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A Computational Theoretical Study of the Diels–Alder Reaction Between β -ionone and Maleic Anhydride. Influence of Lewis Acid Catalyst, and Inclusion of Solvent Effects

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A Computational Theoretical Study of the Diels–Alder Reaction Between β -ionone and Maleic Anhydride. Influence of Lewis Acid Catalyst, and Inclusion of Solvent Effects[#]

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Abstract

Motivation. In order to contribute to a better understanding of the stereochemical outcome of the Diels–Alder reaction between β -ionone and maleic anhydride, the presence of Lewis acid catalyst modeled by the BH_3 and the inclusion of solvent effects are analyzed and discussed. The reaction between β -ionone and maleic anhydride takes place through synchronous transition structures. The transition structure of the *exo* attack is more stable than the *endo* one.

Method. The Diels–Alder reaction of the β -ionone and maleic anhydride has been studied using density functional and conventional ab-initio methods.

Results. The transition structure of the *exo* attack is more stable than the *endo* one. The inclusion of Lewis acid catalyst increases the asynchronicity of transition states and decreases the activation energies of the cycloaddition process, while the inclusion of solvent effect produces a significant increase of the *exo* selectivity.

Conclusions. This study shows that the DFT calculations are useful to obtain qualitatively correct result.

Keywords. Diels–Alder; stereoselectivity; solvent and Lewis acid effect; theoretical study.

Abbreviations and notations

B3LYP, Becke Lee and Yang and Parr	MP2, Møller–Plesset
DA, Diels–Alder	PEB, potential energy barrier
DFT, density functional theory	PES, potential energy surface
HF, Hartree–Fock	RHF, restricted Hartree–Fock
HOMO, highest occupied molecular orbital	SCRf, self consistent reaction field
LUMO, lowest unoccupied molecular orbital	TS, transition structure
MPA, Mulliken population analysis	

1 INTRODUCTION

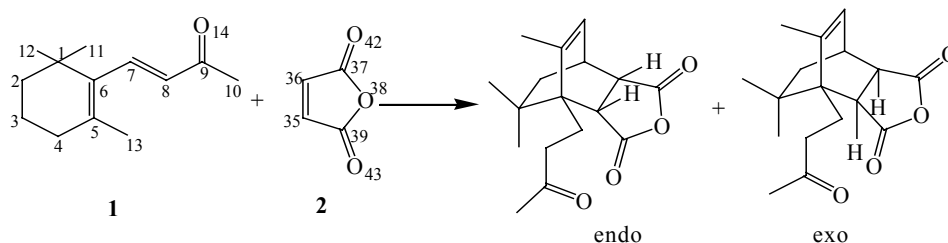
The Diels–Alder reaction is one of the most useful synthetic reactions, and this overwhelming importance is well-known and well documented in organic chemistry. Its usefulness arises from its versatility and from its remarkable selectivity. Many synthetic routes to cyclic compounds are made

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possible through DA reactions, which can involve a large variety of dienes and dienophiles [1].

As a part of our research program devoted to the study of molecular mechanism of the cycloaddition DA reactions that takes place via asynchronous mechanism, we present the result of theoretical study on the normal DA reaction of β -ionone **1** and maleic anhydride **2** (See scheme 1) to give the corresponding cycloadducts.



Scheme 1

Our purpose is to contribute to a better understanding of the origins of the stereo chemical outcome and to shed light on the mechanistic details of this important reaction. Lewis acid catalyst and solvent effect have been also included in order to clarify their role on the nature of the molecular mechanism.

Experimentally, it is well-known that the reaction between β -ionone and maleic anhydride is performed in the presence of AlCl_3 with dichloromethane (CH_2Cl_2) as solvent [2]. Thus, the effects of the Lewis acid catalyst are considered in our study of this reaction with BH_3 as a computational model. BH_3 has been used by different authors to model the presence of Lewis acid with good results [3].

Solvent effects on cycloaddition reactions are well known and have received considerable attention, especially in the last few years. As solvent can modify both activation energy and *endo/exo* selectivity, its effect on the reaction can give useful information about the mechanism.

So the solvent effects have been considered by B3LYP/6–31G* optimizations of stationary points using a relatively simple self-consistent reaction field (SCRFF) [4] method, based on the PCM model (Polarized Continuum model) of Tomasi's group [5]. In this model, the liquid is represented by a dielectric continuum characterized by a macroscopic constant, usually the dielectric relative permittivity.

The solvent used in the experimental work is dichloromethane (CH_2Cl_2). Therefore, we have used at first the dielectric constant at 298.0K $\epsilon = 8.93$ [6], and at second the dielectric corresponding to toluene $\epsilon = 2.379$, and methanol $\epsilon = 32.63$, in order to test the effect of different solvents and to see their impact on the stereo selectivity.

2 COMPUTATIONAL DETAILS

All molecular geometries have been fully optimized using the Gaussian–98 program [7]. Transition states have been located without any geometry restriction on the full potential energy surfaces. Harmonic vibrational frequencies have been computed for all stationary points to verify that for energy minima all frequencies are real, while for transition states there is one and only one imaginary frequency. In DFT calculations we have used the gradient corrected functional of Becke [8] and Lee and Yang and Parr [9] (B3LYP) for exchange and correlation, respectively, and the 6–31G* basis [10]. Conventional *ab initio* calculations have been performed using the 3–21G [10] and 6–31G* basis sets.

Uncatalyzed system. Geometry optimization of the reactants, and the transition states of the uncatalyzed system in the gas phase was performed using the Hartree–Fock (HF) [10], B3LYP hybrid density–functional theory [11], and Møller–Plesset second–order perturbation theory (MP2) [12].

Catalyzed system. For the catalyzed system, a simpler model catalyst (BH₃) was used. For comparison with the uncatalyzed one the B3LYP/6–31G* calculation was performed to obtain more reliable relative energies. Polarized continuum model (PCM) was used to estimate the solvation energy in dichloromethane (CH₂Cl₂) at the optimized geometries.

3 RESULTS AND DISCUSSION

3.1 Gas Phase

We will present first the results corresponding to the uncatalyzed reaction. Figure 1 shows the optimized geometries of **1** and **2**. These structures correspond to the most stable conformation according to a previous study [13].

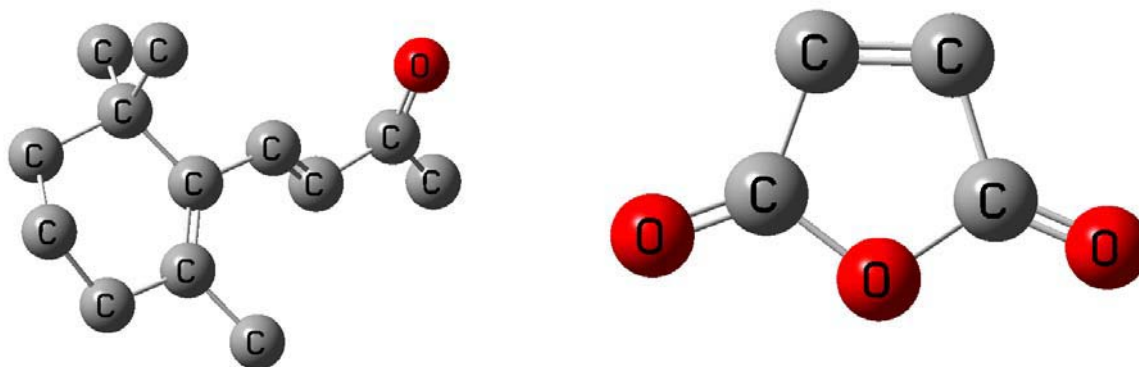
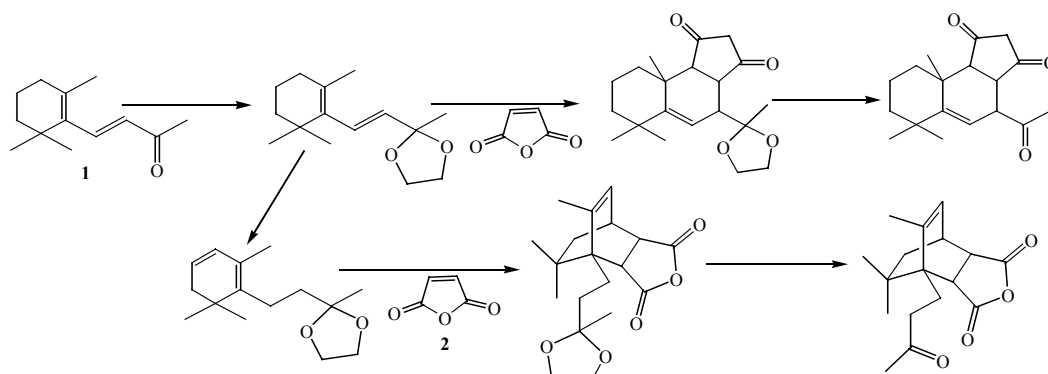


Figure 1. Geometries of β -ionone and maleic anhydride obtained at the B3LYP/6–31G* level.

According to the experiment this diene reacted not in its initial form, but it produces a migration of the double bond of the lateral chain inside the cycle (see Scheme 2) [2]. This experimental study offered the opportunity to carry out a complementary theoretical analysis in order to compare theory and experiment



Scheme 2

The Diels–Alder reaction between this diene and maleic anhydride can lead to two stereo isomeric products through two different transition states: *endo* and *exo*. The optimized geometries of the transition states corresponding to this reaction are illustrated in Figure 2. The values of the most important geometries parameters and the potential energy barrier computed at several levels of calculation are listed in Table 1.

Table 1. Selected Geometry parameters in (Å) and Potential Energy Barriers in (Kcal mol⁻¹) Computed at Several Levels of Calculation for the Reaction of β -Ionone and Maleic Anhydride

		Level of calculation	r_{1a}	r_{2a}	Δr_a	E_{ab}
TS <i>endo</i>		RHF/3-21G	2.13	2.43	0.3	40.10
		RHF/6-31G*	1.91	2.79	0.88	50.48
		MP2/6-31G**/6-31G*	–	–	–	8.52
		B3LYP/6-31G*	2.09	2.58	0.48	28.29
TS <i>exo</i>		RHF/3-21G	2.10	2.41	0.30	30.94
		RHF/6-31G*	2.03	2.50	0.47	46.21
		MP2/6-31G**/RHF/6-31G*	–	–	–	0.44
		B3LYP/6-31G*	1.99	2.66	0.67	21.68

The transition vectors (TVs) [14] are dominated by the motion of the new forming C–C bonds, and the extent of asynchronicity (Δr) can be measured by means of the difference between the distances of the bonds that are being formed in the reaction. The values of the bond lengths presented in Table 1 show that all methods of calculation predict that all transition states are asynchronous, the more formed bond being the one involving the C₃ of β -ionone and the of C₃₅ maleic anhydride (r_1). We can observe that the degree of asynchronicity depends of the level of calculation. For the *exo* stereoisomer the B3LYP/6-31G* calculations predict transition states more asynchronous than the corresponding HF ones.

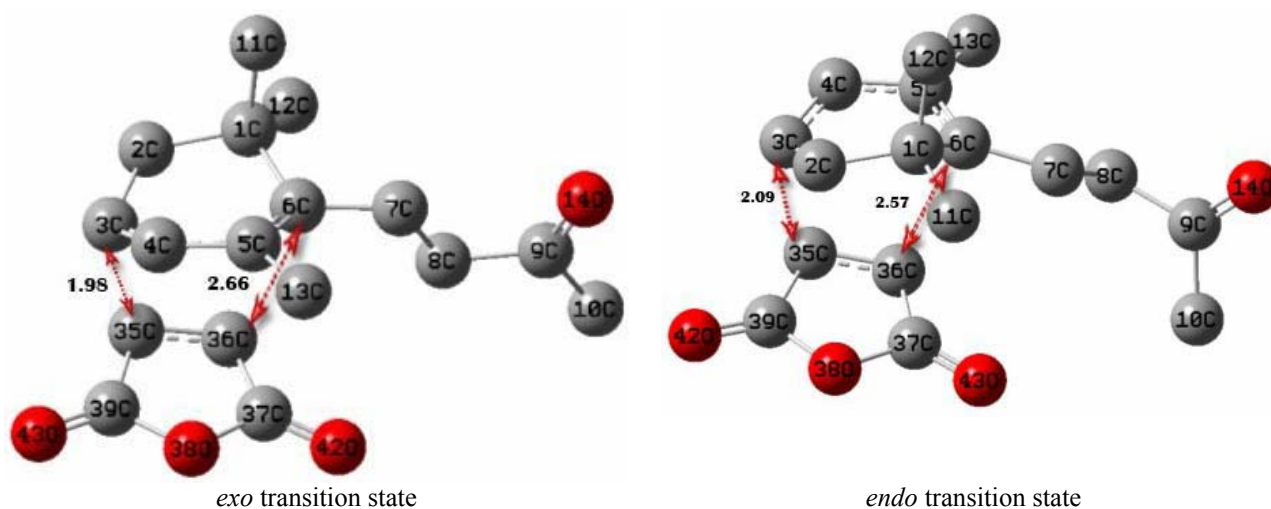


Figure 2. Transitions states corresponding to DA reaction between β -ionone and maleic anhydride in gas phase. Selected bond lengths obtained at B3LYP/6–31G* level of calculation in Å. (Hydrogen atoms have been omitted for clarity).

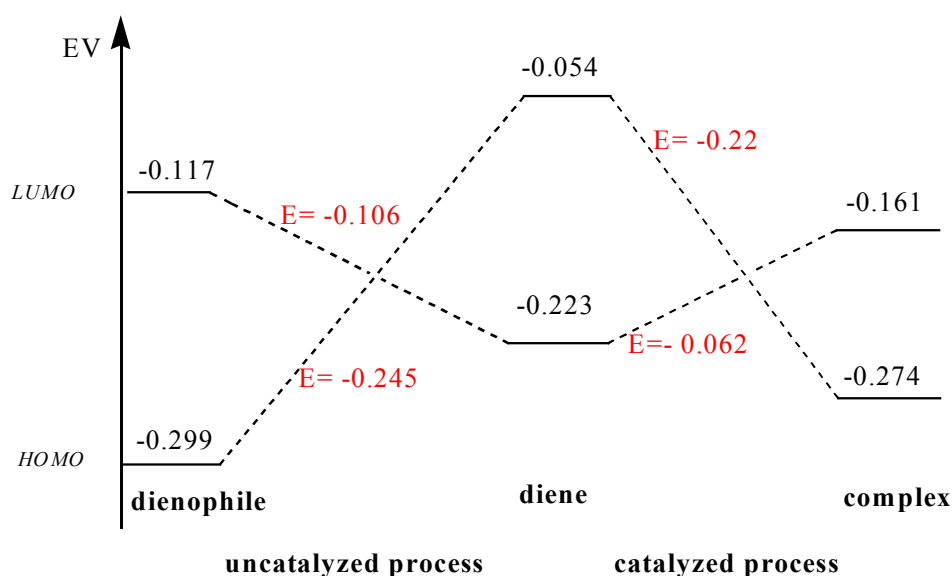


Figure 3. Frontier molecular orbital energy gaps for the catalysed and uncatalysed DA reaction.

Regarding the computed values of the potential energy barrier, we can observe that there is an important dependency on the level of calculation. Upon changing from the 3–21G to the 6–31G* basis set, the potential barriers at RHF level notably increases due to a fortunate error cancellation in HF/3–21G calculations. The inclusion of electron correlation at the MP2 level leads to a dramatic diminution of the barriers. In fact, the potential barriers are clearly underestimated at the MP2 level. The inclusion of electron correlation up to the B3LYP method leads to reasonable values.

As for many other Diels–Alder reactions, RHF methods compute higher activation energies than DFT methods [15–18]. It is well documented that RHF theory gives activations energies

substantially above experimental values, while methods that include electron correlation reproduce activation energy properly [19]. Then we will use in the rest of research the B3LYP/6–31G* method.

Regarding the *endo/exo* selectivity all methods employed, starting with RHF/3–21G gave a good prediction of *exo* stereo–selectivity. Therefore, experimentally, *exo* was found to be preferred over *endo* adduct [2]. The origin of such a result may be attributed to presumable steric repulsions between maleic anhydride and the 11C–methyl group of β -ionone. The *endo/exo* energy difference is 6.6 Kcal mol⁻¹ at the B3LYP/6–31G* level of calculation. It is to be noted that in all these cases the difference between the *endo* and *exo* potential energy barriers changes from 4.3 Kcal mol⁻¹ to 8.1 Kcal mol⁻¹.

The examination of the frontier orbital of β -ionone and maleic anhydride shows that the most favourable interaction is the one involving the *HOMO*_{diene} and the *LUMO*_{dienophile} (see Figure 3). Consequently the reaction between 1 and 2 is a cycloaddition reaction with normal electron demand. Thus, there is a charge transfer from the diene to the dienophile, the values of charge transfer at the transition states determined from Mulliken population analysis range (MPA) from 0.27 to 0.29 au, being slightly larger from the *exo* structure.

3.2 Lewis Acid Catalyst

The Lewis acid–catalyzed Diels–Alder reaction is one of the most investigated areas in organic synthesis. Many regio–, chemo–, diastereo–, and enantioselective Diels–Alder reactions catalyzed by various Lewis acids have been studied to present [3,20]. As mentioned in the introduction, the reaction between β -ionone and maleic anhydride takes place in the presence of Lewis acid. The geometries of BH₃–coordinated TSs are depicted in Figure 4, while Table 2 presents the selected geometries parameters corresponding to these TSs.

Table 2. B3LYP/6–31G* Selected Geometry Parameters (Å) and Potential Energy Barriers in (Kcal mol⁻¹) for the Catalyzed DA Cycloaddition of β -Ionone and Maleic Anhydride ($r_1 = C_3-C_{35}$, $r_2 = C_6-C_{36}$, $\Delta r = r_2 - r_1$)

	r_1	r_2	Δr	Ea
TS <i>endo</i>	1.93	3.07	1.14	18.86
TS <i>exo</i>	1.99	2.85	0.86	17.44

The generally accepted mechanism for Lewis acid catalyzed Diels–Alder reactions assumes the formation of a complex between the dienophile and the catalyst. We have considered the coordination of BH₃ to the different oxygen atoms of the maleic anhydride (see Scheme 3) which showed that the most favourable coordination site is the carbonyl oxygen atom O₄₂. We have also considered several conformations corresponding to the rotation around the C₃₇–O₄₂ bond. The geometries presented in Figure 4 are about 3.3 and 1.5 Kcal mol⁻¹ more stable than the other conformations *endo* and *exo* respectively.

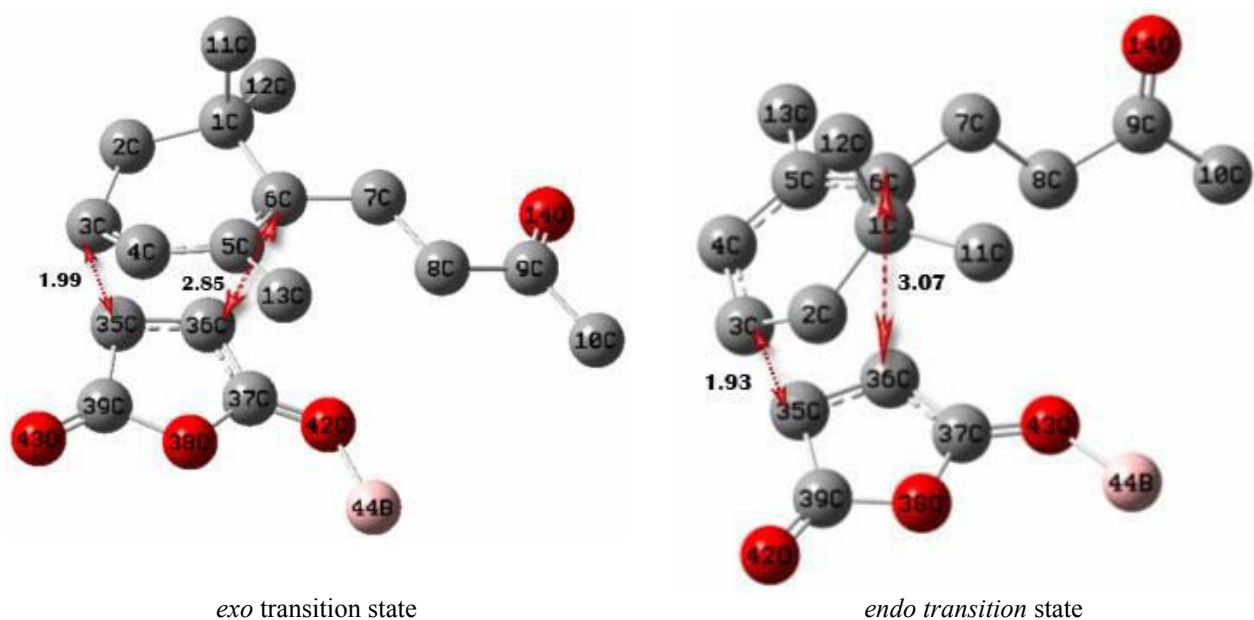
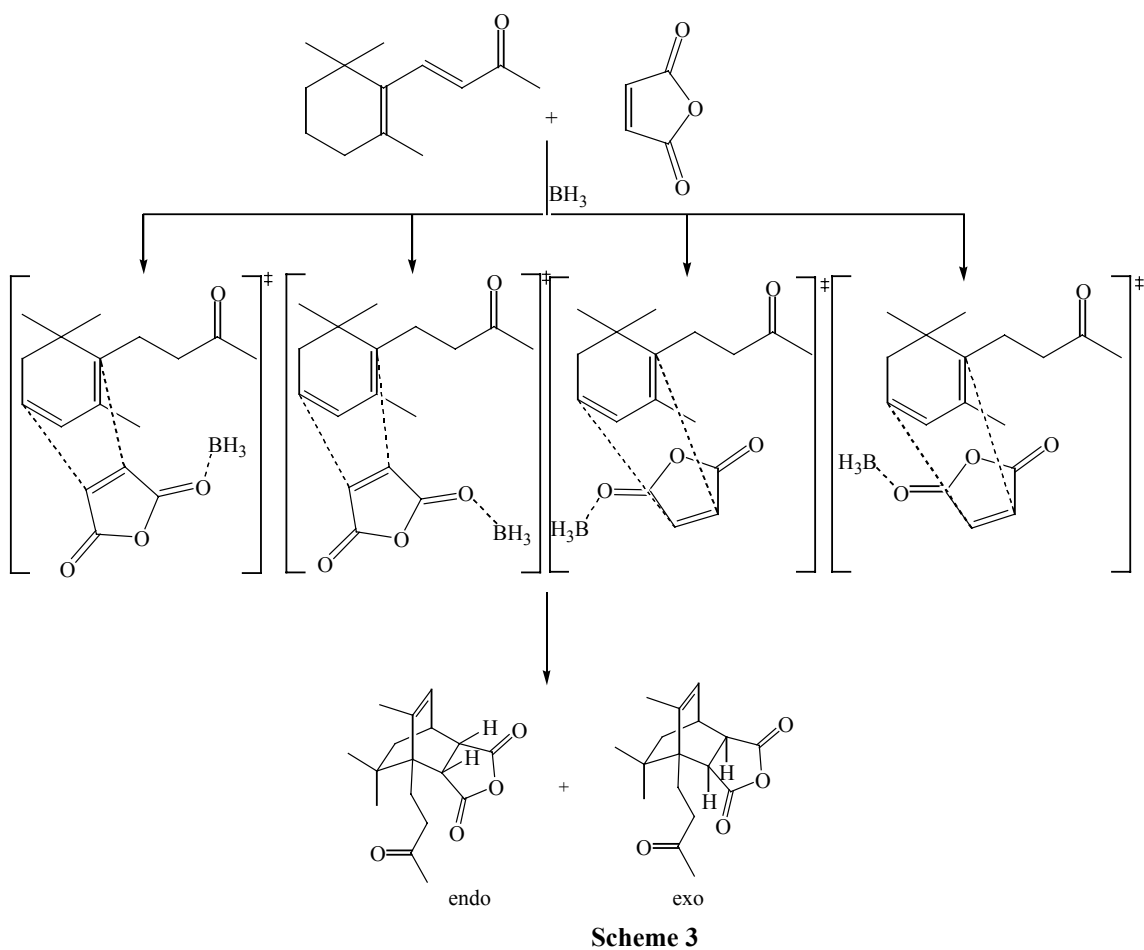


Figure 4. Transitions states corresponding to catalyzed DA reaction between β -ionone and maleic anhydride in gas phase (hydrogen atoms have been omitted for clarity).

If we compare these geometries with the ones corresponding to the uncatalyzed reaction (Table 1), 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 reaction are more asynchronous than those of the uncatalyzed ones. This result has already been observed in other catalyzed Diels–Alder reaction [21] and can be attributed to a polarization of the antibonding π_{C-C} of the dienophile [22].

The potential energies barriers computed at the B3LYP/6–31G* level corresponding to the transition states of the reaction of **1** and **2** for catalyzed reaction are summarized in Table 2. The comparison with those corresponding to the uncatalyzed one (Table 1) shows that the presence of Lewis acid decreases the PEBs for this cycloaddition in the range of 10.8 for *endo* and 3.6 (Kcal/mol) for the *exo* one, so the reaction rates are higher with the addition of this reactant. This behaviour of the Lewis acid catalysts can be understood in terms of a stronger interaction between the $HOMO_{diene} - LUMO_{dienophile}$.

Figure 3 shows the decrease of the $LUMO_{dienophile}$ for the complex. This fact decreases the $HOMO_{diene} - LUMO_{dienophile}$ energy gap, in agreement with the lowering of PES for catalyzed reactions. The MPA shows that the catalyst increases the charge transfer from 0.27 to 0.42 (*endo*) and 0.29 to 0.38 (*exo*). Regarding the stabilities of *endo/exo*, the values listed in Table 1 and 2 show that the catalyst stabilizes through a preference *endo* transition state over the *exo* one. The difference between *exo* and *endo* energy barriers decreases from 6.6 to 1.42 Kcal.mol⁻¹.

The C₅–C₆–C₇–C₈ and C₁–C₆–C₇–C₈ dihedral angles corresponding to the optimized geometry of β -ionone are 45° and –137°, respectively. At the catalyzed transition states, the variations of both dihedral angles with respect to the equilibrium geometry values are, respectively, 55° and 42° for the *endo* transition state, and 17° and 42° for the *exo* one. This steric hindrance due to the ketone group is larger when complex approaches the *endo* face of β -ionone. This larger steric hindrance is translated into geometry distortion of the β -ionone at the transition state. This steric repulsion is also reflected in the value of the C₆–C₃₆ distance in the *endo* transition states (see Table 1 and 2).

The effect of the catalyst on the *endo/exo* selectivity can be also attributed to the change of the conformation of the ketone moiety of β -ionone in the *endo* transition state (Figure 4). Thus the catalyst favours the *s-cis* conformation of the ketone moiety leading to an increase of stabilizing interactions favouring the *endo* transition state.

3.3 Solvent Effect Calculations

Solvent effect on Diels–Alder reactions are well known and have attracted much attention because of the noticeable improvement in reactions achieved by the use of aqueous solvents [23]. Several explanations have been offered to account for the observed solvent effects, such as solvophobicity and enhanced hydrogen bonding to the transition states [24,25].

The *endo/exo* and diastereofacial selectivities are well correlated with polarity parameters for the

solvent used; suggesting that the electrostatic part of the solute–solvent interactions plays an important role [26,27]. In a reaction of Diels–Alder, the role of the solvent has been assumed to be static [28], In other words, its effect is roughly given through the contribution of the solvation energy to the total free energy of the reactants and the transition states. We have then envisaged the study of the reaction of β -ionone with maleic anhydride in different solutions by means of B3LYP/6–31G* calculations. The BH_3 coordinated TSs have been fully used including the solvent effect. Table 3 presents the relative energies corresponding to the TSs of this [4+2] cycloaddition.

Table 3. Potential energies barriers in (Kcal mol^{-1}) for the stationary points of the cycloaddition reaction [4+2] with **1** and **2** ($\Delta \Delta G_{\text{NX}} = \Delta G_{\text{N}} - \Delta G_{\text{X}}$; N= endo; X= exo)

	ΔG_{N}	ΔG_{X}	$\Delta \Delta G_{\text{NX}}$
Gas phase	44.06	37.15	6.58
In solution (CH_2Cl_2)	43.95	36.88	7.00
In solution (CH_2Cl_2) + Catalyst (BH_3)	20.58	19.35	1.22
In solution (MeOH)	43.82	35.77	8.05
In solution (Toluene)	43.71	36.56	7.14

With the inclusion of the solvent effect the TSs are more stabilized relative to those in gas phase. Thus, the solvent effects decrease the barriers in ca. 1–2 Kcal mol^{-1} . The results in Table 3 show that the solvent effects lead to an increase in the *endo/exo* stereoselectivity through a preferential solvation of the *exo* TS over the corresponding *endo* one. The combined effect of the Lewis acid catalyst and solvation on the energy has been investigated for approaching the theoretical study to the experimental conditions. The ordering shows that the *endo* stereoisomer is more stabilized (6 Kcal mol^{-1}) than the *exo* one as shown by free energy of solvation (Table 3). If we compare the effect of different solvent; CH_2Cl_2 , MeOH, and toluene (table 3); we conclude that the polarity of solvent does not induce a clear enhancement of *exo* selectivity for this reaction.

4 CONCLUSIONS

From the present work, we conclude that the [4+2] cycloaddition reaction of the β -ionone with maleic anhydride take place along a highly asynchronous concerted mechanism, and exhibit *exo* selectivity that may be attributed to presumable steric repulsion between this dienophile and the 11C–methyl group of the diene. Consideration of Lewis acid catalysis exemplified here by coordination with BH_3 decreases the activation energies and increases the asynchronicity of the process as well as the charge–transfer from the diene to the dienophile. The inclusion of solvent effect leads to an increase in the *endo/exo* stereo selectivity, through a preferential solvation of the *exo* TS over its corresponding *endo* counterpart. The combined effect of Lewis acid catalyst and solvent decrease the *endo/exo* selectivity.

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