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Potentiometric Selectivities of Ionophore-Doped Ion-Selective Membranes: Concurrent Presence of Primary Ion or Interfering Ion Complexes of Multiple Stoichiometries

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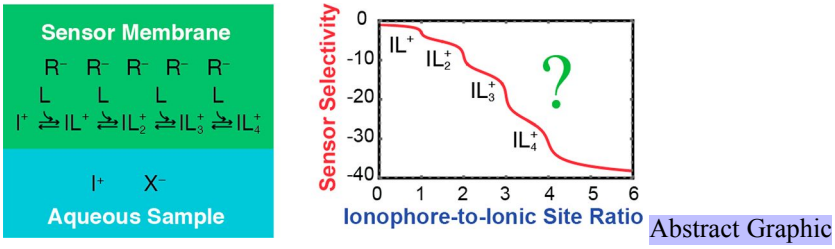
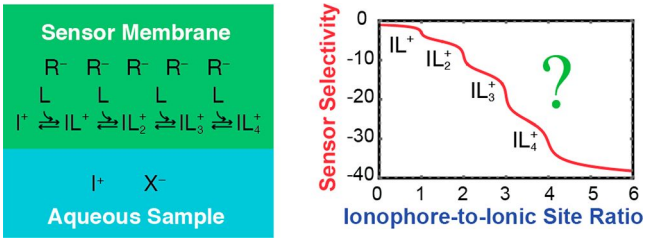
The selectivities of ionophore-doped ion-selective electrode (ISE) membranes are controlled by the stability and stoichiometry of the complexes between the ionophore, L, and the target and interfering ions (I^{z_i} and J^{z_j}, respectively). Well-accepted models predict how these selectivities can be optimized by selection of ideal ionophore-to-ionic site ratios, considering complex stoichiometries and ion charges. These models were developed for systems in which the target and interfering ions each form complexes of only one stoichiometry. However, for a few ISEs, the concurrent presence of two primary ion complexes of different stoichiometries, such as IL^{z_i} and $IL_2^{z_i}$, was reported. Indeed, similar systems were probably often overlooked and are, in fact, more common than the exclusive formation of complexes of higher stoichiometry unless the ionophore is used in excess. Importantly, misinterpreted stoichiometries misguide the design of new ionophores and are likely to result in the formulation of ISE membranes with inferior selectivities. We show here that the presence of two or more complexes of different stoichiometries for a given ion may be inferred experimentally from careful interpretation of the potentiometric selectivities as a function of the ionophore-to-ionic site ratio or from calculations of complex concentrations using experimentally determined complex stabilities. Concurrent formation of JL^{z_j} and $JL_2^{z_j}$ complexes of an *interfering* ion is shown here to shift the ionophore-to-ionic site ratio that provides the highest selectivities. Formation of $IL_{n-1}^{z_i}$ and $IL_n^{z_i}$ complexes of a *primary* ion is less of a concern because an optimized membrane typically contains an excess of ionophore, but lower than expected selectivities may be observed if the stepwise complex formation constant, K_{IL_n}, is not sufficiently large and the ionophore-to-ionic site ratio does not markedly exceed n.



Abstract Graphic



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~~Keywords: Ion-selective electrodes; Ionophore; Ionic Sites; Complex Stoichiometry; Potentiometric Selectivity; Fluorous Membranes~~

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W ~~When~~hen ionophore-based ion-selective electrodes (ISEs) [1–8] ~~1 2 3 4 5 6 7 8~~ were first introduced, their membranes were doped with ionophores, but no deliberate effort was made to introduce ion -exchanger sites. Only later was it shown that ISE membranes with electrically neutral ionophores but no added ionic sites gave the well-known Nernstian responses to the target ions only because the matrix polymer and plasticizers contained charged impurities that functioned as ion -exchanger sites. [9–13] ~~9 10 11 12 13~~ This led to the deliberate introduction of highly hydrophobic ions to provide for ion -exchanger sites. Moreover, it was shown that the ratio of the ionophore and the ionic sites in an ISE membrane can change the potentiometric selectivity by many orders of magnitude. [14–18] ~~14 15 16 17 18~~ This is true ~~both~~ for both neutral and electrically charged ionophores.

The reason for the large effect of the ionophore-to-ionic site ratio on the selectivity lies in the stoichiometry of the target ion complexes in the ISE membrane. [4, 7, 19] Because of the requirement for electroneutrality in bulk phases, the bulk of an ISE membrane must contain an amount of exchangeable ions such that their total charge equals (but is opposite in sign to) the total charge of the ion -exchanger sites (and the ionophore, if the latter is electrically charged). If the ionic site concentration is chosen to be too high, the total concentration of target ions in the bulk of the ISE membrane is too high as well, and there is an insufficient amount of ionophore available for the formation of complexes with the target ion. On the other hand, in a highly selective ISE membrane, all but a minuscule amount of the target ions is bound in the form of ionophore complexes, and the membrane contains an appreciable excess of free ionophore.

In most of the published work on ionophore-based ISEs, the ionophore has been assumed to form only complexes of one stoichiometry with the target ion, although different stoichiometries for primary and interfering ions were considered thoroughly. [14–18] This led, e.g., to the recommendation that membranes doped with an electrically neutral ionophore that forms 1:1 complexes with the monovalent target cation I^+ but 1:2 complexes with the monovalent interfering cation J^+ should be doped with 71 mol % anionic sites to achieve optimum potentiometric selectivity.[18]

Only a small number of publications mentioned the possibility of multiple complex stoichiometries for a given type of ion under different conditions (such as in membranes with different ionophore-to-ionic site ratios). [20–23] Moreover, there are few examples of the concurrent presence of target ion complexes of multiple stoichiometries in ISE membranes. Probably the first example for such a system was given by the Mg^{2+} response of a Mg^{2+} ISE in a background of Ca^{2+}. It was speculated that this Mg^{2+} response was affected by the concurrent presence of 1:1 and 2:1 complexes of the ionophore with Mg^{2+}, but a quantitative discussion was not provided because complex formation constants were not available at the time.[20] More than ~~ten~~10 years later, a report on [9]mercuracarborand-3 as a chloride ionophore gave quantitative evidence for 1:1 and 2:1 complex formation with the target ion Cl^-. [21,22] It was understood that these two types of complexes coexisted in the sensing membrane, but the effect of the ionophore-to-ionic site ratio on the potentiometric selectivity was ~~only~~ referred to only in the context of lower detection limits. A more comprehensive discussion of primary ions that formed complexes of multiple stoichiometries was provided for fluorous [24,25] membrane ISEs doped with an electrically neutral fluorophilic crown ether ionophore. In that case, K^+, Cs^+, and NH_4^+ each formed 1:1 and 2:1 complexes, and it was shown how the concentration of these complexes in the sensing membrane depends on the sample composition.[23] For example, when membranes doped with this ionophore and 71 mol % anionic sites were exposed to samples that contained K^+ as the only cation, this resulted in formation of substantial concentrations of 1:1 and 2:1 complexes of the ionophore and K^+ in the sensing membrane, while the concentrations of both the free ligand and free K^+ in the ISE membrane remained very low. This thermodynamic model explained the apparently super-Nernstian responses [26–28] of those electrodes to K^+ when measured in a background of an interfering ion.[23] Interestingly, the closely related technique of ion-transfer voltammetry has been used to determine sequential

binding constants of ions to ionophores. [29–32] However, ~~since~~because ion-transfer voltammetry is based on the use of hydrophobic sensing membranes that comprise an ionophore and a hydrophobic electrolyte but no ion-exchanger sites, complexes with higher stoichiometry are more likely to be formed preferentially unless the ionophore is depleted or complex stabilities are particularly small.[33]

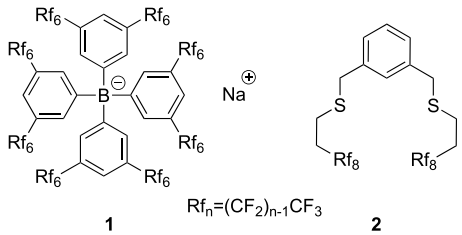
Notably, in the above-mentioned case of [9]mercuracarborand-3, [21,22] the concentration of free ionophore was not considered quantitatively, and, in the case of the fluorophilic crown ether,[23] the free ionophore concentration was low throughout the whole range of the calibration curve. Moreover, in none of the above cases was an attempt made to predict (i) the concentrations of the different complexes and free ionophore in a wider range of ionophore-to-site ratios and (ii) the resulting effects on potentiometric selectivities. To this end, we briefly described earlier the perhaps counterintuitive finding that, for low ionic site concentrations, membranes doped with an ionophore that forms multiple *n*:1 complexes with a monovalent ion will have lower potentiometric selectivities than membranes doped with an ionophore that only forms 1:1 complexes.[7] We are reporting here the theory to explain this finding and discuss the reasons that explain how the ionophore-to-ionic site ratio affects potentiometric selectivities in systems with multiple stoichiometries, using as an example a hypothetical ionophore that forms complexes of 1:1, 2:1, 3:1, and 4:1 stoichiometry. This is followed by experimental data for a fluorophilic Ag^+ ionophore, which appears to be the first example of a highly selective ISE membrane that contains 2:1 and 1:1 complexes in the presence of a substantial excess of free ionophore. Finally, the effect of multiple stoichiometries on the optimum ratio of ionophore and ionic sites is discussed. Both the theoretical and the experimental results illustrate (i) that ignoring higher complex stoichiometries may result in the use of suboptimal ionic site concentrations and, therefore, poor selectivities, and (ii) that even a detailed experimental plot of selectivity versus the ionophore-to-ionic site ratio does not always readily reveal the concurrent formation of multiple complex stoichiometries.

~~EXPERIMENTAL SECTION~~Experimental Section

Reagents

All commercial chemicals were of high purity and were used as received. ~~Perfluoroperhydrophenanthrene~~Perfluoroperhydrophenanthrene and ~~tetraethylammonium~~tetraethylammonium acetate were purchased from Alfa Aesar (Ward Hill, MA) and GFS Chemicals (Powell, OH), respectively. Sodium tetrakis[3,5-bis(perfluorohexyl)phenyl]borate, **1**, [34,35] and 1,3-bis(~~perfluorooctylethylthiomethyl~~perfluorooctylethylthiomethyl)benzene, **2**, [36,37] were synthesized as reported previously (see Figure 1). All sample solutions were prepared with deionized and charcoal-treated water (18.2 MΩ cm specific resistance) purified with a Milli-Q PLUS reagent-grade water system (Millipore, Bedford, MA).

Figure 1. Structure formulas of the fluorophilic site, **1**, and the Ag^+ ionophore, **2**.



Ion-Selective Membranes

Fluorous stock solutions were prepared to contain 1.0 mM ionic site (**1**) and 0 or 5.0 mM ionophore (**2**) in ~~perfluoroperhydrophenanthrene~~perfluoroperhydrophenanthrene as the solvent, and were stirred for at least 24 h to ensure complete dissolution. Sensing phases that contained ionic sites (1.0 mM) and ionophore (in the concentration range from 0.0 to 5.0 mM) were prepared by mixing of appropriate volumes of the two stock solutions. The fluorous sensing phases (30 µL) were then applied with a micropipette onto a stack of ~~6~~six porous filter disks (porous poly(tetrafluoroethylene), without backing; 47 mm diameter, 0.45 µm pore size, 50 µm thick, 85% porosity, Fluoropore, Millipore) that mechanically supported the fluorous sensing phases, as described previously. [34,35,38–42] Full penetration of the sensing phases into the porous supports was spontaneous and was apparent from the translucence of the impregnated filter disks.

Electrode Assembly

The fluorous sensing membranes were mounted into custom-fabricated electrode bodies machined from poly(chlorotrifluoroethylene), as previously reported.[35] In short, a cap with a center hole was screwed onto an electrode body, holding the sensing membrane between the cap and the electrode body but leaving a circular membrane area of 8.3 mm diameter exposed (see ~~Figure 1~~ Figure 1 in ref. 35). An aqueous 0.10 mM $AgNO_3$ solution was used as the inner filling solution, into which a AgCl-coated Ag wire was inserted as the reference electrode. Before measurements, all electrodes were conditioned in a 10 mM $AgNO_3$ solution for at least 10 h.

EMF Measurements

Potentiometric measurements were performed at room temperature in stirred solutions with an EMF 16 potentiometer (Lawson ~~Labs~~Laboratories, Malvern, PA) controlled with EMF Suite 1.02 software (Fluorous Innovations, Arden Hills, MN). A free-flowing double-junction Ag/AgCl electrode with a 1.0 M LiOAc bridge electrolyte and AgCl-saturated 3.0 M KCl reference electrolyte was used as the external reference electrode (DX200, Mettler Toledo, Switzerland).[43] Measurements were performed with polypropylene containers as sample beakers, which were cleaned weekly in 0.10 M HNO_3. All emf values were corrected for liquid-junction potentials using the Henderson equation.[44] Selectivity coefficients were determined with the separate solution method (SSM), fixed interference method (FIM), and fixed primary ion method (FPIM).[45] In the concentration range where selectivities were measured, all ions responded Nernstian, as confirmed by successive dilutions of stock solutions. All reported selectivities are average values for 3 ~~to~~ 6 electrodes. This level of carefulness in the determination of selectivity coefficients is crucial because only unbiased selectivity coefficients[45] are thermodynamically meaningful and lend themselves to the type of thorough interpretation as performed in this work.

~~RESULTS AND DISCUSSION~~Results and Discussion

Dependence of the Potentiometric Selectivity on the Ratio of Ionophore and Ionic Sites

The selectivity of an ISE membrane doped with an ionophore that forms only complexes of one type of stoichiometry with the target ion (Figure 2 A) exhibits a fairly simple dependence of the potentiometric selectivity on the concentration of the ionophore. This is illustrated by the dashed line in Figure 3 for an ionophore that forms 4:1 complexes with the target ion. For ionophore concentrations that are too low in comparison to the ionic site concentration, not all target ions in the ISE membrane can form complexes. As a result, the high concentration of unbound target ions in the membrane results in an ISE selectivity over ~~non-complexing~~noncomplexing interfering ions that is very close to the selectivity of an ionophore-free ion-exchanger membrane (for a definition of the latter, see p 1595 of ref. 5). As the ratio of ionophore -to -ionic sites is increased, there is a rapid increase in selectivity as the total ionophore concentration exceeds the minimum amount necessary to bind all target ions in the membrane. At these high ionophore-to-ionic site ratios, the free ionophore concentration in the membrane is large, and the free target ion concentration in the membrane is lowered by many orders of magnitude below the complex concentration. This is the region where the free ionophore and the complex buffer the free target ion concentration in the membrane, which is a characteristic of a well-functioning ISE.

Figure 2. Schematic representing the effect of multiple complex stoichiometries on the composition of ISE membranes. (A) The ionophore, L, forms exclusively 4:1 complexes with the target ion, I^+; the concentration of free I^+, $[I^+]$, is very small if the complex formation constant is high and the concentration of R^-, $[R^-]$, is smaller than ~~one-fourth~~1/4 of the total ionophore concentration, $[L_{tot}]$. (B) The ionophore forms complexes of 1:1, 2:1, 3:1, and 4:1 stoichiometry; the ratio of the concentrations of I^+ and the different complexes depends on the formation constants of the individual complexes and on the ratio of $[L_{tot}]$ and $[R^-]$.

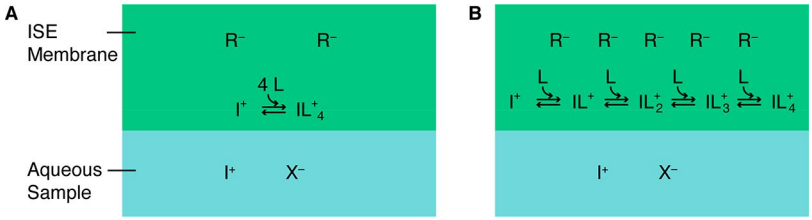
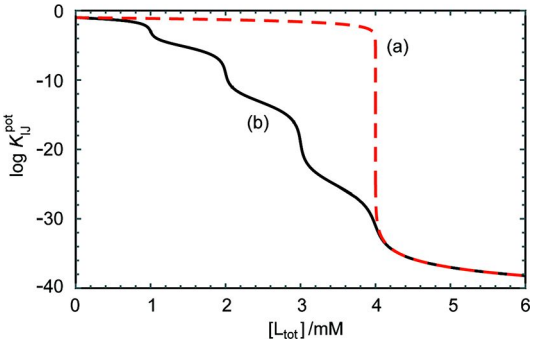


Figure 3. Selectivities, K_{IJ}^{pot}, of ISE membranes for an ion I^+ that forms multiple complexes with the ionophore, L, with respect to an interfering ion J^+ that does not bind to L. Shown are calculated values of log K_{IJ}^{pot} versus $[L_{tot}]$ for

$[R^{z_R}] = 10^{-3}$ M, $K_{IJex} = 0.1$, and (a) $\beta_{IL} = 10^{10}$ M^{-1}, $\beta_{IL2} = 10^{10}$ M^{-2}, $\beta_{IL3} = 10^{10}$ M^{-3}, $\beta_{IL4} = 10^{48}$ M^{-4}; and (b) $\beta_{IL} = 10^{18}$ M^{-1}, $\beta_{IL2} = 10^{32}$ M^{-2}, $\beta_{IL3} = 10^{42}$ M^{-3}, $\beta_{IL4} = 10^{48}$ M^{-4}.



While the above is well -documented, it has not been discussed in detail in prior literature how the potentiometric selectivity depends on the total membrane concentration of an ionophore that forms complexes of multiple stoichiometries with the target ion. Intuitively, one might expect that the selectivity for the target ion over a ~~non-complexing~~noncomplexing ion exhibits multiple steps when it is plotted against the ratio of the ionophore and ionic site concentrations, $[L_{tot}]/[R]$. As $[L_{tot}]/[R]$ is increased, steps may be expected whenever $[L_{tot}]/[R]$ exceeds a threshold value that allows for the exclusive formation of a $IL_n^{z_i + n z_L}$ complex, where z_i and z_L are the charges of the target ion and the ionophore, respectively, and n is the number of ionophore molecules forming a complex $IL_n^{z_i + n z_L}$ with ion i. At these specific $[L_{tot}]/[R]$ ratios, the bulk of the sensing membrane contains only negligibly small concentrations of free ionophore and complexes of other stoichiometry. A decrease in selectivity is expected at lower $[L_{tot}]/[R]$ ratios because complexes of lower stoichiometries are formed due to the lack of available ionophore, and a higher selectivity is expected at higher $[L_{tot}]/[R]$ ratios because either complexes of higher stoichiometries are formed or substantial concentrations of free ionophore are present.

Taking into account both electrically neutral and charged ionophores, specific values of $[L_{tot}]/[R]$ at which selectivity steps may be observed are $|n z_R / (z_i + n z_L)|$, where z_R is the charge of the ionic sites. For example, for a simple case of a monovalent anionic site, an electrically neutral ionophore, and a monovalent target cation that can bind up to ~~4~~four ionophore molecules, steps in the selectivity curve might be expected at $[L_{tot}]/[R]$ values of 1, 2, 3, and 4. Such selectivity steps are indeed predicted for unique combinations of complex stability constants and concentrations of ionic sites, as illustrated by the solid line in Figure 3 . (Notably, for a given set of complex stabilities, complexes of higher stoichiometries are favored by higher ionic site and ionophore concentrations, as illustrated by Figure S1 of the Supporting Information.)

However, as shown in the following, the absence of multiple distinct selectivity steps should not be misinterpreted as an indication that only complexes of one stoichiometry are being formed. Moreover, even when distinct selectivity steps are missing, the careful interpretation of a selectivity plot as depicted in Figure 3 can still give crucial information about the types and stabilities of complexes that are formed.

Calculation of Selectivity Coefficients and Membrane Compositions

~~Potentiometric selectivities and corresponding species concentrations in ISE membranes were calculated in this work for a complex-forming ion I^{z_I} and an interfering ion J^{z_J} that does not form complexes with L, as shown in Figures 3 to 10 and S1 to S4. To do so, the well-established phase boundary model [4, 19] was used, taking into account all relevant equilibria in the ISE membranes. Briefly, considering a monovalent target cation and an electrically neutral ionophore, complex formation constants, β_{IL_n}, were defined as~~

~~(1)~~

~~For an ionophore that forms 1:1, 2:1, 3:1, and 4:1 complexes, the mass balance for the ionophore in the ISE membrane is given by~~

~~(2)~~

~~Assuming a monovalent anion as ionic site, R⁻, electroneutrality in the bulk of the ISE membrane requires that~~

~~(3)~~

Potentiometric selectivities and corresponding species concentrations in ISE membranes were calculated in this work for a complex-forming ion I^+ and an interfering ion J^+ that does not form complexes with L, as shown in Figures 3−10 and S1−S4. To do so, the well-established phase boundary model[4,19] was used, taking into account all relevant equilibria in the ISE membranes. Briefly, considering a monovalent target cation and an electrically neutral ionophore, complex formation constants, β_{IL_n}, were defined as

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Assuming a monovalent anion as the ionic site, R^-, electroneutrality in the bulk of the ISE membrane requires that

(3)

The selectivity, K_{IJ}^{pot}, of the ISE membrane is given by ~~(eqn~~eq 33 in ref~~. 4)~~.

(4)

where $[I^+(I)]$ and $[J^+(J)]$ represent the concentrations of I^+ and J^+ on the ISE membrane side of the phase boundary layer between the ISE and the sample when I^+ and J^+ are measured separately, i.e., when the membrane contains either only I^+ and IL_n^+ complexes or only J^+ and JL_n^+ complexes. K_{IJex} is the equilibrium constant that describes the ion-exchange of uncomplexed target and interfering ions between the aqueous sample and the ISE membrane~~:~~

(5)

where $a_{I(aq)}$ and $a_{J(aq)}$ represent the activities of the respective ions in the aqueous phase.

The set of ~~eqns~~eqs 2~~,~~−~~4~~ 3~~,~~ 4~~,~~ and the ~~4~~four equations corresponding (for n = 1, 2, 3, and 4) to ~~eqn~~eq 1 cannot be solved algebraically to give K_{IJ}^{pot} as a function of $[L_{tot}]$. However, the set of ~~eqns~~eqs 2, 3, and the four equations corresponding to ~~eqn~~eq 1 can be readily solved to give $[L_{tot}]$ as a function of [L]. Moreover, K_{IJ}^{pot} can also be obtained as a function of [L] by (i) solving for $[I^+]$ the set of ~~eqn~~eq 3 and the four equations corresponding to eq 1, (ii) replacing in ~~eqn~~eq 4 the term $[I^+(I)]$ with the thus-obtained expression for $[I^+]$, and (iii) replacing in the resulting equation the term $[J^+(J)]$ with $[R^-]$ (because J^+ does not form a complex with L and, therefore, the two concentrations equal one another). So-called parametric plots of K_{IJ}^{pot} versus $[L_{tot}]$ can then be obtained by numerical calculation of corresponding K_{IJ}^{pot} and $[L_{tot}]$ pairs for a range of [L] values.

Parametric plots of the membrane concentrations of the various complexes in ISE membranes can be obtained similarly by (i) solving for $[I^+]$ the set of ~~eqn~~eq 3 and the ~~4~~four equations corresponding (for n = 1, 2, 3, and 4) to ~~eqn~~eq 1~~,~~ and (ii) solving ~~eqn~~eq 1 for $[IL_n^+]$ for the value of n of interest, followed by insertion of $[I^+]$ from (i) into the resulting equation. This gives $[IL_n^+]$ as a function of [L]. Parametric ~~plot~~plots of $[IL_n^+]$ versus $[L_{tot}]$ are again obtained upon numerical calculation of corresponding $[IL_n^+]$ and $[L_{tot}]$ pairs for a range of [L] values. For further details, see the Supporting Information.

Multiple Complexes IL_n^+ with Equal Stepwise Binding Constants

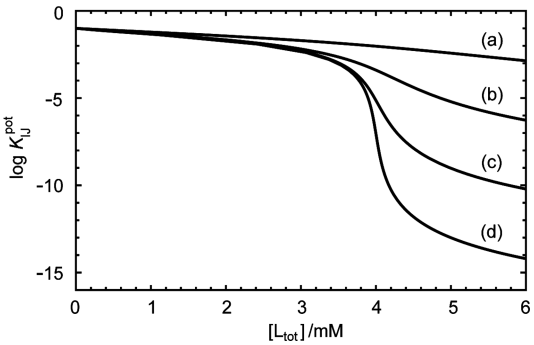
Let us first consider a system in which all four complexes IL^+, IL_2^+, IL_3^+, and IL_4^+ are formed, assuming that the stepwise binding constants K_{IL}, K_{IL2}, K_{IL3}, and K_{IL4} for each of these complexes are the same, i.e., if the free energy of binding of L to IL_{n-1}^+ to give IL_n^+ is identical for all n~~:~~

(6)

where $\beta_{IL_nIL_n}$ and $\beta_{IL_nIL_{n-1}}$ represent cumulative binding constants (i.e.: $\beta_{IL_nIL_n} = [IL_n^+]\,[I^+]^{-1}\,[L]^{-n}$). Figure 4 shows the predicted selectivity for four different systems with stepwise binding constants, $K_{IL_nIL_n}$, of 10^3, 10^4, 10^5, and 10^6 M^{-1} for (a), (b), (c), and (d), respectively. As expected, the larger the complex stability ~~is,~~ the larger the predicted

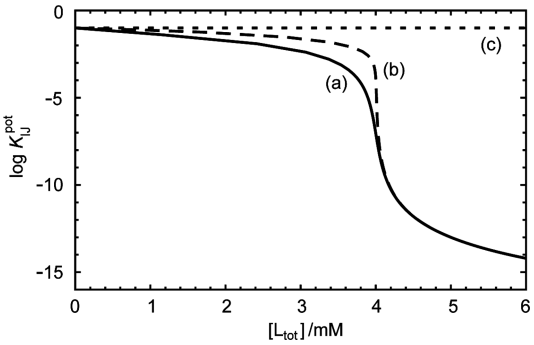
selectivity at high total ionophore concentrations. However, despite the formation of IL^+, IL_2^+, and IL_3^+ complexes of substantial stability, none of the selectivity curves ~~shows~~show more than one step, very unlike the pattern shown in Figure 3 (solid line).

Figure 4. Selectivities of ISE membranes for an ion I^+ that forms multiple complexes with the ionophore, L, with respect to an interfering ion J^+ that does not bind to L. Shown are calculated values of log K_{IJ}^{pot} versus $[L_{tot}]$ for $[R^-] = 10^{-3}$ M, $K_{IJex} = 0.1$, and (a) $\beta_{IL} = 10^3$ M^{-1}, $\beta_{IL2} = 10^6$ M^{-2}, $\beta_{IL3} = 10^9$ M^{-3}, $\beta_{IL4} = 10^{12}$ M^{-4}; (b) $\beta_{IL} = 10^4$ M^{-1}, $\beta_{IL2} = 10^8$ M^{-2}, $\beta_{IL3} = 10^{12}$ M^{-3}, $\beta_{IL4} = 10^{16}$ M^{-4}; (c) $\beta_{IL} = 10^5$ M^{-1}, $\beta_{IL2} = 10^{10}$ M^{-2}, $\beta_{IL3} = 10^{15}$ M^{-3}, $\beta_{IL4} = 10^{20}$ M^{-4}; and (d) $\beta_{IL} = 10^6$ M^{-1}, $\beta_{IL2} = 10^{12}$ M^{-2}, $\beta_{IL3} = 10^{18}$ M^{-3}, $\beta_{IL4} = 10^{24}$ M^{-4}.



For ionophore-to-ionic site ratios larger than 4, the selectivity predicted for a membrane in which IL^+, IL_2^+, IL_3^+, and IL_4^+ can all be formed is indistinguishable from the selectivity for the membranes in which only IL_4^+ is formed. This is illustrated by Figure 5 , which shows the solid line for log K_{IJ}^{pot} of membranes in which IL^+, IL_2^+, IL_3^+, and IL_4^+ can be formed and the dashed line for log K_{IJ}^{pot} of membranes in which only IL_4^+ can be formed. Figure 5 shows that below the ratio of a total ionophore -to -ionic site of 4:1, despite the possibility for the formation of IL^+, IL_2^+, and IL_3^+ complexes, the selectivity of the membrane in which IL^+, IL_2^+, IL_3^+, and IL_4^+ can all be formed (solid line) is only slightly higher than that for an ionophore-free ion-exchanger membrane (dotted line) and the membrane in which only IL_4^+ can be formed (dashed line).

Figure 5. Selectivities of ISE membranes for an ion I^+ that forms multiple complexes with the ionophore, L, with respect to an interfering ion J^+ that does not bind to L. Shown are calculated values of log K_{IJ}^{pot} versus $[L_{tot}]$ for $[R^-] = 10^{-3}$ M, $K_{IJex} = 0.1$, and (a) $\beta_{IL} = 10^6$ M^{-1}, $\beta_{IL2} = 10^{12}$ M^{-2}, $\beta_{IL3} = 10^{18}$ M^{-3}, $\beta_{IL4} = 10^{24}$ M^{-4}; and (b) $\beta_{IL} = 10^{-10}$ M^{-1}, $\beta_{IL2} = 10^{-10}$ M^{-2}, $\beta_{IL3} = 10^{-10}$ M^{-3}, $\beta_{IL4} = 10^{24}$ M^{-4}. (c) For comparison, selectivity of an ionophore-free ion-exchanger electrode.



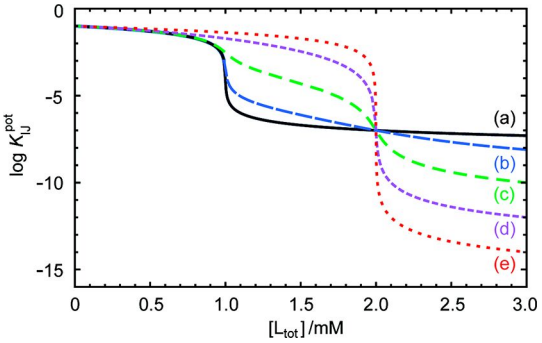
Plots of log K_{IJ}^{pot} versus $[L_{tot}]$ in systems in which IL_n^+ complexes are formed with identical stepwise complex formation constants, $K_{IL_{n-1}IL_n}$, also show an absence of multiple steps when the maximum number of ionophore molecules allowed to bind to I^+ is varied between 1 and 4 (see Figure S2 of the Supporting Information for systems with $K_{IL_{n-1}IL_n} = 10^6$ M^{-1}).

Stepwise Binding Constants Decreasing in Strength with Stoichiometry

Comparison of Figures 3 , 4, and S2 suggests that steps in the plot of the selectivity versus the ionophore-to-ionic site ratio are only possible if the stepwise binding constants decrease with increasing complex stoichiometry. Even if that is true, a selectivity step is not always observed though. This is illustrated in Figure 6 for a system in which only 1:1 and 2:1 complexes can be formed. For all five sets of stability constants, β_{IL} has the same value of 10^9 M^{-1}. For $K_{IL2} = 10^{10}$ M^{-1} (a) and $K_{IL2} = 10^4$ M^{-1} (b), the 1:1 complex dominates how the selectivity depends on the ionophore concentration, resulting in a rapid increase in selectivity only at an ionophore-to-ionic site ratio of 1:1. The opposite is true for $K_{IL2} = 10^8$ M^{-1} (d) and $K_{IL2} = 10^{10}$ M^{-1} (e), for which a rapid increase in selectivity is seen only at an ionophore-to-ionic site ratio of 2:1. Two separate distinctive jumps in selectivity at ~~the~~ ionophore-to-ionic site ratios of 1:1 and 2:1 are observed only for $K_{IL2} = 10^6$ M^{-1} (c). This is consistent with the conclusion that multiple selectivity steps are only possible if the stepwise binding constants decrease with increasing complex stoichiometry.

Interestingly, the concentrations of the membrane species corresponding to Figure 6 (shown in Figure S3 of the Supporting Information) show that at ~~the~~a ionophore-to-ionic site ratio of 1:1 there is a substantial concentration of IL^+ for all of the K_{IL2} values considered (99.4, 94.0, 61.2, and 13.7% of the total ionophore concentration for ~~the~~ values of K_{IL2} of 10^4, 10^6, 10^8, and 10^{10} M^{-1}, respectively). Even when K_{IL2} exceeds K_{IL} by ~~one~~1 order of magnitude and the selectivity appears to be clearly indicative of 2:1 complexation (i.e., curve (e)), the ratio of $[IL_2^+]$ to $[IL^+]$ at ~~the~~a total ionophore-to-ionic site ratio of 1:1 is still only 43.2 : 13.7. This example illustrates how easily multiple complex stoichiometries can remain unrecognized in a qualitative interpretation of log K ~~IL~~IL$_n$ versus $[L_{tot}]$ relationships.

Figure 6. Selectivities of ISE membranes for an ion I^+ that forms IL^+ and IL_2^+ complexes with the ionophore, L, with respect to an interfering ion J^+ that does not bind to L. Shown are calculated values of log K_{IJ}^{pot} versus $[L_{tot}]$ for $[R^-] = 10^{-3}$ M, $K_{IJex} = 0.1$, $\beta_{IL} = 10^9$ M^{-1}, and (a) $\beta_{IL2} = 10^{10}$ M^{-2}, (b) $\beta_{IL2} = 10^{13}$ M^{-2}, (c) $\beta_{IL2} = 10^{15}$ M^{-2}, (d) $\beta_{IL2} = 10^{17}$ M^{-2}, and (e) $\beta_{IL2} = 10^{19}$ M^{-2}.

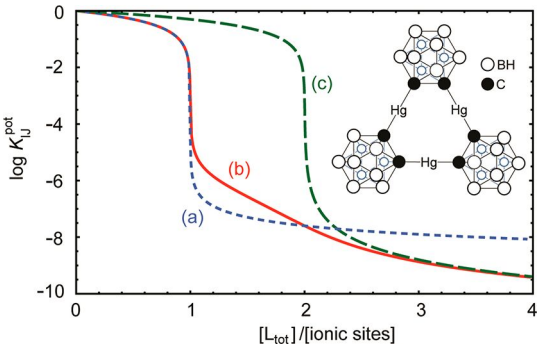


~~The~~ Example of [9]Mercuracarborand-3 ISEs

An experimental example that illustrates how easy it can be to overlook ionophores that form complexes of multiple stoichiometries with the primary ion is given by [9]mercuracarborand-3. An initial report on ISEs based on this ionophore reported 1:1 complex formation with Cl^-.[46] A later study of optode membranes doped with this ionophore found inconsistencies and clarified that this ionophore forms 1:1 and 2:1 complexes with Cl^-, with overall complex formation constants of $\beta_{IL} = 10^{9.9}$ M^{-1} and $\beta_{IL2} = 10^{13.4}$ M^{-2}, respectively. [21,22] ~~[21–22]~~ Using these values of β_{IL} and β_{IL2} and adapting the model described above for the [9]mercuracarborand-3 system, the dependence of log K_{ClJ}^{pot} on the total ionophore concentration as shown by curve (b) in Figure 7 is predicted. For comparison, curves (a) and (c) show log K_{ClJ}^{pot} as calculated for hypothetical ionophores that form either only 1:1 or only 2:1 complexes, respectively, using the same complex formation constants as those for (b). Qualitatively, the most noticeable feature of curve (b) is the abrupt change in selectivity at the ionophore-to-ionic site ratio of 1:1. A second large step in selectivity is missing. This could easily be misinterpreted as an indication for unique 1:1 complex stoichiometry. However, as the comparison of curves (b) and (a) shows, log K_{ClJ}^{pot} is noticeably larger for ionophore-to-ionic site ratios between 1 and 2 than for a system with unique 1:1 stoichiometry. Moreover, at ionophore-to-ionic site ratios larger than 2, log K_{ClJ}^{pot} is noticeably smaller than that for unique 1:1 stoichiometry. Quite remarkable is also the substantial increase in selectivity (i.e., decrease in log K_{ClJ}^{pot}) in the range from ionophore-to-ionic site ratios of 1 to 2, as compared to a system in which only 2:1 complexes are formed (i.e., curve (c)), despite the fact that the complexation constant K

$_{ClL2}$ is ~~with~~that $10^{3.5}$ M^{-1} relatively small in comparison to the K_{ClL} of $10^{9.9}$ M^{-1}. The comparatively weak stability of the 2:1 complex is reflected by the rather modest decrease in log K_{ClJ}^{pot} from curve (a) to curve (c) at high total ionophore concentrations. Indeed, at an ionophore-to-ionic site ratio of 2:1, 11% of the ionophore is in its free form, while at the ionophore-to-ionic site ratio of 1:1 only 0.06% of the ionophore is in its free form, which is consistent with a relatively low affinity of ClL^- for a second ionophore ligand. Arguably, the reported conclusion that the 2:1 complex is "extremely stable" is correct in the sense that ClL_2^- formation from Cl^- and two ionophore molecules can result in Donnan failure. However, with a view to formation of ClL_2^- from ClL^- and L, the ClL_2^- complex has only a comparatively low stability.[22] (Figure S4 of the Supporting Information depicts for the [9]mercuracarborand-3 system the concentration of all membrane species as a function of the ratio of the ionophore and ionic sites concentrations.)

Figure 7. Selectivities of ISE membranes for an ion I^- that forms IL^- and IL_2^- complexes with the ionophore, L, with respect to an interfering ion J^- that does not bind to L. Shown are calculated values of log K_{IJ}^{pot} versus $[L_{tot}]/[\text{ionic sites}]$ for $[R^+] = 5 \times 10^{-3}$ M, $K_{IJex} = 1$, and (a) $\beta_{IL} = 10^{11.3}$ M^{-1}, $\beta_{IL2} = 10^{-10}$ M^{-2}; (b) $\beta_{IL} = 10^{9.9}$ M^{-1}, $\beta_{IL2} = 10^{13.4}$ M^{-2}; and (c) $\beta_{IL} = 10^{-10}$ M^{-1}, $\beta_{IL2} = 10^{13.4}$ M^{-2}. Inset: Structure formula of [9]mercuracarborand-3.



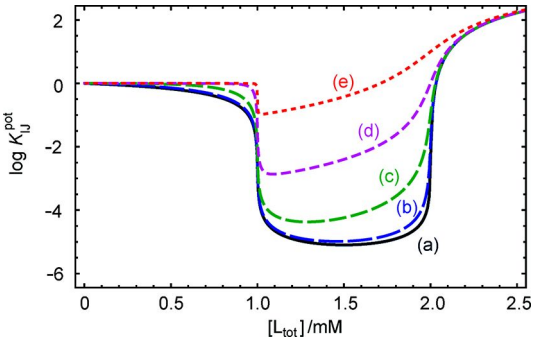
Site Optimization in the Case of Primary and Interfering Ions ~~That~~that Form Complexes of Multiple Stoichiometries

One of the most important tasks in developing a new ISE is the choice of the optimum ratio of ionophore and ionic sites, so that the highest possible potentiometric selectivity is achieved. While this process was entirely empirical in the early days of ISE development, guidelines for optimum ionophore-to-ionic site ratios were introduced first for electrically neutral ionophores [14–16] and subsequently for electrically charged ionophores. [17–18] Even when complex stoichiometries are not known prior to potentiometric measurements, those guidelines are extremely useful because, based on educated guesses of probable stoichiometries, they provide for each system of interest a small number of ionophore-to-ionic site ratios that are most likely to provide the highest selectivities. Unfortunately, those guidelines no longer apply the same way if the primary ion, interfering ion, or both ~~form~~forms complexes of more than one stoichiometry.

An example that illustrates this is given by ISE membranes doped with an ionophore that binds a monovalent primary cation, I^+, with 1:1 stoichiometry and a monovalent interfering ion, J^+, with both 1:1 and 2:1 stoichiometry. Curve (a) in Figure 8 shows the predicted log K_{IJ}^{pot} as a function of the total ionophore concentration for the case of extremely weak 1:1 but very stable 2:1 complexes of J^+ ($\beta_{IL2} = 10^{15}$ M^{-2}). Established theory predicts the highest selectivity for this system for 71 mol % ionic sites with respect to the ionophore,[18] which in Figure 8 (calculated for an anionic site concentration of 1.0 mM) corresponds to a total ionophore concentration of 1.41 mM. Allowing also for 1:1 complex formation of J^+ with complex stabilities of β_{JL} of 10^7, 10^8, 10^9, and 10^{10} M^{-1} not only gradually worsens the optimum selectivity but ~~it~~ also shifts the selectivity optimum steadily closer and closer to a total ionophore concentration of 1.0 mM (curves (b) ~~to (~~e)). Recognizing this shift in the optimum concentration of ionic sites is important for ~~the~~ optimization of the ISE's selectivity. For example, the inadequate assumption of exclusive 2:1 complex formation for J^+ and the ensuing choice of 71 mol % ionic sites based on traditional ionic site theory would give a log K_{IJ}^{pot} of ~~–~~0.56 for $\beta_{JL} = 10^{10}$ M^{-1} (curve (e)), whereas the optimum site ratio of 98% is predicted to give a K_{IJ}^{pot} of ~~–~~0.98.

Figure 8. Selectivities of ISE membranes for a primary ion I^+ that forms only IL^+ complexes ($\beta_{IL} = 10^9$ M^{-1}) with the ionophore, L, with respect to an interfering ion J^+ that ~~that~~ forms both JL^+ and JL_2^+ complexes with L ($\beta_{IL2} = 10^{15}$

M−2). Shown are calculated values of log K_{IJ}^{pot} versus [L_{tot}] for [R−] = 10^{-3} M, K_{IJex} = 1, and (a) $\beta_{JL} = 10^{-10}$ M^{-1}, (b) $\beta_{JL} = 10^{7}$ M^{-1}, (c) $\beta_{JL} = 10^{8}$ M^{-1}, (d) $\beta_{JL} = 10^{9}$ M^{-1}, and (e) $\beta_{JL} = 10^{10}$ M^{-1}.



Another notable fact illustrated by curve (e) is that ISE membranes with an optimized ionophore-to-site ratio may be selective for I^+ over ion J^+ if the ionophore forms a 2:1 complex only with J^+, even when the 1:1 complex of the primary ion, I^+, is less stable than the 1:1 complex with the interfering ion, J^+. It is interesting to consider the reasons for this selectivity at the molecular level. In the case of an ISE membrane with the optimized 71 mol % anionic site concentration and an ionophore that forms only 1:1 complexes with I^+, exposure of this membrane to aqueous solutions of I^+ results in 71% of the ionophore in the membrane bulk forming complexes with I^+, and 29% of the ionophore remaining in the uncomplexed form. If the same membrane is exposed to samples that contain an ion J^+ that forms only 2:1 complexes, all of the ionophore is in the form of the complex JL_2^+, and the membrane contains an additional 21 mol % uncomplexed J^+. The excess of ionophore in the case of I^+ exposure combined with the excess of uncomplexed J^+ in the case of J^+ exposure is the cause for the high selectivity for I^+ over J^+. Instead, if the ion J^+ forms both 2:1 and 1:1 complexes, exposure of this membrane with 71% ionic sites to aqueous solutions of J^+ results in 58% of the ionophore forming 2:1 complexes with J^+ and 42% of the ionophore forming 1:1 complexes with J^+. The good selectivity for I^+ over J^+ is the result of an excess of ionophore in the case of I^+ exposure, combined with the extremely low concentration of free ionophore in the case of J^+ exposure (but not a large concentration of uncomplexed J^+ in the bulk of the ISE membrane). Because it appears improbable that an ionophore that forms 2:1 complexes with an ion will not form 1:1 complexes at all, the ISE literature likely contains a substantial number of publications that failed to recognize complexes of multiple stoichiometries for a given ion.

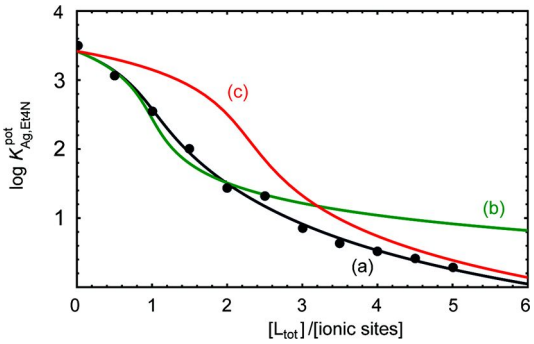
Fluorophilic Ag^+ Ionophore **2**

A detailed study of potentiometric selectivities over a large range of ionophore-to-ionic site ratios has not been performed for any of the above-mentioned systems in which a primary ion forms complexes of multiple stoichiometries. To this end, we reinvestigated the properties of the fluorophilic Ag^+ ionophore **2**. We previously showed that ISEs with fluorous membranes doped with **2** exhibit selectivities ~~of nine to eleven~~9−11 orders of magnitude over those of K^+, Na^+, and Cu^{2+}.[40,47,48] For this work, we focused on the selectivities for Ag^+ over the tetraethylammonium ion, Et_4N^+, because we wanted to avoid complications from multiple stoichiometries for both the primary and the interfering ion. While tetraalkylammonium ions have been shown to bind in fluorous solvents to trialkylamine derivatives by formation of hydrogen bonds of the type R_3N^+−C(R)−H···NR_3 and should not be considered inert under all circumstances,[49] binding of Et_4N^+ to thioethers is not a concern. Thioethers have a pK_a in water of approximately −5.4 (value estimated for $(CH_3)_2SH^+$),[50] a basicity that is approximately 15 orders of magnitude lower than that for trialkylamines. Therefore, Et_4N^+ was assumed for this work to be an ion that does not bind to the ionophore.

Figure 9 shows log $K_{Ag,Et4N}^{pot}$ for ionophore-to-ionic site concentration ratios from 0 to 4. The experimental data were fitted with a model taking into account AgL^+ and AgL_2^+ complexes. As curve (a) shows, the fit is very good, suggesting that the bidentate ionophore **2** forms a tetracoordinated Ag^+ complex and that there is no need for consideration of complexes of higher stoichiometry. This is in agreement with the literature, which reports a strong preference of Ag^+ for low coordination numbers (see ref. 40 and references cited therein).

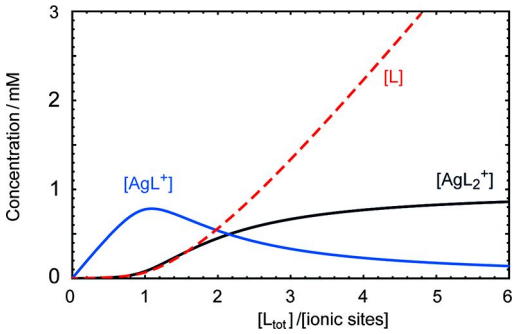
Figure 9. ISE membrane consisting of ~~perfluoroperhydrophenanthrene~~perfluoroperhydrophenanthrene doped with ionic sites **1** and ionophore **2**: Potentiometric selectivities for Ag^+ over Et_4N^+ as a function of the ratio of ionophore and ionic sites ([R^+] = 10^{-3} M~~)~~;, determined with the separate solution method (see Table S1 in the ~~Supporting In-~~

~~formation~~ Supporting Information for numerical values). (a) Experimental log $K_{Ag,Et4N}^{pot}$ values were fitted with the model described in the text, giving the following parameters: $K_{Ag,Et4N,ex}$ = ~~2.6x10~~2.6 × 10^3, β_{AgL} = 7.9 × 10^4 mol^{-1} kg^{-1}, and β_{AgL2} = 1.2 × 10^8 mol^{-2} kg^{-2}. Also shown are selectivities as predicted for the same stability constants but formation of (b) 1:1 complexes only (i.e., β_{AgL} = 7.9 × 10^4 mol^{-1} kg^{-1}, β_{AgL2} = 10^{-10} mol^{-2} kg^{-2}) or (c) 2:1 complexes only (i.e., β_{AgL} = 10^{-10} mol^{-1} kg^{-1}, β_{AgL2} = 1.2 × 10^8 mol^{-2} kg^{-2}).



The fitted values of the stepwise complex formation constants K_{AgL} and K_{AgL2} of 7.9 × 10^4 and 1.5 × 10^3 mol^{-1} kg^{-1}, respectively, are consistent with a common observation for organometallic complexes, i.e., that $K_{IL} > K_{IL2}$. Note that the value of K_{AgL2} is small enough to result in a significant increase in selectivity near the ionophore-to-ionic site ratio of 1:1, which would not be expected in the hypothetical case of exclusive 2:1 complex formation with the same β_{AgL2} (curve (c)). However, K_{AgL2} is also large enough to cause a substantial increase in selectivity at high ionophore concentrations, as compared to the hypothetical case of exclusive 1:1 complex formation with the same value of β_{AgL}, as illustrated in Figure 9 by curve (b). As shown in Figure 10 , in the range of ionophore-to-ionic site ratios from 1 to 5, the cause for the gradual but substantial increase in selectivity is the increase in free ionophore concentration, which steadily changes the ratio of the AgL^+ and AgL_2^+ complex concentrations from 0.10 to 0.84 and 4.77 at the ionophore-to-ionic site ratios of 1:1, 2:1, and 5:1, respectively.

Figure 10. Concentrations of the free ionophore **2** and its complexes with Ag^+ as calculated from the fit of log $K_{Ag,Et4N}^{pot}$ shown in Figure 9 .



~~CONCLUSIONS~~Conclusions

With few exceptions, ~~the~~ ISE literature has overlooked in the past the concurrent formation of primary ion complexes with multiple stoichiometries. This is surprising because typically chemical interactions that lead to the formation of IL_n^+ complexes will also stabilize complexes of a lesser stoichiometry. Because complexation equilibria with $K_{IL_nIL_n}$ ~~>>>~~ ≫ $K_{IL_nIL_{n-1}}$ are few, exclusive formation of complexes such as IL_2^+ or IL_3^+ is unlikely unless the ionophore is used in excess (as illustrated in Figures 6 and S2).

The failure to notice the possible formation of IL_{n-1}^+ complexes of the *primary* ion is of lesser concern if the ratio of ionophore and ionic site is optimized in view of the formation of IL_n^+ complexes. However, if $K_{IL_nIL_n}$ is not sufficiently large, IL_n^+ will coexist with IL_{n-1}^+. In such a case, a higher potentiometric selectivity will be observed at

ionophore-to-ionic site ratios that are larger than what one might expect from the n:1 stoichiometry alone (as shown for [9]mercuracarborand-3 in Figure 7 and for Ag^+ ionophore **2** in Figures 9 and 10). Formation of JL_{n-1}^+ complexes of the *interfering* ion cannot be ignored either as that can affect the ionophore-to-ionic site ratio that provides the optimum selectivity (as illustrated in Figure 8).

To ~~assure~~ensure that ISE membranes are formulated to provide the highest possible selectivities with a given ionophore, experimental selectivities should be determined for a range of ionophore-to-ionic site ratios. Plots of log K_{IJ}^{pot} versus $[L_{tot}]$ are unlikely to exhibit multiple abrupt changes in log K_{IJ}^{pot} that indicate different complex stoichiometries (as for the hypothetical example of Figure 3), but fits of experimental selectivities can provide both stoichiometries and complexation constants (as shown, e.g., in Figure 9). Alternatively, potentiometric selectivities for systems with multiple complex equilibria may be predicted mathematically using complex formation constants determined with other techniques, such as the sandwich membrane technique, optical methods (such as for Figure 7), or ion transfer voltammetry. [51–54]

Whichever experimental approach is taken, investigators should be prepared to consider the concurrent presence of multiple complexes for a given ion, be it the primary ion or interfering ions. Failure to do so can ~~result~~ not only result in the preparation of ISE membranes with inferior selectivity, but it may also provide misleading guidance for the design of new and better ionophores.

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Supporting Information

~~Supporting Information~~
~~The Supporting Information is available free of charge on the ACS Publications website.~~Log~~The~~ ~~K~~Supporting$_{IJ}^{pot}$ ~~in systems analogous to~~Information is available free ~~Figure 3 but with different ionic site concentrations. Log K_{IJ}^{pot} in systems in which IL_n^+ complexes are formed with identical stepwise complex formation constants. Species concentrations in ISE membranes corresponding to Figures 6 and 7 . Numerical values of K~~charge$_{Ag,Et4N}^{pot}$ ~~corresponding to Figure 9 . Details~~ on the ~~preparation~~ACS Publications website ~~of parametric plots~~at DOI: 10.1021/acs.analchem.8b05196 .

Log K_{IJ}^{pot} in systems analogous to Figure 3 but with different ionic site concentrations, log K_{IJ}^{pot} in systems in which IL_n^+ complexes are formed with identical stepwise complex formation constants, species concentrations in ISE membranes corresponding to Figures 6 and 7, numerical values of $K_{Ag,Et4N}^{pot}$ corresponding to Figure 9 , and details of the preparation of parametric plots (PDF)

~~Notes~~
The authors declare no competing financial interest.

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