

A Novel Hybrid Post-Hartree-Fock and Monte Carlo Algorithm for the Characterization of Conformational Isomers in Acyclic Alkanes

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Abstract—Determining the molecular Hamiltonian proves to be an essential tool in understanding a molecule's properties, including energy changes in reactions and molecular stability. Traditional self-consistent field methods such as Hartree-Fock have been long-standing approaches for approximating the Schrodinger equation to help find molecular Hamiltonians. However, their limitation in handling perturbation energies has led to the development of Post-Hartree-Fock methods, including the Møller–Plesset perturbation theory. This research aims to introduce a novel method for the analysis of conformational isomers of acyclic alkanes utilizing the Møller–Plesset perturbation theory. Specifically, the geometric and Hamiltonian characteristics of conformers are analyzed. Conformers are computationally generated, and their molecular Hamiltonians are evaluated. The method uses a single molecular structure as input and combines Monte Carlo simulations with classical geometric clustering to generate possible conformers. Ethane, propane and isobutane are used for the analysis of this methodology. The molecular geometries are evaluated using the Computational Chemistry Comparison and Benchmark Database (CCCBDB) with the MP2/cc-pVDZ basis set. Results from this research showcase that narrower angle bounds lead to more plausible and stable structures, primarily indicated by the low variability in energy values.

Keywords—Hartree-Fock, Post-Hartree-Fock, perturbation theory, Møller–Plesset, conformational isomers, Schrödinger's equation, Monte Carlo

I. INTRODUCTION

Conformational isomerism is a crucial property of certain organic molecules that has profound impacts across many different fields. For example, different conformers can affect drug discovery processes, molecule binding properties, and reaction pathways for both medical and biological purposes [1]. Determination of conformational isomers can advance treatment modalities for cancer since the positioning of conjugate groups plays an important role in cancer treating drugs. For instance, the positioning of glucose-platinum has been shown to determine the effectiveness of the C6-glucose-platinum isomer to target cancer cells [2]. Additionally, the identification of conformational isomers is essential for biomolecular protein folding and unfolding, which has potential in disease diagnosis and treatment. However, a significant challenge lies within the rapid interconversions of conformational isomers, which hampers their analysis and identification [3]. This issue is also evident in other identification methods such as nuclear magnetic resonance, which also lack the ability to identify individual room-temperature isomers due to their tendency for

interconversions [4]. With the importance of conformational analysis for numerous practical applications and the current constraints for existing methods, this research aims to provide a novel computational method for finding new conformational isomers of a molecule while also analyzing their molecular energies i.e. the Hamiltonians.

II. BACKGROUND

Molecular mechanics have been a prominent method for the analysis and minimization of molecular energies. There are a few molecules such as cyclohexane whose steric energies have been well analyzed and pathways between different conformers (chair, half-chair, twist-boat, and boat) have been described [4]. To describe the conformer that a molecule takes, a typical choice is to observe the torsional angles between bonds. Torsional angles provide a detailed 3D configuration of a specific molecule, but quickly become impractical for larger molecule sizes [1].

Furthermore, approaches using force fields have also been utilized for steric energy analysis of organic molecules. These force fields include Molecular Mechanics 2, Molecular Mechanics 3, and Merck Molecular Force Field [5, 6]. These molecular force fields provide precise classical approximations of the dynamics of quantum mechanical systems using a combination of bond lengths, bond angles, bond torsions and electron repulsions. Methods for analyzing these force field factors typically involve stochastic or Monte Carlo analysis, and random sampling methods to approximate solutions [7, 8]. Prior research has generalized the trends in steric energies found through these force fields into geometric transformations [9].

In addition to stochastic methods, more recent research has revealed how different standard clustering algorithms can identify conformational isomerism in molecules. For example, the k-means and affinity propagation methods have been used to identify cluster centers in molecules. However, they hold their own disadvantages, ranging from being too sensitive to noise or being too computationally expensive [1]. Research by Nwerem in [10] used principal component analysis and k-means to create a computational system to identify common conformer structures, but at a loss of accuracy in higher dimensionality situations. Furthermore, new research has shown the use of an improved Fast Search and Find of Density Peaks clustering algorithm to observe conformers of Sildenafil (hypertension medication) and create energy comparisons [1]. Deep learning neural

networks have also been applied to improve molecular property predictions, thus increasing the accuracy of drug development models by including 3D information for many conformers [11].

Despite the aforementioned conformer analysis techniques, finding stable conformers with increased molecule size remains unaddressed. This research attempts to address this issue for acyclic alkanes using a combination of classical geometric clustering and Monte Carlo algorithms. Research by Ghamari *et al.* and Sukurma *et al.* has shown successful use cases of stochastic quantum methods for molecular energy evaluation and transitions [12, 13]. Rather than addressing the issue of finding stable conformers using stochastic quantum methods, this research focuses on using a novel Monte Carlo based approach to classically generate molecules and evaluate their energy characteristics.

III. METHODOLOGY

This research evaluates the molecular Hamiltonian, an operator which when applied to a molecule, provides the total energy of its system as a sum of the potential and kinetic energies. Solving the Schrödinger Eq. (1) provides the value of this Hamiltonian:

$$\mathcal{H}|\Phi\rangle = \mathcal{E}|\Phi\rangle \quad (1)$$

While solving the Schrödinger equation is well-defined for single-electron systems such as hydrogen, multi-electron systems require approximations of their Hamiltonian solutions. Several methods have been proposed to approximate the value of a multi-electron system's Hamiltonian, several of which involve an iterative process for calculating a Hamiltonian. These methods are known as Self-Consistent Field (SCF) methods.

An extremely prevalent SCF method is The Hartree-Fock method, which performs Hamiltonian calculations by iteratively updating the orbitals of a molecule until a convergence is found in its density matrix [14]. The density matrix of the molecule is representative of all the wave functions that are present in a molecule, and its elements provide a probability for quantum elements such as electrons in a specific quantum state.

The Møller-Plesset Perturbation Theory (Eq. (2)), a post-Hartree-Fock method, extends the standard Hartree-Fock method by providing a perturbation factor to account for electron correlation energy. As a result, more accurate energy approximations can be made using the equation below:

$$\mathcal{H} = \mathcal{H}_0 + \lambda\mathcal{V} \quad (2)$$

In this research, a second order Møller-Plesset Perturbation Theory (MP2) was used to evaluate molecular energies and geometries. To computationally find the MP2 energy (in units of Hartrees) of a molecule, Python's PySCF library was used and molecular orbitals were created under a standard Correlation-Consistent Polarized Valence Double Zeta (cc-pVDZ) basis set from the Computational Chemistry Comparison and Benchmark Database (CCCBDB) [15, 16].

CCCBDB provides a systematic organization of the different evaluations of molecular geometries, energies (both in terms of electronic states as well as rotational and

vibrational states), and thermochemical properties. In particular, the CCCBDB contains calculated geometries for several molecules evaluated using a variety of methods and standard basis sets [16]. The CCCBDB was used to find the geometries of the ground states of molecules.

We adapted the following steps for the search of conformers of a given acyclic alkane. First, an alkane's calculated ground state geometry was found using the CCCBDB evaluated under the cc-pVDZ basis set. This ground state conformer geometry provides a starting point for generating new conformers. The geometry found on CCCBDB was set in a 3D cartesian coordinate space. Second, a Monte Carlo method was used to create several random conformers of the alkane and subsequently analyze their MP2 energies.

In particular, the first carbon atom for a given alkane's ground conformer geometry, labeled "C1" by the CCCBDB, was fixed in the 3D coordinate space. Then, the given alkane was considered as an undirected mathematical graph with vertices defined by the atoms and edges defined by bonds. More specifically, two atoms were adjacent in the graph of the alkane if they share a bond. The adjacency matrix defined by atomic bonding was also found on CCCBDB. Note that in this methodology all alkanes are acyclic. Since any connected, acyclic graph is a tree, the given alkanes can also be considered as tree graphs.

Given this graphical representation of the alkane's ground conformer, a Breadth-First Search (BFS) (see Algorithm 1 below) was performed starting with the root vertex as the fixed carbon atom (C1). Then the order of traversal by BFS through the alkane graph was stored into an array.

Algorithm 1. Breadth-First Search (BFS)

Input: Graph G , root r .

```

1  for each vertex  $v \in G$ .Vertices
2     $v$ .visited = False
3   $Q = \emptyset$ 
4  Enqueue( $Q, r$ )
5   $r$ .visited = True
6  traversalOrder = []
7  while  $Q \neq \emptyset$ :
8     $u = \text{Dequeue}(Q)$ 
9    Append(traversalOrder,  $u$ )
10   for each vertex  $w \in u$ .Neighbors
11     if  $w$ .visited = False
12       Enqueue( $Q, w$ )
13        $w$ .visited = True
14  return traversalOrder

```

Note that BFS traverses through a graph in a level-by-level planar manner starting with the root vertex. This means that at any point in the BFS traversal, the current vertex is adjacent to exactly one of the previously traversed vertices. Then the "parent" vertex is defined as this previously traversed vertex which is adjacent to the current vertex. All vertices except the root vertex will have a parent vertex. For a tree graph, if every vertex is appended to its parent vertex starting from the root, the tree graph can be reconstructed if the appending process follows the order returned by BFS traversal. This means the graph representation of the given acyclic alkane can be reconstructed with the BFS traversal order starting from the root vertex, which was the fixed carbon atom.

Note that any two conformers of the given alkane will have the same undirected graphical representation. This is because different conformers will retain their atomic bonding patterns,

regardless of what configuration they are in. Given this key insight, the BFS traversal order could provide a method for the generation of random conformers of the alkane. Specifically, a new conformer can be generated while reconstructing its graph by fixing each bond length in the given alkane and randomly varying the azimuthal and polar angles of each atom around its parent atom. The specific azimuthal angles are also set to have a lower bound of 0 radians, and three upper bound test cases of $\pi/4$, $\pi/8$, and $\pi/16$ radians. The corresponding polar angles for these three test cases are bounded above by $\pi/2$, $\pi/4$, and $\pi/8$ radians respectively. The process by which an atom is appended to its parent in random position within a given angle bound is shown below in Algorithm 2.

Algorithm 2. Appending an atom around its parent

Input:

Angle bound, ψ

Parent atom coordinates in ground conformer, $(x_{\text{ground}}, y_{\text{ground}}, z_{\text{ground}})$

Parent atom coordinates in new conformer, $(x_{\text{new}}, y_{\text{new}}, z_{\text{new}})$

Current atom coordinates in ground conformer: (a, b, c)

```

1  radius =  $\sqrt{(a - x_{\text{ground}})^2 + (b - y_{\text{ground}})^2 + (c - z_{\text{ground}})^2}$ 
2   $\theta = \arccos\left(\frac{c - z_{\text{ground}}}{\text{radius}}\right)$ 
3   $\phi = \text{atan2}(b - y_{\text{ground}}, a - x_{\text{ground}})$ 
4   $\theta' \leftarrow$  random number between  $-\frac{\psi}{2}$  and  $\frac{\psi}{2}$ 
5   $\phi' \leftarrow$  random number between  $-\psi$  and  $\psi$ 
6   $\theta_{\text{new}} = \max(0, \min(\theta + \theta', \pi))$ 
7   $\phi_{\text{new}} = (\phi + \phi' + 2\pi) \% 2\pi$ 
8   $\Delta x = r \cdot \sin(\theta_{\text{new}}) \cdot \cos(\phi_{\text{new}})$ 
9   $\Delta y = r \cdot \sin(\theta_{\text{new}}) \cdot \sin(\phi_{\text{new}})$ 
10  $\Delta z = r \cdot \cos(\theta_{\text{new}})$ 
11 return  $(x_{\text{new}} + \Delta x, y_{\text{new}} + \Delta y, z_{\text{new}} + \Delta z)$ 
```

Once this appending procedure is complete for all atoms in the BFS traversal order, a random conformer of the given acyclic alkane has been created. This trial conformer generation process was repeated 1000 times, creating 1000 possible configurations for the alkane at random azimuthal and polar angles between 0 radians and their respective angle bounds. The choice of 1000 iterations was subjective and was made in order to obtain a sufficient number of conformers to observe a trend in the molecular energy distribution without the requirement of extensive computational power and time. Additionally, it was chosen to vary polar and azimuthal angles to observe patterns in the energy of a conformer with varying atomic positions. Furthermore, the MP2 energies for each trial conformer were also recorded, forming a distribution of energies for the alkane at each angle bound.

Four statistical parameters of each distribution, namely median, Interquartile Range (IQR), skewness, and kurtosis were then recorded. The process of creating the distribution and finding the statistical parameters was performed three times with the aforementioned angle bounds for the azimuthal and polar angles.

With the three different distributions of conformers for the given acyclic alkane (one for each angle bound test case), a classical geometric clustering was used to compare different geometric configurations with each other. More specifically, the centroids for the CH, CH₂, and CH₃ groups (if present) in each conformer were calculated and it was observed how the positions of these centroids varied across the distribution of conformers. The collection of each centroid's location across the entire distribution creates an observable cluster when overlayed on top of the ground conformer. The proposed process is shown in Fig. 1 and was implemented using Python

3 and the following libraries: PySCF, NumPy, and Matplotlib [17–19]. Results were analyzed using the acyclic alkanes ethane (C₂H₆), propane (C₃H₈), and isobutane (C₄H₁₀). Note, however, that this process can work for acyclic alkanes of any given size provided that the computational resources are present.

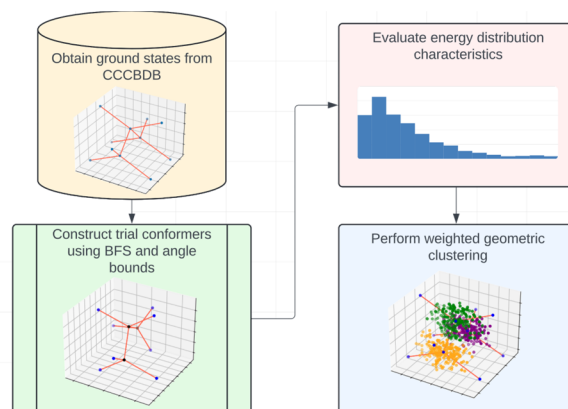


Fig. 1. Methodology: Monte Carlo with classical geometric clustering.

IV. RESULTS

The following Figs. 2(a) and (b), show the ground conformer and median MP2 energy conformers for ethane created from the Monte Carlo trial conformer generation.

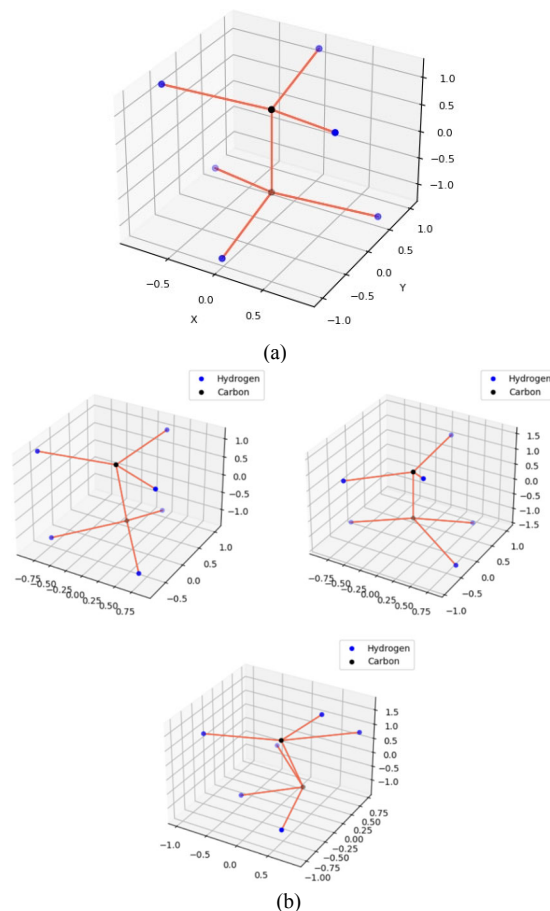


Fig. 2. (a) Ethane ground conformer; (b) Ethane median energy conformer (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

The following Figs. 3(a) and (b) show the ground conformer and median MP2 energy conformers for propane created from the Monte Carlo trial conformer generation.

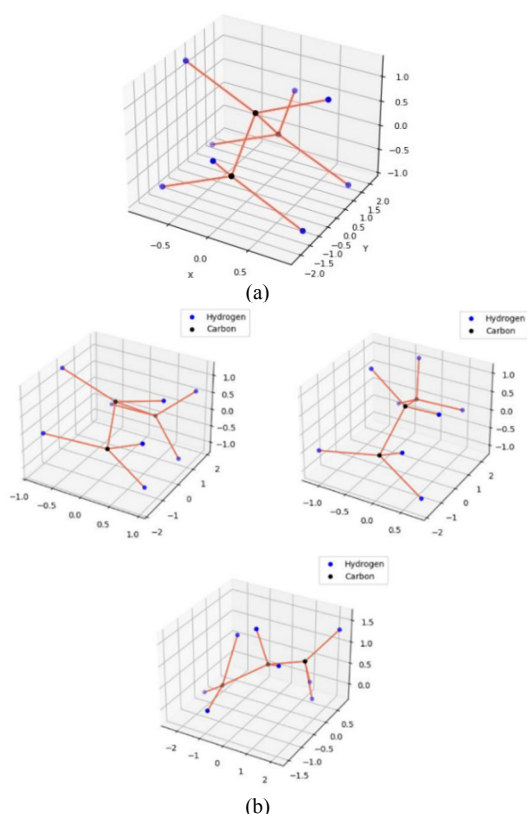


Fig. 3. (a) Propane ground conformer; (b) Propane median energy conformer (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

The following Figs. 4(a) and (b) show the ground conformer and median MP2 energy conformers for isobutane created from the Monte Carlo trial conformer generation.

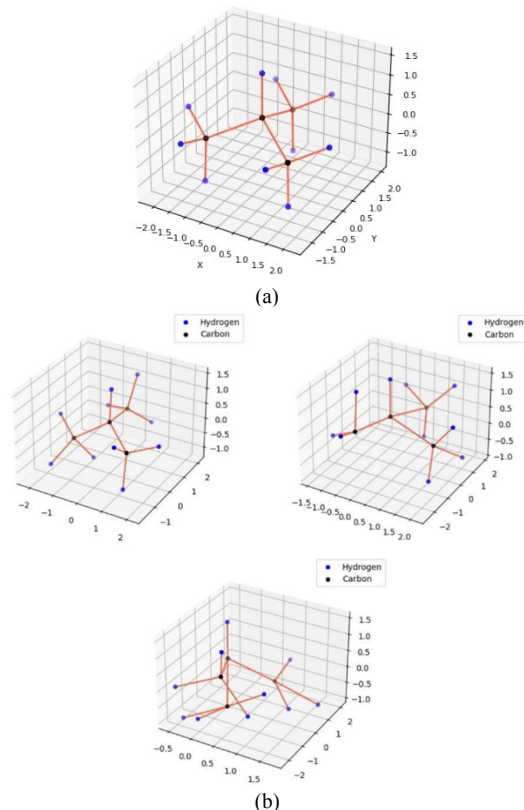


Fig. 4. (a) Isobutane ground conformer; (b) Isobutane median energy conformer (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

From the Monte Carlo methodology, statistical parameters from the trial conformer MP2 energy distributions are shown in Table 1. Molecular energy is in units of Hartrees.

Table 1. Distribution statistics for conformer MP2 energies

Conformer	Azimuthal Angle Bound	PolarAngle Bound	Median Energy (Hartrees)	IQR	Skewness	Kurtosis
Ethane	$\pi/4$	$\pi/2$	-79.1140	0.3182	6.4239	54.4983
Ethane	$\pi/8$	$\pi/4$	-79.4074	0.0880	0.6810	0.4500
Ethane	$\pi/16$	$\pi/8$	-79.5061	0.0222	0.6631	0.2458
Propane	$\pi/4$	$\pi/2$	-117.7483	0.8028	22.5781	595.5804
Propane	$\pi/8$	$\pi/4$	-118.4544	0.1457	4.1881	40.6724
Propane	$\pi/16$	$\pi/8$	-118.6553	0.0348	0.7257	0.5383
Isobutane	$\pi/4$	$\pi/2$	-155.9988	2.5213	7.6761	74.6403
Isobutane	$\pi/8$	$\pi/4$	-157.4520	0.3948	9.1102	127.9822
Isobutane	$\pi/16$	$\pi/8$	-157.8050	0.0594	2.2178	8.4754

Next, the classical geometric clustering of centroids from CH, CH₂ and CH₃ groups for ethane, propane, and isobutane are shown in Figs. 5–7. Note that ethane does not contain a CH or CH₂ group and propane does not contain a CH group. In all the following figures, purple points are for CH group clusters, orange points are used for CH₂ group clusters, and green points are used for CH₃ group clusters.

Below in Figs. 8–10 are box plots showcasing the different distributions of energies for ethane, propane, and isobutane under different angle bounds. Note that the box plots (in units of Hartrees) are not all the same scale for visual purposes.

We start by observing four statistical parameters of conformer energy distributions created by the Monte Carlo methodology, as reported in Table 1. It should be observed that the median MP2 energy increases in magnitude from larger to narrower angle bounds (from $\pi/2$ to $\pi/8$). Furthermore, narrower bounds such as $\pi/4$ and $\pi/8$ have much

smaller interquartile ranges than the $\pi/2$ bounds.

Note that all distributions have a positive skew which decreases as the angle bound changes from $\pi/2$ to $\pi/8$. This positive skew indicates that the Monte Carlo method is producing outlier conformers that are physically improbable. Examples of such outliers can be seen in Figs. 8–10. The positive kurtosis values and leptokurtic behavior of each distribution indicates that outliers have a high deviation from the median. This positive kurtosis allows for an easier separation of physically improbable trial conformers. Additionally, it is evident from the roughly symmetric box plots in Figs. 8–10 that as the angle bounds approaches lower values (i.e. $\pi/8$), the distribution of energies tends toward a normal model. As the angle bound increases to higher values such as $\pi/8$ and $\pi/4$, it can be seen that a larger number of outliers are generated, thus skewing the distribution toward higher energy values.

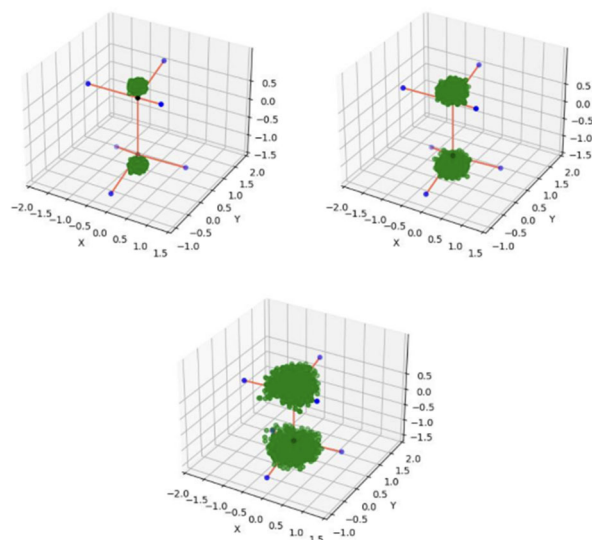


Fig. 5. Ethane centroid clusters (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

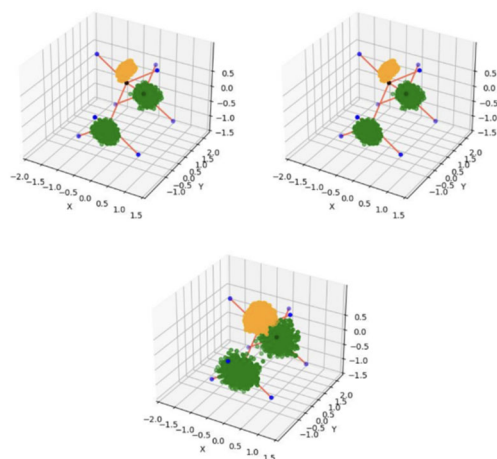


Fig. 6. Propane centroid clusters (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

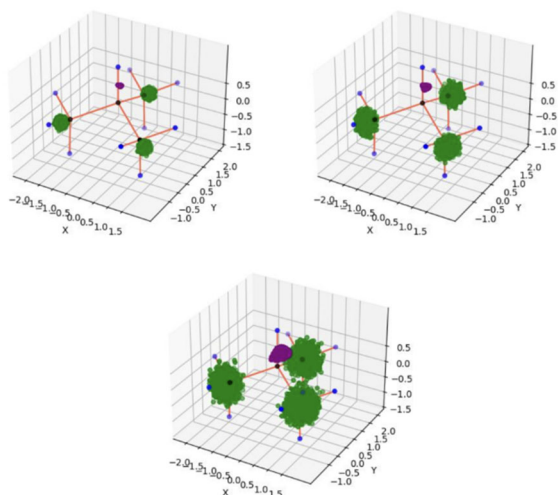


Fig. 7. Isobutane centroid clusters (Top Left: $\pi/8$ polar angle bound, Top Right: $\pi/4$ polar angle bound, Bottom: $\pi/2$ polar angle bound).

It should also be observed that the CH_2 group (orange) in propane has an electron cloud that gets noticeably compressed between the surrounding CH_3 groups (green). This can be seen by the decreased width of the green centroid cluster compared to the orange and purple clusters.

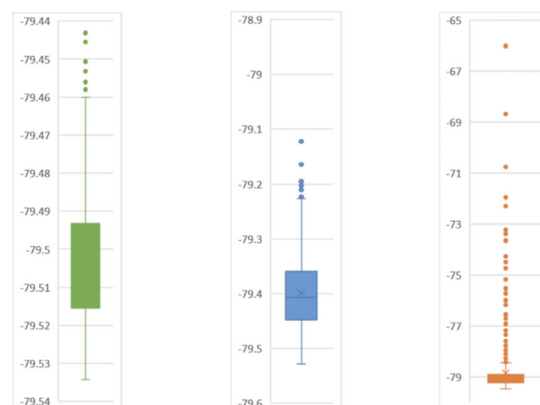


Fig. 8. Ethane MP2 energy distribution box plots (From left to right: $\pi/8$ polar angle bound, $\pi/4$ polar angle bound, $\pi/2$ polar angle bound).

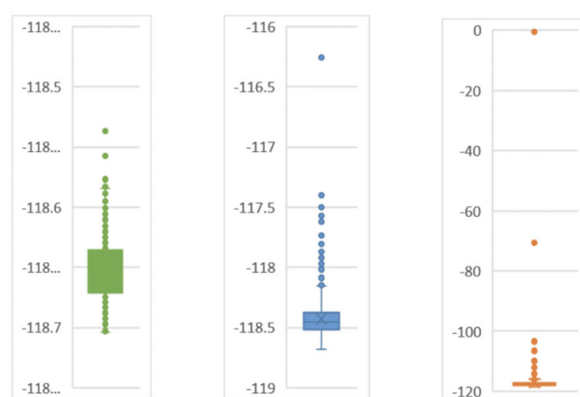


Fig. 9. Propane MP2 energy distribution box plots (From left to right: $\pi/2$ polar angle bound, $\pi/4$ polar angle bound, $\pi/8$ polar angle bound).

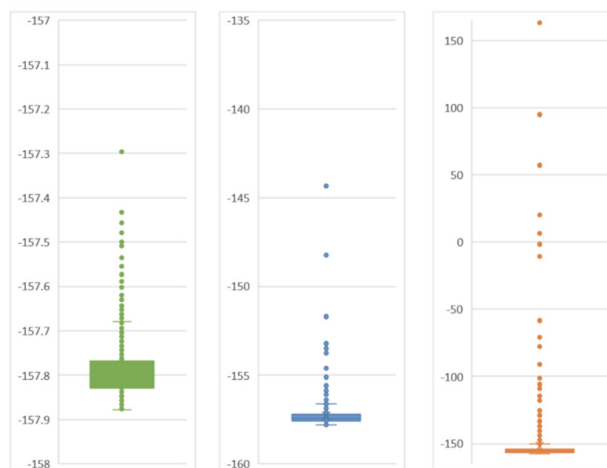


Fig. 10. Isobutane MP2 energy distribution box plots (From left to right: $\pi/2$ polar angle bound, $\pi/4$ polar angle bound, $\pi/8$ polar angle bound).

V. ANALYSIS AND DISCUSSION

As seen in the results, when transitioning to higher angle bounds the number of outliers tends to increase. This likely results from the overlapping of electron clouds between the CH , CH_2 and CH_3 groups of the given molecule. As the angle bounds increase, the range for the random azimuthal and polar angles also increases, meaning bonds gain more rotational freedom. With larger amounts of rotational freedom, the electron clouds of the structural units have a higher chance of overlapping, leading to higher electron-electron repulsion energies. This is reflected in the form of more positive-valued Hartree energies which are seen as

outliers in the distribution as seen in Figs. 8–10. Conversely, when the angle bounds are decreased, the structural units lose their rotational freedom and possess fewer electron-electron repulsions. This is observed as more negative-valued Hartree energies, resulting in an increase in the magnitude of the median energies (see Table 1).

Results from the classical geometric clustering algorithm around the CH, CH₂ and CH₃ groups revealed trends in the overall geometric tendency for ethane, propane, and isobutane (shown in Figs. 5–7). The similarity of new trial conformers with the ground conformer indicates that ethane, propane, and isobutane lack a wide range of stable conformers. This implies that the structure of each conformer is largely dictated by the placement of hydrogen atoms around each CH, CH₂, and CH₃ group as the underlying carbon atoms remain largely fixed. In ethane, as seen in Fig. 5, the lack of centroids between the top and bottom CH₃ centroid clusters suggests that the most stable conformers have hydrogen atoms that tend to stay as far apart from each other as possible. A similar trend is noted in propane, as seen in Fig. 6 and isobutane in Fig. 7.

VI. LIMITATIONS AND FUTURE WORK

Currently, this research presents an analysis of the energies of conformational isomers as well as a novel method for their generation and evaluation. However, while this method works for acyclic alkanes, larger molecules, especially those that are cyclic are generally much more computationally expensive and difficult to work with. This initial computational issue stems from the Monte Carlo methodology, which requires the Møller-Plesset SCF calculations to be run a substantial number of times. The latter issue concerning the difficulty to work with cyclic molecules is a direct result of the proposed BFS method, since it is unable to work with cyclic graphs. As a result, the researchers of this paper have three primary aims for future work:

- 1) the extension of the current approach to observe conformers of cyclic structures such as benzene;
- 2) energy analysis of conformers using alternate methods such as embedding molecules in a force field to vary bond lengths and bond orders;
- 3) the implementation of parallel computing and a machine learning model to optimize SCF calculations.

The researchers hope to use aim 1 to enhance the utility of the Monte Carlo-based analysis and aim 2 to provide new methods to determine molecular energies. The purpose of aim 3 is to directly address the limitation of computational power, which was initially observed through evaluation times when testing ethane, propane, and isobutane, as seen in Table 2.

Table 2. Evaluation time for each conformer

Molecule Conformer	Evaluation Time (minutes)
Ethane	13.99
Propane	18.80
Isobutane	29.50

When implementing the proposed methodology, the evaluation time of propane's Hamiltonian was measured to

be 1.34 times the evaluation time for ethane. Isobutane also followed a similar trend with a Hamiltonian evaluation time 1.56 times that of propane.

Given this polynomial increase in evaluation times, as larger molecules are tested, finding alternate solutions to the ab initio methods is pertinent. This is where aim 3 could prove to be considerably helpful. First, running ab initio methods, specifically Hartree-Fock and Density Functional Theory on a parallel computing system has already been shown to significantly speed up the SCF process [20]. Extending this method to run higher order ab initio methods, such as MP2, could prove to be helpful in reducing evaluation times as larger molecules begin to get tested.

Furthermore, leveraging the use of a machine learning model could also prove to be vital in optimizing SCF calculations. Specifically, machine learning could be beneficial for MP2 by generating better wavefunction corrections and reducing the number of iteration steps when converging to a Hamiltonian. As mentioned in the background, machine learning has already been implemented in the field of molecular dynamics. Particular instances include the Fast Search and Find of Density Peaks clustering algorithm along with deep learning prediction models. Therefore, implementing machine learning for the generation and evaluation of conformational isomers could prove to be a valuable step forward in enhancing this research.

VII. CONCLUSIONS

In conclusion, a novel method for analyzing the conformers of acyclic alkanes was successfully implemented using the Møller-Plesset Perturbation theory, Monte Carlo methodology, and classical geometric clustering algorithm. Conformers were successfully generated and evaluated for ethane, propane, and isobutane. This can potentially be generalized for any acyclic molecule provided the necessary computational power is present. Our results consist of a substantial number of stable conformers, where their structure and median energy were influenced by the position of the CH, CH₂ and CH₃ groups. By observing the kurtosis values and leptokurtic behavior of each distribution, the proposed novel method can also identify outliers, further increasing the accuracy of conformer analysis. Future advancements in computational efficiency and the expansion of our approach to larger, more complex molecular systems can also help improve the scope of our study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

RS, RG, JL, and SK all worked on the implementation of the proposed methodology. LM provided guidance on self-consistent field methods and prior methodologies. RS performed data analysis and visualization. RS, RG, and SK wrote the paper. All authors approved the final version.

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