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INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF INDOMETHACIN

Syrovaya A.O.
Kharkiv National Medical University, professor
Kozub S.N.
Kharkiv National Medical University, assistant professor
Tishakova T.S.
Kharkiv National Medical University, assistant professor
Levashova O.L.
Kharkiv National Medical University, PhD assistant
Chalenko N.N.
Kharkiv National Medical University,PhD assistant

Abstract

The quantum-chemical properties of indomethacin were determined. These properties are very important for understanding explanation the causes of the manifestation of certain biological effects. The geometry optimization for indomethacin molecule was performed by PM3 method, Polak-Ribiere algorithm.

Pharmacological activity of a molecule depends not only on the character and sequence of atoms, but also on their spatial distribution in the molecule, atomic charges, position of the functional groups and active radicals, quantum-chemical properties.

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

INTRODUCTION

Indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]-acetic acid) is an effective anti-inflammatory, analgesic and antipyretic medicine from the NSAID group [2, 8]. Indomethacin has a wide spectrum of action: it is used in ophthalmology, gynecology, surgery, and is effective in the treatment of neuralgia. Indomethacin as a powerful anti-inflammatory agent allows rapid clinical improvement in inflammatory rheumatic diseases. Thus, it is helpful for pain suppression in a treatment of acute arthritis, gout, rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis, and various injuries of soft tissue of the body. It shows a significant reduction of the morning stiffness and the number of inflamed joints, as well as a decrease in the sedimentation rate of erythrocytes (ESR) and C-reactive protein (CRP) in the rheumatoid arthritis treatment [11, 14].

Indomethacin causes weakening or disappearance of the pain syndrome having rheumatic and non-rheumatic nature, including pain in joints at rest and during movement, decrease of a morning stiffness and joints swelling. It contributes to an increase in the volume of movements, in inflammatory processes that occur after operations and injuries, quickly facilitates both spontaneous pain and pain when moving, and reduces inflammatory swelling at the wound site [6, 14].

Indomethacin suppresses the activity of anti-inflammatory factors, reduces the aggregation of platelets. Inhibiting both cyclooxygenases 1 and 2 (COX-1 and COX-2, giving preference to COX-1), it disrupts the metabolism of arachidonic acid, suppresses the exudative and proliferative phase of inflammation, reduces the amount of prostaglandins in both the inflammation focus and in healthy tissues [4, 12, 15].

In this paper, calculations of quantum-chemical properties of indomethacin molecule were carried out with the aim of explanation of specific acting centers of this molecule.

MATERIAL AND METHODS

Research of quantum chemical and pharmacological properties of indomethacin was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [3, 7, 9]. 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), inter-nucleus 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) [16].

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

$$\eta = ½ (E_{LUMO} - E_{HOMO})$$

RESULTS AND DISCUSSION

Molecular model of indomethacin 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 indomethacin molecule are presented in Figure 3. The regions of high electron density reside on oxygen atoms (-0.369; -0.316; -0.303 a.u.) as well as on nitrogen atom (-0.189 a.u.). The electron density on C_1, C_5, C_8, C_{31} atoms: -0.143, -0.176, -0.163 and -0.179 respectively.

The electron deficient areas are observed on carbon atoms directly bonded to oxygen and nitrogen atoms (0.369, 0.311, 0.071 a.u.). Positive charges are located on hydrogen atoms (from 0.167 to 0.072 a.u.).

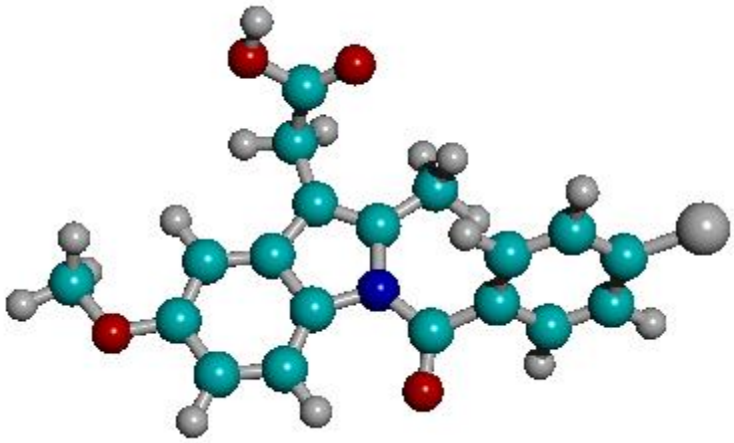

Figure 1. Structure of indomethacin molecule – green colour correspond to carbon atoms, blue – nitrogen, red - oxygen, grey – hydrogen.

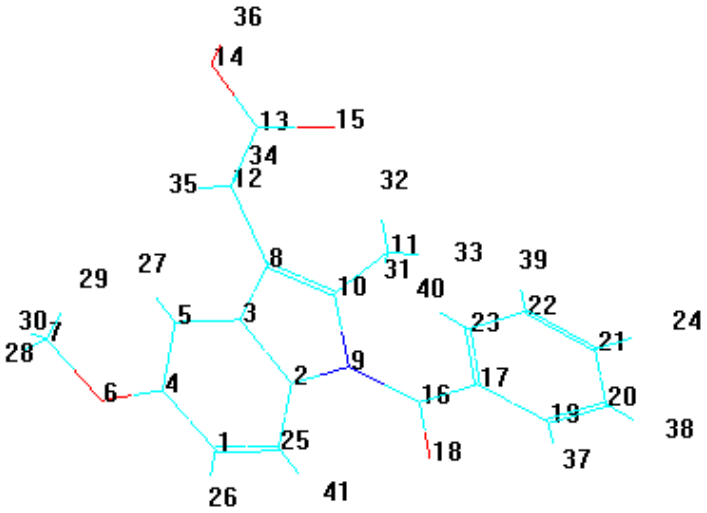

Figure 2. Atom numeration of indomethacin molecule used in calculation of quantum chemical parameters.

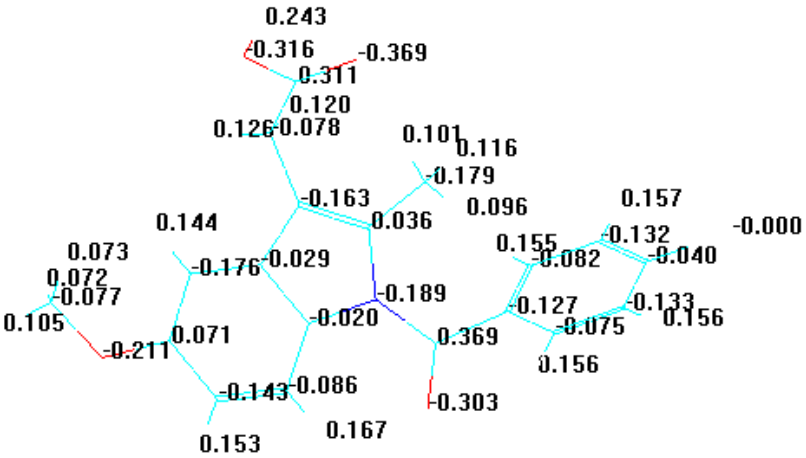

Figure 3. Atomic charges in indomethacin molecule.

The adsorption of the drug molecule from the intercellular fluid to the surface of the biomembrane depends on the projection of the vector of the dipole moment on the plane. It characterizes the extent of charge separation within a molecule. Dipole moment quantitatively determines a static polarization of particle. Its value is also a measure that defines the activity of chemical interaction (Figure 4).

The total dipole moment of indomethacin molecule is 2.5473 D. The distances at axes are X = -2.1338 D, Y = 1.1464 D, Z = 0,7884 D.

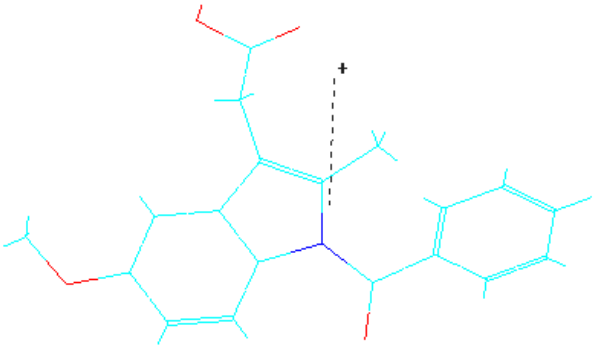

Figure 4. Dipole moment of indomethacin molecule

The distribution of electron density of outer valence electrons of the indomethacin molecule is shown in Figure 5. The highest electron density is observed on oxygen nitrogen and chloride atoms, C_2, C_3, C_5, C_{17} and C_{20} atoms. C_5 atom (+0.176) as a potential electrophile may react with nucleophilic reagent. Hydrogen atoms directly bonded to oxygen are capable to form hydrogen bonds with electro neutral atoms of other molecules.

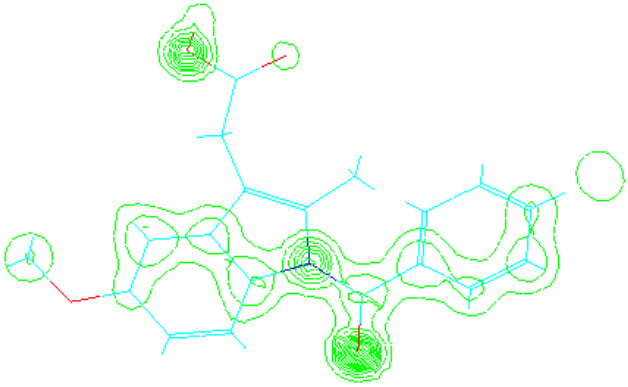

Figure 5. Distribution of electron density of outer valence electrons in the indomethacin molecule

The reactivity of the molecule characterizes by the localization of HOMO LUMO (H. Fukui theory) [1, 10, 19]. 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 indomethacin molecule.

The calculations of the energy levels of the electron orbitals allowed to quantify the value of the HOMO and LUMO energies; -8.6683eV and -0.7765 eV respectively. The value of the HOMO indicates that the molecule of indomethacin is a donor of electrons. Possible centers that can accept or donate electrons are indicated on the Figure 6 (a, b).

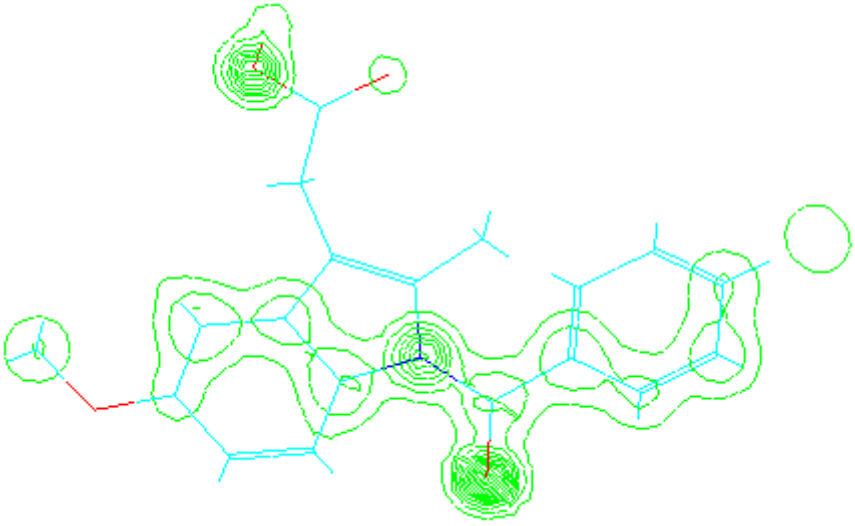

Figure 6a. Localization of HOMO in the indomethacin molecule

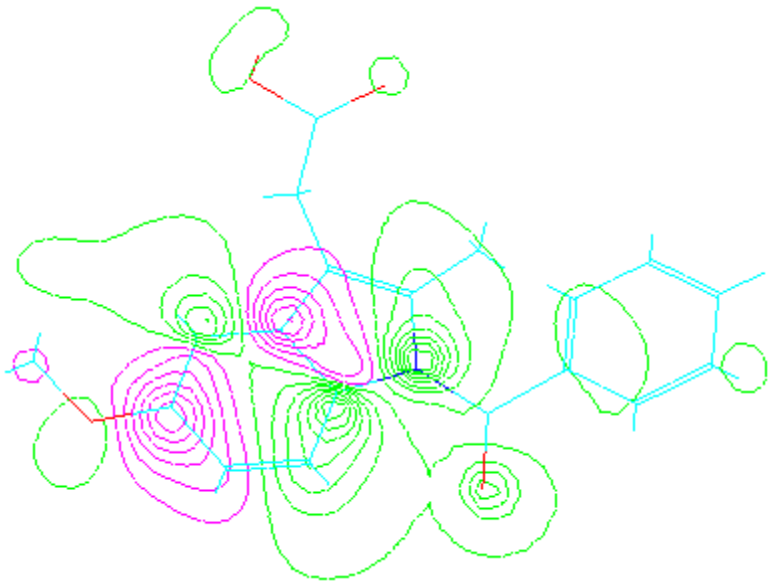

Figure 6b. Localization of LUMO in the indomethacin molecule

The value of absolute hardness represents the basis of the principles of soft and hard acids and bases. Soft substitutes make acids and bases softer, hard substitutes make them more rigid. The interaction energy increases with decrease of the reactants hardness. Based on the energies of HOMO and LUMO, the absolute hardness of the molecule can be computed using data from Table 1. Based on the values obtained for HOMO and LUMO, the hardness of indomethacin molecule is equal to 3.9459.

Table 1.

Electro-optical properties of indomethacin

Property	Value
Total energy (E) (kcal/mol)	-104098.7758
Binding energy (kcal/mol)	-4547.99015
Electronic energy (kcal/mol)	-72.4094
Heat of formation (kcal/mol)	-87.2222
HOMO (eV)	-8.6683
LUMO (eV)	-0.7765
Hardness (η) (eV)	3,9459

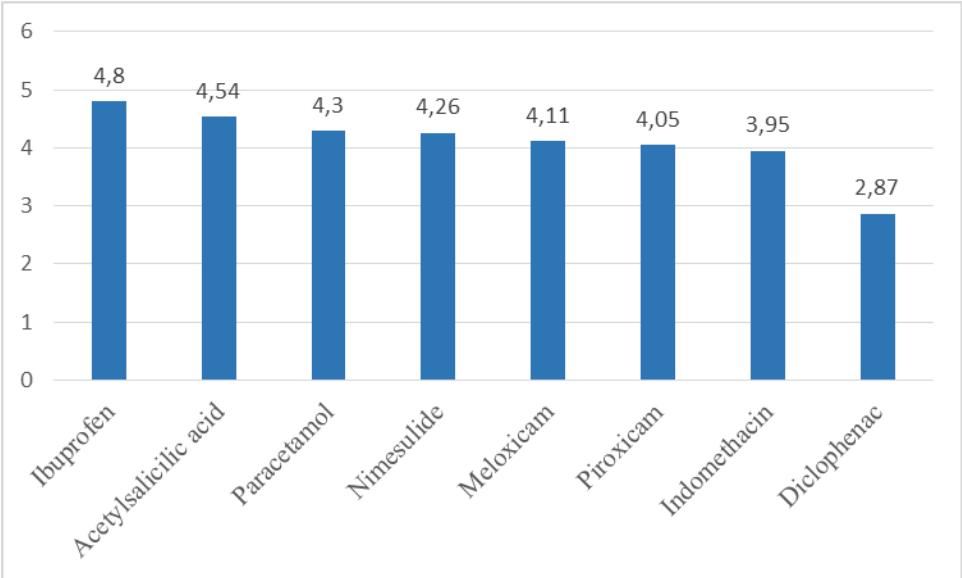

Figure 7. Hardness values (η)

By the comparison of hardness value (η) shown on Figure 7, we can conclude that the studied molecule can be considered as a soft reagent. Thus, indomethacin most actively will react with soft reagents comprising cysteine residues in proteins as evidenced by the published data [5, 13, 17-20].

CONCLUSIONS

Main geometrical and energetic parameters were established for indomethacin molecule. It was shown that negative electrostatic potential is on the oxygen and nitrogen atoms. It was shown that indomethacin is a soft reagent (η=3.9459). The quantum-chemical properties of indomethacin could be the basis of the molecular mechanisms of its pharmacological action.

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