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# Ab Initio Study of the Lewis Acid-Catalyzed Diels–Alder Reaction of Sulfur Dioxide with Isoprene: Regioselectivity and Stereoselectivity

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Hetero Diels–Alder reactions have attracted considerable attention in the last years due to their interesting role in organic synthesis.[1] This methodology allows for the preparation of several types of six-membered-ring heterocycles and acyclic structures and has been used in key steps of the total synthesis of natural products.[1,2] Despite their synthetic appeal, it has been only recently that hetero Diels–Alder reactions have been studied using theoretical methods, in contrast to the case of all-carbon Diels–Alder reactions.[3–7] According to the ab initio calculations, hetero Diels–Alder reactions are predicted to take place through concerted but slightly asynchronous transition structures in a similar way to the all-carbon version.[5–7]

In a very recent communication, Deguin and Vogel reported that 1,3-dienes react with sulfur dioxide to give Diels–Alder adducts.[8] It is well known that sulfur dioxide undergoes cheletropic reactions with conjugated dienes to give sulfolenes, but only a few examples of such Diels–Alder reactions have been reported to date.[9]

In this communication we report the results of ab initio calculations[10] on the Lewis acid-catalyzed ($BH_3$ was used as a model for the Lewis acid catalyst) Diels–Alder reaction of isoprene with sulfur dioxide (Scheme 1). Geometry optimizations were performed at the restricted Hartree–Fock (RHF) level using GAUSSIAN 92.[11] Structures were fully optimized with the 3-21G* basis set,[12] followed by vibrational frequency calculations. Schlegel's algorithm[13] was used to locate the transition structures. Single-point RHF/6-31G* calculations were carried out on the RHF/3-21G* geometries.[14] Four transition structures, corresponding to the "meta" and "para" regioisomeric sultines **2** and to the endo and exo stereoisomers for the reaction between isoprene (**1**) and the $SO_2$–$BH_3$ complex, have been located. Predicted activation energies are given in Table 1, and the transition structures are shown in Figure 1.

**Scheme 1**

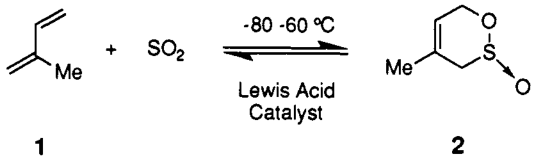

**Table 1.** Calculated Energies (kcal/mol) of the Transition Structures and Products Relative to Those of Reactants

| transition structures | 3-21G* | 3-21G*+ZPE[a] | 6-31G*[b] | $\Delta E_{rxn}$[c] |
|---|---|---|---|---|
| "meta"-endo, **TS1** | 4.2 | 6.3 | 13.6 | –23.9 (–34.7) |
| "meta"-exo, **TS2** | 8.2 | 10.2 | 18.4 | |
| "para"-endo, **TS3** | 8.8 | 10.9 | 19.0 | –23.9 (–34.9) |
| "para"-exo, **TS4** | 12.0 | 14.0 | 23.1 | |

[a] Corrected for zero-point energies. [b] RHF/6-31G*//3-21G* energies. [c] RFH/6-31G*//3-21G* energies (3-21G* energies are in parentheses).

The transition structures located indicate that the reaction of **1** with the $SO_2$–$BH_3$ complex is concerted. The limited asynchronicity shown by the transition structures in Figure 1[15] is consistent with data available on other Lewis acid-catalyzed Diels–Alder reactions recently studied[6,17] and is readily understood when the coefficients of the frontier molecular orbitals collected in Chart 1 are examined (**i** and **o** in Chart 1 stand for the inner and outer parts, respectively, of the 6-31G* $\pi$ orbitals).

The experimentally observed regioselectivity[8] is correctly predicted by the ab initio calculations, being that the "meta" regioisomer transition structure **TS1** is favored by 4.8 kcal $mol^{-1}$ at the RFH/6-31G*//3-21G* theory level. This regioselectivity can be easily rationalized in terms of the coefficients of the frontier molecular orbitals. Indeed, Chart 1 shows that in the case of isoprene the coefficients at C1 of the HOMO are sensibly larger than those at C4, while in the case of the $SO_2$–$BH_3$ complex the large coefficient (corresponding to the inner basis function) on the sulfur of the LUMO causes this terminus to be much more electrophilic than the oxygen, which has a smaller coefficient.

An important point in the study of the Diels–Alder reactivity is the stereoselectivity of the addition. In the present case, the reported endo preference[8] is correctly predicted by the ab initio calculations (see Table 1). This preference can be rationalized as follows: on one hand, we have detected a very important secondary interaction in the "meta"-endo transition structure (**TS1** in Figure 1) which is not present in the rest of the transition structures located. Such an interaction involves the sulfur dioxide oxygen attached to $BH_3$ and one of the hydrogens of the isoprene methyl group (see Figure 1). It is the type of interaction on which much attention has been focused in the recent literature.[18] The CH···O distance is 2.387 Å, and the Mulliken overlap population between the two atoms involved is +0.015. In order to check the order of magnitude of such a secondary interaction, we have computed different conformations corresponding to the rotation of the three hydrogen atoms of the methyl group around the C(methyl)–C2 axis, keeping the geometry of the rest of **TS1** unaltered. These calculations indicated that the contribution of the CH···O secondary interaction to the stabilization of the "meta"-

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(15) The C–S and C–O Pauling bond orders (see ref 16) computed for the four transition structures in Figure 1 are 0.36, 0.05 (**TS1**); 0.28, 0.07 (**TS2**); 0.27, 0.08 (**TS3**); and 0.23, 0.09 (**TS4**).

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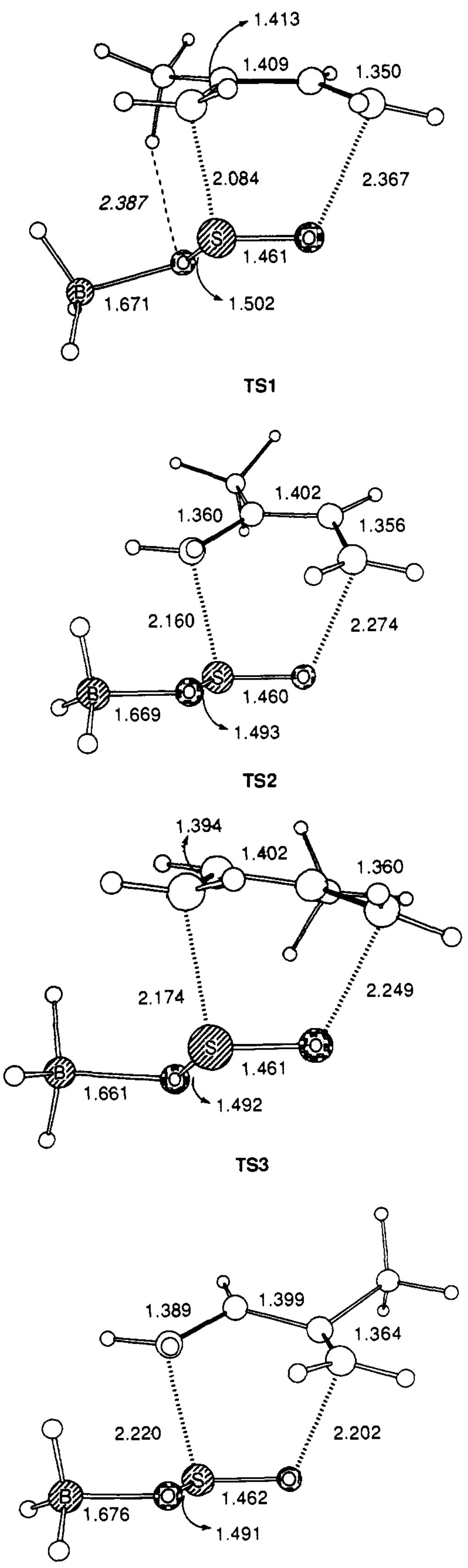
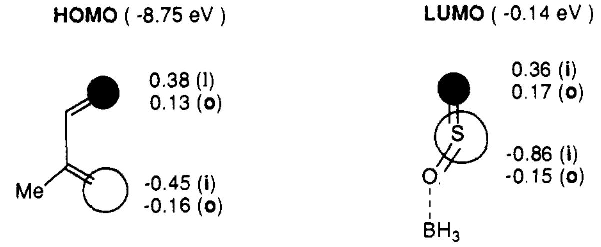


**Figure 1.** "Meta"-endo (**TS1**), "meta"-exo (**TS2**), "para"-endo (**TS3**), and "para"-exo (**TS4**) transition structures, computed at the RHF/3-21G* level, for the cycloaddition of isoprene to sulfur dioxide complexed with BH$_3$. The broken line in **TS1** between an oxygen and a methyl hydrogen corresponds to the secondary interaction discussed in the text. Distances are in angstroms.

**Chart 1**



endo transition structure is 2 kcal mol$^{-1}$ (RHF/6-31G*), which is an appreciable part of the total energetic difference found between "meta"-endo and "meta"-exo transition structures (4.8 kcal mol$^{-1}$; see Table 1).[19] Furthermore, a Bader-type density analysis[20] revealed the existence of a bond critical point between the two above-mentioned atoms (the value of the electronic density at the critical point is 0.01 au). We have looked for HOMO–LUMO secondary orbital interactions[21] and found only very small secondary overlaps which are insufficient by themselves to explain the endo preference. Therefore, it seems that, in the present case, the CH···O electrostatic interaction[18] plays a relevant role in the stabilization of the endo transition state relative to the exo state.[22] On the other hand, the stabilizing interaction between the diene HOMO and the dienophile LUMO, greatly facilitated by Lewis acid complexation, which lowers the dienophile LUMO energy to a large extent[23] (it should be noted in Chart 1 that the SO$_2$–BH$_3$ complex LUMO becomes negative), produces a notable charge transference (0.33, 0.30, 0.29, and 0.29 electrons for **TS1**, **TS2**, **TS3**, and **TS4** in Figure 1, respectively). The resulting charge separation is necessarily destabilizing, but a simple analysis based on the calculation of the relative Coulombic potential energy from the Mulliken charges[17] shows that the geometry of the "meta"-endo transition structure (**TS1** in Figure 1) is such that it minimizes the physical separation of the induced charges and, consequently, has the lower energy (the relative Coulombic energies are 0.0, 1.0, 2.8, and 3.1 eV for **TS1**, **TS2**, **TS3**, and **TS4** in Figure 1, respectively). Finally, the exothermicity of the $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloaddition of SO$_2$–BH$_3$ to isoprene (see last column in Table 1) is relatively low when compared with those of other Diels–Alder reactions,[5] which can be related to the difficulties associated with carrying out those types of additions.[8]

Work is in progress to understand the decisive role played by both the catalyst and the substituents in the control of the Diels–Alder reactions of 1,3-dienes with sulfur dioxide and other sulfur-containing dienophiles.

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**Supplementary Material Available:** Full geometries and energies of the four transition structures (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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