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## Investigation of Quantum-chemical Properties of Acetylsalicylic Acid

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### ABSTRACT

Quantum chemistry provides a physical insight into the sequences of processes that are the basis of drug action related to the pharmacokinetic and pharmacodynamics' phases. The results of computation of such quantum-chemical parameters of acetylsalicylic acid as geometrical structure, atomic charges, high occupied and low unoccupied molecular orbital energies, electrostatic potential, total charge density, etc. were analyzed. Installed quantum-chemical properties of acetylsalicylic acid are the basis of the molecular mechanisms of its pharmacological action.

**Keywords:** Acetylsalicylic acid, Molecular orbitals, Dipole moment

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### INTRODUCTION

Acetylsalicylic acid (aspirin) is a well-known analgesic, antipyretic, anti-inflammatory drug and platelet aggregation inhibitor [1,2]. Quantum-chemical properties of the drug molecules can explain the molecular mechanism of pharmacological action. It was shown in our already published articles about paracetamol, ibuprofen, meloxicam, diclofenac and 2,4-dichlorobenzoic acid [3-7].

In 1763 an English clergyman Edward Stone wrote to president of Royal Society a letter where he described the successful application of dried, powdered willow bark in treatment of fever and agues. The active ingredient of the willow bark is salicin, which forms after the hydrolysis of salicylic acid.

Salicylic acid is a simple acid with a pKa of 3.0, aspirin has a pKa of 3.5. Aspirin absorbed intact and hydrolyzed to acetic acid and salicylate by blood and tissue esterases. The acidic environment of the stomach promotes preservation of most of the salicylates in non-ionized form, which increases absorption. The American Heart Association recommends daily, low-dose aspirin for people at high risk for heart attack, or who have survived a heart attack [8-10]. When a large amount of salicylate accumulated in the cells of the mucous membranes, aspirin can cause mucosal damage; if the pH of the stomach is increased by a buffer of up to 3.5 or higher, no mucous irritation occurs. Also enteric-soluble coating of aspirin may protect against the topical mucosal damage.

Aspirin is characterized by the high value of bioavailability due to rapid biotransformation into active metabolite, salicylate. It has a very short half-life ( $T_{1/2}$ ) about 3-5 h which increases up to 24 h depending on dose [9].

Acetylsalicylic acid is metabolized in the liver and in the blood to form acetic and salicylic acid by hydrolysis [9,10]. A further metabolic pathway is the formation of the pair of compounds with glycine and glucuronic acid and hydroxylation of the aromatic ring. The product of salicylic acid and glycine is salicyluric acid. About 80% of metabolites excreted by the kidney, and the rest are destroyed in the tissues in different ways. From the pharmacodynamics point of view, the mechanism of its action is associated with inhibition of prostaglandins synthesis. As a result of the irreversible blockade of the prostaglandin synthetase (cyclooxygenase) the conversion of arachidonic acid to endoperoxides is inhibited. Besides that, it affects the kallikrein-kinin system: inhibits the adhesion of granulocytes to the site of injury in the vessel stabilizes mesosomes, inhibits migration of leukocytes and macrophages to the site of inflammation. It is known that aspirin has anti-inflammatory, analgesic, antipyretic effects. Small doses (80-100 mg/day) of aspirin are used as antiplatelet agent, as it inhibits thrombocytes aggregation by inhibiting thromboxane [9]. However, despite the widespread practice in the world, there are no data on the quantum-chemical properties and the spatial structure of acetylsalicylic acid in the scientific literature.

The purpose of this work is to perform quantum-chemical research of acetylsalicylic acid molecule and to make computer predictions of pharmacological activity of this compound.

**MATERIALS AND METHODS**

The structure of the molecule was established by quantum-chemical calculation using “HyperChem” program. Optimization of the spatial structure (calculation of the mutual position atoms in space at which the molecule has the lowest energy level) was performed with a help of Polak-Ribiere algorithm. The following parameters were under investigation: 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 ( $\eta$ , eV) [11-14].

**RESULTS AND DISCUSSION**

The optimized structure of acetylsalicylic acid and numerations of atoms are shown in Figures 1 and 2. Due to the presence of polar (carboxylic, hydroxide groups) and non-polar groups acetylsalicylic acid can react with different fragments of other molecules. For example it can interact with polypeptide and amine polar groups and form covalent bond via acetyl group with serine residue in the active site of the cyclooxygenase (COX) enzyme [15].

The atomic charges of investigated molecule calculated in atomic units (Figure 3) show that the highest electron density is localized on oxygen atoms (-0.294, -0.335, -0.376). The electron density on C<sub>1</sub>, C<sub>4</sub>, C<sub>6</sub>, C<sub>12</sub> atoms are -0.139, -0.189, -0.169 and -0.217 respectively. Charges on carbon atoms depend on electronegativity of neighboring atoms. Thus C<sub>7</sub> and C<sub>11</sub> have significantly positive charge (0.324 and 0.360). Specified atoms with the highest positive and negative charge form reactive centers of this molecule.

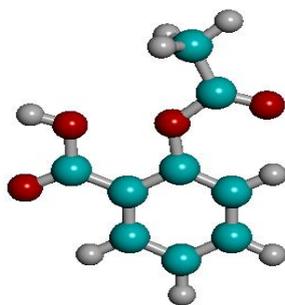


Figure 1: Structure of acetylsalicylic acid molecule-green colour corresponds to carbon atoms, red-oxygen, grey-hydrogen

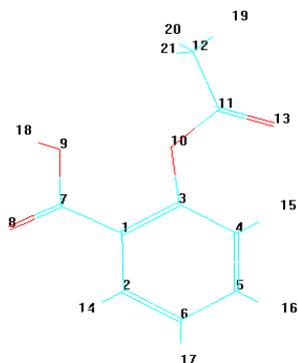


Figure 2: Atom numeration of acetylsalicylic acid molecule used in calculation of quantum chemical parameters

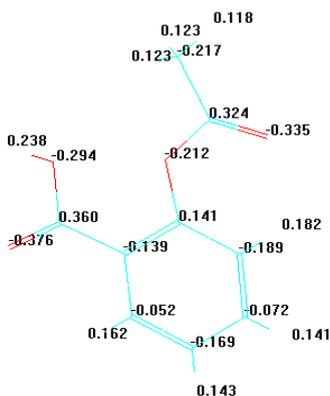
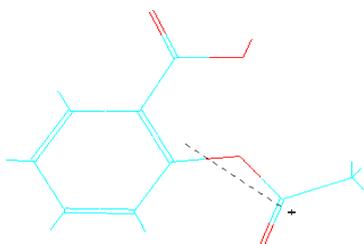


Figure 3: Atom charges in acetylsalicylic acid molecule

Therefore investigated molecule has nucleophilic and electrophilic properties that enable possibility to react with different reactive centers of biosubstrate molecules. Specified atoms that have biggest positive and negative charges form main active centers of the molecule. Spatial distribution of charges forms dipole. Its direction and size are shown on Figure 4.

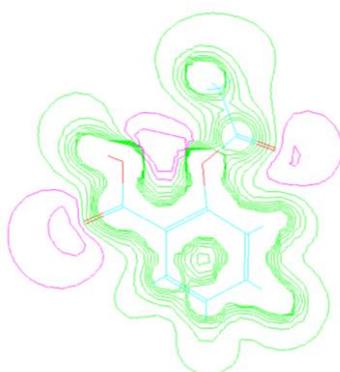
A small dipole moment (1.58592 D) indicates a low polarity of investigated molecule. Therefore acetylsalicylic acid will actively interact with the lipid components of the membrane, rather than with the protein components.



**Figure 4: Dipole moment of acetylsalicylic acid molecule**

Any molecule can be represented as a system of nucleuses surrounded by the electron cloud. Such a system of positive and negative particles in the surrounding space will correspond to the electrostatic field of a molecule with well-defined potential at each point.

Accordingly, the molecular electrostatic potential was defined as the energy of the electrostatic interaction of the nuclei and the electronic distribution of molecules with a single positive point "trial" charge placed at a given point of space surrounding the molecule. Figure 5 shows the distribution of the electrostatic potential of outer valence electrons in the molecule of acetylsalicylic acid (two-dimensional image). The amount of molecular electrostatic potential is an integral characteristic of the molecule, so it cannot be linked to a specific atom or functional group. As shown in Figure 5, the areas with the negative electrostatic potential values are located around the oxygen atoms. Therefore, these atoms can be protonated in the reaction with bioligands of the organism or form most strong hydrogen bonds.



**Figure 5: Distribution of electrostatic potential in the acetylsalicylic acid molecule**

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) as shown on Figure 6a and 6b [16,17]. Electro-optical parameters presented in the Table 1.

**Table 1: Electro-optical properties of acetylsalicylic acid**

Property	Value
Total energy (E) (kcal/mol)	-58669.55667
Binding energy (kcal/mol)	-2333.563042
Electronic energy (kcal/mol)	-284958.9957
Heat of formation (kcal/mol)	226289.439
HOMO (eV)	-9.6335
LUMO (eV)	-0.5483
Hardness (eV)	4.54261

Boundary orbitals (HOMO, LUMO) in the molecule of acetylsalicylic acid are delocalized. The calculations of the energy levels of the electron orbitals allowed quantifying the value of the HOMO and LUMO energies; -9.6335 eV and -0.5483 eV respectively. The value of the HOMO indicates that the molecule of acetylsalicylic acid is a donor of electrons. Possible centers that can accept or donate electrons are indicated on the Figures 6a and 6b.

HOMO of acetylsalicylic molecule is mainly localized on benzene ring, so this part of the molecule will in the first place interact with electron acceptor center of other molecule. LUMO is localized not only on benzene ring but also on oxygen atoms. It indicates that electron-donating center of other molecule will interact primarily with this fragment of investigated molecule.

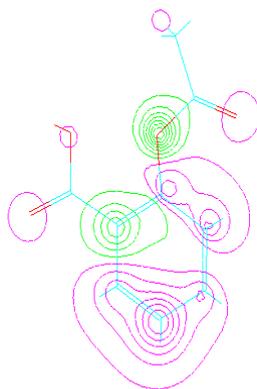


Figure 6a: Localization of HOMO in the acetylsalicylic acid molecule

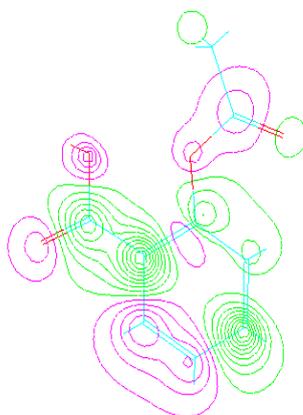


Figure 6b: Localization of LUMO in the acetylsalicylic acid molecule

The value of absolute hardness was calculated on the basis of HOMO and LUMO data: ( $\eta = \frac{1}{2} \text{ELUMO} - \text{EHOMO} = 4,54261$ ). Comparing hardness value of different molecules we can conclude that this molecule belongs to soft reagents [18].

Therefore it will especially react with soft alkaline substances nature (alkaline amino acids and unsaturated aromatic compounds). These properties can help to identify the possible mechanism of pharmacological action of this drug.

### CONCLUSION

The quantum-chemical characteristics of acetylsalicylic acid revealed main active centers of the molecule and established that it is a soft reagent that can interact with polar and non-polar parts of cell membranes due to the presence of different fragments in its molecule. Installed quantum-chemical properties of acetylsalicylic acid could be the basis of the molecular mechanisms of its action pharmacological action.

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