

An S_N2-like Transition State for Alkene Episulfidation by Dinitrogen Sulfide

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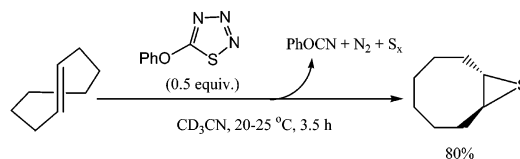
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Abstract: Episulfidation of alkenes by dinitrogen sulfide, generated from thermolysis of 5-aryloxy-1,2,3,4-thiadiazoles, was found to be an S_N2-like reaction involving simultaneous sulfur addition and dinitrogen extrusion. The preference for the one-step S_N2 mechanism instead of the two-step (2+3) dipolar cycloaddition and denitrogenation is attributed to the higher geometry distortion penalty in the (2+3) transition state than that in the S_N2-like transition state.

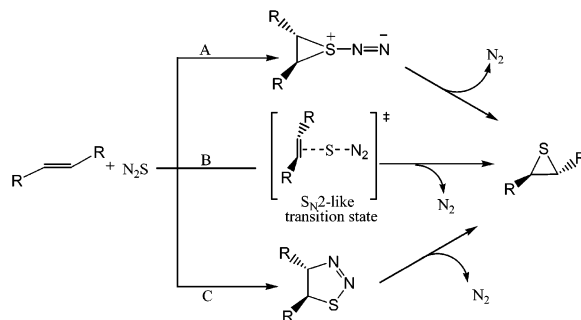
The synthesis of epoxides and aziridines has received intense investigation during the last two decades due to the high synthetic value of these three-membered active species as building blocks in organic chemistry.¹ Synthesis of their sulfur analogues, episulfides or thiiranes, is also receiving considerable attention since episulfides are highly reactive species which can be found in natural products and have potential pharmaceutical applications.² Several methods have been discovered by Adam and co-workers to synthesize episulfides.^{3,4} Among them, the episulfidation of alkenes by using 5-phenyloxy-1,2,3,4-thiadiazole as a sulfur atom donor merits further attention since the detailed mechanism of this transformation is not well understood (Scheme 1).^{3g}

Adam and Bargon proposed that dinitrogen sulfide (N₂S) is the active species generated in situ, which donates sulfur to alkenes. They proposed that the episulfidation process takes place via either pathway A or pathway C (Scheme 2). In pathway A, formation of a

SCHEME 1



SCHEME 2



three-membered zwitterionic species is followed by denitrogenation. By contrast, pathway C proceeds through a (2+3) dipolar cycloaddition and denitrogenation. Detection of the (2+3) adduct 1,2,3-thiadiazoline in pathway C by ¹H NMR was unsuccessful, suggesting that pathway A is more reasonable than pathway C.^{3g} In addition to pathways A and C, however, we speculate that a concerted pathway B involving the simultaneous sulfur addition and N₂ extrusion is also possible since this episulfidation is very similar to the epoxidation of alkenes by performic acid, dioxirane, which were found to proceed via a concerted S_N2-type mechanism.⁵ To differentiate these three competitive pathways and gain more insight into the reaction mechanism, we performed CCSD(T)//MP2/6-31+G* calculations⁶⁻¹⁰ to investigate the model reaction between ethene and N₂S.

First, we investigated the mechanism of thermolysis of 5-phenyloxy-1,2,3,4-thiadiazole by studying the decomposition reaction of 5-methoxy-1,2,3,4-thiadiazole.^{11,12} Our calculations indicated that this is a concerted retro-(2+3) dipolar cycloaddition process with an activation energy of 28.9 kcal/mol and reaction energy of 1.9 kcal/mol.¹³ This unimolecular decomposition is favorable due

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(3) (a) Adam, W.; Weinkötz, S. *Chem. Commun.* **1996**, 177. (b) Adam, W.; Fröhling, B.; Peters, K.; Weinkötz, S. *J. Am. Chem. Soc.* **1998**, *120*, 8914. (c) Adam, W.; Deeg, O.; Weinkötz, S. *J. Org. Chem.* **1997**, *62*, 7084. (d) Adam, W.; Fröhling, B.; Weinkötz, S. *J. Org. Chem.* **1998**, *63*, 9154. (e) Adam, W.; Fröhling, B. *Org. Lett.* **2000**, *2*, 2519. (f) Adam, W.; Weinkötz, S. *J. Am. Chem. Soc.* **1998**, *120*, 4861. (g) Adam, W.; Bargon, R. M. *Eur. J. Org. Chem.* **2001**, 1959. (h) Adam, W.; Bargon, R. M. *Chem. Commun.* **2001**, 1910. (i) Adam, W.; Bargon, R. M.; Schenk, W. A. *J. Am. Chem. Soc.* **2003**, *125*, 3871.

(4) Episulfidation of alkenes has also been reported by other groups: (a) Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* **1988**, *29*, 4177. (b) Kendall, J. D.; Simpkins, N. S. *Synlett* **1998**, 391.

(5) (a) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410. (b) Bach, R. D.; Glukhovtsev, M. N.; Gonzalez, C. *J. Am. Chem. Soc.* **1998**, *120*, 9902. (c) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (d) Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 3790.

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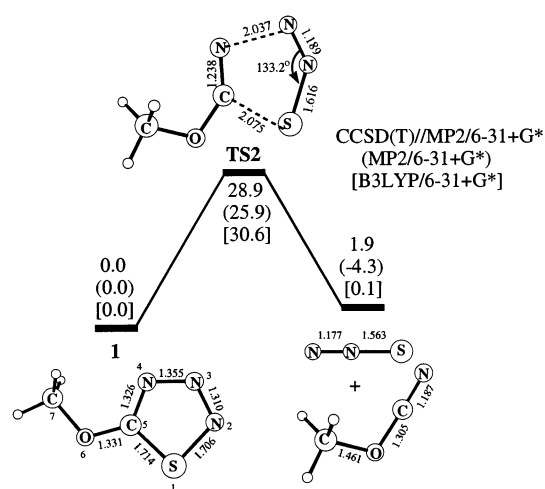


FIGURE 1. The potential energy surface for decomposition of **1**. The geometries (distances in Å) were computed at the MP2/6-31+G* level and energies (in kcal/mol) were computed at the CCSD(T)//MP2/6-31+G* level. The relative energies of MP2/6-31+G* and B3LYP/6-31+G* are given in parentheses and brackets, respectively.

to the entropy gain (25.8 eu) involved in the overall reaction. The geometries of the reactant and transition state are given in Figure 1. Another point worthy of mention is that the methoxy group in the reactant prefers the *s-cis* C₇-O₆-C₅-N₄ conformation in order to avoid the lone pair repulsion between O₆ and N₄ (see Figure 1).¹⁶

The potential energy surface for episulfication of ethene with N₂S is shown in Figure 2 together with the computed structures. Pathway A can be ruled out since no zwitterionic species with a three-membered ring or

(7) All species have been optimized by both the MP2/6-31+G* and B3LYP/6-31+G* methods.^{8,9} Harmonic frequency calculations were performed at both levels to confirm that each species is either a minimum (without imaginary frequency) or a transition state (with only one imaginary frequency). Single point energy calculations were carried out at the CCSD(T)/6-31+G* level.¹⁰ Unless otherwise mentioned, all the relative energies reported are unscaled zero-point energy (ZPE) corrected electronic energies (ΔE_0), which include single-point energies of the CCSD(T) level and ZPEs of the MP2 level. All orbital energies were computed at the HF/6-31G**/B3LYP/6-31+G* level.

(8) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785.

(10) For a review, see: Bartlett, R. J. *J. Phys. Chem.* **1989**, *93*, 1697.

(11) For discussions of thermal denitrogenation of 5-phenyloxy-1,2,3,4-thiaziazole by vacuum flash pyrolysis, see: (a) Wentrup, C.; Kambouris, P. *Chem. Rev.* **1991**, *91*, 363. (b) Wentrup, C.; Flamang, R. *J. Phys. Org. Chem.* **1998**, *11*, 350.

(12) For the experimental and theoretical characterization of N₂S, see: (a) Wentrup, C.; Fischer, S.; Maquestiau, A.; Flammang, R. *J. Org. Chem.* **1986**, *51*, 1908. (b) Kambouris, P.; Ha, T.-K.; Wentrup, C. *J. Phys. Chem.* **1992**, *96*, 2065. (c) Brown, R. D.; Elmes, P. S.; McNaughton, D. *J. Mol. Spectrosc.* **1990**, *140*, 390. (d) Bender, H.; Carnovale, F.; Peel, J. B.; Wentrup, C. *J. Am. Chem. Soc.* **1988**, *110*, 3458. (e) Davy, R. D.; Schaefer, H. F. *J. Am. Chem. Soc.* **1991**, *113*, 1917. (f) Collins, C. L.; Yamaguchi, Y.; Schaefer, H. F. *J. Chem. Phys.* **1993**, *98*, 4777.

(13) The activation energy of the decomposition of **1** in dibutyl phthalate (DBP) was reported to be 24.6 ± 0.1 kcal/mol.¹⁴ The difference between our calculated activation energy of 28.9 kcal/mol in the gas phase and that in DBP is attributed to the solvent effects. Calculations in aniline (which has a dielectric constant of 6.89, very close to 6.58 of DBP) with PCM model¹⁵ at the B3LYP/6-31+G* level indicate that the activation free energy in solvent is reduced by 3.81 kcal/mol compared to that in the gas phase.

(14) Jensen, K. A.; Burmester, S.; Bak, T. A. *Acta Chem. Scand.* **1967**, *21*, 2792.

their transition state could be located in both the gas phase and solvent. Both transition states and intermediates in pathways B and C can be located. Intrinsic reaction coordinate (IRC)¹⁷ calculations have been performed to confirm that these transition states are connected to their respective reactants and products shown in Figure 2. It is interesting to note that the final products in pathway C are vinylthiol and N₂ instead of episulfide and N₂, as proved by IRC calculations.^{18–20} The generation of vinylthiol is understandable: in **TS6**, the migrated hydrogen is elongated to 1.14 Å and is very close to the sulfur atom (1.98 Å). The concerted pathway B with synchronous formations of the two C–S bonds is the most favorable pathway since the activation barrier is 13.1 kcal/mol lower than that for pathway C (11.8 vs 24.9 kcal/mol). In addition, the S_N2-like reaction is exothermic by 42.8 kcal/mol while the (2+3) reaction is slightly endothermic. The denitrogenation step from **5** to produce vinylthiol and N₂ in pathway C is also unfavorable since this step has an activation energy of 14.7 kcal/mol. We must emphasize here that all efforts at both the UMP2 and UB3LYP levels to locate the diradical transition states involved in pathways A–C were unsuccessful.²¹

The solvent effects have been considered by using the PCM model¹⁵ at the B3LYP/6-31+G* level. The geometries for both **TS3** and **TS4** optimized in acetonitrile are very similar to their counterparts in the gas phase (Figure 2). **TS3** is still favored more than **TS4** in solvent by 12.9 kcal/mol in terms of activation energy (11.4 kcal/mol in terms of free energy of activation). The activation energy of the episulfidation in acetonitrile is lower than that in the gas phase by 0.4 kcal/mol (1.6 kcal/mol in terms of free energy of activation).

Figure 2 shows that the PES obtained at the B3LYP/6-31+G* level is very close to that of the CCSD(T)//MP2/6-31+G* level, suggesting that the former method is appropriate to evaluate the episulfidation process. Therefore, we used the DFT method to investigate the realistic reaction between *E*-cyclooctene and N₂S (Figure 3). It is expected that (2+3) cycloaddition between *E*-cyclooctene and N₂S is more efficient than the reaction between ethene and N₂S since *E*-cyclooctene is a very good dipolarophile.²² Calculations support this, showing that

(15) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(16) The atomic Mulliken charges (with hydrogen summed in) in **1** for S₁, N₂, N₃, N₄, C₅, O₆, and C₇ are 0.48, -0.33, 0.09, -0.25, 0.07, -0.42, and 0.36 e, respectively. **1** with *s-trans* C₇-O₆-C₅-N₄ is higher in energy than its *s-cis* conformer by 4.5 kcal/mol.

(17) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.

(18) We speculate that thiirane could also be a product when nitrogen is eliminated from **5** when kinetic energy, which is ignored in IRC calculations, is taken into account. For a discussion of kinetic energy affecting reaction pathways, see: (a) Sun, L.; Song, K.; Hase, W. L. *Science* **2002**, *296*, 875. (b) Ammal, S. C.; Yamataka, H.; Aida, M.; Dupuis, M. *Science* **2003**, *299*, 1555.

(19) Huisgen and Mloston reported that extrusion of a nitrogen molecule from spiro-1,2,3-thiadiazoline generates a mixture of thiirane and thioaldehyde.²⁰ Our preliminary theoretical calculations show that thioaldehyde is the only product predicted by IRC calculations, suggesting a dynamic effect is responsible for the generation of thiirane. A dynamic study of the extrusion reaction from 1,2,3-thiadiazoline will be reported in due course.

(20) Huisgen, R.; Mloston, G. *Tetrahedron Lett.* **1985**, *26*, 1049.

(21) We can locate the stepwise diradical pathway for the denitrogenation from **5**. However, the transition state (at the UCCSD(T)//UMP2/6-31+G* level) is higher in energy than **TS6** by 2.8 kcal/mol.

(22) Mloston, G.; Huisgen, R.; Huber, H.; Stephenson, D. S. *J. Heterocycl. Chem.* **1999**, *36*, 959.

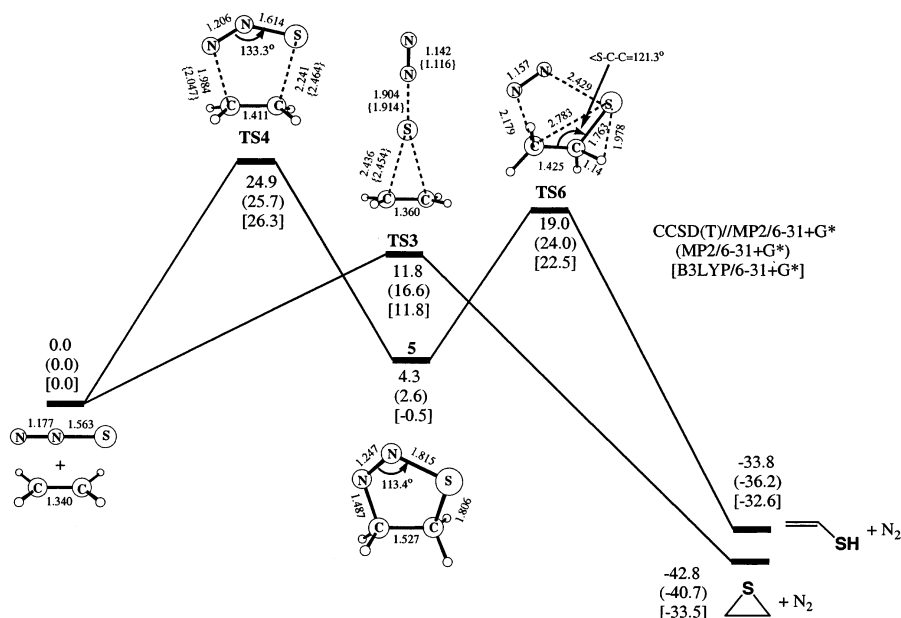


FIGURE 2. The potential energy surfaces of episulfidation of ethene by N_2S . The geometries (distances in Å) were computed at the MP2/6-31+G* level and energies (in kcal/mol) were computed at the CCSD(T)/MP2/6-31+G* level. The relative energies of MP2/6-31+G* and B3LYP/6-31+G* are given in parentheses and brackets, respectively. The distances in parentheses are optimized in acetonitrile with the PCM model.

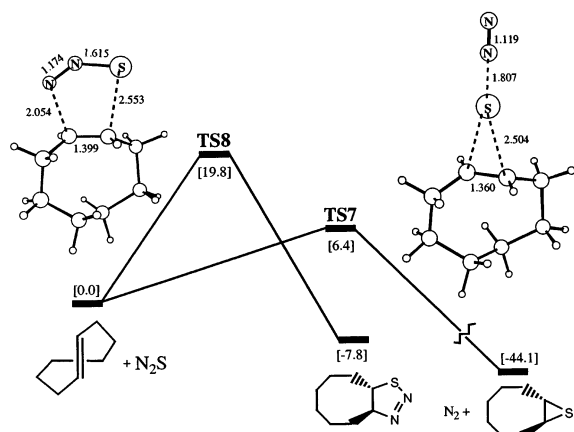


FIGURE 3. The potential energy surface for the episulfidation of *E*-cyclooctene by N_2S computed at the B3LYP/6-31+G* level.

the activation barrier for the former (2+3) cycloaddition is favored by 6.5 kcal/mol over the latter (19.8 vs 26.3 kcal/mol). Despite the easier (2+3) cycloaddition, the direct episulfidation via the S_N2 -type path is still favored by 13.4 kcal/mol (Figure 3).

The characteristics of the S_N2 -like transition state for concerted pathway B are manifested by the electron transfer of 0.09 e from ethene, which acts as a nucleophile, to N_2S in **TS3**. The frontier molecular orbital (FMO) interaction diagram shown in Figure 4 further confirms the similarity between episulfidation **TS3** and traditional organic S_N2 reactions.²³ In **TS3**, one major interaction in the HOMO-2 corresponds to the nucleophilic donation from the alkene's π orbital to the σ^* orbital of the S–N(N). Another orbital interaction between the two reactants in **TS3** is related to the overlap

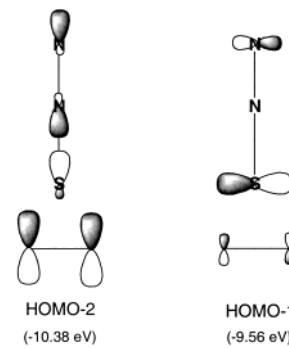


FIGURE 4. FMO interactions in the S_N2 -like episulfidation transition state.

of the lone pair of the S atom with the π^* orbital of the alkene in the HOMO-1. This interaction is less significant than the π – σ^* interaction due to the smaller energy gap of the latter (Figure 5).

Further evidence to support the S_N2 -like character of the episulfidation transition state is that electron-donating substituents on the alkene facilitate the episulfidation while electron-withdrawing substituents have the opposite effect. The activation energies computed at the B3LYP/6-31+G* level for $CH_2=CH-R + N_2S$ are 9.3 (R = OMe), 11.1 (R = Me), 11.8 (R = H), and 15.1 (R = CN) kcal/mol, respectively. The relative activation energies for these reactions correlate with the HOMO energies of $CH_2=CH-R$: the higher the HOMO energy of the alkene, the lower the activation energy for the episulfidation reaction.^{24,25} The very low activation energy for the S_N2 -type transition state for *E*-cyclooctene to N_2S is due

(23) Rauk, A. *Orbital Interaction Theory of Organic Chemistry*; John Wiley & Sons: New York, 1994.

(24) The HOMO energies (eV) of $CH_2=CH-R$ are the following: -9.02 (R = OMe), -9.61 (R = Me), -10.08 (R = H), and -10.63 (R = CN). The geometries for these S_N2 -type transition states of $CH_2=CH-R + N_2S$ are given in Figure S1 of the Supporting Information.

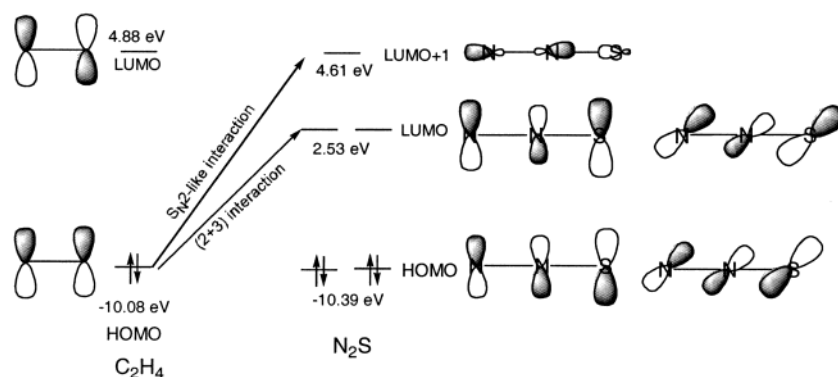


FIGURE 5. FMO interactions in the S_N2 -like and (2+3) transition states. Orbital energies are computed at the HF/6-31G**/B3LYP/6-31+G* level.

to its relative higher HOMO energy (-8.84 eV) compared to those of other alkenes.²⁴

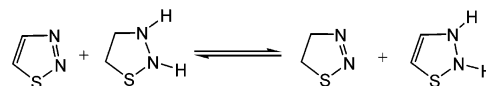
The preference for the generation of episulfide instead of vinylthiol is certainly related to the relative energies of S_N2 -like **TS3** and (2+3) **TS4**. Frontier molecular orbital (FMO) interaction theory²⁶ predicts that in the reaction of ethene with N_2S , the (2+3) step should be easier than the S_N2 -like step since the energy gap between HOMO (ethene) and LUMO (N_2S) is smaller than that between HOMO (ethene) and σ^* (N_2S), as shown in Figure 5. Bear in mind that, as a perturbation method, FMO theory is only useful for reactions with an early transition state and a correct treatment of the interactions is restricted to the beginning of the reaction coordinate.²⁶ Therefore, an understanding of the preference for S_N2 -like reaction pathway B instead of pathway C lies in appreciating the different geometry distortions in S_N2 -like **TS3** and (2+3) **TS4**. In **TS3**, except for an elongation of about 0.34 Å for the S–N bond, the geometries of the ethene and N_2S moieties have only slight changes compared to their free counterparts in the reactants. The calculated total energy penalty for their geometry distortions in **TS3** is 14.7 kcal/mol (0.4 kcal/mol for ethene and 14.4 kcal/mol for N_2S). In **TS4**, the ethene moiety becomes significantly nonplanar and the N_2S moiety has bent to a significant extent. The computed energy penalty for the geometry distortions in **TS4** is 39.3 kcal/mol (11.7 kcal/mol for ethene and 27.6 kcal/mol for N_2S). This means that the (2+3) reaction needs more additional energy (approximately 24.6 kcal/mol) to achieve the (2+3) transition state compared to S_N2 -like **TS3**. Even though the aromatic stabilization in the (2+3) **TS4** can reduce this energy difference to some extent, it cannot compensate for all 24.6 kcal/mol.²⁷ It is difficult if not impossible to estimate the aromatic stabilization

(25) The reaction between cyclohexene and N_2O takes place through (2+3) cycloaddition and denitrogenation reactions to produce cyclohexanone instead of an alcohol or epoxide; see: Avdeev, V. I.; Ruzankin, S. P.; Zhidomirov, G. M. *Chem. Commun.* **2003**, 42. We could not locate the S_N2 -type transition state between ethylene and N_2O . We reason that this is due to the much higher σ^* (LUMO+1) orbital of N_2O compared to N_2S (7.27 vs 4.61 eV) that favors (2+3) cycloaddition instead of the S_N2 -type reaction (see Figure S2 for the orbital energies of N_2O in the Supporting Information).

(26) (a) Dewar, M. J. S. *The Molecular Orbital Theory for Organic Chemistry*; McGraw-Hill: New York, 1969. (b) Zimmerman, H. E. *Acc. Chem. Res.* **1971**, 4, 271.

(27) For discussions of aromatic (2+3) transition states, see: (a) Morao, I.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1997**, 62, 7033. (b) Morao, I.; Cossio, F. P. *J. Org. Chem.* **1999**, 64, 1868.

SCHEME 3



energy (ASE) in **TS4**. However, it is reasonable to assume that the ASE in **TS4** is much less than that of the parent aromatic molecule 1,2,3-thiodiazole, which has an ASE of 17.3 kcal/mol based on the computed homodesmotic reaction shown in Scheme 3.²⁸ Therefore, the ASE of the (2+3) transition state **TS4** is much less than 24.6 kcal/mol resulting in **TS4** being disfavored with respect to the S_N2 -type transition state **TS3**.

In conclusion, episulfidation of ethene by N_2S is an S_N2 -type reaction with simultaneous addition of S to ethene and extrusion of N_2 .²⁹ The preference for the S_N2 -type **TS3** opposed to the (2+3) **TS4** is attributed to a large geometric distortion present in the latter transition state. The concerted S_N2 -type mechanism is in agreement with the fact that the episulfidation reaction is stereoselective (Scheme 1).³⁸ The present study also shows that N_2S does not possess a distinguished dipolarophilic character when considering its reactions with alkenes. This is in contrast to N_2O , which behaves like a dipole to react with alkenes.²⁵

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Supporting Information Available: The calculated Cartesian coordinates and total energies of the reactants, intermediates, and transition states. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(28) For calculations of ASE with homodesmotic reactions, see: (a) Schleyer, P. v. R.; Freeman, P. K.; Jiao, H.; Goldfuss, B. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 337. (b) Katritzky, A. R.; Karelson, M.; Sild, S.; Krygowski, T. M.; Jug, K. *J. Org. Chem.* **1998**, 63, 5228.

(29) The competing reaction for the episulfidation of alkenes is the decomposition of N_2S to S_x and N_2 . Experimental observation suggests that elemental sulfur is not involved in episulfidation.³⁸ For a discussion of the decomposition of N_2S , see: Wentrup, C.; Fischer, S.; Maquestiau, A.; Flammang, R. *J. Org. Chem.* **1986**, 51, 1908.