

Introduction of a Computational Chemistry Course-Based Undergraduate Research Experience (CURE) into an Advanced Organic Chemistry Lab: An Investigation of Propellane Formation

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Received September 27, 2021; Revised November 02, 2021; Accepted November 07, 2021

Abstract The introduction of basic computational chemistry concepts is becoming an integral part of any complete undergraduate curriculum in chemistry. The advanced organic chemistry course affords laboratory time in which some focused study of computational chemistry is possible. Although learning how to carry out basic computational manipulations is important, interest in computational chemistry can be instilled by carrying out a research-like experience. We incorporated a course-based undergraduate research experience (CURE) into our advanced organic chemistry lab course in which students, as a group, studied the spontaneous formation of strained propellane compounds from the corresponding anionic bridgehead bromide precursor compounds. Completing the calculations and data analysis as a class simulated a true research project, and led to the discovery of results from which interesting conclusions were drawn. Student feedback was generally very positive and suggested that this project gave them a strong sense for how computational chemistry research is conducted.

Keywords: organic chemistry, computational chemistry, propellanes, course-based research experience, CURE

Cite This Article: Phillip J. Alexander, Dillon Button-Jennings, Claudia N. Evans, Mason B. Hemstreet, Marissa E. Henager, Stephanie Jacob, Charles S. Jolly, Maayan R. Lantzman, Alexandra Saputo, Nolan R. Stager, Elizabeth L. Whitman, Bohdi J. Young, and Gary W. Breton, "Introduction of a Computational Chemistry Course-Based Undergraduate Research Experience (CURE) into an Advanced Organic Chemistry Lab: An Investigation of Propellane Formation." *World Journal of Chemical Education*, vol. 9, no. 3 (2021): 88-93. doi: 10.12691/wjce-9-3-4.

1. Introduction

Computational chemistry has become an integral part of research in organic chemistry as evidenced by its prevalence in articles published in current organic chemistry journals. Therefore, it is important to ensure that undergraduates completing degrees in chemistry have a working knowledge of the theoretical basis of computational chemistry, how computational chemistry programs generally work, and how to apply computational chemistry to research questions of interest [1-5]. Furthermore, computational chemistry provides an alternative to traditional laboratory-based research, thereby broadening interest in, and access to, research experiences to a greater diversity of students [6].

At Berry College we offer an advanced organic chemistry course that builds upon the content learned in the two-semester introductory sequence. The course enrollment includes students that intend to pursue a graduate education in chemistry, students looking forward

to employment following graduation, and students that are simply interested in learning more about organic chemistry. The course has an associated 3-hour laboratory that has typically been used like other organic chemistry labs in which students carry out lab-based chemical manipulations, albeit at an advanced level relative to the sophomore-level course. However, given the increasing importance and prevalence of computational chemistry in the chemical community, we decided to use some of the laboratory time to provide an introduction to the essential elements of computational chemistry from an organic chemist's standpoint.

Following the introduction of computational chemistry, we felt it important to demonstrate how computational chemistry is commonly utilized by organic chemists. We therefore integrated a research-like computational experience into the lab. Such course-based undergraduate research experiences (CUREs) have proven to be remarkably effective at enhancing positive educational experiences in chemistry labs [7,8]. Small-ring propellanes are a structurally-fascinating class of compounds in which bridgehead carbons exhibit unusual

pyramidalized geometries leading to highly strained C–C bonds [9]. A serendipitous computational discovery (described below) presented an opening for a line of investigation that lent itself to class participation.

In this paper we briefly describe how concepts in computational chemistry were introduced, the research project that was studied by the class, how data was collected and analyzed as a group, and overall impressions of the project as gathered from student feedback.

2. Results and Discussion

2.1. Introduction of Computational Chemistry Concepts

Being at a small college, it made little sense to expect sufficient enrollment in a dedicated course that often serves as the means by which computational chemistry is introduced to undergraduate students at larger institutions. While we have integrated elements of computational chemistry into other courses (e.g., our sophomore-level organic and physical chemistry courses), we wanted to ensure students had a fundamental understanding of what the computational software was doing within “the black box”. The advanced organic chemistry lab seemed to be the perfect place to introduce computational concepts. There are many options for computational chemistry software (commercial and open source) including those programs very familiar to practicing computational chemists such as Gaussian [10], GAMESS [11], ORCA [12], and others. However, we didn’t want students to be intimidated and/or distracted by the difficulties of creating complicated input files as required by most of these programs. We, therefore, opted to utilize *Spartan Student Edition* as a reasonably-priced, user-friendly software package that incorporates an easy-to-use graphical user interface to set up calculations and view results [13,14]. To complete the computational research study, we required more advanced capabilities, which will be discussed below. The results described herein, however, could be adapted to any computational program. Table 1 provides a brief overview of the order in which computational chemistry concepts were introduced to the students over a five-week period along with sample exercises.

2.2. Carrying out the Computational Research Project as a Class

Once the 5 weeks of introductory material were completed as outlined in Table 1, the instructor was confident that the students had a good grasp of the concepts covered and were prepared to use them in a research-like setting. While we initially had a project planned that investigated the limits of Bredt’s rule, a chance observation opened up a new and interesting line of inquiry. In the lecture portion of the class we had analyzed the unusually strained central bond of [1.1.1] propellane (Figure 1). Small-ring propellanes have pyramidalized bridgehead carbons in which all four bonds are directed to one side of the carbon

atom rather than its preferred tetrahedral geometry [9]. This results in very strained bridgehead-bridgehead bonds that often lead to unusual physical and chemical properties [9]. Several propellanes have been synthesized according to the route outlined in Scheme 1 for [1.1.1] propellane [9]. One of us thought it would be interesting to model the energy difference between the starting anionic bridgehead bromide and the resulting propellane. A quick semi-empirical PM3 optimization of the geometries of both the precursor anionic bromide and the final propellane suggested this could be done. However, when we tried to optimize the geometry of the same anionic bridgehead bromide using the more advanced DFT B3LYP/6–31G* level of calculation, the optimization resulted in spontaneous expulsion of the bromine atom (as bromide), and formation of the central bridgehead-bridgehead propellane bond. This led to the question as to what the structural limits (i.e., bridge size) might be for such spontaneous propellane formation (e.g., do ALL such bridgehead anionic bromides undergo spontaneous propellane formation?). Fortunately, the PM3 optimizations could provide a geometry upon which we could calculate an energy at the B3LYP/6–31G* level in order to estimate (albeit crudely) ΔE ’s for the propellane-forming reactions.

We laid out the following initial questions to investigate:

- (1) Does the type (size) of bridging affect the C–Br bond length in the anionic bromides?
- (2) How does the type of bridging affect the ΔE for the conversion of anionic bromides to propellanes?
- (3) Do differing conformations of the anionic bromides affect the reaction?
- (4) Are there types of bridging for which propellane formation is not observed?

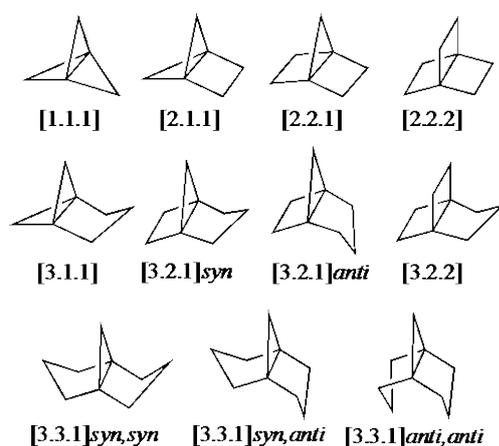
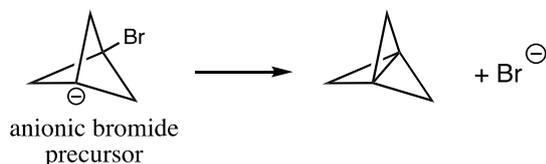
Eight propellanes were selected for investigation (see Figure 1). Two of these propellanes ([3.2.1] and [3.3.1]) and their precursors had two or more possible conformations available. We assigned *syn*- and *anti*-nomenclature to the conformations with regards to the orientation of the three-carbon bridge relative to the one-carbon bridge.

Before starting the project, we discussed the importance of securing reproducible results on all of the calculations conducted. To this end, each of the propellanes and their precursors were assigned to at least two students upon which to conduct *independent* optimizations and energy calculations. Students were tasked with communicating with each other to ensure they had final data (geometrical and energetic) that agreed, and to send the instructor one combined set of data per assigned computation. Three complete sets of data were to be collected as follows:

- (1) All precursor bridgehead bromo compounds with negatively charged bridgehead carbons were optimized using semiempirical PM3 calculations *followed by* single point energy calculations at the B3LYP/6-31G* level.
- (2) All precursor bridgehead bromo compounds with negatively charged bridgehead carbons were optimized using B3LYP/6-31G* calculations.
- (3) All neutral propellane compounds were independently optimized using B3LYP/6-31G* calculations.

Table 1. Description of Sequence of Introduction of Computational Chemistry Concepts and Assigned Exercises in the Advanced Organic Chemistry Course at Berry College

Week	Topic	Concepts Covered	Exercises Assigned
1	Building Input Structures and Making Common Measurements	Building simple and complex structures in three dimensions, performing elementary optimizations, measuring bond distances, bond angles, and dihedral angles.	A series of structures of increasing complexity were assigned for students to build and then perform measurements upon (e.g., progressing from ethyl benzene to cubene).
2	Computational Basics Using Alkanes	Setting up simple optimization calculations; understanding computational iterations and the energetic and structural optimization criteria imposed (e.g., maximum energy gradients and maximum displacement between atoms); defining local and global minima; defining a Hartree; using frequency calculations to differentiate stationary from non-stationary points; learning how to freeze coordinates; conformation searching.	Calculating rotational barriers for amines; running conformation searches on alkanes; examining cyclohexane chair conformations; calculating A-values and visualizing to explain relative values.
3	Computational Methods, Levels of Theory, and Basis Sets	Born-Oppenheimer approximation; understanding uses, limitations and applications of molecular mechanics and semi-empirical models; ab initio and density functional theory; defining basis sets, polarization and diffuse functions, and how to communicate levels of computations.	Examining and contrasting the structures of a series of increasingly complicated molecules via MMFF, PM3 and DFT methods (e.g., progressing from ozone to 1,1-dimethylstyrene).
4	Rendering, Analyzing, and Using Surfaces	Electron density calculations and electrostatic potential maps.	Building, optimizing and viewing the electron densities of bicyclic and propellane molecules; Building, optimizing, and viewing the electrostatic potential maps of DNA bases and some aromatic molecules (including azulene).
5	Rendering, Analyzing, and Using Frontier Orbitals	Rendering images of HOMOs and LUMOs; understanding which orbital to view for prediction of reactivity.	Predicting sites of electrophilic aromatic substitution on a series of aromatic molecules; predicting O vs C alkylation of enolates; predicting direction of nucleophilic attack on cyclohexanones; comparing cis- and trans-cycloheptene; understanding Bredt's rule.

**Figure 1.** The propellanes investigated in this study. The terms *syn* and *anti* are defined with respect to the one-carbon bridge**Scheme 1.** Formation of [1.1.1] propellane via intramolecular attack of the anionic lone pair onto the bridgehead carbon bearing the bromo leaving group.

We had learned through prior experiences in lab that several of the student-owned laptops on which the *Spartan* Student Edition software had been run (Wavefunction, Inc., the company that produces *Spartan* Student, requires that the computers be student-owned) would be inadequate for the optimizations at the B3LYP level [13,14]. While we had available some computers that had a site-license for the full version of *Spartan*, competition for their use in other classes, and the lack of convenience of being able to

submit and analyze calculations in the evenings and over the weekend, sent the instructor in search of an alternative. Fortunately, we discovered access to supercomputer sites via the website ChemCompute (chemcompute.org), a site maintained by Dr. Mark Perri at Sonoma State University [15]. This website grants academic access to supercomputers for educational purposes. The program we utilized was GAMESS [11], which usually requires the generation of complicated input files, but Dr. Perri has ingeniously engineered job submission and visualization to be as simple and intuitive as possible. Therefore, all data related to the propellane project discussed in this paper derives from results on GAMESS by way of the ChemCompute website.

During the first week of the project, the instructor demonstrated how to set up, submit, and analyze calculations through the website. Students in the course then began setting up their own calculations with the help of the instructor as needed. We opted to conduct the calculations using the 6-31G* basis set, even though a basis set containing diffuse functions would have been preferred for anionic substrates, in order to conduct the calculations as efficiently as possible but with acceptable accuracy. Students were provided with explicit conditions to use for each of the calculations described above including ensuring that all optimized structures were at energy minima by running frequency calculations. We quickly realized that the computational platform was becoming overwhelmed with so many simultaneously submitted jobs. Therefore, students were given one week to i) run all of the individually assigned calculations, ii) analyze the results to ensure they were reasonable, and iii) communicate with their partner to confirm the result and re-submit calculations if there were discrepancies.

Armed with their data, in the second week of the project the students completed as a group a series of

editable online tables that summarized the information calculated, including relevant bond lengths, energies, and observations. The class reviewed the compiled data and looked for data points that appeared to be out of the ordinary. These data were double checked and sometimes needed to be corrected. The completed tables containing all of the structural and energy information are available in the Supporting Materials.

A brief summary of the computational observations is provided below:

(1) All of the bridgehead anionic bromide precursor compounds were successfully optimized with PM3 semiempirical calculations with the exception of the [3.3.1] derivatives. The final geometry of the bromide derived from the [1.1.1] derivative is provided as a representative example in Figure 2A. Optimized geometries for all of the anionic bromide precursors are available in the Supporting Materials. Unlike the other derivatives, all three of the conformational isomers of [3.3.1] underwent spontaneous elimination of the bridgehead bromine as a bromide ion along with formation of the central propellane bond even at this low level of computational theory.

(2) All of the bridgehead anionic bromide precursor compounds underwent spontaneous elimination of the bridgehead bromine as a bromide ion along with formation of the central propellane bond upon optimization at the B3LYP/6-31G* level of theory with the exceptions of the [2.2.2] and [3.2.2] derivatives. The final structures resulting from the optimizations for these two derivatives can be observed in Figure 2B and Figure 2C. The [2.2.2] derivative expelled the bromine atom as a bromide but failed to form the central propellane bond. The [3.2.2] derivative underwent a Grob fragmentation during bromine elimination to form the corresponding bis-exocyclic diene. It was visually confirmed by animating the iterative process that the corresponding propellane was never formed during the optimization.

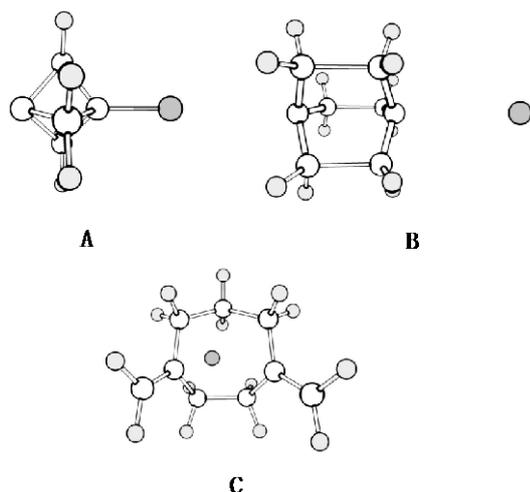


Figure 2. (A) Structure of the PM3-optimized geometry of the [1.1.1] anionic bromide derivative. Note the intact C–Br bond. (B) Final structure observed upon B3LYP-optimization of the [2.2.2] anionic bromide. Note that the C–Br bond has been broken (the bromide ion is to the right of the structure) but no central propellane bond is formed. (C) Final structure observed upon B3LYP-optimization of the [3.2.2] anionic bromide. Note that the C–Br bond has been broken (the bromide ion has migrated behind the structure), and that in addition to the lack of a central propellane bond, one of the C₂ bridges has broken to afford C=C bonds with the former bridgehead carbons

(3) All of the propellane derivatives could be readily optimized as stationary points at the B3LYP/6-31G* level of theory. Optimized geometries for all of the propellanes are available in the Supporting Materials.

Between the 2nd and 3rd weeks of the research project, the instructor double checked the submitted data in the tables to ensure they were correct. The instructor then sent out the finalized tables and a list of questions for the students to consider prior to reconvening for the 3rd, and final, week. These questions not only included the initially-generated set of research questions but also some new questions highlighting some important trends that seemed to be present in the collected data. The questions, and a student-written sample of the answers as generated by class discussion, are included in the Supporting Materials.

Below are some of the salient conclusions generated by the research study:

(1) The [1.1.1], [2.1.1] and [2.2.1] anionic bromide precursor compounds that were optimized at the PM3 level show an interesting trend. As the bridgehead-bridgehead distance becomes closer together (2.19, 2.00, and 1.81 Å, respectively), the C–Br bond length (1.96, 1.98, and 2.03 Å, respectively) increases. Class discussion concluded that the shorter bridgehead-bridgehead distance brings the negative charge into greater overlap with the σ-antibonding orbital of the C–Br bond. Population of this orbital weakens the C–Br bond, thereby resulting in bond lengthening.

(2) The spontaneous propellane formation from the [3.3.1] anionic bromide precursor compounds under PM3 optimization, unlike the other derivatives, was discussed as a class. Upon examination of the structures of the resulting product propellanes, it was concluded that the newly formed bridgehead/bridgehead bonds for these particular derivatives were the most “normal” (i.e., tetrahedral) of the propellanes, and that they were, therefore, expected to be considerably less strained than the others. For these derivatives then, even the lower-level PM3 optimizations were sufficient to form the propellane bonds.

(3) The order of stability of the [3.3.1]propellane conformers according to B3LYP/6-31G* calculations was [3.3.1] *syn,syn* > [3.3.1] *anti,syn* > [3.3.1] *anti,anti*. This appeared surprising at first since the *syn* stereochemistry appeared to be the most sterically congested as it simulates a “boat-like” structure rather than the “chair-like” structure in the *anti*-conformations (see Figure 1). However, upon closer examination of the geometries, two features stand out. First, the bond length of the strained central propellane bond trends upward in the series (1.521, 1.522, and 1.525 Å, respectively). Thus, adopting the *anti*-conformation appears to further strain the already-strained central propellane bond. Second, the dihedral angles between the neighboring CH bonds of the 3-carbon bridges is greatest (34°) for the *syn*-conformation and least (31°) for the *anti*-conformation. Thus, adopting *syn* stereochemistry results in greater relief of torsional strain energy. This appeared to be an interesting case in which the strain energy inflicted upon the molecules by increased steric strain is more than offset by the overall decrease in strain energy due to relief of strain on the central propellane bond as well as relief of torsional strain energy.

(4) The [2.2.2] anionic bridgehead bromide expels the bromine atom as bromide, but resists forming the central propellane bond. Likewise, the [3.2.2] derivative expels its bromine atom, but opts to form a diene rather than the expected propellane. Class discussion of the anomalous behavior of these two derivatives relative to the others ultimately concluded that these two derivatives were exemplifying the general reluctance of molecules to form strained propellane derivatives. The shorter-bridged derivatives (i.e., [1.1.1], [2.1.1], [2.2.1], [3.1.1] and [3.2.1]) formed the corresponding propellanes due to the structurally-enforced proximity of the two bridgehead carbons. The two carbons are simply too close to one another to avoid forming the central bond. On the other hand, the larger-bridged derivatives (i.e., the conformers of [3.3.1]) can easily form the propellanes because the resulting bonds are not particularly strained since the bridgehead carbons can adopt a near normal tetrahedral geometry. The [2.2.2] and [3.2.2] derivatives serve as a transition between these two behaviors. These bridge sizes, while not sufficiently large to avoid strain in the incipient central propellane bonds, are sufficiently large to provide enough distance between the two bridgehead carbons that central bond formation can be avoided, and alternative optimization routes taken. In the case of the [2.2.2] derivative it optimizes as a diradical species [see 4]. The slightly larger [3.2.2] derivative is apparently sufficiently flexible to allow for a Grob fragmentation to occur. It should be noted that experimentally [2.2.2]propellanes are known to undergo a similar Grob fragmentation [9,16]. Animations (mp4 files) of both of these optimizations are provided in the Supporting Materials. It was observed that the fragmentation of the [3.2.2] derivative does not occur via the [3.2.2]propellane as an intermediate. This is consistent with the observation that the [3.2.2]propellane can be independently optimized under B3LYP/6-31G* conditions, and is therefore computationally “stable” as a stationary point relative to fragmentation.

2.3. Student Response to the CURE

Following the final discussion of the results, students were asked to complete a survey in an attempt to determine whether the research experience had any positive effects. Three of the most relevant questions and student responses are provided in Table 2. In summary, while most students did not quite understand how computational chemistry might be integrated into a research project before the project (but notably even after completing the introductory computational chemistry material!) there was *unanimous* consensus

following completion of the project as to how computational chemistry could be utilized in a practical sense.

Several students had very positive things to say about their personal experience with the computational chemistry research project:

“I think that this group research project was overall great.... I do think that this is a unique experience that is valuable for the class, and it should be a component in future classes.”

“I thought the overall research project was extremely efficient for expanding my knowledge on computational chemistry. To be honest, I did not even know computational chemistry existed prior to this class and project. I love how there are endless molecules to create and study. The only limits are the rules of organic chemistry and my imagination.”

“I honestly enjoyed the research project, it wasn't too intense and was illustrative of the applications of computational chemistry when assessing chemical phenomena.”

“The experiment was enjoyable and fun. It had a simple method and was a great way just to understand how things work for a crazy computational chemist.”

“I enjoyed working on this project in pairs. It was helpful to work with a partner to ensure correct results.”

Finally, several students offered constructive criticism for improvement of the CURE experience:

“I think a period of open discussion where the students lead the discussion and make observations would be nice.... I know we individually came to conclusions but being able to have a roundtable discussion about what I got out of it with my equals would have been preferable to me personally.”

“I think if there was a way for us to finish the computations in class, so that we could discuss what we saw within our own group, would have been super helpful to my understanding. I know that the computations were elaborate and took a while, so this was hard to do. I just wish we had more in-group discussion before the big class discussion.”

“I found discussing the anomalies very interesting and what circumstances brought them to be. I would very much have liked to dive a little deeper into the chemistry behind them and maybe discuss computational methods for trying to understand outliers.”

From the instructor's viewpoint, it was pleasing to see that the major criticisms were that students wanted to do *more* than they were asked to do, and asked to spend more time analyzing data and interpreting results. To this end, enhanced discussion periods will be incorporated into the next offering of this course.

Table 2. Results of Survey on Impact of the Computational CURE

Question	Results
Before this project I wasn't sure how computational chemistry could be used as a research tool	67% agree 43% unsure or disagree
After carrying out this research project, I have a better understanding of how computational chemistry can be useful in a research setting	100% agree
Carrying out this research had the following impact on my interest in computational chemistry as a whole	67% increased 25% remained the same 8% decrease

3. Conclusions

Introduction of computational chemistry concepts is important to current chemistry students. Even with an understanding of these foundational concepts, however, the connection to how computational chemistry can be used in a research setting may remain unclear. By following up the introduction of computational concepts with a true computational research project via a CURE experience, students leave not only with a greater appreciation for how computational chemistry can be used in a practical sense, but also with more positive impressions of computational chemistry as a whole. Given that, as one student astutely remarked, that the only limits of computational chemistry “are the rules of organic chemistry and my imagination”, any number of similar class-based computational chemistry research projects can be devised that satisfies the curiosities of both the faculty member and students. We hope that the framework laid out in this article facilitate such course-based collaborations.

Acknowledgements

The authors thank the Department of Chemistry and Biochemistry at Berry College for purchasing the Spartan Student Edition software, Dr. Kenneth Martin for reviewing this manuscript and offering sage advice for its improvement, and Dr. Mark Perri for his assistance with the operation and use of the ChemCompute website. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1548562.

Supporting Materials

Student Handout 1 (PDF) that describes the research project to be carried out; Completed Propellane Results Tables (PDF); a compilation of optimized Propellane Structures (PDF); Student Handout 2 (PDF) containing the questions asked post-calculations; Student Sample Answer Questions (PDF); A sample of how a student answered the Student Handout 2 questions (PDF); movie file of the [2.2.2] optimization at the B3LYP level (mp4); movie file of the [3.2.2] optimization at the B3LYP level (mp4).

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