Chapter 4
Ionophore-Based ISEs

This chapter describes ISEs with membranes based on ionophores. Ionophores are organic lipophilic substances which selectively bind ions. The nature of these interactions makes the basis of the potentiometric selectivity of ISEs with membranes containing ionophores. A large variety of ionophores enables selective sensing of various analytes, mostly ions but sometimes also neutral species. The fundamentals of the ionophore-based potentiometric and optical sensors, as well as brief characterization of a large number of ionophores, are presented in review papers [1, 2]. Although published more than a decade ago, these reviews remain highly relevant. Currently, most of the progress in ISEs theory and its applications is related to ionophore-based membranes. This makes these membranes, probably, the most important kind, and therefore, we start our in-depth discussion of ISEs with this particular kind of sensor membranes: ionophore-based electrodes.

Originally, ionophore-based membranes were comprised of liquids, namely solutions of ionophores in suitable organic solvents. However, already for several decades, solvent-polymeric membranes with polymeric matrixes normally containing plasticizers, and doped with ionophores and ion exchangers, strongly predominate over liquid membranes in most applications. The chapter starts with description of the membrane materials, followed by a brief description of the theory of the response and the selectivity of this kind of ISEs.

4.1 Ion Exchangers and Charged Ionophores

The type of the electrode response (cationic or anionic) and the selectivity of the electrode are determined by ionophores and ion exchangers contained by the electrode membrane. Among the first ion exchangers were potassium salts of the tetraphenylboric acid derivatives (lipophilic anions) [3] and also salts of tetraalkylammonium, tetraalkylphosphonium, and tetraalkylarsonium (lipophilic cations) [4], see Fig. 4.1.

Generally speaking, ion exchangers are lipophilic salts (sometimes acids or bases) which, at least to some extent, dissociate in the membrane phase. The products of the

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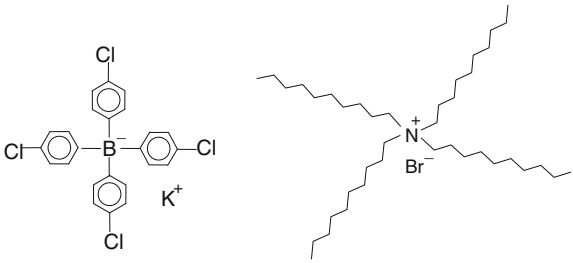

Fig. 4.1 Typical ion exchangers: potassium tetrakis(p-Cl-phenyl)borate (*left*) and tetradecylammonium bromide (*right*)

dissociation are R^{z_R}: a lipophilic organic cation or anion and I^{z_I}: a hydrophilic ion. The lipophilicity is a measure of the affinity of the species to organic phases. Quantitatively, the lipophilicity is defined as decimal log of the partition coefficient of the species between water and normal octanol [5]. Partition coefficients of individual ions (see below) cannot be measured. However, partition coefficients of salts formed by a lipophilic R^{z_R} anion or cation and a water-soluble cation or anion are determined primarily by the lipophilicity of R^{z_R}. The latter must be enough to prevent significant leak of the salt from the membrane phase to the aqueous phase. Ion exchangers and neutral ionophores suitable for the analysis of ordinary aqueous solutions must have the lipophilicity of 7.4 or more, and those for measurements in blood must show the lipophilicity of at least 11 [6]. Thus, the affinity of R^{z_R} lipophilic ions to organic phases is very strong. Therefore, these ions are confined to the membrane phase and (ideally) do not participate in the charge transfer across the membrane/solution interface. The other product of the dissociation, I^{z_I} hydrophilic ion, can be either of inorganic or of organic nature: its hydrophilicity can vary within a broad range, but anyway, I^{z_I} ion is capable of crossing the interface and distribute reversibly between the two phases: membrane and solution.

Very often the term "ion exchanger" is used for R^{z_R} ion—the lipophilic product of the dissociation. For instance, potassium tetrakis(p-Cl-phenyl)borate is a typical cation exchanger in the strict sense of the term. However, tetrakis(p-Cl-phenyl)borate anion is also often called ion exchanger. The lipophilic ions form the so-called ion-exchange sites in membranes. Dependent on whether these ions are covalently bonded to the polymeric matrix of the membrane, or can diffuse freely, the respective membranes are called membranes with fixed or with mobile ion-exchanger sites. Due to the macroscopic electroneutrality, the total number of hydrophilic ions in a membrane is equivalent to the total number of sites, regardless of the dissociation degree.

Historically, I^{z_I} hydrophilic ions (e.g., cations) which counterbalance the charge of (e.g., anionic) R^{z_R} sites were called counter-ions, while ions of the same charge as R^{z_R} sites (anions in this case), which may co-extract by membrane together with I^{z_I} cations, were called co-ions [7]. Nowadays, the term counter-ion often refers to ions of the same charge as the analyte, which interfere with the electrode response to I^{z_I}. Ideally, the presence of ion-exchanger sites in a membrane prevents from co-extraction of aqueous electrolyte, in other words, from co-ions penetration.

The ability of ion exchangers to prevent from co-extraction is also called Donnan exclusion [8]. When the Donnan exclusion holds, the charge transfer across the membrane/solution interface is due to the ion-exchange process, while interfacial partition of the electrolyte as a whole plays only a minor role and often can be neglected. In the latter ideal case, pure ion-exchange is the sole electrochemical process at the membrane/solution interface, and one can expect full Nernstian potentiometric response of the respective electrode. The origin of the response will be discussed in detail below, see Sect. 4.4.

Let us look in more detail on how the Donnan exclusion works. For simplicity, we consider interfacial distribution of an IX 1:1 salt which can dissociate producing I^+ cation and X^- anion. At equilibrium, the activity of IX in the membrane phase is proportional to that in the aqueous phase and to k_{IX} the partition coefficient:

$$a_I{}^{mem}\, a_X{}^{mem} = k_{IX} a_I^{aq} a_X^{aq} \tag{4.1}$$

For simplicity, we now replace the activities of the species in the membrane phase with the respective concentrations (upper indexes denoting the membrane phase now omitted):

$$C_I C_X = k_{IX}\, a_I{}^{aq}\, a_X{}^{aq} \tag{4.2}$$

On the other hand, if the membrane contains IR salt with R^- lipophilic anion, the macroscopic electroneutrality requires the following:

$$C_I = C_R + C_X \tag{4.3}$$

The combination of these equations allows obtaining for the concentration of X^- in the membrane phase:

$$C_X = \left(\sqrt{C_R^2 + 4k_{IX}\, a_I{}^{aq}\, a_X{}^{aq}} - C_R\right) \Big/ 2 \tag{4.4}$$

Thus, the concentration of co-extracted X^- ions in the membrane phase depends on the R^- concentration in the membrane, on the activity of IX electrolyte in the aqueous phase, and on the value of the partition coefficient. One can see that as long as $C_R{}^2 \gg 4k_{IX}\, a_I{}^{aq}\, a_X{}^{aq}$ the concentration of X^- ions in the membrane is negligible, $C_X \ll C_R$ and effectively only I^+ cations cross the interface. This is the Donnan exclusion.

Donnan exclusion fails in the following cases: (1) too low ion-exchange capacity (too low R^- concentration), (2) too high concentration of IX electrolyte in the aqueous phase, or (3) too high partition coefficient value. Then, it may happen that $C_X \cong C_R$ and even $C_X \gg C_R$. These regularities are presented in Fig. 4.2. For most applications, the R^- sites concentration of 0.01 or even 0.001 M is enough.

The selectivity of ISEs with membranes based on ion exchangers is normally low and obeys the so-called Hofmeister series. That is, ISEs are more selective to hydrophobic ions and less selective to hydrophilic ions. Basically, this is because

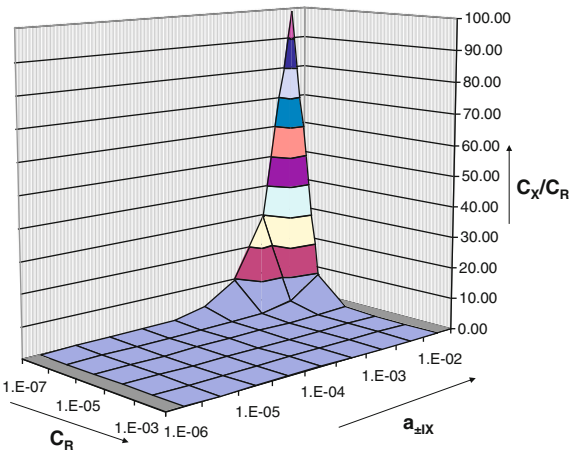

Fig. 4.2 Donnan exclusion. The dependence of the C_X/C_R ratio on the R^- site concentration in membrane and the activity of IX electrolyte in solution. The data refer to $k_{IX} = 10^{-6}$

ion exchangers interact with ions only electrostatically, and the interaction is relatively weak. The detailed explanation of the origin of the Hofmeister series for ISE selectivity is given in Sect. 4.4.2.

Let us turn now to ionophores. Ionophores which are in use for solvent-polymeric membranes are divided into two groups: neutral ionophores (neutral carriers, neutral ligands) and charged ionophores (charged carriers, charged ligands) [1, 2, 9]. We will start the discussion with charged ionophores. Being charged, these ionophores impart some ion-exchange capacity to membranes and therefore prevent from co-extraction of electrolyte and ensure ion-exchange equilibrium at the membrane/solution interface. The first charged ionophore was calcium didecylphosphate used in Ca^{2+}- ISEs [10]. Since then, more charged ionophores have been invented, for example, bis[4-(1,1,3,3-tetramethylbutyl)phenyl]phosphate, also selective to Ca^{2+} ions [11], a number of metal porphyrine complexes [12–16] and guanidinium bases [17] for various non-Hofmeister anionic electrodes, see Fig. 4.3. It must be noted that metal porphyrines may also be neutral and, in this case, act as neutral ionophores [18].

The interaction of charged ionophores with ions in membranes is not of the pure electrostatic nature. Therefore, this interaction is much stronger and more selective than in the case of ion exchangers. From the formal point of view, these differences are quantified by the respective ion-to-ionophore association constants. It is not possible to define a threshold value of the association constant in such a way that lipophilic species with association constants below the threshold value are ion exchangers and those above the threshold are charged ionophores. In this sense, there is no way to set a formal difference between ion exchangers and charged ionophores. However, this does not cause a problem. Although only little data are available on the respective association constants [19–21], the data on the ISE selectivity allow for conclusion that the difference in association constants between ion exchangers and charged ionophores is about several orders of magnitude. Thus, the two groups are far from one another in terms of the association

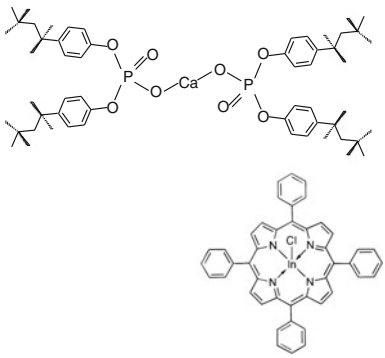

Fig. 4.3 Structures of some complexes of ions with charged ionophores. Target ions given in *parenthesis*. Calcium bis[4-(1,1,3,3-tetramethyl butyl)phenyl]phosphate (Ca^{2+}), *top*; In^{III} teraphenylporphyrine chloride (NO_2^-), *bottom*

constants values, and the question of where exactly the "threshold" must be laid is irrelevant. From the practical point of view, it is widely recognized that a charged ionophore is a species which allows for obtaining non-Hofmeister selectivity, so that the selectivity to the respective ion is in contrast to its position in the Hofmeister series.

4.2 Neutral Ionophores

Neutral ionophores are non-electrolytes, these are nonionic species which are neither intrinsically charged nor dissociate producing charged species. Neutral ionophores are highly lipophilic molecules capable of selective binding of ions with formation of ion-to-ionophore complexes. Among the first and still widely used neutral ionophores were valinomycin for potassium-selective ISEs [22] and nactines for ammonium electrodes [23]. These two, together with crown and bis-crown ethers, belong to ionophores of macrocyclic structure. Later on, a number of synthetic neutral ionophores were invented. These were macrocyclic compounds: crown and bis-crown ethers, acyclic lipophilic diamides (podands), various calixarenes as neutral ionophores for cations. A large number of acyclic ionophores (podands) have been invented by Simon group in ETH Zürich: these ionophores are normally called by their respective ETH numbers.[1] All these ionophores selectively bind cations and are used in membranes for cation-selective electrodes.

Neutral ionophores binding anions are less numerous. These are lipophilic fluoro ketones like trifluoroacetyl-p-heptylbenzene selective to CO_3^{2-} [24–29] for carbonate, phosphate, and sulfate electrodes, salofenes [30, 31], thiourea derivatives selective to Cl^- [32, 33], mercurocarborands [34]. Examples of the neutral ionophore structures are presented in Fig. 4.4.

[1] ETH comes from Swiss-German name for the Swiss Federal Institute of Technology, Zurich.

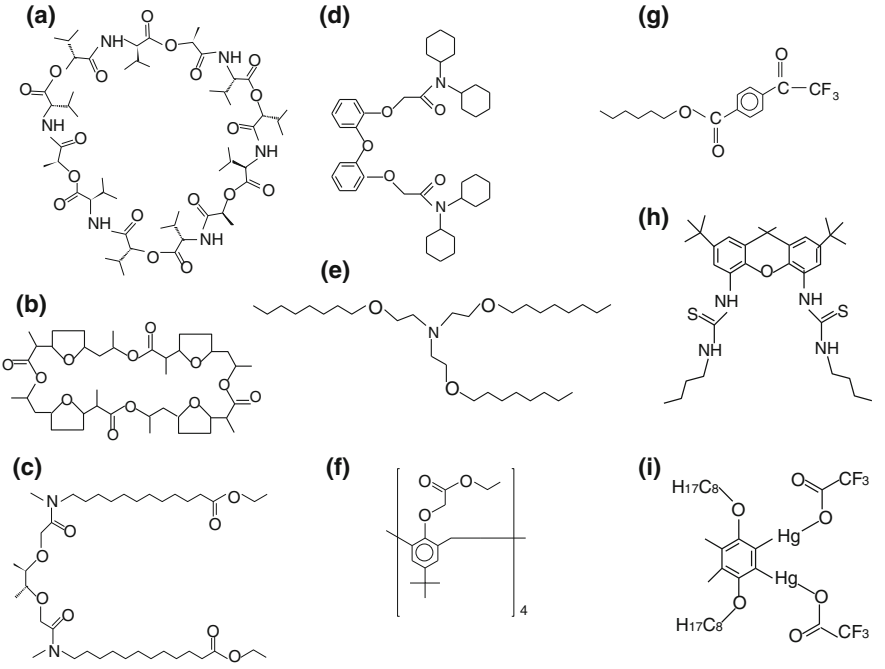

Fig. 4.4 Structures of some neutral ionophores. Target ions given in *parenthesis*. **a** valinomycin (K^+), **b** tetranactin (NH_4^+), **c** ETH 1001 (Ca^{2+}), **d** ETH 231 (Ba^{2+}), **e** Tris(2-octyl-oxy-ethyl)amine (H^+), **f** tert(4)butylcalixarene (Na^+), **g** *p*-hexyltrifluoroacetylbenzoate (CO_3^{2-}), **h** bis(thiourea)derivative (Cl^-), **i** organomercury compound (Cl^-)

Unlike ion exchangers and charged ionophores, neutral ionophores impart no ion-exchange capacity to membranes. Therefore, to exclude co-extraction of aqueous electrolytes, electrode membranes based on neutral ionophores must be doped with ion exchangers. However, in the early years of ISEs with neutral ionophore membranes, these membranes did not contain intentionally added ion exchangers. Surprisingly, the electrodes responded with almost full Nernstian slope [35]. The slope clearly indicated unipolar conductivity of membranes: only cations were permeable across them.[2] A number of theories were proposed to explain this fact. One explanation was rather straightforward. It was assumed that the whole membrane comprises the space-charge region, that is, macroscopic electroneutrality fails, and the membranes are positively charged [36]. This assumption means that the two electrical double layers, on the both sides of the membrane, overlap. According to the Gouy–Chapmen theory, one can relate l, the effective thickness of the space-charge layer (the diffuse part of the electric double layer), to the concentration of ions in the respective phase and the dielectric permittivity of the phase:

[2] At that times only cation-binding neutral ionophores were known.

$$l = \frac{1}{F}\sqrt{\frac{RT\varepsilon_0\varepsilon}{2C}} \tag{4.5}$$

Here, l stands for the effective thickness of the space-charge region (meters), C is the dissociated electrolyte concentration (mol/m^3), ε is the relative dielectric permittivity of the phase, and $\varepsilon_0 = 8.85 \times 10^{-12}$ F/m (Farad per meter) is the vacuum dielectric constant. R, T, F are gas constant, absolute temperature, and Faraday constant. For a membrane with the thickness 0.4 mm (meaning $l = 0.2$ mm), Eq. (4.7) suggests $C = 1 \times 10^{-12}$ mol/m^3 or 10^{-15} M. Assuming the diffusion coefficients of about 10^{-8} cm^2/s [1], the resistivity of such a phase would be in three or more orders of magnitude higher than the experimental value for a site-free membrane. Thus, the space-charge theory is not supported by the experimental data.

A rather elegant theory was proposed by Simon group in ETH Zürich [37] and by Stefanova group at St. Petersburg University [38]. It was suggested that anions are co-extracted by neutral ionophore membranes in quantities equivalent to that of cations. However, the anion mobility in membranes is much lower than that of complexed cations because anions are immobilized in water droplets (inverted micelles) in the membrane phase. Indeed, when being in contact with aqueous solutions, membranes sorb water and become cloudy. This is because of Rayleigh scattering of light by the droplets. Since the scattering refers to the visible range, one can conclude that at least some of the droplets are rather large having diameter commensurable with the wavelength of visible light, that is, about 400–700 nm. The mobility of anions entrapped by water droplets is limited by the mobility of the droplets, and the latter move very slow due to their large size. Cations form lipophilic complexes with neutral ionophores. Therefore, cations are located in the organic phase and can diffuse within membranes relatively freely. In this way, the membrane as a whole is neutral, containing cations and anions in equivalent quantities, but cations move across the membrane much faster than anions. This is how the authors of [37, 38] explained the cationic response of membranes based on neutral ionophores containing no intentionally added ion-exchanger sites.

It was also suggested that the cationic response of these membranes is due to inevitably present lipophilic ionic impurities [39]. These are impurities present in polymers or those originating from plasticizers. The latter are often esters and, due to hydrolysis, produce organic acids and alcohols. Acids at least to some extent dissociate producing lipophilic anions (cation-exchanger sites) and hydrogen ions which are replaced by cations selectively interacting with the ionophore. This opinion got broad experimental support [40–42] and nowadays is generally accepted. Obviously, the content of the intrinsic impurities is difficult to standardize in the ISE manufacturing process. Also, the resistivity of such membranes is often too high, making the signal noisy and sensitive to external electrostatic field, so that screening the cell by use of a Faraday cage is needed for measurements. Therefore, modern ISE membranes based on neutral ionophores are always doped with deliberately added ion exchangers. This not only makes the response more stable and reproducible, but also allows for the optimization of the selectivity

[43–47], see Sect. 4.5.2. Addition of ion exchangers permits significant lowering of the resistance of membranes, facilitating the practical measurements with ISEs.

Some ionophores show a dualistic behavior working either as neutral or as charged ionophores dependent on external conditions. It was shown that some weak lipophilic acids, like monensin, as well as alkylphosphoric acids may act as charged or as neutral ionophores dependent on the pH of the solution [47].

A large number of charged and neutral ionophores are listed and briefly characterized in a review paper [2]. Although this review has been published more than a decade ago, it remains a very useful source of information when a suitable ionophore must be chosen for a certain application.

4.3 Polymers and Plasticizers in ISE Membranes

4.3.1 Poly(vinylchloride) Plasticized Membranes

The ionophore(s) content in ISE membranes is normally only 0.5–2 % of the whole membrane mass, while most of the membrane mass is made of polymer and (normally) also plasticizer. Polymers suitable for ISE membranes must meet a number of requirements. These polymers must be mechanically robust and in the same time elastic—either due to intrinsically low glass transition temperature (T_g) or due to a plasticizer added. Polymers must be processable, stable within a reasonable temperature range, for example, between 0 and 50 °C, must be chemically inert, must not lose their molecular mass spontaneously, must be non-soluble in water, and stable against hydrolysis, at least up to pH 8–9.

In many cases, particularly for poly(vinylchloride) (PVC) membranes, some of the requirements are fulfilled by adding plasticizers. The latter play a dualistic role: plasticizers allow for elasticity of membranes (and for sufficient mobility of ionophores and ions within the membrane phase) at temperatures below T_g, and on the other hand, plasticizers act as solvents for ionophores.

PVC remains the most popular polymer in ISE membranes, wherefore we will discuss this kind of membranes in utmost detail. PVC-based membranes always require a suitable plasticizer because the glass transition temperature of PVC is much higher than the temperature in ISE applications. Different kinds of PVC show T_g from 85 to 102 °C [48, 49]. The mobility of ions and ionophores in polymers at temperatures below T_g is extremely low hindering measurements with such membranes. Also, pure PVC cracks spontaneously. For suitable elasticity, it is enough to add 0.5 mass units of a plasticizer to 1 mass unit of PVC. Obviously, one can dissolve ionophore(s) in this amount of the plasticizer and thus dope the membrane with ionophores. However, even at the 1:1 mass ratio of the plasticizer to the polymer, the electrical resistivity of the membranes is too high, and therefore, the measured signals are noisy. On the other hand, the membrane with the ratio 5:1 is sticky and jelly-like, mechanically non-robust and hardly suitable for real-world sensors. In the pioneering works [50, 51], the plasticizer to PVC

ratio was 3:1 and 2:1, respectively. For decades, the choice of this ratio was rather traditional than scientifically sounded. Only a handful of examples are known when the optimization of the plasticizer to PVC ratio indeed allowed for significant improvement of the ISE performance. These reports highlight the improvement of the lower detection limit of the ISEs by the optimization of this ratio [52]. However, the large majority of PVC-based ISE membranes contain 30–33 % of PVC and 60–66 % of a plasticizer, thus the membranes with the 2:1 ratio predominate.

Plasticizers used in PVC membranes are non-volatile organic liquids compatible with PVC. These are mostly esters, like carboxylic acid esters or phosphorous and phosphonic acid esters, and also some ethers, in first place, 2-nitrophenyloctyl ether. Structures of the most popular plasticizers used in PVC membranes are presented in Fig. 4.5.

The number of plasticizers suitable for PVC membranes is obviously much smaller than that of solvents for liquid membranes. There were suggestions that solvation of ions by plasticizers may significantly modify the selectivity of ISEs [53, 54]. Attempts were made to develop special plasticizers for almost any analyte ion [55]. Indeed, trialkylphosphates or dioctylphenylphosphonate as plasticizers are advantageous for calcium electrodes [56, 57]. A very characteristic example is the water hardness sensor. Membrane containing didecylphosphoric acid in trihexylphosphate provides high selectivity to Ca^{2+} ions in the presence of Mg^{2+} and other alkali-earth cations, while the replacement of trihexylphosphate with n-decanol levels the selectivity between Ca^{2+} and Mg^{2+} ions, and the respective electrode is used as a water hardness sensor [10, 58]. However, all other

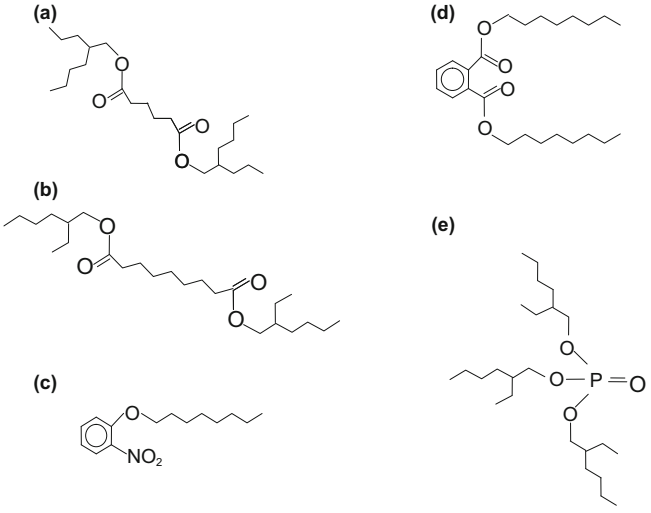

Fig. 4.5 Structures of some plasticizers used in PVC membranes. **a** bis(butylpentyl)adipate, **b** bis(2-ethylhexyl)sebacate, **c** 2-nitrophenyloctyl ether, **d** dioctylphthalate, **e** tri(2-ethylhexyl) phosphate

known PVC membranes can be made with one of the following plasticizers: bis(butylpentyl)adipate (BBPA), bis(2-ethylhexyl)sebacate (DOS), or 2-nitrophenyloctyl ether (oNPOE). The first two are used for ISEs selective for monovalent ions, and oNPOE is more suitable for divalent ion sensors [1, 2].

The point is that the potentiometric selectivity can be achieved if the target analyte is more eager to transfer from the aqueous solution phase to the membrane phase than other ions present in the sample. In principle, in terms of energy, a transfer from a polar phase (aqueous solution) to a low-polar membrane phase is unfavorable for any charged species. However, the energy loss is especially large for a divalent ion. Morf and Simon considered this issue using the Born equation for energy of the transfer of a charged species from vacuum to a phase with a dielectric constant ε [59]. Assuming I^{z+} ions form (in aqueous solution) $[IL]^{z+}$ complexes with L neutral ionophore, and then distribute between the two phases, they obtained for the distribution coefficient

$$\lg k_{IL} \sim \frac{{z_{IL}}^2}{r_{IL}} \left(\frac{1}{78.5} - \frac{1}{\varepsilon} \right). \tag{4.6}$$

Here, z_{IL} is the charge of the ion–ionophore complex, and r_{IL} stands for the complex effective radius, 78.5 is the dielectric constant of water. Equation (4.6) shows that the decrease in ε always causes a decrease in the affinity of the species to the membrane phase. Since the charge appears in Eq. (4.6) in the second power, the effect is more pronounced for divalent ions. Thus, low-polar plasticizers are especially unfavorable for divalent ions and therefore are more suitable for monovalent ions, while ISEs for divalent ions require membranes with polar plasticizers.

All in all, this concept proved to be fruitful, especially for sodium and calcium ISEs [60–62]. However, not all the ISEs follow this simple rule. For instance, the replacement of low-polar bis(hexyl)adipate in Na^+ ISEs with more polar 2-nitro-p-cumol does lead to the increase in the interference from Ca^{2+} ions. However, it does not alter the influence from Mg^{2+}, and the interference from Ba^{2+} is even decreased [63]. Apparently, this is due to different stoichiometry of the complexes of different ions with the same ionophore, so the effective radii of the respective complexes are also different.

Membranes plasticized with polar plasticizer oNPOE show dielectric constant $\varepsilon = 14$ which lies in between $\varepsilon = 2$ for pure PVC and $\varepsilon = 24$ for pure oNPOE. However, the relation between the dielectric constant of plasticized PVC membranes and that of the respective pure plasticizer is not always so trivial. The dielectric constant of pure DOS is $\varepsilon = 4$, but a PVC membrane plasticized with DOS has $\varepsilon = 6$, thus exceeds that of any of the components [64]. This fact can be explained as follows [65]. In pure PVC, the rotation of C–Cl bond around the C–C bond of the polymer backbone is "frozen," but in plasticized PVC it becomes possible. Therefore, in plasticized PVC, the polar C–Cl bonds orientate in an electric field and decrease its intensity, which on the macroscopic level manifests in higher dielectric permittivity. This is why the dielectric constant of a membrane

containing low-polar plasticizer may exceed ε of the pure components. It was shown that the dielectric constants of plasticized PVC membranes lie within the range from 4 to 14 [64].

Plasticized PVC membranes are cast from the so-called membrane cocktails. These are solutions of PVC, plasticizer and ionophores in a volatile organic solvent. Most frequently the latter is tetrahydrofuran (THF), sometimes (seldom) cyclohexanone is used. The amount of THF in the cocktail is normally about 85 %, the rest, the so-called dry mass, is made of PVC, plasticizer and ionophores and ion exchangers (ionic additives). The cocktail can be cast onto a Petri dish, and in this way, a large "master" membrane with a diameter of 3–10 cm can be obtained after the evaporation of THF. The thickness of the membrane, obviously, depends on the dry mass of the cocktail and normally varies from 0.3 to 0.6 mm. Next, smaller discs with diameters of 5–10 mm can be cut from this master membrane with a suitable cork bore. The discs can be fixed in electrode body in different ways. The so-called Philips electrode body is the most popular, see Fig. 4.6. Membrane disc is fixed and sealed with a silicon O-ring in screw cup connected to the body. The latter contains internal reference electrode. In Fig. 4.6, the membrane is shown black to be seen clearly. The Philips body set also includes a special tool (similar to a cork bore) to cut membrane discs from master membrane.

Membrane discs can be glued to PVC bodies with a PVC-cyclohexanone slurry. In the case of solid-contact electrodes, no master membrane is prepared. Instead, portions of membrane cocktails can be drop-cast directly on the respective substrate. The area of the membrane formed after evaporation of THF must be slightly larger than that of the substrate, so that the membrane surely covers all the substrate and some part of the body as well. No glue is used in this case; however, poor adhesion of the membrane to the substrate and/or to the body may cause a

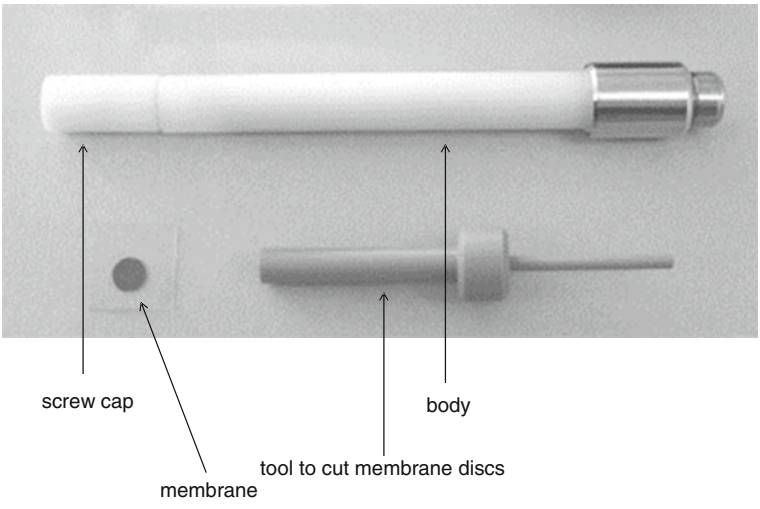

Fig. 4.6 Philips electrode body

shortened lifetime of the electrode. Sometimes membranes can even detach from the substrate.

Plasticized PVC membranes appear macroscopically uniform. However, studies of the component distribution over the membrane volume showed differently. By means of X-ray photoelectron spectroscopy and secondary ion mass spectroscopy [66], as well as by atomic force microscopy [67], it was shown that the layers in the outmost vicinity of the membrane surface are enriched by the plasticizer in comparison with its average content over the whole membrane. Experiments with small-angle neutron scattering revealed tiny PVC clusters the size of about 6 nm which do not dissolve in THF even after lengthy and vigorous mixing of the membrane cocktail [68]. Thus, plasticized PVC membranes are to some extent intrinsically non-homogeneous.

When solvent-polymeric membranes are in contact with aqueous solutions, another kind of non-homogeneity arises. It originates from water sorption by the membranes. Plasticized PVC membranes sorb water in relatively large quantities: from 0.5 to 2 % of the total mass of the membrane [69, 70]. Water in membranes aggregates into large clusters (inverted micelles) which cause scattering of the transmitting light. Because of this, membranes in contact with solutions become dim, sometimes even milk white. When taken out from solutions, membranes lose absorbed water. It evaporates from membranes within several minutes, up to about 1 h depending on the membrane composition and geometry and on the ambient temperature. After that, the membranes became fully transparent again. Water sorption strongly depends on the nature of the plasticizer, membranes plasticized with phosphates and phosphonates sorb water in larger quantities than other kinds of membranes [70].

Water uptake was studied by spectrophotometry and NMR [69, 71–74]. It was shown that water is non-uniformly distributed within the membrane. Membrane layers in the vicinity of the surface are enriched with water when compared with the membrane bulk [69]. The typical size of water clusters is about 16 nm, and the freezing point of water in the clusters may be below zero, within the range from 0 to −15 °C [72]. Water uptake takes place in two stages. During the first hour of contact, membrane sorbs water from solution and forms mobile particles with diffusion coefficients of about $D \approx 10^{-6}$ cm^2/s. After that, light-scattering clusters (water droplets) form with a much lower mobility: $D \approx 10^{-9}$ cm^2/s. The non-uniformity of the water distribution in the membrane is most pronounced during the first few hours of contact with the solution. However, even after 5 days of contact, the content of water in the layers of about 25 μm from the membrane/solution interface is about 20 % higher than the average value over the whole membrane [73, 74]. Analogous non-uniformity was also found for the distribution of ionophores [75].

Further studies of the water uptake were carried out for solid-contact ISEs with conducting polymers in the transducer layer in between ionically conducting PVC membranes and electronically conducting substrates (glassy carbon, graphite). These studies also revealed several kinds of water clusters with diffusion coefficients $D_1 = 4.7 \times 10^{-10}$, $D_2 = 5.1 \times 10^{-11}$, and $D_3 = 4.7 \times 10^{-12}$ cm^2/s in the

poly(trioctylthiophene) layer, that is, in several orders of magnitude lower than in PVC [76, 77]. The absorbed water does not only make a dispersed phase within the membrane, but also form a continuous layer even on hydrophobic substrates like conducting polymers and graphite [76–79]. By the neutron reflectometry and the IR–ATR methods, it was shown that the water layer thickness is about 10 nm [76, 79].

These peculiarities hinder correct theoretical description of the electrochemistry of solvent-polymeric membranes. Most often, however, these peculiarities are neglected in theoretical considerations, and solvent-polymeric membranes are normally treated as liquid phases. The presence of the polymer matrix is only indirectly accounted for. For instance, in considerations of the ion transfer across the ISE membranes, the typical values of the ion diffusion coefficients are 10^{-8} cm^2/s, while those in liquid membranes are in 1.5–2 orders of magnitude higher. The polymer therefore is considered as an inert network which impedes the movement of the species within the membrane, but otherwise does not participate in any chemical interactions.

4.3.2 Non-PVC Polymeric Membranes, ISEs with Ion-Exchanger Sites and Ionophores Covalently Bound to Polymer Backbone

One of the disadvantages of plasticized polymeric membranes, in particular, plasticized PVC membranes, is their sensitivity to elevated temperatures and organic solvents. Indeed, plasticizers simply dissolve in organic solvents, while at elevated temperatures, membranes get depleted in plasticizers and ionophores even in aqueous solutions. Under normal conditions: room temperature and only aqueous samples, the lifetime of ISEs with plasticized PVC membranes is about 1 year, although the shelf time may be up to 10 years [80]. Therefore, for many years, efforts were made and still are made aimed to replace PVC as the membrane matrix polymer with other polymers. The final goal would be a polymer with a low glass transition temperature and with covalently bonded ionophores. Such a membrane may be stable at elevated temperatures as well as in mixed aqueous-organic solutions.

Among polymers, apparently suitable as substitutes of PVC, are silicon rubbers, acrylic polymers, acrylsiloxanes, and urethanes. Low glass transition temperature allows, in principle, use of these polymers without plasticizers. Anyway, these membranes are normally doped with plasticizers which in these cases are mostly needed as solvents for ionophores [81]. Much less is published about ISEs with plasticizer-free membranes containing only a polymer and an ionophore. The latter can be distributed within the polymer bulk as individual molecules, or covalently bonded to the polymer backbone [82].

Historically, first attempts of substitution of PVC were focused on silicon rubbers [35]. Silicon rubbers adhere to various substrates much stronger than PVC, which is an important advantage, especially in production of solid-contact electrodes or ion-selective field effect transistors. Plasticizers must be added to these membranes to increase the solubility of ionophores, to ensure Nernstian response slope, and to reduce Ohmic resistance of the membranes. These goals can be achieved without a decrease in the adhesion of membranes to substrates [83, 84].

Later, photocured polymers, mostly of acrylic or urethane nature, and acrylic-siloxane polymers had became more popular as substitutes of PVC. In addition to good adhesion properties, these polymers allow for photolithographic technology of the sensor manufacturing. This, in turn, strongly facilitates mass production of small-sized sensors with good piece-to-piece reproducibility and low rejection. Calcium electrodes with acrylic membranes are capable of working in the presence of high contents of perchlorate [85]. Methacrylic membranes for ISEs selective to K^+ and to various inorganic anions have been described in [86]. Polyurethane and urethane–acrylic membranes were described in [81, 87–89], among them for carbonate ions [88] and for K^+, NH_4^+, Ca^{2+} [81, 89]. Self-plasticizing membranes with methacryl–acryl copolymer matrixes having glass transition temperatures from −20 to −44 °C can be used for K^+, Na^+, Ca^{2+} and also for pH ISEs [49, 90–93]. A method was developed to obtain acrylic membranes for K^+ and Ca^{2+} ISEs with a given ratio of the concentrations of the target analyte ion and interfering ion, to preset the dynamic range of the ISEs [94]. Ion diffusion coefficients and therefore also trans-membrane fluxes of electrolytes in acrylic polymers are much lower than those in plasticized PVC. This makes ISEs with acrylic membranes promising for measurements in strongly diluted samples [95]. It was also reported about a successful use of ionic liquids as plasticizers in ISEs with acrylic membranes [96–98].

Durability of ISE membranes can be improved by covalent binding of ionophores and/or ion-exchanger sites to polymeric backbone (PVC or other polymers). Poly-crown ethers were used as oligomeric ionophores in plasticized PVC membranes since late 1970s [99]. It was reported on ISEs with crown ethers and calixarenes covalently bonded to silicone rubbers [100–102] or to carboxylated PVC [103]. More recently, membranes with neutral ionophores bound to acrylic polymer backbone were obtained for Ca^{2+} [82] and Pb^{2+} [104] ISEs. Calcium ISEs with alkylphosphoric groups (charged ionophores) were immobilized on polystyrenbutadiene [105, 106] and on vinylchloride–vinylacetate copolymer [107]. Dodecacarboran lipophilic anion known as a promising analog of tetraphenylborates (widely used cation exchangers) [108, 109] can also be covalently bound to acrylic backbone. In this way, a novel Ca^{2+} electrode was made with a polymeric cation exchanger [110]. Polyetherketon functionalized with sulfonated groups was successfully used in NH_4^+ ISEs with nonactin as neutral ionophore [111]. Also, acrylic polymers are sometimes used in solid-state reference electrodes [112, 113].

Fluorous polymers, plasticizers, and ionophores have been reported by Bühlmann [114–117]. The selectivities of ISEs with fluorous membranes significantly exceed those of their PVC analogs. The membranes consisting of these extremely hydrophobic compounds are especially promising for clinical and biological

applications since the ISEs with these membranes do not suffer from bio fouling. The respective sensors are also suitable for measurements at trace levels of analytes, for example, down to 4.1 ppt Ag^+ [117]. Originally, fluorous membranes were of liquid type, more recently it was reported on polymeric fluorous membranes with Teflon AF2400: poly[4,5-difluoro-2,2-bis(trifluoromethyl)-1,3-dioxole]-co-poly(tetrafluoroethylene) as polymer matrix [116].

A totally novel approach was proposed by Gyurcsanyi [118]. Ionophores are immobilized on the surface of gold nanopores. First promising results are obtained with Ag^+—selective sensors with thiacalixarene derivative as neutral ionophore.

4.4 The Theory of the Ionophore-Based Membranes Response and Selectivity

4.4.1 Response and Selectivity of ISEs with Membranes Containing Ion Exchangers and Charged Ionophores

Discussion of the selectivity of ISEs with membranes containing ion exchangers and charged ionophores requires some mathematical apparatus; namely, we will consider the boundary potentials on the two sides of the membrane: the external (sample) side and the internal side, as well as the diffusion potential within the membrane. In this way, we will obtain an equation for the overall membrane potential (the electric potential difference across the whole membrane). To do this, we will use ideas and equations discussed in Chap. 2.

If the membrane/solution interface is at electrochemical equilibrium with regard to I^{z_I} species, the interfacial (boundary) potential:

$$\varphi_b = \varphi^{(\mathrm{mem})} - \varphi^{(\mathrm{aq})} = -\frac{\left(\mu_I{}^{0(\mathrm{mem})} - \mu_I{}^{0(\mathrm{aq})}\right)}{z_I F} - \frac{\mathrm{RT}}{z_I F}\ln\frac{a_I{}^{(\mathrm{mem})}}{a_I{}^{(\mathrm{aq})}} \tag{4.7}$$

This equation, the same as Eq. (2.8), is presented here for the readers' convenience. In most cases, the activities of all the species in the membrane phase are replaced with the concentrations of the respective free (non-complexed, non-associated) ions. Under this assumption, we can rewrite Eq. (4.7) in the following form:

$$\varphi_b = \varphi^{(\mathrm{mem})} - \varphi^{(\mathrm{aq})} = -\frac{\left(\mu_I{}^{0(\mathrm{mem})} - \mu_I{}^{0(\mathrm{aq})}\right)}{z_I F} - \frac{\mathrm{RT}}{z_I F}\ln\frac{C_I{}^{(\mathrm{mem})}}{a_I{}^{(\mathrm{aq})}} \tag{4.8}$$

Since the membrane, generally speaking, separates solutions with different compositions, the values of the species concentrations within the membrane phase may vary across the membrane. The membrane (or its part with non-uniform distribution of ions) constitutes therefore a diffusion layer. The diffusion of the species across this layer results in additional contribution to the membrane

potential: the diffusion potential. Although this phenomenon is discussed in Sect. 2.3.2, here we address this issue again, adopting our consideration closer to ionophore-based membranes.

The flux of I^{z_I} charged species caused by the gradient of the respective electrochemical potential across the membrane obeys the Nernst–Planck equation:

$$\begin{aligned} J_I &= -u_I C_I \frac{\mathrm{d}}{\mathrm{d}x}(\mu_I + z_I F\phi) = -u_I C_I \frac{\mathrm{d}}{\mathrm{d}x}(\mathrm{RT}\ln a_I + z_I F\phi) \\ &= u_I C_I \frac{\mathrm{d}}{\mathrm{d}x}(\mathrm{RT}\ln C_I + z_I F\phi) \end{aligned} \tag{4.9}$$

The electric current density (i) produced by the fluxes of charged species equals the sum of the respective fluxes multiplied by the respective charge numbers, and the whole sum is multiplied by the Faraday constant. Under the potentiometric conditions, the electric current density is zero, so

$$i = F\sum_I z_I J_I = 0 \tag{4.10}$$

Let us consider the case when the membrane containing R^- lipophilic sites is in contact with mixed solutions of IX, JX mono-monovalent hydrophilic electrolytes. We will also assume that the Donnan exclusion holds, and that the electrolytes in the membrane are present as ions R^-, I^+, and J^+, and ion-pairs IR, JR. This means that R^-, I^+, and J^+ are the only charged species present in the membrane. Using Eq. (4.9), we obtain for this simple case:

$$-u_I C_I \frac{\mathrm{d}}{\mathrm{d}x}(\mathrm{RT}\ln \mathrm{C_I} + \mathrm{F}\phi) - u_J C_J \frac{\mathrm{d}}{\mathrm{d}x}(\mathrm{RT}\ln \mathrm{C_J} + \mathrm{F}\phi) + u_R C_R \frac{\mathrm{d}}{\mathrm{d}x}(\mathrm{RT}\ln \mathrm{C_R} - \mathrm{F}\phi) = 0 \tag{4.11}$$

After combining all the terms containing the potential in the left-hand part and all other terms in the right-hand part, we get

$$F\frac{\mathrm{d}\phi}{\mathrm{d}x}(u_I C_I + u_J C_J + u_R C_R) = -\mathrm{RT}\left(u_I \frac{\mathrm{d}C_I}{\mathrm{d}x} + u_J \frac{\mathrm{d}C_J}{\mathrm{d}x} - u_R \frac{\mathrm{d}C_R}{\mathrm{d}x}\right), \tag{4.12}$$

which immediately gives the differential form of the diffusion potential within the membrane:

$$\frac{\mathrm{d}\phi}{\mathrm{d}x} = -\frac{\mathrm{RT}}{F}\frac{\mathrm{d}(u_I C_I) + \mathrm{d}(u_J C_J) - \mathrm{d}(u_R C_R)}{(u_I C_I + u_J C_J + u_R C_R)} \tag{4.13}$$

The macroscopic electroneutrality holds, so that $C_I + C_J = C_R$ in any layer within the membrane. The interaction between I^+ and R^- versus the interaction between J^+ and R^- is generally speaking different. Therefore, profiles of I^+ and J^+ species across the membrane caused by the difference of the solution compositions may also cause a profile of R^- distribution as well. Because of this, Eq. (4.13), although it looks

very simple, for integration thereof requires either the knowledge of the profiles of the species distribution across the membrane or some further simplifications.

One of these simplifications can be the assumption of the complete dissociation of the membrane electrolytes, so that only R^-, I^+, and J^+, that is, only charged species are present in the membrane, and no ion-pairs exist. In such a case, the replacement of I^+ with J^+ counter-ion or vice versa does not produce any driving force for R^- flux: the competing ions are identical for the sites. Then, at least in the steady state, the sites are distributed uniformly, there is no flux of R^-, and the concentration of sites everywhere within the membrane equals their total concentration: $C_R = C_R{}^{\text{tot}} = \text{Const}$. Thus, under the assumption of the complete dissociation of the electrolytes in the membrane, $C_I + C_J = C_R = C_R{}^{\text{tot}} = \text{Const}$. This allows for the integration of Eq. (4.13) which results in the equation for the diffusion potential within the membrane:

$$\varphi_{\text{d}} = -\frac{\text{RT}}{F}\ln\frac{(u_I C_I + u_J C_J)^{(r)}}{(u_I C_I + u_J C_J)^{(l)}} \tag{4.14}$$

Upper indices (l) and (r) denote the external and the internal sides of the membrane. The same result can be obtained in the case when I^+ and J^+ ions do form ion-pairs with R^- sites, but the respective association constants are the same. Here, once again, the competing ions are identical for the sites.

Using the so-called ionic distribution coefficients introduced by Eisenman [119] as $k_I = \exp\left(-\left(\mu_I{}^{0(\text{mem})} - \mu_I{}^{0(\text{aq})}\right)/\text{RT}\right)$,[3] one can express the concentration of J^+ ions in the membrane as a function of the I^+ and J^+ activities in the aqueous solution and of the concentration of I^+ ions in the membrane:

$$C_J = C_I \frac{a_J k_J}{a_I k_I} \tag{4.15}$$

By combining Eq. (4.8) written for the both sides of the membrane, with Eqs. (4.14) and (4.15), we obtain for the overall membrane potential:

$$\begin{aligned}\varphi_{\text{mem}} &= \varphi_b{}^{(l)} + \varphi_b{}^{(r)} + \varphi_{\text{d}} \\ &= -\frac{\text{RT}}{z_I F}\ln\frac{C_I{}^{(l)}}{a_I{}^{(l)}} - \frac{\text{RT}}{z_I F}\ln\frac{a_I{}^{(r)}}{C_I{}^{(r)}} - \frac{\text{RT}}{z_I F}\ln\frac{C_I{}^{(r)}\left(u_I + u_J\frac{a_J{}^{(r)}k_J}{a_I{}^{(r)}k_I}\right)}{C_I{}^{(l)}\left(u_I + u_J\frac{a_J{}^{(l)}k_J}{a_I{}^{(l)}k_I}\right)}\end{aligned} \tag{4.16}$$

[3] Note, in contrast to the electrolyte distribution coefficient, the ionic distribution coefficient does not show the ratio of the activities of the species within the two contacting phases. This ratio for any charged species is also dependent on the value of the interfacial electrical potential. Only combinations of the ionic distribution coefficients like multiples of those for a cation and an anion, or ratios of these values for ions of the same charge are potential independent. These multiples and ratios are equivalent to the ordinary electrolyte distribution coefficients or to the ratios of the latter, respectively. Nevertheless, ionic distribution coefficients are useful, especially for the theoretical descriptions of the boundary and membrane potentials.

Trivial algebra allows obtaining from Eq. (4.16):

$$\varphi_{\text{mem}} = -\frac{\text{RT}}{z_I F}\ln\frac{\left(a_I{}^{(r)} + \frac{u_J k_J}{u_I k_I} a_J{}^{(r)}\right)}{\left(a_I{}^{(l)} + \frac{u_J k_J}{u_I k_I} a_J{}^{(l)}\right)} \tag{4.17}$$

Let us now assume that the right-hand side of the membrane is in contact with the internal solution of the ISE and the composition of this solution is constant, while the left-hand side solution comprises a sample or a calibrator. Then for the membrane potential, we get

$$\varphi_{\text{mem}} = \varphi_{\text{mem}}{}^{0} + \frac{\text{RT}}{z_I F}\ln\left(a_I{}^{(l)} + \frac{u_J k_J}{u_I k_I} a_J{}^{(l)}\right) \tag{4.18}$$

Thus, in the case of the complete dissociation of electrolytes in the membrane, as well when the interactions between sites and both kinds of the competing ions are identical, the membrane potential follows the Nikolsky equation:

$$\varphi_{\text{mem}} = \varphi_{\text{mem}}{}^{0} + \frac{\text{RT}}{z_I F}\ln(a_I + K_{\text{IJ}} a_J), \tag{4.19}$$

and the selectivity coefficient to the target (primary) I^+ ions in the presence of the interfering J^+ ions is

$$K_{\text{IJ}} = \frac{u_J k_J}{u_I k_I} \tag{4.20}$$

Thus, the selectivity coefficient depends on the ratios of the ion mobilities and the ion partition coefficients. The latter may vary in orders of magnitude, while the former may vary in times, at most. Therefore, the selectivity is normally governed by the so-called equilibrium factor: k_J/k_I. However, there are some examples of the selectivity determined by the mobilities ratio [120, 121].

Besides the assumption of the identical interactions between I^+ and J^+ ions with R^- sites (or the lack of interaction: the case of the complete dissociation), some other simplifications allow for the integration of the Eq. (4.13). One can consider the situation when R^- sites are immobilized by covalent binding with the matrix polymer, or the sites are just low mobile for any other reason, meaning $u_R \ll u_I, u_J$. In this case

$$\frac{\text{d}\phi}{\text{d}x} = -\frac{RT}{z_I F}\frac{\text{d}(u_I C_I) + \text{d}(u_J C_J)}{(u_I C_I + u_J C_J)} = -\frac{\text{RT}}{z_I F}\text{d}\ln(u_I C_I + u_J C_J) \tag{4.21}$$

The obtained form comprises a full differential, and the respective integral is the same as that given by Eq. (4.11). Consequently, Eqs. (4.13–4.17) are also valid in this case.

It is also possible that I^+ and J^+ ions have equal mobilities, while the mobility of R^- sites is different: $u_I = u_J \neq u_R$. If this is true, the differential form of the diffusion potential (Eq. 4.15) looks as follows:

$$\frac{\mathrm{d}\phi}{\mathrm{d}x} = -\frac{\mathrm{RT}}{F}\frac{\mathrm{d}(u_I(C_I + C_J)) - \mathrm{d}(u_R C_R)}{(u_I(C_I + C_J)) + (u_R C_R)} \tag{4.22}$$

Because of the macroscopic electroneutrality, $C_I + C_J = C_R$, therefore Eq. (4.22) produces the equation for the diffusion potential within the membrane:

$$\varphi_{\mathrm{d}} = -\frac{\mathrm{RT}}{F}\frac{u_I - u_R}{u_I + u_R}\ln\frac{C_I{}^{(r)} + C_J{}^{(r)}}{C_I{}^{(l)} + C_J{}^{(l)}} \tag{4.23}$$

The combination of Eq. (4.23) for the diffusion potential, with Eq. (4.8) for the two boundary potentials, gives for the overall membrane potential the following expression:

$$\varphi_{\mathrm{mem}} = \frac{u_I - u_R}{u_I + u_R}\frac{\mathrm{RT}}{F}\ln\frac{a_I{}^{(l)} + \frac{k_J}{k_I}a_J{}^{(l)}}{a_I{}^{(r)} + \frac{k_J}{k_I}a_J{}^{(r)}} + \frac{2u_R}{u_I + u_R}\frac{\mathrm{RT}}{F}\ln\frac{a_I{}^{(l)}\,C_I{}^{(l)}}{a_I{}^{(r)}\,C_I{}^{(r)}} \tag{4.24}$$

Here, only the first term in the right-hand side is Nikolsky like, while the second term contains parameters (free ion concentrations in the membrane) which are unknown variables. These variables can be calculated numerically if the respective parameters are known: the ionic distribution coefficients and ion-site association constants [19, 20, 122–127]. As to the Nikolsky-like term, one can see that the selectivity here is entirely determined by the ratio of the ionic distribution coefficients, while the mobilities show up only in the pre-logarithmic factors of the two right-hand terms of Eq. (4.24).

4.4.2 The Hofmeister Series

Whatever the simplifying assumption is which allows for the integration of the differential presented by Eq. (4.13), one can see that the selectivity is determined by the ratio of the ionic distribution coefficients and also by the ratio of the species' mobilities within the membrane. This consideration is useful for the understanding of the regulations in the selectivity of the ISE membranes containing ion exchangers and charged ionophores. The selectivity of ISEs with membranes containing only ion exchangers is relatively low and depends primarily on the free energy of the ion hydration. Below we will try to explain this. If we consider only the equilibrium factor of the selectivity (neglecting the mobilities' ratio), the selectivity is determined by the difference of the free energy of transfer of the two competing ions. Let them be I^+ primary (target) ion and J^+ interfering ion. When distributing from the aqueous solution to the membrane, both ions lose $\Delta G_I{}^h$, $\Delta G_J{}^h$, the free energies of hydration, and gain $\Delta G_I{}^s$, $\Delta G_J{}^s$, the free energies of solvation by the membrane components, and also ΔG_{IR}, ΔG_{JR}, the free energies of the association with R^- sites. Thus, the difference of the free energies

of the ion transfer which refers to the ability of J^+ interfering ion to replace I^+ primary ion in the membrane can be written as follows:

$$\Delta\Delta G_{I/J}{}^{\mathrm{tr}} = \Delta G_J{}^{\mathrm{tr}} - \Delta G_I{}^{\mathrm{tr}} = -\Delta G_J{}^{\mathrm{h}} + \Delta G_I{}^{\mathrm{h}} + \Delta G_J{}^{\mathrm{s}} - \Delta G_I{}^{\mathrm{s}} + \Delta G_{\mathrm{JR}} - \Delta G_{\mathrm{IR}} \tag{4.25}$$

In practically relevant membranes, there are no specific interactions between ions and membrane solvent (plasticizer). Therefore, the values of the free energy of solvation are low for any ion. The interaction between ion exchangers and ions is mostly of pure electrostatic nature, and therefore, the ion-site association constants are relatively low [19–21]. Furthermore, these association constants are virtually independent of the nature of the ion: whichever I^+ or J^+ in our example. This is because R^- lipophilic sites are large and the distances between the centers of the ions in the ion-pairs depend primarily on the effective radius of R^-. Therefore, the electrostatic forces in IR and JR ion-pairs are roughly the same. For instance, ion-site association constant values for K^+, Na^+, Cs^+, and $NH_4{}^+$ cations with $ClTPB^-$ anion in bis(butylpentyl)adipate are 2.5×10^3, 2.0×10^3, 4.0×10^3, and 3.2×10^3 M^{-1}, respectively, thus only weakly dependent on the cation nature [20]. For a typical concentration of ion exchanger in PVC membranes about 0.01 M, these values mean that the fraction of ion-pairs varies from 18 % for NaClTPB to 27 % for CsClTPB.

The only significant impact to the difference of the free energies of the ion transfer comes from the difference in the free energies of hydration, while the other components are of minor importance, so

$$\Delta\Delta G_{I/J}{}^{\mathrm{tr}} = \Delta G_J{}^{\mathrm{tr}} - \Delta G_I{}^{\mathrm{tr}} \approx -\Delta G_J{}^{\mathrm{h}} + \Delta G_I{}^{\mathrm{h}} \tag{4.26}$$

Therefore, the selectivity of ISEs with ion-exchanger–based membranes is governed primarily by the affinity of ions to the aqueous phase: an ion-exchanger–based membrane is more selective to the ion which leaves aqueous phase more easily. In this sense, ions form the so-called Hofmeister series. This series contains ions arranged in order of their free hydration energy, with low hydration on the left-hand side and high hydration on the right-hand side. Originally, Hofmeister revealed these series when studying the influence of inorganic salts on the solubility of proteins in water [128].

Anion-selective electrodes with membranes having only ion exchangers remain widely used. Therefore, we will first discuss the Hofmeister series for anions. It looks as follows:

$$\begin{aligned} R^- > ClO_4{}^- > SCN^- > I^- > NO_3{}^- > Br^- > Cl^- \\ \approx HCO_3{}^- > H_2PO_4{}^- > SO_4{}^{2-} \end{aligned} \tag{4.27}$$

In the series above, R^- represents organic anions. Many of them are lipophilic and prefer an organic phase over an aqueous phase. Therefore, ion-exchanger–based membranes are more selective to most of organic ions, even in the presence

of ClO_4^- or SCN^-. Inorganic ions, obviously, prefer to stay in a polar—aqueous—phase, rather than in membrane phase which is significantly less polar [64]. However, the free hydration energy of ions which measures the adherence of ions to water is dependent primarily on the so-called surface charge density of the ion. This is the ratio of the ion charge over the surface area of the ion considered a sphere with the effective radius. Obviously, the surface charge density of a small divalent or trivalent ion is high, while that of a large monovalent ion is low. Therefore, there is no surprise that perchlorate, thiocyanate, iodide—monovalent ions—which are only weakly hydrated due to relatively large size, belong to the left-hand side of the series. These ions are more eager to get into membrane phase than nitrate, bromide, chloride, and bicarbonate. It is therefore easy to ensure selectivity, for example, to perchlorate over nitrate and chloride, or to nitrate over sulfate. However, when having only the ion exchanger present in the membrane, one cannot make an electrode selective to hydrophilic ions like divalent carbonate, phosphate, or sulfate.

The Hofmeister series for cations is as follows:

$$R^+ > Cs^+ > K^+ > Na^+ > Li^+ > Ca^{2+} > Mg^{2+} > Al^{3+} \qquad (4.28)$$

R^+ represents organic cations. Cation-selective electrodes already in early years of ISEs with liquid and polymeric membranes have been based on ionophores specifically interacting with cations. However, when studying novel ionophores, it is strongly advisable to compare the selectivities of ISEs having ionophores in membranes with those of ISEs having only ion-exchanger sites. In this sense, Hofmeister series for cations is useful as reference.

4.4.3 Selectivity of the ISEs Based on Neutral Ionophores

The first theory of the response and the selectivity of ISEs with membranes containing neutral ionophores selectively binding cations was proposed by Ciani et al. [129]. Their studies were aimed at modeling living cell membranes, and ISE membranes served as model systems. The ISE membranes, therefore, have been assumed very thin, and this assumption allowed neglecting anions in membranes: membranes with thickness comparable with the respective Debye length may deviate from the electroneutrality condition. Thus, in [129], they considered a membrane containing L neutral ionophore and equilibrated with two mixed aqueous solutions of electrolytes IX and JX. Both I^+ and J^+ cations form 1:1 complexes with the neutral ionophore: IL^+ and JL^+. Interestingly, Ciani, Eisenman, and Szabo assumed that the complexes are formed in the aqueous phase with K_{IL}, K_{JL} the respective formation constants, and the complexes distribute between the phases with k_{IL}, k_{JL} the respective ionic distribution coefficients. For this case, according to [129], the membrane potential can be described as follows:

$$\varphi_m = \frac{\mathrm{RT}}{F} \ln \frac{{a_I}^{\mathrm{ex}} + \frac{u_{\mathrm{JL}} k_{\mathrm{JL}} K_{\mathrm{JL}}}{u_{\mathrm{IL}} k_{\mathrm{IL}} K_{\mathrm{IL}}} {a_J}^{\mathrm{ex}}}{{a_I}^{\mathrm{in}} + \frac{u_{\mathrm{JL}} k_{\mathrm{JL}} K_{\mathrm{JL}}}{u_{\mathrm{IL}} k_{\mathrm{IL}} K_{\mathrm{IL}}} {a_J}^{\mathrm{in}}} \tag{4.29}$$

Here, u_{IL}, u_{JL} stand for the mobilities of the complexes within the membrane phase. Thus, the membrane potential follows the Nikolsky equation, and the complex formation constants directly contribute to the selectivity coefficient:

$$K_{\mathrm{IJ}} = \frac{u_{\mathrm{JL}} k_{\mathrm{JL}} K_{\mathrm{JL}}}{u_{\mathrm{IL}} k_{\mathrm{IL}} K_{\mathrm{IL}}} \tag{4.30}$$

If IL^+ and JL^+ complexes are isosteric, the respective distribution coefficients and mobilities must be roughly the same for both kinds of the species: $k_{\mathrm{IL}} \approx k_{\mathrm{JL}}$, $u_{\mathrm{IL}} \approx u_{\mathrm{JL}}$. Then, the selectivity coefficient is determined by the ratio of the complex formation constants in the aqueous phase:

$$K_{\mathrm{IJ}} = K_{\mathrm{JL}} / K_{\mathrm{IL}} \tag{4.31}$$

Macrocyclic neutral ionophores do form isosteric complexes with ions of the same charge. Acyclic ionophores (podands) in most cases form complexes with two molecules of the ionophore per one ion. Effectively, these complexes are also isosteric, while the two molecules of the ionophore in the complex can be (formally) considered as a product of the ionophore dimerization. Thus, according to the Ciani, Eisenman, and Szabo theory, the selectivity of ISEs with neutral ionophores in membranes, at least for ions of the same charge and forming complexes of the same stoichiometry, must be independent of the membrane solvent. The latter seems, probably, the most striking result of the theory, and this result often gets experimental support.

Morf considered the formation of ion-to-ionophore complexes in the membrane phase, while ions distribute between the phases as individual species [130]. His equation for the membrane potential looks very similar to Eq. (4.29):

$$\varphi_m = \frac{\mathrm{RT}}{F} \ln \frac{{a_I}^{\mathrm{ex}} + \frac{u_{\mathrm{JL}} k_J K_{\mathrm{JL}}}{u_{\mathrm{IL}} k_I K_{\mathrm{IL}}} {a_J}^{\mathrm{ex}}}{{a_I}^{\mathrm{in}} + \frac{u_{\mathrm{JL}} k_J K_{\mathrm{JL}}}{u_{\mathrm{IL}} k_I K_{\mathrm{IL}}} {a_J}^{\mathrm{in}}} \tag{4.32}$$

However, the distribution coefficients in Morf's Eq. (4.32) refer to ions (not to complexes), and the complex formation constants refer to the membrane phase.

In principle, if all the necessary equilibria (heterogeneous and homogeneous) are established, the mechanism of the complex formation and of the ion distribution does not matter. Indeed, the Gibbs free energy of ion transfer according to the Ciani, Eisenman, and Szabo theory combines the loss of the Gibbs free energy of the hydration of the free ion, the gain due to the complexation in the aqueous phase, the loss of the Gibbs hydration free energy of the complex, and the gain of the Gibbs free energy of the solvation of the complexed ion in the membrane phase:

$$\Delta {G_I}^{\mathrm{aq} \to m} = -\Delta G_{I,h} + \Delta {G_{\mathrm{IL}}}^{\mathrm{aq}} - \Delta G_{\mathrm{IL},h} + \Delta G_{\mathrm{IL},s} \tag{4.33}$$

According to the alternative approach (like that considered by Morf),

$$\Delta G_I^{\mathrm{aq}\rightarrow m} = -\Delta G_{I,h} + \Delta G_{I,s} + -\Delta G_{\mathrm{IL},h} + \Delta G_{\mathrm{IL},s} \tag{4.34}$$

It was mentioned above that according to the Ciani, Eisenman, and Szabo theory, the selectivity of the membranes with neutral ionophores does not depend on the membrane solvent. This conclusion is often but not always supported by experimental data. The explanation why and when the solvent influences the selectivity, and when it does not, has been proposed by Mikhelson [131–134]. Basically, if both the target analyte ion and the interfering ion form complexes of the same stoichiometry (and therefore isosteric), and these complexes predominate over non-complexed ions in the membrane, the complex solvation free energy contributions are eliminated. Then, solvent does not influence the selectivity to ions of the same charge. Obviously, this conclusion is similar to that proposed by Ciani, Eisenman, and Szabo, however, not limited to thin membranes. If the stoichiometry of the complexation is different for the primary and the interference ions, the nature of the solvent affects the selectivity.

4.4.4 *Co-Ion Interference with the Response of ISEs Based on Neutral Ionophores*

ISEs with membranes based on neutral ionophores show interesting peculiarity. The span of the Nernstian response is strongly dependent on the nature of the co-ion [135]; namely, cation-selective ISEs show interference from anions present in solution, and anion-selective electrodes show interference from cations. An example of the anion interference with the potassium response of membranes based on valinomycin is shown in Fig. 4.7.

With the increase in the concentration of the electrolyte, the response to the potassium ions deviates more and more from the Nernstian law, and after passing a maximum turns into anionic response. It was shown that the ability of the anions to interfere is determined by their position in the Hofmeister series, that is, by their Gibbs free energy of hydration [130, 134, 136]. Less hydrated anions interfere even at low concentrations.

For the theory, the two phenomena, the anion interference with the cationic response and the cation interference with the anionic response, are absolutely symmetrical. Since most of the respective studies have been performed for cationic ISEs, the phenomenon is often called “anion interference with cationic response.” The trivial explanation in terms of high mobility of anions within membranes is not consistent with the data on the ion transference numbers in membranes [137]. Also, it is hardly possible that the anions in membranes are low mobile when in contact with diluted solutions, and the mobility is increasing with the solution concentration. The consistent theory of the co-ion interference was first proposed by Simon’s

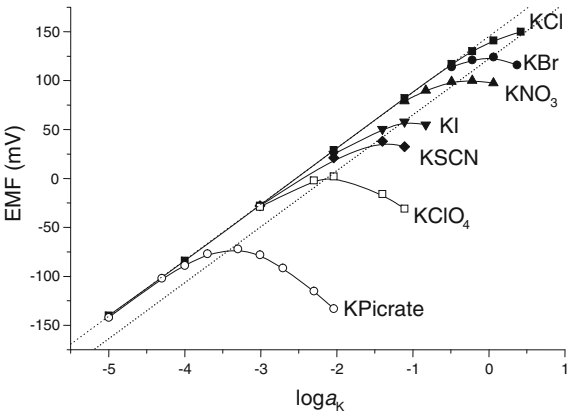

Fig. 4.7 Anion interference with K^+ membranes containing valinomycin and KClTPB in DOP [123]. Adapted with permission from Mikhelson [123]. Copyright 1992 Elsevier

group [138]. According to [138], for the full Nernstian response to, for example, cations, the neutral ionophore must be present in some excess over the complexed ions. The concentration of the latter is roughly equal to the concentration of R^- ion-exchanger sites in the membrane since the concentration of non-complexed ions is very small: $C_{\mathrm{IL}} \approx C_R$, $C_I \ll C_{\mathrm{IL}}$. On the other hand, the concentration of the complexed ions is proportional to that of the free ionophore: $C_{\mathrm{IL}} = C_I C_L K_{\mathrm{IL}}$. Thus, $C_I = C_{\mathrm{IL}} {C_L}^{-1} {K_{\mathrm{IL}}}^{-1} \approx C_R {C_L}^{-1} {K_{\mathrm{IL}}}^{-1}$. Therefore, as long as the Donnan exclusion holds, $C_I \approx$ Const and the boundary potential follows the Nernst equation, while the diffusion potential within the membrane is negligible. With the increase in the concentration of the solution, the membrane extracts the electrolyte in significant quantities (the Donnan exclusion failure) and more and more of the ionophore molecules are consumed by the extracted ions by complexation. Decrease in C_L, the free ionophore concentration, causes increase in C_I the free ion concentration in the membrane. Because of this, the boundary potential deviates from the Nernst equation, and eventually the response appears to be anionic. The latter limiting situation is characteristic to membrane with fully complexed ionophore. This means that the membrane contains a lipophilic cation (the cationic complex) in excess over R^- sites, so, effectively, the membrane works as anion exchanging.

The position of the maximum on the response curve depends on the stoichiometry of the ion-to-ionophore complexation and on the dissociation degree of the complexed electrolyte in the membrane in a complicated way [138, 139]. In the simplest case of 1:1 complexation, and low degree of association with anions, the activity of the target ion in the solution when the response curve reaches maximum is [139]

$$a_I{}^{\max} = \sqrt{\frac{4{C_L}^{\mathrm{tot}}}{3K_e}} \tag{4.35}$$

Here, ${C_L}^{\mathrm{tot}}$ is the total concentration of the neutral ionophore in the membrane, and $K_e = k_{\mathrm{IX}} K_{\mathrm{IL}}$ is the co-extraction constant—the multiple of the electrolyte

distribution coefficient and the complex formation constant. It was shown that in the point of the maximum 1/3 of the total ionophore concentration refers to the complexes, and 2/3 is free [139]. Furthermore, the maxima on the curves belong to a straight line, parallel to the Nernstian response line, and shifted in $\Delta E = (2RT/F) \ln \sqrt{3} \approx 27.7$ mV to more negative values [139]. The experimental value for the valinomycin membrane (see Fig. 4.7) is 24.5 mV [136], supporting this theoretical conclusion. Equation (4.34) shows that the co-ion interference intensifies with the decrease in the hydrophilicity of the electrolyte (therefore, the anions interfere according to their position in the Hofmeister series) and with the increase in the complex formation constant.

A detailed comparison of the anion interference on the cationic response of ISEs with neutral and charged ionophores was performed by Bühlmann [140].

4.5 Generalized Theories of Ionophore-Based ISE Membranes

Theoretical considerations presented in Sects. 4.4.1–4.4.4 contain too many simplifications: the ion-site interactions are either negligible (complete dissociation), or the same for any kind of counter-ion, or sites are immobile, or mobilities of counter-ions are the same. These approaches are very useful giving intuitively clear simple descriptions of the respective limiting cases. On the other hand, these simplifications are hardly true for the real-world ISEs. Low polarity of membranes suggests a rather strong association than complete dissociation of the electrolytes in membranes, the sites, typically, are mobile. Therefore, attempts were made to develop a more realistic description of the ISE response and selectivity. Here, we will briefly outline several generalized approaches to the description of the ISE membrane response and selectivity. Even more advanced theories providing the description of the membrane potential in real time and space are discussed in Sect. 7.1.

4.5.1 The Sandblom–Eisenman–Walker Theory

The Sandblom–Eisenman–Walker theory was proposed already in the mid-1960s [119]. This theory was developed to access the influence of ion-site association with ion-exchanger–based membranes. The theory addressed the boundary potentials as well as the diffusion potential within the membrane. The whole system—membrane and solutions—was considered being in the steady state, while the membrane/solution interfaces were supposed to be at electrochemical equilibrium. Only limiting cases were solved: (1) complete dissociation and (2) strong association of the electrolytes in the membrane.

For the first limiting case, the complete dissociation, the description of the membrane potential in a mixed solution containing I^+ primary ions and n sorts of monovalent interferences, is Nikolsky like

$$\varphi_m = {\varphi_m}^0 + \frac{RT}{F}\ln\left(a_I + \sum_{i=1}^{n}\frac{u_{J_i}k_{J_i}}{u_I k_I}a_J\right) \tag{4.36}$$

Furthermore, Eq. (4.36) shows the additivity of the impacts from the interferences to the membrane potential. Thus, in the case of the complete dissociation, the selectivity coefficient is dependent on the species mobilities and on their ionic distribution coefficients.

Since real membranes are low-polar, the second limiting case, the strong association of the electrolytes in the membrane phase, appears more realistic. For this more complicated situation (and for only two competing ions: I^+ and J^+), Sandblom, Eisenman, and Walker obtained

$$\varphi_m = -\frac{RT}{F}\left\{(1-\tau)\ln\frac{{a_I}^{in} + \left[\frac{u_J+u_R}{u_I+u_R}\frac{k_I}{k_J}\right]{a_J}^{in}}{{a_I}^{ex} + \left[\frac{u_J+u_R}{u_I+u_R}\frac{k_I}{k_J}\right]{a_j}^{ex}} + \tau\ln\frac{{a_I}^{in} + \left[\frac{u_{JR}}{u_{IR}}\frac{k_J K_{JR}}{k_I K_{IR}}\right]{a_J}^{in}}{{a_I}^{ex} + \left[\frac{u_{JR}}{u_{IR}}\frac{k_J K_{JR}}{k_I K_{IR}}\right]{a_J}^{ex}}\right\} \tag{4.37}$$

Here, u_I, u_J, u_R, u_{IR}, u_{JR} are mobilities of I^+, J^+ ions, of R^- ion-exchanger sites and of IR, JR ion-pairs; K_{IR}, K_{JR} stand for the ion-pairs association constants. Upper indexes *in* and *ex* denote the internal and the external solutions.

Equation (4.37) constitutes a sum of two Nikolsky-like logarithmic terms with weighting factor:

$$\tau = \frac{u_R(u_{JR}K_{JR} - u_{IR}K_{IR})}{(u_I + u_R)u_{JR}K_{JR} - (u_J + u_R)u_{IR}K_{IR}} \tag{4.38}$$

The first logarithmic term in Eq. (4.37) shows, basically, the impact of the ionic distribution coefficients to the selectivity. The presence of the ion exchanger manifests in the first term only via u_R: the R^- mobility value. The second term is directly related to the association—via K_{IR}, K_{JR} ion-pair association constants and u_{IR}, u_{JR} mobilities. Thus, Eq. (4.37) is crucially different from the Nikolsky-like equations with only one parameter. According to the Sandblom, Eisenman, and Walker theory, the selectivity of an associated membrane is characterized by three parameters: ${K_{IJ}}^{(1)} = (u_J + u_R)k_J/(u_I + u_R)k_I$, ${K_{IJ}}^{(2)} = (u_{JR}k_J K_{JR})/(u_{IR}k_I K_{IR})$, and τ. This may explain the variability of the selectivity coefficients calculated by the Nikolsky equation: a one-parameter equation is not suitable for ISEs with strong association of the electrolytes in membranes.

4.5.2 Phase-Boundary Potential Approaches, Ionic Additives, Selectivity Optimization

Large variety of the compositions of the ionophore-based membranes, in combination with large variety of analytes and interferences, sometimes causes peculiar dependences of the membrane potential on the activities of ions. Apparently, non-Nernstian responses with slopes approaching one-half, two-thirds, and other multiples of RT/z_IF are frequently observed, especially for membranes with charged ionophores [141]. A consistent theoretical explanation of these facts, taking into account the boundary potentials as well as the diffusion potential within membrane, may be mathematically too complicated and intuitively not clear. On the other hand, accounting for only the boundary potentials allows for rationalization of many of these peculiar facts, like the apparently non-Nernstian slopes [47, 141] and non-monotonous curves for Ca ISEs when the pH is varied [45]. Furthermore, the boundary potential approach allowed inventing the so-called *ionic additives method* for the improvement of the selectivity of the ISEs with membranes containing charged ionophores [43–47]. This fact deserves special consideration presented below.

The selectivity coefficient of an ISE with a membrane containing a neutral ionophore is directly proportional to K_{JL}/K_{IL}, the ratio of the complex formation constants of L, the ionophore with I^+ and J^+, the primary and the interfering ions, see Eq. (4.32). However, in the case of an ISE with a membrane containing R^- charged ionophore, the selectivity coefficient is proportional to $\sqrt{K_{JR}/K_{IR}}$—the square root of the association constants ratio. Thus, the selectivity of ion complexation by a neutral ionophore fully translates into the potentiometric selectivity, whereas the selectivity of the association translates into the potentiometric selectivity only partly. For instance, if $K_{JR}/K_{IR} = 10^{-4}$, the respective increment in the selectivity is only 10^{-2}. Let us see why this happens.

The boundary potential between the membrane and *IX* solution is

$$\varphi_b{}^{IX} = \varphi^{mem} - \varphi^{aq} = \frac{RT}{z_IF}\ln k_I + \frac{RT}{z_IF}\ln\frac{a_I}{C_I} \tag{4.39}$$

Here, a_I is the activity of I^+ ion in solution, and its activity in the membrane is approximated by C_I—the free I^+ concentration. An analogous equation can be written for the interfering ion. We now assume that the selectivity is measured by the SSM method ($a_I = a_J$), so that

$$\ln K_{IJ} = \frac{z_IF}{RT}\left(\varphi_b{}^{JX} - \varphi_b{}^{IX}\right) = \left(\frac{RT}{z_IF}\ln\frac{k_J}{k_I} - \frac{RT}{z_IF}\ln\frac{C_Ja_I}{C_Ia_J}\right)\frac{z_IF}{RT} = \ln\frac{k_JC_I}{k_IC_J} \tag{4.40}$$

In the membrane equilibrated with IX solution, the concentration of IR ion-pairs is $C_{IR} = C_IC_RK_{IR}$. The macroscopic electroneutrality holds, so $C_I = C_R$. Due to the low polarity of membranes, the associates predominate over free ions, so that the concentration of IR ion-pairs approaches the total concentration of the

charged ionophore: $C_{\mathrm{IR}} \approx C_R{}^{\mathrm{tot}}$. Thus, $C_I \approx \sqrt{C_R{}^{\mathrm{tot}}/K_{\mathrm{IR}}}$. The same reasoning is true for J^+ ions, so that

$$K_{\mathrm{IJ}} \approx k_J K_{\mathrm{JR}}{}^{1/2} \Big/ k_I K_{\mathrm{IR}}{}^{1/2} \tag{4.41}$$

Because of this relation, for a long time, it was assumed that charged ionophores are intrinsically inferior to neutral ionophores when it comes to ISEs.

Now, we will turn to membranes also containing S^+—a bulky ionic additive with the charge sign opposite to the sign of the ionophore. The ionic additives are added in excess over I^+ ions, but in such a way that $C_S{}^{\mathrm{tot}} < C_R{}^{\mathrm{tot}}$. The electroneutrality condition for such a membrane looks like: $C_I + C_S = C_R$, and due to the excess of S^+ it turns $C_S \approx C_X$. Since the ionic additives practically do not associate with R^-, $C_S \approx C_S{}^{\mathrm{tot}}$. Therefore, $C_{\mathrm{IR}} \approx C_R{}^{\mathrm{tot}} - C_R \approx C_R{}^{\mathrm{tot}} - C_S^{\mathrm{tot}}$, and $C_I \approx (C_R{}^{\mathrm{tot}} - C_S{}^{\mathrm{tot}})/C_S{}^{\mathrm{tot}} K_{\mathrm{IR}}$.

With the same reasoning for J^+ ions, we come to

$$K_{\mathrm{IJ}} = \frac{k_J K_{\mathrm{JR}}}{k_I K_{\mathrm{IR}}} \tag{4.42}$$

This is how ionic additives allow for the full translation of the selectivity of the association with the potentiometric selectivity. This approach works for various charged ionophores, in particular for metal porphyrine complexes [12]. It is also valid for divalent analytes and helps improving the selectivity to Ca^{2+} ions in more than two orders of magnitude [44, 46, 142].

Membranes containing neutral ionophores are doped with ionic additives (ion-exchanger sites) with a charge sign opposite that of the target analyte ion. In early years of the ionophore-based ISE research, it was assumed that the neutral ionophore must be in excess over sites, otherwise the ratio of the neutral ionophore concentration over the concentration of sites does not play significant role. However, within the frames of the phase-boundary model, it was shown theoretically, and supported experimentally, that the variation of this ratio may produce non-monotonous selectivity curves [1, 143–146]. In other words, this ratio is critical for the optimization of the electrode selectivity. The respective optimal values of ISEs based on charged and neutral ionophores are summarized in Table 4.1, in accordance with [146].[4]

4.5.3 Multispecies Approximation

Detailed description of the membrane potential and selectivity requires detailed consideration of the species present in ISE membranes. To do so, Mikhelson

[4] The table assumes the target and the interfering ions being cations. The situation for anion-selective ISEs is completely symmetric.

Table 4.1 Optimal values of R^{z_R} ionic site concentration over L^{z_L} the ionophore concentration ratios for I^{z_I} primary and J^{z_J} interfering ions forming, respectively, IL_{n_I} and JL_{n_J} complexes with charged or neutral ionophores, in accordance with [146]

Charge		Stoichiometry		Ratio sites over ionophore, mole percentage			
Z_I	Z_J	n_I	n_J	Charged $Z_L = -1$	Ionophore	Neutral $Z_L = 0$	Ionophore
				Z_R	${C_R}^{tot}/{C_L}^{tot}$	Z_R	${C_R}^{tot}/{C_L}^{tot}$
+2	+2	1	2	−1	41	−1	141
		2	3	+1	23	−1	77
		3	4	+1	46	−1	54
+2	+1	1	1	−1	62	−1	162
		2	2	+1	27	−1	73
		3	3	+1	54	−1	46
+1	+1	1	2	+1	29	−1	71

invented an approach called *multispecies approximation* [122–127]. To the best of our knowledge, this approximation is the only one capable of description of the membrane potential for any dissociation degree of the membrane electrolytes.

The approximation is as follows. For each component present in membranes, as many as possible, individual forms are taken into consideration. For instance, for a potassium-selective membrane containing valinomycin (L) and tetrakis(p-Cl-phenyl)borate (R^-), it is assumed that potassium is present as K^+-free ions, KL^+-complexed ions, and also KR and KLR neutral associates. In turn, valinomycin is present as L-free ionophore, KL^+ and KLR, while tetrakis(p-Cl-phenyl)borate exists as R^--free anion, and KR and KLR neutral species. Thus, in this case, six sorts of species are taken into consideration. For higher valencies and for higher complexation stoichiometries, the number of sorts of species increases sharply. The general model also includes S^+ ionic additives and accounts for the possibility of the Donnan exclusion break, so that X^- ions from solution can penetrate into membrane. The model is schematically presented in Fig. 4.8.

It is assumed that the total concentrations of the ionophores and additives are determined by the membrane preparation. This allows using the respective mass balances:

$$C_L{}^{tot} = C_L + \sum_{n=1}^{k}\left[\sum_{q=0}^{z} n\left(C_{ILnRq} + C_{ILnXq}\right) + \sum_{q=0}^{1} n\left(C_{JLnRq} + C_{JLnXq}\right) + \sum_{q=0}^{1} n\left(C_{SLnRq} + C_{SLnXq}\right)\right] \tag{4.43}$$

$$C_R{}^{tot} = C_R + \sum_{n=0}^{k}\sum_{q=1}^{z} qC_{IL_nR_q} + \sum_{n=0}^{k} C_{JL_nR} + \sum_{n=0}^{k} C_{SL_nR} \tag{4.44}$$

$$C_S{}^{tot} = \sum_{n=0}^{k}\sum_{q=0}^{1} C_{SL_nR_q} \tag{4.45}$$

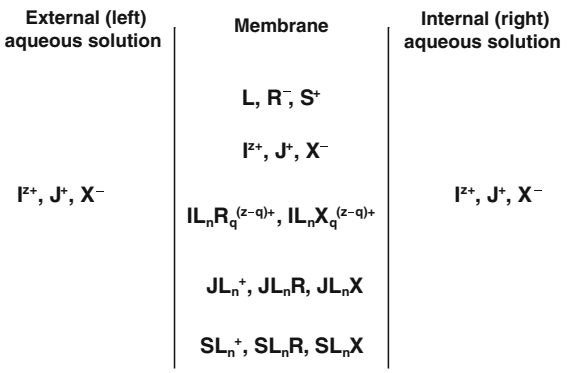

Fig. 4.8 Schematic representation of the multispecies approximation. The stoichiometry coefficients are n = 0, 1,…, k, and q = 0, 1,…, z

The macroscopic electroneutrality holds, so that

$$\sum_{n=0}^{k}\left(\left[\sum_{q=0}^{z}\left((z-q)C_{\mathrm{ILnRq}}+(z-q)C_{\mathrm{ILnXq}}\right)\right]+C_{\mathrm{JLn}}+C_{\mathrm{SLn}}\right)=C_R+C_X \tag{4.46}$$

The system of Eqs. (4.43–4.46), together with the ion-exchange equation $C_J = C_I((a_J k_J)^z/a_I k_I)^{1/z}$ and the co-extraction equation $C_X = (a_I(a_X)^z/k_{\mathrm{IX}}C_I)^{1/z}$, fully determines the membrane composition. However, this system cannot be solved analytically and requires computer simulations. The model assumes the so-called group mobilities, that is, the mobilities of all cationic species are the same: u_+, and the mobilities of all anionic species are also the same: u_-.

For a membrane containing a neutral ionophore and an ion exchanger, when the Donnan exclusion holds, the model yields for the membrane potential:

$$\varphi_m = -\frac{\mathrm{RT}}{F}(1-2\tau)\left[\ln\frac{{a_I}^{\mathrm{in}}+{K_{\mathrm{IJ}}}^{\mathrm{in}}{a_J}^{\mathrm{in}}}{{a_I}^{\mathrm{ex}}+{K_{\mathrm{IJ}}}^{\mathrm{ex}}{a_J}^{\mathrm{ex}}}+\ln\frac{\sum_{n=0}^{k}({C_L}^{\mathrm{in}})^n K_{\mathrm{ILn}}}{\sum_{n=0}^{k}({C_L}^{\mathrm{ex}})^n K_{\mathrm{ILn}}}\right]$$
$$-2\frac{\mathrm{RT}}{F}\tau\ln\left[\frac{{a_I}^{\mathrm{in}}/{C_I}^{\mathrm{in}}+{a_J}^{\mathrm{in}}/{C_J}^{\mathrm{in}}}{{a_I}^{\mathrm{ex}}/{C_I}^{\mathrm{ex}}+{a_J}^{\mathrm{ex}}/{C_J}^{\mathrm{ex}}}\right] \tag{4.47}$$

The weighting factor (τ) depends on the species mobilities: $\tau = u_-/(u_+ + u_-)$. Equation (4.47) contains three logarithmic terms, and only the first one is Nikolsky like with the selectivity coefficient:

$$K_{\mathrm{IJ}} = \frac{k_J}{k_I}\frac{\sum_{n=0}^{k}(C_L)^n K_{\mathrm{JLn}}}{\sum_{n=0}^{k}(C_L)^m K_{\mathrm{ILn}}} \tag{4.48}$$

The second term represents the impact to the membrane potential from the non-uniform distribution of the free neutral ionophore molecules in the membrane. This non-uniformity arises in an initially uniform membrane due to the difference in the solution compositions—external and internal. Also, it may be arranged artificially, and this allows for the studies of the ion-to-ionophore interactions in ISE membranes, see Sect. 4.6.

Equations (4.47) and (4.48) helped rationalizing various shapes of the dependences of the selectivity coefficient on the concentration of the neutral ionophore, including those with minima and maxima, see Fig. 4.9.

The multispecies approach was also successfully applied to the membranes with ionic additives [19, 20, 122–127]. In particular, it was shown that the role of the ionic additives may be more complicated than in accordance with the phase boundary potential models, and the mobilities of the species modify the respective dependences. Curves presented in Fig. 4.10 illustrate this conclusion. One can see how much the improvement of the selectivity caused by an ionic additive depends on the τ value.

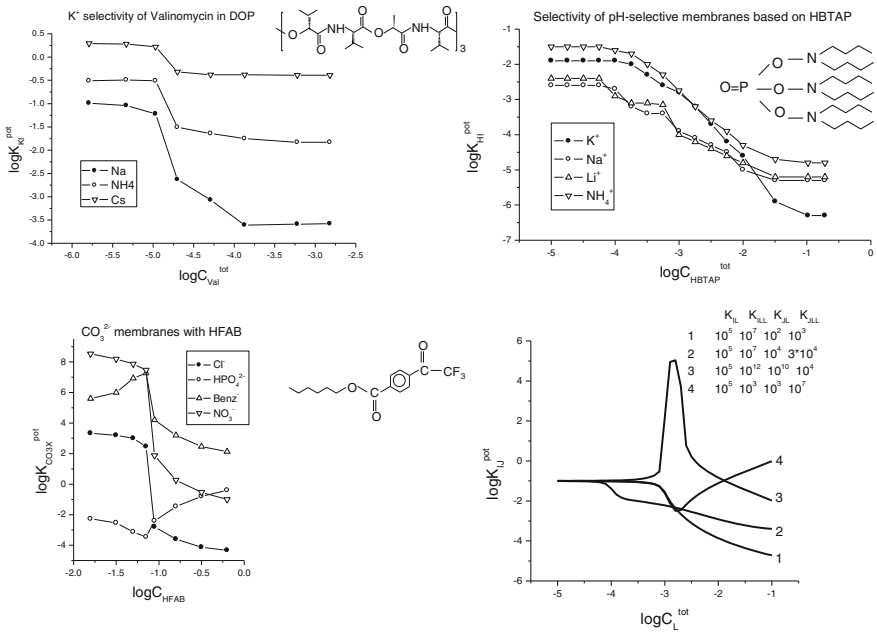

Fig. 4.9 Dependence of the selectivity coefficient on the concentration of the neutral ionophores. Experimental curves, *top* and *bottom*, *left*: valinomycin (Val), K^+ ISEs [122], hexabutyltriamido phosphate (HBTAP), H^+-ISEs [123], *p*-hexyltrifluoroacetylbenzoate (HFAB), CO_3^{2-}-ISEs [122], the ionophore structures shown next to the respective graphs. Calculated curves, *bottom right*, the complex formation constant values shown next to graph. Adapted with permission from Mikhelson and Smirnova [122]. Copyright 1992 Elsevier

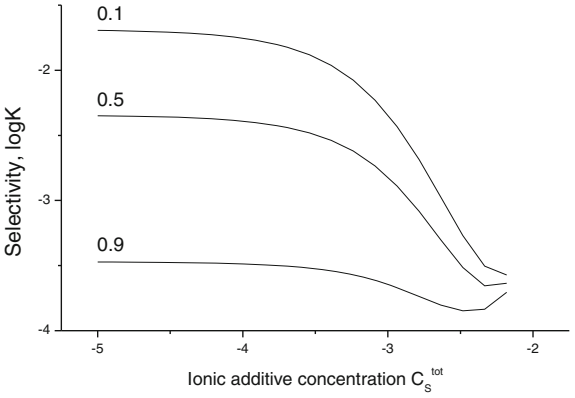

Fig. 4.10 Dependence of the selectivity on the concentration of S^+ ionic additive for different values of $\tau = u_-/(u_+ + u_-)$ [126]. Adapted with permission from Mikhelson and Lewenstam [126]. Copyright 2000 American Chemical Society

4.6 Studies of the Species Interactions in Ionophore-Based Membranes

4.6.1 Complexation of Ions by Neutral Ionophores

Selective complexation of analyte ions by neutral and charged ionophores is commonly recognized as primarily responsible for the selectivity of sensors. Data on the interactions of ions and ionophores in membranes are therefore of great academic and practical interest. In early years of ISEs study, some attempts were made to measure complex stability constants in model solutions, mostly in water–ethanol mixtures [147–150]. The data obtained showed only a poor correlation with the potentiometric selectivity. Later on, a number of methods allowing measuring of complex stability constants in situ have been invented [151–154]. These methods suffer from two intrinsic drawbacks. First, an additional reference is required. The reference is either a chromoionophore [151] or a pH ionophore [152, 153], which supposedly does not interact with the ion of interest, or it is an ion (e.g., tetrabutylammonium) which supposedly does not interact with the ionophore under study [154]. Since the respective interactions may occur (at least to some extent), the usage of references may bias the results. Second, the complex stoichiometry has to be known or postulated beforehand or can be determined only indirectly by means of an iteration procedure [154].

A different approach to measure complex stability constants in ISEs membranes containing neutral ionophores relies on recording electrical potential of segmented sandwich membranes [155]. The sandwich consists of two ordinary membranes attached to one another (see Fig. 4.11). The only difference between the membranes is the ionophore content. An artificial gradient of a neutral ionophore in the segmented membrane dividing two identical aqueous solutions with two identical electrodes immersed (e.g., Ag/AgCl) evokes a nonzero electromotive force in the galvanic cell. Initially, the effect was studied "as such" [155, 156]. Later, it was

utilized to reveal the free ionophore fraction in membranes [132], and finally to measure stability constants of ion-to-ionophore complexes [156–164].

In principle, an EMF signal caused by uneven distribution of a mobile ionophore species across a sandwich membrane is intrinsically unsteady. Initially, there are two flat concentration levels of the ionophore in two respective segments of the sandwich (see Fig. 4.11), horizontal lines 1 and 2. Diffusion of the ionophore from A, the segment with a higher concentration to B, the segment with a lower concentration change the initial step-like profile of the ionophore distribution. The measured EMF is steady (giving a "plateau") when boundary conditions on both sides of the sandwich membrane remain unaltered by the diffusion (see Fig. 4.11, curve 3). When the diffusion front reaches the membrane boundaries (curve 4 in Fig. 4.11), the EMF starts to decrease. Diffusion of the ionophore eventually levels its distribution (horizontal line 5 in Fig. 4.11) and reduces the EMF to zero. A typical example of the respective kinetic curves obtained first by Stefanova and Suglobova for valinomycin membranes [156] is presented in Fig. 4.12.

As one can see from Fig. 4.12, the plateau time gets increased with a decrease in the gradient of the ionophore in the membrane (except for curve 1, which refers to a very low initial concentration of valinomycin). When the segments' geometry and contact area are well defined, it is possible to obtain the diffusion coefficients of the ionophore in the membrane from the kinetic curve. Data obtained for valinomycin in PVC membranes plasticized with dibutyl phthalate: $D \cong 10^{-8}$ cm^2/s [165] agree well with the values obtained by radiotracers [166]. Here, however, we concentrate on the complex formation constants. From now on (in the text and in the figures), by EMF, we mean only the "plateau" values and use the Mikhelson' multispecies approach (see Sect. 4.5.3) and, respectively, Eq. (4.47) for the interpretation of the data [167].

The second term in the Eq. (4.47) represents the contribution from possible non-uniform distribution of the neutral ionophore in a segmented sandwich membrane in contact with two identical pure solutions of electrolyte IX. In the

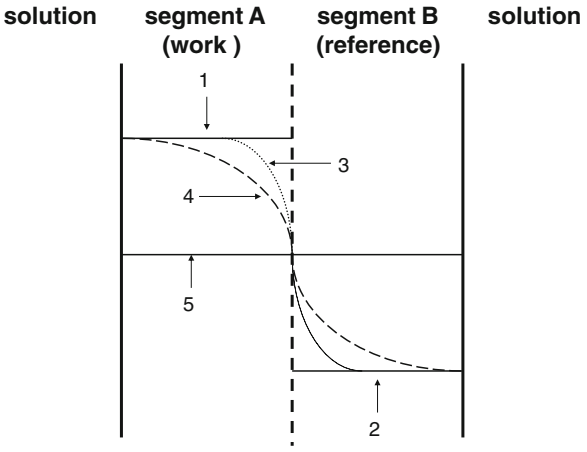

Fig. 4.11 Schematic representation of a segmented sandwich membrane

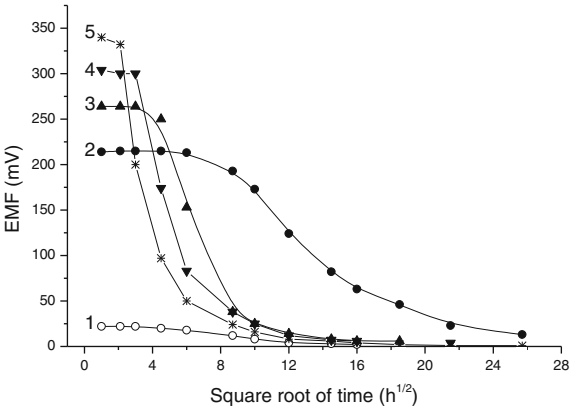

Fig. 4.12 Kinetics of sandwich membrane potential: valinomycin in DBP. $C_{val}{}^{tot}$ (mM): (*1*) 0.022, (*2*) 2.24, (*3*) 11.2, (*4*) 28.0, and (*5*) 270 [156, 167]. Adapted with permission from Shultz et al. [167]. Copyright 2002 American Chemical Society

segments, the total content of L neutral ionophore is different, while the total content of R^- ion-exchanger sites is the same. When only one sort of IL_n^+ complexes is predominating, Eq. (4.47) gets very much reduced:

$$E_m = -\frac{RT}{F}\ln\left(\frac{1+\left(C_L{}^{in}\right)^n K_{IL_n}}{1+\left(C_L{}^{ex}\right)^n K_{IL_n}}\right) \tag{4.49}$$

If on one (internal) side, in the reference segment, $C_L{}^{in,tot} = 0$, while $\left(C_L{}^{ex}\right)^n K_{ILn} \gg 1$, we can obtain from (4.49):

$$E_m = n\frac{RT}{F}\ln C_L{}^{ex} + \frac{RT}{F}\ln K_{IL_n} \tag{4.50}$$

According to Eq. (4.50), the EMF is linearly dependent on the free ionophore concentration in the external (working) segment of the sandwich. If n stoichiometry coefficient is known, the free ionophore concentration can be calculated as $C_L{}^{ex} = C_L{}^{ex,tot} - n\,C_R{}^{tot}$. In membranes with large excess of neutral ionophore over sites $C_L{}^{ex,tot} \gg C_R{}^{tot}$, and therefore concentration of the free ionophore approaches, the total concentration: $C_L{}^{ex} \approx C_L{}^{ex,tot}$. Thus, a domain of the plot EMF versus $\log C_L{}^{ex,tot} C_L{}^{ex,tot}$ has to appear, where EMF linearly depends on $\log C_L{}^{ex,tot}$. The respective slope nRT/F gives n: the stoichiometry coefficient of the complex. In this way, variation of the ionophore concentration in a wide range allows to obtain the stoichiometry of the complex without a priori knowledge. Extrapolation of the straight line to $\ln C_L{}^{ex,tot} = 0$ provides information on the complex formation constant. Examples of the respective experimental curves are given in Figs. 4.13, 4.14.

Detailed description of the advantages and limitation of the segmented sandwich method of the study of the complexation of ions by neutral ionophores is presented in [167].

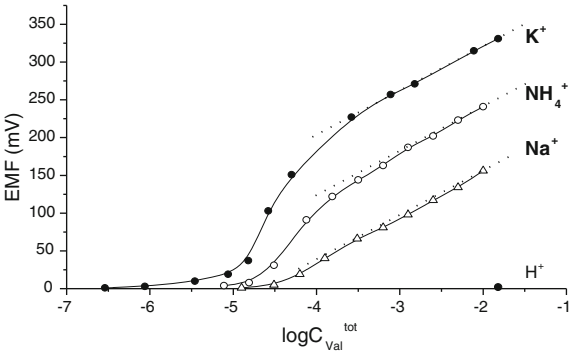

Fig. 4.13 Segmented sandwich potential *curves* obtained with valinomycin membranes [167]. Adapted with permission from Shultz et al. [167]. Copyright 2002 American Chemical Society

4.6.2 Quantification of Ion-Site Association in Membranes

It appears that, in full analogy with neutral ionophores, arranging of artificial gradient of charge ionophore or ion-exchanger sites in membrane will provide with the data on ion-site association. However, the potential of such segmented sandwich membrane does not allow for measurements of ion-site association constants. It is only possible to distinguish between strong and weak association, and it was shown that even tetraphenylborate salts are mostly associated with ISE membranes [161].

A modification of segmented sandwich membrane method which, in principle, may allow for direct measurements of ion-site association constants in real membranes was briefly discussed for the first time in [19]. The theory of the modified method relies on computer simulations using the multispecies approach. The simulations revealed another experimental setup which allows for the quantification of ion-site association with real membranes. The essence of the modified setup is that the total concentration of sites in the working segment must be constant and be the same as in the reference segment. However, the working segment must contain lipophilic ionic additive charged oppositely to the sites, and the concentration of the additive must be varied.

The results of simulations of segmented sandwich membrane potentials are presented in Fig. 4.15. Interaction between S^+ additive and R^- sites was assumed rather weak: $K_{SR} = 1$. This assumption may be realistic for bulky S^+ additive and R^- sites with low density of charge.

One can see that the variation of the concentration of the ionic additive allows obtaining EMF response, increasing with the increase in the content of the additive and also with the increase in the association constant. At relatively high values of K_{IR}, like 10^6 M^{-1}, the simulated curves contain linear domain with Nernstian slope. When the values of association constants are even higher, $K_{IR} \geq 10^{12} M^{-1}$, the simulated curves tend to come close to one another, and the whole response curve is Nernstian. The overall sandwich membrane potential in the linear domain obeys simple equation below [19, 20]:

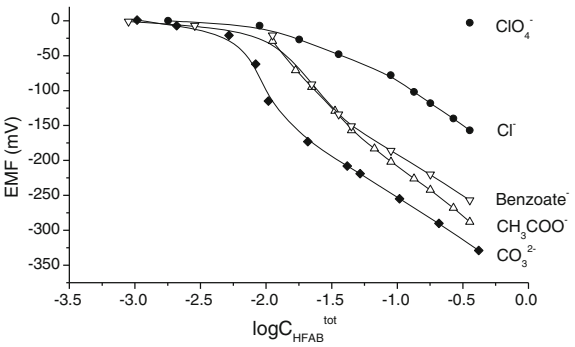

Fig. 4.14 Segmented sandwich potential *curves* obtained with membranes containing *p*-hexyltrifluoroacetylbenzoate [167]. Adapted with permission from Shultz et al. [167]. Copyright 2002 American Chemical Society

$$E = \frac{\mathrm{RT}}{F}\left(\frac{1}{2}\ln K_{\mathrm{IR}} + \ln {C_S}^{\mathrm{tot}} - \frac{1}{2}\ln {C_R}^{\mathrm{tot}}\right) \tag{4.51}$$

Thus, the modified setup for the segmented sandwich membrane method allows for measurement of the ion-site association constants in real membranes. This simple behavior can be anticipated only for membranes with strong ion-site association, and weak interaction between the main sites (or charged ionophores) and lipophilic additive. Otherwise one cannot expect linear domains in the curves of segmented sandwich membrane potential. Interpretation of experimental results obtained for membranes with $K_{\mathrm{IR}} < 10^6\ \mathrm{M}^{-1}$, or with commensurable values of K_{IR} and K_{SR}, may require nonlinear fitting of the data. Simulated EMF curves presented in Fig. 4.15 tend to coincide at very high association constants, so the EMF is not more sensitive to the value of K_{IR}. Thus, the method is limited to membranes with moderate ion-site association.

The method was applied for estimation of the ion-site association constants in membranes containing tetradecylammonium bromide (TDABr) and tetrakis(p-Cl-phenyl)borates (ClTPB^-) [19, 20]. The results are presented in Figs. 4.16, 4.17.

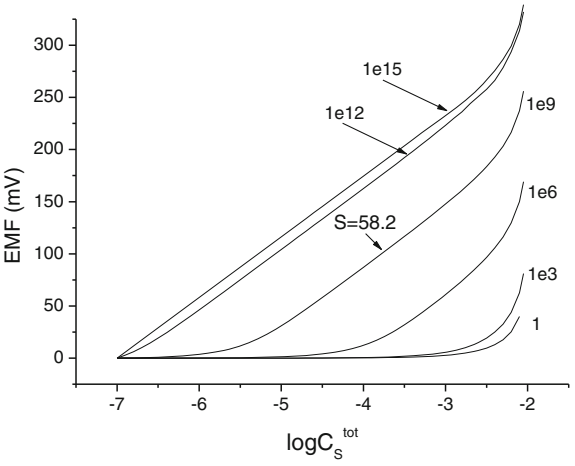

Fig. 4.15 The results of simulations of segmented sandwich membrane potentials [20]. Adapted with permission from Peshkova et al. [20]. Copyright 2008 Elsevier

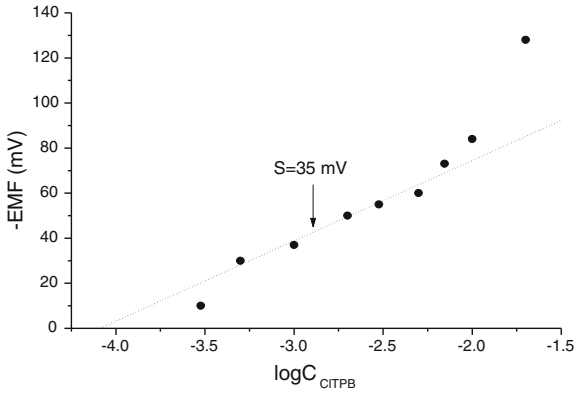

Fig. 4.16 EMF of sandwiches with 0.03 M of TDABr with variation of $ClTPB^-$ concentration in work segment [19]. Adapted with permission from Mikhelson [19]. Copyright 2003 Wiley

According to [20], the estimated values of the association constants of $ClTPB^-$ ion pairs in membranes plasticized with bis(butylpentyl)adipate are as follows: $K_{KClTPB} = 2.5 \times 10^3$, $K_{NaClTPB} = 2.0 \times 10^3$, $K_{CsClTPB} = 4.0 \times 10^3$, $K_{NH4ClTPB} = 3.2 \times 10^3\ M^{-1}$, $K_{TDDAClTPB} = 2.5 \times 10^2\ M^{-1}$. For membrane plasticized with o-nitrophenyl octyl ether, $K_{KClTPB} = 1.6 \times 10^3\ M^{-1}$, $K_{TDDAClTPB} = 10\ M^{-1}$. The association constant of TDABr in dioctylphthalate was estimated as $K_{TDABr} = 10^{6.5}\ M^{-1}$ [19].

Measuring association by the above described modified segmented sandwich method is time and labor consuming. However, the data obtained can be used as reference in the simplified method proposed later by Egorov [21].

4.7 Potentiometric Sensing of Nonionic Species

Ion-selective electrodes are essentially electrochemical sensors, and therefore, it may appear that ISEs are sensitive only to ions. This, however, is not always true. Nonionic species present in samples may interfere with the ISE response, and this makes some problems, especially in clinical applications [168]. On the other hand, the sensitivity to nonionic species may be used for sensing thereof. The nature of the effect can be rationalized with the same reasoning as used in Sect. 4.6 concerning segmented sandwich membranes.

If N, a nonionic species is capable of partitioning into the membrane phase, and bind the potential-determining ion, the result is effectively the same as in the segmented sandwich membrane, see Fig. 4.18. This type of response is most often observed for membranes containing Ba^{2+} ionophores.

In contrast to a segmented sandwich membrane with artificially non-uniform distribution of the ionophore, here the gradient of N, —nonionic species, arises naturally: because it is present only in the sample, not in the internal solution, and therefore penetrates into the membrane only from one side. Due to binding of ions with N in the membrane, N molecules act as water-soluble ionophore. Because of

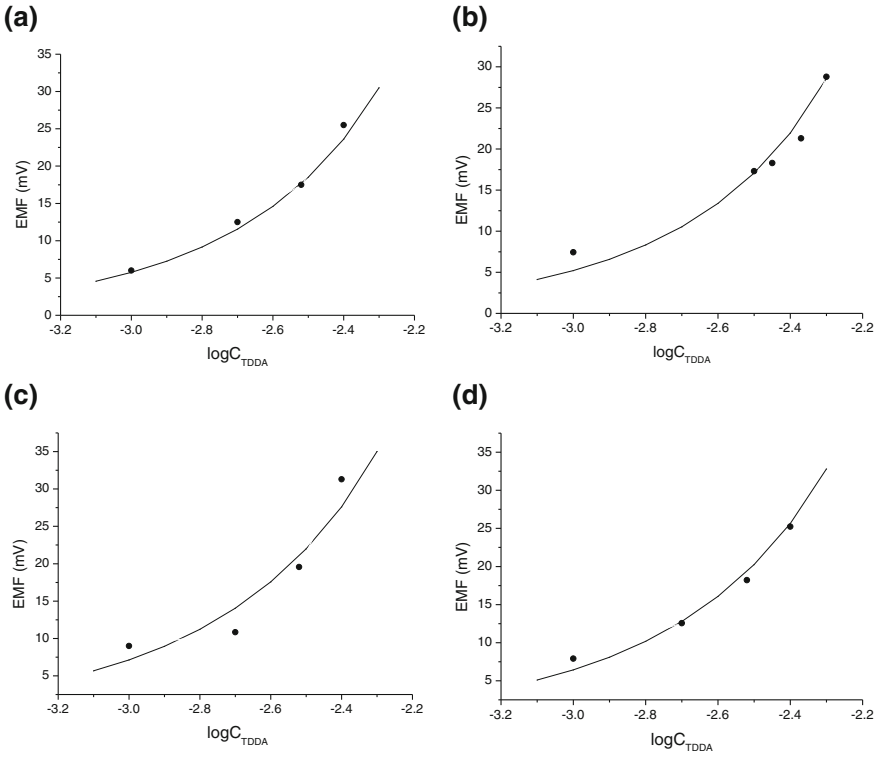

Fig. 4.17 Potentials of segmented sandwich membranes plasticized with BBPA, equilibrated with KCl (**a**), NaCl (**b**), CsCl (**c**), and NH_4Cl (**d**) [20]. Adapted with permission from Peshkova et al. [20]. Copyright 2008 Elsevier

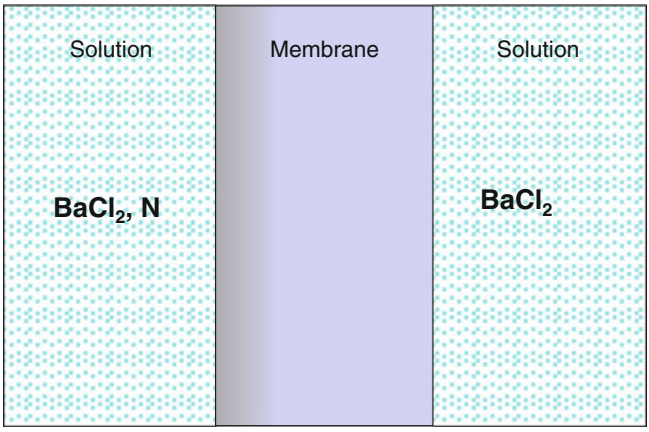

Fig. 4.18 Schematic representation of the mechanism of ISE response to nonionic species

this, a nonzero membrane potential is established, and the respective EMF delivers information on the concentration of N species.

In this way, a number of environmentally relevant species can be measured, in the first place—phenol derivatives [169] and a large number of nonionic surfactants [170, 171].

4.8 Studies of the Interfacial Kinetics at the Membrane/Solution Boundary

The most convenient and most informative method of studying the charge transfer kinetics at the membrane/solution interface relies on measurements of the electrochemical impedance of membrane/solution systems [172]. The method, in principle, provides with the information on the processes in the membrane bulk, in boundary layers, and directly at the interface. The registered impedance spectrum is interpreted with the help of the respective equivalent circuits.

Among the equivalent circuits proposed for an ion-selective membrane in contact with aqueous solutions, the most common is circuit **A** presented in Fig. 4.19 [173, 174]. In the circuit, $R_s{}^l$ and $R_s{}^r$ stand for solution resistance, $R_{\mathrm{ct}}{}^l$ and $R_{\mathrm{ct}}{}^r$ for charge transfer resistance, $C_{\mathrm{dl}}{}^l$ and $C_{\mathrm{dl}}{}^r$ for double-layer capacity, $Z_w{}^l$ and $Z_w{}^r$ for Warburg impedance, R_b is the membrane bulk resistance, and C_g is the geometric capacity of the membrane. Superscripts l and r denote left and right sides of the membrane. It is advisable to make the cell symmetric, that is, the

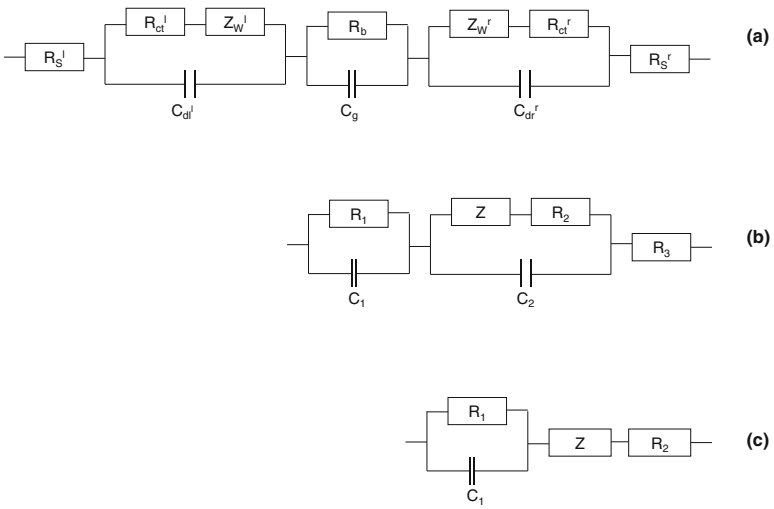

Fig. 4.19 Equivalent circuits used to interpret impedance data. **a** The Randles circuit assumed for membrane dividing two solutions. **b** Circuit for fitting EIS with two semicircles. **c** Circuit for fitting EIS with one semicircle

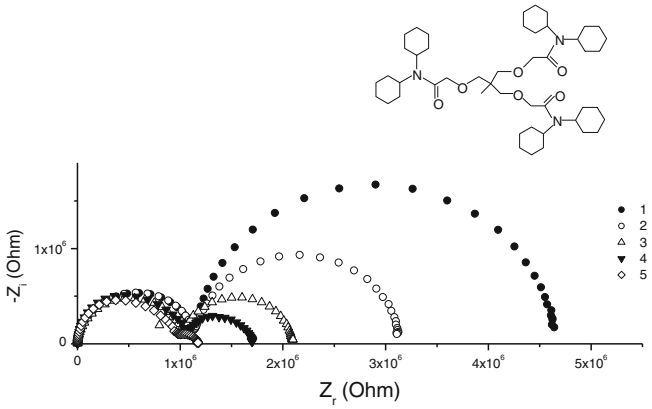

Fig. 4.20 The impedance spectra of Li ISEs in LiCl supported with 0.01 M $MgCl_2$. LiCl concentrations: 10^{-6} M (*1*), 3×10^{-6} M (*2*), 10^{-5} M (*3*), 3×10^{-5} M (*4*), 10^{-4} M (*5*). The ionophore structure shown above the spectrum [163]. Adapted with permission from Mikhelson et al. [163]. Copyright 2002 American Chemical Society

solutions must be identical, and the surface area of both—left and right—sides of the membrane must be the same.

Depending on their shape, the experimentally recorded spectra can be fitted to circuits **B** and **C**, also presented in Fig. 4.19. The symmetry of the cell suggests that the respective values for both sides of the membrane are the same. Consequently, the relation between cell parameters (circuit **A**) and those derivable by experimental impedance spectra (circuits **B** and **C**) is as follows: $R_S = R_3/2, R_{\text{ct}} = R_2/2, C_{\text{dl}} = 2C_2, Z_w = Z/2, R_b = R_1,$ and $C_g = C_1$.

The impedance method was widely used for studies of ionophore-based membranes, but most studies clearly show only one (bulk) semicircle, followed by the Warburg diffusion wave at lower frequencies [142, 173–177]. Only a few reports on well-resolved Faradaic impedance semicircles are known [163, 178–180]. In Fig. 4.20, the impedance spectra are presented, obtained for Li^+-selective electrodes with neutral ionophore [163].

In the spectra, one can see a high-frequency and also a low-frequency semicircle. The latter is regularly dependent on LiCl, NaCl, and KCl concentrations in solutions. The regularity suggests the Faradaic nature of the semicircle. The results allowed estimation of the standard exchange current densities for Li^+, Na^+, and K^+ as 1.7×10^{-5}, $2.9 \times 10^{-7}$and 1.6×10^{-7} A/cm^2. The respective capacity C_2 lies in the range $4 \times 10^{-8} - 7 \times 10^{-8}$ F and in a few cases reaches values up to 1.2×10^{-7} F. These values suggest for the double-layer capacity C_{dl}, the value of $3 \times 10^{-8} - 6 \times 10^{-8}$ F/cm^2. Using the Gouy–Chapman theory, these values allowed estimation of the thickness of the double layer at the interface between an aqueous solution and a polymeric membrane containing ionophores as 100–300 nm. These results also tell about the transient time of the charge transfer process. This time lies in the range from 10^{-5} to 10^{-3} s, dependent on the nature of the membrane

and the ion in question. In particular, the interfacial electrochemical equilibrium establishes in about 10^{-4} to 10^{-2} s, which is much less than the practical response time of ISEs.

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