Effect of Lewis Acid Catalysis on the Diels−Alder Reaction between Methyl (*Z*)-(*S*)-4,5-(2,2-Propylidenedioxy)pent-2-enoate and Cyclopentadiene.   A Theoretical Study

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The Diels−Alder reactions of methyl *(Z)-(S)*-4,5-(2,2-propylidenedioxy)pent-2-enoate and *(Z)-(S)*-4,5-(2,2-propylidenedioxy)pent-2-enoic acid with cyclopentadiene catalyzed by $AlCl_3$ have been theoretically studied at the B-LYP/6-31G* level. The results obtained show that the catalyst increases both the *endo/exo* and *syn/anti* selectivity, in good qualitative agreement with the experimental observations. The origin of the selectivity and the role of the catalyst are discussed.

Introduction

Diels−Alder reactions between chiral pentenoates and cyclopentadiene provide polyfunctionalized adducts that are useful in the synthesis of several products. For instance, key intermediates in the stereoselective synthesis of the thromboxane antagonists S-1452 and ONO-8809,[1,2] and of carbocyclic nucleosides[3] have been prepared from the *endo* adduct resulting of the cycloaddition of methyl *(Z)-(S)*-3-4,5-(2,2-propylidenedioxy)pent-2-enoate, **1**, with cyclopentadiene. For this reason, control of facial and *endo/exo* diastereoselectivities is crucial to obtain adducts in an efficient and stereocontrolled manner.

The cycloaddition between **1** and cyclopentadiene carried out in the absence of catalysts affords a mixture of *endo/exo* isomers, the ratio being dependent on the temperature.[4] *Syn*-facial stereochemistry was predominant in all cases as a result of the attack of the diene on the less hindered π-face of the dienophile in its most stable conformation. The use of catalysts greatly enhanced *endo* and facial selectivities. The influence of several Lewis acids was studied, Et_2AlCl being found to be the most efficient one, allowing the obtention of the *syn-endo* adduct in 90% chemical yield under very mild conditions.[5]

The parent Diels−Alder reaction has been the subject of many theoretical studies.[6] These studies have shown that reliable energy barriers can only be obtained using high-level ab initio methods. Ab initio methods have also been used to study Diels−Alder reactions with unsymmetrical reactants.[7−11] The results obtained have shown that reasonable values of the potential energy barriers

require at least a MP3/6-31G* level of calculation.[9] Reactions of cyclopentadiene and unsymmetrical dienophiles present *endo/exo* stereoselectivity. Theoretical calculations do not always yield results in good agreement with experiments. Recent theoretical studies[9,10] have shown that in order to reproduce the correct *endo/exo* selectivity at least a HF/6-31G* level of calculation is required.

The study of Diels−Alder reactions involving chiral dienes and/or dienophiles involves methodological problems, since the size of the system precludes the use of high level ab initio methods. We have studied the reaction of **1** with butadiene using the semiempirical AM1 method.[4] The *syn/anti* selectivity is correctly reproduced, but the calculations predict the *exo* transition states to be more favorable than the *endo* ones, in disagreement with experimental data. A more recent study[12] of reactions of chiral butenolides and cyclopentadiene shows that the facial selectivity is well reproduced at all levels of calculation but that a correct description of the *endo/exo* selectivity requires at least a HF/6-31G* level of calculation.

The effect of catalysts in Diels−Alder reactions has also been the object of theoretical studies.[13−15] These studies, using both semiempirical[13] and ab initio calculations,[14,15] predict that the catalyst produces a notable increase in the asynchronicity of the transition states.

In recent years, the methods based on the density functional theory[16] have emerged as an alternative to traditional ab initio methods in the study of structure and reactivity of chemical systems. The parent Diels−Alder reaction has been the object of several density functional studies,[17−21] showing that functionals that

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include gradient corrections and hybrid functionals lead to barriers in good agreement with experimental results. More recently, reactions of cyclopentadiene with several dienophiles have also been studied[22,23] using density functional methods, yielding results in excellent agreement with experiments.

The study of systems involving bulky substituents has been considered by Houk *et al.*[24] using a methodology that consists of a combination between standard quantum chemical (QC) calculations and molecular mechanics (MM) calculations. The transition states of a model reaction are located using QC methods, while the steric interactions due to the bulky groups are taken into account through MM calculations. More recently, Jursic[25] has reported a theoretical study of a cycloaddition reaction in which the transition states are located using a semiempirical method, while the energies are computed at the density functional level.

The purpose of the present paper is to study the reaction between cyclopentadiene and **1** catalyzed by $AlCl_3$ in order to rationalize the experimental observations regarding *endo/exo* and *syn/anti* selectivity. In order to check the validity of several theoretical methods, (Z)-(S)-4,5-(2,2-pentylidenedioxy)pent-2-enoic acid, **2**, will also be considered as a model of **1**.

Computational Details

All molecular geometries have been fully optimized using the semiempirical AM1 method[26] implemented in the AMPAC program.[27] Transition states have been located without any geometry restriction and have been characterized through the calculation of the force constants matrix by ensuring that they correspond to saddle points of the potential energy hypersurface; i.e., they have one and only one imaginary frequency.[28,29] For the reaction between **2** an cyclopentadiene, these structures have been taken as starting points for the location of the stationary points using density functional (DF) calculations. We have used the gradient corrected functionals of Becke[30] and Lee and Yang and Parr[31] (B-LYP) for exchange and correlation, respectively, and the 3-21G basis set.[29] Vibrational frequencies have also been calculated at this level of calculation. These B-LYP/3-21G stationary points and the corresponding frequencies have been used to locate the stationary points with the 6-31G* basis set.[29] For the reactions of **1** and **2**, the energies of all AM1 structures have been recomputed at the B-LYP/6-31G*. This level of calculation yields energy barriers in excellent agreement with experimental results for the reactions of cyclopentadiene with ethylene and acrolein.[23] The basis set superposition error (BSSE) on the computed potential energy barriers have been estimated
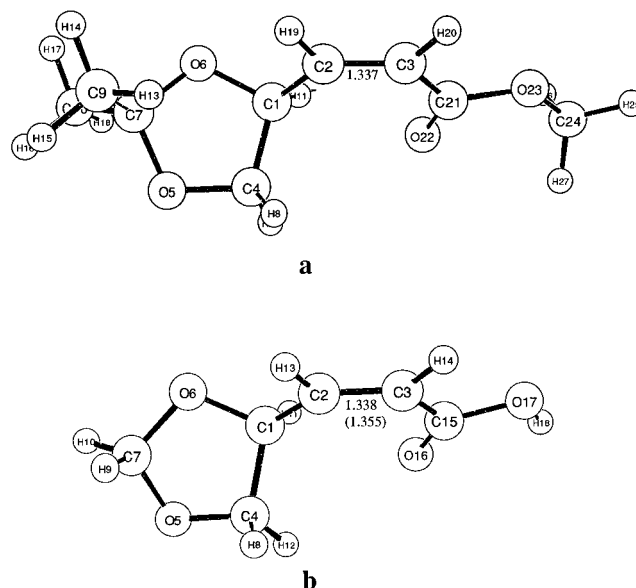

a

b

Figure 1. Geometries of **1** (a) and **2** (b) optimized at the AM1 (B-LYP/6-31G*) level of calculation. Selected bond lengths in Å.

using the counter poise method.[32] DF calculations have been done using the Gaussian-94 program.[33]

Results and Discussion

We will present first the results corresponding to the uncatalyzed reactions. Figure 1 shows the optimized geometries of **1** and **2**. These structures correspond to the most stable conformation according to a previous study of **1**.[4] Figure 2 presents the geometries of the transition states of the reaction between **2** and cyclopentadiene.

All transition states are asynchronous, the more formed bond being the one involving the β carbon atom of the enoate molecules (C2). We can observe that the degree of asynchronicity is larger for the B-LYP structures than for the AM1 ones. The differences between the B-LYP and AM1 values of the C22–C3 distances are in all cases about 0.3 Å. For the rest of the geometry parameters the differences between both methods are smaller. The geometries of the transition states corresponding to the reaction between **1** and cyclopentadiene[34] are very similar to the ones corresponding to the reaction of **2** (AM1 structures).

1   **2**
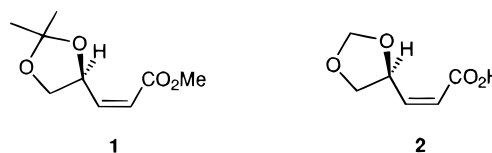
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(34) The values of the lengths of the two forming C–C bonds are as follows: 2.040 and 2.190 Å (*syn-endo*), 2.050 and 2.188 Å (*syn-exo*), 2.074 and 2.166 Å (*anti-endo*), 2.083 and 2.169 Å (*anti-exo*).
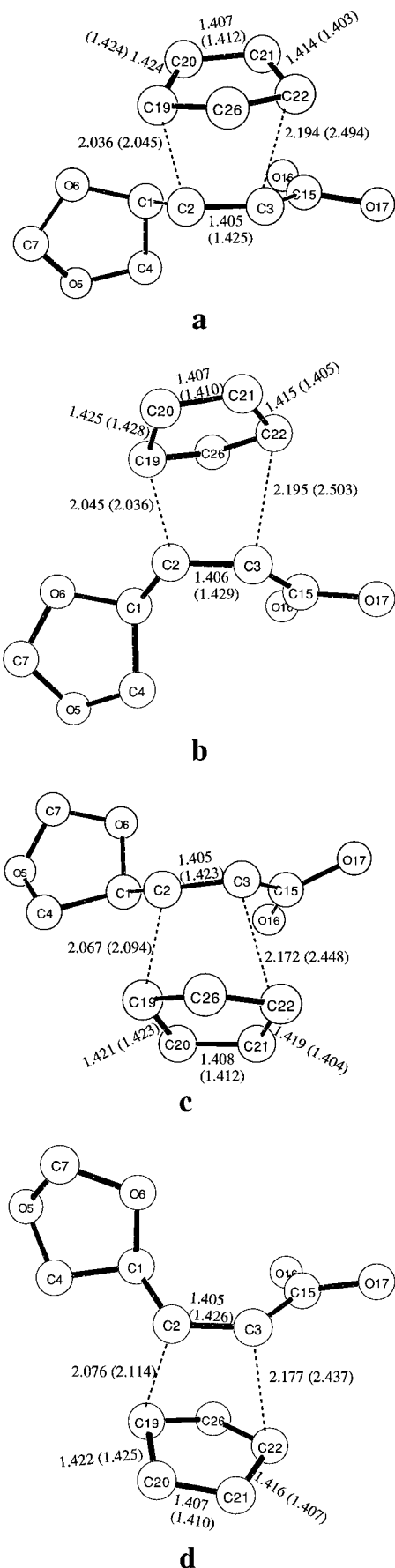
Figure 2. Geometries of the transition states of the reactions between **2** and cyclopentadiene: (a) *syn-endo*, (b) *syn-exo*, (c) *anti-endo*, (d) *anti-exo*. Hydrogen atoms have been omitted for clarity. Selected bond lengths obtained at the AM1 (B-LYP/ 6-31G*) level of calculation in Å.

Table 1. Potential Energy Barriers Computed at the B-LYP/6-31G* Level for the AM1 (B-LYP) Geometries of the Transition States of the Reactions of 1 and 2 with Cyclopentadiene

dienophile	TS	$\Delta E^{\ddagger a}$
1	*syn-endo*	26.3
	syn-exo	27.1
	anti-endo	28.0
	anti-exo	28.6
2	*syn-endo*	25.7 (21.7)
	syn-exo	26.3 (21.8)
	anti-endo	27.9 (24.9)
	anti-exo	28.4 (25.1)

[a] In kcal mol^{-1}. BSSE correction included.

Table 1 presents the values of the potential energy barriers corresponding to these reactions computed at the B-LYP/6-31G* level for geometries optimized at both the AM1 and B-LYP/6-31G* levels. For the reaction between **2** and cyclopentadiene the values computed for the AM1 structures are always 3−4.5 kcal mol^{-1} larger than the ones corresponding to the B-LYP structures. The ordering between the values of the barriers corresponding to the formation of the four isomers is the same for both methods. However, the AM1 structures lead to larger *endo/exo* and smaller *syn/anti* energy differences than the B-LYP structures.

We have computed the values of activation enthalpies and entropies corresponding to the formation of the four isomers of each product. For the AM1 structures we have used the potential energy barriers computed at the B-LYP/6-31G* level along with the AM1 harmonic frequencies. For the B-LYP/6-31G* structures the B-LYP/ 3-21G frequencies have been used. In all the transition states there are several low-frequency vibrational modes.[35] These modes are not well represented by the harmonic oscillator approximation. This fact may lead to errors in the computed values of activation entropies. We have also computed the activation Gibbs energies at 298 and 353 K, which is the experimental temperature for the reaction.[5] The results are summarized in Table 2.

The activation entropies corresponding to the *syn-endo* product are less negative than the one corresponding to the *syn-exo* adduct. A similar result has been obtained for Diels−Alder reactions of chiral butenolides with cyclopentadiene.[12] On the other hand, the ordering between activation entropies corresponding to the *syn/ anti* transition states depends on the level of calculation. The ordering of the Gibbs activation energies is in excellent agreement with the experimentally observed product distribution for the reaction of **1**.[5] The *syn-endo* isomer is predicted to be the most favorable one, and the facial selectivity is larger than the *endo/exo* selectivity. This ordering is mainly dominated by the potential energy barriers, but in the *syn-endo/syn-exo* ratio there is also a contribution of the entropic term.

Let us now consider the results corresponding to the catalyzed reactions. The generally accepted mechanism for Lewis acid catalyzed Diels−Alder reactions assumes the formation of a complex between the dienophile and the catalyst. Figure 3 shows the optimized geometries of the complexes of **1** and **2** with AlCl$_3$. We have considered the coordination of AlCl$_3$ to the different oxygen atoms of the enoate molecules, which showed that

(35) For instance, for the *syn-endo* transition state of the reaction of **2** the number of modes with frequencies lower than 500 cm^{-1} is 14 (AM1) and 15 (B-LYP/3-21G).

Table 2. Activation Parameters[a] for the Reactions of 1 and 2 with Cyclopentadiene

dienophile	TS	$\Delta H^{\ddagger b}$	$\Delta S^{\ddagger c}$	$\Delta G^{\ddagger}_{298}{}^{b}$	$\Delta G^{\ddagger}_{353}{}^{b}$
1	*syn-endo*	25.7	−46.3	39.5	42.1
	syn-exo	26.4	−47.6	40.6	43.2
	anti-endo	27.4	−46.3	41.2	43.8
	anti-exo	28.0	−46.0	41.7	44.2
2	*syn-endo*	25.1 (22.7)	−46.5 (−43.8)	39.0 (35.8)	41.5 (38.2)
	syn-exo	25.6 (23.1)	−48.1 (−45.0)	39.9 (36.5)	42.6 (39.0)
	anti-endo	27.3 (26.0)	−46.7 (−46.0)	41.2 (39.7)	43.8 (42.2)
	anti-exo	27.7 (26.3)	−47.9 (−46.3)	42.0 (40.1)	44.6 (42.7)

[a] Computed from the B-LYP/6-31G*//AM1 energy barriers and the AM1 harmonic frequencies (B-LYP/6-31G*//B-LYP/6-31G* energy barriers and B-LYP/3-21G frequencies). [b] In kcal mol⁻¹. [c] In cal K⁻¹ mol⁻¹.
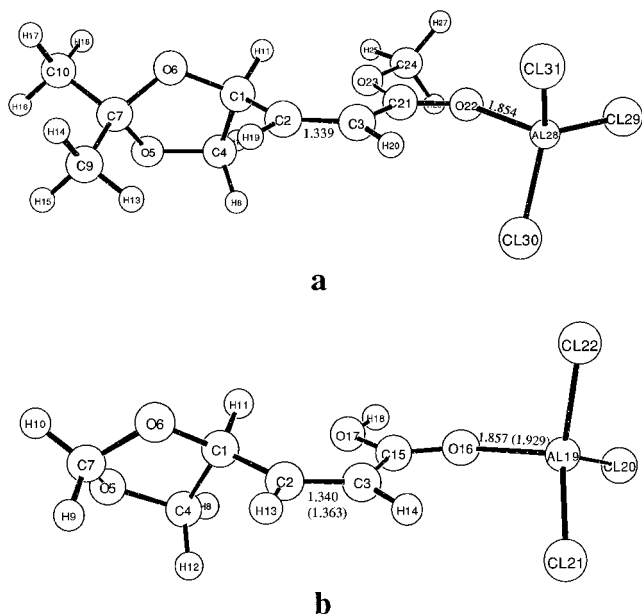

Figure 3. Geometry of the complexes **1**−AlCl₃ and **2**−AlCl₃ obtained at the AM1 (B-LYP/6-31G*) level. Selected bond lengths in Å.

the most favorable coordination site is the carbonyl oxygen atom. We have also considered several conformations corresponding to the rotation around the C1−C2, C3−C15/C21, and Al−O bonds. The geometries presented in Figure 3 correspond to the most stable conformation. The most significant difference with the structures of the uncomplexed molecules is the *s-trans* arrangement of the carbonyl group with respect to the C=C bond. A *s-cis* arrangement would involve important steric hindrance between AlCl₃ and the dioxolane group. A similar change in the conformation of methyl acrylate upon complexation by BH₃ has been observed by Loncharich *et al.*[36]

The value of the Al−O bond length in the complexes can be compared to the ones corresponding to the formaldehyde−AlCl₃ complex optimized at the HF/6-31G* level (1.947 Å)[37] and using a gradient-corrected density functional method (1.951 Å).[38] These results suggest that **1** is a stronger Lewis base than formaldehyde. The values of the formation energy of the **2**−AlCl₃ complex are −28.5 kcal mol⁻¹ (AM1 geometry) and −21.7 kcal mol⁻¹ (B-LYP geometry), while for the complex of **1** the computed value is −30.2 kcal mol⁻¹. These values can

be compared to the one corresponding to the formaldehyde complex, −19.8 kcal mol⁻¹.[38] These results confirm the relative Lewis basicities of **1**, **2**, and formaldehyde suggested by the values of the Al−O bond length.

Figure 4 presents the geometries of the transition states of the reaction between **2** and cyclopentadiene catalyzed by AlCl₃. The geometries of the transition states for the reactions of **1**[39] are very similar to the ones corresponding to the AM1 transition states of the reaction of **2**. Table 3 presents the values of the potential energy barriers of these reactions.

If we compare these geometries with the ones corresponding to the uncatalyzed reaction (Figure 2), we can see that the difference between the lengths of the two forming C−C bonds has increased, so that the transition states of the catalyzed reactions are more asynchronous than those of the uncatalyzed ones. This result has already been observed in other catalyzed Diels−Alder reactions[13−15] and can be attributed to a polarization of the antibonding π_{CC} of the dienophile.[40,41]

For the transition states of the catalyzed reactions the number of vibrational modes with frequencies lower than 500 cm⁻¹ increases by a factor of 2 with respect to the uncatalyzed reactions, so that the error introduced in the computation of activation entropies would be larger. For this reason, we will not present values of such parameters here.

The comparison of the potential energy barriers presented in Table 3 with those corresponding to the uncatalyzed reactions (Table 1) shows that the catalyst produces a drastic lowering of the barriers. In all cases the catalyst stabilizes with preference the *endo* transition states over the *exo* ones and the *syn* over the *anti*. This fact leads to an increase of both the *syn/anti* and *endo/exo* selectivities. For the reaction of **2** the difference between the *syn-exo* and *syn-endo* energy barriers increases from 0.6 to 2.1 kcal mol⁻¹ (AM1 geometries) and from 0.1 to 0.6 kcal mol⁻¹ (B-LYP geometries), and for the reaction of **1** the increase is from 0.8 to 2.0 kcal mol⁻¹. Regarding the differences between the *anti-endo* and *syn-endo* energy barriers the increase is from 2.2 (3.2) kcal mol⁻¹ to 3.0 (3.2) kcal mol⁻¹ for the AM1 (B-LYP) structures of the reaction of **2** and from 1.7 to 2.4 for the reaction of **1**. At a given temperature, the *syn/anti* selectivity slightly increases, while the increase in the *endo/exo* selectivity is larger.

In addition to the changes in the potential energy barriers induced by the catalyst, there is another factor

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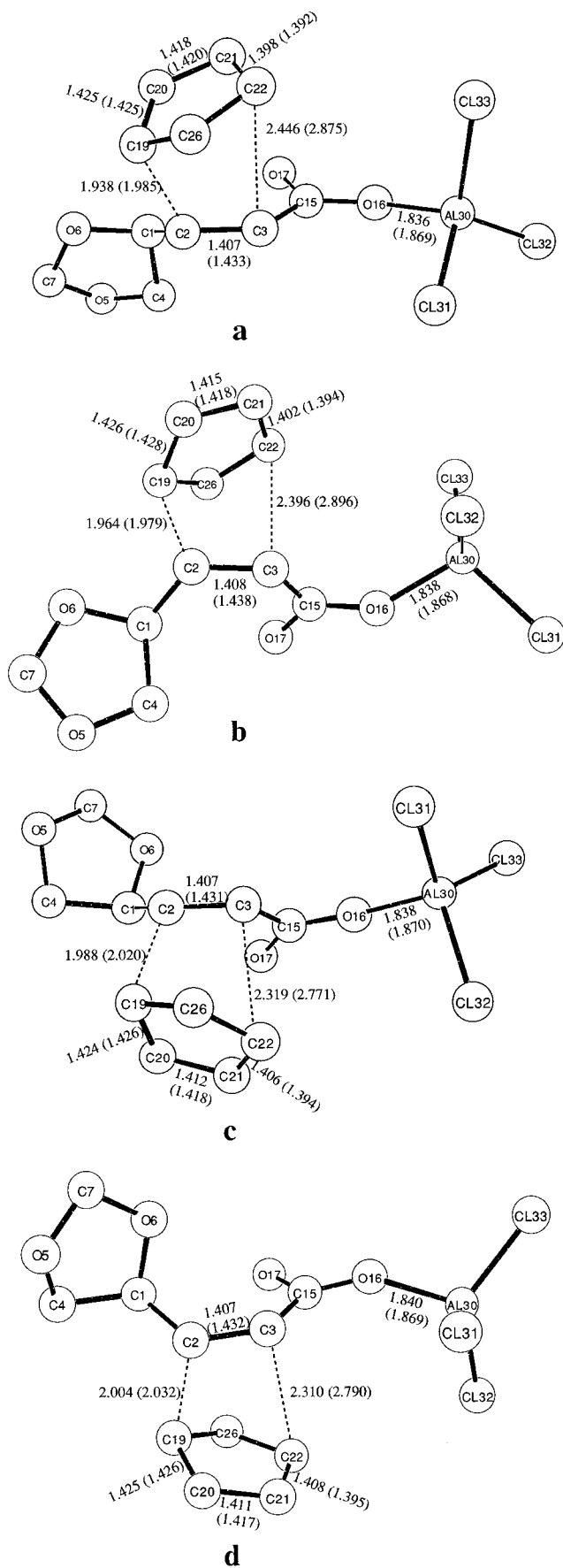
Figure 4. Geometries of the transition states of the reactions between **2** and cyclopentadiene catalyzed by AlCl₃ obtained at the AM1 (B-LYP/6-31G*) level: (a) *syn-endo*, (b) *syn-exo*, (c) *anti-endo*, (d) *anti-exo*. Hydrogen atoms have been omitted for clarity. Selected bond lengths in Å.

Table 3. Potential Energy Barriers Computed at the B-LYP/6-31G* Level for the AM1 (B-LYP) Geometries of the Transition States of the Reactions of 1 and 2 with Cyclopentadiene, Catalyzed by AlCl₃

dienophile	TS	$\Delta E^{\ddagger a}$
1	*syn-endo*	16.9
	syn-exo	18.9
	anti-endo	19.3
	anti-exo	21.0
2	*syn-endo*	14.6 (11.4)
	syn-exo	16.7 (12.0)
	anti-endo	17.6 (14.6)
	anti-exo	19.8 (15.5)

[a] In kcal mol⁻¹. BSSE correction included.

that contributes to the enhancement of the selectivity. The catalyzed reaction takes place in the experiments at 250 K, while the temperature for the uncatalyzed reaction is 353 K.[5] The diminution of the reaction temperature modifies the relative values of the rate constants corresponding to the formation of the different isomers leading to a higher selectivity.

To better understand the origin of the *endo/exo* and *syn/anti* selectivities and how they are modified by the catalyst, we have carried out a partition of the potential energy barriers. The potential energy barrier can be decomposed into two contributions. The first one is the distortion energy, i.e., the energy necessary to distort the reactant molecules from their equilibrium geometries to the geometries they have at the transition state. This term can be split into contributions of both reactant molecules. The second term is the interaction energy between the distorted reactant molecules. This term includes contributions from all stabilizing and repulsive interactions between both addends. The results corresponding to the three experimentally observed isomers of the reaction of **1** with cyclopentadiene are summarized in Table 4.

Let us first consider the uncatalyzed reactions. In all cases, the main contribution to the potential energy barrier arises from the distortion of reactant molecules, the term due to cyclopentadiene being the most important. The interaction energy term is also destabilizing in all cases, but it is much smaller than the distortion term. The difference between *syn-endo* and *syn-exo* barriers is basically due to a difference in the interaction energy term. The interaction between both reactants is more favorable when they approach each other in an *endo* orientation. On the other hand, the difference between the *syn-endo* and *anti-endo* energy barriers is mainly due to the distortion of **1**. This distortion can be easily visualized through the values of the dihedral angles that determine the orientation of the dioxolane group. The C4−C1−C2−C3 and O6−C1−C2−C3 dihedral angles corresponding to the optimized geometry of **1** are −90° and 153°, respectively. At the transition states, the dioxolane group rotates around the C1-C2 bond in order to minimize the steric repulsion with the incoming cyclopentadiene molecule. The variations of both dihedral angles with respect to the equilibrium geometry values are, respectively, 13° and 13° for the *syn-endo* transition state, 15° and 14° for the *syn-exo* transition state, and 80° and 79° for the *anti-endo* transition state. The steric hindrance due to the dioxolane group is larger when cyclopentadiene approaches the *anti* face of **1**. This larger steric hindrance is translated into geometry

Table 4. Decomposition of the Energy Barriers[a] for the Reaction between 1 and Cyclopentadiene

cat.	TS	E_{dist}			E_{int}	ΔE
		1	cp	total		
	syn-endo	9.4 (0.0)	15.9 (0.0)	25.3 (0.0)	1.0 (0.0)	26.3 (0.0)
	syn-exo	9.5 (+0.1)	15.7 (−0.2)	25.2 (−0.1)	1.9 (+0.9)	27.1 (+0.8)
	anti-endo	11.0 (+1.6)	15.5 (−0.4)	26.5 (+1.2)	1.5 (+0.5)	28.0 (+1.7)
AlCl$_3$	syn-endo	7.7 (0.0)	12.9 (0.0)	20.6 (0.0)	−3.7 (0.0)	16.9 (0.0)
	syn-exo	8.0 (+0.3)	13.2 (+0.3)	21.2 (+0.6)	−2.3 (+1.4)	18.9 (+2.0)
	anti-endo	8.8 (+0.9)	14.6 (+1.7)	23.4 (+2.8)	−4.1 (−0.4)	19.3 (+2.4)

[a] Energies obtained at the B-LYP/6-31G*//AM1 level in kcal mol^{-1}. Values relative to the *syn-endo* transition state are given in parentheses.

distortion of the enoate molecule at the transition state.[42] This steric repulsion is also reflected in the values of the C19−C2 distance in the *syn-endo* and *anti-endo* transition states (see Figure 2).

The diminution of the potential barriers in the catalyzed reactions is due both to a diminution of the distortion energy term and to a change in the sign of the interaction energy term. The lowering of the distortion energy term suggests that the transition states are closer to the reactants in the catalyzed reactions.

The increase of the difference between *syn-endo* and *syn-exo* barriers produced by the catalyst is again related to the distortion energy term and to the interaction term (see Table 4). The distance between C19 and C2 decreases with respect to the values corresponding to the uncatalyzed reaction (see Figures 2 and 4). Steric repulsions between cyclopentadiene and the dioxolane group become more important. The degree of geometry distortion in the *exo* transition state is greater than in the *endo* one in order to minimize the larger steric repulsion. The geometry distortion of the enoate moiety is reflected in the variation of the O6−C1−C2−C3 dihedral angle. This angle presents a variation with respect to the value corresponding to the isolated **1**−AlCl$_3$ complex (154°) of 13° and 17° for the *syn-endo* and *syn-exo* transition states, respectively.

The contribution of the interaction term to the increase of *endo/exo* selectivity is mainly due to the change of conformation of the ester moiety of **1**. It has already been observed in other theoretical studies of Diels−Alder reactions that the stabilization of the *endo* transition states relative to the *exo* ones is greater in *s-trans* conformations.[7,9] These results suggest that the increase in *endo/exo* selectivity in the catalyzed reaction is due both to steric effects and to better attractive interactions in a *s-trans* conformation of the enoate molecule.

Regarding the *syn/anti* selectivity, Table 4 shows that the increase in the difference between the *syn-endo* and *anti-endo* energy barriers arises from an increase of the distortion energy term. As the value of the C28−C2 distance becomes smaller in the transition states of the catalyzed reaction, the steric repulsion between the cyclopentadiene moiety and the dioxolane group increases and the geometry of both moieties has to distort in order to minimize this repulsion. As has already been observed for the uncatalyzed reaction, the *anti* transition state involves a greater steric repulsion than the *syn* one. This is reflected in the values of the dihedral angles that measure the rotation of the dioxolane group around the

C1−C2 bond. The C4−C1−C2−C3 and O6−C1−C2−C3 dihedral angles present distortions with respect to the values corresponding to the isolated **1**−AlCl$_3$ complex (−89° and 154°), which are, respectively, 13° and 14° (*syn-endo*) and 90° and 89° (*anti-endo*). The more asynchronous character of the transition states in the catalyzed reactions produces a greater steric differentiation between them.[14]

Concluding Remarks

We have studied the Diels−Alder reactions of **1** and **2** with cyclopentadiene and the effect of catalysis by AlCl$_3$ on their mechanism and selectivity.

The predicted *endo-exo* and *syn-anti* selectivities are in good qualitative agreement with experimental observations. The catalyst increases both selectivities due to an increase of the difference between the corresponding energy barriers. Moreover, the lowering of the potential energy barriers makes the reaction feasible at lower temperatures, thus contributing to an additional enhancement of selectivity.

The effect of the catalyst on the *endo-exo* selectivity can be attributed to both steric and electronic effects. The latter are due to the fact that complexation of the enoate molecule by the catalyst favors a *s-trans* conformation of the ester moiety, thus leading to an increase of stabilizing interactions favoring the *endo* transition state. Regarding the *syn-anti* selectivity, we have found that it is mainly due to steric effects involving the dioxolane group of the enoate molecule. The steric repulsion is amplified in the catalyzed reaction as a consequence of a higher degree of asynchronicity.

Finally, the comparison of the results obtained at the B-LYP/6-31G*//B-LYP/6-31G* and B-LYP/6-31G*//AM1 levels shows that the AM1-optimized geometries are useful to obtain qualitatively correct results. This fact opens the possibility of using such an approach for larger systems.

Supporting Information Available: Cartesian coordinates of **1**, **2**, their complexes with AlCl$_3$, and the transition states of all the reactions (37 pages). This material is contained in 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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