

Tautomeric Equilibrium Modeling: Stability and Reactivity of Benzothiazole and Derivatives

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Abstract

Benzothiazoles are organic compounds with multiple biological activities. Due to their biological interests, these are synthesized on a large scale at the industrial level and used in various fields. Their release into waters causes environmental problems which leads to public health problems. Finding solution which can help for their degradation become necessary.

That is the reason why a theoretical study of the reactivity of five benzothiazole derivatives has been initiated in order to understand some aspect of their biodegradation.

The calculations were carried out in gaseous and aqueous phase with B3LYP functional associated with bases 6-311G(d) and 6-31+G(d).

The results revealed that the thione tautomer of the MBT derivative is more stable than the thiol form. These results are in agreement with previous experimental work which showed that the thiones forms in MBT metal complexes are the most stable. Moreover, the study of the reactivity based on the computation of the global indices of reactivity reveals that the benzothiazoles BT, OBT and MBT are the most reactive. The most electrophilic is BT and the least electrophilic is MTBT. In addition, the thermodynamic parameters and the energy barriers predict a possibility of coexistence of tautomers of one of OBT derivative. Fukui dual descriptors have shown that the carbon C² of BT is the most electrophilic. In substituted derivatives, it is the C⁶ carbon that is the most electrophilic. N³ nitrogen remains the most nucleophilic site in all the studied molecules.

Keywords: Benzothiazoles, DFT / B3LYP, tautomeric equilibrium, Fukui indices, tautomers

1. Introduction

Benzothiazole derivatives have a wide range of biological activities such as anticancer, analgesic, anti-inflammatory, antimicrobial, antimalarial, anticonvulsant (Venkatesh & Pandeya, 2009) (Pritesh, Jagath et al., 2012) (Nadeem, Arpana et al., 2007) (Mishra, Gautam et al., 2010) (Hout, Azas et al., 2004). They are also used as fungicides (Helena, Tomáš et al., 1993) (Drotar, Burton et al., 1987). Some of them are vulcanizing agents in the pneumatic industry (Herrero, Borrull et al., 2014). They are used in large quantities in very different fields such as agriculture, detergent industry, paper industry, automotive industry and pharmaceutical industry (Herrero, Borrull et al., 2013) (Herrero, Borrull et al., 2014) (Speltini, Sturini et al., 2016) (Markiewicz, Björklund et al., 2017) Due to their varied applications, they are synthesized on a large scale at the industrial level. However, these high production of chemicals constitute a real environmental problem (Herrero, Borrull et al., 2014). They end up in the environment through several processes. Their discharge into runoff is likely to affect the functioning of ecosystems, posing a major environmental and public health problem.

Studies have shown that most benzothiazole derivatives are classified as emerging organic pollutants (Hogenboom, Van & De Voogt, 2009) (Richardson & Ternes, 2011) (Richardson, 2012) (Farré Pérez et al., 2008). In the search for a solution to the problem of environmental pollution caused by this type of pollutant, most of the work is focused on the degradation of these pollutants (Li F., Li X. & Hou, 2004) (De Wever & Verachttert, 1997) (Lagarde, Puetz et al., 2006) (Poulain, Mailhot et al., 2003) (Printz, Burauel & Fuhr, 1995). Certain derivatives such as 2-mercaptobenzothiazole (MBT) and 2-hydroxybenzothiazole (OBT) have been shown to be difficult to biodegrade (Lagarde, Puetz et al., 2006) ((Printz, Burauel & Fuhr, 1995).

A theoretical study of the reactivity of these molecules is therefore necessary to help better understand the biodegradation process of these pollutants. For our study, we are interested in five benzothiazoles namely benzothiazole, 2-aminobenzothiazole, 2-hydroxybenzothiazole, 2-mercaptobenzothiazole and 2-methylthiobenzothiazole (Figure 1). Interest for these benzothiazoles is motivated by the fact that these derivatives are commonly found in wastewater (De Wever & Verachtert, 1997) (Reemtsma, Fiehn et al., 1995) (Kloepfer, Gnirss et al., 2004). Also, studies have shown that derivatives studied to be among a family of benzothiazoles which are most toxic according to the Microtox test (Andrei, 2006). In addition, MBT has a carcinogenic and dermatological allergenic activity (De Wever & Verachtert, 1994) (Adams & Warshaw, 2006) (Gold, Slone et al., 1993) (Whittaker, Gebhart et al., 2004). This work aims to study the reactivity of these derivatives in gas and aqueous phase. Precisely we did a theoretical calculation of thermodynamic energies and reactivity parameters. Benzothiazole (BT) mesomers are proposed from Fukui indices calculations. The tautomeric equilibrium and the relative stability of the tautomers of the ABT, OBT and MBT derivatives are also analyzed.

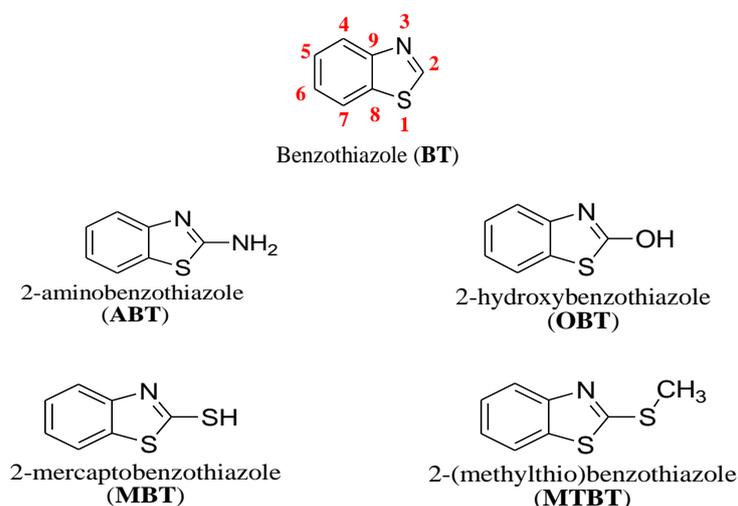


Figure 1. Structures of Benzothiazole Derivatives

2. Material and Methods

2.1 Calculation Level

To carry out this work, the Density Functional Theory (DFT) method (Becke, 1997) (Bauernschmitt & Ahlrichs, 1996) with the functional B3LYP (Lee, Yang & Parr, 1988) (Becke, 1993) associated with the bases 6-311G (d) and 6-31G+(d, p) was used. The calculation software used is the Gaussian 09 (Frisch et al., 2013) quantum chemistry software. Thermodynamic energies were calculated from the ground state geometry of the optimized molecule at the B3LYP/6-311G(d) theory level. The benzothiazoles studied being commonly found in the aquatic environment, the calculations were carried out as well in gas phase as in aqueous phase at the temperature of 298.15 Kelvin and the pressure of 1 atmosphere (1 atm). The Polarized Continuum Model (PCM) (Cancès, Mennucci, Tomasi, 1997) is taken as a solvation model. The optimization of molecular geometries is followed by calculations of vibration frequencies at the same level of theory. The proton affinities (PA) and Fukui functions were determined from optimized geometry at B3LYP/6-31+G(d) level in order to take into account long-range interactions (Van der Waals forces), in the case of charged molecules (anion and cation) (Jensen, 2001) (Lehtola, 2015).

2.2 Reaction Thermodynamic Parameters

Understanding the contributions of variations in energy to internal energy between reagents and products helps to characterize energetically a chemical reaction. The energy characterization of a quantity X is given by the relation below:

$$\Delta_r X = \sum X(\text{products}) - \sum X(\text{reactants}) \quad (1)$$

The thermodynamic parameters considered in this study are the reaction enthalpy ($\Delta_r H$), free reaction enthalpy ($\Delta_r G$), equilibrium constant and rate constant. These parameters are calculated from the following relationships:

$$\Delta_r G = \sum \Delta_f G (\text{Products}) - \sum \Delta_f G (\text{Reactants}) \quad (2)$$

$$\Delta_r H = \sum \Delta_f H (\text{Products}) - \sum \Delta_f H (\text{Reactants}) \quad (3)$$

$$k = \frac{K_B T}{h} \exp\left(\frac{\Delta G^\ddagger}{RT}\right) \quad (4)$$

$$\Delta G^\ddagger = \Delta G(\text{TS}) - \Delta G(\text{reactant}) \quad (5)$$

$$K_{eq} = \exp^{(-\Delta_r G(T)/RT)} \quad (6)$$

ΔG^\ddagger is the free enthalpy of activation and $\Delta G(\text{TS})$, the free enthalpy of the transition state. In this work, the equilibrium constants are determined at 298.15 K:

2.3 Global and Local Indices Derived from Conceptual DFT

Frontier Molecular Orbital Theory (FMO) is used to characterize the chemical reactivity of a compound (Fujimoto & Fukui, 1972). This theory foretells the excitation properties of a molecule. As a result, it constitutes quantum parameters for the determination of molecular reactivity (Michel, Jean-François et al., 2005) (Aihara, 1999). The smaller the energy gap between the energies of the HOMO and LUMO orbitals, the more reactive the molecule is. The condensed Fukui functions are obtained using the procedure based on the finite difference method (Christophe, André Alejandro, 2005) (Bultinck, Dorien et al., 2011) (Melin, Ayers & Ortiz, 2007). The different values of the local descriptors are calculated from equations (7) and (8).

$$f_k^+ = q_k(N+1) - q_k(N) \quad (7)$$

$$f_k^- = q_k(N) - q_k(N-1) \quad (8)$$

$q_k(N)$: electron population of the atom k in the neutral molecule.

$q_k(N+1)$: electron population of the atom k in the anionic molecule.

$q_k(N-1)$: electron population of the atom k in the cationic molecule.

The information contained in the two Fukui functions can be synthesized into a single function called dual descriptor. The expression of this function is given by equation (9).

$$\Delta f = f_k^+ - f_k^- \quad (9)$$

Δf is a function which represents the reactivity of the molecule. The positive or negative value of this function indicates respectively an electrophilic zone or a nucleophilic zone.

The chemical potential μ measures the tendency of the electron cloud to escape from the molecule. This reactivity parameter can be expressed as a function of the ionization potential PI and the electronic affinity AE. It corresponds to the opposite of electronegativity χ as defined by Pauling and Mulliken (Parr, Donnelly et al., 1978) (Mulliken, 1934).

$$\mu = -\frac{PI + AE}{2} = -\chi \quad (10)$$

The hardness η , the softness S and the electrophilic index ω can be expressed as a function of the ionization potentials (PI) and proton affinity (AE) (Pearson, 1987) (Koopmans, 1934).

$$\eta = \frac{1}{S} = (PI - AE)/2 \quad (11)$$

$$\omega = \frac{\mu^2}{2\eta} = \frac{\chi^2}{2\eta} \quad (12)$$

$$PI = -E_{HOMO} \text{ et } AE = -E_{LUMO} \quad (13)$$

E_{HOMO} and E_{LUMO} are respectively the energies of the HOMO and LUMO boundary molecular orbitals.

3. Results and Discussion

3.1 Stability of Tautomers

3.1.1 Tautomeric Equilibrium

The tautomeric structures of the ABT, OBT and MBT derivatives and the tautomeric equilibrium that may exist between these molecules are shown in Figure 2. The values of the thermodynamic energies, energy gaps (ΔE), rate constants and the equilibrium constants of these tautomers is summarized in Table 1. ΔE is the electron energy difference between the HOMO and LUMO molecular orbitals.

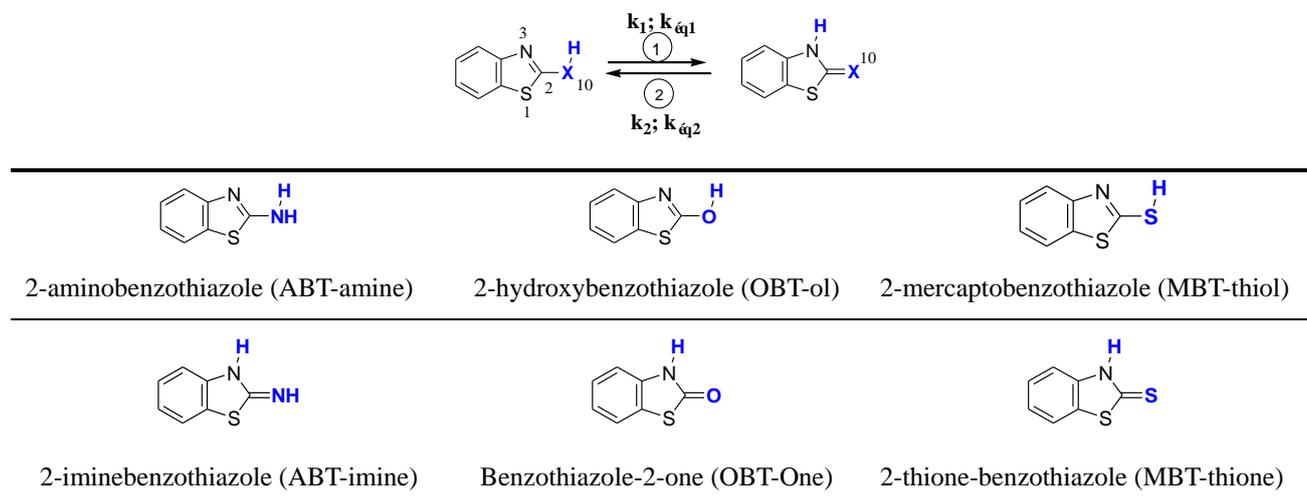


Figure 2. Tautomeric equilibrium and tautomers structures

Table 1. Energy parameters ($\text{kJ}\cdot\text{mol}^{-1}$), energy gap (eV), rate constants (s^{-1}) and equilibrium constants of benzothiazoles ABT, OBT and MBT calculated at B3LYP/6-311G(d) level in aqueous phase

Compounds	ABT		OBT		MBT	
	ABT-amin e	ABT-imin e	OBT-ol	OBT-one	MBT-thiol	MBT-thione
ΔE	3.09	2.97	2.59	2.40	2.64	2.45
Equilibrium	amine \longleftrightarrow imine		ol \longleftrightarrow one		thiol \longleftrightarrow thione	
$\Delta_r H$	14.8		12.0		-11.9	
$\Delta_r G$	9.8		7.1		-6.4	
K_1	$1.7 \cdot 10^{-25}$		$6.2 \cdot 10^{-19}$		$2.8 \cdot 10^{-15}$	
K_2	$1.7 \cdot 10^{-21}$		$1.2 \cdot 10^{-16}$		$1.3 \cdot 10^{-18}$	
K_{eq1}	$1.0 \cdot 10^{-4}$		$5.7 \cdot 10^{-3}$		$2.1 \cdot 10^3$	
K_{eq2}	$9.8 \cdot 10^3$		$1.8 \cdot 10^2$		$4.7 \cdot 10^{-4}$	

The ABT-amine tautomer has a higher ΔE value than that obtained with the ABT-imine form. It is the same for the OBT-ol tautomer. The amine and ol forms of these molecules are therefore the most stable. The energy gap values obtained with the tautomers of the MBT derivative indicate a clear stability of the thione form. Our results are in agreement with those of Yoshida et al. These showed that in MBT metal complexes, thiones are the most stable (Yoshida, Yamasaki, Sawada, 1979).

The values of the equilibrium constants k_1 are small compared to those of k_2 for the amine-imine and ol-one equilibria respectively in the ABT and the OBT. For these derivatives the reaction evolves in the direction number 2 (Figure 2.). This confirms the stability of the amine and ol tautomers with respect to the imine and one tautomers. In the case of the MBT derivative, the value of the rate constant k_1 is larger than k_2 . The reaction should evolve in the direction 1. This indicates the stability of the thione tautomer with respect to the thiol tautomer.

The reaction enthalpies analysis ($\Delta_r H$ and $\Delta_r G$) showed that the ABT and OBT derivatives have positive values. These values reflect an exothermic and non-spontaneous reaction under the conditions of this study. These thermodynamic

quantities are negative with the MBT derivative. Contrary to the ABT and OBT molecules, this reaction is endothermic and spontaneous with the MBT derivative. The values of the equilibrium constants are between 10^{-4} and 10^4 . This shows that the studied systems are in a state of tautomeric equilibrium. These molecules can exist in tautomeric forms.

3.1.2 Activation energies and geometrical parameters

The calculated activation energies for these equilibria are represented in graphical forms (Figure 3).

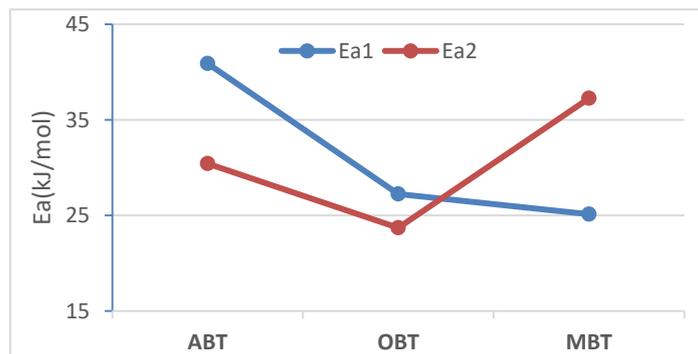


Figure 3. Activation energy (E_{a1} and E_{a2}) calculated at the B3LYP/6-311G(d) theory level

E_{a1} and E_{a2} are respectively the activation energies in direction 1 and 2 of the tautomeric equilibrium reaction (Figure 2). At the tautomers amine and imine of benzothiazole ABT level, the required energetic barrier to pass from the tautomer imine to tautomer amine is about $11.5 \text{ kJ}\cdot\text{mol}^{-1}$ higher than that required in the opposite direction ($E_{a1} = 40.88 \text{ kJ}\cdot\text{mol}^{-1}$) and $E_{a2} = 29.41 \text{ kJ}\cdot\text{mol}^{-1}$). The same observation is made with the tautomers ol and one of the OBT derivative. The transition from ol tautomer to form one requires an energy barrier of $27.24 \text{ kJ}\cdot\text{mol}^{-1}$ and an energy of $23.70 \text{ kJ}\cdot\text{mol}^{-1}$ in the opposite direction. These values indicate a stability of the amine and ol tautomers with respect to the imine and one tautomers respectively. The difference between these two energy barriers (E_{a1} and E_{a2}) in the case of benzothiazole OBT is $3.5 \text{ kJ}\cdot\text{mol}^{-1}$. This difference is small compared to that obtained with the derivative ABT ($11.5 \text{ kJ}\cdot\text{mol}^{-1}$). This assumes a coexistence of the two tautomers ol and one of the OBT derivative in the medium. In the case of the ABT derivative, a predominance of the amine tautomer in the medium can be expected. Contrary to benzothiazoles ABT and OBT, the energy barrier E_{a1} is about $12.1 \text{ kJ}\cdot\text{mol}^{-1}$ lower than the E_{a2} energy with thiols and thione tautomers of MBT. These results predict a predominance of the thione tautomer over the thiol tautomer.

The passage from one tautomer to another necessarily passes through a state of transition. The structures of these different transition states are shown in Figure 4. We were interested in the bond lengths and valence angles of the atoms involved in the structural change during the transition from one tautomer to another.

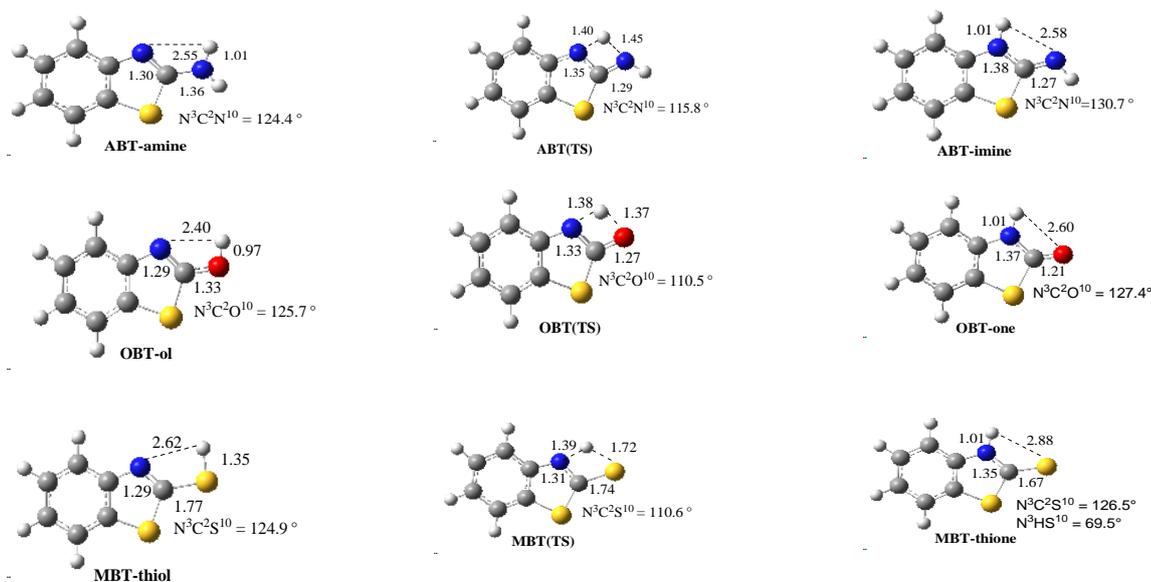


Figure 4. Transition state and different tautomers structures, bond lengths and valence angles are expressed respectively in Angstrom (\AA) and degree ($^\circ$)

The distances between the C²-N³ (1.36 Å) and C²-N¹⁰ (1.29 Å) atoms are closer to those obtained in ABT-imine. It would therefore be easier to obtain the geometry of the transition state from that of the ABT-imine tautomer. This fact can justify the less energetic passage of ABT-imine to ABT-amine. Also the valence angle formed by the three atoms N³, C² and N¹⁰ in the tautomer ABT-amine (N³C²N¹⁰ = 124.4 °) is smaller than that formed by the same atoms in the ABT-imine (N³C²N¹⁰ = 130.7 °). The increase of this angle can lead to a rapprochement of the hydrogen atom (H) of the imine group (H-N¹⁰=C²) to the sulfur atom (S¹). The rapprochement of these two atoms can produce a repulsive effect which would destabilize the ABT-imine tautomer.

The transition state OBT (TS) presents an intermediate geometry between the OBT-ol and OBT-one tautomers. The C²=N³ bond in the transition state is lengthened by 0.04 Å in both OBT-ol tautomers and OBT-one. Similarly, the C²-O¹⁰ bond in the transition state geometry OBT (TS) is shortened by 0.06 Å in these two molecules. These values indicate an intermediate geometry of the OBT (TS) located between that of the OBT-ol and the OBT-one. This can explain the small variation between the activation energies Ea₁ and Ea₂ (3.5 kJ.mol⁻¹) and the possibility of coexistence of the two tautomers in the medium. In the case of the MBT derivative, the calculated geometric parameter values show that the MBT transition state (TS) has a geometry similar to that of the MBT-thiol tautomer. Which can be explained the passage MBT-thiol in MBT-thione less energetic. For this fact, an analysis of the stability of the different conformers of OBT-ol and MBT-thiol molecules was carried out using free enthalpies and energy gaps (Figure 5).

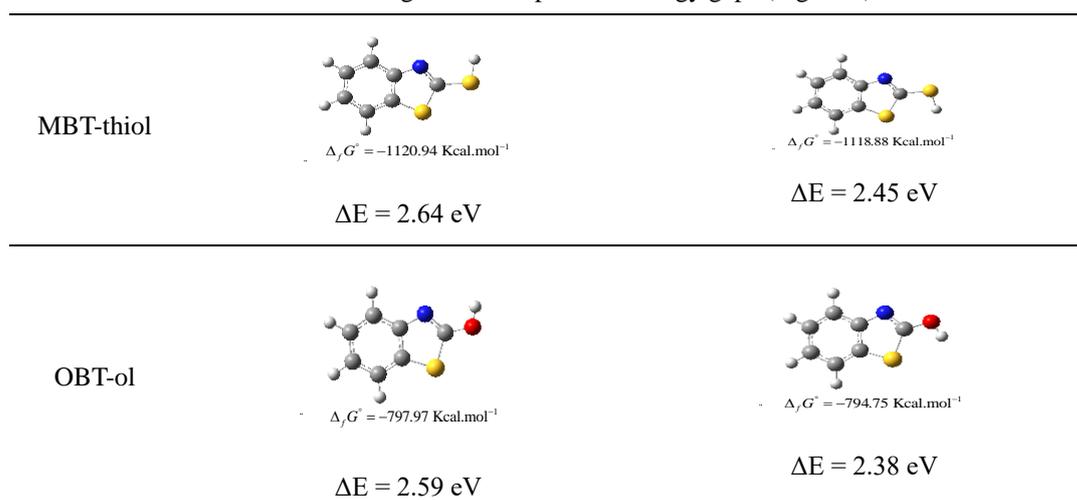


Figure 5. Structures of MBT and OBT benzothiazole conformers with their values of free enthalpies ($\Delta_f G^\circ$) and energy gaps (ΔE) calculated at the B3LYP/6-311G (d) theory level

The relative stability order of the conformers is established by comparing the values of the free enthalpies ($\Delta_f G^\circ$). It emerges from this analysis that the conformers with the hydrogen atom (H) oriented towards the sulfur atom (S¹) are the least stable. Also, the values of ΔE indicate that the same molecules are the most reactive. The possibility of electronic repulsion effect due to the electron-donor nature of the sulfur atom S¹ can be an explanation for the destabilization of these conformers. Therefore, the orientation of the hydrogen atom (H) towards the sulfur atom (S¹) could be justified by the instability of the ABT-imine tautomer.

3.2 Reactivity Study

The analysis of benzothiazole reactivity in this work is based on the determination of global reactivity indices and Fukui indices.

3.2.1 Global Reactivity Indices

The reactivity parameters which have been examined in the study of this benzothiazoles' series are: chemical potential (μ_{pot}), hardness (η), softness (S) and electrophilic index (ω). By taking into account the theory of the Frontier Molecular Orbitals (FMO) (Fujimoto. & Fukui, 1972) (Michel, Jean-François et al., 2005) (Aihara, 1999), the HOMO-LUMO energy gaps (ΔE) have been determined. This theory allows to foretell the reactivity of molecules. It states that the smaller the energy gap, the more reactive the molecule would be. The calculated values of concerned parameters are gathered in Table 2.

Table 2. Energy gaps (eV), chemical potential (eV), hardness (eV), softness (eV⁻¹) and electrophile index (eV) calculated in aqueous phase at B3LYP/6-311G(d).

	BT	ABT	OBT	MBT	MTBT
ΔE	2.43	3.09	2.59	2.64	3.28
μ_{pot}	-2.97	-3.15	-2.96	-2.97	-2.94
η	1.21	1.55	1.29	1.32	1.64
S	0.82	0.65	0.77	0.76	0.61
ω	3.64	3.20	3.39	3.35	2.63

The value of the energy gap ΔE increases with the substituents in position 2 of the cycle. Which leads to the the decrease of the reactivity of benzothiazole (BT). The smallest values of ΔE are obtained with BT, OBT and MBT. These molecules are therefore the most reactive. The BT molecule with the lowest energy gap value (2.43 eV) remains the most reactive molecule. The ABT and MTBT derivatives are the least reactive.

Chemical hardness (η) and overall softness (S) express the resistance of a molecular system to charge transfer. The values of this reactivity parameters of BT, OBT and MBT derivatives are the lowest. This molecules are the softest. The BT derivative is softer than the two others. The hydroxyl (OH) and thiol (SH) groups compared to the thiomethyl (CH₃S) and amine (NH₂) substituents at the position (2) of the benzothiazole ring increase the reactivity of benzothiazoles. The value of the electrophilic index (ω) of benzothiazole BT is the highest. Among the derivatives substituted in position 2, OBT and MBT derivatives have the highest electrophilic index values. The value of this reactivity index varies slightly from one derivative to another. These molecules therefore have an electrophilic character. They are susceptible to undergo a nucleophilic attack. Among the studied molecules, the most electrophilic is BT and the least one is MTBT.

3.2.2. Fukui indices

Previous works have shown that Liquid Chromatography (LC) coupled with Mass Spectrometry (MS) or High-Resolution Mass Spectrometry (HRMS) are the technics which must be chosen for the determination of benzothiazoles pollutants in wastewater (Salas, Borrull et al., 2016) (Asimakopoulos, Ajibola, et al., 2013). The results of this work showed that benzothiazoles appear to be retained on the adsorbent through ionic interactions. The delocalization of the electron density of these molecules is able to stabilize the partial charges in order to interact with the ionic group of the adsorbent. Thus earlier works have proposed BT mesomers (Salas, Borrull et al., 2016) (Hanif, Muhammad et al., 2015). According to the results of these studies, it is important to determine the sites of interaction such as nucleophilic and electrophilic sites of these molecules. Calculations of Fukui indices are necessary for the determination of those interaction sites. The Fukui function analysis was performed using Hirschfeld populations (Roy, Pal & Hirao, 1999) on BT, OBT and MBT derivatives which are found to be the most reactive. The results of these calculations are summarized in Table 3.

Table 3. Fukui indices calculated at B3LYP / 6-31+G (d) level

Atoms	BT			OBT			MBT		
	f^+	f^-	$\Delta f(r)$	f^+	f^-	$\Delta f(r)$	f^+	f^-	$\Delta f(r)$
S ¹	0.175	-0.105	0.28	0.152	-0.107	0.259	0.198	-0.095	0.293
C ²	0.426	-0.027	0.453	0.057	-0.06	0.117	0.079	-0.024	0.103
N ³	-0.085	0.225	-0.31	-0.085	0.193	-0.278	-0.089	0.169	-0.258
C ⁴	0.176	-0.125	0.301	0.305	-0.091	0.396	0.209	-0.098	0.307
C ⁵	-0.037	0.117	-0.154	-0.048	0.156	-0.204	-0.016	0.133	-0.149
C ⁶	0.355	-0.064	0.419	0.321	-0.101	0.422	0.312	-0.081	0.393
C ⁷	-0.019	0.107	-0.126	-0.02	0.139	-0.159	-0.026	0.131	-0.157
C ⁸	-0.018	0.042	-0.060	0.065	0.075	-0.01	-0.081	0.015	-0.096
C ⁹	-0.009	0.059	-0.068	0.063	0.026	0.037	0.038	-0.014	0.052

A positive value of $\Delta f(r)$ indicates an electrophilic site and a negative value reveals a nucleophilic site. In the unsubstituted molecule (BT), this reactivity parameter has a positive value for the atoms S¹, C², C⁴ and C⁶. These atoms are electrophilic sites. A nucleophilic attack would probably occur at these atoms. The decreasing order of priority of a nucleophilic attack is as follows:

$$C^2 > C^6 > C^4 > S^1$$

The C^2 atom is the most favourable site during a nucleophilic attack. This order may justify biodegradation from BT to OBT as the first step (De Wever, Vereecken et al., 1998) (Besse, Combourieu et al., 2001). This leads us to conclude that the electrophilic nature of the C^2 , C^4 and C^6 atoms is strongly implicated in the biodegradation of BT. The N^3 , C^5 , C^7 , C^8 and C^9 atoms have negative $\Delta f(r)$ values. They are therefore nucleophilic sites. The decreasing order of priority of an electrophilic attack is as follows:

$$N^3 > C^5 > C^7 > C^9 > C^8$$

An electrophilic attack will be preferentially on the N^3 atom. The nucleophilic and electrophilic sites of BT are shown in figure 6.

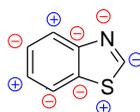


Figure 6. Nucleophilic and electrophilic sites of benzothiazole (BT) given according to Fukui indices. Negative signs (red) represent nucleophilic sites, positive signs (blue) represent electrophilic sites

As mentioned in previous work (Salas, Borrull et al., 2016) (Asimakopoulos, Ajibola et al., 2013), the retention of these compounds on the adsorbent through ionic interactions is more important than the hydrophobic interactions. This fact can be explained by the ability of these molecules to go into several mesomeric forms. Mesomerie is used to describe the displacement of certain electrons in a molecule. The mesomeric effect is an important electronic effect in the reactivity of molecules with double bonds and p electrons (non-binding doublets). It characterizes the property of an atom or a functional group to yield or accept a doublet of electrons.

The sites which are rich in terms of electron of the compound BT are the N^3 , C^5 , C^7 , C^8 and C^9 atoms and the poor ones are the S^1 , C^2 , C^4 and C^6 atoms. Considering these different sites, the delocalization of electrons in benzothiazole leads to five (5) mesomers (Figure 7). These mesomers are the fact of the delocalization of the free doublet (free electrons of the electronic structure) of the sulfur atom.

The OBT and MBT derivatives have the same electrophilic and nucleophilic sites. The atoms, S^1 ; C^2 ; C^4 , C^6 , and C^9 have positive values of $\Delta f(r)$ and C^6 carbon has the highest value. A nucleophilic attack will probably occur at these atoms and preferentially at the level of C^6 carbon. The N^3 , C^5 , C^7 and C^8 atoms have negative values of $\Delta f(r)$ so these atoms are nucleophilic sites. The nitrogen N^3 has the lowest value of $\Delta f(r)$ and the maximum value of f^- in the studied compounds. An electrophilic attack will be happen primarily on this atom (N^3). The carbon C^6 which is the most electrophilic site in these substituted molecules (OBT and MBT), has the greatest value of $\Delta f(r)$. This leads us to conclude that this atom (C^6) will be more reactive face to a nucleophilic attack in the OBT and MBT. In all the studied benzothiazoles, the N^3 atom is the most nucleophilic site. A methylation reaction of the N^3 nitrogen atom of these benzothiazole derivatives can be envisaged in the framework of the degradation process of these compounds. The carbon atoms C^2 , C^4 and C^6 of the benzene ring of the substituted derivatives have an electro-acceptor character. Work has shown that benzothiazoles BT, OBT and MBT are more reactive towards hydroxyl radicals. And the degradation of the OBT and MBT derivatives leads to hydroxylated compounds at the 6 position are majority. The hydroxylated compounds at the 4 position are in minority (Bahnmüller, Loi et al., 2015). The more pronounced electrophilic character of the atom C^6 may justify this experimental observation.

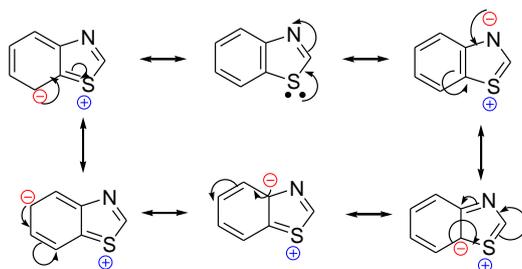


Figure 7. Proposed benzothiazole mesomers

4. Conclusion

This work focused on the study of the stability, tautomeric equilibrium and reactivity of five benzothiazole derivatives by Density Functional Theory (DFT) method.

The results of this study showed that the thione tautomer of MBT derivative is more stable than the thiol form. At this level, our results are in agreement with previous experimental work which showed that the thiones forms in MBT metal complexes are the most stable. The values of the equilibrium constants and rate constants showed the existence of a tautomeric equilibrium in the ABT, OBT and MBT derivatives. The thermodynamic data and the energy barriers calculated predict a possibility of coexistence of the tautomers of one of OBT derivative.

The study of the reactivity based on the calculation of the global reactivity indices shows that the benzothiazoles BT, OBT and MBT are the most reactive. The studied molecules have an electrophilic character. The most electrophilic is BT and the least electrophilic is MTBT.

The calculation of Fukui's functions permit to identify the interaction sites of these molecules. From these calculations, five mesomeric forms of benzothiazole BT have been proposed. These calculations have also shown that carbon C² is the most electrophilic site of BT. In substituted derivatives, it is the carbon C⁶ which is the most electrophilic site. The electrophilic nature of these atoms could be a possible explanation for obtaining hydroxylated biodegradation products at these positions. N³ nitrogen remains the most nucleophilic site in all the studied molecules. An electrophilic attack of atom N³ in the biodegradation process of these compounds may be considered.

The knowledge of the solubility in water and the acidity of these molecules is essential if we want to determine their behavior and final state in the aquatic environment. In this sense, we plan to determine the lipophilicity and acidity of these molecules from calculations of acidity constants (pKa) and partition coefficients (logP).

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