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A DFT Study of the Domino Inter [4 + 2]/Intra [3 + 2] Cycloaddition Reactions of Nitroalkenes with Enol Ethers

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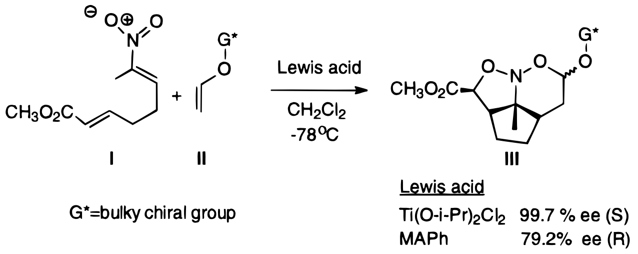
The molecular mechanism of the domino inter [4 + 2]/intra [3 + 2] cycloaddition reactions of nitroalkenes with enol ethers to give nitroso acetal adducts has been characterized using density functional theory methods with the B3LYP functional and the 6-31G* basis set. The presence of Lewis acid catalyst and solvent effects has been taken into account to model the experimental environment. These domino processes comprise two consecutive cycloaddition reactions: the first one is an intermolecular [4 + 2] cycloaddition of the enol ether to the nitroalkene to give a nitronate intermediate, which then affords the final nitroso acetal adduct through an intramolecular [3 + 2] cycloaddition reaction. The intermolecular [4 + 2] cycloaddition can be considered as a nucleophilic attack of the enol ether to the conjugated position of the nitroalkene, with concomitant ring closure and without intervention of an intermediate. For this cycloaddition process, the presence of the Lewis acid favors the delocalization of the negative charge that is being transferred from the enol ether to the nitroalkene and decreases the activation energy of the first cycloaddition. The [4 + 2] cycloaddition presents a total regioselectivity, while the endo/exo stereoselectivity depends on the bulk of the Lewis acid used as catalyst. Thus, for small Lewis acid catalyst, modeled by BH_3, the addition presents an endo selectivity. The [3 + 2] cycloaddition reactions present an total exo selectivity, due to the constraints imposed by the tether. Inclusion of Lewis acid catalyst and solvent effects decrease clearly the barrier for the first [4 + 2] cycloaddition relative to the second [3 + 2] one. Calculations for the activation parameters along this domino reaction allow to validate the results obtained using the potential energy barriers.

Introduction

Domino cycloadditions play a key role in organic syntheses where construction of complex polycyclic structures with an adequate regio- and stereochemical control is needed.[1,2] In this process type, several bonds of the target molecule are formed alongside a continuous sequence of reactions that does not require isolation of intermediates, changes of reaction conditions, or addition of reagents. The interest in this subject is shown by numerous recent reviews.[2−4]

Among domino-type reactions, those involving nitroalkenes have been extensively developed for the stereoselective construction of polycyclic nitrogen-containing compounds.[4] Denmark et al.[5] have recently described the domino reactions of the nitroalkene **I** with the enol ethers **II** in the presence of the Lewis acids, MAPh, or $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ to give the nitroso acetals **III** (see Scheme 1). These domino reactions take place with a total regioselectivity and with a high stereoselectivity to obtain mainly a final cycloadduct along with formation of six stereogenic centers, three of which are controlled by the outcome of the first cycloaddition. The bulk of the Lewis acid together with the use of a bulky chiral enol ether determine the *endo/exo* stereoselectivity for the first [4 + 2] cycloaddition.

Scheme 1



Despite the obvious potential of these domino processes and its many variations, the reaction pathways have not been theoretically studied so far. A deep knowledge of the molecular mechanism is fundamental, however, for a rationalization of the experimental results.

The structural information obtained by theoretical methods based on quantum mechanical calculations of possible intermediates and transition structures (TSs) provide powerful assistance for the study of organic reaction mechanisms.[6] These methods are accepted as available tools for the interpretation of experimental results, since such data are rarely available from experiments.[6d]

Recently, we have described a PM3 semiempirical study for the domino reaction of the nitroalkene **IV** with the silylvinyl ether **V** to give the nitroso acetal **VI** (see Scheme 2).[7] For this domino reaction, the presence of both silyl and methyl ether in the alkene system increase the

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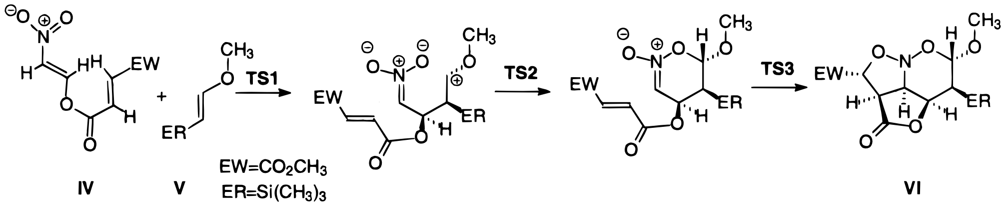
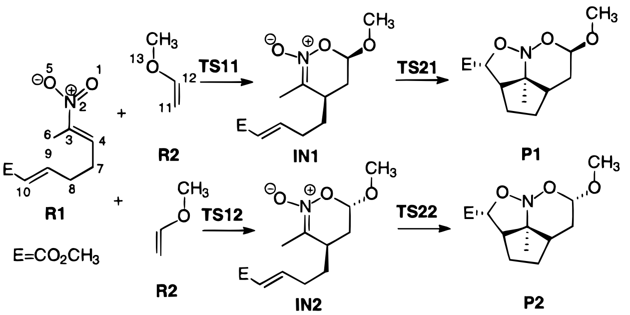
Scheme 2



Scheme 3



nucleophilic character of the silylvinyl ether, allowing a stepwise mechanism for the first cycloaddition, which is enhanced with the inclusion of Lewis acid catalyst and solvent effects. Moreover, the use of a nonchiral methyl enol ether together a small Lewis acid catalyst, Al(CH$_3$)$_3$, afford a large endo selectivity.

The intermolecular [4 + 2] cycloaddition of nitroethene with electron-rich alkenes has been recently studied by us.[8] This study points out that the cycloaddition can be considered as a nucleophilic attack of the enol ether to the nitroalkene with concomitant ring closure instead of a concerted process along a pericyclic mechanism. For these cycloadditions, the reactivity and the *ortho/endo* selectivity increase with the electron-releasing character of the substituent on the alkene. On the other hand, the facial selectivity of the intermolecular [3 + 2] cycloaddition of ethene to cyclic nitronates has been recently studied by Denmark et al.[9]

In the present paper, a density functional theory (DFT) study for the domino inter [4 + 2]/intra [3 + 2] reaction of the nitroalkene **R1** with the enol ether **R2** to yield the nitroso acetal adducts **P1** and **P2** is carried out (see Scheme 3). Our purpose is to contribute to a better mechanistic understanding of this sort of domino processes, specially by characterization of the stationary points on the reactive potential energy surface (PES). The effect of both Lewis acid and polar solvents have been included in the study.

Computing Methods and Models

In recent years, theoretical methods based on the density functional theory[10] have emerged as an alternative to traditional ab initio methods in the study of structure and reactivity of chemical systems. Diels–Alder reactions and related reactions have been the object of several density functional studies showing that functionals that include gradient corrections and hybrid functional, such as B3LYP, together with the 6-31G* basis set, lead to potential energy barriers (PEBs) in good agreement with the experimental results.[11] Thus, in the present study, geometrical optimizations of the stationary points along the PES were carried out using the gradient corrected functional of Becke and Lee, Yang, and Parr (B3LYP)[12] for exchange and correlation, with the standard 6-31G* basis set.[13] The stationary points were characterized by frequency calculations in order to verify that minima and transition structures have zero and one imaginary frequency, respectively. The optimizations were carried out using the Berny analytical gradient optimization method.[14] The transition vectors (TV),[15] i.e., the eigenvector associated to the unique negative eigenvalue of the force constants matrix, have been characterized. All calculations were carried out with the Gaussian 98 suite of programs.[16]

We have used the simplified model **R2** instead of chiral enol ether **II**. In Denmark's enol ether **II**, the bulky chiral appendage has been replaced for a nonchiral methyl group. Optimized geometries of all structures are available from the authors. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[17]

As is known, the use of Lewis acids can lead to significant changes in the nature of the molecular mechanism in comparison with the uncatalyzed process. This fact has led to a huge amount of experimental work, in which a wide variety of this type of catalysts have been employed.[18] The effect of catalysts in DA reactions has also been the object of several

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semiempirical[7,19] and ab initio[8,20] theoretical studies. These works predict that the catalyst produce a notable increase in the asynchronicity of the TS. Experimentally, the reactions between nitroalkenes and alkenes or enol ethers are usually performed in the presence of Lewis acids. In our study, these domino reactions are catalized by MAPh, an aluminum derivative with 69 atoms, or Ti(O-*i*-Pr)$_2$Cl$_2$.[5] However, the large model system of this domino reaction together with the bulk of these Lewis acids prevent the DFT study of the real catalyst models. Thus, the role of the acidic catalyst on the molecular mechanism has been studied using BH_3 as a Lewis acid model.[8] This system has been used by different authors for modeling the presence of Lewis acids with good results.[21] Moreover, the results obtained for this BH_3 catalized domino reaction are closer to those obtained for the PM3 study of the reaction between the nitroethene **IV** and the silylvinyl ether **V**, using Al(CH$_3$)$_3$ as Lewis catalyst.[7]

The vast majority of chemical reactions are performed in solution, and as solvent effects can yield valuable information about the reaction mechanism, the need to increase our knowledge about interactions between solvent and solute remains crucial. The solvent effects have been considered by B3LYP/6-31G* optimizations of stationary points using a relatively simple self-consistent reaction field (SCRF)[22] method, based on the polarizable continuum model (PCM) of the Tomasi's group.[23] In this procedure, the solvent is assimilated to a continuous medium characterized by the dielectric constants (ϵ) that surrounds a molecular-shaped cavity in which the solute is placed. As the solvent used in the experimental work is dichloromethane we have used its dielectric constant, $\epsilon = 8.93$.[24] This methodology has been successfully used for the study of related cycloaddition reactions.[25]

Finally, values of relative enthalpies, entropies and free energies have been estimated by means of the B3LYP/6-31G* potential energy barriers along with the harmonic frequencies. These frequencies have been scaled by 0.96. The activation free energies have been computed at −78 °C, which is the experimental temperature.[5] The enthalpy and entropy changes are calculated from standard statistical thermodynamic formulas.[13,26] These calculations have been carried out including the Lewis acid catalyst and the solvent effect.

Results and Discussion

(a) Gas-Phase Calculations. The domino reaction between **R1** and **R2** can take place along two competitive reactive channels that involve two consecutive cycloaddition reactions (see Scheme 3). The first processes are intermolecular [4 + 2] cycloadditions between **R1** and **R2** in two stereoisomeric possibilities to give two nitronate intermediates, **IN1** and **IN2**, while the second ones are intramolecular [3 + 2] cycloadditions of these intermediates to give the final nitroso acetal adducts **P1** and **P2**.

Table 1. Total Energies (au) and Relative Energies[a] (kcal/mol, in Parentheses) for the Stationary Points of the Domino Reactions between the Nitroalkene R1 and the Enol Ether R2

	B3LYP/6-31G*	
R1	−706.315 704	
R2	−193.110 423	
TS11	−899.402 569	(14.8)
TS12	−899.397 873	(17.7)
TS13	−899.378 395	(30.0)
TS14	−899.375 561	(31.7)
IN1	−899.454 098	(−17.6)
IN2	−899.462 802	(−23.0)
TS21	−899.425 034	(0.7)
TS22	−899.424 977	(0.7)
TS23	−899.413 156	(8.1)
TS24	−899.413 123	(8.2)
P1	−899.472 845	(−29.3)
P2	−899.470 080	(−27.6)

[a] Relative to **R1** + **R2**.

For the first intermolecular [4 + 2] cycloaddition, four attack modes have been considered corresponding to the endo and exo approaches of the methyl vinyl ether **R2** to nitroalkene **R1** in two regioisomeric possibilities: the ortho (head-to-head) and the meta (head-to-tail) ones. However, the larger energies obtained for the meta channels relative to the ortho ones, ca. 15 kcal/mol, allow us to discard the study of these regioisomeric possibilities for this domino reaction (see Table 1). Consequently, two TSs have been considered, **TS11** and **TS12**, corresponding to the endo and exo attack modes of the ortho approaches.

For the second intramolecular [3 + 2] cycloadditions, two stereoisomeric attack modes are possible for each intermediate. These attack modes are related to endo and exo approaches of the unsaturated carboxylic ester to the nitronate group. However, the endo approaches are ca. 7 kcal/mol more energetic that the exo ones, due to the constraints imposed by the tether (see Table 1).[9] This fact allows us to discard the study of the endo attack modes. Thus, two TSs have been considered for the second processes of this domino cycloaddition, **TS21** and **TS22**, corresponding to the exo approach of the unsaturated ester to the nitronate group on the intermediates **IN1** and **IN2**, respectively. The total and relative energies of the different stationary points along this domino reaction are presented in Table 1, while Figure 1 presents the geometries of the TSs.

The PEBs associated with the first intermolecular cycloaddition along **TS11** and **TS12** are 14.8 and 17.7 kcal/mol, respectively, the endo channel being the most favorable one. Thus, the first processes in the gas phase present a large endo stereoselectivity.[8] These intermolecular cycloadditions that are conducive to the formation of a pair of diastereomeric nitronates, **IN1** and **IN2**, are very exothermic processes, −17.6 and −23.0 kcal/mol, respectively. The larger stability of **IN2** relative to **IN1** is due to an anomeric effect that appears between the O1 oxygen atom of the nitronate group and the O13

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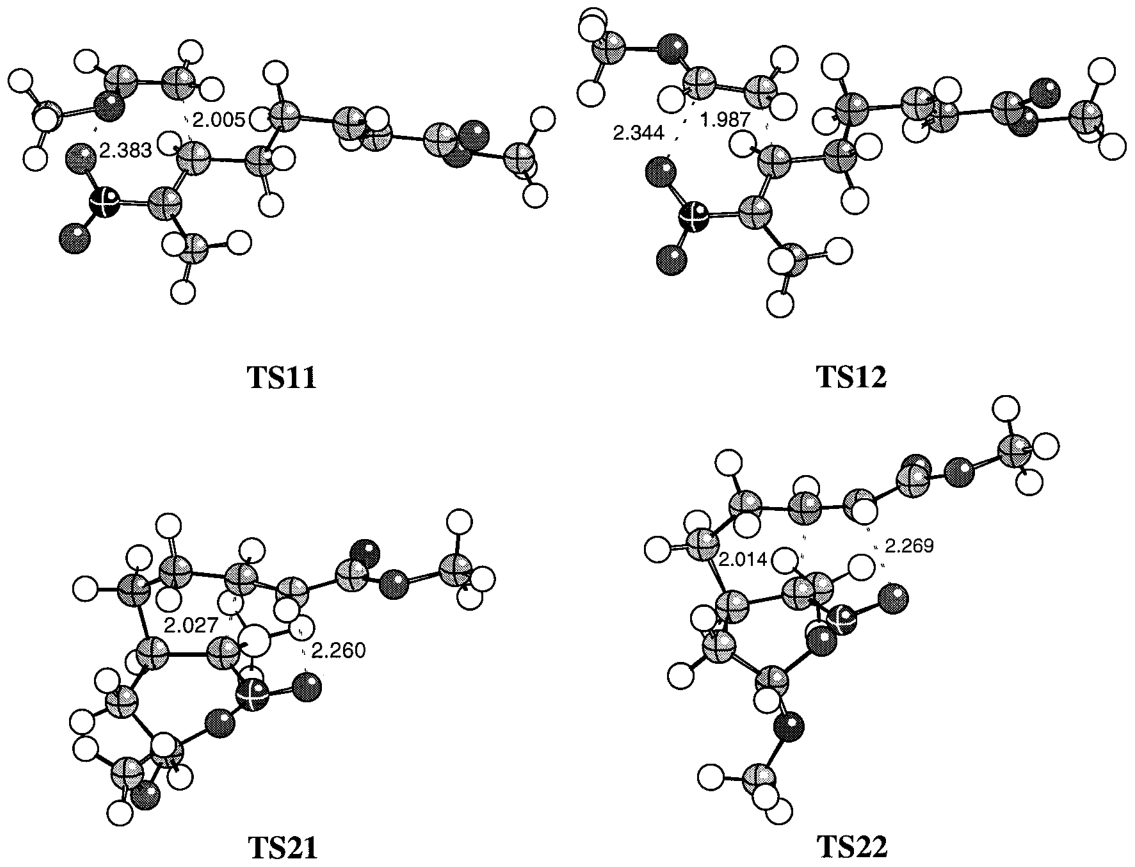

Figure 1. Transition structures corresponding to the uncatalyzed domino reaction between the nitroalkene **R1** and the enol ether **R2**. The values of the bond lengths directly involved in the processes are given in angstroms.

oxygen atom of the methyl ether, which destabilizes the equatorial arrangement of the methyl ether present in **IN1**.[27]

These intermediates, after the corresponding conformational interconversions, carry out the intramolecular [3 + 2] cycloaddition reactions to give the final cycloadducts **P1** and **P2**. Although along these cycloadditions three chiral centers are formed, the constraints imposed by the tether[9] allow the formation of only one isomeric cycloadduct from each intermediate. The PEBs associated with the second intramolecular cycloaddition along **TS21** and **TS22** are 18.3 and 23.7 kcal/mol, respectively. Formation of **P1** and **P2** along this domino reaction are very exothermic processes, −29.3 and −27.6 kcal/mol, respectively.

For the intermolecular [4 + 2] cycloaddition, the length of the C4−C11 forming bond (2.005 and 1.987 Å, for **TS11** and **TS12**, respectively) and the length of the O1−C12 forming bond (2.383 and 2.344 Å, for **TS11** and **TS12**, respectively) indicate that these cycloadditions are asynchronous processes.[8]

For the intramolecular [3 +2] cycloaddition, the length of the C3−C9 forming bond (2.027 and 2.014 Å, for **TS21** and **TS22**, respectively) and the length of the O5−C10 forming bond (2.260 and 2.269 Å, for **TS21** and **TS22**, respectively) show a smaller asynchronicity in the bond formation than for the intermolecular [4 + 2] cycloadditions.

The extent of the asynchronicity for these cycloadditions can be measured by means of the difference between the distances of the two σ-bonds that are being formed in the reaction, indicating that the first [4 + 2] cycloadditions are more asynchronous processes than the second [3 + 2] ones.

Table 2. Wiberg Bond Orders at the Transition Structures TS11, TS12, TS21, and TS22

	TS11	TS12		TS21	TS22
O1−N2	1.26	1.25	N2−O5	1.37	1.14
N2−C3	1.23	1.21	N2−C3	1.21	1.22
C3−C4	1.21	1.22	O5−C10	0.27	0.31
O1−C12	0.17	0.17	C3−C9	0.46	0.46
C4−C11	0.68	0.66	C9−C10	1.43	1.41
C12−O13	1.18	1.15			

A more balanced measure of the extent of bond formation or bond breaking processes along a reaction pathway is provided by the concept of bond order (BO). This theoretical tool has been used to study the molecular mechanism of chemical reactions.[28] Values of the BO can be used to evaluate the asynchronicity of the bond formation processes, and it allows us to understand the nature of the cycloaddition processes. Thus, the Wiberg bond indices[29] have been computed by using the NBO analysis as implemented in Gaussian 98. The results are given in Table 2.

Analysis of the BO values for the C4−C11 (0.68 and 0.66, for **TS11** and **TS12**, respectively) and O1−C12 (0.17 and 0.17, for **TS11** and **TS12**, respectively) forming bonds

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for the intramolecular [4 + 2] cycloadditions indicate that these processes are very asynchronous. While the C4−C11 bond formation processes are very advanced in these TSs, the O1−C12 ones are not at all. This analysis also indicates that the most favorable endo TS is slightly more advanced and more asynchronous than the exo one. The BO values of the C12−O13 single bond (1.18 and 1.15 for **TS11** and **TS12**, repectively) indicate a π-delocalization of the lone pair of the O13 oxygen atom at these TSs, what increases the nucleophilic character of the dienophile.[8]

For the [3 + 2] cycloadditions, the BO values of the O5−C10 (0.27 and 0.31, for **TS21** and **TS22**, respectively) and C3−C9 (0.46 and 0.46, for **TS21** and **TS22**, respectively) forming bonds indicate that these [3 + 2] cycloadditions are less asynchronous and earlier processes than the [4 + 2] ones.

The natural population analysis for these TSs allows us to understand the electronic nature of these cycloadditions processes. The atomic charges in the TSs corresponding to the [4 + 2] cycloadditions have been shared by both the donor enol ether and the acceptor nitroalkene system, while for the TSs corresponding to the [3 + 2] cycloadditions have been shared by fragmentation of the TSs along the C7−C8 single bond.[30]

The values of the charge transferred at **TS11** and **TS12** from dienophile to heterodiene system are 0.40 and 0.38 e, respectively, while the charge transferred at **TS21** and **TS22** from dipole to dipolarophile system are 0.07 and 0.08 e, respectively. The large values found for the TSs corresponding to the [4 + 2] cycloadditions indicate that they have a large zwitterionic character.[8] Thus, both BO and transfer charge analysis indicate that the [4 + 2] cycloaddition processes between the nitroalkene and the enol ether can be undertaken as a nucleophilic attack of the β carbon of the enol ether to the conjugated position of the nitroalkene, with concomitant ring closure and without participation of zwitterionic intermediates to give the corresponding nitronates.[8] Moreover, the slightly larger transfer charge at **TS11** than at **TS21** points out the favorable interaction that appears along the endo approach.[8] The lower charge transferred along the second cycloadditions, together the lower asynchronicity of the processes, indicate that these 1,3 dipolar cycloadditions are associated with pericyclic processes where the HOMO, associated mainly with the dipole nitronate residue, interacts with the LUMO, associated mainly with unsaturated ester fragment, along the intramolecular concerted processes.[7]

For the [4 + 2] cycloadditions, the dominant TV components correspond to the O1−C12 and C4−C11 bond distances, while for the [3 + 2] cycloadditions the dominant TV components correspond to the O5−C10 and C3−C9 bond distances. These distances are associated with the two σ-bonds that are being formed in these cycloaddition processes. The imaginary frequency values for **TS11**, **TS12**, **TS21**, and **TS22** are 426i, 440i, 433i, and 420i cm^{-1}, respectively. These low values indicate that these TSs are associated with the motion of heavy atoms. Moreover, for the [4 + 2] cycloadditions, the most favorable endo TS presents a lower value than the exo one. The previously discussed asynchronicity in the bond formation for the [4 + 2] cycloaddition processes is also confirmed by the fact that the imaginary frequencies of **TS11** and **TS12** have a larger participation on the motion of the C4−C11 forming bond than for the O1−C12 one.

(b) Effects of Lewis Acid Catalyst. As was stated in the Introduction, the domino reactions between the nitroalkenes and enol ethers take place in the presence of Lewis acids. So our next step was the study of the role of Lewis acid on these domino cycloadditions, using borane (BH_3) as a model system of the Lewis acid catalysts (see Computing Methods and Models). The BH_3 can be coordinated to an oxygen atom of the nitro group belonging to the nitroalkene **R1** in an endo or exo orientation. Previous calculations of DA reactions rendered that the exo BH_3-coordinated is favored over the endo one.[20g]

The stationary points along the two reactive channels studied in gas phase were optimized coordinating the BH_3 to one oxygen atom of the nitro or nitronate groups. Thus, one reactant, **R1-B**, two intermediates, **IN1-B** and **IN1-B**, two cycloadducts, **P1-B** and **P2-B**, and four TSs, **TS11-B**, **TS12-B**, **TS21-B**, and **TS22-B**, have been considered. The geometries of BH_3-coordinated TSs are depicted in Figure 2, while Table 3 presents the values of the total and relative energies corresponding to these BH_3-coordinated stationary points.

The presence of Lewis acid decreases the PEBs for the first [4 + 2] cycloadditions in 6.6 and 8.3 kcal/mol, compared with those for the uncatalyzed processes. This behavior of the Lewis acid catalysts has been found in the [4 + 2] cycloaddition reaction between nitroethene and methyl vinyl ether,[8] and it can be understood from a frontier molecular orbital (FMO) analysis in terms of a stronger interaction between the $HOMO_{dienophile}$−$LUMO_{heterodiene}$. These [4 + 2] cycloadditions can be considered as inverse electron demand Diels−Alder reactions. The presence of BH_3 coordinated to nitroalkene decreases the $LUMO_{heterodiene}$ energy, and therefore, there is a decrease of the $HOMO_{dienophile}$−$LUMO_{heterodiene}$ energy gap, which is in agreement with the lowering of PEBs for the catalyzed reactions.[8]

There is a more noticeable change on structural features for the BH_3-coordinated TSs. The Lewis acid catalyst enhances significantly the asynchronicity of the endo TS, due to the increase of the O1−C12 distance. Thus, the values of the geometrical asynchronicity, Δr, for **TS11-B** and **TS12-B** are 0.50 and 0.35, respectively. This fact is also observed in the BO analysis, where a slightly decrease of the O1−C12 BO is observed.

The NPA at **TS11-B** and **TS12-B** shows a decrease of charge transfer (0.05e) from the enol ether to BH_3-coordinated nitroalkene relative to uncatalyzed processes. However, the most noticeable effect of the Lewis acid catalyst is the delocalization of the negative charge that is being transferred at TSs. A partial charge analysis at **TS11-B** and **TS12-B** shows that the BH_3 fragment accepts 0.29 e from the 0.35 and 0.33 e transferred from the enol ether to the nitroalkene. This fact allows a stabilization of the corresponding TSs, lowering the PEBs associated with these cycloadditions and increasing the asynchronicity of the processes. Thus, the role of the Lewis acid catalyst can be understood as an increase of the electrophilic character of the nitroethene due to a stabilization of the corresponding TS through a delocalization of the negative charge that is being transferred along the nucleophilic attack of the enol ether.

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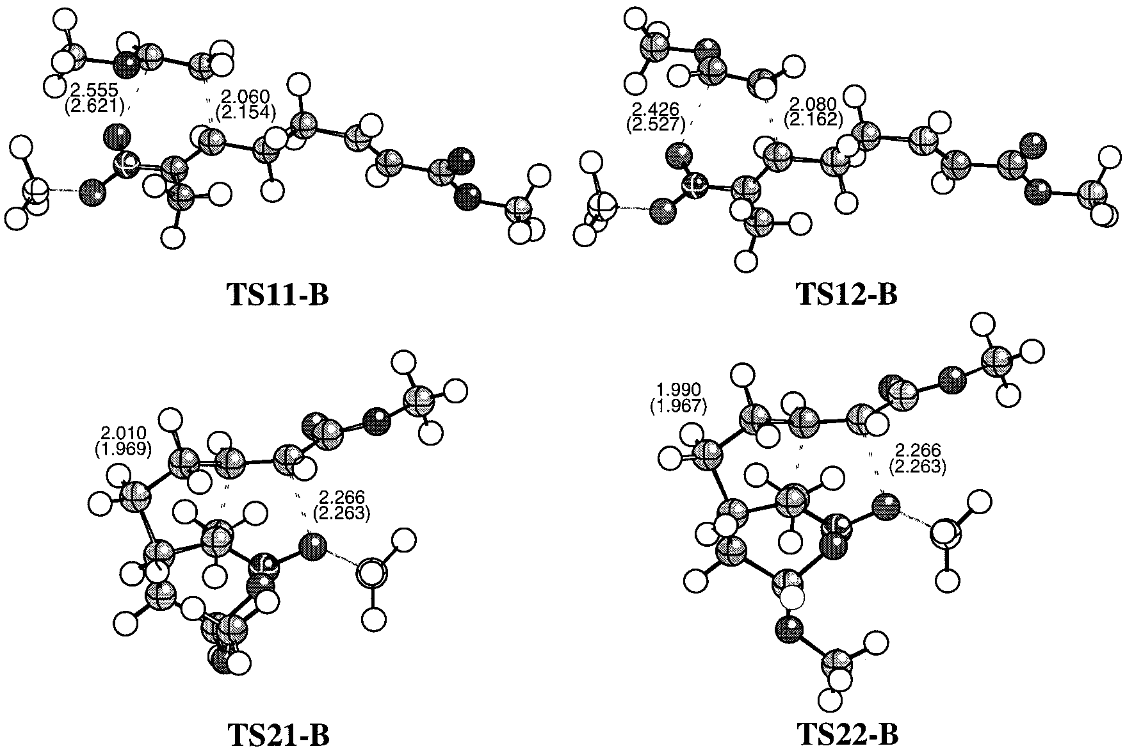
[30] This sharing for **IN1** and **IN2** gives a total charge for each fragment of ca. 0.0 e.



TS11-B **TS12-B**

TS21-B **TS22-B**

Figure 2. Transition structures corresponding to the BH_3-catalyzed domino reaction between the nitroalkene **R1** and the enol ether **R2**. The values of the bond lengths directly involved in the processes are given in angstroms. The values in parentheses correspond to the reaction in dichloromethane.

Table 3. Total Energies (au) and Relative Energies (kcal/mol, in Parentheses) for the Stationary Points of the Catalyzed Domino Reactions between the BH_3-Coordinated Nitroalkene R1 and Enol Ether R2, in Vacuo, B,[a] and in Dichloromethane, S[b]

	B3LYP/ 6-31G*			B3LYP/ 6-31G*	
R1-B	−732.954 594		**R1-S**	−732.966 770	
R2	−193.110 423		**R2-S**	−193.112 393	
TS11-B	−926.051 933	(8.2)	**TS11-S**	−926.068 890	(6.4)
TS12-B	−926.050 058	(9.4)	**TS12-S**	−926.067 217	(7.5)
IN1-B	−926.094 606	(−18.6)	**IN1-S**	−926.117 622	(−24.1)
IN2-B	−926.105 616	(−25.5)	**IN2-S**	−926.123 975	(−28.1)
TS21-B	−926.062 756	(1.4)	**TS21-S**	−926.078 237	(0.6)
TS22-B	−926.072 193	(−4.5)	**TS21-S**	−926.084 181	(−3.1)
P1-B	−926.104 355	(−24.7)	**P1-S**	−926.117 635	(−24.1)
P2-B	−926.112 260	(−29.6)	**P2-S**	−926.122 747	(−27.3)

[a] Relative to **R1-B** + **R2**. [b] Relative to **R1-S** + **R2-S**.

For the intramolecular [3 + 2] cycloadditions the presence of Lewis acid increases the PEB for **TS21-B** in 2.7 kcal/mol, while for **TS22-B** is similar to that found for the uncatalyzed process. The behavior of the Lewis acid catalyst in the intramolecular [3 + 2] cycloaddition reactions is similar to that found in the domino reaction between the nitroethene **IV** and the silyl vinyl ether **V** in the presence of $Al(CH_3)_3$,[7] and it can be understood by a FMO analysis. The 1,3 dipolar cycloaddition reactions of nitrone with unsaturated esters are controlled by a strong $HOMO_{dipole}-LUMO_{dipolarofile}$ interaction.[9] For this intramolecular [3 + 2] cycloaddition the HOMO, mainly associated to the nitronate group, interact with the LUMO, mainly associated to the unsaturated ester. Thus, the presence of BH_3 coordinated to nitronate group decreases the $HOMO_{dipole}$ energy; this fact increases the $HOMO_{dipole}-LUMO_{dipolarophile}$ energy gap and, consequently, increases of PEBs for the second step of these catalyzed reactions.[7]

(c) Study of the Solvent Effects. Solvent effects on [4 + 2] cycloadditions are well-known[31] and have received considerable attention, especially in the past few years, because these studies can clarify the role of the solvent on related pericyclic reactions.[7,8,32] The next step in our investigation was to study the solvent effects on the basic features of the molecular mechanism for these domino cycloadditions. The geometries of these TSs, including the selected geometrical parameters are depicted in Figure 2, while Table 3 presents the relative energies. In Figure 3a, the potential energy profiles for this domino reaction are presented.

The inclusion of the solvent effects appears to be quantitatively significant. Solvent effects decrease the energies of all stationary points along the domino reaction between 7 and 12 kcal/mol relative to the gas-phase calculations. This stabilization is larger for the TSs and intermediates corresponding to the [4+2] cycloadditions than for the [3 + 2] ones, because of the larger polar character of the former process. In consequence, while the PEBs for **TS11-S** and **TS12-S** decrease to 6.6 and 7.5 kcal/mol, for **TS21-S** and **TS22-S** they increase to 23.1 and 24.9 kcal/mol, respectively, due to a larger stabilitation of intermediates than the TSs of the second stage.

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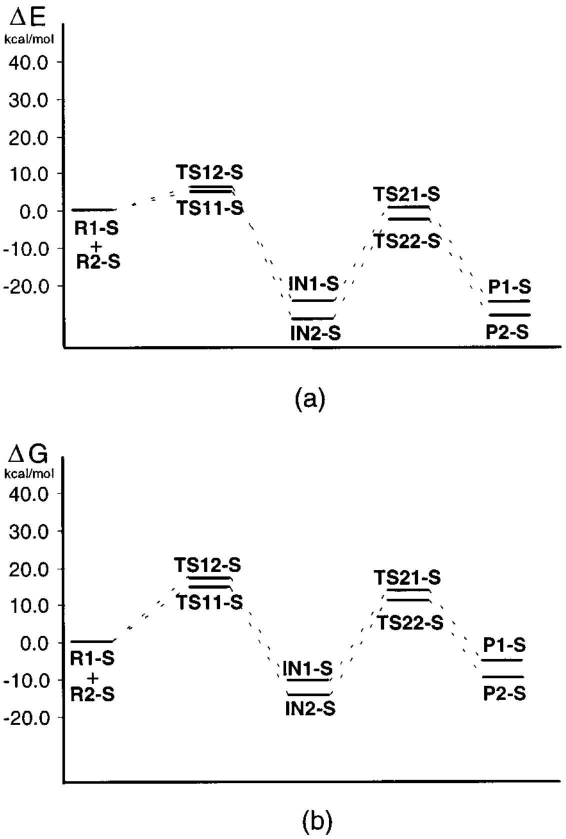

Figure 3. Energy profiles for the domino reactions between the nitroalkene **R1-S** and the enol ether **R2-S**, including Lewis acid catalyst and solvent effects: (a) potential energies and (b) free energies at −78 °C.

Moreover, the inclusion of solvent effects does not modify the *endo/exo* stereoselectivity found in the first cycloaddition of this domino reaction, which experimentally is controlled by the bulk of both Lewis acid catalyst and the quiral substituent on the enol ether.[5b] Finally, a comparison of the geometrical parameters given in Figure 2 shows that the inclusion of solvent effects on the geometry optimization increases ca. 0.1 Å the lengths of the two σ forming bonds along the [4 + 2] cycloadditions relative to the gas-phase geometries; for the [3 + 2] cycloadditions there is not a substantial change.

(d) Study of the Kinetic and Thermodynamic Parameters. Finally, the values of the relative enthalpies, entropies, and free energies, corresponding to the two reactive channels, including the Lewis acid catalyst and solvent effects, have been estimated by means of the potential energy computed at the B3LYP/6-31G* level with inclusion of solvent effects along with the B3LYP/6-31G* gas-phase harmonic frequencies. The free energies have been computed at −78 °C, which is the experimental temperature for these domino reactions.[5] The energetic results are summarized in Table 4, while the free energy profiles are presented in Figure 3b.

The most relevant feature of the free energy profiles relative to the potential energy profiles, Figure 3b relative to Figure 3a, is the increase of the relative free energies due to the intramolecular nature of the first cycloaddition. Moreover, although the first cycloadditions present lower activation free energies than the second ones, the latter have lower relative free energies than the former, 0.8 and 4.9 kcal/mol, justifying the domino character of these reactions.

Table 4. Relative[a] Enthalpies (Δ*H*, in kcal/mol), Entropies (Δ*S*, in kcal/mol·K), and Free Energies (Δ*G*, in kcal/mol) Computed at −78 °C and 1 Atm for the Domino Reactions between the BH$_3$-Coordinated Nitroalkene R1 and the Enol Ether R2 Including Solvent Effects

	Δ*H*	Δ*S*	Δ*G*
TS11	7.5	−48.3	16.9
TS21	8.5	−47.8	17.9
IN1	−21.0	−54.7	−10.3
IN2	−24.9	−56.6	−13.8
TS12	3.6	−64.2	16.1
TS22	0.0	−66.7	13.0
P1	−19.4	−69.2	−5.9
P2	−22.5	−68.7	−9.1

[a] Relative to **R1-B** + **R2**.

A different behavior is found with the inclusion of the zero-point energy and thermal contributions to the potential energy barriers for the two modes of cycloaddition reactions. While for the [4 + 2] cycloadditions the activation enthalpies increase ca. 1 kcal/mol relative to the PEB, for the [3 + 2] ones there is not an appreciable modification.

The relative entropies play a more relevant role to the changes of the free energies along this domino reaction. While for the intermolecular processes the activation entropies are −48.3 and −47.8 kcal/mol·K, for the intramolecular ones are −9.7 and −10.1 kcal/mol·K. These results are similar to those found in related inter and intramolecular cycloadditions, and are responsible for the increase of the activation free energies relative to the PEBs, that is larger for the intermolecular one.

A comparison of the relative free energies for the two intermolecular [4 + 2] cycloadditions shows that the calculated activation parameters do not modify the selectivity found in this domino reaction.

The changes of free energy for the formation of **P1-S** and **P2-S** along this domino reaction are −5.9 and −9.1 kcal/mol, respectively; both processes being very exothermic: −19.4 and -22.5 kcal/mol, respectively. We again find that the decrease of the free energy for the global process is mainly a consequence of the decrease of the entropy along the first cycloadditions.

Conclusions

The molecular mechanism of the domino inter [4 + 2]/intra [3 + 2] cycloaddition reactions of nitroalkenes with enol ethers to give nitroso acetal adducts has been characterized using density functional theory methods with the B3LYP functional and the 6-31G* basis set. Both Lewis acid catalyst, modeled by BH$_3$, and solvent effects have been included in this study in order to take into account the experimental environment.

This domino process comprises two consecutive cycloaddition reactions: the first one is an intermolecular [4 + 2] cycloaddition of the enol ether to the nitroalkene to give a nitronate intermediate, whereas the second one is an intramolecular [3 + 2] cycloaddition to afford the final nitroso acetal adduct.

The intermolecular [4 + 2] cycloaddition can be considered as a nucleophilic attack of the enol ether to the conjugated position of the nitroalkene, with concomitant ring closure and without intervention of an intermediate. For this process, the presence of a Lewis acid coordinated to the nitro group favors the delocalization of the negative charge that is being transferred from the enol ether to the nitroalkene and decreases the activation energy of the cycloaddition process. The [4 + 2] cycloaddition presents a total regioselectivity, while the endo/exo stereoselectivity depends on the bulky of the Lewis acid catalyst. Thus, for small Lewis acid catalyst the addition presents an endo selectivity. The [3 + 2] cycloaddition reaction presents a total exo selectivity, due to the constraints imposed by the tether. Inclusion of Lewis acid catalyst and solvent effects decrease the barrier for the first [4 + 2] cycloaddition and increase that for the second [3 + 2] one due to a large stabilization of the intermediate.

Finally, calculations for the activation parameters along this domino reaction allow to validate the results obtained using the potential energy barriers in the study of the selectivity of these domino reactions.

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