

Density Functional Studies on Reactivity of Thiazole and Some of its Derivatives in the Gas Phase

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المخلص

دراسات في النشاط الكيميائي للثيازول وبعض مشتقاته في الحالة الغازية
بواسطة نظرية الكثافة الوظيفية.

لقد أثبتت أفضلية الكثافة الوظيفية الهجينة B3LYP في وجود الدالة 6-311++G(d,p) و الدالة الممتدة aug-cc-pV(Q+d)Z في حالة عناصر الدورة الثالثة على إحدى عشرة دالة وظيفية هجينة أخرى من خلال التقييم الإحصائي للمعلمات الهندسية المحسوبة بالمقابل مع نظيرتها العملية. لقد تم تحسين مركب الثيازول ومشتقاته من خلال الدالة الوظيفية B3LYP في وجود الدوال السابق ذكرها ومن ثم اثبات الحالة الأرضية (الأساسية) لكل منها من خلال حسابات التردد. لقد تم تقدير الميل البروتوني، القاعدية و موصفات النشاط الكيميائي المتمثلة في طاقة المدارات المتقدمة، الصلابة و النعومة الكيميائيتين، فجوة الطاقة، السالبية الكهربائية و الميل الإلكتروني و النووي باستخدام B3LYP/6-311++G(d,p)//B3LYP/6-311++G(3df,2p). لقد تم تأكيد خصائص الروائح باستخدام نموذج التذبذب التوافقي للعطرية (HOMA)، ونموذج التذبذب التوافقي للإلكترونات الغير متموضعة في المركبات الحلقية الغير متجانسة (HOMHED) والتحول الكيميائي المستقل للنواة (NICS). عكست الحسابات المتعلقة بالتحول الكيميائي للنواة أن الخاصية العطرية (الأروماتية) للثيازول أعلى من أي من مشتقاته، بيد أن الحسابات المتعلقة بنموذجي التذبذب التوافقي أظهرتا التفوق العطري للمركب 2-nitrothiazole. أشارت النتائج إلى أن الثيازول ومشتقاته تتصرف كقواعد نيتروجينية متوسطة القوة كما تم تأكيد الميل البروتوني والسالبية في الحالة الغازية من خلال حسابات التفاعل العالمي. هذا وقد عكست الحسابات المتعلقة بفجوة الطاقة والصلابة الكيميائية ثباتاً ملحوظاً للثيازول. ولقد تناولت الدراسة أيضاً تأثير المستبدلات على الخواص الهيكلية والعطرية و PAs و GBS (واصفات التفاعل العالمية). ولقد أظهرت الحسابات، تقريباً، أن ترتيب التفاعل على أساس المجموعة البديلة هو $\text{Ph} > \text{NH}_2 \geq \text{NO}_2$ وأن مركب 2-فينيل ثيازول كان الأكثر كفاءة في تثبيط عملية التآكل.

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Abstract

The preference of B3LYP functional over eleven different hybrid functional in case of thiazole in the presence of 6-311++G(d,p) and aug-cc-pV(Q+d)Z basis sets was initially established through statistical evaluation of the estimated geometrical parameters with the observed ones. Thiazole and its derivatives were fully optimized at DFT(B3LYP) with the aforementioned basis sets and ground state nature of each was confirmed through frequency calculations. Proton affinity, gas-phase basicity, and chemical reactivity descriptors; frontier orbital, energy gap, chemical hardness, softness, electronegativity, electrophilicity and nucleophilicity were estimated at B3LYP/6-311++G(3df,2p)//B3LYP/6-311++G(d,p). Aromaticity characteristics were confirmed using Harmonic Oscillator Model of Aromaticity (HOMA), Harmonic Oscillator Model of Heterocyclic Electron Delocalization (HOMHED) and Nucleus Independent Chemical Shift (NICS). NICS calculations reflected that the aromaticity of thiazole is higher than any of its derivatives, while HOMA and HOMHED calculations showed that the aromatic characteristic superiority is associated with 2-nitrothiazole. Results indicated that thiazole and its derivatives behave as nitrogen bases with moderate strength. Proton affinity and gas phase basicity calculations were confirmed by Global reactivity calculations. Energy gap and chemical hardness reflected a remarkable thiazole chemical stability. Substituent effect on structural properties, aromaticity, PAs, GBs and global reactivity descriptors has been established. Calculations showed, almostly, the order of reactivity based on the substituent group is $\text{Ph} > \text{NH}_2 \geq \text{NO}_2$ and that 2-phenylthiazole showed the best corrosion inhibition efficiency.

Keywords: Thiazole, B3LYP, Reactivity, Aromaticity and Electronic Properties.

1. Introduction

Heterocyclic compounds as a major classical division of organic chemistry are of immense biological and industrial use (Padwa, and Pearson, 2003; Eicher et al. 2013). Heterocycles are present in all kinds of organic compounds of interest; electronics, biology, optics, pharmacology, material science and so on (Gupta and Kant, 2013). Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents (Bjornsson and Arnason, 2009). Of particular importance, a poly functional heterocycles are considered as a very rich chemically environment in which different heteroatoms therein (Safi, 2016; Fares and Safi, 2014; Safi and Frenking, 2013; Bjornsson and Arnason, 2009; Safi and Abu-Awwad, 2008).

Thiazoles (C_3H_3NS), which were described firstly in the last decades of the nineteenth century, (Hantzsch and Weber, 1887) are one of the most intensively investigated classes of five-membered aromatic heterocycles. Their structure is considered as the resonance hybrid of many resonating structures due to the possibility of the involvement of d-orbitals of sulfur in addition to nitrogen lone pairs of electrons. They exhibit aromatic characteristics and resemble pyridines in their properties.

This five membered ring system containing sulfur and nitrogen heteroatoms at positions (1) and (3), respectively, and three carbon atoms are involved in many of the natural products (such as sesame seed oil and chicken), and in numerous synthetic drugs, dyes, and industrial chemicals.

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture (Burling and Goldstein, 1992; De Souza, 2005; Potewar and Ingale, 2007). These compounds play an important role as synthetic intermediates and common substructures in numerous biologically active compounds such as various derivatives of

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penicillins, thiamine (vitamin B1), and antibacterial thiazoles (Fosbinder and Walter, 1939; Sperry and Wright, 2005; Dolle et al., 2006; Pola, 2016). Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds that are biologically significant (Moulard et al., 1993; Desai and Harsora, 2012). Thiazoles and isothiazoles have an important role in the synthesis of potential medication; antitumor, antimicrobial, anti-infective, cardiovascular and nervous system agents (Geronikaki et al., 2009; Olszewski and Boduszek, 2010). Besides, thiazoles are important precursors for the preparation of other fused compounds, such as oxazoles, pyrazoles, pyrimidines, oxazepines etc. (Jain and Singh, 2016; Ji Ram et al., 2019: 414-421).

In the last few decades, thiazole and its derivatives have been receiving researchers intentions in terms of theoretical, experimental (Frizzo and Martins, 2012; Gümüş and Türker, 2012; Gupta and Kant, 2013; Hegelund et al., 2007; Palmer et al., 2008; Abdelmalek et al., 2011; Belaidi, et al., 2013) and biological investigations (Gupta and Kant, 2013; Jain and Singh, 2016; Sumalatha and Joseph, 2016).

Geometrical structure of thiazole compound was studied using ab initio and density functional (B3LYP) methods with both (6-31G**) and (cc-pVTZ) basis sets (Belaidi et al., 2013). Density functional DFT(B3LYP) prediction of geometrical parameters of thiazoles is found in great consistency with the observed ones obtained by microwave spectrometry (Nygaard et al., 1971).

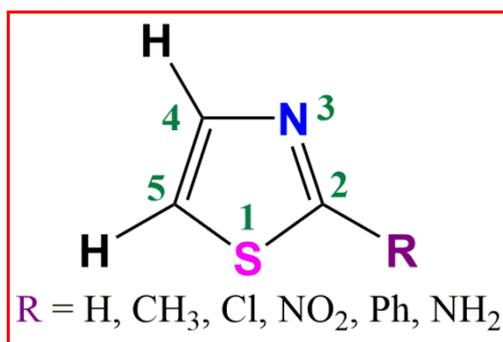
Quantum chemical descriptors such as chemical reactivity and the influence of substituent; either donor or acceptor electron, on the chemical reactivity of thiazoles were investigated (Belaidi et al., 2013; Güray et al., 2007). Semiempirical calculations indicated that the nucleophilicity reduction of 4-nitro thiazole relative to thiazole refers to the reduction of electron density at C4 position as a result of the nitro substituent. (Güray et

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al., 2007). Additionally, theoretical calculations showed that C2 and C4, are the most preferential sites for nucleophilic attack, whereas C5 is more susceptible to electrophilic occurrence (Belaidi et al., 2013).

Thiazole aromaticity studies are limited (Frizzo and Martins, 2012; Gümüş and Türker, 2012). It is found that the aromaticity could be enhanced significantly through NICS calculations upon the introduction of substituent at position-4 in the thiazole ring (Gümüş and Türker 2012). Based on the experimental data from X-ray electron diffraction, the modified Harmonic Oscillator Model of Aromaticity (HOMHED) (Frizzo and Martins, 2012), a modified version of HOMA, has been employed to estimate aromaticity for all heterocycles, except those containing oxygen that reflect weak aromatic characteristics according to Krygowski rHOMA calculations (Raczyńska, 2019). Ab initio method with both 6-31G and 6-31G* basis sets showed that the proton affinity decreases in the order: imidazole < oxazole < thiazole, and it also showed that the proton affinity decreases from nitrogen to oxygen to sulfur. (Kabir and Sapse, 1991)

In this work, Reactivity of thiazole and some of its derivatives (Scheme 1) will be investigated through studying aromaticity indices, basicity to assign the preferred protonation site and the chemical reactivity through local and global reactivity descriptors.



Scheme 1. Schematic representation of thiazole and its derivatives with the numbering scheme.

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2. Computational details

Molecular geometry of 2-phenylthiazole in the gas phase at 1.0 atmospheric pressure and 298 K has been fully optimized followed by frequency calculations at twelve different hybrid functionals; DFT(B3LYP (Becke, 1993; Lee et al., 1988) PBE1PBE(PBE0) (Perdew et al., 1996), mPW1PW91(Adamo and Barone, 1998), LSDA (Vosko et al., 1980) HSEh1PBE(HSE06) (Heyd and Scuseria, 2004), HCTH (Zhao et al., 1994), wB97X-D (Chai and Head-Gordon, 2008), TPSSTPSS (Grimme, 2005; Tao et al., 2003), M06-2X (Zhao and Truhlar, 2006), CAM-B3LYP (Cohen and Handy, 2001) and O3LYP (Yanai et al., 2004), in attempt to assign the most proper functional to be applied in studying such system. The basis set 6-311++G(d,p) (Clark et al., 1983) where diffused and polarized functions were added to both, heavy atoms and hydrogens was used in the calculations. Simulation accuracy of the third row elements; sulfur, were improved through the introduction of extra basis set of Dunning's correlation consistent quadruple-zeta augmented with diffused d-functions; aug-cc-pV(Q+d)Z (Dunning, et al., 2001). Single point energies were calculated at B3LYP/6-311++G(3df,2p)//B3LYP/6-311++G(d,p) and corrected to zero point energies that scaled by the empirical factor 0.9806 as proposed by Scott and Radom (Scott and Radom, 1996). Thermal corrections to the internal energies, enthalpies and free energies were also estimated. Calculations reflected the reliability of the functional B3LYP over the others in simulating such system, as it would be presented in the discussion, so B3LYP/6-311++g(d,p) level of theory will be employed to the entire study unless otherwise stated. Hydrogen proton Nuclear Magnetic Resonance (¹H NMR) chemical shifts were calculated by B3LYP Gauge Independent Atomic Orbital (GIAO) method (Keith and Bader, 1993, 1992) (GIAO-B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) and the isotropic NMR shielding values of a gauss ghost atom probed a distance (0, 0.5, 1.0,

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1.5, 2.0, 2.5 and 3.0 Å) along the principal axis of rotation of thiazone moiety in thiazole and its derivatives were estimated. Aromaticity index based on the Reformulated Harmonic Oscillator Model of Aromaticity (rHOMA) (Krygowski, 1993) and Harmonic Oscillator Model for Heterocycles with π -Eelectrons and/or n-Electron Delocalization (HOMHED)(Kruszewski and Krygowski, 1972) were estimated utilizing the fully optimized wavefunctions. Reactivity of thiazole and its derivatives were investigated through studying some of the global and local reactivity descriptors such as Proton affinity (PA), molecular gas-basicity (GB), electron affinity A , vertical ionization potential I , adiabatic ionization potential (IP), chemical hardness (η), energy gap ΔE_{gab} (the difference between the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO)), electronegativity (χ), chemical potential (μ), electrophilicity (ω) and nucleophilicity (ε) at the B3LYP/6-311++G(3df,2p)//B3LYP/6-311++G(d,p) level of theory. Atomic charges were calculated using Mulliken natural population analysis (Mulliken, 1955). All calculations have been accomplished by using the Gaussian 09 package (Frisch, 2009). Results were visualized by the aid of Gauss View 6.0 Frisch et al., 2010) and Chemcraft (Allouche, 2010). Data manipulations were attained by using MS-Excel. All computations have been carried out on the computational science at the Universidad Autonoma de Madrid (CCC), Spain. Visualization and some simple calculations have been carried out using an office PC; an Intel(R) Core (TM)i7 processor with 8 GB memory.

3.0 Results and discussion

3.1 Validating functional choice

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The optimized geometrical structures; bond distances and bending angles, of thiazole at twelve different hybrid functionals; DFT(B3LYP, B3PW91, M06-2X, wB97X-D, mPW1PW91, HSE06, CAM-B3LYP, O3LYP, PBE0, TPSSTPSS, LSDA and HCTH) with the assigned basis set along with the available experimental values are listed in **Tables S1** and **S2** of the **Electronic supplementary information (ESI)**, for comparative purposes. The results show that all of the assigned functionals are strongly correlated with the experimental values. To decide which functional that will be the optimum choice of them and thus being employed to the entire of the study, statistical, relative and average relative deviations, as it is defined in **Eqs 1** and **2**, were employed , and the results are recorded in **Table 1**.

$$\text{relative deviation} = \frac{1}{N} \left(\sum_{i=1}^N \left| \frac{\text{theoretical value} - \text{experimental value}}{\text{experimental value}} \right| \times 100 \right) \quad (1)$$

$$\text{average deviation} = \frac{\text{bond distance relative deviation} + \text{bending angle relative deviation}}{2} \quad (2)$$

Table 1. Relative and average relative deviations of the calculated geometrical parameters of thiazole from the observed values.

Method	Bond distance relative deviation	Bending angle relative deviation	Average Deviation
B3LYP	0.1940	0.1921	0.1931
B3PW91	0.2827	0.1918	0.2372
M062x	0.3078	0.1918	0.2498
WB97XD	0.3288	0.1930	0.2609
MPW1PW91	0.3459	0.1967	0.2713
HSEH1PBE	0.3686	0.2002	0.2844
CAM-B3LYP	0.3582	0.2320	0.2951
O3LYP	0.2623	0.1727	0.2951
PBE1PBE	0.3949	0.2044	0.2996

TPSSTPSS	0.4777	0.12300	0.3038
LSAD	0.8562	0.3581	0.6027
HCTH	1.3368	0.2011	0.769

As it obvious from **Table 1**, the statistical evaluation reflects the preferentiality of B3LYP functional due to lowest average relative deviation. **Figure 1** presents, as an example, the remarkable correlations between the B3LYP calculated geometrical parameters (bond distances and bending angles) and the corresponding observed ones.

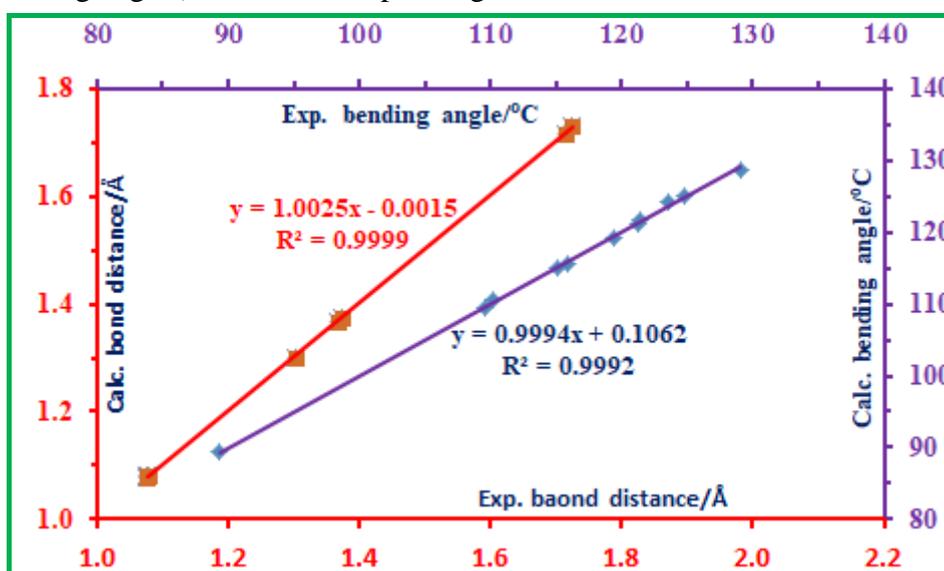


Figure 1. B3LYP/6-311++G(d,p) calculated geometrical parameters vs. the observed ones; bond distances (major axis, red color) and bending angles (minor axis, blue color).

3.2 Molecular geometry

The optimized geometrical structures of the compounds under probe were found ground state on the potential energy surface due to inexistence of imaginary vibrational modes of frequencies. According to **Table S1** in **ESI**,

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for thiazole, the calculated bond distances predicted by B3LYP of S1-C2 and C5-S1 are 1.729 Å and 1.717 Å, respectively, are shorter than that of a typical S-C single bond (1.82 Å) and longer than that of a typical S=C double bond (1.60 Å). Accordingly, the calculated S-C bond length would have a double bond character. The same behavior is also noticed for the N3-C4, C2-N3 and C4-C5 bonds. The calculated bond lengths of N3-C4 and C2-N3 are 1.373 Å and 1.302 Å, respectively, which are shorter than that of a typical C-N single bond (1.47 Å) and longer than that of a typical C=N double bond (1.29 Å), reflecting varied double bond character . Based on that, one could safely conclude that the π -electron density between the bonds S1-C2, C5-S1, N3-C4 and C2-N3 are delocalized implying the existence of hyperconjugation. These results can also be confirmed through displaying the frontier molecular orbitals (HOMO and LUMO), electrostatic potential and contour maps (**Figure 2**), in which the charge density is distributed with more concentration on the highest electronegative moiety. The red color reflects the lowest electrostatic potential and thus electron rich region, while blue one represents the highest electrostatic potential region and thus the lowest charge density distribution.

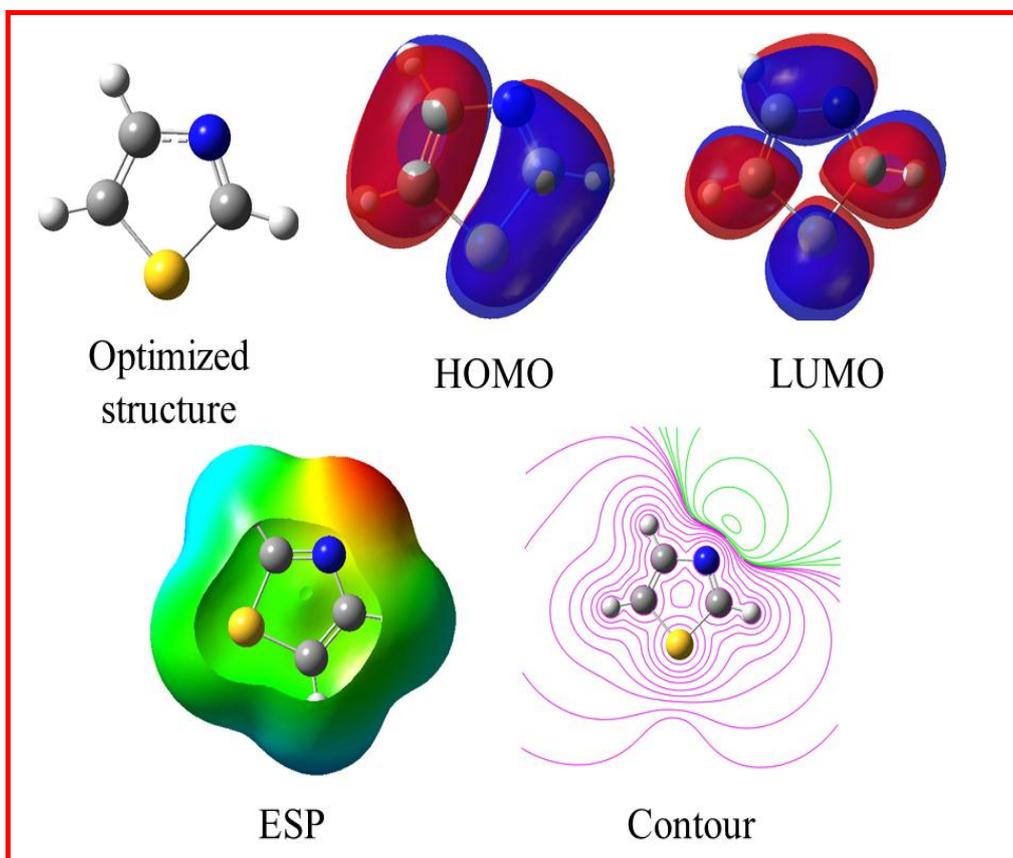


Figure 2 . Optimized geometrical structure, frontier molecular orbitals (HOMO and LUMO) and electrostatic potential (ESP) and contour maps of the unsubstituted thiazole in the gas phase using B3LYP/6-311++G(d,p).

Our results revealed that the calculated C4-C5 bond distance (1.366 Å) is considerably shorter than that of a typical C-C single bond (1.54 Å) by 0.174 Å and slightly longer than that of a C=C double bond (1.34 Å) by 0.026 Å. This bond is closed to the optimum aromatic carbon-carbon bond (1.388 Å), indicating that the π -electron density between C4-C5 might be delocalized. Similar results are also obtained with all other functionals involved in the study.

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3.3 Substituent effect on geometrical structure

It is well known that substituents might significantly influence the geometrical structural parameters relative to that of the parent compound. (Raissi et al., 2013; Raissi et al., 2012; Safi, 2016). The influence of substituents on thiazole geometrical structure has been examined through the introduction of a variety of activating/deactivating groups; CH₃, NH₂, Cl, F, Ph and NO₂ on C2 position. As it is afore mentioned, selected substituted derivatives were found ground states on the PSE. Their optimized geometries along with that of the parent thiazole are given in **Figure 3**, while their optimized molecular parameters are provided in **ESI** as mole files.

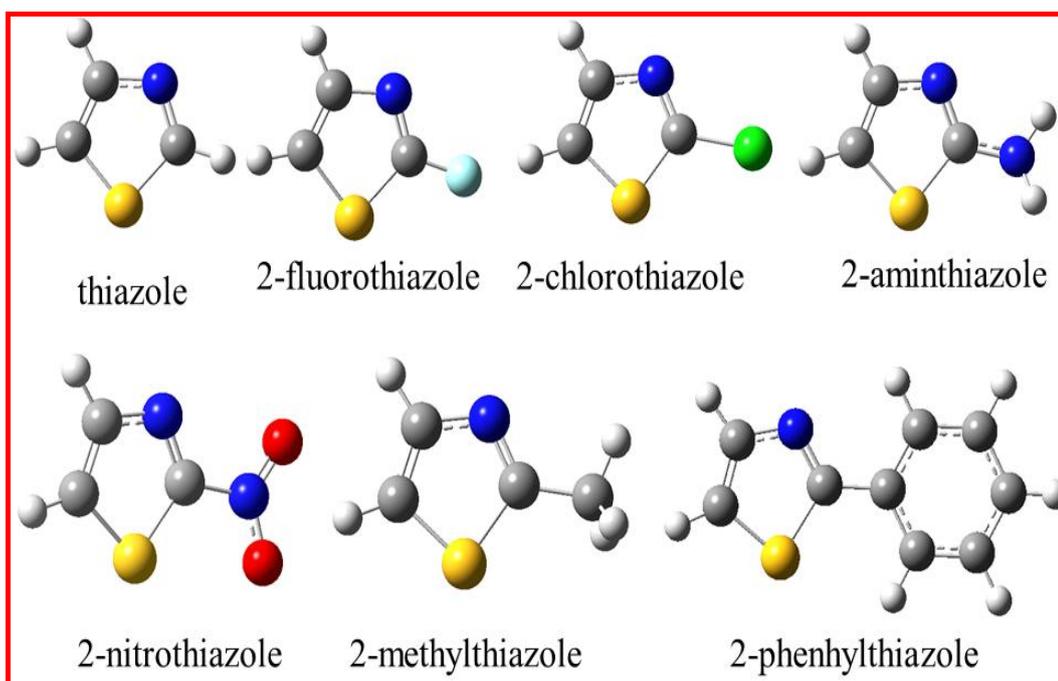


Figure 3. Optimized molecular structure of thiazole and its derivatives.

The most obvious influence were noticed with the electron donating CH₃ group where S1-C2 bond experienced 0.016 Å elongation while the impact of introduction of the electron withdrawing NO₂ group shortens the S1-C2 by 0.007 Å compared to the parent thiazole. Similar results are also shown for the other bonds. This behavior could be rationalized in terms of the impact of increasing/decreasing electron density in the assigned bonds upon push/pull characteristics of substituents.

3.4 Aromaticity index

3.4.1. Nucleus-independent chemical shifts (NICS) indices

The calculated NICS values of neutral thiazole and its selected derivatives at the GIAO- B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory are recorded in **Table 2**. Calculations were accomplished through the introduction of (Bq) ghost atom at the distances, 0, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 Å away from the surface of species under probe.

Table 2. Calculated NICS data (in ppm) for thiazole and its derivatives at the GIAO- B3LYP /6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory.

Substituent	NICS values (ppm)						
	0.0 Å	0.5 Å	1.0 Å	1.5 Å	2.0	2.5 Å	3.0
H	-	-14.15	-11.65	-7.85	-4.83	-2.95	-1.86
CH ₃	-	-12.99	-10.36	-6.89	-4.24	-2.60	-1.64
Cl	-	-12.21	-9.50	-6.28	-3.84	-2.34	-1.48
F	-	-12.09	-9.21	-6.03	-3.66	-2.21	-1.38
NH ₂	-	-10.98	-8.57	-5.72	-3.50	-2.12	-1.33
Ph	-	-11.65	-9.82	-6.45	-3.85	-2.34	-1.52
NO ₂	-	-13.46	-11.24	-7.64	-4.71	-2.89	-1.83

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Table 2 shows that the aromaticity of thiazole and its derivatives decreases significantly at long distances in the order NICS(0) > NICS(0.5) > NICS(1) > NICS(1.5) > NICS(2) > NICS(2.5) > NICS(3). In addition, NICS values varied significantly with substituent so it could be utilized to differentiate between relative aromaticities of thiazole and its derivatives.

3.4.2 The harmonic oscillator model of aromaticity (HOMA)

In this work, rHOMA (Krygowski, 1993) and HOMHED (Frizzo and Martins, 2012) have been chosen to describe π -electron delocalization quantitatively in thiazole compound and some of its derivatives. HOMHED uses the optimized bond length R_{opt} determined experimentally by X-ray diffraction and neutron diffraction. R_{opt} is similar to the bond in aromatic systems where the atoms show the same hybridization (Frizzo and Martins, 2012). HOMHED works in line with rHOMA for all heterocycles, except those containing oxygen, which were found to be weak aromatic from Krygowski rHOMA calculations; Eqs (3) and (4).

$$rHOMA = 1 - \frac{\alpha}{N} \sum (R_{opt} - R_i)^2 \quad (3)$$

$$\alpha = 2 \left\{ (R_{opt} - R_s)^2 + (R_{opt} - R_d)^2 \right\}^{-1} \quad (4)$$

Where N is the number of bonds taken into account, R_{opt} is the appropriate optimum bond length, R_i is the real bond length (experimental or computed bond length), R_s and R_d are the reference single and double bond lengths,

respectively. A normalized α constant for each type of bond is required. The normalized values of α are: 57.21 (N-O), 93.52 (C-N), 94.09 (C-S), 157.38 (C-O) and 257.7 (C-C) (Krygowski, 2001; 1993). HOMHED classifies, compounds as aromatic if HOMA > 0.5, non-aromatic if $0.0 < \text{HOMA} < 0.5$ or anti-aromatic if $\text{HOMA} < 0$ (Mrozeka et al., 2000). The calculated rHOMA and HOMHED values of neutral and substituted thiazole as predicted by B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) level of theory are tabulated in **Table 3**.

Table 3. rHOMA and HOMHED of neutral and substituted thiazole as predicted by B3LYP/6-311++G(d,p)// B3LYP/6-311++G(d,p) level of theory.

substituent	HOMA	HOMHED
H	0.847	0.871
CH ₃	0.800	0.835
Cl	0.804	0.834
F	0.768	0.804
NH ₂	0.740	0.789
Ph	0.814	0.845
NO ₂	0.879	0.888

The calculated values of both rHOMA and HOMHED at the assigned level of theory indicate that thiazole and its derivatives are aromatic compounds since the rHOMA and HOMHED values in all cases are higher than 0.5. According to **Table 3**, the aromaticity of thiazole and its derivatives calculated by rHOMA and HOMHED indices are decreasing in the order $\text{NO}_2 > \text{H} > \text{Ph} > \text{Cl} \approx \text{CH}_3 > \text{F} > \text{NH}_2$.

Inspection of **Table 2** and **Table 3** show that the aromaticity characteristics of thiazole suffer a varied influence which could be generally attributed to diverse inductive behavior of substituents. Thiazole

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experiences, nearly, a significant reduction in aromaticity characteristics with all substituents, whether activating or deactivating. Aromaticity characteristic of thiazole suffers the least reduction in the presence of the strongest electron-withdrawing group NO₂ in case of NICS calculations, but slightly enhanced within the cases of rHOMA and HOMHED. The slight aromaticity de/increment in the case of NO₂ substituent might be referred to the formation of the highly conjugated Zwitterion triene resonating structure **II** in **Figure 8**. Aromaticity reduction within the case of fluoride substituent is more than that of chlorine due to its high electronegative characteristic than that of chloride moiety. Methyl and phenyl groups show varied influence in NICS and the other two aromaticity models, which might be referred to the difference in bond hybridization; sp² in phenyl and sp³ in the case of methyl group. The most remarkable aromaticity reduction is found associated within NH₂ substituent, the strongest electron releasing substituent. This could be attributed to a probable perturbation of charged density due to strong electron pumping behavior of NH₂ moiety where C2 getting more positive (**Table 5**) in addition to aromaticity abolition through the formation of the transient resonating structure **II** as clarified in **Figure 7**. In this case reactivity of thiazole would be enhanced significantly in the presence of a very strong pumping effect.

According to HOMA and HOMHED, it would be safely said that: increasing the substituent electrophilicity (like NO₂ group) brings about an increase in aromaticity (Mrozeka et al., 2000). The predicted aromaticity indices for all, the neutral thiazole and the substituted ones, by HOMHED are larger than that predicted by rHOMA . This behavior could be rationalized in terms of the role played by each theory. HOMHED theory takes into consideration in its postulates the type of bond whether hetero or homo dinuclear bond, while the rHOMA treats all bonds as though, they are C-C bonds only. To facilitate comparison between the results of the two

theories, rHOMA and HOMHED aromaticity indices are displayed in Figure 4.

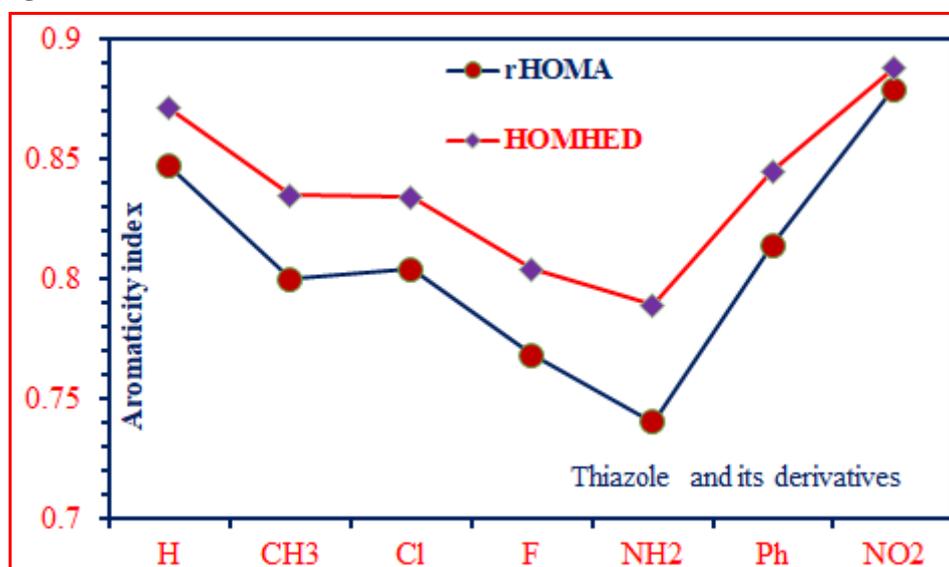


Figure 4. HOMA and rHOMHED aromaticity indices of thiazole and its derivatives as predicted by B3LYP/6-311++G(3f,d)//B3LYP/6-311++G(d,p) level of theory.

3.5 Proton affinity and gas phase basicity

The energy released by the addition of a proton (H^+) to the basic center of a neutral molecule is called proton-affinity (PA), while gas phase basicity (GB) is associated with the electron donating ability.

Global proton affinities and gas phase basicities of neutral thiazole and its derivatives that were predicted by B3LYP/6-311++G(3df,2p)// B3LYP/6-311++G(d,p) in gas phase and corrected to ZPE and thermal energy correction are recorded in **Table 4**, while local PA and local GB values are reported in **Table 5**. Experimental values of PA and GP, where accessible, are also included for comparison. (Linstrom, 2003; Hunter and Lias, 1998).

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Table 4 Calculated proton affinity and gas phase basicity in (kcal mol^{-1}) of thiazole and its derivatives as predicted at B3LYP/6-311++G(d,p)//B3LYP/6-311++G(3df,2p) level of theory. Experimental values are given between brackets in bold face character.

Species	PA (kcal	GB (kcal mol^{-1}
H	217.0	209.4(208.4)
CH ₃	222.5	214.6 (214.8)
Cl	212.5	204.9
F	207.4	199.8
NH ₂	225.0	217.7 (214.8)
Ph	225.9	218.0
NO ₂	201.3	193.8

Table 4 reflects that the computed proton affinity and gas phase basicity values of thiazole and its derivatives are following the order : Ph > NH₂ > CH₃ > H > Cl > F > NO₂. Obviously, the higher the value of proton affinity corresponds to higher basicity. Stated differently, the higher the proton affinity, the stronger the base and the weaker the conjugate acid in the gas phase. Ph, NH₂ and CH₃ substituents are acting in such a way of pumping electrons to the ring and thus reactivity in the direction of proton affinity (nucleophilicity) is enhanced. To the contrary, the electron withdrawing Cl, F and NO₂ substituents reduced the protonation tendency and thus reactivity toward electrophilicity would be enhanced. A highly remarkable correlation between GS and PA is manifested in **Fig 5**, where GB is linearly varied with PA; $\text{GB} = 0.9929\text{PA} - 6.1048$; $R^2 = 0.9995$.

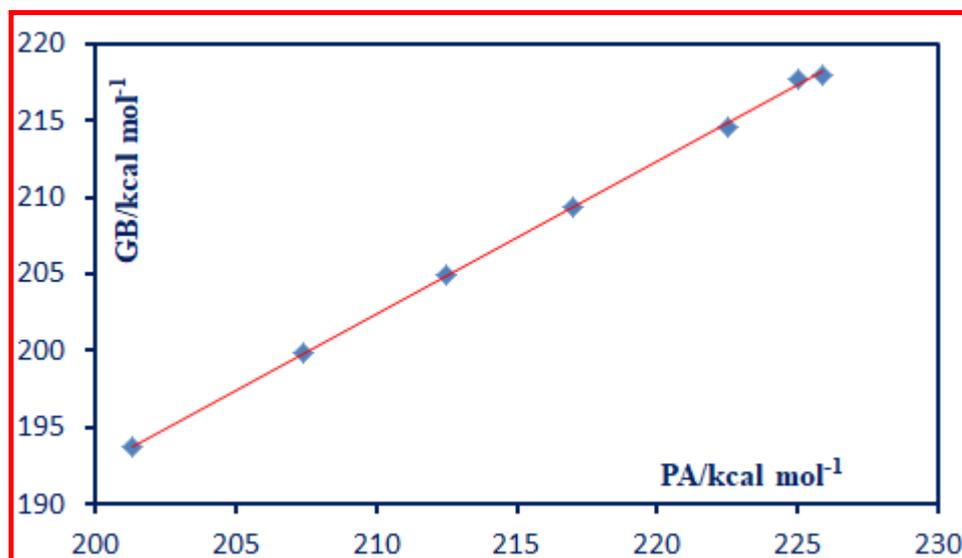


Figure 5. Proton affinity vs. gas basicity of thiazole and its substituted derivatives.

Table 5. Local proton affinity and gas phase basicity in (kcal mol⁻¹) of thiazoles and Mullikan natural population analysis as predicted in gas phase by B3LYP/6-311++G(3df,2p)// B3LYP/6-311++G(d,p) level of theory.

Atom center	Local PA kcal mol ⁻¹	Local GB kcal mol ⁻¹	Atomic charge / eu						
			H	CH ₃	Cl	F	NH ₂	NO ₂	Ph
S1	160.45	153.33	1.536	1.22	1.519	1.162	1.093	1.364	1.371
C2	174.99	167.66	-0.351	-0.01	-0.181	0.511	0.666	0.573	-0.288
N3	208.45	200.79	-0.79	-1.02	-0.93	-0.99	-1.08	-1.03	-1.06

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			6	5	8	7	2	2	4
C4	172.90	165.63	0.33 0	0.16 7	0.11 3	0.06 0	0.82	0.14 7	0.37 8
C5	178.93	171.61	- 0.80 0	- 0.79 6	- 0.79 8	- 0.67 9	- 0.74 9	- 0.75 6	- 0.98 5

Apparently, calculations show the presence of two probable protonation sites; N3 and C5 moieties, but protonation occurs more favorably on the N moiety, due to high accumulation of charge density. C5 could be marked as the primary site for electrophilic substitution (**Figure 6-III**), while nucleophilic substitution could be preferentially associated with C2 moiety. It may also be worthwhile pointing out here that electrophilic substitution might be also accessible on C4 (**Figure 6-II**) in the parent thiazole where PA is 172.90 eV provided that the polarization of π -clouds of S moiety redistributed via 4,5-double bond given rise to the following resonating structures, **Figure 6**.

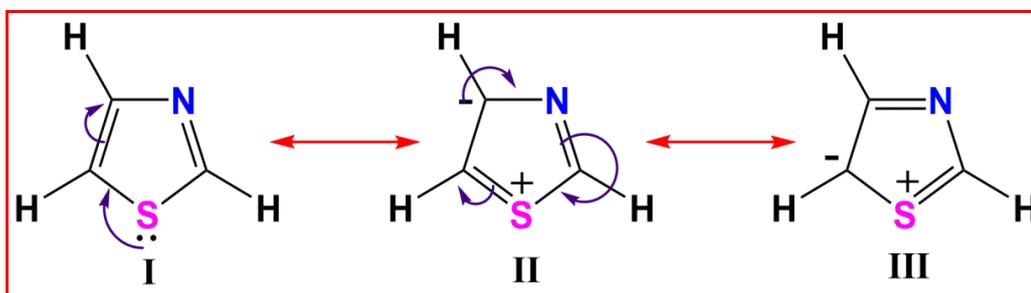


Figure 6. Sites of electrophilic substitution in thiazole.

The least electrophilic and thus nucleophilic characteristic is shown associated with the S moiety. This S behavior could be rationalized in terms of sharing electron density where the S nonbonding electrons are hyperconjugated with the ring charge density to enforce thiazole aromaticity characteristic. The predicted order of electrophilicity as introduced in

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Table 5 is $N3 > C5 > C2 > C4 > S1$. These results are found consistent with the natural population analysis of the charge density on thiazole atoms as it is evident in **Table 5** and **Figure 2**, where the charge density is mostly concentrated at N and C5 moieties while the S moiety is the positive charge center within thiazole compound. The introduction of substituents on position C2 in the parent thiazole compound slightly influenced the charge populations on all atoms, but almost retained its electronic characteristics, whether electrophilic or nucleophilic ones. The most tangible influence is found within the nitrogen center where the charge was found intensified which reflected positively on enhancing aromaticity characteristics as it is already discussed.

3.6 Global reactivity descriptors

Chemical reactivity descriptors such as E_{HOMO} , E_{LUMO} , ΔE , chemical hardness, softness, electronegativity, electrophilicity and nucleophilicity give important clues about electron-donating and accepting abilities of molecules and thus their reactivities. In general, electron-donating ability is associated with high E_{HOMO} , while the lower the value of E_{LUMO} the more likely the molecule to accept electrons (Obot et al., 2016).

3.6.1 Ionization energy and electron affinity

Table 6 displays E_{HOMO} , E_{LUMO} , energy gap ΔE , vertical ionization energy (I) and electron affinity (A), adiabatic ionization and electron affinity potentials (IP and EA) of the studied thiazole along with the selected derivatives in the gas phase at B3LYP/6-311++G(3df,2p)// B3LYP/6-311++G(d,p) level of theory. According to Koopman's theorem, [Koopmans, 1934] I and A could be approximated as the energies of LUMO and HOMO, respectively. **Table 6** shows that the reactivity of thiazoles under probe according to HOMO or I energies obeys the order : $NH_2 > Ph$

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> CH₃ > Cl > H > F > NO₂ which is almost in consistence with the trend obtained from *IP* calculations; NH₂ > Ph > CH₃ > Cl > F > H > NO₂ . On the other hand, reactivity based on ΔE that found in the order Ph > NO₂ > NH₂ > Cl > CH₃ > H > F is in consistence with that predicted from $\Delta E'$; Ph > NH₂ > NO₂ > Cl > CH₃ > F > H. Despite of remarkable similarities in the two predictions, *IP* and *EA* will be considered in estimating global reactivity descriptors due to more reliable *IP* value. In another words, *IP* value is 9.2593 eV, deviated 1.11% from the experimental ionization potential (9.3633 eV), compared to homo prediction of *I* (7.1697 eV) which largely deviate from the observed one (23.43%). It is vital to point out that $\Delta E' = IP - EA$, $IP = E^+ - E^o$ and $EA = E^o - E^-$ where E^+ , E^o and E^- are the energies of cation, neutral and anion species, respectively, calculated at the same level of theory and corrected to the scaled ZPEs. These results indicate that the introduction of groups, whether, activating or deactivating, increases thiazole reactivity and remarkable reactivity enhancement is associated with the strength of electron push/pull capability of substituent groups. Stated differently, a molecule with a low ΔE and $\Delta E'$ is more polarizable and is generally associated with the high chemical activity, and thus, classified as soft molecule. (Bereket and Öğretir, 2002; Ebenso et al., 2010). The order of reactivity here is 2-phenylthiazone > 2-aminothiazone \approx 2-notroamine.

Table 6. E_{HOMO}, E_{LUMO}, Energy gap (ΔE), Ionization energy (*I*) and electron affinity (*A*) of the non-protonated thiazole and its derivatives in the gas phase as predicted by B3LYP/6-311++G(3df,2p)// B3LYP/6-311++G(d,p) level of theory. All values are in eV .

Substituent	E_{HOMO}	E_{LUMO}	ΔE	I	A	IP	EA	$\Delta E'$
H	- 7.169 7	- 1.147 2	6.022 5	7.169 7	1.147 2	9.259 3	- 0.532 2	- 9.791 5
CH ₃	- 6.807 0	- 0.973 9	5.833 1	6.807 0	0.973 9	8.748 4	- 0.639 2	- 9.387 5
Cl	- 7.127 3	- 1.414 7	5.712 5	7.127 3	1.414 7	9.031 6	0.459 7	- 8.571 9
F	- 7.236 9	- 1.198 7	6.038 3	7.236 9	1.198 7	9.266 9	- 0.477 2	- 9.744 1
NH ₂	- 6.052 4	- 0.647 4	5.405 0	6.052 4	0.647 4	7.825 2	- 0.429 5	- 8.254 7
Ph	- 6.342 5	- 1.793 0	4.549 5	6.342 5	1.793 0	7.900 9	0.333 1	- 7.567 8
NO ₂	- 8.075 0	- 3.403 4	4.671 7	8.075 0	3.403 4	9.927 0	1.671 9	- 8.254 7

3.6.2 Electronegativity and chemical potential

Whereas electronegativity (χ) represents the power to attract electrons of a chemical species, chemical potential (μ) describes the escaping tendency of electrons from the system. μ that could be used as a global reactivity descriptor is defined in terms of the derivative of energy E with respect to

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the number of electrons N at constant external potential $v(r)$;

$$\mu^+ = \left(\frac{\partial E}{\partial N} \right)_{v(r)} = -A \quad \text{and} \quad \mu^- = \left(\frac{\partial E}{\partial N} \right)_{v(r)} = -I.$$

The calculated χ and μ of thiazole and its derivatives in the gas phase that derived from IP and EA such as $\mu = -\chi = \left(\frac{IP + EA}{2} \right)$ are given in **Table 7**. Calculations showed that

2-aminothiazole would be the highest reactive one due to possessing maximum potential ($\mu = -3.6978 eV$) and lowest electronegativity ($\chi = 3.6978 eV$), while 2-nitrothiazole would be the least reactive one of all since it is the highest electronegative ($\chi = 5.7994 eV$) and retaining least chemical potential characteristics ($\mu = -5.7994 eV$). According to **Table 7**, reactivity obeyed the order: $NH_2 > CH_3 > Ph > H > F > Cl > NO_2$.

For more clarification, the electronegativity of the 2-aminothiazole is found to be $\sim 0.67 eV$ lower than the corresponding thiazole molecule while the electronegativity of the 2-nitrothiazole is $\sim 1.44 eV$ higher than that of the parent compound; unsubstituted thiazole.

Table 7. Electronegativity, chemical potential, hardness, softness, electrophilicity and energy ($\chi, \mu, \eta, s, \omega$ and ε , respectively, all in eV) thiazole and its substituted derivatives, as predicted by B3LYP/6-311++G(df,3pd)//B3LYP/6-311G(d,p) level of theory.

Substitue	χ	μ	η	s	ω	ε	ΔN_{110}	ΔE_{b-d}
H	4.363	-	4.895	0.204	1.944	0.514	0.269	-
CH₃	4.054	-	4.693	0.213	1.751	0.571	0.313	-
Cl	4.745	-	4.286	0.233	2.627	0.380	0.263	-
F	4.394	-	4.872	0.205	1.982	0.504	0.267	-
NH₂	3.697	-	4.127	0.242	1.656	0.630	0.400	-

Ph	4.117	-	3.783	0.264	2.239	0.446	0.381	-
NO ₂	5.799	-	4.127	0.242	4.074	0.245	0.145	-

3.6.3 Hardness and softness

As it is known that, both the global hardness (η) and softness (S) and energy gap are closely interrelated chemical properties;

$$\eta = \left(\frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \right) = \left(\frac{IP - EA}{2} \right) = \frac{1}{S}$$

According to maximum hardness principle (Pearson, 1993), chemical hardness is a measure of stability of a chemical species. In another meaning, hardness indicates the resistance toward the deformation of electronic atmosphere of a chemical species when exposed to a small perturbation encountered in a chemical reaction. A hard molecule has a large energy gap and thus the electronic cloud is strongly held by the nucleus. A soft molecule has a low energy gap and the electronic cloud is loosely held by the nucleus (Obot, 2010). The global softness describes the capability of a chemical species to accept electrons. Molecules with the least values of global hardness and greatest values of global softness are expected to be good reactive molecules. Hardness (in eV) and softness (in eV^{-1}) of the non-protonated thiazole and its derivatives in the gas phase are presented in **Table 7** where 2-phenyl thiazole has shown to have the least value of global hardness ($\eta = 3.7839 eV$) and hence the highest value of global softness ($s = 0.2643 eV$), so it is expected to be the highest reactive of all. Besides, the neutral thiazole possesses good chemical stability ($\eta = 4.8957 eV$ and $s = 0.2043 eV$). The larger energy gap ($\Delta E = 6.0225 eV$) suggests that it has significant kinetic stability according to softness-hardness rule and thus be classified as a hard one compared to its substituted derivatives, except of 2-florothiazole ($\eta = 4.8721 eV$, $s = 0.2053 eV$ and $\Delta E = 6.0335 eV$) which would be slightly

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harder than it. A last thing to be observed here is that the molecular hardness has decreased upon the introduction of electron donating groups (CH₃, NH₂ and Ph), implying a more reactive species. The order of softness is found Ph > NO₂ ~ NH₂ > Cl > CH₃ > F > H.

3.6.4 Electrophilicity and Nucleophilicity

Electrophilicity (ω) and nucleophilicity (ε) are useful quantum chemical descriptors in prediction of substances chemical reactivities. They are

interrelated such as $\omega = \frac{\chi^2}{2\eta} = \varepsilon^{-1}$. The higher the value of ω , the higher

the capacity of the molecule to accept electrons. Thus, a good nucleophile is characterized by low value of ω ; whereas a high value of ω is a characteristic of a respectable electrophile. Alternatively, a molecule that has a large ε , which is an indication of a higher E_{HOMO} , is a good reactive molecule. Predicted electrophilicity (in eV^{-1}) and nucleophilicity (in eV) of the non-protonated thiazole and its derivatives in the gas phase are recorded in **Table 7**. In the light of ω and ε values given in **Table 7**, reactivity ranking of studied compounds can be given as : NH₂ > CH₃ > H > F > Ph > Cl > NO₂.

An inspection of these results indicates that on going from electron donating groups to the electron withdrawing ones, electrophilicity increases while nucleophilicity decreases. These results indicate that the thiazole nucleophilicity is enhanced on replacing hydrogen atom by an electron donating group. This could be attributed to delocalization promotion of π -electrons of structure **I** through the transient form **II**, facilitating the formation of the canonical structure **III**, as it illustrated in **Figure 7**.

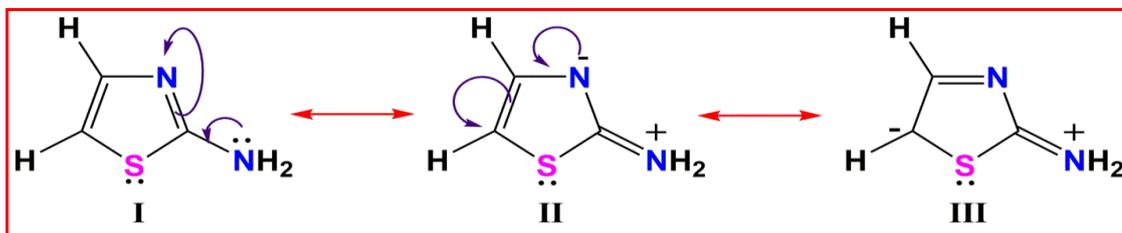


Figure 7. Influence of highly activating substituent on electrophilicity enhancement on C5.

In contrast, thiazole electrophilic characteristic at C5 position is reduced when hydrogen atom at position 2 is substituted by electron withdrawing group. Differently stated, electrophilic substitution at 5-position is very challenging in the presence of electron accepting group like NO_2 due to reverse delocalization as clarified in **Figure 8**.

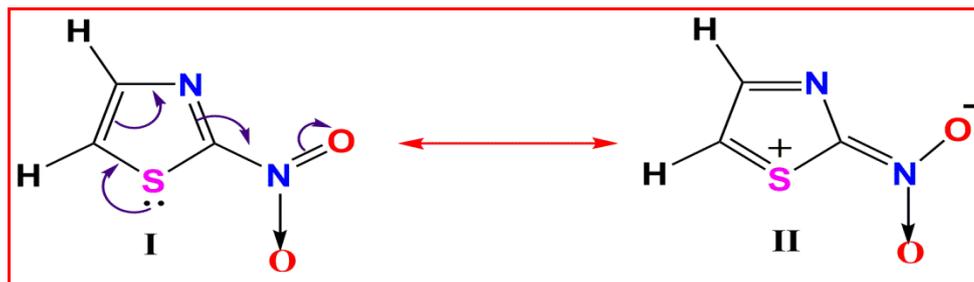


Figure 8. Influence of highly deactivating substituent on electrophilicity enhancement on C5.

3.7 The fraction of electrons transferred

It was reported that the fraction of electrons transferred (ΔN) from the inhibitor molecule to the surface of the metal can be calculated according to **Eq. 5** [Chauhan and Gunasekaran, 2007; Rodriguez et al., 2006].

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$$\Delta N = \frac{\chi_{\text{Fe}} - \chi_{\text{inh}}}{2(\eta_{\text{Fe}} + \eta_{\text{inh}})}$$

(5)

where χ_{Fe} is the electronegativity of Fe metal, which is equal to 7 for Fe(110) plan and the overall hardness $\eta_{\text{Fe}}=0$, assuming that in the metallic bulk $I = A$ [Abreu-Quijano et al., 2011] and χ_{inh} and η_{inh} are the electronegativities and hardnesses of inhibitors (thiazole and its derivatives) given in **Table 7**. The results of ΔN_{110} are gathered in **Table 7**. The calculated values of ΔN_{110} (**Table 7**) show that the trend of reactivity within the studied thiazole derivatives follows the order 2-aminothiazole > 2-phenylthiazol > 2-methylthiazole > thiazole > 2-flurothiazole > 2-chlorothiazole > 2-nitrothiazole >. The highest value of ΔN is associated with the most efficient inhibitor. Even more, our results indicate that 2-amionothiazole is the best inhibitor among the studied molecules, whereas, 2-nitrothiazole has the lowest effective inhibition behavior.

3.8 Energy of electronic back-donation

Gómez et al. [Gomez et al., 2006] showed that the interaction between the inhibitor molecule and the metal surface can be governed by an electronic back-donation process. In this sense, if both processes occur, namely charge transfer to the molecule and back-donation from the molecule, the energy change associated with back donation ($\Delta E_{\text{b-d}}$) is directly proportional to the

hardness of the molecule, such as $\Delta E_{\text{b-d}} = -\frac{\eta}{4}$ [Gomez et al., 2006].

Results obtained for $\Delta E_{\text{b-d}}$ are presented in **Table 7** which shows, the

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calculated ΔE_{b-d} value of each of the studied thiazole derivatives is less than 0. This would implies that, the charge transfer to a molecule followed by a back-donation from the molecule would be energetically favored provided that $\eta > 0$ and $\Delta E_{b-d} < 0$. The order followed is: 2-phenylthiazol > 2-aminothiazole = 2-nitrolthiazole > 2-chlorothiazole > 2-methylthiazole > thiazole > 2-flurothiazole, indicating that 2-phenylthiazole could be of valuable utility in the field of corrosion inhibition.

Conclusion

Reactivity of thiazole and the influence of some push/pull substituents on its reactivity have been theoretically investigated by the aid of B3LYP density functional, which proved to be the most appropriate functional of the set of the hybrid functionals used, in the gaseous state. The studied molecules were ground state on the potential surface energy. Aromaticity indices were calculated by using three different models; NICS, HOMA and HOMHED. Proton affinity, gas phase basicity and global reactivity descriptors; IP , EA , χ , μ , η , s , ω , ε , ΔN and ΔE_{b-d} were examined. Aromaticity calculations showed that the thiazoles in the study are aromatic due to aromaticity indices more than 0.5 of each of them, and aromaticity is invariably, negatively, influenced upon the introduction of substituents where the least recorded aromaticity reduction is found accompanied with the most electrons withdrawing NO_2 substituent. Additionally, NICS calculations showed that the aromaticity of thiazole is higher than those of its derivatives regardless of the substituent group. Reactivity of thiazole is enhanced under the influence of substituents where electrophilicity increases upon the substitution of H2 by electron releasing group; particularly, NH_2 group, while nucleophilicity increases in the presence of electron withdrawing one; particularly, NO_2 group. The most remarkable

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reactivity improvements were found within the phenyl, amine and nitro substituents. Calculations made it clear that thiazole might have a promising future as corrosion inhibitor upon the attachment with either of Ph, NH₂ or NO₂ substituents due to better charge transfer and back-donation capabilities.

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Supplementary material

Table S1. Bond distances of thiazole as predicted by 12 DFT functionals												
R	LSDA	PBEPBE1	B3LYP	B3PW91	MBW1PW91	HSEH1PBE	HCTH	WB97XD	TPSSTPSS	X3LYP	CAM-B3LYP	O3LYP
S1-C2	1.7107	1.7138	1.7287	1.7187	1.7145	1.7149	1.7174	1.715	1.7332	1.7268	1.7141	1.7206
S1-C5	1.6948	1.7046	1.7171	1.7185	1.7054	1.7053	1.7035	1.7077	1.719	1.7165	1.7076	1.709
C2-N3	1.3009	1.2999	1.3019	1.3013	1.2991	1.2997	1.3046	1.2984	1.3109	1.3011	1.2961	1.3043
C2-H6	1.0916	1.083	1.0817	1.0828	1.0815	1.0827	1.0839	1.0821	1.0843	1.0815	1.0814	1.0831
N3-C4	1.3553	1.365	1.3729	1.3672	1.3653	1.3651	1.3638	1.3694	1.3769	1.3718	1.3691	1.368
C4-C5	1.3675	1.3651	1.3662	1.3662	1.3641	1.365	1.3706	1.3618	1.3731	1.3657	1.3594	1.3696
C4-H7	1.092	1.0831	1.0818	1.083	1.0816	1.0828	1.0845	1.0818	1.0849	1.0816	1.0811	1.0834
C5-H8	1.0884	1.0799	1.0787	1.0798	1.0784	1.0796	1.081	1.0788	1.0821	1.0785	1.078	1.08

Table S2. Bending angles of thiazole as predicted by 12 DFT functionals												
Angle	LSDA	PBEPBE1	B3LYP	B3PW91	MBW1PW91	HSEH1PBE	HCTH	WB97XD	TPSSTPSS	X3LYP	CAM-B3LYP	O3LYP
C2-S1-C5	89.88	89.66	89.32	89.58	89.62	89.63	89.65	89.57	89.37	89.39	89.55	89.58
S1-C2-N3	114.46	114.94	114.89	114.91	114.93	114.92	114.93	115.00	115.02	114.85	114.91	115.00
S1-C2-H6	121.10	121.11	121.05	121.09	121.12	121.11	120.93	121.25	120.96	121.11	121.28	120.99
N3-C2-H6	124.45	123.94	124.07	124.00	123.95	123.98	124.13	123.75	124.01	124.04	123.80	124.02
C2-N3-C4	110.75	110.31	110.53	110.38	110.36	110.37	110.25	110.30	110.18	110.57	110.49	110.22
N3-C4-C5	115.52	115.77	115.70	115.77	115.76	115.76	115.79	115.73	115.84	115.72	115.58	115.86
N3-C4-H7	119.75	119.39	119.30	119.38	119.38	119.40	119.51	119.31	119.14	119.32	119.33	119.77
C5-C4-H7	124.73	124.84	125.00	124.85	124.86	124.84	124.70	124.96	125.02	124.96	125.09	124.77
S1-C5-C4	109.39	109.31	109.55	109.37	109.33	109.33	109.38	109.40	109.59	109.47	109.47	109.35
S1-C5-H8	121.76	121.94	121.79	121.88	121.94	121.92	121.71	122.13	121.52	121.86	122.08	121.80
C4-C5-H8	128.85	128.75	128.66	128.75	128.73	128.74	128.91	128.48	128.89	128.68	128.45	128.86

Mol_files

Density Functional Studies



thiazole.mol



thiazole_CH3.mol



thiazole_Cl.mol



thiazole_F.mol



thiazole_NH2.mol



thiazole_NO2.mol



thiazole_Ph.mol