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Integration of Computational Chemistry into the Undergraduate Organic Chemistry Laboratory Curriculum

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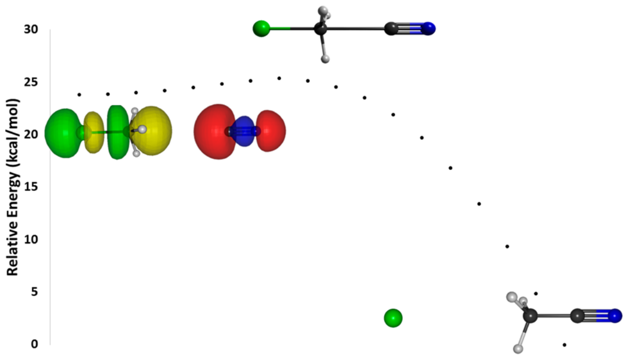
Supporting Information



ABSTRACT: Advances in software and hardware have promoted the use of computational chemistry in all branches of chemical research to probe important chemical concepts and to support experimentation. Consequently, it has become imperative that students in the modern undergraduate curriculum become adept at performing simple calculations using computational software, interpreting computational data, and applying computational data to explain chemical phenomena. We utilize computational chemistry in a high-enrollment (>1200 students/year), undergraduate organic chemistry laboratory course in a manner similar to that of organic chemistry researchers. We have employed WebMO as a web-based, easy-to-use, and free front-end interface for Gaussian09 that allows our students to complete ab initio and density functional theory (DFT) calculations throughout the curriculum. Rather than an isolated exposure to computational chemistry, our students use computational chemistry to obtain a deeper understanding of their experimental work throughout the entire semester. By integrating calculations into the curriculum, the focus moves away from performing the calculations to providing insight into chemical phenomena and understanding experimental results. We provide here both an overview of the introductory laboratory experiment and our integrated approach.

KEYWORDS: *Second-Year Undergraduate, Curriculum, Organic Chemistry, Misconceptions/Discrepant Events, Computational Chemistry, Molecular Modeling, Mechanisms of Reactions*

INTRODUCTION

Until recently, integration of computational chemistry into the undergraduate curriculum was almost prohibitively difficult due to both software and hardware concerns. There have been various implementations of computational chemistry in the undergraduate curriculum in recent years coinciding with the availability of more student-friendly software and the decreased cost of computing resources.[1−9] Given the heavy (and increasing) use of computational techniques in modern chemical research, it is critical to provide means for the effective introduction of this area to undergraduate students, along with examples of the authentic implementation of computational tools to support and enhance student learning in existing laboratory experiments. We present here a ready-to-implement introductory module appropriate for a sophomore organic chemistry laboratory course, along with an overview of how examples of computational chemistry have been integrated into each subsequent experiment. These exercises have been completed by >5000 students and can provide a useful starting point for an interested instructor.

EDUCATIONAL CONTEXT

The University of Wisconsin—Madison typically enrolls >1200 undergraduates per year in the introductory organic chemistry laboratory course. The laboratory course, which is separate from the organic chemistry lecture sequence, meets twice per week for 4 h per session and is offered during the spring, summer, and fall terms. The course is designed for students who require two semesters of organic chemistry including a laboratory course.[2] This course is taken either concurrently with or subsequent to the second semester organic chemistry lecture course. The laboratory course is designed to enhance the student learning of organic chemistry in the two lecture courses, but is an independent course with its own curricular goals and assessments. Most of the classroom and laboratory instruction students receive, including molecular modeling, is provided by teaching assistants or through prerecorded streaming video delivered via the course Web site.[10] This current implementation of computational chemistry, employing a WebMO[11] cluster-based approach, is based upon and has replaced the previously published module[2] that used Spartan Student Edition (SpartanST)[12] on approximately 50 PCs in a computer lab.

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Table 1. Introductory Computational Chemistry Laboratory Exercises

Exercise	Chemistry Concepts	Calculations Performed
Conformational isomers of butane	• Potential Energy Surface • Relative Energy • Hyperconjugation and Steric Repulsion	• optimization and vibrational frequency • relaxed conformational scan
Conformational isomers of cyclohexane derivatives	• Relative Energy • Chemical Equilibrium • Hyperconjugation and Steric Repulsion	• optimization and vibrational frequency
π Electron-donating and withdrawing effects of substituents	• Molecular and Atomic Orbitals • π-conjugation • Limitations of VSEPR	• optimization and vibrational frequency • Natural Bond Orbital (NBO)
^1H NMR and ^{13}C NMR chemical shifts	• Shielding and Deshielding effects	• optimization and vibrational frequency • NMR chemical shift prediction
Basicity of N atom lone pairs	• Relative Energy • Chemical Equilibrium • Hybridization of Lone Pairs • Molecular and Atomic Orbitals	• optimization and vibrational frequency • Natural Bond Orbital
S_N2 reactions	• Molecular and Atomic Orbitals • Transition States • Potential Energy Surfaces	• optimization and vibrational frequency • Natural Bond Orbital • transition state optimization • vibrational frequency • intrinsic reaction coordinate
Bond dissociation energies	• Homolytic Bond Cleavage • Potential Energy Surfaces • Open Shell Species	• optimization and vibrational frequency

■ COMPUTATIONAL METHODS AND RESOURCES

In our implementation, WebMO is installed as a front-end for Gaussian 09 on our departmental computer cluster.[13] The WebMO resource serves as a front-end interface to a variety of computational software, including freely available programs such as PSI4[14,15] or GAMESS.[16,17] Conveniently in our current installation, students can access WebMO via any Internet connection and are thus not required to be physically present in a departmental computer room. We have found that an approximate ratio of 1 processor per 5 students enrolled in the course has been sufficient for all of the calculations described in order to avoid significant backlog of jobs in the queue. Thus, WebMO is a convenient and inexpensive option for computational chemistry regardless of institutional computational resources; the majority of the cost is based upon computer hardware.

All student calculations presented here, as well as those performed by students in the course, were completed in Gaussian 09 using the WebMO interface. We have employed both ab initio (Hartree−Fock) and density functional theory (B3LYP) calculations, using either 3-21G or 6-31G(d) basis sets. Although none of these calculations are considered to be chemically accurate, they provide sufficiently accurate results in an appropriate time frame for the exercises and accompanying student learning described herein. The selection of an ab initio or a DFT method for a specific exercise was based on a combination of data accuracy and calculation time. For all calculated species, students use harmonic frequency calculations to confirm whether an output structure is an energy minimum (reactant, intermediate, or product) or an energy maximum (transition state) on the potential energy surface.

■ INTRODUCTORY COMPUTATIONAL CHEMISTRY EXPERIMENT

The introductory module (details provided in the Supporting Information) is situated in the early, skill-building portion of the laboratory course. This skill-building segment also includes cross-cutting experimental techniques such as extraction, thin-layer chromatography, and spectroscopy. With the presentation of foundational experimental and computational techniques in a combined block of the course, students are encouraged to view computational chemistry as an additional tool to use throughout the semester to support their experimental work and provide deeper conceptual understanding of the material. Prior to attending the two in-class laboratory sessions on molecular modeling, students are required to view three recorded lecture videos and read a section of the lab manual chapter. The introductory video lectures provide detailed demonstrations on the use of WebMO and discuss how to apply computational techniques to chemical problems.[10] Students are provided with a laboratory manual containing an overview of WebMO usage, descriptions of the computational methods, and instructions on how to interpret computational outputs. In addition, students are provided with individual assistance from course instructors and teaching assistants during the two 4 h hands-on laboratory sessions. Our focus as organic chemists has not included an in-depth description of the mathematics or quantum mechanical treatment of molecules in a particular method, but rather the interpretation of computational results and their application to student experimental data.

The first lecture video addresses fundamental concepts of charge distribution and molecular orbitals, material with which students should be familiar from the first-semester organic chemistry lecture course. This provides an excellent opportunity to help students understand the differences between formal atomic charges and a more realistic charge distribution in molecules. In the second video lecture, concepts of molecular and electronic structure are reviewed, and specific instruction on how to use the computational software is provided. For many students, this material signifies their first exposure to the limitations of VSEPR for the accurate prediction of electronic

Table 2. Integration of Computational Chemistry throughout the Laboratory Curriculum

Reaction	Summary of Calculations Performed
Nucleophilic Substitution Reactions (S_N1[24]/S_N2)	NBO analysis and NMR chemical shift prediction of the S_N2 product
Elimination reactions (E1/E2)	Relative energy difference of the two observed reaction products
Oxidation of 4-*tert*-butylcyclohexanol[25]	Exploration of the electronic structure of the active oxidizing agent $[H_2OCl]^+$
Reactions of nitrogen functional groups[26]	Exploration of the hybridization of a number of N atom lone pairs and their impact on physical properties and chemical reactivity
Wittig synthesis of ethyl cinnamate[27]	Comparison of the relative energy of the product isomers and prediction of the ^1H NMR chemical shifts of each
Stereochemistry of a carbonyl reduction[28]	Exploration of the stabilization of an intramolecular H-bond in the starting material
Electrophilic aromatic substitution—nitration	Investigation of the electronic structure of a strong electrophile. Application of Hammond's postulate to predict the outcome of a kinetically controlled reaction
Electrophilic aromatic substitution—acylation[21]	Investigation of the electronic structure of an acylium-type cation
Grignard reaction[20]	Prediction of the ^1H NMR chemical shift of the reaction product
Suzuki-Miyaura coupling[22]	Investigation of the molecular and electronic structure of a biaryl molecule
Cu/TEMPO catalyzed aerobic oxidation of a primary alcohol[23]	Investigation of the molecular and electronic structure of the bipyridyl-type ligand
Biginelli synthesis of a heterocycle[29]	Exploration of the impact of π conjugation on lone pair basicity
Aldol condensation[30]	Relative energy comparison of two conformers of a benzaldehyde derivative
	Exploration of the impact of a nonconjugated lone pair on ^1H NMR chemical shift

structure; for example, the hybridizations of the nondegenerate oxygen atom lone-pairs in water and anisole are calculated and the chemical implications explored.[18,19] The third video lecture explores more complicated issues involved in obtaining appropriately optimized structures and the use of computational tools to explain observable chemical phenomena. Through these resources, students learn (or re-engage with) important chemical concepts and prepare to use computational chemistry throughout the introductory exercises and the entire course.

In this introductory portion of the course, students gain an improved understanding of molecular and electronic structure and potential energy surfaces while obtaining hands-on experience with the WebMO interface. The complexity of the exercises and required data analysis increases in a scaffolded manner during the 8 h of laboratory experience. The exercises are designed to enhance understanding of topics explored in the lecture course and are not directly related to a particular laboratory experiment. Nevertheless, a major goal of the introductory module is to enable students to build a framework in which to apply computational techniques to the results of their lab experiments. In progressing through these introductory exercises, students learn how to optimize the structure of a molecule, determine whether it is an energy minimum (reactant, product, or intermediate) or a transition state, perform a relaxed conformational scan of a structural parameter, and view atomic and molecular orbitals. A brief outline of the concepts studied and calculations performed in each exercise is provided in Table 1. The complete description is provided in the Supporting Information.

The exercises in Table 1 encourage key conceptual and practical learning; however, their scope is necessarily limited and the initial exposure is somewhat inauthentic. Contemporary organic chemistry is increasingly reliant on various computational techniques to predict or rationalize the distribution of products, reaction mechanisms, and electronic structures. In this context, the benefit of the introductory exercise lies in the empowerment of students to better understand aspects of the future laboratory experiments and more effectively interpret their experimental data via use of computational chemistry. With the support provided by video lectures, the student laboratory handout, and the presence of teaching assistants in the computer laboratory, students are able to complete these exercises with a high degree of success. The struggle that students experience is mostly in the interpretation of their results and rationalization of the chemical concepts. Building upon this initial skill development, we have incorporated computational chemistry into all of our laboratory reports and summary assessments (see Supporting Information). In essence, we view (and use) computational chemistry in the same manner as ^1H NMR, ^{13}C NMR, IR, and GC−MS analyses, i.e., as a routine tool for analysis of an experimental outcome. Several examples of this approach have been previously published,[20−23] and all are summarized in Table 2. Our implementation of computational chemistry in these experiments is designed to enhance the interpretation of spectroscopic data, enable deeper analysis of the electronic or molecular structure of a key species in the reaction, and/or rationalize the observed reaction products. A representative course schedule is available in the Supporting Information and computational details for each experiment are available upon request. Although these are the experiments within which we have chosen to incorporate computational chemistry, this is not by any means an inclusive, restrictive, or definitive list of the possibilities.

■ HAZARDS

There are no significant hazards associated with this experiment.

■ CONCLUSIONS

We have created an introductory computational chemistry module for the undergraduate organic chemistry laboratory which can be used as a stand-alone activity to enhance students understanding of key organic chemistry concepts. For improved learning outcomes, the module can be used as a foundation for the authentic integration of computational chemistry into the undergraduate organic curriculum. The WebMO resource provides an inexpensive and effective interface for students to perform simple calculations and support their experimental work using modern computational software packages.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00815.

> A sample course schedule, student handouts, stock NMR FID data for 4′-hydroxyacetophenone, and sample NMR spectra (answers to all student exercises and additional experimental implementations of computational chemistry are available upon request to the authors and are not included to avoid dissemination/misconduct among students), reference for Gaussian 09, examples of Chemistry 344 midterm and final exams including questions related to computational chemistry (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Linenberger, K. J.; Cole, R. S.; Sarkar, S. Looking Beyond Lewis Structures: A General Chemistry Molecular Modeling Experiment Focusing on Physical Properties and Geometry. *J. Chem. Educ.* **2011**, *88* (7), 962−965.

(2) Clauss, A. D.; Nelsen, S. F. Integrating Computational Molecular Modeling into the Undergraduate Organic Chemistry Curriculum. *J. Chem. Educ.* **2009**, *86* (8), 955−958.

(3) McNaught, I. J. Testing and Extending VSEPR with WebMO and MOPAC or GAMESS. *J. Chem. Educ.* **2011**, *88* (4), 421−425.

(4) Johnson, L. E.; Engel, T. Integrating Computational Chemistry into the Physical Chemistry Curriculum. *J. Chem. Educ.* **2011**, *88* (5), 569−573.

(5) Rowley, C. N.; Woo, T. K.; Mosey, N. J. A Computational Experiment of the *Endo* versus *Exo* Preference in a Diels−Alder Reaction. *J. Chem. Educ.* **2009**, *86* (2), 199−201.

(6) Clausen, T. P. Combining a Standard Fischer Esterification Experiment with Stereochemical and Molecular-Modeling Concepts. *J. Chem. Educ.* **2011**, *88* (7), 1007−1009.

(7) Montgomery, C. D. π Backbonding in Carbonyl Complexes and Carbon−Oxygen Stretching Frequencies: A Molecular Modeling Exercise. *J. Chem. Educ.* **2007**, *84* (1), 102−105.

(8) Wang, L. Using Molecular Modeling in Teaching Group Theory Analysis of the Infrared Spectra of Organometallic Compounds. *J. Chem. Educ.* **2012**, *89* (3), 360−364.

(9) Salter, C.; Foresman, J. B. Naphthalene and Azulene I: Semimicro Bomb Calorimetry and Quantum Mechanical Calculations. *J. Chem. Educ.* **1998**, *75* (10), 1341−1345.

(10) Esselman, B. J.; Hill, N. J. Experiment 4: Computational Molecular Modeling (WebMO). https://www.chem.wisc.edu/content/experiment-4-computational-molecular-modeling-webmo (accessed Jan 2016).

(11) Schmidt, J. R.; Polik, W. F. *WebMO Enterprise*, 15.0.002e; WebMO, LLC.: Holland, MI, 2015.

(12) *Spartan Student Edition*, 3; Wavefunction, Inc., 2011.

(13) Phoenix. http://phoenix.chem.wisc.edu/wiki/index.php/Main_Page (accessed Jan 2016).

(14) Turney, J. M.; Simmonett, A. C.; Parrish, R. M.; Hohenstein, E. G.; Evangelista, F. A.; Fermann, J. T.; Mintz, B. J.; Burns, L. A.; Wilke, J. J.; Abrams, M. L.; Russ, N. J.; Leininger, M. L.; Janssen, C. L.; Seidl, E. T.; Allen, W. D.; Schaefer, H. F.; King, R. A.; Valeev, E. F.; Sherrill, C. D.; Crawford, T. D. Psi4: An Open-source *Ab Initio* Electronic Structure Program. *WIREs Comput. Mol. Sci.* **2012**, *2* (4), 556−565.

(15) Fortenberry, R. C.; McDonald, A. R.; Shepherd, T. D.; Kennedy, M.; Sherrill, C. D., PSI4Education: Computational Chemistry Labs Using Free Software. In *The Promise of Chemical Education: Addressing our Students Needs?*; Daus, K., Rigsby, R., Eds.; American Chemical Society: Washington, DC, 2015; Vol. *1193*, pp 85−98.

(16) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. General Atomic and Molecular Electronic Structure System. *J. Comput. Chem.* **1993**, *14* (11), 1347−1363.

(17) Gordon, M. S.; Schmidt, M. W., Advances in Electronic Structure Theory: GAMESS a Decade Later. In *Theory and Applications of Computational Chemistry: The First Forty Years*; Elsevier: Amsterdam, 2005.

(18) Laing, M. No Rabbit Ears on Water. The Structure of the Water Molecule: What Should We Tell the Students? *J. Chem. Educ.* **1987**, *64* (2), 124−128.

(19) Clauss, A. D.; Nelsen, S. F.; Ayoub, M.; Moore, J. W.; Landis, C. R.; Weinhold, F. Rabbit-ears Hybrids, VSEPR Sterics, and Other Orbital Anachronisms. *Chem. Educ. Res. Pract.* **2014**, *15* (4), 417−434.

(20) Hein, S. M.; Kopitzke, R. W.; Nalli, T. W.; Esselman, B. J.; Hill, N. J. Use of ^{1}H, ^{13}C, and ^{19}F-NMR Spectroscopy and Computational Modeling To Explore Chemoselectivity in the Formation of a Grignard Reagent. *J. Chem. Educ.* **2015**, *92* (3), 548−552.

(21) Esselman, B. J.; Hill, N. J. Proper Resonance Depiction of Acylium Cation: A High-Level and Student Computational Investigation. *J. Chem. Educ.* **2015**, *92* (4), 660−663.

(22) Hill, N. J.; Bowman, M. D.; Esselman, B. J.; Byron, S. D.; Kreitinger, J.; Leadbeater, N. E. Ligand-Free Suzuki−Miyaura Coupling Reactions Using an Inexpensive Aqueous Palladium Source: A Synthetic and Computational Exercise for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2014**, *91* (7), 1054−1057.

(23) Hill, N. J.; Hoover, J. M.; Stahl, S. S. Aerobic Alcohol Oxidation Using a Copper(I)/TEMPO Catalyst System: A Green, Catalytic Oxidation Reaction for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2013**, *90* (1), 102−105.

(24) Gilbert, J. C.; Martin, S. F. *Experimental Organic Chemistry: A Miniscale and Microscale Approach*, 6th ed.; Cengage Learning: Boston, MA, 2014; pp 473−479.

(25) Mohrig, J. R.; Hammond, C. N.; Schatz, P. F. *Modern Projects and Experiments in Organic Chemistry: Miniscale and Williamson Microscale*, 2nd ed.; W. H. Freeman and Company: New York, NY, 2003.

(26) Touchette, K. M. Reductive Amination: A Remarkable Experiment for the Organic Laboratory. *J. Chem. Educ.* **2006**, *83* (6), 929−930.

(27) Nguyen, K. C.; Weizman, H. Greening Wittig Reactions: Solvent-Free Synthesis of Ethyl *trans*-Cinnamate and *trans*-3-(9-Anthryl)-2-Propenoic Acid Ethyl Ester. *J. Chem. Educ.* **2007**, *84* (1), 119−121.

(28) Ball, D. B. Diastereoselectivity in the Reduction of α-Hydroxyketones. An Experiment for the Chemistry Major Organic Laboratory. *J. Chem. Educ.* **2006**, *83* (1), 101−105.

(29) Holden, M. S.; Crouch, R. D. The Biginelli Reaction. *J. Chem. Educ.* **2001**, *78* (8), 1104.

(30) Crouch, R. D.; Richardson, A.; Howard, J. L.; Harker, R. L.; Barker, K. H. The Aldol Addition and Condensation: The Effect of Conditions on Reaction Pathway. *J. Chem. Educ.* **2007**, *84* (3), 475.

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