UNDERSTANDING ION SELECTIVE SENSORS

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CHAPTER 1

INTRODUCTION TO ANALYTICAL POTENTIOMETRIC

ELECTROCHEMISTRY

Analytical Potentiometric Ion Selective Sensors

Ion selective sensors are a type of analytical potentiometric electrochemical sensor that is of great interest for use in academia and industry, as they offer a convenient and low-cost option for performing ion measurements in liquid media, both in the laboratory and in the field.[1-3] Alternate analytical techniques that are also commonly employed for such ion analysis in liquid systems include methods such as inductively coupled plasma mass spectrometry (ICP-MS), X-ray fluorescence (XRF), atomic absorption spectroscopy (AA), colorimetry, and other more classical analytical techniques, such as gravimetry.[4,5] While these methods are often unsurpassed for accuracy, detection limit, linearity and selectivity, they are also often significantly too expensive and tedious to be conducted with great regularity and are generally not very portable nor suitable for online continuous measurements. Ion selective sensors allow for both a lower cost and more portable ion selective analysis method. Recent improvements have bridged the gap in analytical quality differences between these higher cost benchtop laboratory analyzers and the lower cost electrochemical measurement systems for laboratory and industry.[5-11] Greater portability also makes ion selective sensors of great interest for remote environmental monitoring.[10]

While very many of the current ion selective sensors could benefit from further develop and improvement, the need for online measurement of nitrate is of broad

interest for environmental measurement and process control at large and constitutes a special area of the current research. Nitrate ion measurement is an area of intense interest due to the impact on biological systems of elevated nitrate levels caused by human activities like farming through the use of fertilizers such as ammonium nitrate and industrial process plant discharge from nitrogen-containing processes.[12,13] The ability to monitor the nitrate levels at many points of potential intrusion into the ground water tables, often measured at locations such as remote well sites, in a low-maintenance cost-effective manner is of interest to many entities such as the EPA and other similar government bodies that promote the health and well being of the citizens and the environment at large in any potentially affected areas.[14-20] It is the lack of such a cost-effective field measurement system that has ultimately restricted the EPA's ability to mandate such a compliance measurement on a broader basis.

Several obstacles remain before the widespread adoption of nitrate ion selective sensors for such measurements. The most notable is the need to achieve sufficient selectivity over the common interference of chloride ions, to achieve sufficient stability to reduce the uncertainty of the measurement, and finally to achieve sufficient sensitivity to detect down to the low parts per million (ppm) and even parts per billion (ppb) levels of interest. In particular, the reduction of sensor drift (which must be corrected by time and labor-intensive recalibration) and a reduction in membrane degradation (which must be addressed by frequent replacement of the sensor) are both critical factors to making any practical continuous environmental measurement possible with such ion selective sensors.

Ion selective sensors have been used for analytical determination of a wide variety of ions since the 1900s. With their utility and simplicity ion selective sensors have replaced other wet analytical methods that were often far slower and more cumbersome to perform. Although it would be impossible to give a comprehensive review of previous work here, a brief overview is desirable to properly assess the areas of interest in the current literature.[21]

<div align="center">Types of Ion Selective Electrodes</div>

Most of the traditional solid-state ion selective analytical potentiometric electrochemical sensors are classified as electrodes of the second kind. Electrodes of the first kind (a metal electrode in contact with a solution of its own metal ion, $[M|M^+]$) do not exhibit a very selective behavior, can often easily be oxidized, and may well also be soluble in many potential solutions of interest for measurement.[22] As such, electrodes of the first kind are rarely used for analytical determination, except in some very special situations. In contrast, electrodes of the second kind being those that respond to changes in concentration by formation of a complex offer the stable and reversible system necessary to achieve a long-lasting and selective electrode potential. This means in practical use that a metal is in contact with sparingly soluble salt of that metal. Some common examples include $Ag(s)|AgCl(s)|Cl^-(aq)||$ and $Pt(s)| Hg(l)|Hg_2Cl_2(sat),KCl(Sat)|Cl^-(aq)||$. This second electrochemical system with platinum and mercury is commonly referred to as calomel. Only the $Ag(s)|AgCl(s)|Cl^-(aq)||$ type electrode is commonly used for field measurements due to the high temperature coefficients of the calomel electrode and some inherent problems with the

use of mercury for sensors that may be damaged and allow this toxic metal to leak into the measured solution. The calomel electrode is most commonly used for laboratory applications due to very good long term stability and since most laboratory tests are run at room temperature (25 degrees Celsius) so that the higher temperature coefficient of this electrode is not a critical factor.[22]

Traditional solid-state ion selective electrodes of the second kind will typically also possess an internal filling solution that will contribute to the overall electrochemical potential of the electrode. Electrodes that have a simple passive barrier such as a porous ceramic, glass or plastic frit are typically used as reference electrodes. These passive (non-selective) barriers are also commonly referred to by the more industry standard terms "junctions," where the number of junctions for a particular electrode is referred to as single junction (one barrier), double junction (two barriers), triple junction (three barriers) and so forth. Electrodes that have an ion selective membrane of some variety (glass, crystalline or polymeric) as the barrier between the electrode of the second kind are commonly referred to as the measuring ion selective electrode. The speed of response and reversibility of any measuring electrode are of critical importance for accuracy and reproducibility of its use in any electrochemical measurements for the purpose of ion analysis.[23] The classical Nernst equation defines the change in the cell potential of an electrochemical system and is shown below in Equation 1.

$$E = E^{0}(T) + (RT/zF) \ln (a(OX) / a(RED)) \qquad (1)$$

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In equation one above, E is the observed potential of the electrode in Volts, E^0 is the standard potential of the electrode in Volts at 25 degrees Celsius, R is the gas constant, T is the temperature in Kelvin, z is the charge on analyte ion, F is Faraday's constant, *ln* is the natural log, and *a(OX)* and *a(RED)* are the molar activity of the oxidized and reduced species, respectively.[24] It is clear that the potential is dependent upon temperature from inspection of the classical Nernst equation, as well as the activity of the species in solution. A simplified form of the Nernst equations can be obtained if only systems at 25 degrees Celsius are considered, with the activity of all solids and liquids taken to be unity, and having been transformed from natural log to base 10 log units. This simplified form is the commonly used form of the Nernst equation for measurements done at 25 degrees Celsius and was used for all work in this thesis.

It should be noted that in general either the oxidized species (OX) or the reduced species (RED) will be a solid, liquid or gas meaning that the equation can be further simplified to contain only one activity term. In the simplified case used for this research work where only one anion exists in a clean deionized (DI) water background, there will in fact only be one ion activity term that is used. For measurements in for a simple set of monovalent electrolyte species in DI water where [ION] is the mean electrolyte activity of the cation or anion, Equation 2 is a complete representation of the electrochemical potential for these specific conditions.

$$E = E^0 - 0.05916*log_{10} [ION] \qquad\qquad (2)$$

It should be noted that the -0.05916 constant which is valid at 25 degrees Celsius for such monovalent anion systems is the theoretical slope (mV per decade

response) of the electrode. Real electrodes will typically not exhibit such an ideal response, but more typically exhibit some percentage of this theoretical value such as 80 to 100%.[25] This percentage is commonly referred to as the sensor efficiency or slope and is one characteristic that is used to judge the quality of the ion selective sensor.

Some critical issues that arise with all ion selective sensors are detection limit, linear measurement range, and selectivity over interfering ions. In addition, the operational pH, temperature, and pressure limits of the sensor greatly determine its usefulness in real world industrial and laboratory applications. Another important criterion for the utility of any given sensor is the expected lifetime. The consideration of usable sensor lifetime and aging effects will be discussed in greater depth for the sensors fabricated in this thesis research project in the results and discussion chapter.

<div align="center">The Reference Electrode</div>

The ideal reference electrode is one where the potential is invariant with respect to any changes in ion concentration of the measured solution and invariant with respect to any changes in temperature. The hydrogen electrode is used to determine the potentials of other reference electrodes.[24] The very simple reversible electrochemical half-reaction for the hydrogen electrode is described in Equation 3.

$$2H^+(aq) + 2e^- \rightarrow H_2(g) \qquad\qquad (3)$$

Making the simple substitution into the general Nernst equation, the potential of the hydrogen electrode can be written as shown in Equation 4.

$$E_H = E°_H + RT/F*ln\left(a_H^+ / p_{H2}^{1/2}\right) \qquad\qquad (4)$$

In Equation 4 E_H is the potential of hydrogen electrode, $E°_H$ is the standard potential of the hydrogen electrode (by convention this is zero at all temperatures), a_{H+} is the activity of the hydrogen ions, p_{H2} is the partial pressure of the hydrogen gas, the R is the universal gas constant, the T is the temperature, in Kelvin, the F is the Faraday constant.[23,26] The general cell notation for the hydrogen electrode is $Pt(s) \mid H_2(g) \mid H^+(aq)$. More specifically, the cell potential for the hydrogen electrode is defined to be exactly zero if it has the condition as given below in Equation 5.

$$ \| \; Pt \mid H_2 \; (g, \; 1 \; atm) \mid H^+(aq), \; 1 \; M \qquad\qquad\qquad (5) $$
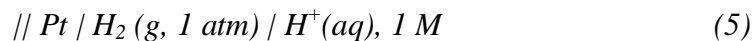
In the cell notation above *Pt* is platinum black, *H_2 (g, 1 atm)* is hydrogen gas at the concentration of one atmosphere wherein the partial pressure is 1 atm, and *H^+(aq), 1 M* is a pure solution of 1 Molar activity hydrochloric acid. This special case of hydrogen electrode cell is referred to as the standard hydrogen electrode (SHE), or the normal hydrogen electrode. It is assigned to have the potential of 0.000 Volts at all temperatures, because the quotient of the natural logarithm term *$(a_H^+ / p_{H2}^{1/2})$* is 1. The SHE is the reference potential standard against which all other electrochemical half-cells can be measured. An illustration of the hydrogen electrode can be found in Figure 1 for discussion and visualization purposes. Platinum black is usually prepared by platinizing platinum by electroplating elemental (shiny) platinum in chloroplatinic acid, although quite a number of other methods are also possible. Platinum black has excellent catalytic properties for conversion of hydrogen and oxygen diatomic gases in electrochemical redox reactions such as those required for a hydrogen electrode.[27]

Both the measuring electrode and the reference electrode contain oxidation and reduction half-cell reactions that exist in equilibrium, and cannot be measured separately from each other as there would not be a complete electrochemical cell to generate a potential.[23] The potential of the measuring electrode must be with respect to a particular reference electrode used to construct a complete electrochemical potentiometric cell. The ability to measure the relative potential differences between the measuring ion selective sensor and standard reference electrode is the foundation of modern liquid analytical electrochemistry.[28-30]

Unfortunately, although the standard hydrogen electrode (SHE) would certainly serve as an excellent reference electrode, as can be seen from inspection of Figure 1, the SHE is complicated, expensive and quite clearly neither very portable nor amenable to miniaturization. The goal of all modern reference electrodes is to obtain as closely as possible the invariance, stability and reproducibility of the standard hydrogen electrode, while achieving the features which are sorely lacking: namely, low cost, manufacturability, portability, and the ability to be miniaturized. Reference electrodes used for real world applications are generally electrodes of the second kind with electrolyte solutions serving as salt bridges to the measured solution with a barrier or "junction" that only permits ion mobility across the junction. The number physical barriers (junctions) is a commonly used parameter to signify the degree of inertness of the reference electrode to any measured solutions whose components could react with or otherwise render the electrode of the second kind inoperable. Various approaches have been undertaken for modern reference

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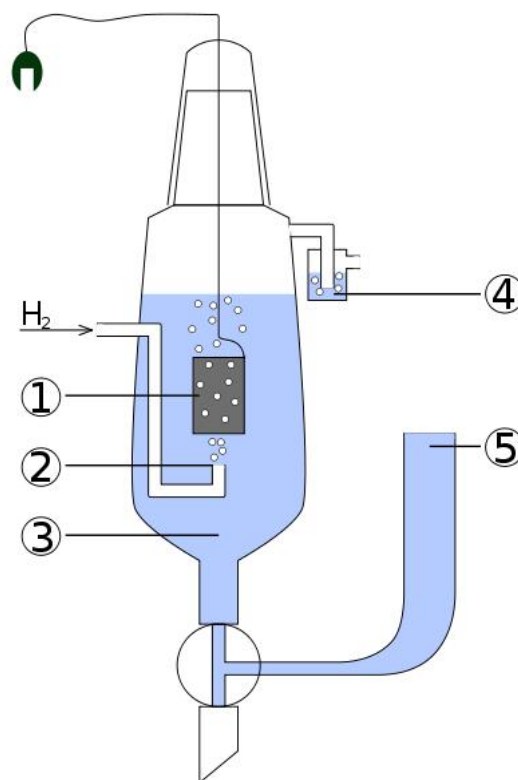
FIGURE 1. Idealized illustration of standard hydrogen electrode. In this illustration,[26] 1 represents the Platinum black electrode, 2 represents the Hydrogen gas, 3 represents the Acid solution (normally hydrochloric acid) with an activity of hydrogen ion (H^+) equal to mol per liter (1 Molar activity), 4 represents a Hydroseal for prevention of oxygen interference and 5 represents the Reservoir via which the second half-element of the galvanic cell should be attached. The function of component 5 is also commonly referred to as an electrochemical bridge.

This illustration is a public domain image.

electrodes, such as different types of ionically conductive gels and polymers, flowing electrolyte with a variety of passive barriers (junctions), and solid contact matrices, all to differing degrees of success.[28,29]

The reference junction potential, which is in part generated by the difference in ion mobility between cations and anion species across the barrier of the reference electrode, can cause significant errors for a number of systems and is more prominent for solutions of very low and very high ionic strength, and for systems with higher concentrations of divalent cations and divalent anions.[24] The single largest source of errors for most mature analytical potentiometric electrochemical measurement systems otherwise at stable equilibrium is in fact this junction potential uncertainty. To complicate real measurement further, often the reference electrodes exhibiting the smallest junction potential (such as flowing type systems) have some of the shortest lifetimes and are impractical for real world measurements outside the laboratory. Often the more rugged systems, with lower ion mobility that is required for more aggressive measured solutions, exhibit higher junction potentials that must be compensated by calibration methods, if such corrective schemes are feasible and repeatable. The most mobile ions in solution are the hydrogen ion and hydroxyl ion. This plainly explains why some of the highest junction potentials are observed in very high and very low pH solutions. Deviations from an ideal invariant reference electrode potential constitute a large percentage of measurement uncertainty. The typical classical reference electrode employs a porous ceramic or plastic interface which is impregnated with an electrolyte solution such as 4 Molar or saturated

potassium chloride (KCl) or an immobilized gel formulation based upon such an electrolyte solution that will behave in a well known manner with changes in temperature and ionic strength. This classical potassium chloride electrolyte inner filling solution is the most well characterized one for reference electrodes, although many others are possible.

The reference potential is most commonly generated by a silver wire that has been chloridized or been dipped into molten silver chloride. The potential of the reference electrode, while ideally invariant to the ion activity of the measured solution, is also a function of the inner filling solution and does, unfortunately, exhibit some dependence on the measured solution. Similar reference electrodes using mercurous chloride, mercury liquid and a platinum or silver electrode ($Pt|Hg| Hg_2Cl_2|Cl^-$) commonly called calomel are substituted for the typical silver silver-chloride reference electrodes ($Ag|AgCl|Cl^-$) for laboratory applications requiring higher accuracy. The more invariant and stable calomel reference electrode is not suitable for use outside of laboratory research applications due to its high temperature sensitivity, its difficulty to manufacture for field style configurations, and its well-known toxicity and disposal issues. The use of a flowing (aqueous electrolyte inner filling solution rather than an immobilized variety) 4 Molar potassium chloride calomel reference electrode is considered standard practice for research applications requiring high accuracy and reproducibility, and all measurements in this paper were made with such a reference electrode. The question of the most suitable field reference electrode for such measurements shall not be considered as it is outside of the scope of this research

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project. The issue of reference uncertainty will also not be considered, as there is no better commercially available reference electrode than the flowing quartz-fiber junction calomel used and it will be considered a truly invariant standard electrode.

<u>Traditional Laboratory Ion Selective Measurement Setup</u>

Figure 2 shows a traditional ion selective laboratory setup identical to the one used for all electrochemical experiments conducted for this thesis. The ion selective membrane is traditionally applied over a porous ceramic or plastic that has been bound to the PVC plastic body with a weak electrolyte inner filling solution, such as 0.01 or 0.001 Molar of an appropriate electrolyte for the particular ion selective measurement of interest, with a Ag|AgCl electrode. It should be noted that the absolute ion selective electrode potential response to the external solution (sample) is a function of the inner electrode filling solution, as is the reference electrode potential. The ion selective electrode and reference electrode have a body housing that is fabricated from a glass or plastic tube with suitable sealing. The two electrodes are typically suspended in the sample with a special holder so as not to touch each other or the walls of the beaker. The electromotive force (EMF) is measured by means of a special electrochemical mV meter able to amplify the very high impedance mV potential generated by the ion selective and reference electrode. The current generated between these two electrodes is about on the scale of picoamps (10^{-12} Amperes) meaning that instrument grounding, circuit isolation, and limiting leakage current are critical to ensure accurate tests.
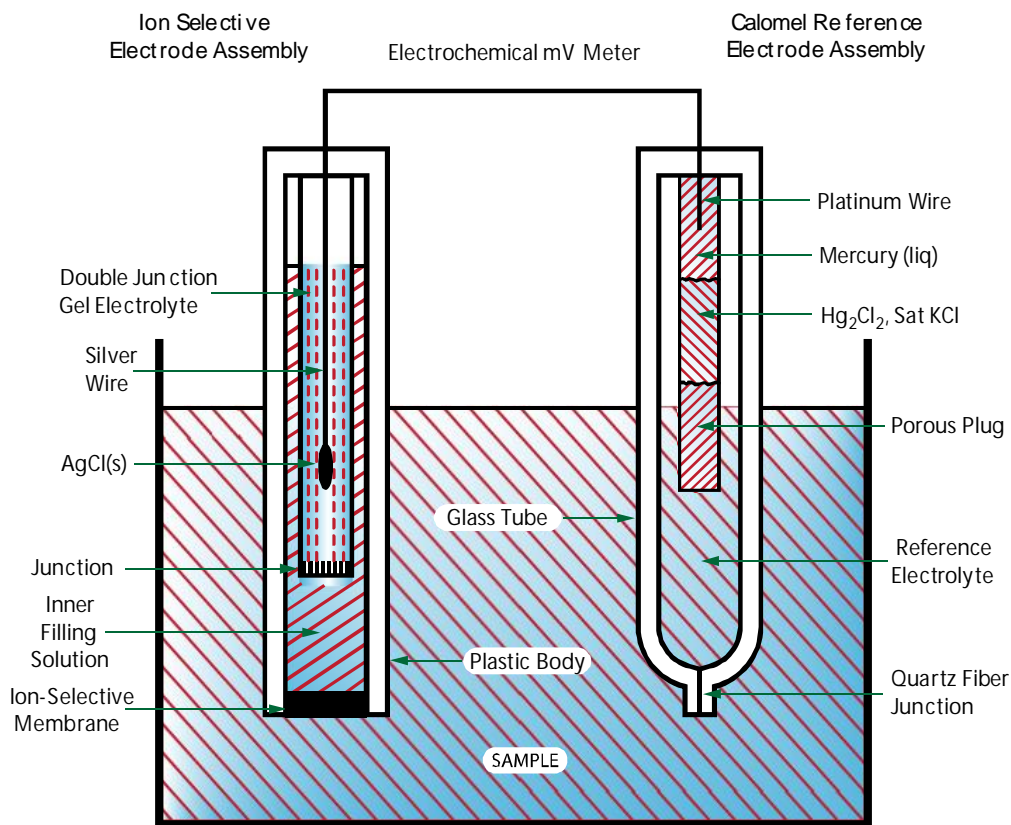
FIGURE 2. Idealized schematic diagram of the quintessential laboratory ion selective measuring circuit and cell assembly. As shown there is a double junction calomel reference electrode on the right and a double junction ion selective measuring electrode on the left. Figure 3 will be a close-up Helmholtz electrical double layer model representation of the "Ion-Selective Membrane" portion of the measuring electrode on the left, including the same "Inner Filling Solution and "Sample Solution" as shown in Figure 2.

Types of Ion Selective Sensors

Ion selective sensor membranes are typically categorized into one of the three clasees: glass, crystalline and polymeric. Some other types may also be reported, but these three types are by far the most prevalent and pertinent. There will not be any discussion about the glass membrane herein except to state that they have been by far the most successful and widely used subset of analytical potentiometric ion selective sensors, finding uses from laboratory to industry, and as such they are considered a rather mature and robust technology. Other types of ion selective glass membranes reported include potassium and sodium, which have achieved some limited success as well, but pale in comparison to that of the glass pH membrane.

Crystalline ion selective membranes have been employed with great success. There is, however, a limited set of issues that inhibits their use for some applications, and only a select few cations and anions can be measured by use of crystalline ion selective membrane. Since their discovery, silver halide precipitate based ion selective crystalline membranes have become widely used for measurement of halide ions, and other related measurements that are possible with this ion selective membranes. These ion measurements that are feasible with such membranes include silver (Ag^+), chloride (Cl^-), bromide (Br^-), iodide (I^-), sulfide (S^{-2}), cyanide (CN^-), and thiocyanate (SCN^-). There also exists an analogous series of mercury salts that can perform the identical measurement, often with better performance. The mercury style crystalline membranes have not been as widely employed due to the typical issues surrounding the use of mercury. While this is not intended as complete list of all

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currently available silver halide based precipitates, these are the most commonly used and accepted ion selective electrodes of this class.[30] It should be noted that $Ag_2S|MS$ co-precipitates based ion selective electrodes (commonly referred to as electrodes of the third kind) where M is usually any divalent heavy metal cation that forms a stable sulfide precipitate such as lead, copper or cadmium have been investigated for quite some time with very limited success. Although these ion selective electrodes have been commercially available, their problems with drift, stability and redox sensitivity have prevented them from being employed to any significant extent.

The halide anions that can be sensed with this type of crystalline membrane are made from the highly purified silver or mercury salt prepared by a dilute precipitation reaction and then pressed into a disc under intensive pressure and vacuum. The performance characteristics for the lowest limit of detection is determined the solubility product of these sparingly soluble silver and mercury salts, and the selectivity coefficients are defined by the ratio of solubility products. The solubility products descend down the periodic table for the halide elements in group VII, meaning that silver chloride is the most soluble (worst detection limit for chloride anions) and silver iodide is the least soluble (best detection limit for iodide anions). Silver sulfide constitutes a special case and is in reality the least soluble of this series, although measurement of sulfide is problematic due to stability and pH considerations. In addition, lanthanum fluoride crystals also constitute a special case where such special crystals formed into a suitable disc can be used to measure fluoride anions. Fluoride ion selective sensors prepared from doped lanthanum fluoride crystal discs

are the gold standard for anion measurement, exhibiting the lowest limit of detection, linear measurement range and selectivity. In fact, there are essentially no interferences for fluoride ion selective sensors using such lanthanum fluoride crystals, except for very high concentration of hydroxide that actually destroys the crystal itself.

The Debye-Huckel ion activity model is commonly used to correct the differences between concentration and activity of a particular electrolyte. Although all ion selective electrodes only measure ion activity, they are typically calibrated with standards that are expressed in concentration units. The Debye-Huckel model expresses that only the ion activity of the cation and anion system as a whole can be determined, but not the individual activity for just the cation or anion species.[22,23] In special cases, the exact electrolytes (or mixture of electrolytes) should be specified as the counterion(s) will contribute to the overall activity coefficient of the system. Corrections accounting for the differences between concentrations and activity are necessary for the ranges where the Debye-Huckel activity coefficients differ significantly from unity. Most weak electrolyte systems have an activity coefficient very near unity for very dilute system (10^{-8} Molar) to solutions of about 10^{-2} or 10^{-1} Molar concentration. The 10^{-2} or 10^{-1} Molar concentration level, in turn, is often the practical limit of many ion selective sensors, or else the top end of the analytical range of interest. In most cases, such activity coefficient correction is not performed as it is not required, or serendipity renders it unnecessary. In cases where activity coefficient correction is in fact required, it is customary to fabricate calibration standards in units of apparent (activity coefficient corrected) concentration.

The Electrical Double Layer

Glass and solvent polymeric ion selective electrodes are a unique and distinct electrode type. The mechanism whereby the electrochemical potential of such electrode types is generated has been an area of interest for quite some time. The concept of an electrical double layer was originally proposed by Helmholtz back in the 1850s as an explanation for the charge accumulation and separation at the surface of a metal electrode in contact with an electrolyte solution of its own salt. For example, a simple case would be copper metal electrode in contact with a solution of copper sulfate as an electrode of the first kind. This model predicts that the excess of electrons on the surface of the metal electrode is charge balanced at the surface by a very close plane of positively charged ions. This charge separation forms the foundation of the electrical double layer theory (sometimes also called a Helmholtz double layer) which is considered to be an electrical capacitor. In a slight refinement, the modern Helmholtz electrical double layer takes into account the solvation effects by proposing an "inner Helmholtz plane" where the counterions have shed their solvation shells very close to the electrode (membrane) surface. The ions in the inner Helmholtz plane are also referred to as contact adsorbed. Any ions outside of this plane are referred to as the "outer Helmholtz plane" and are solvated (to various degrees) and contribute significantly less to the electrical double layer potential generation process. A variety of improvements to the basic Helmholtz model have been proposed by Gouy-Chapman and Stern that better explain the exact charge density and ion transitions between the inner and outer planes, although the

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fundamental concept of the modern Helmoltz model is sufficiently useful for visualization purposes of the basic concept of how a potential is generated at the surface of such an ion selective electrode (membrane).[31,32]

Figure 3 shows an idealized and simplified representation of the modern Helmholtz electrical double layer model for a neutral-carrier ionophore based ion selective membrane in contact with an inner filling solution and outer sample solution. The potential across the ion selective membrane is generated by the difference in activity between the electrical double layer at the inner and outer surface. As the activity of the inner filling solution is constant, the potential observed is then due solely to activity changes at the surface of the outer sample solution. In Figure 3, this electrical double layer model is shown together with a simplified model for the ion migration across a neutral carrier based solvent polymeric ion selective membrane. This ion migration across the membrane must be of a reversible nature so that solutions that are both more dilute and concentrated than the inner filling solution can be measured. The absolute (observed) potential is defined solely by the difference between the activity differences between the inner and outer solutions. As can be observed from this model, since the potential is generated only at the membrane surface, any perturbation to the homogeneity of the inside or outside surface will cause an unwanted instability or error to the potential. These perturbations include but are not limited to air bubbles, systems not at chemical or thermal equilibrium, an electrolytic potential (this phenomenon is typically called polarization of the membrane), or kinetic induced potential from high or irregular flow patterns.

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Modern Helmholtz Electric Double Layer Model

Plastic Body Housing

Inner Filling Solution

Compact Layer

Sample Solution

(Outer Helmholtz Plane)

Diffuse Double Layer

Inner Helmholtz Plane

Ion Selective Membrane

Inner Helmholtz Plane

Diffuse Double Layer

(Outer Helmholtz Plane)

C+   IA-   IA-   I   IA-   C+   IA-   IA-
IA-   C+   I   I   IA-   I   IA-   IA-   I   IA-
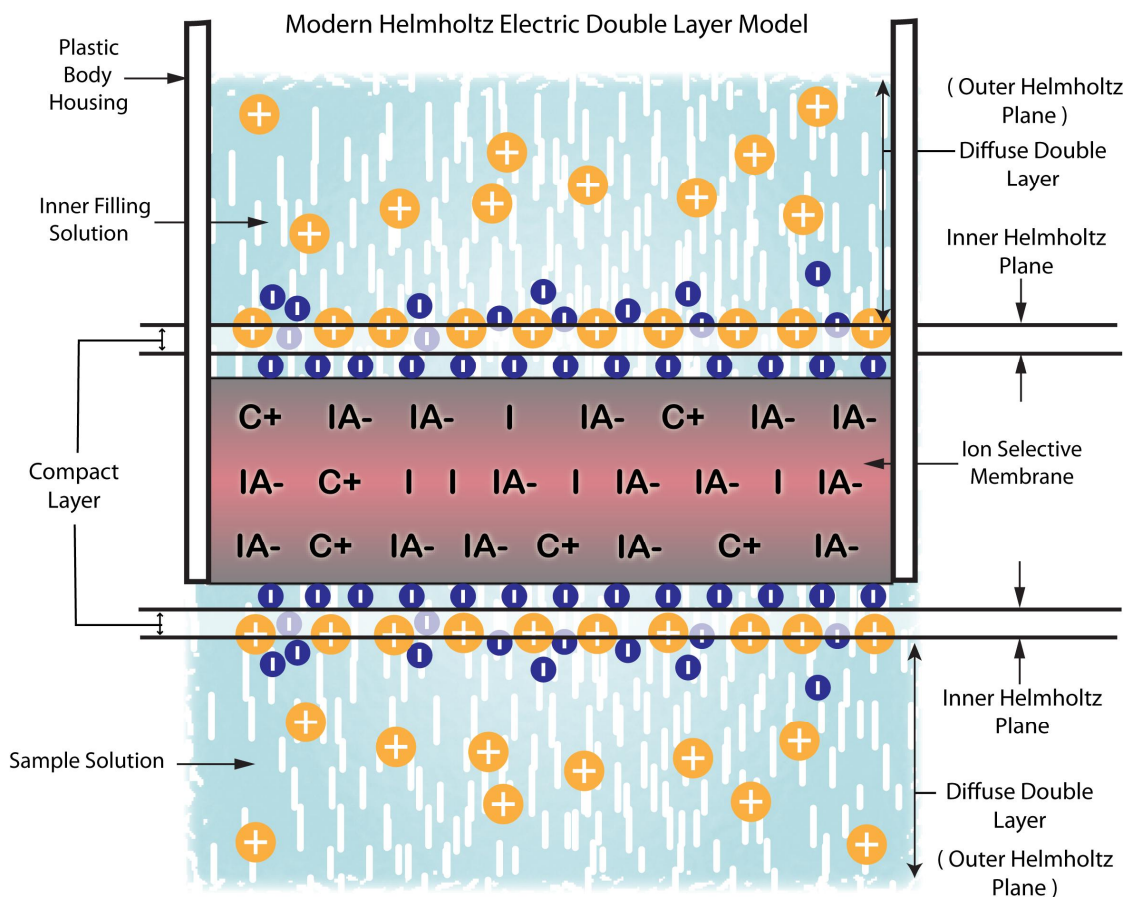IA-   C+   IA-   IA-   C+   IA-   C+   IA-

FIGURE 3. Illustration of electrical double layer in solvent polymeric ion selective sensor membranes. The schematic above illustrates two important processes that occur for a solvent polymeric ion selective sensor membrane. This first is the equilibrium processes that occur at the membrane surface as described by the modern Helmholtz electrical double layer model. The second is a cartoon style visualization of ions migrating across the ion selective membrane as they move from one binding site to another.[33]

Starting with the simplified model of ion migration across an ion selective membrane, the "C+" represents a large immobile organic cation (fixed), the "I" represents an unbound neutral carrier ionophore, and "IA-" represents the anion bound ionophore-ion complex. In this case, the anions (represented by the circles with negative sign) enter into the ion selective membrane and move to an unbound ionophore binding site, or else dislodge an existing anion from a bound site that causes that anion to likewise move to the next available binding site.

The modern Helmholtz electrical double layer model illustrated above expresses the permanent charge accumulation and separation that occurs at the surface of an ion selective membrane. The counterions (in this case, the positive charged species) within the "Inner Helmholtz plane" are considered to be a contact adsorbed layer without solvations and held in place by the strong electrostatic potential to the membrane surface. The counterions in the "Outer Helmholtz plane" are solvated and also commonly referred as the "Diffuse Double layer" with a weaker charge accumulation than the inner adsorbed contact layer.[22,32,33]

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Neutral Carrier-Based Ion Selective Membranes

Many measurements cannot be performed by use of ionically conductive sparingly soluble inorganic salts such as the silver halides, nor by ion selective glass membranes. For the vast majority of measurements, the use of a neutral carrier-based ion selective membrane is required. An ionophore is typically a neutral carrier (uncharged) large organic molecule with a hydrophobic exterior and a hydrophilic interior that enables the selective and reversible binding of an ion.[1,33] It is highly preferable to have the ionophore be neutral rather than charged, as charged carriers will eventually leach out of the membrane due the gradient created by the charged membrane. The ions that selectively bind with such a neutral-carrier ionophore will then slowly move across the membrane matrix, generating a electrochemical potential in the process when combined with an appropriate inner filling solution and electrode of the second kind.[33]

The neutral carrier (I) must have a number of desirable properties to be considered a good ionophore. It must exhibit a high binding constant to the ion of interest over a wide range of concentration, usually from 10^{-1} to 10^{-6} Molar for most ions. Most ionophores will also support measurement above and below these typical limits, although there are adsorption and reference issues for very low level measurements and activity coefficients at the very high level measurements that can make these ranges problematic. The plot in Figure 4 expresses the typical electrochemical response from very low to high concentrations.[34] When an ionophore is embedded into PVC with suitable additives as may be required, such as a plasticizer

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to improve the solubility of the ionophore and overall ion mobility, it is able to selectively transport ions across a relatively lipophilic membrane. The addition of plasticizer not only increases the solubility of the ionophore, but also increases the leaching rate of the ionophore and lowers the overall bulk resistance of the membrane. These additional additives are typical large organic salts that promote reorganization of the ionophore to the most favored binding conformation, also lowers the bulk resistance like most plasticizers, and makes the membrane more lipophilic in cases where biological fluid compatibility is desirable (for whole blood, serum or plasma). The plasticizer and additives are often required to produce a stable electrochemical potential for the ion selective electrode. An ideal membrane would need little or no plasticizer or additives to exhibit good electrochemical performance.

CHAPTER 2

CHARACTERIZATION OF ION SELECTIVE SENSORS

Potentiometric Selectivity Coefficient Determination and Significance

A potentiometric selectivity coefficient describes the ability of an ion selective electrode to distinguish a particular ion from others per the agreed mathematical and experimental conventions as defined by the IUPAC.[34-37] It turns out that the determination of meaningful and reproducible selectivity coefficients is one of the most technically complex areas of characterizing the performance of an ion selective sensor. In fact, the issues of divergent selectivity coefficients and their dependence upon the exact methodology employed has been an area of intense and often conflicting journal articles in the literature for well over forty years,[38-42] and it continues to be an area of very active discussion in even the most recent literature.[43,44] The original conventions and recommended methods as outlined by IUPAC back in 1975 are still in force, although a number of supplements and improvements to original recommendations have been made.[34-37,45-47] Often, the improvements in selectivity coefficients can be the primary experimental data that mark a paradigm shift from previous style of ionophore to a new generation of ionophore. All of the selectivity coefficient determination methodologies are either some form of a single (separate) solution or a mixed solution method.

In principle, as the selectivity coefficient is a fundamental property of the ion selective sensor, any characterization method should yield similar (if not identical) selectivity coefficients. There are many reasons why this is not always the case, and
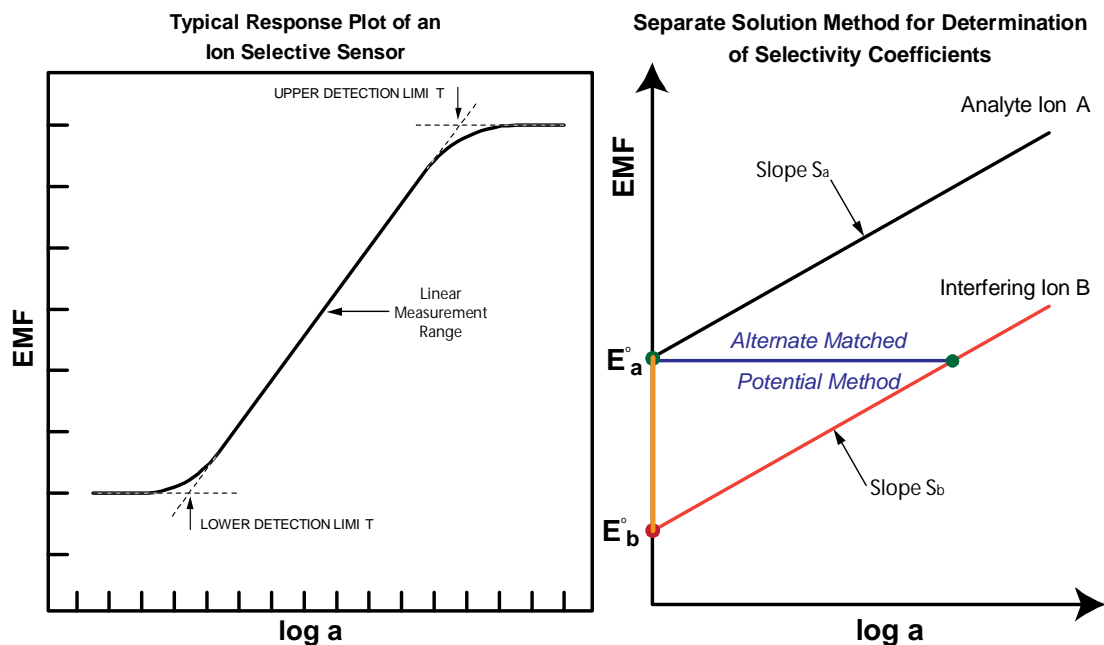
FIGURE 4. Idealized graphs of typical response plots for ion selective sensors. The two plots above collectively illustrate the general electrochemical response characteristic of a typical ion selective measurement cell (see FIGURE 2). The plot on the left illustrates the typical EMF response of an ion selective sensor to various activity of a given ion. The portion of the curve that demonstrates a (near) Nernstian response is called the linear measurement range. The non-ideal (non-Nernstian) behavior at low and high activity may vary slightly from that indicated as very many complex (and often countervailing) effects may be simultaneously at play. The low and high detection limits are defined by the the 1975 IUPAC guidelines.[34]

The plot on the right describes the response of an ion selective sensor to the analyte ion A, and the generalized interfering ion B. In the case where there is a (near) Nernstian response to both analyte and interfering ions, the experimental data lends itself to be an ideal candidate for the practical solution method (PSM)[44] refinement of the separate solution method to find the potentiometric selectivity coefficients as outlined by the 1975 IUPAC guidelines.[34] In this case the selectivity coefficient is simply defined by the equation $K^{pot}_{A,B} (PSM) = 10^{(E°b- E°a)/Sa}$ where all terms are clearly defined by the plot on the right above. An alternative method to find the selectivity coefficient if a (near) Nernstian response is not observed for both the analyte and interfering ions (A and B, respectively) is to use the matched potential method (MP). In this case the selectivity coefficient $K^{pot}_{A,B} (MP)$ is equal to the log a_B where a_B is the activity where the sensor has the same mV potential as $E°_a$ (thus the so-called "matched potential"). The horizontal line above labeled as "Alternate Matched Potential Method" indicates this simple relationship.

Although both of the EMF response plots above are only strictly valid when plotted against ion activity, in the common activity ranges of interest the concentration and activity are nearly identical (activity coefficient very near unity) meaning that concentration can often safely be treated as though it were actual activity.

thus it is the source of great interest and sometimes even controversy in the recent literature.[43]

The single solution method is the most classical and well explored, and is quite suitable for a great many sets of ion selective sensors for characterization, and is also quite simple and practical to perform. The main requirement for the classical single solution method to be valid is that the ion selective sensor exhibit a (near) Nernstian response in at least some portion of the interfering ion concentration range, such that the standard electrode potential (at 25 degrees Celsius and 1 Molar activity) can be extrapolated. The corresponding set of Voltage values at the standard electrode potential for each ion is then mathematically worked up into selectivity coefficients using a suitable formula.

A quick comment about unit conventions is now in order. All electrochemical test results are typically expressed in milliVolts (mV) units rather than Volts for simplicity and convenience of handling data. The use of mV units does not alter any of the previously provided equations in any way as all terms are just divided by 1000. In cases where no (near) Nernstian response is observed for some or most of the interfering ions of interest, an alternate methodology also based upon single solution testing can be performed, called the matched potential method. Without a complete exploration as to the reasons, it is generally preferable to use the classical single solution methodology of finding the standard electrode potential for each interfering ion, and to use these potentials to compute the selectivity coefficient per the IUPAC formulae, versus using the matched potential method formalism to evaluate the result

of a set of single solution experiments. The primary reason is that the matched

potential method can be very sensitive to the exact test conditions employed, whereas

the traditional single solution (and mixed solution) methods are considerably less

dependent on the exact test conditions. This makes the selectivity coefficients

determined with traditional single solution (and mixed solution) method a more useful

set of parameters for comparing the performance of different membranes and

ionophores, as well as for the purposes of determining suitability of the ion selective

sensor for any particular measurement.[35,43]

<div align="center">Constants and Symbols for Selectivity Coefficients</div>

The IUPAC guidelines were released in 1975 by the IUPAC and are

reproduced below for purposes of discussion.[34] The following indented set of

definitions is an excerpt from these IUPAC guidelines germane to this thesis. The

main equation describing the response of an ion selective electrode is hereafter

referred to as Equation 6.

A. The modified Nernst equation for ion-selective electrodes and definition of

$K^{pot}_{A,B}$

$E=constant+(2.303RT/Z_A F)log \: [a_A + K^{pot}_{A,B} \: (a_B)^{Za/Zb} + K^{pot}_{A,C} \: (a_c)^{Za/Zc} ....] \quad (6)$

E is the experimentally observed potential of a cell (in milliVolts)

R is the gas constant and is equal to $8.31441 \: JK^{-1}mol^{-1}$

T is the thermodynamic temperature (in degrees Kelvin)

F is the Faraday constant and is equal to $(9.648670 \pm 0.000054) \times 10^4 \: C \: mol^{-1}$

a_A is the activity of the ion, A

a_B and a_C are the activities of the interfering ions, B and C, respectively

$K^{pot}_{A,B}$ is the potentiometric selectivity coefficient of A with respect to B

z_A is an integer with sign and magnitude corresponding to the charge of the principal ion, A

z_B and z_C are integers with sign and magnitude corresponding to the charge of interfering ions, B and C, respectively

$K^{pot}_{A,C}$ is the potentiometric selectivity coefficient of A with respect to C

The "constant" term includes the standard or zero potential of the indicator electrode, E°_{ISE}, the reference electrode potential, E_{Ref}, and the junction potential, E_J (all in milliVolts).

The two general classes of methods used to find the potentiometric selectivity coefficients are defined using the separate solutions method and fixed interference (mixed solutions) method. The original IUPAC definitions and recommendations to find the selectivity coefficients using this class of methods are reproduced in the indented text below as a direct excerpt. The mixed solution method is shown as Equation 7, and the single solution method is shown as Equation 8.

D. Methods for determining $K^{pot}_{A,B}$

1. Fixed interference method. The potential of a cell comprising an ion-selective electrode and a reference electrode is measured with solutions of constant level of interference, a_B, and varying activity of the primary ion, a_A. The potential values obtained are plotted vs the activity of the primary ion. The intersection of the extrapolation of the linear portions of this curve will

indicate the values of aA which are to be used to calculate K from the equation:

$$K^{pot}_{A,B} = a_A / (a_B)^{Za/Zb} \qquad (7)$$

2. Separate solution method. The potential of a cell comprising an ion-selective electrode and a reference electrode is measured with each of two separate solutions, one containing the ion A at the activity A (but no B), the other containing the ion B at the same activity $a_B = a_A$ (but no A). If the measured values' are E_1 and E_2, respectively, the value of K may be calculated from the equation:

$$log\ K^{pot}_{A,B} = (E_2 - E_1) / (2.303RT/Z_AF) + (1 - Z_a/Z_b)*log\ a_A \qquad (8)$$

This method is recommended only if the electrode exhibits a Nernstian response. It is less desirable because it does not represent as well the actual conditions under which the electrodes are used.

A variety of improvements and considerations have been reported and published since the original 1975 IUPAC recommendations, primarily dealing with situations where there is not a perfectly Nernstian response for all ions but where the single solution method would otherwise seem to perfectly apply.[44] These include conditions such as when there are very low-level measurements where a variety of environmental factors can influence the potential (filling solution leakage, adsorption, hysteresis, et cetra). In such cases, there appear to be differences in the selectivity coefficients that arise from the use of different methodologies and even divergent selectivity coefficients using the same method but where experiments are performed at

different concentration ranges. In general, the matched potential method is only used in cases where it is simply not possible to achieve a Nernstian response for a given interfering ion. In such cases, the absolute mV potential at (or near) 1 Molar activity is used in lieu of the plotted E° intercept values obtained when interfering ions do exhibit a Nernstian response that can be extrapolated to this 1 Molar activity.

A slight improvement to single solution method has been reported in the recent literature whereby observed slope (mV response per decade change in ion activity) for the analyte ion is used instead of the theoretical Nernstian slope.[44] In this modified practical slope method (PSM), if the observed slope of both the analyte ion and the variety of other interfering ions are nearly identical but systematically not perfectly Nernstian (for example only operating at 80-95% of theoretical slope), then this approach is quite reasonable, self-consistent and ultimately more reflective of the actual selectivity coefficients. The simplified empirical form of the potentiometric selectivity coefficients equation using this modified PSM is described in Equation 9 below:[44]

$$10^{(E°_b - E°_a)/S_a} = K^{pot}_{A,B} \; (PSM) \tag{9}$$

In Equation 9, A is the primary analyte ion and B is the interfering ion. The values of $E°_A$ and $E°_B$ can be found using Equations 10 and 11, respectively.

$$E = E°_A + S_A \, log_{10} \, a_A \tag{10}$$

$$E = E°_B + S_B \, log_{10} \, a_B \tag{11}$$

In equations 10 and 11, *E* is the observed electrochemical potential in Volts (or mV), $E°_A$ and $E°_B$ are the electrochemical potential in Volts (or mV) at the standard 1 Molar

activity conditions and S_A and S_B are the slope for the analyte and interfering ion, respectively, obtained from standard linear regression analysis of the data from a region where a (near) Nernstian response is observed. Note that $E°_A$ and $E°_B$ are derived values from computed intercepts (and extrapolated from the linear range to the 1 Molar activity). The practical slope method (PSM) represents the selectivity coefficient method for either single solution or mixed solution methods where the practical slope is used including both Nernstian and near Nernstian responses. This is one of the more common modern single solution selectivity coefficient methods used and shall be used to determine all selectivity coefficients in this thesis, except where no near Nernstian response is observed at all. Figure 4 and Figure 5 gives examples of idealized and typical response and visualize the practical slope method and matched potential methods discussed for determination of potentiometric selectivity coefficients.

For very specific applications, it may also be desirable to use the fixed solution method with the fixed interference being set to the expected typical interference concentration. In this manner, not only is the selectivity coefficient derived in the most realistic way possible, but the specific lowest limit of detection and linear measurement range are simultaneously obtained under the conditions of interest. Such well known sample conditions are often restricted to physiological measurement systems where variance by an order of magnitude is rare if not impossible. The single solution and fixed interference methods should, in principle, result in the same selectivity coefficient, although a significant number of precautions must be taken to
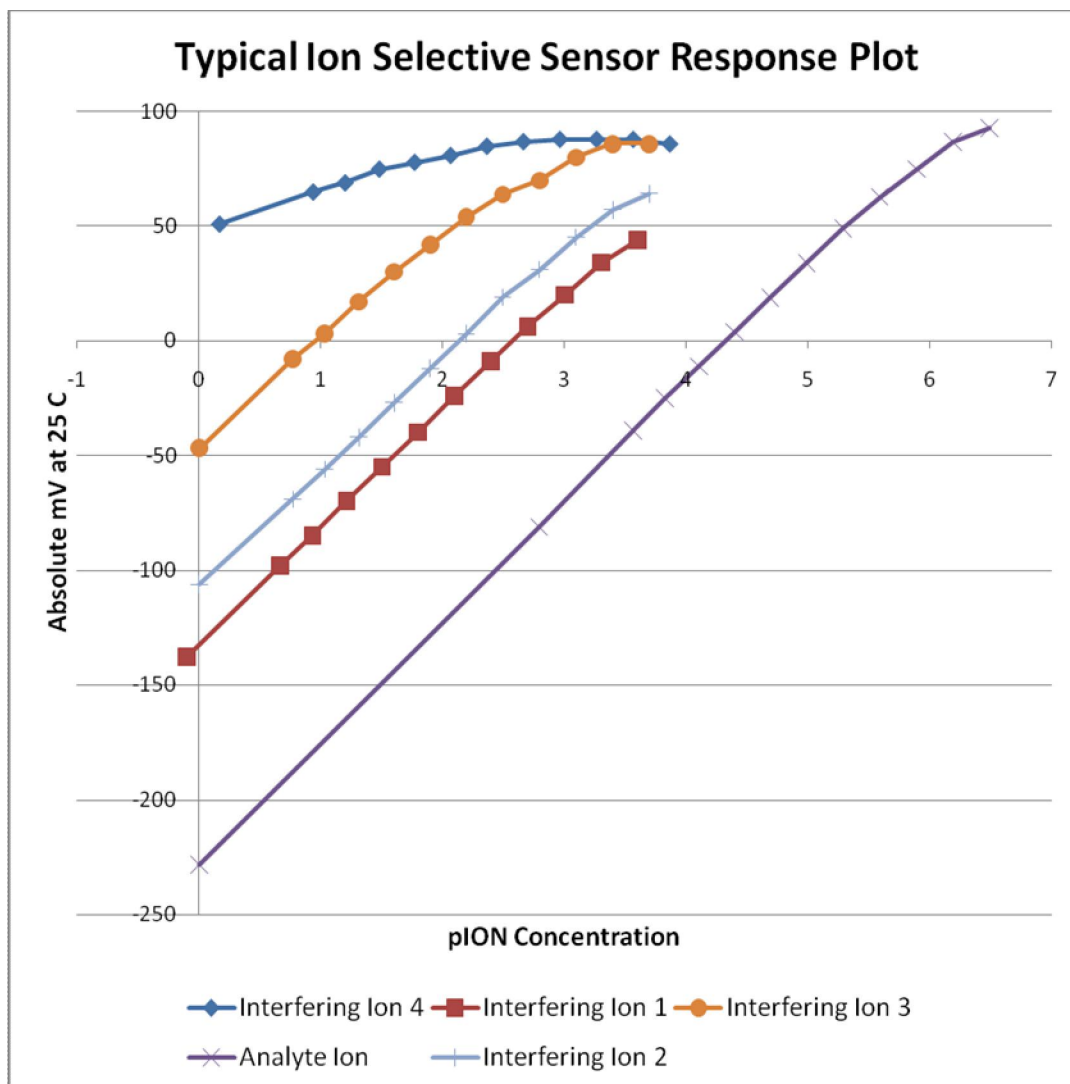
FIGURE 5. Typical ion selective sensor response plot for separate solution experiments. The plot above is for the absolute mV potential of a typical anion selective ion selective sensor plotted against the pION concentration. The pION scale is defined by $-\log_{10}[ION]$ where [ION] is the molar concentration of the given ION. In this anion ion selective sensor case the ion to which the sensor exhbits the strongest response is shown as the lowest mV potential at pION=0 (lowest parallel line). If this was instead a response plot for a cation ion selective sensor, the ion to which the sensor exhibits the strongest response would be the highest mV potential at pION=0 (highest parallel line).

The ion to which the sensor exhibits the highest response is designated as the "Analyte Ion" and it is called an ion selective sensor of that type. For example, if in this plot the Analyte Ion were nitrate (NO_3^-), the the sensor would be called a nitrate ion selective sensor. In the plot above Interferion Ion 1 is the most interfering, whereas Interfering Ion 4 is the least interfering. As intefering Ions 1, 2 and 3 exhibit a(near) Nerstian response that can be extrapolated to the pION intercept, the practical slope method (PSM) can be used to determine the selectivity coefficients for these three interfering ions. For Interfering Ion 4, there is no (near) Nernstian response exhibited so, unfortunately, the Matched Potential Method (MPM) must be employed. It can be seen at all of the response plots converge toward a lower bound of +100 mV, which is near the potential for the lowest limit of detection.

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ensure this is actually the case.[43] Due to the issues of selectivity coefficient

determination dependence upon the method employed and the concentration ranges

selected, the mixed solution method (fixed interference) is often not used for ion

selective electrodes that will be exposed to a wide variety of sample media. The

reason is that the results from a single fixed interference experiment to determine the

selectivity coefficient may actually be less generally relevant than a well performed

practical slope method single solution experiment to find the selectivity coefficient

that has a more broad applicability to most potential analytical uses.

<p align="center">Ionophore Binding Mechanisms and Visualization</p>

Visualizing the selective reversible binding mechanism of an ionophore is

central to designing new ionophores and improving existing ionophores. Not all

electrochemical performance characteristics are defined by the ionophore used. The

plasticizer employed, ratio of PVC to plasticizer, and the role of specific additives

(typically to improve ion mobility or lipophilicity), can affect all electrochemical

performance parameters. It is generally accepted that the role of the ionophore is

crucial and that a series of ionophores can be compared for relative performance

analysis if all membrane formulation options are held constant. The membrane

formulation options are then presumably derived from a well optimized set of options

as previously reported in the literature for a reasonably analogous ionophore as a

starting reference point.

The ionophore nonactin is among the most well known and studied ionophore

and is shown in Figures 5, 6 and 7. This naturally-occurring ionophore is widely used

in ion selective sensors for the detection of ammonium ions. One reason for the common use is because it can be made in large quantities at relatively low cost through industrial fermentation processes rather than a purely synthetic route, and it exhibits rather good overall ionophore characteristics. Although many other ammonium ionophores now exist that demonstrate superior selectivity and performance to nonactin, its stability, excellent lifetime, and reproducible results in a wide range of matrix and plasticizers, continue to make it a widely used and researched ionophore for ammonium measurements.[48,49] A large binding constant to the analyte ion is necessary for the receptor to be considered a good ionophore. This binding must be of a reversible nature, meaning that there must be a pathway for the ion to both enter the largely hydrophilic interior of the ionophore and exit towards to the largely hydrophobic exterior and then migrate to the next binding site. The migration of ions from ionophore binding site to binding site is illustrated in Figure 3 as part of the overall electrical double layer model for an ion selective membrane.

It is common for larger macrocyclic ionophores such as nonactin to have a significant conformational change between the ion bound and unbound conditions. This significant change in conformation is a "preorganization" that reduces the entropic cost of binding and maximizes the enthalpic contribution to binding (in this generated case ion dipole interaction) and can readily be achieved by having all ionophore species bound to the analyte of interest prior to the fabrication of any ion selective membrane.[50-52] The proximity and effectiveness of the charge stabilization between the ionophore and ion (host-guest) is responsible for the binding affinity of

the ionophore (this relates to the lowest limit of detection and linear measurement range). The difference in binding affinities between the desired analyte (ammonium ions for the ionophore nonactin) and other potential ions of like charge and reasonably similar ionic radius is the primary factor for the observed selectivity coefficients. In the case of nonactin binding to ammonium, the placement of the four oxygen atoms in close proximity to the four charged hydrogen atoms of the ammonium ions favors the binding of this ionophore to ammonium ions versus other ions of like charge and similar ionic radius such as potassium. To further improve the percent of binding sites that have the optimal conformation, it is common for ionophores to be highly symmetric molecules (in the case of nonactin it is a meso compound) as this improves the statistical probability that the compound will be in a suitable geometry for binding at any given site.

<u>Typical Characteristics and Expectations for Ion Selective Sensors</u>

Ionophores are molecules that selectively bind and transport ions across a membrane. An ideal ionophore would be neutral in charge to minimize leaching,[53] highly selective to the analyte ion over all potential interfering ions of similar ionic radius and charge (1,000 times or better selectivity on a Molar basis is considered quite good), have a large linear response range (10^{-7} to 1.0 Molar), be soluble in common organic solvents such THF to facilitate fabrication, and be insensitive to reduction and oxidation from common constituents in the measured media.

In addition, an ideal ionophore would be able to operate over a broad pH range (such as 1-13), be stable for many months, and operate over a wide temperature range
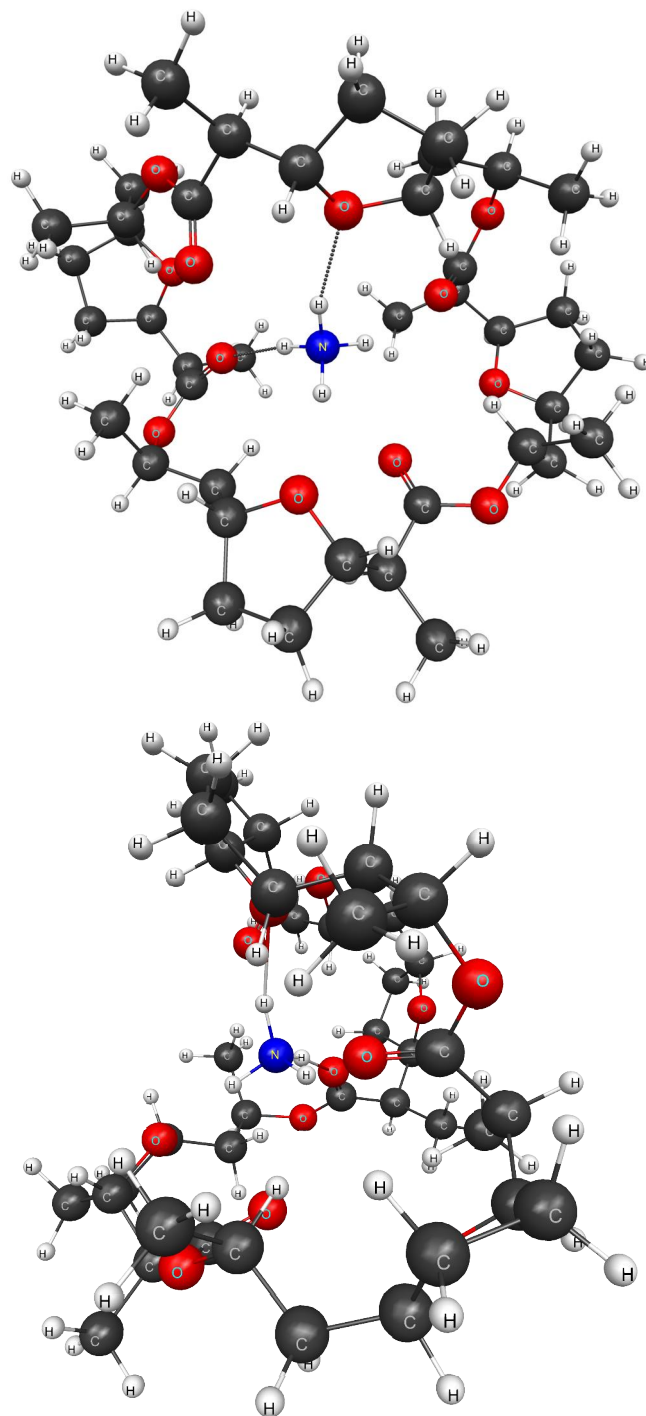
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FIGURE 6. Optimized geometry of nonactin bound to an ammonium ion. The structure above (two views) shows the preferred highly puckered conformation of the nonactin ionophore when bound to an ammonium ion.[48,49,54,55] This optimized structure was obtained by computer modeling with the PC GAMESS/Firefly QC package,[56] which is partially based on the GAMESS (US)[57] source code at the DFT level of theory (in vacuo).

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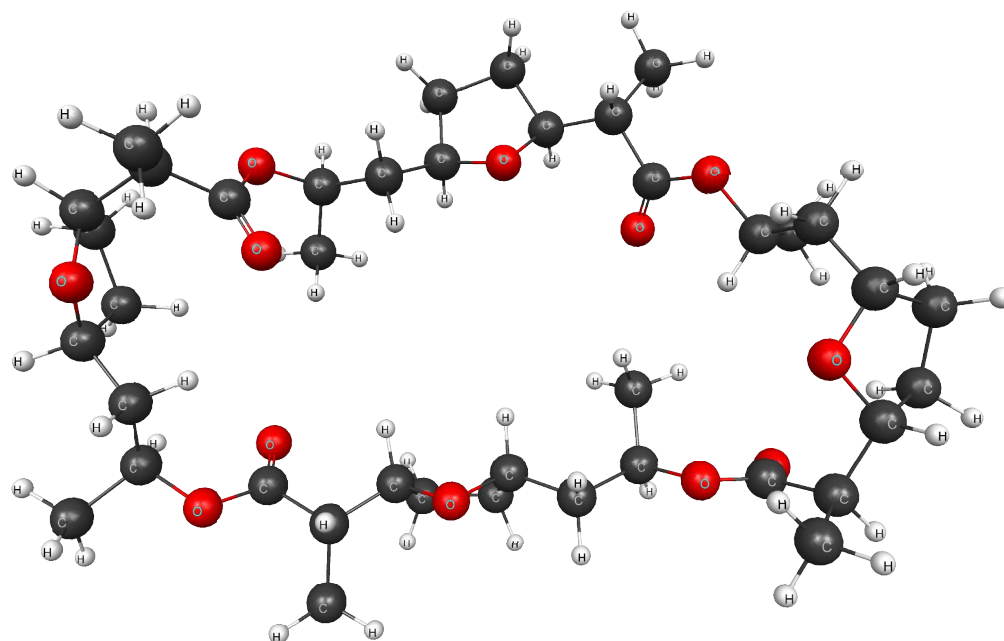FIGURE 7. Optimized geometry of nonactin without any ion present. The structure above shows the preferred largely planar relaxed conformation of the nonactin ionophore when no cation is present.[48,49,54,55] This optimized structure was obtained by computer modeling with the PC GAMESS/Firefly QC package,[56] which is partially based on the GAMESS (US)[57] source code at the DFT level of theory (in vacuo).
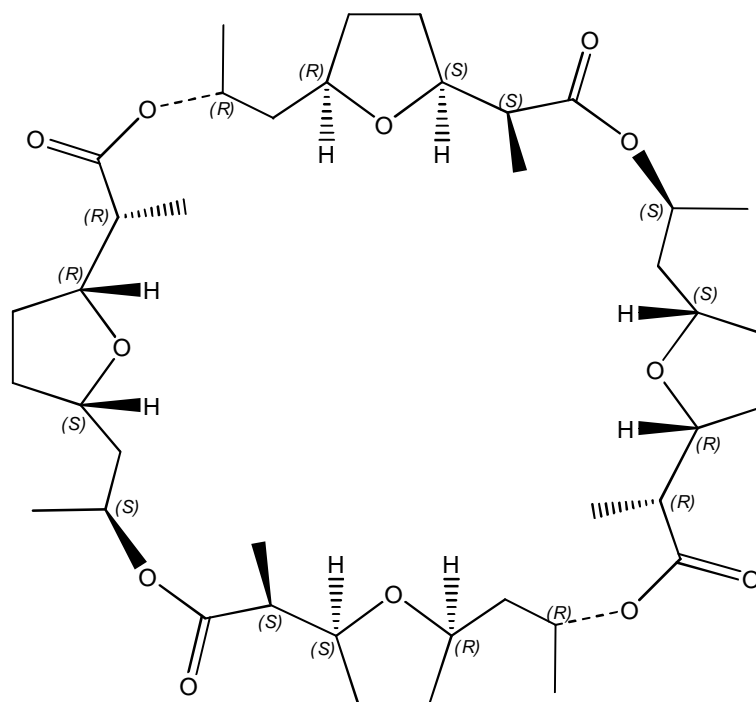
FIGURE 8. A Chemdraw rendering of the naturally occurring antibiotic ionophore nonactin including all stereochemistry. As is often true for such macrocylcic polyether and polypeptide ionophores, nonactin is a meso compound.[48,49,52,54,55,58] Symmetric compounds are often preferable for ionophores because the statistical distribution of ion-binding conformations can often improve as the degree of symmetric rises due to the more limited conformational degrees of freedom.[59]

(such as 5 to 50 degrees Celsius).[33,59] A wide variety of compounds have been reported to act as good ionophores, including naturally produced ionophores as well as synthetically engineered ionophores.[60] Naturally produced ionophores are usually produced by bacteria or other microbes and are discovered during the course of investigating the mechanism of the antibiotic's activity. These naturally occurring antibiotic molecules are usually long-chain macrocyles such as nonactin, which selectively binds ammonium ions, and valinomycin, which selectively binds potassium ions.

Synthesized ionophores typically are smaller molecules that often mimic naturally occurring active sites of proteins or antibiotics. Some good examples include crown ethers, cryptands, porphyrins, and salens. Many ionophores have been reported to selectively detect ions in aqueous solutions when integrated into a suitable solvent polymeric, polyurethane and silicone membranes. This thesis shall only focus on the more ubiquitous solvent polymeric membranes, as they are currently the only viable platform for cost effective ion selective electrodes.

Solvent polymeric membranes consist of four main components, all of which must be dissolved with a suitable organic solvent such as tetrahydrofuran (THF):

Ionophore: about 1 to 10% by weight (typically 1%)

PVC: ultra-high molecular weight, about 20 to 50% by weight (typically 33%)

Plasticizer: (a.k.a. solvent mediators) to improve ionophore solubility and lower membrane bulk resistance - about 50 to 80% by weight (typically 66%)

Additives: large organic salts that promote lipophilicity and are typically required only

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for measurement in blood or serum (about 0.5-2% by weight if used at all)

The quality of an ion selective electrode is characterized by an assortment of criteria. Since many ion selective membranes are used for trace or low level analysis as a lower cost alternative to optical methods, an improved lowest limit of detection is often reported to indicate an improved ionophore or membrane formulation. Although levels as low as 10^{-10} Molar have been reported for some membranes under special testing conditions, a lowest limit of detection at or near 10^{-6} to 10^{-8} Molar is excellent for practical measurements. The lowest limit of detection is largely a function of the thermodynamics of binding (enthalpic and entropic) between the ionophore and ion.

The linear measurement range is another important criterion for determining the quality of a given membrane and ionophore. The linear measurement range is the concentration range at which a single (near) Nernstian response is observed throughout for a given set of pH and temperature condition (these limits and influences are typically considered separately); the most typical values for the linear measurement range are 10^{-5} to 10^{-1} Molar. There are more specialized applications for determination of concentration above 0.1 Molar that are not generally considered in the course of an ordinary evaluation of the quality of an ion selective electrode. Many different effects cause measurements above 0.1 Molar to be more complicated, including the non-linearity of the activity coefficients at higher concentrations and the non-linear variation of such activity coefficients with temperature (in many cases with no data available at the specific concentration and temperature values of interest). For this reason, few if any reports in the literature appear involving solvent polymeric

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ionophore based sensors describing performance characteristics above 0.1 Molar concentrations.

Measurement at levels below the linear measurement range is possible; however, the necessary calibration software to support the non-linear behavior of the sensor is often not supported by commercial ion selective instrumentation and benchtop meters. For example, if a sensor exhibits a highly linear 55 mV per decade response (93% of ideal Nernstian) in the range of 10^{-5} to 10^{-1} Molar, but a reduced 30-40 mV per decade response between the 10^{-6} or 10^{-5} range (50% of ideal Nernstian), the instrument would need to support multi-point calibration or only operate in the most restrictive concentration range to give meaningful analytical data with only a typical two point calibration scheme. As it turns out, the use of the reference value of 50% of typical slope in the full linear measurement range is a far more practical and meaningful benchmark for the lowest limit of detection than the classical IUPAC definition.[34] The lowest limit of detection does not constitute a range that could actually be measured for practical application in the lab or field, even presuming the multi-point calibration scheme described was supported. The same argument regarding the need for multi-point calibration and operational difficulties can be made for measurement in media at or above 0.1 Molar concentrations, with the added complexity of the non-linearity due to the temperature dependence and activity coefficients further compounding the basic concerns. Even for systems where the activity coefficients for high concentration species are known, they are often reported only at 25 degrees Celsius, usually because there is little or no data available at

various temperatures. Even if such data does exist, it would constitute a custom activity coefficient calibration curve that would need to be separately programmed for each particular measurement. Such efforts would only be made for the absolute most mission critical measurements.

In many cases, there are existing membrane formulations and ionophores that offer an acceptable lowest limit of detection and linear measurement range, but the state of the current technology is limited by the selectivity coefficients for interfering ions. In such cases, there exists a typical interfering ion in excess of the analyte ion. The goal for improved ionophore and membrane development is to raise the selectivity coefficients to a value that will support the typical measurement conditions of interest. A selectivity coefficient value from -1 to -2 (meaning a 10 to 100 fold Molar excess of the interfering ion to the analyte ion can be supported for the measurement) is considered poor to average. A selectivity coefficient value from -3 to -4 (meaning a 1,000 to 10,000 fold Molar excess of interfering ion to analyte ion can be supported for the measurement) is considered good to very good. Any selectivity coefficient of -5 or less (meaning a molar excess of interfering ion to analyte ion of 100,000 or more) is considered excellent. It is exceedingly difficult to determine the selectivity coefficients when they are smaller than -5 as no (near) Nernstian response is often observed at any concentration range for the interfering ion, meaning that less desirable methods such as matched potential must be employed. It is clear from inspection and from reviewing the previously discussed IUPAC conventions for the selectivity coefficients that they are expressed on a log base 10

scale, although often reported in ratio of permissible molar or ppm excess for non-analytical electrochemists for simplicity and ease of discussion.

The speed of response is another criterion for evaluating the performance of an ion selective sensor. The speed of response for a given ion selective membrane is a function of the kinetics of ionophore binding and PVC membrane formulation's ion mobility and reversibility. The lack of reversibility is commonly referred to as "hysteresis". The valid pH range is usually defined by a combination of the acid and base reactivity or interactions exhibited by the ionophore, as well as the PVC and plasticizer matrix sensitivity to hydrolysis of the membrane itself. The issue of membrane hydrolysis is much more of an issue for long-term continuous online measurement than for short term laboratory analysis where the ion selective electrode is normally stored dry. Temporary hydrolysis can be reversed with sufficient "drying" time where the membrane is left out in the air. The thermal stability is primarily a function of reactivity and decomposition of the ionophore, although at very high temperatures the plasticizer and PVC may also degrade. In an ideal situation, the ionophore should exhibit a very low reactivity to all potential ions that it may complex. Furthermore, it should also exhibit no reactivity and low sensitivity to heat cycling, light, and exposure to a variety of organic chemicals and to solvents, in addition to being resistant to hydrolysis. As one can imagine, there is in reality no such ideal ionophore, although many will exhibit a number of these desired traits. A typical valid temperature range for most ion selective membranes is 5 to 40 degrees Celsius with most tests conducted only at twenty-five degrees. In general, a speed of

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response of 5 to 10 seconds or less is considered acceptable for most uses, and it is often presumed that this condition is fulfilled if the issue of speed of response is not discussed explicitly. Such fast response is only possible for laboratory style ion selective electrodes. Industrial ion selective sensor assemblies will exhibit considerably longer response times for very many complex reasons not discussed here.

The extent of drift, as measured in mV change per day in a static system, is a stability (equilibrium) issue arising from whether the conditions of the overall electrochemical cell that generate the mV potential are changing. The causes of drift are typically when the membrane is absorbing water into PVC matrix, when the ionophore is migrating out of membrane (typically because it is charged, or too small and labile), or when some other root cause leading to an asymmetry of ion mobility (typically referred to as polarization of the membrane). Changes in the overall ionic strength of the measured solution, or significant changes for the measured analyte concentration or ratio of interfering ions, can also contribute to the extent of drift.

The useable lifetime of a plasticized PVC ion selective electrode or sensor employing a neutral carrier ionophore is typically an indication of the stability of the ionophore itself. This lifetime is also dependent on plasticizer stability, ionophore mobility (leaching) and other factors. The slow decomposition reactions of all components (typically radicals formed from heat, light and air exposure) are another factor affecting sensor lifetime. Naturally, the useful lifetime (as defined by an acceptable mV/decade response and degree of drift) is also diminished by reduction and oxidation chemistry, by photosensitivity, and by sensitivity to hydrolysis, which is

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particularly an issue for smaller more polar plasticizers. It should be noted that the "acceptable" performance is a largely subjective measure based upon the application requirements. Such sensor lifetime is not typically reported as a firm time period for any particular membrane and ionophore composition, and therefore any useable lifetime reported should be considered carefully.

Successful measurements for cations utilizing naturally produced ionophores and well known small molecule (synthetic) ionophores include but are not limited to Na^+, Li^+ (crown ethers), K^+ (Valinomycin), NH_4^+ (Nonactin) and Ca^{2+}. However, there are still many cation measurements where few if any good ionophores have been reported, particularly those having characteristics for practical real world measurements of interest.[3] These measurements include but are not limited to heavy metal ions such as Cu^{2+}, Pb^{2+}, Co^{2+}, Cd^{2+}, Cr^{3+}, $Fe^{2+,3+}$ as well as other larger cations such as Mg^{2+}. In the realm of anionic ionophores there are really just a handful of well respected traditional silver-halide based solid-state ion selective electrodes that are readily available and commonly used.[60] This set of electrodes once again includes fluoride (F^-), chloride (Cl^-), bromide (Br^-), iodide (I^-), cyanide (CN^-), thiocyanate (SCN^-), silver (Ag^+), and sulfide (S^{2-}). All measurements not listed as being supported by the silver-halide type ion selective electrodes (and fluoride) are performed with neutral carrier solvent polymeric ionophore based ion selective membranes. These include a wide variety of measurements of environmental interest including perchlorate (ClO_4^-) for environmental remediation and toxicity applications, and nitrate (NO_3^-) for water quality in agricultural water streams.

It is well known that the measurement of anions using solvent polymeric sensor technology is significantly more complex and problematic than using solvent polymeric sensors for cations. This is because the behavior of anions moving across a membrane potential gradient and the large ionic radius of very many anions makes it difficult to design ionophores to selectively bind to one anion in particular. Unless there is a gross disparity in anionic radius between the analyte and interfering anion (for example iodide versus fluoride might constitute such a special case), most anionic solvent polymeric sensors are likely to respond to some extent to anion with the same formal charge. Analogous to cation solvent polymeric sensors, preference of binding to one anion over another is characterized by the selectivity coefficients for anionic solvent polymeric sensors. In contrast to the relatively poor selectivities exhibited by anionic solvent polymeric sensors, it is quite common that good cation solvent polymeric sensors show excellent selectivity over most interfering cations, or that there are quite a number of cations to which it does not show any response at all. In general, neither cation nor anion ion selective sensors exhibit a significant response to ions of different net charge. For example, a sensor that detects a monovalent anion would be expected to have very good selectivity over an interfering divalent anion. Analogously, a sensor that detects a monovalent cation is expected to have very good selectivity over an interfering divalent cation. Special strategies for anion receptor design constitute a separate subset of supramolecular chemistry, and such concepts are of multidisciplinary interest.[61] The special case of anion ion selective sensors will be further explored in the next chapter.

CHAPTER 3

SPECIAL CASES AND FUTURE DIRECTIONS

The Problems with Anions

The issue of anion mobility across a membrane has been discussed for over a hundred years, based upon the early work in 1888 as reported by Hofmeister.[62] Thus, the observed series of anions from the most protein destabilizing to the most protein stabilizing is still called the "Hofmeister" series. In addition, the Hofmeister series continues to be an active area of research and discussion in several fields.[63] Although the exact causes and ramifications of the Hofmeister series are not fully understood, it is generally agreed that the large solvation shells that surround anions, and the very different electronic state of anions as opposed to cations are at least part of the explanation. The Hofmeister series discusses the impact of salt on biological systems for many significant biological processes such as colloidal assembly and protein folding. More recently, the Hofmeister series has been explored in greater detail for non-biological applications, including ion exchange and selectively permeable membranes.[33,61,64]

Using a solvent polymeric ion selective electrode based on the classical ion exchange quaternary ammonium salt tridodecylmethylammonium chloride organic salt (TDDMACl), the potentiometric response follows the Hofmeister series and is $ClO_4^- >$ $SCN^- > Salicylate > I^- > NO_3^- > NO_2^- > Br^- > Cl^-, HSO_3^- > CH_3COO^-, HCO_3^- > HSO_4^-$ where perchlorate is the most lipophobic (protein destabilizing and denaturing) and bisulfate is the most lipophilic (protein stabilizing). The Hofmeister series also serves

as a quick shorthand for the biotoxicity of simple anions, as the most protein destabilizing will disrupt the normal colloidal assembly and folded protein. Most of these effects have been rationalized on the basis of the water hydration shells for these anions and how the hydration shells impact the overall local water structure.[63] Further research has suggested that direct ion macromolecule interactions and dispersion effects may contribute more significantly to explain the observed Hofmeister series.[65] Upon this basis, the physical organic chemistry description of anions as hard or soft is useful, as is the traditional concept of solvation shells based upon the total charge density and ionic radius.

Unfortunately, anionic systems can be particularly problematic to model computationally, as many weak interactions can significantly impact geometries and electron distribution (density). These issues and other related topics will be addressed further in the discussion chapter. Building anti-Hofmeister selective anion receptors (or at the very least those that distort the natural ratio of preference defined by the Hofmeister series) then presents some very serious difficulties, and is thus an area of intensive research interest.[46,60] Detecting perchlorate and thiocyanate is relatively easy (high in series), while detecting bicarbonate and bisulfate (low in series) is quite difficult and in fact very few good ionophores exist for them. If a nitrate or chloride measurement system is desired, even a trace of iodide or perchlorate present will convert all possible binding sites of the classical organic ion exchange salt to the much more highly favored iodide or perchlorate. In this case, a gross excess of chloride or nitrate would be needed to make any kind of binding for that species possible. The

reversibility of any anionic solvent polymeric ion selective electrode is critical to permit continuous usage in the event the highly interfering ions may be present.

The Hofmeister series is a ranking of the natural "perm" selectivity of these various anions to biological like membranes, and serves as a reasonable guide for their behavior in crossing solvent polymeric membranes as well. Even when detecting an anion high in the series, a significant excess of an anion lower in the Hofmeister series will cause difficulty with selective binding. Although iodide is much higher in the series than is bromide (which is turn higher in the series than chloride), a large excess of either the bromide or chloride species will cause a lack of selectivity. More generally, the selectivity of the favored anions over the less favored anions in the series is not large, and certainly much smaller than for most cations. Lastly, the response of membranes employing the traditional ion exchange organic salt that follows the Hofmeister series can often be quite sluggish (slow equilibrium), with poor detection limits and linear measurement range. In addition, the potentials from such ion-exchange systems drift over time as the equilibrium shifts and various imperfections in this type of membrane technology are exposed.

More special ion selective sensor cases will be added to this chapter in future updates (revisions) to this article in this third chapter. Check back periodically or subscribe to our newsletter to automatically receive notification of such updates. Planned updates include discussions about ultra-low level measurements of sodium (Na^+) for power plant application and calcium (Ca^{2+}) for RO and water softener installations. In addition, field measurement of nitrate (NO_3^-) and total nitrogen in the

presence of strong interferences such as solution containing high chloride

concentrations will be considered. Inline copper (Cu^{2+}) determination will be

explored for very many potential applications such as drinking water, plating,

sterilization, semiconductor and mining each including considerations related to

interfering ions, temperature and pH.

Patko, T.A.D. Understanding Ion Selective Sensors. [Online] **2009**. Available from *Advanced Sensor Technoloiges, Inc.*, http://www.astisensor.com (Last Revised April 2009). **All Copyright Reserved.**

REFERENCES

References are available upon request. Complete an online citation request by accessing the URL link below and you will be provided a complete list of references from this article.

http://www.astisensor.com/cgi-bin/ttx.cgi