Article

A Theoretical Study of Chemical Reactivity of Mefenamic acid Through DFT Reactivity Descriptors

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Abstract

Using density functional theory (DFT), the geometry optimized has been studied at ground state, B_3LYP, and 6-311G basis sets. The identification of donor sites is aided by theoretical features such as shape and the HOMO-LUMO gap detected by DFT simulations. Mefenamic acid's global reactivity properties at the B3LYP/6-311G level have been calculated in Global softness (S), global hardness (η), global affinity (A), ionization potential (I), electro negativity (χ), chemical potential (μ), global electrophilicity index (ω), and global softness (S) are some of the descriptors of global reactivity.

Key- Words: B_3LYP, ΔE gap , 6-311G, DFT, Mefenamic acid.

Research aims

1- Identify chemical properties such as total energy, geometric shape, and charge distribution, which contribute to understanding the behavior of the molecule.

2- Comparative examination of drug binding with body proteins through transition state formation reactions.

3- Analysis of interactions is used to evaluate the stability of the drug under different conditions, which affects its effectiveness and safety.

4- It helps predict how a drug will interact with other molecules, which may be important for avoiding harmful interactions.

Introduction

Mefenamic acid is a high dose non-steroidal anti-inflammatory agent prepared in the form of capsules and tablets that has an anti-inflammatory effect due to its ability to inhibit COX enzymes and phospholipase A_2. It is usually prescribed for oral administration to relieve mild to moderate pain including headache, toothache, and muscle pain. It is a poorly soluble drug in aqueous media[1]. Mefenamic acid has a wide range of effects on cellular ion channels, with this effect being documented mostly for cation channels. Accordingly, such effects are relevant to cellular transport systems for cations and many other molecules. The drug does not appear to be cytotoxic in vitro, although lactic acid production is increased in tissue culture cells. It may enhance the cytotoxicity of some chemotherapeutic agents[2].

Computational methods

We drew the Mefenamic acid complex using the Gauss View program 06 and used Gaussian 09 [3, 4] to calculate it using DFT / B_3LYP in the basis set 6-311G [5], where the engineering optimization structure were built. In addition to calculating the energy of the Mefenamic acid as a whole, the energy of the transition between the lowest electron-occupied orbit (LUMO) and the highest electron-occupied orbit (HOMO), and the energy difference between the orbits [6] In theoretical chemistry, the chemical potential (μ) is defined as the electronegativity's negative (χ) [7] as:

$$\chi = \frac{1}{2}\left(\boldsymbol{E\ Lumo} + \boldsymbol{E\ Homo}\right) \ldots\ldots\ldots\ldots\ldots \mathbf{1}$$

$$\mu = -\chi = \tfrac{1}{2}\left(\boldsymbol{E\ Lumo} + \boldsymbol{E\ Homo}\right) \ldots\ldots\ldots\ldots \mathbf{2}$$

The hardness (η) quantitative description With a total energy power of E, an N-electron device can be expressed as[8]

$$\eta = \frac{1}{2}\left(\boldsymbol{E\ Lumo} - \boldsymbol{E\ Homo}\right) \ldots\ldots\ldots\ldots\ldots \mathbf{3}$$

The worldwide electrophilicity index (ω)[9] In terms of is conveyed as:

$$\omega = -\frac{\mu 2}{2\,\eta} \quad \ldots\ldots\ldots 4$$

where the chemical system's initial potential for vertical ionization and electron affinities are, respectively, IP and EA. Koopmans' theorem can be used to express the aforementioned parameters as an additional approximation[10] .

$I = -E_{HOMO}$ ……. 5

$A = -E_{LUMO}$ …….6

where the lowest unoccupied molecular orbital's energy is known as E_{LUMO} and the highest occupied molecular orbital's energy is known as E_{HOMO}.

Results and Discussion

Geometry optimization of Mefenamic acid

Mefenamic acid optimally structured shapes Fig.1, DFT /B_3LYP /6-311G, covers all of the useful conclusions from the present investigation.

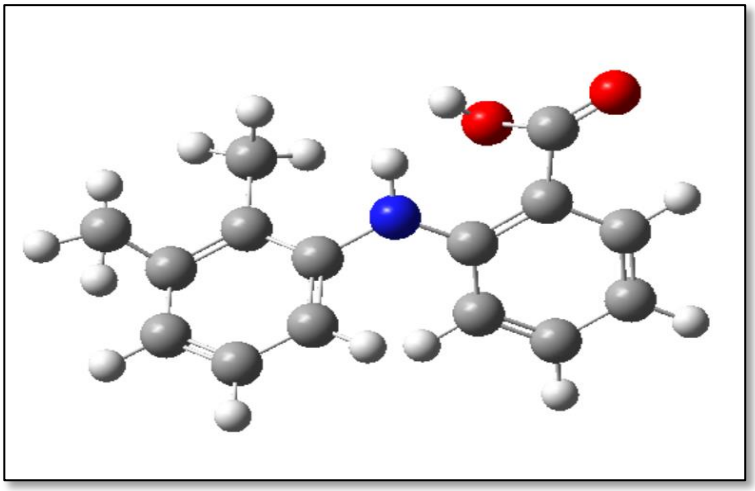


Fig.1 Geometry optimized for Mefenamic acid by DFT/ B_3LYP basis set 6-311G.

Calculating the optimal spatial structure of the drug in the form of a three-dimensional image. Molecular modeling was applied through computer applications that determine the most stable molecular shape resulting from factors related to each

other, such as total energy. The total energy of Mefenamic acid was calculated as -3.2135913*10^{-18}KJ using DFT/B_3LYP/6-311G[11].

Dipole moment

The dipole moment (μ) of Debye is another important electronic parameter resulting from the non-uniform distribution of charges on different atoms in a molecule. It is likely that a high value of dipole moment means increased adsorption between the chemical compound and the adsorbent surfaces and thus the deformation energy increases with increasing μ, making the molecule easier to adsorb on the surface[12].

Then μ =1.3974 was deduced using DFT/B_3LYP/6-311G.

Global Reactivity Descriptors

Determine the values of the following: ionization potential (I), global hardness (η), chemical potential (μ), electronegativity (χ), global electrophilicity index (ω), and electronic affinity (A) in table (2). [13], According to the results, a low stable structure is indicated by a low hardness value, while a tiny ionization potential value suggests a high level of reactivity of the atoms and molecules. The electrophilic energy calculation of a gain the electrophilicity (ω) toward a nucleophile in the molecular process. A molecule's reactivity as an electrophile increases with its electrophilic ability. The design shows low hardness and a strong reactivity, as indicated by its electrophilic value [14].

Table (1): Electronic properties of Mefenamic acid using DFT/B3LYP/6-311G

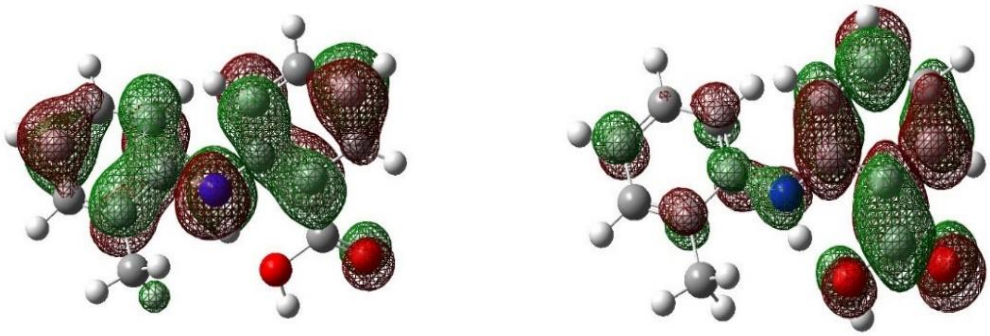
Drug	I	A	Φ	χ	η	S	ω
Mefenamic acid	0.087	0.064	-0.011	0.011	0.075	13.19	-0.0008

Molecular orbital energy levels

The DFT using B_3LYP/6-311G was used to calculate the energy of Mefenamic acid's frontal molecular orbitals, including E_{HOMO}, E_{LUMO}, and Egap Whereas the energy of E_{LUMO} is associated with the potential to take electrons from the molecules, the energy of the electron-donating potential of E_{HOMO} is commonly related to the molecules[15]. Both the LUMO value and the high-value E_{HOMO} indicate a strong tendency to accept electrons and a heavy inclination to give electrons with low empty molecular orbital energy to a suitable acceptor molecule. Table 1 and Figure 5 present the results, which indicate which form of Mefenamic acid has the highest LUMO energy. The disparity in energy between Mefenamic acid's HOMO and LUMO energy levels[16]. Low electronic stability and high reactivity arise from low energy gap values. Low values can be advantageous since they indicate that it would be simple to extract an electron from the HOMO orbital and transfer it to the LUMO orbital. lead to reaction The formula (1) Hartree = (27.211 e.v) converts the energy units of the Hartree to electron volts.

Table (2): Molecular orbital energy of Mefenamic acid

Drug	E_{LUMO}	E_{HOMO}	ΔE gap
Mefenamic acid	-0.09404	-0.17731	0.08327



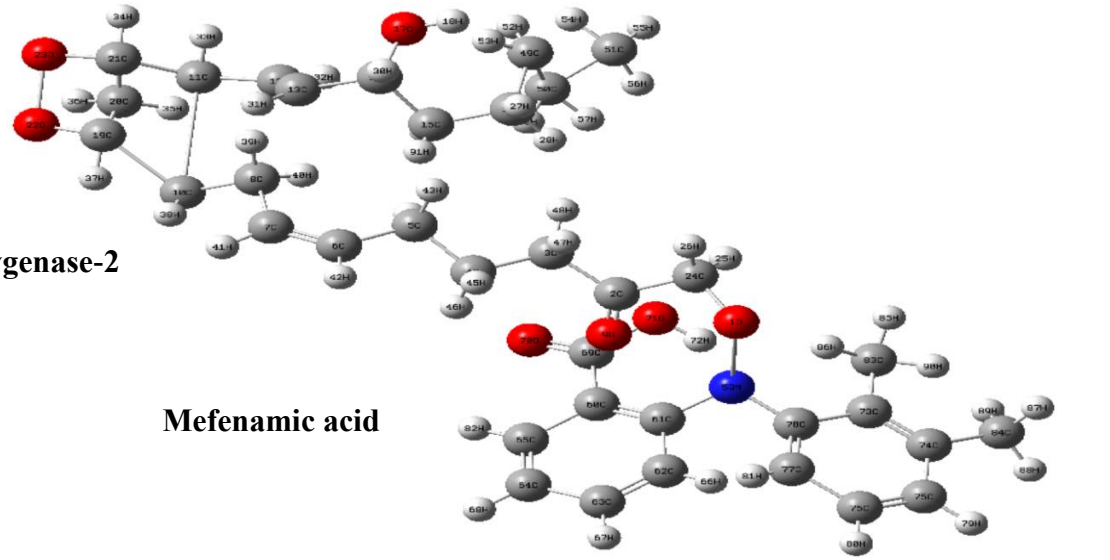
E_{HOMO} = -0.17731 E_{LUMO} = -0.09404

ΔE gap= 0.08327

Fig.2: Energy levels of Mefenamic acid using the DFT/B3LYP/6-311G method

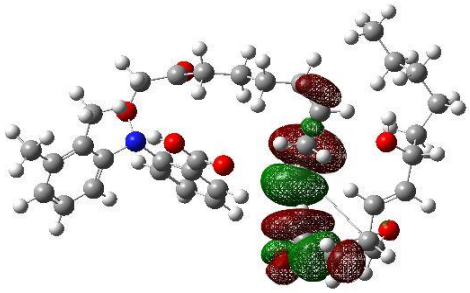
Binding of Mefenamic acid with the enzyme

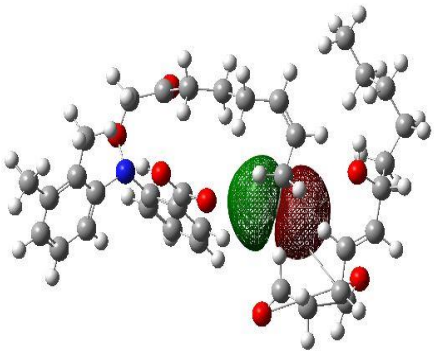
Mefenamic acid binds noncompetitively to a site on the enzyme cyclooxygenase-2 (COX-2), and by inhibiting the enzyme cyclooxygenase-2 (COX-2), mefenamic acid reduces the production of prostaglandins that cause pain and inflammation[17]. Therefore, (N) of Mefenamic acid was linked to (O) of the enzyme (COX-2) through the Gaussian09 program using the DFT/B3LYP/6-311G method.



Cyclooxygenase-2

Mefenamic acid





HOMO= -0.31098

LUMO= -0.04129

ΔE gap=0.26969

Fig.3 : Mefenamic acid binds to the COX-2 enzyme via an energy gap

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