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Research Article

Comparative Thermodynamic Analysis of Pain-Relieving Molecules

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Abstract

This study provides a comprehensive investigation of the thermodynamic properties of common pain-relieving molecules such as morphine, ibuprofen, and aspirin. Initially, the molecular structures of these compounds were determined using geometric optimization calculations performed in the gas phase with Gaussian software. These optimizations aimed to accurately obtain the energy minima and geometric structures of the molecules. Subsequently, the thermodynamic properties of the molecules were calculated using Density Functional Theory (DFT) with the B3LYP/6-311G(d,p) basis set. These calculations assessed critical parameters such as binding energies, free energy changes, and entropy changes. The thermodynamic properties of morphine, ibuprofen, and aspirin were analyzed to understand their effects on binding to biological targets and their effective pain-relieving activities. Additionally, important parameters for optimizing molecular design and pharmaceutical formulations were identified, with the goal of contributing to future drug development processes.

Keywords: dft calculations; pain-relieving molecules; thermodynamic properties

1.Introduction

Pain is a complex symptom affecting numerous medical conditions, and its effective management is a significant focus in both clinical and research fields. In this study, we selected pain-relieving molecules such as morphine, ibuprofen, and aspirin due to their distinct mechanisms of action and pharmacological profiles. Comparing the thermodynamic properties of these molecules can provide insights into their analgesic effects. Morphine [1] is an opioid molecule known for its potent analgesic effects, typically prescribed for severe pain [2-4]. It reduces pain perception by binding to opioid receptors in the brain and spinal cord. Ibuprofen [5], a non-steroidal anti-inflammatory drug (NSAID) [6], is recognized for its ability to alleviate both pain [7] and inflammation [8]. It works by inhibiting cyclooxygenase (COX) enzymes, thereby reducing prostaglandin [9] production and relieving pain and inflammation. Aspirin [10], another NSAID, is known for its effects on pain [11], fever [12], and inflammation [13]. It inhibits COX enzymes to block prostaglandin production, aiding in pain and inflammation management [14].

This study aims to provide a comprehensive analysis of the thermodynamic properties of morphine, ibuprofen, and aspirin. Determining the geometric structures of these molecules and calculating their thermodynamic properties will help us better understand their binding capabilities to biological targets and their analgesic effects. Geometric optimizations performed in the gas phase using Gaussian 5 software and thermodynamic calculations carried out with Density Functional Theory (DFT) using the B3LYP/6-311G(d,p) basis set will be employed. The obtained data will highlight the impact of these molecules on pain management and identify potential areas for improvement in drug development processes.

2. Computational Details

The geometric structures of the pain-relieving molecules morphine, ibuprofen, and aspirin were initially visualized using the Gaussian View 5 program [15]. Following this, a series of comprehensive theoretical calculations were conducted to investigate various aspects of these compounds. Utilizing the Density Functional Theory (DFT) [16] method, calculations were specifically performed using the B3LYP [17-18] functional and the 6-311G(d,p) [19] basis set. This computational approach is particularly effective for predicting molecular structures, energy levels, and diverse chemical properties, including those related to interactions with biological targets. The theoretical calculations aimed to elucidate not only the geometric configurations of the pain-relieving molecules but also to provide insights into their thermodynamic properties such as binding energies, free energy changes, and entropy variations. By employing advanced computational tools, this study enhances the understanding of the

structural characteristics and potential pharmacological activities of these molecules, thereby contributing valuable information for pharmaceutical research and drug development.

3. Results and Discussion

3.1. Geometric Structure

The previously synthesized structures of morphine, ibuprofen, and aspirin were obtained from the Cambridge Crystallographic Data Centre (CCDC). A comparative theoretical analysis of these three molecules is not present in the literature and has been conducted for the first time in this study using the DFT/B3LYP/6-311G(d,p) method.

X-ray single crystal structures of each molecule provided a foundation for theoretical geometric calculations. Density Functional Theory (DFT) calculations were performed using GAUSSIAN 09 software, with the B3LYP methodology and the 6-311G(d,p) basis set to optimize the lowest energy conformations of each molecule. The geometric structures of morphine, ibuprofen, and aspirin were thoroughly examined and optimized using the DFT/B3LYP/6-311G(d,p) approach. These calculations allowed for a detailed analysis of the molecular geometries, energies, and stabilities. The theoretical analyses have provided detailed insights into the electronic density, molecular orbital distributions, and steric interactions of the molecules. Additionally, these analyses assessed potential variations in the geometric structures and reactivity profiles of the molecules. Such theoretical information is crucial for testing the alignment with experimental data and for a better understanding of the physicochemical properties of these molecules. The experimental structure of morphine is shown in Figure 1a, and its optimized structure obtained using DFT/B3LYP/6-311G(d,p) is depicted in Figure 1b.

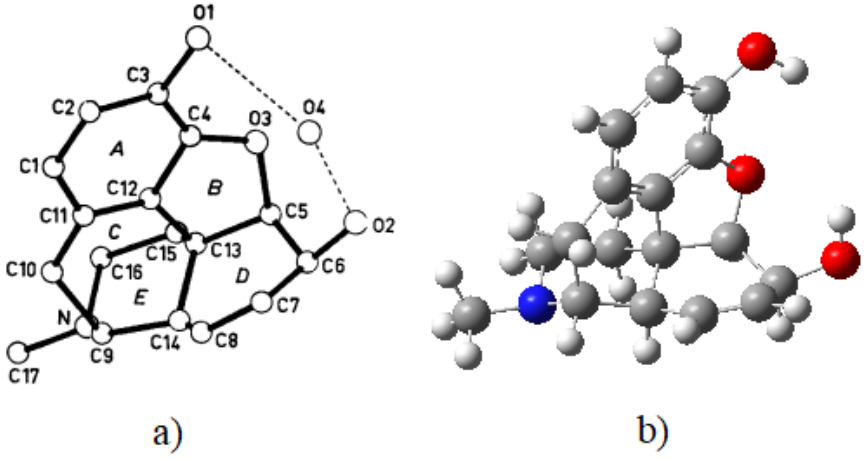

Figure 1a. The Experimantal structure 1b. The optimized geometry of morphine.

The experimental structure of ibuprofen is shown in Figure 2a, and its optimized structure obtained using DFT/B3LYP/6-311G(d,p) is depicted in Figure 2b.

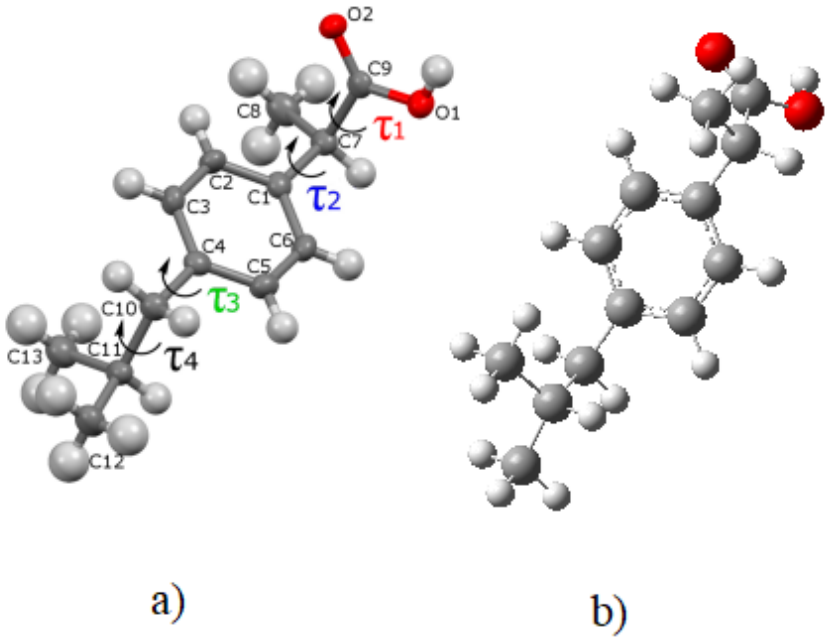

Figure 2a. The Experimantal structure 2b. The optimized geometry of ibuprofen.

The experimental structure of aspirin is shown in Figure 3a, and its optimized structure obtained using DFT/B3LYP/3-311G(d,p) is depicted in Figure 3b.

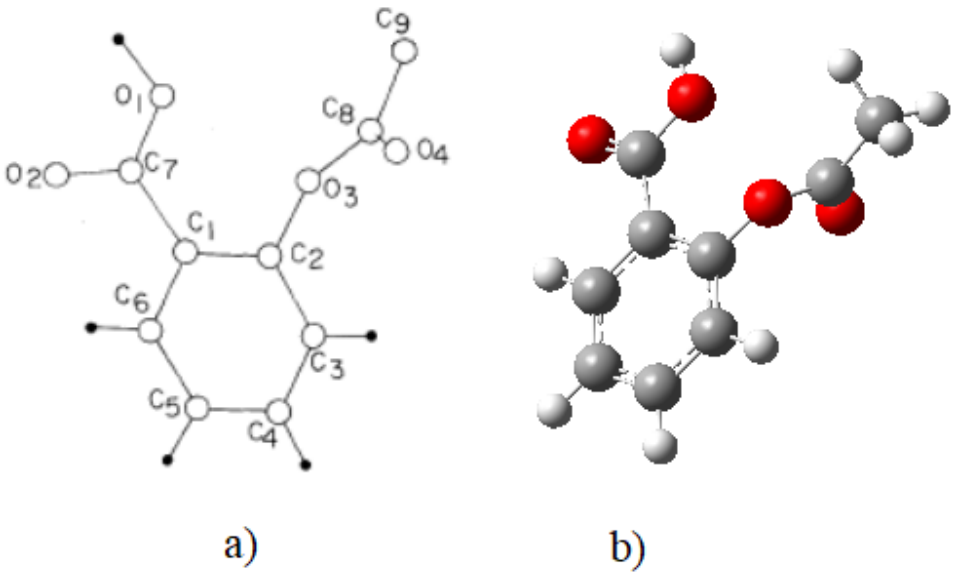

Figure 3a. The Experimantal structure 3b. The optimized geometry of aspirin.

DFT calculations have provided detailed insights into the atomic and electronic distributions within each molecule, facilitating a thorough understanding of chemical bonding and molecular interactions. The structural features of morphine, ibuprofen, and aspirin, including electronic density and molecular orbital distribution, have been analyzed in depth. Furthermore, the calculations have revealed steric interactions and bond lengths, as well as potential reactivity profiles of these molecules.

These analyses enhance our understanding of molecular structures and ensure consistency between experimental observations and theoretical predictions. The optimized structures of the molecules provide valuable information for various scientific applications and test the accuracy of theoretical modeling.

3.2. Calculation and Comparison of Thermodynamic Properties

In this study, the thermodynamic properties of morphine, ibuprofen, and aspirin molecules were calculated using the Gaussian program with the density functional theory (DFT) method, employing the B3LYP/6-311G(d,p) functional. The B3LYP functional provides a precise modeling of electronic structures, while the 6-311G(d,p) basis set offers an expanded basis set for detailed energy calculations. This methodology enables accurate determination of molecular energy levels and thermodynamic properties.The obtained data from the calculations include various thermodynamic parameters for morphine, ibuprofen, and aspirin molecules. These parameters are summarized and compared in Table 1. Table 1 details each molecule's thermal energy, heat capacity, entropy, rotational constants, and thermal corrections, highlighting differences among the molecules.

Termal energy, E (Kcal/mol)	**Morphine**	Ibuprofen	Aspirin
Rotational	0.889	0.889	0.889
Translational	0.889	0.889	0.889
Vibrational	236.106	186.069	103.841
Total	237.884	187.847	105.618
Heat capacity, C_v (cal/mol K)			
Rotational	2.981	2.981	2.981
Translational	2.981	2.981	2.981
Vibrational	73.296	52.938	37.107
Total	79.257	58.900	43.069
Entropy, S (cal/mol K)			
Rotational	33.806	32.556	31.004
Translational	43.024	41.874	41.471
Vibrational	60.129	55.080	37.037
Total	136.959	129.510	109.512
Rotational constants (GHz)			
A	0.47967	1.57357	1.13519
B	0.25566	0.24044	0.74845
C	0.20660	0.23545	0.50026
Rotational temperature (Kelvin)			
A	0.02302	0.07552	0.05448

B	0.01227	0.01154	0.03592
C	0.00991	0.01130	0.02401
Thermal properties (Hartree/particle)			
Zero-point correction	0.359995	0.283597	0.156551
Thermal correction to Energy	0.379092	0.299353	0.168313
Thermal correction to Enthalpy	0.380036	0.300297	0.169257
Thermal correction to Gibbs Free Energy	0.314962	0.238762	0.117225
Sum of electronic and zero-point Energies	-1015.973479	-656.600463	-648.715954
Sum of electronic and thermal Energies	-1015.954383	-656.584707	-648.704192
Sum of electronic and thermal Enthalpies	-1015.953439	-656.583763	-648.703248
Sum of electronic and thermal Free Energies	-1016.018512	-656.645297	-648.755281
Zero-point vibrational energy (kcal/mol)	225.90054	177.95975	98.23744

Table 1: The calculated thermodynamic parameters of molecules.

Table 1 provides a detailed comparison of the thermodynamic properties of morphine, ibuprofen, and aspirin molecules. According to thermal energy data, rotational and translational energies are identical for all three molecules, each being 0.889 kcal/mol. However, significant differences are observed in vibrational energies: morphine has 236.106 kcal/mol, ibuprofen has 186.069 kcal/mol, and aspirin has 103.841 kcal/mol. Consequently, total energy values are calculated as 237.884 kcal/mol for morphine, 187.847 kcal/mol for ibuprofen, and 105.618 kcal/mol for aspirin.

Regarding heat capacity, rotational and translational heat capacities are consistent across all molecules, each being 2.981 cal/mol K. Vibrational heat capacities show variation with morphine at 73.296 cal/mol K, ibuprofen at 52.938 cal/mol K, and aspirin at 37.107 cal/mol K. Total heat capacities are 79.257 cal/mol K for morphine, 58.900 cal/mol K for ibuprofen, and 43.069 cal/mol K for aspirin.Entropy values indicate that the rotational entropy is 33.806 cal/mol K for morphine, 32.556 cal/mol K for ibuprofen, and 31.004 cal/mol K for aspirin; translational entropy is 43.024 cal/mol K for morphine, 41.874 cal/mol K for ibuprofen, and 41.471 cal/mol K for aspirin; vibrational entropy is 60.129 cal/mol K for morphine, 55.080 cal/mol K for ibuprofen, and 37.037 cal/mol K for aspirin. Total entropy values are 136.959 cal/mol K for morphine, 129.510 cal/mol K for ibuprofen, and 109.512 cal/mol K for aspirin. Rotational constants and temperatures are as follows: for morphine, A = 0.47967 GHz, B = 0.25566 GHz, C = 0.20660 GHz, and rotational temperatures are A = 0.02302 K, B = 0.01227 K, C = 0.00991 K; for ibuprofen, A = 1.57357 GHz, B = 0.24044 GHz, C = 0.23545 GHz, and rotational temperatures are A = 0.07552 K, B = 0.01154 K, C = 0.01130 K; for aspirin, A = 1.13519 GHz, B = 0.74845 GHz, C = 0.50026 GHz, and rotational temperatures are A = 0.05448 K, B = 0.03592 K, C = 0.02401 K.Thermal corrections indicate that morphine has a zero-point correction of 0.359995 Hartree/particle, a thermal correction to energy of 0.379092 Hartree/particle, a thermal correction to enthalpy of 0.380036 Hartree/particle, and a thermal correction to Gibbs free energy of 0.314962 Hartree/particle; ibuprofen has a zero-point correction of 0.283597 Hartree/particle, a thermal correction to energy of 0.299353 Hartree/particle, a thermal correction to enthalpy of 0.300297 Hartree/particle, and a thermal correction to Gibbs free energy of 0.238762 Hartree/particle; aspirin has a zero-point correction of 0.156551 Hartree/particle, a thermal correction to energy of 0.168313 Hartree/particle, a thermal correction to enthalpy of 0.169257 Hartree/particle, and a thermal correction to Gibbs free energy of 0.117225 Hartree/particle.These results provide a comprehensive comparison of the thermodynamic properties of morphine, ibuprofen, and aspirin molecules and offer a deep understanding of their thermal behaviors. Such detailed analyses are crucial for drug formulation and stability assessments, aiding in the optimization of molecular stability and performance.

4. Conclusions

In this study, the thermodynamic properties of pain-relieving molecules such as morphine, ibuprofen, and aspirin have been examined in detail. Geometric optimizations performed in the gas phase using Gaussian software determined the energy minima and geometric structures of these molecules. Subsequently, their thermodynamic properties were calculated using Density Functional Theory (DFT) with the B3LYP/6-311G(d,p) basis set. The obtained binding energies, free energy changes, and entropy changes illuminate the ability of these molecules to bind to biological targets and their analgesic activities. The strong pain-relieving effects of morphine can be explained by its high binding energy, while the effectiveness of NSAIDs like ibuprofen and aspirin is related to their binding capacities to COX enzymes. The findings of this study clearly demonstrate how the structural and thermodynamic properties of these molecules shape their efficacy in pain management and potential side effects. Additionally, these results have identified important parameters to consider in molecular design processes and have provided valuable insights for future drug development strategies. Future research may advance by providing more comprehensive examinations of these molecules and developing new pharmaceutical formulations.

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