Resorcin[4]arenes: A Convenient Scaffold to Study Supramolecular Self-Assembly and Host:Guest Interactions for the Undergraduate Curriculum.

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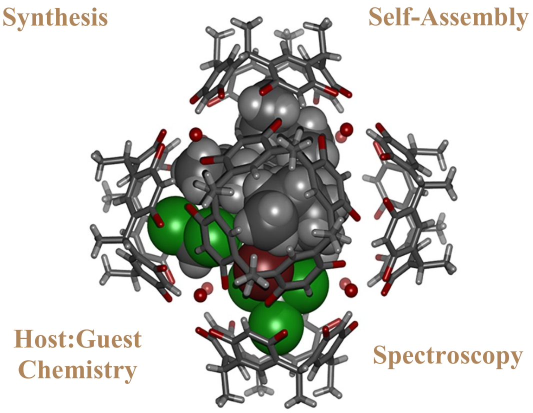
ABSTRACT

In response to the call for an increased emphasis from the American Chemical Society on including macromolecular studies in the undergraduate curriculum, a supramolecular-themed experiment was designed for undergraduate-level organic laboratory courses that provides a convenient platform to study physical behaviors of supramolecular assemblies. Students synthesize an easily purified resorcin[4]arene and characterize the product of its self-assembly via ^{1}H NMR spectroscopy. These bowl-shaped molecules are noteworthy because of their propensity to self-assemble in organic solution in the presence of trace water or alcohol solvents. Upon self-assembly, the resulting hexamer adopts a well-defined molecular cage structure with a large internal cavity that can be used to explore host:guest chemistry. After completing the experiment, students are expected to gain a better understanding of electrophilic aromatic substitution, ^{1}H NMR spectroscopy, supramolecular chemistry and self-assembly, and molecular recognition.

GRAPHICAL ABSTRACT



KEYWORDS

Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Interdisciplinary / Multidisciplinary, Hands-On Learning / Manipulatives, Molecular Recognition, NMR Spectroscopy, Noncovalent Interactions, Analogies / Transfer.

INTRODUCTION

In the quest to improve the quality of college chemistry curricula across the United States, the American Chemical Society has recently announced that nanomaterials, polymers, biological macromolecules, and supramolecular chemistry are areas that need to be better addressed to continue receiving accreditation of undergraduate degree programs.[1] Of these areas, the field of supramolecular chemistry offers perhaps the greatest access to well-defined molecular systems that can be easily analyzed by students, making these types of systems pedagogically appropriate for inclusion at the second-year undergraduate as well as the upper-division levels. In addition, supramolecular chemistry bridges all of the traditional fields of chemistry as well as biochemistry, and is therefore a valuable tool to demonstrate to students the interdisciplinary nature of modern chemistry. Despite their potential to incorporate supramolecular chemistry into appropriate second-year undergraduate level courses such as introductory analytical and organic chemistry, until recently most supramolecular experiments focused on advanced concepts in physical[2] or inorganic chemistry,[3] with few exercises geared towards lower-division organic courses.[4] Given the value and importance of incorporating lessons on supramolecular chemistry into the undergraduate curriculum, more experiments are needed that are appropriate for lower-division students.

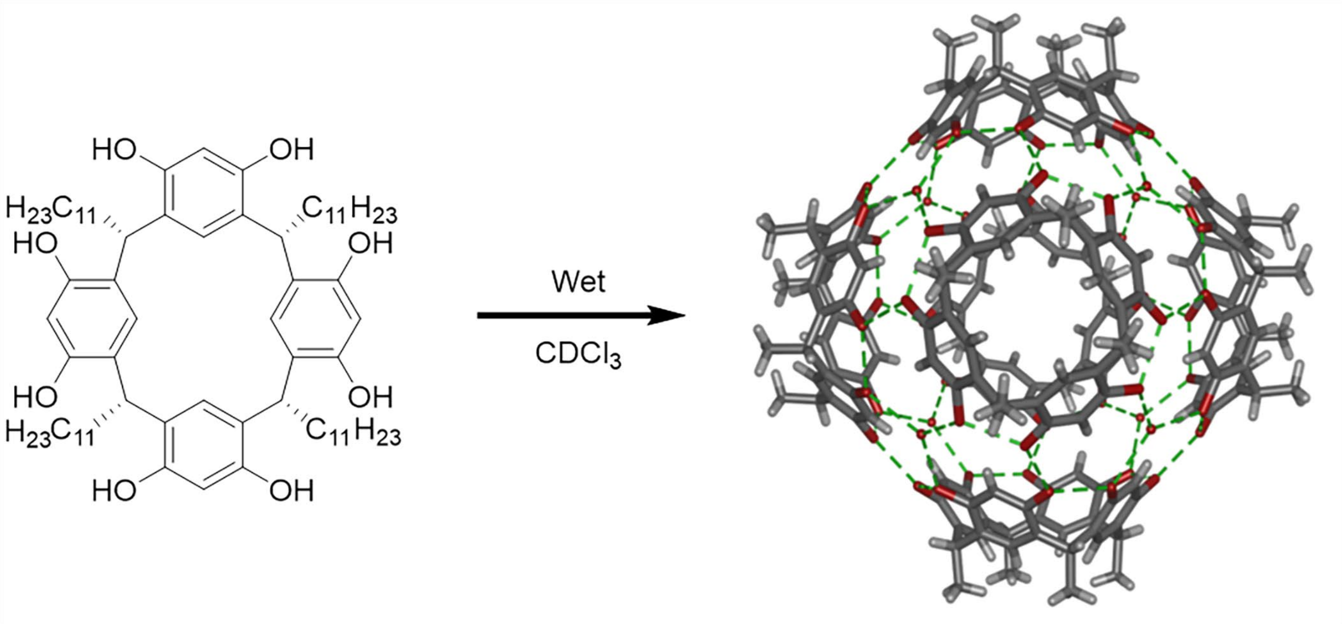


Figure 1. Self-Assembly of *C*-undecylcalix[4]resorcinarene hexamer with hydrogen bonds (denoted by green dashed lines) between phenolic residues and water molecules (denoted by red dotes). Solvent, exchangeable hydrogens, and the majority of the alkyl chains have been removed for clarity.

One class of molecular hosts that is particularly well-suited for introduction into the second-year undergraduate organic lab are the resorcin[4]arenes (Figure 1).[5] These structures are readily prepared from cheap reagents, and offer a diverse range of applications that are of appropriate complexity for study in the second-year undergraduate organic lab. For example, these structures can be used to introduce and cover topics related to conformation,[6] molecular self-assembly and hydrogen bonding,[7] molecular recognition and host:guest chemistry,[8] and catalysis,[9] and they can serve as intermediates to more complex cavitands[10] that can be used to further explore all of these topics.[11] Upon self-assembly, resorcin[4]arene hexamers' high symmetry make them relatively simple to analyze by solution phase ^{1}H NMR techniques, while the reactions necessary to prepare them are generally covered in a second-semester second-year undergraduate organic course. Resorcin[4]arene syntheses are generally facile, and can be performed within 1 h – a positive attribute for the often tight schedules of undergraduate lab courses. Furthermore, given the shape and size of the molecules, they can be easily recrystallized to access relatively pure products.

Here, we present a simple addition to the undergraduate laboratory curriculum involving the synthesis and host:guest chemistry of resorcinarene-based self-assembled hosts. While the experiments are relatively straightforward, there are a number of complex concepts that can be introduced in the discussion, which leads to a wide-ranging set of pedagogical goals for this lab. At the most basic level, students can understand the concept of “lock and key” guest binding, simply in terms of shape-fitting and size matching effects, which is suitable for students of any experience level. Students who have taken/are taking organic chemistry can discuss the concepts of hydrogen bonding and self-assembly, as well as discussions of topics in NMR spectroscopy such as magnetic anisotropy. More advanced students will be able to read, understand, and apply concepts from primary literature into their understanding and discussion of lab results, and partake in a discussion of thermodynamics and equilibrium constants. All students are expected to be able to perform a risk assessment of different compounds and to determine both the most hazardous agent used, as well as to propose how to mitigate the hazards. The discussion contents can be individually tailored at the instructor’s discretion.

EXPERIMENTAL OVERVIEW

The full procedure for this experiment can be found in the Supporting Information. The first portion of the experiment is straightforward, with approximately 2-5 min necessary per student to measure out the two reagents (resorcinol and *n*-dodecanal), the solvent, and finally the acid catalyst. The reaction can be run from between 1-2 h depending on the length of the lab period, and the yields are only slightly reduced when performed for 1 h instead of 2 h. The 1 h reaction time allowed students at the second-year undergraduate level to perform the reaction as well as a recrystallization, followed by use of IR spectroscopy to ascertain the purity of their samples. If the reaction has not gone to completion (most likely from inadequate heating of the reaction), the students will see evidence of the aldehyde in the IR spectrum, either of the aldehyde C–H or C=O bond stretches. Melting point analysis can also be used if equipment is available that can reach the approximately 293-295 °C required to melt the monohydrate of the product.

In larger-sized groups, where access to an NMR spectrometer for students was limited, the students were supplied with pre-recorded ^{1}H NMR data. In addition to the spectrum of the pure cage, spectra were also provided with a poorly or non-binding guest, such as tetramethylammonium bromide or tetraethylammonium bromide, as well as a sample with either tetrabutylammonium bromide or tetrahexylammonium bromide (see below for further discussion). When running the experiment with smaller groups, such as a Chemistry majors-only version of a second-year undergraduate [or introductory undergraduate] organic laboratory course, the experiment could be extended to two 3-h periods. In this scenario the reaction and purification can be performed during the first period, and the students could perform the characterization, including three ^{1}H NMR spectra per student (host, host + poor guest, host + good guest), during the second lab period. A more thorough understanding of the different operational approaches can be found in the Supporting Information (Student Handout 1 versus Student Handout 2).

HAZARDS

Resorcinol can be purchased as a food-grade additive, albeit there are concerns about it being a skin and eye irritant. *n*-Dodecanal is considered a skin irritant. The 95% ethanol used as both reaction and recrystallization solvent poses a slight fire hazard, as well as being a mild eye irritant. Concentrated hydrochloric acid is the most hazardous reagent in the lab due to its corrosiveness, and precautions should be taken to keep it contained in a fumehood to prevent the vapors from causing burns to skin or soft tissues such as the eyes or nasal passage. The tetraalkylammonium bromide guests are non-volatile and relatively safe, although tetramethylammonium bromide is considered toxic by ingestion, while tetrabutylammonium bromide and tetrahexylammonium are considered eye and skin irritants. The product, *C*-undecylcalix[4]resorcinarene, is considered a skin and eye irritant. Data does not exist for the host:guest assembly, but under biological conditions it will likely dissociate to its constituent components and should be considered to have similar hazards as the free host and guest. Chloroform-*d* is a carcinogen as well as an incapacitating agent. Students are provided with the SDS/MSDS information for all of these compounds, and asked to rank the relative hazardousness of each. More information can be found in the Supporting Information in the Student Handout Sections.

RESULTS AND DISCUSSION

This experiment was used for three years in upper-division labs at UC-Riverside, where it was routinely performed with 2 or 3 lab sections, each containing approximately 15-18 students, and run over two 4-h lab periods. It was possible for this advanced class to obtain all of the requisite NMR data within the designated second lab period with access to a single 300 MHz spectrometer. The experiment has also been used for two years at The University of Toledo at the second-year undergraduate organic level, where it was performed by classes of approximately 24 students in the general organic population (approximately 350 students per year) in a single 4-h lab period. Due to time constraints in this population, these students were supplied with the necessary NMR data to complete the experiment, as is common for most experiments during these large-enrollment second-year undergraduate organic labs at both of our universities. We felt it was important to extend this experiment to these students because as non-chemistry majors, these students would not otherwise be exposed to a supramolecular experiment since they do not take advanced laboratory courses in chemistry.

Meanwhile, a chemistry and biochemistry majors-only version of second-year undergraduate organic chemistry at The University of Toledo containing between 5-15 students performed the lab experiment over two 3-h lab periods. In the smaller setting, it was possible for each student to obtain ^{1}H NMR data for all three samples independently on one of two available NMR spectrometers (one 400 MHz and one 600 MHz) during the second 3-h lab period. The students can be asked to partner up for this step if necessary, but we have preferred to give the students as much practice collecting spectra as possible. Attempts to use a 200 MHz spectrometer were unsuccessful, as peaks for mixtures of free and bound host were not consistently well-resolved.

Purified yields for second-year undergraduate students in the general population generally ranged from between 27-80%, with a large amount of the variability coming from the level of skill demonstrated during the recrystallization step. Prior to recrystallization, the crude yields were in the range of 70-200%. In this population some students would not adequately dry their products, leading to >100% yields of crude product being reported occasionally. When necessary, these students were encouraged to further dry their products either in an oven or by using a rotary evaporator. When the experiment was run in the chemistry major-only lab courses, the purified yields were generally in the range of 55-90%, owing to the greater experience with recrystallization.

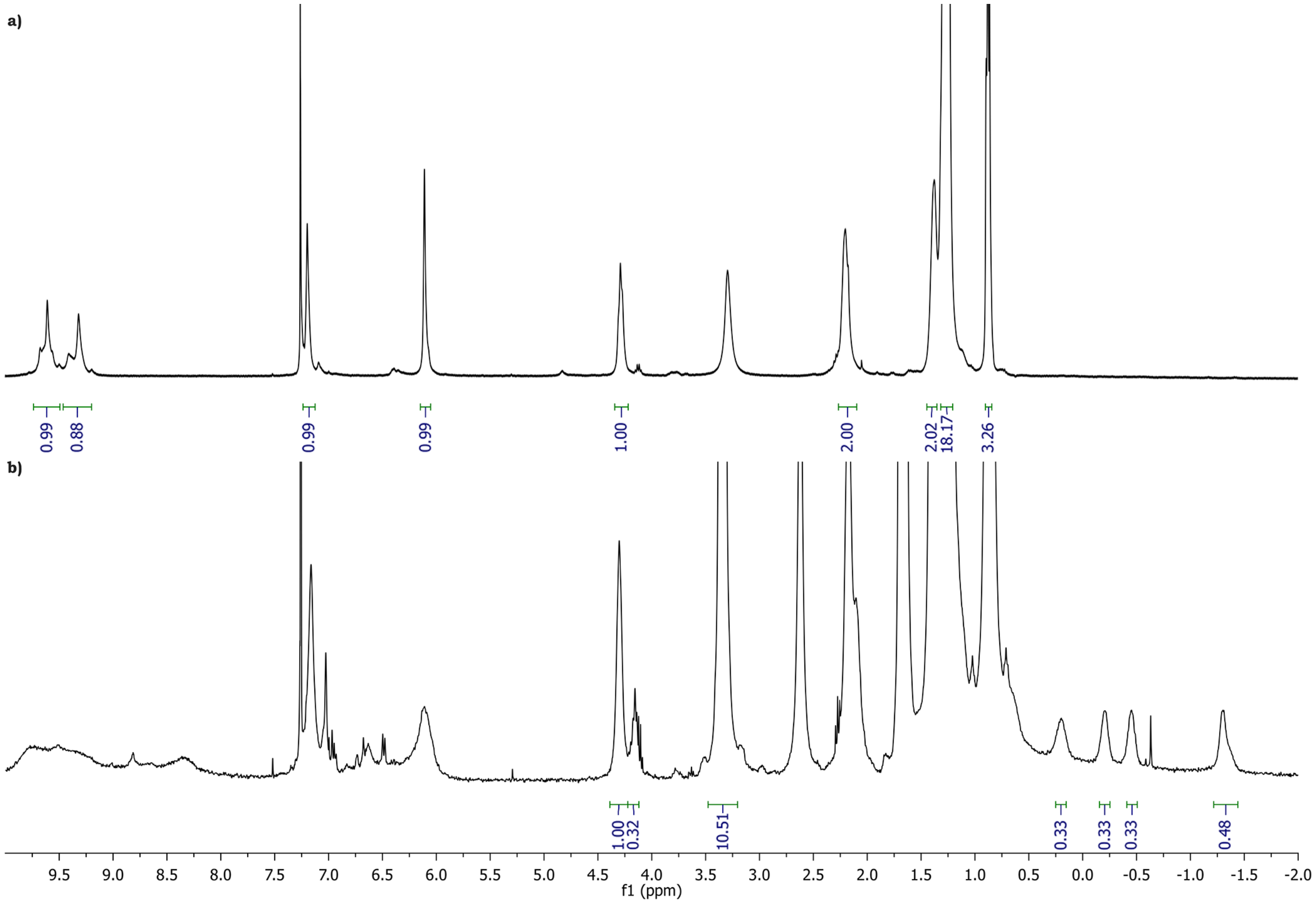


Figure 2. Typical ^{1}H NMR spectra as obtained by second-year students in a majors-only lab section with key peaks integrated (400 MHz, $CDCl_3$, 298 K): a) Free *C*-undecylcalix[4]resorcinarene. b) *C*-undecylcalix[4]resorcinarene host with tetrahexylammonium bromide guest.

Though the resorcin[4]arenes themselves are only sparingly soluble in anhydrous chloroform-*d*, the presence of adventitious water proves advantageous in that it facilitates self-assembly and subsequently solubilization of the hexameric host complex, due to hydrogen bonding between the water and phenolic hydroxides (Figure 1).[12] The presence of these hydrogen bonds leads to highly variable aromatic OH peaks in the ^{1}H NMR spectra of these structures, although they will be shifted further downfield than the signal for $CHCl_3$, which should be at 7.26 ppm (Figure 2a). For the same reason, the water peak is often shifted downfield, and can be between 2 – 4 ppm. Minor peaks can arise in the ^{1}H NMR for the hexamer, and these can usually be attributed to a separate, minor self-assembled species (identity unknown). In our hands, it is also frequently observed that trace amounts of ethanol will be present, although the CH_2 will be shifted to ~4.10 ppm (likely due to replacement of water in the hydrogen bonded self-assembly of the hexamer. Despite significant training, we also still find that students at all levels will frequently run their spectra with acetone as a contaminant from inadequate drying of their NMR tubes or NMR tube caps.

The cavity formed by self-assembly can then be used to study host:guest chemistry. One class of molecules that have been explored for this are the tetraalkylammonium halides.[8] Upon addition of a suitable guest, such as tetrahexylammonium bromide, new peaks are observed for both the free tetrahexylammonium species (δ 3.37 and 1.70 ppm, the remaining peaks will overlap with host peaks), as well as for the bound tetrahexylammonium species (Figure 2b, ~δ 0.20, -0.20, -0.45, and -1.30 ppm). The two sets of clearly resolved peaks for the free and bound guest molecules are due to the slow rate of guest exchange on the ^1H NMR timescale – during the experiment the bound guest remains encapsulated, and thus gives a distinct peak. Due to the presence of 24 aromatic rings flanking the cavity, a significant anisotropic shielding effect is observed, shifting the resonance for the bound guest's terminal CH_3 groups dramatically upfield to approximately -1.30 ppm. The relative integration of the peaks for the bound guest allows students to quickly identify the most upfield peak as the CH_3, and this provides an excellent opportunity to discuss (or for second-year undergraduate-level students to introduce) the concept of ring currents, and how this leads to a more shielding environment inside the self-assembled host. To help students more quickly analyze and label their NMR spectra (especially important for Postlab Question 2), the NMR spectra of the selected tetraalkylammonium salts can be provided (see Supporting Information for more details as well as for sample spectral data). It is worth noting that in addition to the guest exchange being slow on the NMR timescale, it is likely that tumbling may also be restricted, causing significant anisotropy both for the OH protons, as well as the aromatic protons *ortho* to the OH groups, which effectively point towards the inside of the capsule. For this reason, these protons are shifted depending on their proximity to the newly encapsulated guest, leading the aromatic and phenolic regions of the NMR spectrum to become more complex.

Alternatively, addition of a smaller species such as a tetramethylammonium or tetraethylammonium will only provide one new set of resonances in the ^1H NMR spectrum with the C-undecylcalix[4]resorcinarene hexamer. The binding of tetraalkylammonium guests inside of the C-undecylcalix[4]resorcinarene hexamer is unfavorable due to poor space-fitting, and as a result the students can be encouraged to explain why guest binding is observed with larger tetraalkylammonium species, but not with the smaller.[8] The discussion can even be related to concepts learned in general chemistry: guest binding of large tetraalkylammoniums are favored at room temperature (negative ΔG term), but disfavored for smaller guests. The strong guest binding is entropically driven in this case,[8] and this allows a discussion of solvent effects in molecular recognition. The large hexameric capsule is not empty, but rather filled with solvent molecules (six, in the case of $CDCl_3$). As a result, upon guest binding, the bound solvent molecules are displaced from the capsule. If the guest is large enough for a single guest to bind (between tetrapropylammonium and tetraoctylammonium in size), then between three and five of the encapsulated chloroform molecules can be displaced, leading to an increase in entropy, and thus a favorable ΔS term.[8]

Student comprehension was assessed through the use of postlab questions and the student laboratory reports. When the lab was run in a format where students were already accustomed to reading through primary literature (major-specific lab courses at either the upper-division or second-year), we found that around 80-85% of students were able to answer all of the questions correctly, with the weakest students answering as few as 2 questions correctly (Postlab questions 1 and 4 have the highest success rate). Teaching assistants reported that the majority of the students in this population (~65-70%) also successfully incorporated and correctly used the new terminology, such as supramolecular chemistry, host:guest binding, and self-assembly in their postlab reports. This leads us to believe that none of the concepts are too difficult for chemistry or biochemistry students during years 2 – 4 to understand, and that the majority of students had met the learning goals.

Alternatively, when run during the non-major second-year undergraduate organic course, students were less successful at accessing/understanding the primary literature. Despite being instructed in how to access and to approach reading the primary literature, the student buy-in of this population was low, and polling seems to suggest that most students simply chose not to read the primary literature. To alleviate this challenge it became necessary to expand the prelab lectures to provide the information that the primary literature was intended to address. This also required expanding the discussion towards the more advanced topics, especially with regard to the explanation for entropic versus enthalpic driving forces for self-assembly. After this modification, we found that the average student was answering more than half of the postlab questions correctly, although the rate of students successfully incorporating the new terminology into lab reports was lower than desired (~25-35%).

Overall, this experiment provides an opportunity to challenge students with questions that require critical reasoning. Based on our observations, this experiment is completely appropriate for introduction in either an upper-division or second-year organic chemistry laboratory course. There is easily comprehendible primary literature that beginning students can be directed towards to gain a better understanding of the underlying chemistry,[4,7-8] as well as to use for support in answering postlab questions. Besides what is presented herein, extensions to this experiment are also possible (see Supporting Information). We note that the experiment was not as successful when presented in the current format to second-year non-major organic chemistry students, and that caution and patience are advised if trying to implement this lab in a non-major setting, whether it be to upper-division or second-year students.

ASSOCIATED CONTENT

Supporting Information

Student handouts, instructor notes, and spectral data are available on the ACS Publications website at DOI: 10.1021/acs.jchemed.

"Chemicals and general methods; Student handouts (versions 1 and 2); Instructor notes, with answers to prelab and postlab questions (DOCX)"

"C-undecylcalix[4]resorcinarene IR spectrum (PDF)"

"Sample NMR spectra (PDF)"

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