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Investigation of quantum-chemical properties of piroxicam

Abstract: piroxicam is a nonsteroidal anti-inflammatory drug that is commonly used in medical practice.

We have studied the quantum-chemical properties of piroxicam, which are vital for understanding of mechanisms of biological and pharmacological activity at a molecular level. The geometry optimization for piroxicam molecule was performed by PM3 method, Polak-Ribiere algorithm. We have determined the distance between atoms, total charge density, characteristics of molecular orbitals (HOMO, LUMO) of piroxicam molecule.

Established quantum-chemical properties of piroxicam molecule are the basis of molecular mechanisms of its anti-inflammatory and analgesic action.

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

Utilization of nonsteroidal anti-inflammatory drugs (NSAIDs) plays a fundamental role in the control of inflammation and pain management. These drugs inhibit the synthesis of prostaglandins (PG) through the inhibition of cyclooxygenase (COX-1 and COX-2) — enzymes responsible for the synthesis of prostaglandins.

Piroxicam is a synthetic drug that is representative of chemical class oxicam and belongs to the group of NSAIDs. Among oxicams can be distinguished drugs that are non-selective and selective inhibitors of COX-1, COX-2, which causes the differences in the pharmacological properties of these drugs. Piroxicam is the non-selective cyclooxygenase inhibitor of both COX-1 and COX-2. It inhibits the migration of monocytes and leucocytes, the formation of oxygen radicals, lysosomal enzyme action that destroy cartilaginous tissue. In joint syndrome reduce or eliminate inflammation and pain on movement and at rest[1]. Piroxicam has analgesic, antipyretic and anti-inflammatory effects, reduces pain, fever and inflammation[2].

Piroxicam has been successfully used in the treatment of inflammatory and degenerative diseases of the locomotor system: rheumatoid arthritis, rheumatism, osteoarthritis, ankylosing spondylitis, gout.

Piroxicam greatly inhibits collagen synthesis that explains its distinct antiproliferative and weak antyalteratyve activity. It has a pronounced antiproliferative effect[3].

However, despite of widespread occurrence in world practice data about quantum-chemical properties and spatial structure of piroxicam in scientific literature are not available.

Objective. This work is a part of the research work of the Medical and Bioorganic Chemistry Department of Kharkiv National Medical University. Previously, we have conducted quantum-chemical studies of NSAIDs molecules having different chemical structures[4].

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[1] Compendium. Available at: http://compendium.com.ua/akt/77/825/piroxicamum

[2] Mashkovskii M. D. (2012). Medicinal product. Moskow: New wave, 1216.

[3] Winkelmeyer W. C., Waikar S. S., Mogun H., Solomon D. H. (2008). Nonselective and Cyclooxygenase-2-Selective NSAIDs and acute kidney injury. Am. J. Med., 121, 1092–1098; Козачок Н. Н. Оптимальный выбор нестероидного противовоспалительного препарата в современной клинической практике [Текст]/Н. Н. Козачок, М. Н. Селюк, С. А. Бычкова, В. В. Бесача//Новости медицины и фармации. – 2007. – № 8/218. – С. 3–4.

[4] Syrovaya A. O., Levashova O. L., Andreeva S. V. (2015). Investigation of quantum-chemical properties of paracetamol. Journal of Chemical and Pharmaceutical Research. 7 (1), 307–311; Tishakova T. S., Levashova O. L., Singh Sukhdeep et al. (2015) Investigation of quantum-chemical properties of ibuprofen. European applied science. 5, 82–85.

Research of quantum chemical and pharmacological properties of piroxicam was conducted by the method of molecular mechanic MM+ and semi empirical method PM3[1].

All calculations were carried out using the Polak — Ribiere conjugate gradient algorithm.

During the research, the following parameters were studied: interatomic distance (E), atomic charges (a.u./eV), distribution of electron density of outer-shell electrons, the total energy (kcal/mol), bonding energy (kcal/mol), electronic energy (kcal/mol), nuclear 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)[2].

The global hardness corresponds to the gap between the HOMO and LUMO orbitals. The larger the HOMO-LUMO energy gap, the harder the molecule is. Absolute hardness of the piroxicam molecule was determined by the following equation[3].

$$\eta = ½ (E\ LUMO - E\ HOMO)$$

According to the chemical structure piroxicam belongs to the chemical class oxicams. In terms of structure, piroxicam has a simple chemical structure and correspond to hydroxy derivative of acetanilide.

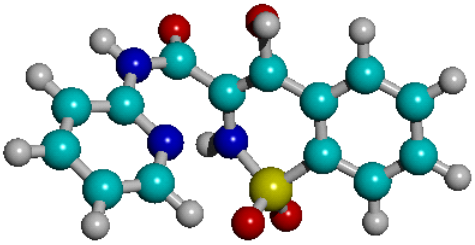

Figure 1. Structure of piroxicam molecule – green colour correspond to carbon atoms, red – oxygen, blue – nitrogen, yellow – sulfur, grey – hydrogen

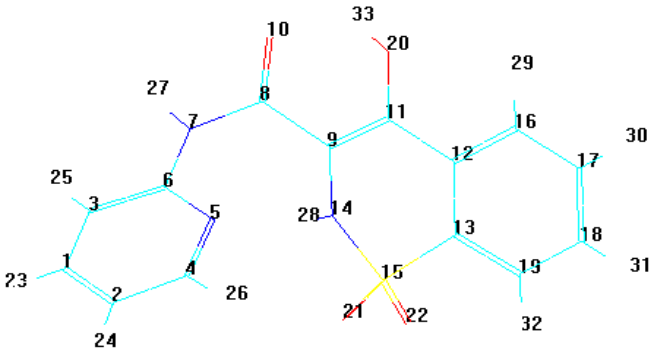

Figure 2. Atom numeration of piroxicam molecule used in calculation of quantum chemical parameters

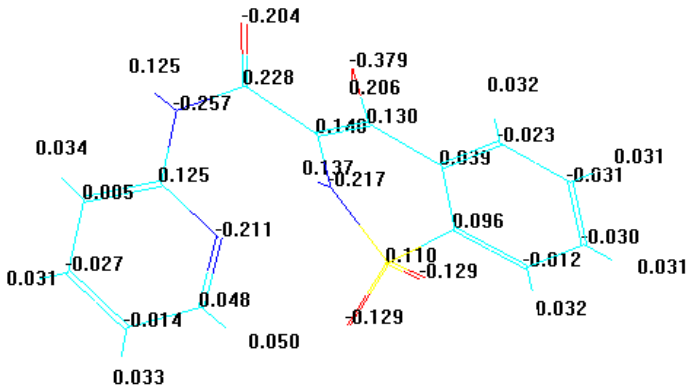

Figure 3. Atom charges in piroxicam molecule

Molecular model of piroxicam molecule was calculated based on geometrical optimization depicted in Figure 1; atoms numeration used in calculation of quantum chemical parameters is depicted in Figure 2. Calculated charges for each atom in the piroxicam molecule are

[1] Chekman I. S., Gorchakova N. O., Nebesna T. U. (2012). Quantum-chemical basis of pharmacokinetics. Medical business. 3/4, 3–13; Chekman I. S., Gorchakova N. O., Tumanov V. A. et al.; Chekman I. S. (Ed.) Pharmacology. Kiiv: Visha shkola., 2001, 598; Chekman I. S. (2012). Quantum Pharmacology. Kiiv: Naukova dumka, 180; Chekman I. S., Kazakova O. O., Nebesna T. U. (2008). Quantum-chemical and topological descriptors in studies of "structure – activity" relationship. Journal of the Academy of medical sciences of Ukraine, 14, 4, 636–650; Minkin V. I., Simkin B. Y., Miniaev R. M. (1997). Theory of molecules structure. Rostov-on-Don: Phoenix, 560; Nebesna T. U., Zagorodnii M. I., Yagupova A. S., Gorchakova N. O., Chekman I. S. (2007). The study of molecular structure and chemical properties of quantum-acetylcysteine. Ukrainian Scientific Medical Youth Journal. 1–2, 19–23.

[2] Soloviev M.E., Soloviev M.M. (2005) Kompyuternaya chimiya. Moskow: Solon-press, 325.

[3] Apostolova E.S., Michayluk A.I., Tserelson V.G. (1999). Quantum chemical description of reactions. – Moskow: Izdat. Center MORPH, 45.

presented in Figure 3. The regions of high electron density reside on oxygen atom of sulfo-, oxo- and hydroxo- groups (–0,379; –0,204; –0,129 a.u.), as well as on nitrogen atoms (–0,257; –0,217; –0,211 a.u.). The electron density is significantly different on the carbon atoms not directly associated with the nitrogen, oxygen and sulfur atoms: from -0,031 a.u. (C17) to 0,096 a.u. (C13) correspondingly. The electron deficient areas are observed on carbon atoms directly bonded to oxygen (C8, C11) and nitrogen (C9, C6) (0,228; 0,130; 0,140; 0,125 a.u. correspondingly). Positive charges are located on hydrogen atoms (from 0,137 to 0,030 a.u.).

Dipole moment of a molecule represents a sum of dipole moments of each chemical bond 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.

The total dipole moment of piroxicam molecule is 4,7469. The distances at axes are: X = 0,9695 D, Y = –1,0302 D, Z = 4,5312 D (Fig. 4).

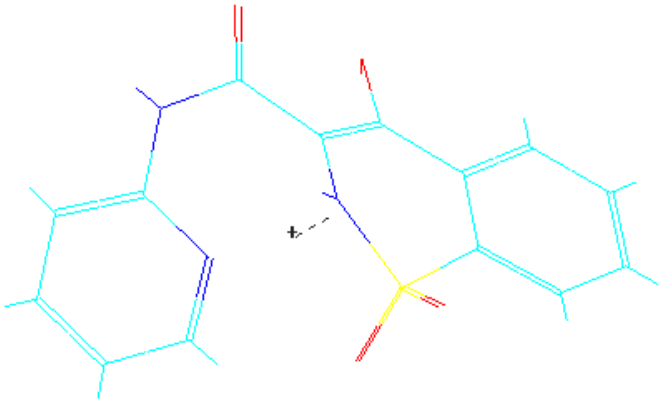

Figure 4. Direction of dipole moment in the piroxicam molecule

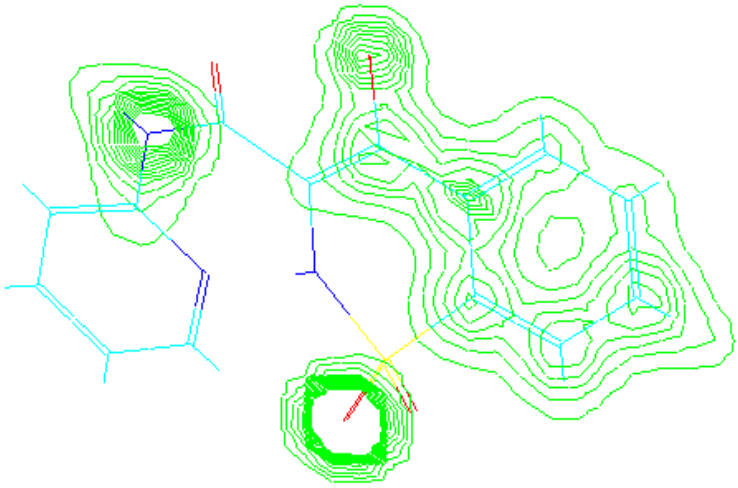

Figure 5. Distribution of electron density of outer valence electrons in the piroxicam molecule

The distribution of electron density of outer valence electrons of the piroxicam is shown in Figure 5. The highest electron density is observed on oxygen, nitrogen, C12, C13, C18 and C19 carbon atoms. Hydrogen atoms directly bonded to oxygen and nitrogen are capable to hydrogen bond with electro neutral atoms of other molecules (oxygen or nitrogen of amino acids at the bonding place with receptors.

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

Table 1. – Electro-optical properties of piroxicam

Property	Value
Total energy (E) (kcal/mol)	–93137,14776
Binding energy (kcal/mol)	–3657,3315
Electronic energy (kcal/mol)	–624564,0543
Nuclear energy (kcal/mol)	531426,9066
Heat of formation (kcal/mol)	–48,1135
Hydration energy (kcal/mol)	–13,02
Polarizability (A)	28,49
HOMO (eV)	–9,06808
LUMO (eV)	–0,95425
Hardness (η, eV)	4,05692

[1] William O Foye (2008). Foye's principles of Medicinal Chemistry. In: Foye WO, Lemke TL, Williams DA, (Eds). Philadelphia: Lippincott Williams & Wilkins.

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).

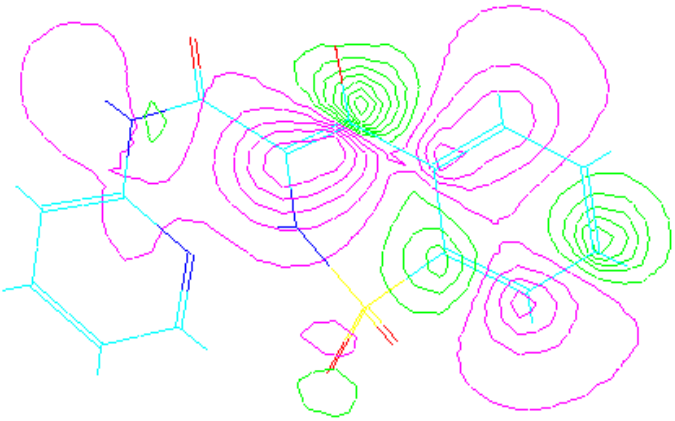

Figure 6 a. Localization of HOMO in the piroxicam molecule

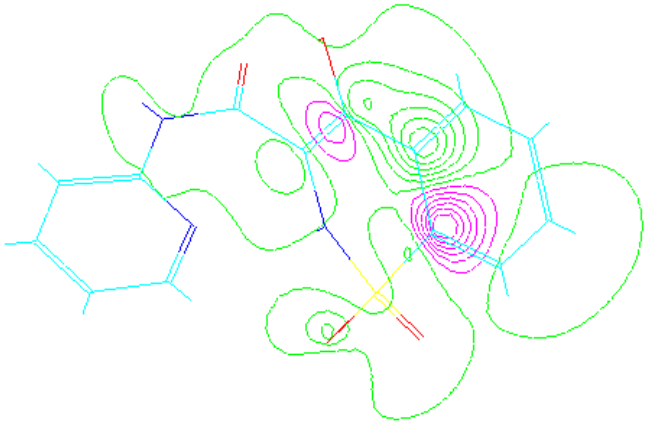

Figure. 6 6. Localization of LUMO in the piroxicam molecule

The frontier orbitals are delocalized in the piroxicam molecule. Calculations of energy levels of electronic orbitals allowed to quantify the values of HOMO and LUMO energy: –9,06808 and –0,95425 eB respectively.

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 4,05692 (η = ½ ELUMO – EHOMO).

By the comparison of hardness value (η) of other NAISD molecules (η, eB) such as paracetamol –4,364926 eV, ibuprofen –4,8036968 eV, meloxicam –4,118919 that are soft molecules, we can conclude that the studied molecule can be considered as a soft reagent. Thus, piroxicam most actively will react with soft reagents comprising cysteine residues in proteins and glutathione.

Main geometrical and energetic parameters were established for piroxicam molecule as a result of conducted studies. It is shown that negative electrostatic potential in piroxicam molecule is observed on oxygen, nitrogen atoms. Piroxicam is a mild reagent according to the values of the HOMO and LUMO energies and the absolute hardness.