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Synthesis & HyperCEST Testing of CTV Derivatives: A Bowl Shaped Compound That Encapsulates Xenon

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SYNTHESIS & HYPERCEST TESTING OF CTV DERIVATIVES: A BOWL SHAPED COMPOUND THAT ENCAPSULATES XENON

BY

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ABSTRACT

The primary focus of this dissertation is the synthesis and testing of cyclotriveratrylenes (CTV) as potential biomedical molecular imaging contrast agents. CTVs are bowl shaped molecules that have a hydrophobic pocket capable of reversibly binding Xenon-129 (^{129}Xe) gas, a spin ½ noble gas, which is diamagnetic and produces a signal when a strong magnetic field is applied to it. These CTVs then create two pools of ^{129}Xe which produce distinct signals in an NMR scan. The creation of the two pools of ^{129}Xe is necessary for the application of an imaging technique named HyperCEST, Hyperpolarized Chemical Exchange Saturation Transfer, which increases the sensitivity of the scan by up to 10,000 times. The ease of synthesis for the CTV as well as its ability to be conjugated to biochemical ligands should expedite the synthesis of targeted ^{129}Xe biosensors.

The last chapter deals with, Process oriented guided inquiry learning (POGIL), which is a pedagogical method that has demonstrated improvement in student performance, increases in attendance, and decreases in failing grades and withdrawals. A three-year study was conducted where attendance was mandatory for all students across both the POGIL and traditional lecture formats to measure the effect of POGIL. There was a decrease in the standard deviation of exam grades in the POGIL lecture sections however there was no statistically significant change in grades received by the students. This is in keeping with previous studies that have found a decrease in grades of D, F, and W's.

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PREFACE

The following work is presented in manuscript format according to the guidelines presented by the University of Rhode Island Graduate School. The dissertation will consist of three manuscripts two of which have been submitted for publication and one of which will be submitted for publication.

Manuscript 1 entitled, “A Bowl-Shaped Molecular Probe for Xenon-129 NMR” was submitted for publication in March of 2015 to Chemical Communications.

Manuscript 2 entitled, “Substituent Effects on the HyperCEST Efficiency of Bowl-Shaped Molecular Probes for Xenon-129 NMR” will be submitted to The Journal of the American Chemical Society in July of 2015.

Manuscript 3 entitled, "Does POGIL Increase Grades with Attendance Held Constant?” has been presented as a poster at the 2014 Biennial Conference on Chemical Education and was submitted for publication in the Journal of Chemical Education in February of 2015.

TABLE OF CONTENTS

LIST OF GRAPHS

LIST OF TABLES

TABLE PAGE

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SPECTRA

INTRODUCTION

The main goals of medical imaging are the diagnosis of diseases and tracking both the progress of and treatment for those diseases. There are six major types of medical imaging currently in use: Magnetic Resonance Imaging (MRI), Ultrasound

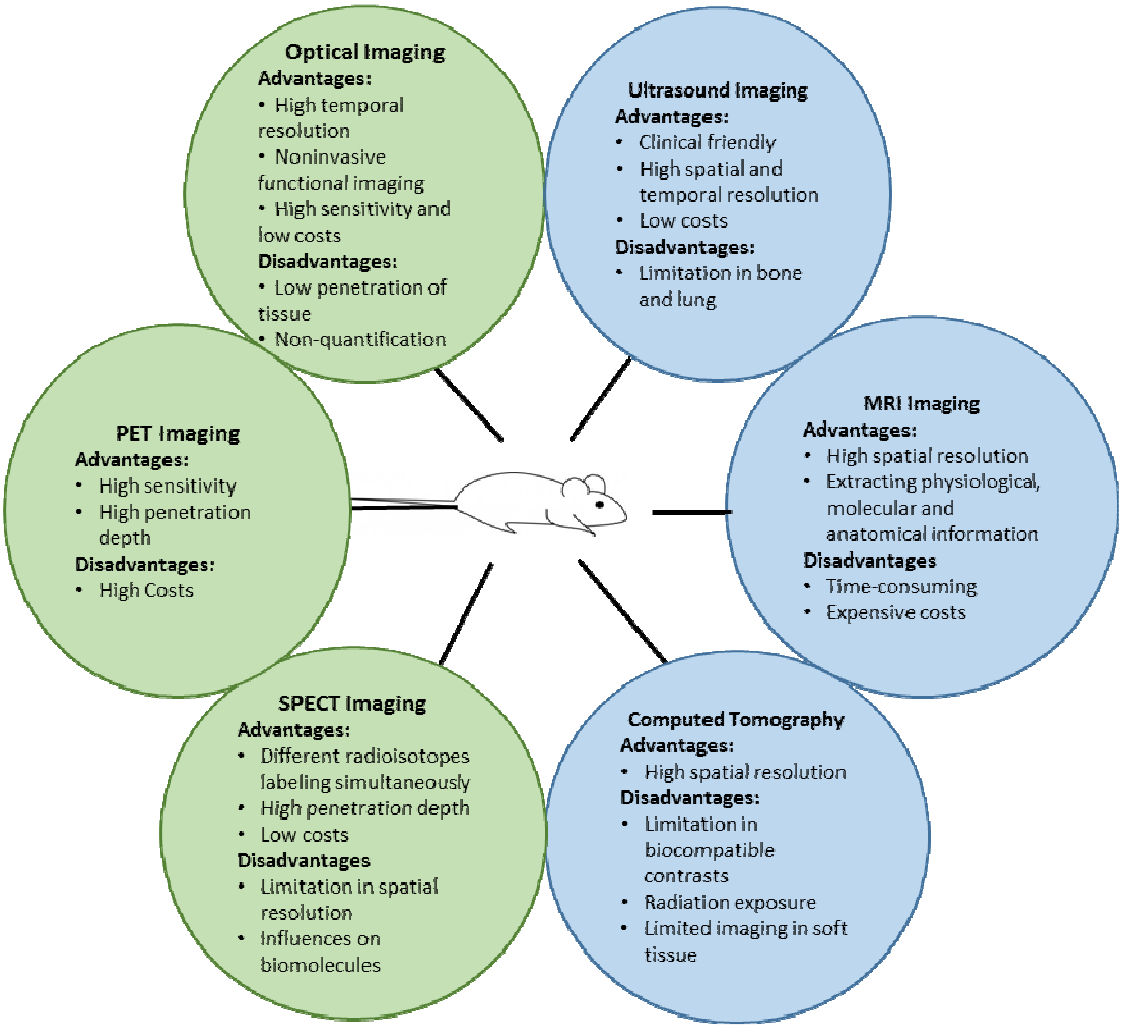


Figure 1 – Six types of medical imaging. Molecular imaging techniques are in green and morphological techniques are in blue. (Adapted from Reference 1.)

(US), Computerized Tomography (CT), Positron Emission Tomography (PET), Single-Photon Emission Computerized Tomography (SPECT), and optical imaging (Figure 1).[1] These six types of imaging are divided into two large categories: morphological, which focuses on the entire body, and molecular, which deals with the processes occurring within the cells. Of these six types none are able to accomplish the three major requirements for the ideal medical imaging technique, high spatial resolution, selectivity, and low toxicity *in vivo*. Selectivity refers to the ability for the imaging technique to detect the molecular process that is indicative of the disease. MRI meets two of the criteria for an ideal imaging technique; it has excellent resolution and is benign to the subject. To obtain an image it exposes a subject to a strong magnetic field causing the magnetic nuclei to align and relax at different rates based upon their chemical environment. This produces a signal that the MRI then uses to make a three dimensional image of the scanned area. The most abundant MRI active isotope in the human body is hydrogen-1, which is contained in water, fats, and soft tissues. Unfortunately the widespread distribution of hydrogen-1 does not allow for the desired selectivity. The current method of increasing selectivity for MRI imaging is to use a gadolinium contrast agent, which has severe side effects in some patients, effectively trading an increase in selectivity at the cost of preserving the health of the subject. Alternatively, if an MRI is paired with another medical imaging technique, such as PET scanner, the two images can be overlaid. This is often an uncomfortable process for the subjects, since they must be immobilized for the images, and any shift of location during the imaging procedures would render the

images useless as a pair. In addition, the subjects are exposed to radiation as part of the PET scan, again trading possible adverse effects to the subject for an increase in selectivity.

However, ^{1}H is not the only nucleus that is MRI active and capable of being introduced into the human body. To be an ideal choice the chosen nucleus would need to be capable of being distributed throughout the body, including crossing the blood brain barrier, would have no background signal in the subjects, and be nontoxic to the subject. Xenon-129 (^{129}Xe) meets all three of those requirements, and is not only benign, but also has been previously approved for medical applications.[2] Furthermore, any MRI scanner that is equipped with a broadband coil is capable of detecting the ^{129}Xe signal. ^{129}Xe is administered orally and is lipid soluble meaning that it diffuses throughout the body and across the blood brain barrier. ^{129}Xe has a large chemcial

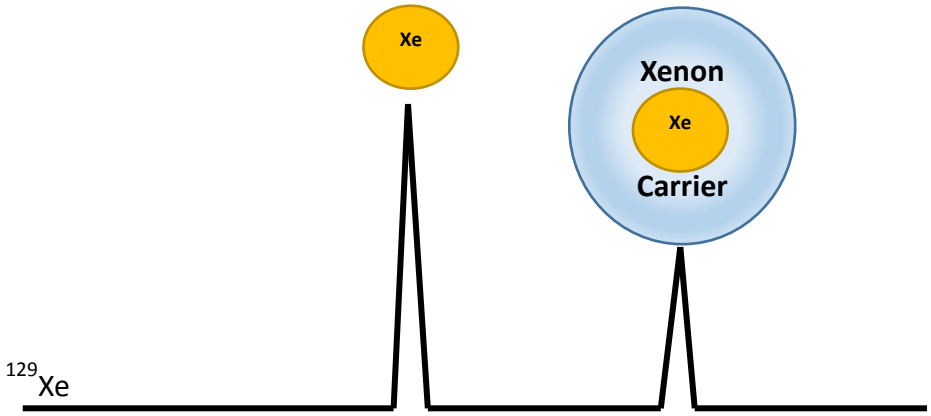


Figure 2 – Representation of the two pools of ^{129}Xe created by the molecular host encapsulation of ^{129}Xe.

shift range of approximately 2000 ppm, and the shift is largely dependent on the environment surrounding the xenon atom. This gives ^{129}Xe the potential to act as a

selective imaging agent. It has already been applied to detect lung activity in MRI scans where it shows the portions of the lungs that are filled with gas when the patient inhales.[3] The major drawback has been the sensitivity of the MRI, which is typically capable of detecting molecules that are present concentrations greater than 10^{-3} to 10^{-5} M, while the typical PET or SPECT molecular imaging technique has a detection limit of 10^{-9} to 10^{-12} M. To overcome this limitation hyperpolarized ^{129}Xe gas has been used providing approximately a 100,000 increase in sensitivity and putting it on approximately the level of the leading molecular imaging techniques.[4]

Conventional NMR/MRI techniques only detect approximately 1.0 ppm of the available nuclei in a given sample. This is because NMR and MRI capitalize on the magnetic moments of certain nuclei, which are caused by the nuclei having odd numbers of protons and/or neutrons. In the case of 129Xe, the nucleus has an odd number of neutrons (75) and an even number of protons (54), and its spin value has been experimentally determined to be ½. This means that when the 129Xe is exposed to a magnetic field, the atoms organize themselves into two energy states – one with the magnetic moments aligned with the external field (lower energy state) and one with the magnetic moments opposed to the external field (higher energy state). The ratio of the states is determined by the energy difference between the two levels, which is determined by the strength of the magnetic field. The Boltzmann distribution predicts that at room temperature the population difference of the two states is on the order of parts per million in the presence of a 7 T magnetic field (a 300 MHz NMR). Hyperpolarization artificially increases the population of the lower energy state, causing an overall increase in signal.

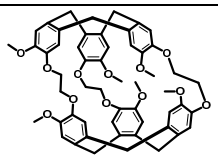
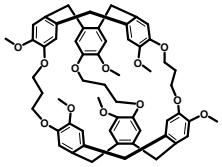
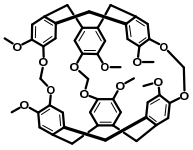
In a typical spin-echo NMR experiment, a radio frequency pulse is applied causing the magnetic moment of the nuclei to become perpendicular to the external magnetic field. Once the pulse is complete, the transverse magnetization begins to decay as the sample returns to equilibrium. This decay is detected by the receiver, producing a free induction decay pattern, or what is commonly referred to as a FID.

The ability to make ^{129}Xe a selective biosensor centers on changing the environment surrounding the xenon. To accomplish this it was hypothesized that xenon atoms could be encapsulated in molecular hosts thus causing a unique signal to appear in the ^{129}Xe NMR spectrum (Figure 2). Cryptophanes, or bis(cyclotriveratrylenyl) macrocage, had historically been used to encapsulate various compounds, including Xenon. In 1981, André Collet discovered that cryptophanes reversibly encapsulated xenon, and more importantly, that the chemical shift of xenon is dramatically changed by the encapsulation. Across the next twenty years, work focused on optimizing the size of the cavity for encapsulation. In 2007 Dutasta's lab reported the synthesis of the smallest cavity to date that was still capable of encapsulating xenon, when they synthesized the Cryptophane-1,1,1 (Table 1).[5]

The cryptophane-1,1,1, so named according to the length of the carbon chains in the diether linkers, has a cavity size of 81 $Å^3$, and xenon has a van deer Waals surface volume of 42 $Å^3$. Building on the work of Mecozzi and Rebek, who determined empirically from a multitude of host guest complexes that rely on London dispersion forces to form the relationship that a cavity to guest size ratio of 55% ± 9% results in optimal binding, they determined that their cryptophane, with a ratio of 51%, was within this optimal binding ratio.[7] This increase in binding strength resulted in an

increased signal intensity from the bound xenon. A three and half times increase in binding constant versus cryptophane-A was observed with the optimal cavity size of cryptophane-1,1,1, which corresponded to an improvement in the signal to noise ratio and a sharpening of the bound xenon peak.

Table 1 - Yield of cryptophanes via three common synthetic methods.

Yield of Cryptophanes via Synthetic Routes	**Template Method**	**"Two Step" Method**	**Capping**
 Cryptophane A	13%[6]	2-5%[6]	N/A
 Cryptophane E	6%[6]	15-20%[6]	N/A
 1,1,1 Cryptophane	N/A	N/A	1.5%[5]

Pines later made a major breakthrough with the advent of the hyperpolarized chemical exchange saturation transfer technique (HyperCEST) (Figure 3).[4] HyperCEST takes advantage of the ability to selectively presaturate at a specific

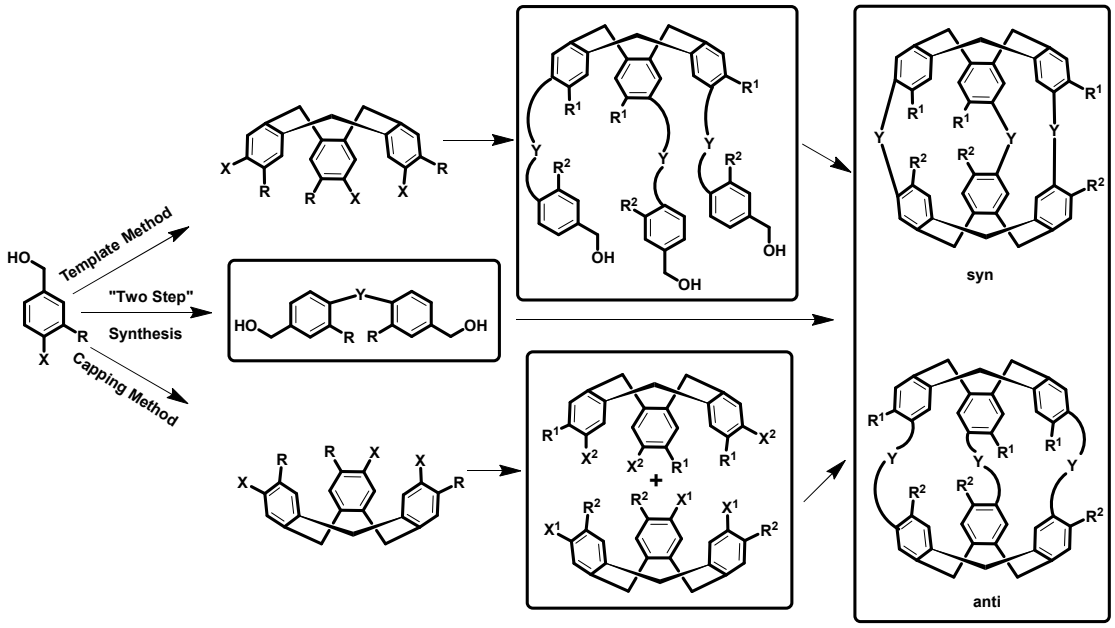
frequency, with a targeted radio frequency pulse. In this technique an initial reading is conducted giving a baseline signal (S_{off}) then the scan is repeated with the presatureation pulse frequency on giving a reduced signal (S_{on}). CEST values (C) can then be obtained by using equation 1.

$$C = \frac{(S_{off} - S_{on})}{S_{off}} \qquad Equation\ 1$$

The higher the value of C the more sensor is present in a given location. The key to this technique is the significant change in signal for the bound xenon and the free exchange of the xenon into and out of the host. HyperCEST shifted our focus from the small peak corresponding to the encapsulated xenon to the large peak corresponding to the unbound xenon. The HyperCEST experiment shifts the focus for an ideal xenon imaging probe from one that tightly binds xenon to that rapidly exchanges xenon in and out of its hydrophobic cavity.

The synthesis of cryptophanes has been accomplished following three main routes: (i) the template method, (ii) "two step" synthesis, and (iii) capping method (Scheme 1).[8] All three methods involve the use of electron donating groups in both the meta and para positions to facilitate the Friedel-Crafts reaction. The two substitutions also act as *ortho/para* directing groups, making it necessary for the *meta* group to be the stronger electron donating to ensure that the substitution occurs at the correct position for ring formation. Each of the three methods has different advantages and accomplishes the synthesis of various cryptophanes with varying degrees of success (Table 1). The capping method is used primarily for the synthesis of 1,1,1 cryptophane. The other two methods are extensively used, but for different cryptophanes, with the template method having better results with shorter linkers, and

the “Two Step” method having higher yields with larger linkers. Cryptophane-A has been extensively researched and functionalized in an effort to make it a selective biosensor.



Scheme 1 - Synthetic strategies for cryptophanes.[8]

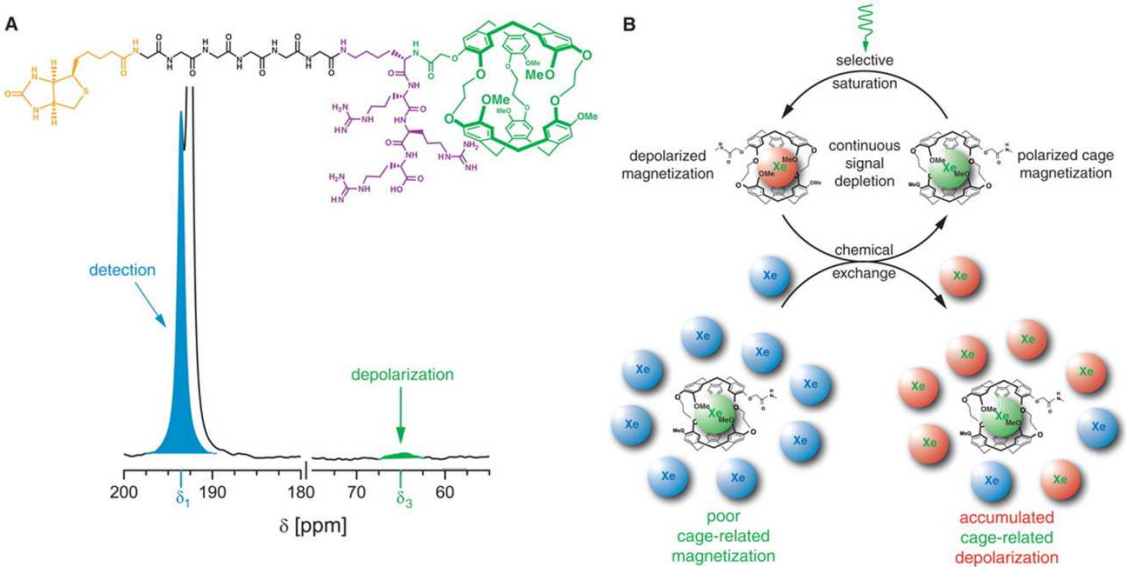


Figure 3 - HyperCEST NMR detection of Xe biosensors.[4]

Current cryptophanes have a long and low yielding synthetic procedure that results in an ether linked macrocycle that can be difficult to functionalize.[9] Functionalization is necessary to make the cryptophane selective and water soluble, critical qualities for a biosensor.

Two of the three synthetic strategies go through cyclotriveratrylenes (CTVs) to obtain cryptophanes. CTVs have further been used in the past to bind large hydrophobic molecules called fullerenes.[10] The volume of a fullerene is 450 $Å^3$, which is approximately 10 times the volume of xenon.[11] There have been multiple previously CTVs synthesized often with high yielding procedures, most notably the aCTG which has a reported cyclization step yield of 95%.[6] Additionally, much of the work on functionalizing the cryptophanes can be directly applied to CTVs. This will facilitate the rapid synthesis of a number of CTV derivatives that can meet the requirements for an effective biosensor. We hypothesize that CTVs will provide a hydrophobic cavity capable of binding ^{129}Xe and changing its chemical shift. That combined with its short high-yielding synthesis will make CTVs an ideal candidate to replace cryptophanes as the primary focus of ^{129}Xe molecular imaging research.

REFERENCES

1. Huang, Y.; He, S.; Cao, W.; Cai, K.; Liang, X. J., Biomedical nanomaterials for imaging-guided cancer therapy. *Nanoscale* **2012,** *4* (20), 6135-49.

2. (a) Schroder, L., Xenon for NMR biosensing - Inert but alert. *Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics* **2011**; (b) Oros, A.-M.; Shah, N. J., Hyperpolarized xenon in NMR and MRI. *Physics in Medicine and Biology* **2004,** *49* (20), R105-R153.

3. Goodson, B. M., Nuclear magnetic resonance of laser-polarized noble gases in molecules, materials, and organisms. *Journal of magnetic resonance* **2002,** *155* (2), 157-216.

4. Schroder, L.; Lowery, T. J.; Hilty, C.; Wemmer, D. E.; Pines, A., Molecular imaging using a targeted magnetic resonance hyperpolarized biosensor. *Science* **2006,** *314* (5798), 446-9.

5. Fogarty, H. A.; Berthault, P.; Brotin, T.; Huber, G.; Desvaux, H.; Dutasta, J. P., A cryptophane core optimized for xenon encapsulation. *Journal of the American Chemical Society* **2007,** *129* (34), 10332-3.

6. Brotin, T.; Dutasta, J. P., Cryptophanes and their complexes--present and future. *Chemical reviews* **2009,** *109* (1), 88-130.

7. Sandro Mecozzi and Julius Rebek, J., The 55 % Solution: A Formula for Molecular Recognition in the Liquid State. *Chemistry A European Journal 4* (6), 1016-1022.

8. Holman, K. T., Cryptophanes: Molecular Containers. In *Encyclopedia of Supramolecular Chemistry*, Atwood, J. L. a. S., J. W, Ed. CRC Press: 2004; pp 340-34.

9. (a) Delacour, L.; Kotera, N.; Traore, T.; Garcia-Argote, S.; Puente, C.; Leteurtre, F.; Gravel, E.; Tassali, N.; Boutin, C.; Leonce, E.; Boulard, Y.; Berthault, P.; Rousseau, B., "Clickable" hydrosoluble PEGylated cryptophane as a universal platform for 129Xe magnetic resonance imaging biosensors. *Chemistry* **2013,** *19* (19), 6089-93; (b) Taratula, O.; Dmochowski, I. J., Functionalized 129Xe contrast agents for magnetic resonance imaging. *Current opinion in chemical biology* **2010,** *14* (1), 97-104; (c) Fairchild, R. M.; Joseph, A. I.; Holman, K. T.; Fogarty, H. A.; Brotin, T.; Dutasta, J. P.; Boutin, C.; Huber, G.; Berthault, P., A water-soluble Xe@cryptophane-111 complex exhibits very high thermodynamic stability and a peculiar (129)Xe NMR chemical shift. *Journal of the American Chemical Society* **2010,** *132* (44), 15505-7; (d) Taratula, O.; Hill, P. A.; Khan, N. S.; Carroll, P. J.; Dmochowski, I. J., Crystallographic observation of 'induced fit' in a cryptophane host-guest model system. *Nature communications* **2010,** *1*, 148.

10. Hardie, M. J., Recent advances in the chemistry of cyclotriveratrylene. *Chemical Society reviews* **2010,** *39* (2), 516-27.

11. Adams, G. B.; O'Keeffe, M.; Ruoff, R. S., Van Der Waals Surface Areas and Volumes of Fullerenes. *The Journal of Physical Chemistry* **1994,** *98* (38), 9465-9469.

MANUSCRIPT 1

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A Bowl-Shaped Molecular Probe for Xenon-129 NMR

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MANUSCRIPT 1

A BOWL-SHAPED MOLECULAR PROBE FOR XENON-129 NMR

Abstract

A novel molecular probe for ^{129}Xe magnetic resonance spectroscopy and imaging is disclosed. Prior work in the field has predominantly relied on the use of cryptophanes, cage-shaped compounds that fully encapsulate xenon atoms, thus giving rise to a unique signal in the ^{129}Xe NMR spectrum. Herein, we report a cyclotriveratrylene (CTV) compound that is capable of reversibly binding xenon, and that the binding event can be detected as a unique peak in the ^{129}Xe NMR spectrum. The ease of synthesis for the CTV as well as its ability to be conjugated to biochemical ligands should expedite the synthesis of targeted ^{129}Xe biosensors.

Main Text

Hyperpolarized xenon-129 magnetic resonance imaging (HP-Xe MRI) is a promising technology for diagnostic imaging which does not rely on ionizing radiation. The non-toxic noble gas ^{129}Xe has a nuclear spin of ½ and can be hyperpolarized by optical pumping to increase the magnetic resonance signal intensity 10,000–100,000-fold.[1] Once inhaled, HP-Xe readily enters the blood stream, and because it is lipid soluble, it distributes into nearly all organs of the body, even crossing the blood-brain barrier. The distribution of the HP-Xe can then be imaged in whole bodies using an MRI scanner that is equipped with a broadband coil.[2] Examples of the current applications of this technology include distinguishing between the white

and gray matter in the brain and the diagnosis of maladies such as chronic obstructive pulmonary disease and stroke.[3]

In light of the extra sensitivity that can be gained via the hyperpolarization process, several research groups have pursued HP-Xe MRI as a method for performing molecular imaging of biochemical receptors via MRI.[4] As first outlined by Pines and Wemmer, a biosensor can be constructed by tethering a ligand for binding a biochemical target to a molecular host that is capable of encapsulating HP-Xe.[5] The most common host molecule used for encapsulating xenon is cryptophane-A, which consists of two bowl-shaped cyclotriveratrylenes (CTVs) joined by three ethylene linkers.[6] The encapsulation of xenon in a cryptophane host creates two pools of ^{129}Xe spins, which can be detected as two distinct peaks in the ^{129}Xe NMR spectrum (Figure 4), as the residence time of xenon in a cryptophane is sufficiently long (tens of milliseconds) to be detected on the NMR time scale.

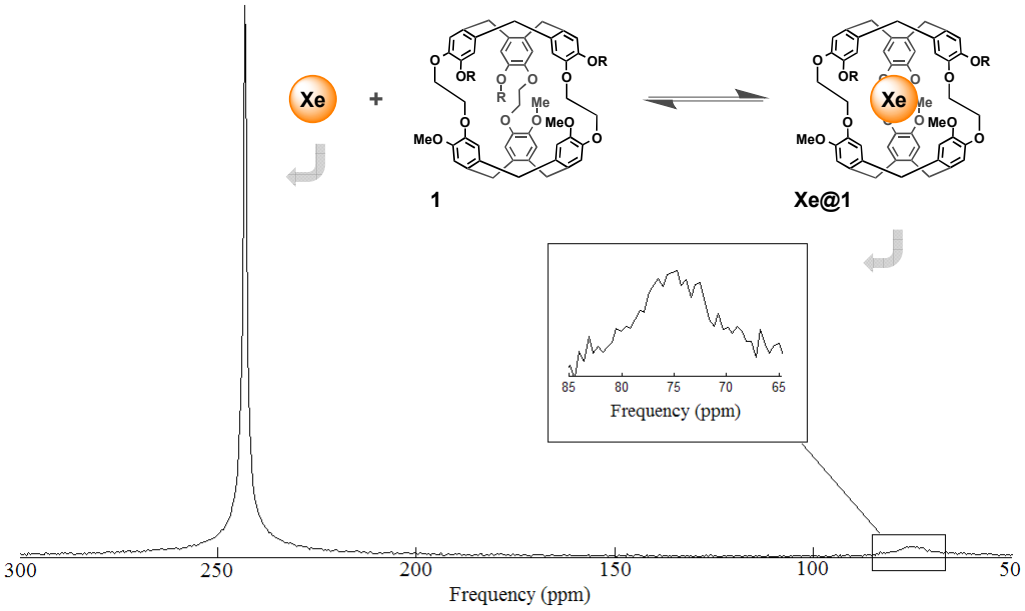


Figure 4 - ^{129}Xe NMR spectrum of a 2.7 mM solution of Dmochowski's cryptophane (**1,** R = propargyl) in DMSO. ^{129}Xe NMR (^{129}Xe polarization ~37%): δ 242 (dissolved Xe), 75 (Xe@1), 0 (Xe gas, not shown).

The exchange of the xenon in and out of the host can be exploited to achieve an additional 10,000-fold sensitivity enhancement.[7] This is achieved by detecting the decrease in the signal of the large pool of unbound ^{129}Xe spins while saturating the signal of the pool of encapsulated ^{129}Xe spins with a targeted radio frequency pulse. Since the xenon atoms are reversibly bound by the host, the targeted pulse also causes the partial saturation of the pool of unbound ^{129}Xe. The reduction of signal intensity for the unbound xenon is easily detected, even in cases where there is a minimal amount of host molecule in solution. In fact, both Dmochowski and Stevens have used this indirect detection technique, called Hyperpolarized Chemical Exchange Saturation Transfer (HyperCEST), to detect sub-picomolar quantities of the host compounds,[8,9] indicating that HyperCEST imaging has the potential to be a viable

alternative to current molecular imaging techniques that rely on probes containing radionuclides.

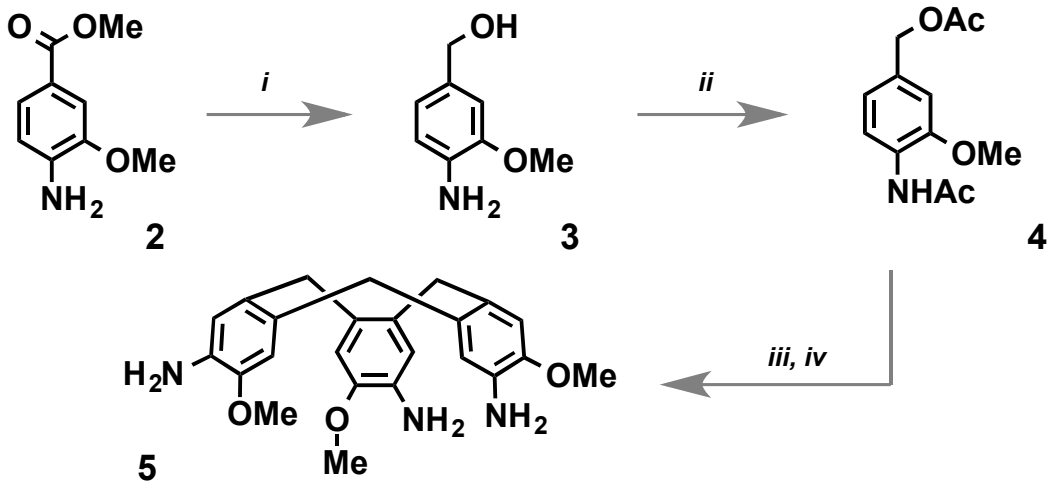
The key requirement for the development of a HP-Xe molecular probe is the presence of a molecular or macromolecular species that can bind the ^{129}Xe atoms and create two distinguishable pools of nuclear spins. Nearly all HP-Xe probes that have been developed to date have used cryptophanes for this purpose.[10,11] One of the biggest impediments to research in this field has been the synthesis of these molecular cages, such as Dmochowski's tri-alkyne, **1** (Figure 4). The 10-step synthesis is expensive, low yielding and technically difficult. It is the bottleneck in the development of HP-Xe biosensors.

Consequently, we hypothesized that the HyperCEST technique created a paradigm shift in the field, and that there now existed a need to develop new xenon hosts that were optimized for exchange kinetics rather than binding affinity. We predicted that bowl-shaped cavitands such as cyclotriveratrylenes (CTVs) would be superior hosts for HyperCEST imaging due to their more open architectures that should allow for faster chemical exchange. Herein, we disclose the first example of ^{129}Xe magnetic resonance spectroscopy using such a bowl-shaped contrast agent, indicating that it has the potential to be a scaffold for constructing HyperCEST biosensors.

While most CTVs contain six ether groups around their rim, Collet reported that substituting one of these ethers for an amide, more than tripled the yield of the key Friedel-Crafts trimerization step.[12] As shown in Scheme 1, we followed this strategy to synthesize the amino-CTV (**5**) in four steps with an excellent yield (average step

yield = 83%, overall yield = 47%). In addition to facilitating the Friedel-Crafts step, we hypothesized that the amines in this CTV derivative could serve as functional handles to conjugate ligands for eventual studies with targeted HP-Xe biosensors.

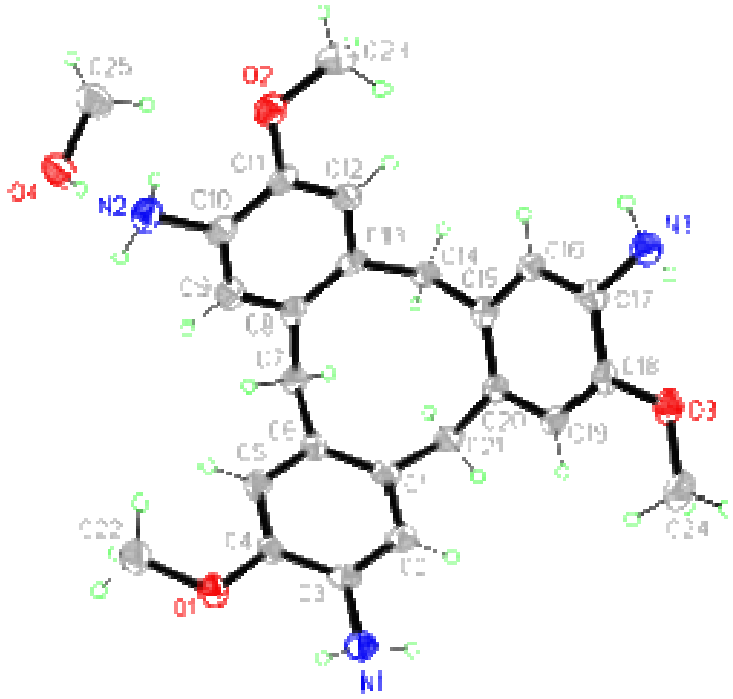
Scheme 2 - Synthesis of Amino-CTV Contrast Agent



(i) $LiAlH_4$ (5 equiv), ether/THF (1:1), 0 ^oC, 2 h, 87% yield; (ii) Ac_2O (3.1 equiv), pyridine 16 h, 81% yield; (iii) $HClO_4$ (60% aq)/AcOH (2:1), 24 h, 91% yield; (iv) HCl/EtOH, 74% yield.

To analyze the size of the cavity of **5** and to compare it with that of a cryptophane cage, X-ray quality crystals were grown in methanol (Figure 5A). The bond lengths and angles of **5** were virtually identical to the CTV portion of Dmochowski's triallyl cryptophane-A,[13] as demonstrated by the superimposed image shown in Figure 5B. The longest diameter of Dmochowski's cryptophane is 9.3 Å, while the depth of the bowl-shaped cavity of the CVT, **5**, is only 3.3 Å. Thus, when compared to cryptophane A derivatives, **5** has approximately 36% of the volume that can be used to accommodate a xenon atom.

To support our hypothesis that CTVs could be used as ^{129}Xe molecular probes, a xenon atom was computationally docked in the cavity of the amino-CTV host, **5**, and the energy was minimized using a Hartree-Fock 3-21G basis set, yielding a calculated binding energy of -0.52 kcal/mol (Figure 5C). Though this is a fraction of the free energies of association that have been previously described for xenon-cryptophane complexes,[14] the computed favorable binding energy indicates that the formation of a host-guest complex between xenon and **5** could possibly produce the two spin pools necessary for HyperCEST.



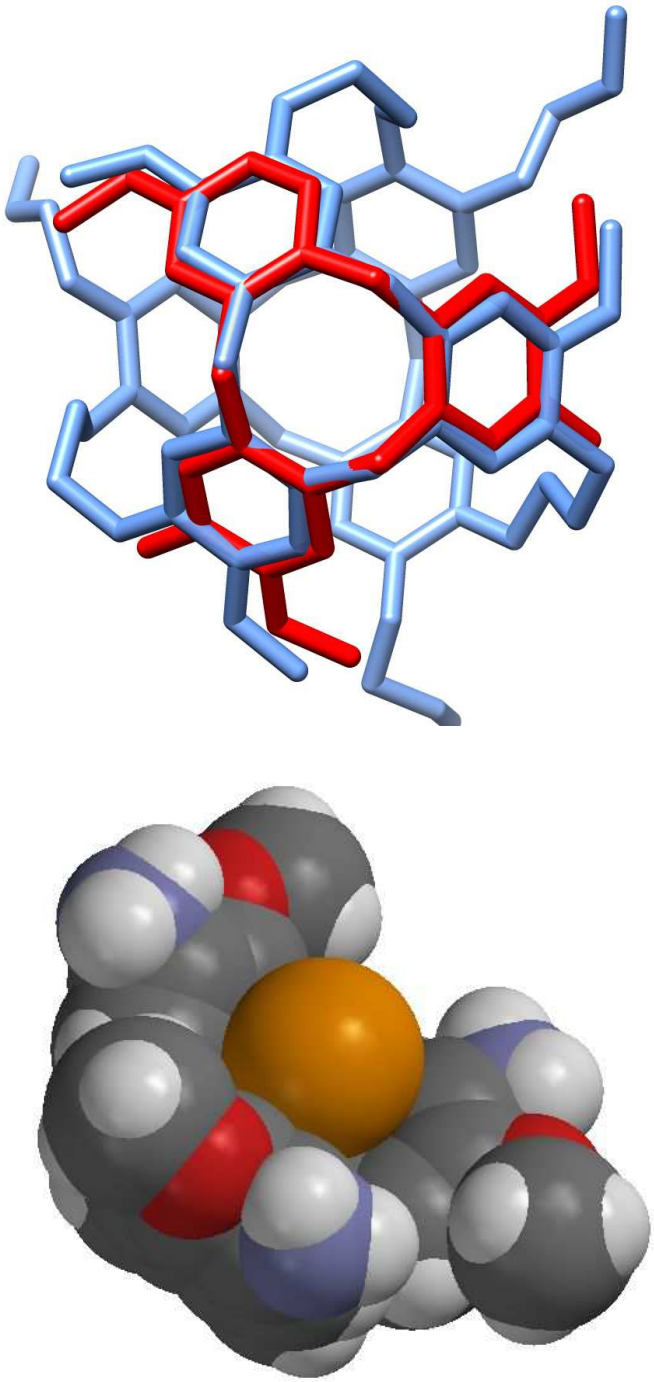


Figure 5 - A/ ORTEP drawing (50%) of the crystal structure of 5. (The unit cell contains 1.687 MeOH molecules.) B/ Superposition of 5 (red) and Dmochowski's triallyl cryptophane-A (blue-gray), showing that the sizes of the CTVs are nearly identical.

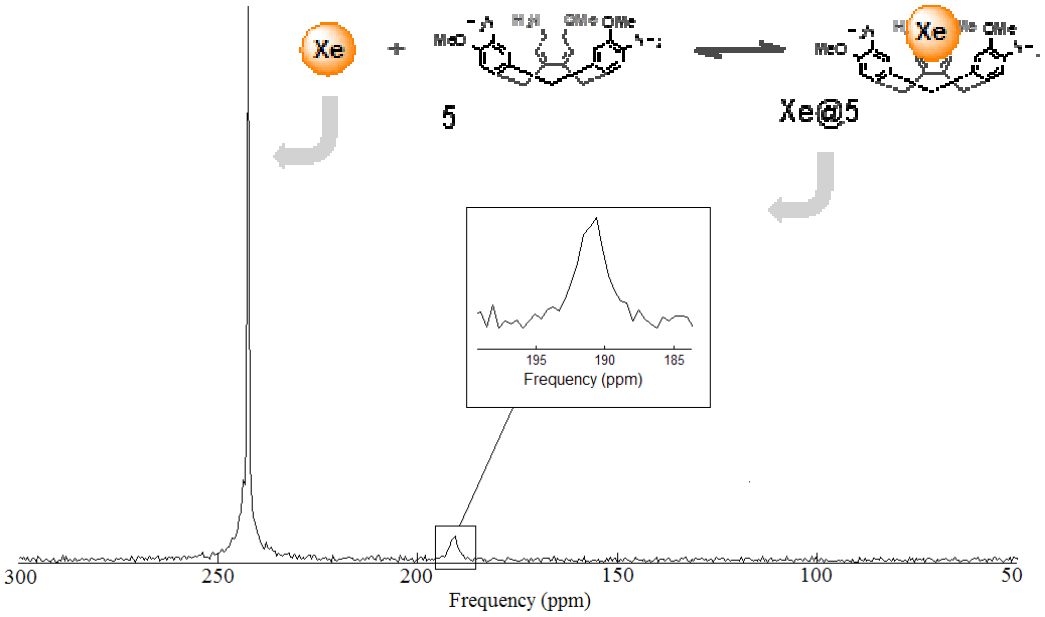


Figure 6 - ^{129}Xe NMR spectrum of a 50 mM solution of amino-CTV 5 in DMSO. ^{129}Xe NMR (^{129}Xe polarization ~37%): δ 242 (dissolved Xe), 190 (Xe@5), 0 (Xe gas, not shown).

Ultimately, ^{129}Xe NMR spectroscopy confirmed that the probe **5** was, in fact, capable of serving as a HP-Xe host (Figure 6). A 50 mM solution of **5** was prepared in DMSO and placed in a syringe containing 1 atm of HP-Xe (polarization ~37%). A ^{129}Xe magnetic resonance spectrum was then acquired using a Phillips 3T MRI scanner. A small peak corresponding to Xe@**5** was observed in the ^{129}Xe NMR spectrum 51 ppm upfield from the free ^{129}Xe peak.

The host-guest relationship of the tri-amino CTV, **5**, with xenon described herein could represent a significant advance in xenon biosensor development. It allows for the rapid synthesis of CTV-derived HP-Xe molecular probes. Future work in our laboratories will be dedicated toward the further optimization of the bowl-

shaped contrast agent for HyperCEST spectroscopy and imaging, as well as the development of targeted CTV-derived contrast agents for use as biosensors. The structure of **5** makes it readily amenable to the synthesis of targeted biosensors, as the three amine groups should serve as functional handles for conjugation to small molecule probes, peptides or antibodies. Additionally, the use of a clinical MRI scanner and a commercially available XeMed Xe-Box polarizer in this study indicates that eventual clinical application of HP-Xe biosensors based on CTVs like **5** should be possible.

Supporting Information

Experimental procedures and characterization data for novel compounds, description of the ^{129}Xe NMR protocol using a clinical MRI scanner, crystal structure data for compound 5, and computational methods are available in appendix 1.

Acknowledgement

We thank A. Fitterman for graphical assistance. This work was funded by a Collaborative Research Grant from the Rhode Island Science and Technology Advisory Council (B.D.B.) an NSERC discovery grant and the Thunder Bay Regional Research Institute.

References

(1) Goodson, B. M. *J. Magn. Reson.* **2002**, *155*, 157–216.

(2) Swanson, S. D.; Rosen, M. S.; Coulter, K. P.; Welsh, R. C.; Chupp, T. E. *Magn. Reson. Med.* **1999**, *42*, 1137–1145.

(3) For examples, see: (a) Kilian, W.; Seifert, F.; Rinneberg, H. *Magn. Reson. Med.* **2004**, *51*, 843–847; (b) Lilburn, D. M. L.; Pavlovskaya, G. E.; Meersmann, T. *J. Magn. Reson.* **2013**, *229*, 173–186; (c) Zhou, X.; Sun, Y.; Mazzanti, M.; Henninger, N.; Mansour, J.; Fisher, M.; Albert, M. *NMR Biomed.* **2010**, *24*, 170–175; (d) Albert, M. S.; Cates, G. D.; Driehuys, B.; Happer, W.; Saam, B.; Springer, C. S.; Wishnia, A. *Nature* **1994**, *370*, 199–201; (e) Mazzanti, M. L.; Walvick, R. P.; Zhou, X.; Sun, Y.; Shah, N.; Mansour, J.; Gereige, J.; Albert, M. S. *PLoS ONE* **2011**, *6*, e21607; (f) Zhou, X.; Sun, Y.; Mazzanti, M.; Henninger, N.; Mansour, J.; Fisher, M.; Albert, M. *NMR Biomed.* **2011**, *24*, 170–175; (g) Sakai, K.; Bilek, A. M.; Oteiza, E.; Walsworth, R. L.; Balamore, D.; Jolesz, F. A.; Albert, M. S. *J. Magn. Reson. B* **1996**, *111*, 300–304; (h) Zhou, X.; Mazzanti, M. L.; Chen, J. J.; Tzeng, Y. S.; Mansour, J. K.; Gereige, J. D.; Venkatesh, A. K.; Sun, Y.; Mulkern, R. V.; Albert, M. S. *NMR Biomed.* **2008**, *21*, 217–225.

(4) (a) Seward, G. K.; Wei, Q.; Dmochowski, I. J. *Bioconjugate Chem.* **2008**, *19*, 2129–2135; (b) Berthault, P.; Huber, G.; Desvaux, H. *Prog. Nucl. Magn. Reson. Spectrosc.* **2009**, *55*, 35–60; (c) Seward, G. K.; Bai, Y.; Khan, N. S.; Dmochowski, I. J. *Chem. Sci.* **2011**, *2*, 1103–1110; (d) Schröder, L. *Phys Med* **2013**, *29*, 3–16.

(5) (a) Ramirez, R. M.; Stevens, T. K.; Smith, M. A.; Wemmer, D. E.; Pines, A. *Proc. Intl. Soc. Mag. Reson. Med.* **2011**, *19*, 3542; (b) Spence, M. M.; Rubin, S. M.;

Dimitrov, I. E.; Ruiz, E. J.; Wemmer, D. E.; Pines, A.; Yao, S. Q.; Tian, F.; Schultz, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10654–10657.

(6) (a) Holman, K. T. Cryptophanes: Molecular Containers. In *Encyclopedia of Supramolecular Chemistry*; Marcel Dekker: New York, 2004; pp 340–348; (b) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88–130.

(7) Schröder, L.; Lowery, T. J.; Hilty, C.; Wemmer, D. E.; Pines, A. *Science* **2006**, *314*, 446–449.

(8) Bai, Y.; Hill, P. A.; Dmochowski, I. J. *Anal. Chem.* **2012**, *84*, 9935–9941.

(9) Stevens, T. K.; Ramirez, R. M.; Pines, A. *J. Am. Chem. Soc.* **2013**, *135*, 9576–9579.

(10) Two nanoscale alternatives to cryptophanes have been reported as potential scaffolds for HP-Xe molecular probes, nanoemulsions (a) and gas vesicles (b), but neither of these moieties have been used for the synthesis of targeted biosensors: (a) Stevens, T. K.; Ramirez, R. M.; Pines, A. *J. Am. Chem. Soc.* **2013**, *135*, 9576–9579. (b) Shapiro, M. G.; Ramirez, R. M.; Sperling, L. J.; Sun, G.; Sun, J.; Pines, A.; Schaffer, D. V.; Bajaj, V. S. *Nature Chemistry* **2014**, *6*, 629–634.

(11) Other macormolecular hosts have been shown to encapsulate xenon, including cucurbiturils (a-c), calixarenes (d) and pillarenes (e), but none of these compounds have been used for the synthesis of targeted biosensors: (a) Haouaj, El, M.; Luhmer, M.; Ko, Y. H.; Kim, K.; Bartik, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 804–807; (b) Kim, B. S.; Ko, Y. H.; Kim, Y.; Lee, H. J.; Selvapalam, N.; Lee, H. C.; Kim, K. *Chem. Commun.* **2008**, 2756–3; (c) Huber, G.; Legrand, F.-X.; Lewin, V.; Baumann, D.; Heck, M.-P.; Berthault, P. *ChemPhysChem* **2011**, *12*, 1053–1055; (d) Brouwer, E.

B.; Enright, G. D.; Ripmeester, J. A. *Chem. Commun.* **1997**, 939–940; (e) Adiri, T.; Marciano, D.; Cohen, Y. *Chem. Commun.* **2013**, *49*, 7082–7084.

(12) Garcia, C.; Malthete, J.; Collet, A. *Bulletin De La Societe Chimique De France* **1993**, *130*, 93–95.

(13) Taratula, O.; Hill, P. A.; Khan, N. S.; Carroll, P. J.; Dmochowski, I. J. *Nat. Commun.* **2010**, *1*, 148.

(14) For examples, see: (a) Hill, P. A.; Wei, Q.; Eckenhoff, R. G.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2007**, *129*, 9262–9263; (b) Brotin, T.; Dutasta, J. P. *Eur. J. Org. Chem.* **2003**, 973–984.

MANUSCRIPT 2

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Substituent Effects on the HyperCEST Efficiency of Bowl-Shaped Molecular Probes for Xenon-129 NMR

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MANUSCRIPT 2

Introduction

There has been a strong interest in developing a contrast agent for magnetic resonance imaging (MRI) for diagnostic biomedical applications that will shift MRI from a primarily morphological imaging tool to a molecular imaging tool. While the majority of work in this field has focused on the development of paramagnetic contrast agents that can perturb the T_1 relaxation time of protons, the use of xenon-based imaging agents is a viable alternative that could prove to be a superior molecular imaging platform. Xenon-129 (^{129}Xe) is a non-toxic noble gas that has a ½ nuclear spin and is capable of being hyperpolarized via optical pumping.[1] ^{129}Xe is delivered through inhalation and distributes throughout the body including crossing the blood brain barrier and is currently used in medical diagnoses.[2]

^{129}Xe magnetic resonance molecular imaging is currently being pursued by several research groups, and until our recent communication, has primarily been pursued using cryptophane hosts that have been functionalized with ligands for binding to a molecular target. To take advantage of these properties, large macrocyclic compounds named cryptophanes were developed to bind xenon. Cryptophanes encapsulate ^{129}Xe reversibly with a residence time of approximately 40 milliseconds. This presents two pools of ^{129}Xe that are detected by the NMR at unique chemical shifts. This phenomenon can be further exploited for an increase in sensitivity by saturating the signal of the encapsulated ^{129}Xe with a targeted radio frequency pulse. This effectively "turns off" the signal from these encapsulated ^{129}Xe

atoms. The scan is designed with a mixing time, to allow the depolarized ^{129}Xe atoms to exchange out of the molecular host's cavity, thus decreasing the intensity of the peak corresponding to unbound ^{129}Xe. Indirectly detecting the presence of the cryptophane probe by observing the decrease in the large peak is 10,000 more sensitive than trying to directly detect the small peak corresponding to encapsulated ^{129}Xe in aqueous solution,[3] thus allowing for the detection of quantities of the molecular probe in sub-picomolar concentrations (Figure 7).[4] The technique that Pines developed, and Dmochowski, Stevens and Schröder have since repeated, is called Hyperpolarized Chemical Exchange Saturation Transfer (HyperCEST). Due to its high sensitivity, HyperCEST has the potential to replace the use of radionuclides that current molecular imaging techniques utilize.

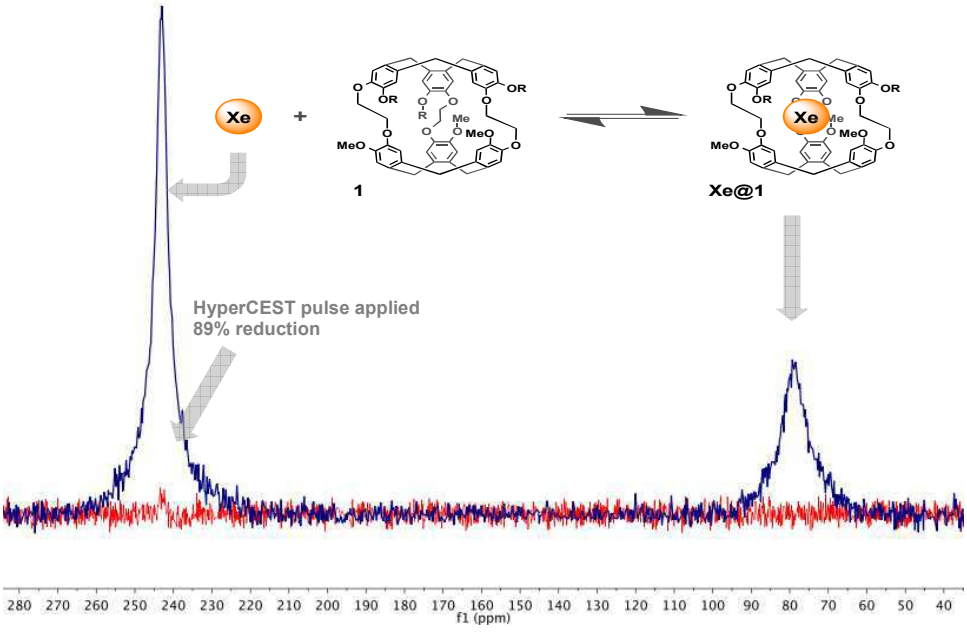


Figure 7 - ^{129}Xe NMR spectrum of a 70 mM solution of Dmochowski's cryptophane (1, R = propargyl) in DMSO (blue, polarization ~5%). HyperCEST spectrum of the

same solution with application of a prepulse at the frequency corresponding to the encapsulated species (red).

With the advent of HyperCEST, we hypothesized that a new xenon host that was optimized for its exchange kinetics, rather than binding affinity, was the next step towards the development ^{129}Xe molecular probes. Cyclotriveratrylenes (CTVs) were chosen due to their open architecture and their known affinity for hydrophobic guest molecules. They have exhibited a ball-and-socket-style binding of large hydrophobic compounds such as C60 fullerenes.[5] Additionally, they are an intermediate in two of the main synthetic strategies currently used to synthesize cryptophanes, which essentially are two CTVs joined by three diether linkers. CTVs are quickly and easily synthesized from cheap, readily available starting materials. As we recently reported in our communication, the amino functionalized CTV binds xenon gas and that this binding is apparent by ^{129}Xe NMR, thus demonstrating the two pool system of ^{129}Xe spins that is necessary for HyperCEST. It has been shown that CTVs, when binding charged substances, can self-assemble with hydrogen bonds to form a dimeric compound encapsulating the guest.[6] In addition, the methoxy and amino groups around the exterior ring of the compound in our earlier publication are within range of each other to have hydrogen bonding interactions (Figure 8). To explore the effects the functional groups around the outer ring of the CTV have on ^{129}Xe binding, a set of CTVs was synthesized that varies the number and type of hydrogen bond donors/acceptors present (Figure 9).

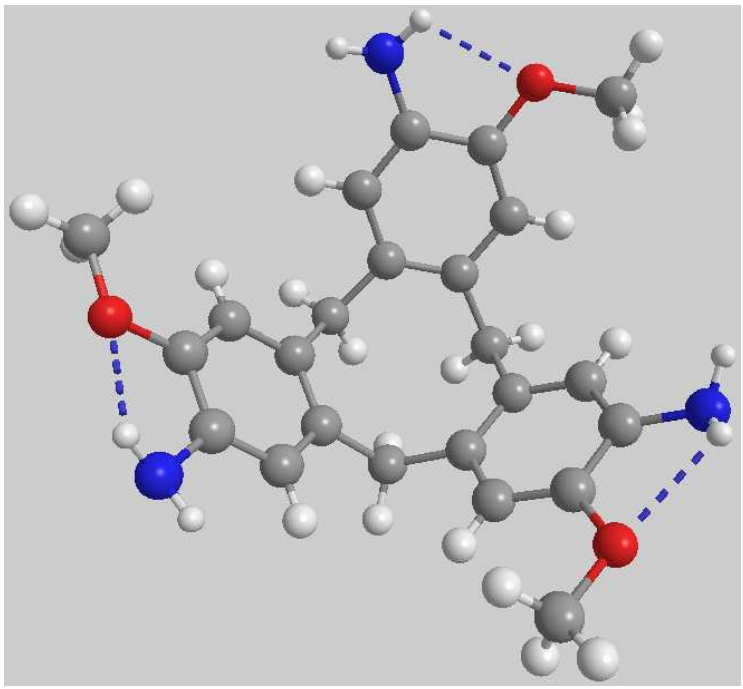


Figure 8 - Crystal Structure of amino-CTV with hydrogen bond interactions shown.

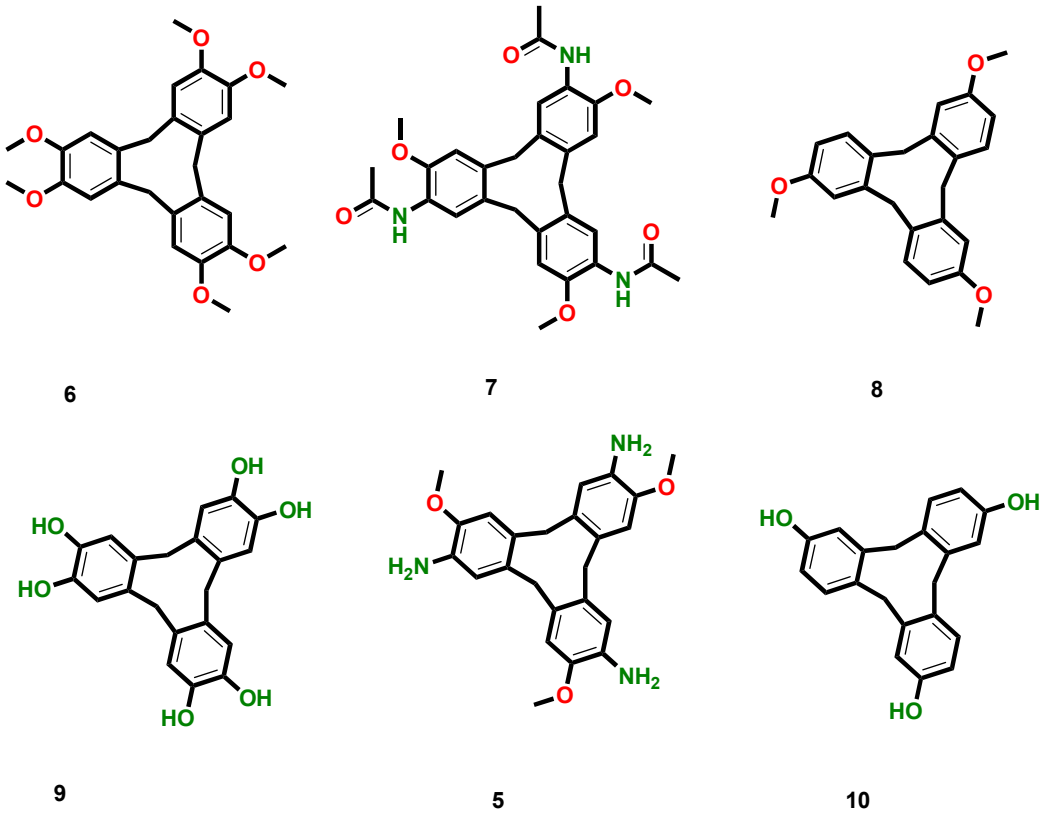
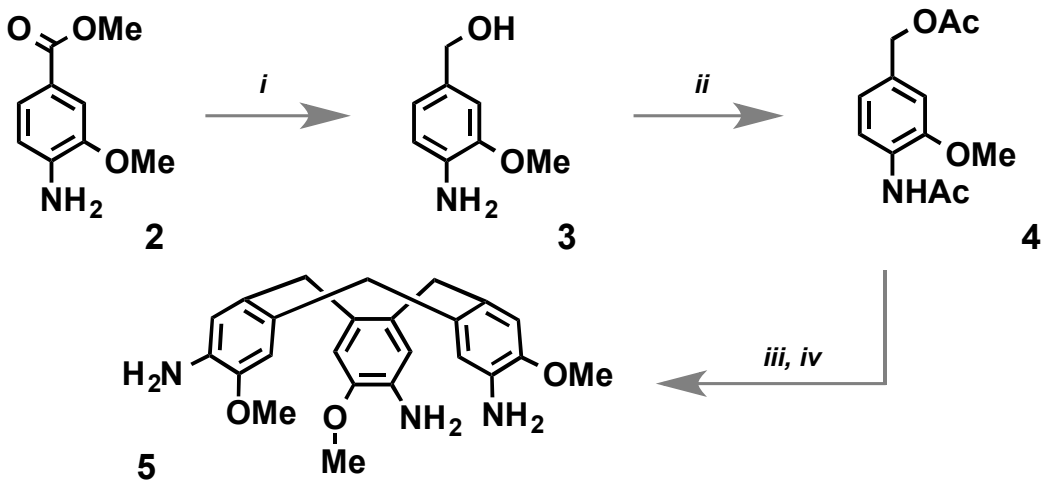


Figure 9 – Synthesized CTVs with hydrogen bond donating and accepting groups varied around the rim of the CTV. Hydrogen bond donors are in red and donors/ acceptors are in green.

Experimental Procedures

Chemical Synthesis

Scheme 3 - Synthesis of Amino-CTV Contrast Agent.



(i) $LiAlH_4$ (5 equiv), ether/THF (1:1), 0 ^oC, 2 h, 87% yield; (ii) Ac_2O (3.1 equiv), pyridine 16 h, 81% yield; (iii) $HClO_4$ (60% aq)/AcOH (2:1), 24 h, 91% yield; (iv) HCl/EtOH, 74% yield.

The amine CTV (**5**) was synthesized in five steps starting with methyl 4-amino-3-methoxybenzoate (**2**) which was reduced to 4-amino-3-methoxybenzol alcohol using five equivalents of lithium aluminum hydride in THF/ether (1:1). After a Fiezer and Fiezer workup, the crude reaction mixture was vacuum filtered, and the solvent was removed via rotary evaporation. The crude product was loaded onto silica gel and purified via automated flash chromatography using a ISOLERA 1® yielding the product (**3**) in 87% yield. The purified product was immediately taken on to the next reaction due to its quick decomposition.

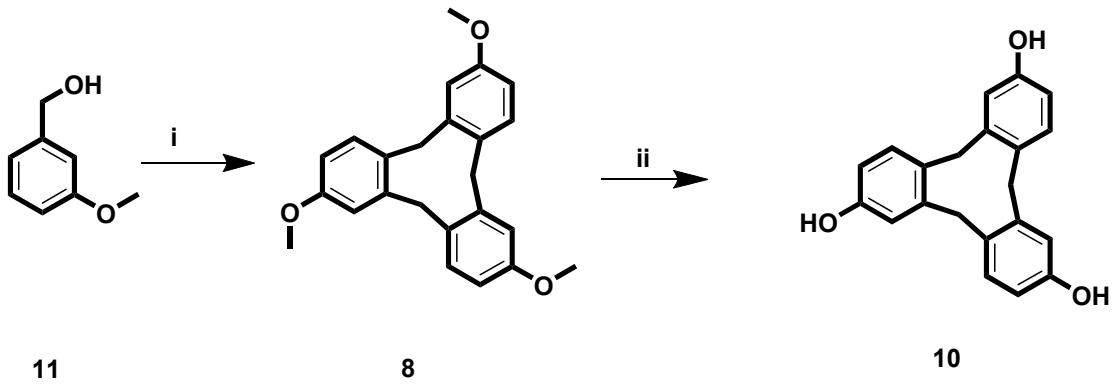
The diacetate (**4**) was synthesized from the amino alcohol (**3**), which was dissolved in pyridine (anhydrous) and acetic anhydride was added drop wise over three minutes at 0 ^oC under an ambient atmosphere. The reaction mixture was capped, warmed to room temperature and allowed to react for 12 hours. The reaction was then

cooled to 0 °C, and ice was added to the reaction mixture. Concentrated hydrochloric acid was added drop wise until the reaction was brought to pH 1. The product precipitated and was vacuum filtered and washed with DI H_2O. The product **4** was dried with a V-10 rapid solvent evaporator, giving a 81% yield of a white crystalline powder. The product was of sufficient purity to take directly on to the next step.

The CTV (**5**) was synthesized from the monomer (**4**), dissolving it in glacial acetic acid and adding percholoric acid (65%) drop wise over five minutes. The reaction mixture was then stirred overnight. After 12 hours, the volume was doubled by adding DI H_2O, and the reaction was stirred for an additional 15 minutes to allow for complete precipitation. Vacuum filtration through a fine sintered glass frit and washing with DI H_2O and acetone provided the pure product the triacetal CTV (**7**) in 91% yield as a white paste.

The deprotected CTV (**5**) was synthesized by suspending **7** in ethanol and adding 12 M hydrochloric acid and refluxing for approximately 5 hours, until a white suspension formed. The reaction was vacuum filtered, and the white suspension was dissolved in dichloromethane and washed first with a saturated sodium bicarbonate solution and then with DI H_2O, giving the product (**5**) in 74% yield.

Scheme 4 - Synthesis of trihydroxy-CTV Contrast Agent



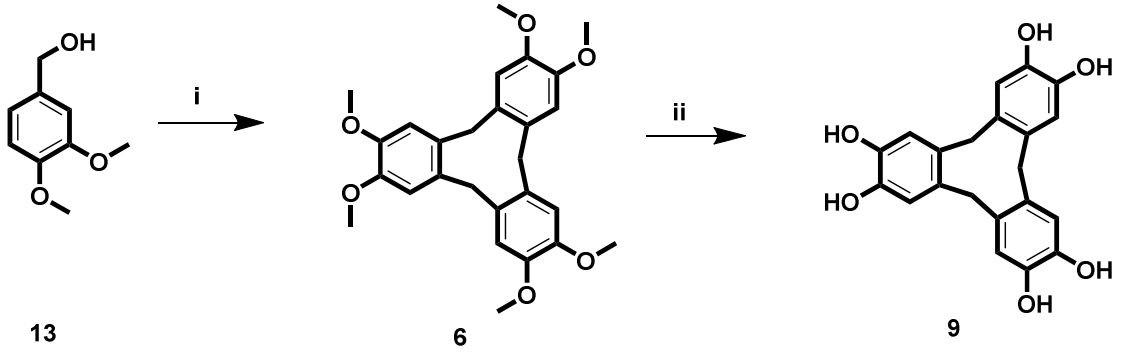
11 **8** **10**

(i) P_2O_5 (5 eq) DCM, 40 °C, 1 h, 1% (ii) BBr_3 in DCM (7 eq), DCM, 40 °C, 2 h, 91.3%

Compound (**8**), the trihydroxy CTV, was synthesized from 3-methoxy benzyl alcohol (**11**) following the previously published procedure.[7] Phosphorous pentoxide was added to a round bottom flask with a stir bar and suspended in dichloromethane. The alcohol (**11**) was added drop wise over five minutes and was heated at 40 °C for one hour. The product (**8**) was obtained by recrystallization in sufficient purity to take on to the next step in 1% yield.

The deprotected CTV (**10**) was synthesized by adding a 1 M solution of BBr_3 in dichloromethane to a suspension of **8** in dichloromethane at 0 °C and then warmed to room temperature and allowed to react overnight. The solution was then poured onto an ice/DI H_2O slurry, and the solid was filtered. The solid was washed with hot DI H_2O and then with acetonitrile, providing pure **10** in 91.3% yield.

Scheme 5 - Synthesis of Hexahydroxy CTV Contrast Agent.



(i) $Sc(OtF)_3$ (5%) ACN, 60 °C, overnight, 26% (ii) BBr_3 in DCM (6 eq), DCM, 40 °C, 2 h, 44%.

The hexahydroxy CTV (**9**) was obtained in two steps from 3,4-dimethoxy benzyl alcohol (**13**).[8] **13** was added to a sealed reaction vessel with $Sc(OTf)_3$ and acetonitrile under a nitrogen atmosphere. The reaction was heated to 60 °C overnight. The reaction was concentrated *in vacuo*, and the residue was then dissolved in dichloromethane and extracted with DI H_2O. The organic phase was collected, and the solvent was removed via rotary evaporation. The product was washed with ethyl acetate, yielding pure **6** in 26% yield.

The hexamethoxy CTV (**6**) was then dissolved in anhydrous dichloromethane and placed in a flask under a nitrogen atmosphere. BBr_3 (1 M in DCM) was added dropwise at 0 °C and then heated to 40 °C for two hours. The reaction was cooled in an ice bath and quenched with DI H_2O. The reaction was vacuum filtered, and the crude product was purified via flash chromatography, producing the product **9** in 44% yield.

Conclusion

Six CTVs were synthesized for HyperCEST testing to determine if they were capable of reversibly binding xenon. The aim of the HyperCEST testing will be to determine if they form a dimeric compound through hydrogen bonding self-assembling a cryptophane like structure to encapsulate ^{129}Xe. These CTVs are currently waiting HyperCEST testing by our collaborator.

References

1. Goodson, B. M., Nuclear magnetic resonance of laser-polarized noble gases in molecules, materials, and organisms. *Journal of magnetic resonance* **2002,** *155* (2), 157-216.

2. Swanson, S. D.; Rosen, M. S.; Coulter, K. P.; Welsh, R. C.; Chupp, T. E., Distribution and dynamics of laser-polarized129Xe magnetization in vivo. *Magnetic Resonance in Medicine* **1999,** *42* (6), 1137-1145.

3. Schroder, L.; Lowery, T. J.; Hilty, C.; Wemmer, D. E.; Pines, A., Molecular imaging using a targeted magnetic resonance hyperpolarized biosensor. *Science* **2006,** *314* (5798), 446-9.

4. Shapiro, M. G.; Ramirez, R. M.; Sperling, L. J.; Sun, G.; Sun, J.; Pines, A.; Schaffer, D. V.; Bajaj, V. S., Genetically encoded reporters for hyperpolarized xenon magnetic resonance imaging. *Nature chemistry* **2014,** *6* (7), 629-34.

5. Hardie, M. J.; Raston, C. L., Confinement and recognition of icosahedral main group cage molecules: fullerene C60 and o-, m-, p-dicarbadodecaborane(12). *Chemical communications* **1999,** (13), 1153-1163.

6. Hardie, M. J., Recent advances in the chemistry of cyclotriveratrylene. *Chemical Society reviews* **2010,** *39* (2), 516-27.

7. Traoré, T. n.; Delacour, L. a.; Kotera, N.; Merer, G.; Buisson, D.-A.; Dupont, C.; Rousseau, B., Scalable Synthesis of Cyclotriphenolene. *Organic Process Research & Development* **2011,** *15* (2), 435-437.

8. Brotin, T.; Roy, V.; Dutasta, J. P., Improved synthesis of functional CTVs and cryptophanes using Sc(OTf)3 as catalyst. *The Journal of organic chemistry* **2005,** *70* (16), 6187-95.

MANUSCRIPT 3

Submitted to ***Journal of Chemical Education***

Does POGIL Increase Grades With Attendance Held Constant?

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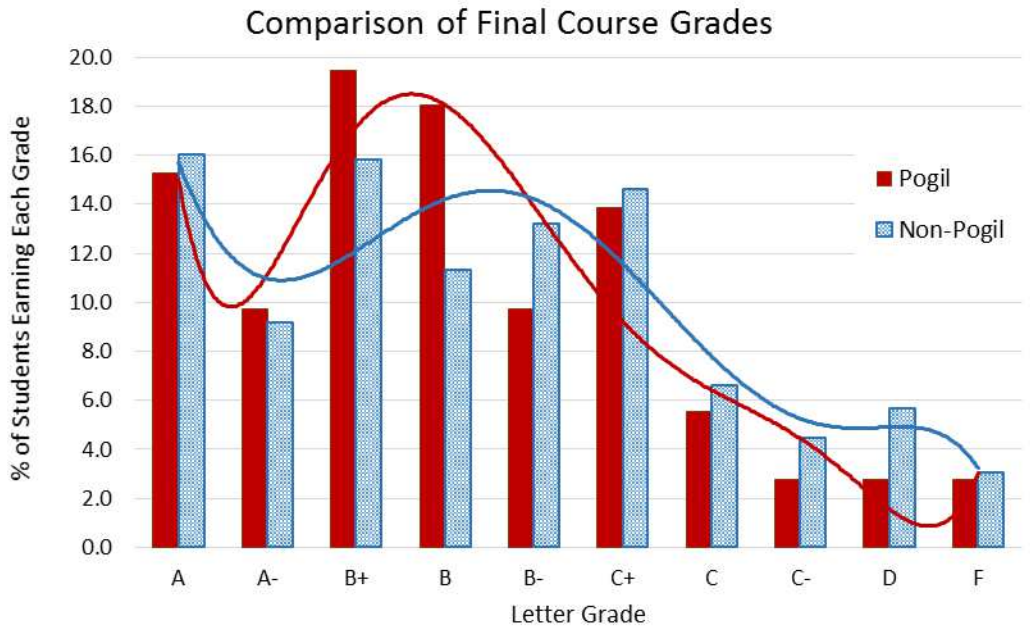
MANUSCRIPT 3

Does POGIL Increase Grades With Attendance Held Constant?

Abstract

Process oriented guided inquiry learning (POGIL) is a pedagogical method that has demonstrated improvement in student performance, increases in attendance, and decreases in failing grades and withdrawals. A three-year study was conducted where attendance was mandatory for all students across both the POGIL and traditional lecture formats to measure the effect of POGIL. There was a decrease in the standard deviation of exam grades in the POGIL lecture sections however there was no statistically significant change in grades received by the students. This is in keeping with previous studies that have found a decrease in D, F, and W's. The increase in student performance that has been observed at other institutions is most likely associated with both the pedagogical method POGIL and an increase in class attendance.

Abstract Graphic



Keywords

First-Year Undergraduate, Cooperative Learning, Chemical Education Research, Inquiry-Based/Discovery Learning, Student-Centered Learning

Introduction

Process-oriented, guided-inquiry learning (POGIL) was first proposed as an alternative method for teaching chemistry in 1999.[1] It is centered on the theory that knowledge is constructed by the learner by relating new knowledge to knowledge that students already possess. Building on previous studies about the way students learn, Farrell, et al (1999) proposed a change to the classroom environment to follow a guided inquiry learning cycle and take advantage of social interaction to construct student knowledge.[2] Since this seminal work, over 50 papers have been published centered around POGIL classroom instruction, including its implementation in both high school and college courses. These classrooms span the fields of anatomy & physiology, computer science, engineering, math, and biochemistry.[3] The student-

centered active learning focuses on the development of "process skills" as well as teaching the core material. These process skills include information processing, critical thinking, problem solving, teamwork, and communication.[4]

The existing body of work on POGIL has demonstrated a variety of results including positive impact on grades, a decrease in D, F, and withdrawal rates, an increase in attendance, and more enjoyment in the classroom.[5] As one study recently pointed out, increased attendance is a challenging outcome to obtain with conventional teaching methods.[6] However, some of those studies have shown that this method does not necessarily result in an increase in grades. In addition, there is some doubt about whether the increase in grades can be attributed to the increase in attendance or due to the pedagogy itself.[7]

Aims and Research Questions

This study aims to investigate the impact of adopting POGIL on student performance in a first semester general chemistry course while holding attendance constant. Specifically, we ask if a full implementation of POGIL improves the performance of the students relative to other non-POGIL sections of the general chemistry class, and relative to the previous year's POGIL section taught by the same instructor.

Methods

Institution

The United States Coast Guard Academy is a four-year public undergraduate college that has an enrollment of approximately 900 students. It has a stated goal of graduating 130 students from STEM majors each year, which is approximately 60% of each class.[8] General Chemistry is a required course for all students in their freshman

year and is made up of students intending to major in science, mathematics, and engineering as well as government and management. Attendance to all class meetings is required.

Students

The students are made up of a diverse body from across the United States. Each incoming class is composed of individuals who were under the age of 26 and who have no dependents on the day that they were required to report. All students are required to live on campus in the student dorms and are on a full scholarship with an additional stipend. Each of the three classes in this study were made up of 73% men and approximately 16% underrepresented minorities. Data on the incoming freshman class's SAT, ACT and incoming high school GPA are given in table 2. All students were required to enroll in General Chemistry I during the fall of their freshman year, unless they showed proficiency on a validation exam. Approximately 5 students in each incoming class successfully validated chemistry.

Table 2 - Student data

Year	*2008*	*2007*	*2006*
Mean SAT Reasoning Score	1256	1259	1262
Mean ACT Composite Score	27	29	27
Mean High School GPA	3.74	3.76	3.76

Course Setup

The lecture portion of General Chemistry I is conducted in seven sections, taught by seven different instructors. The class meets three times per week for 50 minutes in a three-tiered classroom capable of holding 40 students. Class size was approximately 35 students per class. All students are required to attend each class

unless they had an approved excusal to miss from their instructor. Generally, the only approved excusals were for varsity athletes who were missing class for a competition. At the beginning of the semester, chapter-specific objectives for each chapter were handed out to each student (available in supporting information). The objectives were authored and agreed upon by all instructors involved in the course prior to the beginning of the semester and ensured the same material was covered in all seven sections. Exams were administered using a common testing period for all students at the same time. Exam authorship was rotated among the instructors, with all exams being authored by two of the instructors and peer reviewed by the other five to ensure that the material covered was from the chapter-specific objectives. The final exam was the same exam for all three years with minor changes to correct issues identified in previous years.

The lecture course grade was determined by exams, written homework, online homework, and a cumulative final exam. The course grade was combined with the laboratory grade to determine the final grade in the course. This study only deals with the lecture portion of the class, so the laboratory grades have been excluded from the analysis. Therefore the course grade was calculated out of 75 points: There were five exams worth a total of 40 points, written homework accounted for another 10, online homework 5, and the final exam was worth 20 points. All assignments were the same for all seven sections, and all assignments were due on the same date.
Generally, students were not permitted to withdraw from the course without withdrawing from the institution. As a general rule, students do not withdraw from the institution as a result of the chemistry course but instead for a variety of reasons

that lead them to conclude they do not wish to pursue a career in the U.S. Coast Guard. Students who did not complete the semester were excluded from this study. Written homework was graded on a scale of 1 to 5 for each assignment and collected at the end of each chapter by the assigned lecture instructor. Online homework was due at the same time and was graded for completeness. It was assigned through an online homework system, ChemSkill Builder. As long as a student received a score better than 65% on an individual section, they would receive full credit. The grading was completed by the online system. There were five hourly exams given throughout the semester. All exams were administered during a common testing period, where all students enrolled in the course took the exam at the same time. Each page of an exam was graded by one instructor for all seven sections ensuring that all exams were graded equitably across all sections. Finally, online student surveys were taken on a voluntary basis at the end of the course. The surveys were anonymous and not attributed to specific sections or instructors, therefore they were only used for anecdotal conclusions.

Experimental Design

In the first year of data that was collected, all seven sections were taught by different instructors in a traditional lecture format. In the second and third year, one section was taught using POGIL, by an instructor who attended a weeklong implementation workshop offered by the POGIL project. POGIL was implemented following all of the tenets of a basic POGIL classroom[9] including:

- Students worked in groups of 3 or 4.
- The activities follow the learning cycle and were designed using POGIL principles.

- The instructor acted as a facilitator.
- Only short lectures (if any) were used, and the majority of class time was used for student centered learning.
- Students had assigned roles within their groups and rotated through the roles.
- The first time new information was introduced was in class, via POGIL.
- Groups were expected to complete all of the activities together in class, ensuring that all members understood the information.

In lieu of graded quizzes at the beginning of the course, as used in many implementations of POGIL,[1b] an anonymous clicker system was used approximately weekly to give the students immediate anonymous feedback on how they were performing relative to the objectives that had been covered in previous classes.

Data Analysis

In year one, all sections (242 students) were taught using traditional methods. This year was used as a control, comparing the instructor who would later implement POGIL to the remaining sections. In years two and three, one section was taught using a full implementation of POGIL, while the remaining sections continued to be taught using traditional methods. For years two and three, 14% of students enrolled in the General Chemistry course experienced the POGIL implementation, with 241 and 263 students enrolled in the course, respectively.

For all three years, data was analyzed for each of the five exams given during the semester, overall averages on homework assignments and final exam scores. Data analysis was performed using independent two-group t-tests comparing traditional and

POGIL implementations, and results were considered statistically significant (i.e., the null hypothesis is rejected) at the $p = 0.1$ level.

For year one, the instructor who would later implement POGIL had statistically significant higher scores in his section on semester exam averages, $t(52) = 1.71$, $p < 0.10$, and final exam score, $t(58) = 2.17$, $p < 0.05$. Differences on homework assignment averages did not show a statistically significant difference. Table 3 shows averages for year one.

Table 3 - Year one averages (standard deviation)

	Pre-POGIL Instructor	*Traditional*
Homework Average (out of 5)	4.63 (0.22)	4.67 (0.41)
Exam Averages (%)	83.24 (7.28)	80.84 (9.16)
Final Exam (%)	81.48 (9.26)	77.50 (13.41)

Tables 4 and 5 contain averages for each of these categories for years two and three, respectively. In years two and three, with full POGIL implementation, all but one of the average scores for each category noted above are higher for the POGIL sections when compared to the traditional sections. However, none of the differences in exam scores or final exam scores are statistically significant at the $p = 0.1$ level of confidence. There is, however, an advantage in the POGIL section on homework averages in year three, $t(52) = 2.20$, $p < 0.05$.

Table 4 - Year two averages (standard deviation)

	POGIL	*Traditional*
Homework Average (out of 5)	4.71 (0.46)	4.70 (0.40)
Exam Averages (%)	79.75 (7.12)	79.08 (9.80)
Final Exam (%)	78.85 (8.10)	79.45 (11.30)

Table 5 - Year three averages (standard deviation)

	POGIL	*Traditional*
Homework Average (out of 5)	4.66 (0.58)	4.42 (0.66)
Exam Averages (%)	76.42 (11.75)	74.14 (11.47)
Final Exam (%)	76.65 (12.57)	75.21 (12.47)

Of the ten exams given during the semester over years two and three, averages from the POGIL section outscored the traditional section on eight exams, although the differences were only statistically significant for three of those eight exams: Exam two in year 2, $t(60) = 2.01$, $p < 0.05$, Exam three in years three, $t(49) = 1.8$, $p < 0.01$, and Exam 5 in year three, $t(48) = 2.67$, $p < 0.05$. One of the two exams where the traditional sections scored higher than the POGIL section was also significant: Exam three in year two, $t(48) = -2.34$, $p < 0.05$. The averages for each of these exams can be seen in Table 5. However, a paired two-tailed t-test showed that the standard deviation for the exams between the POGIL and traditional classroom was statistically significantly smaller, $t(10) = 2.2912$, $p < 0.05$.

Table 6 - Exam averages (Standard Deviation)

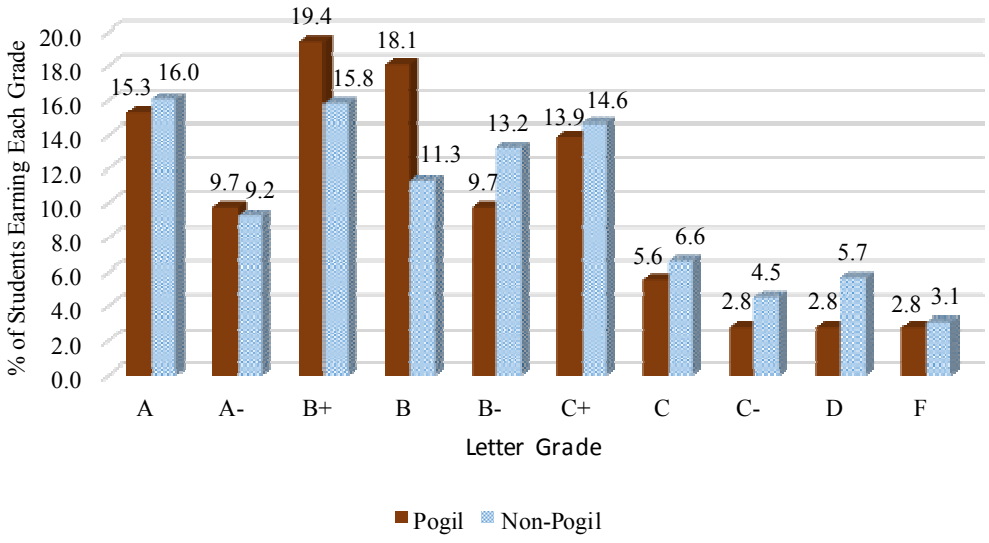
	Exam 1	*Exam 2*	*Exam 3*	*Exam 4*	*Exam 5*
Year 2: POGIL	82.4 (9.0)	81.4 (9.9)	74.5 (11.8)	82.0 (7.1)	78.4 (10.6)
Year 2: Traditional	81.8 (10.2)	77.5 (14.0)	79.6 (12.6)	80.2 (11.4)	76.3 (12.3)
Year 3: POGIL	75.1 (15.8)	73.2 (14.7)	75.6 (12.5)	75.6 (14.4)	82.7 (11.5)
Year 3: Traditional	75.3 (16.2)	73.9 (13.6)	71.5 (12.7)	73.7 (13.9)	77.4 (13.3)

Conclusions and Discussion

In this study, we were able to evaluate the impact of a full POGIL implementation in its first two years for a first-year general chemistry classroom while holding attendance constant. Due to experimental design we were able to convey the

same amount of information and produce the same level of performance as a traditional lecture. A visual representation of the grades appeared to show an improvement in the letter grades obtained by the students in the POGIL sections (graph 1.) A X^2 analysis was conducted to determine if the difference was significant. It revealed that there was no significant difference between the two groups, X^2 (9, N = 424) = 14.68, $p < 0.10$. However, when a paired two-tailed t-test was performed on the standard deviations it showed that the POGIL classrooms standard deviation was significantly smaller. This is in keeping with previously reported results of POGIL decreasing the number of D, F and W's. A visual inspection of the exam averages combined with the decreased standard deviations, allows us to see that the top students are still generally performing at the same level; however, the lower students have begun to perform at a higher level.

Graph 1. Comparison of Final Course Grades During POGIL Implementation



Instructor preparation was important for the successful implementation. The weeklong POGIL workshop combined with ongoing discussions from experienced

practitioners greatly accelerated the learning curve and decreased any negative impacts on the class. Anecdotally, the classroom was much more enjoyable with an increase in interaction with the students. Further study on the impact of POGIL on process skills is definitely warranted and planned for the future. Previous implementations of POGIL have reported an increase in grades and attendance but were unable to determine the interrelation of these two variables. In this implementation, where we were able to hold attendance constant, we did not see a significant increase in grades for the POGIL classroom but did see a decrease in the standard deviation of the grades between the POGIL and traditional lecture sections. At institutions where attendance is not compulsory, an increase in attendance alone should be enough of a positive outcome to warrant POGIL's consideration.

Associated content

Supporting Information

An example syllabus and chapter specific objectives are provided for the course in appendix 3.

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and do not necessarily represent the official views of the U.S. Coast Guard or the federal government.

References

1. (a) Spencer, J. N., New Directions in Teaching Chemistry: A Philosophical and Pedagogical Basis. *J. Chem. Educ.* 1999, *76*, 566; (b) Farrell, J. J.; Moog, R. S.; Spencer, J. N., A Guided-Inquiry General Chemistry Course. *J. Chem. Educ.* 1999, *76*, 570.
2. Abraham, M. R.; Renner, J. W., The Sequence of Learning Cycle Activities in High-School Chemistry. *J Res Sci Teach* **1986,** *23*, 121-143.
3. POGIL Post Secondary. https://pogil.org/post-secondary (accessed October 6, 2014).
4. Minderhout, V.; Loertscher, J., Lecture-free biochemistry: A Process Oriented Guided Inquiry Approach. *Biochem Mol Biol Educ* **2007,** *35*, 172-80.
5. Eberlein, T.; Kampmeier, J.; Minderhout, V.; Moog, R. S.; Platt, T.; Varma-Nelson, P.; White, H. B., Pedagogies of engagement in science: A comparison of PBL, POGIL, and PLTL*. *Biochem Mol Biol Educ* **2008,** *36*, 262-273.
6. Chase, A.; Pakhira, D.; Stains, M., Implementing Process-Oriented, Guided-Inquiry Learning for the First Time: Adaptations and Short-Term Impacts on Students' Attitude and Performance. *J. Chem. Educ.* **2013,** *90*, 409-416.
7. Marcus, N. R. a. L., Student Attitudes and Learning Outcomes from Process Oriented Guided-Inquiry Learning (POGIL) Strategy in an Introductory Chemistry Course for Non-science Majors: An Action Research Study. *Chem Educ* **2009,** *14*, 85-93.
8. Academy, U. S. C. G., Strategic Plan 2013-2018. 2013.

9. Basic POGIL Classroom Implementation. https://pogil.org/uploads/media_items/basic-pogil-implementation.original.pdf (accessed October 6, 2014).

APPENDIX 1

Manuscript 1 Supporting Information

A Bowl-Shaped Contrast Agent for HyperCEST-Enhanced Xenon-129 NMR

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Experimental Section

General Procedures:

Unless otherwise noted the chemicals and solvents used were purchased from Fisher Scientific or Sigma Aldrich, of analytical grade, and were used as received. All reactions were carried out under normal atmosphere unless otherwise noted. Flash chromatography was performed using a Biotage® Isolera 1 with Biotage® SNAP Ultra high performance flash chromatography cartridges (25 micron spherical silica) and Biotage® SNAP NH functionalized silica gel cartridges (50 micron silica).

Instrumentation:

GC/MS analysis was carried out on an Agilent Technologies 6890 GC system fixed with a 5973 mass selective detector. GC/MS Conditions: J & W Scientific DB-1, capillary 25.0m x 200µm x 0.33µm, 1.3 mL/min, 40 °C, hold 0.50 min, 12 °C/min to 320 °C, hold 6.0 min. NMR spectra were acquired with Bruker Avance 300 and 400 MHz spectrometers.

Chemical Synthesis.

Unless otherwise noted all reactions were carried out under normal atmosphere at room temperature.

4-amino-3-methoxy-benzenemethanol (3):

To an oven dried 100 mL RBF with a stir bar lithium aluminum hydride (27.61 mmol) was added under N_2(g). The vessel was capped and cooled to 0°C. The $LiAlH_4$ was suspended in anhydrous diethyl ether (37 mL). Methyl-4-amino-3-methoxy-benzoate

(5.52 mmol) was dissolved in anhydrous tetrahydrofuran (17 mL) and then added to the RBF across 5 min. The reaction was allowed to warm to room temperature and stirred for approximately 4 hours with the reaction progress being monitored via TLC. When the reaction appeared complete by TLC it was cooled to 0 ^{o}C and quenched using the Fieser method. After stirring for an additional hour the reaction was vacuum filtered and the solid was washed with approximately 30 mL of dichloromethane. The filtrate was concentrated via rotary evaporation and the resulting yellow oil was purified via flash chromatography on a 10g Ultra SNAP column. The fractions containing the desired compound were combined and dried via rotoary evaporation and on a V-10 rapid solvent evaporator. 4-amino-3-methoxy-benzenemethanol (**3**) was obtained in 87% yield.

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4):

A magnetic stir bar and anhydrous pyridine (6.5 mL) were added to a 20 mL scintillation flask containing 4-amino-3-methoxy-benzenemethanol, **3** (725.3 mg, 4.735 mmol). The reaction was cooled to 0 ^{o}C and acetic anhydride (2.7 mL, 28.41 mmol) was added across 5 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched after cooling to 0 ^{o}C and adding approximately 2 mL of deinonized water to it by adding 12M HCl until pH ~1. A white precipitate formed. The precipitated was vacuum filtered and washed with 20 mL of DI-H_2O and then dried on the V-10 rapid solvent evaporator. *N*-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (**4**) was obtained in an 81% yield.

(±)-3,8,13-triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7):

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide, **4** (704.5 mg, 2.969 mmol), was dissolved in glacial acetic acid (7 mL) and added with a magnetic stir bar to a 50 mL RBF. 60 % by weight perchloric acid (14 mL) was added drop wise across 10 min and the reaction was stirred for 12 hours. DI-H_2O (25 mL) was then added and the reaction was stirred for an additional 15 mins. The white precipitate was collected by vacuum filtration through a sintered glass funnel. The precipitate was then washed with 25 mL of additional DI-H_2O followed by 25 mL of acetone. The white precipitate was then dried on the V-10 solvent evaporator. (±)-3,8,13-triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (4) was obtained in 91% yield.

(±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5):

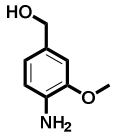
The triacetamide (479 mg) was suspended in ethanol (18 mL) in a 100 mL RBF. A magnetic stir bar was added and then 12M hydrochloric acid (30 mL) was added. The solution was refluxed for five hours. A white precipitate formed during that time. The solution was cooled to 0 ^oC and vacuum filtered. The precipitate was washed with 3 mL of ethanol, ether, and dichloromethane. The white precipitate was then dried on in a 20 mL scintillation vial on the V-10 evaporator. The triamine, **5**, was obtained in a 74% yield.

Characterization of Compounds

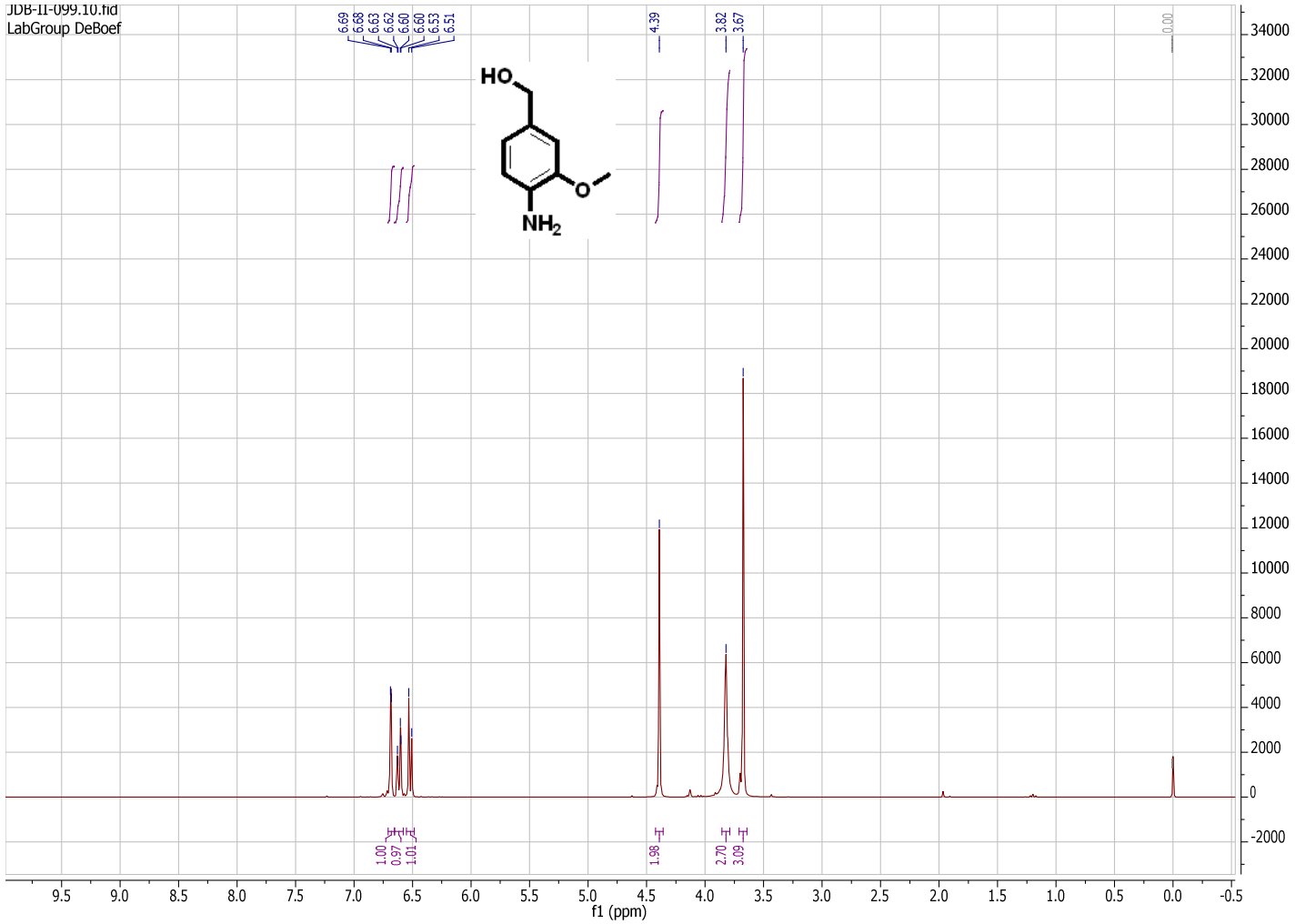
Known compounds were obtained by the procedures above and characterized via NMR spectroscopy; a ^{1}H NMR spectrum was provided for each compound and the relevant reference was cited. All novel compounds obtained have been characterized with ^{1}H NMR, ^{13}C NMR, and either Mass Spectroscopy or Elemental Analysis.

Spectroscopic Data for Compounds in Scheme 1:

4-amino-3-methoxy-benzenemethanol (3)

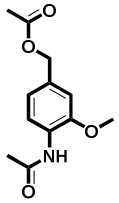


^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.69 (d, *J*=1.7 Hz, 1H), 6.61 (dd, *J*=7.8, 1.7 Hz, 1H), 6.52 (d, *J*=7.8 Hz, 1H), 4.39 (s, 2H), 3.82 (br, 3H), 3.67 (s, 3H)

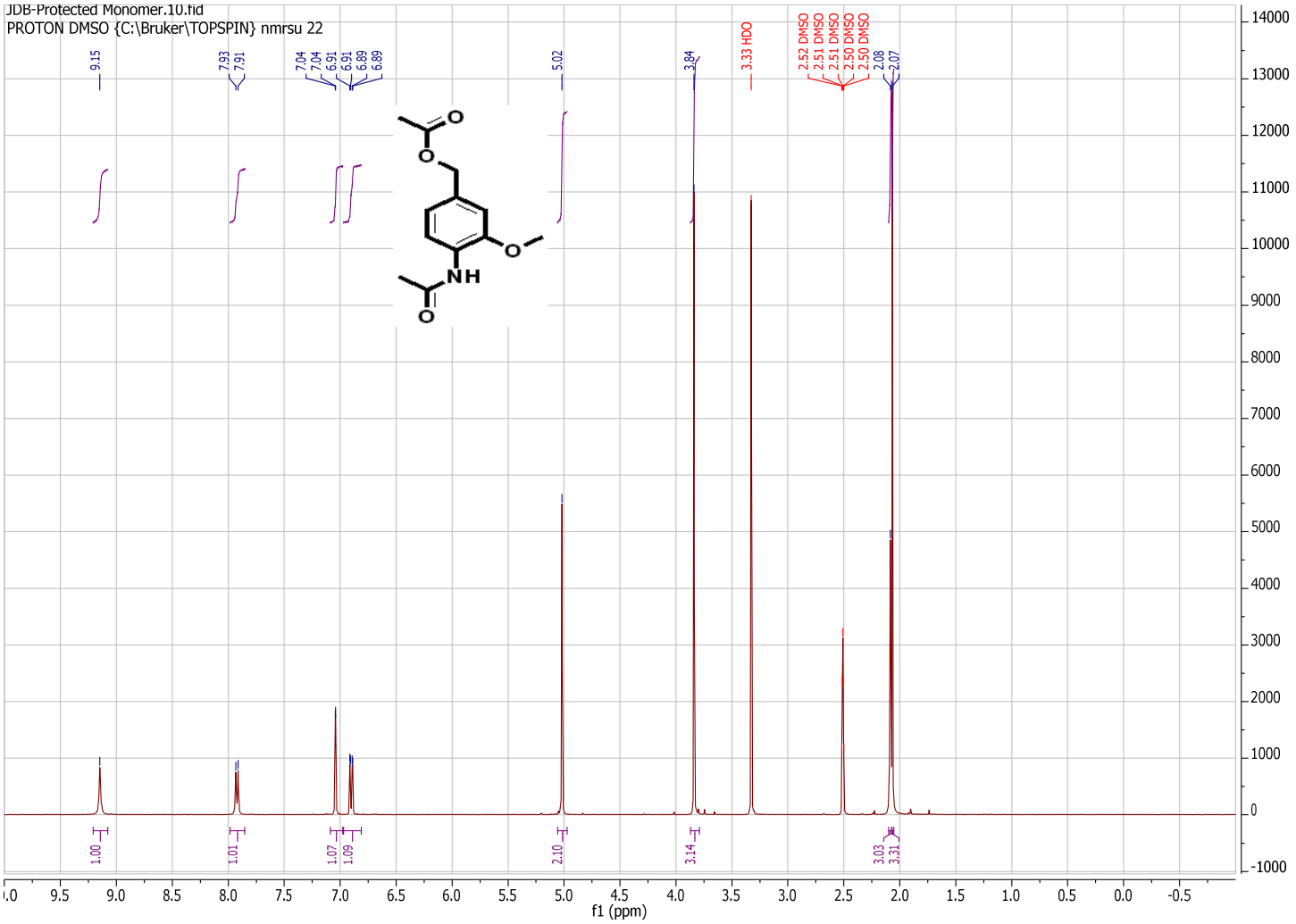


Spectra 1 - ^{1}H NMR of 4-amino-3-methoxy-benzenemethanol (3).

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4):

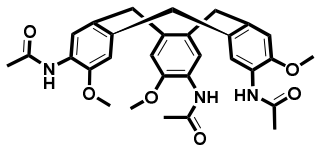


^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.15 (s, 1H), 7.92 (d, *J*=8.1 Hz, 1H), 7.04 (d, *J*=1.8 Hz, 1H), 6.90 (dd, *J*=8.2, 1.7 Hz, 1H), 5.02 (s, 2H), 3.84 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H).

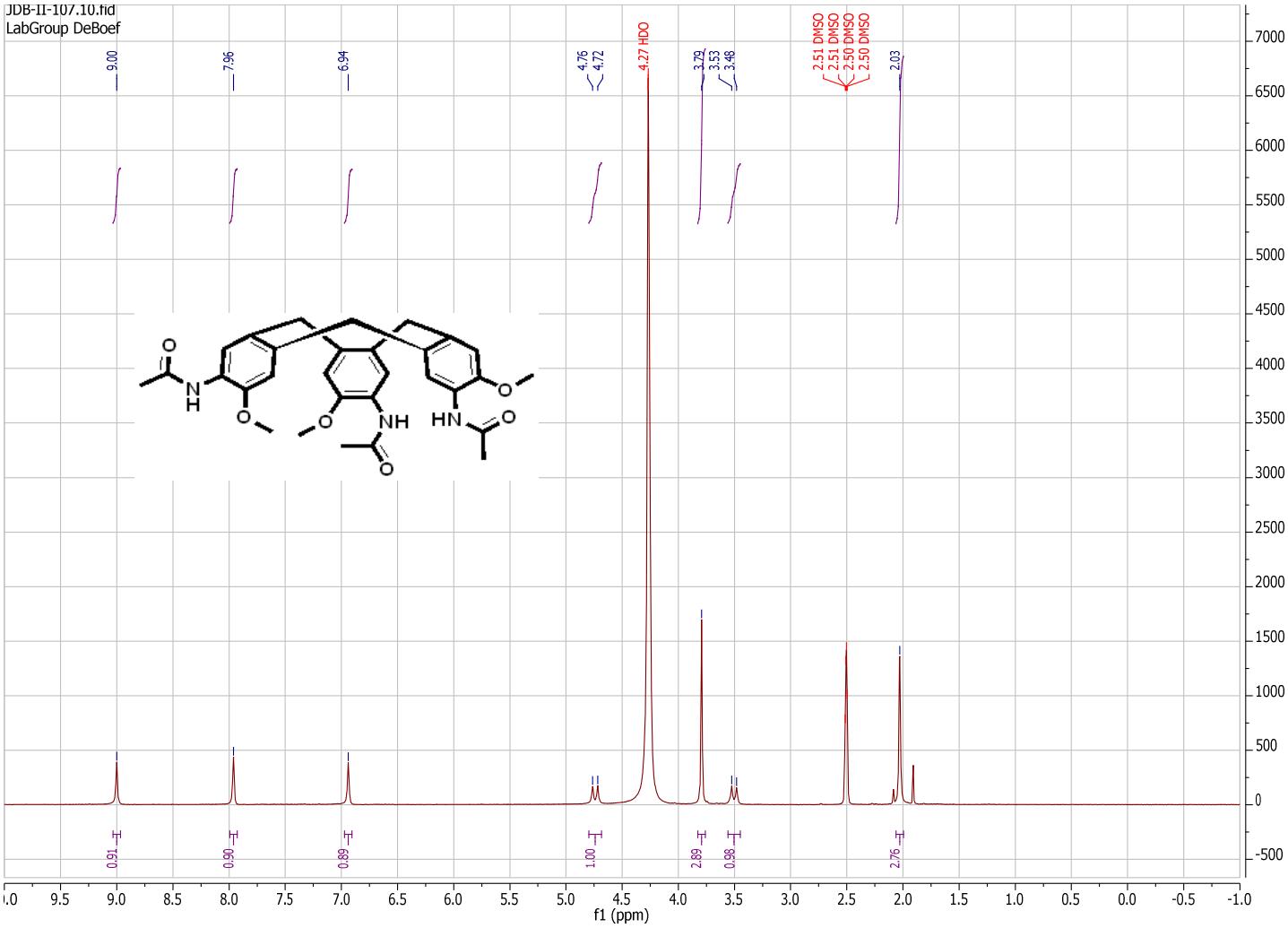


Spectra 2 - ^{1}H NMR of N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4)

(±)-3,8,13-Triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7):

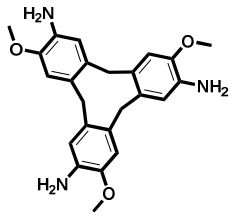


^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 9.00 (s, 1H), 7.96 (s, 1H), 6.94 (s, 1H), 4.74 (d, *J*=13.4 Hz, 1H), 3.79 (s, 3H), 3.50 (d, *J*=13.3 Hz, 1H), 2.03 (s, 3H).



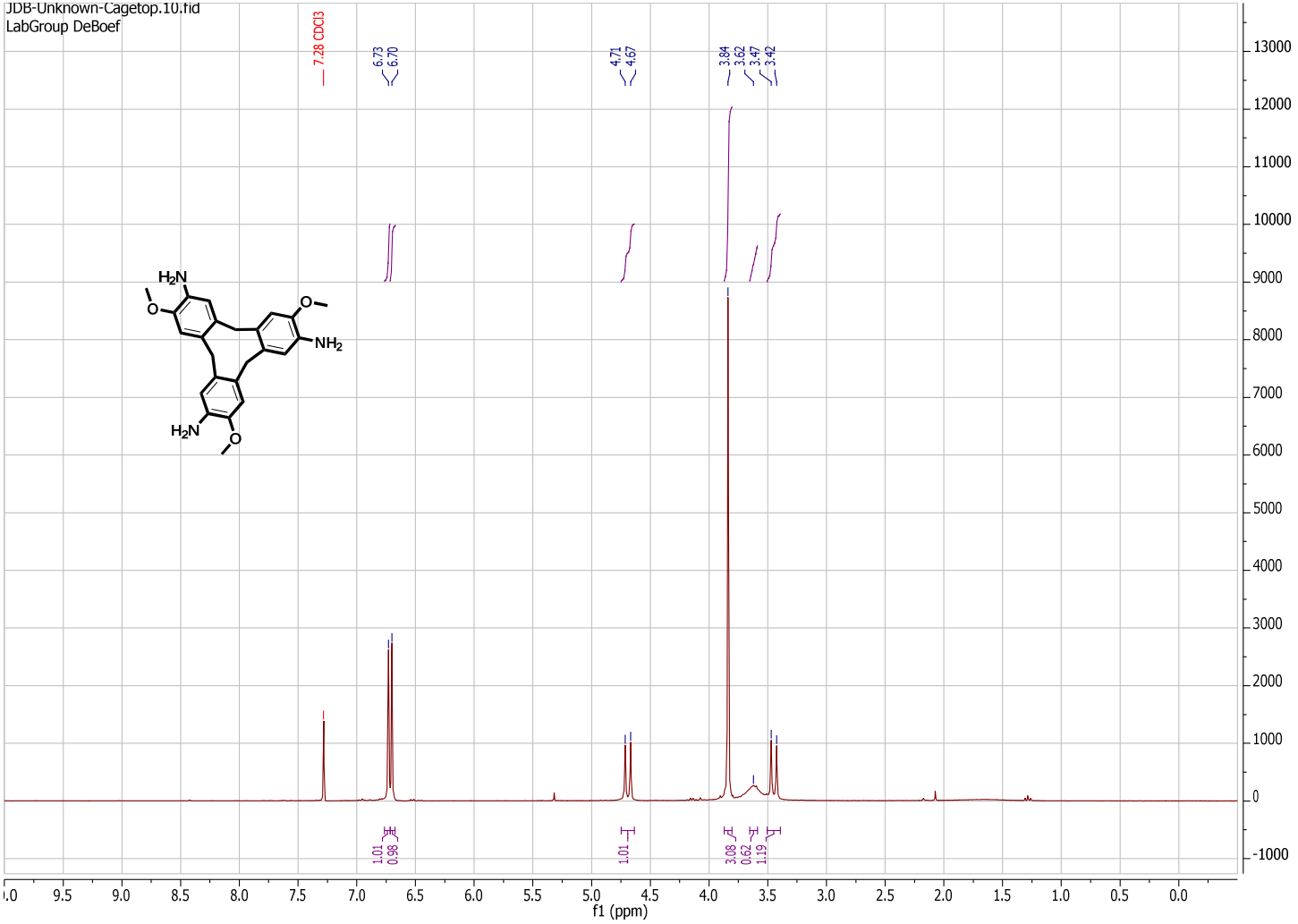
Spectra 3 - ^{1}H NMR of (±)-3,8,13-Triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7).

(±)-3,8,13-tTiamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5):

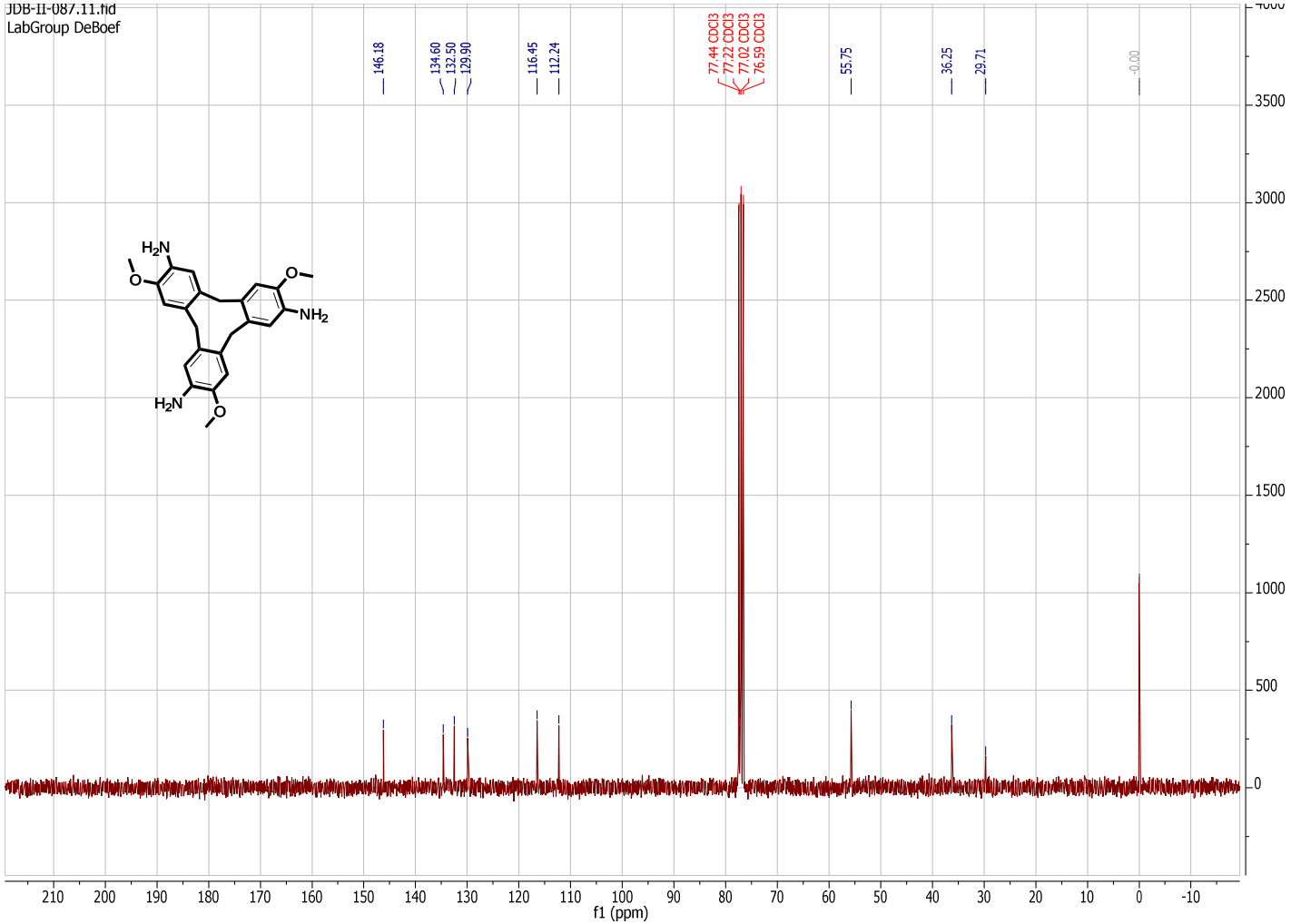


^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.73 (s, 1H), 6.70 (s, 1H), 4.69 (d, *J*=13.7 Hz, 1H), 3.84 (s, 3H), 3.62 (br, 2H, exchangeable protons), 3.45 (d, *J*=13.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 146.18, 134.60, 132.50, 129.90, 116.45, 112.24, 55.75, 36.25, 29.71



Spectra 4 - ^{1}H NMR of (±)-3,8,13-tTiamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5)



Spectra 5 - ^{13}C NMR of (±)-3,8,13-tTiamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5)

Crystallographic Data

A colorless crystal of sample was mounted on a Cryoloop with paratone-N oil and data was collected at 90 K with a Bruker CMOS detector using Mo K alpha radiation generated from a Mo rotating anode. Data were corrected for absorption with SADABS. Structure was solved by direct methods and all non-hydrogen atoms were refined anisotropically by full matrix least squares on F^2. Hydrogen atom H1N was found from a Fourier difference map and was refined isotropically with N-H distance of 0.87 (0.01) Å and 1.20 U_{eq} of parent N atom. All other hydrogen atoms were placed in calculated positions with appropriate riding parameters.

Platon program SQUEEZE used to address issue of diffused solvent. Program found void volume of 1196 $Å^3$ with an electron count of 196. This was assigned to 11 molecules of methanol (CH_4O) and unit card was changed to address changes in chemical formula, molecular mass, density and F000 value. Because of time constraints only 95 % of the data were collected and used in structural refinement.

Table 1. Crystal data and structure refinement for JimStuff.

Identification code	jimstuff (C24 H27 N3 O3) 1.687 (CH4O)	
Empirical formula	C25.69 H33.75 N3 O4.69	
Formula weight	459.56	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 45.923(17) Å	▪ = 90°.
	b = 45.923(17) Å	▪ = 90°.
	c = 4.6253(18) Å	▪ = 90°.

Volume	9754(6) $Å^3$
Z	16
Density (calculated)	1.252 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	3942
Crystal size	0.14 x 0.14 x 0.05 mm^3
Crystal color / habit	colorless / block
Theta range for data collection	3.20 to 25.39°.
Index ranges	-31<=h<=54, -54<=k<=36, -3<=l<=5
Reflections collected	10215
Independent reflections	4273 [R(int) = 0.0722]
Completeness to theta = 25.39°	94.8 %
Absorption correction	multi-scan / sadabs
Max. and min. transmission	0.9957 and 0.9880
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4273 / 9 / 312
Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R1 = 0.0730, wR2 = 0.1630
R indices (all data)	R1 = 0.1361, wR2 = 0.1853
Largest diff. peak and hole	0.241 and -0.268 $e.Å^{-3}$

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103) for JimStuff. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	7257(1)	615(1)	5779(6)	31(1)
O(2)	5495(1)	826(1)	5942(6)	31(1)
O(3)	6576(1)	2288(1)	6181(6)	30(1)
N(1)	7452(1)	1165(1)	6228(7)	28(1)
N(2)	5873(1)	374(1)	5737(7)	32(1)
N(3)	6002(1)	2203(1)	6300(7)	33(1)

C(1)	6861(1)	1254(1)	716(8)	21(1)
C(2)	7092(1)	1312(1)	2616(8)	23(1)
C(3)	7221(1)	1102(1)	4322(8)	24(1)
C(4)	7120(1)	815(1)	4042(8)	23(1)
C(5)	6895(1)	755(1)	2182(8)	26(1)
C(6)	6759(1)	973(1)	501(8)	22(1)
C(7)	6495(1)	887(1)	-1259(8)	27(1)
C(8)	6220(1)	890(1)	532(8)	23(1)
C(9)	6159(1)	648(1)	2245(8)	28(1)
C(10)	5923(1)	629(1)	4056(8)	25(1)
C(11)	5732(1)	862(1)	4155(8)	25(1)
C(12)	5785(1)	1106(1)	2499(8)	25(1)
C(13)	6030(1)	1126(1)	686(8)	22(1)
C(14)	6075(1)	1411(1)	-944(8)	24(1)
C(15)	6227(1)	1643(1)	858(7)	21(1)
C(16)	6055(1)	1817(1)	2660(8)	23(1)
C(17)	6173(1)	2028(1)	4443(8)	25(1)
C(18)	6474(1)	2074(1)	4353(8)	23(1)
C(19)	6643(1)	1908(1)	2531(8)	24(1)
C(20)	6526(1)	1689(1)	792(7)	21(1)
C(21)	6736(1)	1507(1)	-984(8)	26(1)
C(22)	7125(1)	336(1)	6053(10)	37(1)
C(23)	5313(1)	1074(1)	6336(9)	34(1)
C(24)	6882(1)	2328(1)	6297(9)	36(1)
O(4)	5672(1)	-23(1)	1592(7)	44(1)
C(25)	5397(1)	102(1)	885(12)	50(1)

Table 3. Bond lengths [Å] and angles [°] for JimStuff.

O(1)-C(4)	1.373(4)
O(1)-C(22)	1.422(4)
O(2)-C(11)	1.375(4)
O(2)-C(23)	1.423(4)
O(3)-C(18)	1.376(4)
O(3)-C(24)	1.419(4)
N(1)-C(3)	1.411(5)
N(1)-H(1A)	0.905(10)
N(1)-H(1B)	0.902(10)
N(2)-C(10)	1.426(5)
N(2)-H(2A)	0.901(10)
N(2)-H(2B)	0.904(10)
N(3)-C(17)	1.417(5)
N(3)-H(3A)	0.897(10)
N(3)-H(3B)	0.893(10)
C(1)-C(6)	1.379(4)
C(1)-C(2)	1.403(5)
C(1)-C(21)	1.517(5)
C(2)-C(3)	1.380(5)
C(2)-H(2)	0.9500
C(3)-C(4)	1.403(5)
C(4)-C(5)	1.372(5)
C(5)-C(6)	1.411(5)
C(5)-H(5)	0.9500
C(6)-C(7)	1.513(5)
C(7)-C(8)	1.510(5)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.395(5)
C(8)-C(13)	1.395(5)
C(9)-C(10)	1.371(5)
C(9)-H(9)	0.9500

C(10)-C(11)	1.387(5)
C(11)-C(12)	1.379(5)
C(12)-C(13)	1.405(5)
C(12)-H(12)	0.9500
C(13)-C(14)	1.526(5)
C(14)-C(15)	1.521(5)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(20)	1.391(5)
C(15)-C(16)	1.397(5)
C(16)-C(17)	1.382(5)
C(16)-H(16)	0.9500
C(17)-C(18)	1.401(5)
C(18)-C(19)	1.375(5)
C(19)-C(20)	1.393(5)
C(19)-H(19)	0.9500
C(20)-C(21)	1.515(5)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
O(4)-C(25)	1.426(4)
O(4)-H(4)	0.8400
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(4)-O(1)-C(22)	117.4(3)
C(11)-O(2)-C(23)	116.4(3)
C(18)-O(3)-C(24)	116.8(3)

C(3)-N(1)-H(1A)	113(2)
C(3)-N(1)-H(1B)	115(2)
H(1A)-N(1)-H(1B)	111(2)
C(10)-N(2)-H(2A)	108(2)
C(10)-N(2)-H(2B)	115(2)
H(2A)-N(2)-H(2B)	113(2)
C(17)-N(3)-H(3A)	112(2)
C(17)-N(3)-H(3B)	113(2)
H(3A)-N(3)-H(3B)	113(2)
C(6)-C(1)-C(2)	118.7(3)
C(6)-C(1)-C(21)	123.5(3)
C(2)-C(1)-C(21)	117.8(3)
C(3)-C(2)-C(1)	123.2(3)
C(3)-C(2)-H(2)	118.4
C(1)-C(2)-H(2)	118.4
C(2)-C(3)-C(4)	117.7(3)
C(2)-C(3)-N(1)	122.4(3)
C(4)-C(3)-N(1)	119.9(3)
C(5)-C(4)-O(1)	125.4(3)
C(5)-C(4)-C(3)	119.6(3)
O(1)-C(4)-C(3)	115.1(3)
C(4)-C(5)-C(6)	122.5(3)
C(4)-C(5)-H(5)	118.7
C(6)-C(5)-H(5)	118.7
C(1)-C(6)-C(5)	118.2(3)
C(1)-C(6)-C(7)	123.8(3)
C(5)-C(6)-C(7)	117.8(3)
C(8)-C(7)-C(6)	111.8(3)
C(8)-C(7)-H(7A)	109.2
C(6)-C(7)-H(7A)	109.2
C(8)-C(7)-H(7B)	109.2
C(6)-C(7)-H(7B)	109.2
H(7A)-C(7)-H(7B)	107.9
C(9)-C(8)-C(13)	117.6(3)
C(9)-C(8)-C(7)	118.2(3)
C(13)-C(8)-C(7)	124.1(3)

C(10)-C(9)-C(8)	123.7(3)
C(10)-C(9)-H(9)	118.1
C(8)-C(9)-H(9)	118.1
C(9)-C(10)-C(11)	118.3(3)
C(9)-C(10)-N(2)	120.8(3)
C(11)-C(10)-N(2)	120.9(3)
O(2)-C(11)-C(12)	124.9(3)
O(2)-C(11)-C(10)	115.4(3)
C(12)-C(11)-C(10)	119.7(3)
C(11)-C(12)-C(13)	121.7(3)
C(11)-C(12)-H(12)	119.2
C(13)-C(12)-H(12)	119.2
C(8)-C(13)-C(12)	118.9(3)
C(8)-C(13)-C(14)	123.8(3)
C(12)-C(13)-C(14)	117.3(3)
C(15)-C(14)-C(13)	113.2(3)
C(15)-C(14)-H(14A)	108.9
C(13)-C(14)-H(14A)	108.9
C(15)-C(14)-H(14B)	108.9
C(13)-C(14)-H(14B)	108.9
H(14A)-C(14)-H(14B)	107.8
C(20)-C(15)-C(16)	118.9(3)
C(20)-C(15)-C(14)	123.2(3)
C(16)-C(15)-C(14)	117.9(3)
C(17)-C(16)-C(15)	122.4(3)
C(17)-C(16)-H(16)	118.8
C(15)-C(16)-H(16)	118.8
C(16)-C(17)-C(18)	118.4(3)
C(16)-C(17)-N(3)	122.9(3)
C(18)-C(17)-N(3)	118.6(3)
C(19)-C(18)-O(3)	125.5(3)
C(19)-C(18)-C(17)	119.2(3)
O(3)-C(18)-C(17)	115.2(3)
C(18)-C(19)-C(20)	122.6(3)
C(18)-C(19)-H(19)	118.7
C(20)-C(19)-H(19)	118.7

C(15)-C(20)-C(19)	118.4(3)
C(15)-C(20)-C(21)	123.7(3)
C(19)-C(20)-C(21)	117.9(3)
C(20)-C(21)-C(1)	112.5(3)
C(20)-C(21)-H(21A)	109.1
C(1)-C(21)-H(21A)	109.1
C(20)-C(21)-H(21B)	109.1
C(1)-C(21)-H(21B)	109.1
H(21A)-C(21)-H(21B)	107.8
O(1)-C(22)-H(22A)	109.5
O(1)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
O(1)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
O(2)-C(23)-H(23A)	109.5
O(2)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
O(2)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
O(3)-C(24)-H(24A)	109.5
O(3)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
O(3)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(25)-O(4)-H(4)	109.5
O(4)-C(25)-H(25A)	109.5
O(4)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
O(4)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å2x 103) for JimStuff. The anisotropic displacement factor exponent takes the form: -2□2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	31(1)	23(1)	39(2)	9(1)	0(1)	2(1)
O(2)	31(1)	32(1)	30(2)	0(1)	5(1)	-5(1)
O(3)	37(2)	25(1)	28(2)	-3(1)	-7(1)	-1(1)
N(1)	28(2)	28(2)	27(2)	-1(2)	-6(2)	0(1)
N(2)	36(2)	28(2)	33(2)	3(2)	-2(2)	-4(2)
N(3)	35(2)	31(2)	34(2)	-9(2)	4(2)	-2(2)
C(1)	21(2)	24(2)	17(2)	2(2)	8(2)	2(2)
C(2)	23(2)	26(2)	21(2)	-1(2)	8(2)	-2(2)
C(3)	18(2)	32(2)	20(2)	0(2)	5(2)	2(2)
C(4)	23(2)	21(2)	25(2)	6(2)	6(2)	4(2)
C(5)	26(2)	21(2)	30(2)	-1(2)	8(2)	-2(2)
C(6)	25(2)	22(2)	17(2)	-2(2)	4(2)	2(2)
C(7)	29(2)	25(2)	26(2)	-6(2)	0(2)	-1(2)
C(8)	26(2)	24(2)	21(2)	-6(2)	-7(2)	-5(2)
C(9)	33(2)	24(2)	27(2)	-11(2)	-5(2)	-3(2)
C(10)	29(2)	25(2)	22(2)	-6(2)	-3(2)	-7(2)
C(11)	26(2)	29(2)	20(2)	-4(2)	2(2)	-10(2)
C(12)	25(2)	24(2)	25(2)	-4(2)	-6(2)	0(2)
C(13)	20(2)	30(2)	16(2)	-2(2)	-6(2)	-7(2)
C(14)	21(2)	30(2)	22(2)	1(2)	-2(2)	-2(2)
C(15)	28(2)	22(2)	14(2)	2(2)	-3(2)	0(2)
C(16)	24(2)	24(2)	21(2)	3(2)	-1(2)	-2(2)
C(17)	35(2)	22(2)	19(2)	1(2)	4(2)	3(2)
C(18)	35(2)	19(2)	16(2)	-1(2)	-5(2)	0(2)
C(19)	22(2)	25(2)	24(2)	8(2)	-2(2)	-4(2)
C(20)	26(2)	20(2)	16(2)	4(2)	1(2)	-2(2)
C(21)	26(2)	31(2)	23(2)	1(2)	3(2)	-6(2)
C(22)	34(2)	30(2)	48(3)	10(2)	6(2)	2(2)

C(23)	23(2)	50(2)	28(2)	-2(2)	1(2)	-4(2)
C(24)	38(2)	30(2)	41(3)	-11(2)	-3(2)	-8(2)
O(4)	36(2)	37(2)	57(2)	-12(2)	-13(2)	8(1)
C(25)	39(2)	45(3)	67(3)	1(3)	-13(3)	8(2)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3) for JimStuff.

	x	y	z	U(eq)
H(1A)	7473(8)	1029(5)	7630(50)	34
H(1B)	7452(8)	1346(3)	6980(60)	34
H(2A)	5754(6)	423(8)	7210(50)	39
H(2B)	6035(5)	281(7)	6350(70)	39
H(3A)	6103(6)	2267(8)	7830(50)	40
H(3B)	5833(4)	2120(7)	6790(70)	40
H(2)	7164	1506	2733	28
H(5)	6828	560	2018	31
H(7A)	6473	1023	-2903	32
H(7B)	6525	689	-2058	32
H(9)	6288	486	2151	34
H(12)	5653	1265	2587	30
H(14A)	6193	1372	-2696	29
H(14B)	5884	1487	-1577	29
H(16)	5850	1789	2659	28
H(19)	6846	1944	2455	28
H(21A)	6897	1633	-1670	32
H(21B)	6632	1431	-2703	32
H(22A)	7131	236	4185	56
H(22B)	6922	359	6668	56
H(22C)	7231	221	7496	56

H(23A)	5222	1126	4489	51
H(23B)	5430	1238	7034	51
H(23C)	5161	1028	7755	51
H(24A)	6954	2387	4390	54
H(24B)	6976	2144	6864	54
H(24C)	6929	2479	7718	54
H(4)	5755	79	2857	65
H(25A)	5341	42	-1071	76
H(25B)	5411	314	972	76
H(25C)	5250	34	2269	76

Table 6. Torsion angles [°] for JimStuff.

C(6)-C(1)-C(2)-C(3)	-1.0(5)
C(21)-C(1)-C(2)-C(3)	178.6(3)
C(1)-C(2)-C(3)-C(4)	2.4(5)
C(1)-C(2)-C(3)-N(1)	-179.7(3)
C(22)-O(1)-C(4)-C(5)	-11.4(5)
C(22)-O(1)-C(4)-C(3)	166.9(3)
C(2)-C(3)-C(4)-C(5)	-2.0(5)
N(1)-C(3)-C(4)-C(5)	-179.9(3)
C(2)-C(3)-C(4)-O(1)	179.6(3)
N(1)-C(3)-C(4)-O(1)	1.7(5)
O(1)-C(4)-C(5)-C(6)	178.5(3)
C(3)-C(4)-C(5)-C(6)	0.3(5)
C(2)-C(1)-C(6)-C(5)	-0.8(5)
C(21)-C(1)-C(6)-C(5)	179.6(3)
C(2)-C(1)-C(6)-C(7)	174.4(3)
C(21)-C(1)-C(6)-C(7)	-5.2(5)
C(4)-C(5)-C(6)-C(1)	1.2(5)
C(4)-C(5)-C(6)-C(7)	-174.3(3)
C(1)-C(6)-C(7)-C(8)	-92.1(4)
C(5)-C(6)-C(7)-C(8)	83.1(4)
C(6)-C(7)-C(8)-C(9)	-82.2(4)
C(6)-C(7)-C(8)-C(13)	94.8(4)

C(13)-C(8)-C(9)-C(10)	0.0(5)
C(7)-C(8)-C(9)-C(10)	177.1(3)
C(8)-C(9)-C(10)-C(11)	1.3(5)
C(8)-C(9)-C(10)-N(2)	179.6(3)
C(23)-O(2)-C(11)-C(12)	-7.6(5)
C(23)-O(2)-C(11)-C(10)	173.1(3)
C(9)-C(10)-C(11)-O(2)	177.9(3)
N(2)-C(10)-C(11)-O(2)	-0.4(5)
C(9)-C(10)-C(11)-C(12)	-1.4(5)
N(2)-C(10)-C(11)-C(12)	-179.7(3)
O(2)-C(11)-C(12)-C(13)	-179.0(3)
C(10)-C(11)-C(12)-C(13)	0.3(5)
C(9)-C(8)-C(13)-C(12)	-1.1(5)
C(7)-C(8)-C(13)-C(12)	-178.1(3)
C(9)-C(8)-C(13)-C(14)	177.0(3)
C(7)-C(8)-C(13)-C(14)	0.0(5)
C(11)-C(12)-C(13)-C(8)	1.0(5)
C(11)-C(12)-C(13)-C(14)	-177.2(3)
C(8)-C(13)-C(14)-C(15)	-94.9(4)
C(12)-C(13)-C(14)-C(15)	83.2(4)
C(13)-C(14)-C(15)-C(20)	94.6(4)
C(13)-C(14)-C(15)-C(16)	-85.3(4)
C(20)-C(15)-C(16)-C(17)	-1.9(5)
C(14)-C(15)-C(16)-C(17)	178.1(3)
C(15)-C(16)-C(17)-C(18)	2.3(5)
C(15)-C(16)-C(17)-N(3)	-179.4(3)
C(24)-O(3)-C(18)-C(19)	-3.6(5)
C(24)-O(3)-C(18)-C(17)	175.8(3)
C(16)-C(17)-C(18)-C(19)	-0.7(5)
N(3)-C(17)-C(18)-C(19)	-179.1(3)
C(16)-C(17)-C(18)-O(3)	179.9(3)
N(3)-C(17)-C(18)-O(3)	1.5(5)
O(3)-C(18)-C(19)-C(20)	178.1(3)
C(17)-C(18)-C(19)-C(20)	-1.2(5)
C(16)-C(15)-C(20)-C(19)	-0.1(5)
C(14)-C(15)-C(20)-C(19)	179.9(3)

C(16)-C(15)-C(20)-C(21)	177.5(3)
C(14)-C(15)-C(20)-C(21)	-2.4(5)
C(18)-C(19)-C(20)-C(15)	1.6(5)
C(18)-C(19)-C(20)-C(21)	-176.1(3)
C(15)-C(20)-C(21)-C(1)	-92.7(4)
C(19)-C(20)-C(21)-C(1)	85.0(4)
C(6)-C(1)-C(21)-C(20)	99.7(4)
C(2)-C(1)-C(21)-C(20)	-79.9(4)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for JimStuff [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1B)...O(4)#1	0.902(10)	2.420(11)	3.322(4)	177(3)
N(2)-H(2B)...N(1)#2	0.904(10)	2.322(16)	3.189(5)	161(3)
O(4)-H(4)...N(2)	0.84	1.98	2.802(4)	167.6

Symmetry transformations used to generate equivalent atoms:

#1 y+3/4,-x+3/4,z+3/4 #2 -y+3/4,x-3/4,z+1/4

^{129}Xe Magnetic Resonance Spectroscopy

Representative Procedure:

^{129}Xe gas was polarized to 39% polarization using a Xemed polarizer utilizing spin exchange optical pumping (SEOP). Polarized ^{129}Xe was stored in a tetlar bag and kept inside the magnet bore to minimize depolarization. The amino-CTV (**5**) was dissolved in dimethyl sulfoxide (DMSO) within a 5 mL syringe to create a 50 mM solution. 1 mL of hyperpolarized ^{129}Xe was introduced into the syringe and vigorously shaken within the magnet bore. All ambient air was removed from the syringe and ^{129}Xe delivery tubes prior to the introduction of polarized ^{129}Xe into the syringe. The syringe was placed inside a custom built quadrature birdcage RF coil within the magnet bore. A Phillips Achieve 3T clinical MRI scanner was used to obtain NMR spectra utilizing the manufacturer's control software. A RF pulse sequence consisting of 10-5 ms pulses followed by 5-5 ms pulses with a 5 ms pulse interval was applied, and an MR spectrum was collected. MR spectra were processed using MATLAB (v. 8.1.0.604) software.

Computations

All quantum chemical computations were done using Spartan 10 software.[1] Structures were minimized using the Hartree-Fock method using the 3-21G basis set. No imaginary frequencies were found. This is the only basis set in Spartan 10 with basis functions for Xe.

[1] Spartan '10; Wavefunction, Inc.: Irvine, CA, **2010**. Version 1.1.0.

APPENDIX 2

Manuscript 2 Supporting Information

Substituent Effects on the HyperCEST Efficiency of Bowl-Shaped Molecular Probes for Xenon-129 NMR

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Supporting Information

Synthetic Methods.

All reagents were commercially available and used without further purification, unless otherwise stated. All reactions were carried out in oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Column chromatography was performed using a BIOTAGE® ISOLERA 1 with Biotage® SNAP Ultra high performance flash chromatography cartridges (25 micron spherical silica) and Biotage® SNAP NH functionalized silica gel cartridges (50 micron silica).

Instrumentation:

GC/MS analyses were performed on an Agilent Technologies 6890 GC system fixed with a 5973 mass selective detector. GC/MS Conditions: J & W Scientific DB-1, capillary 25.0m x 200µm x 0.33µm, 1.3 mL/min, 40 °C, hold 0.50 min, 12 °C/min to 320 °C, hold 6.0 min. NMR spectra were acquired with Bruker Avance 300 and 400 MHz spectrometers.

Chemical Synthesis.

Unless otherwise noted all reactions were carried out under normal atmosphere at room temperature.

4-amino-3-methoxy-benzenemethanol (3):

To an oven dried 100 mL RBF with a stir bar, lithium aluminum hydride (27.61 mmol) was added under N_2(g). The vessel was capped and cooled to 0 °C. The $LiAlH_4$ was suspended in anhydrous diethyl ether (37 mL). Methyl-4-amino-3-methoxy-benzoate (5.52 mmol) was dissolved in anhydrous tetrahydrofuran (17 mL) and then added to the RBF over 5 min. The reaction was allowed to warm to room

temperature and stirred for approximately 4 hours, and the reaction progress was monitored via TLC. When the reaction appeared complete by TLC, it was cooled to 0 ^{o}C and quenched using the Fieser method. After stirring for an additional hour, the reaction was vacuum filtered, and the solid was washed with approximately 30 mL of dichloromethane. The filtrate was concentrated via rotary evaporation, and the resulting yellow oil was purified via flash chromatography on a 10 g Ultra SNAP column. The fractions containing the desired compound were combined and dried first via rotary evaporation and subsequently using a V-10 rapid solvent evaporator. 4-amino-3-methoxy-Benzenemethanol (**3**) was obtained in 87% yield.

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4):

A magnetic stir bar and anhydrous pyridine (6.5 mL) were added to a 20 mL scintillation vial containing 4-amino-3-methoxy-benzenemethanol, **3** (725.3 mg, 4.735 mmol). The reaction was cooled to 0 ^{o}C and acetic anhydride (2.7 mL, 28.41 mmol) was added over 5 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched after cooling to 0 ^{o}C. First approximately 2 mL of DI H_2O was added followed by 12M HCl until pH ~1. A white precipitate formed. The precipitate was vacuum filtered and washed with 20 mL of DI H_2O and then dried on the V-10 rapid solvent evaporator. *N*-[4-[(acetyloxy) methyl]-2-methoxyphenyl]-acetamide (**4**) was obtained in an 81% yield.

(±)-3,8,13-triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7):

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide, **4** (704.5 mg, 2.969 mmol), was dissolved in glacial acetic acid (7 mL) and added with a magnetic stir bar to a 50 mL RBF. 60 % (w/w) perchloric acid (14 mL) was added drop wise across 10 min, and the reaction was stirred for 12 hours. DI H_2O (25 mL) was then added, and the reaction was stirred for an additional 15 min. The white precipitate was collected by vacuum filtration through a sintered glass funnel. The precipitate was then washed with 25 mL of additional DI H_2O followed by 25 mL of acetone. The white precipitate was then dried on the V-10 solvent evaporator. (±)-3,8,13-triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene, **7**, was obtained in 91% yield.

(±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5):

The triacetamide (479 mg) was suspended in ethanol (18 mL) in a 100 mL RBF. A 1.5 inch magnetic stir bar was added and then 12M hydrochloric acid (30 mL) was added. The solution was refluxed for 5 hours. A white precipitate formed during that time. The solution was cooled to 0 ^{o}C and vacuum filtered. The precipitate was washed with 3 mL of ethanol, ether and dichloromethane. The white precipitate was then dried on in a 20 mL scintillation vial on the V-10 evaporator. The white precipitate was then dissolved in dichloromethane and washed with a saturated sodium bicarbonate solution followed by DI-H_2O. The triamine was obtained in a 74% yield.

Cyclotriveratrylene (6):

Scandium(III) triflate (64 mg) was added to a 5 mL reaction vessel with a magnetic stir bar which was then sealed and purged with dry nitrogen. 3,4-dimethoxybenzyl alcohol (500 mg) was added then added and acetonitrile (3 mL) and it was heated to 60 ^{o}C in an oil bath overnight. The reaction was then rotovaped to dryness and redissolved in dichloromethane and extracted with DI-H_2O. The dichloromethane was rotovaped to dryness. The product was washed with ethyl acetate yielding the 114 mg (26% yield) of the pure product.

Cyclotricatechylene (9):

Cyclotriveratrylene (6) (146.9 mg) was added to a reaction vial and dissolved in anhydrous dichloromethane (2.6 mL) and stirred under dry nitrogen. A solution of boron tribromide (250.5 mg, 2.0 mL) in dichloromethane was added dropwise under dry nitrogen at 0 ^{o}C and allowed to react for 15 minutes. The round bottom flask was warmed to room temperature and stirred for 10 minutes. The reaction was then refluxed at 40 ^{o}C in an oil bath for 2 hours. The reaction was then cooled to 0 ^{o}C and was quenched by adding 5 mL of DI H_2O. The reaction was vacuum filtered and the crude product was loaded onto silica and run through a 10 g SNAP Ultra column using a hexane/ethyl acetate gradient. 52.5 mg of the pure product was obtained (44% yield).

(±)-Cyclotrianisylene (8):

Phosphorus pentoxide (5.13 g) with a stir bar was added to a 100 mL round bottom flask under dry nitrogen and dissolved in anhydrous dichloromethane (40 mL). 3-

Methoxy benzyl alcohol was added to the stirred mixture over approximately 5 minutes. The mixture was heated to 40 °C for 1 hour and then cooled to 5 °C in an ice water bath. The organic phase was drawn off and the solid was washed with 12 mL of dichloromethane two times. The dichloromethane was removed via rotary evaporation. The residue was taken up in dichloromethane and filtered through a silica gel plug. The filtrate was collected, and the solvent was removed via rotary evaporation, leaving a pale wax. The pale wax was dissolved in approximately 15 mL of ether and sonicated for 20 min and then allowed to rest for 30 minutes to form a white precipitate. 82.6 mg of precipitate was collected via vacuum filtration as the pure product (1% yield).

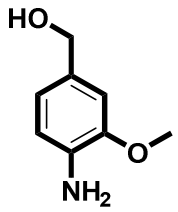
(±)-Cyclotriphenolene (10):

(±)-Cyclotrianisylene (**8**) (146.9 mg) was added to a reaction vial and dissolved in anhydrous dichloromethane (2.6 mL) and stirred under dry nitrogen. A solution of boron tribromide (250.5 mg, 2.0 mL) in dichloromethane was added dropwise under dry nitrogen at 0 °C and allowed to react for 15 minutes. The round bottom flask was warmed to room temperature and stirred for 10 minutes. The reaction was then refluxed at 40 °C in an oil bath for 2 hours. The reaction was then cooled to 0 °C and was quenched by adding 5 mL of DI H_2O. The reaction was vacuum filtered, and the crude product was loaded onto silica and run through a 10 g SNAP Ultra column using a hexane/ethyl acetate gradient. 52.5 mg of the pure product was obtained (44% yield).

Characterization of Compounds:

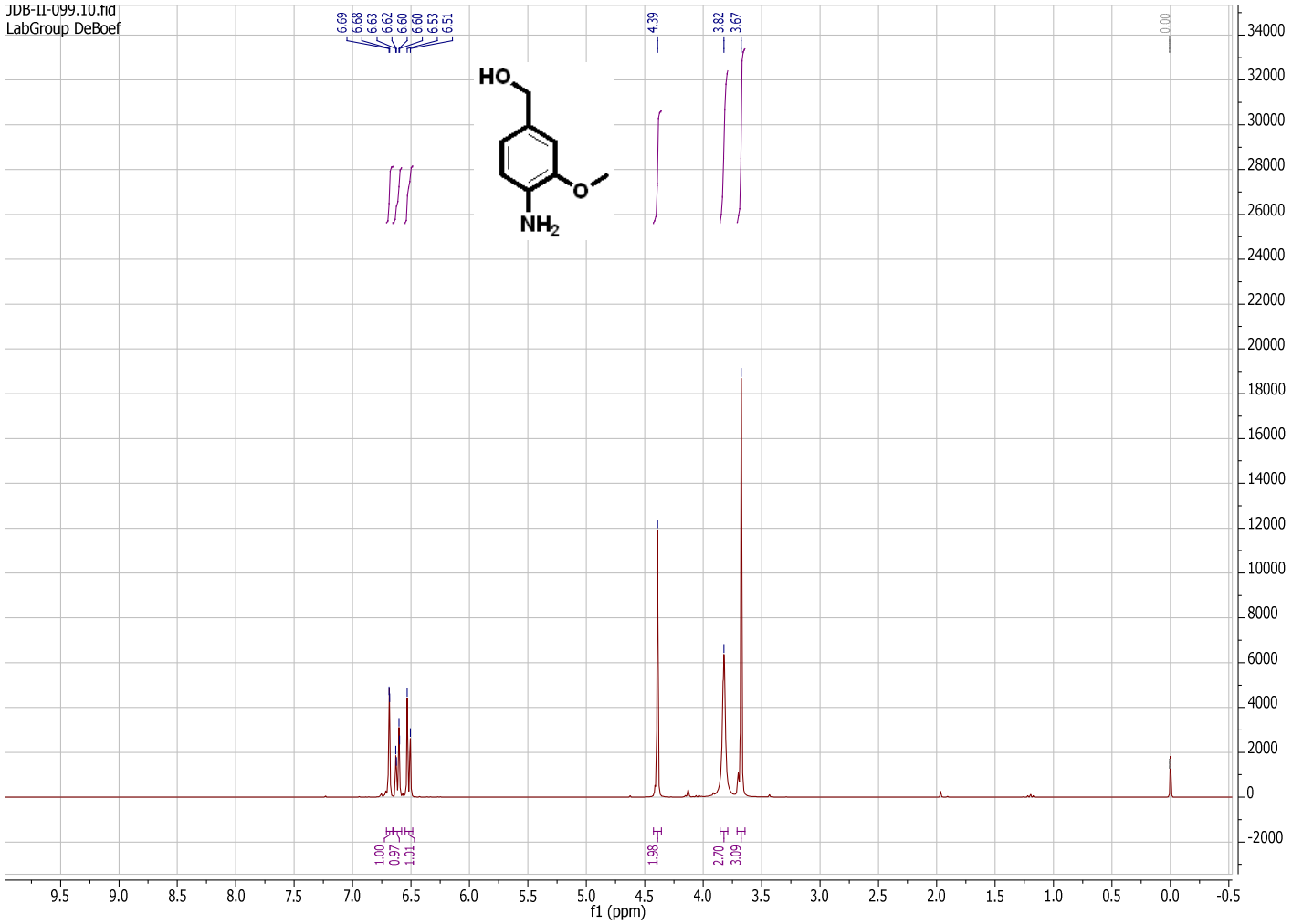
Known compounds were obtained by the procedures above and characterized via NMR spectroscopy; ^{1}H NMR and ^{13}C NMR spectra were provided for each compound, and the relevant reference was cited. All novel compounds obtained have been characterized with ^{1}H NMR, ^{13}C NMR.

4-amino-3-methoxy-benzenemethanol (3)

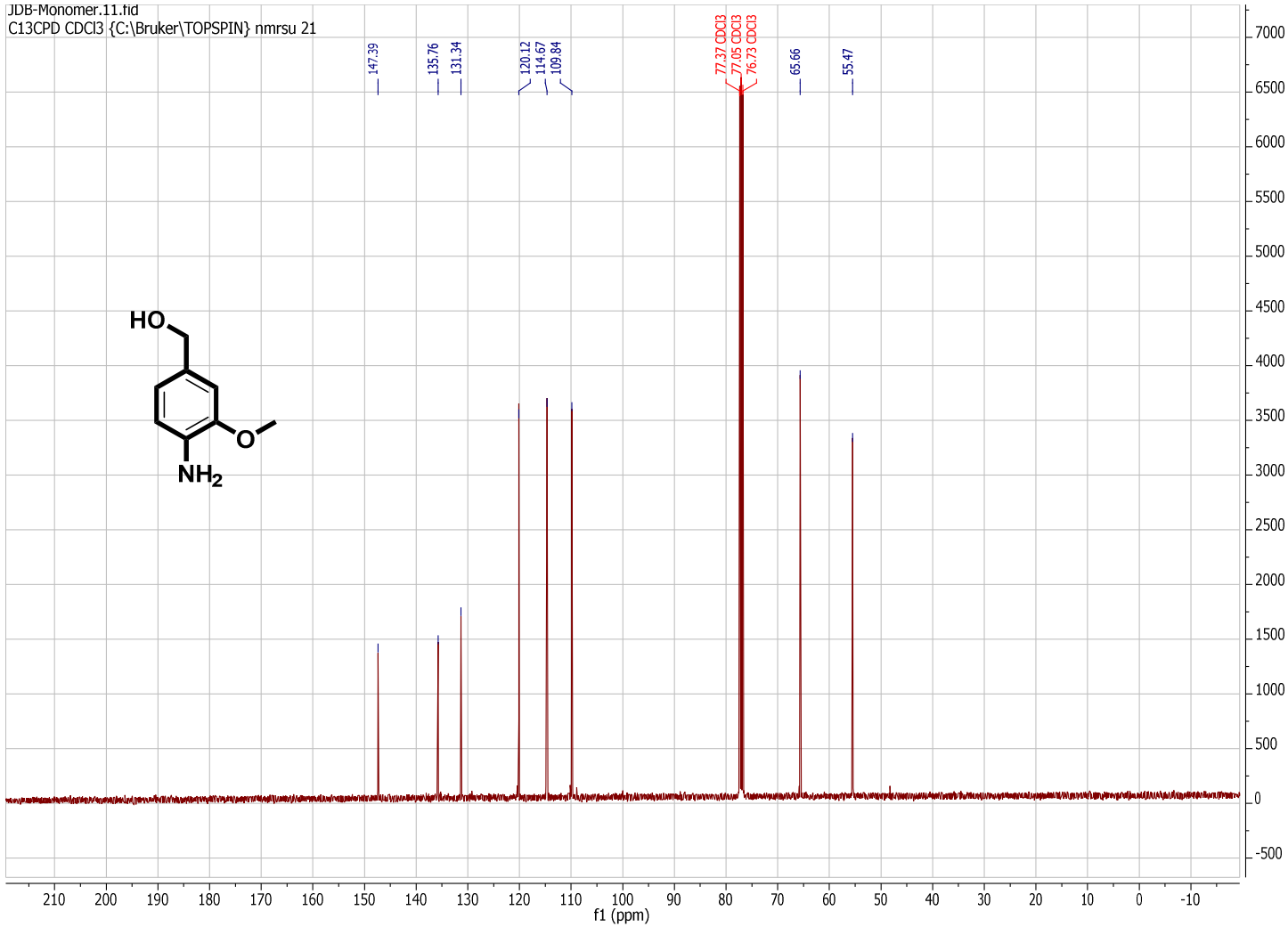


^{1}H NMR (300 MHz, $CDCl_3$)): δ (ppm) 6.69 (d, *J*=1.7 Hz, 1H), 6.61 (dd, *J*=7.8, 1.7 Hz, 1H), 6.52 (d, *J*=7.8 Hz, 1H), 4.39 (s, 2H), 3.82 (br, 3H), 3.67 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.39, 135.76, 131.34, 120.12, 114.67, 109.84, 65.66, 55.47.

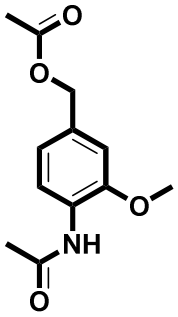


Spectra 6 - ^{1}H NMR 4-amino-3-methoxy-benzenemethanol (3)



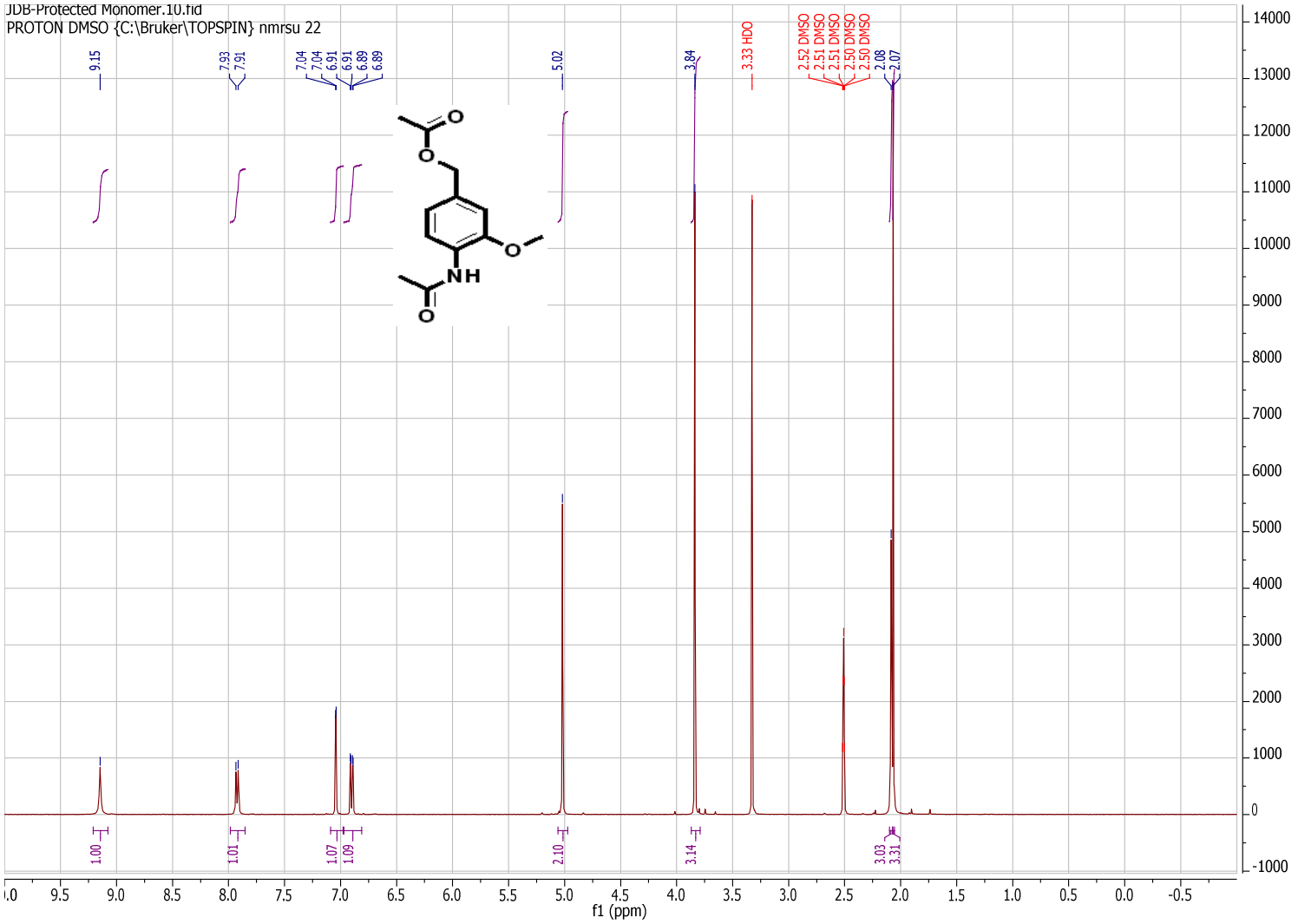
Spectra 7 - ^{13}C NMR of 4-amino-3-methoxy-benzenemethanol (3)

N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4):

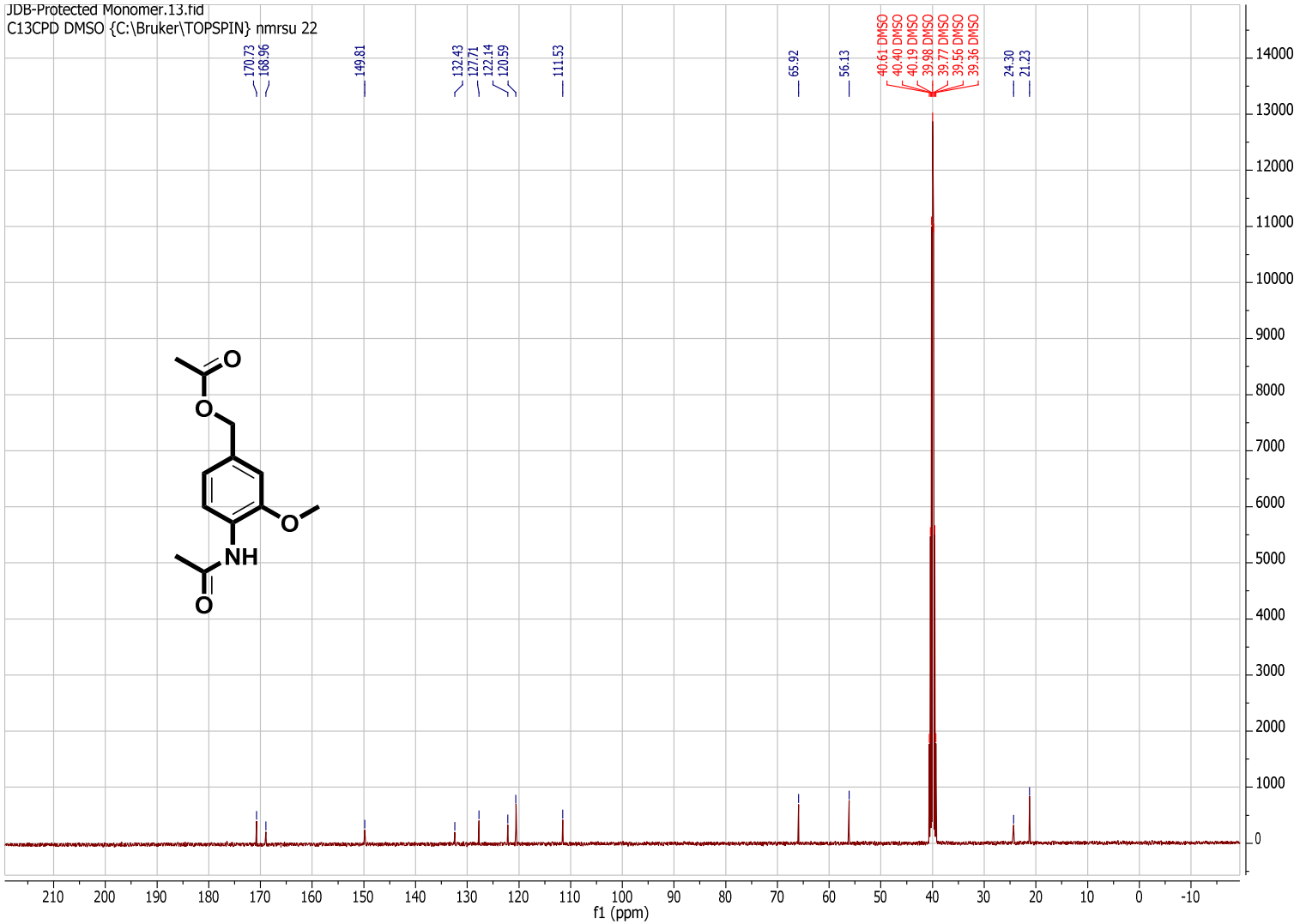


^{1}H NMR(400 MHz, DMSO-d_6): δ (ppm) 9.15 (s, 1H), 7.92 (d, *J*=8.1 Hz, 1H), 7.04 (d, *J*=1.8 Hz, 1H), 6.90 (dd, *J*=8.2, 1.7 Hz, 1H), 5.02 (s, 2H), 3.84 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 170.73, 168.96, 149.81, 132.43, 127.71, 122.14, 120.59, 111.53, 65.92, 56.13, 24.30, 21.23.



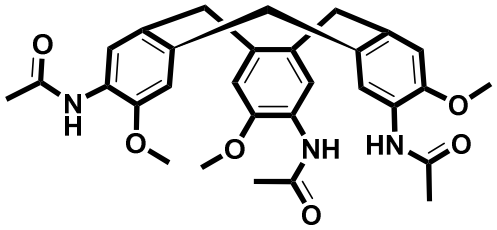
Spectra 8 - ^{1}H NMR of N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4)



Spectra 9 - ^{13}C NMR of N-[4-[(acetyloxy)methyl]-2-methoxyphenyl]-acetamide (4)

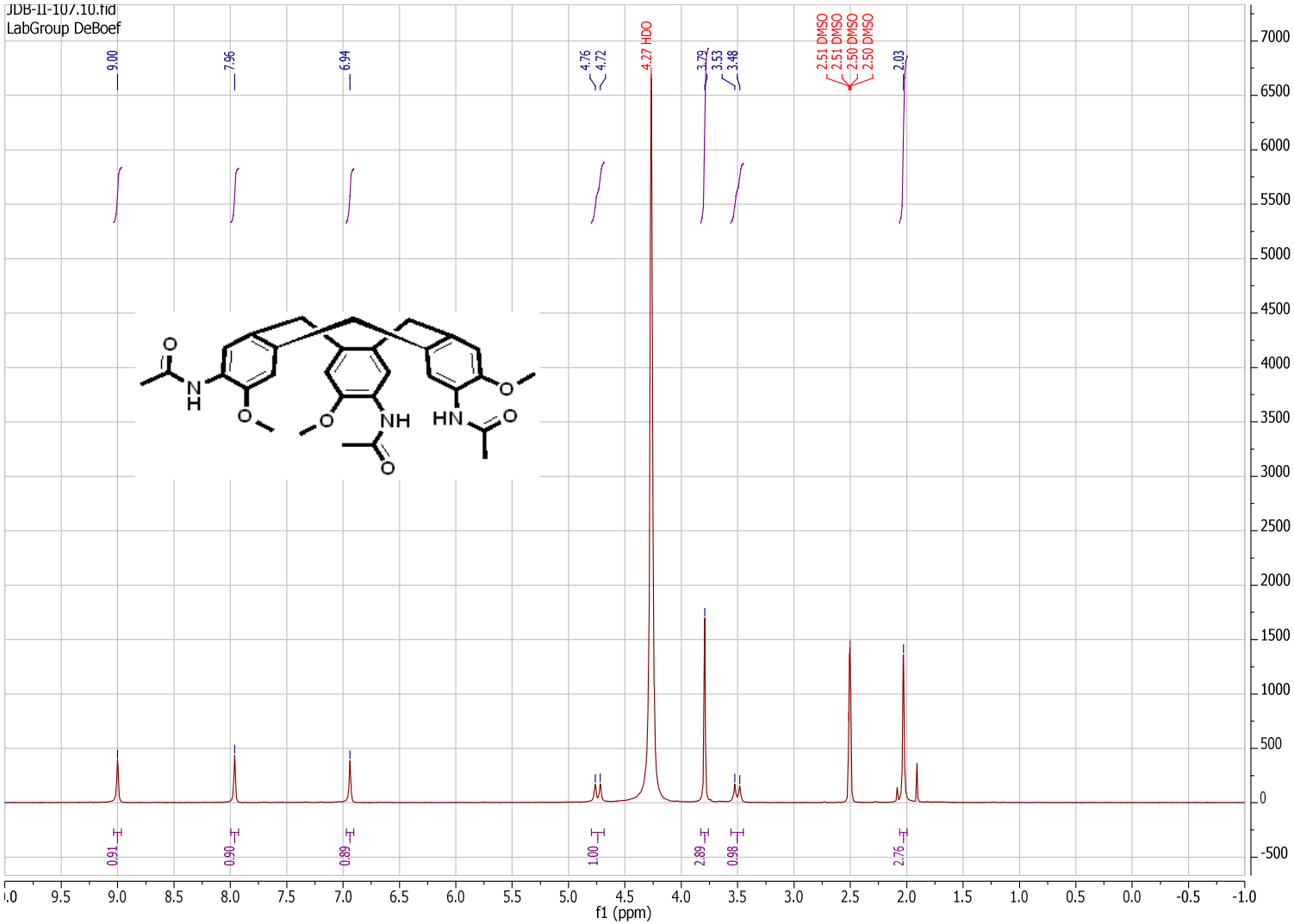
(±)-3,8,13-Triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-

tribenzo[a,d,g]cyclononene (7):

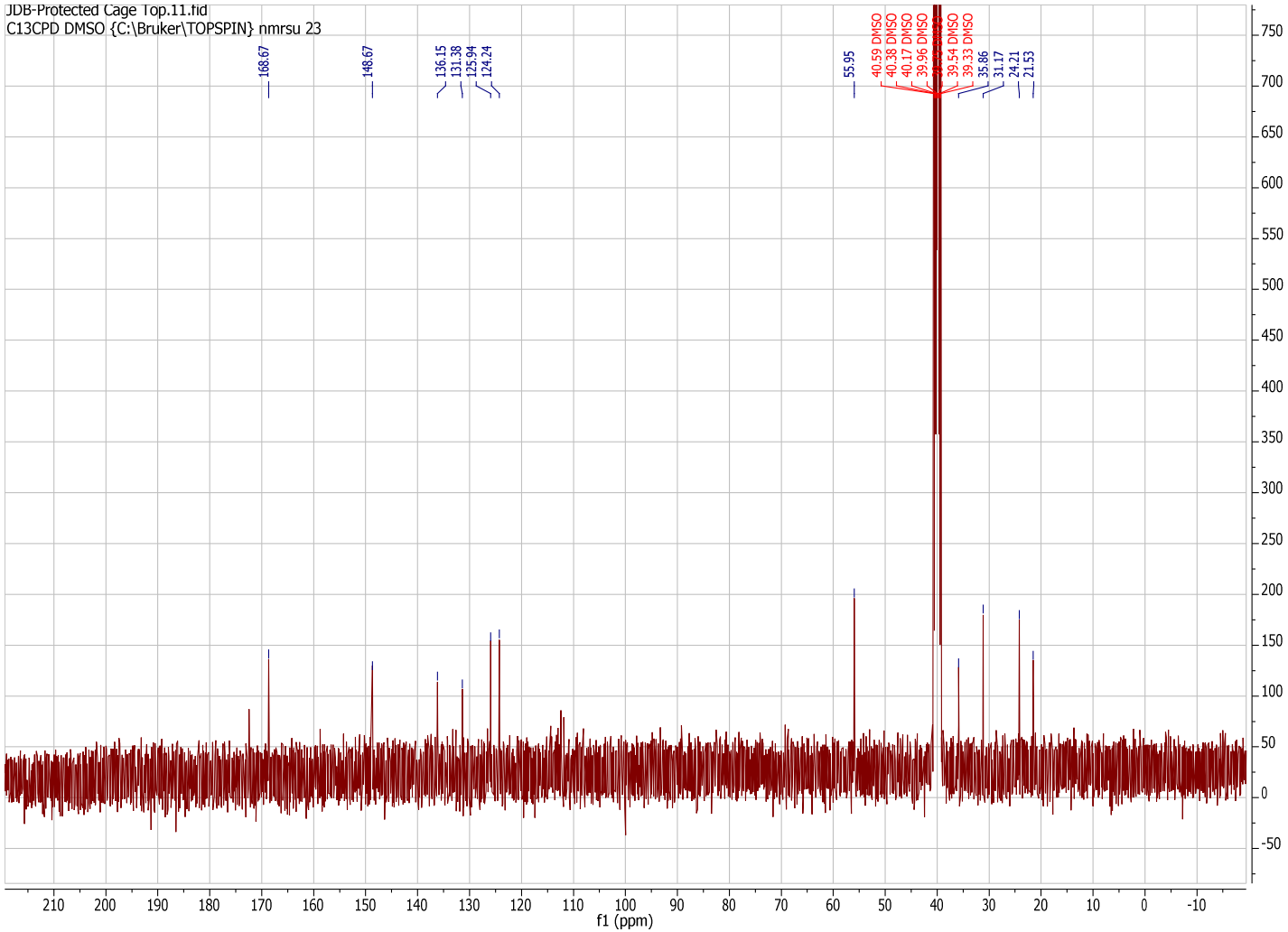


^{1}H NMR(300 MHz, DMSO-d_6): δ (ppm) 9.00 (s, 1H), 7.96 (s, 1H), 6.94 (s, 1H), 4.74 (d, *J*=13.4 Hz, 1H), 3.79 (s, 3H), 3.50 (d, *J*=13.3 Hz, 1H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.67, 148.67, 136.15, 131.38, 125.94, 124.24, 55.95, 35.86, 31.17, 24.21, 21.53.



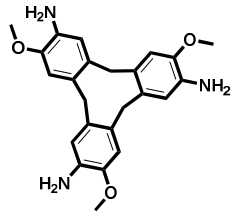
Spectra 10 - ^{1}H NMR of (±)-3,8,13-Triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7)



Spectra 11 - ^{13}C NMR of (±)-3,8,13-Triacetamido-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (7)

(±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-

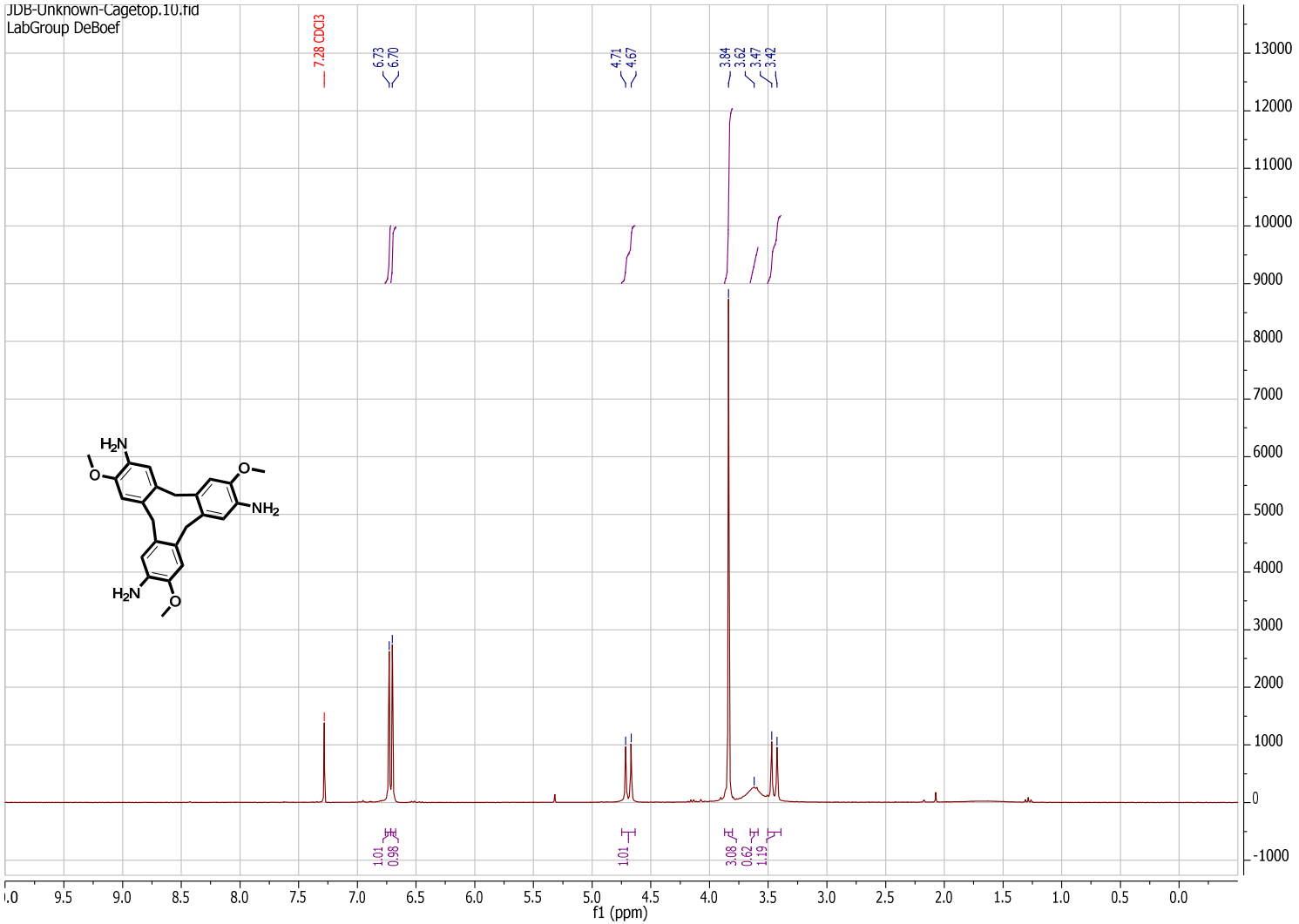
tribenzo[a,d,g]cyclononene (5):



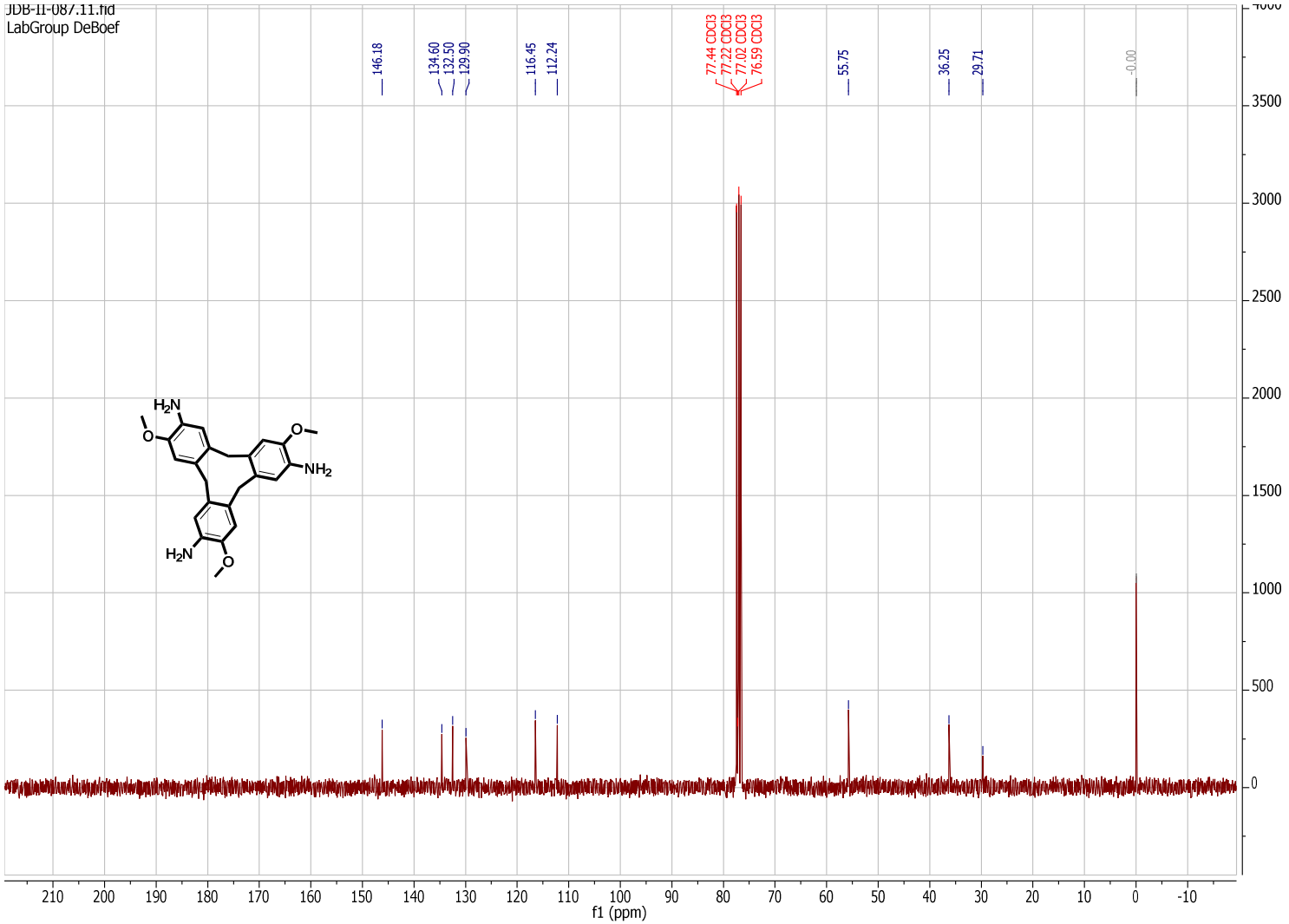
^{1}H NMR(Chloroform-d, 300 MHz): δ (ppm) 6.73 (s, 1H), 6.70 (s, 1H), 4.69 (d, *J*=13.7 Hz, 1H), 3.84 (s, 3H), 3.62 (br, 2H, exchangeable protons), 3.45 (d, *J*=13.7 Hz, 1H).

^{13}C NMR (75 MHz, CDCl3) δ 146.18, 134.60, 132.50, 129.90, 116.45, 112.24, 55.7, 36.25, 29.71.

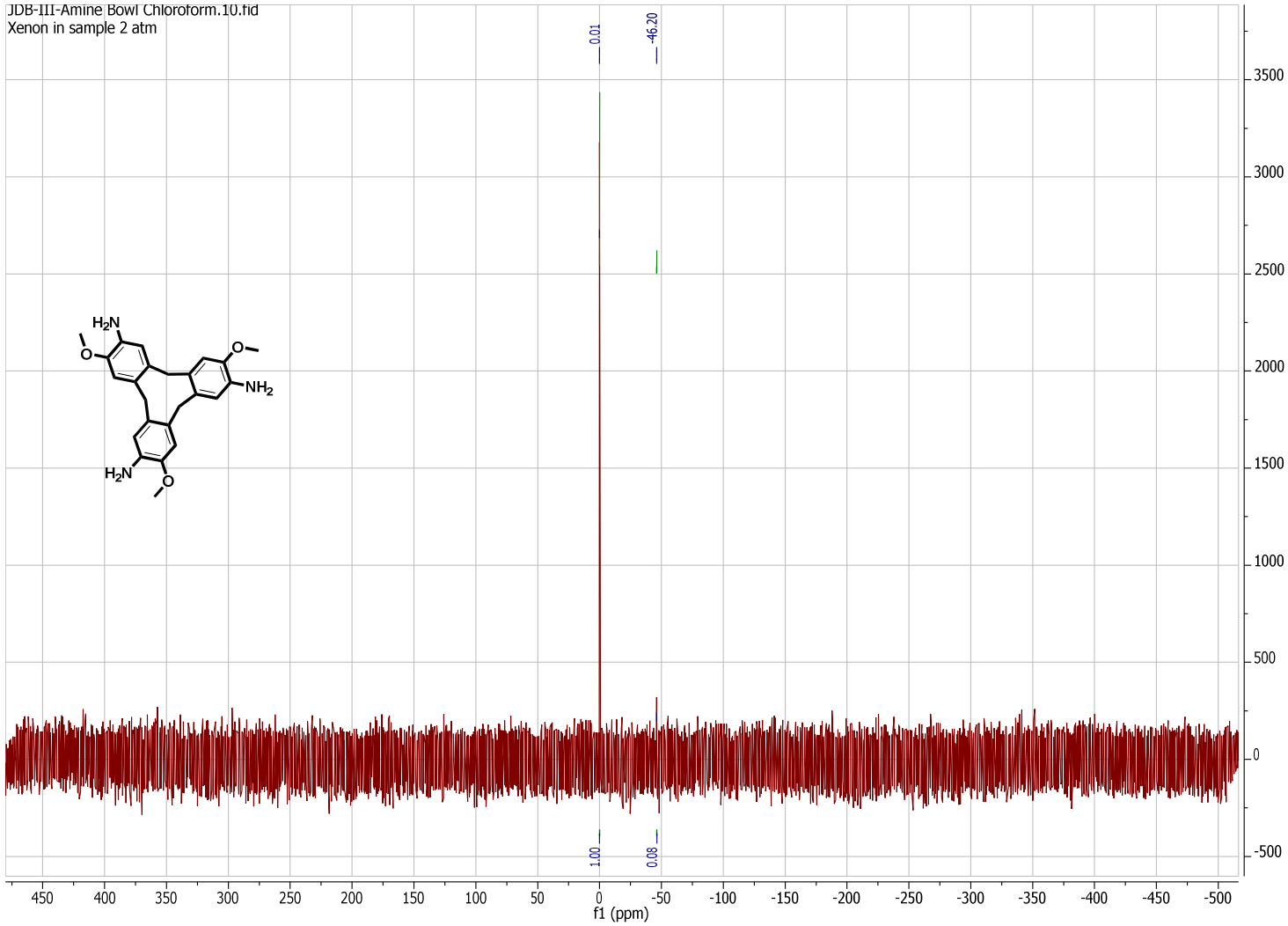
^{129}Xe NMR (111 MHz, $CDCl_3$) δ 0.01 (dissolved, unbound ^{129}Xe), -46.20 (129Xe@**5**).



Spectra 12 - ^{1}H NMR of (±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5)

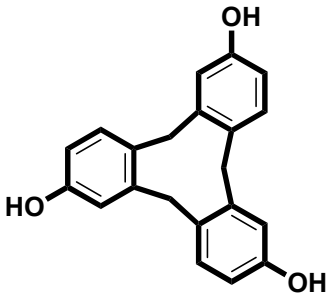


Spectra 13- ^{13}C NMR of (±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5)



Spectra 14 - ^{129}Xe NMR of (±)-3,8,13-triamino-2,7,12-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene (5).

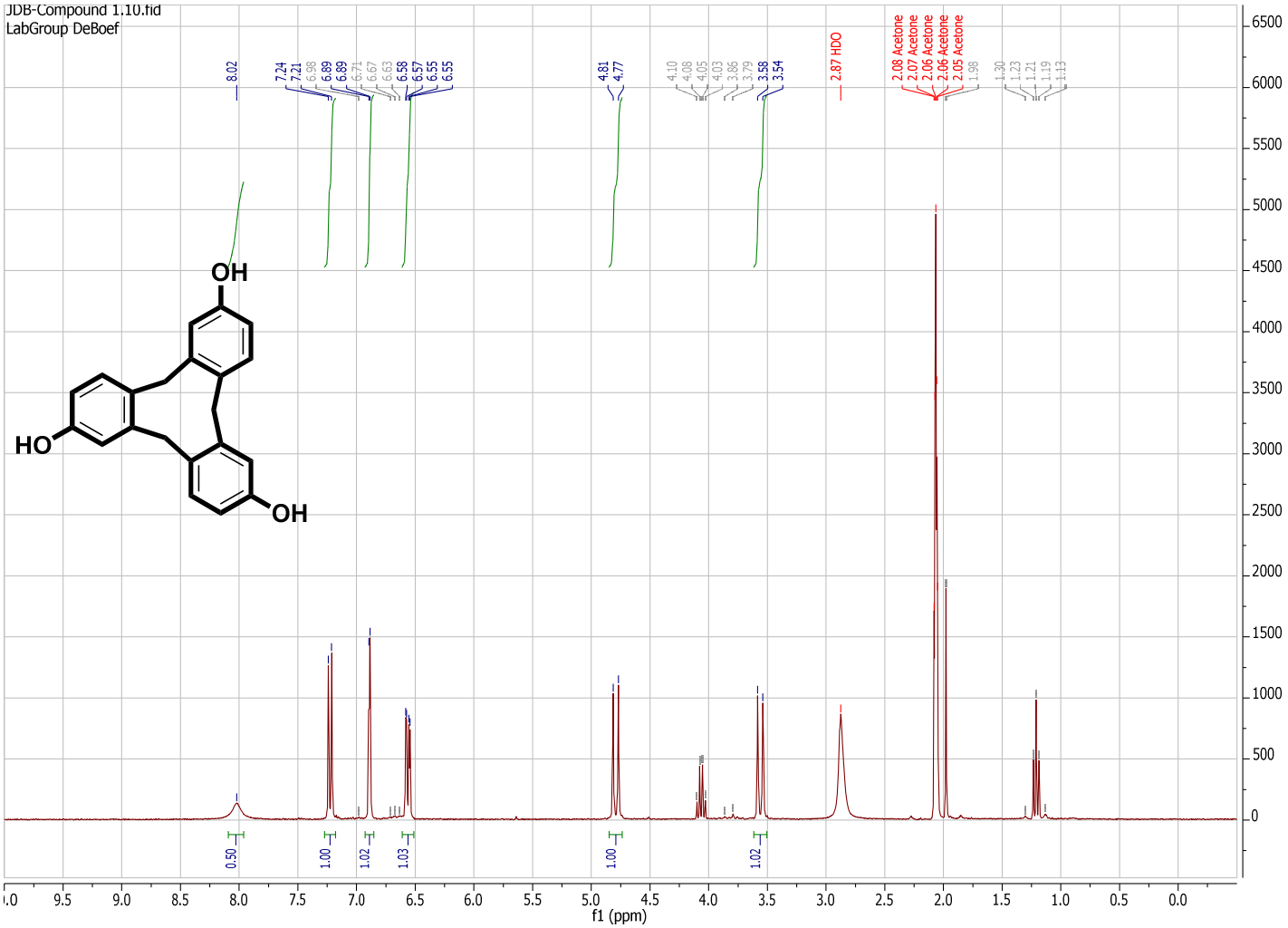
(±)-Cyclotriphenolene (10):



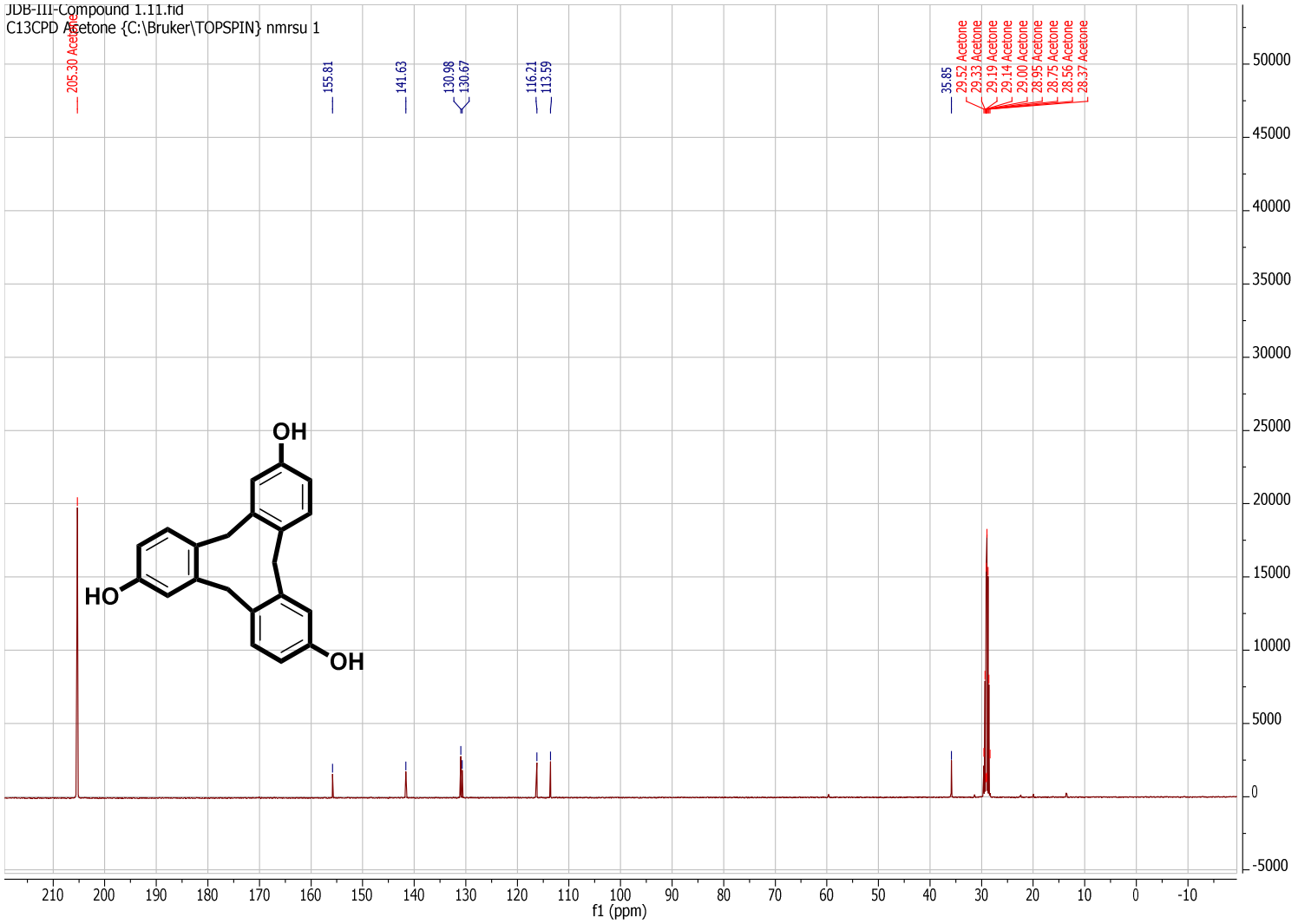
^{1}H NMR(300 MHz, Acetone-d_6): δ (ppm) 8.02 (broad, 1H), 7.23 (d, *J*=8.3 Hz, 1H), 6.89 (d, *J*=2.6 Hz, 1H), 6.56 (dd, *J*=8.3, 2.7 Hz, 1H), 4.79 (d, *J*=13.4 Hz, 1H), 3.56 (d, *J*=13.4 Hz, 1H)

^{13}C NMR (101 MHz, Acetone-d_6) δ 155.81, 141.63, 130.98, 130.67, 116.21, 113.59, 35.85.

.

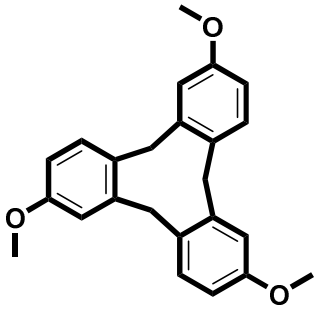


Spectra 15 - ^{1}H NMR of (±)-Cyclotriphenolene (10)



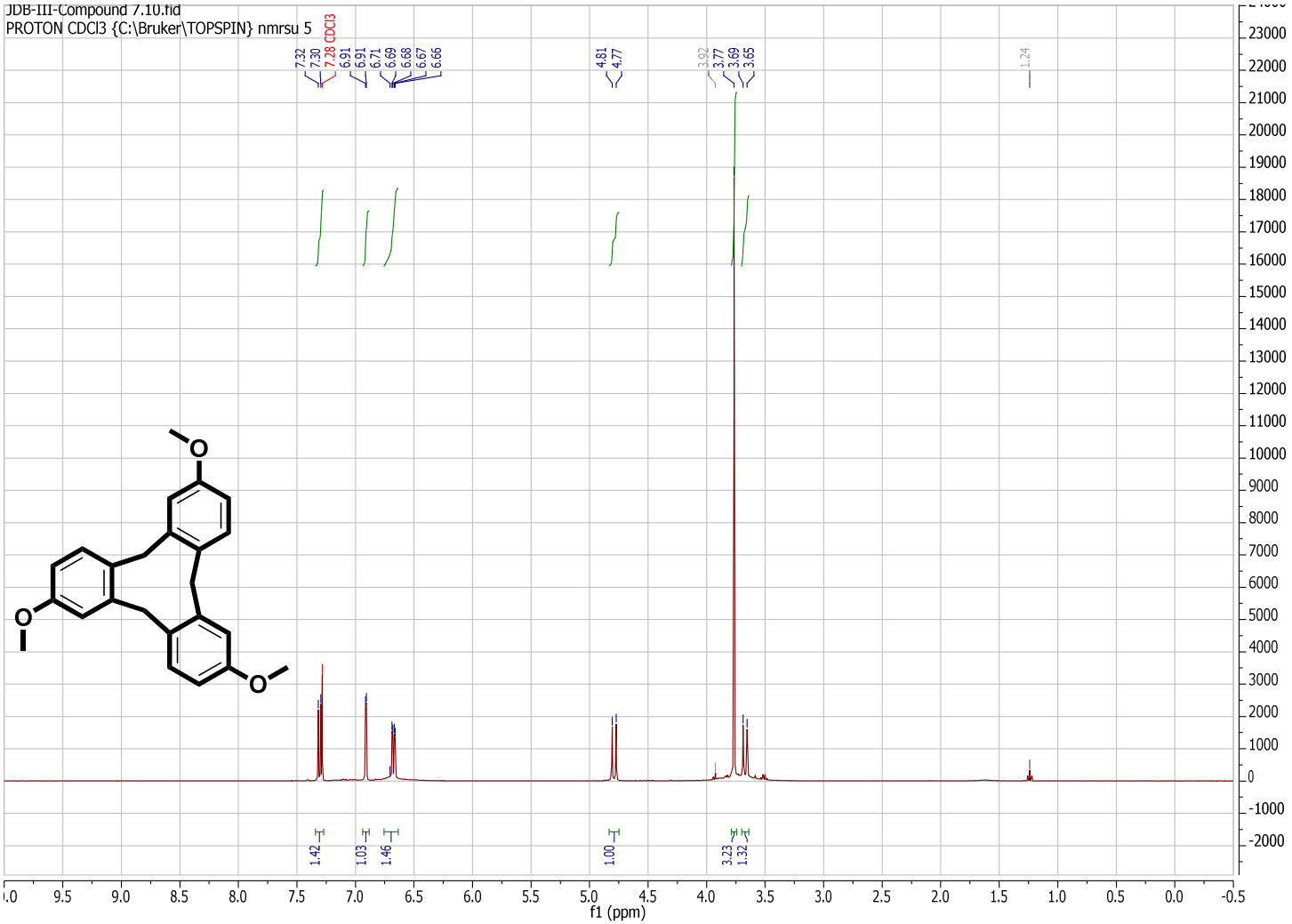
Spectra 16 - ^{13}C NMR of (±)-Cyclotriphenolene (10)

(±)-Cyclotrianisylene (8):

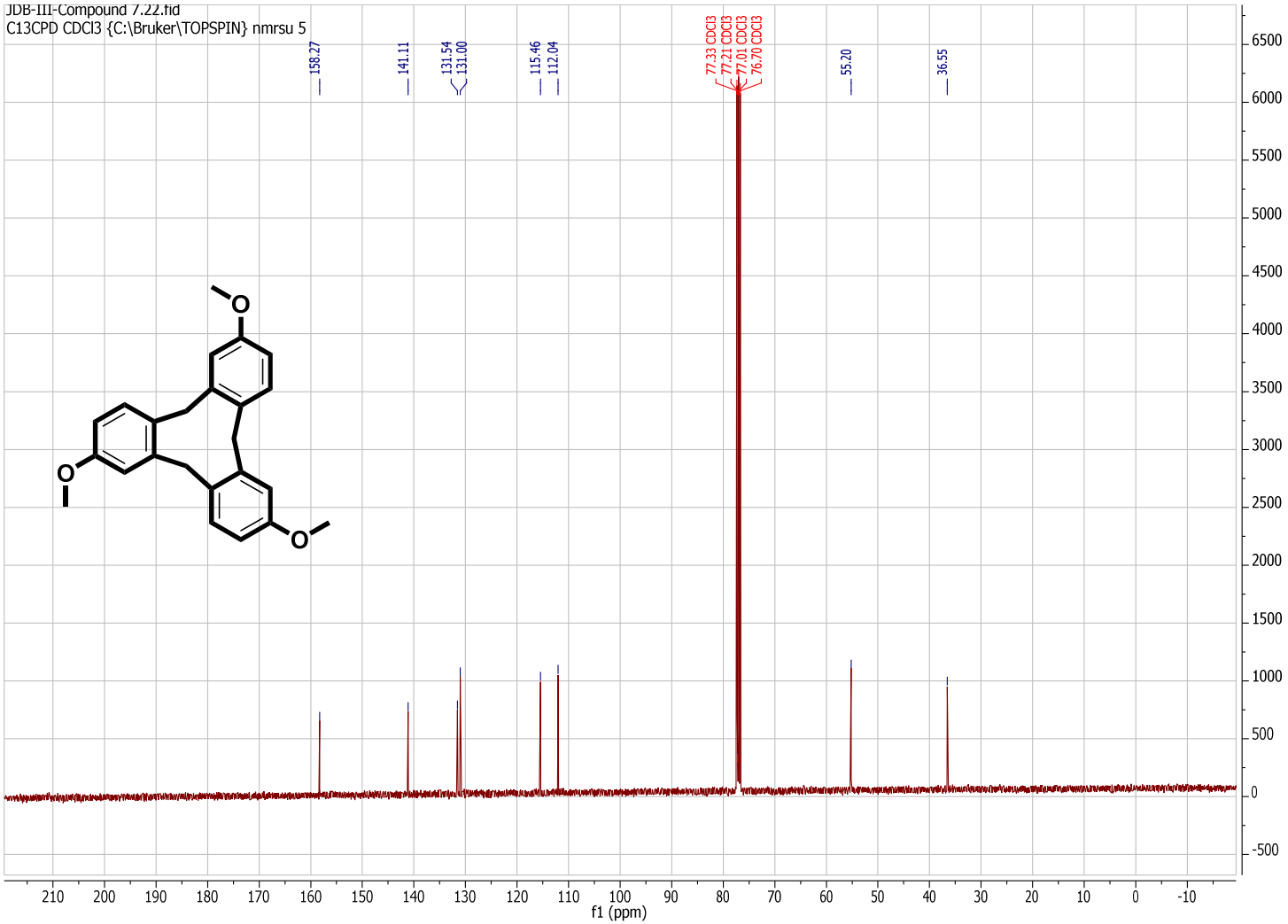


^{1}H NMR(400 MHz, $CDCl_3$): δ (ppm) 7.31 (d, *J*=8.5 Hz, 1H), 6.91 (d, *J*=2.7 Hz, 1H), 6.67 (dd, *J*=8.5, 2.8 Hz, 1H), 4.79 (d, *J*=13.6 Hz, 1H), 3.77 (s, 3H), 3.67 (d, *J*=13.6 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.27, 141.11, 131.54, 131.00, 115.46, 112.04, 55.20, 36.55.

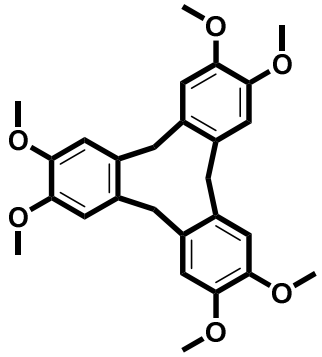


Spectra 17 – ^{1}H NMR of (±)-Cyclotrianisylene (8)



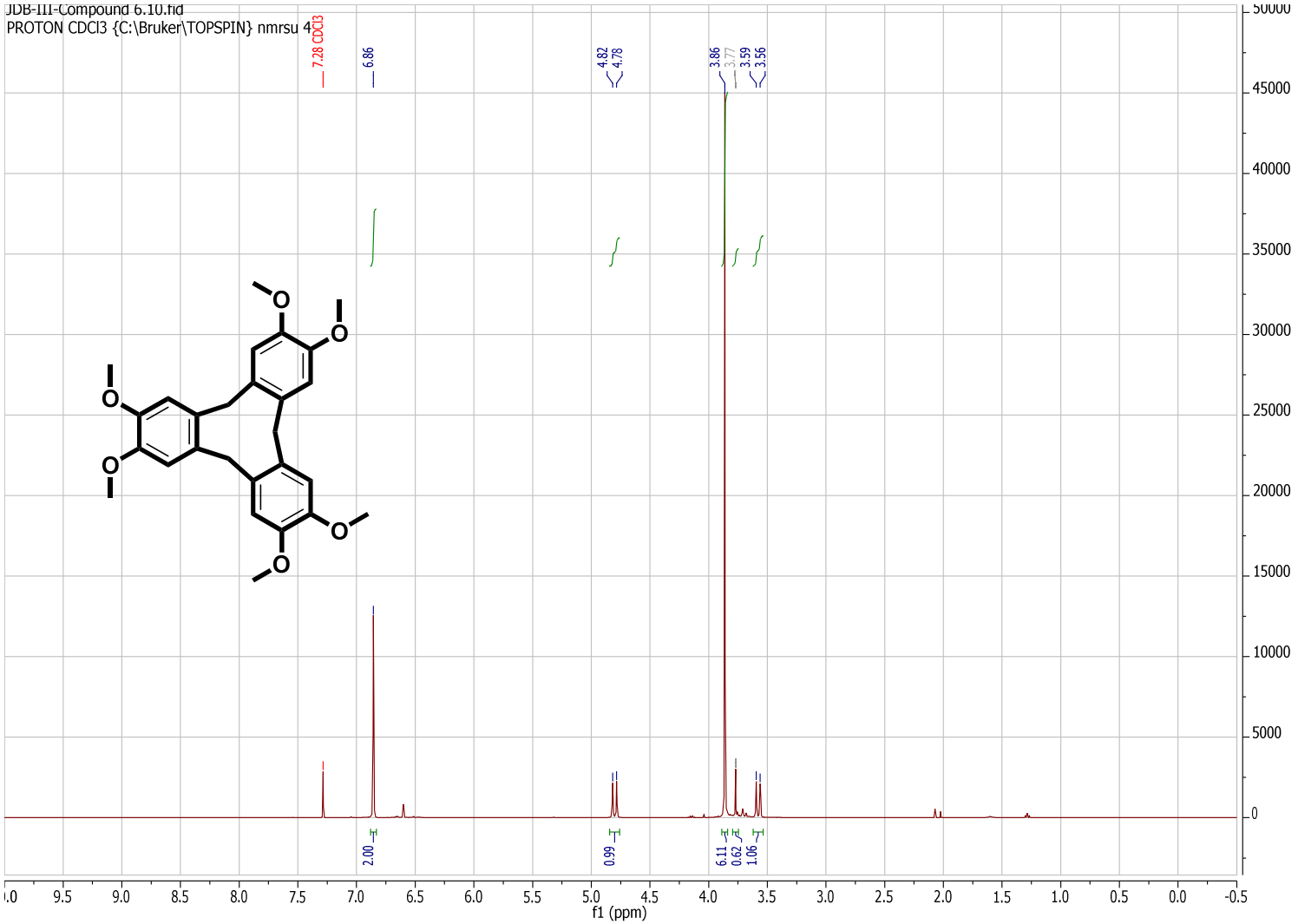
Spectra 18 - ^{13}C NMR of (±)-Cyclotrianisylene (8)

Cyclotriveratrylene (6):

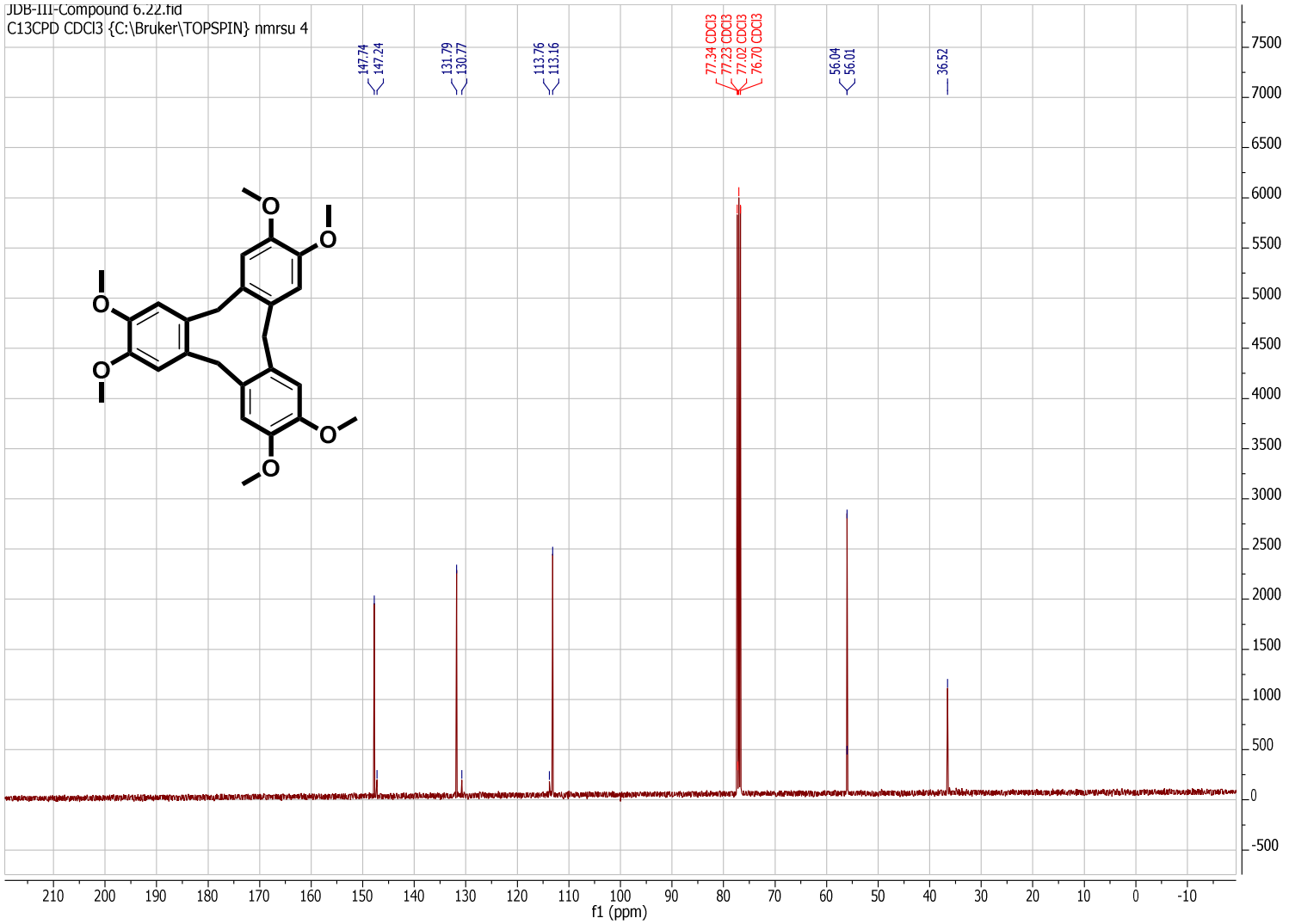


^{1}H NMR(400 MHz, $CDCl_3$,): δ (ppm) 6.86 (s, 2H), 4.80 (d, *J*=13.8 Hz, 1H), 3.86 (s, 6H), 3.58 (d, *J*=13.8 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.74, 147.24, 131.79, 130.77, 113.76, 113.16, 56.04, 56.01, 36.52.

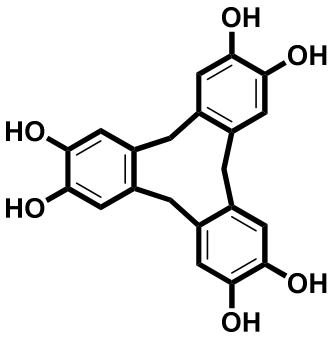


Spectra 19 – ^{1}H NMR of Cyclotriveratrylene (6)



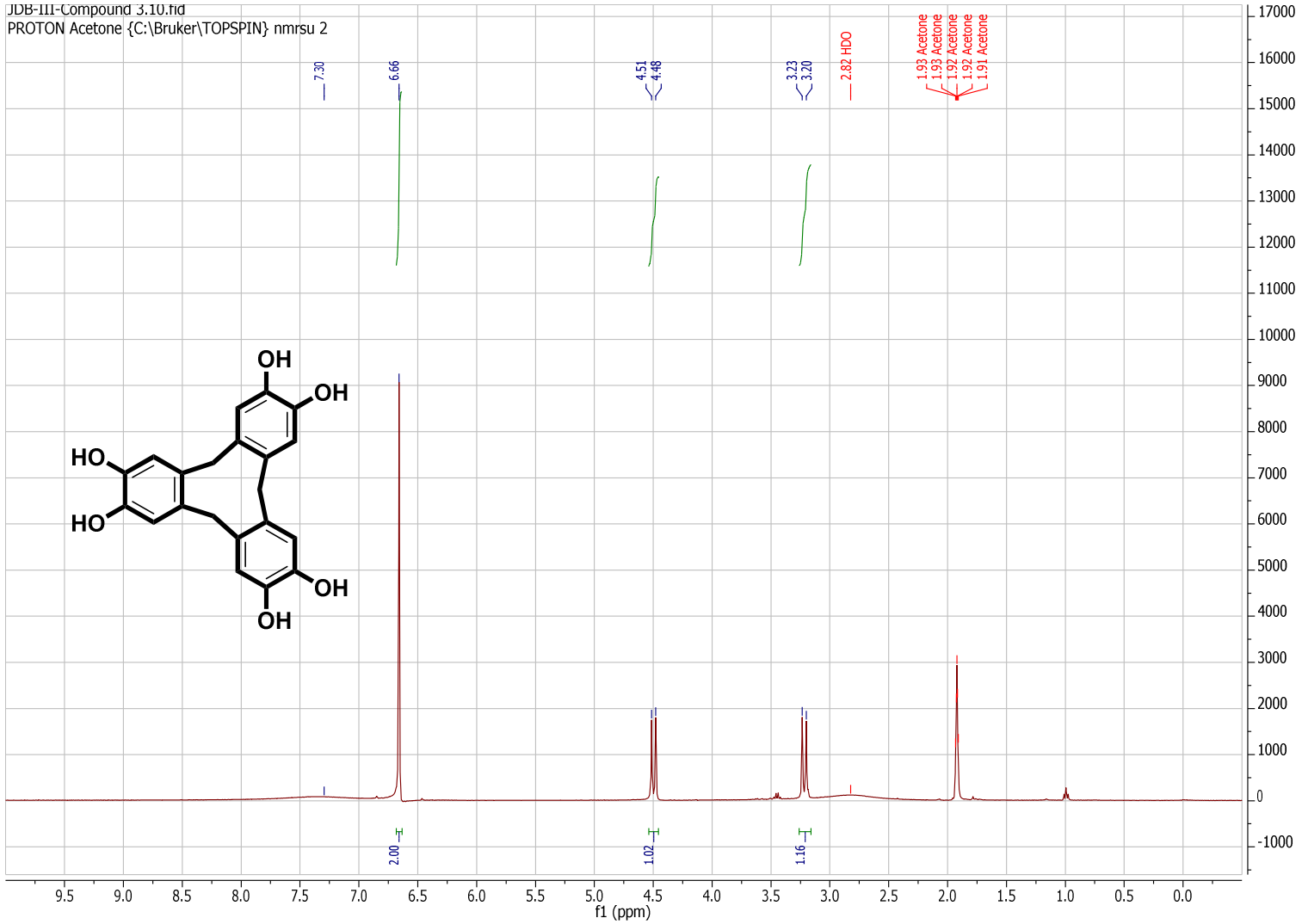
Spectra 20 – ^{13}C NMR of Cyclotriveratrylene (6)

Cyclotricatechylene (9):

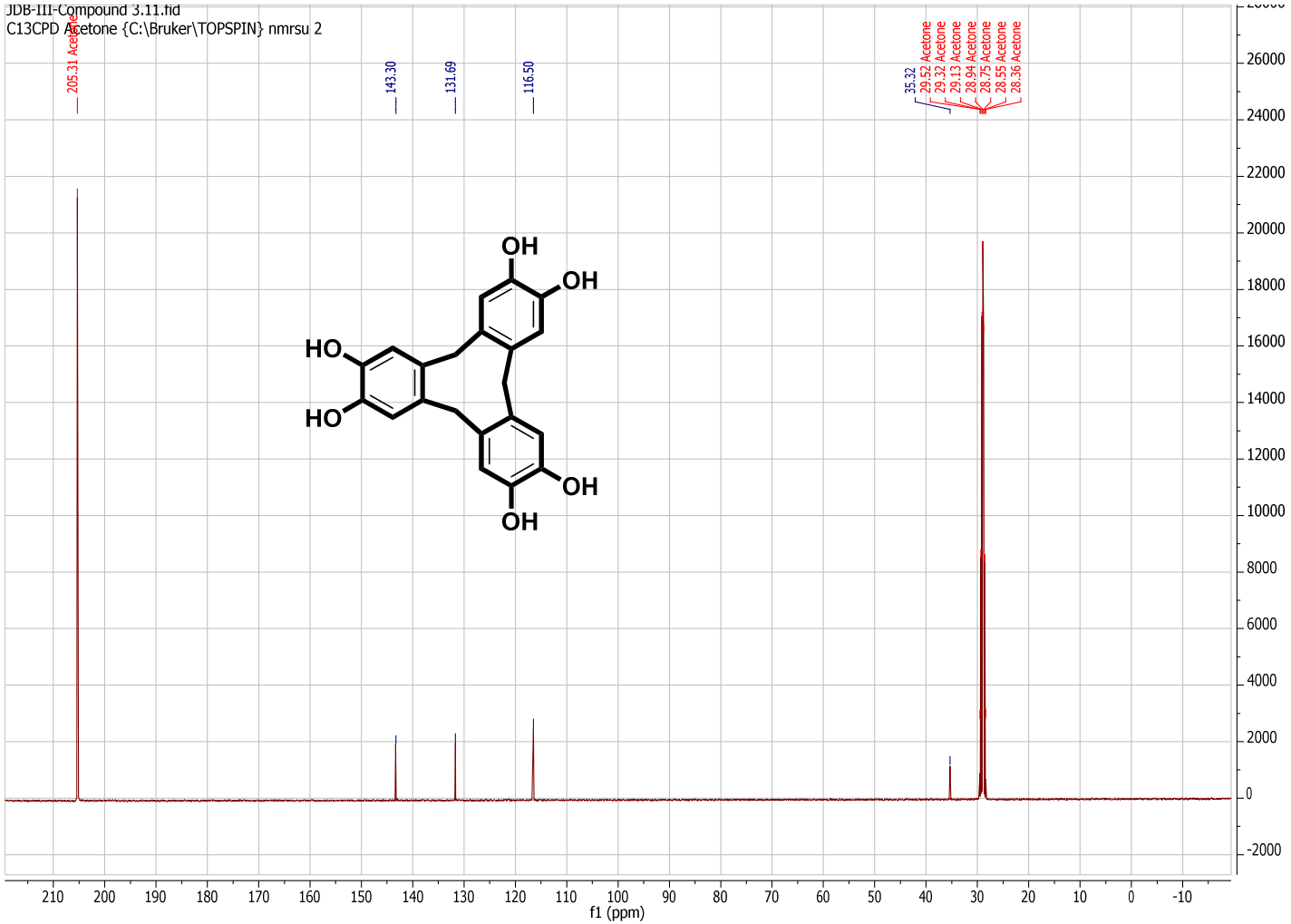


^{1}H NMR(400 MHz, Acetone-d_6): δ (ppm) 7.30 (broad, 1H), 6.66 (s, 2H), 4.50 (d, *J*=13.6 Hz, 1H), 3.22 (d, *J*=13.6 Hz, 1H).

^{13}C NMR (101 MHz, Acetone d_6) δ 143.30, 131.69, 116.50, 35.32.



Spectra 21 - ^{1}H NMR of Cyclotricatechylene (9)



Spectra 22 - ^{13}C NMR of Cyclotricatechylene (9)

APPENDIX 3

Manuscript 3 Supporting Information

Supporting Information for

Does POGIL Increase Grades With Attendance Held Constant?

Joseph Brown[1,2*], Eric Page[1], Brenton DeBoef[2]

Corresponding author:

CDR Joseph Brown

Science Department,

United States Coast Guard Academy

New London, CT, 06320

Joseph.D.Brown@uscga.edu

UNITED STATES COAST GUARD ACADEMY

CHEMISTRY I (5102) - Fall 2006
COURSE INFORMATION SHEET

Course Director	***Office #***	***Phone Ext.***	***E-Mail Address***
Laboratory Director			

Course/Lab Instructors

Text: *Chemistry*, 9th Ed., Raymond Chang

Websites: http://uscg.blackboard.com and http://www.chemskillbuilder.com

Course Description: Chemistry I is the first half of a one-year curriculum in general chemistry. It is a four-credit-hour course that consists of three one-hour lectures and one three-hour laboratory each week. The course presents an introduction to elementary concepts of chemistry, covering topics of matter and measurement, atomic theory and inorganic nomenclature, mass relationships, reactions in aqueous solution, gas laws and reactions, enthalpy, quantum theory, periodic trends in the elements, chemical bonding, and intermolecular forces.

Grade Calculation:

Lecture		
	Online ChemSkill Builder	5
	Homework	10
	Exams	40
	Final Exam	20

Minimum Requirements to Receive a Passing Grade:

A lecture average of **64.0%** or greater.

Letter Grade Assignments:

	A	=	90.0% and above	C+	=	73.0% - 76.9%	
	A–	=	87.0% - 89.9%	C	=	70.0% - 72.9%	
B+	=	83.0% - 86.9%	C–	=	67.0% - 69.9%		
B	=	80.0% - 82.9%	D	=	64.0% - 66.9%		
B–	=	77.0% - 79.9%	F	<	64.0%		

The grade of "H" (Honors) will be given in lieu of "A" for those students who have distinguished themselves by demonstrating mastery of all four overall course objectives.

Course Curriculum

Overall Course Objectives: Successful students will improve in the following performance dimensions:

1. ***Technical proficiency:*** Students will develop a core foundation of critical thinking skills by applying mathematical, statistical and scientific knowledge to various general chemistry problem sets.
2. ***Knowledge:*** Students will acquire information as outlined in the chapter specific objectives. Students will then use this information in conjunction with data—either given in problem sets or observed in laboratory experiments—to develop understanding, awareness, and, ultimately, knowledge.
3. ***Communications:*** Students will demonstrate the ability to effectively read, understand, discuss and summarize single scientific concepts outlined in the chapter specific objectives.
4. ***Leadership:*** Students will become excellent followers and burgeoning personal leaders by incorporating the core values of honor, respect and devotion to duty into their general chemistry course of study.

Chapter Specific Objectives: There is a comprehensive list of objectives that establishes instructor expectations of what each student should learn from each chapter. The objectives are accompanied by online exercises from ChemSkill Builder and a mandatory set of homework problems meant to illustrate the minimum level of mastery expected. Each chapter also includes a list of optional practice problems from the textbook and study guide. Use your list of objectives to study and to help you prepare for exams.

Online ChemSkill Builder: Your textbook has been packaged with ChemSkill Builder, an online study aid, which is designed to improve the quality of your study time by reviewing specific topics with you and providing immediate feedback as to whether or not you are grasping each topic. ChemSkill Builder assignments are listed in the chapter specific objectives. The online software will record your highest score earned for each section completed. You may improve your scores by repeating each section as often as you like, up until the deadline for that unit. Scores will be collected online at 1600 on the dates indicated on the syllabus, and credit will be given for each section on a pass/fail (64%) basis. It is more important that you learn from ChemSkill Builder than to earn high scores on every section.

Written Homework: Written homework assignments out of the textbook are listed in the chapter specific objectives. For each question, you shall include a summary of the question and a detailed, worked answer or written response. Assignments are due during class on the dates indicated in the syllabus. Your work will be graded on a scale of 0-5 points, based on correctness, completeness, neatness, and effort. To receive full credit, the homework shall be submitted on white, 8 ½ by 11, ruled paper or on engineering graph paper. At the top, the first sheet shall include your name, date, lecture instructor, class period, and assignment. All other sheets shall be stapled together in order with your name placed in the upper right hand corner. Late submissions will be collected by your instructor and assigned 0 points. Homework solutions will be posted on http://uscg.blackboard.com after the completion of each chapter.

Collaboration and consultation (explained below) on homework and ChemSkill Builders is highly encouraged. However, the work you submit to your instructor for evaluation must be your own work. On the written homework assignments, you shall acknowledge collaboration and assistance by listing the name(s) of people and the date(s) next to each problem, as appropriate. It is not necessary to annotate help received on ChemSkill Builder.

Exams

Hourly Exams: Unless otherwise directed, exams will be proctored in Dimick Auditorium during the 0800 testing period on Tuesdays and Thursdays, as scheduled in the syllabus. The exams will test your mastery of the course objectives.

Final Exam: The comprehensive final exam will include material from the entire semester, and will be scheduled in accordance with a SUPTNOTE published during the semester.

Course Notebook

Each cadet will maintain a notebook that contains all administrative handouts, lecture notes, homework assignments, exams, and laboratory documents. This notebook can become an indispensable study aid and self-assessment tool. Further, your returned assignments are the only physical record of your graded effort. In the rare event that a mistake is made while entering your grades, a properly-maintained portfolio of your graded assignments may be the only evidence available to correct the problem. Selected notebooks will be collected and retained for submission to the Accreditation Board for Engineering and Technology (ABET) reviewers when they visit during the Fall 2007 semester.

Chemistry Resources

USCGA Chemistry Blackboard: http://uscg.blackboard.com is the official course web site, and it should be your first source in obtaining course information. All course and laboratory documents will be posted there, along with homework and exam solutions, announcements, student grades, textbook resources, and more. Safeguard your BlackBoard password and visit the site frequently.

Chemistry Faculty: Outside of the classroom and laboratory, any member of the Chemistry Faculty will help you with any aspect of the course. Approach the instructor to whom you are assigned before seeking out other faculty members.

Cadet Academic Assistance Program (CAAP): During scheduled CAAP sessions, one or more of the Chemistry Faculty will be available in the evening during study hour to assist students as needed, for lecture or lab questions. An official Chemistry CAAP schedule can be found at http://uscg.blackboard.com.

Chemistry Tutors: Upper-class cadets volunteer to be available in Chase Hall as consultation tutors for Chemistry I. A list of participating cadets can be found at: http://eduportal.uscga.edu:8080/sites/ptp/default.aspx.

Cadet Reading/Writing Center: By appointment, this resource is prepared to help you with your writing (including post-lab questions) and can also help you improve your skills at reading technical textbooks.

Chemistry II

Chemistry I & II are essentially one seamless course. As such, the knowledge you gain from Chemistry I will be important to your understanding of Chemistry II. At the conclusion of this one-year chemistry curriculum you will be administered a standardized, multiple-choice exam, covering both semesters.

Collaboration and Consultation

Collaboration is working together on an assignment with someone who is in the same course and is also responsible for completing the same assignment. Consultation is discussing an assignment with someone who is not currently taking the course but does have the information you need. Consultation with a Chemistry Instructor is always allowed on every assignment. Consultation with anyone outside of the Chemistry Faculty (e.g. an upper-class tutor) is allowed whenever collaboration is allowed. Collaboration is allowed and highly encouraged on ChemSkill Builder, homework problems, and studying for exams.

Individual Effort: If an assignment is marked as an i*ndividual effort* assignment, then all work is expected to be done by one individual with the exception of assistance provided by a Chemistry Instructor. No other collaboration or consultation is permitted. *Individual effort* applies to examinations, quizzes, and when indicated in laboratory reports.

Group Effort: A *group effort* assignment applies to laboratory exercises where two or more students are assigned to a laboratory group. Full collaboration is expected within each assigned group, instructors may be consulted for assistance, but two separate groups may not collaborate together in whole or in part. Many lab assignments are broken up into group effort sections and individual effort sections; each section will be clearly labeled in every laboratory exercise.

If you have any doubt concerning the collaboration policy for an assignment, you shall first assume that collaboration is prohibited, and then you should seek clarification from a Chemistry Instructor.

	CHAPTER 1 - CHEMISTRY: The STUDY of CHANGE	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	1.1 - 1.9		
2	Understand the progression of steps in the "scientific method" and how these steps are applied to written problems and laboratory exercises.	1.3	1.1	
3	Understand difference between elements, compounds, and mixtures.	1.4	1.4, 3.1,3.6	1.13, 1.15
4	Understand the characteristics of the three states of matter: solid, liquid, and gas.	1.5	1.3	
5	Understand and give examples of chemical properties, physical properties, extensive properties, and intensive properties.	1.6	1.2	1.11
6	Memorize and use the SI standard units and decimal multipliers (Tables 1.2 & 1.3).	1.7	1.6	1.18
7	Perform calculations and conversions with mass, volume, and density.	1.7	2.4	1.21,1.22
8	Perform conversions among Fahrenheit, Celsius, and Kelvin temperature scales.	1.7	2.6	1.23, 1.25, 1.26
9	Correctly apply scientific notation conversions and rules to calculations.	1.8	2.1	1.29, 1.30, 1.31, 1.32
10	Determine/Identify the number of significant figures in a calculated result for mult/div/add/sub/log.	1.8 / App 4	2.2, 2.3	1.34, 1.35, 136
11	Understand how precision and accuracy relate to scientific measurements.	1.8		
12	Perform unit conversions using the factor-label method (dimensional analysis).	1.9	2.5	1.37, 1.40, 1.42, 1.45
13	Additional problems.			1.57, 1.92

Optional Practice Problems From Textbook: 1.12, 1.14, 1.16, 1.54, 1.59, 1.72, 1.73, 1.90

Optional Test Preparation Problems From Study Guide: Exercises and Problems: 2, 4, 6, 9, 10, 13, 15, 17, 18
Practice Test: 5, 6, 7, 8, 10, 12, 13, 14, 16

CHAPTER 2 - ATOMS, MOLECULES, and IONS	SECTION	CSB	HW ASSIGNMENT
1 Understand all boldface terms and apply all key equations in the chapter.	2.1 - 2.7		
2 Understand the three hypotheses of Dalton's atomic theory.	2.1		
3 Understand the subatomic particles (protons, neutrons, and electrons) and radioactive products.	2.2		
4 Understand and use the information contained in the chemical notation: ${}^{A}_{Z}X$	2.3	9.1	2.16, 2.18, 2.71
5 Understand the organization of the Periodic Table. Study the chemical characteristics of each group.	2.4		2.22, 2.26
6 Understand the fundamental characteristics and differences of molecules and ions.	2.5		2.49
7 Understand the concept of, and how to determine, molecular, empirical and ionic formulae.	2.6		2.45, 2.47
8 Define and name: ► Simple ionic compounds (Memorize Tables 2.2 and the polyatomic ions handout) ► Simple molecular compounds (Memorize Table 2.4) ► Simple acids, bases, and hydrates (Memorize Table 2.5 and apply Table 2.6) ► Straight chain alkanes (Memorize Table 2.8)	2.7, 2.8	1.5, 3.2, 3.3, 3.4, 3.5	2.57, 2.59, 2.90
9 Additional problems.			2.69, 2.85

Optional Practice Problems From Textbook: 2.35, 2.38, 2.55, 2.58, 2.60, 2.63, 2.68, 2.70, 2.86, 2.87, 2.91

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 3, 5, 10, 11, 12, 13, 14, 15, 16
Practice Test: 1, 2, 3, 4, 7, 8, 9, 10

	CHAPTER 3 - MASS RELATIONSHIPS in CHEMICAL REACTIONS	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	3.1 - 3.3, 3.5 - 3.10		
2	Be able to calculate average atomic mass given natural abundances of isotopes, and vice versa.	3.1		3.6
3	Understand the concept of "the mole" and its relationship to Avogadro's number.	3.2		
4	Convert between mass, moles, and number of particles for a given sample.	3.2	4.1	3.15, 3.26
5	Calculate molecular or molar mass of substances.	3.3	4.2	3.24
6	Determine empirical and molecular formula from “mass percent composition” and molar mass.	3.5	4.5	3.52, 3.53, 3.54
7	Determine empirical and molecular formulas from combustion analysis data.	3.6	4.6	3.136
8	Write and balance chemical equations.	3.7	4.3, 5.4	3.59
9	Master the following types of stoichiometry problems: ► Convert a mass or mole of reactant to a mass or mole of product or vice versa. ► Identify the limiting reactant, determine the mass of a product, and calculate percent yield.	3.8 - 3.10	4.4	3.71, 3.84, 3.90
10	Additional problems.			3.134, 3.144

Optional Practice Problems From Textbook: 3.19, 3.22, 3.25, 3.28, 3.42, 3.44, 3.46, 3.50, 3.60, 3.70, 3.72, 3.76, 3.82, 3.86, 3.92, 3.94, 3.100, 3.104, 3.108, 3.112, 3.120, 3.122, 3.126, 3.128, 3.140

Optional Test Preparation Problems From Study Guide:

Exercises and Problems: 2, 4, 5, 7, 8, 9, 11, 12, 13, 15, 17, 18, 19, 23, 24, 25, 27

Practice Test: 6, 7, 8, 11, 13, 14, 15, 16, 17, 18, 20

CHAPTER 4 - REACTIONS in AQUEOUS SOLUTION		SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	4.1 - 4.5, 15.4		-
2	Understand the concepts of **concentration** and **dilution.** Perform calculations involving molarity, including calculations involving diluted solutions.	4.5	6.1, 6.4	4.59, 4.61, 4.74
3	Understand the difference between ionic and molecular substances as strong electrolytes, weak electrolytes, or nonelectrolytes. (Table 4.1)	4.1		4.9
4	Write molecular, ionic, and net ionic reactions.	4.2	5.3	4.21
5	Apply the solubility rules (Table 4.2) to: ► Classify substances as soluble or insoluble in water @ 25 °C. ► Predict product formation in metathesis (ion-swap) chemical reactions.	4.2	5.1, 5.2	4.19, 4.23
6	Understand both the Brønsted theory of acids and bases and neutralization reactions and stoichiometry.	4.3		4.30, 4.33
7	Understand the terms **strong** and **weak** as they apply to acids and bases. Classify acids and bases as either "strong" or "weak." Memorize all common strong acids and strong bases: ►**STRONG ACIDS:** $HClO_4$, HI, HBr, HCl, H_2SO_4, and HNO_3 ►**STRONG BASES:** LiOH, NaOH, KOH, RbOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, $Sr(OH)_2$, and $Ba(OH)_2$	15.4		15.33, 15.34
8	Understand the concept of an Oxidation-Reduction reaction. Determine oxidation numbers for atoms in molecules and ions.	4.4	10.1, 10.2	4.43, 4.47
9	Additional problems.	-		4.136

Optional Practice Problems From Textbook: 4.22, 4.31, 4.32, 4.34, 4.44, 4.46, 4.62, 4.64, 4.65, 4.70, 4.72, 4.132

Optional Test Preparation Problems From Study Guide:

Exercises and Problems: 1, 2, 3, 4, 5, 6, 8, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 22, 23

Practice Test: 1, 2, 4, 6, 7, 9, 10, 11, 12, 13

	CHAPTER 5 - GASES	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	5.1 - 5.8		-
2	Memorize Table 5.1 (Substances found as gases and their names).	5.1		-
3	Understand the concept of pressure (including atmospheric pressure). Perform conversions between the units of pressure.	5.2	7.1	5.14
4	Derive useful pressure data from barometers and manometers.	5.2		5.4
5	Understand & perform calculations relating moles, volumes, pressures, & temperatures of gases using: ► Boyle's Law ► Charles's and Gay-Lussac's Law ► Avogadro's Law	5.3	7.2	5.18, 5.20, 5.23, 5.26
6	Calculate the condition of a gas (P, V, T, or n) using the ideal gas equation.	5.4		5.31, 5.33
7	Perform advanced calculations involving density and molar mass determination for gases.	5.4	7.3	5.47, 5.48, 5.49
8	Perform stoichiometric calculations for reactions involving gases.	5.5		5.53, 5.57
9	Show the relationship between pressure, mole fraction, and partial pressure through the use of mathematical calculations and Dalton's Law of Partial Pressure.	5.6	7.4	5.63
10	Understand the Kinetic-Molecular Theory of gases and use it to account for the general properties of substances found in the gaseous state.	5.7	7.5	5.72
11	Understand how real gases deviate from ideal behavior.	5.8		5.86, 5.90

Optional Practice Problems From Textbook: 5.22, 5.24, 5.32, 5.34, 5.40, 5.44, 5.50, 5.54, 5.60, 5.70, 5.93, 5.94, 5.103, 5.106, 5.110, 5.114, 5.134

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 3, 4, 6, 7, 8, 10, 12, 14, 16, 18, 20, 21, 29
Practice Test: 5, 6, 8, 12, 16, 17, 18

	CHAPTER 6 - THERMOCHEMISTRY	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	6.1 - 6.6		
2	Understand the Law of Conservation of Energy.	6.1	8.4, 8.5	
3	Understand the difference between endothermic and exothermic reactions.	6.2		6.10
4	Understand the concept of enthalpy and use it in stoichiometric calculations.	6.4	8.6	6.25, 6.59
5	Understand calorimetry and derive thermochemical information from calorimetric experiments.	6.5	8.1, 8.3	6.35, 6.36, 6.82
6	Be able to use tabulated standard enthalpy of formation ($\Delta H°_f$) data to determine the enthalpy of a reaction ($\Delta H°_{rxn}$), and vice versa.	6.6	8.6	6.57, 6.81
7	Be able to use Hess's Law to determine the enthalpy of a reaction ($\Delta H°_{rxn}$).	6.6	21.1	6.62
8	Additional problems.			6.86, 6.88

Optional Practice Problems From Textbook: 6.34, 6.52, 6.64, 6.74, 6.84, 6.100, 6.104, 6.108, 6.118

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 3, 4, 5, 7, 8, 9, 10, 14, 15
Practice Test: 2, 3, 4, 5, 6, 9, 10, 11

	CHAPTER 7 - QUANTUM THEORY and the ELECTRONIC STRUCTURE of ATOMS	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	7.1 - 7.9		
2	Understand and apply the interrelationship of the quantities ν, λ, and E.	7.1	9.2	7.8, 7.15, 7.103
3	Understand Planck's Quantum Theory and the concept of quantization of energy.	7.1		
4	Understand the Photoelectric Effect.	7.2		7.138
5	Understand the Bohr model, its assumptions and shortcomings. Apply the model through calculations.	7.3	9.2	7.32
6	Understand the dual nature of the electron.	7.4		
7	Understand the basic premises of the Quantum Mechanical description of the atom.	7.5		
8	Understand the four quantum numbers. Memorize their designations and assignments.	7.6	9.6	7.75
9	Learn the orbital types, shapes, and sizes.	7.7		
10	Relate quantum numbers to atomic orbital designations (Table 7.2).	7.7		7.57, 7.62, 7.65
11	Predict the electron configuration and orbital diagrams for multi-electron atoms using the Aufbau Principle, the Pauli Exclusion Principle, and Hund's Rule.	7.8 – 7.9	9.3, 9.4, 9.5	7.89, 7.124, 7.87
12	Understand and apply the concept of noble-gas-core notation to ground state electron configurations.	7.9		

Optional Practice Problems From Textbook: 7.10, 7.12, 7.16, 7.18, 7.30, 7.34, 7.42, 7.56, 7.58, 7.64, 7.66, 7.70, 7.76, 7.88, 7.91, 7.96, 7.104, 7.120, 7.132

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 27, 28 **Practice Test**: 1, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15

CHAPTER 8 - PERIODIC RELATIONSHIPS AMONG the ELEMENTS	SECTION	CSB	HW ASSIGNMENT
1 Understand all boldface terms and apply all key equations in the chapter.	8.1 - 8.5	11.3, 11.4	
2 Write electron configurations for ions.	8.2		8.28, 8.29, 8.30
3 Understand Shielding Effect and Effective Nuclear Charge. Use to predict relative size of atoms (atomic and ionic radii).	8.3	11.1	8.42, 8.44
4 Understand the correlation of electron configuration and ionization energy.	8.4	11.2	8.55, 8.56
5 Understand the correlation of electron configuration and electron affinity.	8.5	11.2	8.62, 8.119
6 Additional problems.			8.109

Optional Practice Problems From Textbook: 8.24, 8.54, 8.64, 8.76, 8.86, 8.116

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 4, 5, 6, 7, 9, 11, 12, 13, 15, 16, 17, 18, 21, 23, 25, 26, 30, 31, 32, 33
Practice Test: 4, 5, 6, 7, 8, 9, 11, 12, 15

CHAPTER 9 - CHEMICAL BONDING 1: BASIC CONCEPTS	SECTION	CSB	HW ASSIGNMENT
1 Understand all boldface terms and apply all key equations in the chapter.	9.1 - 9.2, 9.4 - 9.9		
2 Use Lewis dot symbols to denote valence electrons of an atom.	9.1		9.5
3 Use Lewis dot symbols and the octet rule to show the formation of ionic compounds.	9.2		9.18
4 Use Lewis dot symbols to show the formation of covalent bonds.	9.4		
5 Understand the concept of electronegativity and relate it to the designation of ionic, polar covalent, and covalent bonds (Fig 9.7).	9.5	12.1	9.36, 9.40
6 Be able to draw Lewis structures of compounds.	9.6	12.2	9.43, 9.47
7 Use the concepts of formal charge and resonance to draw plausible Lewis structures	9.7 - 9.8	12.4	9.51, 9.54
8 Draw plausible Lewis structures that do not follow the octet rule, including: ► Structures with an incomplete octet ► Structures with an odd number of electrons ► Structures with an expanded octet	9.9		9.63, 9.65
9 Additional problems.			9.102, 9.106

Optional Practice Problems From Textbook: 9.16, 9.20, 9.38, 9.44, 9.48, 9.64, 9.66, 9.74, 9.92, 9.96, 9.116

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 2, 7, 8, 9, 10, 12, 13, 16, 17, 20, 22
Practice Test: 3, 4, 5, 6, 8, 9, 10

CHAPTER 10 - CHEMICAL BONDING 2: MOLECULAR GEOMETRY and HYBRID ORBITALS	SECTION	CSB	HW ASSIGNMENT
1 Understand all boldface terms and apply all key equations in the chapter.	10.1 - 10.5		
2 Apply VSEPR theory to Lewis diagrams in order to describe the electron-group arrangement and geometry of a given molecule. Memorize Tables 10.1 and 10.2.	10.1	12.3	10.10, 10.12
3 Explain the relative effects of lone pair vs. bonding electrons upon molecular shape and geometry.	10.1		
4 Understand the concept of a dipole moment and predict the polarity of a molecule.	10.2	12.5, 13.4	10.18, 10.20, 10.21
5 Understand bond formation through atomic orbital overlap. (Valence Bond Theory)	10.3		10.41
6 Determine the hybridization state of the central atom and sketch the geometry.	10.4	13.2	10.39, 10.42
7 Understand sigma (σ) and pi (π) bonds in Lewis structures.	10.5	13.1, 13.3	10.43
8 Additional problems.			10.79, 10.86

Optional Practice Problems From Textbook: 10.8, 10.14, 10.22, 10.36, 10.40, 10.44, 10.76, 10.78, 10.80, 10.92

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 19, 20
Practice Test: 1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14

	CHAPTER 11 - INTERMOLECULAR FORCES and LIQUIDS and SOLIDS	SECTION	CSB	HW ASSIGNMENT
1	Understand all boldface terms and apply all key equations in the chapter.	11.1 - 11.3, 11.8 - 11.9		
2	Understand the Kinetic Molecular Theory of Liquids and Solids	11.1		11.111
3	Differentiate between ion-dipole, dipole-dipole, and dispersion forces (dipole-induced dipole and instantaneous dipole-induced dipole) and predict which is the dominant intermolecular force between given chemical species.	11.2	14.4	11.10
4	Relate the concept of polarizability to induced intermolecular forces.	11.2		11.100
5	Understand how the hydrogen bond is a special case of dipole-dipole interactivity occurring when N, O, or F are bonded to H.	11.2		11.12
6	Use the concept of IMF's to explain the properties of liquids, including surface tension and viscosity.	11.2 - 11.3		11.31, 11.32
7	Understand the concept of equilibrium vapor pressure and its relationship to temperature.	11.8		11.79
8	Explain boiling point and its relationship to intermolecular forces, pressure, and the molar heat of vaporization.	11.8	14.1	11.13, 11.81
9	Apply heating/cooling curves to the understanding of boiling and melting points, and heats of fusion, vaporization and sublimation.	11.8	14.5	11.77, 11.78, 11.84
10	Perform calculations using heats of fusion and heats of vaporization.	11.8	8.2	11.86
11	Be able to interpret a phase diagram.	11.9	14.6	11.94, 11.99

Optional Practice Problems From Textbook: 11.14, 11.20, 11.82, 11.88, 11.96, 11.104, 11.122, 11.128, 11.134

Optional Test Preparation Problems From Study Guide:
Exercises and Problems: 1, 2, 3, 4, 5, 7, 14, 17, 18, 19, 25, 26
Practice Test: 1, 2, 3, 11, 12, 13, 14, 15