Chapter III

Cryptands

III.1 Introduction

Like crown ethers, cryptands were designed and synthesized as binding receptors of smaller molecular substrates. A simple definition of a cryptand is a bicyclic (or polycyclic) ligand.[1] This definition was derived from Lehn's observations of the behavior of cryptands with alkali metals. Lehn noticed that a 3D structure with flexible linkers having donor groups capable of encapsulating cations would be analogous to the first solvation shell of cations. He named these encapsulating bicyclic cryptands. The root word "crypt" taken from Latin for *crypta* which comes from Greek *kruptos* which means 'hidden or to hide.' The bound cation is hidden from the solvent that previously stabilized it. Lehn's realization led to classes of spherands, cavitands, carcerands, lariat ethers and others.[2] Several reviews of cryptands and their complexes have been published since the late 1960s.[1-5]

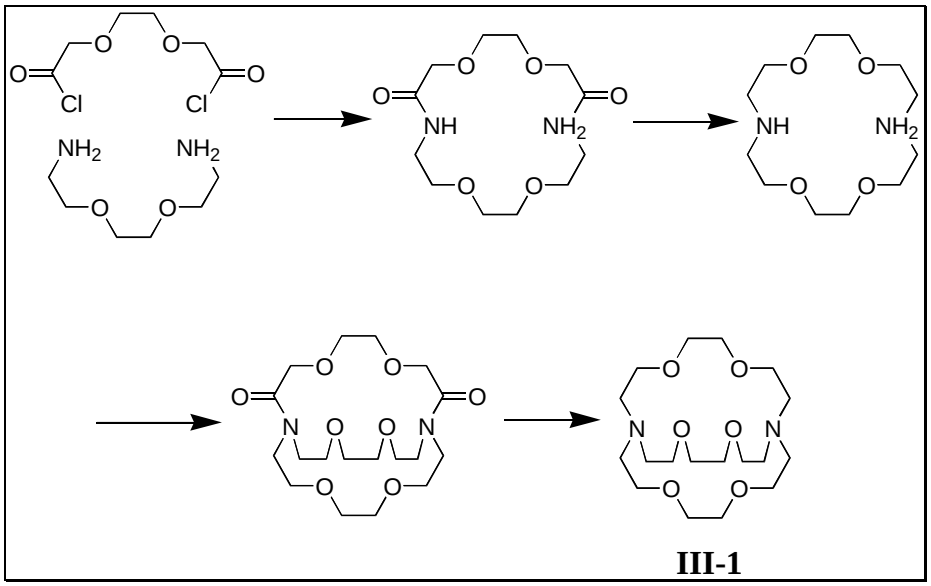


Figure III-1. First reported cryptand.[6]

Cryptands became synthetic realities at the same time Pedersen discovered his crown ethers (see Chapter II). Dietrich, Lehn, and Sauvage reported the first cryptand, **III-1**, in 1968 (**Figure III-1**).[6] It was produced using high dilution reactions and amide formation. Prior to their discovery Simmons had an idea to build a bicyclic 3D structure capable of being flexible and having unique properties when compared to previously known smaller, quite rigid 3D molecules. These unique molecules were known as 'in-out' bicyclic amines, one of which is shown in its "out" (left) and "in" conformations in **Figure III-2**.[2] It is debatable whether these bicyclic amines can be called cryptands, although they do meet the basic definition requirements since the two bridging nitrogens are capable of binding.

Just as Pedersen did for the crown ethers, Lehn developed an abbreviated nomenclature system for cryptands to simplify the complicated IUPAC nomenclature. His presumption was that the heteroatoms were separated by two carbons atoms, and the three ethyleneoxy chains were anchored at the bridgeheads by nitrogen. The number of heteroatoms, n, in each bridge are separated by periods and placed in square brackets, [n.n.n]. This designation is used as a prefix and is then followed by the word "cryptand". As an example, **III-1** is designated as the [2.2.2]-cryptand.

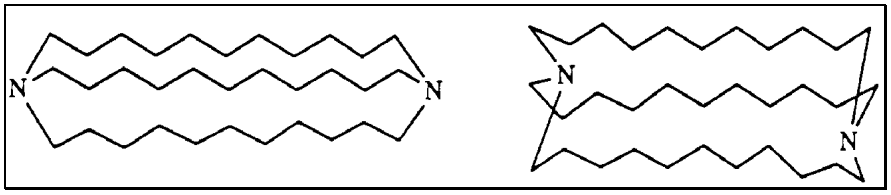
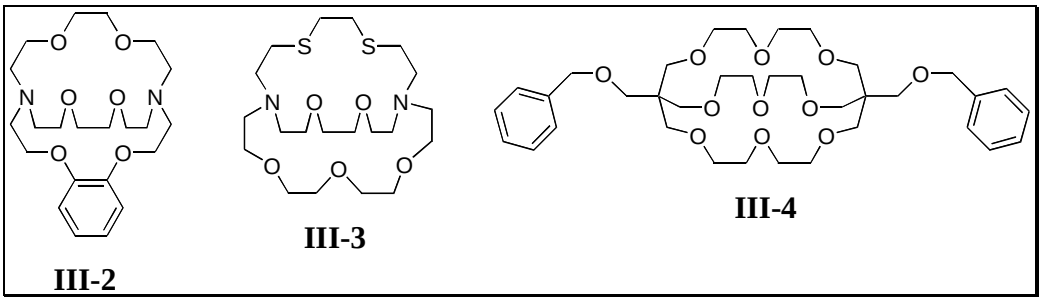
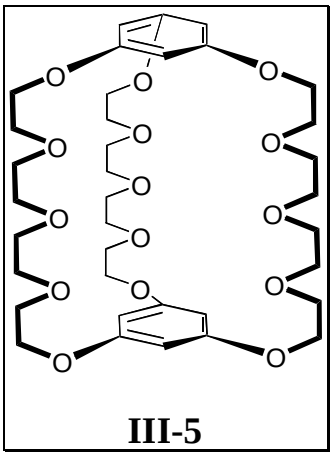


Figure III-2. Simmons' "in-out" bicyclic amines with the "out" conformation on the left and "in" on the right.[2]





The nomenclature system does have some drawbacks, however. For example, both **III-1** and **III-2** could be designated as [2.2.2]-cryptands using Lehn's nomenclature system even though they are obviously different. Since there is no designation as to what type of heteroatom is used in the bridges of the cryptand Gokel suggested a modification to the nomenclature.[2] He suggested that a subscript be used to designate the atom or group that is substituted for oxygen in the bridges. As an example, structure **III-2** would be named $[2.2.2_B]$-cryptand, where the "B" designates the benzo- group in the third bridge, and structure **III-3** would be named $[3.2.2_S]$-cryptand, where the "S" designates the sulfur atoms. However, this suggestion does not fully clarify the nomenclature. What if the bridgehead were a different atom or group, such as a carbon atom or 1,3,5-phenylene group? There are several examples of cryptands with carbons atoms as bridgeheads.[7] There have also been several examples of cryptands containing only

oxygen as the heteroatom, an example of which is **III-4**.[8,9] A suitable designation for this type of cryptand does not exist. Neither does one exist for **III-5**, a target molecule of the research summarized in this chapter. An extension of Lehn and Gokel's nomenclature would be to include a designation for the bridgehead before the bracketed numers. Suggestions include using the letter "c" for carbon, "n" for nitrogen, and the phrase "1,3,5-phenylene" for the 1,3,5-phenylene moiety as examples. Therefore, **III-2**, **III-3**, **III-4**, and **III-5** would be named n-[2.2.2_B]-cryptand, n-[3.2.2_S]-cryptand, c-[3.3.3]-cryptand, and bis-1,3,5-phenylene-[5.5.5]-cryptand, respectively. This suggested nomenclature will be used in this chapter and subsequent chapters.

The research discussed in this chapter involves the synthesis of two bis-1,3,5-phenylene cryptands, **III-17** and **III-5**, containing 3 and 4 ethyleneoxy repeat units in the bridges, respectively (**Figure III-3**). The complexation behavior of **III-5** will be discussed in **Chapter V**.

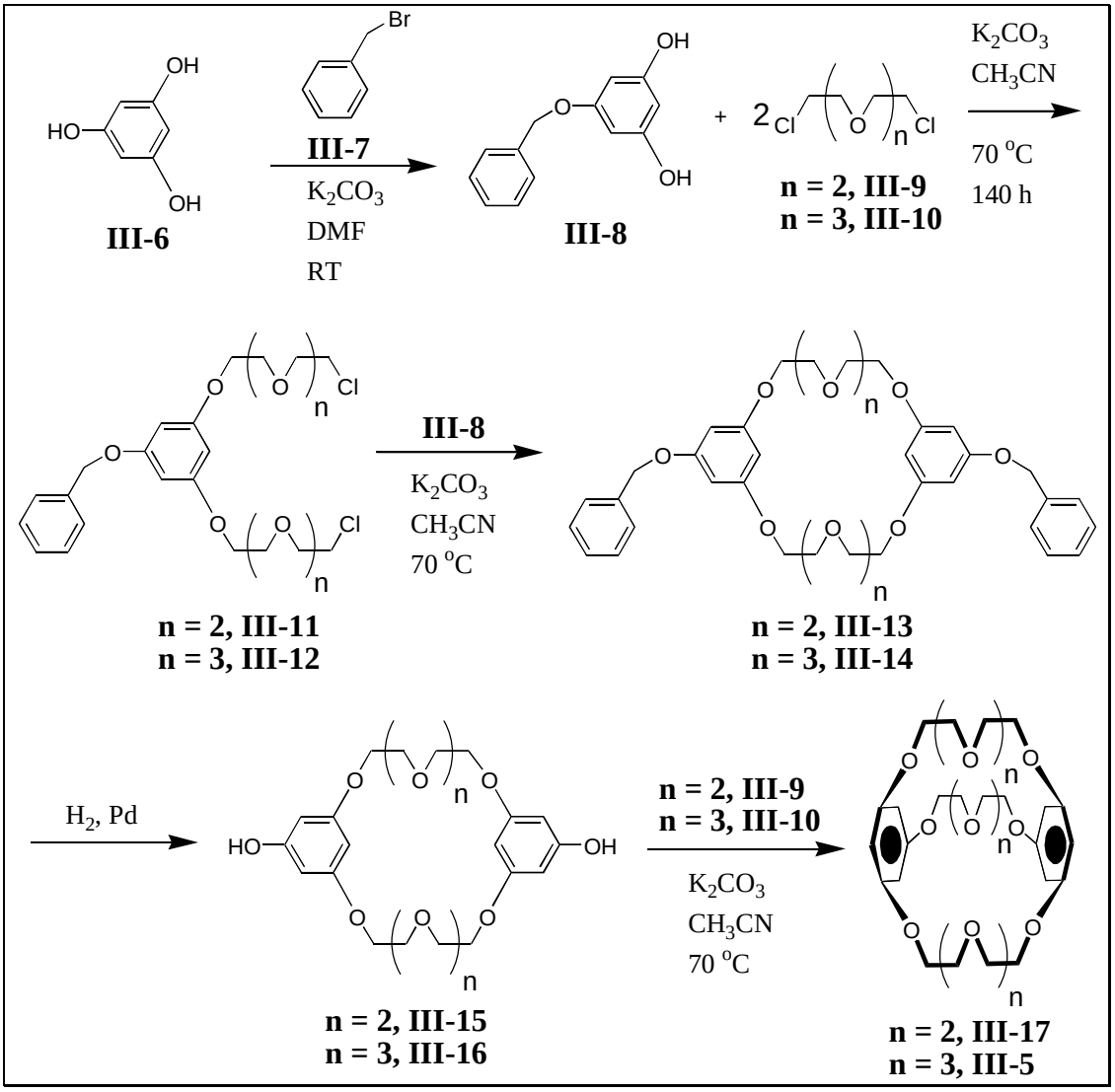


Figure III-3. Synthesis of bis-1,3,5-phenylene cryptands.

III.2 Results and Discussion

As shown in **Figure III-3**, the syntheses of **III-5** and **III-17** were performed in five steps. Both target cryptands required two equivalents of 5-benzyloxyresorcinol (**III-8**). The synthesis of **III-8** was not trivial and was performed via two methods, **Method A** and **B**. In **Method A** (step 1 of **Scheme III-3**), phloroglucinol (**III-6**) was dissolved in a large quantity of DMF in the presence of one equivalent of potassium carbonate. One equivalent of benzyl bromide (**III-7**) diluted with a large quantity of DMF was then added slowly. Purification of **III-8** can be done via two different methods. The first method involves using column chromatography and is outlined in the experimental section of this chapter. However, a solid was not obtained as expected. The second method uses no column and results in the formation of a solid. After removing the DMF from the reaction mixture the unreacted phloroglucinol is removed by triturating the resulting oil with chloroform followed by filtration. The filtrate is then subjected to liquid-liquid extraction using chloroform and water to separate the two undesired by-products, 1,3,5-tribenzyloxybenzene and 3,5-dibenzyloxyphenol, from the desired product **III-8**, which has a limited solubility in water. The water is then removed and the resulting oil is dissolved in methylene chloride. Several washings with 5% HCl, to remove the residual DMF, results in the precipitation of **III-8**. The complete removal of the DMF is important for the crystallization of **III-8**. The best yield obtained for the synthesis of **III-8** from this method is 36.7%.

The synthesis of **III-8** via **Method B** (**Figure III-4**) involved three steps.[10] The first step was the esterification of phloroglucinol (**III-6**) using two equivalents of benzoyl chloride (**III-18**) to produce 1,3,5-tribenzoyloxybenzene (**III-19**) 3,5-dibenzyloxyphenol, (**III-20**) and 5-benzoyloxyresorcinol (**III-21**). The desired intermediate product was the diester **III-20**. **III-21** was removed from the mixture by triturating the resulting oil, after work-up, with ethyl ether followed by filtration. Using ^{1}H NMR the filtrate was determined to contain 85% of **III-20** corresponding to a yield of 56.4%. The two esters **III-19** and **III-20** were not further separated but used directly for the next step. Benzyl bromide (**III-7**) was reacted with **III-20** to give **III-22**. Hydrolysis of the ester groups of

both **III-19** and **III-22** gave **III-6** back and the desired product **III-8**. After the purification work-up the yield was 6.7%, far below the reported yield (85 %) as done by Devdatt Negvekar[10] in our labs. The overall yield for **Method B** was 3.8% as compared to the reported yield of 41%.[10] Obviously, the better method for the synthesis of 5-benzyloxyresorcinol is **Method A**.

III.2.1 Bis-1,3,5-phenylene-[4.4.4]-cryptand

The synthesis of bis-1,3,5-phenylene-[4.4.4]-cryptand, **III-17** required two pseudo-high dilution Williamson ether steps (**Figure III-3**). The synthesis of the dichloride precursor **III-11** was done first using a large excess of tri(ethylene glycol) dichloride (**III-9**) and **III-8**. After removal of the excess **III-9**, the resulting oil was subjected to liquid-liquid extraction using petroleum ether. However, this method was done for 16 days and not all of the desired product was recovered. Flash column chromatography of the residual oil using ethyl ether recovered more material. Therefore, it appears that only a flash column is needed to purify **III-11**. The product was an oil and the reaction resulted in a yield of 62.2%.

The next step required pseudo-high dilution conditions. Another equivalent of **III-8** was reacted with **III-11** in a 1+1 cycloaddition to give the diprotected crown ether bis(5-benzyloxy-1,3-phenylene)-26-crown-8 (**III-13**). As was done for the crown ethers (see Chapter II) the reaction was done using potassium carbonate in a large quantity of acetonitrile and an addition rate of 0.75 mL/h was used for **III-8** and **III-11**. As will be explained in the next section, the desired product was not isolated. The crude material was subjected to the hydrogenolysis step using palladium catalyst of carbon black in a 60 psi hydrogen gas environment. The bisphenol, bis(5-hydroxy-1,3-phenylene)-26-crown-8, **III-15**, an acetonitrile insoluble compound, was then easily isolated by trituration of the resulting brown oil. The yield (8.0 %) was not as high as expected, however.

Another attempt at making **III-15** was conducted. The conditions were similar to the above procedure; however, DMF was substituted for the solvent and the temperature was raised to 110 ^{o}C. The reaction was not completed.

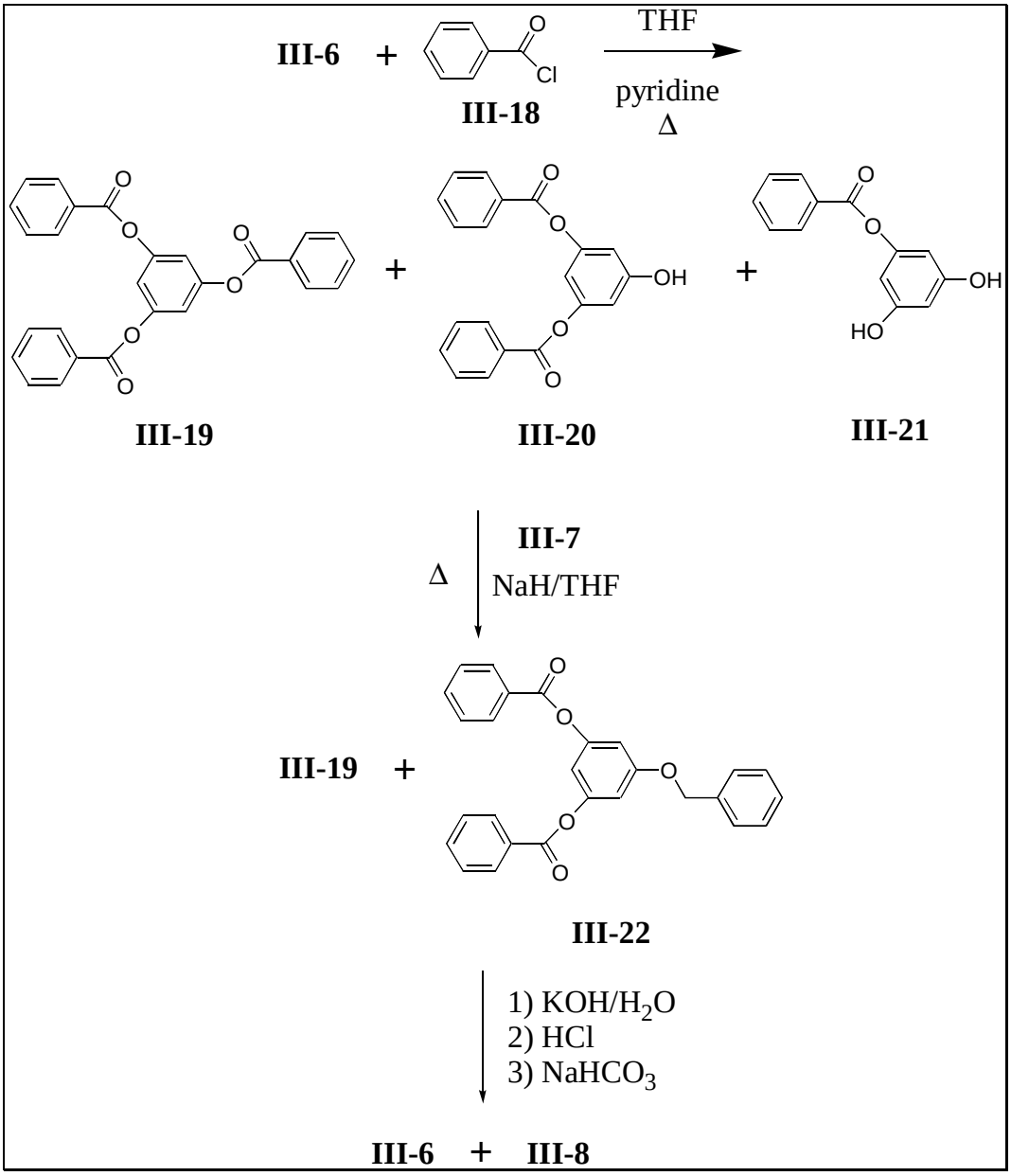


Figure III-4. Synthesis of 5-benzyloxyresorcinol (**III-8**) via **Method B**.

III.2.2 Bis-1,3,5-phenylene-[5.5.5]-cryptand

The synthesis of bis-1,3,5-phenylene-[5.5.5]-cryptand (**III-5**) was similar to that of **III-17**. An excess of dichloride **III-10** was reacted with **III-8** in the presence of potassium carbonate. After work-up the yield of the dichloride precursor **III-12** was

72.5%, ten percent higher than that obtained for **III-11**. The first 1+1 cyclization, **III-8** plus **III-12**, was conducted using pseudo-high dilution conditions and resulted in a yield of 24.0 % for bis(5-benzyloxy-1,3-phenylene)-32-crown-10 (**III-14**).

The deprotection of **III-14** by hydrogenolysis to give bis(5-hydroxy-1,3-phenylene)-32-crown-10 (**III-16**) was not quantitative as expected. However, some leakage did occur during the reaction and some material was lost. **III-16** was very insoluble in many common organic solvents such as acetonitrile, chloroform, and acetone. Therefore, due to the insolubility of **III-16** it may be possible to forgo the use of column chromatography to purify **III-14** and subject the crude oil obtained in the first 1+1 cycloaddition reaction directly to hydrogenolysis. This method was demonstrated to be successful for the synthesis of **III-15** in **Section III.2.1**.

The last step for the synthesis of **III-5** involved another 1+1 cyclization Williamsen ether reaction. **III-16** was reacted with one equivalent of **III-10**. After work-up, however, some of the starting material **III-16** was recovered. The yield, having accounted for the unreacted diphenol **III-16**, was 38.0 %. The desired product **III-5** was purified by column chromatography **(**SiO_2, Et_2O:EtOAc, 9:1; EtOAc**)**.

The melt behavior for **III-5** was rather interesting. Once isolated, the cryptand (**III-5**) was dried overnight in a drying pistol with P_2O_5 present at room temperature. It was then analyzed by differential scanning calorimetry (DSC, **Figure III-5**) at a heating rate of 5 ^oC/min (Sample 1). There was a large endothermic peak between 32.7 and 54.8 ^oC. Another smaller endotherm occurs between 63.9 and 71.1 ^oC. Upon cooling, crystallization did not occur. The second heating did not show any change in the baseline up to 100 ^oC. These results may indicate that the product obtained is possibly a solvate and the endotherm may result from the loss of the solvent molecule(s).

Another sample of **III-5** (Sample 2) was analyzed by DSC. The sample was prepared by dissolving it in acetone and then evaporating the solvent off under argon flow. The DSC (**Figure III-6**) exhibited a large endotherm between 71.9 and 80.0 ^oC with a maximum at 76.5 ^oC. The tailing at the beginning of the endotherm may be due to residual acetone, which may be responsible for the breadth of the peak. The reported

melting temperature for **III-5** from our lab was 77.5 - 78.0 ^{o}C which reasonably concurs with the results from the second DSC experiment. The cryptand did not crystallize during cooling and the second heat did not show a melting endotherm.

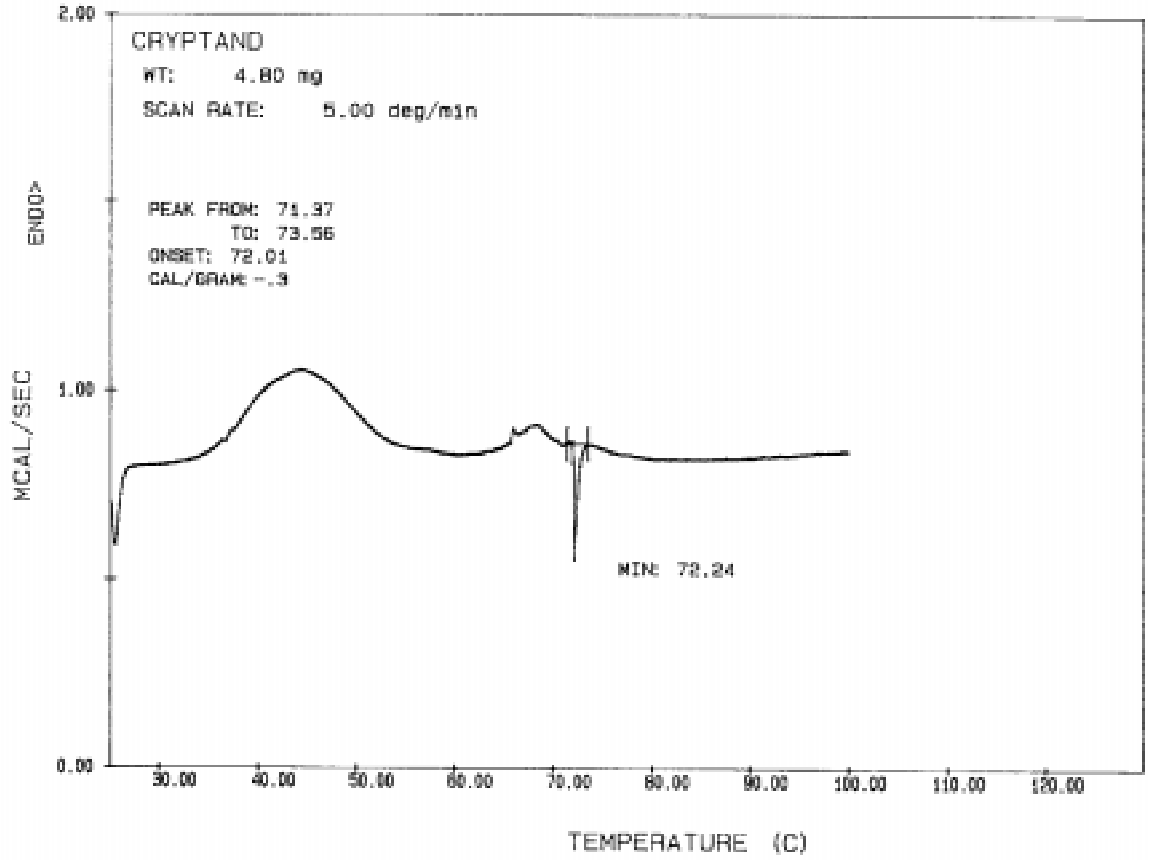


Figure III-5. First DSC (Sample 1) of bis-1,3,5-phenylene-[5.5.5]-cryptand, **III-5**.

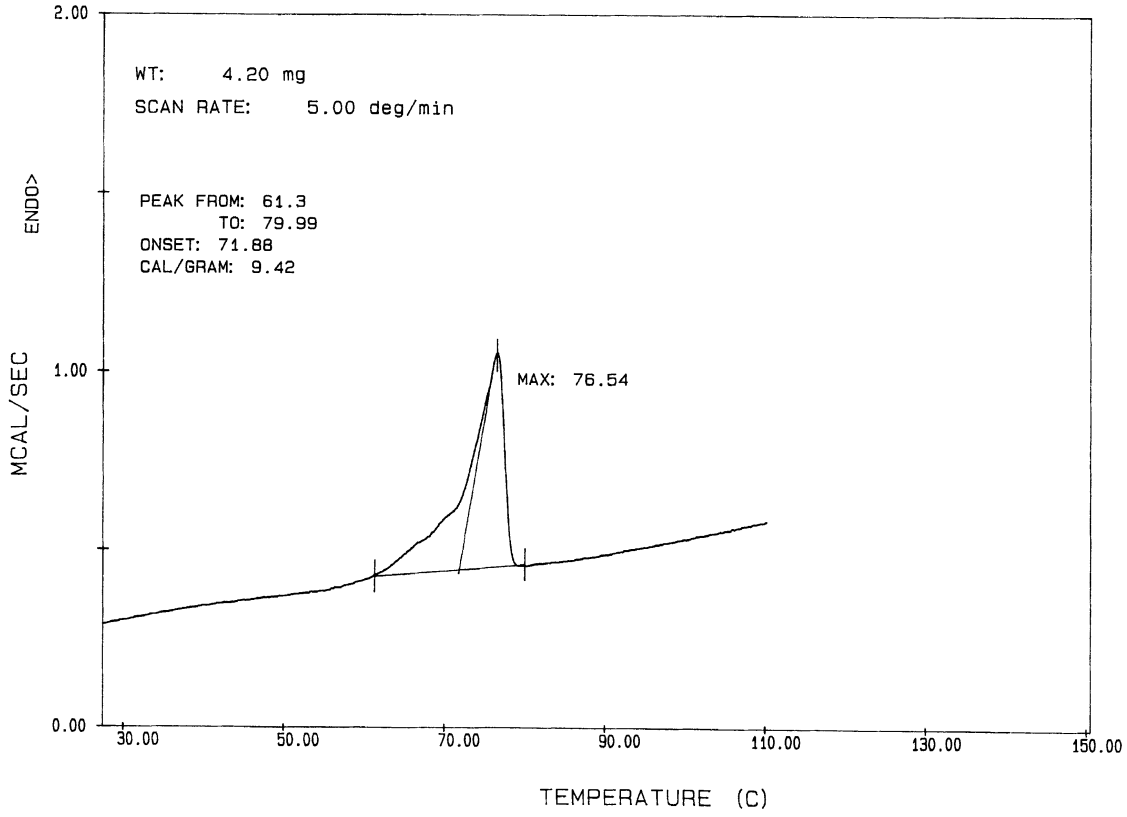


Figure III-6. Second DSC (Sample 2) of bis-1,3,5-phenylene-[5.5.5]-cryptand, **III-5**.

III.3 Conclusions

One cryptand, bis-1,3,5-phenylene-[4.4.4]-cryptand (**III-17**) was synthesized via a five step synthetic route (**Scheme III-3**). The synthesis of bis-1,3,5-phenylene-[4.4.4]-cryptand (**III-5**) was not completed; however, the diphenol precursor **III-15** was made. The mono-protected phloroglucinol (**III-8**) proved to be a rather difficult intermediate to synthesize. A previously published method[10] using several steps **(Method B**, 3.8 %) did not have an overall yield better than that of the one step synthesis (**Method A**, 38.7 %) in our hands. After **III-8** was produced in a reasonable yield the cryptands were synthesized using techniques similar to those used with the crown ethers discussed in **Chapter II**. However, in general the cryptands are difficult to synthesize because: 1) the difficult synthesis of the mono-protected phloroglucinol **III-8**, 2) purification involves one or more column chromatography steps, 3) the two pseudo-high dilution reactions require large reaction flasks, and 4) the yields of 4 of the 5 steps were less than 40 %. The complexation of the 32-membered cryptand **III-17** with a secondary ammonium ion will be discussed in **Chapter VI**.

III.4 Experimental

Chemical Reagents and Measurements

All chemicals were reagent grade and used directly as received from Aldrich except where specified. All solvents were HPLC or GC grade. THF was dried by refluxing in the presence of sodium metal and benzophenone. Melting points were taken in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Varian spectrometer with tetramethylsilane as an internal standard. The following abbreviations have been used in describing NMR spectra: s (singlet), d (doublet), and t (triplet). Elemental Analyses were performed by Atlantic Microlabs of Norcross, GA. Differential scanning calorimetry was conducted using a Perkin-Elmer thermal analyzer at a rate of 5 ^{o}C/min for both heating and cooling.

1. 5-Benzyloxyresorcinol (III-8): **Method A**: Phloroglucinol dihydrate (32 g) was placed in a 100 mL round bottom flask equipped with a Dean Stark trap and dehydrated using toluene (75 mL). After removal of the water and evaporation of the solvent dry phloroglucinol (**III-6**, 11.20 g, 88.8 mmol) was dissolved in DMF (200 mL) and added via a 250 mL addition funnel to a mixture of K_2CO_3 (12.27 g, 88.8 mmol) in DMF (200 mL). The mixture was stirred with a mechanical stirrer for 10 min. Benzyl bromide (**III-7**, 15.19 g, 88.8 mmol) was diluted with DMF (200 mL) and added dropwise over 3 h to the reaction mixture. After complete addition the reaction mixture was stirred for 1 h. The mixture was then filtered and the solvent was removed by rotoevaporation. The residue was dissolved in CH_2Cl_2 and washed with water (3 x 250 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed by rotoevaporation. A brown oil was obtained. The oil was absorbed on silica gel and purified by flash column chromatography (CH_2Cl_2; CH_2Cl_2:Et_2O, 85:15). The desired product was isolated as an oil. Yield = 7.04 g (36.6 %). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 7.94 (s, 2H), 7.32 (m, 5H), 6.08 (d, J = 2.0 Hz, 2H), 6.05 (t, J = 2.0 Hz, 1H), 4.92 (s, 2H); ^{13}C NMR (100 MHz) δ (ppm): 160.7, 157.9, 136.9, 128.4, 127.8, 127.5, 96.1, 94.8, 69.8 (9 carbons as required). **Method B**: **1,3,5-Tribenzoyloxybenzene** (**III-19**) and **3,5-**

Dibenzoyloxyphenol (**III-20**)[10]: Phloroglucinol dihydrate (53.56 g) was dried using refluxing toluene and a Dean Stark trap. The toluene was removed by rotoevaporation to give 43.99 g (349 mmol) of phloroglucinol (**III-6**). **III-6** was dissolved in dry THF (1.7 L) and stirred with pyridine (59.28 mL, 733 mmol). Benzoyl chloride (**III-17**, 49.06 g, 349 mmol) was added dropwise at RT over 1h. The resulting solution was stirred for 3 days. Another portion of **III-17** (49.06 g, 349 mmol) was added dropwise to the solution at RT over 1 h. The solution was stirred at reflux for 24 h, cooled to RT and filtered. The filtrate was concentrated using the rotoevaporator and the resulting tacky oil was stirred in $CHCl_3$ (200 mL). This solution was poured into ethyl ether (500 mL) to give two layers, the botton layer was an orange oil and the top was a cloudy, yellow solution. The two layers were separated. The bottom layer contained pyridine salt and 5-benzoyloxyresorcinol (**III-21**). The top layer was extracted with 2N HCl (200 mL), H_20 (2 x 100 mL) and a saturated solution of NaCl (200 mL). During the extraction a solid was collected (12.15 g) and determined to be **III-19**. The ether was removed by rotoevaporation and the resulting tacky solid (67.16 g) was air dried overnight. It was determined to be a mixture of **III-19** (10.07 g) and **III-20** (57.09 g, 56.4% yield) by ^1H NMR. To a solution of **III-19** and **III-20** (57.68 g, 43.6 g of **III-20**, 124 mmol) in anhydrous THF (400 mL) was added sodium hydride (5.46 g, 136 mmol). Benzyl bromide (**III-7**, 21.21 g, 124 mmol) was added and the resulting mixture was stirred at reflux for 20 h. The solution was cooled, filtered, and the filtrate was dried using a rotoevaporator. The solid was dissolved in ethyl acetate and washed with water (3 x 350 mL). A brown oil was found after removal of the ethyl acetate by rotoevaporation. MeOH was added to the oil and a white precipitate formed. The solid was filtered (21.79 g). The white solid was assumed to contain both **III-19** and **III-22**. The solid was dissolved in 180 mL of water and 18 mL of MeOH. KOH (7.80 g, 139 mmol) was then added. The mixture was heated to reflux overnight. Upon cooling a white solid was filtered. The filtrate was cooled to 0 ^oC and 2 N HCl was added slowly until a brownish-white precipitate was observed. The solid was filtered and washed with a saturated $NaHCO_3$ solution. A brownish-white solid was obtained and was recrystallized from water/ethanol.

Mp = 83.2 - 86.2 ^{o}C (lit.[10] 80 - 82 ^{o}C) Yield = 1.35 g (6.7%). ^{1}H (400 MHz, ambient T, DMSO-d_6) δ (ppm): 9.23 (s, 2H), 7.33 (m, 5H), 5.85 (d, J = 2.0 Hz, 2H), 5.83 (t, J = 2.0 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (100 MHz, ambient T) δ (ppm): 69.3, 93.9, 96.1, 127.9, 128.1, 128.8, 137.8, 159.4, 160.6.

2. 3,5-Bis(8-chloro-3,6-dioxaundecyloxy)benzyloxybenzene (III-11): 5-benzyloxy-resorcinol (**III-8**, 10.3 g, 47.6 mmol) and tri(ethylene glycol) dichloride (**III-9**, 10-fold excess, 89.10 g, 476 mmol) were dissolved in a suspension of potassium carbonate (29.7 g, 215 mmol) in acetonitrile (~ 25 mL) at 70 ^{o}C. The mixture was then stirred with a mechanical stirrer for 140 h. The mixture was cooled to RT and filtered. The solvent was removed from the filtrate by rotoevaporation. The resulting brown oil was dissolved in chloroform and washed with water (2 x 200 mL). The organic layer was evaporated to give a brown oil. The excess dichloride was removed by vacuum distillation (61 ^{o}C @ 0.25 mm Hg). The distillate was subjected to liquid-liquid extraction using petroleum ether for 16 days resulting the isolation of 12.7 g of **III-11**. The crude material was also subjected to flash column chromatography (ethyl ether) and 2.23 g of product was obtained. Yield = 14.9 g (62.2 %). ^{1}H (400 MHz, ambient T, $CDCl_3$) δ (ppm): 3.68 (m, 16H), 3.83 (m, 4H), 4.07 (m, 4H), 4.99 (s, 2H), 6.13 (t, J = 2.0 Hz, 1H), 6.18 (d, J = 2.0 Hz, 2H), 7.35 (m, 5H); ^{13}C NMR (100 MHz, ambient T) δ (ppm): 42.7, 67.4, 69.6, 70.0, 70.6, 70.7, 71.3, 94.4, 94.5, 127.5, 127.9, 128.5, 136.7, 160.5 (14 peaks of 15 needed).

3. Bis(5-hydroxy-1,3-phenylene)-26-crown-8 (III-15): A solution of **III-11** (11.66 g, 23.16 mmol) and **III-8** (5.01 g, 23.16 mmol) was made in acetonitrile (~ 100 mL). In a 3 L, 3-neck Morton flask, equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, rubber septum, and thermometer, acetonitrile (2.5 L) was heated to 70 ^{o}C under nitrogen flow. Potassium carbonate (48.07 g, 347.4 mmol) was then added followed by the above mentioned solution at a rate of 0.75 mL/h. The final mixture was stirred for 10 d. The mixture was then cooled to RT and filtered over Celite®. After removal of the solvent by rotoevaporation the resulting oil (17.55 g) was dissolved in a 50:50 mixture of

chloroform:methanol in a hydrogenation flask. To the flask was added palladium on carbon (500 mg, 5 wt % Pd/wet, Englehard) and the flask was pressurized to 60 psi. The flask was then shaken for 24 h. The mixture was then filtered through Celite®. The solvent was removed from the filtrate by rotoevaporation to give a brown oil. Trituration with acetonitrile gave a brownish precipitate. The precipitate was filtered and washed with acetonitrile. Yield = 833 mg (8.0 %). Mp = 192.2 - 193.1 ^{o}C. ^{1}H (400 MHz, ambient T, DMSO-d_6) δ (ppm): 3.58 (s, 8H), 3.69 (m, 8H), 3.96 (m, 8H), 5.91 (d, J = 2.0 Hz, 2H), 5.93 (d, J = 2.0 Hz, 4H), 9.43 (s, 2H); ^{13}C NMR (100 MHz) δ (ppm): 66.8, 68.7, 69.9, 92.7, 94.0, 159.0, 160.1 (7 peaks as required). EA (found, calculated): C 59.85, 59.99; H 6.89, 6.71.

4. 1-Benzyloxy-3,5-bis[2-(2-[2-(2-chloroethoxy)ethoxy]ethoxy)-ethoxy]benzene (III-12) III-8 (4.50 g, 20.8 mmol) and K_2CO_3 (16.45 g, 119.0 mmol) were stirred in CH_3CN (50 mL) in a 250 mL three-neck round bottom flask equipped with a reflux condenser, magnetic stirrer, and nitrogen bubbler. The reaction mixture was heated at 70 ^{o}C for 4 h under nitrogen. Tetra(ethylene glycol) dichloride (**III-10**, 165 g, 714 mmol) was then added dropwise via an addition funnel. The resulting reaction mixture was heated for 140 h at 70 ^{o}C. The mixture was then cooled, filtered, and the solvent was removed by rotoevaporation to give an orange oil. The oil was dissolved in chloroform (300 mL) and washed with water (2 x 200 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness using a rotoevaporator. The excess **III-10** was removed from the resulting orange oil by vacuum distillation (0.1 - 0.25 mmHg, 98 - 102 ^{o}C). The resulting dark oil was subjected to liquid-liquid extraction using petroleum ether for 14 d at 40 ^{o}C. A yellow oil was collected that still had **III-10** present (~5 - 10% by ^{1}H NMR). Flash column chromatography (EtOAc:hexanes, 1:2, v:v; EtOAc) was employed to remove **III-10**. Yield = 9.13 g (72.5 %). ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 7.78 (m, 5H), 6.18 (d, J = 2.0 Hz, 2H), 6.12 (t, J = 2.0 Hz, 1H), 4.99 (s, 2H), 4.07 (m, 4H), 3.83 (m, 4H), 3.68 (m, 24H); ^{13}C NMR (100 MHz) δ (ppm): 160.5, 160.4, 136.7, 128.5, 127.9,

127.4, 94.5, 94.3, 71.2, 70.7, 70.6, 70.6, 69.9, 69.6, 67.3, 42.7 (16 carbons of 17 expected).

5. Bis(5-benzyloxy-1,3-phenylene)-32-crown-10 (III-14): In a 5 L, 3-neck Morton flask equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, rubber septum, and thermometer, potassium carbonate (85.6 g, 619.6 mmol) was suspended in 4.0 L of acetonitrile. The reaction mixture was heated to 70 ^{o}C. To this mixture was added a solution of dichloride precursor (**III-12**, 25.5 g, 41.4 mmol) and diphenol (**III-8**, 8.93 g, 41.3 mmol) in acetonitrile (75 mL) at a rate of 0.75 mL/h. Upon complete addition the reaction mixture was stirred for an additional 7 d. The reaction mixture was cooled to RT and filtered to remove the salts. The solvent was removed from the filtrate by rotoevaporation to give a brown oil. The desired product was isolated via flash column chromatography (Et_2O, EtOAc) as a white solid. Yield = 7.42 g (24.0 %). Mp = 92.4 – 94.4 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 3.69 (m, 16H), 3.81 (m, 8H), 4.02 (m, 8H), 4.96 (s, 4H), 6.12 (t, J = 2.2 Hz, 2H), 6.16 (d, J = 2.2 Hz, 4H), 7.36 (m, 10H); ^{13}C NMR (100 MHz) δ (ppm): 67.6, 69.6, 70.0, 70.8, 94.4, 94.5, 94.6, 127.5, 127.9, 128.5, 136.8, 160.3, 160.5 (12 carbons of 13 expected).

6. Bis(5-hydroxy-1,3-phenylene)-32-crown-10 (III-16): The diprotected crown ether (**III-14**, 10.00 g, 13.4 mmol) was dissolved in a hydrogenation flask with MeOH:$CHCl_3$ (80:20, 250 mL) containing palladium on carbon (2.00 g, 5 wt. %/wet, Englehard). The flask was pressurized to 60 psi. with hydrogen gas and shaken for 2 d. The mixture was then filtered through Celite®. The solvent was removed from the filtrate to give an orange oil. Recrystallization from methanol gave a white solid. Yield = 5.75 g (75.5 %). Mp = 168.6 – 172.8 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6, ambient T) δ (ppm): 3.53 (m, 16H), 3.67 (m, 8H), 3.95 (m, 8H), 5.90 (d, J = 2.0 Hz, 4H), 5.95 (t, J = 2.0 Hz, 2H), 9.40 (s, 2H); ^{13}C NMR (100 MHz) δ (ppm): 67.0, 69.0, 70.0, 92.2, 94.7, 159.9, 160.3 (7 carbons of 8 expected).

7. Bis-1,3,5-phenylene-[5.5.5]-cryptand (III-5): In a 3 L, 3-neck Morton flask equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, rubber septum, and thermometer, potassium carbonate (20.6 g, 149 mmol) was suspended in 2.0 L of acetonitrile at 70 ^{o}C. To this mixture was added a solution of **III-16** (5.67 g, 9.97 mmol) and dichloride **III-10** (2.30 g, 9.97 mmol) in DMF (100 mL) slowly (0.75 mL/h) via a syringe pump. After addition the reaction mixture was stirred for 14 d. Upon cooling the salts were removed by filtration and the solvent was removed from the filtrate by rotoevaporation. The resulting brown viscous oil (7.68 g, 13.5 mmol) was subjected to column chromatography (SiO_2, Et_2O:EtOAc, 9:1; EtOAc). Some of the starting material **III-16** (0.76 g) was recovered followed by the desired product **III-5**. Yield (based on only 4.46 g, 7.8 mmol, of **III-16** reacting) = 2.17 g (38.0 %). Mp = 71.9 - 80.0 ^{o}C (Dev's = 77.5 - 78.0 ^{o}C) ^{1}H NMR (400 MHz, $CDCl_3$, ambient T) δ (ppm): 3.69 (m, 24H), 3.81 (m, 12H), 3.93 (m, 12H), 6.00 (s, 6H); ^{13}C NMR (100 MHz) δ (ppm): 67.5, 69.7, 70.7, 71.0, 94.2, 160.4 (6 carbons as expected). FABMS (3-nitrobenzyl alcohol, NBA) m/z (rel. int.): 749.1 [$(M + Na)^+$, 100 %)], 727.2 [$(M + H)^+$, 32 %], and 705.3 [$(M + Na)^+ - C_2H_4O$, 15 %]. HR-FABMS (3-NBA): m/z 749.3373 $(M + Na)^+$ [calcd. for $C_{36}H_{54}O_{15}Na$: 749.3360].

III.5 References

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