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Synthesis of Two New Crown-Ether Cyclophanes for Measuring Cation-Aromatic Interactions in Solution

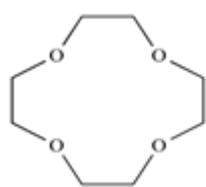
Abstract:

Molecular recognition is the specific noncovalent interaction between two or more atoms or molecules, such as hydrogen bonding, metal coordination, and hydrophobic forces. Molecular recognition plays roles in biological systems as well as in the development of new technologies. Consequently, molecular recognition is crucial for us to study and become more familiar with these interactions. In this study, we have synthesized two new 15-crown-5 ether cyclophanes: compounds **1** and **2**. Compound **1** consists of a phenyl ring as the spacer while compound **2** possesses an anthracenyl spacer. Using the cyclophanes as *host* molecules, we performed molecular-recognition studies using potassium ion as the *guest* cation. With known concentrations of each host and using the proton NMR spectroscopy, we performed a titration experiment with a known aliquots of potassium hexafluorophosphate in acetonitrile. Our goals are (1) to determine the association constant of each host compound with the potassium cation and (2) to ascertain the contribution of cation- π interaction in the molecular recognition process by comparing the association constants of the two cyclophane hosts. Noting that the structural difference between the two host compounds relates to the π electron density of anthracene being superior to that of the benzene, the difference in the association constants was used as a measure of the cation- π interaction. With the aid of the *Bindfit* program, the changes in the proton NMR chemical shift as a function of concentration enabled us to determine an association constant of

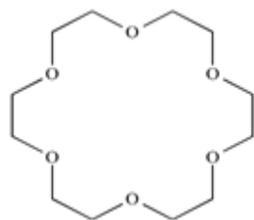
24.60 M⁻¹ for host 1 and an association constant of 49.98 M⁻¹ for host 2, which amounted to association energies of -1.897 kcal/mol for host 1 and -2.316 kcal/mol for the host 2.

Introduction:

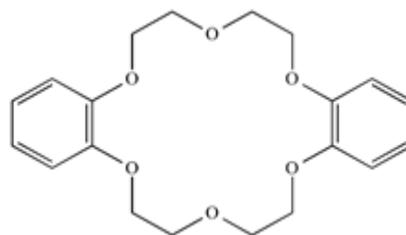
Crown ethers are molecules made up of hydrogen, carbon and oxygen, where each oxygen atom is bound between two carbon atoms, which is called an ether functional group (2). They are called ‘crown’ ethers because their shape resembles that of a crown. Some examples of crown ethers included in Figure 1.



12-Crown-4



18-Crown-6



Dibenzo-18-Crown-6

Figure 1. Examples of crown ethers

Crown ethers are remarkable for their ability to exhibit selective cation binding (3). Atoms like sodium and potassium, which contain specific metallic properties, pass through the center of the ring and are able to attach themselves to the exposed oxygen atoms. They fit somewhat like a key in a lock, depending on the element as well as the size of the ring. The crown molecule can act as a “host,” and it is able to take its “guest” to a place where it would not go

on its own. For example, a crown ether can take a cation through the membrane that makes up the wall of a cell. Crown ethers have high selectivity which allows them to “identify” the guest atom in a solution and effectively wrap around it.

Crown ethers are able to mimic, in a not-so complicated way, the vastly complicated functions of biological systems, enzymes for instance. This mimicry has made them fascinating molecules for various fields and their study and could result in the development of new pharmaceutical systems. Crown ethers could potentially serve as a natural method of crossing the blood-brain barrier and could help us understand how the body moves essential elements for life like sodium and potassium, into cells. Other types of uses for crown ethers include their potential to serve as “scavengers,” where they would be able to remove elements like radioactive strontium from the environment. This property would allow them to also regulate concentrations of sodium in the blood. Researchers have even suggested that crown ethers could someday be used to extract uranium or gold from seawater (2).

In this experiment two host molecules were utilized: host 1 and host 2. Their chemical structures follow:

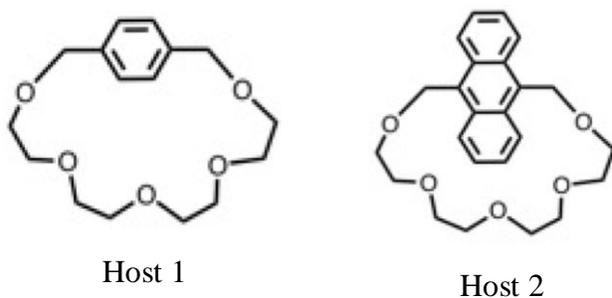


Figure 2. The two newly synthesized crown-ether cyclophanes

The objective was to insert the guest, a potassium cation, into the cavity of the crown ether and calculate the association constants of the resulting complex. This could be done using NMR Spectroscopy and the *BindFit* program, which has been used before for equilibrium/association constant quantification. The association constant is highly dependent on the interactions that are occurring between the host and guest molecules; in this case, the interactions occur between the cation and oxygen atoms and between the cation and the π electrons in the aromatic rings. The cation was obtained from potassium hexafluorophosphate; its structure is shown in Figure 3.

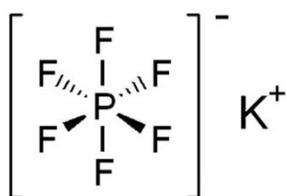


Figure 3: Two-dimensional molecular structure of potassium hexafluorophosphate

When this compound is dissolved in a polar solvent, the K^{+} ion will separate from the negatively charged hexafluorophosphate, and it is able to move freely in the solution and, thus, can bind in the cavity of the crown ethers.

Procedures and Methods:

The experiment was initiated by obtaining two clean vials and 10-uL, 25-uL, and 500-uL syringes. Thereafter, around 25mg of host 1 was measured and added to one of the vials. To

follow, host 2 was required to have the equivalent number of moles as host 1, so the mass of host 2 that provided the same number of moles as the sample of host 1 was calculated, measured, and added to the same vial. To dissolve the two host compounds, 620uL of deuterated acetonitrile was added to the vial, and the vial was shaken. Subsequently, the molarity of each host and the total molarity of the solution was calculated; the guest compound was chosen to have a concentration that is approximately 24 times more as the total concentration of the hosts solution. With the guest concentration and the selected volume of deuterated acetonitrile – 655uL – the mass of potassium hexafluorophosphate to create this concentration was calculated, measured, and added to the second vial. The 655uL of deuterated acetonitrile was measured after and added to the same vial. The vial was shaken until the guest was fully dissolved. After, the solution containing the host was transferred into a NMR tube, and the first NMR reading of the hosts alone (without any of the guest) was taken. The first addition of the guest was made with a chosen volume, the NMR tube was shaken well, and the concentration of the guest added was calculated. An NMR reading was taken after each addition, and the NMR spectrum was compared to the NMR spectrum of the hosts solution with no guest added to it. Afterwards, more additions of the guest and more NMR readings were taken as such until the peaks were not seen to change significantly. Thereafter, one signal for host 1 and one signal for host 2 were chosen to examine; the chemical shifts at the beginning of the titration experiment and the change in chemical shifts after each addition were recorded for both of the chosen signals. Following this, the host concentration, the changes in guest concentration, and the changes in chemical shift were imputed into an Excel sheet, separately for each host. The excel sheets were independently uploaded to the *BindFit* program, and the association constant and a plot was obtained for

each host. Lastly, the association energy of the complex was calculated for each host, and the difference of the association energy was computed as well.

Results:

Figure 4: NMR spectrums of host 1, 2 and guest additions

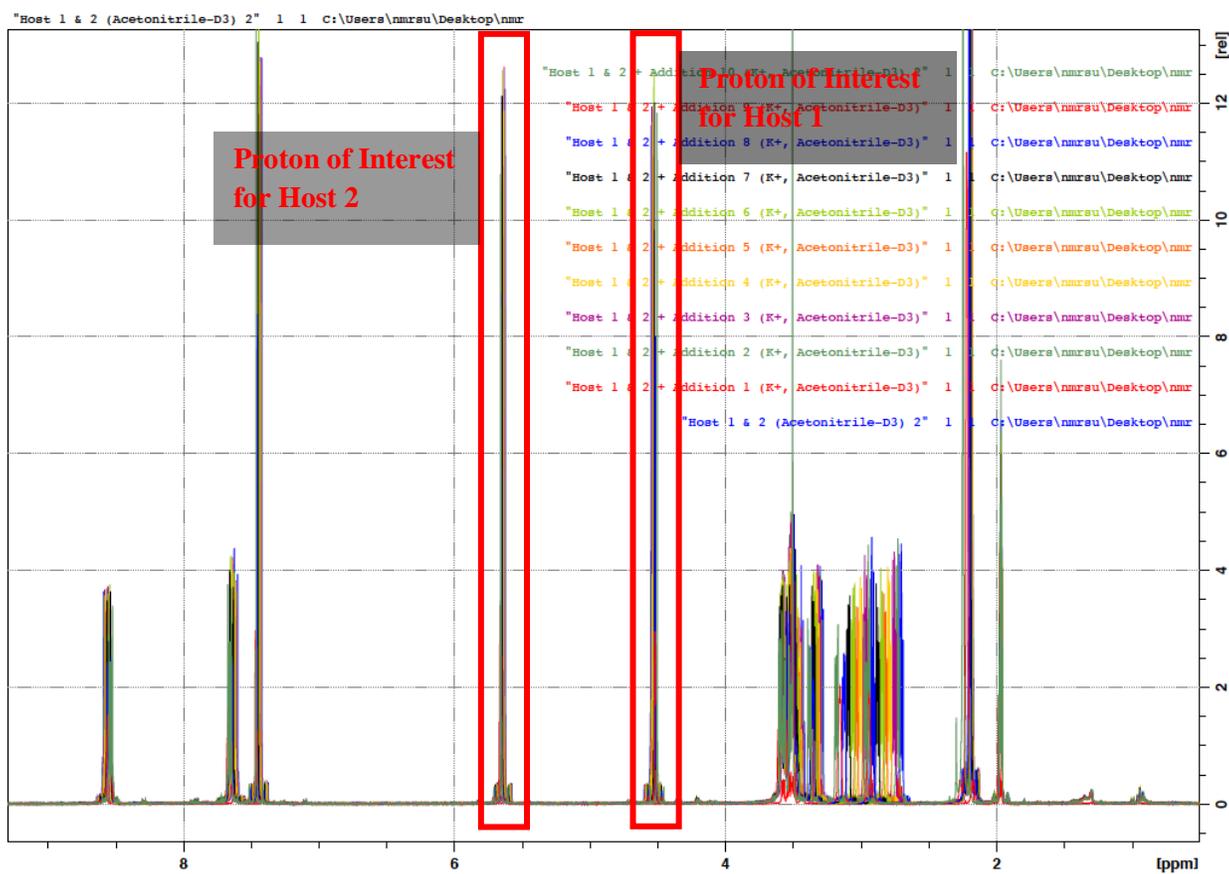


Figure 5: Proton of interest for host 1

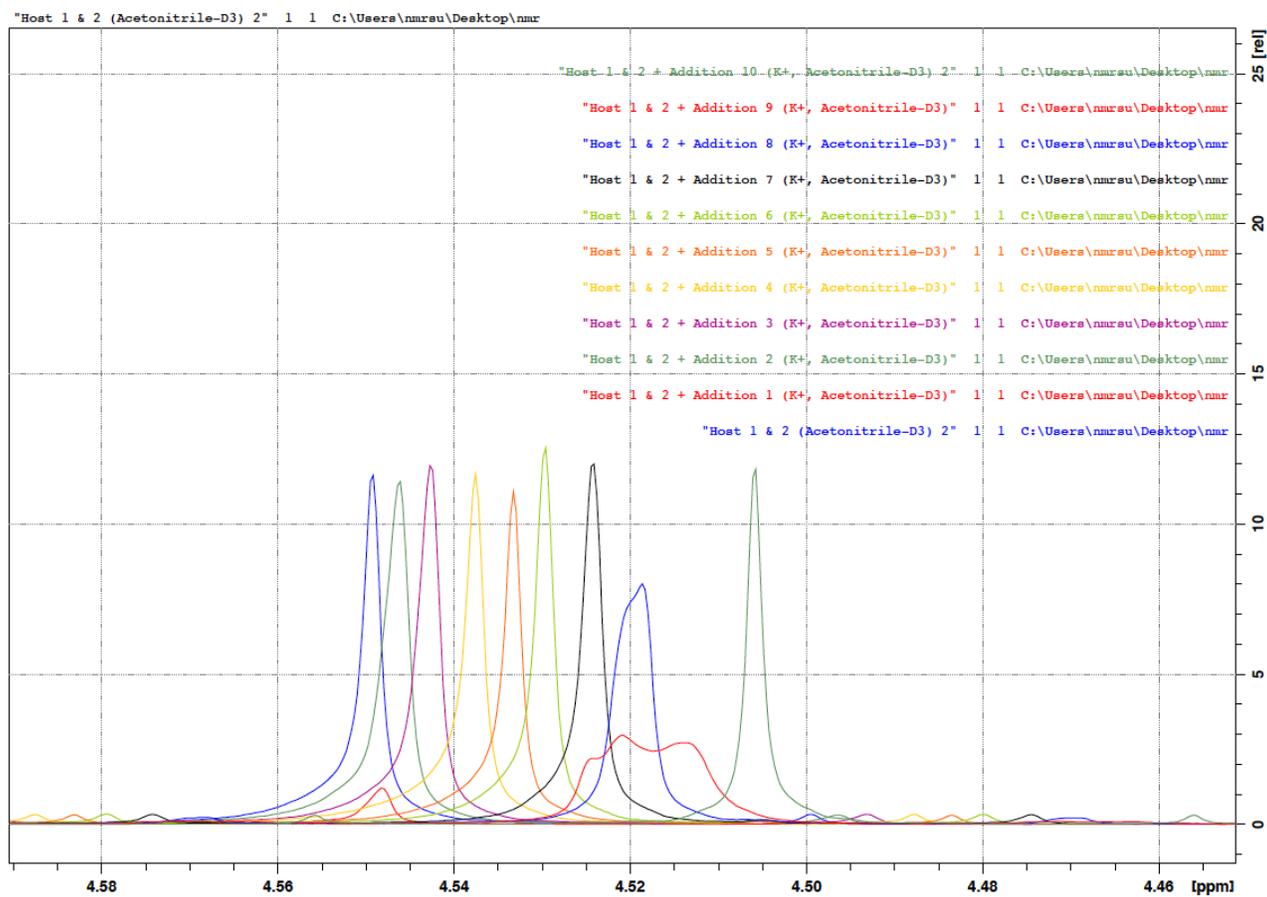
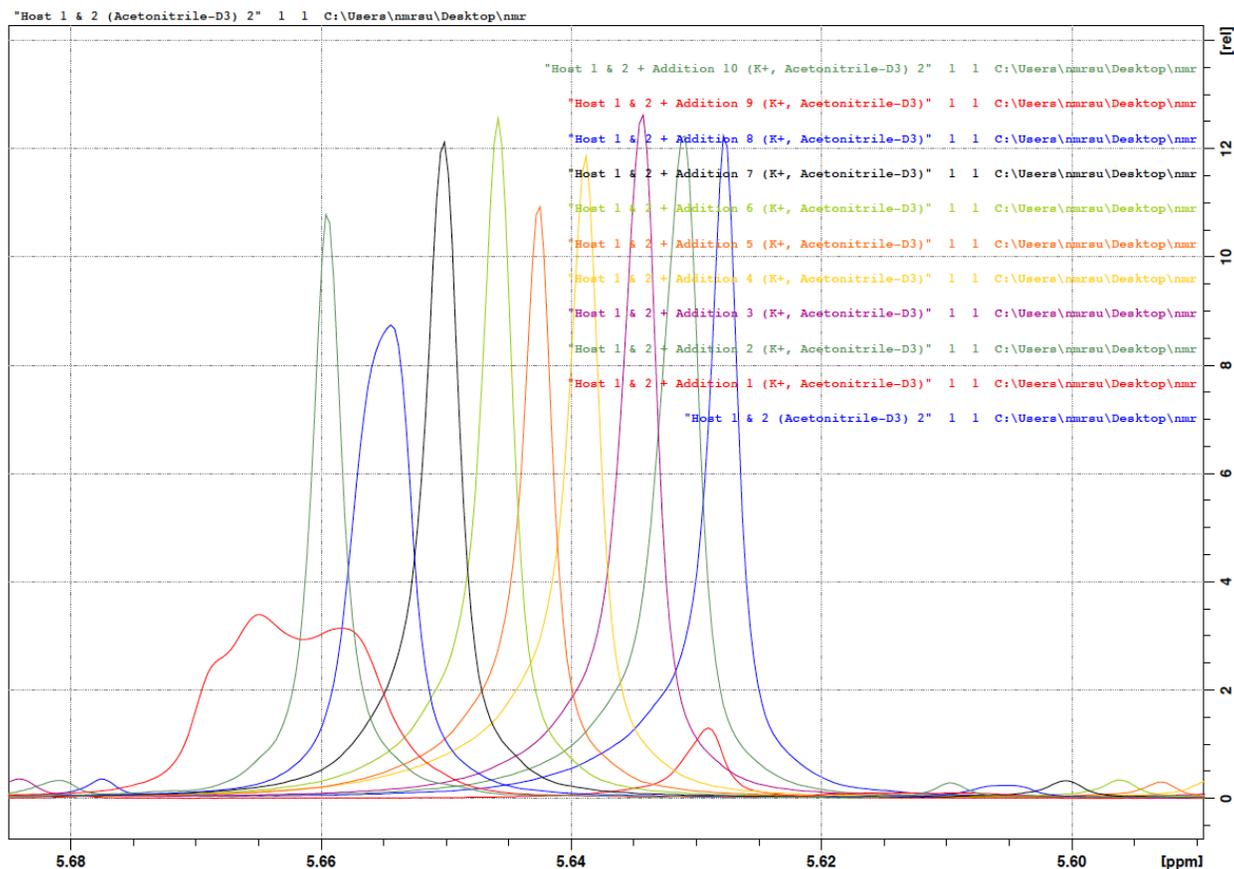


Figure 6: Proton of interest for host 2



Note (for both figures 5 and 6): it was discovered that re-shimming was required prior to taking the NMR reading for the ninth addition. This was not done, so the “Host 1 & 2 Addition 9 (K⁺, Acetonitrile)” peak came out indecisive. Since at least eight data points for the additions are required, this peak was disregarded, and nine of the remaining data points for the additions were used; this did not affect the data.

Table 1: For host 1, host concentration, additions of guest, changes in guest concentration & changes in chemical shift

Host 1 Concentration (M)	Addition of Guest	Guest Concentration (M)	Chemical Shift (ppm)
0.01360610		0	4.5493
0.01360610	Addition 1: 1.0	0.00106721	4.5482
0.01360610	Addition 2: 2.0	0.00319134	4.5462
0.01360610	Addition 3: 5.0	0.00842425	4.5427
0.01360610	Addition 4: 5.0	0.01361068	4.5376
0.01360610	Addition 5: 5.0	0.01869786	4.5333
0.01360610	Addition 6: 5.0	0.02370593	4.5297
0.01360610	Addition 7: 10.0	0.03349192	4.5243
0.01360610	Addition 8: 15.0	0.04762170	4.5197
0.01360610	Addition 9: 95.0	0.12420860	4.5059

Table 2: For host 2, host concentration, additions of guest, changes in guest concentration & changes in chemical shift

Host 2 Concentration (M)	Addition of Guest (uL)	Guest Concentration (M)	Chemical Shift (ppm)
0.01360610		0	5.6277
0.01360610	Addition 1: 1.0	0.00106721	5.6291
0.01360610	Addition 2: 2.0	0.00319134	5.6310
0.01360610	Addition 3: 5.0	0.00842425	5.6344
0.01360610	Addition 4: 5.0	0.01361068	5.6389
0.01360610	Addition 5: 5.0	0.01869786	5.6426

0.01360610	Addition 6: 5.0	0.02370593	5.6459
0.01360610	Addition 7: 10.0	0.03349192	5.6502
0.01360610	Addition 8: 15.0	0.04762170	5.6548
0.01360610	Addition 9: 95.0	0.12420860	5.6595

Figure 7: Fit of chemical shift (ppm) against guest concentration (M) over host 1 concentration (M)

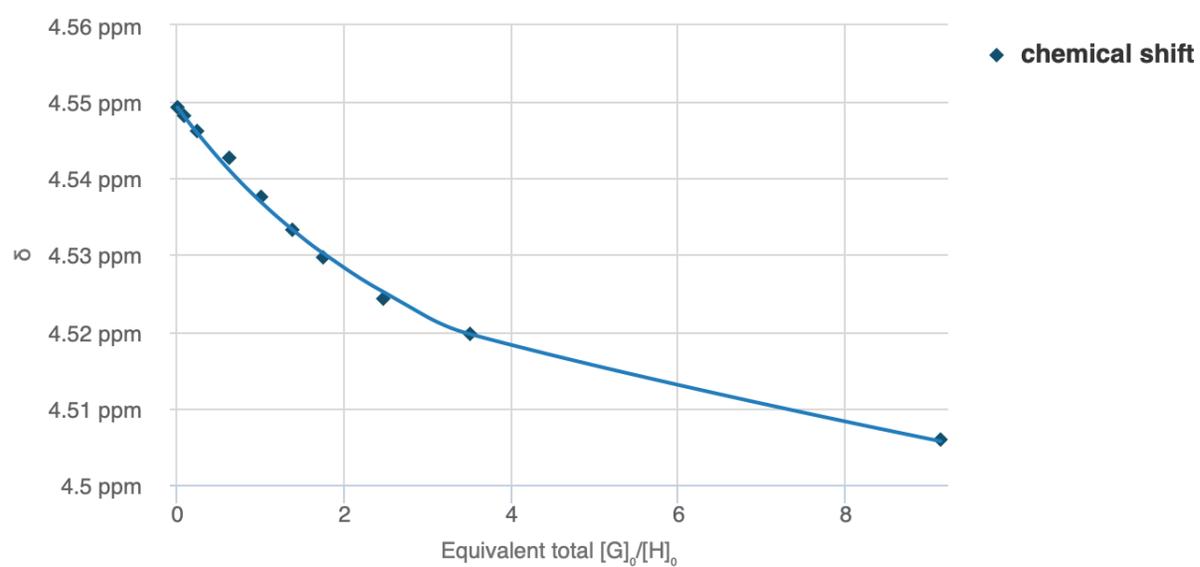


Figure 8: Fit of chemical shift (ppm) against guest concentration (M) over host 2 concentration (M)

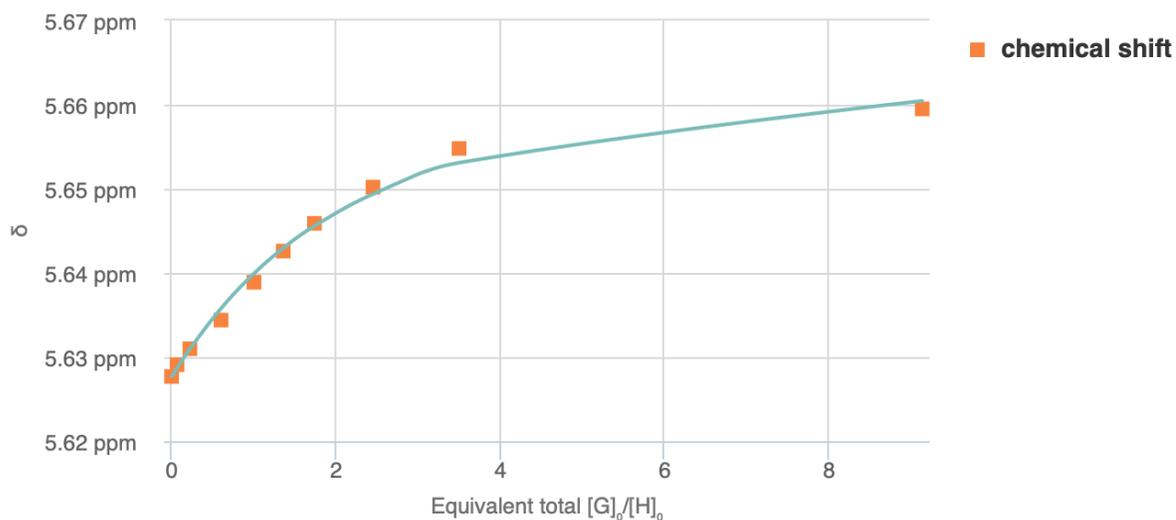


Table 3: Association constants & error in deuterated acetonitrile

	Association Constant (M^{-1})	Error
Host 1 & Guest	24.60	$\pm 6.3264\%$
Host 2 & Guest	49.98	$\pm 13.5864\%$

Table 4: Association energy

	Association Energy
Host 1 & Guest Complex	$\Delta G = -RT \ln K_a$ $= -(8.314 J \cdot K^{-1} \cdot mol^{-1})(298.0 K) \ln(24.60)$ $= -7.935 kJ/mol$ $= -1.897 kcal/mol$
Host 2 & Guest Complex	$\Delta G = -RT \ln K_a$ $= -(8.314 J \cdot K^{-1} \cdot mol^{-1})(298.0 K) \ln(49.98)$ $= -9.691 kJ/mol$ $= -2.316 kcal/mol$
Difference In Association Energy Between The Two Complexes	$\Delta G = (-2.316 kcal) - (-1.897 kcal)$ $= -0.419 kcal/mol$

Discussions:

From the proton NMR spectra, it was seen that each addition of the guest changed the chemical environment of the host compounds, and therefore the chemical shifts of the protons on the host molecules were seen to alter as well. The *Bindfit* program, with the obtained chemical shifts and the corresponding concentrations of the host and the guest, generated the association constants for the two host and guest complexes. The host 1 and guest complex had an association constant of 24.60M^{-1} , and the host 2 and guest complex had an association constant of 49.98M^{-1} . This signified that host 2 had a higher interaction with the K^+ guest. The structures of both hosts are very similar, with the only difference being the number of aromatic rings. The host molecules were purposely synthesized to have some identical structural properties such as the number and location of the oxygen and carbon atoms of the crown ethers. Because of this, the effect of the aromatic rings was solely displayed. Host 2 resulted in a higher association constant, which is explained by the structure of the molecule; host 2 had more aromatic rings that were part of the crown ether than host 1. Aromatic rings have π electrons, and since host 2 had a greater number of aromatic rings, it also had a greater amount of π electrons or greater π electron density; this allowed for a greater cation- π interaction, resulting in more potassium ions to interact with the host and form a higher concentration of the host-guest complex.

Moreover, the association energy was calculated for both complexes. The host 1 and guest complex had an association energy of -1.897kcal/mol , and the host 2 and guest complex had an association energy of -2.316kcal/mol , with a difference being -0.419kcal/mol . The binding of the guest ion to the host molecule was a spontaneous reaction and was exergonic; the energy of the host decreased because the binding of the guest is a stabilizing interaction as a

more stable conformation is achieved with the binding of the guest cation. Host 2 had a higher association energy because of the higher association constant, which informed that host 2 was stabilized by the guest more than host 1 was. Furthermore, the *BindFit* program provided error values for the determination of the association constants. The software has chemical shift and concentration ratios programmed within it in order to compare and validate experimental data. The association constant for host 1 had an error of $\pm 6.3264\%$, and the association constant for host 2 had an error of $\pm 13.5864\%$. This error was largely due to the utilized syringes. The syringes were manual, and therefore obtaining the exact measurements for the titration was extremely difficult and was not always done, as seen by the error. Also, the syringes, sometimes had tiny air bubbles inside them which were unable to be removed even with great effort; this also had introduced some error.

Conclusions:

Crown ether compounds have a variety of uses. Increasing solubility and nucleophilicity, mimicking enzymatic functions, and storing ions are just a few of the incredibly useful properties of crown ethers. Studying these compounds is therefore quite important. These uses all require researching and learning the interactions of these compounds; the most notable interaction of crown ethers is the association with metal ions. Both host 1 and host 2 favored the binding of the potassium ion, with host 2 having a higher association constant (49.98M^{-1}) than host 1 (24.60M^{-1}). There was some error in determining these association constant values: $\pm 6.3264\%$ for the host 1- K^+ complex and $\pm 13.5864\%$ for the host 2- K^+ complex; these deviations were due to the flaw of the manual syringes. Moreover, host 2 had a greater affinity for the guest because of the additional π electrons available for a greater cation- π

electron interaction. This interaction was stabilizing as shown by the spontaneity and by the energy release. Host 2 was stabilized more than host 1, and host 2 had a higher release of energy (-2.316kcal/mol for host 2 and -1.897kcal/mol for host 1) because of the higher association constant. As mentioned before, deploying resources to study these host-guest complexes is vital because of the multiple ways these compounds can be utilized, both in biology and chemistry. Gathering more information through research will increase the efficiency of the uses of crown ethers and make a greater contribution to the fields of science.

Safety Considerations:

In this experiment, standard organic safety protocol was followed by wearing goggles, gloves and lab coats. The potassium hexafluorophosphate compound was handled with extreme care as it may cause chemical conjunctivitis with connect with eyes, causes skin irritation with contact with skin, may cause gastrointestinal irritation with nausea, vomiting and diarrhea if ingested, and causes respiratory tract irritation if inhaled. When working with an NMR spectrometer, it is important to keep in mind the recommended restrictions provided by the manufacturer. Metallic objects must not be brought within 10 feet of the magnets and no objects can be placed inside the NMR except for the NMR tube and the holder. People with medical implants such as cardiac pacemakers and neurostimulators also need to stay away from the NMR; exposure could result in injury or death (4). Another hazard of working with NMR spectroscopy is the fragility of the NMR tubes. These tubes have thin walls and can easily break; therefore, it is important to be careful when placing them into the NMR to prevent injuries.

References:

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- (4) Columbia University. (n.d.). Safety in the NMR lab. Retrieved December 10, 2017, from <https://nmr.chem.columbia.edu/content/safety-nmr-laboratory>

Acknowledgment:

I would like to thank Dr. Bright Emenike for providing the necessary materials and instrumentation required for the execution of this experiment. This project would not have been possible without his guidance and support.