

An Undergraduate Computational Chemistry Experiment: Investigation of the E2 Elimination Reaction of 2-Bromopropane to Propene

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Abstract This paper presents an undergraduate computational chemistry lab experiment of the E2 elimination reaction of 2-bromopropane to form propene. Utilizing the Hartree-Fock (HF) and Density Functional Theory (DFT) methods within the computational frameworks of Avogadro and ORCA, the experiment offers a comprehensive insight into the reaction mechanism, activation energy, and electronic structure changes associated with the reaction. The experiment was structured to enhance students' understanding of key concepts in quantum chemistry and organic chemistry, including molecular orbitals, electron density, and reaction kinetics. By calculating and analyzing the activation energy and reaction pathways, students will gain a deepened understanding of the transition states and the energy profiles of the E2 elimination process. The experiment effectively demonstrates theoretical principles applications to practical scenarios, correlating computational findings with experimental data when available, thereby bridging the gap between theory and practice. It also fosters the development of critical thinking and problem-solving skills through hands-on experience with computational tools and data analysis. This approach not only elucidates the fundamental principles of the E2 elimination reaction but also highlights the versatility and significance of computational methods in modern chemical research and education.

Keywords: E2 elimination reaction, computational chemistry experiment, undergraduate experiment, organic chemistry

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1. Introduction

This undergraduate laboratory experiment is designed to introduce students to the principles and applications of computational chemistry, using the E2 elimination reaction of 2-bromopropane to propene as a model system. By employing computational methods like Hartree-Fock (HF) [1] and Density Functional Theory (DFT) [2], students will explore key concepts in quantum chemistry and organic reaction mechanisms.

The E2 elimination reaction [3] is a fundamental transformation in organic chemistry that involves hydrogen atom removal as a leaving group from adjacent carbon atoms in a molecule, resulting in a double bond formation. Understanding this reaction is crucial for grasping the principles of organic synthesis and reaction mechanisms. Computational chemistry, on the other hand, provides powerful tools to model and predict the behavior of molecules, offering insights that are often difficult or impossible to obtain experimentally.

Educational Objectives:

1. To familiarize students with computational chemistry software (Avogadro for input preparation and visualization and ORCA for quantum mechanical calculations).
2. To understand the mechanism of the E2 elimination reaction, including the roles of the substrate, base, transition state, and product.
3. To calculate and analyze the activation energy and electronic properties of the reaction using HF and DFT methods.
4. To develop skills in interpreting computational data and relating theoretical predictions to experimental observations.

Students will model the reactants, transition states, and products of the E2 elimination reaction using Avogadro [4]. They will then perform quantum mechanical calculations using ORCA [5] to determine the activation energy and analyze the electronic structure of the molecules involved. The experiment aims to enhance students' understanding of reaction mechanisms and the application of computational tools in chemistry.

2. Materials and Methods

Avogadro molecular modeling and visualization software and the ORCA quantum chemistry program are utilized in this experiment. Avogadro is an open-source molecular editor and visualization tool. It is widely used for creating, editing, and visualizing complex molecular structures. Its user-friendly interface makes it particularly suitable for educational purposes. Avogadro will be used for building the initial molecular models of 2-bromopropane, hydroxide ion, and the reaction products (propene, water, and bromide ion). The molecules will then be pre-optimized in Avogadro before ORCA calculations with force field methods like MMFF94. The resulting initially optimized molecule structures can be exported as structure files in various formats such as .xyz or ORCA inputs can be directly obtained from Avogadro. Detailed procedures for this are included in our previous publication [6].

ORCA is a highly sophisticated quantum chemistry program that enables various calculations, including density functional theory (DFT) and Hartree-Fock (HF) methods. It can handle small and large molecular systems, widely utilized in academic research. ORCA will be used to optimize the molecules and obtain the transition state structure and their energies using two different methods, namely HF and DFT (with the B3LYP [7] hybrid functional).

In our experience, Avogadro and ORCA are well integrated to work seamlessly for this experiment. In addition, the accessibility of both Avogadro and ORCA as open-source (Avogadro) and free-for-academic-use (ORCA) software makes them ideal choices for educational settings.

In this experiment, students will utilize HF and DFT methods—two pivotal computational methods used in quantum chemistry to study molecular systems.

Hartree-Fock is a wavefunction-based method that approximates the behavior of electrons in a molecule using a set of mathematical functions. It considers electron-electron interactions and provides a solution to the Schrödinger equation by assuming that each electron moves independently in an average field created by all other electrons. While HF is known for its simplicity and forms the foundation for many methods, it often lacks accuracy in predicting properties that are heavily influenced by electron correlation, such as reaction energies and electronic excited states.

On the other hand, density functional theory is a more sophisticated approach that treats electron correlation more effectively. DFT utilizes electron density rather than wavefunction as its fundamental variable, simplifying the problem of many-body interactions. It incorporates various functionals to account for electron-electron repulsion and correlation effects. DFT is widely acclaimed for its balance between computational efficiency and accuracy. These properties make it a popular choice for studying many chemical systems, from small organic molecules to complex biological systems and materials.

3. Results and Discussion

In this physical chemistry lab experiment (SI) focusing on the E2 elimination reaction of 2-bromopropane using Hartree-Fock (HF) and Density Functional Theory (DFT) methods, students are set to achieve a comprehensive set of learning goals. The experiment is designed to deepen their understanding of the E2 elimination mechanism, including the roles played by the substrate, base, and the resultant alkene product, as well as the crucial aspects of stereochemistry and regioselectivity unique to E2 reactions.

Equally important is the acquisition of a solid grasp of quantum chemical concepts. Students will learn about the basic principles of quantum mechanics as they apply to HF and DFT calculations, gaining insight into molecular orbitals, electron density, and the energy levels within molecules. An integral part of the learning process involves developing proficiency in using computational chemistry tools Avogadro for molecular modeling and ORCA for quantum mechanical calculations. Students will engage in hands-on activities like geometry optimization and transition state analysis to understand organic molecules.

Like the level of theory, the choice of basis set is an integral part of quantum mechanics (QM) calculations. The selected basis set for the experiment is the def2-TZVP [8], a valence triple-zeta polarization basis set. This formalism means def2-TZVP includes three sets of mathematical functions (zetas) to describe each valence electron's orbital shape, with extra functions (polarization) to account for electron density distortions. In quantum chemistry packages, including ORCA, def2-TZVP implementation supports effective core potential (ECP) for atoms He-Kr and Rb-Rn (Def2-ECP). This basis set often provides accurate results for many molecular properties, including geometries, energies, and vibrational frequencies. It also has appreciable accuracy and efficiency, striking a good balance between computational cost and accuracy and making it a popular choice for various quantum chemistry calculations [8,9]. The selection is promising for approximating larger atom units like the bromide component of this reaction.

Several studies have shown the def2-TZVP basis function in predicting electronic properties with appreciable accuracy and agreement with experimental results, even for higher molecular weight molecules like metals and halides. Lawal *et al.* [10], in comparative modeling of acetic acid and acid halides (F, Cl, Br, and I) esterification reaction, explored the accuracy of eight different basis sets and their combinations. Def2-TZVP and its combination with others show the lowest basis set superposition error correction ranging from 0.47 to 1.91 kcal/mol [10]. Although the calculation also identifies mixed aug-cc-pVTZ/def2-TZVP (for halides only) as the finest choice, it is highly computationally expensive [10]. Within the purview of this present study, computing resource accessibility, and undergraduate student involvement, we have selected the def2-TZVP basis set for all atoms calculation at HF and DFT (B3LYP) levels.

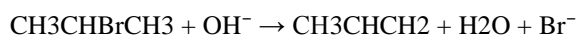
The experiment also aims to sharpen skills in analyzing

reaction pathways. This activity fosters a comprehension of transition states and their impact on reaction kinetics and mechanisms through computational exploration of energy barriers and reaction pathways. This analytical approach encourages the application of theory to practice, as students correlate their computational findings with known experimental data, thereby enhancing their understanding of how theoretical chemistry complements experimental observations.

In addition, students are encouraged to analytically interpret computational data and develop problem-solving skills as they navigate through challenges in performing these computational chemistry simulations. Furthermore, the development of scientific communication skills is a crucial goal. This is achieved through detailed report writing, encompassing methods, results, discussions, and enhanced presentation skills. By sharing their findings with peers and instructors, students foster a collaborative learning environment, which is invaluable in the scientific community. This comprehensive learning approach ensures a well-rounded educational experience, equipping students with the knowledge and skills necessary for advanced studies in chemistry.

As they delve into diverse segments of the experiment, students are tasked with becoming keen observers, logging their insights and any challenges they encounter. This valuable data will ultimately contribute to a well-rounded report. The experiment procedure is provided as supplementary material.

The description of results will start with describing the reaction and writing the chemical equation:



Students should recognize that in this reaction:

- 2-Bromopropane ($\text{CH}_3\text{-CHBr-CH}_3$) is the substrate
- Hydroxide ion (OH^-) is the base.
- Propene ($\text{CH}_3\text{-CH=CH}_2$) is the organic product (alkene).
- Water (H_2O) and Bromide ion (Br^-) are the byproducts.

Figure 1 shows the 2D chemical structures of the reactant 2-bromopropane and the product propene.

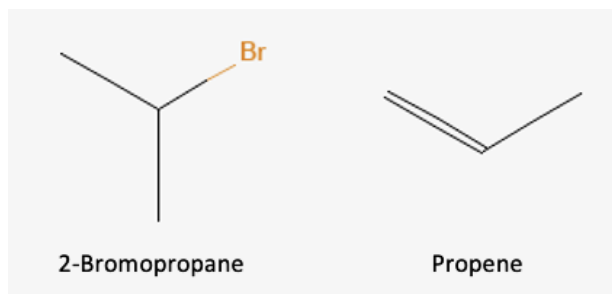


Figure 1. Chemical structures of 2-bromopropane and propene

The hydroxide ion acts as a base, abstracting a hydrogen atom from one of the methyl groups in 2-bromopropane. Simultaneously, the electrons from the broken C–H bond form a double bond between the two carbon atoms (C=C), resulting in propene formation. The bromide ion (Br^-) is released as a leaving group. A summary of the procedure is shown in Figure 2.

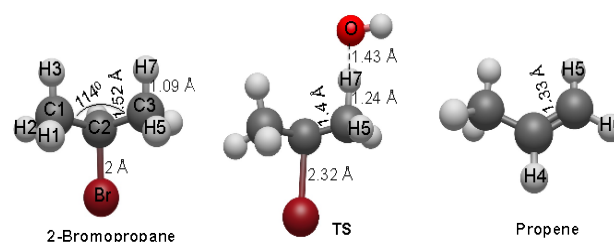


Figure 2. E2 elimination reaction of 2-bromopropane to propene depicted with the optimized starting structure, transition state (TS), and product at the DFT level. The reaction is a one-step with a TS structure showing the bond-breaking and forming process

This stereospecific reaction often occurs in an anti-periplanar geometry, where the hydrogen and the leaving group are on opposite sides of the molecule (Figure 2). The C1–C2–C3 angle of the fully optimized starting geometry of 2-bromopropane is 114° , which became 125.3° at product formation. This geometry change is phenomenal, required for hydrogen atom rearrangement around the C2 and C3 rotating about their axes after being deficient in Br and H7, respectively, to attain the C2=C3 planar geometry of propene. The C2–C3 bond of 1.52 \AA collapses to form a C2=C3 double bond of 1.33 \AA at the end of the alkane-to-alkene reaction.

Students will optimize all the reactant and product molecules and tabulate the optimized values for each, as displayed in Table 1 and Table 2. One expected error during this process shows that ORCA will not run if optimization is requested for the bromide ion since it has a single atom. Therefore, the single point energy keyword (SP) was used instead of the optimization keyword (OPT). The differences between the output energies of the separated reactants and products using HF and DFT are -69.03 and -62.75 kcal/mol after converting Hartree to kcal/mol.

Table 1. Reactant energies (in Hartree) at different levels of theory

Level of theory	2-Bromopropane	Hydroxide ion
HF def2-TZVP	-2690.15	-75.40
DFT def2-TZVP	-2692.55	-75.77

Table 2. Product energies (in Hartree) at different levels of theory

Level of theory	Propene	Water	Bromide ion
HF def2-TZVP	-117.12	-76.06	-2572.48
DFT def2-TZVP	-117.87	-76.43	-2574.12

Following the successful optimization completion, students will delve into the theoretical aspect of predicting the geometry of the reaction's transition state (TS). Although the ORCA/Avogadro combination is a powerful and open-source tool for electronic structure calculation computational chemistry, TS modeling is often challenging. In this experiment, students will obtain the anti-periplanar TS orientation in two stages after several trials and errors. The steps involve relaxed scan optimization at PM3 (a semi-empirical level) and TS optimization at HF and DFT levels. By scanning the bond distances between C3–H7 and HO–H7 from 1.07 \AA to 1.23 \AA and 1.59 \AA to 1.35 \AA for 15 optimization steps, they can obtain an initial guess TS that was subsequently optimized with no restrain to find the exact TS structure. All the input and output files are provided in the

supplementary information for a straightforward implementation of this experiment.

Confirming that a calculated state is a TS structure involves checking its vibrational frequencies. A correct transition state is characterized by having one imaginary frequency in its vibrational frequency analysis. This is a strategic diagnostic criterion in computational chemistry for transition state validation. A transition state, depicting a saddle point on the potential energy surface, is a point of maximum energy along the reaction coordinate but a minimum in all other directions. This unique characteristic leads to one negative eigenvalue in the Hessian matrix (the matrix of second derivatives of the energy relative to atomic positions). This negative eigenvalue manifests as a single imaginary frequency in the vibrational frequency analysis (often denoted by a negative value or an "i" in the frequency list). It represents the direction in which the energy decreases as the system transitions from the reactants to the products.

The vibrational mode associated with the imaginary frequency should correspond to the motion along the reaction pathway. For instance, in a bond-breaking reaction, the imaginary frequency mode corresponds to a vibrational motion where the two atoms separate. As shown in the TS of Figure 2, the C2–C3 bond of the bromopropane decreases from 1.52 Å to 1.4 Å, bromine elongates from 2 Å to 2.32 Å, the hydroxide ion attracts a hydrogen atom to increase the C3–H7 bond from 1.09 Å to 1.24 Å, and the leaving hydrogen is now at 1.43 Å distance to the hydroxide. This TS has a characteristic single imaginary frequency of -977.72 cm^{-1} and -277.18 cm^{-1} at HF and DFT levels of theory, respectively. At TS, the C1–C2–C3 angle gently stretches from 1140 to 121.3°, while the Br–C2–C3–H7 dihedral of 177° in the starting bromopropane is now 179° at TS. The Br–C2–C3–H7 dihedral influences the anti-periplanarity, steric hindrance, orbital interactions, and reactant properties, making it a critical factor in understanding and predicting the rate of this fundamental reaction. Noting the Br–C2–C3–H7 dihedral angle approaching 180° at TS signifies a near-coplanar arrangement of the Br, C2, C3, and H7 atoms during the bond-breaking and making process. This observation with other structurally related outcomes like the C–H bond distance approximate value of 1.09 Å in the minimum structures, consistent with the literature [11], reflects the accuracy of the selected basis set. An animation showing the atoms' motion and displacement vectors for the optimized TS structure is available in Mov. S1 of the supplementary material.

Besides having one imaginary frequency, it is prudent to visually inspect the vibrational mode associated with this frequency to ensure it aligns with the expected reaction mechanism. Performing an intrinsic reaction coordinate (IRC) calculation can provide further confirmation. An IRC traces the path on the potential energy surface from the transition state down to the reactants and products, confirming the connectivity of the transition state to the expected states. In this experiment, the IRC calculation confirms the connection of the TS structure to the intended reactant and product complexes (Figure 3). The input starting structure for IRC computation is the coordinates of the TS output structure. The activation energy (E_a), depicted by subtracting the

energy of the separated reactants from the TS energy, is highly spontaneous. The corresponding calculated E_a values at HF and DFT levels are -12.4 and -27.6 kcal/mol , suggesting a rare scenario based on the classical thermodynamic principle. This negative E_a in the forward reaction direction denotes an exothermic process whereby the saddle point has lower energy than the reactants (Figure 3). In contrast, the energy differences between the products and the TS (backward barrier) are 56.65 kcal/mol (HF) and 35.15 kcal/mol (DFT).

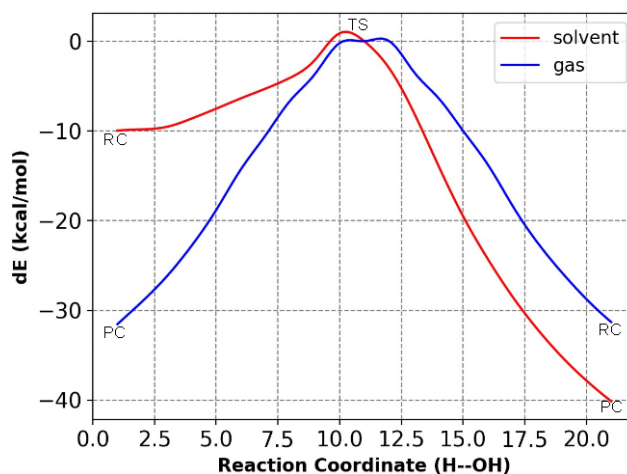


Figure 3. IRC path for E2 elimination reaction of 2-bromopropane to propene at DFT/def2-TZVP level of theory in vacuum and solvent (implicit CPCM ethanol model) showing the product complex (PC), transition state (TS), and reactant complex (RC)

Students can be encouraged to critically evaluate this result with both what they have been learning in the classroom and through a comprehensive literature search. Obtaining a negative activation energy is not unlikely since the calculation was executed in the gas phase and considering factors like the halide presence. Negative E_a has been associated with the homogeneous gas-phase reactions catalyzed by nitrogen, hydrogen, chlorine, and bromine-containing species [12]. Although they pose curiosity, reactions with negative activation energies are plausible and could occur in reality [12]. Even with dispersion correction on the B3LYP and higher basis set (B3LYP-D3/def-QZVP), reports of negative E_a for organic reactions are available in the literature [9]. However, experiences with reaction modeling enabled us to envisage that computing the reaction in a solvent model will push the E_a to a positive or near-positive value. Solvation usually reshapes the reaction process and modifies the activation barrier [10,13], mimicking conventional laboratory experiments.

Students endeavored to model the reaction process in an aqueous medium by solvation with the conductor-like polarizable continuum model (CPCM) [14] implemented in ORCA. This procedure involves optimizing the TS in ethanol (implicitly) and computing the IRC (in solvent) from the output TS geometry. The selected aqueous medium is based on the commonly acceptable reaction medium (KOH, alcohol) for 2-bromopropane conversion to propene. The CPCM is an efficient approach to account for solvent effects in quantum chemical calculations. The formalism entails depicting the solvent as a dielectric polarizable continuum and positioning the solute in a

space near its molecular shape [14]. In the solvated medium, the calculated E_a for 2-bromopropane E2 elimination to propene is 2.34 kcal/mol, making it about 30 kcal/mol energy change compared to -27.6 kcal/mol in vacuum at DFT level. IRC path of the vacuum and aqueous phase show energy disparity with up to 21.6 kcal/mol (Figure 3). Integrating solvent in this E2 elimination reaction path enables a clearer uncoupling of the forward and backward barrier heterogeneity than the vacuum phase. This outcome suggests that solvation in ethanol remodeled the system, including the TS Br–C2–C3–H7 dihedral (179.6°) with an improved anti-periplanarity. The TS structure in solvent tends closely to the product (propene) as reflected in the IRC plus the C1–C2–C3 angle at an absolute value of 120° .

To reinforce knowledge and evaluate the suitability of def-TZVP for higher atoms, students can be encouraged to replace the bromine with iodine using the outlined protocol for 2-iodopropane conversion to propene. This can be used as an additional challenge for students or left out depending on the implementation goals. Figure 4 shows the reactant and TS structural details with only one negative eigenvalue of -225.8 cm^{-1} using the HF method. The difference between the energy of separated reactants and products is -83.97 kcal/mol with the reaction energy barrier of -92.44 kcal/mol and -8.7 kcal/mol for the backward barrier at HF level. Besides the non-solvation effect and OH/I reactivity, these HF/def-TZVP results likely reflect an overestimation often associated with HF, considering the product–reactant difference of -75.8 kcal/mol with DFT modeling. Interestingly, solvating the structures in ethanol yielded an activation energy of 8.66 kcal/mol, accounting for over 100 kcal/mol contribution to the E2 elimination reaction.

The C2–C3 bond of the iodopropane contracts from 1.54 \AA to 1.37 \AA , iodide extends from 2.17 \AA to 2.87 \AA , and the hydroxide abstracts a hydrogen atom within 1.35 \AA to make C3–H7 bond distance become 1.23 \AA at TS. This transition state is characterized by one imaginary frequency of -977.72 cm^{-1} at the HF level of theory. Angle changes include the C1–C2–C3 angle tilted from 112° to $\sim 122^\circ$, while the Br–C2–C3–H7 dihedral of 173.7° in the starting 2-iodopropane changes slightly to 174.2° at TS. The E2 elimination reaction of 2-iodopropane to propene follows the same route as the 2-bromopropane but with a more favorable solvation activation energy (2.34 kcal/mol) than the iodide substrate. The comparative experiment buttresses Br reactivity over iodine, similar to the previous DFT studies of acetyl halide esterification with Br derivatives showing a lower energy barrier than iodine [10,13]. The def-TZVP proved suitable for higher atomic weight calculations, and students could reproduce the 2-bromopropane experiment by switching to 2-iodopropane.

In summary, more than one imaginary frequency presence indicates that the structure is not a transition state but a higher-order saddle point or possibly a reactant/product conformation if all frequencies are realistic. For this student practical, all separated reactant and product structures have nil negative eigenvalue from the vibrational frequency output. Observing a single imaginary frequency associated with the reaction coordinate without other imaginary frequencies is a robust

indicator that the calculated structure is a transition state. Solvation is a crucial component of molecular modeling for improved reactivity prediction and theory establishment.

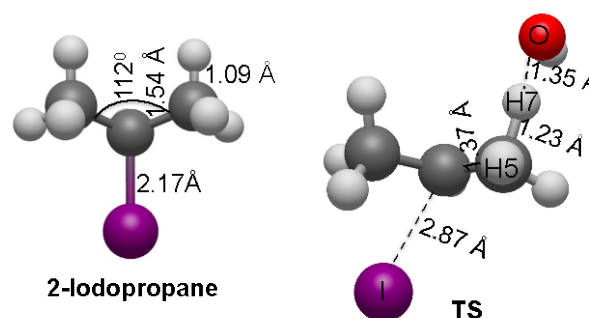


Figure 4. E2 elimination reaction of 2-iodopropane to propene depicted with the optimized starting structure and transition state (TS) at the DFT (B3LYP/def2-TZVP) level

4. Conclusion and Implementation Suggestions

In conclusion, this study demonstrates the effectiveness of integrating computational chemistry, specifically Hartree-Fock (HF) and Density Functional Theory (DFT), into undergraduate education through a lab experiment focusing on the E2 elimination reaction of 2-bromopropane. The experiment offered students a practical understanding of key concepts in quantum mechanics and organic chemistry, such as molecular orbitals, electron density, reaction mechanisms, and energy profiles. By engaging in hands-on computational modeling and analysis, students could visualize and quantify the nuances of the E2 elimination process, enhancing their theoretical knowledge with practical skills in computational chemistry.

Our implementation suggestions for this and similar computational chemistry experiments in the undergraduate curriculum include the following:

Integration into Curriculum: Computational chemistry modules can be incorporated into existing chemistry courses to complement and reinforce theoretical concepts. This could be part of physical chemistry, organic chemistry, or a specialized course in computational methods.

Modifications to this Experiment: The experiment can be adjusted in different ways. Removing the transition state investigation will make it a short and simplified activity. On the other hand, the experiment can be extended by adding other levels of theory and comparing results from each calculation. Students may also explore differing solvent media to predict the more favorable reaction medium and activation energy. Additionally, replacement of bromide with iodide will be a suitable extension.

Collaborative Learning: Group projects and peer learning can be encouraged to foster collaborative skills. Students can work in teams on different molecules or reaction types, promoting knowledge exchange and problem-solving strategies.

Software Training: It will be beneficial to provide a prior lab period or pre-lab assignment on using

computational chemistry software like Avogadro and ORCA [6]. Familiarity with these tools is crucial for the success of such experiments.

Gradual Complexity: We recommend starting with simpler systems and gradually introducing more complex molecules or reactions as students become more comfortable with the computational tools and concepts described in our previous publication. Higher levels of complexity would include simulating the reaction with longer alkanes and replace bromide with other halide atoms.

Research Opportunities: Interested students can be encouraged to undertake independent research projects using these computational tools, potentially leading to publishable findings or conference presentations.

Interdisciplinary Applications: It will be beneficial for students to highlight the cross-functional nature of computational chemistry by showcasing its applications in materials science, biochemistry, environmental chemistry, and other fields.

Computational chemistry incorporation into the chemistry curriculum enriches the student's learning experience and equips them with valuable skills for their future academic and professional pursuits in various scientific domains.

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