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Carrier-Based Ion-Selective Electrodes and Bulk Optodes. 2. Ionophores for Potentiometric and Optical Sensors

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I. Introduction

The first ion-selective electrodes (ISEs) based on bulk membranes containing an ion carrier were introduced more than 30 years ago. It has been estimated that by 1990 more than 7000 papers on ISEs had already been published.[1] ISEs today form one of the most important groups of chemical sensors. On the other hand, bulk membrane optodes have been known for only about 10 years. However, a fairly large number of such optodes have been developed in short time because ionophores originally developed for ISEs can often be used without further modification and because the two types of sensors rely on very similar chemical processes.

The first of this pair of reviews[2] gave a theoretical description of the two sensor types, discussing their response mechanisms, selectivities, detection limits, measuring ranges, response times, and lifetimes. The simultaneous treatment emphasized similarities and differences in the theory of ISEs and optodes and was

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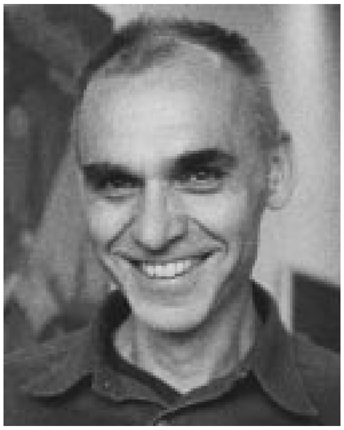

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followed by a general discussion of the requirements on the polymer matrix, membrane solvent, ionic additive, and the carrier. Table 1 of the first of this pair of reviews gave a brief list of the analytes for which carrier-based ISEs and bulk optodes have been developed.

This review describes individual carrier-based ISEs and bulk optodes, ordered according to the analyte for which they have been developed. Many reviews on ISEs have been written,[3−17] selected topics have been covered in the journal *Ion-Selective Electrode Reviews*, and a little-known electronic database summarizes a large number of data on potentiometric sensors (for a first-time user some knowledge of Japanese seems necessary for utilizing this database).[18] A more readily accessible data collection in book form tabulated selectivity data, detection limits, linear ranges, response slopes, and lifetimes of many solid and liquid membrane ISEs up to 1988.[19] However, for many analytes, especially for anions and heavy metal ions, more new carrier-based ISEs have been reported in the last 10 years than before. For other ions, as for example for several clinically relevant blood electrolytes, major improvements in sensor performance were achieved in the 1990s and several new classes of ionophores, such as the cup-shaped calixarenes,[20] were introduced only fairly recently. Therefore, it is not surprising that among the roughly 120 most representative ISEs and optodes whose principal properties have been summarized in Appendix I almost two-thirds have been described in reports published after 1990. This review is intended to document these new developments of carrier-based ISEs, presenting them together with those in the much younger field of the bulk membrane optodes, and tries to put them in a historical perspective. While other articles have reviewed optodes,[21] this is probably so far the most complete review of bulk membrane optodes. This review is intended to be comprehensive enough to mention all analytes for which carrier-based ISEs or bulk membrane optodes have been developed and is supposed to refer to all classes of ionophores that were reported so far for use in bulk membrane ISEs and optodes. It should provide not only a wide overview of relevant work in the field but should also make it possible for the interested reader to quickly find references to specific sensors. For this purpose we have consulted a large number of original publications, reviews and books, searched the literature published between 1981 and November 1996 using the Science Citation Index,[22] and verified many of the references in the original publications found by these means.

To make information on individual sensors easily accessible and emphasize the similarities between ISEs and optodes, the sensors discussed are classified according to the analytes. Cross-references point out similarities in ionophore structures and other sensor characteristics. As a consequence, some issues of general significance are exemplified and discussed in more detail in the sections for particular analytes. Notably, some issues with general relevance to clinical chemistry are discussed in section II.3 on Na^+ sensors, section II.9 on Mg^{2+} sensors, and section II.10 on Ca^{2+} sensors. Furthermore, a few comments on the biocompatibility of ISE membranes have already been made in section III.2.C of the first[2] of this pair of reviews (nitric oxide releasing membranes were suggested recently as a new approach to improve biocompatibility[23]). Apparently "twice-Nernstian" response slopes are discussed in section II.12. Complications in the emf responses to metal cations due to formation of complexes with OH^- or other anions are mentioned in more detail in section II.22 on Pb^{2+}/PbA^+ sensors.

As discussed in the first of this pair of reviews,[2] added ionic sites can be used to control the selectivity of ISEs. Because the full consequences of this have become clear only relatively recently, many of the studies commented on below were performed without consideration of such sites. In quite a number of cases, a reinvestigation of these ISEs by using ionic sites would be of interest (in particular for charged carriers) but to prevent frequent repetitions this was only pointed out where it seemed particularly appropriate.

The methods that were used to determine selectivity coefficients[2] given below are abbreviated as FIM for the fixed interference, as MPM for the matched potential, MSM for the mixed solution,[19] and SSM for the separate solution method. The selectivity coefficients are usually accompanied by a brief description of the sensor membrane composition, indicating the type of ionophore, membrane plasticizer, and ionic sites. Abbreviations for the membrane components and for a some other frequently used terms are given in Appendix II. Because most sensors discussed in this review were prepared with poly(vinyl chloride) (PVC) as membrane matrix, PVC is omitted in the description of the membrane compositions. However, it is always specifically mentioned if the sensor membrane contained no polymer matrix, or if another type of polymer was used instead. Structure formulas of ionophores are usually given in the section discussing sensors on analytes for which these ionophores are selective; the structure formula of a Na^+ ionophore mentioned in the Li^+ sensor section, for example, would be given in the Na^+ sensor section at the place where sensors based on this ionophore are discussed. While often several plasticizers and ratios of ionophore and ionic sites were tested, selectivity data are with few exceptions given in this review only for one membrane composition, which is usually the one that was considered to give the most relevant sensor. All selectivity coefficients given below are either numerical values as reported in the original publications or were obtained from figures given there. The latter technique may have led to minor errors but we expect that these are smaller than experimental errors. Furthermore, it is important to note that the measured selectivities of highly selective ISEs are often not truly determined by interfering ions but rather by the detection limit for the primary ion.[2,24]

The distinction between sensor membranes with and without carrier is less sharp than it may appear at first sight. Many membrane plasticizers have functional groups that may interact with analytes and interfering substances and thereby influence sensor selectivities to some extent. Also, ionic sites form stronger ion pairs with small analyte and interfering ions than with larger ones, which may affect selectivities in case of membranes with a low polarity. However, such electrostatic single point interactions *alone* are rarely large enough to allow for the preparation of a sensor with a selectivity that differs appreciably from the Hofmeister series. Therefore, electrodes and optodes without a ligand that either binds the analyte by multitopic interactions, by formation of a covalent bond or by coordination to a metal center are in this review referred to as ionophore-free ion exchanger electrodes or optodes. Whether the ionic sites or ionophores of these sensors are fixed, i.e., bound covalently to a polymer matrix, or whether they are mobile is, in contrast to earlier assumptions, of no relevance for this classification.

Solid-state ISEs and ionophore-free ion-exchanger ISEs are not topic of this review. For comparison, they are occasionally cited in the chapter on ionophore-based sensors for the same ion. As an exception, ion-exchanger electrodes for complex ions, such as for $Ag(CN)_2^-$ or $Zn(SCN)_4^{2-}$, are mentioned in the chapter on the corresponding metal ion. However, such related sensors are not discussed if a carrier-based sensor for the same ion was not reported.

Numerous ISEs based on enzymes or ion exchangers without carrier function and optical sensors based on enzymes or antibodies were reported for the determination of organic analytes.[25,26] Of particular interest is the measurement of pharmacologically active compounds. However, as in the sections on inorganic analytes too, only carrier-based membrane ISEs and optodes are discussed in this review. References to sensors that do not strictly fall into this category are only given occasionally.

While references related to ionophore-based ISEs will usually lead readers back to the original literature, we often intentionally refer to reviews or recent papers with relevant references when mentioning topics beyond the scope of this review. This is particularly true in case of references to solid-state and ionophore-free ISEs, enzyme-based sensors, and optodes that are not of the bulk membrane type. We did this to aid readers to locate recent references, which will certainly indirectly guide them to the original sources.

The design and synthesis of new selective carriers are not only very important for the ISE and optode development, as is apparent also from this review, but are central issues in modern chemistry. Many interesting carriers, and recently in particular chromoionophores, have been developed but have never been tested for use in ISEs or optodes. However, it would go far beyond the scope of this review to discuss carriers that have not been employed as components of ISEs or bulk membrane optodes.

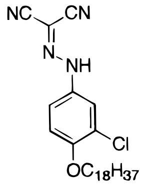
II. Inorganic Cations

1. H^+ Sensors

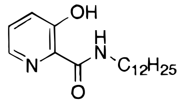
Glass electrodes for pH, widely used for more than 60 years, excel with a high selectivity and have become the standard pH sensor, as recommended for example by the International Federation of Clinical Chemistry (IFCC) and by IUPAC.[27,28] Unfortunately, the very nature of glass presents inherent disadvantages for certain applications. Uses of glass electrodes for in vivo measurements or in food processing, for example, are hazardous because glass easily breaks. The high resistivity of glass also makes miniaturization difficult and leads to relatively large response times for glass microelectrodes.[29] Other problems that were reported are dissolution of glass by hydrofluoric acid, preventing the use with samples containing HF, or the difficulties in integrating glass membranes in sensor arrays. On-line monitoring of pH in tissue of critically ill patients with a disposable polymer sensor, for example, offers distinct advantages over the use of much more expensive, nondisposable glass electrodes because the latter function over a shorter period of time, require more care in application, and have to be carefully sterilized.[30] It has also been claimed that electrode fouling due to protein adsorption on the electrode surface is a more serious in case of glass than for solvent polymeric membranes.[31] However, while protein adsorption may be a problem for miniaturized glass electrodes with a high impedance, regular cleaning of glass electrodes, as recommended by certain manufacturers of clinical analyzers and the International Federation of Clinical Chemistry,[27] can be used to solve this problem if it does occur. Alternatives to pH glass electrodes, such as antimony electrodes[32] or Al_2O_3- or Si_3N_4-based ion-sensitive field-effect transistors (ISFETs),[33] exist but have their own disadvantages, such as for example interference from protein adsorption or phosphate interference in the case of the antimony electrodes.[34]

The pH being defined as the negative logarithm of the activity and not the concentration of H^+, the activity of H^+ is for the vast majority of applications more relevant than its concentration. This can cause problems when samples of very low ionic strength, such as rainwater, are measured and ionic strength adjusters that affect the pH are used to allow for the simultaneous measurement of concentrations of other ions.[35,36] Of course, the same problem also occurs when activities of ions other than H^+ are of interest.

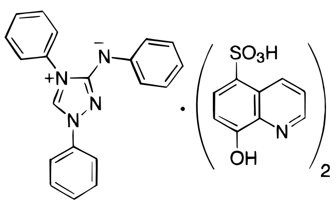
First attempts to develop solvent polymeric H^+-selective electrodes were based on the use of charged ionophores. Inspired by the fact that organic weak acids uncouple oxidative phosphorylation in plant and animal cells by transporting H^+ across mitochondria membranes, mesoxalonitrile *p*-(octadecyloxy)-*m*-chlorophenylhydrazone (**H^+-1**), a lipophilic homologue of a known uncoupler, was incorporated into various membrane matrixes. A block copolymer containing about 60% polysiloxane and 40% poly(bisphenol A carbonate), which can be solvent cast, was found to be the most appropriate matrix.[37−39] According to the same principle, the use of 3-hydroxy-*N*-dodecylpicolinamide (**H^+-2**) was suggested and proved to be of even more general applicability because it could be used in a variety of solvents.[40,41] The use of this carrier in the presence of anionic sites shifts the measuring range by 8 pH units to pH < 4 (applications in HF demonstrated).[41] The anionic sites probably enforced a neutral carrier mechanism while in their absence a charged carrier mechanism prevailed. Isomerides of this carrier have interestingly been reported to give fairly high Cu^{2+} selectivities (e. g., **Cu^{2+}-8**, see section II.15).[42] It was claimed that these charged H^+ carriers are less selective than neutral carriers, but it seems that the selectivities of electrodes based on the former carriers were not fully characterized. An electrode based on Nitron 8-hydroxyquinoline-5-sulfonate (**H^+-3**), was reported to be OH^--selective but seems in fact also to belong to the group of ISEs with charged H^+ carriers.[43]



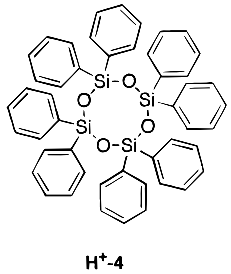
H^+-1



H^+-2



H^+-3



H^+-4

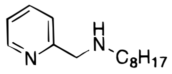
Octaphenylcyclotetrasiloxane (**H^+-4**) was one of the earliest compounds suggested as neutral H^+ carrier but ISE selectivities were moderate and probably determined to a large extent by the plasticizer.[44] An ionophore-free membrane with dioctyl phenylphosphonate as membrane plasticizer and potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (KTpClPB) as added anionic site for example shows quite comparable selectivities.[45]

Inspired by an investigation of ethanolamines as possible anion carriers, the choice of the first highly selective neutral carrier fell on the extremely simple compound tridodecylamine.[46−50] With a linear response over the pH range 4.5−11.0, a Nernstian slope and an excellent selectivity (log $K^{\mathrm{pot}}_{\mathrm{H,J}}$ (FIM): Na^+, −10.4; K^+, −9.8; Ca^{2+}, <−11.1; KTpClPB, DOS), this electrode approached the properties of glass electrodes and was for example used for the measurement of pH in blood serum,[31,51] or as internal sensing element in Severinghaus-type gas sensors for NH_3 and CO_2.[52,53] Microelectrodes based on the same ionophore proved to be equally successful.[29,47,54,55] It was initially reported that electrode membranes that contained besides the ionophore also sodium tetraphenylborate should be pretreated with CO_2. This procedure could not be justified convincingly, and it was later shown to be obsolete when using KTpClPB to provide ionic sites. It was speculated that the CO_2 pretreatment may have increased the solubility of the ionic sites.[56] The use of 68 other mono-, di-, and trialkylamines gave very similar results and also confirmed that a sufficient lipophilicity of the ionophore is a prerequisite for a satisfactory pH response.[57,58]

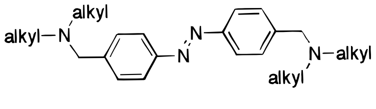
There is some uncertainty on the lipophilicity of the ionophore tridodecylamine. Values for log P_{TLC} of 31[59] and 11.6[48] were reported. The latter is much closer to the log P_{TLC} of 13.5 as estimated on the basis of Hansch parameters. Note, however, that estimated log P_{TLC} values for H^+ carriers only reflect the lipophilicity of the neutral ionophore, whereas as a result of protonation the distribution of the ionophore between sample and membrane is also strongly affected by the sample pH, as discussed in section III.1.D of the first of this pair of reviews.[2] For the same reason, the use of 90% ethanol and 10% distilled water as pH-unbuffered mobile phase for the determination of log P_{TLC} by thin-layer chromatography seems problematic. A further complication in the determination of log P_{TLC} may arise from interactions of the ionophore with residual, uncapped silanol groups on the silica supporting the stationary phase.

To extend the pH range that can be measured, a large number of ISEs based on neutral ionophores (e. g., pyridines, piperazines, morpholines, imidazoles, pyrazoles, anilines, diamines) of very different p*K* values were subsequently tested.[56,59−61] Whereas the dynamic range of an ISE can be shifted to higher pH values as the p*K* of the ionophore increases, and vice versa, as is clear experimentally and was shown also theoretically, the width of the dynamic range cannot be influenced by the p*K* of the ionophore.[62,63] The range of the H^+ response is limited by anion interference at low pH and by cation interference at high pH. To obtain a maximum measuring range, pH electrode membranes based on neutral carriers should ideally contain 50 mol % anionic additives.[62] Interference of cations can be minimized by using membrane plasticizers without coordination sites, such as, e. g., amide, ester, or ether groups. Chloroparaffin, for example, has no such groups and, indeed, its use results in a much larger measuring range than use of bis(2-ethylhexyl) sebacate (DOS), which has potentially complexing ester groups. Even the plasticizer 2-nitrophenyl octyl ether (oNPOE) gives, despite its high polarity, a wider measuring range than DOS. Clearly, the selectivity of the ionophore itself is also likely to decrease if it contains functional groups that interact with interfering ions.[59]

To permit analysis in a wide pH range, two electrodes with different ionophores can be used simultaneously, as was for example demonstrated with a flow injection system (pH range 1−13).[36] On the other hand, incorporation of more than one ionophore into the same membrane, or use of an ionophore with more than one group that can be protonated, does not extend the measurable pH range because the limitations of each carrier (anion and cation interference) narrow the measurable pH range. This was demonstrated for an electrode based on 2-(octylaminomethyl)pyridine (**H^+-5**), the pH range of which was limited by the amino group for low concentrations and by the pyridine group for high concentrations of added anionic sites.[64] At low site concentrations only the amino group is protonated within the range of a Nernstian response to H^+. At site concentrations between 100 and 200 mol %, the amino group is fully protonated and, as long as the electrode responds in a Nernstian way to H^+, the pyridine group is partially protonated. Claims that ionophores with two groups of different basicity increase the range of the H^+ response were made, for example, for 4,4′-bis[(*N*,*N*-dialkylamino)methyl]-azobenzenes (**H^+-6**)[65] or aminated PVC[66] (PVC-NH_2, for references to this polymer see refs 66−69) but experimental data seem not to support this, equally large pH ranges having been found elsewhere also for membranes with ionophores that had only one H^+-coordinating group.

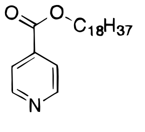


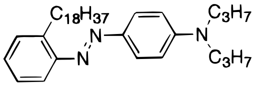
H^+-5



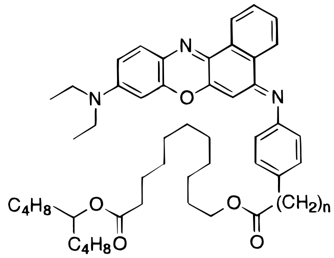
H^+-6

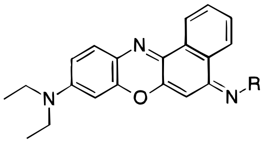
The choice of the ionophore for a specific purpose must therefore depend on the expected pH range of the samples of interest. ISEs with tridodecylamine as ionophore, for example, are appropriate for blood pH measurements,[70−72] detection in ion chromatography[73] and applications in electrophysiology, and quickly replaced glass electrodes to a large extent (linear response range from pH 5 to 11). On the other hand, ISEs based on the less basic 4-nonadecylpyridine are better suited for applications at low pH (linear response range from pH 2 to 9) but give slightly inferior discrimination of interfering cations (log $K^{pot}_{H,J}$:[56] K^+, −8.7; Na^+, −9.7; microelectrode, KTpClPB, oNPOE; log P_{TLC} for this carrier is 20.0[48] but the log P_{TLC} of 11.0 as estimated[48] from Hansch parameters is considerably smaller). For very acidic conditions, such as for measurements in the gastrointestinal tract, ISEs based on octadecyl isonicotinate (**H^+-7** (ETH 1778); log P_{TLC} 15.3; log P_{TLC} estimated as 9.8)[48] can be used, giving a dynamic range down to pH 0. However, the even smaller discrimination of interfering cations (log $K^{pot}_{H,J}$: K^+, −4.4; Na^+, −5.6; Li^+, −6.9; microelectrode, KTpClPB, oNPOE) limits applications of these ISEs to pH < 4.[74] An electrode with the recently introduced ETH 2418 (**H^+-8**), a derivative of propyl red, seems to be a very useful alternative as it allows measurements in the dynamic range from pH < 1 to 10 with a much smaller loss in selectivity (log $K^{pot}_{H,J}$: K^+, −7.4; Na^+, −8.0; Mesamoll H81 (phenylalkylsulfonic acid esters), chloroparaffin 60C, KTpClPB).[75] Interference from the sedative midazolam, which is extracted into the electrode membrane as a neutral species and then seems to act as a second neutral carrier, could be eliminated by using either a silicone rubber membrane or the plasticizer oNPOE.

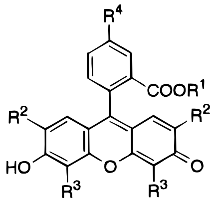

H$^+$-7 (ETH 1778)


H$^+$-8 (ETH 2418)

Recently, H$^+$-selective chromoionophores initially developed for optodes (ETH 2439, ETH 5294, and ETH 5350 (**H$^+$-9** to **H$^+$-11**); all Nile Blue derivatives) were used as ionophores for ISEs.[76–78] Whereas the selectivities of these ISEs are comparable to those based on tridodecylamine (ETH 5294; log $K_{\mathrm{H,J}}^{\mathrm{pot}}$: Na$^+$, −10.9; K$^+$, −10.5; Ca^{2+}, <−11.2; oNPOE, KTpClPB, pH range 4−12),[77] the high lipophilicities of these chromoionophores are an advantage in view of high electrode lifetimes. A comparison of the sensor characteristics for various polymeric matrixes shows the smallest response times for high molecular weight PVC and mobile carriers, whereas carboxylated PVC[49,68,79] (PVC-COOH) gives very sluggish responses and the largest cation interferences. Large response times have also been found for other matrixes of high polarity. On the other hand, the combination of largely immobilized ionophore (4 or 13% impurity of mobile ionophore) and PVC-COOH was found to give intermediate response times, which increased with the amount of free carboxyl groups.[79] While ionophore-free membranes based on aminated PVC (PVC-NH$_2$) membranes and anionic sites or carboxylated[80] PVC show a pH response, incorporation of an ionophore into such membranes leads to improved long-term sensor characteristics, and for the PVC-COOH membranes to considerably higher selectivities (cf. log $K_{\mathrm{H,J}}^{\mathrm{pot}}$: K$^+$, −1.6; Na$^+$, −1.8; NH$_4$$^+$, −1.6; PVC-COOH, 0.3% tetradecylammonium bromide, oNPOE). With the use of chronoamperometry, impedance analysis, and UV−vis spectroscopy, H$^+$ transport in the latter polymer was studied.[68,81] All experimental data confirm that H$^+$ is transported by the ionophore and no evidence for proton hopping between ionophores could be found. On the other hand, H$^+$ hopping seems to be essential in ionophore-free aminated PVC (PVC-NH$_2$) membranes.[69] A good selectivity was found when piperazine was immobilized in PVC membranes (log $K_{\mathrm{H,J}}^{\mathrm{pot}}$: K$^+$, −9.1; Na$^+$, −10.1; Li$^+$, −10.6; PVC-piperazine, KTpClPB, oNPOE, pH range 4−11).[67] Potentiometric pH sensors based on electropolymerized membranes resemble the latter pH electrodes but will not be commented in this review. Interestingly, the only charged H$^+$ carrier that was developed for optodes and was subsequently also used in potentiometry is so far **H$^+$-12** (ETH 7075).[82] While tetrakis(4-chlorophenyl)borate as anionic site enforces a neutral carrier mechanism below pH 2.5 and gives only a poor H$^+$ selectivity (log $K_{\mathrm{H,K}}^{\mathrm{pot}}$ −1.5), use of tridodecylmethylammonium as cationic site results in a much higher selectivity based on a charged carrier mechanism (log $K_{\mathrm{H,K}}^{\mathrm{pot}}$ −8.3) and a measuring range from pH 3.5 to 10.


H$^+$-9 (ETH 2439): n=1
H$^+$-22 (ETH 5418): n=0


H$^+$-10 (ETH 5294): R=COC$_{17}$H$_{35}$
H$^+$-11 (ETH 5350): R=CH$_2$CH(C$_8$H$_{17}$)$_2$
H$^+$-13 (ETH 2430): R=C$_{18}$H$_{37}$
H$^+$-14 (ETH 2458): R=COCH(C$_8$H$_{17}$)(C$_{18}$H$_{37}$)
H$^+$-15 (ETH 2462): R=CH$_2$CH(C$_8$H$_{17}$)(C$_{18}$H$_{37}$)
H$^+$-16 (ETH 2468): R=COCH(C$_{18}$H$_{37}$)$_2$
H$^+$-17 (ETH 3531): R=CO(CH$_2$)$_{11}$N(CH$_3$)COCH(CH$_2$polymer)$_2$
H$^+$-18 (ETH 5348): R=COCH(C$_8$H$_{17}$)$_2$

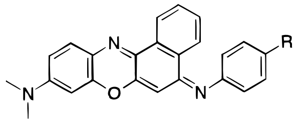

H$^+$-12 (ETH 7075): R^1 = C$_{18}$H$_{37}$; R^2 = H, R^3 = Br, R^4 = H
H$^+$-23 (ETH 5355): R^1 = C$_{18}$H$_{37}$; R^2, R^3 = Br, R^4 = H
H$^+$-24 (ETH 7058): R^1 = C$_{18}$H$_{37}$; R^2, R^3 = I, R^4 = H
H$^+$-25 (ETH 7061): R^1 = C$_{18}$H$_{37}$; R^2, R^3, R^4 = H
H$^+$-26 (ETH 2479): R^1 = CH$_2$CH(C$_8$H$_{17}$)(C$_{18}$H$_{37}$); R^2, R^3, R^4 = H
H$^+$-27 (A 118): R^1 = H; R^2, R^3 = H, R^4 = NHCOC$_{17}$H$_{35}$

Optodes. The use of indicator dyes for the determination of pH is a very old concept, exemplified for example in the classical litmus paper. Since the first detailed report of a fiber-optic pH sensor[83] in 1980, a very large number of pH optodes based on various transduction principles, such as changes in absorption, fluorescence (direct or with energy transfer from a donating to an accepting fluorophore), or refractive index, have been reported.[84] These sensors can be classified as to whether the indicator dye is trapped or immobilized (i) on the surface of an otherwise inert, sometimes porous support, such as glass or an ion-exchanger, (ii) in a hydrophilic polymer, or (iii) in a hydrophobic film that forms a phase clearly distinct from the sample.[2] In reports on sensors of type i or ii, to which the majority of reported pH optodes belong, the influence of co-ions is usually neglected, as has been discussed elsewhere.[84–89] Only type iii optodes, which are based either on phase distribution of H$^+$ and a co-anion, or ion-exchange of H$^+$ against a competing cation, fall within the scope of this review. Consequently, sensors for which the identity of the co-extracted counteranion or competing cation has not been clearly established will not be discussed unless this seemed particularly appropriate.

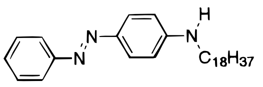
Although the field is still very young, already a quite large number of optodes based on principle iii have been reported. However, most of them will be mentioned only in later chapters because they respond to activity products or ratios involving H$^+$ and were used to determine analytes other than H$^+$ in pH buffered sample solutions. In this chapter only pH bulk optodes and some representative H$^+$ chromoionophores that were repeatedly used in other optodes will be discussed.

On one hand, 13 neutral H$^+$ chromoionophores (**H$^+$-9** to **H$^+$-11** and **H$^+$-13** to **H$^+$-22**), most of them Nile Blue derivatives,[90] were well-characterized by their pK_a in optode membranes, lipophilicity, chemical stability, and absorption properties. Interestingly, they are slightly more basic in the membrane phase than in methanol or water, which may be due to stronger solvation of H$^+$ in the latter. The wide range of their pK_a values (5.2−14.0) makes it possible to design bulk optodes for specific measuring ranges. Chromoionophore decomposition was found to be only a problem under direct sunlight irradiation. On the other hand, nine electrically charged H$^+$ ionophores (fluoresceins **H$^+$-12** and **H$^+$-23** to **H$^+$-27**; hydroxy coumarins **H$^+$-28** and **H$^+$-29**; anthraquinone **H$^+$-30**; hydroxypyridinecarboxamide derivative **H$^+$-2**) were shown to cover a range of more than 10 pK_a units.[91] Other charged H$^+$ chromoionophores that were used in carrier-based optodes are for example *o*-cresolphthalein octadecyl ester (LAD-4; **H$^+$-31**) or substituted diphenylamines (**H$^+$-32**, LAD-3; **H$^+$-33**, LAD) resembling the Takagi reagent (**K$^+$-11**).[92−94] A combination of a Na$^+$ ionophore and one of many charged H$^+$ chromoionophores incorporated into an oNPOE/PVC membrane supported by a filter paper was used for visual and photometric determinations of Na$^+$ in urine.[95] Similar assays, based for example on 4-[(2,6-dibromo-4-nitrophenyl)azo]-2-octadecyloxy-1-naphthol (**H$^+$-34**) as charged H$^+$ chromoionophore, were reported for K$^+$ analysis.[96,97]

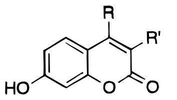
Even though many optodes could be easily used to determine pH, only few have so far served for this purpose. Responses of pH optodes based on coextraction of anion−proton pairs at a constant concentration of the anion were reported for several anions.[98] Whereas H$^+$ was detected by complexation with a Nile Blue derivative as the selective chromoionophore, no ionophore was used for anion binding. Similar efforts based on octyl bis(2,4-dinitrophenyl)acetate (**H$^+$-35**) as a charged carrier for H$^+$ and coextraction of an anion were less successful, probably because of interference from buffer ions.[99] The response of an optode with an azobenzene ionophore (**H$^+$-36**) was based on competitive exchange of Na$^+$ and H$^+$, but no Na$^+$ ionophore was used.[100] Bulk optodes based on an acridine derivative as H$^+$ ionophore (**H$^+$-37**) were found to respond to H$^+$ in the range from pH 6 to 9 but the response mechanism and possible influence and nature of a coextracted anion was not discussed.[101] The same compound was also reported as Ag$^+$ chromoionophore.[102]



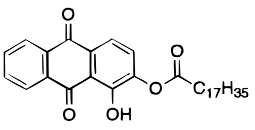
H$^+$-19 (ETH 5300): R=$C_{16}H_{33}$
H$^+$-20 (ETH 5326): R=$OC_{18}H_{37}$



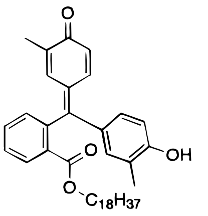
H$^+$-21(ETH 5315)



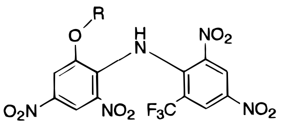
H$^+$-28 (C 828): R = H, R' = $COC_{17}H_{35}$
H$^+$-29 (C 837): R = $C_{17}H_{35}$, R' = H



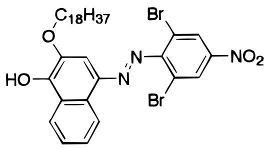
H$^+$-30 (ETH 2425)



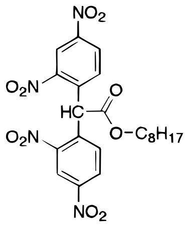
H$^+$-31(LAD-4)



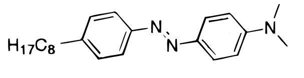
H$^+$-32 (LAD-3): R = $C_{18}H_{37}$
H$^+$-33 (LAD): R = C_8H_{17}



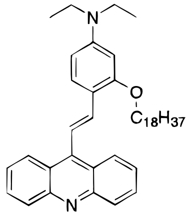
H$^+$-34



H$^+$-35



H$^+$-36



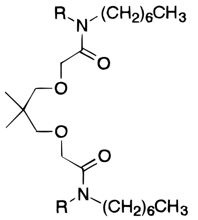
H$^+$-37

2. Li$^+$ Sensors

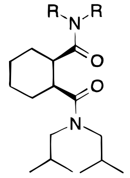
The major interest for Li$^+$ analysis arises from the effective prophylactic and therapeutic action of Li$^+$ in various affective disorders, a purpose for which Li$^+$ was approved by the US Food and Drug Administration in 1970. Because the therapeutic range in blood is very narrow (0.8−1.0 mM) and limited by adverse side effects above 2.0−2.5 mM Li$^+$, monitoring of this analyte is indispensable.[103] Li$^+$-selective electrodes belong therefore to the most investigated types of ISEs.[104] A comprehensive review has covered publications on carrier-based and other Li$^+$-selective electrodes up to 1986.[105] A large number of publications on ionophore-based Li^+-selective electrodes have been published since. Two new classes of Li^+ ionophores (natural carboxylic polyether derivatives and heteroaromatic compounds) were introduced and considerable improvements in selectivity were achieved. The first commercial clinical analyzers with ISEs for Li^+ became available only in 1987 but potentiometric determination of Li^+ has quickly become popular.[106-109]

The major challenge for Li^+-selective electrodes is the required selectivity against Na^+, which is ≈140 mM in blood, thus requiring a log $K^{pot}_{Li,Na}$ of at least −4.3 for less than 1% interference. Li^+ glass or lithium bronze electrodes are inadequate because they are not selective enough.[105] Most Li^+ ionophores used for ISEs are either diamides or crown ethers but derivatives of natural polyether antibiotics, heteroaromatic compounds and polypropoxylates were reported as well.

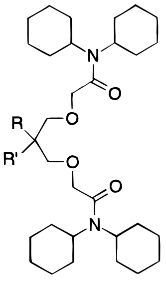
Di- and Triamide Ionophores. The first Li^+ ionophores for ISEs were obtained by increasing the number of carbon atoms between the ether oxygens of 3,6-dioxaoctanoic diamides, which were known to induce Ca^{2+} selectivity (**Li$^+$-1**, log $K^{pot}_{Li,J}$ (SSM): Na^+, −1.3; K^+, −2.1; NH_4^+, −1.3; Ca^{2+}, −3.3; Mg^{2+}, −3.7; TEHP).[110,111] They soon found an application in microelectrodes and became commercially available.[55,112] Over the years, a large number of diamides were investigated, with variations in the backbone connecting the two amide groups and the substituents on the amide nitrogens. Improvements were obtained by using the more rigid, oxygen-free backbone provided by *cis*-cyclohexane-1,2-dicarboxamide.[113,114] In subsequent studies, the substituents of the amide groups were varied, demonstrating their large influence on the selectivity.[115] With ETH 1810 (**Li$^+$-2**; log P_{TLC} ≈ 7.3)[48] it became possible to determine Li^+ in blood within the clinically relevant activity range by making calibrations in LiCl solutions with a constant background of NaCl, KCl, $CaCl_2$, and $MgCl_2$ (log $K^{pot}_{Li,Na}$ (SSM): −2.3; (FIM): −2.5; oNPOE, KTpClPB).[107,116] The membrane plasticizer used for this electrode (oNPOE) leads unfortunately to longer response times and a shorter membrane lifetime. Thus, the slightly less selective ETH 2137 (**Li$^+$-3**; log P_{TLC} 10.3),[48,117] which gives a log $K^{pot}_{Li,Na}$ of −1.9, was preferred for clinical applications (log $K^{pot}_{Li,J}$ (SSM): K^+, −2.5; NH_4^+, −2.4; Ca^{2+}, −3.7; Mg^{2+}, −3.8; bis(1-butylpentyl) adipate) but required corrections based on the Na^+ concentration.[118] Alternatively, the same ionophore can be used to determine Li^+/Na^+ ratios.[119] This ligand is the result of an optimization of the substituents on the amide nitrogens as well.[118,120]



Li$^+$-1: R = CH_3
Li$^+$-8: R = $(CH_2)_2OCH_2CH_3$

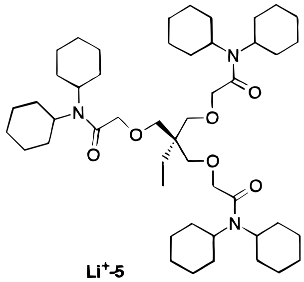


Li$^+$-2 (ETH 1810); R = cyclohexyl
Li$^+$-4 (ETH 1644); R = $CH_2CH(CH_3)_2$

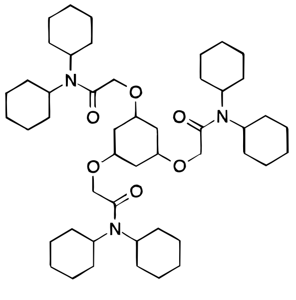


Li$^+$-3 (ETH 2137): R = ethyl, R' = butyl
Li$^+$-7: R, R' = CH_3
Li$^+$-9: R = H, R' = $C(C_6H_5)_3$
Li$^+$-10: R, R' = $CH_2(C_6H_5)_2$
Li$^+$-11: R, R' = CH_2(α-naphthyl)$_2$

Variation of the concentration of added ionic sites in membranes containing *cis-N,N,N′,N′*-tetraisobutylcyclohexane-1,2-dicarboxamide (**Li$^+$-4**) as carrier as well as X-ray structure analysis showed the formation of complexes of one Li^+ ion and two carrier molecules.[115] On the other hand, covalent linkage of two diamides to give a tetraamide, designed in analogy to bis(crown) compounds, was shown to result in 1:1 complexes with Li^+ that are only slightly more stable than the 1:1 complexes of the diamides.[121,122] It is therefore not surprising that an improvement of the potentiometric selectivity with the tetraamides was not achieved.[121,123] Similarly, two triamide ionophores (**Li$^+$-5** and **Li$^+$-6**) with a total of six dicyclohexyl substituents on the nitrogen atoms showed selectivities very comparable or even worse than similar diamides.[124,125]



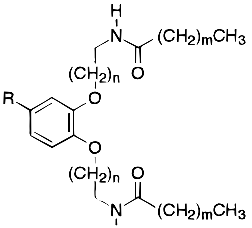
Li$^+$-5



Li$^+$-6

In contrast to the cyclohexane-1,2-dicarboxamide **Li$^+$-4**, a diamide host with two ether oxygens in the backbone (**Li$^+$-7**) was found to form 1:1 complexes, with all four oxygen atoms of the carrier interacting with the metal ion.[118] A 3,7-dioxanonanediamide with two additional ether oxygens in the substituents of the amide groups (**Li$^+$-8**), which was expected to form a 1:1 complex with a coordination number of six,[126] did not give the sought-after selectivity for Li^+ against Na^+.[104,127,128] The same is true for the attachment of pyridine or ether substituents to the carbon in 5-position of 3,7-dioxanonanediamides, and for a reduction of the flexibility of the 3,7-dioxanonanediamide backbone by using 1,8-naphthalenediol, cyclohexane, or cyclopentene units.[129] However, various bulky aromatic substituents (one triphenylmethyl or two benzyl or 1-naphthylmethyl substituents; **Li$^+$-9** to **Li$^+$-11**) in 5-position lead to a slight selectivity improvement (log $K^{\text{pot}}_{\text{Li,Na}}$ (SSM): -2.0).[129] A number of other diamide backbones, based for example on bis-phthalimide, bis-benzothiazole, disubstituted furan, pyridine, or polyethers, were used but neither a clear correlation between structure and selectivity nor improvements in selectivities could be found.[104,127]

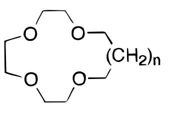
Owing to their tendency to form intramolecular hydrogen bonds, compounds with secondary amides were assumed to give less efficient Li$^+$ ionophores. Indeed, several ionophores with two secondary amide groups (**Li$^+$-12**) were found to be less selective than the above-described ligands, but whether this is only due to the secondary amide groups in these ionophores or also due to changes in other structural features is not clear.[130] Interestingly, Mg^{2+} ionophores with secondary amide groups are superior to corresponding tertiary amides (see section II.9).[131−133]



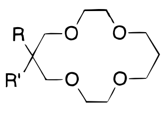
Li$^+$-12: R = H or *tert*-butyl,
n = 1 or 2, m = 2, 6, 10 or 14

Cyclic diamides are a particularly interesting class of compounds because the original assumption for the development of the above-mentioned noncyclic diamides was that cyclic systems might lead to slow decomplexation, and therefore to impairment of the ISE performance. Indeed, sub-Nernstian emf slopes were observed repeatedly for ISEs based on several cyclic diamides, particularly in the presence of trioctylphosphine oxide and even though added ionic sites were used.[134,135] However, the actual reason for these sub-Nernstian slopes has not been investigated.

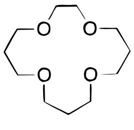
Crown Ether Derivatives. With an ionic diameter of only 68 pm, Li$^+$ fits well into the cavities formed by crown ethers of sizes in the range from 12-crown-4 to 15-crown-4 (**Li$^+$-13** to **Li$^+$-16**). Unfortunately, the discrimination of Na$^+$, the interfering ion of highest concern in clinical analysis, can be impaired by the formation of sandwich complexes between the larger Na$^+$ ion and two crown ether ionophores with ideal fit for Li$^+$. Many relatively simple crown ethers have therefore been found to give only quite small potentiometric discrimination of Na$^+$.[105,136−139] However, with a careful choice of the site concentration the formation of 1:1 complexes with monovalent ions could be enforced and thus the selectivity for Li$^+$ over Na$^+$ could be improved.[2,140]



Li$^+$-13: n = 0
Li$^+$-14: n = 1

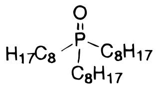


Li$^+$-15: R, R' = H
Li$^+$-17: R = CH$_3$, R' = C$_{12}$H$_{25}$
Li$^+$-18: R = H, R' = C$_{12}$H$_{25}$
Li$^+$-19: R, R' = CH$_2$C$_6$H$_5$
Li$^+$-23: R = C$_{12}$H$_{25}$, R' = CH$_2$CON(CH$_2$CH$_3$)$_2$

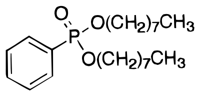


Li$^+$-16

The notion of introducing additional substituents to hinder the formation of sandwich complexes has been introduced early on. Whereas this concept failed when applied to 12-crown-4, 13-crown-4, and 16-crown-4 compounds, showing the importance of the fit of the cavity size, it proved to be very successful for 14-crown-4 and 15-crown-4 ionophores.[137,139] The role of methyl groups to hinder sandwich complex formation is also evidenced by the influence of the ionophore concentration on the potentiometric selectivity. Whereas the selectivity induced by a hindered ionophore hardly altered with its concentration, a pronounced decrease of the selectivity was found with a nonhindered ionophore at high concentrations (3-dodecyl-3-methyl-1,5,8,12-tetraoxacyclotetradecane (**Li$^+$-17**, log P_{TLC} 9.6),[48] log $K^{\text{pot}}_{\text{Li,Na}}$ (FIM): -2.2; 3-dodecyl-1,5,8,12-tetraoxacyclotetradecane (**Li$^+$-18**), log $K^{\text{pot}}_{\text{Li,Na}}$ (FIM): -1.8; oNPOE, KTpClPB). Using a coated-wire ISE and calibrations in pooled serum blanks, the ISE with **Li$^+$-17** was the first potentiometric sensor to be reported for Li$^+$ determinations in clinical serum samples.[141−143] Addition of a small amount of trioctylphosphine oxide (**PL-1**), which may coordinate to Li$^+$, to membranes containing **Li$^+$-17** led to a further improvement of log $K^{\text{pot}}_{\text{Li,Na}}$ (-2.7; oNPOE, KTpClPB and small amount of trioctylphosphine oxide; FIM) but worsened the detection limit and the selectivity toward H$^+$.[144−146] Whereas the complexing properties of compounds containing P=O groups are also shown by the observation that ionophore-free PVC membranes with di-*n*-octyl phenylphosphonate (**PL-2**) have a certain selectivity for Li$^+$ (log $K^{\text{pot}}_{\text{Li,J}}$ (SSM): H$^+$, $+0.6$; Na$^+$, -1.2; K$^+$, -1.8; Mg^{2+}, -1.8),[45] it must also be pointed that out that use of phosphine oxide additives was reported to have no or even an adverse effect on selectivities for several other Li$^+$ ionophores.[142,147] Furthermore, for none of 11 bis(phosphine oxide) ionophores log $K^{\text{pot}}_{\text{Li,Na}}$ values smaller than -0.9 could be obtained.[148]

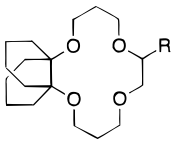


PL-1



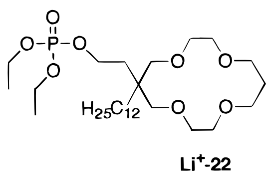
PL-2

Further application of the concept of steric hindrance led to stepwise improvements of log $K^{\text{pot}}_{\text{Li,Na}}$ (**Li$^+$-19**, (FIM): -2.9; NPPE and TEHP (98:2) as plasticizer mixture).[149,150] The formation of sandwich-type 2:1 complexes with interfering ions seems to be at least suppressed by two benzyl groups. Therefore, added ionic sites could not be expected to improve the potentiometric selectivity very much. Nevertheless, KTpClPB slightly improved selectivities (in particular versus H^+).[140] A breakthrough in selectivity was however achieved when bulky substituents were attached to the ethylene rather than the propylene bridge. An investigation of five 14-crown-4 ethers with substituents on only one ethylene bridge and six derivatives with substituents on both ethylene bridges clearly showed that too many bulky substituents do not lead to an optimal selectivity and furthermore lengthen response times, probably owing to a slow complexation reaction.[147,151] This conclusion agrees with the results for some 14-crown-4 ethers substituted on the propylene bridge.[152] However, the ionophores with bulky substituents on only one ethylene bridge give excellent selectivities, the best result being obtained for two ionophores (**Li$^+$-20** and **Li$^+$-21**) with a decalino subunit. The compound **Li$^+$-21**, which has a tetradecyl substituent to ensure high lipophilicity, is presently the only Li^+ ionophore with a Li^+/Na^+ selectivity larger than 1000 that was demonstrated to be useful for measurements in serum (log $K^{pot}_{Li,J}$ (SSM): Na^+, −3.0; K^+, −3.6; Ca^{2+}, −4.9; Mg^{2+}, −5.0; log $K^{pot}_{Li,J}$ (FIM): Na^+, −3.1; K^+, −3.6; Ca, <−5.0; Mg^{2+}, <−5.0; BBPA, KTpClPB).[147]

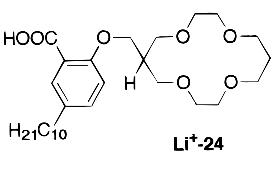


Li$^+$-20: R = H
Li$^+$-21: R = $C_{14}H_{29}$

On the other hand, there were several attempts to improve log $K^{pot}_{Li,Na}$ by introducing additional binding sites as side arms. A first generation of such ionophores had functional substituents on the propylene bridge of the 14-crown-4 skeleton. Whereas ether and ester groups decreased the selectivity, probably because of an increased stability of complexes with cations that are too large to fit the crown cavity ideally, a phosphoric acid triester (**Li$^+$-22**) or an amide group (**Li$^+$-23**) did improve the selectivity, but unfortunately this effect was not as pronounced as the one achieved with the concept of steric hindrance.[149,150,153] With neutral or acid solutions, a carrier with a benzoic acid substituent (**Li$^+$-24**) seemed to function as a neutral carrier in the presence of a tetraphenylborate and led only to a very small response to H^+, whereas in solvent extraction the same carrier is deprotonated to allow for neutrality in the organic bulk phase.[154] The carboxylic acid group seemed to contribute to the potentiometric selectivity by providing an additional coordination site. A quinoline group was reported to have no appreciable effect on selectivity coefficients.[150] Also, functional groups attached to dibenzo-14-crown-4 did not lead to an improvement in potentiometric selectivities.[155]

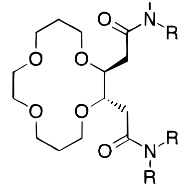


Li$^+$-22



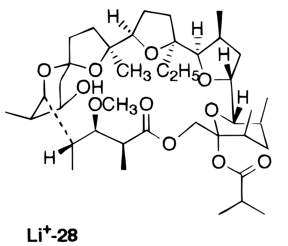
Li$^+$-24

In a series of papers a large number of ISEs with 14-crown-4 ionophores mono- or difunctionalized with ether, alcohol, cyanide, thiophene, carboxylic acid, ester and amide groups on the ethylene rather than on the propylene chain were described.[156−159] A dibutyl and a diisobutyl diamide (**Li$^+$-25** and **Li$^+$-26**), whose bulkiness and ability to provide additional coordination sites seem both to be important, led to log $K^{pot}_{Li,Na}$ −2.9 and −3.3 (FIM; oNPOE, KTpClPB), respectively. Interestingly, there is a certain similarity of these compounds to the above-mentioned very successful decalino-14-crown-4 compounds **Li$^+$-20** and **Li$^+$-21**. Unfortunately, the membrane containing the diisobutylamide compound gave a very poor performance when used in serum. The use of the dibutyl derivative on the other hand resulted in a lifetime of at least 50 d, the selectivity being however slightly inferior to that of the decalino-14-crown-4 ionophores.

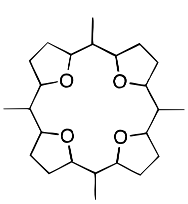


Li$^+$-25: R = $(CH_2)_3CH_3$
Li$^+$-26: R = $CH_2CH(CH_3)_2$

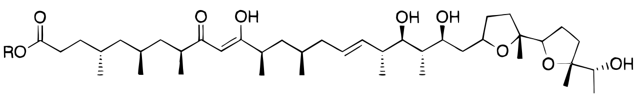
Natural Carboxylic Polyether Derivatives. Natural carboxylic polyether derivatives form a fairly new class of Li^+ ionophores, designed with the idea that relatively small changes in the structure of these rather rigid compounds can lead to large changes in their selectivities. The antibiotic ionomycin, for example, has a high affinity for Ca^{2+}, but its methyl ester (**Li$^+$-27,** R = CH_3) was found to be moderately selective for Li^+ (log $K^{pot}_{Li,Na}$ (FIM): −1.3; dibenzyl ether as plasticizer).[160−162] Analogously, lactone formation decreases the size of the host cavity of the Na^+ ionophore monensin. Further reduction of the guest cavity by acylation of the tertiary hydroxyl group prevents complexation with large cations, resulting in Li^+ selectivity (**Li$^+$-28**, log $K^{pot}_{Li,Na}$ (SSM): −1.8; dibenzyl ether as plasticizer, KTpClPB).[163] Similar but more successful was an attempt to take advantage of the relatively rigid structure of cyclic



Li$^+$-28



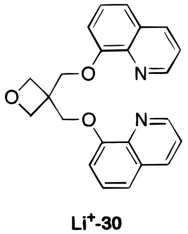
Li$^+$-29



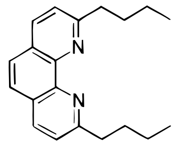
Li$^+$-27: R = CH_3
(ionomycin: R = H)

polyethers containing furan or tetrahydrofuran units (**Li^+-29**: log $K^{pot}_{Li,J}$ (SSM): Na^+, −2.8; K^+, −4.3; NH_4^+, −3.2; Cs^+, −4.6; TEHP, KTpClPB).[164,165]

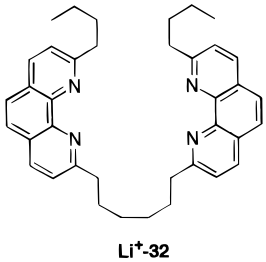
Heteroaromatic Ionophores. To another relatively new class of Li^+ ionophores belong heteroaromatic compounds with nitrogens as ligating atoms. First carriers of this class, which had two 8-quinonyloxy groups, led only to a quite limited selectivity, which could however be improved in the presence of small amounts of organophosphorus compounds, such as trioctylphosphine oxide (**Li^+-30**, log $K^{pot}_{Li,Na}$ (SSM): −2.2; oNPOE and trioctylphosphine oxide; log $K^{pot}_{Li,Na}$ (SSM): −1.5; oNPOE without trioctylphosphine oxide, KTpClPB).[166,167] More successful were phenanthroline derivatives with moderately bulky substituents in 2- and 9-position,[168−170] a very low log $K^{pot}_{Li,Na}$ of −3.3 being obtained for the dibutyl derivative (**Li^+-31**; log $K^{pot}_{Li,J}$ (SSM): H^+, +2.7; Na^+, −3.3; K^+, −3.6; Ca^{2+}, −3.2; NPPE, KTpClPB). Unfortunately, the H^+ interference is strong. Among various oligomethylene-bridged bis-1,10-phenanthroline compounds, an ionophore with a hexanediyl bridge was found to provide the highest selectivity (**Li^+-32**; log $K^{pot}_{Li,J}$ (SSM): H^+, +3.5; Na^+, −3.2; K^+, −3.7; Ca^{2+}, −3.5; oNPOE, KTpClPB).[171] Interference from Mg^{2+}, for whose detection phenanthroline derivatives were also suggested (see section II.9), is no serious problem. Phenanthroline ionophores have also been used in ISEs for transition metal ions (Cu^{2+}, Zn^{2+}; see sections II.15 and II.17) and, therefore, interference from those ions in certain applications might occur.



Li^+-30



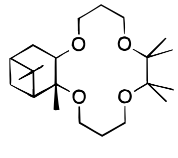
Li^+-31



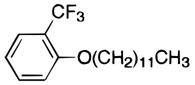
Li^+-32

Poly(propylene glycol) Salts. Only a limited Li^+ selectivity can be obtained with membranes containing the tetraphenylborate-barium complex of poly(propylene glycol) and a phosphonate plasticizer. Also, ISEs based on corresponding Li^+ salts were reported to give very similar selectivities (log $k^{MPM}_{Li,J}$ (0.14 M NaCl): Na^+, −1.4; K^+, −2.4; Ca^{2+}, −0.4; DOPP, Ba(polypropylene glycol $1025)_{0.69}$-$(TPB)_2$).[143,172,173] However, the low cost and ready availability of these ionophores may be an advantage under certain circumstances.

Optodes. A flow-through optode for Li^+, based on a sterically highly crowded 14-crown-4 derivative with a pinane subunit (**Li^+-33**) as Li^+ ionophore and the charged H^+ carrier LAD-3 (**H^+-32**), was reported for determinations in the range from 10^{-6} to 10^{-1} M Li^+, the logarithms of the selectivity coefficients for all alkali and alkaline earth metals being smaller than −4.[93] DOS proved to be superior to the more polar *o*-trifluoromethylphenyl dodecyl ether (**PL-3**), which is a colorless membrane plasticizer that was designed to resemble the slightly yellow oNPOE. The ionophore **Li^+-33** was also employed for an ISE[147] but was less successful there. A slow response of the ISE to Li^+ but not to Na^+ was interpreted as indicating slow complexation of Li^+.



Li^+-33 (PTM14C4)

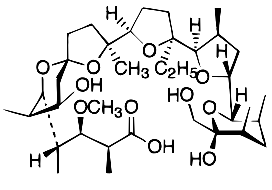


PL-3

3. Na^+ Sensors

More than two-thirds of the publications on Na^+ ISEs were written during the last 10 years, showing that this field, despite its fairly long history, is still very active. A major interest for Na^+ analysis with ISEs comes from clinical chemistry.[174] Whereas the determination of this analyte in blood or urine requires often only a modest selectivity, intracellular measurements are much more demanding. Both in view of miniaturization as well as for in vivo studies, liquid membrane electrodes are preferred over glass electrodes, some of which have a fairly good selectivity (log $K^{pot}_{Na,K} \approx -3$) but suffer from a strong interference from H^+.[175] Nevertheless, glass electrodes are still used in several commercial clinical analyzers,[176,177] in which, however, appropriate electrode cleaning cycles may be necessary to cope with protein adsorption[12] (see also cleaning of pH glass electrodes[27]).

Monensin and Monensin Derivatives. Monensin (**Na^+-1**) was one of the carboxylic acid antibiotics surveyed in the early days of ISEs[178−180] and was also used in early Na^+ microelectrodes.[181] It was shown by use of membranes with added anionic or cationic sites that in contact with pH-unbuffered solutions this ionophore acts as a neutral Na^+ ionophore (log $K^{pot}_{Na,J}$ (SSM): K^+, −1.1; H^+, −2.8; Li^+, −0.6; Ca^{2+}, −3.1; oNPOE, 10 mol % KTFPB).[182] The interference from H^+ was found to depend particularly strongly on the site concentration. A rather high interference from Ba^{2+} was observed (log $K^{pot}_{Na,J}$ (SSM): Ba^{2+}, −0.9 (pH = 6.0), +1.0 (pH = 8); dibenzyl ether).[162,183,184] Note, however, that variaton

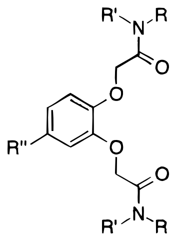


Na^+-1 (monensin)

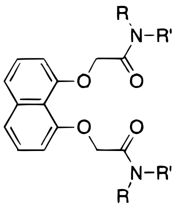
of the sample solution pH confirmed that in the presence of anionic sites and at pH 7.0 monensin is a charged carrier for Ba^{2+} (see section II.12).[185]

A series of monensin esters has been synthesized.[183] They all have relatively similar selectivities and the most lipophilic of them, a dodecyl ester, was shown to be useful for blood serum measurements, even though the discrimination of K^+ was rather poor ($\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (SSM): K^+, −0.7; Ba^{2+}, −2.8; diisodecyl phthalate). The less lipophilic methyl ester has been used for the commercial Ektachem slides, which contain a complete measurement cell with selective membrane and reference electrode but are disposable and intended for one test only.[186,187] Interestingly, ISEs based on PVC membranes plasticized with oNPOE and containing monensin methyl ester as ionophore have recently been suggested as nonspecific detectors for ion chromatography because they have a very similar sensitivity for various monovalent cations.[188] As mentioned above, the lactone of monensin was used as Li^+ ionophore.[163]

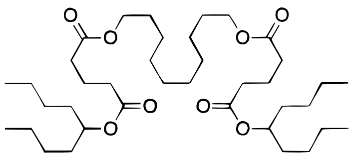
Noncyclic Amide Ionophores. As in the case of Li^+ ISEs, the first class of fully synthetic ionophores that was investigated were the noncyclic di- and triamides.[189−191] One of the most successful diamides was ETH 157 (**Na$^+$-2**, $\log P_{\mathrm{TLC}}$ 4.6:[48] $\log K^{\mathrm{pot}}_{\mathrm{Na,K}}$ −0.3; **PL-4** as plasticizer).[192−195] Even though the discrimination of K^+ is poor, it can be used for measurements in extracellular fluids and has been applied in clinical analyzers. Whereas efforts to improve its selectivity by introducing substituents to the central aromatic ring were not successful,[196] the use of a 1,8-naphthalenediol (**Na$^+$-3**) instead of the catechol unit improved $\log K^{\mathrm{pot}}_{\mathrm{Na,K}}$ (SSM) to −0.7 and, upon further replacing the substituents on the nitrogens by cyclohexyl groups, to −1.3 (**Na$^+$-4**, bis(1-butylpentyl)adipate).[197] A similar improvement in the discrimination of K^+, accompanied by a smaller loss in that of Ca^{2+}, was obtained by replacing the phenyl and benzyl groups of **Na$^+$-2** with cyclohexyl groups (**Na$^+$-5** (ETH 2120): $\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (SSM): K^+, −1.5; H^+, −0.6; Li^+, −1.2; Ca^{2+}, −2.9; BBPA; $\log P_{\mathrm{TLC}}$ 8.3).[195,198] A recent report described the use of **Na$^+$-5** for ISFETs with fluorosilicone membranes ($\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (FIM): K^+, −1.8; Li^+, −1.3; Ca^{2+}, −3.0; NaTPB).[199] For a much more lipophilic version of this ionophore (**Na$^+$-6** (ETH 4120): $\log P_{\mathrm{TLC}}$ 17.2) only small decreases in selectivity and no loss in response time were observed.[200,201]



Na$^+$-2 (ETH 157): R = benzyl, R' = phenyl, R" = H
Na$^+$-5 (ETH 2120): R,R' = cyclohexyl, R" = H
Na$^+$-6 (ETH 4120): R,R' = cyclohexyl, R" = $\mathrm{CH_2OCOC_{17}H_{35}}$

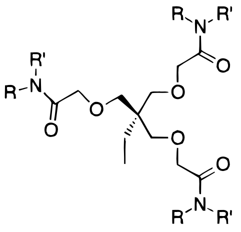


Na$^+$-3: R = phenyl, R' = benzyl
Na$^+$-4: R, R' = cyclohexyl



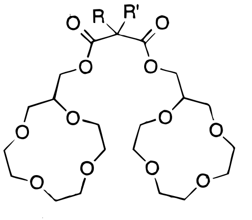
PL-4

The first neutral carrier with a sufficiently large discrimination of K^+ that allowed for intracellular measurements was **Na$^+$-7** (ETH 227), which is a triamide with three ether groups, giving a total of six oxygens as possible coordination sites ($\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (SSM): K^+, −2.3; H^+, −0.7; Li^+, +0.4; Ca^{2+}, −0.5; oNPOE).[175,192,202,203] This ionophore has subsequently been used in many microelectrode studies of intracellular processes.[55,204,205] When using bis(1-butylpentyl) adipate (BBPA) as membrane plasticizer, the discrimination of Ca^{2+} was just good enough to allow for measurements in urine and serum[206,207] but more selective ionophores have become available by now. A recent study of several very similar tripodal amides and esters showed for **Na$^+$-8** (a hexabutyl isomeride of **Na$^+$-7**) a slightly higher discrimination of K^+ but a more pronounced interference from Ca^{2+} ($\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (FIM): K^+, −2.6; Ca^{2+}, −0.1; oNPOE, KTpClPB).[208]

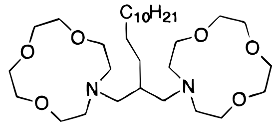


Na$^+$-7 (ETH 227): R = $\mathrm{CH_3}$, R' = $\mathrm{C_7H_{15}}$
Na$^+$-8: R, R' = $\mathrm{C_4H_9}$

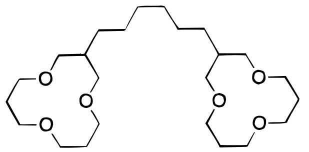
Crown Ether Ionophores. A rather high discrimination of K^+ and Li^+ was obtained[209,210] for several ionophores with two 12-crown-4 units, which form 1:1 complexes with sandwich structure, in analogy for example to the bis(15-crown-5) ionophores used for K^+ selective electrodes (**Na$^+$-9** ($\log P_{\mathrm{TLC}}$ 6.7):[48] $\log K^{\mathrm{pot}}_{\mathrm{Na,J}}$ (MSM): K^+, −2.0; Li^+, −3.0; oNPOE). Slight differences were found for different lengths of the spacer connecting the two crown rings, and it was clearly shown that the bis(12-crown-4)-based electrodes are superior to ISEs based on monocyclic 12-crown-4 ionophores (note also a recent study[211] confirming poor potentiometric Na^+ selectivities for naphtho- and benzo-12-crown-4). For nitrobenzene as the organic phase, it was shown in a voltammetric study[212] that Li^+ forms a slightly more stable complex with **Na$^+$-9** than K^+. This suggests that the much larger discrimination of Li^+ by the ISE must be explained by the much higher free energy of the ion transfer from the aqueous into the membrane phase in the case of Li^+. Experimental optimization of the plasticizer and concentration of added anionic sites allowed measurements with **Na^+-9** in blood serum and led to applications of this ionophore in commercial analyzers.[194,213−215] A recent investigation of 15 bis[(12-crown-4)methyl] malonates with various substituents in the α-position of the malonate unit confirmed the selectivity of this class of compounds but major selectivity improvements were not found (**Na^+-10** (log P_{TLC} 6.7), log $K^{\text{pot}}_{\text{Na,J}}$ (FIM): K^+, −2.1; Li^+, −3.5; Rb^+, −2.4; NH_4^+, −3.6; oNPOE, NaTFPB).[216] Apart from a stronger H^+ response, relatively similar selectivities were also obtained with a bis(12-crown-4) derivative with a nitrogen atom in each crown ether ring (**Na^+-11**).[217] Interestingly, bis(12-crown-3) derivative **Na^+-12** gives a fairly high discrimination of K^+ (log $K^{\text{pot}}_{\text{Na,J}}$ (SSM): K^+, −2.2; Li^+, −1.3; oNPOE, NaTPB)[218] while its bis(13-crown-4) isomeride gives worse selectivities. Therefore, it would be interesting to know the performance of bis(12-crown-3) ionophores with other spacers as well.



Na^+-9: R = CH_3, R' = $C_{12}H_{25}$
Na^+-10: R, R' = $CH_2C_6H_5$

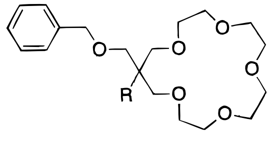


Na^+-11

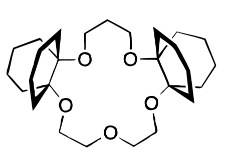


Na^+-12

Several reports were also made on Na^+-selective electrodes based on mono-crown ethers. A simple 16-crown-5 ionophore with a $CH_2Si(OC_2H_5)_3$ group on the central carbon of the propano bridge as the only substituent was successfully immobilized in silicone rubber membranes but the obtained selectivity was much smaller than for a similarly immobilized calix[4]arene ionophore (vide infra).[219] A number of 16-crown-5 derivatives were synthesized with the aim not only to provide an optimal cavity for the primary ion but also to prevent complex formation with larger ions.[220] Two of these ionophores, both with one very bulky benzyloxymethyl and one small substituent (methyl or ethyl) on the central carbon of the propano bridge, gave a high discrimination of K^+ (**Na^+-13** and **Na^+-14**, log $K^{\text{pot}}_{\text{Na,J}}$ (SSM): K^+, −2.7 and −2.8; Li^+, −1.6 and −1.7, respectively; dibenzyl ether, KTpClPB), whereas compounds with two smaller or two larger substituents were found to be less selective. A more recent improvement of this strategy took very successfully advantage of two decalino units to prevent formation of 1:2 complexes with K^+ (**Na^+-15**, log $K^{\text{pot}}_{\text{Na,J}}$ (FIM): K^+, −3.0; Li^+, −3.1; TEHP, KTpClPB).[221]

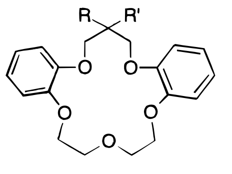


Na^+-13: R = CH_3
Na^+-14: R = C_2H_5

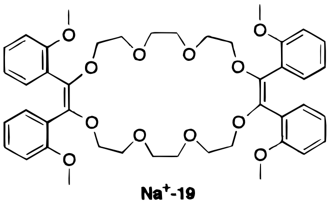


Na^+-15

A very systematic investigation of a large number of the similar dibenzo-16-crown-5 compounds gave evidence for interaction of the complexed cation with ligating pendants.[222−226] The discrimination of K^+ increased with the basicity of the oxygens in the pendant and the introduction of an additional substituent on the ring carbon bearing the pendant. On the other hand, an increased basicity decreased the Li^+ discrimination, and the additional substituent did not influence the Li^+ selectivity. These findings seem to confirm that in these dibenzo-16-crown-5 complexes the Li^+ and Na^+ ions are "nested" within the crown ring, whereas the K^+ ion "perches" on top of it. The Na^+ selectivities of the first dibenzo-16-crown-5 ISEs were clearly inferior to those of ISEs based on 16-crown-5 ionophores but on the other hand the discrimination of Li^+ was significantly higher in the case of the dibenzo-16-crown-5 ISEs (e. g. for a dibenzo-16-crown-5 with a $OCH_2CO_2C_2H_5$ and (a) a propyl substituent (**Na^+-16**), log $K^{\text{pot}}_{\text{Na,J}}$ (FIM):[224] K^+, −1.5; Li^+, −3.7; or (b) a $C_6H_{13}C{\equiv}C$ substituent (**Na^+-17**), log $K^{\text{pot}}_{\text{Na,J}}$ (FIM):[225] K^+, −0.9; Li^+, −3.9; oNPOE, KTpClPB). However, stepwise optimization of the pendant and the alkyl substituent on the polyether ring carbon that also bears the pendant has more recently resulted in considerable selectivity improvements (**Na^+-18**, log $K^{\text{pot}}_{\text{Na,J}}$ (FIM): K^+, −2.4; Li^+, −2.9; oNPOE, KTpClPB).[226] Di(*o*-methoxy)-stilbeno-24-crown-8 (**Na^+-19**) was shown to provide for a modest discrimination of K^+ (log $K^{\text{pot}}_{\text{Na,K}}$ (FIM): −0.7; DOP) but an excellent one of Li^+ (log $K^{\text{pot}}_{\text{Na,Li}}$ −3.7) and Cs^+ (log $K^{\text{pot}}_{\text{Na,Cs}}$ −1.3), while the more flexible dibenzo-24-crown-8 responds strongly to Rb^+ and K^+.[227]

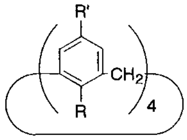


Na^+-16: R = $OCH_2COOC_2H_5$, R' = C_3H_7
Na^+-17: R = $C{\equiv}CC_6H_{13}$, R' = C_2H_5
Na^+-18: R = $OCH_2CON(C_8H_{17})_2$, R' = $CH(CH_3)_2$

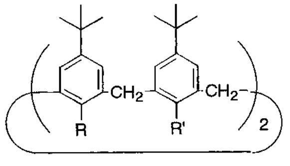


Na^+-19

Calixarene Ionophores. By far the best Na^+ selectivities have been achieved with calix[4]arenes, which were used for the first time as ionophores for Na^+ ISEs only relatively recently.[228] The success of these calix[4]arenes can be ascribed to the phenolic oxygens, which provide for a scaffold on which various functional groups can be attached, giving an optimum cavity for the complexation of Na^+. Electrodes with the relatively simple tetraester **Na^+-20**, which was one of the first compounds of that class, already discriminated K^+ more strongly than any previous ISE ($\log K^{\rm pot}_{\rm Na,J}$ (SSM): K^+, −2.5; Li^+, −2.9 (FIM): H^+, −2.0; oNPOE, KTpClPB).[229] Subsequently, the use of a large number of calix[4]arene derivatives for potentiometric measurements has been reported. Only minor changes in selectivities were found for other *p*-*tert*-butylcalix[4]aryl tetraesters,[230−236] but some improvements were obtained with short-chain esters and a mixed-ester compound (two decyl and two ethyl groups each (**Na^+-21**): $\log K^{\rm pot}_{\rm Na,J}$ (SSM): K^+, −2.6; Li^+, −3.5; H^+, −4.0; DOP, NaTFPB).[237,238] However, better selectivities resulted from the use of a calix[4]aryl tetraester with *tert*-octyl instead of *tert*-butyl groups (**Na^+-22**, $\log K^{\rm pot}_{\rm Na,J}$ (SSM): K^+, −3.1; Li^+, −4.6; Rb^+, −5.1; Cs^+, −5.8; FNDPE, KTpClPB).[239] Tetraesters have been tested for blood serum assays.[231,233,240,241]

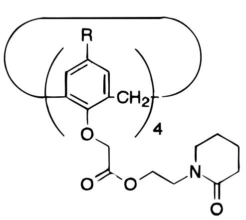


Na^+-20: R = OCH_2COOCH_3, R' = *tert*-butyl
Na^+-22: R = $OCH_2COOCH_2CH_3$, R' = *tert*-octyl
Na^+-25: R = $OCH_2CON(C_4H_9)_2$, R' = *tert*-butyl
Na^+-26: R = OCH_2COCH_3, R' = *tert*-butyl
Na^+-27: R = $OCH_2COC_6H_5$, R' = *tert*-butyl
Na^+-28: R = OCH_2CO(adamantyl), R' = *tert*-butyl
Na^+-29: R = OCH_2CO(*tert*-butyl), R' = *tert*-butyl
Na^+-30: R = OH, R' = *tert*-butyl
Na^+-31: R = $OCH_2CH_2OC_2H_5$, R' = *tert*-butyl
Na^+-32: R = $OCH_2CSN(C_2H_5)_2$, R' = *tert*-butyl

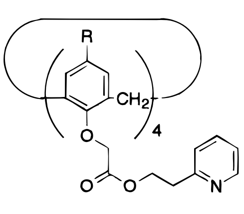


Na^+-21: R = $OCH_2COOCH_2CH_3$,
R' = $OCH_2COOC_{10}H_{21}$

Substituents with more than one ester group were found to result in a decrease of the K^+ discrimination,[235] and introduction of an additional lactam or pyrimidine substituent worsened the H^+ discrimination (**Na^+-23** and **Na^+-24**).[236] While the *tert*-butyl groups on the aromatic rings are known to stabilize the cone conformation of calix[4]arenes and their absence often leads to the occurrence of other conformers, the potentiometric selectivities of several calix[4]arenes without the *tert*-butyl group were found to be rather similar to those obtained with the *tert*-butylated analogues.[236,242,243] In the case of bulky substituents on the complexing groups, the absence of the *tert*-butyl groups leads to decreases in selectivity.



Na^+-23: R = *tert*-butyl

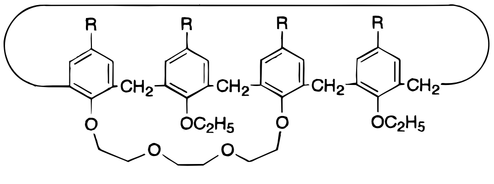


Na^+-24: R = *tert*-butyl

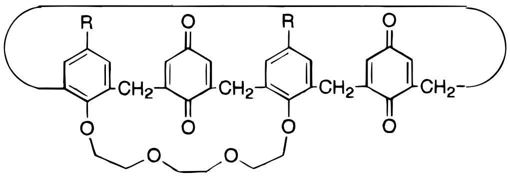
The *p*-*tert*-butylcalix[4]aryl tetraamides, which form more stable host−guest complexes than the esters,[235] provide for similar selectivities than the tetraesters; only H^+ seems to be more strongly discriminated (**Na^+-25**, $\log K^{\rm pot}_{\rm Na,J}$ (FIM): K^+, −2.1 H^+, −2.5; DOS, dipicrylamine sodium salt).[230,231,235,243] A contrary finding as to the H^+ interference reported for a *N*,*N*-diethylamide may be an artifact due to sub-Nernstian slopes[236] and contradicts other results with the same compound.[243] However, direct comparisons of amide and ester derivatives are only meaningful if the ligating substituents are of roughly equal bulkiness. A reported conclusion that *N*,*N*-diethylamides are more selective than *tert*-butyl esters, for example, cannot be generalized.[243]

A similar $\log K^{\rm pot}_{\rm Na,K}$ value as obtained for *p*-*tert*-butylcalix[4]aryl tetraamides and tetraesters was also found for a *p*-*tert*-butylcalix[4]aryl tetraketone with a low degree of steric hindrance ($RCOCH_3$ or $RCOC_6H_5$ for **Na^+-26** and **Na^+-27**, respectively) while the more bulky adamantyl (**Na^+-28**) and *tert*-butyl (**Na^+-29**) ketones lead to significant selectivity decreases and response time increases.[232,235,236,244,245] Furthermore, extraction and potentiometry experiments indicate that calix[4]arene derivatives without carbonyl groups, such as the parent compounds with four phenol oxygens (**Na^+-30**), derivatives with an additional four ether pendants (**Na^+-31**), and thioamides (**Na^+-32**), are much less efficient Na^+ ionophores.[232,235,239]

Very recently an approach not based on carbonyl substituents but rather on a triethylene glycol bridge connecting two opposing aromatic rings (forming a crown loop) was reported to yield extraordinarily high selectivities (**Na^+-33**, $\log K^{\rm pot}_{\rm Na,J}$ (FIM): K^+, −5.3; Li^+, −2.4; Rb^+, −3.7; NH_4^+, −3.9; Mg^{2+}, −5.1; Ca^{2+}, −4.6; H^+, −4.7; oNPOE, KTpClPB; **Na^+-34**, $\log K^{\rm pot}_{\rm Na,J}$ (FIM): K^+, −5.0; Li^+, −2.8; Rb^+, −4.8; NH_4^+, −4.4; Mg^{2+}, −4.5; Ca^{2+}, −4.4; H^+, −5.4; oNPOE, KTpClPB).[246] While independent measurements for **Na^+-33** with the conventional FIM[221] ($\log K^{\rm pot}_{\rm Na,K}$: −2.6 to −2.8; oNPOE, KTpClPB) and for **Na^+-34** with the conventional SSM ($\log K^{\rm pot}_{\rm Na,J}$: K^+, −3.5; Mg^{2+}, −4.5; Ca^{2+}, −4.2; DOS, KTpClPB)[247] gave smaller selectivities, apparently because the electrode response was still partially governed by primary ions being lost from the membrane bulk, the determination of the K^+ selectivity after conditioning of **Na^+-34**-based ISE membranes with the discriminated ion K^+ shows the excellent selectivity properties of this ionophore ($\log K^{\rm pot}_{\rm Na,K}$ (SSM): −4.9; DOS, KTpClPB).[247] **Na^+-34** has recently also been used for a fluorescent fiber-optic Na^+ sensor (vide infra).[248] Unfortunately, protein adsorption seems to be a serious obstacle to the use of ISEs with these ionophores for measuring in blood or cells. The replacement of one or two of the phenol groups of this ionophore by quinones seemed to reduce this problem to some extent,[249] but resulted in a smaller selectivity (**Na^+-35**, log $K^{pot}_{Na,J}$ (FIM): K^+, −3.6; Li^+, −1.8; Rb^+, −3.8; NH_4^+, −3.9; Mg^{2+}, −4.5; Ca^{2+}, −4.1; H^+, −5.0; FNDPE, KTpClPB). Calix[4]arenes with bridges lacking the ether oxygens were found to be less successful.[236,237] Note that these bridged Na^+ ionophores resemble the highly K^+-selective calix[4]arenecrown-5 ionophores **K^+-32** to **K^+-34** (vide infra).[250]

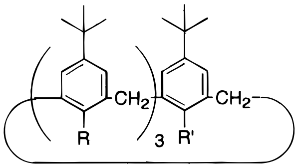


Na^+-33: R = H (*partial cone* conformation)
Na^+-34: R = $C(CH_3)_3$ (*cone* conformation)



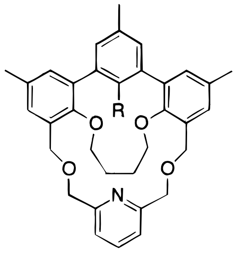
Na^+-35: R = *tert*-octyl

Because calix[4]arenes with high symmetry tend to have a low solubility in ISE membranes, in particular in silicone rubber ones, several unsymmetrical calix[4]arene ionophores have been developed.[251,252] One of these made the first measurements of Na^+ in human blood serum and urine with silicone rubber membrane ISEs possible (**Na^+-36**, log $K^{pot}_{Na,J}$ (FIM): K^+, −2.5; Li^+, −2.8; NH_4^+, −4.2; Mg^{2+}, −3.5; Ca^{2+}, −4.0; H^+, −3.7; silicone rubber).[253,254] Recently, an ionophore with an identical recognition unit (**Na^+-37**) was also covalently immobilized in a silicone rubber membrane (log $K^{pot}_{Na,J}$ (FIM): K^+, −2.4; Li^+, −4.0; NH_4^+, −4.0; Mg^{2+}, −3.5; Ca^{2+}, −4.1 H^+, −3.3; silicone rubber, immobilized anionic sites).[219] Again, measurements in blood serum and urine were demonstrated. A high durability was reported for a chemically modified ion-sensitive field-effect transistor (CHEMFET) with a calixarene ionophore covalently attached to a polysiloxane membrane.[255,256] Another group of unsymmetrical calixarene derivatives is that of the triester monoacids of *p-tert*-butylcalix[4]arene. At intermediate to low pH and in the presence of either only anionic impurity sites or in combination with added anionic sites, these carriers seem to work as neutral carriers. The selectivities of ISE membranes containing either a tris(ethyl ester) monoacid (**Na^+-38**) or a tris(methyl ester) monoacid (**Na^+-39**) ionophore were found to be very similar to those of ISEs with the corresponding tetraesters.[257,258] At high pH, however, deprotonation of the carboxylate group appears to occur, reducing the Na^+ response.



Na^+-36: R = $OCH_2COOC_2H_5$,
R' = $OCH_2COO(CH_2)_{11}(Si(CH_3)_2O)_2Si(CH_3)_3$
Na^+-37: R = $OCH_2COOC_2H_5$,
R' = $OCH_2COO(CH_2)_{11}Si(OC_2H_5)_3$
Na^+-38: R = $OCH_2COOC_2H_5$, R' = OCH_2COOH
Na^+-39: R = OCH_2COOCH_3, R' = OCH_2COOH

Hemispherand Ionophores. The hemispherand ionophores used for Na^+ ISEs can be considered to be crown ether compounds with an extra bridge that enhances ligand preorganization.[259] Shortly after the introduction of these ionophores, at least one of them was used for commercial applications but only a relatively small amount of data has been published.[187,260] A patent states log $K^{pot}_{Na,K}$ to be smaller than −2,[260] and the use of the same ligand (**Na^+-40**; known under the commercial name Hemisodium) was reported to give a log $K^{pot}_{Na,K}$ value of −2.7 (log $K^{pot}_{Na,Li}$ (FIM): −2.2; TEHP; log $K^{pot}_{Na,Li}$ (FIM) −3.3; diphenyl cresyl phosphate).[261,262] In a study on the suitability of several ionophores for measurements in blood serum, **Na^+-40** (log P_{TLC} 10.4)[48] in combination with the plasticizer BBPA was found to give the smallest protein-induced asymmetry potentials.[263,264] Note that other hemispherand ionophores have also been used for K^+ ISEs (vide infra).



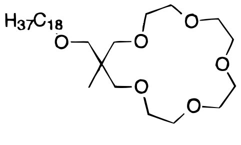
Na^+-40: R = $CH_2C_6H_5$

Application of Na^+ ISEs in Clinical Chemistry. Flame atomic emission spectroscopy (FAES), which measures total ion concentrations, used to be the standard technique for Na^+ determinations in body fluids. However, the introduction in 1972 of the first commercial fully automatic Na^+ and K^+ analyzer[265] for measuring diluted samples was followed in the 1980s by an almost complete change to potentiometric methods. In 1991, the College of American Pathologists Comprehensive Chemistry Survey found 96% of the participating laboratories using Na^+ ISE analyzers,[176] more than 50% of the Na^+ determinations being performed by "direct potentiometry". (In clinical chemistry, the measurement of diluted samples is often called "indirect potentiometry",[176,265,266] which should not to be confused with the more general use of the expressions "indirect determination" or "titration", which mean that the measured chemical species is not the analyte itself.) While initial doubts concerning the usefulness of potentiometric results have given place to the realization that the activities measured by ISEs are of higher physiological relevance than total concentrations, potentiometric results in clinical chemistry are, after appropriate calibration, still usually reported as concentrations.[267,268] Some of the challenges and peculiarities of such measurements are briefly summarized in the following. Reviews of this particular field are recommended for more thorough information.[269−274]

Measurements in whole blood have the advantage that the sample does not need to be centrifuged, which is an important factor when a result is urgently requested or when measurements should be performed in vivo. The variation of activity coefficients in blood samples is very small even at pathological electrolyte concentrations.[275] Only high amounts of heparin salts, which are added to blood samples as anticoagulants, are known to give appreciable changes in ionic strength.[276] However, various other reasons can be responsible for differences between results from FAES and potentiometry.[265] In human whole blood, proteins and lipids occupy about 7% of the sample volume, which is not accessible for free ions. Therefore, high protein and lipid concentrations in blood can falsify measurements by FAES or potentiometry with diluted samples, suggesting too low Na$^+$ concentrations. Activities as measured by "direct potentiometry" are not affected by such anomalies, as was experimentally confirmed.[277−279] On the other hand, complexation of Na$^+$ with other ions in the sample can decrease its activity. While Na$^+$ is usually assumed to bind to proteins only to a very small extent,[266] Na$^+$ binding to bicarbonate is controversial. Inadequate assessment of liquid junction potentials has in certain studies probably further complicated the issue.[177,280−283] Also the influence of erythrocytes on Na$^+$ has been disputed.[284] Clearly, inadequate storage of samples results in hemolysis, leading to changes in the activities of free ions in blood plasma. This effect is however less distinct for Na$^+$ than for K$^+$ because of the higher intracellular concentrations of the latter.[285] Furthermore, addition of dried heparin results in an osmotic pressure and transfer of water from erythrocytes into blood plasma, diluting the plasma.[286] Partial blockage of liquid junctions was reported as a problem[287,288] but can be prevented, for example by using free-flowing free-diffusion reference electrodes with applied pressure.[289] With an electrically symmetric measuring cell, it was shown that with such reference electrodes Na$^+$ and K$^+$ can be measured without a need for calibration.[263] However, well-characterized reference sera are necessary to minimize interlaboratory variability and biases arising at least partially from the use of differing calibration procedures in different commercial analyzers.[176,177] Insufficient selectivities of ISEs can lead to faulty determinations that cannot be fully compensated with appropriate calibration and data handling.[177,290] Use of Li$^+$ as antipsychotic drug or from lithium heparin used as anticoagulant, for example, may cause unexpected interferences.

Another challenge is the determination of Na$^+$ in urine, the ionic strength of urine varying over a range of more than 1 order of magnitude.[278,291] Often this problem has been solved by dilution but it can also be overcome by calculation of activity coefficients in an iterative procedure, allowing for example direct ex vivo measurement in undiluted urine of catheterized patients.[207] Recently, Na$^+$-selective electrodes were also used for direct, continuous measurements in stomach fluid to determine reflux of the duodenal content.[292]

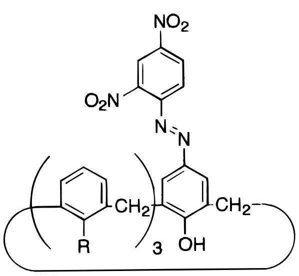
Optodes. Optical Na$^+$ sensors based on modified surfaces and bilayers have been known since the 1980s,[293,294] and combinations of a Na$^+$ ionophore and one of many charged H$^+$ chromoionophores incorporated into oNPOE/PVC membranes supported by filter paper were used for visual and photometric determinations of Na$^+$ in urine.[95] However, bulk Na$^+$ optodes based on a neutral carrier, a H$^+$ chromoionophore and lipophilic anionic sites have been reported only fairly recently.[201,295,296] Because of the required high lipophilicity[2] of the Na$^+$ ionophore, the diamide ETH 4120 (**Na$^+$-6**)[200] was used. The selectivities for K$^+$, Li$^+$, and Ca^{2+} were very close to those of ISEs with the same ionophore (log $K^{opt}_{Na,J}$ (FIM): K$^+$, −1.2; Li$^+$, −1.1; Ca^{2+}, −1.2; Mg^{2+}, −2.5; pH 4.8, Nile Blue isomeride ETH 2439 (**H$^+$-9**), NaTFPB, BBPA; $K^{opt}_{Na,J}$ (FIM): K$^+$, −1.2; Li$^+$, −1.1; Ca^{2+}, −1.4; Mg^{2+}, −3.0; pH 7.6, Nile Blue isomeride ETH 5350 (**H$^+$-11**), NaTFPB, BBPA). Measurements in blood plasma were demonstrated and suffered only from a small interference from Ca^{2+}. Recently, an improved version of this optode was developed by using the tetraethyl ester isomeride of calix[4]arene **Na$^+$-20** ($K^{opt}_{Na,J}$ (SSM): K$^+$, −2.1; Ca^{2+}, −2.3; pH 8.0, Nile Blue isomeride ETH 5294 (**H$^+$-10**), NaTPB).[297] Also for a slightly different optode with an anionic dye (LAD-4, **H$^+$-31**) derived from *o*-cresolphthalein as H$^+$ ionophore and 15-octadecyloxymethyl-15-methyl-16-crown-5 (**Na$^+$-41**) as Na$^+$ ionophore, determinations in diluted blood serum were demonstrated ($k^{Osel}_{Na,K}$ (FIM): −0.6; $k^{Osel}_{Na,Ca}$ (FIM): <−4.0; FNDPE).[92]



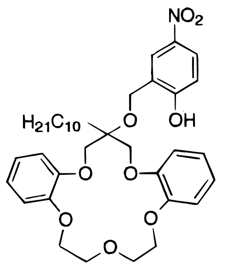
Na$^+$-41

Fluorescence fiber-optic sensors based on the highly selective calix[4]arene ionophore **Na$^+$-34** are so far the only optodes with selectivities that should allow intracellular measurements ($K^{opt}_{Na,J}$ (SSM): K$^+$, <−4.0; Ca^{2+}, <−2.4; Mg^{2+}, <−3.9; pH 7.0, Nile Blue isomeride ETH 2439 (**H$^+$-9**), KTFPB, DOS).[248] Three different Nile Blue isomerides (**H$^+$-9** to **H$^+$-11**) initially developed as H$^+$ chromoionophores were used as fluoroionophores. Three operation modes for sensors with this ionophore were demonstrated: (a) simple fluorescence intensity measurements at a single emission wavelength, (b) determination of the ratio of the fluorescent intensities at two different wavelengths to compensate for fluctuations in excitation power, collection geometry, and photobleaching, and (c) measurement of the fluorescence intensity of a second absorber that was excited by either emission or direct energy transfer from the primary H$^+$ fluoroionophore.

An optode based on a chromogenic calix[4]arene (**Na$^+$-42**), which can form a Na$^+$ complex but can also be deprotonated, was recently reported.[298] While it can be also used only with added anionic sites (reported were results for pH 10.4; oNPOE, KTpClPB), further addition of the H^+ carrier tridecylamine somewhat decreased the detection limit (oNPOE, NaTFPB, tridecylamine). Potentiometric sensors with the same ionophore were also tested but selectivities were inferior to those obtained with other calix[4]arenes. A dibenzo-16-crown-5 chromoionophore with a nitrophenol group (**Na^+-43**) was found to allow for Na^+ determinations with a detection limit of 10^{-5} M and complete absence of interference from Li^+ and K^+ up to 0.10 M (membrane components: oNPOE, cellulose triacetate as matrix; response time several minutes).[299] Many other chromogenic ionophores were developed but have so far not been used for sensors but rather for more costly assay applications.[300]



Na^+-42: R = $OCH_2COOC_2H_5$

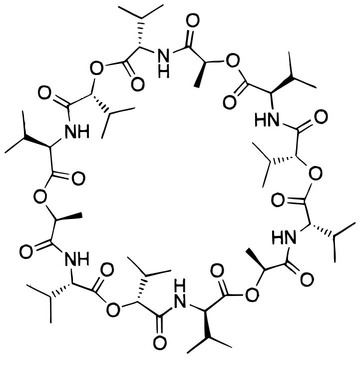


Na^+-43

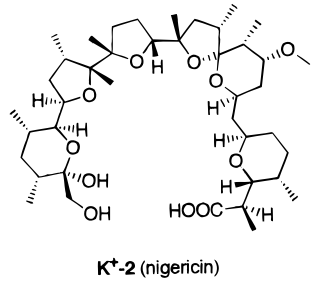
4. K^+ Sensors

A major interest for K^+ analysis comes from clinical chemistry because changes in K^+ concentration in human serum bring along the risk of acute cardiac arrhythmia. Continuous K^+ monitoring is of particular interest when K^+ concentrations may rapidly and greatly change, such as during or after surgery, or after a diabetic coma or burn shock. Most ionophores for K^+ can be classified into four groups, that is, antibiotics (e. g. valinomycin), mono- and biscrown ethers and hemispherands.

Antibiotics as Ionophores. K^+-selective electrodes based on nonactin (**NH_4^+-1**), monactin (**NH_4^+-2**) or a mixture of actin homologues were the first neutral carrier-based K^+ ISEs to be proposed.[301−304] As compared to previously known glass electrodes (log $K^{\mathrm{pot}}_{\mathrm{K,Na}} > -1.5$), remarkable selectivities were achieved (log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$ −2.9 for the mixture of actin homologues).[301] Shortly afterward, complexation constants of K^+ and valinomycin (**K^+-1**), an antibiotic from cultures of *Streptomyces fulvissimus*, and the formation of 1:1 complexes of valinomycin and K^+ in crystalline form were reported,[304−306] followed by the first valinomycin based ISE with a quick response time and a very good selectivity (log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$ (SSM):[307] −3.6; diphenyl ether).[1,307−309] Therefore, not much interest went to the less selective electrode based on nigericin (**K^+-2**), a natural carboxylic acid with antibiotic character, which was investigated at the same time.[162,178,179] Furthermore, nonactin was found to prefer NH_4^+ over K^+[308] and first applications in NH_4^+ and NH_3 sensors were demonstrated. Valinomycin electrodes were shown to be of use for measurements in blood serum[310] and were soon commercialized, initially even without a change of the membrane solvent.[311,312] However, PVC-based solvent polymeric membrane electrodes followed soon[312−314] as well as coated wire ISEs,[315] silicone rubber membranes (log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (SSM):[51] H^+, −4.4; Li^+, −4.3; Na^+, −4.0; Rb^+, +0.6; Cs^+, −0.2; NH_4^+, −1.8; Mg^{2+}, −4.3; Ca^{2+}, −4.2; Sr^{2+}, −4.2; Ba^{2+}, −3.8; silicone rubber)[51,316−320] and tubes,[321] fluorosilicone,[199] PVC-OH (for references to this polymer see refs 79 and 195),[195] polyurethane (log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (SSM):[322] H^+, −1.8; Li^+, −3.4; Na^+, −3.2; Mg^{2+}, −3.3; Ca^{2+}, −4.2; KTpClPB, DOS, photocurable polyurethane),[322,323] cellulose acetate,[324] methacrylate−acrylate,[325] decyl methacrylate−hexanedioldimethacrylate[326] and poly(vinyl pyrrolidone-*co*-vinyl acetate)[327] membranes, and microelectrodes.[55,328,329] The latter were the first K^+-selective electrodes with membranes containing added anionic sites. They had much higher selectivities than previously used ionophore-free microelectrodes, whose selectivities were determined by the difference between the standard free energies of the primary and the interfering ions in the sample and in the membrane phases and were only slightly influenced by the membrane solvent.[330] In 1990, an estimated 64 million valinomycin-based sensors were used.[331] Almost 30 years after its introduction and despite a large number of new K^+ ionophores (see below), valinomycin is still the carrier most often used in clinical analyzers.[176,177,186,291,332] The high selectivity of the ionophore valinomycin has recently been demonstrated by using electrodes conditioned in K^+-free solutions (log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (SSM, Na^+ conditioning): Na^+, −4.5; Ca^{2+}, −6.9; Mg^{2+}, −7.5; DOS, NaTFPB).[333] A distinct disadvantage of valinomycin is unfortunately its relatively low lipophilicity (log, P_{TLC} 7.8;[48] the insufficient lipophilicity of valinomycin was also observed in a recent investigation of fiber-



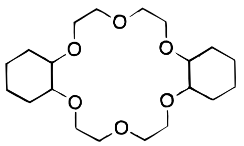
K^+-1 (valinomycin)



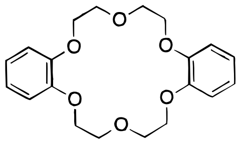
K^+-2 (nigericin)

optic sensors[334]). To eliminate this problem, valinomycin derivatives have been immobilized by formation of covalent bonds to a polymer matrix,[335] and more lipophilic valinomycin derivatives have been synthesized.[336]

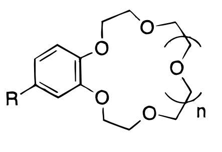
Crown Ionophores. One of the first reports of crown ether based K^+ ISEs described nitrobenzene membranes containing dicyclohexano-18-crown-6 (**K^+-3**), dibenzo-18-crown-6 (**K^+-4**), benzo-15-crown-5 (**K^+-5**), or dibenzo-30-crown-10 (**K^+-6**).[337] However, most of the selectivities of those ISEs were not very different from those of ionophore-free ion-exchanger membranes (e. g. best attained log $K^{\text{pot}}_{\text{K,Na}}$ −1.8).[338,339] Also, rather poor selectivities (log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −0.4) were obtained in a more recent investigation on 18-crown-6 covalently attached to poly(acrylic acid), which was then incorporated into a PVC matrix.[340] In the first study of solvent polymeric membrane K^+ ISEs based on crown ethers,[341,342] 20 crown compounds with 5−12 ether oxygens were tested with a special view to their selectivity for K^+ over Na^+ (for the characterization of some similar ionophores see also a more recent investigation[343]). The highest selectivities were obtained for the two dibenzo-30-crown-10 derivatives **K^+-7** and **K^+-8** (**K^+-7**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM):[342] −2.7; dipentyl phthalate), which owing to their flexibility and large size were suggested to be able to wrap around K^+. Similarly, dinaphtho-30-crown-10 (**K^+-9**) also gave a fairly high selectivity (log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.0; oNPOE, KTpClPB).[344] Among the smaller macrocycles, benzo-18-crown-6 compounds showed the highest selectivity (4-nitrobenzo-18-crown-6 (**K^+-10**): log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −2.6; dipentyl phthalate),[342] whereas dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 seem to be too rigid to accommodate the cation optimally.[345,346] On the other hand, the very similar ionophore 4′-picrylamino-5′-nitrobenzo-18-crown-6 (**K^+-11**), which had been developed as a chromogenic polyether reagent for spectrophotometric determinations following solvent extraction, gives only a modest selectivity when incorporated into oNPOE (log $K^{\text{pot}}_{\text{K,Na}}$ (SSM): −1.8 to −0.3; KTpClPB).[346]



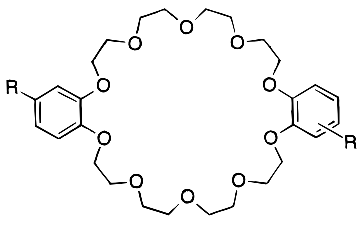
K⁺-3



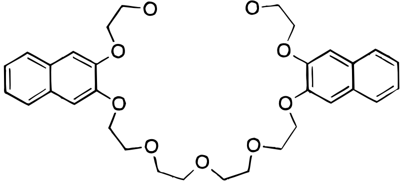
K⁺-4



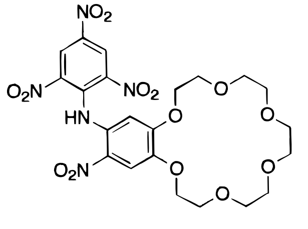
K⁺-5 (R = H, n = 1)
K⁺-10 (R = NO_2, n = 2)



K⁺-6: R = H
K⁺-7: R = CH_3
K⁺-8: R = $C(CH_3)_3$

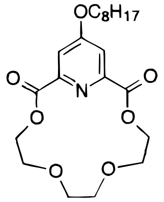


K⁺-9



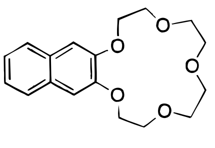
K⁺-11 (Takagi reagent)

A study of cyclic polyethers with lactam and lactone groups in the macrocyclic ring is interesting in view of the ionophore design. Whereas most lactams were found to give strong responses to divalent ions, lactones gave preferences for alkali metal ions and, in some cases, selectivities similar to those observed for common monocyclic crown ethers (typical log $K^{\text{pot}}_{\text{K,Na}}$ (SSM): ≈−1.7; 1,2-dichloroethane).[347] Two ionophores with a thiolactone and two lactone groups were not distinguishable in this respect from the pure lactones but responses to transition metal ions were not determined. Exceptions to these common trends should, however, be interpreted with care as the slopes of the K^+ response were not reported. Also sub-Nernstian slopes were observed for ISEs based on various propeller crown ethers, which are compounds containing three aryl groups attached to one carbon that is part of the crown ring and provide for a moderately good selectivity for K^+.[348] A crown ether with a pyridine unit and two lactone groups (**K^+-12**) has been suggested as an inexpensive substitute for valinomycin for applications for which a very high selectivity against Na^+ is not required but an improved discrimination of NH_4^+ would be desirable (log $K^{\text{pot}}_{\text{K,J}}$ (MSM): Na^+, −2.1; NH_4^+, −2.3; oNPOE, KTpClPB).[349] No H^+ response was observed for this ionophore in the pH region between 3 and 11. A systematic investigation of a variety of other compounds with pyridine groups did not result in any further ionophores with interesting selectivities.[350]

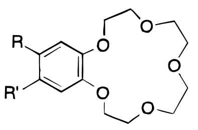


K⁺-12

It was shown that certain mono-15-crown-5 compounds can also give quite high K^+ selectivities, as for example naphtho-15-crown-5 (**K^+-13**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.4; oNPOE, potassium dipicrylaminate),[344,351] (hexanoyloxymethyl)benzo-15-crown-5 (**K^+-14**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.0; oNPOE),[352] octadecanoyloxymethyl-15-crown-5 (**K$^+$-15**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −2.7; oNPOE),[353] or disubstituted benzo-15-crown-5 ethers (e. g. **K$^+$-16**: log $K^{\text{pot}}_{\text{K,Na}}$ (SSM): −3.5; oNPOE).[354] Improvements in detection limits and selectivities were also found when the benzo-15-crown-5 ring was covalently attached to carboxylated PVC (log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −2.0 with free ionophore, −2.6 with covalently bound ionophore; KTpClPB, oNPOE, carboxylated PVC).[355] Some monocyclic polyethers have been used in the preparation of ISFETs[356] and coated wire electrodes.[357] In comparison, results with 1,4-cubyl diester-25-crown-7 ethers reported recently are not too encouraging (log $K^{\text{pot}}_{\text{K,Na}}$ > −1.6).[358]



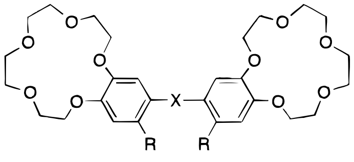
K$^+$-13



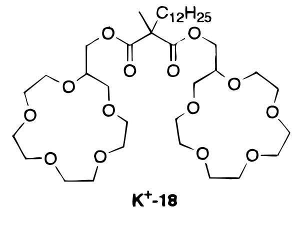
K$^+$-14: R = $CH_2OCOC_5H_{11}$, R' = H
K$^+$-15: R = $CH_2OCOC_{17}H_{35}$, R' = H
K$^+$-16: R, R' = CH_2O(2-biphenyl)

Bis-crown Ionophores. Complexation of bis(crown ether) and alkali metal ions is quite specific when the size of the cation is slightly larger than the internal cavity formed by one crown ether ring. This can be explained by formation of intramolecular sandwich complexes. High Na$^+$ selectivities were, for example, obtained with bis(14-crown-4) compounds, even though the 14-crown-4 cavity is too small for Na$^+$. In the same way, K$^+$ selectivity can be obtained with bis(15-crown-5) compounds and Cs$^+$ selectivity with bis(18-crown-6) ionophores (see sections II.4 and II.6, respectively).[359,360]

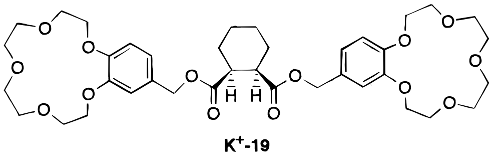
In a series of bis(benzo-5-crown-5) compounds with a dicarboxylic acid backbone, the highest K$^+$ selectivity was found for a pimelic acid diester (**K$^+$-17**), log $K^{\text{pot}}_{\text{K,Na}}$ with −3.5 (FIM, oNPOE) being only slightly larger than for valinomycin, and discrimination of Rb$^+$, Cs$^+$, and NH_4^+ being even somewhat higher (log $K^{\text{pot}}_{\text{K,J}}$: Rb$^+$, −0.7, Cs$^+$, −2.0, NH_4^+, −2.0)[352] than for valinomycin ISEs.[210,213,214,352,361] Use of dipentyl phthalate as plasticizer instead of oNPOE gave slightly less selective electrodes. An improvement in selectivity was obtained by elimination of the benzene ring by using a 2,2-dodecylmethylmalonate diester, which provides for a very short backbone (**K$^+$-18**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.7; oNPOE).[362] Interestingly, discrimination of Cs$^+$ dropped sharply when the methyl group was eliminated, probably because of an increased flexibility of this compound.[353] While the selectivities of membranes hardly varied with the concentration of this compound, a strong dependence on the ionophore concentration has been found for the corresponding monocyclic 15-crown-5. Very similar selectivities as for the 2,2-dodecylmethylmalonate were also obtained with a bis(benzo-15-crown-5) derivative based on a *cis*-1,2-cyclohexanedicarboxylic acid backbone (**K$^+$-19**, log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.3; oNPOE), whereas both the corresponding *trans*-1,2- and the *cis*-1,4-isomer gave a much weaker discrimination of Na$^+$ (log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −0.5 and −2.5, respectively).[363] All these results seem to confirm the formation of intramolecular sandwich complexes in case of the bis(benzo-15-crown-5) ionophores. Replacement of an oxygen by a nitrogen leads to strong interference by H$^+$ and an unsatisfactory selectivity for K$^+$ (log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −2.0; oNPOE, pH 13).[217] A high discrimination was also obtained for three bis(benzo-15-crown-5) compounds in which the two aromatic rings of the macrocycles were linked by a $-CH_2OCH_2-$ (**K$^+$-20**, log $K^{\text{pot}}_{\text{K,J}}$ (FIM): Na$^+$, −3.6; Li$^+$, −4.0; DBP)[359] or propylene bridge (**K$^+$-21**, log $K^{\text{pot}}_{\text{K,J}}$ (MSM): Na$^+$, −3.6; Li$^+$, −2.8; oNPOE).[364] Extending the length of this spacer by one or two more ether units led to decreased selectivities.[359] Bis(benzo-15-crown-5) ethers with an azoxy (**K$^+$-22**: log $K^{\text{pot}}_{\text{K,J}}$ (SSM): Na$^+$, −4.0; Li$^+$, −5.0; DBP), a phenylene (e. g. **K$^+$-23**: log $K^{\text{pot}}_{\text{K,Na}}$ (FIM): −3.7; log $K^{\text{pot}}_{\text{K,Li}}$ (SSM): −5.0; DOP) or a thioether group (**K$^+$-24**: log $K^{\text{pot}}_{\text{K,Na}}$ (MSM): −4.0; log $K^{\text{pot}}_{\text{K,Li}}$ (SSM): −5.0; DOP)[365] in the backbone were reported to have very attractive selectivities but their interpretation requires caution because sub-Nernstian slopes were observed, probably owing to a too low lipophilicity of the ionophores or simply an insufficient concentration of anionic sites in the membrane.[365,366]



K$^+$-17: X = $-CH_2OCO(CH_2)_5COOCH_2-$, R = H
K$^+$-20: X = $-CH_2OCH_2-$, R = H
K$^+$-21: X = $-CH(OC_{16}H_{33})CH_2CH_2-$, R = H
K$^+$-22: X = -N=N(O)-, R = H
K$^+$-23: X = $-COCH(CH_3)O(o\text{-}C_6H_4)OCH(CH_3)CO-$, R = H
K$^+$-24: X = $-COCH_2SCH_2CO-$, R = H
K$^+$-25 (BME 44): X = $-NHCOOCH_2C(CH_3)(C_{12}H_{25})CH_2OCONH-$, R = NO_2



K$^+$-18



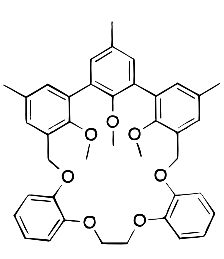
K$^+$-19

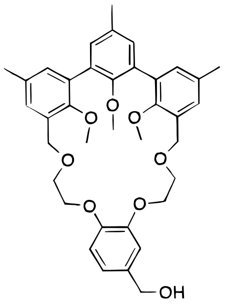
In a very comprehensive study of 28 ionophores, the effect of structural changes in bis(nitrobenzo-15-crown-5) ionophores with two urethane groups in the spacer between the two crown rings was analyzed.[367−369] It was suggested that hydrogen bonds have a decisive influence on the ionophore conformation, probably promoting the formation of a relatively rigid cavity stabilized by hydrogen bonds between NH and nitro groups situated at opposite ends of the bis-crown ether molecules. The most selective of these compounds has a 2,2-dodecylmethylpropano bridge connecting the two urethane units

(**K$^+$-25**, BME−44) and gives a smaller discrimination of Na$^+$ (log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$ (SSM): −3.3; dinonyl adipate, KTpClPB) than valinomycin but has a higher lipophilicity (log, P_{TLC} 10.7;[368] valinomycin: log, P_{TLC} 8.6), which is very desirable for clinical applications (for comments on lipophilic and immobilized valinomycin, vide supra).[370] This ionophore was used in microelectrodes for scanning electrochemical microscopy,[371] for in vivo measurements in rat brain, and in a commercial analyzer for measurements of undiluted serum and of in situ diluted urine samples.[369,372] Slow crystallization of this ionophore when incorporated at high concentration in an optode membrane based on DOS and PVC has been reported.[373]

The favorable K$^+$ selectivity of a phthalocyanine ionophore with four 15-crown-5 ether substituents was explained by the strong tendency of the phthalocyanine to dimerize. However, strongly sub-Nernstian slopes complicate the evaluation of this selectivity.[374] Finally, it should be mentioned that the selectivity for K$^+$ over Rb$^+$ is much higher for almost all ISEs based on crown ionophores than for valinomycin-based electrodes, whereas a higher discrimination of Cs$^+$ with ISEs based on crown ether ionophores is occasionally observed but is less general.

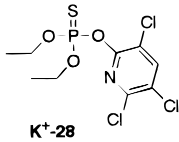
Hemispherands as Ionophores. A quite high discrimination of Na$^+$ was obtained for two hemispherands (**K$^+$-26** and **K$^+$-27**) incorporated into silicone rubber based membranes (log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$ (FIM): ≤−3.3 and ≤−3.1, respectively).[320,375−377] Very high sensor lifetimes as tested for horticultural conditions were obtained when the ionophore was covalently attached to the membrane. Although the emf response slopes were found to quickly become sub-Nernstian, they reached a level of about 40 mV/decade within a few weeks and then remained constant for over half a year. Leaching of the anionic sites, which were not attached covalently to the membrane matrix, was suggested to be responsible for this behavior but the presence of noncovalently bound ionophore could play a role as well.


K$^+$-26

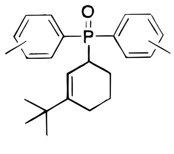


K$^+$-27

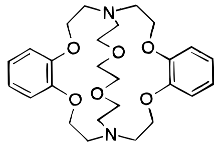
Miscellaneous Ionophores. Several alkyl thiophosphate compounds (e. g. **K$^+$-28**) were used as carriers for tetraarylborate containing membranes[378] but the reported selectivities are not very different from those of ion-exchanger membranes based on a tetraphenylborate alone.[328] Somewhat better results were found for several phosphine oxide ionophores (**K$^+$-29**, log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (SSM): Na$^+$, −2.5; Li$^+$, −2.1; DBP).[379] A dibenzo derivative (**K$^+$-30**) of Kryptofix 222, a cryptand with three 3,6-dioxaoctane bridges connecting two nitrogens, was found to give only a small discrimination of Na$^+$ but did seem to work as ionophore, Rb$^+$ and Cs$^+$ being discriminated fairly well (log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (SSM): Na$^+$, −1.0; Li$^+$, −3.6; Rb$^+$, −2.6; Cs$^+$, −3.2; DBP).[380] On the other hand, it was reported that covalent attachment of a monobenzo derivative of Kryptofix 222 to poly(acrylic acid) did not give a useful electrode membrane.[340]



K$^+$-28

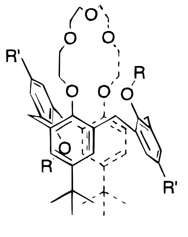


K$^+$-29

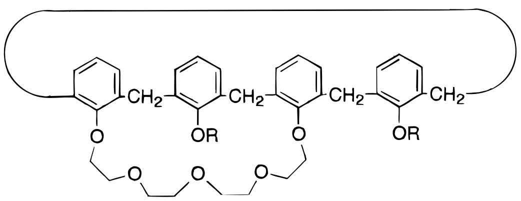


K$^+$-30

For three conformers of a bridged calix[4]arene-crown-5 ionophore different selectivities were observed and the selectivities of membranes prepared from two conformers was reported to change with time, which was explained by isomerization (**K$^+$-31**, log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$ (SSM): −3.7; DOS, KTpClPB).[381] Excellent discrimination of Na$^+$ has recently also been obtained with CHEMFETs based on one of three calix[4]arenecrown-5 ionophores (**K$^+$-32**, log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (FIM): Na$^+$, −3.9; Li$^+$, −3.6; NH$_4^+$, −1.5; Ca^{2+}, −3.6; DOS, KTFPB; **K$^+$-33**, log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (FIM): Na$^+$, −4.2; Li$^+$, −3.7; NH$_4^+$, −1.4; Ca^{2+}, −4.0; DOS, KTFPB; **K$^+$-34**, log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (FIM): Na$^+$, −3.9; Li$^+$, −3.7; NH$_4^+$, −1.4; Ca^{2+}, −3.5; DOS, KTFPB).[250] Measured under identical conditions, valinomycin-based electrodes gave a similar discrimination of Na$^+$ (log $K^{\mathrm{pot}}_{\mathrm{K,Na}}$, −3.9) but K$^+$ complexation in chloroform was found to be significantly more selective for these calix[4]-



K$^+$-31: R = CH$_2$CH$_3$, R' = C(CH$_3$)$_3$
K$^+$-32: R = CH(CH$_3$)$_2$, R' = H



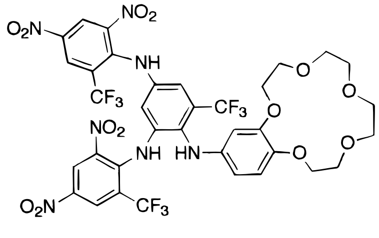
K$^+$-33: R = CH(CH$_3$)$_2$ (*alternate* conformation)
K$^+$-34: R = CH$_2$CH$_3$ (*alternate* conformation)

arenecrown-5 ionophores than for valinomycin. It seems therefore quite likely that loss of K^+ from these ISE membranes determines their detection limits and that conditioning with an interfering ion, as performed for valinomycin electrodes (vide supra),[247] would show significantly higher selectivities. Note the large similarity between these calix[4]arenecrown-5 ionophores and the equally successful Na^+ ionophores **Na^+-33** and **Na^+-34**.

Applications. Since the beginning of the 1980s, potentiometry has been the dominant technique for the determination of K^+ in blood.[107] Many problems of such measurements are similar to those discussed in the chapter on Na^+ ISEs (see section II.3).[174,177,186,214,263,283,287,382,383] A factor characteristic for K^+ determinations is leaching of intracellular K^+ into extracellular space, such as the efflux of K^+ from thrombocytes during coagulation.[284] The continuous on-line measurement of K^+ in whole blood during human open-heart surgery is an impressive example of the advantages of the sensor approach as compared to batch analysis.[207,384] Whereas in analyzers urine is usually diluted[369] and makes the use of PVC membranes possible, silicone rubber membranes proved to be superior for bedside monitoring of K^+ in undiluted urine owing to smaller anionic interferences.[207,318] Various other applications, such as use in saliva,[385] muscles of various animals (microelectrodes[386] and in thick-film sensor arrays[78]), or retina (microelectrodes),[387,388] and the determination of exchangeable potassium in soils[389,390] were reported. Contrary to theoretical expectations, it was claimed that the use of added lipophilic anionic sites leads to an increased interference of acetate for a valinomycin membrane.[391] The scarcity of the data, the fact that one of the two membranes with sites contained 112 mol % sites, a ratio at which the concentration of noncomplexed carrier is negligible, as well as the use of unbuffered solutions for solid-contact electrodes, which are notoriously sensitive to CO_2, indicate, however, that this finding should be interpreted with care.

Optodes. Several K^+ bulk optodes based on K^+/H^+ exchange were reported in the past few years. For an optode based on the K^+ ionophore valinomycin and the neutral H^+ chromoionophore ETH 5294 (**H^+-10**) selectivities ($K^{\mathrm{opt}}_{\mathrm{K,J}}$ (FIM): Li^+, -3.7; Na^+, -3.5; Ca^{2+}, -3.7; Mg^{2+}, -4.0; DOS, KTpClPB) close to those of valinomycin ISEs were obtained.[296,373] Results from K^+ measurements in human blood plasma were in excellent agreement with determinations by potentiometry and flame photometry, and response times for the 4 μm thick membrane were on the order of seconds. Analogous membranes with the same chromoionophore were reported for the more lipophilic K^+ ionophore BME−44 (**K^+-25**),[373] which, however, slowly crystallized in the DOS membrane, and for the less selective calix[6]arene compound **Cs^+-4**.[392] Another optode based on valinomycin as K^+ ionophore was constructed with **H^+-33** (LAD) as anionic H^+ chromoionophore, eliminating the need for added ionic sites (log $k^{\mathrm{Osel}}_{\mathrm{K,J}}$ (SSM): Li^+, <-4.5; Na^+, -4.0; Ca^{2+}, <-4.5; Mg^{2+}, <-4.5; DBS).[94] Its detection limit under otherwise identical conditions was two orders of magnitude lower than that of an optode based on dibenzo-18-crown-6 (**K^+-4**; see also similar optode[92] with *o*-cresolphthalein octadecyl ester (LAD-4; **H^+-31**) as anionic chromoionophore).

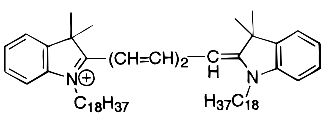
By combining the H^+ chromoionophore and K^+ ionophore functionality in one molecule, the number of different membrane components can be reduced. However, such systems have the disadvantage that they have little flexibility because the measuring range for a given pH cannot be easily modified by choosing a chromoionophore of appropriate basicity. Instead, a new dye that complexes both H^+ and K^+ must be prepared, which is synthetically more demanding. An example of such a K^+ optode is a PVC membrane containing an anionic crown ether dye (**K^+-35**) that provides a good selectivity but unfortunately allows detection limits as low as 10^{-6} M only at pH 10 and higher (log $k^{\mathrm{Osel}}_{\mathrm{K,J}}$ (SSM): Li^+, <-4.0; Na^+, -3.0; Ca^{2+}, <-4.0; Mg^{2+}, <-4.0; oNPOE).[393]



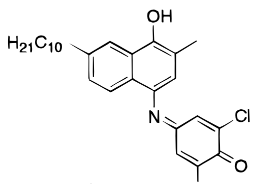
K^+-35

Bulk optodes containing the Takagi reagent (**K^+-11**) as K^+ chromoionophore were reported to be inferior to corresponding optodes with ionophores immobilized on the nonionic polymer resin Amberlite XAD2 (a polystyrene).[394] Whereas a longer lifetime for the latter sensors may, indeed, be an advantage when using ionophores of such a high hydrophilicity, the reported response time of 8 min for the bulk optodes is due to the exceptionally large thickness of the membranes (70 μm) used in that study and not typical for bulk optodes. An influence of the ionic strength on the sensor signal, as demonstrated by these authors only for the bulk optode, certainly occurs for any type of chemical sensor relying on chemical equilibria because the activity coefficient of the ion of interest depends on the ionic strength.

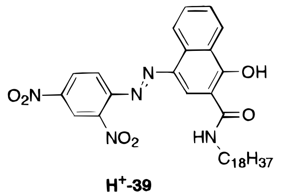
A fiber-optic K^+ sensor with a membrane containing valinomycin (**K^+-1**), a H^+ chromoionophore (**H^+-38**) and a pH-independent fluorescence indicator **Ind-1** demonstrates that detection with bulk optodes is not limited to vis absorption. Energy transfer between the indicator and the free chromoionophore, whose concentration rises with the K^+ concentration, leads to a decrease in the measured fluorescence of the indicator.[395] For another optode with a membrane containing valinomycin, KTpClPB, a charged H^+ chromoionophore (**H^+-39**) and a fluorescence indicator (FluoSphere particles), the fluorescence intensity became smaller as the concentration of K^+ increased because the free chromoionophore absorbed the photons emitted by the fluorophore.[396] This method gives a detection limit of 10^{-6} M, which signifies only a moderate improvement of about 1.5 orders of magnitude as compared to absorption measurements with the same membranes. Furthermore, it was accompanied by a substantial and not fully satisfactorily explainable increase of the response time to 5 min. A combination of valinomycin (**K$^+$-1**) and the charged H$^+$ chromoionophore **H$^+$-34**,[97] or 2,3-(naphtho)-15-crown-5 (**K$^+$-13**) and an unspecified dye[96] incorporated into a nonpolar phase, were reported for K$^+$ analysis on the basis of reflectance photometric analysis. Problems due to the low lipophilicity of valinomycin were found in an investigation of fluorescent fiber-optic sensors.[334]



Ind-1

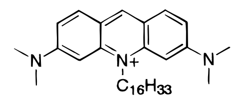


H$^+$-38



H$^+$-39

The response mechanism of K$^+$ optodes based on valinomycin and the alkyl-acridine orange derivative **Ind-2** as surface-active dye was explained by transfer of the charged acridine headgroup from the bulk membrane into the aqueous sample solution upon transfer of K$^+$ into the membrane, maintaining electroneutrality.[397−399] However, a rigorous control of the dye concentration in the membrane was not attempted and an alternative response mechanism seems possible. Similar sensors were also reported for NH_4^+ (see section II.7).

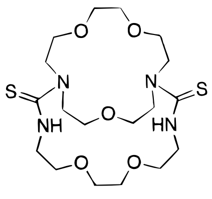


Ind-2

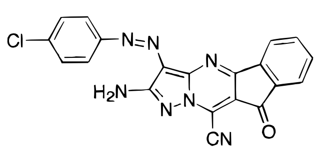
5. Rb$^+$ Sensors

The valinomycin (**K$^+$-1**) electrode is commonly used for K$^+$ analysis (see section II.4) but has in fact a preference for Rb$^+$ over K$^+$ (log $K^{pot}_{K,J}$ (SSM): Rb$^+$, +0.5; Cs$^+$, −0.3; DOP, KTpClPB).[324,328] This was explained by the fact that the valinomycin complex of K$^+$ is slightly less stable than the Rb$^+$ complex,[400] but because the Gibbs free energy of hydration is smaller for the slightly larger Rb$^+$ ion than for K$^+$ it is not surprising that also ionophore-free ion-exchanger ISEs respond more strongly to Rb$^+$ than to K$^+$.[401] On the other hand, the more lipophilic Cs$^+$ ion[401] interferes more strongly in case of the ionophore-free ISEs (log $K^{pot}_{K,J}$ (SSM): Rb$^+$, +0.7; Cs$^+$, +1.2; 2,3-dimethylnitrobenzene as membrane, KTpClPB).[328] Commercial valinomycin ISEs were used to determine Rb$^+$ efflux from yeast cells[402] and to measure the effect of Rb$^+$ on rod membrane photoreceptors in isolated retina.[387]

More recently, the use of seven cryptand ionophores with thiourea groups was reported, resulting in high selectivities for Rb$^+$ over Cs$^+$ (**Rb$^+$-1**: log $K^{pot}_{Rb,Cs}$ (SSM): −1.9; oNPOE) and other alkali and alkaline earth metal ions.[403] Response times were reported to be fast (2−5 s) but very long conditioning periods necessary for obtaining stable potentials and sub-Nernstian emf responses (42−48 mV/decade for Rb$^+$, but 52−58 mV/decade for Cs$^+$) may indicate kinetic limitations in complex formation or dissociation. A comparably high discrimination of Cs$^+$ but with Nernstian slopes was found for an indanopyrazolo[1,5-*a*]pyrimidine carrier (**Rb$^+$-2,** log $K^{pot}_{Rb,J}$ (SSM): K$^+$, −1.6; Cs$^+$, −2.0; Na$^+$, −2.4; oNPOE, KTpClPB).[404] In comparison, the discrimination of K$^+$ and Cs$^+$ as reported for several ISEs based on bisbenzocrown ethers[364] or ionophores with lactam or/and lactone groups[347] is only moderate. As for similar K$^+$ ISEs, sub-Nernstian slopes complicate the interpretation of the selectivity of propeller crowns that provide a certain selectivity for Rb$^+$.[348]



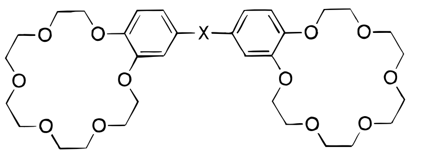
Rb$^+$-1



Rb$^+$-2

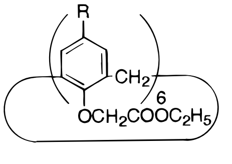
6. Cs$^+$ Sensors

Because of the high lipophilicity of Cs$^+$, a fair selectivity for this ion can be obtained with ionophore-free ion-exchanger ISEs based on cesium tetrakis(*m*-trifluoromethylphenyl)borate (log $K^{pot}_{Cs,J}$ (MSM):[405] Rb$^+$, −0.7; K$^+$, −1.1; Na$^+$, −2.1; 4-ethyl nitrobenzene, no polymer matrix) or KTpClPB (log $K^{pot}_{Cs,J}$ (SSM):[406] Rb$^+$, −0.5; K$^+$, −1.2; Na$^+$, −2.7; NH_4^+, −1.5; oNPOE).[405−407] The selectivities of ISEs based on dibenzo-18-crown-6 derivatives[408] or 2,3-benzoquinone-15-crown-5 ethers[409] were found to be very similar to these of ionophore-free ion-exchanger ISEs. Also only moderate improvements were obtained by use of three bis(benzo-18-crown-6) ethers with a diester spacer between the two macrocycles (e. g. for **Cs$^+$-1**: log $K^{pot}_{Cs,J}$ (FIM): Rb$^+$, −1.1; K$^+$, −1.1; Na$^+$, −3.0; NH_4^+, −2.0; oNPOE).[353,360] With the exception of a better Rb$^+$ discrimination, the same is also true for compounds with ether spacers connecting two bis(benzo-18-crown-6) macrocycles (e. g. **Cs$^+$-2**, log $K^{pot}_{Cs,J}$ (FIM): Rb$^+$, −1.9; K$^+$, −1.0; Na$^+$, −2.0; NH_4^+, −1.7; DBP),[359] whereas ISEs based on an ionophore with a propylene spacer have recently been shown to be somewhat more selective (**Cs$^+$-3**, log $K^{pot}_{Cs,J}$ (MSM): K$^+$, −2.3; Rb$^+$, −1.4; Na$^+$, −4.5; oNPOE; selectivity estimated here from log $K^{pot}_{K,J}$ as given in the original paper).[364] The use of a carrier with a fumaric acid diester spacer that excludes the formation of intramolecular sandwich complexes showed however clearly the effectiveness of the bis(18-crown-6) approach.[410] For oNPOE membranes containing a 14-membered macrocycle with oxygens and nitrogens in the ring, on the other hand, the best discrimination of interfering ions was obtained in the presence of 200 mol % tetraphenylborate, which suggests that the action of the ionophore is completely suppressed.[411] Indeed, the selectivities at that tetraphenylborate concentration seem to be, within experimental error, identical to those obtained with membranes free of ionophore.

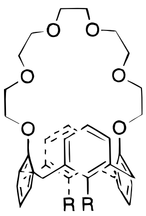


Cs$^+$-1: X = -$CH_2OCO(CH_2)_5COOCH_2$-
Cs$^+$-2: X = -$CH_2(OCH_2CH_2)_3OCH_2$-
Cs$^+$-3: X = -$CH_2CH_2CH_2$-

By far the best Cs^+ selectivities have been obtained with the two calix[6]arene hexaesters **Cs$^+$-4** and **Cs$^+$-5** (for the more selective **Cs$^+$-4**: log $K_{\mathrm{Cs,J}}^{\mathrm{pot}}$ (SSM): Rb^+, −1.9; K^+, −2.7; Na^+, −3.9; NH_4^+, −2.8; oNPOE).[406] Also good are the selectivities of bridged calix[4]arenes containing ether groups as the only type of functional groups (e. g. **Cs$^+$-6**: log $K_{\mathrm{Cs,J}}^{\mathrm{pot}}$ (FIM):[412] Rb^+, −0.9; K^+, −2.2; Na^+, −4.5; NH_4^+, −2.0; oNPOE, KTpClPB).[412,413]



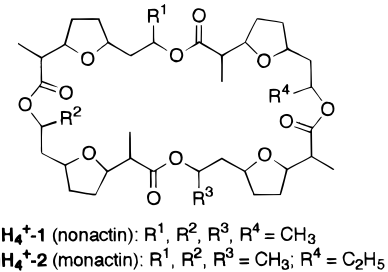
Cs$^+$-4: R = H
Cs$^+$-5: R = $C(CH_3)_3$



Cs$^+$-6: R = $OCH(CH_3)_2$

7. NH_4^+ Sensors

Even though the interest for NH_4^+ analysis for various applications such as in environmental control and clinical chemistry is large, the number of ammonium ion carriers that have been used for ISEs and optodes is very small. Only few studies with ionophores other than the antibiotics nonactin (**NH$_4^+$-1**) and monactin (**NH$_4^+$-2**) were reported. A very high activity was seen in the past years in optical sensors for the neutral analyte ammonia, which will be discussed separately (see section V.2). A particular interest in NH_4^+ sensors arises from the fact that this analyte is the product of many enzymatically catalyzed reactions. Many enzyme-based ISEs and optodes for various organic nitrogen compounds, such as for urea or creatinine, have been developed.[414−416] A commercial clinical analyzer using urease and a nonactin-based NH_4^+ ISE, for example, was introduced in the late 1980s.[109]

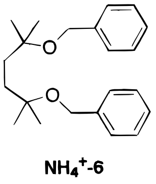


NH$_4^+$-1 (nonactin): R^1, R^2, R^3, R^4 = CH_3
NH$_4^+$-2 (monactin): R^1, R^2, R^3 = CH_3; R^4 = C_2H_5
NH$_4^+$-3 (dinactin): R^1, R^3 = CH_3; R^2, R^4 = C_2H_5
NH$_4^+$-4 (trinactin): R^1 = CH_3; R^2, R^3, R^4 = C_2H_5
NH$_4^+$-5 (tetranactin): R^1, R^2, R^3, R^4 = C_2H_5

NH^{4+}-Selective Electrodes. Nonactin was initially tested as ionophore for K^+, but it was soon found that this macrotetrolide antibiotic provides for a slight preference for NH_4^+ over K^+.[303,308,417] Interestingly, four hydrogen bonds are formed between NH_4^+ and the ether oxygens and not the carbonyl groups of nonactin, as shown by ^{13}C NMR and IR spectroscopy as well as crystallography.[418−420] Several plasticized PVC, silicone rubber, polyurethane, and cellulose acetate membranes were reported to give fairly similar discrimination of alkali and alkaline earth ions (75% nonactin, 25% monactin (note typographical error in the ratio of the ionophores in this reference):[421] log $K_{\mathrm{NH_4,J}}^{\mathrm{pot}}$ (SSM): Li^+, −2.9; Na^+, −2.3; K^+, −1.1; oNPOE, KTpClPB; 72% nonactin, 28% monactin:[51] log $K_{\mathrm{NH_4,J}}^{\mathrm{pot}}$ (SSM): Li^+, −4.6; Na^+, −2.8; K^+, −0.7; silicone rubber; nonactin:[422] log $K_{\mathrm{NH_4,J}}^{\mathrm{pot}}$ (SSM): Li^+, −3.5; Na^+, −2.4; K^+, −1.0; DOS, KTpClPB).[50,423,424] The plasticizer oNPOE was also shown to be very suitable as solvent for microelectrodes (log $K_{\mathrm{NH_4,J}}^{\mathrm{pot}}$ (SSM): Li^+, −3.6; Na^+, −2.0; K^+, −0.6; H^+, −2.2; oNPOE, KTpClPB)[55,425−429] and scanning electrochemical microscopy.[371] Interference by Na^+ and even more by K^+ is a critical problem but can be overcome by chemometric correction for these interfering ions. The use of an array of ISEs selective for NH_4^+, Na^+, K^+, and Ca^{2+} in FIA has for example been shown to be very useful for improving the accuracy of NH_4^+ determinations in the presence of K^+.[430]

Incidentally, the majority of investigations of ISEs based on nonactin were not performed with pure nonactin but rather a commercially available mixture of ≈75% nonactin and ≈25% monactin. Very similar selectivities were reported for an ISE based on a very different macrotetrolide[304] mixture (5% dinactin (**NH$_4^+$-3**), 30% trinactin (**NH$_4^+$-4**), 65% tetranactin (**NH$_4^+$-5**): log $K_{\mathrm{NH_4,J}}^{\mathrm{pot}}$ (SSM): K^+, −0.5; Na^+, −2.4; Cs^+, −2.5; Li^+, −4.4; DBS).[431] Also the discrimination of various alkylammonium ions was not very different when using the ionophores nonactin, dinactin, and tetranactin.[432]

Little is known on nonactin/monactin alternatives. The use of other antibiotics, that is narasin, monensin, and salinomycin, resulted in inferior electrodes.[162,433] Promising on the other hand is a new family of glycol dibenzyl ethers that can be used as ionophoric membrane plasticizers.[422] While the discrimination of all other alkali and alkaline earth ions is similar or even worse than when using nonactin, discrimination of the most troublesome K^+ improves to log $K_{\mathrm{NH_4,K}}^{\mathrm{pot}}$ −1.7 by use of a sterically hindered representative of this ionophore class (**NH$_4^+$-6**, log



NH$_4^+$-6

$K^{\mathrm{pot}}_{\mathrm{NH_4,J}}$ (SSM): Na^+, −2.3; Cs^+, −0.1; Li^+, −1.9; ionophore as membrane plasticizer).

Optodes. An optode based on nonactin and a H^+-selective neutral chromoionophore gives an absorbance response to NH_4^+ with a dynamic range from 10^{-5} to 10^{-3} M and has very similar selectivities as corresponding ISEs (nonactin/monactin log $K^{\mathrm{opt}}_{\mathrm{NH_4,J}}$ (FIM): K^+, −1.2; Na^+, −2.7; Li^+, −3.4; ETH 5294 (**H^+-10**), KTpClPB, DOS; pH 7.35).[434,435] Because this optode responds to the ratio of NH_4^+ and H^+, the activity of the latter must be either measured simultaneously or be kept constant by means of an appropriate buffer. Alternatively, one can however also say that this optode formally responds to NH_3. Very similar optodes will be discussed below for ammonia. NH_4^+ optodes based on nonactin and a surface-active alkyl-acridine orange derivative (**Ind-2**) as dye were suggested and were used as a component of a biosensor for urea.[436,437] Their response mechanism has not been fully elucidated but seems to be very similar to that of K^+ optodes with the same dye (see section II.4).

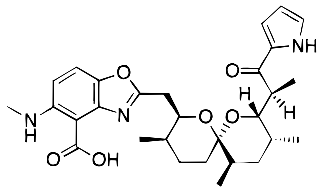
8. Be^{2+} Sensors

Beryllium has found many applications in aerospace, nuclear, telecommunication, and computer industries. Because of its high toxicity and debated carcinogenicity, analysis of this element is necessary in the vicinity of ore processing plants and their waste disposal sites as well as in the industry using beryllium products.[438,439] Unfortunately, the interest in Be^{2+} ISEs has been dampened by the fact that this ion, owing to its very small size and high charge, is very strongly hydrated. Its Gibbs free energy of hydration is 31% and 404% larger than that of Mg^{2+} and Li^+, respectively, making an appropriate ionophore design very difficult.[401] Because of the small size of the ion, which limits the maximum coordination number, and the high required complex stabilities, it has been suggested that the search for ISEs for this analyte ion might be hopeless.[304] A further reason for the lack of interest in Be^{2+} ISEs is probably that the high toxicity of beryllium compounds requires determinations at concentrations that are too low for conventional direct measurements with ion-selective electrodes. The only reported Be^{2+} ISEs were based on phosphate ester ionophores.[440−442] A commercial Ca^{2+} ISE electrode based on an alkyl phosphate ionophore was found to respond more strongly to Be^{2+} than to Ca^{2+} (log $K^{\mathrm{pot}}_{\mathrm{Ca,Be}}$ (FIM): +0.9), and an electrode membrane with the Ca^{2+} ionophore bis[4-(1,1,3,3-tetramethylbutyl)phenyl)] phosphate (**Ca^{2+}-3**) responded to Be^{2+} with a response slope of 31 mV/decade and a detection limit of 1.1×10^{-5} M.[442]

9. Mg^{2+} Sensors

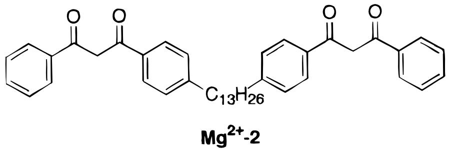
With 78 pm, Mg^{2+} has the same ionic radius as Li^+ and is the second smallest alkaline earth metal ion. As a result, its hydration energy is very large (free energy of hydration −1920 kJ mol^{-1} as compared to −1650 kJ mol^{-1} for Ca^{2+}) and ligand exchange reactions are relatively slow. Hydration water exchange, for example, is about 3 orders of magnitude slower than for Ca^{2+}. Most ionophores for Mg^{2+} fall into one of the three classes of antibiotics, β-diketones, and di- and triamides.[443] The major challenge in the design of Mg^{2+} ionophores lies for many applications in the discrimination of Ca^{2+}. The determination of water hardness with ISEs with equal selectivity for Mg^{2+} and Ca^{2+} was one of the first achievements in the development of ISEs (see “Noncyclic Amide Ionophores” below as well as “Phosphoric Acid Esters” in section II.10), and because of the low intracellular Ca^{2+} concentrations satisfactory intracellular Mg^{2+} determinations were possible with microelectrodes of low selectivity since the early 1980s. However, truly Mg^{2+}-selective electrodes are newcomers and have been used routinely in clinical chemistry only for a few years.[286,444−449] The first clinical analyzer measuring Mg^{2+} potentiometrically was introduced only in 1994.[109]

Antibiotics as Ionophores. ISEs with the antibiotic calcimycin A23187 (**Mg^{2+}-1**) as ionophore, nitrobenzene as membrane solvent and a cellulose ester as support were reported to give a selectivity in the order $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$, contrasting the sequence $Mn^{2+} \gg Ca^{2+} \approx Mg^{2+} \gg Sr^{2+} > Ba^{2+}$ found in extraction studies.[450] A neutral carrier mechanism for the ISE membranes with low concentration of anionic sites and at the fairly low pH of unbuffered sample solutions, on one hand, and dissociation of the carboxylic group of A23187 followed by H^+/Mg^{2+} exchange in the extraction experiments, on the other hand, are the likely explanations for these findings.[182] A similar case was reported for several not very selective dicarboxylic acid monoamide ionophores (vide infra).[451] Another example of an ionophore that, when incorporated in ISE membranes, did not give a Mg^{2+} selectivity as in extraction experiments was antibiotic-6016.[452] On the other hand, in an optical sensor based on A23187 but no added ionic sites the carboxylate anion acts as a charged carrier and gives a selectivity similar to the one observed in extraction (log $k^{\mathrm{Osel}}_{\mathrm{Mg,J}}$: Ca^{2+}, −0.4; Ba^{2+}, <−5; Li^+, <−5; Na^+, <−5; K^+, <−5; DBS).[453] A reinvestigation of ISEs with the above carriers and added ionic sites with sample solutions of controlled pH would therefore be of interest.

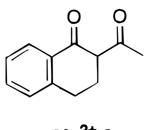


Mg^{2+}-1 (A23187)

***β*-Diketone Ionophores.** Because β-diketones form stronger complexes with Mg^{2+} than with Ca^{2+}, a number of diketones were tested as ionophores for Mg^{2+}-selective electrodes. Whereas ISE membranes without added ionic sites and either a β-diketone or a bis-β-diketone ionophore (e.g. **Mg^{2+}-2**) were reported to give emf slopes typical for divalent ions (pH ≥ 8) and log $K^{\mathrm{pot}}_{\mathrm{Mg,Ca}}$ of only >0.1 (membrane plasticizer 31.8% w/w TEHP, 31.8% w/w 5-phenyl-1-pentanol),[454,455] results from a study with added anionic sites show emf slopes typical for monovalent cations (pH = 10) and improved discrimination of Ca^{2+}.[456] The best results were obtained for 2-acetyl-1-tetralone (**Mg^{2+}-3**, log $K^{pot}_{Mg,J}$ (SSM): Ca^{2+}, −2.2; K^+, −1.9; Na^+, −2.7; dibenzyl ether, KTpClPB) but the limitation to measurements at pH > 8 poses a problem for many applications. The response slopes of the ISEs based on the β-diketone ionophore **Mg^{2+}-3** indicate an unusual response mechanism. A recently developed theoretical model predicts that in case of such acidic ionophores response slopes typical for divalent ions are expected at any pH with cationic sites (leading to a charged carrier response mechanism) and, at low and high pH, with anionic sites (leading to a neutral and charged carrier mechanism, respectively).[185] However, a slope typical for monovalent cations (so-called apparently "twice-Nernstian" response) can occur for membranes with anionic sites in an intermediate pH range, where these membranes contain predominantly the neutral form of the ionophore and complexes of the deprotonated ionophore with the divalent cation. So far, this model has been tested for Ca^{2+} and Ba^{2+} ionophores (vide infra) but not for Mg^{2+} ISEs.



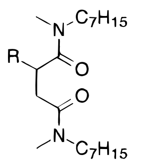
Mg^{2+}-2



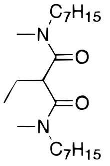
Mg^{2+}-3

Cyclic Peptides as Ionophores. More successful were cyclic peptides, as shown in a study of eight octa-and decapeptides.[457] With a log $K^{pot}_{Mg,Ca}$ of −2.0, *cyclo*(LPro-DLeu)$_5$ was found to give a very promising selectivity but unfortunately the discrimination of monovalent cations was poor. On the other hand, *cyclo*(LPro-LLeu)$_5$ was satisfactory from the latter point of view but showed only a small discrimination of Ca^{2+}. Both ionophores furthermore have a lipophilicity that is too low for clinical applications.

Noncyclic Amide Ionophores. The first strategy for the development of Mg^{2+}-selective amide ionophores was based on the preference of octahedral coordination of this ion, contrasting the preference of Ca^{2+} for larger coordination numbers. An extensive search in the Cambridge Structural Database a few years ago has reconfirmed this trend.[458] The early screening of various amide ionophores that were designed accordingly (among them EDTA and NTA derivatives) failed however to give Mg^{2+} selectivity.[459] Because most early ionophores of the noncyclic amide class contained only two or three amide groups, the stoichiometry of the ionophore−analyte complex had a decisive influence on the potentiometric selectivity. A typical, disappointing surprise was the formation of 1:3 complexes of Ca^{2+} with the tridentate *N,N,N′,N′*-tetracyclohexyl-3-oxapentane diamide, which had been expected to form 1:2 complexes with Mg^{2+}.[452,460] First moderate improvements in Ca^{2+} discrimination were obtained with *N,N′*-diheptyl-*N,N′*-dimethylsuccinamide (**Mg^{2+}-4** (ETH 1117, log P_{TLC} 5.8),[48] log $K^{pot}_{Mg,Ca}$ (SSM): +1.3; oNPOE, KTpClPB) and *N,N′*-diheptyl-*N,N′*-dimethylethylmalonamide (**Mg^{2+}-5**, log $K^{pot}_{Mg,Ca}$ (SSM): +0.8; oNPOE, KTpClPB). Owing to satisfactory discrimination of alkali ions, these ionophores made intracellular determinations of Mg^{2+} possible.[122,452,461−464] Higher discrimination of Ca^{2+} and satisfactory discrimination of all alkali metal ions could be achieved by substituting the malonic backbone with an amino group in 2-position. Not surprisingly, this was accompanied by a strong H^+ interference. ISEs with this ionophore could only be used at pH = 8−9 (**Mg^{2+}-6** (ETH 2220, log P_{TLC} ≈ 8):[48] log $K^{pot}_{Mg,J}$ (SSM): Ca^{2+}, −2.5; H^+, 10.8; oNPOE, KTpClPB).[140,465]

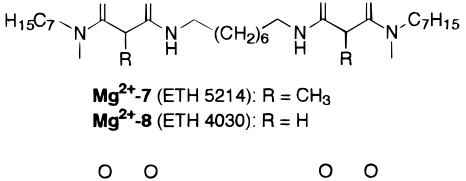


Mg^{2+}-4 (ETH 1117): R = H
Mg^{2+}-6 (ETH 2220): R = NH_2

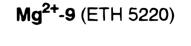


Mg^{2+}-5

In an attempt to reduce selectivity losses arising from variable stoichiometries, later ionophores of the amide class contained more than two and in some cases up to six amide groups. This concept, similar for example to that of bis-crown ethers, was very successful even though ionophore optimization turned out to be very laborious. Several bis(malonic acid diamide) ionophores reduced the Ca^{2+} interference to give roughly equal response to Mg^{2+} and Ca^{2+}.[132] Water hardness determinations with these as well as other ionophores were suggested but it must be realized that there is a basic problem underlying such measurements: the activity coefficients of Ca^{2+} and Mg^{2+} differ substantially at high concentrations and without knowledge of their ratio water hardness cannot be deduced exactly from the measured emf (see also "Phosphoric Acid Esters" in section II.10).[466−470] Electrodes with **Mg^{2+}-7** (ETH 5214, log P_{TLC} ≈ 3.4),[48] differing from **Mg^{2+}-8** (ETH 4030) only by one additional methyl group in 2-position on each malonic acid group, gave inferior selectivities (log $K^{pot}_{Mg,Ca}$ (SSM): +0.6; oNPOE, KTpClPB). However, microelectrodes based on **Mg^{2+}-7** proved to be much more adequate for intracellular measurements than **Mg^{2+}-8** because of a much better solubility of **Mg^{2+}-7** in relatively polar membrane solvents.[55,131,471] The selectivity of the isomeride **Mg^{2+}-9** (ETH 5220, log P_{TLC} 11.4)[48] was just large enough for measurements in real serum samples.[444,472]

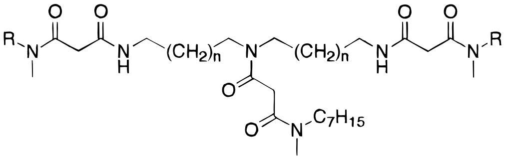


Mg^{2+}-7 (ETH 5214): R = CH_3
Mg^{2+}-8 (ETH 4030): R = H



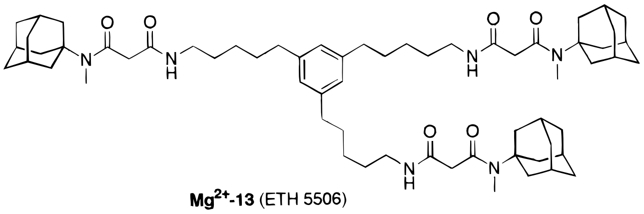
Mg^{2+}-9 (ETH 5220)

The first accurate Mg^{2+} determinations in undiluted blood serum were only achieved with an ISE based on an ionophore with six amide groups, but here too correction for Ca^{2+} interference was necessary (**Mg^{2+}-10** (ETH 5282, log P_{TLC} 5.5),[48] log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM); Ca^{2+}, −0.8; Na^{+}, −3.9; K^{+}, −2.4; oNPOE, KTpClPB).[140,473] Given the known preference of the primary ion for octahedral coordination, it can be expected that this ionophore forms a 1:1 complex with Mg^{2+} and thus theory predicts the highest selectivity if the polymer membrane contains anionic sites in a molar ratio of 1.62 to the ligand (cf. Bakker et al.,[2] Table 3). This was experimentally confirmed by an optimum selectivity for 120 and 150 mol % KTpClPB, whereas for 90 and 170 mol % anionic sites the selectivity was found to be already clearly reduced. Subsequently, isomerides of this hexaamide with spacers of various lengths ($(\mathrm{CH}_2)_n$, $n = 6-10$) connecting the malonamide groups were investigated and the octano bridge of **Mg^{2+}-11** (ETH 7025) was found to be optimal.[339,446,474−477] With a good selectivity, in particular in view of K^{+} discrimination for intracellular measurements, microelectrodes based on **Mg^{2+}-11** are superior to previously reported microelectrodes (**Mg^{2+}-11**, log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM):[478] Ca^{2+}, +0.7; Na^{+}, −3.1; K^{+}, −3.1; acetylcholine, −0.3; oNPOE, 60 mol % KTpClPB, tetradodecylammonium tetrakis(*p*-chlorophenyl)borate (ETH 500); a higher concentration of anionic sites reduces the Ca^{2+} interference on the cost of a higher acetylcholine interference). While for intracellular measurements discrimination of K^{+} is most important and consequently a rather low concentration of added ionic sites (60 mol %) is preferable, discrimination of Ca^{2+} is more important for extracellular measurements, requiring a higher site concentration (150 mol %). The ionophore **Mg^{2+}-11** has found application in commercial clinical analyzers.[479]

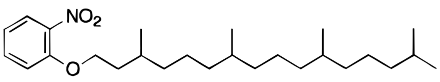


Mg^{2+}-10 (ETH 5282): n = 4, R = $\mathrm{C_7H_{15}}$
Mg^{2+}-11 (ETH 7025): n = 6, R = $\mathrm{C_7H_{15}}$
Mg^{2+}-12 (ETH 7160): n = 6, R = 1-adamantyl

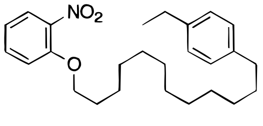
Systematic variation of the number of secondary amide groups in hexaamide isomerides of **Mg^{2+}-11** showed no large changes in selectivities except for a better discrimination of H^{+} in the case of ionophores with two or three secondary amide groups and an inferior Mg^{2+} preference for those with four and five secondary amide groups.[132] The position of the secondary amide groups was found not to affect the selectivity for Mg^{2+} over Ca^{2+} and Na^{+} very strongly. While none of the isomerides was found to be superior to **Mg^{2+}-11**, substitution of three amides with an adamantyl group led to appreciable selectivity improvements for **Mg^{2+}-12** (ETH 7160, log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM): Ca^{2+}, −1.2; K^{+}, −2.0; Na^{+}, −4.2; Li^{+}, −4.3; H^{+}, +1.9; oNPOE, KTpClPB), which is an isomeride of **Mg^{2+}-11**, as well as for a more recent hexaamide ionophore with three malonamide units attached to a benzene ring via pentano bridges (**Mg^{2+}-13** (ETH 5506): log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM): Ca^{2+}, −1.7; K^{+}, −2.7; Na^{+}, −4.4; Li^{+}, −4.7; H^{+}, +0.1; oNPOE, KTpClPB).[133] Further selectivity improvements with hexaamide ionophores can be achieved by using the plasticizer ETH 5373 (**PL-5**), which is an oNPOE isomeride (ETH 5506: log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM): Ca^{2+}, −1.9; K^{+}, −3.7; Na^{+}, −4.7; Li^{+}, −4.8; H^{+}, +0.9; ETH 5373, KTpClPB).[133] An only slightly smaller discrimination of Ca^{2+} was obtained with an isomeride of **Mg^{2+}-13** with heptyl instead of adamantyl groups (ETH 3832 log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM): Ca^{2+}, −1.5; ETH 8045 (**PL-6**) as plasticizer,[480] KTpClPB, tetradecylammonium tetrakis(*p*-chlorophenyl)borate).[133,443,481]



Mg^{2+}-13 (ETH 5506)

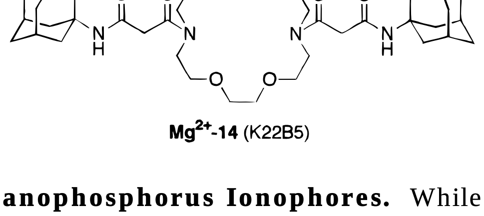


PL-5 (ETH 5373)



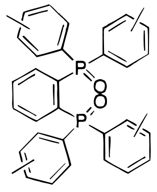
PL-6 (ETH 8045)

Presently, the best discrimination of Ca^{2+} is, however, achieved with double-armed diazacrown ether ionophores.[482] A very systematic study has shown that 18-membered rings are superior to both 15- and 21-membered rings and that among a variety of malonamide type side chains again the ones substituted with adamantyl groups are most favorable (**Mg^{2+}-14** (K22B5), log $K^{\mathrm{pot}}_{\mathrm{Mg,J}}$ (SSM): Ca^{2+}, −2.5; K^{+}, −1.5; Na^{+}, −3.2; oNPOE, KTpClPB). Unfortunately, the spectacular discrimination of Ca^{2+} is accompanied by sizable increases in the interference from alkali metal ions. Analogous ionophores with more than two malonamide units were much less successful.



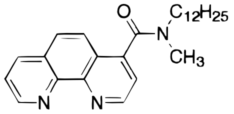
Mg^{2+}-14 (K22B5)

Organophosphorus Ionophores. While many ISE membranes containing phosphoric acid esters are known to be Ca^{2+} selective (see section II.9) and membranes additionally containing 1-decanol have log $K^{\mathrm{pot}}_{\mathrm{Mg,Ca}}$ that approach unity, Mg^{2+}-selective ISEs based on this ionophore class are not known. Nevertheless, such electrodes had been used in intracellular Mg^{2+} determinations before more appropriate ionophores were available.[290,483] Very recently, 1,2-bis(diarylphosphine oxide)benzenes have, however, been reported to give an excellent discrimination of Ca^{2+} (**Mg^{2+}-15**, log $K^{pot}_{Mg,J}$ (MSM): Na^+, −3.1; K^+, −3.3; Ca^{2+}, −2.8; NPOE, KTpClPB).[484] The electrodes do not respond to H^+ in the pH range 5−10 but unfortunately the response times, reported as being within 3 min, were rather long.



Mg²⁺-15

1,10-Phenanthroline Ionophores. Membranes containing the Mg^{2+} complex of 1,10-phenanthroline, tetraphenylborate to provide for ionic sites, and *o*-nitrophenyl lactate as plasticizer were reported to have a good selectivity for Mg^{2+}.[485] Furthermore, some 1,10-phenanthroline derivatives that were least successful as Li^+ ionophores (see section II.2, e. g. **Li^+-31** and **Li^+-32**) showed a preference for Mg^{2+} over Li^+, Na^+, K^+, and Ca^{2+} (2,9-di-*tert*-butyl-1,10-phenanthroline, log $K^{pot}_{Li,J}$ (SSM): Mg^{2+}, +0.5; H^+, +3.7; Na^+, −0.9; K^+, −1.0; Ca^{2+}, −0.8; oNPOE, KTpClPB).[168,169] A recent patent describes the use of compounds such as **Mg^{2+}-16** for Mg^{2+} selective electrodes[486] and Mg^{2+} analysis with a commercial analyzer[487] may be based on such an ionophore. The patent does not report selectivity coefficients but claims that substituents other than hydrogen in 2- and 9-position decrease the selectivity for Mg^{2+}. This effect seems just opposite to the influence of substitution on similar phenanthroline ionophores with Li^+ selectivity (vide infra).



Mg²⁺-16

Optodes. As mentioned previously, an optical sensor based on the fluorescent antibiotic A23187 (**Mg^{2+}-1**) was found to have a small preference for Mg^{2+} (log $k^{Osel}_{Mg,J}$: Ca^{2+}, −0.4; Ba^{2+}, <−5; Li^+, <−5; Na^+, <−5; K^+, <−5; DBS).[453] More recently, an optode has been reported that contained as Mg^{2+} ionophore an isomeride of **Mg^{2+}-14** in which one of the adamantyl groups is replaced by an octadecyl group to increase the ionophore lipophilicity. A physiological background of 3.0 mM LiCl, 150 mM NaCl, and 1.2 mM $CaCl_2$ interfered only weakly for measurements of Mg^{2+} at concentrations higher than 5 mM, but even though the membrane composition was carefully optimized this optode cannot be used for measurements in human serum, which contains typically about 0.1 mM Mg^{2+}.[488] Unfortunately, most Mg^{2+} ionophores developed in recent years for potentiometry seem not suited for use in optodes because their selectivities depend strongly on the stoichiometry of the analyte−ionophore complexes and therefore vary within the measuring range of a bulk membrane optode.[489]

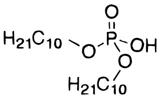
Application of Mg^{2+} ISEs in Clinical Chemistry. A number of general considerations on potentiometric measurements in clinical chemistry have been given above (see section II.3) and apply also to measurements with Mg^{2+} ISEs. A problem particular to Mg^{2+} analysis arises from Mg^{2+} binding to heparin.[286,445] Furthermore, it was suggested that falsely high Mg^{2+} results may be attributed to Zn^{2+} impurities in heparin.[490] Care must be taken to prevent loss of CO_2 from blood samples because the concentration of complexed Mg^{2+} in plasma increases by 1−2% per 0.1 unit increase in pH.[286,490] The concentration of protein-bound Mg^{2+} is very high,[491] accounting normally for about 30% of the total Mg^{2+} but acidification to pH 6.75 can decrease the protein-bound fraction to 7%.[472] Silicone as used in vacutainer linings was reported as causing falsely increased Mg^{2+} readings but independent investigations have shown that this effect seems to be limited to certain types of silicone.[490,491] A satisfactory explanation for this finding has so far not been found.

The availability of ISEs with sufficient selectivity for Mg^{2+} has recently initiated a number of clinical investigations.[487] The Mg^{2+} activity in blood serum was shown to decrease during liver transplantations due to accumulation of citrate and concomitant chelation of Mg^{2+}.[491] Low Mg^{2+} activities were also found for pregnant women, certain sufferers of acute migraine headaches, and patients with cardiac diseases, to name just a few examples.[487] It was also shown by use of potentiometry that the activity of Mg^{2+} in human blood undergoes substantial circadian changes.[447]

10. Ca^{2+} Sensors

Ca^{2+} ISEs were among the first commercially available ISEs.[1,309,492,493] Clinical situations in which in vivo monitoring of Ca^{2+} are of interest include for example organ transplantations, hemodialysis, or exchange transfusion, during which rapid changes in the concentration of ionized calcium may occur. Such applications have made Ca^{2+} one of the analytes of top interest in ion-selective potentiometry. Important industrial applications are Ca^{2+} measurements in boiler water,[494] soils, and fertilizers.

Phosphoric Acid Esters. The use of phosphoric acid esters as ionophores dates back into the early days of carrier-based ISEs and reflects in an exemplary way the history of ISE membrane technology.[1,271,309,495] However, surprisingly little has changed over the years in the structure of the ionophoric unit. The well-known stability of complexes of Ca^{2+} and phosphate or polyphosphate led to the proposition of bis(2-ethylhexyl) phosphate[496] and didecyl phosphate[497] (**Ca^{2+}-1**) as the first carriers of this class.[309] Incidentally, the choice of a dialkyl ester was intended to avoid the problems arising from formation of mixed Ca^{2+}/H^+ complexes in the ISE membrane.[495] Later it has repeatedly been reported that membranes with monocalcium dihydrogen tetrakis(didecyl phosphate) as sensing compound give the best membrane performance.[498−500] Clearly, appropriate membrane conditioning before measurements should eliminate differences between membranes based on different Ca^{2+}/H^+ salts of the same phosphoric acid ester.

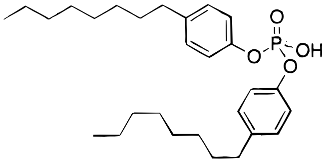


Ca^{2+}-1

The quite good selectivities of these ISEs soon led to several commercial products[1,309,499] and the investigation of various other dialkyl phosphates,[500] even though problems with a limited lifetime and H^+ interference were observed. Those could be significantly reduced when PVC was introduced as the membrane matrix.[501−503] No other membrane matrix has been as successful for Ca^{2+} sensing with phosphate esters.[498,504,505] In terms of selectivity, ethylene vinyl acetate copolymer (EVAC), for which substantially smaller interferences of Cu^{2+} but a slightly smaller discrimination of Mg^{2+} was found (log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (FIM): Mg^{2+}, −1.4; Cu^{2+}, −1.7; Zn^{2+}, −1.5; Mn^{2+}, −0.5; EVAC, calcium didecyl phosphate, DOPP, DOP, nitrobenzene; cf. by the same authors log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (FIM): Mg^{2+}, −1.6; Cu^{2+}, +1.0; Zn^{2+}, −1.4; PVC, calcium didecyl phosphate, DOPP, DOP, nitrobenzene),[506] is an interesting exception but loss of the membrane component nitrobenzene must be expected. Several attempts to covalently attach the ionophore to the matrix were made but were reported to fail to give the expected improvement in the electrode lifetime[507] or to result in only a reduced selectivity.[508−510]

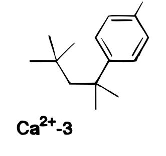
The choice of the excellent plasticizer di-*n*-octyl phenylphosphonate was not explained in the literature but might have been based on the properties of this compound as known from solvent extraction. Other di-*n*-alkyl phenylphosphonates,[502,511] di-(2-ethylhexyl) 2-ethylhexylphosphonate,[500,512] and trialkyl phosphates[513,514] were, however, shown to give rather comparable selectivities as long as their lipophilicity and solubility in the membrane were high enough. On the other hand, 1-decanol as plasticizer leads to a complete loss of selectivity versus Mg^{2+} (log $K_{\mathrm{Ca,Mg}}^{\mathrm{pot}} \approx 1$), making it the plasticizer of choice for so-called divalent ion-selective electrodes, which have found application in the determination of water hardness.[504,515−517] Recently, several neutral carriers have been reported for determinations of water hardness. However, as mentioned previously (see "Noncyclic Amide Ionophores" in section II.9), it must be pointed out that the activity coefficients of Ca^{2+} and Mg^{2+} differ significantly from one another at high ionic strength, which complicates the interpretation of such measurements.

It was argued that a more acidic ionophore would be desirable for a high discrimination of H^+. Indeed, the use of the ionophore bis(*n*-octylphenyl) phosphate (**Ca^{2+}-2**) resulted in a shift of the proton interference in the presence of 10 mM Ca^{2+} by about 1.5 pH units to pH < 4 and an improved selectivity versus Na^+.[499,512,518] If the pH is reduced at a constant Ca^{2+} background, the potential first decreases and only at even lower pH starts to increase, as expected for a usual cation interference. This "dip" seems to result from ionophore protonation[182] and was predicted to occur with all organophosphate ionophores for which the type of complex formed in the membrane depends on the pH.[493,499,519] Nitration of the phenyl ring eliminates the "dip", probably by further increasing the acidity of the ionophore.[493,520,521]



Ca^{2+}-2

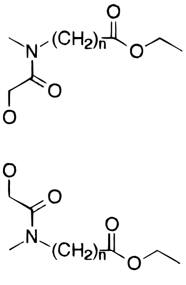
Microelectrodes prepared with the similar bis[4-(1,1,3,3-tetramethylbutyl)phenyl)] phosphate (**Ca^{2+}-3**, an isomer of **Ca^{2+}-2**), were reported to give either a fairly good selectivity but sub-Nernstian emf response slopes[522] or the reverse[523] (log $K_{\mathrm{Ca,Mg}}^{\mathrm{pot}}$ (SSM): −2.4 to −3.5; 1:2 mixture of acid and salt of the ionophore, DOPP). On the other hand, macroelectrodes based on the same ionophore exhibited nearly Nernstian responses (log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (FIM): Mg^{2+}, −2.3 to −2.7; H^+, −2.2; Na^+, −6.3; DOPP).[524] Recently, the effect of added ionic sites on such macroelectrodes was investigated.[182] While the selectivity of dioctyl phenylphosphonate membranes cannot be appreciably improved by addition of anionic or cationic sites (log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (SSM): Mg^{2+}, −3.1; H^+, +0.3; Li^+, −2.2; NH_4^+, −3.0; Na^+, −4.0; DOPP, no sites), membranes with DOS as plasticizer and added anionic sites give a higher discrimination of divalent cations than DOS membranes without added sites. The DOS membranes with added anionic sites discriminate Li^+ and H^+ particularly well but unfortunately this plasticizer allows only low ionophore concentrations and leads to slight deviations from Nernstian responses (log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (SSM): Mg^{2+}, −3.0; H^+, −2.5; Li^+, −4.1; NH_4^+, −3.4; Na^+, −4.0; DOS, KTFPB).[182] Also ISEs with membranes obtained by polymerization of an aromatic epoxyacrylate and 1,6-hexanedioldiacrylate in the presence of the plasticizer dioctyl phenylphosphonate (DOPP), the ionophore **Ca^{2+}-3** and KTpClPB were found to have a good selectivity (log $K_{\mathrm{Ca,J}}^{\mathrm{pot}}$ (FIM): Mg^{2+}, −1.7; Li^+, −4.9; NH_4^+, −4.5; Na^+, −4.5).[525] They were used to measure Ca^{2+} in milk samples that had been digested with $HNO_3/HClO_4$ to hydrolyze proteins and liberate complexed Ca^{2+}.[525] Concentrations of ClO_4^- as high as 0.2 M did not interfere, which was attributed to the beneficial effect of the anionic sites, tetrakis(4-chlorophenyl)borate.



Ca^{2+}-3

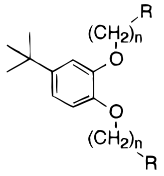
Because of possible applications of Ca^{2+} selective electrodes in the surfactant industry, the influence of surfactants on these ISEs was extensively investigated. To reduce problems from the presence of surfactants, so-called desensitization of the membrane by exposure to anionic surfactants (see also sections IV.6 and V.5),[526] partial replacement of the phosphonate plasticizer by 1-alkanols,[527,528] or use of trioctyl phosphate as plasticizer were suggested. Trioctyl phosphate has the advantage that unlike alcohol plasticizers it does not impair the selectivity and that it seems also to be suited for measurements in body fluids.[528−530] The effectiveness of desensitization with surfactants may be partly explained by extraction of the anionic surfactants, which then provide for anionic sites. A fairly large influence on ISE selectivities may occur by extraction of a small amount of surfactant into the membrane, whereas further extraction would bring the site concentration in a range where minor changes in it do not alter selectivities that much any more.[182]

Amide Ionophores. First attempts at Ca^{2+} sensing were based on neutral macrocyclic ionophores resembling crown ethers derivatives. They were inspired by the cryptands developed by J.-M. Lehn and co-workers and not by to the famous chelating reagents introduced by G. Schwarzenbach, as might be guessed from a certain similarity in structure of many diamide ionophores and, for example, EDTA. The first cyclic ionophores were, however, not very selective[531] and thus several modifications led finally to noncyclic 3,6-dioxaoctanedioic diamides as the first successful neutral Ca^{2+} carriers. They were designed on the notion that an adequate ligand should have no functional groups that could be easily protonated and have preferably six coordinating groups (**Ca^{2+}-4**, log $K^{pot}_{Ca,Mg}$ (SSM): −4.5; *p*-ethyl-nitrobenzene, no polymer matrix).[532,533] An investigation of a variety of very similar ligands showed the important points in the design of these ligands:[534] Ionophores with secondary amide groups have a low selectivity, most probably because of formation of hydrogen bonds to the potential coordination sites (see however refs 131−133, where successful ionophores for Mg^{2+} with secondary amide groups are reported). Furthermore, the two ether oxygens are essential and their elimination led to complete loss of selectivity. The variation of the bridge between the two ether oxygens allowed further ligand optimization.[191] Whereas in general the preference for Ca^{2+} over monovalent cations and larger cations is enhanced by a large dipole moment of the substituents, very bulky substituents shift the selectivity toward monovalent ions, as was also expected theoretically.[304,482,534]



Ca^{2+}-4: R = H, n = 10
Ca^{2+}-5 (ETH 1001): R = CH_3, n = 11

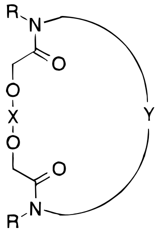
As a result of this optimization, **Ca^{2+}-5** (ETH 1001, log P_{TLC} ≈7.2)[48] was found[535] and more than 20 years after its introduction is still one of the best Ca^{2+} ionophores (log $K^{pot}_{Ca,J}$ (SSM): H^+, −4.4; Li^+, −2.8; Na^+, −3.4; K^+, −3.8; Mg^{2+}, −4.4; FIM (in Ca^{2+}-buffered solutions): Na^+, −6.1; K^+, −6.6; FIM (without Ca^{2+} buffer): Mg^{2+}, −5.1; oNPOE, KTpClPB).[51,117,195,199,536,537] It has found broad application, especially in clinical chemistry.[177,538,539] Replacing the ethylene bridge between the ether oxygens by *o*-phenylene and increasing the number of methylene groups between the ether oxygens and the amide groups to three[540] (**Ca^{2+}-6**), and also replacement of the amide groups by sulfinyl groups (**Ca^{2+}-7**) led to considerable losses in Ca^{2+} selectivity.[541] The ester groups of ETH 1001 (**Ca^{2+}-5**) are, in contrast to initial expectations, normally not involved in complexation, as was shown by spectroscopy for solutions and solvent polymeric membranes.[533,534,542−545] Therefore, it is not surprising that very similar potentiometric selectivities have also been obtained with ligands lacking the ester groups.[546] Depending on the choice of solvent and the concentration of Ca^{2+} and ETH 1001, at least three different complexes of ETH 1001 may be formed. Complexes of 1:2 stoichiometry are, however, predominant in ISE membranes of standard composition, as was also confirmed by impedance methods.[547]



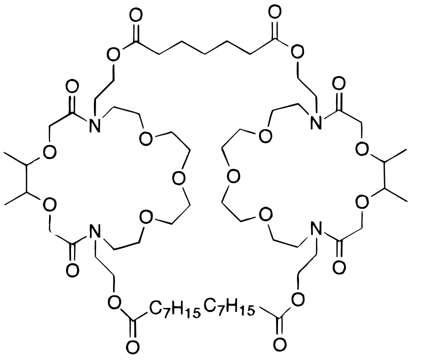
Ca^{2+}-6: n = 3, R = $CONHC_{16}H_{33}$
Ca^{2+}-7 : n = 2 or 3, R = $S(O)C_6H_5$, $S(O)C_8H_{17}$, or $S(O)CH_2C_6H_5$

Macrocyclic 3,6-dioxaoctanedioic diamides with alkane bridges connecting the two diamide groups (e. g. **Ca^{2+}-8**) have brought no selectivity improvements.[548] Whereas the very large 20-membered ring of **Ca^{2+}-8** provides for selectivities comparable to those for noncyclic ionophores, ligands with smaller rings are less selective. An ionophore with a 12-membered ring, for example, was totally inefficient in potentiometric and extraction experiments. A 1:2 complex geometry as known from the crystal structure[549] of the Ca^{2+} complexes of a tetrapropyldiamide does not seem possible in case of these smaller macrocycles. An attempt to improve the selectivity of the diamide macrocycles by incorporating ether oxygens into the bridge connecting the two amide groups (e. g. **Ca^{2+}-9**) was reported.[550,551] The observed selectivities were smaller than those of the 20-membered macrocycle but a direct comparison of the selectivities of the two studies is difficult because added anionic sites were not used optimally. The use of membranes containing anionic sites and an ionophore with the same ring structure but additional ester groups attached to the ring nitrogens (**Ca^{2+}-10**) performed better but not as well as ETH 1001

(**Ca^{2+}-5**).[552,553] Incorporation of two macrocycles in one compound on the other hand leads to a marked improvement in the discrimination of Mg^{2+} (**Ca^{2+}-11**, log $K^{\text{pot}}_{\text{Ca,Mg}}$ (FIM): −5; oNPOE, KTpClPB).[553] As for all of these macrocyclic polyether ionophores, interferences from Sr^{2+} and Ba^{2+} are quite high. Special among the macrocycles is a highly lipophilic synthetic hexapeptide, which is the only cyclic peptide that was reported for Ca^{2+} ISEs. Unfortunately the obtained selectivities were not very high (log $K^{\text{pot}}_{\text{Ca,Mg}}$ (MSM): −2.8; NPPE, KTpClPB).[554]

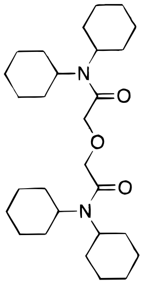


Ca^{2+}-8: R = C_6H_{13}, X = *o*-phenylene or $-CH_2CH_2-$
Y = $(CH_2)_n$, n = 2, 6 or 10
Ca^{2+}-9 : R = $CH_2C_6H_5$, X = $-CH_{2-m}(CH_3)_mCH_{2-n}(CH_3)_n-$,
Y = $-CH_2(CH_2OCH_2)_3CH_2-$; m,n = 0, 1or 2
Ca^{2+}-10 : R,R' = $(CH_2)_2OCOC_7H_{15}$, X = $-CH(CH_3)CH(CH_3)-$
Y = $-CH_2(CH_2OCH_2)_3CH_2-$



Ca^{2+}-11

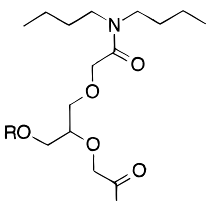
Another class of Ca^{2+} ionophores based on diamides was discovered by serendipity. Because the above-mentioned 3,6-dioxaoctanedioic diamides gave 1:2 complexes in which eight oxygens were coordinated to Ca^{2+} and because Mg^{2+} is known to prefer coordination with six ligands, it was assumed that 3-oxapentane- and 4-oxaheptane-diamides might be selective for Mg^{2+}. However, a selectivity for Ca^{2+} over Mg^{2+} of about 4 orders of magnitude was observed.[460] Again, the ether oxygen was found to be essential and minor changes in the backbone, such as introduction of additional methylene groups or incorporation of the ether oxygen into a tetrahydrofuran ring, led to appreciable changes in selectivity.[452,460] The ionophore **Ca^{2+}-12** (ETH 129, log, $P_{\text{TLC}} \approx 7.4$)[48] is the ionophore with the most favorable selectivities in this class. The structure of a Ca^{2+} salt of this ionophore shows 1:3 complexes in which nine oxygens are coordinated to Ca^{2+},[555] and the dependence of the potentiometric selectivity on the concentration of anionic sites confirms that the same stoichiometry occurs in ISE membranes. Membrane impedances were interpreted as indicating the predominance of 1:2 complexes but relatively large experimental errors cast some doubt on this conclusion.[547,556] Whereas a relatively high interference of H^+ has been observed, the advantage of **Ca^{2+}-12** lies in the high discrimination of K^+ and Na^+ (log $K^{\text{pot}}_{\text{Ca,J}}$ (SSM): H^+, −1.6; Li^+, −3.3; Na^+, −3.7; K^+, −4.0; Mg^{2+}, −4.9; FIM (Ca^{2+} buffered solutions): Na^+, −7.4; K^+, −8.0; oNPOE, KTpClPB).[339,536] Such high selectivities could for long only be accurately measured with Ca^{2+}-buffered solutions[536,557] because otherwise Ca^{2+} impurities from various sources determine the Ca^{2+} concentration in the calibration solutions (note that ref 557 incorrectly cites selectivity data of ref 536). In Ca^{2+}-buffered solutions containing 125 mM K^+, the Ca^{2+} detection limit of **Ca^{2+}-12** based ISEs was found to be $10^{-10.1}$ M Ca^{2+}, which is 1.4 logarithmic units lower than for ETH 1001 (**Ca^{2+}-5**) under identical conditions. Recently, the excellent selectivity of **Ca^{2+}-12** was reconfirmed by using oNPOE- and DOS-based electrodes conditioned in Ca^{2+}-free solutions (log $K^{\text{pot}}_{\text{Ca,J}}$ (SSM, Na^+ conditioning): K^+, −10.1; Na^+, −8.3; Mg^{2+}, −9.3; oNPOE, NaTFPB; log $K^{\text{pot}}_{\text{Ca,J}}$ (SSM, Na^+ conditioning): K^+, −7.7; Na^+, −6.2; Mg^{2+}, −9.7; DOS, NaTFPB).[247] The lipophilic isomeride ETH 5234 with two octadecyl rather than two cyclohexyl substituents on one of the amide nitrogens was found to have a selectivity similar to that of **Ca^{2+}-12** but the much higher lipophilicity of this compound makes it particularly suitable for the preparation of optodes and ISEs with a high lifetime (log $K^{\text{pot}}_{\text{Ca,J}}$ (SSM): H^+, −3.1; Li^+, −5.7; Na^+, −5.8; K^+, −6.7; Mg^{2+}, −4.3; oNPOE, KTpClPB).[558]



Ca^{2+}-12 (ETH 129)

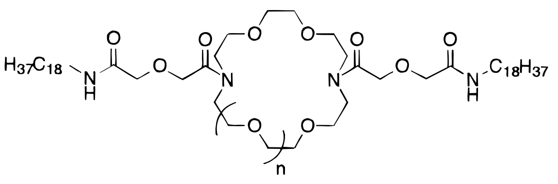
ETH 1001 (**Ca^{2+}-5**), which had dominated intracellular Ca^{2+} determinations after quickly replacing phosphate esters,[204,492,559−563] has recently been replaced itself by ETH 129 (**Ca^{2+}-12**) for intracellular measurements[55,564] and applications in soil sciences, where the K^+ background concentration is often high. On the other hand, the selectivity of the more lipophilic ETH 1001 is more suitable for clinical applications. Furthermore, smaller emf shifts upon serum contact were observed for oNPOE-plasticized membranes with ETH 1001 than for membranes with ETH 129. It was suggested that this presumable disadvantage of ETH 129 can be eliminated by using polyurethane membranes.[565] Very favorable selectivities have recently also been reported for plasticized silicone and fluorosilicone rubber membranes containing either of these two ionophores.[199,537] Covalent attachment of the ionophore, as demonstrated for a chemically sensitive field effect transistor

(CHEMFET) with a 3,6-dioxaoctanedioic diamide (**Ca^{2+}-13**),[566] is a promising way to solve some of the problems associated with membrane degradation in long-term applications.

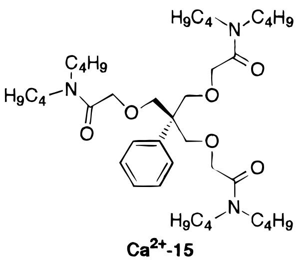


Ca^{2+}-13: R = polymer

Recently, outstanding selectivities were achieved with double-armed diazacrown ether derivatives.[482] As in the case of a similar excellent Mg^{2+} ionophore, both the ring size and the diamide type arms were very systematically optimized by testing a large number of compounds. The best size of the diazacrown ring was found to be at 21 atoms, which is three atoms more than for the Mg^{2+} carriers. The most suitable diamide type arms are derived from 3-oxapentanedioic acid (**Ca^{2+}-14** (K23E1), log $K^{\mathrm{pot}}_{\mathrm{Ca,J}}$ (SSM): Mg^{2+}, −5.0; K^{+}, −4.4; Na^{+}, −4.1; H^{+}, −3.6; Li^{+}, −4.1; oNPOE, KTpClPB). The isomeride K23E5 with adamantyl in place of the octadecyl substituents of **Ca^{2+}-14** was found to have comparable selectivities but is less lipophilic.

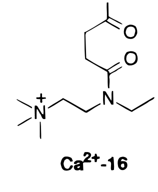


Ca^{2+}-14 (K23E1): n = 2
Ca^{2+}-19 (K22E1): n = 1



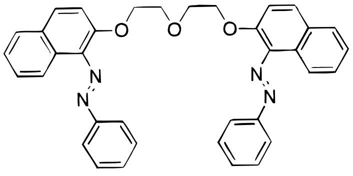
Ca^{2+}-15

A very good discrimination of Mg^{2+} but inferior selectivity for alkali ions was also obtained for a triamide (**Ca^{2+}-15**) with similarity to the Na^{+} ionophore **Na^{+}-7** (ETH 227) (log $K^{\mathrm{pot}}_{\mathrm{Ca,J}}$ (FIM): Mg^{2+}, −4.8; K^{+}, −3.2; Na^{+}, −2.3; oNPOE, KTpClPB),[208] whereas almost complete loss of selectivity was obtained by incorporation of a diamide unit into a tetraalkylammonium salt (**Ca^{2+}-16**).[567]

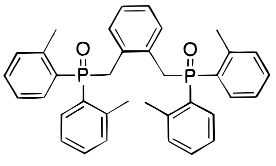


Ca^{2+}-16

Miscellaneous Neutral Ionophores. An ionophore of rather different design (**Ca^{2+}-17**) was reported recently to give a promising discrimination of both Na^{+} and Mg^{2+} (log $K^{\mathrm{pot}}_{\mathrm{Ca,J}}$ (FIM): Na^{+}, −4.2; K^{+}, −4.4; Mg^{2+}, −4.6; dinonyl sebacate, KTPB) and a detection limit of 10^{-8} M Ca^{2+} in Ca^{2+} buffered solutions.[568] Analysis of water and urine samples was demonstrated. Somewhat worse is the selectivity of neutral organophosphorus ionophores, the tetratolyl-*o*-xylylenediphosphine dioxide **Ca^{2+}-18** being best characterized (log $K^{\mathrm{pot}}_{\mathrm{Ca,J}}$ (SSM): Na^{+}, −4.0; K^{+}, −4.1; Mg^{2+}, −3.3; oNPOE, NaTPB).[569] While the corresponding meta isomer was claimed to be superior, it was not used together with added ionic sites and, not surprisingly, sub-Nernstian slopes were reported.[570,571] Note that very similar ionophores were also used for uranyl-selective electrodes (e. g. **UO$_2$$^{2+}$-2**, section II.23). Several natural products and synthetic isomerides with a bis-tetrahydrofuran unit were recently tested as neutral carriers but the observed potentiometric selectivities were relatively poor.[572] Benzo-15-crown-5 coupled to polyacrylamide was successfully used to thermodynamically characterize the interaction of Ca^{2+} with various organic solvents.[573]



Ca^{2+}-17



Ca^{2+}-18

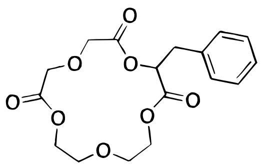
Clinical Application of Ca^{2+} ISEs. A review[574] of the history of Ca^{2+} measurements with ISEs from the clinical point of view has discussed the properties of many commercial clinical analyzers and well documented how organophosphate carriers started to be replaced by neutral amide carriers in the end of the 1970s.[574,575] General comments on the use of ISEs in clinical chemistry were given above (cf. section II.3) and apply also to Ca^{2+} measurements.[177,271,288,539,574,576−584] Furthermore, binding of Ca^{2+} to heparin may cause erroneous Ca^{2+} determinations.[276,576] Special care must also be taken to prevent loss of CO$_2$ from the sample because the amount of Ca^{2+} bound to proteins is very large,[539,585] and the concentration of free Ca^{2+} depends even more strongly on the pH than in the case of Mg^{2+}.[286,586] Moreover, a temperature dependence of the free calcium concentration was reported.[587] Contrary to theoretical expectations, acetate interference was reported to increase with the concentration of lipophilic anionic sites in ETH 1001 (**Ca^{2+}-5**) membranes.[588] In addition to reasons discussed above for a similar case of K^{+} solid-contact electrodes by the same authors,[391] doubts on this interpretation arise from the fact that high acetate concentrations strongly affect the responses of nearly all the Ca^{2+} sensors tested in that particular investigation.

Optodes. The first bulk optode with a fairly large response to Ca^{2+} was based on the carboxylic antibiotic A23187 (**Mg^{2+}-1**) as charged carrier and had selectivities similar to those obtained in solvent extraction studies (log $k_{\mathrm{Mg,J}}^{\mathrm{Osel}}$: Ca^{2+}, −0.4; Ba^{2+}, <−5; Li^{+}, <−5; Na^{+}, <−5; K^{+}, <−5; DBS).[453] More recently, much better selectivities were achieved by use of the more selective Ca^{2+} ionophores ETH 1001 (**Ca²⁺-5**), K23E1 (**Ca²⁺-14**) or K22E1 (**Ca²⁺-19**).[92,296,435,589,590] Selectivities comparable to those of the corresponding ISEs were observed (ETH 1001: log $K_{\mathrm{Ca,J}}^{\mathrm{opt}}$ (SSM):[589] K^{+}, −3.8; Na^{+}, −3.6; Li^{+}, −3.1; Mg^{2+}, −4.1; NaTFPB, DOS Nile blue derivative ETH 5294; K22E1: log $k_{\mathrm{Ca,J}}^{\mathrm{Osel}}$ (FIM):[590] K^{+}, −4.3; Na^{+}, −4.9; Li^{+}, −4.2; Mg^{2+}, −4.4; *o*-trifluoromethylphenyl dodecyl ether, lipophilic anionic dye LAD-3 (**H⁺-32**)). The immobilization of chromoionophore and anionic sites for optodes based on ETH 1001 was found to increase not only lifetimes but unfortunately response times too.[591] On the other hand, a high lipophilicity was reported as an advantage of K23E1 (**Ca²⁺-14**, log $P_{\mathrm{o/w}}$ 14.6). Membranes with ETH 1001 and ETH 5294 (**H⁺-10**) were also used in an optical sensor based on refractometry.[592]

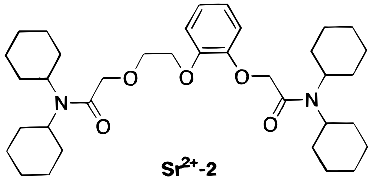
11. Sr^{2+} Sensors

Probably mainly owing to the absence of a known biological role of Sr^{2+}, only a small number of sensors for this ion have been demonstrated. Natural antibiotics that selectively bind this ion seem not to be available. Whereas the intermediate position of Sr^{2+} within the alkaline earth metal ions led to the serendipitous discovery of Sr^{2+} ionophores, an ionophore optimization has so far not been performed. A possible application of Sr^{2+} sensors would be the analysis of radioactive waste.[593]

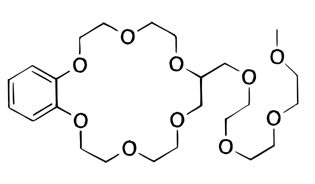
The Sr^{2+} complex of nonylphenoxypoly(ethyleneoxy)ethanol (**Ba²⁺-1**) was used in an ISE with the aim of Sr^{2+} determinations in a nuclear waste program, but the response to Ba^{2+} was found to be larger than that to the primary ion.[594] A higher discrimination of Ba^{2+} was obtained with a macrocyclic triester diether compound (**Sr²⁺-1**, log $K_{\mathrm{Sr,Ba}}^{\mathrm{pot}}$ (SSM): −1.6; 1,2-dichloroethane, cellophane film) but in this case Ca^{2+} interfered more strongly (log $K_{\mathrm{Sr,Ca}}^{\mathrm{pot}}$ −0.5).[347] The best characterized Sr^{2+} ISE with a discrimination of both Ba^{2+} and Ca^{2+} seems to be an ISE with a diamide that was synthesized in the course of a study of Ba^{2+} selective electrodes (**Sr²⁺-2**, log $K_{\mathrm{Sr,J}}^{\mathrm{pot}}$ (SSM): Ba^{2+}, −0.7; Ca^{2+}, −1.4; other alkali and alkaline earth metal ions <−3.3; oNPOE, KTpClPB; selectivity estimated here from log $K_{\mathrm{Ba,J}}^{\mathrm{pot}}$ as given in the original paper).[595] A promising discrimination of Mg^{2+} and Ca^{2+} was also found for several rather hydrophilic benzo-18-crown-6 derivatives, suggesting that the Sr^{2+} selectivity is markedly enhanced by the introduction of a side arm with two or more oxygens. Unfortunately, log $K_{\mathrm{Sr,Ba}}^{\mathrm{pot}}$ values were not reported (**Sr²⁺-3**, log $k_{\mathrm{Sr,J}}^{\mathrm{MPM}}$ (in the presence of 140 mM NaCl): Ca^{2+}, −1.8; Mg^{2+}, −2.8; oNPOE, KTpClPB).[343] An electrode based on poly(dibenzo-18-crown-6) showed very interesting selectivities but the sensor lifetime was rather short (log $K_{\mathrm{Sr,J}}^{\mathrm{pot}}$: Mg^{2+}, −2.6; Ca^{2+}, −3.0; Ba^{2+}, −0.3).[596] Interestingly, this ISE gave a strontium ion response with a slope typical for monovalent cations. Note also the use of a similar electrode for Ba^{2+} (see section II.12).[597]



Sr²⁺-1



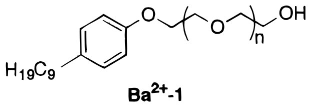
Sr²⁺-2



Sr²⁺-3

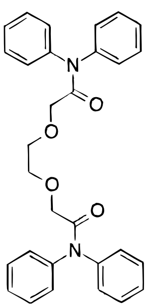
12. Ba^{2+} Sensors

With a size almost identical to that of the monovalent K^{+} ion, Ba^{2+} is the largest stable alkaline earth metal ion. The first class of neutral carriers that was suggested for this analyte is based on poly(ethylene glycol) derivatives, forming complexes with typically one Ba^{2+} ion and two tetraphenylborate ions per 12 ethylene oxide units of the ionophore.[598,599] Although several poly(ethylene glycol) derivatives were investigated, the initially suggested nonylphenoxypoly(ethyleneoxy)ethanol (**Ba²⁺-1**), also known as Antarox CO-880, Igepal CO-880 or Nonidet P 40, proved to be superior.[600] The most favorable plasticizers for membranes with this carrier and PVC as matrix were found to be di-2-nitrophenyl or 2-nitrophenyl phenyl ether, whereas other conventional plasticizers, such as dinonyl phthalate or dioctyl phenylphosphonate failed owing to the insolubility of the ionophore complex (log $K_{\mathrm{Ba,J}}^{\mathrm{pot}}$ (FIM): Na^{+}, −2.1; K^{+}, −1.7; Ca^{2+}, −3.2; di-2-nitrophenyl ether).[601,602] A long recovery time of these electrodes after contact to Cu^{2+} was reported. Note that **Ba²⁺-1** has also been suggested as ionophore for Pb^{2+}-selective electrodes (see section II.22).[603] Tripodal "scorpion-like" ionophores with various types of "pincers" and an "oligoether tail" were found to be less efficient.[604]

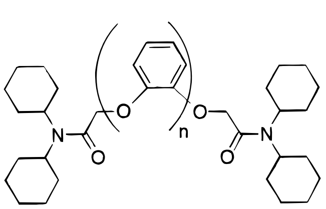


Ba²⁺-1

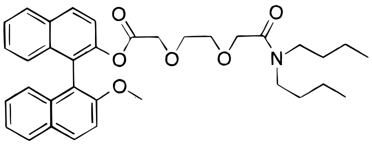
Another class of Ba^{2+} ionophores is the result of a very early study of diamide ionophores. The diamide **Ba²⁺-2**, which has a very similar backbone as the very successful Ca^{2+} ionophore ETH 1001 (**Ca²⁺-5**), was found to have a fair selectivity for Ba^{2+} (log $K_{\mathrm{Ba,J}}^{\mathrm{pot}}$: Na^{+}, −0.2; K^{+}, −0.5; Ca^{2+}, −2.2; oNPOE, no PVC).[545] Because no polymer matrix was used in that study and the concentration of ionic sites was therefore very low, this result should however be interpreted with care. A variety of more lipophilic derivatives with a longer backbone containing more oxygens was subsequently investigated, giving very diverse patterns for the discrimination of interfering ions.[595,605,606] The choice of an appropriate ionophore for a specific application would depend strongly on the type of possibly interfering ions. Whereas two ionophores with four ether oxygens showed a good discrimination of Ca^{2+} and Sr^{2+} but a rather weak discrimination of alkali ions (e. g. **Ba^{2+}-3**, log $K^{pot}_{Ba,J}$ (SSM): Ca^{2+}, −2.3; Sr^{2+}, −2.0; K^{+}, −1.2; Na^{+}, −1.7; oNPOE, KTpClPB), an ionophore with only three ether oxygens showed an opposite selectivity pattern (**Ba^{2+}-4**, log $K^{pot}_{Ba,J}$ (SSM): Ca^{2+}, −1.7; Sr^{2+}, −0.2; K^{+}, −2.7; Na^{+}, −2.7; oNPOE, KTpClPB).[595] The use of ISEs with the latter ionophore, which discriminates Na^{+} and K^{+} more strongly than ISEs based on Antarox CO-880, was demonstrated to be suitable for titrimetric sulfate determinations in elemental analysis.[595] An ISE based on the very similar 3,6-dioxaoctanedioic acid monoamide monoester **Ba^{2+}-5** has recently been reported as an indicator electrode for the determination of sulfate in mineral waters (log $K^{pot}_{Ba,J}$ (SSM): Ca^{2+}, −2.5; Sr^{2+}, −1.9; K^{+}, −2.1; Na^{+}, −2.4; oNPOE, NaTPB, ethylene-vinyl acetate copolymer as matrix).[607] Indeed, the major interest for Ba^{2+} sensors stems not from a need for Ba^{2+} determinations but rather from their use as endpoint indicators in titrimetric measurements.[605]



Ba^{2+}-2

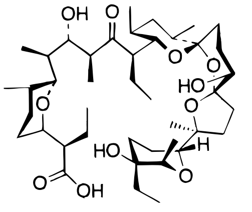


Ba^{2+}-3: n = 3
Ba^{2+}-4: n = 2

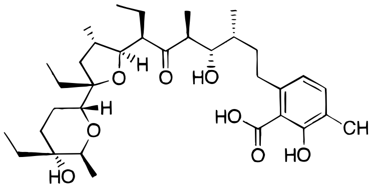


Ba^{2+}-5

ISEs based on antibiotics were also reported for Ba^{2+} detection. It was already mentioned above that the antibiotic A23187 (**Mg^{2+}-1**, a carboxylic acid), when used with nitrobenzene as membrane solvent and cellulose ester as support, gave a selectivity in the order $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$ and slopes typical for divalent ions.[450] On the other hand, an optode using this compound as a charged carrier was Mg^{2+} selective.[453] ISEs with PVC membranes of DOS and salinomycin (**Ba^{2+}-6**, which is also a carboxylic acid polyether antibiotic), but no added ionic sites responded to Ba^{2+} with a slope of 59 mV/decade (log $K^{pot}_{Ba,J}$ (SSM; with treatment of Ba^{2+} as monovalent ion): Na^{+}, −3.6; K^{+}, −2.9; Ca^{2+}, −2.7; Rb^{+}, −2.8; DOS).[162,608] Rb^{+} being the most strongly interfering alkali metal ion, this electrode is outstanding in its discrimination of monovalent ions. Also for monensin- and nigericin-based ISEs (**Na^{+}-1** and **K^{+}-2**) Ba^{2+} response slopes typical for monovalent ions have been reported, while for the similar lasalocid (**Ba^{2+}-7**), which is highly Ba^{2+} selective, originally only Ba^{2+} responses with slopes typical for divalent cations were observed (log $K^{pot}_{Ba,J}$ (SSM): Na^{+}, −3.5; K^{+}, −1.6; Ca^{2+}, −2.2; Rb^{+}, −1.7; DBS),[162] and slopes typical for monovalent cations have only been reported recently.[185] To understand such response slopes more quantitatively, a model that describes divalent cation responses of liquid membrane ion-selective electrodes based on acidic ionophores and ionic sites was developed.[185] It predicts that response slopes for membranes with ionophore and anionic sites change from Nernstian to apparently “twice-Nernstian”, and then back to Nernstian again as the pH of the sample solution decreases. On the other hand, membranes with ionophore and cationic sites are expected to give only Nernstian responses, either to divalent cations at high pH or to H^{+} at low pH. The validity of this model was experimentally confirmed with the two Ba^{2+}-selective carboxylate ionophores monensin (**Na^{+}-1**) and lasalocid (**Ba^{2+}-7**), and the Ca^{2+}-selective organophosphate ionophore bis(2-heptylundecyl) phosphate. Addition of anionic sites gave apparently “twice-Nernstian” slopes for monensin at pH 7.0 (56.6 mV/decade), for lasalocid at pH 4.0 (53.3 mV/decade), and for bis(2-heptylundecyl) phosphate at pH 3.5 (53.6 mV/decade). Membranes with cationic sites showed only pH responses at the respective pH values. Such apparently “twice-Nernstian” responses are the first examples of super-Nernstian responses that can be explained with a quantitative model based on thermodynamic equilibria.



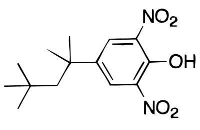
Ba^{2+}-6 (salinomycin)



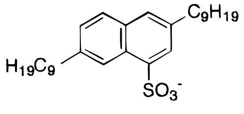
Ba^{2+}-7 (lasalocid)

Also for ISEs based on 4-(1,1,3,3-tetramethylbutyl)-2,6-dinitrophenol (**Ba^{2+}-8**) a high discrimination of monovalent cations was observed, which seems interesting from the point of view of selectivity. Unfortunately, these ISEs exhibit strongly sub-Nernstian response slopes.[609] Added ionic sites might improve the sensor characteristics, as was shown for the charged carrier dinonylnaphthalene sulfonate

(**Ba^{2+}-9**, DNNS; the commercial form of this ionophore seems to contain a number of stereoisomers and probably also monoalkylated isomerides[610]).[611] While ISE membranes containing DNNS but no added sites are Cs^+ selective and give sub-Nernstian slopes, addition of 48 mol % cationic sites led to a moderate Ba^{2+} selectivity and Nernstian responses (log $K^{\text{pot}}_{\text{Ca,J}}$ (SSM): Na^+, −1.4; K^+, −1.1; Ba^{2+}, +0.3; Sr^{2+}, 0.0; oNPOE, TDDMACl). Some macrocyclic ionophores with several lactam or/and lactone groups gave moderate discrimination of many common cations.[347] A reinvestigation with added ionic sites might reveal some interesting Ba^{2+} ionophores.



Ba^{2+}-8

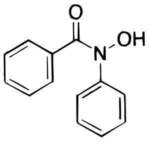


Ba^{2+}-9

Finally, the use of a Ba^{2+}-selective electrode based on immobilized dibenzo-18-crown-6 was reported for use in acetonitrile but unfortunately the response to all interfering ions was either sub-Nernstian or poorly reproducible.[597] A similar electrode for Sr^{2+} has also been reported (vide supra).[596]

13. Mo(VI) Sensors

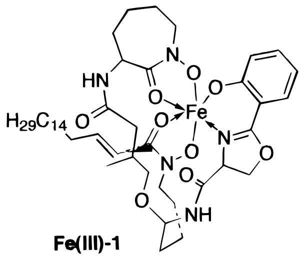
An ISE based on the chelating reagent *N*-benzoyl-*N*-phenylhydroxylamine (**Mo(VI)-1**) was shown to give a MoO_2^{2+} response with a nearly Nernstian slope (log $K^{\text{pot}}_{\text{MoO}_2\text{,J}}$ (MSM): Fe^{3+}, −3; Ni^{2+}, −2.4; Cu^{2+}, −2.9; nitrobenzene, no matrix polymer; note the similarity of **Mo(VI)-1** and **Pb^{2+}-9**).[612] The largest range of linear response was found for nitrobenzene, which was the most polar solvent that was used.



Mo(VI)-1

14. Fe(III) Sensors

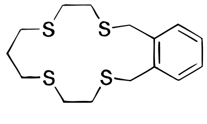
A few examples for the use of solid-state ISEs for Fe(III) were reported.[19,613] Also ionophore-free ion-exchanger electrodes for iron complexes, such as tetrachloroferrate(III) or iron(II)-1,10-phenanthroline, were described and may find applications in special cases, but the selectivity arising from complexation in the aqueous solution is in neither of these two cases fully satisfactory.[614,615] On the other hand, electrodes with membranes containing myobactin S (**Fe(III)-1**; a hydrophobic siderophore) as a triply charged carrier for Fe(III) were found not to respond to Fe(III) but rather to salicylate (see section IV.3).[616] Because the complex of Fe(III) with the triply charged ionophore seems to be extremely stable, the use of cationic sites is not likely to improve the performance of this sensor. The same is probably also true for a number of ISEs based on sulfur atom-containing ionophores that give strong responses to Fe(III).[617]



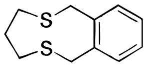
Fe(III)-1

15. Cu^{2+} Sensors

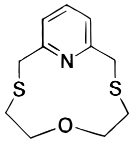
Cu^{2+}-selective electrodes based on an *S*-alkyl thioglycolic acid ($RSCH_2COOH$, R = C_{9-11}) as ionophore were already commercially available in the late 1960s.[1,618,619] They suffered from a number of interferences[620] and were withdrawn from the market when superior solid-state electrodes based on CuS-Ag_2S were invented.[1] The latter are now well-established but unfortunately Hg_2^{2+}, Hg^{2+}, Ag^+, and Fe^{3+} are serious interferents, and complications in the presence of high concentrations of halides were reported.[621] The first one of a new generation of carrier-based Cu^{2+}-selective electrodes was based on a macrocyclic tetrathioether (**Cu^{2+}-1**, log $K^{\text{pot}}_{\text{Cu,J}}$ (MSM): Zn^{2+}, −2.0; Cd^{2+}, −2.7; K^+, −1.7; oNPOE, KTpClPB).[622,623] Because macrocyclic tetrathioethers showed high affinities for Hg^{2+}, Cu^+, and Ag^+ in solvent extraction,[624,625] one might expect a large interference of these ions, but unfortunately no corresponding potentiometric data are available. Interference of Ag^+ would not be surprising as rather similar thioethers have also been used for Ag^+-selective electrodes with appreciable discrimination of Cu^{2+}.[626] Note also that recently a very similar compound was reported as ionophore for Tl^+-selective ISEs with a considerable discrimination of Cu^{2+} (**Tl^+-4,** see section II.20).[627] On the other hand, a macrocyclic dithioether (**Cu^{2+}-2**) resulted in a quite unsatisfactory selectivity for Cu^{2+} (log $K^{\text{pot}}_{\text{Cu,J}}$ (MSM): Cd^{2+}, −1.2; K^+, +1.1; oNPOE, KTpClPB).[623] A macrocyclic dithioether with a pyridine group as an additional coordination site (**Cu^{2+}-3**) led to an unsatisfactory discrimination of Ni^{2+} and Co^{2+} (log $K^{\text{pot}}_{\text{Cu,J}}$: Ni(II),



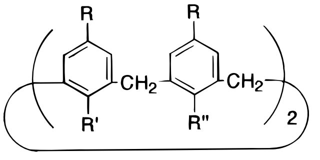
Cu^{2+}-1



Cu^{2+}-2



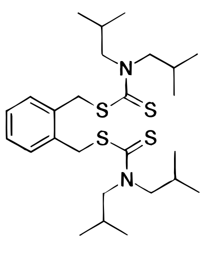
Cu^{2+}-3

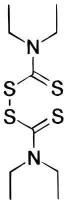


Cu^{2+}-4: R = *tert*-butyl, R′, R″ = $OCH_2CH_2SC(S)N(C_2H_5)_2$
Cu^{2+}-5: R = *tert*-butyl, R′ = $OCH_2CH_2SC(S)N(C_2H_5)_2$,
R″ = $OCH_2CH_2CH_3$

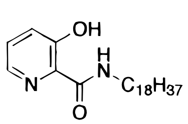
−1.0, Co(II); −1.0; DOP).[628,629] The extraction selectivity of certain macrocyclic tetrathioethers for Cu^+ over Cu^{2+} is quite interesting,[625] as there are only a limited number of electrodes available that can be used for the speciation of copper.[630] Also into the group of macrocyclic Cu^{2+} ionophores belong two calix[4]arenes with thiocarbamoyl substituents (**Cu^{2+}-4** and **Cu^{2+}-5**).[631] Their potentiometric selectivity is, however, inferior to that of the macrocyclic dithioether and noncyclic dithiocarbamates.

As an alternative to these macrocycles and inspired by the well-known properties as chelating reagents, several noncyclic ionophores with dithiocarbamate groups have been investigated more recently. Among several *o*-xylylene bis(dithiocarbamates), a diisobutyl derivative was most promising (**Cu^{2+}-6**, log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$ (FIM): Zn^{2+}, −2.3; Pb^{2+}, −0.8; Ni^{2+}, −3.3; Cd^{2+}, −4.4; K^+, −2.4; oNPOE, KTpClPB).[632,633] Even more selective are however ionophores in which the dithiocarbamates are directly linked by a disulfide bridge (**Cu^{2+}-7**, log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$ (FIM): Zn^{2+}, −3.9; Pb^{2+}, −1.8; Ni^{2+}, −3.9; Cd^{2+}, −4.3; K^+, −3.7; oNPOE).[634] This strategy was also more successful than a very similar approach in which the two thiocarbonyl groups are linked by one sulfur atom only.[635] Unfortunately, no selectivities toward Hg^{2+} and Ag^+ were reported for these electrodes.

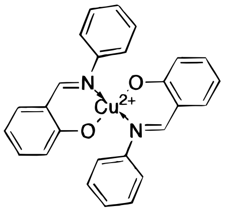

Cu^{2+}-6

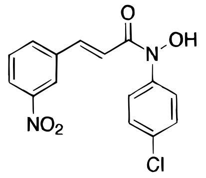

Cu^{2+}-7

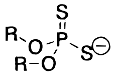
A survey of a large number of neutral ionophores with nitrogen atoms, including phenanthroline, pyridine, amide, carboxamide, and amine derivatives and spectrophotometric reagents, has shown that several of these ionophores respond more strongly to Cu^{2+} than to many other transition metal ions.[42] The best selectivities were interestingly obtained for *N*-octadecyl-3-hydroxypicolinamide (**Cu^{2+}-8**, log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$ (FIM): Ni^{2+}, −2.2; Pb^{2+}, −3.0; Cd^{2+}, −2.8; didecyl phthalate, KTpClPB), an isomeride of the H^+ carrier **H$^+$-2**. Not surprisingly, interference by H^+ was serious. This problem was almost absent for a series of 12 sulfur-containing ionophores with various functional groups.[636] The response of these electrodes in the presence of the possible interferents Ag^+ and Hg^{2+} was not reported.


Cu^{2+}-8

The most attractive aspect of electrodes based on several Schiff's bases, which upon deprotonation form complexes as charged carriers, is the discrimination of Hg^{2+} and to a lesser extent of Ag^+ (**Cu^{2+}-9**, log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$ (MSM): Zn^{2+}, −3.0; Pb^{2+}, −2.7; Ni^{2+}, −3.0; Hg^{2+}, −2.0; Cd^{2+}, −2.7; Ag^+, −0.1; chlorobenzene, no polymer matrix).[637] The selectivity coefficients for these two ions compare quite favorably to those of solid-state electrodes. Another class of compounds that provides charged ionophores without sulfur atoms is that of the hydroxamates, for which even smaller interference by Hg^{2+} and Ag^+ was reported (**Cu^{2+}-10**, log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$ (FIM): Fe^{3+}, −0.2; Ni^{2+}, −3.2; Hg^{2+}, −2.0; Cd^{2+}, <−4.0; Ag^+, <−5.0; DBP).[638] Very similar ionophores were also reported for Pb^{2+} electrodes (see section II.22, **Pb^{2+}-8** and **Pb^{2+}-9**).[639] The interference of Fe^{3+} could be eliminated by masking Fe^{3+} with NaF. In contrast, an ISE with dialkyl dithiophosphate (**Cu^{2+}-11**) as ionophore was reported to completely lose its response to Cu^{2+} in solutions of Pb^{2+}, Hg^{2+}, and Ag^+.[640] Note also that very similar ionophores were reported for use in Tl^+-selective electrodes and that recently thiophosphorylated calix[6]arene ionophores[641] were also used for Pb^{2+}-selective electrodes (**Pb^{2+}-7**). The selectivities of ISEs based on Cu^{2+} complexes of 6-nitroquinoxaline-2,3-dithiol seem very attractive (log $K_{\mathrm{Cu,J}}^{\mathrm{pot}}$: Ni^{2+}, −3.0; Fe^{2+}, −3.2; nitrobenzene, no PVC, tetrabutylammonium as counterion for the charged complex).[642] Surprisingly, an ISE for Ni^{2+} based on the Ni^{2+} complex of the same ligand was reported to strongly discriminate Cu^{2+} (log $K_{\mathrm{Ni,Cu}}^{\mathrm{pot}}$: −2.9),[642] which seems hard to understand. A carrier mechanism based on a thermodynamic equilibrium can certainly not explain such a selectivity.


Cu^{2+}-9


Cu^{2+}-10


R = $(CH_2)_nCH_3$, n = 19 to 23

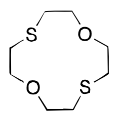
Cu^{2+}-11

16. Ag^+ Sensors

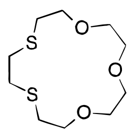
Unlike many other sulfide-based solid-state electrodes, the Ag_2S electrode has a very high primary ion selectivity and only weakly responds to most other transition metal ions. Only Hg^{2+} gives a serious interference.[19] This may be one reason the interest in developing liquid membrane ISEs for Ag^+ has for a long time been fairly small. However, there have recently been an increasing number of reports on carrier-based Ag^+ selective electrodes.[643] An interesting application of Ag^+ ionophores is also the incorporation of Ag^+ complexes of such ionophores into membranes that directly contact a Ag^0 surface. The reversible Ag^+/Ag^0 redox couple gives a well-defined phase boundary potential at the membrane-solid interface, eliminating the need for an internal solution.[644] Incorporation of a further ionophore and anionic sites into the same membrane gives electrodes with a selectivity governed by the latter ionophore.

Not only carrier-based ISEs but also exchangers for silver complex ions can be used for Ag^+ determinations.[645] Furthermore, ionophore-free ion-exchanger ISEs have some selectivity for Ag^+ and were reported to discriminate even K^+ (log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM):[626] K^+, −3.2; Pb^{2+}, −4.4; Cu^{2+}, −4.6; Cd^{2+}, −4.5; DOP, KTpClPB, pH 4.0; log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM):[646] K^+, −1.0; Pb^{2+}, −3.1; Cu^{2+}, −3.1; Cd^{2+}, −2.8; oNPOE, KTpClPB, pH 4.0; log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM):[626] K^+, −2.5; Hg^{2+}, −2.1; Pb^{2+}, −3.7; Ca^{2+}, −3.7; Cu^{2+}, −3.8; Cd^{2+}, −3.6; oNPOE, KTpClPB, pH 4.0).[626,647]

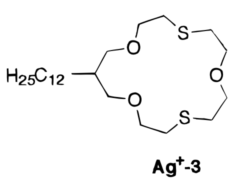
While cryptands were used without success, dithiacrown ethers gave the first neutral carrier Ag^+-selective electrodes with a discrimination of alkali metal ions.[648] Although one of the ionophores, 1,7-dithia-12-crown-4 (**Ag^+-1**), led to an almost Nernstian response, selectivities have only been reported for 1,4-dithia-15-crown-5 (**Ag^+-2**), which gave a super-Nernstian slope that reportedly could not be eliminated by use of NaTpClPB. Five lipophilic mono- and di-thiacrown ethers gave however a much improved selectivity for Ag^+ over Hg^{2+} and Fe^{3+}.[649−651] Despite differences in the number of sulfur atoms, and in the ring size of the 15-crown-5, 16-crown-5, and 18-crown-6 skeletons, very similar selectivities for all five ionophores were obtained (e. g. **Ag^+-3**, log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM): Hg^{2+}, −2.1; Zn^{2+}, −3.2; H^+, −3.5; Pb^{2+}, −3.8; Cu^{2+}, −4.2; Fe^{3+}, −3.9; Cd^{2+}, −4.3; K^+, −4.6; DOP, dipicrylamine sodium salt). Similar are also the results for two 14-membered macrocyclic tetrathioethers, whereas introduction of carbonyl groups lowers the Ag^+ selectivity.[626] Note also that one of these tetrathioethers, as well as similar compounds were used for Tl^+-selective electrodes (see section II.20).[627] A recent study has confirmed the Ag^+ selectivity of ISEs based on macrocyclic tetrathioethers, but showed that a better discrimination of Hg^{2+} can be achieved with two noncyclic dithioethers (e. g. **Ag^+-4**: log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM): Hg^{2+}, −2.5; Pb^{2+}, −6.1; Cu^{2+}, −6.3; Cd^{2+}, −6.6; K^+, −5.4; oNPOE, KTpClPB).[646]



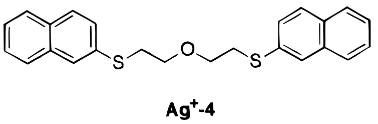
Ag⁺-1



Ag⁺-2

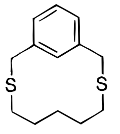


Ag⁺-3

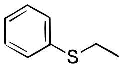


Ag⁺-4

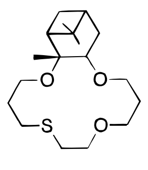
The Ag^+ ion preferring a linear coordination, three thiamacrocyclic derivatives of *m*-xylene-α,α′-dithiol with two or three sulfur atoms were designed (e. g. **Ag^+-5**: log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM): Hg^{2+}, −2.6; Zn^{2+}, −5.4; Pb^{2+}, −5.2; Cd^{2+}, −5.0; K^+, −4.9; DOP).[629,652] Their potentiometric selectivities are similar to those of other thiacrown ethers, but the detection limits of down to 0.3 μM were appreciably lower. Interestingly, similar selectivities were also obtained with acyclic *m*-xylene-α,α′-dithiol derivatives.[653] Also the use of monothioethers such as diethyl sulfide, ethyl phenyl sulfide, and diphenyl sulfide as ionophores has recently been shown to give electrodes with similar selectivities (e. g. ethyl phenyl sulfide (**Ag^+-6**): log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (FIM): Zn^{2+}, −5.5; Pb^{2+}, −6.0; Cd^{2+}, −5.6; DOP), from which it was concluded that steric factors are not very important for the ionophores described above (unfortunately, selectivities for Hg^{2+} and Fe^{3+} have not been reported).[654,655] A similar conclusion was also obtained from the study of 14 noncyclic and cyclic thioether, sulfoxide, and sulfone ionophores.[656] The best of these ionophores (**Ag^+-7**) is a thioether compound and does not give a high selectivity for Ag^+ because it has an ideal shape for Ag^+ complexation but rather because the bulky substituents on this ionophore prevent formation of stable complexes with interfering ions (**Ag^+-7**, log $K_{\mathrm{Ag,J}}^{\mathrm{pot}}$ (SSM): Hg^{2+}, −1.4; Zn^{2+}, −6.2; Fe^{3+}, −5.4; Cu^{2+}, −5.6; Cd^{2+}, −5.9; K^+, −4.1; BBPA, KTpClPB).[656] Oxidation of the thioether unit to sulfoxide on the other hand results in selectivity for Hg^{2+}.[656] It has therefore been concluded that thioether type compounds are not suited as ionophores for ions other than Ag^+.



Ag⁺-5



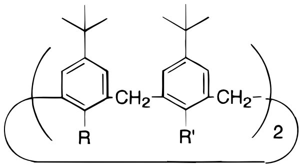
Ag⁺-6



Ag⁺-7

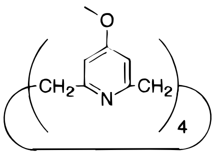
The very low selectivity coefficients of roughly −6 for many highly discriminated ions as observed with the above Ag^+ ISEs when measuring with the conventional separate solution or fixed interference method seem to be determined by a constant release of very small amounts of Ag^+ from the sample into the membrane solution.[2,657] A manifestation of structural features of the ionophore in such cases cannot be expected. However, under conditions that allow to decrease this Ag^+ background (membrane conditioning with an interfering and not the primary ion),[247,658] much higher selectivities can be measured, as was demonstrated also for other ISEs (see sections II.2 and II.3). Even though the general finding that any thioether group gives a surprisingly high selectivity for Ag^+ is not likely to change, application of non-primary ion conditioning to ISEs based on the above thioether ionophores is likely to show some influence of structural properties of the ionophore on potentiometric selectivities. Certainly this applies not only to the above-commented ISEs based on thioether ionophores but to other carrier-based Ag^+ ISEs.

A study of several calix[4]arenes showed that as long as the ionophore contains four ester groups, introduction of nitrogen- or sulfur-containing functional groups is not sufficient to eliminate a very strong Na^+ interference.[659,660] In view of the Na^+ selectivity of some calix[4]arenes this is not too surprising and agrees well with reductions in selectivities due to keto carbonyl groups.[626] Interestingly, the Na^+ interference was also large for an ionophore with four thioamide groups. Hg^{2+} and Pb^{2+} poisoned these electrodes and detection limits were quite high. In contrast, a more recent investigation has shown an excellent discrimination of alkali metal ions by a calix[4]arene with two hydroxy and two 2-methylthioethyl groups and a smaller interference from Pb^{2+} and Hg^{2+} (**Ag^+-8**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (FIM): Hg^{2+}, −2.5; Zn^{2+}, −5.6; Pb^{2+}, −4.7; Cu^{2+}, −5.3; Cd^{2+}, −5.3; K^+, −4.7; bis(butylpentyl) adipate, KTpClPB).[631,647] Only slightly inferior were the selectivities for an isomeride with four 2-methylthioethyl groups. Conditioning of electrodes based on **Ag^+-8** with solutions of a salt of an interfering ion rather than with a silver salt shows that the underlying ion-exchange selectivity, and thus the selectivity of the ionophore, is even higher (log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (SSM, conditioning with 0.01 M NaCl): Na^+, −6.2; K^+, −5.7; Pb^{2+}, −6.0; Cu^{2+}, −7.7; Ca^{2+}, −8.0; DOS, NaTFPB).[247] Furthermore, it was also demonstrated that ISEs based on **Ag^+-8** respond to Ag^+ when $AgNO_3$ solutions are used, and to Cl^- when $AgNO_3$ conditioned membranes are exposed to NaCl solutions (cf. "I^- and I_3^- Sensors").[657] Similarly, triisobutylphosphine-based membranes respond to Ag^+ as well as to I^-, Br^-, and SCN^- (cf. "I^- and I_3^- Sensors").[661] The selectivity of the cationic response has, however, not been determined.

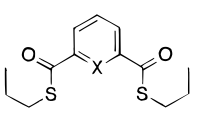


Ag^+-8: R = OH, R' = $OCH_2CH_2SCH_3$

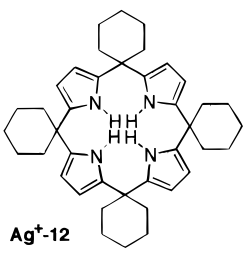
Pyridophanes belong to the few Ag^+ ionophores that have been used for ISEs but do not contain sulfur atoms.[662] The potentiometric selectivity for Hg^{2+} as interfering ion has not been investigated, but membrane transport was irreversibly inhibited by Hg^{2+}. Only Tl^+ interfered strongly but the alkali ion discrimination was less pronounced than for sulfur-containing ionophores (e. g. **Ag^+-9**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (SSM): Zn^{2+}, −4.2; Pb^{2+}, −3.1; Cd^{2+}, −3.4; K^+, −2.7; DBS, KTpClPB). Similarly, a loss in selectivity toward various metal ions is observed when an aromatic carbon in 2-position of benzene-1,3-bis(thioic) acid bis(*S*-propyl) ester (**Ag^+-10**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (MSM): Zn^{2+}, −4.0; Pb^{2+}, −4.0; Na^+, −3.0; oNPOE, KTpClPB) is replaced by a nitrogen atom (**Ag^+-11**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (MSM): Zn^{2+}, −2.9; Pb^{2+}, −2.7; Na^+, −2.2; oNPOE, KTpClPB).[663] A pyrrole-based tetraazacrown ether is a further example of a sulfur atom-free compound that was used as Ag^+ ionophore (**Ag^+-12**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (SSM): Hg^{2+}, −1.9; Pb^{2+}, −5.1; Na^+, −4.1; H^+, −1.6; NPPE, KTpClPB).[664] A dithio-azauracil (**Ag^+-13**) is another ionophore with an unusual structure. Its use gave only a very limited linear range (10^{-4} to 10^{-1} M) and almost no discrimination of Hg^{2+}.[665]



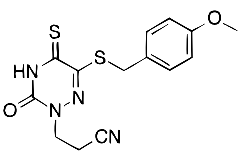
Ag^+-9



Ag^+-10: X = CH
Ag^+-11: X = N

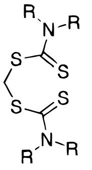


Ag^+-12



Ag^+-13

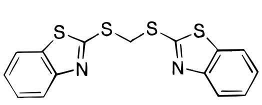
The ionophore methylene bis(diisobutyldithiocarbamate) (**Ag^+-14**) was first introduced as Pb^{2+} ionophore.[666,667] However, a very high selectivity for Ag^+ was lately demonstrated for ISEs with this ionophore by conditioning of the electrode membrane with a salt of the discriminated ion Na^+ rather than the primary ion Ag^+ (log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (SSM, conditioning with 0.01 M NaCl): Na^+, −8.7; K^+, −8.2; Cu^{2+}, −10.5; Pb^{2+}, −10.3; DOS, NaTFPB).[247] As also shown for ISEs based on **Ag^+-8**, membranes containing **Ag^+-14** respond to Ag^+ in $AgNO_3$ solutions but exhibit anionic responses to Cl^- in NaCl solutions after overnight conditioning with $AgNO_3$ (cf. "I^- and I_3^- Sensors").[657] The ionophore **Ag^+-14** was also used for Ag^+ optodes.



Ag^+-14: R = $CH_2CH(CH_3)_2$
Ag^+-15: R = CH_2CH_3

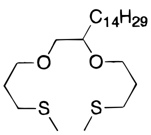
Optodes. Ag^+ optodes based on dithiocarbamate, thioether, and acridine ionophores were reported. The dithiocarbamate optodes contain a neutral H^+ chromoionophore (ETH 5418 (**H^+-22**) or ETH 5315 (**H^+-21**)) as the second carrier and are based on Ag^+/H^+ exchange.[668] While only the selectivity of an optode with the ionophore **Ag^+-14** was fully characterized (log $k^{\mathrm{Osel}}_{\mathrm{Ag,J}}$ (SSM): Hg^{2+}, +0.7; K^+, −9.3; Cu^{2+}, −9.6; Pb^{2+}, −13.4; Cd^{2+}, −14.6; DOS, KTFPB, **H^+-22**), a tetraethyl-substituted isomeride (**Ag^+-15**) gave a much better discrimination of Hg^{2+} (log $k^{\mathrm{Osel}}_{\mathrm{Ag,Hg}}$ (SSM): −1.6) and use of a mono-dithiocarbamate resulted in a good discrimination of Pb^{2+} and Cd^{2+} too (log $k^{\mathrm{Osel}}_{\mathrm{Ag,J}}$: Pb^{2+}, −9.9; Cd^{2+}, −10.7), indicating that a proper choice of the nitrogen substituents is very important. With detection limits for Ag^+ of down to 2.5×10^{-9} M at pH 4.7, the **Ag^+-14** optode is very promising for environmental monitoring (note also the use of **Ag^+-14** for ISEs, vide supra). A considerably improved discrimination of Hg^{2+} was recently obtained with **Ag^+-16**, with which Ag^+ was determined in drinking water (log $k^{\mathrm{Osel}}_{\mathrm{Ag,J}}$ (SSM):

Hg^{2+}, −2.7; Na^+, −6.0; K^+, −5.6; Cu^{2+}, −5.6; Pb^{2+}, −7.2; DOS, KTFPB, ETH 5315 (**H^+-21**), pH 4.5).[669]

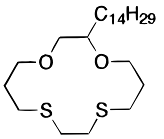


Ag^+-16

Three thiacrown ether ionophores used in optodes share with similar ionophores used for Ag^+ ISEs that they have not only one or two sulfur atoms but also ether oxygens.[670] To obtain a high discrimination of large cations, a sterically blocking subunit was introduced. Interestingly, for one of these ionophores 2:2 complexes of ionophore and Ag^+ were found to be formed in $CDCl_3$ upon coextraction of Ag^+ and picrate from aqueous solutions. While all three ionophores as well as two noncyclic control compounds responded selectively to Ag^+, the highest discrimination of Hg^{2+} in combination with a good response reproducibility was found for a noncyclic ionophore (**Ag^+-17**) and the lowest detection limit (10^{-6} M) for a dithiacrown ether (**Ag^+-18**), which unfortunately responded to Hg^{2+} irreversibly. Because pH 7 was used for this study, the concentration of many potentially interfering transition metal ions could not be made higher than 10^{-3} M. None of them led to a response at this concentration and neither did alkali and alkaline earth metal ions in concentrations up to 1 M.



Ag^+-17

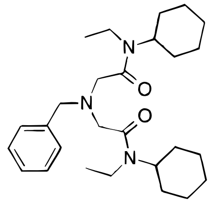


Ag^+-18

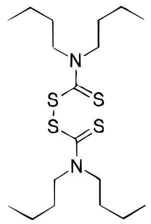
The idea for a Ag^+ optode based on a TEHP-plasticized PVC membrane containing KTpClPB and an acridine chromoionophore (**H^+-37**; see Koncki et al.[101] for a use of this compound as H^+ ionophore) came from the observation that the latter gives three distinctly different absorbance spectra in the neutral, the protonated, and the Ag^+ complex form.[102] Due to this peculiar response mechanism, interfering ions mimic a lower Ag^+ sample activity instead of a higher one, as usually observed for optodes with two ionophores. While interferences from a series of alkali, alkaline earth, and transition metal ions are quite small, Hg^{2+} again poisons the optode.

17. Zn^{2+} Sensors

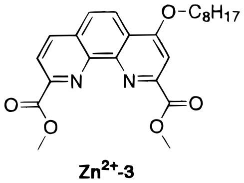
Several 3-azaglutaric acid diamides were studied as ionophores, giving the most promising selectivities with benzyl as the substituent on the nitrogen in 3-position (**Zn^{2+}-1**, log $K^{\mathrm{pot}}_{\mathrm{Zn,J}}$ (SSM): H^+, +0.6; Cu^{2+}, +0.2; Pb^{2+}, −2.1; K^+, −2.5; Na^+, −2.7; oNPOE, KTpClPB).[671] A decrease of the basicity of that nitrogen by acetylation, tosylation, or substitution with phenyl groups was unfortunately not able to decrease the interference of H^+ but rather resulted in a substantial loss of selectivity for Zn^{2+}. These ionophores have a quite close structural resemblance to certain Pb^{2+} ionophores, which have an oxygen in 3-position.[672] The selectivity of the Pb^{2+} electrode is however very different, with a high preference for Ca^{2+} and PbA^+ over Zn^{2+} and a high discrimination of Cu^{2+}. The interference of the latter ion, on the other hand, is substantial in the case of the 3-azaglutaric acid diamides. Whereas strong interference of H^+ limits the use of these ionophores to buffered samples with pH ≥ 6, tetrabutyl thiuram disulfide as ionophore (**Zn^{2+}-2**) allows a good response to Zn^{2+} in the pH range 3.5−6.5. Cu^{2+}, Pb^{2+}, Ag^+, and Hg^{2+} interfere significantly but alkali ions are well discriminated (log $K^{\mathrm{pot}}_{\mathrm{Zn,J}}$ (SSM): Cu^{2+}, +1.0; Pb^{2+}, +0.8; K^+, −3.8; Na^+, −3.3; Ca^{2+}, −2.8; oNPOE, KTpClPB).[634,673] On the other hand, ISEs based on phosphoric acid esters, as they were also used for Ca^{2+} ISEs, suffer invariably from large interferences from alkali and/or alkaline earth ions[674,675] and the same is also true for the use of a phenanthroline-2,9-dicarboxylic acid diester (**Zn^{2+}-3**, log $K^{\mathrm{pot}}_{\mathrm{K,J}}$ (MSM): Zn^{2+}, +0.8; Cu^{2+}, +0.2; Ba^{2+}, +0.3; Na^+, −0.1; oNPOE, KTpClPB or NaTPB).[676] Likewise, alkali ion interference is a serious problem for an ISE based on 2,2,2-cryptand (**Zn^{2+}-4**, log $K^{\mathrm{pot}}_{\mathrm{Zn,J}}$ (FIM): Cu^{2+}, −0.8; Pb^{2+}, −0.8; K^+, +1.3; Na^+, +1.3; Cd^{2+}, −0.7; DBP; note the similarity between **Zn^{2+}-4** and **K^+-30**),[677] which may, however, be alleviated by using added anionic sites. Increases in selectivity might be obtained by using a more lipophilic derivative of this quite hydrophilic ionophore. Finally, it should be mentioned that a rather high selectivity for Zn^{2+} can be obtained indirectly by determination of $Zn(SCN)_4{}^{2-}$ in thiocyanate solutions.[678]



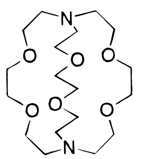
Zn^{2+}-1



Zn^{2+}-2

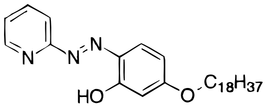


Zn^{2+}-3



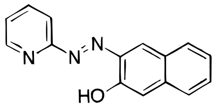
Zn^{2+}-4

Optodes. A preliminary report on an optode based on the 3-azaglutaric acid diamide (**Zn^{2+}-1**) in combination with the H^+ ionophore ETH 5294 (**H^+-10**) has shown a Zn^{2+} response in the range of 5 × 10^{-6} to 5 × 10^{-2} M.[671] In the case of an optical sensor based on a lipophilic isomeride (**Zn^{2+}-5**) of the well-known 4-(2-pyridylazo)resorcinol (PAR) no second ionophore is needed because this indicator dye functions as a charged carrier that has different absorption spectra for the H^+ and the Zn^{2+} complex.[679] Response times are in the range of several minutes even at high analyte concentrations and are larger than for other optodes of comparable thickness. This suggests that not diffusion but complex formation and dissociation are the steps determining the response time.[435] Interference from Cu^{2+} and Co^{2+} is unfortunately strong so that these ions have to be removed from the sensing film by treatment with 10^{-2} M HCl.



Zn²⁺-5

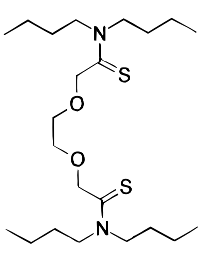
Optodes based on the very similar complexation reagent PAN (**Zn^{2+}-6**) respond strongest to Ni(II) and to a lesser extent in decreasing order to Cu(II), Zn(II), Hg(II), Pb(II), and Cd(II).[680] Binding of these ions is so strong that regeneration of the optode membranes requires treatment with a strong acid, which is easily feasible in a FIA system. The highly hydrophilic nature of the Nafion matrix on which the PAN ionophore was immobilized distinguishes these sensors from the optodes based on hydrophobic membranes, which are the main subject of this review. Note that the use of the same ionophore was reported for a Hg^{2+} ISE with high discrimination of Zn^{2+} (section II.19).[681]



Zn²⁺-6

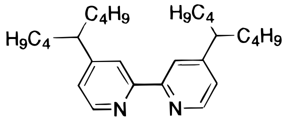
18. Cd^{2+} Sensors

Hg^{2+}, Ag^{+}, and Cu^{2+} are serious interferents for solid-state Cd^{2+}-selective electrodes based on CdS-containing solids, making alternative sensors very desirable. ISEs based on a 3,6-dioxaoctanedithioamide (**Cd^{2+}-1**) offer a reasonable discrimination of all alkali and alkaline earth metal ions but are poisoned by Cu^{2+}, Pd^{2+}, Pt^{2+}, Ag^{+}, and Hg^{2+}, the latter two inducing decomposition of the ionophore (note also the similarity of this ionophore to **Pb^{2+}-1** and **Pb^{2+}-2**).[682−684]



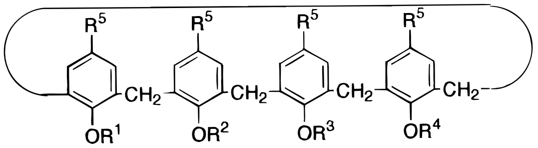
Cd²⁺-1

A recent study of a lipophilic 2,2′-bipyridine carrier (**Cd^{2+}-2**) shows an interesting Cd^{2+} selectivity over Co^{2+} and Ni^{2+} but strong interference from Cu^{2+} and Zn^{2+}.[685] It was suggested that despite the use of added anionic sites, the lifetime of this sensor is limited by extraction of a Cd^{2+} salt into the membrane, as evidenced by the anionic responses that are obtained after prolonged use and the spectroscopically confirmed increase in the concentration of the Cd^{2+} complex in the membrane. The experiments having been performed at pH 6.85, it would seem possible that the response slope of 34 mV/decade does not indicate a slightly super-Nernstian response to Cd^{2+} but rather a sub-Nernstian CdA^{+} response, where A^{-} represents an anion (similar MA^{+} responses are shown for Pb^{2+} in section II.22, where the topic is discussed in more detail). Results of ion transfer voltammetry show phase transfer of a doubly charged species but were performed with dichloroethane containing an electrolyte salt rather than with the membrane itself. That a too high affinity of the ionophore is detrimental to the sensor function is also indicated by the observation that after conditioning of this electrode in solutions of Cu^{2+}, for which the ionophore has an even higher affinity, no Cd^{2+} responses can be observed anymore. Interesting is the observation that the response to Ni^{2+}, for which the carrier has a very high thermodynamic affinity, was very small. Ion transfer voltammetry indicates that kinetic limitations, which are also evidenced by the slow water exchange of this ion, may play an important role in determining the selectivity of this ISE.



Cd²⁺-2

A higher discrimination of Cu^{2+} was reported for an ISE based on benzo-15-crown-5 (**K^{+}-5**, log $K^{\mathrm{pot}}_{\mathrm{Cd,J}}$ (FIM): Pb^{2+}, −0.7; K^{+}, −1.0; Na^{+}, −0.9; Cu^{2+}, −0.7; Zn^{2+}, −1.0; Hg^{2+}, −1.0; DBP).[686] Note, however, the high hydrophilicity of this ionophore. Best for discrimination of Cu^{2+} seem to be electrodes based on calix[4]arenedithioamides (**Cd^{2+}-3** and **Cd^{2+}-4**), which were reported to give Nernstian responses to Cd^{2+} at pH 4.0 but do not show a response to K^{+}, Cu^{2+}, and Pb^{2+} at all.[631]

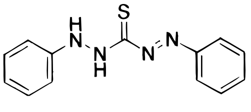


Cd²⁺-3: R^1, R^2 = $OCH_2C(S)N(CH_3)_2$; R^3, R^4 = OH; R^5 = *tert*-butyl
Cd²⁺-4: R^1, R^3 = $OCH_2CH_2OCH_2C(S)N(CH_3)_2$; R^2, R^4 = OC_3H_7; R^5 = *tert*-butyl

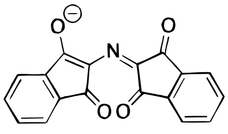
Optodes. The carrier **Pb^{2+}-2**, an isomeride of the ionophore **Cd^{2+}-1**, was incorporated in an optode that gives an excellent discrimination of alkali and alkaline earth metal ions. This optode was characterized primarily in view of possible Pb^{2+} determinations (see section II.22) but responds more strongly to Cd^{2+} than to Pb^{2+} (log $k^{\mathrm{Osel}}_{\mathrm{Pb,Cd}}$(SSM): +1.2).[687]

19. Hg^{2+} Sensors

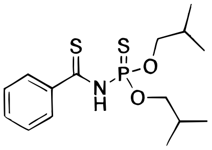
Hg^{2+}-selective electrodes based on chelating reagents as charged carriers were reported repeatedly. The dithizone (**Hg^{2+}-1**) chelate of Hg^{2+} has for example been used to make electrodes with the typical selectivity of the chelating agent ($Au^{3+} > Hg^{2+} > Ag^{+} > Cu^{2+} > Zn^{2+} > Pb^{2+} > H^{+}$)[688] and a similar electrode based on palladium dithizonate was also reported for Hg_2^{2+} detection.[689] ISEs based on mercury diketohydrindylidene-diketohydramine[690] (**Hg^{2+}-2**) give a high discrimination of most transition metal ions except Ag^+ (log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (SSM): Ag^+, +0.3; Zn^{2+}, −3.0; Pb^{2+}, −3.4; Cu^{2+}, −1.9; $CHCl_3$, no PVC). The use of the 1-(2-pyridylazo)-2-naphthol (**Zn^{2+}-6**, PAN) chelate of Hg^{2+} gives an even better discrimination of many transition metal ions but Ag^+ and Fe^{3+} interfere seriously (log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (SSM): Ag^+, +0.9; Fe^{3+}, +5.4; Zn^{2+}, −4.6; Pb^{2+}, −4.4; Cu^{2+}, −3.9; $CHCl_3$, no PVC; see also use of **Zn^{2+}-6** for optodes).[681] In the case of a *N*-(thiophosphoryl)thiobenzamide ionophore (**Hg^{2+}-3**) a good discrimination of most transition metal ions including Fe^{3+} was observed but again Ag^+ interferes appreciably (log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (MSM): Ag^+, 0.0; Fe^{3+}, −3.4; Zn^{2+}, −2.9; Pb^{2+}, −2.6; Cu^{2+}, −2.7; CCl_4).[691] With Hg^{2+} buffers, the detection limit could be lowered from 10^{-5} to $10^{-15.2}$ M with a response slope of 29 mV/decade.



Hg^{2+}-1

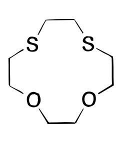


Hg^{2+}-2

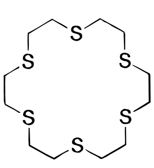


Hg^{2+}-3

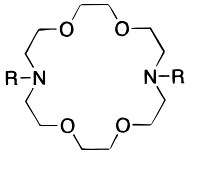
On the other hand, only few neutral carriers were presented for use in Hg^{2+} electrodes. A very interesting discrimination of both Fe^{3+} and Ag^+ was obtained with a very simple 1,4-dithia-12-crown-4 ionophore (**Hg^{2+}-4**, log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (fixed primary ion method): Ag^+, −3.4; Fe^{3+}, −1.5; Zn^{2+}, <−5.0; Pb^{2+}, −3.6; Cu^{2+}, −3.1; Na^+, −2.8; DBP, NaTPB).[648] While Nernstian slopes were observed for $Hg(NO_3)_2$ solutions, the use of the chloride salt led to a nearly complete disappearance of an emf response. The major interfering ion for an electrode based on hexathiacyclooctadecane (**Hg^{2+}-5**) is Fe^{3+}, followed by Bi^{3+} and Pb^{2+} but Ag^+ was not measured (log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (FIM): Fe^{3+}, +0.7; Bi^{3+}, +0.1; Pb^{2+}, −0.8; DOP).[617] For two *N,N′*-substituted 1,10-diaza-18-crown-6 ethers (**Hg^{2+}-6** and **Hg^{2+}-7**) a high discrimination of most tested ions and only a severe interference from Ag^+ was found (**Hg^{2+}-6**, log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (SSM): Ag^+, +2.6; Zn^{2+}, −3.5; Pb^{2+}, −3.7; Na^+, −5.3; Cd^{2+}, −3.9; oNPOE, KTpClPB).[692,693]



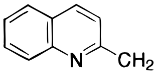
Hg^{2+}-4



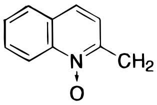
Hg^{2+}-5



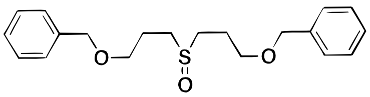
Hg^{2+}-6: R =



Hg^{2+}-7: R =

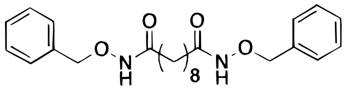


From the study of 14 noncyclic and cyclic thioether, sulfoxide and sulfone ionophores, sulfoxides have emerged as an interesting new Hg^{2+} ionophore class.[656] While the ISEs with thioether ionophores were found to give invariably a preference for Ag^+, oxidation of the thioether to a sulfoxide group results in a preference for Hg^{2+} (**Hg^{2+}-8**, log $K^{\mathrm{pot}}_{\mathrm{Ag,J}}$ (SSM): Hg^{2+}, +0.8; Zn^{2+}, −3.6; Pb^{2+}, −2.0; Na^+, −1.6; Cd^{2+}, −3.1; BBPA, KTpClPB). Further oxidation to the sulfone leads to strong interferences from alkali metal ions by eliminating the possibility of direct interaction between Hg^{2+} and the sulfur atom.



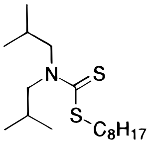
Hg^{2+}-8

While *N*-substituted hydroxylamide derivatives with an OH group have been used as ionophores for detection of Mo(VI) (**Mo(VI)-1**, section II.13) and Pb^{2+} (**Pb^{2+}-9**, section II.22), hydroxylamides with an NH but no OH group have been recently found to provide a high selectivity for Hg^{2+} (**Hg^{2+}-9**, log $K^{\mathrm{pot}}_{\mathrm{Hg,J}}$ (SSM): Ag^+, −3.9; Zn^{2+}, −7.6; Pb^{2+}, −4.8; Cd^{2+}, −7.4; oNPOE, KTpClPB, selectivity calculated with the super-Nernstian slope).[694] The origin of the response slope of 70 mV/decade for the ISE based on **Hg^{2+}-9** has not been explained yet. It seems possible that these compounds are charged Hg^{2+} carriers, and that at an appropriate pH, a response mechanism prevails that is similar to the apparently "twice-Nernstian" responses that have been observed for ISEs with monensin, lasalocid, or bis(2-heptylundecyl) phosphate as acidic ionophore.[185] Alternatively, there may be a response to the monocation mercury acetate.

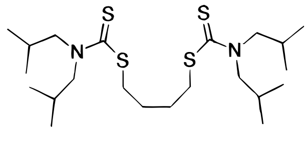


Hg^{2+}-9

Optodes. Optodes based on a dithiocarbamate ionophore and a neutral H^+ chromoionophore, giving responses of similar extent to Ag^+ and Hg^{2+}, have been discussed in the section on Ag^+ optodes.[668] Several bis(dialkyl dithiocarbamate) ionophores were shown to give a slight preference for Hg^{2+} over Ag^+ and an excellent discrimination of other ions (log $k^{\mathrm{Osel}}_{\mathrm{Ag,Hg}}$ (SSM): +0.7, +0.9, and +1.0 for **Ag^+-14**, **Hg^{2+}-10**, and **Hg^{2+}-11**, respectively; DOS, KTFPB).



Hg^{2+}-10

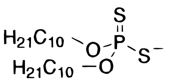


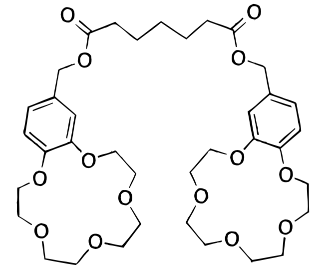
Hg^{2+}-11

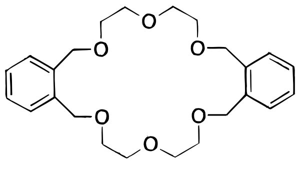
20. Tl^+ Sensors

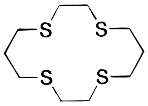
The Tl^+ ion has an ionic radius of 144 pm (K^+: 138 pm; Rb^+: 148 pm) and a fairly small molar Gibbs free energy of hydration (−300 kJ/mol, which is nearly equal as for K^+).[401] It therefore relatively easily enters organic membranes, as can be seen for example from the selectivity of an ionophore-free ion-exchanger electrode based on a tetraphenylborate salt (log $K^{\mathrm{pot}}_{\mathrm{Tl,J}}$ (MSM): Ag^+, −0.7; K^+, −0.6; Na^+, −1.6; Rb^+, −0.1; NH_4^+, −0.9; thallium tetrakis(*m*-trifluoromethylphenyl)borate, ethylnitrobenzene, no PVC).[405] The analytical interest arises primarily due to the high toxicity of Tl^+.

The use of electrodes based on the thallium(I) salt of *O*,*O*′-didecyl dithiophosphate (**Tl^+-1**) was reported to provide for good selectivity for Tl^+ over alkali and alkaline earth metal ions but Cd^{2+}, Hg^{2+}, Ag^+, Pb^{2+}, and Cu^{2+} interfere seriously.[695] Indeed, a very similar ionophore was reported for Cu^{2+} detection (**Cu^{2+}-11**),[640] thiophosphorylated calix[6]arene ionophores were reported for use in Pb^{2+}-selective electrodes (e. g. **Pb^{2+}-7**),[641] and an ionophore with thiophosphate groups was also reported for Hg^{2+} (**Hg^{2+}-3**). However, a much improved selectivity for Tl^+ over Ag^+ and Pb^{2+} is found for bis(benzo-15-crown-5) derivatives (e. g. **Tl^+-2**, log $K^{\mathrm{pot}}_{\mathrm{Tl,J}}$ (FIM): Ag^+, −3.2; K^+, −0.5; Na^+, −4.0; Pb^{2+}, −4.7; Rb^+, −1.0; NH_4^+, −2.1; oNPOE).[696] The improvement in selectivity as compared to a benzo-15-crown-5 ionophore was found to be fairly large for the interfering ions Na^+ and Ag^+, whereas selectivities against other ions hardly changed. Incidentally the same ionophores were also characterized in view of their K^+ selectivities and indeed K^+ is strongly interfering.[210,352,361] A somewhat higher discrimination of K^+ is obtained by using ring-enlarged dibenzo-20-crown-6 and dibenzo-22-crown-6 compounds but these improvements are accompanied by a decreased discrimination of other cations (dibenzo-22-crown-6 (**Tl^+-3**): log $K^{\mathrm{pot}}_{\mathrm{Tl,J}}$ (MSM): Ag^+, −1.4; K^+, −1.7; Na^+, −3.0; Pb^{2+}, −3.4; oNPOE, NaTFPB).[697] Recently, the use of a series of oligothia-crown ethers was investigated, giving the best results for 1,4,8,11-tetrathiacyclotetradecane (**Tl^+-4**) as carrier (log $K^{\mathrm{pot}}_{\mathrm{Tl,J}}$ (MSM): Na^+, −2.3; Fe^{3+}, −2.9; Zn^{2+}, −3.5; DOP, KTpClPB).[627] A comparison to the benzo-15-crown-5 ionophores is however difficult because selectivity coefficients were reported only for a few interfering ions. Note that the same compound and other similar ionophores were also used for Ag^+ selective electrodes.[626]


Tl^+-1


Tl^+-2

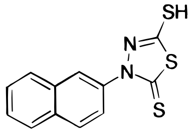

Tl^+-3


Tl^+-4

For Tl(III) determinations only ionophore-free ion-exchanger electrodes for $TlCl_4^-$ were reported.[19]

21. Bi^{3+} Sensors

The large interference of Bi^{3+} on the response of a Hg^{2+}-selective electrode based on a hexathiacyclooctadecane was mentioned above.[617] In view of Hg^{2+} discrimination, a Bi^{3+}-selective electrode with the chelating reagent Bismuthiol III (**Bi^{3+}-1**), log $K^{\mathrm{pot}}_{\mathrm{Bi,J}}$ (MSM): Hg^{2+}, ≫0; Fe^{3+}, −3.9; Zn^{2+}, < −4.4; Pb^{2+}, −5.0; tetrachloroethane, no polymer matrix) seems to be inferior, but on the other hand the Fe^{3+} selectivity of the latter is far superior.[698,699]

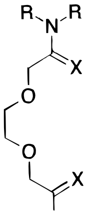

Bi^{3+}-1

22. Pb^{2+}/PbA^+ Sensors

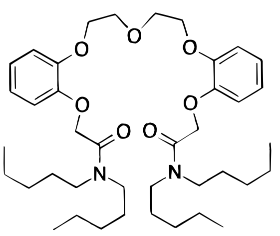
The most serious drawback of PbS based solid-state ISEs is their susceptibility to interference from Hg_2^{2+}, Hg^{2+}, Ag^+, and Cu^{2+}. This has recently led to a substantial interest in carrier-based sensors for Pb^{2+}. Whether these sensors respond to Pb^{2+} or to PbA^+, where A^- stands for OH^-, OAc^-, NO_3^-, or another anion present in the sample solution, not only depends on the membrane components but also on the pH and the type and concentration of anions in the sample solution. Because emf response slopes typical for monovalent and divalent ions as well as intermediate slopes were observed, great care should be taken in interpreting selectivity coefficients.

The first neutral-carrier based lead ion selective electrodes were based on oxa- or dioxadicarboxylic acid diamides,[672,684,687,700] giving nearly Nernstian responses to PbA^+ ($A^- = Cl^-$, OH^-, OAc^-, or NO_3^-). Selectivity coefficients for different lead species were calculated from the emf responses at different pH values (**Pb^{2+}-1** (ETH 322), log $K^{\mathrm{pot}}_{\mathrm{PbOH,J}}$ (FIM):[672] $PbCl^+$, −1.8; $PbNO_3^+$, −1.8; $PbOAc^+$, −1; Pb^{2+}, −4.8; H^+, −4.2; log $K^{\mathrm{pot}}_{\mathrm{PbA,J}}$ (SSM): Li^+, −2.9; Ca^{2+}, −5.2; Cu^{2+}; −5.0; Cd^{2+}; −3.7; Ba^{2+}, −4.7; BBPA; note the similarity of this ionophore to **Cd^{2+}-1**). No added ionic sites were used, and it has been speculated that the concentration of impurity sites in the membrane components may have played a crucial factor in determining selectivities and response slopes.[687] A recent reevaluation of the selectivity of Li^+, Na^+, Mg^{2+}, and UO_2^{2+} ionophores showed that the relatively similar UO_2^{2+} ionophore **UO_2^{2+}-4** (ETH 295) gives a selectivity for Pb^{2+} that is almost as good as that of ISEs based on **Pb^{2+}-1**. Added ionic sites lead to a response slope of 35.3 mV/decade, suggesting a mixed response to PbA^+ and Pb^{2+} (log $K^{\mathrm{pot}}_{\mathrm{Pb,J}}$ (SSM):

Li^+, −2.9; Cu^{2+}, −3.9; Cd^{2+}, −4.1; Ba^{2+}, −2.4; Ag^+, +0.1; oNPOE, KTpClPB; sample solution: nitrate salts, pH 4).[701] Furthermore, use of membranes containing added anionic sites and a 3,6-dioxaoctanedithioamide carrier (**Pb^{2+}-2**, ETH 5435) resulted in Nernstian slopes typical for doubly charged Pb^{2+}.[702] A slope of the Pb^{2+} response of 28.5 mV/decade was obtained with an ISE based on added anionic sites and the noncyclic ionophore **Pb^{2+}-3** with two tertiary amide groups (log $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (FIM): Li^+, −1.6; Cu^{2+}, −4.3; Fe^{3+}, −3.4; Ca^{2+}, −3.2; Na^+, +0.0; K^+, −0.6; oNPOE, KTpClPB).[703]



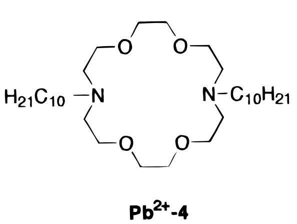
Pb^{2+}-1 (ETH 322): R = C_3H_7, R' = $C_{18}H_{37}$, X = O
Pb^{2+}-2 (ETH 5435): R, R' = $C_{12}H_{25}$, X = S



Pb^{2+}-3

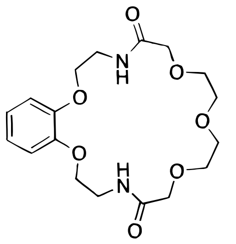
The ionophore **Pb^{2+}-2** has recently been used to demonstrate that the lower detection limit of ion-selective polymer membrane electrodes (ISEs) of typically 10^{-6} M can be improved by a factor of $\geq 10^6$, making measurements down to the picomolar range possible. This was achieved by using the complexing agent EDTA to reduce the primary ion activity in the internal electrolyte. The latter also contains a salt of a highly discriminated interfering ion, which partly replaces Pb^{2+} at the reference side of the membrane. The thus generated concentration gradient of primary ions in the membrane lowers the detection limit and yields improved selectivities toward strongly discriminated ions. By eliminating a fundamental limiting factor, this opens up new dimensions of ISE applications in trace metal analysis for environmental and biochemical studies (log $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (SSM): Li^+, −5.1; Na^+, −4.7; K^+, −4.1; Mg^{2+}, −9.4; Ca^{2+}, −8.6; Cu^{2+}, −0.4; Zn^{2+}, −5.0; Cd^{2+}, +0.4; oNPOE, KTpClPB).[24]

It was reported that among some of the above dioxadicarboxylic amide ionophores, two other 3,6-dioxaoctane diamides, dicyclohexano-18-crown-6, tetrakis(2-pyridylmethyl)ethylenediamine, and the diazamacrocycle Kryptofix 22DD (**Pb^{2+}-4**), only the Kryptofix ionophore allows the determination of 2 × 10^{-6} M Pb^{2+} in the presence of 10^{-2} M Ca^{2+}, which interferes substantially in lead detection in drinking water.[704] However, no selectivity coefficients have been reported.

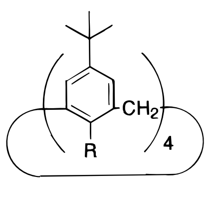


Pb^{2+}-4

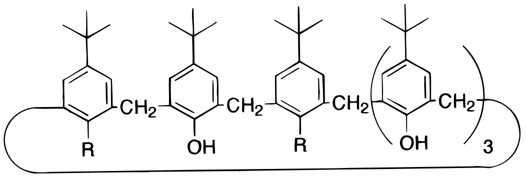
Among 14 diamide and two diamine macrocycles investigated with the aim to take advantage of the macrocyclic effect, two diamides with a 3,6,9-trioxaundecane-1,11-diamide unit gave the most favorable selectivities (**Pb^{2+}-5**, log $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (SSM): Cu^{2+}, −1.6; Cd^{2+}, −2.8; Ca^{2+}, −2.4, Ag^+, Cs^+, Rb^+, > 0; oNPOE, KTpClPB; response slope for lead 37 mV/decade, pH 4, $Pb(NO_3)_2$ solutions).[705] Higher selectivities could be obtained with calix[4]arenes carrying two amide[631] or four thioamide[706,707] groups (**Pb^{2+}-6**, $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (FIM): Cu^{2+}, −3.3; Cd^{2+}, −3.8; Ca^{2+}, −4.8; oNPOE, KTpClPB; note the similarity of **Pb^{2+}-6** and **Cd^{2+}-3**). Electrodes based on the latter were affected by Ag^+ and Hg^{2+}. Potentiometric selectivities for seven mono-, bis-, and pentakis(thiophosphate) derivatives of *p-tert*-butylcalix[6]arene were determined in another attempt to take advantage of the rigid calixarene platform (for the most selective **Pb^{2+}-7**, $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (SSM): Cu^{2+}, −2.4; Cd^{2+}, −2.6; Ca^{2+}, −1.4; oNPOE, KTpClPB).[641] Note the similar use of ligating groups in dialkyl dithiophosphate ionophores, which were suggested for Cu^{2+} and Tl^+ detection, and in the Hg^{2+} ionophore **Hg^{2+}-3** (see sections II.15, II.20, and II.19, respectively).



Pb^{2+}-5



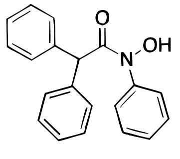
Pb^{2+}-6: R = $OCH_2C(S)N(CH_3)_2$

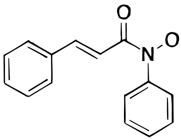


Pb^{2+}-7: R = $OP(=S)(OCH_2CH_3)_2$

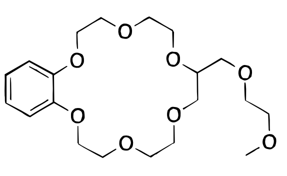
Diphenylmethyl-*N*-phenylhydroxamic acid (**Pb^{2+}-8**), reported to be a charged carrier, was shown to give a quite high selectivity for Pb^{2+} and a response slope of 28 mV/decade ($K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (SSM): Cu^{2+}, −4.5; Cd^{2+}, −2.9; Ca^{2+}, −4.0; Ag^+, −2.6; Hg^{2+}, −1.8; DOS; sample solution: nitrate salts, pH 5−6).[708] Particularly interesting seems to be the high discrimination of Ag^+ and Hg^{2+}. ISEs based on chelates of *N*-benzoyl-*N*-phenylhydroxylamine derivatives, on the other hand, showed substantial interference from Cu^{2+} and Hg^{2+} (**Pb^{2+}-9**, $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (FIM): Cu^{2+}, −0.7;

Cd^{2+}, −3.6; Ca^{2+}, −4.4; Hg^{2+}, 0.0; DBP; response slope 29 mV/decade, pH 3.3−5.5, adjusted with HNO_3; note the similarity of **Mo(VI)-1** and **Pb^{2+}-9**).[639] Indeed similar ionophores were reported for Cu^{2+} electrodes (e. g. **Cu^{2+}-10**, section II.15).[638]

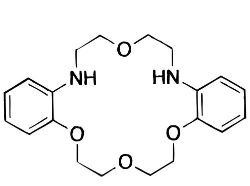

Pb^{2+}-8

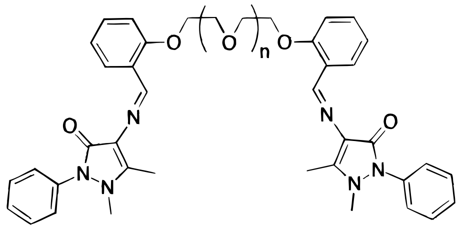

Pb^{2+}-9

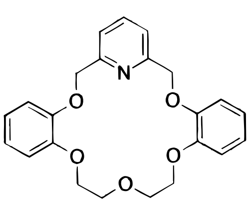
A disadvantage of electrodes based on tetraphenylborate salts of polyalkoxylate complexes with Pb^{2+} are the quite large interference from Ba^{2+} and a very strong interference from Ag^{+} and Hg^{2+} (**Ba^{2+}-1** (nonylphenoxypoly(ethyleneoxy)ethanol), $K^{pot}_{Pb,J}$ (FIM): Li^{+}, −2.8; Ca^{2+}, −3.6; Cd^{2+}, −3.9; Ba^{2+}, −0.5; NPPE, tetraphenylborate salt of polyalkoxylate; $Pb(NO_3)_2$ solutions, pH 2.5−5.5; **Ba^{2+}-1** was also used for Ba^{2+} selective electrodes;[602] see section II.12).[603] The response slopes indicate Pb^{2+} to be the potential-determining ion, in contrast to the response slope typical for a monocation ($PbOH^{+}$) reported for a membrane containing a noncyclic polyether but no added anionic sites (sample solutions: nitrate salts, pH 5−6).[709] Near-Nernstian slopes indicative for PbA^{+} (where A^{-} is OH^{-}, OAc^{-}, or NO_3^{-}) were also reported for membranes with dicyclohexano-18-crown-6 (**K^{+}-3**, as $Pb(NO_3)_2$ complex in the presence of an equimolar amount of sodium tetraphenylborate; measurement in 0.1 M $Mg(OAc)_2$)[710] and a variety of other crown ethers (no ionic sites added, membrane solvent: dibutyl sebacate).[709] Selectivities were reported only briefly but indicate quite a good discrimination of Ag^{+}, K^{+}, Tl^{+}, and NH_4^{+} ($K^{pot}_{Pb,J} < -2$). Interestingly, the introduction of ether oxygen containing sidearms to benzo-18-crown-6 has little influence on the discrimination of alkaline earth ions (**Pb^{2+}-10**, $K^{pot}_{Pb,J}$ (SSM): Mg^{2+}, −4.0; Ca^{2+}, −3.5; Sr^{2+}, −1.8; oNPOE, KTpClPB; $Pb(OAc)_2$ solutions).[343]


Pb^{2+}-10

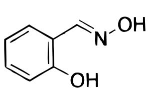
On the other hand, membranes containing either dicyclohexano-18-crown-6 or a diazadibenzo-18-crown-6 ether (**Pb^{2+}-11**) but no added ionic sites were found to respond to the doubly charge Pb^{2+} with Nernstian slopes.[711−714] Not a single factor, such as the presence or absence of added sites, but rather a number of factors seem relevant in determining the response slope. The sample pH, the type and concentration of counteranions in the sample solution, the concentration of ionic sites (introduced as impurities or added intentionally) and the ionic strength in the membrane, the ionophore structure, and probably also the type of membrane solvent seem all to be able to influence which lead species becomes potential determining. The lack of a Pb^{2+} response of ISEs based on 1,10-dithia-18-crown-6 and dicyclohexano-18-crown-6[711] was most probably due to the lack of anionic sites in those membranes. Similarly, the experimentally obtained superiority of DBP over DOS and oNPOE observed for Pb^{2+} ISEs based on di-, tri-, and tetraethylene glycol ionophores with two terminal antipyryliminomethinylphenyl groups (**Pb^{2+}-12** to **Pb^{2+}-14**)[715] may be not the result of intrinsic properties of these plasticizers but rather an artifact due to different concentrations of impurities contained in those plasticizers.[716] Cu^{2+} and Ag^{+} are moderately discriminated by the tetraethylene glycol derivative ISE (**Pb^{2+}-14**, $K^{pot}_{Pb,J}$ (MSM): Li^{+}, −4.0; Ca^{2+}, −4.0; Cu^{2+}, −0.5; Cd^{2+}, −2.4; Ag^{+}, −0.3; DBP; sample solution prepared from $Pb(NO_3)_2$, response slope ≈ 22 mV/decade). The ionophore **Pb^{2+}-15**, which resembles **K^{+}-12**, gives an ISE that responds to the analyte dication even though no added anionic sites were used ($K^{pot}_{Pb,J}$ (FIM): K^{+}, +0.9; Ca^{2+}, −2.6; Cu^{2+}, −1.8; Cd^{2+}, −2.7; oNPOE).[717]


Pb^{2+}-11


Pb^{2+}-12: n = 1, **Pb^{2+}-13:** n = 2, **Pb^{2+}-14:** n = 3


Pb^{2+}-15

The lack of information on the possible influence of added ionic sites is also a drawback of an investigation on the use of spectrophotometric reagents in ISEs.[718] Non-Nernstian response slopes make the interpretation of selectivities difficult, but salicylal-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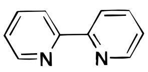
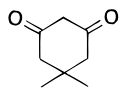
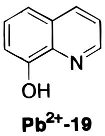

Pb^{2+}-17


Pb^{2+}-18


Pb^{2+}-19

doxime (**Pb^{2+}-16**), 2,2′-bipyridyl (**Pb^{2+}-17**), dimedone (**Pb^{2+}-18**), and 8-hydroxyquinoline (**Pb^{2+}-19**) may have some potential for Pb^{2+} sensors, even though sensor lifetimes are certainly very limited as long as no attempt is made to use more lipophilic derivatives of these reagents. Alternatively, such reagents might be used for optical sensors.

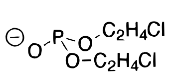
With two bidentate bis(dithiocarbamate) ionophores (**Ag^{+}-14**, **Hg^{2+}-11**) slopes typical of ions with a double charge were obtained.[666,667] Cu^{2+} leads to a strong interference (**Ag^{+}-14**: $K_{\mathrm{Pb,J}}^{\mathrm{pot}}$ (FIM): Ca^{2+}, −5.4; Cu^{2+}, +0.7; Cd^{2+}, −3.5; Fe^{3+}, −2.6; oNPOE, KTpClPB; sample solutions prepared from metal nitrates, pH 3.1−5.4), and it is thus not surprising that bis(dithiocarbamate) ionophores were reported for use in Cu^{2+} ISEs (**Cu^{2+}-6** and **Cu^{2+}-7**, section II.15). These ionophores have recently also been used in Ag^{+} and Hg^{2+} optodes. The higher selectivity of the ionophore in which the dithiocarbamate units are linked by a methylene unit as compared to its butylene isomeride corresponds well with results from extraction experiments.

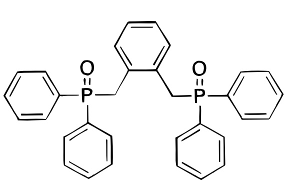
Optodes. In contrast to Pb^{2+} selective electrodes prepared without added anionic sites, optodes based on dioxaoctanediamide ionophores strongly respond to Ca^{2+} (**Pb^{2+}-1**, log $k_{\mathrm{Pb,Ca}}^{\mathrm{Osel}}$ (SSM): −0.6; **H^{+}-9** (ETH 2439), DOS, KTFPB; sample solution: acetate buffer, pH 5.04). Furthermore, all optode functions can be perfectly explained by presuming a response to Pb^{2+} only.[687] Both facts are probably mainly due to the presence of anionic sites in the optode membrane and indicate that anionic sites would certainly also strongly affect the selectivities of dioxaoctanediamide ISEs. Whereas also optodes based on the uranyl ionophore **UO$_2$$^{2+}$-4** (ETH 295) suffer from Ca^{2+} interference, the use of **Pb^{2+}-2** (ETH 5435) results in a very high discrimination of all alkali and alkaline earth metal ions (log $k_{\mathrm{Pb,J}}^{\mathrm{Osel}}$ (SSM): Na^{+}, −5.6; K^{+}, −5.3; Mg^{2+}, −10.9; Ca^{2+}, −10.8; Cu^{2+}, +0.7; Zn^{2+}, −4.6; Cd^{2+}, +1.2; ETH 5294 (**H^{+}-10**), ETH 5418 (**H^{+}-22**) or ETH 5315 (**H^{+}-21**), DOS, KTFPB; sample solution: acetate buffer, pH 4.7). Pb^{2+} cannot be selectively measured in the presence of Ag^{+}, Cu^{2+}, and Cd^{2+} but for environmental monitoring, in which often the total amount of toxic heavy metal ions is most important, this optode seems to be nearly perfect because the selectivity coefficients for the heavy metal ions are in the order of their toxicity.[687] The detection limit of $10^{-13.1}$ M Pb^{2+}, as determined with sample solutions containing a metal buffer, seems particularly attractive for such applications. It is almost 4 orders of magnitude lower than that of conventional ISEs[702] but closer to the detection limit of $10^{-11.3}$ M Pb^{2+} of ISEs with internal electrolyte solutions in which Pb^{2+} is buffered (vide supra).[24]

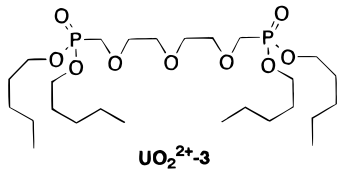
23. U(VI) Sensors

There is special interest for U(VI) analysis in nuclear industry, in particular for use in fuel separation and processing. Because Fe(II) is often used as a reducing agent, Fe(II) and Fe(III) are interfering ions of particular concern. Characteristic for the determination of uranyl is the small available pH range, which is limited by the occurrence of several U(VI) species in aqueous solution. Besides the linear UO$_2$$^{2+}$ species, UO$_2$OH^{+}, UO$_2$OH^{+} dimers, and complexes of UO$_2$$^{2+}$ with anions in solution are formed.[719,720] While above pH 3.5 UO$_2$(OH)$_2$ starts to precipitate, at pH 3.5 or lower free UO$_2$$^{2+}$ accounts for more than 96% of the uranyl species if the concentration of the total amount of uranyl is 10^{-4} M or smaller. However, the occurrence of other forms has usually not been taken into account when calculating selectivity coefficients. Furthermore, activities and concentrations were used alternately to evaluate selectivities.

The first uranyl ionophores were organophosphorus compounds analogous or even identical to those used in Ca^{2+} electrodes. Various alkyl phosphates were investigated,[720−723] bis-[4-(1,1,3,3-tetramethylbutyl)phenyl] phosphate (**Ca^{2+}-3**) being one of the most successful ones (**Ca^{2+}-3**, log $K_{\mathrm{U(VI),J}}^{\mathrm{pot}}$ (SSM):[720] Fe(III), 0.4; Fe(II), −2.9; Ca^{2+}, −2.0; Cu(II), −2.8; DOPP; Tris buffer, pH 3; in disregard of the occurrence of other forms, values of log $K_{\mathrm{U(VI),J}}^{\mathrm{pot}}$ refer to the total concentration of each cation). Fe(III) was reported not to poison these electrodes but H^{+} starts to interfere seriously below pH 2. On the other hand, several neutral organophosphorus carriers were used as well. Three phosphites gave quite a high discrimination of mono- and divalent cations, but trivalent ions interfered substantially (**UO$_2$$^{2+}$-1**, log $K_{\mathrm{U(VI),J}}^{\mathrm{pot}}$ (SSM): Fe^{3+}, +0.5; Ca^{2+}, −2.7; Cr^{3+}, −1.3; HCl, pH 3, log $K_{\mathrm{U(VI),J}}^{\mathrm{pot}}$ referring to the activity of the uranyl dication).[721] Even though phosphites have a fairly high reactivity, no oxidation of the ligand was observed in the ISE membranes. Use of the more strongly complexing ligand tri-*n*-octylphosphine oxide (**PL-1**; see under "Crown Ether Derivatives" in section II.2) required the presence of tetraphenylborate to prevent serious anion interference and, in the presence of nitrate, gave emf responses typical for monovalent ions (log $K_{\mathrm{UO_2,J}}^{\mathrm{pot}}$ (fixed primary ion method): Fe^{3+} (at pH 2), −2.1; Ca^{2+}, −2.5; Cu^{2+}, −2.8; tributyl phosphate, KTPB; HNO$_3$, pH 3, log $K_{\mathrm{UO_2,J}}^{\mathrm{pot}}$ referring to activities).[724] For the bidentate ionophore tetraphenyl-*o*-xylyldiphosphine dioxide (**UO$_2$$^{2+}$-2**), the most favorable among three similar diphosphine dioxides, on the other hand, again a response slope typical of divalent ions was observed (log $K_{\mathrm{UO_2,J}}^{\mathrm{pot}}$ (SSM): Al^{3+}, −2.9; Ca^{2+}, −3.1; Cu^{2+}, −3.0; oNPOE; HNO$_3$ or HCl, pH 3, log $K_{\mathrm{UO_2,J}}^{\mathrm{pot}}$ referring to activi-

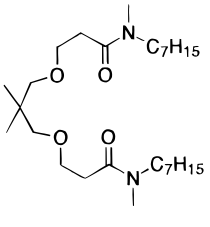

UO$_2$$^{2+}$-1


UO$_2$$^{2+}$-2

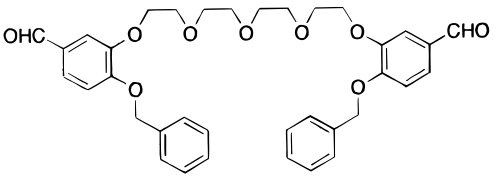

UO$_2$$^{2+}$-3

ties).[570,725] The same ligand was reported to give a sub-Nernstian response when used for a Ca^{2+}-selective electrode, even though a tetra-*o*-tolyl derivative (**Ca^{2+}-18**) led to Nernstian responses for Ca^{2+}.[569] Similar selectivities and also a slope indicating a response to a divalent cation were obtained with acyclic oligoethers with terminal phosphonate groups (**UO_2^{2+}-3**, log $K^{\mathrm{pot}}_{\mathrm{UO_2,J}}$: Pb^{2+}, −3.5; Ca^{2+}, −2.2; Cu^{2+}, −3.0; nitrobenzene, no PVC, NaTPB, HNO_3, pH 3, log $K^{\mathrm{pot}}_{\mathrm{UO_2,J}}$ referring to activities).[726]

Very different from the above-mentioned ionophores but again in similarity to corresponding Ca^{2+} ionophores are diamides that were reported as UO_2^{2+} carriers. Within a series of such compounds, **UO_2^{2+}-4** (ETH 295) was found to give the most selective electrodes, responding with a slope typical for the monovalent UO_2OH^+ (log $K^{\mathrm{pot}}_{\mathrm{UO_2A,J}}$ (SSM): Ag^+, −2.5; Ca^{2+}, <−4.1; Cu^{2+}, <−4.0; 1-chloronaphthalene; HNO_3, pH 3, log $K^{\mathrm{pot}}_{\mathrm{UO_2A,J}}$ referring to a monovalent uranyl species, which was suggested to be most likely UO_2OH^+).[114,727] The authors claimed to have found no ion that poisoned the electrode. Fears reported elsewhere that Fe(II) or Fe(III) might poison the electrode are probably not justified as the same ionophore was successfully used for an UO_2^{2+} optode with a completely reversible response to these interfering ions.[719] Because that optode responded however to UO_2^{2+}, it can be concluded that just as in the case of Pb^{2+} electrodes based on diamide carriers the selectivities and response mechanism of these UO_2^{2+} electrodes are very sensitive to the presence of ionic sites. Membranes containing **UO_2^{2+}-4** and anionic sites were characterized as Pb^{2+} ISEs but UO_2^{2+} was not measured (see section II.22).[701] A recently reported electrode based on an ionophore with seven ether and two aldehyde groups (**UO_2^{2+}-5**) suffered from a rather high detection limit and a sub-Nernstian slope for the response to the primary ion even in the presence of tetraphenylborate.[728]



UO_2^{2+}-4 (ETH 295)



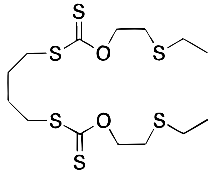
UO_2^{2+}-5

An ISE reported as being based on the ternary mixture of $(UO_2(C_6H_5COO)_3)^-$ and methylene blue as countercation requires use of benzoate and pH 4 in the sample solution and is an ion exchanger for $(UO_2(C_6H_5COO)_3)^-$. Its dynamic range of 10^{-6} to 4 × 10^{-4} M is unfortunately very small.[729]

Optodes. The first bulk membrane optodes for UO_2^{2+} were only introduced very recently.[719] By using **UO_2^{2+}-4** and chromoionophore **H^+-21** (ETH 5315), a measuring range from 10^{-7} to 10^{-4} M UO_2^{2+} could be obtained, giving a detection limit lower than for any reported UO_2^{2+}-selective electrode. As demonstrated for other primary ions, the use of a more acidic ionophore could, however, result in even lower detection limits, even though this would be accompanied by increased response times owing to slow convective mass transport from the bulk of the aqueous phase.[687] This optode discriminated several important heavy metal ions but Pb^{2+}, Ca^{2+}, Ag^+, and Li^+ interfered substantially (log $k^{\mathrm{Osel}}_{\mathrm{U(VI),J}}$ Fe^{3+}, −3.3; Fe^{2+}, −3.2; Ca^{2+}, −1.8; Cu^{2+}, −5.0; Pb^{2+}, −0.6; Ca^{2+}, −1.8; Ag^+, −1.9; Li^+, −2.1; DOS, KTFPB; formate buffer, pH 3; log $k^{\mathrm{Osel}}_{\mathrm{U(VI),J}}$ referring to the total uranyl concentration, assuming divalent uranyl species). This problem might be reduced by taking advantage of the intrinsic luminescence properties of UO_2^{2+}.[730]

24. Sm(III) Sensors

ISEs based on bis(thiaalkylxanthato)alkanes have been shown to respond selectively to Sm(III) and thereby represent the first case of neutral carrier-based ISEs for rare earth metal ions.[731,732] The response slopes indicate a response to the tricationic species Sm^{3+}. While the presence of sulfur atoms in these cation receptors not unexpectedly leads to serious interference from Cu^{2+} and Fe^{3+} and a similar problem might be expected for Ag^+ and Hg^{2+}, alkali, alkaline earth, and other rare earth metal ions are fairly well discriminated (**Sm(III)-1**, log $k^{\mathrm{MPM}}_{\mathrm{Sm,J}}$($c_{\mathrm{1,Sm}}$ = 10^{-5} M): Cu^{2+}, +1.2; Fe^{3+}, +0.1; Pb^{2+}, −0.9; Gd^{3+}, −1.2; Pr^{3+}, −1.5; K^+, −2.9; Na^+, −3.2; oNPOE, KTpClPB).



Sm(III)-1

III. Inorganic Anions

1. CO_3^{2-} and HCO_3^- Sensors

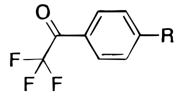
Bicarbonate, carbonate, and carbon dioxide coexist in aqueous solutions. A particular need for bicarbonate analysis comes from the wish of clinical chemists to determine the blood plasma concentration of so-called "unidentified anions" from $[Na^+] - [Cl^-] - [HCO_3^-]$ or a similar formula.[28,733,734] To these "unidentified" anions belong for example lactic acid and di- and tricarboxylic acids. Potentiometric bicarbonate measurements are also frequently used in studies of gastric secretion.[735] Carbonate, on the other hand, occurs only in very small concentrations under physiological conditions. The same is also true for CO_2, whose analysis will be discussed below (section V.1). The so-called "total CO_2 content", $c_{\mathrm{tCO_2}}$, of blood plasma equals approximately the bicarbonate concentration but comprises besides dissolved CO_2, H_2CO_3, HCO_3^-, and CO_3^{2-} also carbon dioxide bound to amino groups of proteins in form of carbamino groups (Pr-NH-COO$^-$).[28] It can be determined by acidification of a sample followed by extraction of CO_2 into a gas phase.[736]

The relation between the partial pressure of CO_2, the activities of CO_3^{2-} and HCO_3^-, and the pH is given by the Henderson–Hasselbalch equation:[733,737]

$$\mathrm{pH} = \mathrm{p}K' \log\{[\mathrm{HCO_3}^-]/(S_{\mathrm{CO_2}} p_{\mathrm{CO_2}})\}$$

where S_{CO_2} is the solubility coefficient of CO_2, p_{CO_2} its partial pressure, and pK' is an empirical "constant". Measurements of p_{CO_2} and the pH allow [HCO_3^-] to be calculated. This is the conventional approach in clinical chemistry because sensors for direct bicarbonate determination in blood samples are not available. The value 6.1 is commonly used for pK' but a value of 6.105 was recently recommended by the secretariat of the clinical laboratory technical committee of the International Standards Organization (ISO),[734] which also gives S_{CO_2} as 0.0307 mM (mmHg)$^{-1}$. However, the use of a single value for pK' was repeatedly questioned and data that suggest a decrease of pK' in patients with a metabolic acidosis were presented.[738,739] Other investigators suggested that this apparent variability in pK' is due to artifacts in sample handling.[740,741] Electrolyte changes seemed to have only a minor influence on pK'.[736] Because determinations of the value of pK' are based on measurements of pH, p_{CO_2}, and c_{tCO_2} and require the assumption that the activity coefficients of HCO_3^- and dissolved CO_2 are constant, a certain variation in pK' would indeed not seem very surprising.

Carbonate. Whereas ionophore-free ion-exchanger ISEs show only a weak response to hydrogen carbonate, a presumably improved selectivity for this analyte was obtained when trifluoroacetyl-*p*-alkylbenzenes were introduced as membrane solvents for ISEs based on quaternary ammonium salts.[742] However, it was soon realized that such ISEs do not respond to hydrogen carbonate but rather to carbonate (trifluoroacetyl-*p*-butylbenzene (**CO_3^{2-}-1**), log $K^{\mathrm{pot}}_{\mathrm{CO_3,J}}$ (SSM):[743] Cl^-, −3.7; OAc^-, −1.6; SO_4^{2-}, −3.8; NO_3^-, −0.5; HPO_4^{2-}, −3.6; Aliquat 336S, no polymer matrix).[743–746] The high selectivity for carbonate quickly led to uses in microelectrodes[747–749] and commercial analyzers.[750–752] As typical for ISEs based on ionophores, the ratio of carrier and added charged sites was shown to be crucial for obtaining high selectivities, confirming that trifluoroacetophenone derivatives are carriers.[753,754] Only fairly recently has it been spectroscopically confirmed that trifluoroacetophenones are indeed neutral ionophores and that carbonate directly attacks the carbonyl carbon of the ketone, thereby selectively and reversibly forming a 1:1 adduct.[755] In ISE membranes, in which there is usually a large excess of the ketone, this 1:1 adduct can react with another ionophore molecule, forming a 1:2 adduct.



CO_3^{2-}-1: R = C_4H_9
CO_3^{2-}-2: R = $C(O)N(C_8H_{17})_2$
CO_3^{2-}-3: R = $C(O)OC_7H_{15}$
CO_3^{2-}-4: R = $S(=O)_2C_{12}H_{25}$
CO_3^{2-}-5: R = $C_{10}H_{21}$
CO_3^{2-}-6: R = $C(O)OC_6H_{13}$

Replacement of the alkyl substituent on the benzene ring by various functional groups showed that strong electron acceptors such as amide, ester, and sulfone groups (**CO_3^{2-}-2** to **CO_3^{2-}-4**) lead to a higher discrimination of interfering ions; selectivity coefficients for various anions decrease by up to 1.5 logarithmic units (**CO_3^{2-}-2**, log $K^{\mathrm{pot}}_{\mathrm{CO_3,J}}$ (SSM): Cl^-, −5.0; SCN^-, +1.0; SO_4^{2-}, −5.0; NO_3^-, −1.4; phosphate, −5.0; salicylate, +3.3; DOS, TDDMACl).[756] A limit of the lifetime of these electrodes to about one month accompanies this selectivity enhancement, but reactivation by storage in hydrochloric acid and subsequent reconditioning is possible.[756] Interferences by the highly lipophilic salicylate and perchlorate anions could be reduced by using asymmetric membranes with a surface layer of ionophore-free cellulose triacetate, which seems to provide for a kinetic discrimination.[757,758] An alternative approach to alleviate the same interference problem is based on the use of plasticized silicone rubber membranes (trifluoroacetyl-*p*-decylbenzene (**CO_3^{2-}-5**), log $k^{\mathrm{MPM}}_{\mathrm{CO_3,J}}$ (at interfering ion concentration of 0.1 M): Cl^-, −4.0; SCN^-, +0.9; NO_3^-, −0.8; salicylate, +2.1; OH^-, +1.1; silicone rubber, bis(2-ethylhexyl) adipate, TDDMACl).[759] With the purpose of demonstrating the potential of a new alternative to the PVC matrix, the ionophore **CO_3^{2-}-5** was also incorporated into photopolymerized decyl methacrylate-hexanedioldimethacrylate membranes plasticized with DOS.[326]

Recently, the hexyl ester of 4-(trifluoroacetyl)benzoic acid (**CO_3^{2-}-6**) was reported as a carrier for a sulfate sensing electrode.[760] The measured selectivities were however very far from ideal for selective sulfate detection. Furthermore, trifluoroacetophenones were also used as carriers for the neutral analytes alcohol and H_2O (see sections V.5 and V.3, respectively) and the organic anions salicylate,[761] benzoate,[762] and phenylpyruvate[763] (see sections IV.3).

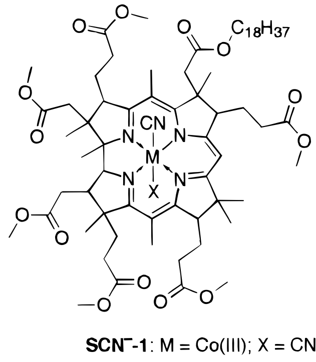
Because the reaction of trifluoroacetophenones with carbonate leads to a loss in the electron delocalization between the carbonyl group and the benzene ring, it is accompanied by a large hypsochromic shift in the UV spectrum of these chromoionophores.[755,764] Taking advantage of this principle, optodes measuring the activity ratio $a_{CO_3^{2-}}/(a_{Cl^-})^2$ or the product $(a_{NH_4^+})^2 \cdot a_{CO_3^{2-}}$ were demonstrated.[765]

Bicarbonate. Whereas carbonate selective electrodes and optodes have attracted much attention, very little is known on bicarbonate selective electrodes. A high selectivity for HCO_3^- was reported for membranes with a very high concentration of tributyltin chloride, which is a compound usually used as ionophore for Cl^-, but unfortunately the requirements for clinical applications have not been quite met.[766] The response slope of -46 mV/decade in the linear range from $10^{-2.5}$ to $10^{-1.2}$ M HCO_3^- casts some doubt on whether this ISE really responds to HCO_3^- and not to CO_3^{2-}. A “bicarbonate-selective” electrode based on a membrane with a H^+ ionophore and an unbuffered internal electrolyte solution should probably be better considered to be CO_2 selective and is discussed below in section V.1.[51,767,768] The same seems also to be true for a “HCO_3^--selective” electrode with tridecylamine as carrier.[769]

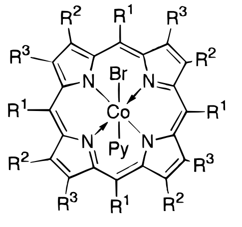
2. SCN^- Sensors

Solid-state thiocyanate-selective electrodes are commercially available but show a large interference from I^- and S^{2-}.[19] For certain applications, such as thiocyanate determinations in serum,[770] ionophore-free ion-exchanger electrodes without a carrier give satisfactory results because the concentrations of potentially interfering ions, such as perchlorate, iodide and nitrate, are very low in the samples of interest (log $K^{pot}_{SCN,J}$ (MSM):[771] ClO_4^-, -0.3; Cl^-, <-3.5; NO_3^-, -1.2; Aliquat 336S, 1-decanol). Nevertheless, more selective ISEs for this analyte are of interest.

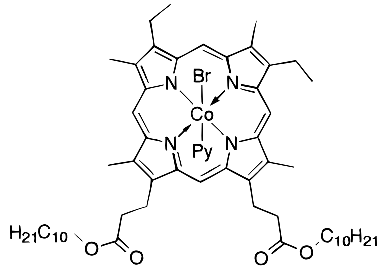
ISEs with trioctyltin chloride as carrier respond strongly to SCN^- but little was done to characterize this selectivity in detail (log $K^{pot}_{SCN,J}$ (SSM): ClO_4^-, -2.7; I^-, -2.6; Cl^-, -3.8; *R*,*R*-2,3-dimethoxysuccinic acid bis(1-butylpentyl) ester, selectivity estimated from log $K^{pot}_{Cl,J}$ indicated in the original paper).[772] Whereas electrodes based on cobyrinate ionophores (**SCN^--1**, **SCN^--2**) show comparable selectivities[773] for SCN^- and NO_2^- and ISEs with a Co(III) porphyrin ionophore (**SCN^--3** to **SCN^--5**) respond quite strongly also to I^-, the only serious interfering ion for several electrodes with a Mn(III) porphyrin ionophore was found to be N_3^- (**SCN^--6**, log $K^{pot}_{SCN,J}$ (SSM): ClO_4^-, -2.0; I^-, -2.3; Cl^-, -3.4; N_3^-, -0.6; NO_2^-, -3.0; **PL-7** (ETH 469), selectivity estimated from log $K^{pot}_{Cl,J}$ indicated in the original paper).[774-776] The choice of the membrane solvent was found to strongly influence the potentiometric performance of membranes based on (tetraphenylporphyrinato) manganese(III) (**SCN^--7**) and molybdenum(V) (**SCN^--8**; a Mo(V) tetraporphyrinate was also reported as carrier of an OH^- ISE; see section III.5) but because no added ionic sites were used in these studies, this result should be interpreted with care.[777,778] Note that the carrier **SCN^--7** has also been used for Cl^-, I_3^-, and salicylate analysis.[779-781] ISEs based on a ruthenium(II) porphyrin ionophore (**SCN^--9**) suf-



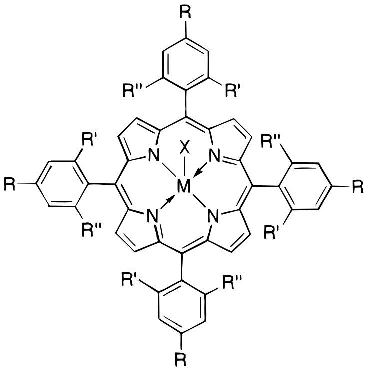
SCN^--1: M = Co(III); X = CN^-
SCN^--2: M = Co(III); X = H_2O



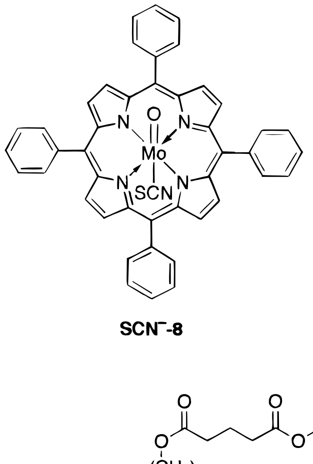
SCN^--3: R^1 = $C_4H_6C(O)OC_6H_{13}$; R^2, R^3 = H
SCN^--4: R^1 = H; R^2 = $(CH_2)_2C(O)OCH(CH_3)_2$, R^3 = CH_3



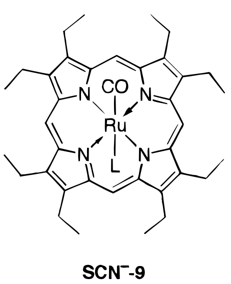
SCN^--5



SCN^--6: M = Mn(III); R = $COOC_6H_{13}$; R', R'' = H; X = Cl^-
SCN^--7: M = Mn(III); R, R', R'' = H ; X = SCN^-
SCN^--10: M = Mn(III); R, R', R'' = C_6H_5; X = Cl^-
SCN^--11: M = Co(III); R'' = $NHC(O)C(CH_3)_3$; R, R' = H; X = ClO_4^-
SCN^--12: M = Co(III); R, R', R'' = H ; X = SCN^-



SCN^--8



SCN^--9

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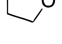
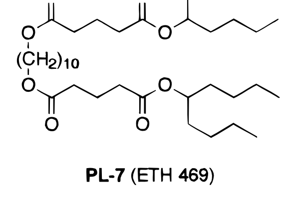
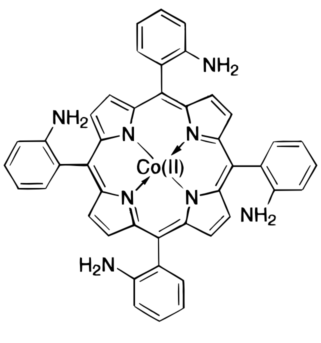




PL-7 (ETH 469)

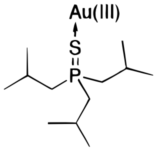
fered from a rather higher interference from ClO_4^- but showed a good discrimination of many other anions (log $K^{pot}_{SCN,J}$ (SSM): Cl^-, −5.6; ClO_4^-, −0.1; I^-, −1.9; NO_2^-, −4.4; oNPOE, tetraoctylammonium bromide, selectivity estimated from log $K^{pot}_{Cl,J}$ indicated in the original paper).[774]

A series of papers has reported on how changes in the axial ligation of Mn(III) and the substitution pattern of the porphyrin ring affect the potentiometric selectivity.[776,782−785] Using sterically very crowded porphyrin derivatives with an axial cavity, the access of the large anions ClO_4^- and IO_4^- to the metal center could be strongly restricted, resulting in a high selectivity for SCN^- (5,10,15,20-tetrakis[2,4,6-triphenylphenyl]porphyrinato)manganese(III) (**SCN^--10**), log $K^{pot}_{SCN,J}$ (SSM): salicylate, −1.6; Cl^-, −4.6; I^-, −3.0; ClO_4^-, −2.3; DBS).[783] A less crowded but markedly hydrophobic environment at the coordination site, on the other hand, was reported to lead to an enhanced response to salicylate.[776] The interpretation of the selectivity obtained with a very crowded Co(III)porphyrin with four *o*-pivalamidophenyl substituents (**SCN^--11**) is less straightforward (log $K^{pot}_{SCN,J}$ (FIM): NO_2^-, −0.7; I^-, −2.8; ClO_4^-, −2.0; oNPOE),[786] the small I^- being more discriminated but NO_2^- interfering more strongly than in case of ISEs based on (tetraphenylporphyrinato) cobalt(III) (**SCN^--12**; log $K^{pot}_{SCN,J}$ (SSM): NO_2^-, −1.1; I^-, −0.9; Cl^-, −3.6; oNPOE; selectivity estimated from log $K^{pot}_{Cl,J}$ indicated in the original paper)[787,788] or **SCN^--3**.[774] A recent investigation with **SCN^--12** showed that ISEs based on this ionophore respond according to a neutral carrier mechanism.[789] A high discrimination of I^- was also reported for electrochemically polymerized cobalt(II) tetrakis(*o*-aminophenyl)porphyrin (**SCN^--13**; log $k^{MPM}_{SCN,J}$: I^-, −3.3).[790] The selectivity of ISEs based on Cu(II) complexes of 1,3-bis(diphenylphosphino)propane) was not very large but results for membranes with added ionic sites have not been reported (log $K^{pot}_{SCN,J}$ (SSM): I^-, −0.9; ClO_4^-, −0.9; oNPOE).[791]

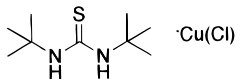


SCN^--13

ISEs based on a 1:1 complex of triisobutylphosphine sulfide and Au(III) (**SCN^--14**) show a fair selectivity for SCN^-,[792] in contrast to I^- electrodes based on the corresponding Ag(I) or Hg(II) complexes. The selectivity for most ions corresponds well with the strength of their coordination to Au(III) (log $k^{MPM}_{SCN,J}$: Br^-, −0.4; Cl^-, −1.9; NO_2^-, −2.2; DOS). The response times of around 20 s are shorter than for the corresponding I^- electrodes. Thiosulfate, I^-, and thiourea poison this electrode. Similar electrodes based on $Cu^I(Cl)L$ salts, where L is a lipophilic thiourea derivative, also resulted in a rather high sensitivity to SCN^- (**SCN^--15,** log $K^{pot}_{SCN,J}$: ClO_4^-, −0.3; Cl^-, −2.9; NO_3^-, −2.9; nitrobenzene, no polymer matrix).[793]

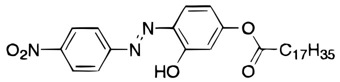


SCN^--14



SCN^--15

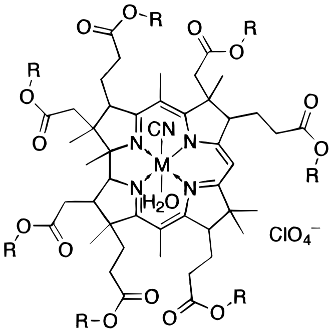
Optodes. The high lipophilicity of SCN^- made the measurement of this analyte in human saliva possible with bulk optodes based on coextraction of SCN^- and H^+, using a H^+ chromoionophore but no carrier for the anion.[794,795] On the other hand, an optode membrane containing a ruthenium(II) porphyrin ionophore (**SCN^--9**) was used to measure the ratio of activities of SCN^- and ClO_4^-.[774] Recently, fluorescence optodes based on **SCN^--9** as SCN^- ionophore and the H^+ chromoionophore ETH 2412 (**H^+-40**) responding to log $[a_{H^+}a_{SCN^-}]$ were demonstrated.[796]



H^+-40 (ETH 2412)

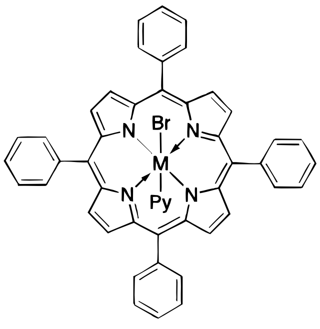
3. NO_2^- Sensors

The first ISEs based on lipophilic derivatives of vitamin B_{12} (**SCN^--1** and **SCN^--2**), a corrin containing a cobalt(III) center, were reported to show a very comparable selectivity for nitrite and thiocyanate, but a high discrimination of perchlorate.[773,797,798] UV−vis absorption spectra showed that water exposure of membranes containing a Co(III) complex with two CN^- ligands results in the exchange of one of these CN^- for an oxygen ligand. Subsequent contact of these membranes to NO_2^- solutions leads to the replacement of the oxygen substituent by NO_2^-. Two similar compounds with much slower ligand-exchange kinetics on the other hand led to potentiometric selectivities comparable to those of blank membranes. Only recently has it been shown unequivocally that these Co(III) aquocyanocobyrinates are charged carriers, as can be seen from the optimum selectivity obtained in the presence of 10−60 mol % KTFPB as anionic additive and the Hofmeister selectivity induced by the presence of 50 mol % TDDMACl (log $K^{pot}_{NO_2,J}$ (SSM): SCN^-, +0.2; Cl^-, −3.7; I^-, −2.2; ClO_4^-, −2.2; oNPOE, KTFPB).[611,789] Given these observations and the fact that CN^- is known to form very stable cobalamin complexes, one may suspect CN^- to interfere strongly with NO_2^- analysis. Indeed, high CN^- concentrations lead to long-term potential drifts of these electrodes.[798] However, 10^{-7} M concentrations of this ion were found to be tolerable irrespective of the nitrite concentration in the sample. An improved lifetime but almost identical selectivities were obtained with more lipophilic derivatives (e. g. **NO$_2^-$-1**),[799] which were also used to demonstrate selective anion transport through solvent polymeric membranes.[800,801] Use of cobyrinate carriers in microelectrodes resulted in slightly reduced selectivities as compared to macroelectrodes, as often observed for this type of electrode.[802]



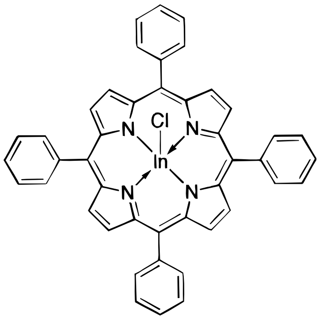
NO$_2^-$-1: M = Co(III); R = CH$_2$CH$_2$C$_6$H$_5$

Selectivity patterns do not change drastically when the corrin-ring system of vitamin B$_{12}$ is replaced by a porphyrin ring but the Co(III) as center is retained; only discrimination of iodide becomes slightly inferior.[775,787,803,804] For one of these carriers, ligand exchange kinetics were investigated and found to be very fast.[803] In contrast to the cobalt(III) cyanocobyrinate, the systematic use of added charged sites showed chloro(tetraphenylporphyrinato)cobalt(III) to be a neutral carrier, giving an optimal selectivity only when the ISE membranes contain cationic additives or no added ionic sites at all but not when they contain anionic additives.[789] However, the response in absence of added charged sites was observed to be only short-lived. The much improved selectivity over chloride when using **NO$_2^-$-2**, which has a bromide ion and a pyridine group as axial ligands on the cobalt(III) center, had been originally suspected to be due to the choice of the plasticizer, but recent studies on the role of the axial ligands of (tetraphenylporphyrinato)cobalt(III) carriers indicated that site theory may explain this finding as follows:[804] The formation of $\sigma-\pi$ bonds between nitrite and Co(III), which seems to explain the high selectivity of these carriers, destabilizes the binding of axial pyridine ligand. Upon dissociation of this organic ligand, the pyridine can be protonated and function as sites that temporarily improve the sensor performance until they are washed out of the membrane due to their relatively high hydrophilicity. The large strength of the bond between nitrite and Co(III) also explains why (tetraphenylporphyrinato)cobalt(III) salts with anions that form only weak bonds to the metal center are not suitable as sensor components in the absence of cationic sites. Such salts can dissociate within the membrane, giving charged carriers for nitrite. Upon exposure of such membranes to sample solutions, nitrite ions enter and the initially present anions leave the membrane, leading temporarily to super-Nernstian slopes. When this ion exchange with the aqueous solution is completed, a large neutral carrier concentration is obtained but in the absence of cationic sites no further nitrite ions may enter the membrane, and complexes with two NO$_2^-$ ligands cannot be formed.



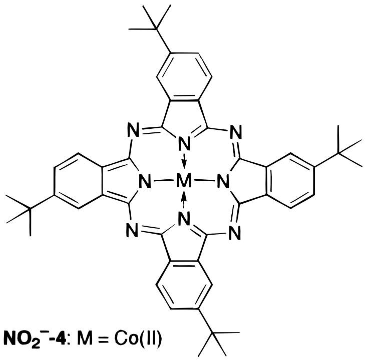
NO$_2^-$-2: M = Co(III)

Replacing the Co(III) for In(III) (**NO$_2^-$-3**) does not affect the high nitrite selectivity but was found to give a relatively strong response to fluoride (log $K^{\mathrm{pot}}_{\mathrm{NO_2,J}}$ (SSM): SCN$^-$, -1.0; Cl$^-$, -1.8; I$^-$, -1.0; ClO$_4^-$, -2.4; F$^-$, -1.2; didecyl sebacate).[805] The same study also describes the influence of methoxy and nitro substituents on selectivities. Partly sub-Nernstian slopes were reported and it would be interesting to know the effect of added sites on selectivities of ISEs with these In(III) ionophores. Interestingly, a recent study[789] has shown that the very similar compound chloro(octaethylporphyrinato)indium(III) (**Cl$^-$-4**; see section III.10),[806] which provides a smaller discrimination of Cl$^-$ (log $K^{\mathrm{pot}}_{\mathrm{Cl,NO_2}}$(SSM): $+0.3$; oNPOE, 30 mol % KTFPB) and gives super-Nernstian slopes even in the presence of anionic sites, functions as a charged carrier. Finally, it should be mentioned that OH$^-$ gives a serious interference in nitrite sensing with metalloporphyrins, often making measurements at low pH mandatory.[804] As HNO$_2$ is only a weak acid (pK_a = 3.37), one is, however, often limited to a fairly narrow pH range for nitrite measurements.



NO$_2^-$-3

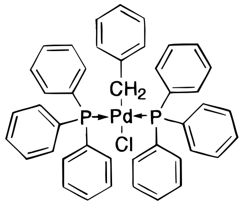
In a further variation of the Co(III) theme, the corrin ring was replaced by phthalocyanine (**NO$_2^-$-4**, log $K^{\mathrm{pot}}_{\mathrm{NO_2,J}}$ (SSM): SCN$^-$, -1.0; Cl$^-$, -3.5; I$^-$, -1.6; ClO$_4^-$, -1.6; DBP, hexadecyltrioctylammonium iodide).[807,808] The relatively good discrimination of thiocyanate seems very promising. Although a Co(II) salt was used to prepare these ISE membranes, the change in membrane selectivities upon addition of cationic sites indicates a charged-carrier mechanism, which was speculated to be due to oxidation of the metal center to Co(III). A version of this electrode with an electrochemically polymerized membrane was reported as well.[809] Interestingly, a change of the metal center for Cu(II) resulted in Hofmeister selectivities. Note that a very similar compound was also reported as phosphate carrier (**phosphate-7**, see section III.6).[810,811]



NO_2^--4: M = Co(II)

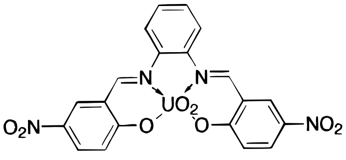
The Co(III) center does however not guarantee nitrite selectivity, as shown by use of an ionophore similar to the above-mentioned corrins, in which a peripheral lactone ring and a proximal base, reminding of vitamin B_{12}, are introduced (**I^--2**).[812,813] The result is a high selectivity for iodide. Similarly, an ISE based on electrochemically polymerized cobalt-(II) tetrakis(*o*-aminophenyl)porphyrin is selective for thiocyanate.[812]

Recently, palladium complexes have been shown to be a very promising new class of NO_2^- ionophores.[814] The use of cationic and anionic added sites in potentiometric measurements and preliminary electrodialysis experiments have suggested that both charged and neutral carrier mechanisms are possible for such ionophores. A mixed-mode response mechanism was suggested as a probable explanation for the non-Nernstian slope of ≈−74 mV/decade found for an electrode based on benzylbis(triphenylphosphine)palladium(II) chloride (**NO_2^--5**; log $K^{pot}_{NO_2,J}$ (SSM): SCN^-, +0.6; Cl^-, −1.8; I^-, +0.5; ClO_4^-, +0.1; salicylate, −0.8; oNPOE, TDDMACl). A particular advantage of the latter electrode is the lack of a response to H^+ and OH^- in the range of pH 3.5−12.



NO_2^--5

Another very new class of NO_2^- ISEs is based on complexes of UO_2^{2+} as Lewis acidic binding sites.[815] Among six very similar compounds, a dinitro-substituted UO_2-salophen (**NO_2^--6**; log $K^{pot}_{NO_2,J}$ (SSM): Br^-, −2.6; SO_4^{2-}, −2.8; ClO_4^-, −1.5; BBPA, TDDMACl) was found to provide the highest selectivity for NO_2^-, which seems to be the result of the electron-withdrawing nitro groups. The discrimination of Cl^-, being of particular concern for possible applications, is quite high when using electrodes based on this ionophore (log $K^{pot}_{NO_2,J}$ (SSM): NO_3^-, −2.4; Cl^-, −2.5; $H_2PO_4^-$, −2.3; BBPA, no added sites; selectivity estimated from log $K^{pot}_{NO_3,J}$ indicated in the original paper). Because $H_2PO_4^-$ forms stronger complexes with **NO_2^--6** than Cl^-, NO_2^-, SO_4^{2-} and NO_3^-, it is not surprising that $H_2PO_4^-$ gives a stronger response than in case of ionophore-free ion-exchanger electrodes. The high hydrophilicity of $H_2PO_4^-$ explains, however, why there is no serious interference from this anion.



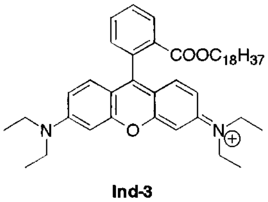
NO_2^--6

Nitrite-selective membranes find an interesting application as internal sensor element in Severinghaus-type sensors for NO_x.[812,816] Nitrogen oxide (NO_x) permeates across a gas-permeable membrane that separates the sample from a pH-buffered inner solution, in which NO_x disproportionates. As a result, nitrite is formed and is measured with a nitrite-selective electrode. The internal detection eliminates interferences from nitrate, acetate, salicylate, bicarbonate, benzoate, and chloride.

Optodes. In view of the many publications on nitrite-selective electrodes and the various UV−vis spectroscopy-based studies of the complexation of these carriers, it seems astonishing that so far very few efforts were aimed at nitrite-selective optodes. A recent report on such a sensor, based on a electrochemically deposited cobalt(II) porphyrin, gives the very low detection limit of 6×10^{-9} M. A disadvantage of this sensor is unfortunately its large response time in the range from 15 to 35 min.[817]

Two fluorescence optodes based on the ionophore **NO_2^--1** and either the H^+ chromoionophore ETH 2439 (**H^+-9**) or ETH 5350 (**H^+-11**) give further examples for the tunability of the dynamic response range of coextraction based optodes by choosing an appropriate H^+ chromoionophore.[796] Diffusion of unbleached chromoionophore from nonirradiated parts of the sensor membrane into the photoexcitation zone continuously replaces photobleached ionophore, increasing the lifetime of these fluorescence sensors.

The organopalladium ionophore **NO_2^--5** has recently been incorporated together with the fluorescent rhodamine B octadecyl ester (**Ind-3**) into PVC-based fluorescence sensors, resulting in good selectivities for nitrite (log $k^{Osel}_{NO_2,J}$ (SSM): NO_3^-, −2.1; Cl^-, −2.8; SO_4^{2-}, <−3.5; oNPOE, **Ind-3**, pH 7.13).[818] It was argued that microemulsions are formed in such sensor membranes, which was expected to shorten response times. However, the



Ind-3

response times of 10−15 min for this optode are fairly long as compared to those of other optode membranes with similar thicknesses.

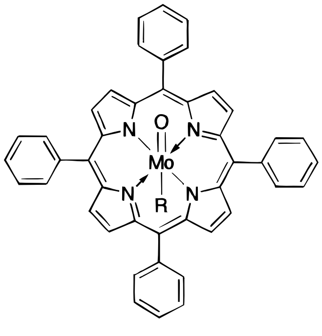
4. NO_3^- Sensors

Numerous reports on the development and application of nitrate ISEs[13,55] were given and a few bulk membrane optodes were described as well.[819,820] Almost all of these sensors are based on ion exchangers that provide Hofmeister-type selectivities.[820,821] Typically, salts of tris(1,10-phenanthroline)nickel(II) or tris(4,7-diphenyl-1,10-phenanthroline)nickel(II) are used.[822] However, it is evident from the potentiometric selectivities and from crystal structures, such as of tris(1,10-phenanthroline)nickel(II) nitrate,[823] that there is no specific interaction between typical anions and these nickel(II) complex dications. Because of the fairly high lipophilicity of nitrate, such electrodes are nevertheless often sufficiently selective and have found many applications, such as for measurements in food, fertilizers, plant tissues, soils, or wastewater. They are probably the largest-selling anion electrodes outside the medical field. However, use of reagents to reduce interferences from certain interfering ions, such as for precipitation of chloride or hydrolysis of pyrophosphate, were necessary in several cases.[824,825] "Standard Methods",[826] for example, recommends using a buffer solution containing Ag_2SO_4 to remove Cl^-, Br^-, I^-, S^{2-}, and CN^-, sulfamic acid to remove NO_2^-, a buffer at pH 3 to eliminate HCO_3^- and to maintain a constant pH and ionic strength, and $Al_2(SO_4)_3$ to complex organic acids. The lack of nitrate ionophores makes worth mentioning molecular imprinting, which is a very different approach to achieve potentiometric selectivity. It was realized by polymerization of pyrrole in the presence of a nitrate salt, producing films with pores that are complementary to the analyte. High potentiometric selectivities for nitrate over larger lipophilic anions, such as salicylate or perchlorate, were demonstrated.[827]

5. OH^- Sensors

While interference from the hydroxide ion has been reported for several anion selective electrodes with an organometallic ionophore, little is known on hydroxide selective electrodes. Because the activities of H^+ and OH^- in aqueous samples depend on each other, an emf response alone does not allow distinguishing between responses to H^+ and OH^-. Plots of the emf versus the H^+ or OH^- activity give both reasonable response slopes for the respective species. Also the investigation of carrier-based membranes with anionic or cationic sites, as recently repeatedly used for distinguishing between neutral and charged carrier-based response mechanisms, would not allow differentiation between H^+ and OH^- responses. Anionic sites, for example, have been shown to be beneficial for neutral carrier-based H^+-selective electrodes but would also be expected to improve selectivities of OH^--selective electrodes based on a cationic carrier.

An ISE based on Nitron 8-hydroxyquinoline-5-sulfonate (**H^+-3**) was reported to be selective for hydroxide ions.[43] However, it may actually rather respond to H^+, the influence of anions other than the hydroxide ion being a counterion effect. No OH^--carrier function of **H^+-3** is apparent. More evident seems to be the case of a membrane-coated wire electrode with oxomolybdenum(V) tetraphenylporphyrin as active compound (**OH^--1**; besides axial ligand identical to **SCN^--8**), which was found to respond to a variety of anions (log $K_{SCN,J}^{pot}$ (FIM): ClO_4^-, +1.6; NO_2^-, +1.3; F^-, +0.1; OH^-, +6.2; bis(2-ethylhexyl) adipate) but not to cations.[828] The OH^- carrier function of **OH^--1** seems confirmed by the isolation of its hydroxide complex. The highly selective and nearly Nernstian response to OH^- may, however, alternatively be interpreted as the deprotonation of the hydrated, electrically charged ionophore, and as such as a response to H^+. A comparison of the activity of free H^+ and OH^- in the electrode membrane might be used as an arbitrary guideline to distinguish between H^+ and OH^- selective electrodes, but so far such a criterion has not been used.

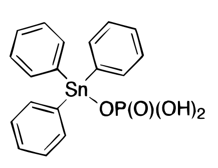


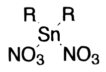
OH^--1: R = OCH_2CH_3

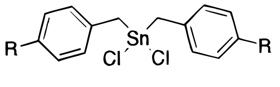
6. Phosphate Sensors

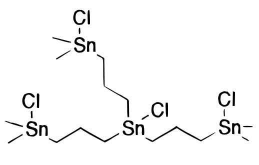
Due to the very high hydration energy of phosphate, ion exchanger based electrodes have a very poor selectivity for phosphate, even when membrane components with potentially hydrogen bond donating groups are used.[829,830] Interestingly, ionophore-free ion-exchanger electrodes discriminate pyrophosphate and tripolyphosphate much less than orthophosphate,[825] a trend that is analogously also observed for nucleotides.[831] Phosphate ionophores can be classified into four types, that is, organotin compounds, Co(II) and Ni(II) complexes, and cyclic polyamines.

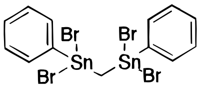
The carrier property of organotin compounds is based on coordination of the tin center with HPO_4^{2-}, the organic substituents on the metal center governing the anion selectivity. The idea of using organic tin(IV) compounds for phosphate selective electrodes was inspired by the observation that triphenyltin compounds are good reagents for phosphate extraction.[832] First attempts with triphenyltin dihydrogenphosphate (**phosphate-1**) as carrier resulted in a quite good sensitivity but poor selectivities and very slow responses (see also use of triphenyltin chloride for Cl^- ISEs).[833] Indeed, most phosphate selective organotin compounds have only two organic substituents on the tin center. In contrast, trialkyltin carriers are often selective for Cl^-. Dialkyltin dinitrate ionophores (**phosphate-2**) were reported to give the sought-after selectivity pattern, with a slight preference for HPO_4^{2-} over $H_2PO_4^-$. The discrimination of other anions was found to increase in the series of octyl, nonyl, and lauryl with the length of the alkyl chain.[834,835] Interestingly, these electrodes were also reported[835,836] to strongly respond to arsenate. ^{119}Sn NMR spectroscopy has shown that dioctyltin dichloride forms 2:1 complexes as well as 1:1 and/or oligomer complexes with HPO_4^{2-}.[837] While later efforts to make phosphate selective electrodes with dialkyltin salts were unsuccessful, they resulted in the suggestion of derivatives of dibenzyltin dichloride as carriers for HPO_4^{2-} (**phosphate-3**, log $K^{\text{pot}}_{\text{HPO}_4,\text{J}}$ (FIM): Cl^-, 0.0; NO_3^-, +1.0; I^-, +2.1; Br^-, +0.3; OAc^-, −0.1; DBS; pH 7.0 (Tris buffer adjusted with H_2SO_4), response slope for HPO_4^{2-} −33.0 mV/decade).[838,839] The investigation of dibenzyl tin dichlorides with several substituents in the para position of the benzene ring indicated an increase of the phosphate selectivity with an increase of the Hammett constant of the substituent (bis(*p*-fluorobenzyl)-tin dichloride (**phosphate-4**), log $k^{\text{MPM}}_{\text{HPO}_4,\text{J}}$: Cl^-, −4.2; NO_3^-, −3.5; I^-, −2.2; Br^-, −3.1; OAc^-, −3.2; DBS; pH 7.0 (Tris[hydroxymethyl]aminomethane buffer adjusted with H_2SO_4), response slope for phosphate −31.5 mV/decade).[840,841] Electrodes based on bis(*p*-chlorobenzyl) tin (**phosphate-3**) or bis(*p*-fluorobenzyl) tin (**phosphate-4**) carriers were also shown to strongly respond to the highly hydrophilic, tribasic citrate. The mechanism of this response was not clarified, but seems to be somewhat different from the phosphate response as no correlation with the electronegativity of the substituents on the benzyl rings was found.[841] The most serious limitation of all dibenzyltin electrodes is their functional lifetime, which is limited by degradation of the response within days. An excellent selectivity (phosphate > Sal^- > ClO_4^- > NO_3^- > SO_4^{2-} > Cl^- > Br^- > SCN^- > NO_2^-) was recently reported for a multidentate carrier with four tin centers (**phosphate-5**) but here the sensor lifetime of less than 1 day was even shorter (response slope for phosphate −40 mV/decade at pH 5.5; −30 mV/decade at pH 8.5).[842] Unfortunately, information on lifetimes has not been reported for a series of ISEs based on one of several distannyl derivatives, among which some gave good selectivities (e. g. **phosphate-6**, log $K^{\text{pot}}_{\text{H}_2\text{PO}_4,\text{J}}$ (SSM): ClO_4^-, −3.3; NO_3^-, −3.6; I^-, −3.3; SCN^-, −2.0; DOS, pH 5.5 (MES buffer adjusted with NaOH), response slope for phosphate −53.1 mV/decade).[843]


phosphate-1

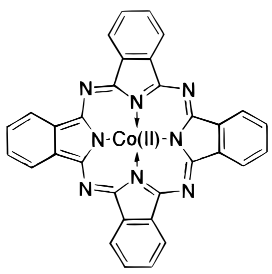

phosphate-2: R = C_8H_{17}, C_9H_{19} or $C_{12}H_{25}$


phosphate-3: R = Cl
phosphate-4: R = F

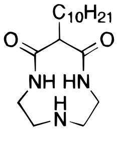

phosphate-5


phosphate-6

Cobalt phthalocyanine (**phosphate-7**) was used as an ionophore for phosphate, resulting in interesting selectivities (log $K^{\text{pot}}_{\text{H}_2\text{PO}_4,\text{J}}$ (FIM): NO_3^-, −2.1; I^-, −1.3; OAc^-, −2.8; Br^-, −1.9; Cl^-, −1.2; DOS) and non-Nernstian slopes (−45 mV/decade).[810,811] Note, however, that a very similar compound has recently been used for potentiometric NO_2^- measurements, the selectivity for phosphate not being reported explicitly but phosphate being used as a component of the pH buffer.[807] ISEs with membranes containing mixed ligand Ni(II) complexes (Ni[dike][diam] where dike = *β*-diketonate, diam = *N*,*N'*-di-, tri-, or tetra-alkylated ethylenediamine) were found to respond to phosphate with response slopes of −21 mV/decade but selectivities were not commented (note a similarity to dodecyl sulfate ISEs based on Cu(II) complexes of ethylenediamine derivatives;[844] see section IV.6).[845,846]


phosphate-7

Polyamines form a special group of phosphate carriers because they have no metal center.[847] Among four macrocyclic polyamines, a macrocycle with one secondary amine and two lactam groups was claimed to give the highest selectivity for phosphate (**phosphate-8**, log $K^{\text{pot}}_{\text{HPO}_4,\text{J}}$ (modified SSM): NO_3^-, −2.8; SO_4^{2-}, −3.0; OAc^-, −3.2; SCN^-, −2.3; Cl^-, −2.3; DBS, at pH 7.2 response slope for phosphate −28.9 mV/decade), giving a Nernstian response down to 10^{-6} M HPO_4^{2-}. The authors suggest that this ionophore is doubly protonated in its active form, which seems however unlikely in view of the p*K* of the lactam groups. It would therefore be very interesting to know the influence of added anionic sites on the lifetime and selectivity of this ionophore.

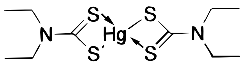

phosphate-8

7. Sulfide Sensors

Potentiometric sulfide detection is most often performed with solid-state membranes,[19] but use of ISE membranes based on electrochemically polymerized binaphthyl-20-crown-6 (linear range 2 × 10^{-7} to 2 × 10^{-5} M; response slope −110 mV/decade)[848] or an electrochemically deposited phthalocyanine have also been reported (linear range 1 × 10^{-6} to 1 × 10^{-2} M; response slopes for several electrodes between −61 and −92 mV/decade).[849] Decomposition of the latter sensing films at high pH was reported as a problem but could be avoided when using electrochemically polymerized tetraaminophthalocyanatocobalt(II) instead, which also responds to 2-mercaptoethanol.[850] Solvent polymeric carrier-based ISEs and optodes have however so far not been reported for this analyte.

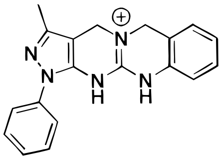
8. Sulfite Sensors

Sulfite ISEs based on bis(diethyldithiocarbamato)mercury(II) (**sulfite-1**) provide for an excellent selectivity over many common, nonreducing anions. Their response mechanism was originally conceived as being of the neutral carrier type (log $k^{\mathrm{MPM}}_{\mathrm{SO_3,J}}$ (separate solution, matched potential method): NO_2^-, ≤−4; OAc^-, ≤ −4; SCN^-, 0.0; Br^-, 0.0; Cl^-, ≤ −4, I^-, +7.0; $S_2O_3^{2-}$, +0.5; pH 10, DBP; sulfide strongly interferes).[851] The selectivities of these ISEs, the effect of conditioning, extent of ionophore leaching, and the influence of stirring rate, ionophore and plasticizer content on the emf response suggest, however, a response based on reduction of the metal center to Hg(I) by sulfite.[852] Therefore, the potentiometric response is kinetic in nature and determined by mass transfer to and from the membrane surface. Use of a gas-permeable membrane allows further improvement on the selectivity and was used in flow injection analysis (FIA) to demonstrate sulfur dioxide and thus indirect sulfite detection in wine.[852] Owing to short contact times between membrane and sample, FIA also reduces the Hg(II) consumption, which leads to an improved sensor lifetime.



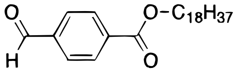
sulfite-1

A more conventional ISE based on a guanidinium derivative (**sulfite-2**) as charged ionophore was shown to give a surprisingly high discrimination of lipophilic anions such as salicylate and ClO_4^- (log $K^{\mathrm{pot}}_{\mathrm{HSO_3,J}}$ (FIM): ClO_4^-, −2.2; salicylate$^-$, −2.3; Cl^-, ≤−3.0; pH 6.0, oNPOE).[853] The emf response had a slope of −47 ± 2 mV/decade, changed only slightly with pH, and was interpreted as a sub-Nernstian response for HSO_3^- rather than as a response to the divalent SO_3^{2-}. The counterion of the ionophore being BF_4^-, the lifetime of this ISE is limited to a few days but an investigation to eliminate this disadvantage was reported to be in progress.



sulfite-2

Optodes. In contrast to the guanidine derivative **sulfite-2**, the carrier **sulfite-3** (octadecyl-4-formylbenzoate; ETH 5444) of an optode reported for hydrogen sulfite is not electrically charged (log $k^{\mathrm{Osel}}_{\mathrm{HSO_3,J}}$ (SSM): ClO_4^-, 0.0; SCN^-, −0.3; Cl^-, −2.3; NO_3^-, −1.7; pH 7.9, oNPOE, PVC−OH, ETH 5350 (**H^+-11**)).[854] The analyte reversibly binds, by formation of a covalent bond, to the aldehyde group of the carrier. Similar recognition mechanisms are the basis of ethanol, humidity, and CO_3^{2-} sensors with trifluoroacetophenone derivatives as ionophores (**ALC-1**, **CO_3^{2-}-1** to **CO_3^{2-}-6**; see sections III.1, V.3, and V.5). Response times are in the range of several minutes. For measurements at low pH, PVC/DOS membranes were found to be more suitable than OH-PVC/oNPOE membranes, because many inorganic acids are more strongly extracted into the latter. Unfortunately, the selectivity of the PVC/DOS optodes is smaller. The same carrier can also be employed for SO_2 detection down to 4 ppb$_v$ in humid gas samples (see section V.4).[855]

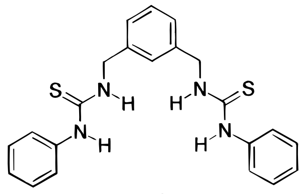


sulfite-3 (ETH 5444)

9. Sulfate Sensors

A number of solid-state and ionophore-free ion-exchanger electrodes have been reported but, lacking adequate selectivities, none of them has been very satisfactory.[829] The use of triphenyllead salts as carriers led to only very short sensor lifetimes, and because very poor selectivities were found it was concluded that Ph_3Pb^+ does not act as a sulfate carrier.[856] ISEs containing trifluoroacetyl-4-butylbenzene (**CO_3^{2-}-1**) or (trifluoroacetyl)benzoic acid hexyl ester (**CO_3^{2-}-6**), the latter being a homologue of a CO_3^{2-} ionophore mentioned above, were reported as sulfate sensing electrodes but selectivities were poor.[760,857] Furthermore, titrimetric sulfate determination is possible by end-point detection with Pb^{2+}-selective electrodes.[858]

The use of α,α′-bis(*N*′-phenylthioureylene)-*m*-xylene (**SO_4^{2-}-1**) as ionophore gives an ISE with a very unusual selectivity for sulfate.[859] It responds to sulfate in a Nernstian manner in the concentration range from 10^{-6} to 10^{-2} M. In comparison to ionophore-free anion-exchanger electrodes, the interference from SCN^-, NO_3^-, Br^-, and Cl^- is significantly reduced (log $k^{\mathrm{MPM}}_{\mathrm{SO_4,J}}$ (for a step of the primary ion concentration from $10^{-3.0}$ to $10^{-2.0}$ M): SCN^-, +2.9; NO_3^-, +1.6; Br^-, +1.1; Cl^-, −0.1; oNPOE, TDDMACl). Cl^- interferes significantly at high concentrations but because the Cl^- and SO_4^{2-} responses



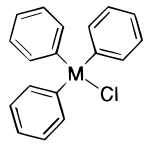
SO_4^{2-}-1

have different slopes sample dilution might be used to bring the Cl^- concentration in a range where there is no Cl^- response but where there is still a Nernstian response to SO_4^{2-}.

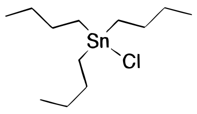
10. Cl^- Sensors

The use of solid-state Cl^- selective electrodes based on AgCl is limited by a relatively unsatisfactory selectivity and, in the case of biological samples, the interference by proteins that bind through their sulfur groups to Ag^+ and adsorb to the electrode surface.[19,186,806,860] Liquid ionophore-free ion-exchanger ISEs based on tetraalkylammonium chloride,[19,861] on the other hand, have been used widely in clinical chemistry for blood, urine, and sweat[862] samples and in physiology for intracellular measurements (microelectrodes). Bicarbonate interference is however a shortcoming (log $K^{pot}_{Cl,J}$ (SSM):[863] ClO_4^-, +3.7; NO_3^-, +1.6; NO_2^-, +0.7; HCO_3^-, −1.0; Br^-, +1.0; SO_4^{2-}, −1.7; TDDMACl, PVC, no plasticizer; log $K^{pot}_{Cl,J}$ (SSM):[776] ClO_4^-, +4.6; SCN^-, +3.0; I^-, +2.8; salicylate, +2.7; Br^-, +0.6; TDDMACl, PVC, DBS).[332,766,863] Although the interference of lipophilic anions can be considerably reduced by using ion-exchange type ISEs based on plasticizers with alcohol functions (log $K^{pot}_{Cl,J}$ (SSM):[864] ClO_4^-, +1.1; NO_3^-, +0.5; SCN^-, +1.3; HCO_3^-, −0.7; Br^-, +1.0; SO_4^{2-}, −2.1; oNPOE, higher aliphatic alcohol, *N*-methyl-*N*,*N*-dioctadecyl-*N*-octadecylammonium chloride),[863–865] the development of Cl^- selective electrodes based on carriers is still of prime interest. For this purpose a wide variety of metal ion complexes have been investigated.

Tin organic compounds belong to the earliest carriers used for Cl^- ISEs (triphenyltin chloride; **Cl⁻-1**)[866] but were also used for phosphate-selective electrodes. In general, trialkyltin compounds give an analytically relevant selectivity for Cl^-, whereas for dialkyl- or diaryltin compounds phosphate selectivity is found. NMR spectroscopy shows a direct interaction of Cl^- with the tin center and was used to determine the strength of the relatively weak, negatively charged complex in which the tin center is pentacoordinated (for trioctyltin chloride and Cl^- in $CDCl_3$: 52 M^{-1}; for tributyltin chloride (**Cl⁻-2**) and Cl^- in chlorobenzene: 1.1×10^3 M^{-1}). The order of the latter was confirmed by vapor pressure osmometry.[772,867,868] While a charged carrier mechanism is also conceivable, electrodialytic transport experiments indicated a response mechanism based on a neutral carrier.[837] Pentacoordination was also confirmed by ^{13}C and ^{119}Sn NMR spectroscopy.[772,867,869] However, the inorganic substituent on the tin center of many trialkyltin carriers gets exchanged and thus reflects the composition of the sample solution. This ligand exchange alters the structure of the neutral ionophore and is probably accounting for the long response times and unstable potentials often observed for ISEs with these ionophores.[870] This problem can only partly be eliminated by using nucleophiles as membrane additives (log $K^{pot}_{Cl,J}$ (SSM): NO_3^-, −0.9; HCO_3^-, −1.9; Br^-, +0.1; SO_4^{2-}, −1.3; I^-, +0.8; SCN^-, +0.6; OAc^-, −0.1; phosphate, −4.8; diethylhexyltin acetate, octadecanethiol, BBPA).[871] It has however recently been shown that more reproducible measurements can be made by using flow-injection analysis, which allows to recondition the electrode after each sample and to correct more easily for potential drifts (trioctyltin chloride, log $K^{pot}_{Cl,J}$ (SSM): NO_3^-, −2.1; Br^-, +0.3; I^-, +2.0; SCN^-, +1.4; OAc^-, −0.1; ClO_4^-, −1.4; BBPA).[872]



Cl⁻-1: M = Sn
Cl⁻-10: M = Ge

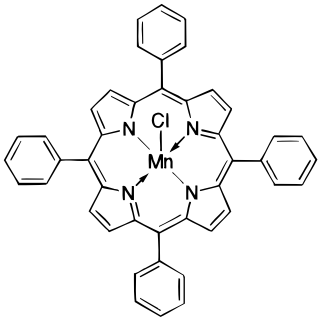


Cl⁻-2

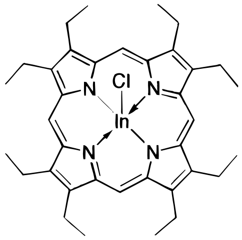
The selectivities of trialkyltin chloride based ISEs depend heavily on the carrier concentration.[870] Sodium tetraphenylborate and a quarternary ammonium salt (TDDMACl) in concentrations of a few mole percent relative to the tin compound were both found to worsen selectivities.[868] The use of a tetraphenylborate salt of Capriquat with impurities (Capriquat is known to contain besides trioctylmethylammonium chloride several other tetraalkylammonium salts)[873] or a carrier concentration effect may be responsible for the fairly different selectivities found with coated wire electrodes (trioctyltin chloride, log $K^{pot}_{Cl,J}$ (SSM): NO_3^-, 0.0; Br^-, +0.4; I^-, ≥5.0; SCN^-, +3.0; OAc^-, −0.9; SO_4^{2-}, −2.1; tetraphenylborate salt of Capriquat, 1-octadecanol, triphenyl phosphate).[505] Triphenyltin chloride, the first reported carrier of this class,[866] was not very successful when used in later studies,[833,870,874] probably because of the low stability of the complex of Cl^- and triphenyltin chloride.[869] Similarly, Cl^- was reported not to bind to tetraalkyltin compounds.[869]

Another very early Cl^--selective electrode was based on the use of $Cu^I(Cl)L$ salts, where L is a lipophilic thiourea derivative. Using chloroform as membrane solvent resulted in quite a high sensitivity to chloride, whereas a change to nitrobenzene led to high preference for ClO_4^- over Cl^- (log $K^{pot}_{Cl,J}$: NO_3^-, −1.0; ClO_4^-, +0.7; L = *N*,*N′*-di-*tert*-butylthiourea, chloroform).[793] The SCN^- interference was however large (log $K^{pot}_{SCN,Cl}$: −1.6).

Microelectrodes based on chloro(5,10,15,20-tetraphenylporphyrinato)manganese(III) (**Cl⁻-3**)[779] offer a higher discrimination of acetate and HCO_3^- (log $K^{pot}_{Cl,J}$ (SSM): HCO_3^-, −1.5; NO_3^-, +1.2; Br^-, +0.9; I^-, +2.4; SCN^-, +3.4; OAc^-, −1.3; ClO_4^-, −3.6; tetradodecylammonium tetrakis(*p*-chlorophenyl)borate (ETH 500), oNPOE) than the often used ionophore-free ion exchanger microelectrodes. Interference from I^- and SCN^- is no serious problem for most applications (cf. use of this and very similar carriers for SCN^- and salicylate ISEs) but it was reported that some individual electrodes exhibit a pH sensitivity at pH > 7.6. Because the selectivity coefficients for most anions other than acetate and SO_4^{2-} fall into a smaller range than those of ionophore-free anion-exchanger ISEs, this microelectrode is also well suited as detector for capillary electrophoresis.[875] Asymmetric cellulose acetate membranes were used to reduce the interference of large ions such as salicylate on macroelectrodes with this ionophore.[758] Similar results were reported for CO_3^{2-} electrodes. Replacement of the Mn(III) by an In(III) center was shown to lead to a larger discrimination of ClO_4^-, SCN^-, and salicylate and a response slope of −80 to −85 mV/decade. With an ISE based on a corresponding octaethyl derivative (**Cl$^-$-4**), Cl^- in human serum samples was measured (log $K^{\mathrm{pot}}_{\mathrm{Cl,J}}$ (SSM): HCO_3^-, −2.2; Br^-, +0.3; I^-, +1.6; SCN^-, +0.9; OAc^-, −1.4; salicylate, +1.6; oNPOE; pH 7.2).[806] Depending on the number of charged axial substituents of this carrier, both a charged and a neutral carrier response mechanism seemed conceivable. An increase in the selectivity of ISEs with this carrier upon use of anionic sites and a selectivity decrease in the presence of cationic sites shows, however, that **Cl$^-$-4** is a charged carrier (log $K^{\mathrm{pot}}_{\mathrm{Cl,J}}$ (SSM): I^-, +0.9; SCN^-, +1.4; salicylate, +2.2; NO_2^-, +0.3; NO_3^-, −3.8; oNPOE, 30 mol % KTFPB).[789]

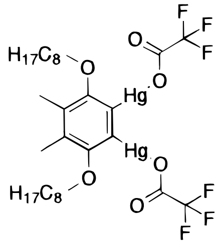


Cl$^-$-3

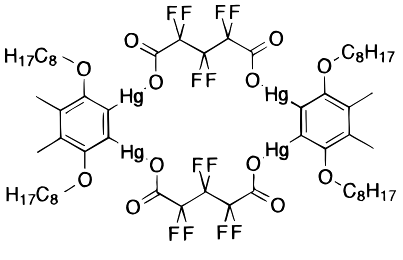


Cl$^-$-4

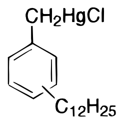
Very good selectivities for Cl^- were obtained with two organomercury compounds as neutral carriers, which prefer Cl^- over SCN^-, ClO_4^-, NO_3^-, and salicylate (**Cl$^-$-5**, log $K^{\mathrm{pot}}_{\mathrm{Cl,J}}$ (SSM): HCO_3^-, −5.5; Br^-, +0.0; I^-, +1.0; SCN^-, −0.2; HPO_4^{2-}, −5.9; salicylate, −0.4; DOS, TDDMACl).[876] For a macrocyclic tetramercury carrier (**Cl$^-$-6**), ^{199}Hg NMR titrations showed the formation of 1:4 complexes with both Cl^- and SCN^- but, interestingly, the selectivities obtained with membranes containing this compound differed only slightly from those for membranes with the nonmacrocyclic dimercury carrier. A recent investigation of various organomercury compounds has confirmed adequate selectivities for physiological measurements[877] but found a limited stability of all ionophores with acetoxy or trifluoroacetoxy substituents on the mercury centers. While the ionophores with chloro substituents proved to be more stable, they too are still prone to substituent exchange. This leads to the formation of new ionophoric species and a dependence of the ISE selectivity on the sample composition. In agreement with findings of an earlier, fruitless investigation on ISEs with dodecylbenzylmercury(II) chloride (**Cl$^-$-7**) as carrier,[1] organomercury compounds with only one Lewis center did not show any ionophoric properties.[877] Note also the use of mercurated polystyrene with RC_4H_4HgOAc groups (**SF-2**) for detection of anionic surfactants (see section IV.6).[878,879]



Cl$^-$-5

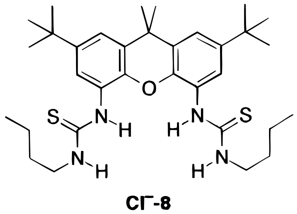


Cl$^-$-6



Cl$^-$-7

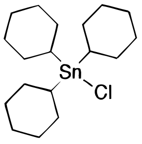
A highly preorganized bis-thiourea (**Cl$^-$-8**) is one of the few neutral, hydrogen bond forming compounds that were used as ionophores for ISEs. At pH 7.0 (HEPES buffer), this electrode responds to chloride in a linear range from 10^{-5} to 10^{-2} M with a slope of −54.0 mV/decade.[880] As compared to ionophore-free anion-exchanger electrodes, the interference from SCN^-, Br^-, NO_3^-, I^-, and even salicylate is considerably reduced (log $k^{\mathrm{MPM}}_{\mathrm{Cl,J}}$ (for step of the primary ion concentration from $10^{-2.34}$ to $10^{-2.04}$ M): salicylate, +1.8; SCN^-, +1.6; NO_3^-, +0.7; I^-, +0.5; Br^-, +0.4; log $k^{\mathrm{MPM}}_{\mathrm{Cl,J}}$ (for step of the primary ion concentration from $10^{-5.00}$ to $10^{-4.70}$ M): SO_4^{2-}, −1.2; HSO_3^-/SO_3^{2-}, −2.0; OAc^-, −2.3; HCO_3^-, −2.6; $H_2PO_4^-/HPO_4^{2-}$, <−3.5; oNPOE, TDDMACl). Chloride determinations in horse serum were demonstrated. In contrast to many ISEs based on organometallic ionophores, this electrode still works satisfactorily after storage in aqueous solution for four weeks. Note that an ISE based on a similar, hydrogen bond-forming ionophore was found to have a remarkable sulfate selectivity (**SO_4^{2-}-1**, see section III.9).



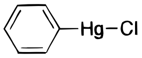
Cl$^-$-8

A Ag^+ ionophore-based ISE has been recently found to respond to Cl^-, and it was suggested that this electrode may be used for Cl^- measurements in whole blood.[657] The response mechanism of this electrode seems to resemble that of an I^--selective electrode and is discussed below (see section III.13).

Optodes. While the first bulk membrane optodes for Cl^- were based on ionophore-free ion exchanger membranes with a selectivity following the Hofmeister series,[98] several organometallic carriers have been developed more recently. As compared to corresponding ISEs, optodes with trioctyltin chloride as an ionophore give a much better stability and a faster response.[296,881] The use of this optode for the determination of Cl^- in human plasma was demonstrated and it was shown that SCN^- did not interfere significantly at concentrations typically occurring in samples from smokers (trioctyltin chloride, log $k_{\mathrm{Cl,J}}^{\mathrm{Osel}}$ (SSM): ClO_4^-, −0.7; NO_3^-, −1.8; Br^-, +0.3; SO_4^{2-}, −2.8; SCN^-, +1.1; I^-, +1.0; ETH 7075 (**H$^+$-12**), BBPA). A similar selectivity was also found for tricyclohexyltin chloride (**Cl$^-$-9**), which under otherwise identical conditions seems to allow lower detection limits than tributyltin and trioctyltin chloride, while optodes based on triphenylgermanium chloride (**Cl$^-$-10**) and phenylmercuric chloride (**Cl$^-$-11**) as well as hafnocene dichloride (**CA$^-$-2**; for use of this ionophore see also "Sensors for Carboxylates", section IV.3) only weakly respond to Cl^-.[92,874] A better discrimination of several interfering ions was found for optodes with chloro(octaethylporphyrinato)indium(III) (**Cl$^-$-4**) and either ETH 2412 (**H$^+$-40**) or fluorescein as chromoionophore (log $k_{\mathrm{Cl,J}}^{\mathrm{Osel}}$ (SSM): ClO_4^-, −2.2; NO_3^-, −2.8; Br^-, +0.1; I^-, +0.2; SCN^-, −1.8; ETH 2412, oNPOE, PVC and Tecoflex polyurethane matrix; pH 4.2).[794]



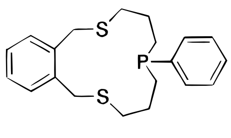
Cl$^-$-9



Cl$^-$-11

11. ClO_4^- Sensors

A number of ClO_4^- ISEs with ionophore-free ion exchanger membranes were reported.[19,882] In some of these membranes, ion pair formation between ClO_4^- and the cationic site may occur with some selectivity but none of these electrodes can be considered to be carrier-based. A recent report on a CHEMFET suggests that this is, however, the case when membranes are prepared with a dithiamacrocycle with a phosphine group (**ClO$_4^-$-1**).[883] ^{31}P NMR spectra showed that this ionophore occurs only in an oxidized form in the membrane. It was suggested that ion−dipole interactions between analyte and P=O groups may be responsible for the ClO_4^- selectivity (log $K_{\mathrm{ClO_4,J}}^{\mathrm{pot}}$ (FIM): SCN^-, −1.0; I^-, −2.9; NO_3^-, −3.4; Cl^-, −4.9; oNPOE; CHEMFET), which is better than that reported for most ionophore-free ion exchangers. Because PVC contains anionic and not cationic impurities, it seems that the anionic response of this CHEMFET is only possible after the occurrence of Donnan failure, i.e., extraction of a perchlorate salt into the electrode membrane. Therefore, the carrier may actually (also?) complex cations. Such cationic complexes could be the cationic sites necessary for neutral carrier (and ion exchanger) based anion-selective electrodes.

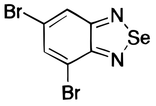


ClO$_4^-$-1

The selectivities of perchlorate-selective electrodes based on Hg^{2+} complexes of calix[4]arenes with thioamide groups were found to be very similar to the selectivities of ionophore-free ion exchanger ISEs.[815] Coordination of ClO_4^- to the metal center is not evident. On the other hand, the strong interference from I^- may be due to interaction between Hg^{2+} and I^- (log $K_{\mathrm{ClO_4,I}}^{\mathrm{pot}}$ (SSM): +0.5; oNPOE; selectivity estimated from log $K_{\mathrm{NO_3,J}}^{\mathrm{pot}}$ as given in the original paper). A response mechanism similar to that found for I^--selective electrodes based on complexes of Hg^{2+} and triisobutylphosphine sulfide seems possible (see section III.3).

12. SeO_3^{2-} Sensors

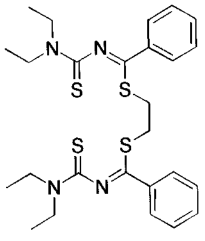
The response mechanism of a selenite-selective electrode with a linear but slightly sub-Nernstian slope was reported to be based on the formation of two covalent bonds between SeO_3^{2-} and the amino groups of the carrier 1,2-diamino-3,5-dibromobenzene (**selenite-1**).[884] While the selectivity of this electrode as determined by SSM is indeed very good, even ClO_4^- being highly discriminated, and selenium determinations in hair were demonstrated, the evidence for the proposed response mechanism does not seem fully conclusive.



selenite-1

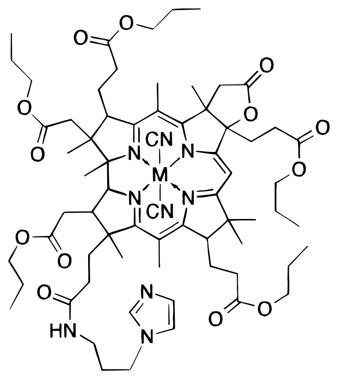
13. I^- and I_3^- Sensors

ISE membranes for iodide have been known for long. First developed were those based on ionophore-free ion exchangers (log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (MSM):[771] Cl^-, −2.0; NO_3^-, −0.7; Br^-, −1.0; Aliquat 336S, 1-decanol) or precipitates[19,861] (log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (SSM):[885] Cl^-, −5.2; Br^-, −2.3; AgI dispersed in silicone rubber; very similar electrodes are based on a pressed mixture of AgI and Ag_2S). On the other hand, carrier-based iodide ISEs have been reported only relatively recently. The response mechanism of solvent polymeric membranes containing a complex of triisobutylphosphine sulfide (TIBPS) and either Ag^+ or Hg^{2+} (cf. **SCN$^-$-14**) has not been fully clarified but was suggested to be due either to reversible association of the analyte anions with the metal complex or the formation of a surface layer of an insoluble salt.[661,886] The good selectivity for iodide (log $k_{\mathrm{I,J}}^{\mathrm{MPM}}$: Cl^-, −5.3; Br^-, −2.5; DOS, Ag(I)-TIBPS) is somewhat set back by fairly long response times of several minutes. The same mechanism may also explain the response of an ISE based on the Ag(I) complex of **I$^-$-1**, which has shorter response times of about 10 s (log $k_{\mathrm{I,J}}^{\mathrm{MPM}}$: Cl$^-$, -4.0; Br$^-$, -2.1; DOS).[887] A similar system based on Au(III) was reported for SCN$^-$ as analyte (see section III.2). More recently, it has also been shown that ISEs based on a calix[4]arene bisthioether (**Ag$^+$-8**) or a bis(dithiocarbamate) ionophore (**Ag$^+$-14**) respond to Ag$^+$ in AgNO$_3$ solutions, and to Cl$^-$ in NaCl solutions after overnight conditioning in 0.01 M AgNO$_3$.[657] During measurements, Ag$^+$ seems to be constantly released in very small amounts from the membrane into the sample solution. The most likely explanation for this release appears to be leaching of Ag$^+$ and negatively charged impurities contained in the membrane. The Cl$^-$ response can be explained by coprecipitation of Ag$^+$ and Cl$^-$, resulting in a decrease of the Ag$^+$ activity on the aqueous side of the sample−membrane phase boundary. No anionic emf response is, however, observed for I$^-$. It seems that AgI precipitation lowers the activity of Ag$^+$ in the sample phase and promotes cation-exchange between sample and membrane phase. This quickly depletes the Ag$^+$ in the membrane and replaces it with a sample cation, resulting in a cationic emf response.

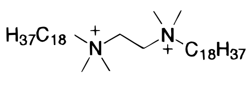


I$^-$-1

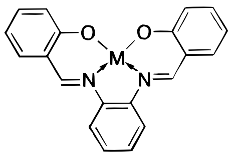
While cobyrinate derivatives that contain only the corrin ring but not the dimethylbenzimidazole ligand of vitamin B12 were used in ISEs with selectivity for NO$_2^-$ and SCN$^-$, a vitamin B12 analogue with an imidazole group coordinated to the metal center gave a good selectivity for I$^-$ (**I$^-$-2**, log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (SSM): SCN$^-$, -1.6; ClO$_4^-$, ≈ -2.0; salicylate, -2.1; DOS), which was explained by simultaneous interaction of this anion with the metal center and the protonated imidazole ring.[812,813] This recognition mechanism resembles the ditopic recognition of I$^-$ by hydrophobic diquaternary ammonium salts, which give the best selectivity for iodide when the two ammonium groups are separated by two carbon atoms (**I$^-$-3**; log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (FIM): ClO$_4^-$, -1.9; acetate, -4.3; SCN$^-$, -1.5; salicylate, -1.9; oNPOE; selectivities estimated here from log $K_{\mathrm{X,OAc}}^{\mathrm{pot}}$ of original publication).[888] An increase to three carbons leads to Hofmeister selectivities. Schiff base complexes of Co(II) provide for similar selectivities as **I$^-$-2** (**I$^-$-4**, log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (SSM): Cl$^-$, -4.3; Br$^-$, -2.5; ClO$_4^-$, -2.4; SCN$^-$, -2.2; NO$_2^-$, -2.2; *o*-nitrophenyl dodecyl ether; note the similarity of **I$^-$-4** and **NO$_2^-$-6**) but this metal center is very sensitive to oxidation such as by oxygen or ascorbate.[889] As mentioned in section III.10, ISE membranes of mercurated polystyrene, which contain a large number of RC$_4$H$_4$HgOAc units, were reported[878,879] to weakly respond to inorganic anions with a preference for I$^-$ (I$^-$ $\gg$ SCN$^-$ > Br$^-$ $\gg$ Cl$^-$ > NO$_3^-$ > F$^-$).



I$^-$-2: M = Co(III)



I$^-$-3



I$^-$-4: M = Co(II)

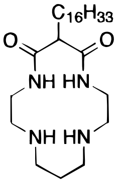
One of the earliest I$^-$-selective electrodes was based on organic solutions of I$_2$, which probably acted as a neutral carrier by forming I$_3^-$ complexes, the phase boundary potential at the liquid−solid interface being determined by the redox couple I$_2$/I$_3^-$ (log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (MSM): Cl$^-$, ≤ -2.4; Br$^-$, ≤ -2.4; ClO$_4^-$, <-5.0; NO$_3^-$, ≤ -4.1;benzene, no polymer matrix).[890] In contrast, (5,10,15,20-tetraphenylporphyrinato) manganese(III) (cf. **Cl$^-$-3** and **SCN$^-$-7**) was used to measure I$_3^-$ as analyte (log $K_{\mathrm{I_3,J}}^{\mathrm{pot}}$ (FIM): Cl$^-$, <-4.0; Br$^-$, <-4.0; ClO$_4^-$, <-4.0; salicylate, -3.3; FNDPE; super-Nernstian response of -87 mV/decade to I$_3^-$).[781] This electrode was also shown to be applicable for the indirect determination of oxidizing agents. More recently, a potentiometric sensor for the detection of tributyl phosphate vapor based on iodine incorporated into a chemically inert matrix of poly(cyclophosphazene-benzoquinone) has been demonstrated. The response was explained to be due to specific charge-transfer interactions between analyte and I$_2$, and allowed for detection of tributyl phosphate in the range from 1.1 ppb to 8.8 ppm.[891]

Optodes. An optode based on coordination of iodide to the metal center of the carrier chloro(5,10,15,20-tetraphenylporphyrinato)manganese(III) (**Cl$^-$-3**), resulting in changes of the vis spectra of this complex, exhibited a fairly complicated selectivity pattern.[794] Salicylate and perchlorate for example gave only a very small response by themselves but considerably weakened the response to I$^-$, which seems to be due to extraction of these lipophilic ions into the membrane, in competition with I$^-$. A relatively large interference would also be expected for SCN$^-$, as potentiometric studies mentioned above suggest (cf. **SCN$^-$-7**).

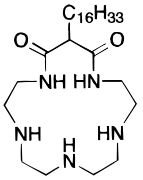
I$_2$ was determined optically by measuring fluorescence quenching of fluoranthene but the reported analysis of table salt did not take into account that iodine added to table salt for dietary reasons is in an ionic form.[892]

14. Sensors for Metal Cyano Complexes

Numerous electrodes for metal cyano complexes based on ionophore-free ion exchangers with a Hofmeister selectivity were reported.[19] Noticeable exceptions are ISEs with lipophilic macrocyclic dioxopolyamines (**$M(CN)_4^{2-}$-1**, **$M(CN)_4^{2-}$-2**) as ionophores, which were shown to discriminate between hexacoordinated complexes with an octahedral structure ($[Fe(CN)_6]^{3-}$, $[Fe(CN)_6]^{4-}$) and tetracoordinated complexes ($[Ni(CN)_4]^{2-}$, $[Pt(CN)_4]^{2-}$) with a square planar structure (**$M(CN)_4^{2-}$-1**: $\log k^{\mathrm{MPM}}_{\mathrm{Ni(CN)_4,J}}$ (for step of primary ion concentration from 1.0×10^{-4} M to 2.0×10^{-4} M): $[Pt(CN)_4]^{2-}$, 0.0; $[Fe(CN)_6]^{3-}$, <-3.0; $[Fe(CN)_6]^{4-}$, <-3.0; oNPOE; acetate buffer pH 4.0).[893] As the ISEs with the corresponding macrocyclic polyamines without carbonyl groups did not exhibit such a discrimination, the two lactam groups seem to be a prerequisite for this selectivity. The exact nature of the recognition mode has, however, not been fully clarified. Similar macrocyclic polyamines were also used as ionophores for ISEs developed for phosphate (**phosphate-8**, section III.6), nucleotides (**NT-3**, section IV.5), and carboxylates (**CA-7**, section IV.3).[831,894−898]



$M(CN)_4^{2-}$-1



$M(CN)_4^{2-}$-2

IV. Organic Ionic Analytes

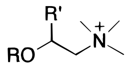
1. Sensors for Organic Ammonium Ions

The interest for organic ammonium sensors arises primarily due to the physiological activity of a variety of ammonium ions. Other fields of applications, such as herbicide detection, were also suggested.[899] Crown ethers were the first ionophores in this field but more recently applications of calixarene and cyclodextrin ionophores were also demonstrated. While many ionophores that form hydrogen bonds to primary ammonium ions are known, and cyclodextrins and crown ethers were reported to complex quaternary ammonium ions, examples of carriers for secondary and tertiary ammonium ions are very few. Steady-state and equilibrium responses of polyion sensors based on ion pair forming ion exchangers,[900] which were successfully used for the determination of the polycationic protamine (a low-molecular-weight protein, rich in arginine) and the polyanion heparin (a highly sulfated polysaccharide), will be discussed in section IV.7.

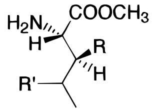
All the ISEs and optodes reviewed in this chapter respond to ionic analytes, that is, either to ammonium ions formed by protonation of primary, secondary, or tertiary amines, or to quaternary ammonium ions. However, for better comprehensibility, the names of the neutral form of primary, secondary, and tertiary amines, such as benzylamine, ephedrine, or isoleucine methyl ester, will be given in the following.

ISEs for Primary Amines and Amino Acid Esters. In the 1970s and 1980s, enantioselectivity was the major focus of reports on ISEs for primary ammonium ions. Advances in host−guest chemistry recently led to a shift in interest to the discrimination among organic cations that are not stereoisomers but several reports on enantioselective ISEs have also been published in the 1990s. The first ISE of this type discriminated between the enantiomers of 1-phenylethylamine (**A-1**) by a factor of 1.1.[901] It was followed by many other enantioselective ISEs, often based on ionophores that were not specifically developed for potentiometry. Using noncyclic diamides,[901,902] crown ethers,[902−910] cyclodextrins,[911−914] tartaric acid esters (the latter as chiral plasticizers),[905,906] and derivatives of monensin[909,910,915,916] and other antibiotics,[916] enantioselectivities for 1-phenylethylamine (**A-1**),[901−904,906−910,915,916] 1-(1-naphthyl)-ethylamine (**A-2**),[910,915,916] ephedrine (**A-3**),[902,905,906,911,913,914] norephedrine (**A-4**),[911,913,914] pseudoephedrine (**A-5**; also called Ψ-ephedrine),[902,911,913,914] amphetamine (**A-6**),[912,914] propranolol (**A-7**),[912] amino acid methyl esters,[902,903,908−910,915,916] α-amino-ϵ-caprolactam (**A-8**),[908] and amino acid amides[902] were determined (Chart 1). While several of the ISEs based on these ionophores would probably yield interesting selectivities toward other, nonenantiomeric organic cations, with few exceptions (such as for three crown ethers (e. g. **AM-1**)[904] or for the cyclodextrins **AM-3** and **AM-4** (Chart 1);[912,917−919] vide infra) only selectivities for inorganic cations were investigated.

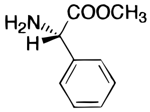
Whereas a comprehensive theoretical treatment for enantioselectivity was presented,[905] many electrodes were simply characterized by $\log K^{\mathrm{pot}}_{(+)/(-)} = [E_{(+)} - E_{(-)}]/S$, where $E_{(+)}$ and $E_{(-)}$ are emf values determined for the two enantiomers at a given analyte concen-



A-9 (acetylcholine): R = COCH3; R' = H
A-23 (choline): R = H; R' = H
A-24 (methacholine): R = COCH3; R' = CH3

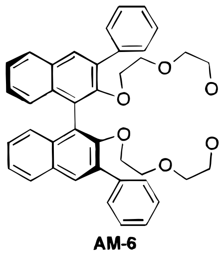


A-10 (L-isoleucine methyl ester):
R = CH3; R' = H
A-11 (L-leucine methyl ester):
R = H; R' = CH3



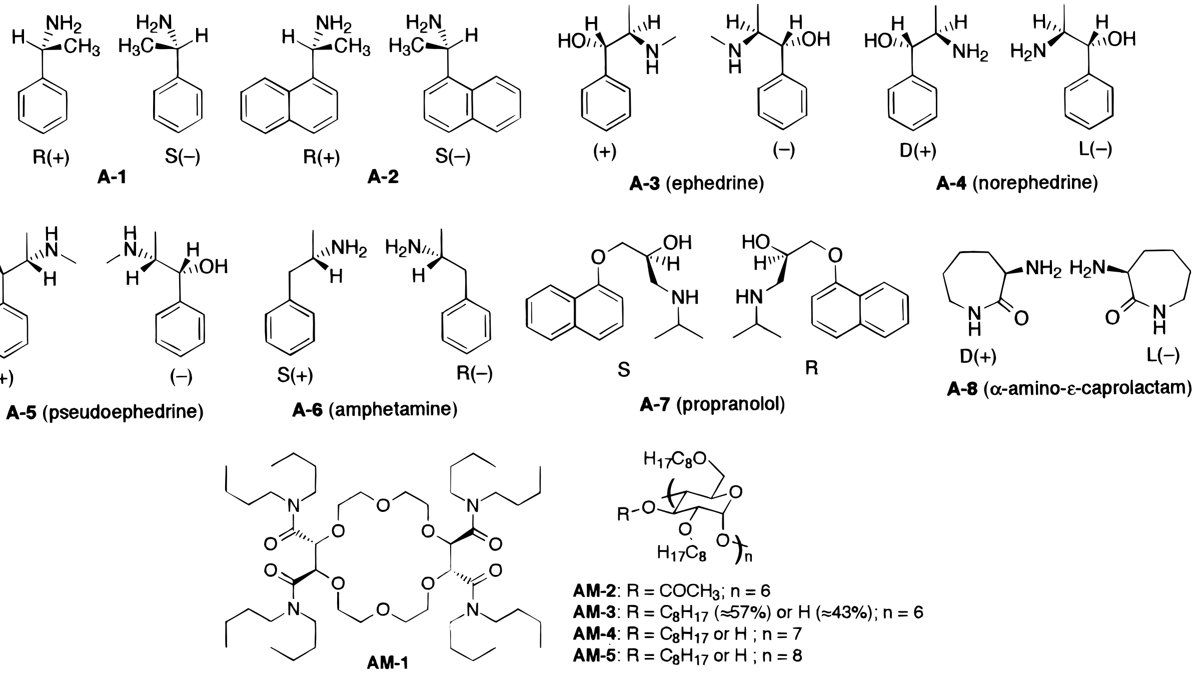
L(+)

A-12 (phenylglycine methyl ester)



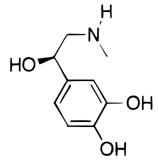
AM-6

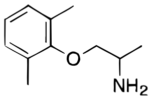
Chart 1

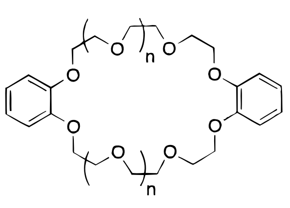


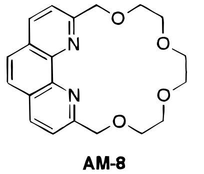
tration and S is the experimental slope. Among the largest observed selectivity coefficients (caveat: these are $K^{\mathrm{pot}}_{(+)/(-)}$ and not log $K^{\mathrm{pot}}_{(+)/(-)}$ values) were 2.7 for 1-phenylethylamine (**A-1**) with the crown ionophore **AM-1**,[907] 3.0 for ephedrine (**A-3**) with the α-cyclodextrin ionophore **AM-2**,[914] 2.7 for propranolol (**A-7**) with either one of two β-cyclodextrin ionophores (e. g. **AM-4**; this ionophore was also used in enantiodiscrimination of propranolol (**A-7**) and detection of acetylcholine (**A-9**), and secondary, tertiary, and quaternary amines),[912] and 11.5 for isoleucine methyl ester (**A-10**),[908] 10.4 for leucine methyl ester (**A-11**) [909] and 18.4 for phenylglycine methyl ester (**A-12**) with an ISE based on the crown ether ionophore **AM-6**.[909] For the accurate determination of enantiomeric excesses, a cell assembly with two solvent polymeric membranes containing each one an enantiomer of the ionophore was proposed.[907]

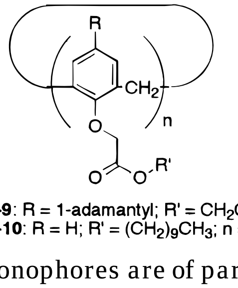
Electrodes based on dibenzo-18-crown-6 (**K$^+$-4**) and dibenzo-24-crown-8 (**AM-7**) were used for the detection of amphetamine (**A-6**), no consideration being given to enantioselectivity.[920] The fairly high discrimination of several inorganic cations and a number of organic cations, such as adrenaline (**A-13**), ephedrine (**A-3**), and some alkaloids, was obviously not only due to specific interactions between the primary ammonium group and the ionophore but also due to the highly hydrophobic character of the 1-phenyl-2-propyl substituent on the primary analyte (see also section IV.6 on ionic surfactants, commenting the use of dibenzo-18-crown-6 for the detection of primary alkylammonium ions[921]). For sensing the very similar analytes benzylamine and mexiletine (**A-14**), macrocyclic polyether derivatives of *o*-phenanthroline and 2,2′-dinaphthol with various ring sizes were incorporated into PVC membranes.[922−924] Due to specific interactions between the primary ammonium ions and the ionophore, the selectivity sequence for an electrode with a bridged *o*-phenanthroline (**AM-8**; $RNH_3^+ > R_4N^+ > R_3NH^+ > R_2NH_2^+$; R = ethyl) clearly differs from that for typical ion-exchanger ISEs ($R_4N^+ > R_3NH^+ > R_2NH_2^+ > RNH_3^+$), which is determined by the lipophilicities of the measured ions. A similar but smaller effect was also observed for ISEs with a calix[6]arene[925] (**Cs$^+$-4**) or a *p*-1-adamantylcalix[8]arene[926,927] (**AM-9**) ionophore. For the latter, selectivities versus phenylalanine methyl ester were reported and use in monitoring of phenylglycine methyl ester (**A-11**) during the enzymatic synthesis of the antibiotic ampicillin was suggested.[927]


A-13 (L-adrenaline)

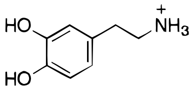

A-14 (mexiletine)


AM-7: n = 1
AM-13: n = 2


AM-8

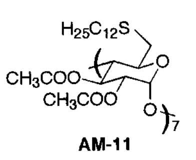

AM-9: R = 1-adamantyl; R′ = CH2CH3; n = 8
AM-10: R = H; R′ = (CH2)9CH3; n = 6

Calixarene ionophores are of particular interest for the recognition of organic analytes by inclusion into the ionophore. This makes not only discrimination among different functional groups of the analyte possible but also allows for steric recognition of nonpolar moieties.[928,929] An ISE based on a calix[6]-arene hexaester (**AM-10**) responds less strongly to primary ammonium ions with bulky groups (log $K^{\mathrm{pot}}_{\text{2-phenylethylamine,J}}$ (SSM): octylamine, +0.1; benzylamine, −1.1; adamantylamine, −2.8; *tert*-butylamine, −4.1; DOS) than an electrode based on dibenzo-18-crown-6 (**K^+-4**; log $K^{\mathrm{pot}}_{\text{2-phenylethylamine,J}}$ (SSM): octylamine, +1.3; benzylamine, −0.3; adamantamine, +0.5; *tert*-butylamine, −1.6; DOS; see also above us of this ionophore for amphetamine, **A-6**). Steric hindrance also improved the selectivity of the former electrode for dopamine (**A-15**) versus noradrenaline and adrenaline (**A-13**). On the other hand, α-amino acid esters are guests that cannot form three hydrogen bonds to the ammonium group when accommodated within the calix[6]arene cavity. Other ISEs that were used to measure dopamine were based on polyoctylated α- or β-cyclodextrins (**AM-3**, **AM-4**) as ionophores.[917,918] Strong interference from K^+ prevents use of these electrodes for the analysis of blood samples. **AM-3** and **AM-4** were also used for detection of various other organic cations (propranolol (**A-7**), guanidine, acetylcholine (**A-9**), secondary, tertiary, and quaternary amines). Note that because of deprotonation of dopamine (**A-15**) at high pH, anionic and not cationic, responses were obtained at pH 9.4 with an ISE based on poly(binaphthyl-20-crown-6).[930−932]



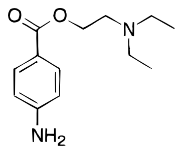
A-15 (dopamine)

Inclusion complexes seem also to determine the responses of electrodes based on a long-chain derivative (**AM-11**) of β-cyclodextrin,[933] resulting in an enhanced selectivity for 2-phenylethylamine and a sequence of the selectivity for methoxy-substituted benzylamines that differs from that for ionophore-free membranes.

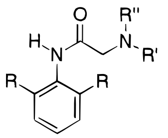


AM-11

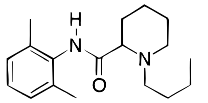
ISEs for Secondary and Tertiary Amines. Nernstian responses to the local anaesthetics procaine (**A-16**), prilocaine (**A-17**), lidocaine (**A-18**; also called lignocaine), or bupivacaine (**A-19**) and negligible interferences from serum levels of inorganic cations were reported for ISEs based on 2,6-di-*O*-dodecyl-β-cyclodextrin[912,934,935] (**AM-12**) or the polyoctylated **AM-4** already mentioned above.[912,934,935] Note that the same electrodes also respond well to acetylcholine (**A-9**) and creatinine (see section IV.2) and in the case of the ISEs with the latter ionophore, to propranolol (**A-7**; enantioselective response), acetylcholine (**A-9**), dopamine (**A-15**), and secondary and tertiary amines.



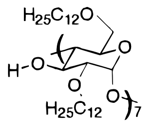
A-16 (procaine)



A-17 (prilocaine): R,R''=H; R'=CH$_2$CH$_2$CH$_3$
A-18 (lidocaine): R=CH$_3$; R',R''=CH$_2$CH$_3$

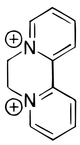


A-19 (bupivacaine)

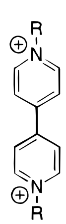


AM-12

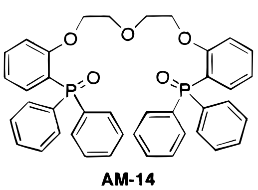
ISEs for Quaternary Ammonium Compounds. The diquat dication (**A-20**), a dipyridyl derivative with a positive charge on both nitrogens, was found to form complexes with dibenzocrown ethers. Interactions between the nitrogen atoms of diquat and the phenolic oxygen lone-pair p-orbitals of the crown ether stabilize this complex. These findings led to the development of ISEs based on dibenzo-30-crown-10 (**AM-13**) for the detection of the contact herbicides paraquat (**A-21**), diquat, and 4,4′-dipyridinium (**A-22**).[899,936] While the molar ratio of tetraphenylborate and ionophore of 3.1 to 1 used for the preparation of those membranes seems to be too large, the selectivity of the ionophore-incorporated ISE is higher than that of typical ionophore-free ion-exchanger electrodes, suggesting that the excess borate may have leached out of the membrane during conditioning before measurements. Electrodes based on phosphoryl group-containing podands (e. g. **AM-14**) were reported for measuring the similar alkylpyridinium cations,[937] and various calix[8]arenes were used in ISEs with modest selectivities for dodecylpyridinium and dodecyltrimethylammonium surfactants[938] (uses of ionophores similar to **AM-14** were reported for octylammonium ISEs;[939] see section IV.6).



A-20 (diquat)



A-21 (paraquat): R=CH$_3$
A-22 : R=H

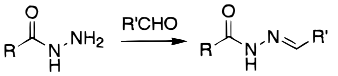


AM-14

Selective recognition of tetramethyl- and tetraethylammonium ions was reported for ISEs based on polyoctylated β- and γ-cyclodextrins (**AM-4** and **AM-5**), respectively, whereas corresponding electrodes with an α-cyclodextrin derivative (**AM-3**) as ionophore responded more strongly to NH_4^+.[912,917,918] In the case of the former two ionophores attractive interactions between the ionophore oxygens and the methylene hydrogens next to the quaternary nitrogen of the guest seem to stabilize the respective complexes. On the other hand, residual hydroxy groups in the ionophore seem to be relevant in the complexation of NH_4^+ by **AM-3**. An important example of a quaternary ammonium analyte is acetylcholine (**A-9**; responses to choline, **A-23**, and methacholine, **A-24**, were reported too).[917,918,934] Interferences from Na^+, K^+, Ca^{2+}, NH_4^+, and bovine serum albumin on acetylcholine (**A-9**) determinations with an ISE based on 2,6-di-*O*-dodecyl-β-cyclodextrin (**AM-12**) were reported to be very small.[912] Polyoctylated β-cyclodextrin (**AM-4**) was also used to measure long-chain alkyl trimethylammonium ions,[940] which are cationic surfactants with antibacterial and antifungal properties, and to detect propranolol (**A-7**), dopamine (**A-15**), and anaesthetics.[912,917–919,934,935]

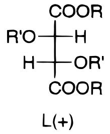
Formaldehyde and a few other aldehydes were determined indirectly by in situ reaction with Girard reagents (Scheme 1), which react with aldehydes to give hydrazones.[941,942] Concentrations of the latter could be measured potentiometrically because Girard reagents with a positively charged *N*-alkylpyridyl substituent were used. However, whether the *p-tert*-butylcalix[4]arene-based ISEs that were used for these measurements are better suited for indirect aldehyde measurements than ionophore-free ion-exchanger ISEs was not demonstrated.

Scheme 1

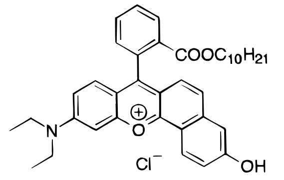


Optodes. Much fewer optodes for organic amines than ISEs have been reported so far. The first two optodes for this class of analytes were developed for the determination of enantiomeric excesses (ee) with nonpolarized light. Remarkably matching enantioselectivities for the (*R*) and (*S*) enantiomers of 1-phenylethylammonium, and vice versa, were obtained for membranes containing ETH 5294 (**H$^+$-10**) and either the (+) or the (−) enantiomer of a 18-crown-6 derivative (**AM-1**; $\log K^{\mathrm{opt}}_{R,S} = 0.421$ and $K^{\mathrm{opt}}_{R,S} = 0.426$, respectively).[943] The precision of ee determinations could be even improved by measuring the difference in vis absorption of those two membranes and was found to be limited by the error in the absorbance readings. Further improvements in precision most importantly require ionophores with a higher enantioselectivity. Another factor that seems to deserve more attention is the temperature at which such measurements are performed. Because enantiomer selectivities depend on enthalpic and entropic terms, the extent of enantioselectivity of optodes and ISEs depends on the temperature. A lack of enantioselectivity at the isoenantioselective temperature and opposite enantioselectivities below and above that temperature were observed for complex formation in organic solvents.[944] Reversals in enantioselectivity were so far not observed for ISEs and optodes but could very likely be demonstrated by temperature variation.

Enantioselectivities were also measured with fluorescence sensors. Membranes containing the charged fluorescing H^+ chromoionophore DZ-49 (**H$^+$-41**) and one of four (*R*,*R*)-tartrate esters (**AM-15** to **AM-18**) were used to detect enantioselectively 1-phenylethylamine (**A-1**), propranolol (**A-7**), and norephedrine (**A-4**).[945]



AM-15: R = menthyl; R' = H
AM-16: R = $C(CH_3)_3$; R' = H
AM-17: R = $CH_2C_6H_5$; R' = H
AM-18: R = $C(CH_3)_3$; R' = $CHCCl_2$

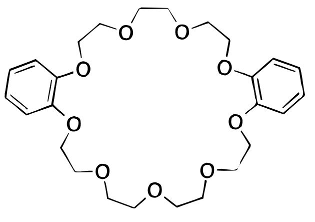


H$^+$-41

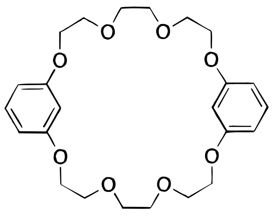
Fluorescence and vis spectrometric measurements of organic ammonium ions were also performed with membranes containing calixarenes. The measuring range of a vis optode[946] based on a calix[6]arene hexaester (**Cs$^+$-4**) and the neutral H^+ chromoionophore ETH 5294 (**H$^+$-10**) was found to be 1×10^{-6} to 1×10^{-3} M for octylamine, the selectivities for several organic ammonium ions indicating specific host−guest complexation ($\log K^{\mathrm{opt}}_{\mathrm{octylamine,J}}$ (SSM): hexylamine, −1.2; tetrabutylammonium, −1.7; butylamine, −2.0; triethylamine, −3.3; DOP, NaTPB, ETH 5294, pH 8.0). Interference from H^+, probably due to phenolic ionophore impurities, was suggested to be responsible for the unfavorable detection limit (≈1 mM) of a fluorescence optode for 2-phenylethylamine based on a calix[6]arene (**Cs$^+$-5**) as ionophore and hexadecyl-acridine orange (**Ind-2**; see section II.4) as dye.[947]

2. Sensors for Guanidinium, Guanidinium Derivatives, and Creatinine

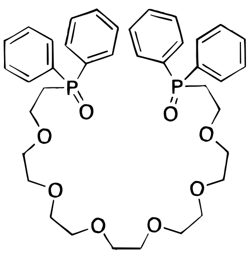
A relatively high selectivity for guanidinium can be obtained with ion-exchanger electrodes if an appropriate membrane plasticizer is used ($\log K^{\mathrm{pot}}_{\mathrm{Gua,J}}$ (SSM): creatinine, −1.2; H^+, −1.8; Na^+, −1.9 K^+, −1.5; NH_4^+, −1.7; DOS, KTpClPB; creatinine, −0.4; H^+, −2.5; Na^+, −2.0; K^+, −1.2; oNPOE, KTpClPB; creatinine, −1.0; H^+, −1.2; Na^+, −2.1; K^+, −2.9; NH_4^+, −1.8; TEHP, KTpClPB),[948] but it was repeatedly reported that such ISEs have an unsatisfactory response time.[949,950] First attempts to use carrier-based ISEs for guanidine measurements were made with benzocrown ethers[949–951] that were known to form guanidine complexes. However, the selectivity improvements due to use of such ionophores were relatively small (dibenzo-27-crown-9 (**GU-1**): $\log K^{\mathrm{pot}}_{\mathrm{Gua,J}}$ (FIM): Na^+, −1.7; K^+, −1.0; NH_4^+, −1.5; dibutyl phthalate;[951] di([1,3]benzeno)-26-crown-8 (**GU-2**): $\log K^{\mathrm{pot}}_{\mathrm{Gua,J}}$ (SSM): Na^+, −1.9; K^+, −1.2; NH_4^+, −1.8; dibutyl phthalate, guanidinium tetraphenylborate).[950] The same is also true for ISEs based on noncyclic polyethers with two terminal phosphoryl groups (**GU-3**, $\log K^{\mathrm{pot}}_{\mathrm{Gua,J}}$ (MSM): Na^+, −0.0; K^+, −1.2; NH_4^+, −1.2; oNPOE, NaTPB).[952] An improved discrimination of Na^+ and NH_4^+ was obtained with bis-sulfonamide cryptands as ionophores and TEHP as membrane plasticizer (**GU-4**: log $K^{pot}_{Gua,J}$ (SSM):[948] creatinine, −0.8; H^+, −0.4; Na^+, −2.5; K^+, −3.1; NH_4^+, −2.2; TEHP, KTpClPB). While use of **GU-4** and DOS gives a better discrimination of H^+, the use of this plasticizer results in a much larger interference from K^+.[948] Also, ISEs based on several noncyclic bis-sulfonamides discriminate K^+ to a lesser extent (log $K^{pot}_{Gua,J}$(SSM): K^+, >−1.7; Na^+, >−2.2).[948,953,954] Comparable results were found for the best membranes based on one of eight calixarenes (log $K^{pot}_{Gua,J}$ (FIM): Na^+, −1.9; K^+, −1.8; NH_4^+, −1.8; dibutyl phthalate, KTpClPB).[955] Most attractive in view of a simultaneous discrimination of Na^+ and H^+ are probably electrodes based on alkylated cyclodextrins (e. g. **AM-3**: log $K^{pot}_{Gua,J}$ (FIM): Na^+, −2.9; K^+, −1.4; NH_4^+, −1.7; oNPOE, NaTFPB),[919] which seem to be well-suited for recognition of "onium" ions that have a highly delocalized positive charge[934] (note also the use of **AM-3** in enantioselective sensors and for detection of dopamine, **A-15**).



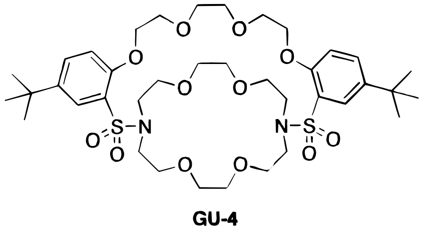
GU-1



GU-2

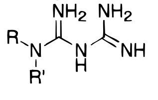


GU-3

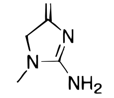


GU-4

ISEs based on cyclodextrin ionophores were not only used for guanidine and amine measurements (see sections IV.1 and IV.2) but also for detection of the guanidinium derivatives metformin (**A-25**; drug used in treatment of diabetes mellitus) and phenformin (**A-26**) and the structurally similar creatinine (**A-27**).[912,940] For four ISEs based on an α- or β-cyclodextrin derivative with varying degree of alkylation, only small differences in selectivities versus the primary analyte creatinine were observed (2,6-di-*O*-dodecyl-β-cyclodextrin (**AM-12**): log $K^{pot}_{creatinine,J}$ −2.7;[940] oNPOE, NaTFPB; determined under FIM conditions in mixed solutions of creatinine and a mixed background of 145 mM Na^+, 4.3 mM K^+ and 1.26 mM Ca^{2+}, using the equation log $K^{pot}_{creatinine,J} = c_{creatinine}/\sum c_J^{z_I/z_J}$; for details on this method see Kataky et al.[935]).



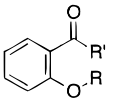
A-25 (metformin): R,R'=CH_3
A-26 (phenformin): R = $CH_2CH_2C_6H_5$, R'=H



A-27 (creatinine)

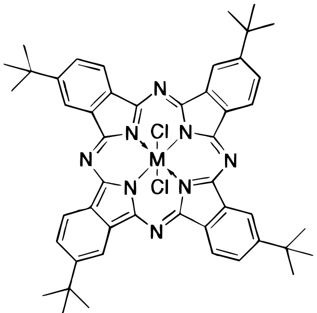
3. Sensors for Carboxylates

Salicylate. Because of the widespread use of 2-acetoxybenzoic acid (**A-28**; also called *O*-acetylsalicylic acid or aspirin) as analgesic and recently also as a preventive of heart attacks, 2-acetoxybenzoic acid and even more its hydrolysis product salicylate (**A-29**) have become analytes of considerable interest. Importantly, binding of salicylate to proteins is strong and cannot be neglected when trying to compare results from potentiometric salicylate measurements and more conventional methods used to determine total salicylate.[761,956] Furthermore, other aspirin metabolites than salicylate were reported to react in standard salicylate tests.[956]



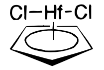
A-28 (*O*-acetylsalicylic acid): R = $COCH_3$; R' = OH
A-29 (salicylic acid): R = H; R' = OH
A-33 (2-hydroxybenzhydroxamate): R = H; R' = NHOH

Ionophore-free ion-exchanger electrodes for salicylate offer a fairly good discrimination of hydrophilic anions[956−959] but discrimination of lipophilic anions such as ClO_4^- is poor (log $K^{pot}_{Sal,J}$ (SSM): ClO_4^-, +1.8; SCN^-, +0.7; Cl^-, −2.1; OAc^-, −2.2; DBP, Aliquat-336S).[956] However, a number of organometallic species with better selectivities were reported as carriers for salicylate. While the strong interference from Cl^- excluded the use of chloro(5,10,15,20-tetraphenylporphyrinato)manganese(III) (**SCN$^-$-7**) membranes for direct measurements (log $K^{pot}_{Sal,J}$ (SSM): ClO_4^-, −0.6; SCN^-, −0.8; Cl^-, −2.1; DBS),[956] an analysis method based on sample acidification leading to selective permeation of salicylic acid across a silicone membrane and subsequent measurement with an ISE based on this carrier was demonstrated.[776,780] A very significant improvement in selectivity was obtained upon replacing the Mn(III) by a Sn(IV) center (log $K^{pot}_{Sal,J}$ (SSM): ClO_4^-, −3.4; SCN^-, −2.5; Cl^-, −3.8; OAc^-, −3.9; log $K^{pot}_{Sal,OH}$ (FIM): +4.2 (pH 7.2−7.6); DBS).[782,789,956] Unfortunately, OH^- interference does not allow salicylate determinations at physiological pH with this ISE, and response times are in the range of minutes. While it was originally assumed that direct binding of salicylate to the metal center, giving an inner-sphere complex, explained the response mechanism of this ISE, super-Nernstian responses, cationic responses at high salicylate concentrations and unusual response time variations indicated a more complex mechanism. Subsequent spectroscopic and conductometric measurements indicated that direct binding of salicylate to the Sn(IV) center occurs only at high analyte concentrations, whereas at low concentrations of salicylate water competes with the analyte, which then probably is bound by hydrogen bonds and $\pi-\pi$ interactions to the diaquo porphyrin complex.[68,960] Replacement of the porphyrin macrocycle by phthalocyanine while retaining the Sn(IV) center (**CA-1**) was recently shown to give not only high selectivities (log $K^{\mathrm{pot}}_{\mathrm{Sal,J}}$ (SSM): $\mathrm{ClO_4^-}$, −3.3; $\mathrm{SCN^-}$, −2.9; $\mathrm{Cl^-}$, −4.8; $\mathrm{OAc^-}$, −3.4; dinonyl sebacate, KTPB) but also fast response times of 6−20 s.[961] Loss of selectivity versus most interfering ions (in particular for $\mathrm{ClO_4^-}$, $\mathrm{SCN^-}$, and $\mathrm{I^-}$) as obtained for membranes without the tetraphenylborate confirm that this tin(IV) phthalocyanine acts as a charged carrier. This electrode was used to demonstrate assays of aspirin in tablets and of salicylate in urine. On the other hand, tin(IV) tetraphenylporphyrins were recently reported for the determination of 2-hydroxybenzhydroxamate (see section IV.4).



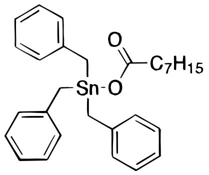
CA-1: M = Sn(IV)

Among seven metallocenes, bis(cyclopentadienyl)-hafnium dichloride (**CA-2**) was found to be a very promising salicylate carrier (log $K^{\mathrm{pot}}_{\mathrm{Sal,J}}$ (SSM): $\mathrm{ClO_4^-}$, −0.9; $\mathrm{SCN^-}$, −0.9; $\mathrm{Cl^-}$, −1.9; $\mathrm{OAc^-}$, −1.8; BBPA).[959] Otherwise rather attractive, this electrode unfortunately gives a fairly low discrimination of $\mathrm{Cl^-}$. The response mechanism of an Fe(III)-siderophore complex (**Fe(III)-1**) based electrode with sub-Nernstian slopes and a high detection limit was not fully elucidated.[616,962]



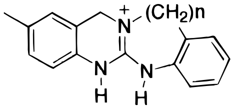
CA-2

While organotin(IV) ionophores were widely used for $\mathrm{Cl^-}$ and phosphate selective electrodes (see sections III.10 and III.6 for **Cl⁻-1**, **Cl⁻-2**, and **Cl⁻-9**, and **phosphate-1** to **phospate-6**, respectively), use of this compound class for salicylate electrodes is very new. A good selectivity was reported for several electrodes based on tribenzyltin carboxylates and their application for salicylate determinations in urine was demonstrated (**CA-3**, log $K^{\mathrm{pot}}_{\mathrm{Sal,J}}$ (SSM): $\mathrm{ClO_4^-}$, −3.1; $\mathrm{SCN^-}$, −2.1; $\mathrm{Cl^-}$, −4.9; $\mathrm{OAc^-}$, −3.9; oNPOE).[963]

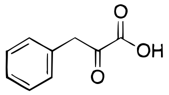


CA-3

Two electrodes based on guanidinium derivatives (**CA-4** and **CA-5**)[964] are examples of carrier-based salicylate electrodes whose selectivities are not based on an ionophore with a metal center. The two ionophores strongly resemble the carrier **sulfite-2** but lack its phenyl group, which was suggested to interact with the sulfur and provide for hydrogen sulfite selectivity. Indeed, the selectivities of both salicylate electrodes (**CA-5**, log $k^{\mathrm{MPM}}_{\mathrm{Sal,J}}$: $\mathrm{ClO_4^-}$, −2.7; hydrogen sulfite, −2.7; benzoate, −1.7; DOS) differ impressively from that of the hydrogen sulfite ISE. The major advantage of the ISE with **CA-5** is a lower detection limit. In view of the low lipophilicity of **CA-4** (log P_{TLC} 3.4), the likely explanation for this finding is the enhanced lipophilicity (log P_{TLC} 5.0), owing to the additional methylene group in **CA-5**. Heptyl 4-trifluoroacetylbenzoate (**$\mathbf{CO_3^{2-}}$-3**) is another example of a carrier without metal center.[761] While developed originally for carbonate (see section III.1), a salicylate ISE with this carrier gives a good discrimination of $\mathrm{Cl^-}$ (log $K^{\mathrm{pot}}_{\mathrm{Sal,J}}$ (FIM): $\mathrm{HCO_3^-}$, −2.4; $\mathrm{Cl^-}$, −4.4; $\mathrm{OAc^-}$, −3.9; oNPOE, TDDMACl). In view of the selectivities of the carbonate ISEs, a reported slight bicarbonate interference may be rather a carbonate interference. ISEs with the same ionophore were also used to detect phenylpyruvate (**A-30**) in urine (log $K^{\mathrm{pot}}_{\mathrm{phenylpyr.,J}}$ (FIM): $\mathrm{HCO_3^-}$, −2.2; $\mathrm{Cl^-}$, −3.3; $\mathrm{OAc^-}$, −3.1; lactate, −3.0; salicylate, +0.2; oNPOE, TDDMACl)[763] and benzoate formed by the enzymatic hydrolysis of benzoylcholine, allowing to determine cholinesterase activity in blood serum (log $K^{\mathrm{pot}}_{\mathrm{benzoate,J}}$ (FIM): $\mathrm{HCO_3^-}$, −1.0; $\mathrm{Cl^-}$, −3.4; $\mathrm{Br^-}$, −2.5; $\mathrm{OAc^-}$, −2.6; lactate, −2.6; salicylate, +0.4; oNPOE, TDDMACl).[762]

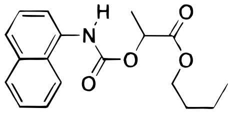


CA-4: n = 2
CA-5: n = 3



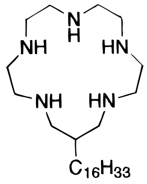
A-30 (phenylpyruvic acid)

Only few salicylate optodes were demonstrated so far. The selectivity of an indium(III) octaethylporphyrin (**Cl⁻-4**) based optode for salicylate over lipophilic ions was found to be very good, but the interference from $\mathrm{Cl^-}$ was quite large.[794] However, interesting selectivities were found for an optode based on coextraction of salicylate and hydrogen ions.[965] While fluorescence measurements were used to detect the protonation of the underivatized dye Nile Blue, butyl *O*-(1-naphthylaminocarbonyl)lactate (**CA-6**) was used as the carrier that presumably binds salicylate by $\pi-\pi$ interactions. The selectivity of this optode for a variety of inorganic and organic anions was measured (log $k^{\mathrm{Oscl}}_{\mathrm{Sal,J}}$ (SSM): ClO_4^-, +0.1; Cl^-, −2.8; OAc^-, <−3; DOP).

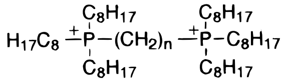


CA-6

Other Carboxylates. Discrimination between the ortho, meta, and para isomers of phthalate is possible even with ionophore-free ion-exchanger electrodes (log $K^{\mathrm{pot}}_{o-\mathrm{pht.,J}}$ (FIM): *m*-phthalate, <−2; *p*-phthalate, <−2; nitrobenzene, pH 4).[966,967] Because of the fairly large differences in the p*K* values of the three isomers, the selectivities depend strongly on the pH, which also determines whether mono- or dianions are detected. Also the choice of the membrane solvent seems to have a notable influence on selectivities. Using an ISE based on a macrocyclic polyamine (**CA-7**),[895] a selectivity in the order ortho > meta > para was observed at pH 7.4, and the detection limit for phthalate dianions was significantly lower than that reported for an ion-exchanger electrode.[967] In contrast, a selectivity order of para > ortho was found at pH 11 for an ISE with an anion-exchanger membrane based on the dicationic decamethylenebis(trioctylphosphonium) (**CA-8**) and the plasticizer DOP, which is just the reverse to the selectivity order for a membrane containing Capriquat and the same plasticizer.[968] However, a preference for the para isomer at pH ≥ 8 was also reported for a simple ion exchanger membrane with a 85:15 mixture of the plasticizers dibutyl phthalate and tributyl phosphate.[967] Similarly, hexamethylenebis(trioctylphosphonium) dication (**CA-9**), an isomeride of **CA-8**, was reported to be more selective for 1,5-naphthalenedisulfonate than a corresponding Capriquat ion exchanger.[969]



CA-7



$$H_{17}C_8-\overset{C_8H_{17}}{\underset{C_8H_{17}}{\overset{+}{P}}}-(CH_2)_n-\overset{C_8H_{17}}{\underset{C_8H_{17}}{\overset{+}{P}}}-C_8H_{17}$$

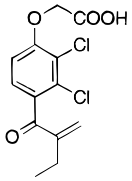
CA-8: n = 10
CA-9: n = 6

At neutral or acidic pH, ionophore-free anion-exchanger electrodes respond more strongly to maleate than to fumarate (log $K^{\mathrm{pot}}_{\mathrm{mal,fum}}$ (FIM): <−3; nitrobenzene, pH 4).[966] While the maleate selectivity of these ISEs is nearly completely lost at pH 8.22, where both isomers occur almost exclusively in their dianionic form, an ISE based on the macrocyclic polyamine **CA-7** discriminates fumarate even at this high pH and has a much lower detection limit than the ionophore-free anion-exchanger ISE.[895]

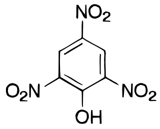
Membranes containing a classical ion exchanger, a cyclic polyamine, or a macrocycle with either a diaminopyridine or a diaminopyrimidine unit were used for the potentiometric detection of carboxylates in liquid chromatography. The ISE based on the macrocyclic polyamine **CA-7** was found to have the shortest response time, giving only small tailing of the elution peaks.[970] However, it should be noticed that due to the logarithmic response to concentration changes some tailing is inevitable when using ISEs as detectors for chromatography: ISEs always respond more slowly to concentration steps from a concentrated to a more diluted solution than to concentration steps in the opposite direction.[2]

ISEs with bis(*p*-chlorobenzyl)tin (**phosphate-3**) or bis(*p*-fluorobenzyl)tin (**phosphate-4**) as carrier were found to strongly respond to tribasic citrate. Because no correlation between the electronegativity of the substituents on the benzyl rings was found, it was concluded that the mechanism of this response is different from that of the phosphate response.[841]

Fluorescence optodes with lipophilized fluorescein derivatives (e. g. **H^+-25**) incorporated into PVC membranes were found to respond to many carboxylic acids, the selectivities being governed by the lipophilicity of the analyte.[971] For benzoic acid, for example, a detection limit below 1 × 10^{-4} M was determined. The response mechanism was not clarified, but it was speculated that hydrogen-bond formation between the carboxylic acid and the fluorescence dye decreases the probability of collision of two dye molecules, enhancing the fluorescence intensity. A decrease of the measured fluorescence on the other hand is observed in the presence of phenol as interferent, which acts as a fluorescence quencher. Similarly, hydrogen bonding seems to play a role in the response of a 1,4-bis(1,3-benzoxazol-2-yl)benzene-based fluorescent sensor for the diuretic ethacrynic acid (**A-31**) and for picric acid (**A-32**).[972,973] Optical sensors for carboxylic acids that are based on extraction of the neutral species and either nonspecific hydrogen bonds or protonation of a membrane dye that does not bind the thus formed carboxylate specifically will, however, not be discussed here further. Note also the use of Severinghaus-type ISEs (see also sections V.1. and V.2)[974] to measure acetic acid, and the use of solid-state ISEs to determine acetic acid in ethanol with the fluoride isoconcentration method[975] (see also section V.5. for use of isoconcentraton method[976] for H_2O measurements in organic solvents).



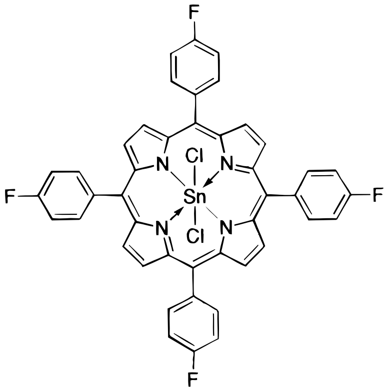
A-31 (Ethacrynic acid)



A-32 (picric acid)

4. A Sensor for 2-Hydroxybenzhydroxamate

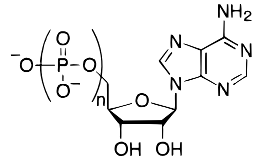
It was recently found that ISEs based on tin(IV) tetraphenylporphyrins, which were previously reported for salicylate analysis (see **SCN^--7**, section IV.3), are very suited for the potentiometric determination of 2-hydroxybenzhydroxamate (**A-33**; HBHA).[977] This analyte is a chelating agent that is also used for photometric measurements of soft metal ions and as a drug in prevention of kidney stone formation. The good selectivities of electrodes with **HB-1** as ionophore and tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate as anionic site indicate a charged carrier mechanism (**HB-1**; $\log K^{\mathrm{pot}}_{\mathrm{HBHA,J}}$ (SSM): ClO_4^-, −2.5; SCN^-, −2.2; Cl^-, −2.6; salicylate, −1.5; oNPOE, KTFPB). The response slopes of −76 to −73 mV/decade were reported to be reproducible and are probably due to a dependence of the ratio of 1:1 and 2:1 complexes in the ISE membrane on the 2-hydroxybenzhydroxamate concentration in the sample. A photometric titration and the relatively slow response (≈90 s) seem to confirm this interpretation. An assay of 2-hydroxybenzhydroxamate in drug capsules with this ISE was demonstrated.



HB-1

5. Sensors for Nucleotides

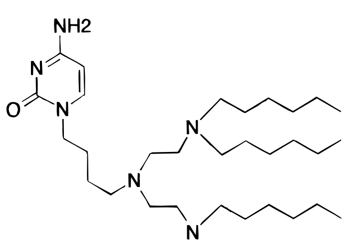
Protonated macrocyclic polyamines and adenosine 5′-mono-, 5′-di-, or 5′-triphosphate (5′-AMP, 5′-ADP and 5′-ATP; **A-34** to **A-36**, respectively) form stable 1:1 complexes in aqueous solutions ($\log \beta = 3.12$, 3.13, 3.62, respectively). This observation led to the development of ISEs with either a lipophilic macrocyclic tetra- or pentaamine as carrier.[831,894] For the latter, the range of the linear response to 5′-ATP^{4-} (−14.5 mV/decade) from 10^{-7} to 10^{-3} M was larger than for ionophore-free anion exchanger electrodes and the discrimination of many anions was fairly high (**CA-7**; $\log k^{\mathrm{MPM}}_{5'\text{-ATP,J}}$ (for step of primary ion concentration from 1.0×10^{-5} M to 2.0×10^{-5} M): 5′-ADP^{3-}, −1.4; 5′-AMP^{2-}, −1.5; Cl^-, −3.2; NO_3^-, −0.9; DOP; pH 6.7). The lack of a response to anions at high pH and the effect of the pH on the measured emf suggest that protonation of the carrier is a prerequisite for the emf response, as also reported for carrier-based pH electrodes.[62] Note that macrocyclic polyamines were also suggested for the potentiometric detection of organic acids and inorganic phosphate (e. g. **phosphate-8**; see section III.6).



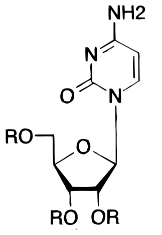
A-34 (5'-AMP): n = 1
A-35 (5'-ADP): n = 2
A-36 (5'-ATP): n = 3

Similar response slopes of −14.2, −21.4, and −28.5 mV/decade have been observed as responses to 5′-ATP, 5′-ADP, and 5′-AMP, respectively, of ISEs with (bis(*p*-chlorobenzyl)tin dichloride (**phosphate-4**) as ionophore.[840] For 5′-ATP a detection limit of $10^{-6.1}$ M was determined. Dibenzyltin dichloride ionophores were also used in the development of ISEs for inorganic phosphate (see section III.6).

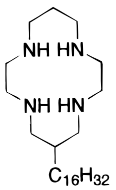
To obtain discrimination among nucleotides with different base pairs, electrodes containing either a triamine ionophore with a cytosine pendant (**NT-1**) or a lipophilic derivative of cytidine (**NT-2**) in the presence of a macrocyclic polyamine (**CA-7** or **NT-3**) were presented.[896,897] In the case of the former electrode, nearly all-or-none selectivities for guanosine 5′-triphosphate (5′-GTP; **A-37**) and 5′-monophosphate (5′-GMP; **A-38**) over 5′-ATP and 5′-AMP, respectively, were obtained and explained by ditopic recognition based on complementary base pairing and electrostatic interactions between the phosphate and the protonated amine groups. However, sub-Nernstian slopes (−10 mV/decade for 5′-GMP) reduced the sensitivity. Similarly, the two electrodes with a cytidine derivative and one of two macrocyclic tetraamines gave slopes of −40 and −23 mV/decade for 5′-GMP. Multiple protonation equilibria seem to complicate the response of these electrodes. Their selectivity seems to arise at least partly due to formation of ternary complexes formed by the analyte, cytidine derivative, and protonated tetraamine.



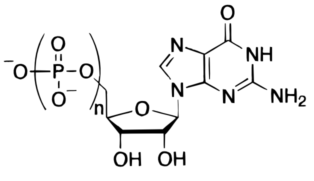
NT-1



NT-2: R = Si[CH(CH3)2]3

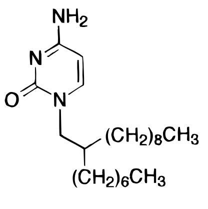


NT-3

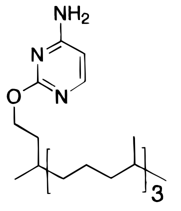


A-37 (5'-GTP): n = 3
A-38 (5'-GMP): n = 1

While anion-exchanger electrodes without ionophore do not discriminate between 5′-GMP and 5′-AMP, it was recently shown that use of neutral derivatives of cytosine (**NT-4**, **NT-5**) in the presence of tridodecylmethylammonium sites allows discrimination between these two nucleotides (log $K^{\mathrm{pot}}_{5'-\mathrm{GMP},5'-\mathrm{AMP}}$ (SSM): −0.35; DOP, TDDMACl).[929,978] Such electrodes represent the first cases of ISEs with Nernstian slopes in which potentiometric selectivities are only due to the formation of hydrogen bonds between a neutral ionophore and a neutral moiety of the analyte. Because of non-Nernstian slopes, it is difficult to interpret the selectivity of the above-mentioned nucleotide electrodes based on ionophores with multiple amine groups. On the other hand, the selectivity of the ISE based on **NT-4** or **NT-5** can be discussed on the basis of thermodynamic equilibria at the phase boundary between sample and ISE membrane. The potentiometric selectivity was smaller than expected for formation of three hydrogen bonds between analyte and ionophore and required a more elaborate investigation. Variation of the ionophore/site ratio indicated different stoichiometries for the complexes of 5′-GMP and 5′-AMP, and ^{13}C NMR spectroscopy with PVC membranes showed ionophore solvation and self-association in the membrane. Such factors are expected to diminish the potentiometric selectivity and, in hindsight, very likely played a role for previous nucleotide electrodes too. They must be sufficiently considered when designing future electrodes for analytes with hydrogen-bond donor and acceptor groups.

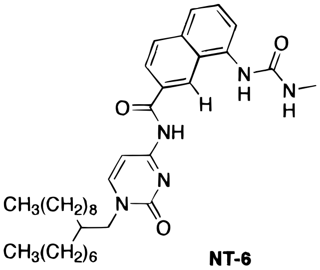


NT-4



NT-5

In an attempt to obtain higher complexation selectivity, ionophore **NT-6**, which can form five hydrogen bonds to the guanine base, was synthesized.[979] The UV/vis spectra of **NT-6** in a mixed solvent of $CHCl_3$ and DMSO (4:1, v/v) undergo no significant changes upon complexation of this ionophore with a guanosine derivative but the fluorescence emission is quenched, whereas complexation with a lipophilic adenosine derivative was not found to result in fluorescence quenching at all. A smaller but still significant selectivity for 5′-GTP (**A-37**) was found for a fluorescence optode based on a membrane containing **NT-6** and ionic sites.

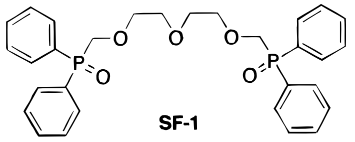


NT-6

6. Sensors for Ionic Surfactants

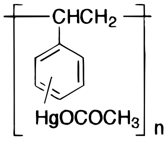
Because analysis of surfactants is of major interest for the detergent industry, environmental control, and the determination of physical surfactant properties such as the critical micelle concentration, a large number of ISEs for anionic, cationic, and neutral surfactants were reported.[19,980] The vast majority of these sensors is, however, based either on ion exchangers without any specific interactions with the analyte or, for neutral analytes, on the formation of a charged complex with an inorganic cation initially present or added to the sample solution.[981−983] Similarly, optical sensors based on the formation of nonspecific ion pairs with charged surfactants were reported.[984] The number of truly carrier-based surfactant electrodes is very limited.

It could be expected that many ionophores used for the determination of NH_4^+ or organic ammonium ions can also be used for sensing surfactants with ammonium groups. Indeed, an ISE based on dibenzo-18-crown-6 (**K$^+$-4**) was reported to have an alkylammonium/1-dodecylpyridinium selectivity that is roughly 100 times larger than that of a corresponding ISE without ionophore.[921] As for ionophore-free ion-exchanger ISEs too, the ISE based on **K$^+$-4** had a selectivity for a homologous series of surfactants that increased with the surfactant lipophilicity, i.e., with the length of the alkyl chain. Little interference from inorganic ions was observed in the measurement of typical surfactants. As compared to such electrodes with dibenzo-18-crown-6 as ionophore, ISEs based on podands with diphenylphosphine oxide terminal groups (e. g. **SF-1**) showed a much higher discrimination of alkali metal ions.[939] Unfortunately, data that would allow comparison of such selectivities with that of a classical ion exchanger seem not available (note that ionophores similar to **SF-1** were also incorporated into ISEs for dodecylpyridinium and dodecyltrimethylammonium measurements;[937] e. g. **AM-14**, see section IV.1). For the determination of long-chain alkyl trimethylammonium ions with ISEs based on cyclodextrin derivatives see above under “ISEs for Quaternary Ammonium Compounds” (section IV.1).



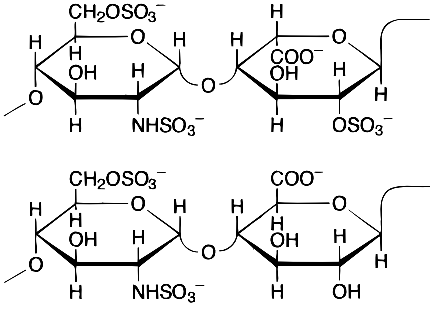
SF-1

Mercurated polystyrene with RC_4H_4HgOAc groups (**SF-2**) was reported for the detection of anionic surfactants.[878,879] The response to inorganic anions was weak ($I^- \gg SCN^- > Br^- \gg Cl^- > NO_3^- > F^-$) but clearly deviated from the Hofmeister sequence, giving evidence for specific interactions with the mercury centers. For several sulfonates and dodecyl sulfate, a selectivity sequence deviating from that of the lipophilicities was observed, but the differences were relatively small. Note that organomercury ionophores were also used in Cl$^-$ ISEs (e. g. **Cl$^-$-5** and **Cl$^-$-6**; see section III.10). Another group of ISEs for dodecyl sulfate was based on Cu(II) complexes of ethylenediamine derivatives.[844] Hydrogen bonding between analyte and the Cu(II) complex may explain this selectivity (note a similarity to anion ISEs based on Ni(II) complexes;[846] see section III.6). Similarly, anion-exchanger electrodes with *o*-dichlorobenzene as plasticizer and alkylphenols as additives have a selectivity for *p*-toluenesulfonate over ClO_4^-, whereas use of *o*-dichlorobenzene alone results in a high selectivity for ClO_4^- (log $K^{pot}_{p\text{-toluenesulfonate},ClO_4}$(SSM): -0.6; *o*-dichlorobenzene, 0.5 M *p*-(1,1,3,3-tetramethylbutyl)phenol, methyltrioctylammonium *p*-toluenesulfonate; log $K^{pot}_{p\text{-toluenesulfonate},ClO_4}$ (SSM): $+2.3$; *o*-dichlorobenzene, methyltrioctylammonium *p*-toluenesulfonate).[985] Here too, hydrogen bonding to the analyte seems to be the crucial factor that provides sulfonate selectivity.

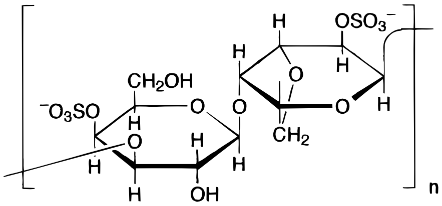


SF-2

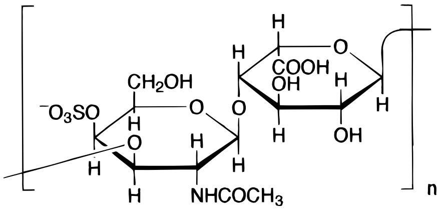
7. Sensors for Polyionic Analytes Such as Heparin and Protamine



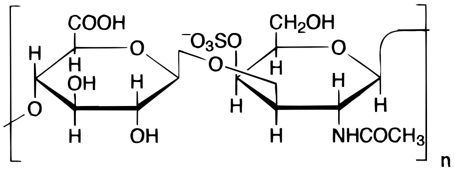
A-39 (heparin is a natural polymer composed mainly of two repeating disaccharide units)



A-40 (iota-carrageenan)



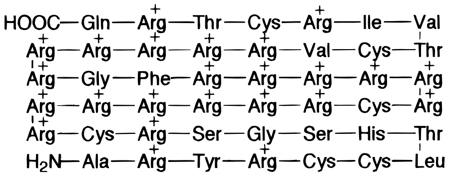
A-41 (dermatan sulfate)



A-42 (chondroitin sulfate A)

Polyanions such as highly sulfated polysaccharides are widely used in medicine as anticoagulants (e. g., heparin, **A-39**) and in the food industry as thickening agents (e. g., carrageenan, **A-40**, a synthetic polysaccharide derivative). It is well-known that lipophilic quaternary ammonium ions can bind heparin tightly. Meyerhoff and co-workers exploited this observation to develop potentiometric sensors for the direct detection of heparin (for a review, see ref 986). Early studies revealed several unusual effects associated with the heparin response. In particular, it was observed that the response depends significantly on the plasticizer content of the sensor membrane, as well as on the geometry of the sensor configuration and stirring rate of the sample. Furthermore, such sensors normally exhibit super-Nernstian response slopes, a feature that is welcomed in view of the fact that Nernstian slopes toward highly charged species (typical polyion valencies range from 20 to 70) would otherwise render the electrode insensitive to analyte concentration changes. The response mechanism of these sensors was recently established.[987] Typical polyion samples are rather dilute so that the analyte extraction from the sample into the membrane leads to significant depletion of polyions in the aqueous diffusion layer. Under such conditions, the uptake of analyte is roughly proportional to its concentration in the sample bulk, which leads to super-Nernstian response slopes. Such a non-Nernstian steady-state response is essential for optimum functioning of the sensor. It must be emphasized that this effect, while usually undesired, is observed with many other ion-selective electrode membranes as well, provided that they are conditioned with a discriminated ion and the solution contains low analyte levels. Optimized heparin-sensitive electrode membranes typically contain a high mass ratio of PVC to plasticizer (DOS) of about 2 to ensure sensitivity at low analyte concentrations, and contain tridodecylmethylammonium chloride (TDDMACl) as the active membrane component. Extended potentiometric studies revealed the equilibrium ion-exchange selectivity of such membranes.[988] It was found that polyions with a high charge density were preferred by the membrane, and the selectivity toward sulfonated polysaccharides was found to follow the order: beef lung heparin > porcine heparin, carrageenan (LC-5) > dermatan sulfate (**A-41**) > kappa-carrageenan > chondroitin sulfate A (**A-42**), which corresponds quite well to the order of charge densities of these species. Interestingly, membranes containing symmetric tetraalkylammonium species such as tetradodecylammonium ions showed nearly no preference among these polyions. This indicates that cooperative interactions between the anion-exchanger site and the extracted polyion can amount to analytically useful selectivity, even with membranes containing only so-called ion-exchanger sites. An optical heparin sensor was recently also described.[989] It makes use of the coextraction of H^+ and heparin into a membrane that contains TDDMACl and a lipophilic anionic dye. The color change associated with the protonation of the dye is related to the sample heparin concentration.

Analogous potentiometric sensing membranes, with an incorporated cation exchanger such as a tetraphenylborate derivative or dinonylnaphthalene sulfonic acid, were developed for polycationic analytes such as protamine (**A-43**).[900] Protamine is routinely used as antidote for heparin, because addition of protamine to the sample will bind to excess heparin. Titration of heparin with protamine was used to accurately determine heparin in whole blood with the potentiometric heparin sensor. A recent clinical study involved 162 samples from 24 patients undergoing cardiopulmonary bypass, and good agreement was found with values obtained with a commercial assay system.[990]



A-43 (protamine)

V. Neutral Analytes

1. CO_2 Sensors

Carbon dioxide is often determined by Severinghaus-type potentiometric sensors, which are based on permeation of carbon dioxide through a gas-permeable membrane into an internal hydrogen carbonate solution and indirect determination carbon dioxide by measuring the pH of that internal solution.[974,991,992] Severinghaus-type sensors are well-accepted for measurements in aqueous samples, such as bacterial cultures, carbonated beverages, or wine, for transcutaneous use and as sensing element in enzyme electrodes, but they fall out of the scope of the present review. The latter is also true for optodes based on an analogous principle, i.e., measurement of the pH of an internal solution or a membrane layer by use of a proton-selective chromo- or fluoroionophore.[993−995] In contrast to CO_3^{2-} sensors (see section III.1), ISEs and optodes for CO_2 based on a carrier (for CO_3^{2-} or CO_2) seem so far not to be known.

An approach with a sensor assembly similar to that of Severinghaus-type electrodes is based on the use of a membrane containing a H^+ ionophore separating the pH-buffered sample solution from an unbuffered internal electrolyte solution (typically 10 mM NaCl to minimize changes in the ionic strength and diminish water permeation through the membrane due to osmotic pressure) with an internal reference electrode. Using a planar sensor design, response times, which had been very long in early versions of this sensor, could be reduced to as low as 30 s and suitability for clinical measurements was shown (log $K^{\mathrm{pot}}_{\mathrm{CO_3,J}}$ (SSM): Cl^-, <-2.7; OH^-, <2.7; $H_2PO_4^-$, <-1.9; HPO_4^{2-}, <-3.0).[768,996] Responses of this electrode result because carbon dioxide permeates through these membranes and changes the pH of the unbuffered internal electrolyte solution. This changes the phase boundary potential at the interface between membrane and internal electrolyte solution. Because the emf response depends on the HCO_3^- activity with a response slope indicative of a monoanion, as shown in theory and practice, this type of electrode was called HCO_3^--selective.[51,767] It resembles a Severinghaus-type ISE with a carrier-based H^+ ISE to monitor the internal pH in many respects: (i) one solution is unbuffered and is in contact with a reference electrode (R), (ii) the emf response arises due to a change in the phase boundary potential at the interface of this unbuffered solution and a pH selective membrane, and (iii) a second solution on the other side of the membrane is pH-buffered and contains a second reference electrode (R′). In the case of the "HCO_3^--selective" electrode, the buffered solution is the sample solution, and in case of the Severinghaus-type ISE it is the internal reference solution of the pH sensor. The two setups differ in the fact that the two reference electrodes R and R′ are connected to the millivolt meter in opposite sense, explaining the opposite signs of the response slope. Because the same "monoanionic" response as observed with the "HCO_3^--selective" electrode should also be obtainable with a Severinghaus-type ISE by simply inverting the sign of the measured emf, it seems justifiable to consider this electrode to be a CO_2 sensor rather than a HCO_3^--selective electrode. In view of very long response times of 15−20 min, the same may be true for a "HCO_3^--selective" electrode with tridecylamine as carrier.[769]

Severinghaus-type CO_2 sensors offer the advantage that they can be very compactly combined with potentiometric sensors for ionic analytes such as alkali metal ions. An ionophore for the ionic analyte is incorporated into the CO_2 permeable membrane and an internal solution of the ionic analyte with an inner reference and a pH electrode is used.[992] The activity of the ion of interest can then be monitored by measuring the potential across the CO_2 permeable membrane, using the inner reference electrode and a reference electrode in the sample. CO_2 is determined with the circuit containing the pH and the inner reference electrode.

2. Sensors for Ammonia and Organic Amines

Severinghaus-type NH_3 electrodes are based on a gas-permeable membrane that separates the sample from an internal solution in which a glass electrode monitors the pH.[974,997−999] Methods to determine ammonia in drinking, surface, and saline waters and wastewaters with such electrodes have been approved by the United States Environmental Protection Agency (EPA)[1000] and are also described in "Standard Methods".[826] Other applications include determinations in air and stack gases, plating baths, fish tanks, food, and beverages. Better selectivities and lower detection limits can be obtained when the internal NH_4^+ activity is measured with an ISE based on nonactin (**NH_4^+-1**).[1001−1004] Whereas many amines have a higher pK_a than ammonia and therefore interfere particularly strongly with internal pH measurements, the internal nonactin electrode responds to ammonium roughly 100 times stronger than to many alkylamines.[1002] The unsatisfactory selectivity of nonactin for NH_4^+ over Na^+ and K^+ is obviously not relevant here. While such electrodes can also be used for monitoring NH_3 in air,[1005] the majority of reported applications concern NH_3 measurements in aqueous solutions.

An NH_3 optode that differs from the nonactin-based NH_4^+ optode described in section II.7 by an additional gas-permeable membrane between the aqueous sample solution and the PVC membrane, was used for ammonia determinations in aqueous samples.[432] Essential in the preparation of this NH_3 optode is conditioning of the KTpClPB-containing PVC membranes with aqueous NH_4Cl solution to allow exchange of K^+ for NH_4^+ ions before the gas-permeable membrane is applied. By replacing nonactin with valinomycin (**K^+-1**), which forms weaker complexes with NH_4^+ than nonactin, the dynamic range of the optode can be shifted from roughly $10^{-6}-10^{-4}$ M to $10^{-5}-10^{-3}$ M. The high selectivity of NH_4^+ carrier based optodes is certainly their major advantage as compared to the many similar devices based on a pH indicator alone.[1006−1010]

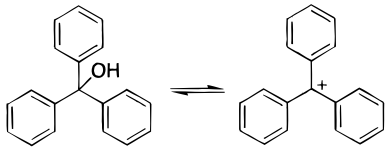
For measurements of ammonia in gaseous samples, the Na^+ ionophore **Na^+-2** (ETH 157), which also binds NH_4^+, was found to be very useful because, in contrast to valinomycin-based optodes, humidity did not influence the response of corresponding optodes.[1011] Such optodes had a measuring range of 0.002 to 100 ppm_v NH_3, and no interferences from SO_2, CO_2, and NO_2 were observed. Alkylamines interfere, however, and thus in their presence the more selective valinomycin should be chosen. Another NH_3 optode was based on the Mn(II) complex of 5,10,15,20-tetra(phenyl)porphyrin (cf. **SCN^--7**) as carrier,[1012] giving a detection limit of 0.63 ppm NH_3. The humidity dependence of the response of this sensor varies with the wavelength and could probably be eliminated chemometrically.

Detection of organic amines, which evolve in spoiled fish and other food, is possible by use of acidic dyes, as for example demonstrated for trimethylamine.[1013] Because the only factor influencing the selectivity of such sensors is the pK_a of the amine, discrimination of different organic amines is not possible but could probably be achieved by additional use of a carrier for organic ammonium ions (see section II.7). Similar optical sensors based on an acidic dye but no ionophore for the analyte were also reported for ammonia.[1014−1016]

3. Sensors for Humidity and Water

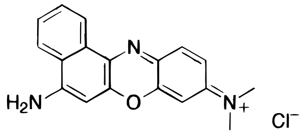
Many different types of sensors for measuring moisture in air were developed for an abundance of applications, such as in industry, agriculture, medicine, and domestic households. Typical humidity sensors are based on the humidity dependence of the impedance or capacitance of porous ceramics, electrolytes, or organic polymers with ionic groups,[1017,1018] but also coulometric, dew point, gravimetric, microwave, piezoelectric, psychrometric, thermal conductivity, and recently optical humidity sensors were reported. Most often water is physically adsorbed, absorbed or chemisorbed to an inorganic salt, such as $CoCl_2$.

Nafion membranes containing triphenylcarbinol[1019] (**HU-1**) and plasticized PVC membranes incorporated with trifluoroacetophenone derivatives[1020] (**CO_3^{2-}-3**, **CO_3^{2-}-4**) are the basis of two carrier-based optical humidity sensors whose response arises due to formation of a covalent bond to the ionophore. In the case of the triphenylcarbinol ionophore, conversion of the triphenylcarbenium cation in the presence of water to triphenylcarbinol can be followed by absorbance measurements at 430 nm, allowing determination of the relative humidity (RH) of air up to 30%. Wider ranges of 1−53% RH and 5−100% RH were found for sensors based on two trifluoroacetophenone derivatives, to which water is chemically bound by reaction of the trifluoroacetyl group (optical detection at 253 and 261 nm, respectively). Incorporation of small amounts of the quaternary ammonium salt TDDMACl and dipping the membrane into water before use leads to acceleration of the ionophore hydration, shortening the response times to a few seconds. This effect was explained by partial exchange of Cl^- by OH^- when the membrane is contacted with water. The absence of interferences from acetic acid (2000 ppm), ammonia (100 ppm), NO_2 (10 ppm), and SO_2 (10 ppm) at 10% RH, as observed for **CO_3^{2-}-3**, demonstrates the high selectivity of these sensors. While other trifluoroacetophenone derivatives were used as carbonate carriers in ISEs, the trifluoroacetophenone-based humidity sensors do not respond to concentrations of CO_2 as occurring in normal air.

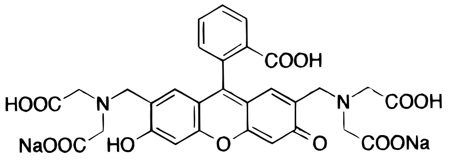


HU-1 (carbinol)

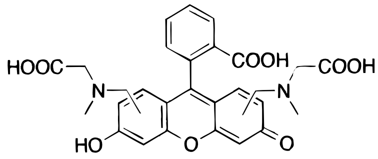
Fluorescence sensors for humidity based on the organic dyes cresyl violet (**HU-2**),[1021] calcein (**HU-3**; also called fluorexon),[1010] methyl calcein (**HU-4**),[1022] or umbelliferone[1023] (**HU-5**) were demonstrated. With the exception of the last sensor, these optodes were also found to respond to ammonia up to 2500 ppm. While in the above cases the optode response was reported to arise from shifts of protonation equilibria in the presence of water, formation of unidentified complexes between the dye and H_2O was suggested for an optode based on rhodamine 6G (**HU-6**).[1024]



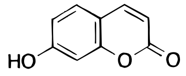
HU-2 (cresyl violet)



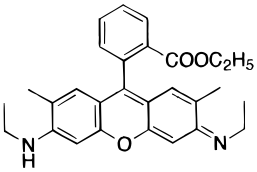
HU-3 (calcein)



HU-4 (methyl calcein)



HU-5 (umbelliferone)



HU-6 (rhodamine 6G)

The effect of water on the activity of H^+ at a constant concentration, as measured with solid-state pH electrodes, was used to determine water in organic solvents such as methanol, ethanol, propanone, acetonitrile or acetic acid.[976,1025,1026] Applications of carrier-based electrodes for the determination of water in organic solvents seem not to be known.

4. SO_2 Sensors

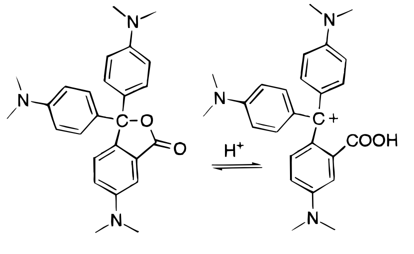
In presence of water, sulfur dioxide reacts by formation of a covalent bond with the neutral carrier octadecyl-4-formylbenzoate (**sulfite-3**), which was also used for an optode for hydrogen sulfite (see section III.8).[854] This carrier was employed for SO_2 detection down to 4 ppb_v in humid gas samples.[855] Use of a lipophilic alcohol as membrane additive or of PVC-OH makes responses to SO_2 also in absence of humidity possible, and a secondary amine improves response times from 20 to several minutes by catalyzing the bisulfite addition reaction. While elimination of the carrier further decreases response times to 0.5 min, this is accompanied by less favorable detection limits and selectivities. Virtually no responses to CO_2 were observed, but NO_x seemed to react with the H^+-selective chromoionophore. Note that also Severinghaus-type electrodes (see also sections V.1. and V.2) were described for the determination of SO_2.[974]

5. Sensors for Alcohols and Nonionic Surfactants

The cationic responses to aqueous solutions of methanol, ethanol, and propanol at concentrations between 10 and 90% as obtained with potassium stearate gel membranes were some of the earliest reported potentiometric responses to neutral compounds.[1027] They were explained by the influence of these alcohols on the stearate gel structure and the activity of the potential-determining K^+ in the sample solution. Similarly, solid-state electrodes were used to measure the effect of water in organic solvents on the activity of an ion of constant concentration (isoconcentration method),[976] allowing the determination of, for example, water in methanol, ethanol, propanone, acetonitrile, or acetic acid.[1025,1026] Also, the effect of ethanol on the activity of nitrate was used to determine ethanol in alcoholic beverages.[1028] Whereas the potentiometric responses to a series of nonionic alcohols (e. g. nonan-1-ol, benzyl alcohol, 2-phenylethanol) for valinomycin and crown ether-based ISEs were relatively small,[374,1029] larger effects of nonionic poly(ethylene oxide)-based surfactants were observed for hydrogen ion selective electrodes.[72] In the latter case, interactions between the surfactant and the polymeric polyamine in the membrane apparently shift the pK_a values of the amine sites, which changes the H^+ activity in the membrane phase. The potentiometric responses to catechols as observed for PVC membranes containing a macrocyclic pentaamine (**CA-7**),[898] a tetraalkylammonium chloride,[1030] or electrochemically polymerized crown ethers,[931] and to phenols as obtained with tetraalkylammonium chloride-based ISEs[1030,1031] seem all to be based on similar principles.

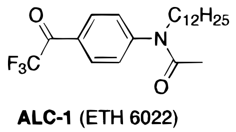
An application of ISEs for the determination of nonionic surfactants is the analysis of detergent formulations. Barium ion selective electrodes based on the tetraphenylborate salts of Ba^{2+}-alkoxylate complexes respond to nonionic alkoxylates (e. g. nonylphenoxypoly[ethyleneoxy]ethanol) in a range from 2×10^{-5} to 10^{-3} M.[600,1032−1038] Unfortunately, the response times of these sensors are in the minute range, reaching up to 15 min at low surfactant concentrations. So far, a potentiometric sensor with a synthetic carrier that selectively binds an alcohol or surfactant seems not to be known.

An optical sensor based on bis(phenol) as acid and **H^+-42** as base was found to respond to various polar solvents (ethanol, methanol, ethyl acetate, acetone).[1039] It was suggested that these alcohols disturb the hydrogen bond network of bis(phenol) and **H^+-42** but a carrier mechanism in a narrow sense is not evident.



H^+-42

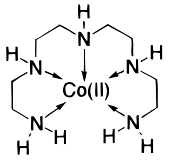
Formation of the hemiacetal of the trifluoroacetophenone derivative **ALC-1** by reaction with ethanol leads to loss in electron delocalization between the trifluoroacetyl and benzene group and results in a large hypsochromic shift of the absorption band of **ALC-1**. Optodes based on this principle respond 11 times stronger to ethanol than to water, allowing ethanol determinations in alcoholic beverages after dilution with pH buffer and decolorization with activated charcoal.[1040] 2-Propyl and *tert*-butyl alcohol are relatively well discriminated but several primary alcohols lead to responses comparable to those for ethanol (log $k^{\mathrm{Osel}}_{\mathrm{ethanol,J}}$ (SSM): H_2O, −1.1; methanol, +0.2; 1-propanol, ≈-0.1; 1-butanol, ≈+0.2; *tert*-butyl alcohol, −1.1; 2-propyl alcohol, −0.9; DOS, TDDMACl). Just as in the case of humidity sensors based on very similar ionophores (see section V.3), incorporation of TDDMACl into the optode membrane catalyzes the reaction of the ionophore with the analyte, giving response times of less than 30 s. For several other optical ethanol sensors, formation of hydrogen bonds between ionophore and analyte seems very probable[1041] but an influence of such interactions on the sensor selectivity was not confirmed.



ALC-1 (ETH 6022)

6. Sensors for O$_2$

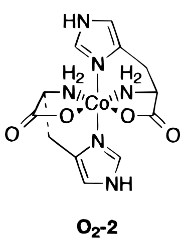
The potentiometric response of an oxygen sensor based on an in situ formed complex of tetraethylenepentaamine and cobalt(II) (**O$_2$-1**), incorporated into a membrane in direct contact to a platinum electrode, was attributed to a mixed response mechanism.[1042] The cobalt(II) compound binds oxygen reversibly, which is accompanied by a change in the redox potential of cobalt(II). A response of bare platinum electrodes with an oxide-free surface was, however, also observed. More recently, it was shown for copper electrodes that the potentiometric O_2 response is the result of O_2 reduction and simultaneous slow corrosion of copper.[1043] Potentiometric O_2 sensors based on yttrium-stabilized zirconia give responses with very small drifts but require operation at high temperatures.[1044]



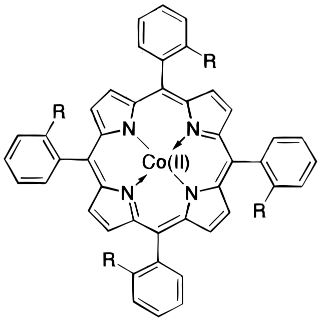
O$_2$-1

Many optical oxygen sensors that are based on quenching of the fluorescence or phosphorescence of organic or organometallic dyes were reported.[1045,1046] Two quenching mechanisms can be distinguished, i.e., dynamic quenching, which is due to collisional encounters of the excited molecules and the quencher oxygen, and static quenching, which is based on complex formation between the dye and oxygen. Most optical oxygen sensors are based on the former quenching mechanism and will not be discussed here further because the dye in these cases does not take the role of a carrier. On the other hand, examples of oxygen optodes based on oxygen binding, which is usually followed by vis absorption spectrometry, are only few. A smaller sensitivity to slight changes in the membrane medium and a better selectivity were suggested as their possible advantages. While at present sensors based on collisional fluorescence quenching seem to be more appropriate for measuring oxygen in blood gas analysis, oxygen carriers may be more suited for relatively inexpensive sensors and test strips.

The response of an early version of an optical, carrier-based oxygen sensor resulted from the shift in the spectrum of hemoglobin (a protein with four polypeptide chains and four oxygen-binding sites) upon oxygen binding.[1047] Unfortunately, the hemoglobin degraded within days. Sensors with bis(histidinato)cobalt(II) (**O$_2$-2**) as oxygen carrier required pH buffering and a wet environment to keep the carrier concentration constant but allowed detection limits that are as low as 0.2% in oxygen−argon mixtures.[1048,1049] A cobalt(II) porphyrin (**O$_2$-3**; cf. the similar **SCN$^-$-11**) was found to bind oxygen reversibly by interaction with the cobalt(II) centers. Its immobilization on poly[(octyl methacrylate)-*co*-1-vinylimidazole] or poly[(2,2,3,3,4,4,5,5-octafluoropentyl methacrylate)-*co*-1-vinylimidazole] was used to make optodes for the determination of oxygen in gas samples. Their response range was 1−1000 hPa of oxygen partial pressure and response times were between 5 and 15 s.[1050] Use of the latter polymer, which is the more hydrophobic one, decreases the influence of humidity on O_2 determinations to experimental errors of less than 5−10%, which can be further decreased if humidity is measured separately and its influence is compensated chemometrically. No interference from CO and CO_2 was observed, but other possibly interfering gases were not studied. Following an initial conditioning period, the response characteristics of these sensors remain nearly constants for at least 1 to 2 months.



O$_2$-2



O$_2$-3: R = NHC(O)C(CH$_3$)$_3$

VI. Conclusions

Carrier-based ion-selective electrodes and bulk optodes have been described for over 60 and 30 analytes, respectively. This impressive number reveals that these sensor classes are generic and highly successful approaches to chemical sensing. The chemistry that enables these electrodes and optodes to function selectively in complicated sample matrixes is rich and versatile. In most cases, a number of different ionophores are available for the same ion. Moreover, the sensor selectivity can be dramatically improved for a given ionophore by optimizing other membrane parameters, such as the type of plasticizer and polymer, and the charge type and concentration of added ionic sites. Only in recent years has it been fully realized that selective lipophilic ionophores can be used in transduction principles other than potentiometry. It has been one of the goals of this two part review to document this development.

Although, as shown in the first part of this article, there is no fundamental difference between ISEs and bulk optodes as to response range and selectivities, bulk optodes are currently much less spread than their potentiometric counterparts. This fact can be explained with the relatively short time since their introduction. One must not forget that the breakthrough of ISEs in fields where other methods were already well established, as for example in clinical chemistry, was the result of a development that took up to two decades. It may appear as a drawback of optodes that the optical signal is directly proportional to the concentration of relevant components. Whereas ISEs are much more robust in this respect, and substantial concentration changes have only minor effects on EMF responses, minor concentration changes in optode membranes due to leaching or decomposition directly affect the signal. However, covalent immobilization of the membrane components may offer a solution to this problem. Moreover, disposable test strips that are based on the same principles as bulk optodes are not expected to suffer from leaching at all. Given the large potential for developing many sensitive optical detection methods, e. g., inexpensive ones by using photodiodes, miniaturized ones with fluoroionophores instead of chromoionophores, or sophisticated ones with integrated optical technologies, a rapid spread of optical sensors is expected.

Ion-selective electrodes are very well established in automated clinical analyzers for blood and urine electrolyte measurements. Furthermore, bulk optodes and electrodes seem now also to be suitable for trace level analysis, since recent reports have demonstrated detection limits in the picomolar range for both type of sensors.[24,669,687] Given these developments and the availability of modern microfabrication technology, the class of carrier-based sensors will surely further expand into many other areas of chemical sensing. Undoubtedly, the development and improvement of highly selective ionophores that will allow measurements of new analytes in complex real-life samples will remain a central issue in the development of such sensors. Whereas a number of satisfactory ionophores are already available for many more common metal cations, there is still a lack of more selective ionophores for anions and only fairly few carriers for organic and neutral analytes have already found wider application. General requirements that new carriers will have to fulfill have been summarized in section III.1 of the first[2] of this pair of reviews. Predictions on what type of ionophores will be important in the coming years are of course difficult. However, it seems quite likely that a number of interesting new ionophores will have a fairly high degree of three-dimensional preorganization, such as the very successful calixarenes. As for cation ionophores, more and more anion ionophores will probably bind their guests not by single point interaction, as has for example been the case for most of the organometallic ionophores so far, but by multitopic recognition. Due to the recent advances in theory, electrically charged carriers can also be expected to gain in importance. The interest of many organic chemists with chromophoric host compounds is expected to result in the development of many new interesting carriers but the preoccupation of these researchers with aqueous solvents casts some doubt on whether these results will soon have an influence on bulk membrane optodes. Unclear is the influence that the certainly very promising approach of combinatiorial chemistry will have for the development of new ionophores for ISEs and optodes. Despite enormous efforts, designing new ionophores is still not trivial. However, researchers involved in this type of molecular recognition will certainly continue to be drawn to such work, not only because it is of practical relevance but also, because of the intellectual challenge, or, from the words from S. H. Gellman[1051] in the editorial of a recent special issue of *Chemical Reviews* on molecular recognition, because “it is, well, cool”.

VII. Acknowledgments

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VII. Appendix I. Properties of a Selection of Representative ISEs and Bulk Optodes

Table 1 summarizes major characteristics of a small selection of carrier-based ion-selective electrodes and bulk membrane optodes that have been used either for measurements in real life samples, that have been found to be more selective than other ISEs or optodes for the same analyte, or that we have considered otherwise as particularly representative. For the convenience of potential users of these sensors, ionophores that we could easily identify as commercially available are marked with an asterix (*). It should be noted that the listed selectivity coefficients have been measured with several different methods and, therefore, cannot always be compared directly with one another.

Table 1

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M) primary ion	concentration (M) interfering ion	slope (mV/decade)	linear range (M)	remarks	literature refs
H^+-Selective Electrodes								
*Tridodecylamine**								
tridodecylamine (1.0 wt %), KTpClPB (63.1 mol %), DOS (65.6 wt %), PVC (32.8 wt %)	Na^+, −10.4; K^+, −9.8; Ca^{2+}, <−11.1	FIM	−	1.0	57.8	10^{-11}−$10^{-4.5}$	20 °C	31,46, 51,70
*4-Nonadecylpyridine (ETH 1907)**								
4-nonadecylpyridine (6.0 wt %), KTpClPB (11 mol %), oNPOE (93 wt %)	Na^+, −9.7; K^+, −8.7	FIM	−	−	56.7	10^{-9}−10^{-2}	micro-electrode	56
***H^+-7** (octadecyl isonicotinate; ETH 1778)**								
H^+-7 (1.0 wt %), KTpClPB (76 mol %), oNPOE (68 mol %), PVC (30 wt %)	Li^+, −6.9	FIM	−	0.06	57.2	10^{-8}−10^{0}	20 °C	74
	Na^+, −5.6		−	0.14				
	K^+, −4.4		−	0.20				
***H^+-8** (4′-(dipropylamino)azobenzene-2-carboxylic acid octadecylester; ETH 2418)*								
H^+-8 (9.2 wt %), KTpClPB (10 mol %), Mesamol H81 (= phenylalkylsulfonic acid esters; 36.4 wt %), chloroparaffin 60C, (18.7 wt %), PVC (35 wt %)	Na^+, −8.0; K^+, −7.4	−	−	−	Nernstian	10^{-10} to $>10^{-1.0}$		75
***H^+-10** (9-(diethylamino)-5-octadecanoylimino-5*H*-benzo[a]phenoxazine; ETH 5294)**								
H^+-10, KTpClPB (70 mol %), oNPOE, PVC	Li^+, <−10.8; Na^+, −10.9; K^+, −10.5; Ca^{2+}, <−11.2	FIM	−	−	58.2	10^{-12}−10^{-4}		77
Li^+-Selective Electrodes								
***Li^+-19** (6,6-dibenzyl-14-crown-4)**								
Li^+-19 (1 wt %), KTpClPB (50 mol %), *o*-nitrophenyl phenyl ether (68 wt %), TEHP (2 wt %), PVC (28 wt %)	Na^+, −2.9; K^+, −3.2; Rb^+, −3.3; Cs^+, −2.7	FIM	−	0.05	58	−		149,150
	H^+, −3.1; NH_4^+, −3.6; Mg^{2+}, −4.6; Ca^{2+}, −4.5; Sr^{2+}, −4.5; Ba^{2+}, −4.5		−	0.5				
***Li^+-21** (7-tetradecyl-2,6,9,13-tetraoxatricyclo[12.4.4.$0^{1,14}$]docosane)*								
Li^+-21 (2−3 wt %), KTpClPB (20−30 mol %), BBPA (70 wt %), PVC (26−27 wt %)	Na^+, −3.1; K^+, −3.6; Rb^+, −3.7; Cs^+, −3.6; NH_4^+, −3.8; Mg^{2+}, <−5.0; Ca^{2+}, <−5.0; Sr^{2+}, <−5.0; Ba^{2+}, <−5.0	FIM	−	0.15	−	−		147
***Li^+-26** ((2S,3S)-(−)-2,3-bis(diisobutylcarbamoylmethyl)-1,4,8,11-tetraoxacyclotetradecane)*								
Li^+-26 (1.2 wt %), KTpClPB (0.4 wt %), oNPOE (66 wt %), PVC (33 wt %)	Na^+, −3.3	FIM	−	0.1	61	−	does not perform well in serum	159
***Li^+-29** (16-crown-4 derivative with all ether oxygens being part of tetrahydrofuran rings)*								
Li^+-29 (2.5 wt %), KTpClPB (0.5 wt %), TEHP (64 wt %), PVC (33 wt %)	Na^+, −2.8; K^+, −4.3; Cs^+, −4.6; NH_4^+, −3.2; Mg^{2+}, −5.8; Ca^{2+}, −5.5; Ba^{2+}, −5.5	SSM	0.1	0.1	58.2	10^{-5}−10^{0}	rt < 0.5 min	164,165
Na^+-Selective Electrodes								
***Na^+-15** (2,6,13,16,19-pentaoxapentacyclo[18.4.4.$4^{7.12}$.0.$^{1.20}0^{7.12}$]dotriacontane; a 16-crown-5 derivative with two decalino subunits; DD16C5)**								
Na^+-15 (3 wt %), KTpClPB (10 mol %), TEHP (68 wt %), PVC (29 wt %)	Li^+, −3.1; K^+, −3.0; Rb^+, −3.6; Cs^+, −4.0; NH_4^+, −3.3; Mg^{2+}, −4.2; Ca^{2+}, −4.0; Sr^{2+}, −3.9; Ba^{2+}, −4.3	FIM	−	0.1	−	10^{-5}−10^{-1}		221
***Na^+-33** (a calix[4]arenecrown-4 ionophore with H substituents on the upper rim; partial cone conformation)*								
Na^+-33 (3.2 wt %), KTpClPB (0.6 wt %), oNPOE (64.1 wt %), PVC (32.1 wt %)	Li^+, −2.4; K^+, −5.3	FIM	−	0.05	−	−		246
	H^+, −4.7; Rb^+, −3.7; Cs^+, −3.2; NH_4^+, −3.9 Mg^{2+}, −5.1; Ca^{2+}, −4.6; Sr^{2+}, −4.2; Ba^{2+}, −4.6		−	0.5				
***Na^+-34** (a calix[4]arenecrown-4 ionophore with tert-butyl substituents on the upper rim; cone conformation)*								
Na^+-34 (3.2 wt %), KTpClPB (0.6 wt %), oNPOE (64.1 wt %), PVC (32.1 wt %)	Li^+, −2.8; K^+, −5.0	FIM	−	0.05	−	−		246
	H^+, −5.4; Rb^+, −4.8; Cs^+, −5.0; NH_4^+, −4.4; Mg^{2+}, −4.5; Ca^{2+}, −4.4; Sr^{2+}, −4.1; Ba^{2+}, −5.5		−	0.5				

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs $\log K^{pot}_{I,J}$ (SSM), $\log K^{pot}_{I,J}$ (FIM), or $\log k^{MPM}_{I,J}$ (as specified in next column to the right); for optodes $\log k^{Osel}_{I,J}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Na^+-Selective Electrodes								
Na^+-34 *(a calix[4]arenecrown-4 ionophore with tert-butyl substituents on the upper rim; cone conformation)*								
Na^+-34 (10 mmol kg^{-1}), KTpClPB (50 mol %), DOS (≈66 wt %), PVC (≈33 wt %)	K^+, −4.9; Mg^{2+}, −8.0; Ca^{2+}, −7.7	SSM	–	–	61.3	–	conditioned with 0.01 M KCl in absence of primary ion	247
Na^+ Optode								
Na^+-34 *(a calix[4]arenecrown-4 ionophore with tert-butyl substituents on the upper rim; cone conformation)/**H^+-9** (Nile Blue isomeride ETH 2439)*								
Na^+-34 (30 mmol/kg), KTFPB (50 mol %), DOS (66 wt %), PVC (33 wt %)	K^+, <−4.0; Mg^{2+}, <−3.9; Ca^{2+}, <−2.4	SSM ($\log K^{opt}_{Na,I}$)	–	–	–	–	pH 7.0	248
K^+-Selective Electrodes								
K^+-1 *(valinomycin)**								
K^+-1 (2.5 wt %), cross-linking agent KA-1 (14.5 wt %), Silopren K1000 (83 wt %)	Li^+, −4.3; Na^+, −4.0; H^+, −4.4; Rb^+, +0.6; Cs^+, −0.2; NH_4^+, −1.8; Mg^{2+}, −4.3; Ca^{2+}, −4.2; Sr^{2+}, −4.2; Ba^{2+}, −3.8	SSM	–	0.1	59.5	10^{-4}–10^{-1}		51
K^+-1 (1.2 wt %), NaTFPB (60 mol %), DOS (65 wt %), PVC (33 wt %)	Na^+, −4.5, Mg^{2+}, −7.5; Ca^{2+}, −6.9	SSM	0.0367	0.0367	59.5	–	conditioning with 0.01 M NaCl in absence of primary ion	333
K^+-17 *(bis[(benzo-15-crown-5)-4′-ylmethyl] pimelate)*								
K^+-17 (2.8 wt %), oNPOE (69 wt %), PVC (28 wt %)	Na^+, −3.5 Rb^+, −0.7; Cs^+, −2.0 NH_4^+, −2.0	FIM	– – –	0.1 0.001 0.01	58	10^{-5}–10^{-1}		352
K^+-18 *(bis[(benzo-15-crown-5)-4′-ylmethyl] 2-dodecyl-2-methylmalonate)**								
K^+-18 (3.8 wt %), oNPOE (64.2 wt %), PVC (32 wt %)	Na^+, −3.7 Rb^+, −0.7; Cs^+, −2.0 NH_4^+, −1.4	FIM	– – –	1 0.001 0.01	55	10^{-4}–10^{-1}		362
K^+-25 *(2,2-bis[3,4-(15-crown-5)-2-nitrophenylcarbamoxymethyl]tetradecane; BME-44)**								
K^+-25 (1 wt %), NaTPB (0.4 wt %), DOS (66 wt %), PVC (32.6 wt %)	Li^+, −3.8; Na^+, −3.2; Cs^+, −2.4; NH_4^+, −2.1; Ca^{2+}, −4.2	SSM	0.1	0.1	58.1	–		370
K^+-33 *(25,27-bis(2-propyloxy)calix[4]arenecrown-5; 1,3-*alternate *conformation)**								
K^+-33 (1 wt %), KTFPB (50 mol %), DOS (65.5 wt %), PVC (33 wt %)	Na^+, −4.2 Li^+, −3.7; NH_4^+, −1.4; Mg^{2+}, −4.0; Ca^{2+}, −4.0	FIM	1.0 0.1	– –		–		250
K^+ Optodes								
K^+-1 *(valinomycin)*/**H^+-33** (N-2,4-dinitro-6-octyloxyphenyl-2′,4′-dinitro-6′-trifluoromethylphenylamine, LAD)*								
K^+-1 (3.3 wt %), LAD (1.6 wt %), DBS (70.0 wt %), PVC (25.1 wt %)	Li^+, <−4.5; Na^+, −4.0; Rb^+, 0; NH_4^+, −3.0; Mg^{2+}, <−4.5; Ca^{2+}, <−4.5; Ba^{2+}, <−4.5	SSM	1	1	–	–	pH 7.0	94
K^+-35 *(an anionic crown ether dye derived from benzo-15-crown-5)*								
K^+-35 (5.0 wt %), oNPOE (65 wt %), PVC (30 wt %)	Li^+, <−4.0; Na^+, −3.0; Rb^+, +0.1; Mg^{2+}, <−4.0; Ca^{2+}, <−4.0	SSM	0.1	0.1	–	–	dl 10^{-6} M at pH ≥10	393
Rb^+-Selective Electrodes								
K^+-1 *(valinomycin*, vide supra)*								
Rb^+-2 *(indano-3-amino-4-*p*-chlorophenylazopyrazolo[1,5-a]pyrimidine)*								
Rb^+-2 (1 wt %), KTpClPB (50 mol %), oNPOE (65.5 wt %), PVC (33 wt %)	Li^+, −2.7; Na^+, −2.4; K^+, −1.6; Cs^+, −2.0; NH_4^+, −1.9; Mg^{2+}, −3.3; Ca^{2+}, −3.2; Sr^{2+}, −3.1; Ba^{2+}, −2.7	SSM	0.01	0.01	59	10^{-4}–10^{-1}		404
Cs^+-Selective Electrodes								
Cs^+-2 *(bis([benzo-18-crown-6]-4′-yl)-2,5,8,11-tetraoxadodecane)*								
Cs^+-2 (12.5 wt %), DBP (63 wt %), PVC (25 wt %)	Li^+, <−4.3 Na^+, −2.0; K^+, −1.0; Rb^+, −1.9; NH_4^+, −2.0	FIM	– –	0.01 0.1	57	$10^{-4.3}$–$10^{-1.1}$		359

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Cs^+-Selective Electrodes								
Cs^+-3 *(1,3-bis([benzo-18-crown-6]-4′-yl)propane)*								
Cs^+-3, (7 wt %), oNPOE (63 wt %), PVC (30 wt %)	Li^+, −4.7; Na^+, −4.3; K^+, −2.2; Rb^+, −1.2; NH_4^+, −3.2; Mg^{2+}, −5.6; Ca^{2+}, −5.4	MSM	–	–	–	–	selectivity estimated from log $K_{K,J}^{pot}$	364
Cs^+-4 *(hexakis(*p-tert-*butyl)calix[6]arene hexakis(carboxymethyl ether) hexakis(ethyl ester))*								
Cs^+-4 (0.4 wt %), oNPOE (66 wt %), PVC (33 wt %)	H^+, −3.7; Li^+, −4.2; Na^+, −3.9; K^+, −2.7; Rb^+, −1.9; NH_4^+, −2.8; Mg^{2+}, −4.0; Ca^{2+}, −3.4	SSM	0.1	0.1	51	–		406
NH_4^+-Selective Electrodes								
NH_4^+-1 *(nonactin) and* ***NH_4^+-2*** *(monactin)**								
NH_4^+-1, **NH_4^+-2** (75:25, 1 wt %), KTpClPB (0.25 wt %), oNPOE (66 wt %), PVC (33 wt %)	Li^+, −2.9; Na^+, −2.3; K^+, −1.1; Mg^{2+}, −4.0; Ca^{2+}, −4.0	SSM	–	–	57	–	dl $10^{-5.3}$	421
NH_4^+-1, **NH_4^+-2** (72:28, 1.1 wt %), cross-linking agent KA-1 (13.6), silicone rubber (83 wt %)	Li^+, −4.6; Na^+, −2.8; K^+, −0.7; Rb^+, −1.1; Cs^+, −2.3; H^+, −4.7; Mg^{2+}, −4.9; Ca^{2+}, −4.8; Sr^{2+}, −5.1; Ba^{2+}, −5.3	SSM	–	0.1	57.8	10^{-6}–10^{-1}		51
NH_4^+-1 (3 wt %), KTpClPB (0.5 wt %), DOS (66.5 wt %), PVC (30 wt %)	Li^+, −3.5; Na^+, −2.4; K^+, −1.0; Rb^+, −1.5; Cs^+, −2.4; Mg^{2+}, −4.0; Ca^{2+}, −3.8; Sr^{2+}, −3.6; Ba^{2+}, −4.0	SSM	0.1	0.1	–	–		422
NH_4^+-6 *(2,5-dibenzyloxy-2,5-dimethylhexane)*								
NH_4^+-6 (69 wt %), KTpClPB (1 wt %), PVC (30 wt %)	Li^+, −1.9; Na^+, −2.3; K^+, −1.7; Rb^+, −1.1; Cs^+, −0.1; Mg^{2+}, −3.2; Ca^{2+}, −3.4; Sr^{2+}, −3.2; Ba^{2+}, −3.4	SSM	0.1	0.1	–	–		422
NH_4^+ Optode								
NH_4^+-1 *(nonactin)* and* ***NH_4^+-2*** *(monactin)/****H^+-10*** *(ETH 5294)**								
NH_4^+-1, **NH_4^+-2** (2.4 wt %), **H^+-10** (1.6 wt %), DOS (63 wt %), KTpClPB (1.5 wt %), PVC (31 wt %)	K^+, −1.2; Na^+, −2.7; Li^+, −3.4	FIM	–	–	–	–	pH 7.35	434,435
Mg^{2+}-Selective Electrodes								
Mg^{2+}-6 *(*N,N′*-diheptyl-*N,N′*-dimethylaspartamide, ETH 2220)*								
Mg^{2+}-6 (1 wt %), KTpClPB (73 mol %), oNPOE (65 wt %), PVC (33 wt %)	Li^+, −2.6; Na^+, −2.6; K^+, −2.3; Rb^+, −2.0; Cs^+, −1.3; H^+, +10.8; Ca^{2+}, −2.5; Sr^{2+}, −3.2; Ba^{2+}, −3.1	SSM	–	0.1	32	–	pH 8.8; rt ≈ 4 s	140,465
Mg^{2+}-14 *(a double-armed 18-membered diazacrown ether ionophore with two adamantyl-substituted malonamide side chains, K22B5)*								
Mg^{2+}-14 (2 wt %), KTpClPB (100 mol %), oNPOE (66 wt %), PVC (32 wt %)	Li^+, −3.7; Na^+, −3.2; K^+, −1.4; Rb^+, −0.5; Cs^+, +0.6; NH_4^+, −2.0; Ca^{2+}, −2.5; Ba^{2+}, −2.3; Sr^{2+}, −2.9	SSM	0.1	0.1	29.3	$10^{-4.7}$–10^{-1}		482
Mg^{2+}-15 *(1,2-bis(ditolylphosphine oxide)benzene)*								
Mg^{2+}-15 (2.66 wt %), (100 mol %), oNPOE (64 wt %), PVC (32 wt %)	Li^+, −3.8; Na^+, −3.1; K^+, −3.3; Cs^+, −3.2; NH_4^+, −3.4; Ca^{2+}, −2.8; Sr^{2+}, −3.6; Ba^{2+}, −3.2; Co^{2+}, −3.7; Ni^{2+}, −4.0; Cu^{2+}, −4.1; Cd^{2+}, −3.9; Al^{3+}, −3.8	MSM	–	–	30	–	rt < 3 min; dt $10^{-4.2}$	484
Ca^{2+}-Selective Electrodes								
Ca^{2+}-5 *(a 3,6-dioxaoctanediamide, ETH 1001)**								
Ca^{2+}-5 (1 wt %), KTpClPB (69 mol %), oNPOE (64 wt %), PVC (34.5 wt %)	Li^+, −2.8; Na^+, −3.4; K^+, −3.8; H^+, −4.4; Mg^{2+}, −4.4	SSM	0.1	0.1	–	–		536
	Na^+, −6.1 K^+, −6.6	FIM	– –	0.094 0.125	–	–	in Ca^{2+}-buffered solutions	536

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Ca^{2+}-Selective Electrodes								
Ca^{2+}-12 *(N,N,N′,N′-tetracyclohexyl-3-oxapentanediamide, ETH 129)**								
Ca^{2+}-12 (1 wt %), KTpClPB (53 mol %), oNPOE (65.6 wt %),	Li^+, −3.3; Na^+, −3.7; K^+, −4.0; H^+, −1.6; Mg^{2+}, −4.9	SSM	0.1	0.1	−	−		536
PVC (32.8 wt %)	Na^+, −7.4 K^+, −8.0	FIM	− −	0.094 0.125			in Ca^{2+}-buffered solutions	536
Ca^{2+}-12 (10 mmol kg^{-1}), NaTFPB (50 mol %), oNPOE (≈66 wt %), PVC (≈33 wt %)	Na^+, −8.3; K^+, −10.1; Mg^{2+}, −9.3	SSM	−	−	33.5	−	conditioning with 0.01 M NaCl in absence of primary ion	247
Ca^{2+}-14 *(a double-armed 21-diazacrown ether ionophore with two octadecyl-substituted 3-oxapentanediamide side chains, K23E1)**								
Ca^{2+}-14 (2 wt %), KTpClPB (100 mol %), oNPOE (66 wt %), PVC (32 wt %)	Li^+, −4.1; Na^+, −4.1; K^+, −4.4; Cs^+, −4.0; Rb^+, NH_4^+, −4.2; H^+, −3.6; Mg^{2+}, −5.0; Ba^{2+}, −2.1; Sr^{2+}, −1.0	SSM	0.1	0.1	29	10^{-5}−10^{-1}		482
Ca^{2+}-17 *(1,7-di[2-(1-phenylazo)naphthyl]-1,4,7-trioxaheptane)*								
Ca^{2+}-17 (2.5 wt %), KTPB (17 mol %), dinonyl sebacate	Na^+, −4.2; K^+, −4.4; Mg^{2+}, −4.6; Mg^{2+}, −3.3	FIM	−	0.5	28.8	$10^{-7.5}$−10^{-1}	Ca^{2+}-buffered solutions; rt 10−30 s	568
(66.8 wt %), PVC (30 wt %)	Zn^{2+}, −2.1	FIM	−	0.1				
Ca^{2+} Optode								
Ca^{2+}-19 *(a double-armed 18-diazacrown ether ionophore with two octadecyl-substituted 3-oxapentanediamide side chains, K22E1)/**H^+-32** (LAD-3)*								
Ca^{2+}-19, **H^+-32**, *o*-trifluoromethylphenyl dodecyl ether, octadecyl-derivatized silica beads	Li^+, −4.2; Na^+, −4.9; K^+, −4.3; NH_4^+, −4.7; Mg^{2+}, −4.4; Ba^{2+}, −2.8	SSM	0.1	0.1	−	−	pH 7.0; rt ≈ 2 min	590
Sr^{2+}-Selective Electrodes								
Sr^{2+}-2 *(2-[(2-[(dicyclohexylcarbamoyl)methoxy]phenoxy)ethoxy]*-N,N-*dicyclohexylacetamide)*								
Sr^{2+}-2 (1 wt %), oNPOE (≈66 wt %), KTpClPB (67 mol %), PVC (≈33 wt %)	H^+, −2.9; Li^+, −3.8; Na^+, −3.2; K^+, −4.1; Rb^+, −4.5; Cs^+, −4.9; NH_4^+, −4.2; Mg^{2+}, −7.6; Ca^{2+}, −1.4; Ba^{2+}, −0.7	SSM	−	0.1	30.1	−	selectivity estimated from log $K_{Ba,J}^{pot}$	595
Sr^{2+}-3 *(11-(2,5,8,11-tetraoxadodecyl)-2,3-benzo-18-crown-6)*								
Sr^{2+}-3 (1.5 wt %), KTpClPB (33 mol %), oNPOE (65 wt %), PVC (33 wt %)	Mg^{2+}, −2.8; Ca^{2+}, −1.8	MPM	−	−	−	−	140 mM, NaCl	343
Ba^{2+}-Selective Electrodes								
Ba^{2+}-1 *(nonylphenoxypoly(ethyleneoxy)ethanol)*								
Ba^{2+}-1, di-2-nitrophenyl ether, PVC	Na^+, −2.1; K^+, −1.7; Mg^{2+}, −3.6; Ca^{2+}, −3.2; Sr^{2+}, −2.4	FIM	−	0.1	28	10^{-4}−10^{-1}	rt < 1 min	602
Ba^{2+}-4 *(oxybis[2-(1-phenyleneoxy)*-N,N-*dicyclohexylacetamide])**								
Ba^{2+}-4 (1 wt %), oNPOE (≈66 wt %), KTpClPB (67 mol %), PVC (≈33 wt %)	H^+, −1.5; Li^+, −3.1; Na^+, −2.7; K^+, −2.7; Rb^+, Cs^+, −2.8; NH_4^+, −3.1; Ca^{2+}, −1.7; Sr^{2+}, −0.2	SSM	−	0.1	29.7	−		595
Ba^{2+}-5 *(3,6-dioxaoctanedioic acid monoamide monoester)*								
Ba^{2+}-5 (≈1 wt %), NaTPB (≈0.1 wt %), oNPOE (≈88 wt %), ethylene−(vinyl acetate) copolymer (≈6 wt %)	Li^+, −3.7; Na^+, −2.4; K^+, −2.1; Rb^+, −2.5; Cs^+, −2.1; NH_4^+, −2.4; Ca^{2+}, −2.5; Sr^{2+}, −1.9; Cu^{2+}, Zn^{2+}, −4.6; Mn^{2+}, Mg^{2+}, −4.7	SSM	0.1	0.1	30	−	dl $10^{-5.7}$	607
Ba^{2+}-6 *(salinomycin; a carboxylic acid polyether antibiotic)**								
Ba^{2+}-6 (3 wt %), DBS (70 wt %), PVC (27 wt %)	Li^+, −4.6; Na^+, −3.5; K^+, −2.9; Rb^+, −2.8; Cs^+, −3.5; Mg^{2+}, −4.0; Ca^{2+}, −2.7	SSM	−	0.1	58	−	for determination of selectivities the primary ion was assumed to be monovalent	162,608

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (SSM), log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (FIM), or log $k_{\mathrm{I,J}}^{\mathrm{MPM}}$ (as specified in next column to the right); for optodes log $k_{\mathrm{I,J}}^{\mathrm{Osel}}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
MoO_2^{2+}-Selective Electrode								
Mo(VI)-1 *(N-benzoyl-N-phenylhydroxylamine)*								
Mo(VI)-1 (1 mM), nitrobenzene, no polymer matrix	Na^+, −5.8; V(V), −1.8; W(VI), −3.8; Mn(II), −2.7; Fe(III), −3.0; Co(II), −3.4; Ni(II), −2.4; Cu(II), −2.9	MSM	–	0.01	nearly Nernstian	10^{-5}–10^{-1}		612
Cu^{2+}-Selective Electrodes								
Cu^{2+}-7 *(tetraethylthiuram disulfide)*								
Cu^{2+}-7 (4.1 wt %), oNPOE (54.8 wt %), PVC (41.1 wt %)	Na^+, K^+, −3.7; Mg^{2+}, −4.0; Ca^{2+}, −4.4; Mn^{2+}, −3.7; Co^{2+}, Ni^{2+}, Zn^{2+}, −3.9; Cd^{2+}, −4.3; Pb^{2+}, −1.8	FIM	–	0.1 0.01	30	10^{-7}–10^{-1}	rt 27 s; pH range 3.2–5.4	634
Cu^{2+}-9 *(salicylaniline)*								
Cu^{2+}-9 (1.7 wt %), chlorobenzene, no polymer matrix	Mg^{2+}, Ca^{2+}, −3.3; Cr^{3+}, Fe^{3+}, Co^{2+}, Ni^{2+}, −3.0; Mn^{2+}, Pb^{2+}, Cd^{2+}, −2.7; Ag^+, −0.1; Zn^{2+}, −3.0; Hg^{2+}, −2.0; Tl^+, −2.5	MSM	0.001	0.001	28.3	$10^{-5.3}$–10^{-1}	0.1 M $NaNO_3$; pH 4.0–5.0	637
Cu^{2+}-10 (N-*(*m*-nitrocinnamoyl),*N-*(*p*-chlorophenyl)hydroxylamine)*								
Cu^{2+}-10 (as chelate, 3–5 wt %), DBP (65–70 wt %), PVC (30–33 wt %)	Na^+, K^+, Mg^{2+}, Co^{2+}, Cd^{2+}, <−4.0; Ca^{2+}, −3.7; Fe^{3+}, −0.2; Ni^{2+}, −3.2; Ag^+, <−5.0; Hg^{2+}, −2.0	FIM	–	–	30	10^{-6}–10^{-1}	rt 10–15 s for >1 mM Cu^{2+}	638
Ag^+-Selective Electrodes								
Ag^+-4 *(bis[2-(2-naphthylsulfanyl)ethyl] ether)*								
Ag^+-4 (1 wt %), oNPOE (≈66 wt %), KTpClPB (75 mol %), PVC (33 wt %)	K^+, −5.4; Ca^+, Pb^{2+}, −6.1; Cu^{2+}, −6.3; Cd^{2+}, −6.6; Hg^{2+}, −2.5	FIM	–	0.01	Nernstian	–	pH 4; rt < 10 s	646
Ag^+-6 *(ethyl phenyl sulfide)**								
Ag^+-6 (7 wt %), DOP (31 wt %), PVC (62 wt %)	Na^+, −4.9; Ca^{2+}, −5.4; Co^{2+}, −5.9; Ni^{2+}, −5.6; Cu^{2+}, −4.2; Zn^{2+}, −5.5; Cd^{2+}, −5.6; Pb^{2+}, −6.0	FIM	–	–	62	–	rt < 5 s	654,655
Ag^+-8 *(a calix[4]arene with two methylthioethyl groups)**								
Ag^+-8 (1 wt %), bis(butylpentyl) adipate (≈66 wt %), KTpClPB (75 mol %), PVC (33 wt %)	Li^+, NH_4^+, Cu^{2+}, Cd^{2+}, −5.3; Na^+, Ni^{2+}, −5.0; K^+, Pb^{2+}, −4.7; Mg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, −5.6; Zn^{2+}, −5.6; Hg^{2+}, −2.5	FIM	–	–	54.7	–		631,647
Ag^+-8 (14 mmol kg^{-1}), DOS (≈66 wt %), NaTFPB (29 mol %), PVC (≈33 wt %)	Na^+, −6.2; K^+, −5.7; Ca^{2+}, −8.0; Cu^{2+}, −7.7; Pb^{2+}, −6.0	SSM	–	–	58.2	–	conditioning with 0.01 M NaCl in absence of primary ion	247
Ag^+-14 *(methylene bis[diisobutyldithiocarbamate])**								
Ag^+-14 (14 mmol kg^{-1}), DOS (≈66 wt %), NaTFPB (29 mol %), PVC (≈33 wt %)	Na^+, −8.7; K^+, −8.2; Ca^{2+}, −11.0; Cu^{2+}, −10.5; Pb^{2+}, −10.3	SSM	–	–	58.8	–	conditioning with 0.01 M NaCl in absence of primary ion	247
Ag^+ Optodes								
Ag^+-14 *(methylene bis[diisobutyldithiocarbamate])*/**H^+-22** (ETH 5418)*								
Ag^+-14 (12.5 mmol kg^{-1}), **H^+-22** (3.1 mmol kg^{-1}), KTFPB (3.5 mmol kg^{-1}), DOS (≈66 wt %), PVC (≈33 wt %)	Li^+, −11.2; Na^+, −9.9; K^+, −9.3; Cu^{2+}, −9.6; Cd^{2+}, −14.6; Hg^{2+}, +0.7; Pb^{2+}, −13.4	SSM	–	–	–	–	dl $10^{-8.6}$ (pH 4.7)	668
Ag^+-16 *(methylene bis[2-thiobenzothiazole])/**H^+-21** (ETH 5315)*								
Ag^+-16 (267 mmol kg^{-1}), **H^+-21** (18.3 mmol kg^{-1}), KTFPB (18.3 mmol kg^{-1}), DOS (≈65 wt %), PVC (≈33 wt %)	Na^+, −6.0; K^+, −5.6; Ca^{2+}, Mg^{2+}, −9.0; Co^{2+}, −10.9; Cu^{2+}, −5.6; Hg^{2+}, −2.7; Pb^{2+}, −7.2	SSM	–	–	–	–	pH 4.5	669

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Zn^{2+}-Selective Electrodes								
Zn^{2+}-1 *(N-benzyliminodiacetic acid bis(N-ethyl-N-cyclohexylamide)*								
Zn^{2+}-1 (2 wt %), oNPOE (65 wt %), KTpClPB (70 mol %), PVC (33 wt %)	H^{+}, +0.6; Li^{+}, Na^{+}, −2.7; K^{+}, −2.5; NH_4^{+}, −3.1; Mg^{2+}, −3.5; Ca^{2+}, −2.8; Cu^{2+}, +0.2; Cd^{2+}, −3.6; Pb^{2+}, −2.1	SSM	−	0.1	29.5	$10^{-5.3}-10^{-1.3}$	pH 6.0 for selectivity; pH 7.0 for lin. range	671
Zn^{2+}-2 *(tetrabutyl thiuram disulfide)**								
Zn^{2+}-1 (5.4 wt %), oNPOE (53 wt %), KTpClPB (12 mol %), PVC (40 wt %)	Na^{+}, −3.3; K^{+}, −3.8; NH_4^{+}, −3.3; Mg^{2+}, −3.1; Ca^{2+}, −2.8; Mn^{2+}, −2.1; Fe^{3+}, −2.4; Co^{2+}, −1.5; Ni^{2+}, −1.4; Cu^{2+}, +1.0; Pb^{2+}, +0.8	SSM	−	−	28	$10^{-6}-10^{-1}$	pH range 3.5−6.5; rt 2 to 10 s; serious interference from Ag^{+} and Hg^{2+}	673
Cd^{2+}-Selective Electrode								
Cd^{2+}-4 *(a bis(dimethylthiocarbamoylmethoxyethoxy)calix[4]arene)*								
Cd^{2+}-4 (2.1 wt %), DOS (≈65 wt %), KTpClPB (0.8 wt %), PVC (≈32 wt %)	Ca^{2+}, −3.2; K^{+}, no response	FIM	−	0.1	29	−	pH 4	631
	Cu^{2+}, Pb^{2+}, no response		−	0.01				
Hg^{2+}-Selective Electrodes								
Hg^{2+}-4 *(1,4-dithia-12-crown-4)*								
Hg^{2+}-4 (17 wt %), DBP (28 wt %), NaTPB, PVC (55 wt %)	Li^{+}, −3.3; Na^{+}, −2.8; K^{+}, Ba^{2+}, Ni^{2+}, −3.1; Rb^{+}, −4.2; Cs^{+}, −3.9; Mg^{2+}, −2.9; Ca^{2+}, Sr^{2+}, Co^{2+}, Zn^{2+}, <−5.0; Fe^{3+}, −1.5; Cu^{2+}, Cd^{2+}, −3.1; Ag^{+}, −3.4; Pb^{2+}, −3.6;	FPIM	10^{-5}	−	30	$10^{-6}-10^{-3}$	rt ≤ 1 min; (FPIM: fixed primary ion method)	648
Hg^{2+}-6 *(N,N′-bis(2-methylquinolyl)-4,13-diaza-18-crown-6)*								
Hg^{2+}-6 (1 wt %), oNPOE (68−69 wt %), KTpClPB (70 mol %), PVC (30 wt %)	Na^{+}, −5.3; Ca^{2+}, Pb^{2+}, −3.7; Ag^{+}, +2.6; Ni^{2+}, Zn^{2+}, −3.5; Cd^{2+}, −3.9	SSM	0.01	0.01	41	$10^{-5}-10^{-3}$		693
Hg^{2+}-9 *(N,N′-dibenzyloxysebacic acid diamide)*								
Hg^{2+}-9 (2 wt %), KTpClPB (5 mol %), oNPOE (66 wt %), PVC (32 wt %)	Li^{+}, −6.0; Na^{+}, −6.1; K^{+}, −5.5; NH_4^{+}, −5.8; Mg^{2+}, −7.6; Ca^{2+}, −7.5; Cr^{3+}, −8.1; Mn^{2+}, −7.5; Fe^{3+}, −7.9; Co^{2+}, −7.4; Ni^{2+}, −7.5; Cu^{2+}, −7.6; Zn^{2+}, −7.6; Cd^{2+}, −7.4; Ag^{+}, −3.9; Pb^{2+}, −4.8	SSM	−	0.01	70	$10^{-5}-10^{-2}$	selectivity calcd based on super-Nernstian response	694
Tl^{+}-Selective Electrodes								
Tl^{+}-2 *(bis[(benzo-15-crown-5)-4′-ylmethyl] pimelate)*								
Tl^{+}-2 (1.4 wt %), oNPOE (70 wt %), PVC (28 wt %)	Na^{+}, −4.0; K^{+}, −0.5; Rb^{+}, −1.0; Cs^{+}, 2.0; NH_4^{+}, −2.1; Mg^{2+}, −5.3; Ca^{2+}, −5.0; Sr^{2+}, <−5.2 Ba^{2+}, −4.5; Ag^{+}, −3.2; Cd^{2+}, <−5.4; Pb^{2+}, −4.7; As^{3+}, −4.0	FIM	−	−	59	$10^{-5}-10^{-2}$		696
Tl^{+}-3 *(dibenzo-22-crown-6)*								
Tl^{+}-3 (2.8 wt %), oNPOE (69 wt %), NaTFPB (9 mol %), PVC (28 wt %)	H^{+}, −3.9; Li^{+}, −4.6; Na^{+}, −3.0; K^{+}, −1.7; Rb^{+}, −1.6; Cs^{+}, −1.5; NH_4^{+}, −2.3; Mg^{2+}, −5.1; Ca^{2+}, −5.0; Sr^{2+}, −4.5; Ba^{2+}, −4.0; Cr^{3+}, −4.9; Fe^{3+}, −3.9; Co^{2+}, −4.8; Ni^{2+}, −4.5; Cu^{2+}, −4.9; Ag^{+}, −1.4; Zn^{2+}, −5.0; Cd^{2+}, −4.8; Hg^{2+}, −3.5; Pb^{2+}, −3.4	MSM	−	−	59	$10^{-4.5}-10^{-2}$	rt ≤ 10 s	697
Bi^{3+}-Selective Electrode								
Bi^{3+}-1 *(Bismuthiol III)*								
Bi^{3+}-1 (5 mM), tetrachloroethane	Mg^{2+}, <−5.1; Ca^{2+}, <−5.2; Mn^{2+}, <−5.5; Fe^{3+}, <−3.9; Co^{2+}, <−5.5; Ni^{2+}, <−4.9; Ag^{+} ≫0; Al^{3+}, <−6.2; Th(IV), −6.3	MSM	10^{-4}	10^{-2}	18.7	$10^{-9.5}-10^{-6.5}$	pH 3−4; rt ≈ 10 s for 0.1 to 10 mM solutions	698,699
	Cu^{2+}, −0.7		10^{-2}	10^{-2}				
	Pb^{2+}, −4.0		10^{-2}	10^{-3}				

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K^{\mathrm{pot}}_{\mathrm{I,J}}$ (SSM), log $K^{\mathrm{pot}}_{\mathrm{I,J}}$ (FIM), or log $k^{\mathrm{MPM}}_{\mathrm{I,J}}$ (as specified in next column to the right); for optodes log $k^{\mathrm{Osel}}_{\mathrm{I,J}}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Pb^{2+}/PbA^+-Selective Electrodes								
Pb^{2+}-1 (N,N-*dioctadecyl*-N′,N′-*dipropyl-3,6-dioxaoctane-1,8-diamide, ETH 322)**								
Pb^{2+}-1 (1 wt %), BBPA (66 wt %), PVC (33 wt %)	H^+, −3.5; Li^+, −2.9; Na^+, −3.5; K^+, −3.7; NH_4^+, −3.9; Rb^+, −4.2; Cs^+, −4.6; Mg^{2+}, −5.6; Ca^{2+}, −5.3; Sr^{2+}, −5.2; Ba^{2+}, −4.8; Cu^{2+}, −5.1; Zn^{2+}, −5.2; Cd^{2+}, −3.7; Mn^{2+}, −5.7	SSM	0.01	0.1	57.6	10^{-5}−10^{-2}	pH 4; $Mg(OAc)_2$, HCl	672
UO_2^{2+}-4 (N,N′-*diheptyl*-N,N′,*6,6-tetramethyl-4,8-dioxaundecanediamide, ETH 295)**								
UO_2^{2+}-4 (1 wt %), oNPOE (67 wt %), KTpClPB (40 mol %), PVC (30 wt %)	H^+, −0.1; Li^+, −2.9; Na^+, −3.8; K^+, −3.9; NH_4^+, −3.6; Mg^{2+}, −4.7; Ca^{2+}, −2.3; Sr^{2+}, −1.7; Ba^{2+}, −2.4; Co^{2+}, −4.2; Ni^{2+}, Cu^{2+}, −3.9; −4.7; Ag^+, +0.1; Zn^{2+}, −4.4; Cd^{2+}, −4.2	SSM	0.1	0.1	35.3	$10^{-5.2}$−10^{-1}	pH 4; nitrate salts	701
Pb^{2+}-8 (*diphenylmethyl*-N-*phenylhydroxamic acid)*								
Pb^{2+}-8, DOS (≈66 wt %), PVC (≈33 wt %)	Ca^{2+}, −4.0; Co^{2+}, −3.4; Ni^{2+}, −2.8; Cu^{2+}, −4.5; Ag^+, −2.6; Zn^{2+}, −2.1; Cd^{2+}, −2.9; Hg^{2+}, −1.8	SSM	0.1	0.1	28	$10^{-5.3}$−$10^{-2.3}$	pH 5−6; nitrate salts	708
Ba^{2+}-1 (*nonylphenoxypoly(ethyleneoxy)ethanol)**								
antarox CO-880·$Pb(TPB)_2$ (6.6 wt %), NPPE (66 wt %), PVC (28 wt %)	Li^+, Na^+, −2.8; K^+, −2.0; Mg^{2+}, −4.0; Ca^{2+}, −3.6; Sr^{2+}, −2.7; Ni^{2+}, −4.2; Zn^{2+}, −3.5; Cd^{2+}, −3.9; Al^{3+}, −4.1	FIM	−	0.05	28.5−30.5	10^{-5}−10^{-1}	pH 2.5−5.5; $Pb(NO_3)_2$ solutions; Ag^+ and Hg^{2+} interfere strongly	603
	Ba^{2+}, −0.5; La^{3+}, −3.4		−	0.005				
Pb^{2+} Optodes								
Pb^{2+}-2 (N,N,N′,N′-*tetradodecyl-3,6-dioxaoctanedithioamide, ETH 5435)*/**H^+-10** (ETH 5294),* **H^+-22** (ETH 5418) or **H^+-21** (ETH 5315)*								
Pb^{2+}-2 (36.7 mmol kg^{-1}), **H^+-10** (12.5 mmol kg^{-1}), KTFPB (13.1 mmol kg^{-1}), DOS (≈66 wt %), PVC (≈33 wt %)	Na^+, −5.6; K^+, −5.3	SSM	−	−	−	−	pH 4.7; acetate buffer	687
Pb^{2+}-2 (29.7 mmol kg^{-1}), **H^+-22** (9.9 mmol kg^{-1}), KTFPB (9.9 mmol kg^{-1}), DOS (≈66 wt %), PVC (≈33 wt %)	Mn^{2+}, −3.0; Cu^{2+}, +0.7; Cd^{2+}, +1.2	SSM	−	−	−	−	pH 4.7; acetate buffer	687
Pb^{2+}-2 (52.2 mmol kg^{-1}), **H^+-21** (12.0 mmol kg^{-1}), KTFPB (13.7 mmol kg^{-1}), DOS (≈66 wt %), PVC (≈33 wt %)	Mg^{2+}, −10.9; Ca^{2+}, −10.8; Co^{2+}, −6.5; Ni^{2+}, −4.8; Zn^{2+}, −4.6	SSM	−	−	−	−	pH 4.7; acetate buffer	687
U(VI)-Selective Electrodes								
UO_2^{2+}-2 (*tetraphenyl*-o-*xylyldiphosphine dioxide)*								
UO_2^{2+}-2 (0.56−1 wt %), oNPOE (≈66 wt %), NaTpClPB (50 mol %), PVC (≈33 wt %)	Li^+, Na^+, K^+, −3.0; NH_4^+, −3.3; Mg^{2+}, Ca^{2+}, −3.1; Sr^{2+}, −3.7; Ba^{2+}, −3.7; Mn^{2+}, −2.9; Co^{2+}, −3.0; Ni^{2+}, −3.1; Cu^{2+}, −3.0; Zn^{2+}, −2.6; Cd^{2+}, −3.9; Al^{3+}, −2.9	SSM	0.1	0.1	29	10^{-4}−10^{-1}	pH ≈3	570,725
UO_2^{2+}-4 (N,N′-*diheptyl*-N,N′,*6,6-tetramethyl-4,8-dioxaundecane diamide, ETH 295)**								
UO_2^{2+}-4 (2.8 wt %), 1-chloronaphthalene (64 wt %), PVC (33 wt %)	H^+, −1.8; Li^+, −3.2; Na^+, <−3.6; K^+, <−3.7; NH_4^+, <−3.6; Mg^{2+}, <−4.0; Ca^{2+}, <−4.1; Ba^{2+}, <−4.0; Mn^{2+}, <−3.9; Co^{2+}, <−4.0; Ni^{2+}, <−4.1; Cu^{2+}, <−4.0; Ag^+, −2.5; Zn^{2+}, <−4.1; Cd^{2+}, <−4.0; Pb^{2+}, −3.7; Tl^+, −3.2	SSM	0.1	0.1	59.2	$10^{-4.5}$−$10^{-1.5}$	pH 3 (HNO_3); log $K^{\mathrm{pot}}_{\mathrm{UO_2A,J}}$ refers to a monovalent uranyl species	114,727

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (SSM), log $K_{\mathrm{I,J}}^{\mathrm{pot}}$ (FIM), or log $k_{\mathrm{I,J}}^{\mathrm{MPM}}$ (as specified in next column to the right); for optodes log $k_{\mathrm{I,J}}^{\mathrm{Osel}}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
U(VI) Optode								
UO_2^{2+}-4 (N,N′-*diheptyl*-N,N′,*6,6-tetramethyl-4,8-dioxaundecanediamide, ETH 295)*/**H^+-21** (ETH 5315)*								
Pb^{2+}-2 (38.1 mmol kg^{-1}), (11.9 mmol kg^{-1}), KTFPB **H^+-21** (28.1 mmol kg^{-1}), DOS (≈66 wt %), PVC (≈33 wt %)	Li^+, −2.1; Na^+, −3.4; K^+, −3.5; Mg^{2+}, −4.8; Ca^{2+}, −1.8; Fe^{3+}, −3.3; Fe^{2+}, −3.2; Cu^{2+}, −5.0; Ag^+, −1.9; Cd^{2+}, −5.0; Pb^{2+}, −0.6	SSM	–	–	–	–	pH 3.0 (formate buffer); given are log $K_{\mathrm{U(VI),J}}^{\mathrm{opt}}$ referring to divalent species	719
Sm(III)-Selective Electrode								
Sm(III)-1 *(bis[3-thiapentylxanthano]butane)*								
Sm(III)-1 (10.2 wt %), oNPOE (60 wt %), KTpClPB (5.7 mol %), PVC (29 wt %)	Na^+, −3.2; K^+, −2.9; NH_4^+, −3.0; Mg^{2+}, −2.7; Ca^{2+}, −1.9; Cr^{3+}, −2.4; Fe^{3+}, +0.1; Ni^{2+}, −2.7; Cu^{2+}, +1.2; Zn^{2+}, −2.8; Pb^{2+}, −0.8, Tl^+, −3.2; Al^{3+}, −2.9; La^{3+}, −2.4; Ce^{3+}, −1.6; Pr^{3+}, −1.5; Nd^{3+}, −1.9; Gd^{3+}, −1.3	MPM	10^{-5}	–	19.5	10^{-6}–$10^{-2.3}$	pH 5.5	731,732
CO_3^{2-}-Selective Electrodes								
CO_3^{2-}-1 *(trifluoroacetyl-*p-*butylbenzene)**								
CO_3^{2-}-1 (99 vol %), Aliquat 336S (1 vol %)	ClO_4^-, +1.4; NO_3^-, −0.5; Cl^-, −3.7; OAc^-, −1.6; SO_4^{2-}, −3.8	SSM	0.001	0.1	–	–		743
	HPO_4^{2-}, −3.6		0.001	0.25				
	borate, −1.3		0.001	0.01				
	hydrogen phthalate, −1.9		0.001	0.5				
CO_3^{2-}-2 (N,N-*dioctyl-4-trifluoroacetylbenzamide)*								
CO_3^{2-}-2 (3.4 wt %), MTDDACl (41 mol %), DOS (54 wt %), PVC (41 wt %)	SCN^-, +1.0; NO_3^-, −1.6; Br^-, −3.5; Cl^-, −5.0; SO_4^{2-}, −5.0; HPO_4^{2-}, −5.0; salicylate, +3.3	SSM	0.014	0.1	–	–		756
CO_3^{2-}-3 *(heptyl 4-trifluoroacetylbenzoate, ETH 6010)**								
CO_3^{2-}-3 (2.7 wt %), MTDDACl (41 mol %), DOS (55 wt %), PVC (41 wt %)	SCN^-, +0.7; NO_3^-, −1.6; Br^-, −3.5; Cl^-, −4.8; SO_4^{2-}, −4.9; HPO_4^{2-}, −4.7; salicylate, +3.8	SSM	0.014	0.1	–	–		756
SCN^--Selective Electrodes								
SCN^--6 *(chloro[5,10,15,20-tetrakis[4-(hexyloxycarbonyl)phenyl]porphyrinato]manganese(III))*								
SCN^--6 (1.0 wt %), **PL-7** (ETH 469,* 66 wt %), PVC (33 wt %)	ClO_4^-, −2.0; I^-, −2.3; NO_3^-, −3.6; Br^-, −3.1; NO_2^-, −3.0; Cl^-, −3.4; HCO_3^-, −5.1; OAc^-, −5.2; SO_4^{2-}, −7.1; HPO_4^{2-}, −6.0; F^-, −4.4; N_3^-, −0.6	SSM	0.1	0.1	−56.0	$10^{-4.1}$–$10^{-1.0}$	pH 7.4; selectivity estimated from log $K_{\mathrm{Cl,J}}^{\mathrm{pot}}$	774–776
SCN^--10 *((5,10,15,20-tetrakis[2,4,6-triphenylphenyl]porphyrinato)manganese(III) chloride)*								
SCN^--10 (1.0 wt %), DBS (66 wt %), PVC (33 wt %)	ClO_4^-, −2.3; I^-, −3.0; salicylate, −1.6; Br^-, −3.8; Cl^-, −4.6; OAc^-, −4.2; ascorbate, succinate, urate, citrate, <−3.7; CN^-, −3.2	SSM	–	–	≈−64	10^{-5}–10^{-2}	rt < 1 min	783
SCN^--11 *((meso-α,α,α,α-tetrakis(*o*-pivalamidophenyl)porphyrinato)cobalt(III))*								
SCN^--11 (1.0 wt %), oNPOE (74 wt %), PVC (25 wt %)	ClO_4^-, −2.0; I^-, −2.8; NO_3^-, −3.2; Br^-, −3.8; NO_2^-, −0.7; Cl^-, −4.2; SO_4^{2-}, −5.5; HPO_4^{2-}, −2.5	FIM	0.1	0.1	−55 ± 1	10^{-4}–10^{-1}	1–2 min	786

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
NO_2^--Selective Electrodes								
SCN^--2 *(aquocyanocobalt(III) heptakis(phenylethyl)cobyrinate perchlorate)**								
SCN^--2 (1.0 wt %), KTFPB (37 mol %), oNPOE (65 wt %), PVC (33 wt %)	ClO_4^-, −2.2; SCN^-, +0.2; I^-, −2.2; NO_3^-, −3.5; Br^-, −3.3; Cl^-, −3.7; SO_4^{2-}, −4.1; HCO_3^-, 3.7; OAc^-, −3.8; F^-, −3.9	SSM	0.1	0.1	−56.3	−		611,789
NO_2^--3 *(chloro(5,10,15,20-tetraphenylporphyrinato)indium(III))*								
NO_2^--3 (1.0 wt %), didecyl sebacate (66 wt %), PVC (33 wt %)	ClO_4^-, −2.4; SCN^-, −1.0; I^-, −1.0; NO_3^-, −2.6; Br^-, −1.4; Cl^-, −1.8; F^-, −1.2	SSM	−	−	−	−		805
NO_2^--4 *((2,9,16,23-tetra-*tert*-butylphthalocyanine)cobalt(III))*								
NO_2^--4 (2.5 wt %), hexadecyltrioctylammonium iodide (2 mol %), DBP (66.5 wt %), PVC (31 wt %)	ClO_4^-, −1.6; SCN^-, −1.0; I^-, −1.6; NO_3^-, −3.1; Br^-, −2.9; Cl^-, −3.5	SSM	0.1	0.1	−57	10^{-5}−10^{-1}	rt s to 2 min, depending on conc	807,808
Phosphate-Selective Electrodes								
phosphate-4 *(bis(*p*-fluorobenzyl)tin dichloride)*								
phosphate-4 (20 wt %), DBS (41 wt %), PVC (38 wt %)	SCN^-, −1.8; I^-, −2.2; NO_3^-, −3.5; Br^-, −3.1; Cl^-, −4.2; OAc^-, −3.2	MPM	−	−	−31.5	−	pH 7.0	841
phosphate-6 *(bis(dibromophenylstannyl)methane)*								
phosphate-6 (2 wt %), DOS (65 wt %), PVC (33 wt %)	ClO_4^-, −3.3; SCN^-, −2.0; I^-, −3.3; NO_3^-, −3.6; F^-, −3.7; Br^-, −4.0; Cl^-, −4.2; SO_4^{2-}, −4.8	SSM	0.009	0.009	−53.1	−	pH 5.5	843
phosphate-8 *(3-decyl-1,5,8-triazacyclodecane-2,4-dione)*								
phosphate-8 (20 wt %), DBS (35 wt %), PVC (45 wt %)	SCN^-, −2.3; NO_3^-, −2.8; Cl^-, −2.3; OAc^-, −3.2; SO_4^{2-}, −3.0; lactate, −3.0; acetate, −3.2	modified SSM	−	−	−28.9	10^{-6}−10^{-1}	pH 7.2	847
Hydrogen Sulfite-Selective Electrode								
sulfite-2 *(a guanidinium derivative)*								
sulfite-2 (1.0 wt %), oNPOE (66 wt %), PVC (33 wt %)	ClO_4^-, −2.2; Cl^-, ≤−3.0; salicylate$^-$, −2.3	FIM	−	0.005	−47 ± 2	$10^{-4.3}$−$10^{-0.3}$	pH 6.0	853
Hydrogen Sulfite Optode								
sulfite-3 *(octadecyl-4-formylbenzoate; ETH 5444)*/**H^+-11** (ETH 5350)*								
sulfite-3 (0.279 M), **H^+-11** (0.035 M), oNPOE (62.6 wt %), PVC-OH (28.1 wt %)	ClO_4^-, −0.0; SCN^-, −0.3; NO_3^-, −1.7; Cl^-, −2.3	SSM	−	−	−	−	pH 7.9; dl $10^{-3.2}$ M	854
Sulfate-Selective Electrode								
SO_4^{2-}-1 *(α,α′-bis(*N′*-phenylthioureylene)-*m*-xylene)*								
SO_4^{2-}-1 (1.0 wt %), TDDMACl (50 mol %), oNPOE (65 wt %), PVC (32 wt %)	SCN^-, +2.9; NO_3^-, +1.6; NO_2^-, +0.6; Br^-, +1.1; Cl^-, −0.1; HSO_3^-/SO_3^{2-}, −0.3; HCO_3^-, −0.9; OAc^-, −1.5; $H_2PO_4^-$/HPO_4^{2-}, −1.5	MPM	0.001 to >0.01	−	−28.1	10^{-6}−10^{-2}	pH 7.0	859
Cl^--Selective Electrodes								
Cl^--3 *(chloro(5,10,15,20-tetraphenylporphyrinato)manganese(III))*/ETH 500 (tetradodecylammonium tetrakis(*p*-chlorophenyl)borate)**								
Cl^--3 (5.0 wt %), 1-decanol (4 wt %), ETH 500 (1 wt %), oNPOE (33 wt %)	ClO_4^-, −3.6; SCN^-, +3.4; I^-, +2.4; NO_3^-, +1.2; Br^-, +0.9; NO_2^-, +0.7; HCO_3^-, −1.5; OAc^-, −1.3; SO_4^{2-}, −2.6; HPO_4^{2-}, −2.9; salicylate, +3.0	SSM	−	0.1	−57.5	−	microelectrode	779
Cl^--4 *(chloro(octaethylporphyrinato)indium(III))*								
Cl^--4 (0.6−1.0 wt %), KTFPB (30 mol %), oNPOE (≈66 wt %), PVC (≈33 wt %)	ClO_4^-, −2.6; SCN^-, +1.4; I^-, +0.9; NO_3^-, −3.8; NO_2^-, +0.3; salicylate, +2.2	SSM	−	0.01	−93.2	−		789

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K_{I,J}^{pot}$ (SSM), log $K_{I,J}^{pot}$ (FIM), or log $k_{I,J}^{MPM}$ (as specified in next column to the right); for optodes log $k_{I,J}^{Osel}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Cl^--Selective Electrodes								
Cl^--5 *([γ-[4,5-dimethyl-3,6-bis(octyloxy)-1,2-phenylene]]bis(trifluoroacetato-*O*)dimercury)**								
Cl^--5 (2.0 wt %), TDDMACl (2.5 mol %), DOS (65 wt %), PVC (33 wt %)	ClO_4^-, −1.8; SCN^-, −0.2; I^-, +1.0; NO_3^-, −3.1; Br^-, +0.0; HCO_3^-, −5.5; OAc^-, −5.1; SO_4^{2-}, −6.3; HPO_4^{2-}, −5.9; F^-, −5.5; salicylate, −0.4	SSM	0.1	0.1	−57.6	–	rt < 10 s; dl ≈ 10^{-5} M	876
Cl^--8 *(2,7-di-*tert*-butyl-9,9-dimethyl-4,5-xanthenediamine)*								
Cl^--8 (1 wt %), TDDMACl (50 mol %), oNPOE (66 wt %), PVC (33 wt %)	salicylate, +1.8; SCN^-, +1.6; NO_3^-, +0.7; I^-, +0.5; Br^-, +0.4 SO_4^{2-}, −1.2; HSO_3^-/SO_3^{2-}, −2.0; OAc^-, −2.3; HCO_3^-, −2.6; $H_2PO_4^-/HPO_4^{2-}$, <−3.5	MPM	$10^{-2.34}$ to $10^{-2.04}$ $10^{-5.00}$ to $10^{-4.70}$	–	−54.0	10^{-5}–10^{-2}	pH 7.0	880
Cl^- Optodes								
Trioctyltin chloride/**H^+-12** (ETH 7075)*								
trioctyltin chloride (2.1 wt %), **H^+-12** (50 mol %), BBPA (63 wt %), PVC (31 wt %)	ClO_4^-, −0.7; SCN^-, +1.1; I^-, +1.0; NO_3^-, −1.8; Br^-, +0.3; SO_4^{2-}, −2.8	SSM	–	–	–	–		296,881
Cl^--4 *(chloro(octaethylporphyrinato)indium(III))/**H^+-40** (ETH 2412)*								
Cl^--4 (2.0 wt %), **H^+-40** (1 wt %), oNPOE (67 wt %), PVC (15 wt %), Tecoflex polyurethane matrix (15 wt %)	ClO_4^-, −2.2; SCN^-, −1.8; I^-, +0.2; NO_3^-, −2.8; Br^-, +0.1; NO_2^-, +0.2; OAc^-, −2.2; $H_2PO_4^-$, <−3.5; salicylate, +0.7	SSM	–	–	–	–		794
ClO_4^--Selective Electrode								
ClO_4^--1 *(3,4-benzo-10-phenyl-1,6-dithia-10-phosphacyclotridecane)*								
ClO_4^--1 (4.7 wt %), oNPOE (64 wt %), PVC (31 wt %)	SCN^-, −1.0; I^-, −2.9; NO_3^-, −3.4; NO_2^-, −3.8; Cl^-, −4.9; Br^-, −4.7; Cl^-, −3.7; SO_4^{2-}, −4.8; HCO_3^-, −4.4; HPO_4^{2-}, −3.8; BF_4^-, −2.0	FIM	0.1	0.1	−54	$10^{-6.2}$–10^{-2}	rt < 10 s; CHEMFET	883
I^--Selective Electrodes								
I^--2 *(a vitamin B12 isomeride with an imidazole group coordinated to the metal center)*								
I^--2 (1.0 wt %), BBPA (66 wt %), PVC (33 wt %)	SCN^-, −1.6; salicylate, −2.1	SSM	–	–	Nernstian	–	rt < 1 min	813
I^--3 *(*N,N,N′,N′*-tetramethyl-*N,N′*-dioctadecylethylene-1,2-diammonium iodide)*								
I^--3 (1.0 wt %), oNPOE (66 wt %), PVC (33 wt %)	ClO_4^-, −1.9; SCN^-, −1.5; acetate, −4.3; salicylate, −1.9	FIM	–	–	−59 to −55	–	selectivity estimated from log $K_{X,OAc}^{pot}$; dl $10^{-6.4}$	888
I^--4 *(bis(salicylaldehyde)phenyldiiminecobalt(II))*								
I^--4 (2.5 wt %), *o*-nitrophenyl dodecyl ether (66.5 mol %), PVC (31 wt %)	ClO_4^-, −2.4; SCN^-, −2.2; NO_3^-, −4.2; NO_2^-, −2.2; Br^-, −2.5; Cl^-, −4.3; SO_4^{2-}, −4.5	SSM	–	–	−56.2	10^{-6}–10^{-1}	rt < 1 min; pH 2.5	889
I_3^--Selective Electrode								
*(5,10,15,20-tetraphenylporphyrinato)manganese(III)**								
(5,10,15,20-tetraphenylporphyrinato)manganese(III) (5 wt %), FNDPE (68 wt %), PVC (27 wt %)	ClO_4^-, <−4.0; salicylate, −3.3; benzoate, −3.4; Br^-, NO_3^-, Cl^-, HCO_3^-, F^-, <−4.0	FIM	–	0.1	−87	–		781
Guanidinium-Selective Electrodes								
GU-4 *(a cryptand with two sulfonamide groups)*								
GU-4, TEHP, KTpClPB, PVC	H^+, −0.4; Na^+, −2.5; Li^+, −1.4; K^+, −3.1; NH_4^+, −2.2; creatininium, −0.8; $N(CH_2CH_3)_4^+$, −3.5	SSM	–	0.01	56	$10^{-5.5}$–10^{-1}		948
AM-3 *(a polyoctylated α-cyclodextrin)*								
AM-3 (1.2 wt %), oNPOE (32.8 wt %), NaTFPB (0.4 wt %), PVC (65.6 wt %)	Na^+, −2.9; K^+, −1.4; NH_4^+, −1.7; Ca^{2+}, −3.9	FIM	–	0.1	61.7	–	dl $10^{-5.7}$	919

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K^{pot}_{I,J}$ (SSM), log $K^{pot}_{I,J}$ (FIM), or log $k^{MPM}_{I,J}$ (as specified in next column to the right); for optodes log $k^{Osel}_{I,J}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Salicylate-Selective Electrodes								
CA-1 *((2,9,16,23-tetra-*tert*-butylphthalocyanine)tin(IV))*								
CA-1 (2 wt %), dinonyl sebacate (67 wt %), PVC (31 wt %)	ClO_4^-, −3.3; SCN^-, −2.9; Cl^-, −4.8; OAc^-, −3.4	SSM	0.1	0.1	−54 to −50	10^{-5}−10^{-1}	rt 6 to 20 s; 10 °C; pH 5.5; dl $10^{-5.2}$	961
CA-3 *(tribenzyltin octanoate)*								
CA-3 (1.5 wt %), oNPOE (64 wt %), PVC (34.5 wt %)	ClO_4^-, −3.1; SCN^-, −2.1; I^-, −3.8; Br^-, −4.0; NO_3^-, −4.2; NO_2^-, −3.1; Cl^-, −4.9; OAc^-, −3.9; lactate, −3.0, citrate, −3.4; benzoate, −1.3	SSM	0.1	0.1	−57.5	$10^{-5.3}$−10^{-1}	pH 5.5	963
CA-5 *(a guanidinium)*								
CA-5 (1 wt %), DOS (66 wt %), PVC (33 wt %)	ClO_4^-, −2.7; hydrogen sulfite, −2.7; benzoate, −1.7	MPM	−	−	−60	−	rt 0.5 to 5 min; dl 3 × $10^{-3.2}$ M	964
CO_3^{2-}-3 *(heptyl-4-trifluoroacetyl benzoate)**								
CO_3^{2-}-3 (2.7 wt %), oNPOE (48 wt %), TDDMACl (40 mol %), PVC (48 wt %)	HCO_3^-, −2.4; Cl^-, −4.4; OAc^-, −3.9	FIM	−	−	−55 (in serum)	−	rt 6 < 10 s	761
Salicylate Optode								
CA-6 *(butyl* O*-(1-naphthylaminocarbonyl)lactate)/Nile Blue*								
CA-6 (11.3 wt %), Nile Blue (5.7 wt %), DOP (57 wt %), TDDMACl (3.8 wt %), PVC (23 wt %)	ClO_4^-, +0.1; NO_3^-, −1.9; Cl^-, −2.8; OAc^-, <−3 benzoate, −1.8; ascorbate, 0; acetate, phosphate, SO_4^{2-}, <−3	SSM	−	−	−	−	rt 2−4 min	965
2-Hydroxybenzhydroxamate-Selective Electrode								
HB-1 *(dichloro(5,10,15,20-tetrakis(4-fluorophenylporphyrinato)tin(IV))*								
HB-1 (1.0 wt %), oNPOE (66.0 wt %), KTFPB (10 mol %), PVC (33 wt %)	ClO_4^-, −2.5; SCN^-, −2.2; Cl^-, Br^-, NO_3^-, −2.6; salicylate, −1.5	SSM	0.01	0.01	−76 to −73	−	rt ≈ 90 s; pH 7.2; dl 3 × 10^{-5} M	977
Heparin Optode								
TDDMACl *(tridodecylmethylammonium chloride)*/**H^+-40** (ETH 2412)**								
TDDMACl (2.0 wt %), **H^+-40** (1.7 wt %), DOS (66.3 wt %), PVC (30 wt %)	ClO_4^-, −1.5; SCN^-, −2.8; I^-, −2.5; salicylate, −2.5; NO_3^-, −3.3; Br^-, −3.7; NO_2^-, −4.6; Cl^-, −5.8; HCO_3^-, OAc^-, SO_4^{2-}, HPO_4^{2-}, citrate, <−6.0	SSM	−	−	−	(1.2−18 μg/mL)	rt ≈ 20 min	989
NH_3 Optodes								
NH_4^+-1 *(nonactin)* and **NH_4^+-1** (monactin)/**H^+-11** (ETH 5350); measurements in aqueous samples (membrane covered with gas-permeable membrane)*								
NH_4^+-1, **NH_4^+-2** (32 mmol/kg), **H^+-11** (27 mmol/kg), KTpClPB (31 mmol/kg), DOS (≈64 wt %), PVC (≈32 wt %)	methylamine, −2.7; ethylamine, −3.4; propylamine, −3.7; dimethylamine, −4.0; trimethylamine, −4.6	SSM	−	−	−	(dynamic range 10^{-6}−10^{-4} M)	rt ≤ 1 min	432
K^+-1 *(valinomycin)*/**H^+-11** (ETH 5350); measurements in aqueous samples (membrane covered with gas-permeable membrane)*								
K^+-1 (32 mmol/kg), **H^+-11** (27 mmol/kg), KTpClPB (31 mmol/kg), DOS (≈64 wt %), PVC (≈32 wt %)	methylamine, −0.4; ethylamine, −1.7; propylamine, −1.9; dimethylamine, −2.0; trimethylamine, −2.9	SSM	−	−	−	(dynamic range 10^{-5}−10^{-3} M)	rt ≤ 1 min	432
Na^+-2 *(*N,N′*-dibenzyl-*N,N′*-diphenyl-1,2-phenylenedioxydiacetamide; ETH 157)*/TBPE (3′,3″,5′,5″-tetrabromophenolphthalein ethyl ester); measurements in gas mixtures*								
Na^+-2 (≈2 wt %), TBPE (≈110 mol %), KTFPB (≈ 110 mol %), DOS (≈60 wt %), PVC (≈30 wt %)	methylamine, 0.0; ethylamine, 0.0; no interferences from SO_2, CO_2, NO_2, and humidity observed	SSM	−	(0.1 ppm_v)	−	(msm. range 0.002 to 100 ppm_v NH_3)		1011

Table 1 (Continued)

membrane composition	selectivity coefficients: for ISEs log $K^{pot}_{I,J}$ (SSM), log $K^{pot}_{I,J}$ (FIM), or log $k^{MPM}_{I,J}$ (as specified in next column to the right); for optodes log $k^{Osel}_{I,J}$	method of selectivity determination	concentration (M)		slope (mV/decade)	linear range (M)	remarks	literature refs
			primary ion	interfering ion				
Humidity Optodes								
CO_3^{2-}-3 *(heptyl* p*-(trifluoroacetyl)benzoate; ETH 6010);* measurements in gas mixtures*								
CO_3^{2-}-3 (3.5 wt %), TDDMACl (1.9 wt %), DOS (63.1 wt %), PVC (31.5 wt %)	ethanol, +0.4 (at 10% relative humidity no interference from 2000 ppm HOAc, 100 ppm NH_3, 10 ppm NO_2, 10 ppm SO_2	SSM	–	–	–	(5–100% relative humidity)	few s	1020
CO_3^{2-}-4 *(4-(*n*-dodecylsulfonyl)-1-(trifluoroacetyl)benzene; ETH 6019);* measurements in gas mixtures*								
CO_3^{2-}-4 (4.5 wt %), TDDMACl (1.9 wt %), DOS (62.4 wt %), PVC (31.2 wt %)	ethanol, −0.3 (no measurable interference from CO_2 at a concentration 9 times higher than in normal air)	SSM	–	–	–	(1–53% relative humidity)	few s	1020
SO_2 Optode								
sulfite-3 *(octadecyl-4-formylbenzoate; ETH 5444)*/**H^+-11** (ETH 5350); measurements in gas mixtures*								
sulfite-3 (66 mM), **H^+-11** (36 mM), oNPOE (64.0 wt %), PVC (31.4 wt %)	(<1% interference from 50 vol % CO_2 at 50% relative humidity)	–	–	–	–	–	dl 4 ppb_v at 98% relative humidity (10.5 $\mu g/m^3$)	855
Ethanol Optode								
ALC-1 *(*N*-acetyl-*N*-dodecyl-4-(trifluoroacetyl)aniline; ETH 6022)**								
ALC-1 (4.9 wt %), TDDMACl (1.6 wt %), DOS (40.5 wt %), PVC (53.0 wt %)	H_2O, −1.1; CH_3OH, +0.2; $CH_3(CH_2)_2OH$ ≈−0.1; $CH_3(CH_2)_3OH$, ≈+0.2; $C(CH_3)_3OH$, −1.1; $CH(CH_3)_2OH$, −0.9	SSM	–	–	–	0.5–35% (v/v)	rt < 30 s	1040
O_2 Optode								
O_2-3 *((*meso*-α,α,α,α-tetrakis(*o*-pivalamidophenyl)porphyrinato)cobalt(II)); measurements in gas mixtures*								
O_2-3 (1.1 wt %), poly[(2,2,3,3,4,4,5,5-octafluoropentyl methacrylate)-*co*−1-vinylimidazole] (98.9 wt %)	(influence of H_2O on O_2 measurements <5–10%; no interference from CO and CO_2)	–	–	–	–	1–1000 hPa of O_2 partial pressure	rt 5–15 s	1050

* Ionophores that we could easily identify as commercially available.

XI. Appendix II. Abbreviations

BBPA	bis(1-butylpentyl) adipate
CHEMFET	chemically modified ion-sensitive field-effect transistor
DBS	dibutyl sebacate
DBP	dibutyl phthalate
dl	detection limit
DOP	bis(2-ethylhexyl) phthalate (“dioctyl phthalate”)
DOPP	dioctyl phenylphosphonate
DOS	bis(2-ethylhexyl) sebacate (“dioctyl sebacate”)
FAES	flame atomic emission spectroscopy
FIM	fixed interference method
FNDPE	2-fluorophenyl 2-nitrophenyl ether
ISE	ion-selective electrode
ISFET	ion-sensitive field-effect transistor
KTFPB	potassium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate[a]
KTPB	potassium tetraphenylborate[a]
KTpClPB	potassium tetrakis(4-chlorophenyl)borate[a]
MPM	matched potential method
MSM	mixed solution method[19]
NaTFPB	sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate[a]
NaTpClPB	sodium tetrakis(4-chlorophenyl)borate[a]
NPPE	2-nitrophenyl phenyl ether
oNPOE	2-nitrophenyl octyl ether
PVC	poly(vinyl chloride)
PVC-COOH	“poly(vinyl chloride) carboxylated”; typical carboxyl content 1.8 wt % [49,68,79]
PVC-NH_2	“poly(vinyl chloride) aminated”[66−69]
PVC−OH	“poly(vinyl chloride) hydroxylated”; either a hydrolyzed copolymer of vinyl chloride and vinyl acetate, or a polymer of vinyl chloride, vinyl acetate and vinyl alcohol[79,195]
rt	response time
SSM	separate solution method
TDDMACl	tridodecylmethylammonium chloride
TEHP	tris(ethylhexyl) phosphate
TOPO	trioctylphosphine oxide
log P_{TLC}	logarithm of the partition coefficient, *P*,[b] between 1-octanol and water as estimated experimentally by use of thin-layer chromatography[48]

[a] Compare with Figure 54 in Bakker et al.[2] [b] Compare with section III.1.D in Bakker et al.[2]

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