Using Molecular Modeling in the Organic Chemistry Course for Majors

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Abstract: Molecular modeling provides a way to correlate theoretical concepts with experimental data; therefore, we have introduced organic chemistry students to molecular modeling early in the first semester. This approach provides students with additional skills for clarifying chemical and theoretical concepts by means of demonstrations in the classroom and hands-on tutorial modules. In this manner the impact of the active-learning process is increased. In addition, this tool allows us to further enhance laboratory experiments already developed using a guided-inquiry approach and to design new experiments. Chemical concepts such as conformational analysis, stereochemistry, IR spectra, molecular and electronic properties, molecular orbitals, and chemical reactivity are emphasized through this approach.

Introduction

We have developed several strategies aimed at improving student performance for the majors organic chemistry course at UPR-RP. These include increased utilization of technologically oriented inquiry-based laboratory experiences and molecular modeling. The fast development of computer technology and software has allowed the field of molecular modeling to become a powerful tool in chemistry, including at the academic level. In our classroom, this type of technology is being used to enhance student learning experiences through the visualization of three-dimensional molecular structures, stereochemistry, energy profiles, infrared spectroscopy, and molecular orbitals. Molecular modeling is also being used to enhance inquiry-based laboratory experiences that have been developed for this class.

Our goal is to introduce molecular modeling across the organic chemistry curriculum and to develop connections between the interpretation of data gathered in the laboratory and the theory discussed in class. This is accomplished with the use of molecular computation and modeling, which helps the students develop a more compelling understanding of laboratory results. According to recent literature, molecular modeling has been used for laboratory experiments [1, 2], for new courses in computational chemistry for undergraduate students [1–4], to calculate the value of some physical properties [5], to understand stereoselectivity [6], to predict the three-dimensional structure of molecules [7, 9], to compute molecular surface areas [8], and to predict the most reactive site of a molecule [9, 10]. The interactive relationship between lecture, laboratory, and molecular modeling provides a rich learning opportunity to accomplish fundamental skills such as (1) recognizing the reaction pathways that might be possible (given the conditions) and predict the principal products, (2) proposing plausible reaction mechanisms, (3) integrating this knowledge in the solution of synthetic problems, (4) proposing structures based on spectroscopic analysis, (5) integrating concepts in solving complex problems, (6) applying this knowledge to new situations, and (7) recognizing the importance of organic chemistry.

By the introduction and implementation of molecular modeling experiences in the organic chemistry course we also want to addresses the following objectives: (1) to improve students' creativity and critical thinking, (2) to introduce students to literature and library research, (3) to improve students' understanding of fundamental concepts, (4) to improve students' ability to work in teams, (5) to improve students' ability to organize ideas, (6) to improve students' written and oral communication skills, and (7) to provide students with experiences in computer technology and chemistry software. Using computational chemistry and molecular modeling in the organic chemistry course provides an opportunity to enrich the students learning process [1] and to enhance their critical thinking [2]. With this in mind, we have introduced undergraduate students to the world of molecular modeling to reinforce their understanding of how organic molecules look, beyond the simple representation on paper or the ball-and-stick models. For these calculations, we are using the CAChe molecular modeling software (Computer-aided chemistry, Ver. 4.5, Fujitsu), although other molecular modeling packages can be used (i.e., MacSpartan Pro, Ver. 1.0.4, Wavefunction). The software is used in classroom demonstrations as well as hands-on student assignments and is available to students at the Educational Resource Center of the Department of Chemistry and several research laboratories. Our software license agreement (CAChe) even allows highly motivated students to have their own personal copies. Although software vendors have developed many molecular modeling tutorials and courseware, (and our students are encouraged to visit their Web sites), we have produced our own series of modules to aim at our goal. This has allowed us to tackle specific needs tailored to our approach and scope, to teach organic chemistry based on higher-order cognitive skills and critical thinking. In addition, this has allowed us to produce materials in Spanish, which is our students' first language. Five molecular modeling modules were developed:

I. Tutorial—How to Construct and Prepare Molecules for Modeling
II. Conformational Analysis and Energy Profiles: Alkanes and Cycloalkanes

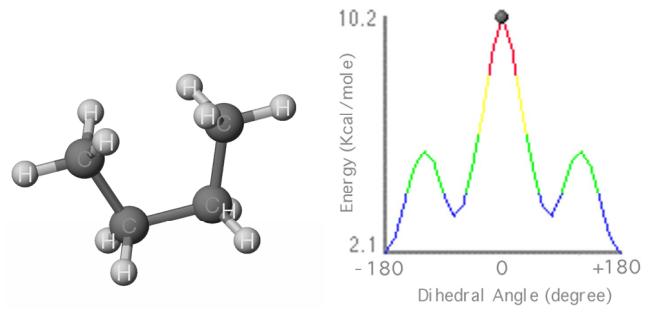

Figure 1. Conformational analysis and energy map for butane.

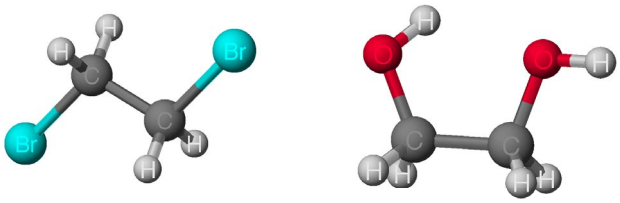

Figure 2. 1,2-Dibromoethane and 1,2-ethanediol.

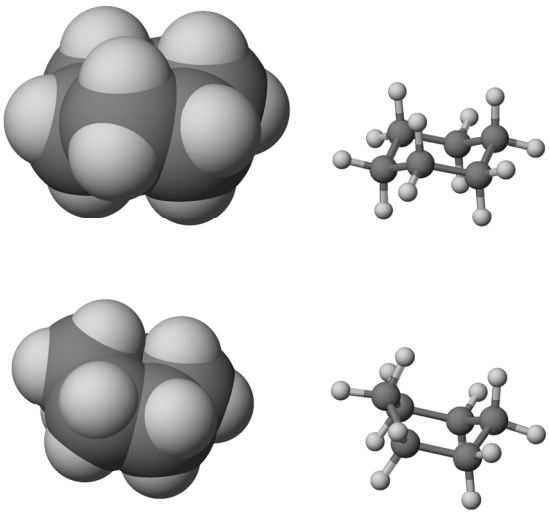

Figure 3. Cyclohexane chair and boat conformations.

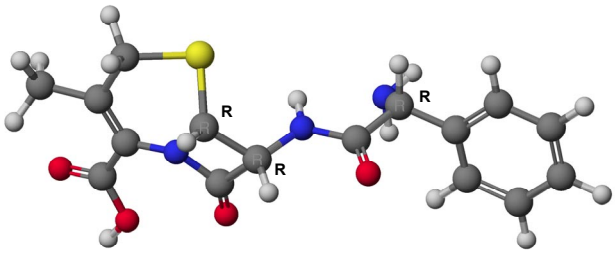

Figure 4. Cephalexin ball-and-stick model with CIP descriptors.

III. Stereochemistry
IV. Infrared Spectroscopy
V. Molecular Orbitals and Graphical Representations

This material is available on the home page [11].

Tutorial

Building a molecule is an important process. A basic tutorial module has been developed to familiarize the students with the software and the fundamentals of model building. This tutorial includes a general introduction to some software features and menu structure with a complete explanation of building a molecule from scratch, creating a molecule from fragments using the fragment library, representing different type of models (cylindrical bonds, space-filling model, etc.), and producing good starting geometries for later computation.

Conformational Analysis and Energy Profiles. A tutorial for performing conformational analysis has been developed for ethane and butane. After constructing the molecules, they are minimized using the molecular mechanics MM2 force field (conjugate-gradient method). Then, the conformational analysis is performed (MM2 exhaustive search method). The results are analyzed and each conformer is correlated to its corresponding position at the energy profile generated by the software (Figure 1). The concepts of energy minimization and types of computational methods are addressed only superficially because we believe that it is somewhat premature at this stage for an in-depth treatment.

Another exercise is a comparison between the conformational analysis of 1,2-dibromoethane and 1,2-ethanediol (ethylene glycol). In this activity, the students have to work on the conformational analysis for 1,2-dibromoethane (in which the most stable conformation is anti); then, they perform the same analysis for 1,2-ethanediol. In this case, the most stable conformation is gauche (Figure 2). Students are asked to discuss and present an explanation of the apparent discrepancy. After some discussion, they are able to correlate this finding with the presence of hydrogen bonding in 1,2-ethanediol and its importance in conformation. Usually conformational analysis at the undergraduate level is presented with emphasis on destabilizing, repulsive, torsional, and steric interactions. Here, students discover that stabilizing attractive interactions can be important as well.

A complete classroom demonstration for cyclohexane conformations, including the planar representation, was developed. Different types of models (cylindrical bonds, ball-and-stick and space-filling) were used and compared with the classical boat and chair representations. By rotating the molecules on the screen, Newman projections were generated. This is an ideal tool to illustrate torsional and 1,3-diaxial interactions. The space-filling representation was used to illustrate the 1,3 diaxial as well as the flagpole interactions and to point out the fact that molecular shape is governed by electron density (Figure 3).

Stereochemistry. After the topic on absolute configuration is presented and students have learned to work with 3-D projections on paper, a demonstration on stereochemistry is given in the classroom using the CAChe software. Initially, simple molecules with one stereogenic center, such as alanine, D- and L-glyceraldehyde, and epinephrine, are presented. After briefly stressing their importance in biochemistry, the structures are presented in wire-frame, cylindrical, ball-and-stick, and CPK models. The Cahn–Ingold–Prelog (CIP) R/S descriptors for each stereogenic center is determined using the different model types and structure orientations. The software then corroborates their conclusions. Successively, molecules with several stereogenic centers, such as menthol, camphor, and the β-lactam cephalexin, are similarly analyzed and the

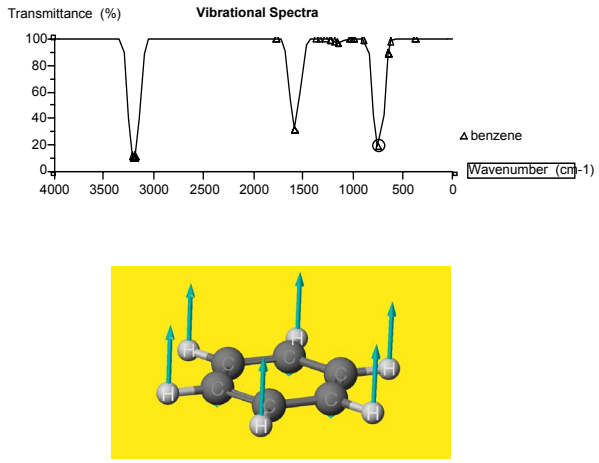

Figure 5. Calculated IR spectrum and out of plane bending mode for benzene.

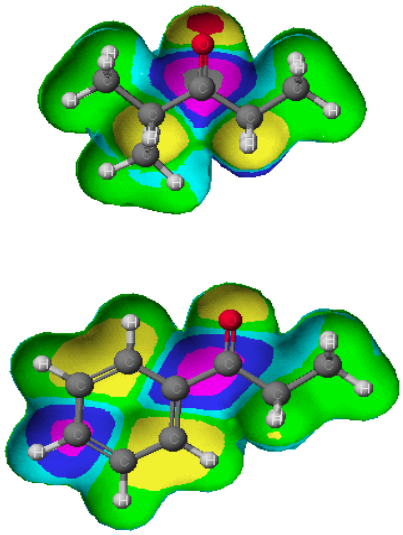

Figure 6. Color-coded LUMO electron density maps (isosurface) for 2-methyl-3-pentanone and propiophenone.

R/S designation for each center is established (Figure 4). Finally, the stereogenic centers for the androsterone steroid are analyzed. During these demonstrations, students become energized, fully participating in the class discussions, asking and answering questions, and showing increased interest. After the class, student visits to the Resource Center dramatically increase, requesting access to the computer stations. At the Center, they have access to the molecules presented in class and many other interesting molecules provided by the CAChe compound library.

A module on stereochemistry has been designed as supplementary material and is available at the Chemistry Resource Center and the class Home Page [11]. This module includes basic theory on stereochemistry, exercises regarding stereogenic centers, absolute configuration, and applications in the pharmaceutical industry. Drugs such as Prozac, Captopryl, Zocor, and many others are used for stereogenic center CIP designation exercises. This activity emphasizes the importance of stereochemistry in chiral drugs and the pharmaceutical industry.

Infrared Spectroscopy. Another application of molecular modeling and computational chemistry that has been introduced to the students is the generation of the vibrational spectra of organic molecules. For this, we use the AM1 semi-empirical method that can calculate the vibrational frequencies and graphically present the results as an IR spectrum. Although the calculation is performed in the gas phase and there is a 12% error inherent to quantum mechanical electronic methods [12], useful correlation between experimental and calculated peaks are obtained. The software even provides a graphical representation of the spectral frequencies and the vibration (stretching, bending, etc.) modes as illustrated in Figure 5. The students are required to apply this tool in several laboratory exercises during the academic year.

As shown in Figure 5, the CAChe software package provides the sense and direction of molecular vibrations using a static representation (out-of-plain bending in this example). This approach has been similarly used in a classroom demonstration using the MacSpartan Pro molecular modeling software (Ver. 1.0.4, Wavefunction). Using simple molecules such as methane, propane, methanol, formaldehyde, benzene, and others, we can graphically illustrate the different vibrational modes with on-screen real-time animations. Again, during these demonstrations the students become fully energized, significantly increasing their visits to the Resource Center.

Systematic Study of the Grignard Reaction Complemented with Molecular Modeling. Because computational chemistry is becoming essential in experimental chemistry [8], undergraduate students should be introduced to this tool by performing relevant basic calculations. As a prototype application of molecular modeling in the organic chemistry laboratory, an experiment dealing with the Grignard reaction is presented. The specific objective of this guided-inquiry experiment is to study how the reactivity of a carbonyl group in a Grignard reaction is affected by different carbonyl substituents. This laboratory experience includes the use of molecular modeling as the prelaboratory assignment to predict reactivity. The students are asked to perform a semi-empirical (AM1) calculation for each ketone to calculate and visualize the LUMO, the electrostatic potential, and the vibrational frequency associated with the carbonyl group. The electronic properties are graphically displayed on color-coded electron density maps (isosurfaces) and then used to predict carbonyl relative reactivity.

During the prelaboratory discussion, students are asked to predict the expected difference in the reactivity of a series of ketones and explain their reasoning using the results obtained from their molecular computations. For example, the results from LUMO calculations (isosurface) are used to compare and predict the relative carbonyl reactivity for the members of the series. As can be seen in Figure 6, the LUMO for 2-methyl-3-pentanone is more localized at the carbonyl carbon (based on the color-coded intensity) than that of 1-phenyl-1-propanone (propiophenone) indicating its greater reactivity towards a nucleophilic attack. This is further corroborated by a LUMO energy calculation. Their predictions are then sustained by the experimental results.

From this and other experiments, it is our experience that using molecular electronic calculations for predicting relative reactivities of simple chemical reactions does not always

produce good correlation between a selected property and the experimental results. For example, in the above Grignard experiment, while the AM1 evaluation of the LUMO properties for the ketones fits the expected reactivity, a similar approach on substituted benzaldehydes does not work for some substrates. A judicious evaluation of the proposed reaction mechanism, the type of calculation (molecular mechanics, semi-empirical, etc.), and the interpretation of the calculation results have to be thoroughly addressed.

Results and Discussion

We have introduced our students to molecular modeling, which provides them with additional skills for clarifying the chemical processes involved in their laboratory experiments and classes. In this manner the impact of the problem-based learning process is increased. As stated recently by Paul Lahti, "Far from being merely effective for production of attractive graphical presentations, modern computational chemistry allows a knowledgeable scientist to explore the effect upon properties caused by various substituents and structural changes in known materials, and in some cases even allows evaluation of completely novel materials" [13]. This approach has been used to further enhance those experiments already developed and to design new applications.

Through this additional tool we have addressed the aforementioned objectives to improve students' creativity and critical thinking, to improve students' understanding of fundamental concepts, to improve students' ability to work in teams, to improve students' ability to organize ideas, to improve students' written and oral communication skills, and to provide students with experiences with computer technology and chemistry software. A statistical study of student performance for the last six years reflects a significant improvements during the last three years, the time in which we have implemented the use of molecular modeling. According to this study, there has been an increase of 15% in students that obtained an A, B or C. Although this improvement has been the result of different approaches that have included the active-learning, inquiry-based laboratory experiences and molecular modeling, we firmly believe that the interactive relationship between class, laboratory, and molecular modeling have been important contributors to this improvement.

To access the impact of molecular modeling on the overall understanding of organic chemistry, a questionnaire, given at the end of the academic year, included some questions related to this approach. When asked about the contribution of molecular modeling to enhance their learning process, the students provided meaningful feedback. The results of the questionnaire showed that 36 % of the students considered molecular modeling very helpful, 60% considered it helpful, and only 4% considered molecular modeling not relevant or helpful to them.

On the question of whether the students continued to use molecular modeling on their own after the classroom- and laboratory-required uses, we have seen that during the second semester, student visits to the Resource Center for the purpose of using molecular modeling are mostly related to required laboratory work; however, there is an increasing tendency for students working on their research proposal (this is a second-semester course requirement where students form small groups and formally propose a new organic experiment for the teaching laboratory or address a current relevant chemical question) to include molecular modeling and computation in their work. In the latest proposal activity, 25% of the students included molecular modeling as part of their proposals.

Conclusions

Computational chemistry is becoming a standard tool for the experimental chemist. Through different classroom demonstrations, homework, and prelaboratory assignments our students are introduced to molecular modeling, which provides them with additional skills for clarifying the chemical processes involved in theoretical as well as their laboratory experiences. In many cases, a student's interest and motivation are greatly enhanced by demonstrations, and in this manner, the impact of the problem-based learning process has been increased.

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