Cyclic Vinyl *p*-Tolyl Sulfilimines as Chiral Dienophiles: Theoretical Study on the Stereoselectivity, Lewis Acid Catalysis, and Solvent Effects in Their Diels−Alder Reactions

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The theoretical study reported in the present work deals with chiral cyclic vinyl sulfilimines and their reactivity as dienophiles in [4 + 2] cycloaddition reactions, using B3LYP/6-31G(d)//AM1 and B3LYP/6-31G(d)//B3LYP/6-31G(d) model chemistries. Consideration of Lewis acid catalysis, illustrated by BF_3, decreases the activation energies of the cycloaddition process while the charge transfer from the diene to the sulfilimine is augmented. The [4 + 2] cycloaddition reactions of sulfilimines with both furan and cyclopentadiene occur in the gas phase with *endo* stereoselectivity, which is more pronounced with the latter diene. *Endo-exo* energy differences in the gas phase with the B3LYP/6-31+G(d)//B3LYP/6-31+G(d), B3LYP/6-31G(d)//B3LYP/6-31G(d), and B3LYP/6-31G-(d)//AM1 model chemistries are almost the same. Solvent effects are responsible for the inversion of the stereoselectivity in the reactions of sulfilimines with furan because of the great difference in the dipole moments in *endo* and *exo* approaches.

Introduction

The high regio- and stereoselectivity exhibited and the formation of two new carbon−carbon double bonds and up to four new stereogenic centers make Diels−Alder reactions one of the most powerful and versatile synthetic strategies in organic synthesis. Chiral precursors in Diels−Alder reactions have been brought into play successfully to enhance the stereocontrol of the cycloadditive process. In this context, our group has been using chiral vinyl sulfoxides as dienophiles with a remarkable π-facial stereoselectivity.[1] The recent synthesis of the novel cyclic vinyl sulfilimines[2] starting from such chiral vinyl sulfoxides has extended our project to a new class of dienophiles with an improved stereoselection, which is also opposite to that found with the sulfoxides.

The cycloaddition reactions of cyclic vinyl *p*-tolyl sulfilimines proceed with complete π-facial selectivity to the less hindered face of the dienophile, since the *p*-tolyl substituent sterically hinders the diene approach to the face of the sulfilimine bearing the aromatic moiety.[2,3] Moreover, the cycloaddition reaction of the title sulfilimines with furan[3] exhibits a high *exo* selectivity, which is opposite to that found with cyclopentadiene[2] and acyclic dienes.[3]

Herein, we report the first theoretical study on cyclic vinyl sulfilimines and their [4 + 2] cycloaddition reactions with cyclopentadiene and furan as model dienes. The process was studied at a semiempirical level that has been previously employed for simulating π-facial selectivities of cycloadditon processes with chiral reactants.[4] We also performed a full B3LYP/6-31G(d) study of a simplified model in which the *p*-tolyl group on the sulfur atom has been replaced by a methyl group, thereby reducing the computational cost. Our DFT analysis has been focused on the *endo* and *exo* stereoselectivities when the dienes approach to the less hindered face of the dienophile. Finally, solvent effects in these reactions have been evaluated at a semiempirical level.

Computational Methods

All gas-phase calculations were performed with GAUSSIAN 98.[5] The structures were fully optimized with the AM1 semiempirical method[6] and with the B3LYP functional,[7] based on the density functional theory (DFT), along with the 6-31G-(d) basis set. All minima and transition states were characterized by their vibrational frequencies. Unless otherwise indicated, all energy changes of the B3LYP/6-31G(d) optimizations reported in this paper include zero-point energies without scaling. The semiempirical quantum chemistry program AM-SOL[8] was used to calculate free energies of solvation in order to establish the effect of solvent on the stereoselectivities. The structures were optimized in solution of dichloromethane[9] with the SM5.4 solvation model and the AM1 Hamiltonian (SM5.4/AM1).[10]

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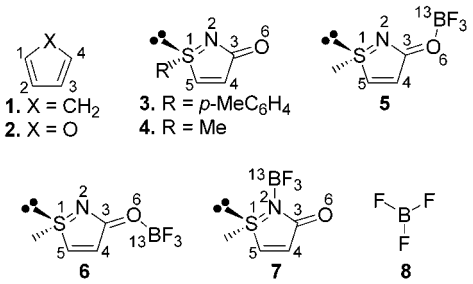

Figure 1. Structures of the reactants studied at the B3LYP/6-31G(d) level.

Results and Discussion

DFT Study. We have optimized the structure of the sulfilimine **3** at the B3LYP/6-31G(d) level. However, the sulfilimine **4** has been used as the model in the course of our theoretical study of the cycloaddition reactions. In Tables 1−3, the most significant results of the calculation of structure **3** are presented. The energies and atomic coefficients of the frontier molecular orbitals, the bond distances, bond orders, and the dipole moments of structures **3** and **4** are very similar, thus validating our model. We have also considered the effects of BF_3 coordination on the oxygen and nitrogen atoms in the sulfilimine **4** (**5**−**7**).

The carbon−carbon double bond present in the sulfilimine **3** and in the model **4** exhibits a clear electrophilic character because it is substituted by a carbonyl group and a positive sulfur atom. This is reflected by the values of the interaction $LUMO_{dienophile}-HOMO_{diene}$, which is 1.5 eV lower than the $LUMO_{diene}-HOMO_{dienophile}$ energy difference (see Supporting Information). Consequently, the reactions between the dienes **1** or **2** with **3** are [4 + 2] cycloaddition reactions with normal electron demand. However, the presence of these two electron-withdrawing groups in each end of the double bond results in an almost nonpolarized LUMO (Table 1).

Table 1. Energies and Atomic Coefficients ($2p_z$) of FMOs Involved in [4 + 2] Cycloaddition Reactions of Reactants 1 and 2 (HOMO) and 3−7 (LUMO) and Their Dipole Moments

	E (eV)	c_4	c_5	dipole moment (D)
1	−5.8	+0.35	−0.35[a]	0.4
2	−6.1	+0.38	−0.38[a]	0.6
3	−1.4	+0.34	−0.33	7.9
4	−1.6	+0.33	−0.30	7.2
5	−2.8	+0.31	−0.30	13.4
6	−2.7	+0.32	−0.31	12.4
7	−2.6	+0.34	−0.33	10.8

[a] Coefficient on atom 1 (c_1).

The addition of the Lewis acid BF_3 makes the sulfilimine **4** more electrophilic (LUMO energies in **5**−**7** ∼1.1 eV lower than in **4**) and its reactivity toward cyclopentadiene and furan is enhanced by lowering the $LUMO_{dienophile}-HOMO_{diene}$ gap. In addition, sulfilimine−BF_3 complexes **5**−**7** present almost the same values in the atomic coefficients of C4 and C5.

The most favorable point of coordination of boron trifluoride with the sulfilimine **4** is at the nitrogen atom of the heterocycle (**7**, $\Delta E = -19.1$ kcal/mol), which is only 0.7 kcal/mol more stable than the coordination at the oxygen atom of the carbonyl group *anti* to the C−N bond (**6**, $\Delta E = -18.4$ kcal/mol). The less stable sulfilimine−BF_3 complex is the one in which the Lewis acid is coordinated at the oxygen atom of the carbonyl group *syn* to the C−N bond (**5**, $\Delta E = -13.9$ kcal/mol).

Another important issue of these sulfilimines to be addressed is the bond distribution in the heterocycle. Table 2 collects the most important bond orders in terms of the Wiberg indices[11] obtained by an analysis of the natural bond orbitals (NBO).[12] In contrast with the Lewis structure used to represent the sulfilimines **3** and **4** throughout the text, the Wiberg index of the S1−N2 bond is close to 1.0, which means that there is no significant retrodonation from nitrogen to sulfur and therefore this bond is strongly polarized. The negative charge on the nitrogen atom is delocalized by the carbonyl group: the bond order of the N2−C3 bond is higher than the bond order of the S1−N2 bond, and the bond order of C3−O6 is clearly lower than the corresponding one for a double bond. This bond distribution explains the high dipole moment of the sulfilimine and its direction: from positive sulfur to negative oxygen.

The coordination of sulfilimines with BF_3 increases the polarization of the molecule by withdrawing the electrons of the π-delocalized system toward the heteroatom to which it is attached (Table 2). In **5** and **6**, the carbonyl bond order (C3−O6) is reduced by electrodonation to form the new O6−B13 bond and the delocalization of the negative charge on the nitrogen atom by the carbonyl-BF_3 group is higher (N2−C3). When BF_3 is coordinated to the nitrogen atom of the sulfilimine (**7**), the negative charge on this atom is stabilized by the new bond with the Lewis acid and the delocalization with the carbonyl group is reduced from the sulfilimine **4**, i.e., lower N2−C3 and higher C3−O6 bond orders.

The geometries obtained for sulfilimines from the B3LYP/6-31G(d) calculations are in good agreement with

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Table 2. Bond Orders (Wiberg Indices) for Sulfilimines 3−7

	S1−N2	N2−C3	C3−C4	C4−C5	C5−S1	C3−O6	O6−B13	N2−B13
3	1.13	1.23	0.98	1.91	0.92	1.66		
4	1.14	1.23	0.98	1.91	0.93	1.66		
4 diff[a]	1.12	1.25	0.98	1.90	0.94	1.64		
5	1.08	1.41	1.02	1.88	0.96	1.38	0.39	
6	1.07	1.43	1.02	1.87	0.97	1.35	0.44	
7	1.01	1.11	1.00	1.89	0.98	1.73		0.48

[a] B3LYP/6-31+G(d).

Table 3. Bond Distances (Å) for Sulfilimine 3 in Crystal Structure Compared with DFT Optimized Structures

	S1−N2	N2−C3	C3−C4	C4−C5	C5−S1	C3−O6
3 [crystal]	1.64	1.36	1.49	1.30	1.75	1.24
3 [B3LYP/ 6-31G(d)]	1.64	1.39	1.53	1.33	1.82	1.22
4 [B3LYP/ 6-31G(d)]	1.64	1.39	1.53	1.33	1.81	1.22
4 [B3LYP/ 6-31G+(d)]	1.64	1.38	1.53	1.33	1.81	1.22

Scheme 1. B3LYP Optimized Geometries of TS9-TS10 Showing the Forming C−C Bond Distances in Å

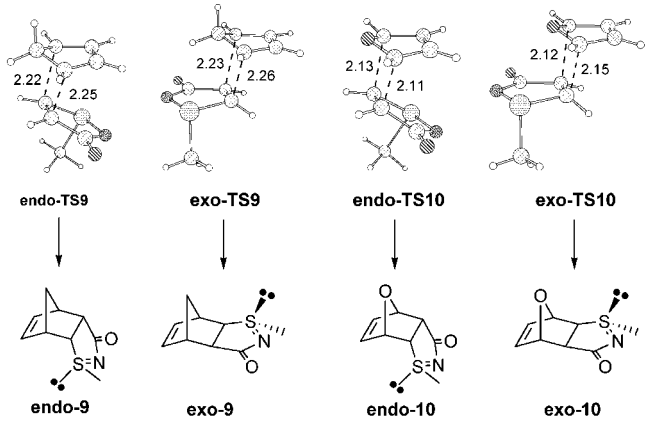

Table 4. B3LYP/6-31G(d) Computed Activation and Reaction Energies for Reactions of 4 with Cyclopentadiene and Furan, with Dipole Moments and Charge Transfer[a] in the Transition States

		$\Delta E^{\ddagger}$ (kcal/mol)	dipole moment (D)	charge transfer (au)	ΔE (kcal/mol)
9	*endo*	+18.6	6.9	+0.17	−17.0
	exo	+19.3	6.8	+0.16	−18.1
10	*endo*	+23.7	6.3	+0.19	−0.4
	exo	+24.0	7.6	+0.19	−2.4

[a] Residual charge of the diene fragment in the transition state.

the X-ray crystal structure of **3** (Table 3).[2] The bond distances in the heterocycle for the calculated structures are slightly longer than the experimental ones (0.07 Å is the highest difference for the C5−S1 bond) with the sole exception of the carbonyl bond distance (C3−O6), which is 0.02 Å shorter.

Full optimizations at the B3LYP/6-31G(d) level have been done on the transition states of the concerted [4 + 2] cycloaddition processes of **4** with **1** (**endo-TS9** and **exo-TS9**) and with **2** (**endo-TS10** and **exo-TS10**) (Scheme 1). The optimized geometries correspond to synchronous and concerted processes being **endo-** and **exo-TS9** earlier transition structures than **TS10**. The energy barriers and the reaction energies of the concerted [4 + 2] cycloadditions of **1** and **2** with **4** leading to **9** and **10**, respectively, are collected in Table 4. The reaction of sulfilimine with cyclopentadiene exhibits activation energies ∼5 kcal/mol lower than the corresponding ones for the reaction with furan. The *endo* adduct is kinetically favored in the reaction of sulfilimine **4** with cyclopentadiene, but in the reaction with furan, **endo-TS10** is only 0.3 kcal/mol lower in energy than **exo-TS10**. The electrophilic character of the sulfilimine **4** is illustrated by the values of the charge transfer from the diene to the dienophile in the transition states, which are higher in the reaction with furan, an electronically richer diene (Table 4). These values agree with normal electron demand processes.

These reactions are exothermic processes with the *exo* adducts the most stable ones. If we consider that the [4 + 2] cycloaddition reactions are entropically disfavored processes, the yield in the reaction of the sulfilimine **4** with furan is predicted to be low because the adducts have almost the same energy than the reactants.

The concerted [4 + 2] cycloaddition reactions of **4** with cyclopentadiene and furan in the presence of BF_3 have also been explored. We have located the *endo* and *exo* transition states for the reactions with both dienes and with BF_3 coordinated at each of the three positions already mentioned (**TS11-TS16** in Figure 2). Transition structures in which BF_3 is coordinated to the nitrogen atom (**TS13** and **TS16**) exhibit the same synchronicity as the uncoordinated ones. However, when coordination with BF_3 takes place at the oxygen atom of the carbonyl group, the resulting transition structures (**TS11-TS12** and **TS14-TS15**) are less synchronous with the longest forming bond distance being the one that is closest to the point of coordination. The activation energies of the concerted [4 + 2] cycloaddition processes studied are collected in Table 5. The third column of this table shows the energy differences of the transition states with respect to the three separate reactants (diene, sulfilimine, and BF_3). Likewise, the energy differences of the transition states relative to the diene and the sulfilimine−BF_3 complex are presented in the fourth column. The most favorable coordination occurs at the oxygen atom of the carbonyl group and *anti* to the C−N bond (**TS12** and **TS15**).

In the presence of BF_3, the reaction takes place by formation of the sulfilimine−BF_3 complex in the first stage followed by concerted [4 + 2] cycloaddition of the diene with that complex afterward. The activation energy of the cycloaddition process is therefore the energy difference of this last step (Table 5, column 4). The use of BF_3 decreases significantly the activation energies of the cycloadditions of the sulfilimine **4** with both dienes, so the reaction rates are higher with the addition of this reactant. The more significant catalytic effect of BF_3 in the reaction of cyclopentadiene with **4** occurs when the coordination takes place at the oxygen atom of the carbonyl group and *anti* to the C−N bond (sulfilimine **6**, **TS12** and **TS15**), which are also the most stable transition structures. In addition, the coordination of BF_3 to the most favorable position in the transition states

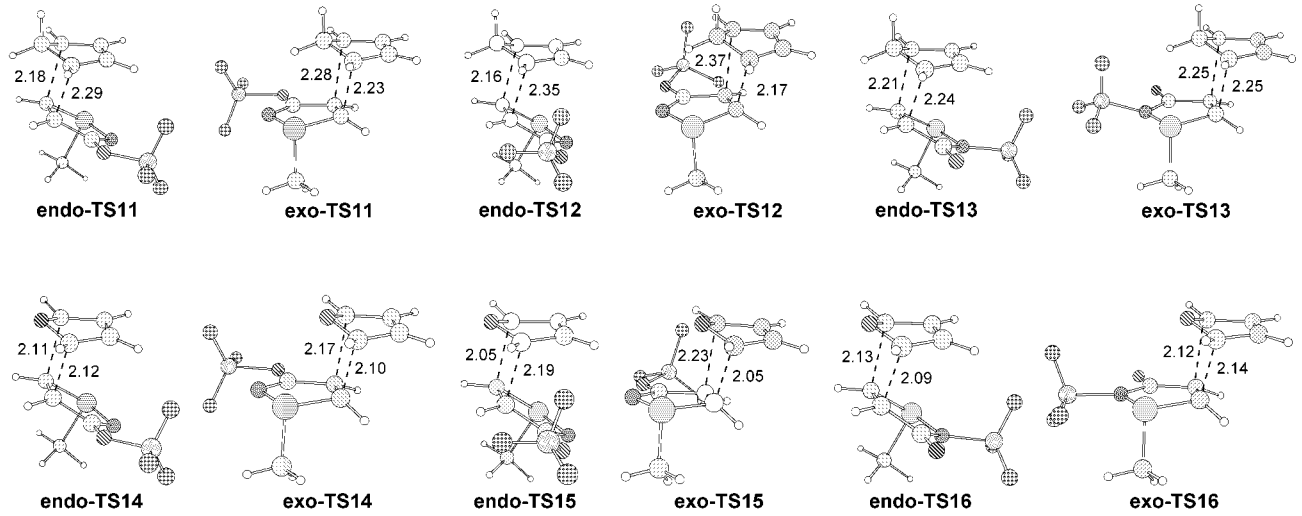

Figure 2. B3LYP optimized geometries of **TS11-TS16** showing the forming C−C bond distances (Å).

Table 5. B3LYP/6-31G(d) Computed Activation Energies for Reactions of 4 with Cyclopentadiene and Furan in the Presence of BF_3, with Dipole Moments and Charge Transfer[a] in the Transition States

		$\Delta E_i^{\ddagger}$ [b] (kcal/mol)	$\Delta E^{\ddagger}$ (kcal/mol)	dipole moment (D)	charge transfer (au)
TS11	*endo*	−1.1	+12.9	13.6	+0.25
	exo	+2.0	+16.0	13.9	+0.24
TS12	*endo*	−6.5	+11.9	12.2	+0.25
	exo	−4.3	+14.0	12.3	+0.24
TS13	*endo*	−4.6	+14.5	11.2	+0.25
	exo	−3.6	+15.5	11.3	+0.23
TS14	*endo*	+4.1	+18.0	12.9	+0.26
	exo	+6.7	+20.6	14.7	+0.26
TS15	*endo*	−2.2	+16.2	11.9	+0.27
	exo	−1.2	+17.2	12.5	+0.26
TS16	*endo*	+0.5	+19.7	10.3	+0.27
	exo	+2.4	+21.5	12.6	+0.25

[a] Residual charge of the diene fragment in the transition state. [b] Energy differences from the three separate reactants (diene, sulfilimine and BF_3) with respect to transition states.

enhances the stereoselectivity of this cycloaddition. Thus, in the reaction of **4** with cyclopentadiene the *endo* adduct is kinetically favored by 2.2 kcal/mol (vs 0.7 kcal/mol without BF_3), whereas in the reaction with furan the preference for the *endo* adduct is 1.0 kcal/mol (vs 0.3 kcal/mol without BF_3).

As stated above, the coordination of BF_3 with the sulfilimine **4** increases the electrophilic character of the latter. The reactions of dienes **1** and **2** with the sulfilimine−BF_3 complexes **5**−**7** take place with a strong charge transfer from the diene to the dienophile, which is higher in the reactions with furan than in the reactions with cyclopentadiene. The same holds also true for the *endo* versus *exo* approaches, the former exhibiting higher charge transfer.

From the above-mentioned theoretical results we conclude that the [4 + 2] cycloaddition reactions of the title sulfilimines with cyclopentadiene or furan exhibit an *endo* stereoselectivity that is stronger with the former. The *exo* stereoselectivity of the reaction of the sulfilimine **4** with furan found in the experiments cannot reasonably be explained in the terms considered in the present study. However, it should be noted that in the transition states of the concerted [4 + 2] cycloaddition reactions of the sulfilimine **4** and sulfilimine−BF_3 complexes **5**−**7** with furan, the dipole moments of the *exo* approaches are much higher than those arising from *endo* orientations (Tables 4 and 5). This contrast with the situation encountered in the transition states of the reactions with cyclopentadiene for which the values of the dipole moments are almost identical for both approaches. This fact suggests that solvent effects should be taken into account in the reactions of sulfilimines with furan because the interactions of the dipoles of the transition states with the medium should be different in both approaches.

In a final point of this DFT study, we have investigated the effect of diffuse functions in the basis set on the results of this theoretical analysis. The 6-31+G(d) basis set was used for the optimization of the sulfilimine **4**, BF_3 (**8**), the sulfilimine−BF_3 complexes **5**−**7**, furan (**2**), and the transition structures **TS10** and **TS14-TS16**. The geometry, bond orders and FMOs of sulfilimine **4** are similar to those obtained with the 6-31G(d) basis set. The polar character of the structures **4**−**7** is enhanced by about 1 D. Again, the most favorable coordination site for BF_3 in the sulfilimine **4** is at the nitrogen atom and the least favorable one is at the oxygen atom and *syn* to the C−N bond.

The main effect of the inclusion of diffuse function in the basis set is a significant increase in the energy barriers (∼2 kcal/mol) of the cycloaddition processes. In the presence of BF_3, the most stable transition structures and the lowest energy barriers correspond to the coordination to the oxygen atom and *anti* to the C−N bond (**TS15**). Although the effect of the diffuse functions in the energy barrier of the cycloadditive process is significant, the stereochemical preference (*endo*-*exo*) is the same with both basis sets. Anew, the *endo* approach is favored and the energy differences between both orientations are nearly identical with both 6-31(d) and 6-31+G(d) basis sets. As was found before, the dipole moment for the *endo* approaches are also lower than those of the *exo* ones. These two results support the hypothesis that the explanation for the observed stereoselectivity in the reaction with furan should arise from the consideration of solvation effects.

AM1 Study. At the AM1 semiempirical level, we have carried out full optimizations of the reactants cyclopentadiene (**1**), furan (**2**), and the sulfilimine **3**, and the transition states of the concerted [4 + 2] cycloaddition

Scheme 2. Cycloaddition Processes of Sulfilimine 3 with Cyclopentadiene and Furan Studied at the B3LYP/6-31G(d)//AM1 Level of Theory

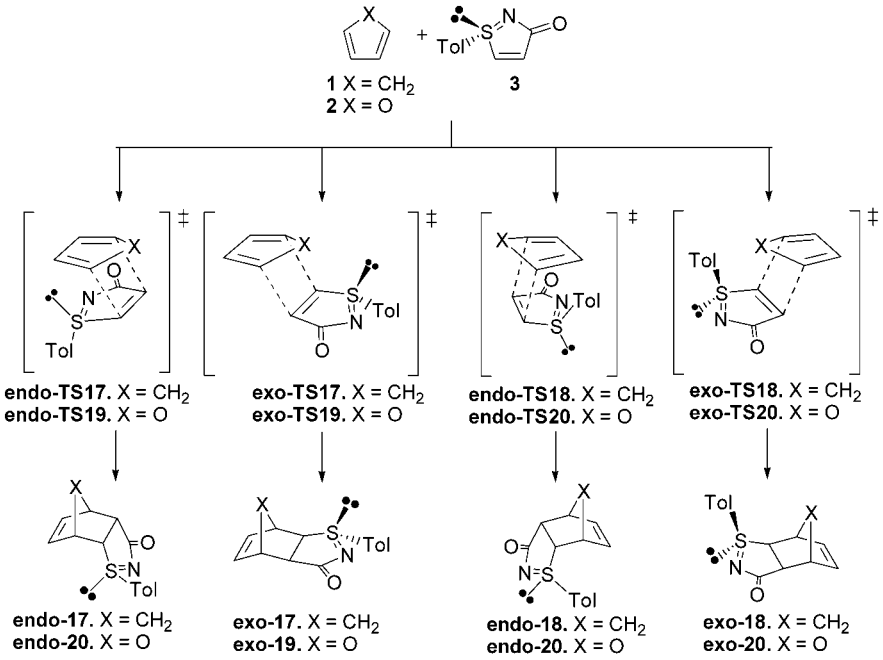

Table 6. B3LYP/6-31G(d)//AM1 Computed Activation and Reaction Energies for Reactions of 3 with Cyclopentadiene and Furan

		$\Delta E^{\ddagger}$ (kcal/mol)	dipole moment (D)	ΔE (kcal/mol)
17	*endo*	+19.3	7.5	−21.5
	exo	+20.2	7.5	−22.2
18	*endo*	+23.5	8.4	−17.3
	exo	+22.9	8.3	−19.8
19	*endo*	+25.2	7.0	−3.9
	exo	+25.8	8.3	−5.6
20	*endo*	+28.4	8.2	+0.2
	exo	+27.1	8.6	−4.9

processes of **3** with **1** (**TS17-TS18**), along with those of **3** with **2** (**TS19-TS20**) (Scheme 2).

AM1 calculations in GAUSSIAN 98 comprising molecules with boron and sulfur use MNDO parameters for both atoms.[13] This mixture of methods has not been fully tested, and therefore we decided to perform B3LYP/6-31G(d) single-point energy calculations on the AM1 optimized structures. All energy barriers are relative to the B3LYP/6-31G(d)//AM1 calculations.

Table 6 shows the energy barriers and the reaction energies of the concerted [4 + 2] cycloadditions of **1** or **2** with **3** that lead to **17**−**18** and **19**−**20**, in each case. These results confirm that cyclopentadiene is much more reactive than furan because the activation energies of **TS17** structures are ∼5 kcal/mol lower than the corresponding ones for the reaction of **3** with furan (**TS19**). The energy barriers found at this level of calculation are in very good agreement with the ones obtained at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level with the sulfilimine **4**, thus validating AM1 geometries. In all cases, the DFT transition structures present lower activation barriers than the semiempirical ones by ∼1 kcal/mol in the case of the reaction with cyclopentadiene and ∼1.5 kcal/mol in the reaction with furan.

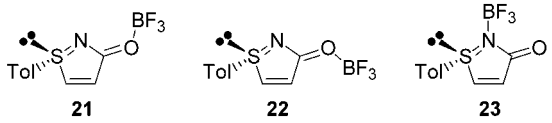

Figure 3. Sulfilimine−BF_3 complexes studied at the B3LYP/6-31G(d)//AM1 level.

The high π-facial stereoselectivity showed by the cycloaddition reactions of the sulfilimine **3** is reflected in the lower energy barriers for **TS17** versus **TS18** (higher than 3 kcal/mol) and **TS19** versus **TS20** (higher than 2 kcal/mol). When the cycloaddition takes place through the less hindered face of the sulfilimine the most favored approach is *endo* with cyclopentadiene but less significant preference is found with furan. The energy differences between *endo* and *exo* approaches are almost the same with both methods, B3LYP/6-31G(d)//B3LYP/6-31G(d) (Table 4) and B3LYP/6-31G(d)//AM1 (Table 6). However, in **TS18** and **TS20** the *exo* approaches present lower activation barriers than the *endo* ones, which could be explained by a higher sensitivity to steric effects in the latter approach.

We have also considered the reactions of **3** with **1** or **2** in the presence of BF_3 (**8**). In all cases, the formation of the complex sulfilimine−BF_3 is exothermic. The structure in which the coordination of boron trifluoride takes place at the oxygen atom of the carbonyl group of the sulfilimine **3** and *anti* to the C−N bond (**22**) is the most stable structure (ΔE = −18.9 kcal/mol). In structures **21** (ΔE = −15.8 kcal/mol) and **22**, in which boron trifluoride is coordinated to the oxygen atom of the sulfilimine, the energy values are quite similar to the ones calculated for the corresponding DFT structures (**5** and **6**). In contrast, the AM1 structure in which the coordination takes place at the nitrogen atom (**23**) is the least stable one (ΔE = −15.2 kcal/mol), whereas the corresponding DFT structure was the most stable one.

(13) (a) MNDO parameters for sulfur atom: Dewar, M. J. S.; Reynolds, C. H. *J. Comput. Chem.* **1986**, *2*, 140. (b) MNDO parameters for boron atom: Dewar, M. J. S.; McKee, M. L. *J. Am. Chem. Soc.* **1977**, *99*, 5231.

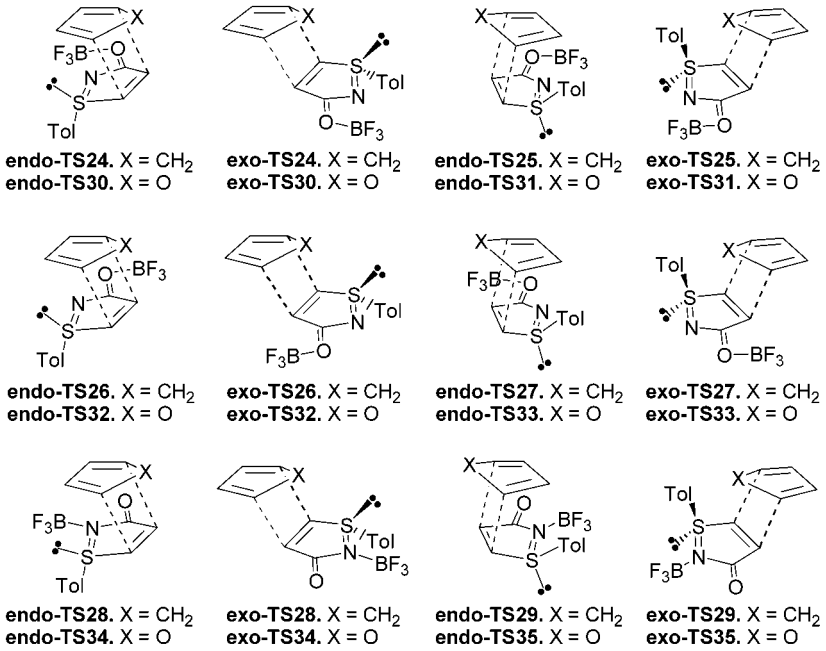

Figure 4. BF_3-coordinated transition structures studied at the B3LYP/6-31G(d)//AM1 level.

The transition states of the reactions of **1** or **2** with the sulfilimine **3** in the presence of BF_3 (**TS24-TS35**) have been located (Figure 4). Now, there are three groups of four transition structures with each diene, one for each coordination site of BF_3.

In all cases, the activation energies are lower than the corresponding ones for the same process in the absence of BF_3 (Table 6). Again, the most favorable coordination occurs at the oxygen atom of the carbonyl group and *anti* to the C−N bond, the same as in the starting sulfilimine (**TS26-TS27** and **TS32-TS33**). The coordination of BF_3 to this position increases the *endo* selectivity because the energy difference between *endo* and *exo* is 0.9 kcal/mol higher than for the uncatalyzed process when the diene approach to the less hindered face of **3**. The π-facial selectivity of the cycloaddition is also enhanced by the inclusion of BF_3 (more than 1 kcal/mol higher). Compared to the DFT geometries, the energy barriers for the AM1 transition structures are higher by 1.3−2.3 kcal/mol with the exception of the structures in which BF_3 is coordinated to the nitrogen atom. The preference for the *endo* approach is well reproduced at this level of calculation.

In the cycloaddition reaction of furan with the sulfilimine **3** in the presence of BF_3, the coordination of this Lewis acid to the oxygen atom of **3** and *anti* to the C−N bond exhibits the lowest activation energies (Table 7). The activation energies for *endo* and *exo* approaches are 5.8 and 6.0 kcal/mol lower than for the uncatalyzed process so, in that case, the energy difference between them is negligible. Once again, the activation barriers obtained by this method are higher than those determined at the B3LYP/6-31G(d) level. Anyway, these barriers are lower than the ones obtained at the B3LYP/6-31+G(d) level. Moreover, the semiempirical and DFT geometries exhibit a similar *endo* preference although it is slightly lower in the first ones.

Solvent Effects. The small energy differences that are responsible for either high *endo* or high *exo* selectivity complicate the theoretical rationalization of the problem because the observed final effect can be the sum of several different contributions. Secondary orbital overlap in the *endo* transition structures[14] and steric[15,16] or solvent[15,17]

Table 7. B3LYP/6-31G(d)//AM1 Computed Activation Energies for Reactions of 3 with Cyclopentadiene and Furan in the Presence of BF_3

		$\Delta E_i^{\ddagger}$ [a] (kcal/mol)	$\Delta E^{\ddagger}$ (kcal/mol)	dipole moment (D)
TS24	*endo*	−0.5	+15.2	13.4
	exo	+1.6	+17.3	13.4
TS25	*endo*	+2.8	+18.5	14.0
	exo	+3.5	+19.2	14.1
TS26	*endo*	−5.1	+13.8	12.0
	exo	−2.9	+16.0	12.0
TS27	*endo*	−0.9	+18.5	13.8
	exo	−0.4	+19.2	13.7
TS28	*endo*	−1.6	+13.6	12.6
	exo	+0.2	+15.4	12.3
TS29	*endo*	+6.3	+21.5	13.9
	exo	+3.6	+18.8	13.6
TS30	*endo*	+5.5	+21.2	12.7
	exo	+6.8	+22.6	14.1
TS31	*endo*	+7.3	+23.0	13.3
	exo	+7.8	+23.5	14.5
TS32	*endo*	+0.5	+19.4	11.8
	exo	+0.8	+19.8	12.4
TS33	*endo*	+3.8	+22.7	13.5
	exo	+2.0	+20.9	13.6
TS34	*endo*	+5.5	+20.7	11.5
	exo	+5.8	+21.0	13.7
TS35	*endo*	+11.2	+26.4	13.2
	exo	+7.8	+23.0	14.0

[a] Energy differences from the three separate reactants (diene, sulfilimine, and BF_3) with respect to transition states.

(14) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 4388. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970. (c) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976. (d) Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 4170. (e) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095. (f) Gleiter, R.; Bohm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237. (g) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Eur. J.* **2000**, *6*, 267 (h) Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **2001**, *66*, 6178.

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Table 8. SM5.4/AM1 Free Energies of Solvation, Activation Barriers, and Reaction Energies (in kcal/mol) for the Reaction of 3 with Furan in Dichloromethane[a]

		ΔG_{sol} (TS)	$\Delta E^{\ddagger}$ [b]	$E^{\ddagger}_{endo}-E^{\ddagger}_{exo}$ [b]	$\Delta H_f^{\ddagger}$ [c]	$H_f^{\ddagger}{}_{endo}-H_f^{\ddagger}{}_{exo}$ [c]	ΔG_{sol}	ΔE [b]	ΔE [c]
1							−3.9		
2							−4.4		
3							−27.2		
17	*endo*	−29.6	+20.7	−2.5	+30.9	−2.2	−28.0	−18.5	−22.7
	exo	−28.1	+23.2		+33.1		−27.1	−18.3	−22.7
18	*endo*	−28.9	+25.6	−1.1	+34.9	−0.4	−28.3	−14.6	−19.6
	exo	−27.2	+26.7		+35.3		−27.4	−16.1	−21.4
19	*endo*	−28.8	+28.0	+1.8	+32.1	+2.8	−27.4	+0.4	−10.6
	exo	−31.2	+26.2		+29.3		−30.4	−4.5	−15.4
20	*endo*	−27.9	+32.1	+3.5	+35.3	+3.7	−27.6	+4.1	−7.9
	exo	−30.1	+28.6		+31.6		−30.5	−3.8	−13.7

[a] Columns 3−7 refer to transition structures, and columns 8−10 refer to minima. [b] E = B3LYP/6-31G(d) single point energy (gas) + free energy of solvation. [c] H_f = SM5.4/AM1 heat of formation (gas) + free energy of solvation.

effects have been suggested as an explanation of the experimental results.

Sustmann and co-workers[18] studied the influence of solvent effects on the stereoselectivity of several Diels−Alder reactions at a semiempirical level. The solvent favors the transition structure that exhibits the higher dipole moment. Therefore, in that case the selectivities obtained cannot be directly compared with calculations that simulate gas-phase conditions. In fact, for the reactions studied by Sustmann et al. in which an *exo* selectivity was experimentally found, the gas-phase calculations predicted an *endo* preference. These results clearly suggest that besides all other influences, solvent effects may select which addition mode is followed and should be particularly significant in these cases where the transition structures are highly polarized.

In our study of the cycloaddition reactions of the sulfilimines **3** and **4** we have also found that the dipole moment in the *exo* transition states are higher than in the *endo* ones. Contrary to the reactions studied by Sustmann et al., wherein the high polarity of the transition structure came from its strong asynchronous and almost stepwise character, the transition structures for the cycloaddition reactions of sulfilimines are very synchronous and the high dipole moment of these structures arises from the strong polarity of these dienophiles.

Uncatalyzed cycloaddition reactions of cyclopentadiene and furan with the sulfilimine **3** in dichloromethane solution have been explored. The AMSOL[8] program has been used for this purpose because of its ability to include solvent effects in semiempirical calculations. The solvation models used by this program include solvation effects by considering the polarization of the solvent based on a distributed monopole representation of the solute charges in conjunction with the solute polarization in a self-consistent manner and by computing the solvent-accessible-surface area based on the local nature of the solute and the atom's or group's interface with the solvent. This represents a very advanced model to take into account solvent effects. The SM5.4[10] solvation model with the AM1 semiempirical method was used in our study, and the parameters for the solvent were taken from the ones specified by the program.[9]

Accordingly, the structures of the dienes **1** and **2**, the sulfilimine **3**, the transition structures **TS17-TS20**, and the cycloadducts **17**−**20** with the SM5.4/AM1 method in dichloromethane have been reoptimized. Table 8 shows the most significant results of these calculations. Only the uncatalyzed reactions were studied because of the lack of parameters for the boron atom in AMSOL.

All of the stationary points along the reaction path are stabilized by solvation, the latter effects being more important for the reactants (ΔG_{sol}[**1**+**3**] = −31.1 kcal/mol, ΔG_{sol}[**2**+**3**] = −31.6 kcal/mol; Table 8 and Figure 5) than for transition states and products, which exhibit similar values for ΔG_{sol}. Consequently, the activation barriers are higher in solution, by >1 kcal/mol, than in the gas phase whereas the exothermic character of the reaction is reduced by about the same quantity. The *endo* transition structures for the reaction of cyclopentadiene with **3** in solution are more stabilized than the *exo* ones by ∼1.6 kcal/mol as shown by the free energies of solvation (Figure 5). The absolute values of the activation barriers ($\Delta H_f^{\ddagger}$), determined from the heat of formation at a semiempirical level, are less significant because the energy barriers discussed before for the gas-phase reactions were obtained from a B3LYP/6-31G(d) energy calculation. For comparative purposes, we have also calculated the energy in solution for the optimized structures as the sum of the B3LYP/6-31G(d) energy in the gas-phase and the SM5.4/AM1 free energy of solvation. The differences in energy between the *endo* and *exo* transition structures are in very good agreement with the experimental results (Table 8). The *endo* approach is favored in the reaction with cyclopentadiene, the same as in the gas phase. On the other hand, there is a complete inversion in the stereoselectivity of the cycloaddition with furan from a slightly favored *endo* approach in the gas phase to an important *exo* preference in solution (Figure 5).

Conclusions

The analysis of the dipole moment, bond orders, and frontier molecular orbitals of sulfilimines shows that these are electron-poor dienophiles that undergo normal

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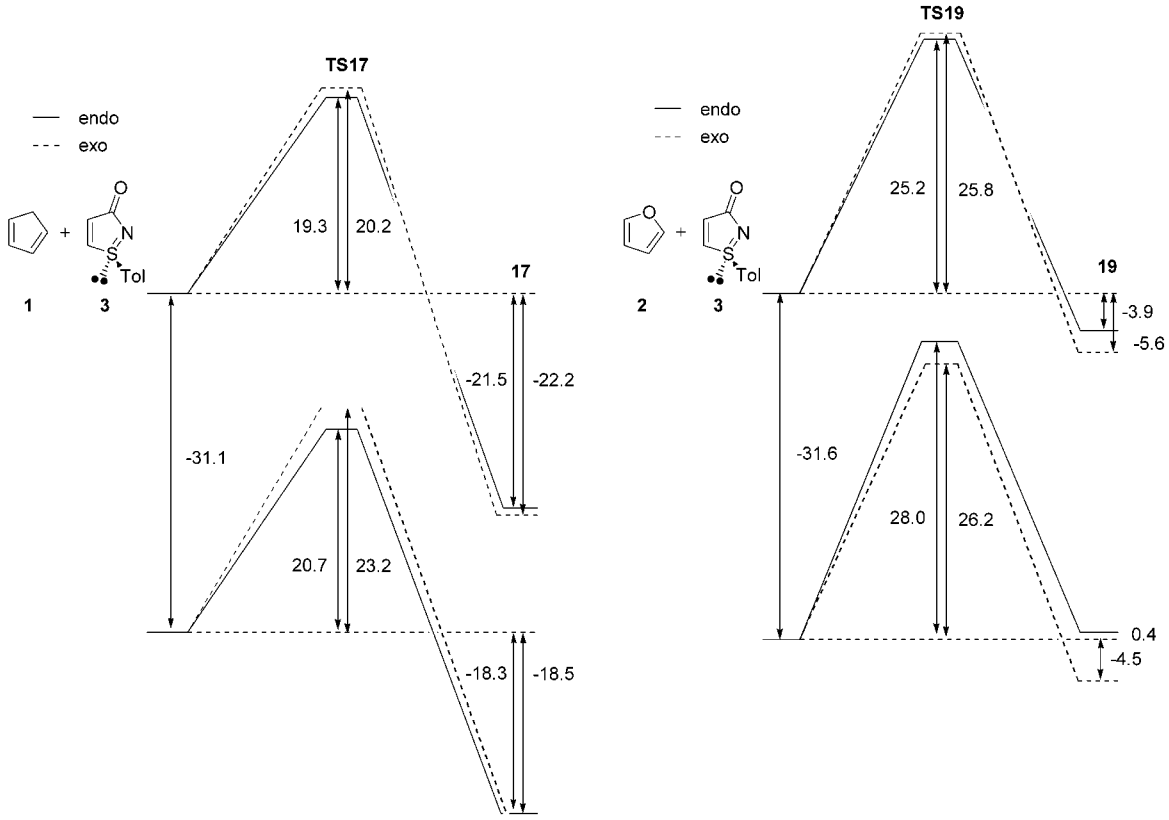

Figure 5. Solvent effects on the most favorable cycloadditive pathway of **1** or **2** with **3**.

electron-demand [4 + 2] cycloaddition reactions and that their LUMOs are almost nonpolarized. The most favorable coordination of boron trifluoride at the sulfilimine occurs at the oxygen atom of the carbonyl group and *anti* to the C−N bond.

The molecular mechanism of the reaction of cyclic vinylsulfilimines with cyclopentadiene and furan corresponds to a concerted [4 + 2] cycloaddition process, which also exhibits a high degree of synchronicity. Consideration of Lewis acid catalysis exemplified here by coordination with BF_3 decreases the activation energies of the cycloaddition process, whereas the charge transfer from the diene to the sulfilimine is augmented.

The [4 + 2] cycloaddition reactions of sulfilimines with furan and cyclopentadiene occur with *endo* stereoselectivity in the gas phase, which is more important in the reaction with cyclopentadiene. Solvent effects are responsible for the inversion of the stereoselectivity in the reactions of sulfilimines with furan because of the great difference of the dipole moments in *endo* and *exo* approaches.

Finally, the economical B3LYP/6-31G(d)//AM1 model chemistry works reasonably well in comparison with the B3LYP/6-31G(d)//B3LYP/6-31G(d) one, and the former is validated as a good and feasible approximation in the study of concerted [4 + 2] cycloaddition processes. The inclusion of diffuse functions in the basis set slightly increases the energy barriers for the reaction of sulfilimine with furan as well as the dipole moment of the transition structures. Conversely, the *endo-exo* energy differences in the gas-phase with the B3LYP/6-31+G(d)//B3LYP/6-31+G(d), B3LYP/6-31G(d)//B3LYP/6-31G(d), and B3LYP/6-31G(d)//AM1 model chemistries remain practically unaffected.

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Supporting Information Available: Cartesian coordinates of all of the structures with their computed total energies as well as tabular data regarding bond distances and thermodynamical energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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