Rapid Racemization in Thiazolidinediones: A Quantum Chemical Study†

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Ab initio molecular orbital (MO) and density functional studies have been carried out on the keto−enol tautomerization process in thiazolidinediones to understand the mechanism of rapid racemization observed in these systems. MP2(full)/6-31+G* results on model thiazolidinedione **1** indicate that the energy difference between keto and enol tautomers is 24.04 kcal/mol, which is larger than that in acetaldehyde (16.23 kcal/mol). Neither the ring strain in **1** nor the electron delocalization in its tautomers is significant enough to facilitate rapid racemization through this mechanism. Reversible S-oxide formation increases the acidity of the hydrogen at the chiral center as well as provides an alternative path for tautomerization, suggesting that such a mechanism is responsible for the rapid racemization observed under physiological conditions.

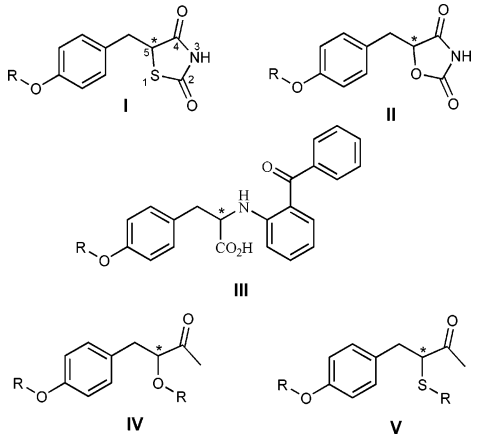
Introduction

Glitazones (I) are insulin sensitizers useful for the treatment of Type-II Diabetes Mellitus.[1−5] They are agonists for the peroxisome proliferator activated receptor gamma (PPAR-γ), a member of the nuclear hormone receptor superfamily involved in lipid homeostasis.[6] Several hundreds of derivatives of thiazolidinediones have been synthesized and tested for antidiabetic activity and of them two compounds, i.e., rosiglitazone[2] and pioglitazone,[3] are presently in clinical use.

Glitazones contain a stereogenic center at the C5 position of the thiazolidone-2,4-dione ring, the two enantiomers show differential activity with the *S*-enantiomer being more active than the *R*-enantiomer.[4a] The two enantiomers of rosiglitazone have been separated by chiral HPLC (high performance liquid chromatography). Competitive binding assay to PPAR-γ receptor indicated higher affinity for the *S*-enantiomer as compared to the *R*-enantiomer. The finding has been further strengthened by the crystal structure analysis of the bound receptor with the *S*-enantiomer of rosiglitazone.[7] It has also been established that the higher binding affinity of the *S*-enantiomer correlates with better antidiabetic activity.[8] But attempts to use only the eutomer for therapeutic purpose turned futile when it was observed that the pure enantiomer underwent rapid racemization under physiological conditions, giving no net advantage of the tedious separation or synthesis of enantiomerically pure compounds.[5] The IC_{50} (inhibitory concentration 50 is the concentration of the material estimated to inhibit the biological endpoint of interest by 50%) values for rosiglitazone in the assay referred above, were monitored over the course to estimate the rate of racemization. The $t_{1/2}$ for racemization was determined to be 3 h at pH 7.2.[4a] Several nonthiazolidinedione insulin sensitizers such as oxazolidinediones (II),[9] tyrosine based PPAR-γ agonists (III)[10] and alkoxypropionic acid derivatives (IV)[11] (Chart 1) have shown no tendency for racemization unlike glitazones and as a result show better activity of the pure compound.[9−12]

It has been proposed that the 1,3-H shift leading to the formation of the enol isomer of the thiazolidinedione ring is mainly responsible for rapid racemization.[5,13−15] The differential

CHART 1



rates of racemization between thiazolidinediones and other insulin sensitizers have been attributed to the differential rates of keto−enol tautomerism in these compounds.[9−12] However, to the best of our knowledge, there is no evidence available to show the existence of enols of thiazolidinediones and no studies are available reporting the percentage enol content in these systems. The π donating substituents in CH_3-CXO (X = F, NH_2) have been shown to reduce the probability of keto−enol tautomerism[16] and hence the tautomerization in glitazones may not be a very favorable process.

Hulin et al. have rationalized the observed rapid racemization in ciglitazone by comparing the activity of (+) and (−) isomers of (alkylthio)propionic acids V with that of the alkoxypropionic acids IV.[17a,b] They have observed (alkylthio)propionic acids are less active than the corresponding alkoxypropionic acids because the former can undergo rapid racemization whereas the latter does not. They proposed that reversible S-oxide formation in vivo[17c] may be causing the observed difference. They also pointed out that the α-sulfinyl carboxylic acid shows greater acidity by losing the chiral hydrogen. Hence it is important to verify whether enolization or sulfoxide formation in glitazones is of importance in the mechanism for rapid racemization. A clear understanding of the mechanism of racemization would help in designing new molecules with controlled racemization

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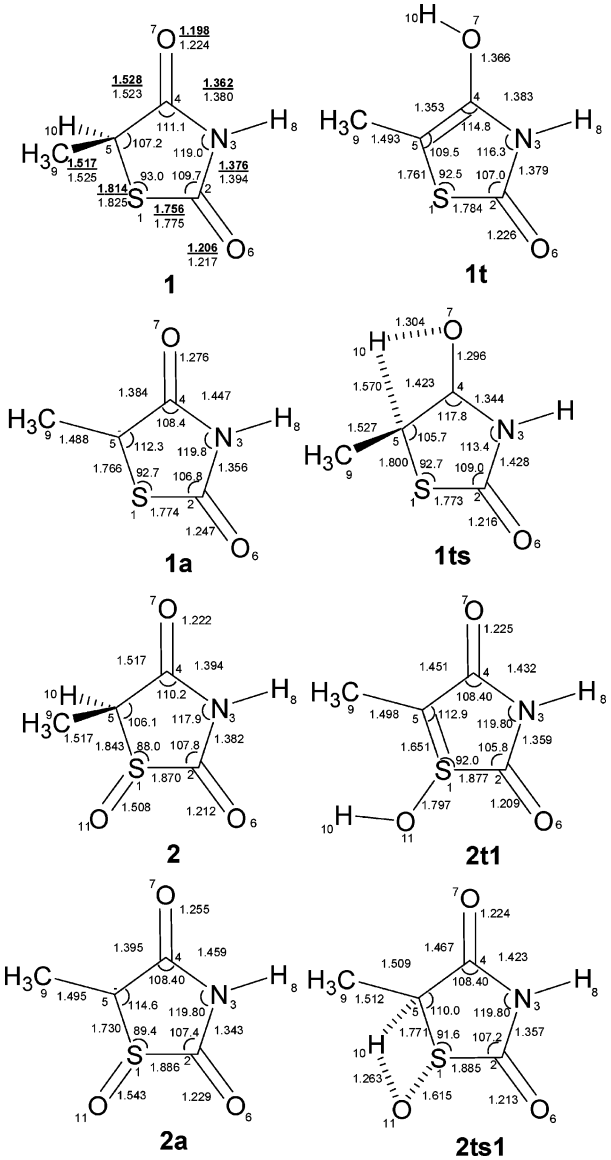


Figure 1. Geometries of **1**, **1t**, **1a**, **1ts**, **2**, **2t1**, **2a**, and **2ts1**. The top bold and underlined values in **1** are obtained from the crystal structure. The normal text values in all geometries are MP2(full)/6-31+G* values.

property; computational studies are ideally suited for this purpose.[18−28]

In this paper we report ab initio MO[29] and density functional[30,31] studies on the keto−enol tautomerism in thiazolidinedione **1** and its S-oxide derivatives **2** and **3** by estimating acidity at the chiral carbon, the barrier for 1,3-H shift, etc.

Methods of Calculations

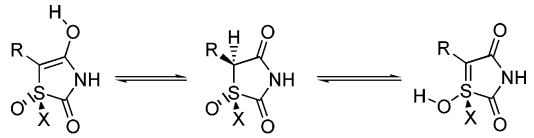
Ab initio MO and DFT calculations were performed with the GAUSSIAN98[32] suite of programs. Geometry of 5-methylthiazolidinedione (**1**), its tautomeric form (**1t**), its anion (**1a**), and the corresponding transition state structure for 1,3-H shift (**1ts**) were optimized at HF, MP2(full) and B3LYP levels of theory using 6-31+G* basis set;[29b] all the representative structures are displayed with their important geometrical parameters in Figure 1. Analytical frequencies were calculated on all systems at HF/6-31+G* and B3LYP/6-31+G* levels to recognize minima (zero negative frequency)/transition state (one negative frequency) on the potential energy (PE) surface and to estimate zero point vibrational energies (ZPE).[33] ZPE values obtained using HF/6-31+G* are scaled by the corresponding scaling factor of 0.9153.[34] The relative energies (ΔE), 1,3-H shift barriers (E_a), and the ionization energies (IE) are tabulated in Table 1. The natural population analysis (NPA) method was used in estimating partial atomic charges.[35] Similar calculations have also been carried out on the sulfoxide derivatives of 5-methylthiazolidinedione (**2** and **3**), their two tautomeric forms (**2t1, 3t1** and **2t2, 3t2**), anions (**2a** and **3a**), and their corresponding transition states (**2ts1, 3ts1** and **2ts2, 3ts2**) (Scheme 1). To understand the influence of solvent on the tautomerization process, self-consistent reaction solvent fields[36] (SCRF) calculations have been carried out in water medium ($\epsilon = 78.39$) using the Onsager method. Earlier computational work on the keto−enol tautomerism showed that the energy difference between the two tautomers is highly dependent on the method used, high-accuracy methods showing smaller ΔE, though the trends are independent of the method employed.[20−24] G2MP2 calculations performed on **1**, **1t**, **1ts,** and **1a** confirmed the same observation. The ΔE between **1** and **1a** is 19.11 kcal/mol according to G2MP2, which is smaller (by ~4.93 kcal/mol) than that obtained at the MP2 level. Similarly, the barrier for the 1,3-H shift is smaller by 4.19 kcal/mol and the ionization energy is larger by 3.47 kcal/mol. These deviations indicate that the relative energies reported in Table 1 need to be scaled by about 0.80, 0.95, and 1.01 to obtain numerically accurate estimates of the tautomerization energies. In this work trends in the energy values are more important than the absolute energies. MP2(full)/6-31+G* geometries and energies are employed in the discussion unless otherwise specifically mentioned.

TABLE 1: Energy Parameters (kcal/mol) Associated with Tautomerization in 1, 2, and 3 in the Gas Phase at B3LYP/6-31+G* and MP2(full)/6-31+G* and the Solvent Phase (Solvent Water $\epsilon = 78.6$) at B3LYP/6-31+G* and MP2(full)/6-31+G*//B3LYP/6-31+G* [a]

	ΔE		E_a		IE	
molecules	B3LYP	MP2(full)	B3LYP	MP2(full)	B3LYP	MP2(full)
			Gas Phase			
1 ⇄ **1t**	22.54	24.04	75.49	77.41	345.32	344.72
2 ⇄ **2t1**	14.55	15.66	38.38	39.65	331.57	330.68
2 ⇄ **2t2**	23.34	25.27	75.96	78.02	331.57	330.68
3 ⇄ **3t1**	30.87	34.67	52.16	55.76	323.25	323.22
			Solvent Phase			
1 ⇄ **1t**	19.27	20.8	75.45	77.64	345.51	344.93
2 ⇄ **2t1**	15.87	17.01	39.34	40.59	332.44	331.32
2 ⇄ **2t2**	19.02	20.9	74.62	76.66	332.44	331.32
3 ⇄ **3t1**	29.51	33.00	53.96	57.49	324.92	324.53

[a] All the values are ZPE corrected. ΔE: energy difference between the tautomers. E_a: activation energy for 1,3-H shift. IE: ionization energy for deprotonating chiral center.

SCHEME 1: Two Tautomeric Forms of Derivatives of 2 (X═:) and 3 (X═O) of 5-Methylthiazolidinedione



Results and Discussion

Keto−Enol Tautomerism in 1. Complete optimizations have been carried out on **1**, **1t**, **1a**, and **1ts** at B3LYP/6-31+G* and MP2(full)/6-31+G* levels to understand the tautomerization in glitazones. Figure 1 gives the important geometric parameters of **1**, **1t**, **1a,** and **1ts** at various levels. The calculated bond

lengths and geometric data are comparable to that reported for the thiazolidinedione ring in various crystal structures such as those of thiazolidinedione,[37a,b] phenyl thiazolidinedione,[37c] and troglitazone.[37d] A significant deviation is seen in the estimation of C−S bond lengths at the B3LYP/6-31+G* level. This is in accordance with the known limitations of the B3LYP method in estimating X−S bond lengths.[38]

The TZD ring has been found to adopt a planar arrangement at all the computational levels, as in the case of related crystal structures. The C5 center is expected to be highly acidic because the loss of H from this center would induce sp^2 character to C5 and increase π-delocalization.

The geometric changes between **1** and its enol tautomer **1t** are according to the expectations in a typical keto−enol pair. **1ts** is a nonplanar transition state similar to that in the keto−enol tautomer of acetaldehyde, with the migrating H slightly above the molecular plane. All parameters (Figure 1) suggest that transition state **1ts** is a true transition state connecting the minima **1** and **1t** and this has been verified by performing IRC (intrinsic reaction coordinate) calculation.

Energy estimations have been carried out for these compounds at HF, B3LYP, and MP2 levels (Table 1), the keto form is more stable than the enol form at all levels. The energy difference (ΔE) between the two tautomers **1** and **1t** at B3LYP/6-31+G* and MP2/6-31+G* levels are 22.54 and 24.04 kcal/mol, respectively. The energy barrier for the 1,3-H shift estimated at the same levels are 75.49 and 77.41 kcal/mol, respectively. The keto−enol energy difference at the MP2(full)/6-31+G* level in **1** (24.04 kcal/mol) is much larger than the same in acetaldehyde (16.23 kcal/mol). The 1,3-H shift barrier (77.41 kcal/mol) in **1** is also larger than that in acetaldehyde (71.4 kcal/mol) at the MP2(full)/6-31+G* level. Even under solvent conditions, ΔE and 1,3-H shift barriers are higher in **1** (20.80 and 77.64 kcal/mol) than that of acetaldehyde (18.27 and 72.50 kcal/mol) at the MP2(full)/6-31+G* level. Higher values of ΔE and 1,3-H shift barriers suggest the enol content in **1** should be less than that of acetaldehyde. Hence, keto−enol tautomerism in glitazones is not expected to be a very favorable process.

The ionization energy in **1** to give **1a** has been estimated to be 344.72 kcal/mol at the MP2(full)/6-31+G* level. This value is much less than that of acetaldehyde (363.90 kcal/mol) at the same level, indicating that the ionization of **1** by removing hydrogen at C5 is much more facile than ionization of acetaldehyde. The calculated ionization energies in the gas phase (344.72 kcal/mol) and water medium (344.93 kcal/mol) are comparable and hence the observed greater acidity at C5 is expected in all media. This further indicates that the acidity at C5 is much higher than that of the methyl group in acetaldehyde. The greater acidity at C5 may be attributed to the planar structure of **1** and to the extra stability of **1a** due to enhanced electron delocalization. These data indicate that the higher acidity at C5 indeed can be implicated in the rapid racemization of thiazolidinediones, as suggested by Sohda et al.[5] and Gaupp and Effenberger.[14] But considering the large ΔE between the tautomers **1** and **1t**, it appears that the higher acidity at the chiral center in thiazolidinediones may not contribute to keto−enol tautomerism.

Atomic charges on various elements in **1**, **1t**, **1a,** and **1ts** have been estimated using the NPA method with MP2(full)/6-31+G* geometries and MP2 densities (Figure 2). The C4−O7 bond in **1** is highly polarized as indicated by the differences in the atomic charges at these centers ($\Delta q = 1.522$ e), which is much higher than that of acetaldehyde ($\Delta q = 1.131$ e). Upon ionization, this strongly polarized bond in **1** does not show any increase in polarization as most of the charge in **1a** gets delocalized in the ring. Upon ionization, O7 attracts some electron density (0.213 e) but much less than that of acetaldehyde (0.298 e). Upon ionization, C5 also gains electron density, though less than that at O7. The difference in the charges gained by O7 and C5 is $0.213 - 0.067 = 0.146$ e; the corresponding value for acetaldehyde is much higher (0.187 e). Hence the relative probability of proton attack at oxygen in **1a** is less than that of acetaldehyde, and thus the relative enol content in **1** is expected to be less than that of acetaldehyde. As a result it can be confirmed that the keto−enol tautomerization is a much less pronounced process in thiazolidinediones, compared to that of acetaldehyde.

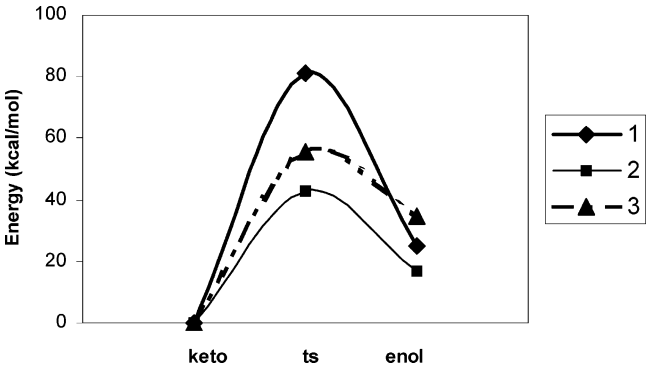


Figure 2. Potential energy (PE) surface representing **1** ⇄ **1t**, **2** ⇄ **2t1**, and **3** ⇄ **3t1** tautomeric processes at MP2(full)/6-31+G* level.

The planar structure of **1** causes the electron cloud to be π-delocalized over the whole system. This delocalization increases the acidity of the hydrogen atom at the chiral center, as indicated by the lower values of ionization energies calculated for **1** in comparison to acetaldehyde. Hence acid−base catalyzed ionization of glitazones is expected to play a crucial role in racemization process; however, the energy and charge considerations indicate less feasibility for tautomerization in **1**. The tautomerization energies in **1** are more comparable to that in acetamide ($\Delta E = 31.1$ kcal/mol) where $CH_3-C(=O)NH_2 \rightleftarrows CH_2=C(OH)-NH_2$ tautomerization is not expected to take place.[16] All these factors indicate that the keto−enol tautomerism in the thiazolidinedione ring is much less feasible than that in acetaldehyde and hence keto−enol tautomerism is not the driving force for the rapid racemization in glitazones, though greater acidity is observed at C5.

Keto−Enol Tautomerism in 2 and 3. Hulin et al. proposed that a reversible S-oxidation path might be playing a role in the rapid racemization in glitazones.[17] Single S-oxidation of **1** would give **2**, and double oxidation would give **3**. The MP2 estimated energy release during the S-oxide formation in **1** is ∼128.8 kcal/mol. Double oxidation at sulfur in **1** showed a release of ∼290.2 kcal/mol. Complete optimizations on the S-oxide derivative **2** showed that it can exist in two structural forms differing in the pyramidalization at S1. The 1*R*,5*S* diastereomer is marginally more stable and it is also convenient for 1,3-H shift; hence this structure was considered in the following discussion. Enolization in the sulfoxide derivatives is possible in two ways (Scheme 1): either the sulfoxide is involved **2** ⇄ **2t1** (**3** ⇄ **3t1**) or the carbonyl group is involved **2** ⇄ **2t2**, (**3** ⇄ **3t2**) in tautomerism. However, the tautomerization involving carbonyl carbon has been found not to be effected by the S-oxide, as indicated by tautomerization energies of (**2** ⇄ **2t2**) path (Table 1) and this path was not considered further.

The calculated ΔE between **2** and its tautomer **2t1** is 15.66 kcal/mol and the 1,3 H-shift barrier is 39.65 kcal/mol at MP2-

TABLE 2: Comparison of Ionization Energies of Acetic Acid, 1, 2, and 3 for C5−H and the N−H Proton in kcal/mol at the MP2(full)/6-31+G* Level

molecule	IE (C)	IE (N)
acetic acid	368.14	338.50[a]
1	344.72	324.87
2	330.68	313.77
3	323.22	308.02

[a] COOH group ionization energy.

(full)/6-31+G* level (Table 1). On the other hand the ΔE and E_a values between **2** and **2t2** are 25.27 and 78.02 kcal/mol, respectively, similar to that of the **1** ⇄ **1t** process. **2** ⇄ **2t1** tautomerization values are much smaller than the tautomerization energy values in **1** ⇄ **1t** and **2** ⇄ **2t2** processes. Hence it can be concluded that **2** ⇄ **2t1** tautomerization is a much freely accessible path after S-oxidation. The MP2(full)/6-31+G* calculated ionization in **2** at the chiral center C5 is 330.68 kcal/mol, which is much less than that in **1** (344.72 kcal/mol) at the same level. Also NPA (Figure 2) showed that O11 is the most negative center in **2a**. Thus S-oxidation of **1** leads to an increase in the probability of the 1,3-H shift at S═O group as well as an increase in the acidity at the chiral center, thus increasing the probability of tautomerization in this system. The lower ΔE values between **2** and **2t1** indicate much larger percentage of S−OH tautomer content in solution compared to that of **1t**. The smaller E_a in **2** ⇄ **2t1** process indicates the kinetic control on this process is high. Hence, thermodynamically as well as kinetically the reversible single S-oxidation increases the probability of racemization. This observation leads to the conclusion that rapid racemization in thiazolidinediones appear to involve the formation of **2**. The **3** ⇄ **3t1** tautomerization process requires slightly higher energy (Figure 2) for the tautomerization in terms of both 1,3-H shift barrier (55.76 kcal/mol) and ΔE (34.67 kcal/mol), in comparison to the **2** ⇄ **2t1** process. Hence, **3** ⇄ **3t1** tautomerization is not a highly favorable path in the rapid racemization of thiazolidinediones. Also, considering that the double oxidation at sulfur is irreversible under in vivo conditions, the mechanistic path involving **3** in the rapid racemization of thiazolidinediones does not seem to play any role.

Acidity of Thiazolidinediones. The acidity of the thiazolidinediones has been shown to be the most important factor in the binding of glitazones in the active site of PPAR-γ. Blaney[39] reported that the transfer of H from the N−H of thiazolidinedione ring in rosiglitazone to the Arg-286 takes place when it binds with PPAR-γ. Also mutation of Arg-286 in PPAR-γ with methionine[39] as well as the methylation of N−H of 5-(naphthalenylsulfonyl)-2,4-thiazolidinedione has been shown to cause complete loss of activity.[12] Hence it is important to compare the N−H acidity vs C−H acidity (Table 2).

The ionization energy of the N−H unit in **1** is 324.87 kcal/mol, which is much less than that of the COOH group in acetic acid (338.50 kcal/mol) at the MP2(full)/6-31+G* level, indicating greater acidity of **1**. Upon oxidation in **2** the acidity of the N−H unit increases as indicated by about a 12 kcal/mol decrease in the ionization energy. Upon double oxidation in **3**, the acidity of glitazone increases further. Similarly, the C−H acidity at the chiral center also increases upon single and double oxidation, from 344.72 to 330.68 and 323.22 kcal/mol, respectively. In fact, the C−H ionization energy in **3** is smaller than N−H ionization in **1**. The data indicate that the reversible S-oxidation contributes not only for the enhanced rapid racemization but also to improve the acidity of the N−H unit. From this discussion it may be inferred that the SO or SO_2 derivative of glitazones enhances the desirable acidic character of glitazones. But the crystal structure of rosiglitazone with PPAR-γ does not show the involvement of any of the oxide derivatives.[7] Hence, the rapid racemization should involve only a reversible S-oxidation, i.e., single oxidation.[17c]

AM1 calculations were performed on some important molecules of glitazones series (I). The ΔE 1,3-H shift barriers and the study on corresponding sulfoxides support the ab initio studies on **1**−**3**.

Conclusions

Computational studies on the model thiazolidinedione **1** showed that the ΔE between the tautomers **1** and **1t** is ∼24 kcal/mol, which is much higher than that in acetaldehyde (∼16 kcal/mol). Even the barrier for the 1,3-H shift has been found to be much higher than that in acetaldehyde. The ionization energy for the loss of H^+ at the chiral center is ∼345 kcal/mol, which is much less than that in acetaldehyde ∼363 kcal/mol, indicating greater acidity of thiazolidinediones at the chiral center. The greater acidity does not seem to contribute toward the keto−enol tautomerization because of the higher ΔE between the tautomers as well as the relatively reduced charge gain at enolic oxygen as a function of ionization in **1** as compared to that in acetaldehyde. Solvent phase studies also support the above observations. Hence the probability of keto−enol tautomerization is very less in thiazolidinediones. The computational study indicates that higher acidity at the chiral center but not rapid keto−enol tautomerization is responsible for the observed racemization. Reversible S-oxidation of thiazolidinediones greatly enhances the acidity at chiral center as indicated by the smaller ionization energy of **2** (∼330 kcal/mol) as compared to that in **1**. S-oxidation also favors 1,3-H shift by lowering the ΔE between S−O ⇄ S−OH tautomers and also by lowering the barrier for 1,3-H shift. In conclusion, the mechanism involving the formation of S-oxide derivative (**2**) is thermodynamically and kinetically more favorable in the rapid racemization of thiazolidinediones.

Supporting Information Available: Archive entries of **1**, **2**, and related structures at MP2(full)/6-31+G*, in the gas phase. Geometries of **3**, **3t1**, **3a**, and **3ts**. NPA estimated atomic charges of **1**, **2**, **3**, and their isomeric forms using MP2(full)/6-31+G* geometries. Tables of absolute energies and energy parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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