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INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF NIMESULIDE

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Abstract

Nimesulide is a widely used drug in pain and fever treatment. The quantum-chemical study of nimesulide molecule is very important for understanding the mechanisms of its biological and pharmacological activity at a molecular level. The geometry optimization of nimesulide molecule was performed by PM3 method, Polak-Ribiere algorithm. The following quantum-chemical properties were investigated in this work: geometrical structure, atomic charges, high occupied and low unoccupied molecular orbital energies and total charge density of nimesulide molecule.

Keywords: Nimesulide, spatial structure, quantum-chemical properties.

Quantum-chemical properties of the drugs molecules can explain the molecular mechanism of pharmacological action. Non-steroid anti-inflammatory drugs (NSAID) having anti-inflammatory, analgesic and antipyretic pharmacological activities are among the most commonly used medications in the world [1, 2].

We have studied the quantum-chemical properties of molecules of NSAID: paracetamol, ibuprofen, meloxicam, diclofenac, aspirin, mefenamic acid [3-8]. Nimesulide (N-(4-Nitro-2- phenoxyphenyl)methanesulfonamide) is a sulphonanilide non-steroidal anti-inflammatory drug (NSAID). It is widely used in the treatment of acute pain (back pain, lower back, pain in the pathology of the musculoskeletal system including trauma, sprains and dislocations of joints, tendinitis, bursitis, dental pain), symptomatic treatment of osteoarthritis pain syndrome, algodismenorrhea, myalgia, rheumatic and nonrheumatic genesis, headache, arthralgia, lumboischialgia.

It inhibits the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins (PGs) preferentially COX-2 (an enzyme involved in the synthesis of PG) mediators of edema, inflammation and pain in the area of inflammation.

The selectivity of nimesulide decreases with increase of the dosage, leading to severity of side effects and increase the risk of GI tract and kidneys damage. In addition, nimesulide is a drug that has a low allergenic potential, so it can be used by people who suffer from hypersensitivity to NSAIDs drugs.

Nimesulid reversibly inhibits PGE2 formation in the area of inflammation as well as in ascending pathways of the nociceptive systems, including pathways of spinal cord pain impulses. It reduces the concentration of short-lived PGN2 of which under the influence of GHG isomerase PGE2 is formed. Reducing the concentration of PGE2 leads to a decrease in the degree of activation of prostanoid EP receptor type, resulting in anti-inflammatory and analgesic effects. It inhibits the release of TNF-α, which is responsible for cytokinins formation.

It prevents the destruction of cartilage tissue by suppression of histamine release, inhibition the synthesis of IL-6 and urokinase. It inhibits synthesis of metalloproteases (elastase, collagenase), preventing the destruction of proteoglycans and collagen of cartilage tissue. It interacts with the glucocorticoid receptors, activating them by phosphorylation, which also increases its anti-inflammatory effect. It inhibits platelet aggregation. [9-11].

The purpose of this work was to conduct quantum-chemical study of nimesulide molecule and their effect on pharmacological activity of this compound.

Materials and methods.

Research of quantum chemical and pharmacological properties of nimesulide was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [12-16]. All calculations were carried out using the Polak – Ribiere conjugate gradient algorithm. During the research, the following parameters were studied: charges of atoms (a.u./eV), distribution of electron density of outer-shell electrons, the total strain energy (kcal/mol), bonding energy (kcal/mol), electronic energy (kcal/mol), internucleus interaction energy (kcal/mol), heat of formation (kcal/mol), localization and energy of highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals (eV) and absolute hardness (η, eV) [15].

Absolute hardness of the nimesulide molecule was determined using the following equation:

$$\eta = ½ (E_{LUMO} - E_{HOMO})$$

Results and discussion

Molecular model of nimesulide molecule was calculated based on geometrical optimization depicted in Figure 1; atoms numeration used in calculation of quantum chemical parameters is shown in Figure 2.

Calculated charges for each atom in the nimesulide molecule are presented in Figure 3. The regions of high electron density reside on oxygen atoms (-0.929; -0.927; -0.357; -0.355 a.u.) as well as on nitrogen atom (-0.818). The electron density on C_4, C_{10}, C_{13}, C_{21}, atoms are -0.131, -0.162, -0.129, and -0.953 respectively.

The electron deficient areas are observed on sulfur atom (2.831) and carbon atoms directly bonded to O_7 and N_{17} atoms (0.033, -0.010 and 0.121 a.u.). Positive charges are located on hydrogen atoms (from 0.188 to 0.140 a.u.).

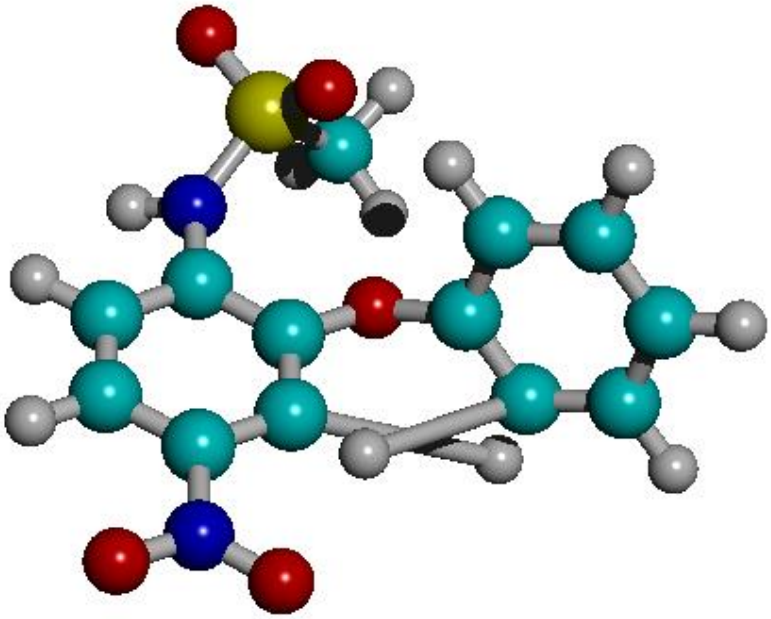

Figure 1. Structure of nimesulide molecule: green colour correspond to carbon atoms, red - oxygen, blue – nitrogen, yellow – sulphur, grey - hydrogen.

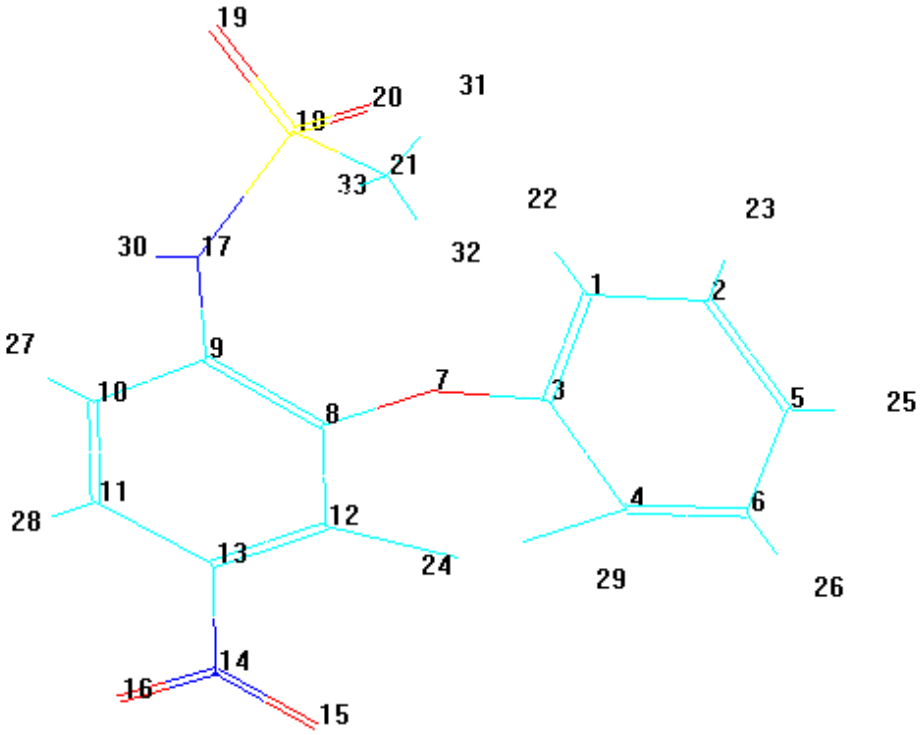

Figure 2. Atom numeration of nimesulide molecule used in calculation of quantum chemical parameters.

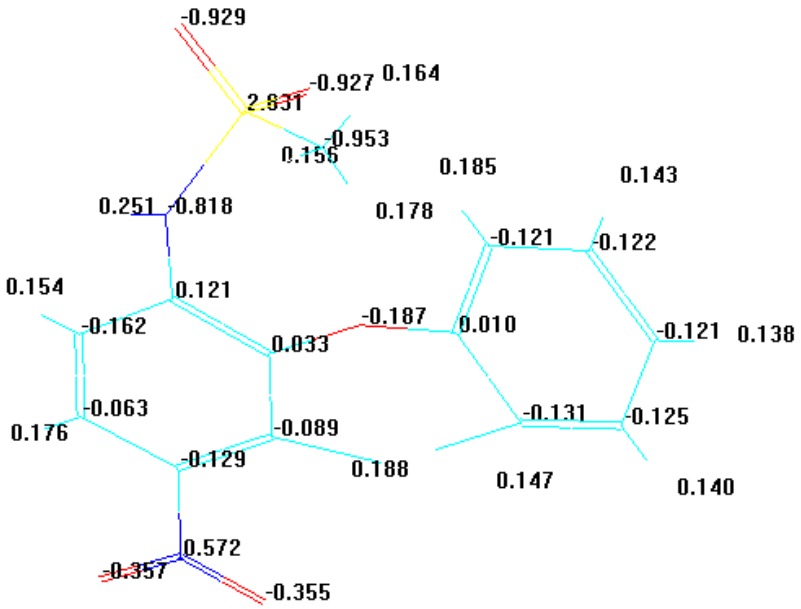

Figure 3. Atomic charges in nimesulide molecule.

The overall dipole moment of a molecule may be approximated as a vector sum of bond dipole moments and having the directionality from the center of negative charges to the center of positive charges. It characterizes the asymmetry of charge distribution in electro-neutral system. Dipole moment quantitatively determines a static polarization of particle. Its value defines the activity of chemical interaction (Figure 4).

The total dipole moment of nimesulide molecule is 4.12398 D. The distances at axes are X = 1.2817 D, Y = -1.9302 D, Z = 3.4116 D.

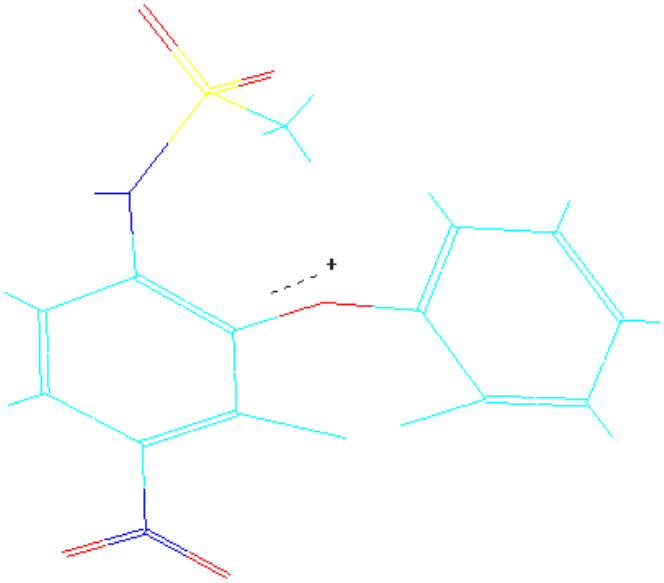

Figure 4. Dipole moment of nimesulide molecule

The distribution of electron density of outer valence electrons of the nimesulide is shown in Figure 5. The highest electron density is observed on oxygen and nitrogen atoms, C_3, C_{11}, C_{12} and C_{13} atoms. C_9 atom (+0.121) as a potential electrophile and can react with nucleophilic reagent. Hydrogen atoms directly bonded to oxygen are capable to form hydrogen bonds with electro neutral atoms of other molecules.

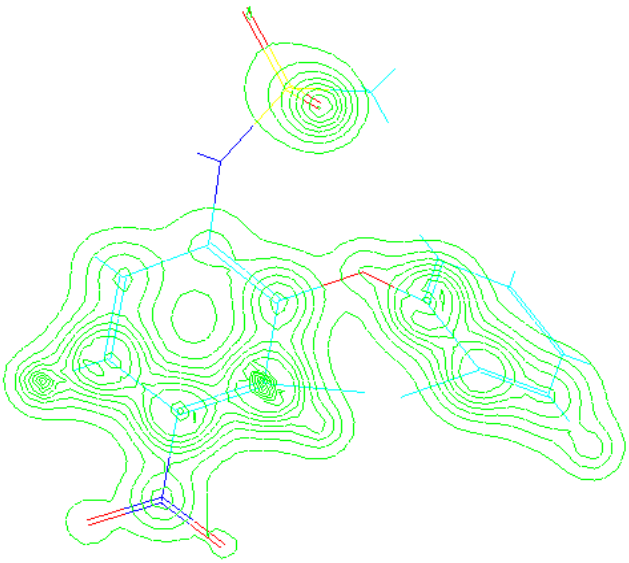

Figure 5. Distribution of electron density of outer valence electrons in the nimesulide molecule

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) [16]. Table 1 shows some electro-optical parameters of the nimesulide molecule. Localization of electron density of HOMO LUMO depicted in Fig. 6 (a, b).

Table 1

Electro-optical properties of nimesulide molecule

Property	**Value**
Total energy (E) (kcal/mol)	-93050.1396
Binding energy (kcal/mol)	-3471.8067
Electronic energy (kcal/mol)	-594595.6466
Heat of formation (kcal/mol)	-34.8177
HOMO (eV)	-9. 8375
LUMO (eV)	-1. 3099
Hardness (η) (eV)	4.2638

HOMO characterizes the molecule ability to interact with electron acceptors, LUMO – with electron donors. According to the Koopmans' theorem, energies of boundaries surfaces correspond to the ionization energy (HOMO energy) and electron affinity (LUMO energy). The frontier orbitals are delocalized in the nimesulide molecule.

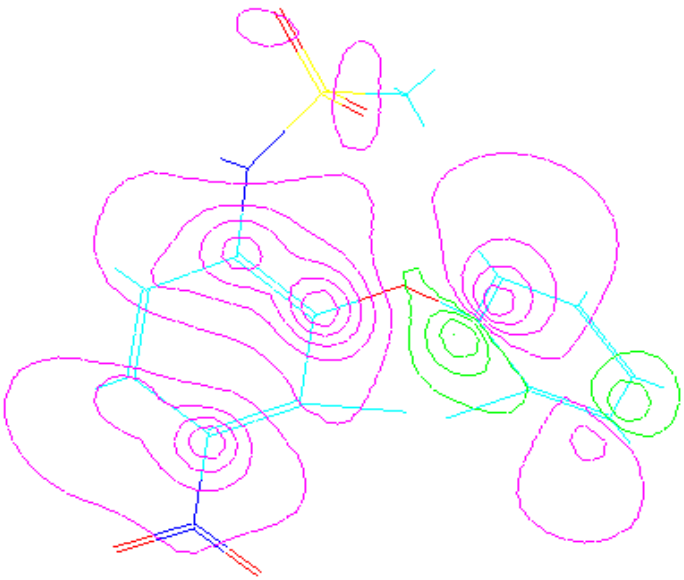

Figure 6a. Localization of HOMO in the nimesulide molecule

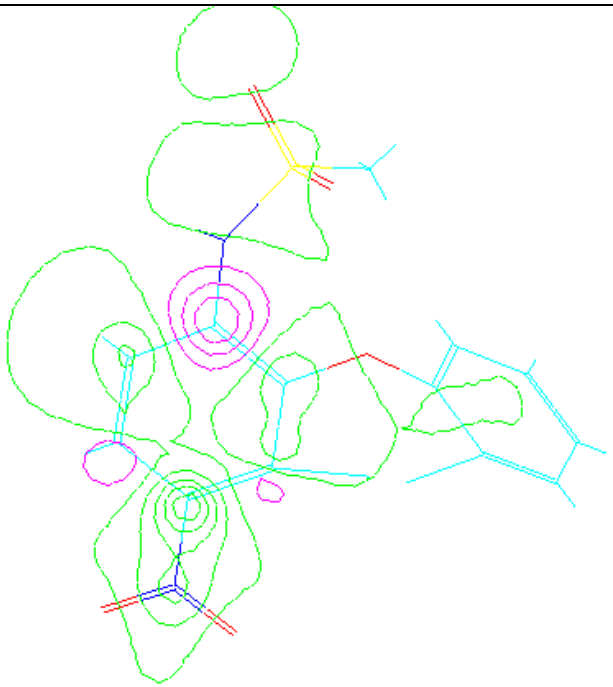

Figure 6b. Localization of LUMO in the nimesulide molecule

Boundary orbital (HOMO, LUMO) in the molecule of nimesulide are delocalized. The calculations of the energy levels of the electron orbitals allowed to quantify the value of the HOMO and LUMO energies; -9.837501eV and -1.30998 eV respectively. The value of the HOMO indicates that the molecule of nimesulide is a donor of electrons.

Molecular parameters such as hardness can be computed using data from Table 1. Based on the values obtained for HOMO and LUMO, the hardness is equal to 4.2638 ($\eta = ½ E_{LUMO} – E_{HOMO}$).

By the comparison of hardness value (η) of hard molecules (BF_3 – 7.8 eV, HCL – 8.0 eV) and soft molecules (paracetamol – 4.3649 eV, ibuprofen – 4.8036968 eV, meloxicam – 4.1189 eV, diclofenac – 2.8746, acetylsalicylic acid – 4.5426, mefenamic acid – 3.8656) we can conclude that the studied molecule can be considered as a soft reagent. Thus, nimesulide most actively will react with soft reagents comprising cysteine residues in proteins as evidenced by the published data [3-8, 18].

Conclusions

Main geometrical and energetic parameters were established for nimesulide molecule. It was shown that nimesulide is a soft reagent. Established quantum-chemical properties of nimesulide could be the basis in the study of molecular mechanisms of its pharmacological action.

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