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Two New Resorcinarenes: A Pyridine & Acetic Acid Ligand for Metal Coordination and a Deep-Cavity Nitroquinoxaline Resorcinarene

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TWO NEW RESORCINARENES:

A PYRIDINE AND ACETIC ACID LIGANDS FOR METAL COORDINATION AND A DEEP-CAVITY NITROQUINOXALINE RESORCINARENE

by

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GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

Samantha Sizemore Vernetti

This thesis has been read by each member of the following graduate committee and by majority vote has been found satisfactory.

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As chair of the candidate's graduate committee, I have read the thesis of Samantha Sizemore Vernetti in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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Harrison and Fleming group

Department of Chemistry and Biochemistry

DEDICATION

To my loving husband, Bryan

To my son, Dominic

To my parents

To Tippy and Diasy

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1. Acetic Acid and Pyridine Resorcinarene Ligand

Abstract: Functionalizing the upper rim of resorcinarene-based cavitands allows a variety of compounds to be synthesized from a single scaffold. Using the upper-rim moieties as ligands for a variety of transition metal ions further increases the versatility of this class of host compounds. A new resorcinarene-based molecule functionalized with four pyridine and acetic acid ligands has been successfully prepared to explore the properties of metal-assembled complexes. To synthesize this compound, tetra(bromomethyl)cavitand was reacted with N-(2-pyridylmethyl)-N-ethylacetate amine to give ethyl acetate pyridine resorcinarene. Hydrolysis of the ester gave acetic acid pyridine resorcinarene (APRes) in good yield. Complexes with Cu^{2+}, Co^{2+}, and Zn^{2+} are currently being investigated and characterized by MS and ^{1}H and ^{13}C NMR.

1.1 Introduction

1.1.1 Calixarenes

Calixarenes are a group of cyclic compounds composed of four, six, eight or more aryl groups. The name calixarene refers to the shape of the compounds, which is similar to that of a Greek vase called a calix crater (Figure 1-1).[1]

Figure 1-1. Richard Milette, Calix Crater, 2001

Calixarenes were first discovered in 1872 by Johann Friedrich Wilhelm Adolph von Bayer.[2] Bayer discovered that formaldehyde condensed with phenol in the presence of mineral acid to form a hard, cement-like resin. Bayer proposed a structure with aromatic rings linked by methylene and ether ($-CH_2OCH_2-$) bridges. The true structure of calixarenes remained a puzzle until 1949 when several researches independently proposed cyclic tetrameric structures for compounds obtained by the acid-catalyzed treatment of aldehydes and phenols (Figure 1-2).

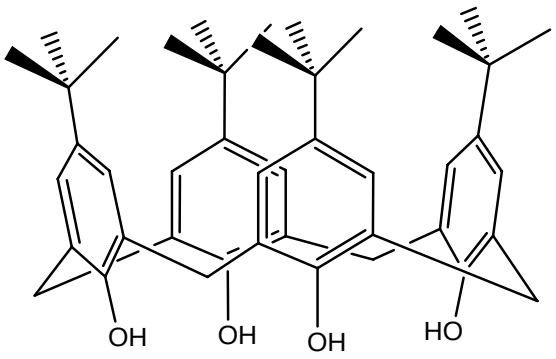


Figure 1-2. Calixarene from condensation of formaldehyde and 4-t-butyl alcohol

Calixarenes can be synthesized by either acid- or base-catalyzed condensation of phenols and aldehydes. The base-catalyzed syntheses have been known to give better yields. Nevertheless, the acid-catalyzed reactions have synthetic utility as they are known to produce cyclooligomers with as many as twenty phenol units connected at the 2' and 6' positions.

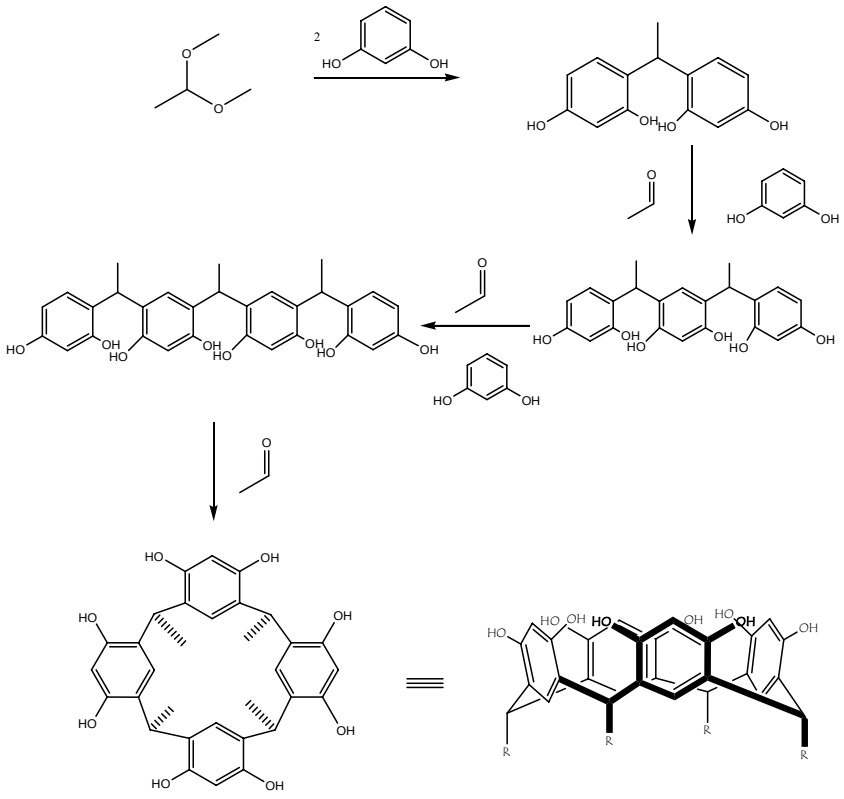
Today, the name calixarene which was originally used to describe phenol-derived calixarenes is applied to a wide variety of structurally-related compounds which include resorcinarenes and thiocalixarenes.

Calixarenes are applied in enzyme mimetics, ion sensitive electrodes or sensors, selective memberanes, non-linear optics[3] and in HPLC stationary phase.[4] They are also able to catalyze reactions that occur inside the cavitand by a combination of local concentration effect and polar stabilization of the transition state. An example of this is

an extended pyrogallol[4]arene which has been found to accelerate the reaction rate of a Menshutkin reaction between quinuclidine and butylbromide by a factor of 1600.[4]

1.1.2 Resorcinarenes

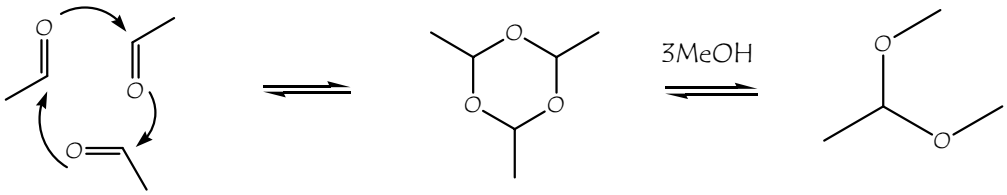
Resorcinarenes are cyclic oligomers formed when resorcinol condenses with aliphatic or aromatic aldehydes under acidic or basic conditions.[5] They are also referred to as calixresorcarenes, or simply, resorcarenes. They are easier to synthesize than cyclodextrins and spatially more interesting than crown ethers. Scheme 1-1 shows studies done by Weinelt and Schneider.[6]



Scheme 1-1. Synthesis of tetraresorcinarene

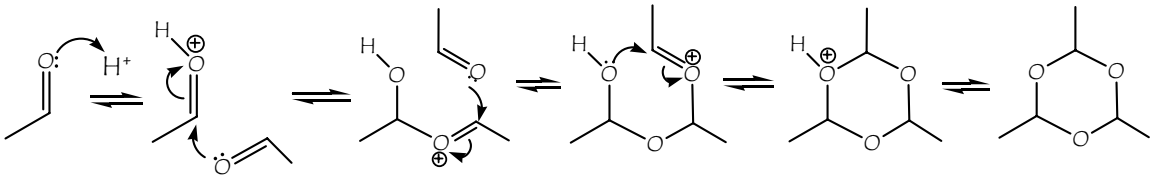
In their paper, Weinelt and Schneider's group proposed that the synthesis starts with the formation of a cyclic acetal which then reacts with three molecules of methanol to form another acetal, 1,1-dimethoxyethane (Scheme 1-2). This new acetal is the molecule that

further reacts with two molecules of resorcinol to form the dimer, the first of a series of additions which ultimately leads to the formation of the tetraresorcinarene.



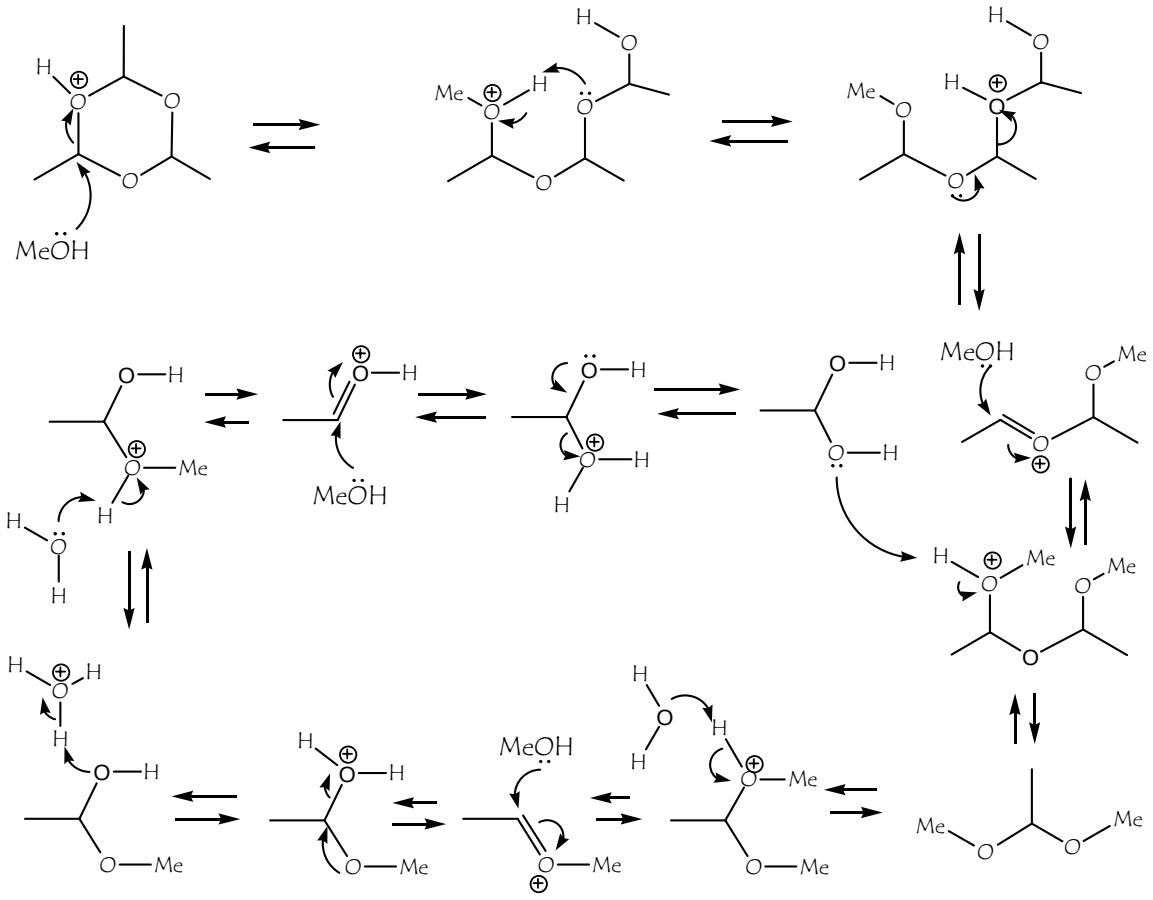
Scheme 1-2. Formation of the acetal

The mechanism illustrates why the group suggested the formation of the cyclic acetal (Scheme 1-3). The condition is a classic acid-catalyzed process learned in introductory organic chemistry. This cyclic acetal is then hydrolyzed by the methanol solvent, another classic mechanism.



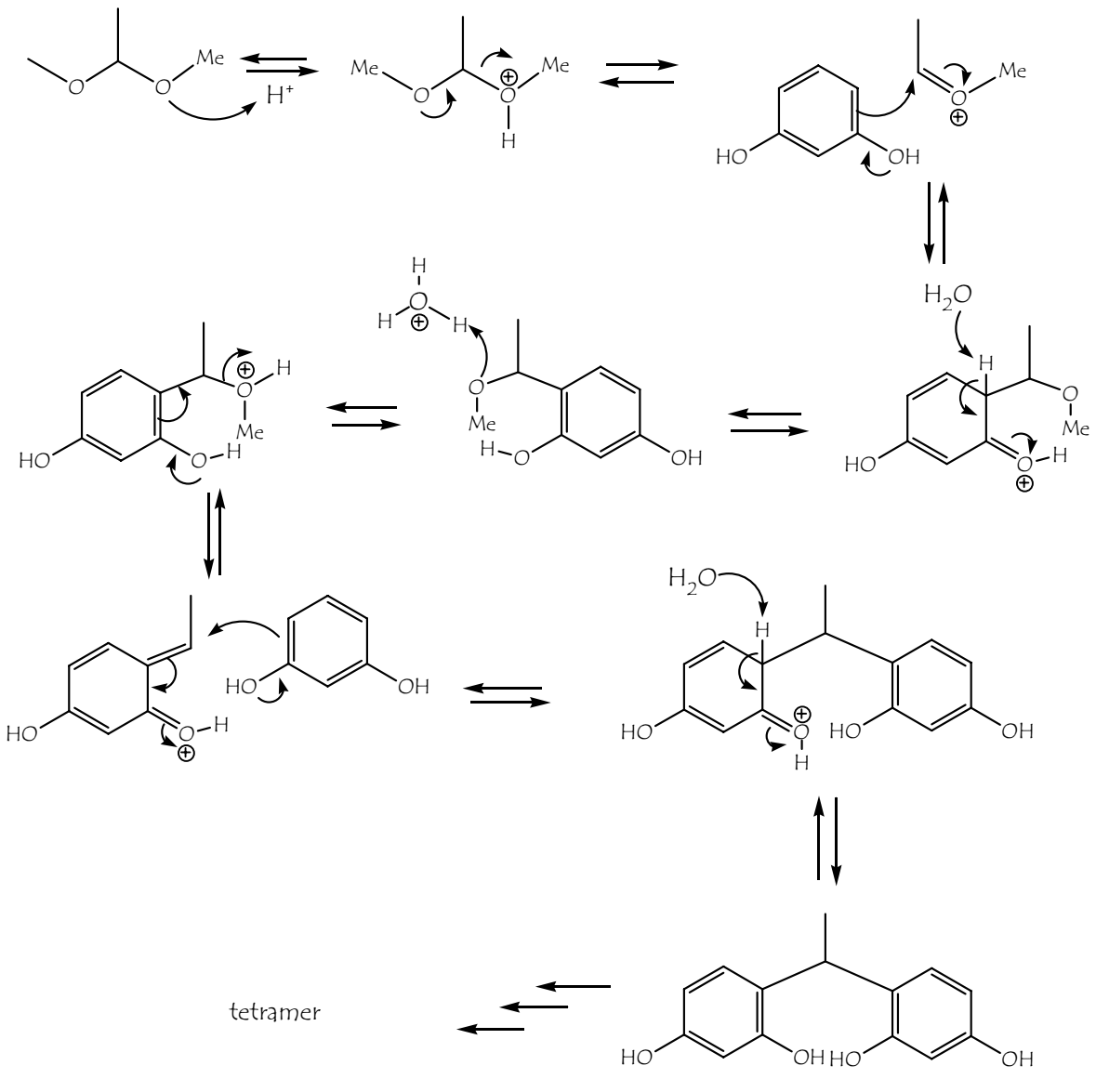
Scheme 1-3. Mechanism for the cyclic acetal

Although we are not totally convinced that the acetal steps are necessary in forming tetraresorcinarene, we have proposed a mechanism showing the solvolysis of the cyclic acetal to form 1,1-dimethoxyethane (Scheme 1-4).



Scheme 1-4. Mechanism for 1,1-dimethoxyethane

Furthermore, we suggest a mechanism which demonstrates how 1,1-dimethoxyethane reacts with two molecules of resorcinol to form the dimer (Scheme 1-5). It begins with the acid-catalyzed hydrolysis of the acetal. The electrophilic carbon formed by the elimination of a molecule of methanol is attacked by the nucleophilic resorcinol aromatic ring. This is made possible because of the two electron-donating hydroxyl groups on resorcinol. Moreover, the electron-rich resorcinol group eliminates the second methoxy group upon protonation. Subsequently, another resorcinol molecule attacks the electrophilic carbon created by the methanol elimination. The final dimer is formed after the aromatization of the second resorcinol group.



Scheme 1-5. Mechanism for formation of the dimer

The dimer and the trimer from the aforementioned reaction can be isolated. But the tetramer cylices too quickly to form a resorcinarene ring (Figure 1-3); hence, the tetramer could not be isolated as a linear structure. The tetramer usually precipitates from the reaction mixture; although, water is sometimes added to assist in the crystallization.[7] This tetramer is the most common and most useful condensation product as it has been used as substrate in many resorcinarene studies; nevertheless, many cyclooligomers can be formed under various conditions.

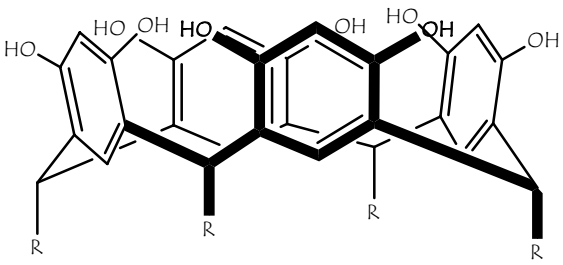


Figure 1-3. Tetramer made from resorcinol.

Resorcinol has been studied extensively in condensation reactions with different aldehydes.[8] The reaction with formaldehyde is excluded in these studies as it only forms linear polymers. This may be due to the high reactivity of formaldehyde. In the presence of acids, polymerization occurs, disabling any cyclization.

The two electron-donating hydroxyl groups in resorcinol make it an excellent substrate in synthesizing functionalized calixarene analogs. Whereas calixarenes have flexible cavities, resorcinarenes have more rigid conformations because of the two hydroxyl groups in resorcinol. This rigidity enables resorcinarenes to host different guest molecules from metallic ions to neutral compounds.

The top of the bowl is the wide, upper rim on which the hydroxyl groups are attached. Furthermore, the upper rim of resorcinarenes is easily functionalized, making it a versatile molecular vessel. It is at the upper rim that spacer moieties are added to deepen the cavity.

The lower rim is where the feet are attached. The feet of the resorcinarene can be changed to alter solubility or even to bond with metals or with other bowls. To synthesize water-soluble cavitands, the feet must be a short-chain alkane or contain a water-soluble group. Resorcinarenes formed from the condensation of acetaldehydes are water-soluble.[9] Resorcinarenes with alkyl chains of two carbons or more are less soluble in polar solvents and can be made soluble upon addition of a polar moiety to the upper

rim. Resorcinarenes with alkyl feet are typical. These conformationally-mobile hydrocarbon chains increase the solubility in nonpolar organic solvents.[10]

Polar groups such as phosphates and hydroxyl have been added to the lower rim of the bowl as well.[11] In addition to making the resorcinarenes more soluble, these polar groups help in metal coordination. Cram[12] and coworkers synthesized a butanol-footed bowl which was later characterized by Sherman[13] and coworkers. Sherman's group also synthesized several hydroxyl-footed bowls attached to chains of three to four carbon atoms in length. These bowls were made under similar conditions with ethanol as the preferred solvent and hydrochloric acid as the catalyst.

1.1.3 Cavitands

Cavitands are synthetic open-ended structures with enforced cavities that are capable of binding complementary organic compounds and ions.[14] Resorcinarenes are one type of cavitands. The inclusion complexes of cavitands and guest molecules are called caviplexes. Cram gave the name caviplex to a class of synthetic organic compounds that has a cavity large enough to accommodate different guest molecules.[15] A 1996 report delineated four general classifications of cavitands based on the type of bridges in the structure.[16] They are alkylenedioxy-, dialkylsilicon-, heterophenylene-, and phosphoryl-bridge cavitands (Figure 1-4).

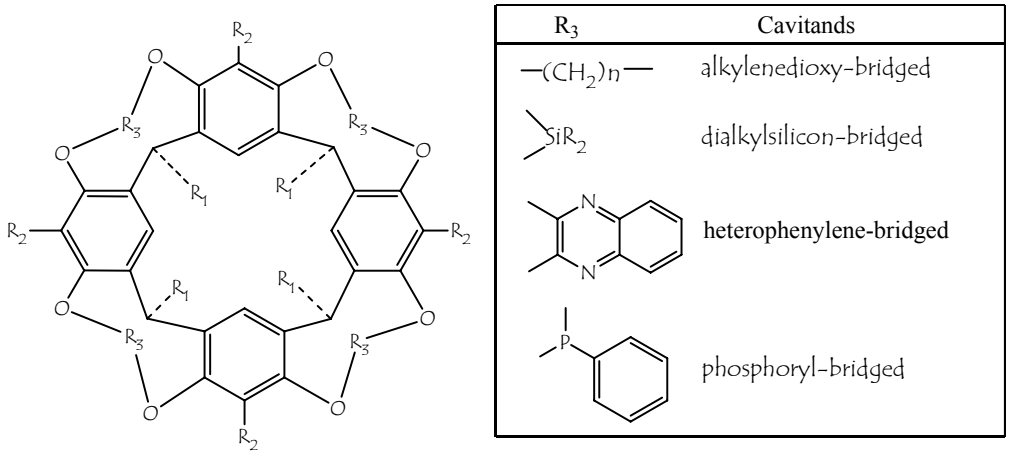


Figure 1-4. Classes of cavitands based on linkages (R_1= CH_3, R_2=H or CH_3).

1.1.4 Carcerands and Hemicarcerands

Carcerands are molecular cages formed when two cavitands are bonded at their upper rims (Figure 1-5). These enclosures have been compared to the shape of an American football with enough space to accommodate small organic molecules. One of the weaknesses of covalently bonded carcerands is they cannot released molecules which are imprisoned during synthesis. Covalent bonds must first be broken before any guest exchange is made. Carcerands that enable guest molecules to enter and leave are more useful. The synthesis of hemicarcerands which allow for guest exchanges broadened the application of these cages. Some of these hemicarcerands showed enantioselective binding based on differences in the activation energy of decomplexation. Other types carry out chemical reactions inside the cavity or inhibit reactions by protecting small molecules from larger molecules which cannot pass through the small portals. Other possible medical and veterinary applications for hemicarcerands are matrixes for time-release drugs or for target-release release.

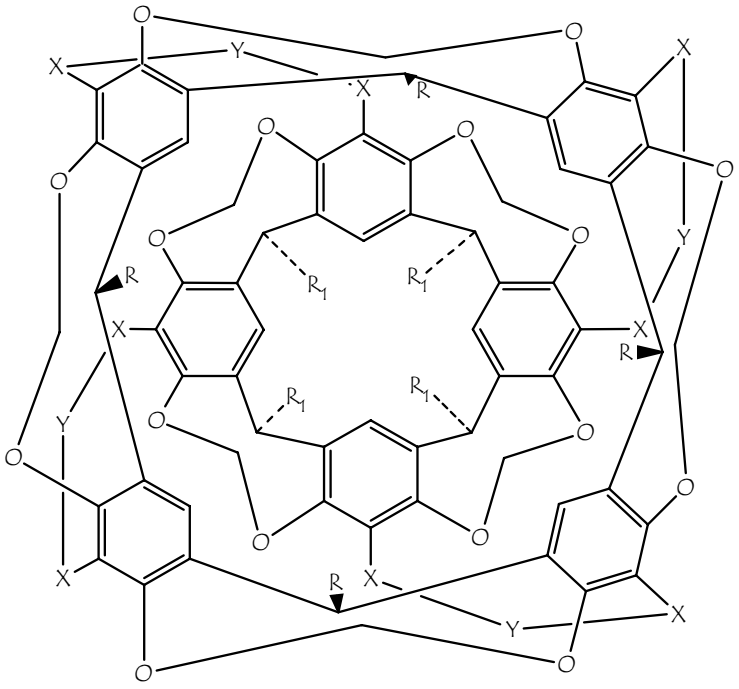


Figure 1-5. Top view of a carcerand

1.1.5 Metal Complexes

Cage complexes can be formed by a variety of interactions between complementary molecules. Hydrogen bonding, guest templates, and metal coordination have been used to form cage compounds. A cage compound must contain an interior cavity in which one or more molecules or ions can be trapped.

Metal-assembled cages consist of multi-dentate ligands held together by metal cations.[17] Unlike cages whose components are bound covalently, metal-assembled cages are unique because their bonds are more easily broken, thus allowing the movement of guest molecules through the cavity (Figure 1-6).[18] These cages have potential applications in the areas of molecular recognition, light harvesting, biomolecular transport and delivery systems, waste clean-up and time-released medicine.[19]

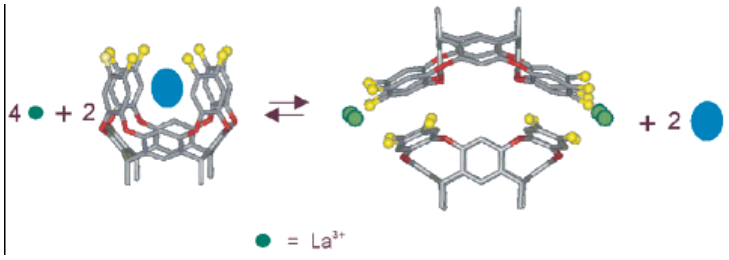


Figure 1-6. Metal-assembled cage

Scientists took a cue from nature when they began to research the guest-binding properties of certain metal ion-assembled cages. These molecules capture guest molecules in a way that is similar to the mechanism of enzyme and substrates.[14] Self-assembly of molecules also has roots in biology. In fact, it is believed that molecular self-assembly must have played a large role in the development of the first life on earth.

A variety of cationic metals are used to link ligands of the assemblies. Cages linked by transition metals have been studied. The most commonly used transition metals are iron, nickel, zinc, and cobalt. Coordination geometry plays a role in the choice of metal. For example, Pt(II) and Pd(II) are frequently used for their square-planar geometry.

The most commonly used ligands are those with aromatic components.[20] Their electron-rich π molecular orbitals provide ample space for host-guest interactions. Each ligand has one or more donor sites that coordinate with the metal ion. Nitrogen, sulfur,

oxygen and phosphorus are common donor atoms. The ligands can be either cup-shaped or linear.

1.1.6 More recent studies on cages

To create a large, enantiomerically selective cavity, Shinkai and coworkers used Pd^{2+} to link two calixarene half-bowls. They synthesized a dimeric capsule in which [60]-fullerene was captured.[21] The selective encapsulation of [60]-fullerene by the cage is a promising purification method. Capture of [60]-fullerene is dependent upon a pre-organized cone conformation of the bowls and the flexibility of the benzene rings comprising the outer rims of the bowls. The ^{13}C signal of [60]-fullerene shifts upfield after capture of the cage. The ^{1}H NMR signal of the cage shifts downfield due to the interaction between protons and the p-electron ring current of the guest molecule.

Capture was improved by the addition of two Li^{+} "plugs" to the ends of the capsule. The cation plugs partially flatten the aromatic rings at the ends of the capsule to help the cavity achieve the rounder conformation needed for guest inclusion. Interestingly, sodium ion has the opposite effect. Addition of sodium cation gives the capsule a more elliptical shape and induces the release of the guest molecule.[16]

Studies on this cage have shown its potential as a chiral receptor.[22] Interaction between the p-electrons of the pyridinyl groups and the lithium or sodium cations cause the cage to twist into a right- or left-handed conformation. Studies of the cage's interaction with alkylammonium guests show that it is enantiomerically selective.[19]

Several cage compounds capture cationic species. Raymond and coworkers synthesized an M_4L_6 (four metal ions, six ligands) supramolecular cluster which captures alkylammonium guests of various sizes.[23] The truncated tetrahedron is formed by six ligands held together by four Ga^{3+} or Fe^{3+} cations. The trigonal planar ligands are formed by three dimethoxybenzoyl groups attached to the nitrogen of a tri-amino benzene.[24] Encapsulation of guest molecules can be confirmed by NMR analysis. For example, the capture of one Et_4N^{+} molecule is accompanied by a dramatic upfield shift in the ^{1}H NMR spectrum (δ= -0.689 (m), -1.58 (t)). The free Et_4N^{+} is found at δ =3.46 (q), 1.27 (t). A set of six Et_4N^{+} signals are found at δ =2.42 (q), 0.68 (t).[21]

Raymond and coworkers found that guest molecules served as a template for the cages.[25] They described two conditions of guest-templated assembly:

1- Cage does not exist in the absence of guest.

2- Cage decomposes upon removal of guest.

The group showed the cage is not formed in the absence of certain guest molecules. However, they have not been able to remove the guest without destroying the host in acidic conditions. This is consistent with a thermodynamically-driven process in which the guest molecule drives the complex formation.[22]

A different type of cage adopts an adamantine-like structure to capture small organic cations. Saalfrank and coworkers synthesized M_4L_6 adamantoid cages using malonate ester-derived ligands and a variety of metal cations (Mg^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}).[26] The metal cations form a nearly tetrahedral shape. The net charge of the cage compound is negative four. It is believed the cage assembly is driven by one of its guests – the ammonium cation. Metal cations and other small organic molecules have also been captured by this cage.[27]

Park and coworkers added pyridine moieties to the upper rim of each cup.[28] The nitrogen from the pyridines coordinates to Pd^{2+} and Pt^{2+} moieties to form a cage that encapsulates N-methylpyridine derivatives. This is surprising because the cage has a net charge of plus eight. This is due to cation-π interactions. Neutral guests were not captured. Anionic guests, such as $CF_3SO_3^-$, were captured. Fujimoto and coworkers synthesized another calixarene cage that recognized diamines.[29] Dalcanale and coworkers synthesized a dimeric capsule using resorcinarene-based ligands and Pd^{2+} and Pt^{2+} binding moieties.[30] The cage was found to capture $CF_3SO_3^-$.

Fujita and coworkers used the induced fit model to describe their self-assembling cages.[31] This means the host does not assemble in the absence of the guest. For example, the assembly of two pyridine-based ligands with Pd^{2+} moieties occurs only in the presence of certain guests. In the absence of guest, the ligands form oligomers. Upon addition of guest, the oligomers disappear as the host is formed. Fujita's group found that guests with large hydrophobic moieties assembled host compounds in the highest yields. The hydrophobic cavity stabilizes hydrophobic guests. Anionic, electron-rich, and neutral guests were used as templates in these studies.[32]

Kusukawa and coworkers synthesized an M_4L_6 cage that encapsulated large, neutral guests.[33] In D_2O experiments, hydrophobic guests were transferred to the aqueous phase in the presence of the cage compound. The cage, having a net charge of plus twelve, is readily miscible in water. The encapsulation was accompanied by ^1H NMR shift of the hydrophobic protons. This shift was not observed for the hydrophobic protons, presumably because these protons stick out of the openings of the cage and are not shielded by the cage electrons.

Another interesting observation is the significant color changes that accompany the π-donor-π-acceptor interaction between the interior of the cavity and certain electron-rich guests, e.g. 1,3,5-trimethoxybenzene and toluene. These results revealed the interior of the cage to be a hydrophobic, electrophilic microspace whose environment is different from the bulk phase.

The cage can remain intact after removal of guest molecules when it has been thermally "locked" into place.[34] After encapsulation at higher temperatures, the host-guest complex is cooled to give a rigid framework. The guest molecule can be removed as an acid by acidification of the aqueous cage solution. Since the cage is locked into place, it remains intact and later, forms a salt with the anion PF_6^-.

This compound is also known to form hydrophobic dimmers of cis-azobenzene and cis-stilbene derivatives in a "ship-in-a-bottle" reaction.[35] The cage selectively encapsulates the cis-conformations of these molecules in succession. Once inside the cavity, the two molecules are positioned so that they dimerize. NMR and NOESY analysis show the dimmer is present only inside the cage. This reaction cannot take place outside the cage because the dimmer is too large to pass through cage windows. This equilibrium reaction favors the formation of the dimer so much that in some cases, the cage is never observed for long with only one guest molecule. In addition to steric requirements, participating guest molecules for this reaction must be electron-rich and hydrophobic.

1.2. Research Rationale

Our group reported the synthesis of an iminodiacetate resorcinarene cage that is assembled with cobalt (Figure 1-7, page 16).[36] This cage captures neutral organic

molecules from water. It also acts as an NMR shift reagent, causing ^{1}H NMR signals of guest molecules to shift 25-40 ppm.[37] X-ray crystallography revealed the cages form a grid in the solid state to create a porous material.[38] Two oxygen donor atoms from each moiety coordinate with Co^{2+}. We later used Fe^{2+} to bind the ligands together. This cage was found to be pH-sensitive. The cage captured various guests such as aromatic molecules, alkanes, haloalkanes, alcohols and other organic molecules from aqueous solutions. These guests were released in acidic conditions. Lastly, our group has also synthesized a cavitand with N,N-bis(pyridinylmethyl)amine (bpa) ligands.[39]

This thesis reports the synthesis of a new resorcinarene with a ligand designed to coordinate metal ions. Upon hydrolysis of the aminopyridine ester, the compound was complexed with several metals and characterized.

We also synthesized a resorcinarene with four N,N-bis(pyridylmethyl)amine ligands which coordinated with metals. The metal complexes of this compound were all cationic. The iminodiacetate resorcinarene synthesized by our group formed neutral or anionic complexes with metals. The bpa resorcinarene forms a cationic cage with Co^{2+} or Fe^{2+}. Acetic acid pyridine resorcinarenes (APRes) should form neutral complexes with the same cations. The iminodiacetate resorcinarene forms a neutral species when complexed with Cu^{2+}. APRes is expected to form a cationic complex with Cu^{2+}. The new resorcinarene ligand will have different solubility properties due to its different charge states. APRes may also be capable of using its acetate groups to coordinate other metal ions such as Ca^{2+}or Mg^{2+}.

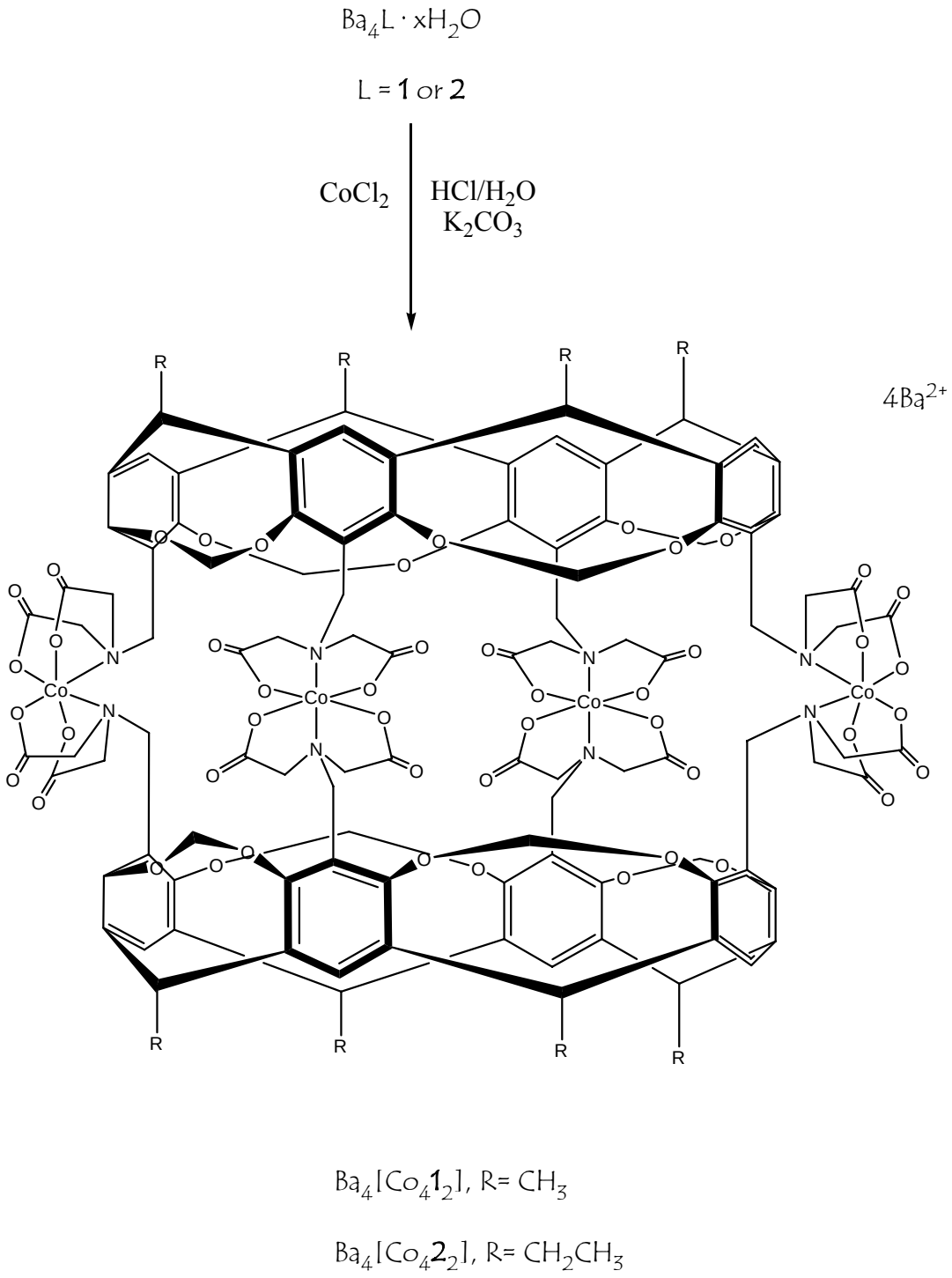
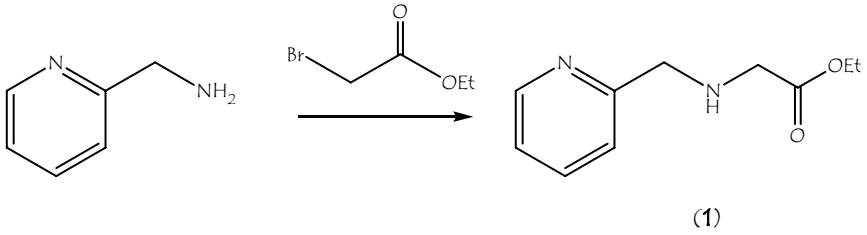


Figure 1-7. Cobalt resorcinarene cage

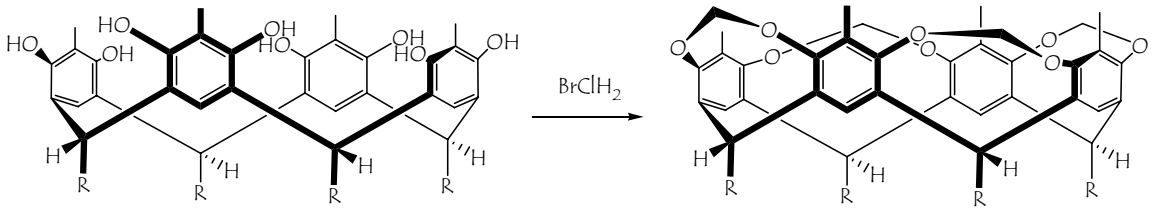
1.3. Results and Discussion

A new cavitand was synthesized by adding an amine moiety with pyridine and acetate ester arms to the upper rim of a brominated bowl. The amine ligand (**1**) was synthesized via nucleophilic substitution of ethylbromoacetate by 2-(aminomethyl)pyridine under mildly basic conditions (Scheme 1-6). **1** was a pale yellow liquid. The brominated bowl (**4**) was synthesized using literature preparations, converting the upper rim of tetraresorcinarene into ether linkages before brominating with NBS (Scheme 1-7). The amine ligand was added to the resorcinarene bowl by the substitution at the four brominated carbons (Scheme 1-8). This compound was hydrolyzed to give acetic acid pyridine resorcinarene (APRes).



(1)

Scheme 1-6. Synthesis of amine ligand



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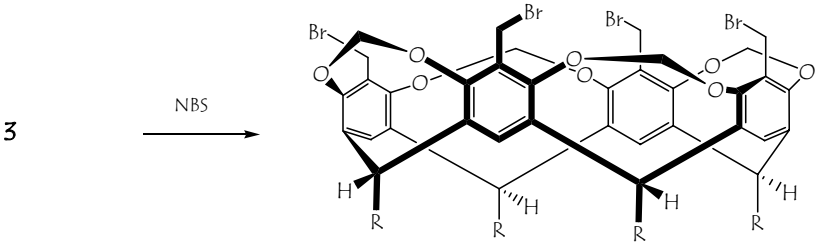

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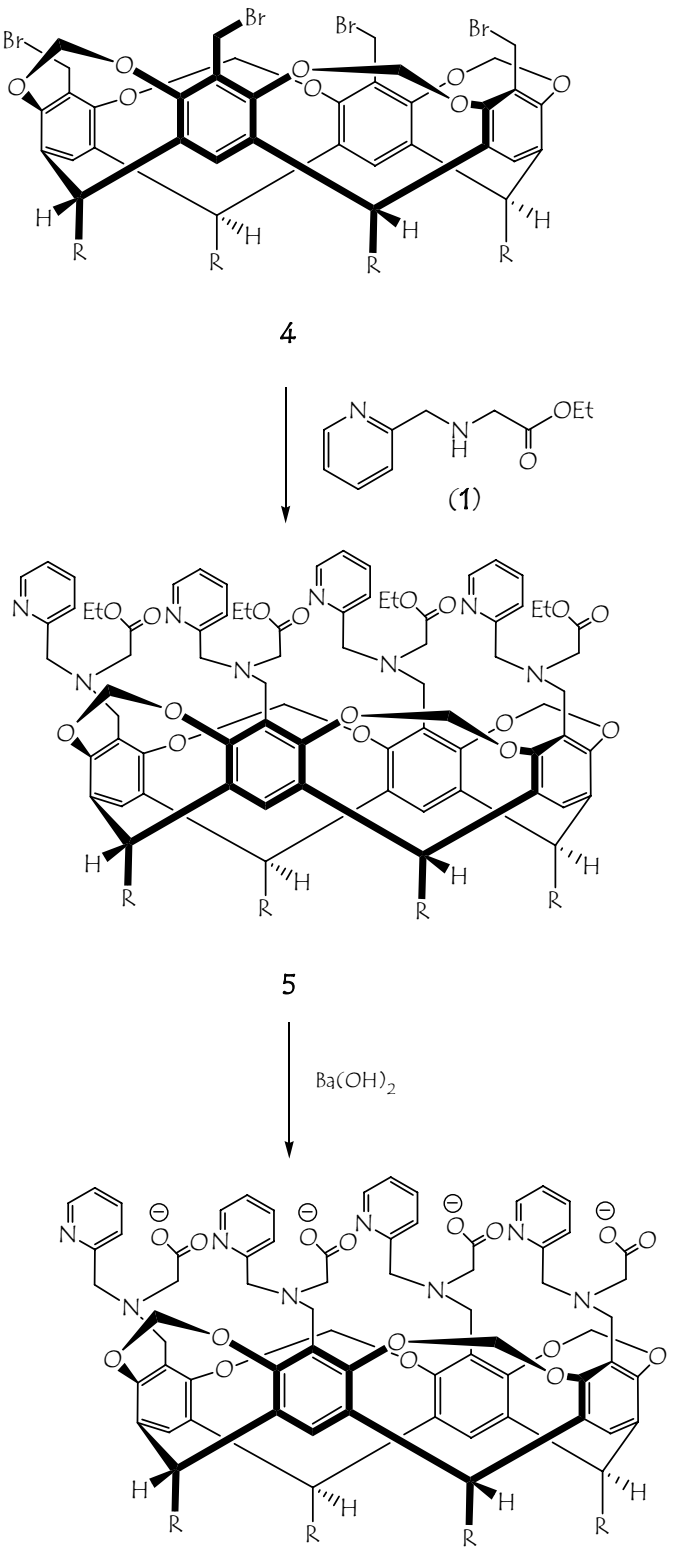
Scheme 1-7. Formation of brominated bowl



Scheme 1-8. Addition of amine ligand to the bowl

The low yields of these supramolecule are not really surprising as most published works on the synthesis of cavitands have reported similar low yields. The yield for acetic acid pyridine resorcinarene (APRes) ester is relatively low which may be due to the route chosen.

1.4 Conclusions

A new resorcinarene with four pyridine and acetic acid ligands capable of metal coordination has been synthesized. N-(2-pyridylmethyl)-N-ethylacetate amine was synthesized by a substitution of methylpyridine amine onto ethylbromoacetate. The amine product was added to brominated methyl resorcinarene to give the product acetic acid pyridine resorcinarene (APRes). Metal complexes of APRes (**6**) are currently being studied and characterized. Future studies will include further characterization of the metal complexes and host-guest studies.

1.5 Experimental

Literature preparations were followed in the synthesis of compounds **1**[40], **2**[7], **3**[41] , and **4**[42]. All reagents and solvents were obtained from Aldrich or other commercial suppliers. Solvents were dried over molecular sieves. ^{1}H NMR spectra were collected at 23^{o}C using a Varian INOVA 300 MHz Multinuclear FT-NMR Spectrometer. ^{13}C NMR spectra were collected at 23^{o}C using a Varian INOVA 75 MHz Multinuclear FT-NMR Spectrometer. ^{1}H and ^{13}C NMR shifts were reported in parts per million (ppm) relative to external reference, tetramethylsilane. Fast atom bombardment (FAB) and electron impact (EI) mass spectra were obtained using a Joel JMS-SX 102 A spectrometer.

_N_-(2-pyridylmethyl)-_N_-ethylacetate amine (1)

Ethylbromoacetate (9.88 mL, 0.089 mol) was dissolved in 51.5 mL THF. Potassium carbonate (10.71 g, 0.077 mol) was added to 2-(aminomethyl)pyridine (8.84 mL, 0.087 mol). The K_2CO_3 mixture was cooled to 0°C and the THF solution was dripped into the K_2CO_3 mixture. The reaction mixture was stirred at 0°C for 30 minutes and warmed to room temperature and stirred overnight. The mixture was filtered to remove solids. The solvent was removed by rotovaporation to give a clear orange liquid. The liquid product was purified by distillation. Yield was 66%.

Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (m, 1H, J = 0.9 Hz, Ar*H*), 7.65 (t, 1H, J = 7.8 Hz, Ar*H*), 7.35 (d, 1H, J = 7.8 Hz, Ar*H*), 7.16 (t, 1H, J = 1.2 Hz, Ar*H*), 4.20 (q, 2H, J = 7.2 Hz, -OC*H*$_2$CH$_3$), 3.95 (s, 2H, -NHC*H*$_2$COO-), 3.47 (s, 2H, ArC*H*$_2$NH-), 2.34 (s, 1H, -N*H*-), 1.27 (t, 3H, J = 6.9 Hz, -CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.3, 159.2, 149.4, 136.6, 122.2, 122.1, 60.8, 55.0, 54.6, 52.3, 50.5, 44.3, 14.3. MS (EI^+) found 195, (100), calcd 195.10 for $[C_{10}H_{15}N_2O_2]^+$.

Methyl-Footed Resorcinarene (2)

To a solution of 65.22 g (0.504 mol) of 2-methylresorcinol in 250 mL of 95% ethanol were added 250 mL of water and 126 mL of concentrated hydrochloric acid under nitrogen. The stirred solution under nitrogen was cooled to 0°C and 30 mL of acetaldehyde were added drop-wise over a 30-minute period. The mixture was then stirred at 55°C for 1 h and then allowed to cool to 22°C. The product precipitated after several hours. The mixture was stirred under nitrogen for 6 days. The solid product was isolated by vacuum filtration and was triturated twice with water. Yield was 88%. ^{1}H

NMR (DMSO, 300 MHz): δ 8.66 (s, 8H, ArO*H*), 7.38 (s, 4H, Ar*H*), 4.45 (q, 4H, J = 7.2 Hz, -C*H*CH_3), 1.94 (s, 12H, Ar-CH_3), 1.71 (d, J = 6.9 Hz, -CHCH_3). ^{13}C NMR (DMSO, 75 MHz): δ 128.6, 125.7, 120.9, 111.5, 28.6, 20.1, 10.0. MS(FAB$^+$) found 623, (100), calcd 600.26 for $[C_{36}H_{40}O_8 \cdot Na]^+$.

Protected Methyl-Footed Resorcinarene (3)

Compound **2** (0.3 g, 0.5 mmol) was dissolved in 25 mL DMF. To the solution of **2** was added K_2CO_3 (6.25 g, 45.2 mmol). CH_2BrCl (1.13 mL, 17.4 mmol) was then added to the reaction mixture. The mixture was stirred and heated to 47°C under a nitrogen atmosphere. A solution of **2** (0.3 g, 0.5 mmol) in 25 mL DMF was dripped into flask overnight. On the second day, another solution of **2** (0.3 g, 0.5 mmol), K_2CO_3 (0.9 g, 6.5 mmol) and $BrClCH_2$ (0.5 mL, 7.7 mmol) in 25 mL DMF was dripped into the flask overnight. The solution was dripped over a period of 6 hours. On the second and third days, a similar solution was dripped into the flask under the same conditions as the second day. The reaction mixture was stirred for another 3 days. The reaction mixture was filtered through a celite pad. The solvent was removed by rotovaporation. Acetonitrile (50 mL) was added to the solid. The mixture was stirred at reflux for 2 hours. Upon filtration, a red solid was obtained. The yield was >90%.

Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.11 (s, 4H, Ar*H*), 5.90 (d, 4H, J = 6.9 Hz, outer –OCH_2O-), 5.00 (q, 4H, J = 7.5 Hz, -C*H*CH_3), 4.28 (d, 4H, J = 6.9 Hz, inner –OCH_2O-), 1.97 (s, 12H, Ar-CH_3), 1.75 (d, J = 7.5 Hz, -CHCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.1, 139.1, 123.9, 117.2, 98.7, 31.4, 16.3, 10.5.

Brominated Methyl-Footed Resorcinarene (4)

Compound **3** (0.4 g, 0.5 mmol) was dissolved in 125 mL chlorobenzene. To this solution NBS (2.02 g, 11.3 mmol) was added. Benzoyl peroxide (0.0200 g, 0.08 mol) was added to reaction mixture under a nitrogen atmosphere. The mixture was then heated to 110°C for 9 hours and allowed to cool to room temperature. NBS (0.69 g, 3.9 mmol) and benzoyl peroxide (0.0123 g, 0.05 mmol) were added to the flask. The reaction mixture was heated to 110°C for 5 hours. The solvent was removed by rotovaporation. The resulting solid was stirred overnight in 200 mL acetonitrile. The product was collected by vacuum filtration. The yield was 89%.

Spectral data: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25 (s, 4H, Ar*H*), 6.05 (d, 4H, J = 6.6 Hz, outer –OCH_2O-), 5.03 (q, 4H, J = 7.4 Hz, -C*H*CH_3), 4.58 (d, 4H, J = 7.2 Hz, inner –OCH_2O-), 1.97 (s, 12H, Ar-CH_2Br), 1.77 (d, J = 7.6, -CHCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.3, 139.2, 124.6, 120.6, 99.2, 31.3, 23.1, 16.2. MS (FAB^+) found 964, calcd 964.6 for $[C_{40}H_{37}Br_4O_8]^+$.

APRes Ester (5)

Compound **1** (3.00 g, 0.0155 mol) was dissolved in THF (600 mL). K_2CO_3 (18.6 g, 0.135 mol) was added to this solution. Compound **4** (3.73 g, 0.0039 mol) was added to the reaction mixture. This solution was heated to 65°C for 21 hours. A dark orange solid formed and was isolated by vacuum filtration. The yield was 53%.

Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.49 (d, 4H, J = 4.8 Hz, Ar*H*), 8.43 (t, 4H, J = 3.9 Hz, Ar*H*), 7.58 (t, 4H, J = 7.2 Hz, Ar*H*), 7.48 (d, 4H, J = 7.8 Hz, Ar*H*) 7.09 (s, 4H, Ar*H*), 5.24 (d, 4H, J = 7.2 Hz, outer –OCH_2O–), 4.84 (q, 4H, J = 7.5 Hz, –C*H*CH_3), 4.11 (t, 8H, J= 7.5 Hz, –COOC$H_2$$CH_3$), 4.03 (s, 12H, Ar-C$H_2$N), 3.90 (d, 4H, J = 4.2 Hz, inner –OCH_2O–), 3.49 (s, 8H, NCH_2Pyr), 3.20 (s, 8H, –NCH_2COO), 1.65 (d, 12H, J =

7.2 Hz, –CHC*H*$_3$), 1.18 (q, 12H, J= 6.9 Hz, –COOCH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.5, 159.8, 154.0, 149.1, 138.9, 136.5, 123.3, 122.1, 119.5, 98.9, 60.7, 60.1, 54.7, 53.4, 50.6, 46.5, 31.3, 16.3, 14.4. HRMS found 1439.6205, (100), calcd 1439.62 for $[C_{80}H_{88}N_8O_{16}Na]^+$.

Hydrolyzed APRes (6)

Compound **5** (0.53 g, 0.37 mmol) was dissolved in THF (117 mL). $Ba(OH)_2 \cdot 8H_2O$ (0.61 g, 1.9 mmol) was dissolved in water (116 mL) and added to **5**. The solution was heated to 80°C and stirred for 18 hours. The precipitate that formed was isolated by vacuum filtration and washed with water. The yield was 16%.

Spectral data: ^{1}H NMR (D_2O, 300 MHz): δ 8.43 (d, 4H, J = 5.1 Hz, Ar*H*), 8.03 (t, 4H, J = 7.8 Hz, Ar*H*), 7.57 (t, 4H, J = 6.3 Hz, Ar*H*), 7.45 (d, 4H, J = 8.1 Hz, Ar*H*) 7.09 (s, 4H, Ar*H*), 5.62 (d, 4H, J = 7.2 Hz, outer –OC*H*$_2$O-), 4.42 (q, 4H, J = 7.5 Hz, -C*H*CH_3), 4.22 (s, 12H, Ar-C*H*$_2$N), 3.86 (d, 4H, J = 6 Hz, inner –OC*H*$_2$O-), 3.75 (s, 8H, NC*H*$_2$Pyr), 3.71 (s, 8H, NC*H*$_2$COO), 1.48 (d, J = 8.7 Hz, -CHC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.7, 145.5, 141.7, 139.3, 128.8, 128.3, 126.5, 126.4, 99.5, 57.0, 55.8, 48.9, 31.1, 15.4.

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2. Deep-Cavity Resorcinarenes

Abstract: Synthesis of a novel resorcinarene-based molecule functionalized with four dinitroquinoxaline moieties has been proposed. Functionalizing the upper rim of resorcinarene-based cavitand allows a variety of compounds to be synthesized from a single scaffold. The synthetic methodology is based on the addition of quinoxaline to Cram's resorcinarene bowls. 1,2-dichloro-6,7-dinitroquinoxaline was synthesized to be added to the rim of a resorcinarene compound. The synthesis involved the addition of oxalic acid to 4-nitro-o-phenylenediamine. The quinoxaline product was nitrated to give 6,7-dinitroquinoxaline-1,2-dione. Chlorination of the dione gives 1,2-dichloro-6,7-dinitroquinoxaline, which can be readily added to resorcinarene.

2.1 Introduction

Simple resorcinarenes have rigid but shallow cavities. Attempts to deepen the cavity usually involve functionalization of the rim of the resorcinarene. Resorcinarenes are well-suited to deepen their cavities. The eight hydroxyl groups at the upper rim hold the compound in a vase-like conformation through hydrogen-bonding. Further functionalization of the upper rim can lead to a deep, rigid cavity. Aromatic groups have been used to build upon the existing scaffold of the resorcinarene by bridging the hydroxyl groups. Bridging the hydroxyl groups with the phenylene moieties deepens the cavity without compromising the rigid structure (Figure 2-1).[43]

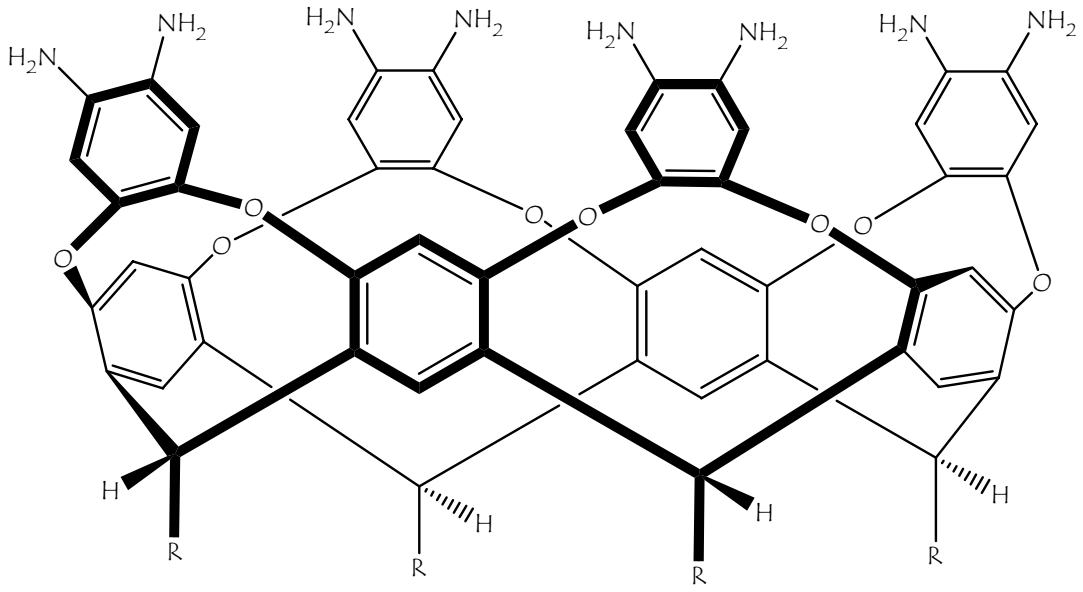


Figure 0-1. Octaaminoresorcinarene

Rebek and coworkers added 1,2-difluoro-4,5-dinitrobenzene to ethyl-footed resorcinarene to given an octanitro compound that encapsulates the large biological compounds choline and carnitine.[44] The nitro groups on the rim were reduced to amine groups for further functionalization (Figure 2-1). These compounds form kinetically stable complexes in water despite the presence of a hydrophobic cavity. They are able to capture tetra-alkylammonium salts and some amines from water.[45]

Quinoxaline compounds are one type of aromatic compound that can be added to resorcinarenes. They were first synthesized by Cram and coworkers in 1982 when

dichloroquinoxaline derivatives were added to resorcinarene to give a deeper cavitand (Figure 2-2).[46]

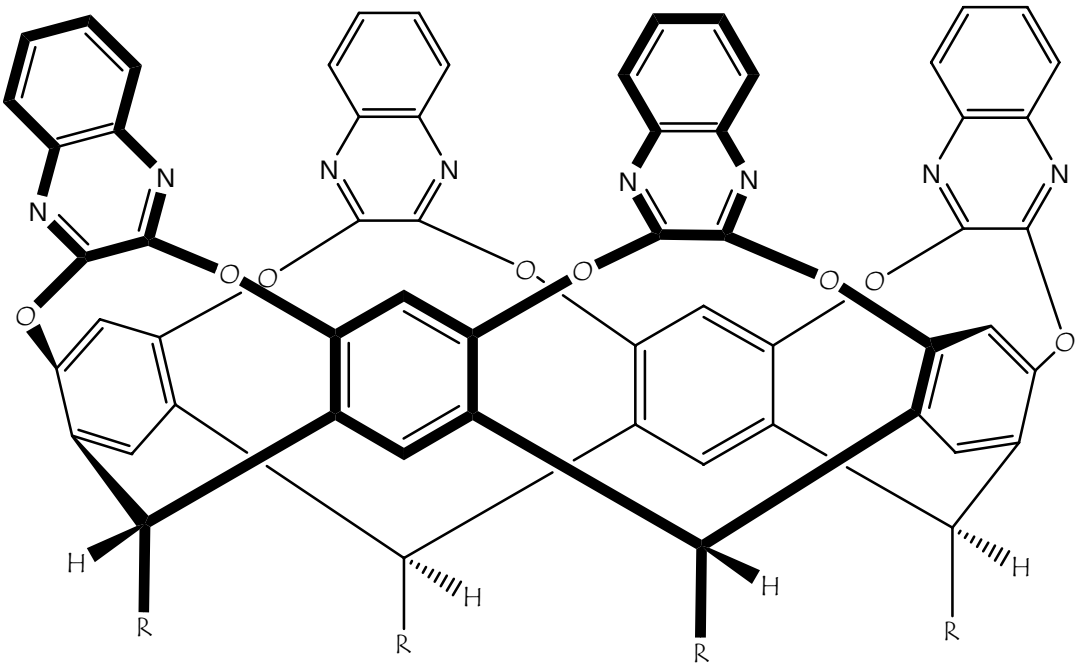
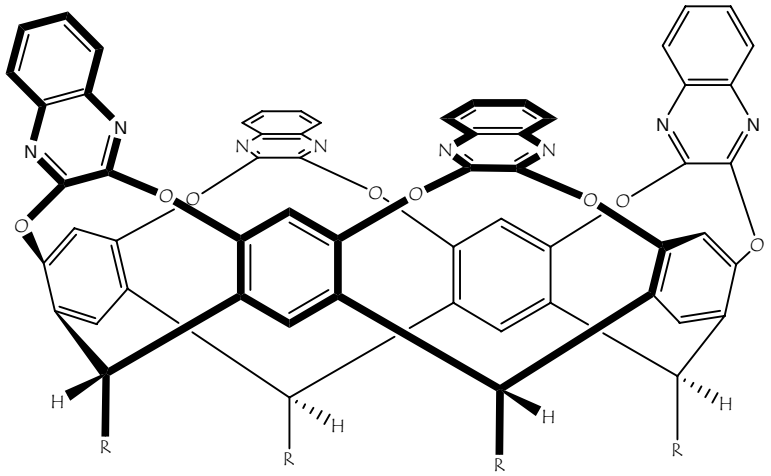
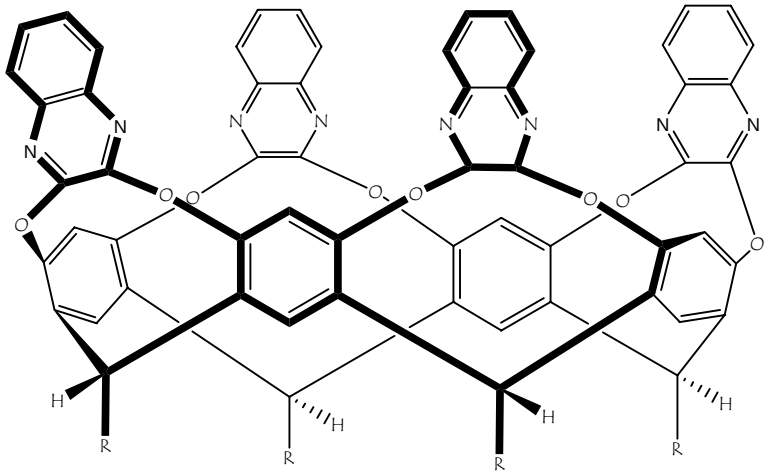


Figure 0-2. Cram's quinoxaline cavitand

Each quinoxaline flap can be found in an axial or equatorial position. Thus, two main conformations were discovered to exist: all axial (aaaa), and all equatorial (eeee). These conformations were found to be temperature-dependent.[47] The aaaa conformation was the main species at $T \geq 5^{o}C$. The eeee conformation dominated at $T \leq -60^{o}C$. The aaaa conformation has been termed a "vase" structure. The eeee conformation is called the "kite" structure (Figure 2-3). The vase conformation led to solubility problems which made those compounds difficult to characterize. Substitution of methyl or bromide on the six and seven positions of the quinoxaline also decreases solubility.[48]



(A)



(B)

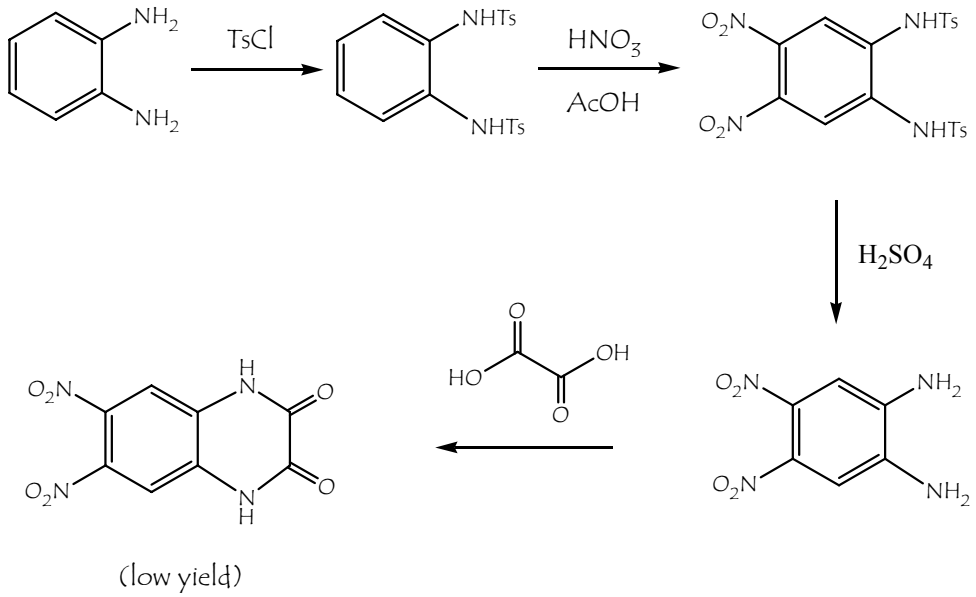
Figure 0-3. Deep-cavity conformations: (A) Kite; (B) Vase

The quinoxaline bowl selectively binds some aromatic compounds in acetone. Compounds such as benzene, toluene, chlorobenzene, fluorobenzene, and benzonitrile were encapsulated whereas benzaldehyde, anisole, benzoic acid, and phenol were not bound.[49]

We have designed a deep-cavity cavitand by adding quinoxaline-derived moieties to the upper rim of the tetrameric bowl. We have added 2,3-dichloro-6,7-dinitroquinoxaline to the bowl via an S_NAr reaction with the hydroxyl groups of upper rim. This cavitand has a larger cavity size and provides amine groups along its upper rim for further functionalization. These functionalizations can be accomplished via reactions with acid chlorides or aldehydes.

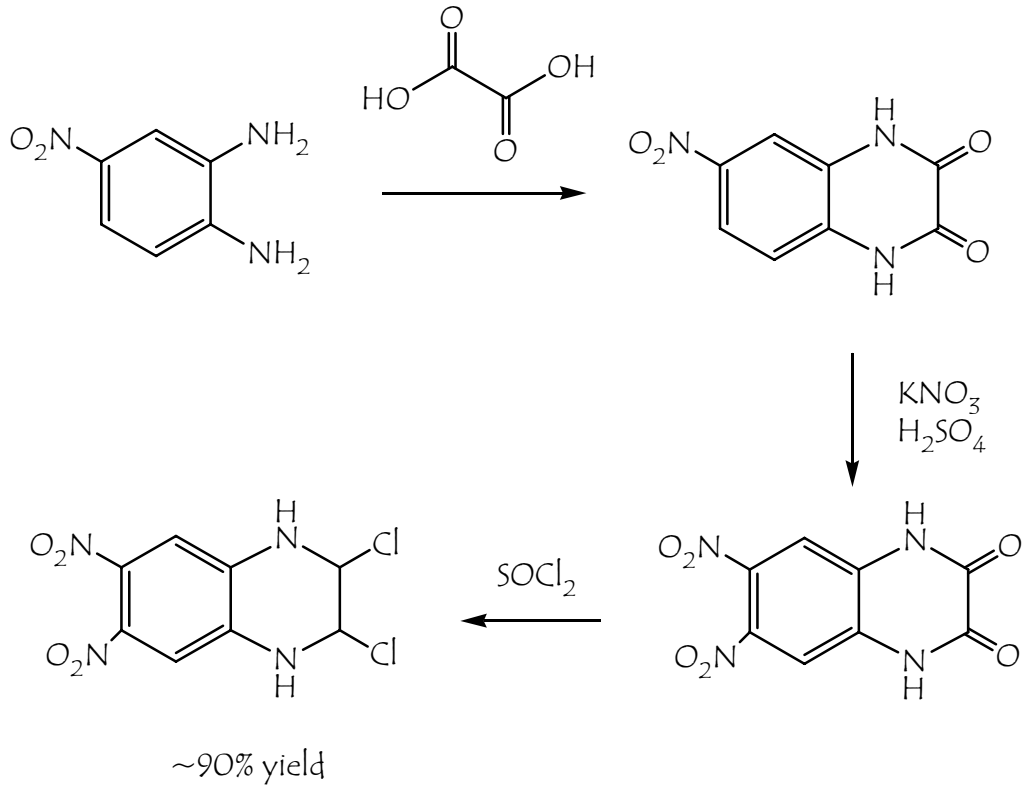
2.2 Results and Discussion

Initially, 1,2-dichloro-6,7-dinitroquinoxaline was synthesized via the usual synthetic route which involved the protection[50] of the amine group of ortho-phenylenediamine using toluene-*p*-sulfonyl chloride (TsCl), followed by nitration[51] (Scheme 2-1). The yields in the multi-step process were decent until the deprotection step (~15% yield based on recovered starting materials).



Scheme 0-1. Synthesis of 6,7-dinitroquinoxaline-1,2-dione

Better yields were achieved when instead of starting with orthodiphenylenediamine, 4-nitro-*o*-phenylenediame was used to form the quinoxaline-1,2-dione (Scheme 2.2). The yield jumped to 90% yield based on recovered starting material.



Scheme 0-2. Route with the better yield

The reaction mechanism involves the protonation of the carbonyl oxygen, resulting in larger electrophilicity of the carbonyl carbon. The amine nitrogen then attacks the carbonyl carbon. Proton exchange follows which leads to the formation of an amide bond upon water expulsion.

2.3 Conclusions

The synthesis of a new resorcinarene with four dinitroquinoxaline moieties attached to the upper rim has been proposed. The ligand to be added to the rim of the resorcinarene has been synthesized and is currently being fully characterized. Oxalic acid was reacted with 4-nitro-*o*-phenylenediamine to give 6-nitroquinoxaline-1,2-dione. This product was

nitrated to give 6,7-dinitroquinoxalinedione. Chlorination of the quinoxaline compound with thionyl chloride leads to an adduct that can be added to the resorcinarene rim. Future studies will involve the addition of the quinoxaline moiety to the rim. The nitro groups on the quinoxaline moieties will be reduced to amine groups in preparation for further functionalization of the rim. Eventually, metal complexes of this compound will be synthesized and studied.

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2.4 Experimental

All reagents and solvents were obtained from Aldrich or other commercial suppliers. ^{1}H NMR spectra were collected at 23°C using a Varian INOVA 300 MHZ Multinuclear FT-NMR Spectrometer. ^{13}C NMR spectra were collected at 23°C using a Varian INOVA 75 MHZ Multinuclear FT-NMR Spectrometer. ^{1}H NMR and ^{13}C NMR shifts were reported in parts per million (ppm) relative to external tetramethylsilane. Fast atom bombardment (FAB) and electron impact (EI) mass spectra were obtained using a Joel JMS-SX 102A spectrometer.

6-nitroquinoxaline-1,2-dione (7)

Compound **7** was synthesized using literature preparations.[52]

4-nitro-1,2-phenylenediamine (15.37 g, 0.100 mol) and oxalic acid dihydrate (13.79 g, 0.109 mol) were dissolved in 30 mL water and 30 mL concentrated hydrochloric acid. The solution was heated to 135°C for 8-12 hours. A red solid was isolated by vacuum filtration. The yield was 90%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.39 (s, 1H, -N*H*-), 12.18 (s, 1H, -N*H*-), 7.96 (d, 1H, J = 8.7 Hz, Ar*H* ortho to NO_2), 7.93 (s, 1H, Ar*H*, ortho

to NO_2), 7.26 (d, 1H, J = 7.8 Hz, Ar*H* meta to NO_2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 155.11, 154.71, 142.08, 131.59, 126.04, 118.55, 115.48, 110.33. MS (FAB^+) found 208.0353 (67), calcd 208.03 for $[C_8H_4N_3O_4]^-$.

6,7-dinitroquinoxaline-1,2-dione (8)

Compound **8** was synthesized using a modified literature preparation.[53] Potassium nitrate (0.3 g, 0.003 mol) was dissolved in 3.2 mL concentrated sulfuric acid. This solution was cooled to 0°C. Compound **7** (0.62 g, 0.003 mol) was added to the cooled solution with stirring. The reaction mixture was stirred at 0°C for 40 minutes and allowed to return to room temperature. The solution was then stirred 18 hours. A yellow solid was collected by vacuum filtration and purified by recrystallization in aqueous DMF. Yield was 67%. ^1H NMR (DMSO-d_6, 300 MHz): δ 12.50 (s, 2H, -N*H*-), 7.72 (s, 2H, Ar*H*). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 154.74, 136.92, 129.55, 111.81. MS (FAB-) found 251.0049 (100), calcd 251.01 for $[C_8H_3N_4O_6]^-$.

1,2-dichloro-6,7-dinitroquinoxaline (9)

Compound **8** (0.2337 g, 0.9 mmol) was dissolved in 1.0 mL dioxane. The mixture was heated to 80°C. When DMF (0.03 mL) was added to the mixture, the solid **8** dissolved. Thionyl chloride (0.21 mL, 2.9 mmol) was added slowly to the solution with stirring. The reaction mixture was heated to 100°C for 3 hours. The solution was rotovapped. The yield was 32%. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 156.1, 116.7, 112.8, 111.7. MS (FAB^-) found 288 (33) calcd 288.02 for $[C_8HN_4O_4Cl_2]^-$.

Ethyl-footed Resorcinarene (10)

Compound **10** was synthesized following a modified literature preparation.**Error! Bookmark not defined.**To a solution of resorcinol (110.16 g, 1 mol) in 500 mL of 95%

ethanol were added 500 mL of water and 250 mL of concentrated hydrochloric acid under nitrogen. The solution was cooled to 0°C. Propanal (75 mL, 1 mol) was dripped into the reaction mixture over a 30-minute period. The solution was clear and pale orange. The mixture was then stirred at 50°C for one hour and then allowed to cool to 22˚C. A precipitate formed after several hours. The mixture was stirred under nitrogen for 6 days. Ice was added and the solution was filtered to give an orange solid. The yield was >90%. ^{1}H NMR (Acetone-d_6, 300 MHz): δ 8.01 (s, 4H, Ar*H*), 7.53 (s, 4H, Ar*H*), 6.36 (s, 4H, Ar*H*), 4.40 (t, 4H, J = 7.5 Hz, -C*H*CH_2CH_3), 3.01 (s, 8H, Ar-O*H*), 2.11 (m, J = 7.2 Hz, -CHC*H*$_2CH_3$), 0.827 (t, J = 7.2 Hz, -$CHCH_2$C*H*$_3$). ^{13}C NMR (Acetone-d_6, 75 MHz): δ 153.2, 125.6, 124.9, 103.3, 35.7, 13.3.

Quinoxaline Bowl (11)

Compound **11** will be synthesized by adding **9** to **10** or to other resorcinarene with a longer foot (possibly pentyl-footed resorcinarene). The compound will be synthesized following the literature procedure for similar compounds.

2.5 References

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Appendix

^{1}H NMR Unprotected Methyl bowl

^{13}C NMR Unprotected Methyl bowl

^{1}H NMR Protected Methyl bowl

^{13}C NMR Protected Methyl bowl

^{1}H NMR Bromomethyl bowl

^{13}C NMR Bromomethyl bowl

^{1}H NMR Amine bowl

^{13}C NMR AP amine

^{1}H NMR AP Res

^{13}C NMR Methyl AP Res bowl #7

^{1}H NMR Barium-hydrolyzed carb-pyridine #2

^{13}C NMR Acid hydrolyzed AP Rex #8

^{1}H NMR Ethyl footed bowl

^{1}H NMR Nitroquinoxalinedione

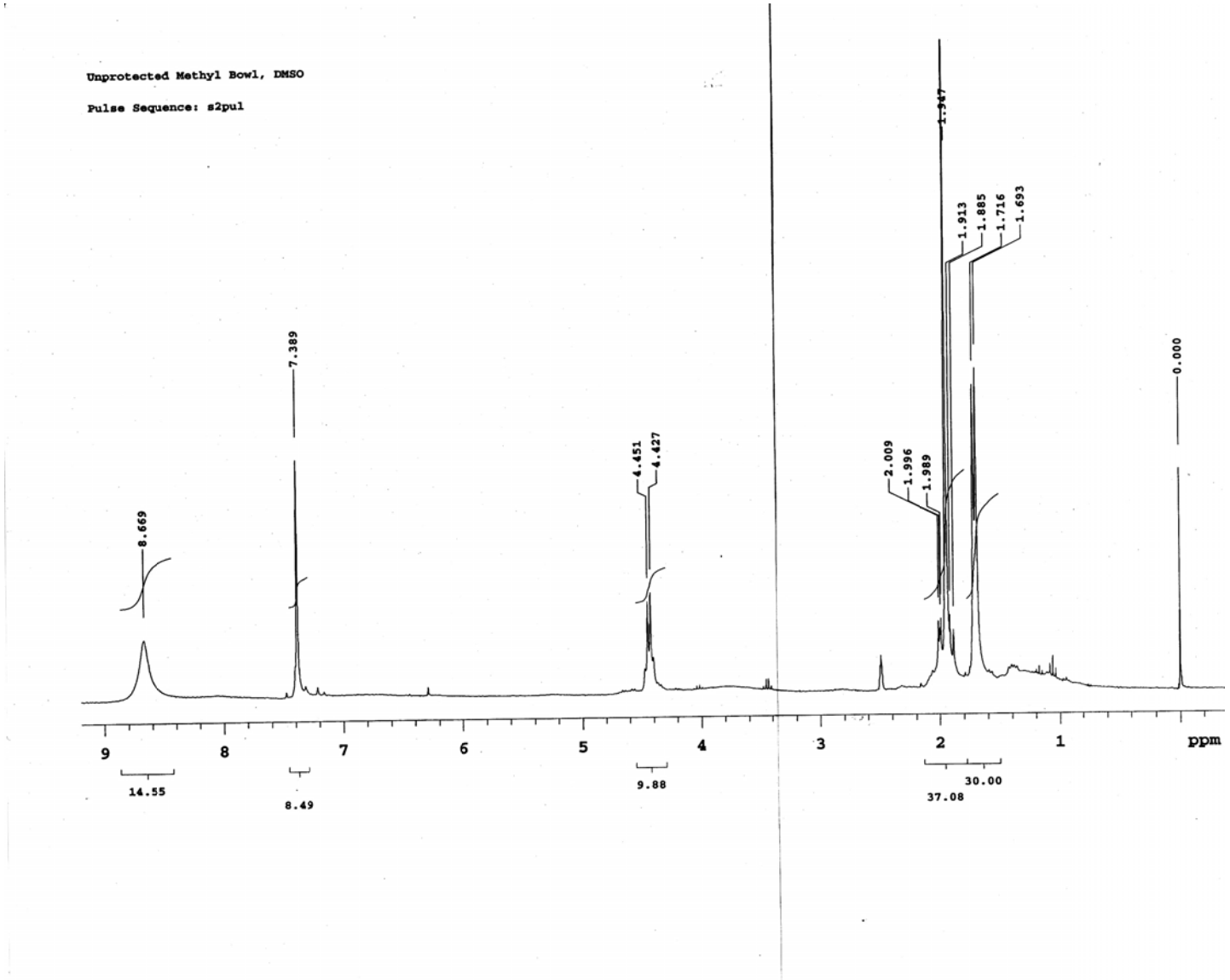
^{13}C NMR Nitroquinoxalinedione

^{1}H NMR Dinitroquinoxalinedione

^{13}C NMR Dinitroquinaxalinedione

^{1}H NMR Dichlorodinitroquinoxaline

^{13}C NMR Dichlorodinitroquinoxaline


Unprotected Methyl Bowl, DMSO
Pulse Sequence: s2pul
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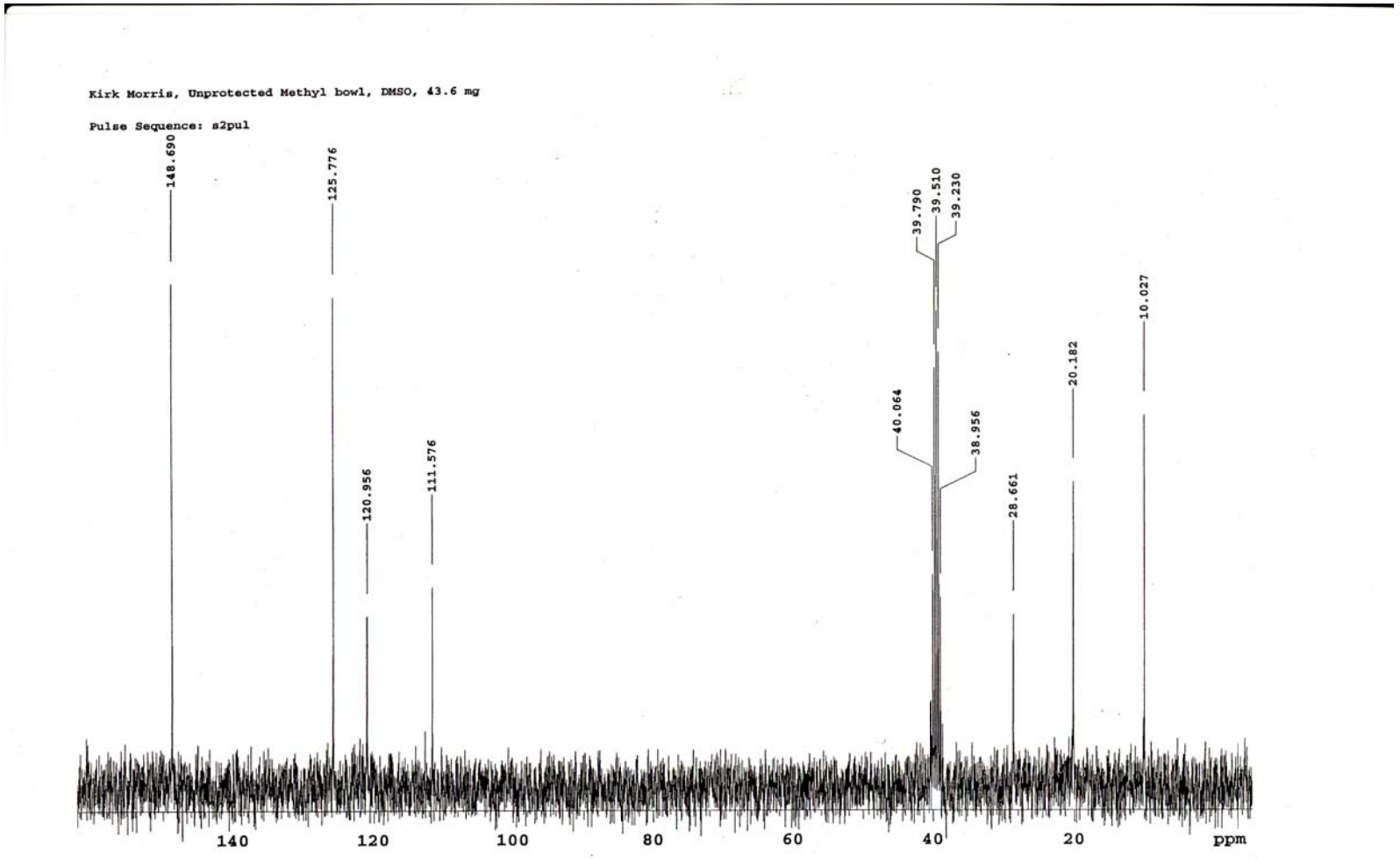
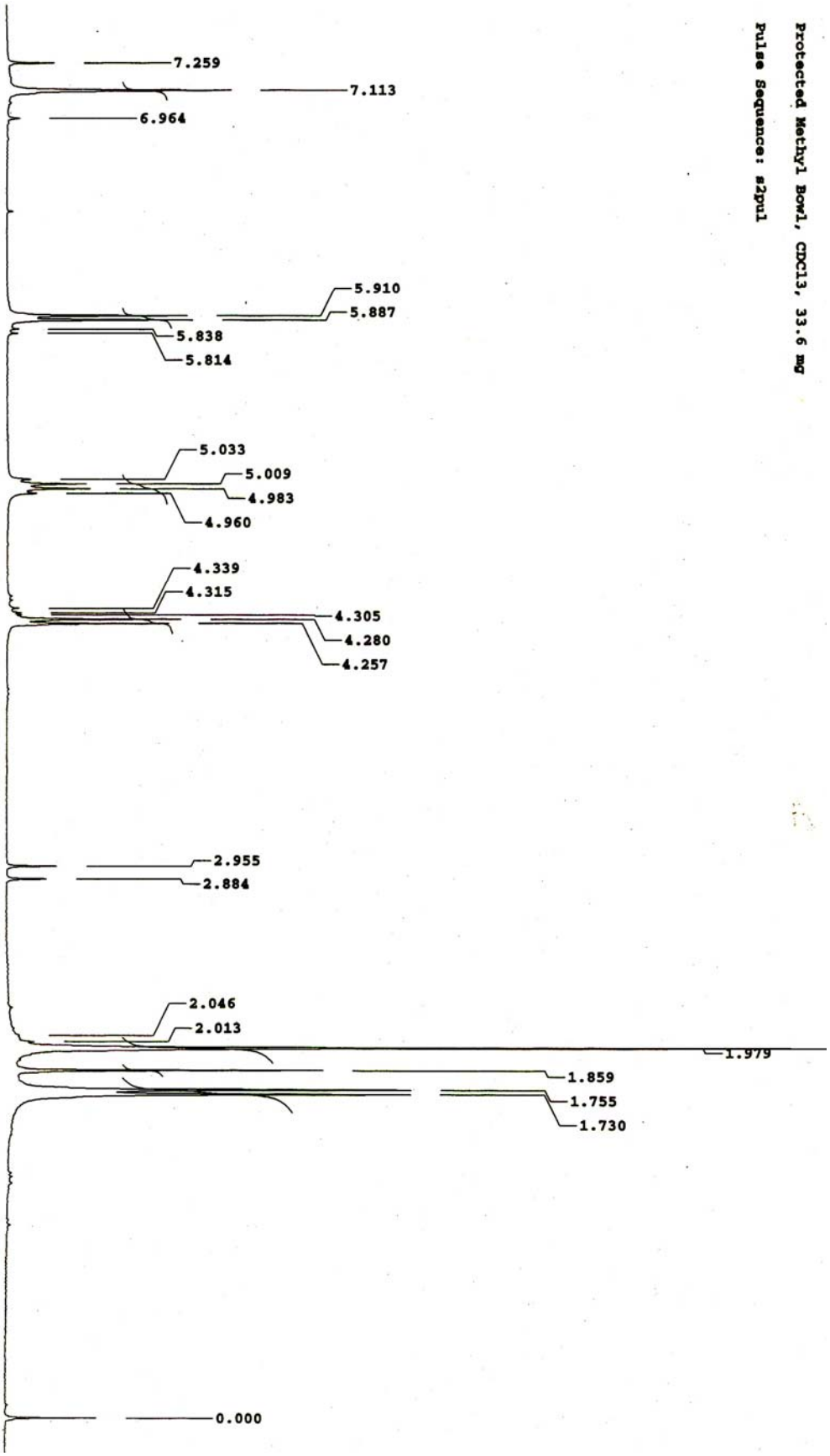
7.389
4.451
4.427
2.009
1.996
1.989
1.947
1.913
1.885
1.716
1.693
0.000
9
8
7
6
5
4
3
2
1
ppm
14.55
8.49
9.88
37.08
30.00


Kirk Morris, Unprotected Methyl bowl, DMSO, 43.6 mg
Pulse Sequence: s2pul
148.690
125.776
120.956
111.576
40.064
39.790
39.510
39.230
38.956
28.661
20.182
10.027
140
120
100
80
60
40
20
ppm


Protected Methyl Bowl, CDCl3, 33.6 mg
Pulse Sequence: s2pul
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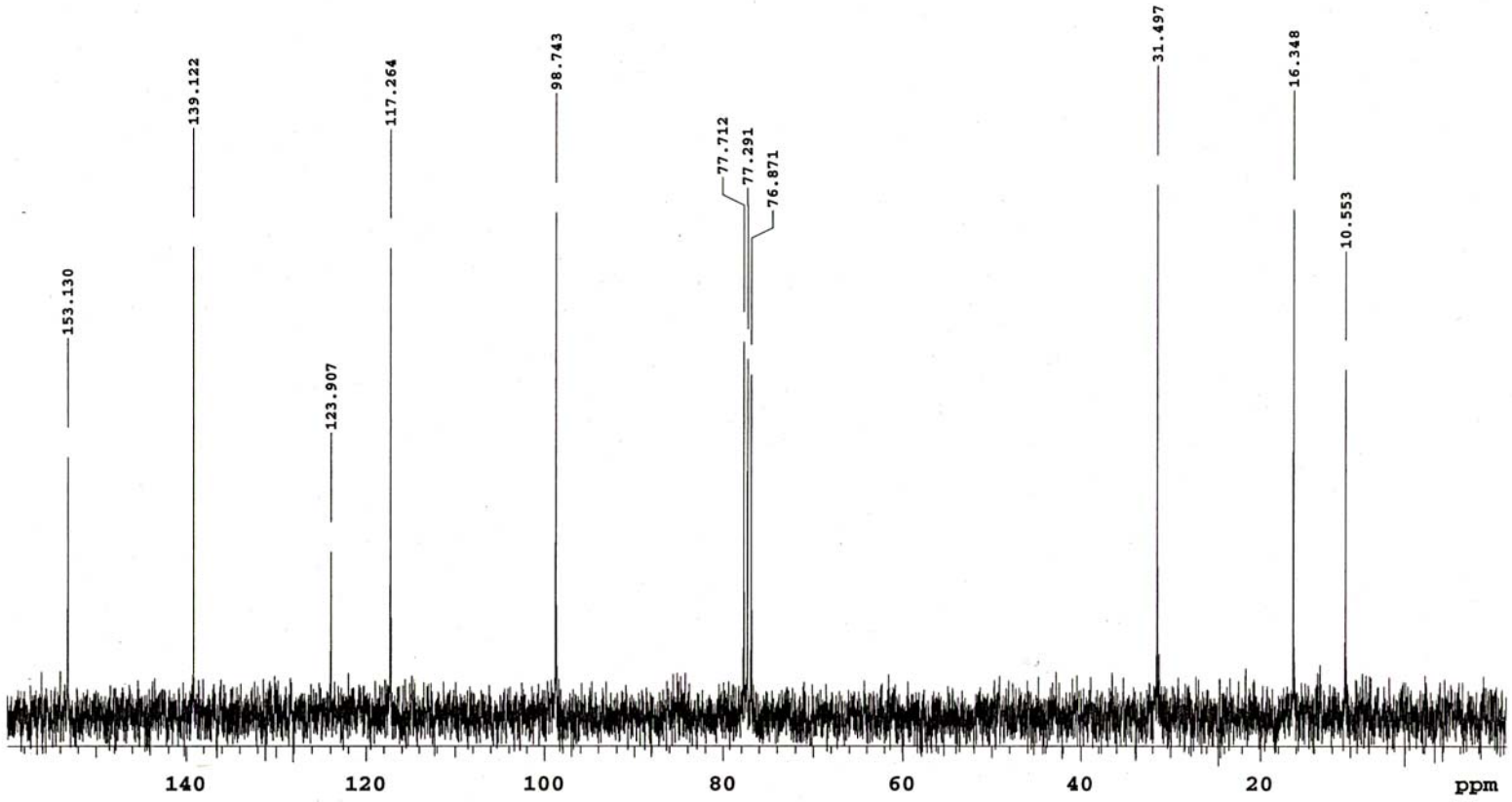
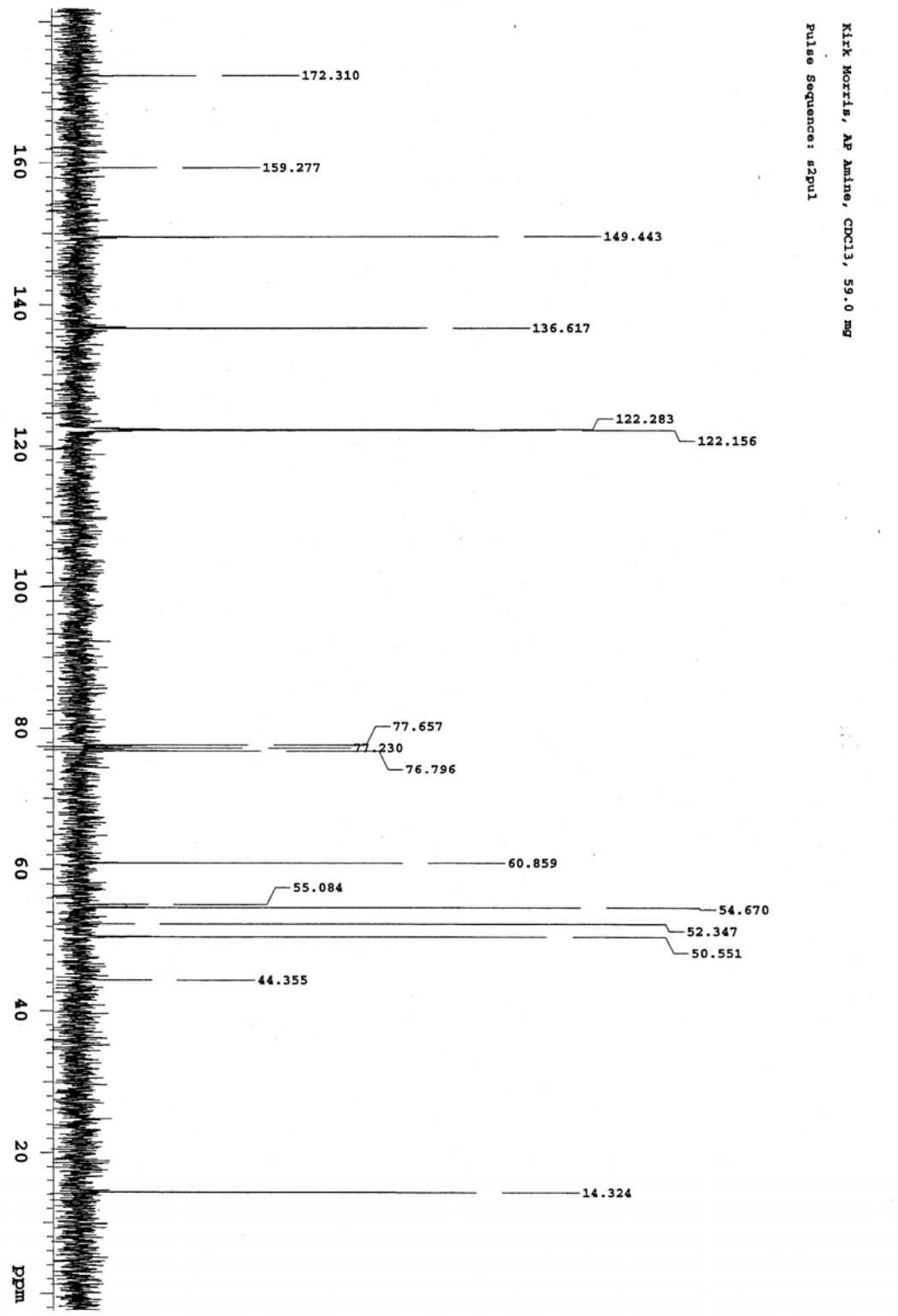
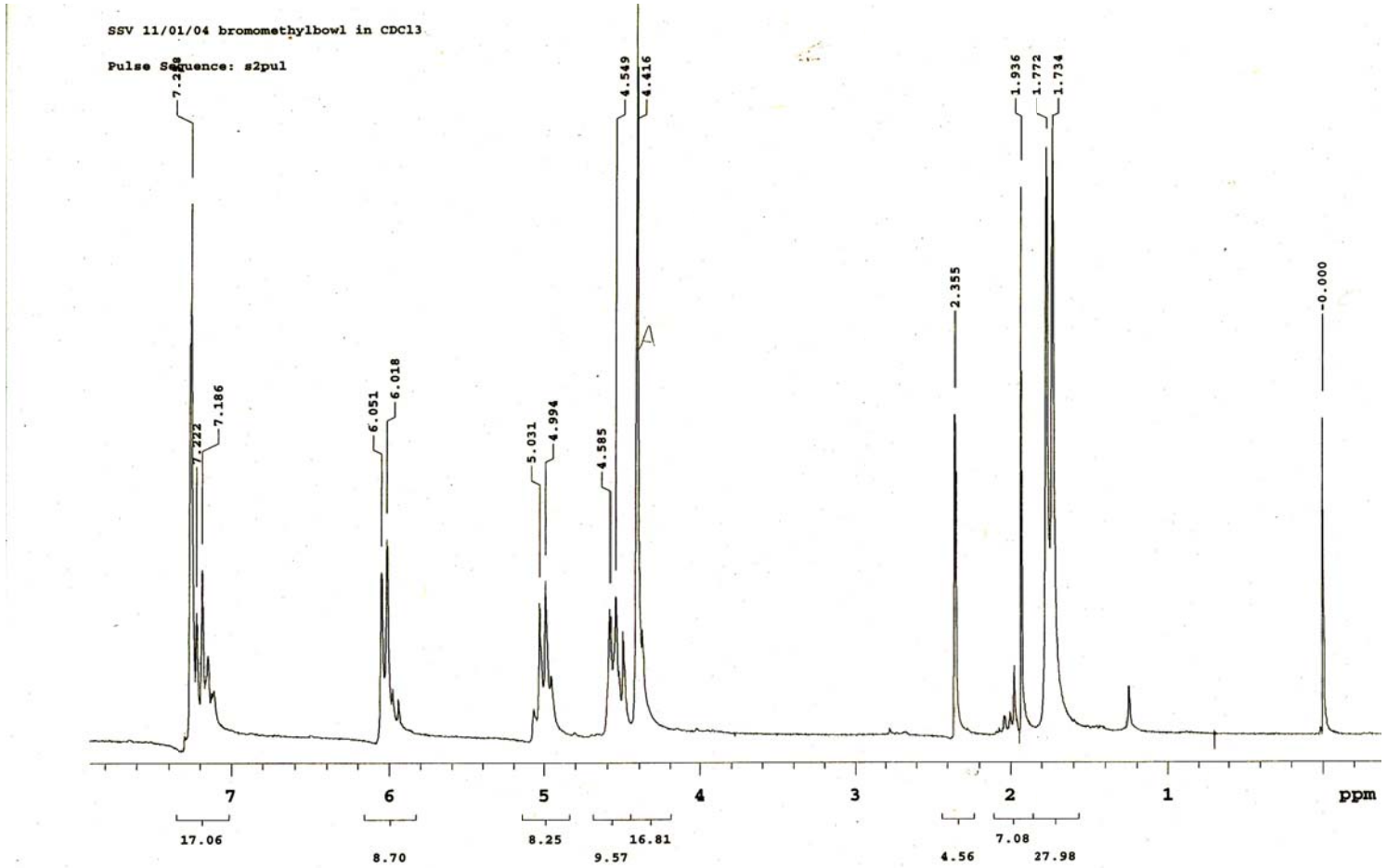
7.113
6.964
5.910
5.887
5.838
5.814
5.033
5.009
4.983
4.960
4.339
4.315
4.305
4.280
4.257
2.955
2.884
2.046
2.013
1.979
1.859
1.755
1.730
0.000

Protected Methyl Bowl, CDCL3, 33.6 mg

Pulse Sequence: s2pul




Kirk Morris, AP Amine, CDCl3, 59.0 mg
Pulse Sequence: s2pul
172.310
159.277
149.443
136.617
122.283
122.156
77.657
77.230
76.796
60.859
55.084
54.670
52.347
50.551
44.355
14.324
160
140
120
100
80
60
40
20
ppm


SSV 11/01/04 bromomethylbowl in CDCl3
Pulse Sequence: s2pul
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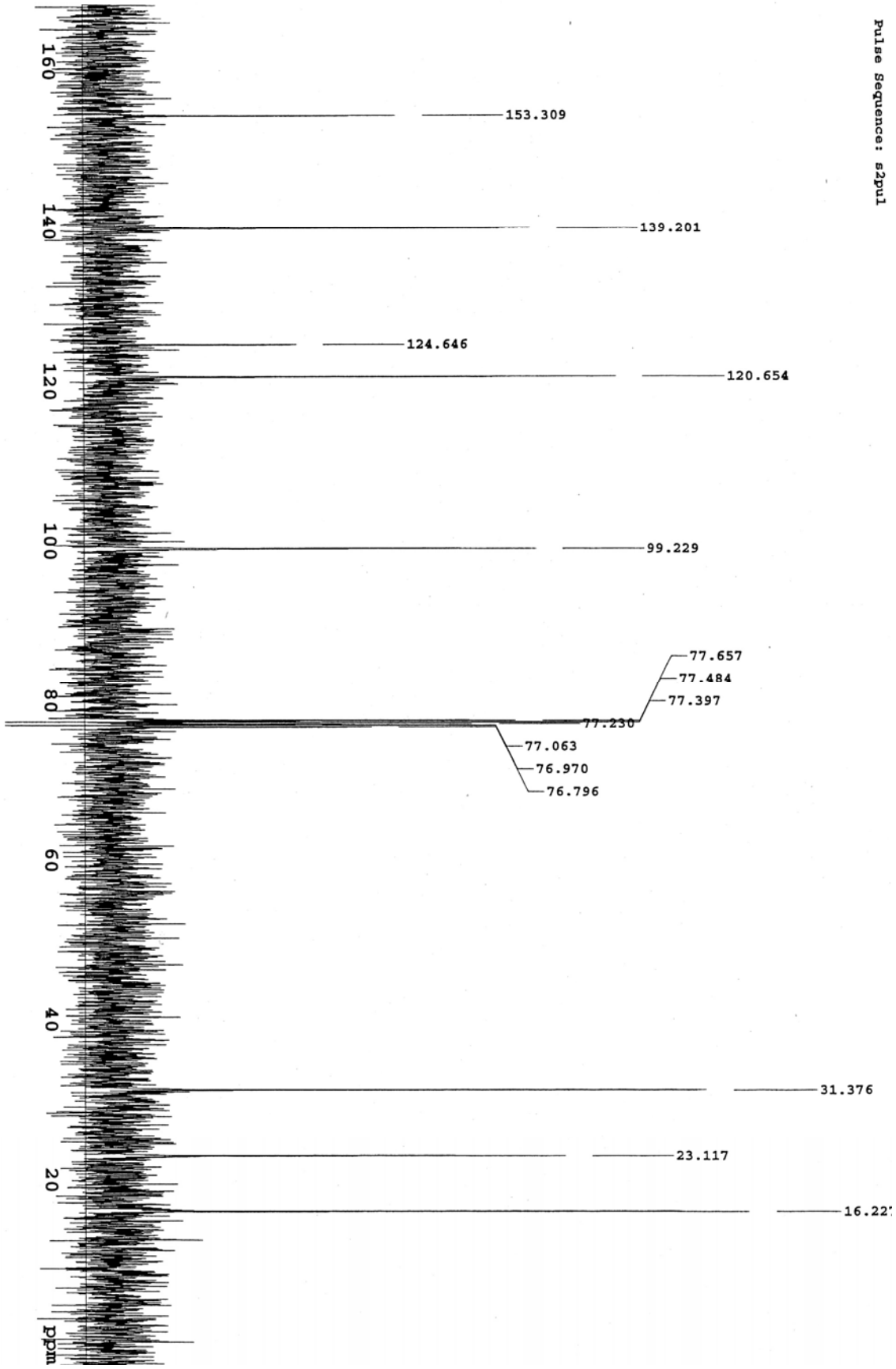
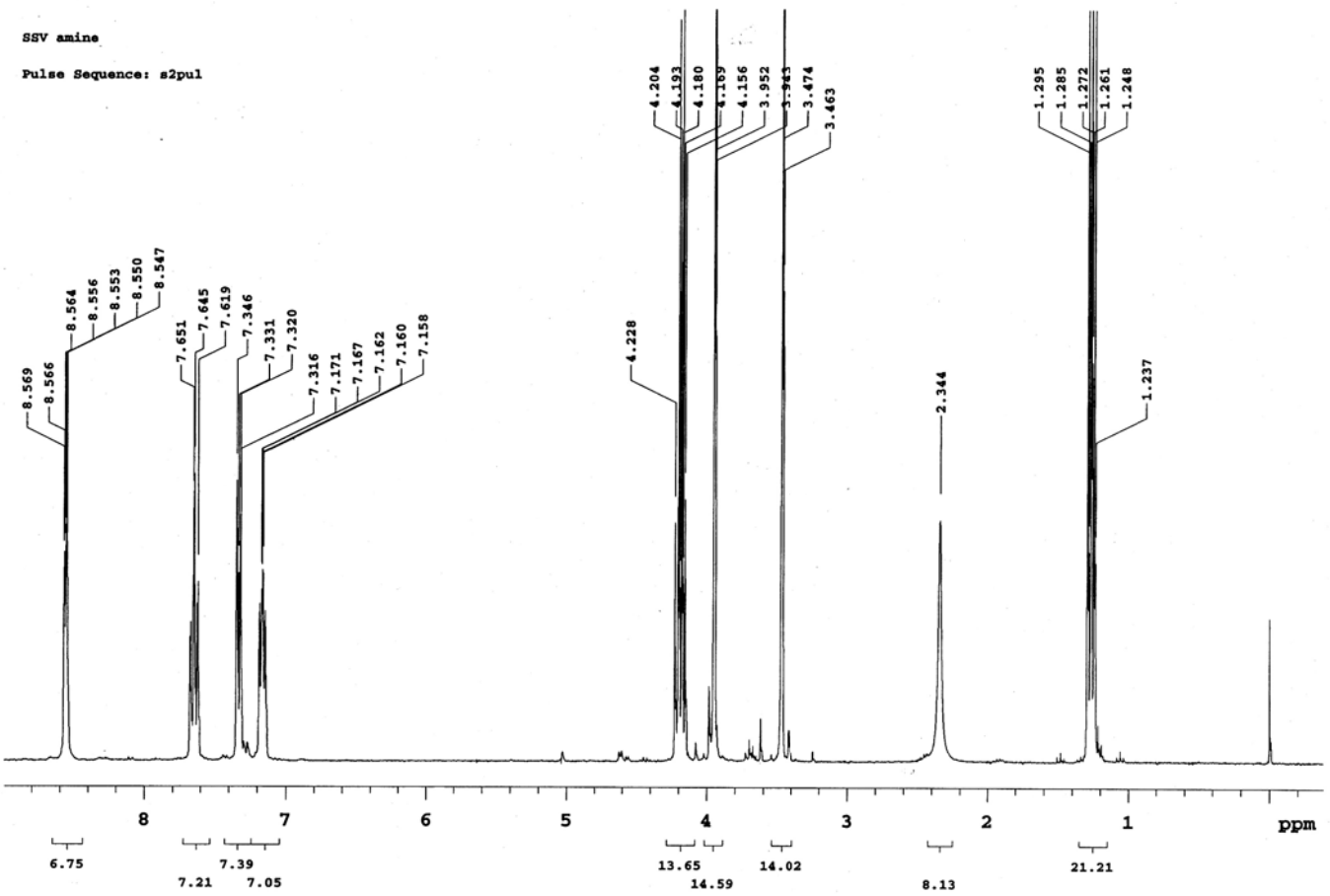
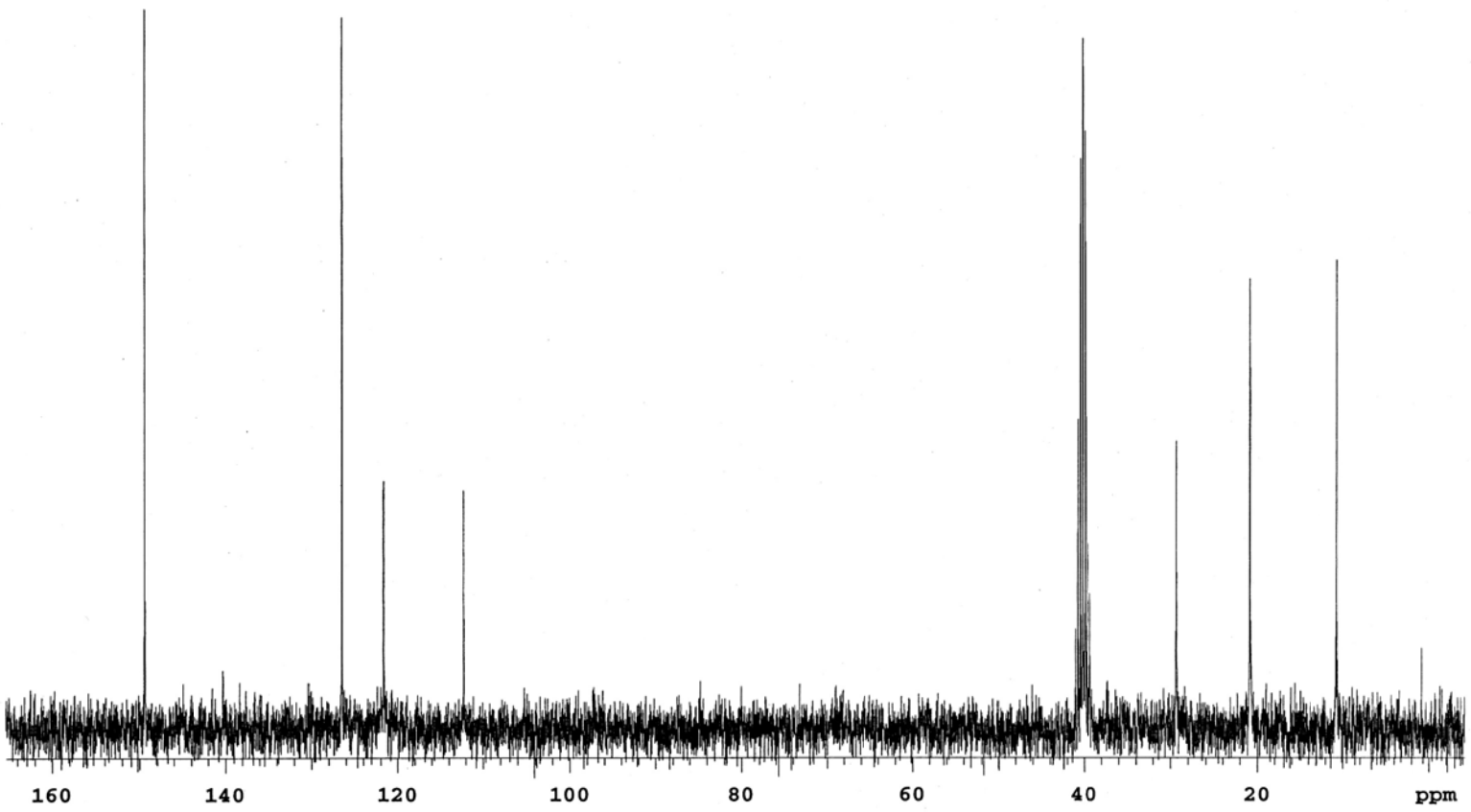
7.186
6.051
6.018
5.031
4.994
4.585
4.549
4.416
2.355
1.936
1.772
1.734
0.000
A
7
6
5
4
3
2
1
ppm
17.06
8.70
8.25
16.81
9.57
4.56
7.08
27.98

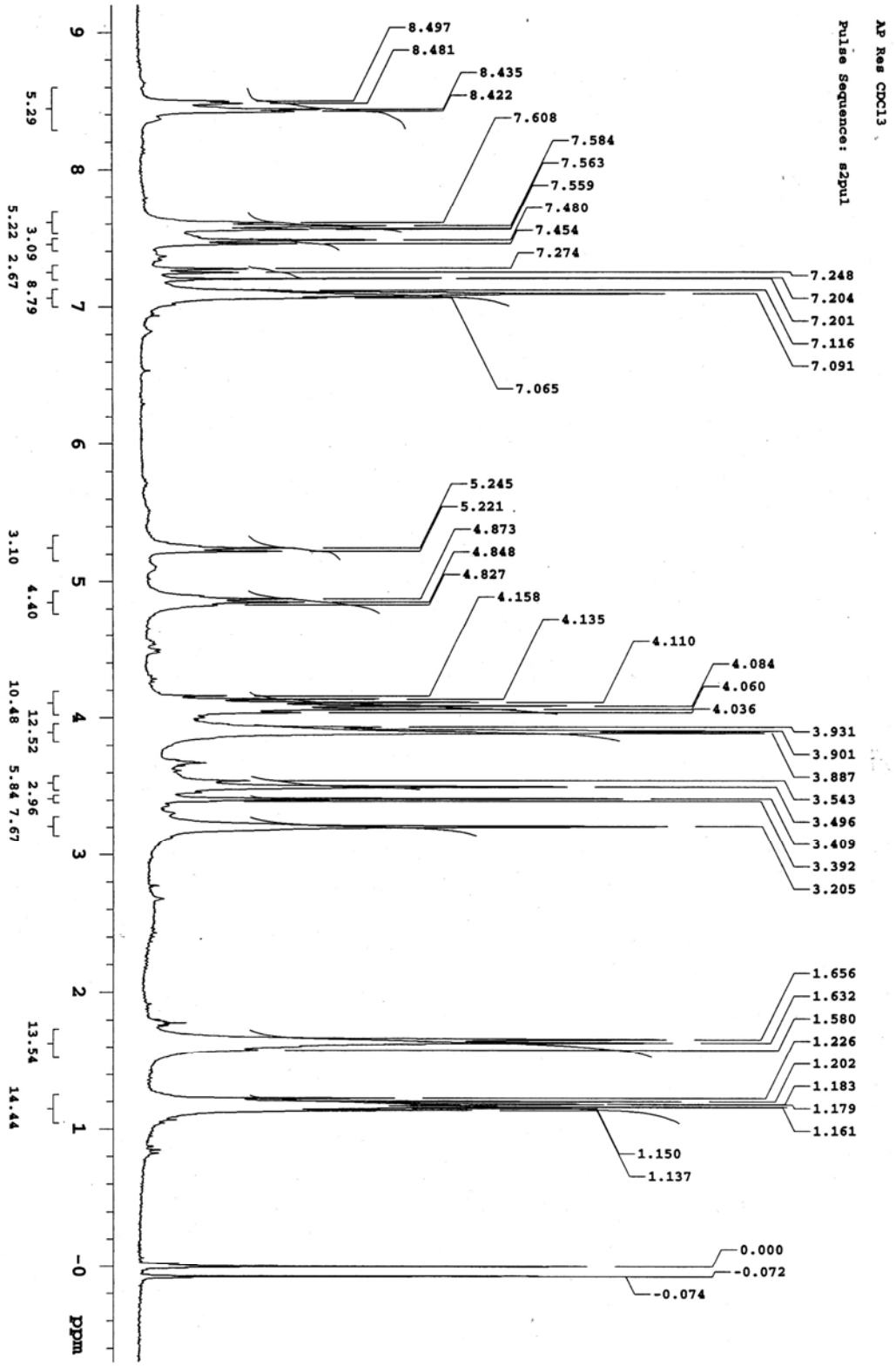

Pulse Sequence: s2pul
153.309
139.201
124.646
120.654
99.229
77.657
77.484
77.397
77.230
77.063
76.970
76.796
31.376
23.117
16.22
160
140
120
100
80
60
40
20
ppm

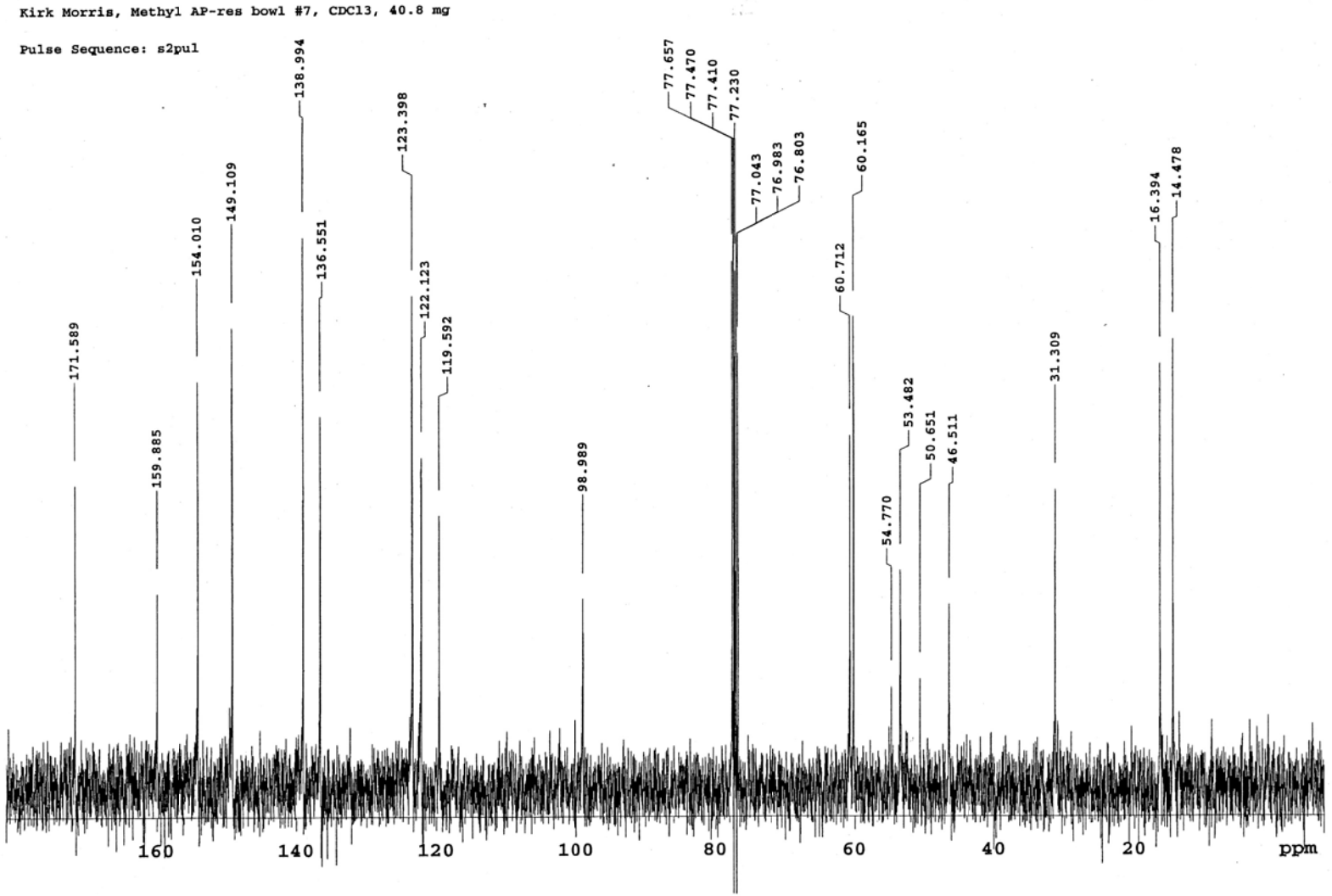

SSV amine
Pulse Sequence: s2pul
8.569
8.566
8.564
8.556
8.553
8.550
8.547
7.651
7.645
7.619
7.346
7.331
7.320
7.316
7.171
7.167
7.162
7.160
7.158
4.228
4.204
4.193
4.180
4.169
4.156
3.952
3.943
3.474
3.463
2.344
1.295
1.285
1.272
1.261
1.248
1.237
8
7
6
5
4
3
2
1
ppm
6.75
7.21
7.39
7.05
13.65
14.59
14.02
8.13
21.21

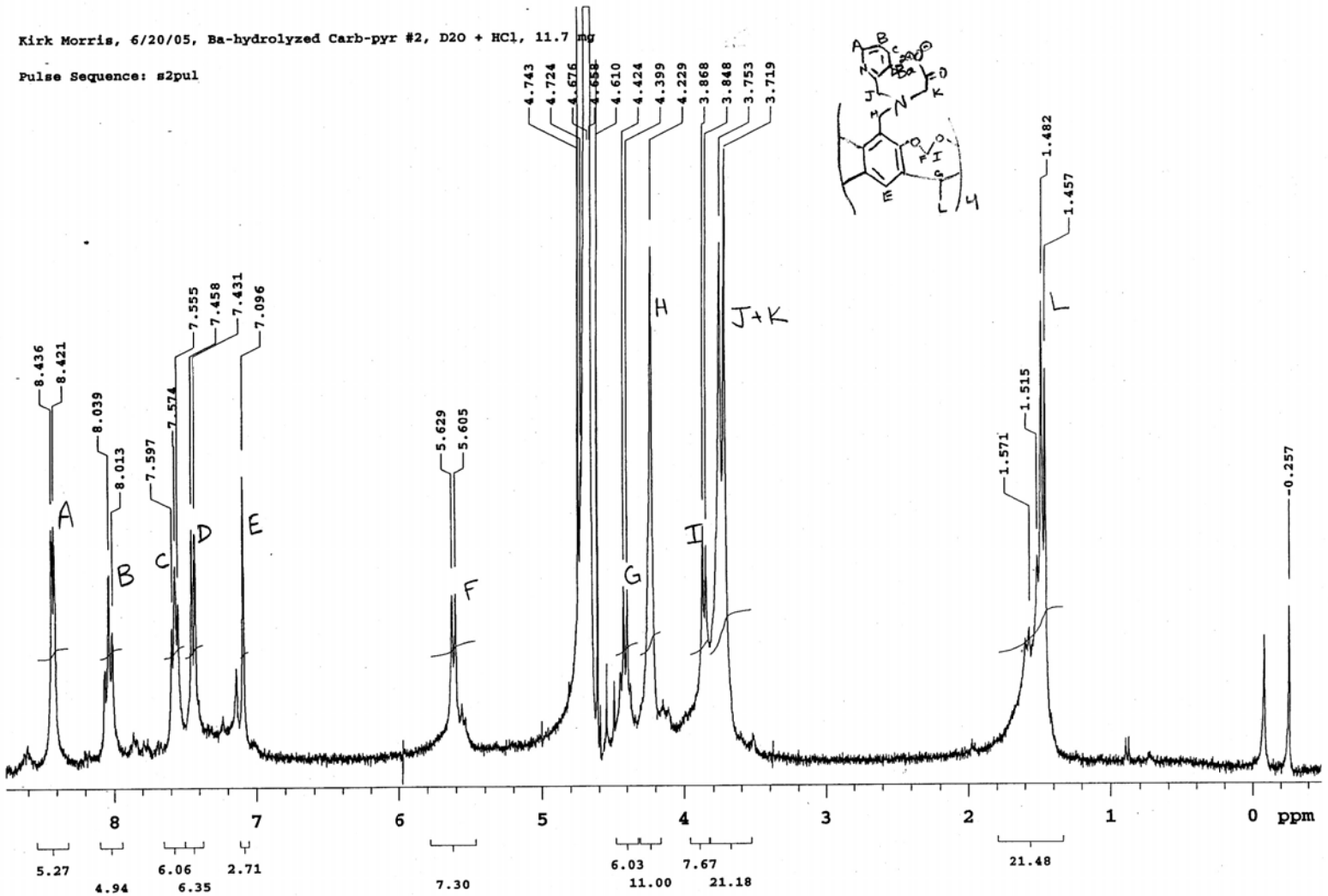
Unprotected Methyl Bowl, DMSO

Pulse Sequence: s2pul



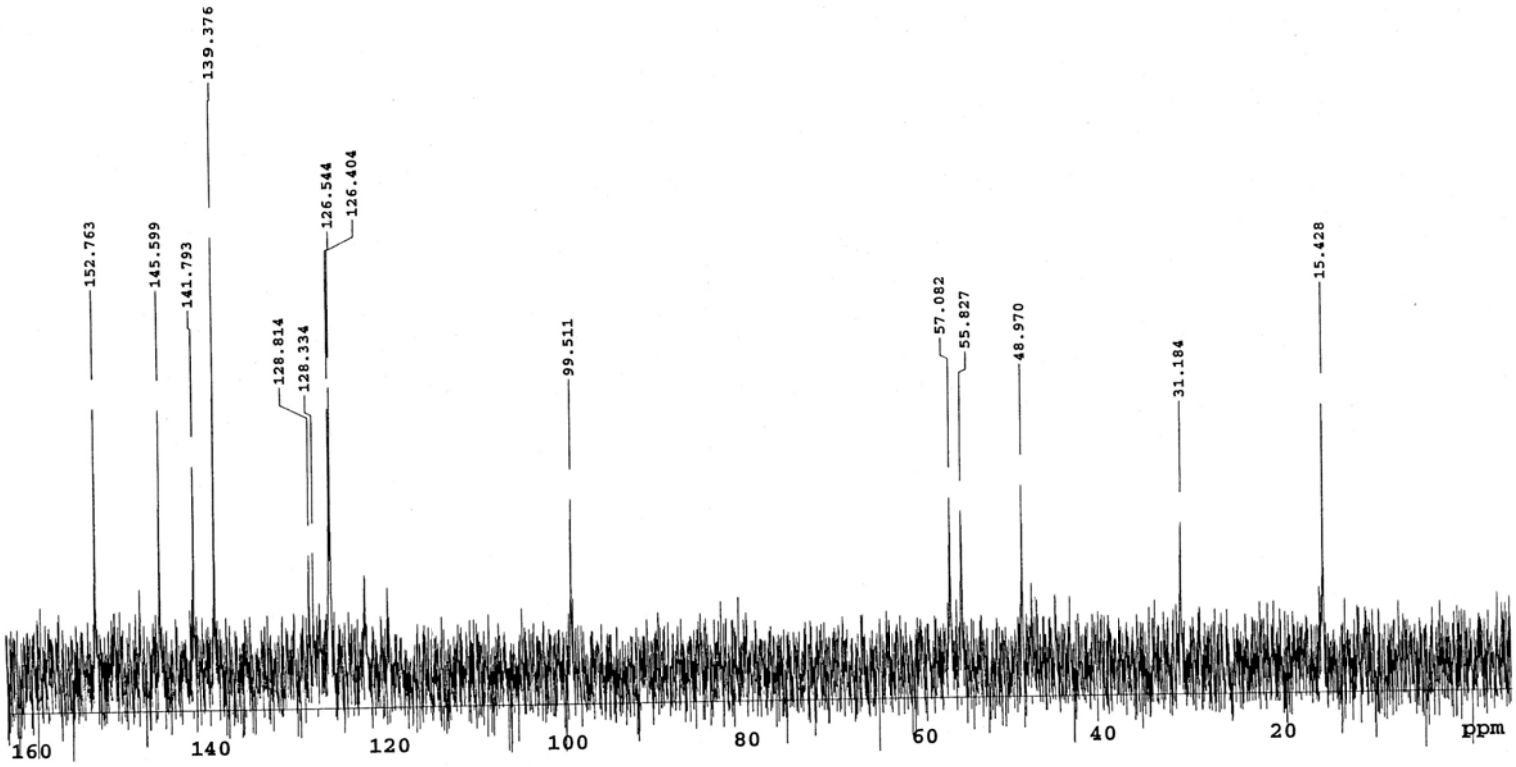

AP Res CDC13
Pulse Sequence: s2pul
8.497
8.481
8.435
8.422
7.608
7.584
7.563
7.559
7.480
7.454
7.274
7.248
7.204
7.201
7.116
7.091
7.065
5.245
5.221
4.873
4.848
4.827
4.158
4.135
4.110
4.084
4.060
4.036
3.931
3.901
3.887
3.543
3.496
3.409
3.392
3.205
1.656
1.632
1.580
1.226
1.202
1.183
1.179
1.161
1.150
1.137
0.000
-0.072
-0.074
ppm

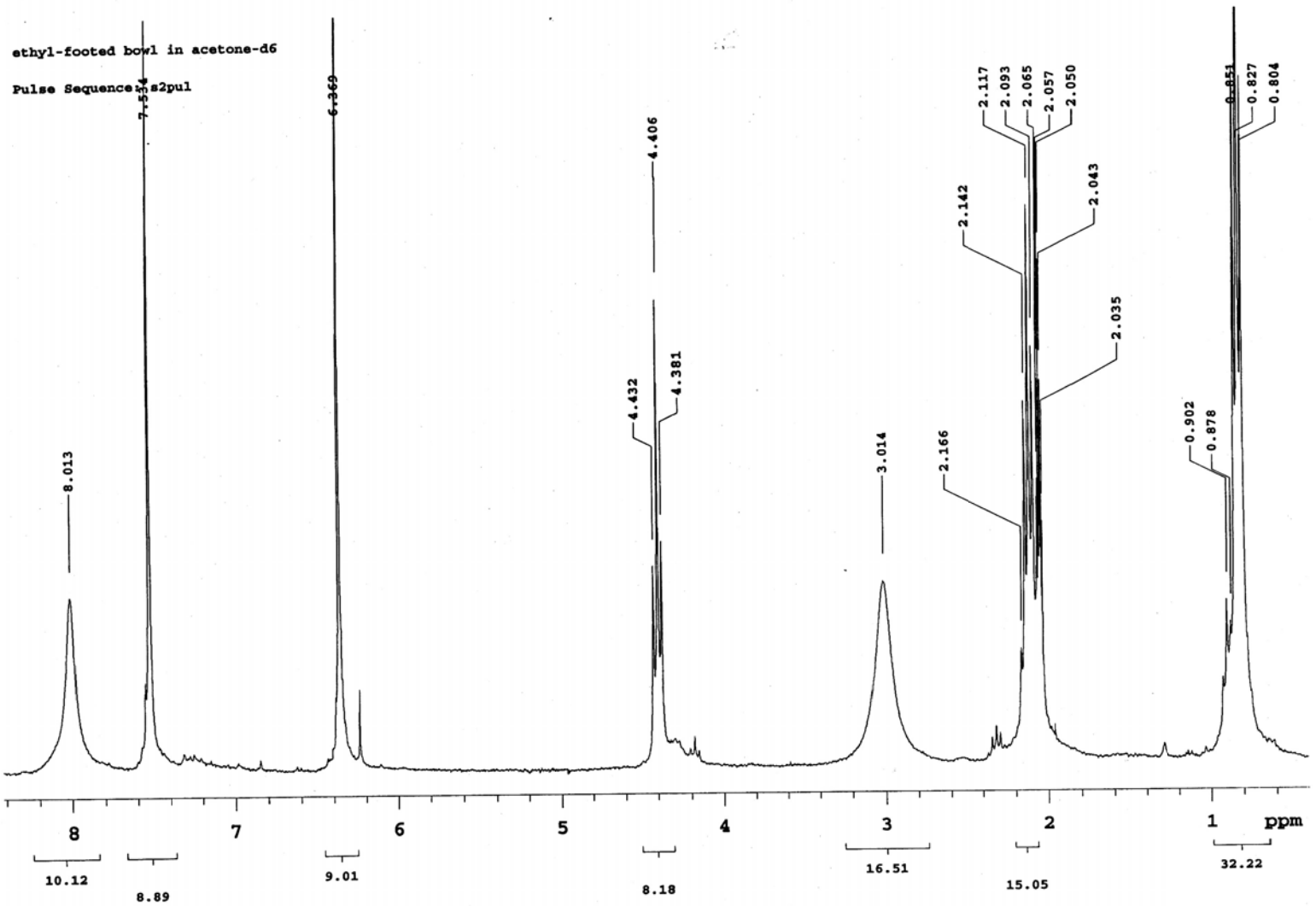

Kirk Morris, Methyl AP-res bowl #7, CDCl3, 40.8 mg
Pulse Sequence: s2pul
171.589
159.885
154.010
149.109
138.994
136.551
123.398
122.123
119.592
98.989
77.657
77.470
77.410
77.230
77.043
76.983
76.803
60.712
60.165
54.770
53.482
50.651
46.511
31.309
16.394
14.478
160
140
120
100
80
60
40
20
ppm

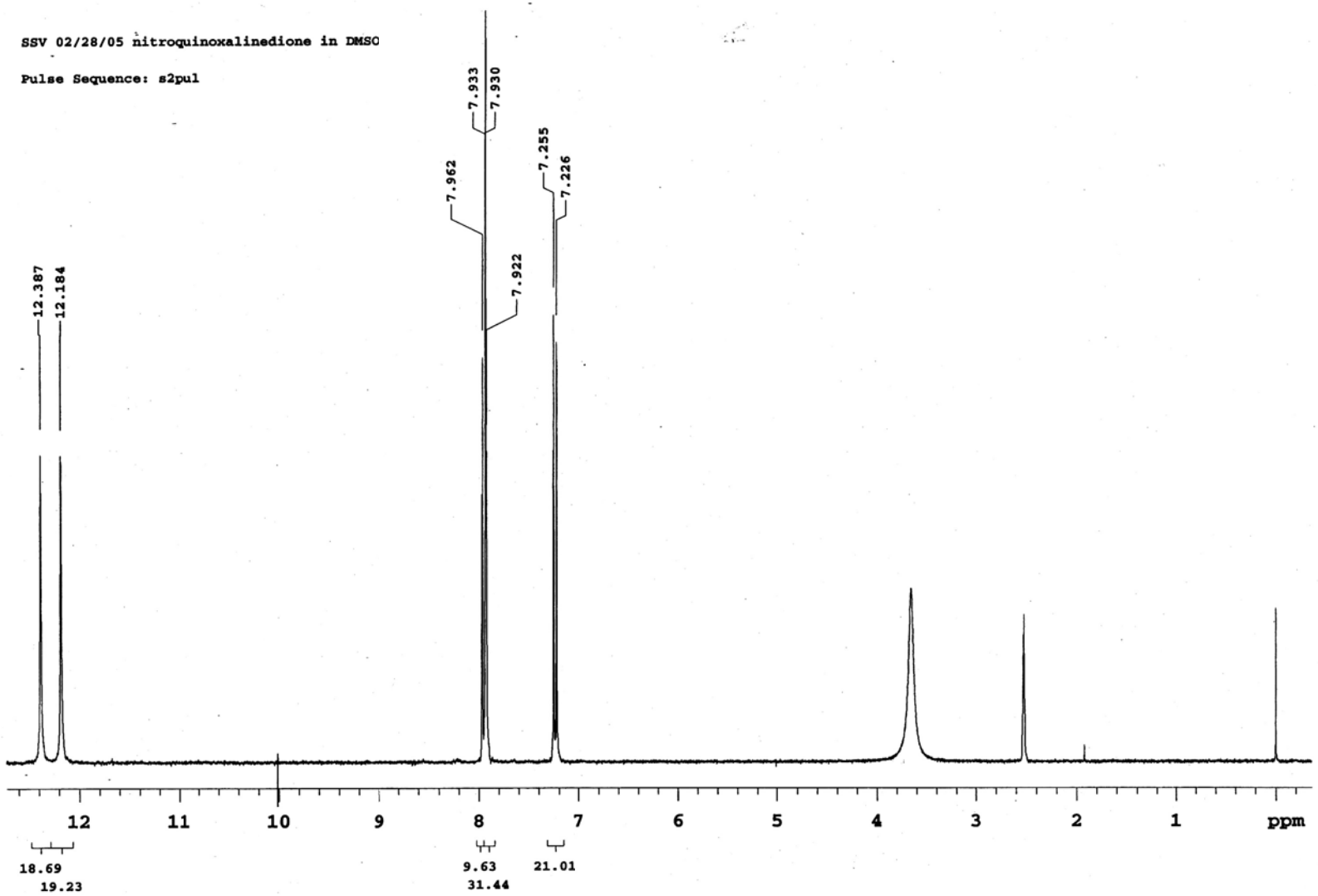

Kirk Morris, 6/20/05, Ba-hydrolyzed Carb-pyr #2, D2O + HCl, 11.7 mg
Pulse Sequence: s2pul
8.436
8.421
8.039
8.013
7.597
7.574
7.555
7.458
7.431
7.096
5.629
5.605
4.743
4.724
4.676
4.658
4.610
4.424
4.399
4.229
3.868
3.848
3.753
3.719
1.571
1.515
1.482
1.457
-0.257
A
B
C
D
E
F
G
H
I
J+K
L
ppm
5.27
4.94
6.06
6.35
2.71
7.30
6.03
11.00
7.67
21.18
21.48

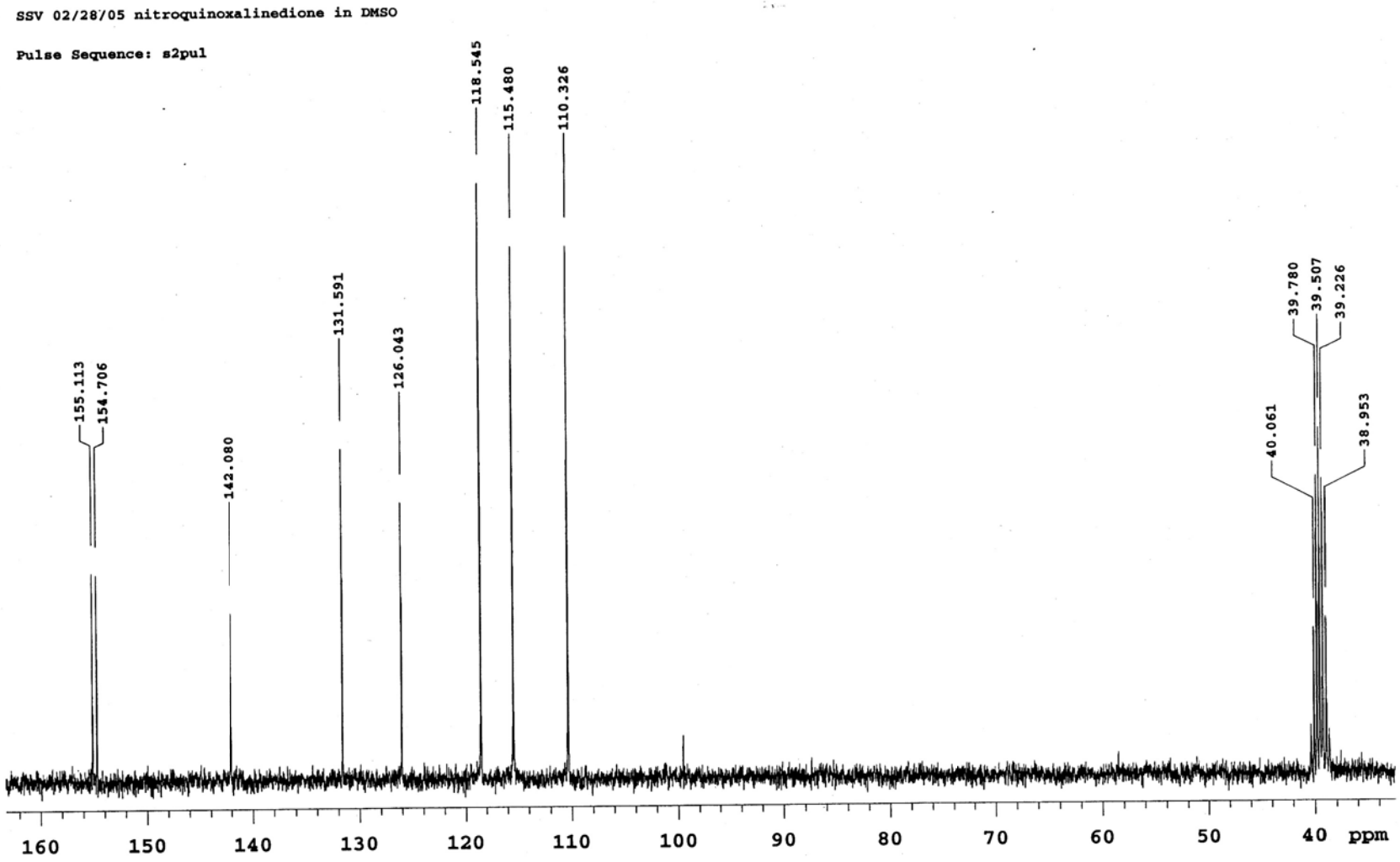
Kirk Morris, 6,/30/05, Acid Hydrolyzed AP-res #8, D2O, 39.9 mg

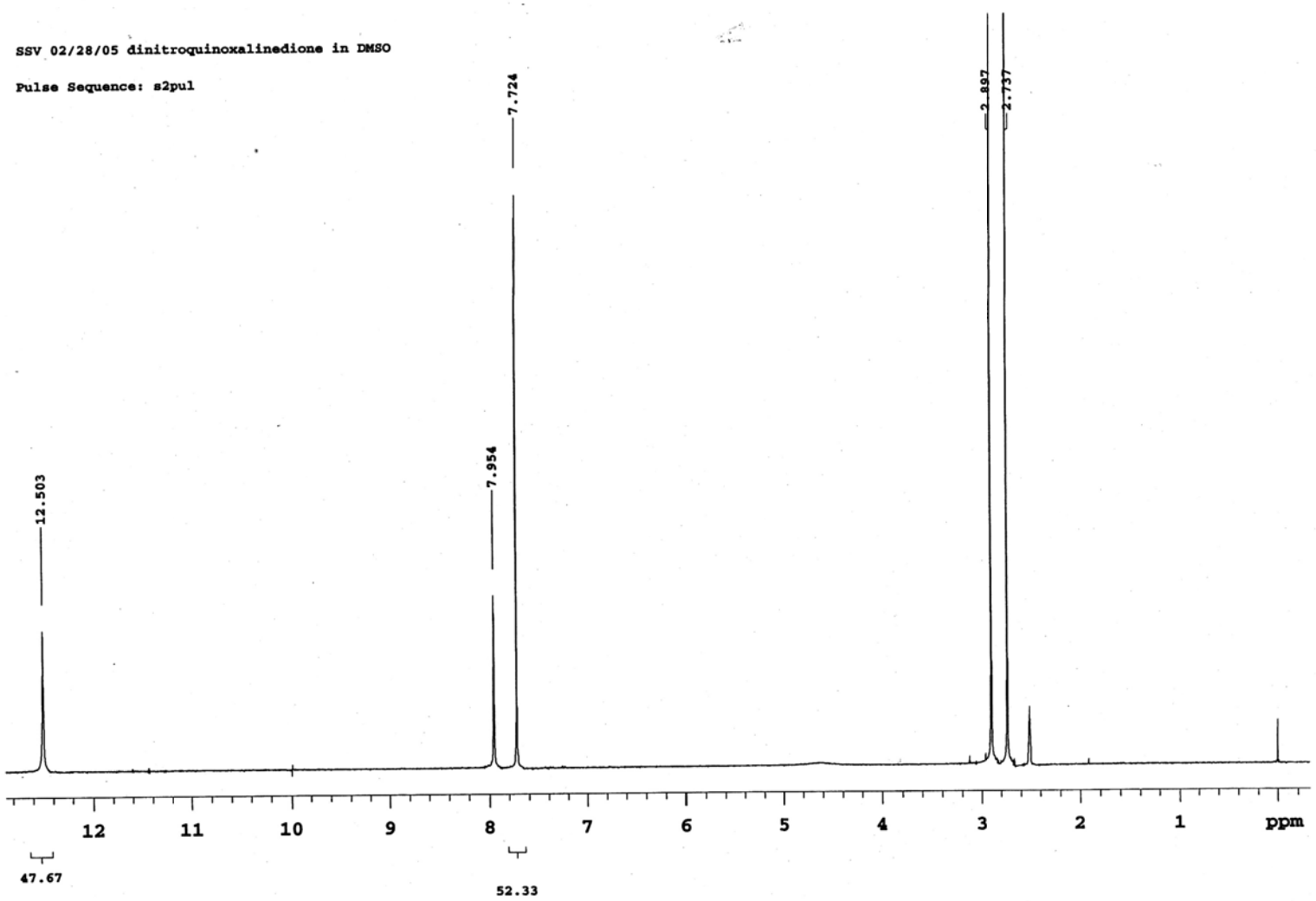
Pulse Sequence: s2pul

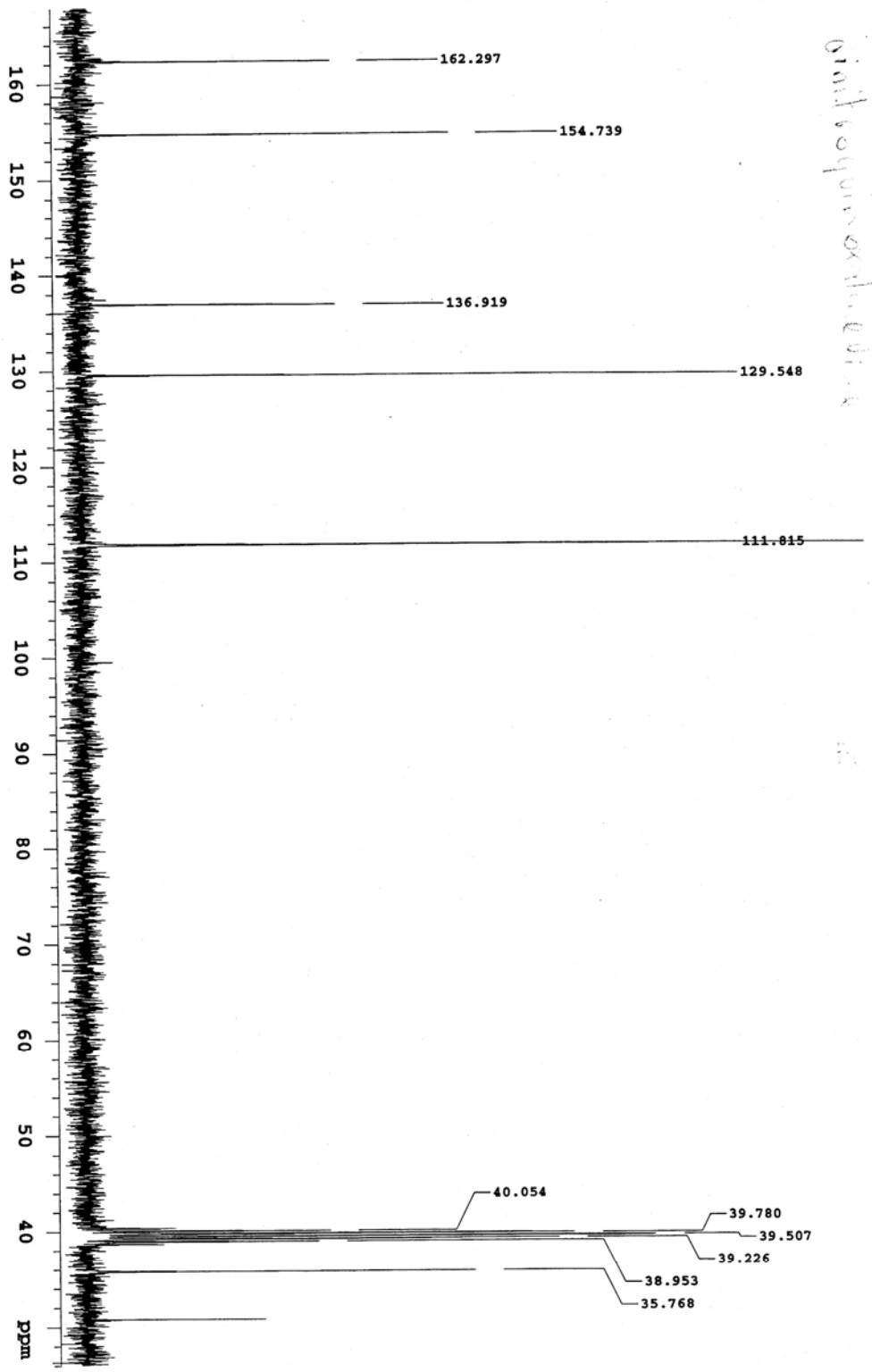


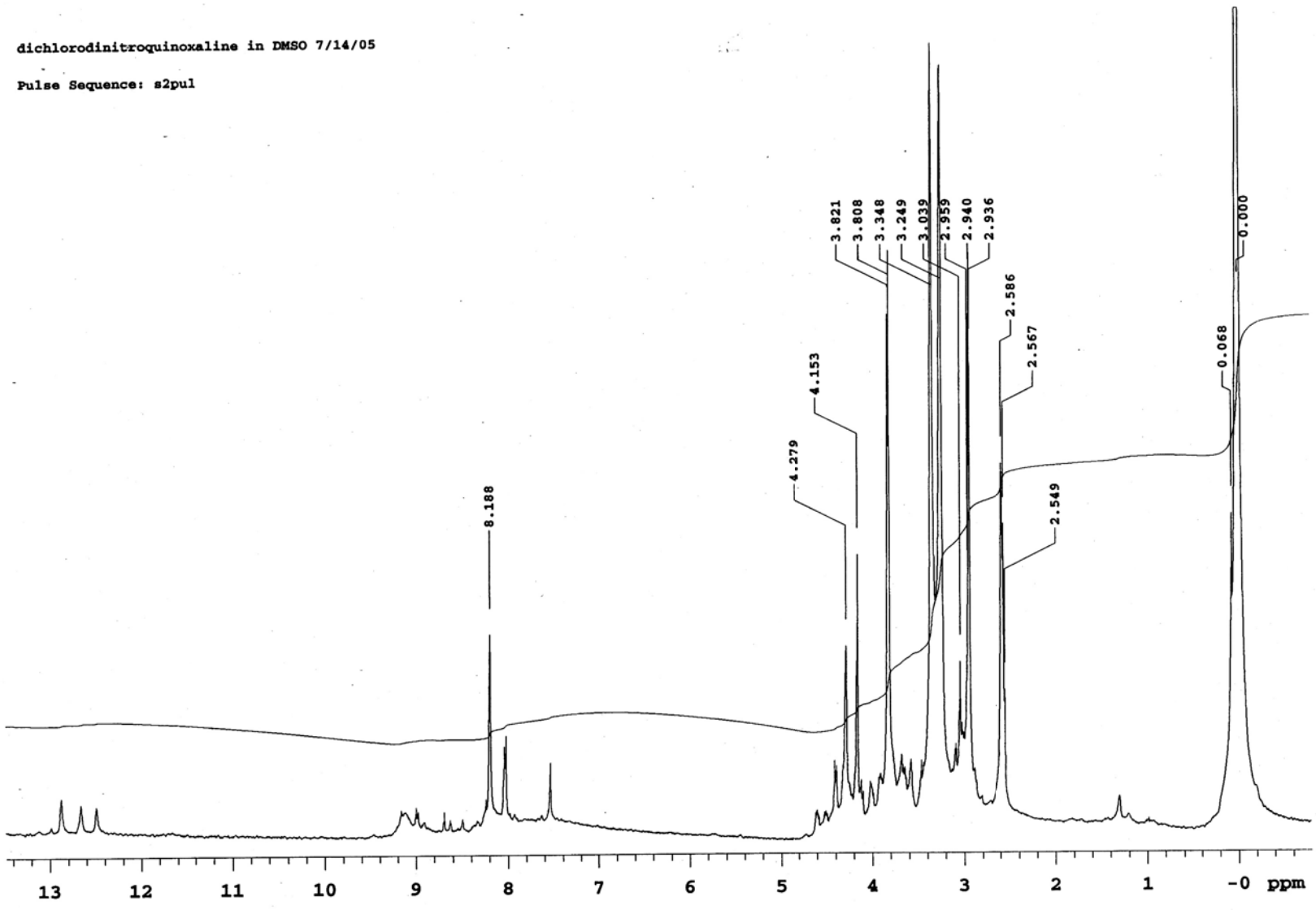

ethyl-footed bowl in acetone-d6
Pulse Sequence: s2pul
8.013
7.534
6.369
4.432
4.406
4.381
3.014
2.166
2.142
2.117
2.093
2.065
2.057
2.050
2.043
2.035
0.902
0.878
0.851
0.827
0.804
8
7
6
5
4
3
2
1
ppm
10.12
8.89
9.01
8.18
16.51
15.05
32.22


SSV 02/28/05 nitroquinoxalinedione in DMSO
Pulse Sequence: s2pul
12.387
12.184
7.962
7.933
7.930
7.922
7.255
7.226
12
11
10
9
8
7
6
5
4
3
2
1
ppm
18.69
19.23
9.63
31.44
21.01


SSV 02/28/05 nitroquinoxalinedione in DMSO
Pulse Sequence: s2pul
155.113
154.706
142.080
131.591
126.043
118.545
115.480
110.326
40.061
39.780
39.507
39.226
38.953
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


SSV 02/28/05 dinitroquinoxalinedione in DMSO
Pulse Sequence: s2pul
12.503
7.954
7.724
2.897
2.737
12
11
10
9
8
7
6
5
4
3
2
1
ppm
47.67
52.33


162.297
154.739
136.919
129.548
111.815
40.054
39.780
39.507
39.226
38.953
35.768
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


dichlorodinitroquinoxaline in DMSO 7/14/05
Pulse Sequence: s2pul
8.188
4.279
4.153
3.821
3.808
3.348
3.249
3.039
2.959
2.940
2.936
2.586
2.567
2.549
0.068
0.000
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm