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Design and Synthesis of Crown Ether Ligands for Use in Metal Organic Frameworks

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Design and Synthesis of Crown Ether Ligands for Use in Metal Organic Frameworks

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Abstract

In recent years research focused on the development of porous solids derived from metal-organic frameworks (MOFs), or coordination polymers, has exploded with the number of articles discussing the synthesis, structures, properties and applications of these materials increasing dramatically every year. Porous MOFs are crystalline solids permeated by channels that exhibit a high internal void volume and surface area with tunable properties that make them ideal for a range of applications. Those properties include high thermal stability, MOFs diverse framework architectures, and adjustable pore size, void volumes, and reactivity. The research described here focused on two areas related to synthesis of MOFs. In the first part of this project, the synthesis of a cadmium-based MOF, 1-Cd featuring 4-(imidazol-1-yl)benzoic acid ligands coordinated to cadmium(II) ions was investigated at room temperature resulting in a MOF with a crystal structure differing from the crystal structure of the cadmium-based MOF obtained previously in our group via hydrothermal synthesis. TGA experiments showed that this new MOF structure was able to reversibly absorb DMF as a guest molecule, indicating that the solid material is porous. The second part of this research explored several synthetic strategies to prepare two new ligands for use in MOF synthesis that incorporated macrocyclic crown ethers into the structure of the ligand either as part of the ligand backbone or as a pendant side-chain. The synthetic approaches investigated to prepare the two new ligands, dimethyl 2-(((1,4,7,10-tetraoxacyclododecan-2-yl)methyl)amino)terephthalate and 4,4'-(1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarbonyl)dibenzoic acid are described.

Acknowledgements

I would like to thank my MQP advisor for this project, Professor John C. MacDonald. Professor MacDonald provided many opportunities to learn about the chemistry and equipment used in these experiments and was always willing to help with and explain any problems I may have had. I also would like to thank Professor James. P. Dittami as well as Moqing Hu and Pranoti Navare.

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1. Introduction

Porous metal-organic frameworks (MOFs) are a class of highly-ordered crystalline solids that has attracted considerable attention over the last two decades.[1] Porous MOFs are constructed of metal ions or ion clusters covalently bound to organic ligands that serve as linking components to create a continuous framework, or coordination polymer, in one, two, or three dimensions. The resulting solids are permeated by channels typically ranging from 4-20 Å in diameter that impart porosity.[1] Analogous to porous inorganic zeolites, MOFs exhibit exceptionally high pore volume and surface area . Unlike zeolites, which have porous properties that generally cannot be modified without changing their structures, MOFs allow chemists to customize the framework structures and surface properties of channels with desired specifications via synthetic modification of the organic components. Because of this ability it is possible to incorporate a wide range of ligands, functional groups, metal ions, and reactive chemical species within the structure of frameworks and as such, the materials properties of MOFs are being widely explored. For example, MOFs with interesting physical behavior such as lumincence,[5] magnetism,[28] and a range of optical properties[28] have been demonstrated.

Of all the properties of MOFs, the most interesting are the exceptionally high internal void volume and surface area created by the channels. The ability to modify the dimensions of channels by lengthening organic ligands, and to tune their surface properties by varying the functional groups and substituents present on the ligands in the framework makes MOFs a unique class of porous materials. Since their discovery almost 15 years ago, the majority of research on MOFs has focused on developing synthetic methodology necessary to prepare MOFs and on cataloging the different types of framework architectures that can be created.[29] More recently, research on MOFs as turned toward exploring the functional behavior of MOFs and their application in processes that take advantage of their porosity. For example, considerable research is now focused on developing MOFs as porous hosts for applications involving hydrogen or methane storage,[2,3] heterogeneous catalysis,[4] and environmental remediation[29] to name a few. Highly porous materials have been used for many decades for applications such as environmental remediation or as chemical adsorbents in industrial settings. The ability to create custom three-dimensional structures allows chemist to tailor solids to have ideal properties for removing potential toxins from chemical wastes and separating them from useful materials. For example, the well-known MOF developed by Yaghi known as IRMOF-5, which derives its porosity based on a cubic framework comprised of zinc ion clusters linked by benzene-1,4-dicarboxylic acid ligands, has been shown previously in our laboratory to provide roughly an 8-fold excess adsorption of phenanthrene over naphthalene. That work demonstrated selectivity by IRMOF-5 for sorbing larger amounts of phenanthrene compared to naphthalene due to its larger surface area.[6]

Research in our group currently is focusing on two areas related to the investigation of new MOF systems. One area is synthesis of novel organic ligands for the development of new families of MOFs that exhibit non-cubic, lower-symmetry architectures. The other area is investigation of the sorption behavior of our MOFs and known MOFs toward hydrophobic and hydrophilic guest molecules such as polyaromatic hydrocarbons (PAHs) and pharmaceutical drugs in an effort to develop MOFs as sorbents for environmental remediation and drug delivery. Recent efforts have focused on investigating the sorption characteristics and kinetics toward PAHs for IRMOF-5 and 2-Cd MOF (a MOF developed in our lab). [6]

The aims of this project were to further increase our knowledge of MOFs in two ways. The first objective was to explore the development of a synthetic method to carry out fast, room temperature synthesis of IRMOF-5 that could also be employed to prepare Cd MOFs in high yield as an alternative to the time-consuming hydrothermal synthesis traditionally used to prepare those MOFs.[4] That new synthesis produced Cd MOF-1 as a fine white powder in high yield and demonstrated a fast and easy method to prepare gram quantities of MOF in a far shorter time frame (i.e., 30 minutes) than normally is required utilizing hydrothermal methods (days). The experimental procedures, characterization of the Cd MOF-1 solid by thermogravimetric analysis and X-ray powder diffraction, and analysis comparing the structure and properties of the product to Cd MOF-1 prepared hydrothermally are described . The second object of this project was to explore the synthesis of two new ligands for generating MOFs. The target ligands consisted of aromatic dicarboxylic acids that contain macrocylic crown ethers either as the backbone of the ligand, or as a substituent covalently linked to the ligand. Those ligands were prepared with the intention that they could be utilized to generate novel MOFs featuring crown ethers within or dangling off the framework. MOFs featuring crown ethers have not been reported previously. We are interested in developing crown-based MOFs because crown ethers are well-known to bind alkali metal ions such as Li, Na, and K with high selectivity. Therefore, it is likely that MOFs derived from those ligands also should exhibit high selectivity for ionic guests containing those ions. The design and synthesis of these ligands is described.

2. Background

2.1 Porous solids

Porous solids are a group of materials that have pores or channels that run through their structures that are large enough to permit the diffusion of guest molecules. In addition, to be classified as porous solids, those materials must continue to exhibit porosity after evacuation of solvent or guest molecules. This porosity is necessarily linked to increased surface area, which in turn provides solids that have great potential to act as molecular adsorbents – a property that researchers have been able to exploit to develop safe and cost effective production of commercial sorbent materials.

Several porous solids have been well known for a number of years in the scientific community. Activated carbon has long been considered the 'gold standard' of highly porous materials. Typically produced through the pyrolysis of organic compounds, activated carbon has the advantages of being very cost effective to make as well as providing a very high surface area material that is non-toxic for use in a number of applications. Sorbent materials based on activated carbon are used for catalysis,[7] environmental remediation,[8] and medical applications,[8] to name just a few.

Another popular choice for highly porous materials are inorganic zeolites. Those materials consist of porous aluminosilicate solids that are formed either naturally and mined from the earth, or synthetically using a sol-gel process to create a wide array of possible structures and properties. With approximately 3 million tons of zeolites produced annually, those materials are used for a number of different applications that require the use of porous solids.[9] Zeolites possess a wide range of channel sizes (typically 3-8 Å) and pore volumes, but the ability to modify their porous properties is somewhat limited by their restricted compositions and synthetic requirements.

As previously described, metal-organic frameworks (MOFs) have been shown to have exceptional porosity and surface areas that can far exceed those of zeolites. Accordingly, MOFs are quickly emerging as the new leaders in custom made high surface area materials. Ordered frameworks in MOFs have been shown to have surface areas as high as 3000 m^2/g compared to 904 m^2/g for the most porous zeolites known and 2030m^2/g for disordered carbon[10]. In fact, some MOFs have been reported with estimated surface areas of roughly 4500m^2/g. Scientists and engineers have made use of these materials by exploiting their increased surface areas to create a number of commercial and industrial applications where materials are required that can adsorb a large amount of guest molecule relative to the mass of adsorbent used. More specifically, a large amount of research has been done to investigate MOFs for use in energy storage and catalysis. In addition, fields such as molecular separation and environmental

remediation have seen great breakthroughs by applying newly designed MOFs to challenging problems.

2.2 Crown Ethers

2.2.1 Properties of Crown Ethers

Crown ethers represent a group of compounds with an exceptional ability to selectively coordinate to ions of alkali ions that has made them the target of extensive research since their discovery. The term crown ether refers to cyclic compounds constructed with ethylene bridges separated by oxygen atoms. Since their initial discovery, that name has evolved to refer to a number of similar structures that make use of different heteroatoms joining carbon bridges of differing sizes and properties. Typically constructed using a modified Williamson Ether Synthesis to join individual monomers, these reactions can be adapted to create unique structures with similar basic pieces.[11] In addition, substituted crown ethers can be used to impart a huge range of properties to these compounds. Examples of several commonly used crown ethers are shown in Figure 1.

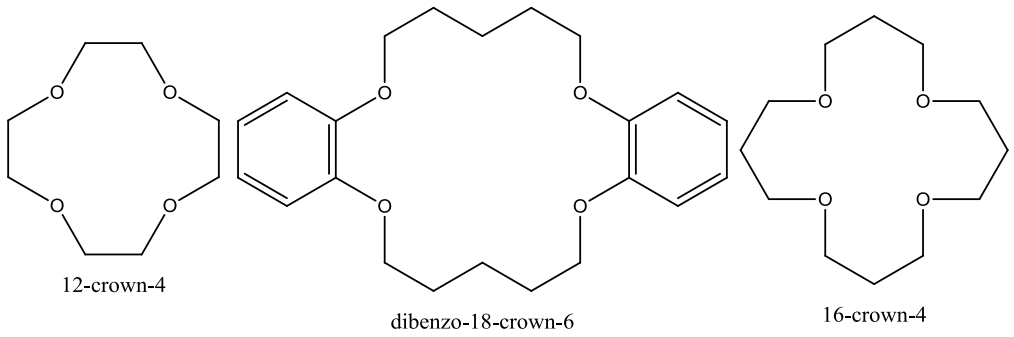

Figure 1. Examples of commonly used crown ethers.

One interesting property of crown ethers is that the electron pairs present in the ring heteroatoms provide the molecule with the ability to complex a wide range of cations in the empty cavity present in the center of the ring[11]. A space filling model of 18-crown-6 is shown in Figure 2 illustrating the central cavity in which K^+ ions bind by coordinating to the six surrounding ether oxygen atoms. In the case of 18-crown-6, the diameter of the interior hole is about 4.0 Å.[11] That structural feature allows for crown ethers to form a number of complexes with cationic species.[12]

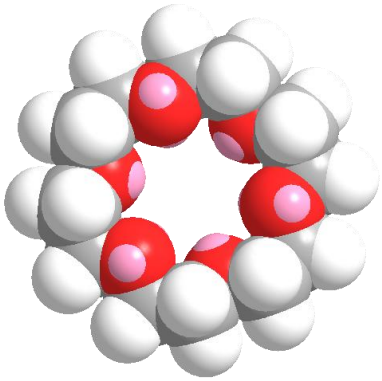

Figure 2. A space filling model of 18-crown-6 showing the open space at the center of the crown and electron pairs present on the exposed oxygen atoms (in pink).

Coupled with the hydrophobicity of the aliphatic bridges within the structure, these features allow crown ethers to help overcome some obstacles that often plague organic synthesis. For example, crown ethers are often used to solubilize ionic species such as sodium hydroxide in non-aqueous solvents by shielding the resulting ionic species.[13, 14] In addition to increasing solubility, crown ethers have been shown to increase reactivity of the exposed counter ions within aprotic solvents for a number of species.[14]

Because of the spatial restrictions defined by the dimensions of the void at the center of the molecule and the corresponding variation of those dimensions depending on the size of the ring, crown ethers show different affinity toward specific cations. For example, 18-crown-6 shows a strong interaction for the K^+ ion, but limited complexing power for the Cs^+ ion.[11] These properties allow three of the most common crown ethers (12-crown-4, 15-crown-5, and 18-crown-6) to be used to complex different metal ions – Li^+, Na^+, and K^+ respectively.[12] It is this property that our group hopes to exploit in creating MOFs that show selective uptake of specific salts versus those salts that should have lower uptake based on the well understood binding properties of crown ethers. The synthetic work to prepare crown-substituted ligands described later in this report serves as a first step toward development of crown-based MOFs.

2.2.2. Applications of Crown Ethers

Aside from the applications to wet chemistry described above, crown ethers have found a home in various fields in chemistry and biology. The important complexing power of crown ethers has allowed them to be used in a number of ion selective electrodes. Gokel, Leevy, and Weber identified crown ethers unique structural properties and relative ease of synthesis as important characteristics in their widespread use in such electrodes and as ionophores for other

applications.[13] One such application is to the use of specialized dyes to indicate the presence of one or more cation in a multiphase solution. By utilizing modified 18-crown-6 and 15-crown-5 ethers, one group has successfully synthesized dyes which have been used in extraction spectroscopy to detect the presence of sodium in blood serum as well as lithium.[14] These dyes were successfully able to extract these cations from an aqueous/organic interface.

In addition to normal colorimetric spectroscopic methods, crown ethers have been used to create ions sensors which respond to the presence of target ions by fluorescence. Typically, these sensors contain a receptor unit (crown ether) and a fluorphore which is quenched by the free lone pair of one of the heteroatom within the crown ether. Binding a cation to these lone pairs removes the quenching effect and allows the fluorphore to fluoresce freely. [13]

Due to the chiral nature of some substituted crown ethers, scientists have been able to separate a number of optically active compounds from racemic mixtures. One study has shown that optically active amines can be separated using the chiral 18-crown-6-tetracarboxylic acid as a pseudo-stationary phase for capillary zone electrophoresis.[15] Additionally, Armstrong et. Al. have shown that specialized chiral crown ethers can be used in columns constructed for reverse phase HPLC to separate optically active amino acids. [16]

2.3. Synthesis of MOFs

Over the past few decades a number of models have been presented to describe the nature of MOF structures and their essential 'building blocks'. To help develop an understanding of the construction and basic structure of MOFs it is informative to consider MOFs as the combination of a discrete metal ion center coordinated to discrete organic ligands of fixed length and well-defined organization, as illustrated in Figure 3 for a MOF with a simple cubic structure. Although in reality, that type of representation is highly simplified, its simplicity provide a clear picture of basic connectivity between the organic and ionic components present in MOFs.

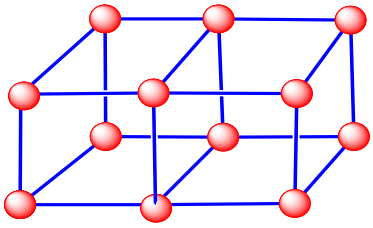

Figure 3. Illustration of the connectivity between rigid organic ligands (blue) and metal ions (red) present in a MOF with a simple cubic structure. Channels are present in the spaces between the components.

2.3.1. Hydrothermal Synthesis of MOFs

In the synthesis of MOFs, it is generally desirable to work under reaction conditions that allow the components to react slowly, so that assembly of the MOF results in formation of large single crystals suitable for analysis by X-ray diffraction in order to determine the crystal structures. As such, early synthetic methodology to create MOFs evolved toward approaches that generally lead to the formation of large single crystals. The most common method used for that purpose today is hydrothermal synthesis, which generally involves heating a mixture of organic ligands and metal salt in solution in a high-pressure reaction vessel at elevated temperature over several days. MOFs are typically created under hydrothermal conditions through the slow deprotection of carboxylic acid methyl or ethyl esters in aqueous solutions at elevated temperatures. Those conditions allow slow conversion of the protected ester to the corresponding carboxylate ions, which then coordinate reversibly to the metal ions, driving formation of extended three-dimensional coordination networks that define the framework. That type of reversible reaction leads to slow generation of crystals over the course of hours, days, or weeks in some cases.

2.3.2. Room Temperature Synthesis of MOFs.

Applications where MOFs are utilized generally require that large crystals of MOF be crushed to a fine powder to maximize surface area of the MOF particles and expose a reasonable amount of the solid for sorption of molecular guests. Therefore, when large single crystals of MOFs are not required for structural determination, alternative synthetic methods that allow more rapid synthesis of microcrystalline MOF particles are desirable. Toward that goal, Huang *et al* developed a rapid room temperature procedure to synthesize MOFs. That approach utilizes ligands with free carboxylic acids (deprotonated by organic bases) to create MOFs in high yield within minutes as fine precipitates that can be recovered easily by filtration.

2.3.3. Activation of MOFs

Many applications require MOFs to be ‘activated’ before the solids can be effectively employed. That process is used to remove solvent and unused reagent from the surface of the MOF as well as in the pores and channels (for example, our unactivated 1-Cd MOF showed evidence of triethylamine remaining despite repeated washings). Although some MOFs exhibit higher strength adsorption, heating just past the boiling point of the particular solvent and reagents for extended periods (>6 hours) is typically sufficient to remove the vast majority of guests. The

samples can then be stored under vacuum or at elevated temperatures until they are ready to be used with little or no consequence to their properties.

3. Experimental

3.1. Synthesis of Ligands

3.1.1. Synthesis of ethyl 4-(imidazol-1-yl)benzoate

Synthesis of the 1-Cd ligand was carried out using a procedure developed previously by our group.[17] The synthesis involved two steps: (1) coupling a fluoro-substituted ester to imidazole via nucleophilic aromatic substitution, and (2) deprotecting the ethyl ester via hydrolysis to yield the carboxylic acid as shown in Figure 4. Although samples of previously synthesized 1-Cd ligand were used for these experiments, the general reaction scheme is outlined below.

Ethyl 4-fluorobenzoate (1 eq.) was dissolved in 10mL DMSO in a round bottom flask. Imidazole (1 eq.) and potassium phosphate (2 eq.) were added to the solution. The solution was refluxed under a nitrogen atmosphere at 120°C for 24 hours. The resulting pale yellow solution was cooled to room temperature and then then poured into 200mL of cold water to produce a white precipitate. The precipitate was then collected by filtration and dried to yield a white solid in 65% yield.

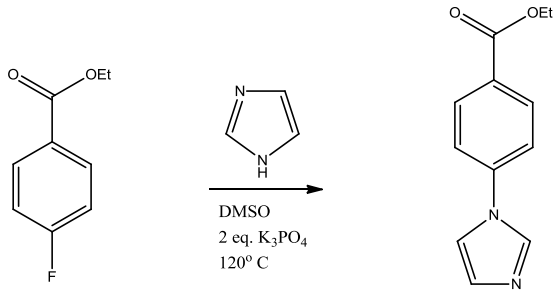

Figure 4. Scheme used to couple the fluroester to imidazole.

Hydrolysis of the ester to the carboxylic acid. As shown in Figure 5, ethyl 4-(1*H*-imidazol-1-yl)benzoate (0.200g 0.927mmol, 1 eq.) was added to a round bottom flask. To that flask 10mL of a 19:1 Ethanol/H_2O solution was added such that the total volume contained 0.1M ligand. Sodium hydroxide pellets (0.146g, 3.65mmol, 3.9 eq.) were crushed and added to the solution. The solution was then refluxed for 2 hours, then cooled to room temperature. The pH of the

solution was adjusted to pH 7 using HCl, which caused a fine white precipitate to form. The resulting solid was collected by suction filtration and washed with cold 19:1 ethanol/H_2O and dried to give .1630g of a white solid (94% yield).

4-(1*H*-imidazol-1-yl)benzoic acid: ^{1}H NMR ($CDCl_3$) δ (ppm) 8.18 (d, 2H), 7.39 (d, 2H), 7.05 (m, 2H), 4.42 (q, 2H), 2.41 (s, 3H), 1.43 (t, 3H). IR(cm^{-1}): 1700, 1600, 1290, 1245. Mass Spectrometry mass 230.1 amu.

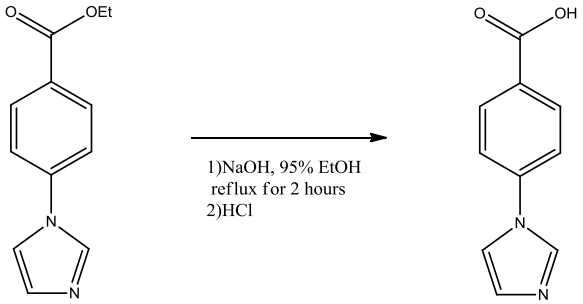

Figure 5. Reaction scheme used to deprotect the carboxylic acid.

3.1.2. Synthesis of the 12-Crown-4 ligand - dimethyl 2-(((1,4,7,10-tetraoxacyclododecan-2-yl)methyl)amino)terephthalate

The proposed synthesis of the title 12-crown-4 ligand was designed in two steps. First, the corresponding 12-crown-4 alcohol was converted to the mesylate using methanesulfonyl chloride and then the mesylate was reacted with the aminoterephthalate to yield the final product. Although these two steps seem straight forward, there are a few inherent difficulties presented by this synthesis. In the first portion of the experiment, the reaction must be kept very dry to avoid deactivating the methanesulfonyl chloride. In addition, any water present could potentially regenerate the starting materials through nucleophilic attack of the hydroxide ions in water. These delicate conditions are easily achieved by flame drying glassware and careful control of the atmosphere exposed to the reactants. All experiments detailed here were conducted under nitrogen gas to ensure limited exposure to water vapor in the laboratory air.

In addition to the difficulties outlined above, this reaction was also potentially complicated by the fact that primary amines such as is present on dimethyl 2-aminoterephthalate, are typically poor nucleophiles. In addition, the primary amine is present on a bulky terephthalate group, and the target for nucleophilic attack sits adjacent (alpha) to the large crown ether. Furthermore, the

aromatic esters present are known electron-withdrawing groups that further reduce the nucleophilicity of the amine. To help overcome some of these problems, the relatively poor alcohol leaving group was converted to a mesylate using a method adapted from Crossland and Servis[25]. That reaction was shown to be rapid and to proceed in high yield, making it ideal for our synthesis. After replacement of the alcohol proton by the mesylate group, the nucleophilic amine was able to react much more readily.

In attempting a direct alkylation of primary amines under appropriate conditions there are often many potential competing side products to consider. One of the most common is the over-alkylation of the amine to yield tertiary amines. [6] To combat this problem, and the typically low yields of such reactions, our N-alkylation scheme was adapted to utilize the cesium effect described by Salvatore, Nagle, and Jung[18]. In their paper, the authors described a method which utilized monohydrated CsOH to yield N-alkylated secondary amines in yields ranging from 90% to 52%. The authors theorized that the in polar aprotic solvents such as DMF, the primary amine may complex with the positive Cs ion (which behaves as a Lewis acid) to yield an ionic complex which can lose water to increase the reactivity of the amine toward alkylation. In addition, since secondary amines are too hindered to undergo this process, the catalytic CsOH helps to eliminate side products which further increases yield. Our group attempted to make use of these novel reactions to increase the yield of our secondary amine detailed below.

Initial attempts to synthesize the target ligand are described on the following pages.

First Trial - Conversion to the mesylate. The reaction scheme (Figure 6) used to convert alcohols to mesylates was previously described by Crossland and Servis.[5] (1,4,7,10-tetraoxacyclododecan-2-yl)methanol (0.0313g , 1.15×10^{-4}mol, 1 eq.) was dissolved in a minimum amount of methylene chloride and the solution was added to a 10mL round bottom flask. Triethylamine (0.0254g , 2.51×10^{-4} mol, 1.1 eq) was added to the solution, and the flask was flushed with nitrogen and placed in an ice bath to cool the solution to 0^{o}C. Methanesulfonyl chloride (0.025g , 2.18×10^{-4} mol, 1.1 eq.) was dissolved in a minimal amount of methylene chloride and added to the cooled solution over approximately 10min. The solvent was then removed under vacuum. A white crystalline solid resulted.

The white solid was then redisolved in 10mL methylene chloride and washed with ice water, cold HCl, cold saturated sodium bicarbonate solution and cold brine. The organic phase was then dried over anhydrous sodium sulfate. The remaining solution was stripped of solvent in a rotovap. A pale yellow oil remained that was used without further purification in the next step.

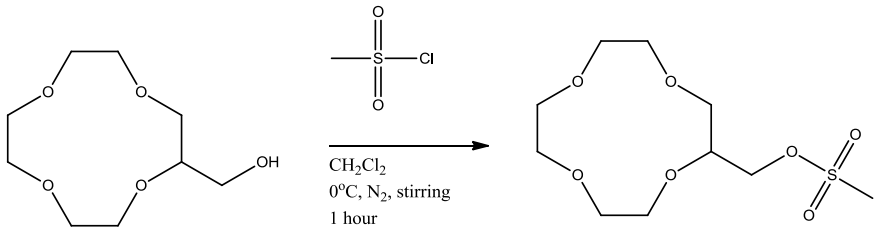

Figure 6. Scheme used to convert our alcohol to a mesylate ester.

First Trial – Reaction of the mesylate ester with the aminoterephthalate . The pale yellow oil from the previously reaction was dissolved in 5mL DMF and transferred to a 25mL round bottom flask equipped with a magnetic stir bar. CsOH: H2O (0.0515g, $3.07x10^{-4}$mol, catalytic) was added to the flask along with dimethyl 2-aminoterephthalate (.0315g, $1.51x10^{-4}$ mol, 1 eq.). Upon addition of the yellow solid, the solution began to turn a faint red color. The reaction (Figure 7) was allowed to stir under nitrogen for 24h, by which time the red color had faded and the solution was the pale, yellow, slightly opaque color of dimethyl 2-aminoterephthalate. The reaction was quenched with 10mL H_2O which clarified the solution leaving it a clear yellow solution. The solution was extracted with 4x20mL ethyl acetate and the organic layers were combined and washed with brine. The organic layer was then dried over anhydrous sodium sulfate and reduced via rotovap. The resulting pale yellow oil was first analyzed by TLC. The resulting plate indicated the presence of a compound which was unique from the starting materials with an R_f value of 0.65 The pale yellow oil was separated using a silica gel column using 1:1 ethyl acetate/hexane (v:v). The fractions collected which contained the assumed product were combined and dried in a rotovap. It is interesting to note that, after leaving the dried sample on the bench for ~1 week, the sample no longer contained any observable amount of the compound with $R_f = 0.65$

Analysis of the proton NMR spectrum indicated that the product did not form and that only starting reagents were present. Therefore, the procedure was altered and repeated for a second trial.

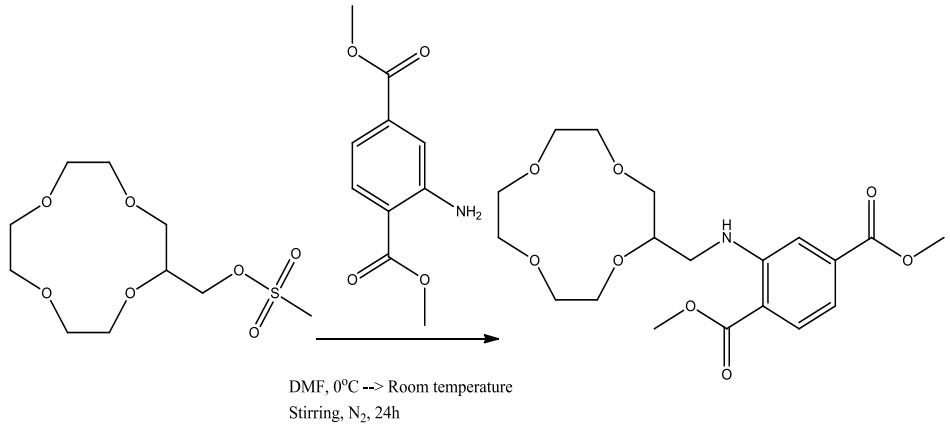

Figure 7. Reaction scheme used to couple our mesylate ester to the aminoterephthalate.

Trial 2. After considering the approach from the previous experiment, it was decided that the method used may have deactivated the mesylate produced by the addition of water to the reaction flask. Although this step was called for in the mesylate procedure presented by Crossland and Servis, that step may have been problematic. As such, the reaction scheme was modified to a one-pot synthesis in which the reaction was kept under nitrogen in an attempt to prevent water from deactivating the mesylate produced as follows.

(1,4,7,10-tetraoxacyclododecan-2-yl)methanol (0.0825g , $4.0x10^{-4}$mol, 1 eq.) was added to a 10mL pear shaped flask followed by 2mL DMF. The flask was placed in an ice bath and cooled. Methanesulfonyl chloride (.0509g, $4.44x10^{-4}$ mol, 1.11eq) was dissolved in ~1mL DMF and added to the solution followed by triethylamine (.0435g, $4.298x10^{-4}$ mol, 1.07eq). The reaction was stirred for 10min, then removed from the ice bath. The reaction was allowed to stir at room temperature for an additional 1hour. Dimethyl 2-aminoterephthalate (.0836g, $4x10^{-4}$ mol, 1eq) was added to the reaction flask. $CsOH:xH_2O$ (.049g) was quickly ground in a mortar and pestle and added to the solution. The solution turned a pale yellow color upon addition of the amine. The CsOH did not dissolve in the DMF solution, and instead remained a fine white powder. After 2 weeks the solution maintained its pale yellow color and the solid CsOH remained unchanged. The reaction was quenched with 5mL deionized H_2O and extracted with 4x15mL EtOAc. The resulting organic phase was washed with brine and dried over anhydrous sodium sulfate. The resulting solution was filtered, and evaporated via rotovap to yield a pale yellow oil. The reaction mixture was characterized by TLC using 1:1 EtOAc/Hexane which is shown in Figure 8. Analysis by TLC revealed the presence of new compound at R_f 0.60 as well as some unreacted starting material.

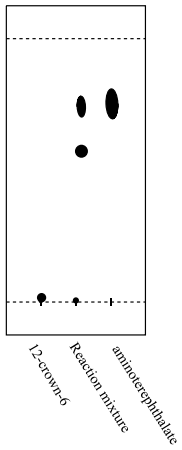

Figure 8. TLC plate showing unknown product at R_f = .60.

The product mixtures was then separated using a silica gel column with 1:1 EtOAc/Hexane (v:v) as the developing solvent. The fractions that contained a portion of the possible product were combined and sealed to be used for later analysis. An interesting side note is that the dimethyl 2-aminoterephthalate starting material appear in almost all of the fractions collected, yielding poor separation of this reagent from the possible product.

After an additional 2 weeks had passed, the solution was again tested by TLC for presence of the possible product, and it appears that it was no longer present. The product may have reverted to starting materials.

3.1.3. Synthesis of the Diaza-crown ligand - 4,4'-(1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-dicarbonyl)dibenzoic acid

The synthesis of the diaza-crown ligand was also attempted in two steps. The first step involved synthesis of the amide via the reaction shown in Figure 9 (next page). The second step involved conversion of the acid chloride to the carboxylic acid via treatment of the acid chloride product with H_2O.

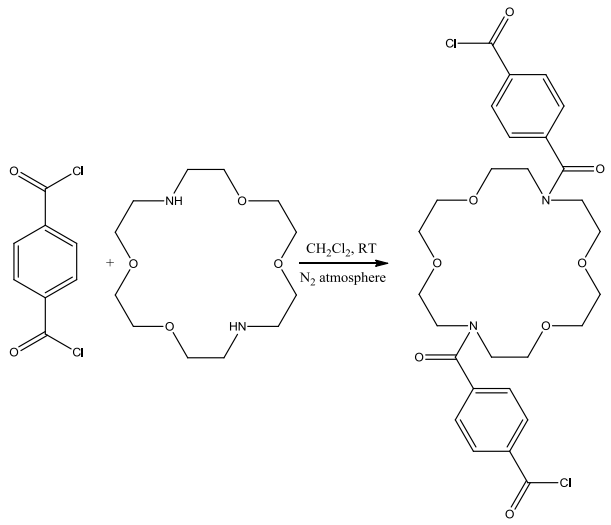

Figure 9. Reaction scheme used to couple diaza-18-crown-6 to terephthaloyl chloride.

Diaza-crown ligand Trial 1. A 25mL round bottom flask was equipped with terephthaloyl chloride (0.3888g, $1.92x10^{-3}$ mol, 10eq.) and a small magnetic stir bar. 10ml methylene chloride was added to the flask which was then sealed with a rubber septum and kept under nitrogen. Diaza-18-crown-6 (.0504g, $1.92x10^{-4}$ mol, 1 eq.) was dissolved in 8mL methylene chloride and loaded in to a syringe. The solution was cooled in an ice bath and the crown solution was added drop wise over 10min under constant agitation. No visible reaction took place. The solution was removed from the ice bath and left to react for 40min. The solution was monitored by TLC using 1:1 EtOAc/hexane as the developing solvent. The reaction mixture streaked the plate and left no indication of the relative concentration of starting materials or products. Despite this, the reaction was quenched with excess H_2O (5mL). The organic layer became slightly cloudy and white, presumably because of the conversion of terephthaloyl chloride to the insoluble diacid, although no visible ppt was observed. The solution was left to stir for an additional 15min. The organic and aqueous layers were separated using a seperatory funnel, and the organic layer was washed once more with an equal volume of H_2O and then twice with brine. The organic layer was dried over anhydrous sodium sulfate and evaporated on a rotovap. As the solvent was stripped the solution began to turn a bright yellow color, and when evaporated to dryness a bright yellow solid remained. Upon evaporation under high vacuum the solid lost some of its color and became a pale yellow. TLC of the crude product yielded the same streaking present on previous plates. The product was then analyzed by proton NMR to determine if the product formed.

Proton NMR of the starting materials was performed. As expected, the acid chloride provided a large singlet at 8.1ppm (8.36 predicted). In addition, the protons present in the crown ether appeared as expected. δ=4.17 (t, 1 H), 3.94 (t, 1 H), 3.79 (s, 2 H). A telltale indication of the production of the desired product will be the splitting of aromatic protons in the sample – an indication of broken symmetry of the terephthaloyl chloride and non-equivalency of these

protons. In addition, the same basic structure of crown ether protons is expected (two triplets and a singlet). These two indications were used as standards with which to assess the reaction in all trials of this experiment. Proton NMR of the crude product from trial 1 did not indicate the presence of target product – it contained only starting material indicating no reaction took place.

Diaza-crown ligand Trial 2. To increase the reactivity of the acid chloride (and presumably the yield of this reaction), triethylamine was added as an acyl transfer reagent for trial 2. That tertiary amine is known to increase the reactivity of acid chlorides toward nucleophilic attack in general, and in the context of this work, toward hindered secondary amines presumably as indicated in the mechanism shown in Figure 10. [19]

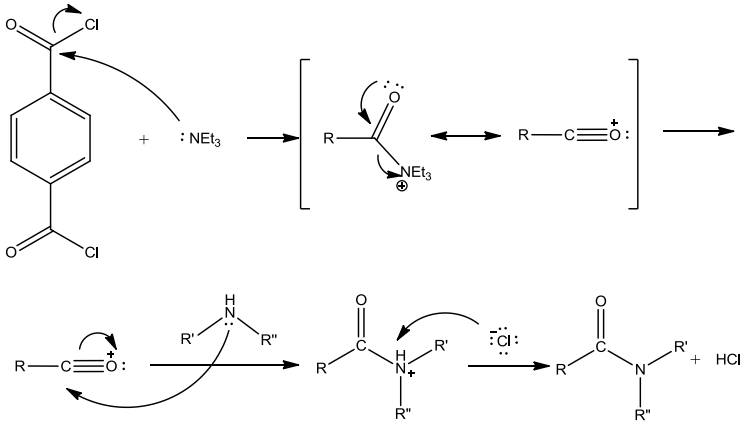

Figure 10. Mechanism by which triethylamine should work as an acyl transfer agent.

In addition to acting as an acyl transfer catalyst, additional triethylamine was required in order to react with HCl produced by the reaction. As such, slightly more than 2 equivalents of TEA used to account for the HCl produced by the reaction at both secondary amines present in the diaza-crown.

The second trial was performed following the procedure described in the first trial. In addition to the steps in that procedure, triethylamine (0.066mL, 4.765×10^{-4} mol, 2.5eq) was added to the reaction before addition of the crown solution. The solution turned a bright yellow color upon addition of the TEA. The reaction proceeded as before to yield a bright yellow solid. Analysis of the crude solid by NMR showed no evidence of the target product but the crude product contained evident starting material again indicating the reaction failed to take place.

Diaza-crown ligand Trial 3/4. In a paper published by Subramanyam and Pinkus a complex between triethylamine and terephthaloyl chloride is described that I believed may have hindered the bases ability to remove HCl from solution and promote the reaction.[20] As such, trial 3 and 4 were designed such that an excess of TEA was supplied as to complex all of the acid chloride in solution. Trial 3 contained 17.5 eq of TEA, and trial 4 contained 32.5 eq. The 32.5 equivalents

should provide enough TEA to complex both acid chloride moieties on the compound (30 eq. required) as well as provide enough additional base to react with the HCl produced. The reaction otherwise was performed as described previously for trial 1 above. The crude product was evaporated to dryness yielding a yellow solid in both trials. This solid appeared very similar to the known solid complex between TEA and terephthaloyl chloride.

Proton NMR analysis of the crude solid recovered from trial 4 provided two singlets in the aromatic region δ = 8.2958, 8.2567. It is believed that one of these corresponds to the diacid terephthalate produced by hydrolysis of the starting acid chloride, while the second corresponds to the diacid chloride starting material.

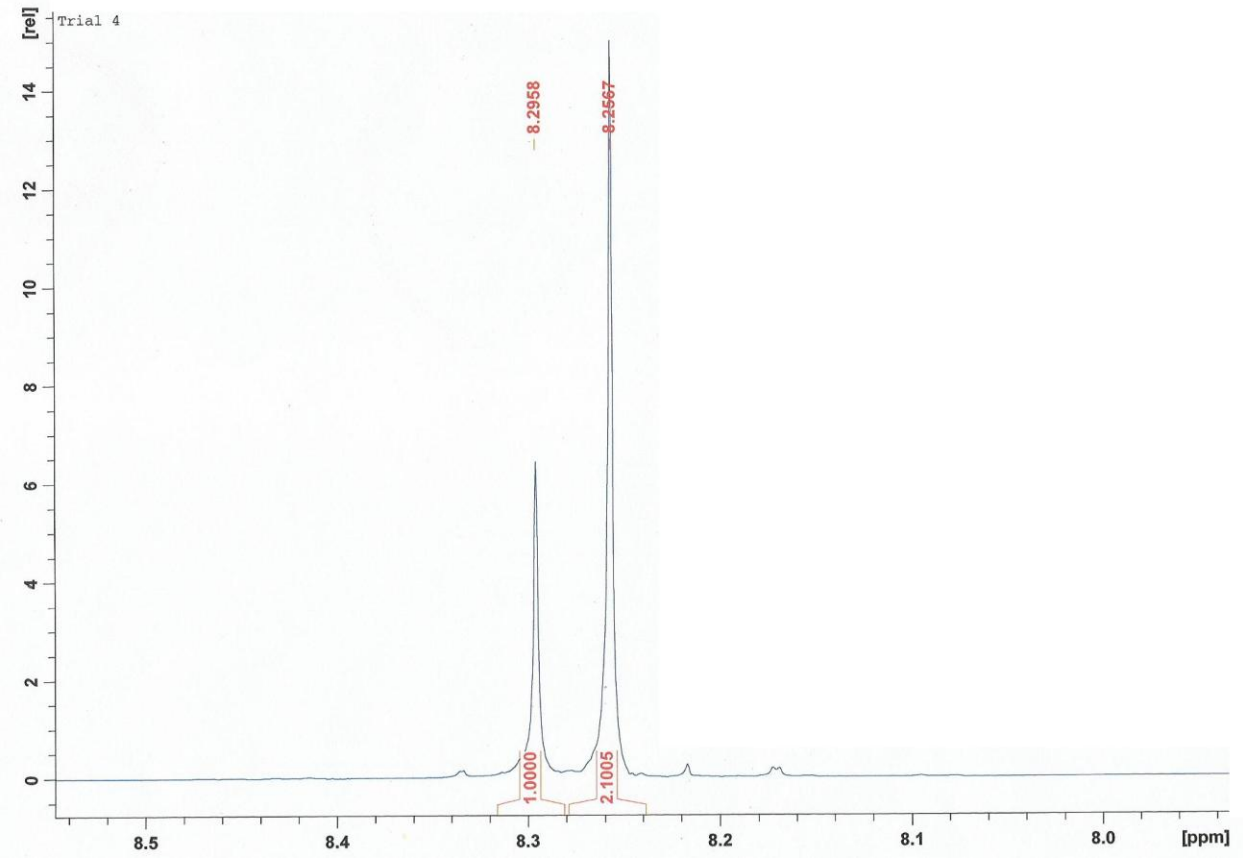

Figure 11. ^{1}H NMR data obtained in $CDCl_3$ for the crude product collected from trial 4. These two singles are believed to correspond to starting materials. Also note the lack of expected aromatic splitting for the target product.

NMR analysis of the trial 3 crude product showed two small doublets (δ = 8.19, 7.86)indicating what may be a small amount of product. However, due to the small signal to noise ratio it is difficult to say with certainty that these peaks do correspond to the target product.

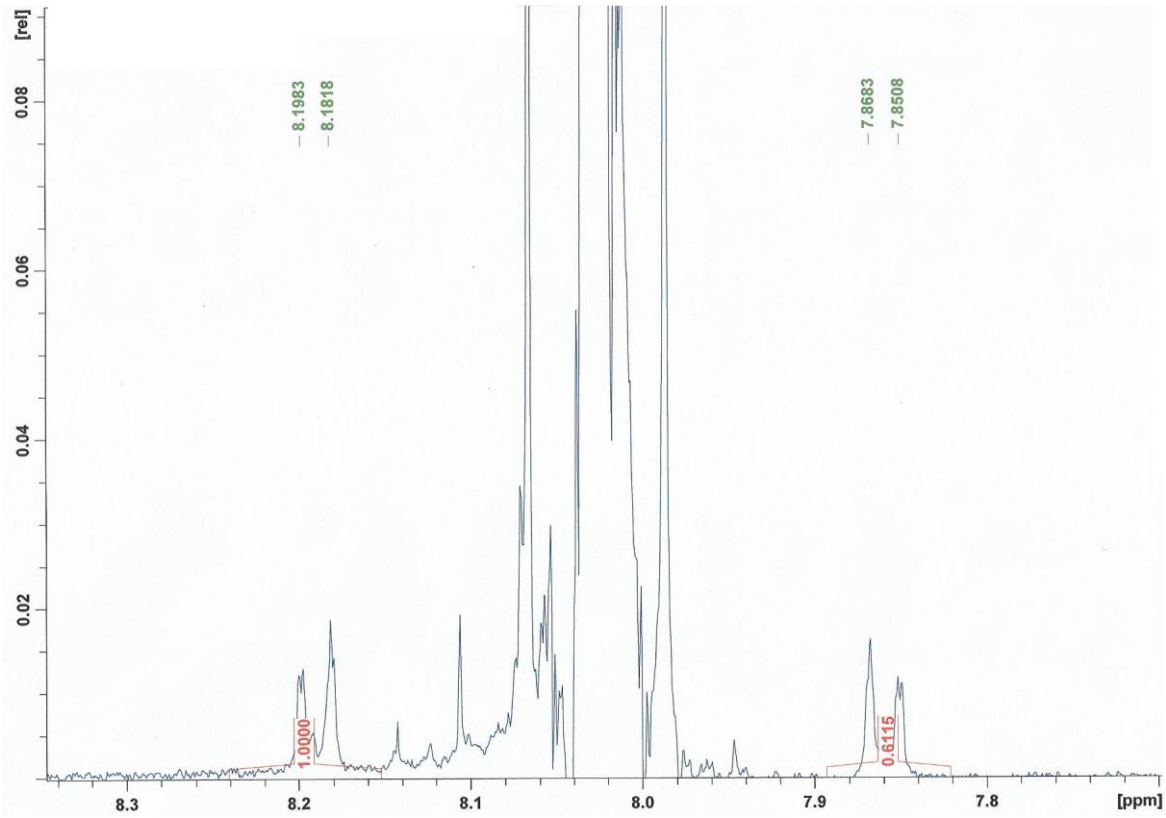

Figure 12. ^{1}H NMR data obtained in $CDCl_3$ which indicates two small doublets which may correspond to the target product. More research is needed to determine the identity of these peaks.

Diaza-crown ligand Trial 5. Several studies have demonstrated reactions to produce amides by the reaction of secondary amines and acid chlorides in the presence of aqueous inorganic base[21, 22, 23]. Trial 5 of the diaza-crown ligand synthesis was performed as in trial 1 with the use of KOH as the base (2.5eq). The reaction was still carried out in methylene chloride, and the insoluble base was crushed in a mortar and pestle before addition to the reaction flask. NMR analysis of this product revealed no indication of the target product – that is, no indication of aromatic splitting of the terephthalate protons. In addition, both starting materials are still readily visible.

Diaza-crown ligand Trial 6. In this trial, the reaction was repeated using deionized H_2O as the solvent and KOH as the base. The reaction was adapted from Survey of Organic Synthesis[22]. Terephthaloyl chloride (.6088g, $3x10^{-3}$ mol, 15 eq.) were added to a 25mL round bottom flask equipped with a magnetic stir bar. The white solid remained in the solution. Diaza-18-crown-6 (.0486g, $1.85x10^{-4}$ mol, 1 eq.) was added to the flask. Both solids did not dissolve in the H_2O. The reaction flask was sealed with a rubber septum and flushed with nitrogen. KOH (.0428g, $7.63x10^{-4}$ mol, 4.1 eq.) was dissolved in 5mL deionized H_2O and added drop wise to the flask via

syringe over 10min. The solution warmed slightly upon addition of the aqueous base. The reaction was left for 60min under constant agitation.

The remaining solid was collected by suction filtration. Proton NMR indicated the solid contained only unreacted starting materials. The aqueous reaction solvent was extracted with methylene chloride which was then dried over anhydrous sodium sulfate. The organic and aqueous layers were rotovaped to dryness. The resulting solid from each flask was analyzed using proton NMR. The aqueous phase indicated no aromatic splitting expected of the target product. The organic phase however, did indicate two small doublets which could indicate the expected reaction. This data is presented and discussed in section 4 at the end of the report.

Diaza-crown ligand Trial 7. Trial 7 was designed to address two of the major problems affecting our synthetic efforts so far. First, the reaction would be heated in reflux to encourage the reaction and increase the yield. In addition, anhydrous ethanol will be used as a quench for the reaction instead of H_2O. The intention of the ethanol is twofold. First, it should make for a product which is more soluble in organic solvents such as methylene chloride. In addition, it should affect the polarity of the molecule and make it considerably less polar (ethyl ester as opposed to a carboxylic acid). This will allow for better separation on a TLC plate and eventual ease of separation by column chromatography.

Terephthaloyl chloride (0.8130g, $4x10^{-3}$ mol, 20eq) was dissolved in 10mL methylene chloride and added to a 25mL round bottom flask. Triethylamine (.139mL, $1x10^{-3}$ mol, 5 eq.) was added to the flask which was then sealed and flushed with nitrogen. The solution turned yellow upon addition of the TEA. Diaza-18-crown-6 (.0503g, $1.92x10^{-4}$ mol, 1 eq.) was dissolved in 5mL methylene chloride and added drop wise to the reaction vessel using a syringe. The rubber septum was removed and the flask was equipped with a water cooled condenser. The solution was heated in reflux for 1 hour during which time the color changed from yellow to a dark orange. The reaction was removed from heat and quenched with excess anhydrous ethanol (5mL). Upon addition of the ethanol, the solution returned to the its original yellow color. The solution was then washed with 2x10mL 9% HCl upon which some gas bubbles could be seen evolving at the aqueous-organic interface. Following the acid washes, the solution was washed with 2x10mL deionized water. The organic phase was dried over anhydrous sodium sulfate and rotovaped. Despite heating to $95^{o}C$ under vacuum, the sample would not evaporate to dryness. A pale yellow liquid remained. The sample was set aside and saved for further analysis.

3.2. Room Temperature MOF Synthesis

Our group has previously developed a synthesis for the 1-Cd MOF based on reaction of ethyl 4-(1H-imidazol-1-yl)benzoate with zinc nitrate under hydrothermal conditions.[6, 17] The following synthesis describes an alternative approach to that reaction carried out at room temperature.

3.2.1. Room Temperature Synthesis of [(4-(1*H*-imidazol-1-yl)benzene dicarboxylic acid)cadmium(II)] (1b-Cd MOF)

The following synthesis was adapted from a rapid room temperature synthesis developed previously to prepare Yaghi's IRMOF-5.[24] 4-(1*H*-imidazol-1-yl)benzene dicarboxylic acid (.3501g, $1.86x10^{-3}$mol, 1eq) was dissolved in 25mL DMF in a beaker containing $Cd(NO_3)_2$:$4H_2O$ (.5735g, $1.86x10^{-3}$mol, 1eq). Triethylamine (3mL, .0215mol, 11.5eq) was added drop wise over 10min to afford a fine white ppt. After addition of the Triethylamine the solid was isolated via suction filtration and washed with clean DMF. The solid was collected and resuspended in 50mL clean DMF. The solid was again collected via suction filtration. The solid product was washed 3 times in total. The washed solid was transferred to a large watch glass and heated in a programmable over at 245^{o}C for 24 hours. The resulting dry, white powder was stored in a 160^{o}C oven until use in the adsorption and PXRD experiments. 0.2011g recovered.

4. Discussion

4.1. Room temperature MOF synthesis

TGA data was collected using a TA instrument, Hi-Res TGA 2950 Thermo Gravimetric Analyzer at a heating rate of 10^{o}C/min. A Bruker D8 Focus instrument was used to collect powder x-ray data. Initial powder x-ray and TGA analysis indicate that the solid white ppt produced by the previously described method has yielded a new structure. The powder x-ray trace is unique and does not match those determined presented previously by our group for Cd MOFs prepared with 4-(1*H*-imidazol-1-yl)benzene dicarboxylic acid.[17]

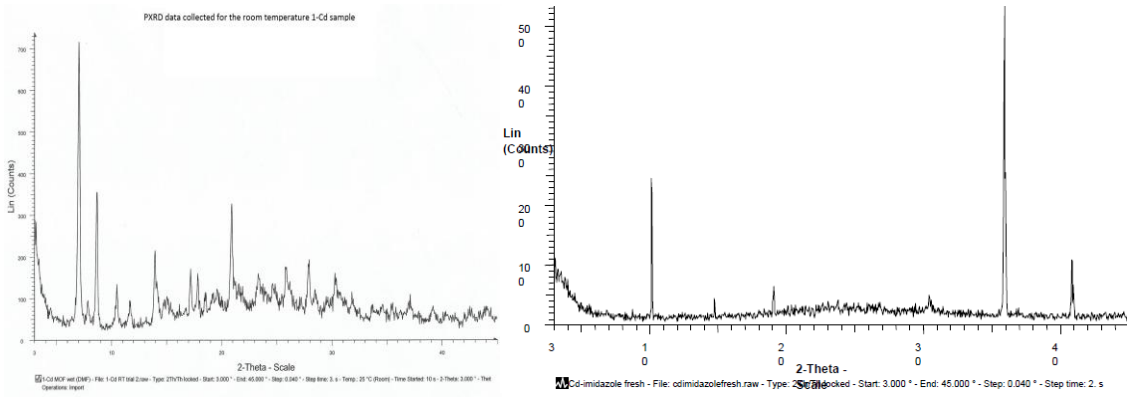

Figure 13. PXRD data for the room temperature 1-Cd MOF (left) and hydrothermal 1-Cd (right).

In addition to the unique powder x-ray pattern collected, TGA analysis has provided good insight into the structure of the MOF samples synthesized. Note in the TGA data presented in figure 14 below the loss of guest at 83^{o}C and 178^{o}C. We believe these areas correspond to the loss of triethylamine and DMF. The sample pictured below lost a total of 11% by mass of adsorbed guest while typical porous MOFs lose anywhere from 10-30% of their mass.

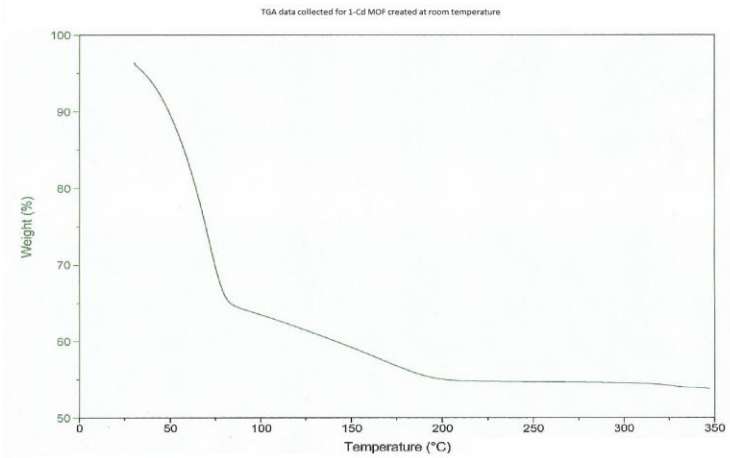

Figure 14. TGA data collected for a sample of 1-Cd MOF prepared by room temperature synthesis. Slope changes are evident at 83^{o}C and 178^{o}C corresponding to the loss of TEA and DMF respectively. The total mass loss of bound guest is 11%.

Further experimentation has revealed that DMF and TEA can be stripped from the white powder through washings with methylene chloride and subsequent evaporation under high vacuum. These samples exhibited a 4.5% mass loss upon heating to 350^{o}C which is notably smaller than the unwashed samples. More experimentations is needed to determine if the guest molecules can be removed entirely by washing. Figure 15 below details this data.

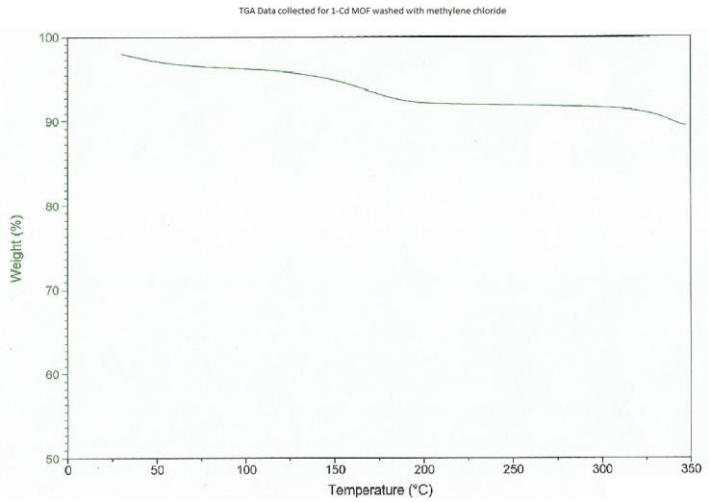

Figure 15. TGA data collected for the 1-Cd MOF which has been rinsed with methylene chloride and air dried at room temperature for 1 hour. This data indicates a 4.5% mass loss which is much smaller than the unwashed samples.

Moreover, initial experiments seem to indicate that process appears reversible – that is upon reintroduction of DMF to preheated samples, the MOF adsorbed guest molecules and desorbed DMF at approximately the same temperature. More work is needed to determine if the MOF is in fact adsorbing and desorbing reversibly, or if there is some degradation to the MOF structure which allows for less adsorption after multiple activation cycles.

4.2. Ligand Synthesis

Although attempts to synthesize the 12-crown-4 and 18-crown-6 ligands were not successful at creating any useable product, there is a great deal of information to be gathered from the experiments that were conducted.

4.2.1. 12-crown-4 Ligand Synthesis

Before this experiment began, we anticipated that synthesis of the 12-crown-4 ligand would be difficult and present some issues to us as described in section 3.1.2. Therefore, it was not completely unexpected that synthesis of that ligand was unsuccessful. Separation of the suspected product from reaction mixtures yielded no usable product. More careful selection of a solvent system could improve the ability to separate the suspected product from the starting materials. Suitable solvent systems would be less polar than the 1:1 EtOAc/Hexane used for initial separation. R_f values of .75 and .60 for the starting amine and suspected product respectively could be better separated on a column using an EtOAc/Hexane system utilizing

more hexane, or a MeOH/CH_2Cl_2 system. While investigating solvent choice in future work, a 1% MeOH solution would be a good target to investigate.

In addition to seperatory methods, there are a few steps that might be taken to make these reactions work. All previous synthetic attempts were done at room temperature. Heat could be used to encourage the reaction, potentially heating in reflux. In order to do so, however, a new solvent system other than DMF may need to be investigated

4.2.2. Diaza-18-crown-6 Ligand Synthesis

Athough also unsuccessful, synthesis of the diaza-18-crown-6 ligand provides possibly the greatest opportunity for improvement since successful synthesis should be easy to observe via NMR analysis, and the short timescale allows for multiple trials. Although no product was obtained, several trials seemed to indicate at least a small amount of product may have formed. Trial 4 and Trial 6 showed the most promise, and either of them might provide a good starting point for adaptation in future work. Although time constraints prevented the appropriate analysis and follow up of Trial 7, it may be that heating the reaction will allow the reaction to proceed to yield the product. In trial 6 (aqueous trial using KOH as a base), analysis of the NMR data of the reaction mixtures that were recovered showed NMR peaks that may correspond to the expected splitting of aromatic protons present on the terephthalate group. Figure 14 below presents the proton NMR taken of the crude trial 6 product with an inset to show splitting of aromatic protons indicating the presence of potential product.

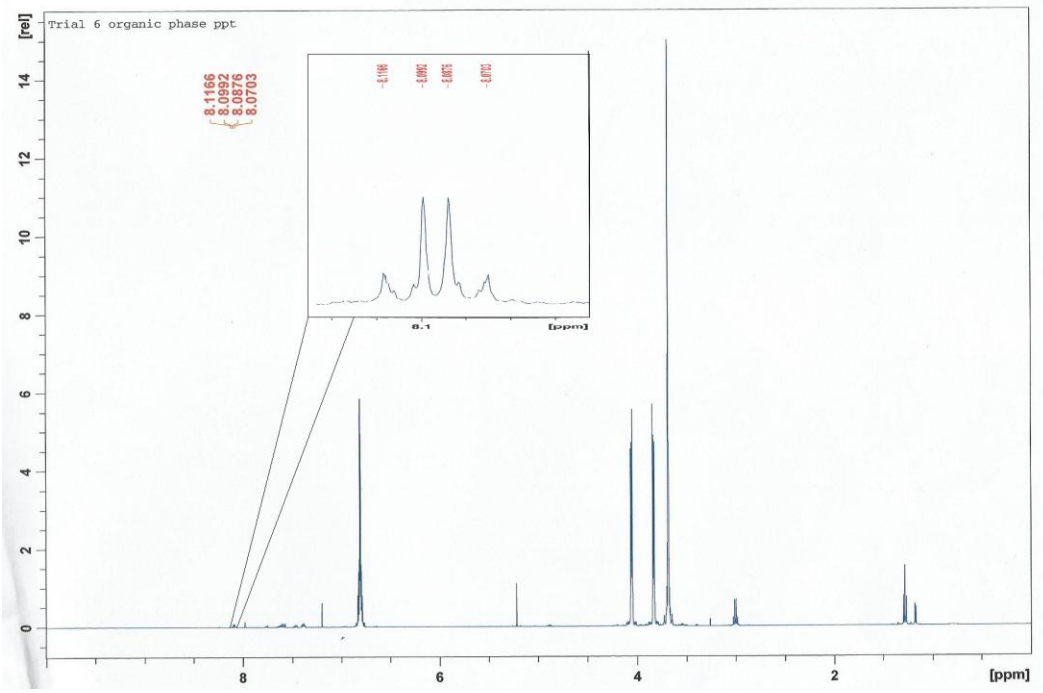

Figure 16. ^1H NMR data obtained in $CDCl_3$ for the crude product obtained through trial 6 (aqueous trial using KOH as a base).

Although the relative size of these aromatic peaks is quite small compared to the other peaks in the sample these results are promising.

Since neither of the crown-containing ligands were obtained, it was not possible to carry out research aimed at synthesizing MOFs from those ligands. Had either ligand been synthesized, we would have attempted to prepare Cd MOFs from them hydrothermally in the presence of cadmium nitrate. The target ligands feature either ester groups or free carboxylic acid groups that should enable the ligand to be used directly under hydrothermal conditions. Appropriate procedures for the hydrothermal production of new MOFs have been described previously in a number of articles as well as developed in our group.[3, 4] Attempts would have been made to produce single crystals of these MOFs for crystal structure determination and structure analysis. Following that, the crown-containing Cd MOFs would have been used to perform adsorption experiments similar to those described previously by our group.[6, 17] Those sorption experiments would have included measuring sorption of lithium, sodium, and potassium salts of pharmaceutical drugs such as aspirin and indomethacin to determine if the crowns showed specificity for taking up higher concentrations of those salts with cations that show the highest affinity for unsubstituted crown ethers. In addition, competitive sorption experiments would also have been carried out that assess the selectivity of the MOFs from mixtures of salts containing the different cations.

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