Molecular Modeling Exercises and Experiments

Integrating Computational Molecular Modeling into the Undergraduate Organic Chemistry Curriculum

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Advances in the speed and memory capacity of desktop computers, combined with advances in molecular modeling software have made molecular mechanics (MM) and molecular orbital (MO) calculations practical, readily available tools for the organic chemist to analyze molecular structures, predict products of reactions, and rationalize reactions and mechanisms.¹ These advances have also made it practical to routinely use MM and MO calculations in undergraduate organic chemistry instruction. Not surprisingly, there has been a dramatic increase in chemical education publications involving computational molecular modeling. Figure 1 shows the number of publications by year obtained from a search of the JCE Online database using the key words “molecular modeling”.

Nearly all of these publications describe the use of computational molecular modeling in the undergraduate chemistry curriculum, and many of them describe specific modeling experiments for use in organic chemistry (1), but only a few of the articles published to date describe broad-based use of molecular modeling in introductory- or intermediate-level organic chemistry. In 1993, Casanova described a program, very progressive for the time, in which students made regular use of computational molecular modeling starting in introductory organic chemistry (2). In 1998, Martin described an undergraduate chemistry curriculum that integrated computational molecular modeling progressively into the course work starting with organic chemistry laboratory (3). In 2001, two articles by Hull described specific modeling experiments for organic chemistry and made reference to an introductory organic chemistry course in which molecular modeling was a component of each lab experiment (4). In 2002, Paselk and Zoellner described a program that included an intermediate-level molecular modeling course for chemistry majors and implementation of computational molecular modeling throughout the undergraduate curriculum starting with some experiments in first-year general chemistry (5).

Organic chemistry textbooks now include numerous representations of molecules based on MO calculations. Most commonly, these are in the form of colorful electrostatic potential maps superimposed on electron density surfaces. Additionally, most organic chemistry textbooks now include computer modeling exercises for the students, either in the text or as part of the online materials (6).

Considering the extent to which computational modeling has been featured in the organic chemistry education literature and integrated into organic chemistry textbooks and how readily available the tools are, there are surprisingly few undergraduate programs that involve students in computational molecular modeling as part of their organic chemistry course work. A survey was recently conducted among chemistry graduate students at this university to determine how many were involved in any kind of computational molecular modeling in their undergraduate programs. The survey obtained responses from 71 graduate students representing a broad crosscut of 26 public universities and 31 private universities or colleges in the United States and 4 non-U.S. universities. Of the 71 respondents, 35 had no experience with computational modeling as part of their undergraduate course work whereas 24 had some experience with computational modeling in a physical chemistry or other upper-level course. Only 12 out of the 71 respondents were involved with modeling as part of their introductory- or intermediate-level organic chemistry course work.

It appears that for the majority of undergraduate organic chemistry programs use of computational molecular modeling has not extended beyond looking at colorful pictures in the textbook. There are probably numerous reasons for this situation. One likely reason is that the logistics of involving students in computational modeling, as part of the classroom experience, are somewhat complex. Students need access to computers equipped with the appropriate modeling software, and they need a certain amount of training in the use of the software before they can conduct modeling exercises. Another likely reason for the limited use of computational modeling is that MO descriptions of molecules, while more accurate and realistic than the simple localized bonding descriptions typically used in teaching introductory organic chemistry, are more difficult for students to understand. Consequently, most organic chemistry instructors rely heavily on simplified descriptions of structure, bonding, and reactivity with infrequent use of MO descriptions. As a consequence, students exposed to MO depictions of molecules often find them initially contradictory and confusing. Helping students overcome this confusion is one of the challenges we have faced as we have integrated computational molecular modeling into our organic laboratory curriculum. Considering the challenges associated with using computational molecular modeling in the teaching of introductory- and intermediate-level organic chemistry, combined with the fact that most instructors devote the majority of time to...
formula manipulation exercises rather than bonding and reactivity concepts and theory, it is not altogether surprising that many instructors feel that the pedagogical benefits of computational molecular modeling are not worth the time or “trouble”.

We present a positive viewpoint on the value of molecular modeling in teaching introductory- and intermediate-level organic chemistry and a success model for integrating computational modeling into the organic lab curriculum. Importantly, we contend that the pedagogical benefits of using computational modeling to teach organic chemistry outweigh the “inconveniences”. However, making the most effective use of computational modeling in undergraduate chemistry instruction calls for some rebalancing of the way we teach structure, bonding, and reactivity.

### Molecular Modeling Instructional Unit

The molecular modeling instructional unit was developed for use in a two-credit introductory organic laboratory course that fulfills the laboratory requirement for all majors that require one year of organic chemistry with lab. For programs in which organic chemistry lab is divided over two semesters as two one-credit labs, this molecular modeling unit would be most appropriate to incorporate into the second semester.

**List 1. Computational Modeling Unit for Introductory Organic Chemistry Lab**

**Introduction**
- Building molecules
- Visualizing and manipulating structures

**Using Molecular Mechanics Calculations To Analyze Conformations of Hydrocarbons**
- Butane
- Substituted cyclohexanes

**Using MO Calculations To Understand Electron Distribution within Molecules**
- Formal charges and charge distribution
- MOs for aromatic hydrocarbons
- Valence bond theory and VSEPR models compared with MO theory

**$S_{N}1$ and $S_{N}2$ Reactivity**
- Prediction of relative $S_{N}1$ reaction rates based on calculated energies of carbocation intermediates
- Prediction of relative $S_{N}2$ reaction rates based on transition-state energies

**EAS Reactivity: Predicting Regiochemistry of Reactions**
- Predictions based on partial charges in aromatic starting materials
- Predictions based on energies of arenium ion intermediates

**Diels–Alder Reactions**
- Rationalization of relative reaction rates based on the HOMO–LUMO gap
- Prediction of stereoisomerism based on transition-state energies

The molecular modeling unit was developed with the following objectives:

- Introduce students to computational molecular modeling and provide them with a conceptual understanding of molecular mechanics calculations versus molecular orbital calculations and what each is most useful for.
- Give all students individual hands-on training and experience using computational modeling software.
- Have students use computational modeling as a practical problem-solving tool to analyze the results of reactions already conducted in the chemistry lab and predict results of reactions to be conducted subsequently.

Inherent in the last objective is an emphasis on connecting molecular modeling in a meaningful and useful way to the compounds and reactions that students explore in the organic laboratory. We feel that this last objective has been key to successful introduction of modeling into our curriculum with a student response that has been generally favorable.

The computational modeling unit is summarized in List 1. The computational exercises were designed using Spartan Student Edition (Spartan ST) software from Wavefunction Inc. and were carried out during two, four-hour lab periods. The design calls for students to work in pairs, but every exercise calls for individual hands-on computer work by each student, making it unlikely that one of the students in a pair becomes the active partner while the other becomes an observer. This design requires a dedicated computer work station for each student for the two lab periods. In our lab program, we have accommodated a course enrollment of about 500 students with 36 computer work stations by using a three-week schedule rotation in which one third of the lab sections complete the modeling unit each week. The lab manual chapter containing detailed background and procedures for the experiments, as provided to the students, is included in the online material, along with instructor’s notes and an answer key.

The instructional unit begins with a classroom session (ca. 30–45 minutes) in which the lab instructor reviews general background information and concepts pertinent to computational molecular modeling. This initial classroom session expands on the introduction section of the lab manual chapter, reviews definitions and terminology, sets objectives and expectations for the molecular modeling unit, and begins to familiarize students with the Spartan software. After the classroom session, the students begin work in the computer lab. The first exercise is a general tutorial to further familiarize them with the software and how to build structures using the model kit. This is followed by a progression of computational modeling exercises that start with molecular mechanics calculations to explore conformations of hydrocarbons and proceed through a series of MO (semiempirical PM3 and some ab initio 6–31G*) calculations. Students first explore how these calculations can be used to understand electron distribution within molecules, then how they can be used to analyze various reactions including $S_{N}1$ or $S_{N}2$, electrophilic aromatic substitution, and Diels–Alder reactions. The reactions analyzed include examples from the students’ laboratory experience. The modeling experiments described here were those used during the fifth semester in which modeling was used in the course. Based on student and teaching assistant (TA) feedback, the experiments were revised each semester to improve their instructional value and success of execution by the students.
Student Feedback on Computational Modeling

Each semester, feedback from students on their molecular modeling experience has been solicited via e-mail near the end of the course. The feedback request encourages candid comments, and students are given the option of responding anonymously. Out of 23 students who responded to the request for feedback during the fifth semester, 16 expressed an overall favorable opinion about their experience with the computational modeling lab and 7 expressed a neutral or negative overall opinion with negative comments offsetting any positive comments. Among the 16 students who expressed an overall favorable opinion, 10 of those also offered criticisms or suggestions for improvement. The verbatim student comments are included in the online material.

Pedagogical Implications from Student Feedback

Over the five semesters that we have incorporated computational modeling throughout all sections of our introductory-level organic chemistry lab course, common themes among the favorable comments have been the value of visualizing the molecules in 3D and better understanding the basis for reactivity differences observed in reactions performed in lab. Common themes among the unfavorable comments have been that the modeling lab was “confusing”, and using a new, unfamiliar computer program was “frustrating”. Through many one-on-one discussions with students and TAs, it has become evident that much of the confusion relates to students’ lack of prior familiarity with MO concepts and descriptions of molecules. Although MO theory is covered to some extent in general chemistry and the organic chemistry lecture courses, and all of these students have completed those courses, it is evident that retention of the information and familiarity with MO concepts and terminology is generally low.

Additionally, in MO representations, students are exposed to some features that appear to be in direct contradiction with what they have learned about electronic structure and bonding from Lewis structures and the valence shell electron pair repulsion model (VSEPR) combined with the hybridization concepts of valence bond theory. For example, based on bonding and hybridization descriptions in their general chemistry and organic chemistry textbooks, students expect to see evidence of sp³ hybridized oxygen in water, alcohol, and ether molecules. They expect the oxygen atoms in these molecules to have two equivalent nonbonded electron pairs (lone pairs) projecting from the oxygen atom in orbitals that look similar to “rabbit ears”. Instead, their computational models of these molecules using semiempirical (PM3) or ab initio (6–31G*) calculations show something very different. In the case of the water molecule, the students see evidence for only one apparently nonbonding electron pair on oxygen that resides in a pure p orbital. Their molecular modeling result is a more accurate description of the electronic structure of the water molecule, consistent with experimental results, whereas the sp³ hybridized description with two equivalent lone pairs on oxygen is not [7]. In the case of alcohols and ethers, molecular modeling results indicate that there are no lone pairs of electrons localized on oxygen that can be considered strictly nonbonding. In the section of our instructional unit titled “Using MO Calculations To Understand Electron Distribution Within Molecules” we include an exercise “Lewis Structures and VSEPR Models Compared with MO Theory” where students use the results of their MO calculations on water to explore these apparent contradictions.

In the broader context, we conclude from our molecular modeling experience that the students would be better served by gaining greater exposure to MO descriptions of structure, bonding, and reactivity throughout their general and organic chemistry courses. There are many topics in general and organic chemistry that can be (and usually are) taught without invoking MO theory, but can be taught more accurately and effectively using MO theory. For example, consider the S_N2 reaction taught in introductory organic chemistry. The mechanism of this reaction is commonly taught without reference to MOs. Reasonable steric and geometric arguments can be made for backside attack of the nucleophile and formation of a trigonal bipyramidal transition state. However, recognizing the reaction as a Lewis acid–base or donor–acceptor interaction between the HOMO of the nucleophile and the LUMO of the substrate provides a more accurate and complete rationale for the reaction and the structure of the transition state. There are numerous other examples of topics and reactions taught in organic chemistry that can be better understood and to some extent “demystified” by invoking MO theory. These topics include aromaticity, conjugation, hyperconjugation, electrophilic aromatic substitution reactions, electrocyclic reactions, among others. It is our opinion that students can benefit by gaining a more complete understanding of these topics in the context of MO theory and then be better prepared to make practical use of computational molecular modeling as an analysis tool.

Summary and Conclusions

Although prominently featured in introductory organic chemistry textbooks, computational molecular modeling has not yet been widely adopted as an instructional tool in the undergraduate organic chemistry curriculum. We have presented an approach to integrating computational modeling into introductory organic chemistry as part of the laboratory program. This approach avoids some of the limitations of using molecular modeling in the classroom. We have used this approach in a large enrollment organic chemistry lab program for five semesters with favorable results. We believe, through individual hands-on experience with computational modeling, students are gaining a more complete and correct understanding of structure, bonding, and reactivity.

Note

1. Molecular modeling is a general term that can refer to a wide range of activities, from constructing “ball-and-stick” models of molecules to doing sophisticated computational modeling carried out on computers. Computational modeling generally falls into two categories: (i) molecular mechanics (MM) models that are based on force field calculations and (ii) molecular orbital (MO) models that are quantum chemical models based on approximating solutions to the Schrödinger equation.

Literature Cited


Supporting JCE Online Material

Abstract and keywords

Full text (PDF) with links to cited JCE articles

Supplement
  Lab manual chapter covering molecular modeling
  Molecular modeling notes for the teaching assistants
  Molecular modeling answer key
  Student feedback on molecular modeling experiences