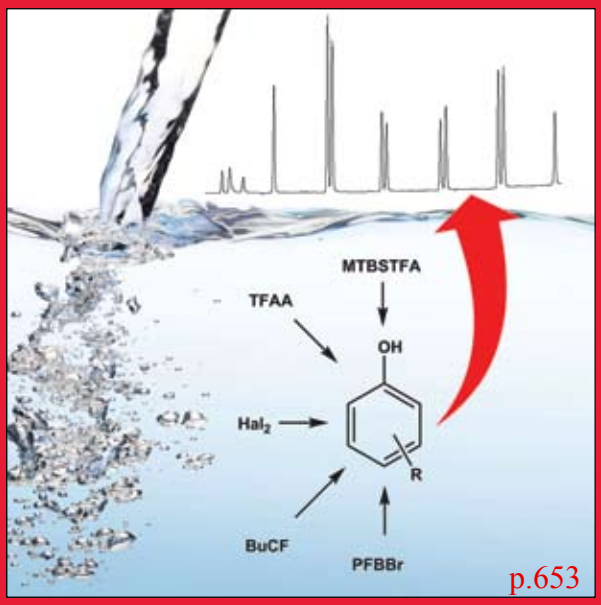
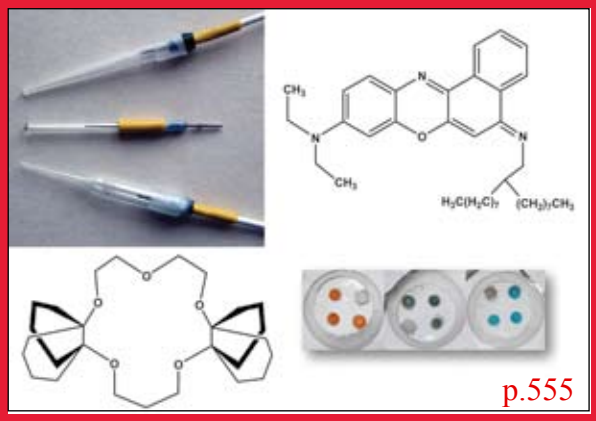
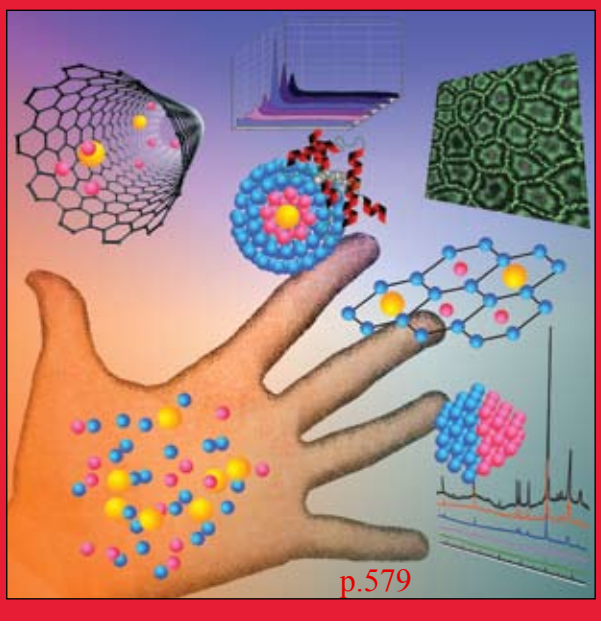
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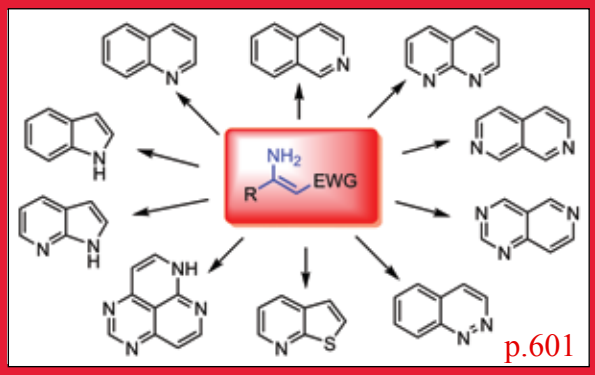
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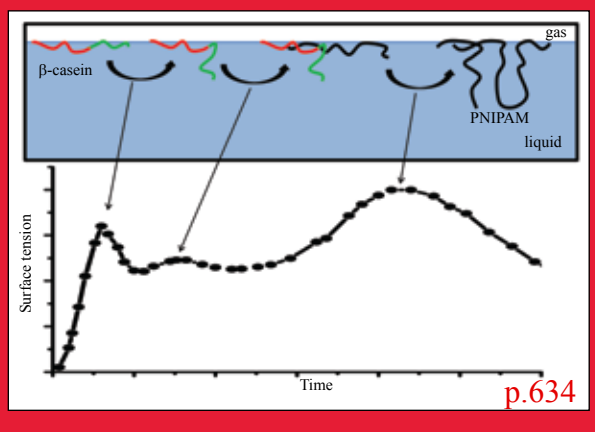
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Reviews on current topics in chemistry

The Chemistry at the Saint Petersburg State University

Volume 84 2015 Number 6

Russian Chemical Reviews **84** (6) 555 – 578 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4506

Advances and trends in ionophore-based chemical sensors

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The recent advances in the theory and practice of potentiometric, conductometric and optical sensors based on ionophores are critically reviewed. The role of the heterogeneity of the sensor/sample systems is emphasized, and it is shown that due to this heterogeneity such sensors respond to the analyte activities rather than to concentrations. The basics of the origin of the response of all three kinds of ionophore-based sensors are briefly described. The use of novel sensor materials, new preparation and application techniques of the sensors as well as advances in theoretical treatment of the sensor response are analyzed using literature sources published mainly from 2012 to 2014. The basic achievements made in the past are also addressed when necessary for better understanding of the trends in the field of ionophore-based sensors.
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I. Introduction

Chemical sensors are devices capable of transducing information on the chemical composition of certain media into a signal which can be registered relatively easily.[1,2] Most often, this is an electric signal (electromotive force, current, conductance, capacitance),[3,4] but it also can be an optical, acoustic or some other kind of signal.[2] Normally, chemical sensors allow for a non-destructive analysis *in situ* and for *in line* monitoring, they are energy- and cost-efficient, easy in use and in maintenance, and require relatively simple and inexpensive secondary instrumentation. Due to these advantages, chemical sensors are widely used in various applications from clinical analysis, control of industrial and agricultural samples and environmental monitoring to food analysis, *etc*.[1,2,5–8]

Some kinds of chemical sensors contain ionophores as active components. Ionophores (earlier also called membrane-active ligands) are neutral or ionogenic substances capable of selective ion binding. Ionophore-based chemical sensors include potentiometric sensors (ion-selective electrodes, ISEs),[9–14] ion-selective conductometric sensors (ISCOMs)[15–17] and optodes.[10–12,18] These sensors are used primarily in aqueous samples: blood, urine and other biological fluids, industrial or agricultural solutions, pulps or suspensions, wet soils, natural and waste waters, laboratory samples, *etc*. These three kinds of sensors share similar chemistry of their recognition components. The similarity goes beyond the use of ionophores: similar matrix materials, in particular, polymers, most often, polyvinyl chloride (PVC), and the same variety of plasticizers are used as membrane components or sensing layers of these sensors. In principle, ionophore-based sensors can have liquid membranes, and historically, this was the case for ISEs.[19,20] However, liquid membranes are inconvenient for handling and the respective sensors have very sophisticated design. Using matrix materials, it is possible to manufacture sensors containing membranes or sensing layers with well-defined geometry easily mounted in sensor bodies or deposited on suitable substrates. Plasticizers play a dual role in polymeric membranes providing elasticity of matrix polymers with high glass transition temperature and at the same time acting as solvents for the ionophores.

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Received 6 October 2014
Uspekhi Khimii **84** (6) 555 – 578 (2015)

Here we do not go deep into the sensor construction issues, which were reported in detail.[10,12,14–16]

There are a number of reviews that separately discuss ionophore-based ISEs, optodes or conductometric sensors, despite the similarity of the chemistry of these devices.[3,4,10–13] Excellent reviews[10–12] describe ISEs and optodes together, but these reviews, although still very useful, have been published long ago, and since then, many new sensor systems have been invented and better understanding of their work principles has been achieved. On the other hand, reviews regularly published in *Analytical Chemistry* (*e.g.*, see Ref. 3) combine brief descriptions of various kinds of sensors but normally lack in-depth discussion of the sensor features.

In this review we briefly discuss the response mechanisms of the ionophore-based chemical sensors, the similarities and differences between ISEs, ISCOMs and optodes. While addressing the recent achievements in this branch of science, we use the results published starting from 2012 and available *via* Scopus and Science Direct. However, given the broad audience of the *Russian Chemical Reviews*, we also use older sources to better show the trends in the development of the theory and practice of the ionophore-based chemical sensors.

II. Heterogeneous processes as the basis of the sensor response

It is critically important that the response of ISEs, optodes and conductometric sensors relies on heterogeneous processes: ion exchange between the sensor and the solution phases, and/or extraction of analytes by the sensor phase from the solution phase. From the practical point of view, heterogeneous processes as the basis of the sensor response comprise the ultimate reason for the sensor analysis being non-destructive. In most other analytical techniques, some reagents are added to the sample, or the sample undergoes some physical treatment, so the composition of the sample after the analysis is significantly different from what it was before. On the contrary, analysis with ISEs, ISCOMs and optodes does not cause changes in the sample composition: sensor and sample are put in contact and the sensor develops a signal which depends on the activity of the analyte in the sample. Strictly speaking, some changes of the sample composition do take place due to, *e.g.*, ion-exchange processes between the sample and the sensor phases. However, these are only minute changes which typically can be neglected.

From the fundamental point of view, the formation of the sensor response due to heterogeneous processes results in another important feature: ISEs, ISCOMs and optodes respond to the activities of the analytes, and not to their concentrations.The sensor signal is determined by the changes at the sensor/solution interface or in the whole bulk of the sensors phase. These changes may be caused by the intrinsic processes in the sample (in the cases of, *e.g.*, in-line monitoring) or simply by the replacement of the previous sample with the next one. For obvious reasons, the sensor response must be fast, otherwise sensor delivers biased data. However, even in the case of fast-responding sensors, the ion exchange and extraction processes reach at least a local equilibrium in the vicinity of the sensor/solution interface. On the other hand, these equilibria get established when the chemical or electrochemical potentials of the respective species (neutral or charged, respectively) became equal in the two phases in contact. This is the fundamental reason for such sensors being responding to the activities rather than to the concentrations of the analytes, in contrast to either classical methods based on homogeneous processes happening directly in the solution phase (*e.g.*, colorimetric analysis) or to voltammetric analysis or other numerous modern physicochemical analytical methods.

Measuring activities instead of concentrations is often advantageous because it is activity rather than concentration that correlates with the chemical potential of the component. Therefore, the activity values characterize the equilibrium states, and the gradients of activities determine the driving forces of chemical processes. Thus, ultimately, the knowledge of the species activities is required for guiding chemical processes. The activities of ions in blood and other body liquids provide more information for the clinical diagnosis than the respective concentrations.

At the same time, measuring activities instead of concentrations presents also some difficulties, which must be clearly understood by sensor users. Energy and free energy are differential quantities lacking absolute values. These quantities can be determined only against a chosen standard state. The same is true for activities. Furthermore, only the activities of components, whatever electrolytes or non-electrolytes, are rigorously defined by thermodynamics. The activities of individual ions are beyond strict thermodynamics and any procedures aimed at assessing these values rely on several extra-thermodynamic assumptions.[1,9,14]

III. Ionophore-based electrochemical sensors

III.1. Ion-selective electrodes

III.1.a. The basics of the ion selective electrode signal formation

In contrast to similar chemistry, the presumed response mechanisms of ISEs, ISCOMs and optodes differ significantly. In this Section, we briefly describe the basics of the ISE response.The main part of an ISE is the membrane (sensing layer), which separates the sample solution from the internal half-cell of the ISE. The latter may be an internal electrode (*e.g.*, Ag/AgCl) immersed into a suitable solution or so-called solid-contact system (Fig. 1). For more details on the ISE design, see books.[14,21]

The measured signal is the electromotive force (EMF) of the corresponding galvanic cell. In most practically-relevant cases, this is a cell with a remote reference electrode and a salt bridge: a cell with a liquid junction. The reference electrode is kept in a separate vial filled with a suitable solution, most often, saturated or 3.5 M KCl. The potential of the reference electrode is, therefore, constant. The reference electrode is connected to the sample solution *via* the so-called salt bridge. In the domain of the contact of the salt bridge with the sample solution (the liquid junction), due to the diffusion of the electrolytes from the bridge to the sample and back, the so-called diffusional (or liquid-junction) potential arises. Measures are always taken to minimize this potential using the so-called equitransferent electrolytes at high concentrations, *e.g.*, 3.5 M KCl, or 1 M LiOAc. Thus, the EMF change upon the variation of the sample composi-

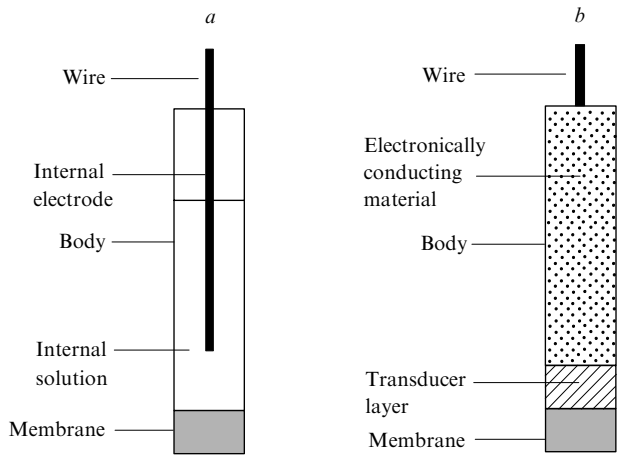


Figure 1. Ion selective electrode with internal solution (*a*) and with solid contact (*b*).

tion is due almost exclusively to the variation of the ISE potential, and, ideally, it obeys the Nernst equation (1):

$$E = E^\circ + \frac{RT}{z_i F} \ln a_i^{\mathrm{s}} \tag{1}$$

The E° value includes all constant contributions to the EMF, and it is called standard EMF value, a_i^{s} is the activity of $I_i^{z_i}$ ion in the solution phase, z_i is the charge number ion $I_i^{z_i}$; R, T and F are the gas constant, the absolute temperature and the Faraday constant.

The detailed theory of ISE response may be rather complicated depending on the generality of the assumed model,[9, 10, 14] and results in implicit mathematical descriptions, which require computer simulations.[13, 14, 22] However, the basic requirements for an ISE exhibiting Nernstian response to the chosen $I_i^{z_i}$ ion can be understood by considering only the boundary electrical potential:[10, 23] the Galvani potential difference at the interface between the electrode membrane and the sample solution:

$$\Delta\varphi_{\mathrm{b}} = \varphi_{\mathrm{m}} - \varphi_{\mathrm{s}} = \frac{\mu_i^{\circ,\mathrm{s}} - \mu_i^{\circ,\mathrm{m}}}{z_i F} + \frac{RT}{z_i F} \ln \frac{a_i^{\mathrm{s}}}{a_i^{\mathrm{m}}} \tag{2}$$

Here $\Delta\varphi_{\mathrm{b}}$ is the boundary potential; φ_{m}, φ_{s} are the Galvani potentials in the membrane and in the solution phases in the immediate vicinity of the interface; $\mu_i^{\circ,\mathrm{m}}$, $\mu_i^{\circ,\mathrm{s}}$ are the standard values of the chemical potential of the $I_i^{z_i}$ ion in the membrane phase and in the solution phase, and a_i^{m}, a_i^{s} are $I_i^{z_i}$ ion activities in the membrane and in the solution phase.

Physically, the Galvani potential difference arises over the space charge region (electrical double layer) on both sides of the interface. The width of this region amounts to 300 nm.[4, 24] The values of $\mu_i^{\circ,\mathrm{m}}$, $\mu_i^{\circ,\mathrm{s}}$, a_i^{m} and a_i^{s} refer to the respective phases outside the space charge region. Normally, due to the lack of reliable data on activities, a_i^{m} is replaced by C_i^{m} the concentration of free $I_i^{z_i}$ ions in the membrane. Also, the use of concentrations allows for the direct application of mass balances, thus simplifying the theory of the ISEs and optodes. Then Eqn (2) can be written as

$$\Delta\varphi_{\mathrm{b}} = \varphi_{\mathrm{m}} - \varphi_{\mathrm{s}} = \frac{\mu_i^{\circ,\mathrm{s}} - \mu_i^{\circ,\mathrm{m}}}{z_i F} + \frac{RT}{z_i F} \ln \frac{a_i^{\mathrm{s}}}{C_i^{\mathrm{m}}} \tag{3}$$

Obviously, the EMF obeys the Nernst equation (1) only if a_i^{m} in Eqn (2) or C_i^{m} in Eqn (3) are constant over the considered range of solution compositions. Considering only the boundary potential, this is an indispensable condition for an ISE to exhibit Nernstian potentiometric response. This condition is fulfilled only if the membrane interacts with the solution *via* an ion-exchange process: $I_i^{z_i}$ ions move from one contacting phase to the other and back, whereas ions of the opposite charge are each confined to a particular phase. For instance, if a cation-sensitive membrane containing potassium tetrakis(*p*-chlorophenyl)borate is in contact with aqueous KCl solution, the K^+ cations move from the membrane to solution and back, while the $[(4\text{-}ClC_6H_4)B]^-$ anions remain in the membrane phase and the Cl^- anions stay in the solution. Thus, the $[(4\text{-}ClC_6H_4)B]^-$ concentration in the membrane is constant and, due to the macroscopic electrical neutrality of the membrane, K^+ concentration is also constant. This is why ISEs obey the Nernst law. For an anion-sensitive membrane containing, *e.g.*, tetradecylammonium nitrate (TDA-NO_3) and placed into $NaNO_3$ solution, the NO_3^- anions exchange between the phases, while the TDA^+ cations are confined to the membrane and the Na^+ cations are in the solution phase. Lipophilic species confined to the membrane phase and interacting with ions only electrostatically, like $[(4\text{-}ClC_6H_4)B]^-$ anions and TDA^+ cations in the above examples, are called ion-exchange sites.

If the solution contains several electrolytes, the ion-exchange process involves several sorts of ions. For instance, if a membrane containing R^- cation exchange sites is in contact with a mixed solution containing I_iX and I_jX electrolytes with the common X^- anion, the ion-exchange equilibrium can be written as follows:

$$I_i^{+,\mathrm{m}} + I_j^{+,\mathrm{s}} \overset{K_{ij}}{\rightleftharpoons} I_i^{+,\mathrm{s}} + I_j^{+,\mathrm{m}} \tag{4}$$

If this process takes place, the EMF of the galvanic cell obeys the Nikolsky equation, derived originally for glass pH electrodes:[25]

$$E = E^\circ + \frac{RT}{z_i F} \ln\left(a_i + K_{ij}^{\mathrm{pot}} a_j\right) \tag{5}$$

Here a_i, a_j are the activities of I_i^+ and I_j^+ ions in solution and the parameter K_{ij}^{pot} is called potentiometric selectivity coefficient of the electrode to the I_i^+ ions in the presence of I_j^+ ions. The lower is the selectivity coefficient, the higher excess of a_j over a_i is tolerated, *i.e.*, the ISE response does not significantly deviate from the Nernst behaviour towards a_i.

Normally, ion-exchange sites interact with ions only non-specifically, and the ion-exchange equilibrium con-

stant can be expressed using the so-called ionic partition coefficients introduced [26] as

$$k_i = \exp\left(-\frac{\mu_i^{\circ,\mathrm{m}} - \mu_i^{\circ,\mathrm{s}}}{RT}\right) \quad (6)$$

If we still consider only the boundary potential, the selectivity coefficient is determined by the ion-exchange equilibrium constant K_{ij}.

$$K_{ij}^{\mathrm{pot}} = K_{ij} = \frac{k_j}{k_i} \quad (7)$$

Membranes containing only ion-exchange sites are typically of low selectivity. The selectivity is enhanced by use of ionophores due to stronger, partly covalent or host–guest specific interactions between these species and ions. This interaction is normally described in terms of formation of ion-to-ionophore complexes, *e.g.*, 1 : 1 complexation of the I^+ cation with the neutral L ionophore:

$$\mathrm{I}_i^+ + \mathrm{L} \overset{K_{\mathrm{I}_i\mathrm{L}}}{\rightleftharpoons} \mathrm{I}_i\mathrm{L}^+ \quad (8)$$

The complex formation constant refers to the membrane phase and is normally expressed *via* the respective species concentrations:

$$K_{\mathrm{I}_i\mathrm{L}} = \frac{C_{\mathrm{I}_i\mathrm{L}}^{\mathrm{m}}}{C_{\mathrm{I}_i}^{\mathrm{m}} C_{\mathrm{L}}^{\mathrm{m}}} \quad (9)$$

The expressions for more complicated complexes are analogous.

Hence, the selectivity coefficient of a membrane containing ionophore L depends also on the ion-to-ionophore complex formation constants for the I_i^+ and I_j^+ ions:

$$K_{ij}^{\mathrm{pot}} = \frac{k_j K_{\mathrm{I}_j\mathrm{L}}}{k_i K_{\mathrm{I}_i\mathrm{L}}} \quad (10)$$

Neutral ionophores must be used together with suitable ion-exchange sites to maintain constant composition of the membrane phase whatever the composition of the solution. Charged ionophores can, in principle, be used without ion exchangers. However, the combination of charged ionophores with ion-exchange sites often allows for drastic improvement of the electrode selectivity.[10, 14, 27–31]

For decades after the classical Nikolsky work on glass pH electrode,[25] the ion exchange at the ISE/sample solution interface in ISEs has been assumed to be the basic electrochemical process underlying the electrode response.

III.1.b. Novel materials in ion-selective electrode membranes

The use of novel materials for ionophore-based ISE membranes is aimed, primarily at improved selectivity, stability (in particular for solid-contact ISEs), better compatibility of the electrodes with clinical and biological samples and longer lifetime of these sensors.

The required selectivity to the target analyte is achieved by using of appropriate ionophore, although other components of the membrane also play a role. In the early days of ISEs with ionophore-based membranes, the progress in thi s field mainly related to the invention of novel lipophilic complexing agents so that more and more analyte ions became accessible *via* direct potentiometric measurements. A large number of ionophores for monovalent and divalent cations have been invented by the end of the 1990s (see a relevant review [11]).

During the last two decades, the frequency of the development of new ionophores has significantly decreased. Anyway, there is some progress in the synthesis of novel ionophores, even for alkali metal cations, which have been accessible for analysis with ISEs for decades. For instance, new bis-crown ionophores were synthesized from azobenzocrown ethers containing hydroxyl groups in the *para* position relative to the azo group. The synthesized host molecules act as sodium or potassium ionophores.[32] Silver ion sensors have been proposed with azathiacrown ethers,[33] calix[4]arene derivatives [34, 35] and new carbon paste ion-selective electrode based on a newly synthesized *N*,*N*-bis(benzophenoneimine)formamidine as an ionophore.[36] Three new calixarene-based Tl^+-selective ionophores have been utilized in Tl^+ ISEs. The complex formation constants (log K_{IL}) for two of the calixarene derivatives with Tl^+ were measured to be 6.44 and 5.85 using the sandwich membrane technique,[37] while measurements with the third ionophore were impossible due to precipitation of the ionophore during these long-term experiments.[38] An ISE with PVC membrane containing dibenzo(perhydrotriazino)aza-14-crown-4 ether showed selectivity to Be^{2+} (see Ref. 39) A new Zn^{2+}-ion PVC membrane sensor with 2-(2-hydroxy-1-naphthylazo)-1,3,4-thiadiazole as the ionophore has been developed. In electrode construction, ionic liquids, various alkylmethylimidazolium chlorides, were used as transducer media and as lipophilic ionic membrane components.[40] A number of Pb^{2+}-selective ionophores have been reviewed.[41] A new copper-selective electrode with a succinimide derivative as ionophore was described.[42]

A new trend is the development of ISEs sensitive to trivalent ions. Due to the correspondingly decreased Nernst factor, the potentiometric determination of these ions requires more precise signal recording than for mono- or divalent ions. Unlike a few years ago, the modern secondary instrumentation such as multichannel computerized potentiometric stations with the resolution of 0.01 mV and better meets the required precision criteria, and this may be a motive for the development of ISEs for trivalent ions. Among these are ISEs for Al^{3+} with various ionophores.[43, 44] Particular attention is attracted by ISEs for determination of lanthanides, probably because of the use of the lanthanide compounds in nonlinear optical devices. Electrodes were proposed for the determination of Ln^{3+} (Ref. 45), Nd^{3+} (Ref. 46), Gd^{3+} (Refs 47 and 48) and Ho^{3+} (Ref. 49).

Quantification of metal cations in samples containing surfactants is very challenging;[50] however, determination of surfactants themselves is not trivial as well. Therefore a novel class of ionophores for surfactant-selective electrodes is of interest. A PVC membrane doped with a stoi-

chiometric polyelectrolyte–surfactant complex was used for the design of ISE responsive to cetyltrimethyl ammonium and related surfactants. The polyelectrolyte platform allows for designing of a wide range of different ionophores responsive to organic cations.[51]

Among clinically-relevant analytes, dopamine,[52] acetylcholine[53] and rivastigmine[54] can be now selectively measured as cationic forms using ISEs; the sulfadimethoxine anion can also be determined.[55]

Amino acids may become a new interesting class of ionophores. In particular, L-tryptophan and L-tyrosine were used as ionophores for Cu^{2+} over the concentration ranges of 3.0×10^{-4}–1.0×10^{-1}M. These ISEs exhibit a good selectivity to alkali, alkaline earth and some transition and heavy metal ions and the ammonium ion.[56,57] Unfortunately, the authors do not indicate the life-time of the ISEs, which can be expected to be short due to hydrophilicity of amino acids. Most probably, relatively narrow dynamic range of these ISEs is also caused by the hydrophilicity of the ionophores. Immobilization of amino acids in the membrane, *e.g.*, by grafting to the polymer backbone may make them more promising as ionophores.

Turning to anion-selective electrodes, it is necessary to mention new chloride ISEs based on polymeric resin ion exchanger[58] and metal porphyrin complexes.[59] A CN^--selective electrode was developed based on the nickel complex of *N,N′*-bis-(4-phenylazosalicylidene)-*o*-phenylenediamine as an ionophore.[60] The bis(*N*-3-methyl phenyl salicylidenaminato)Cu(II) complex was utilized as an SCN^--selective ionophore.[61] Tweezer type carbonate ionophore-based ISE coupled with a glass pH-electrode provided determination of dissolved CO_2 using a cell without liquid junction.[62]

A special example presents synthetic hydrotalcite: an inorganic 'ionophore' in polyvinylbutyral membrane, which showed some selectivity to HPO_4^{2-}.[63] The difficulty of designing ISEs for phosphates, sulfate and other hydrophilic ions is due to low affinity of such ions to non-polar membrane phase.[10,14] A new way of solving this problem relies on the use of Donnan exclusion ion-exchange membranes. These membranes *per se*, as well as the 'ionophores' are hydrophilic, and, therefore, ions are not stripped of their hydration shell as they interact with such membranes. Because of this, lipophilic ions are no longer preferred over hydrophilic ones, making such membranes promising candidates for the measurements in the presence of lipophilic contaminants.[64]

Now we will turn to the materials utilized in solid-contact sensors. The elimination of the aqueous internal electrolyte in ISEs allows for significant miniaturization of the electrodes. Another goal is to make electrodes maintenance-free (no need to refill the ISE with a fresh portion of the internal electrolyte). However, the simple design with direct contact of ion-conducting membrane and electronically conducting substrate ultimately forms a capacitor which behaves as an ideally polarizable electrode. The potentials of such electrodes are very unstable. The potential stabilization requires an intermediate (transducer) layer with combined ionic and electronic conductivity and a redox reaction for coupling ionic and electronic transfer. This is why, when it comes to such sensors, the most challenging issue is the potential stability, especially the long-term stability.[65] Various materials are used for the intermediate layers. Electron-ion-exchange resins[66,67] and conducting polymers were the first to be used.[13,68] More recently, the variety of materials for the transducer layer has been extended and now it includes graphenes,[69] carbon black,[70–72] metal nanoparticles,[73] carbon–epoxy composites[74] and mesoporous carbon.[75] Non-covalent functionalization of multi-walled carbon nanotubes by a pyrene derivatives of benzo-18-crown-6 ether leads to nanostructure assemblies that play both the role of an ion-to-electron transducer and a selective recognition element in solid-contact K^+ ISEs.[76] The use of nanomaterials, in particular, carbon nanotubes, is increasingly popular in making solid-contact ISEs, and also in modifying membranes themselves with such materials.[77–79] For details on the use of carbon and metal nanomaterials dispersed in sensor membranes, see review.[80] Unfortunately, the authors of most of these papers neglect the inevitable effect of redox species on the potentials of membranes containing an electronic conductor. Typically, this important issue is not addressed at all.

Ionic liquids are also used as components of ISEs, including solid contact electrodes. The triblock copolymer polystyrene-block-polybutadiene-block-polystyrene and its composites with 1-butyl-3-methylimidazolium hexafluorophosphate have been applied for preparing various solid contact ion-selective potentiometric sensors.[81] Trihexyltetradecylphosphonium chloride was used for triple function: as ionophore, as lipophilic ionic component in order to reduce membrane resistance and as transducer medium in order to stabilize the potential of internal Ag/AgCl electrode in a solid-contact nitrate ISE.[82] More data on the use of ionic liquids in ISEs are presented elsewhere.[83,84]

A very promising approach for stabilization of solid contact ISE potentials relies on using redox buffer with a well-controlled concentration ratio of oxidized and reduced species of a redox couple (*e.g.*, Co^{II}/Co^{III} porphyrins) in the intermediate layer.[85]

Unfortunately, coupling of the ion and electron transfer is not enough to produce good solid-contact ISEs with ionophore-based membranes. Unlike glass and crystalline membranes, the membranes based on ionophores sorb water from aqueous solutions, and a thin water layer between the membrane and the transducer layer or the substrate causes instability of the potential.[64,70,86]

Very recently, a new approach was proposed aimed at artificial stabilization of the solid-contact ISE potentials *via* the shift of the standard potentials of the electrodes by applying an external voltage or by passing current pulses in the nA range.[87]

An important trends related to novel membrane materials refers to the replacement of all traditional membrane components: polymer, plasticizer and ionophore with their fluorinated analogues. Fluorinated compounds provide enhanced selectivity, longer lifetime and higher robustness of ISEs in biological samples.[88–92] More recently, a new carbonate electrode with fluorinated membrane was devised with largely reduced interference from chloride and salicylate, which is especially important for clinical analysis.[93]

Immobilization of ionophores on the polymer matrix backbone provides another way to improve the ISE lifetime and also the robustness against blood and other

biological fluids capable of extracting ionophores from membranes. Recently, this approach was used for a K^+-selective ionophore: a crown ether containing a terminal triple bond in the substituent was immobilized in azide-modified poly(vinyl chloride) matrix by azide–alkyne Huisgen cycloaddition ('click' chemistry).[94]

The nature of the plasticizer plays a significant role in the performance of polymer membrane ion sensors. Conventional plasticizers suffer leaching from the membrane and exudation, which can limit the lifetime of sensors based on plasticized membranes. Polymeric plasticizers may be a good remedy against these problems. Recently, a polyester sebacate was used as a model polymeric plasti-

Table 1. Selected characteristics of novel ISEs listed in Section III.1.b.

Analyte	Dynamic range /mol litre^{-1}	Slope /mV/log a	Selectivity coefficients /log$K$	Ref.
K^+	6×10^{-5}–1×10^{-1}	55	Na^+ −3.3; NH_4^+ −1.2; Cs^+ −2.8; Li^+ −4.0; Ca^{2+}, Mg^{2+} −5.0	32
K^+	1×10^{-5}–1×10^{-2}	51.7	Na^+ −2.5; NH_4^+ −0.9; Li^+ −4.6; Ca^{2+} −5.2	76
K^+	1×10^{-6}–1×10^{-1}	58.0	Na^+ −1.4; Li^+ −3.2; Mg^{2+} −3.4; Ca^{2+} −3.8	94
Ag^+	1×10^{-8}–1×10^{-3}	55.1	–	33
Ag^+	1×10^{-6}–1×10^{-2}	58.8	Hg^{2+} −2.5; Cu^{2+} −3.5; K^+ −4.5; Na^+, Pb^{2+} < −6	34
Ag^+	5×10^{-7}–1×10^{-3}	59.8	Na^+ −4.0; NH_4^+ −3.9; K^+ −4.3; Mg^{2+} −4.7; Cu^{2+} −4.7; Pb^{2+} −5.3; Hg^{2+} −3.4	35
Ag^+	2.2×10^{-7}–2.2×10^{-2}	59.5	Na^+ −3.3; NH_4^+ −4.3; Mg^{2+} −4.0; Cd^{2+} −3.7; Pb^{2+} −2.7; Cu^{2+} −3.0; Hg^{2+} −2.8	36
Tl^+	1×10^{-6}–1×10^{-2}	58.4	Na^+, NH_4^+ −3.6; K^+ −3.3; Ca^{2+}, Cu^{2+} −5.9; Pb^{2+} −4.8; Cd^{2+} −6.2; Zn^{2+} −6.1	38
Be^{2+}	7.6×10^{-6}–1.0×10^{-1}	30.7	Li^+ −1.1; Na^+ −1.4; Mg^{2+} −1.0; Ca^{2+} −1.2	39
Zn^{2+}	3×10^{-7}–1×10^{-1}	29.8	Li^+, Na^+, K^+ < −5.0; Cu^{2+}, Pb^{2+} −2.2; Hg^{2+} 0.2, Ag^+ 0.9	40
Cu^{2+}	10^{-8}–10^{-2}	37.4	Ca^{2+} −2.4; Co^{2+} −3.5; Ni^{2+} −1.4; Zn^{2+} −2.1; Pb^{2+} −0.6	42
Cu^{2+}	3×10^{-4}–1×10^{-1}		Pb^{2+} −0.5; Cs^+ −1.0; K^+, Ag^+ −1.8; Na^+, Mg^{2+} −2.5	56
Cu^{2+}	1×10^{-6}–1×10^{-2}	29.9	Na^+, K^+, NH_4^+ ⩽ −3.7; Ca^{2+}, Mg^{2+} ⩽ −3; Pb^{2+} −4.5; Cd^{2+} −4.1	98
Al^{3+}	1×10^{-6}–1×10^{-2}	18.4	Fe^{3+} −1.1; Zn^{2+}, Pb^{2+} ⩽ −1.2; Cu^{2+} −2.4; Na^+, K^+ ⩽ −1.6	43
Al^{3+}	1×10^{-7}–1×10^{-1}	20.7	Na^+, K^+ ⩽ −3.9; Ca^{2+}, Mg^{2+} ⩽ −4.2; Cd^{2+} −4.4; Ni^{2+} −4.0; Ag^+ −2.0	44
Ln^{3+}	1×10^{-9}–1×10^{-3}	17.8	Li^+, K^+, NH_4^+ ⩽ −7; Ca^{2+}, Ba^{2+} ⩽ −6; Pb^{2+} −5.0; Al^{3+}, Nd^{3+} ⩽ −5.3	45
Nd^{3+}	1×10^{-6}–1×10^{-2}	21.2	Na^+, K^+ ⩽ −2.7; Ca^{2+}, Co^{2+}, Pb^{2+} ⩽ −2.7; Ho^{3+}, Eu^{3+}, Gd^{3+} ⩽ −2.5	46
Gd^{3+}	1×10^{-6}–1×10^{-2}	19.5	Li^+, Na^+, K^+ ⩽ −3.4; Zn^{2+}, Cu^{2+}, Ni^{2+} ⩽ −2.7; Nd^{3+} −1.7; Ce^{3+} −1.2; La^{3+} −1.6	47
Gd^{3+}	1×10^{-6}–1×10^{-2}	19.9	Na^+, K^+ ⩽ −3.3; Mg^{2+}, Ca^{2+}, Pb^{2+} ⩽ −3.1; La^{3+}, Pr^{3+}, Dy^{3+} ∼ −3.1; Nd^{3+} −2.6	48
Ho^{3+}	3×10^{-8}–1×10^{-2}	21.1	Li^+, Na^+, K^+ ⩽ −3.8; Mg^{2+}, Ca^{2+} ⩽ −2.9; La^{3+} −3.1; other lanthanides ⩽ −3.4	49
Dopamine [a]	1×10^{-3}–1×10^{-1}	∼50	–	52
Acetylcholine [a]	1×10^{-6}–1×10^{-3}	49.1	choline$^+$ −2.5; NH_4^+, NMe_4^+, NEt_4^+ −1.9; Na^+ −1.8; dopamine [a] −1.5	53
Rivastigmine [a]	1×10^{-5}–1×10^{-2}	56.8	K^+ −4.0; Na^+ −3.8; Ca^{2+} −3.7; NH_4^+ −4.0	54
Citalopram [a]	5×10^{-7}–1×10^{-2}	60.4	Na^+, K^+ ⩽ −3.5; Mg^{2+}, Ca^{2+} ⩽ −2.4; Co^{2+} −3.4; Fe^{3+} −2.3	99
Cl^-	1×10^{-4}–1×10^{-2}	59.2	F^- −6.6; Br^- −1.3; I^- −0.8; NO_3^- −4.5; ClO_4^- −3.0	58
CN^-	6.3×10^{-7}–1.2×10^{-2}	−59.8	Cl^-, Br^- −3.8; SCN^- −2.9; NO_3^-, SO_4^{2-} < −5	59
CN^-	1×10^{-6}–1×10^{-1}	−58.7	Br^- −3.1; Cl^-, SCN^- −3.0; NO_3^- −2.8; ClO_4^- −1.8	60
SCN^-	1×10^{-6}–1×10^{-1}	−59.3	Cl^- −3.3; Br^-, NO_3^- −2.8; CN^- −3.0; I^- −1.9	61
HPO_4^{2-}	5×10^{-5}–2×10^{-2}	−29.2	Cl^-, Br^- −1.8; NO_3^- −1.4; SCN^- −1.5; CO_3^{2-} −1.3	63
Sulfadimethoxine anion	2.4×10^{-8}–3.0×10^{-3}	−54.1	Cl^- −1.5; NO_3^- −1.2; HCO_3^- −1.9; salicylate −0.3	55

[a] Cationic (protonated) form

cizer in the fabrication of PVC membrane with valinomycin as ionophore.[95] Data on the non-PVC membranes containing ionophores are critically reviewed elsewhere.[84]

Some new approaches focusing on the preparation procedure of ionophore-based membranes were also developed. It turned out to be possible to introduce ionophores and ion exchangers into membranes being enclosed in acrylic microspheres.[96] The authors of this work claim that the novel technology ensures more uniform distribution of ionophores and ion exchangers over the membrane bulk. Screen-printing technique was utilized to prepare flat-designed ISEs. A film of nanodispersed silver ink (nanosilver film) synthesized by reduction of $AgNO_3$ with $NaBH_4$ was screen printed on paper.[97] Screen-printed ion selective electrodes were fabricated for Cu^{2+} (Ref. 98) and for some pharmaceutical analytes like citalopram.[99]

The data on the dynamic range, slope and selectivity of the novel ISEs discussed in this section are presented in Table 1.

III.1.c. Ion selective electrodes in trace analysis and under non-zero current conditions

Since the late 1990s, the trace-level analysis was the mainstream in the ISE theory and application (see reviews [13, 14, 100]). Before, for decades, ISEs have been considered as being suitable for the analysis of samples containing analyte ions at the concentration levels not lower than 10^{-5} or, at best, 10^{-6} mol litre^{-1}. Therefore, a drastic improvement of the lower detection limit down to 10^{-9} mol litre^{-1} and even lower was a breakthrough in the measurements with ISEs.[101] The deviations from Nernstian response of ISEs in micromolar and sub-micromolar concentration range are caused by the local increase in the concentration of the analyte in the sample in the vicinity of the sensor membrane (Fig. 2). It is now generally recognized that this local increase in the analyte concentration is caused by transmembrane fluxes of ions co-extracted from the internal filling solution to the sample and by the fluxes caused by the replacement of the primary ions in the membrane by the interfering ions due to ion exchange.[102–105]

Interestingly, the effects of co-extraction were thoroughly studied since the mid-1970s.[27, 106–109] It was shown that the co-extraction of the electrolyte from the external solution causes deviations from the Nernstian response of ISEs, and eventually the cationic response of an ISE turns to anionic, and *vice versa*. For obvious reasons, this effect is observed either in relatively strong solutions (>0.1 mol litre^{-1}), or in solutions containing lipophilic (hydrophobic) ions. For instance, K^+-selective electrodes with membranes containing valinomycin exhibit Nernstian response in KCl solutions up to 1 mol litre^{-1}; however, in $KClO_4$ solutions, the electrodes show cationic response only up to 10^{-3} mol litre^{-1}. At higher concentrations of $KClO_4$, the potentials deviate from the Nernstian response and at concentrations higher than 10^{-2} mol litre^{-1}, ISEs give anionic response.[14] Typically, cationic ISEs are filled with the 0.01 M solutions of the corresponding chlorides and anionic ISEs are filled with 0.01 M solutions of a sodium or potassium salt. Thus, the internal electrolytes in ISEs are essentially hydrophilic and cannot be co-extracted in large quantities. Therefore, for decades, the co-extraction from the internal solution was neglected at all. Nowadays, however, this phenomenon is always taken into consideration, as well as the respective fluxes of the co-extracted electrolyte across the membrane. Furthermore, the transmembrane fluxes have been detected experimentally by electrochemical scanning microscopy method.[110]

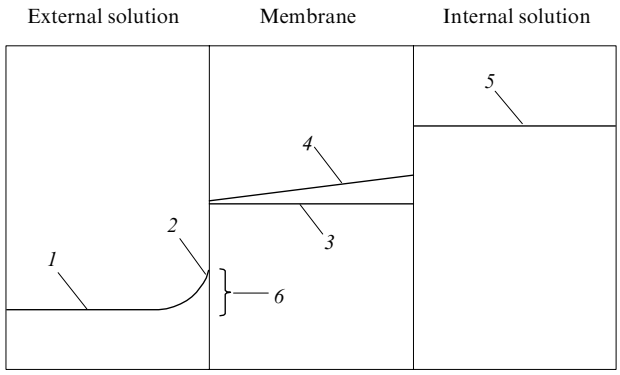


Figure 2. Schematic representation of the electrolyte profiles in a membrane/solution system.
(*1*) Electrolyte concentration in the solution bulk; (*2*) electrolyte concentration in the vicinity of the membrane; (3) 'ideal' flat analyte ion concentration profile determined by the ion-exchanger concentration; (*4*) real analyte concentration profile (the deviations from the flat profile *3* are caused by the co-extraction from the internal solution); (*5*) electrolyte concentration in the internal solution; (*6*) deviation of the surface concentration of the analyte from its bulk value.

It may appear that in the case of solid-contact ISEs (having no internal aqueous solution), no such transmembrane fluxes exist because of the lack of the internal electrolyte. However, the internal reference system of a solid contact ISE based on, *e.g.*, a conducting polymer is also a source of analyte ions, which eventually contaminate sample solutions, although to somewhat lesser extent than in the case of ISEs with internal aqueous filling.[111–114]

Thus, both in a conventional ISE filled with an aqueous electrolyte and in a solid-contact ISE, the membrane is a source of the analyte ions contaminating the external solution, so that the surface concentration of the analyte deviates from the bulk value. This deviation is insignificant if the bulk concentration of the sample is large compared with the impact caused by the transmembrane flux. But with dilution, the deviation increases and at the analyte concentrations of $<10^{-5}$ mol litre^{-1}, the ions brought to the sample by the transmembrane flux determine the surface concentration of the analyte. This is responsible for the 'ordinary' lower detection limit of ISEs in the micromolar concentration range.

A number of approaches aimed at the improvement of the lower detection limit of ISEs *via* minimization of the transmembrane fluxes or compensation of their effects have been proposed.[101, 105, 115] In particular, transmembrane fluxes can be reduced by maintaining the activity of the target analyte in the internal filling solution of an ISE at a very low level by means of a suitable buffer at a sufficiently high activity of an interfering ion.[101] If no suitable buffer exists, low activity of the analyte in the

internal solution may be kept by using, *e.g.*, ion-exchange resins.[105, 116, 117] The disadvantage of this approach is that the transmembrane fluxes of ions are eliminated, rigorously speaking, at only one concentration of the analyte in the sample. The electrode response slope in even more dilute solutions becomes super-Nernstian and nonlinear.

More advanced approaches suggest modifications of the membrane geometry or composition.[105, 118] The magnitude of the transmembrane flux can be decreased by lowering the driving force, namely, the gradient of the analyte ion concentration by using thicker membranes.[105, 119, 120] Also, the flux can be decreased by reducing ion diffusion coefficients, *e.g.*, by higher content of the polymer in the membrane[105, 121] or by means of dispersing silica gel microparticles in the membrane.[105, 122] These (chemical) approaches were critically analyzed and evaluated.[105]

An alternative way to eliminate the transmembrane fluxes or to compensate the consequences of these fluxes is based on galvanostatic polarization of the ISE. This (electrochemical) approach was proposed back in 1999,[123] and since then, it has been utilized by several groups of researchers.[112, 113, 124–127] By passing across the membrane a current of a suitable density, one can eliminate the transmembrane ion flux. Galvanostatic polarization is much more flexible approach aimed at the improvement of the low detection limit of an ISE than the modification of the composition of the internal solution, leaving alone the modification of the composition and/or the geometry of the membrane.

Obtaining linear Nernstian response in a broad concentration range requires specific values of the polarizing current density tuned for particular concentrations of the analyte in the sample. This approach called tuned galvanostatic polarization (TGP) method was first proposed and successfully used first for Ca^{2+}-electrodes.[128] More recently, the TGP method has been significantly improved using Cd^{2+} ISEs as a model system.[129–131] The TGP approach was successfully implemented also for Pb^{2+}-selective crystalline ISEs.[132, 133] The optimal density of the polarizing current is dependent on the analyte concentration; therefore, for real samples, it cannot be known beforehand. This problem was successfully solved on the basis of the found relationship between the analyte concentration in the sample and the optimal current density.[129–131]

Ion selective electrodes are used under non-zero current conditions not solely to improve the lower detection limit. Another promising area of the use of polarized ISEs refers to modification of the types of electrode response (cationic or anionic) and selectivity. Basically, the types of the ISE response and selectivity are determined by the membrane composition. However, using an ISE under non-zero current conditions, it is possible to impose a certain type of response and also to modify the selectivity by passing current across the electrode membrane.[134] This can be done with ISEs having membranes with neutral ionophores and lipophilic background electrolyte [*e.g.*, tetradodecylammonium tetrakis(*p*-chlorophenyl) borate] but without ion-exchange sites. The concentration of the analyte ion in the membrane is then adjusted by passing current of a tuned density for a certain time.[134] Polarization of a membrane containing Na^+-selective neutral ionophore with low cathodic current (~ 3 μA cm^{-2}) resulted in pseudo-Nernstian response to Na^+ ions with the selectivity coefficient determined by the ion partition coefficients and ion-to-ionophore complexation constants:

$$K_{NaK} = \frac{k_K}{k_{Na}} \frac{K_{KL}}{K_{NaL}} \tag{11}$$

When the electrode is polarized with cathodic current of higher density (~ 30 μA cm^{-2}), the concentration of the extracted ions exceeds the ionophore content, and the selectivity is determined by ionic partition coefficients only, as in the case of ionophore-free membranes:

$$K_{NaK} = \frac{k_K}{k_{Na}} \tag{12}$$

By changing the sign of the polarizing current, a cationic response can be replaced by anionic one. It was shown that use of small anodic current (~ 3 μA cm^{-2}) results in a response of the same electrode to Cl^- anions.[134]

Non-zero current measurements are also suitable for sensing polyions, *e.g.*, heparin ($z \approx -70$) and protamine ($z \approx 20$). The classical equilibrium measurements do not allow sensing these ions because the large denominator in the Nernst factor (RT/zF) results in a negligible response slope. A non-equilibrium procedure for the measurements was developed when the process is under the diffusion contro, and the potential change upon addition of Y^- polyionic analyte obeys Eqn (13) [135–137]

$$\Delta E = \frac{RT}{F} \ln\left(1 - \frac{z_Y D_{aq} \delta_m}{C_R D_m \delta_{aq}} C_Y\right) \tag{13}$$

Here z_Y is the charge of Y^- species, C_Y is their concentration in the sample solution, C_R is the concentration of R^+ ion-exchange sites in the membrane, D_{aq} and D_m are the ion diffusion coefficients in the aqueous phase and in the membrane phase, δ_{aq} and δ_m are the thicknesses of the diffusion layers in these phases.

The linearity and the reproducibility of the response of ISEs under diffusion control were poor.[135–137] However, by applying alternating galvanostatic and potentiostatic pulses, very good reproducibility of the response to polyions was attained. Furthermore, the calibration curve was linear with the the same slope as for monovalent ions:[138]

$$E = \frac{RT}{F} \ln C_Y \tag{14}$$

Hence, non-zero current measurements provide new opportunities also for polyion sensing.

Recently, yet another advantage of measurements with ISEs under non-zero current conditions was demonstrated: the possibility of coulometric measurements with ISEs. The measurement protocol consists of the following sequence of actions. First, the open circuit potential (OCP), which essentially equals the EMF, is determined. Subsequently, a controlled potential pulse of a fixed

duration is applied leading to a complete electrolysis of the cationic or anionic analyte. The potential is raised with respect to the OCP. Then, in order to eliminate an undesired buildup of polarization of the membrane, the latter is held at zero current. After that, a second potential pulse of the same magnitude and duration is imposed. The final part of the sequence is a regeneration of the membrane at the OCP.[139–141] The charge passed during the polarization is determined by the analyte concentration in solution.

Historically, chronopotentiometry was used mainly for fundamental studies of the ISEs response mechanism.[142, 143] However, measurements with ISEs in chronopotentiometric mode provide direct control of the concentration (not activity) of the analyte due to the depletion of the species in the vicinity of the membrane surface.[144, 145] In the case of quantification of carbonates, the chronopotentiometric readout is especially attractive because it may provide additional information on the sample speciation compared to zero-current potentiometry and detect the sum of labile carbonate species instead of only the ion activity.[145, 146]

Ion selective electrodes can be applied in a small area detection system using nanopipettes. This, however, requires a special measurement method in order to avoid the enhanced background signal problem caused by a cation-rich layer near the charged inner surface of the nanopipette and the selectivity change problem due to relatively fast saturation of the ISE membrane with the analyte inside the nanopipette. To solve the above problems, a new ion selective detection system was developed using a nanopipette that implies measurements of an alternating current signal mediated by the analyte-saturated ionophores in a PVC membrane located at the conical shank of the nanopipette. Low but reliably recorded K^+ and Na^+ ion currents passing through a PVC membrane containing saturated bis(benzo-15-crown-5) and bis(12-crown-4) ionophores, respectively, were selectively detected using the alternating current signal measurement system equipped with a lock-in amplifier.[147]

The use of ionophore-based membranes in the voltammetric mode was first proposedt in the mid-1990s.[16] Recently, this approach was upgraded for ultrasensitive measurements based on stripping voltammetry down to 0.1 nmol litre^{-1} of Ca^{2+} ions by using a thin-polymer-coated electrode.[148]

III.1.d. Non-classical reference electrodes

The most common reference electrodes (REs) are silver/silver chloride electrodes immersed in 3.5 M KCl and connected to the sample solution *via* salt bridge, which is also filled with 3.5 M KCl. Saturated KCl is also used. These REs are called single junction REs. There are also REs with an additional chamber and salt bridge filled with 1 M LiOAc, which are called double junction REs. The latter are used when contamination of samples with K^+ and Cl^- ions must be avoided.[14] Both designs are rather cumbersome. Therefore, the use of these classical REs hinders the miniaturization of the potentiometric devices. This is why during the recent years, a lot of efforts were invested into the development of solid REs without liquid junction.

One of the approaches to make miniature REs relies on the use of ionic liquids as the salt bridge electrolytes. In particular, an RE was described comprising Ag/AgCl electrode immersed in or coated with an AgCl-saturated ionic liquid: 1-methy-3-octylimidazolium bis(trifluoromethylsulfonyl)imide.[149] The ionic liquid phase plays a dual role, that is, as a medium dissolving AgCl and a salt bridge upon contact with an aqueous solution. The gelation of the ionic liquid phase allowed preparing coated-wire type solid-state REs. Other ionic liquids shown to be useful for the preparation of REs are tributyl(2-methoxyethyl)phosphonium bis(pentafluoroethanesulfonyl)amide[150] and bis(trifluoromethanesulfonyl)amides with 1-alkyl-3-methyl-imidazolium, phosphonium or ammonium cations.[151] The application of conducting polymer films doped with biological ligands as the electroactive parts of the reference electrodes was also proposed.[152]

Conducting polymers are also used for the development of miniature REs. A new kind of all-solid-state reference electrode suitable for potentiometry with ISEs was proposed, where a poly(n-butyl acrylate)-based membrane was deposited on a glassy carbon substrate with conducting polymer–polypyrrole transducing layer.[153] These REs are compatible with poly(acrylate)-based ISEs in simple disposable cells, where both the indicator and reference electrode can be produced in a single fabrication process, using the same or similar methods.

Reference electrodes based on a polymer/inorganic salt composite and a silver/silver chloride reference element demonstrated insensitivity of the potentials to the sample matrix effects, excellent stability of the potential readings and relatively long lifetime.[154]

The idea to utilize the so-called distribution potential to produce reliable REs fully compatible with the ionophore-based ISEs technology appears especially interesting. The distribution of a salt with roughly the same lipophilicity of the cation and anion between organic and aqueous phases determines the interfacial potential, and the latter is roughly constant whatever the composition of the aqueous phase. This approach was implemented using tetra(alkyl)ammonium tetra(butyl or phenyl)borates.[155, 156] A detailed discussion on new types of REs is presented in a review.[157]

III.1.e. Recent advances in the ion selective electrode theory

The electric potential and selectivity of the ionophore-based membranes in a quasi-steady state has been described rather successfully by the so-called multispecies approximation.[29, 30, 158–161] More recently, a number of attempts have been made aimed at description of the membrane potential in the real time and space. A simple but efficient model has been devised describing the propagation of ions over an ionophore-based membrane.[162] Unfortunately, this description does not account for the non-compensated charges in the double layer at the membrane/solution interface.

More advanced theory relies on the numerical solution of the system of the Nernst–Planck (15) and Poisson (16) equations (NPP).[163–170]

$$J_k(x,t) = -D_k\left[\frac{\partial C_k(x,t)}{\partial x} - z_k C_k(x,t)\frac{F}{RT}E(x,t)\right] \qquad (15)$$

$$I(t) = F\sum_k z_k J_k(x,t) + \varepsilon\frac{\partial E(x,t)}{\partial t} \qquad (16)$$

Equation (15) describes $J_k(x,t)$ — the place- (x) and time- (t) dependent flux of the species k as a function of D_k, $C_k(x,t)$ and $E(x,t)$, *viz*., the species k diffusion coefficient, concentration and electric field. In Eqn (16) [the Poisson equation re-written for the time-dependent total current density $I(t)$], z_k stands for the species charge and ε is the dielectric permittivity of the medium. This approach allows for tracing the formation of the boundary and the diffusion potentials in membranes over time and space. Furthermore, the theory provides guidelines for the optimization of the membrane and of the internal solution compositions for the improvement of the ISE sensitivity. In this way the theory can be used to optimize the membrane and internal solution compositions of ISEs for trace analysis.[164–170] A striking power of this theory is in predicting the optimal response time needed in the case of ultra-low concentration measurements and unique possibility for inverse simulations., *i.e*., accessing the ISE properties directly from the empirical results, omitting representation by the equivalent circuits.[168]

Originally, the NPP model implied liquid or plasticized membranes. More recently, it was applied to a new kind of ionophore-based membranes: permselective gold nanopores with ionophores immobilized on the pore surface with thiol deri vatives.[171] Comparative reviews of different theoretical descriptions of the ISE membrane potential and selectivity have been published.[13, 22]

The advances in theory, with the main benefits, *i.e*., the access to space (including membrane, diffusion layers, solid or liquid internal contacts) and time domains (including interpretation of time-dependent selectivity and detection limit), and in general 'non-equilibrium potentiometry'[168] are not without cost. Some simple facts, although formally feasible for modelling by the NPP, are still beyond consideration, *e.g*., the possibility for simultaneous occurrence of multiple target ion complexes with different stoichiometries. Simultaneous formation of 1 : 1 and 1 : 2 complexes of a fluorophilic crown ether with ions in fluorinated ISE membranes and how this results in what looks like super-Nernstian responses has been reported recently.[172] Also, it is normally assumed that ion–ionophore complexes include only one ion and one or several ionophore molecules. It was shown, however, that Ba^{2+} ions form also polynuclear complexes with some new ionophores.[173]

It is also worth mentioning here that the mixed-potential theory (as an alternative to equilibrium approaches) has been proven to be useful to optimize the membrane composition for a higher selectivity and a lower detection limit.[174]

A simple, fast and theoretically substantiated experimental method for the determination of the so-called unbiased selectivity coefficients[10, 175, 176] has been proposed recently.[177]

III.2. Ion-selective conductometric sensors

Ion-selective conductometric sensors (ISCOMs) were invented in the mid-1990s.[15, 16, 178] The conductometric mode of measurements allows for drastic miniaturization of sensor devices. This advantage of ISCOMs is due to the lack of the reference electrode needed for the potentiometric measurements. The relatively large size of reference electrodes hampers the miniaturization of potentiometric sensors even if the ISEs themselves can be rather small (see also Section III.1.d). In ISCOMs (Fig. 3), two planar interdigitated metal electrodes are covered with a thin layer of a suitable membrane material. The working area of an ISCOM is about 1 mm^2, and the whole device is of only slightly larger size, except for the wires.

Despite this advantage and unlike ISEs and optodes, ISCOMs have been less developed and applied. However, these sensors are currently used in sensing clinically-relevant analytes like creatinine,[179] sugars (maltose, lactose, sucrose and glucose)[180] and aflatoxin B[181] as well as ions, *e.g*., ammonium[182] and cationic surfactants.[183]

The ISCOM response relies on the co-extraction of electrolytes from the solution phase to the sensor layer phase (it is necessary to distinguish between conductometric sensors based on metal oxide nanostructures widely used for the analysis of gases[184] and ionophore-based conductometric sensors). In principle, the sensor phase can contain neutral ionophores L and M to bind the cation and the anion of the electrolyte, respectively. In the real practice, however, the sensor phase is doped with only one ionophore, typically, the cation binding one. Without going into the details of the theory of the conductometric response formulated by the inventors of these devices,[15, 16] here we will only present the final theoretical relationship between the specific conductivity of the sensor phase (κ),the mean activity of the electrolyte in the solution ($a^{s}_{\pm IX}$), the total ionophore concentration in the membrane ($C_L^{m,tot}$), the ionic partition coefficients (k_I, k_X) and the ion–ionophore complex stability constant (K_{IL}):

$$\kappa \sim a^{s}_{\pm IX}\left(C_L^{m,tot} k_I k_X K_{IL}\right)^{1/2} \qquad (17)$$

This equation was derived with the assumption of complete dissociation of the electrolyte in the sensor phase.[15] The formation of ion pairs in ISCOM membranes caused primarily by low polarity of the sensor phase does not alter this relationship, although the higher consumption of the ionophore may shorten the working range of the sensor in the high analyte concentration domain. Thus,

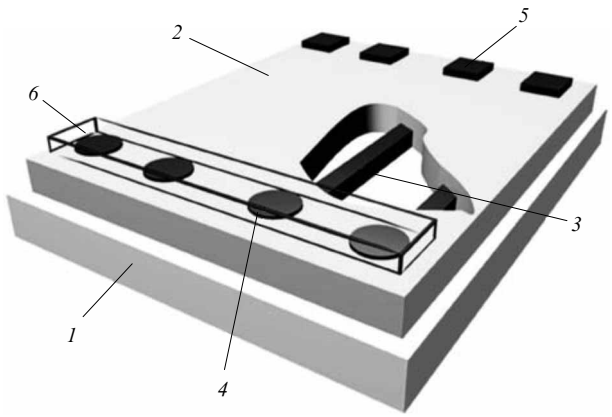


Figure 3. Schematic representation of a planar conductometric sensor: (*1*) substrate, (*2*) insulator, (*3*) conductive track, (*4*) metal electrode, (*5*) contact pads, (*6*) sensing layer.

Eqn (17) derived by the inventors of the ISCOMs[15] predicts a linear relationship between the membrane conductivity and the analyte concentration (rigorously, the activity). However, the experimentally recorded ISCOM signals give sigmoidal curves comprising a linear domain when plotted against the logarithm of the analyte concentration.[15–17, 79] In other words, the experimental results do not support the existing interpretation of the ISCOM response.

IV. Ionophore-based optochemical sensors (optodes)

IV.1. Operating principles and characteristics of optodes

Optodes are defined as chemical sensors transforming the analyte concentration into the optical signal. The optical signal is induced by a specific interaction of the analyte with an active component of the optode. Upon binding the analyte, this component changes its absorbance, luminescence or other optical properties. These changes can be detected with spectral instruments, digital camera and sometimes even visually.

The optode response may be based either on the surface equilibrium (surface optodes) or on the equilibrium establishing in the bulk of the sensor (bulk optodes). Optodes based on the interfacial phenomena are less explored and their response mechanism is a lot more cumbersome to quantitatively describe as compared to the bulk optodes.[185]

The 'classical' example of an optical chemical sensor is a hydrophobic bulk optode which is typically based on PVC or similar polymer matrix and contains lipophilic active components. The same lipophilic compounds are exploited in such optodes as in the membranes of ISEs. However, besides ionophores and ionic additives typical of the ISEs, optodes contain optically detectable molecules, most often chromoionophores or luminophores, which can change their colour or luminescence being protonated or complexed with the analyte, respectively. A typical example of the response of the PVC bulk optode to pH change is shown in Fig. 4.

As opposed to the ISE potentiometric response, the optical signal is proportional to the concentration of the detectable component in the sensor phase. To optically detect changes in analyte activity in the aqueous sample solution, the corresponding changes in the detectable form of the active component in the membrane phase need to be



Figure 4. Optical response of the ETH 5350-containing PVC membrane to the pH change from 5 to 9 in physiological saline.[186] ETH 5350 is 5-(2-octyldecyl)imino-9-diethylaminobenzo[*a*]-phenoxazine.

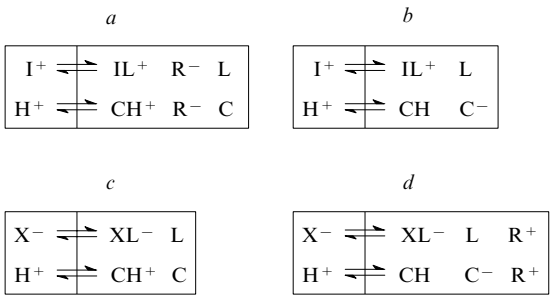


Figure 5. Schematic response of the optode membrane containing neutral ionophore L.
(*a*) Membrane selective to I^+ (R^- is cation-exchange additive) contains neutral chromoionophore C; (*b*) membrane selective to I^+ contains charged chromoionophore C^-; (*c*) membrane selective to X^- contains neutral chromoionophore C; (*d*) membrane selective to X^- (R^+ is anion-exchange additive) contains charged chromoionophore C^-. The left-hand side in all schemes is the aqueous phase, while the right-hand side is the organic phase.

significant relative to its total concentration. Since one of the forms of the active component is always charged, the concentration of the charged species in the membrane also changes significantly. Therefore, since the electroneutrality must hold in the phase bulk, optodes do not respond to a single ion. Instead, the distribution equilibrium between the aqueous and polymer phases must hold for a pair of ions. Depending on the charge sign of these ions, this can be either competitive ion-exchange equilibrium or ionophore-mediated co-extraction. The corresponding response mechanisms are schematically shown in Fig. 5 for the case of neutral ionophore and neutral or charged chromoionophore present in the membrane.

For the membranes containing charged ionophore, fully analogous schemes can be given, as well as for the luminescent membranes containing luminophore. In some cases, the charge-compensating ionic additives must be entrapped in the optode membrane.

It is generally known that the acquired optical signal gives information on the bulk concentrations of the optically detectable species in the phase rather than their activities. However, in the case of the optodes which form a phase separate from the sample, these concentrations are dictated by the activities of the ions in the aqueous solution, as explained in Section II. Thus, while retaining the advantages of the optical readout, the optodes are sensors of the sample activity, in contrast to the traditional optical methods.

Here we briefly describe the quantitative formulation of the colorimetric optode response for the case of polymeric membranes containing neutral chromoionophore C with its protonated form CH^+, neutral cation-selective ionophore L forming complexes IL_n^{z+} with the cation I^{z+} and cation exchange sites R^-. Other systems shown in Fig. 5, as well as luminescent optodes, can be described in similar way. The overall ion-exchange equilibrium between the aqueous solution and the membrane phase can be written as

$$I^{z+,aq} + n\,L^{org} + (z\,CH^+ + z\,R^-)^{org} \rightleftharpoons \rightleftharpoons (IL_n^{z+} + z\,R^-)^{org} + z\,C^{org} + z\,H^{+,aq} \quad (18)$$

For luminescent optodes containing neutral luminophore P binding the analyte cation I^{z+} to form complexes IP_n^{z+} and cation exchange site R^- in the form of the M^+R^- salt with the hydrophilic cation M^+, the corresponding ion exchange equilibrium can be given as

$$I^{z+,\mathrm{aq}} + n\,P^{\mathrm{org}} + (z\,R^- + z\,M^+)^{\mathrm{org}} \rightleftharpoons \rightleftharpoons (IP_n^{z+} + z\,R^-)^{\mathrm{org}} + z\,M^{+,\mathrm{aq}} \quad (18a)$$

The equilibrium constant of (18), *i.e.*, the ion exchange constant of an optode is given by expression (19)

$$K_{\mathrm{exch}}^{\mathrm{IL}_n} = \left(\frac{a_{\mathrm{H}}[\mathrm{C}]}{[\mathrm{CH}^+]}\right)^z \frac{[\mathrm{IL}_n^{z+}]}{a_{\mathrm{I}}[\mathrm{L}]^n} = \left(\frac{K_{\mathrm{a}}}{k_{\mathrm{H}}}\right)^z k_{\mathrm{I}}\beta_{\mathrm{IL}_n} \quad (19)$$

which is a function of the ionic partition coefficients (see Eqn 6) k_{I} and k_{H} for I^{z+} and H^+ ions between the aqueous solution and membrane phase, the stability constant for the ion–ionophore complex ($\beta_{\mathrm{IL}n}$) and the chromoionophore acidity constant (K_{a}) in the membrane.[10, 187] It is assumed that equilibrium (18) holds throughout the whole bulk of the membrane contacting with the solution and that the concentrations in the organic phase are proportional to activities. By combining Eqn (19) with the mass balance and electroneutrality condition for the membrane phase, one can obtain the optode response function [188]

$$a_{\mathrm{I}} = \left(zK_{\mathrm{exch}}\right)^{-1}\left(\frac{\alpha a_{\mathrm{H}}}{1-\alpha}\right)^z \frac{C_{\mathrm{R}^-}^{\mathrm{tot}} - (1-\alpha)C_{\mathrm{C}}^{\mathrm{tot}}}{\left\{C_{\mathrm{L}}^{\mathrm{tot}} - [C_{\mathrm{R}^-}^{\mathrm{tot}} - (1-\alpha)C_{\mathrm{C}}^{\mathrm{tot}}](n/z)\right\}^n} \quad (20)$$

where α is the relative portion of the unprotonated form of the chromoionophore in the membrane:

$$\alpha = \frac{[\mathrm{C}]}{C_{\mathrm{C}}^{\mathrm{tot}}}$$

Equation (20) describes an implicit S-shaped response function that cannot generally be solved for α. The measured absorbance A in a given solution can be related to α by measuring the absorbances of the fully protonated (A_{P}) and deprotonated form (A_{D}) of the chromoionophore:

$$\alpha = \frac{A_{\mathrm{P}} - A}{A_{\mathrm{P}} - A_{\mathrm{D}}} \quad (21)$$

Analogous relationships were derived for the luminescent optodes.[189]

As noted above and becomes clear from Eqn (20), only the ratio of two ion activities ($a_{\mathrm{I}}/a_{\mathrm{H}}$) can be measured with the chromoionophore-based optode, and individual activity of the analyte ion I^{z+} remains inaccessible without independent data on the sample pH. This is in line with the well-known fact that single ion activities cannot be accessed without additional extra-thermodynamic assumptions. For anion-selective optode, only the product ($a_{\mathrm{X}} \cdot a_{\mathrm{H}}$) (were X^- is the analyte anion) can be measured.

In the case of luminescent optodes, the response will be determined by the ratio $a_{\mathrm{X}}/a_{\mathrm{M}}$ or the product $a_{\mathrm{I}} \cdot a_{\mathrm{H}}$, where M^+ is the hydrophilic cation which provides the electrical neutrality in the membrane phase upon establishing of equilibrium (18a). Since the anionic additive R^- does not show any pronounced selectivity to a particular cation, M^+ (reference ion) is the cation whose sample concentration is the highest. As such, it essentially determines the ionic strength.

The cross-sensitivity of the optode response to the activities of the two ions restricts, to some extent, their application. Meanwhile, this dependence can be utilized to tune the sensitive range of the optode to the target sample activity range by changing pH [see Eqn (20)] or ionic strength of the sample. Another way to shift the ion-exchange equilibrium to the activity range of interest is choosing a system with a different exchange constant, *i.e.*, by changing either the ionophore or chromoionophore by the one which forms a complex with a different stability. In addition, Eqn (20) suggests the dependence of the response function and, in turn, of the experimental optode calibration curve on the charge of the extracted cation and the stoichiometry of the membrane complex. This information cannot be retrieved from potentiometric measurements within the Nernstian response range of corresponding ISEs.

Optodes can demonstrate impressively low detection limits as compared to the conventional ISEs.[190] The analyte concentrations down to 10^{-10}–10^{-12} mol litre^{-1} can be accessed due to the absence of the inner filling solution and the arising problem of the transmembrane ion fluxes.[102] A new mathematical model for estimation of the anion-selective optode detection limit was developed based on IUPAC methodology.[191] The model accommodates for the non-linearity of the optode response and can be generally utilized to any analytical system with S-shaped response function.

The response time of the bulk optodes is typically longer as compared to the ISEs since in the case of optodes, the equilibrium response means uniform distribution of the components in the membrane, *e.g.*, diffusion within the whole bulk of the polymeric phase. The mathematical description of the dynamics of the optode response has been reported.[187] The simple equation to estimate the time when the distribution of the components in the membrane reaches 95% of the equilibrium state was derived.[187]

$$t_{95\%} = 1.13\,\frac{d^2}{D_{\mathrm{m}}} \quad (22)$$

Here d is the membrane thickness, D_{m} stands for the diffusion coefficient of the moving species in the membrane (it is assumed that diffusion coefficients of all species are equal). Thus, given the membrane thickness of about 1 μm and the diffusion coefficient of about 10^{-8} cm^2 s^{-1}, which is typical of PVC-based membranes, the response time should be $\sim$1 s.

The selectivity of optodes is mainly determined by the ionophore selectivity since the proton-to-chromoionophore binding is extremely selective.[192] The mathematical

description of the colorimetric optode selectivity was proposed and, as the authors demonstrated, required somewhat different considerations than the Nikolsky–Eisenman formalism.[188] It was shown that, as opposed to the ISEs, selectivity of the optodes can be formalized accurately for the full range of the ion charge numbers and that it is pH-dependent.[188]

The lifetime of the optodes is typically shorter than that of ISEs. This is because the intensity of the optical signal is proportional to the bulk concentration of the photoactive component in the optode membrane; therefore, its leakage and/or decomposition causes much bigger loss in signal intensity and sensitivity than in the case of the ISEs.

Optodes have been known since the 1970s and have been developed over the decades along with the ISEs, due to the similarity of the active components and membrane matrices. Nowadays, optodes represent a good alternative to the ISEs having a number of advantages, such as low detection limits and insensitivity to the electromagnetic interferences. Optodes do not require a separate reference sensor or electrical connection with power source or detector. This enables the design of a broad variety of sensor configurations, including submicro-size devices. Coupled with the optical fibre, optodes provide minimally invasive and remote measurements. The ease of handling, capability of continuous in-line analysis, low energy consumption, low cost, and possibility of mass production make optodes a good solution for industrial, environmental, pharmaceutical, biological, and especially *in vivo* medical applications. Real-time imaging using optical sensors, which is attractive in medical and biological applications, is an emerging field.

In the next sections we overview the main trends in optode development, namely, (*i*) advancing the readout techniques; (*ii*) implementing new sensing materials in optodes; (*iii*) implementing new matrices for optode membranes; (*iv*) advancing the design of optical sensing platforms; (*v*) state-of-the-art concepts of the optode response.

IV.2. Optical signals and optode readout modes

The most commonly measured optical properties are absorption and reflectance of visible light; luminescence intensity and decay time; and, in addition, refractive index, light scattering and light polarization.[193, 194] Spectrofluorimetry in the near-infrared (NIR) region is an area of increasing interest for biology and medicine because NIR waves penetrate skin and adjacent live tissue as deep as a few millimetres, and most biological matter exhibits relatively low levels of background interference in this wavelength region.

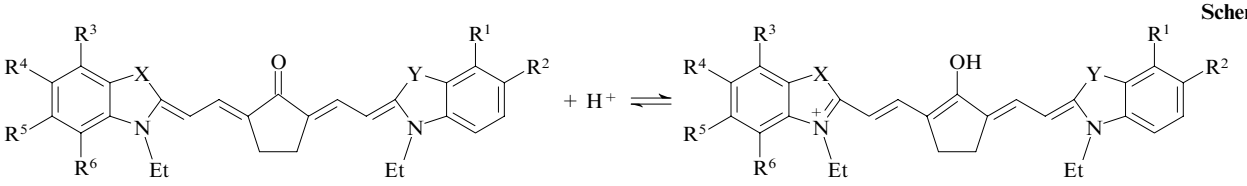
Most of optodes operate in the visible absorbance/reflectance and in fluorescent modes. Colorimetric signal can be readily acquired while fluorescent molecule must be excited prior to detection. However, fluorescent signal is typically more intense as compared to the absorbance readings.

The optode film absorbance was earlier commonly measured by spectrophotometers; today, this technique loses its relevance due to expensive and bulky equipment. Instead, simple methods based on the light reflectance such as digital camera readout are used for signal acquisition. Photographing of the sensors in contact with the sample solution is followed by digital colour analysis (DCA) which can be performed with commercial (MatLab) and free (ImageJ) software. Typically, these programmes deliver the sensor colour as a 3D vector in RGB colour coordinates with the estimation of the respective red, green and blue intensities. However, direct colour acquisition as the intensity of a single colour component is dependent on the fluctuations in light source intensity, detector sensitivity, concentration of the chromoionophore in the membrane, photobleaching and changes in the optical alignment. In addition, inhomogeneous indicator distribution and varying thickness of the sensor film can influence the signal. The effect of these factors can be minimized using referenced detection techniques, namely, ratiometric readout mode. The simplest approach is to take the ratio of two of the most changing colour components. A digital consumer camera readout, and ratiometric referencing based on the red and green camera channels was used to image pH gradients in marine sediments with hydrogel pH-sensitive optode.[195] DCA was implemented to acquire the signal of Cu^{2+}-, Ag^{+}- and Co^{2+}-sensitive poly(methacrylate) optodes.[196] A simple and low-cost imaging setup for film optodes based on NIR-emitting dyes was introduced.[197] It is based on a commercially available 2-CCD colour near infrared camera and LEDs as light sources. The common ratiometric RGB imaging was extended by an additional NIR channel. Oxygen partial pressure and pH gradients were imaged simultaneously with sufficient resolution. A readout device based on greyscale CCD detector and red, green and blue narrow-band LEDs as light sources was proposed and provided minimal interference from sample absorbance and illumination instability.[198] Hue, saturation, value (HSV) colour space was studied as possible substitute for commonly used RGB colour space.[199, 200] It was demonstrated that the use of the hue component of the HSV as a quantitative analytical parameter for bitonal optical sensors is promising for minimizing signal interferences which arise from indicator concentration, membrane thickness, detector spectral responsivity and illumination.

Fluorescent optodes respond to the analyte concentration change by changing the lifetime or intensity of fluorescence. The lifetime-based sensing and its referencing cannot be briefly explained and, therefore, it will not be discussed here. The intensity of the fluorescence can be measured with spectral devices or with a digital camera and suffers from the same interferences as the colour change. There are two ways of referencing the fluorescent signal. Classical approach implies a reference fluorophore introduced into the optode membrane along with the indicator fluoroionophore. The ratio of intensities of these two components is then acquired as a signal. More recent approach relies on the use of dual-wave emitting compounds. These molecules being excited with a single wavelength emit light of two distinct wavelengths and the ratio of the respective intensities forms the optical reading in this case.[201]

At the more advanced level the modes of the optical readout and approaches to the signal referencing are discussed in the recent review.[18]

Scheme 1



R^1, R^2, R^5, R^6 = H; R^1-R^2, R^5-R^6 is benzo; R^3, R^4 = H, OH, NHAc, NH_2; X, Y = CMe_2, S

IV.3. Novel sensing compounds for the optode membranes

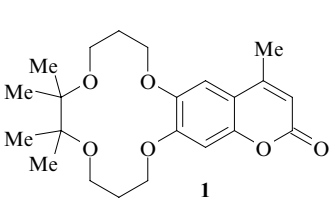
A number of new classes of organic compounds and novel principles of synthesis were investigated recently for application in optical sensing.

New chromogenic and fluorescent compounds were proposed as H^+-selective carriers. Asymmetric perylene bisimide dyes entrapped in polyurethane hydrogel and poly(hydroxyalkyl methacrylate) matrix were shown to be suitable for fluorimetric pH-sensing.[202] The new fluoroionophores demonstrated excellent photostability. A ratiometric fluorescent pH-sensor with extremely high resolution based on pyrene-derivatives of the disulfonic acid was described.[203] Nile blue derivative-based nanosized pH sensors were applied for simultaneous far-red and near-infrared qualitative imaging of hypoxia in tumour models.[204] Twenty ketocyanine dyes were examined as potential pH fluoroionophores (Scheme 1).[205] The basicity, reversibility, photostability, leaching and calibration curves were determined for the new compounds.

A more detailed overview on the existing pH-selective optical sensors and novel trends in this area are given in review paper.[206]

Among the most recent advances in synthetic methods reported recently, clickable crown ether type K^+-selective ionophore was synthesized for the first time.[94] The ionophore can be easily immobilized in azide-modified poly(vinyl chloride) to produce optode, as well as ion-selective electrode membrane. A new fluorescent optode was developed for measuring lithium therapeutic concentrations, with newly synthesized crown ether type fluoroionophore and its polymer-immobilizable hydrophilic derivative.[201] Compound **1** incorporates simultaneously 14-crown-4 ether as a Li^+-selective binding site and 4-methylcoumarin as a fluorophore. The intramolecular charge transfer between the two sites causes wavelength shift, which is utilized for fluorescence measurements. The sensors demonstrated no response to major biological interfering cations (K^+, Ca^{2+}, Mg^{2+}) and selectivity over Na^+ of $\log k_{Li/Na} = -2.4$.

Structure 1



1

Colorimetric optodes for nickel detection were fabricated by immobilization of indophenol or triazene oxide in triacetylcellose matrix.[207,208] A luminescent zinc-selective sensor based on a Schiff base was developed.[209] The sensor functioned in the range of 10^{-9} to 10^{-3} mol litre^{-1} and was successfully applied to detect Zn^{2+} in human hair samples, different brands of powdered milk and some pharmaceuticals.

New chromogenic calix[4]arenes functionalized with a phenyl azo group were investigated as potential fluoroionophores for optical sensing of Hg^{2+}, Ni^{2+} and Eu^{3+} (Ref. 210). Thin calix[4]arene amide derivative layers deposited on a glass Suprasil substrate demonstrated reversible response after regeneration with hydrochloric acid.

Due to the extremely low detection limits that optodes can demonstrate they are an attractive tool for monitoring of heavy metal ions. There is a relatively old review on heavy metal detection with optodes[211] and we list here the most recent findings in this area. A new class of lead-selective optodes based on dithizone derivatives entrapped in different matrices was evaluated.[212] The optodes sensed lead down to 10^{-8} to 10^{-9} mol litre^{-1} in several types of natural water samples and showed reversible response upon an appropriate regeneration procedure. Rhodamine B derivative was utilized to prepare fluorescent mercury sensor with the detection limit of 10^{-9} mol litre^{-1} in the batch solution.[213] The optode was shown to be functional in a flow-through mode and applicable for mercury determination in environmental water samples and fish. A newly synthesized rhodamine B type fluorescent chromoionophore with a spirolactam ring was evaluated for use in bulk optodes.[214] Optode membranes loaded with the new dye and containing copper ionophore exhibited a nanomolar detection limit for copper ion at pH 5.5. An absorbance-based optode for detection of cadmium was developed by the immobilization of a functionalized naphthol-based dye in the plasticized cellulose triacetate matrix.[215] Various combinations of the dye immobilized in the cellulose triacetate and polystyrene matrices with different plasticizers were studied. The optode found to be reversible upon treating it with 0.01 M HNO_3.

Multifunctional membrane for visual warning and enhanced adsorptive removal of cadmium ions in aqueous solutions was prepared and examined.[216] Porphyrin-based optical indicator for cadmium ions was immobilized onto a porous chitosan/cellulose acetate blend base membrane. The prepared membrane was found to be capable of displaying distinct colour changes in response to the presence of cadmium ions in aqueous solutions. In addition, it also showed significantly enhanced performance for adsorptive removal of cadmium ions.

Fluorescent and colorimetric optodes are widely used for detection of noble metal ions. The advances in optical sensing of silver, gold and platinum ions were overviewed recently.[217]

New photoactive compounds for lanthanide recognition were tested.[218,219] Dysprosium and europium ions

were measured in fluorescent and absorbance modes, respectively.

In analogy with the ISEs, the number of cationic analytes which are detectable with optodes is significantly higher than of the anionic species. However, corrole-derivative complex with cobalt(III) and functionalized porphyrin complex with rhodium(III) were utilized as chromoionophores for detection of nitrite anion in PVC-plasticized optodes.[220] The sensors exhibited enhanced nitrite selectivity over other anions including thiocyanate and perchlorate.

It was shown quite long ago that optodes and ion selective electrodes are suitable for gaseous analyte sensing.[11] The most common gas optical sensors are oxygen-sensitive luminescent optodes.[221] Carbon dioxide partial pressure is also assessable with optodes. For example, it is reported on a lifetime-based optical sensor for measuring partial pressure of dissolved CO_2 gas in natural waters in the range of about 0 to 50000 μatm.[222] It was shown that after preconditioning, these sensors are stable in water for time periods longer than 7 months. A novel, rapid response, fluorosensor for 2D-imaging of CO_2 distributions and dynamics in marine sediments was described.[223] An optical fibre gas-phase biosensor (bio-sniffer) for assessment of indoor formaldehyde was fabricated and tested.[224] The sensor measures formaldehyde vapour as fluorescence of reduced nicotinamide adenine dinucleotide, which is the product of formaldehyde dehydrogenase reaction.

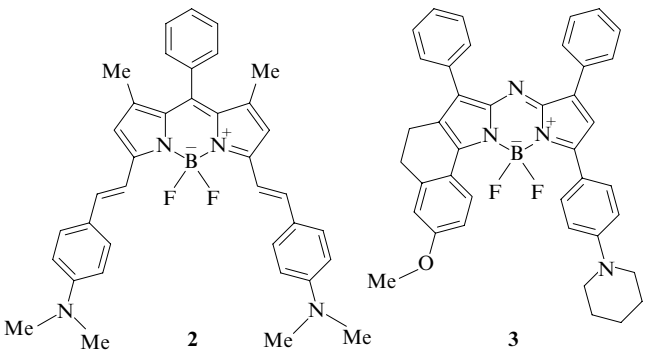
Biological analytes are also accessible with the optodes. An amine-reactive ionophore was utilized for the development of micro-optodes for *in vitro* and *in vivo* monitoring of histamine levels.[225] Similarly to the ISEs, optodes can be modified into biosensors with the respective enzymes in order to sense neutral biologically relevant analytes. Glucose is among the most important analytes of the kind, an overview on luminescent glucose sensing has been published recently.[226]

It was found recently that boron-dipyrromethene (BODIPY) functionalized with appropriate substitutes can be effectively utilized in optode development. We show here several applications of this novel class of compounds. Highly stable near-infrared fluorescent (NIRF) BODIPY derivatives (structures **2** and **3**) have been utilized as chromoionophores in ion-selective optodes.[227] The pK_a values of the chromoionophores were tuned by using different substituted aniline groups. Ion optodes prepared with NIRF chromoionophores and cation exchanger were pH-sensitive and exhibited fully reversible response. This study was continued[228] by utiliziation of a calix[4]arene-functionalized boron dipyrromethene (CBDP) as a charged fluorescent chromoionophore for different metal ion optodes. The plasticized PVC films containing CBDP and anion exchanger exhibited reversible response to pH from 2 to 10. CBDP was applied to prepare optodes for Cl^-, K^+, Na^+ and Ca^{2+}, which were successfully tested in rabbit plasma. Boron dipyrromethene functionalized with a phenylboronic acid group was synthesized and characterized for application in polymeric optodes for monosaccharides detection in the concentration range of 0.1–100 mM with an improved selectivity toward D-fructose.[229] The optical response is based on the increase in the emission intensity of fluoroionophores when binding to the analytes with diol groups and forming boronic esters at fixed pH. Boronic acid-functionalized boron dipyrromethene (BABDP) was studied as a new fluorescent probe for the detection of catechols and catecholamines.[230] Dopamine-selective optode was prepared by using hydrophobic polymer films containing BABDP and cation exchanger. The results measured from both optical and electrochemical sensors confirmed the selective measurement of dopamine in the range of 10^{-4} to 10^{-2} mol litre^{-1} at physiological pH.

A novel class of nanomaterials demonstrating up-converting luminescence, in particular, up-converting nanorods, appears promising for use in optode measurements. Their advantage is that their fluorescence can be induced at several wavelengths simultaneously upon IR excitation (at 980 nm). Since it does not cause any background fluorescence, the sensitivity of the optical readout can be drastically increased. Up-converting nanorods allow transforming an analyte-dependent colorimetric signal of a non-fluorescent pH-indicator into a fluorescence signal. Provided that there is a good spectral overlap between the absorbance peak of the chromoionophore and the emission peak of the up-converting nanorods, the emission signal can be reabsorbed by the chromoionophore due to the inner filter effect. Hence, a change in visible absorbance directly translates into a change in fluorescence which can be detected using ratiometry. Optodes incorporating $NaYF_4$:Er,Yb up-converting nanorods, neutral ionophores and different chromoionophores in hydrophobic polymer matrices have been developed to measure pH, Na^+, K^+, Ca^{2+}, Cu^{2+} and Pb^{2+} (Refs 231–233) The sensors were tested in sheep plasma, whole blood samples and artificial samples of industrial wastewater (for detection of toxic metals). The results were comparable with those obtained by ICP MS and potentiometric methods.

Optodes can also operate based on the redox reactions. An optical sensor for the determination of ascorbic acid has been developed.[234] The optode membrane was constructed by immobilization of methyltrioctylammonium chloride on triacetylcellulose polymer. The exchange of I_3^- ions in the membrane and its redox reaction with ascorbic acid were monitored spectrophotometricaly. The change in the absorbance of the membrane was used for determination of ascorbic acid with the detection limit of 10^{-6} mol litre^{-1} (Ref. 235). The concentration of Cr^{VI} in paint samples was assessed using redox optode.[236] The detection was based on the colour obtained from the

Structures 2, 3



reaction of Cr^{VI} with 1,5-diphenylcarbazide in the presence of sulfuric acid. The redox product was immobilized on a poly(styrene-divinylbenzene) membrane optode and sensed spectrophotometrically. A functional redox-sensitive optical sensor based on a phenosafranine-containing Nafion film was described.[237] The synthetic cationic photoactive dye phenosafranine, 3,7-diamino-5-phenylphenazinium chloride, responds with changes in light absorbance between its oxidized and reduced forms.

IV.4. Novel matrices for the optode membranes

Matrices used for the bulk optode preparation can be generally divided into two classes: materials where the active components can be physically entrapped and the ones where the components must be covalently (or in some other way) immobilized, either on the surface of the matrix or in its depth. The matrix material should enhance (or at least not hamper) selectivity and provide permeability for the target analyte, flexibility and mechanical and chemical stability. Entrapment of the components into hydrophobic polymers such as PVC is straightforward and easy method to implement; however, the components tend to slowly leak out from such a membrane to the solution, which significantly shortens the sensors lifetime. Covalent binding is usually more complex and requires a specific material with a functional group suitable for the immobilization. This method is reliable with respect to component leaching; however, the response of the sensors is typically longer. In addition, the span and the range of the response are sometimes reduced and optical properties of a photoactive component may be altered.

The most common polymer utilized in the optode membranes is plasticized PVC due to its high hydrophobicity. Using ionic liquids as plasticizers is a relatively new and promising approach. It was shown [238] that hydrophobic room-temperature ionic liquid, trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl)phosphinate, used as a plasticizer for bulk optode membranes enhanced the selectivity and improved the lifetime of the sensors. It was found [239] that the ionic liquid trihexyltetradecylphosphonium dicyanamide can act as a plasticizer, a ligand and a chromogenic indicator when used in PVC membranes. Upon exposure to an aqueous Cu^{2+} solution, a yellow colour is generated within the membrane, while exposure to an aqueous Co^{2+} solution generates a blue colour. Owing to two distinct absorption maxima, simultaneous dual-analyte recognition is possible.

Examples of polymer matrices used in optical sensing reported to date include: cellulose acetate,[207, 208, 215] poly(vinyl alcohol),[240] Nafion,[237] ethylcellulose [241] and hydrogels such as polyurethane and poly(alkyl metacrylates).[242] Lee *et al.*[243] used electrostatic layer-by-layer assembly of poly(allylamine hydrochloride) and poly(acrylic acid). The listed materials are well suited also for chemical immobilization of the active optode components, for example a pH-sensitive azo-dye covalently grafted onto cellulose nanocrystals yielded nanostructured optodes in the form of membranes, sticks and water-based inks for optical pH determination.[244]

Immobilization of membrane components into the porous glass [245] and mesoporous silica [246] was implemented to obtain durable Li^+-sensing optical device. The results demonstrated that not only the design of the fluoroionophore, but also the matrix for immobilization and the microscale distribution of the fluoroionophore affect the characteristics of an ion sensor.

Another promising class of matrices for immobilization of the optode components is sol–gel based materials. They provide very good optical transparency as compared to the polymers. Moreover, versatile application tuned sol-gel formulations can be developed. In particular, organically modified silicates (ORMOSILs) can be prepared with desired hydrophobicity, flexibility, hardness, porosity and stability and can be easily fabricated at room temperature.

Ratiometric fluorescent pH sensors operating in a wide pH range from 4 to 10 were prepared based on double sol-gel silica layers with the first layer embedding two types of quantum dots and the second layer embedding light-absorbing pH indicators.[247] The optodes had high durability against continuous light exposure, even under severe acidic condition (1 M HCl), and the shelf life over 6 months. Fibre optic pH sensor with ORMOSIL-based sensitive membrane was proposed for on-body monitoring in biological fluids.[248] Optode membranes were prepared using sol-gel technology from a mixture of tetraethyl orthosilicate and methyltriethoxysilane (MTES) or phenyltriethoxysilane, forming a porous hybrid organic-inorganic layer upon drying. The ORMOSILs were doped with bromophenol blue and the formulation was optimized to suppress dye leaching by varying the fraction of organic precursor, the sol ageing time and the drying conditions. Homogeneous crack-free films were obtained with an optimal MTES content of 50%. Leaching from these films was greatly reduced. The entrapped indicator showed pronounced increase of apparent pK_a and a broader response range compared to the free form in solution. The sensor demonstrated good sensitivity from pH 3 to 9. Monitoring between pH 5 and 8 with a precision of 0.2 pH unit was demonstrated in human serum as a model biological fluid, without degradation of the sensing fibre for 24 h.

A novel trend in the optical sensor materials is the development of biodegradable matrices for *in vivo* applications. The development of biodegradable optode-based Na^+-nanosensors with the polymer matrix composed of polycaprolactone and a citric acid ester plasticizer has been reported.[249] The optodes had a lifetime of at least 14 days at physiological temperature and three-day lifetime in the presence of lipase in concentrations found in serum.

IV.5. Optode-based sensing platforms

While the ISE construction and the potentiometric cell design are relatively strictly determined by the need of the reference electrode and of the physical connection with power supply, on the one hand, and potentiometer, on the other hand, optode-based analysis is versatile with respect to the configuration of the sensing devices. The variety of the optode-based devices has been surveyed recently.[206, 250] Optodes can be prepared in two forms: as thin films, and then planar diffusion determines their response, or as small-size particles (beads, capsules), which have an advantage of spherical diffusion and thus faster response.

Sensing films have been used for a long time and can be fabricated using dip-coating, spin-coating and drop-casting procedures. Novel preparation procedures include

screen-printing, spray coating, knife coating, and inkjet or pinprinting. Recently, very homogeneous sol–gel-derived films have been achieved using a hemiwicking process.[251]

Optode membranes can be readily coupled with either fibre optic or planar platforms. Planar films deposited on plastic or glass slide serving as an inert support is a commonly used setup. Planar platforms can utilize waveguide phenomenon just as fibre optic sensors. The waveguide layer installed in the optode support increases the path length of the light, which significantly improves the sensor sensitivity.[252] The active waveguide mode in which the light passes through the optode film itself seems to be a very promising approach.

Planar optodes are more attractive than optical fibres in terms of their compatibility with a range of advanced microfabrication technologies and deposition techniques, and their geometry facilitates integration with microfluidic, lab-on-a-chip systems. Planar devices are an ideal platform for integrated optical sensor development and are also well suited for multianalyte sensing. Integrated optode platform, so-called microplate reader, was fabricated by casting polymer membranes into the 96-well polypropylene-based plate and by screen printing them on an optically transparent substrate with 96-well pattern.[253] Arrays of colorimetric sodium-selective and potassium-selective bulk optodes were tested in serum samples. It was demonstrated that microtiter plate-format optodes can provide high sample throughput (100 samples in less than 5 min) and analytical performance comparable to that of a potentiometric clinical analyzer. This concept was later converted into microtiter plate (MTP) reader, by adding a titrant that binds the analyte, to the sample solution. Fluorescein derivative-based bulk optodes were integrated in MTP reader for determination of several polycations (pentosan polysulfate, xanthan, Na-alginate, and carrageenan [254]) and some anionic surfactants [255] with the respective titrants. A miniature biocompatible optical platform was developed for simultaneous monitoring of pH, potassium and glucose.[256] Four types of BODIPY-based fluorescent optodes were integrated into plate format reader for simultaneous detection of Cl^-, K^+, Na^+ and Ca^{2+} (Ref. 228).

Planar structures can be effectively used for 2D real-time imaging of analyte distribution at the surfaces of different objects. Planar colorimetric and luminescent optodes were able to image the distribution and dynamics of ammonium,[257] oxygen,[195] pH and CO_2 [258] in soil and rhizosphere.

Film optodes attached to the flexible optical fibres are very well suited for remote sensing due to their ability to transfer the optical signal over long distances, and are attractive tools for *in vivo* diagnostics. The main challenge in fibre-optic sensor development is the precise alignment required to couple light efficiently to the fibre. A novel system for simultaneous operation of multiple oxygen sensitive luminescent fibre optic sensors was described.[259] Reading ends (opposite to sensing ends) of the fibre optodes were fixed in a 10×10 matrix and placed in front of a CCD camera and a LED-light source. Oxygen measurements were conducted by simultaneous excitation of all optodes with the LEDs followed by simultaneous imaging with the camera. The overview on the recent advances in fibre optic optodes was presented by one of the leading research groups in this area.[260]

Optical sensing with micro- or even nano-size beads is a rapidly developing area in the optode research. Growing interest in the use of ultra-small sensing particles is connected with their potential as minimally invasive and non-destructive 3D imaging tools for *in vivo* intracellular sensing. Recently, silica nano-optodes have been officially approved for a first-in-human clinical trial.[261]

Small size polymeric optode particles can be prepared by means of various kinds of emulsification. One of the methods, solvent displacement method, has been described in detail.[262] The polymer optode composition is rapidly injected into a stirred aqueous solution of a surfactant. By varying the solvent for the optode composition, rotation speed of a stirrer and nature of the surfactant one can obtain beads of a desired size with relatively narrow size distribution. In another procedure, spray dry method,[256] an optode membrane composite solution is sprayed with a nebulizer under heated air stream from a heat gun. Few micron-size sensing particles can be obtained in this way. Convenient precipitation procedure to fabricate ultrasmall fluorescent Na^+- and pH-selective bead-type nanosensors was described.[263] The bead matrix was composed of bis(2-ethylhexyl) sebacate and the triblock copolymer Pluronic® F-127, which also functioned as a surfactant to stabilize the nanoparticle. Surface area effects on the response mechanism of optode beads were studied.[264] A shift of the dynamic range of the optodes was observed for optodes with identical composition but of different size. A strong correlation was found between the calculated specific surface area and the apparent ion-exchange constant for several types of ion optodes. The selectivity did not substantially correlate with the optode size. The reported results show that one must be cautious while applying the response models established for macroscopic optodes to micrometre and submicrometre sensors.

A significant enhancement in the photoactive indicator brightness and stability can be achieved in microbead optodes, for example, in one of the pioneering works in this area,[265] the dynamic range of oxygen nano-optodes was found to be broader than that of the existing film-based micro-optodes. The inert protective bead material, for example, silica, can minimize contamination of biological environment with toxic optode components and reduce biofouling. So called 'sliver-sensor' was proposed for *in vivo* monitoring of metabolites.[256] Optode beads for multiple analytes were encapsulated in biocompatible hydrogel and tested for simultaneous measurement of several biologically relevant analytes. A mathematical model of the sliver-sensor response was recently proposed.[266] It was shown that gel encapsulation of glucose nanosensors provides for prolonged *in vivo* lifetime.[267] Several pH-responsive components (Nile blue A, bromophenol blue, and acid fuchsin) were entrapped in hollow nanocapsules with nanometre-thin walls of controlled porosity.[268] The porous nanocapsules retain molecules larger than the pore size but provide ultrafast access to their interior for molecules and ions smaller than the pore size. Dye-loaded nanocapsules were immobilized in a polyvinyl alcohol matrix with high solvent permeability and rapid analyte diffusion. The porous nanocapsule loaded films were stable and reproducible in long-term monitoring experiments.

A huge number of research articles are dedicated to analyte mapping and 3D imaging with optical microsensors. Mesoporous silica nanobeads were used for pH mapping inside cells.[269] Other nanostructures tested in pH intracellular sensing include magnetic core nanoparticles,[270] carbon nanodots labelled with pH-sensitive dyes,[271] dendrimer-based fluorescent pH nanomaterials.[272] Ratiometric sodium imaging with sodium-responsive polymer-free nanosensors was introduced.[273] Colorimetric sensors were shown to be fully reversible having a dynamic range centred at 20 mM. The same research group proposed also glucose-sensitive fluorescent nanosensors.[274] The nanosensors demonstrated glucose response *in vitro* and also when injected subcutaneously into mice. In the latter case the estimated glucose levels were comparable to those measured with a glucometer.

Disposable sensing devices play an important role in modern diagnostics, where biofouling and sterility are crucial issues. A facile preparation method of a disposable enzymatic urea biosensor was described.[275] The colorimetric PVC-based optode and a dissolvable poly(ethylene glycol) membrane containing an enzyme were assembled inside a thin capillary and provided for single-step biosensing by wicking the sample with capillary action. Paper-based single-use system was evaluated for redox determination of Zn^{2+} (Ref. 276). The colour change originated from complexation of zinc with products of redox reaction and was detected with simple office scanner and analyzed using appropriate software. Disposable optodes with chromogenic ionophores entrapped in polymeric matrix were developed for determination of heavy metals;[277] Zn^{2+}, Cu^{2+}, Ni^{2+}, Fe^{2+} and Fe^{3+} were simultaneously measured in a commercial nasal spray of isotonic seawater.

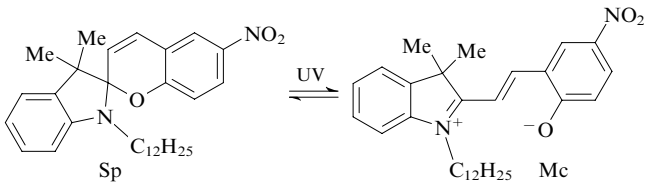
IV. 6. Novel operation principles of optodes

There are only few works dealing with novel operating principles of the optodes. One of them is a dynamic, or active, analyte-sensing mode. To make an optode switchable from sensing mode to passive off mode, one should replace one of the sensor components with a dynamically changeable alternative. The externally induced change of the complexing ability of the ionophore, the charge of the ion exchanger, or the pK_a of the lipophilic pH-indicator will lead to a controlled change in sensor responsivity. Light is most often used for triggering such reactions. Optical sensors operating in an active mode can be controllably switched on or off at defined times allowing for modulation of the sensor signal and, consequently, correction for a non-modulated background signal. Moreover, analyte exchange between sample and sensor phase may be blocked during sensor delivery or storage in the off-state, which will, without doubt, extend the sensor lifetime.

Bulk optodes were converted into photoresponsive nonequilibrium sensors by introducing a photochemical acid generator into the optode membrane.[278] The aim of this work was to demonstrate the general applicability of nonequilibrium detection methods to optical ion-selective sensors by using a photochemical reaction to generate and control ion fluxes in an optical ion-selective membrane in the same manner as nonequilibrium electrochemical methods have been used in ISEs.[128] It was shown that light can be used both to control an optode with a photochemical reaction and at a different wavelength to readout the response *via* absorbance detection. Essentially the proposed technique can be used to titrate the sample with the titrant generated directly within the probe upon illumination and thus to detect the buffer capacity of the sample, in addition to the activity of hydrogen ions.

Absorbance-based sensors with reversible photoinduced response to Cl^- utilizing spiropyran derivative as switchable chromoionophore were proposed.[279] Upon exposure to visible light, spiropyran exists in a ring-closed (Sp) form with a very low basicity. When illuminated by UV light, it transforms into a strongly coloured ring-opened merocyanine (Mc) form with high basicity (Scheme 2). This transformation triggers the co-extraction of H^+ and Cl^- from the contacting aqueous solution into the sensing film where Cl^- is stabilized by the neutral ionophore and H^+ protonates Mc to McH^+. The spectral difference between Mc and McH^+ is large enough to visualize the co-extraction process using optical techniques. Visible light will reverse the process by promoting the ring closure reaction. Highly hydrophilic H^+ and Cl^- will then leave the organic phase to the contacting aqueous solution.

Scheme 2



A new class of switchable chromoionophores, oxazinoindolines, was proposed for developing dynamic pH-optodes.[280] Same as for spiropyrans, ring-closed and ring-opened forms of the dye differ in their absorbance and basicity. The difference is that the ring-opening transformation and, consequently, overall protonation equilibrium is governed by third species, which arise from the thermal isomerization of the molecules in polar solvents, rather than by light.

The recently emerged trend in optode research is modulation of the optode response in order to overcome pH or ionic strength dependence, *i.e.*, the development of single-ion optodes.

Co-extraction based optodes responding to individual K^+ (Ref. 281) and Cl^- (Ref. 282) activities were prepared in the form of the two-phase system where phases of dramatically different polarity, namely, plasticizer and hydrogel, were combined. A solvatochromic fluorescent dye was entrapped in the hydrogel. When the ionophore extracts the analyte from the aqueous solution into the plasticizer phase, the oppositely charged dye rather than proton is co-extracted for reasons of electrical neutrality. This reaction causes a decrease of micro-polarity near the dye, resulting in an increase of its fluorescence intensity. pH-independent potassium and chloride responses were obtained with the developed optodes.

A polymer film optode for the determination of CO_2 concentration in aqueous and gaseous samples was pro-

posed.[283] A novel detection principle based on direct molecular recognition of the carbonate ion by a highly selective tweezer-type ionophore was implemented. The carbonate ion is extracted together with hydrogen ions into a polymeric film that contains the anion exchanger and charged chromoionophore. Such an optical sensor responds to the product of the carbonate ion activity and the square of hydrogen ion activity. This quantity is thermodynamically linked to the activity of carbon dioxide. This provides for the direct carbon dioxide sensing that does not make use of the traditional Severinghaus sensing principle of measuring a pH change upon CO_2 equilibration across a membrane.

A novel optical readout, electrically generated chemiluminescence, was utilized to provide for the pH-independent optode response.[284] Luminescence was induced by the potential of the ion-selective electrode in contact with the sample solution. Since the ISE potential is determined by the analyte activity, the generated luminescence will be proportional to the analyte activity as well. Ca^{2+}, Na^+ and K^+ ion-selective membranes were readout individually and sequentially with this methodology.

The concept of exhaustive nanospheres was proposed in order to overcome pH dependence of the optode response. Calcium-selective optode nanospheres were added in excess to the sample solution.[285] The analyte from the sample gets consumed by the sensor particles in this mode. Therefore, the measured absorbance will be pH-independent and determined only by total calcium content. Sensors were characterized at different pH and the same linear calibration was obtained in the Ca^{2+} concentration range from 10^{-7} to 10^{-5} mol litre^{-1}.

IV.7. Application of optodes in real environment

Planar luminescence lifetime-based polymeric and sol-gel (ORMOSIL) optodes were applied for spatio-temporal 2D imaging of oxygen distribution in living biofilms.[286, 287] Using a simple digital camera for signal acquisition made this technique faster and more inexpensive as compared to widely used spectral devices. Simultaneous confocal imaging of biomass distribution allowed for direct linking it to O_2 distribution.

Chromoionophore-based optodes were used for monitoring potassium and calcium in plant nutrient solutions.[288, 289] Monitoring of calcium and other nutrients is necessary for optimization of hydroponic solution composition and improving the yield, which is especially critical for the space-based plant production systems. Polymeric plasticized chromoionophore-based sodium and potassium optodes and sol-gel pH-optode were tested[290] for potential application for dry-eye syndrome diagnostics from tear fluid samples. It was shown that pH can be measured with accuracy of 0.03 pH units in the tear fluid sample of 20 μl.

Luminescent pH nanosensors were immobilized in agarose gel, which at the same time was used as culture medium for *Escherichia coli*. The embedded nanosensors permitted ratiometric referenced imaging of pH during the growth period of the bacteria.[291]

The applicability of novel aza-BODIPY dyes in pH sensors for marine research was demonstrated by inserting a fibre-optic pH optode into the gastric cavity of a single coral polyp and measuring the pH gradient inside the coral.[292]

Wolfbeis group[293] performed the pH and oxygen ratiometric luminescent imaging based on sprayable optode sensor films. The sensor films were sprayed over acute and chronic wounds on human skin.

High scattering properties of the biological tissue is a well-known problem for optode-based measurements *in vivo*. A deterministic approach for optimization of number of optodes and their location, as well as light source location and intensity for successful measurements in biological tissue was described and verified.[294]

* * *

Ionophore-based chemical sensors with an electrochemical or optical signal registration, ISEs, ISCOMs and optodes, although being invented decades ago, are still being developed and demanded. Novel materials and novel application techniques of the sensors were proposed during the recent years. More and more analytes, including those earlier hardly accessible for sensor control (*e.g.*, lanthanides, polyions, hydrophilic anions) can be reliably measured in various media, and often at trace concentration level. ISEs traditionally perceived as sensors utilized exclusively at zero-current are increasingly used under polarization conditions. Novel approaches to making reference electrodes, in particular using ionophore-like agents with moderate lipophilicity may revolutionize the analytical electrochemistry as a whole. The variety of the sensing agents, matrices and sensing platforms for optodes is growing continuously. Significant results have been achieved in the theory of the sensor response, especially for ISEs. One can envisage further progress in the field of ionophore-based sensors, in particular the development of optodes sensitive to the individual analyte activity.[295]

This review was prepared with the financial support from Saint Petersburg State University, Grant 12.38.235.2014.

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