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Research Article

Molecular Structure and Thermodynamic Properties of Morphine, Ibuprofen and Aspirin Using DFT Method

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Abstract

This study investigates the thermodynamic properties of commonly used pain-relieving molecules such morphine, ibuprofen, and aspirin. The molecular structures were determined through geometric optimizati calculations performed in the gas phase using Gaussian software, ensuring accurate determination of ener minima and structural configurations. Following this, thermodynamic properties were evaluated using Densi Functional Theory (DFT) with the B3LYP/6-311G(d,p) basis set, analyzing parameters such as binding energi free energy changes, and entropy variations. The study aims to enhance the understanding of how these molecul interact with biological targets and their potential effectiveness in pain relief.

Key Words: DFT calculations; morphine; ibuprofen; aspirin

1.Introduction

Pain is a multifaceted symptom associated with various medical conditions, and its effective management remains a central focus in both clinical and research domains. In this study, we have selected three widely used pain-relieving molecules morphine, ibuprofen, and aspirin due to their distinct mechanisms of action and varied pharmacological profiles. By comparing the thermodynamic properties of these molecules, this research aims to provide valuable insights into their analgesic effects and potential for clinical application.

Morphine, an opioid, is renowned for its potent analgesic properties and is commonly prescribed for the management of severe pain [1-4]. It exerts its effects by binding to opioid receptors in the brain and spinal cord, altering the perception of pain. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is effective in relieving both pain and inflammation [5-8]. It achieves this by inhibiting cyclooxygenase (COX) enzymes, reducing the production of prostaglandins, and consequently alleviating pain and inflammation. Aspirin [9], another widely used NSAID, also works by inhibiting COX enzymes to block prostaglandin production, helping to manage pain, inflammation, and fever [10-14].

This study seeks to offer a comprehensive analysis of the thermodynamic properties of morphine, ibuprofen, and aspirin. By determining their geometric structures and calculating key thermodynamic parameters, we aim to better understand their binding affinities to biological targets and their overall analgesic effectiveness. Geometric optimizations in the gas phase will be carried out using Gaussian 5 software, and thermodynamic calculations will be performed through Density Functional Theory (DFT) with the B3LYP/6-311G(d,p) basis set. The data obtained will shed light on the role of these molecules in pain management and highlight potential areas for improvement in future 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.

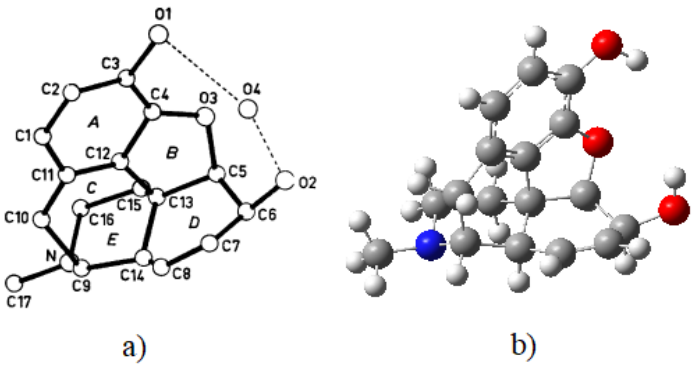

Figure 1a: The Experimantal structure **1b.** The optimized geometry of morphine.

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.

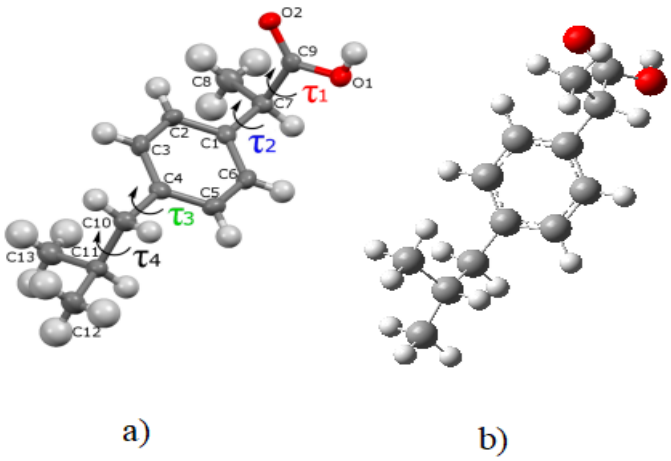

Figure 2a: The Experimantal structure **2b.** The optimized geometry of ibuprofen.

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.

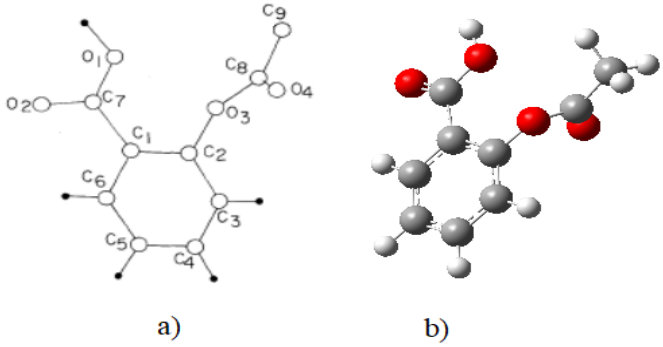

Figure 3a: The Experimantal structure 3**b.** The optimized geometry of aspirin.

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, including morphine, ibuprofen, and aspirin, have been thoroughly examined. Geometric optimizations performed in the gas phase using Gaussian software allowed for the accurate determination of energy minima and molecular structures. Following this, the thermodynamic properties of these molecules were calculated through Density Functional Theory (DFT) with the B3LYP/6-311G(d,p) basis set. The analysis of key parameters, including binding energies, free energy changes, and entropy variations, provided

important insights into the molecules' interactions with biological targets and their analgesic mechanisms.

The strong analgesic effect of morphine can be attributed to its high binding energy, which reflects its potent interaction with opioid receptors in the brain and spinal cord. In contrast, the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin is primarily linked to their ability to bind to cyclooxygenase (COX) enzymes, which play a critical role in the synthesis of prostaglandins involved in pain and inflammation. These findings underscore the significance of the molecular structure and thermodynamic properties in determining the effectiveness of these molecules in pain relief, as well as their potential side effects.

Furthermore, this study highlights essential parameters for optimizing the molecular design of analgesic agents. By understanding the binding affinities and thermodynamic behaviors of these drugs, new avenues for enhancing drug efficacy and minimizing adverse effects in future pharmaceutical formulations can be explored. The insights gained from this research will be crucial for the development of more effective pain management therapies. Future studies could expand on these results by conducting more detailed investigations of these molecules and exploring novel drug formulations to further improve therapeutic outcomes.

References

1. Bye, E., (1976). The Crystal Structure of Morphine Hydrate. *Acta Chemica Scandinavica* B 30, 549-554.
2. Ofoegbu, A., Ettienne, E. B. (2021). Pharmacogenomics and morphine. *The Journal of Clinical Pharmacology*.
3. Voza, A., Ruggiano, G., Serra, S., Carpinteri, G., Gangitano, G., & Intelligente, F. (2020). Inhaled methoxyflurane versus intravenous morphine for severe trauma pain in the emergency setting: Subgroup analysis of MEDITA, a multicenter, randomized, controlled, open-label trial. *Journal of Pain Research*, 13, 491–502.
4. Sharpe, E. E., Molitor, R. J., Arendt, K. W., Torbenson, V. E., Olsen, D. A., Johnson, R. L., Schroeder, D. R., Jacob, A. K., Niesen, A. D., & Sviggum, H. P. (2020). Intrathecal morphine versus intrathecal hydromorphone for analgesia after cesarean delivery: A randomized clinical trial. *Anesthesiology*, 132(6), 1382–1391.
5. Ostrowska, K., Kropidłowska, M., & Katrusiak, A. (2015). High-pressure crystallization and structural transformations in compressed R,S-Ibuprofen. *Crystal Growth & Design*, 15(4), 1512–1517.
6. Sagdinc, S., & Pir, H. (2009). Spectroscopic and DFT studies of flurbiprofen as dimer and its Cu(II) and Hg(II) complexes. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 73(1), 181–194.
7. Zhang, M., Huang, Y., Hao, D., Ji, Y., & Ouyang, D. (2020). Solvation structure and molecular interactions of ibuprofen with ethanol and water: A theoretical study. *Fluid Phase Equilibria*, 510, 112454.
8. Orlando, B. J., Lucido, M. J., & Malkowski, M. G. (2015). The structure of ibuprofen bound to cyclooxygenase-2. *Journal of Structural Biology*, 189(1), 62-66.
9. Mousa, T. H., Al-Obaidi, Z. M. J., & Alkhefaji, S. L. (2021). Molecular docking studies and evaluation of the anti-inflammatory activity of ibuprofen-tranexamic acid codrug. *Latin American Journal of Pharmacy*, 40(special issue), 128-134.
10. Vishweshwar, P., McMahon, J. A., Oliveira, M., Peterson, M. L., & Zaworotko, M. J. (2005). The predictably elusive form II of aspirin. *Journal of the American Chemical Society*, 127(48), 16802-16803.
11. Jiang, Y., Ye, F., Du, Y., Zong, Y., & Tang, Z. (2021). P2X7R in mast cells is a potential target for salicylic acid and aspirin in the treatment of inflammatory pain. Journal of Inflammation Research, 14, 2913–2931.
12. Uzzaman, M., & Mahmud, T. (2020). Structural modification of aspirin to design a new potential cyclooxygenase (COX-2) inhibitor. *In Silico Pharmacology*, 8(1).
13. Nyambuya, T. M., Dludla, P. V., Mxinwa, V., Mokgalaboni, K., Ngcobo, S. R., et al., (2020). The impact of metformin and aspirin on T-cell mediated inflammation: A systematic review of in vitro and in vivo findings. Life Sciences, 255, 117854.
14. Fierro, I. M., & Serhan, C. N. (2001). Mechanisms in anti-inflammation and resolution: The role of lipoxins and aspirin-triggered lipoxins. *Brazilian Journal of Medical and Biological Research*, 34(5), 555-566.
15. Frisch, M.J., Trucks, G.W., Schlegel, H.B., et al. (2009). Gaussian 09, Revision A.1. Gaussian, Inc., Wallingford CT.
16. Ipek, C., Gümüş, H., Şimşek, M., & Tosun, M. (2023). DFT and molecular docking study of 1-(2´-Thiophen)-2-propen-1-one-3-(2,3,5-trichlorophenyl) (TTCP) molecule as antiviral to Covid-19 main protease. *Arabian Journal for Science and Engineering*, 48(10), 1031–1040.
17. Becke, A.D. (1993). J. Chem. Phys. 98, 5648.
18. Lee, C., Yang, W., & Parr, R.G. (1988). Phys. Rev. B 37, 785.
19. Costa Jr., A. C., Ramos, J. M., Téllez Soto, C. A., Martin, A. A., Raniero, L., et al., (2013). Fourier transform infrared and Raman spectra, DFT: B3LYP/6-311G(d,p) calculations and structural properties of bis(diethyldithiocarbamate)copper(II). Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 105, 259–266.

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