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COMPARATIVE QUANTUM CHEMISTRY STUDY OF IBUPROFEN VS NAPROXEN

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ABSTRACT:

This study presents a comparative quantum chemical analysis of two widely used non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen and naproxen. Using computational approaches such as Hartree–Fock (HF), Density Functional Theory (DFT), and the Fragment Molecular Orbital (FMO) method, the electronic structures, interaction parameters, and molecular properties of both drugs were investigated. DFT calculations performed with the B3LYP/6-31G(d,p) level of theory revealed notable differences in key quantum chemical descriptors, including ionization potential, electron affinity, dipole moment, electrophilicity index, global hardness, and softness. Naproxen exhibited higher electrophilicity (21.05), reflecting greater reactivity, whereas ibuprofen displayed higher global hardness (3.03), suggesting enhanced resistance to charge transfer. These insights provide a deeper understanding of their molecular behavior and pharmacological action, supporting the rational design of improved NSAIDs with optimized therapeutic profiles.

KEY WORDS: Quantum Chemistry, Density Functional Theory (DFT), Hartree–Fock (HF), Fragment Molecular Orbital (FMO) ,Ibuprofen, Naproxen, NSAIDs, Electronic Structure, Ionization Potential, Electron Affinity, Electrophilcity Index, Global Hardness

INTRODUCTION:

The goal of quantum chemistry is to create comprehensive, physics-based models that accurately describe the structure, characteristics, and reactivity of molecules and molecular systems**.** The behavior of matter and energy at the atomic and subatomic levels is governed by quantum mechanics, or QM. Quantized energy levels, probabilistic outcomes, and wave–particle duality are among the phenomena that are included in QM. Although precise solutions are rarely achievable for complicated systems, the Schrödinger equation establishes the fundamental framework for QM. Molecular characteristics and interactions are simulated using Hartree–Fock (HF), density functional theory (DFT), quantum mechanics/molecular mechanics (QM/MM), and fragment molecular orbitals (FMO). Their relative strengths are discussed in this review, which contains particular drug applications and methodological tables. Molecular characteristics and interactions are simulated usingHartree–Fock (HF), density functional theory (DFT), quantum mechanics/molecular mechanics (QM/MM), and fragment molecular orbitals (FMO). This study discusses their relative advantages, including methodological tables and particular medication uses(2).NSAIDs are weak organic acids with a carboxylate unit and a pKa of 3 to 5. There are numerous NSAID medications. Among many others, aspirin is the most commonly used. Essential NSAID medications, because NSAIDs are more soluble in water and have a polar character, are difficult to remove effectively from household water and wastewater treatment facilities (WWTPs). Adsorption is one of the most used methods for efficiently removing NSAIDs.

BASICS OF QUANTUM CHEMISTRY AND DFT

Molecules containing hundreds or thousands of nuclei and electrons interact with one another through long-range Coulombic interactions, whereas the three-body problem only involves three interacting bodies. Subatomic particles must be described as probability densities rather than point charges because of their delocalization (caused by wave–particle duality). This makes it challenging to assess how they interact. (1)
Density Functional Theory (DFT) focuses on the electron density ρ(r), a three-dimensional function representing the probability of finding an electron at position *r*. Unlike wave function-based methods, DFT relies on the Hohenberg–Kohn theorems, which establish that the total energy of a system is determined by its electron density, and that the ground-state properties are uniquely defined by this density. DFT is widely used in drug development as a computational quantum mechanical approach for accurately and efficiently simulating electronic structures.

In Density Functional Theory (DFT), the total energy is expressed as:

$$E[\rho] = T[\rho] + Ve_xt[\rho] + Vee[\rho] + E_xc[\rho]$$

Here,E[ρ] represents the total energy functional; T[ρ] denotes the kinetic energy of non-interacting electrons; Vext[ρ] corresponds to the external potential energy such as electron–nucleus interactions; Exc[ρ] accounts for the classical electron–electron repulsion; and Exc[ρ] represents the exchange–correlation energy. Since the exact form of is unknown, it is typically approximated using methods such as the Local Density Approximation (LDA**).**

Hartree–Fock Method in Drug Discovery

The Hartree–Fock (HF) method is a fundamental wave function–based quantum mechanical (QM) approach used to calculate the electronic structures of molecules in drug development. To satisfy the Pauli exclusion principle and maintain anti-symmetry, HF represents the many-electron wave function as a single Slater determinant. This method simplifies the complex many-body problem by assuming that each electron moves within the average electrostatic field generated by all other electrons.

$$E\_HF=\langle \Psi\_HF|\hat{H}|\Psi\_HF\rangle$$

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In the Hartree–Fock method, the wave function is expressed as a single Slater determinant, while denotes the Ψ_HF andE_HF is Hartree–Fock energy. The operator Ĥ represents the electronic Hamiltonian, which accounts for kinetic energy, electron–nucleus attraction, and electron–electron repulsion. The Hartree–Fock energy is obtained as the expectation value (quantum mechanical average) of this Hamiltonian with respect to the wave function.
The HF equations are:

$$\hat{f}\,\varphi i=\epsilon i\varphi i f\hat{}\varphi i=\epsilon i\varphi i$$

In this framework,φi the molecular orbitals and their corresponding energies epsilon are determined from the eigenvalue equation involving the Fock operator which serves as an effective one-electron Hamiltonian. The indistinguishability of electrons is accounted for through the exchange term. These equations are solved using the self-consistent field (SCF) method, in which the solutions are obtained iteratively until convergence is reached.

Hartree–Fock (HF) provides baseline electronic structure descriptions for small molecules relevant to drug development. These results often serve as a starting point for more accurate methods such as density functional theory (DFT) or post-HF approaches. In ligand design, HF calculations can yield electronic properties, dipole moments, and optimized molecular geometries. Such information supports force field parameterization and facilitates the modeling of ligand–receptor interactions in structure-based drug design (SBDD).

QUANTUM PARAMETERS USED FOR EVALUATION

The fragment molecular orbital (FMO) method is a quantum mechanical (QM) approach designed for large biomolecular systems and is widely applied in drug discovery. to accurately examine protein–ligand interactions. A big molecule is broken up into smaller pieces by FMO. (such as ligands and amino acid residues), handling each piece quantum mechanically while taking their interactions into consideration. When compared to full quantum mechanical (QM), this fragmentation lowers the computing cost. The total energy in FMO is approximated as:

$$E\_FMO = \Sigma i E'i + \Sigma i \Sigma i{>}j \Delta E'ij$$

Here, E′ i represents the energy of fragment in the presence of the other fragments, with the interaction energy between fragment pairs and denoted asΔE′Delta . The Σi>j notation indicates the summation over all fragments, while refers to the summation over all unique fragment pairs. The electronic structure of each fragment is calculated using quantum mechanical (QM) methods such as Hartree–Fock (HF) or density functional theory (DFT), with the corresponding Hamiltonian defined for each fragment.

$$Hi = \hat{}Hi + VESP\_i$$

where VESP_i is the electrostatic potential from all other fragments, ˆHi is the isolated fragment Hamiltonian, and ˆH′ i is the fragment Hamiltonian including environmental effects [9]. To guarantee self-consistency, FMO computations are carried out iteratively.

CASE STUDY: IBUPROFEN VS NAPROXEN

STRUCTURAL OVERVIEW

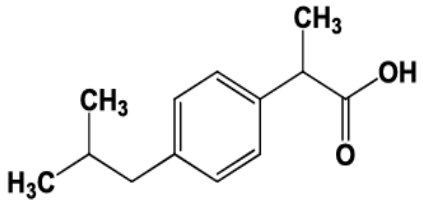
Ibuprofen belongs to the group of medications known as non-steroidal anti-inflammatory medicines (NSAIDS), which have analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen has recently been shown to prevent several types of cancer, such as those of the prostate, colon, breast, and lung. and stomach malignancies asHere's a cleaner, paraphrased version of your passage:As a consequence of cyclooxygenase-2 (COX-2) inhibition,. examined the potential of selective COX-2 blockade to reduce the risk of human lung cancer. Notably, 2-arylpropanoic acids, which represent a major class of non-steroidal anti-inflammatory drugs (NSAIDs), play an important role in this context are classified as racemic mixtures due to their asymmetric carbon atoms.

A common anti-inflammatory medication with a naphthalene backbone is naproxen, a nonsteroidal anti-inflammatory medicine (NSAID). in relation to antipyretic and analgesic properties

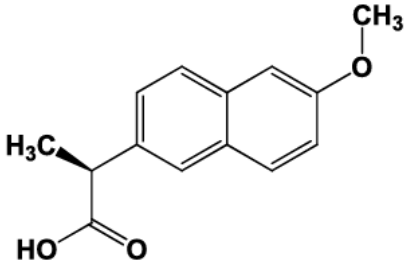
Inhibiting cyclooxygenase (COX) can prevent the formation of prostaglandins [3]. Depending on the kind and severity of the peculiar physical condition, as well as the dosage restriction, it has some drawbacks. Long-term and excessive dosages can result in cardiovascular and gastrointestinal

disorders. It exhibits in vivo selectivity towards the human cyclooxygenase (COX) enzyme by inhibiting COX-2, while inhibiting COX-1 results in undesirable events on the gastrointestinal tract, such as mucosal ulcers and perforation

Both medication concentration and dose differentiation affect COX selectivity.



Ibuprofen (IBU)



Naproxen (NAP)

DFT CALCULATED PARAMETERS :

The GAUSSIAN 03 software was used to do computational analyses on the separated molecules in the gas phase. The semi-empirical AM1 approach has been used to achieve minimum energy structures. The closed shell method was used to calculate the minimal energy structures for DFT.
Becke's Hartree-Fock, The Lee, Yang, and Parr correlation functional B3LYP is used in conjunction with three-parameter density functional theory, or DFT. Based on the total energy difference, which was computed using SCF using RHF for these kinds of molecules and UHF for the molecular anions, the conformers R and S of the medication ibuprofen were distinguished from one another.
. The energy of the DFT theory can be expressed as a function of the electron density, and the DFT calculations have been performed as B3LYP/6-31.

$$E|\rho| = \frac{-\hbar^2}{2m_e}\sum_{i=1}^{n}\int \psi_i^*(r_1)\nabla^2\psi_i(r_1)\,dr_1 - \sum_{i=1}^{n}\int \frac{z_i e^2}{4\pi\varepsilon_0 r_{11}}\rho(r_1)\,dr_1 + \frac{1}{2}\int \frac{\rho(r_1)\rho(r_2)e^2}{4\pi\varepsilon_0 r_{12}}dr_1 dr_2 + E_{xc}|\rho| \quad \text{where } \hbar = \frac{h}{2\pi}$$

DFT-based ligand optimization, Quantum mechanical (QM) techniques have more
focus on calculating molecular orbital features, dipole moment, atomic partial charge, molecular electrostatic potential, thermodynamic parameters, and interpreting various interaction types. The initial geometry of Naproxen (N) was obtained from the ChemSpider Molecular Geometry Optimization online structure database. The Gaussian 09 program was used to further modify all medicationss.Density functional theory (DFT) was employed to optimize all drug molecules using Becke's three-parameter hybrid model combined with the Lee–Yang–Parr (LYP) correlation functional and Pople's 6-31G(d,p) basis set. This combination is well established for providing accurate ground-state geometries. In the gas phase, all compounds underwent initial optimization. For every chemical, the dipole moment, electronic energy, enthalpy, free energy, electrostatic potential, and atomic partial charge are computed. geometries. In the gas phase, all compounds underwent initial optimization.

QCPs of the four investigated NSAIDs for naproxen and ibuprofen
Ionization potential 5.70 6.60
Electron affinity 1.26 0.53
Dipole moment 1.85 1.37
Electrophilicity index 21.05 8.44
Global hardness 2.22 3.03
Global softness 0.45 0.33
Electronegativity 3.48 3.5

CONCLUSION:

The usefulness of DFT and HF-based computational techniques in comprehending the electronic, thermodynamic, and molecular interaction features of NSAIDs is illustrated by the comparative quantum chemical analysis of Ibuprofen and Naproxen. Ibuprofen demonstrated more global hardness, indicating chemical stability, but naproxen demonstrated stronger electrophilicity and electron affinity, indicating a more marked propensity for molecular interactions. Their pharmacological action, adverse effect profiles, and capacity for selective COX-2 inhibition may all be correlated with these differences in quantum characteristics. By improving molecular behavior predictions and enabling the development of safer and more effective NSAIDs, the work emphasizes the significance of computational quantum chemistry in drug design and development.

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