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INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF ROFECOXIB

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ABSTRACT

Rofecoxib is a widely used drug in medical practice. We have studied the quantum-chemical properties of rofecoxib, which are vital for understanding of mechanisms of biological and pharmacological activity at a molecular level. The geometry optimization for rofecoxib molecule was performed by PM3 method, Polak-Ribiere algorithm. We have determined the distance between atoms, total charge density, characteristics of molecular orbitals of rofecoxib molecule.

Installed quantum-chemical properties of rofecoxib are the basis of the molecular mechanisms of its pharmacological action.

Keywords: Rofecoxib, 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) are among the most commonly used medications in the world for pain, fever and inflammation treatment [1, 2].

We have studied the quantum-chemical properties of molecules of NSAID: paracetamol, ibuprofen, meloxicam, diclofenac, 2,4-dichlorobenzoic acid [3-10].

The main criterion for choosing NSAIDs is considered the rate of clinical effect achievement. Particular significance this parameter plays in relieving acute pain syndromes. However, most NSAIDs are non-selective having a large number of side effects and significantly reduce the possibility of their use. In this regard, for the pain management in injuries of the musculoskeletal system is preferable the prescription of the selective COX-2 inhibitors. Rofecoxib is a highly selective inhibitor of cyclooxygenase-2, which has anti-inflammatory, analgesic and antipyretic action, reduces post-traumatic swelling of the tissues and provides sufficient and stable analgesia. It has no effect on COX-1 activity at therapeutic concentrations.

Rofecoxib is characterized by a rigid side chain that can penetrate the hydrophilic side of the COX-2 molecule cavity and block the active site of the isoenzyme in a non-competitive manner. Because of this, the incidence of erosive and ulcerative lesions of the upper gastrointestinal tract is less than the frequency of their occurrence in patients receiving placebo and significantly lower than for non-selective NSAIDs. Rofecoxib has no cross-reactivity with acetylsalicylic acid and other non-selective NSAIDs, and hence does not induce "Aspirin-sensitive Asthma" attacks. Hence, it can be suggested for patients with this disease.

The mechanism of acute pain development during the tissue damage associated with the release of pain mediators - prostaglandins formed from arachidonic acid under the influence of the enzyme COX-2. Prostaglandins have effect on peripheral nociceptors, cause their sensitization, reduction of pain threshold, which leads to the development of lesions in the primary zone of hyperalgesia. Rofecoxib inhibits the synthesis of COX-2, and therefore affects both peripheral and central mechanisms on the development of acute pain. Therefore, its use is necessary and pathogenetically justified for treatment of musculoskeletal and postoperative pain syndromes.

Rofecoxib is indicated for sprains, bruise of joints, it is effective for the relief of pain in trauma limbs, back. It can be used in the treatment of acute post-operative pain associated with surgery [11-13].

The purpose of this work is to conducting quantum-chemical research of rofecoxib molecule and conduct computer predictions of pharmacological activity of this compound.

Materials and methods.

Research of quantum chemical and pharmacological properties of rofecoxib was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [14-18]. All calculations were carried out using the Polak – Ribiere conjugate gradient algorithm. During the research, the following parameters were studied: interatomic distance (E), the angles between the bonds (°), atomic charges (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) [17].

Absolute hardness of the rofecoxib molecule was determined by the following equation:

$$\eta = ½ (E_{LUMO} - E_{HOMO})$$

Results and discussion

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

Calculated charges for each atom in the rofecoxib molecule are presented in Figure 3. The regions of high electron density reside on oxygen atoms (-0.936; -0.929; -0.272; -0.246 a.u.). The electron density on C_3, C_6, C_{16}, C_{18}, C_{22}, atoms are -0.815, -0.133, -0.132, -0.137 and -0.942 respectively.

The electron deficient areas are observed on sulfur atom (2.861) and carbon atoms directly bonded to oxygen atoms (0.325, -0.012 a.u.). Positive charges are located on hydrogen atoms (from 0.169 to 0.121 a.u.).

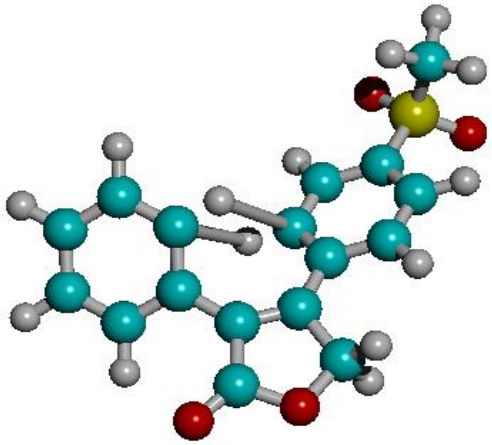

Figure 1. Structure of rofecoxib molecule – green colour correspond to carbon atoms, red - oxygen, yellow – sulfur, grey - hydrogen.

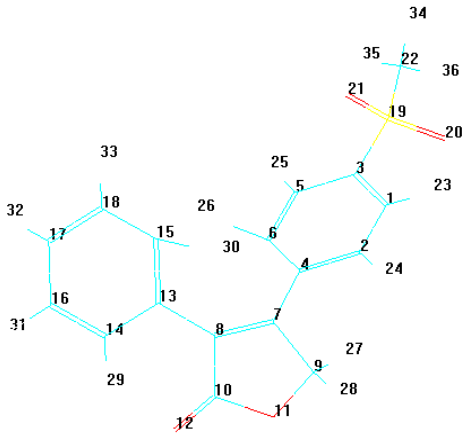

Figure 2. Atom numeration of rofecoxib molecule used in calculation of quantum chemical parameters.

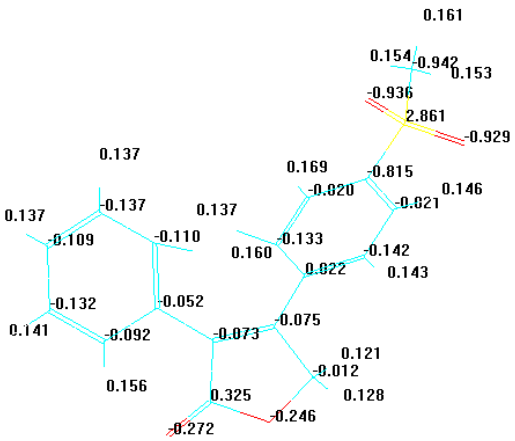

Figure 3. Atom charges in rofecoxib molecule.

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 electroneutral system. Dipole moment quantitatively determines a static polarization of particle. Its value is a measure that defines the activity of chemical interaction (Figure 4).

The total dipole moment of rofecoxib molecule is 3.49402 D. The distances at axes are X = 0.72915 D, Y = -1.09230 D, Z = 3.23781 D.

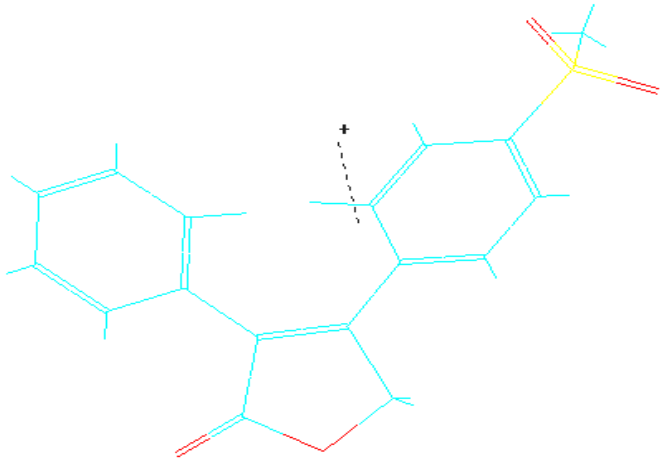

Figure 4. Dipole moment of rofecoxib molecule

The distribution of electron density of outer valence electrons of the rofecoxib is shown in Figure 5. The highest electron density is observed on oxygen and nitrogen atoms, C_3, C_4, C_{13} and C_{17} atoms. C_{10} atom (+0.325) 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.

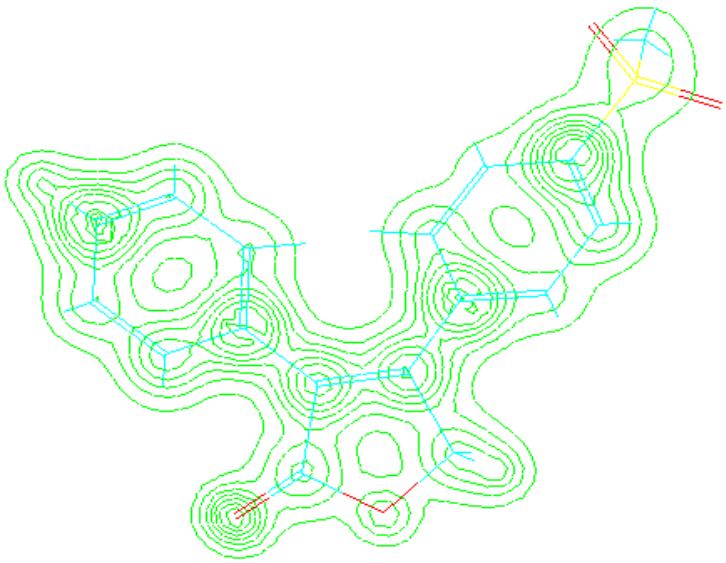

Figure 5. Distribution of electron density of outer valence electrons in the rofecoxib molecule

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) [18]. Table 1 shows some electro-optical parameters of the rofecoxib molecule. Localization of electron density of HOMO LUMO depicted in Fig. 6 (a, b).

Table 1.

Electro-optical properties of rofecoxib

Property	**Value**
Total energy (E) (kcal/mol)	-88625.84916
Binding energy (kcal/mol)	-4002.402728
Electronic energy (kcal/mol)	-582864.4716
Heat of formation (kcal/mol)	-63.20872843
HOMO (eV)	-9.46820
LUMO (eV)	-1.72821
Hardness (η) (eV)	3.8699

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 rofecoxib molecule.

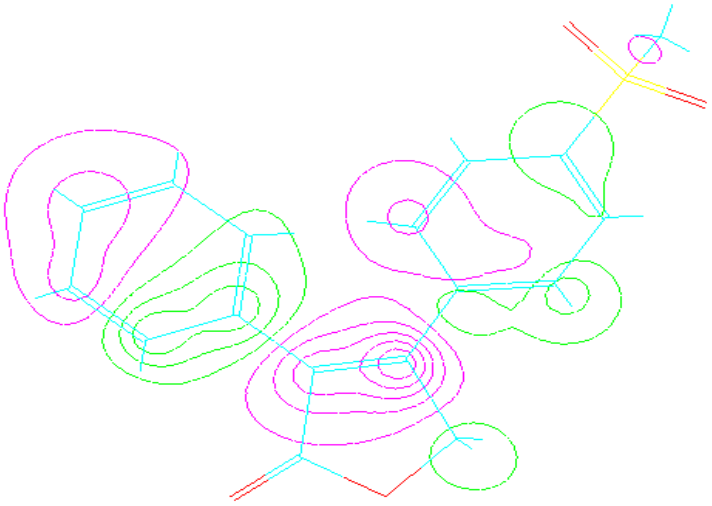

Figure 6a. Localization of HOMO in the rofecoxib molecule

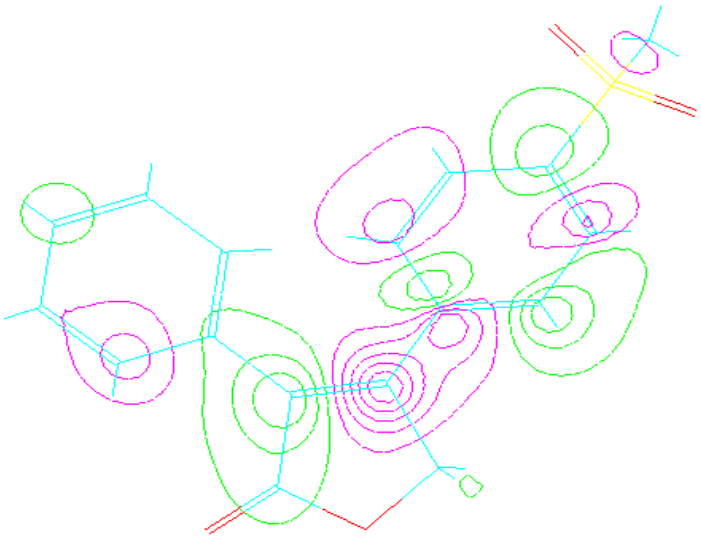

Figure 6b. Localization of LUMO in the rofecoxib molecule

Boundary orbital (HOMO, LUMO) in the molecule of rofecoxib are delocalized. The calculations of the energy levels of the electron orbitals allowed to quantify the value of the HOMO and LUMO energies: -9.4682 eV and -1.7282 eV respectively. The value of the HOMO indicates that the molecule of rofecoxib 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 3.8699 ($\eta = ½ (E_{LUMO} – E_{HOMO})$).

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 – 4,8037 eV, meloxicam – 4,1189 eV, diclofenac – 2.8746) we can conclude that the studied molecule can be considered as a soft reagent. Thus, rofecoxib most actively will react with soft reagents comprising cysteine residues in proteins as evidenced by the published data [3-10].

Conclusions

Main geometrical and energetic parameters were established for rofecoxib molecule.

It was shown that negative electrostatic potential is on the oxygen and nitrogen atoms.

It was shown that rofecoxib is a soft reagent.

Installed quantum-chemical properties of rofecoxib could be the basis of the molecular mechanisms of its action pharmacological action.

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