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SYNTHESIS OF ADJACENT-BRIDGED BENZO-ANNELATED CYCLAM AND STUDIES OF MONO- AND DI-BENZO-ANNELATED CYCLAM DERIVATIVES

BY

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B.S., University of Asmara, 2004

THESIS

Submitted to the University of New Hampshire

in Partial Fulfillment of

the Requirements of the Degree of

Master of Science

in

Chemistry

September, 2013

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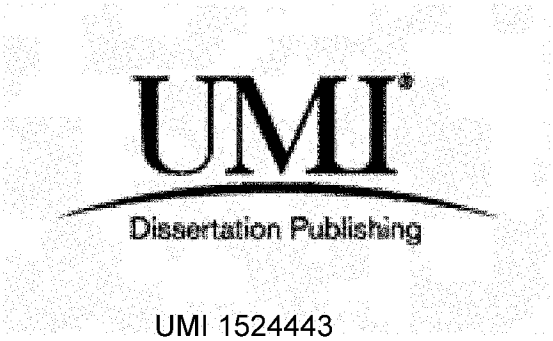

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Assistant Professor of Chemistry

Aug 22, 2013
Date

DEDICATION

I dedicate this thesis to my family, my wife and my friends. For the unlimited blessings, prayers and caring bestowed to me from my family hard to describe and differentiate my parents from my siblings, one from the other remembering me with almost every heartbeat they make. It is your collective effort that made me reach at this stage of my life.

And to my beloved wife, love of my life and the queen of my heart, without her I can't imagine life and this wouldn't be real. I love you eternally.

And last but not least to my friends and group SHABIO, your support and love has some kind of mysterious energy which always raised me up and kept me strong, our brotherhood and union is the mystery to success and flavor to life.

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I would first like to acknowledge my elder brother, Dr. Tesfamichael B. Ghidey, who was always there for me to shape my life in the right way and who always inspired me to be a scientist. For as long as I remember starting from the time while I was at my home country Eritrea, he would always provide me with the necessary advices and would be there to answer any questions. Despite being a Ph.D. student with all the stresses of science and research and very limited time and finance for other activities, he would respond emails on daily basis if not in hourly and would react to situations on time and apply to the number of universities I selected to pursue my graduate studies. While in the States he would be there to explain things and care to take the responsibilities of an elder brother in guiding, watching and supporting us with our life. I can't thank him enough.

I would like to express my special gratitude to my group members and post-docs Dr. Leon Wong and Dr. Barbara Li. I am so lucky and privileged to have them both in my research group. Leon and Barb are among the most important people in my student life in UNH. They taught me all the necessary lab skills and technics as well as great ethics; they are indeed my role models. I don't think I would be able to possess all these skills without them in that I owe them a lot. Whenever I had a question I would go and ask Leon "Leon, I have a question?" and he would be happy and reply "you should." And he will give me his whole time as necessary in solving my problem and teaching me how to solve problems. He is an awesome and superb person. Outside the lab, they were also there for us helping with transport and other services we would need. They taught me how to approach people and students, and how to be friends and help each other so I can do the same for others. Chemistry department stuff, Cindi and Peg, are very special and

pleasant people, they are there to soothe your pains and solve your problems, without them I can't imagine the atmosphere of Parsons Hall, they deserve huge thanks.

Chemistry librarian, Bob Constantine, what an amazing person, friend and colleague, whatever you are looking for through the library is in your hands in a moment. He has provided and taught me how to use and benefit the library and other sources through the library. He would always welcome you with his warm greetings and nice chats, one of the first people I would discuss soccer with at Parsons. Pat Wilkinson, many many thanks for the NMR training on time; she would always be there to answer questions and fix problems with NMR.

I am again lucky to have two advisers, Prof. Gary R. Weisman and Prof. Edward H. Wong. Dr. Wong such a skilled, proficient, very encouraging and supportive professor and Dr. Weisman one of the best Professors in my life time, in that I am honored to work under their guidance. It is more than a research group it feels like your family, and they are there to help and solve with every kind of problems specially science and life. I will always admire the professionalism of Dr. Weisman, impressive way of analyzing NMR data, acquiring every tiny details and phenomenal memory. I would be remiss if I didn't mention and acknowledge Dr. Weisman for his special attention towards safety and precautions inside the lab. I have learnt a lot, I feel like I am a different person, I am transformed. I will definitely miss, the 6:00 or 7:00 o'clock farewell from Dr. Weisman "Be Careful!"

I would like to acknowledge Mr and Mrs. Frank, from Durham Community Church, at the age of 80s and 70s, what an incredible loving people. I want to witness that I am among the thousands of students specially international students who they have helped

with the necessary furniture and utensils one needs to settle, and they would bring it to you regardless of the weather conditions, they deserve a huge thanks and they have taught me kindness and love.

I won't forget expressing my gratitude to the Parsons Hall community, starting from faculty members and the awesome graduate student and undergrads. Having them in Parsons, they made my life a lot easier and they also made this place like home. They are so pleasant, helpful, loving and caring I owe them big thanks and I will never forget all the fun and experiences we have shared. I will definitely miss "ultimate Frisbee" and thanks to all who played and spent their time with me, I really appreciate it.

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I once again want to thank my beloved family who in the first place accepted and supported my long way trip from home and supported me survive to date, you have a special place in my heart. The family of my wife who believed in us and supported us to go out and live our life, I appreciate your love and support and won't fail you down.

Finally, my beloved wife, I can't mention one by one they are so plenty but as Matt Mower has pointed it out once, "she deserves the honorary degree". All these long nights, she would come and keep me accompanied and makes sure I am safe in the lab. All those lunch talk desserts, cooking, inviting my friends home, she is so full of love and patience and unlimited energy. She was still there during her difficult and hard moments that we

will never forget. She is my first teacher of love. I just want to say I will always love you more, maybe that's the best I can do.

Thank you – to all.

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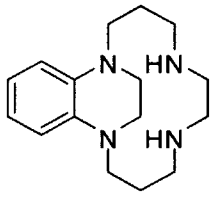
By Amanuel B. Ghidey

University of New Hampshire, September 2013

A new synthetic methodology for the preparation of a novel adjacent-bridged benzo-annelated cyclam is presented. This methodology utilizes reductive ring expansion followed by deallylation to give the desired adjacent-bridged benzo-annelated cyclam. This novel ligand is designed to complex metal cations with a trans coordination geometry. Derivatives of this ligand can be prepared by attaching pendant arms on the nitrogens which can aid as coordinating arms and linkers for potential use of this ligand as bifunctional chelator (BFC).



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Coupling chemistry studies have been carried out in an attempt to increase the lipophilicity of a dibenzo-annelated tetracyclic bisaminal and to functionalize at the *para* positions to provide a site for bio-conjugation.

September, 2013.

CHAPTER I

SYNTHESIS OF ADJACENT-BRIDGED BENZO-ANNELATED CYCLAM AND STUDIES OF MONO- AND DI-BENZO-ANNELATED CYCLAM DERIVATIVES

I. Introduction

Polyazamacrocyles are cyclic organic molecules having three or more nitrogens in their cyclic backbone. Polyazamacrocycles attract persistent interest due to their ability to effectively bind various inorganic and organic ions as well as some polar molecules. Among these are "cyclam" and "cyclen", 14- and 12-membered cyclic tetraamine respectively which bind heavy and transition metals ions to form stable complexes.[1,2] Metal complexes of these ligands exhibit enhanced thermodynamic stability relative to acyclic ligands, which may be attributed to the macrocyclic effect. This effect has been attributed to the macrocycles having both larger enthalpy and smaller entropy of complexation than their open-chain analogues.[3] The replacement of O with N changes the properties of polyazamacrocycles significantly with respect to their crown ether analogues. The decreased electronegativity of nitrogen with respect to oxygen in addition to the increased basicity contributes to many observed differences in the complexation of various metal ions.[4] Polyazamacrocyclic ligands also have the ability to be functionalized at the nitrogen atoms of the parent cyclic backbone.[5-9] The attachment of pendant arms or

the formation of bridged polydentate derivatives allows for a variety of ligands to be prepared from a single polyaza macrocycle.[10] Structural modifications were made by Wainwright[11,12] to the parent polyazamacrocycles "cyclam" and "cyclen" ligands (**1** and **2,** Figure 1.1) whereby two "adjacent" nitrogens (those separated by 2 or 3 methylene units) were bridged with an ethylene unit (**3** and **4**), reinforcing the tendency towards square planar coordination of metal cations.

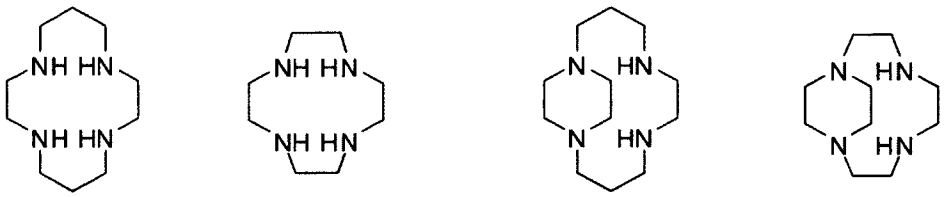


Figure 1.1 Cyclam (1) and cyclen (2) and their reinforced structures (3 and 4).

"Cross-bridged" tetraazamacrocycles, having nonadjacent nitrogens bridged with an ethylene unit, were first reported by Weisman and Wong in 1990.[13] The three common cross-bridged tetraazamacrocycles cross-bridged cyclam (**5**), cross-bridged cyclen (**6**) and cross-bridged homocyclen (**7**) are illustrated in (Figure 1.2).

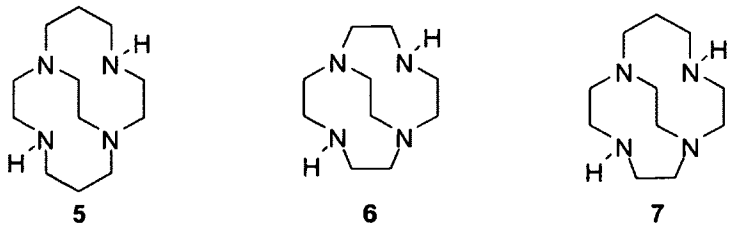


Figure 1.2 Cross-bridged tetraazamacrocycles of cyclam (5), cyclen (6) and homocyclen (7).

By replacement of the N-H hydrogens with alkyl, alkenyl, aryl, or functional pendant arms, many other derivatives may be prepared. Cross-bridged tetraazamacrocycles adopt cis-folded coordination geometry when coordinated with small metal cations. The bridge creates a bicyclic system of two fused triazamacrocycles that can jointly bind a metal cation; a clamshell-shaped cavity or cleft is created as a result of this bridging. While these free ligands are flexible, upon coordination to metal cations "they adopt a low energy conformation having all four nitrogen lone pairs convergent upon the cleft of the ligand".[14] Figure 1.3 shows "cross-bridged cyclam, demonstrating its ability to adopt a low energy, diamond-lattice-type conformation in which all four nitrogen lone pairs are convergent upon the cleft of the ligand for complexation of a metal cation (M)".[14]

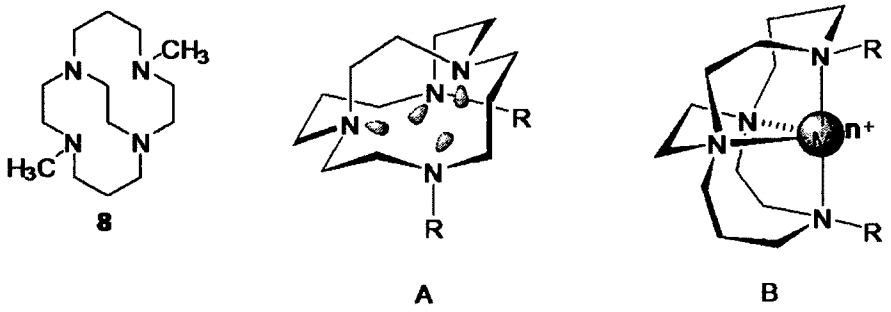


Figure 1.3 The incorporation of an ethylene cross-bridge (8) allows all four nitrogen lone pairs convergent to the cleft (A) and *cis*-V coordination geometries are observed in complexes of small metal ions (B).

A proton, with its small size and its positive charge, will interact with amine lone pairs of these ligands in a manner similar to that of metal cations. A proton fits snugly in the ligand's cavity, and is located on one of the amines and hydrogen bonded to the remaining three nitrogen lone pairs. Unlike the case for small metals cations, the cavity can fit more than one proton. The dimethyl cross-bridged cyclam **8** (Figure 1.3) has been diprotonated and an X-ray structure indicates that both protons are located within the

ligand's cleft.[13] The protonated ligand arranges itself in a slightly distorted diamond-lattice conformation with each proton involved in the hydrogen bonding to two amino nitrogens. This ability to form a hydrogen-bonding network stabilizes the protonated ligand, resulting in a low strain, C_2 conformation in which each of the two 10-membered ring adopts a [2323] diamond-lattice type conformation, and increases the free ligand's basicity as compared to its unbridged analogues. These ligands are such strong bases that a lower limit of the pK_a of the conjugate acid of the dimethyl cross-bridged cyclam (**8**) has been established at 24.9 in MeCN.[13] In water, the conjugate acid of compound **8** has been estimated to have a $pK_{a1} > 13.5$ and the di-conjugate acid a $pK_{a2} = 10.8$,[13,15] whereas an analogous unbridged species, tetramethylcyclam, has corresponding pK_{a1} and pK_{a2} values of 9.7 and 9.3 respectively.[16,17] Due to this strongly basic nature, these ligands are considered proton sponges and they are almost entirely mono-protonated in protic solvents such as alcohols or water.[13]

A. Common Applications

Polyazamacrocycles have attracted a persistent interest by researchers because of their ability to bind different substrates and vast biomedical applications. Clinical applications for these tetraazamacrocycles have been developed in bioinorganic and nuclear medicine.[18-20] Others include the use of polyazamacrocycles as therapeutics against cancer cells, microbes and viruses such as HIV. Apart from the traditional applications of azacrown compounds in nuclear medicine and radiopharmaceuticals, of special interest is the use of those ligands in which the nitrogen atom is conjugated with a chromophore as part of photosensitive, chromogenic, fluorescent and photochromic ligands. These

compounds can form the heart of optical sensors for metals and ammonium ions, photoswitched molecular devices and transporting agents for photocontrolled membrane transport of metal cations.[21]

B. Radiopharmaceutical Applications

Some of the highly investigated and common applications include imaging that are used in diagnostic medicine and radiopharmaceutical therapeutics. Polyazamacrocycles with coordinating pendant arms have shown to be excellent ligands for a wide range of metal ions (Fig. 1.5) compound **9**. The resulting complexes are generally thermodynamically very stable, which has resulted in these systems being used in a range of different applications.[22,23] "For example, coordination of this type of ligand to metals cations such as ^{90}Y, ^{68}Ga and ^{111}In yields complexes that have been successfully used as radiopharmaceuticals for imaging and therapy. On the other hand, complexes of substituted polyazamacrocycles with lanthanides (*e.g.* Eu(III), Tb(III) and Gd(III)) and Fe(II) and Mn(II) have been shown to be excellent molecular probes for optical and magnetic resonance imaging (MRI)."[24-27] "MRI images display sharp contrast differences across tissue boundaries as a result of their different water contents and water environments. Contrast agents help improve the quality of the image providing better visualization of several different types of tissue abnormalities and disease development compared to ordinary MRI."[28] The Gd(III) ion is the most common metal that MRI contrast agents utilize due to its high magnetic moment, a result of having seven unpaired electrons. However it is too toxic at the levels used in MRI imaging and it cannot be injected as such. The choice of a tetraazamacrocycle as a ligand that forms a stable

chelate and facilitates renal excretion is among the most important aspects being studied and developed.[29]

An alternative imaging technique is positron emission tomography (PET), which images physiological processes that are occurring within a living system. "PET imaging requires the delivery of a pharmacologically significant molecule containing a positron-emitting radionuclide to a tissue or organ of interest. As the radionuclide decays it ejects a positron from its nucleus that travels a short distance before being destroyed by an electron to release two 511 keV gamma rays at 180° directions. The emitted gamma rays are detected by PET scanner detectors, and following sufficient acquisition time the data are constructed to give images of the radiotracer's location within the body."[30] Selection of the right radionuclide in radiopharmaceutical design is of essential importance and depends on different factors. "Radionuclides like ^{94m}Tc, ^{66}Ga, ^{68}Ga, ^{86}Y, ^{90}Y, ^{45}Ti and $^{60/61/62/63/64}$Cu have been prepared and used as imaging or radiotherapeutic agents. A significant amount of research has been performed on copper radionuclides because of the different range of half-lives and positron energies."[30] ^{64}Cu has a half-life of 12.7 h, which is higher than the other copper radionuclides, providing better contrast and quality images. This copper radionuclide can then undergo coordination chemistry to different bifunctional chelators (BFC's) that are linked to proteins, peptides, antibodies and other medicinally relevant molecules as illustrated in (Figure 1.4). "To improve the *in vivo* stability of ^{64}Cu complexes researchers have turned their attention to tetraazamacrocyclic ligands as BFC's.

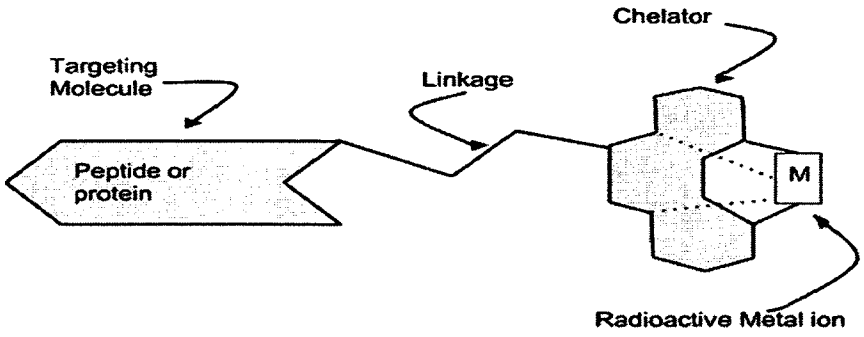


Figure 1.4 Schematic representation of a radiopharmaceutical showing a bifunctional chelator complexed with a radioactive metal attached to a bioactive molecule (peptide or protein).

Among the wide range of chelators that have been studied and investigated, the class of ethylene cross-bridged tetraamine ligands and their pendant armed derivatives, which were developed by Weisman and Wong and coworkers,[13,31] have attracted attention as chelators for radiocopper."[30] Structural data of copper complexes with these cross-bridged ligands demonstrate a *cis*-folded coordination geometry in all cases.[30] The attachment of two carboxymethyl pendant arms to cross-bridged cyclam (CB-cyclam) (**5**) to give CB-TE2A (**9**) further insured the complete enclosure of six-coordinate Cu(II) (**10**) as shown in (Figure 1.5). High stability toward metal loss is of considerable interest in systems designed for the in vivo delivery of copper radionuclides for nuclear medicine applications. The stability constants, of Cu-CB-cyclam complexes is log $K_f = 27.1$, compared to unbridged Cu-cyclam log $K_f = 27.2$ is similar,[32] however their kinetic inertness particularly in proton assisted decomplexation in aqueous solution have a significant difference. A remarkable resistance of Cu-CB-cyclam (**10**) towards strong acid was shown by Woodin and coworkers.[33]

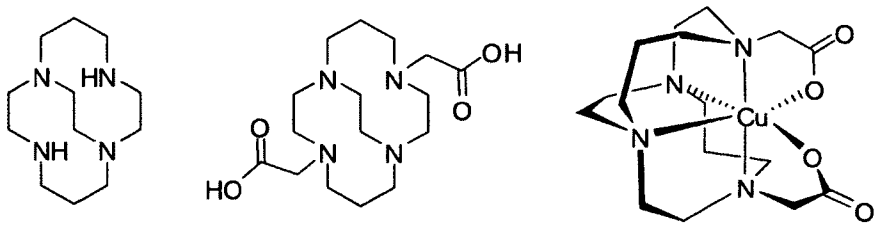


Figure 1.5 Structures of CB cyclam (5), CB-TE2A (9) and Cu(II)-CB-TE2A (10) complex based on the crystal structure found by Wong et al.[14]

Cu-CB-cyclam is almost one order of magnitude more inert compared to Cu-cyclam complexes in 5 M HCl at 90 °C whereas Cu-CB-TE2A (**10**) shows a magnificent resistance to acid decomplexation, showing improved inertness by four orders of magnitude over Cu-CB-cyclam. *In vivo* studies also show that positively-charged complexes exhibit high accumulation in the kidneys and liver, whereas neutral or negatively-charged complexes show lower accumulation in liver and higher clearance through the kidneys.[34] In addition, if Cu(II) is dissociated from the complex it will bind to proteins and remain in the tissue preventing its clearance.[32] Due to the above mentioned reasons, the charge-neutrality of the Cu (II)-CB-TE2A complex and its improved resistance to acid assisted decomplexation made it a strong and promising candidate for PET imaging purposes.

Another potential application of cross-bridged ligands can be found in lithium-selective electrodes. Li(I) has been used as a therapeutic element in the treatment of neurological and psychiatric disorders such as bipolar, schizoaffective disorders and cyclic major depression, in addition to exhibiting antiviral activity.[35] The harsh side effects, which include nausea, kidney damage and possibly death, have inspired investigations to

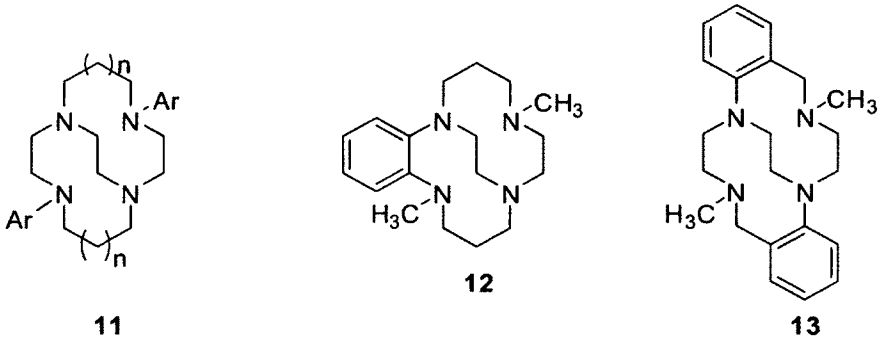
investigate the cellular activity of Li(I) and blood lithium levels. It has been determined that lithium, has a therapeutic dosage of 0.8-1.0 mM in blood, close to the lethal dosage of approximately 2-2.5 mM in blood.[35] In order to monitor blood lithium levels, ion-selective electrodes or fluoroionophores could be used to track ions.[36] There are many ligands for this application that show a reasonable degree of selectivity of lithium relative to sodium ion.[37] Because these ions exhibit similar properties, a ligand which is designed to be a better ionophore for lithium-selective electrodes should distinctly identify lithium from sodium based on the smaller atomic radius and a lower coordination number. Weisman and coworkers have prepared a dimethyl cross-bridged cyclam (**8**) that exhibits a higher degree of lithium to sodium selectivity, which has been explained due to the small cleft size suitable for coordination of lithium over sodium and the presence of only 4 donor atoms in the ligand, favoring lower coordination number.[13] An NMR competition experiment of dimethyl cross-bridged **8**, $LiClO_4$ and $NaClO_4$ in a 1:1:1 ratio showed a lower limit of the relative complexation constant, $K_{rel} = K_{Li+}/K_{Na+} \geq 2 \times 10^2$, which explained that the dimethyl cross-bridged cyclam **(8)** selectively complexes Li^+ in the presence of Na^+.[13] Based on this high degree of selectivity cross-bridged cyclams were proposed to be excellent candidates as ionophores for lithium-selective electrode.

Unfortunately, the strongly basic nature of these cross-bridged ligands hampers their use and application as good ionophores in lithium-selective electrodes. When these ligands are exposed to conditions simulating those of an electrode (monitoring blood samples in protic solvents), the ligand protonation becomes very competitive with lithium complexation. A considerable amount of research was done in order to minimize this strong basicity and lower the competition of protonation with complexation of these

cross-bridged tetraaza macrocyclic ligands.[38] Presumably, the decrease in basicity of these ligands will decrease the complexation ability to lithium while the selectivity of lithium to sodium should remain intact.

C. Decreasing the Basicity of Dimethylated Cross-bridged Cyclam

A number of methods have been investigated in an effort to minimize the strongly basic nature of the cross-bridged ligands. Incorporation of pyridine and its derivatives in the backbone of the tetraazamacrocycle or attaching phenyl rings to the nitrogens were among other strategies which were investigated to increase the rigidity of the ligand and enhance metal complexation selectivity of metal.[21,39,40] The method of conjugating the amine lone pairs with an aryl π-system is of great interest in this study. Some approaches that utilized the amine conjugation to minimize the basicity of these ligands are incorporation of N-aryl groups and annulation of one or two benzo rings to the backbone of the macrocycle[41,42] as illustrated in the (Figure 1.6).

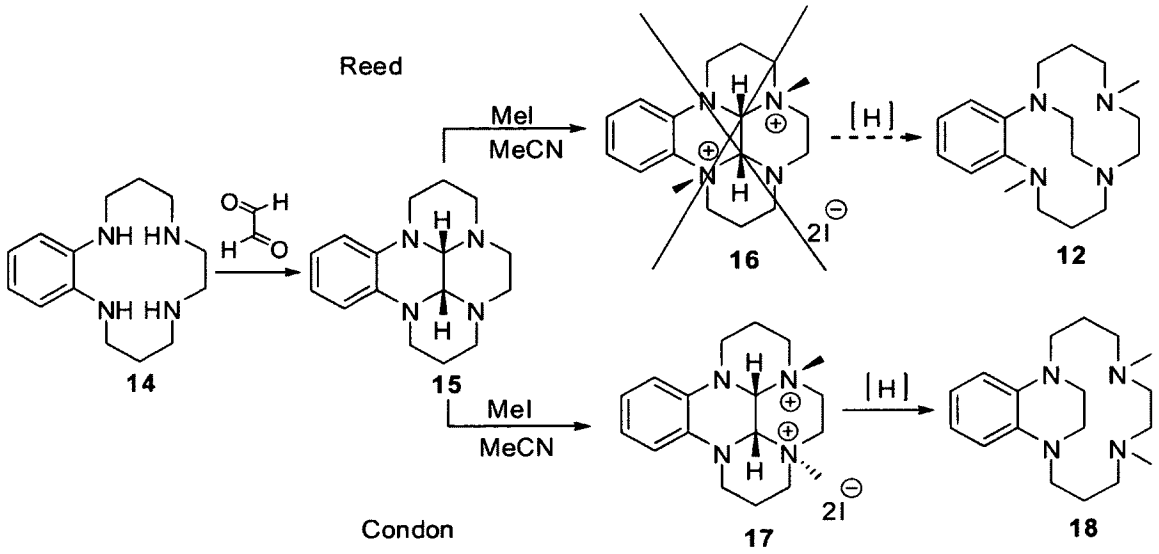


11 12 13

Figure 1.6 Some of the proposed structures of incorporating benzene ring to decrease the basicity of the cross-bridged cyclam, conjugating aromatic ring (11), benzo-annealed (12) and dibenzo-annelated cyclam (13).

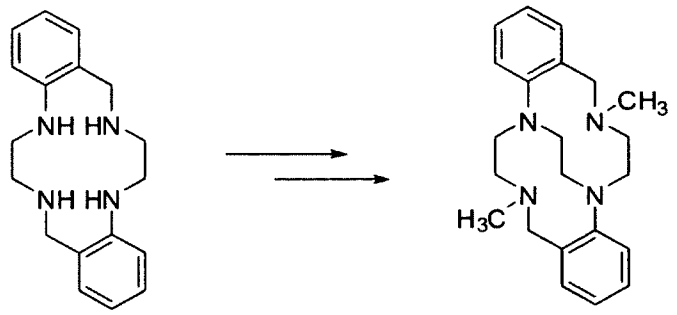
Reed and Zhou, former Weisman-Wong group members, investigated the synthesis of ligand **11** with aryl groups ranging from simple phenyl groups to aryl groups containing multiple electron withdrawing substituents.[41,42] As hypothesized, these compounds exhibit decreased basicity and lowered complexation ability. Some of these compounds exhibit very poor solubility in almost all organic solvents. Reed also performed an initial study towards the synthesis of benzo-annelated cross-bridged cyclam (**12**), and in doing so established a rational synthesis of its main precursor benzo[*b*]cyclam (**14**).[41] Molecular modeling and calculations have indicated that the benzo-annelated cross-bridged cyclam (**12**) will have similar if not better lithium to sodium selectivity than **8** as the result of the decreased cleft size of the ligand. In his approach towards the synthesis of the first benzo-annelated cross-bridged cyclam (**12**), Reed followed the protocol towards the synthesis of dimethyl cross-bridged cyclam (**8**) reported by Weisman and coworkers,[13] and proposed the methylation at non-adjacent nitrogens of benzo-annelated *cis*-fused tetracyclic bisaminal (**15**) to give the di-methylated bis-quaternary ammonium salt **16**. His hypothesis was based on two points: (1) the steric environment imposed by the glyoxal adduct (**15**) would prevent methylation at an endo nitrogen lone pair, which would give rise to dialkylation on non-adjacent nitrogens; and (2) the dialkylation of compound **15** at non-adjacent nitrogens minimizes the coulombic repulsion in the dicationic product. The target ligand can then be obtained after reductive ring opening (expansion), as illustrated in (Scheme 1.1). However, due to time constraints, he was unable to get to the desired product and characterize the proposed intermediate **16**.[41] The work was resumed by Condon,[17] following the same exhaustive methylation conditions, Condon was able to fully characterize and identify the adjacent methylated benzo-annelated *cis*-fused

tetracyclic bisaminal. He explained that the alkylation had taken place at adjacent nitrogen atoms to give compound **17** rather than the originally proposed compound **16**. Condon was able to observe that methylation resulted in a symmetrical compound following reductive ring expansion of the bis-quaternary ammonium salt (**17**), which led to the first synthesis of di-methylated adjacent-bridged benzo-annelated cyclam (**18**).[17]



Scheme 1.1 Proposed route towards the dimethyl cross-bridged benzo-annelated cyclam (12) by Reed and synthesis of the dimethylated adjacent-bridged benzocyclam.

The third proposed methodology to decrease the basicity of cross-bridged cyclams was to prepare di-benzo-annelated cross-bridged cyclam (**12**) to get two *anilino*-type nitrogens, resulting in decreased ligand basicity (Scheme 1.2).[17,43]



19 13

Scheme 1.2 Condon's path to get in to the dibenzo-annelated cross-bridged cyclam

This proposed structure has an interesting C_2 symmetry, and thus could potentially be used as a chiral reagent, in resolution, catalysis, or asymmetric synthesis in addition to the proposed application. This structure could also potentially be further functionalized to aid in coordination and bio-conjugation by securing a charge-neutral or anionic site and retaining the coordination ability of the CB-TE2A motif (Figure 1.7). [17,43]

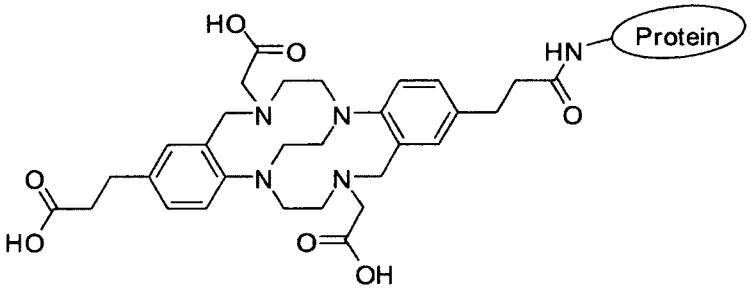
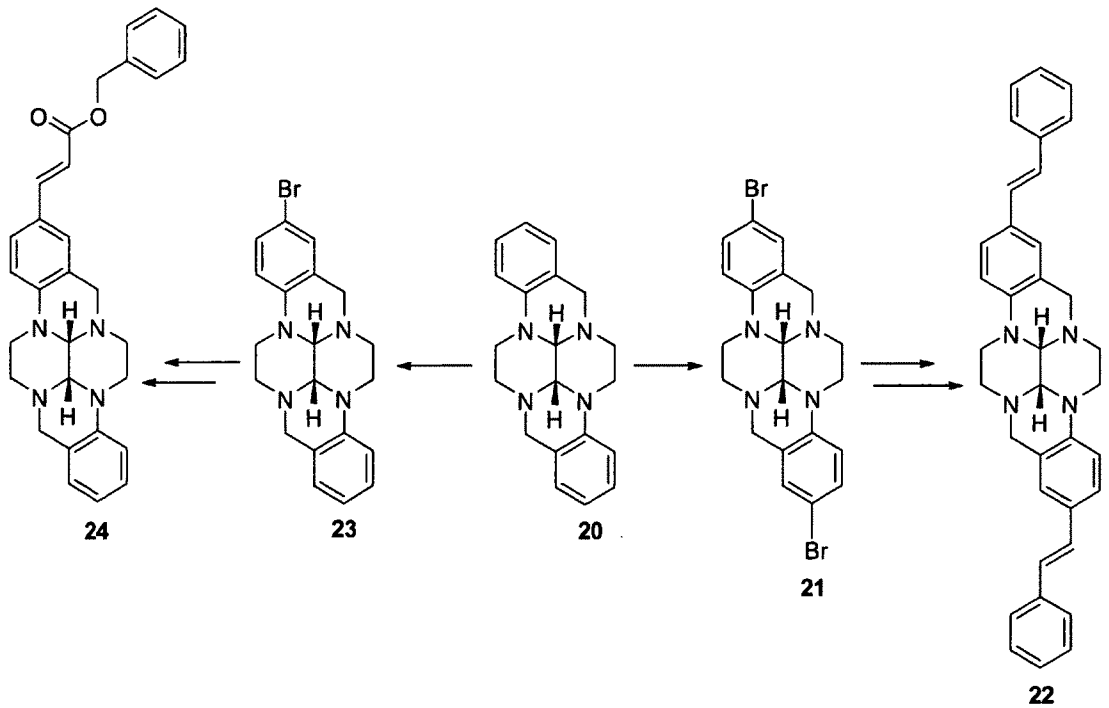


Figure 1.7 Hypothetical structure of dibenzo-annelated cross-bridged cyclam BFC containing *para*-functionalized sites for bio-conjugation.

Employing different aromatic functionalization or coupling chemistry to functionalize at the *para*-position for bio-conjugation will make both carboxymethyl arms available for coordination and a charge-neutral Cu(II) complex will remain reserved. By having an extra ionizable functionality it will serve as a third anionic site for extra ionization at this

position which will enable an overall negatively-charged Cu(II) complex, or charge-neutral bio-conjugation with Ga(III) or In(III). This modified analog might be anticipated to exhibit improved labeling kinetics and clearance from nontarget organs while retaining some of the kinetic stability of the model Cu(II)-CB-TE2A to acid decomplexation.[44] In order to overcome the poor solubility of this chelator and enhance its lipophilicity, different coupling chemistry or aromatic functionalization methods would have to be employed to attach a variety of functionalities, allowing subsequent structural modification. A former Weisman-Wong group member, Yijie Peng, has explored Heck coupling to attach styrene or benzyl acrylate at both *para*-positions following bromination at *para*-positions of the C_2-di-benzo-annelated *cis*-fused tetracyclic bisaminal (**20**), which was previously synthesized by Condon as illustrated in (Scheme 1.3).[17,44]



Scheme 1.3 Structural modifications at the *para*-position of C_2-dibenzobisaminal utilizing Heck coupling chemistry.

The work of this thesis focuses on the synthesis of benzo-annelated cross-bridged cyclam, structurally modified adjacent bridged benzo-annelated cyclam, and *para*-functionalization of the C_2-dibenzo-annelated *cis*-fused tetracyclic bisaminal. Some works of Reed's and Condon's will be revisited, and different methodologies attempted to form one of the target ligands will be discussed. The synthesis of a new benzo-annelated adjacent-bridged ligand amenable to modification by attaching arms or linkers at the secondary nitrogens will also be discussed. This research also investigates different coupling methods to functionalize at the para-position of the C_2-dibenzo macrocyclic ligand **20**, thereby enhancing the lipophilicity of this interesting molecule.

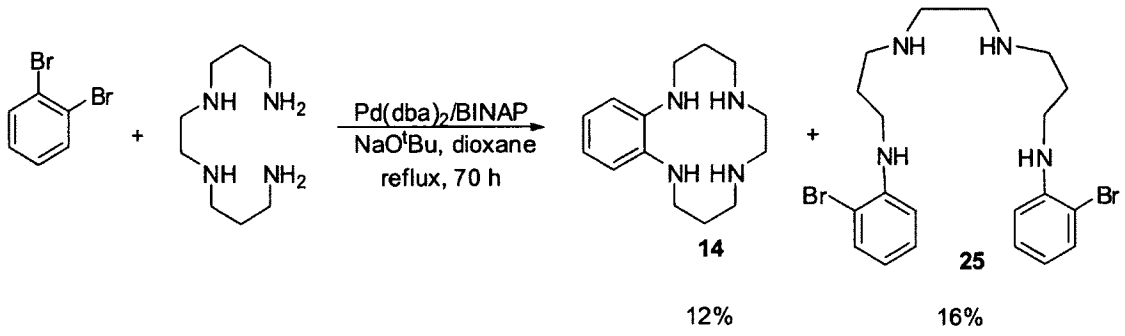
II. Background: Benzo-annelated Cross-bridged Cyclam

A. Synthesis of Benzo[*b*]cyclam (14)

As was stated in the introduction, the goals of this research are based on the interest of investigating and synthesizing a dimethylated cross-bridged cyclam with decreased basicity. We hypothesize that this can be achieved through incorporation of either one or two benzene rings to the macrocyclic frame of the dimethylated cross-bridged cyclam (**8**). Conjugating two of the nitrogen lone pairs to benzene rings will create two *anilino* nitrogens, thereby decreasing the strong basic nature of the cross-bridged cyclam. The two proposed structures targeted are the *mono* or *di* benzo-annelated cross-bridged cyclam illustrated in Figure 1.6 compounds **12** and **13**.

Unlike benzocrown ethers, mono-benzo analogs of saturated polyazamacrocycles are poorly investigated even though such systems potentially possess versatile and useful coordination abilities. Mono-benzo incorporation along the macrocyclic backbone of tetraazamacrocycles has been sparsely reported and very little literature has emerged in the last decade. Less than a handful of reports discuss the benzo incorporation in the carbon chain of the polyazamacrocycle for the purpose of enhancing and reinforcing the framework of the macrocycle. This structural modification will increase the rigidity of the macrocyclic ligand and enhance metal selectivity for coordination.[21,40,45-47] The synthesis of benzo[*b*]cyclam (**14**) which is the main precursor in the preparation of the proposed benzo-annelated cross-bridged cyclam was reported by former Weisman-Wong group member David Reed[41] in 1998 and subsequently in the literature twice by Beletskaya and coworkers.[46,47] The first published synthesis of benzo[*b*]cyclam (**14**) was

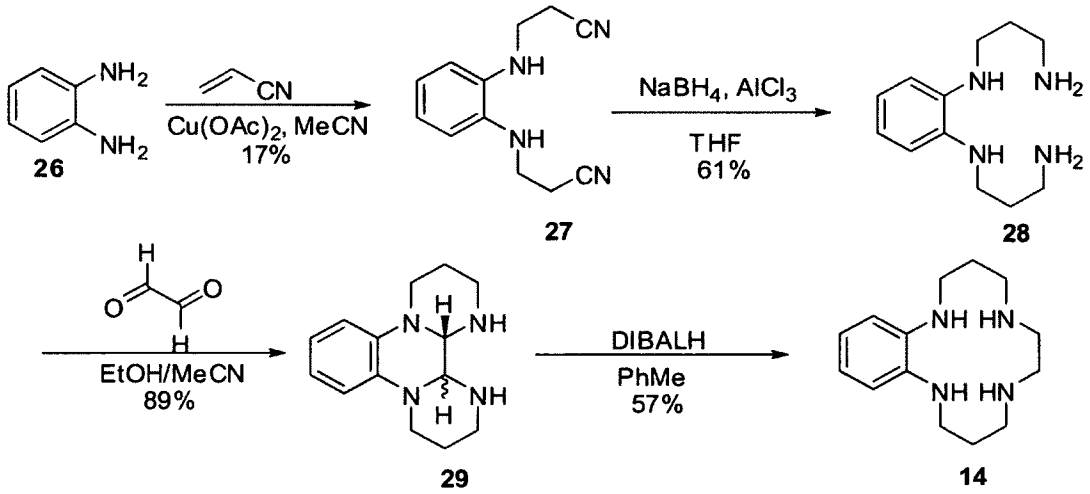
reported by Beletskaya and coworkers, utilizing the Buckwald-Hartwig amination. They reported a one-pot Pd-catalyzed synthesis of benzo[*b*]cyclam (**14**) starting from *o*-dibromobenzene and a linear tetraamine, as shown in (Scheme 1.2). The percent yield achieved with this procedure was very poor and the reaction also led to an undesired open-chain byproduct as a result of the diarylation reaction of the polyamine. It was also reported that arylation with 1-bromo- 2,6-dichlorobenzene promoted the substitution reaction affording a 47% yield of *ortho*-chloro benzo[*b*]cyclam and the undesired byproduct.



Scheme 1.4 Beletsekaya's synthesis of benzo[*b*]cyclam (14).

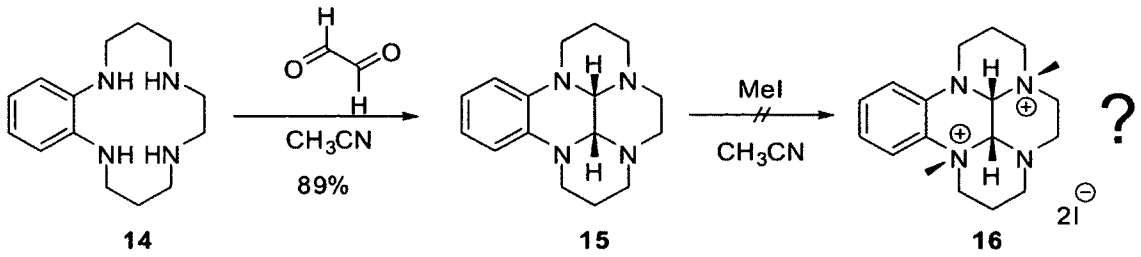
Reed's initial investigation towards the synthesis of benzo-annelated cross-bridged cyclam (**12**) was promising and further investigation was needed. Utilizing the synthetic approach of Weisman *et al.*[13] for converting cyclam to benzo[*b*]cyclam (**14**), Reed devised the first rational synthetic approach for the synthesis of benzo[*b*]cyclam (**14**) as shown in (Scheme 2.2). Michael addition of *o*-phenylenediamine (**26**) to acrylonitrile in the presence of $Cu(OAc)_2$ gave the bis-nitrile species (**27**) by a modification of a literature procedure.[48] Sodium borohydride reduction of the nitrile groups in the presence of Lewis acid $AlCl_3$ gave the benzo-annelated linear tetraamine (**28**), which was

subsequently condensed with glyoxal to give a mixture of the *cis*- and *trans*-benzo-annelated tricyclic bisaminal diastereomers (**29**). Highly



Scheme 1.5 Reed's method towards the synthesis of benzo[*b*]cyclam (14).

regioselective DIBALH reduction of this bisaminal afforded benzo[*b*]cyclam (**14**) in a moderate yield of 57%. Reed was able to make this important intermediate (**14**) in four steps; however the overall yield of these reactions was low to moderate yield due to incomplete conjugate addition and moderate yield of DIBALH reduction to the oxidatively labile benzo[*b*]cyclam (**14**). However the low cost of the starting materials and straightforward experimental procedure made this work practical. A second glyoxal condensation was performed to benzo[*b*]cyclam (**14**), to obtain the *cis*-fused glyoxal adduct compound (**15**).[41] Reed then subjected benzo[*b*]cyclam glyoxal adduct (**15**) to exhaustive methylation conditions (MeI/MeCN/2weeks) as shown in (Scheme 1.3).



Scheme 1.6 Reed's attempt to dimethylate the glyoxal adduct 25.

The methylation product that Reed obtained, which was recrystallized from acetonitrile, exhibited an ^{1}H NMR spectrum consistent with an unsymmetrical dimethyl salt. Reed postulated that the dimethylation has taken place at non-adjacent nitrogens to give dimethyl diiodide (**16**). His interpretation was based on two reasons explained as follows: a) the steric environment imposed by the glyoxal adduct (**15**) would prevent methylation of an *endo* nitrogen lone pair, which would give rise to dialkylation on non-adjacent nitrogens; b) the dimethylation of compound **15** at non-adjacent nitrogens would minimize the Coulombic repulsions of the dication. However Reed was not able to prove his hypothesized structure **16**, as time constraints prevented his exploration of the reductive ring expansion of the dimethylated salt.

B. Synthesis of Dimethylated Adjacent-bridged Benzo-annelated Cyclam (18)

Jeffrey Condon, another Weisman-Wong group member, continued the project trying to achieve the cross-bridged benzocyclam. He repeated the synthesis of benzo-annelated *cis*-fused tetracyclic bisaminal (**15**) and was able to obtain an X-ray structure of that glyoxal adduct (**15**), further verifying the *cis* stereochemistry established by Reed's DNMR results on **15**. The structure of **15** verified that two non-adjacent lone pairs are

pointing *endo* towards the cleft of the molecule, and the other two non-adjacent lone pairs are pointing *exo*, outside the face of the cleft of the molecule. This study explained that the two *exo* lone pairs present are contributed one from the anilino nitrogen and one from the amino nitrogen as shown in (Figure 1.8).

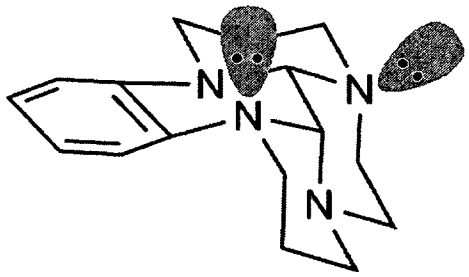
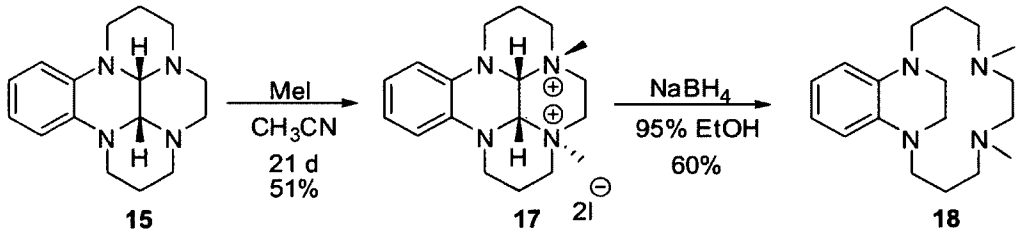


Figure 1.8 *Exo*-lone pairs pointing out of the cleft of compound 15.

The X-ray structure also showed that the anilino nitrogen lone pairs are slightly twisted out of the conjugation with the benzene ring because of the cis-fused conformation. "It indicated that the geometry of the anilino nitrogens is between pyramidal and trigonal planar, shown by the summation of the exo anilino C-N-C bond angle at 345°. This slight twist of the anilino lone pairs out of conjugation should create more nucleophilic character than ordinary anilino nitrogen."[17] Because of the stronger nucleophilicity of the anilino nitrogens discussed above, Reed hypothesized the alkylation to take place at an *exo* site of non-adjacent nitrogens under kinetically controlled conditions. Condon subjected the glyoxal adduct (**15**) to exhaustive methylation conditions for 21 days in acetonitrile to obtain the dimethylated salt compound **17** in 51%. The ^{1}H NMR of this salt was consistent with the spectra of the salt obtained by Reed. The ring expansion and complete characterization of this compound was then finalized by Condon[17] and Reed's initial assignment of structure **16** was found to be incorrect as illustrated in (Scheme 1.4).

The correct structure **17** was deduced based on the results of the reductive ring expansion of compound **17** using sodium borohydride to give compound **18**. The symmetrical ring opened adjacent-bridged compound **18** has simplified $^{13}C\{^1H\}$ NMR spectra compared to the proposed structure **13** because of the presence of a plane of symmetry that bisects it through the benzene ring.



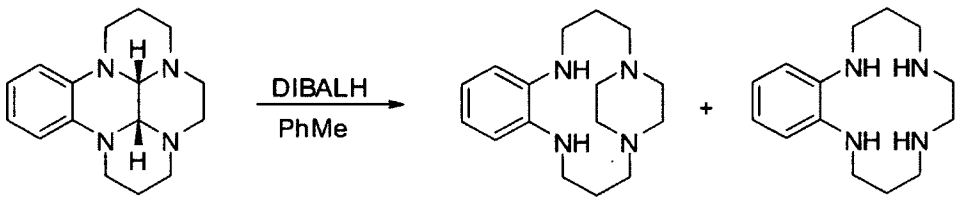
Scheme 1.7 Condon's methylation of compound 15 and reductive ring expansion of the salt 17 that led to the adjacent bridged dimethylated benzocyclam 18.

The $^{13}C\{^1H\}$ NMR spectrum confirmed the structure of **18**. The rationale for the formation of **17** instead of **16** is that amino lone pairs are more nucleophilic than anilino lone pairs. Because of the flattened geometry of compound **15**, the cleft of this compound is broadened and the steric hindrance is decreased enabling the more nucleophilic tertiary amino *endo* lone pair to undergo methylation and accommodate the small size methyl group. Subsequent reduction of **17** gives rise to the adjacent-bridged compound **18** having methyl groups at adjacent amino nitrogens.

C. Other Attempts To the Synthesis of Benzo-annelated Cross-bridged Cyclam

The designed synthetic route (Scheme 1.7) resulted in the synthesis of an adjacent-bridged isomer of the target molecule while the ultimate goal was to synthesize the

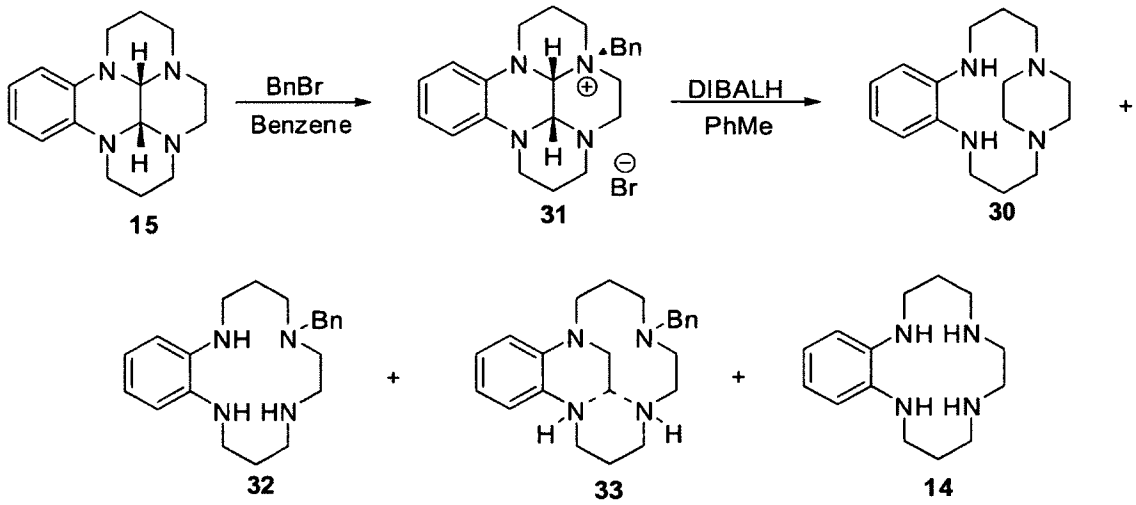
dimethylated benzo-annelated cross-bridged cyclam (**12**). Condon carried out reduction of the aminal **15** using DIBALH.[49] Yamamoto and Marouka have reported the successful DIBALH cleavage of N-tosyl aminal bond preferentially to the other N-aminal bond.[49] According to the report of Yamamoto and coworker DIBALH reduction of the glyoxal adduct **15** would be expected to give selective cleavage of the aminal to anilino nitrogen. Condon envisioned the utilization of this work to synthesize the cross-bridged benzo-annelated cyclam (**12**), in doing so he observed the formation of the structurally reinforced piperazine containing compound (**30**) and unexpected product benzo[*b*]cyclam (**14**) as illustrated in (Scheme 1.8). "The formation of compound of **30** indicated DIBALH reduction could lead to the desired product if it could selectively cleave only one aminal to anilino nitrogen bond."[17]



Scheme 1.8 Regioselective reduction of the glyoxal adduct using DIBALH.

Knowing that the DIBLAH reduces the anilino aminal bond of the benzo[*b*]cyclam-glyoxal adduct, it was envisioned that alkylating at one amino site to get a mono-ammonium salt of the benzo[b]cyclam-glyoxal adduct might lead to the desired cross-bridged benzo[*b*]cyclam. It was hypothesized that the initial reduction would take place between the monoalkylated ammonium nitrogen and the aminal carbon, and the second DIBALH reduction would occur at the anilino-nitrogen aminal bond. Condon synthesized

mono-benzylated quaternary ammonium salt (**31**), and subjected the salt to reduction using excess DIBALH as shown in Scheme 2.6.



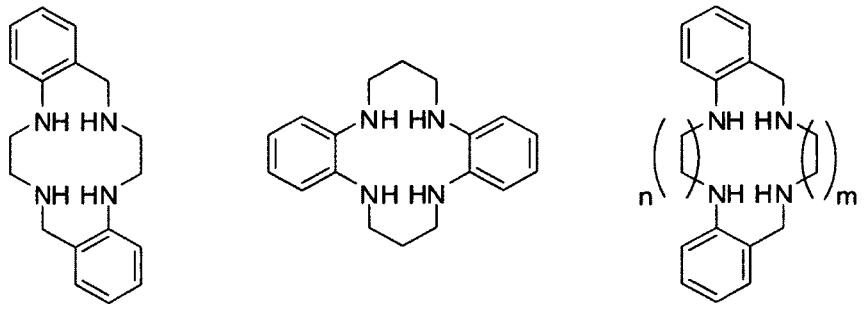
Scheme 1.9 Attempted DIBALH reduction of mono-quaternized ammonium salt to synthesize the cross-bridged benzocyclam.

However, $^{13}C\{^{1}H\}$ NMR analysis showed that the product was a mixture of four different compounds **30**, **32**, **33** and **14** in an approximate ratio of 6:6:2:1. This reaction resulted in debenzylation to yield two of the products which were previously known and a small amount of bicyclic compound **33.** The isomeric identity of the bridging (cross or adjacent) of **33** was not determined. Condon also attempted to employ a weaker reducing agent ($NaBH_4$) to avoid the debenzylation, however again NMR analysis revealed the presence of the debenzylated product, the benzo[*b*]cyclam glyoxal adduct **15** and a bicyclic bridged product, which was different from that previously obtained and of unknown isomeric identity.[17] This thesis will revisit some of the previous work and will discuss further investigations and studies made to synthesize the cross-bridged benzo[*b*]cyclam **12**. The synthesis of a novel structurally-reinforced adjacent-bridged benzo[b]cyclam will also be presented.

III. Background: Dibenzo-annelated Cross-bridged Cyclam

A. Synthesis of Dibenzo-annelated Cyclam (19)

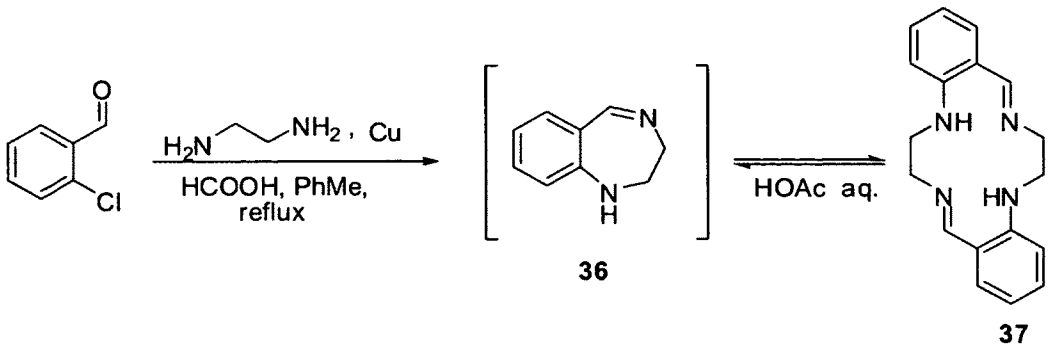
It was discussed in the introduction part that the second goal related to benzo-annelated cyclams was to synthesize a dibenzo-annelated cross-bridged cyclam and increase its lipophilicity by functionalizing at the *para* positions of the benzene ring using different coupling chemistries. Another goal was to add extra pendant arms/linking sites to serve as bifunctional chelator linkers. A number of reports exist for the preparation of dibenzo-annelated cyclam, which vary in the position of the benzene ring around the perimeter or backbone of the carbon chain as illustrated in (Figure 1.9).[50-55]



19 **34** **35**

Figure 1.9 Examples of dibenzo-annelated cyclam structures.

Condon, aiming at C_2 dibenzo-annelated cyclam **19**, followed the work of Ried and coworkers[51] to synthesize the dibenzo-annelated bisimine **37** via a Ullman reaction as shown in Scheme 1.10. The report by Reid and coworkers corrected the earlier characterization of **37** as 2,3-dihydro-1*H*-1,4-benzodiazepine **36**.[56]



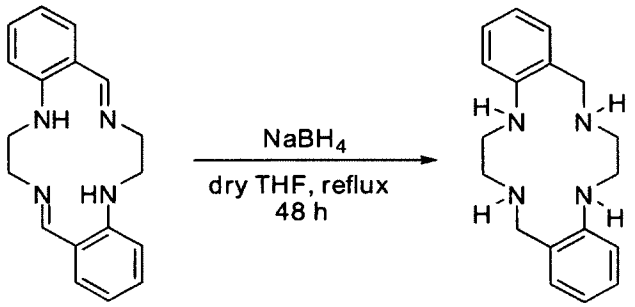
36

37

Scheme 1.10 Ullman Chemistry for the preparation of the dibenzo-bisimine 37.

It also discussed that Coffen and coworkers had reported the same compound in 1974 but with a different melting point.[57] However, Bergman and Brynolf[52] pointed out that the differences in melting point was due to the fact that the 14-membered ring **37** reported by Ried[51] and Uskokovic,[56] was the thermodynamically favored structure, whereas the 7-membered ring **36** was the kinetic product. They explained that "heating the 14-membered ring in aqueous acetic acid gave, via a hydrolytic ring-opening and recyclization, the 7-membered monomeric species **36**, which is the kinetic product as indicated by the fact that it slowly converted back to the 14-membered ring dimer when dissolved in DMSO."[52] The procedure of Betakis afforded a low yield (30-40%) of the dibenzo bisimine **37** following recrystallization. This procedure was improved and a new recrystallization method was developed by Lindoy and coworkers that afforded a 70% yield.[50] Following the synthesis of compound **37**, the next step involved was the reduction to **19**. Mattes and coworkers[58] reported reduction of the imine using lithium aluminum hydride (LAH) in THF to give 87% conversion, while Lindoy and coworkers[50] reported a 95% yield using sodium cyanoborohydride instead as the reductant. However,

Condon was able to reduce the bisimine using sodium borohydride in 83% yield to obtain dibenzo-annelated cyclam **19** as shown in the (Scheme of 1.11).[17]



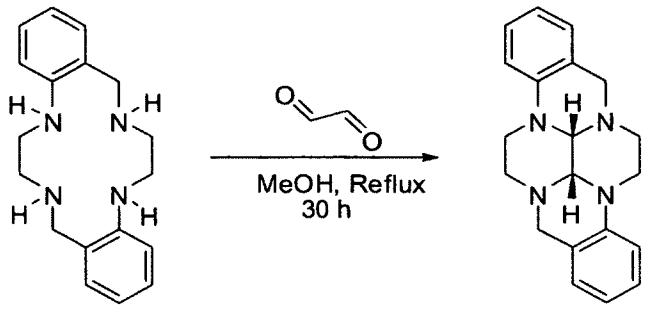
37 **19**

Scheme 1.11 Reduction of the bisimine 37 to dibenzo-annelated cyclam 19.

It is also worth mentioning that Mattes and coworkers have extensively investigated on the coordination ability of ligand **19** with Ni(II), Cu(II), Zn(II) and Pd(II).[59] They also reported that ligand **19** can adopt both *cis* and *trans* coordination geometries and doesn't discriminate well between metals. They also reported the crystal structure of diprotonated ligand **19** and two pendant armed derivatives of **19**.

B. Synthesis of Dimethylated Dibenzo-annelated Cross-bridged Cyclam (13)

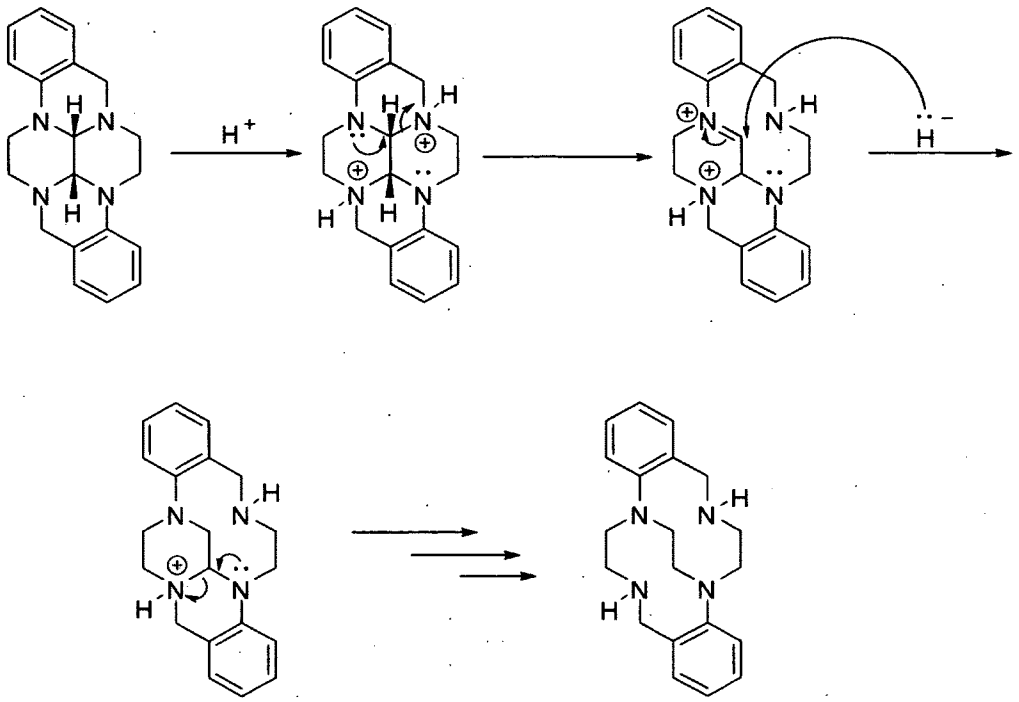
Condon then utilized the conditions developed by Weisman, Wong, and coworkers using glyoxal condensation of compound (**19**) in methanol to make C_2 symmetric dibenzo cis-fused tetracyclic bisaminal (**20**) in 82% yield, which is an interesting chiral compound as illustrated in (Scheme 1.12).



19 20

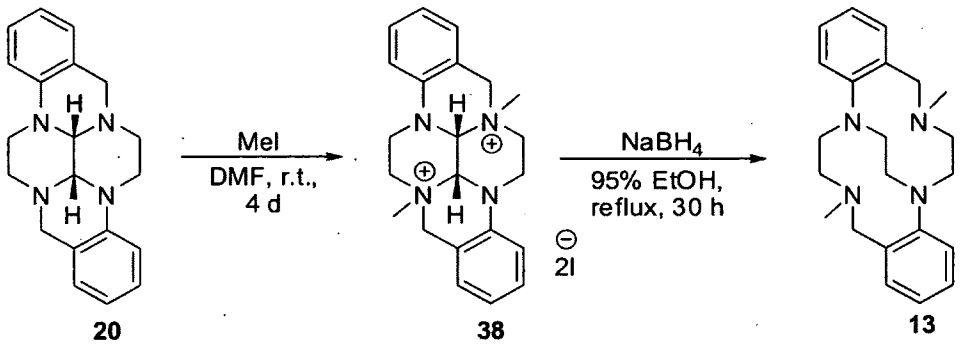
Scheme 1.12 Glyoxal condensation of the dibenzo cyclam to the cis-fused tetracyclic dibenzo bisaminal 20

Condon then attempted to reduce the bisaminal **20** to the dibenzo cross-bridged cyclam taking advantage of the regioselective DIBALH reduction reported by Yamamoto and Marouka[49] in the synthesis benzo[*b*]cyclam (**14**). However, this method was not effective enough and resulted in the formation of a mixture of products of cross-bridged, adjacent-bridged and compound **19**. He then attempted an acid catalyzed borohydride reduction in which protonation of the amino nitrogens generated an iminium ion *in situ*, leading to reduction and thereby generating the desired product as illustrated in Scheme 1.13. But again this method was not very effective, and it was necessary to follow the protocol of Weisman, Wong and coworkers that was developed for cyclam. Alkylation of the amino nitrogens of **20** using methyl iodide (MeI) to generate the *N,N'*-dimethyl *bis*-quaternary ammonium iodide salt **38** would be necessary, which would allow reduction and produce the desired product.



Scheme 1.13 Proposed in situ iminium ion formation and reductive ring expansion to afford the target cross-bridged dibenzo cyclam

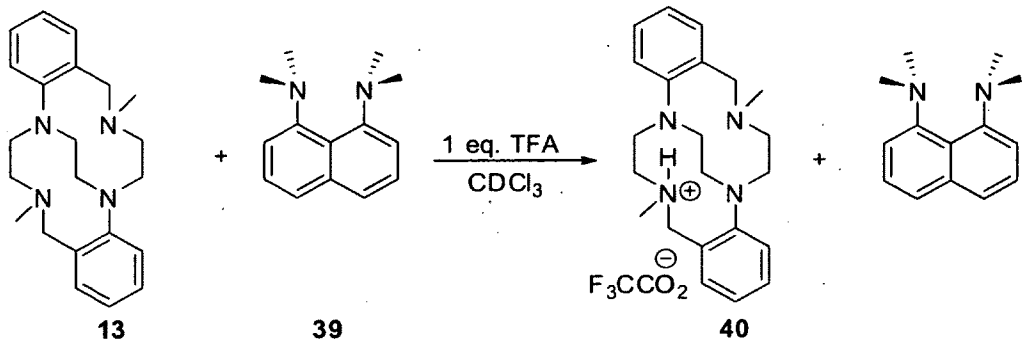
Unfortunately compound **20** was insoluble in most organic solvents, but it did show limited solubility in DMF. So the alkylation with MeI was carried out in DMF, which presented a tedious purification process due to the formation of an insoluble dimethyl ammonium iodide byproduct. This impurity showed improved solubility in isopropanol and was therefore subjected to Soxhlet extraction for 10 days to afford the dimethylated *bis*-quaternary ammonium salt in 82% with ≥ 97% purity as illustrated in Scheme 1.14. Condon, then subjected **38** to reductive ring expansion using sodium borohydride in 95% EtOH at reflux to obtain cross-bridged ligand **13** in an excellent 92% yield and ~98% purity as shown in Scheme 1.14.



Scheme 1.14 Dimethylation of dibenzo bisaminal and reductive ring expansion of the salt 38 to get the target dimethylated dibenzo cross-bridged cyclam 13.

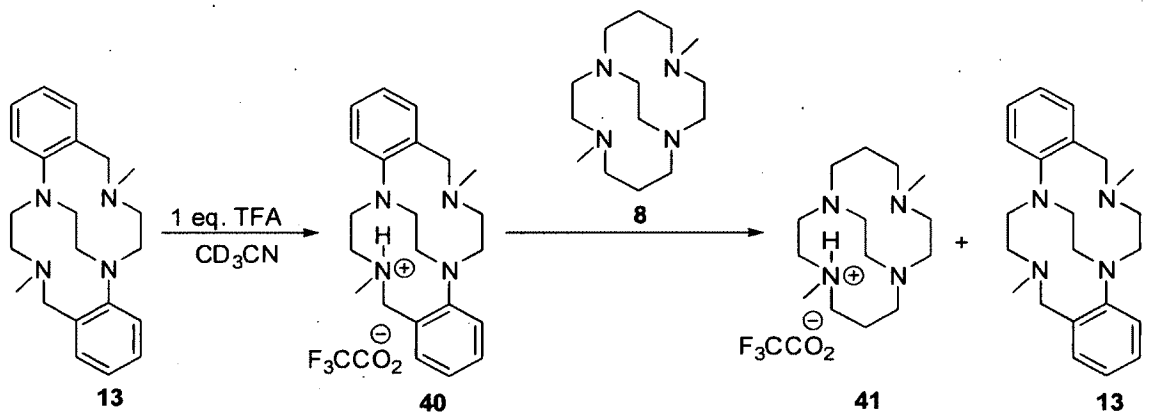
C. Basicity Comparison Between Dimethylated Cross-bridged Cyclam (8) and Dimethylated Dibenzo-annelated Cross-bridged Cyclam (13)

Condon was able to synthesize the dibenzo-annelated cross-bridged cyclam (**13**), and the next step involved was to analyze its basicity compared to cross-bridged cyclam (CB-cyclam). As discussed in the introduction the target of this project was synthesis of a less basic ligand relative to CB-cyclam. Qualitative experiments were performed by Condon following the procedures of Hill[60] that involved the reaction of a 1:1:1 ratio of cross-bridged dibenzo cyclam (**13**), proton sponge (**39**) and trifluoroacetic acid (TFA) in an NMR tube using $CDCl_3$ as the solvent (Scheme 1.15).



Scheme 1.15 Basicity comparison between dibenzo cross-bridged 13 and proton sponge 39.

NMR analysis of this homogenous reaction mixture showed the free proton sponge **39** and the protonated cross-bridged dibenzo cyclam (**40**), while continuous monitoring of the reaction mixture over 10 days resulted in no change. A second qualitative experiment was performed by Condon that compared the basicity of the dibenzo cross-bridged cyclam **13** to the free dimethylated cross-bridged cyclam (**8**). The dibenzo cross-bridged cyclam was allowed to react with one equivalent of TFA in CD_3CN to yield the protonated salt (**40**) which is a homogenous solution. An NMR spectrum was obtained and this protonated ligand **40** was allowed to react with one equivalent of the dimethyl cross-bridged cyclam (**8**) to give an instant precipitate as illustrated in Scheme 1.16. While the precipitate was believed to be the free ligand (**13**), a trace of protonated ligand **40** was observed, though the major product formed was the protonated dimethylated cross-bridged cyclam (**41**).



Scheme 1.16 The qualitative experiment that demonstrated the basicity comparison of 13 and 8; and confirmed 13 is less basic compared to 8.

This study concluded that the dimethyl cross-bridged cyclam **8** is more basic compared to compound **13** indicating that the basic nature of compound **13** was decreased by conjugation of phenyl ring with two nitrogen lone pairs. In summation from the above

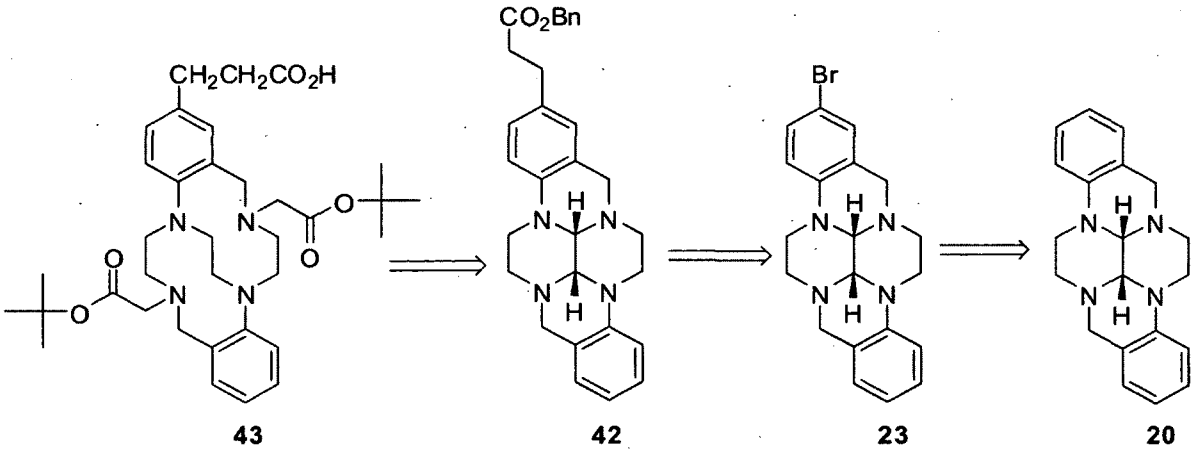
qualitative experiments it can be concluded the pK_a of the conjugate acid of the cross-bridged C_2-dibenzocyclam can be placed between the corresponding pK_a of the proton sponge **39** and the dimethylated cross-bridged cyclam (**8**).[17]

Condon also investigated the coordination ability of ligand **13**. Cu(II) was the first transition metal chosen due its coordination stability. He was able to successfully coordinate Cu(II) with the ligand by refluxing the ligand with one equivalent of copper chloride dihydrate ($CuCl_2 \cdot 2H_2O$), in methanol for 24 hours. The ability of ligand **13** to complex with Li(I) was also investigated. It was predicted that a decrease in basicity would decrease its complexation ability, while it would still be able to coordinate with Li(I). However due to the poor solubility of the ligand in MeCN and of lithium salts in aprotic solvents such as $CHCl_3$, CH_2Cl_2, benzene and toluene, the formation of the complex did not happen. For protic solvents ligand protonation dominated, resulting in the formation of the ammonium salt. An X-ray structure of the protonated ligand revealed that the four nitrogen lone pairs are pointing towards the cleft of the ligand and it is noteworthy that the solid state structure is not symmetrical, although the NMR spectra showed a time averaged C_2 symmetry in solution.

D. Synthesis of Mono and Dibromo Dibenzo-annelated Tetracyclic Bisaminal (21 and 23)

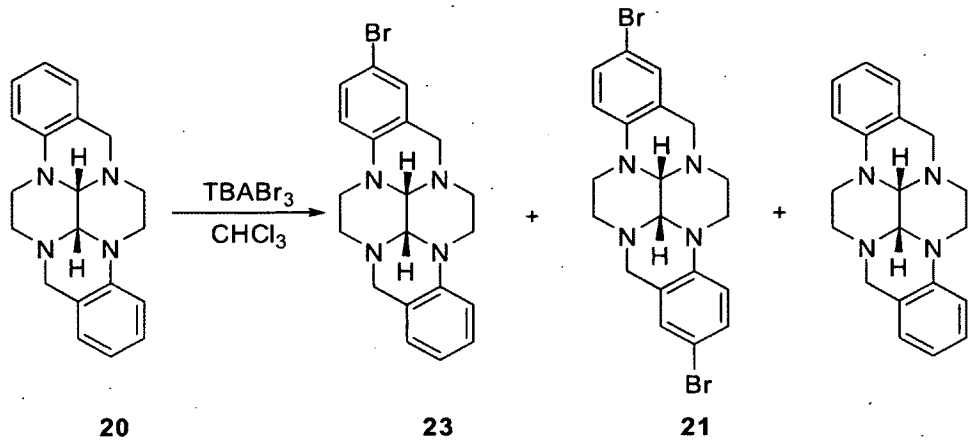
As discussed in the introduction, one of the goals of the dibenzo cross-bridged cyclam was to increase its lipophilicity and to remotely functionalize the phenyl ring which would provide alternate linking sites on the chelator, thereby rendering a charge-neutral

or a charge-negative Cu(II) complex. Yijie Peng, a former Weisman-Wong group member, also investigated synthesis of the bifunctional chelator (BFC), in which the proposed retrosynthetic route is outlined in Scheme 1.17.[44]



Scheme 1.17 Peng's retrosynthetic route towards the synthesis of the proposed BFC 43

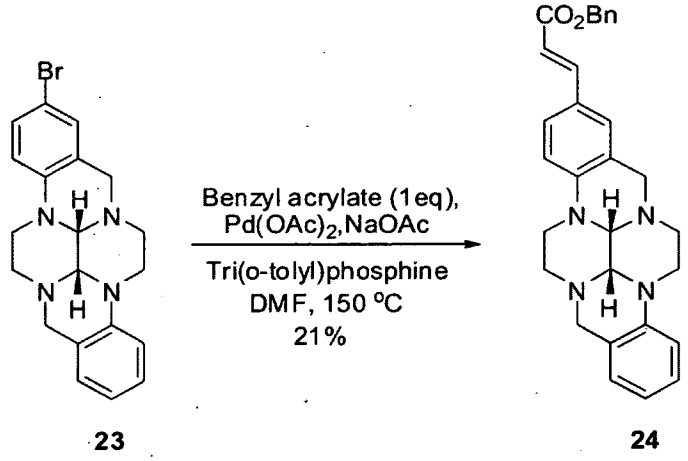
Peng's [44] approach towards the synthesis of BFC **43** started with bromination of the *cis*-fused dibenzo tetracyclic *bis*-aminal (**20**) using one equivalent of tetrabutylammonium tribromide ($TBABr_3$) to get a mixture of monobrominated **23**, dibrominated **21** and starting material **20** as indicated in (Scheme 1.18). Upon increasing the amount of $TBABr_3$ from one equivalent to slight excess of two equivalents the di-brominated species **21** became the major product. The solubilities of the brominated compounds were very poor and the purification/isolation of the mono-brominated compound using chromatography was tedious. Following repeated chromatographic purification of dilute samples Peng obtained the monobrominated compound **23** in 40% yield.



Scheme 1.18 Synthesis of the monobrominated dibenzo bisaminal 23.

E. Attempts to Remotely Functionalize Dibenzo-annelated Tetracyclic Bisaminal for Bifunctional Chelator (BFC)

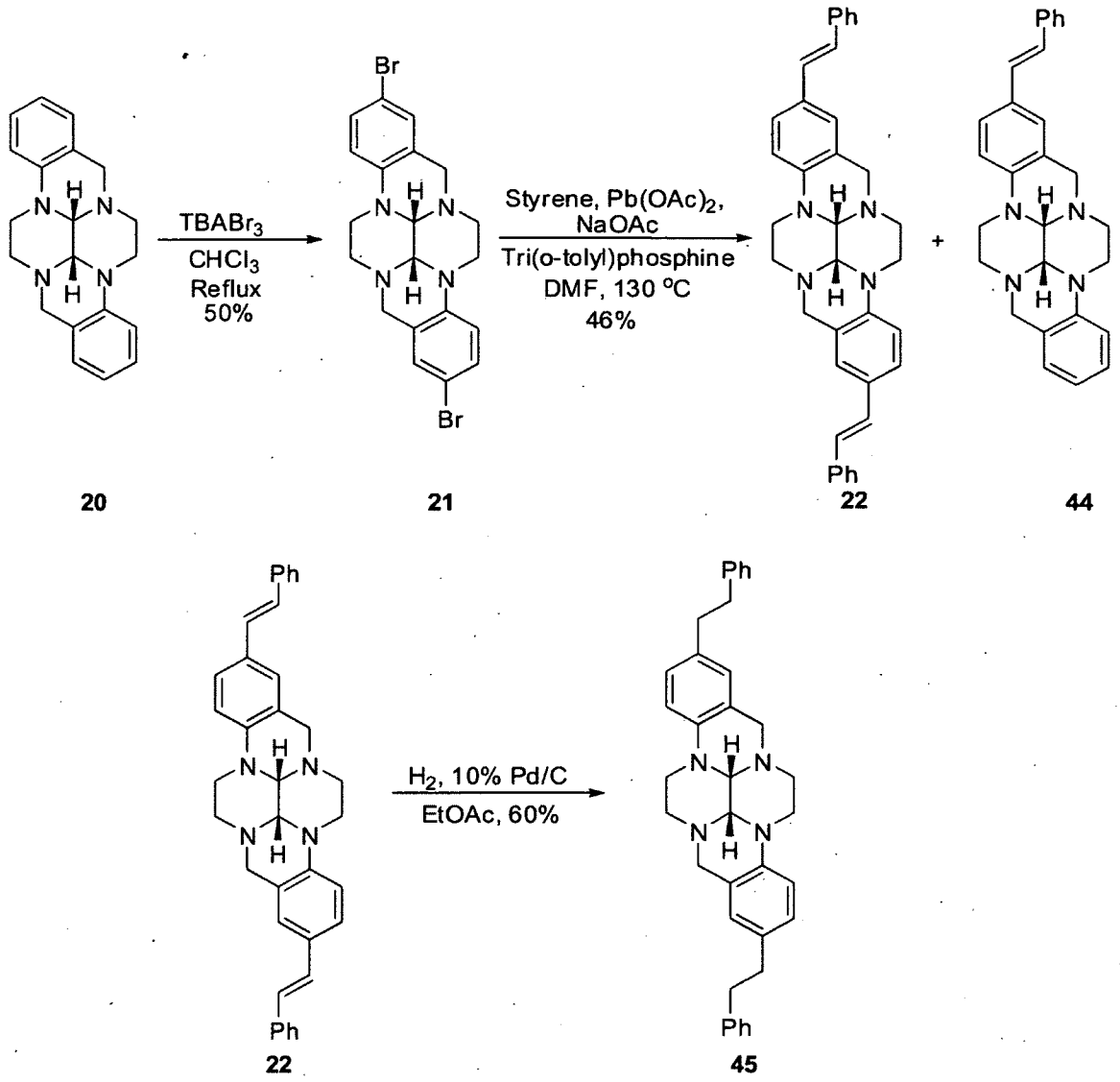
Peng then performed Heck coupling chemistry on **23** with one equivalent of benzyl acrylate in the presence of $Pd(OAc)_2$, tri(o-tolyl)phosphine and NaOAc in DMF as illustrated in Scheme 1.19, compound **24** being synthesized in a low yield of 21%. He attempted the hydrogenolysis-free hydrogenation of the olefin compound **24** following the procedure of Maki and coworkers.[61]



Scheme 1.19 Synthesis of 24 using Heck coupling chemistry.

However, upon attempting their procedure the reaction was unsuccessful on compound **24** and due to time constraints further investigation was not possible. Peng also investigated on the modification of dibenzotetracyclic bisaminal **20** in order to improve its solubility in common organic solvents. Peng prepared the dibromo compound **20** using a slight excess of two equivalents of $TBABr_3$. Recrystallization from hot chloroform gave the desired product **21** in a moderate yield of 50% as shown in Scheme 1.20. The X-ray structure obtained for **21** showed C_2 symmetry with the flanking phenyl rings about the cleft of the molecule. Heck coupling chemistry was also carried out for the dibromo species **22** with styrene in the presence of $Pd(OAc)_2$ with NaOAc and tri(o-tolyl)phosphine in DMF (Scheme 1.20), which resulted in the formation of two mixtures of products in the ratio of 4.7:1, where the major product is the desired product compound **22** in 46% yield and minor product was the mono-coupled component **44**. Hydrogenation of the olefin functionality under standard hydrogenation conditions using 10% Pd/C and atmospheric H_2 in ethyl acetate afforded compound **45** in a moderate yield of 60% after purification by chromatography. However, upon the introduction of two aryl groups, the solubility of **45** didn't improve. Further alkylation attempts on compound **45** to get the desired BFC product were not successful due to the poor solubility of the starting material similar to that of its parents.[44]

As discussed in the introduction, the next chapter of this thesis will re-visit and expand on the work started by Condon and Peng. The dibenzo tetracyclic bisaminal **20** is a chiral molecule and resolution of this chiral compound is among the goals of this thesis.



Scheme 1.20 Synthesis of the dibromo species 21 followed by Heck coupling to styrene to get 22 and hydrogenation of 22.

In order to increase the lipophilicity of this compound and be able to resolve it, Suzuki and Sonogashira coupling chemistries will be utilized to couple an aryl or alkyl component with different functionality. In addition to enhancing the solubility of this compound this methodology will enable us to take advantage of the benzo ring to remotely functionalize it for BFC and/or linking site.

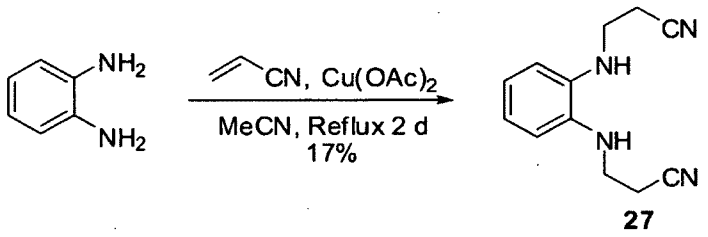
CHAPTER II

RESULT AND DISCUSSION

I. Benzo-annelated Cyclam and Its Derivatives

A. Synthesis of Benzo[*b*]cyclam (14) and Its Metal Complexation Studies

To synthesize the target material cross-bridged benzo[*b*]cyclam **12**, Reed's methodology was initially followed[41] (See Scheme 1.5). *N*, *N'*-bis(3-aminopropyl)-*ortho*-phenylenediamine (**28**) is the appropriate tetraamine required for the preparation of the benzo-annelated tricyclic bisaminal **29,** a precursor for benzo[*b*]cyclam (**14**). The synthesis of **28** has been reported, by Klenke and Gilbert,[62] but they were unable to purify and isolate it. However, Reed was able to synthesize **28** in 78% yield, by reduction of *N,N'*-bis(2-cyanoethyl)-*ortho*-phenylenediamine (**27**). The bis-nitrile species **27** can be prepared by aza-Michael addition of *ortho*-phenylenediamine to acrylonitrile as reported in the literature.[48,63-66] By modification of a literature procedure,[48] Reed synthesized compound **27** from *ortho*-phenylenediamine and acrylonitrile in CH_3CN in the presence of copper(II) acetate ($Cu(OAc)_2$) in 17% yield following recrystallization from $EtOH/H_2O$ as illustrated below Scheme 2.1.

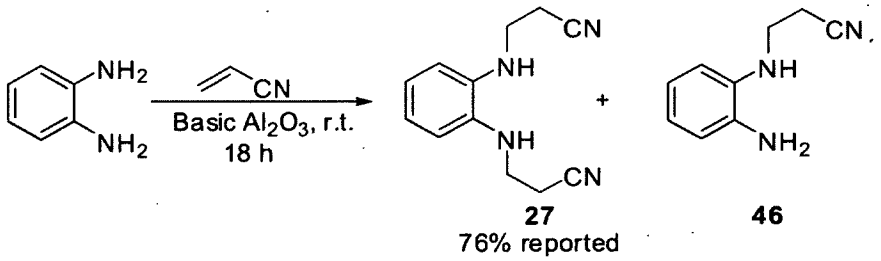


Scheme 2.1 Reed's method of preparing compound 27.

This reaction is a very low yielding reaction, although the starting materials were not costly. We sought to improve the yield of **27**. Several literature procedures were investigated with varying catalyst loading and employing different solvent systems and different purification methods were tried.

1. Reactions to optimize the synthesis of N,N'-Bis(2-cyanoethyl)-*ortho*-phenylenediamine (**27**)

Wang, L,i and co-workers reported aza-Michael addition in the presence of basic alumina without solvent to afford bis-nitrile **27** in 76% yield.[63] Their report was not clear and there was some missing information. The same reaction procedure without solvent was followed, but the reported yield was not achieved. Solvent-assisted modified procedures were performed (Table 2.1) including ball mill assisted neat reaction, however, the maximum yield obtained after attempting all these experiments was 8%.



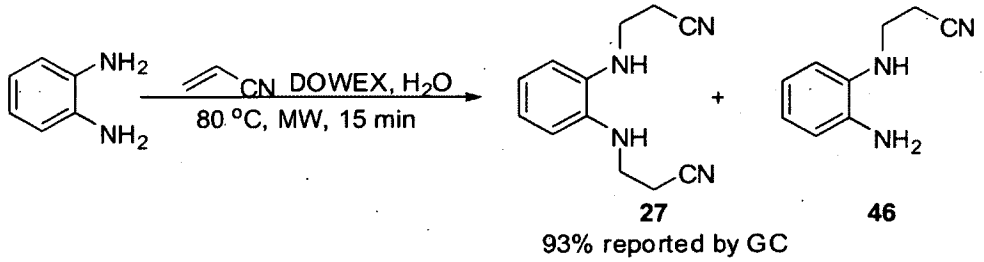
Scheme 2.2 Michael addition in the presence of basic Al_2O_3.

Acrylonitrile (eq)	Basic Al_2O_3 (eq)	Solvent	Yield (%)
3.0	9.8	-	SM [a]
3.0	9.8	MeCN (20 mL)	SM
3.0	9.8	H_2O (5 mL)	8%
3.0	9.8	ball mill (3.5 h)	SM

a = SM is an abbreviation for starting material

Table 2.1 Results of the Aza- Michael addition in the presence of basic alumina.

Varma and coworkers reported aza-Michael addition reactions using microwave heating in the presence of polystyrene sulfonic acid (PSSA) in water at 80 °C (Table 1.2) and claimed a 93% yield of bis-nitrile **27**.[64] The reported procedure was followed and reaction was monitored by TLC, which showed the consumption of starting material and formation of the *mono*-substituted nitrile species **46** as the major product. Reaction conditions were modified by varying the reaction temperature, stoichiometry of reagent, and reaction time (Table 2.2), but the reported yield couldn't be achieved. It is hypothesized that PSSA is protonating one of the anilino nitrogens of **46** and preventing it from being further alkylated.



Scheme 2.3 Aza-Michael addition in the presence of PSSA.

Acrylonitrile (equiv)	MW temp. (°C)	Time (min)	Products **27 : 46**
2.0	80	15	10:90 [a]
2.0	100	30	20:80 [a]
3.0	100	60	47:53 [b]
3.0	130-140	15	45:55 [b]
3.0	140	60	40:60 [b]

a = ratio estimated by TLC
b = ratio estimated by ^{1}H NMR of the crude reaction mixture

Table 2.2 Aza-Michael addition in the presence of PSSA in the microwave.

A similar microwave-induced aza-Michael reaction in the absence of PSSA was reported by Banik and coworkers.[66] This method was attempted with microwave heating and with conventional heating (Table 2.3) but the yield obtained was not satisfactory, with the *mono*alkylated species being the dominant product in all reactions. Sodium chloride was used as an additive in these reactions to increase the polarity of the solvent, allowing the microwave reactor to attain the high temperature we wished to explore. However this methodology was not found to be satisfactory.

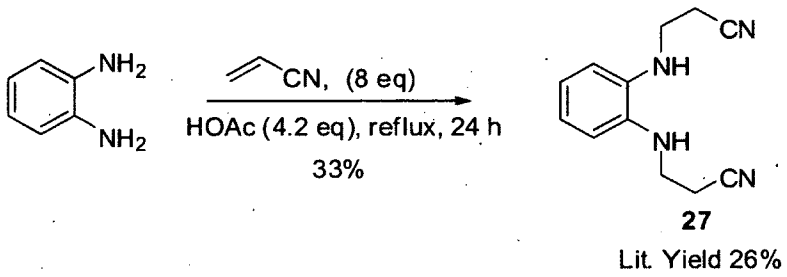
Acrylonitrile (equiv)	NaCl (eq)	MW (°C)	Time	Conversion **27:46**
2.0	-	120	30 min	22:78
2.0	0.5	160	30 min	22:78
2.0	0.5	160	60 min	31:69
2.0	1.0	160	60 min	30:70
2.0	-	Reflux*	5 d	33:67

*conventional heating,

Table 2.3 Aza-Michael addition in water using microwave irradiation.

The last procedure attempted on this study was carried out by following the report of Braunholtz and Mann, where 26% yield was reported for the aza-Michael addition

reaction of *o*-phenylenediamine with acrylonitrile in the presence of glacial acetic acid (Scheme 2.4). By adopting the same procedure, a 33% yield of bis-nitrile **27** was obtained following recrystallization with MeOH (≥ 95% purity as estimated by ^{1}H NMR). Although this yield is still poor, it is a better yield than provided by the other procedures. The low cost of the starting material and the ability to run this reaction easily and in a short period of time with a simple purification method allows for the preparation of multi-gram quantities of bis-nitrile **27** as illustrated in (Scheme 2.4).

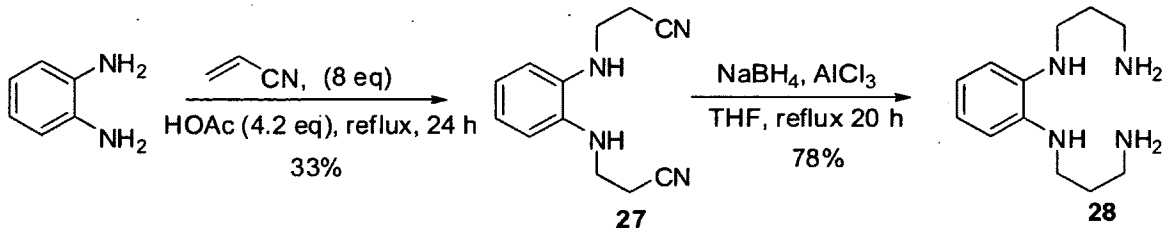


Scheme 2.4 Aza-Michael reaction in acetic acid.

2. Synthesis of benzo-annelated tetraamine **28**

The next intermediate that was required in the Reed synthetic path was *N,N'*-bis(3-aminopropyl)-*ortho*-phenylenediamine (**28**). Adopting Reed's reduction procedure of *N,N'*-bis(2-cyanoethyl)-*ortho*-phenylenediamine (**27**) using $NaBH_4$ in the presence of $AlCl_3$ in dry THF afforded the tetraamine **28** as shown in (Scheme 2.5). Product was obtained from a basified reaction medium, following continuous extraction from toluene, in 78% yield as a brown oil that solidified in the flask.[41] Kugelrohr distillation can also be used for further purification. As a free amine the tetraamine **28** is extremely labile towards oxidation by atmospheric oxygen. The oxidation can be avoided either by using compound **28** immediately to the next reaction or by storing it as hydrochloride salt. To

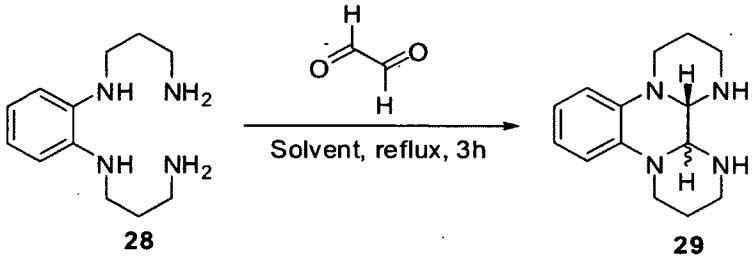
prevent oxidation during the workup all solutions were purged of oxygen and kept under nitrogen atmosphere.



Scheme 2.5 Reduction of bis-nitrile 27 to give the linear teraamine 28.

3. Procedural modification for the synthesis of the benzo-annelated tricyclic bisaminal stereoisomeric mixtures (**29**)

The subsequent material needed is the benzo-annelated tricyclic bisaminal **29,** a precursor of benzo[*b*]cyclam (**14**). Following Reed's procedure, condensation of the tetraamine **28** with aqueous glyoxal was attempted (Scheme 2.6). However, the procedure followed didn't provide the desired product. The desired bisaminal couldn't be obtained even after modifying the reaction conditions by varying solvent systems, reaction times, concentrations and work up procedures, as shown in (Table 2.4). The reaction was also repeated with pure starting materials and different batches of glyoxal including a freshly-opened bottle, but product was not obtained. ^{1}H NMR of the crude reaction mixture showed broad peaks and many multiplets, indicating the presence of complex mixture or polymer.

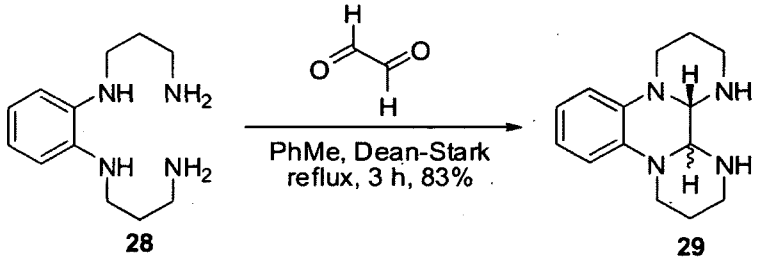


Scheme 2.6 Attempted glyoxal condensations using Reed's procedure.

Glyoxal (equiv)	Solvent	Result
1.3	EtOH/MeCN	Complex mixture
1.3	EtOH	Complex mixture
1.3	MeCN	Complex mixture

Table 2.4 The condensation of the tetraamine 28 with glyoxal.

Searching for better reaction conditions, the idea of modifying the reaction procedure by incorporating a Dean-Stark trap for azeotropic removal of water was suggested. The benzo-tetraamine **28** was dissolved in dry toluene and aq 40% glyoxal was added and was refluxed for 5 h at which time TLC showed the reaction to be complete. Following proper workup procedures, product was obtained as a brown oil that solidified in the round-bottomed flask to afford 83% of **29** (Scheme 2.7). The reproducibility difficulty noted by Reed for the procedure was also resolved (Scheme 2.6).



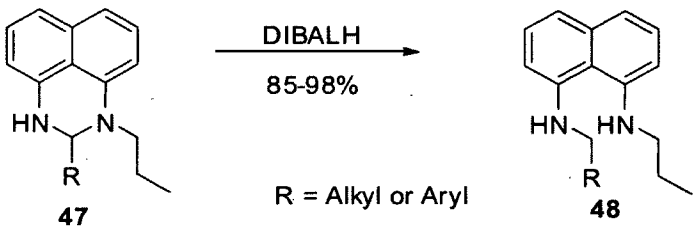
Scheme 2.7 Modified synthesis of compound 29 using Dean-Stark trap.

Several reactions were carried out with Dean-Stark trap and all the reactions successfully afforded the anticipated desired product **29**. ^{1}H NMR analysis showed presence of a mixture of *cis-* and *trans*-tricyclic bisaminals **29** with relative ratio of approximately 54:46, with the presence of residual solvent PhMe.

The complex mixtures obtained in previous attempts (Scheme 2.6) were heated under Dean-Stark trap but no conclusive result was obtained; ^{1}H NMR analysis still showed a complex mixture.

4. Synthesis of benzo[*b*]cyclam (**14**)

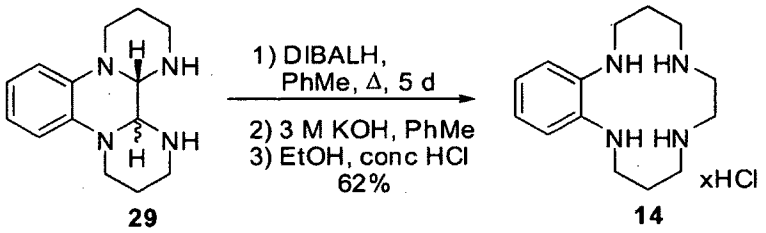
The next step is the regioselective ring expansion of the tricyclic bisaminal **29.** Yamamoto and Marouka[49] reported a highly regioselective reductive cleavage of C-N bond in cyclic amidines by diisobutylaluminum hydride (DIBALH) as shown in Scheme 2.8.



Scheme 2.8 Yamamoto's regioselective reductive C-N bond cleavage.

Reed employed the method of Yamamoto and Marouka for the highly regioselective reduction of compound **29** to benzo[*b*]cyclam (**14**). Repeating the same methodology, the *cis- and trans-* mixture of benzo-annelated tricyclic bisaminals **29** was subjected to the regioselective reductive ring expansion using excess DIBALH for 5 days. Following basic workup of the reaction, benzo[*b*]cyclam (**14**) was isolated successfully as a brown

oil. To prevent oxidation and avoid the necessity of further purification, compound **14** was dissolved in 95% EtOH and protonated with conc. HCl (12 M) to give a pink colored solid. This was recrystallized from absolute EtOH to give light pink colored solid of ≥ 96% purity in moderate yield of 62% (Scheme 2.9). Mass calculations indicate **14** is tri-protonated in the absence of water or di-protonated with some presence of water.



29 **14**

Scheme 2.9 The preparation of hydrochloride salt of benzo[*b*]cyclam 14.

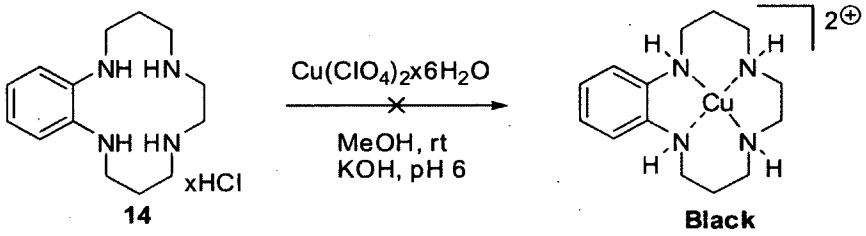
As discussed in the previous chapter, the above synthesis of benzo[*b*]cyclam (**14**) was first performed by former group member David Reed.[41] A different method employing the Buchwald-Hartwig amination was reported later in the literature[46] (Scheme 1.4). While it is a one pot reaction, it is very low yielding with undesired byproducts.

5. Attempted copper(II) complexation of benzo[*b*]cyclam (**14**)

Benzo[*b*]cyclam (**14**), a new variation of cyclam was synthesized for the first time. Coordination of transition metals to this new ligand **14** has not been reported. It's believed that the ligand will have similar coordinating ability to cyclam with various transition metal cations.

To study the complexation ability of **14**, complexation of **14** was attempted with Cu(II). The hydrochloride salt of benzo[*b*]cyclam (**14**) was dissolved in dry degassed MeOH and slightly less than one equivalent of copper perchlorate hexahydrate ($Cu(ClO_4)_2 \cdot 6H_2O$)

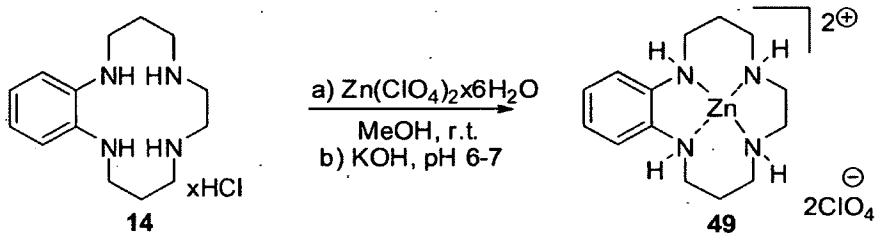
was added while N_2 was bubbled into the reaction mixture. The pH was adjusted to 6-8 by dropwise addition of aq KOH (0.3 M) with gentle stirring. The reaction mixture turned green and then black from which no UV or IR data could be collected. It is believed that ligand had undergone oxidation, accelerated by aqueous buffer in presence of traces of oxygen even in an anaerobic solution.[67] Ligand **14** is a redox active ligand and Cu(II) is a possible oxidant, it can reduce to Cu(I) which in turn can disproportionate to Cu(II) and Cu(0) (dark brown color).



Scheme 2.10 Attempted complexation of Benzo[*b*]cyclam with Cu(II).

6. Zinc (II) complexation of benzo[*b*]cyclam (**14**)

Since the first attempted complexation of the ligand was not successful, the next metal to investigate was Zn(II). Analogous conditions as above were used with zinc perchlorate hexahydrate ($Zn(ClO_4)\cdot 6H_2O$). The pH was adjusted from highly acidic (0-1) to neutral (6-7) by dropwise addition of aq KOH (0.3 M) (Scheme 2.11). The reaction was run for 2 days at room temperature while N_2 was bubbled through the solution, which upon workup yielded a red-brown solid.



Scheme 2.11 Zinc(II) complexation of benzo[*b*]cyclam (14).

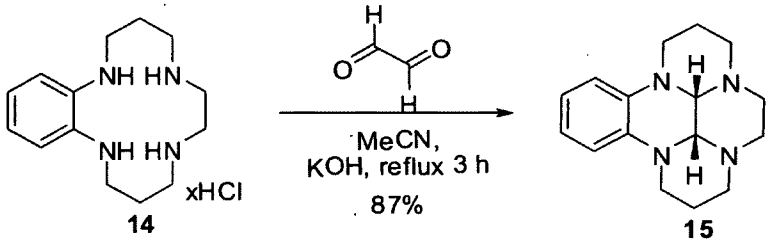
Comparing the ^{1}H NMR of the complex with the starting material showed the appearance of broad peaks and multiplets, evidence of successful complexation. ^{1}H NMR analysis showed the possible formation of two or more coordinated isomeric product, as there are small peaks in the upfield and downfield (aromatic) region. IR spectra showed the disappearance of the strong N-H stretching band at ~3250 cm^{-1} of the free ligand suggesting successful complexation. The N-H bending band at 1615, 1595 and 751 also decreased significantly. Washing the product with CH_2Cl_2 removed the red-brown color to afford an off-white solid. Slow ether diffusion to grow X-ray quality crystals was not successful.

B. Kinetic and Thermodynamic Alkylation and Protonation Studies of Benzo-annelated Tetracyclic Bisaminal (15)

1. Di-methylation studies of benzo-annelated tetracyclic bisaminal (15) using methyl triflate

The *cis*-fused tetracyclic benzo-annelated bisaminal (**15**) was prepared following Reed's method by glyoxal condensation with benzo[*b*]cyclam (**14**). Suspension of the hydrochloride salt of benzo[*b*]cyclam (**14**) in MeCN, subsequent addition of glyoxal solution (40 wt. % in H_2O), adjustment of the pH to 7 by addition of KOH pellets, and

refluxing the reaction mixture for 3 h resulted in an 87% yield of **15** as shown in Scheme 2.12.



Scheme 2.12 Glyoxal condensation of benzo[*b*]cyclam to prepare 15.

Chromatographic purification on basic Al_2O_3 using neat CH_2Cl_2 gave pure **15**. Variable temperature dynamic NMR experiments done by Reed demonstrated that the glyoxal adduct is a *cis*-fused bisaminal; this result was later confirmed by Condon's X-ray structure, which showed the spatial arrangements of the anilino and amino nitrogens as shown in Figure 2.1. As discussed previously, two of the four non-adjacent nitrogen lone pairs are oriented in an *endo* fashion pointing towards the cleft of the compound and the other two non-adjacent nitrogen lone pairs are oriented *exo* facing outside the cleft of the molecule.

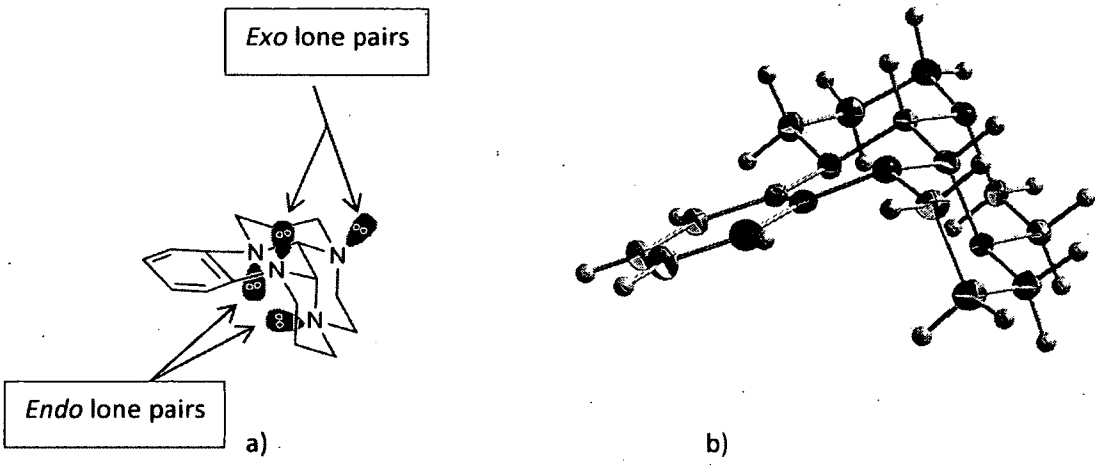


Figure 2.1 a) Conformation of *cis*-fused tetracyclic bisaminal 15 and

b) Crystal structure of compound 15 obtained by Condon.[17]

Both the *exo* and *endo* lone pairs are composed of one anilino and one amino lone pair. Reed attempted dimethylation using MeI assuming kinetically-controlled conditions aiming to get methylation at non-adjacent *exo* nitrogens (one amino and one anilino) (Scheme 1.6). However it was shown indirectly by Condon that the methylation takes place at adjacent amino nitrogens (Scheme 1.7). The X-ray structure of **15** illustrated that the anilino lone pairs are slightly twisted out of conjugation with the benzene ring as the result of the *cis*-fused tetracyclic bisaminal configuration. The sum of the *exo* anilino C-N-C bond angles is 345° making that nitrogen slightly pyramidal. This twisting and partial deconjugation of the anilino lone pairs from conjugation with the benzene ring makes the anilino lone pairs more nucleophilic than ordinary anilino lone pairs. Reed and Condon's methylation conditions were conducted for an extended period of 21 days, which might well correspond to thermodynamic conditions or at least allow an approach to equilibrium. Methyl iodide can undergo reverse S_N2 reaction in extended time as shown in Figure 2.2. Taking this into account, it was then hypothesized that methylation

should be investigated using a strong alkylating agent like methyl trifluoromethanesulfonate (methyl or 'magic' triflate) to get the bis-quaternary ammonium salt at non-adjacent *exo* nitrogen lone pairs. Using such a strong methylating agent under kinetically controlled conditions, it was expected that methylation at the accessible *exo* lone pairs would be the fastest.

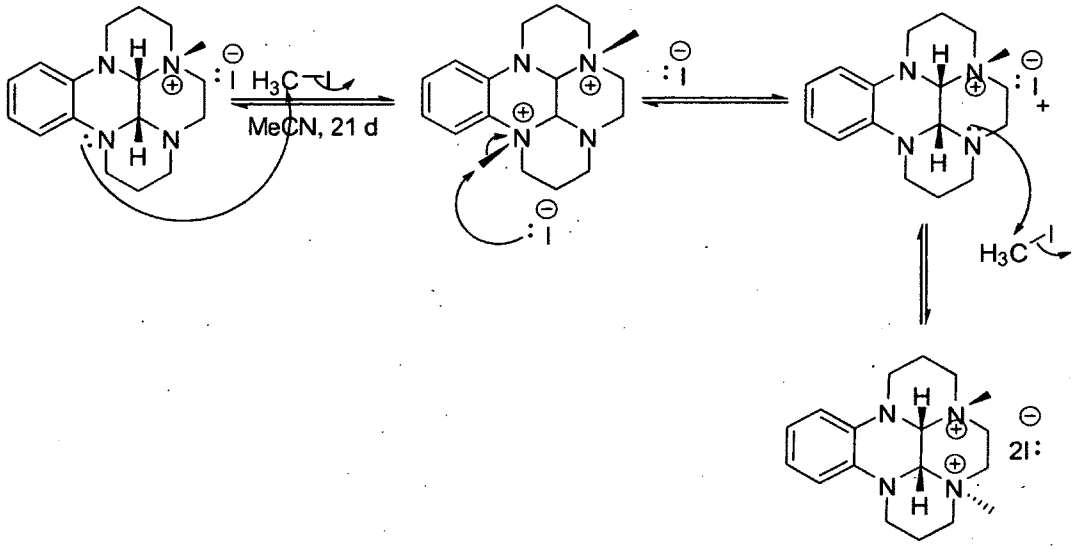
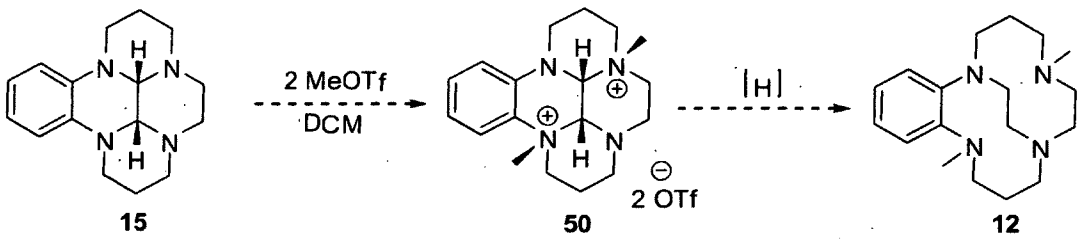


Figure 2.2 The S_N2 nucleophilic attack of iodide on methylated bisaminal 15.

Since triflate anion is a very weak nucleophile compared to iodide, the reverse nucleophilic substitution was not expected, thus providing kinetic control. Because of the easy steric accessibility of the *exo* oriented lone pairs, we hoped the methylation would occur at non-adjacent nitrogens on the convex side of the bisaminal (Scheme 2.13).

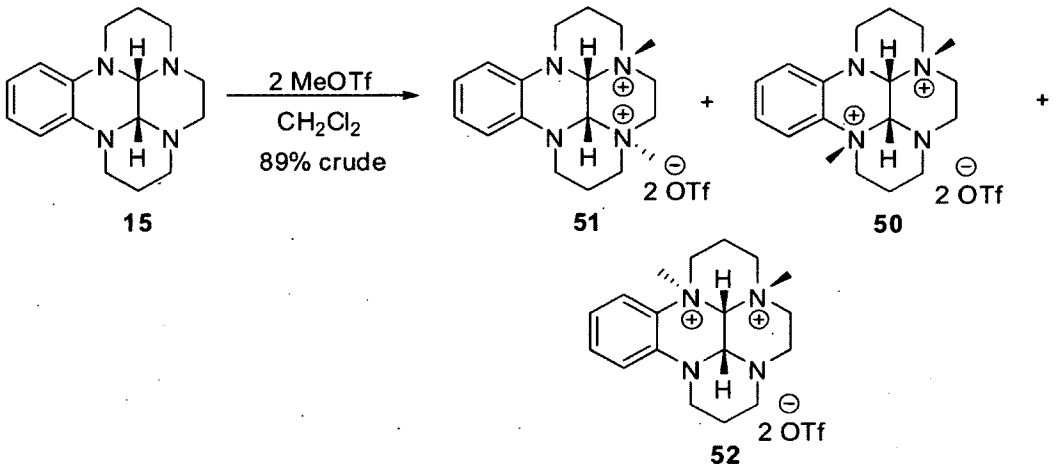


Scheme 2.13 Hypothesized synthesis of cross-bridged benzocyclam 12.

It is known that tertiary amino nitrogens are more basic and nucleophilic than anilino nitrogens. The initial methylation should take place at the more nucleophilic and accessible site which is the *exo* tertiary amino nitrogen, but due to the steric environment caused by the ligand cleft, the *endo* tertiary amino nitrogen will be less accessible. Therefore it was hypothesized that the second alkylation would kinetically take place at an *exo*-anilino lone pair. Reduction of the bis-quaternary ammonium salt **50** was expected to give the reductively ring opened desired product dimethylated benzo-annelated cross-bridged cyclam (**12**).

The dimethylation of benzo[*b*]cyclam-glyoxal adduct by methyl triflate **15** under different conditions was investigated. Trial (1) was the benzo[*b*]cyclam-glyoxal adduct **15** was dissolved in dry CH_2Cl_2 and two equivalents of methyl trifluoromethanesulfonate (MeOTf) was added dropwise via a gas tight syringe while stirring at -78 °C under nitrogen. [SAFETY NOTE: *This reaction should be carried out in a well-ventilated hood. Extra precautions are needed in handling MeOTf as it is a strong alkylating agent and very toxic if inhaled or through skin contact. It is also advisable to prepare the quenching agent (aq KOH) to decompose remaining any material. The MSDS should be consulted.*] The reaction was then warmed to room temperature and stirred for two days under N_2 atmosphere. Following two days of reaction and removal of solvent by rotary evaporation (40 °C bath) in a hood, product was collected as a foam/glass of crude yield 89% assuming all the crude material is dimethylated product. Although the ^{1}H NMR spectrum was complicated, it revealed the presence of three components of mixtures (**A**, **B** and **C**) having five aminal peaks between 5.0 – 6.5 ppm, where the peak at 5.65 ppm

corresponds to residual CH_2Cl_2 solvent but an aminal resonance is overlapped with it where it is clearly observed in other experiments. The sixth aminal peak that corresponds to the compound with aminal peak at 5.25 ppm may be buried among further upfield resonances. The $^{13}C\{^1H\}$ spectra showed three types of major carbon peaks totaling to 53 counts which also corresponds to three components (**A**, **B** and **C**) possibly dimethylated compounds on the basis of $^{13}C\{^1H\}$ at the upfield region. However, it is also possible that the third component could be a mono-methylated isomer, as the ^1H NMR spectrum showed only five *N*-methyl peaks that can correspond to two di-methylated and one mono-methylated species. Among the four dimethylated possibilities, the three most likely products that can be obtained are those resulting from dimethylation at non-adjacent nitrogens (**50**), dimethylation at adjacent amino nitrogens (**51**), and dimethylation at adjacent amino and anilino nitrogens (**52**) as illustrated in Scheme 2.14.



Scheme 2.14 Dimethylation of 15 using MeOTf resulting in three different stereoisomers.

An approximate ratio of 42:33:25 were identified for trial (1) corresponding to components **A**:**B**:**C** on the basis of $^{13}C\{^1H\}$ at the upfield region and ^1H NMR integration of the aminal peaks (where the aminal peak at 5.25 was doubled because its counter

aminal peak is buried among up field resonances). Upon comparison of the $^{13}C\{^1H\}$ spectrum with that of the dimethylated adjacent-bridged benzocyclam (**18**) synthesized by Condon, the major component **A** is identified to be **51**.The other two isomers show similar relative ratios and it is difficult to identify one from the other. Since the methylations were expected to be rapid, we also attempted to run the reactions at lower temperature where regio- and stereoselectivity of kinetically-controlled reaction would to be maximized. To investigate the role of time and temperature, two trails were run at at low temperature (-78 °C) and room temperature. Following a similar procedure, handling and safety precautions, the methyl triflate was added in one portion and two parallel reactions were run at 20 °C (trial 2) and -78 °C (trail 3) for 15 minutes. Each reaction mixture was worked up in the same fashion as above and each afforded similar crude yield of 89% and 90% of brown foam/glass solid, respectively assuming dimethylation. The ^1H and $^{13}C\{^1H\}$ NMR spectra (Figure 2.3) for the reaction at -78 °C (trail 1) were obtained in acetone-d_6 and the result were consistent with the spectra obtained in (trail 1) having a relative ratio of 50:26:24 corresponding to components **A**:**B**:**C**, component **A** (compound **51)** being the major component and the other two components exist in similar ratio . The $^{13}C\{^1H\}$ NMR (for trail 2) between 17.0 ppm and 20.0 ppm show six carbon resonances corresponding to the methylene carbons between two other methylene carbons next to the amino and anilino nitrogens indicating the presence of a mixture of three different compounds. However, for the reaction which run at room temperature for 15 minutes (trial 3), the relative ratio is 27:46: "27" corresponding to components **A**:**B**:**C**, and extra (fourth compound) at 20.61 and 20.53

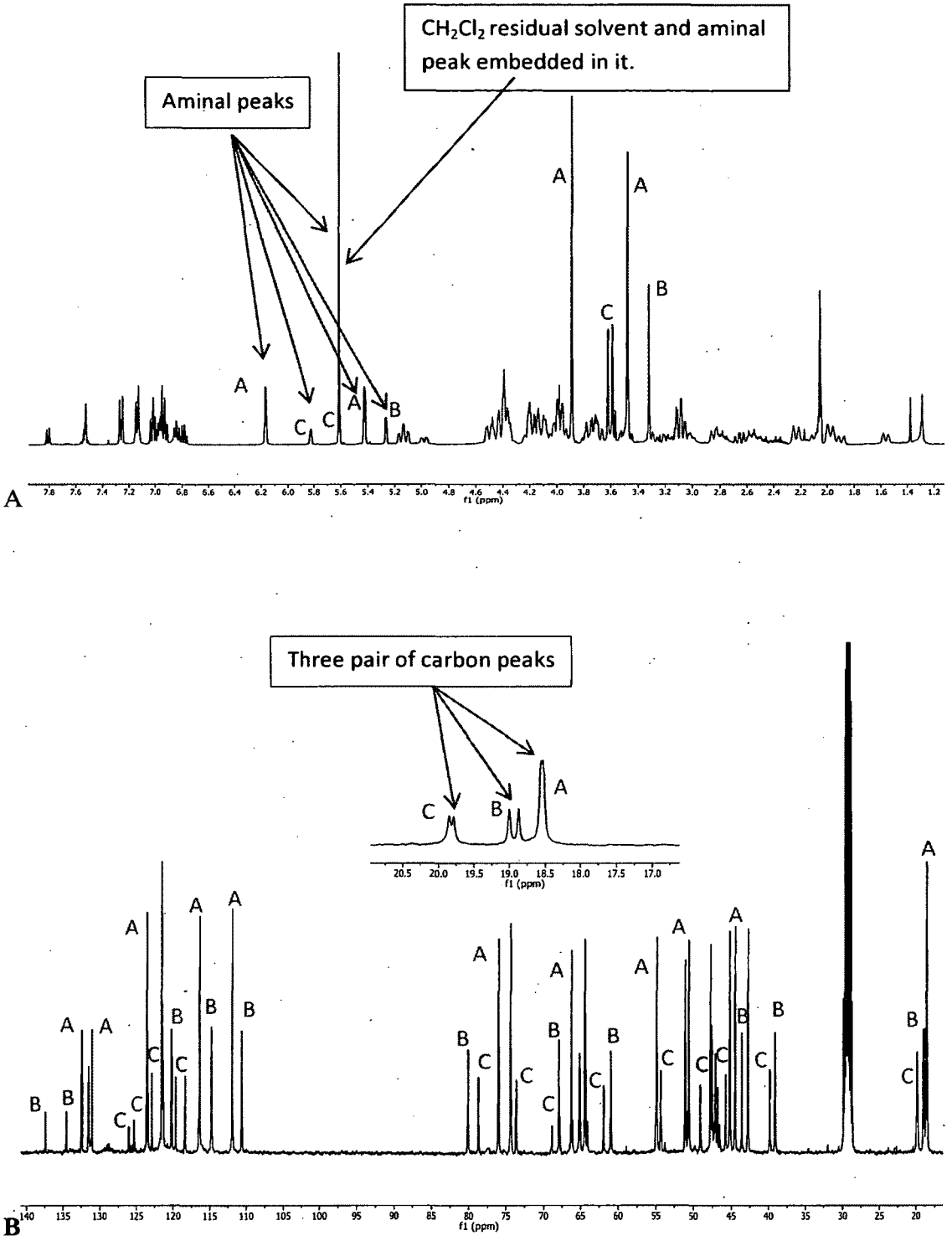


Figure 2.3 The ^{1}H (A) and $^{13}C\{^{1}H\}$ (B) NMR of the dimethylation reaction using MeOTf at -78 °C (Trial 2) labeled for three components.

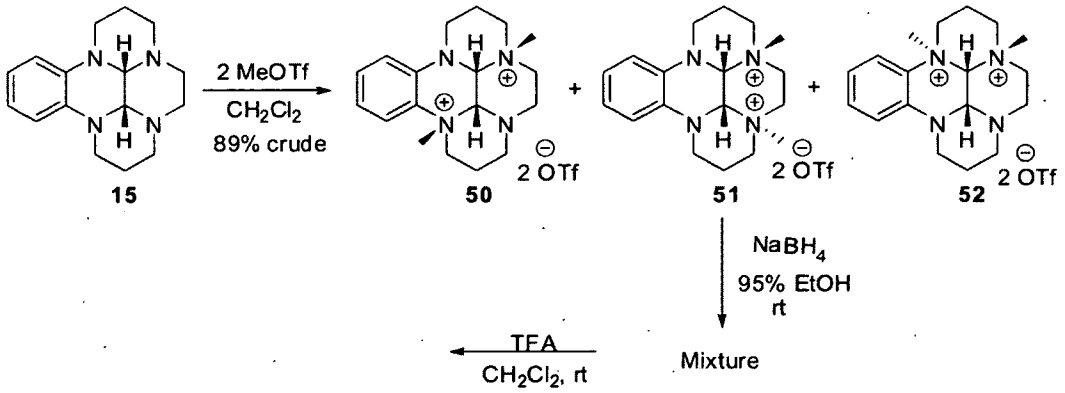
ppm was as observed at the upfield region of the $^{13}C\{^1H\}$ overlapped with either component **B** or **C**, and the ratio "27" included this new resonance. However, on the basis of ^1H spectra for *N*-methyl peak at 3.36 ppm and aminal peak at 5.25 ppm and also $^{13}C\{^1H\}$ spectrum at 19.60 and 19.47 ppm which grew higher for component **B** compared to the previous two experiments. On the basis of the above data and further mono-methylation studies discussed in later section, it can be rationalized component **B** could possibly be either the mono-methylated component which is the third candidate in the mixture as no other methyl peak was observed to grew higher or possibly the dimethylated compound **52**. The methylation was certainly taking place, but it was not selective. MeOTf, being a strong methylating agent, was methylating all of the nitrogens even at low temperature. The steric environment imposed by the cleft of the ligand was not enough to prevent methylation at *endo* lone pairs. However, it was suspected that alkylation might be taking place while concentrating the reaction mixture by rotary evaporation at 40 °C. In order to investigate this point, a different experiment (trial 4) was carried out at -10 to 0 °C for two days and the reaction mixture was concentrated at low temperature (≤ 0 °C). However, the result obtained following this experiment was similar to the previous reactions with a relative ratio of 49:30:21 corresponding to components **A**:**B**:**C** with an extra broad peak at 20.04 ppm. Component **C** most likely is the dimethylated compound **50** on the basis of methylation accessibility (*exo*-lone pairs) and sufficient nucleophilicity of the amino-nitrogen. The relative proportions of these components depending on $^{13}C\{^1H\}$ integration at upfield region and ^1H NMR integration of the aminal resonances in terms of components **A**:**B**:**C** are listed in the order of trials in Table 2.5.

	Trial 1 (-78 °C to rt) 2 d **A:B:C**	Trial 2 (-78 °C) 15 min **A:B:C**	Trail 3 (rt) 15 min **A:B:C**	Trail 4 (≤ 0 °C) 2 d **A:B:C**
$^{13}C\{^1H\}$[a]	42:33:25	50:26:24	27:46:27[c]	49:30:21
^1H[b]	40:33:27	52:26:22	33:48:19	42:36:22
Crude yield	89%	90%	89%	85%

Table 2.5 The relative ratio of the components and their crude yield.

a. based upon $^{13}C\{^1H\}$ integration at upfield
b. based upon ^1H integration of aminal peaks
c. extra set of peak was observed at the upfield region in $^{13}C\{^1H\}$

The crude mixture of product was reduced using $NaBH_4$ to see if simple spectra could be obtained; however, the data collected was not very helpful. The crude reaction mixture was then protonated with TFA to precipitate out any ammonium salt and isolate it as shown in Scheme 2.15, but this was also not productive.



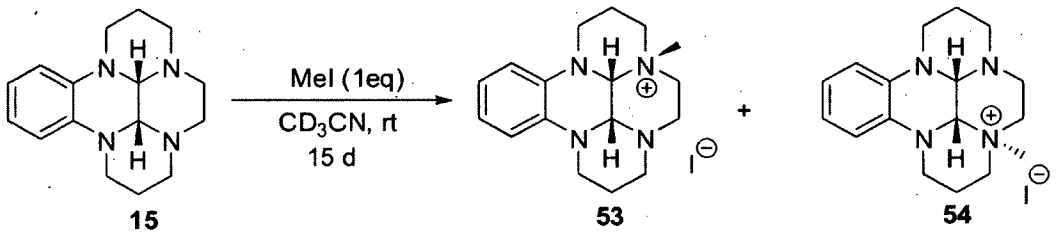
Scheme 2.15 Isolation attempt of the mixture of products.

The reaction was not as selective as we had anticipated for the methylation to occur at non-adjacent nitrogens. The *exo* and *endo* amino nitrogens are both sufficiently nucleophilic to undergo methylation. Methyl triflate is small in size which enables it to

undergo alkylation at the cleft (concave side) of the molecule; a bulkier alkylating agent could possibly give selective alkylation at the convex side of the molecule.

2. Mono-methylation studies of benzo-annelated tetracyclic bisaminal (**15**) using methyl iodide

An investigation and further study of the kinetic *vs* thermodynamic controlled product was carried out by methylating the benzo-annelated tetracyclic bisaminal **15** using one equivalent of methyl iodide (MeI). The experiment was carried out in an NMR tube by the addition of one equivalent of MeI to a solution of bisaminal **15** in deuterated acetonitrile (CD_3CN) as shown in Scheme 2.16.



Scheme 2.16 Monomethylation of bisaminal 15 using MeI.

The reaction was monitored using ^1H and $^{13}C\{^1H\}$ NMR for more than two weeks while sitting at room temperature to observe the progress of the reaction. After 20 hours at room temperature a minor amount of starting material was observed with two major products and one very minor product. Following 60 h, peaks which correspond to starting material were observed to disappear in the downfield aromatic region. By 90 hours all the starting material was consumed, as determined by both ^1H and $^{13}C\{^1H\}$ NMR, and no change was observed in the resonances and integration of the product resonances. However, due to the complexity of the ^1H NMR very little information was obtained, the aminal resonances which correspond to **53** show two doublets at 5.52 and 5.83 ppm and

the methyl resonance at 3.36 pp. While the aminal resonances which correspond to **54** show two doublet at 4.41 and 5.18 ppm and its methyl peak at 3.21 ppm. But $^{13}C\{^{1}H\}$ NMR showed a total of 34 carbon peaks, which corresponds precisely to the number of carbons present in a mixture of two mono-methylated stereoisomers. According to ^{1}H NMR integration of aminal resonances, the mono-methylation is not very selective, the relative ratio is (63:37) of (**53**:**54**) before heating. Presumably, product **53** existed as the major product due to the accessibility of *exo* lone pair and its strong nucleophilicity. Although the *endo* amino nitrogen can have the same inherent nucleophilicity as the *exo* amino nitrogen, it is slightly hindered by the cleft of the compound. Therefore under kinetic conditions a lower proportion of **54** might be expected. Subsequently the sample was heated in a closed vessel at 70 °C for 8 days, monitoring the progress by NMR. A gradual equilibration was observed and the relative ratio ultimately became (51:49) of the presumed *exo* methylated **53** to the presumed *endo* methylated **54**. The process was very slow as it approached equilibrium. But we cannot definitely say that the reaction has achieved equilibrium. It can be concluded that at this stage **53** and **54** have similar energy level, the steric effect favored isomer **53** is in almost equal amount with the anomeric effect favored isomer **54**.

3. Computational studies of mono-methylated benzo-annelated tetracyclic bisaminals **53** and **54**

In order to acquire relative energy data to compare to our experimental observations, geometry optimizations and energy calculations were carried out on **53** and **54**. A conformational search of the bisaminal **15** was first carried out in Spartan '10[68] using molecular mechanics force field calculations (MMFF) to give only one conformation, which was optimized using M06-2X at cc-pVTZ using Gaussian 09[69] (Figure 2.4).

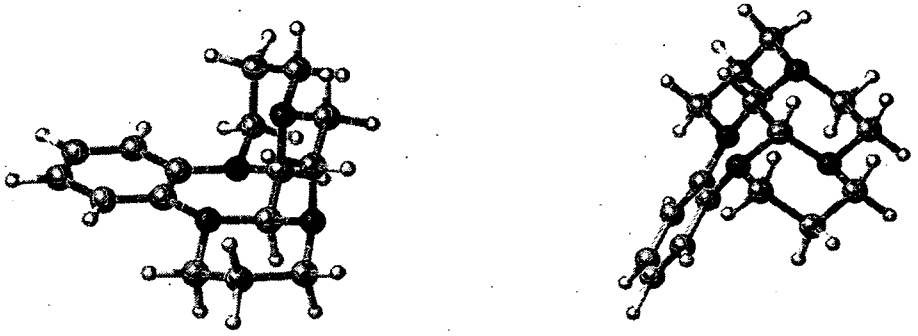


Figure 2.4 Optimized structures of 15 facing up and down using Gaussian 09 at M06-2X/cc-pVTZ adopted from CYLview[70]

Mono-methylation products **53** (*exo*) and **54** (*endo*) were modeled in Spartan '10 and imported in to Gaussian 09. Density functional theory (DFT) was used to calculate the relative energies of the two optimized stereoisomers using Gaussian 09. These structures were first run at lower DFT level of B3LYP/6-31+G(d) and further screened at higher-level of basis set B3LYP/6-311+G(p,d). Then the Truhlar M06-2X functional was used with a large basis set, M06-2X/cc-pVTZ. The relative energies of the stereoisomers are listed in Table 2.6. For each series of calculations, the *endo*-methylated stereoisomer showed consistently the lower relative energy in comparison to the *exo* isomer (difference of 3.59 to 3.91 kcal/mol) in all calculations. It can be explained that the *endo* methylated structure is the thermodynamic product as it is the lowest energy isomer in the gaseous phase. The stability of the *endo* isomer can be rationalized by considering the anomeric effect which has a dominant stabilizing effect of the amino-nitrogen's aminal bond which has an *endo*-substituent *antiperiplanar* to the anilino-nitrogen lone pair which creates a stabilizing resonance structure as shown in Figure 2.6.[71]

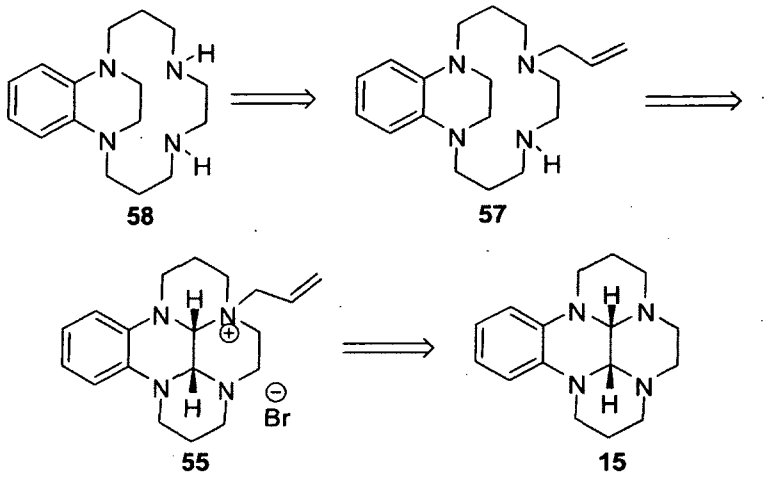
Calculations	*Exo*-methylated **53** Cation (kcal mol^{-1})	*Endo*-methylated **54** cation (kcal mol^{-1})	ΔE (*Exo-Endo*) (kcal mol^{-1})
DFT-B3LYP/6-31+G(d)	-881.64729195 a.u.	-881.65302013 a.u.	3.59
DFT-B3LYP/6-311+G(d, p)	-881.84660638 a.u.	-881.8525845 a.u.	3.75
M062X/cc-pVTZ	-881.57451858 a.u.	-881.58074826 a.u.	3.91

Table 2.6 The relative energy calculations of the two configurational diastereomers of mono-methylated bisaminal using Gaussian.[69]

In this case the experimental results observed agree to the computational energy calculation obtained. The major presence of the *exo*-methylated material at lower temperature can be explained by kinetic control reaction where the *exo*-amino lone pairs are strong nucleophiles and easily accessible and undergoes the S_N2 reaction fast (at higher rate) to get the major *exo*-methylated product. However, upon heating the mixture of isomers for few days, gradual increase of the *endo*-isomer was apparent. The *endo*-isomer is believed to be more stable due to the presence of anomeric effect, and the computational result also supports that hypothesis having lowest relative energy compared to exo-methylated isomer, which can be rationalized at higher temperature and extended time the isomers equilibrate and the *endo*-methylated species increases in concentration being the possible thermodynamic controlled product.

4. Allylation of benzo-annelated tetracyclic bisaminal **15**

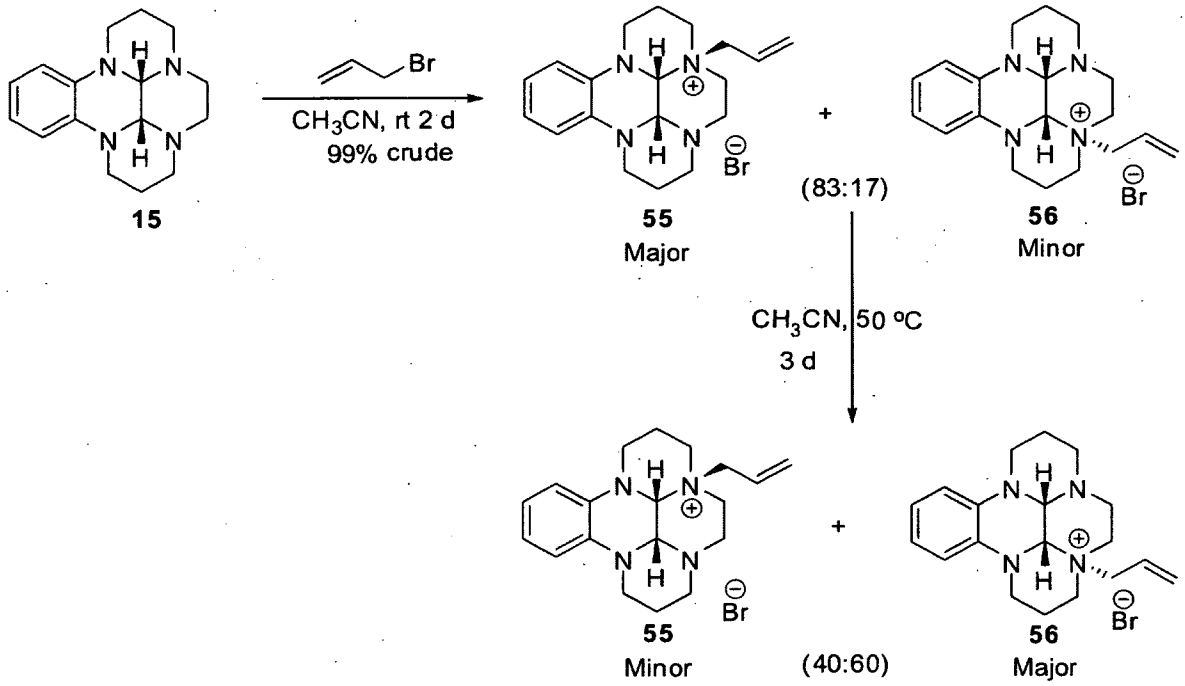
To further investigate the kinetics/thermodynamics of allylation and also shift the synthetic target to another interesting adjacent-bridged benzo-annelated ligand (**58**), the strong nucleophilicity of the amino nitrogens was utilized to allylate either one or both of the amino nitrogens.



Scheme 2.17 Retrosynthetic route 56 utilizing allylation and deallylation chemistry.

Allylation was expected to occur preferentially on the *exo* oriented amino lone pair, however there is a possibility of forming di-allylated material which could be deallylated in the subsequent steps (Scheme 2.17). The desired product **58** could then be prepared by the deallylation of synthetic intermediate **57.** Reductive ring expansion of allylated salt **55** will result in the formation of **57**. S_N2 reaction of compound **15** with allyl bromide was expected to lead to the formation of **55**. Allylation of the glyoxal adduct of benzo[*b*]cyclam (**15**) was done by stirring compound **15** in dry MeCN and in excess allyl bromide for 2 days, followed by work up to give brown solid in a crude yield of 99%. Due to the hygroscopic nature of the product several attempts to recrystallize the product with different solvent pairs failed to give pure product. The solvent pairs that were used in recrystallization attempts were: acetonitrile-diethyl ether, acetonitrile-hexanes, methanol-toluene, methanol-diethyl ether, methanol-chloroform, methanol-benzene. The ^{1}H NMR analysis of the crude product showed proton resonances between 5.50 and 6.20 ppm confirming successful allylation of the product. However due to the presence of many multiplets it was hard to assign the resonances to their corresponding protons.

$^{13}C\{^{1}H\}$ showed two isomers of allylated product with one being the major isomer than the other minor with the presence of a small amount of di-allylated postulated species of relative ratio (80:16:4) as illustrated in Scheme 2.18. The major mono-allyl isomer is presumably the *exo*-allylated isomer **55,** which is expected to be the kinetic product whereas the minor mono-allyl isomer **56** is hypothesized to be the result of allylation at the *endo* site of the amino lone pair which is hindered. In order to prove this hypothesis, the crude mixture was dissolved in acetonitrile and heated at 50 °C for 3 days to see if isomerization occurred (Scheme 2.18).

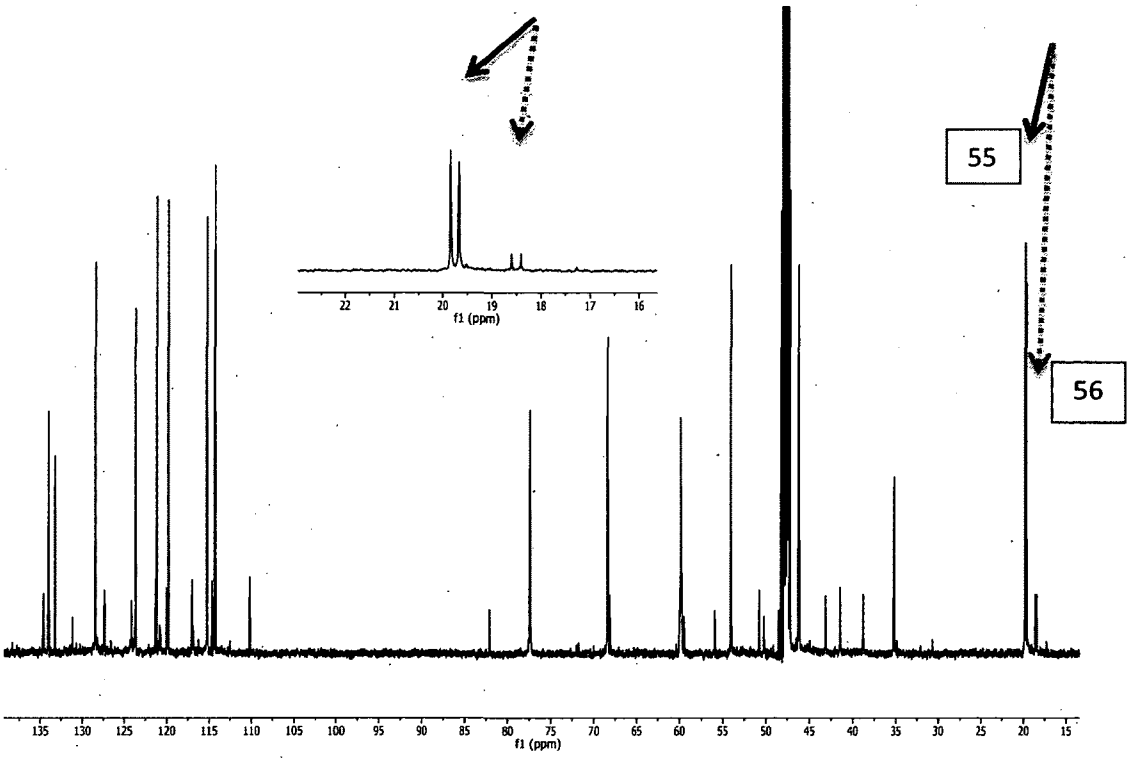


Scheme 2.18 Allylation of 25 and isomerization of 57 and 58.

After a few days of heating the reaction mixture, the ^{1}H NMR spectrum showed some changes; however, careful study of $^{13}C\{^{1}H\}$ NMR revealed a significant change in the ratio of the heights of the carbon peaks of the two isomers. The carbon resonances of the

initial major isomer before heating, presumed to be **55**, were observed to decrease significantly after heating. The carbon resonances of the initial minor isomer **56** increased after heating, becoming as the major isomer with relative ratio of (39:54:7). A small percentage of supposed di-allylated material was still present. Figure 2.5 shows $^{13}C\{^{1}H\}$ spectra before and after heating of the mixture.

A) Before heating



B) After heating

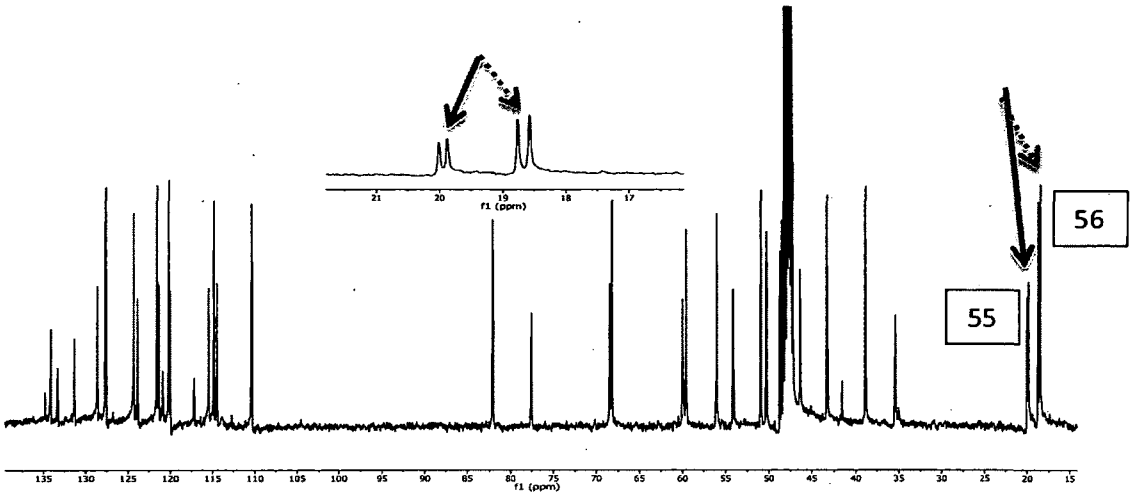


Figure 2.5 $^{13}C\{^{1}H\}$ NMR showing the isomerization of the allylated salt.

Our interpretation is similar to above for mono-methylation studies, in which this isomerization is due to the conversion of the possibly kinetically favored *exo*-product **55** into the more stable thermodynamically favored *endo*-product **56** after a few days of heating. The anomeric effect is hypothesized to stabilize the *endo*-allylated **56** [71] as illustrated in Figure 2.6 having a resonance stabilizing structure for the *endo*-substituted isomer, which doesn't exist for the *exo*-substituted isomer. This isomerization can also involve the free tetracyclic bisaminal (**15**) or traces of dialkylated material, both of which will facilitate the exchange of the allyl.

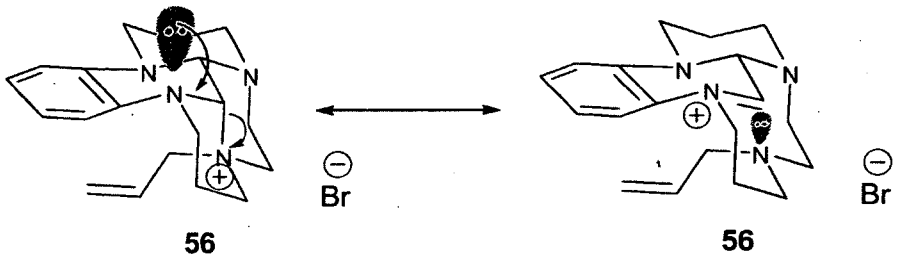
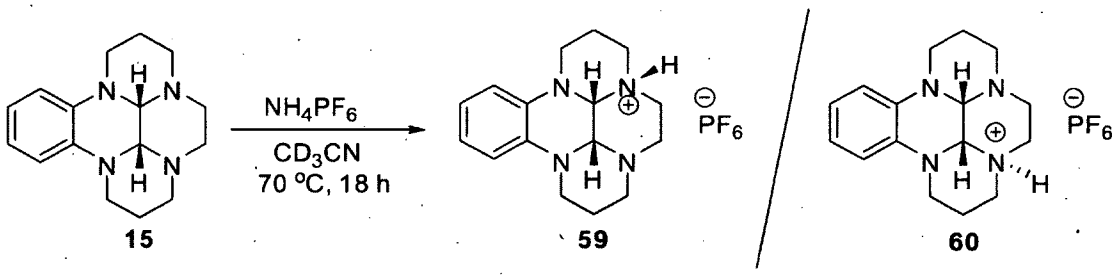


Figure 2.6 The anomeric stabilizing effect for compound 56.

5. Mono-protonation of benzo-annelated tetracyclic bisaminal and computational Analysis

Direct protonation of the tetracyclic bisaminal **15** using one equivalent of ammonium hexafluorophosphate (NH_4PF_6) was also investigated. Compound **15** and NH_4PF_6 was dissolved in CD_3CN and the mixture was heated at 70 °C for 18 hours (Scheme 2.19).



Scheme 2.19 Mono-protonation of bisaminal using NH_4PF_6.

^{1}H NMR of the reaction mixture showed more than 90% protonation of the bisaminal and also the presence of a water peak which disappeared after storing the reaction mixture over 3 Å molecular sieves for one day. The ^{1}H NMR also showed significant shift of the spectra downfield, especially the aminal peak, which had shifted from 3.80 ppm to 4.27 ppm. However, ^{1}H NMR after protonation showed only 9 resonances (2-fold symmetry). If compound **15** had been completely protonated at one site and proton transfer was slow, 11 resonances would have been observed. It is also noteworthy that if two isomers were present, the ^{1}H NMR spectrum would be much more complicated than the one observed. So the ^{1}H NMR must be the time averaged spectrum of mono-protonated species **59** and **60**. ^{13}C{^{1}H} NMR also confirmed protonation by showing dynamic broadening and slight downfield shifts, which resulted in overlapping of peaks. But based on ^{1}H and ^{13}C{^{1}H}

NMR analysis, unlike the methylation case studied above, no mixture of isomers were observed. At this stage no conclusion can be drawn as to whether the protonation has taken place at the *exo* lone pair to form **59** or at the *endo* lone pair to form **60**.

Computational calculations were carried out to determine the most energy favorable isomer between the two. The *exo* and *endo* protonated bisaminal was modeled in Spartan '10, and conformational distribution search was carried out using molecular mechanics force field (MMFF) for bisaminal **15** as above. These structures were then imported to Gaussian '09 and geometry optimization calculations were done using DFT methods and at higher-level of basis sets starting with B3LYP/6-31+G(d) followed by M062X/cc-pVTZ. The results obtained are listed in Table 2.7.

Calculations	*Exo*-protonated **59** cation ($kcalmol^{-1}$)	*Endo*-protonated **60** cation ($kcalmol^{-1}$)	ΔE (*Exo-Endo*) ($kcalmol^{-1}$)
B3LYP/6-31+G(d)	-842.34202844 a.u.	-842.35033980 a.u.	5.26
M062X/cc-pVTZ	-842.27257941 a.u.	-842.28112066 a.u.	5.36

Table 2.7 Conformational relative energy calculations of exo and endo protonated bisaminal using Spartan '10[68] and Gaussian '09.[69]

The table above showed that the *endo*-protonated conformer having the lower relative energy of 5.26 to 5.36 kcal/mol compared to the *exo*-protonated species. Although a time averaged ^{1}H NMR spectrum is observed as discussed above, the major component could possibly be the *endo*-protonated isomer which resulted after heating the reaction mixtures

at extended time. Similar to the discussions above in the cases of methylation and allylation, it can be rationalized that the *endo*-protonated bisaminal would be the more stable and thermodynamically product as a consequence of the favorable anomeric effect for *endo*-protonated salt.

C. Synthesis and Characterization of the Adjacent-bridged Benzo-annelated Cyclam (2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (58))

1. Failed attempt to reduce benzo-annelated tetracyclic bisaminal (15)

One of our goals was to synthesize the cross-bridged benzo-annelated cyclam **12**. Several methods and approaches had been attempted by previous students in the Weisman-Wong group, including efforts to synthesize **12** as reported in this thesis. Unfortunately **12** was unable to be prepared, and further research and study would be needed to prepare the target material. We are also interested in the synthesis and transition metal complexation investigation of another bridged variation of benzo[*b*]cyclam, where the ligand is structurally reinforced to form benzo-annelated cyclam with the adjacent-nitrogens bridged with an ethylene unit (**58**), which would be able to adopt trans coordination geometry when coordinated with transition metal cations.[72] Derivatives of ligand **58** could be prepared by attaching pendant arms to the nitrogens. Such derivatives could serve as bifunctional chelator (BFC) for bio-conjugation to proteins or peptides. As it was discussed in the background of this section, Condon has synthesized the dimethylated adjacent bridged benzocyclam (**18**) (See Scheme 1.7) during his attempt to make the cross-bridged benzo[*b*]cyclam (**12**). However, the synthesis of the di-NH analogue **58** (Figure 2.7) has never been reported.

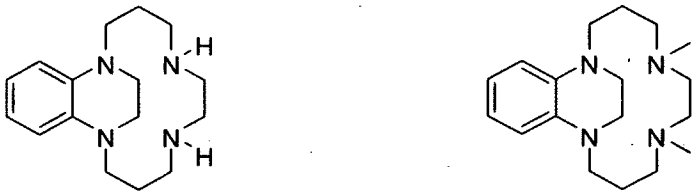
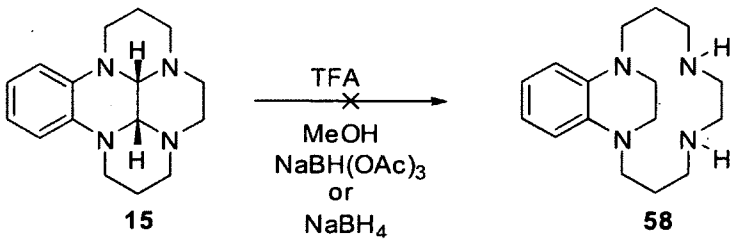


Figure 2.7 The proposed structurally reinforced adjacent-bridged di-NH (58) and the dimethylated adjacent-bridged benzo[*b*]cyclam (18) by Condon.

In an effort to prepare the adjacent-bridged **58** the first proposed method was to reductively ring open *cis*-fused tetracyclic bisaminal **15** under acidic conditions. The tertiary amino nitrogens are more basic than the anilino nitrogens, so we expected the protonation to take place at these tertiary amino nitrogens. The reaction was carried out using trifluoroacetic acid (TFA) in MeOH as the proton source and sodium triacetoxyborohydride ($NaBH(OAc)_3$) as the reducing agent (Scheme 2.20). Upon addition of $NaBH(OAc)_3$ the reaction evolved H_2 gas and was run at room temperature. After 7 days of stirring, the excess reducing agent was quenched with 3 M aq HCl, and following basic work up and extraction, the crude product material was analyzed by ^1H NMR. Unfortunately the material obtained was found to be starting material with a decent percent recovery of 81%.

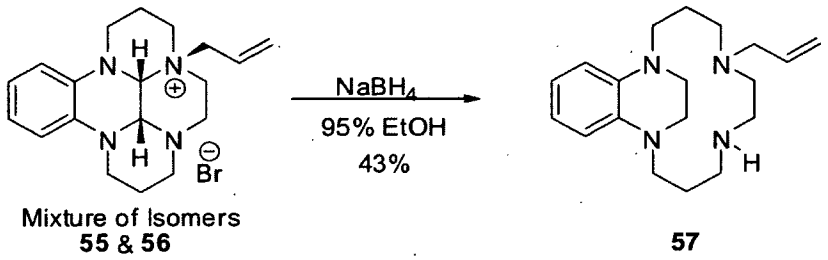


Scheme 2.20 Failed synthesis of 58.

Since this methodology didn't afford the desired product, a different synthetic route was designed to get the desired product that involved allylation, reductive ring opening, and then deallylation to get target compound.

2. Synthesis and characterization of adjacent-bridged benzo-annelated cyclam (**58**)

As discussed above in the retrosynthetic path of Scheme 2.15, the next step that was required for the synthesis of **58** was reductive ring opening of the mixture of allylated salt **55** and **56.** The mixture of *exo* and *endo* allylated bromide salts **55/56** was reduced using a mild reducing agent $NaBH_4$ in 95% EtOH at room temperature as illustrated in Scheme 2.21.



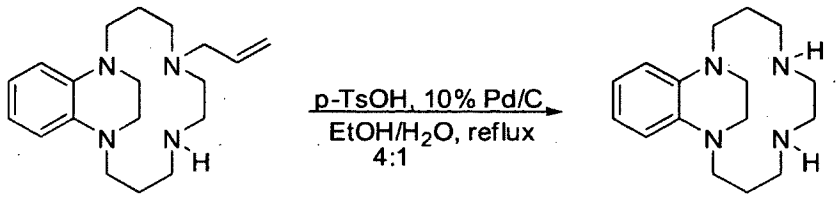
Scheme 2.21 Reductive ring opening of the mixture of 55 and 56

Following a 3 M aq HCl acid quench and workup, crude product **57** was obtained as yellow oil (crude mass recovery of 86%). Several attempts to purify and fully characterize this product were not successful. Chromatography through basic alumina using (1-3%) MeOH and CH_2Cl_2 was the first to be attempted and it gave the best purity of ~90%. Protonation with conc HCl and attempted recrystallization of the precipitate from EtOH didn't yield nice crystals because the material oiled out during the filtration (the compound is hygroscopic). ^1H NMR analysis of the oily hydrochloride salt indicated the presence of pure material, however after base workup was performed the ^1H NMR of

the free compound didn't look as pure as its salt form. Another purification attempt involved chromatography on silica using (2-10%) *i*-$PrNH_2/CHCl_3$. This method also afforded a purity of ~90% by ^1H NMR. Normal-phase chromatography on silica using 10% MeOH and CH_2Cl_2 didn't produce a satisfactory result either. One of the impurities present included the *cis*-fused tetracyclic bisaminal **15** (very high R_f value of 0.9), formed by deallylation of **55/56**. Another impurity that coelutes with the desired compound has a very similar R_f value, where only one spot can be seen by TLC. However, ^1H NMR reveals the presence of the impurity. Therefore it was hard to separate one from the other. The best purified product that was obtained in 43% yield with ~90% purity. It was finally concluded that crude product **57** would have to be carried on through the next step.

Once the reductively open adjacent-bridged monoallylated benzocyclam **(57)** was formed, it was necessary to deallylate (deprotect) the amine to the free secondary amine. Deallylation was first attempted using Pd(0) catalyzed deallylation was carried out in the presence of *para*-toluenesulfonic acid (*p*-TsOH) and (4:1) ratio of absolute EtOH to H_2O.[73] The reaction takes place through Pd(0) isomerization of the allyl to an enamine and subsequent acid catalyzed enamine hydrolysis to the secondary amine. This experiment was first conducted with 100 wt % of 10% Pd/C (palladium on activated carbon), 1.5 equivalents of p-TsOH using (4:1) EtOH:H_2O in concentration of (0.03 M). After 20 hours of reflux and aqueous workup followed by normal phase chromatography using basic alumina and 5% $MeOH/CH_2Cl_2$, the desired product was obtained in 34% yield as off-white solid. It is noteworthy that the yield is approximate since the starting material was impure. ^1H and $^{13}C\{^1H\}$ analysis confirmed the successful formation of the

desired product adjacent-bridged benzo[*b*]cyclam (**58**) as illustrated in Scheme 2.22. However, upon trying to optimize the reaction conditions using lower catalyst loading and at higher concentration as shown in Table 2.8, entry 2, the reaction did not produce the desired product, but returned starting material. It was necessary to step back and study the original successful reaction. The initial reaction conditions were repeated in an effort to reproduce the result. This time the reaction failed to produce the desired product, giving instead a complex mixture. The purity of starting material and reagents were verified. A freshly opened bottle of 10% Pd/C was also used to carry out the reaction. Unfortunately this reaction didn't produce the desired product. The catalyst loading was increased to as high as 150 wt % of starting material at higher concentration with various reaction times in an effort to force the reaction, as indicated in entry 4, resulting in a mixture of desired product and undesired product. The attempts conducted at different catalyst loading, concentration and reaction time are listed in Table 2.8.



57 **58**

Scheme 2.22 The synthesis of the adjacent-bridged benzo[*b*]cyclam 58

Leon Wong, a previous group member who had studied the conditions for deallylation reaction on a cross-bridged cyclam, found that deallylation reaction was favored at low catalytic loading of 10-15 wt % and in a dilute reaction of 150-220 mL/g of starting material. In his studies, he observed that reaction times of more than 4 hours and the use

of high concentrations gave unwanted byproducts.[74] Following Wong's advice similar reaction conditions were tried as shown in entry 6 of Table 2.8 and the reaction was monitored by ^{1}H NMR. After 30 hours at reflux, complete deallylation was observed.

Entry	10% Pd/C Wt. %	Concentration (M)	Time (h)	Yield (%)
1	100	0.0321	20	34
2	17	0.1450	18	a
3	100	0.0493	22	b
4	150	0.0374	5	c
5	100	0.0158	72	b
6	15	0.0186	31	31
7	15	0.0176	30	42

a = starting material b = complex (unknown) mixture
c = mixture of desired product and unknown

Table 2.8 Investigation of reaction conditions for the deallylation 57.

The same reaction conditions were repeated entry 7 and were able to be reproduced, and these reaction conditions were concluded to be the best for this deallylation reaction. The desired product, adjacent-bridged benzo[*b*]cyclam (**58**) was thus synthesized using the above conditions. After base work up and purification using reversed-phase chromatography silica C-18 (gradient elution 5-20% MeCN/H_2O (1%TFA)), the novel ligand (**58**) was obtained in a moderate yield of 42% and excellent purity.^{1}H spectra confirmed the disappearance of the allyl peaks between 4.8 and 5.8 ppm, and formation of **58.** $^{13}C\{^1H\}$ spectra revealed 8 carbon peaks having three peaks at the downfield aromatic region corresponding for the benzene carbons and the remaining five

corresponds to the methylene carbons indicating a time averaged symmetry of **58**. Full characterization of compound **58** was completed by 2-D NMR (COSY and HSQC), IR, and HRMS (ESI+), with the spectrum exhibiting the appropriate *m/z* [M+H] ion at 275.2207.

3. Computational conformation analysis of adjacent-bridged benzo-annelated cyclam (**58**)

Attempts to obtain X-ray quality crystals of **58** were not successful, yet the determination of the most favorable conformation of this novel compound was a point of interest. The structure of **58** has a very flexible 14-membered ring with two secondary amines, and it would be very interesting to know the most stable conformation of this structure. One might expect transannular hydrogen bonding between the amine hydrogens and the anilino nitrogens. In order to study and investigate the conformations, a computational conformational search was first performed using a molecular mechanics force field (MMFF) in Spartan '10,[68] which gave 100 different conformations. The first 30 conformations with lowest relative energies between 0.0 kcal/mol to 8.30 kcal/mol were selected. These structures were re-optimized using DFT at the B3LYP/6-31G(d) in Spartan '10. This optimization screened and narrowed the selection of conformations to seven structures within the range of 2.00 kcal/mol relative to the global minimum. These seven structures were further geometry-optimized at higher level of basis set B3LYP/6-311+G(d, p) using DFT in Spartan '10 to give the relative energies in gas phase shown in (Table 2.9).

Label	rel. E (kcal/mol)
M0001	0
M0010	0.01
M0011	0.66
M0007	0.86
M0006	0.97
M0005	1.66
M0026	2.4

Table 2.9 Relative energies of calculation using DFT method at B3LYP/6-311+G(d, p) for compound 58.

These conformations show the amine N-Hs orienting themselves towards the anilino nitrogens forming H-bonds (Figure 2.8). This result was further re-optimized at higher level of basis set using DFT M06-2X at cc-pVTZ in Spartan '10, the relative energies obtained ranged from 0.0 to 3.07 kcal/mol and are shown in (Table 2.10). The results obtained using M06-2X/cc-pVTZ compared to the previous optimization at DFT/ B3LYP/6-311+G(d, p) are significantly different, showing the lowest energy conformer in B3LYP/6-311+G(d, p) was no longer the lowest energy conformer in M06-2X/cc-pVTZ as shown in Table 2.11.

Label	rel. E (kcal/mol)
M0011	0
M0001	1.28
M0007	1.42
M0006	1.54
M0005	3.01
M0010	3.03
M0026	3.07

Table 2.10 Relative energies calculations using M06-2x/cc-pVTZ for compound 58.

Label	rel. E (kcal/mol) B3LYP/ 6-311+G(d, p)	rel. E (kcal/mol) M06-2X/ cc-pVTZ
M0011	0.66	0.00
M0001	0.00	1.28
M0007	0.86	1.42
M0006	0.97	1.54
M0005	1.66	3.01
M0010	0.01	3.03
M0026	2.4	3.07

Table 2.11 Relative energy comparison between B3LYP/6-311+G(d, p) and M06-2x/cc-pVTZ for compound 58 conformer.

The lowest relative energy conformer of **58** obtained using the basis set M06-2X/cc-pVTZ is shown in Figure 2.8. The figure shows the two hydrogens of the secondary amine orienting themselves towards the anilino nitrogens to form transannular hydrogen bonds.

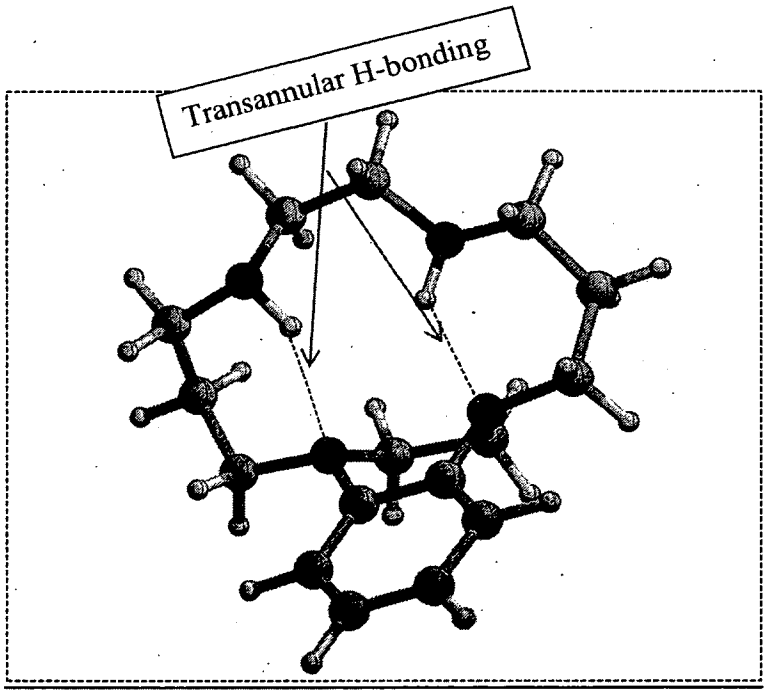
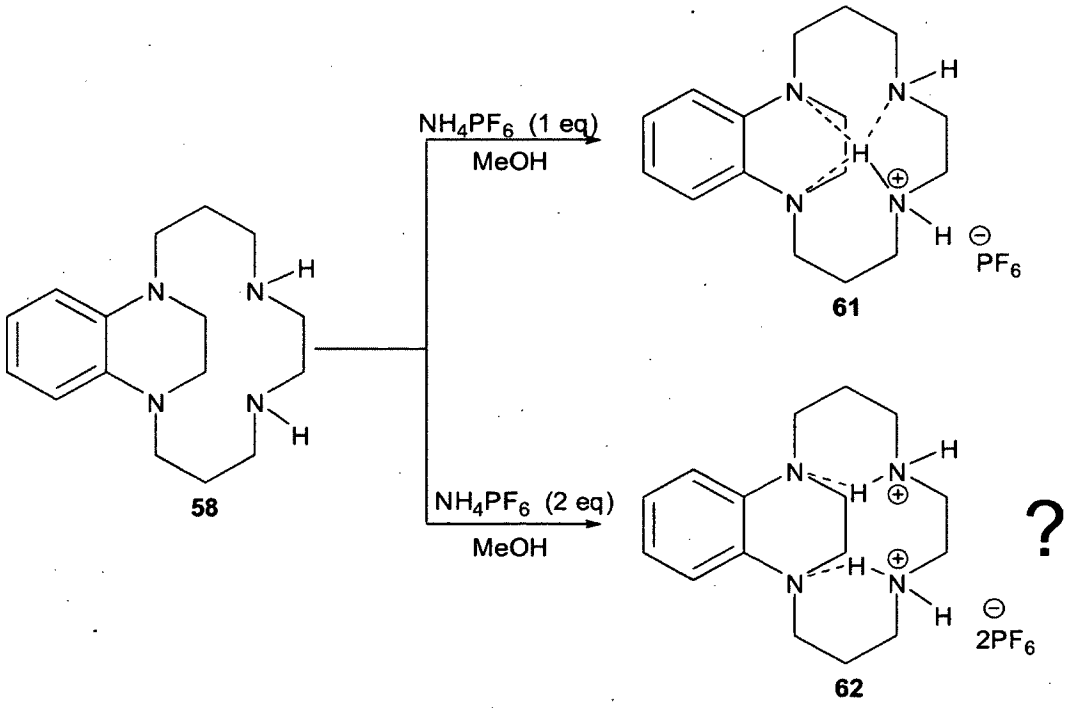


Figure 2.8 The lowest energy conformer calculated using Spartan at M06-2X/cc-pVTZ[68] from CYLview.[70]

4. Experimental and computational studies of mono and di-protonated adjacent bridged benzo-annelated cyclam (**58**)

The free adjacent-bridged **58** was protonated with one or two equivalents of ammonium hexafluorophosphate (NH_4PF_6) to investigate the mono- and diprotonate conjugate acids respectively, as illustrated in Scheme 2.23. This study also investigated the possibility of transannular hydrogen bonding between the new ammonium proton and the amino and/or anilino nitrogens of the mono and diprotonated species. ^{1}H NMR spectra of these experiments showed successful protonation and shifted to downfield, similar resonances were observed for the supposed mono- and diprotonation attempts, indicating only mono-protonation took place even with two equivalents of NH_4PF_6.



Scheme 2.23 Investigation of mono- and diprotonation of ligand 58.

This can be interpreted that, once the mono-protonation has taken place, the formation of hydrogen bonds between an ammonium N-H and the other nitrogen lone pairs decreases

the basicity of the other nitrogens. The above hypothesis would have been proved if an X-ray structure of these protonated ligands were obtained. In order to access X-ray quality crystals slow ether diffusion experiments with various solvent pairs are underway. Mono-and di-protonated structures of the adjacent-bridged **58** was modeled in Spartan '10. A conformational search using molecular mechanics (MMFF) was performed and the conformers with the lowest relative energies between 0.0 and 5.0 kcal/mol were selected.

DFT/B3LYP/6-31G(d)		DFT/B3LYP/6-311+G(d, p)	
Label	rel. E (kcal/mol)	Label	rel. E (kcal/mol)
M0031	0	M0031	0
M0019	0.22	M0019	0.26
M0024	0.60	M0024	0.47
M0011	0.64	M0017	0.76
M0020	0.81	M0016	0.84
M0017	0.81	M0011	0.87
M0016	0.94	M0020	1.05
M0021	1.42	M0021	1.18
M0013	1.59	M0013	1.61
M0006	1.67	M0033	1.75
M0029	1.68	M0030	1.81
M0010	1.71	M0029	1.98
M0030	1.74		
M0033	1.79		

Table 2.12 Relative energy values for mono-protonated compound 61 using B3LYP/6-31G(d) and B3LYP/6-311+G(d, p).[69]

DFT/B3LYP/6-31G(d)		DFT/B3LYP/6-311+G(d, p)	
Label	rel. E (kcal/mol)	Label	rel. E (kcal/mol)
M0001	0	M0001	0
M0003	0.58	M0003	0.63

Table 2.13 Relative energy values for di-protonated compound 62 using B3LYP/6-31G(d) and B3LYP/6-311+G(d, p).[69]

These conformers for both compounds were then further screened using the DFT method at B3LYP/6-31G(d) and narrowed to relative energy between 0.0 to 2.0 kcal/mol resulting in 14 conformers for mono- and 2 conformers for di-protonated. These conformers were then re-optimized at a larger basis set (B3LYP/6-311+G(d, p)). The final calculation resulted in 12 conformers for the mono-protonated species and 2 conformers for the di-protonated compound between 0.0 to 2.0 kcal/mol.

Relative energy values are given in Table 2.12 and Table 2.13 for mono-protonated **61** and diprotonated **62** respectively.

A.

B.

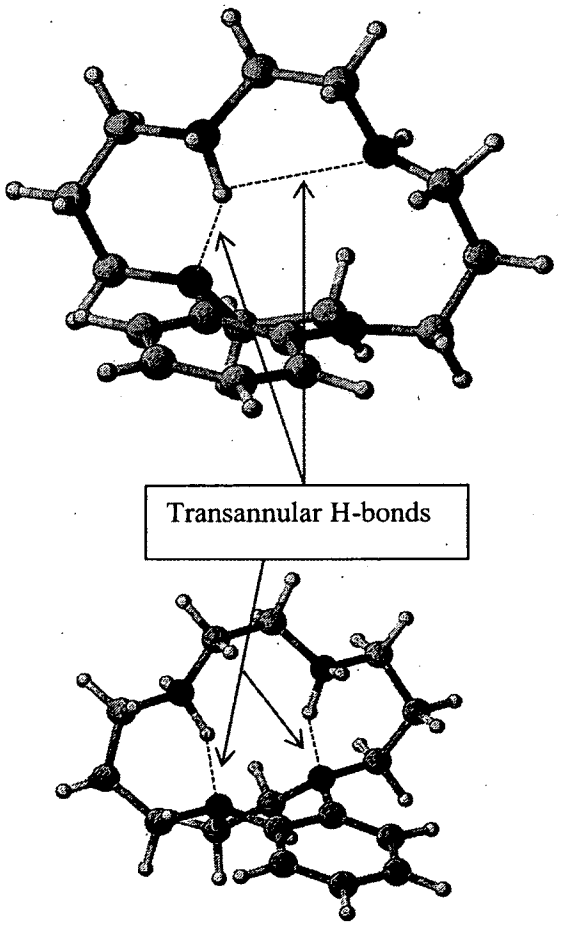
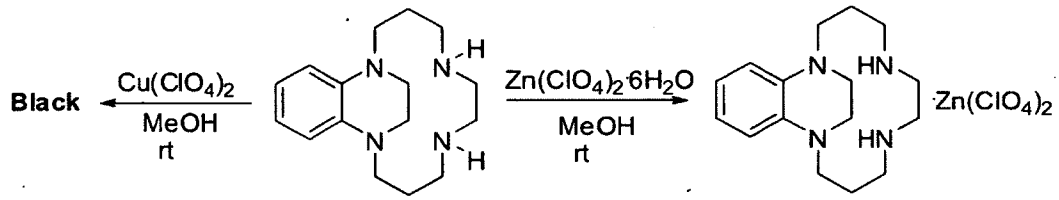


Figure 2.9 The lowest energy conformers of: (A) mono-protonated compound 61 and (B) diprotonated compound 62 calculated using Spartan at B3LYP/6-311+G(d, p)[68] from CYLview.[70]

5. Zinc (II) complexation of adjacent bridged benzo-annelated cyclam (**58**)

An initial investigation towards metal complexation of the adjacent-bridged benzocyclam **58** was first carried out with copper(II). The ligand **58** was dissolved in a dry degassed MeOH and was bubbled with N_2 gas. Slightly less than one equivalent of copper perchlorate hexahydrate ($Cu(ClO_4)_2 \cdot 6H_2O$) was allowed to react with the solution. Following a few seconds of reaction at room temperature while N_2 gas was bubbling through the solution, the blue reaction mixture turned to dark black. The reaction was continued for 24 hours at room temperature. No useful data could be obtained from the reaction mixture. This complexation attempt suggests that ligand **58** is a redox non-innocent ligand and Cu(II) can oxidize the ligand and get reduced to Cu (I). Cu(I) can disproportionate into elemental Cu(0) and Cu(II). Since Cu(0) is a dark brown solid, the dark color of the reaction mixture could be a result of this disproportionation or due to possible oxidation of non-innocent ligand **58**. A possible oxygen assisted oxidative decomposition could have also taken place. Sadly, similar properties were observed in the investigation of copper(II) complexation with benzo[*b*]cyclam **14**, which is another non-innocent ligand.

The next metal candidate for the investigation of coordination chemistry was zinc(II), since a promising result was obtained when studying the complexation of benzo[*b*]cyclam **14** with the same metal. The complexation of the adjacent-bridged ligand **58** with zinc was performed, using one equivalent of zinc perchlorate hexahydrate ($Zn(ClO_4)_2 \cdot 6H_2O$) in MeOH at room temperature for 20 h as illustrated in Scheme 2.24.



58 63

Scheme 2.24 Transition metal complexation of 58.

Following centrifugation to remove small insoluble particles and concentration by rotary evaporation, off-white to yellow glassy solid of crude yield of 73% was obtained. Zinc complexation was judged to be successful on the basis of the ^{1}H NMR spectrum (Figure 2.10).

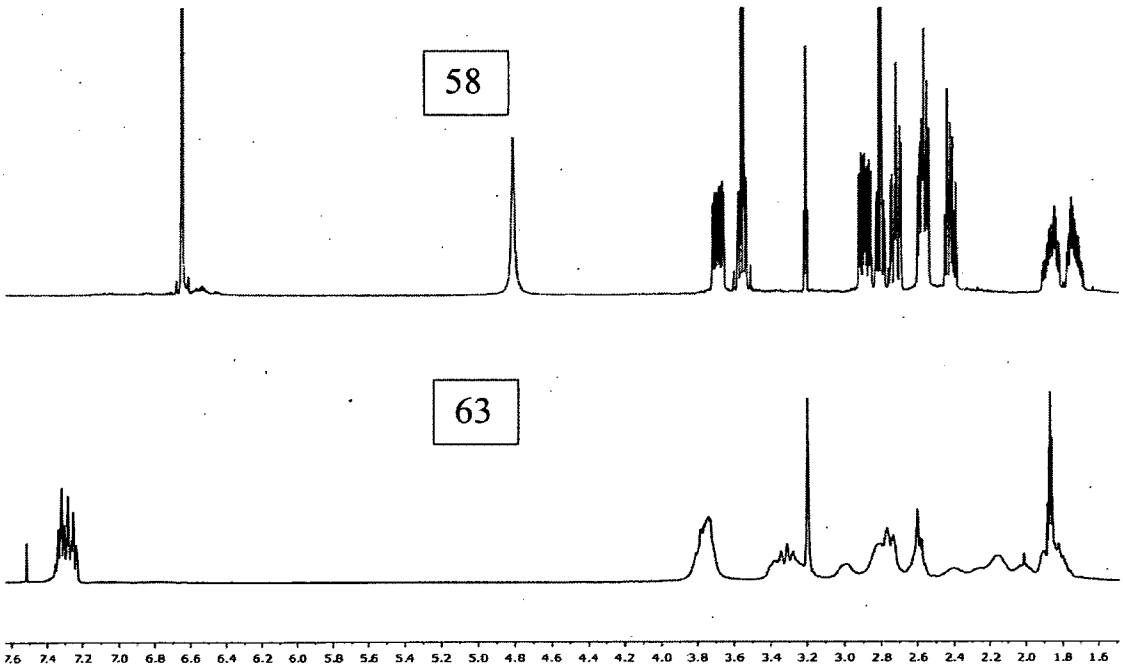
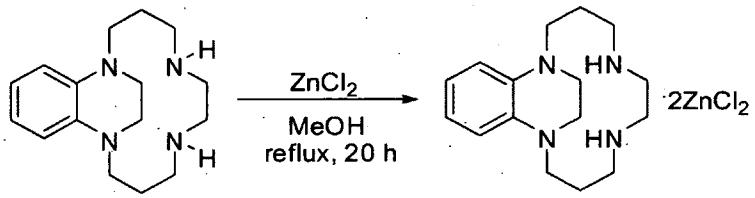


Figure 2.10 ^{1}H NMR spectra of 58 before complexation and 63 after complexation with $Zn(ClO_4)\cdot 6H_2O$.

Resonances of the ^{1}H NMR spectrum of **63** shifted downfield, particularly in the case of the aromatic protons, which shifted from 6.65 ppm to ~ 7.30 ppm. A dynamic broadened

set of peaks were observed in the upfield region. Purification through slow ether diffusion was attempted, but unfortunately no X-ray quality crystals were produced. Another zinc coordination was carried out using anhydrous zinc chloride ($ZnCl_2$) in an attempt to get a better purity product for X-ray. A solution of ligand **58** in MeOH was combined with two equivalents of anhyd $ZnCl_2$ in a glove bag (Scheme 2.25). A precipitate was observed during the addition of $ZnCl_2$. After refluxing for 24 hours, centrifugation to remove some insoluble solids, and rotary evaporation, a brown solid was obtained. ^{1}H NMR spectroscopy showed a significant downfield shift of the resonances, with very broad peaks suggesting successful complexation of the ligand with zinc. The presence of a mixture of isomers of the complex material is possible as there are two sets of major resonance in ^{1}H NMR. Slow ether diffusion is underway in an effort to purify the complex and characterize it completely.



58 **64**

Scheme 2.25 Zinc complexation of 58 using $ZnCl_2$.

D. Conclusions

The targeted compound benzo-annelated cross-bridged cyclam **12** was not successfully synthesized. However, because of its potential applications as discussed, this ligand is of interest and further studies and investigations should be considered to get the target material. The methylation using strong methylation agent under kinetic conditions was proposed to provide the desired product, but the methylation was not

selective. Other undesired products also formed. In general, the reaction did not proceed as planned. A method that could be investigated in the future is to use a bulky alkylating agent that can easily alkylate at the convex side of the bisaminal **15** but would not access the *endo* or concave side of the bisaminal.

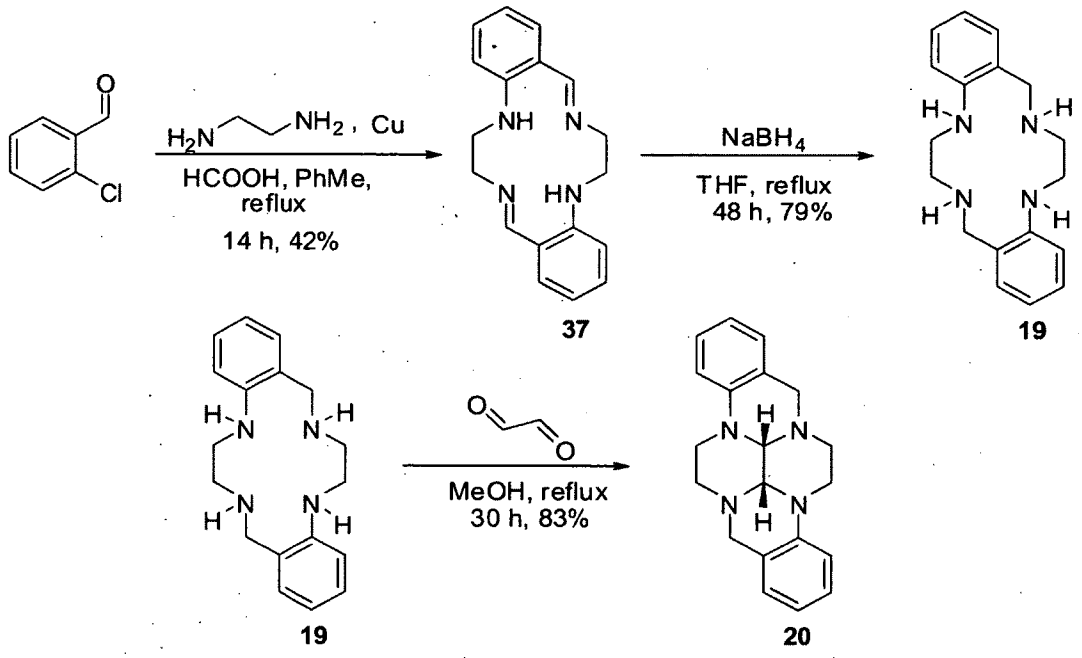
Although compound **12** was not successfully synthesized, the synthesis of the new ligand adjacent-bridged benzo-annelated cyclam (**58**) is of great interest. This species could have potential as a ligand to form trans-coordinated complexes with transition metals. The ligand successfully complexed with Zn(II), but further investigation on its ability to complex other transition metal cations could be studied. The redox chemistry of **58** could also be investigated.

II. Results and Discussion on Dibenzo-annelated Cyclam and Its Derivatives

A. Synthesis of Dibromo Dibenzo-annelated Tetracyclic Bisaminal (21)

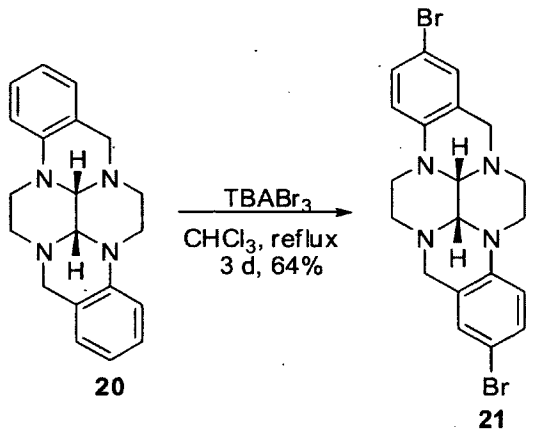
Studies to functionalize at the *para* positions of the dibenzo-annelated bisaminal **21** were started with the synthesis of dibenzo-annelated cyclam **19.** Condon's[17] work was repeated to prepare the 14-membered diimine ring **37**, following the procedure of Ried and coworkers[51] as shown in Scheme 2.26. Following purification by recrystallization from absolute EtOH, of 42% of **37** was obtained in ≥ 94% purity. A better yield was reported by Lindoy and coworkers in which recrystallization from chloroform and diethyl ether over several weeks was followed by washing the crystals with methanol and diethyl ether.[50] But due to the extensive time required for crystallization this method was not

utilized. To prepare the dibenzo-annelated cyclam **19**, the diimine **37** was reduced using $NaBH_4$ following Condon's procedure[17] to give a **19** as a white solid (79% yield) after purification by recrystallization from absolute EtOH.



Scheme 2.26 Preparation of bisaminal 20 following Condon's procedure.

Having the dibenzo-annelated cyclam **19**, glyoxal condensation was carried out in MeOH according to Condon's method.[17] This reaction mixture is heterogeneous and after 30 hours of reflux pure white, dibenzo-annelated cis-fused tetracyclic bisaminal was produced in 83% yield. Repeating Peng's[44] procedure, the dibromo dibenzo-annelated derivative **21** was prepared by bromination of the bisaminal **20** using tetrabutylammonium tribromide ($TBABr_3$) under reflux. Product was obtained as a finely divided white solid following recrystallization from chloroform (63% yield) as shown in Scheme 2.27.



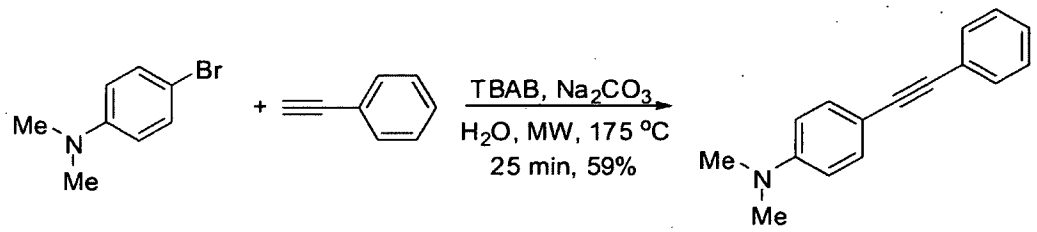
Scheme 2.27 Synthesis of dibromo dibenzo 21.

B. Attempts to Remotely Functionalize the Dibenzo Bisaminal 20

Once compound **21** had been prepared, our plan was to investigate different coupling methods to attach alkyl, alkenyl, alkynyl or aromatic substituents at the *para* positions (relative to N) of the benzo rings to enhance the solubility of compound **20** and provide extra possible functionalization sites. Once the coupling chemistry is achieved and a more soluble derivative of **20** is available, then efforts to resolve chiral bisaminal **20** could be undertaken.

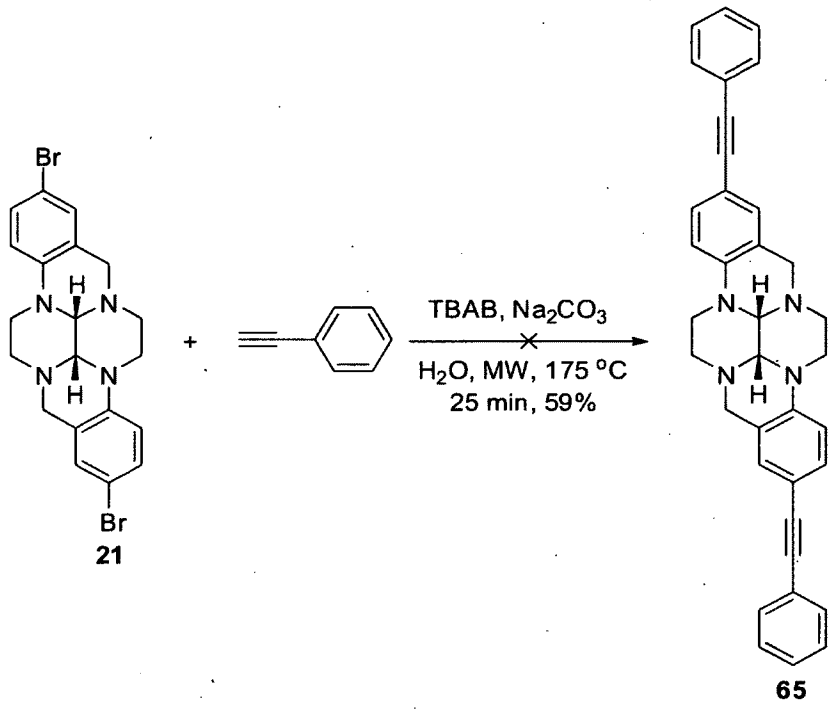
1. Attempted Sonogashira coupling of **21** with phenylacetylene

Van der Eycken and coworkers[75] reported a microwave-assisted transition-metal-free Sonogashira-type reaction in water where a tertiary amine 4-bromo-*N*,*N*-dimethylaniline undergoes a Sonogashira-type reaction with phenylacetylene as shown in Scheme 2.28.



Scheme 2.28 Microwave-assisted Sonogashira-type coupling in water.

Although they mentioned the reaction was slow and didn't run to completion, it was worthwhile of attempting the reaction. The same method was followed and compound **21** was mixed with 4 equivalents of phenylacetylene and an equivalent of the phase transfer catalyst TBAB (tetrabutylammonium bromide) and 8 equivalents of the base Na_2CO_3 in water as shown in Scheme 2.29.



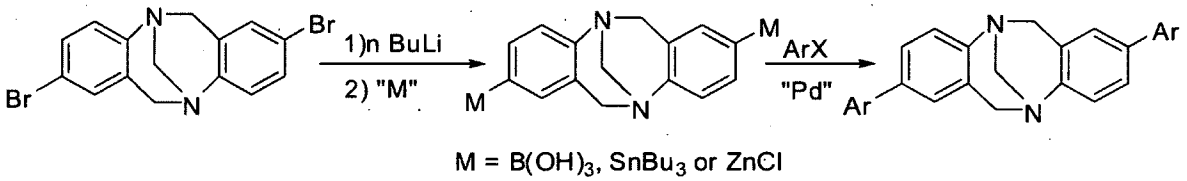
Scheme 2.29 Attempted Sonogashira-type reaction of 21.

Following 25 minutes of microwave irradiation at 150 °C (MW set to 175 °C but was not achieved) a yellow-colored reaction mixture was collected. Following work-up, ^{1}H NMR analysis showed that starting material was recovered. We thought that the use of higher temperature in a closed-vessel microwave reaction could dissolve the starting material with the aid of microwave effect. It can be concluded that either the insoluble nature of the starting material or the absence of transition metal were the reasons for not getting the

desired product. The possibility also exists that traces of transition metals were present in Van der Eyken's reactions.[71,72]

2. Diboronic acid formation of dibenzo-annelated tetracyclic bisaminal

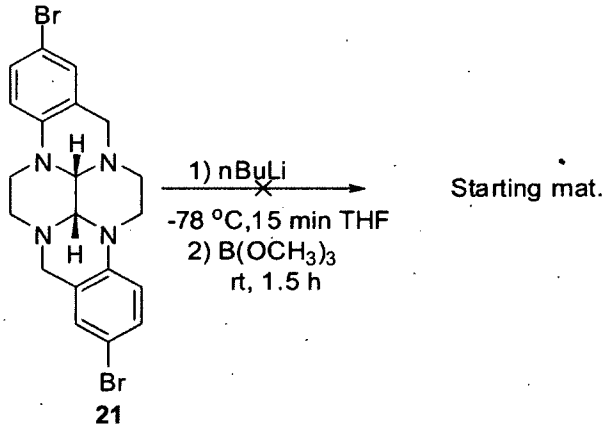
Further literature searching for structures similar to the dibenzo bisaminal **20** on which coupling chemistry has been studied was also carried out. Tröger's base has similar structure to compound **20**, in that both compounds have anilino and amino nitrogens. Warnmark and coworkers[76] reported successful introduction of aromatic and heteroaromatic groups in the 2- and 8- positions of the Tröger's base core by Suzuki, Stille and Negishi cross-coupling reactions as shown in Scheme 2.30. In their detailed comparative study of three palladium-catalyzed cross-coupling reactions, they reported that the Suzuki coupling was the most successful approach for the attachment of aromatic or heteroaromatic moieties to the Tröger's base core.



Scheme 2.30 Cross-coupling reactions of Tröger's base.

We, therefore, decided to carry out a similar experiment on the dibromo bisaminal **21**. Unfortunately the first step, metallation via halogen/lithium exchange was not successful. The reaction was carried out in dry THF and the dibromo species **21** was suspended in the solvent (Scheme 2.31). Once the reaction time was reached, the reaction mixture was

quenched with the addition of water and extracted with $CHCl_3$. The clear aqueous layer was acidified with HCl, but and no precipitate was observed.



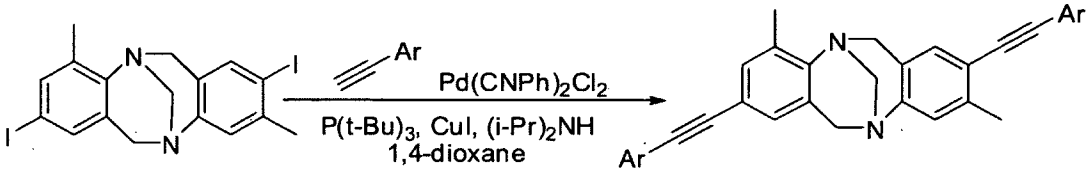
Scheme 2.31 Attempted borylation of compound 21.

After concentration of the aqueous layer a white solid was obtained. However, ^{1}H NMR spectrum showed no significant resonance and did not correspond to either desired product or starting material. Again acid workup was performed on the organic layer in an attempt to isolate the desired product in the aqueous layer. Following concentration of the aqueous solution resulted in fine white precipitate, but ^{1}H NMR showed not much material was present. Upon concentration of the organic layer a white precipitate was obtained. The ^{1}H NMR spectrum revealed the starting material was present in quantitative amount. Poor solubility of the starting material could be the reason for the failure of this reaction, since a very good yield was reported in literature.

3. Attempted Sonogashira couplings of **21**with 1-hexyne and phenylacetylene

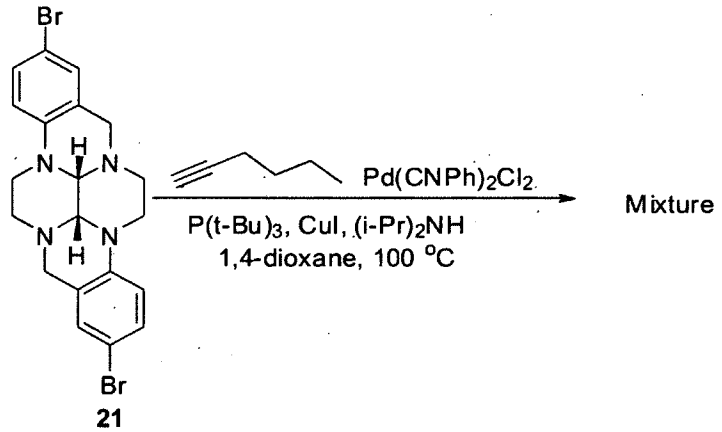
Wärnmark and coworkers[77] reported a successful introduction of an aromatic terminal alkyne utilizing a Sonogashira coupling of diiodo Tröger's base in the presence of an electron rich ligand tri-tert-butylphosphine (P(*t*-Bu)$_3$) and Bis(benzonitrile)

palladium(II)chloride ($Pd(PhCN)_2Cl_2$) as shown in (Scheme 2.32). Similar work was previously reported by Fu and coworkers in which Sonogashira coupling of 4-bromo-*N*,*N*-dimethylaniline was performed in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$.[78]



Scheme 2.32 Sonogashira reactions of Tröger's base.

Introduction of an alkyl terminal alkyne using similar Sonogashira coupling methodology was attempted on dibromo dibenzo species **21** as shown in Scheme 2.33. The reaction was run for 36 h, monitoring it by TLC, however no progress was observed. An ^{1}H NMR spectrum analysis revealed complex spectra that do not correspond to starting material. The same experiment was repeated twice. The first reaction used dimethylsulfoxide (DMSO) and the second reaction using dimethylformamide (DMF). The same reaction conditions and stoichiometry were followed, and the temperature was raised to 140 °C in both cases.



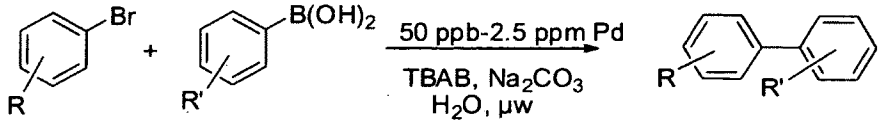
21

Scheme 2.33 Sonogashira attempt of compound 21.

Similar ^{1}H NMR spectra were observed for these reactions, showing starting material and a large peak at the upfield region that corresponds to alkyl chain which could possibly result from homo-coupling of 1-hexyne. We wouldn't expect the proton peaks of the ring for the starting material to be affected by introduction of alkyl chain at the remote positions of the molecule. TLC using SiO_2 and 40% EtOAc/Hexanes was also used to monitor the reaction and showed the starting material and two other components at R_f = 0.36, 0.42 and 0.9. The first spot (0.36) corresponded to starting material and the second spot (0.42) could possibly be the desired material or half reacted material, while the third spot corresponded to the 1-hexyne. Homo-coupling could have been taking place between alkyne, as well. A basic work up was performed to purify the amine from other residual reagents, but the same spectrum was again obtained.

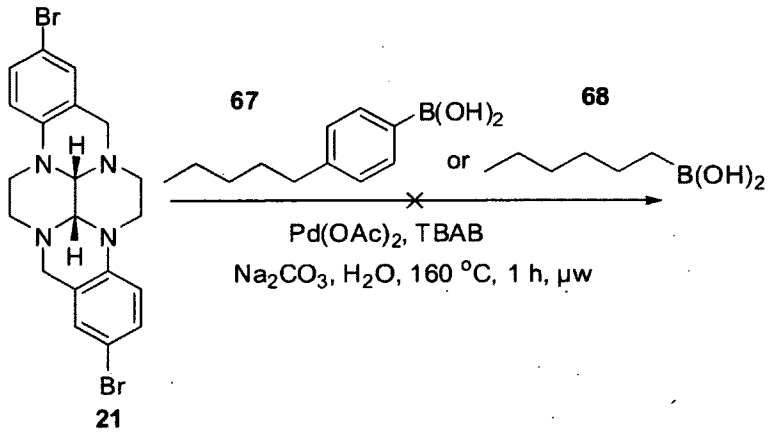
4. Suzuki cross-coupling chemistry using aryl and alkylboronic acids

The next coupling chemistry that was investigated was Suzuki coupling, which is one of the most versatile and utilized reactions for selective construction of carbon-carbon bonds. Leadbeater and coworkers[79] reported a successful microwave-assisted Suzuki coupling using very low amount of palladium (Pd(0)) in the presence of the phase transfer catalyst tetrabutylammonium bromide (TBAB), in water as shown in (Scheme 3.34).



Scheme 2.34 Suzuki-type coupling chemistry reported by Leadbeater and coworkers.

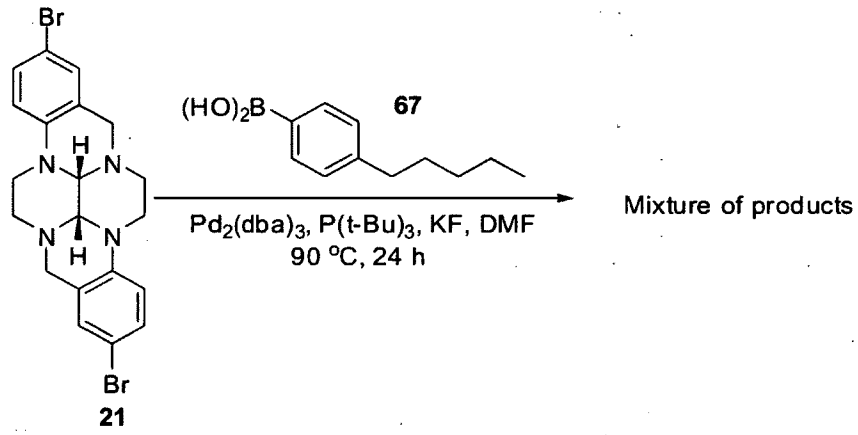
This methodology was utilized in our system for Suzuki-type coupling chemistry in water. Even though we know that our starting material is not soluble in water, we hoped that partial dissolution could take place at higher temperature and pressure when irradiated in a closed microwave vessel. This Suzuki-type coupling chemistry was attempted (Scheme 2.35). A mixture of starting material, three equivalents of the boronic acid reagent **67**, 10 mol% $Pd(OAc)_2$, an equivalent of TBAB and four equivalents of the base Na_2CO_3 was heated at 160 °C using microwave method, ABG315, dynamic, 160 °C, 1h, in a closed-vessel microwave tube. Following half an hour of reaction the crude product was washed and extracted from a basic solution using $CHCl_3$. ^1H NMR analysis of the green colored reaction mixture showed complex and messy spectra; unfortunately no conclusive result could be drawn. The same procedure was repeated with hexylboronic acid (**68**) for an hour following the same conditions; however similarly complex spectra were observed.



Scheme 2.35 Attempted Suzuki-type coupling chemistry.

In search of a better methodology for Suzuki coupling chemistry that could work in our system, a report by Fu and coworkers[78] was attempted. They have reported that the use of

$Pd_2(dba)_3/P(t\text{-}Bu)_3$ as a catalyst can induce reactivity in a wide range of arylboronic acids undergo Suzuki coupling with aryl, vinyl and triflates. They have reported Suzuki coupling of 4-bromo-*N*,*N*-dimethylaniline with arylboronic acid in the presence of potassium fluoride (KF), with product isolated in 98% yield. Even though their procedure reported the use of THF at ambient temperature, we knew that our starting material **21** was not soluble in THF at room temperature. However, by modifying the reaction conditions with different solvent and at higher temperature, we hoped for a better result. The Suzuki cross-coupling of dibromo bisaminal **21** with arylboronic acid **67** (3 equivalents) was carried out using approximately 2 mol% of $Pd_2(dba)_3$, and 2.4 mol% of $P(t\text{-}Bu)_3$ with 6.6 equivalents of KF in DMF for one day at 90 °C(Scheme 2.36).



Scheme 2.36 Attempted Suzuki cross-coupling using arylboronic acid.

Following the workup of the reaction, a crude product was collected. NMR analysis of the crude product showed the presence of a mixture of compounds. Although it was difficult to draw a good conclusion from the spectra, two sets of resonances were observed in the ^1H NMR. The resonances correspond to starting material and possibly

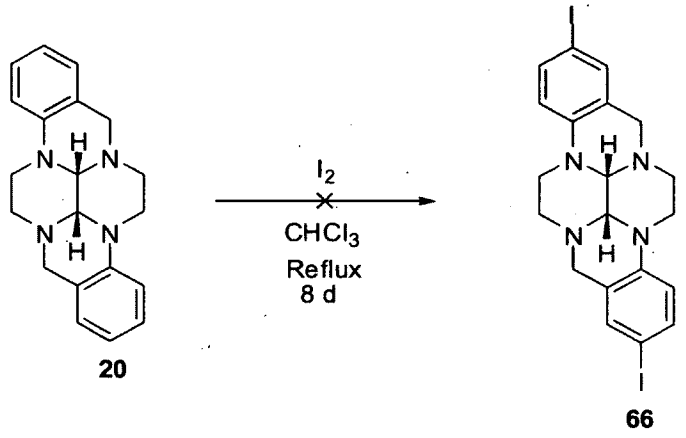
traces of half reacted or product. TLC showed the presence of two components, starting material and another spot. A similar reaction was run parallel to this, in which the arylboronic acid **67** was replaced by hexylboronic acid (**68**). A similar mixture of products was obtained; acid/base workup was carried out on the crude product to remove unreacted reagents and residual catalysts ($Pd_2(dba)_3$). A better purity ^1H NMR spectrum was observed, where impurities around the aromatic region that corresponded to $Pd_2(dba)_3$ were removed. Some of the impurities in the upfield region were also significantly decreased. But the product is still a mixture of starting material and another species. More work and study is needed in this experiment.

C. Attempted Diiodination Reactions of Dibenzo-annelated Tetracyclic Bisaminal (20)

1. Attempted diiodination of **20** using molecular iodine (I_2)

Through the use of Suzuki/Sonogashira coupling methodologies, a wide range of aryl and vinyl halides can be coupled with aryl or alkyl boronic acids/alkynes. Depending on the nature of the sp^2-carbon halide or triflate, different reaction conditions provide varying results. The use of special catalysts can also enhance a diverse array of aryl and vinyl halides and triflates to cleanly react at room temperature. The reactivity series of some of the sp^2-carbon halides or triflates is: vinyl iodide > vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate > aryl bromide >>> aryl chloride.[80] Based on our previous coupling attempts with bromide **21** and considering the above reactivity series, formation of a di-iodo analog **66** seemed a reasonable goal. Even though I_2 is a sluggish reagent for direct electrophilic halogenation, it was worthy of attmepting. The dibenzo

bisaminal **20** was dissolved in chloroform and refluxed with molecular iodine (I_2) as shown in Scheme (2.37).



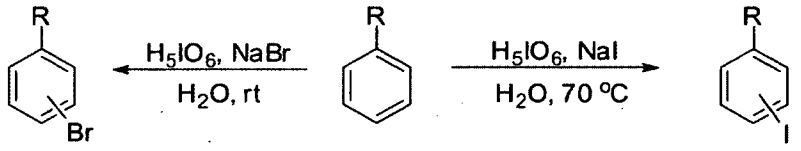
20 **66**

Scheme 2.37 Attempted diiodination of 20 using I_2.

The reaction was monitored for 8 days for any change using TLC; however, no change was observed, and it was concluded that iodine is very slow to undergo reaction with compound **20**.

2. Attempted diiodination reaction of **20** using H_5IO_6/NaI

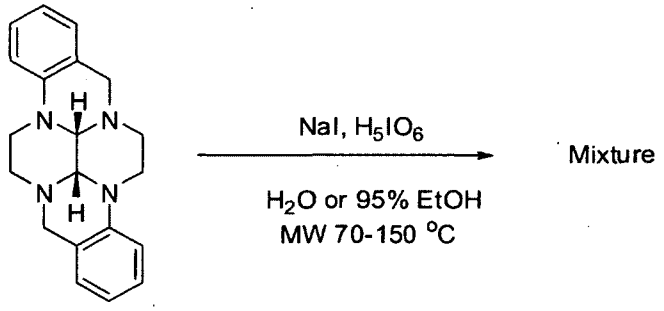
An alternative method that was considered was a green protocol for the bromination or iodination of aromatic compounds using H_5IO_6/NaBr and H_5IO_6/NaI in water reported by Kolavari, Koukabi and coworkers[81] as shown in Scheme 2.38.



Scheme 2.38 Iodination and bromination of aromatic compounds in water.

This method was followed in an attempt to diiodinate the dibenzo tetracyclic bisaminal **20**. Slightly more than 4 equivalents of NaI was dissolved in H_2O (0.7 mL) and compound **20** was suspended over it. This mixture was stirred for few minutes followed

by the addition of a sight excess of 2 equivalents of H_5IO_6. The reaction mixture turned yellow and then dark, and the reaction was heated to 70 °C (Scheme 2.39).



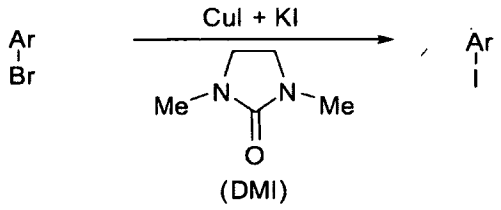
20

Scheme 2.39 Attempted Iodination of 20.

The resulting reaction mixture was treated with a satd solution of $Na_2S_2O_3$ (10.0 mL) before the basic workup and extraction with chloroform. ^{1}H NMR showed mainly starting material with small peaks of new product. In an effort to optimize this reaction and enhance the solubility of the bisaminal, ethanol (95%) was used as a solvent and the reaction was performed in microwave. The same stoichiometry was used and the reaction mixture was irradiated in the microwave for 30 min at 70 °C. The same workup procedure gave the product as a yellow solid, and once again ^{1}H NMR comparison and analysis was similar to the previous result. The same microwave assisted reaction was performed using H_2O as a solvent and irradiating the reaction to 150 °C for 30 min. Some minor product, which closely matched to mono-iodinated species, was observed; however, the starting material was still the dominant component as determined by ^{1}H NMR.

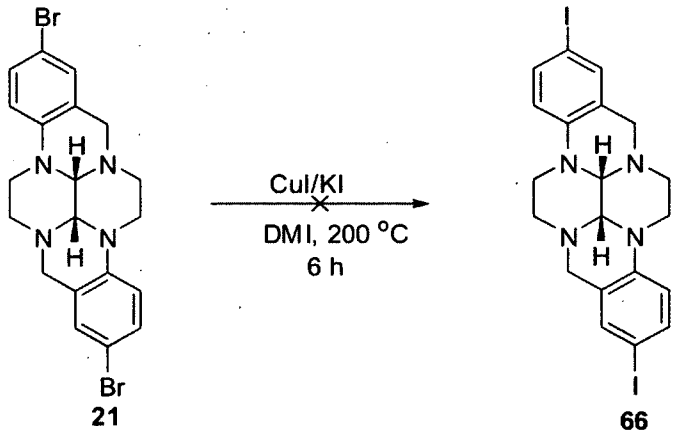
3. Attempted halogen exchange of dibromo dibenzo-annelated tetracyclic bisaminal (**21**) in 1,3-dimethyl-2-imidazolidinone (DMI)

The last experiment attempted was a halogen exchange reaction based on the report of "facile aromatic Finkelstein iodination (AFI) reaction in 1,3-dimethyl-2-imidazolidinone (DMI)" by Segiura and coworkers[82] as shown in Scheme 2.40.



Scheme 2.40 Aromatic Finkelstein iodination in DMI.

The authors reported that using the high boiling point (225 °C) solvent, DMI, gave good to excellent yields. This protocol was followed to carry out the attempted halide exchange of the dibromo **21** to diiodo species **66**, using a slight excess of three equivalents of CuI and nine equivalents of KI in freshly opened DMI with heating to 200 °C for 6 hours as shown in Scheme 2.41.



Scheme 2.41 Attempted halide exchange following aromatic Finkelstein iodination.

Following the proper workup procedure of the resulting black mixture, a yellow oil was obtained. Upon Kugelrohr distillation to remove residual DMI, yellow oil remained in the

distillation flask. ^{1}H NMR analysis of the yellow material showed a complex spectrum which belongs to neither starting material nor the expected product.

D. Conclusions

The targeted product could have many potential applications as bifunctional chelator, chiral resolving agent, catalysts, etc. Unfortunately, the attempts made to remotely functionalize the dibenzo bisaminal (**20**) using different coupling chemistry methods didn't afford the desired product. The attempted coupling chemistries (Sonogashira and Suzuki) appeared to provide mixture of starting material and another component but due to lack of time these studies were not completed. Further investigations are needed to find the right conditions to synthesize the targeted products. One of the main problems hindering the progress of this coupling chemistry is the poor solubility of the starting material **21**. We know that **21** dissolves at higher temperature, therefore employing high boiling point solvents or solid state cross-coupling should be considered in reinvestigation of this chemistry. Further studies on microwave-assisted Sonogashira/Suzuki coupling could result in better conditions to synthesize the targeted materials. A promising trace of mono-iodinated material was observed in our attempt to di-iodinate the bisaminal **20**. This result requires further investigation at different conditions. Good literature reports that describe efforts to perform the halogen exchange should be studied, since this could possibly speed up the cross-coupling reactions.

CHAPTER III

EXPERIMENTAL SECTION

I. General Methods

^{1}H and $^{13}C\{1H\}$ NMR Spectra were acquired on a Varian Unity INOVA 500 MHz NMR Spectrometer with broadband probe operating at 500 and 125.7 MHz, respectively, with VNMR 6.1c software or on a Varian Mercury 400 MHz NMR Spectrometer with broadband probe operating at 400 and 100.5 MHz respectively with VNMR 6.1c software. Chemical shift (δ) values are reported in parts per million (ppm) relative to Me_4Si (TMS) at δ 0.00 ppm unless otherwise noted. For spectra run in CD_3CN, the central solvent peak of residual CHD_2CN was set to δ 1.94 ppm for ^{1}H spectra and central solvent peak of CD_3CN (methyl carbon) was set to δ 1.32 ppm for $^{13}C\{1H\}$ spectra.[83] For spectra run in $CDCl_3$, the solvent peak of residual $CHCl_3$ was set to δ 7.26 ppm for ^{1}H spectra and central solvent peak of $CDCl_3$ was set to 77.16 ppm for $^{13}C\{1H\}$ spectra.[83] For spectra run in D_2O, a small amount of MeCN was added as a secondary reference set at δ 2.06 ppm for the methyl proton ^{1}H resonance of MeCN and 1.47 ppm for the methyl $^{13}C\{1H\}$ resonance of MeCN spectra.[83] Coupling constants (*J* values) are reported in Hertz (Hz). Spectra were processed using MNova software v 8.1.0.

Infrared Spectra (IR) were run on a Nicolet MX-1FT-IR spectrometer with EZ OMNIC 6.0a software. Absorptions are reported in wavenumbers (cm^{-1}).

Melting Points (mp) were recorded on a Mel-Temp capillary melting point apparatus (Laboratory Devices, Cambridge MA) and are uncorrected.

High Resolution Mass Spectra (HRMS) were obtained at the Department of Chemistry and Biology at the University of Notre Dame using a Bruker microTOF II high resolution mass spectrometer under electrospray ionization (HRMS–ESI $[M + H]^+$) mode.

Molecular Modeling calculations were performed on a Dell Computer Intel® Core™ i7-2600CPU running at 3.4 GHz with 16.0 GB RAM or HP Pavilion dv6 notebook PC operating with Intel® Core™ i3 CPU M350 running at 2.27 GHz with 4.00 GB RAM. Molecular modeling was done with Wavefunction, Inc.'s Spartan '10[68] and was imported to Gaussian, Inc. Gaussian® 09[69] for higher level geometry optimization calculations using DFT methods. Conformational searching using MMFF molecular mechanics and higher level equilibrium geometry calculations using DFT methods were also done using Wavefunction, Inc.'s Spartan '10 v 1.0.0.

Centrifugation was performed on an international Equipment Company International Clinical Centrifuge Model CL.

Rotary Evaporation was used for removal of bulk solvents under reduced pressure and traces of solvent were removed by high vacuum pump.

Lyophilization was used to remove water by sublimation under high vacuum (0.15 Torr) to constant mass was carried out using a Freezone (2.5 Plus) lyophilizer (Labconco, Kansas City, MO).

Thin Layer Chromatography (TLC) was performed using 250 μm pre-coated Sorbent silica gel (with UV 254) or alumina glass-backed plates.

Reverse Phase Chromatography (RPC) was carried out using glass-backed C18-W silica TLC plates w/UV 254 (250μm) from Sorbent. Flash chromatography cartridge columns were filled with C18 60A silica gel (40-63 μm, loading = 0.73 $mmolg^{-1}$) from Silicycle or were pre-fabricated: Siliasep C18 cartridges from Silicycle or Redisep C18 cartridges from Isco. RPC was carried out on a CombiFlash Retrieve chromatography system at a pressure of 25 psi for 14 g cartridges.

Microwave reactions were performed using a CEM Discover® research-scale manual microwave synthesizer using Synergy v.1.21 software. Reactions were carried out a closed vessel system using a 10 ml crimp sealed thick walled glass vial equipped with pressure sensor and magnetic stirrer.

Conventional reactions were run under nitrogen atmosphere with magnetic stirring in oven-dried glassware unless otherwise noted. Conventional heating was carried out using a mineral oil bath.

Anhydrous sodium sulfate (anhyd Na_2SO_4) was used to dehydrate organic solutions.

II. Solvents

Absolute ethanol (EtOH, ACS/USP grade) was obtained from Pharmco Products Inc. and was used without further purification.

Acetonitrile (CH_3CN, HPLC grade) was obtained from EMD Chemicals Inc. and stored in an Innovative Technology Inc. Pure-Solv Solvent Purification System. Solvent was passed through the system's silica column under low pressure. Prior to use, it was stored over 3 Å molecular sieves.

Benzene (C_6H_6, ACS grade) was obtained from EMD Chemicals Inc. and was used without further purification.

Chloroform ($CHCl_3$, HPLC grade) was obtained from EMD Chemicals Inc. and was used without further purification.

Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves.

Diethyl ether (Et_2O, Reagent grade, Stabilized with 2,6-*di*-tert-butyl-*p*-cresol (BHT)) was obtained from EMD Chemicals Inc. and was used for extraction without further purification.

Dimethylformamide (DMF, 99+ %) was obtained from EMD Chemicals Inc. It was vacuum distilled and stored over 3 Å molecular sieves prior to use.

Dimethyl sulfoxide (DMSO, ACS grade) was obtained from EMD Chemicals Inc. and was stored over 3 Å molecular sieves prior to use.

Dimethylimidazolidinone (DMI, $\geq$ 98.0 %) was obtained from Fisher Scientific. It was used without further purification.

Ethanol (95% EtOH, ACS grade) was obtained from EMD Chemicals Inc. and was used without further purification.

Glacial acetic acid (HOAc, ACS grade) was obtained from Fisher Scientific and used without further purification.

Isopropylamine (*i*-$PrNH_2$, 99+ %) was obtained from Fisher Scientific and used without further purification.

Methanol (MeOH, Reagent/ACS/USP/NF grade) was obtained from Pharmco Products Inc. and stored over 3 Å molecular sieves prior to use.

Methylene chloride (CH_2Cl_2, HPLC grade) was obtained from Fisher Scientific and was used without further purification.

Tetrahydrofuran (THF) was obtained from Fisher Scientific and stored in an Innovative Technology Inc. Pure-Solv Solvent System. Solvent was passed through the system's silica column under low pressure to remove trace impurities. It was subsequently distilled from benzophenone-ketyl immediately prior to use.

Toluene (PhMe, ACS grade) was obtained from EMD Chemicals Inc. and stored in an Innovative Technology Inc. Pure-Solv Solvent System. Solvent was passed through the system's silica column under low pressure to remove trace impurities and dry the solvent.

III. Reagents

Acrylonitrile was obtained from Sigma-Aldrich.

Aluminum chloride was obtained from Fisher Scientific and was stored in a desiccator.

Ammonium hexafluorophosphate (NH_4PF_6) was obtained from Fisher Scientific.

Celite (diatomaceous earth) was obtained from VWR International, LLC.

Cupric acetate hexahydrate was obtained from J.T.Baker Chemicals.

Cupric perchlorate hexahydrate was obtained from Sigma-Aldrich.

Dichlorobis(benzonitrile)palladium(II) ($PdCl_2(C_6H_5CN)_2$ was obtained from Strem Chemicals Inc. and was stored in a desiccator.

Diisobutylaluminum hydride (DIBALH) was obtained as a 1.0 M solution in toluene from Sigma-Aldrich.

Ethylenediamine was obtained from Sigma-Aldrich and was vacuum distilled prior to use.

Formic acid was obtained from Sigma-Aldrich.

Glyoxal (40% aq solution) was obtained from Sigma-Aldrich.

Hexylboronic acid was obtained from Fisher Scientific.

Hydrochloric acid (12 M HCl) was obtained from Fisher Scientific.

Methyl iodide (MeI) was obtained from Sigma-Aldrich.

Methyl trifluoromethanesulfonate was obtained from Sigma-Aldrich.

10% Palladium on carbon (10%Pd/C) was obtained from Strem Chemicals Inc. and was stored in a desiccator.

4-Pentylbenzene boronic acid was obtained from Fisher Scientific.

1,2-Phenylenediamine was obtained from Sigma-Aldrich.

Potassium hydroxide (KOH) was obtained from Fisher Scientific.

Potassium iodide (KI) was obtained from Fisher Scientific.

Sodium borohydride ($NaBH_4$) was obtained from Sigma-Aldrich.

Sodium carbonate (Na_2CO_3) was obtained from Fisher Scientific.

Sodium hydroxide (NaOH) was obtained from EMD Chemicals Inc.

Sodium sulfate (Na_2SO_4, anhydrous) was obtained from Fisher Scientific.

Sodium triacetoxyborohydride ($NaBH(OAc)_3$) was obtained from Fisher Scientific.

p-Toluenesulfonic acid monohydrate was obtained from Sigma-Aldrich.

Trifluoroacetic acid (TFA) was obtained from Sigma-Aldrich.

Tri-t-butylphosphine was obtained from Strem Chemicals Inc.

Tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) was obtained from Sigma-Aldrich and was stored in a desiccator.

Zinc chloride ($ZnCl_2$, anhydrous) was obtained from Strem Chemicals Inc. and was stored in a desiccator.

Zinc perchlorate hexahydrate was obtained from Sigma-Aldrich.

IV. Syntheses

Note: All reactions were run under nitrogen atmosphere with a magnetic stirring unless otherwise noted. All reactions requiring elevated temperature were heated using mineral oil bath unless indicated otherwise. All routine solvent evaporations were carried out on standard rotary evaporator under reduced pressure using vacuubrand PC 3001 pump. Residual solvent was removed under high vacuum pump unless otherwise noted.

N,N'-Bis(2-cyanoethyl)-*ortho*-phenylenediamine (27). The preparation of this compound was modeled on the procedure for the reaction of aromatic primary amines and acrylonitrile reported by Braunholtz and Mann.[65] A mixture of *o*-phenylenediamine (**26**) (2.02 g, 18.5 mmol), acrylonitrile (9.80 mL, 148 mmol) and glacial acetic acid (4.40 mL, 77.7 mmol) was placed in a 50 mL round-bottomed flask and refluxed for 24 h. After cooling to rt, the reaction mixture was made alkaline by addition of saturated aq sodium carbonate (30 mL) and then extracted with diethyl ether (4 × 40 mL). The combined ether extracts were dried over anhyd Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The solid residue was recrystallized from MeOH to give product as light pink needles (1.31 g, 6.11 mmol, 33%). NMR spectra were consistent with spectra of authentic material.[41,48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, J = 6.5 Hz, CH_2CH_2CN, 4H), 3.48 (q, J = 6.5 Hz, $NHCH_2CH_2$, 4H), 3.72 (br t, J = ~6.6 Hz, N*H*, 2H), 6.685 – 6.745 (m, XX' of AA'XX', 2H), 6.85 – 6.905 (m, AA' of AA'XX', 2H); ^{13}C{^{1}H} NMR (100.51 MHz, $CDCl_3$) δ 136.37, 121.00, 118.78, 113.89, 40.62, 18.59.

N,N'-Bis(3-aminopropyl)-*ortho*-phenylenediamine (28). N,N'-Bis(2-cyanoethyl)-*o*-phenylenediamine (**27**) (0.501 g, 2.30 mmol) was dissolved in dry THF (13.0 mL) in a 100 mL three-necked round-bottomed flask equipped with a reflux condenser with N_2 inlet tube and pressure-equalizing addition funnel. $NaBH_4$ (0.525 g, 13.8 mmol) was added portionwise over a period of 20 min while the mixture was vigorously stirred and cooled with an ice/water bath. A solution of anhyd $AlCl_3$ (0.482 g, 3.60 mmol) in dry THF (10.0 mL) was delivered dropwise through the addition funnel over a period of 20 min. The resulting mixture was refluxed for 20 h. The reaction mixture was then cooled in an ice/water bath and aq HCl (12 M, 8.0 mL) was added dropwise with vigorous stirring to quench the reaction. The reaction mixture was then concentrated, the residue was dissolved in H_2O (20 mL), the solution was made strongly basic by the addition of KOH pellets (pH14), and the aq solution was extracted with toluene (5 × 40 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and solvent was removed by rotary evaporation. Residual solvent was removed to afford light brown oil which solidified upon storage (0.330 g, 1.48 mmol, 65%). NMR spectra matched those of authentic material.[411] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (br s, N*H*, 6H), 1.83 (p, J = 6.7 Hz, $CH_2CH_2CH_2$, 4H), 2.89 (t, J = 6.7 Hz, $CH_2CH_2NH_2$, 4H), 3.19 (t, J = 6.7 Hz, $NHCH_2CH_2$, 4H), 6.64 – 6.70 (m, XX' of AA'XX', 2H), 6.755 – 6.81 (m, AA' of AA'XX', 2H); ^{13}C{^{1}H} NMR (100.51 MHz, $CDCl_3$) δ 33.24, 40.80, 42.81, 111.45, 119.15, 137.59.

***Cis/trans*-1,2,3,4,11,12,13,14,14a,14b-decahydrodipyrimido[1,2-a:2',1'-c]quinoxaline diastereomeric mixture (29)**. N,N'-Bis(-3-aminopropyl)-1,2-diphenylenediamine (**28**)

(1.65 g, 7.40 mmol) was dissolved in toluene (40 mL) in a 100 mL round-bottomed flask. Aqueous glyoxal (40 wt. % aq solution, 1.02 mL, 8.90 mmol) was added via syringe, the flask was fitted with a Dean-Stark trap and reflux condenser, and the reaction was refluxed for 6 h. The resultant toluene solution was decanted from a black sticky precipitate corresponding to neither starting material nor the desired product. The solution was concentrated and the brown oily material was dissolved in toluene and dried over anhyd Na_2SO_4. Solvent was then removed by rotary evaporation and the residue pumped down to give product as a brown oil, which is a mixture of diastereomers in a ratio of (0.56 : 0.46) of mass (1.59 g, 6.51 mmol, 88%). ^1H and $^{13}C\{^1H\}$ NMR data was consistent with previously reported data.[41] ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 – 1.43 (dm, J = 13.4 Hz, $CH_2CH\mathit{H}_{eq}CH_2$), 1.47 –1.56 (dm, J = 13.6 Hz, $CH_2CH\mathit{H}_{eq}CH_2$), 1.56 – 2.01 (m, $CH_2C\mathit{H}_{ax}HCH_2$), 1.51 – 2.08 (br, NH of both isomers), 2.80 – 3.22 (m), 3.90 (s, NC*H*N), 3.94 – 4.035 (m), 4.04 (s, NC*H*N), 6.74 – 6.84 (m, Ar *H* for both isomers). $^{13}C\{^1H\}$ NMR (100.51 MHz, $CDCl_3$) δ Isomer A 23.78, 45.17, 47.38, 73.92, 73.92, 113.57, 119.62, 134.55; δ Isomer B 25.48, 44.19, 47.06, 70.02, 112.99, 119.44, 135.10.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,5,8,12-tetraaza-benzocyclotetradecane ("Benzo[*b*]cyclam") (14). Compound **14** was synthesized following Reed's procedure.[41] *Cis/trans*-1,2,3,4,11,12,13,14,14a,14b-decahydrodipyrimido[1,2-a:2',1'-c]quinoxaline (**29**) (1.59 g, 6.55 mmol) was dissolved in dry toluene (25.0 mL) in an oven-dried 3-neck round-bottomed flask equipped with magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. 1.0 M DIBALH in toluene (65.5 mL, 65.5 mmol) was added dropwise through the addition funnel while the reaction mixture

was stirred for 0.5 h with ice/H_2O cooling. Once the addition of DIBALH was completed, the reaction mixture was refluxed for 5 days. The reaction mixture was then cooled to room temperature and diluted with the addition of dry toluene (50 mL). The reaction mixture was cooled (ice/H_2O bath) and DIBALH was quenched by careful dropwise addition of 3.0 M aq KOH (90 mL). The aq layer was washed with toluene (5 × 65 mL), the combined organic extracts were dried over anhyd Na_2SO_4, and solvent was removed under reduced pressure to give the crude desired product as a thick brown oil (1.10 g, 4.43 mmol, crude yield 68%). The crude oil was then further purified and protonated to avoid oxidation by dissolving it in 95% EtOH (30 mL) followed by dropwise addition of aq HCl (6 M, 35 mL) with vigorously stirring and cooling (ice/H_2O), (the solution turned pinkish). Solvent and excess acid was stripped off by rotary evaporation to give a light pink precipitate. This precipitate was further suspended in absolute EtOH and triturated at reflux, and filtered to afford a pure product as hydrochloride salt (1.58 g, according to mass calculations 99% yield (assuming tri-protonated and no presence of water) or 91% yield(assuming tetra-protonated). ^1H and $^{13}C\{^1H\}$ NMR spectra were consistent with spectra of authentic material.[41] ^1H NMR (400 MHz, D_2O, secondary ref. CH_3CN set at 2.06 ppm) δ 2.12 (p, J = 6.5Hz, $CH_2CH_2CH_2$, 4H), 3.34 (t, J = 6.7 Hz, CH_2CH_2NH, 4H), 3.48 (s, $NHCH_2$, 4H), 3.55 (t, J = 6.4 Hz, $ArNHCH_2CH_2$, 4H), 7.20 – 7.27 (m, Ar *H*, 4H); $^{13}C\{^1H\}$ NMR (100.51 MHz, D_2O, secondary ref CH_3CN set at 1.47) δ 22.77, 42.29, 44.18, 46.23, 119.55, 125.68, 133.56.

Attempted Cu(II) complexation with 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-1,5,8,12-tetraaza benzocyclotetradecane (Cu(II) complex of benzo[*b*]cyclam) .

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,5,8,12-tetraaza-benzocyclotetradecane· 3HCl

(HCl salt of benzo[*b*]cyclam) (**14**) (51.7 mg, 0.133 mmol) was suspended in dry and degassed MeOH (2.0 mL) and $Cu(ClO_4)_2 \cdot 6H_2O$ (61.2 mg, 0.164 mmol) was combined with it. The pH was adjusted to 6 – 7 by a dropwise addition of aq KOH (0.3 M). The reaction mixture turned dark green in few minutes, and it was left stirring for 18 h at rt under N_2. The resulting reaction mixture was concentrated by rotary evaporation to give a dark black solid. No UV or NMR spectrum could be obtained.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,5,8,12-tetraaza-benzocyclotetradecane·$Zn(ClO_4)_2 \cdot 6H_2O$ (Zn complex of Benzo[*b*]cyclam) (49). 1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,5,8,12-tetraaza-benzocyclotetradecane·3HCl (HCl salt of benzo[*b*]cyclam) (**14**) (69.6 mg, 0.181 mmol) was suspended in dry and degassed MeOH (1.5 mL) and $Zn(ClO_4)_2 \cdot 6H_2O$ (61.2 mg, 0.164 mmol) was added. The pH was adjusted to 6 – 7 by a dropwise addition of aq KOH (0.3 M), the reaction mixture was left stirring for 2 d at rt under N_2. The resulting reaction mixture was concentrated by rotary evaporation and washed with (2 × 20 mL) CH_2Cl_2. Residual solvent was removed under reduced pressure to give a light brown solid (0.109 g, 0.176 mmol, 97%). Slow ether diffusion was attempted to grow crystals but was not successful. ^{1}H NMR (400 MHz, CD_3CN, ref. central peak of CHD_2CN set at 1.94) δ 0.92 (dt, J = 8.5, 7.3 Hz, 13H), 1.50 – 1.27 (m, 20H), 1.69 (p, J = 6.0 Hz, 2H), 1.78 – 1.88 (m, 3H), 2.20 (s, 12H), 2.92 (s, 2H), 3.10 (s, 6H), 3.62 – 3.71 (m, 4H), 4.20 (dd, J = 5.7, 2.7 Hz, 4H), 4.49 (s, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.37 – 7.42 (m, 1H), 7.45 – 7.55 (m, 1H), 7.60 – 7.68 (m, 2H), 7.69 – 7.78 (m, 2H).

(12bα,12cα)-1,2,3,8,9,10,11,12,12b,12c-Dodecahydro-3a,7b,10a,12a-tetraazabenzo[*e*] pyrene (15). Compound **15** was synthesized following Reed's procedure. 1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,5,8,12-tetraaza-benzocyclotetradecane "Benzo[b]cyclam" (**14**) (387 mg, 1.56 mmol) was dissolved in MeCN (45 mL). 40% aq glyoxal (0.214 mL, 1.87 mmol) was added via a syringe. The reaction mixture was refluxed for 3 h. The resulting brown solution was concentrated in vacuo and dissolved in $CHCl_3$ (50.0 mL), dried over anhyd Na_2SO_4, suction filtration followed by removal of solvent by rotary evaporation to afford a brown solid (0.346 g, 1.28 mmol, 82%). Further purification can also be done by normal phase chromatography on basic Al_2O_3 and neat CH_2Cl_2. ^1H and $^{13}C\{^1H\}$ NMR spectra were consistent with spectra of authentic material.[41] ^1H NMR (400 MHz, CD_3CN, ref. central peak of CHD_2CN set at 1.94) δ 1.32 – 1.40 (dm, J = 13.42 Hz, 2H), 2.00 – 2.15 (m, 2H), 2.27 (td, J = 8.9, 3.3 Hz, 2H), 2.64 (br t, J = 11.6, 2H), 2.84 (td, J = 13.0, 3.0 Hz, 2H), 2.88 – 2.97 (dm, J = 12.7, 2H), 3.08 (br s, 2H), 3.80 (s, 2H), 3.98 – 4.07 (dm, J = 13.3 Hz, 2H), 6.60 – 6.67 (m, XX' of AA'XX', 2H), 6.70 – 6.77 (m, AA' or AA'XX', 2H). $^{13}C\{^1H\}$ NMR (100.51 MHz, CD_3CN ref. central peak of CD_3CN set at 1.32) δ 21.26, 48.24, 49.65, 54.53, 73.54, 113.60, 119.61, 136.31.

Dimethylation of 15 using methyl trifluomethanesulfonate (methyl triflate) (50, 51 & 52).

Safety Note: This reaction should be carried out in a well-ventilated hood. Extra precautions are needed in handling MeOTf as it is a strong alkylating agent and very toxic if inhaled or through skin contact. It is also advisable to prepare the quenching agent (aq KOH) to decompose remaining any material. The MSDS should be consulted.

The *cis*-fused tetracyclic bisaminal compound **15** (31.9 mg, 0.117 mmol) was dissolved in dry dichloromethane (0.30 mL) in a 10 mL pear-shaped flask under nitrogen. Then in a zip-lock plastic bag filled with N_2 gas, (25 μL, 0.23 mmol) of methyl trifluoromethanesulfonate (methyl triflate) was withdrawn via a syringe and transferred to a vial of dry dichloromethane (0.70 mL). To study the kinetic methylation at different conditions, the same way was used each time to carry out the following four different trials:

i) The solution of methyl triflate was added dropwise with stirring over a period of 1 h to the reaction flask at -78 °C (acetone dry ice bath). The reaction mixture was then left to warm to room temperature following complete addition of methyl triflate. The reaction mixture was stirred for 2 days before excess reagent and solvent were removed at 40 °C (water bath of the rotary evaporator) under the hood to give a foamy light brown solid of crude yield 89%.

ii) The solution of methyl triflate was added in one portion to a stirred solution of compound **15** at -78 °C. The reaction was stirred for 15 min at the same temperature. Excess reagent and solvent was removed at 40 °C (water bath of the rotary evaporator) under the hood to give a foamy light brown solid of crude yield 90%.

iii) The solution of methyl triflate was added in one portion to a stirred solution of compound **15** at room temperature. The reaction was run for 10 - 15 min at room temperature. Excess reagent and solvent was removed by rotary evaporation at 40 °C (water bath) under the hood to give a foamy light brown solid of crude yield 89%.

iv) The solution of methyl triflate was added in one portion to a stirred solution of compound **15** under ice/H_2O bath cooling. Then the reaction was run at -10 °C – 0 °C for 2 days maintaining the same temperature by adding ice every 6 hours in big bowl. Then excess reagent and solvent was removed by rotary evaporation at ice/H_2O temperature to afford a brown glassy and foamy solid of crude yield 85%.

^1H and $^{13}C\{^1H\}$ spectra from all four experiments revealed an identical mixtures in different relative ratios of (**51**:**50**:**52** or **51**:**52**:**50**) since we don't know the spectra of either **50** or **52**. These ratios are based on $^{13}C\{^1H\}$ integration of the resonance at the upfield region, they are listed according to the procedures performed: (i) 42:33:25, (ii) 27:46:27, (iii) 50:26:24 and (iv) 49:30:21. The spectral data below corresponds to run (iii) and is selected because of good signal to noise ratio.

^1H NMR (400 MHz, acetone-d_6) δ 1.565 (d, J = 14.2 Hz, **51/52**), 1.85 – 2.19 (m, **50** and **51** and or **52**), 2.24 (d, J = 15.8 Hz, **50**), 2.30 – 2.90 (m, **50** and **51** and or **52**), 2.94 – 3.32 (m, **50** and **51** and or **52**), 3.33 (s, N^+CH_3, **50**), 3.43 – 3.88 (m), 3.48 (s, N^+CH_3, **50**), 3.59 (s, N^+CH_3, **51/52**), 3.62 (s, N^+CH_3, **51/52**), 3.89 (s, N^+CH_3, **51/52**), 3.90 – 4.28 (m, **50** and **51** and or **52**), 4.30 – 4.58 (m, **50** and **51** and or **52**), 4.98 (d, J = 13.8 Hz), 5.07 – 5.20 (m, **50** and **51** and or **52**), 5.27 (d, J = 2.7 Hz, **51/52**), 5.43 (br s, **50**), 5.61 (br s, **51/52**), 5.82 (d, J = 3.6 Hz, **51/52**), 6.17 (d, J = 2.4 Hz, **50**), 6.75 – 6.89 (m, **51** and or **52**), 6.92 – 7.06 (m, **50** and **51** and or **52**), 7.11 – 7.17 (m, **51** and or **52**), 7.26 (d, J = 8.3 Hz, **50**), 7.50 – 7.58 (m, **51** and or **52**), 7.81 (d, J = 8.2 Hz, **51** and or **52**). $^{13}C\{^1H\}$ NMR (100.51 MHz,

acetone-d_6) δ 18.52 (**50**), 18.55 (**50**), 18.87 (**51/52**), 19.00 (**51/52**), 19.78 (**51/52**), 19.85 (**51/52**), 39.13 (**51/52**), 39.83 (**51/52**), 42.77 (**50**), 43.59, 44.50 (**50**), 45.20 (**50**), 45.77 (**51/52**), 46.84 (**51/52**), 47.15 (**51/52**), 47.55 (**51/52**), 47.74 (**50**), 49.06 (**51/52**), 50.61 (**50**), 51.04 (**51/52**), 54.37 (**51/52**), 54.87 (**50**), 54.94 (**51/52**), 60.94 (**51/52**), 61.91 (**51/52**), 64.43(**50**), 65.08 (**51/52**), 65.16 (**51/52**), 66.22 (**50**), 67.92 (**51/52**), 73.59 (**51/52**), 74.34 (**50**), 76.01(**50**), 78.69 (**51/52**), 80.09 (**51/52**), 110.62 (**51/52**), 111.92 (**50**), 114.76 (**51/52**), 114.83 (**51/52**), 116.40 (**50**), 118.37 (**51/52**), 119.71 (**51/52**), 120.21 (**51/52**), 121.34 (**51/52**), 121.44 (**51/52**), 121.51 (**50**), 122.90 (**51/52**), 123.56 (**50**), 131.06 (**50**), 131.51 (**51/52**), 131.56 (**51/52**), 132.44 (**50**), 134.53 (**51/52**), 137.44 (**51/52**).

Monomethylation of 15 to give stereoisomers (53 and 54).

An NMR monomethylation study of 15 using one equivalent of methyl iodide was carried out.

I. In a screw cap NMR tube (12bα,12cα)-1,2,3,8,9,10,11,12,12b,12c-dodecahydro-3a,7b,10a,12a-tetraazabenzo[e]pyrene (**15**) (26.8 mg, 0.099 mmol) was dissolved in CD_3CN (0.80 mL). Methyl iodide (6.2 μL, 0.099 mmol) was added via a gas tight micro-syringe and this mixture was studied periodically by NMR. A mixture of two isomeric products **53** and **54** was revealed in a relative ratio of 63:37 after 14 d. ^{1}H NMR (400 MHz, CD_3CN, ref. central peak of C*H*D_2CN set at 1.94) δ 1.32 – 1.46 (dm, J =14.0 Hz, 2H, **53**), 1.50 – 1.58 (dm, J = 14.0 Hz, 1H, **54**), 1.74 – 1.87 (m, 1H, **54**), 1.99 – 2.11 (m, 1H, **53**), 2.18 (s, 1H), 2.23 (s, 1H), 2.25 – 2.46 (m, 3H), 2.55 – 2.76 (m, 3H), 2.78 – 2.94 (m, 4H), 2.96 – 3.09 (m, 2H), 3.08 – 3.26 (m, 7H), 3.18 (s, 3H, N^+CH_3, **54**), 3.36 (s, 3H, N^+CH_3, **53**), 3.40 – 3.86 (m,

8H), 3.87 – 4.07 (m, 4H), 4.09 – 4.22 (m, 2H), 4.23 – 4.36 (m, 3H), 4.34 (d, J = 2.56 Hz, **54**), 4.50 (d, J = 3.3 Hz, 2H, **53**), 4.88 (d, J = 3.3 Hz, 2H, **53**), 5.21 (d, J = 2.56 Hz, **54**), 6.73 – 7.04 (m, 8H), $^{13}C\{^{1}H\}$ NMR (100.51 MHz, CD_3CN ref. central peak of CD_3CN set at 1.32 ppm) δ Isomer **53** 20.64, 20.66, 39.63, 44.07, 47.16, 47.83, 48.36, 51.28, 54.81, 64.56, 69.18, 115.34, 116.01, 120.64, 121.85, 134.37, 134.94. Isomer **54** 19.33, 19.54, 40.81, 47.83, 48.06, 51.51, 61.44, 65.42, 68.26, 78.15, 80.64, 111.24, 115.34, 120.86, 121.97, 132.06, 135.12.

II.

The NMR sample was transferred to a 10 mL pear shaped flask; 0.7 mL of CD_3CN was used to rinse the tube and transfer the sample. The resulting solution was heated at 60 °C in a closed vessel for 8 d. Aliquots were removed to monitor the reaction by NMR. NMR of mixtures showed the ratio of (46:54) after 8 days: ^{1}H NMR (400 MHz, CD_3CN, ref. central peak of CHD_2CN set at 1.94) δ 1.41 – 1.51 (dm, J = 13.26, 1H, **53**), 1.56 – 1.64 (dm, J = 14.14, 1H, **54**), 1.88 (d, J = 15.4 Hz, 1H, **54**), 1.95 – 2.00 (m, 1H, **53**), 2.03 – 2.12 (m, 1H), 2.29 (s, 13H), 2.30 – 2.50 (m, 2H), 2.66 – 2.76 (m, 2H), 2.81 (d, J = 13.5 Hz, 1H), 2.85 – 3.02 (m, 3H), 3.04 – 3.24 (m, 5H), 3.23 (s, 3H, $N^{+}CH_3$, **54**), 3.36 (s, 3H, $N^{+}CH_3$, **53**), 3.46 (ddd, J = 14.8, 13.1, 3.5 Hz, 1H), 3.53 – 3.93 (m, 7H), 4.01 – 4.13 (m, 2H), 4.18 – 4.27 (dm, J = 13.2 Hz, 1H), 4.29 – 4.43 (m, 2H), 4.34 (d, J = 2.56 Hz, 1H, **54**), 4.413 (d, J = 2.85 Hz, 1H, **53**), 4.52 (d, J = 3.3 Hz, 1H, **53**), 4.84 (br s, 1H, **54**), 5.17 (d, J = 2.8 Hz, 1H), 6.82 – 6.96 (m, 7H), 7.02 (dd, J = 7.4, 2.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100.51 MHz, CD_3CN ref. central peak of CD_3CN set at 1.32 ppm) δ Isomer **53**: 20.64, 20.66, 39.63, 44.07, 47.16, 47.83, 48.36, 51.28, 54.81, 64.56,

69.18, 115.34, 116.01, 120.64, 121.85, 134.37, 134.94. Isomer **54**: 19.33, 19.54, 40.81, 47.83, 48.06, 51.51, 61.44, 65.42, 68.26, 78.15, 80.64, 111.24, 115.34, 120.86, 121.97, 132.06, 135.12.

(12c*R*,12d*R*)-3a-(prop-2-en-1-yl)-2,3,4,5,7,8,12c,12d-octahydro-1*H*,6*H*-5a,8a,12b-triaza-3a-azoniabenzo[*e*]pyrene bromide stereoisomers (55 and 56). (12bα,12cα)-1,2,3,8,9,10,11,12,12b,12c-Dodecahydro-3a,7b,10a,12a-tetraazabenzo[e]pyrene (**15**) (256 mg, 0.947 mmol) was dissolved in dry MeCN (3.0 mL). Allyl bromide (0.916 mL, 7.60 mmol) was added via a syringe and the mixture was stirred at room temperature for 2 d in the dark under nitrogen. Excess reagent and solvent were removed rotary evaporation and the brown solid was washed with Et_2O (3 × 10 mL) and the solution of ether was concentrated by rotary evaporation to give product mixture as a major and minor of relative ratio (80:16:4) as a brown foam/glass (0.366 g, 0.937 mmol, 99%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 1.47 (d, J = 13.7 Hz, 1H, **55**), 1.61 (d, J = 14.1 Hz, 1H, **56**), 1.91 – 1.80 (m, 1H, **56**), 2.09 – 2.00 (m, 2H, **55**), 2.20 – 2.09 (m, 1H), 2.33 – 2.25 (m, 1H), 2.50 – 2.33 (m, 2H), 2.84 (m, 2H), 3.00 – 2.92 (m, 1H), 3.04 (td, J = 13.3, 3.0 Hz, 1H), 3.32 – 3.09 (m, 4H), 3.29 (d, J = 2.7 Hz, 1H) 3.36 (dddd, J = 3.7, 1.9, 1.3, 0.4 Hz, 1H), 3.84 – 3.52 (m, 4H), 4.05 – 3.87 (m, 1H), 4.15 – 4.08 (m, 1H), 4.34 – 4.21 (m, 3H), 4.78 – 4.71 (m, 2H, **55**), 4.91 – 4.84 (m, 2H), 5.24 – 5.13 (m, 1H), 5.39 (d, J = 2.7 Hz, 1H, **56**), 5.70 – 5.63 (m, 1H, **56**), 5.85 – 5.80 (m, 1H, **55**), 5.94 (d, J = 16.9, 1H, **55**), 6.20 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H, **55**), 6.94 – 6.82 (m, 4H), 7.01 (ddd, J = 15.3, 8.1, 1.4 Hz, 1H, **56**), 7.09 (dd, J = 7.8, 1.6 Hz, 1H, **55**), ^{13}C{^{1}H} NMR (125.67 MHz, CD_3OD) δ Major Isomer

55 19.67, 19.83, 35.19, 46.18, 47.40, 47.47, 54.01, 59.81, 59.88, 68.39, 77.41, 114.30, 115.24, 119.83, 121.16, 123.65, 128.45, 133.21, 133.99. Minor Isomer **56** 18.41, 18.60, 38.77, 41.48, 43.16, 48.55, 50.81, 55.91, 59.47, 68.14, 82.08, 110.20, 114.66, 117.01, 120.03, 121.34, 124.12, 127.40, 134.61.

Isomerization of (12c*R*,12d*R*)-3a-(prop-2-en-1-yl)-2,3,4,5,7,8,12c,12d-octahydro-1*H*,6*H*-5a,8a,12b-triaza-3a-azoniabenzo[*e*]pyrene bromide stereoisomers (55 and 56). Isomerization of the exo allylated **55** to the endo allylated salt **56**, the mixture of the two mono-allylated isomers (**55** and **56**) and di-allylated salt (82.0 mg) of ratio (80:16:4) was dissolved in dry MeCN (1.50 mL) and was heated at 50 °C for 3 d in a closed vessel. The solvent was removed by rotary evaporation and traces of solvent were removed by pump to give product as brown oil. The $^{13}C\{^{1}H\}$ NMR spectrum showed successful isomerization to the ratio of (39:54:7) corresponding to mono-exo-allylated salt **55**, mono-endo-allylated salt **56** and the di-allylated salt respectively.

Attempted monoprotonation of 15 to give stereoisomers (59 and 60). A protonation studies of compound **15** using one equivalent of ammonium hexafluorophosphate was carried out. (12bα, 12cα)-1,2,3,8,9,10,11,12,12b,12c-Dodecahydro-3a,7b,10a,12a-tetraazabenzo[e]pyrene (**15**) (24.6 mg, 0.091 mmol) was dissolved in deuterated-MeCN (0.70 mL) and ammonium hexafluorophosphate (14.9 mg, 0.091 mmol) was added to the solution. The reaction mixture was heated under reflux at 70 °C under nitrogen for 18 h. Aliquots were removed to monitor the progress of the reaction by NMR. A broad water peak was observed, so the reaction mixture was stored over activated 3Å molecular

sieves for a day to give the following spectra: ^{1}H NMR (400 MHz, CD_3CN, ref. central peak of CHD_2CN set at 1.94) δ 1.48 – 1.51 (dm, J = 14.0 Hz, 2H), 2.02 – 2.23 (m, 2H), 2.58 – 2.69 (m, 2H), 2.95 (td, J = 14.0, 13.5, 4.1 Hz, 4H), 3.07 – 3.17 (dm, J = 13.0 MHz, 2H), 3.29 (br s, 2H), 4.02 – 4.13 (dm, J = 13.0 MHz, 3H), 4.26 (s, 2H), 6.72 – 6.80 (m, 2H), 6.82 – 6.89 (m, 2H). ^{13}C{^{1}H} (100.51 MHz, CD_3CN ref. central peak of CD_3CN set at 1.32 ppm) δ 20.14, 47.38, 47.38, 53.55, 72.56, 114.86, 121.79, 134.19.

Attempted reduction of 15 to 2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (58). Compound **15** (64.7 mg, 0.239 mmol) was dissolved in (0.50) mL of MeOH in a 25 mL round-bottomed flask. Trifluoroacetic acid (TFA) (36.6 μL, 0.478 mmol) of was added via syringe. Following 5–8 min of reaction time, $NaBH_4$ or sodium triacetoxyborohydride ($NaBH(OAc)_3$) (90.0 mg, 2.39 mmol) was added in one portion to the reaction mixture. The reaction was run for 5 d at room temperature, monitoring the reaction progress by TLC. No change was observed in TLC. The reaction was worked up by addition of aq HCl (3.0 M, 15mL) to pH ≤ 0. The solvent was removed and the resulting mixture was dissolved in H_2O (10mL), and the pH was adjusted to 14 by addition of KOH pellets with stirring and cooling (ice/H_2O bath). The basic solution was extracted with toluene (3 × 15 mL), the combined organic extracts were dried over anhyd Na_2SO_4, and the filtrate was concentrated to afford a yellow oil which solidified upon storage (52.0 mg, 89%). ^{1}H NMR in acetone-d_6 showed only starting material **15**.

5-(prop-2-en-1-yl)-2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (57). A (39:54) mixture of (12c*R*,12d*R*)-3a-(prop-2-en-1-yl)-2,3,4,5,7,8,12c,12d-octahydro-1*H*,6*H*-5a,8a,12b-triaza-3a-azoniabenzo[*e*]pyrene bromide stereoisomers (**55** & **56**) (0.706 g, 1.80 mmol) was dissolved in 95% EtOH (10 mL). $NaBH_4$ (0.684 g, 18.1 mmol) was added batchwise over a period of 5 min while stirring at rt and the reaction was run 4 d at room temperature. The reaction mixture was then cooled in ice/H_2O bath and was quenched by dropwise addition of aq HCl (3.0 M, 15.0 mL) to pH ≤ 1 with vigorous stirring. The acidic mixture was concentrated in vacuo and the resulting material was dissolved in H_2O (25.0 mL) before the pH was adjusted to 14 by the addition of KOH pellets. This basic solution was extracted with toluene (4 × 75 mL), the combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to give product as a yellow oil. The product was purified by normal phase chromatography on silica (gradient elution 1% to 10% *i*-$PrNH_2$/$CHCl_3$) to give yellow oil (0.396 g, 1.26 mmol, 70% of ≥ 94% purity by ^1H NMR). ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 – 1.59 (m, 1H), 1.80 – 1.90 (m, 1H), 1.93 – 2.08 (m, 2H), 2.32 – 2.41 (m, 2H), 2.47 – 2.66 (m, 5H), 2.71 – 2.86 (m, 3H), 2.87 – 2.99 (m, 3H), 3.22 (ddd, *J* = 10.2, 4.4, 3.3 Hz, 1H), 3.52 (ddd, *J* = 11.0, 6.4, 3.3 Hz, 1H), 3.69 (ddd, *J* = 13.4, 9.7, 3.3 Hz, 1H), 3.87 (ddd, *J* = 9.2, 5.7, 3.6 Hz, 1H), 3.93 (ddd, *J* = 10.1, 9.0, 6.4 Hz, 1H), 4.90 – 5.03 (dm, J = 13.7, 2H), 5.52 – 5.62 (m, 1H), 6.57 – 6.66 (m, 3H), 6.68 – 6.74 (m, 1H). $^{13}C\{^1H\}$ NMR (125.67 MHz, $CDCl_3$) δ 22.74, 25.62, 46.73, 47.63, 49.00, 49.59, 50.18, 51.59, 52.41, 54.33, 54.37, 111.27, 111.31, 116.59, 117.16, 119.10, 134.86, 137.33, 137.53.

2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (**58**). Crude 5-(prop-2-en-1-yl)-2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (≥ 94% purity) (**59**), (105 mg, 0.334 mmol) was dissolved completely in EtOH/H_2O (4:1, 19.0 mL) and *p*-TsOH (95.7 mg, 0.50 mmol) was added to the solution. 10% Pd/C (15.7 mg, 15 wt% of **59**) was added to the reaction mixture with stirring and the mixture was refluxed for 30 h under nitrogen. The reaction mixture was cooled to room temperature, filtered through plug of Celite and washed with 95% EtOH (30 mL). The filtrate was concentrated by rotary evaporation dissolved in ice cold aq KOH (3.0 M, 25.0 mL), and the pH was adjusted to ≥ 14 by further addition of KOH pellets under ice/H_2O bath. The basic solution was extracted with $CHCl_3$ (4 × 20 mL) and crushed ice to keep it cold, the combined chloroform extracts were dried over anhyd Na_2SO_4, and the filtrate was concentrated to give the crude product as yellow oil of (78.6 mg, , crude yield 86% and purity ≥ 80%). The product was purified by reversed-phase chromatography (RPC) on a siliasep C18 cartridges (gradient elution 5% to 20% CH_3CN/H_2O (1% TFA)) to give a brown glassy product. The protonated material was dissolved in H2O (mL) and the pH was adjusted to 14 by addition of KOH pellets. The basic solution was extracted with $CHCl_3$ (5 × 20 mL). The combined $CHCl_3$ solution was dried over anhyd Na2SO4, and the filtrate was concentrated by rotary evaporation. Following removal of residual solvent by the pump the desired product was obtained as an off-white solid (28.6 mg, 0.104 mmol, 31%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.37 – 1.46 (m, $CH_2CH_2CH_2$, 2H), 1.66 – 1.76 (m, $CH_2CH_2CH_2$, 2H), 1.47 – 1.76 (br s, N*H*, 2H), 2.33 – 2.41 (m, 2H), 2.49 – 2.59 (m, 8H), 2.68 – 2.76 (XX' of AA'XX', 2H), 3.42 – 3.50 (AA' of AA'XX', 2H), 3.56 (ddd, *J* = 14.2, 7.2, 3.4 Hz, 2H), 6.56 – 6.61 (m, 2H, Ar *H*),

6.81 – 6.87 (m, 2H, Ar *H*). $^{13}C\{^1H\}$ NMR (125.67 MHz, C_6D_6) δ 25.66, 48.32, 49.63, 49.78, 50.35, 117.93, 111.02, 117.93, 137.03. IR (cm^{-1}): 3301, 2918, 2872, 2811, 1593, 1513, 1473, 1348, 1242, HRMS–ESI (*m/z*) $[M + H]^+$ exact mass calcd for $C_{16}H_{26}N_4$, 275.2191; found, 275.2207. mp 86-88 °C.

Protonation of 2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine to prepare compounds (61 & 62).

2,3,4,5,6,7,8,9,10,11-Decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine **(58)** (10.0 mg, 36.4 μmol) was dissolved completely in dry MeOH (110.0 μL) and (6.30 mg, 38.6 μmol) of NH_4PF_6 was added to the solution and stirred for one hour at room temperature. The reaction mixture color slightly changed from yellow to brown. The solvent was removed by rotary evaporation and residual solvent was pumped off overnight. A brown solid of mass (15.0 mg, 98%) crude yield was obtained. In an attempt to purify and grow X-ray quality crystals, slow ether diffusion was carried out, but this didn't produce the good crystals. The same procedure was followed except with two equivalents of NH_4PF_6 to prepare diprotonated ligand **58**. However, ^1H NMR showed identical spectra as the above mono protonation. ^1H NMR (400 MHz, CD_3CN, ref. central peak of CHD_2CN set at 1.96) δ 1.78 – 1.89 (m, 2H), 1.97 – 2.07 (m, 2H), 2.76 – 3.12 (m, 12H), 3.65 – 3.75 (AA' of AA'XX', 2H), 3.86 (ddd, J = 14.2, 5.9, 3.5 Hz, 2H), 6.80 (s, 4H).

Complexation of 2,3,4,5,6,7,8,9,10,11-decahydro-1,12-ethano-1,5,8,12-benzotetraazacyclotetradecine (58) with $Zn(ClO_4)_2 \cdot 6H_2O$ to prepare 63. The adjacent-bridged compound **56** (19.9 mg, 0.073 mmol) was dissolved in dry degassed MeOH (0.7 mL) and N_2 gas was bubbled to it for 10-15 min. $Zn(ClO_4)_2 \cdot 6H_2O$ (26.3 mg, 0.071 mmol) was added to the reaction flask, and the reaction was stirred at room temperature for 24 h. The resulting clear yellow reaction mixture was filtered through a pad of Celite to remove small insoluble particles and the filtrate was concentrated by rotary evaporation to give a beige glassy solid (34.3 mg, 0.053 mmol, 75%). Slow ether diffusion is underway in an attempt to obtain X-ray quality crystals of the complex. ^1H NMR (400 MHz, CD_3OD) δ 1.84 – 2.04 (m, 4H), 2.05 – 2.17 (m, 1H), 2.18 – 2.57 (m, 4H), 2.62 – 2.77 (m, 2H), 2.78 – 2.30 (m, 4H), 3.09 (br s, 1H), 3.25 – 3.52 (m, 3H), 3.70 – 3.99 (m, 4H), 7.30 – 7.48 (m, 4H).

Attempted complexation of compound 58 to $Cu(ClO_4)_2 \cdot 6H_2O$. Compound **58** (28.4 mg, 0.103 mmol) was dissolved in dry degassed MeOH (0.5 mL) and the solution was degassed with bubbling N_2 for 20 min. Then $Cu(ClO)_4 \cdot 6H_2O$ (38.6 mg, 0.104 mmol) was added and blue reaction mixture was observed, but that didn't last long. After a few seconds of stirring at room temperature the reaction mixture turned dark. The reaction was left to stir at room temperature for 1 d in the dark. The dark reaction mixture was concentrated by rotary evaporation and traces of solvent were removed in the vacuum pump to afford a black solid of (77.3 mg). Attempts to get IR data of the mixture were not helpful to draw any conclusion and no other conclusive data was obtained.

2,3,9,10-Dibenzo-1,5,8,12-tetraazacyclotetradeca-4,11-diene (37). Compound **36** was prepared according to the procedures of Betakis, Piesch and Reid.[51] In an oven dried 1 L 2-neck round bottom flask equipped with pressure equalizer addition funnel and reflux condenser, a mixture of dry toluene (225 mL), ethylenediamine (91.0 mL, 1.36 mol), Cu powder (14.3 g, 0.225 mol), and formic acid (4.5 mL, 0.119 mol) were combined at reflux for 35 min to give a blue heterogeneous mixture. This reaction mixture was allowed to cool to room temperature and then a solution of 2-chlorobenzaldehyde (25.0 mL, 0.222 mol) in toluene (26 mL) was added dropwise through the addition funnel over 45 min while stirring. This mixture was refluxed for 12 h and was hot filtered to remove residual Cu. The filtrate was separated in to blue aqueous layer and green organic layer. The aqueous layer was extracted with toluene (3 × 100 mL), the combined organic extracts were azeotropically distilled to remove additional H_2O under a Dean-Stark trap for 24 h, and then dried over anhyd Na_2SO_4. The solvent was removed by rotary evaporation to give yellow solid suspended over yellow viscous oil. The product was recrystallized from hot absolute EtOH to afford a yellow solid (4.4 g, 15.0 mmol, 14%, > 99% purity). Further crystals were harvested after 10, 26 and 40 days to yield an additional of (7.8 g, 26.7 mmol, 24%) combined to give a total of (12.2 g, 41.7 mmol, 38%). ^1H and $^{13}C\{^1H\}$ NMR spectra were consistent with spectra of authentic material.[17,51]

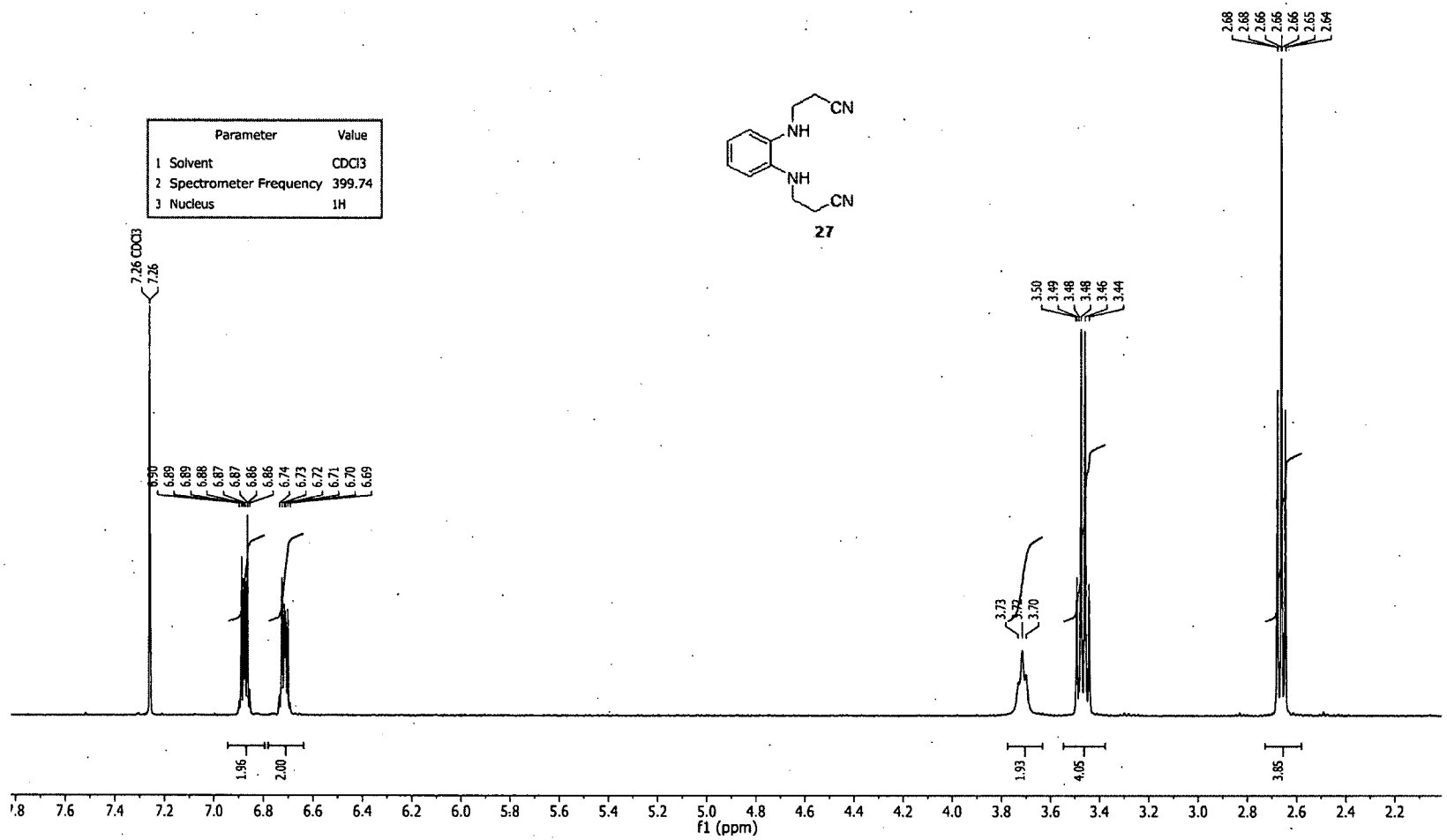
1,2,3,4,5,6,7,8,9,10-Dodecahydro-dibenzo[e,l][1,5,8,12]tetraazacyclotetradecine (19). This compound was prepared following J. Condon's procedure.[17] In an oven dried 1 L round-bottomed flask, 2,8,9,10-dibenzo-1,5,8,12-tetraazacyclotetradeca-4,11-diene (**37**)

(8.16 g, 27.9 mmol) was suspended in dry THF (560 mL). $NaBH_4$ (21.2 g, 0.559 mol) was addedbatch wise over 25 min while stirring under ice/H_2O bath, the resulting mixture was refluxed for 40 h to give a yellow heterogeneous mixture. The reaction was quenched by slow dropwise addition of 3 M aq HCl with vigorous stirring and cooling (ice/H_2O bath) to pH $\leq$ 1. The reaction mixture was concentrated by rotary evaporation, and dissolved in H_2O (270 mL), and the pH was adjusted to 14 by the addition of KOH pellets. The aq layer was extracted with $CHCl_3$ (6 × 150 mL), the combined organic extracts were dried over anhyd Na_2SO_4, and solvent was evaporated to afford an off-white solid crude product. The product was purified by recrystallization from hot absolute EtOH to give a white solid (6.29 g, 21.2 mmol, 76%). NMR spectra were consistent with spectra of authentic material.[17]

(13bα,13cα)-5,6,7,12,13,13b,13c,14-Octahydro-4b,6a,11b,13a-tetraazadibenzo[b,def]chrysene (20). 1,2,3,4,5,6,7,8,9,10-Dodecahydro-dibenzo[e,l][1,5,8,12]tetraazacyclotetradecine **19** (1.38 g, 4.62 mmol) was suspended in MeOH (83.0 mL) in a 200 mL round-bottomed flask equipped with a reflux condenser and magnetic stirrer. 40% aqueous glyoxal (0.64 mL, 5.55 mmol) was added dropwise via a syringe with stirring and the heterogeneous reaction mixture was refluxed for 35 h. The reaction mixture was cooled to room temperature and the white solid was isolated by vacuum filtration and washed with MeOH. Residual solvent was removed by vacuum pump to give product as white solid (1.22 g, 3.83 mmol, 83%). NMR spectra were consistent with spectra of authentic material.[17]

Di-bromo-dibenzo-tetraaza-bisaminal (21). Compound **21** was prepared following Yijie Peng's procedure.[44] (13bα,13cα)-5,6,7,12,13,13b,13c,14-Octahydro-4b,6a,11b,13a tetraazadibenzo[b,def]chrysene (**20**) (199.0 mg, 0.625 mmol) was dissolved in $CHCl_3$ (36 mL). Tetrabutylammonium tribromide ($TBABr_3$) (0.669 g, 1.387 mmol) was added to with stirring and the reaction was stirred at room temperature under nitrogen for 2 d. The reaction mixture was diluted with $CHCl_3$ (400 mL) and H_2O (200 mL), the pH was adjusted to $\geq$ 14 by the addition of KOH pellets. The basic solution was extracted (2 × 150 mL) with saturated sodium thiosulfate ($Na_2S_2O_3$) solution, the aqueous layer was extracted (2 × 150 mL) $CHCl_3$ and the combined organic extracts were washed (2 × 150 mL) with H_2O, and (2 × 85 mL) with saturated NaCl solution. The organic layer was dried over anhyd Na_2SO_4, filtration followed by removal of solvent gave crude product as off-white solid. The product was purified by recrystallization from hot $CHCl_3$ to afford product as white powder (186.3 mg, 0.391 mmol, 63%). NMR spectra were consistent with spectra of authentic material.[44]

Spectral Index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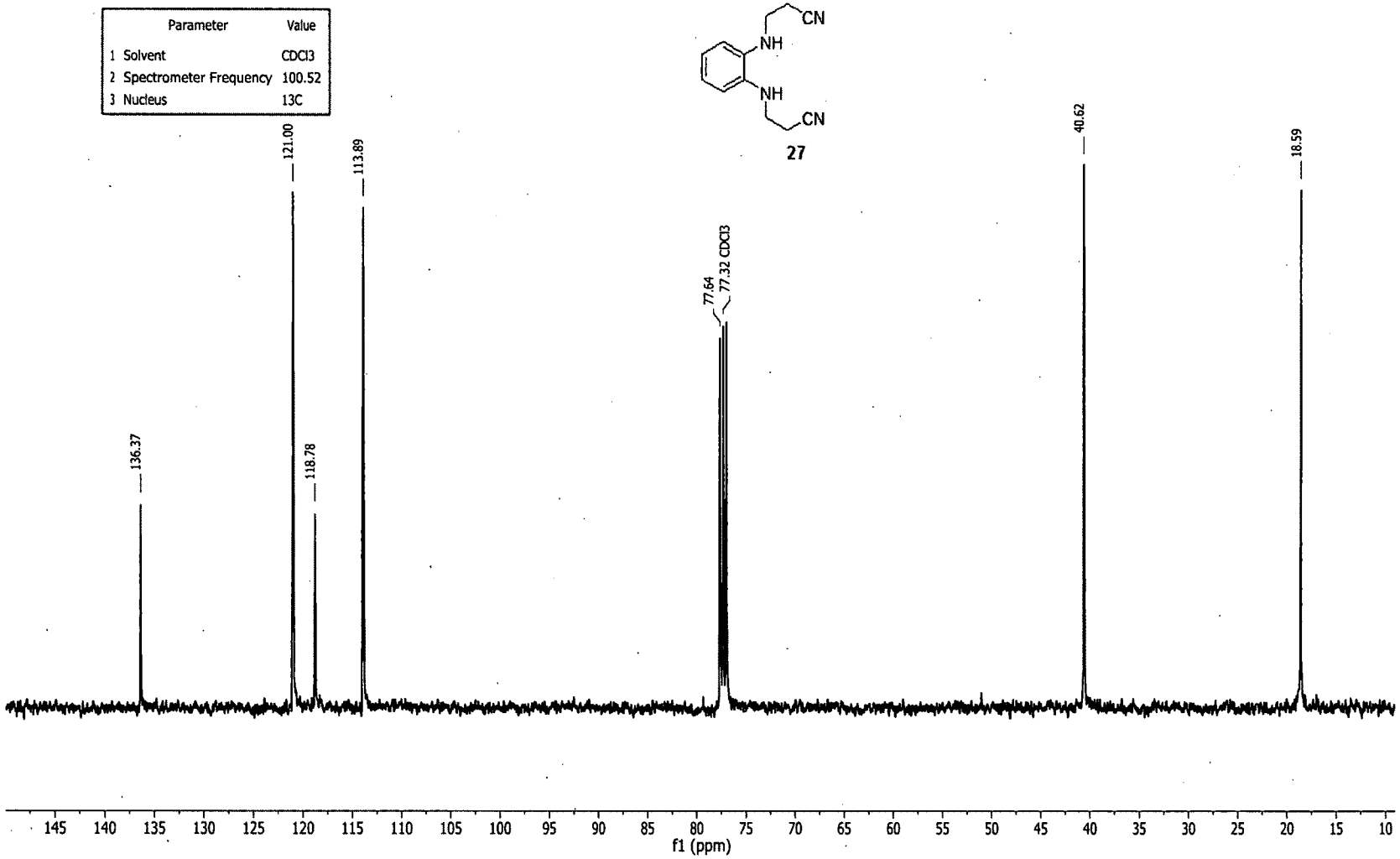
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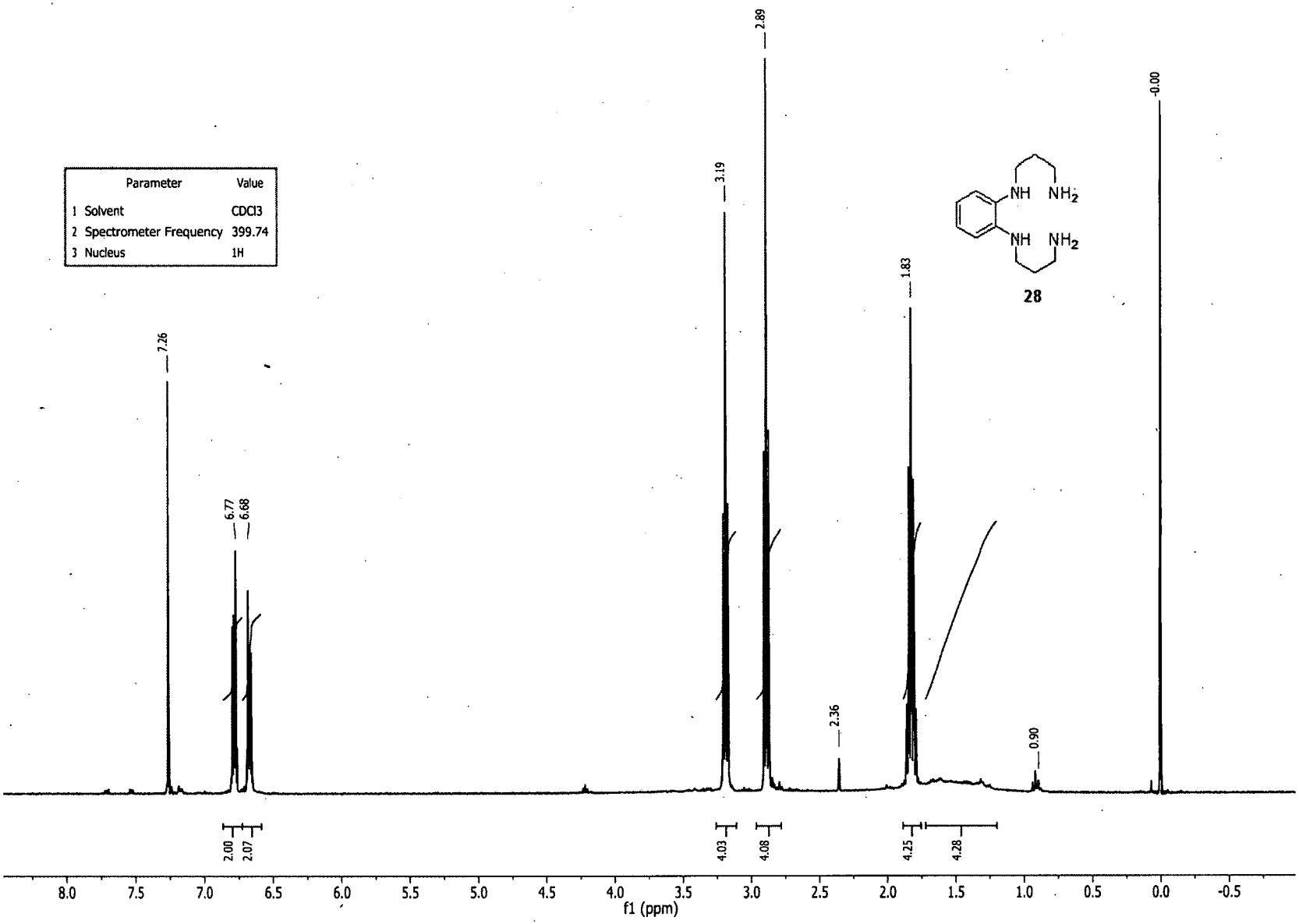
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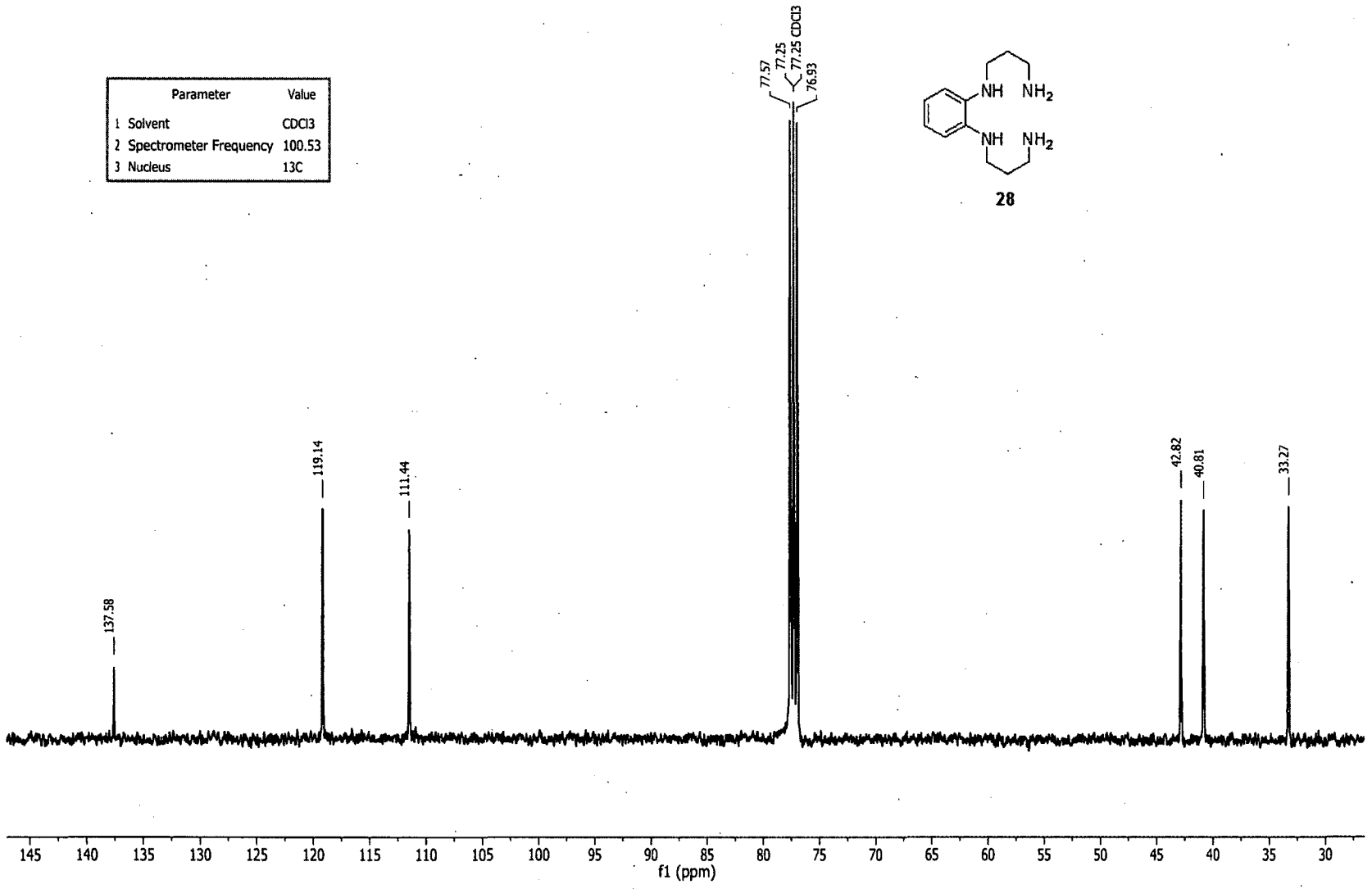
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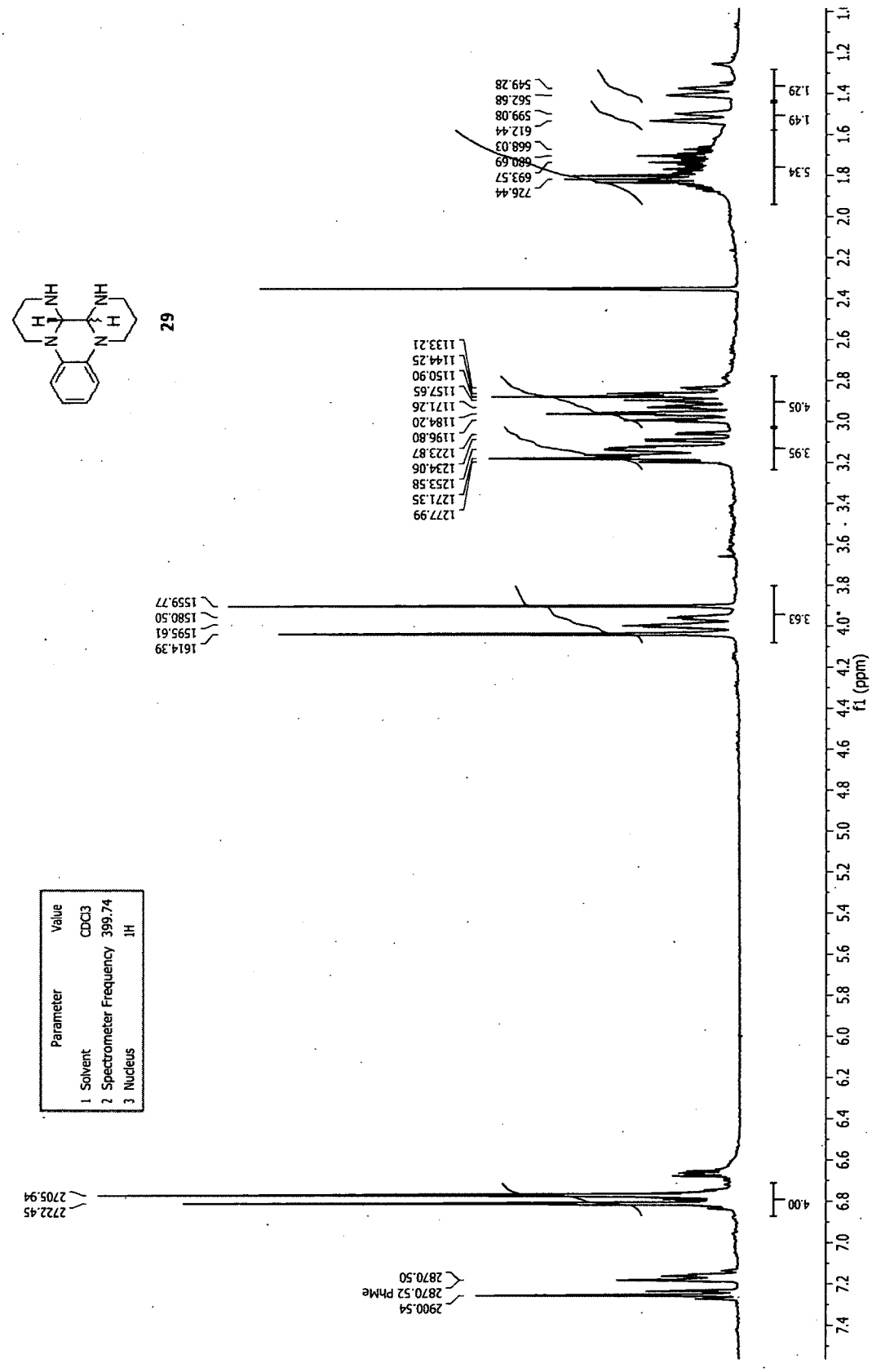
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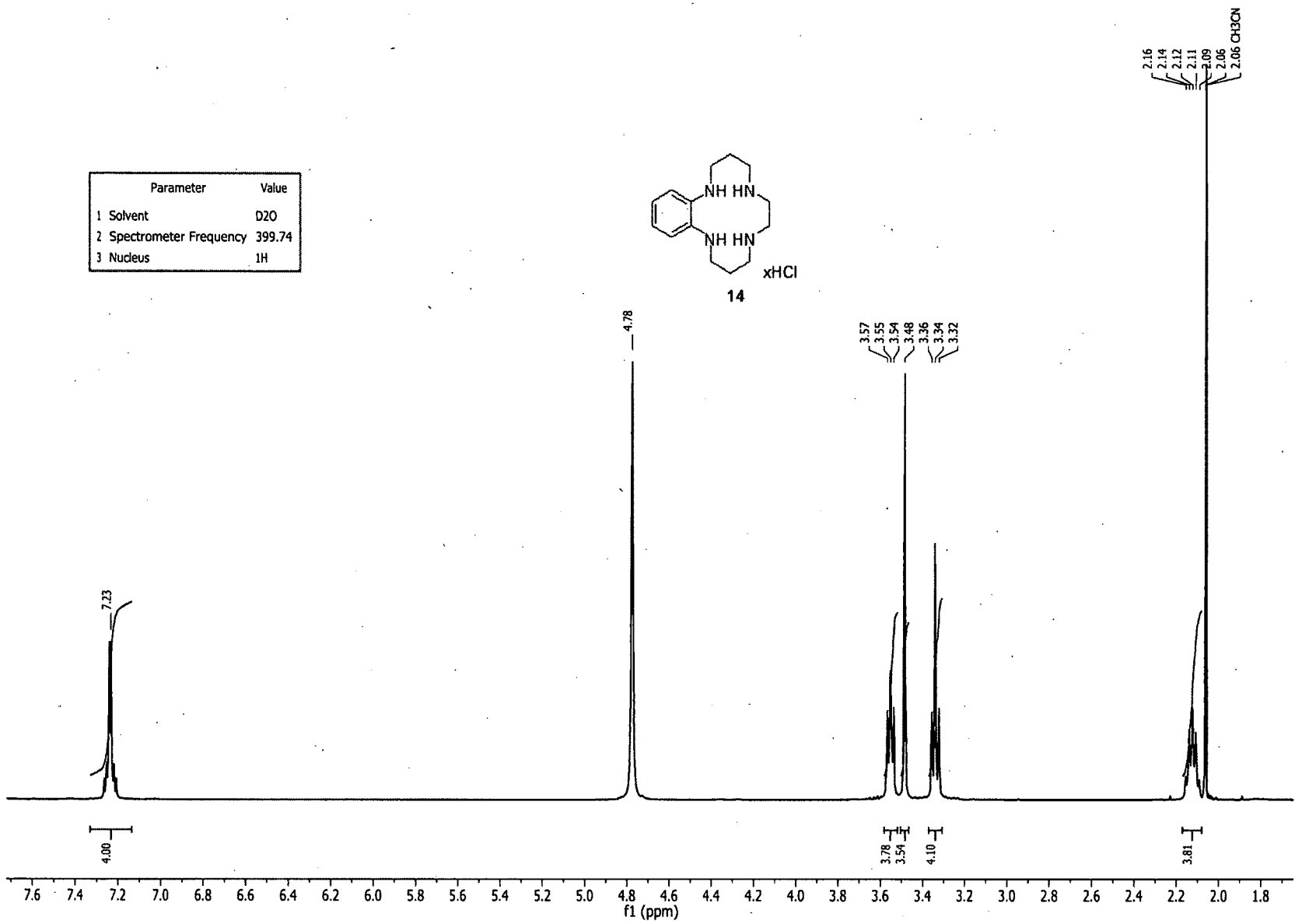
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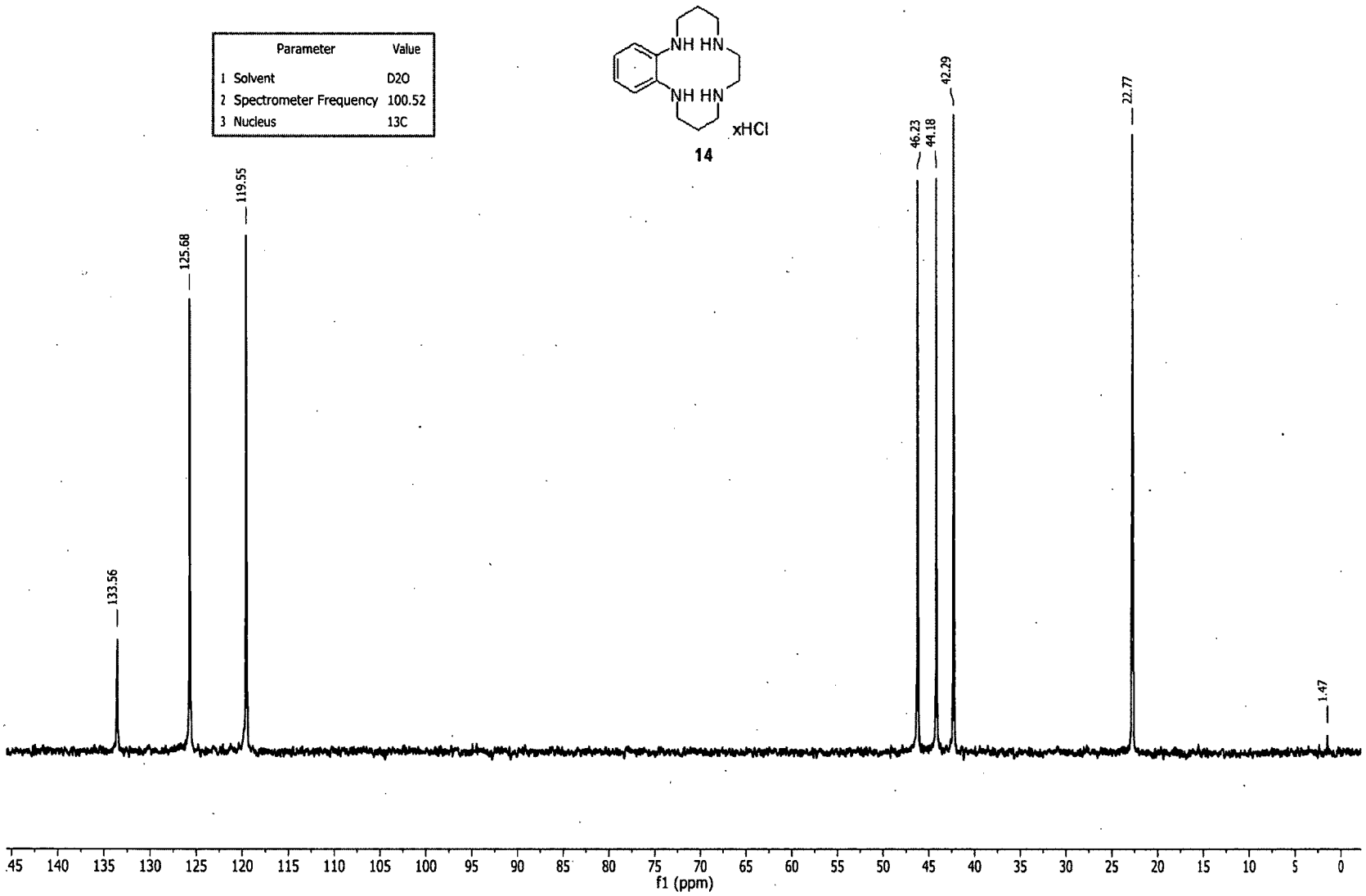
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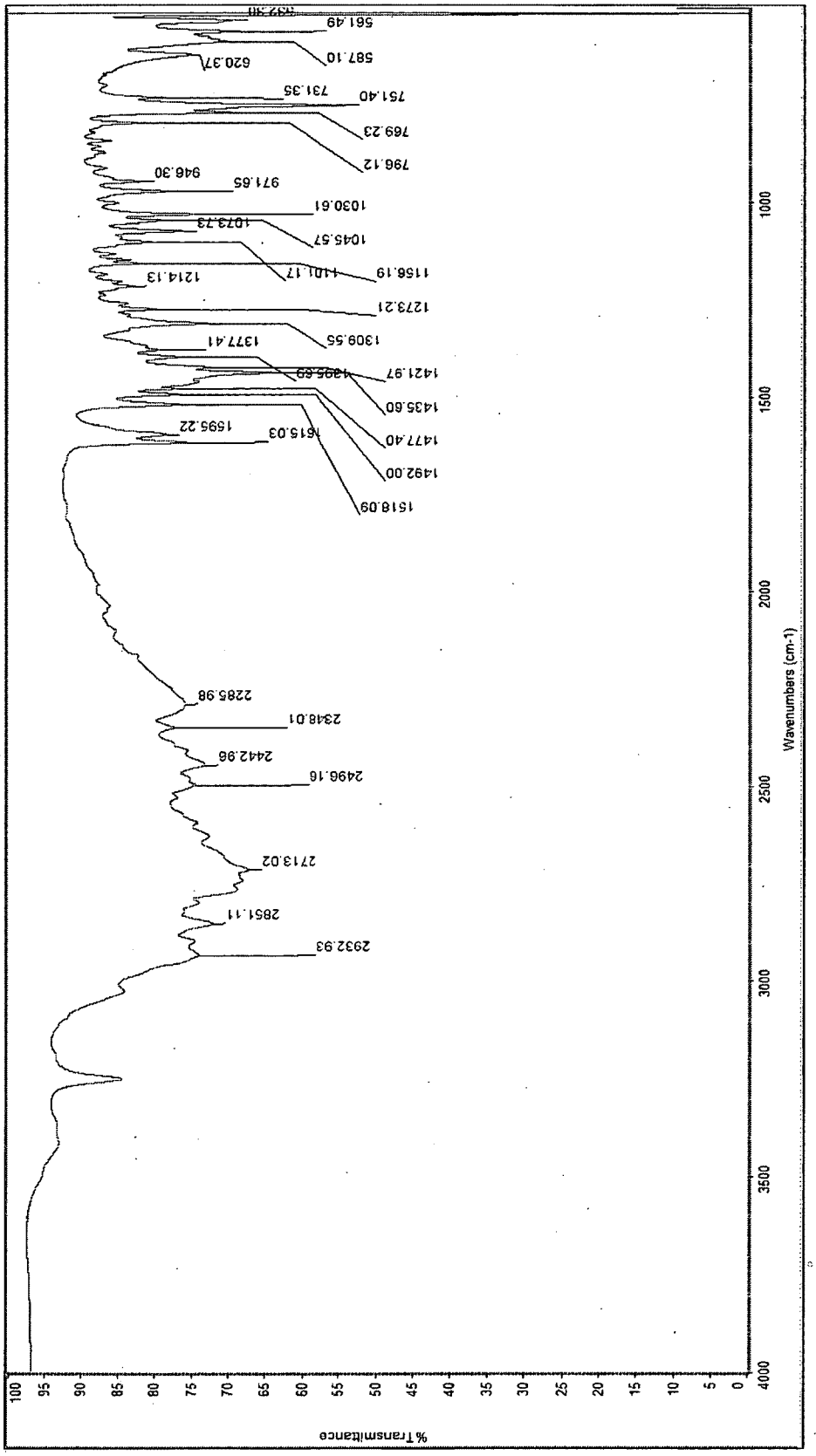
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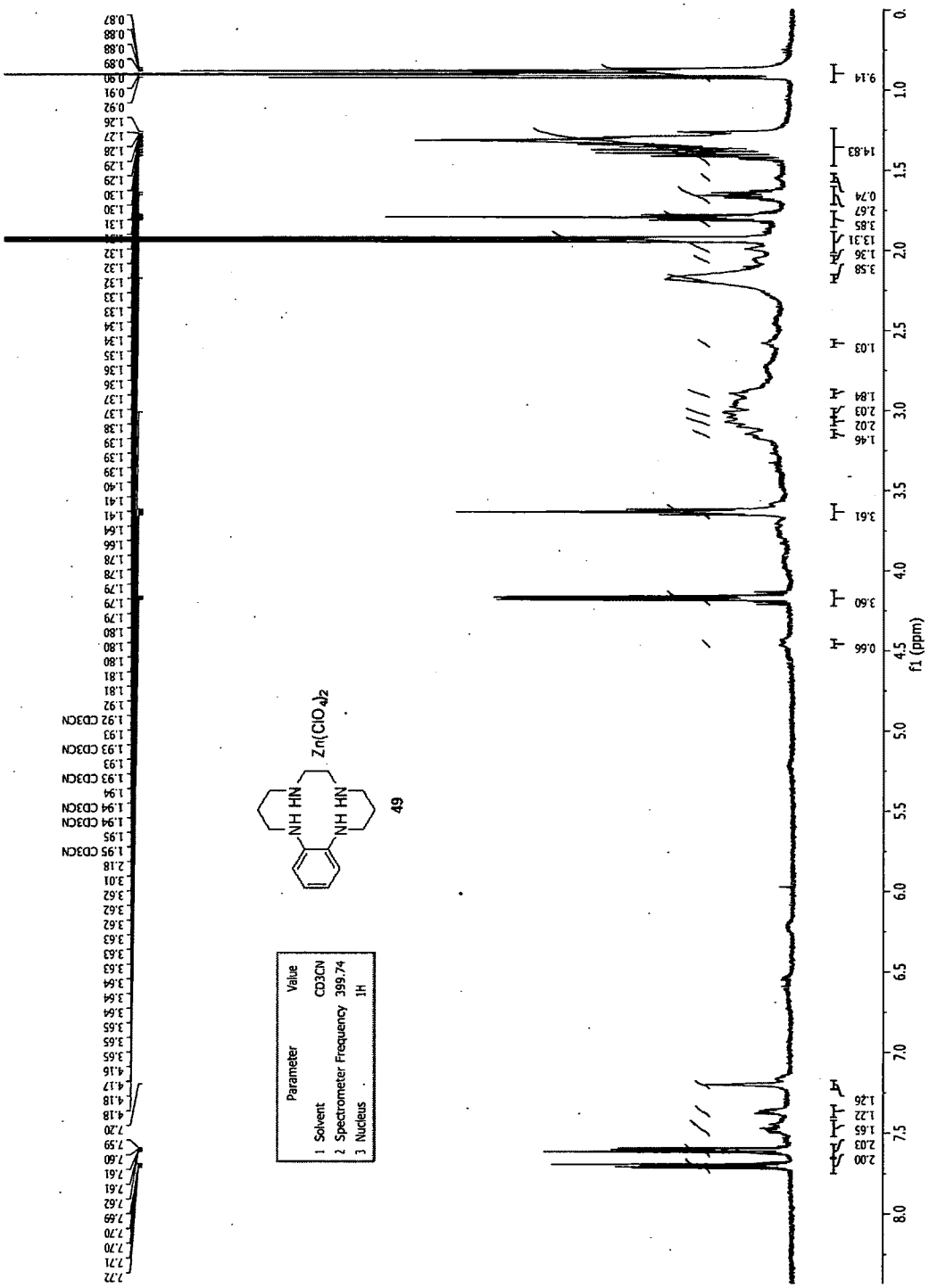
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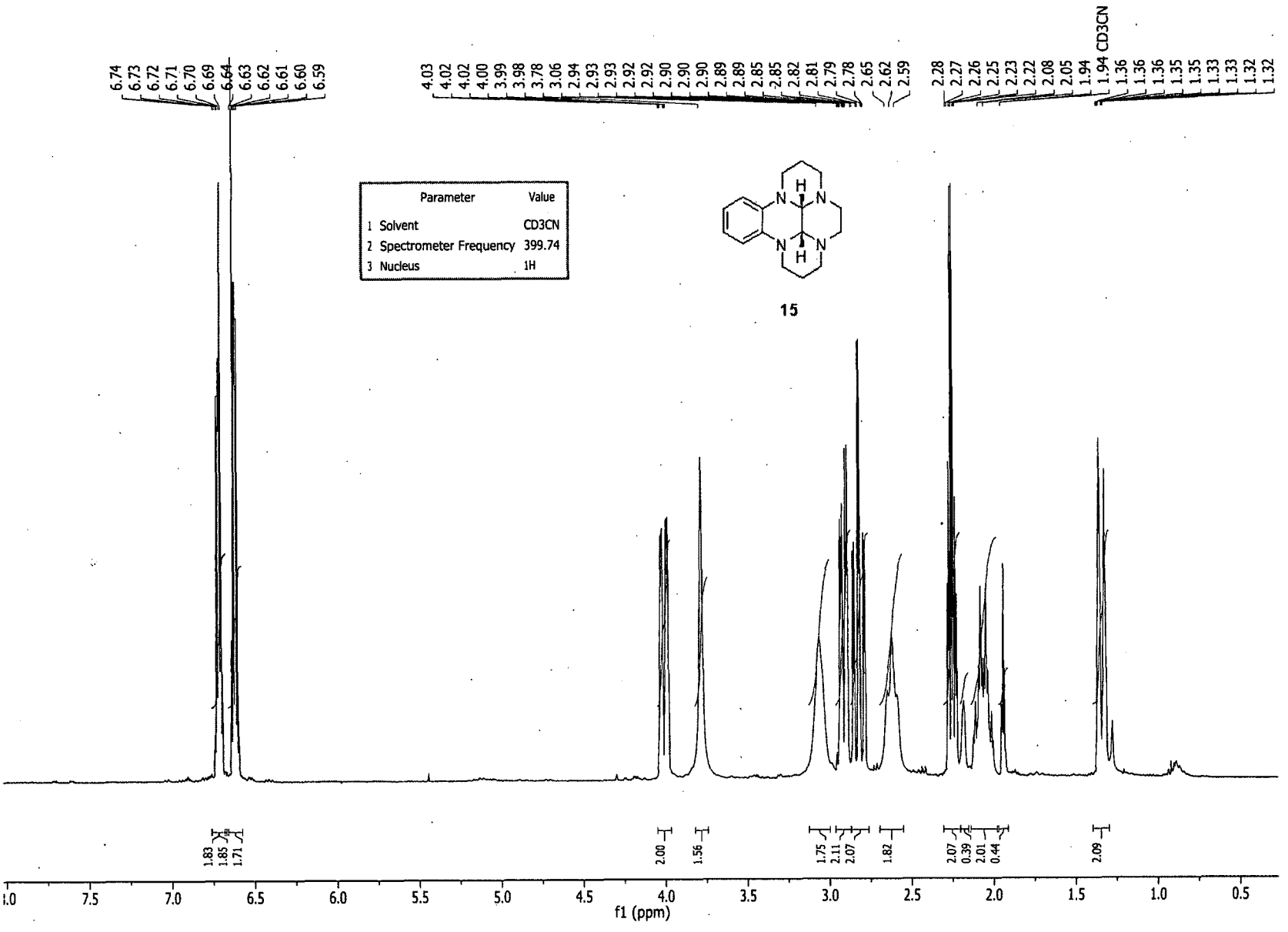
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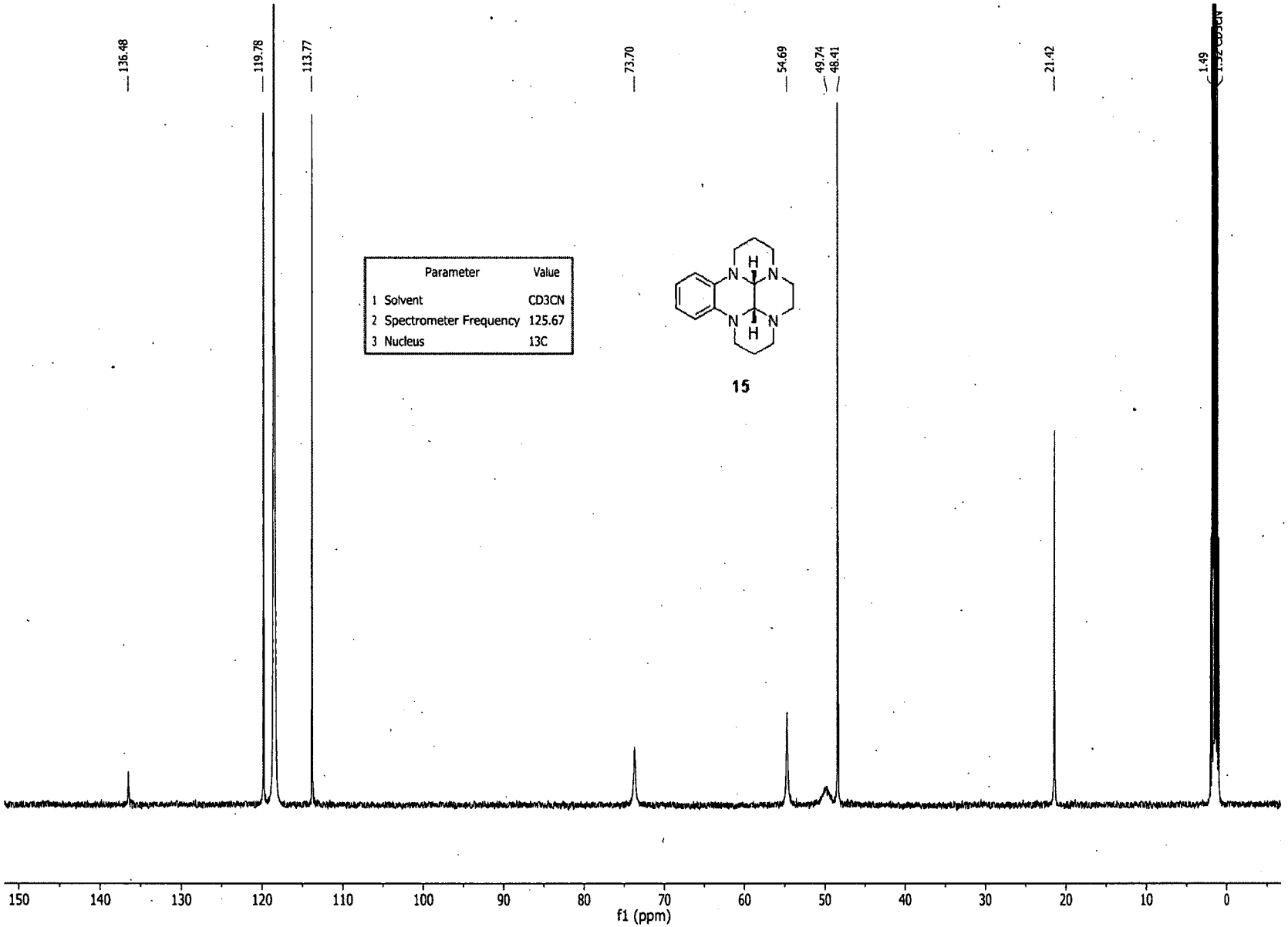
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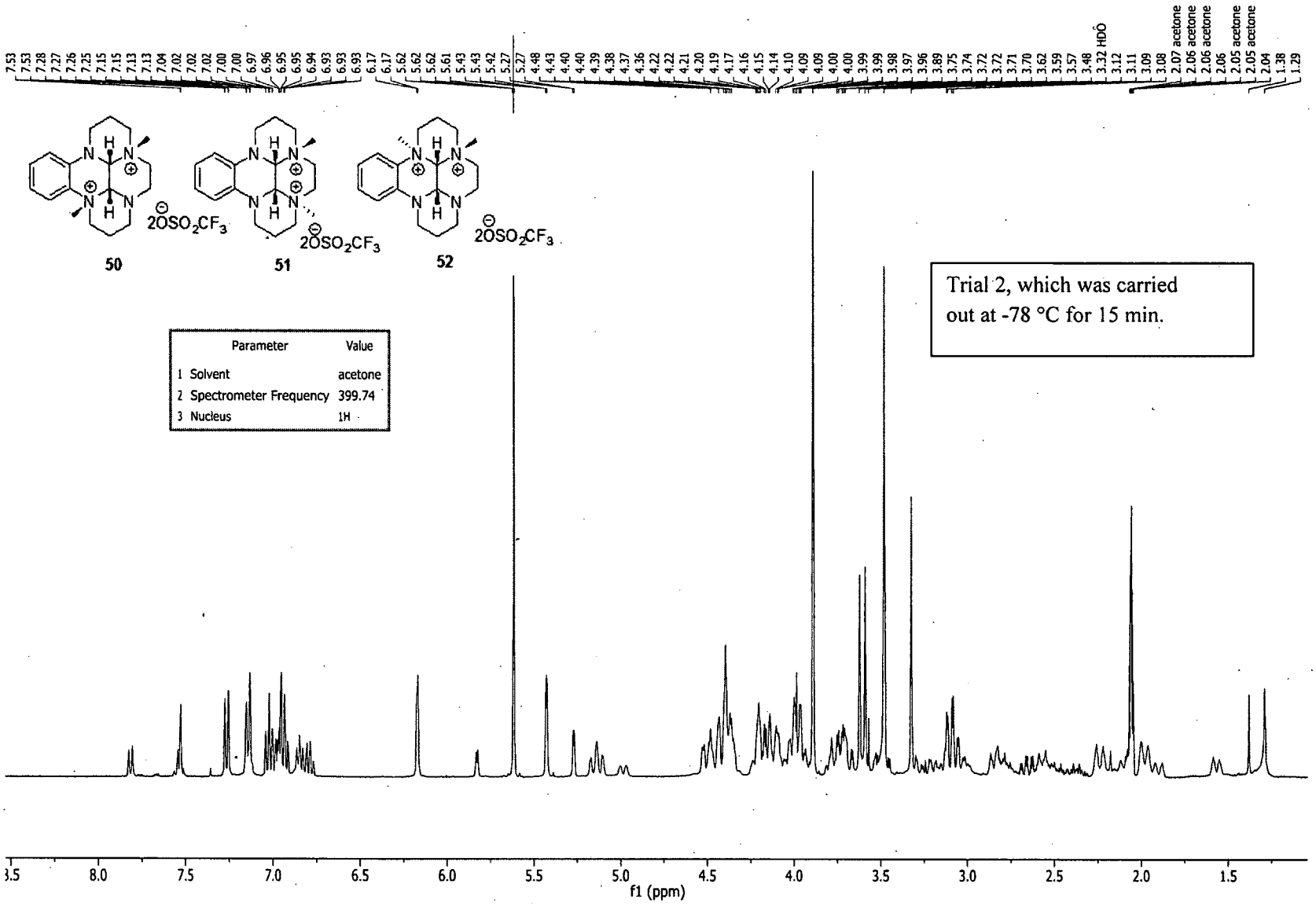
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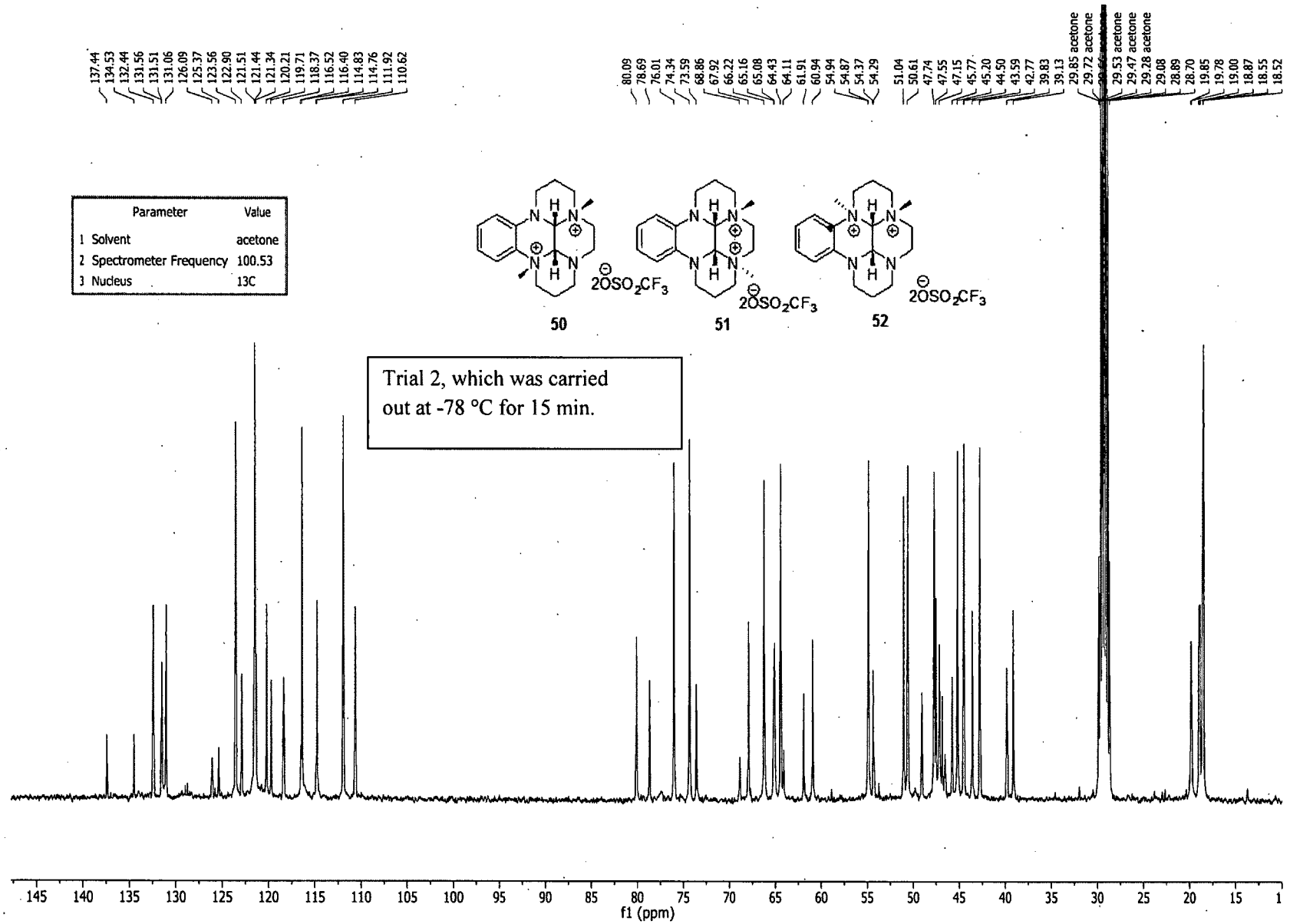
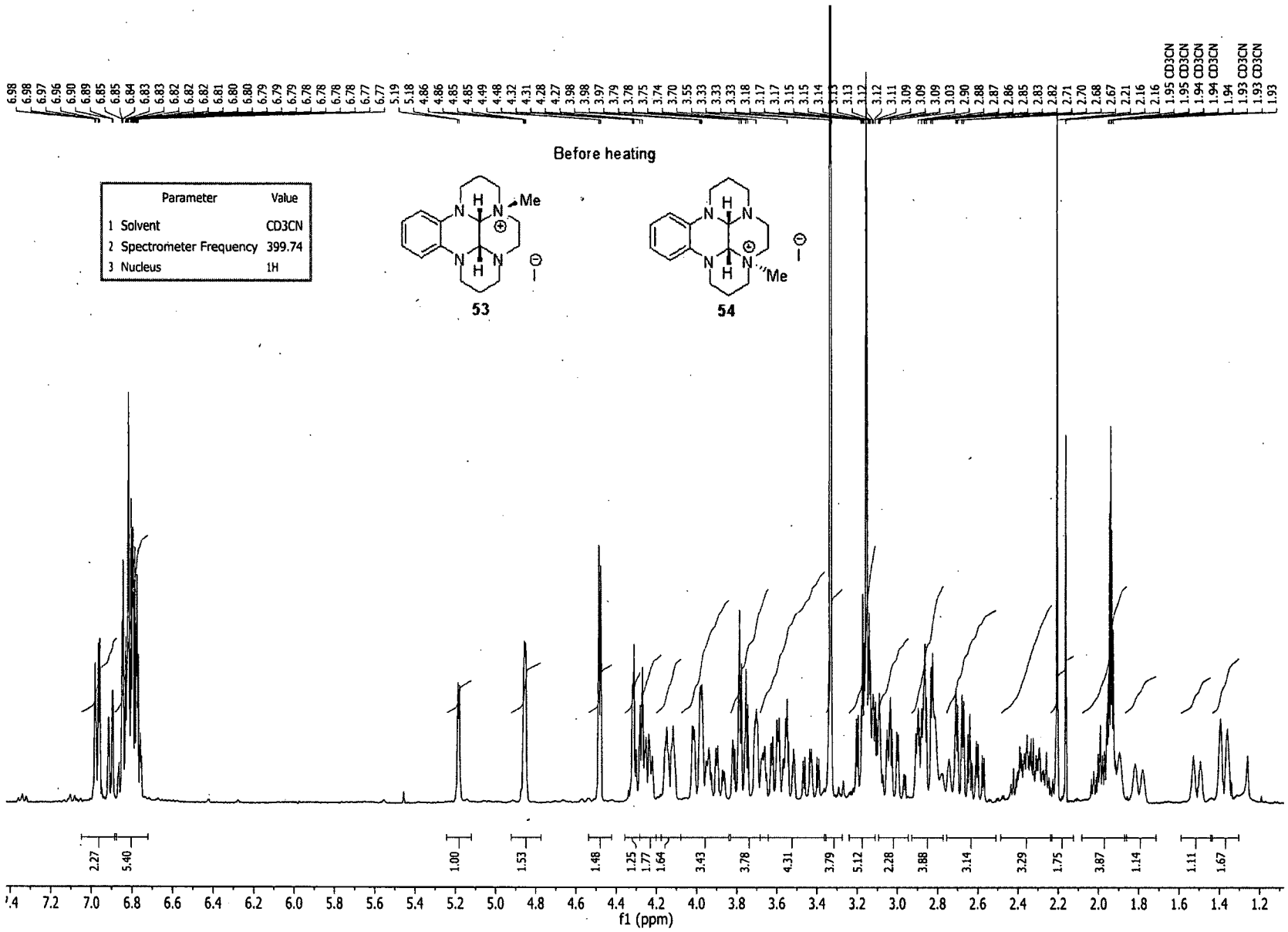
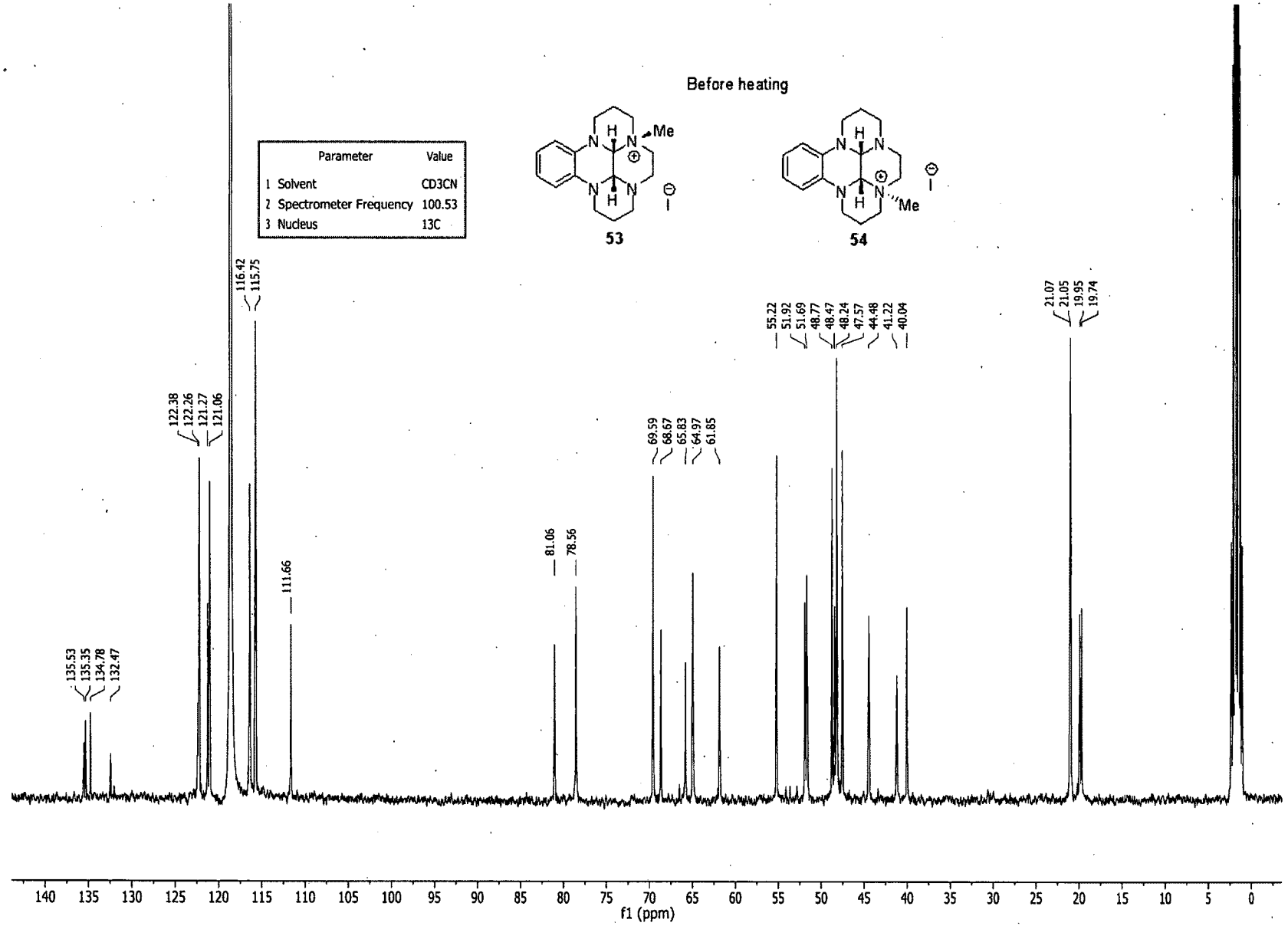
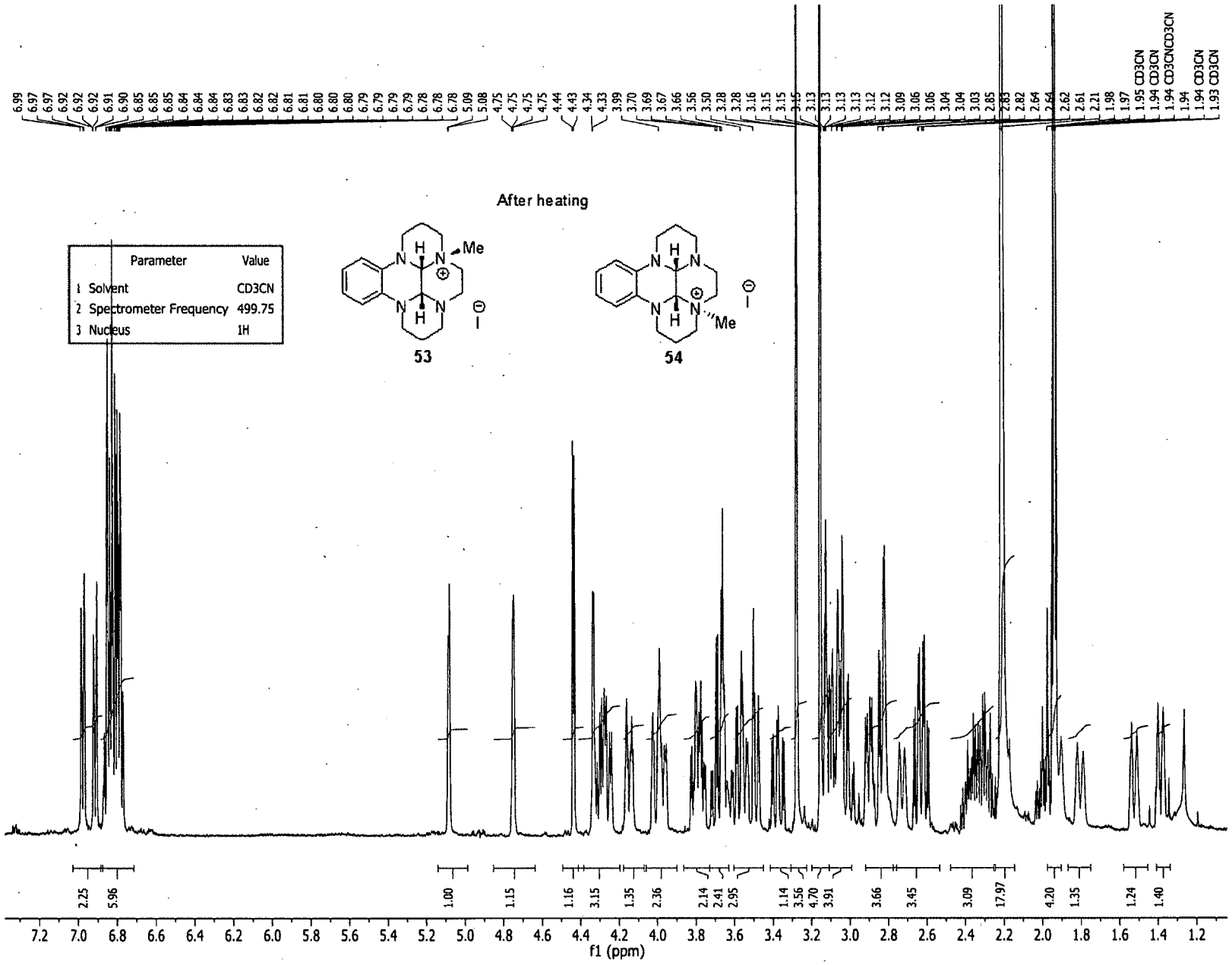
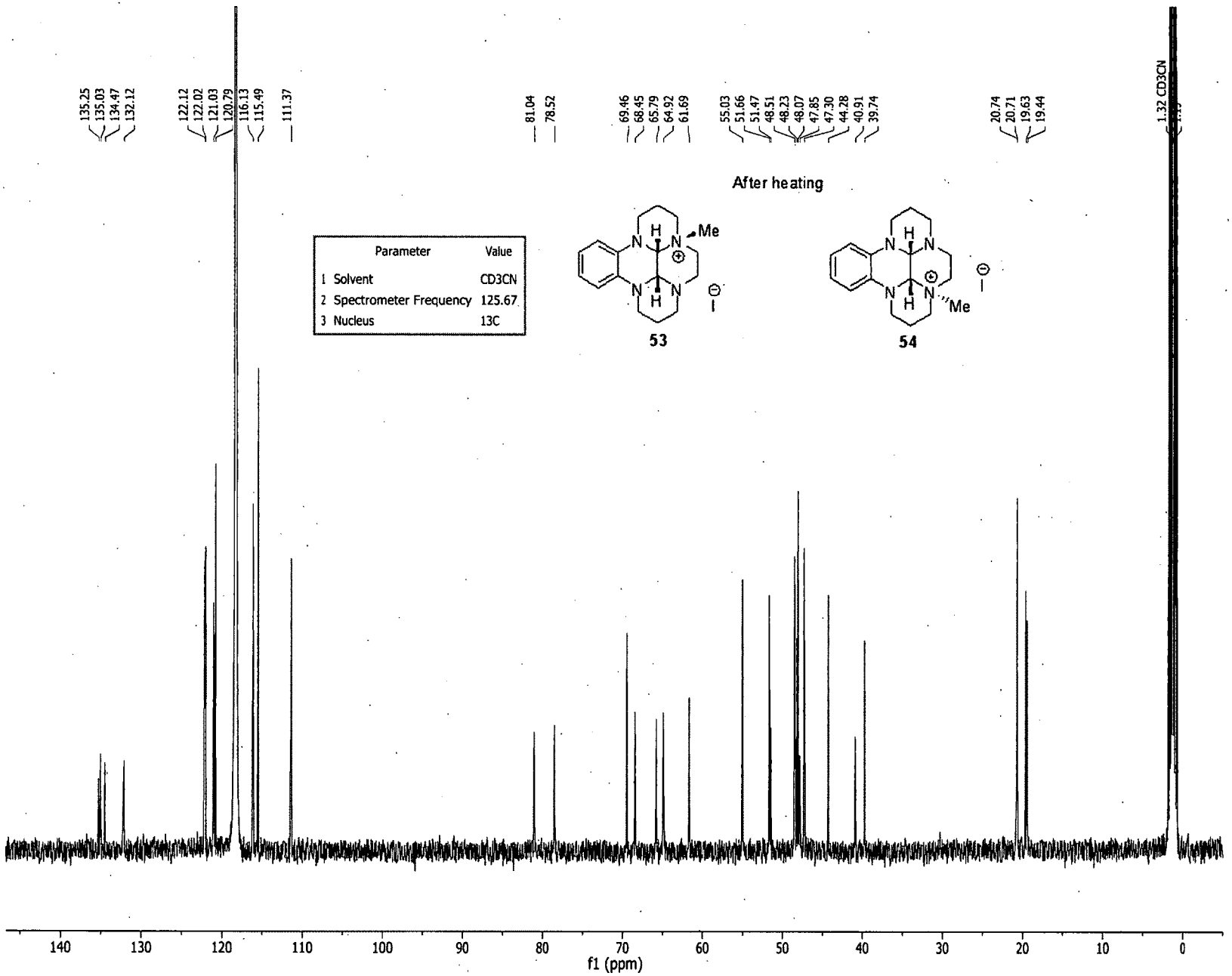
3 Nucleus 1H
f1 (ppm)

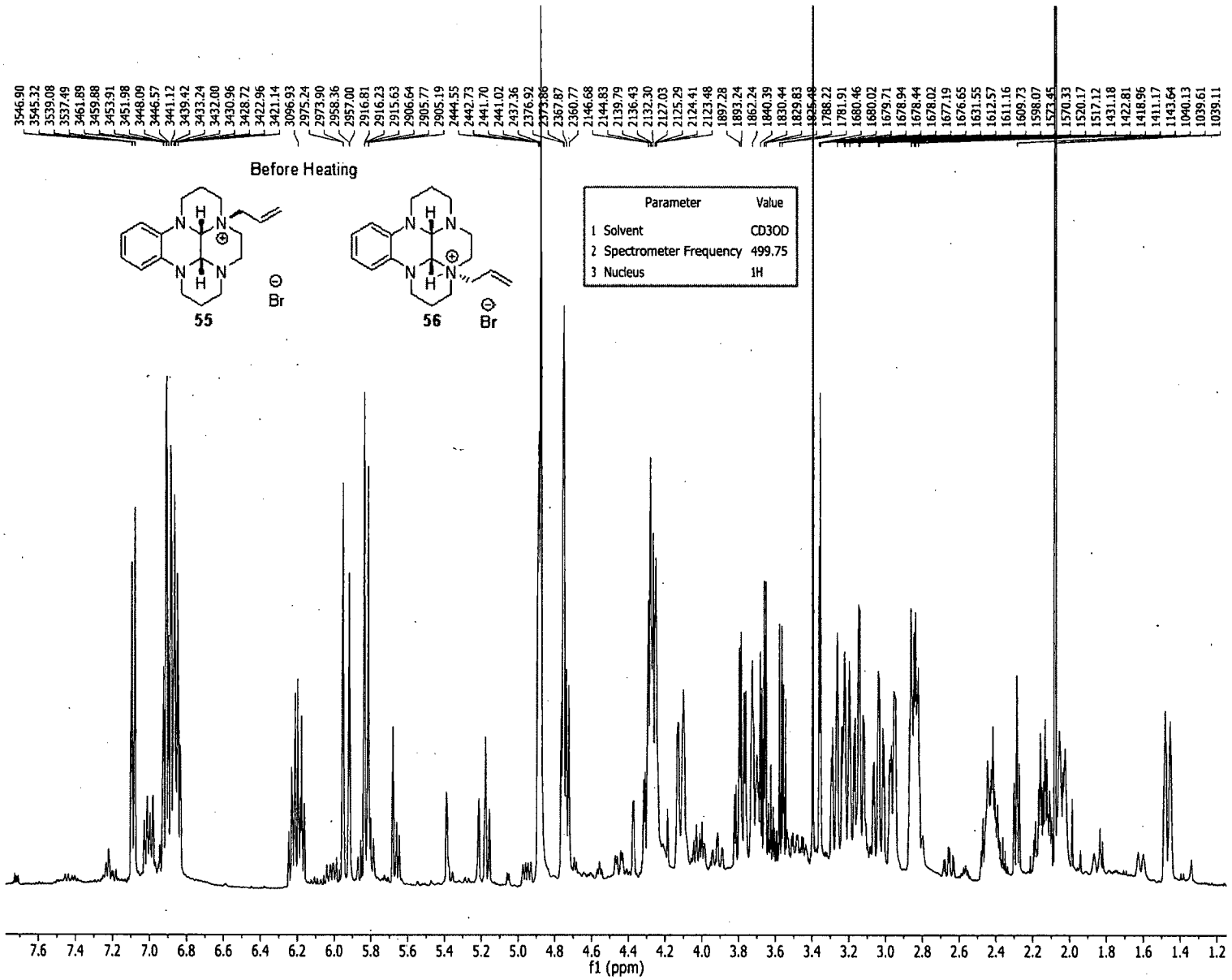

137.44
134.53
132.44
131.56
131.51
131.06
126.09
125.37
123.56
122.90
121.51
121.44
121.34
120.21
119.71
118.37
116.52
116.40
114.83
114.76
111.92
110.62
80.09
78.69
76.01
74.34
73.59
68.86
67.92
66.22
65.16
65.08
64.43
64.11
61.91
60.94
54.94
54.87
54.37
54.29
51.04
50.61
47.74
47.55
47.15
45.77
45.20
44.50
43.59
42.77
39.83
39.13
29.85 acetone
29.72 acetone
29.53 acetone
29.47 acetone
29.28 acetone
29.08
28.89
28.70
19.85
19.78
19.00
18.87
18.55
18.52
Parameter Value
1 Solvent acetone
2 Spectrometer Frequency 100.53
3 Nucleus 13C
2OSO2CF3
50
2OSO2CF3
51
2OSO2CF3
52
Trial 2, which was carried out at -78 °C for 15 min.
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 1
f1 (ppm)

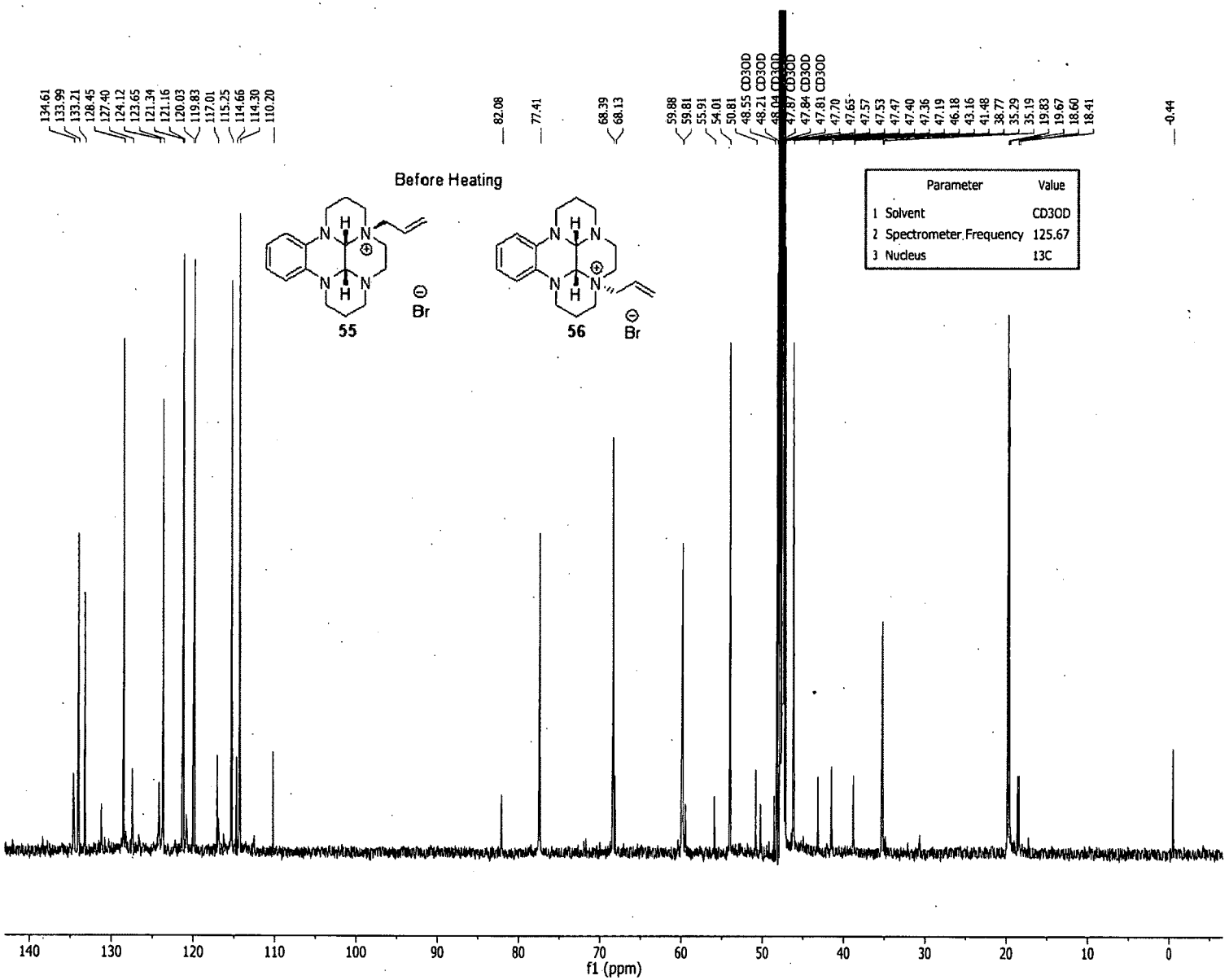

Before heating
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 399.74
3 Nucleus 1H
53
54
f1 (ppm)

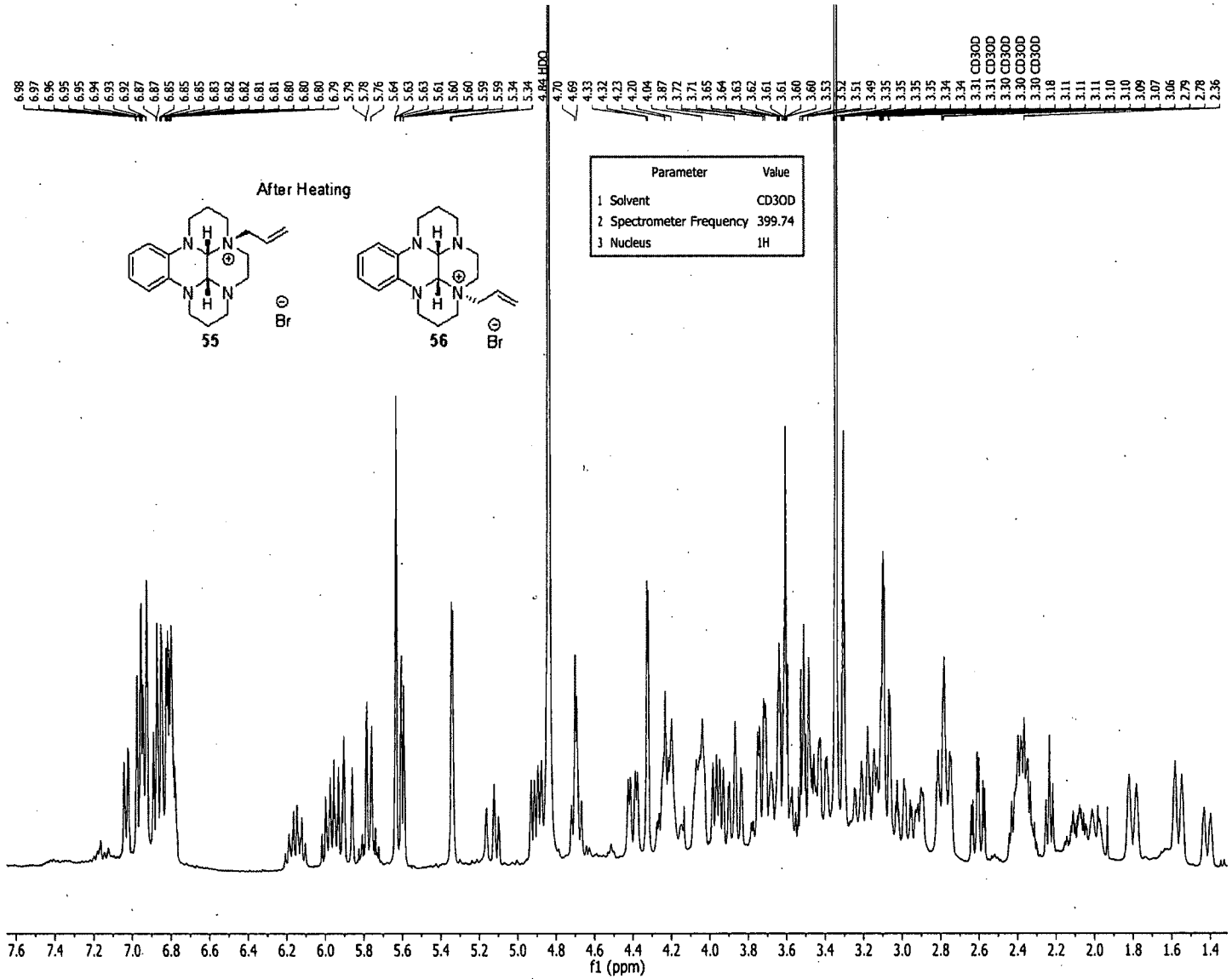

Before heating
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 100.53
3 Nucleus 13C
53
54
135.53
135.35
134.78
132.47
122.38
122.26
121.27
121.06
116.42
115.75
111.66
81.06
78.56
69.59
68.67
65.83
64.97
61.85
55.22
51.92
51.69
48.77
48.47
48.24
47.57
44.48
41.22
40.04
21.07
21.05
19.95
19.74
f1 (ppm)

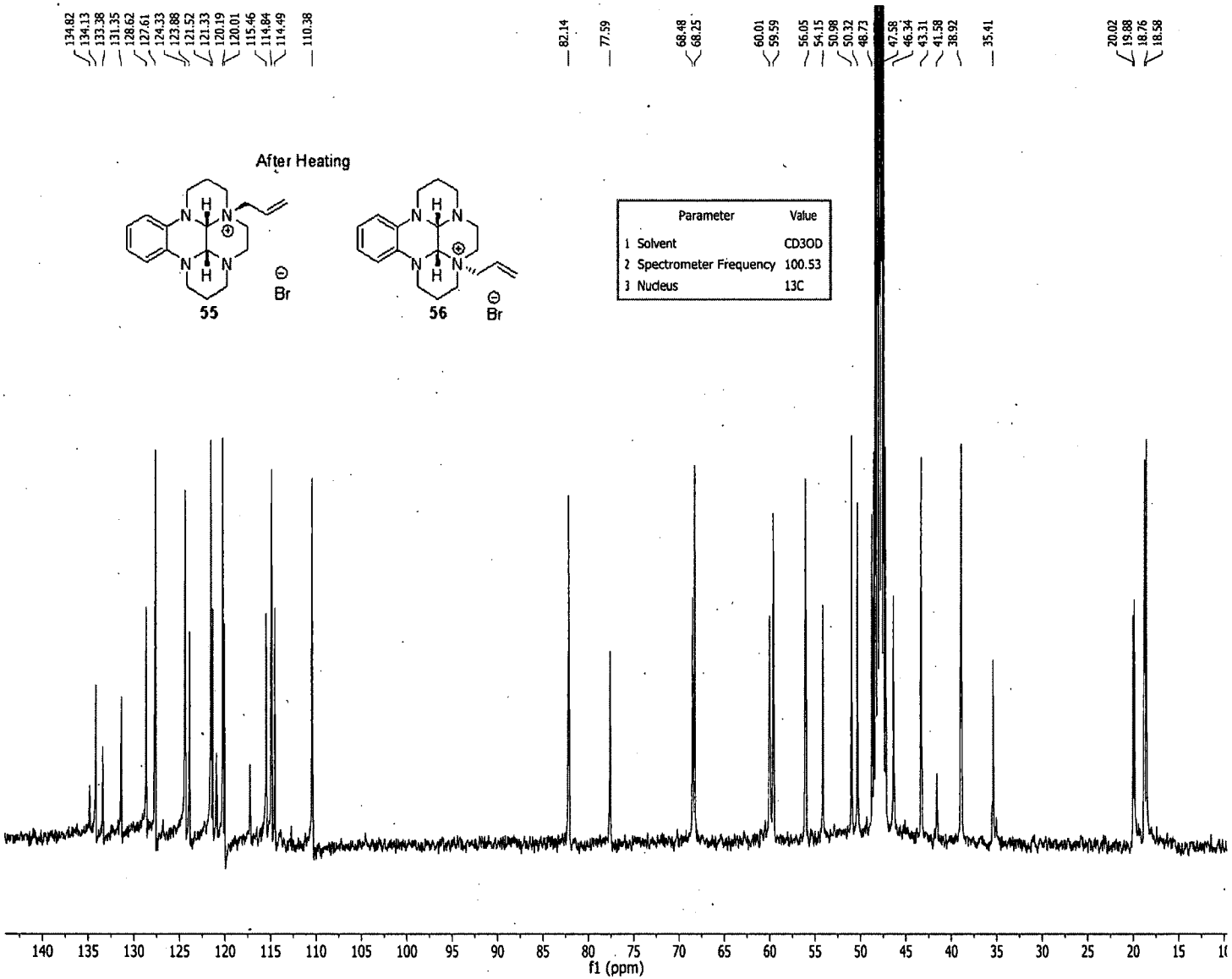

After heating
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 499.75
3 Nucleus 1H
53
54
f1 (ppm)


135.25
135.03
134.47
132.12
122.12
122.02
121.03
120.79
116.13
115.49
111.37
81.04
78.52
69.46
68.45
65.79
64.92
61.69
55.03
51.66
51.47
48.51
48.23
48.07
47.85
47.30
44.28
40.91
39.74
20.74
20.71
19.63
19.44
1.32 CD3CN
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 125.67
3 Nucleus 13C
After heating
Me
53
54
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

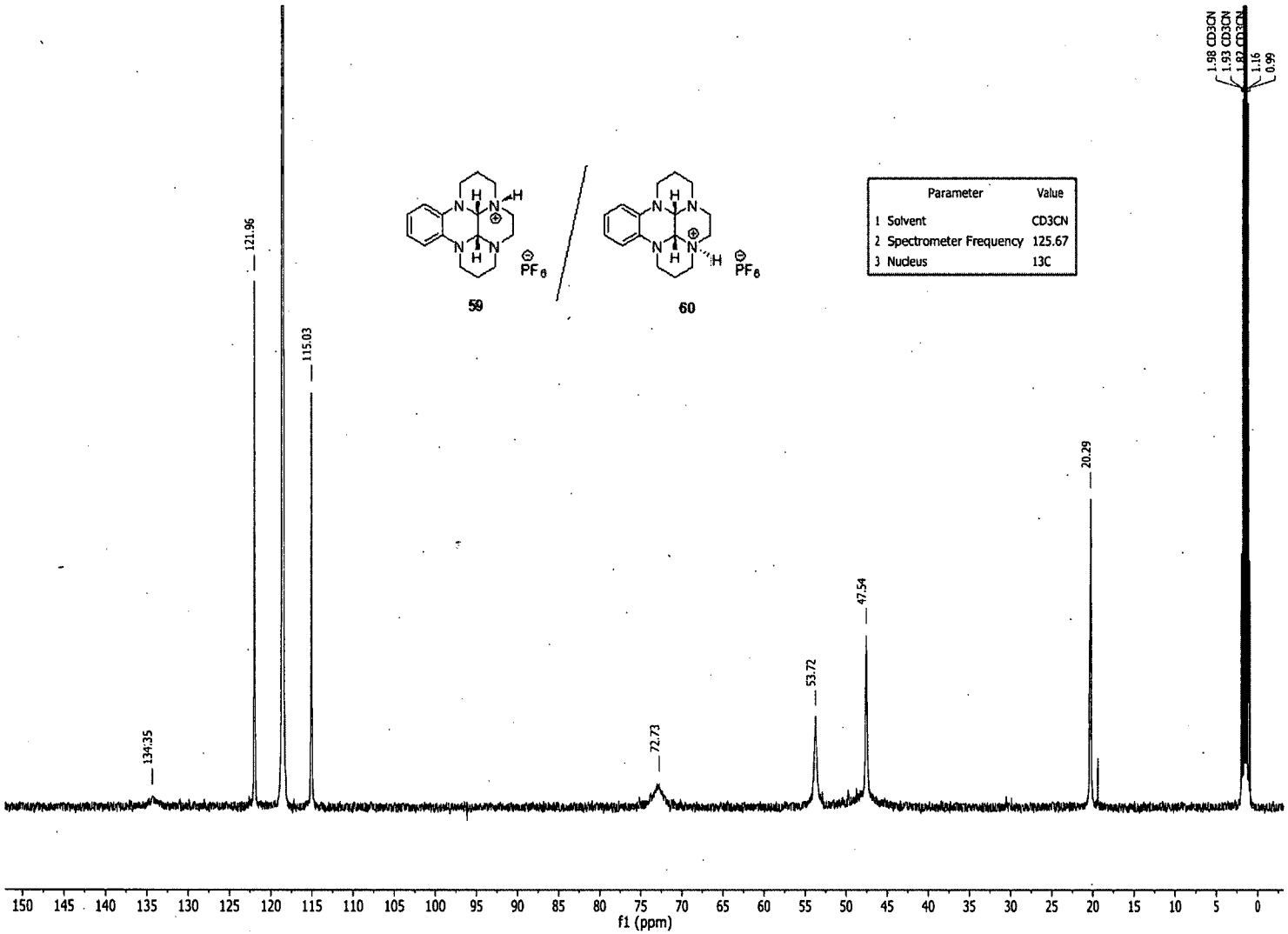

Before Heating
55
Br
56
Br
Parameter Value
1 Solvent CD3OD
2 Spectrometer Frequency 499.75
3 Nucleus 1H
f1 (ppm)

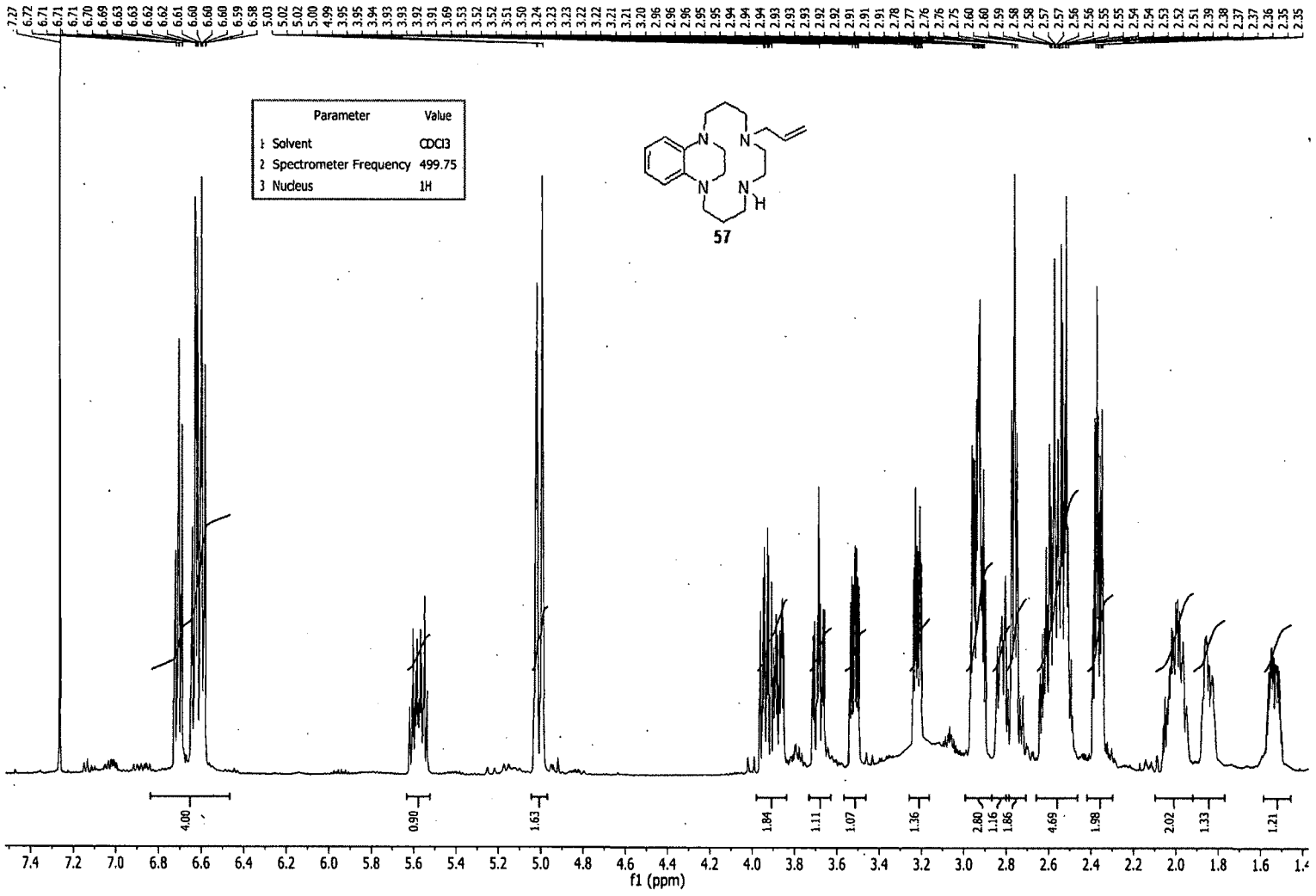

Before Heating
55
Br
56
Br
Parameter Value
1 Solvent CD3OD
2 Spectrometer Frequency 125.67
3 Nucleus 13C
f1 (ppm)

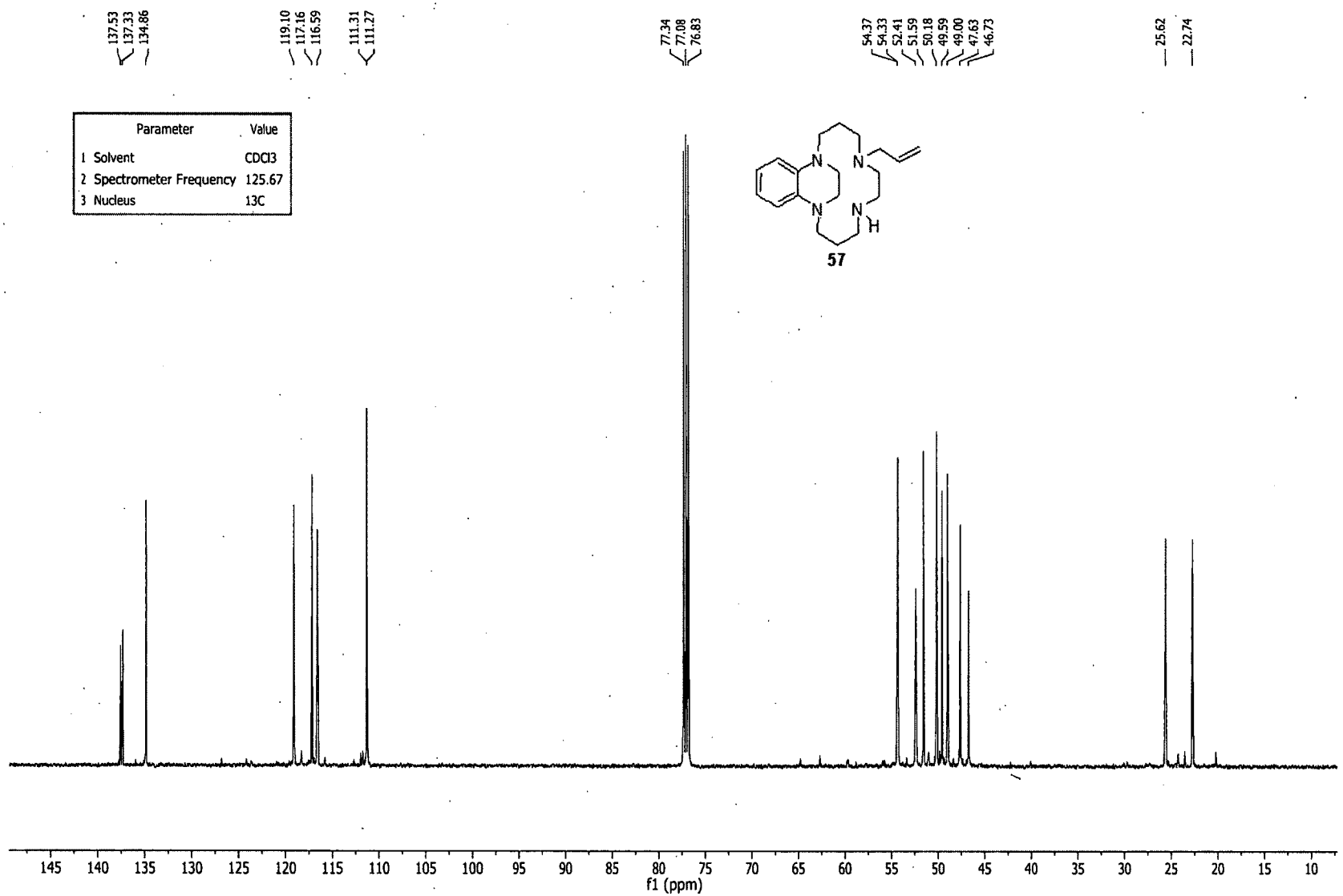

After Heating
55
Br
56
Br
Parameter Value
1 Solvent CD3OD
2 Spectrometer Frequency 399.74
3 Nucleus 1H
f1 (ppm)

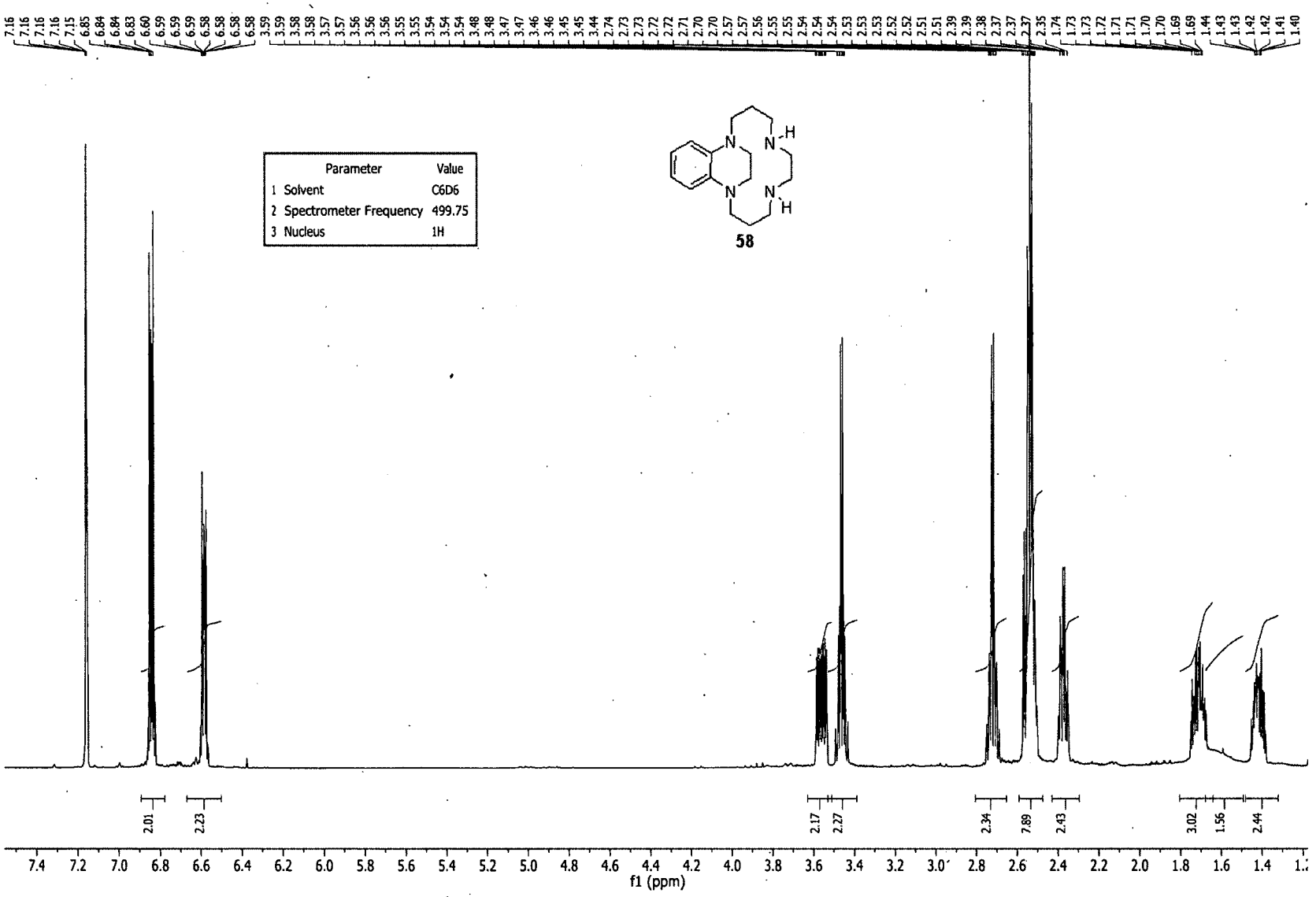

134.82
134.13
133.38
131.35
128.62
127.61
124.33
123.88
121.52
121.33
120.19
120.01
115.46
114.84
114.49
110.38
82.14
77.59
68.48
68.25
60.01
59.59
56.05
54.15
50.98
50.32
48.73
47.58
46.34
43.31
41.58
38.92
35.41
20.02
19.88
18.76
18.58
After Heating
55
Br
56
Br
Parameter Value
1 Solvent CD3OD
2 Spectrometer Frequency 100.53
3 Nucleus 13C
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)

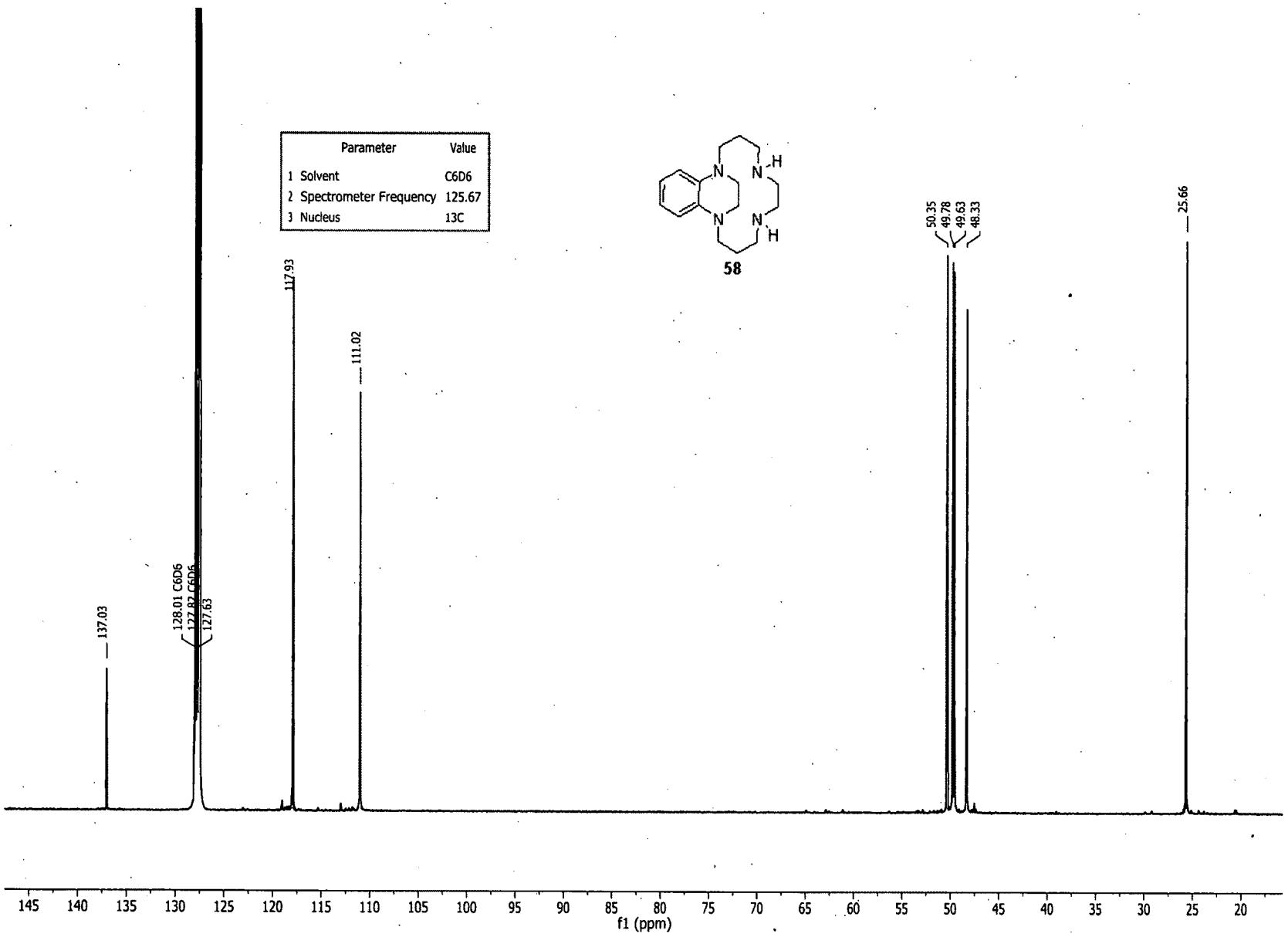
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 399.74
3 Nucleus 1H
59
60
PF6
f1 (ppm)
2.00
1.80
2.13
3.02
2.06
2.40
4.10
2.02
2.19
2.11
2744.00
2740.99
2740.36
2738.17
2737.42
2734.90
2734.30
2731.18
2730.68
2712.10
2708.34
2704.95
2702.24
2698.82
1702.69
1640.00
1637.51
1634.91
1627.01
1624.33
1621.93
1621.45
1316.77 HDO
1254.12
1252.47
1251.99
1243.69
1241.48
1239.09
1238.68
1195.76
1192.20
1188.78
1183.33
1182.72
1179.23
1175.38
1169.82
1165.28
1062.96
1055.25
1051.12
1044.67
859.14
857.54
854.14
846.42
840.98
794.02
793.71
793.36
793.02
792.71
792.36
792.00
791.68
791.35
790.86
790.29
789.71 CD3CN
789.28
788.74
788.05
787.22 CD3CN
786.77
786.43
785.65
784.75 CD3CN
784.08
782.28 CD3CN
781.24
779.79 CD3CN
614.90
613.57
611.55
609.49
608.24
606.26
600.97
599.41
597.50
595.76
594.51
593.98
592.13
523.41
516.84

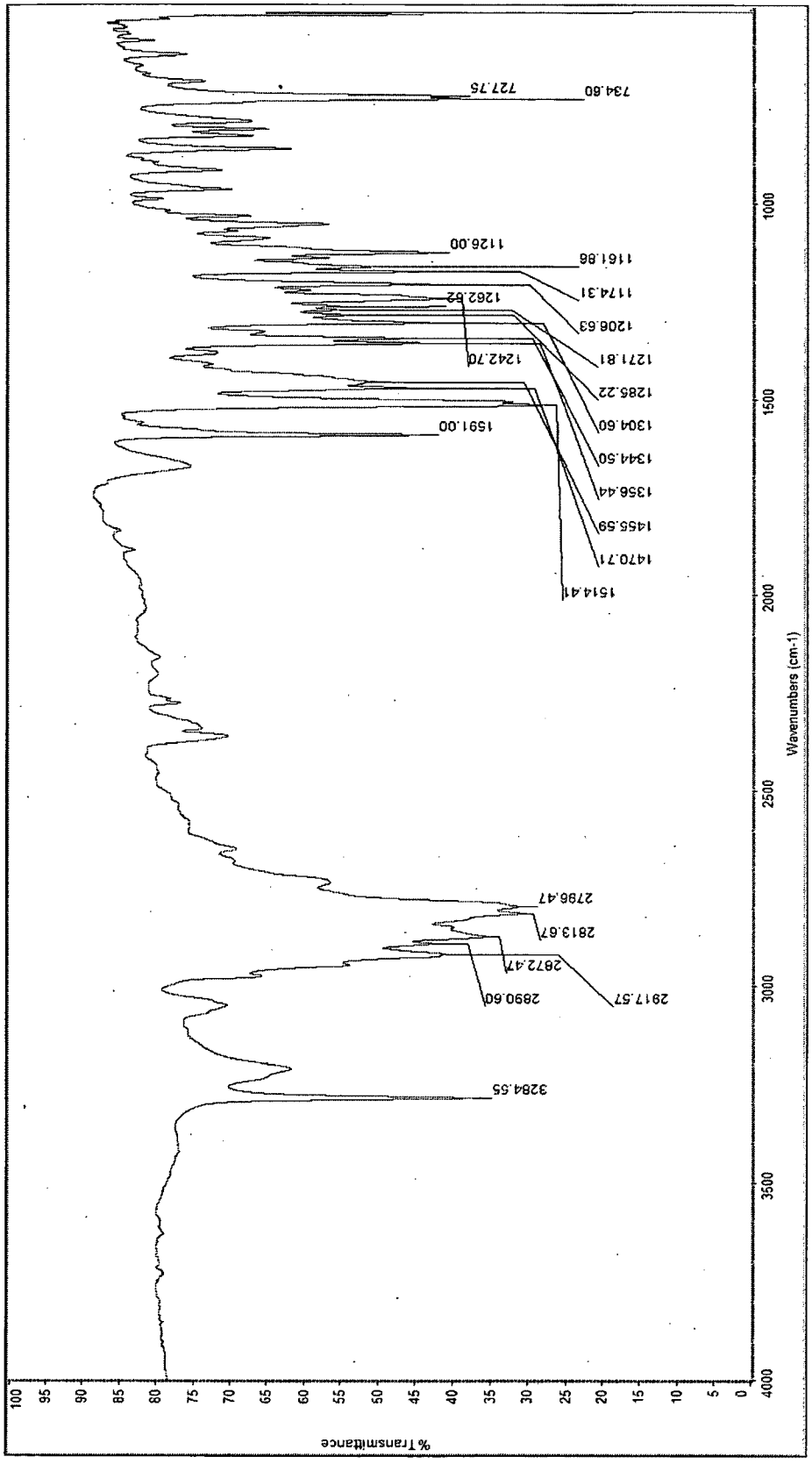

59
60
PF6
Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 125.67
3 Nucleus 13C
134.35
121.96
115.03
72.73
53.72
47.54
20.29
1.98 CD3CN
1.93 CD3CN
1.92 CD3CN
1.16
0.99
f1 (ppm)

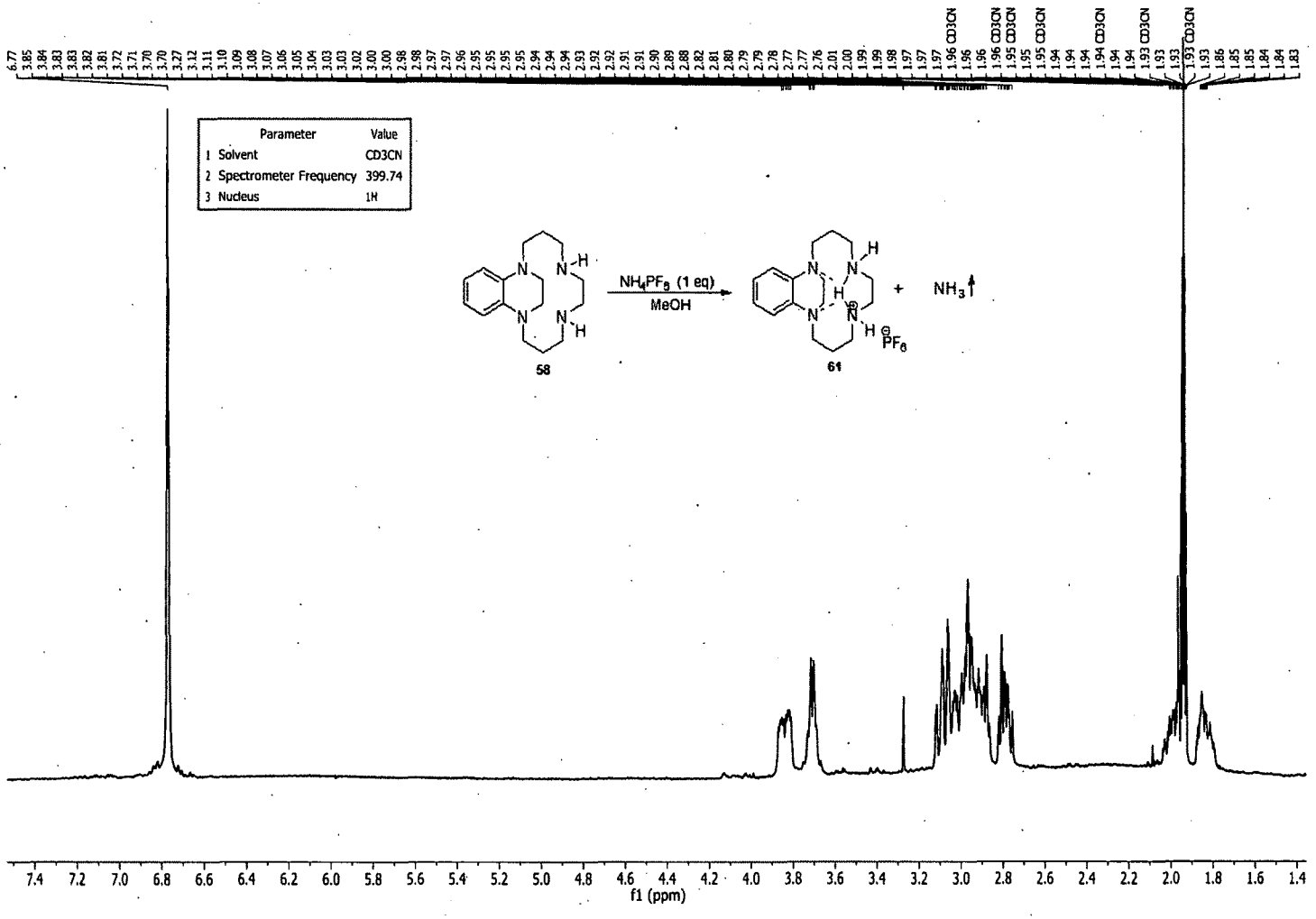

Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 499.75
3 Nucleus 1H
57
f1 (ppm)

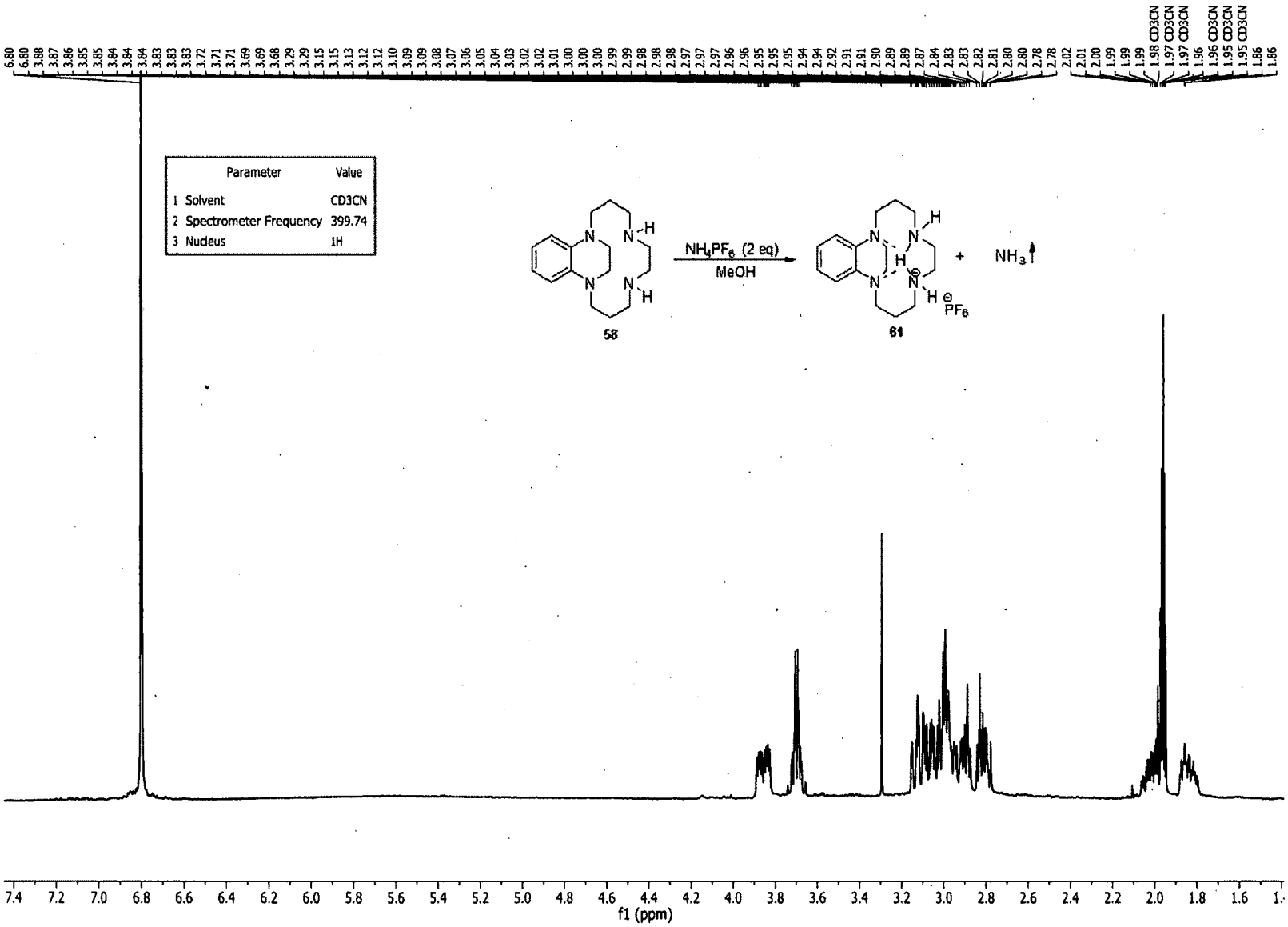

137.53
137.33
134.86
119.10
117.16
116.59
111.31
111.27
77.34
77.08
76.83
54.37
54.33
52.41
51.59
50.18
49.59
49.00
47.63
46.73
25.62
22.74
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 125.67
3 Nucleus 13C
N
N
N
N
H
57
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

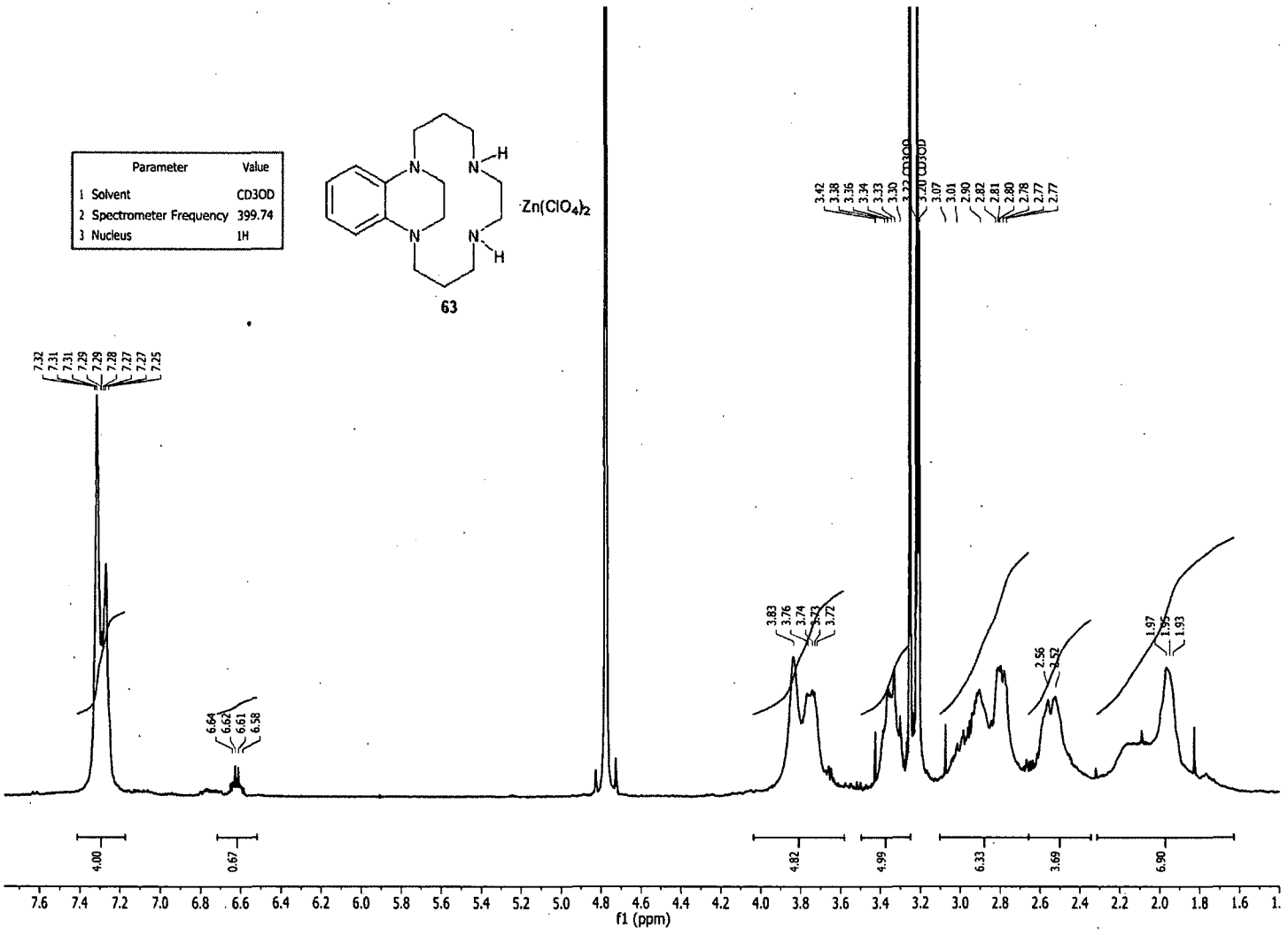

Parameter Value
1 Solvent C6D6
2 Spectrometer Frequency 499.75
3 Nucleus 1H
58
f1 (ppm)

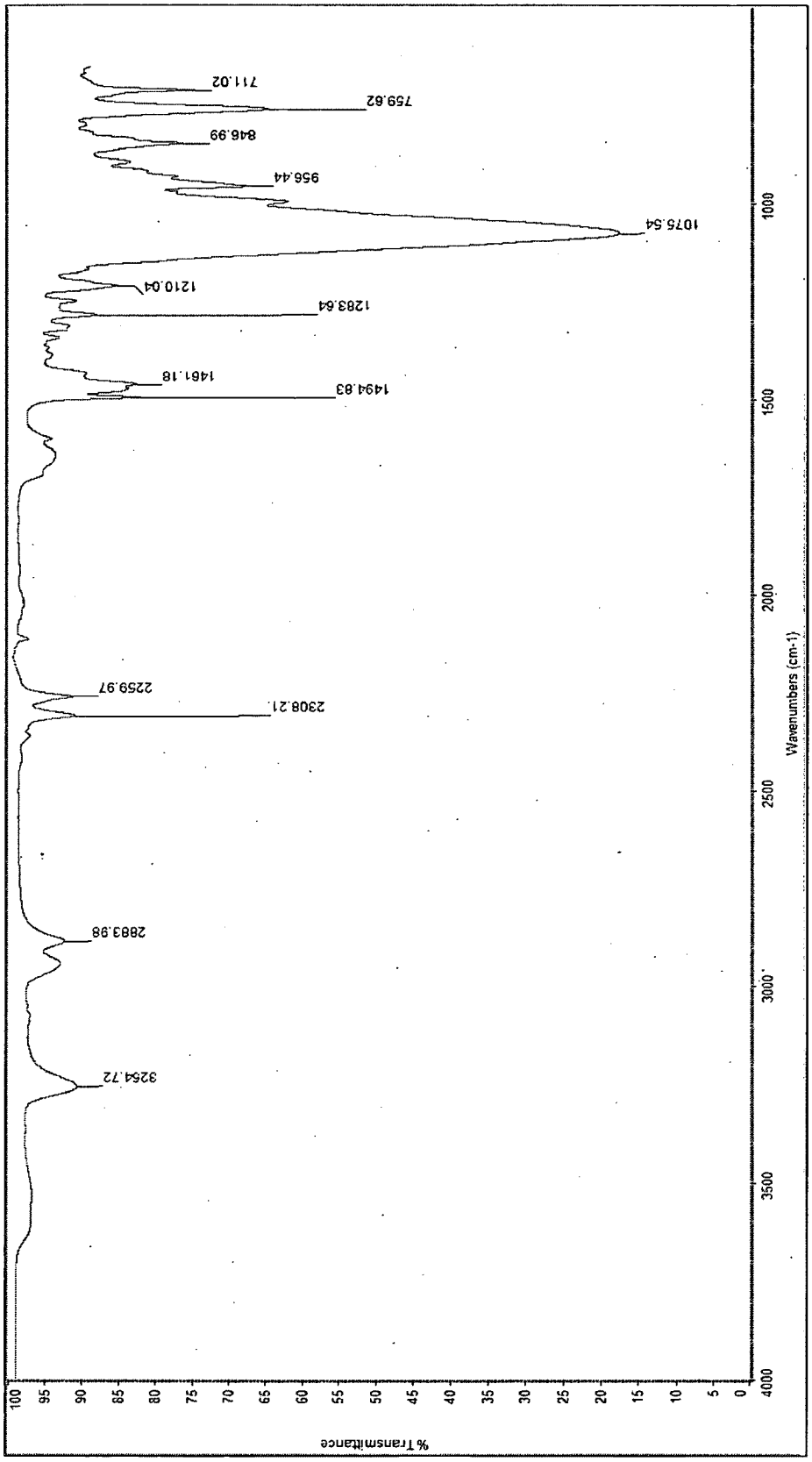

Parameter Value
1 Solvent C6D6
2 Spectrometer Frequency 125.67
3 Nucleus 13C
58
137.03
128.01 C6D6
127.82 C6D6
127.63
117.93
111.02
50.35
49.78
49.63
48.33
25.66
f1 (ppm)

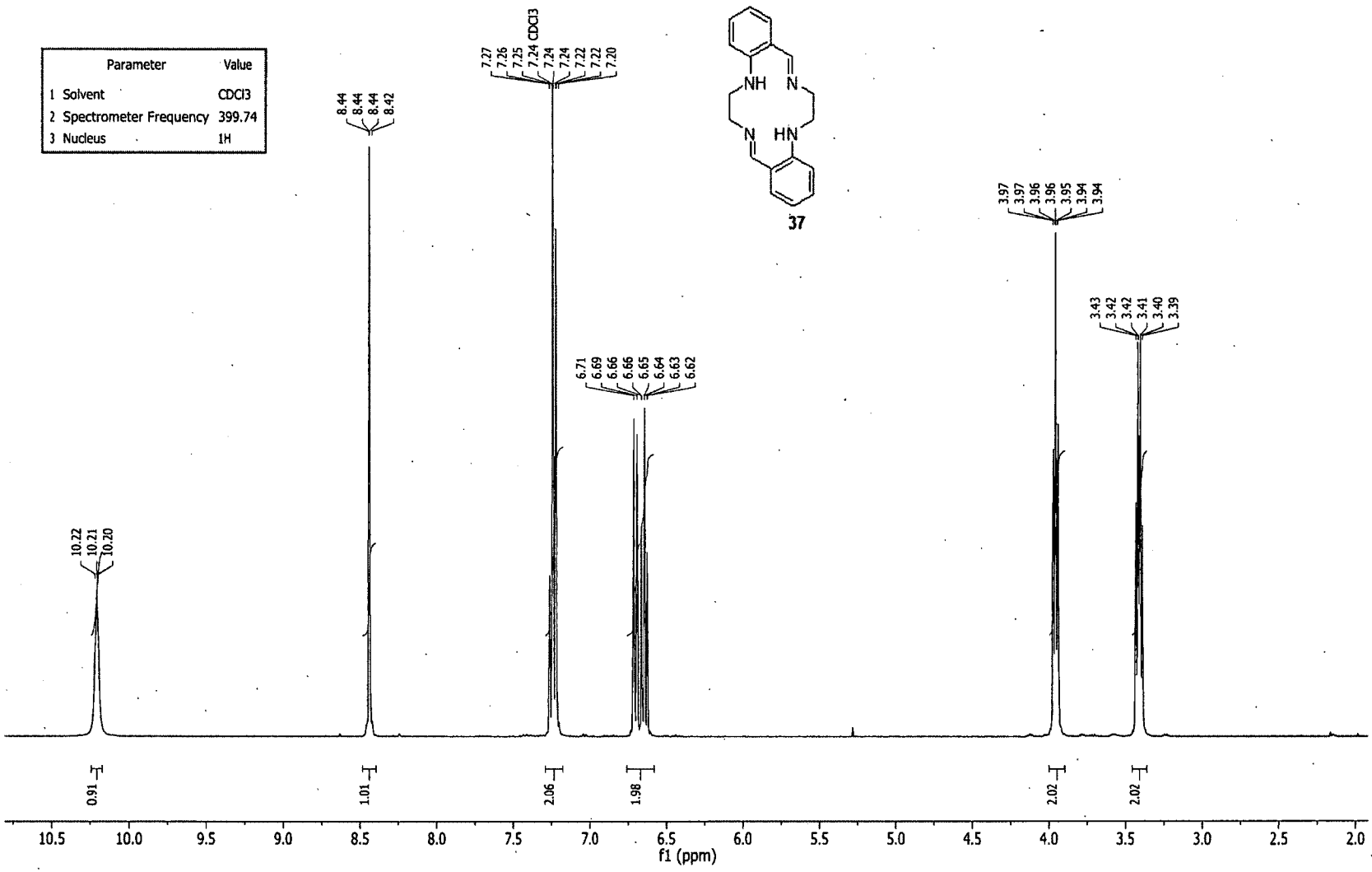

%Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
3284.55
2917.57
2890.60
2872.47
2813.67
2786.47
1591.00
1514.41
1470.71
1455.59
1356.44
1344.50
1304.60
1285.22
1271.81
1242.70
1208.63
1174.31
1162.52
1126.00
1161.86
734.80
727.75

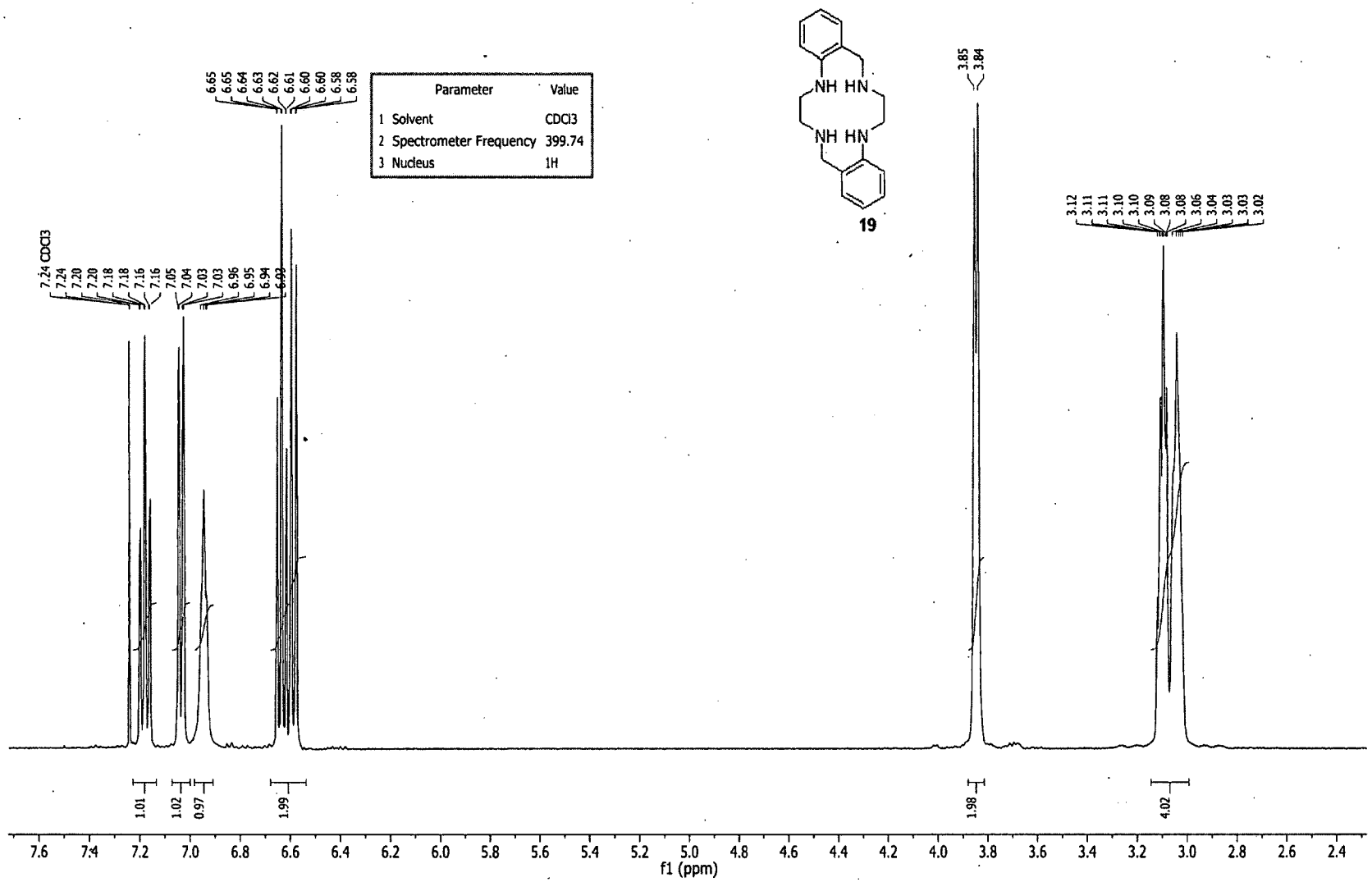

Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 399.74
3 Nucleus 1H
NH4PF6 (1 eq)
MeOH
NH3
58
61
f1 (ppm)

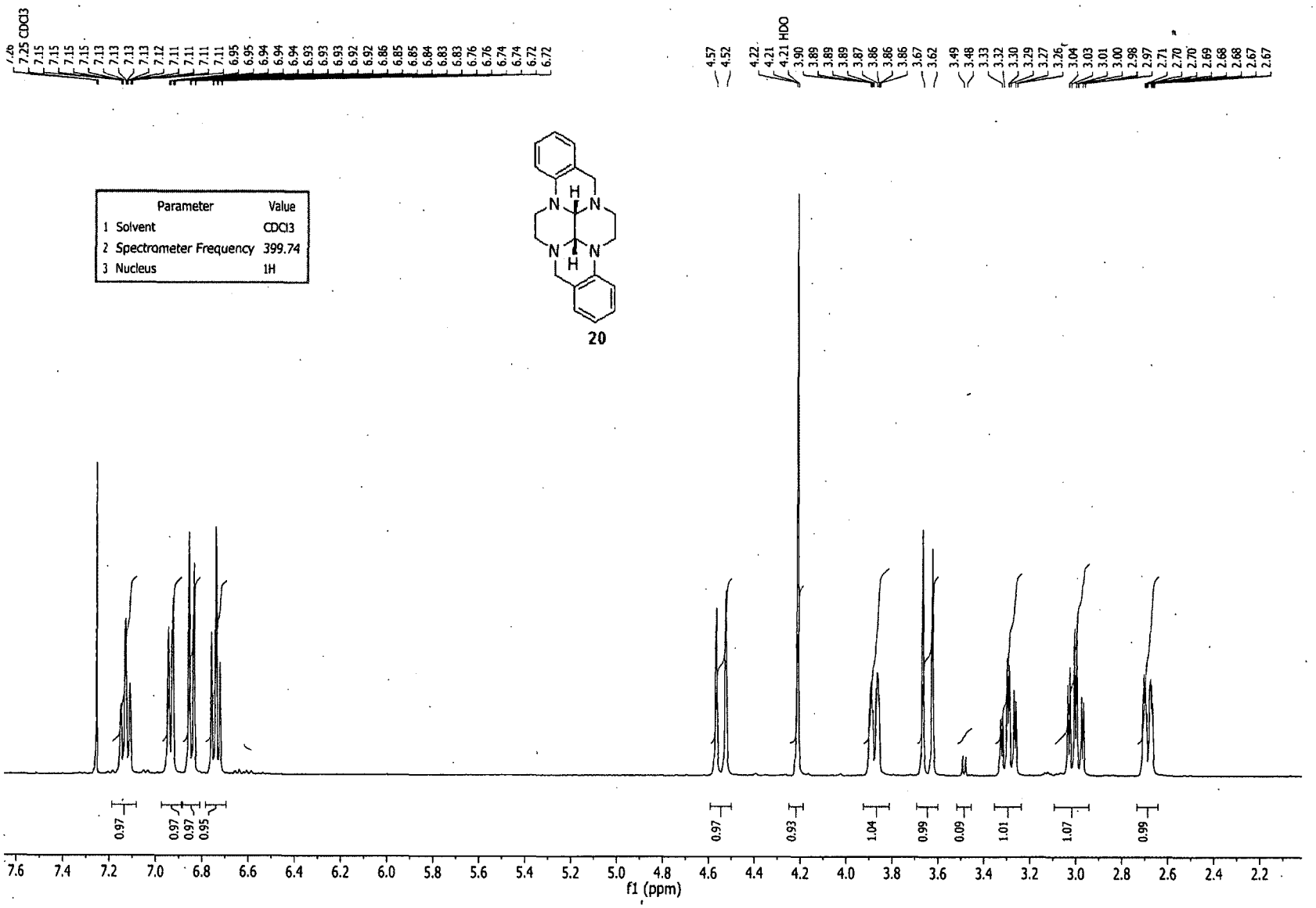

Parameter Value
1 Solvent CD3CN
2 Spectrometer Frequency 399.74
3 Nucleus 1H
NH4PF6 (2 eq)
MeOH
+ NH3
58
61
f1 (ppm)

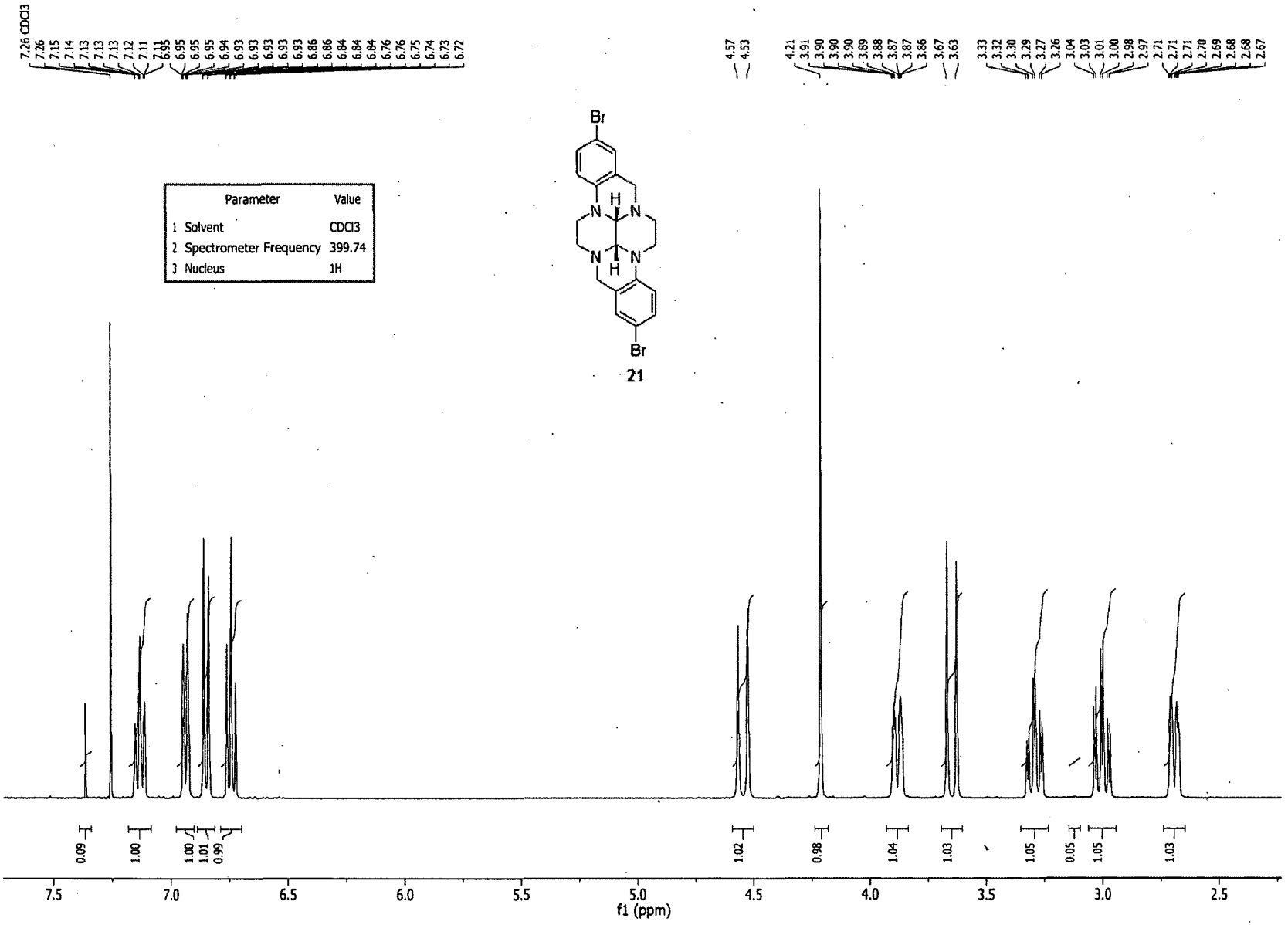

Parameter Value
1 Solvent CD3OD
2 Spectrometer Frequency 399.74
3 Nucleus 1H
Zn(ClO4)2
63
f1 (ppm)


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
3254.72
2883.98
2259.97
2308.21
1494.83
1461.18
1283.64
1210.04
1075.54
956.44
846.99
759.62
711.02

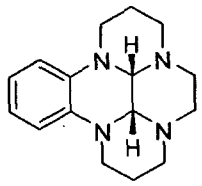
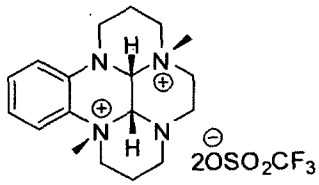
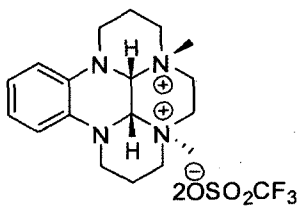
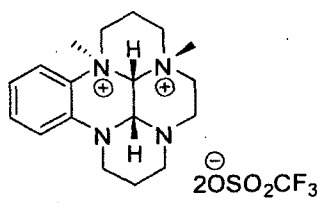
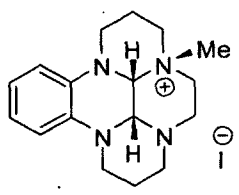

Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 399.74
3 Nucleus 1H
NH
N
N
HN
37
f1 (ppm)

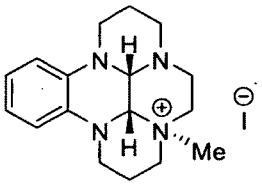
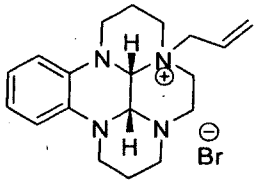
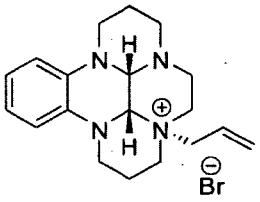
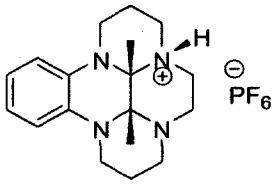
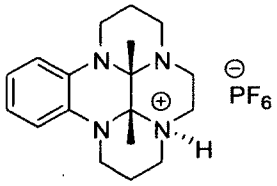

Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 399.74
3 Nucleus 1H
NH HN
NH HN
19
7.24 CDCl3
6.65 6.65 6.64 6.63 6.62 6.61 6.60 6.60 6.58 6.58
3.85 3.84
3.12 3.11 3.11 3.10 3.10 3.09 3.08 3.08 3.06 3.04 3.03 3.03 3.02
1.01 1.02 0.97 1.99 1.98 4.02
f1 (ppm)

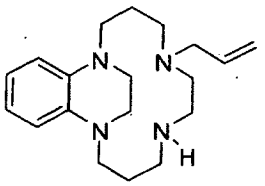
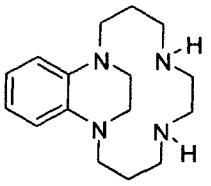
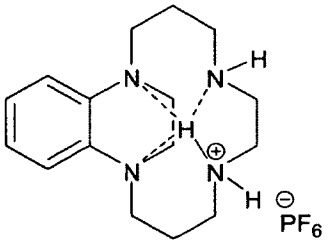
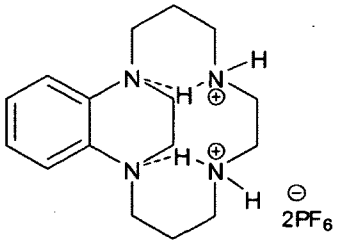
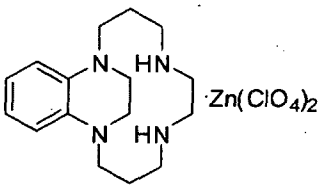

CDCl3
HDO
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 399.74
3 Nucleus 1H
20
0.97
0.97
0.97
0.95
0.97
0.93
1.04
0.99
0.09
1.01
1.07
0.99
f1 (ppm)

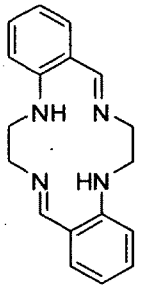
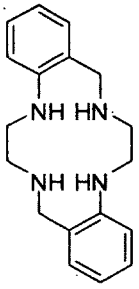
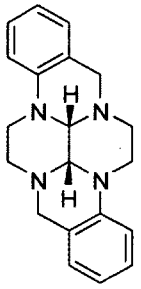
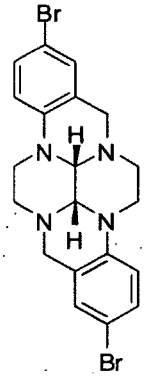

7.26 CDCl3
7.26 7.15 7.14 7.13 7.13 7.13 7.12 7.11 7.11 6.95 6.95 6.95 6.94 6.93 6.93 6.93 6.93 6.93 6.86 6.86 6.84 6.84 6.84 6.76 6.76 6.75 6.74 6.73 6.72
4.57 4.53
4.21 3.91 3.90 3.90 3.90 3.89 3.88 3.87 3.87 3.86 3.67 3.63
3.33 3.32 3.30 3.29 3.27 3.26 3.04 3.03 3.01 3.00 2.98 2.97 2.71 2.71 2.71 2.70 2.69 2.68 2.68 2.67
Parameter Value
1 Solvent CDCl3
2 Spectrometer Frequency 399.74
3 Nucleus 1H
Br
H
N
N
N
N
H
Br
21
0.09 1.00 1.00 1.01 0.99 1.02 0.98 1.04 1.03 1.05 0.05 1.05 1.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5
f1 (ppm)

Compound Index

Compound		Experimental	Spectra
15		107	134
50		107	136
51		107	136
52		107	136
53		110	138

Compound		Experimental	Spectra
54		110	138
55		112	142
56		112	142
59		113	146
60		113	146

Compound		Experimental	Spectra
57		114	148
58		115	150
61		117	153
62		117	153
63		117	154

Compound		Experimental	Spectra
37		118	156
19		119	157
20		120	158
21		120	159

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