SYNTHESIS AND PROPERTIES OF RESORCIN[4]ARENE BASED QUADRUPOLES AND DIMERIC ELECTROSTATIC CAPSULES

BY

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B.S., University of Illinois at Urbana-Champaign, 2003

AN ABSTRACT OF A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry

College of Arts and Sciences

KANSAS STATE UNIVERISTY

Manhattan, Kansas

2009

Abstract

In the present study, the rescorcin[4]arenes decorated with an alternating arrangement of pyridinium and sulfonate moieties were synthesized to establish a molecular quadrupole. These rescorcin[4]arenes are capable of undergoing conformational changes from a 'collapsed' to 'open' state. The stability of the two state are controlled by the polarity of the solvent environment. The electrostatic interactions between pyridinium and sulfonates enforced a 'quadrupolar collapse' in solvents such as chloroform. While these interactions are disrupted in dimethylsulfoxide.

A major synthetic challenge was functionalizing the resorcin[4]arene in a positive/negative/positve/negative pattern was successfully addressed. Comparison to dipolar resorcin[4]arene were undertaken to establish a quantitative measurement of the quadrupolar forces and to address the question of cooperatively provided addition attraction beyond two dipoles.

A,C-functionalized-bis sulfonate resorcin[4]arenes and A,C function bis-pyridinium resocin[4]arenes were synthesized independently. Combining these dicationic and dianionic moieties provided an interdigitating dimeric unit with overall quadrupolar charge distribution.

Disruption of the quadrupolar salt bridges in $CDCl_3$ was accomplished through the addition of DMSO or through dilution. ΔG^o, ΔH^o, and ΔS^o have been determined for the dimer formation. Addition of pyridinium salts led to a disruption of the dimeric capsule.

Host-guest binding studies established attractive binding to CS_2. Larger guests such as toluene, diiodobenzene, dicynanobenzene could not be encapsulated.

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Dr. Stefan Kraft

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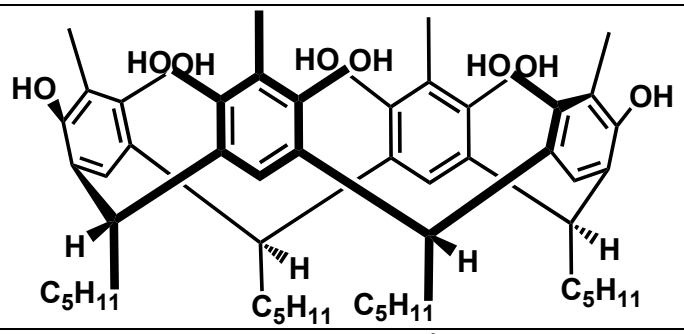
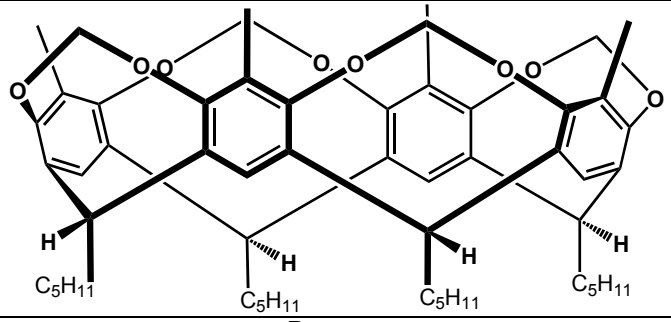
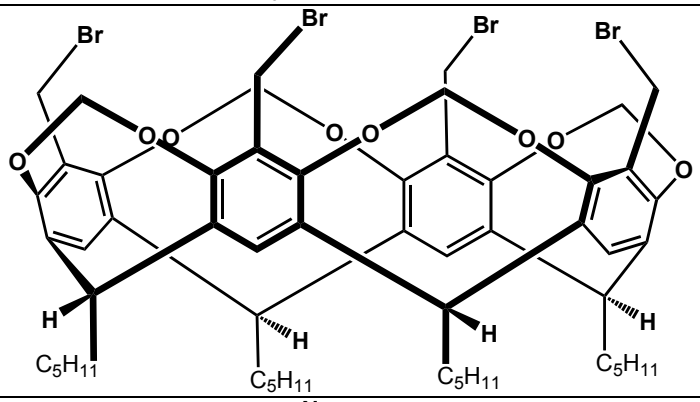
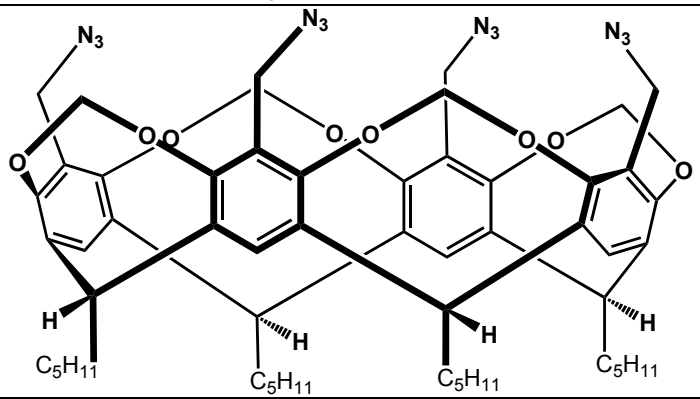
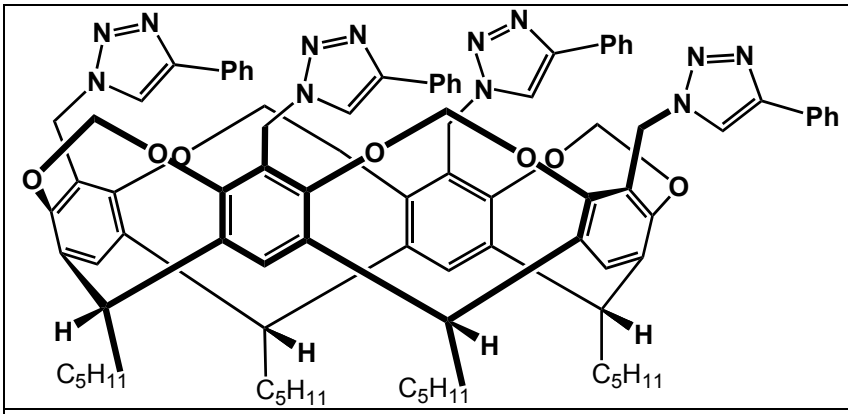
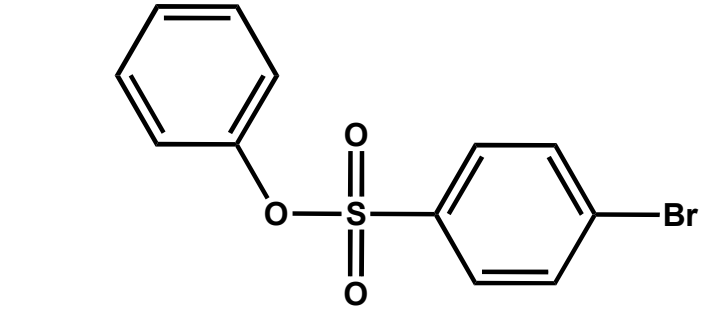
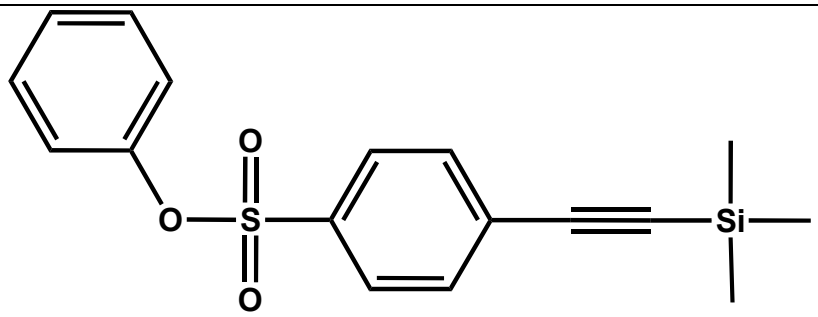
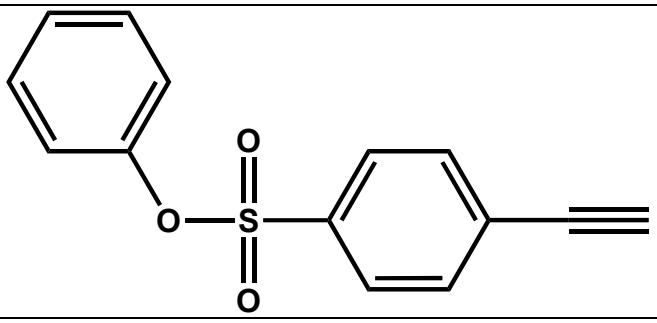
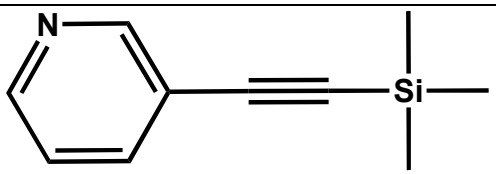
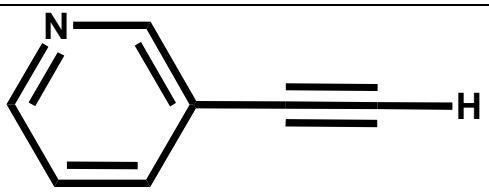
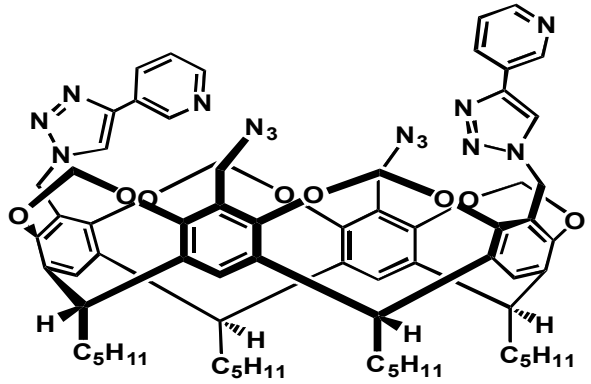
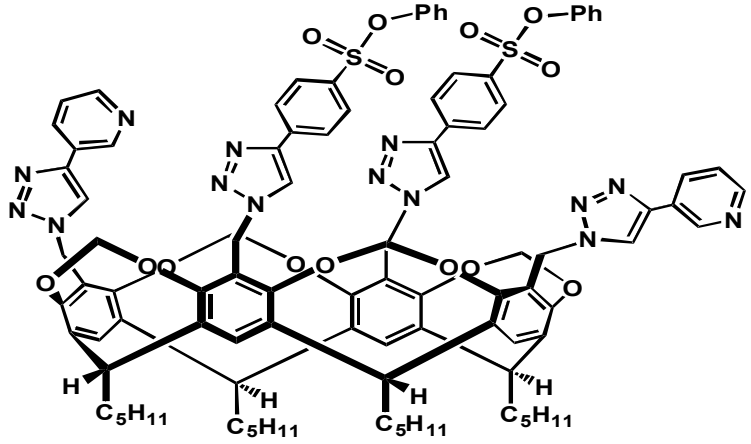
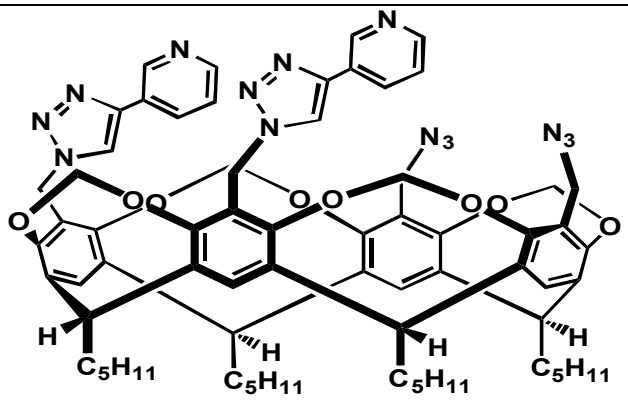
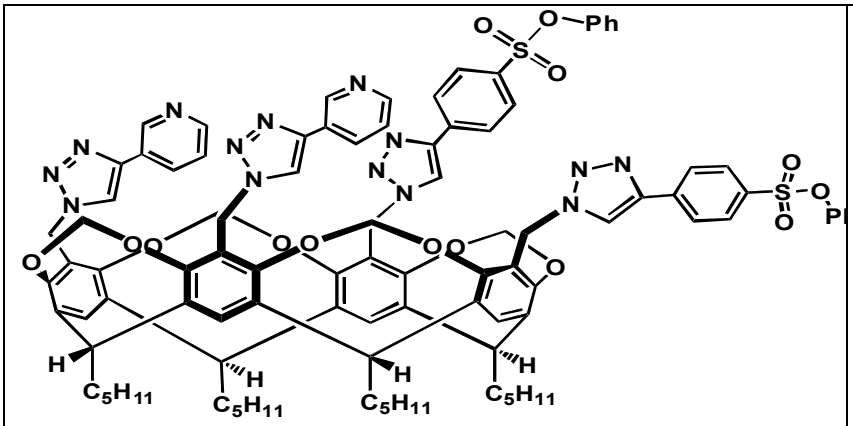
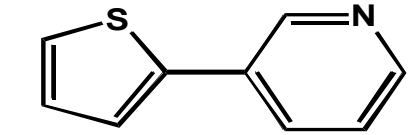
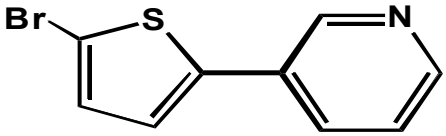
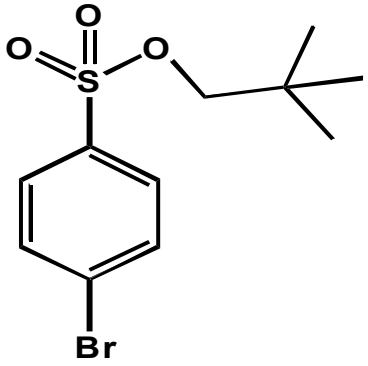
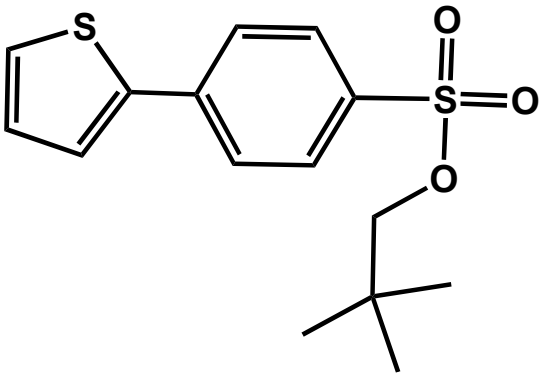
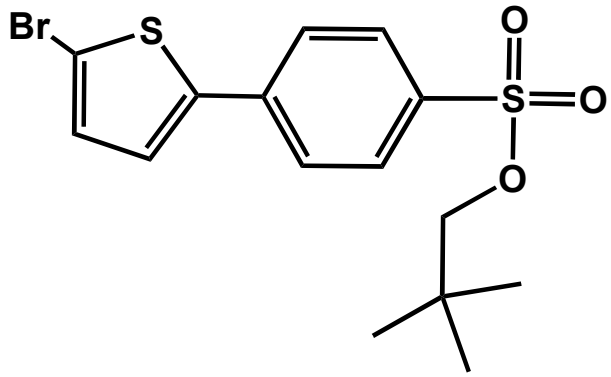
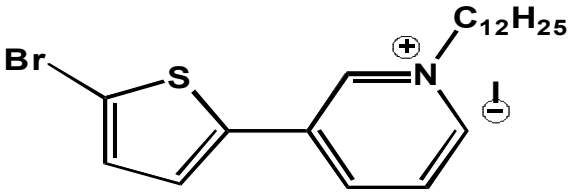
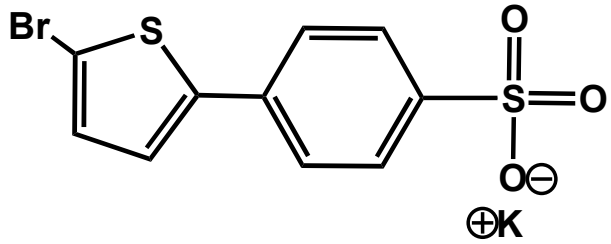
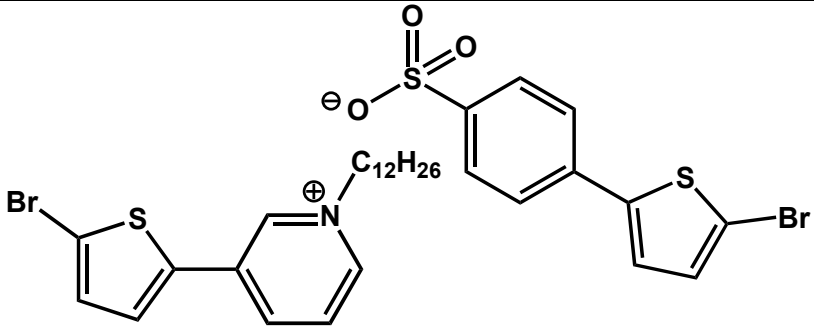
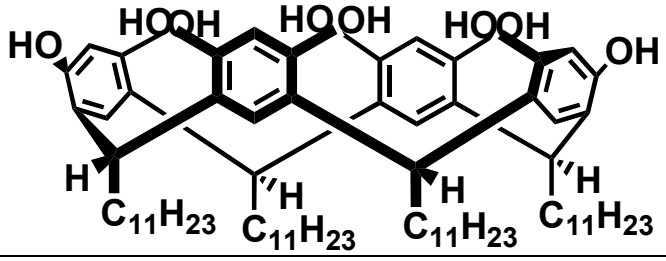
	2-1
	2-2
	2-3
	2-4

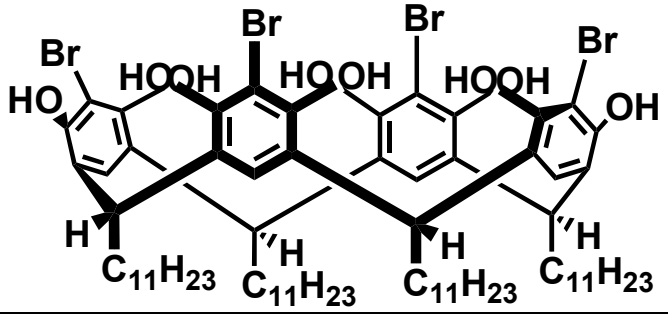
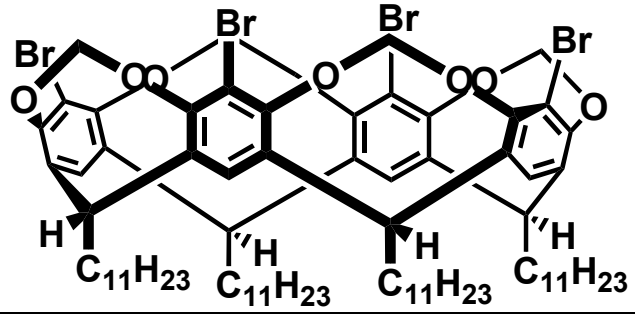
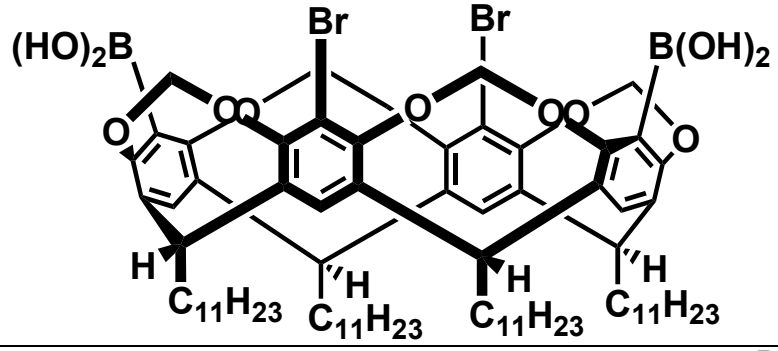
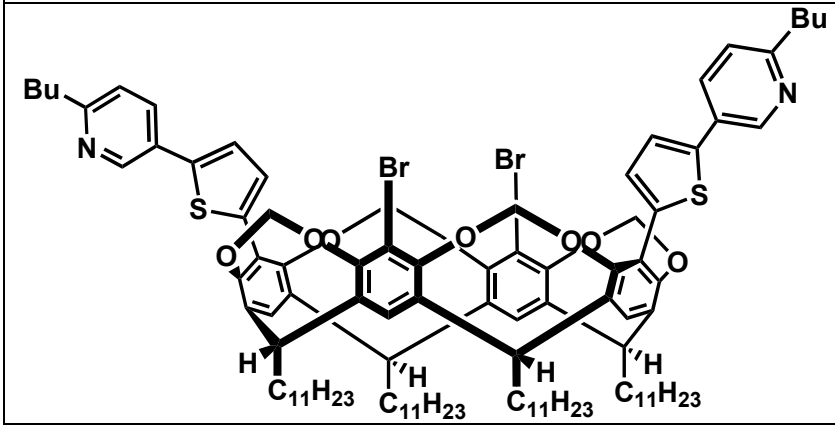
	2-5
	2-6
	2-7
	2-8

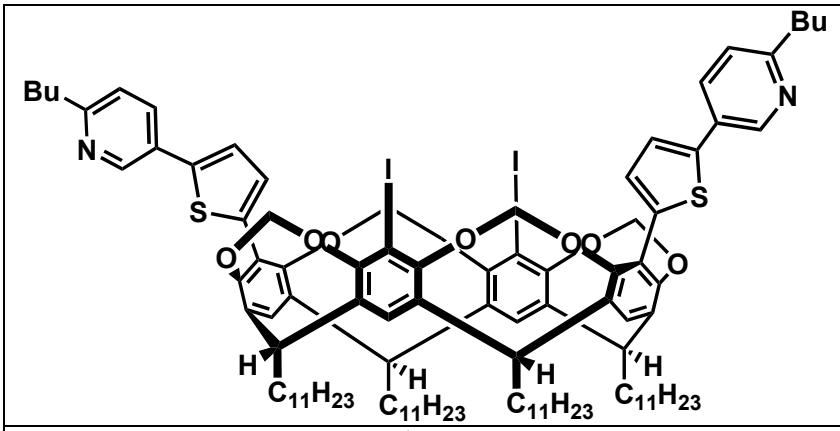
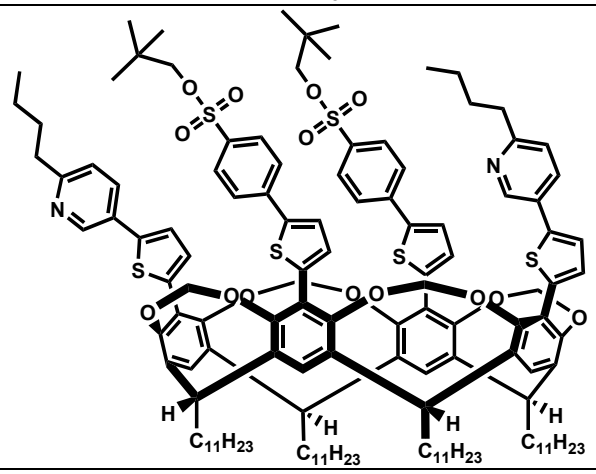
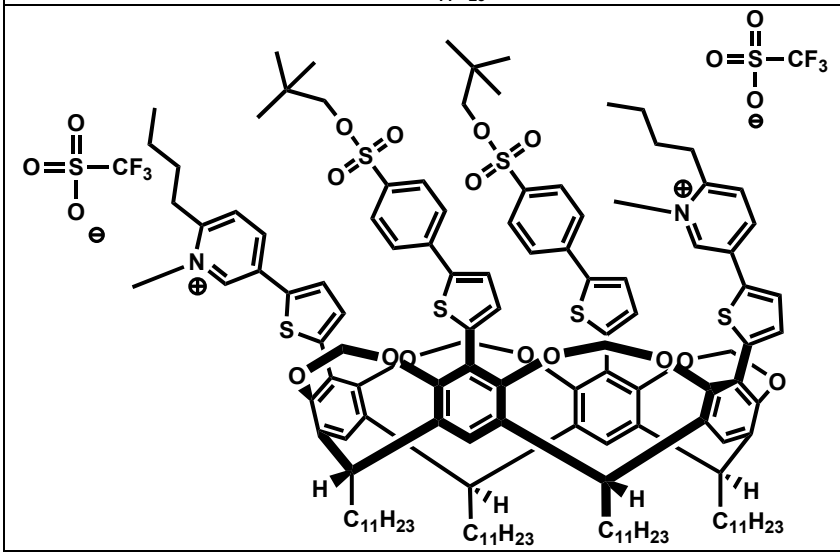
	2-9

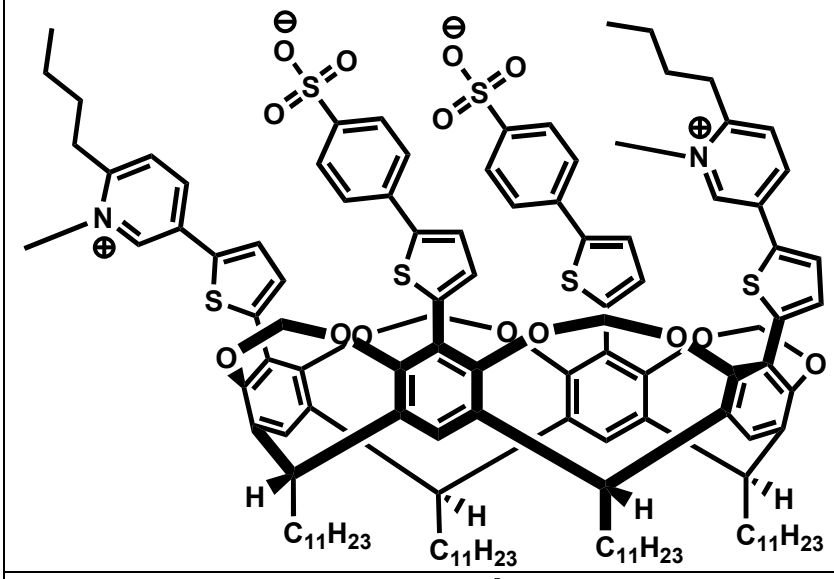
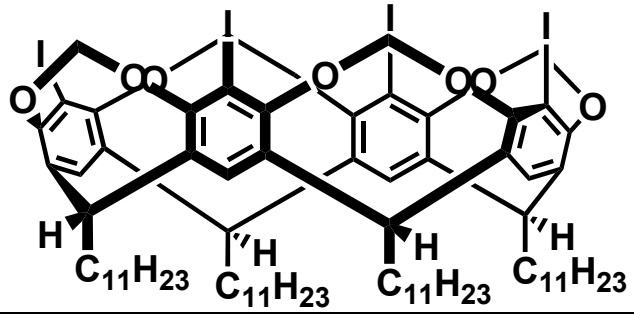
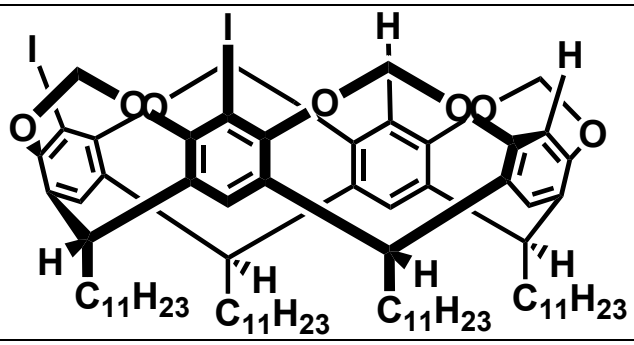
	2-10
	2-11
	2-12
	2-13

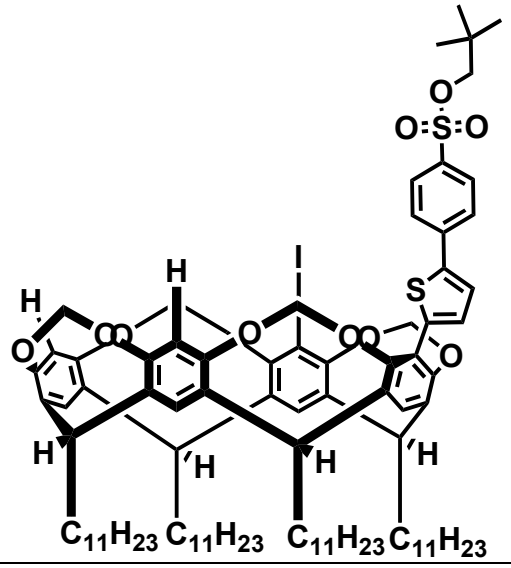
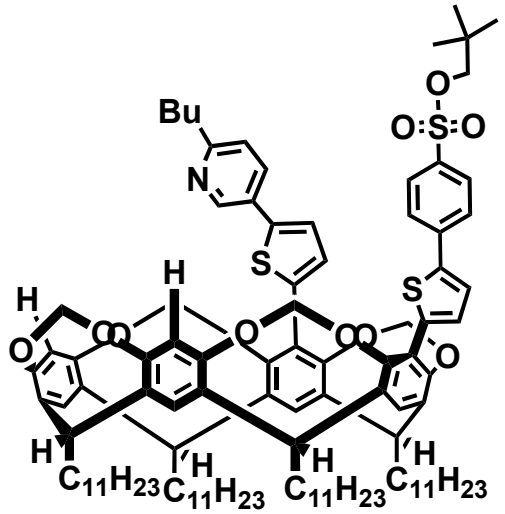
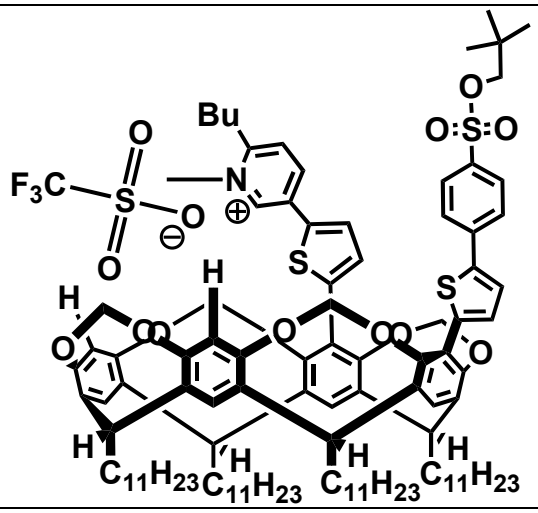
	2-14
	3-1
	3-2
	3-3
	3-4

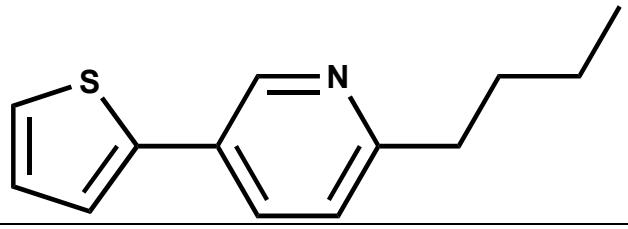
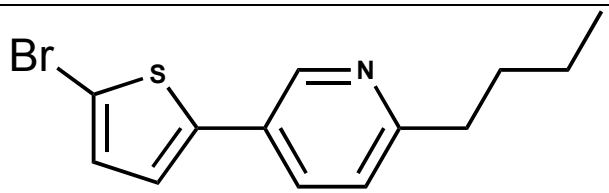
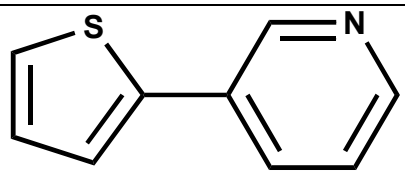
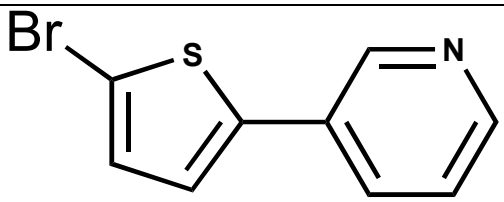
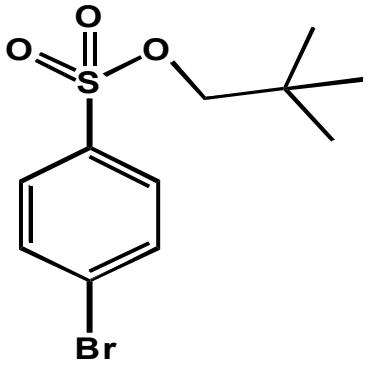
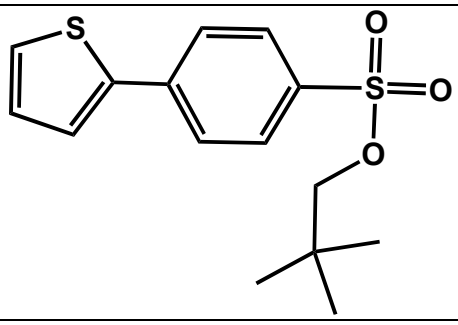
	3-5
	3-6
	3-7
	3-8
	3-9

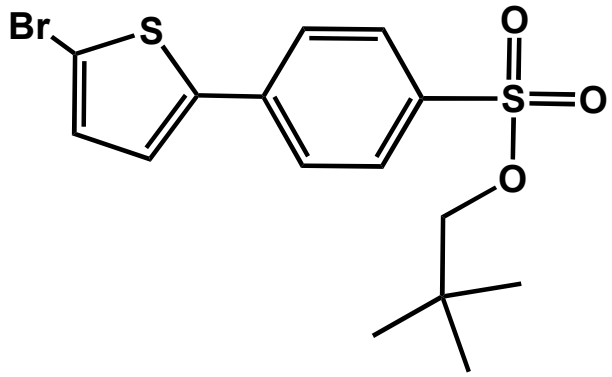
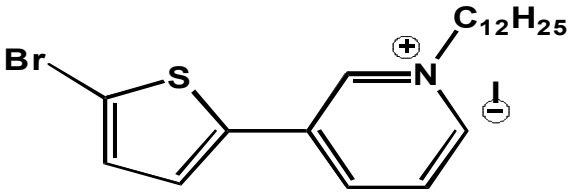
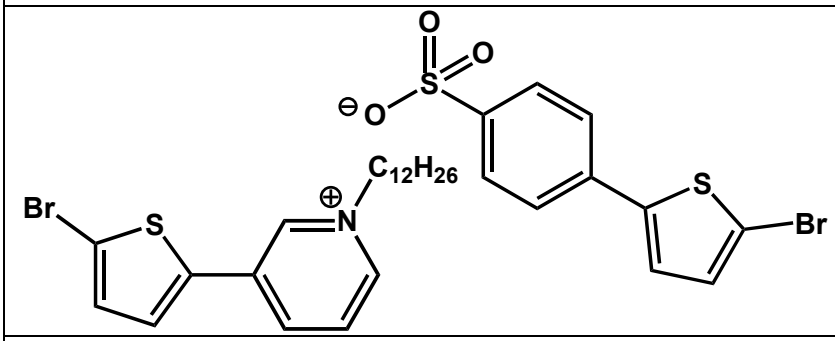
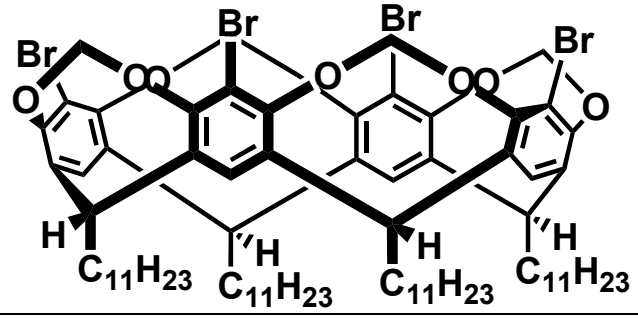
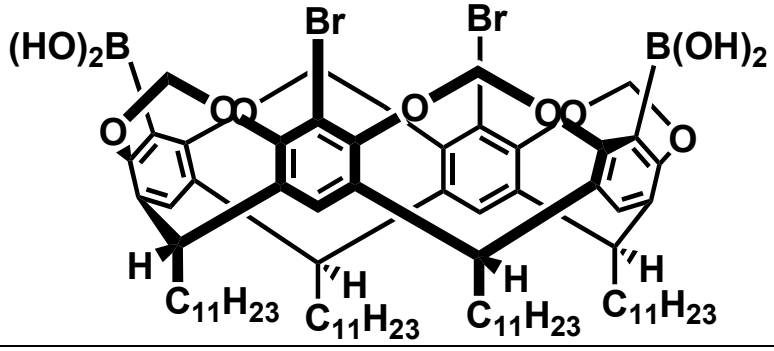
	3-10
	3-11
	3-12
	3-13

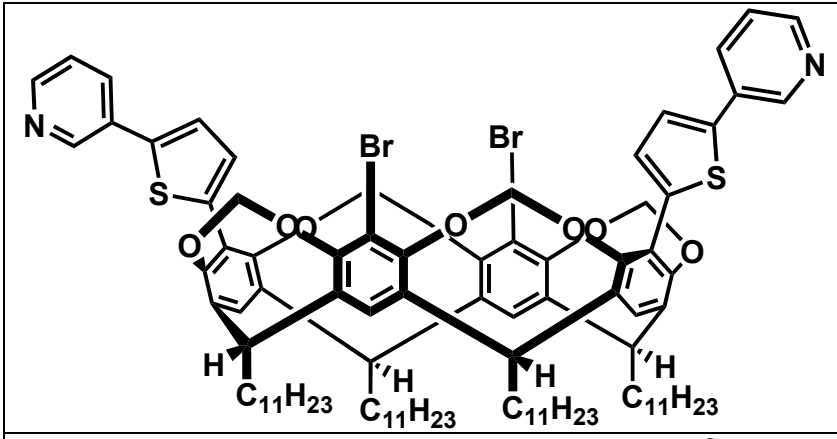
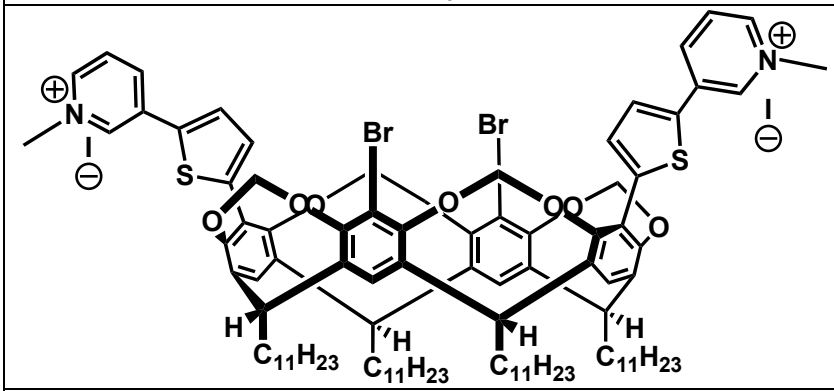
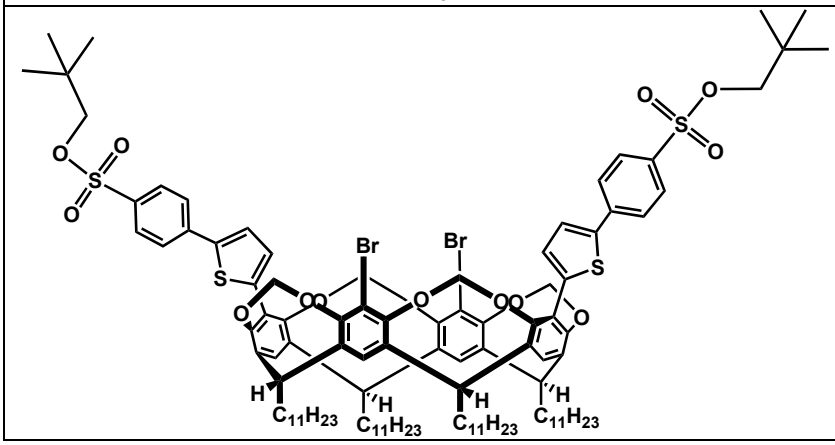
	3-14
	3-15
	3-16

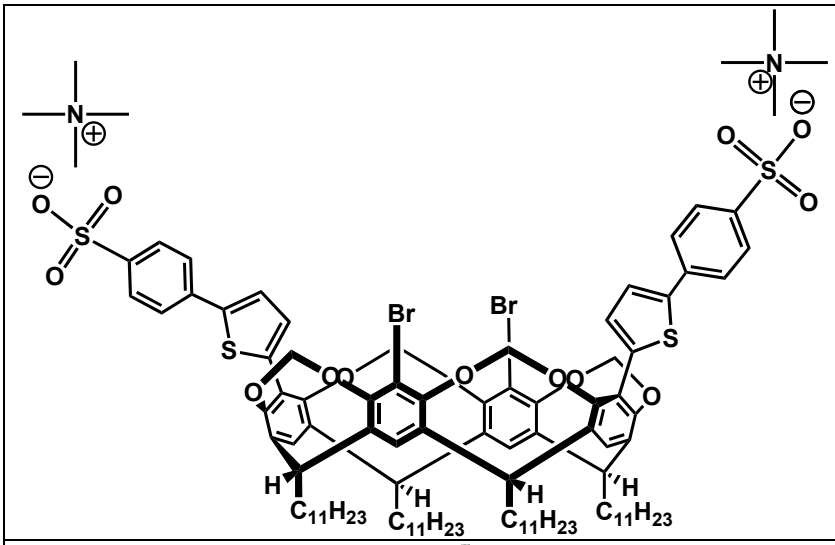
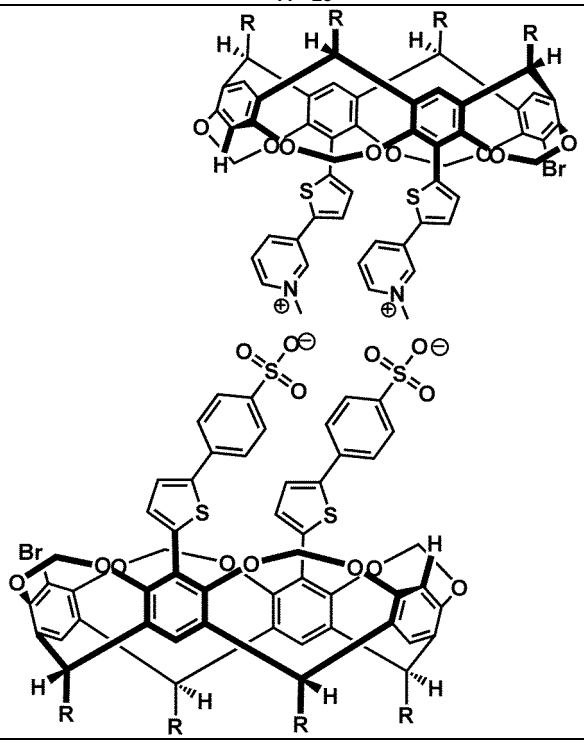
	3-17
	3-18
	3-19

	3-20
	3-21
	3-22

	3-23
	3-24
	4-1
	4-2
	4-3
	4-4

	4-5
	4-6
	4-7
	4-8
	4-9

	4-10
	4-11
	4-12

	4-13
	4-14

Dedication and Acknowledgements

First, I would like to thank my Lord and Savior Jesus Christ for the guidance and strength to face the exciting challenges of graduate school. I would like to thank to my undergraduate mentors, Dr. Peter Wuts and Dr. Jeffery Moore for their encouragement to continue my education.

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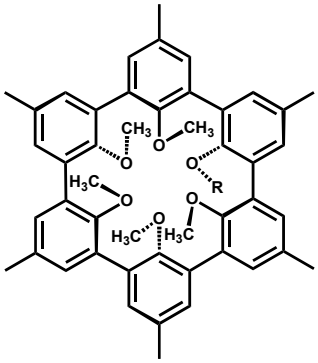
Lastly, I would like to extend a special thanks to my family and my fiancée for their love and unlimited support throughout my graduate career.

Chapter 1 Introduction

.1.1 What is a Cavitand?

In 1982 Cram proposed the term 'cavitand' as a molecule with an inner cavity large enough to accommodate guest molecules or ions.[1] Spherands (**1**)[2] which are useful alkali metal ion complexion, cycloteveratrylene (**2**)[3], which has a saucer shape which can be stitched together to generate a capsule-like molecule (**3**)[3]. Cavitands (**5-7**) generated from resorcinol-acetaldehyde condensations which can be decorated with various functional groups.[1] Cram, Rebek, and Diederich have had great contributions to the diazanapthalene bridged cavitands**(7)** which exhibit a conformational change between vase C_{4v} to kite C_{2v} conformation. The diazanapthalene bridged **(7)** cavitand undergoes a conformation change from a vase to kite conformation which is the upper arms are held together based on an external stimulus. The arms of the aromatic walls are distant relative to each other in the kite while the arms are held together by hydrogen bonding in the vase conformation.



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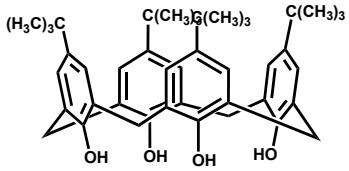

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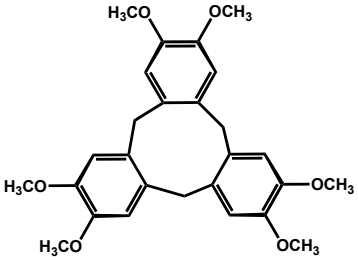

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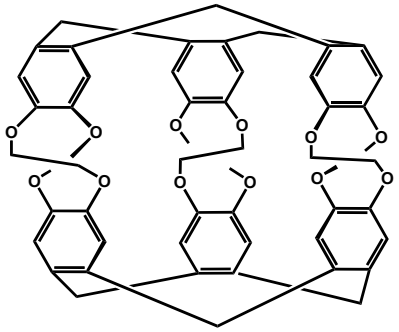

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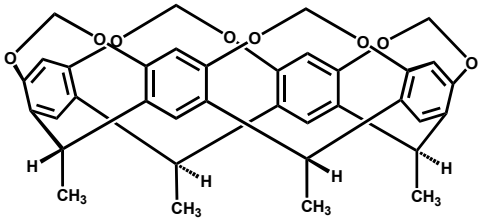

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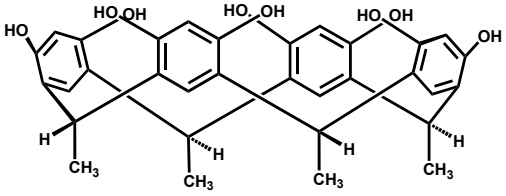

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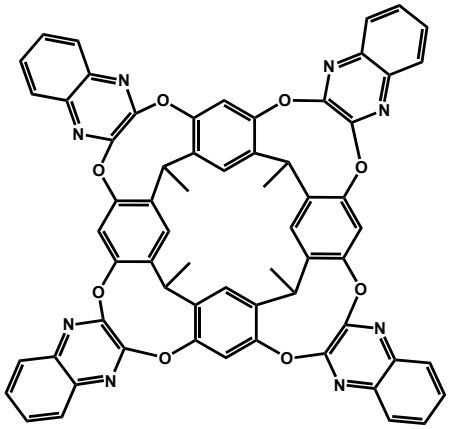

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Figure 1.1 Different types of cavitands.

1.2 What are cavitand's uses?

Cavitands contain cavities, which are capable to accommodate guest molecules or ions. Rebek introduced self-folding capsules (**8**) which can accommodate adamatanes, lactams, and cyclohexanes in amide substituted cavitands[4] (Figure 1.2). These supramolecular structures can reversibly change from a vase C_{4v} to kite C_{2v} conformation. Eight intramolecular hydrogen bonds stitch together the seams of the cavitand's upper arms holding the aromatic walls together for a stable vase-like structure. These intramolecular hydrogen bonds can be ruptured to release solvents molecules and pre-bind guest molecules while reforming the intramolecular hydrogen bonds to generate a stable host guest complex.

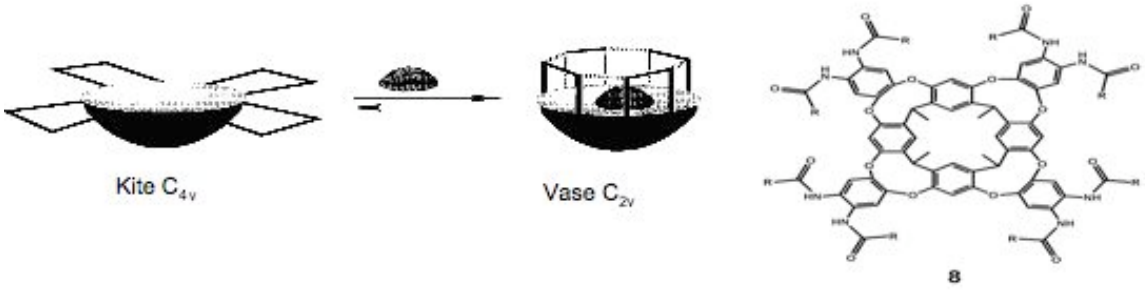


Figure 1.2 Rebek's reversible self-folding Cavitand.

Rebek and co-workers[5] generate molecular capsules through a hydrogen bonding network with two cavitands (Figure 1.3). These complexes are generated with guest molecules such as quniclinidine, with recystillization from methanol yielding dimeric capsules. These studies demonstrate solvents such as methanol, wet acetonitrile, and water is essential to promote formation of these networks.

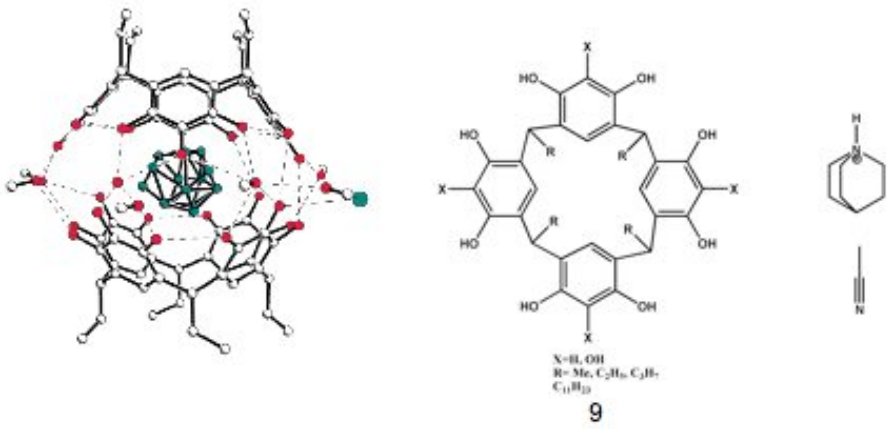


Figure 1.3 shows Cram's solvent stabilized capsule.

Cavitands decorated with pyrazine dicarboximide, which are hydrogen bond donors, and acceptors (**9**), can form 1:1 complexes, which accommodate guest molecules and amplify chemicals reactions such as ring/chain isomerization reaction. The use of a

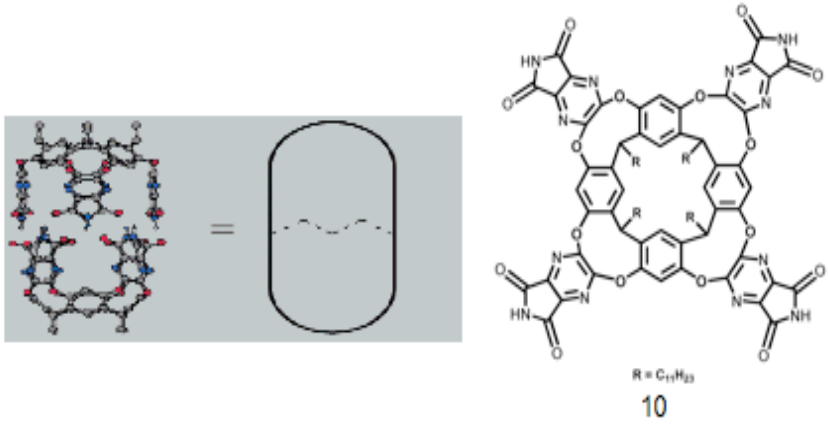


Figure 1.4 Dimeric Capsule through Hydrogen Bonding

cavitand based molecular capsule can shift the equilibrium to the oxazine from the Schiff's base. As shown in the diagram below the use of the 1:1 capsule creates an environment more conducive for the isomerization of the Schiff's base to oxazine. As shown in the scheme below amount of 10 and 12 is greatly diminished with the use of a molecular capsule held together by hydrogen bonds.

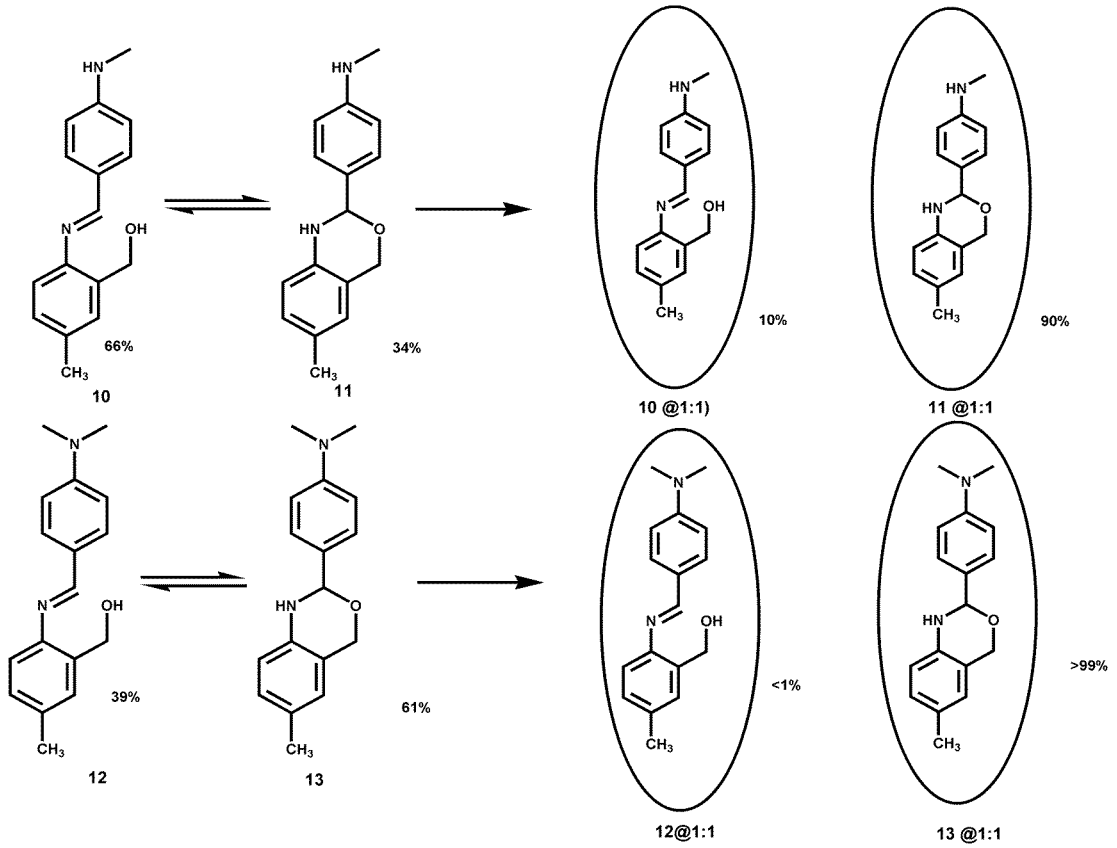


Figure 1.5 shows capsule promoted ring isomerization

1.3 Conformational Change

1.3a What is conformational change?

Conformational change is when a molecule changes its morphology due to functional moieties changing their relative orientation through space. For example this biopolymer undergoes a conformational change from a random coil to a helical type conformation[6]. The helical conformation is held together by

aromatic π-stacking units (**15**). Polar solvents such as acetonitrile drive these oligomers to fold into an ordered state while chloroform pushes the equilibrium to the random coil.

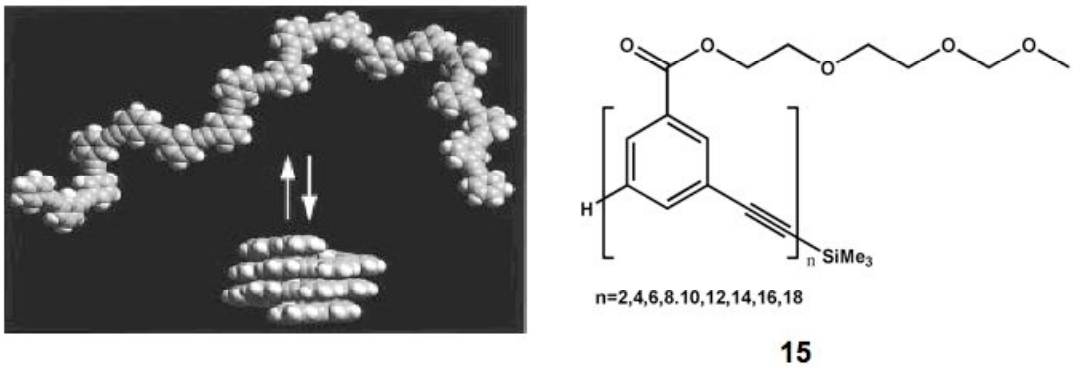


Figure 1.6 Jeffery Moore's conformational change from random coil to ordered helices.

The most significant conformational change was established with Cram's quinoxaline bridged cavitands.[1] External stimuli such as temperature and pH exerted a change from a vase C_{4v} to kite C_{2v} conformation.

Others such as Diederich et al[7] have used chloroform-d($CDCl_3$) or methylene chloride (CD_2Cl_2) with trifluoro acetic acid (TFA) led to the kite conformation. Potassium carbonate was employed to raise the pH thus changing the conformation from a kite vase.

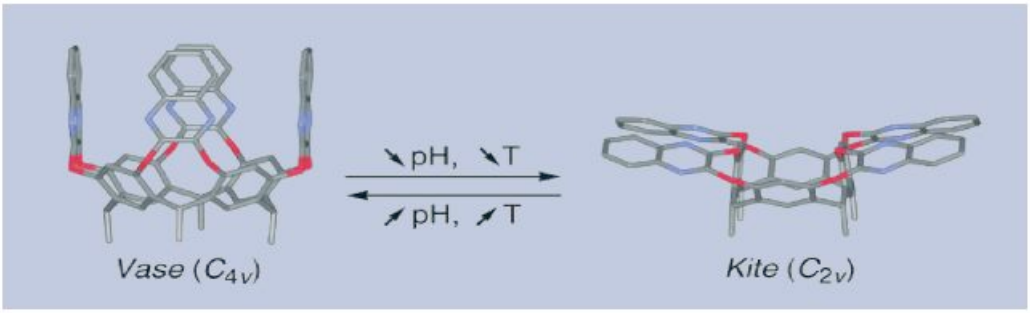
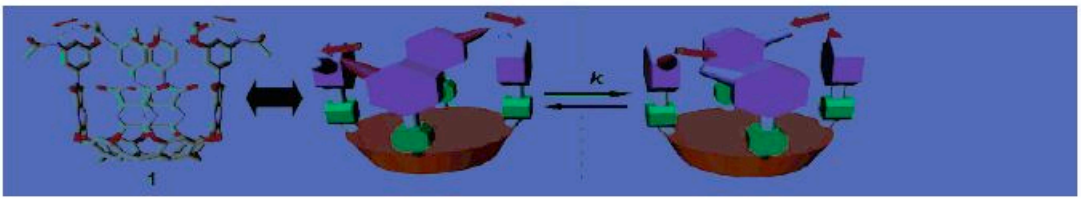


Figure 1.7 Cram's quinoxaline bridged cavitand which undergo transformation from vase to kite.

Conformational dynamics in enzymes is important to understand the allosteric regulation for binding of substrates. This conformational change that occurs within the enzyme is due to an allosteric activator, which is transmitted to the active site. [8] Similar to Cram's system[1] Badjic



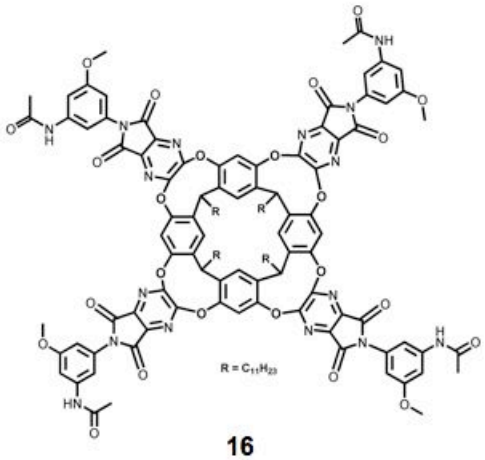


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Figure 1.7 Badjic Cavitand with flaps capable of interconverting by enantiomers.

designed a cavitand **(15)** with flaps capable of interconverting between two enantiomers. Their results demonstrated chloroform with triflouroacetic acid slowed down the interconversion between the two enantiomers. They found a ΔG^{o} = 13.3 kcal/mol for 0 equivalents of TFA and ΔG^{o} = 15 kcal/mol for 17 equivalents of TFA. As a result the allosteric effect is regulated by acid.

1.4 Electrostatics

1.4a How are electrostatics forces implemented in supramolecular systems?

Ion pairing are attractive forces present in many biological systems. For example proteins contain ammonium and carboxylate salts such as lysine and glutamic acid. These electrostatic forces are termed as Coulomb attractions, which are defined as:

$$E = \frac{q_1 \, q_2}{4 \, \pi \varepsilon \varepsilon_o \, r^2}$$

Equation 1.1 calculation for electrostatic forces.

where *q* is the force on the charge, *r* is the separation of the charges, ε is the permittivity of the vacuum and E is the electric field in the space around the charge.[9] The electrostatic forces are great diminished in solvents with high dielectric constants. As a result solvents with low dielectric constants are employed to observe electrostatic forces in ionic pairs. For our purposes the paper involves the study of electrostatic forces within supramolecular host structures therefore solvents with low dielectric constants are employed.

Hans-Jorg Schneider studied association constants of 10 ion pairs in water by NMR titrations.[10] All ten ion pairs were around 16 $kJmol^{-1}$ meaning each ion pair is 8 kJ/mol^{-1}. The difference between the strongest and weakest complexes in ΔG^o values is -12.6 and 16.3 $kJmol^{-1}$, which is surprisingly small. A linear correlation was found between the ΔG and number of bonds, which yields a ΔΔG of 0.5 $kJmol^{-1}$

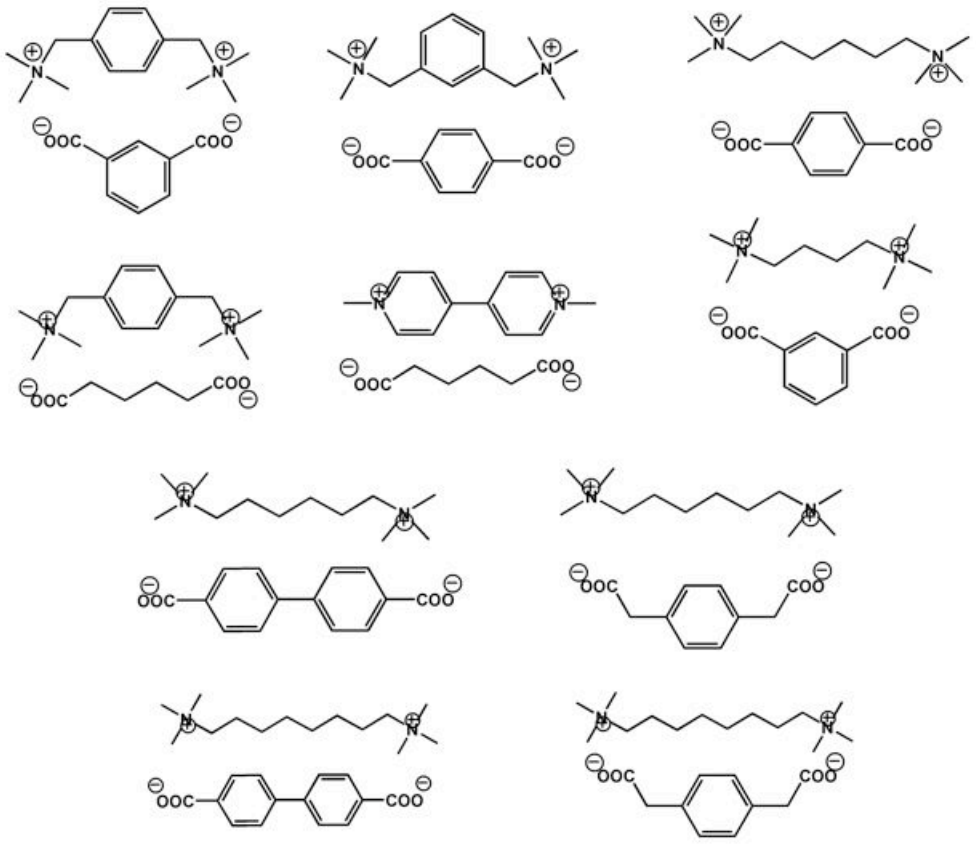


Figure 1.8 shows 10 ion pairs studied by Schneider et al.

.1.5 Supramolecular Electrostatic Assemblies

Many are interested in forming assemblies based on electrostatic forces. This section will focus on the current uses of cavitand-based assemblies of molecular capsules. Reinhoudt has done fabulous work with uses electrostatics for generating molecular capsules. Reinhoudt and coworkers[11] employ two pyridium half capsules with held together by sulfonates through electrostatic self-assembly.

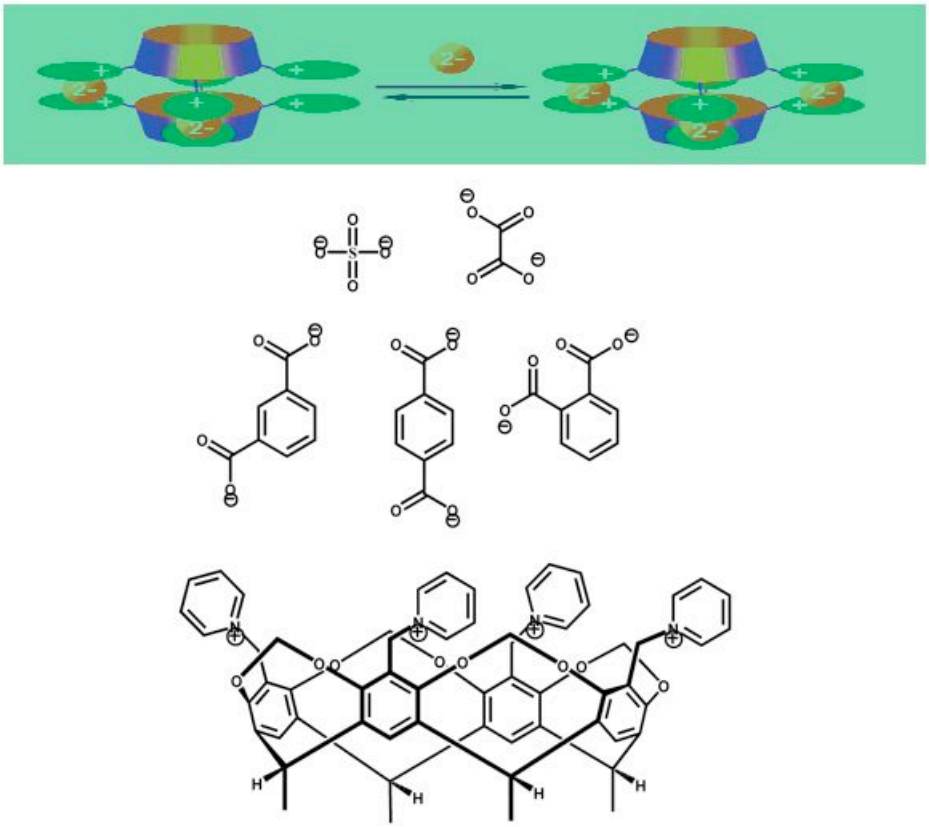


Figure 1.9 tetra(kis)-methylpyridinium half capsule and doubly charged anions that are complexed.

Tetra(kis)-methylpyridium half capsule are complexed with a doubly charged anions such as sulfonate and carboxylates to generate a capsule based on salt bridges. An electrostatic self-assembly generates H_2A_4 and H_2A_3 dimers where 'H' is the half bowl and 'A' is the anionic species. NMR dilution studies were performed in methanol d-4 and H_2A_3 is 3.25 $x10^{12}$ M^{-4} and H_2A_4 is 3.45 x 10^{15} H_2A_4. These capsules possess cavities capable of accommodating methyl and ethyl esters of 4-aminio benzoic acid, 4-iodophenol and 4-iodoaniline. Reinhoudt and coworkers[12] decorate a cavitand with pyridiums and complex it with a sulfonate functionalized calixarene. By NMR and UV dilution studies K_a Values of $2•10^6$ M^{-1} were determined in methanol and water-methanol mixtures.

These molecular capsules inner cavity are smaller than Rebek's[13] systems due there ability to encapsulate molecules such as methanol, ethanol, propanol, and n-amyl alcohol.

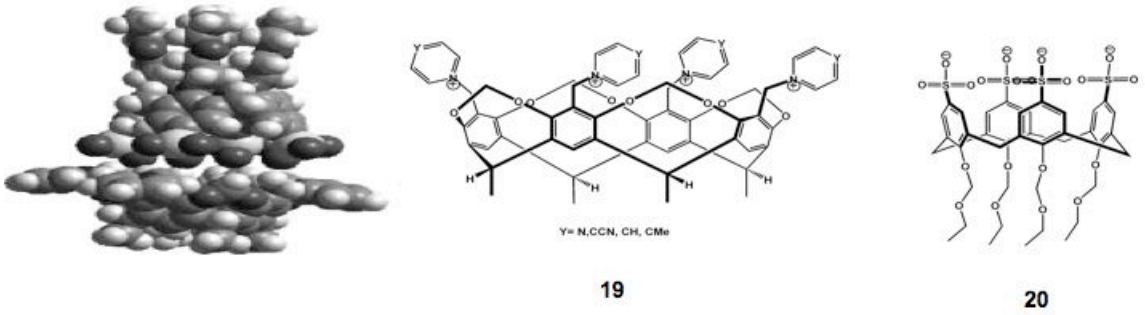


Figure 1.10 shows the sulfonate caliaxarene and tetrapyridinium cavitand.

Reinhoudt also developed a water-soluble electrostatic assembly between a tetra-carboxylate and tetra-amidinium capsule. There studies proved two oppositely charged calixarenes could accommodate small guest molecule such as N-methyl quinuclidinium in water. They calculated ΔH = -3.3 kcal/mol^{-1} due to the favorable interaction between the two oppositely charged calixarenes and $T\Delta S$= 2.9 kcal/mol^{-1}. This evidence supports supramolecular complexes can potentially serve as drug delivery tools.[14]

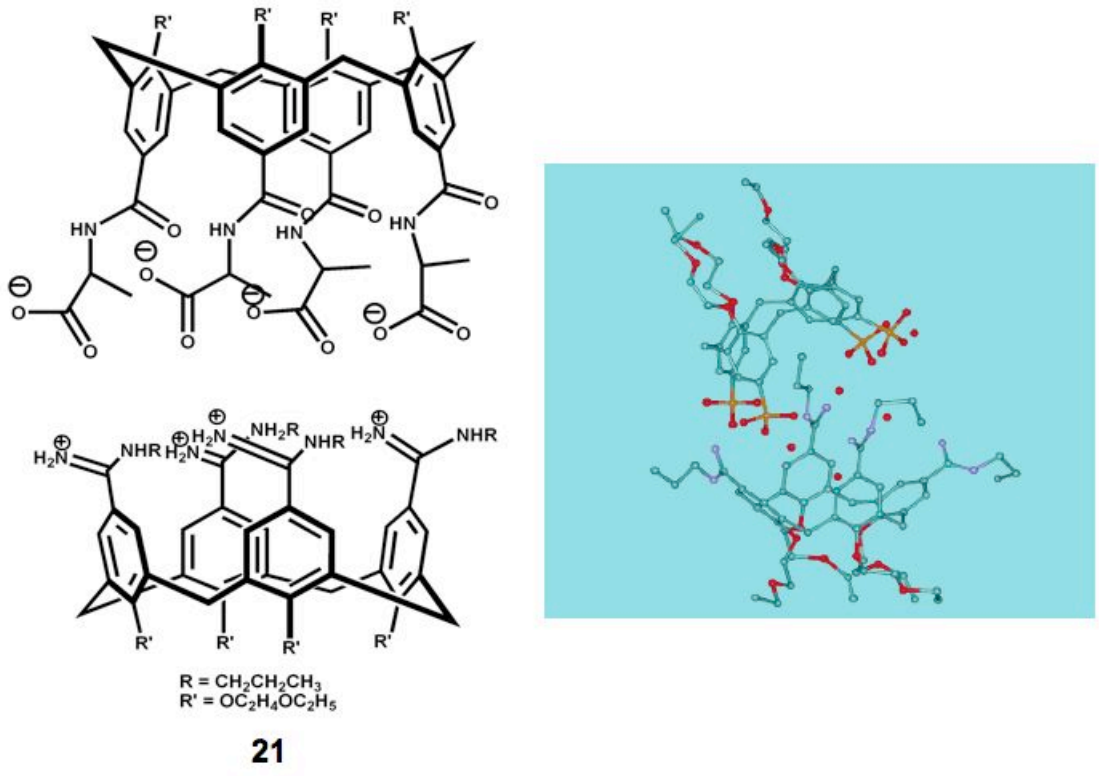


Figure 1.11 shows the tetracaboxylate and tetramidinium capsule.

1.6-References

1. John R. Moran, S. K., and Donald J. Cram, Cavitands: synthetic molecular vessels. *JACS* **1982,** 104, (21), 5826-5828.
2. Donald J. Cram, T. K., Roger C. Helgeson, and George M. Lein, Spherands - ligands whose binding of cations
relieves enforced electron-electron repulsions. *JACS* **1979,** 101, 6752-6754.
3. COLLET, J. G. a. A., Synthesis of a (0,)-B is(c yclotriveratrylenyl) Macrocage by Stereospecific
Replication of a (C,) -Subunit. *J.C.S. CHEM. COMM* **1981**, 1137-1139.
4. Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Self-folding cavitands. *Journal of the American Chemical Society* **1998,** 120, (47), 12216-12225.
5. Shivanyuk, A.; Friese, J. C.; Doring, S.; Rebek, J., Solvent-stabilized molecular capsules. *Journal of Organic Chemistry* **2003,** 68, (17), 6489-6496.
6. Ryan B. Prince, J. G. S., ‡ Peter G. Wolynes, and Jeffrey S. Moore, Cooperative Conformational Transitions in Phenylene Ethynylene
Oligomers: Chain-Length Dependence. *JACS* **1999,** 121, (13), 3114-3121.
7. Vladimir A. Azov, A. B., Martina Cacciarini,; Andrew G. Cheetham, F. D., Markus Frei,; James K. Gimzewski, V. G., Bert Hecht, Bernhard Jaun,; Tatiana Latychevskaia, A. L., Yoriko Lill, Federica Marotti,; Anna Schlegel, R. R. S., Philip J. Skinner, Paul Seiler,; Yamakoshi, a. Y., Resorcin[4]arene Cavitand-Based Molecular
Switches. *Advanced Functional Matter* **2006,** 16, 147-156.
8. Moran, L., Scrimgeour, K., Horton, H., Ochs, R., Rawn, J., *Biochemistry*. Neil Patterson: 1994.
9. Chang, R., *Physical Chemistry for the Chemical and Biological sciences*. University Science Books: Sausalito,, 2000.
10. M. Alamgir Hossain, H.-J. S., Flexibility, Association Constants, and Salt Effects in Organic Ion Pairs:
How Single Bonds Affect Molecular Recognition. *Chemistry European Journal* **1999,** 5, (4), 1284-1290.
11. Gennady V. Oshovsky, D. N. R., and Willem Verboom, Self-Assembled Hemicapsules with Inherent Functionalities:
Modeling of a Supramolecular Electrostatic Self-Assembly. *Journal of Organic Chemistry* **2006,** 71, (19), 7441-7448.
12. Shovsky, G. V.; Reinhoudt, D. N.; Verboom, W., The underestimated role of counter ions in electrostatic self-assembly: [1+1] cavitand-calix[4]arene capsules based on azinium-sulfonate interactions. *European Journal of Organic Chemistry* **2006**, (12), 2810-2816.
13. Rebek, J., Simultaneous encapsulation: Molecules held at close range. *Angewandte Chemie-International Edition* **2005,** 44, (14), 2068-2078.
14. Ionic, G. E. i. a. W.-S. M. C. B. o.; Interactions; Francesca Corbellini, L. D. C., Mercedes Crego-Calama, Silvano Geremia, and; David N. Reinhoudt, Guest Encapsulation in a Water-Soluble Molecular Capsule Based on Ionic
Interactions. *JACS* **2003,** 125, (33), 9946-9947.

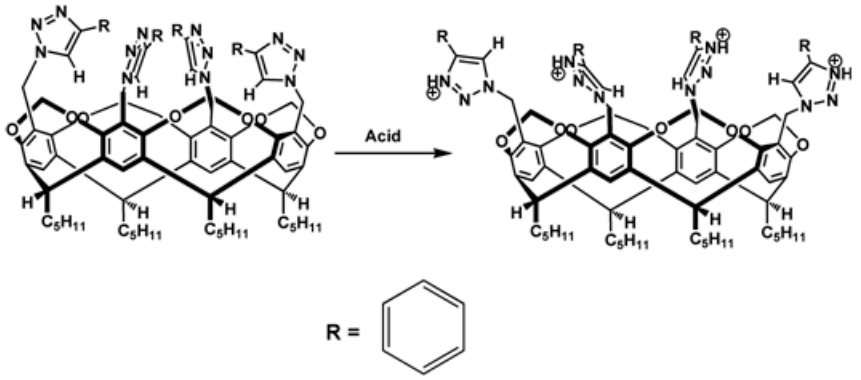
Chapter 2 Early Efforts Toward Conformational Change with 1,2,3 Triazole based Resorcin[4]arenes

2.1,1 Introduction

The use of benzyl substituted resorcin[4]arenes were synthesized to provide flexible arms capable changing there orientation in space generating an overall change in the morphology of the cavitand. These arms are decorated with 1,2,3 triazoles which act as linkers to position aromatic groups on the upper rim of the cavitand. The 1,2,3 triazoles were synthesized via a 1,3 dipolar addition. The use of external stimuli such as acid and solvent environment is employed to promote a conformational change in the cavitand. The use of ^{1}H NMR and 2D NOESY is utilized to monitor the conformational change.

2.1,2-1,2,3 triazole methylene cavitands for conformational control

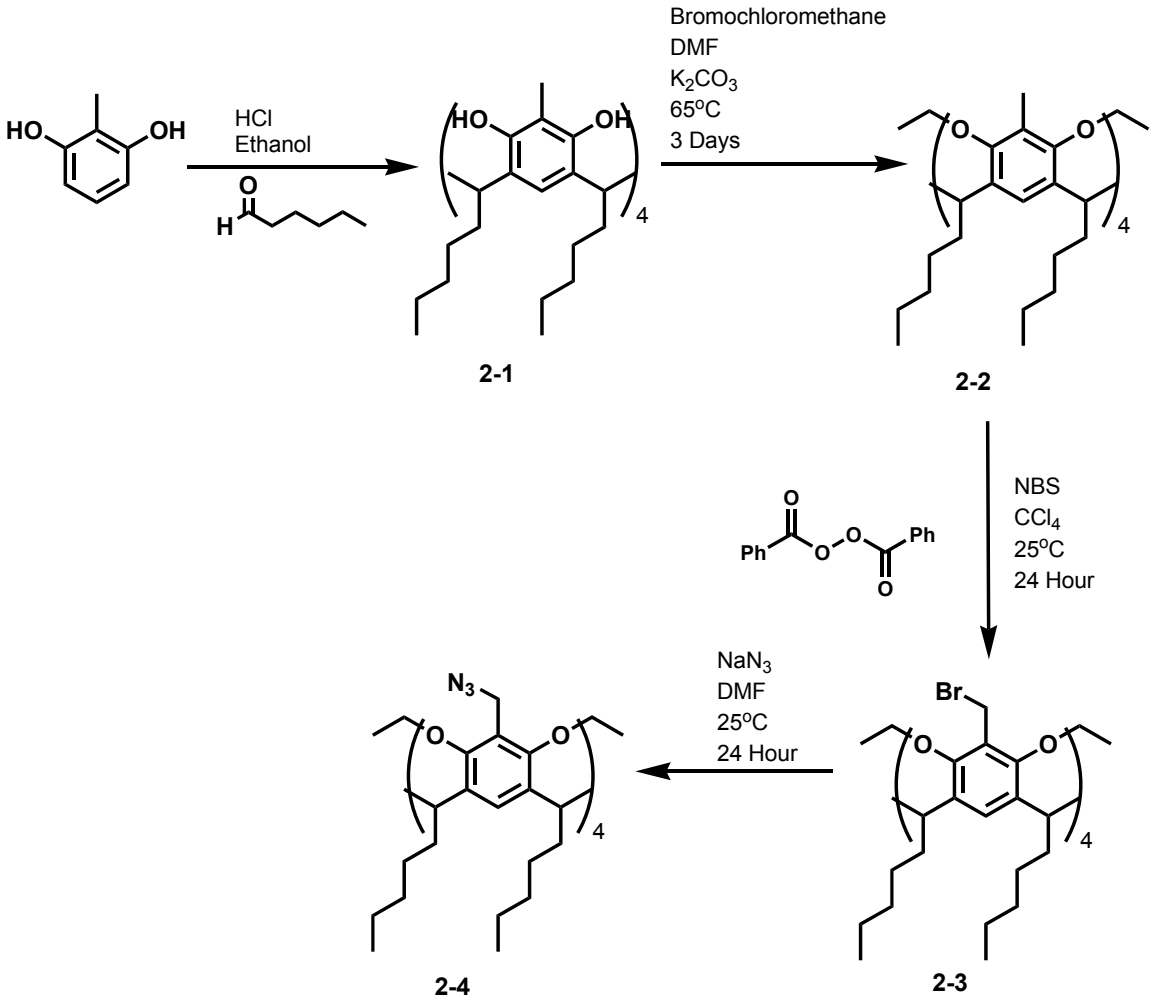
Initially, our focus was directed on conformational change with supramolecular host structures mediated by a pH control switching mechanism. We envisioned an 'open state' that is closed conformation mediated, for example, by the hydrophobic effect[16]. By lowering the pH we envisioned the triazoles would be protonated and through charge repulsion a conformational change would undergo. The 'open state' is an open conformation capable of binding guest molecules as seen in Figure 2.1.



Scheme 2.1 pH mediated conformation of 1,2,3 triazole cavitand.

2.1,3-Synthesis of 1,2,3 tetratriazole phenyl cavitand:

The synthesis of the tetrabromo methylene cavitand **2-2** has been well established by Sherman[17] (Figure 2.2). The first step is the acid catalyzed condensation with hexanal and methyl resorcinol. After drying under high-vacuum the octanol **2-1** was suitable for bridging the seams with bromochloromethane in DMF.[1] The bridged methyl cavitand **2-2** was brominated via an oxidative addition with NBS and diphenyl peroxide to give **2-3**[17]. The benzyl bromides **2-3** were converted to azides with sodium azide in DMF to yield the tetra-azide cavitand **2-4**. 1,3 dipolar cycloadditions of phenyl acetylene and the tetraazide cavitand to generate the tetra phenyl triazole cavitand **2-5**[18]. 2D-NOESY[19] was employed to confirm the presence of the 1,4 regioisomer from the cycloaddition by NOE signal between the triazole hydrogen and methylene connecting the triazole and the phenyl (Figure 2.3). This was consistent with other acetylenes that were reacted with the tetra-azide cavitand such as pyridine alkynes.



Scheme 2.2 Tetrabromo methylene cavitand reaction scheme.

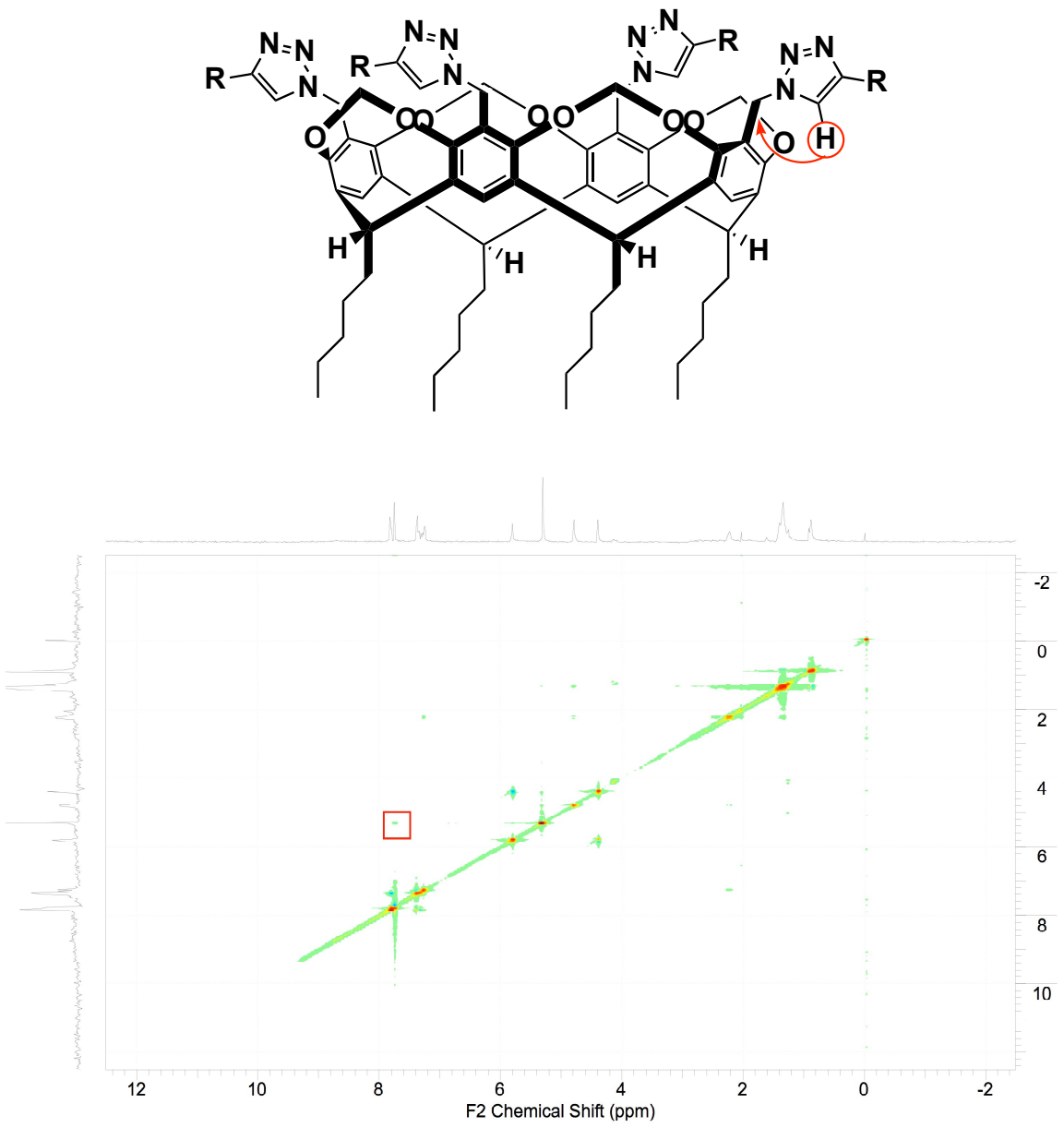
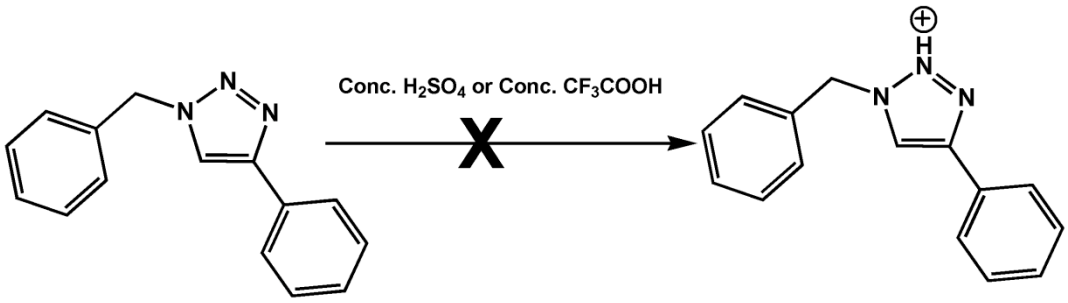


Figure 2.1 2-D NOESY of tetratriazole phenyl methylene cavitand 2-5.

Our efforts were focused on the decorating cavitands with 1,2,3 triazoles via 1,3 dipolar addition with benzyl azides and terminal alkynes. This research established a new synthetic method for decorating cavitands with aromatic motifs. Ultimately, hydrophobic effects would yield an attractive state generating a closed conformation. Unfortunately, the 1,2,3 trizoles cavitands were not

soluble in water. Attempts were made to protonate the triazole with concentrated sulfuric acid to generate a tetra-protonated triazole cavitand. Attempts with a model compound using an excess of H_2SO_4 and CF_3COOH were unsuccessful (scheme 2.4).



Scheme 2.2.3 Model Compound for protonation of triazole.

Several studies were performed to bind substrates such as toluene, benzene, and *para*-toluene sulfonic acid. Unfortunately, no cross-peaks were detected between the substrate and cavitand. From these studies we established our cavitands were not water soluble or capable of binding small aromatic guests.

2.1,4-1,2,3 triazole quadrupole cavitand:

Our efforts altered from “closed” to “open” confirmation to an “open” to “closed” conformation. We envisioned the use of a quadrupolar orientation of charges on the upper rim of the cavitand would yield an attractive force to bring aromatic moieties together. The 1,2,3 triazoles would act as linkers between the cavitand and aromatic moieties (Figure 2.4). The methylene bridges provide flexibility for the charged species to orient themselves through space for a positve/negative/positve/negative pattern on the upper rim of the cavitand.

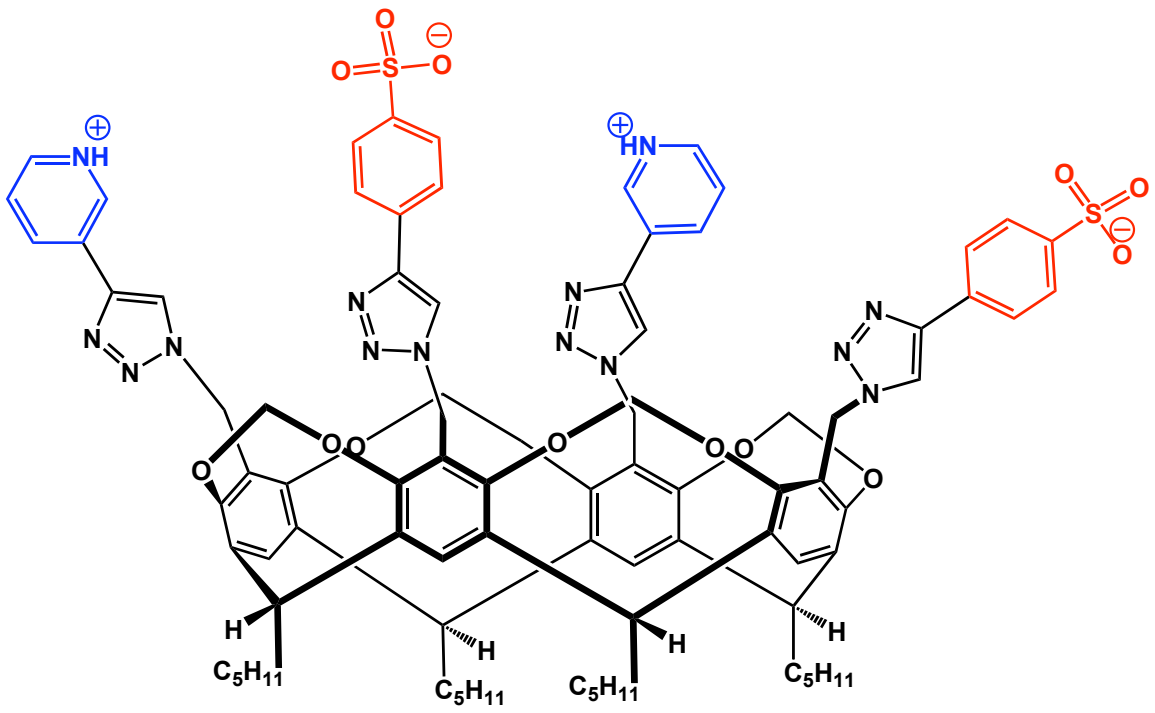


Figure 2.4: 1,2,3 triazole quadrupole

2.1,5-Synthesis of 1,2,3 triazole based Quadrupole

The key challenge to the synthesis of a molecular quadrupole is the functionalization cationic and anionic functional moieties on the upper rim in an alternating pattern. The established 1,3 dipolar addition was employed to generate molecular quadrupole. Key intermediates A,C-bis-pyridinium cavitands or A,C-bis-sulfonate cavitands became key synthetic targets in our endeavors (Figure 2.5).

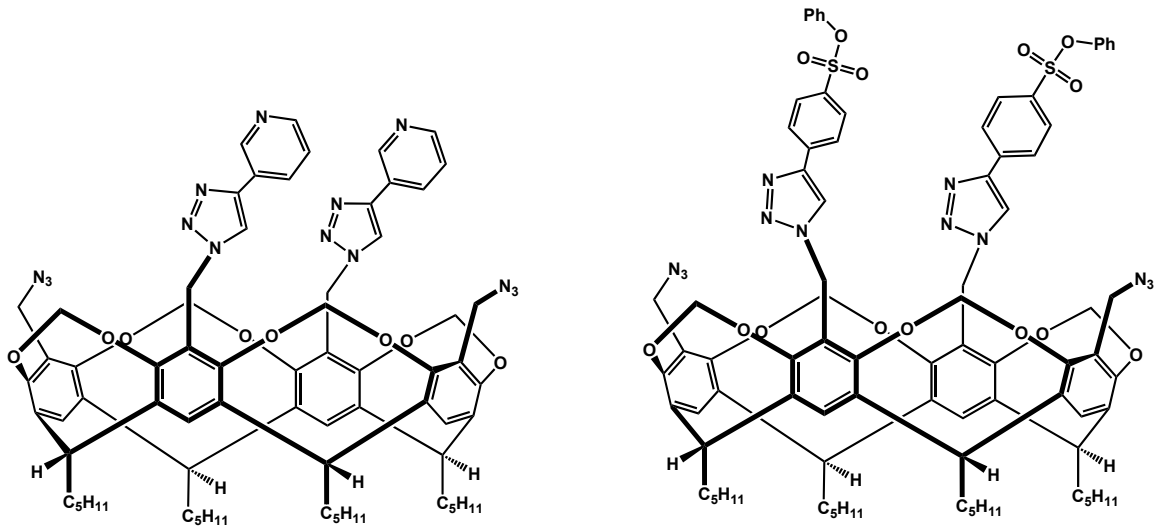


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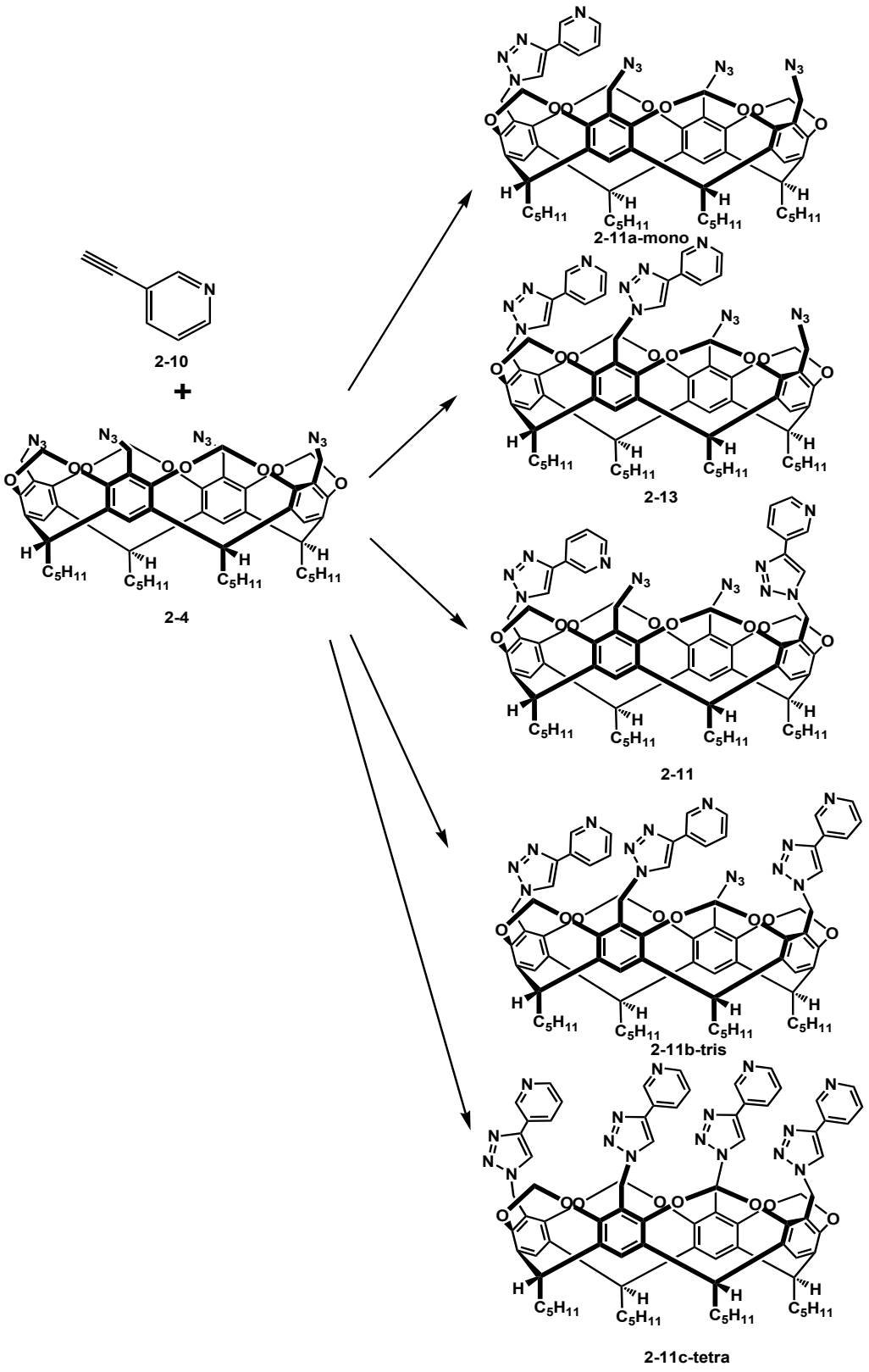
Figure 2.5 Bis-A,C functionalized 1,2,3 triazole cavitand.

2.1,6 Key Intermediate:bis-A,C pyridine, sulfonate 1,2,3 triazole

Our approach to the partial A,C fuctionalization of the upper rim of a cavitand is inherently statistical in nature as we missed 2-11 (Figure 2.6) and approximately two equivalents of pyridinium acetylene in a cycloaddition reaction. The reaction showed essentially no chemo- or regioselectivity. This gave rise to a mixture of mono-, bis-, tris- and tetrafunctionalized cavitands (Figure 2.7). Furthermore, the bis-functionalized cavitand was formed as a 1:2 mixture of the A,B **2-13** and the desired A,C-cavitand **2-11**. The use different isolation techniques such as flash chromatography and reverse phase HPLC with different columns such as C18, C8 and cyano was utilized. After surveying different isolation techniques, flash chromatography with chloroform/methanol mixtures yielded the isolation of the desired bis-A,C pyridine cavitand. The isolation of the bis-A,C sulfonate cavitand was not successful even after many attempts with hexane/ethyl acetate mixtures.



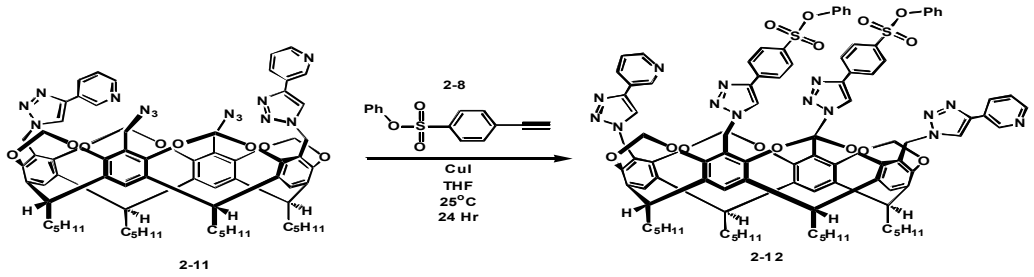
Scheme 2.4 Mixture of isomers generated from 1,3 dipolar addition

The most challenging separation is the bis-A,B functionalized cavitand from the desired bis-A,C cavitand. These two isomers are similar in polarity and cause separation of these isomers a challenging task. The A,B isomer is also statistically preferred over the A,C isomer due to by a factor of 2. After isolating the desired compound **2-11** in low yield, the remaining azides were functionalized with phenyl-substituted sulfonates (Table 2.1).

Isomer	Yield (Isolated)
Mono **2-11a**	17.5 %
A,B Bis **2-13**	24.0%
A,C Bis **2-11**	5.0%
Tris **2-11b**	35.0%
Tetra **2-11c**	18.0%

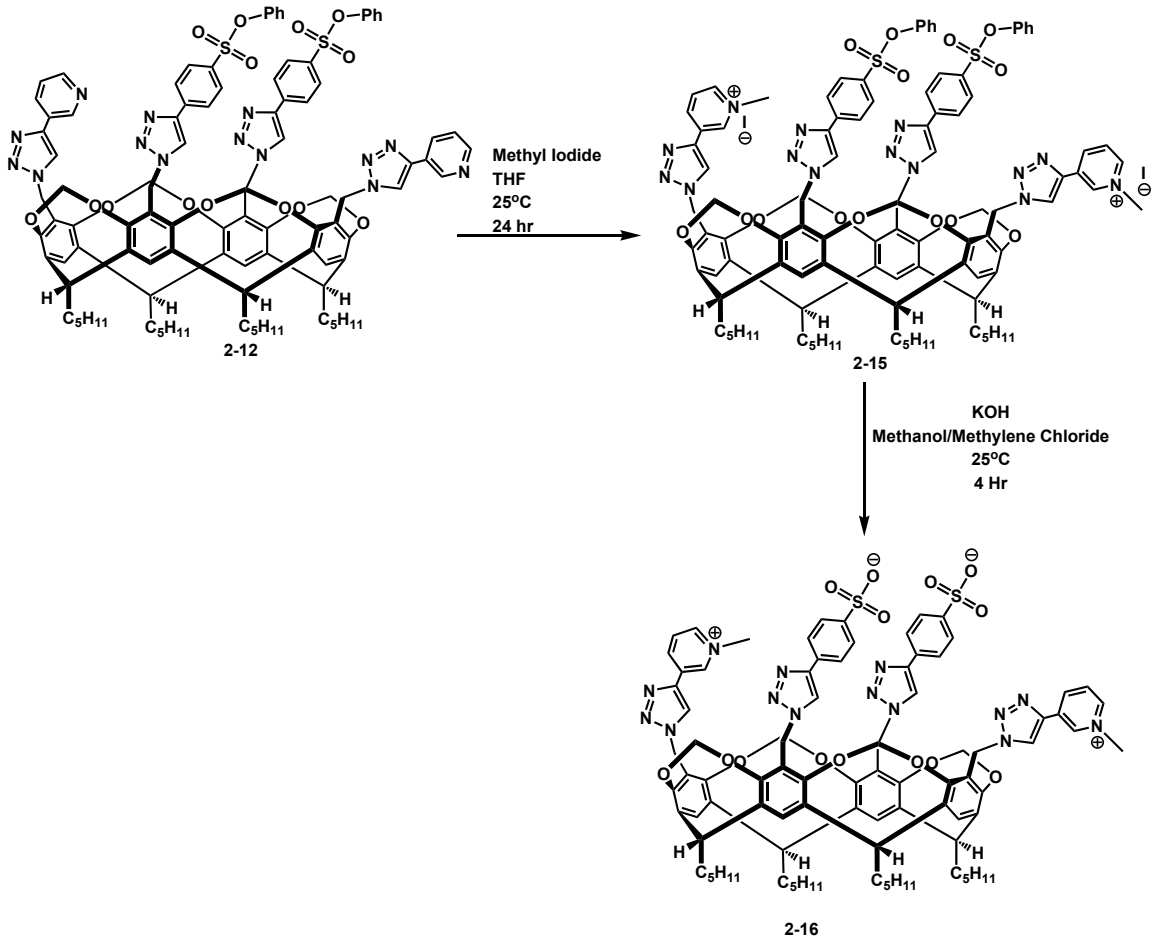
Table 2-1 Isolated Yields from 1,3 dipolar addtion for A,C bis intermediate.

The remaining two steps involve creating cationic and anionic changes in the molecule. The pyridine is alkylated with methyl iodide to yield pyridinium iodide **2-15** (Figure 2.8). Subsequently the anionic sulfonates are released by KOH in methanol and methylene chloride to yield an overall neutral compound **2-16**. After several NMR tests in chloroform I was unable to detect any signals to observe an electrostatic effects. Due to the poor solubility of in chloroform, which is a solvent conducive for tight ion pairing. As a result, this synthetic method was abandoned.



Scheme 2.5 shows 1,3 dipolar addition with sulfonate alkyne and B,D-bis-azide, A,C-bis-pyridine cavitand.shows

The focus was altered to extend the feet of the cavitand to increase the solubility of the cavitand in non-polar solvents.



2-12 2-15 2-16

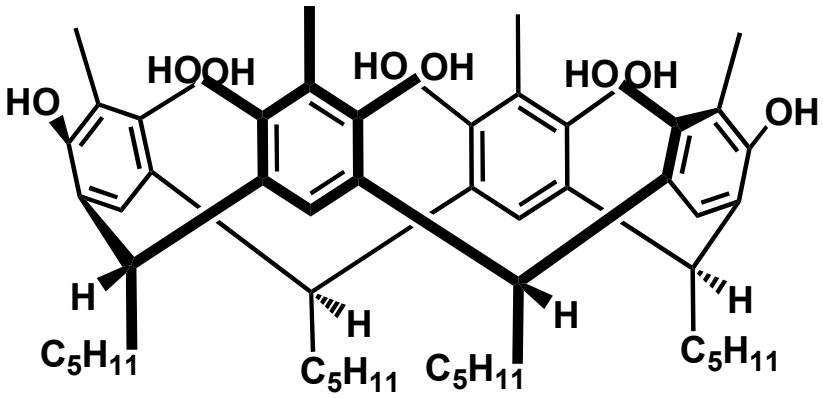
Scheme 2.6 shows the alkylation of the pyridine and deprotection of the sulfonate from the cavitand.

2.1,7-Conclusion

The use of benzyl substituted resorcin[4]arenas was synthesized via a 1,3 dipolar addition. A quadrupolar arrangement of an alternating pyridinium/sulfonate/pyridinium/sulfonate was successfully addressed. Unfortunately, poor solubility of these resorcin[4]arenes in non-polar solvents such as chloroform is not a conducive environment for electrostatics. Future efforts were focused to increase the solubility of the cavitand in non-polar solvent by extending the chain length of the feet of the resorcin[4]arene.

2.2 Experimental Section

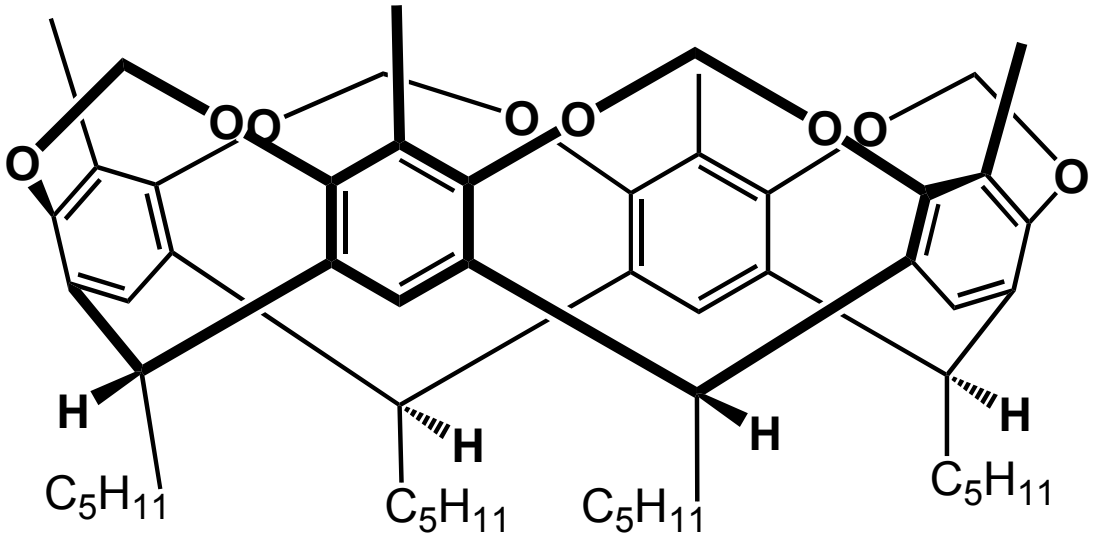
C-pentyl methyl calix[4]resorcinarene[2-1]



Compound 2- 1

To a solution of 2 methyl-resorcinol (17.0 g, 136 mmol) and hexanal (13.7 g, 137 mmol) in ethanol (136 mL) was added concentrated HCl (37.0 mL) at 0ºC under an inert atmosphere. A condenser was attached and the mixture heated to 70°C overnight. The reaction was allowed to cool to room temperature upon completion, then diluted with water. A white precipitate formed which was filtered and dried under high vacuum (80.0 g; 70% Yield)of the title compound **2-1**.[15] ^{1}H NMR (400 MHz, DMSO-d_6) □ δ 0.85 (t, *J*=7.05 Hz, 12 H) 1.27 (s, 32 H) 1.94 (s, 12 H) 2.16 - 2.27 (m, 5 H) 4.19 (s, *J*=9.71 Hz, 4 H) 7.25 (s, 4 H) 8.65 (s, 8 H);^{13}C NMR (101 MHz, $CDCl_3$) □ δ 9.98, 13.9, 22.3, 27.6, 31.4, 33.0, 34.3, 111.6, 121.0, 124.8, 148.9,

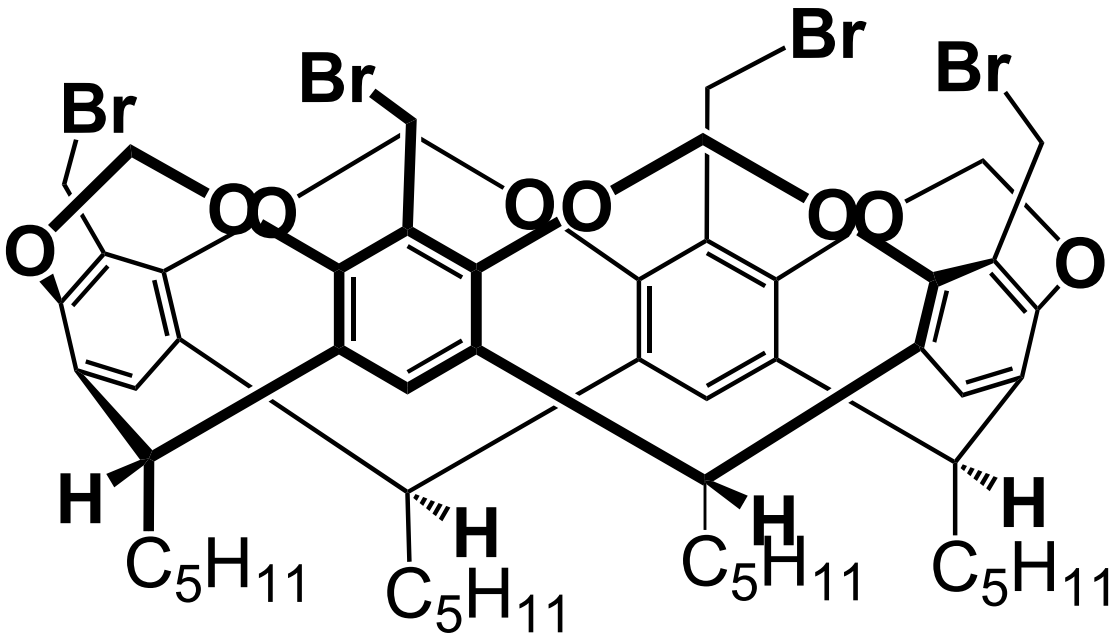
C-Pentyl tetramethyl resorcin[4]arene[2-2]



Compound 2- 2

Dried methyl octanol cavitand **2-1** (12.6 g, 15.3 mmol), bromochloromethane(14.0 g, 108 mmol), and potassium carbonate (44.3 g 320 mmol) in dimethylformamide (340 mL) was stirred under an inert atmosphere for 3 days. After 24 hours the (3.95 g 30.5 mmol 2.00 mL) was added to the solution and repeated on the following day. The solvent was removed via distillation and the remaining residue was dissolved in dichloromethane. The organic layer was washed with 2M HCl, water, and brine and then dried with magnesium sulfate, filtered and concentrated under vacuum. The crude was purified by column chromatography 4:1 hexane:ethyl acetate to give (10.6 g 80% yield) of the title compound **2-2** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.91 (t, *J*=7.1 Hz, 12 H) 1.29 - 1.48 (m, 26 H) 1.97 (s, 12 H) 2.12 - 2.27 (m, *J*=8.1 Hz, 8 H) 4.26 (d, *J*=7.0 Hz, 3 H) 4.76 (t, *J*=8.10 Hz, 4 H) 5.88 (d, *J*=7.00 Hz, 4 H) 6.98 (s, 3 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 10.3, 14.10, 22.7, 27.7, 30.1, 32.07, 37.0, 98.5, 117.6, 123.6, 137.9, 153.2

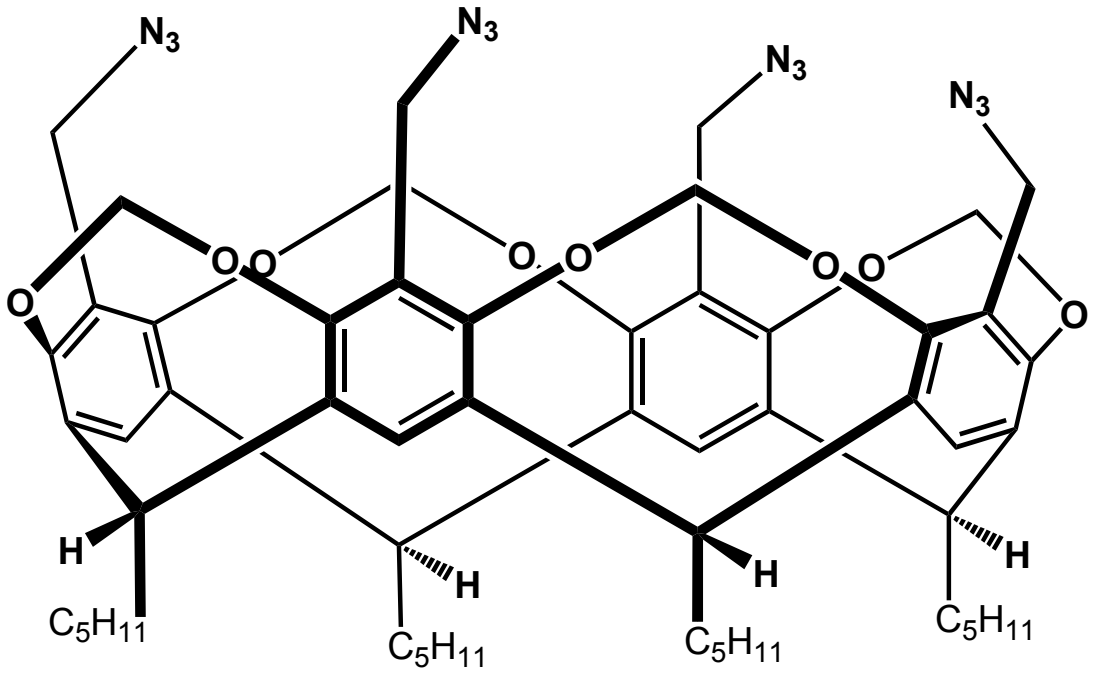
C-Pentyl tetrabenzyl bromidel resorcin[4]arene[2-3]



Compound 2- 3

Tetramethyl bridged cavitand **2-2**(3.00 g 3.30 mmol), N-bromosuccinimide (2.41 g 13.6 mmol), and benzoyl peroxide (0.040 g, 0.170 mmol) in carbon tetrachloride was stirred at 70^{o}C overnight. The reaction was allowed to cool to room temperature and filtered. The solvent was removed via rotatory evaporator and the crude material was purified via column chromatography (4:1 Hexane: Ethyl Acetate) to give (3.50 g 90% Yield) of the title compound **2-3** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.910 (t, *J*=7.00 Hz, 12 H) 1.18 - 1.53 (m, 24 H) 2.21 (q, 8 H) 4.42 (s, 8 H) 4.56 (d, *J*=6.80 Hz, 4 H) 4.78 (t, *J*=8.00 Hz, 3 H) 6.02 (d, *J*=6.40 Hz, 4 H) 7.13 (s, 4 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 22.65, 22.9, 27.5, 30.0, 32.0, 36.9, 99.2, 120.9, 124.5, 138.1, 153.5

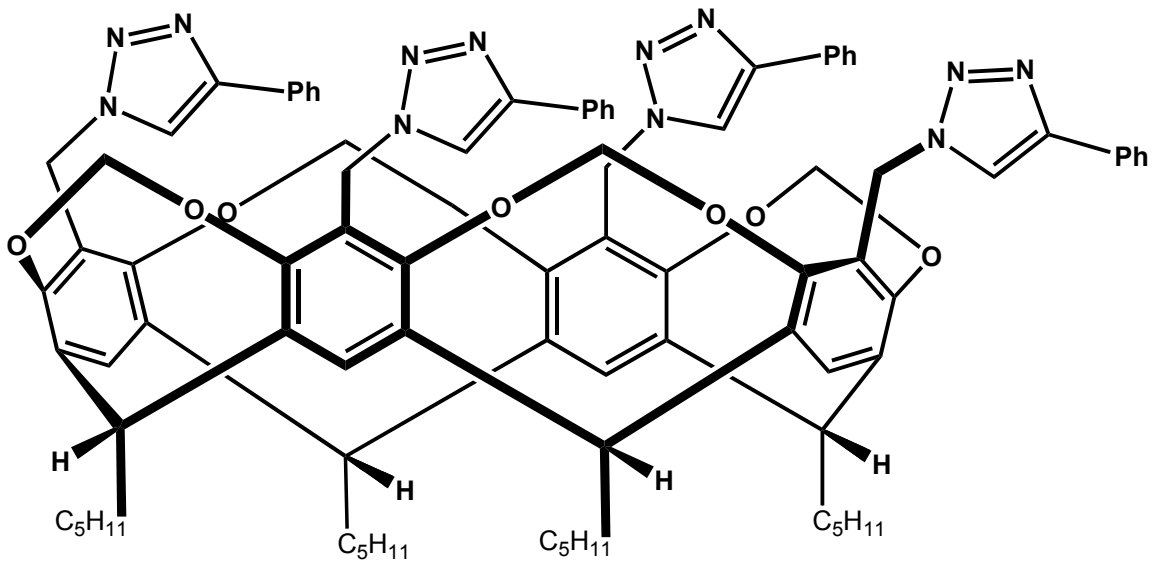
C-Pentyl tetrabenzyl azide resorcin[4]arene[2-4]



Compound 2- 4

2.20 g (2.32 mmol) of tetrabromo cavitand **2-3** was dissolved in 77.0 mL of DMF. 0.904 g (13.9 mmol) of NaN_3 was added and the reaction vessel was stirred at room temperature overnight. DMF was removed by distillation to yield a brown residue which was dissolved in methylene chloride and extracted with saturated brine solution. The organic layer was dried with $MgSO_4$, filtered and concentrated to give (2.21 g 92.0% yield) of the title compound **2-4**. ^{1}H NMR (200 MHz, $CDCl_3$) d δ 0.910 (t, *J*=6.96 Hz, 12 H) 1.21 - 1.47 (m, 24 H) 2.24 (q, *J*=8.42 Hz, 8 H) 4.33 (s, 8 H) 4.39 (d, *J*=6.96 Hz, 4 H) 4.78 (t, *J*=8.24 Hz, 4 H) 5.94 (d, *J*=6.96 Hz, 4 H) 7.15 (s, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) d δ 14.3, 22.8, 27.7, 30.2, 32.1, 37.1, 45.3, 99.9, 120.9 , 122.4, 138.3, 153.9

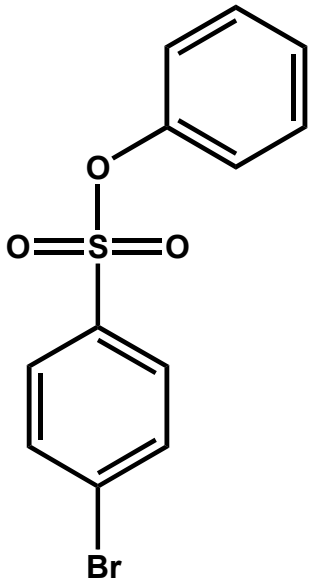
C-Pentyltetraphenyl-1,2,3-triazole resorcin[4]arene[2-5]



Compound 2- 5

0.100 g (0.010 mmol) of tetraazide **2-4**, phenyl acetylene 0.049 g (0.483 mmol) and copper(I)iodide 0.002 g (0.001 mmol) was added to sealable reaction container. The reaction contents were degassed by freeze-pump-thaw and allowed to stir overnight at room temperature. After monitoring by TLC 4:1 Hexane:Ethyl Acetate the reaction contents were transferred to a separtory funnel and extracted with ammonium chloride. The organic and aqueous layers were separated and the organic layer was dried with magnesium sulfate, filtered, and concentrated. The crude was purified via column chromatography 4:1 hexane:ethyl acetate to give (0.070 g 50% yield) of the title compound **2-5**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.900 (t, *J*=7.05 Hz, 12 H) 1.30 - 1.47 (m, 24 H) 2.25 (q, *J*=10.3, 8.61 Hz, 8 H) 4.41 (d, *J*=7.14 Hz, 4 H) 4.79 (t, *J*=8.06 Hz, 4 H) 5.30 (s, 8 H) 5.82 (d, *J*=7.51 Hz, 4 H) 7.25 (s, 4 H) 7.27 - 7.33 (m, *J*=7.51 Hz, 4 H) 7.36 (t, *J*=7.87 Hz, 8 H) 7.76 (s, 4 H) 7.82 (d, *J*=7.33 Hz, 8 H) ^{13}C NMR (50 MHz, $CDCl_3$) □ δ 14.1, 22.7, 27.5, 30.2, 32.0, 37.0, 43.6, 44.7, 99.5, 120.7, 121.4, 125.8, 128.1, 128.7, 130.5, 138.1, 147.7, 153.8

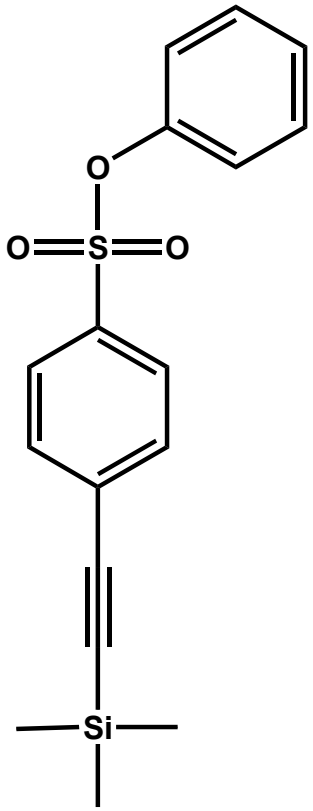
.Phenyl 4-bromobenzenesulfonate[2-6]



Compound 2- 6

To a round bottom flask sulfonyl chloride 0.500 g (1.96 mmol), phenol 0.220 g (2.30 mmol), triethyl amine 0.400 g (3.90 mmol) and 5.00 mL of methylene chloride was added. The reaction was allowed to stir at room temperature for 3 hours and 2.50 M HCl was added to reaction solution. The solution was transferred to separtory funnel and extracted with diethyl ether. The organic and aqueous layers were separated and the organic layer was extracted twice with 2.50 M HCl. The organic layer was dried with magnesium sulfate, filtered, and concentrated. The crude was purified by recystallization from diethyl ether and hexane to give (0.599 g 98% yield) of the title compound **2-6**.^{1}H NMR (400 MHz, $CDCl_3$) □ δ 6.95 - 7.04 (m, 2 H) 7.21 - 7.36 (m, 3 H) 7.61 - 7.73 (m, 4 H)

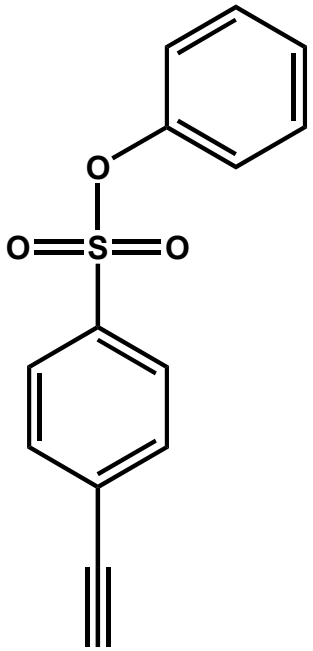
.Phenyl 4-ethynyltrimethylsilanebenzenesulfonate[2-7]



Compound 2- 7

To a sealable tube phenyl 4-bromobenzenesulfonate **2-6** 0.580 g (1.84 mmol), $PdCl_2(PPh_3)_4$ 0.065 g (0.092 mmol), copper(I) iodide 0.018 g (0.092 mmol), diisopropyl amine 2.20 g (22.0 mmol), and tms-acetylene 0.217 g (2.20 mmol) was added. The reaction was degassed by freeze-pump-thaw and heated to 65^{o}C for 8 hours. Methylene chloride was added to the reaction vessel and transferred to a reaction vessel. The organic layer was extracted with ammonium chloride and brine solution was then dried with magnesium sulfate, filtered, and concentrated. The crude product was purified via column chromatography to givle (0.53 g, 87% yield) of the title compound **2-7**. ^{1}H NMR (200 MHz, $CDCl_3$) □ δ 0.21 - 0.35 (m, 9 H) 6.91 - 7.03 (m, *J*=1.83 Hz, 2 H) 7.23 - 7.39 (m, 3 H) 7.52 - 7.64 (m, *J*=8.79 Hz, 2 H) 7.76 (d, *J*=8.79 Hz, 2 H)

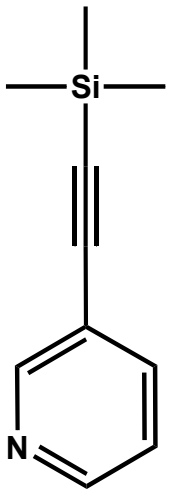
Phenyl 4-ethynylbenzenesulfonate[2-8]



Compound 2- 8

0.660 g (2.01 mmol) phenyl 4-trimethylsilanebenzenesulfonate and 2.00 mL of the THF was added to a round bottom flask. Tetra-butyl ammonium fluoride (0.790 g 3.03 mmol) was added to the solution. The reaction was allowed to stir for one hour at room temperature. The solution was then passed through a silica plug with methylene chloride to give (0.520 g 55% yield) of the title compound **2-8** ^{1}H NMR (200 MHz, $CDCl_3$) □ δ 3.32 (s, 1 H) 6.94 - 7.04 (m, 2 H) 7.23 - 7.39 (m, 3 H) 7.57 - 7.66 (m, *J*=8.79 Hz, 2 H) 7.79 (d, *J*=8.79 Hz, 2 H)

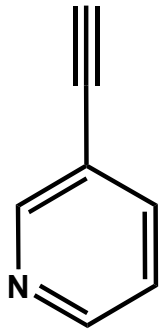
Silane - 3-(3,3-dimethylbut-1-yn-1-yl)pyridine[2-9]



Compound 2- 9

Bromopyridine 4.00 g (25.3 mmol), $PdCl_2(PPh_3)_4$ 0.890 g (1.30 mmol), CuI 0.241 g (1.27 mmol), TMS-acetylene 2.98 g (30.4 mmol), and diisopropyl amine 31 (304 mmol) was charged to a sealable tube. The reaction vessel was degassed by freeze-pump-thaw and heated to 70^{o}C for 8 hours. The reaction allowed to reach room temperature and methylene chloride was added to the reaction vessel. The organic layer was extracted with ammonium chloride, brine and dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography to give 3.81 g (85% yield) of the title compound **2-9**. ^{1}H NMR (200 MHz, $CDCl_3$) □ δ 0.19 - 0.32 (m, 9 H) 7.20 - 7.25 (m, 1 H) 7.68 - 7.83 (m, 1 H) 8.53 (dd, *J*=4.94, 1.65 Hz, 1 H) 8.70 (d, *J*=2.20 Hz, 1 H) ^{13}C NMR (50 MHz, $CDCl_3$) □ δ -0.18, 122.9, 138.8, 148.7, 152.6

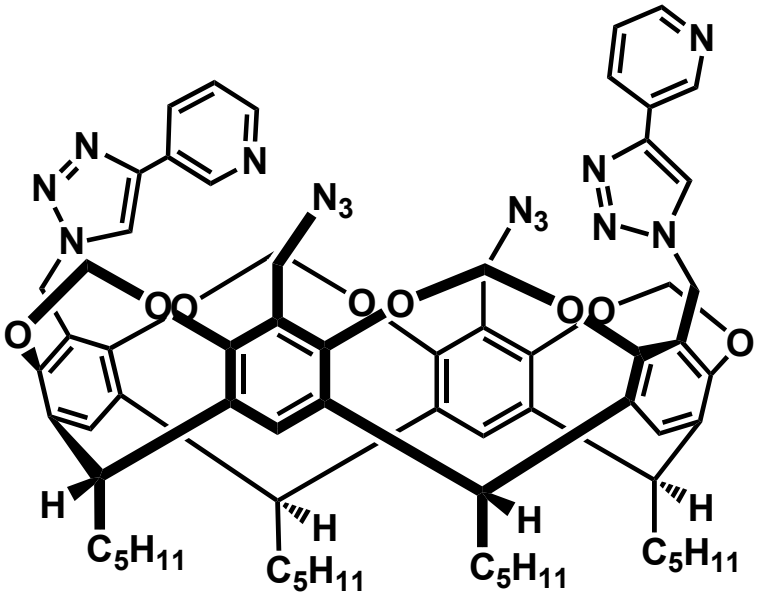
.3-ethynylpyridine[2-10]



Compound 2- 10

3-[2-Trimethylsilyl ethynl]-pyridine **2-9** 0.698 g (3.98 mmol), 0.45 g (7.96 mmol) 10.0 mL of methanol and 5.00 mL of methylene chloride was added to round flask. The reaction was allowed to stir at room temperature for 3 hours. The reaction was quenched with water and extracted with methylene chloride. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude was passed through a silica plug with methylene chloride to give (0.366 g 89%) of the title compound **2-10**. ^{1}H NMR (200 MHz, $CDCl_3$) □ δ 3.22 (s, 1 H) 7.20 - 7.32 (m, 1 H) 7.73 - 7.83 (m, 1 H) 8.57 (dd, *J*=4.94, 1.65 Hz, 1 H) 8.73 (d, *J*=2.20 Hz, 1 H) ^{13}C NMR (101 MHz, $CDCl_3$) d δ 80.6, 123.1, 139.1, 149.2, 152.8

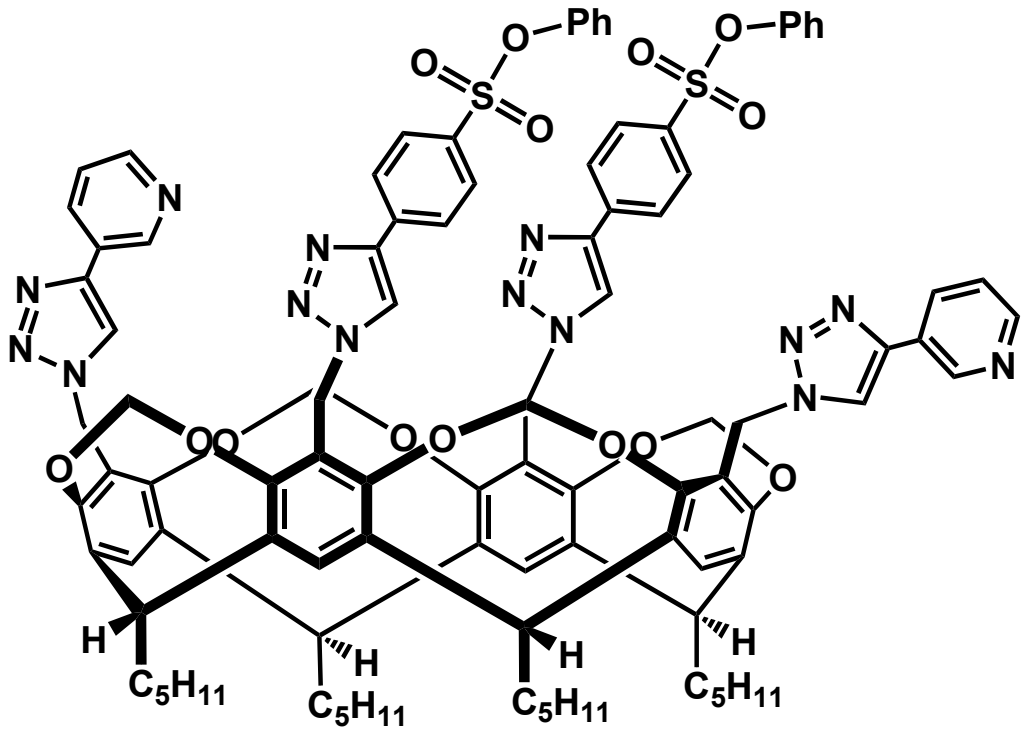
.A,C Bis-1,2,3, triazole 3-pyridine resocinarene[2-11]



Compound 2- 11

Tetra-azide cavitand **2-4** (2.00 g 1.93 mmol), (0.438 g, 4.25 mmol) of 3-ethyl pyridine **2-10**, (.037 g 0.190 mmol) of CuI, and 5.00 mL of dry THF was placed into a sealed tube. The reaction vessel was degassed by freeze-pump-thaw and the reaction was allowed to stir overnight. The reaction monitored by TLC 91:9 chloroform:methanol. Methylene chloride and a saturated ammonium chloride solution were added to the reaction solution. The organic and aqueous layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified via column chromatography. A gradient was applied starting with 50:50 hexane:ethyl acetate. Then slowly a gradient was ran from 98:2 chloroform:methanol to 91:9 chloroform:methanol. The desired A,C 1.2.3 triazole was isolated to give (0.125g 5% yield) of the title compound **2-11** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.91 (t, *J*=6.64 Hz, 12 H) 1.31 - 1.45 (m, 24 H) 2.16 - 2.32 (m, 8 H) 4.31 (s, 4 H) 4.42 (d, *J*=7.03 Hz, 4 H) 4.80 (t, *J*=7.61 Hz, 4 H) 5.41 (s, 4 H) 5.91 (d, *J*=6.64 Hz, 4 H) 7.18 (s, 2 H) 7.25 (s, 2 H) 7.86 (s, 2 H) 8.24 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.4, 22.4, 27.8 , 29.9 ,32.2, 36.7, 44.7, 45.4, 99.8, 120.9, 122.0, 122.8, 133.2, 138.6, 139.1, 145.0, 147.3, 150.0, 154.0

.A,C-Bis-1,2.3 triazole 3-pyridine-B,D-1,2,3-triazole phenyl benzene sulfonate[2-12]

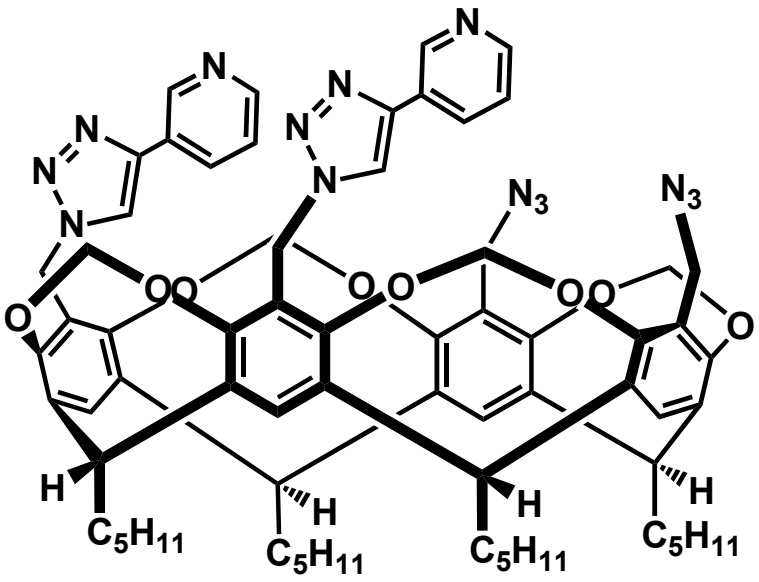


Compound 2- 12

A,C bis-1,2,3 triazole **2-11** (0.061 g 0.049 mmol), phenyl 4 ethynylbenzenesulfonate **2-8** (0.032 g 0.12 mmol) and CuI (0.001 g 0.005 mmol) and 0.500 mL of dry THF was added to a sealable vessel. The reaction vessel was degassed by freeze pump thaw. The reaction was allowed to stir at room temperature overnight. The reaction was monitored by TLC 91:9 chloroform:methanol. The reaction mixture was dissolved in methylene chloride and transferred to a separtory funnel. The organic layer was extracted with a ammonium chloride solution. The organic and aqueous layers were separated. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography with a slow gradient from 100% chloroform to 91:9 chloroform:methanol to give (0.040g 46.0% yield) of title compound **2-12**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.900 (t, *J*=7.03 Hz, 12 H) 1.23 - 1.48 (m, *J*=6.64 Hz, 24 H) 2.17 - 2.32 (m, 8 H) 4.39 (d, *J*=7.42 Hz, 4 H)

4.80 (t, *J*=8.00 Hz, 4 H) 5.34 (d, *J*=13.7 Hz, 8 H) 5.33 (s, 4 H) 5.36 (s, 4 H) 5.82 (t, *J*=7.03 Hz, 4 H) 6.92 - 7.06 (m, 4 H) 7.19 - 7.33 (m, 11 H) 7.80 (d, *J*=8.20 Hz, 4 H) 7.88 (d, *J*=6.64 Hz, 4 H) 7.91 - 8.01 (m, *J*=8.59 Hz, 4 H) 8.19 (d, *J*=6.25 Hz, 2 H) 8.54 (s, 1 H) 8.96 (s, 2 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.4, 22.7, 27.5, 30.1, 31.9, 37.0, 44.4, 99.4, 120.4, 120.5, 121.3, 121.6, 122.3, 126.1, 127.2, 129.1, 129.7, 134.4, 136.3, 138.2, 138.3, 145.6, 149.6, 153.8, 153.9

.A,B Bis 1,2,3, triazole 3-pyridine resorcin[4]arene[2-13]

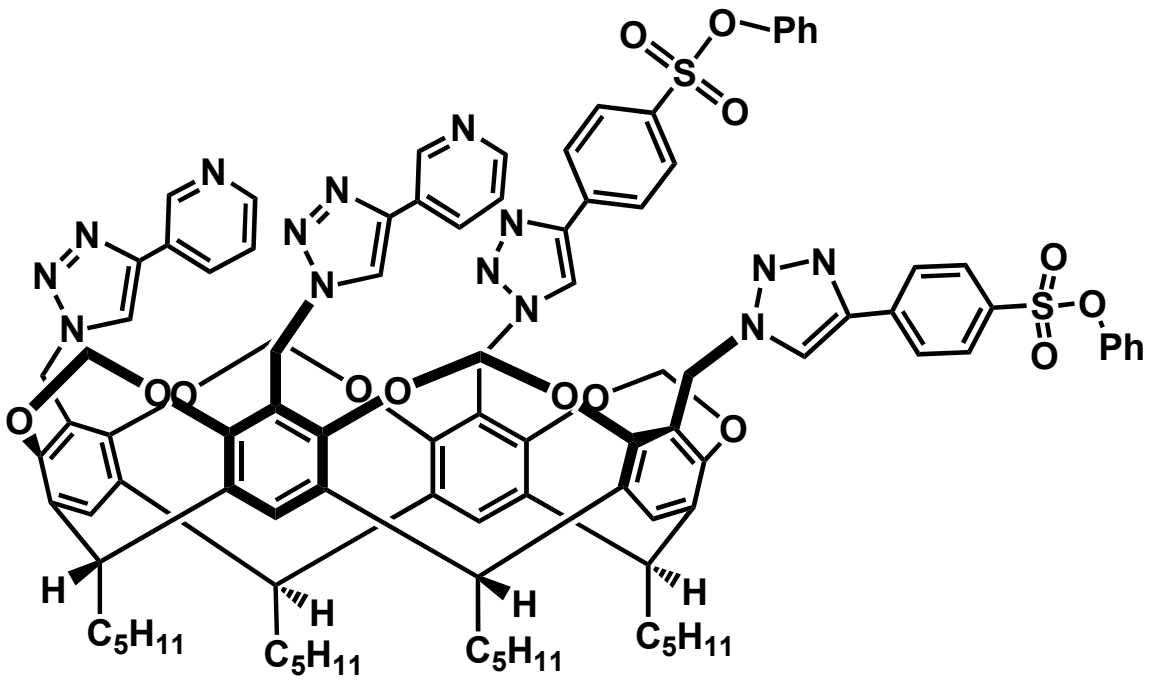


Compound 2- 13

Tetra-azide cavitand **2-4** (2.00 g 1.93 mmol), (0.438 g, 4.25 mmol) of 3-ethynl pyridine **2-10**, (0.037g 0.190 mmol) of CuI, and 5.00 mL of dry THF was placed into a sealed tube. The reaction vessel was degassed by freeze-pump-thaw and the reaction was allowed to stir overnight. The reaction monitored by TLC 91:9 chloroform:methanol. Methylene chloride and a saturated ammonium chloride solution were added to the reaction solution. The organic and aqueous layers were separated. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified via column chromatography. A gradient was applied starting with 50:50 hexane:ethyl acetate. Then slowly a gradient was ran from 98:2 chloroform:methanol to 91:9 chloroform:methanol.

The desired A,C 1.2.3 triazole was isolated to give (0.575 g 25.0% yield) of the title compound **2-13**. ^{1}H NMR (200 MHz, $CDCl_3$) □ δ 0.85 - 1.00 (m, 12 H) 1.21 - 1.50 (m, 24 H) 2.12 - 2.36 (m, 8 H) 4.23 - 4.29 (m, 4 H) 4.29 - 4.42 (m, *J*=7.33, 7.33 Hz, 3 H) 4.48 (d, *J*=6.96 Hz, 1 H) 4.79 (t, *J*=8.06 Hz, 4 H) 5.33 - 5.47 (m, 4 H) 5.84 (d, *J*=7.33 Hz, 3 H) 5.92 (d, *J*=6.96 Hz, 1 H) 7.18 (s, 1 H) 7.25 (s, 1 H) 7.34 (dd, *J*=7.51, 4.58 Hz, 2 H) 7.80 - 7.94 (m, 2 H) 8.07 - 8.27 (m, *J*=8.06 Hz, 2 H) 8.47 - 8.66 (m, *J*=4.40 Hz, 2 H) 8.96 (d, *J*=1.83 Hz, 2 H) ^{13}C NMR (50 MHz, $CDCl_3$) □ δ 13.8, 14.7, 22.2, 23.4, 26.7, 28.4, 29.7, 31.6, 37.1, 44.1, 45.7 , 99.7, 121.9, 122.5, 137.9, 138.1, 138.2, 138.4, 138.7, 154.0

.A,B-Bis-1,2.3 triazole 3-pyridine-C,D-1,2,3-triazole phenyl benzene sulfonate[2-14]



Compound 2- 14

A,B bis-1,2,3 triazole **2-13** (0.103 g 0.082 mmol), phenyl 4-ethynylbenzenesulfonate **2-8** (0.053 g , 0.210 mmol) and CuI (0.002 0.008 mmol) and 1.00 mL of dry THF was added to a sealable vessel. The reaction vessel was degassed by freeze pump thaw. The reaction was allowed to stir at room

temperature overnight. The reaction was monitored by TLC 91:9 chloroform:methanol. The reaction mixture was dissolved in methylene chloride and transferred to a separtory funnel. The organic layer was extracted with a ammonium chloride solution. The organic and aqueous layers were separated. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography with a slow gradient from 100% chloroform to 91:9 chloroform:methanol to give (0.050g 34.0% yield) for the title compound **2-14**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.86 - 0.94 (m, 12 H) 1.30 - 1.46 (m, 24 H) 2.25 (s, 8 H) 4.39 (qd, *J*=7.03 Hz, 4 H) 5.28 - 5.34 (m, 4 H) 5.35 (s, 4 H) 5.70 - 5.91 (m, *J*=7.03, 7.03, 5.86, 5.86 Hz, 4 H) 6.98 (d, *J*=7.03 Hz, 4 H) 7.80 (d, *J*=7.81 Hz, 4 H) 7.87 (s, 4 H) 7.94 (d, *J*=7.81 Hz, 4 H) 8.21 (s, 2 H)

2.3-Reference:

1. Cram D., K. S., Kim, H., Knobler, C., Maverick, E., Ericson, J., and Helgeson, R., Host-guest complexation. 46. Cavitands as open molecular vessels form solvates. *Journal of American Chemical Society* **1988,** 110, 2229-2237.
2. Blokzijl, W., Engberts, J., Hydrophoic Effects. Opinions and Facts. *Angew. Chem. Int. Ed* **1993,** 32, 1545-1579.
3. Mezo, A. S., J., Water-Soluble Cavitands: Synthesis of Methylene-Bridged Resorcin[4]arene Containing Hydroxyls and Phosphate at Their Feet and Bromomethyls and Thiomethyls at Their Rims. *Journal of Organic Chemistry* **1998,** 63, 6824-6829.
4. John R. Moran, S. K., and Donald J. Cram, Cavitands: synthetic molecular vessels. *JACS* **1982,** 104, (21), 5826-5828.
5. Kolb, C. F., G., Sharpless, B., Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed* **2001,** 40, 2004-2021.
6. Braun, S., Kalinowski, H., Berger, S., *150 and More Basic NMR Experiments: A Practical Course*. 1999.

Chapter 3 Thiophene Based Quadrupoles

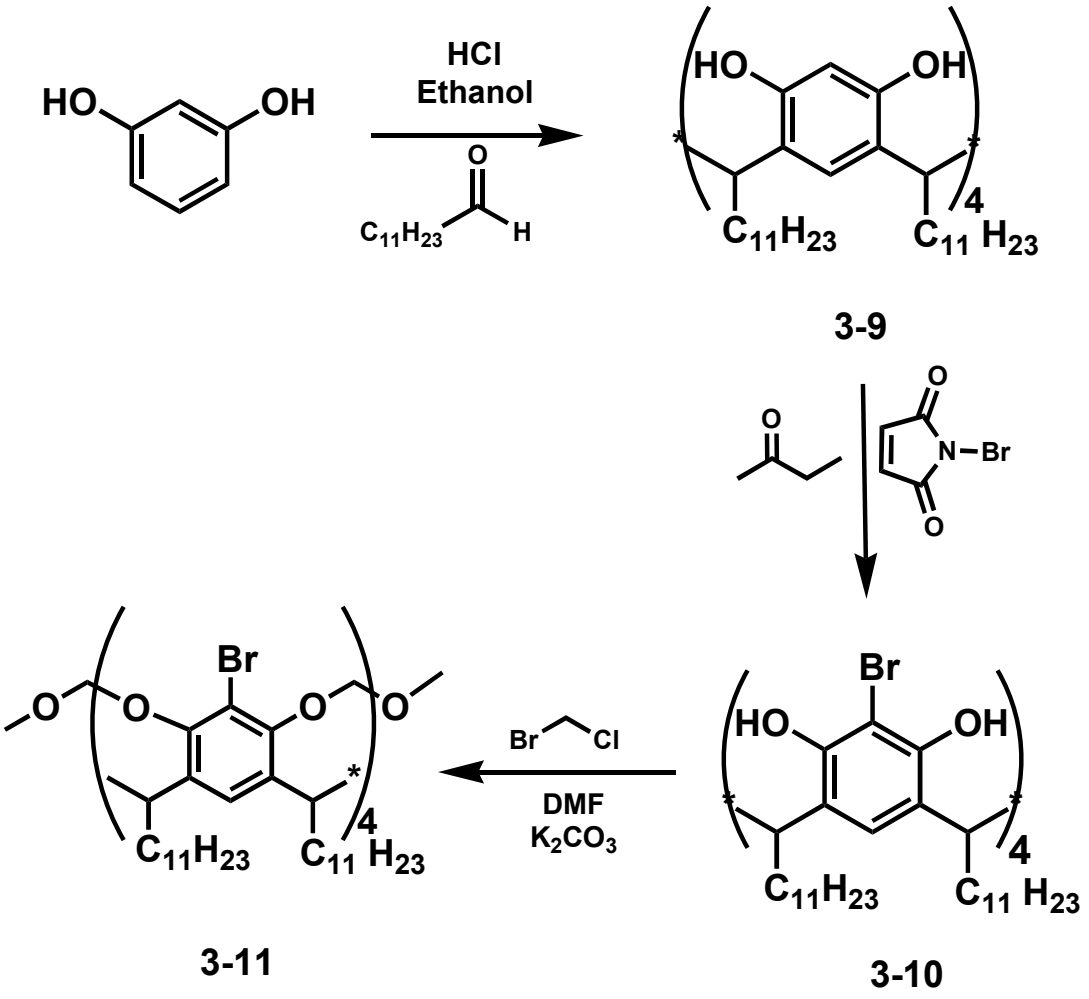
3.1,1-Introduction:

The synthesis of quadrupoles was addressed with thiophene-decorated cavitands. Longer feet were obtained by utilizing dodecanal in the acid condensation to improve solubility in non-polar solvents. Thiophenes were employed as linkers to place sulfonates and pyridiniums on the upper rim. The upper rim was functionalized with boronic acids in an alternate pattern and palladium catalyzed Suzuki cross coupling were utilized to functionalize the upper rim with 2-bromothiophenes. The remaining arms are converted to iodides functionalized with palladium catalyzed Negishi cross coupling. Titrations with chloroform were executed to transition from an 'open' state to an 'attractive' state. A dipole cavitand is also outlined to compare the energy to the quadrupole. Similar synthetic methods are utilized to synthesize the dipole.

3.2-Synthesis of Quadrupole:

A resorcin[4]arene based quadrupole is synthesized to study electrostatic interactions between sulfonates and pyridiniums. The quadrupole is unique due to the pattern of the cationic and anionic charges in a postive/negavtive/positive/negative orientation. The use of a concave shaped molecule allows the for the measurement of intramolecular electrostatic attractions between the functional moieties on the upper rim of the resorcin[4]arene. The main synthetic challenge is the positioning of the cations and anions on the upper rim of the resorcin[4]arene. The main scaffold has been well established Cram[1, 2], Rebek[3], and Sherman[4]. An acid catalyzed condensation between resorcinol and dodecyl aldehyde produces the dodecylcalix[4]arene **3-9**. The use of dodecyl aldehyde was employed to increase solubility in non-polar solvents such as chloroform and carbon-tetrachloride. **3-9** is treated N-bromo succinimide in methyl ethyl ketone to give **3-10** via oxidative addition. The phenolic seams of the octanol are stitched

together with bromochloro methane in the presence of potassium carbonate to give compound **3-11** tetra-bromo cavitand. The tetra-bromo cavitand **3-11** is a starting material that is commonly utilized in many of the synthetic schemes for this research project.



Scheme 3.1 shows the synthesis of the tetra-bromocavitand.

The key step is the fuctionalization of the tetra-bromo cavitand into an A,C pattern as shown in figure **3-1** for synthesizing a alternating pattern of cation/anion/cation/anion moieties on the upper rim of the cavitand. Initially our focus was the synthesis of 1,2,3 triazoles with dodecyl chains for A,C functionalization as described in Chapter 2. Sonogashira chemistry was employed on the upper rim of the cavitand with A,C-iodo-B,D-bromo cavitand. As shown in the scheme **3-2** below several attempts were made to purify the A,C-

iodo-B,D-bromo cavitand from the A,B-iodo-C,D bromo cavitand (Figure 3-1). Unfortunately, the separation of these compounds was not successful while progression of the synthesis was not fruitful for the isolation the A,C cavitand from the A,B isomer.

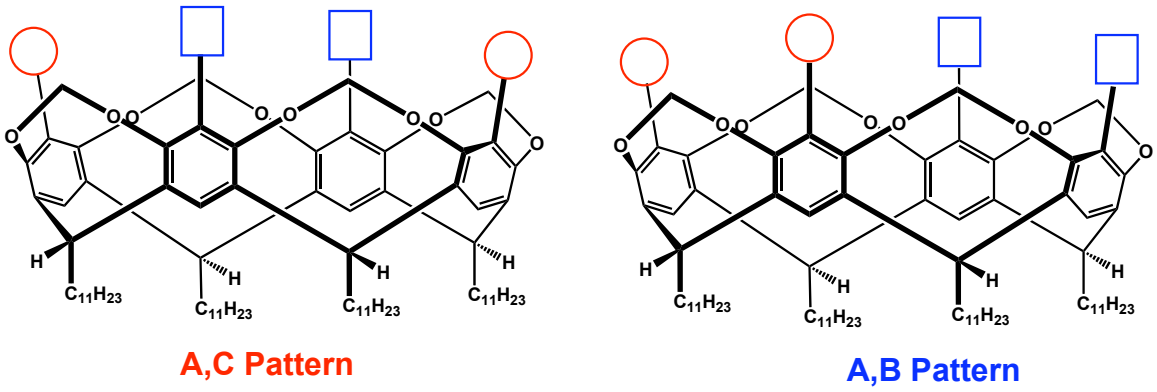
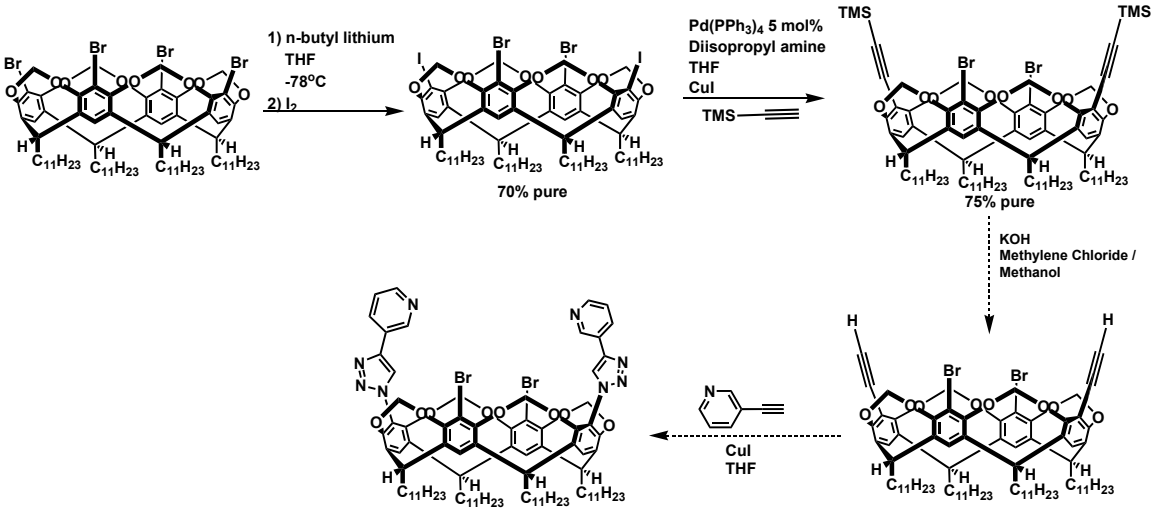


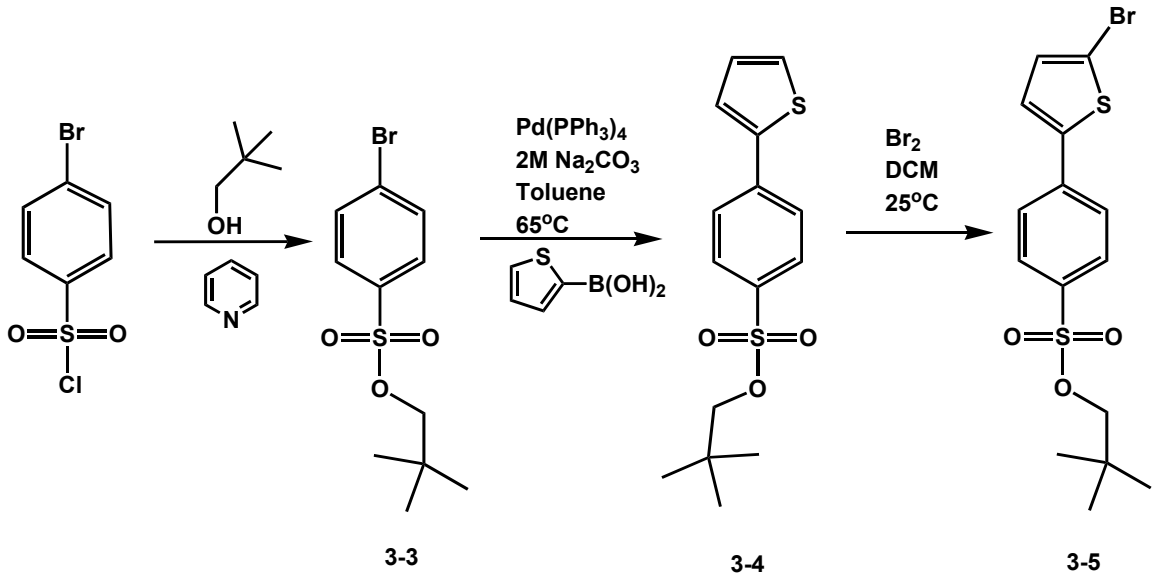
Figure 3.1 shows the A,C and A,B pattern of the upper arms.



Scheme 3.2 shows1,3 dipolar addition with dodecyl feet cavitand.

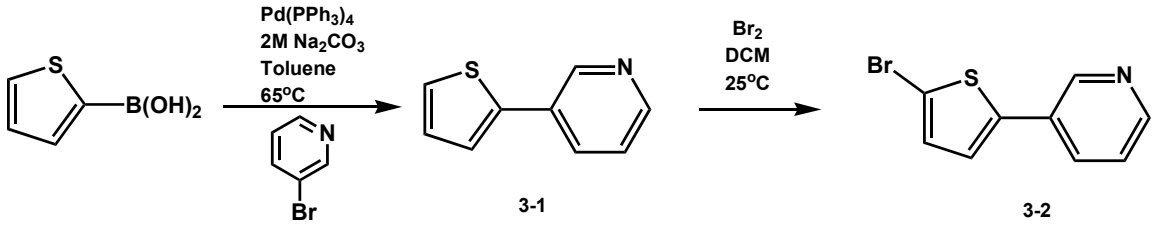
The main challenges in isolating A,C iodo-B,D bromo cavitand was their small surface interaction with the silica gel for allowing separation of the two isomers. These compounds eluded with 95:5 Hexane: Ethyl Acetate. The use of a boronic acid was employed to increase the polarity and yield an easier separation of the

A,C from the A,B cavitand. With the addition of the boronic acids on the upper rim of the cavitand Suzuki chemistry was employed for decorating the upper rim with pyridine and sulfonate moieties. Thiophenes were selected due to synthetic precedence for functionalizing the 2 and 4 position for creating 2- bromo-4 aromatic thiophenes[5]. **3-5** was synthesized by reacting 4-bromosulfonyl chloride with neopentyl alcohol in the presence of pyridine to give **3-3**[6]. **3-4** was achieved by a Suzuki cross-coupling with 2-thiophene boronic acid in presence of tetrakis(triphenylphosphine)palladium[5]. **3-4** was treated with bromine in methylene chloride to yield 2,2-dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **3-5**[5].



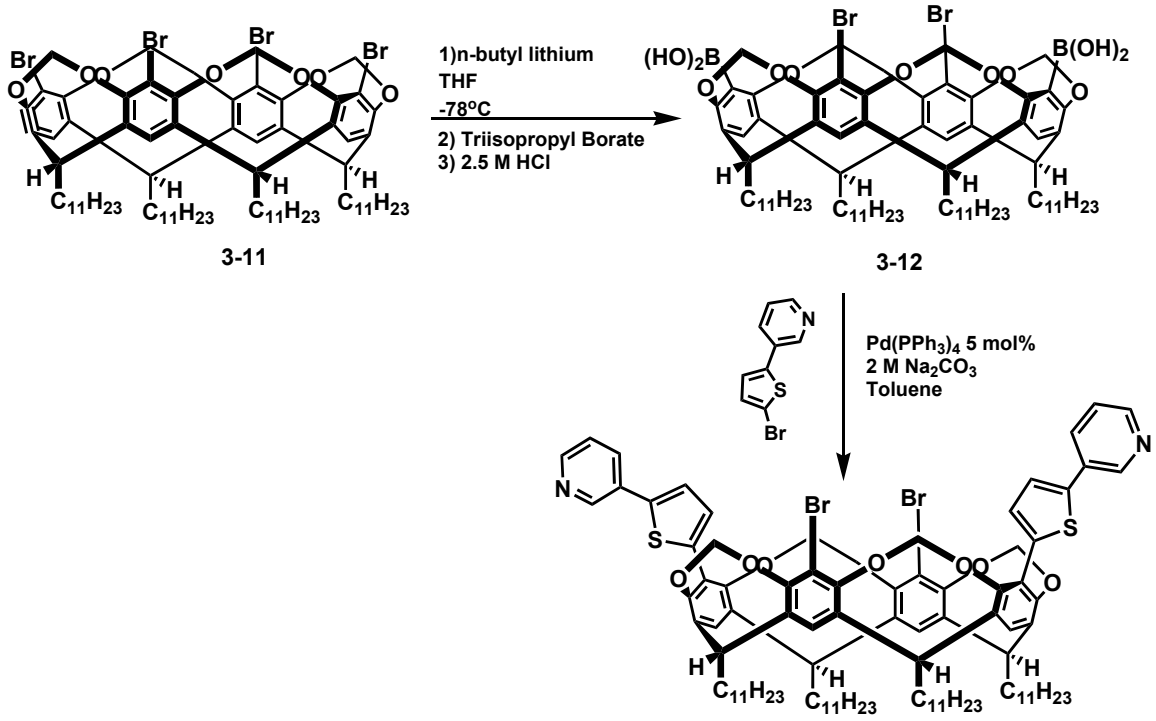
Scheme 3.3 shows the synthesis of the bromo-thiophene sulfonate

3-(5-bromo-2-thienyl)pyridine **3-2** was prepared in a similar manner as the sulfonate thiophene. 2-thiophene boronic acid, 3-bromopyridine, tetrakis(triphenyl phosphine) palladium, sodium carbonate, and toluene were placed together to give **3-1** via a cross-coupling[5]. **3-1** was treated with bromine to yield **3-2** in 83% yield[5] (scheme 3-3).



Scheme 3.4 shows the synthesis of bromothiophene pyridine.

The 3-(5-bromo-2-thienyl)pyridine **3-2** and 2,2-dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **3-5** are basic building blocks are utilized to functionalize the upper rim of resorcin[4]arene to synthesize a molecular quadrupole. The pyridine moiety **3-2** can be alkylated to generate a cationic species and the 2,2 dimethylpropyl sulfonate **3-5** can be suponified to yield an anionic species.

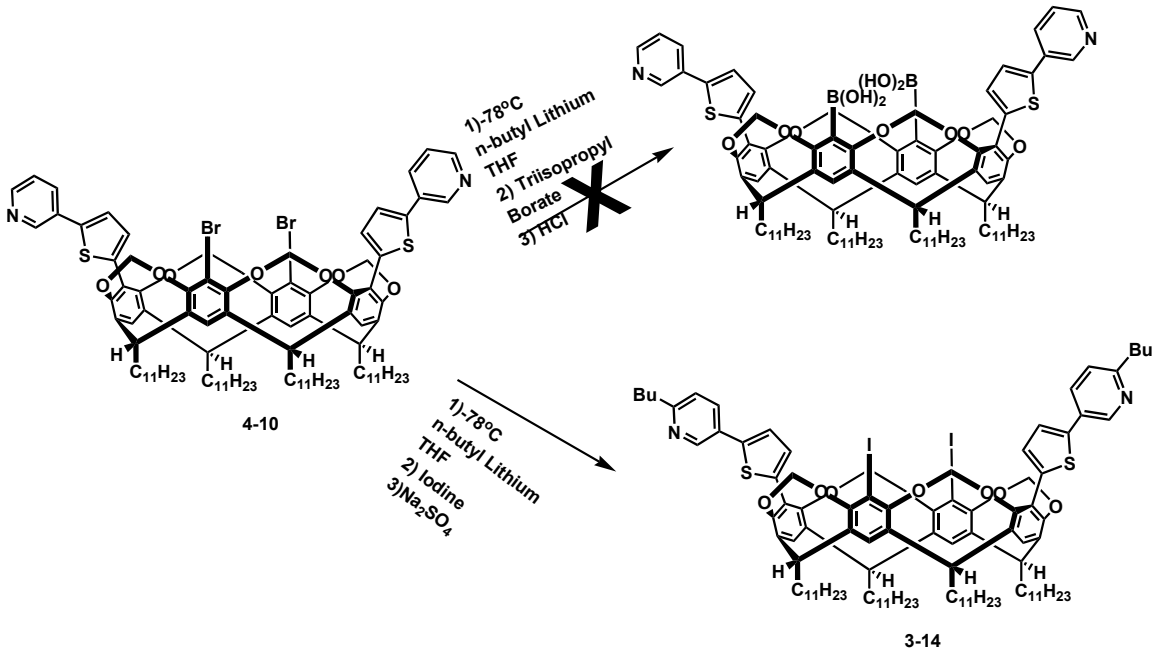


Scheme 3.5 shows the synthesis of the bis-pyridine,bis-bromo cavitand.

3-11 was treated with 1.6 M n-butyl lithium in dry THF at -78°C then triisopropyl borate was added to solution to give **3-12** in 46% yield. The bis-

boronic acid was treated with **3-2** in toluene to give the A,C-bis thiophene pyridine resorcin[4]arene in 55% yield **4-10** (Scheme 3-4)**.**

4-10 was treated with 1.6 M n-butyl lithium in dry THF then triisopropyl borate to convert the remaining bromines to boronic acids. Unfortunately, the boronic acid was never isolated. Concentration, time of reaction with n-butyl lithium, and equivalents of n-butyl lithium was varied. Unfortunately, the bis-boronic acid, bis-pyridine was never isolated. Following the lithiation the electrophile was changed from triisopropyl boronate ester to iodine. The iodine gave a successful conversion from bromide to iodide but a poor yield of 17% was obtained (scheme 3-6).



Scheme 3.6 shows the conversion of the bromides to iodides on the upper rim.

Interestingly, the n-butyl lithium alkylated the pyridine via a nucleophilic addition[7]. An increase in the concentration of n-butyl lithium alkylated the pyridine more and decreased the yield of **3-14**. The butyl chains were confirmed by 2-D NOESY[8] from cross peaks from the butyl chains and the pyridines (figure 3-2).

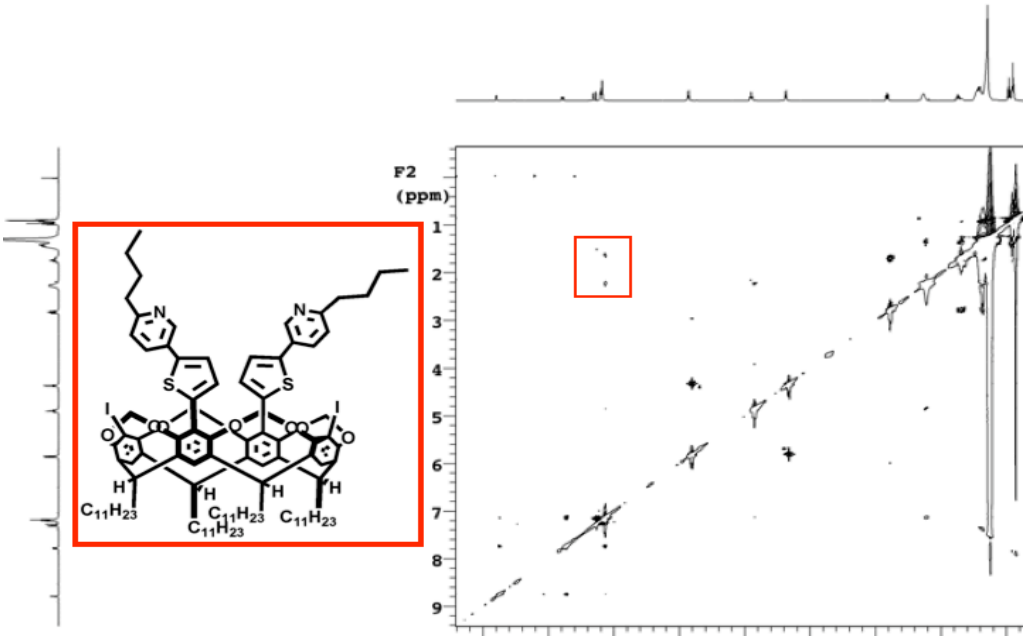
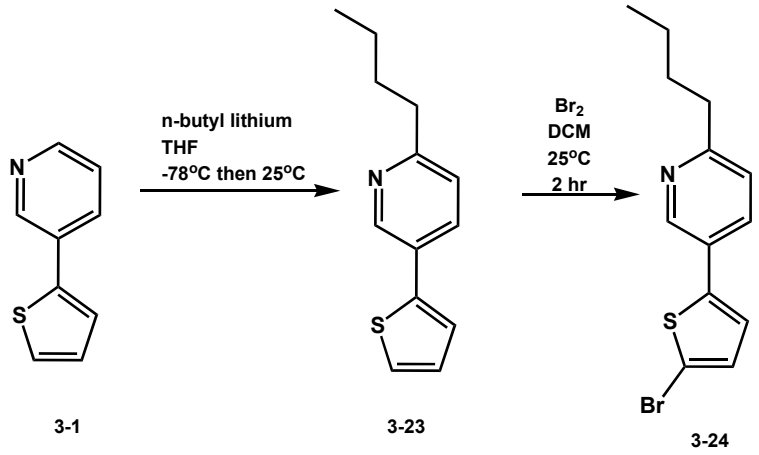


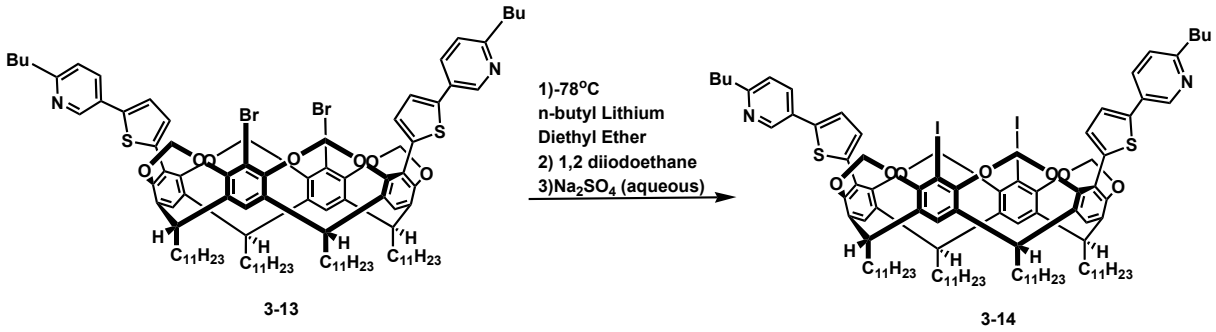
Figure 3- 2 shows a 2-D NOESY confirming the presence of butyl chains on the pyridines.

pyridine aromatic and the alkyl chain of the butyl group. To increase the yield butyl chains were decorated on the pyridines prior to the Suzuki cross-coupling. This was implemented to prevent the nucleophilic addition from occurring at other positions on the pyridine. Unfortunately, upon the addition of the n-butyl lithium the alkylation still occurred.



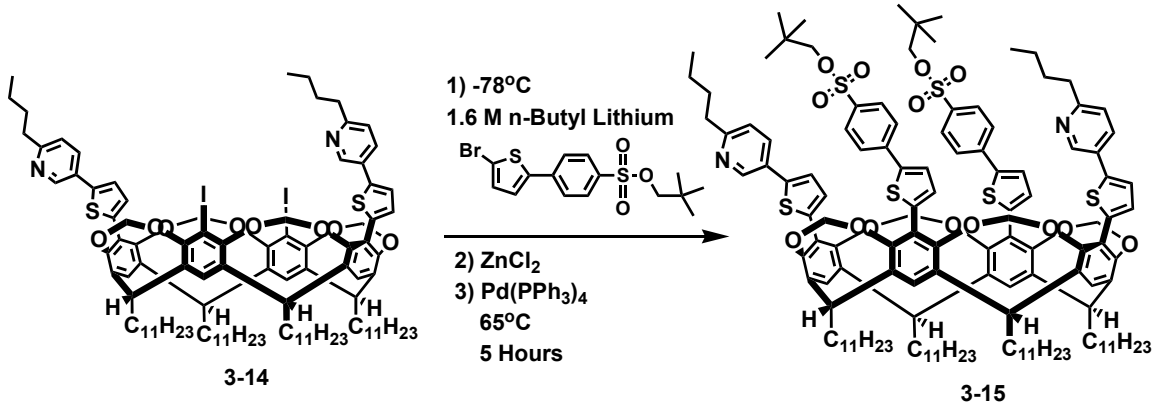
Scheme 3.7 shows the synthesis of the bromothiophene pyridine with butyl chains.

A solvent change from THF to diethyl ether and decreasing the concentration provided a 65% yield. It is uncertain why the yield is increase but a solvent effect could be responsible for suppressing the nucleophilic addition. The use of diethyl ether retards the nuclelophilic addition of the n-butyl lithium.



Scheme 3.8 shows the optimized conversion of the bromide to iodide.

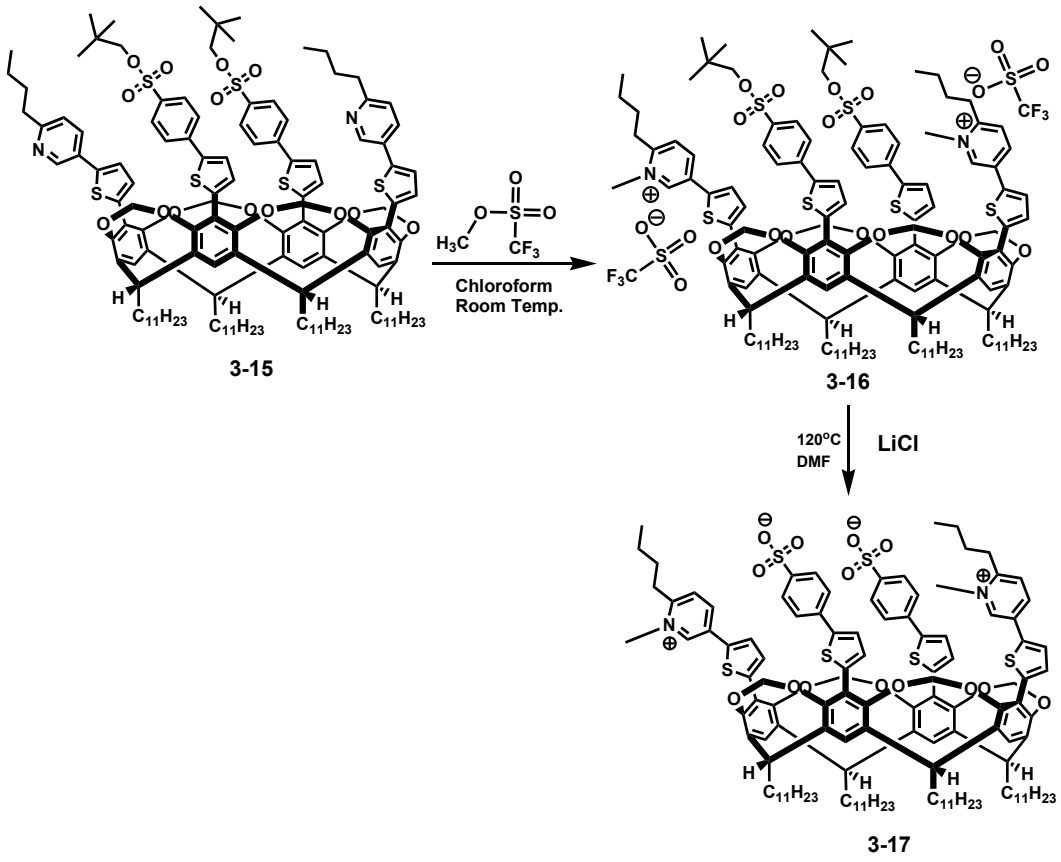
The conversion of an aromatic bromide to an aromatic iodide allowed the use of Negishi chemistry[9] to be employed. **3-13** was converted to **3-14** to accelerate the cross coupling for the addition of the **3-5** to the upper rim. In previous synthetic schemes a phenyl-substituted sulfonate was utilized which was not compatible with n-butyl lithium. Therefore, the use of a neo-pentyl protecting group was utilized which was compatible with n-butyl lithium at -78°C[6]. **3-5** was treated with 1.6 M n-butyl lithium at -55°C inside of the cold well and a THF-zinc chloride solution was added to **3-5**.



Scheme 3.9 shows the Negishi cross coupling with bis-iodo, bis-pyridine cavitnad.

Tetrakis(triphenylphosphine)palladium, zinc chloride tetrahydrofuran solution with **3-5** and **3-14** was placed in a schlenck and heated at 70^{o}C for 6 hours to give **3-15** in 65 % yield. To the best of my knowledge the use of a Negeshi cross-coupling has never been employed to functionalize the upper rim of a resorcin[4]arene.

The alkylation of the pyridine was initially performed with methyl iodide with heating to 80^{o}C. This yielded mixtures of mono and bis-methylated products due to the steric hindrance of the butyl chains of the ortho-substituted nitrogen. A more aggressive agent methyl triflate was employed with is more reactive than methyl iodide.[10] N-ethyldiisopropylamine was added to the solution to act as a buffer to remove any protonated pyridinium to give **3-16** in 55 % yield.



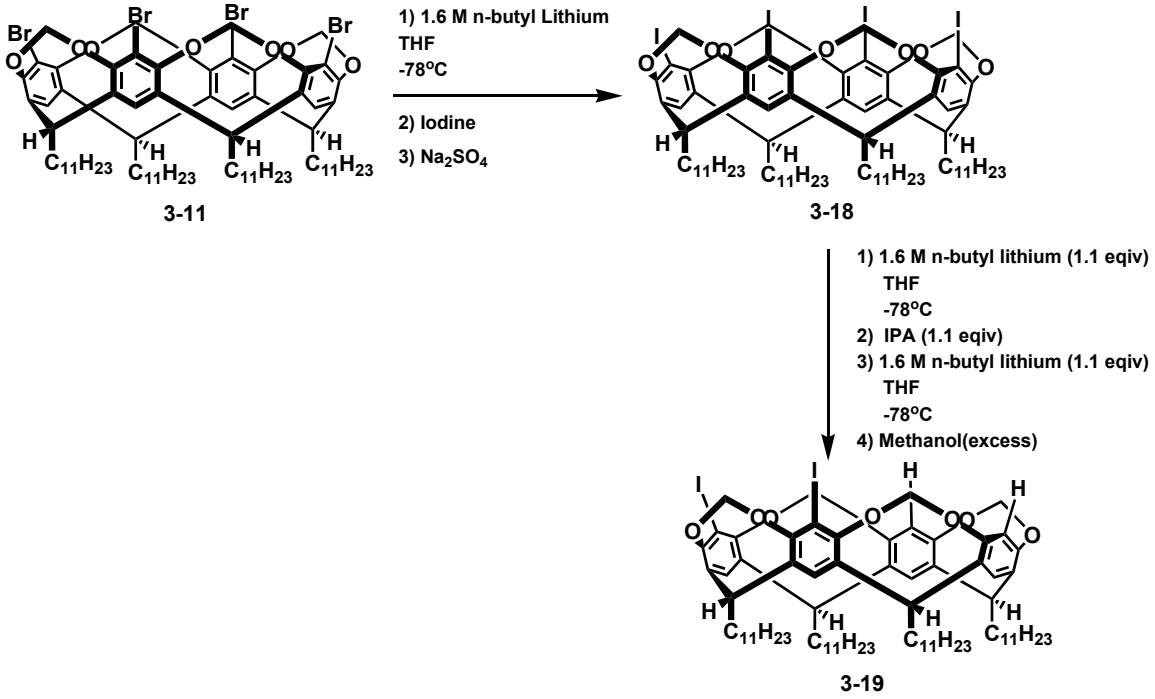
3-15 **3-16** **3-17**

Scheme 3.10 shows the alkylation of the nitrogens and the removal of the neopentyl groups.

Next, the neo-pentyl groups were removed by heating tetra-methyl ammonium chloride and dimethylformamide to 150^{o}C for 24 hours. The chloride ion displaces the neopentyl groups from the sulfonate. After careful analysis, the ^{1}H NMR spectrum indicates the methyl group at 4.3 ppm in compound **3-16** was no longer present. There is literature precedence that pyridinium chloride was used as a N-demethylation reagent via an S_n2 reaction[11]. Lowering the temperature and utilizing lithium chloride in the place of tetramethyl ammonium chloride, the demethylation was controlled. This is the synthesis of the first resorcin[4]arene based quadrupole.

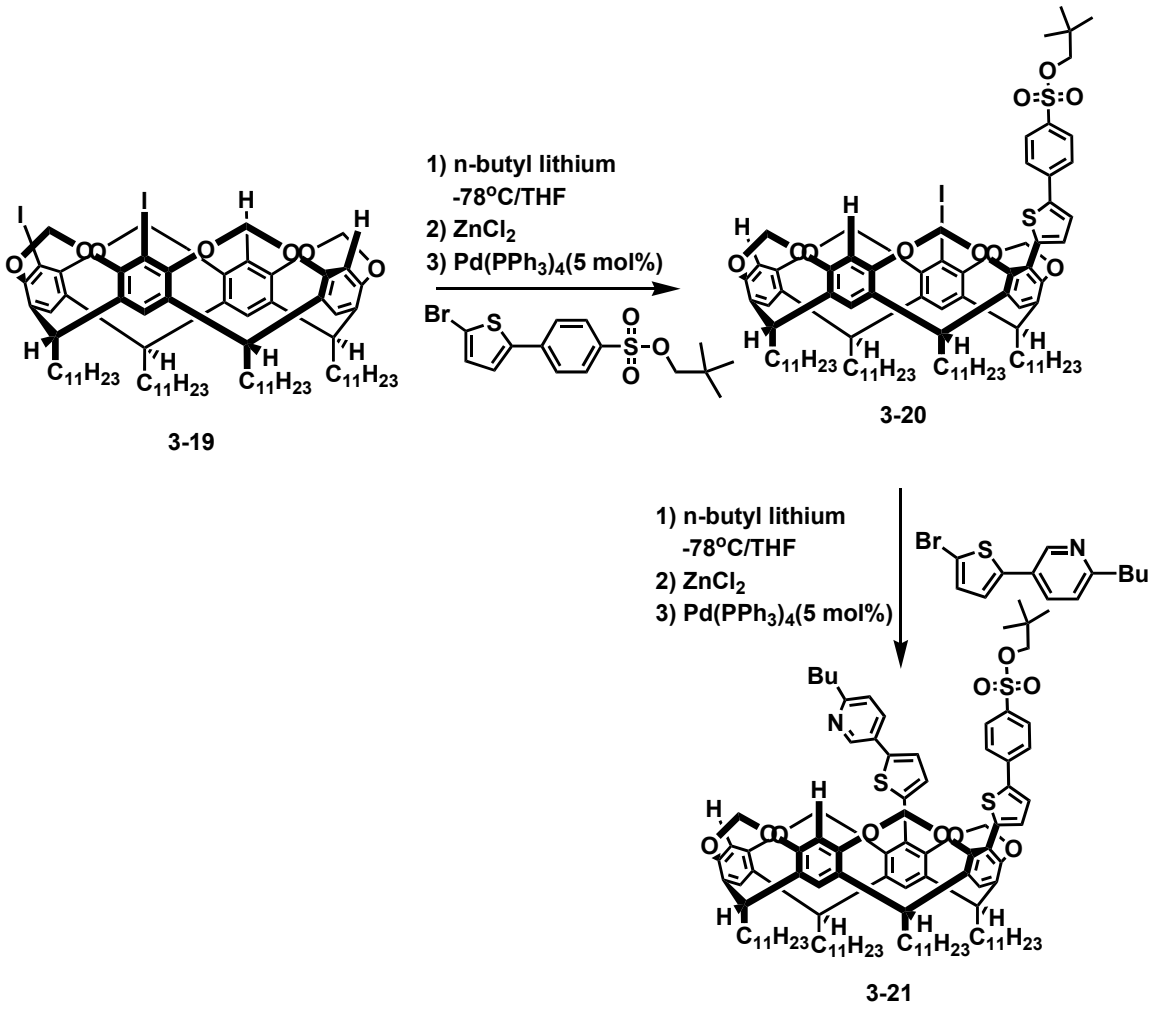
.3.2,1-Synthesis of the A,B Model resorcin[4]arene [3-23]:

The main synthetic challenge to model cavitand was the A,B bis-iodo resorcin[4]arene **3-19**. Two aromatic iodides directly adjacent to each other would allow for mono functionalization of the sulfonate and then the subsequent functionalization of the pyridine (scheme 3.11)**.** Negishi chemistry[9] was employed as a synthetic method for functionalizating of the upper rim with **3-5** and **3-24**. The first step involved the converting the tetrabromo **3-11** to the tetraiodo cavitand **3-18**. After drying **3-11** under high-vacuum, dry THF was added to the tetrabromocavitand **3-11** followed by the rapid addition of 1.6 M n-butyl lithium to give the tetraiodo cavitand **3-18** in 50% yield. The tetraiodo cavitand **3-18** was dried under high vacuum and treated with 1.1 equivalents of 1.6 M n-butyl lithium then 1.1 equivalents of methanol.



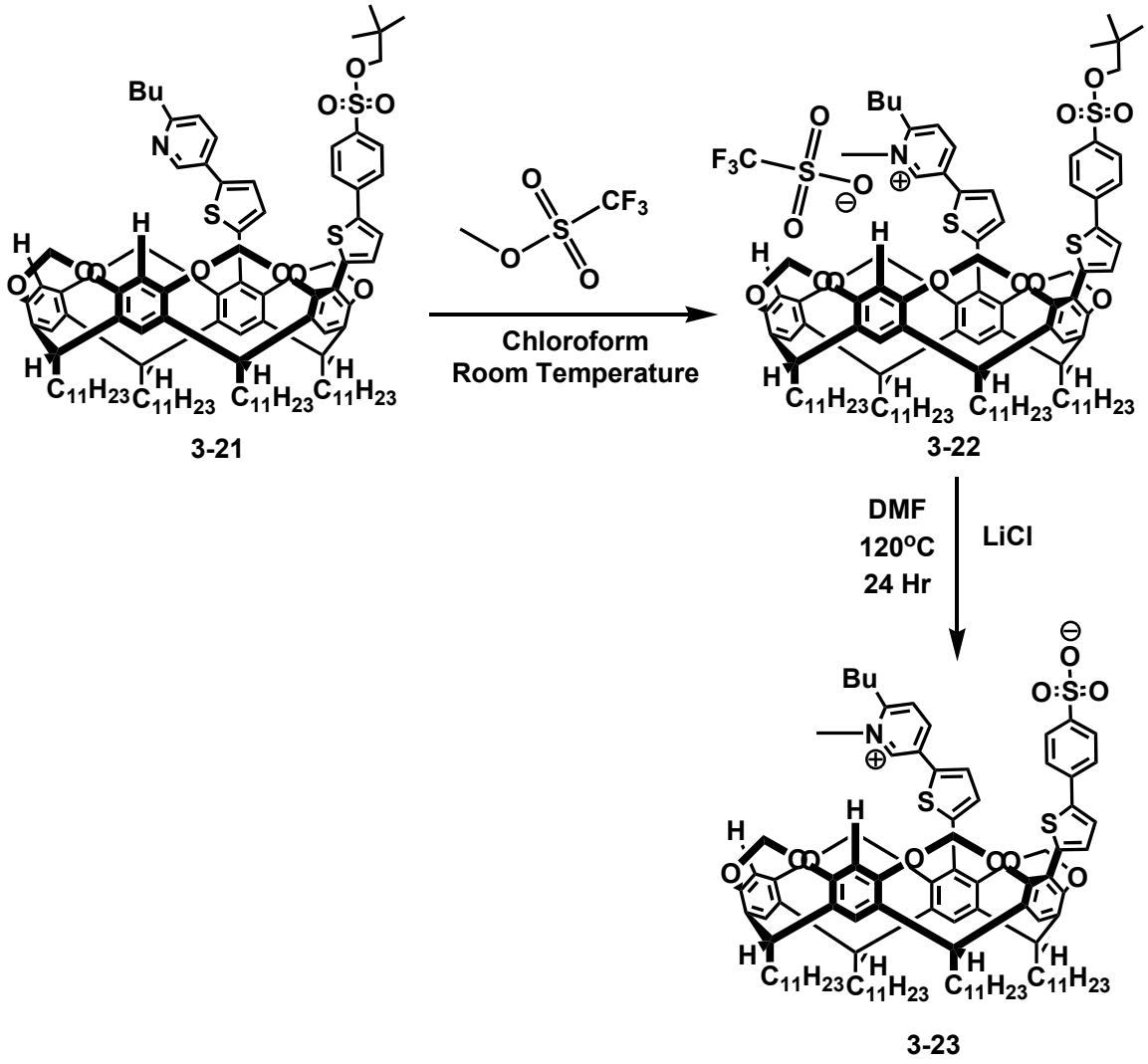
Scheme 3.11 shows the synthesis of the bis, A,B iodo cavitand.

Another equivalent of n-butyl lithium was added followed by an excess of methanol. The resulting compound was purified by column chromatography to yield the A,B bis-iodo cavitand **3-19** in 15 % yield . Negishi chemistry[9] was employed to functionalize one of the iodides with **3-5** on the upper rim of the cavitand. Using 1.2 equivalents of **3-5** yielded a mixture of the bis and mono functionalized sulfonate cavitands. The mixture was purified via column chromatography generating the mono sulfonate **3-20** in 24 % yield. 2-bromothiophene pyridine **3-2** was subjected to similar Negeshi conditions while this method produced the nucleophilc addition of the pyridine upon the addition of n-butyl lithium. Yielding an unfruitful method for the addition of the pyridine onto the upper rim. Therefore, the **3-1** was treated with 1.6 M n-butyl lithium to generate **3-23** and subsequently brominated to give **3-24**. **3-24** was placed in a cold well at -55^{o}C and 1.6 M n-butyl lithium was added rapidly. A zinc chloride solution was added to **3-24** and transferred to schlenck flask with tetrakis(triphenylphosphine)palladium and 3-20 to give 3-21 in 67% yield (scheme 3-12)**.**



Scheme 3.12 functionalization of the model cavitand with Negishi chemistry.

3-21 was treated with methyl triflate due to the steric for an *ortho*-substituted nitrogen to give **3-22** in 37% yield[10]. **3-22** was treated with tetramethyl ammonium chloride in dimethylformamide at 150°C for 24 hours and the methyl group at 4.3 ppm was no longer present. With the addition of methyl triflate and N-ethyldiisopropylamine the desired **3-23** was achieved (scheme 3-13).



Scheme 3.13 shows the alkylation with methyl triflate and deprotection of the sulfonate.

.3.3,1-Conformational Transition

It has been established that sulfonates and pyridiniums can attract to each other. Schneider has measured sulfonate and pyridinium ion-pair complexes in water[12]. As mentioned in chapter one of this thesis their studies of intermolecular ion pairs between sulfonate and pyridinium they found 5 $\pm$ 1 kJ/mol. The focus is to measure the attractive forces in an intramolecular system between sulfonate and pyridinium moieties. The goal is to observe a transition between an 'open

state' and a 'collapsed state'. Conformational transitions such as the denaturation of proteins follow a two-state transition model. To observe these transitions solvent plays a critical role in establishing the equilibrium between the 'open' and 'collapsed' state. Electrostatic forces are less attractive in polar solvents compared to non-polar solvents such as chloroform and carbon tetrachloride. Solvents with high dielectric constants such dimethylsulfoxide and dimethylformaide can align between ion-pairs. To observe the transition between 'open' and 'close,' titrations are performed to observe the two-transition states.

The quadrupole **3-17** and reference compounds **3-22** and **3-8** are titrated to measure the electrostatic forces between the sulfonate and pyridiniums on an intramolecular system. To observe these transitions, chloroform is titrated into a dimethysulfoxide-d_6 stock solution and monitored by ^{1}H NMR. Upon the addition of the chloroform-d to dimethylsulfoxide-d_6 the change in chemical shift is monitored from 100% dimethylsulfoxide-d_6 as chloroform-d is added. As the concentration of dimethysulfoxide-d_6 decreases, the chemical shift changes as a result. Multiple spectrums are obtained at different concentrations of dimethylsulfoxide-d_6 to chloroform-d. These spectrums are stacked in order of increasing concentration of chloroform-d. Monitoring the stacked spectrums peaks are analyzed by patterns. Linear patterns are due to solvent effects while S-shaped patterns are potential transitions.

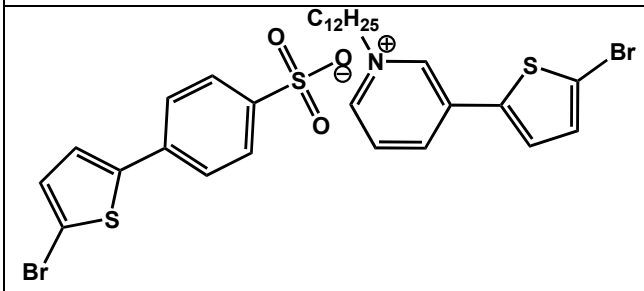
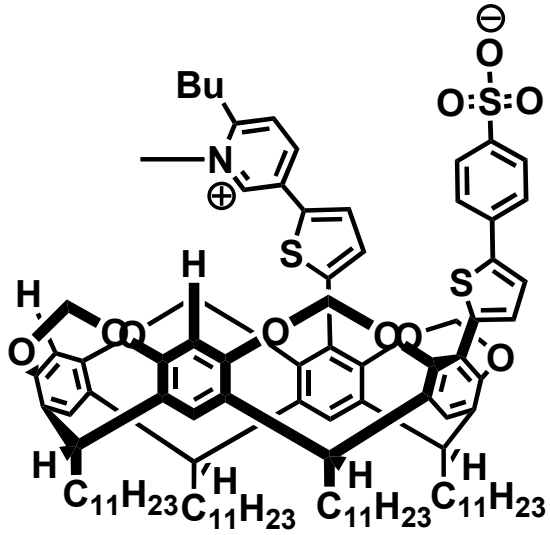
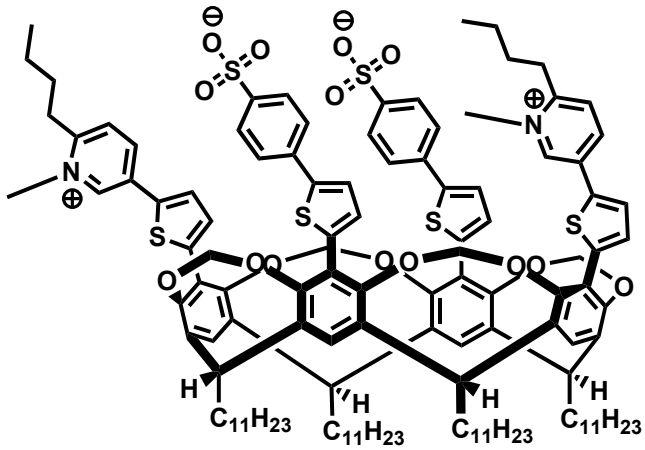
Compound	Intermolecular or Intramolecular
	intermolecular thiophene salt model Compound
	Intramolecular a,b cavitand model Compound
	Intramolecular Quadrupole cavitand

Table 3.1 shows quadrupole cavitands and two reference compounds.

.3.3,2-Titrations

Titrations were executed with chloroform-d and dimethylsullfoxide-d_6 to observe the 'open' and 'attractive' states between the pyridinium and sulfonates. Chloroform-d was utilized as a non-polar media suitable for observing electrostatic interactions. Dimethysulfoxide-d_6 was utilized as a polar media to disrupt the electrostatic interactions. The use of 1H NMR spectroscopy was utilized to monitor the transition. Initially, compounds 3-22 and 3-17 were dissolved in 100% dimethylsulfoxide-d_6 and titrated with aliquots chloroform-d. Both products were titrated as stock solutions with equal concentrations for both solutions of dimethylsulfoxide-d_6 and chloroform-d. This was performed to observe a transition to determine the disassociation energies of sulfonates and pyridiniums. After several titrations, the concentration domain of chloroform-d in dimethylsulfoxide-d_6 was determined and careful titrations were attempted to observe the transition of 'open' and 'attractive.' The model compound was titrated with a 65%:35% chloroform-d:dimethylsulfoxide-d_6 mixture and .05 mL of a chloroform stock solution was added to the NMR tube. The peak at 9.4 ppm which is a singlet from the pyridinium shows a solvent effect moving to the left but a sharp kink is observed, which identifies a transition has occurred.

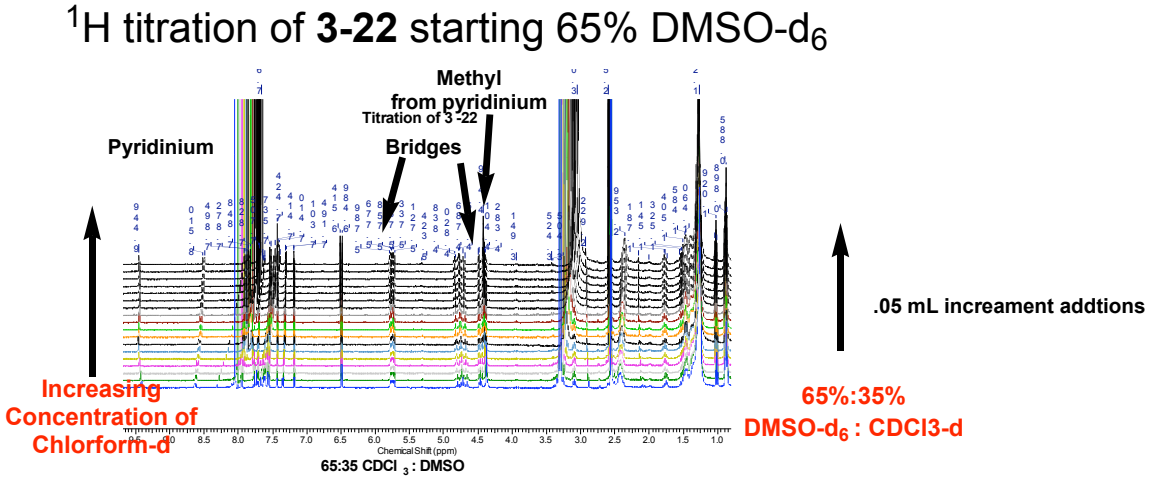


Figure 3.3 shows the NMR titration of 3-23 with bottom spectrum 65% chloroform-d with increasing concentration of chloroform of .05 mL with stacked spectrums.

The NMR spectrums are stacked on top of each other with the each spectrum referenced to trimethylsilane. The pyridinium peak is monitored for a transition and the chemical shifts are recorded in excel against the concentration of the chlorform-d. As shown in the excel plot below a transition occurs at 70% $CDCl_3$ suggesting the onset of conformational change of an open state to a closed state between the sulfonate and pyridinium capsules.

The transition was examined by relating the kink to $\Delta G = RT \ln K$. With K being the equilibrium constant for 'open' vs. 'attractive.' Solvent effects are determined by linear relationship between change in chemical shift and concentration of chloroform in the stacked ^1H NMR spectrums. The kink is identified as a potential transition of 'open' to 'attractive.' Upper and lower plateaus are identified as ‘open’ for 0% to 65% chloroform-d. In the range of 85% to 100% chloroform-d are identified as 'attractive'. With the upper and lower plateaus identified the kink is identified as the onset of a transition. Each data point within the kink is quantified as a percentage of 'open' vs. 'attractive.' This ratio is quantified as the equilibrium value for a disassociation constant for 'open' and 'attractive.' The equilibrium value is then utilized in the $\Delta G = RT \ln K$ to provide a ΔG value for 100% chloroform. A linear extrapolation to the 'y' axis for 100% chloroform provides a ΔG value for attractive state. The extrapolation to 100% chloroform identifies the point in which equilibrium is more pronounced for the 'attractive' state. The linear extrapolation to 100% $CDCl_3$ gives a ΔG of 5.1 Kcal/mol for **3-22**.

The same method was performed for the quadrupole **3-17** to determine the ΔG. To map out the onset of a transition, **3-17** was dissolved in 100% dimethylsulfoxide-d_6 and aliquots of chloroform-d were added. The concentration of 3-17 is equal the stock solutions that were made. After surveying from 100% dimethylsulfoxide-d_6 to 80% chloroform-d, no transitions were observed by ^1H NMR. At higher concentrations of chloroform (>75%) the quadrupole was insoluble in the media. This was determined by a precipitation that occurred and poor quality ^1H NMR spectrums were obtained in this concentration domain.

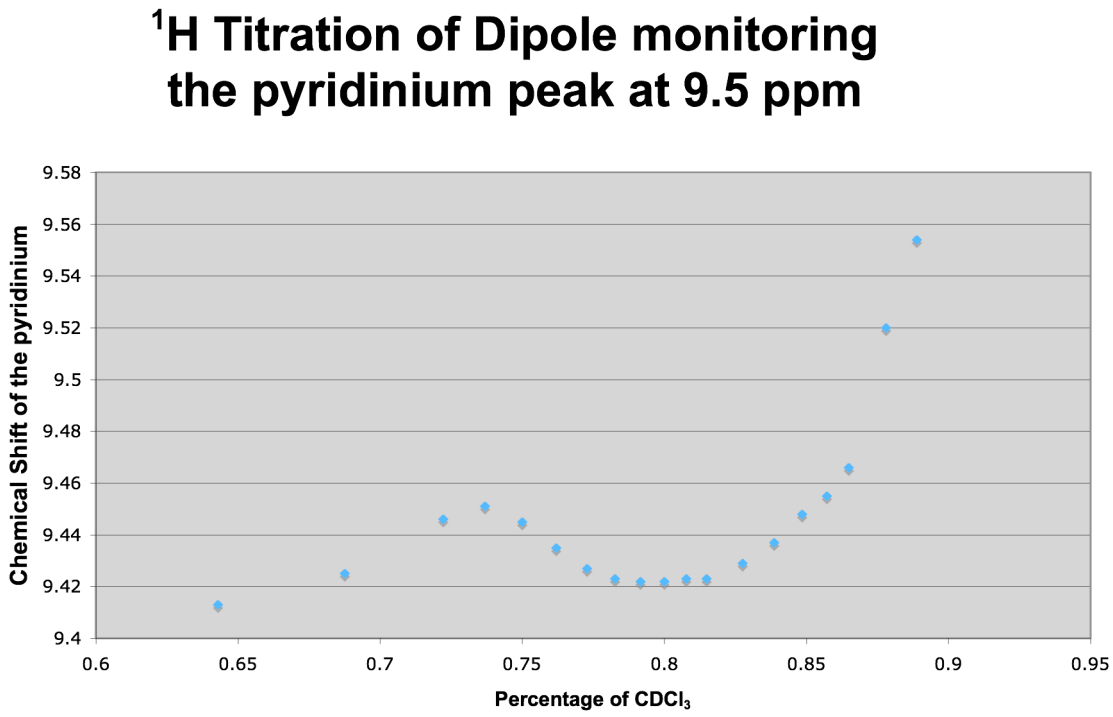


Figure 3.4 shows the titration of the dipole 3-22 from 60% to 85% $CDCl_3$ monitoring the change in chemical shift of the pyridinium peak at 9.5 ppm

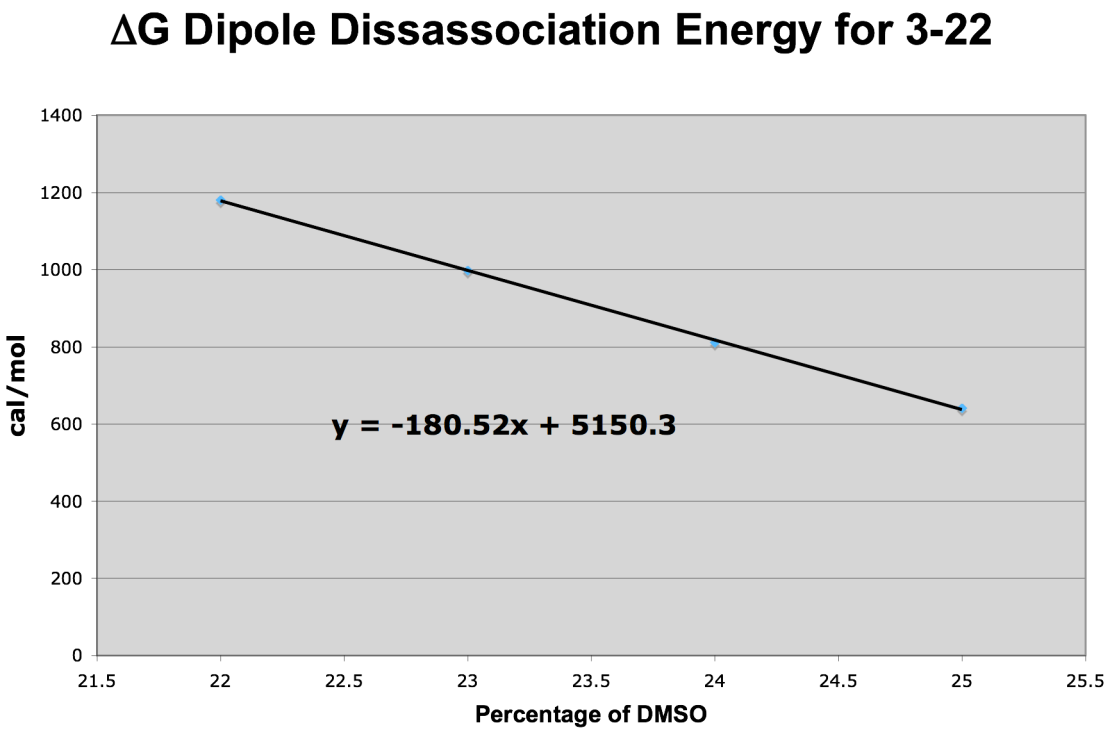


Figure 3.5 shows a solvent dependent-conformational change that is linear.

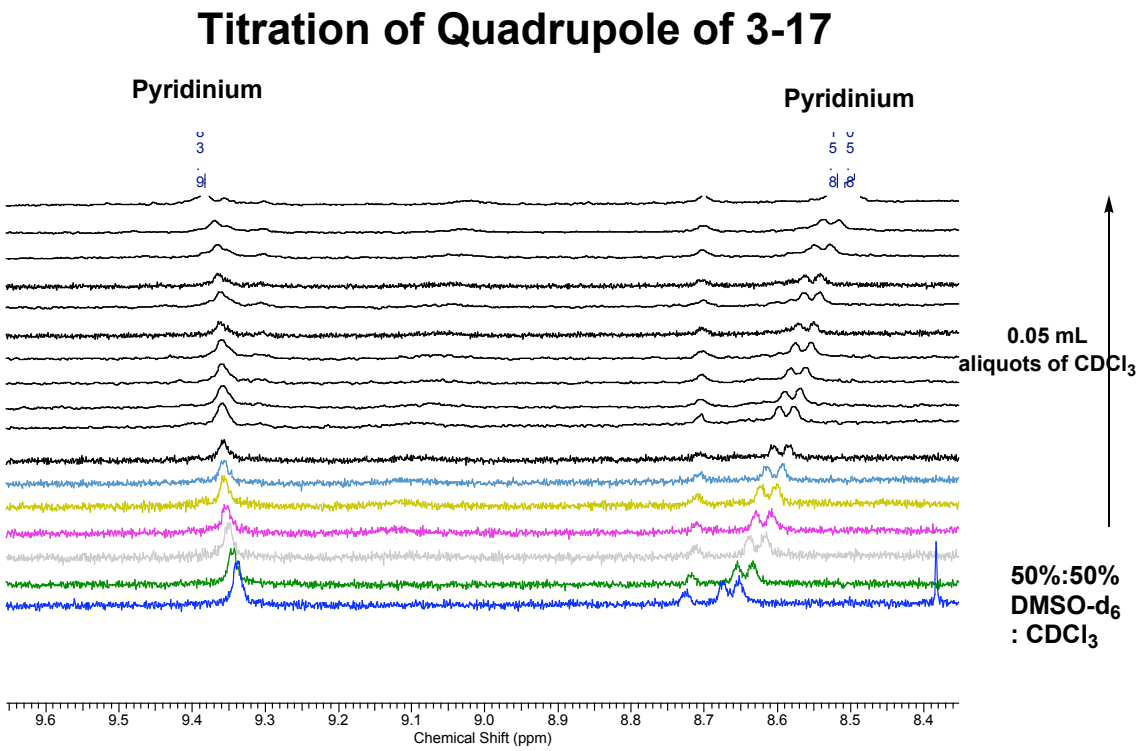


Figure 3.8 shows the titration of the quadrupole

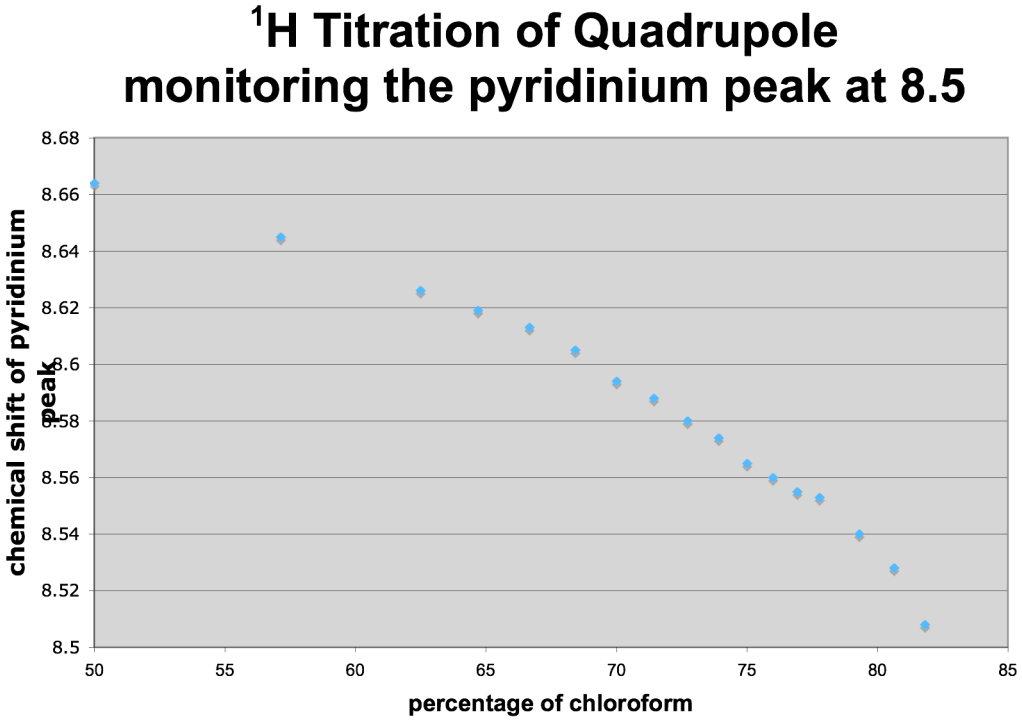


Figure 3.7 shows the titration of the quadrupole 3-17 from 50% chloroform to 85% chloroform-d.

Compound	**ΔG kcal/mol**
Quadrupole (**3-17**)	No transition
Dipole (**3-22**)	5.1 kcal/mol

3.4-Conclusions and Outlook

Synthesized was a molecular quadrupole based resorcin[4]arene. Suzuki and Negishi cross couplings were utilized to decorate the upper rim of the cavitand. A model dipole was also synthesized as a reference to compare ΔG values. Titrations were performed by titrating dimethylsulfoxide-d_6 with chloroform-d. The monopole showed a transition between 75% and 80% chloroform while the quadrupole did not show a clear titration. Solubility problems occurred with quadrupole with 75% chloroform in dimethylsulfoxide. The poor

solubility of the quadrupole in chloroform made it difficult to observe a transition for the quadrupole.

3.5-Future Studies

A practical method for the synthesis of a molecular quadrupole has been established. Unfortunately, poor solubility of quadrupole in chloroform was found. Titrations with other non-polar solvents can be employed such as methylene chloride-d_2 and tetrahydrofuran-d_6. Ortho to the pyridine are butyl chains from nucleophilic attack from the n-butyl lithium. The use of a longer alkyl chain could improve solubility. For example, employing dodecyl lithium in the place of n-butyl lithium could increase the solubility of the quadrupole in non-polar solvents.

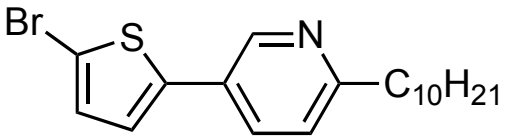
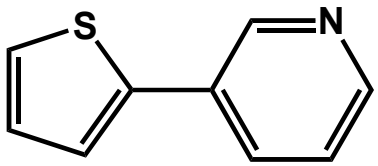


Figure 3.9 shows the use of longer alkyl chains on the pyridine to increase solubility.

3.5-Experimental

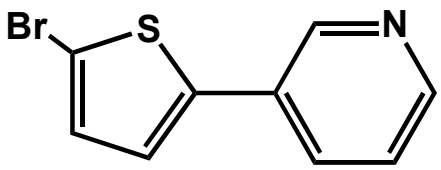
3-(2-thienyl)pyridine [3-1][5]



compound 3- 1

To a reaction vessel 3- bromo-pyridine (1.01g, 6.42 mmol, 0.619 mL), 2-thiophene boronic acid (0.685 g, 5.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.310 g, 0.268 mmol), 2.00 M sodium bicarbonate (6mL), and toluene(13mL) were added. The reaction vessel was degassed by freeze-pump-thaw. The reaction was heated at 80^{o} C for 10 hours. The solution was allowed to reach room temperature and a saturated sodium bicarbonate solution was added. Methylene chloride was added and the aqueous and organic layers were separated. The organic layer was dried with magnesium sulfate, filtered, and concentrated. The product was isolated by column chromatography with 3:1 hexane: ethyl acetate to yield a light brown oil of 1 g (80% yield) of the title compound **3-1** [5] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 7.12 (dd, *J*=4.29 Hz, 1 H) 7.30 (dd, *J*=7.22, 4.88 Hz, 1 H) 7.36 (d, *J*=3.90 Hz, 2 H) 7.86 (d, *J*=8.20 Hz, 1 H) 8.51 (d, *J*=4.69 Hz, 1 H) 8.89 (d, *J*=1.95 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 123.6, 124.1, 125.9, 128.2, 130.3, 132.9, 140.4, 147.0, 148.4

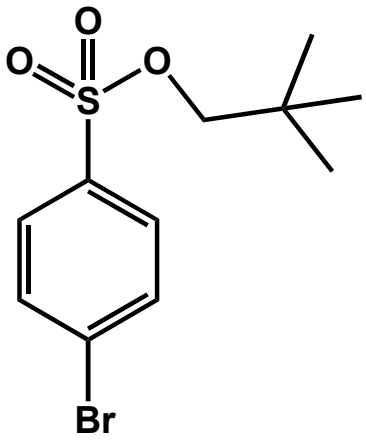
3-(5-bromo-2-thienyl)pyridine [3-2][5]



compound 3- 2

The reaction vessel was wrapped in foil to prevent exposure to light. Compound (**3-1)** 3-(2-thienyl)pyridine (4.36 g, 27.1 mmol) was dissolved in DCM (91.0 mL). A solution of bromine (1.81 mL, 35.0 mmol) in dichloromethane (45.0 mL) was added drop wise over 30 min. The reaction was stirred at ambient temperature for 2 hrs. A 1.00 M aqueous solution of sodium carbonate (30.0 mL) was added, and the mixture was stirred. The layers were separated. The aqueous phase was extracted with additional dichloromethane (30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 5.87 g (90% yield) of of the title compound **3-2**.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.057 (d, *J*=3.55 Hz, 1 H) 7.08 - 7.11 (m, *J*=3.81 Hz, 1 H) 7.29 (dd, *J*=7.86, 7.48, 5.20, 4.06 Hz, 1 H) 7.71 - 7.78 (m, *J*=2.28 Hz, 1 H) 8.53 (dd, *J*=4.82, 1.52 Hz, 1 H) 8.783 (d, *J*=1.78 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) □ δ 112.7, 123.6, 124.4, 129.5, 131.0, 132.6, 141.7, 146.5, 148.7

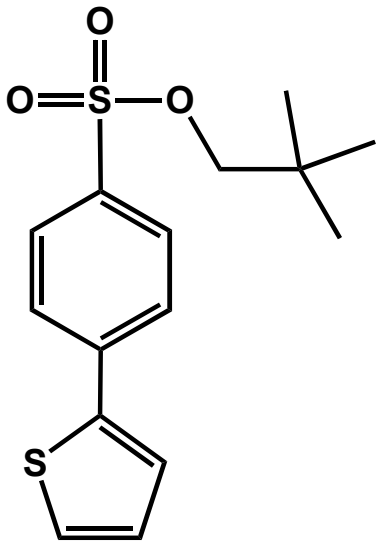
2,2-dimethylpropyl 4-bromobenzenesulfonate [3-3][6]



compound 3- 3

4-bromo-sulfonyl chloride 0.660 g (2.60 mmol), neopentyl alcohol 0.230 g (2.60 mmol) and 26.0 mmol (2.00 mL) of pyridine was added to a round-bottom flask. The pyridine was removed in vacuo and the remaining contents were dissolved in diethyl ether 10.0 mL. The ether was washed with 2.50 M HCl (15.0 mL). The organic and aqueous layers were separated and the organic layer was washed again with 2.50 M HCl. The organic layer was separated dried with magnesium sulfate, filtered, and concentrated. The crude was dissolved in diethyl ether and layered with hexane to induce precipitation of needle-like crystals of the title compound **3-3** (0.662 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.88 - 0.94 (m, 9 H) 3.70 (s, 2 H) 7.69 - 7.73 (m, *J*=8.20 Hz, 2 H) 7.75 - 7.80 (m, *J*=8.20 Hz, 2 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 26.2, 31.9, 80.1, 129.0, 129.5, 132.7, 135.3

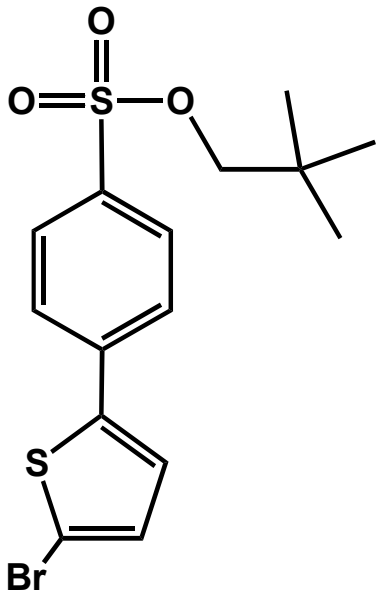
2,2-dimethylpropyl 4-(2-thienyl)benzenesulfonate [3-4][5]



compound 3- 4

To a sealable reaction vessel, 2,2-dimethylpropyl 4-bromobenzenesulfonate **3-3** (0.580 g, 1.89 mmol), 2-thiophene boronic acid (0.220 g, 1.72 mmoles), and tetrakis(triphenylphosphine)palladium(0) (0.080 g, 0.070 mmol), 2.00 M sodium bicarbonate (2.10 mL) and toluene (4.00 mL) were added. The reaction vessel was degassed by freeze-pump-thaw. The reaction was heated for 10 hours at 70^{o}C. The reaction was quenched by the addition of a saturated sodium bicarbonate solution. The aqueous layer was extracted with methyl chloride and the organic layer was dried with magnesium sulfate, filtered and concentrated. The product was isolated by column chromatography with 4:1 hexane:ethyl acetate to produce a white solid of the title compound **3-4** (0.310 g, 57% yield).[5] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.91 (s, 9 H) 3.70 (s, 2 H) 7.14 (dd, *J*=3.90 Hz, 1 H) 7.41 (dd, *J*=5.08, 1.17 Hz, 1 H) 7.45 (dd, *J*=3.90, 1.17 Hz, 1 H) 7.76 (d, *J*=8.59 Hz, 2 H) 7.89 (d, *J*=8.20 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 26.2, 31.9, 79.9, 125.5, 126.2, 127.3, 128.7, 128.8, 134.4, 139.7, 142.1

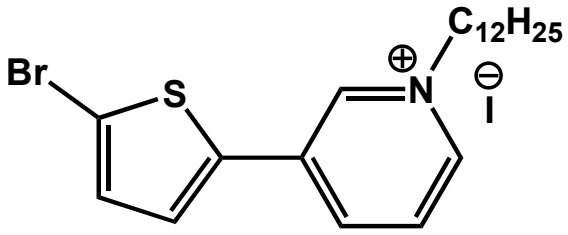
Dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate[3-5]



compound 3- 5

The reaction vessel was wrapped in foil to prevent exposure to light. Compound 2,2-dimethylpropyl 4-(2-thienyl)benzenesulfonate **3-4** (0.260 g, 0.850 mmol) was dissolved in DCM (3.00 mL). A solution of bromine (0.050 mL, 1.02 mmol) in dichloromethane (1.40 mL) was added drop wise over 30 min. The reaction was stirred at ambient temperature for 2 hours. A 1.00 M aqueous solution of sodium carbonate (5.00 mL) was added, and the mixture was stirred. The layers were separated and the aqueous phase was extracted with additional dichloromethane (15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 0.320 g (96% yield) of the title compound **3-5**.[5] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.86 - 0.95 (m, 9 H) 3.71 (s, 2 H) 7.09 (d, *J*=3.90 Hz, 1 H) 7.20 (d, *J*=3.90 Hz, 1 H) 7.62 - 7.70 (m, *J*=8.59 Hz, 2 H) 7.90 (d, *J*=8.20 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 25.3 - 27.3, 31.9, 80.0, 114.3, 125.6, 125.9, 128.9, 131.6, 134.9, 138.8, 143.4

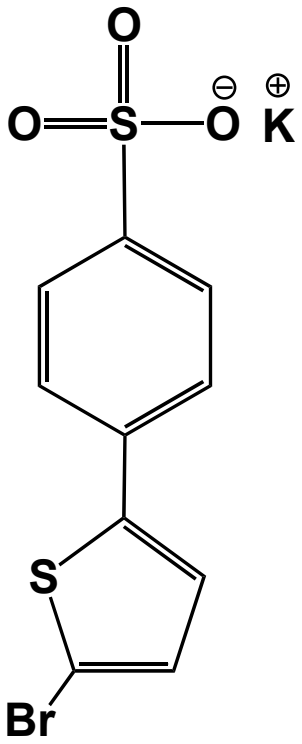
3-(5-bromo-2-thienyl)pyridine [3-6]



compound 3- 6

3-(5-bromo-2-thienyl)pyridine (**3-2)** (0.220 g, 0.920 mmol) was placed into a round bottom flask with 1-Iodododecane (0.410g, 1.40 mmol) neat. The reaction was allowed to stir overnight at room temperature. The reaction solution was dissolved in hexane and the solvent was decanted. This was repeated twice to yield 3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium iodide a brown oil (0.416 g, 85% yield) of the title compound **3-6**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.87 (t, *J*=6.64 Hz, 3 H) 1.17 - 1.50 (m, 20 H) 2.01 - 2.12 (m, *J*=7.03 Hz, 2 H) 5.06 (t, *J*=7.42 Hz, 2 H) 7.12 (d, *J*=3.90 Hz, 1 H) 7.98 (d, *J*=3.90 Hz, 1 H) 8.16 (dd, *J*=8.20, 6.25 Hz, 1 H) 8.52 (d, *J*=8.20 Hz, 1 H) 9.15 (d, *J*=5.86 Hz, 1 H) 9.85 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 13.9, 22.4, 25.7, 28.9, 29.1, 29.2, 29.3 - 29.5. 31.6, 31.8, 61.8, 116.9, 128.6, 130.0, 132.1, 134.0, 135.8, 140.0, 140.3, 141.9

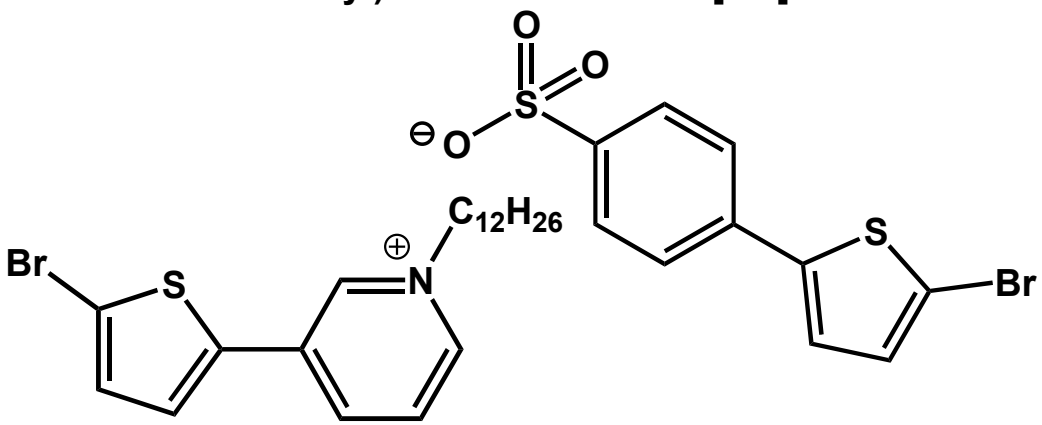
Potassium 4-(5-bromo-2-thienyl)benzenesulfonate [3-7]



compound 3- 7

Phenyl 4-(5-bromo-2-thienyl)benzenesulfonate (0.520 g, 1.31 mmol), 10.0 mL of CH_2Cl_2 and 10.0 mL of methanol was placed into a small round bottom flask. 0.730 g (13.0 mmol) of KOH was dissolved in 5.00 mL of CH_3OH. The reaction was cooled to 0^{o}C and slowly the KOH solution was added. A precipitate was filtered to produce 0.435 g (1.22 mmol, 93% yield) of the title compound **3-7**. $_1$H NMR (200 MHz, DMSO-d_6) d δ 7.26 (d, *J*=3.66 Hz, 1 H) 7.39 (d, *J*=3.66 Hz, 1 H) 7.60 (d, *J*=8.42 Hz, 4 H) ^{13}C NMR (101 MHz, DMSO-d_6) d δ 110.8, 124.5, 124.7, 126.4, 131.8, 132.7, 144.6, 147.9

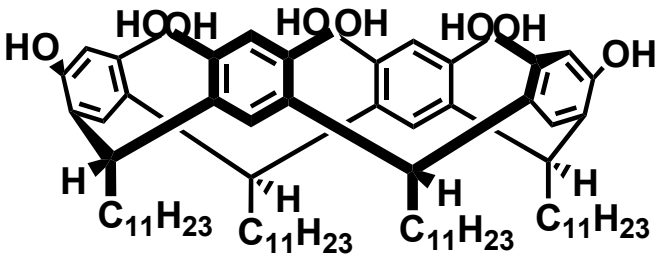
3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium-4-(5-bromo-2-thienyl)benzenesulfonate [3-8]



compound 3- 8

3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium iodide **3-6** (0.086 g, 0.160 mmol) was dissolved in 1.00 mL of DMSO and the potassium 4-(5-bromo-2-thienyl)benzenesulfonate **3-7** (0.057g, 0.160 mmol) was dissolved and 1.00 mL of DMSO. The two solutions were then combined and the addition of water (1.00 mL) produced the desired salt as an off white solid (0.090 g, 74% yield) of the title compound **3-8**. ^{1}H NMR (400 MHz, DMSO-d_6) □ δ 0.85 (t, *J*=6.83 Hz, 2 H) 1.19 - 1.33 (m, 20 H) 1.95 (q, *J*=6.64 Hz, 2 H) 4.59 (t, *J*=7.61 Hz, 2 H) 7.25 (d, *J*=3.90 Hz, 1 H) 7.38 (d, *J*=3.90 Hz, 1 H) 7.47 (d, *J*=3.90 Hz, 1 H) 7.53 - 7.59 (m, *J*=8.59 Hz, 2 H) 7.59 - 7.64 (m, *J*=8.59 Hz, 2 H) 7.76 (d, *J*=3.90 Hz, 1 H) 8.15 (dd, *J*=8.20, 6.25 Hz, 1 H) 8.76 (d, *J*=8.98 Hz, 1 H) 8.98 (d, *J*=6.25 Hz, 1 H) 9.43 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) □ δ 13.8 - 14.2, 21.6 - 22.3, 25.2 - 25.6, 28.3 - 28.5, 28.7 - 28.8, 28.7 - 28.8, 28.9 – 29.0, 28.9 - 29.1, 30.4 - 30.9, 31.3 , 61.1, 110.8, 115.5, 124.8, 126.4, 128.3, 129.2, 129.3, 131.8, 132.4, 132.5, 132.7, 133.0, 137.1, 140.5, 141.1, 142.9, 144.6, 148.0

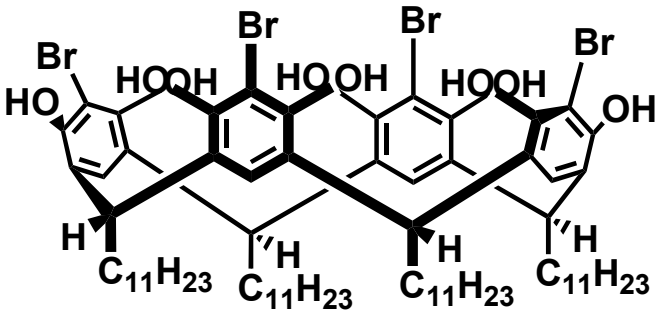
C-dodecylcalix[4]resorinarene [3-9][13]



compound 3- 9

A solution of 20.0 g (182 mmol) of resorcinol in 75.0 mL of ethanol and 25.0 mL of concentrated HCl was cooled to 0°C. Dodecanal (33.5 g, 182 mmol) in 50.0 mL of ethanol was added dropwise to the solution and stirred for 2 hour. The solution was allowed to warm up to room temperature and heated to 75°C for 10 hours. The precipitate that was separated by filtration was washed repeatedly with water. The crude solid was recrystallized from methanol to give the title compound **3-9** (48.5 g, 43.5 mmol). 1H NMR (400 MHz, acetone) δ ppm 0.90 (t, *J*=6.64 Hz, 12 H) 1.22 - 1.44 (m, 72 H) 2.29 (q, *J*=6.64 Hz, 8 H) 4.30 (t, *J*=7.81 Hz, 4 H) 6.24 (s, 4 H) 7.54 (s, 4 H) 8.47 (s, 8 H) LRMS calc. for $C_{72}H_{112}O_8$ found 1106.0 (M + H_2O)1123.0

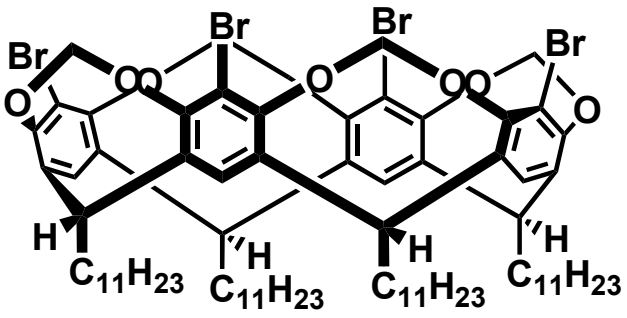
C-dodecyltetrabromocalix[4]resorinarene [3-10][13]



compound 3- 10

C-dodecylcalix[4]resorinarene (50.0 g, 45.2 mmol) **3-9** and N-bromosuccinimide 48.0 g (271 mmol) was added to a flask. Methyl Ethyl Ketone 2.60 L was added to the reaction and stirred at room temperature overnight. The precipitate from the reaction was filtered and washed with cold methyl ethyl ketone, then cold water. The remaining solvent was removed via high-vacuum to give 61.5 g (43.3 mmol) of title compound **3-10.** LRMS calculated for $C_{72}H_{108}Br_4O_8$ 1416.48 found 1421.7

C-dodecyltetrabromorescorcin[4]arene [3-11] [13]

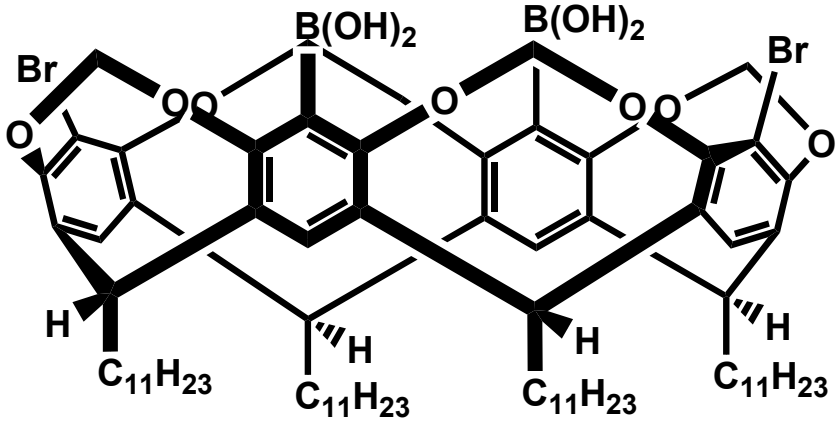


compound 3- 11

To a slurry of C-dodecyltetrabromocalix[4]resorinarene **3-10** (50.0 g, 35.0 mmol), potassium carbonate (68.0 g, 493 mmol), DMF 1350 mL and bromochloromethane (493 mmol, 33.0 mL) was added and the mixture was stirred at 65°C for three days under nitrogen. Every 24 hours more bromochloromethane (4.70 mL, 70.0 mmol) was added. The DMF was removed in vacuo to give a dark brown gum. Diethyl Ether was added to the residue followed by 2.00M HCl, with stirring. The aqueous phase was separated and extracted with more diethyl ether. The combined organic layers were washed with water and saturated brine, dried over magnesium sulfate and filtered. Evaporation of the solvent yielded a clear brown gum which was purified with column chromatography 9:1 hexane:ethyl acetate to produce the pure product as a light brown oil of the title compound **3-11**.[13] **70% Yield** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.89 (t, *J*=6.64 Hz, 12 H) 2.20 (d, *J*=7.81 Hz, 8 H) 4.33 (d, *J*=7.42 Hz, 4 H) 4.86 (t, *J*=8.00 Hz, 4 H) 5.98 (d, *J*=7.42 Hz, 4 H) 7.07 (s, 4 H); ^{13}C NMR

(101 MHz, $CDCl_3$) □ δ 14.3 , 22.9, 27.9, 29.6, 29.9, 30.3, 32.1, 38.1, 93.2, 98.9, 120.9, 138.9, 155.1, LRMS calculated for $C_{76}H_{108}Br_4O_8$ 1464.48 (M^+)1468.6 (M+Na)1486.7

A,C Bis-boronic acid- C,D-bis-bromo resocin[4]arene [3-12] [14]

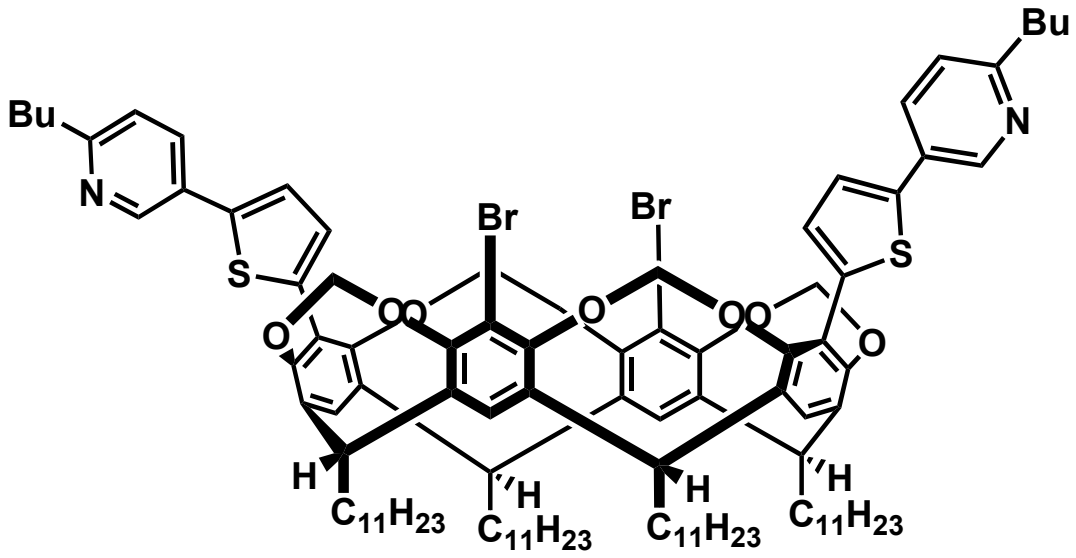


compound 3- 12

C-dodecyltetrabromorescorcin[4]arene **3-11** (4.10 g, 2.80 mmol) and dry THF (40.0 mL) was added to a sealed tube with a stir-bar. The resulting solution was evaporated to dryness and heated to 80°C for one hour. The vacuum was replaced with nitrogen and the procedure was repeated two more times. Dry THF (200 mL) was added to the dried tetrabromo cavitand. The reaction vessel was chilled to -78° C with a dry ice temperature bath and n-butyllithium (0.380 g, 3.70 mL of 1.60 M in hexanes, 2.1 eqiv.). After 20 minutes of stirring, triisopropyl borate (4.20 g, 22.0 mmol, 5.20 mL) was added to the reaction vessel at - 78° C. After stirring for 30 minutes, 2.50 M of HCL was added to the reaction vessel and allowed a stir for an additional 30 minutes. The reaction solution was transferred to a separtory funnel and methylene chloride and brine were added to the flask. The organic and aqueous layers were separated and the aqueous layer was washed a second time with methylene chloride. The organic layers were combined, dried with magnesium sulfate, filtered and concentrated. The resulting oil was purified by column chromatography with the product eluting with

50:50 hexane:ethyl acetate of the title compound **3-12** (1.82 g, 46% yield).[14] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.89 (none, *J*=6.64 Hz, 8 H) 1.36 (q, 99 H) 2.23 (q, *J*=7.81 Hz, 8 H) 4.45 (d, *J*=7.42 Hz, 4 H) 4.81 (s, 3 H) 5.60 (s, 4 H) 5.90 (d, *J*=7.42 Hz, 4 H) 7.06 (s, 2 H) 7.20 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.3, 22.9, 28.0, 29.6, 29.9, 30.3, 32.1, 37.4, 98.9, 113.3, 118.8, 123.4, 138.1, 139.2, 152.1, 158.6

A,C Bis-thiophene pyridine- C,D-bis-iodo resocin[4]arene [3-13]

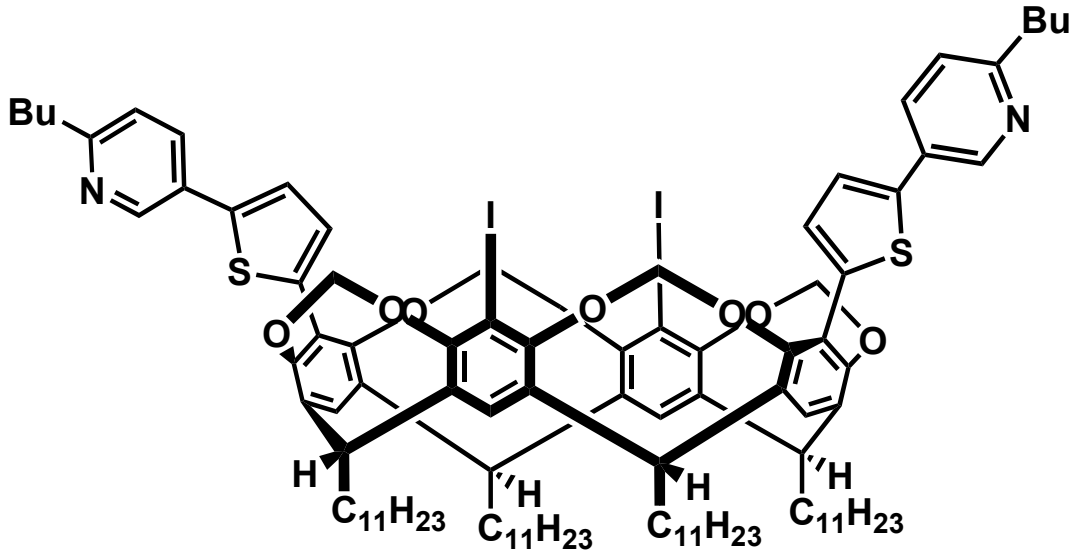


compound 3- 13

The A,C bis boronic acid cavitand **3-12** (1.00 g, 0.715 mmol), tetrakis(triphenylphosphine)palladium(0) (0.083 g, 0.071 mmol), 5-(5-bromo-2-thienyl)-2-butylpyridine(0.470 g, 2.14 mmol), 2.00 M sodium bicarbonate (1.50 ml) and toluene (4.00 ml) was placed in a sealed tube. The reaction vessel was de-gassed by freeze-pump-thaw three times and heated for eight hours at 70°C. The reaction vessel was allowed to reach room temperature and the contents were washed with a saturated sodium bicarbonate solution. Methylene chloride was added and the organic layer was washed with a brine solution. The organic

layer was dried with magnesium sulfate, filtered and concentrated to yield a light-brown residue. The product was isolated by column chromatography to yield the desired A,C-bis 5-(5-bromo-2-thienyl)-2-butylpyridine resorcin[4]arene as a light brown residue (0.810 g, 65% yield) of the title compound **3-13**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 1.23 - 1.51 (m, 80 H) 2.27 (d, *J*=3.90 Hz, 8 H) 4.42 (d, *J*=7.42 Hz, 4 H) 4.90 (t, *J*=8.00 Hz, 3 H) 5.85 (d, *J*=7.42 Hz, 4 H) 7.15 (s, 2 H) 7.19 (s, 1 H) 7.20 (d, *J*=3.90 Hz, 1 H) 7.33 (dd, *J*=5.08 Hz, 2 H) 7.36 (d, *J*=3.51 Hz, 2 H) 7.87 (dd, *J*=6.05, 2.15 Hz, 2 H) 8.54 (d, *J*=3.51 Hz, 2 H) 8.89 (d, *J*=1.95 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 22.7, 27.8, 29.4, 29.7, 30.2, 31.9, 37.4, 99.5, 113.2, 119.0, 120.4, 122.2, 122.7, 123.6, 127.2, 129.9, 133.1, 138.5, 139.1, 141.3, 146.2, 152.1 152.5 161.7 LRMS calculated for $C_{102}H_{136}Br_2N_2O_8S_2$ 1738.8 found (M+1)1742.9

A,C Bis-thiophene pyridine- C,D-bis-iodo resocin[4]arene[3-14]

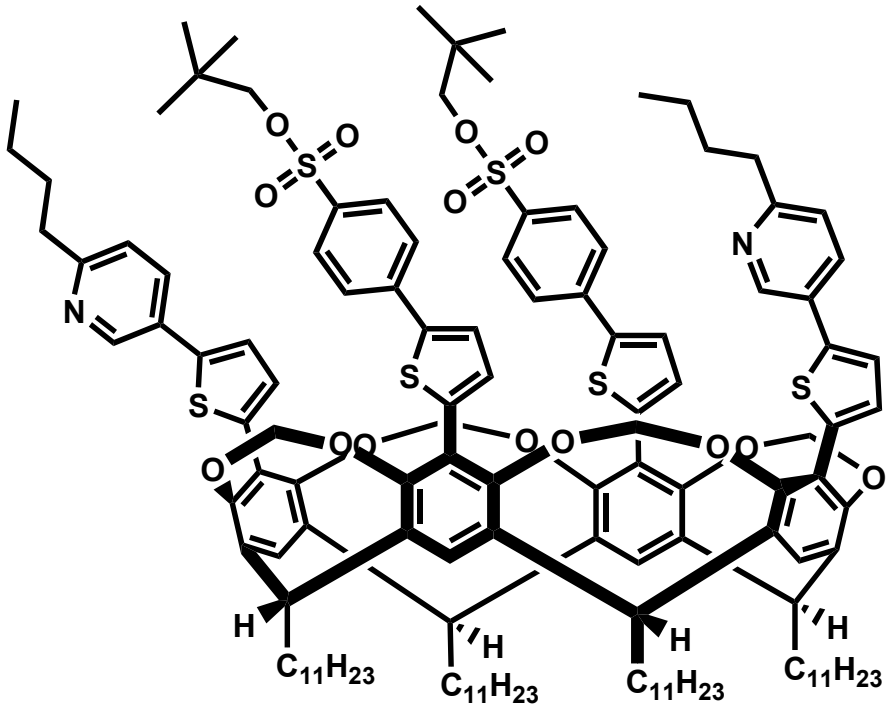


compound 3- 14

The A,C bis-thiophene pyridine with butyl groups bis-bromo cavitand **3-13** (0.330 g, 0.190 mmol) and 5.00 mL of dry diethyl ether was added into a sealable reaction vessel. The solvent was evaporated to dryness and the remaining

residue was heated with an oil bath under high vacuum at 80°C for one hour. This step was repeated twice. After drying, the substrate was suitable for metal halogen exchange. 20.0 mL of dry diethyl ether was added. After chilling to -78^{o}C, (0.590 mL, 0.950 mmol) of n-butyl lithium 1.6 M in hexanes was added rapidly to the solution. The reaction immediately turned a reddish color and was allowed to stir for 10 minutes. Diiodoethane (0.375 g, 1.33 mmol) was added to the reaction vessel and immediately the solution turned dark brown. 20.0 mL of 2.00 M sodoium thiosulfate solution was added and extracted with a 25.0 mL portion of methylene chloride. The aqueous and organic were separated and the organic layer was washed with brine, dried with magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography with the desired product eluting with a gradient from 99:1 hexane:ethyl acetate to 3:1 hexane:ethyl acetate, yielding a clear residue (0.230 g, 65% yield) of the title compound **3-14** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.88 (t, *J*=6.64 Hz, 12 H) 0.95 (t, *J*=7.42 Hz, 6 H) 1.24 - 1.50 (m, 98 H) 1.67 - 1.79 (m, *J*=7.42 Hz, 5 H) 2.26 (d, *J*=2.73 Hz, 8 H) 2.78 - 2.84 (m, *J*=7.81 Hz, 4 H) 4.36 (d, *J*=7.03 Hz, 4 H) 4.89 (t, *J*=8.20 Hz, 4 H) 5.85 (d, *J*=7.42 Hz, 4 H) 7.17 (s, 5 H) 7.19 (d, *J*=3.51 Hz, 2 H) 7.30 (d, *J*=3.51 Hz, 1 H) 7.77 (dd, *J*=8.20, 2.34 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 13.9, 14.1, 22.4, 22.7, 27.8, 29.4, 29.6 - 29.9, 30.3, 31.9, 37.5, 37.77, 92.8, 99.5, 120.3, 120.7, 122.1, 122.7, 123.6, 127.3, 130.0, 133.1, 133.2, 138.5, 138.6, 141.3, 146.2, 152.4, 155.0, 161.8, LRMS calculated for $C_{102}H_{136}I_2N_2O_8S_2$ 1834.8 found (M+H) 1840

A,C Bis-Thiophene pyridine-C,D Bis-thiophene dimethylpropylbenzenesulfonate[3-15]

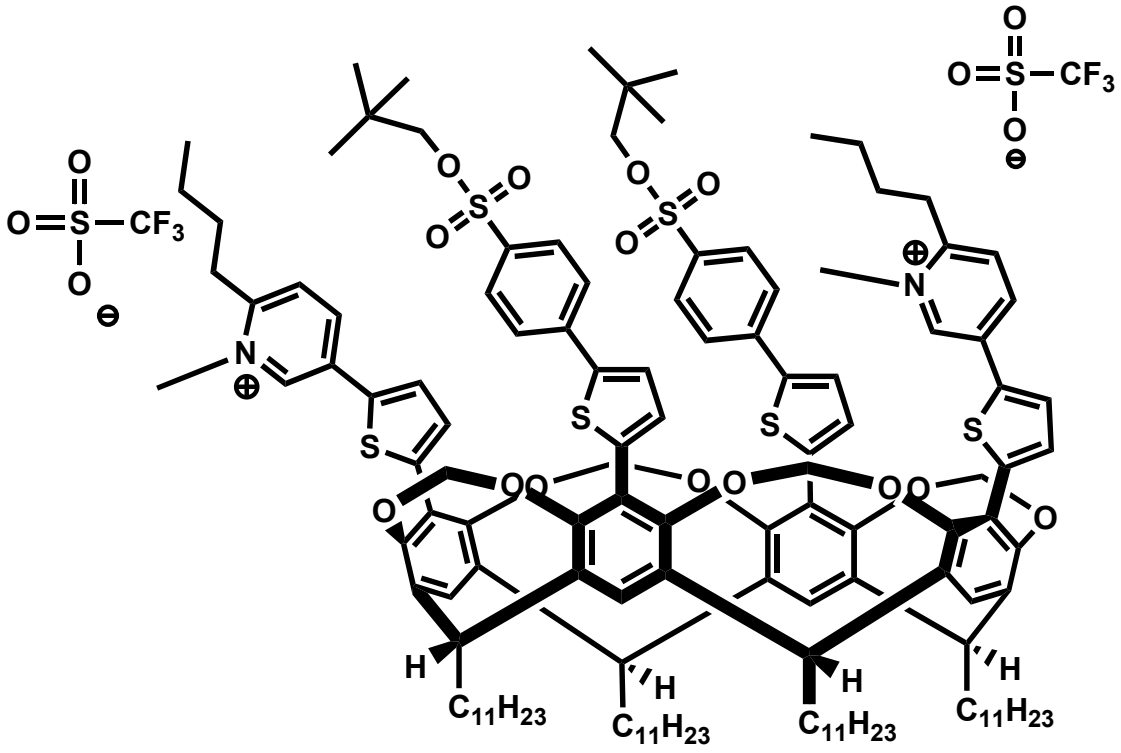


compound 3- 15

The bis-pyridine bis iodo cavitand **3-14** (0.090 g, 0.050 mmol) was transferred to a sealable reaction vessel. The dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **3-5** (0.060 g, 0.150 mmol) was pre-weighed into a vial and both reaction vessels were taken into a glove box. In a cold well inside a glove box, a solution of compound A in 2.00 mL of dry THF was treated with n-butyl lithium (0.100 mL, 0.160 mmol) at -55^{o}C. After 5 minutes of stirring, 0.060 g (0.41 mmol) of zinc chloride solution was added to the reaction vessel and allowed to stir for five minutes. The solution was transferred into the scklenk-flask and (0.009 g, 0.008 mmol) of tetrakis(triphenylphosphine)palladium was added to the reaction vessel. The vessel was taken outside of the glove box and heated to 70° C for eight hours. The reaction was quenched with 2.00M HCl and extracted with 20.0 mL of methylene chloride. The organic and aqueous layers were separated and the organic layer was washed with brine, dried with

magnesium sulfate, filtered and concentrated. The crude oil was purified via column chromatography with a gradient from 99:1 hexane:ethyl acetate to 2:1 hexane: ethyl acetate to produce the desired product as a clear oily residue (0.050 g, 52% yield) of the title compound **3-15**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.85 - 0.97 (m, 36 H) 1.23 - 1.53 (m, 90 H) 1.65 - 1.74 (m, *J*=7.61, 7.61 Hz, 4 H) 2.28 - 2.37 (m, *J*=5.86 Hz, 8 H) 2.78 (t, *J*=7.81 Hz, 4 H) 3.68 (s, 4 H) 4.42 (d, *J*=7.03 Hz, 4 H) 4.94 (t, *J*=7.81 Hz, 4 H) 5.81 (d, *J*=7.42 Hz, 4 H) 7.15 (d, *J*=8.20 Hz, 2 H) 7.23 - 7.25 (m, 3 H) 7.27 - 7.30 (m, 5 H) 7.39 (d, *J*=3.90 Hz, 2 H) 7.71 (d, 4 H) 7.75 (d, *J*=2.34 Hz, 2 H) 7.87 (d, *J*=8.59 Hz, 4 H) 8.73 (d, *J*=2.34 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 14.3, 22.6, 22.9, 26.0 - 26.5, 28.1, 29.6, 29.8 - 30.2, 30.8, 31.9, 32.1, 32.2, 37.4, 37.9, 79.9, 100.5, 120.5, 120.7, 121.6, 121.9, 123.0, 123.8, 125.3, 126.2, 127.5, 128.8, 130.3, 130.5, 133.3, 133.4, 134.5, 135.4, 138.7, 138.8, 139.3, 141.3, 142.3, 146.4, 152.5, 152.6, 162.1, LRMS calculated for $C_{132}H_{170}N_2O_{14}S_6$ 2199.1 found (M+H) 2201.3 (M+Na) 2223.3

A,C Bis-Thiophene pyridinium triflate-C,D Bis-thiophene dimethylpropylbenzenesulfonate resorcin[4]arene[3-16]

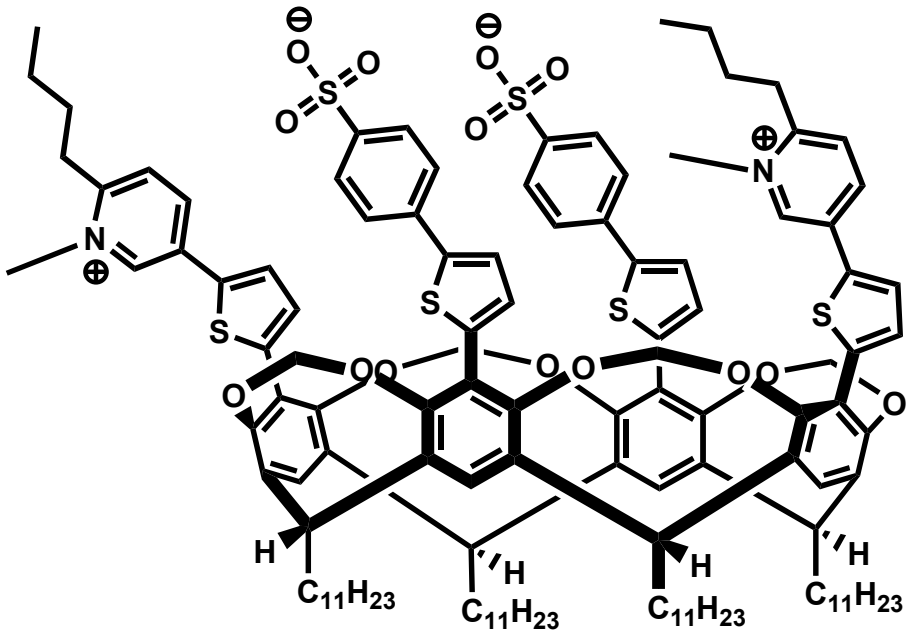


compound 3- 16

0.051 g (0.023 mmol) of the tetrafuctionalized resorcin[4]arene **3-15**, 0.019 g (0.116 mmol) of methyl triflate, and 1.00 mL of dry chloroform was transferred into a sealable reaction container. A drop of N-ethyldiisopropylamine was added to the solution. The reaction was allowed to stir overnight at room temperature. The solvent and excess methyl triflate was removed via high vacuum. The crude was purified via column chromatography 92:8 chloroform:methanol to produce 0.032 g (55% yield) of the title compound **3-16** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.85 - 0.87 (m, 9 H) 0.87 - 0.92 (m, 24 H) 0.94 (t, 6 H) 1.25 - 1.51 (m, 90 H) 1.67 - 1.75 (m, 4 H) 2.28 - 2.37 (m, *J*=6.64 Hz, 8 H) 2.95 - 3.01 (m, 4 H) 3.61 - 3.66 (m, 4 H) 4.35 - 4.38 (m, 6 H) 4.41 (d, *J*=7.42 Hz, 4 H) 4.93 (t, *J*=7.81 Hz, 4 H) 5.78 (d, *J*=7.03 Hz, 4 H) 7.25 (d, *J*=3.51 Hz, 2 H) 7.28 (s, 2 H) 7.30 - 7.34 (m, *J*=3.90 Hz, 4 H) 7.43 (d, *J*=3.90 Hz, 2 H) 7.64 (d, *J*=3.51 Hz, 2 H) 7.68 (d, *J*=8.59

Hz, 2 H) 7.72 (t, *J*=8.00 Hz, 4 H) 7.79 - 7.85 (m, 4 H) 8.27 - 8.36 (m, 1 H) 9.13 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 13.5, 14.1, 22.2, 22.7, 25.9, 28.0, 29.2, 29.4, 29.6 - 30.0, 30.6, 31.6, 31.9 , 32.2 , 37.2, 45.9, 79.8, 100.2, 118.6, 120.3, 120.9, 121.6, 121.8, 125.6, 125.9, 127.8, 128.0, 128.5, 130.5, 131.0, 132.9, 133.6, 134.8, 135.0, 137.4, 138.3, 138.4, 139.4, 140.4, 141.9, 142.7, 152.4, 152.5, 156.0, LRMS calculated for $C_{134}H_{176}N_2O_{14}S_6$ 2199.1 found (M+1) 2229.4

A,C Bis-Thiophene pyridinium C,D Bis-thiophene-benzenesulfonate resorcin[4]arene[3-17]

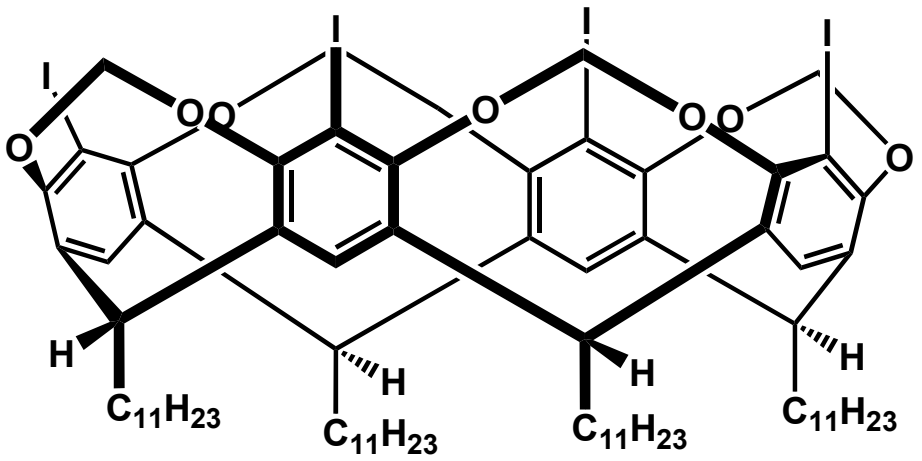


compound 3- 17

A,C Bis-Thiophene pyridinium triflate-C,D Bis-thiophene dimethylpropylbenzenesulfonate resorcin[4]arene**[3-16]** was placed in a schlenck flask with LiCl, and DMF. The reaction was degassed and refilled with nitrogen. After heating for 16 hours at 130^{o}C, the reaction was allowed to reach room temperature. The solvent was removed under high-vacuum and the remaining residue was dissolved in methylene chloride. After concentrating the methylene chloride, the residue was recystallized with methanol to produce the title compound **3-17**. 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (t, *J*=3.51 Hz, 12 H) 0.97 (t, *J*=7.22 Hz, 6 H) 1.20 - 1.53 (m, 97 H) 1.64 - 1.75 (m, 8 H) 3.02 - 3.12 (m, *J*=7.42 Hz, 4 H) 4.27 - 4.32 (m, 6 H) 4.37 (d, *J*=6.64 Hz, 4 H) 4.83 (d, *J*=6.64 Hz, 4 H) 6.02 (d, *J*=7.03 Hz, 4 H) 7.24 (d, *J*=3.90 Hz, 2 H) 7.30 (d, *J*=3.90 Hz, 1 H) 7.41 (d, *J*=3.12 Hz, 1 H) 7.49 (d, *J*=3.90 Hz, 1 H) 7.57 (d, 2 H) 7.77 (d, *J*=3.90 Hz, 2 H) 7.87 (m, 4 H) 8.04 (d, *J*=8.98 Hz, 4 H) 8.73 (d, *J*=8.20 Hz, 2 H) 99.32

(s, 2 H) Concentration in DMSO-d_6 was too low to record ^{13}C within 1d LRMS calc for $C_{124}H_{154}N_2O_{14}S_6$ 2088.9 found (M+) 2090.2 (M+Na) 211.2.1

Tetraiodo resorcin[4]arene [3-18]

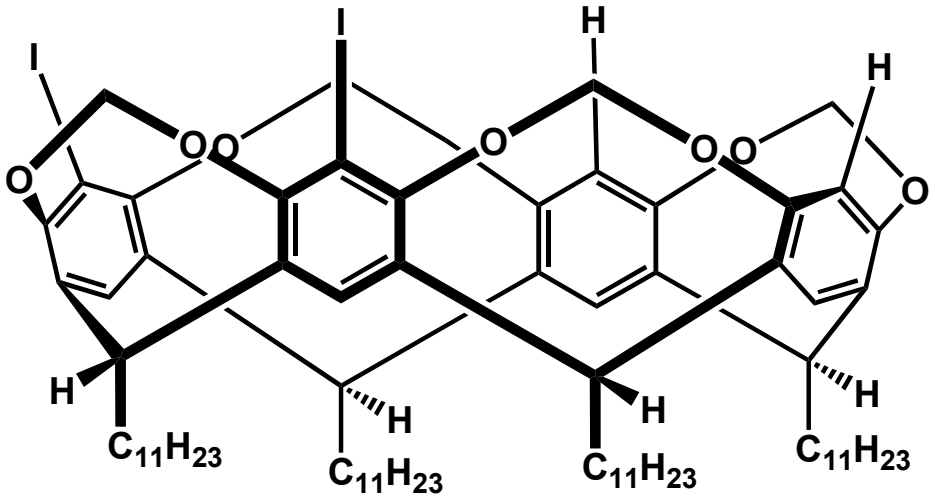


compound 3- 18

Tetrabromo cavitand **3-11** (0.250 g, 0.170 mmol) was transferred to a schlenk flask. 2.00 ml of dry THF was added to vessel and evaporated to dryness. The resulting residue was heated to 80^oC for one hour under high vacuum. This step was repeated twice. This provided suitable conditions for metal-halogen exchange. 5.00 mL of dry THF was added to the reaction vessel. After chilling to -78^oC, 0.530 mL (0.850 mmol) of 1.6 M n-butyl lithium in hexanes was added rapidly to the flask. The reaction was allowed to stir for 30 minutes at -78 ^oC and 0.259 g (1.02 mmol) of iodine was added to the reaction at -78 ^oC. The contents were stirred for 10 minutes and the reaction was quenched with 15.0 mL of 2.00 M sodium thiosulfate. The product was extracted with 25.0 mL of methylene chloride and the layers were separated. The organic layer was washed with saturated brine, dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography with a gradient from 99:1

hexane:ethyl acetate to 9:1 hexane:ethyl acetate to yield tetraiodo cavitand as a light-brown residue of the title compound **3-18** (0.140 g, 50% yield) ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.89 (t, *J*=6.64 Hz, 12 H) 2.20 (d, *J*=7.81 Hz, 8 H) 4.33 (d, *J*=7.42 Hz, 4 H) 4.86 (t, *J*=8.00 Hz, 4 H) 5.98 (d, *J*=7.42 Hz, 4 H) 7.07 (s, 4 H) ^{13}C NMR (101 MHz, CDCl3) □ δ 14.3 , 22.9, 27.9, 29.6, 29.9, 30.3, 32.1, 38.1, 93.2, 98.9, 120.9, 138.9, 155.1

A,B-bis-iodo-C,D-bis-hydrogen resorcin[4]arene [3-19][15]

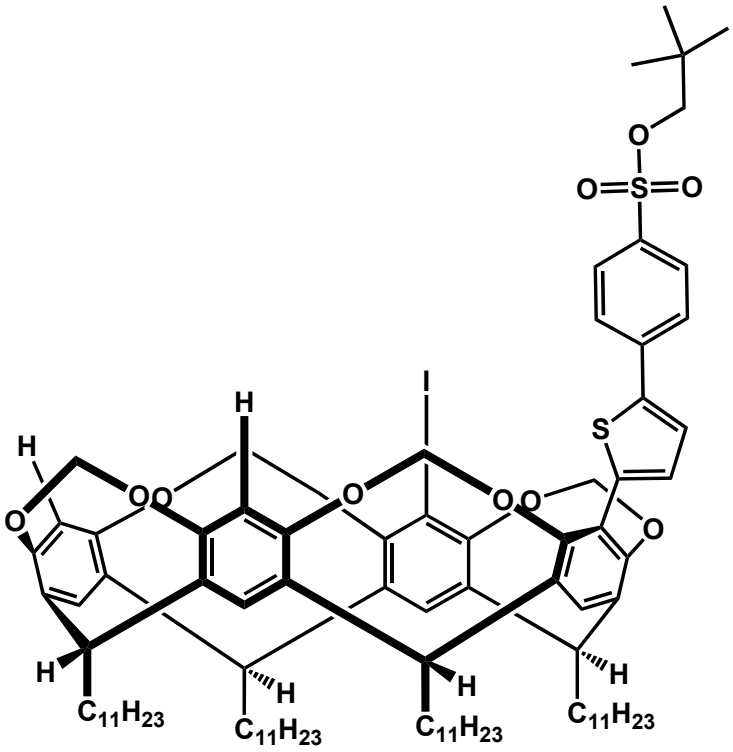


compound 3- 19

Tetraiodo cavitand **3-18** (1.32 g, 0.796 mmol) was placed into a sealable reaction vessel and 10.0 mL of dry THF was added. The THF was evaporated to dryness and heated to 80° C for one hour. This step was repeated twice. 50.0 mL of dry THF was added. After chilling to -78°C, 0.550 mL (0.880 mmol) of 1.6 M. n-butyl lithium in hexane was added rapidly and the reaction was stirred vigorously. After 30 minutes, 0.067 mL (0.876 mmol) methanol was added at -78° C and the solution was stirred for an additional 30 minutes. 0.550 mL (0.880 mmol) of 1.60 M n-butyl lithium in hexane was added rapidly and the reaction was stirred vigorously. After 30 minutes, an excess of isopropanol was added to the reaction

solution. The temperature was allowed to warm up room temperature and the solvent was removed via a rotatory evaporator. The remaining residue was dissolved in diethyl ether and washed with brine. The layers were separated and the organic layer was dried with magnesium sulfate, filtered and concentrated. The resulting crude product was purified via column chromatography with a gradient from 99:1 hexane:ethyl acetate to 92:8 hexane:ethyl acetate yielding a mixture of A,B and A,C bis-iodo-bis-hydrogen. The A,B and A,C isomers were resolved by repeating the column with the same gradient from 99:1 hexane: ethyl acetate to 92:8 hexane:ethyl acetate to produce the A,B bisiodocavitand as an oily residue of the title compound **3-19** (0.168 g, 15% yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.88 (t, *J*=6.83 Hz, 12 H) 1.15 - 1.50 (m, 72 H) 2.21 (q, *J*=7.03 Hz, 8 H) 4.29 (d, *J*=7.42 Hz, 1 H) 4.37 (d, *J*=7.42 Hz, 2 H) 4.46 (d, *J*=7.03 Hz, 1 H) 4.65 - 4.90 (m, 4 H) 5.74 (d, *J*=7.42 Hz, 1 H) 5.85 (d, 1 H) 5.97 (d, *J*=7.42 Hz, 1 H) 6.51 (s, 2 H) 7.08 (s, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.3, 22.9, 27.78 - 28.2, 29.6, 29.7 - 30.4, 32.1, 36.5, 37.3, 38.1, 93.0, 99.0, 99.3, 99.6, 116.9, 120.8, 120.9, 138.2, 138.9, 139.3, 154.8 154.9, 155.2, LRMS calculated for $C_{76}H_{110}I_2O_8$ 1404.6 found (M+H) 1405.9 (M+H_2O) 1422.9

Mono- thiophene-dimethylpropylbenzenesulfonate-mono-iodo-bishydrogen resocin[4]arene[3-20]

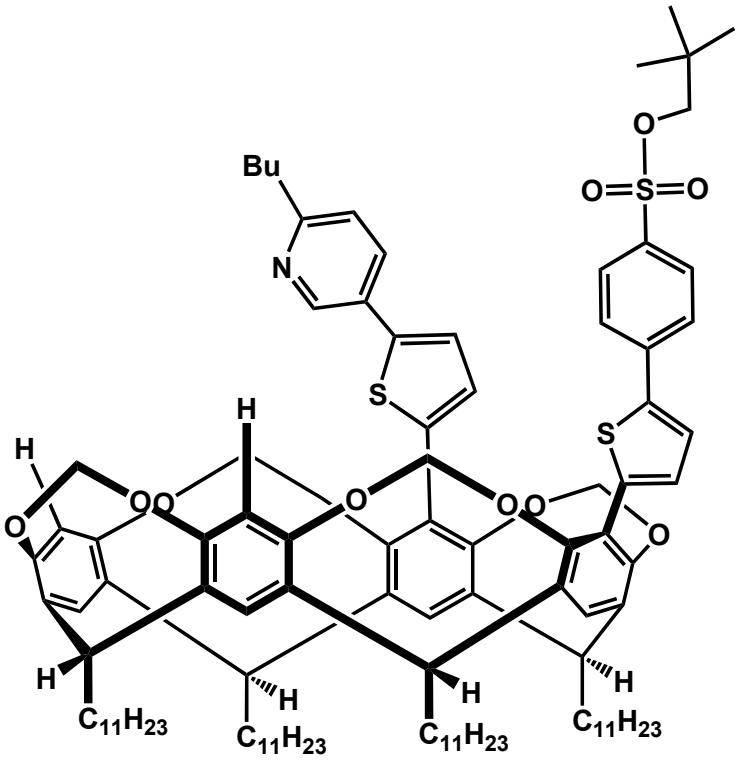


compound 3- 20

A,B bis iodo bis-hydrogen cavitand **3-19** (0.322 g, 0.229 mmol) was transferred to a sealable reaction container. 0.103 g (0.275 mmol) of dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate was weighed into a vial. Both containers were taken inside of a glove box and 3 mL of dry THF was added to the vial. After chilling to -78°C, (0.200 mL, 0.320 mmol) n-butyl lithium 1.6 M in hexanes was added rapidly. After 5 minutes of stirring, (0.156 g, 0.115 mmol) zinc chloride dissolved in 1.00 mL of dry THF was added to the reaction vessel. The zinc species was transferred to the sealable reaction vessel and (0.026 g, 0.023 mmol) tetrakis(triphenylphosphine)palladium(0) was added. The reaction container was taken out of the glove box and heated for 10 hours at 70°C. The reaction was allowed to reach room temperature and 15.0 mL of methylene chloride was added. The product was extracted with 10.0 mL of saturated brine

solution and the layers were separated. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography with a gradient from 99:1 hexane:ethyl acetate to 4:1 hexane:ethyl acetate as a clear oily residue of the title compound **3-20(0**.100 g, 28% yield) ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.82 - 0.98 (m, *J*=6.64 Hz, 21 H) 1.15 - 1.52 (m, 70 H) 2.15 - 2.34 (m, 8 H) 3.66 - 3.76 (m, 2 H) 4.35 (dd, *J*=11.52, 7.22 Hz, 1 H) 4.45 (dd, *J*=7.22, 3.71 Hz, 1 H) 4.69 - 4.90 (m, *J*=8.20, 8.20 Hz, 3 H) 5.74 (dd, *J*=15.23, 7.03 Hz, 1 H) 5.85 (dd, *J*=16.59, 7.22 Hz, 1 H) 6.50 (s, 1 H) 6.52 (s, 1 H) 7.12 - 7.16 (m, 2 H) 7.21 (d, *J*=3.90 Hz, 1 H) 7.43 (d, *J*=3.90 Hz, 1 H) 7.74 (d, *J*=8.20 Hz, 1 H) 7.90 (d, *J*=8.59 Hz, 1 H) ^{13}C NMR (101 MHz, $CDCl_3$) d δ 14.1, 22.7, 26.0, 27.8, 27.9, 29.4, 29.7, 29.9, 30.0, 30.1, 30.2, 31.7, 31.9, 36.3, 36.7, 37.2, 37.5, 79.7, 92.6, 99.2, 99.5, 99.5, 99.8, 116.5, 120.6, 120.7, 120.8, 121.6, 125.1, 125.8, 128.6, 130.2, 134.1, 135.4, 137.8, 138.1, 138.4, 138.6, 138.7, 138.9, 139.1, 139.2, 142.0, 152.2, 152.7, 154.8, 154.9, 155.0, 155.1

A,B-Mono- thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridine-bishydrogen resocin[4]arene[3-21]

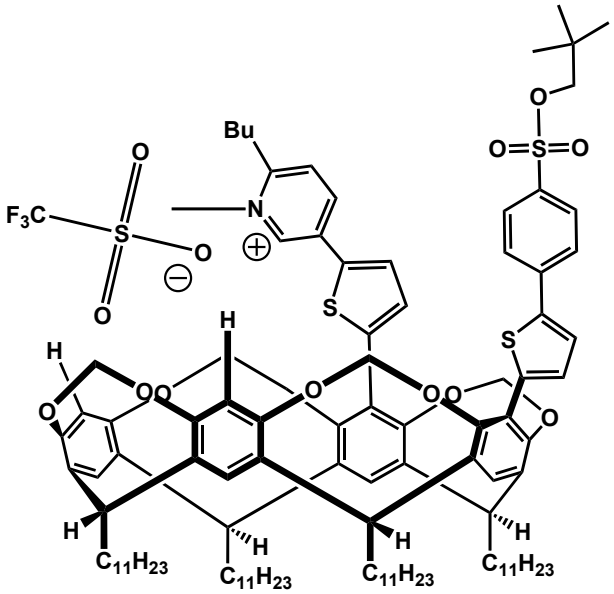


compound 3- 21

3-20 (0.100 g, 0.063 mmol) of mono dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate cavitand was placed into a sealable reaction vessel. 5-(5-bromo-2-thienyl)-2-butylpyridine (0.056 g, 0.189 mmol) was placed into a vial and both containers were brought into the glove box. 1.00 mL of dry THF was added to the thiophene and the solution was chilled to -78° C. Then, (0.120 mL, 0.200 mmol) 1.6 M n-butyl lithium in hexanes was added rapidly. After 5 minutes, (0.068 g, 0.504 mmol) zinc chloride was dissolved in 1.00 mL of dry THF was transferred to the thiophene solution. The zinc species and (0.007 g .006mmol) tetrakis(triphenylphosphine)palladium(0) was added to the sealable reaction vessel. The reaction vessel was taken out of the glove box and heated to 70°C for 8 hours. The reaction was allowed to reach room temperature and

15.0 mL of methylene chloride was added to quench the reaction. The methylene chloride was washed with 15.0 mL of brine. The layers were separated and the organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was isolated via column chromatography with a gradient from 99:1 hexane:ethyl acetate to 75:25 hexane:ethyl acetate to produce A,B sulfonate,pyridine cavitand **3-21** as an oily residue (0.070 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.85 - 0.98 (m, 25 H) 1.21 - 1.49 (m, 72 H) 1.67 - 1.75 (m, 2 H) 2.22 - 2.33 (m, 8 H) 2.79 (t, *J*=7.42 Hz, 2 H) 3.69 (s, 2 H) 4.37 (d, *J*=7.03 Hz, 1 H) 4.40 - 4.49 (m, *J*=7.03, 7.03 Hz, 3 H) 4.73 - 4.93 (m, *J*=8.20, 8.20 Hz, 4 H) 5.68 - 5.81 (m, *J*=7.03, 7.03, 7.03 Hz, 4 H) 6.51 (s, 1 H) 6.51 (s, 1 H) 7.16 (d, *J*=7.81 Hz, 1 H) 7.18 - 7.22 (m, *J*=4.29, 4.29 Hz, 5 H) 7.24 (d, *J*=3.90 Hz, 1 H) 7.40 (d, *J*=3.90 Hz, 1 H) 7.72 (d, *J*=8.59 Hz, 2 H) 7.74 - 7.77 (m, *J*=2.34 Hz, 1 H) 7.88 (d, *J*=8.59 Hz, 2 H) 8.73 (d, *J*=1.95 Hz, 1 H); ^{13}C NMR (101 MHz, CDCl3) □ δ 14.1, 14.3, 22.6, 22.7, 22.9, 26.2, 28.1, 29.6, 29.7 - 30.2, 30.4, 30.7, 31.9, 32.2, 36.6, 36.9, 37.3, 38.0, 38.0, 79.9, 99.8, 100.1, 100.2, 116.5, 116.6, 120.5, 120.7, 120.9, 121.6, 121.9, 122.9, 123.7, 124.6, 125.0, 125.3, 126.0, 127.5, 128.9, 130.1, 130.4, 133.2, 133.6, 134.4, 135.6, 137.2, 138.3, 138.4, 138.6, 138.8, 138.9, 139.0, 139.4, 139.9, 141.1, 142.1, 146.3, 146.4, 152.5, 152.6, 152.7, 155.0, 155.1, 155.2, 161.9

A,B-Mono-thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridinium-triflate-bishydrogen resorcin[4]arene[3-22]

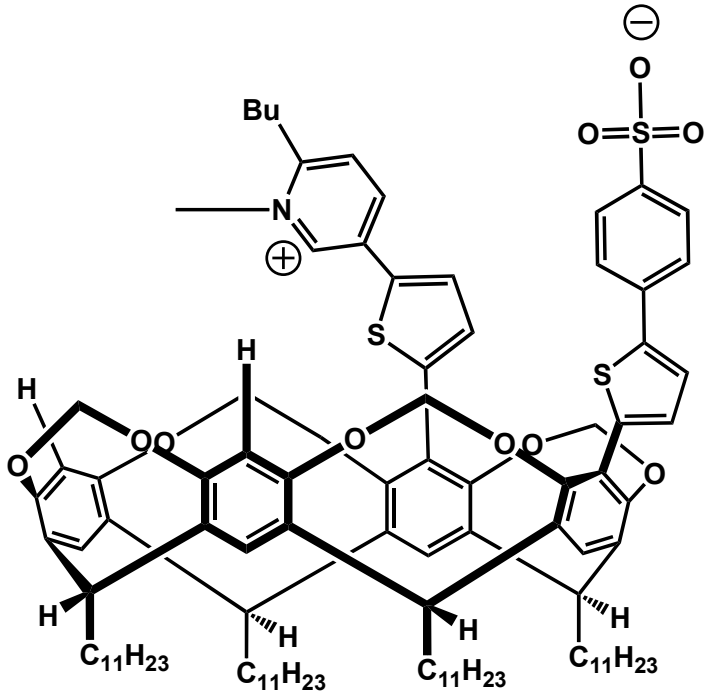


compound 3- 22

(0.071 g 0.023 mmol) A,B sulfonate,pyridine cavitand, **3-21** (0.014 g, 0.116 mmol) methyl triflate, and 1.00 mL of dry chloroform was transferred to a sealable reaction container. The reaction was allowed to stir overnight at room temperature. The solvent and excess methyl triflate was removed via high vacuum. The remaining residue was extracted with 5.00 mL of hexane, which was decanted off to yield A,B sulfonate, methyl pyridinum cavitand as the desired product as an oily light brown residue. By NMR the reaction showed 100% conversion from starting materials to products. Purification by column chromatography 95:5 chloroform : methanol produced 0.030 g (37% yield) of the title compound **3-22**.^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.98 (t, *J*=7.42 Hz, 4 H) 1.18 - 1.53 (m, 50 H) 1.68 - 1.79 (m, *J*=8.20 Hz, 2 H) 2.12 - 2.48 (m, 8 H) 2.95 - 3.02 (m, *J*=7.81 Hz, 2 H) 3.67 (s, 2 H) 4.34 (d, *J*=7.42 Hz, 1 H) 4.43 - 4.51 (m, *J*=7.03 Hz, 3 H) 4.74 - 4.92 (m, *J*=7.81, 7.81, 7.81 Hz, 4 H) 5.67 (d, *J*=7.42 Hz, 1 H) 5.72 - 5.81 (m, *J*=7.42, 7.42, 7.42 Hz, 3 H) 6.50 (s, 1 H) 6.56 (s, 1 H) 7.15 - 7.24 (m, 5 H) 7.40 (d, *J*=3.51 Hz, 1 H) 7.66 (d, *J*=4.29 Hz, 1 H) 7.71 (d, *J*=8.59 Hz, 2 H)

7.85 (d, *J*=8.20 Hz, 2 H) 8.33 (d, *J*=7.81 Hz, 1 H) 9.23 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 13.6, 14.1, 22.3, 22.7, 26.0, 27.9, 28.0, 29.3, 29.4, 29.6 - 30.0, 30.0 - 30.3, 30.4, 31.6, 31.9, 32.3, 36.4, 36.7 - 36.8 (m, *J*=4.42 Hz, 2) 37.1, 45.9 , 79.8, 99.6, 99.8, 99.9, 100.4, 116.6, 120.4, 120.5, 120.8, 121.0, 121.6, 125.3, 125.8, 127.9, 128.5, 130.3, 130.8, 133.0, 133.9, 134.7, 135.4, 137.7, 137.9, 138.0, 138.3, 138.5, 138.6, 138.9, 139.3, 140.2, 141.8, 142.9, 152.3, 152.4, 152.6, 154.7, 154.9, 155.1, 155.8

A,B-Mono-thiophene-benzenesulfonate-mono-thiophene-pyridinium-triflate-bishydrogen resocin[4]arene[3-22][6]

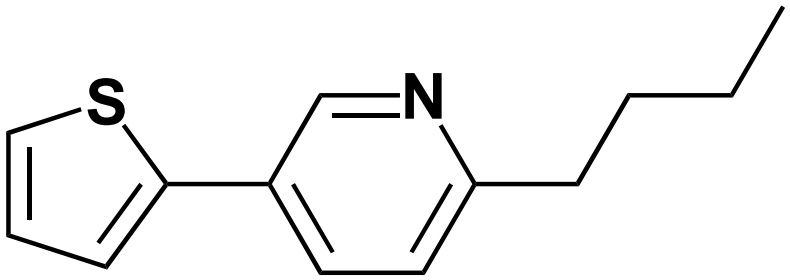


Compound 3-22

The A,B sulfonate, methyl pyridinum cavitand **3-21** (0.085 g, 0.046 mmol), (.015 g 0.138 mmol) tetramethylammonium chloride and 1.00 mL DMF was transferred to a sealable reaction container. The flask was evacuated then purged with nitrogen. The reaction was heated for 24 hours at 150°C. After cooling to room temperature, the reaction solution was evaporated to dryness via high vacuum. 15.0 mL of methylene chloride was added and washed with saturated brine solution. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was purified via column chromatography with a gradient from 100% chloroform to 85:15 chloroform:methanol yielding the deprotected A,B sulfonate, methyl pyridinum cavitand as an oily residue of the title compound **3-22** (0.040 g, 52% yield) .^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.86 - 0.93 (m, 15 H) 1.24 - 1.48 (m, 72 H) 1.64 - 1.74 (m, 2 H) 2.29 (s, 8 H) 2.78 (t,

J=7.42 Hz, 2 H) 4.36 (d, *J*=7.03 Hz, 1 H) 4.46 (d, *J*=7.03 Hz, 3 H) 4.72 - 4.92 (m, *J*=7.81 Hz, 4 H) 5.69 - 5.80 (m, 4 H) 6.50 (s, 1 H) 6.50 (s, 1 H) 7.12 - 7.20 (m, 4 H) 7.21 - 7.29 (m, 6 H) 7.34 - 7.43 (m, 1 H) 7.54 (d, *J*=7.81 Hz, 2 H) 7.75 (d, *J*=9.37 Hz, 1 H) 7.94 (d, *J*=7.81 Hz, 2 H) 8.73 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) □ δ 13.7 - 13.7, 13.7 - 13.9, 21.6 - 21.8, 21.9 - 22.2, 27.5 - 27.8, 28.7 - 28.8, 29.1, 29.3, 29.6, 31.2, 31.3, 36.2, 36.7, 36.8 - 37.3, 98.9, 99.3, 99.6, 116.2, 121.4, 121, 121.5, 121.7, 122.3, 122.6, 123.4, 123.8, 124.5, 126.2, 126.9, 130.0, 132.8, 132.9, 133.1, 133.6, 137.9, 138.0, 138.4, 140.2, 143.2, 145.2, 146.9, 151.6, 151.7, 154.1, 160.6

2-butyl-5-(2-thienyl)pyridine [3-23]

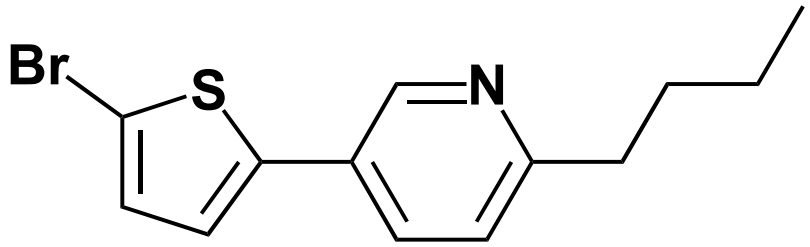


compound 3- 23

3-1 (0.400 g, 2.48 mmol) and 6.00 mL of dry THF was placed in a schlenck flask. The vessel was chilled to -78^{o}C and (0.400 g, 6.2 mmol, 3.9 mL) n-butyl lithium was added to the reaction vessel. The solution was allowed to warm to 0^{o}C then to room temperature and then monitoring by TLC for disappearance of starting material 4:1 hexane:ethyl acetate. 5.00 mL of H_2O was added to the reaction vessel and the solution was extracted with DCM. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude was purified via column chromatography with 4:1 hexane:ethyl acetate to get 0.230 g (1.0 mmol, 43% yield) of the title compound **3-23**.^{1}H NMR (400 MHz, $CDCl_3$) d δ 0.953 (t, *J*=7.42 Hz, 3 H) 1.35 - 1.46 (m, *J*=15.23, 7.42 Hz, 2 H) 1.68 - 1.79 (m, *J*=7.42 Hz, 2 H) 2.81 (t, *J*=7.81 Hz, 2 H) 7.11 (dd, *J*=3.90 Hz, 1 H) 7.157 (d, *J*=8.20 Hz, 1 H) 7.30 - 7.34 (m, 2 H) 7.31 - 7.33 (m, *J*=2.73 Hz, 1 H) 7.33 - 7.33 (m, *J*=1.17 Hz, 1

H) 7.77 (dd, *J*=8.00, 2.54 Hz, 1 H) 8.78 (d, *J*=2.34 Hz, 1 H); ^{13}C NMR (101 MHz, CDCl3) d δ 13.9, 22.5, 32.0, 37.8, 122.6, 123.6, 125.4, 127.7, 128.1, 133.5, 140.8, 146.4, 161.5

5-(5-bromo-2-thienyl)-2-butylpyridine [3-24][5]



compound 3- 24

The reaction vessel was wrapped in foil to prevent exposure to light. 2-butyl-5-(2-thienyl)pyridine **[3-23]** (0.200 g, 0.920 mmol) was dissolved in DCM (4.00 mL). A solution of bromine (0.191 g, 0.060 mL, 1.2 mmol) in DCM (1.40 mL) was added dropwise over 30 min. The reaction was stirred at ambient temperature for 2 hrs. A 1.00 M aqueous solution of sodium carbonate (5.00 mL) was added and the mixture was stirred. The layers were separated and the aqueous phase was extracted with additional dichloromethane (15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give 0.200 g (76% yield) of the title compound **3-24.** ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.88 - 1.03 (m, *J*=7.42 Hz, 3 H) 1.32 - 1.49 (m, *J*=7.42 Hz, 2 H) 1.63 - 1.80 (m, *J*=7.42 Hz, 2 H) 2.82 (t, *J*=7.81 Hz, 2 H) 7.06 (s, 2 H) 7.18 (d, *J*=8.20 Hz, 1 H) 7.71 (d, *J*=8.20 Hz, 1 H) 8.70 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 22.6, 32.1, 37.9, 122.7, 123.8, 125.5, 127.8, 128.3, 133.6, 140.9, 146.5, 161.7

References

1. Cram D., K. S., Kim, H., Knobler, C., Maverick, E., Ericson, J., and Helgeson, R., Host-guest complexation. 46. Cavitands as open molecular vessels form solvates. *Journal of American Chemical Society* **1988,** 110, 2229-2237.
2. John R. Moran, S. K., and Donald J. Cram, Cavitands: synthetic molecular vessels. *JACS* **1982,** 104, (21), 5826-5828.
3. Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Intramolecular hydrogen bonding controls the exchange rates of guests in a cavitand. *Journal of the American Chemical Society* **1997,** 119, (41), 9911-9912.
4. Mezo, A. S., J., Water-Soluble Cavitands: Synthesis of Methylene-Bridged Resorcin[4]arene Containing Hydroxyls and Phosphate at Their Feet and Bromomethyls and Thiomethyls at Their Rims. *J. Org. Chem. FIELD Full Journal Title:Journal of Organic Chemistry* **1998,** 63, 6824-6829.
5. Burger, M. T.; Lin, X. D.; Chu, D. T.; Hiebert, C.; Rico, A. C.; Seid, M.; Carroll, G. L.; Barker, L.; Huh, K.; Langhorne, M.; Shawar, R.; Kidney, J.; Young, K.; Anderson, S.; Desai, M. C.; Plattner, J. J., Synthesis and antibacterial activity of novel C-12 vinyl ketolides. *Journal of Medicinal Chemistry* **2006,** 49, (5), 1730-1743.
6. Roberts, J. C.; Gao, H.; Gopalsamy, A.; Kongsjahju, A.; Patch, R. J., Neopentyl ester protecting groups for arylsulfonic acids. *Tetrahedron Letters* **1997,** 38, (3), 355-358.
7. O'Byrne, A., Evans, P., Rapid synthesis of the tetrahydroquinoline alkaloids: angustureine,
cuspareine and galipinine. *Tetrahedron* **2008,** 64, 8067–8072.
8. Braun, S., Kalinowski, H., Berger, S., *150 and More Basic NMR Experiments: A Practical Course*. 1999.
9. Corbet, J. P., Mignani, G., Selected Patented Cross-Coupling Reaction Technologies. *Chemical Reviews* **2006,** 106, 2651-2710.
10. Kawazoe, Y., Ninomiya, S., Kohda, K., Quantitative structure-chemoslectivity relationship among alkanesulfonate of primary alcohols. *Tetrahedron Letters* **1986,** 27, 2897-2900.
11. Ruiz, A., Rocca, P., Marsais, F., Godard, A., Queguiner, G., Pyridinium Chloride: a New Reagent for N-Demethylation of N-Methylazinium Derivatives. *Tetrahedron Letters* **1997,** 38, 6205-6208.
12. Schneider, H. J.; Schiestel, T.; Zimmermann, P., Host-guest supramolecular chemistry. 34. The incremental approach to noncovalent interactions: coulomb and van der Waals effects in organic ion pairs. *J. Am.*

Chem. Soc. FIELD Full Journal Title:Journal of the American Chemical Society **1992,** 114, (20), 7698-703.
13. Peter Timmerman, B. M. G. A., van Mook,B Willem Verboom,B Gerrit J. van Hummel,b; Reinhoud@*, S. H. a. D. N., Selective Functionalization of Cavitands:
Synthesis of a New Hemicarcerand. *Tetrahedron Letters* **1992,** 33, (23), 3377-3380.
14. Altamore, T. M.; Barrett, E. S.; Duggan, P. J.; Sherburn, M. S.; Szydzik, M. L., Cavitand boronic acids mediate highly selective fructose transport. *Organic Letters* **2002,** 4, (20), 3489-3491.
15. Irwin, J. L.; Sherburn, M. S., Monolithiocavitands: Versatile intermediates for new cavitand-based hosts. *Organic Letters* **2001,** 3, (2), 225-227.

Chapter 4 Dimeric Capsule by Electrostatic interactions

.4.1,1-Introduction

Molecular capsules have been studied extensively for their ability to encapsulate molecular species and lower activation barriers in kinetically unfavorable reactions[1-3]. Many have used molecular capsules in aqueous environments as a model for enzymes and proteins[4]. Non-covalent forces are commonly utilized to yield cooperative systems for the encapsulation of guests[5]. It is known that tight ion pairs that exist in both non-polar and polar media can disrupt electrostatic interactions.

In this project, the synthesis of a dimeric electrostatic capsule and the quantification of the underlying forces for dimerization are presented. In comparing binding enthalpies (ΔH°) to analogous binding enthalpies of non-capsule forming model salt bridges, we are able to elucidate cooperatively due to quadrupolar change alignment. In figure 4.1, the two most energetically favored alignments are shown below. In alignment 1 the salt bridge is parallel where the electrostatic interaction is linear.

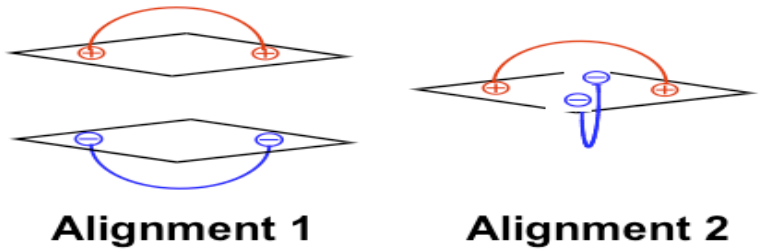


Figure 4.1 shows parallel and anti-parallel configurations for the dimeric capsule.

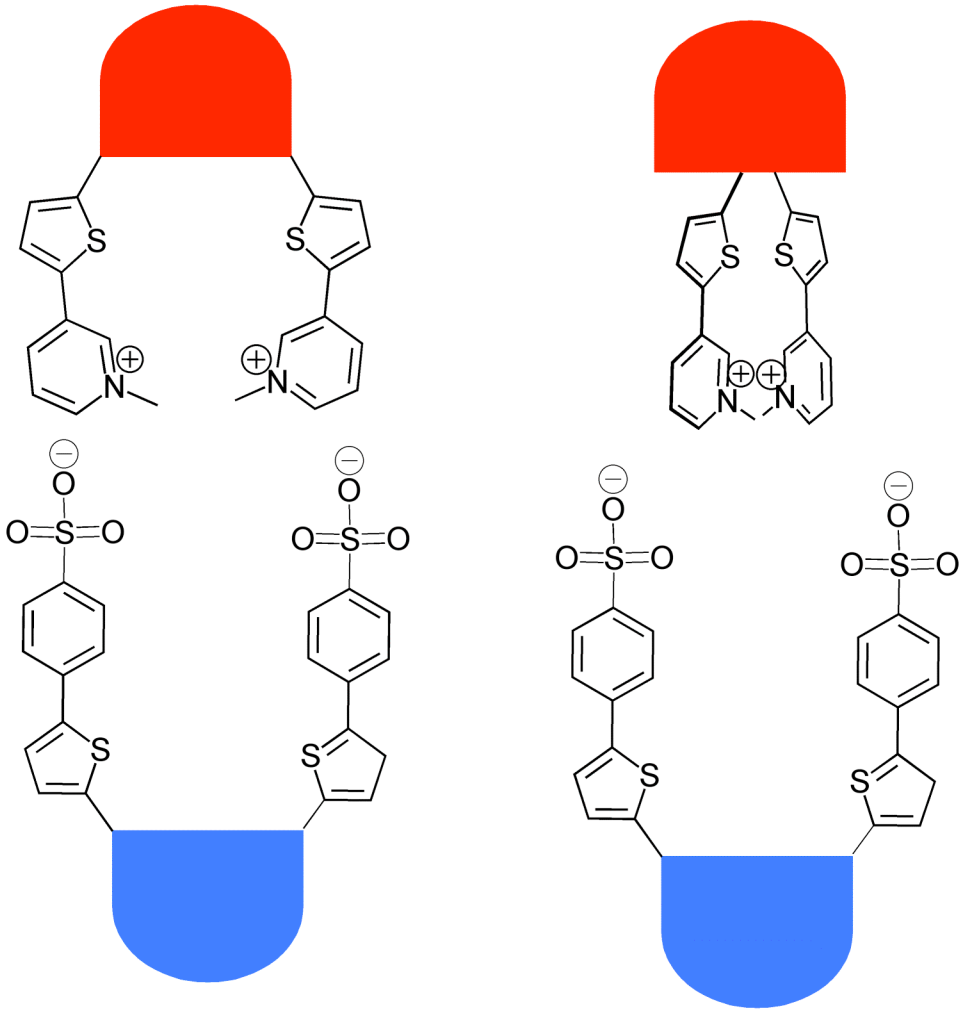
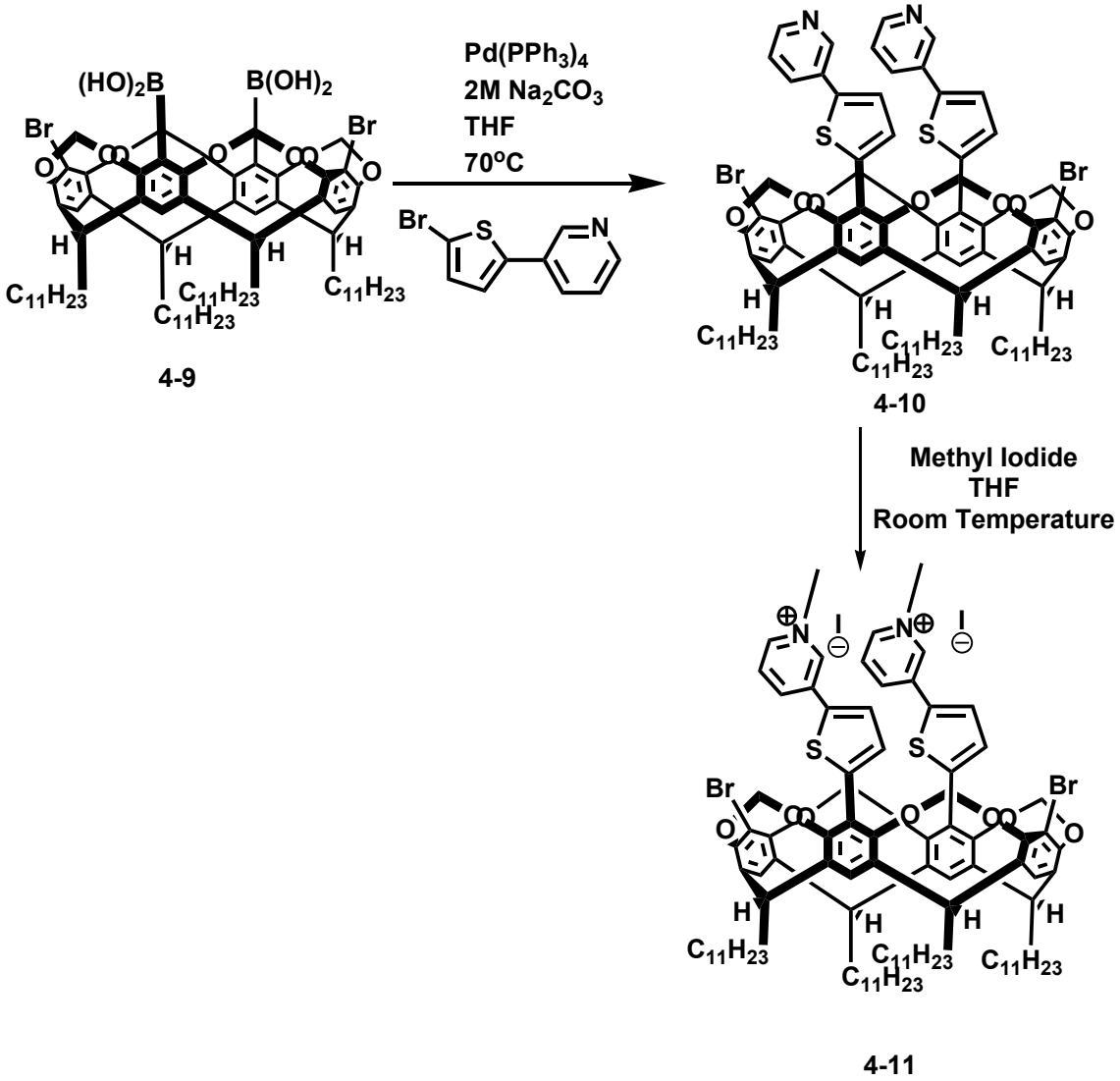


Figure 4.2 Most favorable alignment for the dimeric capsule.

In alignment 2 the salt bridge is antiparallel while the two resorcin[4]arenes are interdigitating between each other. In contrast, alignment 1 constitutes two parallel dipoles. It was expected that the quadrupole would yield tight ion pairs that are lower in energy than two separate dipoles. To demonstrate that our capsules have a quadrupolar arrangement, the association constants are compared to those of single dipoles.

4.1,2-Synthesis of half-capsules

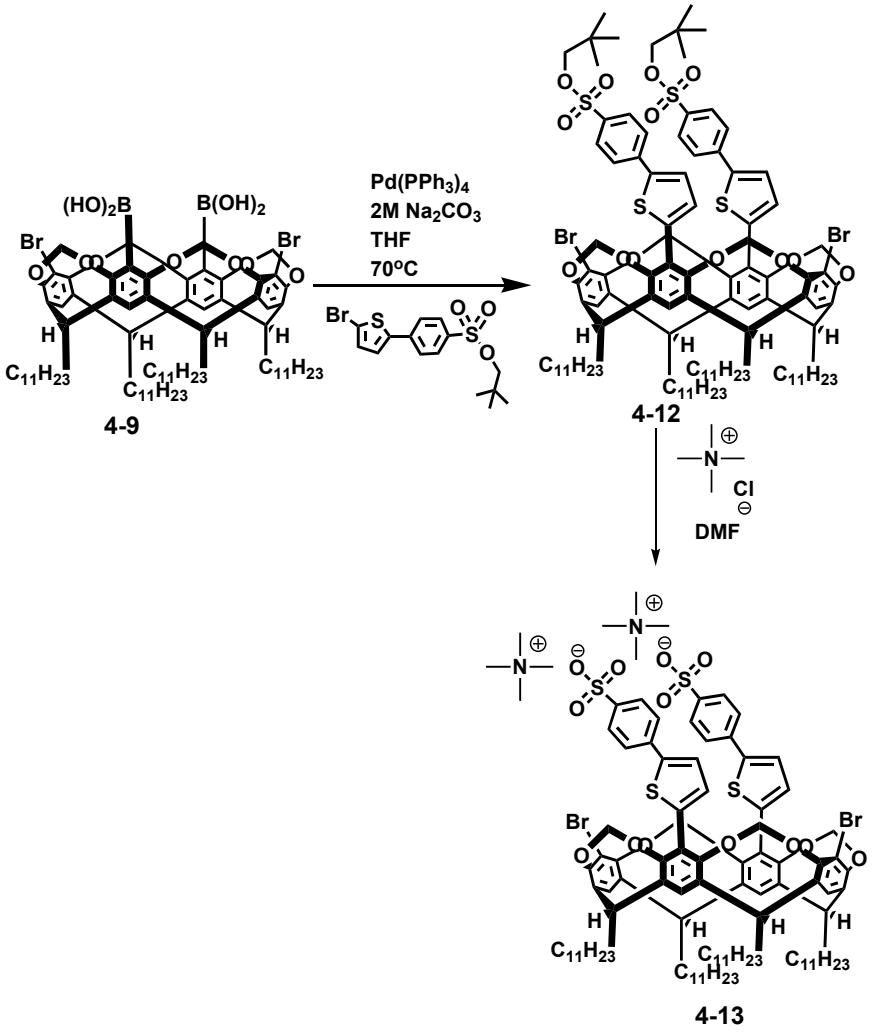
The capsule is based on two hemi-capsules with an A,C distribution on the upper rim as described in chapter 2. This A,C pattern is generated from the lithiation of the tetrabromo cavitand followed by tri-isopropyl borate. The Sherburn group has established precedence for the formation of the A,C pattern due to the charge repulsion of two lithium species on the upper rim.[6]



Scheme 4.1 synthesis of the A,C bis-pyridinium salt a)Pd(PPh3)4, 2 M Na2CO3, THF 55 % yield b) Methyl iodide, THF 85% yield.

Suzuki couplings were employed to decorate the upper rim of the resorcin[4]arene (Figure 4.3). The use of a 3-(5-bromo-2-thienyl)pyridine **3-2** and 2,2-dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **3-5** was utilized as a linker to position the charged species for a cooperative geometry to synthesize a dimeric capsule. This five-membered ring provided a curvature to direct the functional groups on the upper rim to orientate them in a positive/negative/positive/negative quadrupolar pattern.

Both hemicapsules **4-11** and **4-13** were synthesized as neutral components that contained functional groups capable of generating a charged species. The pyridine resorcin[4]arene **4-10** was treated with methyl iodide to generate **4-11**. The use of 2,2-dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **4-5** was employed to generate an anionic species through the removal of the 2,2-dimethylpropyl group using tetramethyl ammonium chloride in DMF. Compound **4-13** was purified via reverse phase column chromatography in THF. In a 1:1 ratio, the two cavitands **4-11** and **4-13** were each dissolved in DMSO and mixed together to generate a dimeric insoluble capsule.



Scheme 4.2 Synthesis of the A,C bis sulfonate tetramethyl ammonium salt.

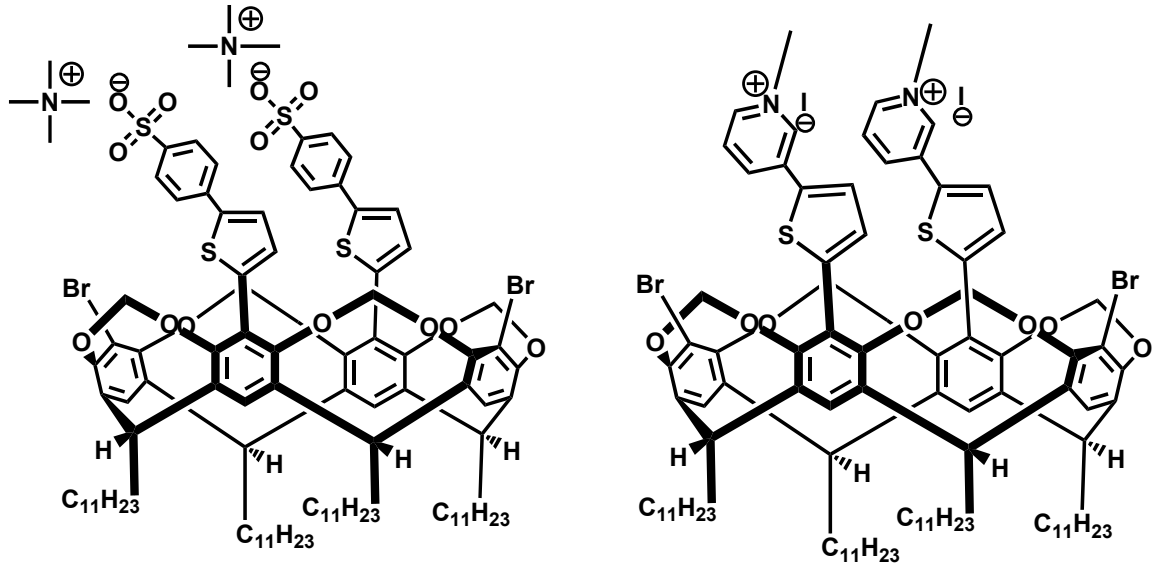


Figure 4.3 A,C bis-pyridinium and A,C bis-sulfonate half capsules.

The H^1 NMR spectrum shows a 1:1 ratio of 1 and 2 and displays both pyridinium and sulfonate moieties relative to their precursors. The pyridinium signals at 9.65, 9.00, 8.57 and 8.06 became broad signals at 9.40, 8.90, 8.10 and 7.98. Noticeable shifts were also observed in the sulfonate. Sharp doublets at 7.84 and 7.58 yielded broad singlets at 7.84 and 7.57. Changes were also observed for the methyl group from the pyridinium with an upfield shift of 0.11 δ relative to 1. Figure 4.7 shows ^{1}H NMR spectrum of the **4-11, 4-13** and **4-14.** The bottom spectrum of C shows the ^{1}H of the **4-11**. The middle spectrum B shows **4-13** and the A is the dimeric capsule **4-14**. The box ■ represents the pyridinium peaks, the circle ● represents the sulfonate peaks present and the star * represents the outer bridges from the resorcin[4]arene. The **x** represents the methyl group from the pyridinium. The stacked spectrum (figure 4.7) shows the sulfonate **4-13** and pyridinium **4-11** hemicapsules are present in the dimeric capsule **4-14**.

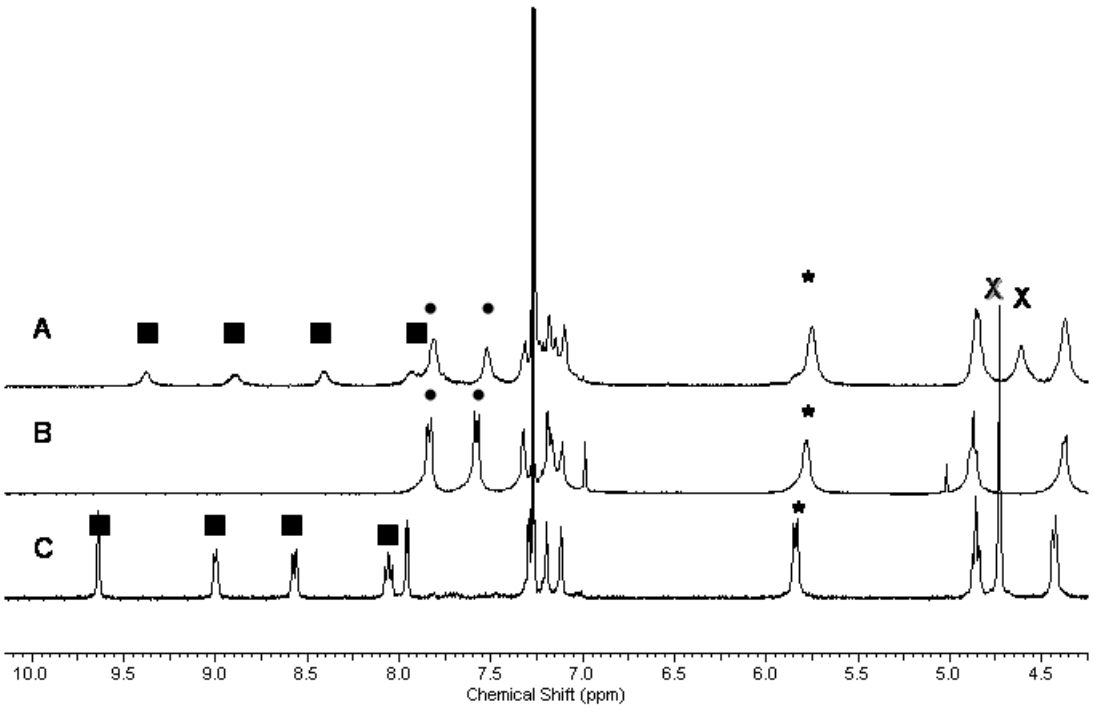


Figure 4.4 H^1 NMR in $CDCl_3$ a) capsule b)sulfonate hemicapsule c) pyridinium hemicapsule.

The use of 2D NOESY in $CDCl_3$ was employed to confirm the contact between the sulfonate and pyridinium species. The NOESY spectrum shown below yields a cross peak between the sulfonate at 7.81 ppm and the methyl group of the pyridinium cavitand. The methyl group was used as probe to determine the proximity of hemicapsule **1** to hemicapsule **2** in the dimeric species.

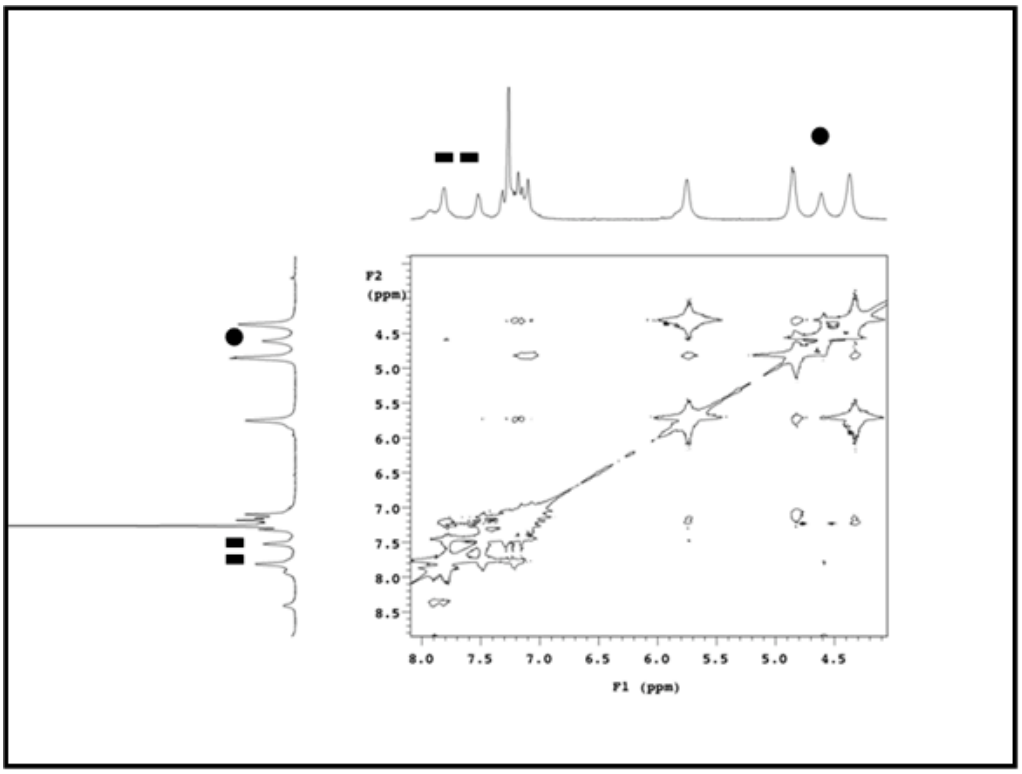


Figure 4.5 2-D NOESY of dimeric capsule in CDCl3; ■ = sulfonate, ● = methyl from pyridinium.

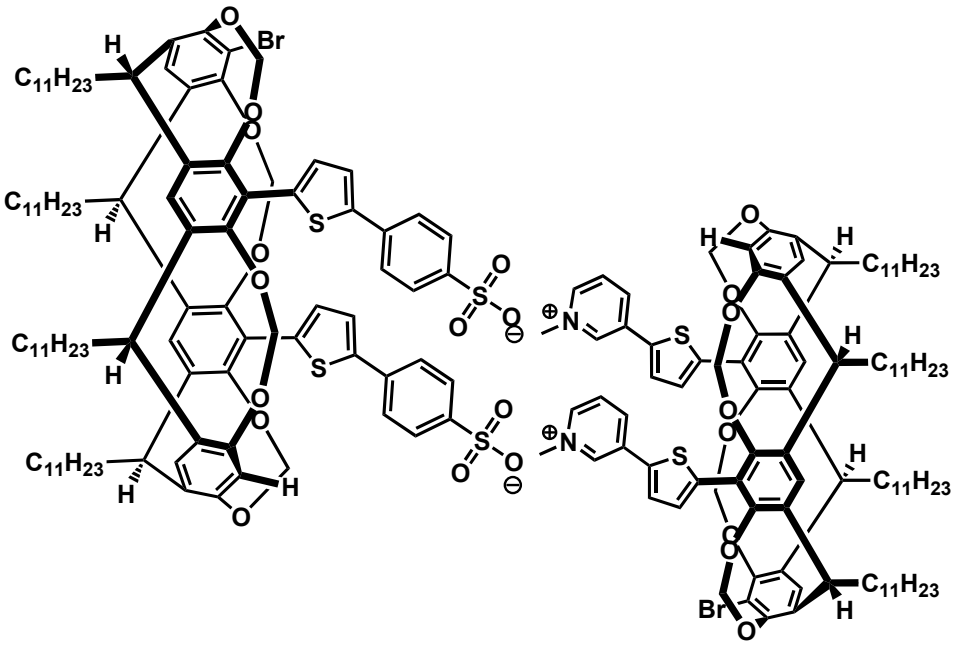


Figure 4.6 Dimeric capsule of bis sulfonate and bis pyridinium cavitand 1-2 complex R= $C_{11}H_{23}$.

4.2,1-Model Studies

A reference salt was synthesized to compare the energies of electrostatic attractions of capsule to a 'non-capsule' analog.

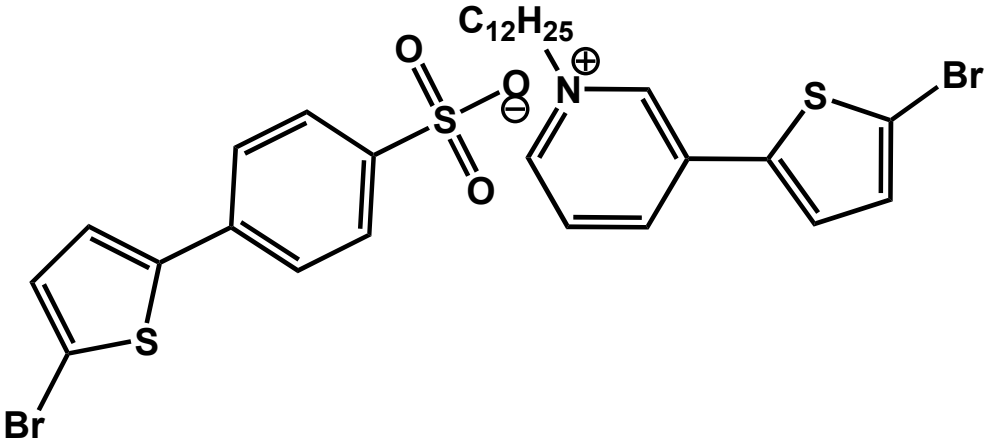


Figure 4.7 Complex 4-7 thiophene-based model salt.

A decoupling experiment was performed to confirm contact between sulfonate and pyridinium. The decoupling experiment was executed in a polar media such as dimethylsulfoxide and a non-polar media such as chloroform. It is known that ion pairs are solvent dependent and polar solvents such as water and dimethyl sulfoxide, dimethylformamide would disrupt ion pairs. The objective was to understand which solvent would provide the tightest ion pair contact. The use of ^{1}H NMR spectroscopy was employed to determine a suitable solvent for a tight ion pair between the sulfonate and the pyridinium. In the decoupling experiment a signal enhancement determines the proximity of one C-H bond to another C-H bond. Here, the focus is to determine the proximity of the sulfonate to the pyridinium in polar and non-polar solvents. As shown in the Figure 4.11, the α-methylene of pyridinium was utilized as a probe to determine the proximity of the sulfonate to the pyridinium. The α-methylene of pyridinium at 4.89 ppm was irradiated and signals from 9.48 ppm and 8.93 ppm were affected. The signal at 9.48 ppm and 8.93 ppm are representative of the pyridinium. The sulfonate doublet at 7.84 ppm showed a positive NOE, which demonstrates the sulfonate is within 5.00 Å from the pyridinium. The same decoupling experiment

was performed in dimethylsulfoxide and the same α-methylene of pyridinium was irradiated. This yielded an irradiated signal from 9.49 ppm and 8.93 ppm from pyridinium. The sulfonate doublets did not show enhancement in dimethylsulfoxide-d_6. This study demonstrates that tight ion pairs of 1 and 2 are formed in chloroform-d, but not dimethylsulfoxide-d_6.

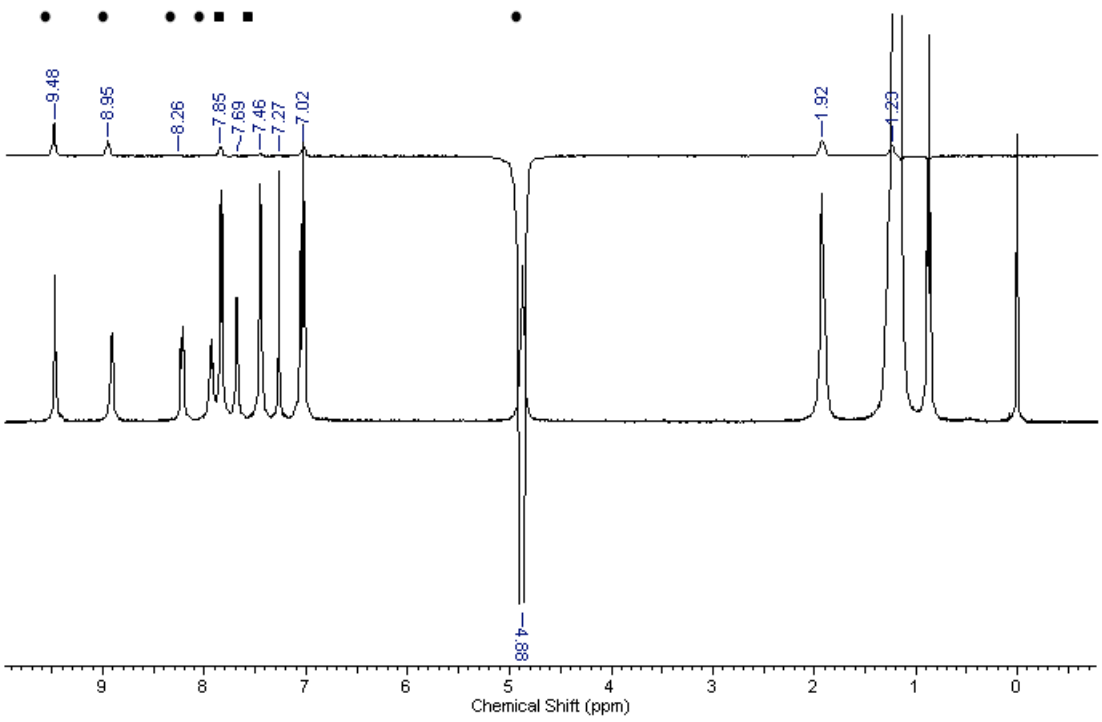


Figure 4.8:decoupling experiment of 4-7 in chloroform-d.

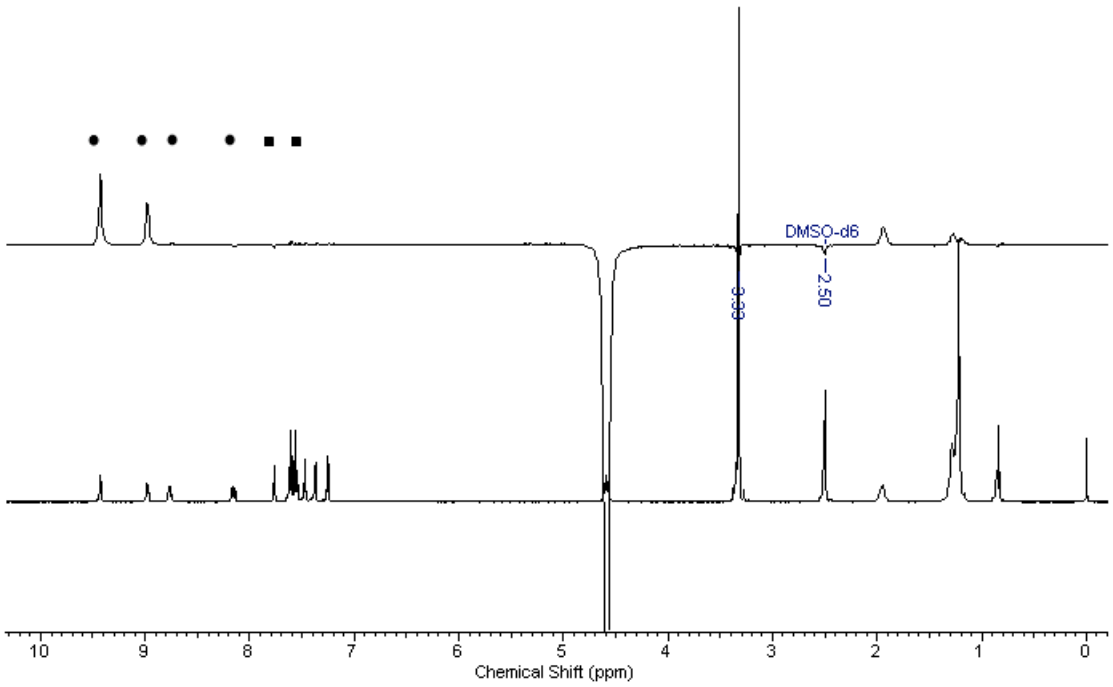


Figure 4.9 is a decoupling experiment of 4-7 in dimethylsulfoxide-d_6.

4.3-Dilution Studies by NMR

Dilution studies were employed to determine binding constants to ultimately compare energies of the model salt thiophene and the dimeric capsule. The use of ^{1}H NMR spectroscopy allowed for measurements of chemical shifts in the range of 40.0 mM and 0.006 mM, assuming a 2-state model that favors ion-pairs at high concentrations. With complexation-induced NMR shifts, one can determine the K_{diass} by establishing an aggregated and disaggregated state. In this system, the complex 4-7 and 4-14 is concentration dependent and dilution can be employed to disaggregate the complex. Studies were performed in chloroform to yield adequate electrostatic interactions between the sulfonate and pyridinium. It has been established in other systems that complexation can be

observed by NMR-monitoring of the changes in chemical shifts of pyridinium and sulfonate; therefore, dilution of our salts would provide a quantitative method for determining the strength of the sulfonate and pyridinium ion pairs.

Measurements were executed in chloroform to provide insight for the binding constant of the sulfonate-pyridinium complex in chloroform. Studies were performed to determine the equilibrium between the AB_{ass} and AB_{diss} based on the apparent NMR shifts with dilution studies. For a 1:1 complex with an disassociation constant, K_{diass}, is kept constant but dilution lowers the ratio of sulfonate-pyridinium complex compared to the sulfonate half-capsule and the pyridinium half-capsule. This way we disrupt the salt bridges via dilution even though $\Delta G°_{diass}$ is favorable for binding.

$$K_a = \frac{[A \cdot B]}{[A][B]} = \frac{\left(\frac{n_{A \cdot B}}{V}\right)}{\left(\frac{n_A}{V}\right)\left(\frac{n_B}{V}\right)} = V\left(\frac{n_{A \cdot B}}{n_A n_B}\right)$$

Equation 4.1 shows the calculation for equilibrium constant for the dilution studies

Dilution studies were performed in concentrations from 38.0 mM (100% aggregation) to 0.019 mM (100% deaggregation). Data points that showed chemical shifts between the plateaus for 100% aggregation and 100% deaggregation were analyzed according to equation below.

$$x_{aggregated} = \frac{S - S_{dissoc}}{S_{total}}$$

Equation 4.2 shows the calucation for the plateaus in the dilution studies

Upon dilution by a factor of two, chemical shifts changes up to 0.200 δ were observed. The NMR studies lead to K_{ass} value of 9.2 M^{-1} and $\Delta G°_{ass}$ energy of 1.3

kcal/mol. This provides insight for the binding energy of a single dipole attraction between a sulfonate and pyridinium in chloroform. This was used as a model compound for the sulfonate-pyridinium complex in our dimeric capsule.

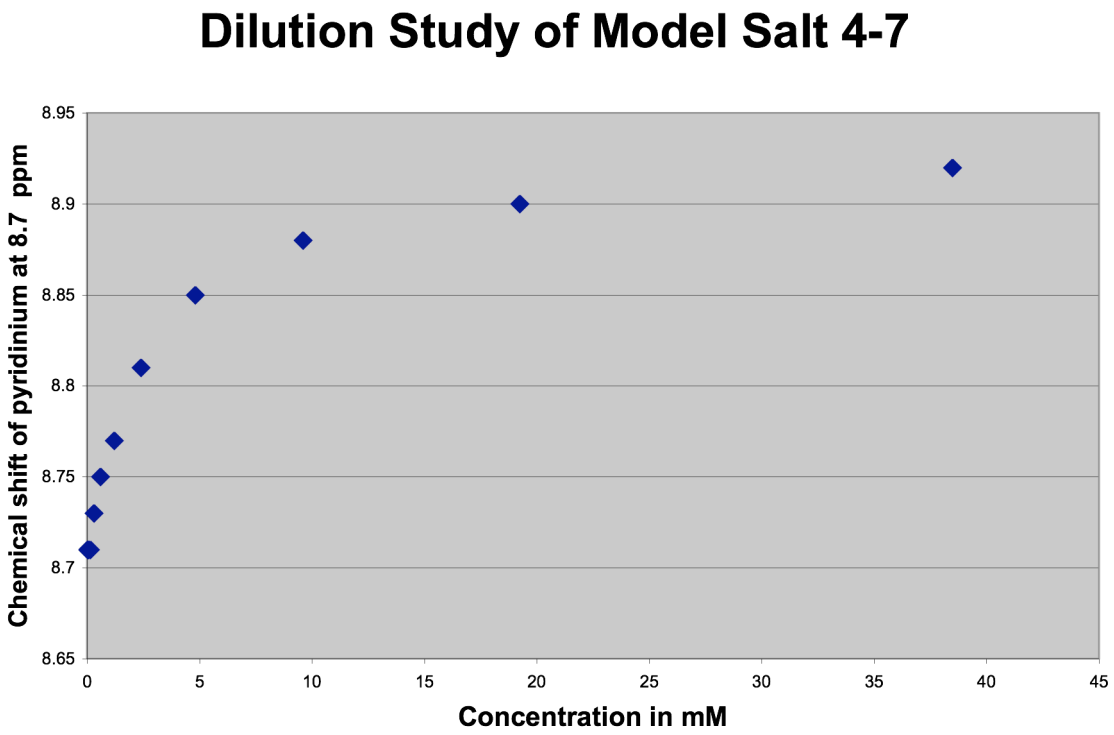


Figure 4.10 Dilution curve for 4-7 thiophene model salt.

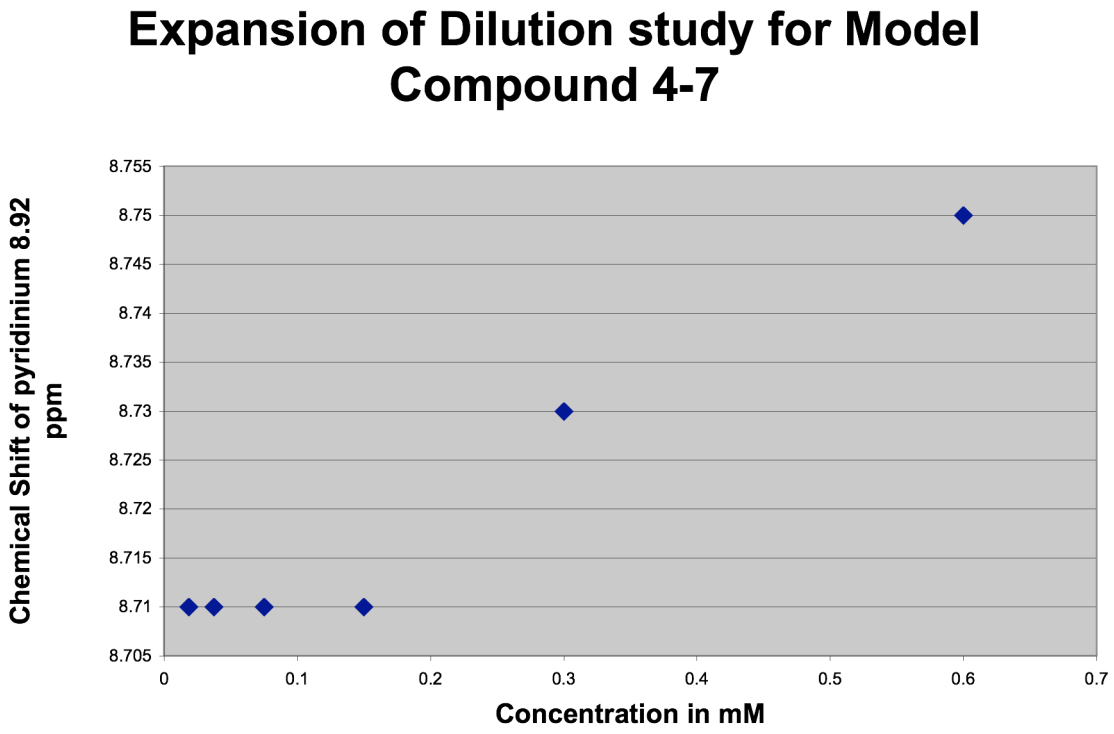


Figure 4.12a Expansion of the dilution curve for 4-7 thiophene model salt which identifies the deaggreated plateau.

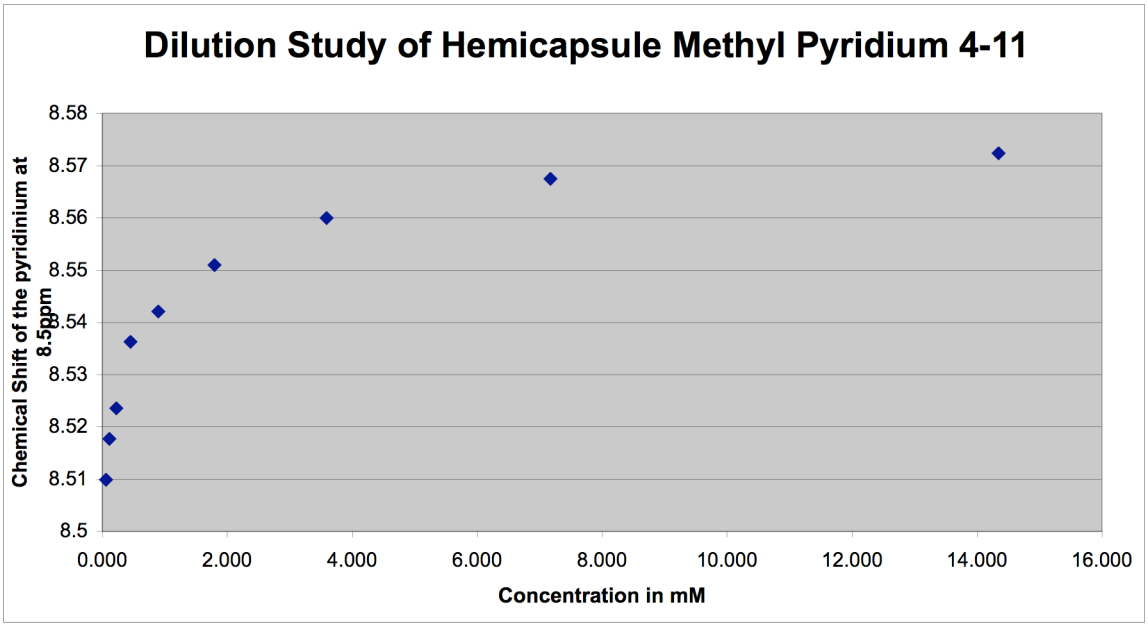


Figure 4.11 Dilution study for the A,C bis-pyridinium iodide 4-11.

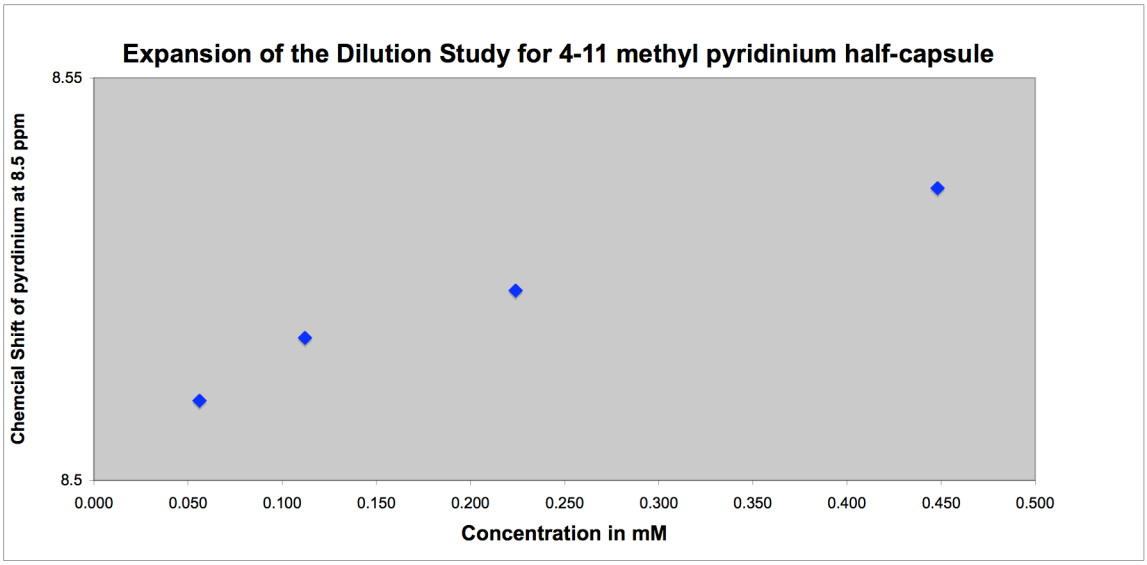


Figure 4.13a shows the expansion of the dilution study which identifies the deaggregated plateau.

^{1}H NMR studies were also employed with the pyridinium iodide **4-11** as a reference compound to determine the affinity of the iodide to the pyridinium. Dilution studies were executed in chloroform to determine a K_{disass} of -50.3 M^{-1} and - 2.3 kcal /mol. Our measurements were based on establishment of the fully aggregated state with 14.4 mM and fully disaggregated at 0.056 mM. The disaggregated state was based on the reproducible chemical shifts at low concentrations of substrate. Similarly, the aggregated state was based on the small changes in chemical shift with high concentrations.

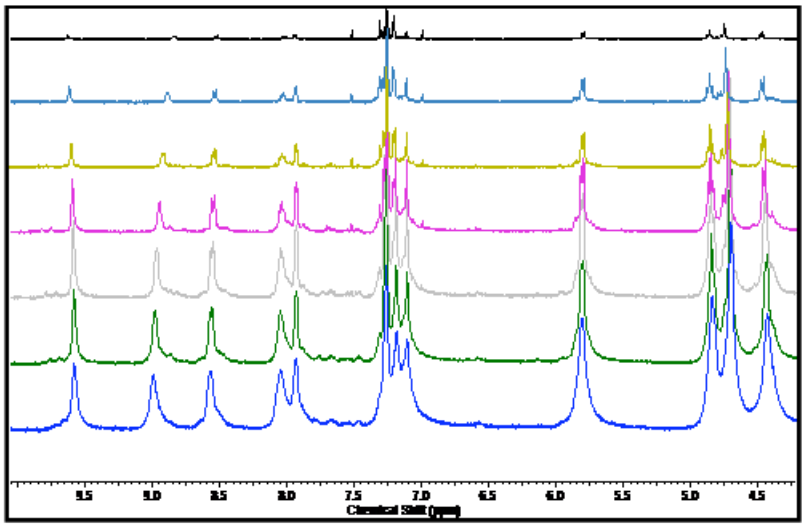


Figure 4.12 Dilution study of the A,C bis pyridinium iodide cavitand.

Similar studies were employed on the **4-14** capsule to calculate the K_{diass} in chloroform. Based on dilution studies, K_{disass} constant of -96.0 M^{-1} and $\Delta G°_{ass}$ of -2.70 kcal/mol were calculated. From the dilution curve it is apparent that in the concentration domain of 3.00 to 6.00 mM, only the dimeric species **4-14** exists while in the domain of 0.012 and 0.006 mM disaggregation is observed (Figure 4-16).

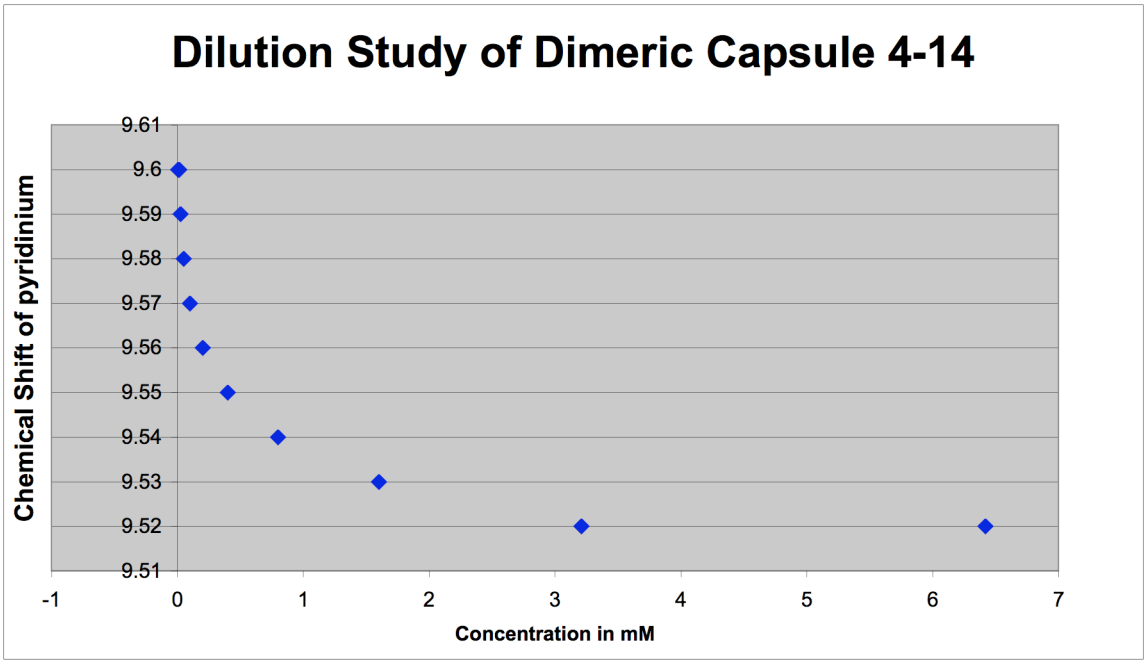


Figure 4.13 Dilution curve for the 4-14 dimeric capsule.

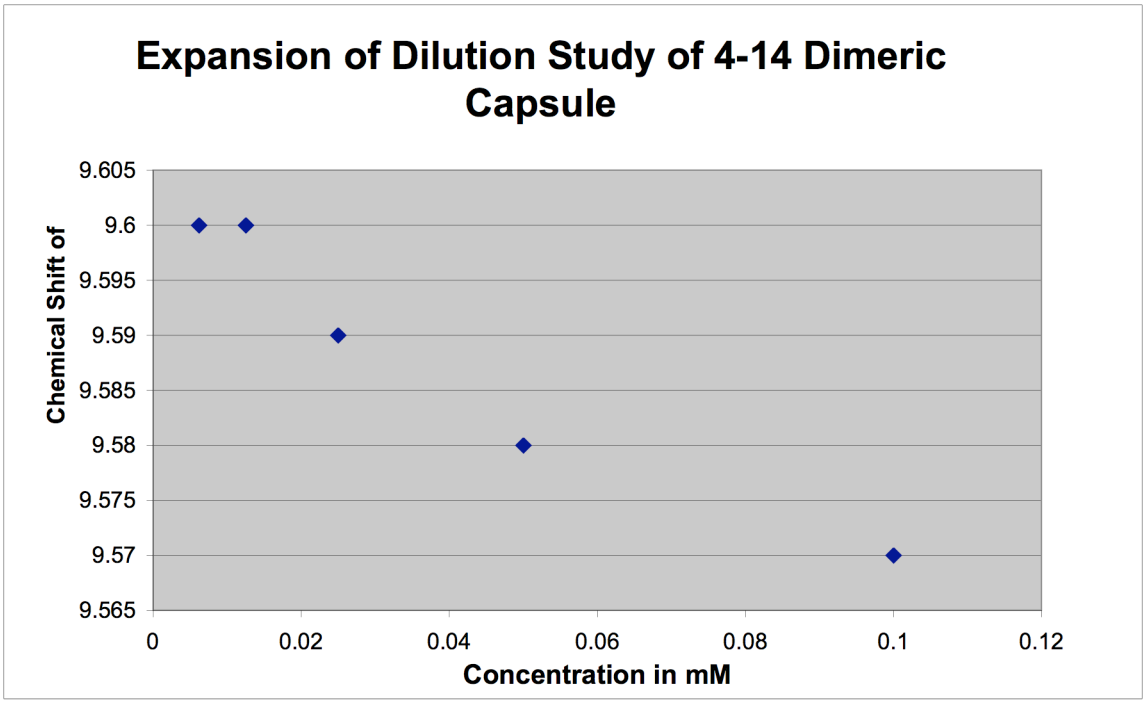


Figure 4.15a shows expansion of dilution curve, which demonstrates the deaggregated plateau.

The comparison of the K_{disass} constants of **4-14** complex and **4-7** complex provides insight for the strength of the electrostatic interactions between the

dimeric species and the single dipole. We anticipated the dimeric capsule to yield ΔG°_{ass} values higher than our experimental values. A ΔG^{o} of -2.70 Kcal/mol for dimeric capsule does not suggest a quadrupolar alignment is not the most thermodynamically preferred for the **4-14** complex, based on the comparison of ΔG^{o} values. It is possible the **4-7** complex can align in a more cooperative fashion than the **4-14** capsule, due to fewer alignment constraints. The difference of 1.40 kcal/mol implies that two dipole-dipole interactions are present in the dimeric capsule. Dilution studies yielded measurable changes in chemical shift (figure 4.17). The methyl group at 4.63 ppm changes to 4.73 ppm due to the dilution in chloroform-d. Sharpening of signals was also observed as the concentration of **4-14** was decreased.

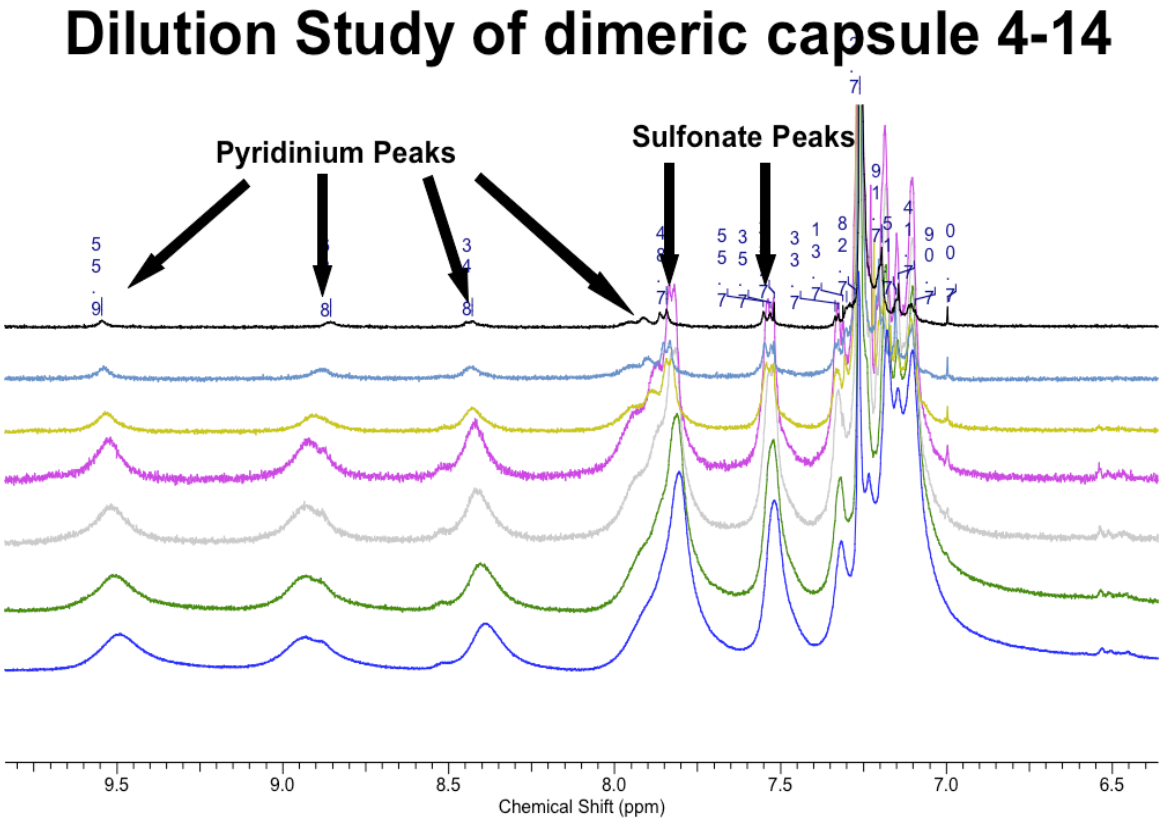


Figure 4.14 Dilution study of 4-14 dimer capsule in chloroform

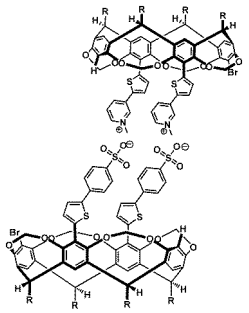
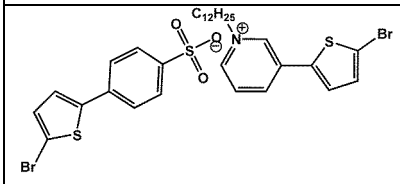
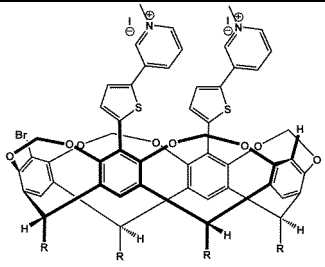
Compound	K_{disass}	ΔG^{o}_{disass}
4-14 	-96 M^{-1}	-2.7 kcal/mol
 **4-7**	-9.2 M-1	-1.3 kcal/mol
 **4-11**	-50.3 M^{-1}	-2.3 Kcal/Mol

Table 4-1 Disassociation constants and ΔG values.

These findings are consistent with the data of Schneider et al who found 5.00 + 1.00 kJ/Mol per salt bridge in sulfonate pyridinium ion-pair complex in water.[7] These studies seem to favor the notion that the dimeric capsule is held together by two independent salt bridges (alignment 1 in Figure 4.2).

4.4-Competitive Binding Study:

Salt brides between sulfonates and pyridiniums hold these capsules together. Initially, the plan was to use 1,4-dimethyl pyridinium iodide as a guest molecule to bind inside the inner cavity of the capsule. After performing a titration experiment with 76-fold excess of the 1,4-dimethyl pyridinium a new stable species formed. The main question was whether there was 2:1 binding or 1:1 binding in the system.

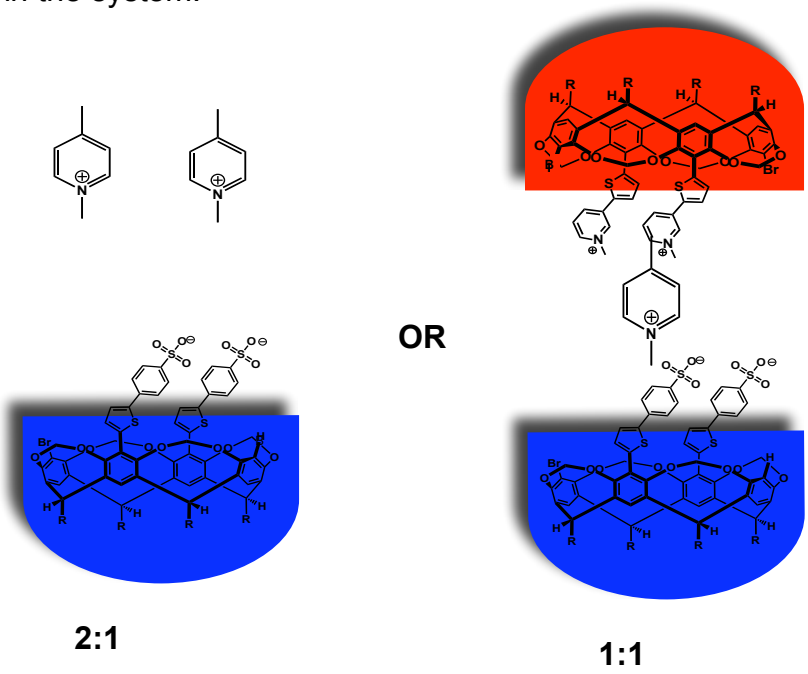


Figure 4.15 Competitve Binding Study.

A Job Plot (Figure 4.19) established 2:1 binding (maximum at 0.3) rather than 1:1 binding, consistent with capsule disruption rather than with encapsulation.

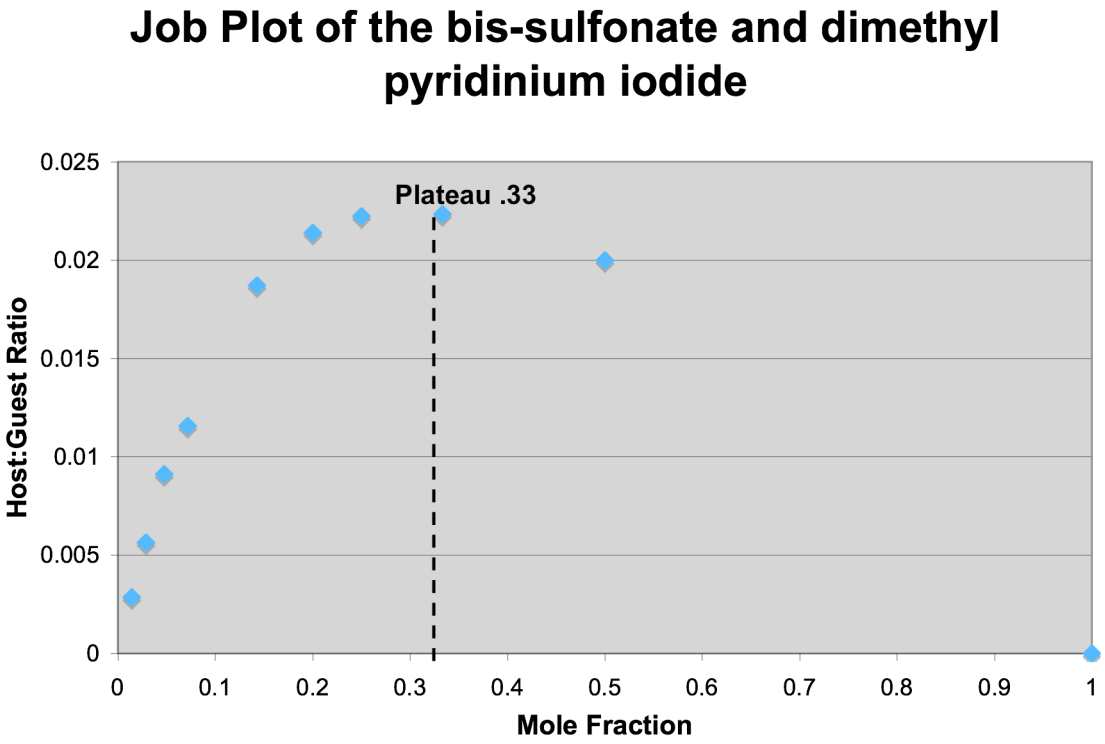


Figure 4.16 Job plot of the bis-sulfonate dimethyl pyridinium salt

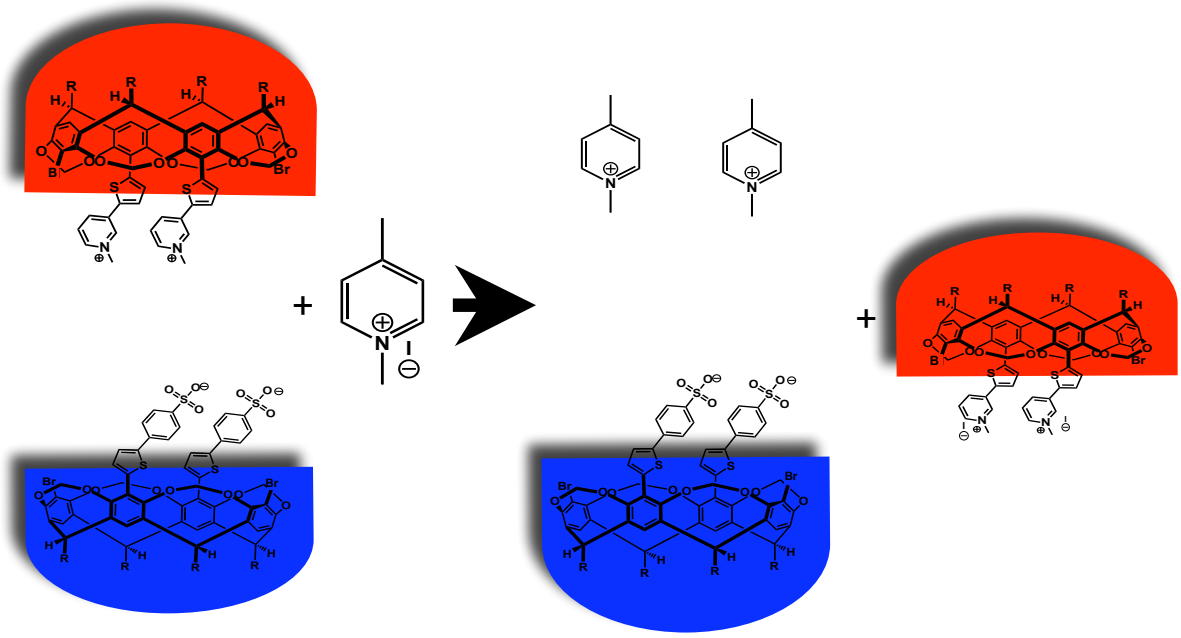


Figure 4.17 Disruption of the dimeric capsule with dimethyl pyridinium iodide

Determination of K_{bind} was possible via the Bernesi-Hildebrand approach (Figure 4.21). The ^{1}H NMR signals show averages of the free sulfonate cavitand and the sulfonate dimethyl pyridinium cavitand. From plotting the inverse of the guest concentration $1/[G]_o$ versus the inverse of the mole fraction slope, the $\mathbf{K_a}$ equilibrium constant can be calculated using the equation below.

$$\Delta\delta = \frac{\Delta\delta_{tot} K_a [G]}{1 + K_a [G]}$$

Equation 4.3 is used to determine K_{bind} via Bernesi-Hildebrand

A K_a of 3.8 M^{-1} was calculated from the slope which is similar to the value determined by dilution studies with the pure dimethyl pyridinium bis sulfonate salt **4-16**.

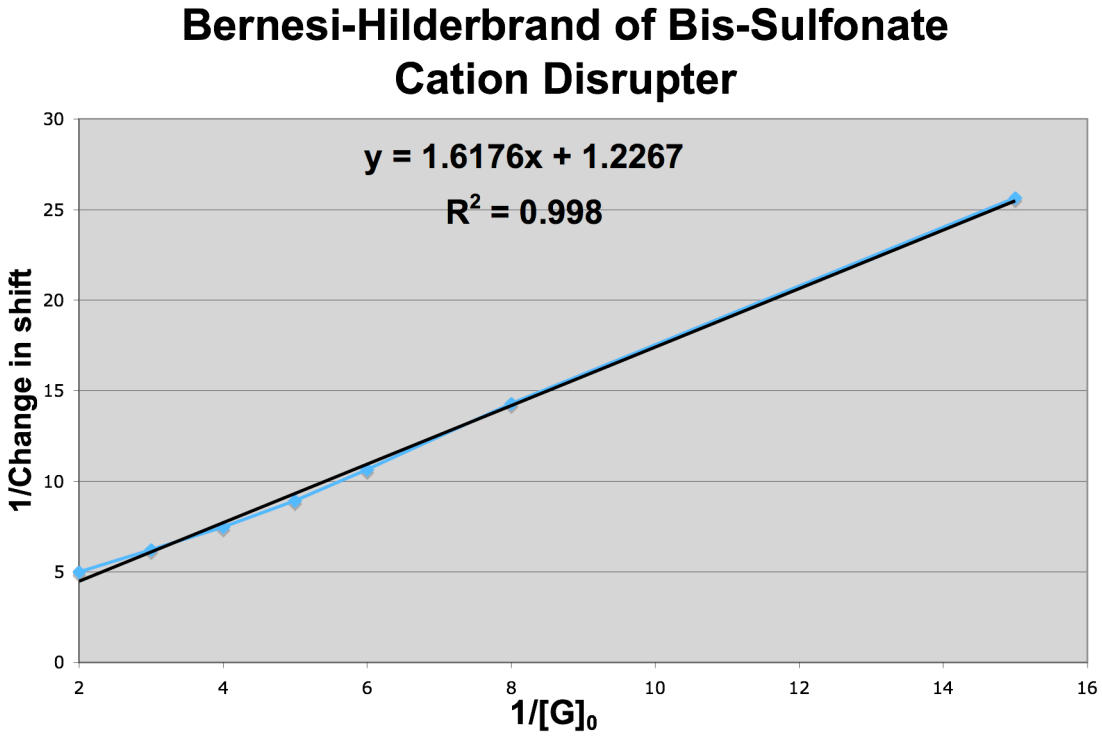


Figure 4.18 Bernesi-Hilderbrand Plot

4.5-Host:Guest Studies

A series of guest molecules were surveyed to gain insight on the size and shape of the cavity. Initially, efforts were focused on binding aromatic molecules such as toluene, benzene, 1,4 dimethoxy benzene, 1,4 dicyanobenzene and 1,4 diiodobenzene. Unfortunately, none of these aromatic substrates would bind to the inner cavity. Cram established small molecules such as acetonitrile and carbon disulfide to bind to the inner cavity of some his capsules and hemi-carcerands[8]. The major challenge with uncovering a guest molecule is that it must have good size and shape matches, but it should not disrupt the electrostatic interactions between the sulfonate and pyridinium; therefore, molecules with large dielectric constants were avoided in other studies because they may disrupt the electrostatic interactions.

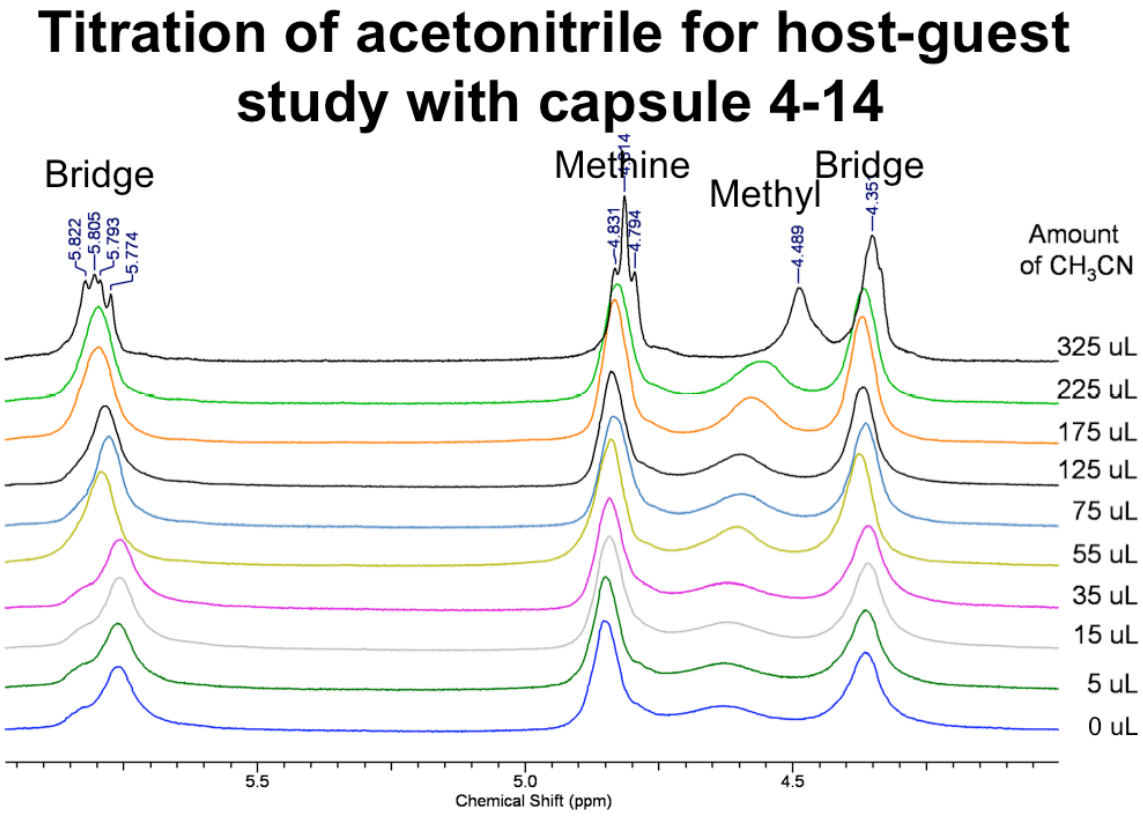


Figure 4.19 Titration of acetonitrile guest of compound 4-14 in ghloroform-d

As shown in the figure 4.27 above, as the concentration of acetonitrile is increase an upfield shift occurs but at high concentrations a drastic shift occurs. Also, the peaks begin to sharpen and doublets are resolved for the bridges. Therefore, acetonitrile is a poor candidate for host: guest studies.

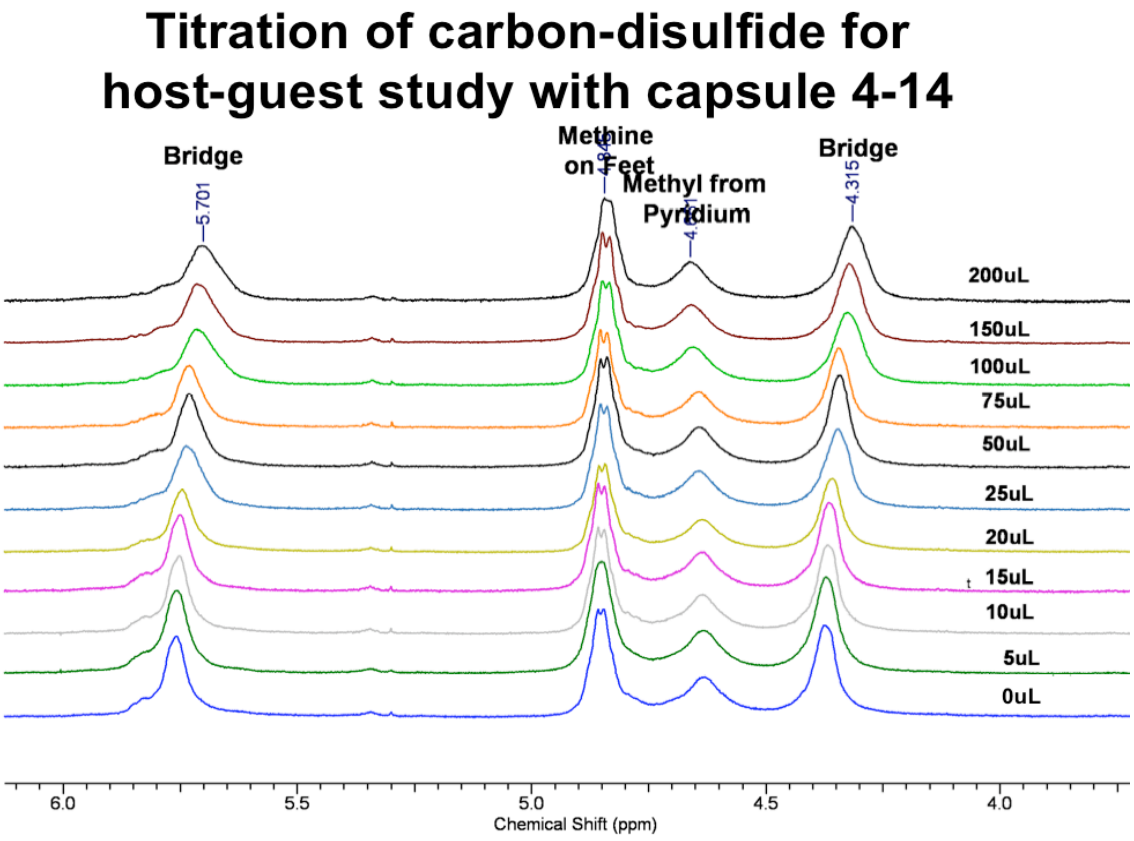


Figure 4.20 Titration of carbon-disulfide guest of compound 4-14 in chloroform-d.

The use of carbon disulfide was employed which has no net dipole moment. After an 800 fold excess 200uL complete 1:1 binding was observed by NMR. As shown in the diagram below the bridges and methyl group from the pyridinium changed upon binding. In some cases the pyridinium peaks shifted as much as 0.120 ppm.

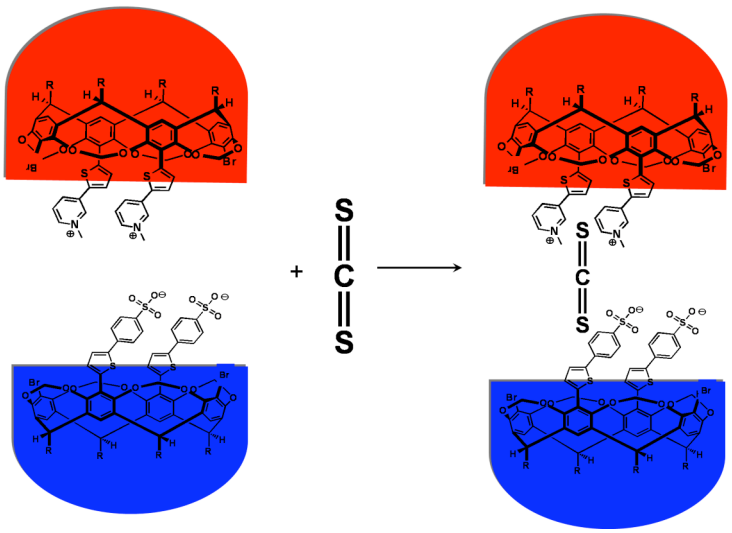


Figure 4.21 Host-guest study with carbon disulfide.

To establish that binding occurred in the capsule binding studies were performed with the sulfonate half-capsule and pyridinium half-capsule. No changes were observed in the ^{1}H NMR spectra even at high concentration of CS_2 support the notion that half-capsules are unsuitable for CS_2 binding.

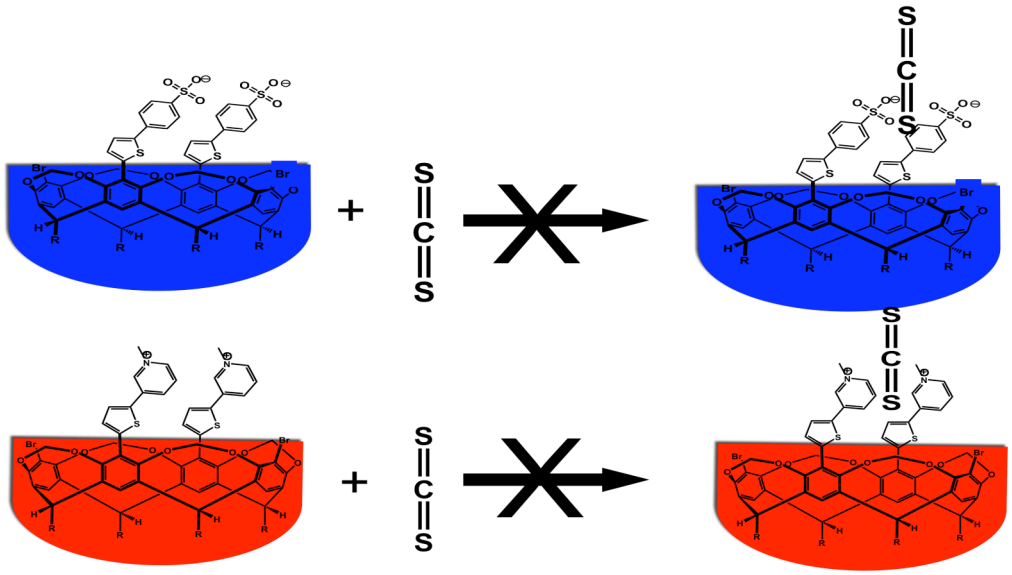


Figure 4.22 Host-guest study with A,C bis sulfonate and A,C bis pyridinium hemicapsules.

4.6-Van't Hoff Studies

Complexation between the sulfonate and pyridinium half capsules may be driven by entropy and/or enthalpy; therefore, ΔH° and ΔS° had to be determined. A series of ^{1}H NMR spectra of 1-2 were acquired over a temperature range of 60°C (-10°C to 50°C) and the amount of 1,2 and 1-2 was determined at each temperature.

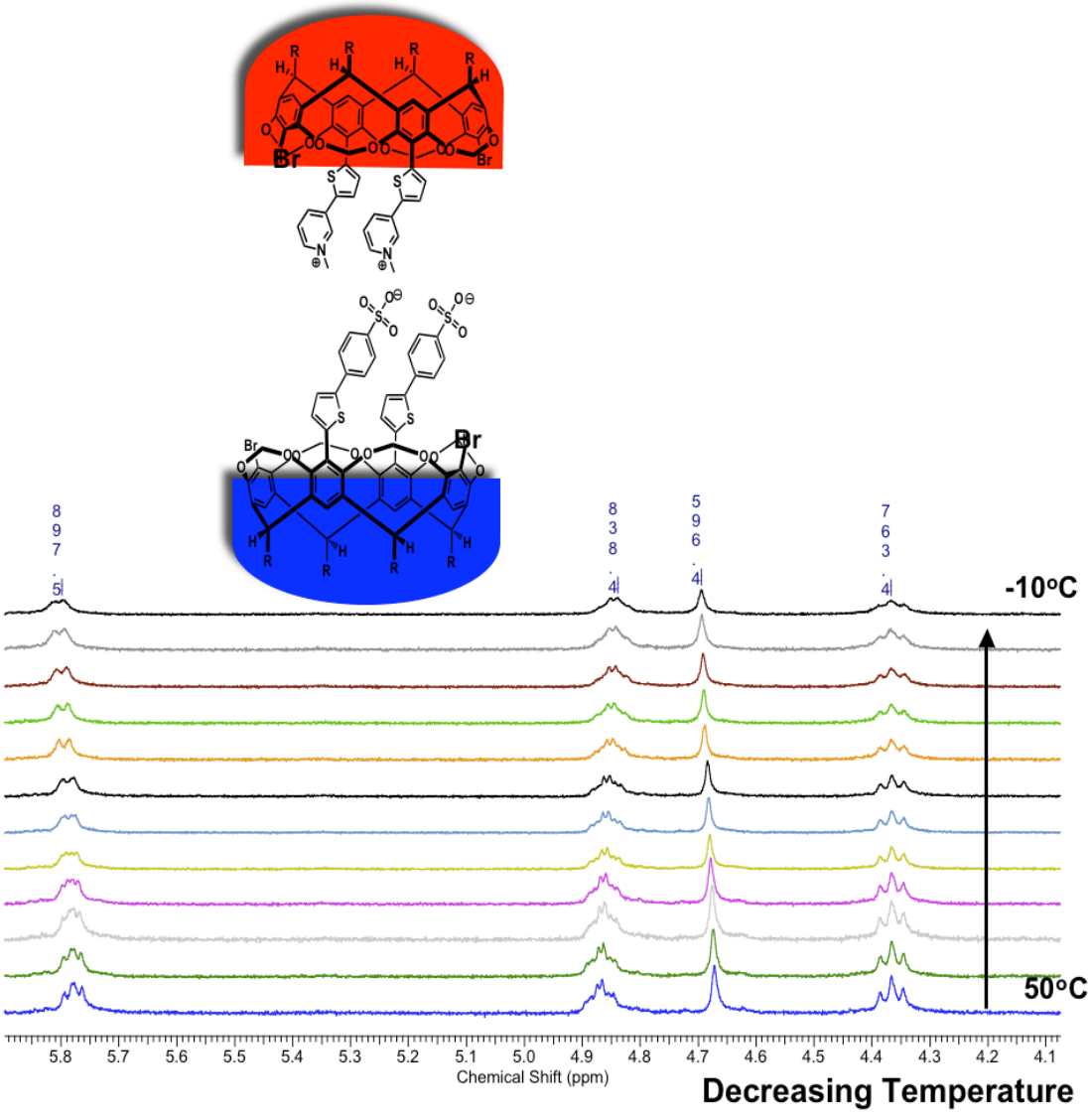


Figure 4.23 Variable temperature studies for dimeric capsules.

To calculate the ΔH° and ΔS° dilution studies were performed to map out extreme plateaus for aggregated and disaggregated states for the capsule and bis-dimethyl bis-sulfonate cavitand. The concentration was kept constant in a range in which the equilibrium is not between the two components of the capsule. An increase in temperature results in the deconvolution of the bridges from the two hemicapsules **4-11** and **4-13**.

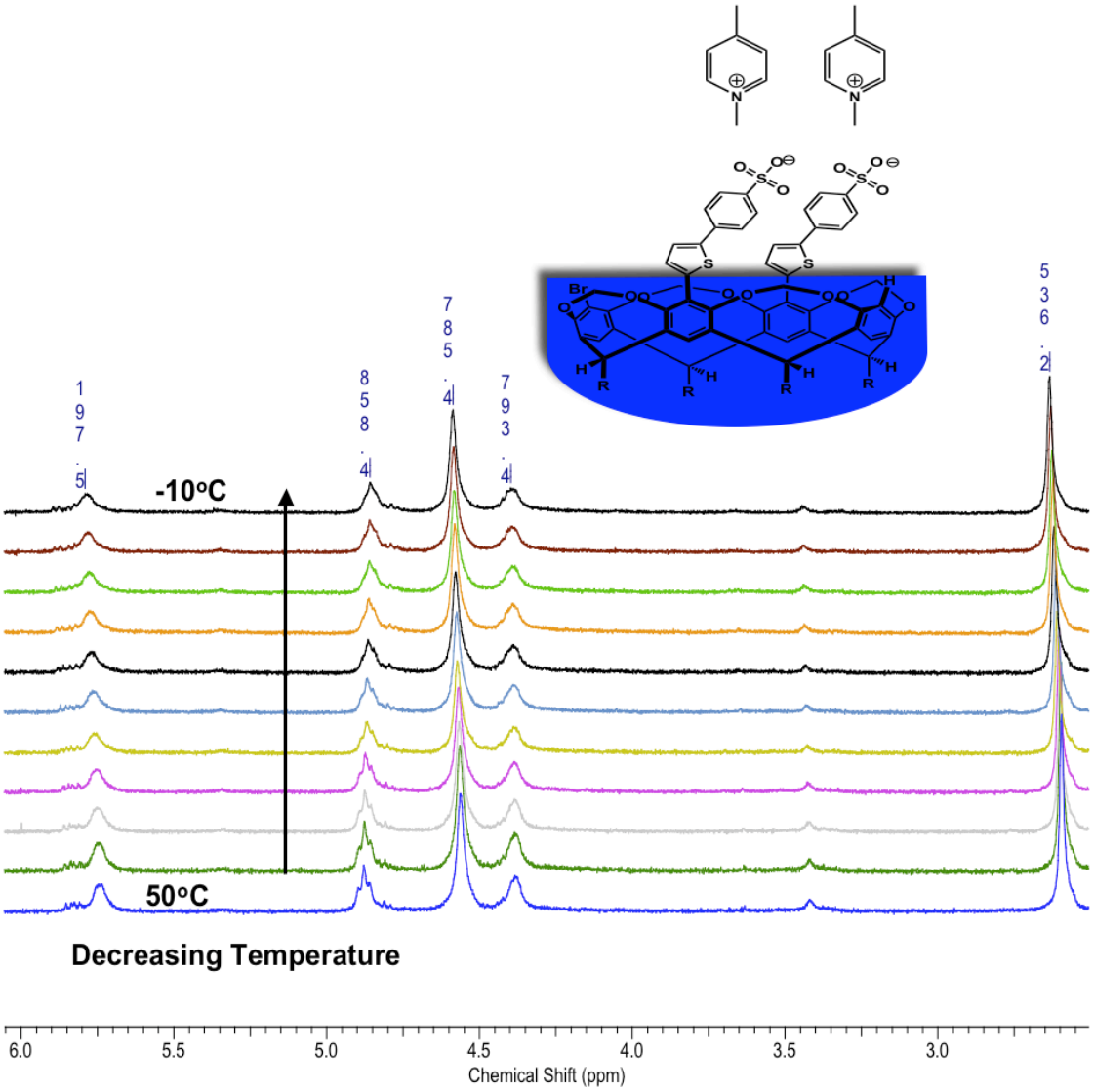


Figure 4.24 Variable temperature studies of bis-sulfonate dimethyl pyridinium salt.

By varying the temperature, a total change in chemical shift of 0.100 ppm for the capsule and 0.030 ppm for the bis-dimethyl pyridinium bis-sulfonate cavitand was observed.

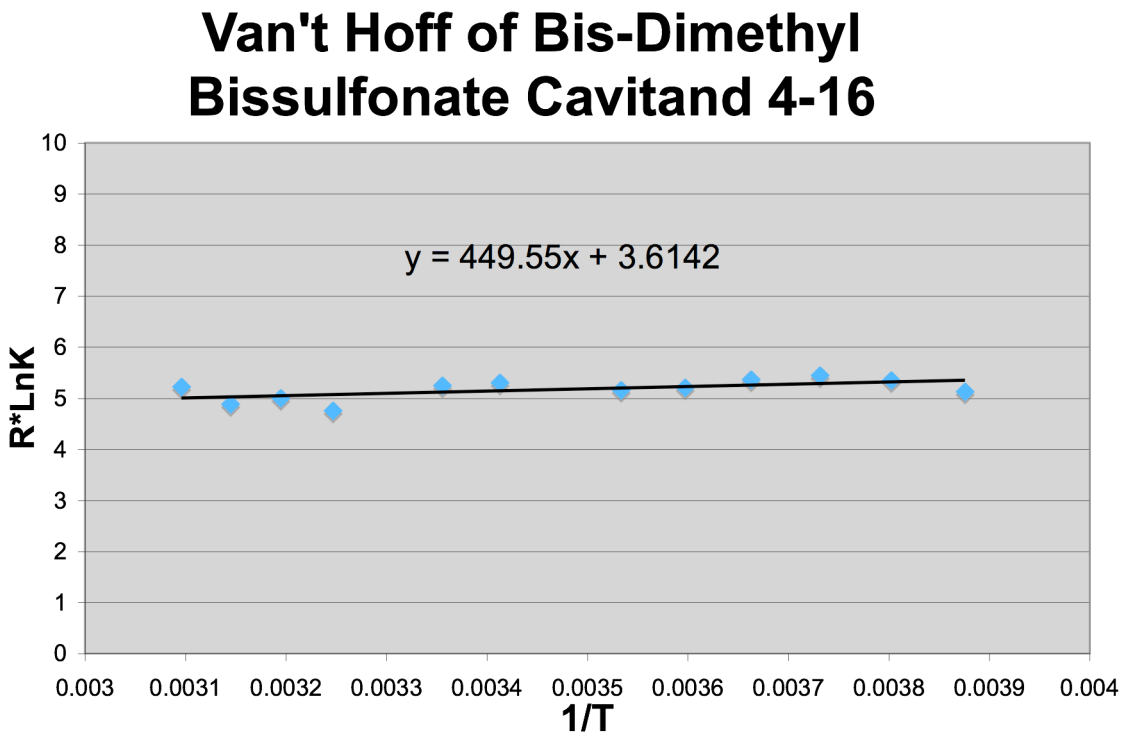


Figure 4.25 Van't Hoff plot for bis-sulfonate dimethyl pyridinium.

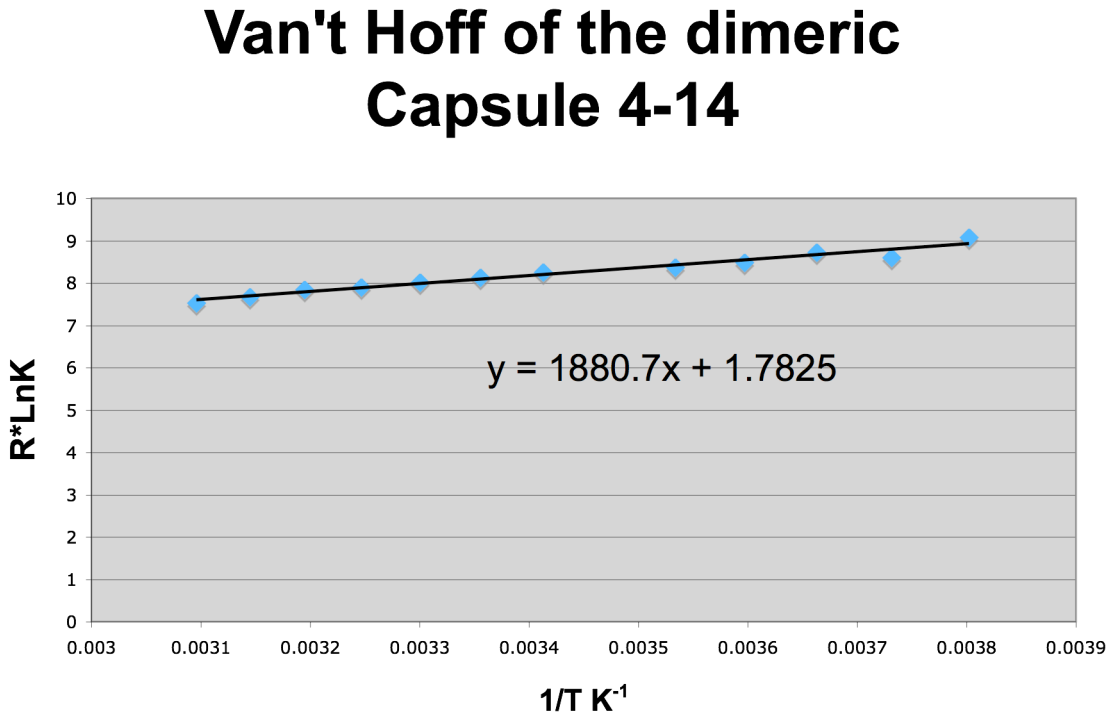


Figure 4.26 Van't Hoff plot for dimeric capsule.

From Van't Hoff plots, ΔH° and ΔS° were determined according to:

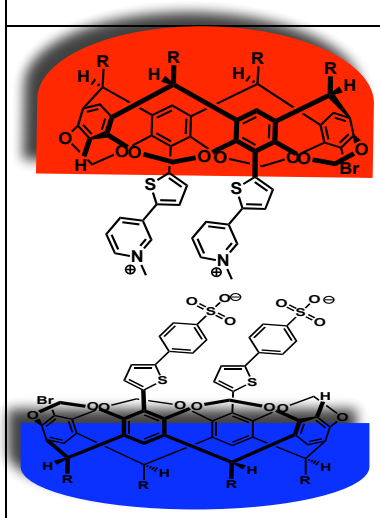
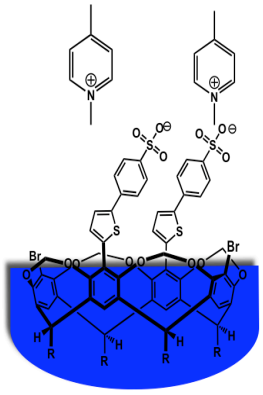
$$\ln K_{eq} = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

Equation 4.4 is used for the Van't Hoff experiment to calculate enthalpy and entropy

As shown in Table 4.2, the capsule ΔH^o and ΔS^o is -1.90 kcal/mol^{-1} and 1.80 kcal mol^{-1} K^{-1}, respectively and the ΔG° is -0.45 kcal/mol^{-1} and 3.60 kcal/mol^{-1}. This underlined that capsule formation in $CDCl_3$ is both enthalpy and entropy driven, while the reference compound forms ion pairs demonstrate this is an entropy driven process. The capsule is slightly enthalpy driven and the 4-16 bis-dimethylpyridinium bis-sulfonate is more entropy driven. Since the capsule is a more enthalpy driven process, this suggests that solvent-to-surface attractions are present in our system. These attractions are driving forces that are dominant

in the formation of the capsule. These enthalpy driven forces are present in Crams Velcraplexes, which are also driven by ‘solvophobic’ binding driving forces.[9]

Table 4-1 shows the ethalpy, entropy, and ΔG disassociation values determined for 4-14 and 4-16

Compound	Enthalpy (ΔH^{o}_{dissoc})	Entropy(ΔS^{o})	Gibbs (ΔG^{o}_{assoc})
 **4-14**	-1.88 kcal/mol^{-1}	1.8 kcal mol^{-1} K^{-1}	2.7 kcal/mol^{-1}
 **4-16**	-0.45 kcal/mol^{-1}	3.6 kcal/mol^{-1}	1.6 kcal/mol^{-1}

4.7 Conclusions and Outlook

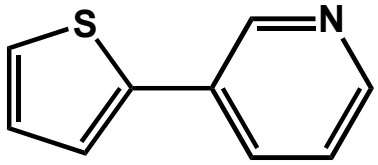
The use of dilution studies through ^{1}H NMR was utilized to determine ΔH, ΔS, and ΔG for the dimeric capsule **4-14**, bis-sulfonate-dimethylpyridinium iodidie **4-16** and thiophene model salt **4-7**. Van't Hoff studies were implemented to compare the ΔH values to compare the capsule to a system that can align itself as two dipoles. The ΔH value for the capsule **4-14** is -1.88 kcal/mol and the -0.45 kcal/mol for **4-17**. This suggests something is special about the alignment of the dimeric capsule **4-14** relative to the **4-17**.

4.8 Future Studies

The use of 3-bromopyridine was employed as starting building block for the synthesis of the pyridinium half-capsule. Also, 4-bromo-sulfonyl chloride was utilized as the starting building block for the synthesis of the sulfonate cavitand. The use of two *para* functionalized pyridinium and sulfonate aromatics could generate a more cooperative binding system. Studying the effect of different *para* versus *meta* substituted pyridinium and sulfonate aromatics could lead to different disassociation constants.

Chapter 5 4.9-Experimental

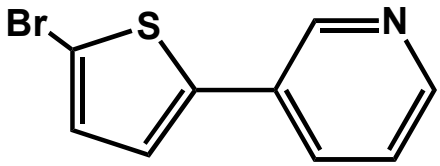
3-(2-thienyl)pyridine [4-1]



Compound 4 - 1

To a reaction vessel, 3- bromo-pyridine (1.01g, 6.42 mmol, 0.619 mL), 2-thiophene boronic acid (0.685 g, 5.35 mmol), tetrakis(triphenylphosphine)palladium(0) (0.310 g, 0.268 mmol), 2.00 M sodium bicarbonate (6.00 mL) and toluene (13.0 mL) were added. The reaction vessel was degassed by freeze-pump-thaw. The reaction was heated at 80^{o} C for 10 hours. The reaction was quenched by the addition of a saturated sodium bicarbonate solution. Methylene chloride was added and the aqueous and organic layers were separated. The organic layer was dried with magnesium sulfate, filtered and concentrated. The product was isolated by column chromatography with 3:1 hexane:ethyl acetate to yield a light brown oil 3-(2-thienyl)pyridine to give (1.00 g, 80% yield) as the title compound **4-1**. [10] ^{1}H NMR (400 MHz, CDCl3) □ δ 7.12 (dd, *J*=4.29 Hz, 1 H) 7.30 (dd, *J*=7.22, 4.88 Hz, 1 H) 7.36 (d, *J*=3.90 Hz, 2 H) 7.86 (d, *J*=8.20 Hz, 1 H) 8.51 (d, *J*=4.69 Hz, 1 H) 8.89 (d, *J*=1.95 Hz, 1 H) ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 123.6, 124.2, 125.9, 128.2, 130.3, 132.9, 140.4, 146.9, 148.4

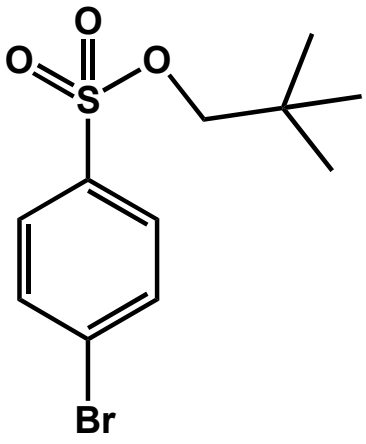
3-(5-bromo-2-thienyl)pyridine [4-2]



Compound 4 - 2

The reaction vessel was wrapped in foil to prevent exposure to light. Compound 3-(2-thienyl)pyridine **4-1** (4.36 g, 27.1 mmol) was dissolved in DCM (91.0 mL). A solution of bromine (1.81 mL, 35.0 mmol) in dichloromethane (45.0 mL) was added drop wise over 30 min. The reaction was stirred at ambient temperature for 2 hrs. A 1.00 M aqueous solution of sodium carbonate (30.0 mL) was added, and the mixture was stirred. The layers were separated and the aqueous phase was extracted with additional dichloromethane (30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give 5.87 g (90% yield) of 3-(5-bromo-2-thienyl)pyridine of the title compound **4-2**.[10] 1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 7.057 (d, *J*=3.55 Hz, 1 H) 7.079 - 7.112 (m, *J*=3.81 Hz, 1 H) 7.292 (dd, *J*=7.86, 7.48, 5.20, 4.06 Hz, 1 H) 7.712 - 7.784 (m, *J*=2.28 Hz, 1 H) 8.525 (dd, *J*=4.82, 1.52 Hz, 1 H) 8.783 (d, *J*=1.78 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$) □ δ 112.7, 123.6, 124.4, 129.5, 131.0, 132.6, 141.7, 146.5, 148.7

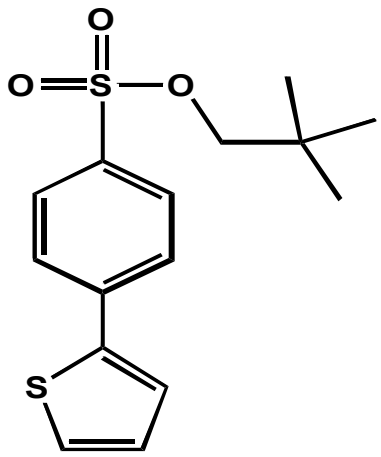
2,2-dimethylpropyl 4-bromobenzenesulfonate [4-3][11]



Compound 4 - 3

4-bromo-sulfonyl chloride (0.66 g, 2.60 mmol), neopentyl alcohol (0.23 g, 2.6 mmol) and 26 mmol (2.00 mL) of pyridine were added to a round-bottom flask. The pyridine was removed in vacuo and the remaining contents were dissolved in 10.0 mL of diethyl ether. The ether was washed with 2.50 M HCl (15.0 mL). The organic and aqueous layers were separated and the organic layer was washed again with 2.50 M HCl. The organic layer was separated, dried with magnesium sulfate, filtered and concentrated. The crude was dissolved in diethyl ether and layered with hexane to induce precipitation on the needle-like crystals of 2,2-dimethylpropyl 4-bromobenzenesulfonate to give (0.662 g 83% yield) of the title compound **4-3**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.880 - 0.940 (m, 9 H) 3.70 (s, 2 H) 7.69 - 7.73 (m, *J*=8.20 Hz, 2 H) 7.75 - 7.80 (m, *J*=8.20 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 26.2, 31.9, 80.1, 129.0, 129.5, 132.7, 135.3

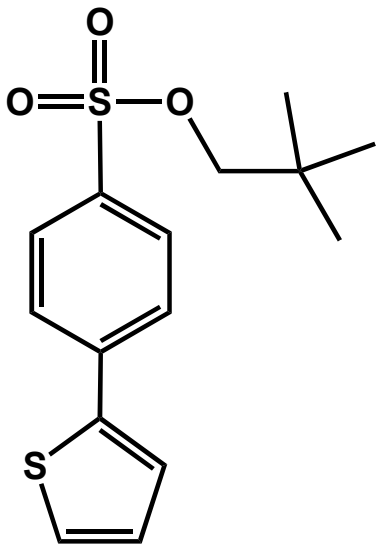
2,2-dimethylpropyl 4-(2-thienyl)benzenesulfonate [4-4][10]



Compound 4 - 4

To a sealable reaction vessel, **4-3** 2,2-dimethylpropyl 4-bromobenzenesulfonate (0.580 g 1.89 mmol), 2-thiophene boronic acid (0.220 g, 1.72 mmoles), tetrakis(triphenylphosphine)palladium(0) (0.080 g, 0.070 mmol), 2 M sodium bicarbonate (2.10 mL) and toluene (4.00 mL) were added. The reaction vessel was degassed by freeze-pump-thaw. The reaction was heated for 10 hours at 70^{o}C. The reaction was quenched by the addition of a saturated sodium bicarbonate solution. The aqueous layer was extracted with methyl chloride and the layers were separated. The organic layer was dried with magnesium sulfate, filtered and concentrated. The product was isolated by column chromatography with 4:1 hexane:ethyl acetate to yield 2,2-dimethylpropyl 4-(2-thienyl)benzenesulfonate a white solid to give (0.310 g, 57% yield) as the title compound **4-4**.[10] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.910 (s, 9 H) 3.70 (s, 2 H) 7.14 (dd, *J*=3.90 Hz, 1 H) 7.41 (dd, *J*=5.08, 1.17 Hz, 1 H) 7.45 (dd, *J*=3.90, 1.17 Hz, 1 H) 7.76 (d, *J*=8.59 Hz, 2 H) 7.89 (d, *J*=8.20 Hz, 2 H);^{13}C NMR (101 MHz, $CDCl_3$) □ δ 26.2, 31.9, 79.9, 125.5, 126.3, 127.3, 128.7, 128.8, 134.4, 139.7, 142.1

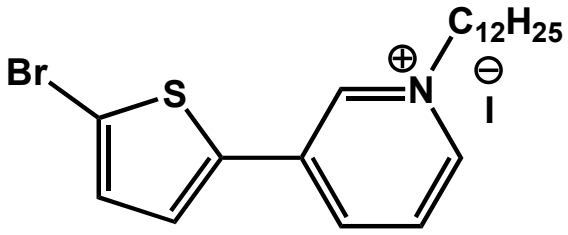
Dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate[4-5]



Compound 4 - 5

The reaction vessel was wrapped in foil to prevent exposure to light. Compound **4-4** 2,2-dimethylpropyl 4-(2-thienyl)benzenesulfonate (0.260 g, 0.850 mmol) was dissolved in DCM (3.00 mL). A solution of bromine (0.050 mL, 1.02 mmol) in dichloromethane (1.40 mL) was added dropwise over 30 min. The reaction was stirred at ambient temperature for 2 hrs. A 1.00 M aqueous solution of sodium carbonate (5.00 mL) was added and the mixture was stirred. The layers were separated and the aqueous phase was extracted with additional dichloromethane (15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give 0.320 g (96 yield%) of dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **4-5** .[10] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.860 - 0.950 (m, 9 H) 3.71 (s, 2 H) 7.09 (d, *J*=3.90 Hz, 1 H) 7.20 (d, *J*=3.90 Hz, 1 H) 7.62 - 7.70 (m, *J*=8.59 Hz, 2 H) 7.90 (d, *J*=8.20 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 25.3 - 27.3, 31.9, 80.0, 114.4, 125.6, 125.9, 128.9, 131.5, 134.9, 138.8, 143.4

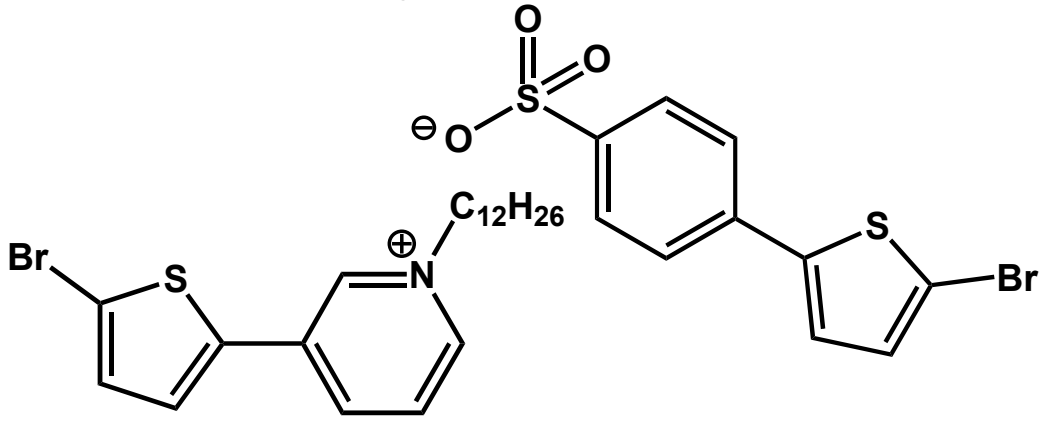
3-(5-bromo-2-thienyl)pyridine [4-6]



Compound 4 - 6

The **4-2** 3-(5-bromo-2-thienyl)pyridine (0.220 g, 0.920 mmol) was placed into a roundbottom flask with 1-Iodododecane (0.410 g, 1.40 mmol) neat. The reaction was allowed to stir overnight at room temperature. The reaction solution was dissolved in hexane and the solvent was decanted. This was repeated twice to yield 3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium iodide, a brown oil of 0.416 g (85.0% yield) as the title compound **4-6**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.87 (t, *J*=6.64 Hz, 3 H) 1.17 - 1.50 (m, 20 H) 2.01 - 2.12 (m, *J*=7.03 Hz, 2 H) 5.06 (t, *J*=7.42 Hz, 2 H) 7.12 (d, *J*=3.90 Hz, 1 H) 7.98 (d, *J*=3.90 Hz, 1 H) 8.16 (dd, *J*=8.20, 6.25 Hz, 1 H) 8.52 (d, *J*=8.20 Hz, 1 H) 9.15 (d, *J*=5.86 Hz, 1 H) 9.85 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 13.9, 22.4, 25.7, 28.9, 29.1, 29.2, 29.3 - 29.5 (m, *J*=4.42 Hz, 3) 31.6, 31.8, 61.8, 116.9, 128.5, 130.0, 132.1, 134.1, 135.8, 140.0, 140.3, 141.9

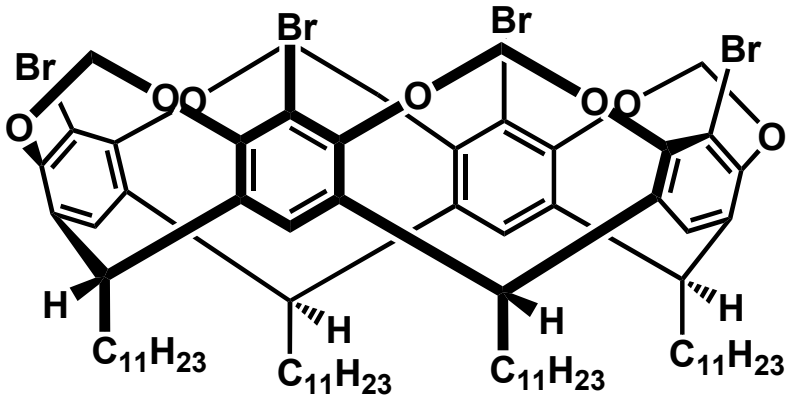
3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium-4-(5-bromo-2-thienyl)benzenesulfonate [4-7]



Compound 4 - 7

4-6 3-(5-bromo-2-thienyl)-1-dodedecanylpyridinium iodide (0.086 g, 0.160 mmol) was dissolved in 1.00 mL of DMSO and a solution of 4-(5-bromo-2-thienyl)benzenesulfonate (0.057g, 0.160 mmol) in 1.00 mL of DMSO was added. After addition of water (1.00 mL) the desired salt was obtained as an off white solid (0.090 g, 74% yield) to the title compound **4-7**. ^{1}H NMR (400 MHz, DMSO-d_6) □ δ 0.85 (t, *J*=6.83 Hz, 2 H) 1.19 - 1.33 (m, 20 H) 1.95 (q, *J*=6.64 Hz, 2 H) 4.59 (t, *J*=7.61 Hz, 2 H) 7.25 (d, *J*=3.90 Hz, 1 H) 7.38 (d, *J*=3.90 Hz, 1 H) 7.47 (d, *J*=3.90 Hz, 1 H) 7.53 - 7.59 (m, *J*=8.59 Hz, 2 H) 7.59 - 7.64 (m, *J*=8.59 Hz, 2 H) 7.76 (d, *J*=3.90 Hz, 1 H) 8.15 (dd, *J*=8.20, 6.25 Hz, 1 H) 8.76 (d, *J*=8.98 Hz, 1 H) 8.98 (d, *J*=6.25 Hz, 1 H) 9.43 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) □ δ 13.8 - 14.2, 21.6 - 22.3, 25.2 - 25.6, 28.3 - 28.5, 28.7 - 28.8, 28.7 - 28.8, 28.9 – 29.0, 28.9 - 29.1, 30.4 - 30.9, 31.3, 61.1,110.8, 115.5, 124.8, 126.3, 128.3, 129.2, 129.3, 131.8 ,132.4, 132.5, 132.7, 133.0, 137.1, 140.5, 141.1, 143.9, 144.6, 148.0

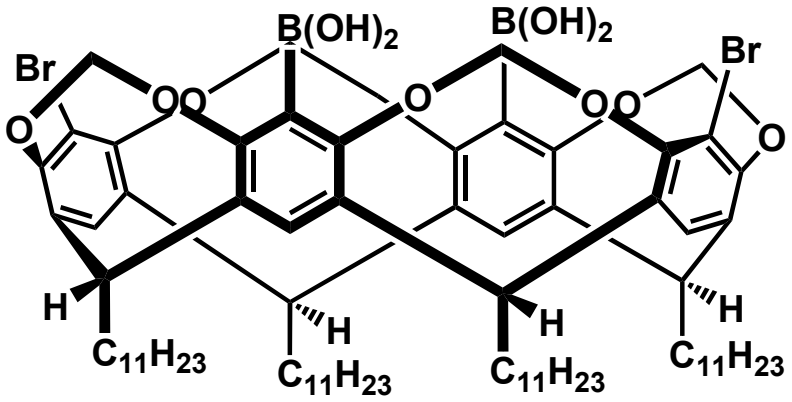
C-dodecyltetrabromorescorcin[4]arene [4-8] [12]



Compound 4 - 8

Bromochloromethane (493 mmol 33 mL) was added to a slurry of C-dodecyltetrabromocalix[4]resorinarene (50.0 g, 35.0 mmol), potassium carbonate (68.0 g, 493 mmol) and DMF 1350 mL and the mixture was stirred at 65° C for three days under nitrogen. Every 24 hours, more bromochloromethane (4.70 mL, 70.0 mmol) was added. The DMF was removed in vacuo to give a dark brown gum. Diethyl Ether was added to the residue followed by 2.00 M HCl with stirring. The aqueous phase were separated and extracted with more diethyl ether. The combined organic layers were washed with water, saturated brine, dried over magnesium sulfate and filtered. Evaporation of the solvent yielded a clear brown gum that was purified with column chromatography, 9:1 hexane:ethyl acetate, to yield pure product as a light brown oil to give the title compound **4-8**.[12] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.890 (t, *J*=6.64 Hz, 12 H) 2.20 (d, *J*=7.81 Hz, 8 H) 4.33 (d, *J*=7.42 Hz, 4 H) 4.86 (t, *J*=8.00 Hz, 4 H) 5.98 (d, *J*=7.42 Hz, 4 H) 7.07 (s, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.3, 22.9, 27.9, 29.6, 29.9, 30.3, 32.1, 38.1, 93.2, 98.9, 120.8, 138.9, 155.1 LRMS calculated for $C_{76}H_{108}Br_4O_8$ 1464.48 found (M+)1468.6

A,C Bis-boronic acid- C,D-bis-bromo resocin[4]arene [3-12] [6]

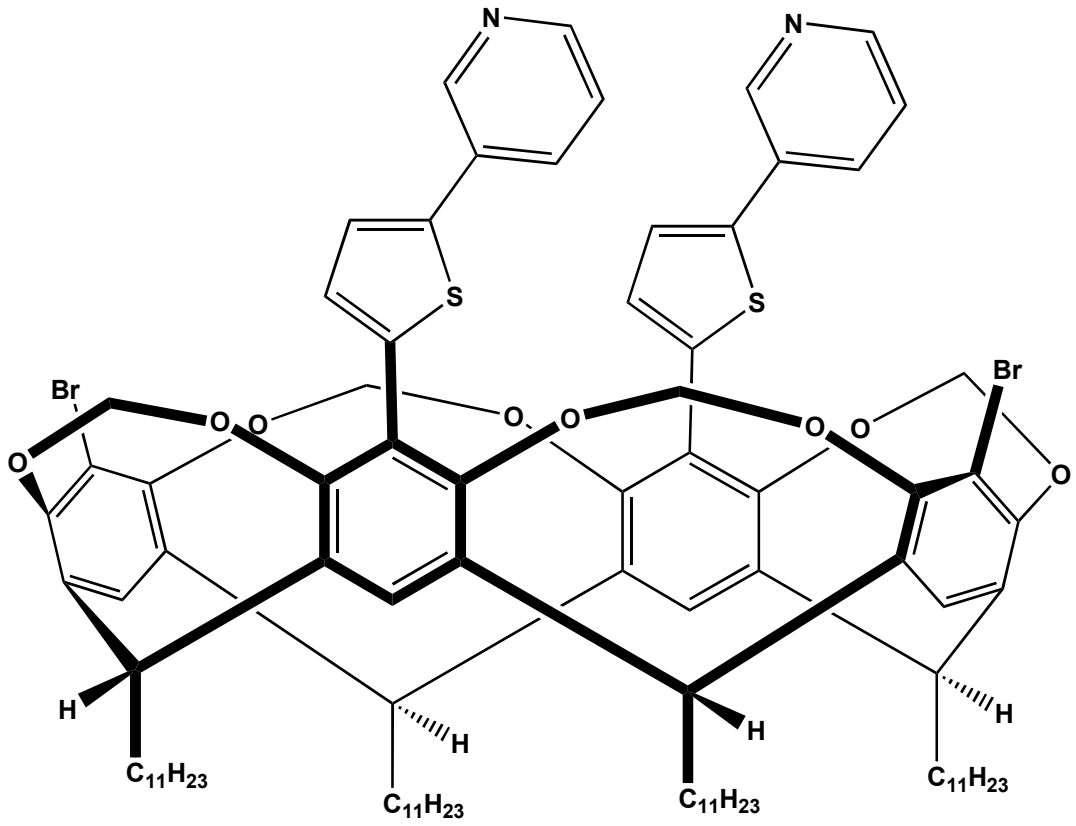


Compound 4 - 9

Dry THF (40.0 mL) was added to a sealed tube with a stir-bar containing tetrabromo cavitand **4-8** (4.10 g, 2.80 mmol). The resulting solution was evaporated to dryness and heated to 80°C for one hour. The vacuum was replaced with nitrogen and the procedure was repeated two more times. Dry THF (200 mL) was added to the dried tetrabromo cavitand. The reaction vessel was chilled to -78°C with a dry ice temperature bath and n-butyllithium (0.380 g, 3.70 mL of 1.60 M in hexanes, 2.10 eqiv.) was added. After 20 minutes of stirring, triisopropyl borate (4.20 g, 22.0 mmol, 5.20 mL) was added to the reaction vessel at -78°C. After stirring for 30 minutes, 2.50 M of HCl was added to the reaction vessel and allowed a stir for an additional 30 minutes. The reaction solution was transferred to a separtory funnel. Methylene chloride and brine were added to the flask. The organic and aqueous layers were separated and the aqueous layer was washed a second time with methylene chloride. The organic layers were combined, dried with magnesium sulfate, filtered and concentrated. The resulting oil was purified by column chromatography with the product eluting with 50:50 hexane:ethyl acetate (1.82 g, 46% yield) to give the title compound **4-9**.[6] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.89 (none, *J*=6.64 Hz, 8 H)

1.36 (q, 99 H) 2.23 (q, *J*=7.81 Hz, 8 H) 4.45 (d, *J*=7.42 Hz, 4 H) 4.81 (s, 3 H) 5.60 (s, 4 H) 5.90 (d, *J*=7.42 Hz, 4 H) 7.06 (s, 2 H) 7.20 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.0 - 14.3, 22.5 - 22.9, 27.5 - 28.0, 29.2 - 29.6, 29.5 - 29.9, 29.9 - 30.3, 31.8 - 32.1, 36.6 - 37.4, 98.9 - 99.5, 113.3, 118.8, 123.4, 138.1, 139.2, 152.1, 158.6

A,C-bis 3-(5-bromo-2-thienyl)pyridine resocin[4]arene [4-10]

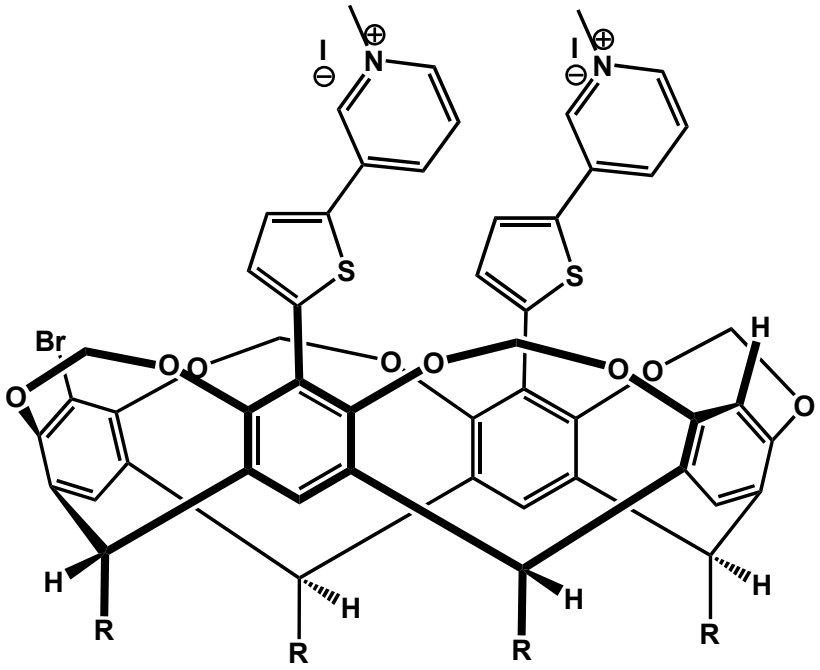


Compound 4 - 10

A,C bis boronic acid cavitand **4-9**(1.00 g, 0.715 mmol), tetrakis(triphenylphosphine)palladium(0) (0.083 g, 0.0710 mmol), 3-(5-bromo-2-thienyl)pyridine **4-2** (0.515 g, 2.14 mmol), 2.00 M sodium bicarbonate (1.50 ml) and toluene (4.00 ml) was placed in a sealed tube. The reaction vessel was de-gassed by freeze-pump-thaw three times and heated for 8 hours at 70°C. The

reaction vessel was allowed to reach room temperature and the contents were washed with a saturated sodium bicarbonate solution. Methylene chloride was added and the organic layer was washed with a brine solution. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield a light-brown residue. The product was isolated by column chromatography to yield the desired A,C-bis 3-(5-bromo-2-thienyl)pyridine resocin[4]arene to give 0.850 g (73% yield) as a light brown residue of the title compound **4-10**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 1.23 - 1.51 (m, 80 H) 2.27 (d, *J*=3.90 Hz, 8 H) 4.42 (d, *J*=7.42 Hz, 4 H) 4.90 (t, *J*=8.00 Hz, 3 H) 5.85 (d, *J*=7.42 Hz, 4 H) 7.15 (s, 2 H) 7.19 (s, 1 H) 7.20 (d, *J*=3.90 Hz, 1 H) 7.33 (dd, *J*=5.08 Hz, 2 H) 7.36 (d, *J*=3.51 Hz, 2 H) 7.87 (dd, *J*=6.05, 2.15 Hz, 2 H) 8.54 (d, *J*=3.51 Hz, 2 H) 8.89 (d, *J*=1.95 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1,22.7,27.8,29.4,29.7, 30.2, 31.9, 37.4, 99.5, 113.2, 119.0, 120.5, 122.1, 123.7, 124.2, 130.0, 130.1, 132.8, 133.8, 138.6, 139.2, 140.9, 146.8, 148.6, 152.2, 152.5 LRMS calc. for $C_{94}H_{120}Br_2N_2O_8S_2$ 1626.7 found (M+) 1629.9

A,C-bis 3-(5-bromo-2-thienyl)methyl pyridinium iodide resorcin[4]arene [4-11]

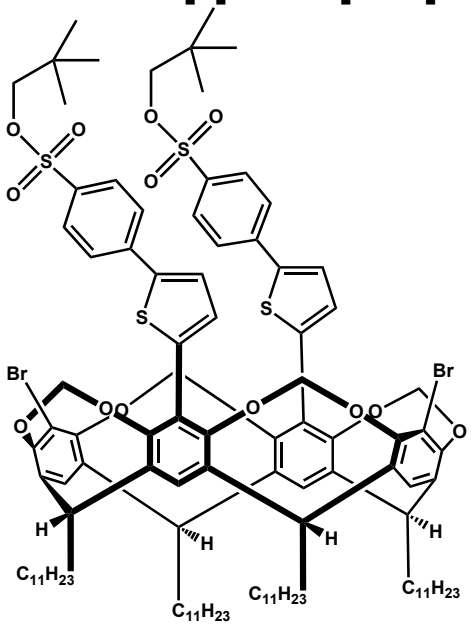


Compound 4 - 11

The A,C-bis 3-(5-bromo-2-thienyl)pyridine resorcin[4]arene **4-10** (0.23 g 14.0 mmol), methyl iodide (0.847 mmol 0.050 mL) and THF (1.00 mL) were added to a sealed reaction container. The reaction was allowed to stir overnight at room temperature. The solvent was removed via vacuum and the remaining residue was dissolved in methyl chloride. The methylene chloride was washed with brine. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the desired A,C-bis 3-(5-bromo-2-thienyl)methyl pyridinium iodide cavitand as a brown residue to give 0.19 g (85.0% yield) of the title compound **4-11**. ^{1}H NMR (400 MHz, CDCl3) □ δ 1.19 - 1.51 (m, 84 H) 2.25 (s, 8 H) 4.42 (d, *J*=7.03 Hz, 4 H) 4.72 (s, 6 H) 4.85 (t, *J*=8.00 Hz, 4 H) 5.83 (d, *J*=7.03 Hz, 2 H) 7.11 (s, 2 H) 7.19 (s, 2 H) 7.29 (d, *J*=3.90 Hz, 1 H) 7.95 (d, *J*=3.90 Hz, 1 H) 8.05 (dd, *J*=6.64 Hz, 1 H) 8.56 (d, *J*=8.20 Hz, 1 H) 8.99 (d, *J*=5.08 Hz, 2 H);

^{13}C NMR (101 MHz, CDCl3) d δ 14.1,22.6,27.9,29.4,29.7 29.9, 30.2, 31.5, 31.9, 37.4, 49.5, 99.5, 113.4, 121.2, 128.3, 128.9, 130.4, 130.6, 131.0, 133.2, 133.3, 134.7, 135.1, 137.8, 138.5, 138.9, 140.2, 141.4, 142.7, 152.1, 152.3 LRMS calc for $C_{96}H_{126}Br_2N_2O_8S_2$ 1910.5 found 1786.8

A,C-bis-3-Dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate resorcin[4]arene [4-12]

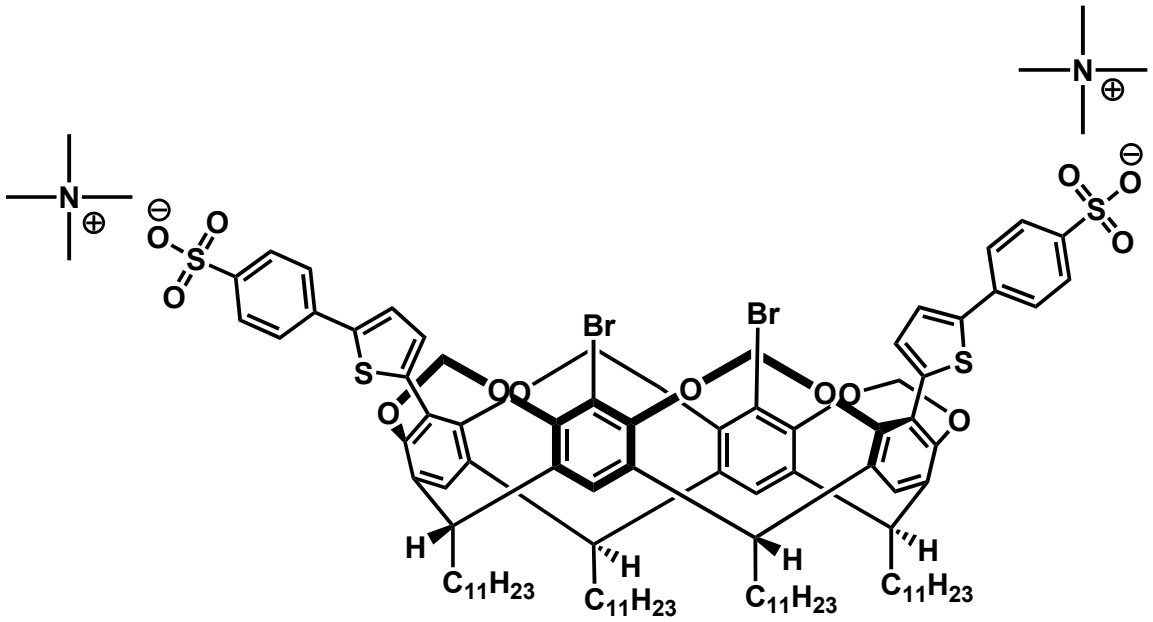


Compound 4 - 12

The A,C bis boronic acid cavitand **4-9** (0.320 g, 0.230 mmol), tetrakis(triphenylphosphine)palladium(0) (0.030 g, 0.023 mmol), 2,2-dimethylpropyl 4-(5-bromo-2-thienyl)benzenesulfonate **4-5** (0.270 grams 0.690 mmol), 2.00 M sodium bicarbonate (1.00 ml) and toluene (3.00 ml) was placed in a sealed tube. The reaction vessel was then de-gassed by freeze-pump-thaw three times and heated for eight hours at 80°C. The reaction vessel was allowed to reach room temperature and the contents were washed with a saturated sodium bicarbonate solution. The organic layer was washed with a brine solution, dried with magnesium sulfate, filtered and concentrated to yield a light-brown residue. The product was isolated by column chromatography to yield the A,C dimethylpropylbissulfonate-cavitand as an off-white residue to give (0.340 g, 77%

yield) of the title compound **4-12**. ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.790 - 1.01 (m, 34 H) 1.15 - 1.65 (m, 83 H) 2.28 (s, 8 H) 3.71 (s, 4 H) 4.41 (d, *J*=7.42 Hz, 4 H) 4.90 (t, *J*=8.00 Hz, 4 H) 5.86 (d, *J*=7.03 Hz, 4 H) 7.17 (s, 1 H) 7.21 (s, 2 H) 7.23 (d, *J*=3.90 Hz, 2 H) 7.44 (d, *J*=3.90 Hz, 2 H) 7.75 (d, *J*=8.59 Hz, 3 H) 7.91 (d, *J*=8.59 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 22.7, 26.0, 27.8, 29.4, 29.7, 30.1, 31.6, 31.9, 37.4, 79.7, 99.4, 113.1, 119.1, 120.7, 121.8, 125.2, 125.8, 128.6, 130.3,134.3,134.9,138.6,139.0,139.2,142.2,152.1,152.4

A,C Bis sulfonate thiophene tetramethyl ammonium resocin[4]arene [4-13]

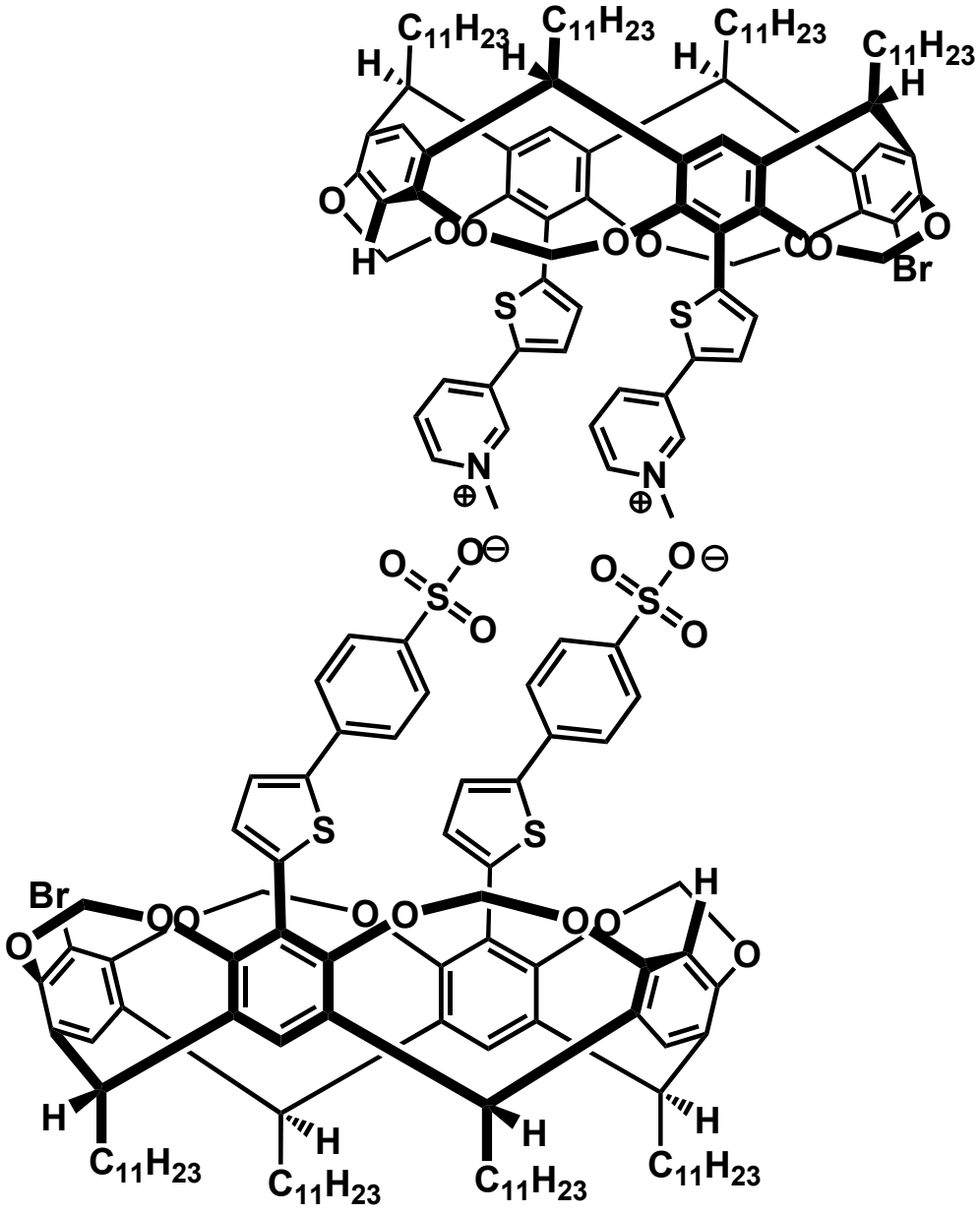


Compound 4 - 13

The A,C dimethylpropylbissulfonate-cavitand **4-12** (0.073 g, 0.038 mmol), tetramethyl ammonium chloride (0.041 g, 0.380 mmol) and DMF (0.500 mL) was placed in a sealed tube. The reaction vessel was heated at 150°C for 24 hours. The reaction solution was allowed to cool to room temperature and the DMF was removed in vacuo. The remaining residue was dissolved in methylene chloride and washed with brine solution. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield a light brown residue. The product was isolated using C18 reverse phase column chromatography with 100% THF to yield the product as an off white solid to give (0.213 g, 99% yield) of the title compound **4-13**.[11] ^{1}H NMR (400 MHz, $CDCl_3$) □ δ 0.880 (t, *J*=6.64 Hz, 12 H) 2.27 (s, 8 H) 3.31 (s, 24 H) 4.36 (d, 4 H) 4.36 (s, *J*=5.47 Hz, 2 H) 4.86 (t, *J*=7.22 Hz, 4 H) 4.86 (t, *J*=7.22 Hz, 2 H) 5.77 (d, *J*=5.47 Hz, 4 H) 5.77 (d, *J*=5.47 Hz, 4 H) 7.11

(s, 2 H) 7.11 (s, 2 H) 7.16 (s, 2 H) 7.16 (s, 2 H) 7.18 (d, *J*=3.51 Hz, 2 H) 7.18 (d, *J*=3.51 Hz, 2 H) 7.32 (d, *J*=3.51 Hz, 1 H) 7.32 (d, *J*=3.51 Hz, 2 H) 7.57 (d, *J*=8.20 Hz, 4 H) 7.57 (d, *J*=8.20 Hz, 4 H) 7.83 (d, *J*=7.81 Hz, 4 H) 7.83 (d, *J*=7.81 Hz, 4 H) 7.83 (d, *J*=7.81 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ δ 14.1, 22.7, 27.9, 29.4, 29.7, 29.8, 30.2, 30.3, 31.9, 37.4, 55.4, 99.4, 113.3, 118.9, 120.4, 122.4, 124.0, 125.4, 126.5, 130.5, 132.95, 135.1, 138.5, 139.1, 143.5, 145.5, 152.2, 152.5

A,C Bis sulfonate-A,C bis pyridinium capsule 4-14

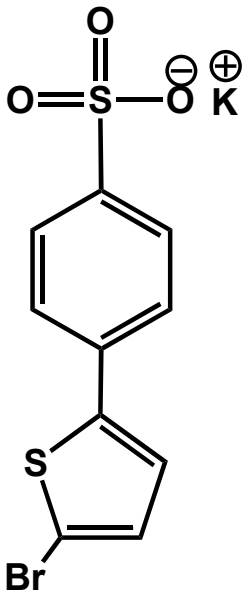


Compound 4 - 14

The A,C-bis methyl pyridinium iodide cavitand **4-11**(0.021 g, 0.0109 mmol) and the A,C bissulfonate-cavitand **4-13**(0.0108 g, 0.0108 mmol) was dissolved separately in 1.00 mL of DMSO. The two solutions were mixed together at room

temperature and immediately a white precipitation occurred. The precipitation was isolated via filtration to yield an off white solid of 0.030 g to give (79% yield) as the title compound **4-14**. ^{1}H NMR (400 MHz, CDCl3) □ δ 0.670 - 1.00 (m, 24 H) 1.18 - 1.50 (m, 164 H) 2.24 (s, 16 H) 4.26 - 4.45 (m, 8 H) 4.61 (s, 6 H) 4.75 - 4.94 (m, 8 H) 5.68 - 5.86 (m, 8 H) 7.06 - 7.25 (m, 12 H) 7.29 - 7.36 (m, 2 H) 7.53 (s, 4 H) 7.82 (s, 6 H) 7.88 - 8.01 (m, 2 H) 8.40 (s, 2 H) 8.94 (s, 2 H) 9.48 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) □ δ 12.5, 20.9, 26.3, 27.6, 27.9, 28.0, 30.1, 36.1, 46.8, 97.6, 110.8, 110.9, 119.2, 119.4, 119.5, 120.3, 120.5, 121.3, 121.8, 123.2, 125.0, 126.4, 126.5, 128.6, 129.3, 131.2, 132.5, 132.8, 133.8, 135.8, 137.0, 137.1, 137.8, 138.6, 140.4, 141.5, 142.2, 145.3, 150.1, 150.2, 150.3

Potassium 4-(5-bromo-2-thienyl)benzenesulfonate [3-7]



compound 3- 25

phenyl 4-(5-bromo-2-thienyl)benzenesulfonate .52 grams (1.31 mmol) and 10 mL of CH_2Cl_2 and 10 mL of methanol was placed into a small round bottom flask. .73 grams (13 mmol) of KOH was dissolved in 5 mL of CH_3OH. The reaction was

cooled to 0^{o}C and slowly the KOH solution was added to reaction. A precipitate was filtered to produce .435 grams (1.22 mmol) 93 % yield of the title compound **3-7**. 1H NMR (200 MHz, DMSO-d_6) d ppm 7.264 (d, *J*=3.66 Hz, 1 H) 7.393 (d, *J*=3.66 Hz, 1 H) 7.598 (d, *J*=8.42 Hz, 4 H) 13C NMR (101 MHz, DMSO-d_6) d ppm 110.817, 124.521, 124.675, 126.403, 31.786, 132.687, 144.589, 147.94

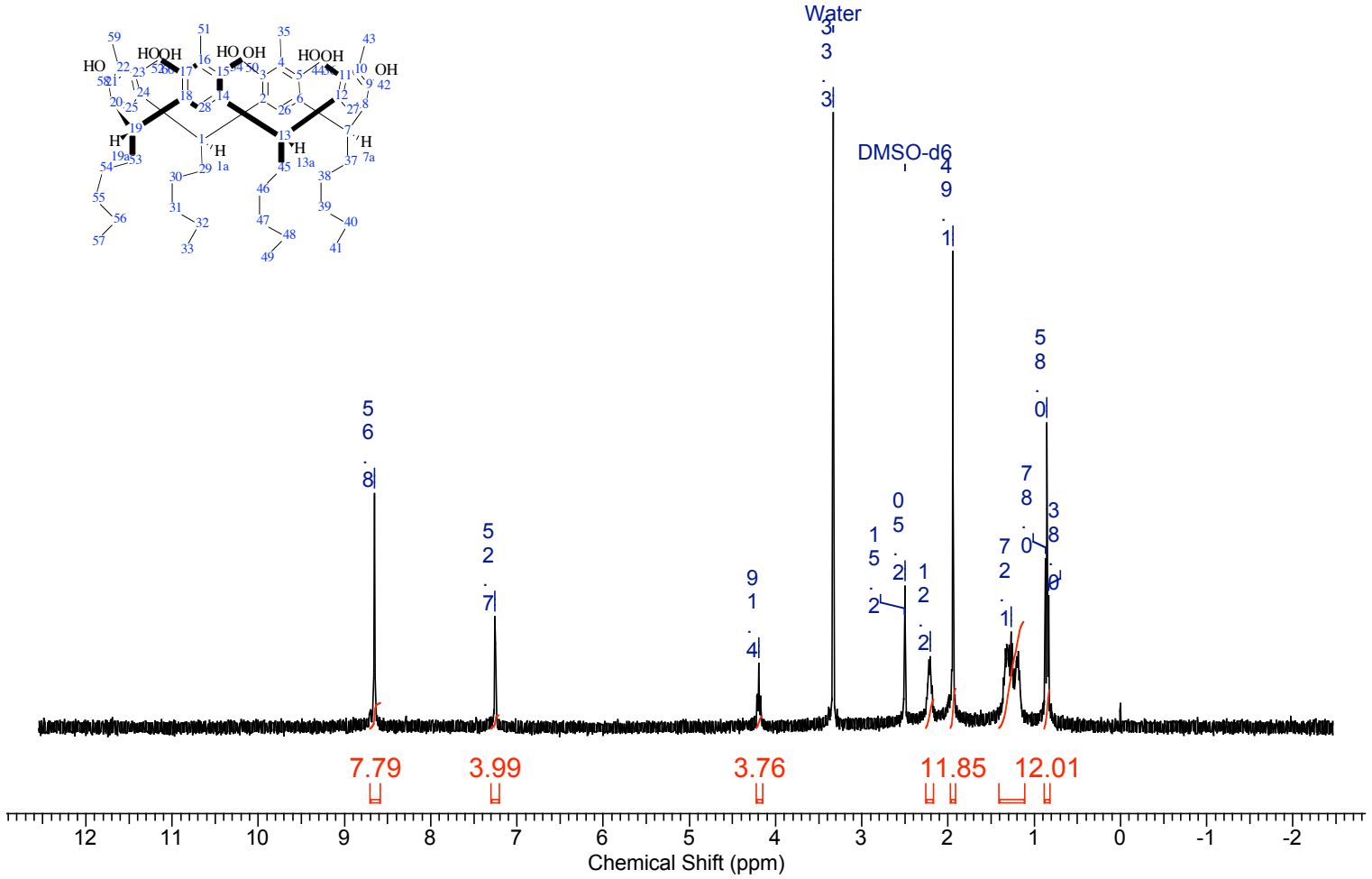
.References

1. Branda, N.; Wyler, R.; Rebek, J., Encapsulation of Methane and Other Small Molecules in a Self-Assembling Superstructure. *Science* **1994,** 263, (5151), 1267-1268.
2. Hamann, B. C.; Shimizu, K. D.; Rebek, J., Reversible encapsulation of guest molecules calixarene dimer. *Angewandte Chemie-International Edition in English* **1996,** 35, (12), 1326-1329.
3. Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Molecular encapsulation. *Angewandte Chemie-International Edition* **2002,** 41, (9), 1488-1508.
4. Ionic, G. E. i. a. W.-S. M. C. B. o.; Interactions; Francesca Corbellini, L. D. C., ‡ Mercedes Crego-Calama,*,† Silvano Geremia,‡ and; David N. Reinhoudt*, Guest Encapsulation in a Water-Soluble Molecular Capsule Based on Ionic Interactions. *JACS* **2003,** 125, (33), 9946-9947.
5. Shovsky, G. V.; Reinhoudt, D. N.; Verboom, W., The underestimated role of counter ions in electrostatic self-assembly: [1+1] cavitand-calix[4]arene capsules based on azinium-sulfonate interactions. *European Journal of Organic Chemistry* **2006**, (12), 2810-2816.
6. Altamore, T. M.; Barrett, E. S.; Duggan, P. J.; Sherburn, M. S.; Szydzik, M. L., Cavitand boronic acids mediate highly selective fructose transport. *Organic Letters* **2002,** 4, (20), 3489-3491.
7. M. Alamgir Hossain, H.-J. S., Flexibility, Association Constants, and Salt Effects in Organic Ion Pairs:
How Single Bonds Affect Molecular Recognition. *Chemistry European Journal* **1999,** 5, (4), 1284-1290.

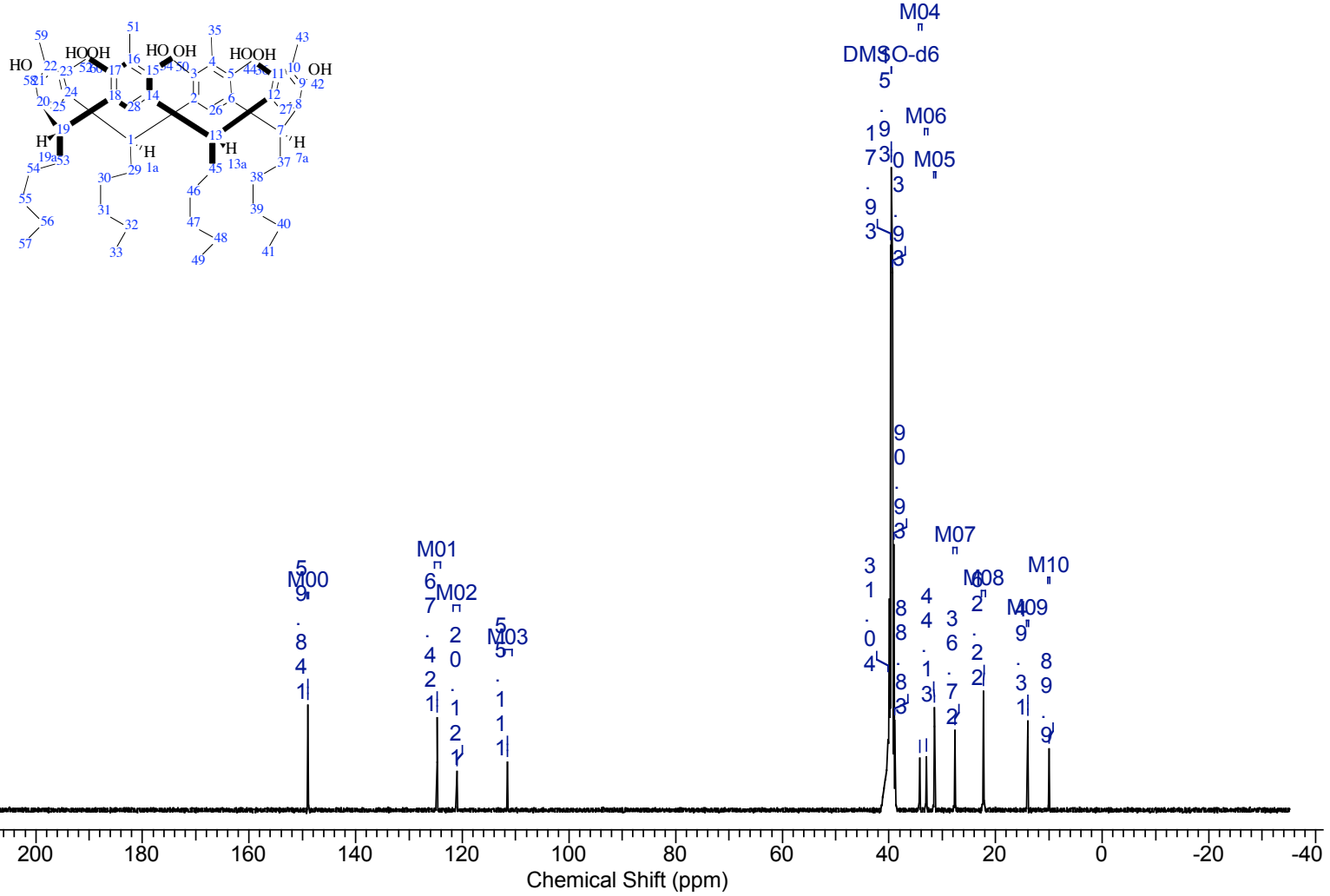
8. Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J., Host-guest complexation. 49. Cavitands containing two binding cavities. *J. Am. Chem. Soc. FIELD Full Journal Title:Journal of the American Chemical Society* **1989,** 111, (10), 3688-99.
9. Cram, D. J.; Choi, H. J.; Bryant, J. A.; Knobler, C. B., Host-Guest Complexation .62. Solvophobic and Entropic Driving Forces for Forming Velcraplexes, Which Are 4-Fold, Lock-Key Dimers in Organic Media. *Journal of the American Chemical Society* **1992,** 114, (20), 7748-7765.
10. Burger, M. T.; Lin, X. D.; Chu, D. T.; Hiebert, C.; Rico, A. C.; Seid, M.; Carroll, G. L.; Barker, L.; Huh, K.; Langhorne, M.; Shawar, R.; Kidney, J.; Young, K.; Anderson, S.; Desai, M. C.; Plattner, J. J., Synthesis and antibacterial activity of novel C-12 vinyl ketolides. *Journal of Medicinal Chemistry* **2006,** 49, (5), 1730-1743.
11. Roberts, J. C.; Gao, H.; Gopalsamy, A.; Kongsjahju, A.; Patch, R. J., Neopentyl ester protecting groups for arylsulfonic acids. *Tetrahedron Letters* **1997,** 38, (3), 355-358.
12. Peter Timmerman, B. M. G. A., van Mook,B Willem Verboom,B Gerrit J. van Hummel,b; Reinhoud@*, S. H. a. D. N., Selective Functionalization of Cavitands:
Synthesis of a New Hemicarcerand. *Tetrahedron Letters* **1992,** 33, (23), 3377-3380.

Appendix

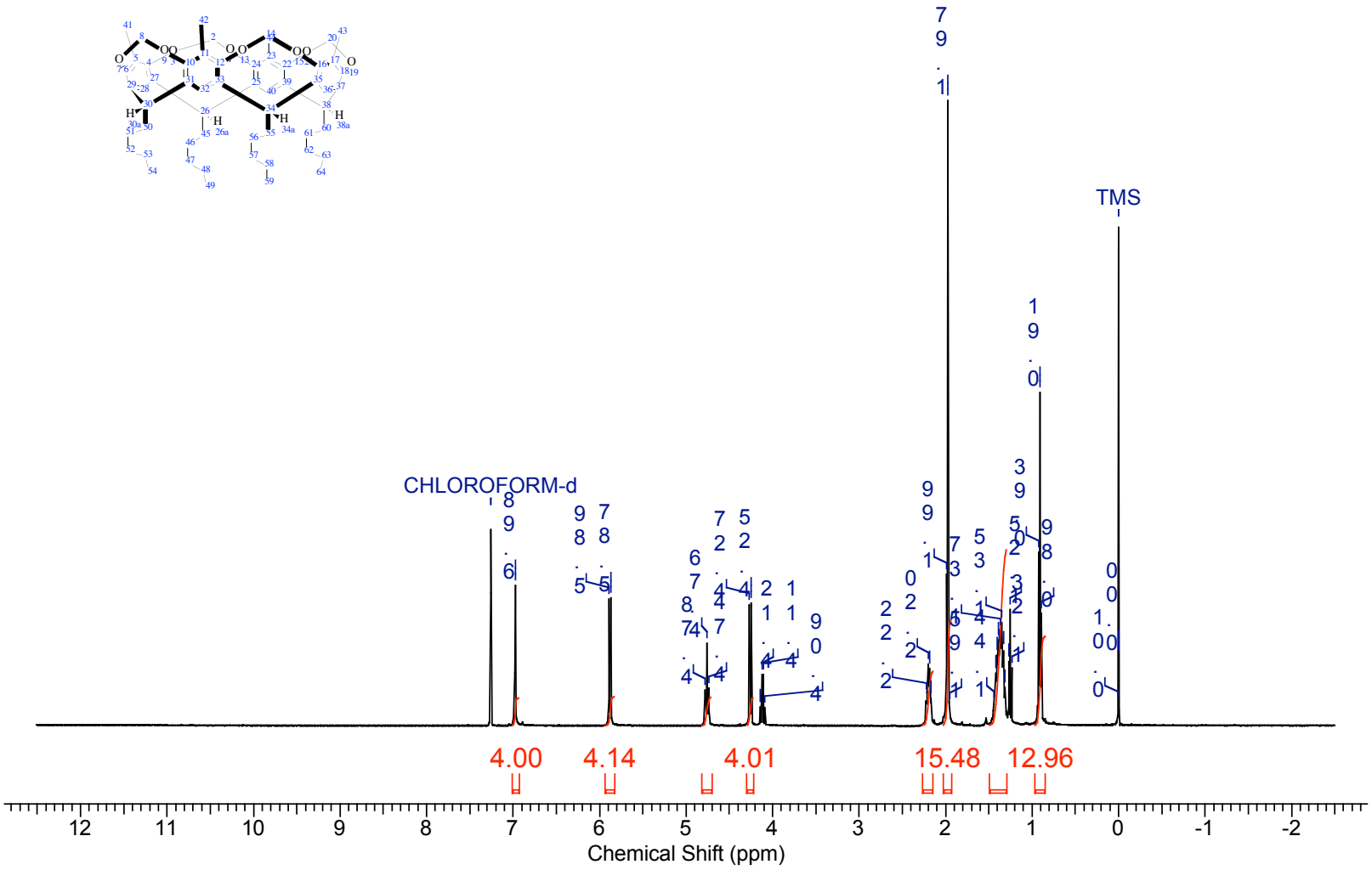
C-pentylmethylcalix[4]resorcinarene**[2-1]** ^{1}H



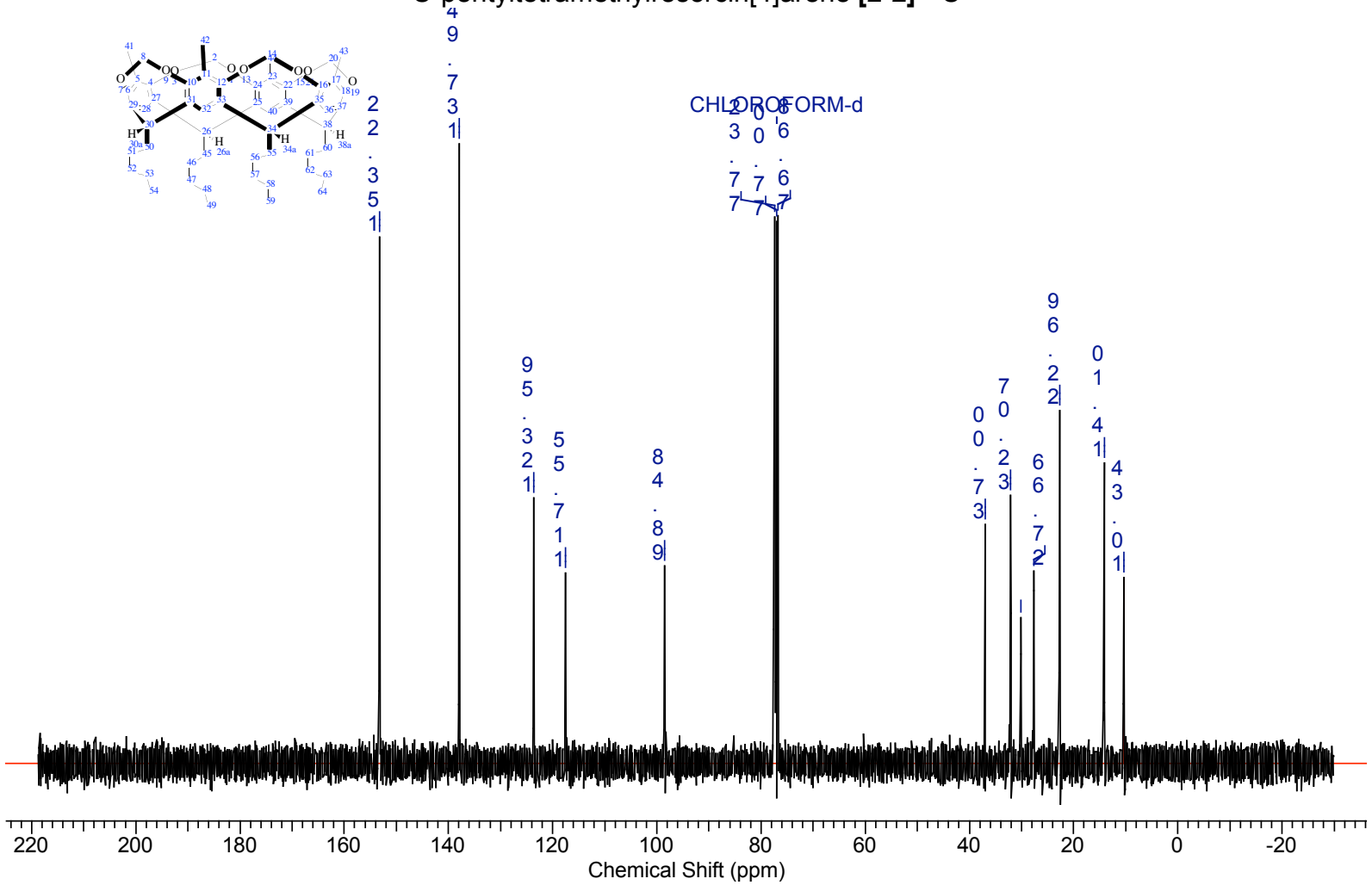
C-pentylmethylcalix[4]resorcinarene**[2-1]** ^{13}C



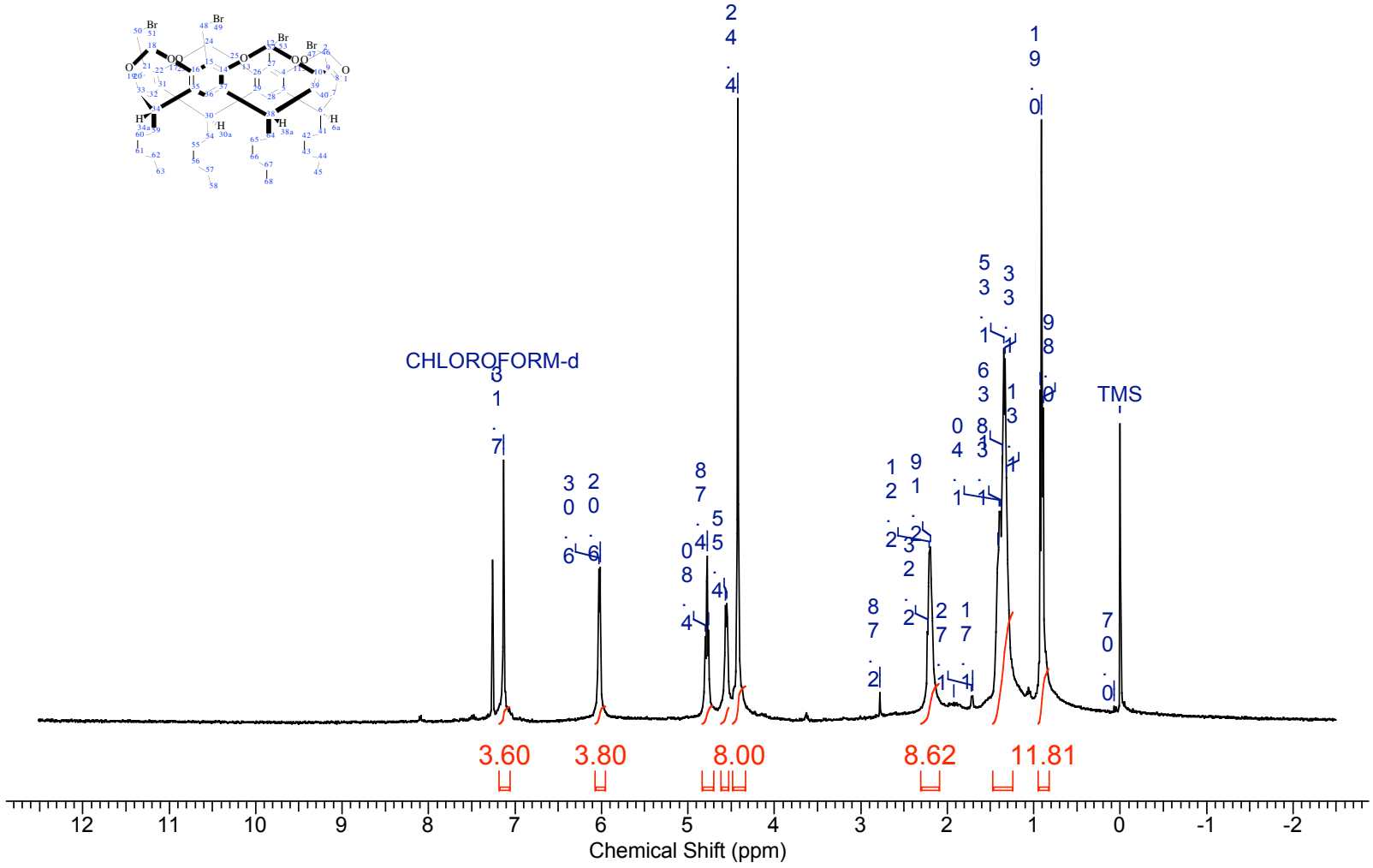
C-pentyltetramethylresorcin[4]arene **[2-2]** ^{1}H



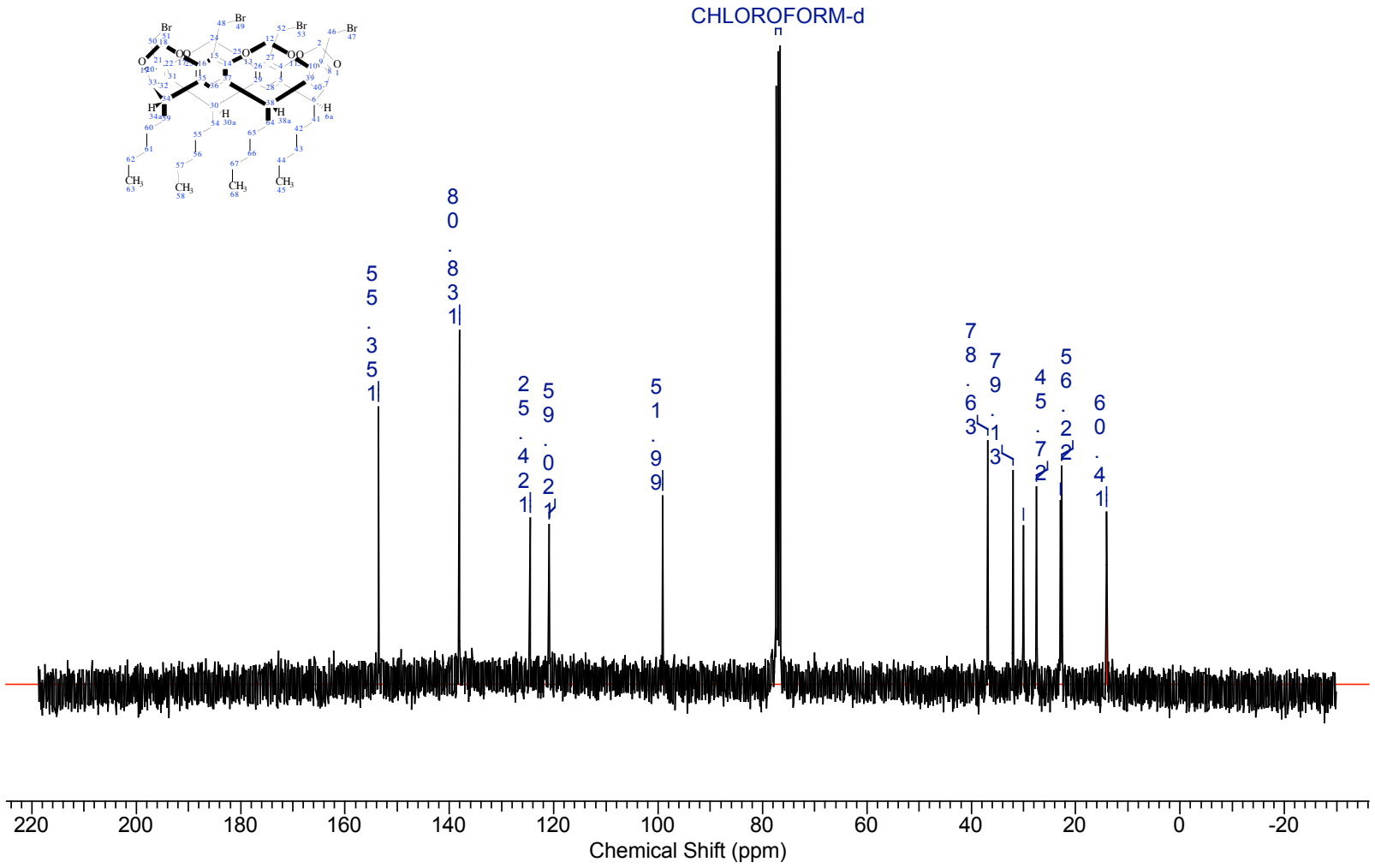
C-pentyltetramethylresorcin[4]arene **[2-2]** ^{13}C



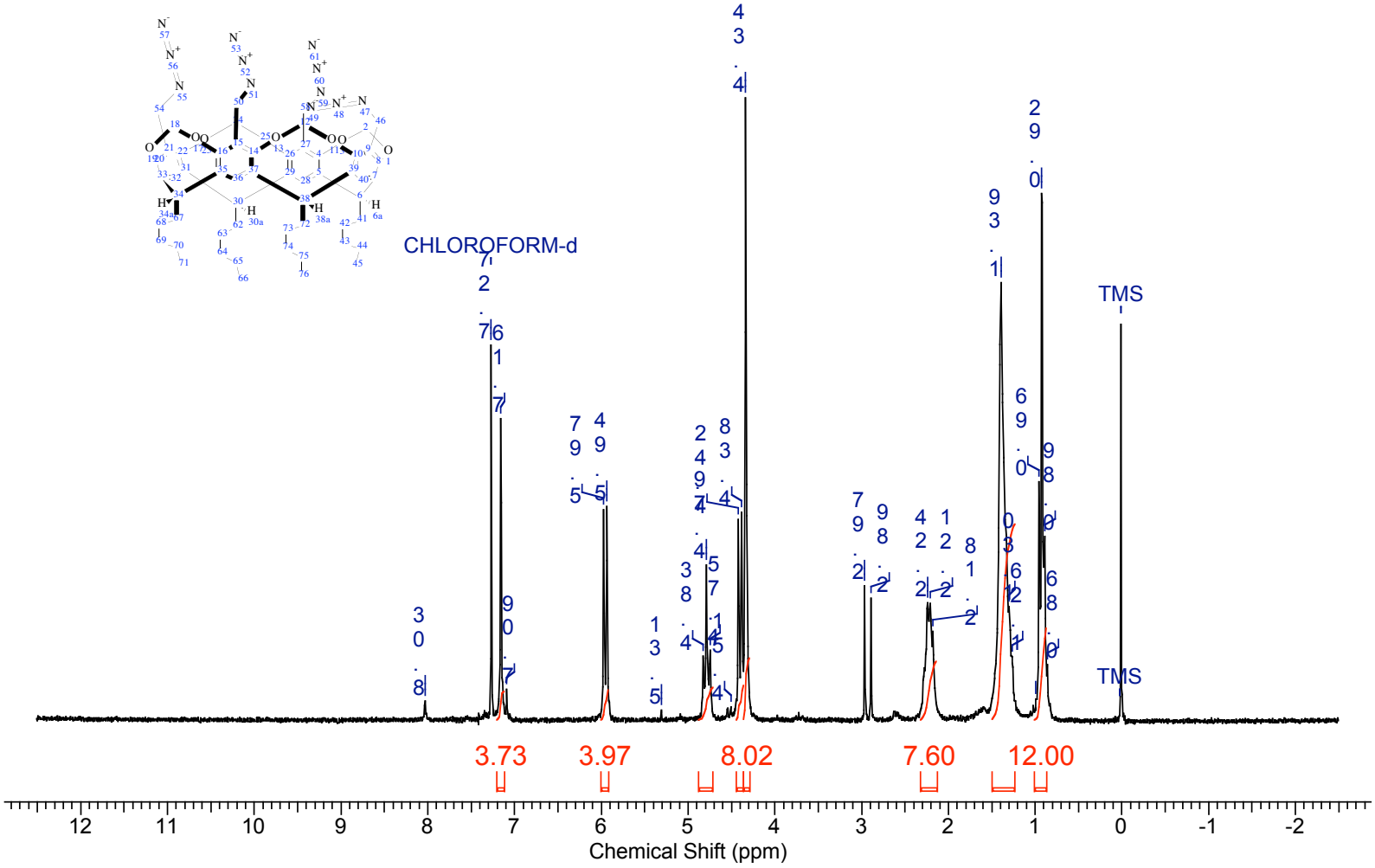
C-Pentyltetrabenzylbromideresorcin[4]arene **[2-3]** ^{1}H



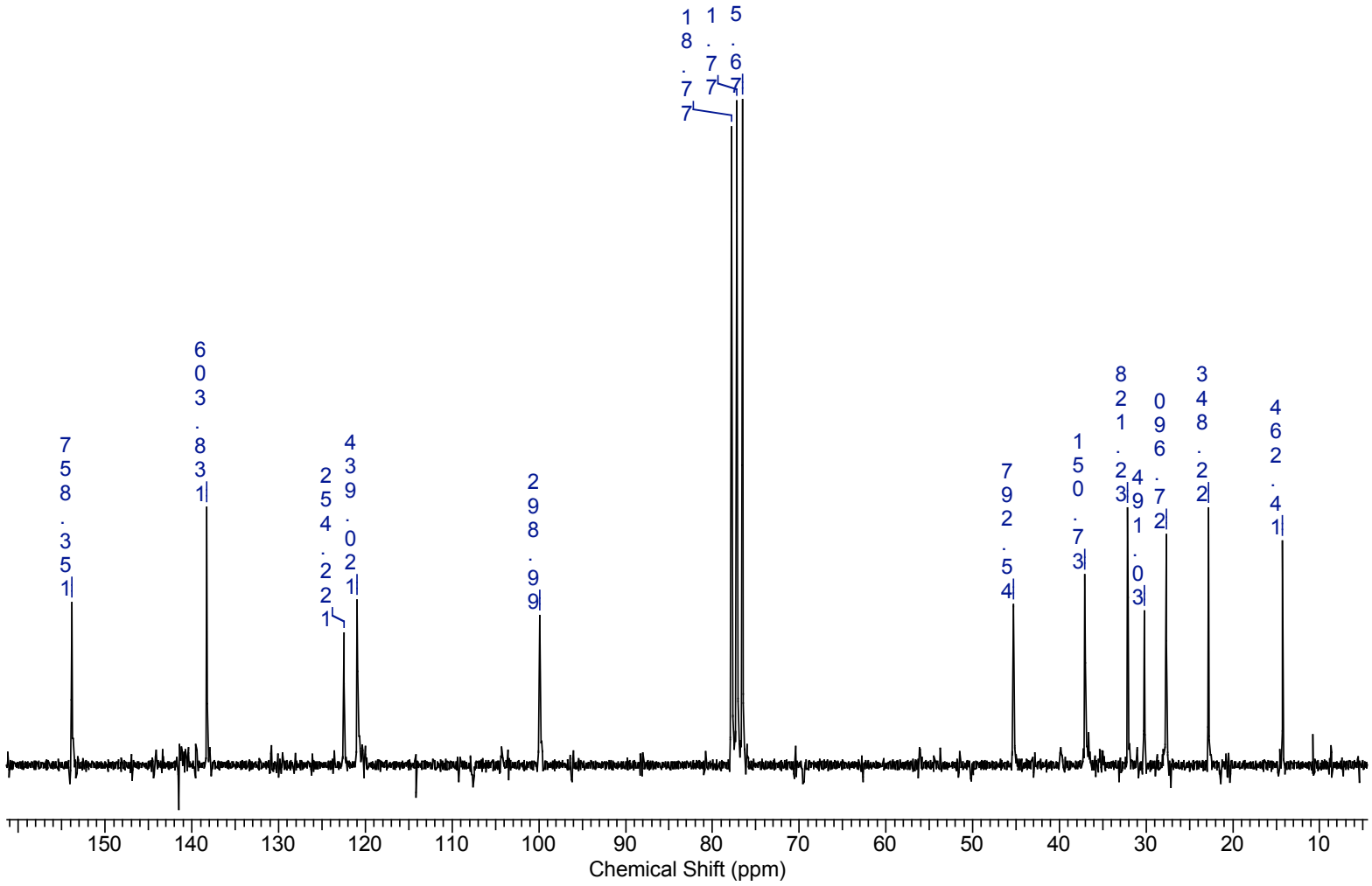
C-Pentyltetrabenzylbromideresorcin[4]arene **[2-3]** ^{13}C



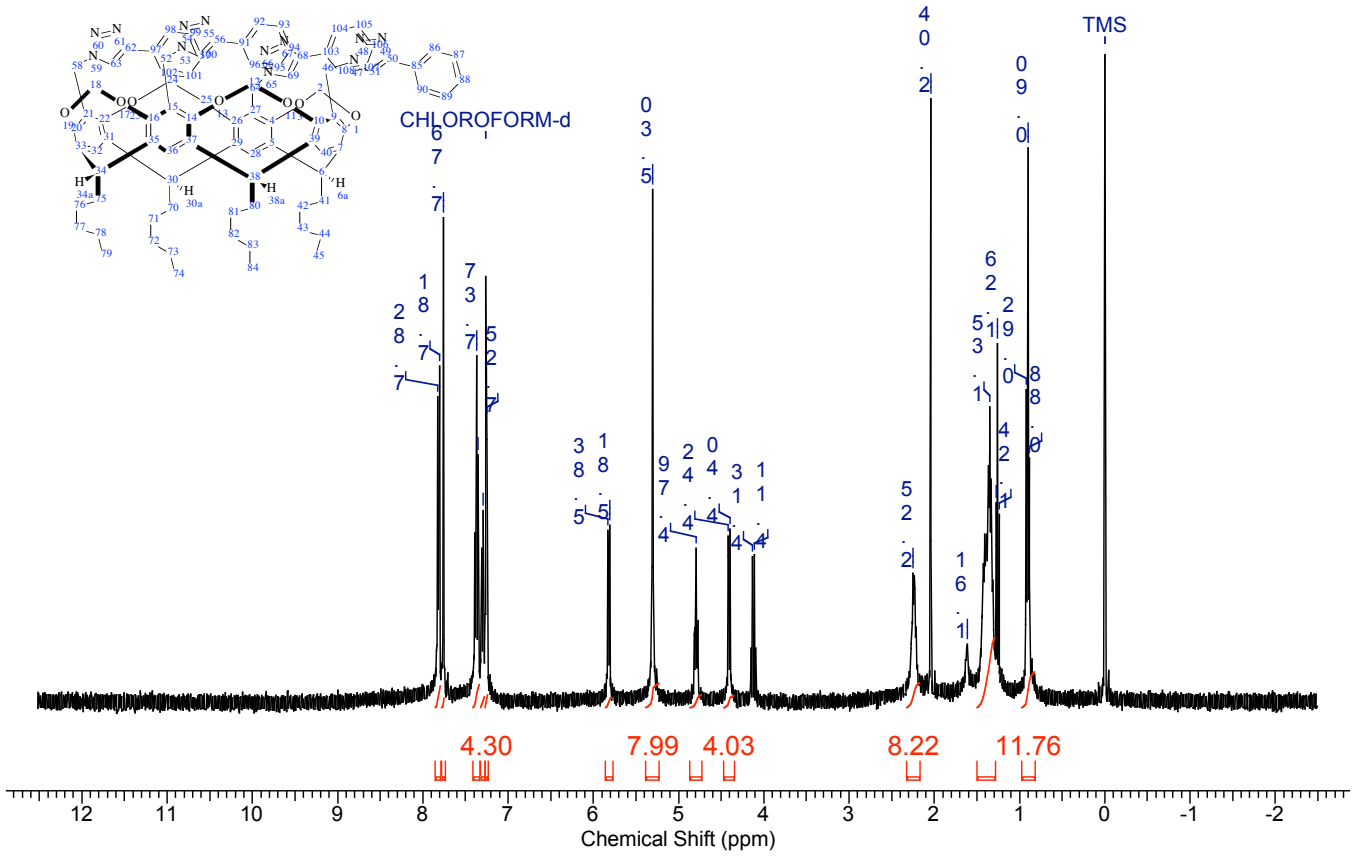
C-Pentyltetrabenzylazide resorcin[4]arene **[2-4]** ^{1}H



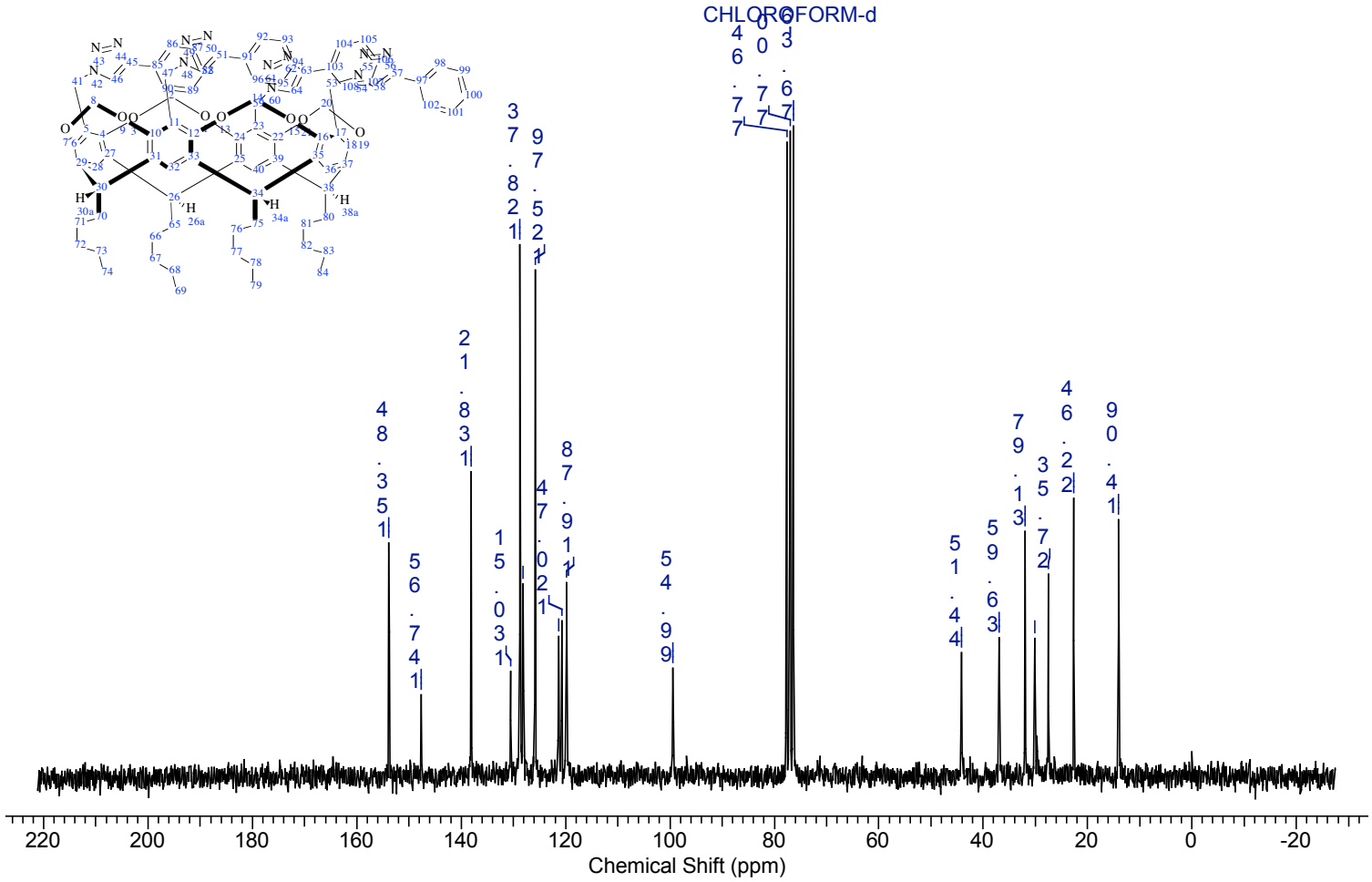
C-Pentyltetrabenzylazide resorcin[4]arene **[2-4]** ^{13}C



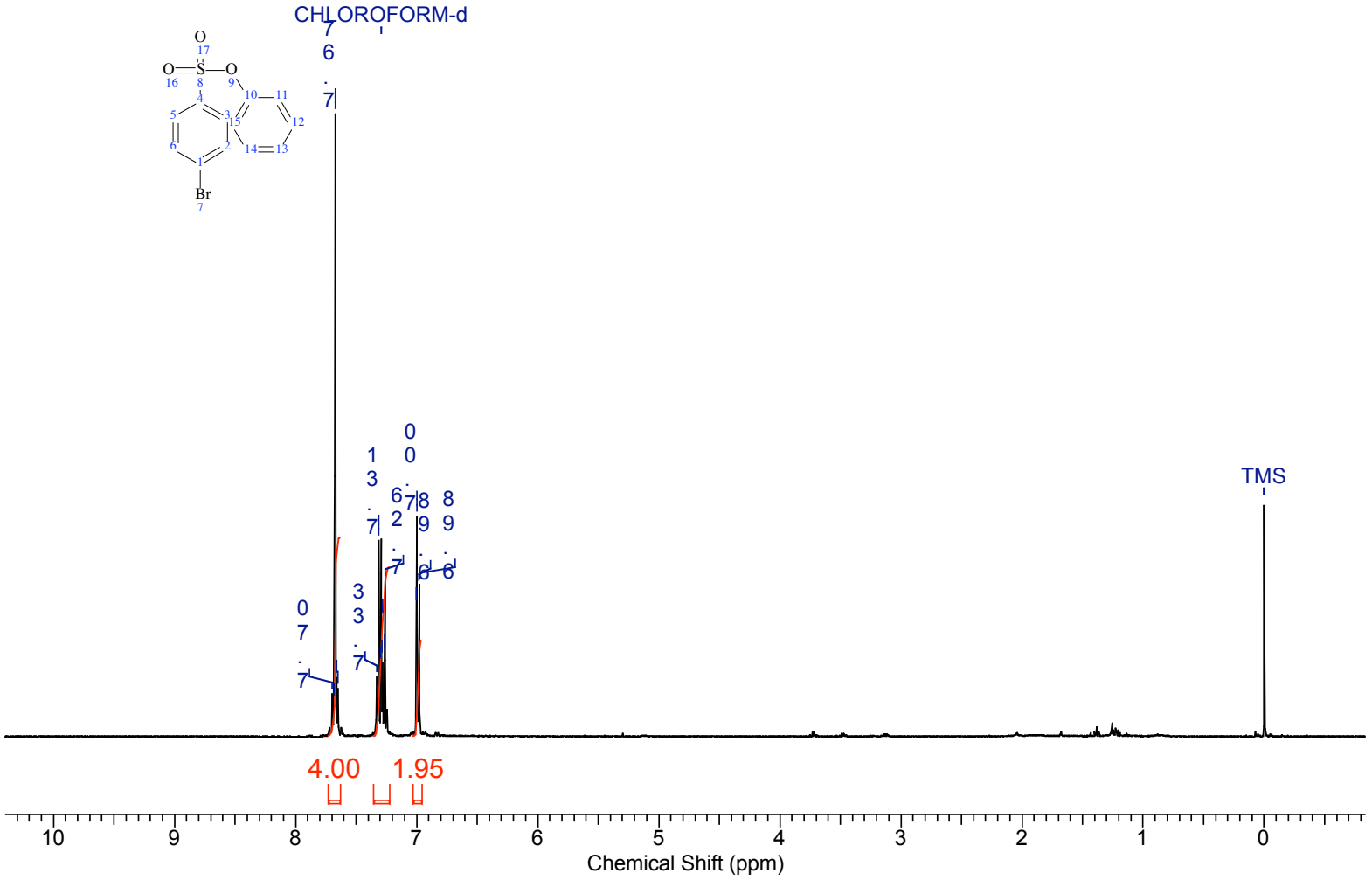
C-Pentyltetraphenyl-1,2,3-triazoleresorcin[4]arene **[2-5]** ^{1}H



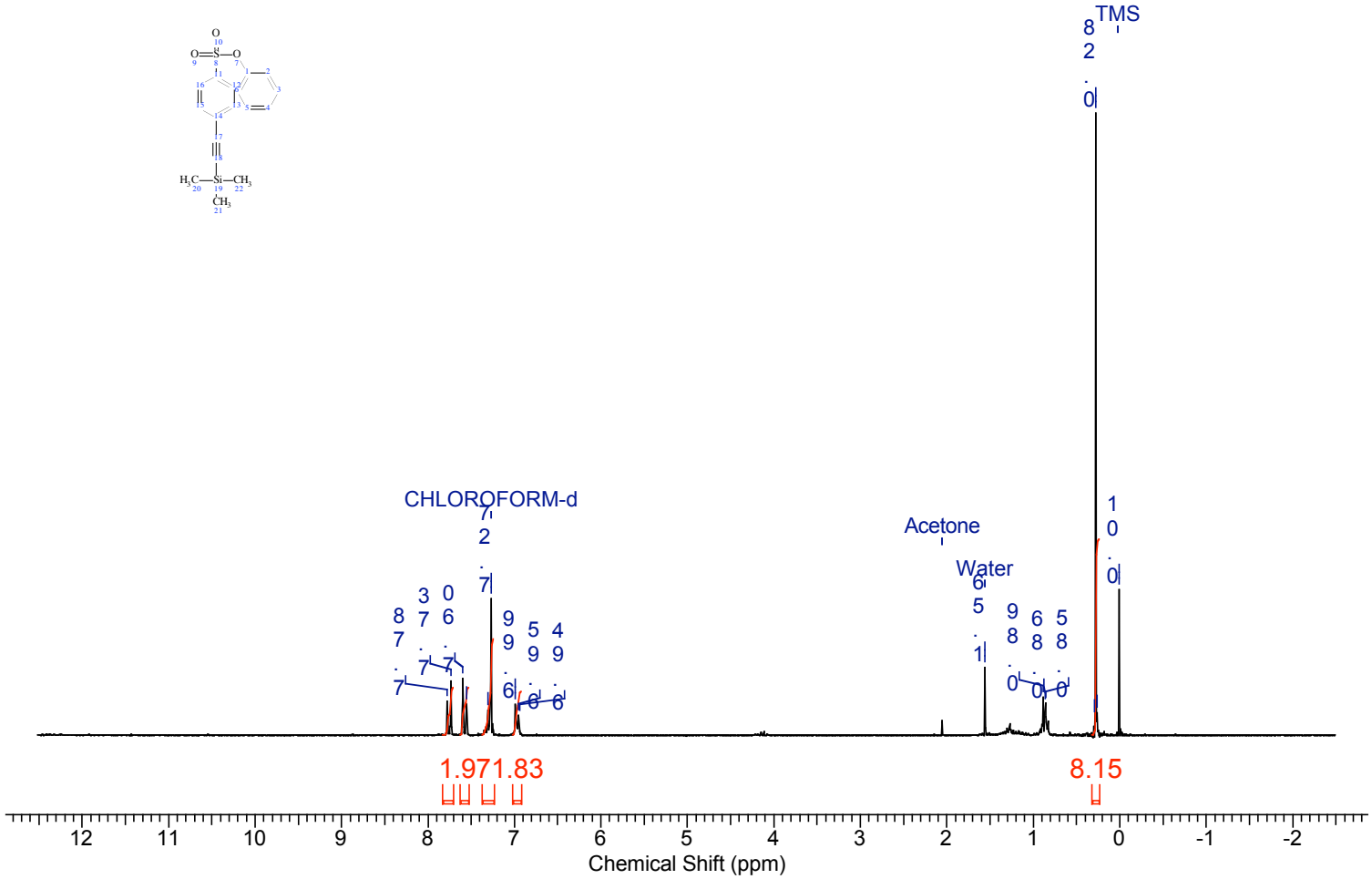
C-Pentyltetraphenyl-1,2,3-triazoleresorcin[4]arene **[2-5]** ^{13}C



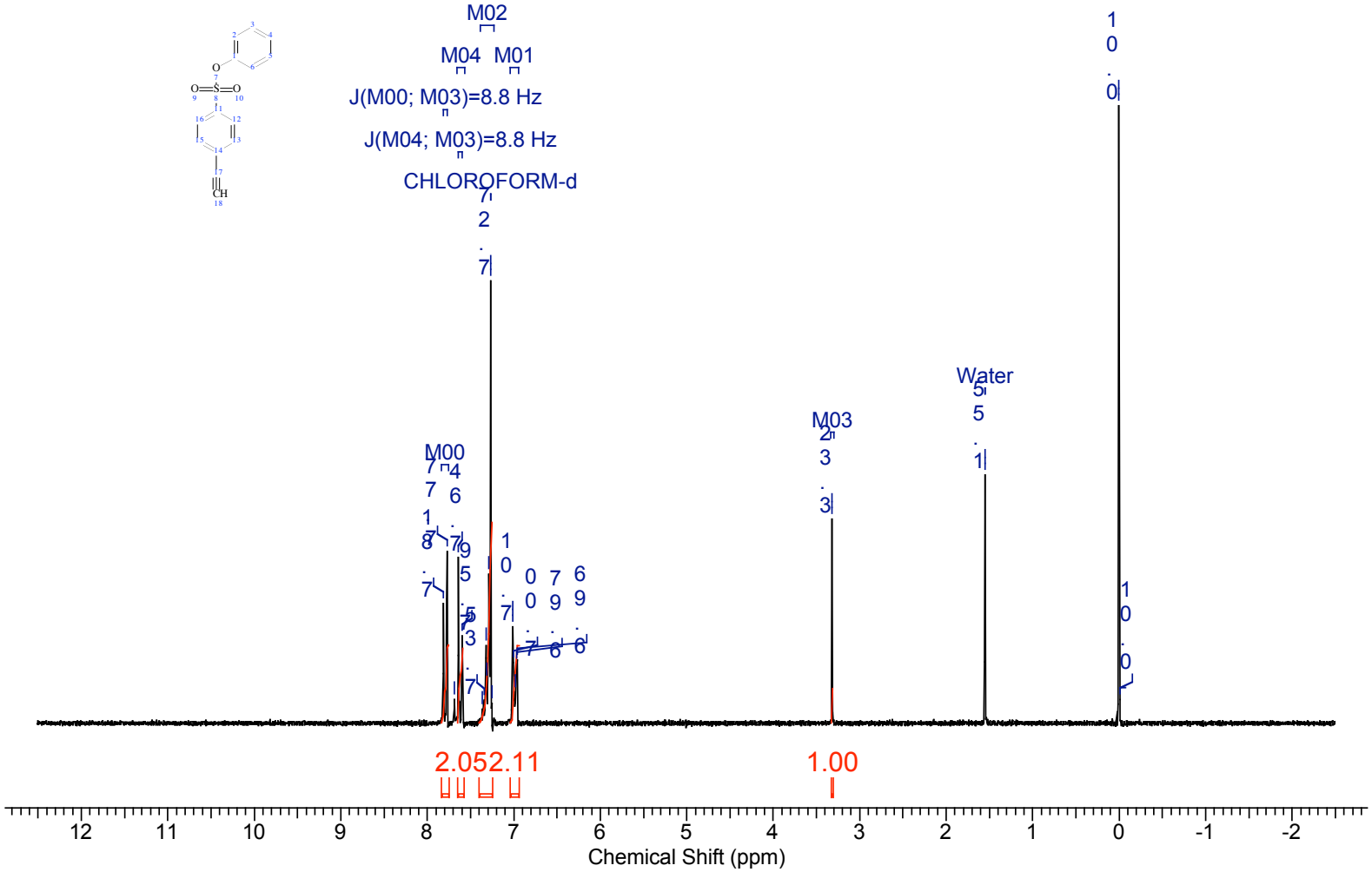
Phenyl 4-bromobenzenesulfonate**[2-6]** ^{1}H



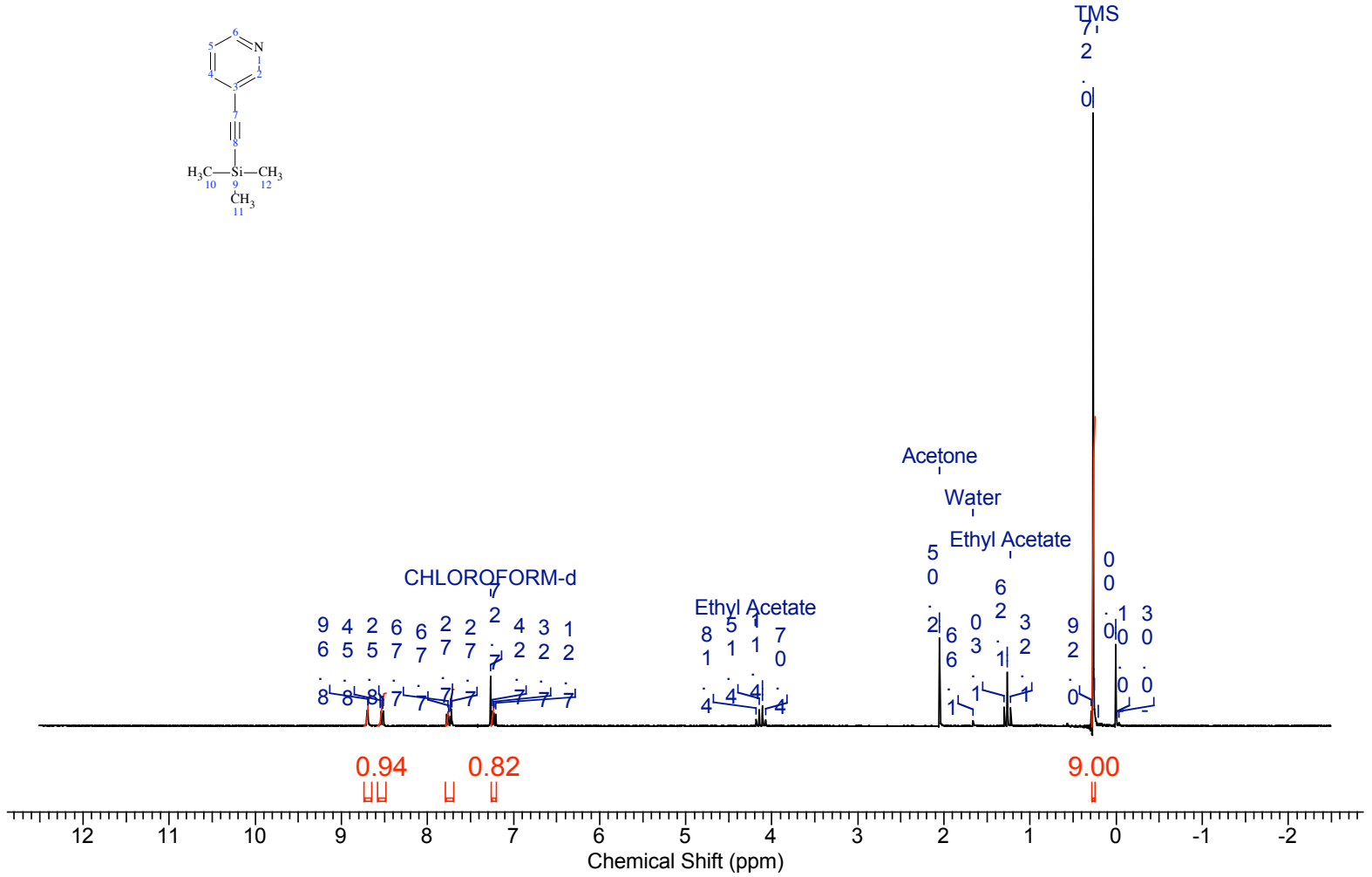
Phenyl 4-ethynltrimethylsilanebromobenzenesulfonate**[2-7]** ^{1}H



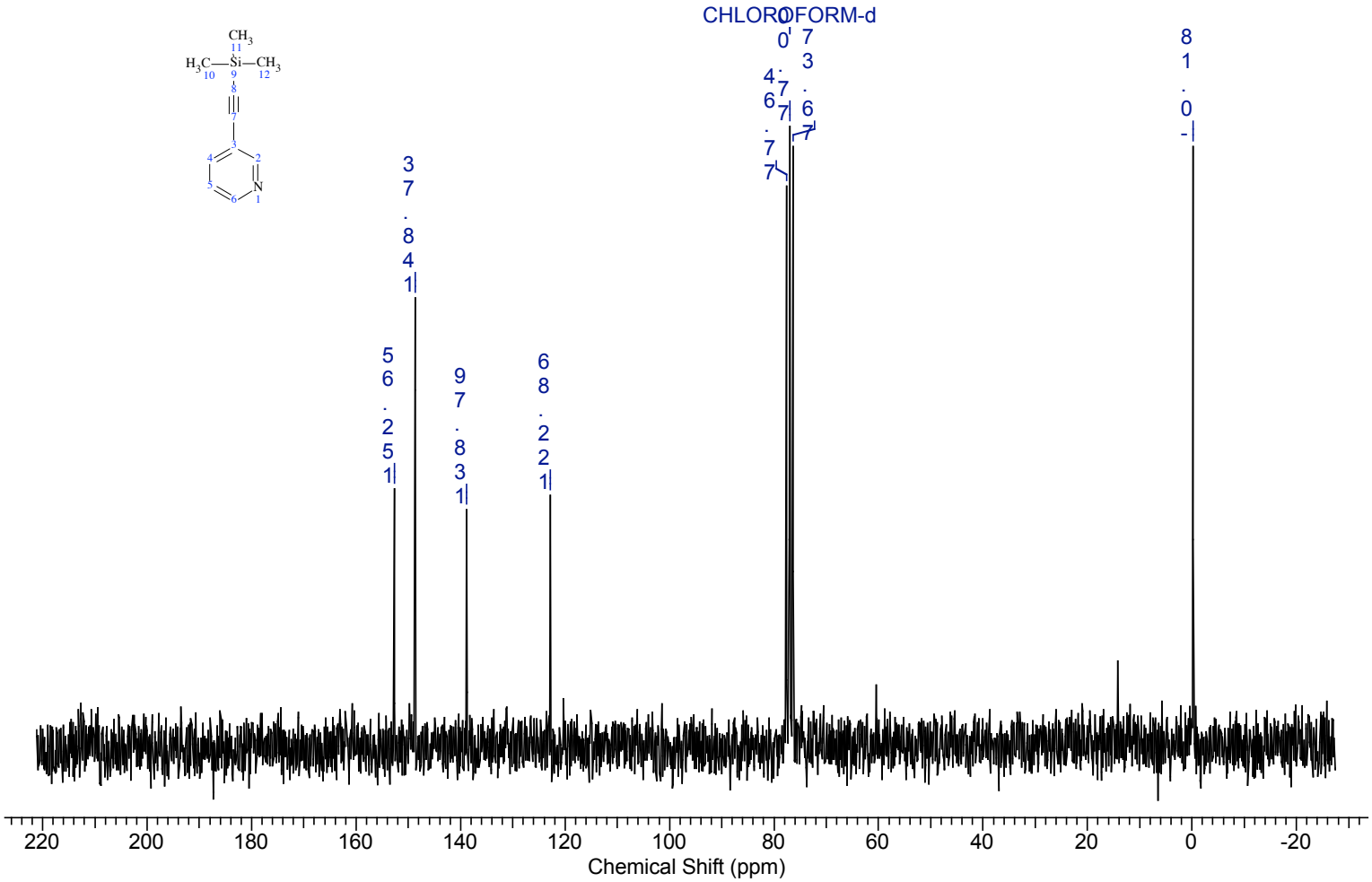
Phenyl 4-ethynylbenzenesulfoate **[2-8]** ^{1}H



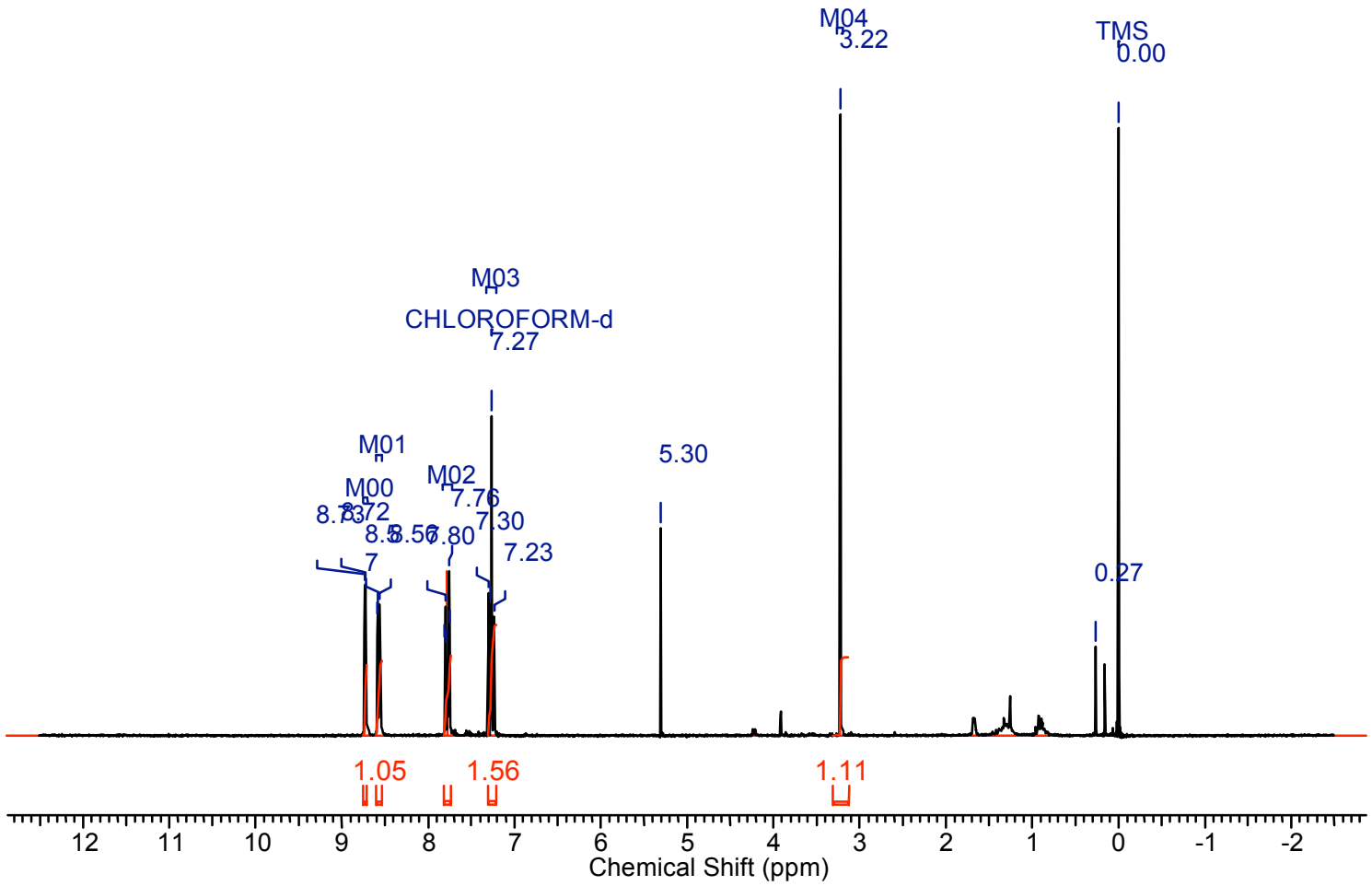
Silyl-3-(3,3-dimethylbut-1-yn-1-yl)pyridine**[2-9]** ^{1}H



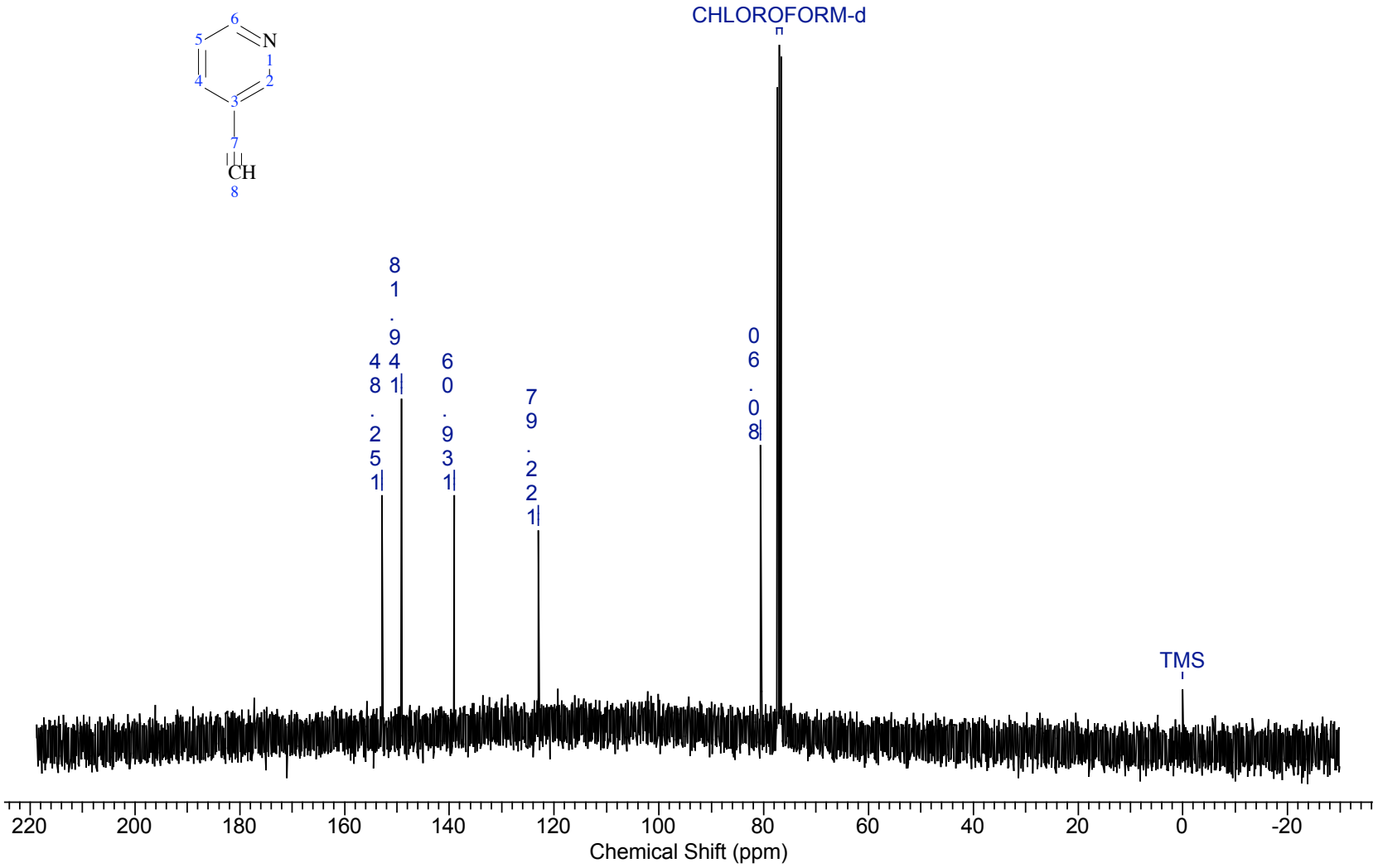
Silyl-3-(3,3-dimethylbut-1-yn-1-yl)pyridine**[2-9]** ^{13}C



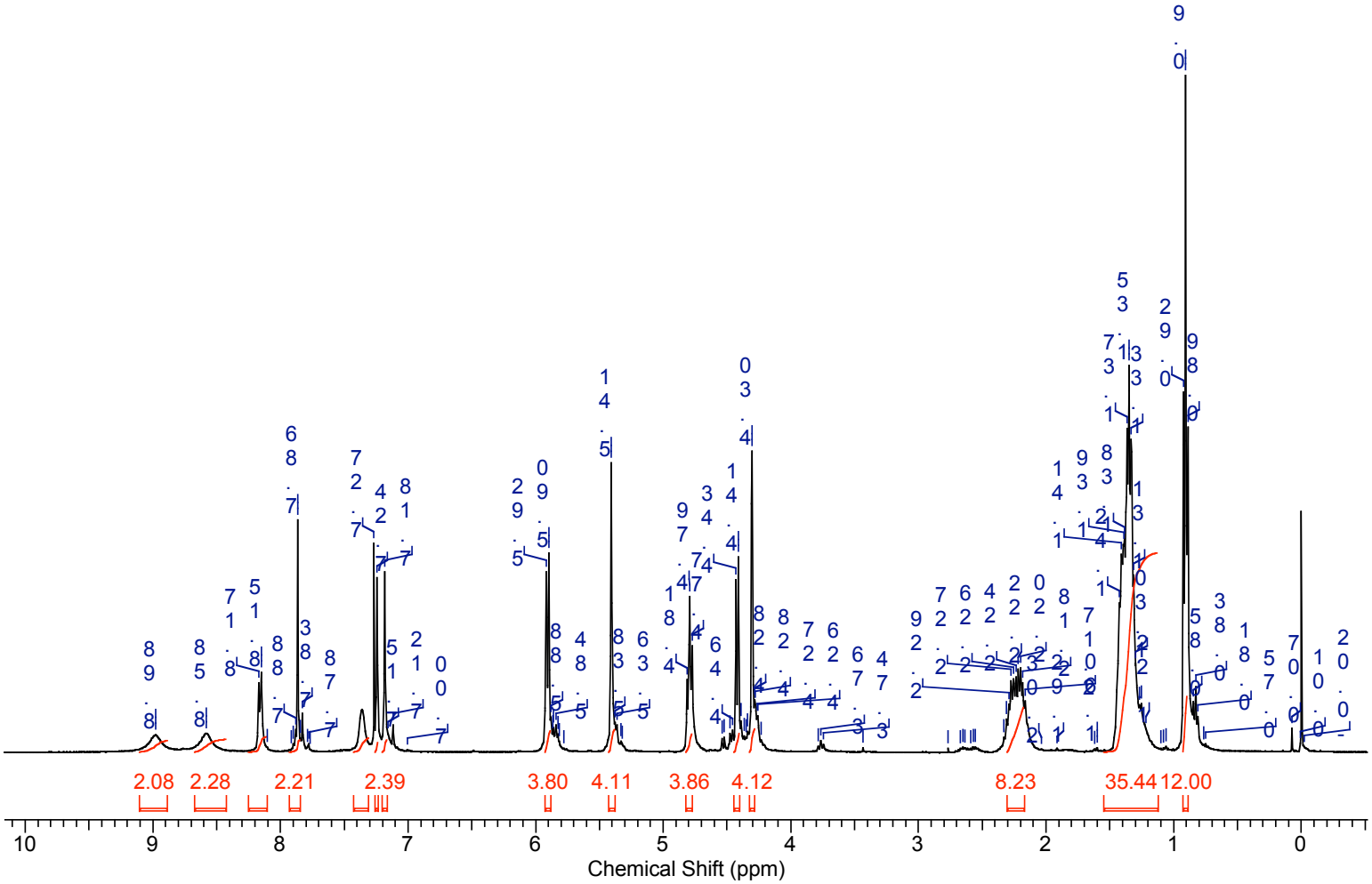
3-ethynylpyridine **[2-10]** ^{1}H



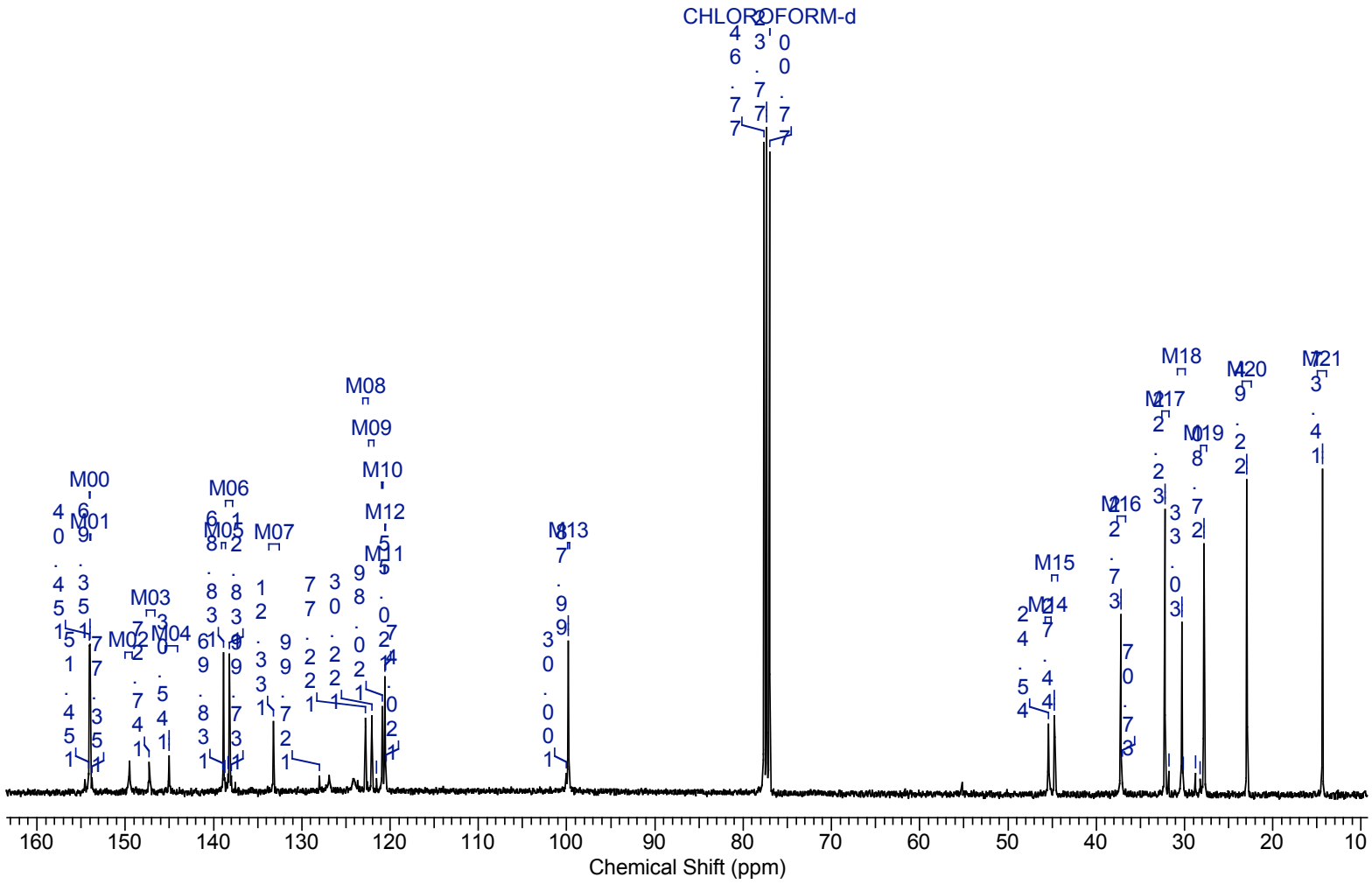
3-ethynylpyridine **[2-10]** ^{13}C



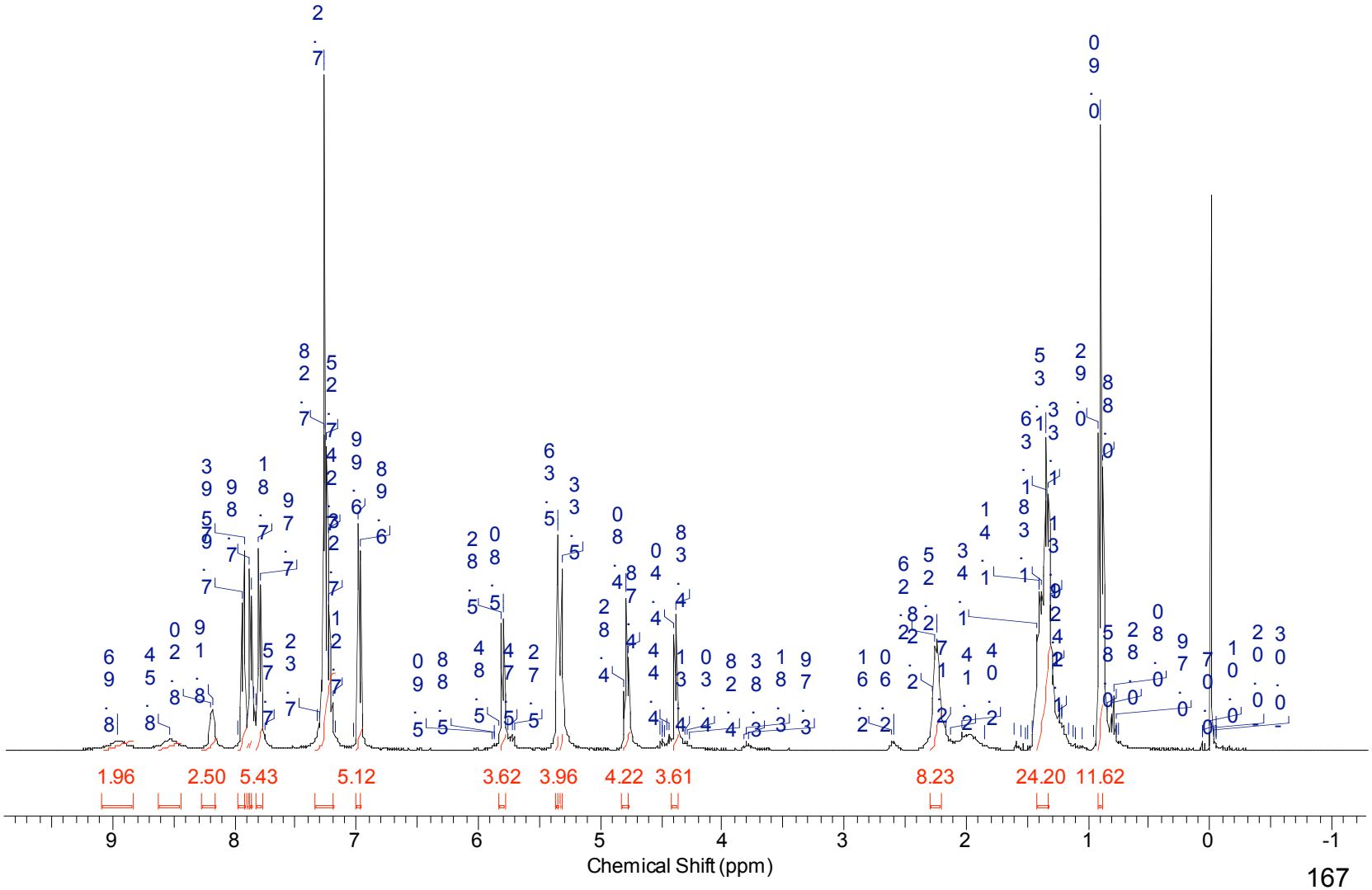
A,C-Bis-1,2,3-triazole 3-pyridine resorcin[4]arene **[2-11]** ^{1}H



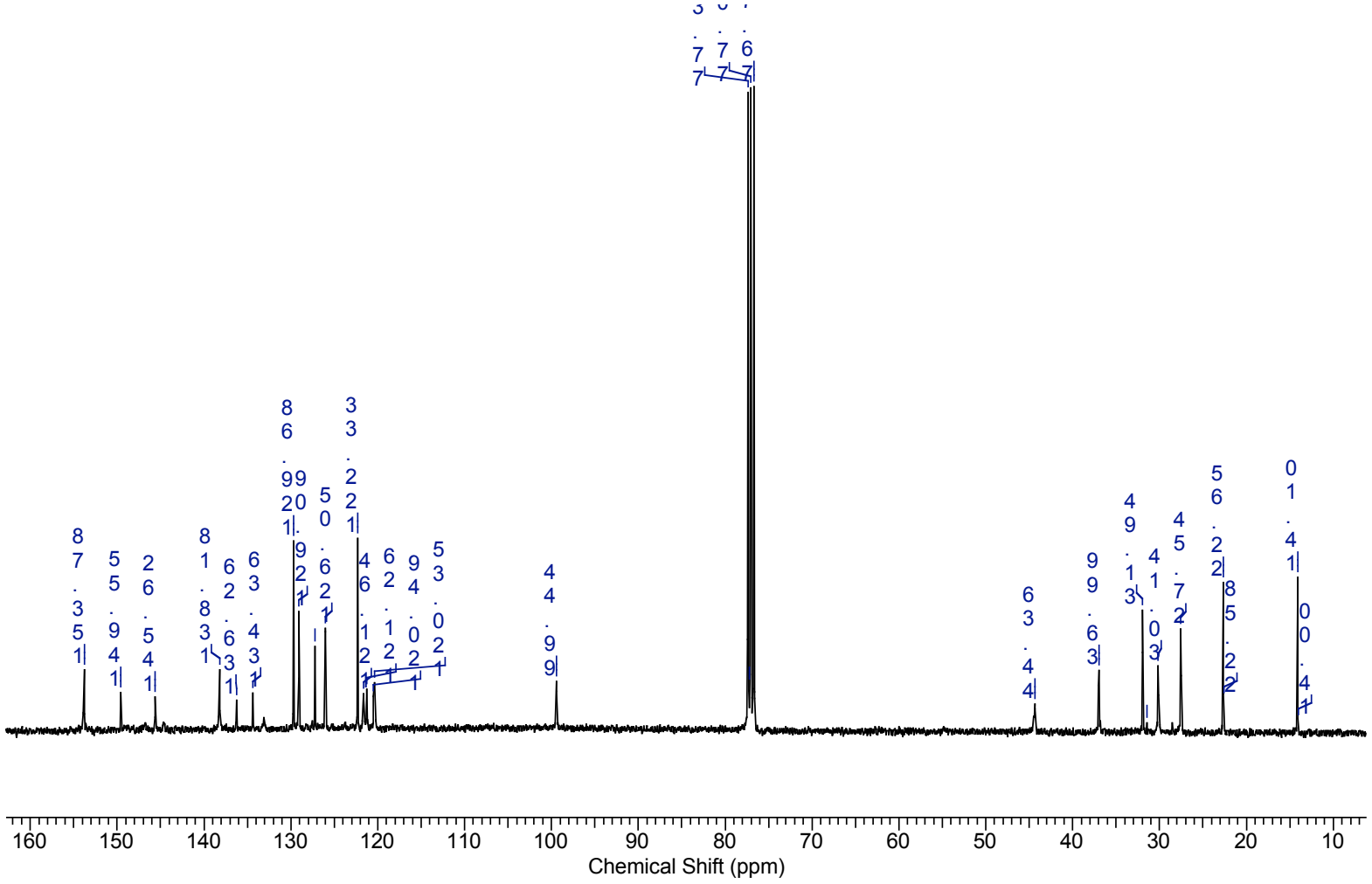
A,C-Bis-1,2,3-triazole 3-pyridine resorcin[4]arene **[2-11]** ^{13}C



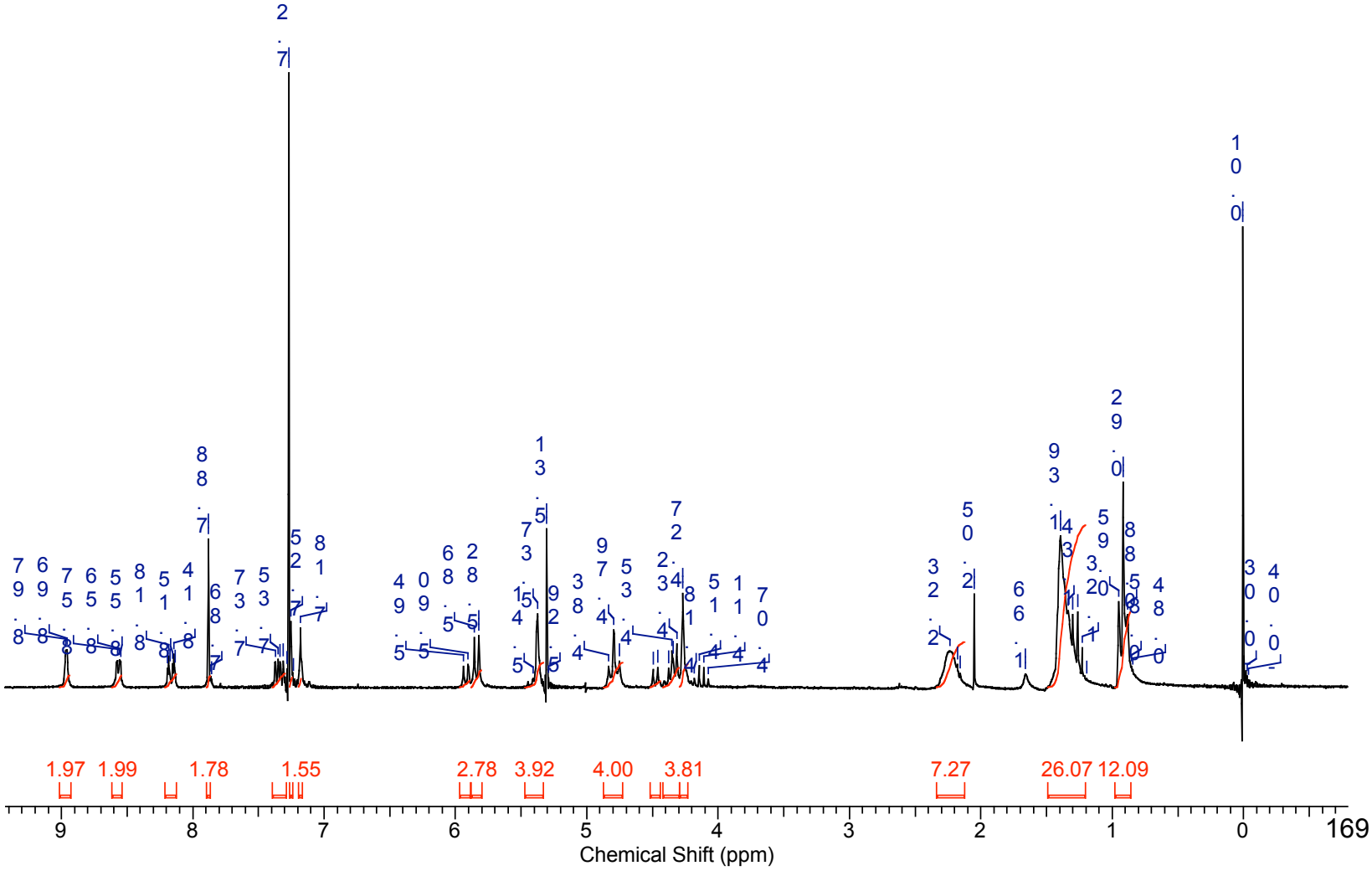
A,C-bis-1,2,3-triazole 3-pyridine-B,D-1,2,3-triazole phenyl benzene sulfonate **[2-12]** ^{1}H



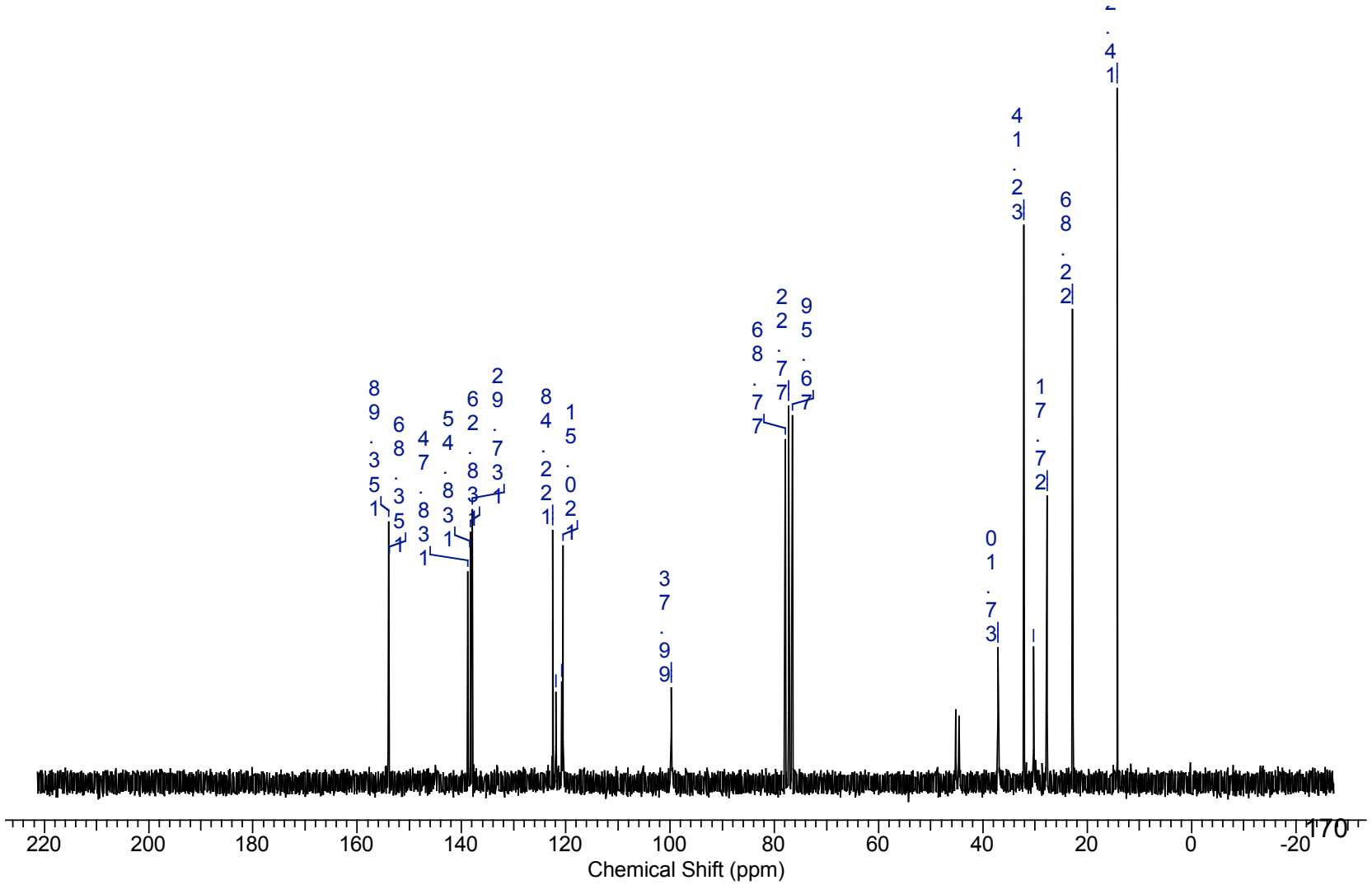
A,C-bis-1,2,3-triazole 3-pyridine-B,D-1,2,3-triazole phenyl benzene sulfonate **[2-12]** ^{13}C



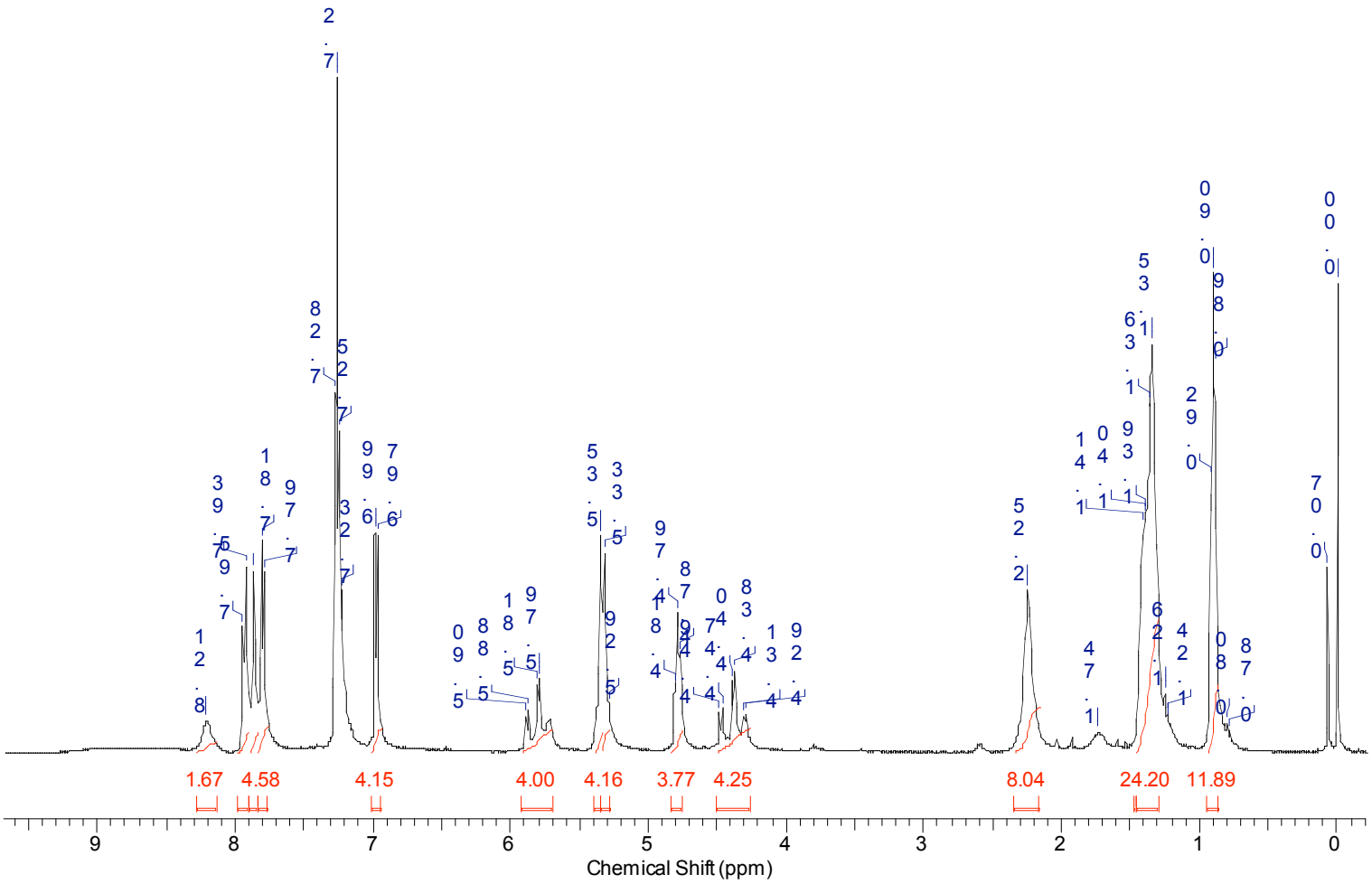
A,B-Bis-1,2,3,triazole 3-pyridine resorcin[4]arene **[2-13]** ^{1}H

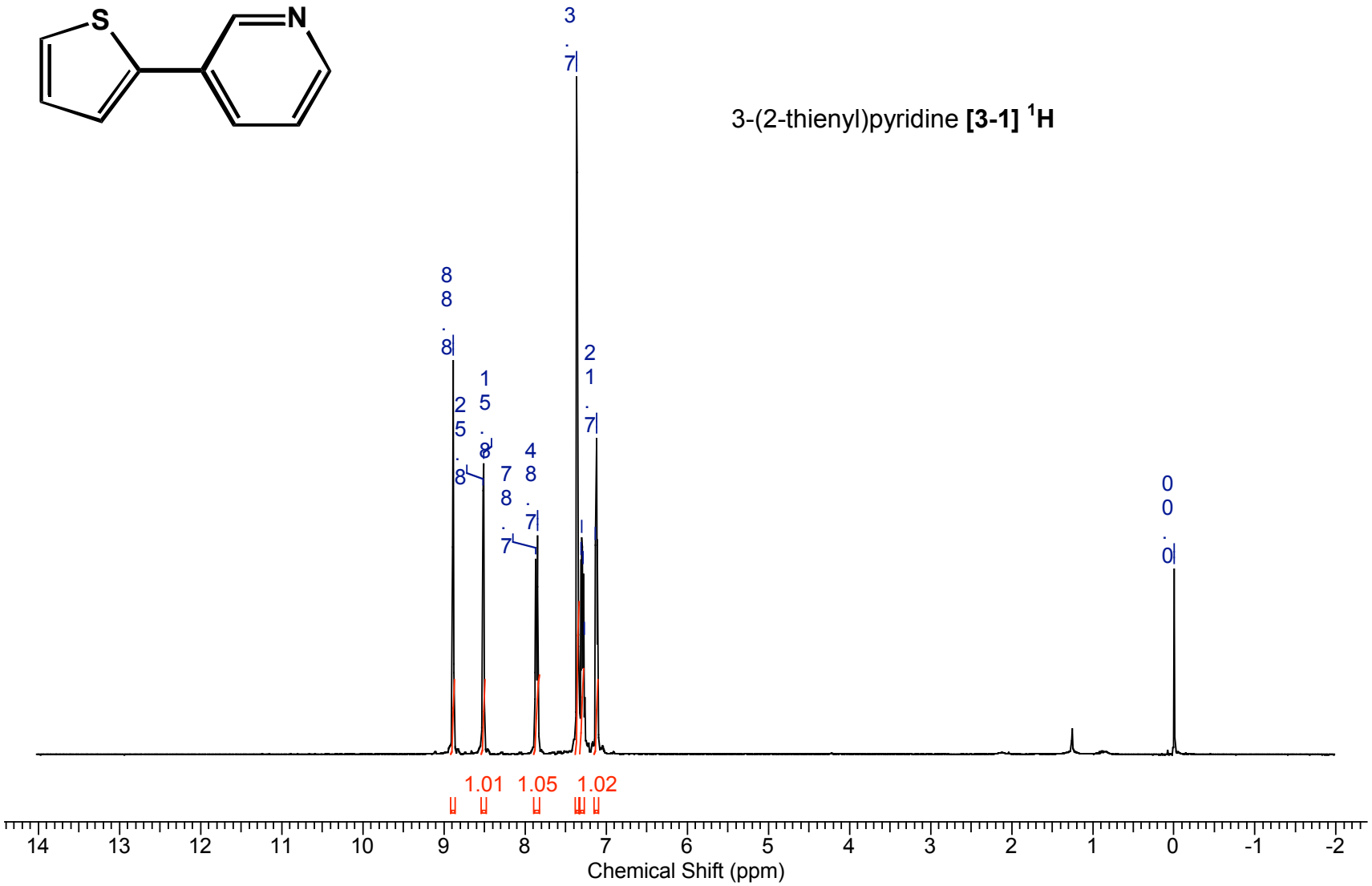


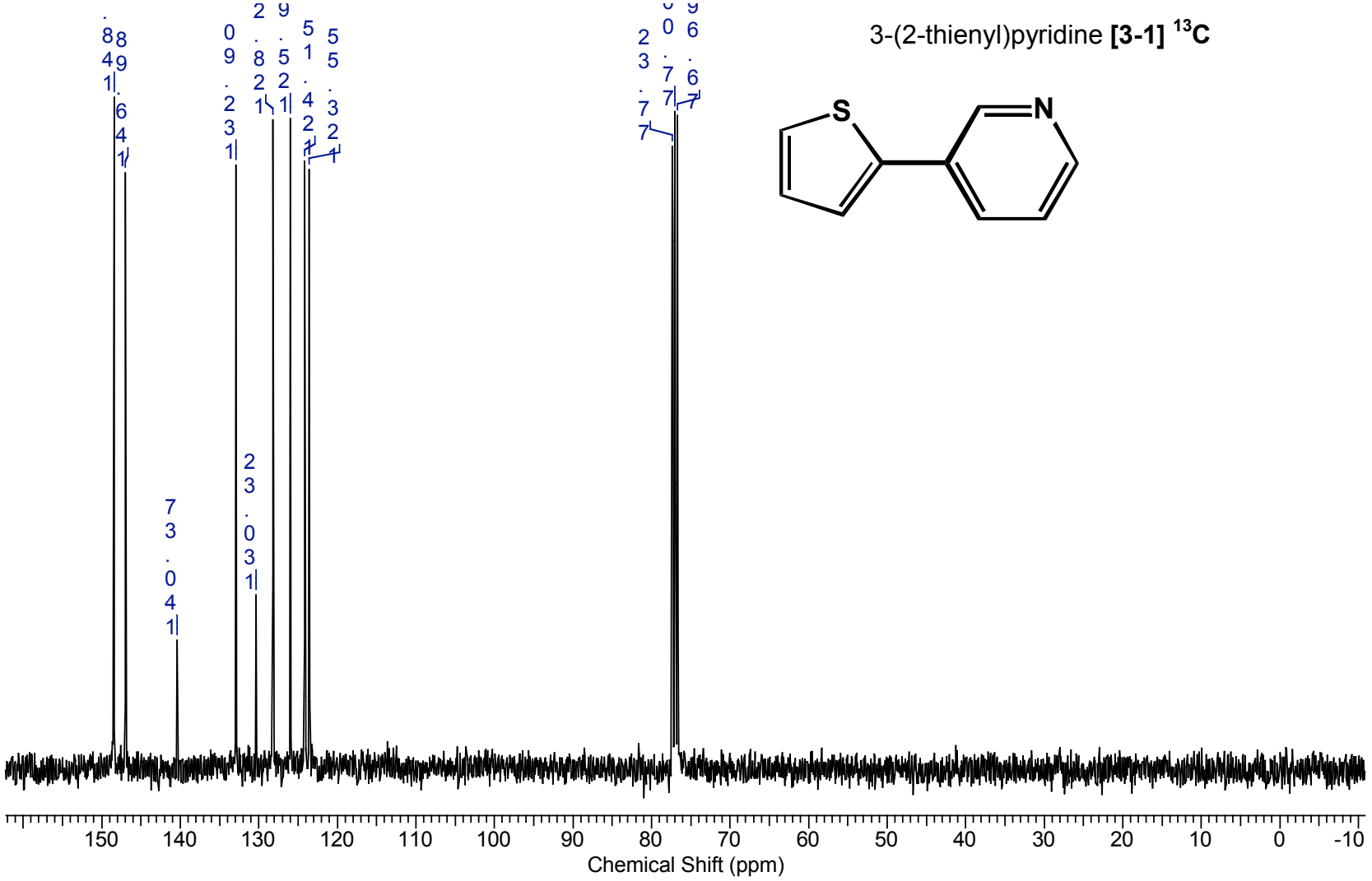
A,B-Bis-1,2,3,triazole 3-pyridine resorcin[4]arene **[2-13]** ^{13}C



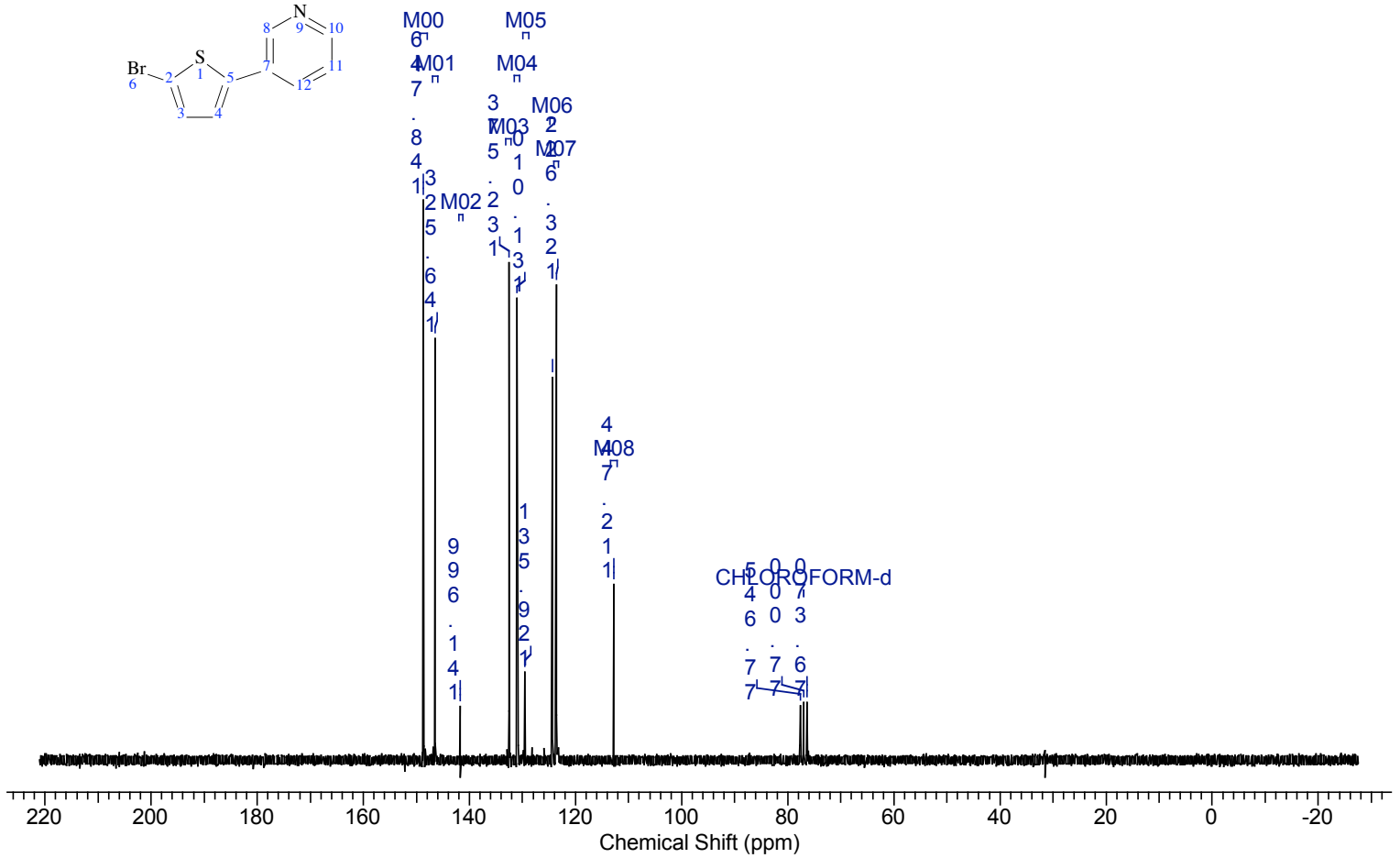
A,B-Bis-1,2,3 triazole 3-pyridine-C,D-1,2,3-triazole phenyl benzne sulfonate **[2-14]** ^{1}H



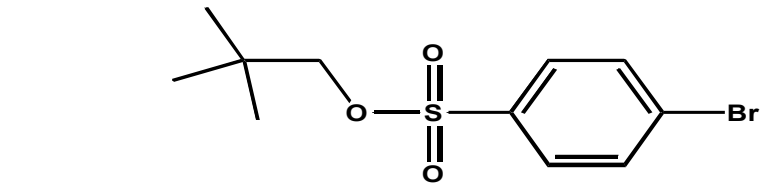

S
N
3-(2-thienyl)pyridine [3-1] 1H
8.88
2.58
15.8
7.87
48.7
3.77
21.7
0.00
1.01
1.05
1.02
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

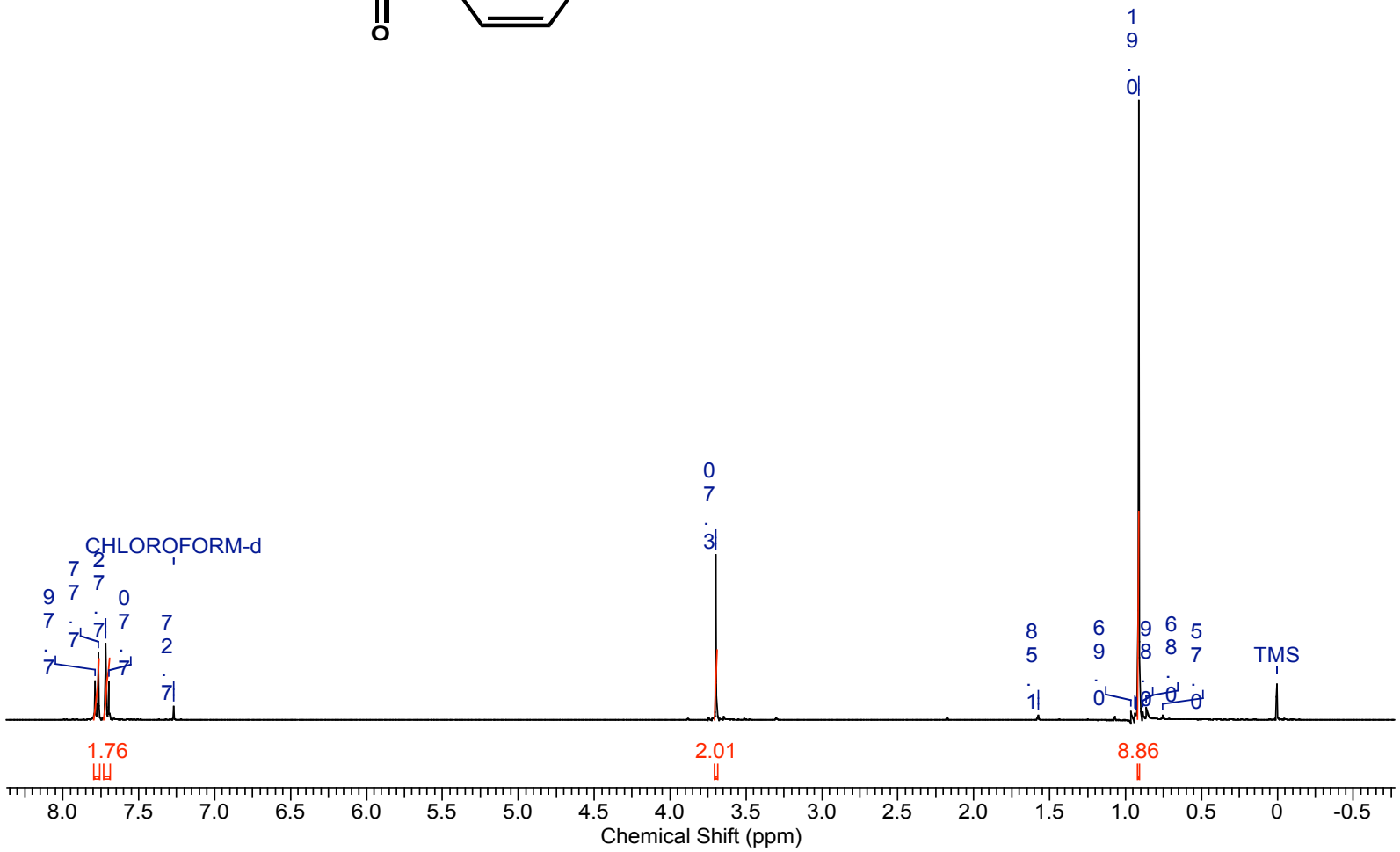

3-(2-thienyl)pyridine [3-1] 13C
S
N
Chemical Shift (ppm)

3-(5-bromo-2-thienyl) pyridine^{13}C

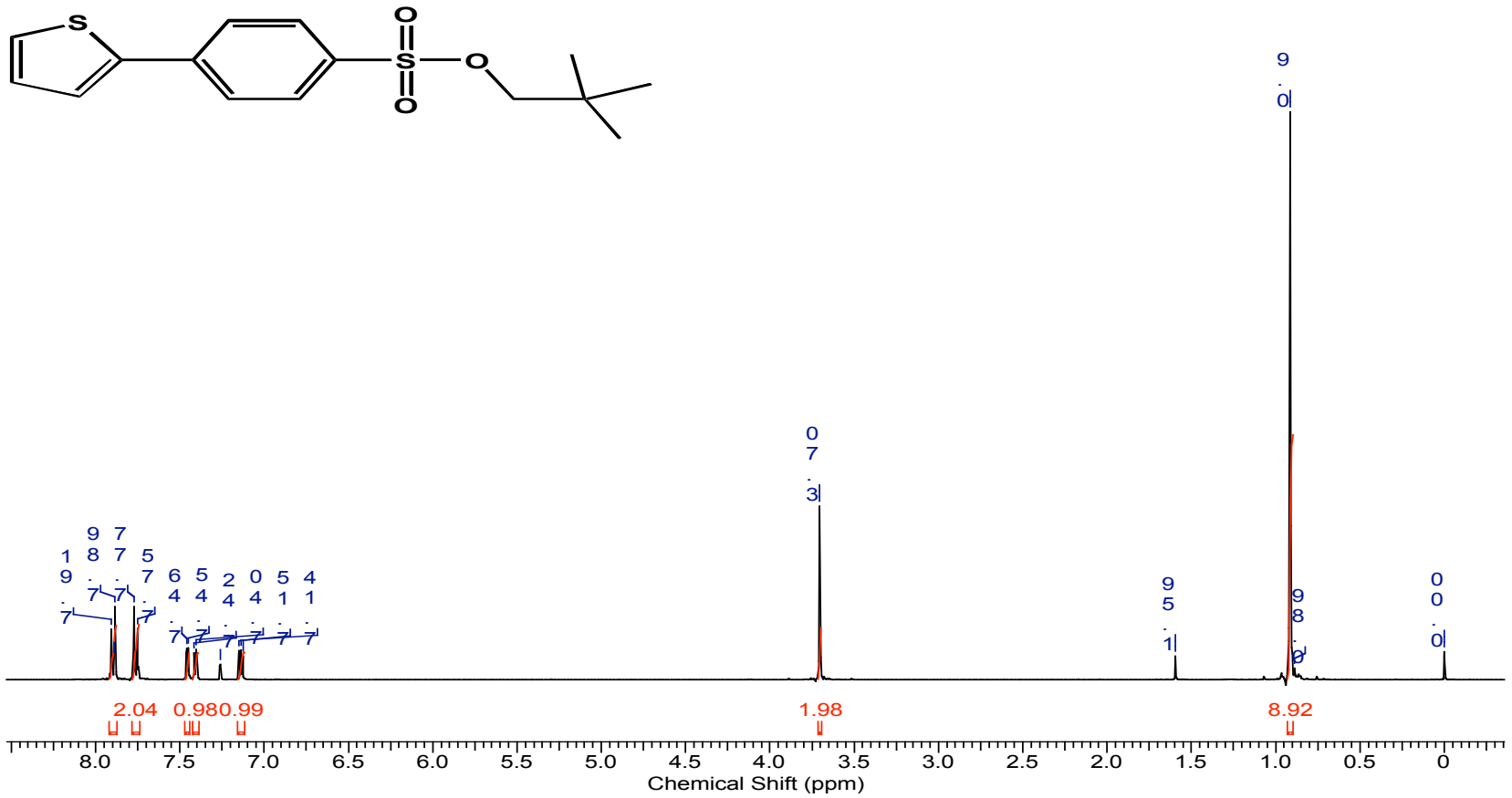


2,2-dimethylpropyl4-bromobenzenesulfonate [**3-3**]^{1}**H**

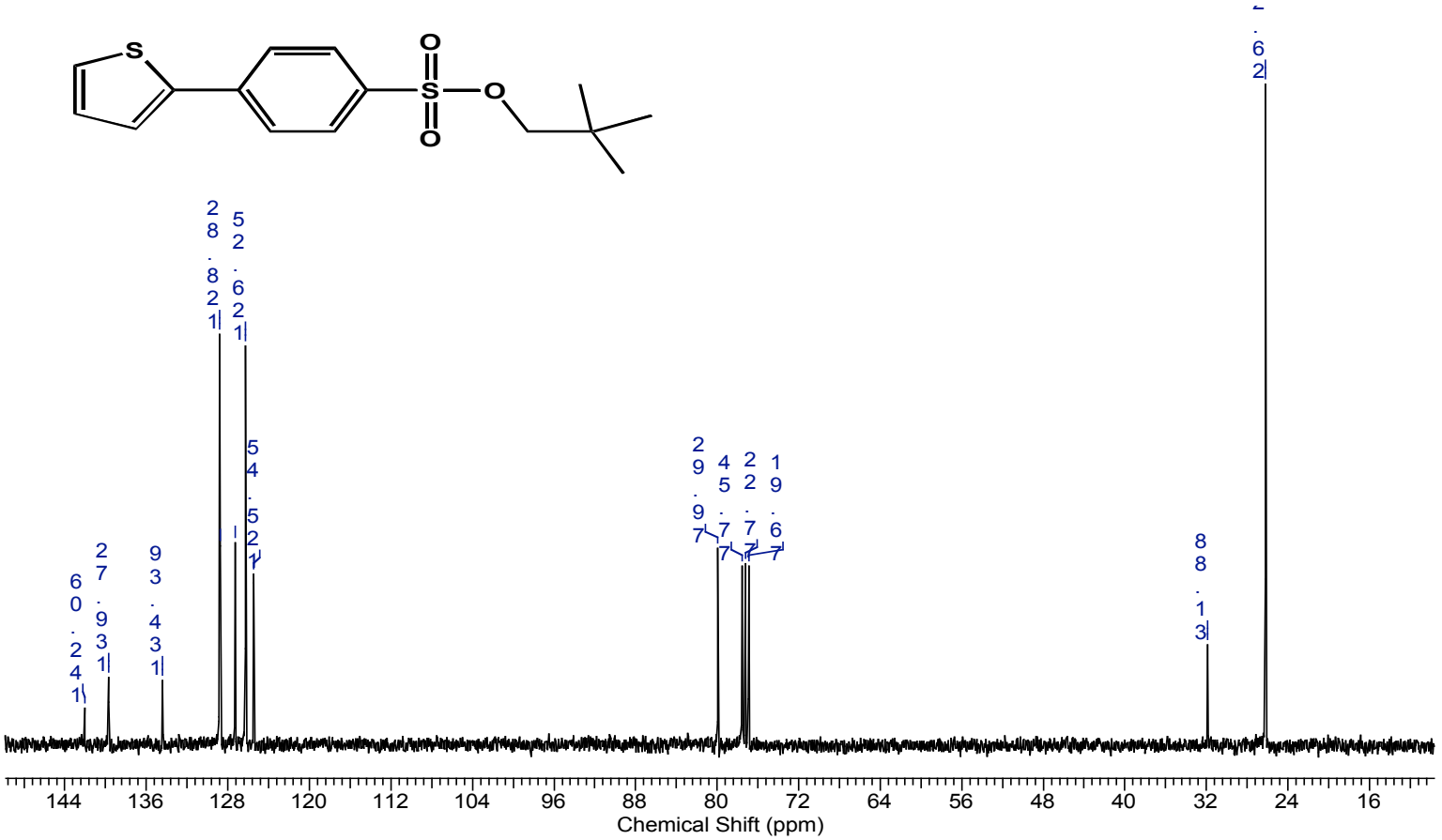




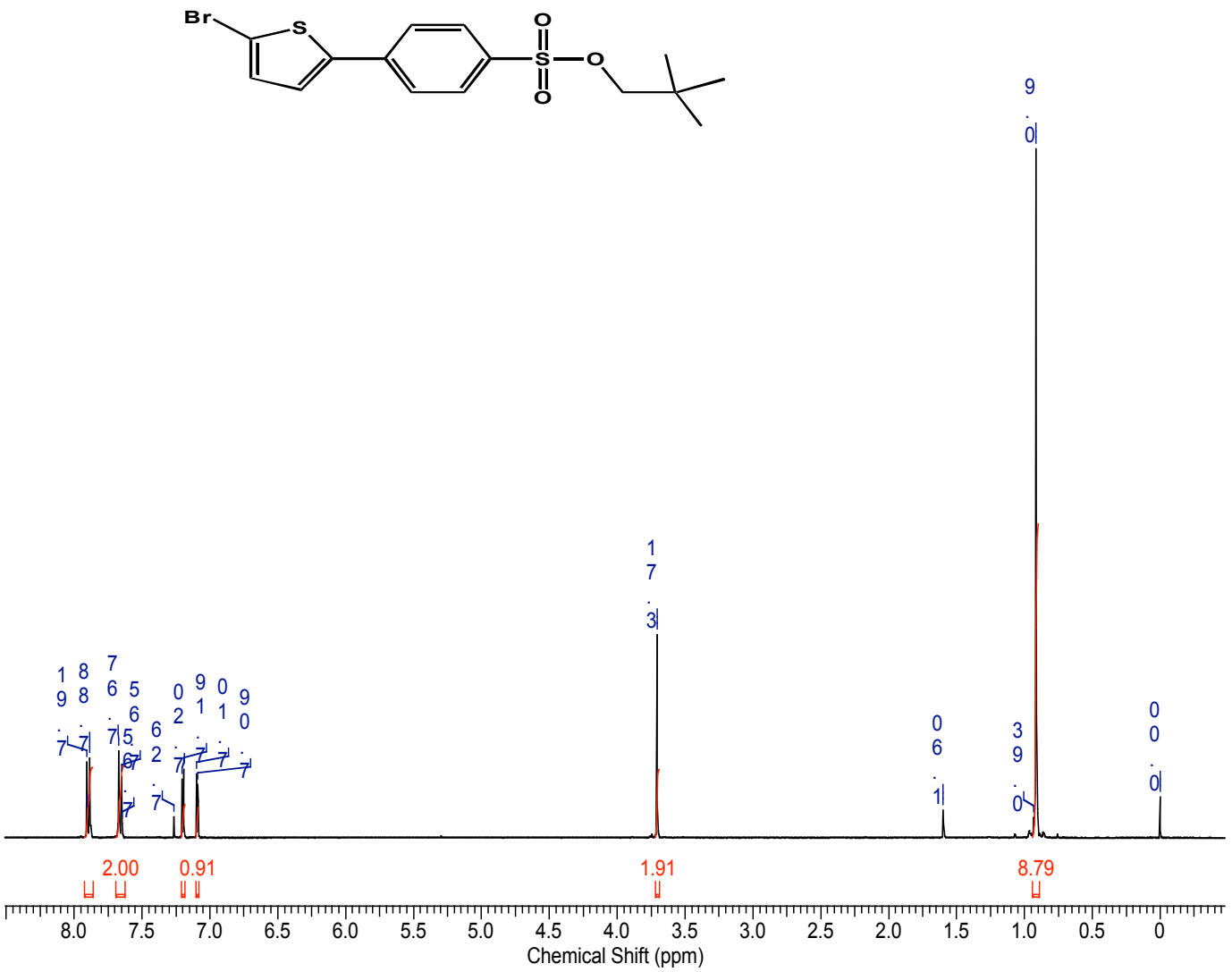
2, 2 dimethylpropyl 4-(2-thienyl)benzenesulfonate[3-4] **^{1}H**

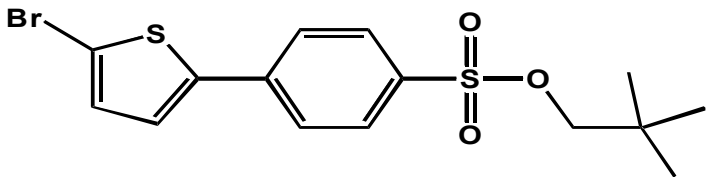


2, 2 dimethylpropyl 4-(2-thienyl)benzenesulfonate**[3-4]** ^{13}**C**



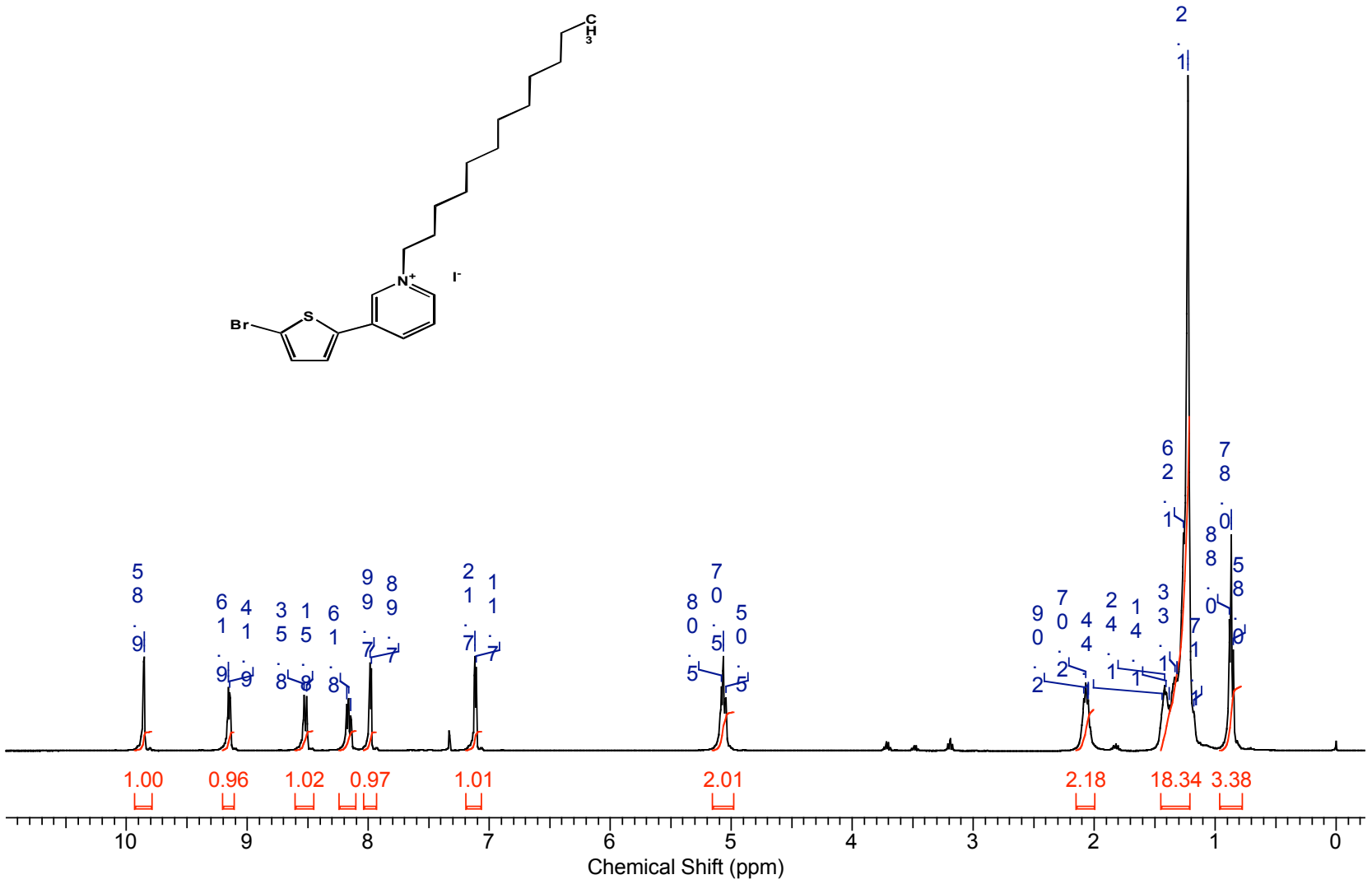
Dimethylpropyl 4-(5-bromo-2thienyl)benzenesulfonate **[3-5]** ^{1}**H**

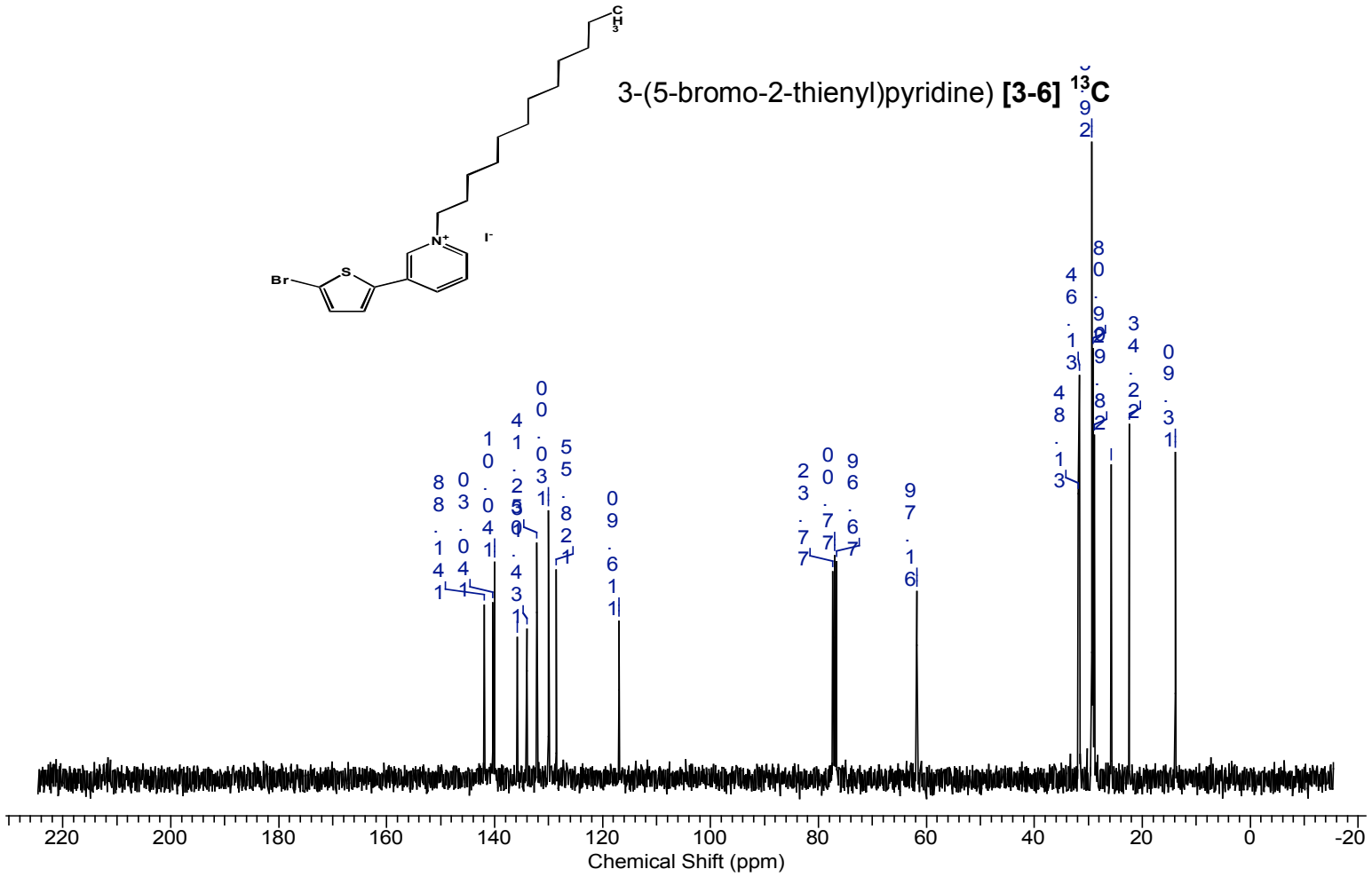




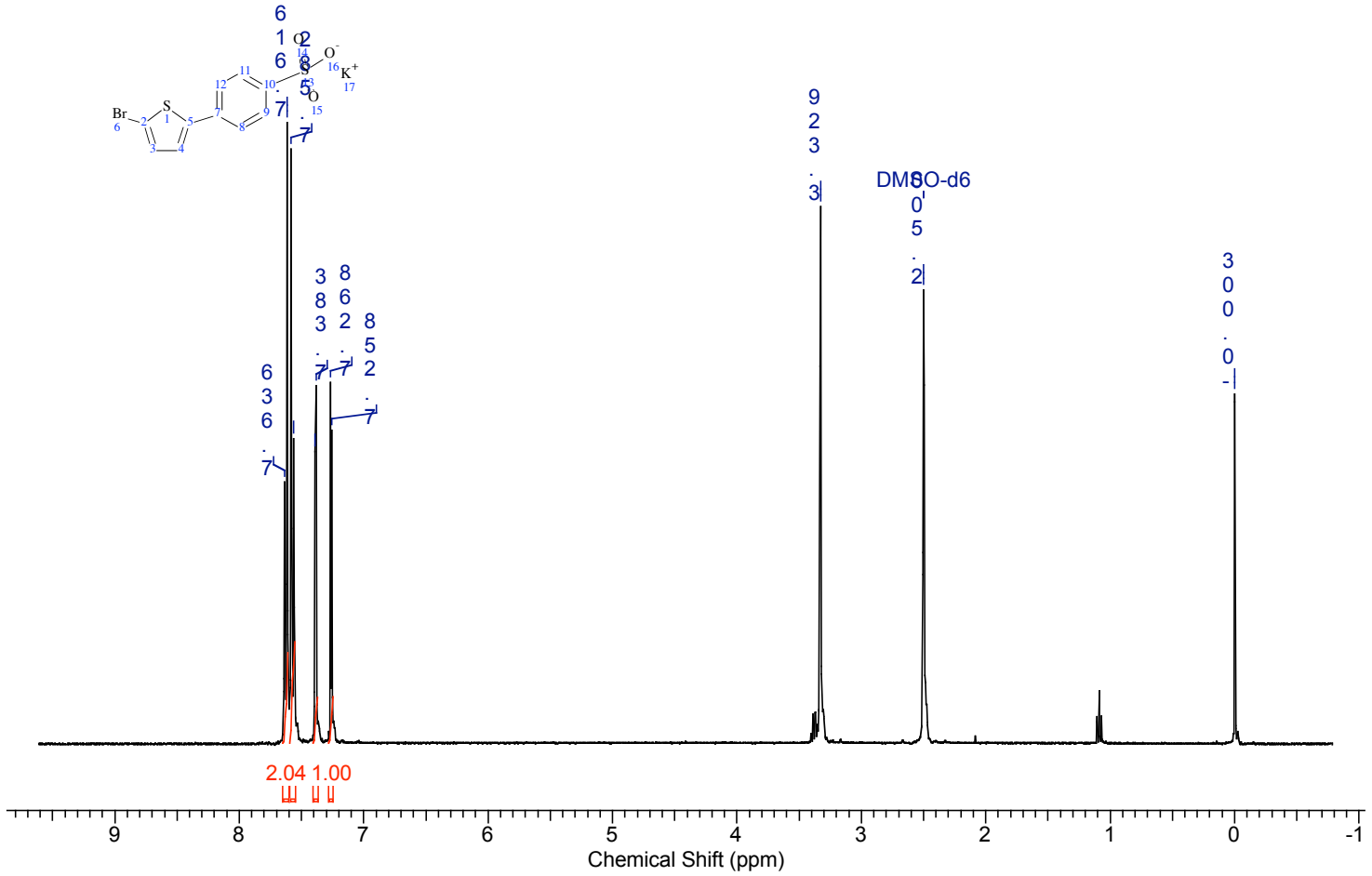
Dimethylpropyl 4-(5-bromo-2thienyl)benzenesulfonate **(3-5)^{13}C**

3-(5-bromo-2-thienyl)pyridine **[3-6]** ^{1}**H**

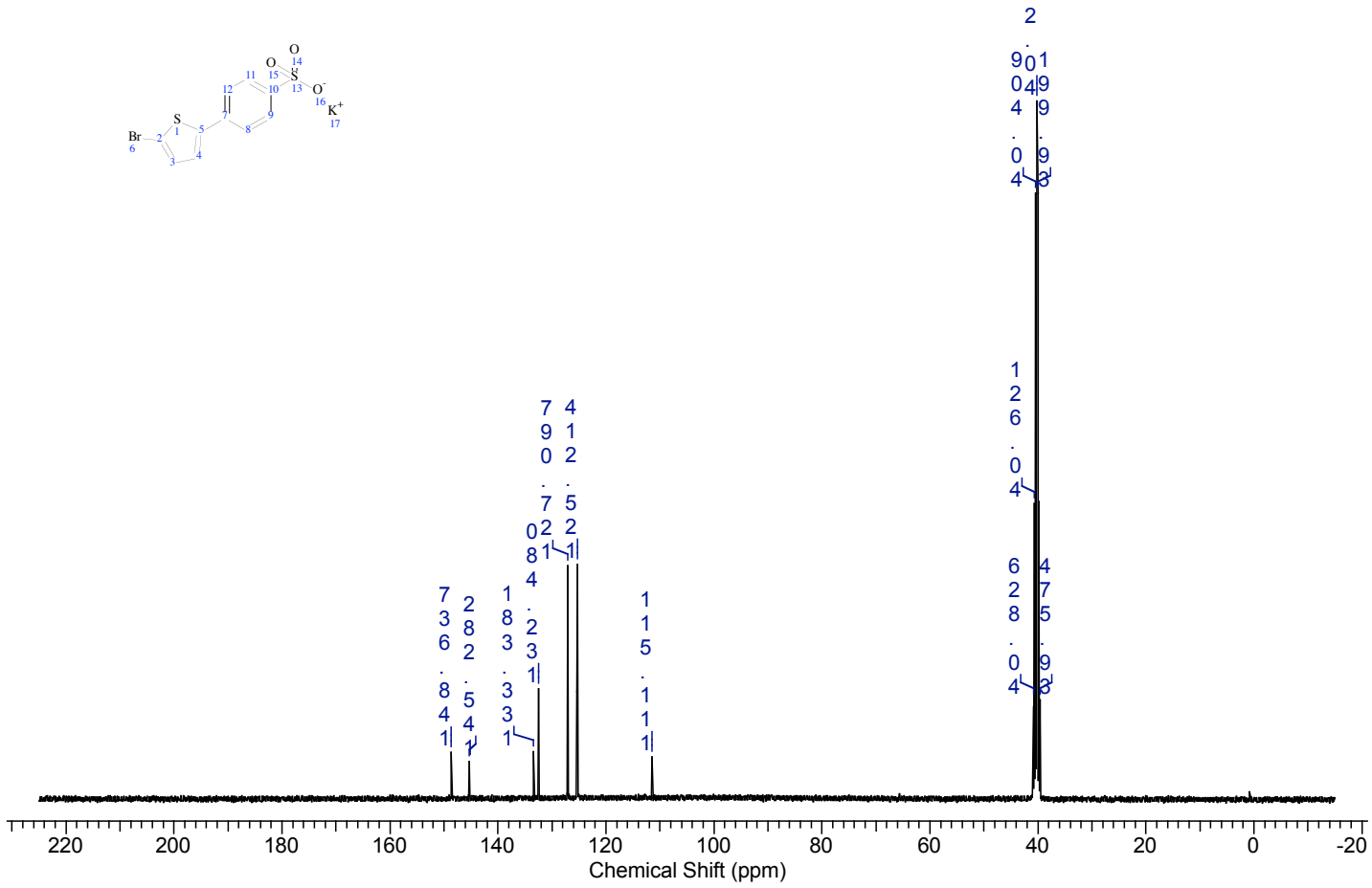



3-(5-bromo-2-thienyl)pyridine [3-6] ^{13}C
Br
S
N+
I-
CH3
Chemical Shift (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20

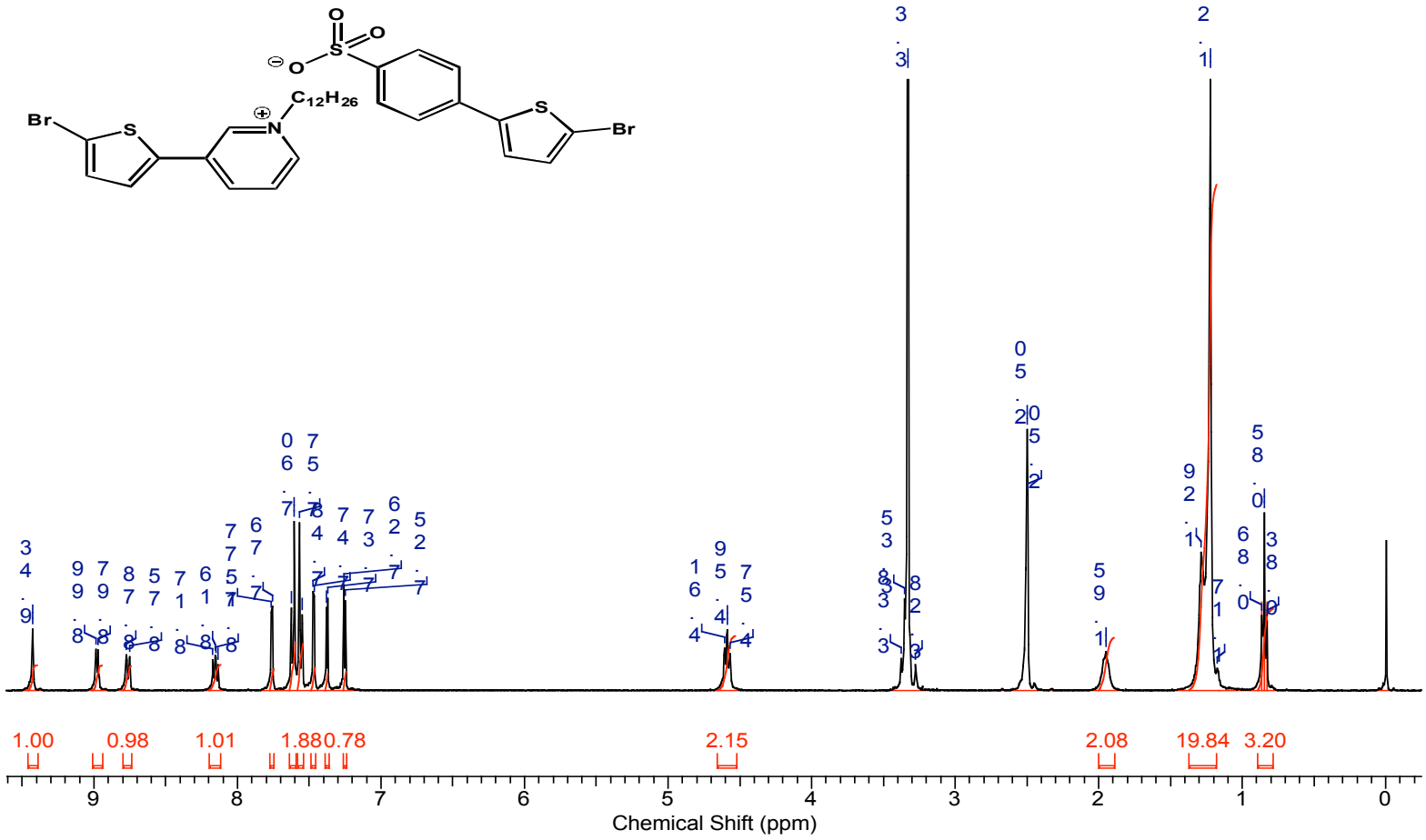
Potassium 4-(5-bromo-2thienyl)benzensulfonate) **[3-7]** ^{1}**H**



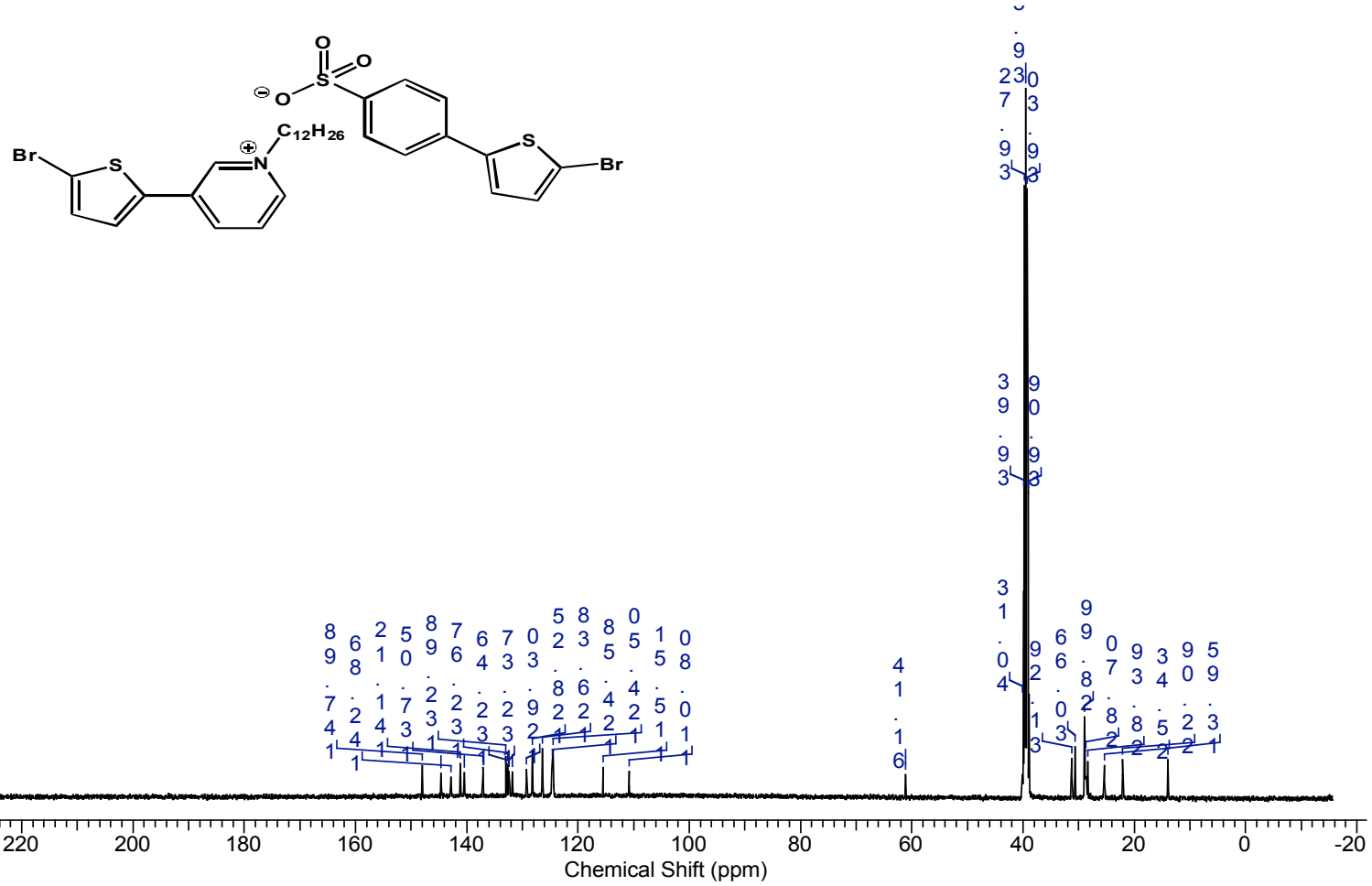
Potassium 4-(5-bromo-2thienyl)benzensulfonate) **[3-7]** ^{13}C



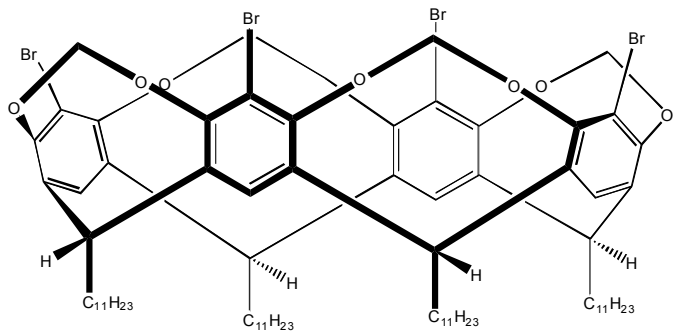
3-(5-bromo-2-thienyl)-1-dodecanylpyridinium -4-(5-bromo-2-thienyl)benzenesulfonate **[3-8]** ^{1}**H**



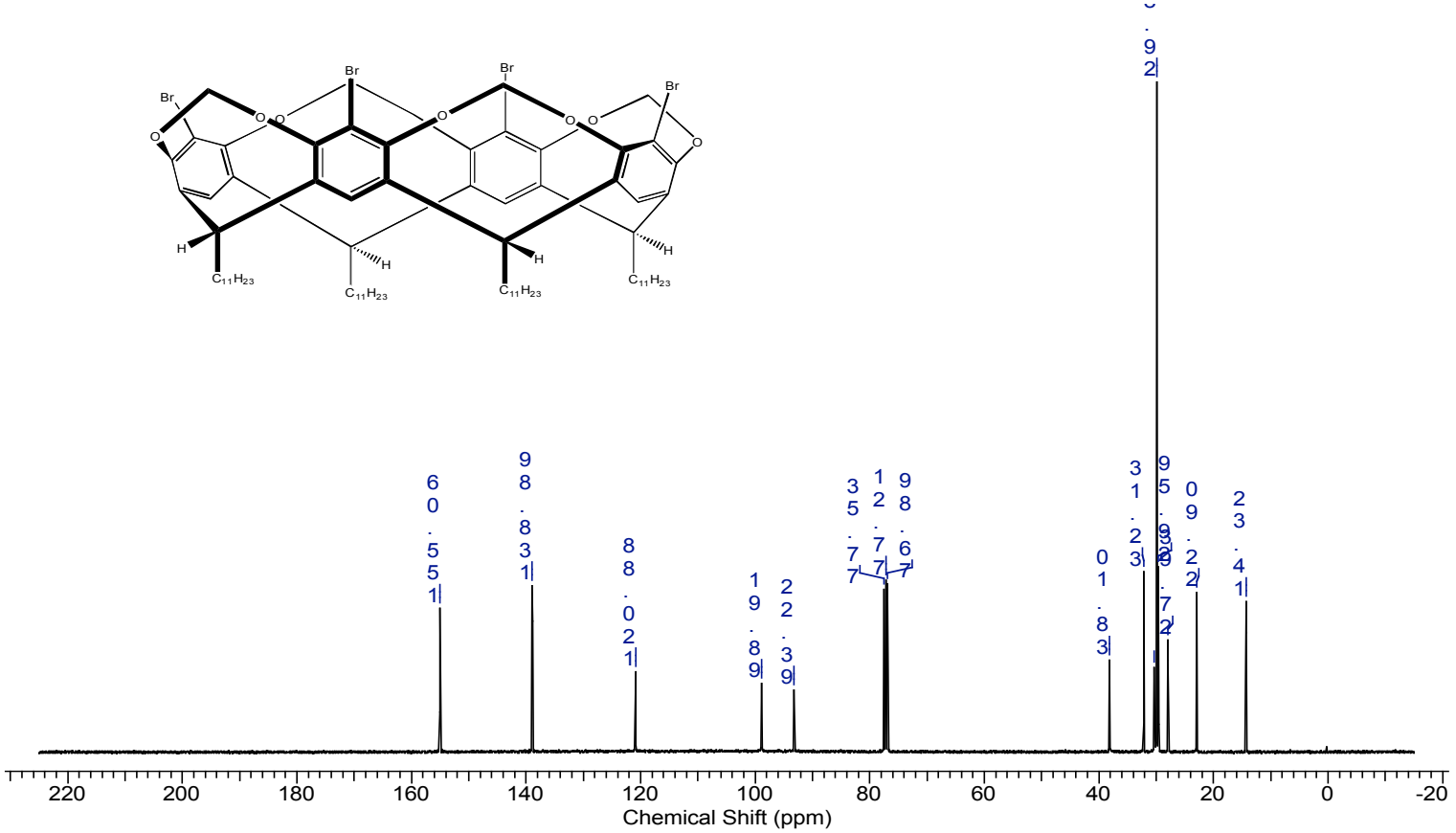
3-(5-bromo-2-thienyl)-1-dodecanylpyridinium -4-(5-bromo-2-thienyl)benzenesulfonate **[3-8]** **^{13}C**



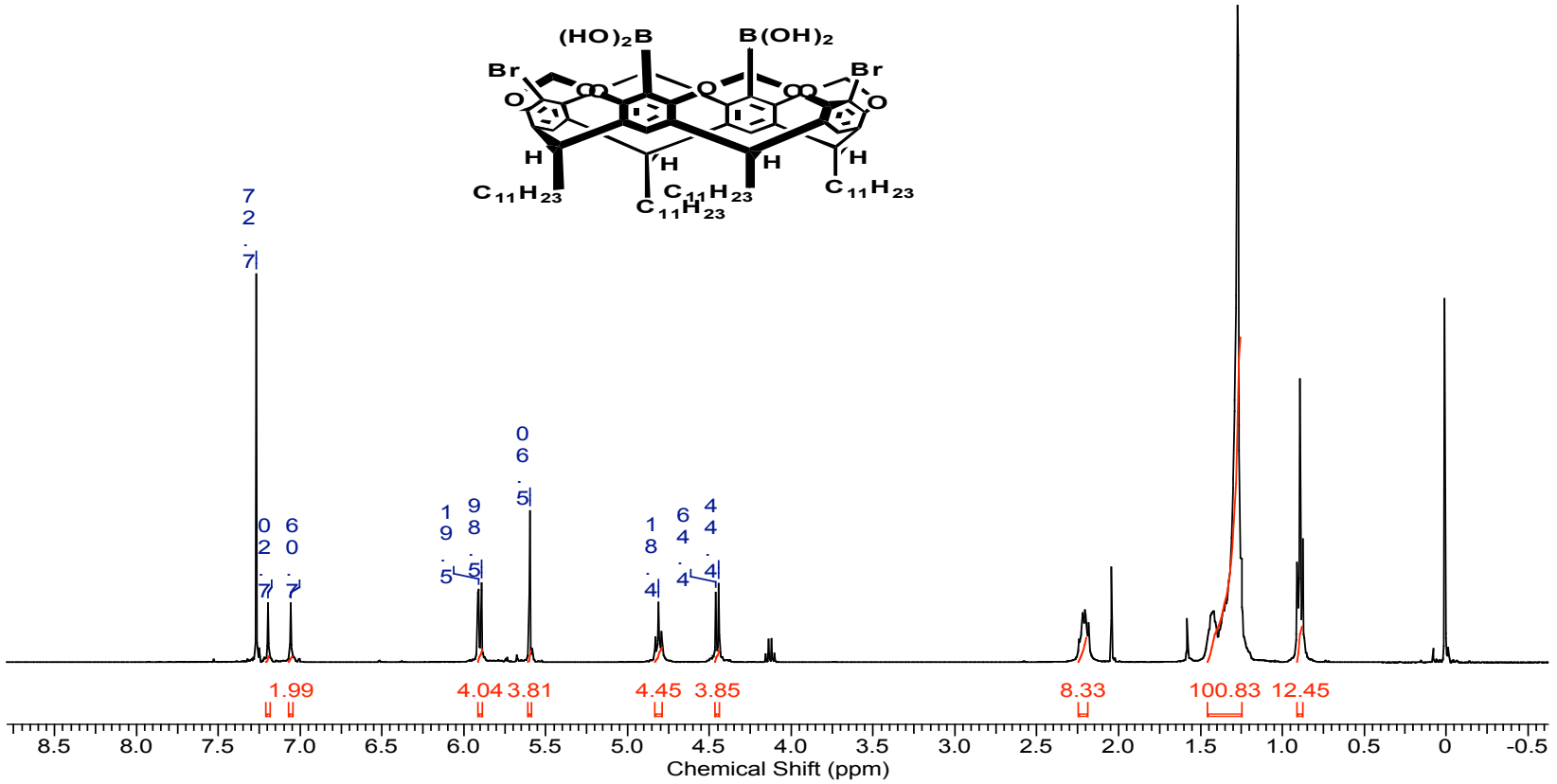
C-dodecyltetrabromorescorcin[4]arene **[3-11]** ^{1}**H**



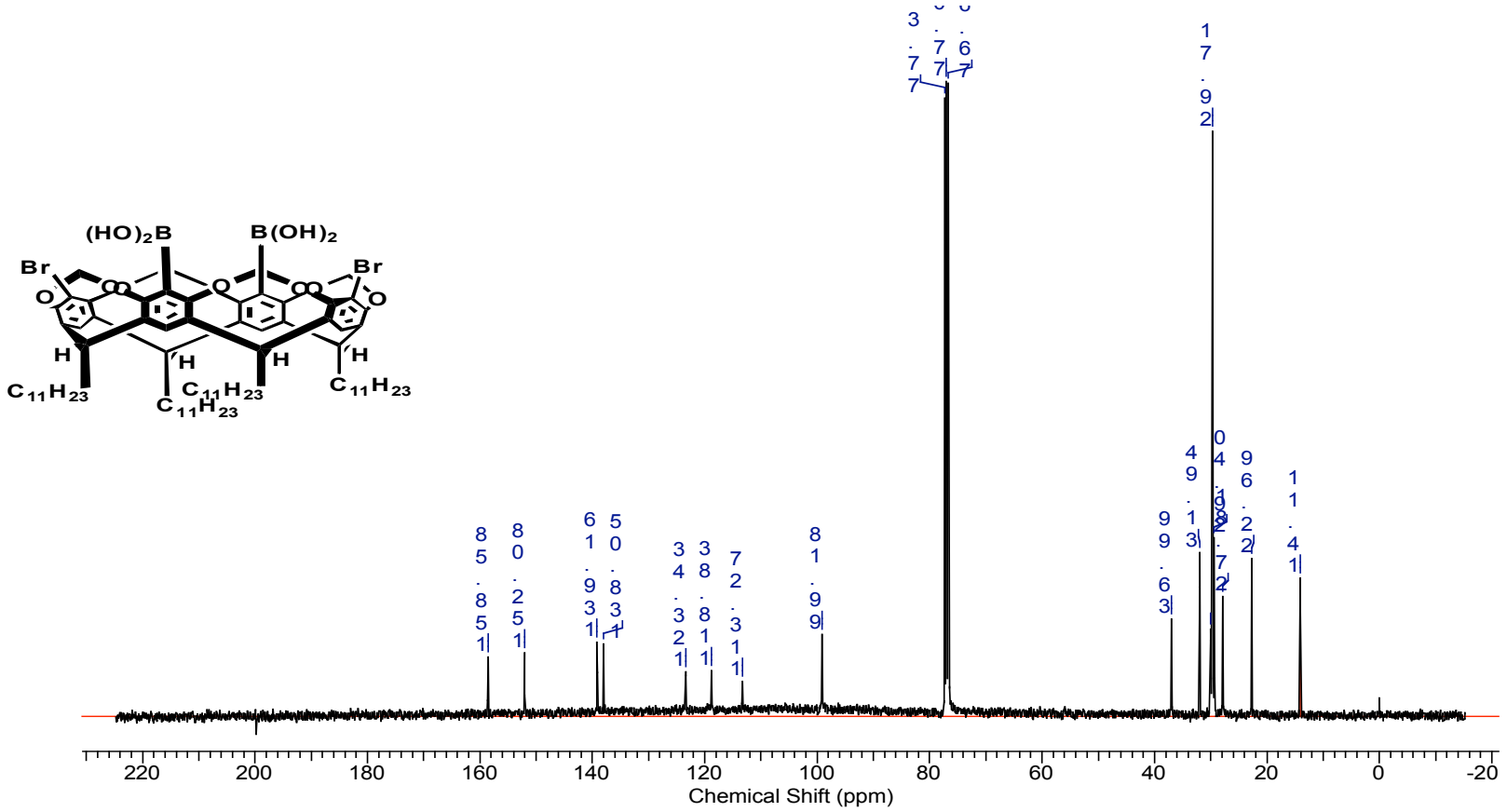
C-dodecyltetrabromorescorcin[4]arene **[3-11]** ^{13}**C**



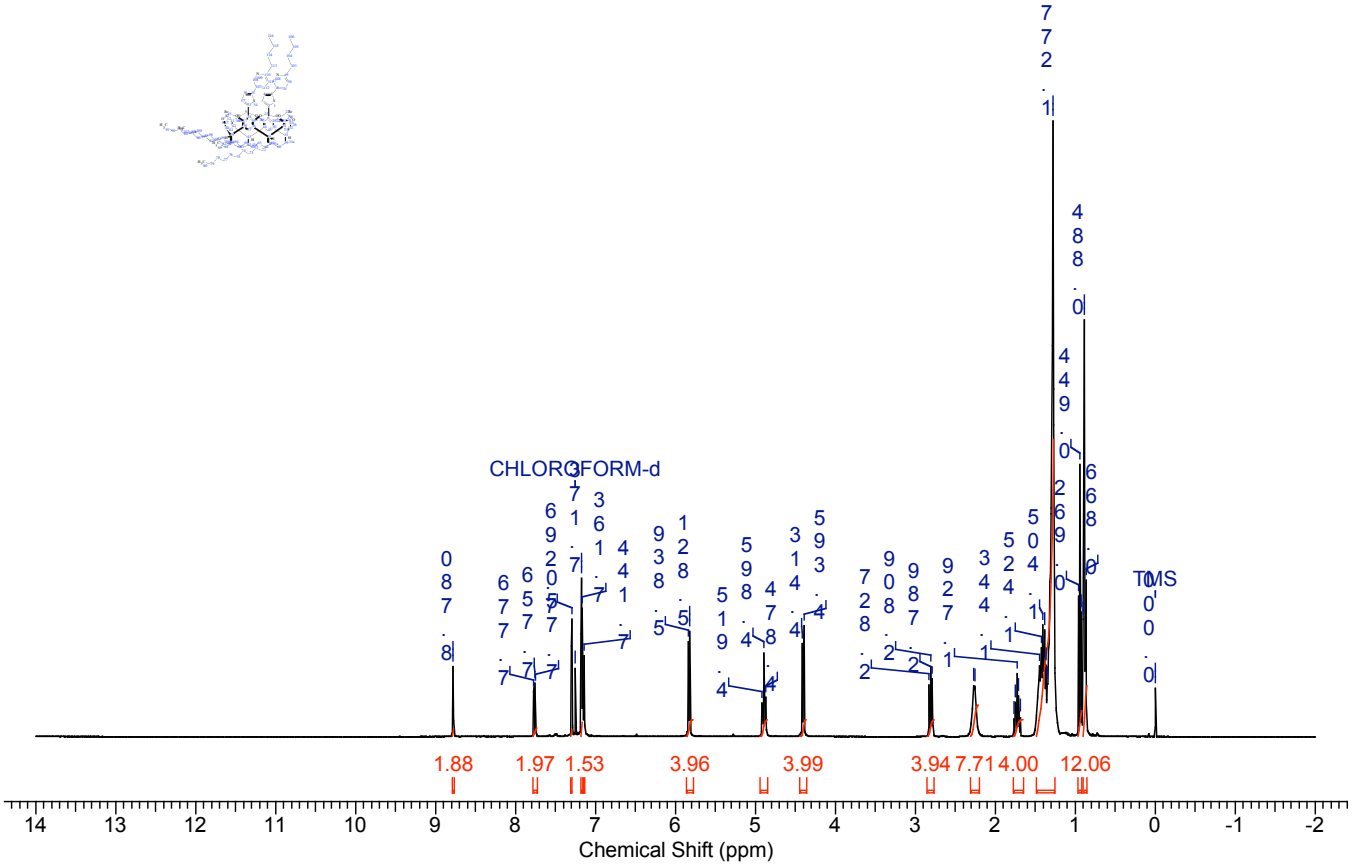
A,C Bis-boronic acid-C,D bis-bromo resorcin[4]arene **[3-12]** ^{1}**H**



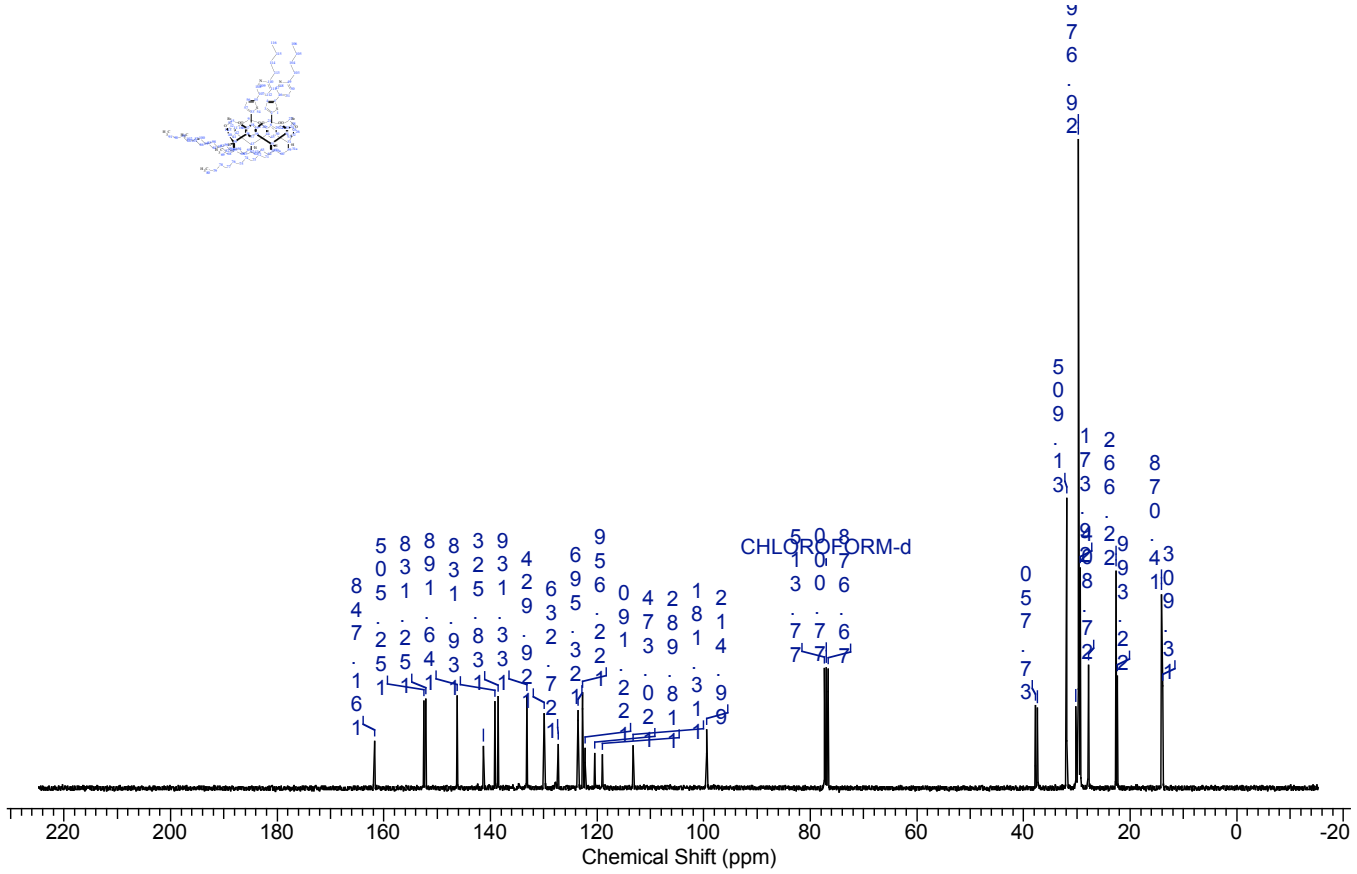
A,C Bis-boronic acid-C,D bis-bromo resorcin[4]arene **[3-12]** ^{13}C



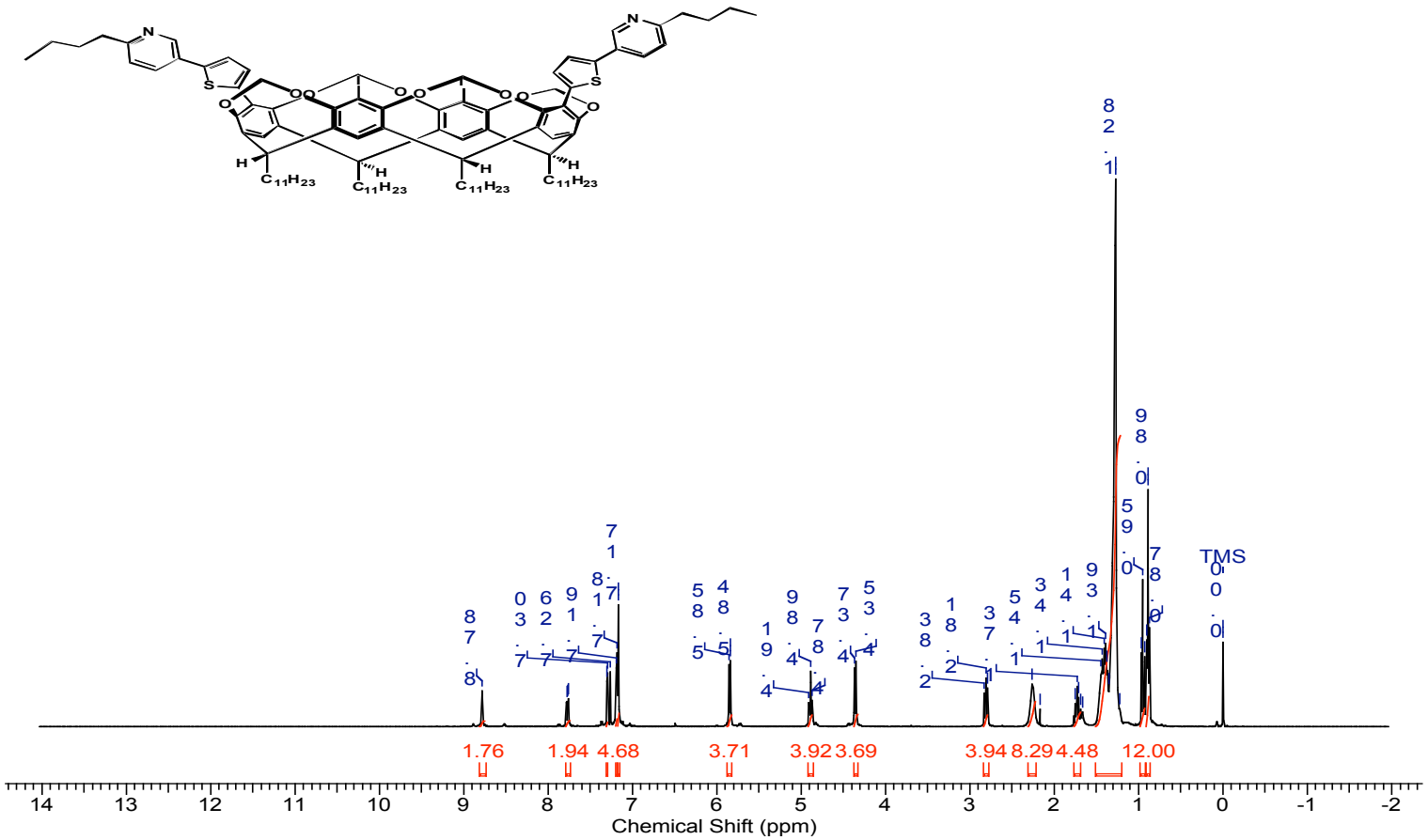
A,C Bis-thiophene pyridine-C,D-bis-bromo resorcin[4]arene **[3-13]** ^{1}**H**



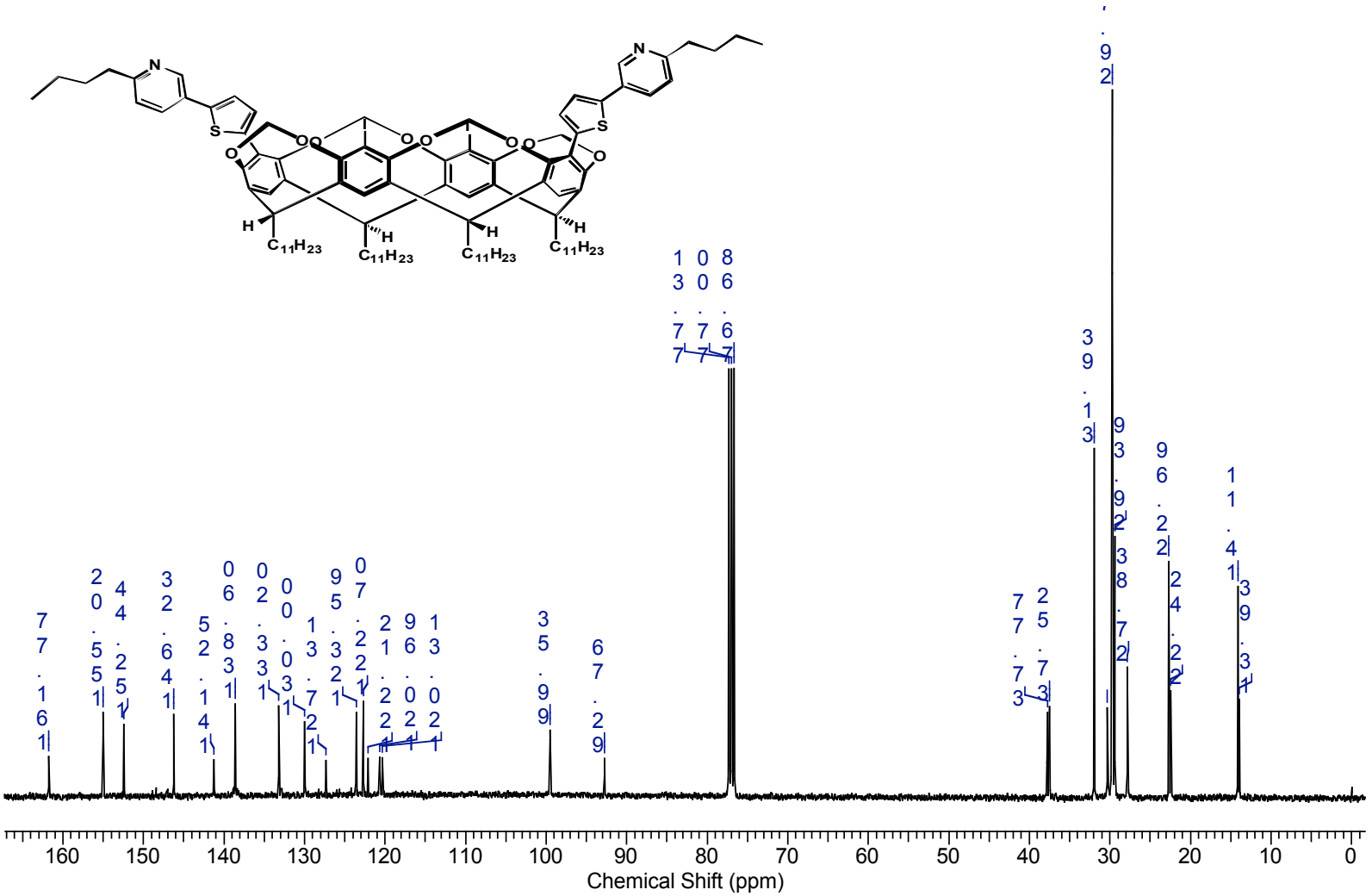
A,C Bis-thiophene pyridine-C,D-bis-bromo resorcin[4]arene **[3-13]** ^{13}C



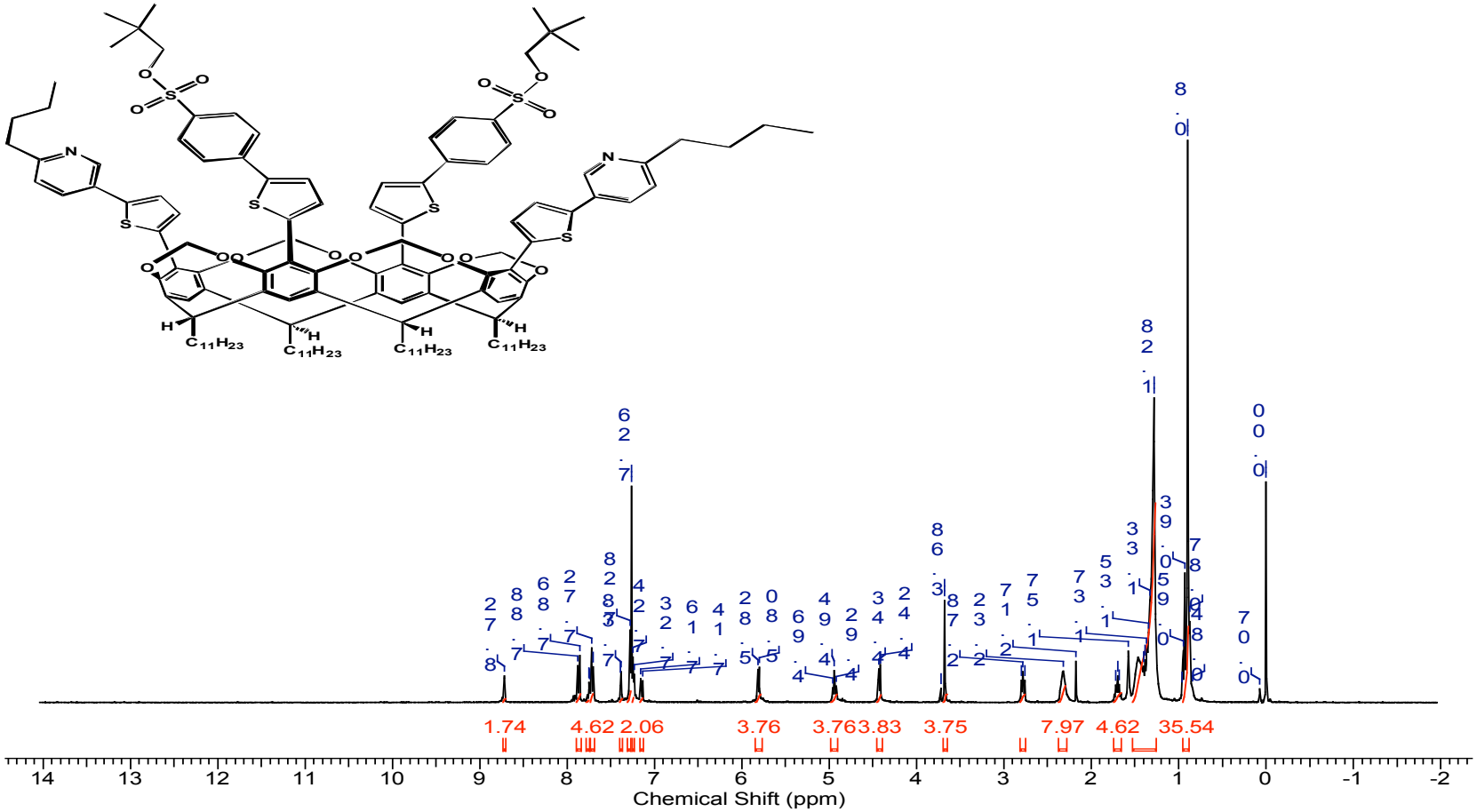
A,C Bis-thiophene pyridine-C,D-bis-iodoresorcin[4]arene **[3-14]** ^{1}**H**



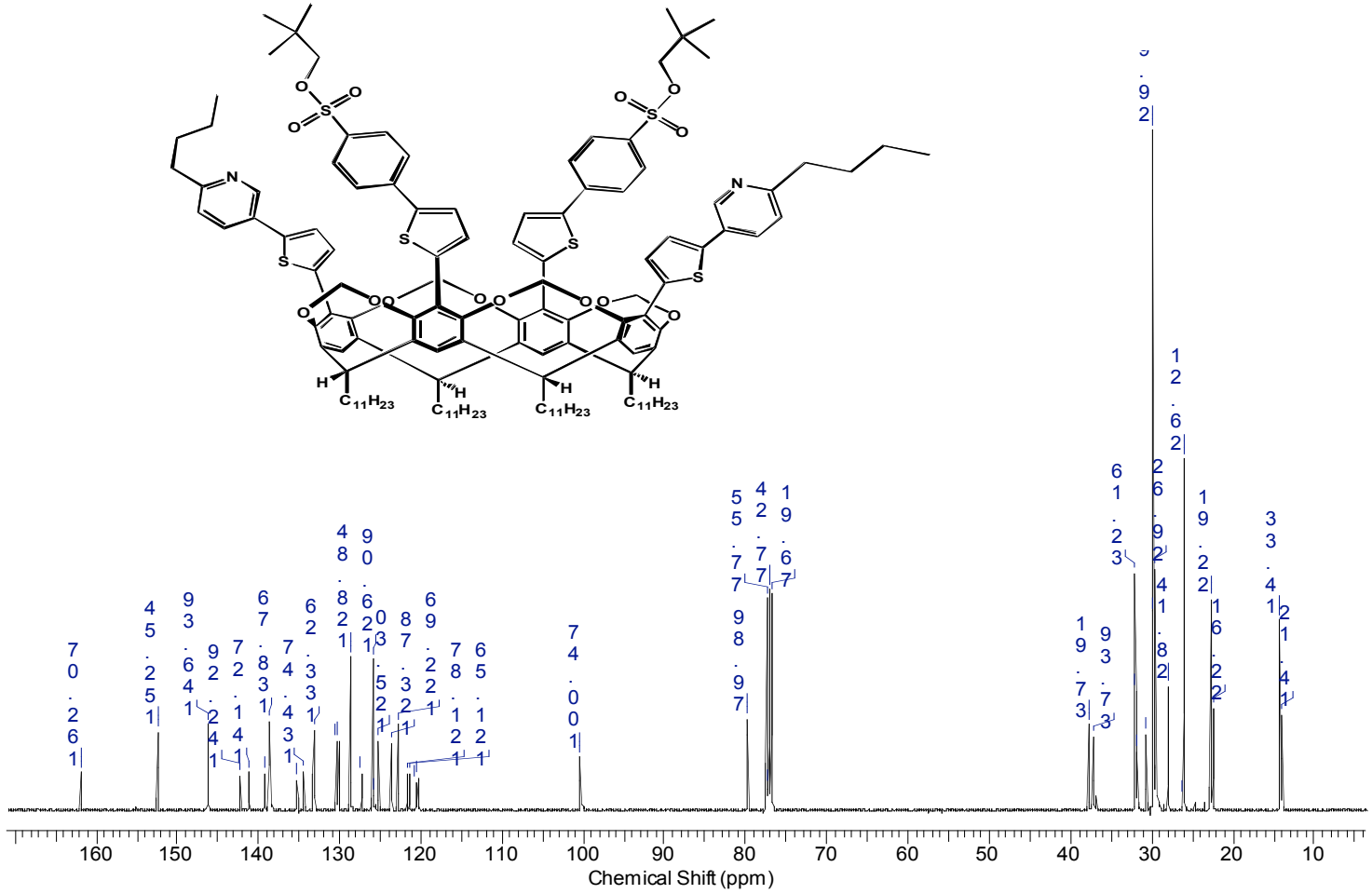
A,C Bis-thiophene pyridine-C,D-bis-iodo resorcin[4]arene **[3-14]** ^{13}**C**



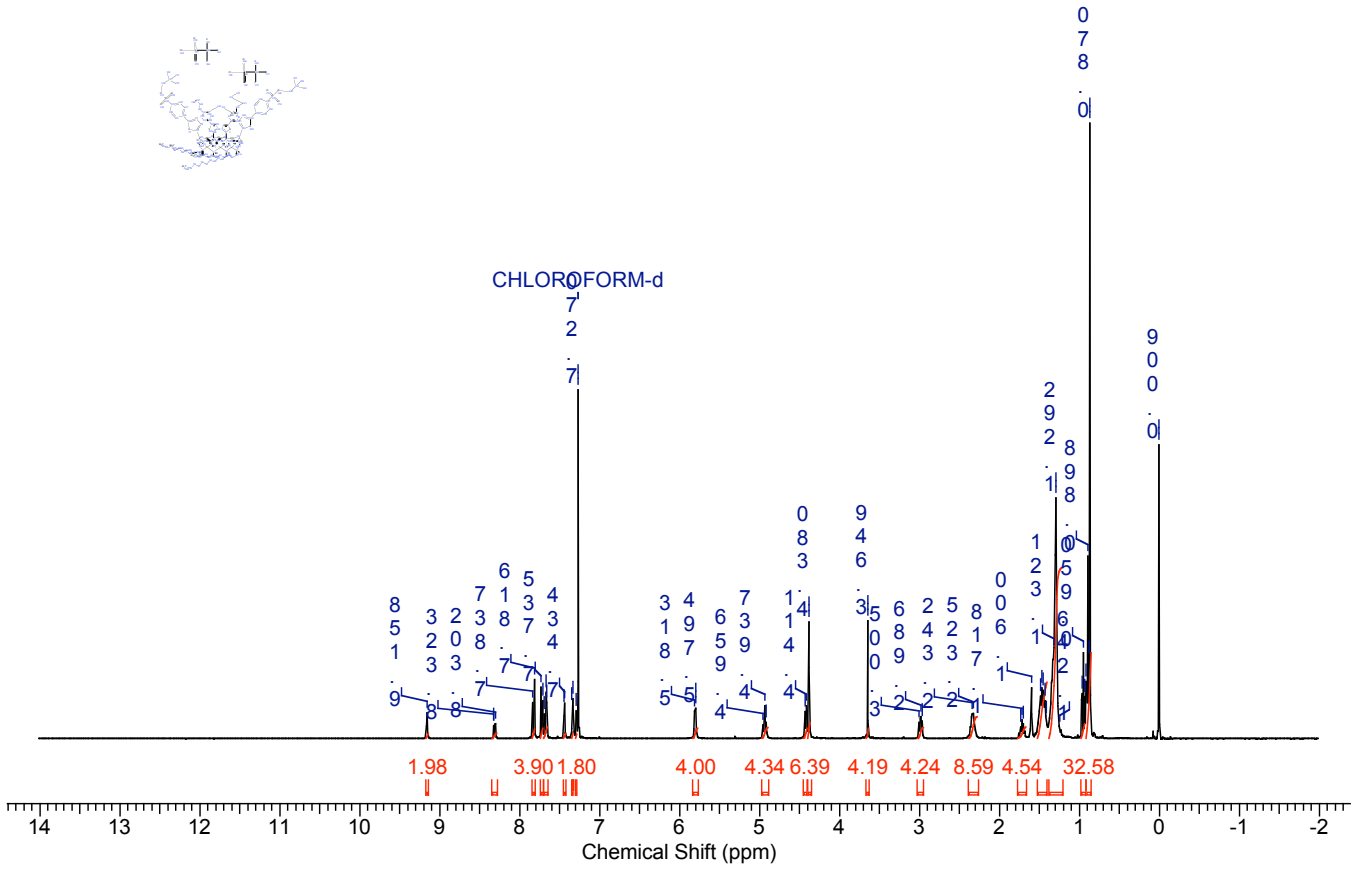
A,C Bis-thiophene pyridine-C,D Bis thiophene dimethylpropylbenzenesulfonate**[3-15]** ^{1}**H**



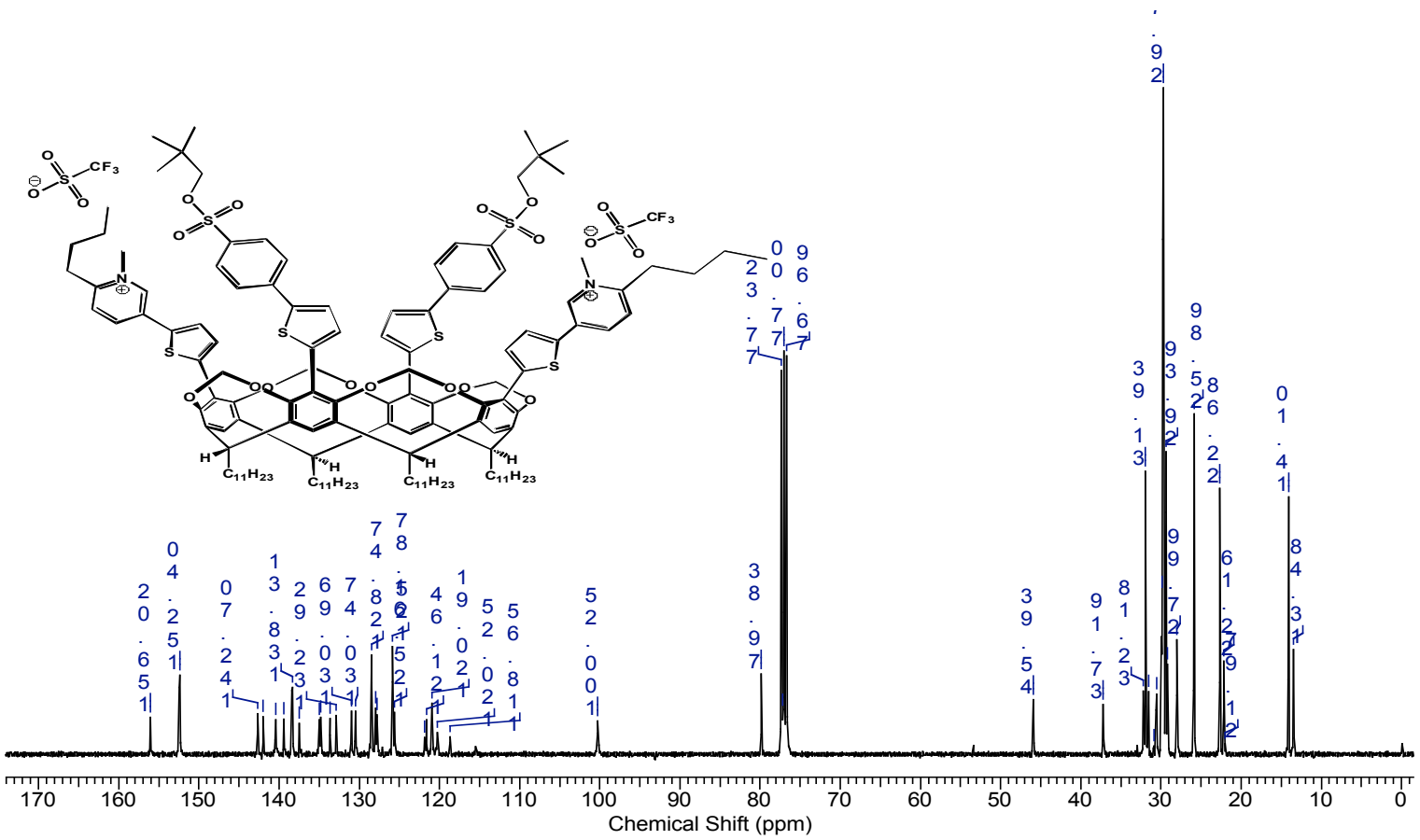
A,C Bis-thiophene pyridine-C,D Bis thiophene dimethylpropylbenzenesulfonate**[3-15]** ^{13}C



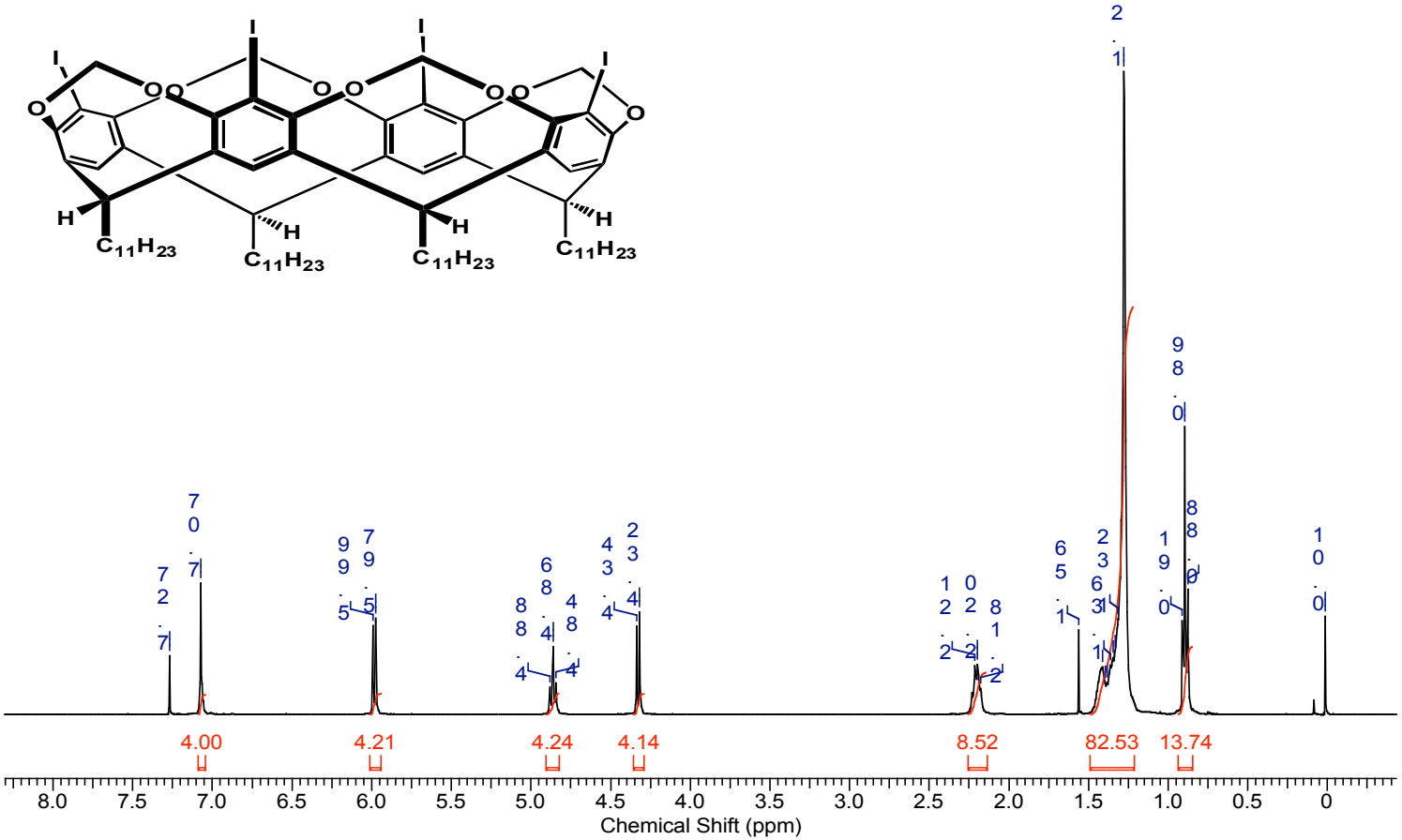
A,C Bis-thiophene pyridinium triflate-C,D bis-thiophene dimethylpropylbenzesulfonate resorcin[4]arene **[3-16]** ^{1}**H**



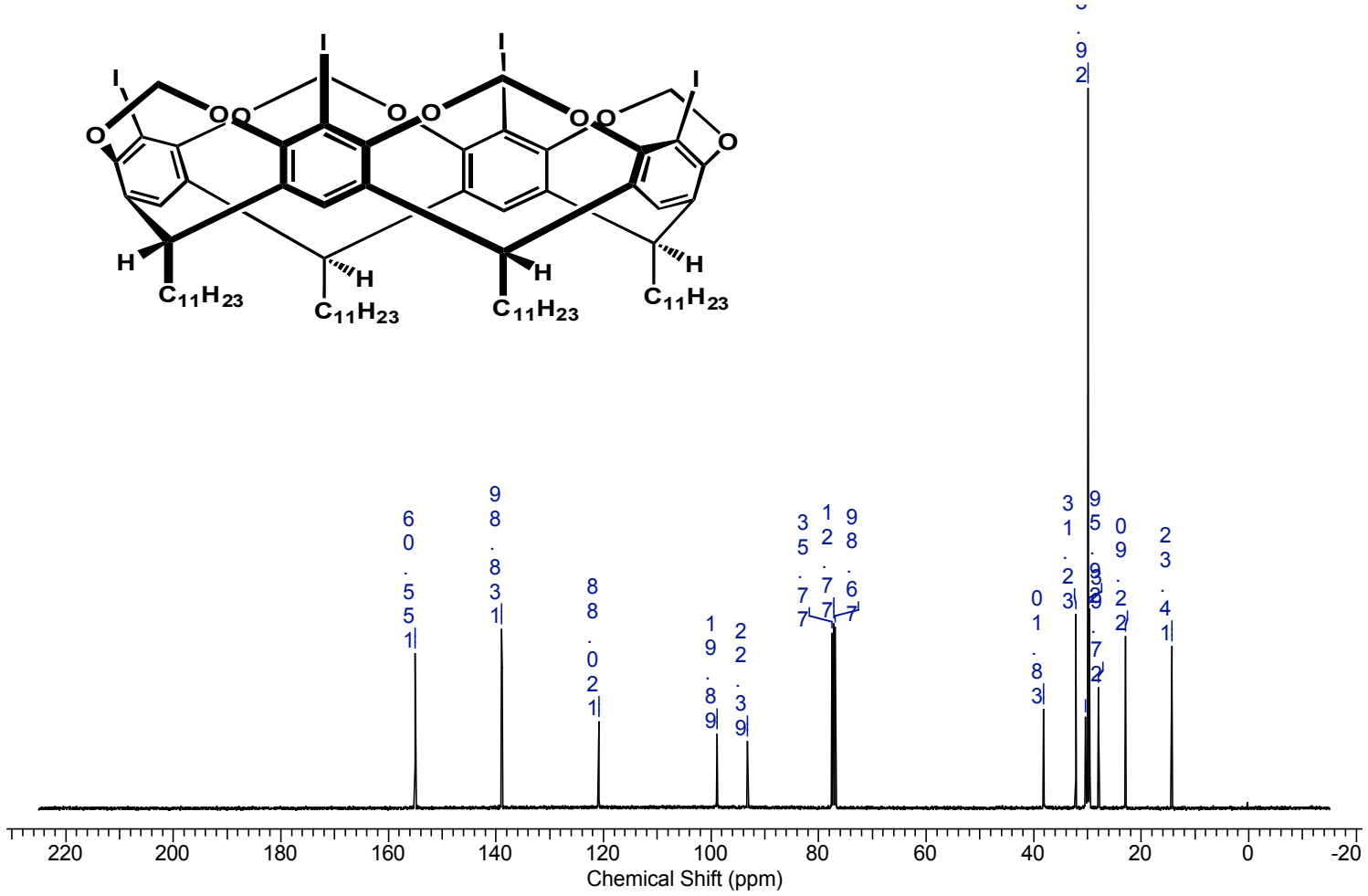
A,C Bis-thiophene pyridinium triflate-C,D bis-thiophene dimethylpropylbenzesulfonate resorcin[4]arene **[3-16]** ^{13}C



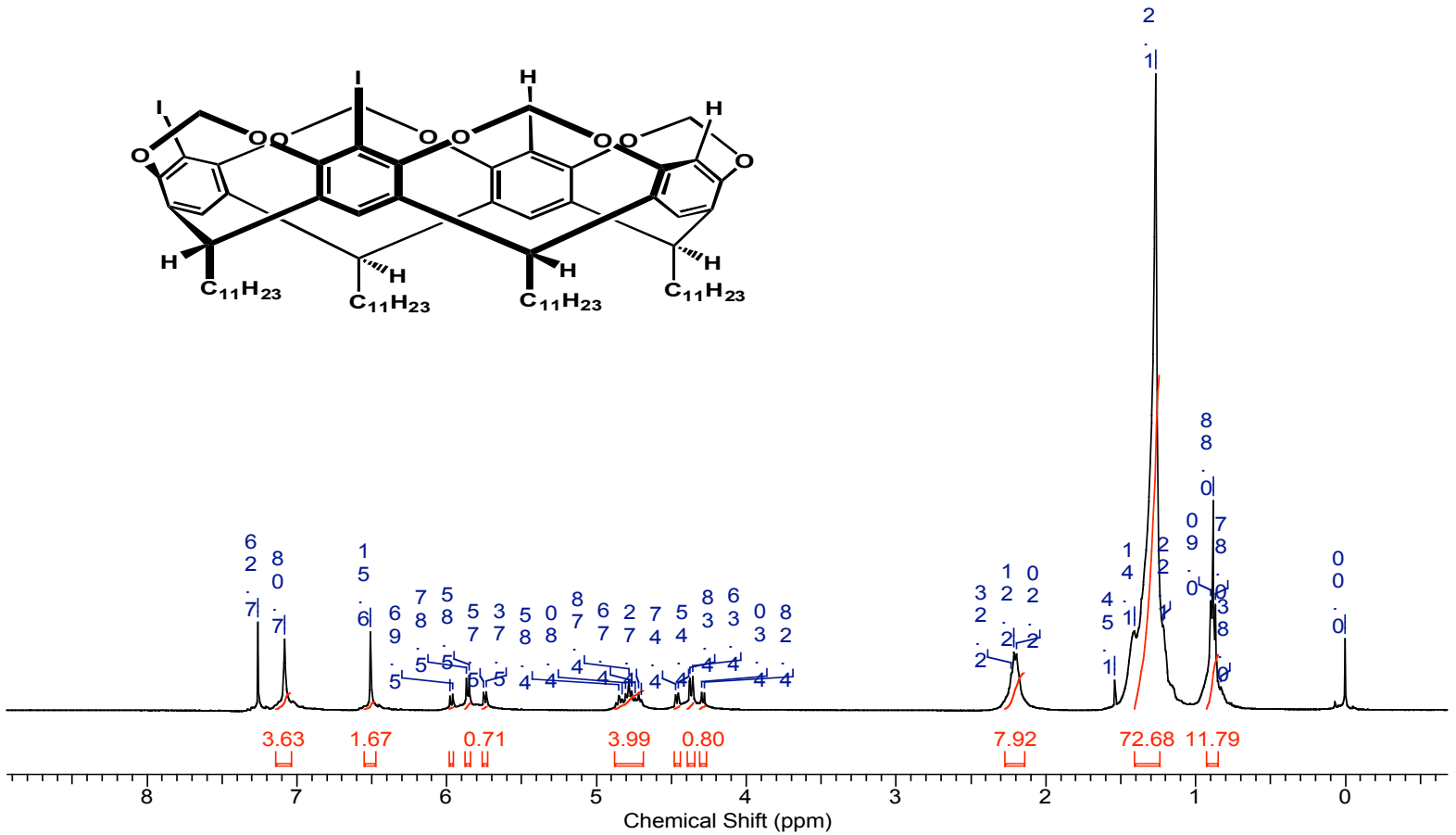
Tetraiodo resorcin[4]arene **[3-18]** ^{1}**H**



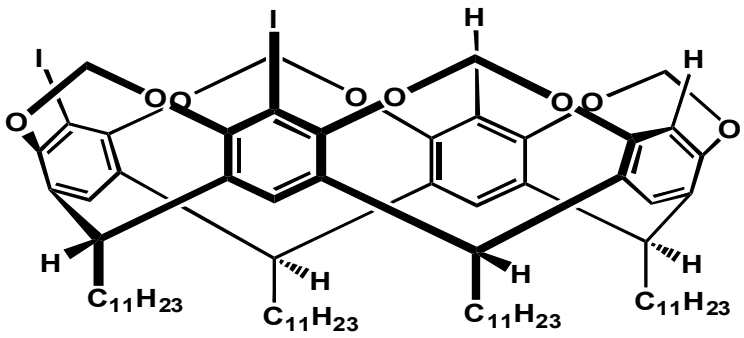
Tetraiodo resorcin[4]arene **[3-18]** ^{13}C



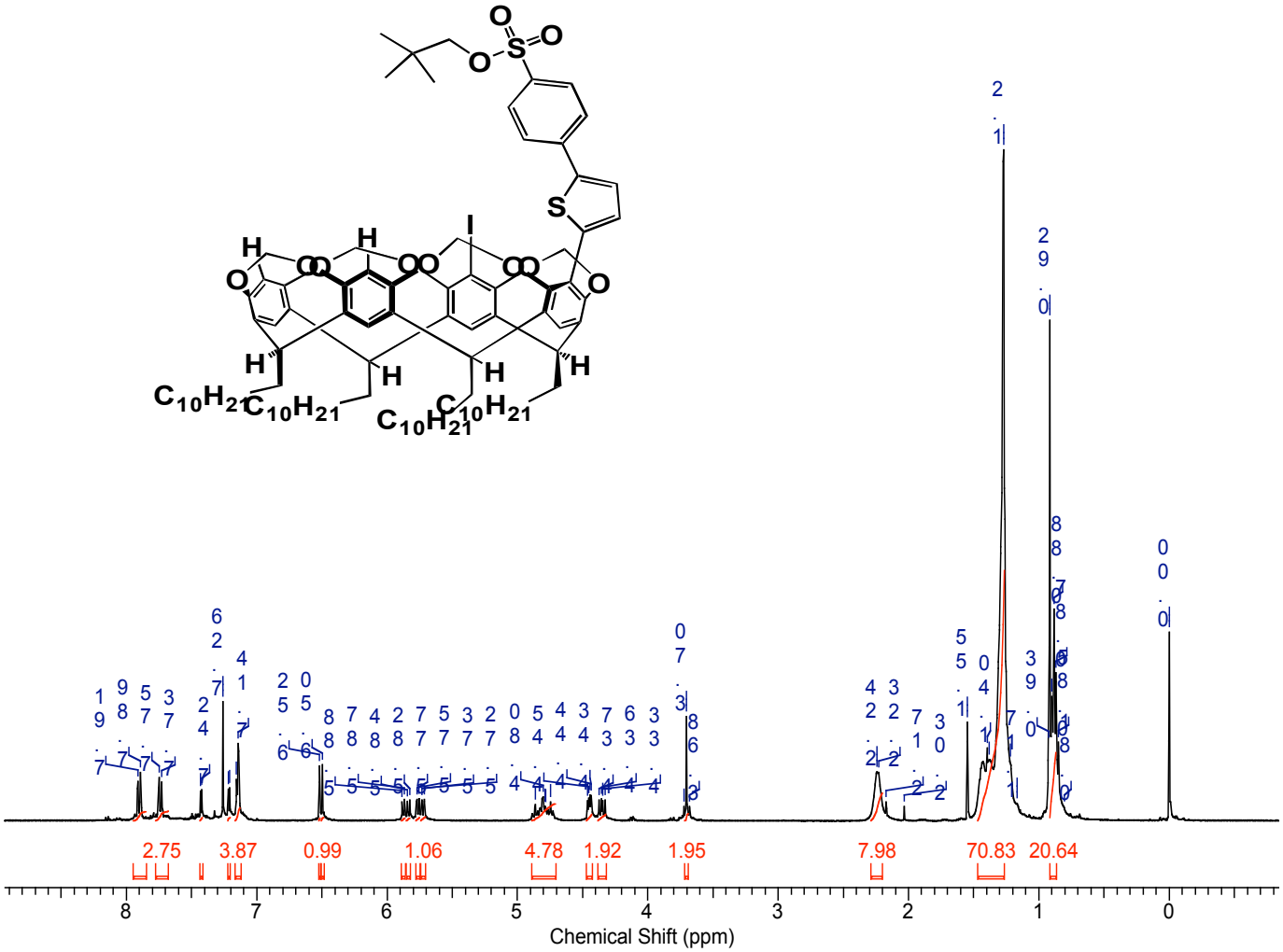
A,B-bis-iodo-C,D-bis-hydrogen resorcin[4]arene **[3-19] ^{1}H**



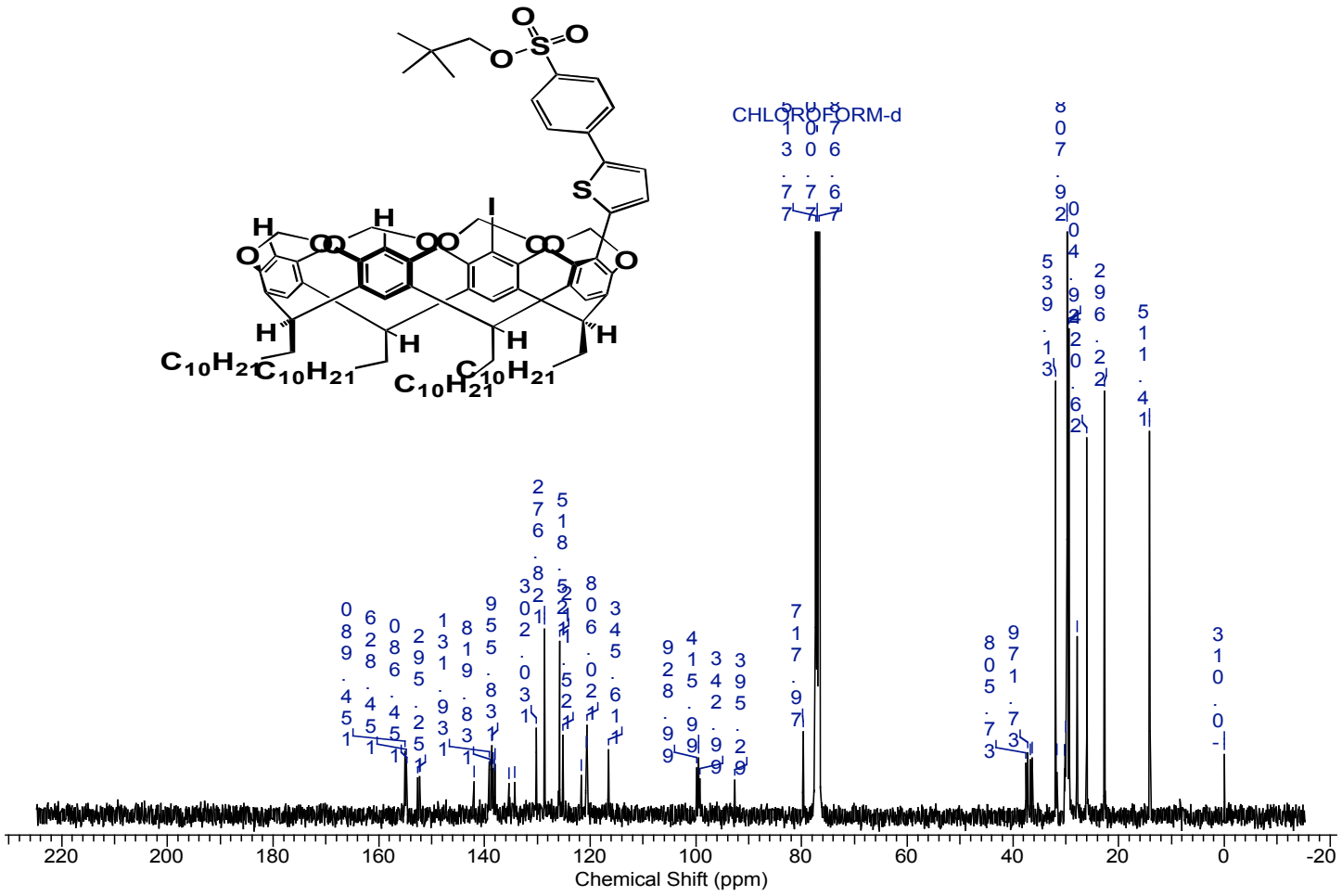
A,B-iodo-C,D-bis-hydrogen resorcin[4]arene **[3-19]** ^{13}C



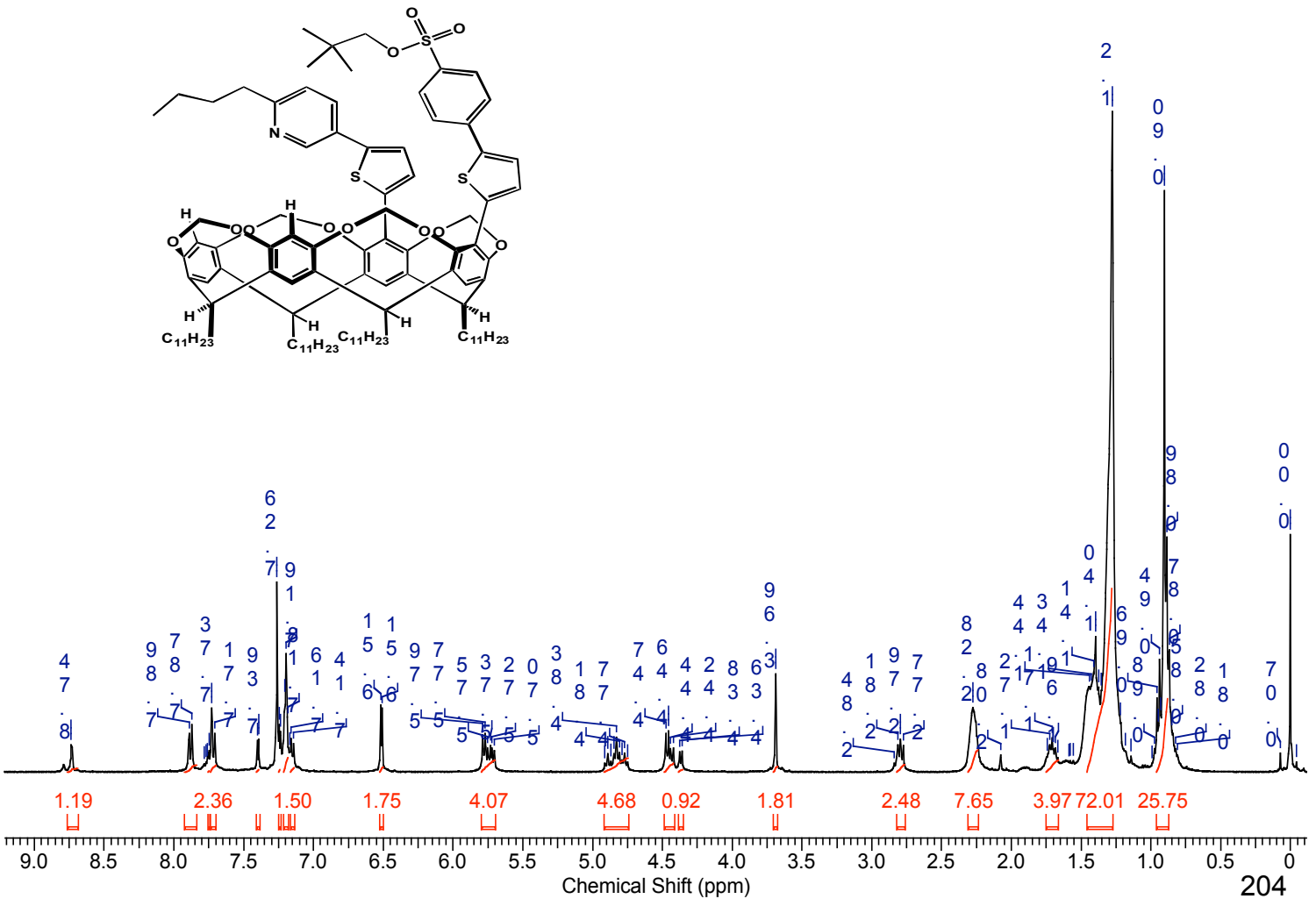
Mono-thiophene-dimethylpropylbenzenesulfonate-mono-iodo-bishydrogne resorcin[4]arene **[3-20]** ^{1}**H**



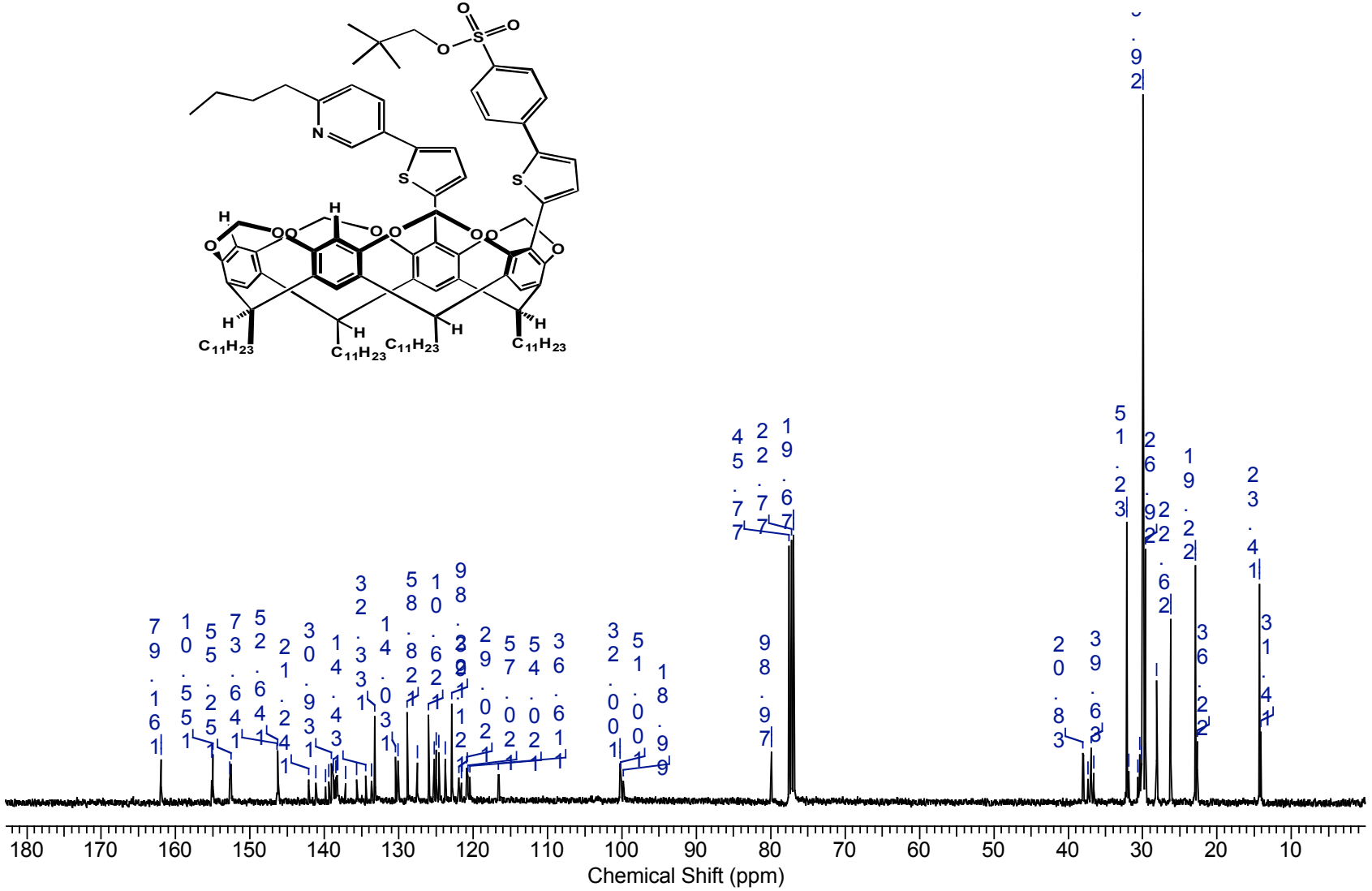
Mono-thiophene-dimethylpropylbenzenesulfonate-mono-iodo-bishydrogne resorcin[4]arene **[3-20]** ^{13}C



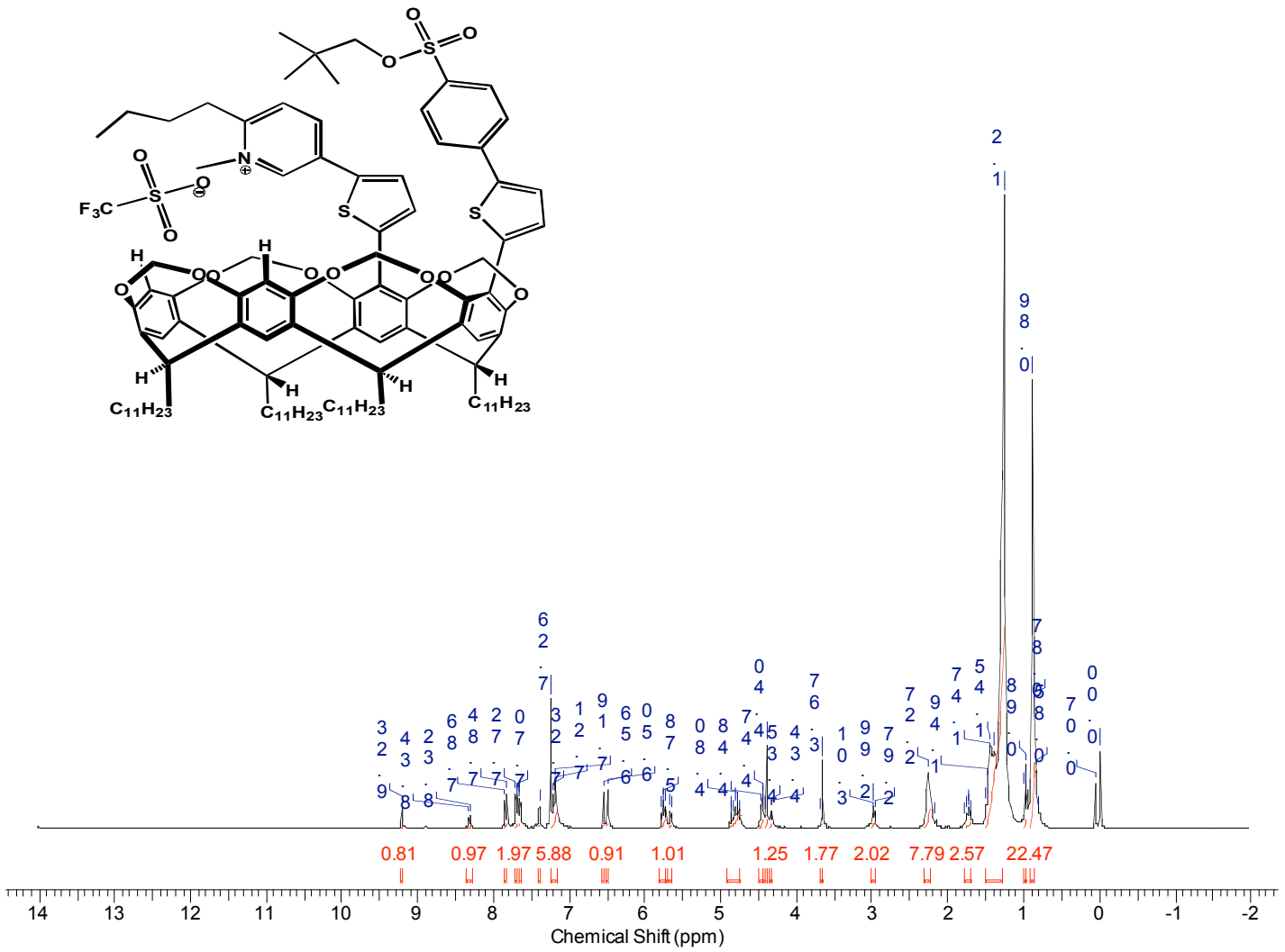
A,B-Mono-thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridine bis hydrogen resorcin[4]arene **[3-21]** ^{1}**H**



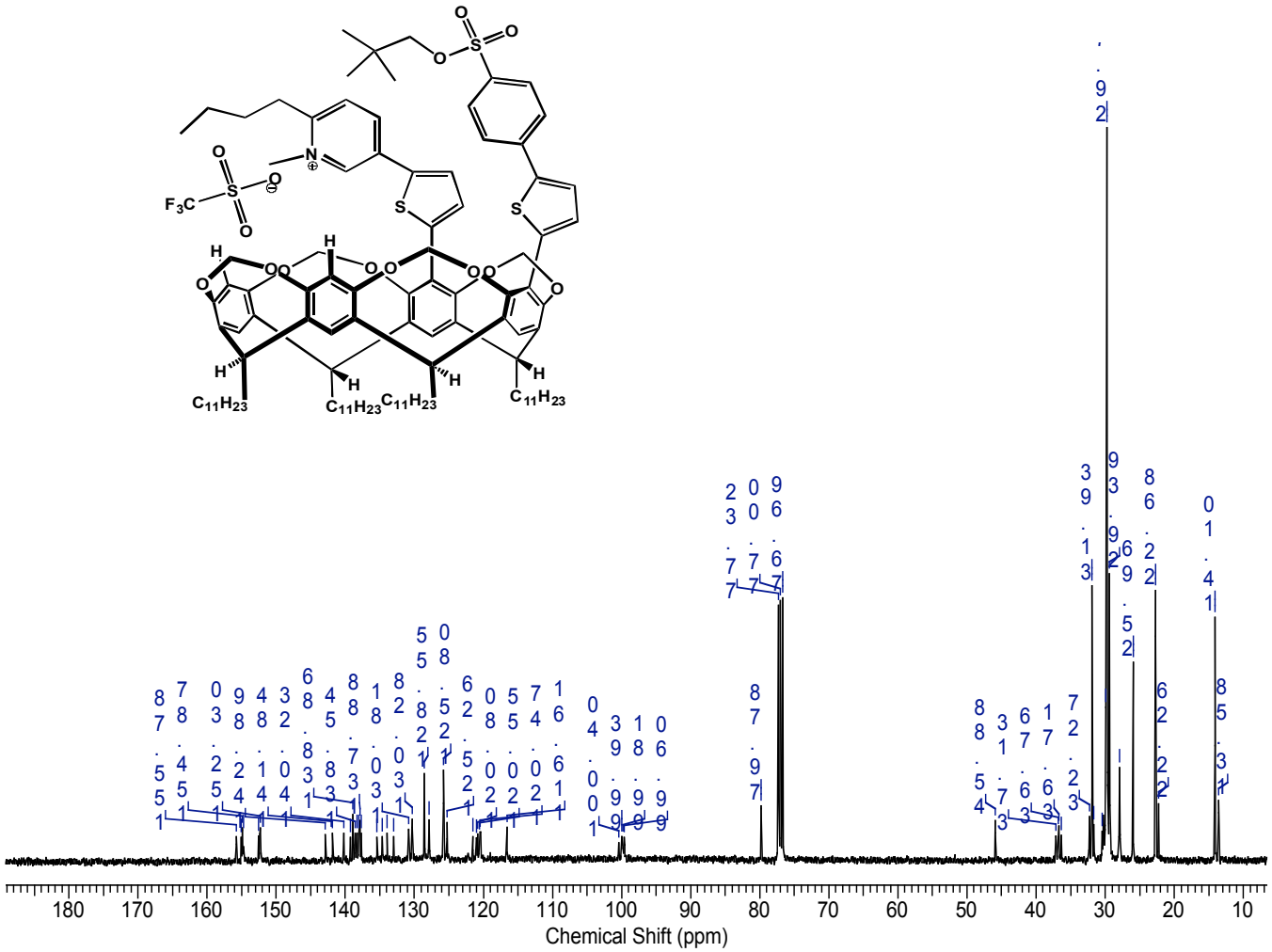
A,B-Mono-thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridine bis hydrogen resorcin[4]arene **[3-21]** ^{13}C



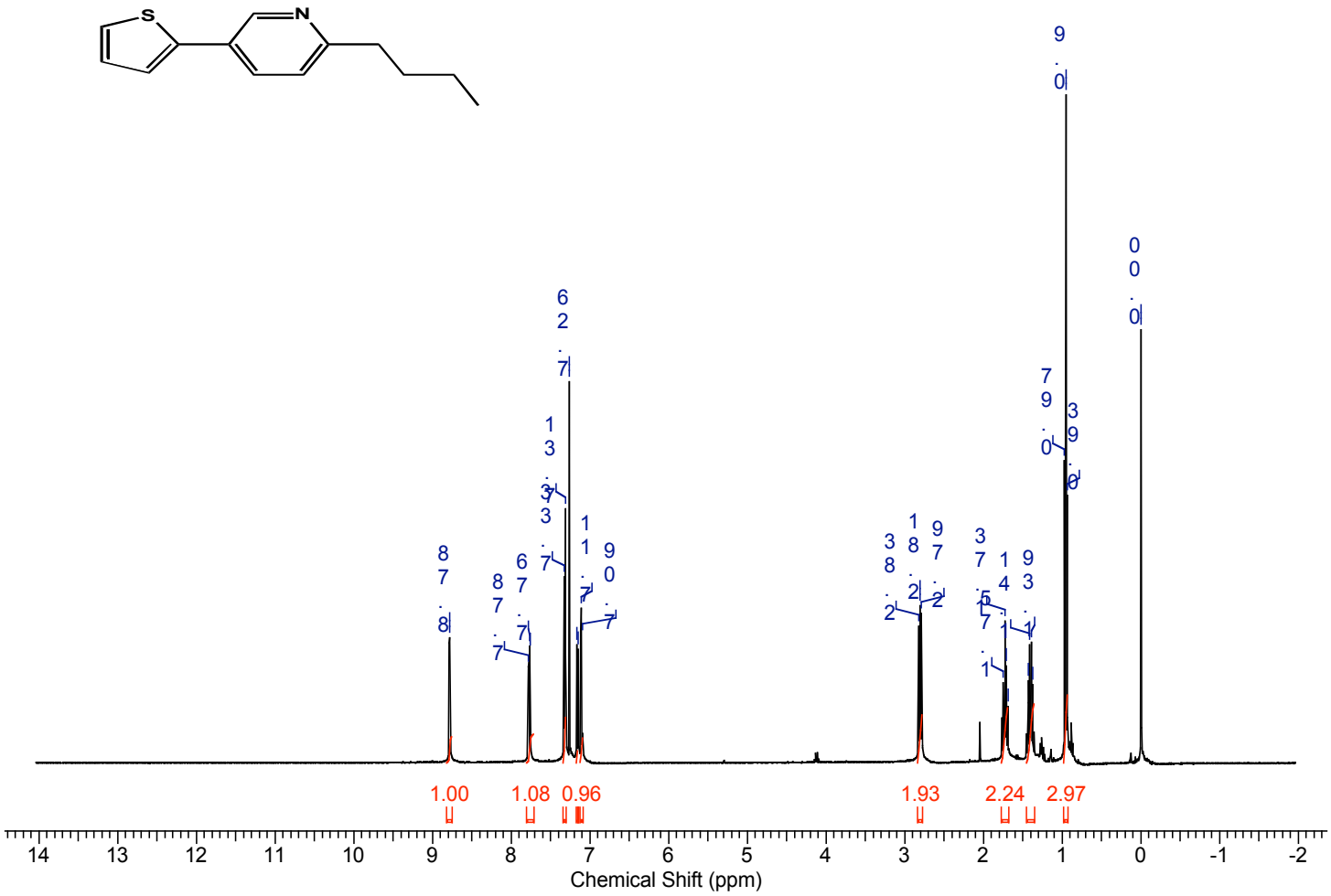
A,B-Mono-thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridinium-triflate-bis hydrogen resorcin[4]arene **[3-22]** ^{1}**H**



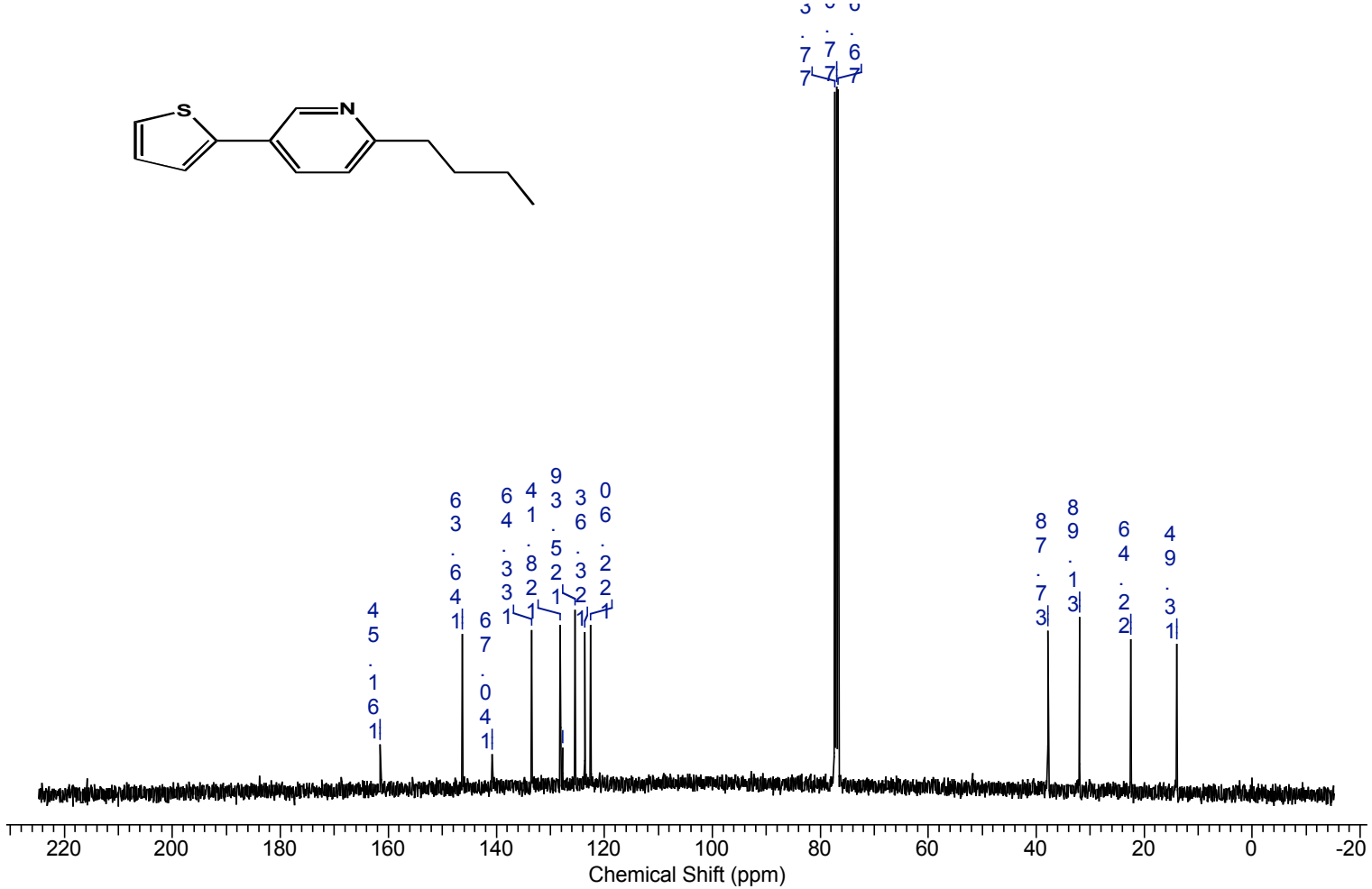
A,B-Mono-thiophene-dimethylpropylbenzenesulfonate-mono-thiophene-pyridinium-triflate-bis hydrogen resorcin[4]arene [**3-22**] ^{13}C



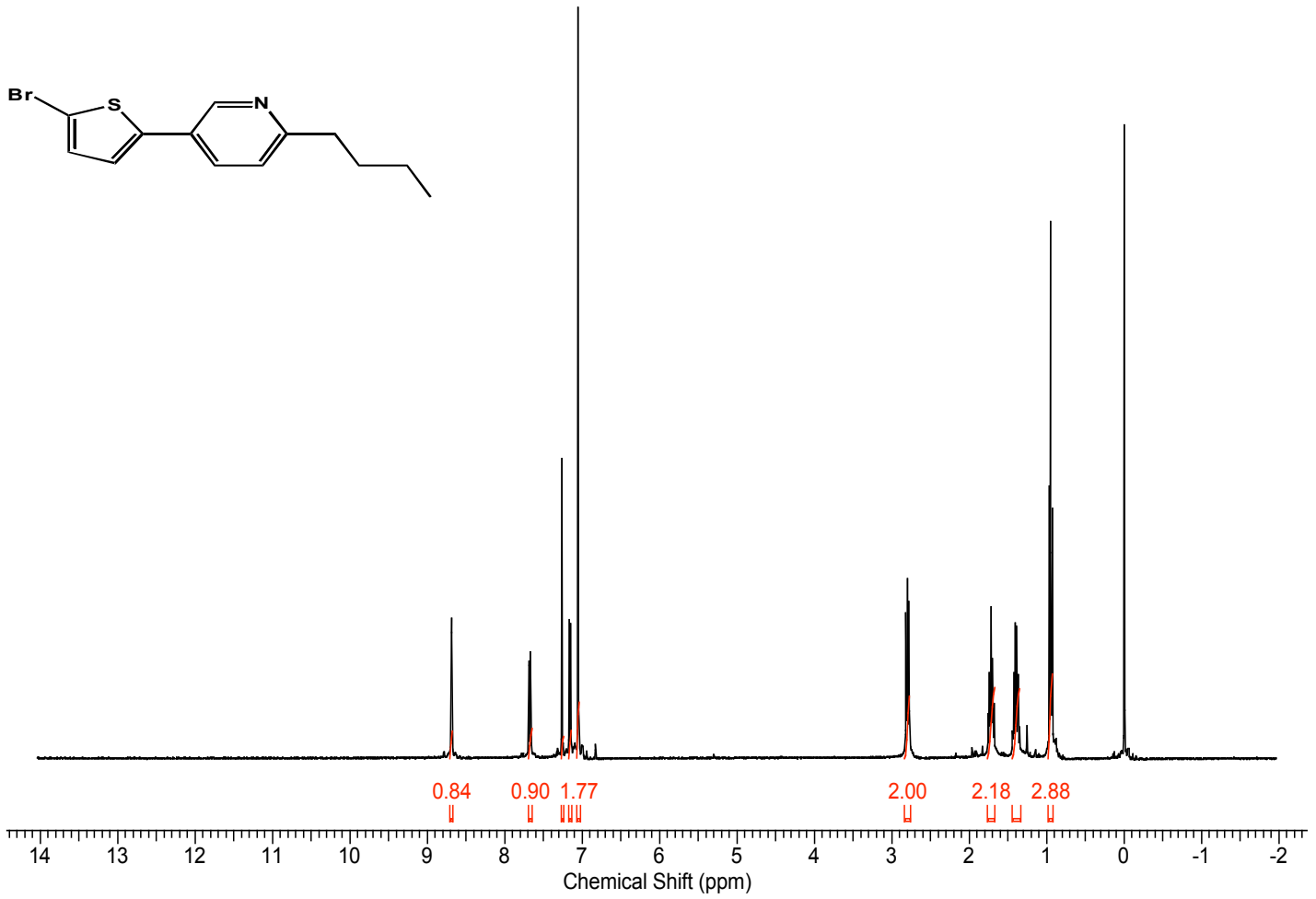
2-butyl-5-(2-thienyl)pyridine**[3-23]** ^{1}**H**



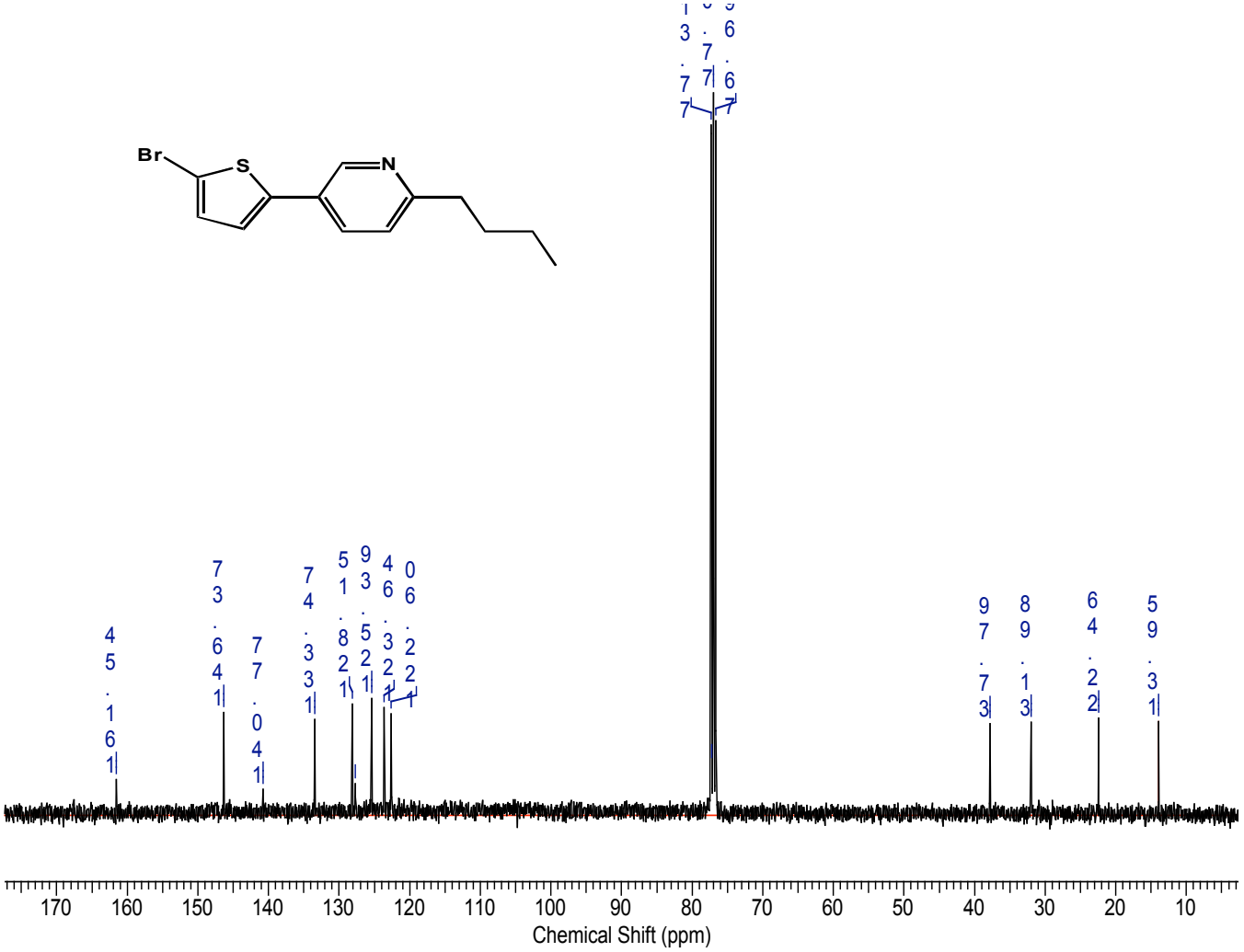
2-butyl-5-(2-thienyl)pyridine**[3-23]** ^{13}C



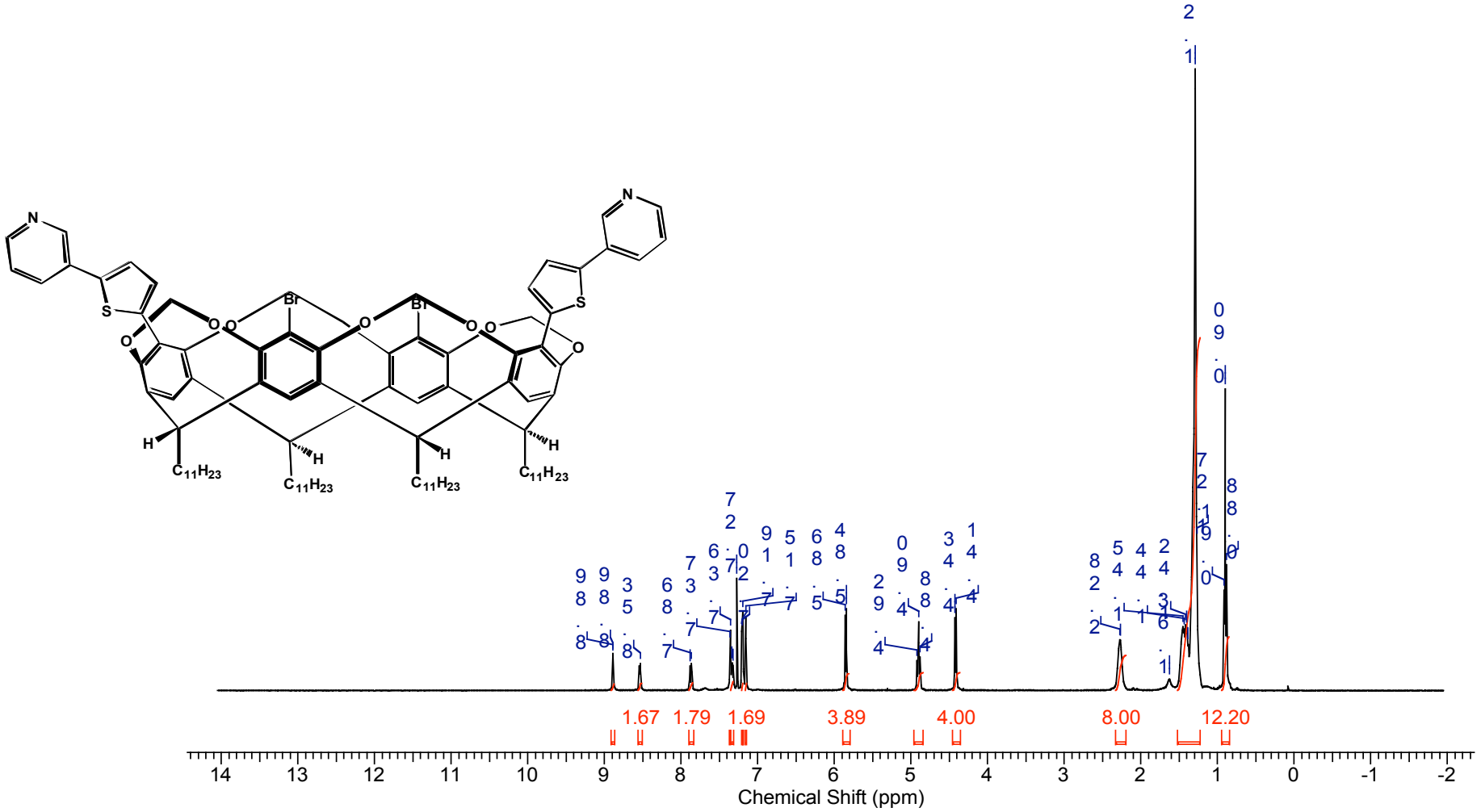
5-(5-bromo2-thienyl)-2-butyl-5-(2-thienyl)pyridine**[3-23]** ^{1}**H**



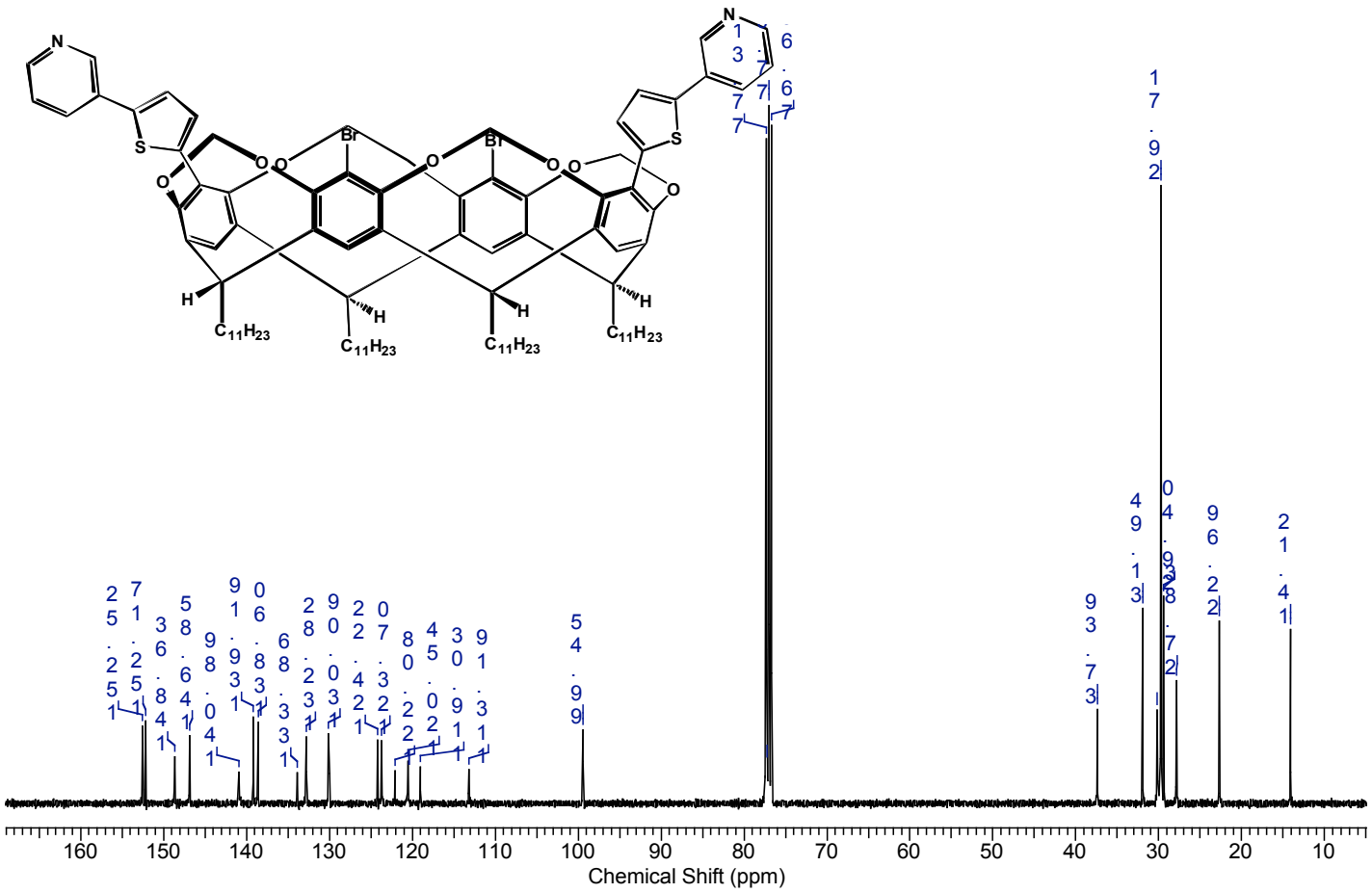
5-(5-bromo-2-thienyl)-2-butyl-5-(2-thienyl)pyridine**[3-23]** ^{13}C



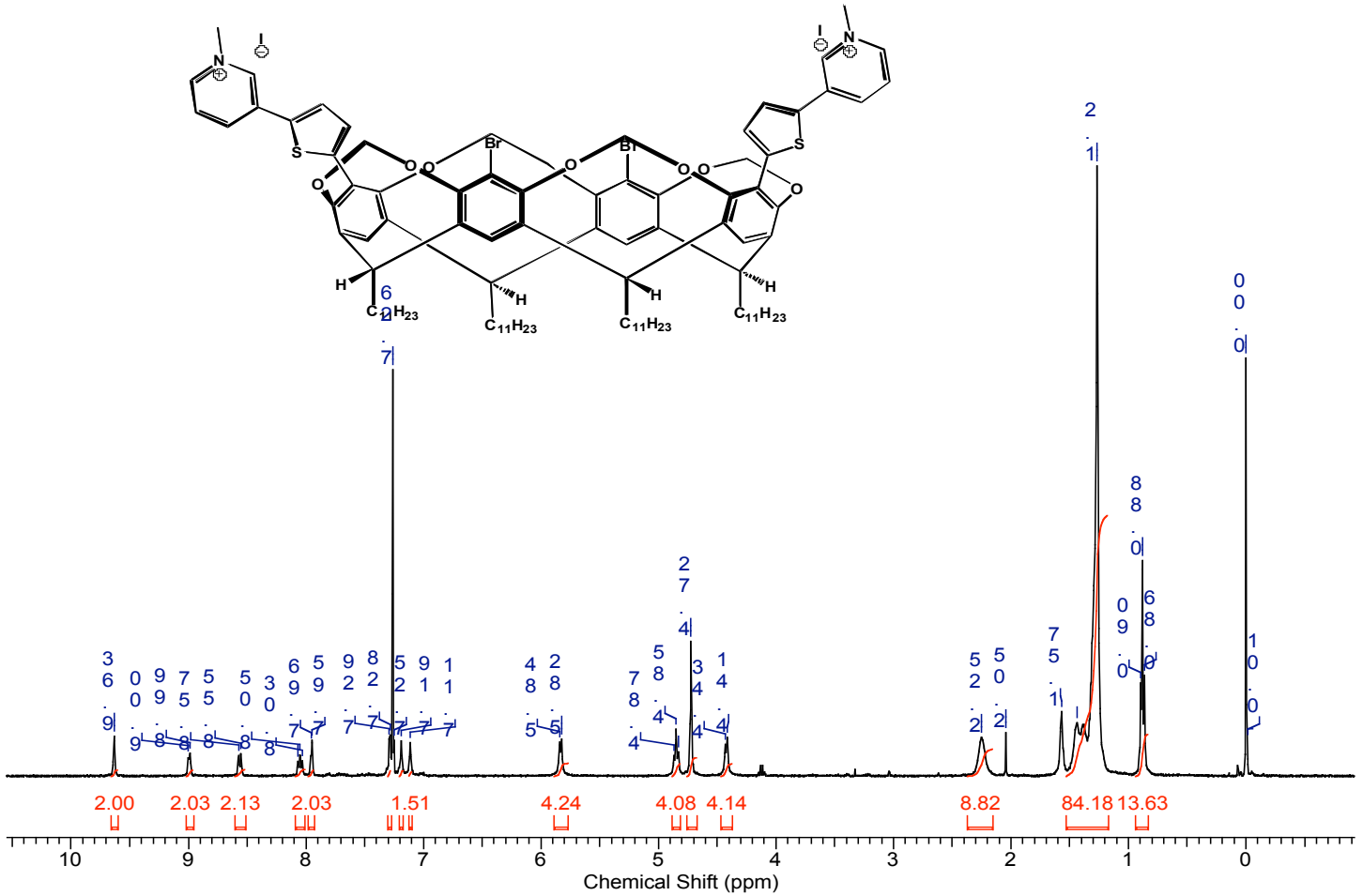
A,C Bis 3-(2-thienyl)pyridine resocin[4]arene [**4-10**] ^{1}**H**



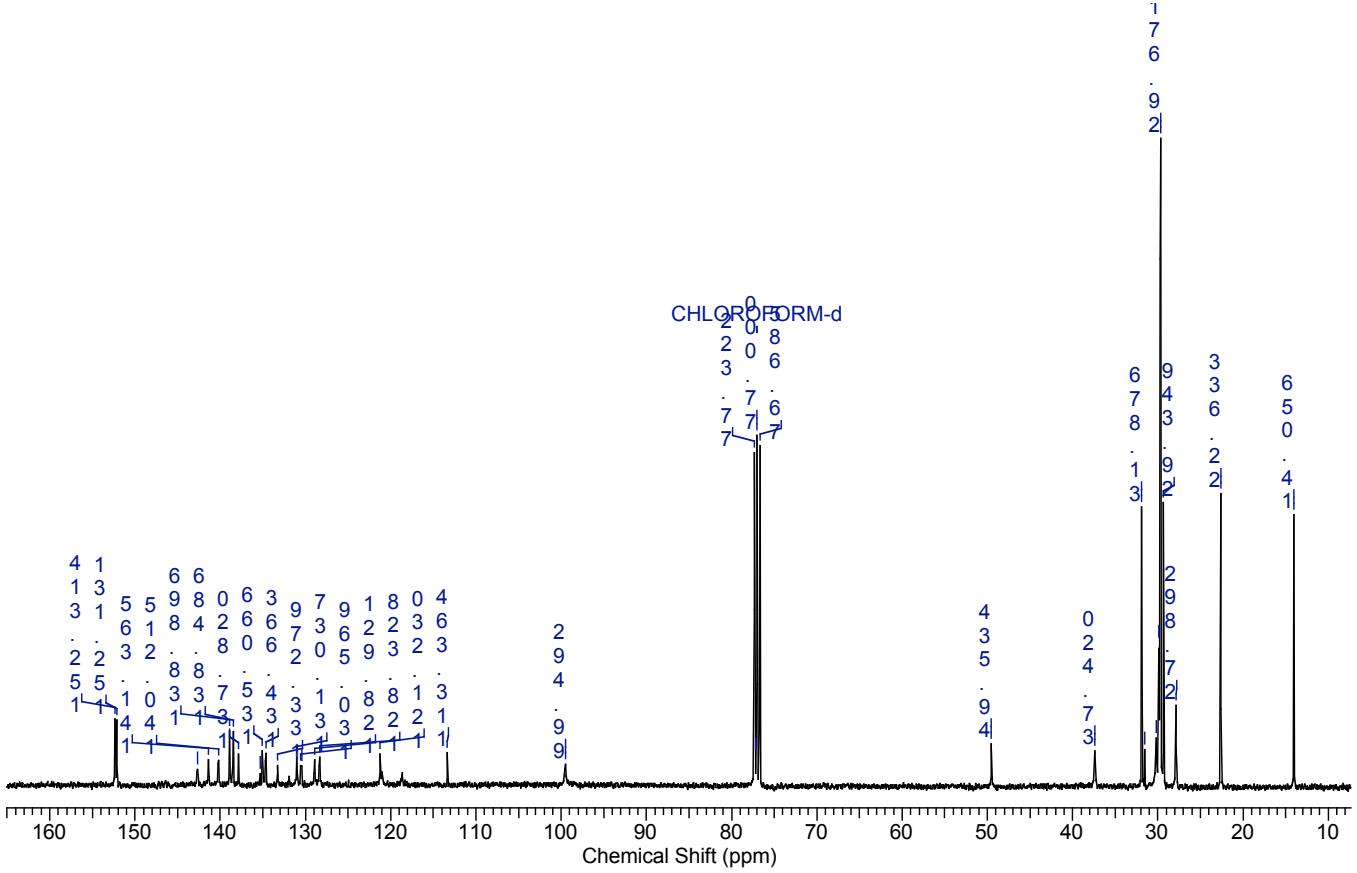
A,C Bis 3-(2-thienyl)pyridine resocin[4]arene [**4-10**] ^{13}**C**



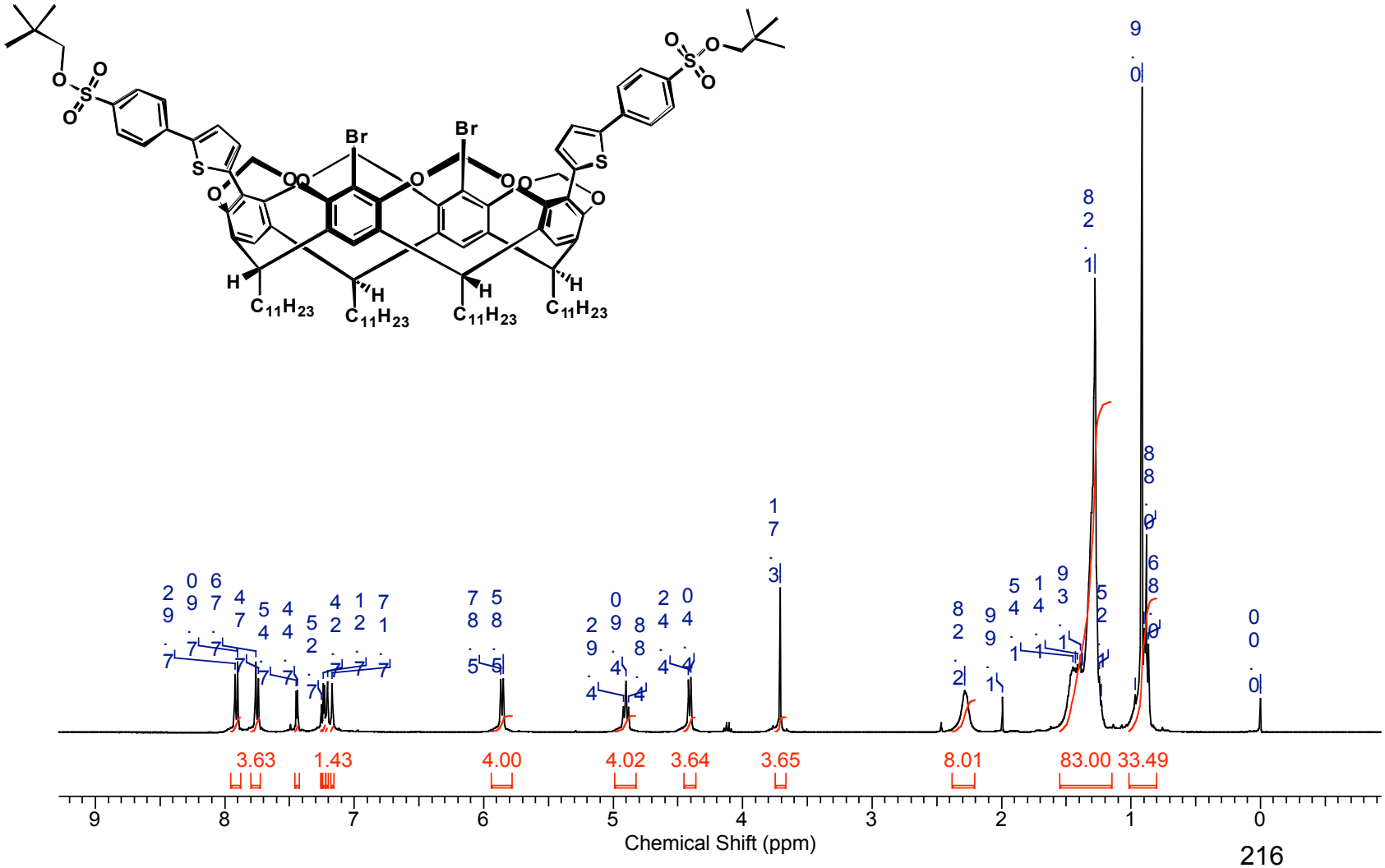
A, C- Bis 3-(2-thienyl)methyl pyridinium iodide resorcin[4]arene [**4-11**] ^{1}**H**



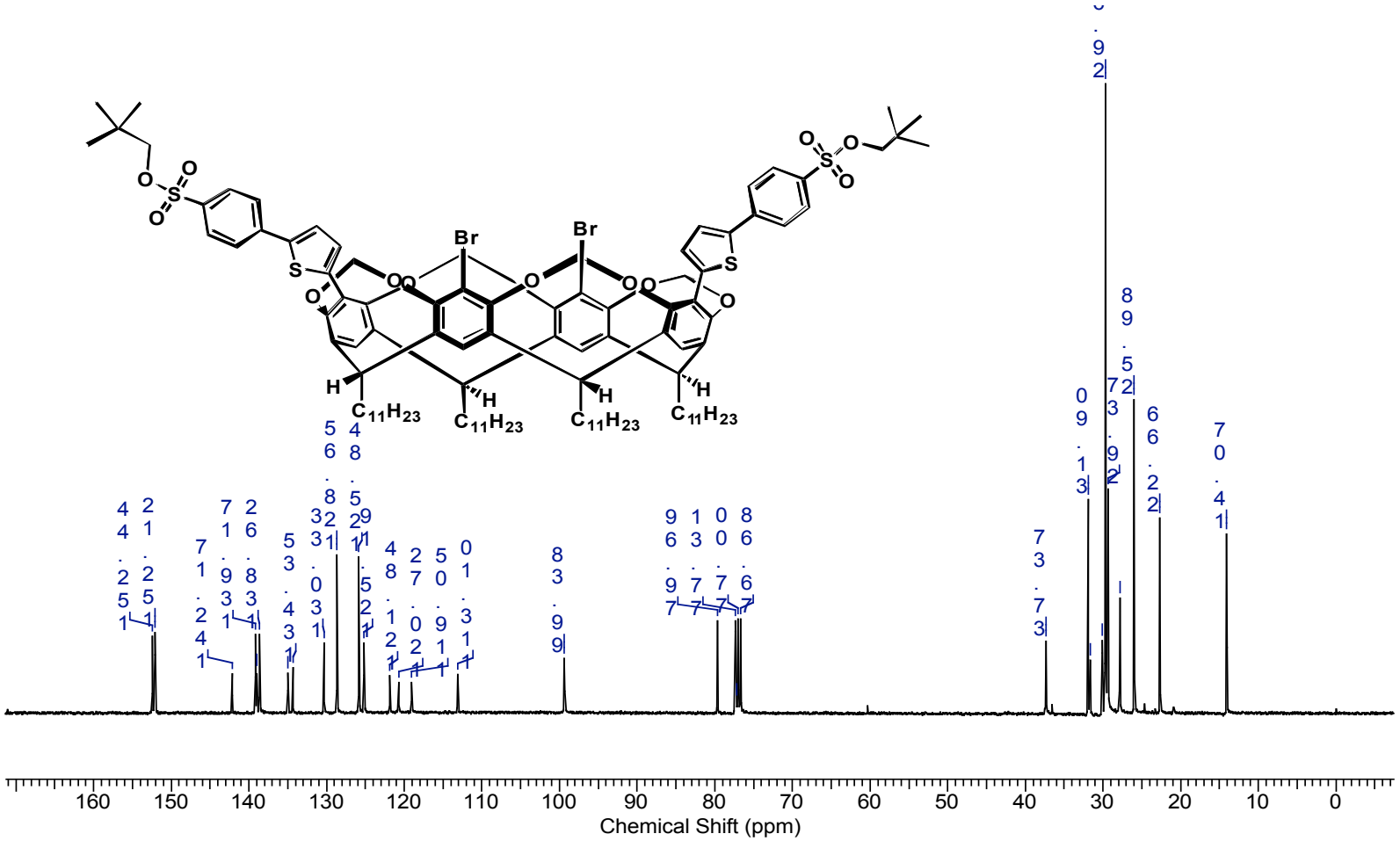
A, C- Bis 3-(2-thienyl)methyl pyridinium iodide resorcin[4]arene **[4-11]** ^{13}C



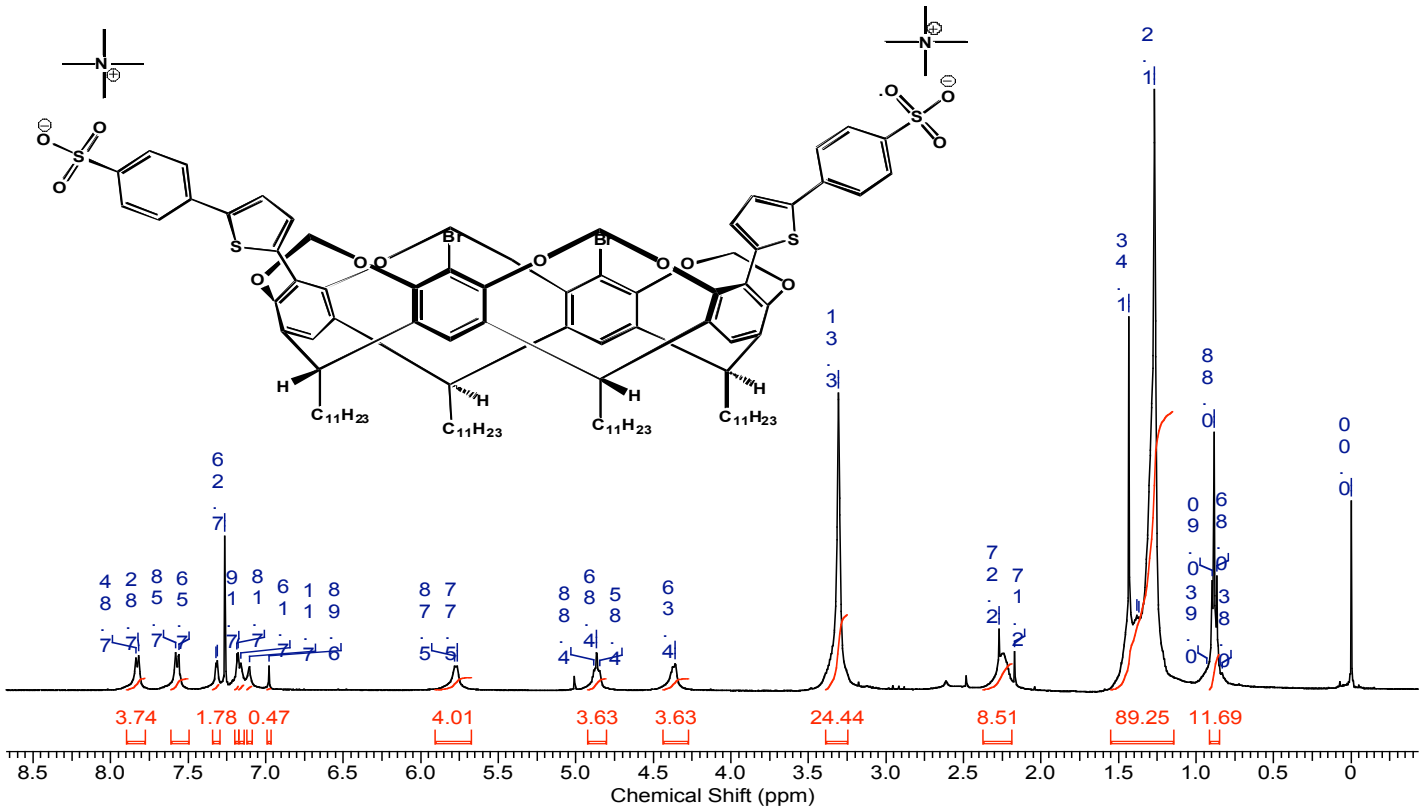
A, C-bis-3-dimethylpropyl 4-(2-thienyl)benzenesulfonate resorcin[4]arene **[4-12]** ^{1}**H**



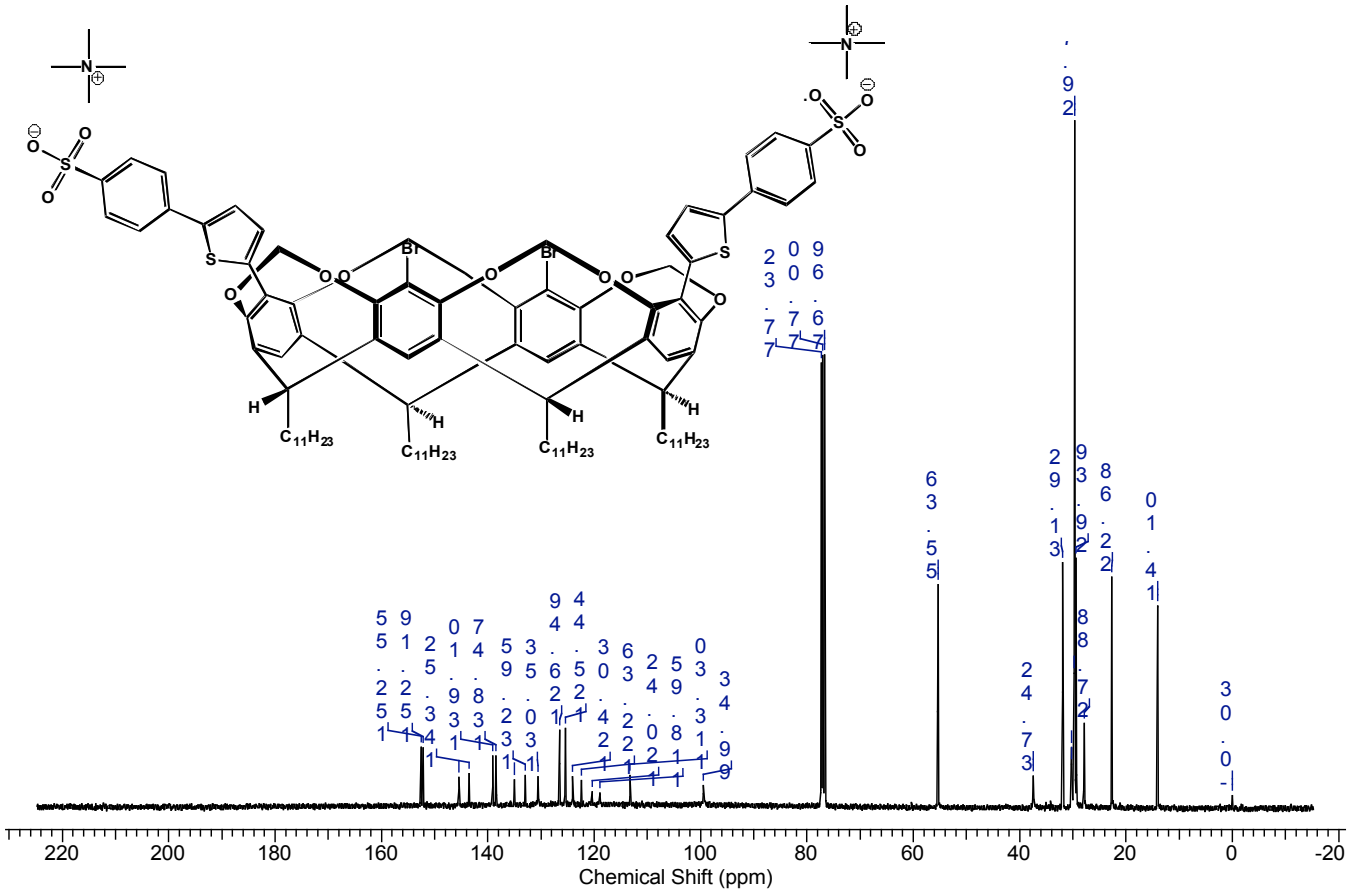
A, C-bis-3-dimethylpropyl 4-(2-thienyl)benzenesulfonate resorcin[4]arene **[4-12]** ^{13}C



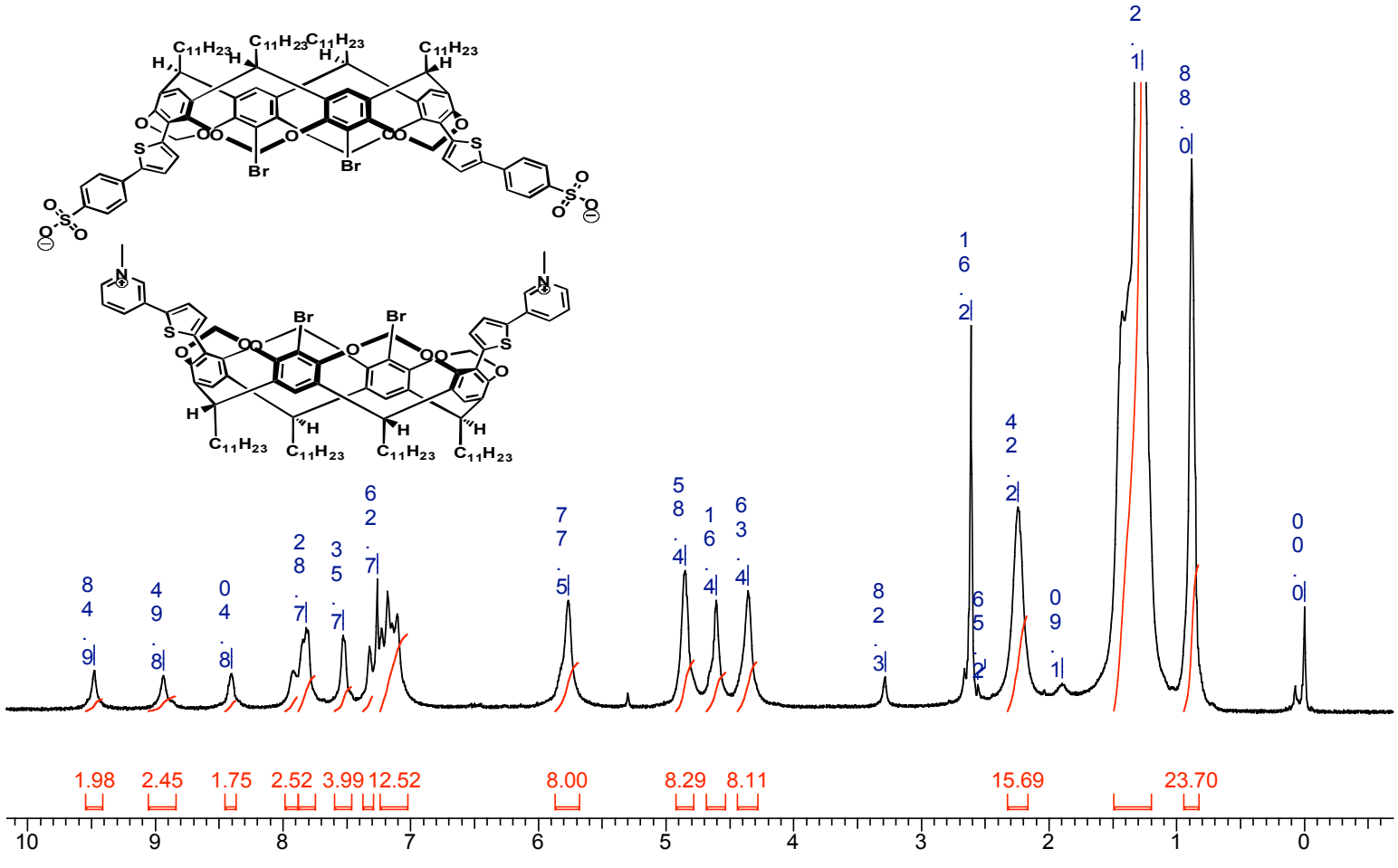
A,C Bis sulfonate thiophene tetramethyl ammonium resorcin[4]arene [**4-13**] ^{1}**H**



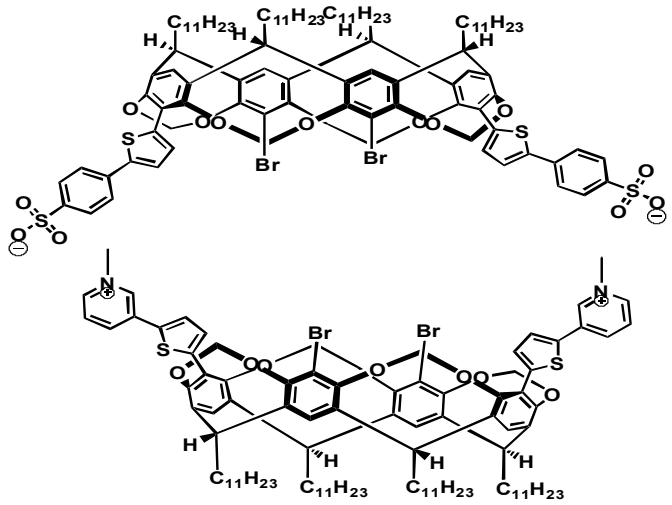
A,C Bis sulfonate thiophene tetramethyl ammonium resorcin[4]arene [**4-13**] ^{13}**C**



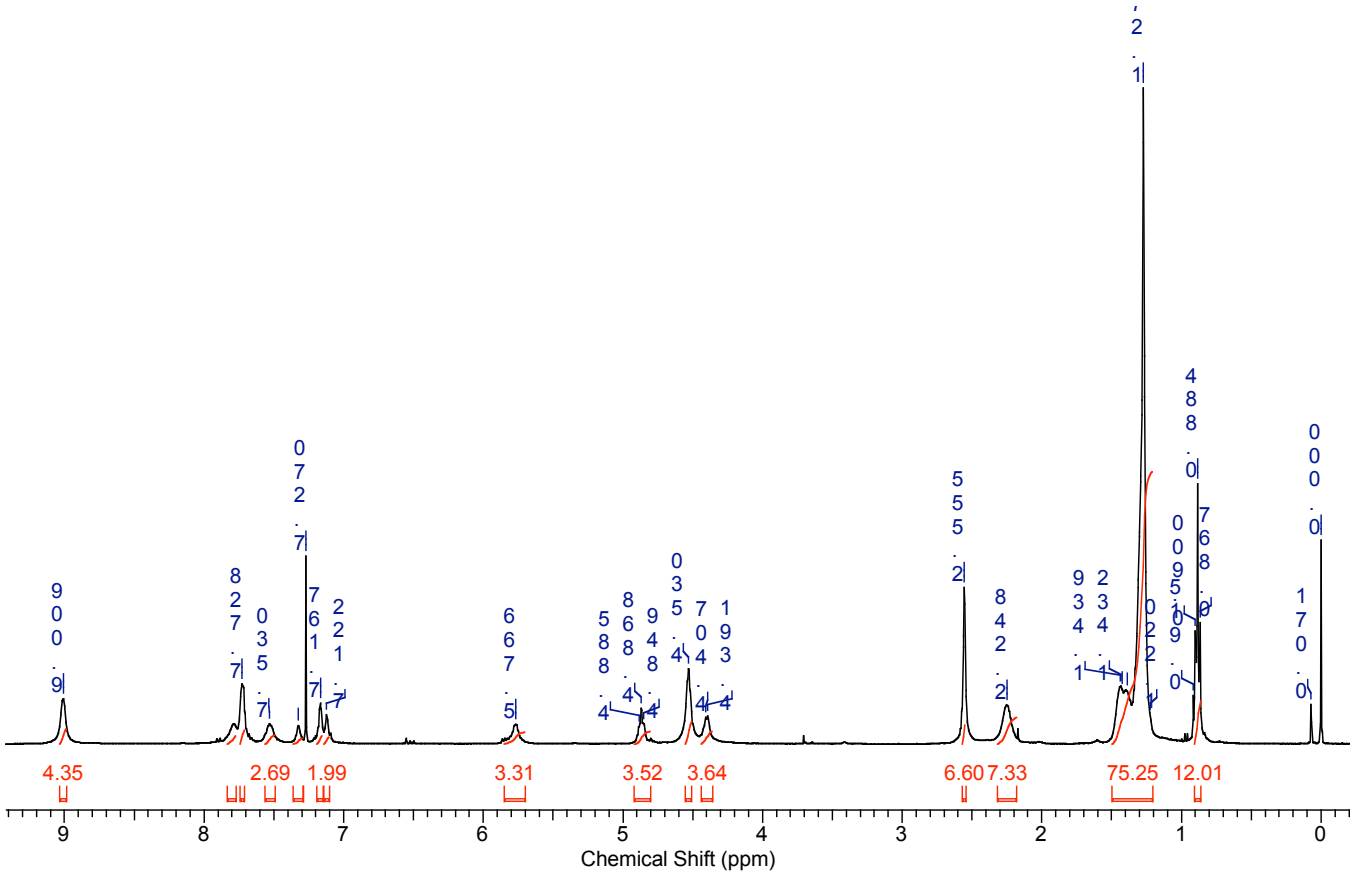
Sulfonate-pyridinium Dimeric Capsule **[4-14]** ^{1}**H**



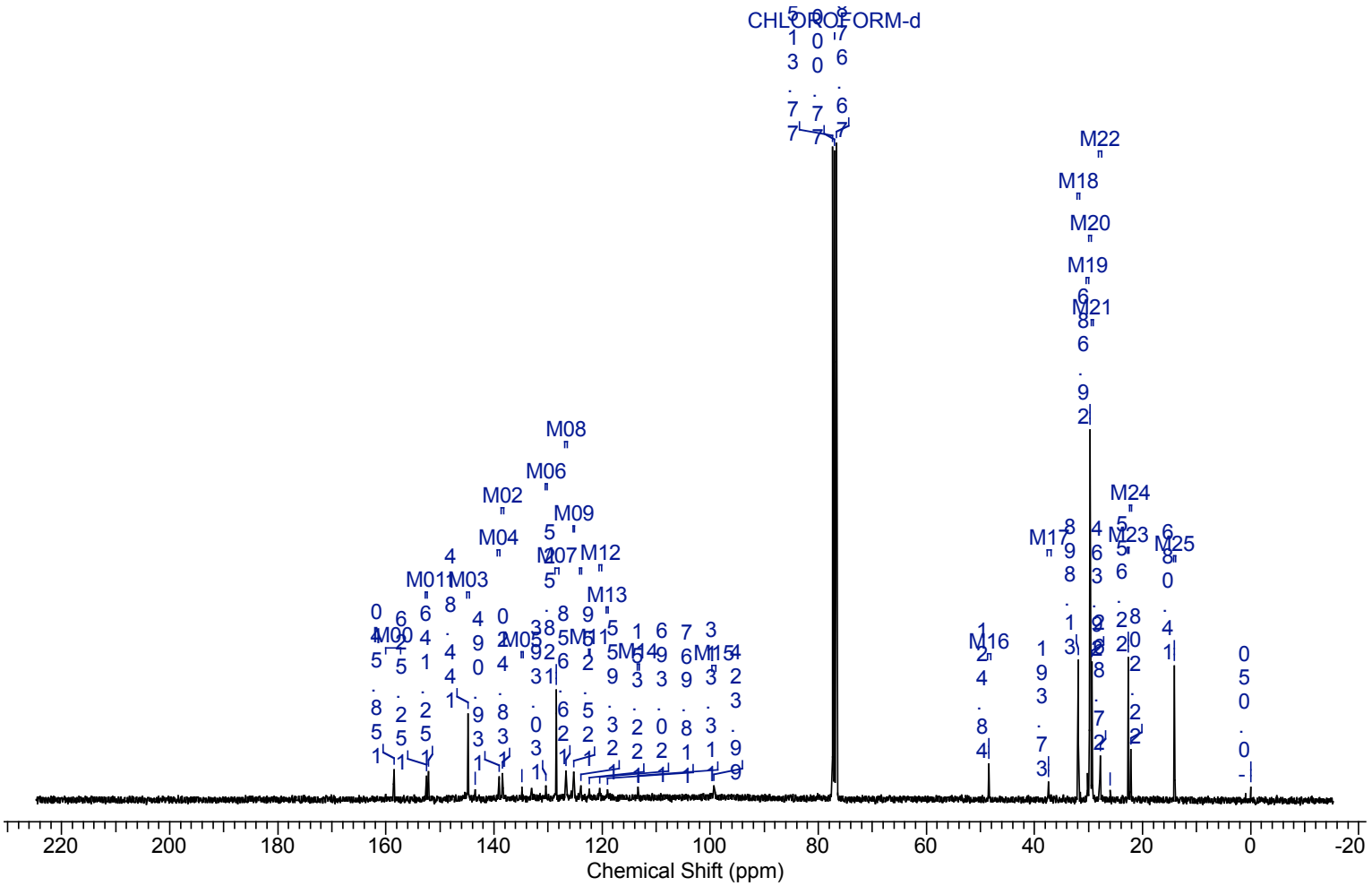
Sulfonate-pyridinium Dimeric Capsule **[4-14]** ^{13}C



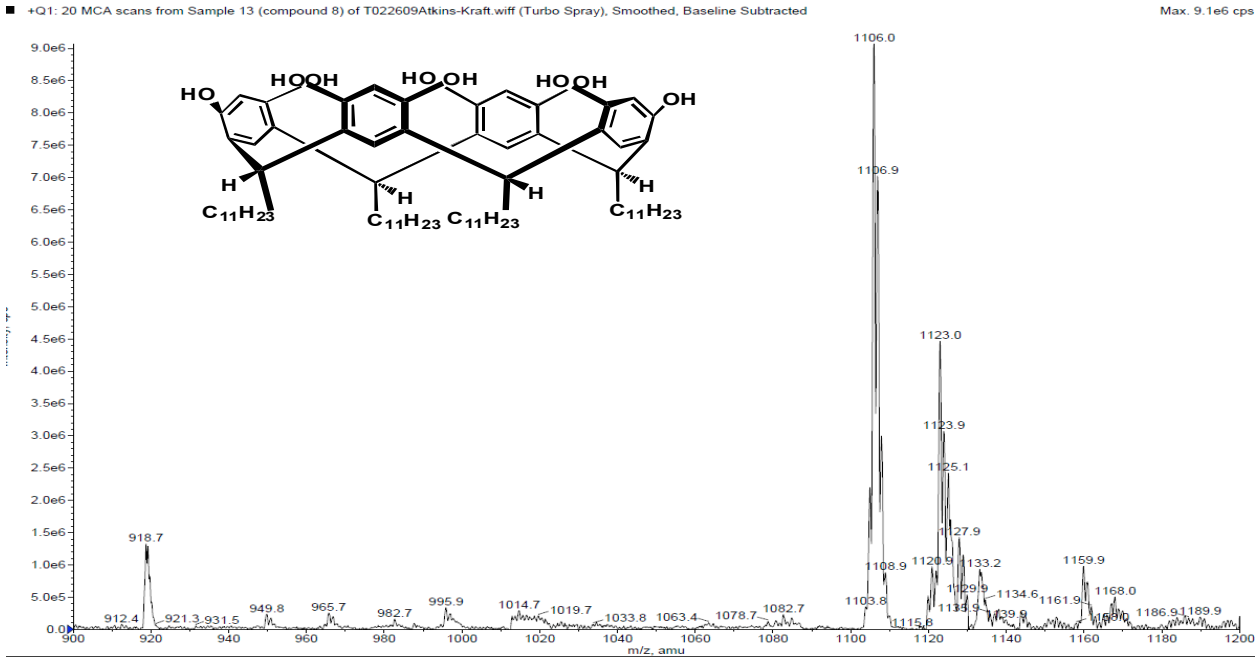
Bis-sulfonate-para-dimethylpyridinium ^{1}H [4-15]



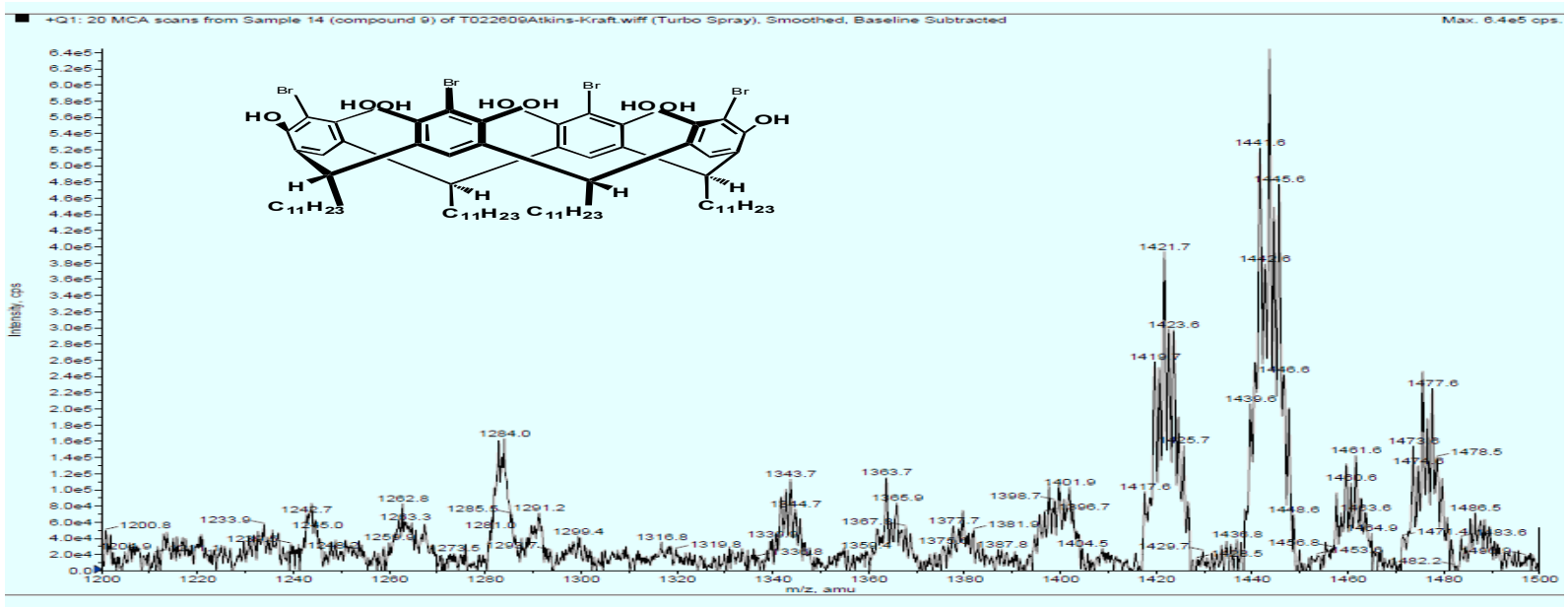
Bis-sulfonate-para-dimethylpyridinium [4-15] ^{13}C



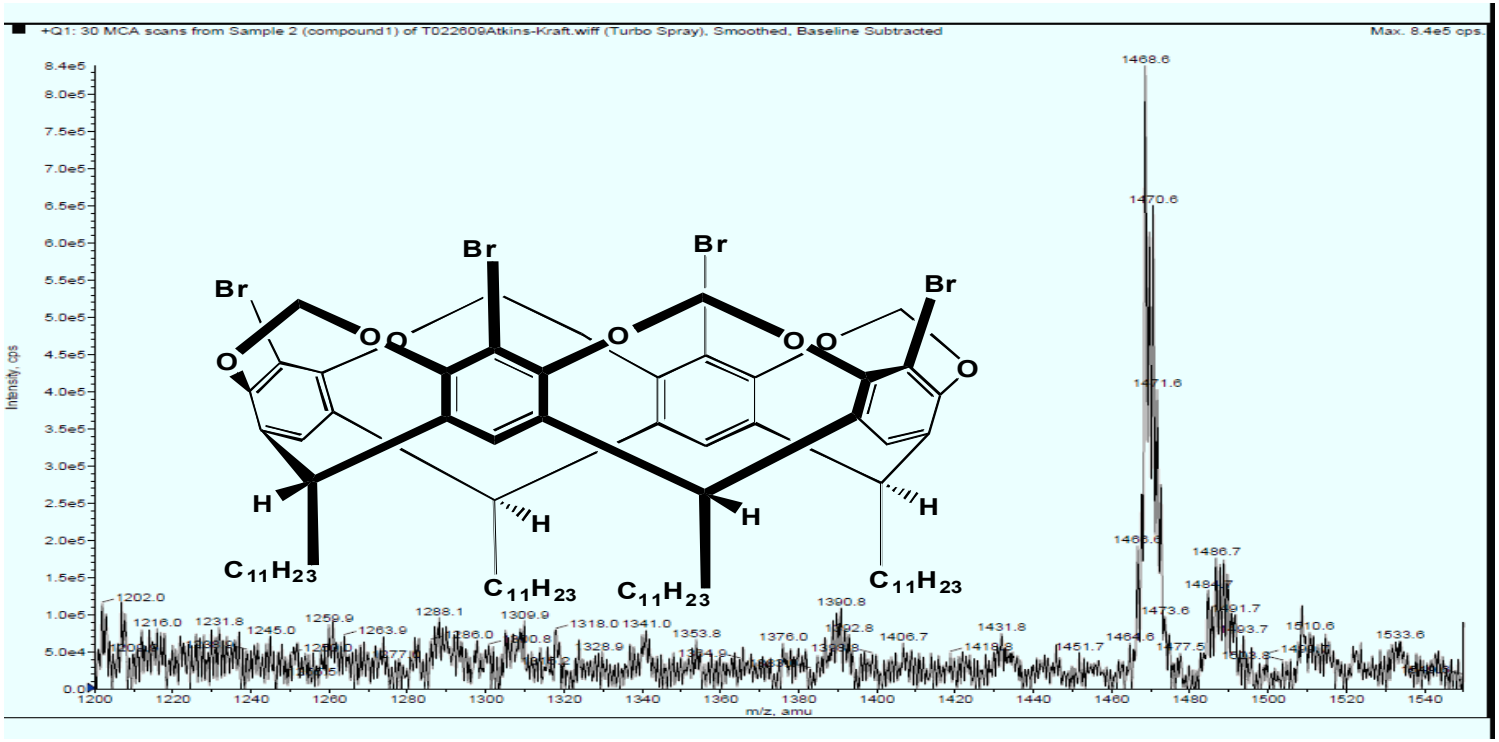
C-dodecy calix[4]resorcinarene **[3-9] LRMS**



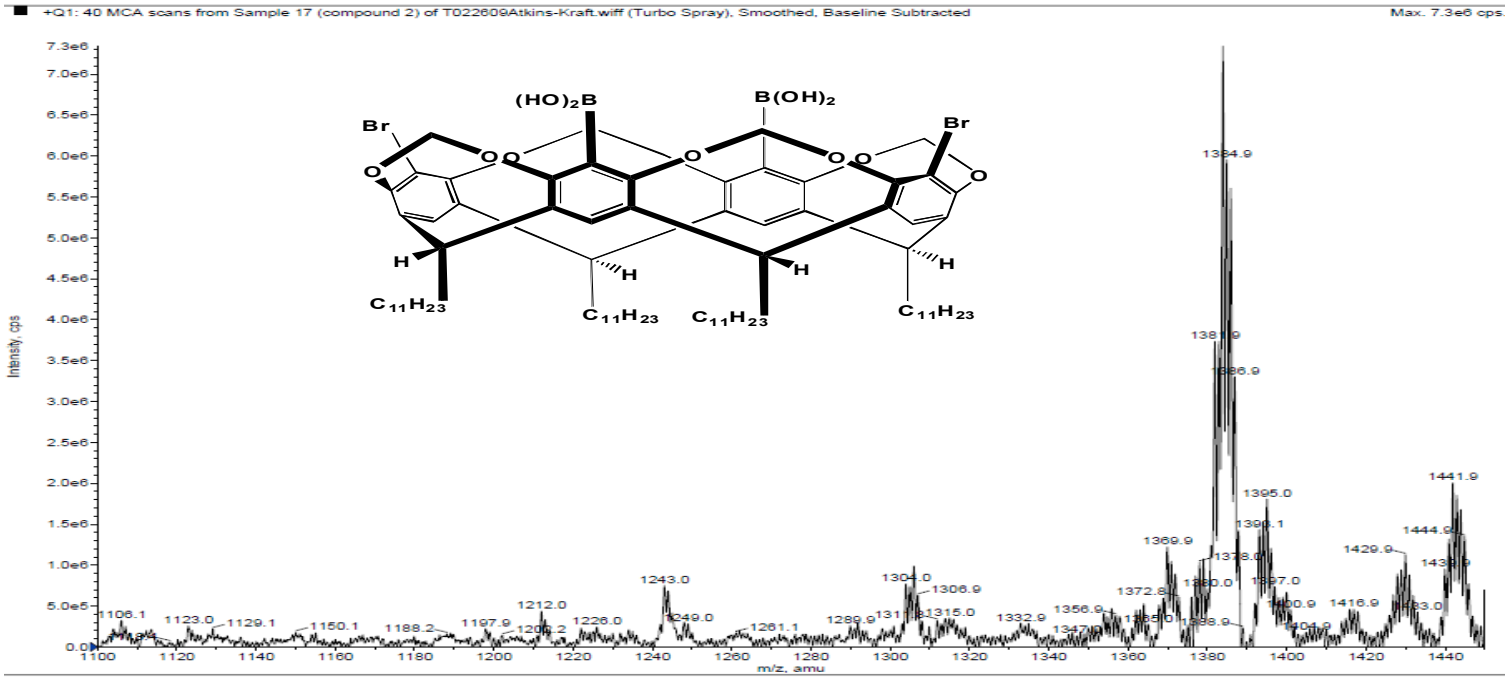
C-dodecytetrabromocalix[4]resorinarene **[3-10] LRMS**



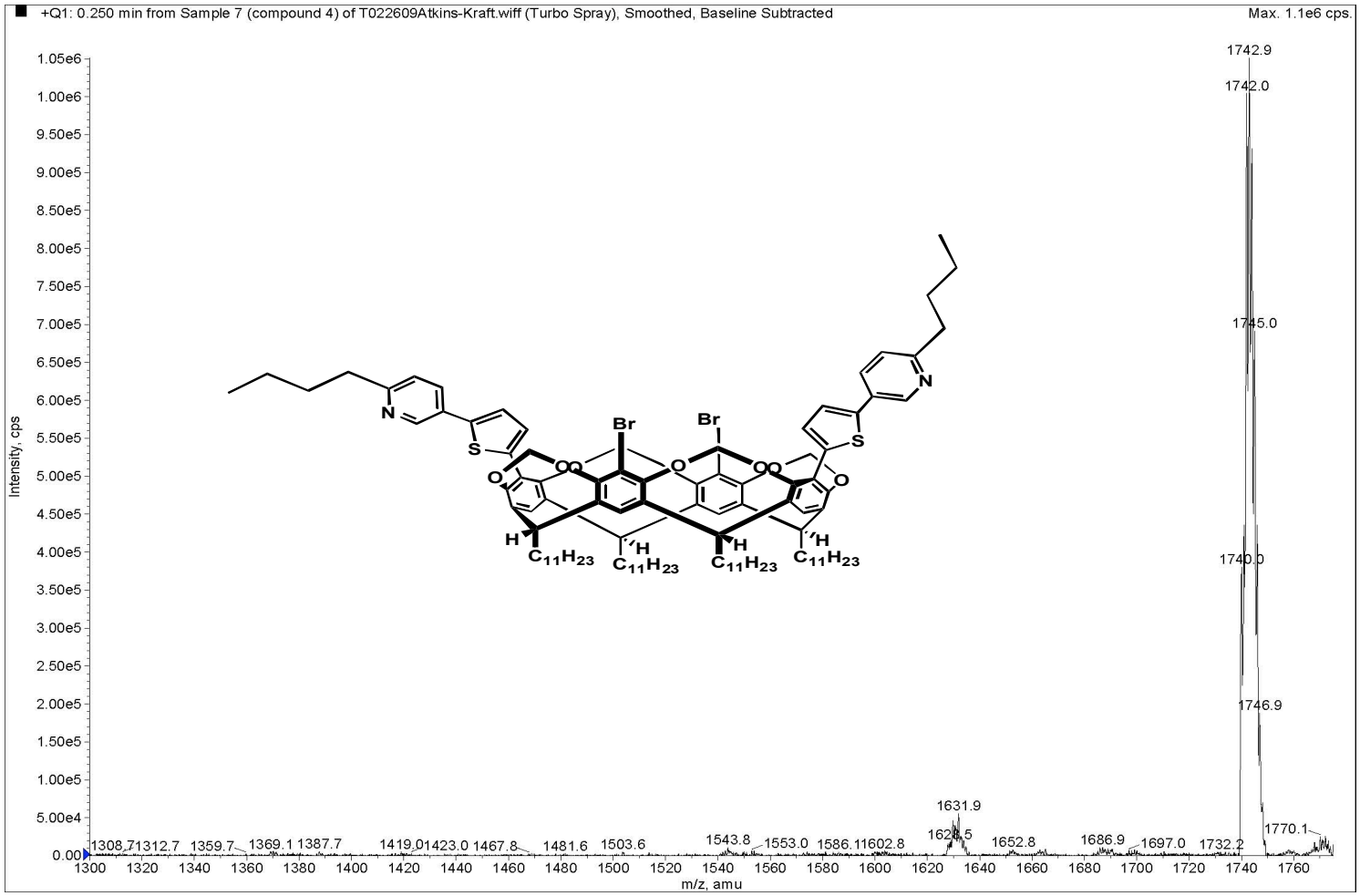
C-dodecyltetrabromo resorcin[4]arene **[3-11]** **LRMS**



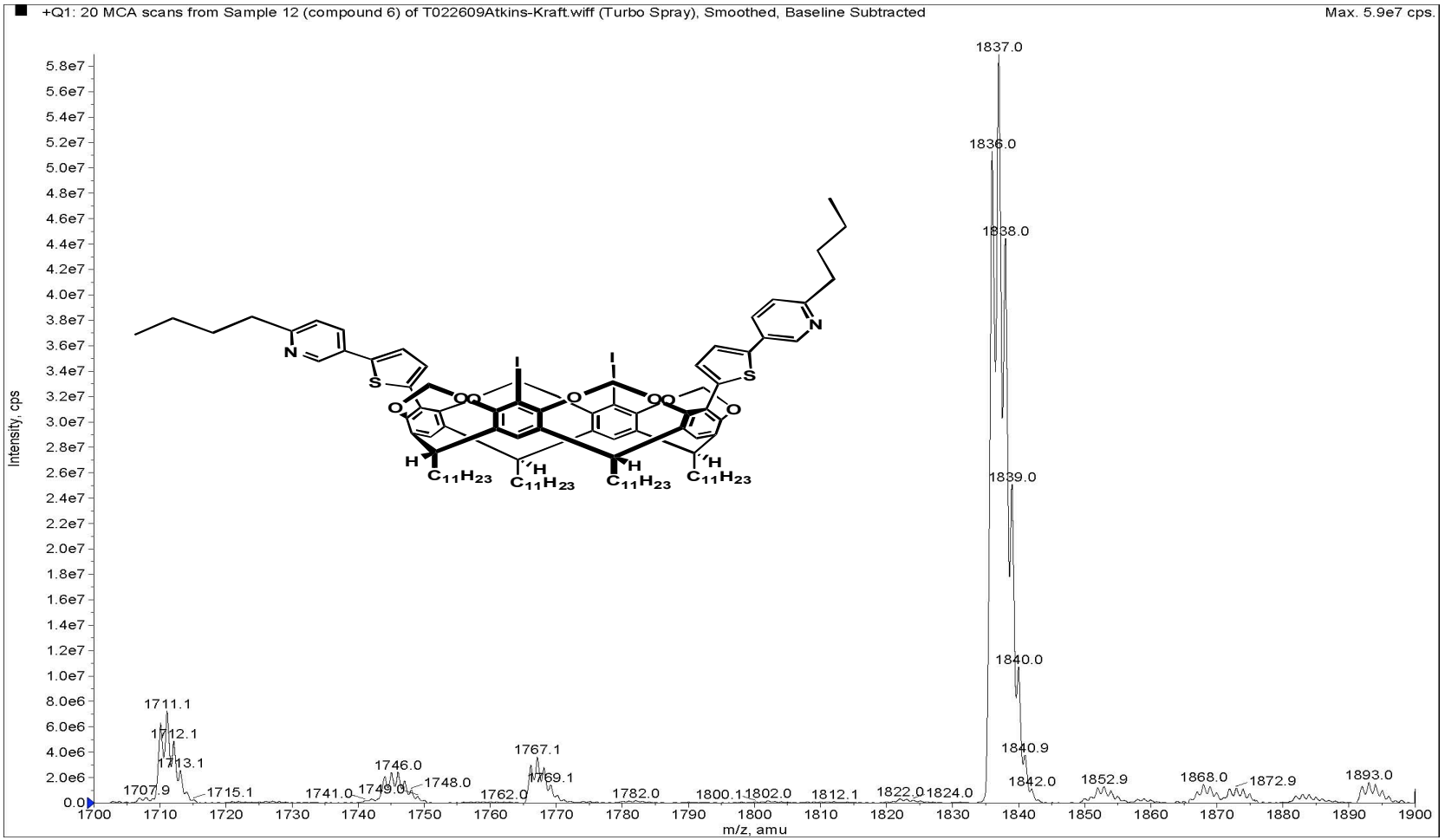
A,C Bis-boronic acid-C,D-bis-bromo resorcin[4]arene **[3-12] LRMS**



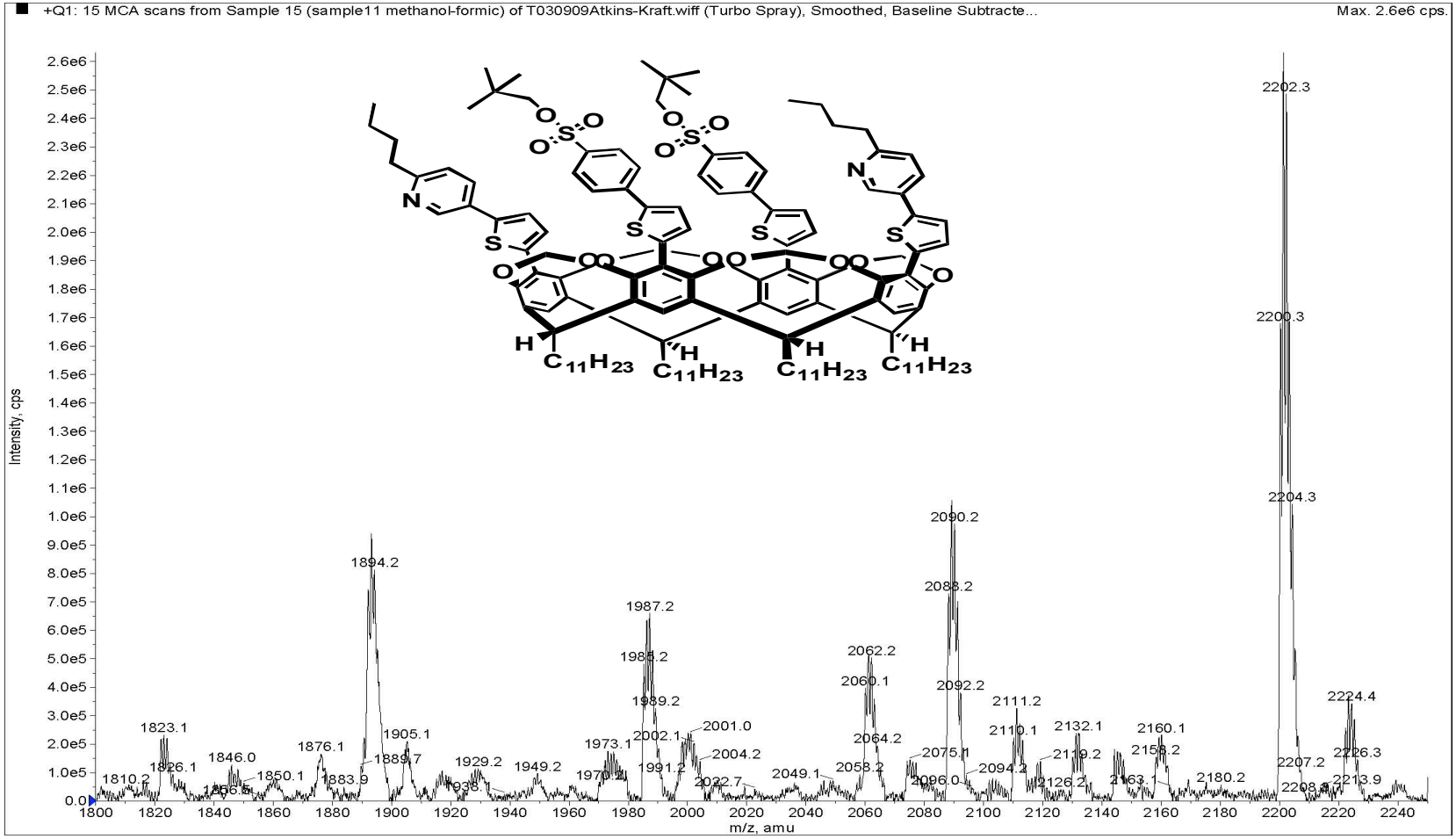
A,C Bis-thiophene-C,D-bis-bromo resorcin[4]arene **[3-13] LRMS**



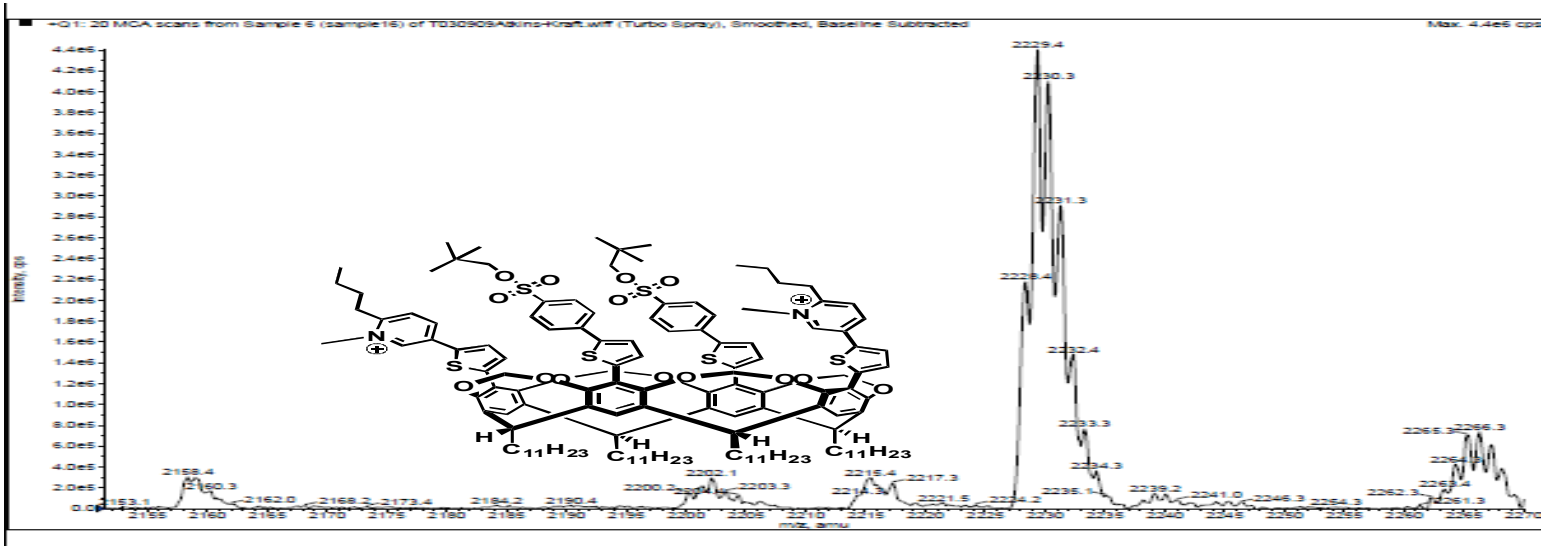
A,C Bis-thiophene-C,D-bis-iodo resorcin[4]arene **[3-14] LRMS**



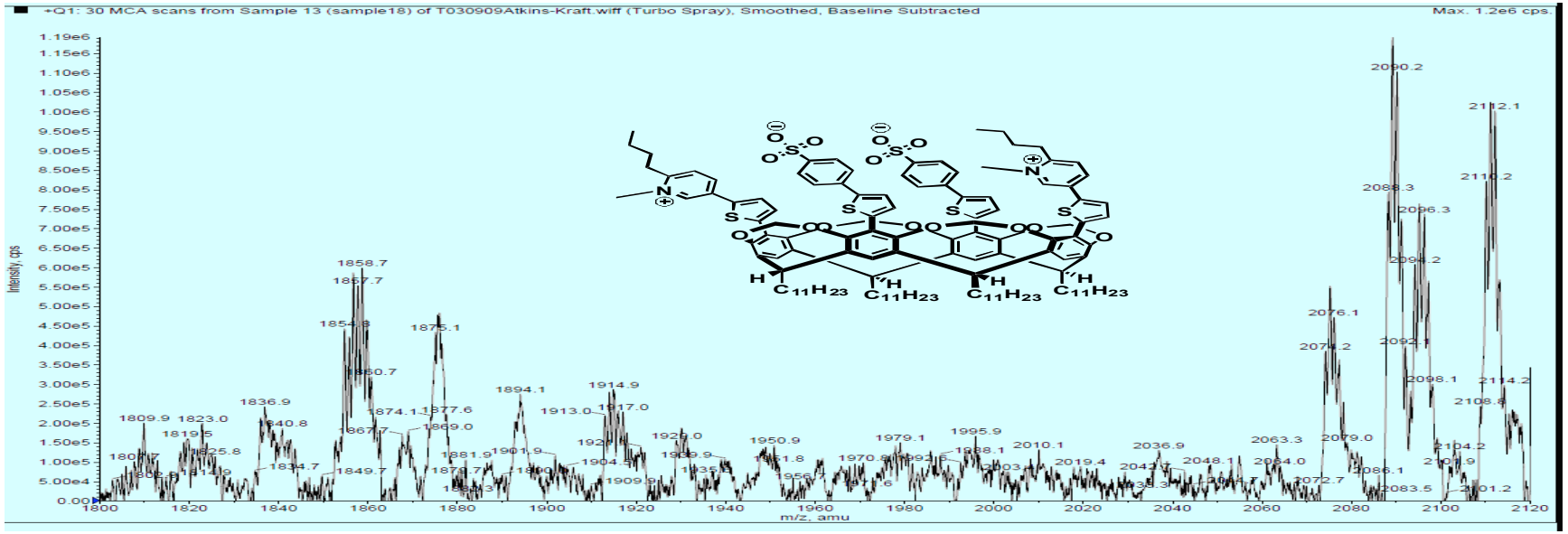
A,C bis-thiophene pyridine-C,D bis-thiophene dimethylpropylbenzenesulfonate **[3-15] LRMS**



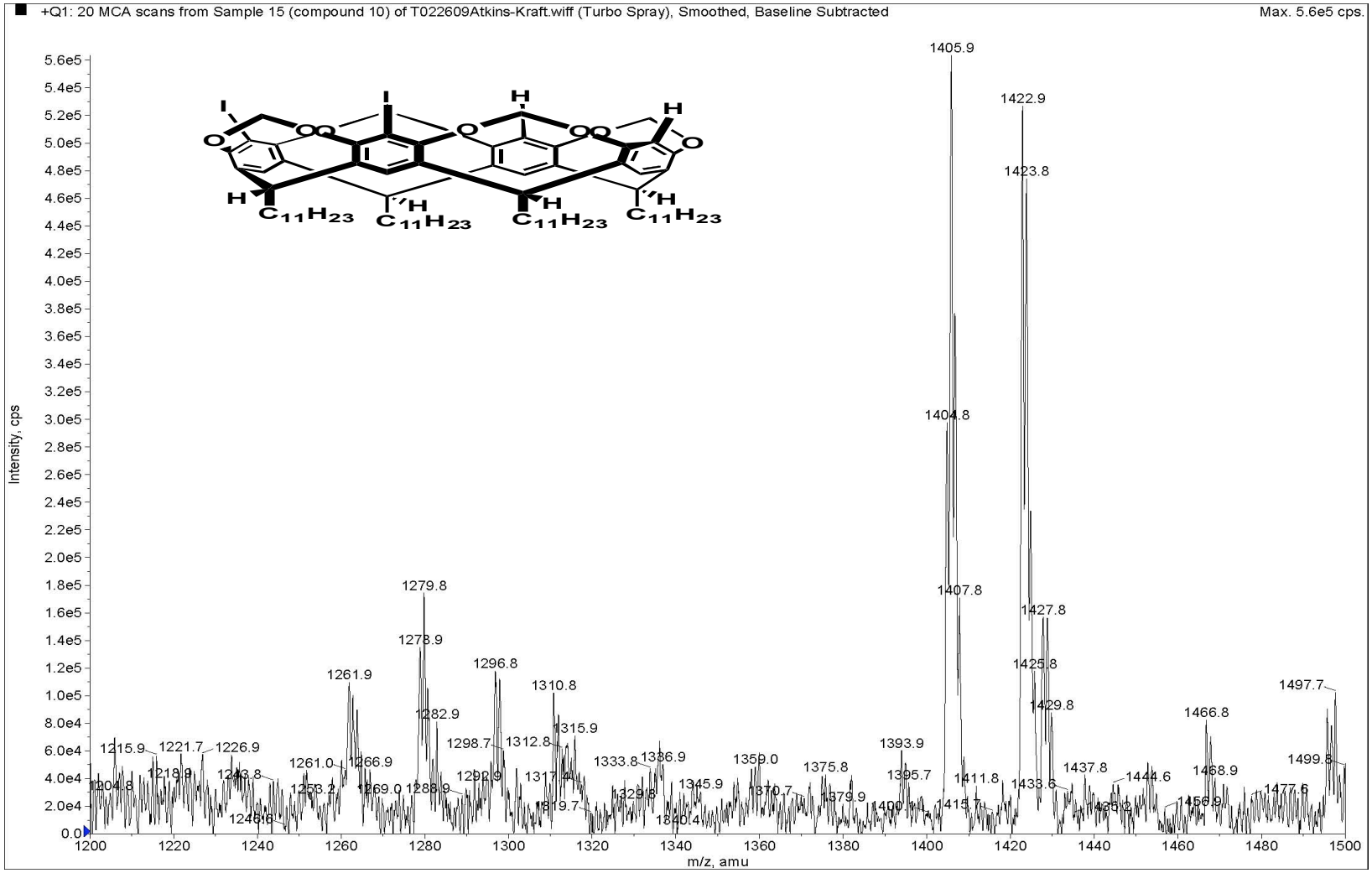
A,C Bis-thiophene pyridinium triflate-C,D bis-thiophene dimethylpropylbenzenesulfonate resorcin[4]arene **[3-16] LRMS**



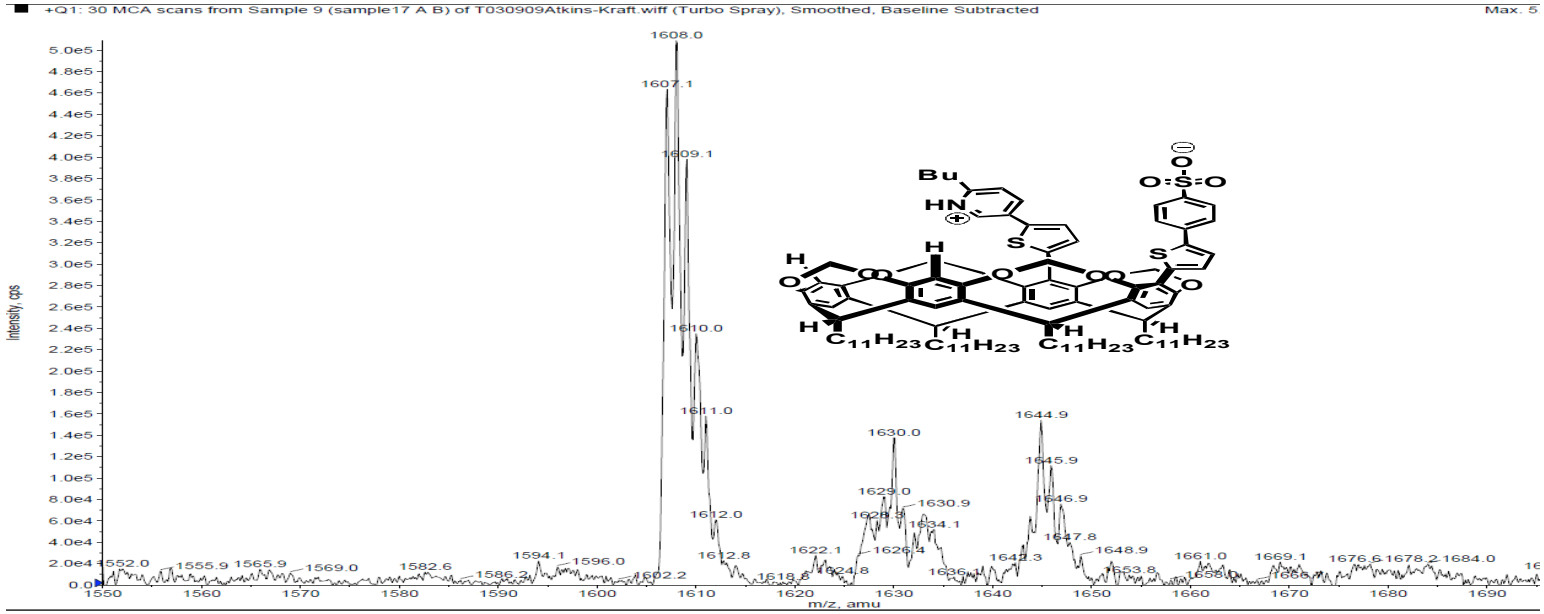
A,C bis-thiophene pyridinium C,D bis-thiophene-benzenesulfonate resorcin[4]arene **[3-17] LRMS**



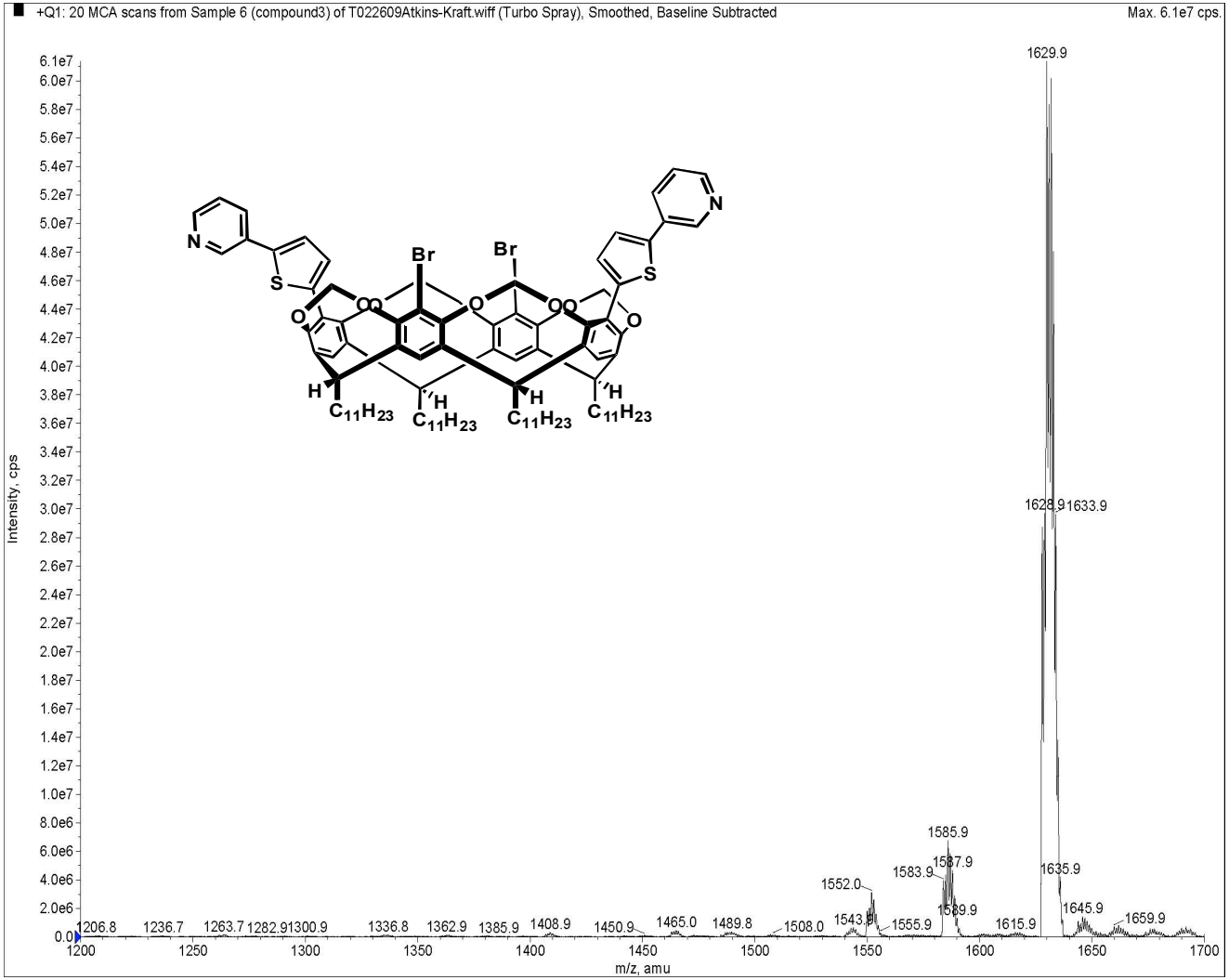
A,B-bis-iodo-C,D-bis-hydrogen resorcin[4]arene **[3-19] LRMS**



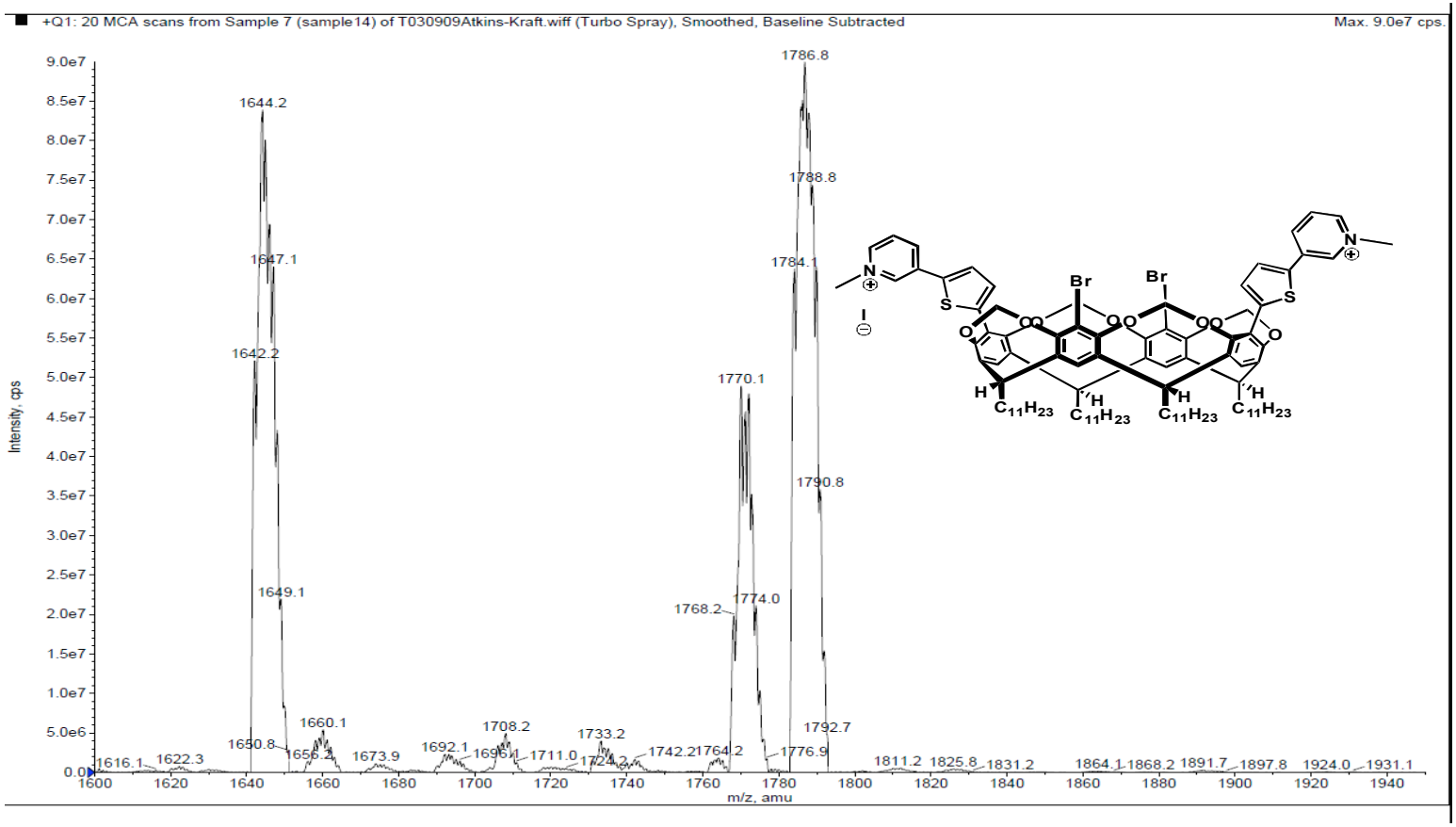
A,B-3(2-thienyl)pyridinium-4(2-thienyl)benzenesulfonate **LRMS**



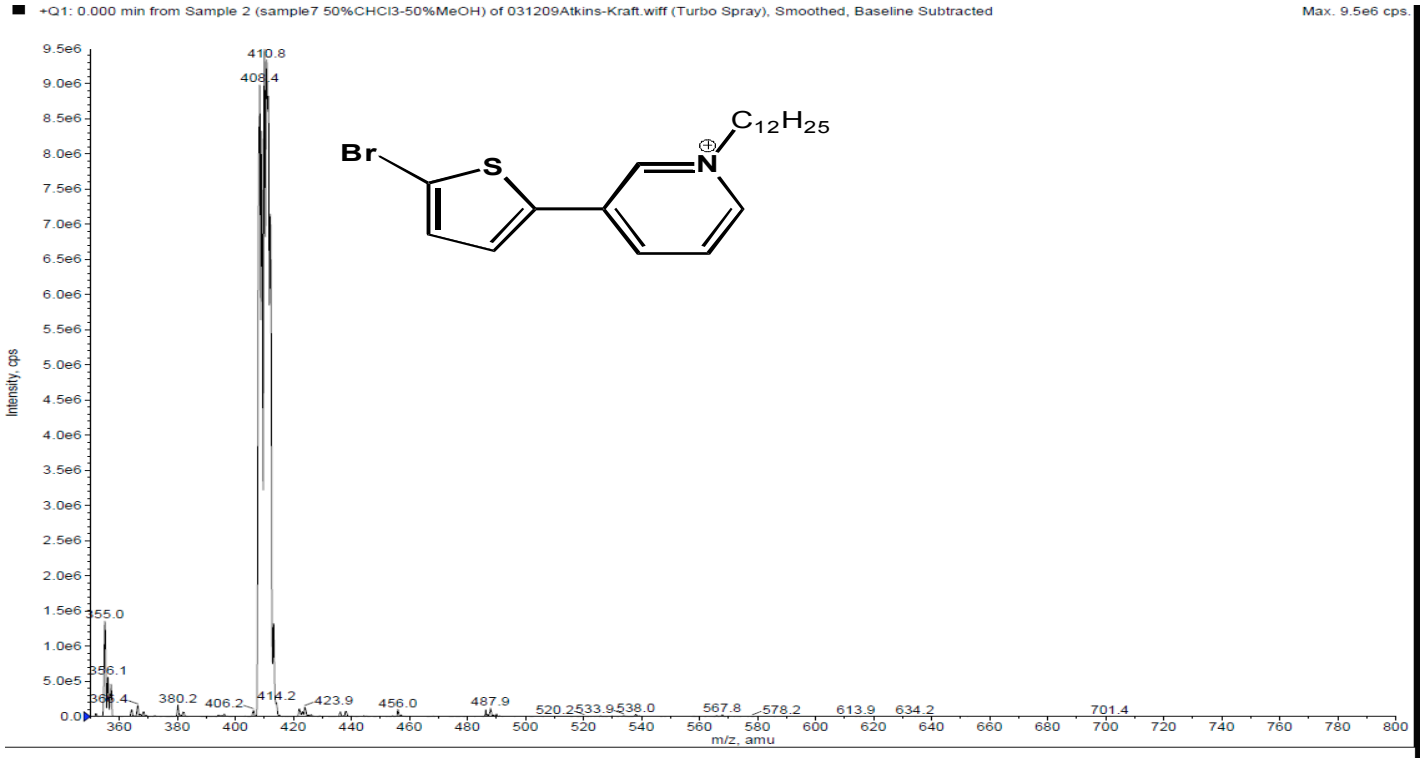
A,C Bis-3(2-thienyl)pyridine resorcin[4]arene **[4-10]**



A,C-bis 3(2-thienyl) methyl pyridinium iodide resorcin[4]arene **[4-11] LRMS**



3-(5-bromo-2-thienyl)pyridinium **[4-6] LRMS**



4-(5-bromo-2-thienyl)sulfonate **[4-6] LRMS**