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QUANTUM MECHANICAL CHARACTERIZATION OF THYMOL BLUE

BY

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Abstract. Thymol blue (TB) is an important acid basic color indicator used in various applications. Its parameters in the ground state are very important for applications, so a comparative study of physical parameters of TB was realized by three methods from Spartan 14, in order to establish the more convenient method to be used in our spectral applications.

After the geometrical optimization, the TB main parameters like length of the chemical bonds, charges near the component atoms, the dihedral angles, dipole moments, polarizability of this molecule were computed.

Keywords: thymol blue; atomic charges; dipole moment; polarizability.

1. Introduction

The molecule of 4-[3-(4-hydroxy-2-methyl-5-propan-2-ylphenyl)-1,1-dioxobenzo[c]oxathiol-3-yl]-5-methyl-2-propan-2-ylphenol also named thymol blue (TB) (Balderas-Hernandez, 2007) is formed by three benzene rings bonded to a central carbon, with a sulphonic group attached to one of the rings and keto-enol groups bonded to other rings (see the structural formula displayed in Fig. 1).

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The chemical formula of TB is $C_{27}H_{30}O_5S$, its molar mass is 466.592 g/mol, its melting point is 221-224°C and its flash point is 36°C. TB is a brownish-green or reddish-brown crystalline powder, insoluble in water but soluble in alcohol and dilute alkali solutions.

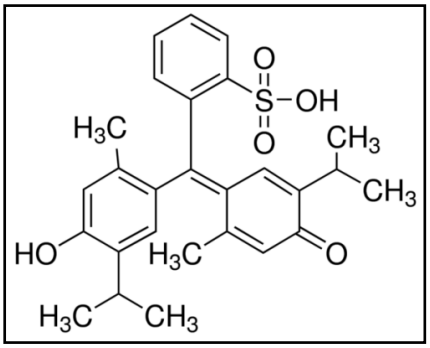


Fig. 1 – Structural formula of TB.

TB is an acid-base indicator from the family of sulphonephtalein, which has two color transition intervals, passing from red to yellow at pH 1.2 – 2.8 and from yellow to blue at pH 8.0 – 9.6 (Pub. Chem. Database https: pubchem ncbi.nlm.nih.gov, access 2018).

The purpose of this paper is to carry out a quantum-chemical study of the TB molecule to establish its molecular parameters.

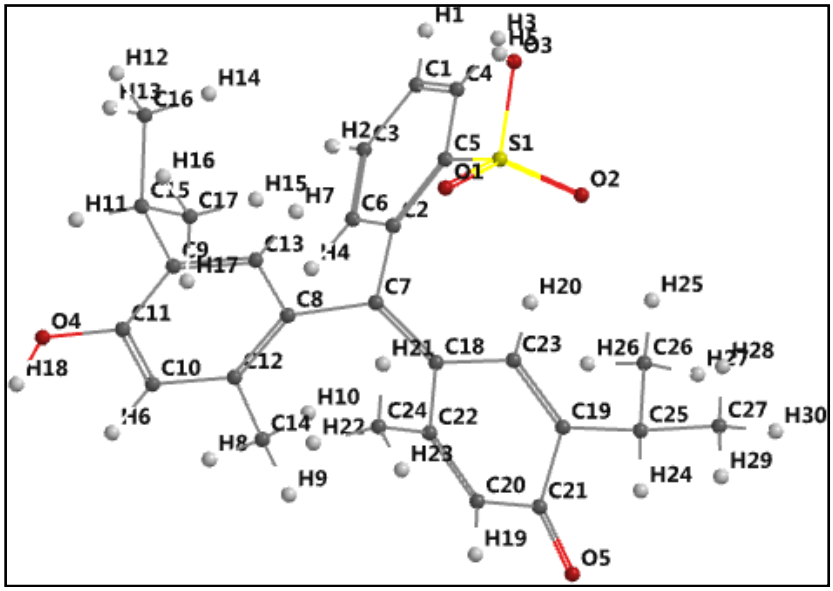


Fig. 2 – Skeletal formula with labeled atoms (Hartree-Fock Method).

Fig. 2 shows the TB skeletal formula. The atoms are labeled to be able to subsequently express the lengths of chemical bonds between the atoms of the molecule as well as the dihedral angles.

2. Simulation Details

The Spartan program provides the access to a number of modern computational methods (molecular mechanics, semi-empirical and Hartree-Fock molecular orbital models) and correlated models including density functional models and Møller-Plesset models. Spartan program offers the access to several spectral quantities, such as infrared spectra, Raman spectra, NMR spectra and UV/visible spectra. Experimental spectra from public online databases may be accessed and overlay onto calculated spectra

Spartan provides graphical tools to improve the interpretation of the results of calculations. Molecular orbitals, electron and spin densities, local ionization potentials and electrostatic potentials can be displayed as surfaces, slices and property maps. Spartan can display some important graphical quantities resulting from quantum chemical calculations: the electron density (shows how much space a molecule occupies), the bond density (reveals chemical bonds) and key molecular orbitals (that provide information about chemical reactivity) (Young, 2001).

The molecular mechanics module calculates the energy, equilibrium geometry and vibrational frequencies. The semi-empirical module calculates the heat of formation, wavefunction, equilibrium and transition-state geometries and vibrational frequencies. The Hartree-Fock module calculates the energy and wave function, equilibrium and transition-state geometries and vibrational frequencies. The density functional module calculates the energy and wave function, equilibrium and transition-state geometries and vibrational frequencies.

Semi-empirical models are the simplest methods based on quantum mechanics. They are applicable to molecules containing 100 - 200 atoms and provide geometries in good accord with experimental structures. Semi-empirical models are suitable for evaluation of properties that depend solely on geometry (such as polar surface area). Semi-empirical models are available for the calculation of IR spectra but do not provide a very good account. They are not available for the calculation of Raman, NMR or UV/visible spectra.

Hartree-Fock models follow from the Schrödinger equation by requiring that the electrons be independent particles (the Hartree-Fock approximation). The motions of electrons in molecules (molecular orbitals) are approximated by a sum of the motions of electrons in atoms (atomic orbitals). Hartree-Fock models are available for the calculation of IR, Raman, NMR and UV/visible spectra. IR (Raman) frequencies are typically overestimated by 10-15% and NMR chemical shifts show large variations from experimental values. Density functional models are to be preferred (Spartan'14 for Windows, 2014).

3. Computational Results

Fig. 3 illustrates the chemical structure of the thymol blue molecule, optimized by Spartan'14 program, using Hartree-Fock method. The arrow indicates the orientation of the dipole moment, a vectorial physical quantity that is a measure of the separation of the electrical charges of a molecule.

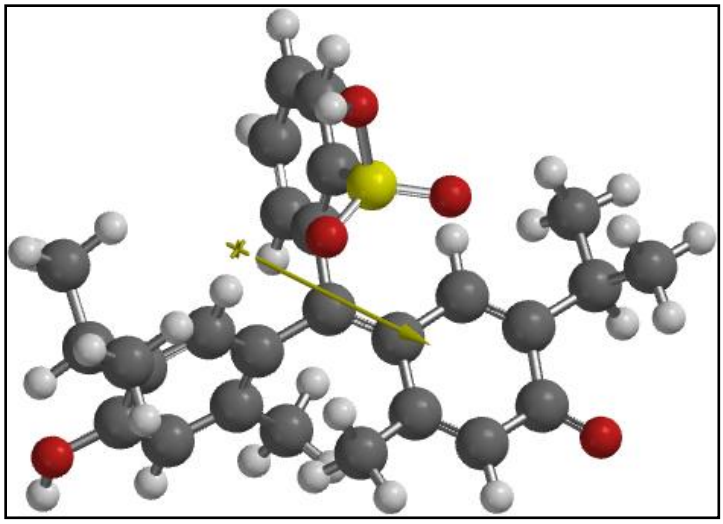


Fig. 3 – Chemical structure of thymol blue, optimized by Spartan'14 program (C – grey, S – yellow, O – red, H – white), Hartree-Fock Method.

The properties of thymol blue molecule were computed using three different methods offered by Spartan program: Hartree-Fock models, semi-empirical models and molecular mechanics models. The molecular parameters obtained in quantum-chemical analysis are listed in Table 1. One can see that the three methods give appropriate values for some information such as weight, number of tautomers, area, volume, polar surface area, ovality, log P, polarizability, hydrogen bond donor count and hydrogen bond acceptor count. The values obtained for energy, energy (aq.), solvation energy, E_{HOMO}, E_{LUMO}, dipole moment and conformers are different.

The charge distribution in a molecule can provide critical insight into its physical and chemical properties. Chemical reactions are also associated with charged sites, and the most highly-charged molecule, or the most highly-charged site in a molecule, is often the most reactive. The sign of the charge is also important. Positively-charged sites in a molecule invite attack by bases and nucleophiles, while negatively-charged sites are usually targeted by acids and electrophiles (http://www.quimica.urv.es/~bo/).

One way to describe a molecule's charge distribution is to give a numerical atomic charge for each atom. A particularly simple and familiar recipe yields so-called formal charges directly from Lewis structures.

Table 1
Molecular Properties of Thymol Blue Molecule, Computed with Spartan'14 Program

Method of Spartan'14	Hartree-Fock Models	Semi-Empirical PM3 Models	Molecular Mechanics Models
Molecule Properties			
Formula	$C_{27}H_{30}O_5S$	$C_{27}H_{30}O_5S$	$C_{27}H_{30}O_5S$
Weight	466.598 amu	466.598 amu	466.598 amu
Energy	-1801.97521 au	-589.36 kJ/mol	201.78 kJ/mol
Energy (aq)	-1802.00114 au	-660.64 kJ/mol	110.14 kJ/mol
Solvation E	-68.08 kJ/mol	-71.28 kJ/mol	-91.64 kJ/mol
E HOMO	-8.11 eV	-9.06 eV	-
E LUMO	1.35 eV	-1.08 eV	-
Dipole Moment	7.88 debye	5.31 debye	6.27 debye
Tautomers	5	5	5
Conformers	384	768	768
Quantitative Structure-Activity Relationship (QSAR)			
Area	476.90 $Å^2$	484.73 $Å^2$	489.68 $Å^2$
Volume	472.19 $Å^3$	475.34 $Å^3$	478.23 $Å^3$
PSA	83.390 $Å^2$	88.354 $Å^2$	86.359 $Å^2$
Ovality	1.63	1.65	1.66
Log P	2.54	2.54	2.54
Polarizability	77.45 $Å^3$	78.05 $Å^3$	-
HBD Count	1	1	1
HBA Count	2	2	2
Temperature	298.15 K	298.15 K	298.15 K

Unfortunately, formal charges are arbitrary. In fact, all methods for assigning charge are arbitrary and necessarily bias the calculated charges in one way or another. This includes methods based on quantum mechanics. Mulliken Charge, Electrostatic Charge and Natural Charge for thymol blue molecule, computed using Hartree-Fock and Semi- Empirical PM3 methods of Spartan program, are displayed in Figs. 4-9. The most used charge partitioning scheme are Mulliken Populations which assign charge to an atomic center on the basis of the total electron density in basis functions located on that center. Natural Population Analysis (NPA) is an algorithm that involves partitioning the charge into atomic orbitals on each center, constructed by dividing the electron density matrix into sub-blocks with the appropriate symmetry. NPA is much less basis set dependent than Mulliken Populations (Leach, 2001; Manz and Gabaldon-Limas, 2016; Reed *et al*., 1985).

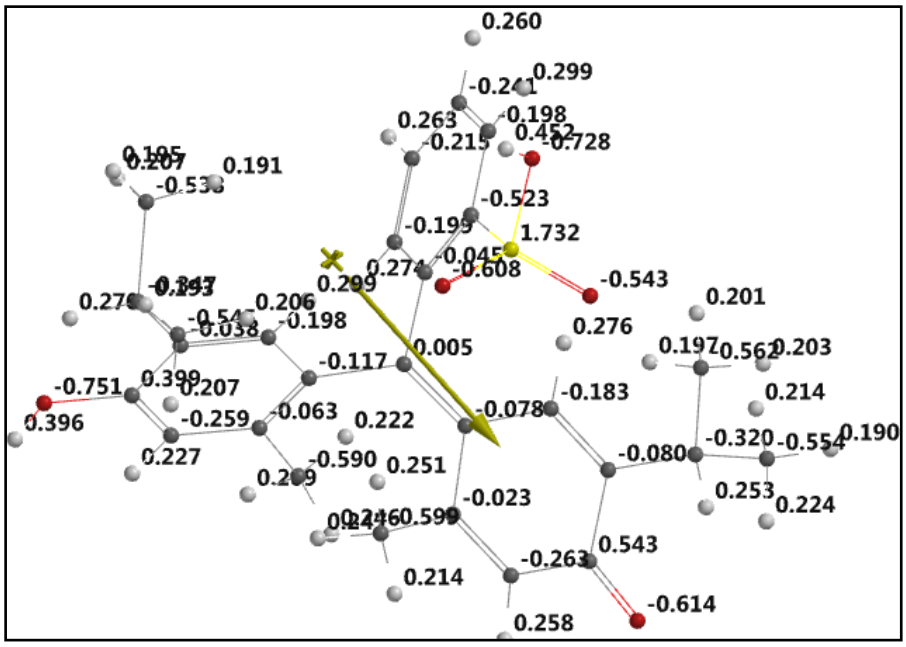


Fig. 4 – Mulliken Charge of molecule, using Hartree-Fock Method of Spartan.

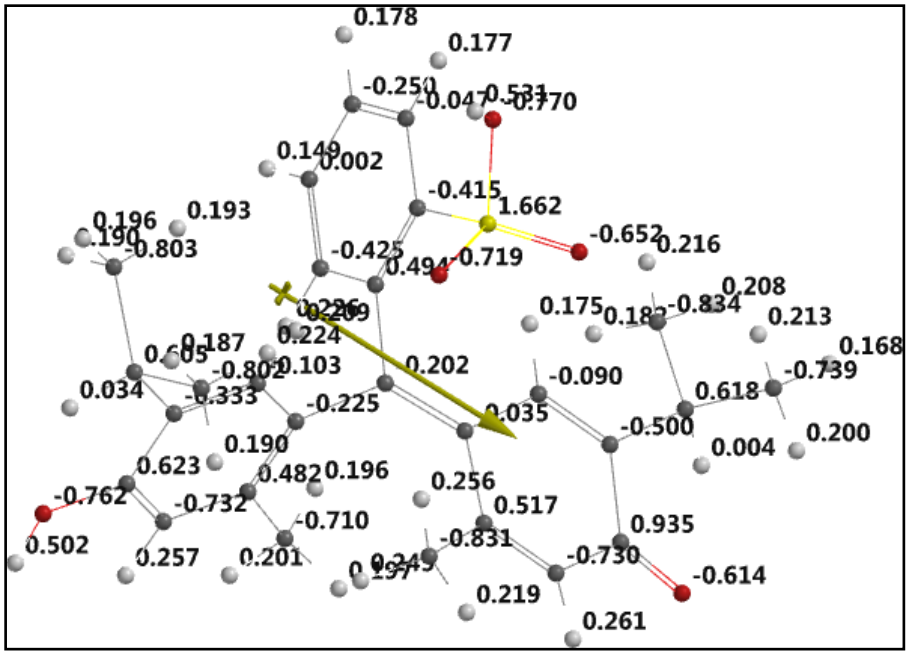


Fig. 5 – Electrostatic Charge of molecule, using Hartree-Fock Method of Spartan.

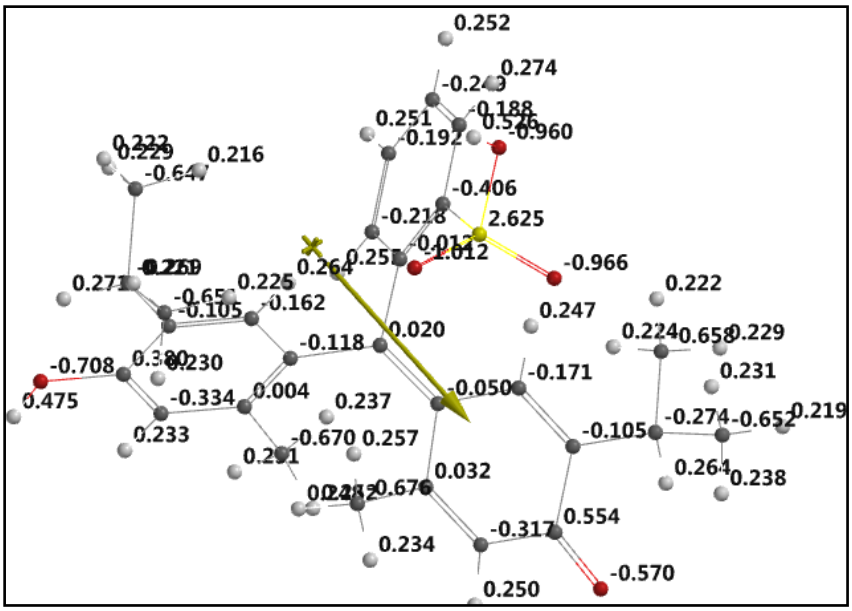


Fig. 6 – Natural Charge of molecule, using Hartree-Fock Method of Spartan.

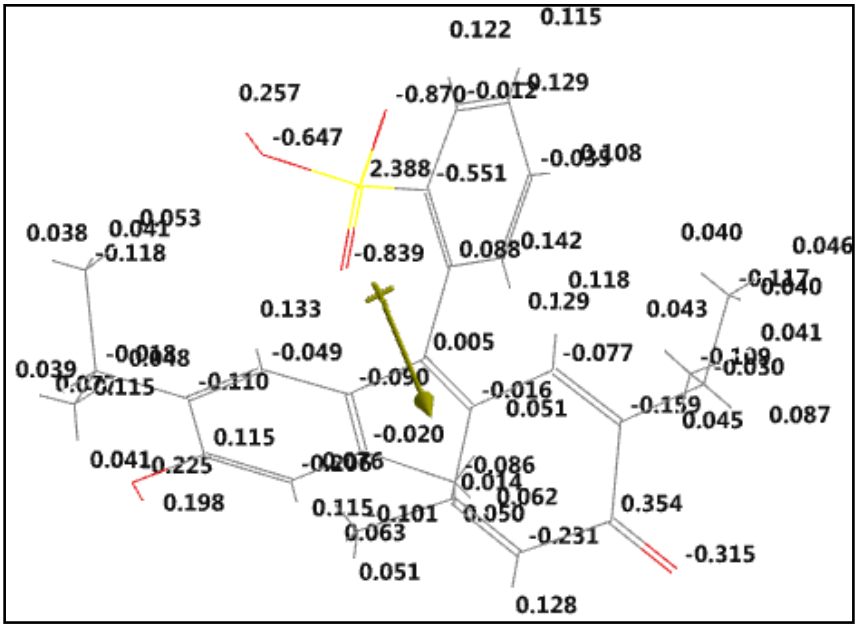


Fig. 7 – Mulliken Charge of thymol blue molecule, using Semi-Empirical PM3 Method of Spartan.

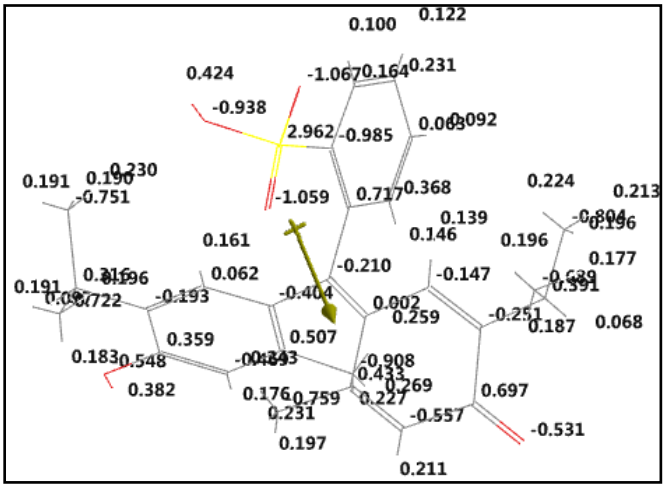


Fig. 8 – Electrostatic Charge of of thymol blue molecule molecule, using Semi-Empirical PM3 Method of Spartan.

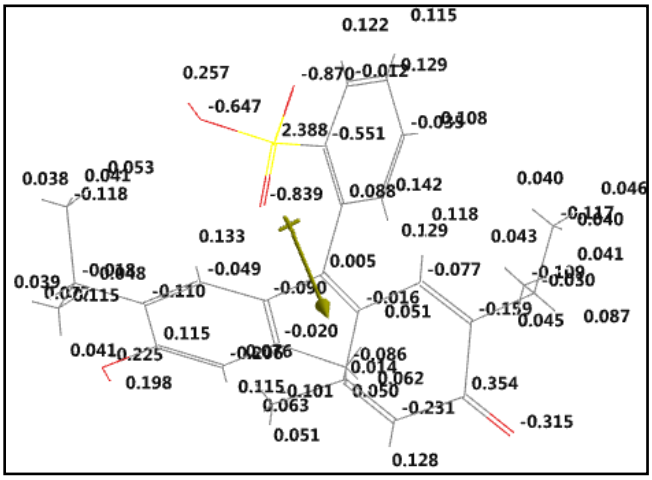


Fig. 9 – Natural Charge of of thymol blue molecule molecule, using Semi-Empirical PM3 Method of Spartan.

The Spartan program can be used to calculate the lengths of chemical bonds between the atoms of the molecule, the angles between these bonds and dihedral angles. The lengths of chemical bonds are listed in Table 2. As can it be seen, the longest chemical bonds are C5-S1 (1.777 Å), S1-O3 (1.616 Å), C25-C26 (1.534 Å), C15-C16, C15-C17, C25-C27 (1.532 Å), while the shortest chemical bonds are O4-H18 (0.971 Å), O3-H5 (0.981 Å), C23-H20 (1.083 Å), C20-H19 (1.084 Å), C10-H6, C13-H7 (1.087 Å), C1-H1, C3-H2, C6-H4 (1.088 Å), C4-H3 (1.089 Å).

Table 2
Lengths of Chemical Bonds of Thymol Blue Molecule, Computed by Hartree-Fock Method of Spartan Program

Chemical bond	Bond length (Å)	Chemical bond	Bond Length (Å)	Chemical bond	Bond Length (Å)	Chemical bond	Bond Length (Å)
C1=C4	1.393	C7-C8	1.503	C15-H11	1.096	C23-H20	1.083
C4-C5	1.406	C8-C13	1.407	C15-C16	1.532	C22-C24	1.506
C5=C2	1.409	C13=C9	1.407	C16-H12	1.096	C24-H21	1.095
C2-C6	1.408	C9-C11	1.396	C16-H13	1.096	C24-H22	1.092
C6=C3	1.397	C11=C10	1.396	C16-H14	1.095	C24-H23	1.097
C3-C1	1.391	C10-C12	1.406	C15-C17	1.532	C20-H19	1.084
C1-H1	1.088	C12=C8	1.413	C17-H15	1.096	C21=O5	1.226
C3-H2	1.088	C13-H7	1.087	C17-H16	1.095	C19-C25	1.519
C6-H4	1.088	C10-H6	1.087	C17-H17	1.096	C25-H24	1.098
C4-H3	1.089	C11-O4	1.367	C7=C18	1.372	C25-C26	1.534
C5-S1	1.777	O4-H18	0.971	C18-C22	1.485	C26-H25	1.096
S1-O3	1.616	C12-C14	1.506	C22=C20	1.345	C26-H26	1.096
S1-O2	1.445	C14-H8	1.096	C20-C21	1.478	C26-H27	1.096
O3-H5	0.981	C14-H9	1.094	C21-C19	1.494	C25-C27	1.532
S1=O1	1.445	C14-H10	1.093	C19=C23	1.346	C27-H28	1.096
`C2-C7	1.503	C9-C15	1.521	C23-C18	1.478	C27-H29	1.095
						C27-H30	1.095

The measure of some dihedral angles is listed in Table 3.

Table 3
The Measure of Some Dihedral Angles for Thymol Blue Molecule, Computed by Hartree-Fock Method of Spartan Program

Dihedral angle	Measure	Dihedral angle	Measure
(C5,C2,C6,C7)	178.77°	(C5,S1,O1,O2)	128.87°
(C6,C2,C7,C8)	63.77°	(C2,C7,C8,C18)	173.63°
(C2,C7,C8,C13)	68.11°	(C2,C7,C18,C22)	169.19°
(C18,C7,C8,C12)	26.60°	(C2,C7, C18,C23)	11.35°
(C7,C8,C12,C10)	178.98°	(C23,C18,C22,C20)	20.39°
(C12,C10,C11,O4)	179.89°	C18,C23,C19,C21)	2.66°
(C13,C9,C11,O4)	0.92°	(C19,C21,C20,C22)	14.53°
(C9,C11,C10,O4)	179.99°	(C18,C22,C20,C24)	173.35°
(C13,C9,C15,C16)	60.77°	(C19,C21,C20,O5)	1.71°
(C9,C15,C16,C17)	124.68°	(C23,C19,C21,C25)	179.06°
(C2,C5,C4,S1)	0.22°	(C23,C19,C25,C26)	9.13°
(C6,C2,C5,S1)	0.33°	(C25,C19,C21,O5)	171.13°
(C5,S1,O1,O3)	111.71°	(C19,C25,C26,C27)	127.23°
(C5,S1,O2,O3)	112.23°	(C21,C19,C25,C27)	78.55°

HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) frontier orbitals (Miller, 2004) for thymol blue molecule are displayed in Fig. 10 (*a*, *b*) and Fig. 11 (*a*, *b*), using Hartree-Fock method of Spartan and Semi-Empirical PM3 method of Spartan, respectively. The energy difference between the HOMO and LUMO is generally the lowest energy electronic excitation that is possible in a molecule. The energy of the HOMO-LUMO gap offers information about what wavelengths are absorbed by the compounds (Holtjie *et al*., 2003).

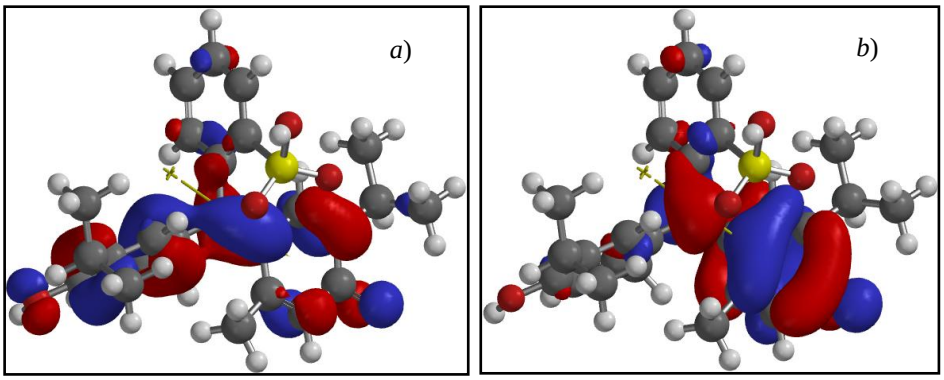


Fig. 10 – HOMO (*a*) and LUMO (*b*) surfaces for thymol blue molecule, obtained with Hartree-Fock method.

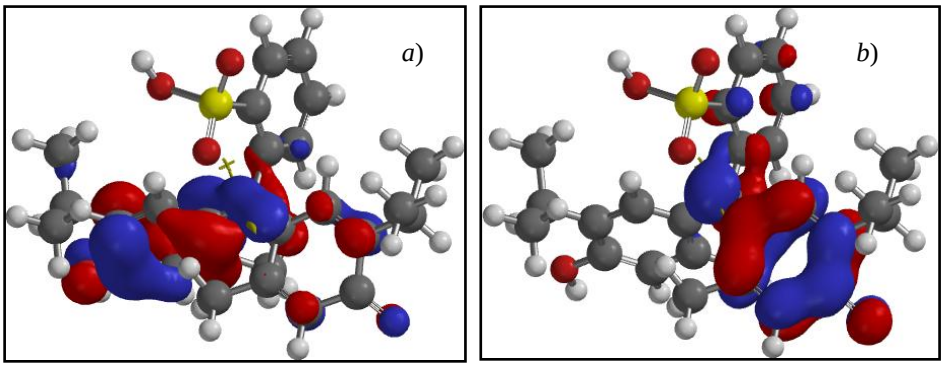


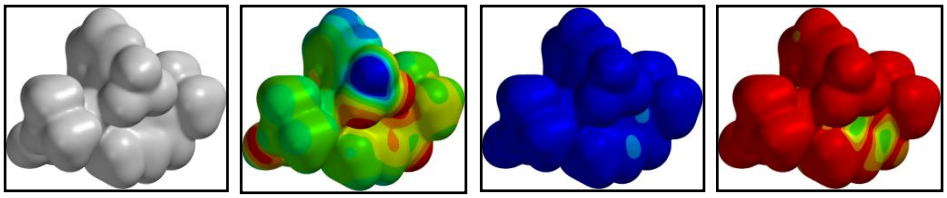
Fig. 11 – HOMO (*a*) and LUMO (*b*) surfaces for thymol blue molecule, obtained with Semi-Empirical PM3 method.

The electron density surface depict overall molecular size and shape of the molecule. Electrostatic potential maps illustrate the space distribution of the electrical charge of a molecule (Shusterman and Shusterman, 1997).

Knowing the distribution of the electrical charge of a molecule, one can determine how the molecule interacts with other molecules (Hehre *et al*., 1998;

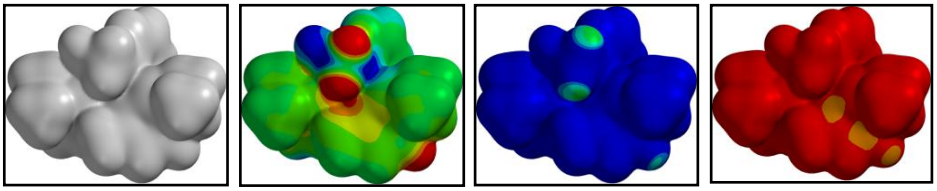
Hehre, 2003). The local ionization potential provides a measure of the relative ease of electron removal ("ionization") at any location around a molecule. In |LUMO| map, the absolute value of the lowest-unoccupied molecular orbital is mapped onto an electron density surface. This offers information about where an electron pair (a nucleophile) might attack. The LUMO map show the regions of a molecule that are are most electron deficient, and therefore, the regions that may be subject to nucleophilic attack (Schlick, 2002).

Density surface, electrostatic potential map, local ionization potential map and |LUMO| map, obtained using the two different methods of Spartan, are displayed in Fig. 12 (*a-d*) and Fig. 13 (*a-d*), respectively.



a) *b*) *c*) *d*)

Fig. 12 – Density surface (*a*), electrostatic potential map (*b*), local ionization potential map (*c*) and |LUMO| map (*d*) with Hartree-Fock method.



a) *b*) *c*) *d*)

Fig. 13 – Density surface (*a*), electrostatic potential map (*b*), local ionization potential map (*c*) and |LUMO| map (*d*) with Semi-Empirical PM3 method.

4. Conclusions

Some differences between the computed molecular parameters using three methods from Spartan 14 are observable, but the order of magnitude and sign of the charges values, of the electron density, electron gap and of the other molecular characteristics is kept in the computational results. The three methods of Spartan show similar more reactive zones of TB molecule both for nucleophilic or electrophylic attack. The sign obtained for logP is the same in all three methods, emphasizing the hydrophilicity of TB.

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CARACTERIZAREA CUANTO-MECANICĂ A TIMOLULUI BLUE

(Rezumat)

Timol blue (TB) este un important indicator acido-bazic de culoare utilizat în diverse aplicații. Parametrii acestuia în starea fundamentală sunt foarte importanți, așa încât am realizat un studiu comparativ al parametrilor fizici ai TB cu trei metode diferite din programele Spartan 14, în vederea stabilirii celei mai bune metode pentru a fi utilizată în viitoarele noastre aplicații spectrale.

După optimizarea geometrică, principalii parametri ai TB, cum sunt lungimea legăturilor chimice, sarcinile electrice din vecinătatea atomilor componenți, unghiurile diedre, momentul de dipol și polarizabilitatea moleculară, au fost calculați.