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THE COMPUTED THERMODYNAMIC PARAMETERS OF SALICYLIC ACID

BY

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Abstract. Some thermodynamic parameters (free energy, entropy, volume, mass) and QSAR properties of molecules (dipole moment, polarizability, refractivity, energy values HOMO and LUMO) were determined using the HyperChem 8.0.6 program. The computed parameters have a significant role in estimation the therapeutic action in the human body. Quantum-mechanical calculations made by us can provide useful information about stability, reactivity and structure of pharmaco-therapeutic compounds.

Keywords: HyperChem 8.0.6; salicylic acid; QSAR properties; thermodynamic parameters.

1. Introduction

Salicylic acid (or 2-hydroxybenzoic acid), has an -OH group adjacent to a carboxyl group. This colorless and crystalline organic acid, is widely used in organic synthesis and functions as a hormone made from plant which generates a major impact on growth and development of plants, photosynthesis, transpiration, ion uptake and transport (Ştefănescu *et al*., 2004).

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Salicylic acid is the best known chemical compound similar, but not identical, to the active component of aspirin. It is a basic ingredient for multiple products indicated in the treatment of skin diseases (acne, psoriasis, corns, warts, follicular keratosis, dandruff). Salicylic acid salts and esters are known as salicylates. Salicylic acid works as a keratolytic and bacteriostatic agent, opens clogged pores and neutralizes bacteria inside, allowing room for new cell growth (Madan and Levitt, 2014).

Unripe fruits and vegetables are natural sources of salicylic acid, especially blackberries, blueberries, cantaloupes, grapes, figs, kiwi fruits, apricots, green pepper, olives, tomatoes, radish, chicory, mushrooms. Some herbs and spices contain quite high amounts, while meat, poultry, fish, eggs and dairy, legumes, grains, nuts, cereals, only almonds, peanuts, water have significant amounts (Swain *et al*., 1995). Salicylic acid is known for its ability to relieve pain and reduce fever. These medicinal properties have been known since Antiquity and it is used as an anti-inflammatory. In modern medicine, salicylic acid and its derivatives are used as components of some rubefacient products (Tarţău and Mungiu, 2007).

2. Theoretical Background

2.1 Fundamentals of Thermodynamics

Thermodynamics studies the properties of the general macroscopic physical systems and their laws of evolution, taking into account all forms of movement and the heat. The various activities of living organisms means, a suite of conversions of energy, more complex, governed by physical laws of converting one form of energy to another (Lazăr, 2013).

A thermodynamic system is a set of macroscopic size bodies, with specific volume, consisting of molecules and atoms which are in a constinuous movement and disordered by interacting with the external environment as a whole. The system behavior is determined by the internal properties and its interaction with the outside.

From the point of view of the relations with the external environment, systems are of three types: isolated systems (outside of any substance does not change, no energy), closed systems (energy only exterior changes, but not the substance), open systems (exterior changes both substance and energy).

All living organisms are thermodynamically open systems and biological processes are irreversible thermodynamic processes. Steady state of a system is called equilibrium if all the parameters characterizing it does not vary over time and feeds are not caused by external sources that involve transport of the substance. Switching system from initial state to a final state, passing through intermediate states, it is called thermodynamic process or transformation of state (Cristea *et al*., 2006).

Classification of thermodynamic parameters:

a) according to their dependence on the number of particles (N):

− intensive parameters: does not depend on the extent of the system and have the same value in the balance throughout the system (temperature T, pressure p, chemical potential μ);

− extensive parameters: depend on the extent of the system (volume V, mass m, entropy S, the number of particles in the system N). They have the property of being additive.

b) according to their dependence on the position of surrounding bodies:

− external parameters: systems depend on the environment (the intensity of an external field, volume, surface area of a liquid);

− internal parameters: depends on the system considered (pressure, temperature, density, electrical polarization, coefficient of tension of a liquid).

2.2. Molecular Modeling

Molecular modeling is used in many fields such as chemistry, physics, biology, medicine, pharmacy and allows graphical representation of a molecule configuration and calculation of physico-chemical its parameters.

In the pharmacological research, molecular modeling plays an important role. Implemented in various molecular modeling programs, these methods are used to determine properties of drugs found in draft before the actual synthesis.

Molecular modeling methods are numerous, mostly relying on the principles of quantum mechanics and Schrödinger's equation solving (Gottlieb *et al*., 1999) which can be written as:

$$H\,\psi = E\,\psi \tag{1}$$

where: H is the Hamiltonian operator, E and total energy of the system ψ is the wave function of the system (which depends on the coordinates of cores and electrons).

For molecule Schrödinger's equation can be solved only with some approximations. A first approximation was carried out by Born and Oppenheimer. He considers that the motion of cores in a molecule can be separated from that of the electrons, given that the mass of the electron is much smaller than a core.

The most important methods that are used in molecular modeling programs are (Humelnicu, 2003): ab-initio methods, empirical methods, semi-empirical methods. The most important methods semi - empirical: AM1, PM3.

In addition to the methods mentioned above, in recent years there was an expansion of the two methods, the method of molecular dynamics and Monte

Carlo method, which refers to theoretical models that takes an intermediate between theory and experiment, called numerical methods.

Among the most used molecular modeling programs include: Spartan, Gaussian and HyperChem. Most molecular modeling techniques based on the principles of quantum mechanics and Schrödinger's equation solving. Depending on the parameters studied molecular system that are intended to be obtained choosing one or another method.

3. Experimental Part

HyperChem 8.0.6 (www.hyper.com) is a sophisticated molecular modelling program which permits to build and analyze different molecular structures and to determine their physico-chemical properties.

The PM3 method (Parametric Method number 3) from computational chemistry is a semi-empirical method for the quantum calculation of molecular structure. PM3 (Stewart, 1989) uses the Hamiltonian and it is parameterized to reproduce a large number of molecular properties.

In order to generate the spatial chemical structure of each studied molecule, two-dimensional structure of the molecule shall be build step-by-step by drawing. Then hydrogen atoms are automatically added and chemical structure is converted into one 3D.

The first step in getting the main characteristic parameters of molecules is to optimize the molecular structure to obtain a configuration characterized by a minimum free energy. This is usually done using the algorithm Polak - Ribiere with maximum gradient set at 0.001 kcal /(mol*Å).

After optimization is achieved, the theoretical properties of the studied compound are calculated. It aimed to obtaining the value of total energy, the bonding energy, the heat of formation, the energy of frontier orbitals, HOMO (Occupied Molecular Orbital Highest) and LUMO (Lowest Unoccupied Molecular Orbital), the dipole moment, the polarizability and parameters QSAR (Quantitative Structure - Activity Relationship).

4. Results and Discussions

A representation of the molecular structure optimized which contain the values of the reactivity indices is called the reactive molecular diagram. The optimized structure of salicylic acid using the HyperChem 8.0.6. program is represented in Fig. 1.

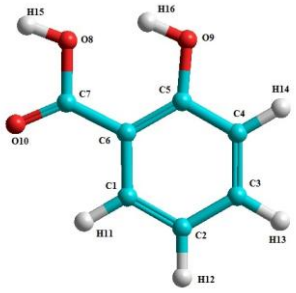

Fig. 1 − The optimized structure of salicylic acid and the denomination of the atoms (colors: red is oxygen, green is carbon, white is hydrogen).

The symmetry (Lide, 2005) is a very powerful tool established on the basis of Hyperchem. Salicylic acid belongs to the CS class symmetry: the molecules of this group are planar and they have only one element of symmetry; the plane of the molecule.

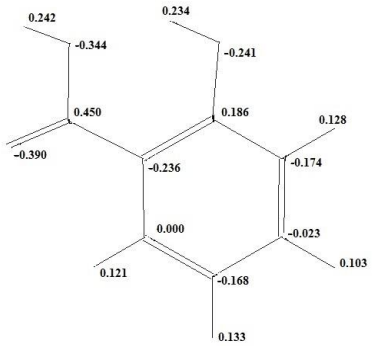

Fig. 2 − The atomic charges computed by HyperChem.

It is seen from Fig. 2 that the negative charges are located near C and O atoms (the highest negative value is -0.390 in O10 atom), and the positive charges are located near H atoms (the highest positive value is 0.450 in C7 atom).

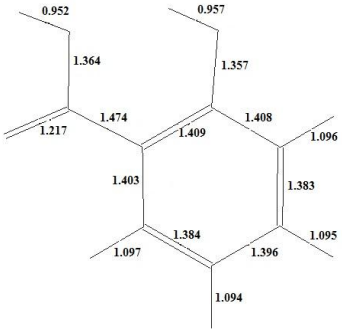

Fig. 3 − The computed bond lengths of molecule (in Å).

The simple bonds C6-C7, C4-C5 are longer than the rest of simple and double bonds than C1-C2, C3-C4 and C7-O10 (Fig. 3). The bond lengths O8-H15 and O9-H16 are the shortest lengths have values below 1 Å.

The energy levels of the molecular orbitals border HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) for salicylic acid molecule give information on the possible electronic transition. They are highlighted in Fig. 4 (color: green is positive value and blue is negative value).

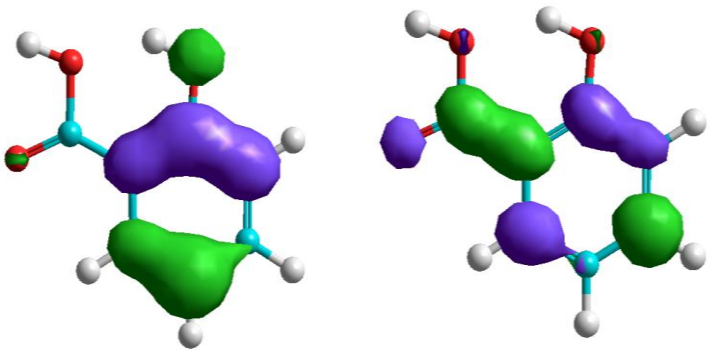

Fig. 4 − The frontier orbitals: a) HOMO and b) LUMO (eV).

The electrophilic attack occurs most likely to the atomic site with a high density of orbital HOMO while nucleophilic attack site is correlated with atomic high-density of orbital LUMO.

The ionization potential (I) and electron affinity (A) can be estimated from the HOMO and LUMO energy values by applying Koopmans theorem (Koopmans, 1934):

$$I = -E_{HOMO} \quad (2)$$

$$A = -E_{LUMO} \quad (3)$$

Table 1

The Values Energies for Salicylic Acid Molecule in the Ground State

Total energy, [kcal/mol]	−41582.53
Heat of formation, [kcal/mol]	−113.079
Binding energy, [kcal/mol]	−1800.599
Electronic energy, [kcal/mol]	−184688.456
Nuclear energy, [kcal/mol]	143105.926
E_{HOMO}, [eV]	−9.456
E_{LUMO}, [eV]	−0.598
$\Delta E = \lvert E_{HOMO} - E_{LUMO} \rvert$, [eV]	8.858

The stability of the studied molecular structure is given by the higher negative values of total energy.

The biological activity of a compound can be estimated on the basis of the energy difference ΔE frontier orbitals. This difference represents the smallest electronic excitation energy which is possible in a molecule.

The surface distribution of molecular electrostatic potential, is an indicator of the specific reactive regions of the molecule.

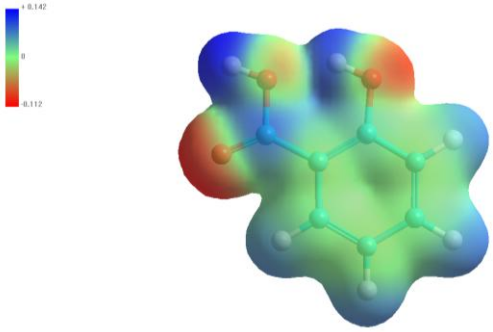

Fig. 5 − 3D geometry of the distribution electrostatic potential.

The three-dimensional geometry of molecular electrostatic potential distribution (Fig. 5), highlights the existence of three regions with increased electronegativity in which oxygen atoms are involved, and that play a role in their coupling to different structures in which ions are positively charged.

Quantitative Structure - Activity Relationships (QSAR) correlate the molecular structure or properties derived from molecular structure with a particular chemical or biochemical activity (Gallegos, 2004). This method is widely used in pharmaceutical chemistry in the environment and in the search for certain properties.

Table 2

QSAR Parameters Calculated by HyperChem

Surface area, [Å^2]	228.00
Volume, [Å^3]	410.17
Mass, [u.a.m]	138.12
Hydration energy, [kcal/mol]	−12.19
Log P	−0.04
Refractivity, [Å^2]	38.56
Dipole moment, [D]	2.17
Polarizability, [Å^3]	13.63

The hydration energy is defined as the energy absorbed when the substance is dissolved in water.

A negative value of log P indicates the hydrophilicity, for the studied compound, that plays an important role in biochemical interactions (Parthasarathi *et al*., 2012).

Hydrophobic drugs tend to be more toxic because, in general, are kept longer, have a wider distribution in the body, are somewhat less selective in their binding to proteins and finally are often extensively metabolized. Therefore ideal distribution coefficient for a drug is usually intermediate (not too hydrophobic nor too hydrophilic).

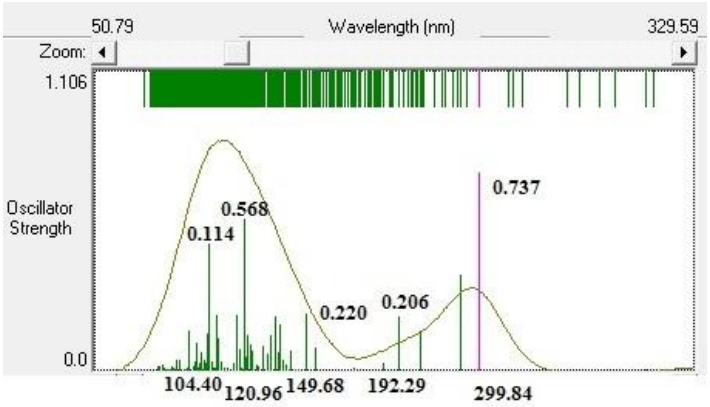

Fig. 8 − The electronic absorbtion spectrum of salicylic acid.

The highest peak corresponding to the absorption bands is at 299.84 nm and it has the oscillator strength with the value of 0.737 (Fig. 8).

The thermodynamic parameters calculated with HyperChem 8.0.6. at too temperatures, do not show big differences (Table 3).

Table 3

Thermodynamic Parameters Determinated Using HyperChem

Temperature	298.15 K	0 K
Entropy, [kcal/mol/deg]	0.08951	0.00509
Free energy, [kcal/mol]	−41528.1	−41582.5
Heat capacity, [kcal/mol/deg]	0.03171	0.00596
Internal energy, [kcal/mol]	−41501.4	−41582.5

In the Kelvin scale the absolute zero temperature (0 K) is the lowest possible and in substance no more energy as heat. The normal room temperature is 298.15 K equivalent to 25°C. In the vicinity of absolute zero (zero Kelvin), the entropy of a thermodynamic system is approximately constant.

The internal energy is a function of the state which represents the total energy of the thermodynamic system that includes the energy for all forms of motion and interaction between the particles of the system (the energy of translational motion, rotation of the molecules, the energy of oscillation of the atoms in the molecules).

From Table 4 shows that the reaction enthalpy (ΔHf and ΔHc) has a negative value such as the reaction enthalpy of a substance is less, the substance is more stable.

Table 4
Condensed Phase Thermochemistry Data -Solid
(http://en.wikipedia.org)

Density, [g/cm^3]	1.443 (20°C)
Pressure, [mPa]	10.93
Acidity, [pKa]	2.97 (25°C)
Melting point, [K]	431.8
Heat capacity, [J/mol*K]	160.9
Entropy, [J/mol*K]	172.4
Enthalpy of formation, [kJ/mol]	−582.45
Enthalpy of combution, [kJ/mol]	−3029.6

The acid dissociation constant pKa, for an acid is a direct consequence of the underlying thermodynamics of the dissociation reaction. A high value of pKa indicates a small degree of disociation at a given pH. The compounds which have pKa value between −2 and 12, are acids. In this case (Table 4) salicylic acid molecule is a weak acid.

5. Conclusions

1. The semi-empirical PM3 method of the program HyperChem 8.0.6. was used to characterize salicylic acid.

2. Were determined the physico-chemical parameters specific to each molecules: the bond lengths, the atomic charges, the formation energy, the binding energy, the molecular descriptors QSAR, the mass, the volume, the dipole moment, the polarizability, the total energy and the energies border).

3. Using molecular modeling programs one can be determined the vibration and electronic spectra of the compound studied. Obtaining by modeling the distribution of molecular electrostatic potential reactive sites led to the identification of the molecules studied.

4. Using some of the program options one could determine some thermodynamic parameters (entropy, enthalpy, free energy).

5. Even if the values obtained by these theoretical methods are slightly different from those experimental they can provide an overview on the compound studied by helping researchers to make "adjustments" required to create a drug as safely and effectively.

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REFERENCES

Cristea M., Popov D., Barvinschi F., Damian I., Luminosu I., Zaharie I., *Fizic*a. *Elemente fundamentale*, Edit. Politehnica, Timişoara, 2006.

Gallegos S.A., *Molecular Quantum Similarities in QSAR: Applications in Computer – Aided Molecular Design*, Ph. D. Thesis, Universitat de Girona, 2004.

Gottlieb I., Dariescu M.A., Dariescu C., *Mecanică cuantică*, Edit. Bit, 1999.

http://en.wikipedia.org/wiki/Salicylic_acid, accessed may 2015.

Humelnicu I., *Elemente de chimie teoretică*, Edit. Tehnopress, Iaşi, 2003.

Koopmans T., *Uber die Zuordnung von Wellenfunktionen und Eigenwerten zu den Einzelnen Elektronen Eines Atoms*, Physica (Elsevier), **1**, *1–6*, 104–113, 1934.

Lazăr I., *Elemente de termodinamică biologică* – curs 2013, http://upmf.ub.ro/Ilazar/Cap5termo.pdf, acccesed may 2015.

Lide R.D., *Handbook of Chemistry and Physics*, Boca Raton, Florida, CRC Press, 2005.

Madan R.K., Levitt J., *A Review of Toxicity from Topical Salicylic Acid Preparations*, J. Am. Acad. Dermatol., **70**, *4*, 788–792, 2014.

Parthasarathi R., Subramanian V., Roy D.R., Chattaraj P.K., *Bioorganic & Medicinal Chemistry*, In Advanced Methods and Applications in Chemoinformatics: Research Progress and New Applications, E.A. Castro, A.K. Haghi (Eds.), 2012.

Stewart J.J.P., *Optimization of Parameters for Semi-Empirical Methods I-Method*, Computational Chemistry, **10**, *2*, 209, 1989.

Swain A.R., Dutton S.P., Truswell A.S., *Salicylates in Foods*, Journal of the American Dietetic Association, **85**, *8*, 1995.

Ştefănescu E., Dorneanu M., Rogut O., Tătărîngă G., *Chimie organică*, Vol. **2**, Edit. Cermi, Iaşi, 2004.

Tarţău L., Mungiu O.C., *Analgezice şi antiinflamatoare nesteroidiene*, Ghid Practic, Iaşi, Edit. Dan, 2007.

www.hyper.com (HyperChem, Molecular Visualisation and Simulation Program Package, Hypercube, Gainsville, Fl, 32601).

PARAMETRII TERMODINAMICI CALCULAŢI AI ACIDULUI SALICILIC

(Rezumat)

Utilizând programul HyperChem 8.0.6. au fost determinati unii parametri termodinamici (energia liberă, entropia, volum, masa) şi unele proprietăţile QSAR ale moleculei (moment de dipol, polarizabilitate, refractivitate, valorile energiilor HOMO şi LUMO). Parametrii obţinuţi au un rol important în estimarea acţiunii terapeutice în organism. Calculele cuanto-mecanice realizate de noi pot aduce informaţii utile despre stabilitatea, reactivitatea sau structura compușilor farmaco-terapeutici.