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TOPOLOGICAL ANALYSIS OF THE CONFORMATIONAL SPACE AND ENERGY LANDSCAPE OF THE BIPHENYL MOLECULE: A TOPOLOGICAL DATA ANALYSIS PERSPECTIVE

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Abstract

The Gaussian 16 program, together with the Gauss-View graphical interface, was used to perform a dihedral scan of the angle defined by four consecutive carbon atoms in the biphenyl molecule, which connects the two benzene rings. A sample of 720 conformers was generated at the PBE0-D3BJ/def2-TZVP level of theory. The rotation around this dihedral angle constitutes a periodic degree of freedom; therefore, the associated conformational space is topologically equivalent to the circle S^1.

Using techniques from Topological Data Analysis (TDA), the conformers were represented as points in the space R^{3N}. Structural similarity between conformations was evaluated using the RMSD metric, from which the corresponding distance matrix was constructed. Consistent with the periodic nature of the system, the persistent homology analysis yielded the Betti numbers β_0=1 and β_1 = 1, indicating the presence of a single connected component and a cyclic topological structure.

Subsequently, a dimensionality reduction method (MDS) was applied to project the point cloud from R^{3N} into a space R^3, preserving the structural and energetic information associated with each conformation. Finally, sublevel-set persistent homology was employed to analyze the topological features of the potential energy landscape of the biphenyl molecule. The results obtained from the geometric analysis, dimensional projection, and sublevel-set structure revealed a consistent global topological agreement.

Keywords: conformational space; potential energy landscape; topological data analysis; sublevel-set persistent homology.

Introduction

Since the hypothesis of Democritus' atomic model, science has sought to understand the nature of matter and its behavior. The concept of the atom has evolved from the idea of a solid and indivisible object to the current description of a system composed of a nucleus with subatomic particles surrounded by electrons.[1,2] The union of atoms gives rise to molecules, which constitute the fundamental structural units of matter, and chemical bonding theory explains the different types of bonds that hold atoms together within them.[1]

In the molecular context, some molecules exhibit isomerism, in which compounds with the same molecular formula display different chemical structures and, consequently, different properties. Isomerism is classified into structural and spatial types; within the latter are enantiomers and diastereomers. The latter include conformational isomers or molecular conformers, which are the main focus of this research.[3–7] Conformers interconvert through rotations around single bonds, and the set of all possible conformations

defines the conformational space of the molecule.[5,8] This space can be conceived as a mathematical manifold embedded in R^{3N}, where N is the number of atoms in the molecule.[8]

If the potential energy values of each conformer are calculated, the potential energy function or energy landscape is obtained. This function can be interpreted as a scalar function $E: R^{3N+1} \rightarrow R$, defined over the conformational space, whose structure describes the energy landscape of the molecule.[10,11] Knowledge of this function is essential because it provides information about physicochemical, spectroscopic, and photochemical properties of molecules.[9,12] Furthermore, the geometric and topological characterization of the conformational space has applications in drug design, structure–activity relationship (SAR) studies, and protein folding analysis.[13–19]

Theoretically, the potential energy of a molecule can be computed for a specific conformer using quantum mechanics (QM) or molecular mechanics (MM) methods.[10] The combination of both approaches, known as QM/MM, provides a balance between accuracy and computational efficiency, which is crucial for studying complex molecular systems such as proteins or reactions in solution.[21] This approach allows a quantum mechanical treatment to be as- signed to the region of interest, while the rest of the system is modeled using classical force fields.[22] Potential energy surfaces obtained from these calculations are essential for under- standing reaction mechanisms and molecular properties, providing a solid theoretical basis for predicting chemical behavior.[9,13]

In recent years, one of the main challenges has been the efficient generation of representative sets of conformers that describe the conformational space, both theoretically and experimentally. The development of computational programs has facilitated the generation of these samples, which can be represented as datasets in R^{3N}.[24–34] This opens the door to the application of topological approaches, in particular persistent homology, to reconstruct the conformational space and explore the potential energy function.[35,36] Previous works, such as those by Menbrillo Solís and collaborators, have employed persistent homology and discrete Morse theory to study the topology and geometry of conformational spaces and energy landscapes.[11] Sublevel-set persistent homology has also been used with samples of conformers together with their associated potential energies to study the topological features of energy landscapes in molecules such as the family of n-pentane.[37]

Based on the above, this work investigates the topological characteristics of the conformational space and the potential energy landscape of the biphenyl molecule. To this end, computational tools from topological data analysis are employed. Persistent homology is used to characterize the structure of the set of conformations in the geometric space, while sublevel-set persistent homology is applied to analyze the topology of the energy landscape. This approach makes it possible to robustly identify local minima associated with stable conformers, as well as the energy barriers that separate different conformational regions. Moreover, the topological analysis allows the detection of cyclic structures related to the periodic nature of the angular degree of freedom connecting the biphenyl rings. In this way, the proposed method complements traditional approaches for the analysis of potential energy surfaces, providing a quantitative and topological description of the global structure of the energy landscape.[40,41]

Theoretical Foundations

The Biphenyl Molecule

The biphenyl molecule is an aromatic hydrocarbon whose molecular formula is $C_{12}H_{10}$. This molecule is formed by the union of two benzene rings through a single bond between two carbon atoms (Figure 1). In this molecule, the single bond connecting the two benzene rings (C7–C1) acts as a rotational axis with respect to the dihedral angle formed by the four consecutive atoms C8, C7, C1, and C2 or C6. The rotation of the molecule around this dihedral angle generates a set of conformers that form the conformational space of the biphenyl molecule. The molecular potential energy values associated with each conformer of the conformational space define the potential energy function of the biphenyl molecule.

Mathematical Framework of the Research

We begin by considering the atom as a solid sphere that exists in a three-dimensional space R^3, whose position is represented by a point in space (x_0, y_0, z_0).

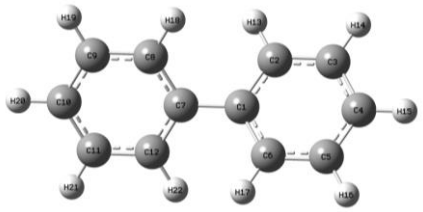

Figure 1: Biphenyl molecule.

In the case of a molecule, a space R^{3N} is required to represent it as a point, where N is the number of atoms in the molecule. For example, for the biphenyl molecule ($C_{12}H_{10}$), which contains 22 atoms, a space R^{66} is required to represent it as a point in space.

Molecular Graph: A molecular graph is a tuple M consisting of the following elements:
M = (V, E, c_v, L, Θ), where: Γ=(V, E) is a finite undirected graph, that is, V is a finite set and E ⊆ V ×V is a subset such that, for any v, w ∈ V , (v, v) ∉ E and (v, w) ∈ E if and only if (w, v) ∈ E. We refer to V as the set of vertices of M and to E as the set of edges. The elements of V correspond to the atoms of the molecule, and the elements of E correspond to the bonds between atoms.
c_v: V → N is a vertex coloring; for v ∈ V , c_V (v) is interpreted as the chemical element represented by the atom corresponding to v, and is defined as the atomic number of that element.

L: E → (0, ∞) is a set of edge lengths; L(e) is called the length of an edge e ∈ E.
Θ : E_2 → (0, π] is a set of angles, where
E_2 ={(v, w_1, w_2) ∈ V × V × V | (v, w_1), (v, w_2) ∈ E, ; $w_1 \neq w_2$}
represents the set of adjacent edges in Γ. We refer to Θ(v, w_1, w_2) as the angle between the edges (v, w_1) ∈ E and (v, w_2) ∈ E, representing the angle between two bonds sharing a common vertex.
For consistency, we also require that L(v, w) = L(w, v) for each (v, w) ∈ E and Θ(v, w_1, w_2) = Θ(v, w_2, w_1) for each (v, w_1, w_2) ∈E_2.

Conformer and Conformational Space: A conformation or conformer of a molecular graph M = (V, E, c_v, L, Θ) is a function φ: V → R^3 that satisfies the following conditions:[11]
1. |φ(v) − φ(w)| = L((v, w)) for all (v, w) ∈ E.
2. For all (v, w_1, w_2) ∈ E_2,

$$\arccos\left(\frac{\varphi(v)\vec{\varphi}(w_1)\cdot\varphi(v)\vec{\varphi}(w_2)}{|\varphi(v)\vec{\varphi}(w_1)||\varphi(v)\vec{\varphi}(w_2)|}\right)=\Theta(v,w_1,w_2).$$

The conformational space of a molecular graph M, denoted C_M, is the set of all conformations φ of M. Each conformation φ can be viewed as a 3N-tuple (φ(v1),...,φ(v_n)) ∈ R^{3N}. Therefore, C_M is a subset of R^{3N}. If E is the molecular potential energy function, then E: C_M → R. The graph of E is denoted by G_E:= {(x, y) |x∈ C_M}, y=E(x) ⊂ R^{3N+1}.

The conformational space must satisfy certain properties to ensure that it aligns with chemical intuition, such as: (1) being path-connected, (2) possessing a spatial metric, and (3) being bounded (that is, the limit of the conformational space must exist).
A conformer φ(v1) consisting of N atoms can be expressed as a vector in R^{3N} :

$$\varphi(v_1)=\begin{pmatrix}x_1 & y_1 & z_1\\ x_2 & y_2 & z_2\\ \vdots & \vdots & \vdots\\ x_n & y_n & z_n\end{pmatrix}=(x_1,y_1,z_1,x_2,y_2,z_2,\ldots,x_n,y_n,z_n)$$

A sample m from the conformational space C_M can be written as:

$$\begin{pmatrix}\varphi(v_1)\\ \varphi(v_2)\\ \vdots\\ \varphi(v_m)\end{pmatrix}=\begin{pmatrix}x_{1,1} & y_{1,1} & z_{1,1} & x_{2,1} & y_{2,1} & z_{2,1} & \cdots & x_{n,1} & y_{n,1} & z_{n,1}\\ x_{1,2} & y_{1,2} & z_{1,2} & x_{2,2} & y_{2,2} & z_{2,2} & \cdots & x_{n,2} & y_{n,2} & z_{n,2}\\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots\\ x_{1,m} & y_{1,m} & z_{1,m} & x_{2,m} & y_{2,m} & z_{2,m} & \cdots & x_{n,m} & y_{n,m} & z_{n,m}\end{pmatrix}$$

Spatial Metric and Distance Matrix: Let M=(V, E, c_v, L, Θ) be a molecular graph such that |V |=n. The conformational space c_M^{int}can be endowed with a metric. A commonly used distance metric in molecular sciences is the root-mean-square deviation (RMSD)

$$RMSD(\varphi(v_1),\varphi(v_2))=\sqrt{\frac{1}{N}\sum_{i=1}^{n}\left(\sum_{\alpha\in\{x,y,z\}}|\alpha_{i,1}-\alpha_{i,2}|\right)}$$

A convenient way to represent the relative distance information among all conformers is through a distance matrix, a simplified version of which is presented below:

$$\begin{pmatrix}0 & Conf1 & Conf2 & Conf3 & Conf4 & Conf5 & \ldots & Confn\\ Conf1 & 0 & d_{12} & d_{13} & d_{14} & d_{15} & \ldots & d_{1n}\\ Conf2 & d_{21} & 0 & d_{23} & d_{24} & d_{25} & \ldots & d_{2n}\\ Conf3 & d_{31} & d_{32} & 0 & d_{34} & d_{35} & \ldots & d_{3n}\\ Conf4 & d_{41} & d_{42} & d_{43} & 0 & d_{45} & \ldots & d_{4n}\\ Conf5 & d_{51} & d_{52} & d_{53} & d_{54} & 0 & \ldots & d_{5n}\\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ldots & d_{31}\\ Confn & d_{n1} & d_{n2} & d_{n3} & d_{n4} & d_{n5} & \ldots & 0\end{pmatrix}$$

Multidimensional Scaling Analysis (MDS): Multidimensional Scaling Analysis (MDS) is a method that projects high-dimensional points into a lower-dimensional space while preserving, as much as possible, the relative distances among the points.[42] Given a set of points in R^p (where p = 3), MDS seeks to find a configuration of points y_1, y_2,

$\ldots, y_n \in R^3$ that minimizes the stress function:

$$\text{Stress}(\mathbf{y}_1, \ldots, \mathbf{y}_n) = \sqrt{\sum_{i<j} (d_{ij} - \|\mathbf{y}_i - \mathbf{y}_j\|)^2}$$

Here, $\|y_i - y_j\|$ represents the Euclidean distance between the projected points y_i and y_j in the lower-dimensional space.

Once the stress function has been minimized, the projected coordinate's y_i are obtained for each conformer i, allowing the conformers to be visualized in a three-dimensional space. Additionally, it is possible to associate further properties, such as the conformer energy, with the projected points.

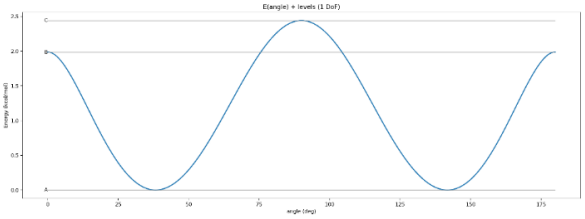

Figure 2: Relative energy vs. scan coordinates for the biphenyl molecule. Letters A–C indicate energy levels in kcal/mol.

Persistent homology: This is a method for computing homological features at different scales. Features that persist over a wider range of the parameter are considered to have greater topological relevance, whereas short-lived features are usually associated with noise. To compute the persistent homology of a set of points, the sample is represented as a simplicial complex.[38,39] For a set of points S, with $|S|=k$, the most common approach is to define the k-simplex S with the points as vertices.

Persistent homology can be summarized into two main approaches:

1. **Distance-based approach:** Estimate C_M by filling the sample S with open balls centered at each point, that is, $U_\varepsilon = U_{x_i \in S} B(x_i, \varepsilon)$, and computing the homology of the nerve of the covering Nrv U. Varying the radius ε generates a filtration of complexes (e.g., Vietoris–Rips).
2. **Sublevel-set approach:** When a scalar function defined on the space is available (for example, the potential energy E of a molecule), the sublevel sets

$$L(r) = \{ x \in C_M \mid E(x) \leq r \},$$

are considered, and the evolution of the Betti numbers β_i is studied as r varies. In this context: (i) local minima generate bars in H_0 (new connected components); (ii) local maxima cause the death of components (merging of energy basins); (iii) in periodic domains (e.g., S^1 for a dihedral angle), cycles may appear in H_1 reflecting the intrinsic topology of the space.

This second approach, known as sublevel-set persistent homology, is especially suitable for studying the energy landscape of molecules. Unlike distance-based methods, it allows the critical structure of the energy function to be directly identified: minima, maxima, and transition barriers, together with the global connectivity of the conformational space. In the case of biphenyl, the application of this approach naturally reveals the existence of the trans and cis conformers, as well as the barrier connecting them[40,41].

Computational Methods

Gaussian 16[43] together with the Gauss-View graphical interface[44] was used to perform a dihedral scan of the biphenyl molecule around the single bond connecting the two benzene rings (atoms C8–C7–C1–C2; see Fig. 1). The calculations were carried out at the PBE0- D3BJ level of theory with the def2TZVP basis set.[45,46] The scan was performed considering the molecular symmetry of the biphenyl molecule. A sweep of 180° was carried out starting from the planar conformation, using a uniform angular step Δθ, generating a sample of conformers together with their corresponding potential energy values E(θ) in kcal/mol.

The conformers were represented as points in R^{3N} (N atoms). Structural similarity was measured using the root-mean-square deviation (RMSD), implemented with RDKit,[47] from which the corresponding distance matrix was constructed. Persistent homology (PH) was computed on this matrix to obtain information about the topological features of the conformational space function, using GUDHI[48] through a Python interface.

Additionally, the topology of the energy landscape E: $S^1 \to R$ was analyzed using sublevel-set persistent homology, and the evolution of the Betti numbers $\beta_0(r)$ and $\beta_1(r)$ was studied.[40,41]

Results and Discussion

Angular scan calculations were performed to

generate the underlying representation of the conformational space function of the biphenyl molecule. Starting from the planar conformation (angle 0°), 30 increments of 3° were carried out up to 90°, yielding a semicircular representation of the conformational space. By continuing with 60 increments of 3°, the molecule returned to the planar conformation, collectively describing a circular trajectory. This behavior is consistent with the molecular symmetry of biphenyl.

In order to refine the characterization, a sampling of 720 conformers was performed, generated from 720 angular increments of 0.250°, computing the potential energy of each conformer (kcal/mol) (see Fig. 2). These conformers were represented as points in a space R^{3N}, where N=22 atoms in biphenyl, that is, a space R^{66}.

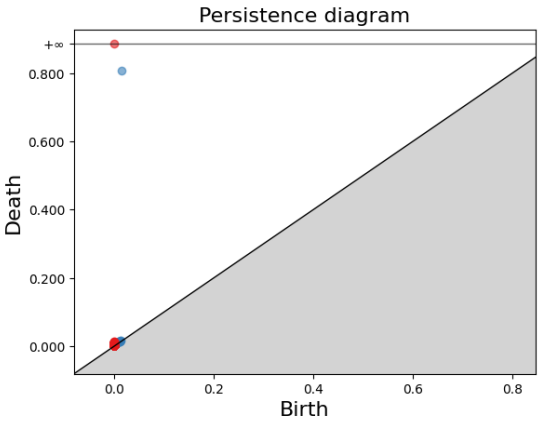

Figure 3: Persistence diagram computed from the RMSD distance matrix for biphenyl.

Using the RMSD metric, the distance matrix between conformers was constructed. The computation of persistent homology on this matrix yielded the Betti numbers β_0=1 and β_1=1 (Fig. 3), confirming that the conformational space of biphenyl possesses the topology of a circle, in agreement with the rotational symmetry of the molecule. Subsequently, Multidimensional Scaling (MDS) was applied to obtain a projection of the conformers represented as points in R^{3N} onto points in a space R^3, preserving the energetic information associated with each conformer. Figure 4 shows the projection of the points, where the color bar represents the relative energy: blue corresponds to minima and yellow to maxima. The presence of two minima and two maxima agrees with the results observed in Figs. 2 and 3.

Finally, sublevel-set persistent homology was applied to analyze the topological features of the torsional energy landscape of biphenyl. According to the formulation of Flegg et al. (2020) and Story et al. (2022), the births of H_0 classes correspond directly to the appearance of local minima on the energy surface, while the deaths of these classes coincide with saddle points (critical points of index 1) where energy basins merge.[40,41] Higher homology classes (H_1,H_2,...) represent the emergence of cyclic structures in the sublevel sets; in a one–dimensional system with angular domain S^1, an H_1 bar corresponds to the energy level at which the sublevel set fully connects the circle, capturing the cyclic topology of the conformational space.

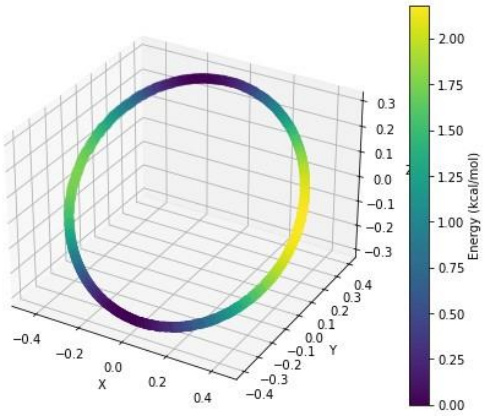

Figure 4: Three-dimensional projection of the biphenyl conformational space using MDS. Colors indicate relative energy (kcal/mol).

In Fig. 5, two H_0 class bars can be observed. The semi-infinite bar represents the global minimum, while the finite bar represents a local minimum. Both bars are born at the same energy level within the torsional profile. The death of the finite H_0 bar gives rise to a transition state connecting the two minima.

Similarly, the blue H_1 bar appears near the maximum energy of the landscape. Its short persistence reflects the fact that, in a one–degree-of-freedom system defined on the domain S^1, the H_1 class is born when the sublevel sets reach sufficient energy to completely wrap around the torsional angle, and dies immediately afterward due to the one–dimensional nature of the problem. This H_1 bar therefore represents the cyclic connectivity of the angular domain, linking both minima through the torsional maximum. The global minimum corresponds to the non-planar conformation around 38°, while the local minimum (finite bar) appears around 141°. In both conformations, the benzene rings twist in order to

reduce steric repulsions between the ortho hydrogens. The transition state where the finite bar dies coincides with the planar conformation (0° and 180°), whose relative energy is approximately 1.95 kcal/mol.

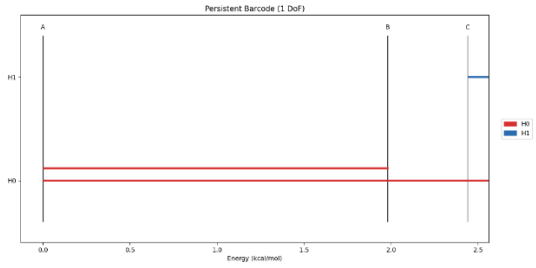

Figure 5: Sublevel-set persistent homology of the biphenyl energy landscape. Red bars: H_0 (minimum); blue bar: H_1 (cycle associated with the S^1 periodicity).

The blue H_1 bar appears at the energy level corresponding to the torsional maximum located at 90°, where the energy reaches its highest value (2.37 kcal/mol). This topological analysis is fully consistent with the computed energy profile and with the theoretical interpretation of persistent homology for one–dimensional energy landscapes.

Conclusions

This work applied advanced methods from topological data analysis to represent the conformational space of the biphenyl molecule. The representation of conformers as points in a high-dimensional space (R^{66}) and their subsequent projection into R^3 using MDS while preserving the associated energetic information allowed for a clear representation of the molecular conformational space. Persistent homology analysis applied to the RMSD distance matrix confirmed that the conformational space of biphenyl possesses a circular topological structure, consistent with the periodic nature of the dihedral angle. In addition, through sublevel-set persistent homology, a topological description of the energy landscape of the biphenyl molecule was obtained. Local minima (corresponding to the cis and trans conformations) were identified, as well as the maximum associated with the transition barrier. This result directly connects the topology of the energy landscape with the chemical intuition regarding stability and interconversion pathways.

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Conflict of interests

The authors declare no conflict of interest.

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