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Applications of Benchtop NMR in the Organic Chemistry Instructional Laboratory

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ABSTRACT

The instructional organic chemistry laboratory has been substantially improved through the implementation of benchtop NMR analysis. When used in conjunction with unknown reaction components in multi-outcome experiments, NMR analysis transforms the laboratory exercise into an investigative inquiry wherein students elucidate structures for their products and thereby deduce their unknown reaction components. This analytical approach closely models the research laboratory and is a valuable preparatory tool for undergraduate researchers. Three newly developed multi-outcome experiments based upon the Diels-Alder cycloaddition, the synthesis of carboxylic amides, and the Friedel-Crafts alkylation are herein described to illustrate the utility of benchtop NMR analysis in the instructional laboratory.

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BACKGROUND

Historically, the introduction of NMR spectroscopy into the organic chemistry instructional laboratory faced several significant challenges.[1-3] Perhaps the most significant of these was the cost of the instrument. Even early 60MHz and 90MHz fixed magnet instruments were cost prohibitive for many institutions. With the advent of high field instruments, purchase and maintenance costs increased significantly.[4,5] Consequently, NMR analysis in the instructional laboratory remained out of reach for several decades.

Chemistry departments that were fortunate to find sufficient resources to purchase NMR spectrometers, either internally or externally through large equipment grants, grappled with the second major challenge: user time and access to the instrument. Research use of high field spectrometers was prioritized, rendering instructional access infrequent. The development and implementation of robotic arms to introduce NMR sample tubes to the spectrometer somewhat increased access to the NMR for instructional purposes. However, the logistics of processing several hundred student sample tubes were daunting, making sample turnaround time a serious obstacle. Therefore, NMR analysis as an analytical tool in instructional laboratories for students at large enrollment institutions remained unfeasible.

Benchtop NMR spectrometers provide a remedy for these formidable challenges. Modern benchtop NMR spectrometers can be obtained for less than ten percent of the cost of a new high field instrument. Their compact size allows them to be placed in the instructional laboratory, circumventing the need for a separate space or facility. They do not require additional personnel specially trained for maintenance and upkeep. Such duties can be successfully performed by graduate student assistants. And, undergraduate students can obtain a spectrum of their sample within two minutes, thereby substantially reducing individual user time on the instrument.

With all of these advantages, there has remained some reluctance to incorporate benchtop NMRs into the instructional laboratory. Indeed, spectra can be produced by computer applications, and idealized spectra that depict excellent signal dispersion and resolution can simplify NMR interpretation for inexperienced students. However, spectra obtained individually by students from samples they prepare in a laboratory experiment constitute a powerful instructional tool. Students acquire a sense of individual ownership of their results. And, exposure to actual results in contrast to idealized results better prepares students for further studies as undergraduate researchers beyond the introductory instructional laboratory. Thus, a well-considered set of experiments yielding product spectra that can be successfully interpreted by newcomers to NMR analysis is transformative, changing the undergraduate instructional laboratory from a brief introduction of experimental techniques and organic transformations to a robust preparatory experience that produces researchers that are prepared to engage in actual research projects in faculty research laboratories.

EXPERIMENT DESIGN AND DEVELOPMENT

Experiment design for the organic chemistry instructional laboratory is constrained by several requirements within which the instructional curriculum must operate. First of all, laboratory experiments must be safe for inexperienced students. This requires that experimental procedures minimize the use of chemicals and reagents that are potentially dangerous.

Secondly, experiments must be designed to consistently give results in good yield. In a research laboratory, the apparent failure of an experiment can be helpful in planning and modifying future experiments. However, failure to achieve a positive result in the instructional laboratory is problematic because of the time required to trouble shoot the problem, identify the cause for the unsuccessful outcome, and modify the experiment procedure for a second trial. This analysis may lead a student investigator far astray from the desired objective of the experiment and consequently from the intended exposure to procedures and techniques associated with the experiment. Thirdly, there is a significant time constraint in the instructional laboratory. A synthetic transformation that requires a 6-hour traditional reflux followed by a 1-hour workup is suitable for the research laboratory but not for a 3-hour instructional laboratory period.

Perhaps the most challenging aspect of experiment design and development pertains to its pedagogical value. A typical laboratory exercise requires all students to perform the same procedure thereby obtaining the same product or result. For example, if all students perform the Fischer esterification reaction to form aspirin, the grade or assessment for each student is determined by the calculated percent yield of the product and its purity, most commonly analyzed by melting point determination, along with the standard lab report submission. This experiment design is woefully lacking in exposure to modern analytical instrumentation and it does not fully engage students in experimentation and analysis. Furthermore, a newly designed experiment of this type that is introduced into the instructional laboratory curriculum has diminishing pedagogical value in subsequent semesters as the same unoriginal results and analyses are shared with the next generation of students.

NMR ANALYSIS OF UNKNOWNS

The introduction of benchtop NMR analysis into the organic chemistry instructional laboratory represents a significant advancement that addresses several of the aforementioned challenges.[6-8] NMR analysis is best applied with the use of *unknowns*. An unknown is a component of the reaction, such as a starting substrate or reagent set, that leads to an individualized result. The identity of the substrate or reagent is unknown to the student researcher. Thus, unknowns allow all students to explore the same transformation while obtaining different products. The product structures are determined by NMR analysis. As a result of pairing NMR analysis with unknown reaction components, structure elucidation becomes a standard and integral component of an instructional laboratory experiment and the instructional laboratory more closely models the actual research experience.

At the University of Georgia, we have developed and implemented a library of experiments with unknown substrates or reagent sets, called multi-outcome Experiments (MOEs). For example, we modified the Fischer esterification reaction to include several unknown alcohols.[9,10] Students perform a standard acid-catalyzed esterification using the same carboxylic acid but with individually assigned unknown alcohols. The structures for the product esters are elucidated by ^{1}H NMR analysis using the benchtop NMR spectrometer. The identity of the unknown alcohol is thus deduced. In this manner, the incorporation of unknowns individualizes the experimental results for all students without significantly changing the experimental procedure. And, analysis of these individualized experimental results entails the use NMR spectrometry, the most common and powerful analytical tool presently available for structure elucidation.

THREE EXAMPLES OF NMR ANALYSIS IN MULTI-OUTCOME EXPERIMENTS

Example 1: The Diels-Alder Cycloaddition

The Diels-Alder cycloaddition reaction is an important reaction in organic synthetic methodology.[11-13] A common example is the reaction of anthracene and maleic anhydride which is driven to completion by the formation of an insoluble and easily isolated solid. However, the Diels-Alder cycloaddition reaction is not widely explored in the instructional laboratory due in large part to the equilibrium under reaction conditions between the starting diene, dienophile and cycloaddition product and also the time required for the reaction to go to completion.

These challenges can be successfully addressed in an MOE by reacting freshly prepared cyclopentadiene and one of four unknown dialkylacetylene dicarboxylates in a microwave promoted reaction using a catalyst. The reaction is completed in 30-minutes, leaving the balance of the time for structure analysis by benchtop NMR. **Figure 1** shows a student-generated ^{1}H NMR spectrum of the cycloaddition product obtained from the reaction of cyclopentadiene and dimethylacetylene dicarboxylate. The product spectrum allows students to assign the methyl protons of the methyl esters (b), the bridgehead protons of the norbornadienyl ring (c), and the vinylic protons (d). Moreover, the spectrum clearly shows the diastereotopic bridge protons (a,a'), which is an important instructional aspect of this NMR analysis.

For comparison, **Figure 2** shows a student-generated ^{1}H NMR spectrum of the cycloaddition product obtained from the reaction of cyclopentadiene and diisopropylacetylene dicarboxylate. Again, the proton signals can be readily identified and assigned.

Example 2: Amide Synthesis

Given the biological importance of the peptide bond, inclusion into the instructional laboratory of an amide synthesis is a worthwhile and informative exercise.[14] An MOE that utilizes acetic anhydride and an array of unknown amines to synthesize amides can be accomplished in a facile 10-minute reaction that is catalyzed by Al_2O_3. Structures of the product amides can be elucidated by benchtop ^{1}H NMR and the unknown amine reactants are thus deduced. **Figure 3** shows the ^{1}H NMR spectrum for *N*-benzylacetamide. The spectrum resolution is excellent and the doublet at δ 4.25 ppm stimulates an in-depth discussion of spin coupling. For comparison, **Figure 4** shows the ^{1}H NMR spectrum for *N*-(*tert*-butyl)acetamide.

Example 3: Friedel-Crafts Alkylation

Electrophilic substitution on an aromatic ring is a widely used synthetic transformation.[15,16] One important example, the Friedel-Crafts alkylation reaction, is explored through an MOE that utilizes benchtop ^{1}H NMR. The acid-catalyzed reaction of 1,4-dimethoxybenzene with an array of unknown alcohols produces white solids in good yields within 30 minutes. The products are recrystallized in hot methanol. The identity of the unknown alcohol is deduced by ^{1}H NMR analysis of the corresponding alkylation products. **Figure 5** shows the ^{1}H NMR spectrum of 1,4-di-*tert*-butyl-2,5-dimethoxybenzene, formed by the Friedel-Crafts alkylation reaction of 1,4-dimethoxybenzene with *tert*-butyl alcohol. The ^{1}H NMR spectrum of 1,4-di-*tert*-pentyl-2,5-dimethoxybenzene is shown in **Figure 6**.

Conclusions

The instructional organic chemistry laboratory is greatly enhanced by the inclusion of ^{1}H NMR analysis using benchtop spectrometers. These instruments are easily maintained and operated. In conjunction with multi-outcome experiments, students are now able to study a given transformation and obtain individualized results. Students are more engaged and invested in their own experimental results thus enriching their instructional laboratory experience. Product structures are elucidated through analysis of student generated ^{1}H NMR spectra and unknown components are thereby deduced. The laboratory experience models reactions and analyses performed in faculty research labs and in this way it more thoroughly prepares undergraduate researchers. It is clear that benchtop NMR analysis has transformed the instructional laboratory experience into an exciting investigative experience for students and is a welcome addition for chemistry faculty that work with undergraduate researchers in their faculty research laboratories.

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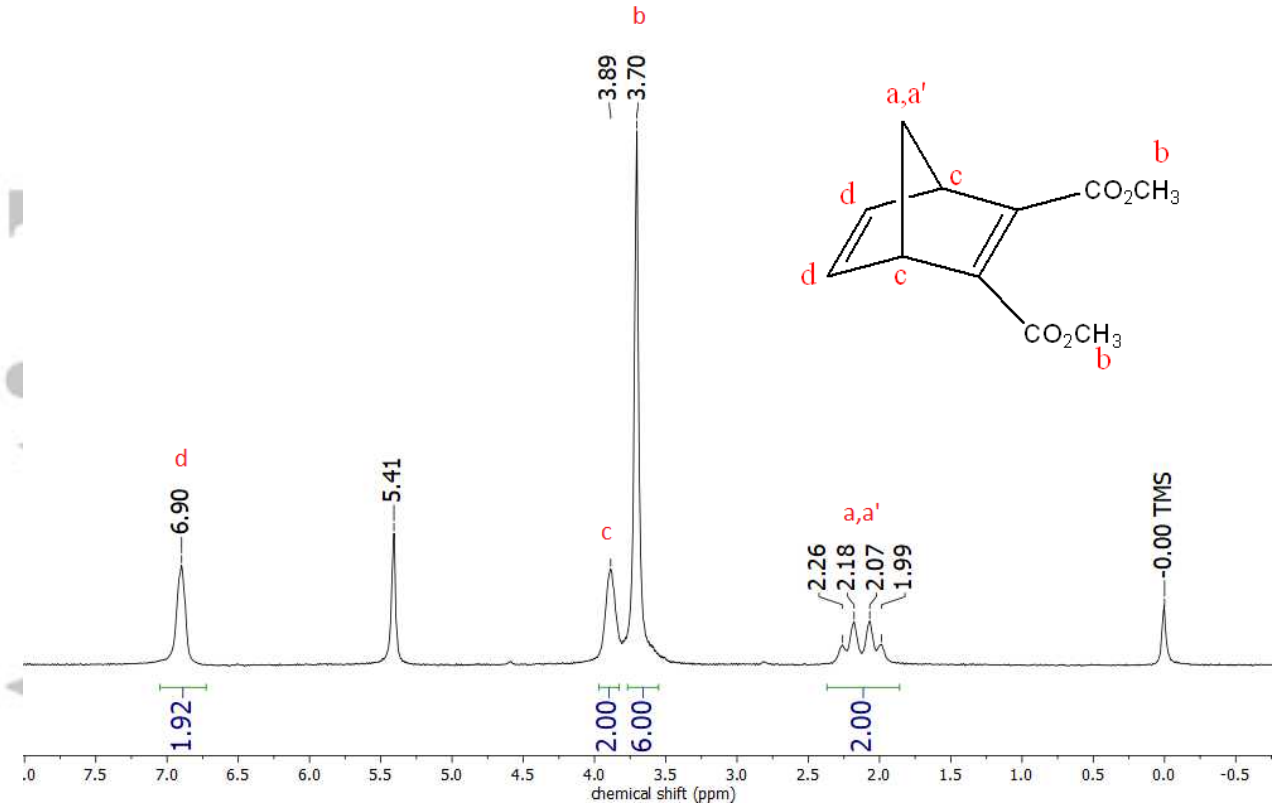

Figure 1. ^{1}H NMR spectrum of dimethyl (1R,4S)-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate obtained from an 82MHz PicoSpin benchtop NMR. The signal at δ5.41 is residual solvent.

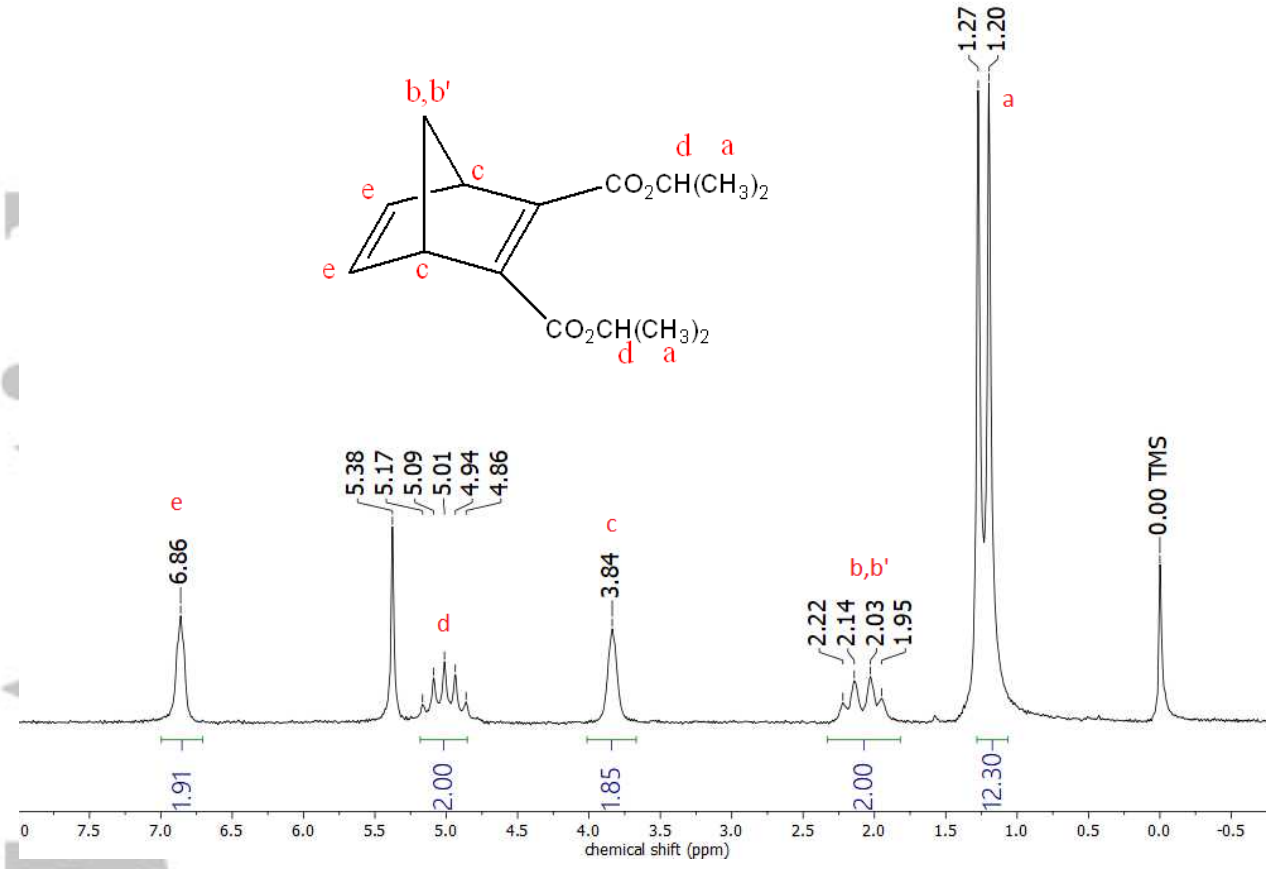

Figure 2. ^{1}H NMR spectrum of diisopropyl (1R,4S)-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate obtained from an 82MHz PicoSpin benchtop NMR. The signal at δ5.38 is residual solvent.

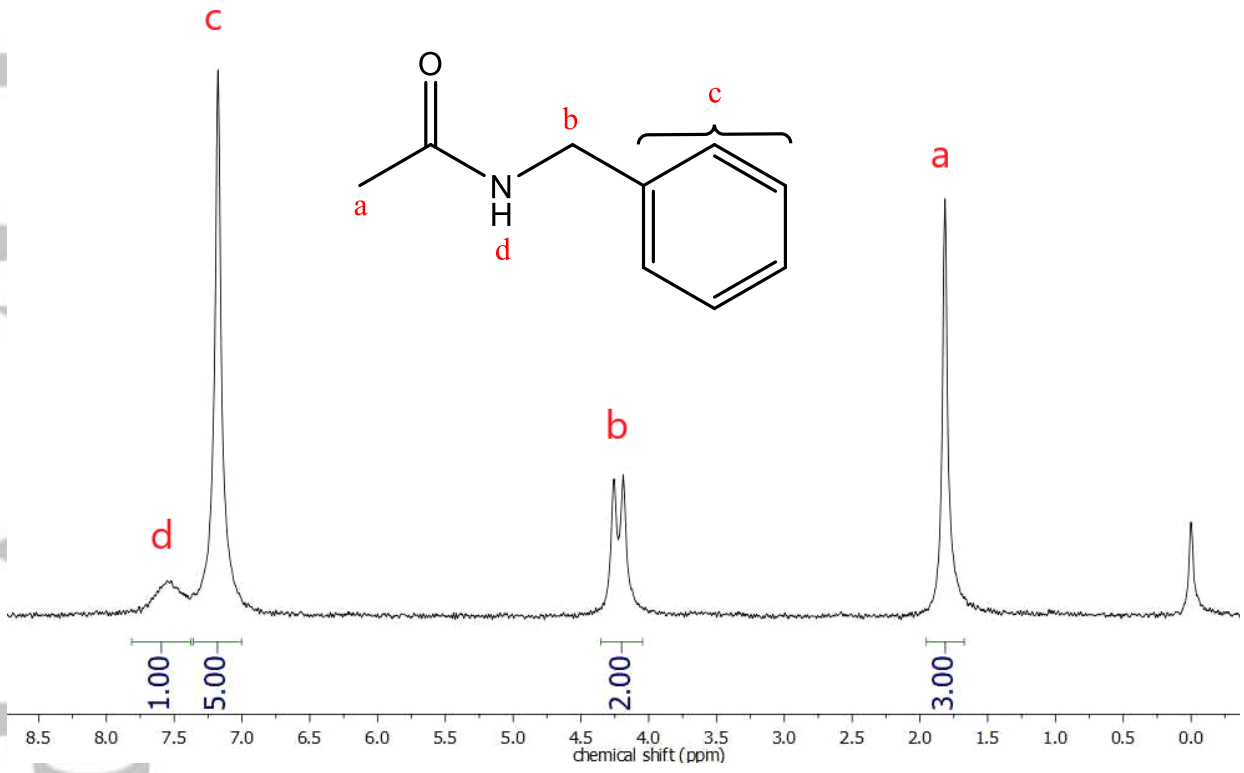

Figure 3. ^{1}H NMR spectrum of *N*-benzylacetamide obtained from an 82MHz PicoSpin benchtop NMR.

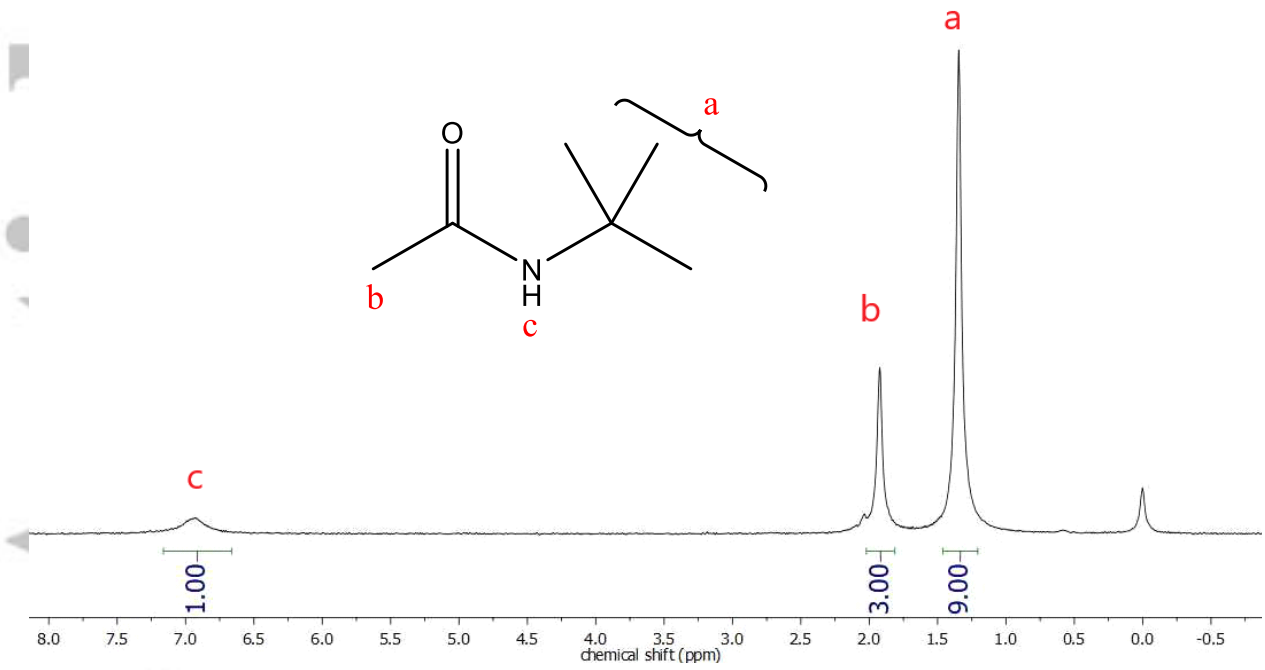

Figure 4. ^{1}H NMR spectrum of *N*-(*tert*-butyl)acetamide obtained from an 82MHz PicoSpin benchtop NMR.

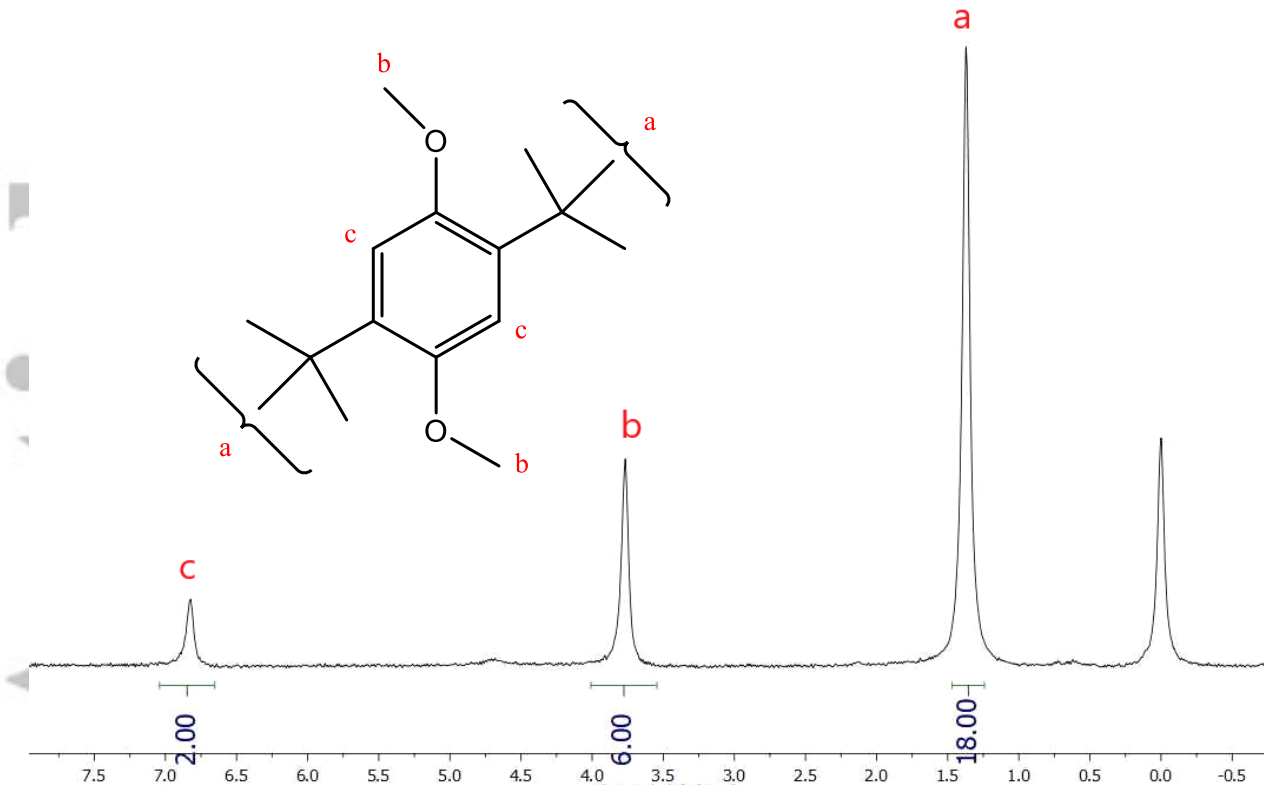

Figure 5. ^{1}H NMR spectrum of 1,4-di-*tert*-butyl-2,5-dimethoxybenzene obtained from an 82MHz PicoSpin benchtop NMR.

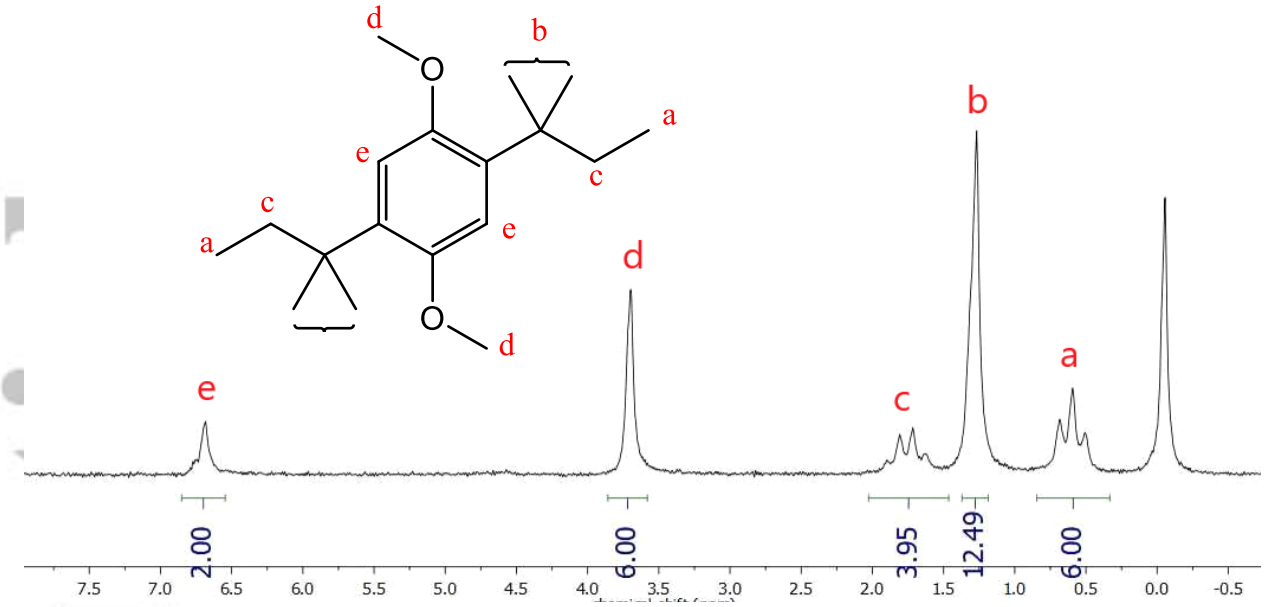

Figure 6. ^{1}H NMR spectrum of 1,4-di-*tert*-pentyl-2,5-dimethoxybenzene obtained from an 82MHz PicoSpin benchtop NMR.

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