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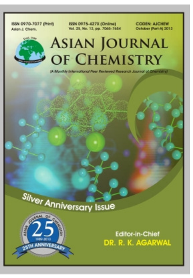

Electronic Structure and Physico-Chemical Property Relationship for Thiazole Derivatives

SALAH BELAIDI[1,*], RADHIA MAZRI[1], HOUMAM BELAIDI[1], TOUHAMI LANEZ[2] and DJEMOUI BOUZIDI[3]

[1]Group of Computational and Pharmaceutical Chemistry, LMCE Laboratory, Department of Chemistry, Faculty of Sciences, University of Biskra, Algeria
[2]Chemistry Department, University of El-Oued, B.P.789, El-Oued 39000, Algeria
[3]Scientific Approach Institute, Waterman Ave Suite 5 1264, San Bernardino, CA 92408, USA

*Corresponding author: Tel:/Fax: +213 33 748687; E-mail: salah_belaidi@hotmail.com

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Electronic structure, effect of the substitution and structure physico-chemical property relationship for thiazole derivatives, has been studied by *ab initio* and DFT method. In the present work, the calculated values, *i.e.*, net charges, bond lengths, dipole moments, electron-affinities, heats of formation and QSAR properties, are reported and discussed in terms of the reactivity of thiazole derivatives.

Key Words: Thiazole, Structure, DFT, *ab initio*, QSAR.

INTRODUCTION

The emerging resistance to antimicrobial drugs demands the synthesis of new remedies, which are effective against organisms resistant to currently available drugs for microbial infections[1, 2].

Thiazoles and isothiazoles have an important role in the synthesis of potential medication, including antitumor, antimicrobial, antiinfective, cardiovascular and nervous system agents[3,4]. There are various experimental methods and theoretical studies, developed for the synthesis of thiazole and isothiazole derivatives[5-8].

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive *ab initio*/HF electron correlation methods are required[9]. Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules[10].

Quantitative structure-activity relationships (QSAR) are attempts to correlate molecular structure, or properties derived from molecular structure, with a particular kind of chemical or biochemical activity. The kind of activity is a function of the interest of the user: QSAR is widely used in pharmaceutical, environmental and agricultural chemistry in the search for particular properties. The molecular properties used in the correlations relate as directly as possible to the key physical or chemical processes taking place in the target activity[11].

In present case, we have studied the structure of thiazole and some of thiazole derivatives, by using the *ab initio* method. For a complete and comparative study, we have also used DFT method.

EXPERIMENTAL

All calculations were performed by using HyperChem 8.03 software[12] and Gaussian 09 program package[13]. The geometries of thiazole and heir methyl, mercapto derivatives and the series of thiazole derivatives, were first fully optimized by molecular mechanics (MM) with Amber force-field (RMS = 0.001 Kcal/Å). We also used the molecular dynamics for the conformational research, with the following options: 1000 K, steep size: 0.001 ps, relaxation time: 0.1 ps. Further, geometries were fully re-optimized by RM1 method (SFC controls). A parallel study has been made using *ab initio*/HF (6-31G**)[14] and DFT/B3LYP exchange-correlation potential with 6-31G** basis[15]. The calculation of properties QSAR is performed by the module (QSAR Properties, version 8.0). QSAR Properties are a module that, together with HyperChem, allows several properties commonly used in QSAR studies to be calculated. The calculations are empirical and, so generally, are fast. The calculated results have been reported in the present work.

RESULTS AND DISCUSSION

Geometric and electronic structure of thiazole and thiazole systems: The efficiency of DFT/B3LYP method may be scrutinized by comparison with the results obtained by more elaborate calculation such as *ab initio*/HF. Present results concerning bond length values for thiazole (Table-1), bond angles (Table-2) and charge densities (Table-3). A very good agreement between predicted geometries (bond lengths, bond angles) and corresponding experimental data. Charge densities calculated by the *ab initio*/HF are similar than DFT/ B3LYP method. The geometry of the oxazole is planar; dihedral angles are almost equal to zero.

TABLE-1
CALCULATED BOND LENGTHS (ANGSTROM) OF THIAZOLE MOLECULE

Bond length	Exp[16]	HF (6-31G**)	HF (cc-PVTZ)	B3LYP (6-31G**)	B3LYP (cc-PVTZ)
S1-C2	1.724	1.727	1.721	1.749	1.737
C2-N3	1.304	1.275	1.273	1.300	1.296
N3-C4	1.372	1.378	1.373	1.377	1.371
C4-C5	1.367	1.342	1.340	1.365	1.360
C5-S1	1.713	1.726	1.721	1.733	1.724
C2-H	1.077	1.073	1.071	1.083	1.079
C4-H	1.079	1.072	1.070	1.084	1.079
C5-H	1.076	1.070	1.067	1.080	1.076

TABLE-2
ANGLES IN DEGREE OF THIAZOLE MOLECULE

Angles	Exp[16]	HF (6-31G**)	HF (cc-PVTZ)	B3LYP (6-31G**)	B3LYP (cc-PVTZ)
C5-S1-C2	089.33	088.53	088.77	088.51	089.03
S1-C2-N3	115.18	115.53	115.29	115.28	114.93
C2-N3-C4	110.12	110.49	110.68	110.39	110.74
N3-C4-C5	115.81	115.91	115.87	116.06	115.79
C4-C5-S1	109.57	109.55	109.39	109.76	109.71
N3-C2-H	123.56	123.55	123.61	124.31	124.34
S1-C2-H	121.26	120.92	121.11	120.41	120.73

TABLE-3
NET CHARGE DISTRIBUTION FOR THIAZOLE MOLECULE

Thiazole atoms	HF (6-31G**)	HF (cc-PVTZ)	B3LYP (6-31G**)	B3LYP (cc-PVTZ)
S1	0.270	-0.036	0.245	0.151
C2	-0.064	-0.431	-0.075	-0.406
C3	-0.454	-0.261	-0.362	-0.278
C4	0.098	-0.599	0.101	-0.440
C5	-0.390	-0.293	-0.301	-0.328

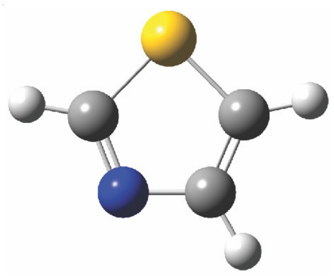

Fig. 1. 3D conformation of thiazole (GaussView 5.0.8)

The calculated values of methyl substituted thiazoles and mercapto substituted thiazoles Fig. 2 are given in Tables 4-7. In Tables 4 and 5, heat of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (ΔE) are reported for thiazole and its methyl and mercapto derivatives. In Tables 6 and 7, net atomic charges are also reported.

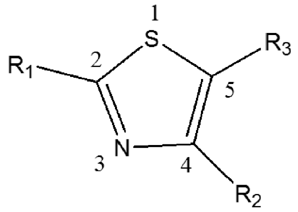

Fig. 2. Scheme of thiazole systems

Series 1	Series 2
a. R1= R2= R3 = H	a'. R1 = R2= R3 = H
b. R1=CH3, R2=R3=H	b'. R1=SH, R2=R3=H
c. R1=R3=H, R2=CH3	c'. R1=R3=H, R2= SH
d. R1=R2=H, R3=CH3	d'. R1=R2=H, R3=SH
e. R1=R2=CH3, R3=H	e'. R1= R2= SH, R3= H
f. R1= R3=CH3, R2=H	f'. R1= R3= SH, R2= H
g. R1=H, R2=R3=CH3	g'. R1=H, R2=R3=SH
h. R1= R2= R3=CH3	h'. R1= R2= R3=SH

It can be seen from the heat of formation data that approximately 28 kcal/mol is increased at each addition of methyl group, in the base compound thiazole irrespective of the number of substitutions.

The ionization potential values in compounds **a-h** show a decreasing trend, which means increasing trend in the easy flow of charges in higher energy states of these compounds. Sulfur and nitrogen contribute 16 and 7 electron density of thiazoles, respectively.

The atomic charge of sulfur is decreased for methyl derivatives and increased for mercapto derivatives, but for nitrogen is approximately unchanged except for compounds **c** and **h** (Tables 6 and 7).

In the mono-substituted methyl group category, the 4-methyl thiazole (compound **c**) showing maximum charge on 5th position carbon (-0.433) which leads to electrophilic substitution Table-6. This is further supported by the least HOMO-LUMO energy gap (12.63) Table-4 which depicts the chemical reactivity of the compound; higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecule hard and less reactive.

On the other hand in lesser HOMO-LUMO gap, there is easy flow of electrons to the higher energy state making it softer and more reactive (HSAB principle: hard and soft acids and bases). Hard bases have highest occupied molecular orbitals (HOMO) of low energy and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy[16,17]. Compound **c** also shows a high dipole moment value. These results are in close agreement with the experiment[18].

In the case of dimethyl substituted thiazole the C4 position (compound **g**) shows a maximum positive charge (0.234), least HOMO-LUMO energy gap (12.46) and high dipole moment value Tables 4-6 which leads to preferential site of nucleophilic attack.

This conclusion finds support from experimental evidence. In search of basicity, N atom is predicted to be the main basic centre of the thiazole systems in accordance with the electron densities Table-4. The C-H hyper-conjugation is the principal mode of electron release by the methyl group (pseudo-hetero atom) and stabilizes excited states more than ground state[19]. In the order of increasing number of conjugated methyl groups,

TABLE-4
ENERGIES OF THIAZOLE AND METHYL SUBSTITUTED THIAZOLES

Compound	System	Heat of formation (kcal/mol)	HOMO (eV)	LUMO (eV)	ΔE (eV)	μ (D)
A	Thiazole	259.667	-9.468	3.348	12.816	1.552
B	2-Methyl thiazole	287.121	-9.135	3.512	12.647	1.036
C	4-Methyl thiazole	285.574	-9.117	3.508	12.625	1.124
D	5-Methyl thiazole	359.742	-9.174	3.462	12.636	1.843
E	2,4-Methyl thiazole	313.079	-8.821	3.668	12.489	0.616
F	2,5-Methyl thiazole	314.204	-8.862	3.620	12.482	1.310
G	4,5-Methyl thiazole	313.413	-8.862	3.602	12.464	1.526
H	2,4,5-Methyl thiazole	340.939	-8.592	3.758	12.350	0.950

Heat of formation calculated by RM1, ΔE and μ (D) by *ab initio*/HF.

TABLE-5
ENERGIES OF THIAZOLE AND MERCAPTO SUBSTITUTED THIAZOLES

Compound	System	Heat of formation (kcal/mol)	HOMO (eV	LUMO (eV)	ΔE (eV)	μ (D)
A'	Thiazole	259.667	-9.468	3.348	12.816	1.552
B'	2- Mercapto thiazole	400.584	-8.876	3.213	12.089	1.322
C'	4- Mercapto thiazole	402.064	-8.712	3.103	11.815	2.510
D'	5- Mercapto thiazole	400.636	-8.791	3.146	11.937	0.392
E'	2,4-Mercapto thiazole	543.106	-8.538	2.995	11.533	1.743
F'	2,5- Mercapto thiazole	580.621	-8.478	3.032	11.510	1.330
G'	4,5- Mercapto thiazole	544.172	-8.478	2.940	11.418	1.319
H'	2,4,5-Mercapto thiazole	683.123	-8.306	2.855	10.856	0.900

TABLE-6
NET ATOMIC CHARGES FOR THIAZOLE AND METHYL SUBSTITUTED THIAZOLES

Compound	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
Sulphur 1	0.2701	0.2669	0.2693	0.2660	0.2503	0.2480	0.2498	0.2399
C 2	-0.0641	0.0962	-0.0694	-0.0753	0.0840	0.0810	-0.0744	0.0861
Nitrogen 3	-0.4544	-0.4993	-0.4778	-0.4561	-0.5025	-0.4841	-0.4655	-0.5024
C 4	0.0984	0.0994	0.2645	0.0723	0.2579	0.0787	0.2342	0.2436
C 5	-0.3901	-0.4131	-0.4337	-0.2446	-0.4284	-0.2509	-0.2777	-0.2796
C-Methyl 2	–	-0.4038	–	–	-0.3875	-0.3868	–	-0.3871
C-Methyl 4	–	–	-0.3742	–	-0.3563	–	-0.3565	-0.3568
C-Methyl 5	–	–	–	-0.3751	–	-0.3585	-0.3541	-0.3539

Net charge calculated by *ab initio*/HF (6-31G**).

TABLE-7
NET ATOMIC CHARGES FOR THIAZOLE AND MERCAPTO SUBSTITUTED THIAZOLES

Compound	**a'**	**b'**	**c'**	**d'**	**e'**	**f'**	**g'**	**h'**
Sulphur 1	0.2701	0.3004	0.2879	0.3010	0.3157	0.3373	0.3230	0.3497
C 2	-0.0641	-0.0819	-0.0718	-0.0822	-0.0759	-0.0814	-0.0683	-0.0730
Nitrogen 3	-0.4544	-0.4747	-0.4506	-0.4396	-0.4790	-0.4784	-0.4526	-0.4839
C 4	0.0984	0.0984	0.0824	0.0895	0.0949	0.1039	0.0831	0.0983
C 5	-0.3901	-0.4115	-0.4034	-0.4181	-0.4113	-0.4300	-0.4315	-0.4406
C-Mercapto 2	–	-0.4115	–	–	0.1131	0.1097	–	0.1196
C-mercapto 4	–	–	0.1234	–	0.1262	–	-0.1541	0.1557
C-Mercapto 5	–	–	–	0.1286	–	0.1335	0.1541	0.1559

ionization potentials (IPs) decrease in the case of compounds **a-h** as expected from those listed in Table-6.

The 2,4,5-trimethyl thiazole (compound **h**) is predicted to be the most reactive with least HOMO-LUMO energy gap of all the thiazole systems and, respectively C2, C4, are the most preferential sites for nucleophilic attack and C5 for electrophilic attack (Table-4).

These results are in close agreement with the experiment[19] and we found in literature that the majority of tri-substituted thiazoles have an important biological activity (3, 4, 19).

It is also noted that the methyl substituent (donor effect) has the effect of increasing the energy of the HOMO, with little change of the LUMO (Table-4).

In the present work, we have studied mercapto substituted thiazoles along the same line of methyl substituted thiazoles for a comparative study. Heat of formation which is approximately 143 Kcal/mol is increased, for each addition of mercapto group irrespective of sulfur in the ring.

In mono-substituted mercapto derivatives, 4-mercapto thiazole (compound **c'**) is predicted to be more chemically reactive than 5- mercapto thiazole and 2- mercapto thiazole on the basis of least HOMO-LUMO energy gap (Table-5). The carbon 5 in 4-mercapto thiazole shows a maximum negative charge (-0.4034) leading to favoured site for electrophilic attack Table-6. In disubstituted mercapto derivatives, 4,5-dimercapto thiazole (compound **g'**) seems to be more reactive than the other two compound **e'** and **f'**, due to least HOMO-LUMO energy gap (11.41) (Table-5). For nitrogen atom the negative atomic charge varies very little, for all mercapto derivatives (Table-7).

It is noted that the mercapto substituent (attractor effect) lowers the energies of HOMO and LUMO. Its influence on the energy of the LUMO is more important (Table-5).

Study of structure and physico-chemical properties relationship for thiazoles derivatives: We have studied six physico-chemical proprieties of thiazole derivatives using HyperChem. We will continue this work in the future by a quantitative calculation. These properties are van der Waals-surface-bounded molecular volume, the log of the octanol-water partition coefficient (log p), polarizability, solvent-accessible surface bounded molecular volume and molecular mass (M). Calculation of log p is carried out using atomic parameters derived by Ghose and coworkers[20].

Computation of molar refractivity was made *via* the same method as log p. Ghose and Crippen presented atomic contributions to the refractivity[21]. Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bodor *et al.*[22], using the atomic radii of Gavezzotti[23].

Polarizability was estimated from an additivity scheme given by Miller[24] with a 3 % in precision for the calculation, where different increments are associated with different atom types. Hydration energy is a key factor determining the stability of different molecular conformations[25]. The calculation is based on exposed surface area and employs the surface area as computed by the approximate method (above), weighted by atom type.

Structural comparison of thiazole derivatives: Based on our conclusions on the effect of substitution on the thiazole molecule, we chose a series of thiazole derivatives (thiazolopyridines); some of them have a biological activity. This series of thiazole derivatives which, have been synthesized and characterized by Anthosen *et al.* [26]. Initially, we performed a structural comparison of this series (Fig. 3). Fig. 4 shows the favoured conformation in 3D of the compound **3**. These molecules have a weak conformational flexibility, with regard to the other macrocycles of macrolide type[27-33]. In a window of 2 kcal/mol (MM), only one favoured conformations is found, for each structure.

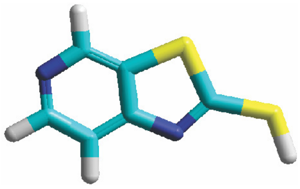

Fig. 4. 3D Conformation of compound 3 (HyperChem 8.03)

Structure and physico-chemical properties relationship: Polarizability values are generally proportional to surfaces and of volumes. The decreasing order of polarizability for these studied thiazoles is: 5, 7, 4, 6, 8, 3, 2 and 1 (Table-8). The order of polarizability is the same one for volumes, but it is a little different for surfaces. This is due primarily to the folding up of surfaces of some structures compared to the majority of the extended structures. This is also explained by the relation between polarizability and volume for the relatively non polar molecules.

The polarizability of the molecule depends only on its volume, which means that the thermal agitation of non polar molecules does not have any influence on the appearance of dipole moments in these molecules. On the other hand, for the polar molecules, the polarizability of the molecule does not depend solely on volume, but also depends on other factors such as the temperature because of the presence of the permanent dipole[34].

Surface and distribution volume of these molecules are definitely higher than those of more polar molecules like the lipopeptides or beta-lactams. For example, Deleu *et al.* used TAMMO software[35] on the surfactins C13, C14 and C15 having cores similar to the macrolides. They found that their surfaces vary from 129 to 157 Å^{2} [36], contrarily for these thiazoles, surfaces vary from 280.79-434.68 Å^{2}. These thiazoles have a great variation of distribution volume, in particular compound **7** and compound **5** which have respective volumes: 668.14 and 663.16 Å^{3} Table-7. The most important hydration energy in the absolute value, is that of compound **8** (19.27 kcal/mol) and the weakest is that of compound **2** (4.47 kcal/mol) (Table-7). Indeed in biological environments, the polar molecules are surrounded by water molecules. They establish hydrogen bonds between water molecule and these ones. The donor sites of proton interact with the oxygen atom of water and the acceptor sites of proton interact with the hydrogen atom. The

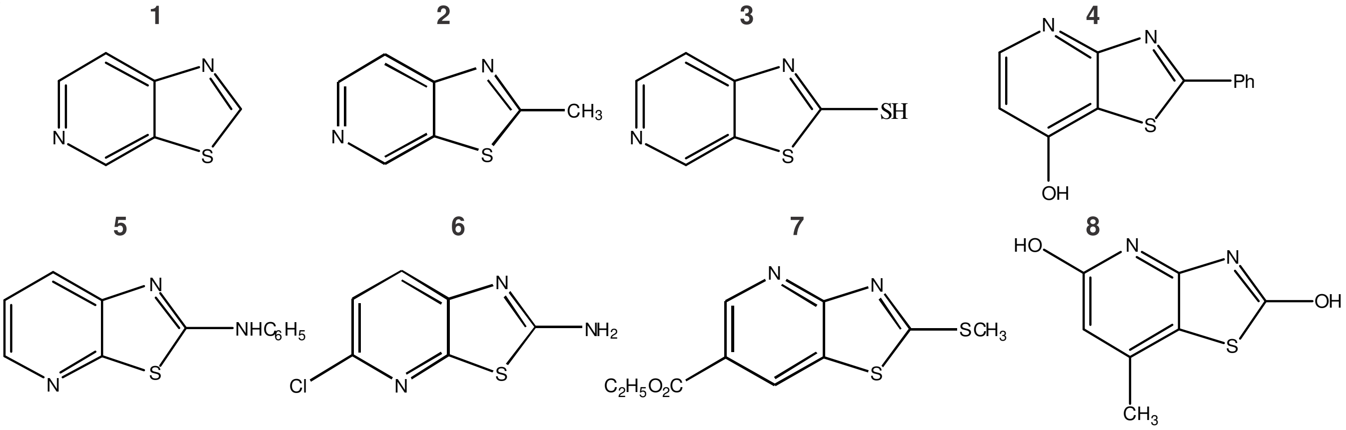

Fig. 3. Structural comparison of the thiazole derivatives

TABLE-8
QSAR PROPRIETIES FOR THIAZOLE DERIVATIVES

Thiazole derivative	Molecular volume (Å^3)	Molecular surface (Å^2)	Partition coefficient (log p)	Hydration energy (Kcal/mol)	Polarizability (Å^3)
1	406.58	280.79	-0.23	-6.07	14.72
2	463.53	313.47	-0.41	-4.47	16.56
3	469.77	319.13	-0.15	-7.37	17.72
4	646.15	412.12	1.10	-13.04	25.02
5	663.16	421.78	1.52	-8.58	25.73
6	492.82	332.01	1.62	-10.46	18.00
7	668.14	434.68	0.79	-7.22	23.95

first corresponds to the composite with the strongest hydrogen bond. These hydrated molecules were dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible[37].

Compound **8** has two donor sites of proton (2 OH) and three acceptor sites of proton (2 N and 1S). On the other hand compound **2** does not possess any donor site, but possesses three acceptor sites of proton (2 N and 1S). The first having higher value, it has two more donor sites of protons. This property supports the first compound, not only by fixing on the receiver, but it activates it more. It is thus an agonist.

Compound **3** presents low coefficient of division (-0.15) and comes after the compound **1** (-0.23) .These molecules are the most absorbent products. When the coefficient of division is rather low, it has as a consequence of a better gastric tolerance. Compounds **8** and **6,** which have, respectively higher values 1.82 and 1.62, have capacities to be dependent on plasmatic proteins.

Conclusion

The present work on the thiazoles reveals that the substitution of methyl and mercapto group does not affect the heat of formation but the electronic parameters due to charge disturbance in the ring. The 2,4,5-trimethyl thiazole (compound **h**) is predicted to be the most reactive with least HOMO-LUMO energy gap of all the thiazole systems and, respectively C2, C4, are the most preferential sites for nucleophilic attack and C5 for electrophilic attack. The RM1and *ab initio* method can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron. Compound **1** in the series of thiazole derivatives, presents the lower coefficient of division (log p). This molecule is the most absorbent product. Compound **8** has important hydration energy leading to a better distribution in fabrics.

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