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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

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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.

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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

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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 intramolecular 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.

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).

R = -H, -CH₃, -Cl, -CN, -F, -NO₂
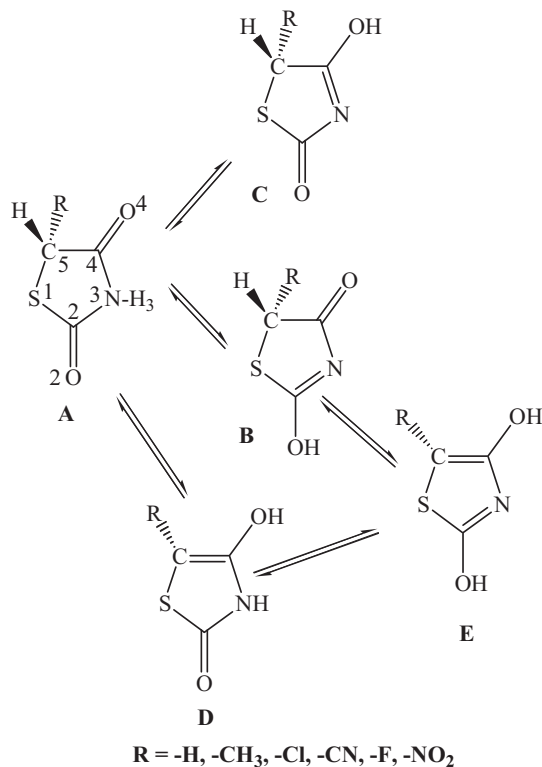
Scheme 1 Schematic representation of the tautomeric forms of Thiazolidine-2,4-dione.