COMPUTATIONAL STUDY OF ALANINE DIPEPTIDE CONFORMATIONS

Exploring the Energy Landscape of Alanine Dipeptide Conformations through Computational Methods

Abstract

Investigating the conformational stability of alanine dipeptide using computational chemistry techniques to calculate Gibbs free energies and analyze the effects of different torsion angles on structural properties

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Introduction

Alanine dipeptide serves as a model compound for studying peptide conformations due to its simplicity. Understanding the stability and energy landscape of various conformations provides insights into the behavior of larger peptide chains. The conformational dynamics of proteins play a crucial role in their biological function, as the three-dimensional structure of a protein determines its interactions, stability, and activity. The spatial arrangements of atoms in a protein can alter its ability to function and influence its biochemical properties. By exploring the Gibbs free energy landscape of different conformations of alanine dipeptide, even isolated, we can gain insights into the stability and preferences of various torsion angles, which may have broader implications for the study of more complex proteins and their functional dynamics. This project explores the energy differences between alpha-helix, beta-sheet, and various other conformations using computational methods, contributing to our understanding of protein structure and function.

Methodology

This project involves the computational study of different conformations of alanine dipeptide, including alpha-helix and beta-sheet conformations. Molecule visualizing software such as Avogadro and Avogadro2 were used to build the proteins and visualize the different conformers by altering torsion properties. Using the ORCA quantum chemistry software, the structures of various conformers were optimized, and Gibbs free energies were calculated to compare their stabilities. MATLAB was used for data analysis and visualization, including the creation of energy landscapes, further improving our understanding of the differences in each conformer.

In Avogadro2, a base alanine dipeptide protein was created and then altered to create multiple conformers by numerically adjusting the torsion angles on significant atoms. For the most significant conformers, Alpha Helix was characterized by torsion angles of $\varphi = -60°$, $\psi = -40°$ and Beta Sheet was characterized by torsion angles of $\varphi = -120°$, $\psi = 120°$. Other conformers were randomly generated and optimized to create a broad sample range.

In Orca, frequency calculations were performed to verify the nature of the optimized structures and to obtain thermodynamic properties. A basis set of def2-SVP and each conformer was optimized prior to frequency calculations.

Results

The calculated Gibbs free energies (in Hartrees) for each conformation were:

Alpha Helix, $\varphi = -60°$, $\psi = -40°$: -492.33052547 Eh

Beta Sheet, $\varphi = -120°$, $\psi = 120°$: -492.33186378 Eh

$\varphi = 54°$, $\psi = -74°$: -492.33261610 Eh

φ = -73°, ψ = 72°: -492.33165235 Eh

φ = -20°, ψ = -55°: -492.33049380 Eh

φ = 168°, ψ = -79°: -492.32740611 Eh

Analyzing these free energy values, it appears that φ = 54°, ψ = -74° was the most stable conformer in this sample. The comparisons between these conformers can be better seen in the 3D plot created in MATLAB (Figure 1).

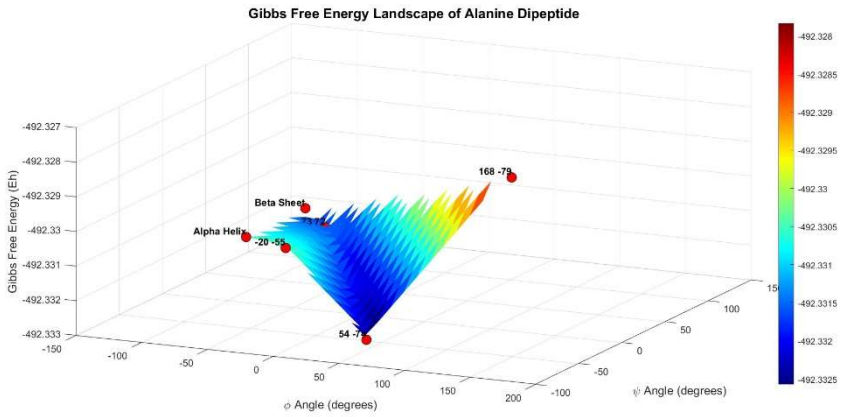

Figure 1: Gibbs Free Energy Landscape

From this chart, it appears that the Alpha Helix and Beta Sheet conformers are relatively stable when compared to other conformers. The vast difference between the stability of φ = 54°, ψ = -74° and φ = 168°, ψ = -79° can also be seen. The least stable conformer, with torsion angles φ = 168°, ψ = -79°, showed a much higher (less negative) energy, likely due to unfavorable steric interactions and torsional strain. These findings highlight that stability is not only a matter of typical secondary structures but can also depend heavily on the precise spatial arrangement of atoms.

Interestingly, one of these random conformers, characterized by torsion angles φ = 54°, ψ = -74°, was found to be the most stable, with a Gibbs free energy slightly lower than those of the alpha-helix and beta-sheet. This suggests that, while specific secondary structures like alpha-helices and beta-sheets are commonly found in proteins due to their stability, other torsion angle arrangements can also exhibit significant stability under isolated conditions. To compare these two methods, it is beneficial to compare this plot to a previously created plot.

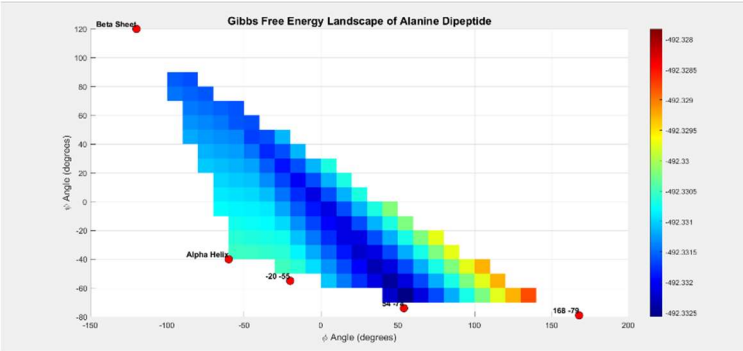

Figure 2: 2D Gibbs Free Energy Landscape

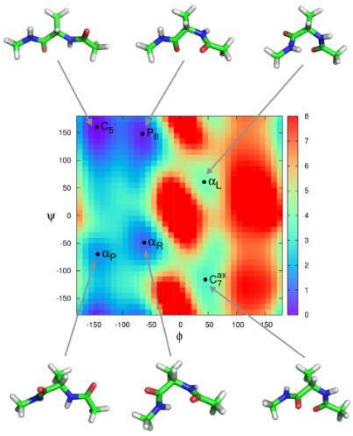

Figure 3: ResearchGate Ramachandran Plot (Chodera et al. 2006; Jaillet et al. 2011)

By comparing our 2D plot (Figure 2) to a Ramachandran Plot (Figure 3) on ResearchGate (Chodera et al. 2006; Jaillet et al. 2011), the results for stability draw significant similarities. For the small sample size calculated, the general trend in the plots match in the area where points connect, and certain conformers such as Alpha Helix, Beta Sheet, and the least stable conformer can be found having the same relative energies.

Errors and Limitations

While the study yielded valuable insights, there were several limitations and potential sources of error. One significant limitation was the use of isolated alanine dipeptide molecules, which may not perfectly replicate the conditions under which proteins naturally fold. In biological systems, solvent interactions, temperature fluctuations, and the presence of other molecules can significantly affect the stability of certain conformers. Additionally, the computational constraints required the use of a relatively small basis set (def2-SVP), which might not capture all electronic effects accurately.

The reliance on frequency calculations for Gibbs free energy estimation also introduces potential errors, especially if the optimization does not reach a true global minimum. Lastly, the sample size of random conformers was limited, and expanding this set could provide a more comprehensive view of the energy landscape, particularly if advanced sampling methods like molecular dynamics simulations were employed. Despite these limitations, the results aligned well with known trends, supporting the robustness of the methodology.

Conclusion

The computational study of alanine dipeptide conformers has provided valuable insights into the stability of various torsion angle arrangements, highlighting the significant differences in Gibbs free energy between conformers. While the alpha-helix and beta-sheet conformers were expected to be among the most stable, this analysis revealed that other conformations, such as $\varphi = 54°$, $\psi = -74°$, could be more stable in isolated conditions. The results align well with existing Ramachandran plots, supporting the

methodology used. However, the deviations from previous studies may indicate the importance of considering environmental factors when analyzing protein conformations. Overall, this project demonstrates how computational chemistry can be used to explore peptide structures, contributing to a deeper understanding of protein dynamics and stability. Further studies could involve larger systems, enhanced sampling, or the inclusion of solvent effects to better mimic biological environments.

References

Devaurs, Didier & Vaisset, Marc & Siméon, Thierry & Cortés, Juan. (2013). A multi-tree approach to compute transition paths on energy landscapes. 10.13140/RG.2.1.1734.6402.