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Ionophore Analysis of 1-Aza-18-crown 6-Ether using an Ion Selective Electrode

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By

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Abstract

Ion selective electrodes are widely used tools in the analysis of ion concentration in liquid media. They offer a low cost tool for performing continuous measurements of ionic activity in liquid samples. Ionophores or ion carriers are the key component of these electrodes. They facilitate the transport of unbound ions across hydrophobic membranes. Ionophores are usually cast into polymeric membranes with other ingredients such as plasticizers and lipophilic salts. These membranes are incorporated into electrodes, and in conjunction with a reference electrode and a potentiometer are able to give accurate concentration readings that are based on the potential generated across the electrode membrane. 1-Aza-18-crown 6-ether was used as the ionophore in preparation of polymeric membranes to test its selectivity to potassium and ammonium. The membranes were incorporated into a Philips body electrode for testing, which inconsistently exhibited a near Nernstian slope of 51.3 mV per decade and a linear range of 10^{-5}- 1 M for potassium chloride. A comparison of the ionophore's selectivity against Valinomycin and Nonactin, the mainly used ionophores for potassium and ammonium respectively was conducted.

Acknowledgements

I would like to sincerely thank all of the following for their generous help and support: Professor Grant McGimpsey, Professor Christopher Lambert, Elizabeth Stepien, Morgan Stanton, Jordan Lackner and all of the other faculty, staff, and graduate students in the WPI department of chemistry and biochemistry.

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Introduction

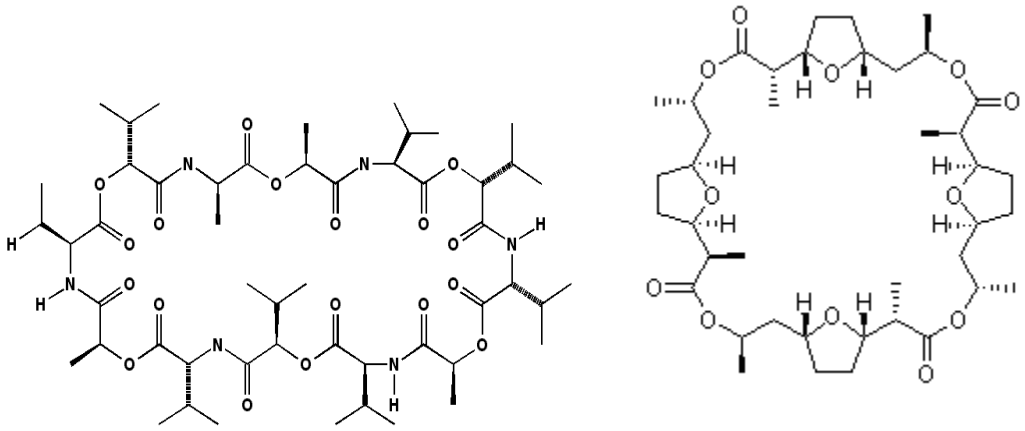
The goal of this research is to use Philips body electrodes to determine the relative selectivity of 1-Aza-18-crown 6-ether to potassium ions. The 1-Aza-18-crown 6-ether was cast into a plasticized-PVC membrane and analyzed using a standard two-electrode setup. The selectivity of the electrode to potassium over ammonium was examined. Ammonium and potassium have similar ionic radii which makes determination of selectivity coefficients a crucial aspect of ionophore analysis.

1.1 Ion sensing

Ion selective electrodes are commonly used as a tool for potentiometric measurements in aqueous solutions. They provide a convenient method for ion analysis in both the academic and industrial field. The ability for these electrodes to be selective to particular ions is largely due to the ionophore or site of ion complexation[1]. Ionophores are lipophilic molecules that are able to catalyze the transport of ions across hydrophobic membranes. They are usually large, organic molecules that function as neutral carriers. Neutral carriers refer to the uncharged nature of most ionophores. Uncharged ionophores are preferable because charged carriers have been shown to leach out of their membranes due to the gradient created by the charged membrane[2]. Symmetry is also a common quality shown in ionophores. Symmetrical ionophores have limited conformational degrees of freedom, which improves the statistical chance that the ionophore will have suitable geometric positioning for binding at any site.

Desirable ionophores have an ion-binding site that is similar in size to a specific target ion. This site is a cavity in which a target ion can bind; when ions bind to the

ionophore, an ion-ionophore complex is formed. The close match of the ionic radius to the ion-binding site allows for a greater number of electrostatic interactions, a smaller ion would experience less electrostatic interactions causing a decrease in stability. A larger ion is not able to utilize all of the electrostatic interactions offered by the ionophore. The proximity and effectiveness of charge stabilization experienced by the ionophore and ion determines the selectivity of the ionophore[2]. The selectivity of an ionophore can be discussed in terms of thermodynamic stability. The binding of an ion causes a conformational change in the ionophore, which has enthalpic and entropic effects. Ion complication is an enthalpically favorable process and there exist a relative correlation between the enthalpy of complexation and the size match between the ion and ionophore[1]. However, there exist multiple entropic costs of complexation that contribute to decreased stability. As the ion binds to the ionophore, it experiences a significant loss of translational entropy. Upon ion binding, the ionophore experiences a loss of entropy due to its loss of conformational freedom. A reduction of this entropic cost can be achieved by preorganization of the ionophore conformation upon binding which also improves the enthalpic contribution to binding[3]. Valinomycin and Nonactin (**Figure 1**) are great examples of ionophores that can preorganize themselves for more efficient ionic binding. Valinomycin has six amide linkages that allow the six carboxyl carbonyls to bind potassium in an octahedral fashion[2]. Whereas the close positioning of the four oxygen molecules on Nonactin interact with the four charged hydrogen molecules of ammonium, making it an effective ionophore for ammonium[4]. Ammonium and potassium are molecules with similar ionic radius and charge but are relatively distinguishable with these two ionophores.



Valinomycin Nonactin

Figure 1: 2D structures of Valinomycin and Nonactin

In order for the ionophore to be used in an electrode, it must be cast into a polymeric membrane, usually consisting of poly(vinyl chloride) and other additives. A plasticizer is often used to improve the solubility and overall ion mobility of the ionophore[2]. Plasticizers effectively increase the diffusion rate of target ions as well as reduce the bulk resistance of the membrane. Commonly used plasticizers include dioctyl phthalate, dipentylphthalate and o-nitrophenyloctylether. Large organic salts are also included to increase the lipophilicity of the membrane. These salts are commonly referred to as lipophilic salts. They also serve to organize the ionophore in its favored binding conformation[2]. These additives help produce stable potential readings for ion selective electrodes.

1.2 Philips body electrodes

Philips body electrodes are commonly used as ion-selective electrodes in testing of polymeric membranes. The Philips body electrode consists of a two-piece epoxy body that encases the important components of the electrode. The tip of the electrodes

unscrews allowing for placement of a membrane. The tip of the electrode has a 5 mm opening, which serves as the interface of the membrane with aqueous solutions. The tip encases an inner teflon insert and a circular rubber component (**Figure 2**) that attaches to the base of the teflon insert. The teflon-rubber component is easily removed and a membrane is placed to sit flush over the opening in the tip. The teflon component is reinserted into the tip, which creates a pressure seal of the membrane through the 5 mm opening. This along with the force of a spring that resides in the base of the epoxy body seals the membrane tightly in order to prevent any of the internal fill solution from leaking out or sample solution from penetrating inward.

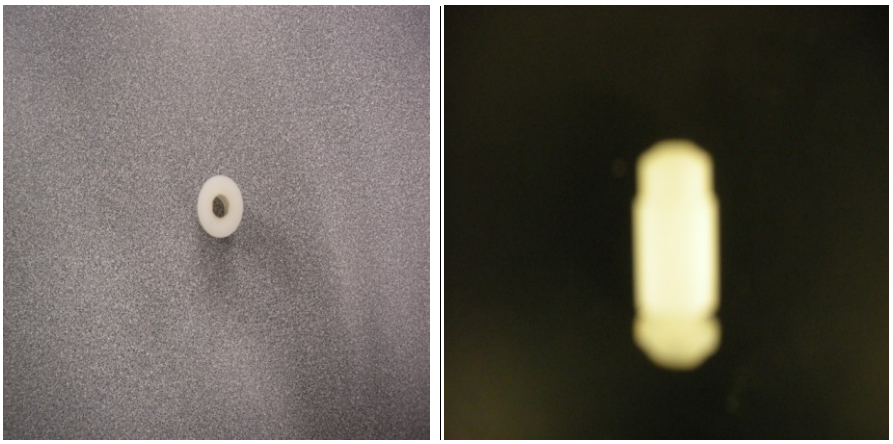


Figure 2: A membrane is placed over the hole in the Philips body electro tip (left) and removable inner teflon insert (right) is positioned back inside the tip to enable a pressure seal.

The base of the epoxy body spans approximately 10.5 cm and holds the glass tubing which acts as an internal reference electrode **(Figure 3).** The 11 cm tubing holds the inner fill solution as well as a chloridated silver-silver chloride wire. The glass tubing is longer than the base of the electrode causing the internal reference electrode to protrude upward to gain close proximity to the membrane.

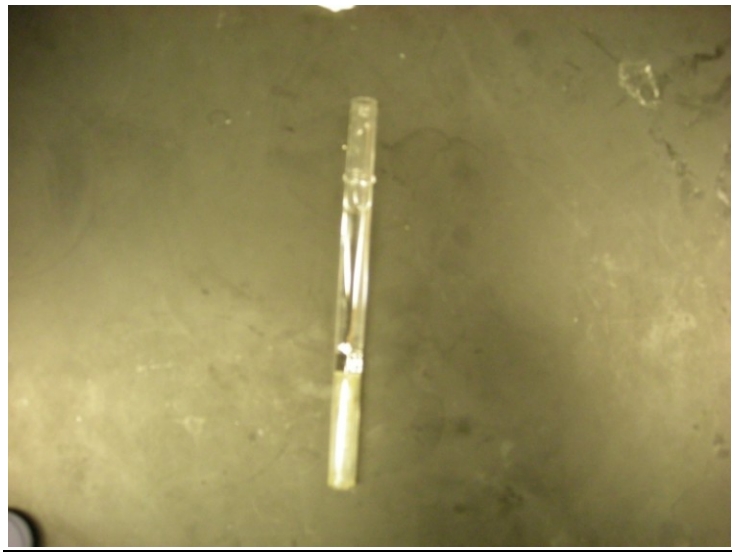


Figure 3: Internal glass reference electrode

A steel tube fits in between the internal reference electrode and the outer epoxy body to increase stability. The silver-silver chloride wire is sealed within the glass tubing and soldered to a gold spring about 3 cm from the end of the tube. The bottom of the inner glass tubing is thicker, and the diameter is narrowed allowing the gold spring to stay securely inside the end of the tube. This narrow bottom also allows the copper contact to fit securely into the internal reference electrode where it makes direct contact with the gold spring. The copper contact resides within a steel cap that easily attaches to the bottom of the epoxy base. There is a 1.2 cm removable metal spring that surrounds the base of the copper contact. This spring provides the force to push the internal reference electrode upward, which helps maintain a secure fit when the electrode tip is screwed on. The outside of the steel cap is designed to connect with low noise coaxial cables. This connection allows potentiometric measurements to be conducted in conjunction with a potentiostat or ISE meter. The components of the Philips body electrode (**Figure 4**.) must be assembled properly in order to attain accurate potential readings.

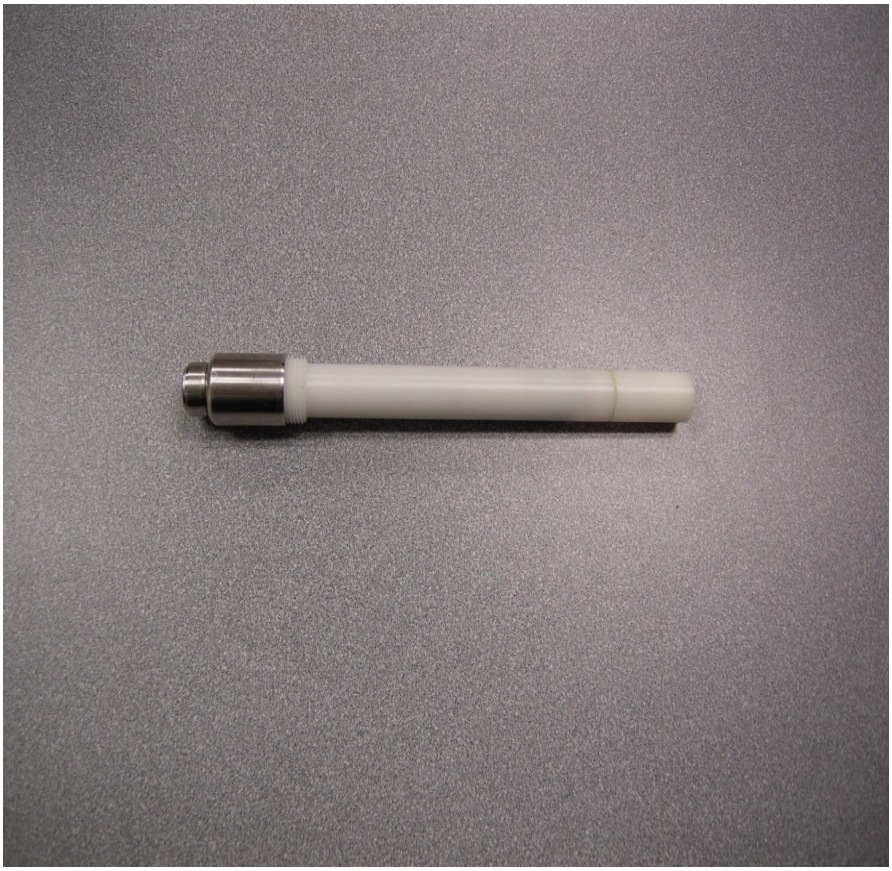


Figure 4: Fully assembled Philips body electrode

Background

2.1 Uses & Limitations

Ion selective electrodes have many practical uses as analytical potentiometric sensors. They are widely used as an effective tool in environmental monitoring. They are used in termination of nitrate levels in soil and in ground water[5]. Nitrates are released into ground water often through fertilizers and in the form of discharge from industrial processes. They have transformed from being referred to as a common pollutant to now as a potential health hazard. Nitrate toxicity causes a dangerous blood condition known as methaemoglobinaemia[5] and is possibly linked with the development of cancer in humans.

In the medical field, ion-selective electrodes are used in blood serum to determine concentration of the alkaline earth metals, magnesium and calcium. Calcium and magnesium play important roles in the human body. Calcium functions as a signal ion for many intracellular responses and plays a vital role in nutrition such as in the formation of healthy bones and teeth as well as muscle stimulation. Magnesium is active in cellular metabolism and the production of energy through its help with enzyme activity[6]. Deficiencies in both magnesium and calcium has been shown to cause osteoporosis

Ion selective electrodes serve as a low cost alternative to expensive, time-consuming methods for ion analysis. They lack some of the accuracy and reproducibility of such methods like X-ray fluorescence, colorimetry, and atomic absorption spectroscopy. These methods are however tedious and expensive, which makes it difficult to conduct constant experiments. Most ion selective electrodes are used over a range of 10^{-5}-10^{-1}M. The performance of these electrodes is constantly improving with further understanding of the membrane electrochemical processes[7]. For decades there has

been issues concerning the ability to increase the electrode's lower limit of detection (LOD). Through further understanding of ion fluxes through the ion selective membrane, the LOD has been expanded as low as 10^{-10} M[7]. The flux of ions from the membrane to the sample causes a limiting concentration of the primary ions near the sensing membrane. This phenomenon is observed even if the sample solution is diluted causing the LOD to be shifted upward. With the use of ionic buffers to control pH, ion flux has been greatly reduced, drastically improving the performance of ion selective electrodes.

The portability of ion selective electrodes is another advantage to conducting real world analysis. They are easily assembled and there is little prep time needed to use these tools. If any problems occur during potentiometric analysis, the electrodes can be quickly examined. If necessary a new membrane can be used and the inner fill solution can be easily replaced. It is recommended to precondition the electrodes prior to use[8]. Once this process is complete, the electrodes are ready for testing. Electrodes are also recommended be stored in the preconditioning solution so they are always available for immediate use. Electrodes must be rinsed of any preconditioning solution prior to use and should be rinsed of any sample solution prior to storage.

2.2 Electrochemical process

The electrochemistry involved in ion selective electrodes can be related to a galvanic cell. An example typical cell used for potentiometric measurements for potassium is:

Ag-AgCl|10^{-1} M KCl|PVC Membrane||Sample Solution||Sat KCl|Ag-AgCl

The single bar represents a phase boundary between the solid Ag-AgCl wire and the internal fill solution of the working electrode and reference electrode. The double bar

represents the liquid junction between the sample solution and reference electrode, and the membrane potential as the ions diffuse across the ion selective membrane. A typical setup for ion selective electrodes is shown in **Figure 5**.

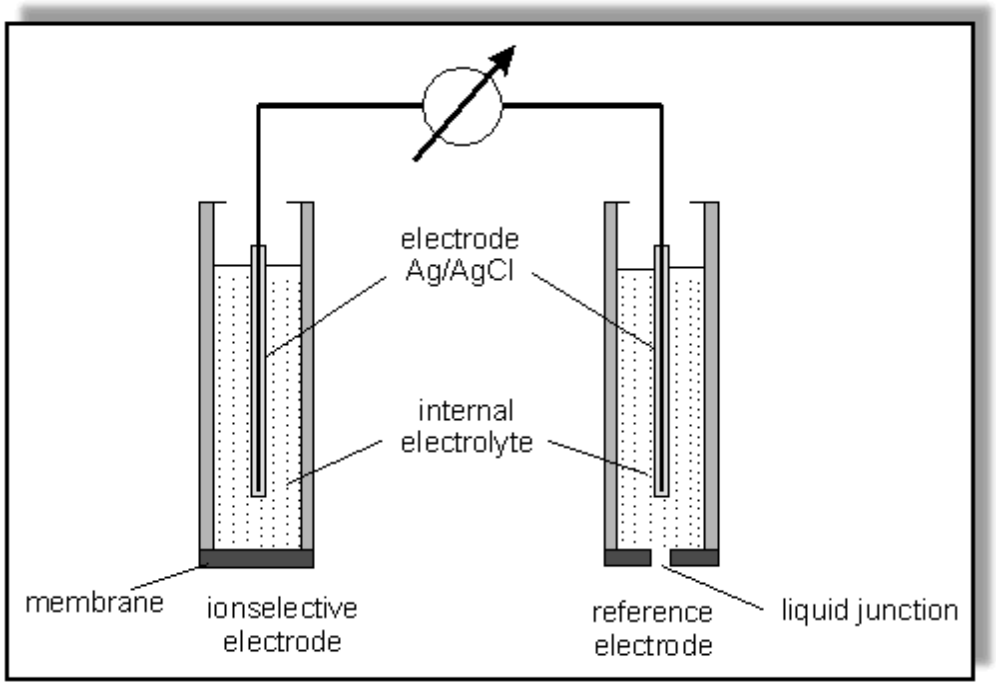


Figure 5: Standard two-electrode setup used for ISE Testing; both electrodes are connected to a potentiometer

The effectiveness of an ion selective electrode is dependent upon the potential difference between the sample solution and the internal electrolyte of the electrode. This potential difference is formed at the interface between the membrane and sample solution. Membranes containing selective ionophores have a potential difference that depends on the activity of a specific ion measured against an external reference electrode[9]. Activity is the number of ions interacting with the membrane. Activity is shown to be less than the actual concentration of ions in solution because ionic mobility is reduced by the presence of other ions[10]. The higher the concentration of other ions, either the same or different

from the species being measured, makes the difference between activity and concentration greater. In dilute solutions, this interference is very small and can be ignored in many practical applications. The function of the potential difference and the activity ideally follow the Nernst equation:

$$E = E° - (2.303RT/nF)Log(a) \quad (1)$$

In which E is the sum of the total potential generated across the working and reference electrode. E° is the cell constant corresponding to a particular reference electrode and ion selective electrode. **a** is the activity of the analyte of interest while **n** is the corresponding charge of the ion. T is the absolute temperature of system in Kelvin, R is the widely used gas constant (8.314 J K^{-1} $mole^{-1}$), and F is the Faraday Constant (96,500 C $mole^{-1}$). A plot of the Log(a) against potential will give a linear graph with the slope corresponding to 2.303RT/nF. The slope for ion selective measurements of monovalent cations should show a Nernstian response of 59.16/dec[9].

The selectivity of an ionophore is dependent on its ability to distinguish between a primary ion verses an interfering ion (**Fig. 6**). Selectivity is given as a logarithmic value using the equation:

$$\text{Log } K_{ij}^{POT} = \text{Log}([i]/[j]) \quad (2)$$

[j] represents the concentration of the interfering ion in the plateau region of an ISE measurement. [i] is the concentration of the primary ion at the potential where the interfering ion begins to plateau. The "POT" refers to the fact that the selectivity was determined using potentiometric methods.

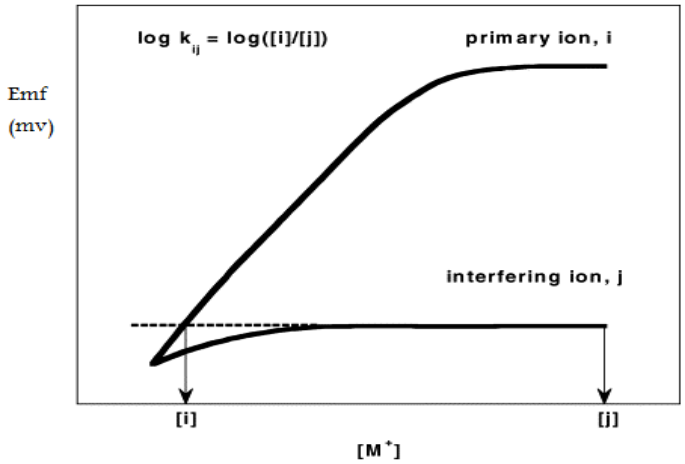


Figure 6: An example of a Selectivity plot

The Fixed Interference Method (FIM) and Separate Solution Method (SSM) are the two commonly used methods used to calculate these coefficients[10]. The FIM involves the use of a solution with constant concentration of an interfering ion while varying the concentration of the primary ion. SSM involves the use of two separate solutions, one only comprised of the primary ion and the other comprised only of the interfering ion[10]. These methods are recommended to be used with electrodes that demonstrate Nernstian or near Nernstian responses to both the primary and interfering ions.

Experimental

3.1 Reagents & Materials

All chemicals used were of analytical reagent grade. 1-Aza-18-crown 6-ether was purchased from TCI (Tokyo, Japan). Potassium tetrakis(p-chlorophenyl)borate (KTpClPB), Dioctyl phthalate (DOP), and Poly(vinyl chloride) high molecular weight (PVC) and Tetrahydrofuran (THF) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All electrolyte solutions were freshly prepared with high-purity Millipore deionized water.

1 M potassium chloride and ammonium chloride were prepared in .1M Tris buffer (pH 7.15). The Tris buffer was prepared in 4 liter glass container using deionized water. 48.456 g of tris(hydroxymethyl)aminomethane was dissolved in 4 liters of the deionized water. The pH of the buffer was lowered with constant stirring, hydrochloric acid (HCL) was added dropwise until desired pH was reached. Ammonium chloride solution was prepared by dissolving 54.5 g of ammonium chloride in 1000 ml of Tris buffer. The same process was repeated with 74.55 g of potassium chloride. Serial dilutions (10^{-1}-10^{-7}) were freshly prepared and kept in Erlenmeyer flasks covered with parafilm.

3.2 Membrane & Electrode Preparation

The 1-Aza-18-crown 6-ether membranes were prepared in standard ISE format[11]. The membrane casting solution had a composition of 1 wt% 1-Aza-18-crown 6-ether, 30 wt% PVC and 69 wt% Dioctyl phthalate (DOP) as the plasticizer. The membrane cocktail consisted of 240 mg of high molecular weight PVC, 552 mg of DOP and 8 mg of 1-Aza-18-crown 6-ether dissolved in 8 ml of THF. 2 mg of Potassium tetrakis(p-

chlorophenyl)borate was added to the membrane cocktail in an effort to improve lipophilicity of the membrane. The ingredients were dissolved in a 4 dram vial and allowed to stir overnight to completely dissolve in the THF. Sonication was attempted as described in previous articles[11] to shorten the mixing process, but it has been shown that sonication can destroy polymers. Sonicated membrane cocktails often seemed completely dissolved; however the lipophilic salt would precipitate out of solution and form crystals in the membranes. Once completely dissolved the membrane cocktail was poured into a glass ring (3 cm diameter) which had been sanded and smoothly seated on a flat glass surface. The membrane solution was covered with filter paper an allowed to dry overnight at room temperature for slow evaporation of the solvent. Master membranes were cut using a "size 3" cork borer (7mm) and were incorporated into a Philips body electrode. A master membrane was placed in the removable cap of the electrode using tweezers, and the teflon stabilizer was inserted to secure the membrane was seated properly with no apparent leakage. 0.1 M potassium chloride was added as the internal electrolyte. The electrodes were allowed to precondition over night in a dilute solution of potassium chloride (10^{-3} M).

3.3 Thickness Determination

The thicknesses of the membranes were determined using the goniometer. The thickness determination was done in a simple fashion. A gold slide of known thickness (1mm) was placed on the Goniometer platform. The Goniometer pump was turned to an intensity where the light was able to distinguish between the gold slide and the platform. A line was set using the appropriate software. The relative screen height of the slide was

recorded. A master membrane was cut out and placed on top of the gold slide. This was done carefully to ensure the membrane was positioned evenly on the slide. A new line was set from the top of the slide to the top of the membrane. The relative screen height was recorded. The ratio of the screen height of the slide to the membrane was compared to the known thickness of the gold slide. The thickness of the membranes was determined to be approximately .5mm.

3.4 ISE Testing

Potentiometric experiments were conducted using the Gamy Reference 600^{TM} Potentiostat/Galvanostat/ZRA. A two-electrode set up was used with an Orion double junction Ag/AgCl reference and the PBISE as the working electrode. A membrane area of .012 cm^2 was exposed to electrolyte solution. Calibration graphs were constructed using solutions (10^{-7}-1M) of ammonium chloride and potassium chloride in 0.1 M Tris buffer (pH 7.15). The electrodes were rinsed with deionized water between each immersion in solution. Standard additions of ammonium chloride were used to determine exact concentration of the ion in the plateau region of the calibration graph. This was performed using 200 ml solutions of 0.1 M ammonium chloride to which 4 ml aliquots of 1 M ammonium chloride were added until the corresponding potential ceased increasing. The same process was repeated with 1 ml aliquots of 1 M potassium chloride to identify the corresponding concentration of potassium ions at the potential where the ammonium ion plateau occurred. Selectivity of the electrode was determined using the previously described Separate Solution Method. The effect of pH was examined using 10^{-3} M solutions of the ammonium and potassium chloride. The pH was altered using dropwise addition of dilute sodium hydroxide and hydrochloric acid. The change in pH was

recorded using the Denver Instrument pH meter.

Results and Discussion

4.1 Electrode Characteristics

The electrochemical performance of the Philips body electrode varied with consistency on a day-to-day basis. Initially there existed problems with improper placement of the membrane inside the electrode. This produced poor results of about 10-15 mV/decade for the 1-Aza-18-crown 6-ether-based electrode. The electrodes were evaluated thoroughly and several steps were taken to try and solve the poor performance. In an attempt to eliminate the perceived causes of the poor performance, the electrodes were disassembled and cleaned of any salt build up. The copper contacts were cleaned of any oxidation and were smoothed using 500 and 4000 grit sand paper. The inner reference electrode was emptied of its internal fill solution and the silver wire was chloridated using bleach that was available in the lab. Some of the electrode tips were noticeably worn and were removed from use. The membranes were initially cut using a "size 4" cork borer, which resulted in master membranes that were too large (9mm). A switch was made to using the "size 3" cork borer which allowed for ideal membrane size (7mm). However, the results did not improve after any these attempts. It was realized soon after that there was a removable teflon insert inside the tip of the electrode. Once a membrane was properly inserted into the electrode the performance drastically improved.

The electrode responses were inconsistently linear over a concentration range of 10^{-5} – 1 M. The typical slope of the calibration plots ranged from 50 – 53 mV/decade. The average slope was 51.3 mV/decade as shown in **Figure 7**. At each decade the stable e.m.f. readings were obtained within 30 s for 10^{-5}-1M solutions. In dilute solutions ($< 10^{-5}$ M), the response times were observed within 40 s. The electrodes only showed a

useful lifetime of 48 hrs, in which the potentials were reproducible within ±5 mV. The variation of the slope did not exceed ±10 mV.

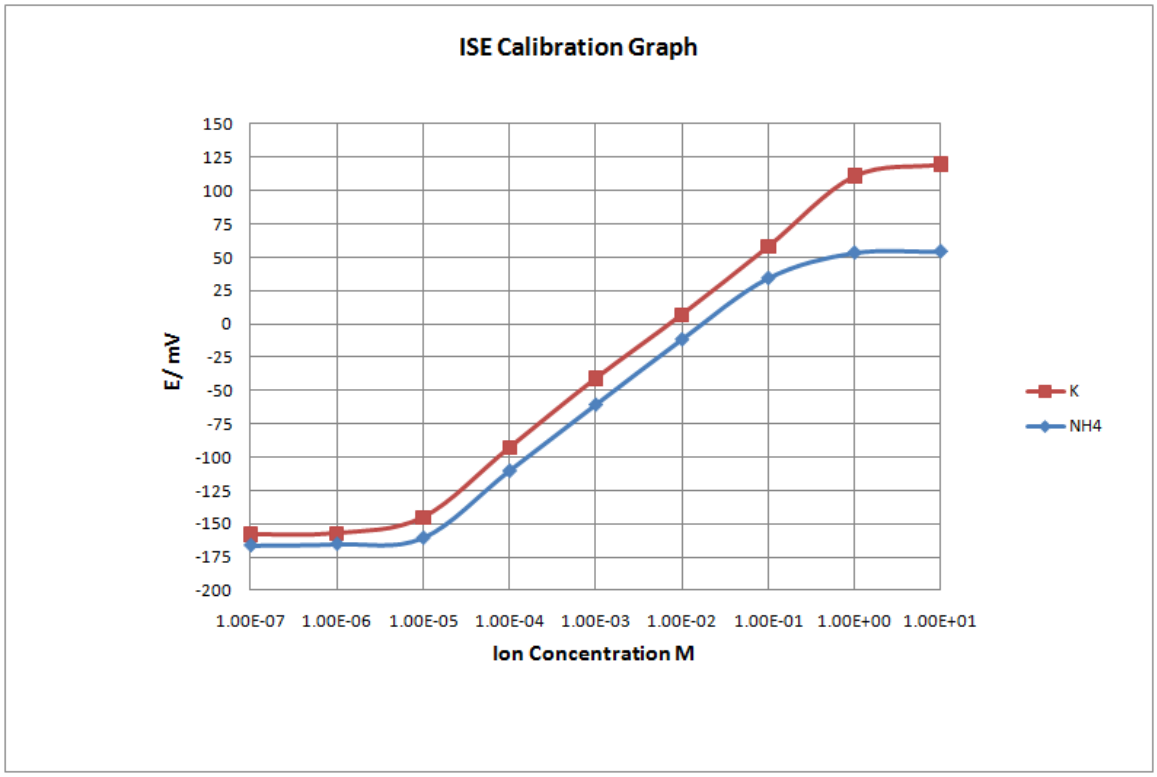


Figure 7: Calibration graph for 1-Aza-18-crown 6-ether electrode for Ammonium and Potassium

4.2 Electrode Difficulties

The electrode did not give stable readings for more than two consecutive days. New membranes had to be used every day or every other day. Similar electrodes have been reported to have a useful lifetime around four weeks[12, 13]. Membranes often became opaque after substantial time in aqueous solutions. Fully discolored membranes produced basically the same results as membranes that were allowed to precondition for a short period time. There was a dilemma because electrodes are recommended to precondition in a dilute solution of the analyte of interest prior to use. This preconditioning time has

been reported to be as short as one hour[13] or as long as two days[14]. When the electrodes were not allowed to precondition, they displayed poor performance in potentiometric experiments. The electrodes were also stored in the same dilute solution while not in use, which caused any membrane to eventually become opaque. Different methods were used to try to eliminate the discoloration of the membranes. After the membranes had been allowed to completely air dry, they were transferred to a dessicator and kept under vacuum for an additional day to evaporate any residual solvent. These membranes were removed from the dessicator and exposed to a 10^{-2} M solution of potassium chloride. The additional drying process had no effect upon eliminating the rapid discoloration. Instabilities in lipophilic salts have been shown to cause membrane degradation[15]. Two membranes were prepared without potassium tetrakis(p-chlorophenyl)borate (KTpClPB) as a lipophilic salt. A control membrane was prepared with KTpClPB to compare the occurrence of discoloration. Master membranes were cut from each of the three membranes and stored in a petri dish containing 10^{-2} M potassium chloride and discoloration occurred within two hours for all three membranes.

4.3 Selectivity

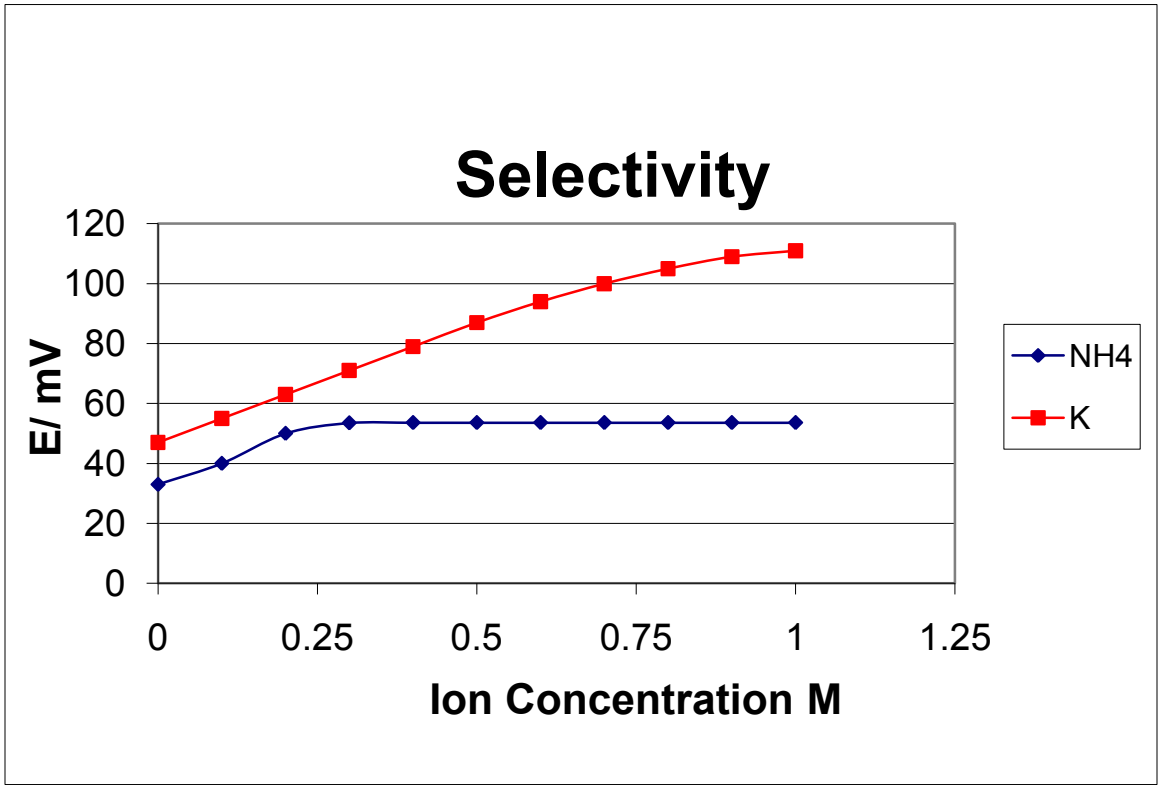
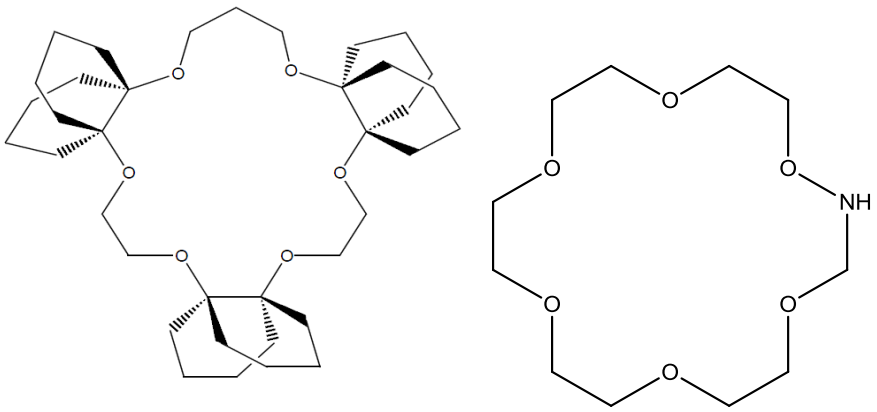


Figure 8: ISE potential as a function of ion concentration for potassium and ammonium. The results show poor selectivity for potassium over ammonium

The selectivity of the electrode to potassium is illustrated in **Figure 8**. This graph shows the dependence of the potential of the 1-Aza-18-crown 6-ether on concentrations for potassium and ammonium. The results show the low selectivity of 1-Aza-18-crown 6-ether to potassium in comparison to its primary interfering ion ammonium. The results show that potential increases relative to the ion concentration up to a certain plateau area where it remains constant. The potential curve for ammonium loses its linearity beyond 0.1 M concentrations. The selectivity was determined using eq. 2 where the primary ion **i,** is potassium ion and the interfering ion **j,** is the ammonium ion. The selectivity

coefficient of potassium versus ammonium yields, log $K_{K^+,NH4^+}^{POT} \sim -.317$. This value indicates that the 1-Aza-18-crown 6-ether is much less selective than Valinomycin, the mainly used ionophore in detection of potassium. Valinomycin selectivity has been reported as log $K_{K^+,NH4^+}^{POT} \sim -1.92$[16]. This logarithmic value indicates that Valinomycin is nearly a hundred times more selective to potassium versus ammonium, in comparison to the 1-Aza-18-crown 6-ether being less than ten times more selective. The poor performance of the 1-Aza-18-crown 6-ether is largely due to its basic crown structure[17,18]. Basic crown ether structures are able to change conformation to bind smaller and larger interfering ions. The ionophore is able to form a wrapping complex around a smaller ions and a sandwich complex with larger ions. Despite the close match of the ionic cavity (~138 pm)[19] of the ionophore to the ionic radius of potassium (133 pm)[19] selectivity will be poor due to the lack of the ionophore's molecular rigidity (**Figure 9**).



TD19C6 1-Aza-18-crown 6-ether

Figure 9: Basic structure of 1-Aza-18-crown 6-ether hinders its ability to be highly selective to potassium. TD19C6[18] is an ammonium ionophore with three decalino subunits to enhance molecular rigidity which improves its selectivity.

4.4 Effect of pH

The effect of pH on the potassium chloride and ammonium chloride test solutions on the electrode potential were examined by observing the potential change over a pH range of 4-10. Dilute solutions of sodium hydroxide and hydrochloric acid were added dropwise to 10^{-3} M solutions for pH adjustment. The results are shown below in plots of potential versus pH (**Figure 10 & 11**). The Philips body electrode worked consistently over the range while immersed in potassium chloride. The potential did not change by more than ± 2 mV. The electrode worked over a pH range of 4~7.3 while immersed in ammonium chloride. As the pH was brought to 8 and above the potential significantly decreased. This behavior can be attributed to the disassociation of ammonium ions as the pH approached its pKa. The pKa of ammonium is 9.23, as the pH was raised above 7.23 the ammonium ions begin to disassociate into ammonia.

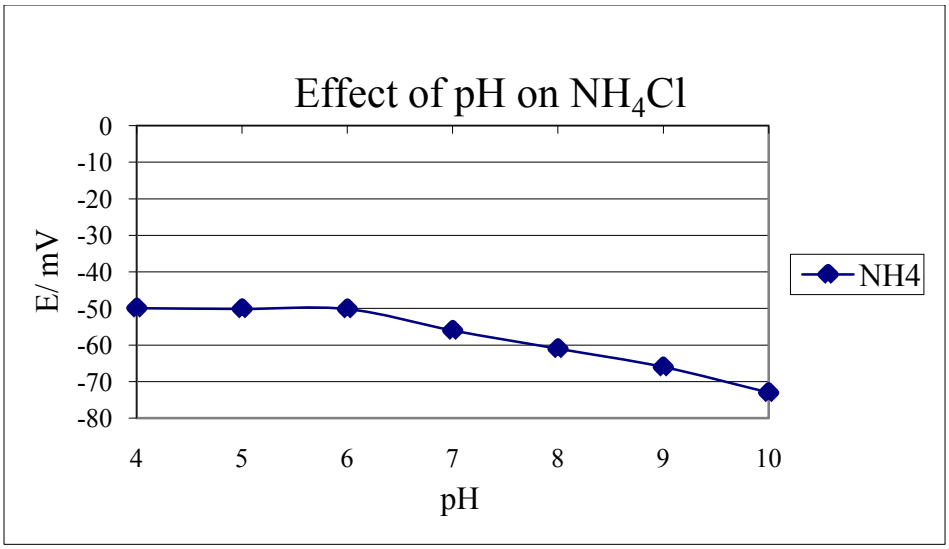


Figure 10: Effect of pH on the electrode response while in KCl

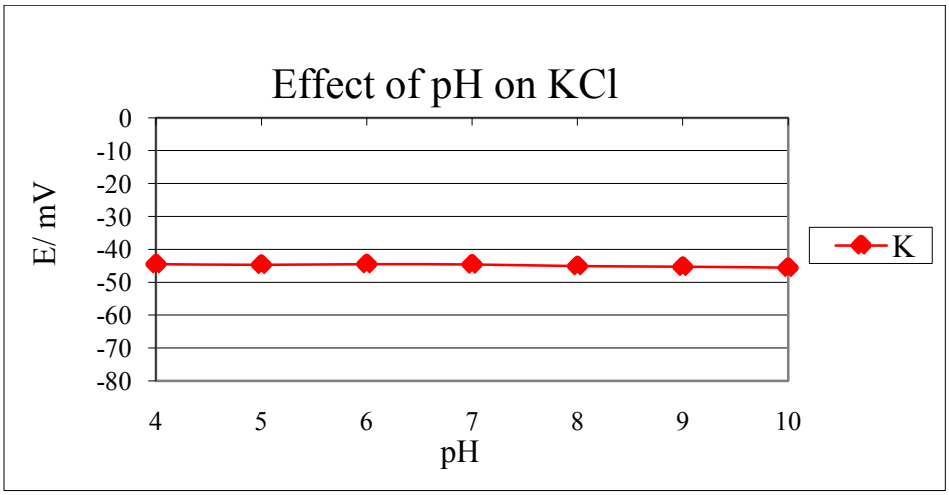


Figure 11: Effect of pH on the electrode response while in NH_4Cl

Conclusions

The ion selective membranes that were fabricated using the 1-Aza-18-crown-6 ether showed poor selectivity to binding potassium ions versus ammonium ions. Philips body electrodes were used as the working electrode in a standard two-electrode setup to perform ion selective electrode potentiometry experiments. The electrode displayed a relatively poor selectivity of potassium over ammonium, $\log K_{K^+,NH4^+}^{POT} \sim -.317$, which is much worse than the reported values for Valinomycin, $\log K_{K^+,NH4^+}^{POT} \sim -1.92$. The basic structure of 18-crown-6-ether without blocking subunits makes it difficult to differentiate ammonium from potassium. The crown ether is flexible enough to accommodate ions with similar sizes. The ionic radii of ammonium (143 pm) and potassium (133 pm) fall within a 10 pm range of the ionic cavity of the 1-Aza-18-crown 6-ether. Nonactin is a fairly flexible ionophore, but utilizes the specific placement of its four ethereal oxygen atoms to somewhat selectively bind ammonium. The ionophore displays a selectivity of $\log K_{NH4^+,K^+}^{POT} \sim -1.0$[20], meaning it is around ten times more selective to ammonium.

I would recommend research focusing on of the synthesis of similar 18-crown compound with additional subunits to increase the molecular rigidity as well as create the block-wall effect[18] in an effort to increase selectivity. Careful consideration must be used in the placement of bulky blocking subunits. The bulky subunit should be positioned on the 18-crown compound in manner that allows its size to be oriented in a vertical position in respect to the crown ring. This large subunit should add support to the molecular rigidity allowing the ring size to remain in a fixed state. The placement of the subunit should be in close proximity to the oxygen donor atoms in the crown ether compound

eliminating the space and availability for the larger cations to bind[18]. The number of blocking subunits in the crown ether must also be considered. An appropriate amount of subunits should be added to increase the block wall effect, but not sterically interfere with the binding of the primary cation. The addition of blocking subunits will help decrease the affinity to bind larger molecules like ammonium.

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