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Theoretical Study on the Selectivity of Asymmetric Sulfur Ylide Epoxidation Reaction

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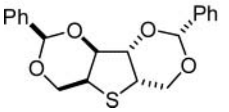
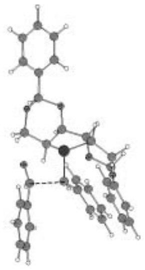
ABSTRACT





We report the first theoretical studies on the asymmetric sulfonium ylide epoxidation reaction using a chiral sulfide that successfully reproduces the experimentally determined high enantiomeric excess. Calculations at the DFT level suggest that the transition states for the addition of the sulfonium ylide to benzaldehyde have energies which account for the observed enantioselectivity.

The formation of asymmetric epoxides by the addition of a chiral sulfonium ylide to a carbonyl compound represents a useful approach to these reactive and versatile intermediates in organic synthesis.[1] A handful of new chiral sulfides and sulfonium ylides[2] have recently been developed which mediate the sulfur ylide epoxidation reaction with different levels of selectivity.[3] Our group has recently reported the synthesis of C_2-symmetric sulfide **1** in high yield and only three steps from D-mannitol and its use in the formation of diaryl epoxides.[4] The enantiomeric excess of 94% obtained for the one-pot sulfur ylide mediated epoxidation was remarkably good.[3a] A major effort has been made to understand and clarify the reaction mechanism and the stereoselectivities observed, both theoretically and experimentally.[5]

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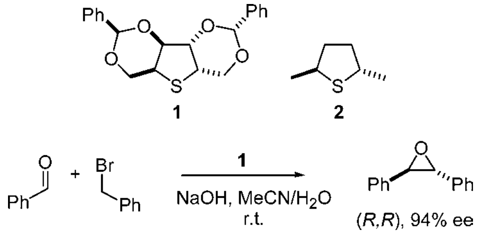
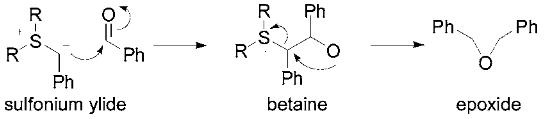
The aim of our theoretical study was to explain the selectivity observed for the sulfonium ylide epoxidation reaction using the chiral sulfide **1** as a catalyst, with formation of (*R*,*R*)-stilbene oxide in high enantiomeric excess (Scheme 1). We initially carried out a study on a less complicated chiral sulfide (2*S*,5*S*)-dimethylthiolane (**2**), for which experimental results have been recently published.[1f] This sulfide would be a good model of **1**, as it reproduces the principal structural characteristics of the sulfide used experimentally in our group.

Scheme 1



Recent computational studies from Aggarwal et al.[5a] have provided an important insight into the mechanism and the factors controlling the selectivity of this reaction (Scheme 2). Based on their results, they concluded that the rotation around the C−C single bond in the betaines appears to be the rate-determining step for the reaction. However, the activation energies for the initial addition step are very similar to the rotation of the betaine step. In the case of the *trans*-epoxide, the highest activation barrier is the first step, the addition of the sulfonium ylide to the aldehyde. Aggarwal and co-workers have suggested that the initial C−C bond formation step takes place at a similar rate for the formation of *cis*- and *trans*-epoxides, based on the small energy difference found for the model they calculated. This study, with a nonchiral sulfide, only considers the diastereoselectivity of the reaction. We have extended this study with the use of chiral sulfides, and suggest that this explanation does not account for the enantioselectivity. Unlike diastereoselectivity, enantioselectivity may be controlled by the C−C bond formation step of the reaction.

Scheme 2. General Mechanism for the Sulfonium Ylide Epoxidation Reaction via a Betaine Intermediate



The transition structures connecting the sulfonium ylide and the benzaldehyde with the corresponding betaine were investigated for chiral sulfides **1** and **2**. The use of a smaller sulfide **2** enabled us to model the system including the solvent effects. We optimized the geometries of the reactants, located the transition structures (TSs), and calculated the activation energies using Jaguar[6] with the B3LYP[7] functional and the 6-31G* basis set.[8]

The study began by investigating the sulfonium ylide conformations. For each of the chiral sulfides considered, two ylide conformations are possible after alkylation with a benzyl group and deprotonation. The conformation with the benzyl group pointing away from the sulfide is labeled the *out* conformation, and the alternative, with hydrogen pointing away, is the *in* conformation (Figure 1). The small difference in energies found for the *in* and *out* conformations of the ylide derived from sulfide **2** showed that neither of the conformers was particularly preferred. It has been suggested that the conformation of the sulfonium ylide could be a factor responsible for enantioselectivity,[3a,9] but our calculations contradict this hypothesis, as both sulfides **1** and **2** give good enantioselectivity, and the ylide derived from sulfide **2** shows low *in/out* selectivity.

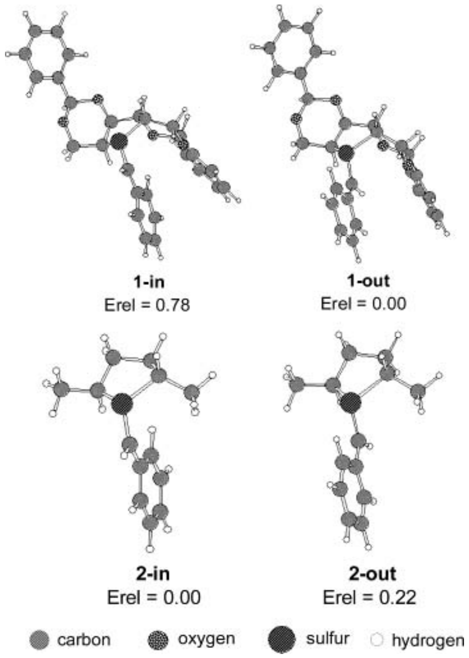


Figure 1. B3LYP/6-31G* geometries and relative energies (in kcal/mol) for the benzyl ylides derived from sulfides **1** and **2**.

Attack can occur from either face (*Re* or *Si*) of benzaldehyde to both faces of the sulfonium ylide (*Re* or *Si*) leading to four possible addition transition structures (Figure 2). All transition structures found showed a cisoid or gauche addition, and all attempts to find the corresponding transoid

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(6) Jaguar 4.2, Schrodinger, Inc., Portland, OR, 2000.

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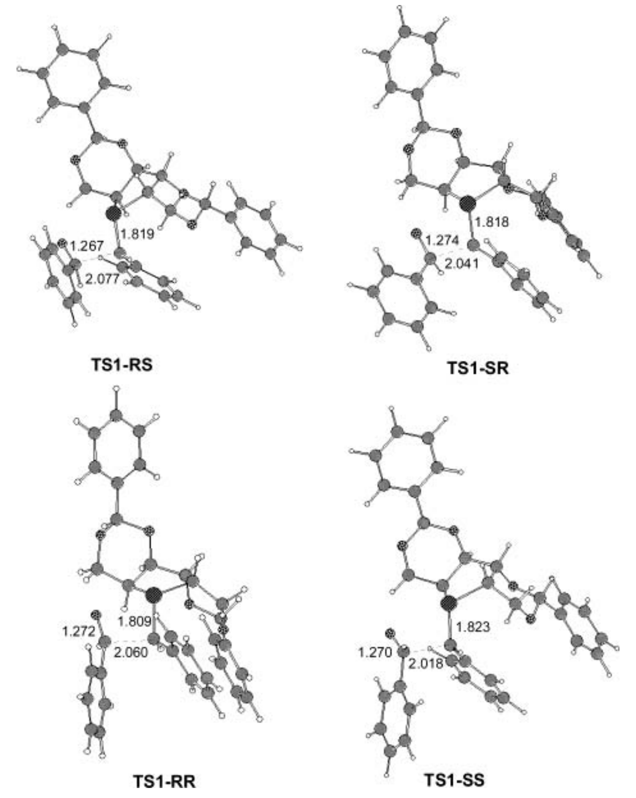

TS1-RS **TS1-SR** **TS1-RR** **TS1-SS**

Figure 2. B3LYP/6-31G* geometries for the addition transition structures **TS1**.

transition structures were unsuccessful.[5g,10] All the transition structures were verified with frequency calculations and found to have only one negative normal mode, corresponding to the movement in the direction of the reaction coordinate. Additionally, in the case of **TS2**s, we also performed QRC calculations[11] (see the Supporting Information) to link transition states with reactants and intermediate betaines. For all the transition structures, the aldehyde always approaches the sulfonium ylide from the less hindered face. All the TSs located showed very similar structural features with C−C distances between 2.04 and 2.08 for **TS1**s and slightly shorter C−C distances, between 1.92 and 2.00 Å, for **TS2**s.

The energies and ratios calculated are collected in Table 1. For the dimethylthiolane system **(2)** we found that the preferred TS is **TS2-SR** corresponding to the formation of a *cis*-epoxide. Nevertheless, for trans-pathway calculations, the Boltzmann factors predict an enantiomeric excess of 74% in favor of the *trans*-stilbene oxide (*R*,*R*), the major isomer is correctly predicted, and the enantiomeric excess is close to that observed experimentally. With these promising results for the model sulfide **2** in hand, we extended the study to our system with sulfide **1**. We were very pleased to observe that the calculated enantioselectivity predicts the formation of the (*R*,*R*)-stilbene oxide, in good agreement with the experimental data, although slightly overestimated.

Table 1. B3LYP/6-31G* Activation Energies (in kcal/mol) for the Addition Transition Structures between Sulfides **1** and **2** and Benzaldehyde[a]

			calcd ratios		exptl ratios	
sulfide	ts	$\Delta E^{\ddagger}_{298}$ (kcal mol^{-1})	trans/ cis	ee (%) (*R*,*R*)	trans/ cis	ee (%) (*R*,*R*)
1	**TS1-RS**	16.92 (4.86)	1:0.04	99.99	1:0.12	94
	TS1-SR	13.98 (1.92)				
	TS1-RR	12.06 (0.00)				
	TS1-SS	17.92 (5.86)				
2	**TS2-RS**	11.00 (1.72)	1:4.86	74.30	1:0.11	80
	TS2-SR	9.28 (0.00)				
	TS2-RR	10.28 (1.00)				
	TS2-SS	11.42 (2.14)				

[a] Relative energies (in kcal/mol) in parentheses. Calculated and experimental[1f,3a] trans/cis ratio and ee.

Further investigation on the potential energy surface after the first addition step performed on the system with chiral sulfide **2** led us to find TSs for the trans pathway connecting the betaines and the epoxides, confirmed by QRC calculations (see Supporting Information). Although energies for these TSs are ca. 14−16 kcal/mol higher than their addition TS counterparts, when we calculated single-point energies including the effect of solvent (acetonitrile: dielectric constant = 37.5; solvent probe radius = 2.18) the addition step TSs had the highest energies, by 1−6 kcal/mol. This is as expected, as the charge separation is much higher in the epoxide-forming TSs than in the addition step, and so the solvent has a greater stabilizing effect. This result is consistent with the hypothesis that the addition step transition state controls the enantioselectivity of the formation of the *trans*-epoxides.

Optimizations including the solvent effect (acetonitrile) were carried out for the transition structures **TS2**s.[12] The results show that calculated enantioselectivity is overestimated, with 99.95% ee, in favor of the experimentally observed *trans*-stilbene oxide.

In summary, calculations show that the transition states for the addition of the sulfonium ylide to benzaldehyde have energies which account for the experimentally observed enantioselectivity. We have been able to reproduce the experimental results of enantioselectivity observed for the chiral sulfides under study.

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Supporting Information Available: Cartesian coordinates, absolute energies, and number of imaginary frequencies of all stationary points reported in the paper; values of

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(10) Aggarwal et al., in their theoretical work using a solvent model, describe a transoid addition transition structure which had not fully converged.

(11) Silva, M. A.; Goodman, J. M. *Tetrahedron Lett.* **2003**, *44*, 8233.

(12) Solvent effect were evaluated by the Poisson−Boltzmann solver as implemented in the Jaguar program. A continuum dielectric constant was selected in order to reproduce the solvent used experimentally, acetonitrile. The optimized transition structures were characterized by frequency calculations. All the transition structures had just one negative mode corresponding to the displacement in the direction of the reaction coordinate, except in one case when we also found small negative frequencies (less than 25 cm^{-1}) that were not associated with the reaction coordinate.

imaginary frequencies of all transition structures. QRC calculations[11] at the B3LYP/6-31G* level for **TS2**s; plots of the relative energy (in kcal mol^{-1}) versus mass-weighted coordinates (in bohr $amu^{1/2}$). Transition structures connecting betaines with epoxides for the trans pathway and with the chiral sulfide **2** and QRC calculations (at B3LYP/6-31G*) for these TSs. This material is available free of charge via the Internet at http://pubs.acs.org.

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