A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex

ARTICLE *in* ARABIAN JOURNAL OF CHEMISTRY · APRIL 2015

Impact Factor: 3.73 · DOI: 10.1016/j.arabjc.2015.03.016

1 AUTHOR:

Zaki Safi

Al-Azhar University - Gaza

18 PUBLICATIONS **39** CITATIONS

SEE PROFILE

Arabian Journal of Chemistry (2015) **xxx**, xxx–xxx

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex

Zaki S. Safi

Chemistry department, Faculty of science, Al Azhar university-Gaza, Gaza city, P.O. Box 1277, Palestine

Received 4 February 2015; accepted 29 March 2015

KEYWORDS

Thiazolidine-2,4-dione;
Cyclic water complexes;
Density functional theory;
Natural bond orbital;
Hydrogen bonds;
Relative stability

Abstract The results of a detailed DFT (B3LYP) investigation on five tautomers of thiazolidine-2,4-dione and their 5-substituted derivatives (—CH_3, —NH_2, —Cl, —F, —CN- and NO_2) are presented here. The energy, geometrical parameters, topological parameters of all species in the gas phase have been calculated at B3LYP6–311 + + G(3df,2p)//B3LYP/311 + G(d,p) level of theory. The proton affinities (Pas), molecular electrostatic potential (MEP), natural valence atomic orbital energies (NNAO) of the basic center exist in the title compound in the gas phase have been calculated at the same level of theory. The specific hydration of the title compound by one water molecule has been also investigated at the same level of theory. Among the thiazolidine-2,4-dione tautomers and its derivatives, the most stable tautomer corresponds to the diketo forms (A), regardless of the substituent type. Results reveal that the oxygen atom of the carbonyl group at position 2 is more basic than the one at position 4. The existence of different hydrogen bond donor and acceptor centers in these molecules led to different kinds of intermolecular hydrogen bonds (CH···O, N—H···O and C═O···H) and different kinds of complexes. The stability of the cyclic complexes has been investigated using the analysis of Natural Bond Orbital (NBO), Atoms In Molecules topology, and the thermodynamic data. Results suggest that the water molecule prefers to bind with the oxygen atom, which has low intrinsic character.

1. Introduction

Compounds containing heterocyclic ring system and both nitrogen and sulfur atoms are of great importance and receiving a special attention as they belong to class of compounds with proven utility in medicinal chemistry. The importance of the sulfur atom in drugs as sulfide or disulfide linkages

E-mail addresses: z.safi@alazhar.edu.ps, zaki.safi@gmail.com

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2015.03.016

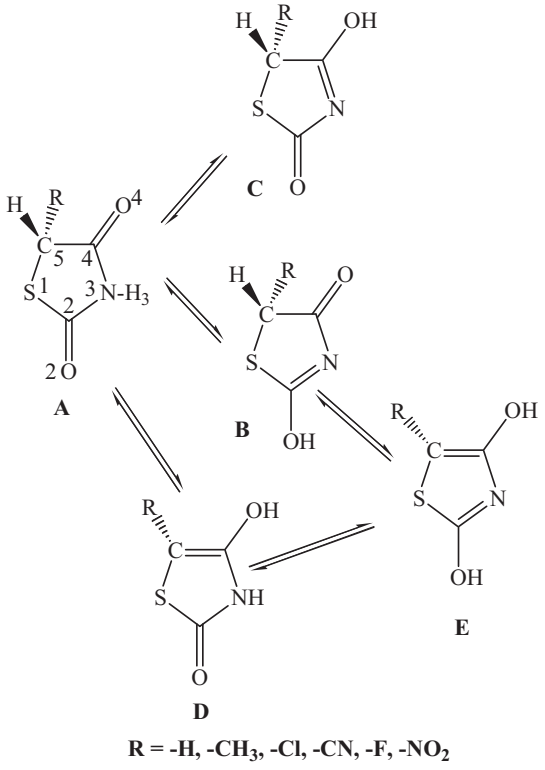
provides great stability for the three-dimensional structure within the molecule (Cecil, 1963). Thiazolidine-2,4-dione derivatives have been studied extensively and found to have diverse chemical reactivity (Jain et al., 2013; Faiyazalam et al., 2013). Thiazolidine derivatives displayed a broad spectrum of biological activities including antimicrobial (Gouveia et al., 2009; Tuncbilek and Altanlar, 2006), antidiabetic (Murugan et al., 2009; Pattan et al., 2005), antiobesity (Bhattarai et al., 2009), anti-inflammatory (Youssef et al., 2010), antioxidant (Bozdag-Dundar et al., 2009), antiproliferative (Patil et al., 2010), and antitumor (Shimazaki et al., 2008). They inhibit corrosion of mild steels in acidic solution (Donnelly et al., 1974).

The tautomerism in the compound under probe is a type of prototropic tautomerism (PT) or intrtamolecular proton transfer (IPT). *It is well known that tautomerism* refers to an equilibrium between two or more different isomeric forms of the same compound called tautomers (Gold, 1979; Raczynska et al., 2005). This phenomenon exists in structures having more than one position to which the transferred proton can be bound. Due to this property one molecule may have more than one structure. Keto-enol tautomerism is a very common process, and is acid or base catalyzed. Typically the 'keto' form of the compound is more stable, but in some instances the 'enol' form can be the more stable (Cederstav and Novak, 1994). It is noteworthy that solvents and substituents have a considerable effect on isomerization.

Tautomerism of Thiazolidine-2,4-dione (Scheme 1) has received a great extensive experimental (Form et al., 1975) and theoretical studies (Tahmassebi, 2003; El-Gogary et al., 2002; Andreocci et al., 1984; Enchev et al., 2002, 1994; Spassova and Enchev, 2004; Ray et al., 2008). All of these studies showed that the predominant tautomer is the thiazolidine-2,4-dione form (diketo tautomer) and there was no evidences supporting thiazoline (oxo-enol) form (Scheme 1). The thiazoline (oxo-enol) system can be formed by the direct 1,3-hydrogen migration of the hydrogen atom to the adjacent carbonyl group at either position 2 or position 4 (structures **B–E**).

In the present work, we have studied the 5-substituted thiazolidine-2,4-dione heterocyclic systems containing keto group in position 2 and 4 of the heterocyclic system (see Scheme 1). So that the main purposes of this work are to:

(1) Study the molecular geometry of the title compound and compare the theoretical results with the available crystallographic data.
(2) Investigate the thermodynamic parameters of the different tautomeric forms (**A–E**) of the 5-substituted thiazolidine-2,4-dione systems in gas phase using the B3LYP/6–311 + + G(3df,2p)//6–311 + G(d,p) level of theory.
(3) Calculate the proton affinities (PAs), molecular electrostatic potential (MEP) and the natural valence atomic orbital energies (NVAO) of the basic center exist for the title compound and its derivatives.
(4) Explore the effect of substituent type on the structure of thiazolidine-2, 4-dione tautomers, relative stabilities of the different tautomeric forms and on the PAs, MEP and NVAO values of the basic centers.
(5) Investigate the specific hydration of the title compound by one water molecule, paying special attention on the relative stabilities of the cyclic complexes and the intermolecular hydrogen bondings, resulting by the interaction of the water molecules with the basic centers of the thiazolidine.



Scheme 1 Schematic representation of the tautomeric forms of Thiazolidine-2,4-dione.

2. Computational details

All electronic structure calculations were performed using the Gaussian 09 suite of programs (Frisch et al., 2009). Geometry optimizations for all tautomers/rotamers and the cyclic thiazolidine-2,4-dione-water complexes have been performed using Density Functional Theory (DFT) at the B3LYP (Beck, 1993; Lee et al., 1988) functional in conjunction with the 6–311 + G(d,p) basis sets. For each stationary point, we carried out vibrational frequency calculation at the same levels to characterize their nature as minima. The calculations were also used to estimate the zero-point energy corrections (ZPE) that were scaled by the empirical factor 0.9806 (Scott and Radom, 1996), absolute entropies, and thermal corrections to calculate enthalpies (*H*). The transition states for isomerization process, which connect between the keto and enol structures, have been located at the same level of theory. The nature of the transition states was confirmed by the presence of one negative eigenvalue in the Hessian matrix. In order to obtain more reliable energies for the local minima, final energies were evaluated by using the same functional combined with the 6–311 + + G(3df,2p) basis set. It has been shown that this approach is well suited for the study of this kind of systems, yielding PAs with good agreement with experimental values (Safi and Frenking, 2013).

Please cite this article in press as: Safi, Z.S. A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.03.016

Analysis of the electron densities at bond critical points (bcps) of the optimized structures was performed by generating the wave functions through a single point calculation on the geometrized structures at the same level of theory and analyzed these wavefunctions by means of the Bader's quantum theory of atoms in molecules (QTAIM) (Bader, 1990) as implemented in AIM2000 program package (Biegler-König, 2000). Finally, a single point calculation was ensued to compute the molecular electrostatic potential (MEP) on each of the nuclei followed by a full Natural Bonding Orbital (NBO) calculations (Reed and Weinhold, 1983) to calculate the overlap interactions of the intermolecular hydrogen interactions between the thiazolidine-2,4-dione compound and to obtain the natural valence atomic orbital energies were calculated using the natural population analysis (NPA) method (Reed et al., 1985).

3. Results and discussion

3.1. Optimized geometries of Thiazolidine-2,4-dione tautomeric forms

Thiazolidine-2.4-dione could exist in different tautomeric forms as shown in Scheme 1. Crystallographic study of Form et al. (Form et al. (1975) and theoretical investigation (Enchev et al., 2002, 1994; Spassova and Enchev, 2004; Ray et al., 2008; Tahmassebi, 2003) showed that the predominant tautomer is the diketo form, structure (**A**), and there was no evidence supporting thiazoline (oxo-enol) or thiazole (dienol) forms (Scheme 1). In addition, experimental results showed that all the bonds in the molecule show significant multiple character, with the exception of those belonging to the saturated methylene carbon atom, C(5). The calculated optimized geometrical parameters, in accordance with the atom-numbering scheme given in Scheme 1, and the available crystallographic data (Form et al., 1975) the investigated compound are listed in Table 1. A close look at Table 1 indicates that our gas phase theoretical results are agreed with the available experimental data. Plotting of the theoretical data versus the experimental ones indicates a strong linear dependencies (see Fig. 1). These figures suggest that the B3LYP/6–311 + G(d,p) bond lengths and bond angles are well fitted to X-ray experimental data, with the correlation coefficients, respectively, 0.9956 and 0.9785. Nevertheless, it is found that the most substantial deviations from X-ray results are found for the S(1)—C(2) bond which is longer by 0.049 Å. The difference is more substantial for the bond angles. For example, our calculation predicts that S(1)—C(5)—C(4) to be expanded by 4.4° in comparison with the experiment.

It is well known that the tautomerization process, in which carbonyl and thiocarbonyl heterocyclic with a hydrogen undergo rabid equilibration with their enol tautomers, is believed to play a crucial role in chemistry of heterocyclic compounds. Moreover, molecular geometries can be specified in terms of bond lengths, bond angles and torsional angles. In the present case, the geometrical structures of the tautomeric forms (**A–E**) are shown in Fig. 2. It is clearly shown that the keto-enol process is associated by the expected significant changes of the corresponding molecular geometries. For example, the C2═O2 bond is elongated by 0.126–0.135 Å. At the same time, there is also an increase in the bond angles S(1)—C(2)—N(3) by 11.5° and a decrease of the bond angles

Table 1 Calculated Optimized structural parameters of thiazolidine-2,4-dione compound obtained at B3LYP/6-311G + (d,p) and the crystallographic data reported by Form et al., 1975.

	Calculated	Experimental
Bong length (Å)		
S(1)—C(2)	1.800	1.751
C(2)—N(3)	1.393	1.372
N(3)—C(4)	1.383	1.373
C(5)—C(4)	1.524	1.547
C(5)—S(1)	1.833	1.845
C(2)═O(2)	1.199	1.209
C(4)═O(4)	1.206	1.219
Bond angle (degree)		
S(1)—C(2)—N(3)	109.3	111.2
C(2)—N(3)—C(4)	119.8	117.5
N(3)—C(4)—C(5)	110.5	113.6
S(1)—C(5)—C(4)	108.0	103.6
C(2)—S(1)—C(5)	92.3	94.2
S(1)—C(2)—O(2)	125.2	124.9
O(2)—C(2)—N(3)	125.4	123.9
O(4)—C(4)—N(3)	124.8	122.7
O(4)—C(4)—C(5)	124.7	123.7

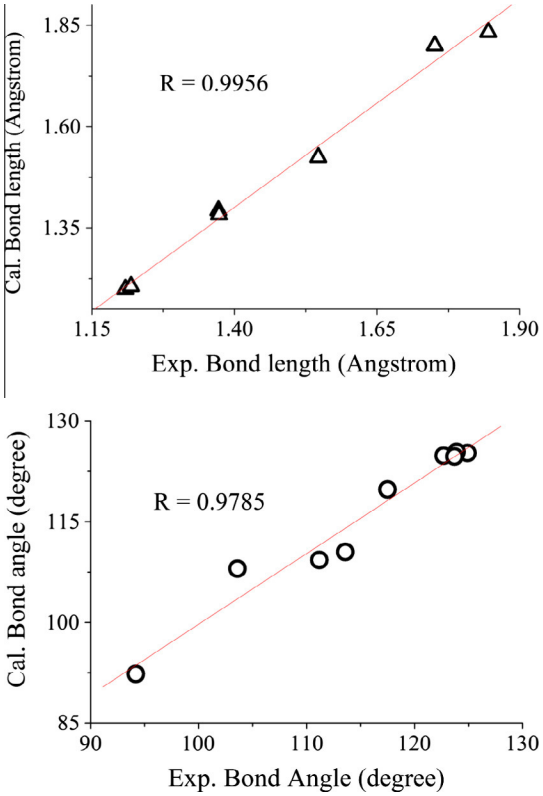


Figure 1 *Upper*: linear correlation dependencies of *Upper:* calculated bond lengths vs. Experimental bond lengths (Å) and *Lower*: calculated bond angle vs. experimental bond angle (degree).

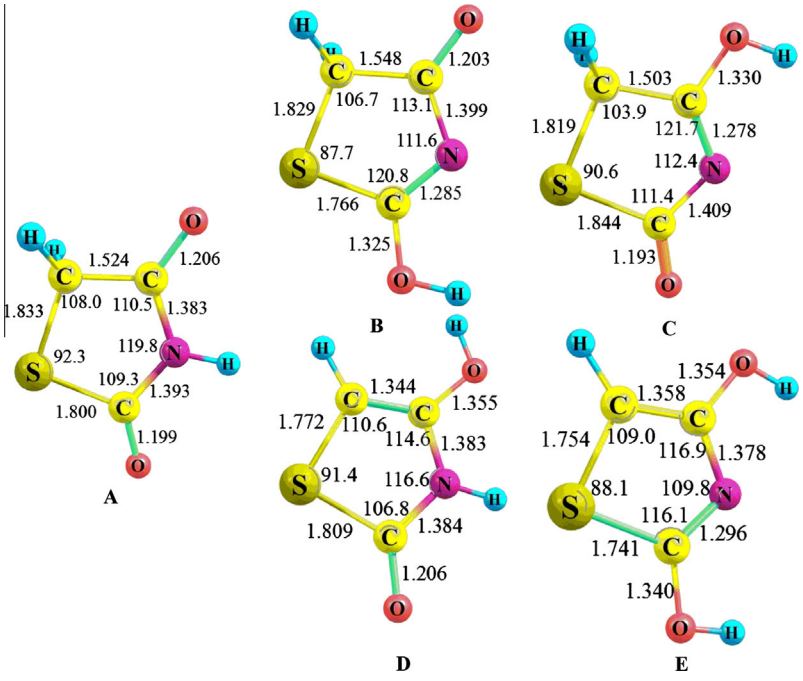


Figure 2 Optimized geometrical structures of the thiazolidine-2,4-dione compound (A) and its tautomers (**B-E**).

S(1)—C(2)—O(2) and N(3)—C(2)—O(2) by 9.7–1.6°. Same changes are also detected for C(4)═O(4) bond. Detailed distances and angles values of **A** optimized tautomer are given in Table 1. In addition, our results, in accordance with analog rhodanine compound (Al-Sehemi and El-Gogary, 2009), all of the intra-ring distances and angles in the tautomers (**A–E**) show the pronounced changes. This non-rigid structure of thiazolidine-2,4-dione tautomers gives their ability to fit with the receptors in the biological systems. In addition, our calculations show that all ring atoms of thiazolidine-2,4-dione tautomers (**A–E**) form planar structures, with all the internal torsion angles are very close to 0°.

Furthermore, it is well known that substituents affect the geometrical structures greatly (Raissi et al., 2012, 2013; Al-Sehemi and El-Gogary, 2009). In the present study, some representative 5-substituted thiazolidine-2,4-dione (—CH_3, —NH_2, —Cl, —F, —CN and —NO_2) were chosen to calculate their tautomerization equilibrium. Comparing the geometrical parameters of the 5-substituted thiazolidine-2,4-dione with that of **A**, **B**, **C**, **D** and **E** tautomers revealed that, at this level, little effects of substituent type position were observed on the structural parameters. For example, comparing the geometrical parameters of the substituted thiazolidine-2,4-dione with that of **A** tautomer shows that the C(2)═O(2) and C(4)═O(4) bonds elongated by ~0.006 Å when changing from electron-withdrawing groups to electron-releasing group. The S(1)—C(2)—N(3) and N(3)—C(4)—C(5) bond angles are increased in the range of 0.4–0.9° when going from electron-withdrawing groups to electron-donating one.

3.2. Analysis of relative thermodynamic data

Calculated thermodynamic parameters such as relative energies, ΔE, enthalpies, ΔH, Gibbs free energies, ΔG, of the various tautomers of thiazolidine-2,4-dione and its derivatives are presented in Table 2. Total set of energetic data are available in Table S1 of the supplementary materials. The B3LYP/6–311 + + G(3df,2p)//B3LYP/6–311 + G(d,p) method at 298.15 K and 1 atm pressure was performed to calculate all of these data. ΔE, ΔH and ΔH of each tautomer are defined as the difference between its total energy or enthalpy or Gibbs free energy with respect to the most stable tautomer **A**.

A cursory examination of Table 2 indicates that in all cases the most stable tautomeric structure corresponds to the diketo structure, tautomer **A**. The second interesting find is that, in contrast to the hydantoin system (Safi and Abu-Awwad, 2008) and in agreement with the analog rhodanine (Al-Sehemi and El-Gogary, 2009), the next-low lying tautomer corresponds to the C tautomer, which is formed by a 1,3-hydrogen transfer from the hydrogen atom at position 3 to the carbonyl oxygen at position 4. The relative energy difference is ~60 kJ mol^{-1}. The relative stability order (ΔE in kJ mol^{-1}) of the tautomeric forms of the compound under probe is as follows:

A > C > B > D > E.

Our results shows that the **A** tautomer is about 60–106 kJ mol^{-1} more stable than the other tautomers (**B–E**); that is, the high positive ΔH demonstrates that tautomerization of the investigated system process is highly endothermic. As it is shown in Fig. 3, the activation barrier requires to get the most stable enolic structure, the **C** tautomer, through the transition state **TS(A–C)** is about 196 kJ mol^{-1}. However, the **B** tautomer, which is formed by a 1,3-hydrogen migration from N3 to O2, is less stable than the tautomer **C**, the activation barrier requires to achieve this tautomer through the transition state **TS(A–B)** is found to be ~5 kJ mol^{-1} lower than that of tautomer **C**.

It is obvious that these large positive ΔG values indicate that the prototropic isomerization process, which leading to

Please cite this article in press as: Safi, Z.S. A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.03.016

Table 2 Relative thermodynamic data (in kcal/mol) of thiazolidine-2,4-dione derivatives calculated at B3LYP/6-311 + + G(3df,2p)/6-311 + G(d,p).

	ΔE					ΔH					ΔG				
	A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
H	0.0	71.5	58.9	79.1	106.9	0.0	72.5	59.4	81.5	109.1	0.0	72.2	59.8	78.7	107.6
CH_3	0.0	72.0	61.8	101.5	79.7	0.0	73.0	62.0	104.6	83.6	0.0	72.6	63.0	99.9	77.4
Cl	0.0	70.8	58.4	100.7	67.7	0.0	71.8	58.8	102.4	69.4	0.0	71.3	59.2	101.2	67.1
CN	0.0	65.7	58.5	47.9	60.0	0.0	66.8	58.9	49.8	60.3	0.0	66.5	59.6	47.3	61.6
F	0.0	72.3	59.5	91.6	122.5	0.0	73.2	59.9	94.5	125.4	0.0	72.8	60.5	90.1	121.3
NO_2	0.0	69.1	58.1	76.0	65.5	0.0	70.3	58.7	76.7	68.2	0.0	69.3	58.8	79.0	65.5
NH_2	0.0	71.4	71.3	61.0	103.1	0.0	72.4	72.2	61.5	106.1	0.0	71.1	71.8	62.2	103.5

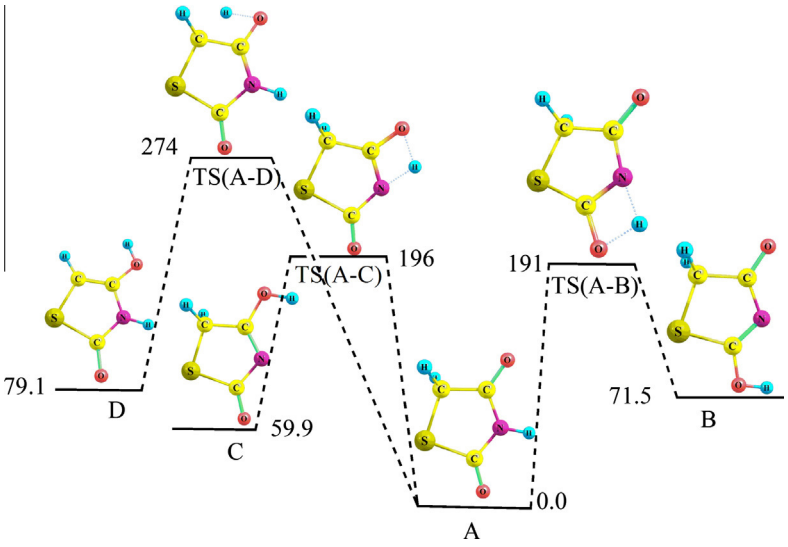


Figure 3 Energy profile for the prototropic isomerization process of thiazolidine-2,4-dione. All values are in kJ mol^{-1}.

the transition from the keto to enol form is quite disfavored, i.e., it is nonspontaneous. It implies, in agreement with analogs polyfunctional heterocyclic systems (Safi and Abu-Awwad, 2008; Safi and Frenking, 2013) that this reaction in gas phase is thermodynamically and kinetically unfavored, meaning that the reverse reaction is both thermodynamically and kinetically favored and the **A** tautomer is the dominant in gas phase.

3.3. Analysis of the substitution effect

Close inspection to our theoretical results (Table 2) shows that the nature of the substituent groups has no effect on the stability order of thiazolidine-2,4-dione tautomers, except. However, there is some exchange of the stability order of thiazoline (oxo-enol) or thiazole (dienol) forms. According to Table 2, the stability order (ΔE in kJ mol^{-1}) of substituted thiazolidine-2,4-dione tautomers is as follows:

$-NH_2$:	**A > D > B > D > E.**
$-CH_3$:	**A > C > B > E > D**
—H:	**A > C > B > D > E**
$-NO_2$:	**A > C > B > E > D**
—CN:	**A > D > C > E > B**
—F:	**A > C > B > D > E**
—Cl:	**A > C > E > B > D**

A closer inspection of Table 2 shows that the substituents with π-electron donating capacity or lone pair electrons (e.g. NH_2, NO_2, CN, Cl, F) tend to lower the relative energies, ΔE, of the enolic tautomers (B-E) in comparison with the keto form (**A**). The NO_2 and CN substituents tend to lower the relative energies between the keto and enol structures more than other substituents. This energy difference becomes higher when going from electron withdrawing groups to electron donating ones. The reason for this finding can be explained in terms of the inductive effect of the substituent groups, which is as follows: NO_2 > CN > F > Cl > NH_2.

On the other hand, when the substitution takes place, the tautomer C becomes more stable than tautomer B, except for CN and NH_2. The interchange of the stability order can be accounted for by the inductive effect and resonance effect of the amino group, which increases the intrinsic basicity of the oxygen atom attached to position 4.

3.4. Analysis of PA, MEP, and NVAO

We will now discuss the proton affinities (PAs), molecular electrostatic potential (MEP) and natural valence atomic orbital energies (NVAO) of the basic centers (O2, N3 and O4) exist for thiazolidine2-4,dione. The PA is defined as the negative of the enthalpy change associated with the gas phase protonation reaction $B + H^+ \rightarrow BH^+$. Table 3 displays the PAs

of the basic sites (O2, O4 and N3) exist for the heterocyclic system under probe. The PAs have been calculated using B3LYP/6–311 + +G(3df,2p)//B3LYP6–311 + G(d,p) methods. Total energies, zero point energies and thermal corrections to enthalpies for all the protonated 5-susbtituted derivatives of Thiazolidine-2,4-dione compound are given in Tables S2 of the supplementary materials.

An inspection of Table 3 indicates that in all of the thiazolidine derivatives the most basic center is the carbonyl oxygen atom at position 2, O2. The calculated PA of O2 of the parent thiazolidine-2,4-dione compound is ~802 kJ mol^{-1} and it is ~9 and 100 kJ mol^{-1} higher than O4 and N3, respectively. Furthermore, it is found that the PA is increased when changing from electron-withdrawing group to electron-releasing group. Our results show that the highest PA corresponds to 5-amino derivatives (~830 kJ mol^{-1}) where the smallest one corresponds to the 5-cyano derivatives. The electron releasing group makes the electron pairs on the oxygen atom more available by donating the electron to the system. The reverse is true in the case of the electron withdrawing group. These results lead us to classify the compound under probe as a moderate basic compound, and the basic centers in this compound can be arranged in order of its strength as follows: O2 > O4 > N3.

To better understand the PA, we will discuss now the results of the molecular electrostatic potential (MEP) and the valence natural atomic orbital energies (NVAO). It was pointed out that the molecular electrostatic potential (MEP) on the nuclei of a molecule originally invoked to study electrophilic reactivity (Yuang et al., 2013). The MEP of a molecule is a real physical property, and it can be determined experimentally by X-ray diffraction techniques (Suresh, 2006). Yuang et al. proposed a theoretical model to calculate this quantum descriptor can be found in Ref. (Yuang et al., 2013). They suggested that the more negative the MEP value, the stronger the molecular basicity, the larger the proton affinity and gas-phase basicity. Also they proposed that for systems with multiple sites of the same basic element type, the most basic site (largest energy decrease) has the most negative MEP value (Yuang et al., 2013). The numerical values of the MEP on the nuclei of basic centers and the valence natural atomic orbital energies of these centers for all species investigated here are also listed in Table 3.

Our theoretical results show that the MEP values on the nuclei of the two oxygen atoms (O2 and O4) are almost degenerate and they are more negative than that on the nitrogen atom, MEP(N3), by about 4.042–4.045 a.u. The degeneracy in the MEP values of the two oxygen atoms suggests again that there is a competitiveness between the two sites. Based on these findings, one expects that the two oxygen atoms should be the site to preferably bond with the incoming proton. These numerical data lead us to suggest,, in accordance with our studies on benzamide derivatives (Safi and Omar, 2014), that the analysis of MEP on the nuclei of the basic centers can be used as a good descriptor to the intrinsic basicities of the heterocyclic compounds containing different type of the basic centers.

It is worth noticing that the MEP and NVAO values become more negative when changing from electron withdrawing group to electron-releasing one in comparison with the parent thiazolidine2,4-dione compound. The most negative MEP value corresponds to the 5-CH_3 derivatives where the least one belongs to the 5-Cl and 5-NO_2 ones. The least negative NVAO energy value corresponds to substituted methyl derivative (−1.829 a.u.) while the highest one corresponds to the substituted nitro derivative (−1.935 a.u.).

3.5. Analysis of thiazolidine-2,4-dione-water complex

In this section we will now discuss the stability of the cyclic thiazolidine-2,4-dione-water complex as a function of the acidity or the basicity of the different sites of the title compound. The interaction of thiazolidine-2,4-dione with one water molecule is guided by the possibility of the water molecule behaving as a hydrogen-bond donor or as a hydrogen-bond acceptor when respectively interacting with the basic centers (C2═O2 and C2═O4) and the acidic groups (N3─H and C5─H) existing in these compounds. Three possible structures may exist in which water behaves simultaneously as hydrogen-bond acceptor and donor (**A–C**). To the best of the author Knowledge, the thiazolidine-2,4-dione-water complexes have not been investigated neither theoretically nor experimentally. However, some systems such as uracil–water (Del Bene, 1983; Nguyen et al., 1998) and triazepine-water (Lamsabhi, 2008) complexes have been studied. The stability of the super-water systems has been explained according to the binding energies. On the other hand, some relevant vibrational frequencies of uracil have also been calculated for the uracil-water (1/2) supersystem (Ghomi et al., 1997). Fig. 4 shows the three stable cyclic structures A, B and C of the thiazolidine-water complexes along with the intermolecular geometrical parameters and the corresponding molecular graphs based on quantum theory of atoms in molecules QTAIM of Bader (Bader, 1990).

Table 3 Proton affinities (PAs) of the basic sites (in kJ mol^{-1}), molecular electrostatic potential on the nuclei of the basic sites (MEP) (in a.u.) and the valence natural atomic orbital energies (NNAO) (in a.u.).

	PA			MEP			NVAO		
	O2	O4	N3	O2	O4	N3	O2	O4	N3
H	803	793	702	−22.356	−22.358	−18.313	−1.842	−1.823	−1.525
CH_3	815	803	717	−22.359	−22.360	−18.316	−1.829	−1.814	−1.511
Cl	782	779	680	−22.343	−22.343	−18.301	−1.890	−1.873	−1.571
CN	759	749	654	−22.335	−22.334	−18.290	−1.920	−1.911	−1.611
F	773	767	673	−22.341	−22.341	−18.299	−1.898	−1.879	−1.577
NO_2	755	768	660	−22.330	−22.330	−18.288	−1.935	−1.921	−1.615
NH_2	831	824	–	−22.356	−22.355	−18.313	−1.841	−1.834	−1.525

Please cite this article in press as: Safi, Z.S. A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.03.016

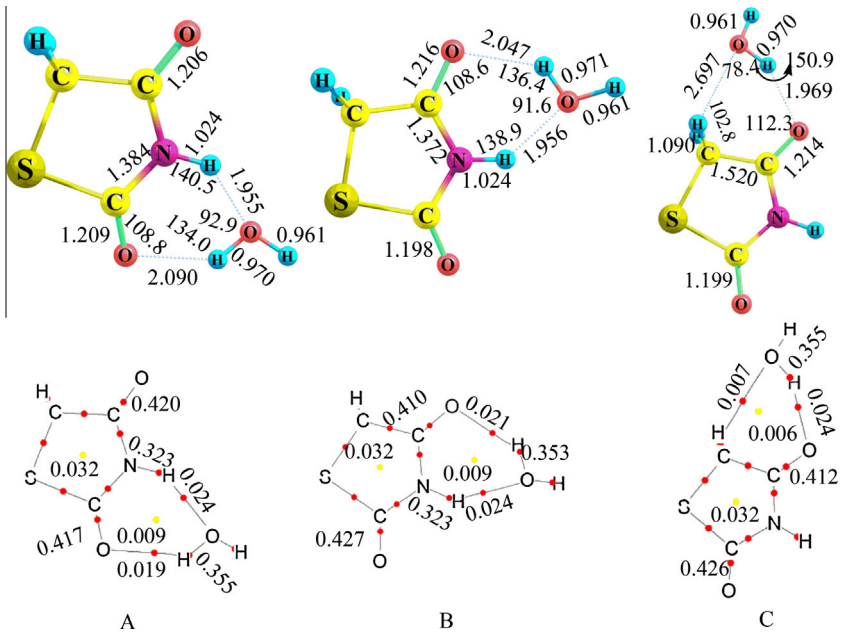


Figure 4 *Upper*: Optimized structures of the complexes A, B and C between uracil and water from B3LYP/6–311 + G(d,p) calculations (distances (Å), angles (degree)). *Lower*: Molecular graphs of Thiazolidine-2,4-diones-water complexes. The charge densities at the bond critical points (red) and ring critical points (yellow) are in e au^{-3}.

Table 4 Relative energies, ΔE (kJ mol^{-1}), hydration enthalpy, ΔH (kJ mol^{-1}), electron transfer energy, E_{CT}, (kJ mol^{-1}) E_{CT} values are in kJ mol^{-1}, electron density at BCP (au^{-3}), local electronic potential energy, $V(r)$ (au), the hydrogen bond strength, E_{HB} (kJ mol^{-1}) of the thiazolidine-2,4-dione-water cyclic complexes and the electron density at the ring critical point of the cyclic complexes, ρ_{RCP} (au^{-3}).

Complex	ΔE	ΔH[a]	Hydrogen bond	Orbital interaction	E_{CT}[b]	ρ_{BCP}	$V(r)_{BCP}$	E_{HB}[c]	ρ_{RCP}
A	0.1	−30.6	O2···Hw	LP(O2) → σ^*_{Hw-Ow}	13.9	0.0189	−0.0131	−17.2	0.0090
			N3H···Ow	LP(Ow) → σ^*_{H-N3}	34.4	0.0243	−0.0182	−23.9	
B	0.0	−28.5	O4···Hw	LP(O4) → σ^*_{Hw-Ow}	17.9	0.0243	−0.0182	−23.9	0.0093
			N3H···Ow	LP(Ow) → σ^*_{H-N3}	33.4	0.0209	−0.0148	−19.4	
C	8.5	-18.4	O4···Hw	LP(O4) → σ^*_{Hw-Ow}	24.9	0.0235	−0.0171	−22.5	0.0057
			C5H···Ow	LP(Ow) → σ^*_{H-C5}	0.0	0.0066	−0.0042	−5.6	

[a] $\Delta H_{hydratioon} = \Delta H_{complex} - (\Delta H_{compound} + H_2O)$.
[b] E_{CT} is the electron charge transfer energy due to the orbitals interaction.
[c] $E_{HB} = 1/2\ V(r)$, where $V(r)$ is the potential energy the bcp of hydrogen bonds.

Our results show that the three complexes are characterized by C1 symmetry, one of the hydrogen atoms of water being out-of-plane of the uracil molecule. Inspection of Table 4 indicates that the **A** and **B** complexes are almost degenerate with a difference only of ~0.1 kJ mol^{-1} in favor of the B complex. The complex **C** is found to be ~8.5 kJ mol^{-1} less stable than the most stable one (Table 4). The hydration energies of the complexes A, B and C due to the binding with water molecule are ~ −30.6, −28.5 and −18.4 kJ mol^{-1}, respectively. These results suggest that the thiazolidine-2,4-dione compound is characterized by a weak interaction with water, which allows classification of the strength of the corresponding hydrogen bonds as moderate. It is worth noting that, in the structure **A** and **B**, the carbonyl groups at position 2 and 4 act as a hydrogen-bond acceptor with respect to water and both kinds of complexes have in common the N3—H group at position 3 acting as a HB donor. In complex **C**, the group acting as HB donor is a C5—H group rather than a N3—H group while the carbonyl group at position 4 acts as a hydrogen-bond acceptor with respect to water.

As it is shown in Fig. 4, the N3—H···Ow and O6(7)···Hw–Ow distances do not markedly differ and this suggests that the two intermolecular hydrogen bonds in the considered complexes have about the same contribution to the total binding energy. Our results show that O6···Hw–Ow distance (2.047 Å) is shorter than the O6···Hw–Ow one (2.090 Å). This seems to indicate that the carbonyl group at position 4 is a weaker HB acceptor than the carbonyl group at position

2. This is in accordance with our recent findings showing that the carbonyl group at position 2 has a larger intrinsic basicity than the one at position 5. The two N3—H···Ow interaction in both complexes has almost the same distance (1.995(6) Å).

In the **C** complex, the distances C5—H···Ow and O7···Hw–Ow are markedly different, suggesting that the two intramolecular hydrogen bonds have not the same contribution to the total binding energy. It is found that the C5—H···Ow (2.697 Å) is longer than the O7···Hw–Ow one (1.969), suggesting that the O7···Hw—Ow hydrogen bond has a more contribution in the total binding energy than the C5—H···Ow one.

In order to confirm the above results, the topology of the electron density of the complexes (**A–C**) based on the AIM analysis of Bader (Bader, 1990) has been studied. The topological parameters of the hydrogen bond interaction (electron densities, ρ_{BCP}, local electronic potential energy at the corresponding BCPs, hydrogen bond strengths, $E_{HB} = 1/2\ V(r)$ (in kcal/mol), and the electron charge densities at the corresponding ring critical points of the quasirings, ρ_{RCP}) are given in Table 4. Inspection of these result strongly supports the above finding in which the complex B is the most stable complex among the three cyclic complexes. It is found that the highest ρ_{RCP} value belongs to the complex **B**, reflecting that the five-membered quasicyclic structure of the complex **B** is the most stable one where the analog cyclic structure of the complex is the least stable one. Additionally, inspection of our results reflected in the value of the electron density at the BCP of the corresponding bonds. In fact, as can be shown in Fig. 4 and Table 4, according to ρ_{BCP} values, the most stable hydrogen bond corresponds to the interaction between the oxygen of water molecule and the amino hydrogen atom, N3—H···O_w. Also, importantly, however, O4 is less PA than O2, inspection of our results indicates that the O4···H_w interaction (ρ_{BCP} = 0.0243 au^{-3}, complex **B**) is stronger than the corresponding O2···H_w (ρ_{BCP} = 0.0189 au^{-3}, complex **A**). These findings are in line with those obtained for uracil–water complexes (Nguyen et al., 1998) and triazepine-water complexes (Lamsabhi, 2008).

In order to confirm the above findings, analysis of Natural Bond Orbital (NBO) has been carried out. The electron transfer energies due to the orbital interaction are also included in Table 5. NBO calculations show that the two lone pairs of the O2 and O4 are not equivalent and their overlap interactions with the N3—H antibonding are quite different. Theoretical results revealed, in accordance with the relative energies of the complexes, that the strongest interaction was observed for the **B** complex. In complex **B**, the total orbital interaction energy, E_{CT}, is ~3 kJ mol^{-1} higher than that in the **A** complex. These results indicate, in complex **A** and **B**, that the water molecule acts as a hydrogen bond acceptor and the N3-H group acting as a hydrogen bond acceptor.

At last it should be pointed out that the vibrational frequency shifts of the harmonic asymmetric ν^{as}(OH) and ν^{as}(C═O) and symmetric ν^{s}(C═O) and ν^{as}(OH) stretching vibrations, together with the ν(NH) stretching vibrations are listed in Table 5. Inspection of the frequency results indicates that the highest frequency shifts are observed for the **A** complex with respect to the other complexes.

Table 5 Frequency shifts (cm^{-1}) of the $\Delta\nu^{s}$(C═O), $\Delta\nu^{s}$(-C═O), $\Delta\nu^{as}$(OH), $\Delta\nu^{s}$(OH) and $\Delta\nu$(N—H) stretching vibrations for structures A, B and C of the thiazolidine-2,4-dione-water complexes.

	Complex		
	A	B	C
$\Delta\nu^{as}$(C═O)[a]	25	21	17
$\Delta\nu^{s}$(C═O)	12	8	10
$\Delta\nu$(N—H)	188	188	1
$\Delta\nu^{as}$(OH)[b]	100	123	123
$\Delta\nu^{s}$(O—H)	22	23	28

[a] The frequencies of ν^{as}(C═O), ν^{s}(C═O) and ν(N—H) of thiazolidine-2,4-dione are 1791, 1830 and 3595 cm^{-1}, respectively.
[b] The frequencies of ν^{s}(O—H) and ν^{as}(O—H) of water are 3819 and 3902 cm^{-1}, respectively.

4. Conclusions

In this work we have performed a theoretical study on the stability order and the prototropic isomerization processes of thiazolidine-2,4-dione using B3LYP functional at 6–311 + + G(3df,2p)//6–311 + G(d,p) basis sets. The proton affinities, the molecular electrostatic potential and the natural valence atomic orbital energies of the basic centers of the title compound have been calculated using the same level. Furthermore, the cyclic complexes, which were formed by the interaction of thiazolidine-2,4-dione compound with one water molecule have been investigated and characterized using NBO and AIM. The results obtained can be summarized as follows:

1. The B3LYP/6–311 + + G(3df,2p)//6–311 + G(d,p) calculations predict that tautomer **A** (diketo form) of thiazolidine-2,4-dione and its 5-substituted derivatives (CH_3, NH_2, NO_2, Cl, F and CN) are the most stable tautomer in the gas phase. This result corresponds to the known experimental and theoretical data. The stability order is as follows: **A > C > B > D > E**. The stability order of the keto-enol and dienol forms influences some changes upon substitution. The prototropic isomerization process, which connects between the diketo form and the enolic forms, requires very high activation energy and the isomerization process is thermodynamically disfavored. Strong linear correlations between the available experimental data and the corresponding theoretical ones were found, which indicate that B3LYP method is a good choice to study such these system.
2. The PA values suggest that the thiazolidine-2,4-dione compound is of a moderate basic heterocyclic compound. These values increase when going from electron withdrawing group to electron-releasing group. These results have been confirmed by MEP and NVAO results.
3. The most stable cyclic thiazolidine-2,4-dione-water complexes correspond to complex **B** in which the water interacts with the nitrogen atom at position 3 and with the oxygen atom of the carbonyl group at position 4. This finding is confirmed by the geometrical and topological parameters, the electron transfer energy, E_{CT}. The strongest hydrogen bond corresponds to O4····Hw and N3H····Ow interactions, which exit for the A and B complexes, respectively. Finally,

Please cite this article in press as: Safi, Z.S. A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.03.016

it should be concluded that the water molecule interacts with the oxygen atom with the lowest PA. This result corresponds to the known theoretical data.

Acknowledgment

A generous allocation of computational time at the Scientific Computational Center (CCC) of the Universidad Autónoma de Madrid (Spain) is acknowledged.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2015.03.016.

References

Al-Sehemi, A.G., EL-Gogary, T.M., 2009. Geometry and thermodynamic stabilities of rhodanine tautomers and rotamers: quantum chemical study. J. of Mol. Struct. (THEOCHEM) 907, 66–73.

Andreocci, M.V., Cauletti, C., Sestili, L., 1984. Electronic structure of some penta-atomic heterocyclic molecules studied by gas-phase He(I) and He(II) photoelectron spectroscopy. Spectrochim Acta. 40 (11), 1087–1093.

Bader, R.F.W., 1990. Atoms in Molecules: A Quantum Theory. Clarendon Press, Oxford Univ, Oxford.

Becke, A.D., 1993. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 98, 5648–5652.

Bhattarai, B.R., Kafle, B., Hwang, J., Khadka, D., Lee, S., Kang, J., Ham, S.W., Han, I., Park, H., Cho, H., 2009. Thiazolidinedione derivatives as PTP1B inhibitors with antihyperglycemic and antiobesity effects. Bioorg. Med. Chem. Lett. 19, 6161–6165.

Biegler-König, F., 2000. A.I.M2000, University of Applied Sciences, Bielefeld, Germany, 2000.

Bozdag-Dundar, O., Coban, T., Ceylan-Unlusoy, M., Ertan, R., 2009. Radical scavenging capacities of some thiazolylthiazolidine-2,4-dione derivatives. Med. Chem. Res. 18, 1–7.

Cecil, R., 1963. Intramolecular bonds in proteins. I. The role of sulfur in proteins. Proteins 1, 379–476.

Cederstav, A.K., Novak, B.M., 1994. Investigations into the chemistry of thermodynamically unstable species. The direct polymerization of vinyl alcohol, the enolic tautomer of acetaldehyde. J. Am. Chem. Soc. 116, 4073–4074.

Del Bene, J.E., 1983. Molecular orbital theory of the hydrogen bond. Water-cytosine complexes. J. Comput. Chem. 4, 226–233.

Donnelly, B., Downie, T.c., Grzeskow, R., Hamburg, Hr., Short, D., 1974. Study of inhibiting properties of some derivatives of thiourea. Corrosion Sci. 14 (10), 597–606.

El-Gogary, T.M., El-Bindary, A.A., Hilali, A.S., 2002. Temperature and substituent effects on the dissociation constants of 5-azorhodanine derivatives. Semi-empirical quantum mechanical calculation. Spectrochim. Acta A 58 (3), 447–455.

Enchev, V., Petkov, I., Chorbadjiev, S., 1994. Tautomerism of rhodanine. Struct. Chem. 5 (4), 225–231.

Enchev, V., Chorbadjiev, S., Jordanov, B., 2002. Comparative study of the structure of rhodanine, isorhodanine, thiazolidine-2,4-dione, and thiorhodanine. Chem. Heterocycl. Comp. 38 (9), 1110–1120.

Faiyazalam, M.S., Navin, B.P., Dhanji, R., 2013. Synthesis of new thiazolidine-2,4-dione derivatives and their antimicrobial and antitubercular activity. Indian J. Res. Pharm. Biotechnol. 1 (4), 496–503.

Form, G.R., Raper, E.S., Downie, C., 1975. The crystal and molecular structure of thiazolidine-2,4-dione. Acta Cryst. B31, 2181–2184.

Frisch, M.J., Trucks, Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G.A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H.P., Izmaylov, A.F., Bloino, J., Zheng, G., Sonnenberg, J.L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., MontgomeryJ.A., Jr., Peralta, J.E., Ogliaro, F., Bearpark, M., Heyd, J.J., Brothers, E., Kudin, K.N., Staroverov, V.N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J.C., Iyengar, S.S., Tomasi, J., Cossi, M., Rega, N., Millam, J.M., Klene, M., Knox, J.E., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Martin, R.L., Morokuma, K., Zakrzewski, V.G., Voth, G.A., Salvador, P., Dannenberg, J.J., Dapprich, S., Daniels, A.D., Farkas, Ö., Foresman, J.B., Ortiz, J.V., Cioslowski, J., Fox, D.J., 2009. Gaussian, Inc., Wallingford CT.

Ghomi, M., Aamouche, A., Cadioli, B., Berthier, G., Grajcar, L., Baron, M.H., 1997. Effect of molecular environment on the vibrational dynamics of pyrimidine-bases as analyzed by nis, optical spectroscopy and quantum-mechanical force-fields. J. Mol. Struct. 410, 323–326.

Gold, V., 1979. Glossary of terms used in physical organic chemistry. Pure Appl. Chem. 51, 1725–1801.

Gouveia, F.L., de Oliveira, R.M.B., de Oliveira, T.B., da Silva, I.M., do Nascimento, S.C., de Sena, K.X.F.R., de Albuquerque, J.F.C., 2009. Synthesis, antimicrobial and cytotoxic activities of some 5-arylidene-4-thioxo-thiazolidine-2-ones. Eur. J. Med. Chem. 44, 2038–2043.

Jain, V.S., Vora, D.K., Ramaa, C.S., 2013. Thiazolidine-2,4-diones: progress towards multifarious applications. Bioorg. Med. Chem. 21, 1599–1620.

Lamsabhi, A.M., 2008. Specific hydration effects on oxo-thio triazepine derivatives. J. Phys. Chem. A 112, 1791–1797.

Lee, C., Yang, W., Parr, R.G., 1988. Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B 37, 785–798.

Murugan, R., Anbazhagan, S., Lingeshwaran, Narayanan, S.S., 2009. Synthesis and in vivo antidiabetic activity of novel dispiropyrrolidines through [3 + 2] cycloaddition reactions with thiazolidinedione and rhodanine derivatives. Eur. J. Med. Chem. 44, 3272–3279.

Nguyen, M.T., Chandra, A.K., Zeegers-Huyskens, T., 1998. Protonation and deprotonation energies of uracil. Implications for the uracil. water complex. 94 (9), 1277–1280.

Patil, V., Tilekar, K., Mehendale-Munj, S., Mohan, R., Ramaa, C.S., 2010. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives. Eur. J. Med. Chem. 45, 4539–4544.

Pattan, S.R., Suresh, C., Pujar, V.D., Reddy, V.V.K., Rasal, V.P., Koti, B.C., 2005. Synthesis and antidiabetic activity of 2-amino [5′(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole. Ind. J. Chem. 44B, 2404–2408.

Raczynska, E.D., Kosinska, W., Osmialowski, B., Gawinecki, R., 2005. Tautomeric equilibria in relation to pi-electron delocalization. Chem. Rev. 105 (10), 3561–3612.

Raissi, H., Yoosefian, M., Zamani, S., Farzad, F., 2012. Conformational study, molecular structure, and S...H \ N, S \ H...N intramolecular hydrogen bond in thioformyl-3-aminoacrylaldehyde. J. Sulfur Chem. 33, 75–85.

Raissi, H., Khan mohammadi, A., Yoosefian, M., Mollania, F., 2013. Ab initio and DFT studies on 1-(thionitrosomethylene) hydrazine: conformers, energies, and intramolecular hydrogen-bond strength. Struct. Chem. 24, 1121–1133.

Ray, J., Panja, N., Nandi, P.K., Martin, J.J., Jones, W.E., 2008. J. Mol. Struct. 874, 121–127.

Reed, A.E., Weinhold, F., 1983. Natural bond orbital analysis of near-Hartree–Fock water dimer. J. Chem. Phys. 78, 4066–4073.
Reed, A.E., Weinstock, R.B., Weinhold, F., 1985. Natural population analysis. J. Chem. Phys. 83, 735–746.
Safi, Z.S., Abu-Awwad, F.M., 2008. Tautomerism of 5-methyl imidazolidine thio derivatives in the gas phase: a density functional study. J. Chem. 5 (4), 884–893.
Safi, Z.S., Frenking, G., 2013. Protonation of 5-methylhydantoin and its thio derivatives in the gas phase: a theoretical study. Int. J. Quant. Chem. 113 (7), 908–915.
Safi, Z.S., Omar, S., 2014. Proton affinity and molecular basicity of m- and p-substituted benzamides in gas phase and in solution: a theoretical study. Chem. Phys. Lett. 610–611, 321–330.
Scott, A.P., Radom, L., 1996. Harmonic vibrational frequencies: an evaluation of Hartree−Fock, Møller−Plesset, quadratic configuration interaction, density functional theory, and semiempirical scale factors. J. Phys. Chem. 100, 16502–16513.
Shimazaki, N., Togashi, N., Hanai, M., Isoyama, T., Wada, K., Fujita, T., Fujiwara, K., Kurakata, S., 2008. Anti-tumour activity of CS-7017, a selective peroxisome proliferator-activated receptor gamma agonist of thiazolidinedione class, in human tumour xenografts and a syngeneic tumour implant model. Eur. J. Cancer. 44, 1734–1743.
Spassova, M., Enchev, V., 2004. Ab initio investigation of the structure and nonlinear optical properties of five-membered heterocycles containing sulfur. Chem. Phys. 298 (1), 29–36.
Suresh, C.H., 2006. Molecular electrostatic potential approach to determining the steric effect of phosphine ligands in organometallic chemistry. Inorg. Chem. 45, 4982–4986.
Tahmassebi, D., 2003. Theoretical studies of the tautomerism in oxazolidine and thiazolidine heterocyclic systems. J. Mol. Struct. (Theochem) 638, 11–20.
Tuncbilek, M., Altanlar, N., 2006. Synthesis of new 3-(Substituted Phenacyl)-5-[39-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinediones and their antimicrobial activity. Arch. Pharm. Chem. Life Sci. 339, 213–216.
Youssef, A.M., White, M.S., Villanueva, E.B., El-Ashmawy, I.M., Klegeris, A., 2010. Synthesis and biological evaluation of novel pyrazolyl-2,4-thiazolidinediones as anti-inflammatory and neuroprotective agents. Bioorg. Med. Chem. 18, 2019–2028.
Yuang, H., Lianghong, L., Shubin, L., 2013. Towards understanding proton affinity and gas-phase basicity with density functional reactivity theory. Chem. Phys. Lett. 527, 73–78.

Please cite this article in press as: Safi, Z.S. A theoretical study on the structure of thiazolidine-2,4-dione and its 5-substituted derivatives in the gas phase. Implications for the thiazolidine-2,4-dione -water complex. Arabian Journal of Chemistry (2015), http://dx.doi.org/10.1016/j.arabjc.2015.03.016