No 11 (11) (2017)
P.1
The scientific heritage

(Budapest, Hungary)

The journal is registered and published in Hungary.
The journal publishes scientific studies, reports and reports about achievements in different scientific fields. Journal is published in English, Hungarian, Polish, Russian, Ukrainian, German and French.
Articles are accepted each month. Frequency: 12 issues per year.
Format - A4
ISSN 9215 — 0365

All articles are reviewed
Free access to the electronic version of journal

«The scientific heritage»
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E-mail: public@tsh-journal.com
Web: www.tsh-journal.com

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INVESTIGATION OF QUANTUM-CHEMICAL PROPERTIES OF MEFENAMIC ACID

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ABSTRACT

Mefenamic acid is a widely used drug in medical practice. The quantum-chemical properties of mefenamic acid were determined. These properties are very important for understanding explanation the causes of the manifestation of certain biological effects. The geometry optimization for mefenamic acid molecule was performed by PM3 method, Polak-Ribiere algorithm. The main spatial, energetic and electronic properties of the molecule of mefenamic acid molecule was determined: distance between atoms, total charge density, characteristics of molecular orbitals.

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

Keywords: Mefenamic acid, spatial structure, quantum-chemical properties.

INTRODUCTION

Benzoic acid derivatives have a broad spectrum of biological activity, making this group of compounds perspective for the research of new drugs.

Benzoic acid is a well-known medicament used externally as an antimicrobial and antifungal agent, and upon oral administration has expectorant effect.

In human organism, benzoic acid is the end product of oxidation of fatty acid with odd number of carbons. Benzoic acid occurs naturally free and bound as benzoic acid esters in many plant and animal species. For example, hippuric acid consists of benzoic and aminoacetic acid residues, and forms during the detoxification of aromatic substances in the liver of mammals.

According to the literature data the enhancement of the spectrum of benzoic acid derivatives biological activity is achieved by introducing into its molecule amino acid fragments, nitrogen-containing heterocyclic compounds (pyrazole, pyridine), which may contribute to the presence in these derivatives anti-inflammatory, analgesic, and other types of activity.

Currently, a group of drugs non-steroidal anti-inflammatory drugs (NSAIDs) have representatives of benzoic acid (sodium salicylate, mefenamic acid, and voltaren al.) which characterized by significant analgesic, anti-inflammatory and antipyretic activities.

Mefenamic acid (2-[(2,3-Dymetylfenyl)amino] benzoic acid or N-(2,3-dimethylphenyl)anthranilic acid) is a non-steroidal anti-inflammatory, anti-rheumatic drug used for treatment diseases of the musculoskeletal system, fever syndrome. It has moderate antipyretic and analgesic properties; analgesic activity of mefenamic acid is comparable to butadion (Phenylbutazonum).

Antipyretic effect relates to its property to reduce the production of prostaglandins and exert influence on the thermoregulatory center. It stimulates the production of interferon. [1]

Mefenamic acid inhibits the synthesis of inflammatory mediators (PG, serotonin, kinins, etc.), reduces the activity of lysosomal proteases involved in the inflammatory response, and affects exudation and proliferation phases. It stabilizes protein ultrastructure and cell membranes, reduces vascular permeability and tissue edema. Uncouples oxidative phosphorylation, inhibits the synthesis of mucopolysaccharide. It suppresses pro-inflammatory activity of serotonin. It stops cell proliferation in area of inflammation, increases the resistance of the cells and stimulates the healing of wounds.

In the mechanism of the analgesic effect, along with the influence of the central mechanisms of pain sensitivity, an important role is played by a local effect on the area of inflammation, the ability to inhibit algogenity of endogenous substances (kinins, histamine, and serotonin). The analgesic effect of mefenamic acid associated with its effect on the peripheral and central mechanisms of pain sensitivity.

The pharmacological action of mefenamic acid associated with its ability to increase the activity of T-lymphocytes that stimulates the interferon production and provides anti-inflammatory effect.

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 [3-7]. Mefenamic acid has the greatest number of prescriptions compared to other NSAID (non-steroid anti-inflammatory drugs), the class of drug known as "aniline analgesics", which is commonly employed in medical practice [8-10].

The purpose of this work is to study quantum-chemical properties of mefenamic acid molecule.

MATERIAL AND METHODS

Research of quantum chemical and pharmacological properties of mefenamic acid was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [11-15]. 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), 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) [14].

Absolute hardness of the mefenamic acid molecule was determined by the following equation:

$$\eta = ½ (E_{LUMO} – E_{HOMO})$$

RESULTS AND DISCUSSION

Molecular model of mefenamic acid 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 mefenamic acid molecule are presented in Figure 3. The regions of high electron density reside on oxygen atoms (-0.379; -0.343 a.u.) as well as on nitrogen atom (-0.277 a.u.). The electron density on C_4, C_5, C_{11}, C_{12}, C_{14} atoms: -0.113, -0.187, -0.203, -0.221 and -0.199 respectively.

The electron deficient area are observed on carbon atoms directly bonded to oxygen and nitrogen atoms (0.360, 0.195, 0.111 a.u.). Positive charges are located on hydrogen atoms (from 0.251 to 0.085 a.u.).

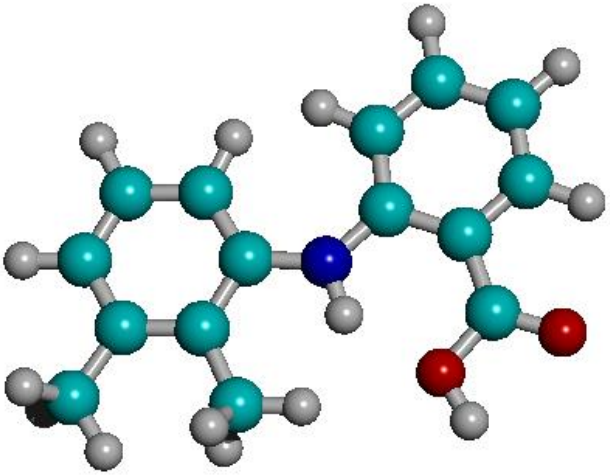


Figure 1. Structure of mefenamic acid molecule – blue colour correspond to carbon atoms, red - oxygen, grey - hydrogen.

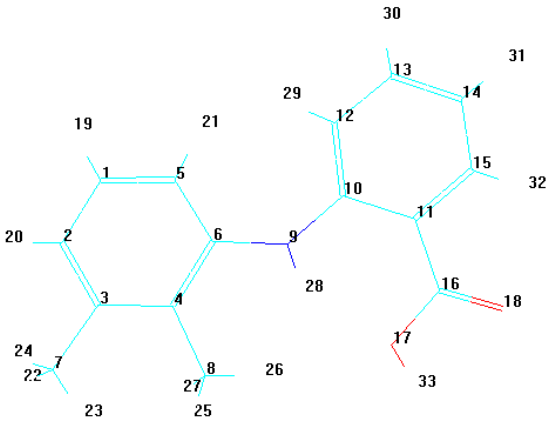


Figure 2. Atom numeration of mefenamic acid molecule used in calculation of quantum chemical parameters.

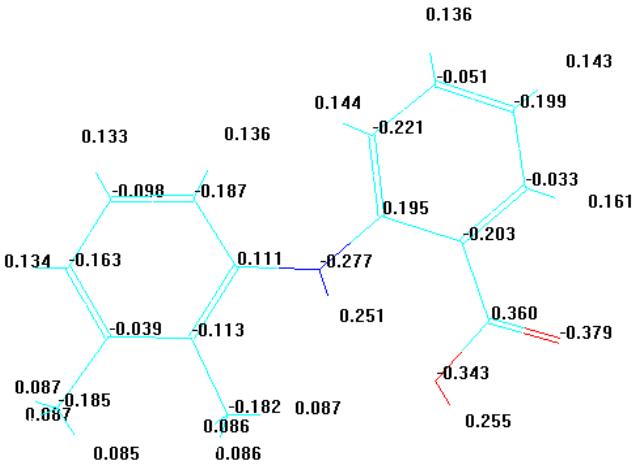


Figure 3. Atom charges in mefenamic acid molecule.

The overall dipole moment of a molecule may be determined by the magnitudes of the partial charges and by the distances between them. It characterizes the extent of charge separation within a molecule. 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 mefenamic acid molecule is 2.46268 D. The distances at axes are X = -2.46268 D, Y = 1.28849 D, Z = 0,00000 D.

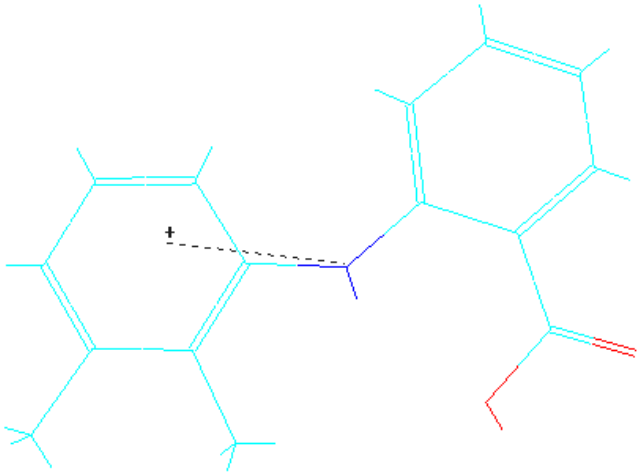


Figure 4. Dipole moment of mefenamic acid molecule

The distribution of electron density of outer valence electrons of the mefenamic acid is shown in Figure 5. The highest electron density is observed on oxygen and nitrogen atoms, C_3, C_4, C_{11} atoms. C_{16} atom (+0.360) 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.

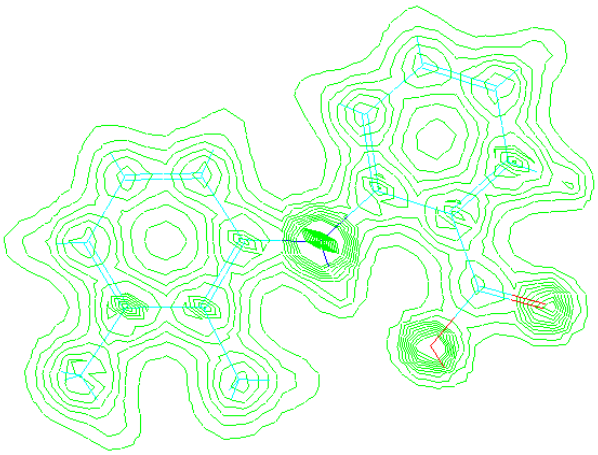


Figure 5. Distribution of electron density of outer valence electrons in the mefenamic acid molecule

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) [15]. Table 1 shows some electro-optical parameters of the mefenamic acid molecule. Localization of electron density of HOMO LUMO depicted in Fig. 6 (a, b).

Table 1.

Electro-optical properties of mefenamic acid

Property	Value
Total energy (E) (kcal/mol)	-68594.86658
Binding energy (kcal/mol)	-3613.8575
Electronic energy (kcal/mol)	-430271.7198
Heat of formation (kcal/mol)	-36.8595
HOMO (eV)	-8.2209
LUMO (eV)	-0.4898
Hardness (η) (eV)	3,8656

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 mefenamic acid molecule.

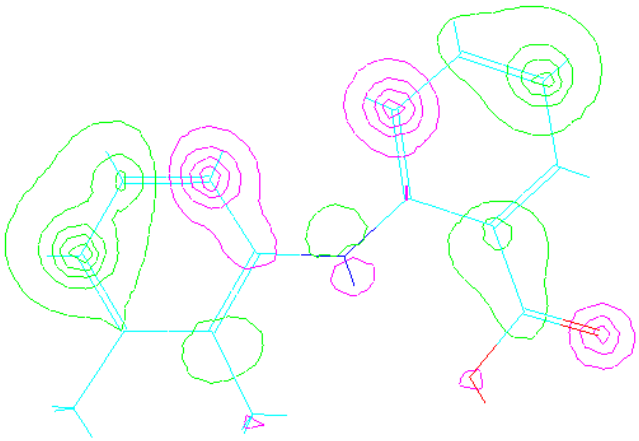


Figure 6a. Localization of HOMO in the mefenamic acid molecule

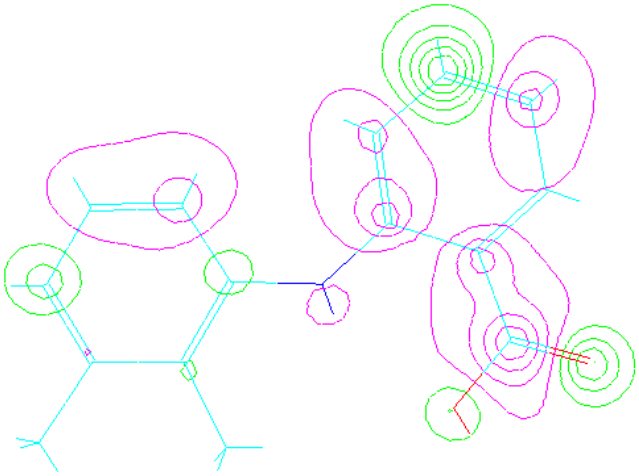
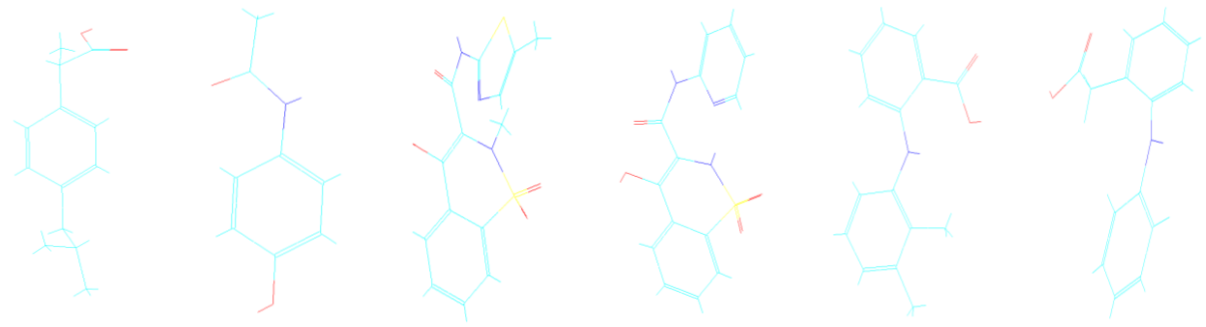


Figure 6b. Localization of LUMO in the mefenamic acid molecule

Boundary orbital (HOMO, LUMO) in the molecule of mefenamic acid are delocalized. The calculations of the energy levels of the electron orbitals allowed to quantify the value of the HOMO and LUMO energies; -8.2209 eV and -0.4898 eV respectively. The value of the HOMO indicates that the molecule of mefenamic acid 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 3.8656 ($\eta = ½ E_{LUMO} – E_{HOMO}$).



Ibuprofen 4.8 > *Paracetamol 4.3* > *Meloxicam 4.11* > *Piroxicam 4.05* > *Mefenamic acid 3.86* > *Diclofenac 2.87*

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, mefenamic acid most actively will react with soft reagents comprising cysteine residues in proteins as evidenced by the published data [3-7, 17].

CONCLUSIONS

Main geometrical and energetic parameters were established for mefenamic acid molecule.

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

It was shown that mefenamic acid is a soft reagent (η=3.8656).

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

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