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ARTICLE

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S-Oxidation of Thiazolidinedione with Hydrogen Peroxide, Peroxynitrous Acid, and C4a-Hydroperoxyflavin: A Theoretical Study

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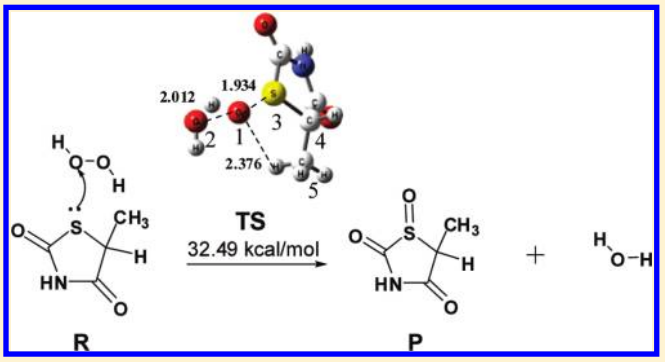
Supporting Information

ABSTRACT: Quantum chemical analysis was carried out to model metabolism of glitazone class of drugs through oxygen transfer process to the sulfur atom of thiazolidinedione ring with different oxidants such as H_2O_2, HOONO, and C4a-hydroperoxyflavin. Complete optimization (geometric and energy parameters) of all the required structures and transition states on the reaction path was carried out using MP2-(full)/6-31+G(d,p). Charge and second-order delocalization analyses of important structures were carried out using the NBO method. The effect of solvent on the oxygen transfer to sulfur of thiazolidinedione was studied by including one, two, or three explicit water molecules. These calculations revealed that explicit solvent (water) effectively contributed in the sulfoxidation of thiazolidinedione and led to remarkable reduction in the energy barrier by ~10 kcal/mol as compared to the gas phase. These results were found to be consistent with previously reported S-oxidation of dimethyl sulfide. When explicit water molecules were included, solvent molecules stabilize the charge separation at the transition state via specific interactions, and oxidation occurs via stretching of the O−O bond of oxidants and gradual formation of S−O bond. This study is helpful in understanding the metabolite generation due to the S-oxidation process in the glitazone series of antidiabetic drugs under physiological conditions.



INTRODUCTION

Metabolism (biotransformation) is a very important biochemical process through which various xenobiotics including drug molecules are converted into highly polar derivatives that can be easily excreted from the body.[1] Various metabolic pathways such as oxidation, reduction, alkylation, etc., are involved in metabolism, generally to detoxify potentially harmful xenobiotic compounds.[2] In some cases, nontoxic compounds are bioactivated to toxic reactive intermediates, precarcinogens, and finally carcinogens.

Sulfur oxidation is one of the important oxidative reaction mechanisms that play a major role in phase I metabolism of drugs with sulfide unit (−S−). Sulfur-containing drugs (Figure 1) like Methimazole, Cimetidine,[3] Artemiside,[4a,4b] Ranitidine,[5a,b,6] Thioridazine,[7,8] 7-(1,3-thiazolidin-2-methyl) theophylline, (+)-*cis*-3,5-dimethyl-2-(3-pyridyl)-thiazolidin-4-one, Sulindac sulfide,[9] etc., are reported to undergo change in metabolic state through sulfur oxidation process. The S-oxidized metabolites may be excreted as such (e.g., sulfoxide and sulfone metabolite of tazarotenic acid,[10] cevimeline[11]), may be therapeutically active (e.g., albendazole,[12] flosequinan[13]), may be toxic (e.g., fenthion sulfoxide[14]), or may have reduced activity as compared to the original substrate (e.g., omapatrilat, sulindac sulfide,[15] *S*-carboxymethyl cysteine,[16] ziprasidone,[17] chlorpromazine[1]). Thorough understanding of the sulfur oxidation process at the molecular level is an essential first step in the prediction of the complex pathway of metabolite generation and its action.

Rosiglitazone and Pioglitazone (Figure 2) are the thiazolidinedione[18,19] class of drugs, which are being employed in the treatment of Type-II Diabetes Mellitus through their insulin sensitizing effect,[20,21] whereas Troglitazone has already been withdrawn from market due to its hepatotoxicity. These compounds bind to nuclear peroxisome proliferator activated receptors (PPARs) in tissues and activate them.[22,23]

These regulators are associated with the differentiation of adipocytes and increased expression of a number of genes involved in the regulation of glucose and lipid metabolism.[24] Early study by Hulin et al.[25,26] on thiazolidinedione class of compounds suggested that in vivo rapid racemization may be due to sulfoxide formation. Kassahun et al. suggested that the hepatotoxicity of the withdrawn drug Troglitazone may be due to the reactive oxidative metabolites.[27] However, later Reddy et al. suggested that the withdrawal of troglitazone was due to the toxicity of its quinine-methide metabolites, whereas thiazolidinedione ring scission following S-oxidation played a minor role.[27] Moreover, it

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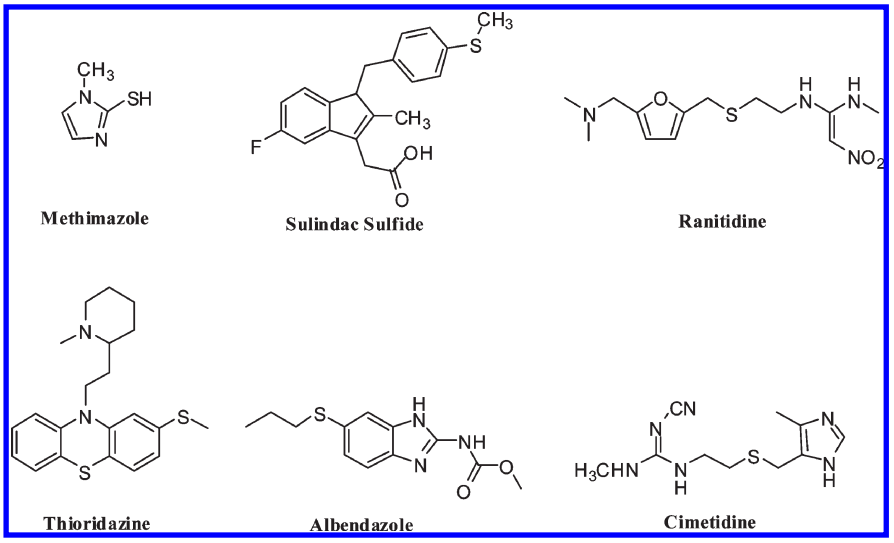

Figure 1. Sulfur-containing drugs, which undergo metabolism through sulfur oxidation.

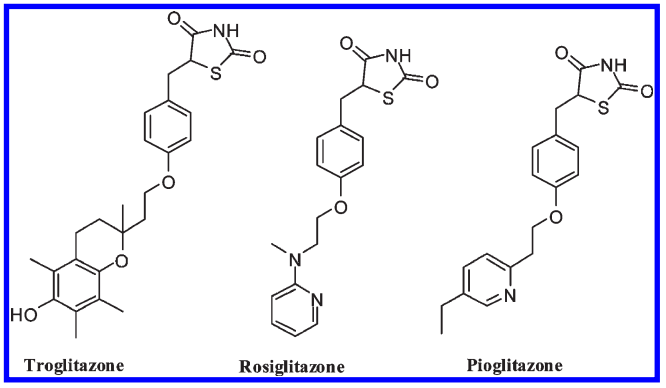

Figure 2. Structures of the glitazone class of drugs.

was observed that the glitazone class of molecules possessing a thiazolidinedione ring (troglitazone, pioglitazone, and rosiglitazone) is shown to form S-oxidation-based ring-opened products in vivo as one of their metabolites. Liu et al.[28] and Baughman et al.[28] showed that the probable metabolic pathway for ring-opened reactive intermediate includes oxidative cleavage of thiazolidinedione ring by sulfur oxidation. This study showed that S-oxidation of thiazolidinedione ring accelerated the formation of ring-opened reactive intermediate of thiazolidinedione and further converted into other metabolites. Experimental evidence for the presence of reactive ring-opened structure of thiazolidinedione ring for glitazone series of drugs like Troglitazone, Pioglitazone, Rosiglitazone, Ciglitazone, MK-0767, etc., is also reported.[27,28] Uchiyama et al. recently reported the metabolites generated by oxidative thiazolidinedione ring-opening in pioglitazone and rosiglitazone.[28] However, the mechanistic details of formation of metabolites have not been explored at the molecular level. Because various in vitro studies support the existence of an initial S-oxidation step in the mechanistic aspects of thiazolidinedione ring cleavage, it is important to have a detailed understanding of the process of S-oxidation at the molecular level, so we explored this using model catalysts **I**, **II**, **III**, and **IV** (Figure 3).

Various experimental and theoretical studies were reported to understand the oxygen transfer mechanism from different model oxidants (Figure 3) like H_2O_2 (**I**),[29,30] HOONO (**II**),[31−34] and

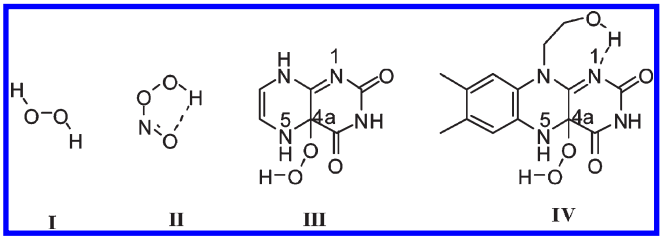

Figure 3. Structures of all oxidants used for this study.

C4a-hydroperoxyflavin (**III**, **IV**),[35] cytochrome P450, etc., to small substrates like dimethyl sulfide,[36] trimethyl amine,[37,38] trimethyl phosphine, etc.

Bach et al. studied a two-step S_N2 oxidation mechanism by H_2O_2 in which the first step included the hydrogen transfer of hydrogen peroxide (1,2 H-shift) to form water oxide, and in the second step was the transfer of oxygen to dimethyl sulfide (DMS) by hydrogen peroxide to form dimethyl sulfoxide.[29,37]

In this mechanism, ab initio gas-phase calculations showed a very high energy barrier of 56 kcal mol^{-1} for transfer of oxygen to substrates like DMS, which was in contrast to the observed experimental value of 10−20 kcal mol^{-1}. Later, Chu and Trout[39] suggested the importance of explicit water molecules (one, two, or three) in the transfer of oxygen to organic sulfides; in contrast to the two-steps mechanism, they suggested that solvent molecules stabilize the charge separation at the transition state via specific interactions and oxidation occurs via stretching of the O−O bond of H_2O_2 and reduction in the S−O distance. In this study, the energy barrier for the oxidation of DMS by H_2O_2 (12.7 kcal/mol) was found to be in the range of experimental values (10−20 kcal/mol). Sulfoxidation of dimethyl sulfide by cytochrome P450 was reported by Shaik et al.[40,41] in which it was noted that direct oxygen transfer to sulfur (sulfoxidation[42]) was favored by high-valent iron-oxo porphyrin complex (Cpd1) via a regioselective spin-state reactivity. Moreover, it was found to be 10 kcal/mol more favorable over previously assumed oxidation via concerted nucleophilic displacement with departure of OH^- from ferric peroxide porphyrin (Cpd0, the precursor of Cpd 1). It was also noted that sulfoxidation by Cpd 0 has a much higher energy barrier (17.8 kcal/mol) than Cpd 1 (7.1 kcal/mol) even

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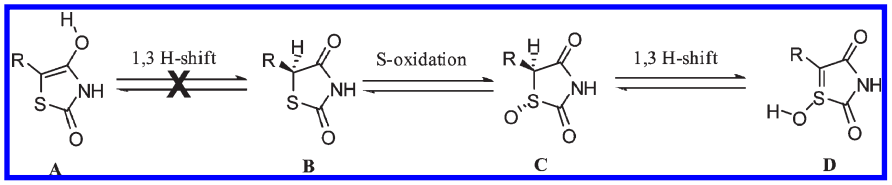

Figure 4. Rapid racemization in thiazolidinedione ring.

in the presence of putative and potent acid catalysis. Thus, the oxygen transfer mechanism from Cpd 1 to DMS is a single step reaction mechanism.[43,44] Thus, the above-mentioned studies have been reported on the standard oxidation of small molecules containing sulfide unit. The detailed mechanism of oxygen transfer to xenobiotics has not been explored and correlated with their metabolism; such a study would help to explain the in vivo oxidation.

Recently, we have carried out a computational study on the importance of sulfur oxidation in rapid racemization of glitazones class of molecules. Ab initio MO and DFT calculations suggested that reversible S-oxidation of thiazolidinediones increases the acidity at adjacent carbon (chiral center), which facilitates rapid racemization. It was shown that C⇌D tautomerization (Figure 4) was more favorable path after S-oxidation, and thus the reversible S-oxidation has been suggested to be an essential step.[45a] Similarly, the sulfur oxidation of nitrosothiols has been shown to be important for the release of nitric oxide using computational analysis. These studies explored the consequences of sulfur oxidation on NO releasing species such as *S*-nitrosocaptopril.[45b]

Although a few studies as above are reported on the model system, the mechanism of oxygen transfer to sulfur in sulfur-containing drugs has not been thoroughly explored. The involvement of one, two, or three solvent molecules during oxygen transfer needs to be evaluated. Detailed analysis of the structure and energetic factors associated with the oxygen transfer to sulfur present in thiazolidinediones help in understanding the sulfur oxidation of glitazone series of drugs under in vivo condition. In this study, we address the proposed S-oxidation mechanisms on methylthiazolidinedione using high level ab initio DFT calculations with the objective of finding feasibility of oxygen transfer in thiazolidinedione containing drugs. In this study, we have used different model oxidants such as **I**, **II**, **III**, and **IV** to understand oxidation of the model system, methyl thiazolidinedione. We have also explored the specific effects of water molecule as solvent in oxidation of methylthiazolidinedione. Moreover, a comparative analysis of the process of S-oxidation in dimethyl sulfide and methylthiazolidinedione is presented.

COMPUTATIONAL DETAILS

Methods of Calculations. All ab initio MO (Molecular Orbital)[46] and DFT (Density Functional Theory)[47,48] calculations were carried out using the Gaussian 03[49] package utilizing gradient geometry optimization. Geometries were fully optimized using the B3LYP functional with the 6-31+G(d,p) basis set.[46a] The energetics of all the reactants, transition states, and products were also calculated using the same basis set. This method and basis set were reported to provide reasonably accurate energy estimates in the studies related to S-oxidation. A full set of vibrational frequency calculations[50] for all minima and transition structures at the same level of geometry optimization were performed to characterize as either minima or first-order saddle points. Each transition state is first-order saddle point with only one imaginary vibrational mode. On the B3LYP estimated energies, a scaling factor of 0.9806 was used for zero-point energies corrections.[51] To understand the influence of quantum chemical method on the energy profile of the reaction, calculations were repeated using MP2(full) methods and 6-31+G(d,p) basis sets.[46a,49] To understand the influence of solvent on the sulfoxidation reaction mechanism, explicit water molecules were included in transition state calculations at the same levels of geometry optimization and reoptimized. AIM (atom in molecules) analysis was carried out to identify weaker hydrogen-bonding interactions.[52] The energy barriers for all transition states were computed relative to their reactant cluster at the B3LYP and MP2(full) levels. In the discussion, the geometric parameters and the energies obtained using MP2(full) level are included unless otherwise specifically mentioned.

RESULTS AND DISCUSSION

Several mechanisms have already been considered for S-oxidation by hydrogen peroxide.[29,30] The simplest of all mechanisms is the S_N2-like cleavage of the O−O bond along with a 1,2 hydrogen shift leading to sulfoxide formation along with generation of neutral molecule (water) as a byproduct. Other mechanisms include involvement of (i) general acids,[30,37] (ii) both general acid and protonated solvent,[37] (iii) water oxide,[30] and (iv) OH^+ group transfer followed by H^+ migration to distal oxygen (especially in case of ROOH),[35] etc. Moreover, in the presence of solvent (water) molecule(s), the mechanism proposed by Bach et al. involved the stabilization of the cyclic transition state formed due to H-bonding influence of water with the oxidant resulting in lowering of energy barriers by 10 kcal/mol.[30] However, the mechanism suggested by Bach et al. implies pH dependency, which does not find support from experimental studies. Later, Chu and Trout proposed pH-independent transfer of oxygen to sulfur of dimethyl sulfide in aqueous solutions in which transfer of hydrogen occurs after the oxygen transfer to sulfur of the substrate.[39] Involvement of one, two, and three water molecules in the mechanism was emphasized by these scientists.

In this study, we employed the simplest mechanism involving up to three water molecules to address the following questions: What is the mechanism of oxygen transfer from the oxidant to sulfur of methylthiazolidinediones? What are the transition state structures for oxygen transfer from oxidant to sulfur atom of methylthiazolidinediones? What is the influence of water molecule(s) on oxygen transfer from oxidant to sulfur atom of methylthiazolidinediones? How can the oxygen transfer to methylthiazolidinediones be compared to that of dimethyl sulfide? The nucleophilic attack on **I** may involve two paths depending on the configuration at the C_5 chiral center in the proposed model, methylthiazolidinedione. Glitazones are known to be more active PPARγ agonists in their S-configuration (on a relative scale). This may not have any bearing on the S-oxidation pathway; however, to analyze the possible differences, transition states on the path of

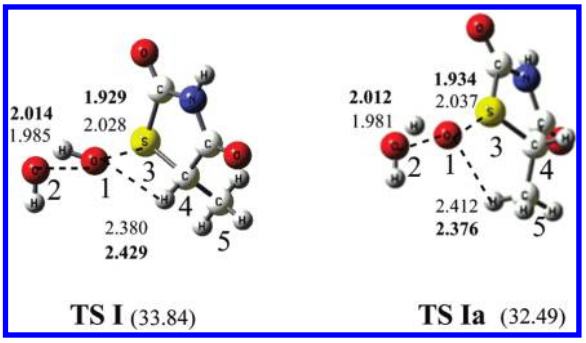

Figure 5. 3D structure of transition states of S-oxidation of methylthiazolidinedione on two paths (*R*) and (*S*) configuration with oxidant **I** (HOOH). The distance data are given in angstroms (normal font, B3LYP level; bold, MP2(full) level). The values in parentheses represent the energy barriers in kcal/mol at the MP2(full) level of theory.

S-oxidation involving both the (*R*) and the (*S*) configurations of model methylthiazolidinedione were studied. Figure 5 shows the 3D structure of the transition states on the above two paths. The S---O_1 distance in the transition state **TS I** is on the order of 1.929 Å. The O_1-O_2 distance elongated as expected to 2.012 Å. The O−O−H angle is quite small (40.28°); also, the O_2---H_1 distance (1.39 Å) is suitable for hydrogen transfer. In addition, a O_1---H−C_4 (chiral) distance of 2.43 Å was noted in **TS I**, whereas a O_1---H−C_5 distance of 2.37 Å was noted in **TS Ia**. These distances are quite within C−H---O_1 hydrogen-bond interactions, indicating that the oxygen transfer involves a supporting (C−H---O_1) interaction from the hydrogen or methyl groups (at chiral center) of methylthiazolidinedione. The hydrogen atom at the chiral center is highly acidic and is characterized by a positive charge of 0.318 units (NBO method), thus contributing toward stabilization of the **TS I**, whereas, on the other hand, methyl hydrogen (0.275 units) in **TS Ia** is proximal to O_1 due to the additional C−C bond. Moreover, the C−H---O_1 hydrogen bond in **TS I** is much weaker than that in **TS Ia** as indicated by AIM analysis. This indicates that the S-oxidation on methylthiazolidinediones may be considered to be more favorable in the S-enantiomer as depicted in **TS Ia**.

The energy barrier for S-oxidation involving **TS I** is 33.04 and 32.64 kcal/mol at the B3LYP and MP2 (full) levels, respectively. On the other hand, barriers are 33.84 and 32.49 kcal/mol in **TS Ia**. These marginal differences in S-oxidation barriers indicate that there is no specific kinetic control of the configuration of methylthiazolidinedione on the S-oxidation reaction. The product thermodynamic energies were found to be −30.61 and −30.16 kcal/mol for sulfoxide formation in (*R*) and (*S*) enantiomers, respectively, indicating a marginal stability of the (*R*) enantiomer. Considering the above factors, especially the energy barrier into consideration, it can be concluded that the S-oxidation involving the (*S*) enantiomer of glitazones is favorable (marginally), and the rest of the work was carried out using the (*S*) enantiomer of methylthiazolidinedione.

Computational analyses on the S-oxidation of methylthiazolidinedione were carried out on the (*S*) enantiomer with other oxidizing agents (**II**, **III**, and **IV**). The structures of the transition states are given in Figure 6; all these are on the path following an S_N2-type reaction mechanism. The transition state structures illustrate elongation of the distance between two oxygen atoms (O_1-O_2) and decrease in the S−O_1 distance, thus depicting the process of S-oxidation of methylthiazolidinediones.

The involvement of peroxynitrous acid (HOONO) and peroxynitrite anion ($^-$OONO) in the process of S-oxidation of dimethyl sulfide has been studied extensively.[32] It was found that biradicaloid character of peroxynitrous acid is not necessary in the process of S-oxidation. Moreover, the mechanism involved is an S_N2-like attack of lone pair of sulfur atom on electrophilic oxygen (O_1) followed by 1,4-H shift resulting in the exclusive formation of sulfoxide and nitrous acid (HONO). Therefore, in this study, peroxynitrous acid is utilized as an oxidant without invoking the biradicaloid nature. In **TSII**, the S−O_1 distance is 1.899 Å. An intramolecular hydrogen transfer noted within the peroxynitrous acid in **TSII**. O_1 in **TSII** also shows a strong C−H---O_1 (2.388 Å) stabilizing interaction, which is supported by AIM analysis. The barrier for the S-oxidation process is 14.61 kcal/mol using **II**, which is much smaller than that of **I**. Energy stabilization gained in the final product (sulfoxide) is −20.87 kcal/mol on the reaction path.

Because a wide variety of oxygen transfer reactions (S-, N-oxidation) in our biological system are carried out by flavoprotein monooxygenases (FMOs), it became critical to analyze the mechanism of oxygen transfer by theoretical studies. Thus, extensive theoretical studies on the process of oxygen transfer in S-containing substrates (dimethyl sulfide, dimethylselenide) were undertaken by Canepa et al.,[35] Bach and co-workers,[29] using bicyclic and tricyclic C4a-flavin hydroperoxides as models (**III** and **IV**) to mimic FMOs in the process of oxygen transfer. They proposed the S_N2-like attack of the nucleophile on O_1 of bicyclic and tricyclic C4a-flavin hydroperoxide. **IV** is the model C-4a-hydroperoxyflavin consisting of tricyclic isoalloxazine moieties, which resemble flavoenzymes (versatile redox cofactors). Flavoenzymes are effectively utilized as oxygen donors for a number of oxidative reactions. **III** is only a model of **IV**, where the aromatic ring is removed and is employed in computational studies to reduce the computational requirements. Because **III** and **IV** constitute as models for the study of flavoprotein monooxygenases (FMOs), they were included as oxidants in the current study of S-oxidation of methylthiazolidinediones also.

Figure 6 includes the 3D structures of the transition states **TSIII** and **TSIV**. The interactions between the catalyst and glitazone in **TSIII** and **TSIV** are quite comparable to that of **TSI**. The S−O_1 distances in **TSIII** and **TSIV** are 1.898 and 1.848 Å. The O_1-O_2 distances are elongated as expected. The O_2-O_1−H angles in **TSIII** and **TSIV** respectively are 47.83° and 55.41°, which are larger than the same angle of O_2-O_1−H in **TSI**. In both **TSIII** and **TSIV**, the oxidation process takes support of the CH_3 group on the thiazolidinedione ring through the C_5−H---O_1 interaction. The barriers for S-oxidation using **III** and **IV**, respectively, are 22.53 and 18.85 kcal/mol, which are much less than that of **I** (32.49 kcal/mol) as shown in Table 1. This is mainly due to the greater oxidative ability of **III** and **IV** in relation to **I**.[29,35,36] This is an expected trend as reported by Bach et al. on the reaction of dimethyl sulfide with **I**, **III**, and **IV**. The above results confirm that the mechanism involving the attack of nucleophile (S atom in glitazone ring) on O_1 followed by S_N2-type O_2 elimination can be confirmed to be the preferred oxidation path for sulfoxidation of glitazones. Moreover, the geometric and energetic factors associated with S-oxidation reaction are quite parallel to that of S-oxidation of dimethyl sulfide with the same model oxidants (**I**−**IV**).[29a−29d,37] These data also indicate that the quantum chemical methods employed in this study are sufficiently rigorous in modeling the S-oxidation of glitazones.

Table 1 lists the barriers for the oxygen transfer reaction (E_a) and stability of the oxidized product (ΔE) on the reaction path.

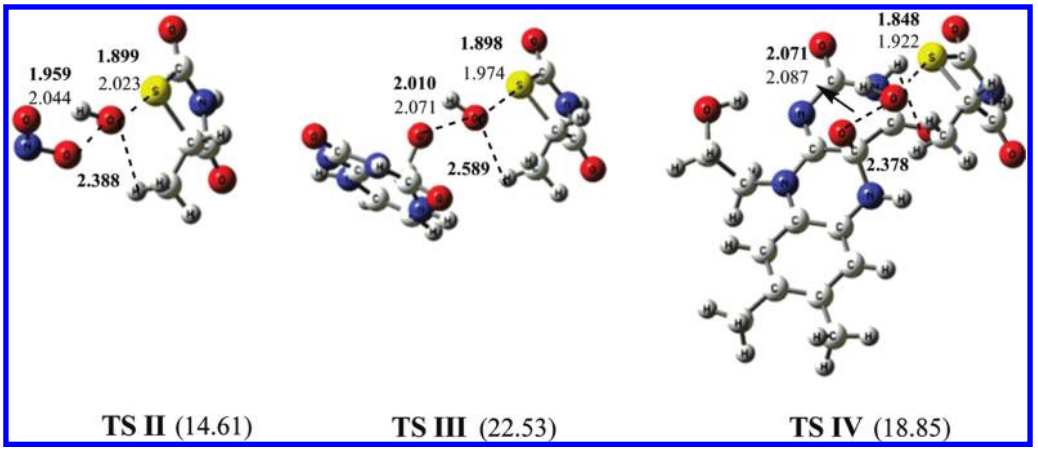

Figure 6. 3D structures of transition states of S-oxidation of methylthiazolidinedione with different oxidants **II** (HOONO), **III** (bicyclic C4a-flavin hydroperoxide), and **IV** (tricyclic C4a-flavin hydroperoxide) in the gas phase. The distance data are given in angstroms (normal font, B3LYP level; bold, MP2(full) level). The values in parentheses represent the energy barriers in kcal/mol at the MP2(full) level of theory.

Table 1. Relative Energies on the S-Oxidation Path of Methylthiazolidinedione and Dimethyl Sulfide with Catalysts I−IV Calculated at Different Levels of Theory Using the 6-31+G(d,p) Basis Set

	methylthiazolidinedione					
	B3LYP			MP2 (full)		
	gas phase		explicit water (one)	gas phase		explicit water (one)
transition state	E_a	ΔE	E_a	E_a	ΔE	E_a
I	33.84	−23.35	26.20	32.49	−30.16	22.49
II	12.56	−14.50		14.61	−20.87	
III	26.79	−18.88	17.93	22.53	−21.96	9.72
IV	24.55	−18.82	17.65	18.85	−21.58	8.40

	dimethyl sulfide			
	B3LYP		MP2 (full)	
	gas phase		gas phase	
transition state	E_a	ΔE	E_a	ΔE
I	25.69	−37.44	22.75	−45.08
II	1.88	−28.08	2.91	−35.79
III	10.81	−32.97	7.73	−36.88
IV	10.60	−32.91	5.98	−36.51

In all cases, the S-oxidation process is found to be exothermic with stabilization energy values in the order of about 14−40 kcal/mol. The activation barriers are in the range of 12−35 kcal/mol. The activation energies for the S-oxidation of methylthiazolidinedione are much larger than that of dimethyl sulfide using the same set of model oxidants. This may be attributed to the reduced nucleophilicity at sulfur in methylthiazolidinedione as compared to dimethyl sulfide. The S_N2 reaction is triggered by the p-type lone pair on sulfur in both dimethyl sulfide and

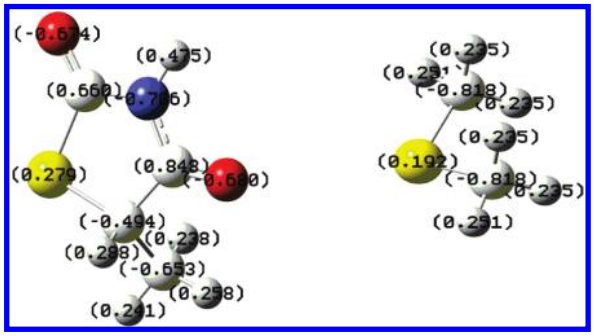

Figure 7. Comparison of charge values calculated by the NBO method for methylthiazolidinediones and dimethyl sulfide at the MP2(full)/6-31+G(d,p) level.

methylthiazolidinedione. It was found that the electron occupancy in the p-type lone pair of S in methylthiazolidinedione is less (1.866) in comparison to that of dimethyl sulfide (1.954). This is because the p-type lone pair in methylthiazolidinedione is involved in $n_{p(S)} \rightarrow \pi^*_{C=O}$ delocalization (NBO analyses), thus reducing nucleophilicity originating from the p-type lone pair on S. Also, the NBO electron density at S in methylthiazolidinedione is also less by 0.087 units than that in dimethyl sulfide, leading to the decreased nucleophilicity of methylthiazolidinedione in relation to dimethyl sulfide.

The reaction enthalpy in the S-oxidation reaction in the methylthiazolidinedione by **I** is about −30.16 kcal/mol at the MP2 (full) level of theory, whereas the same reaction enthalpy is about 14.92 kcal/mol more favorable in case of dimethyl sulfide (Figure 7). A similar difference in the reaction enthalpies was observed while employing other catalysts (**II** −**IV**). This indicates that sulfoxide formation is relatively less favorable in the case of methylthiazolidinedione. This may be attributed to the fact that the S atom in methylthiazolidinedione is already involved in some stabilizing interactions due to conjugation, which are absent in dimethyl sulfide. The C−S bond lengths in dimethyl sulfide are 1.80 Å each, whereas these are 1.82 Å [S−C(O)] and 1.77 Å [S−C(Me)] in methylthiazolidinedione (Figure 8). Upon oxidation, the C−S bond lengths are only marginally elongated in dimethyl sulfoxide, whereas these are significantly increased in methylthiazolidinedione sulfoxide S−C(Me) elongated by 0.03 Å

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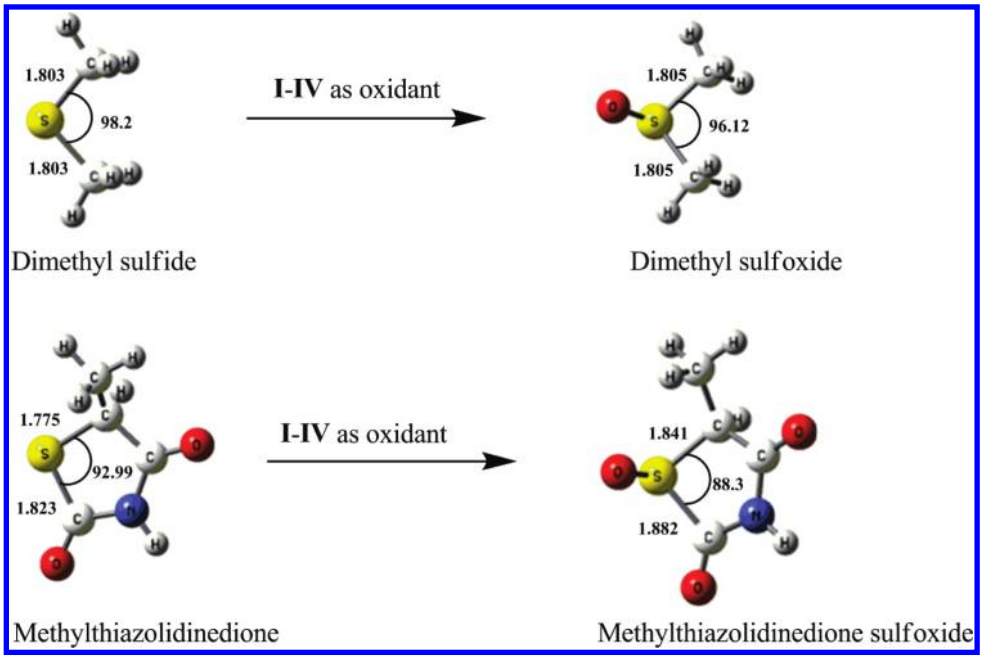

Figure 8. Comparison of geometries of reactants (dimethyl sulfide; methylthiazolidinedione) and products (dimethyl sulfoxide; methylthiazolidinedione sulfoxide) at the MP2(full)/6-31+G (d,p) level of theory. All distances are in angstroms, and bond angles are in degrees.

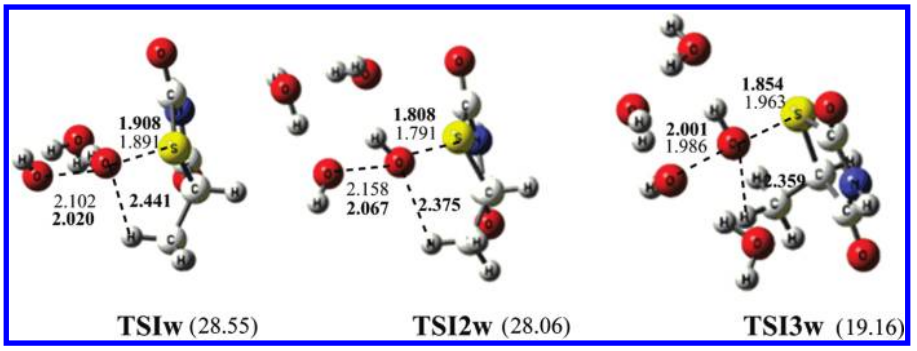

Figure 9. Comparison of transition state structures for S-oxidation of methylthiazolidinedione with **I** (HOOH) in the presence of one, two, and three explicit water molecules at the MP2(full)/6-31+G (d,p) level. All bond distances are in angstroms (normal font, B3LYP level; bold, MP2 (full) level). The values in parentheses represent the energy barriers in kcal/mol with respect to the water complexes of the oxidizing agents and methylthiazolidinedione at the MP2(full) level of theory.

and S−C(O) elongated by 0.11 Å. Moreover, the C−S−O−C torsional angle in methylthiazolidinedione sulfoxide is 93.11°, whereas the C−S−O−C torsional angle in dimethyl sulfoxide is 101.94°; as a result, the S═O bond remains almost perpendicular to the methylthiazolidinedione ring in methylthiazolidinedione sulfoxide. The C−S−C angle in methylthiazolidinedione is 92.99°, which gets shrinked to 88.3° in methylthiazolidinedione sulfoxide, whereas the C−S−C angle in dimethyl sulfide is 98.2°, which gets only marginally reduced to 96.12° in dimethyl sulfoxide. The pyramidalization at S in methylthiazolidinedione (sum of angles: 301°) is much stronger in comparison to that in dimethyl sulfoxide (sum of angles: 309.5°). All these may have influence in the observed differences in the reaction enthalpies for S-oxidation of dimethyl sulfide and methylthiazolidinedione.

Influence of Explicit Water. The estimated barriers for the S-oxidation in gas-phase conditions are quite high, and hence these reactions are not expected to be very favorable under these conditions. Earlier studies indicated that the reaction from dimethyl sulfide to dimethyl sulfoxide might involve the participation of explicit solvent molecules (mostly water).[39] Under in vivo conditions, participation of water in the catalytic process is very much expected. To evaluate the importance of water, explicit water-mediated S_N2 reaction path was analyzed for the above reactions, with 1−3 water molecules, using B3LYP and MP2(full) levels. The 3D structures of the transition states on the S-oxidation path involving explicit water molecules are shown in Figure 9. The network of hydrogen bonds in the transition state complexes is clearly visible from the structures. Indeed, the barrier for the S-oxidation gradually decreases after inclusion of water molecules; however, the stabilizations are dramatic. For example, the barrier for S-oxidation became −5.61 kcal/mol after including three water molecules (**TSI3w**). This is because of the overestimation of stabilization in the presence of the network of hydrogen bonds.

Thus, due to overestimation of stabilization observed, it became clear that consideration of prereaction complex is required in the reaction enthalpies and reaction barrier analysis. The prereaction complex consisting of methylthiazolidinedione, oxidant, and water molecule (s) was identified, but the precise structure

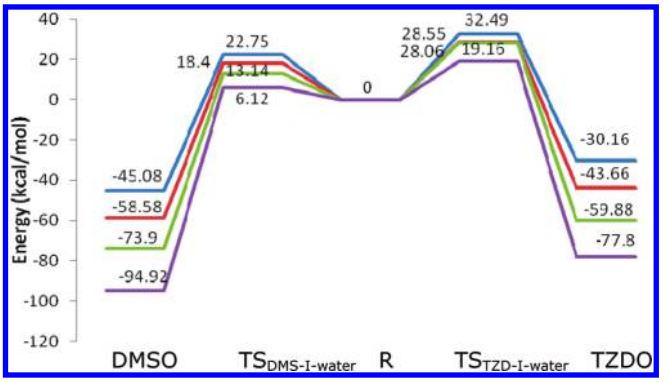

Figure 10. Potential energy surfaces of oxygen transfer reaction from **I** to dimethylsulfide and methylthiazolidinedione in gas and solvent (water) phases (DMSO, dimethyl sulfoxide; $TS_{DMS\text{-}I\text{-}water}$, transition state of dimethylsulfide with oxidant I (H_2O_2) and 1−3 water molecules; R, reactant; $TS_{TZD\text{-}I\text{-}water}$, transition state of methylthiazolidinedione with oxidant I (H_2O_2) and 1−3 water molecules; TZDO, methylthiazolidinedione sulfoxide).

could not be obtained because of the overstabilization due to the hydrogen-bond network. The H-bonding network between water molecule(s) and the carbonyl group of methylthiazolidinedione was found to be more prominent as compared to that with oxidant; therefore, identification of interaction between the oxidant and methylthiazolidinedione became impractical. Hence, the potential energy (PE) surfaces are analyzed with reference to the water complexes of the oxidizing agents, that is, $E_{TZD} + E_{oxidant-water\ complex} \rightarrow E_{TS\text{-}water} \rightarrow E_{TZDO} + E_{water\ molecules\ complex}$. Figure 10 shows the PE surface as per this equation. In this approach, the influence of water on the reaction mechanism became more clearly visible, while the overestimation of stabilization due to the network of hydrogen bonds is drastically reduced. As shown in Figure 10, the barrier of S-oxidation in the absence of water is 32.49 kcal/mol. After including one water molecule, the barrier is reduced to 28.55 kcal/mol; after the inclusion of second and third water molecules, the barriers get reduced further to 28.06 and 19.16 kcal/mol. Participation of one water molecule reduces the barrier by 3.94 kcal/mol. Similarly, the inclusion of a second water molecule causes further reduction in the barrier by 0.49 kcal/mol. However, inclusion of a third water molecule tremendously reduces the barrier by 8.90 kcal/mol. For comparison purpose, the barriers of S-oxidation on dimethylsulfide are also depicted in Figure 10. A near similar trend for lowering in energy barriers was observed for S-oxidation by **I** in both methylthiazolidinedione and dimethylsulfide in the presence of one and three water molecules.

The oxidized products under the explicitly solvated conditions (one, two, and three water molecules) are exothermic by −43.66, −59.88, and −77.80 kcal/mol. Thus, inclusion of explicit water molecules makes the reaction more exothermic than in the gas phase (−30.16 kcal/mol). The above results indicate that the actual oxygen transfer process is indeed influenced by the presence of solvent molecules, in terms of both kinetic and thermodynamic controls.

Because the energy barrier value for process of S-oxidation by **II** was found to be 14.61 kcal/mol (well within the experimental range) and intramolecular hydrogen-bonding interactions occur between terminal oxygen and hydrogen in **II**, the explicit water molecule(s) were not included in the study for S-oxidation by **II**. Moreover, Musaev and co-workers observed only slight changes in energy barrier values for PCM model (implicit solvent conditions) for S-oxidation of dimethyl sulfide as compared to the gas-phase study.[32] The reaction mechanisms involving the oxidizing agents **I**, **III**, and **IV** are quite similar, and hence the influence of explicit water solvent is also expected to be similar.

CONCLUSIONS

Quantum chemical analysis was carried out on the S-oxidation of methylthiazolidinedione as a model of antidiabetic drugs, rosiglitazone, and pioglitazone. Barriers for the oxygen transfer reaction from four different oxidants are estimated using the B3LYP/6-31+G(d,p) and MP2(full)/6-31+G(d,p) levels of theory. The (*S*)-stereoisomer of methylthiazolidinedione was employed in the study, because the barriers for S-oxidation are equally favorable on both isomers ((*S*)-stereoisomer is marginally more favorable). This theoretical study suggests an S_N2-like reaction mechanism of nucleophilic attack of S on the distal oxygen (O_1 toward sulfur) causing the cleavage of O_1-O_2 bond, thereby leading to the formation of a new S=O bond.

In the gas phase, S-oxidation by H_2O_2 (**I**) requires 32.49 kcal/mol. When model organic catalysts based on the peroxide moiety (**III** and **IV**) are employed, the barriers are found to be reduced to 22.53 and 18.85 kcal/mol, respectively. All the above catalysts follow a path involving an intramolecular 1,2-H shift while transferring oxygen to methylthiazolidinedione. On the other hand, the intramolecular 1,4-H shift is involved in the oxygen transfer from peroxynitrous acid (**II**), facilitating the reaction with low energy barrier of 14.64 kcal/mol. S-Oxidation of methylthiazolidinedione is found to be less favorable than S-oxidation of dimethylsulfide. Participation of water in the S-oxidation reduces the barrier to 10−20 kcal/mol, indicating that this reaction mechanism involves the participation of explicit water molecule(s).

ASSOCIATED CONTENT

Supporting Information. Tables S1−S4 with absolute energies of all the geometries under consideration. Cartesian coordinates of all the optimized transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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