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Understanding the role of the Lewis acid catalyst on the 1,3-dipolar cycloaddition of *N*-benzylideneaniline *N*-oxide with acrolein: a DFT study

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Abstract—The Lewis acid (LA) catalyzed 1,3-dipolar cycloaddition of *N*-benzylideneaniline *N*-oxide with acrolein has been studied using DFT calculations. Coordination of $AlCl_3$ to the acrolein oxygen atom produces a drastic change in the mechanism along the more favorable *meta* reactive channel. The process is characterized by a strong nucleophile/electrophile interaction allowing the formation of a zwitterionic intermediate, a Michael-type addition. The subsequent ring closure constitutes the rate-determining step. The energies obtained with the inclusion of solvent effect by means of the polarizable continuum model are in good agreement with experimental findings. Analysis of the global and local electrophilicity allows to explain correctly the reactivity and regioselectivity of the LA catalyzed cycloaddition.

1. Introduction

The 1,3-dipolar cycloaddition (13DC) offers a versatile route for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds[1] and also for the synthesis of natural products.[2] High stereospecificity and stereoselectivity are the reasons why these reactions are synthetically so useful in organic synthetic field.[3] Several theoretical treatments have been devoted to the study of regio- and stereoselectivities of 13DC reactions of nitrones with substituted alkenes.[4] Whether the 13DC reaction proceeds through a concerted mechanism or a stepwise mechanism is a question. This question has been rarely answered.[5] During the last years, several computational studies have been reported to understand the origin of the mechanism of this reaction[6] and the effect of Lewis acid (LA) catalysts.[7] Jørgensen et al. have reported semiempirical calculations of the magnesium catalyzed nitrone cycloaddition reactions to α,β-unsaturated carbonyl acceptors.[8] Tanaka and Kanemasa[9] have performed an ab initio study, at the HF/6-31G++G(d,p) level of theory, of the 13DC reaction of nitrones with acrolein in the presence of BH_3 and BF_3 catalysts[9] and showed that the nitrone cycloaddition reaction with electron-deficient alkenes may occur through a stepwise mechanism when catalyzed by a strong LA. Other experimental studies on the rate and selectivity of 13DC reactions of nitrones with α,β-unsaturated carbonyl compounds can be found in the literature.[10,11] The use of LA catalysts in modern organic synthesis has been expanding uninterruptedly during the last decade.[12] The use of metal catalysts in asymmetric 13DC reactions of nitrones with electron-rich[13] and electron-deficient alkenes[14] remained an unexplored area until recently. When electron-deficient alkenes such as α,β-unsaturated carbonyl compounds are activated by coordination to a LA catalyst, the carbon–carbon double bond of the alkene should be highly polarized and the electrophilicity of the β-carbon should be increased. In 13DC reactions of α,β-unsaturated carbonyl acceptors activated by a LA, the nucleophilic attack of the dipole is kinetically favored. As a result, it is to be expected that the bond formation at the β-carbon of the dipolarophile would take place preferentially with respect to that at the α-carbon.[9,15]

Kanemasa et al.[16] did important pioneering work in this field, although the reactions performed were racemic. Experimentally, the same methods demonstrated that a catalytic amount of aluminum tris (2,6-diphenylphenoxide), designated as ATPH, catalyses cycloaddition reaction between *N*-benzylideneaniline *N*-oxide **1** and α,β-unsaturated carbonyl acceptors as acrolein **2**, and induces a dramatic rate enhancement showing high to exclusive control of regioselectivity in favor of the formation of the isoxazolidine-4-carboxaldehyde **3** (see Scheme 1). According to Kanemasa et al.,[17] in the case of catalyzed reactions via

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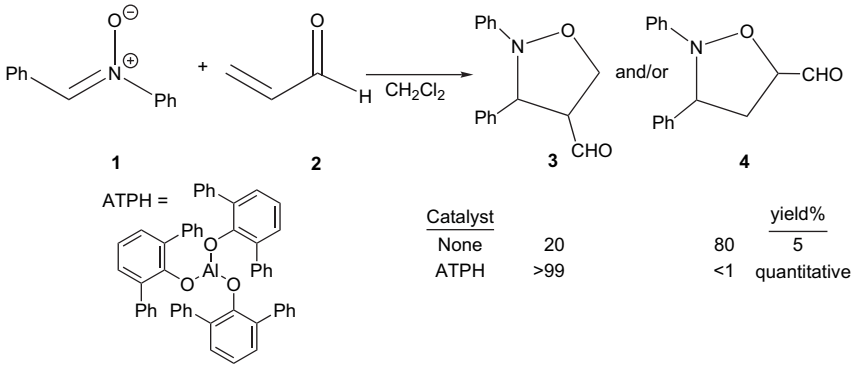
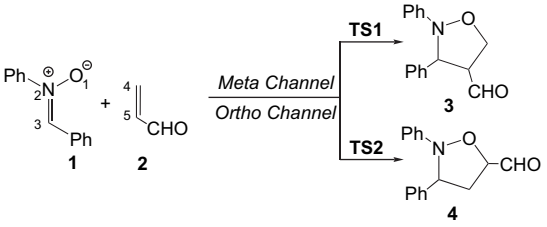


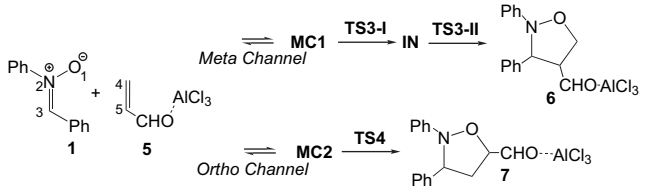
Scheme 1.

the ATPH/dipolarophile complex, the α-position of dipolarophiles is sterically so hindered that the concerted bond formation in the 13DC becomes rather difficult since it contains a bond formation at the congested α-position. The betaine intermediate formed through the stepwise reaction is followed by cyclization, which results in serious steric hindrance.[17]

Our aim in this work is to present a quantum chemical investigation of the electronic effects of the pinhole LA catalyst on the mechanism of the 13DC reaction between *N*-benzylideneaniline *N*-oxide (**1**) and acrolein **2**. We performed a density functional theory (DFT) study with the aim to localize the stationary points for reactants, transition structures (TSs), products, and possible intermediates on the potential energy surface (PES) for these cycloadditions. Firstly, an analysis based on the reactivity indexes defined on the conceptual DFT is used to explain the effects of the LA catalysts in these 13DC reactions. Then, the 13DC reaction between the nitrone **1** and acrolein **2** in the absence (see Scheme 2) and in the presence of the LA catalyst (see Scheme 3) will be analyzed. The effects of the aluminum based LA catalyst $AlCl_3$, as a reduced model of ATPH, on the reaction mechanism of this 13DC reaction allowing the regioselective formation of the cycloadduct **3** will be discussed.



Scheme 2.



Scheme 3.

2. Computational details

DFT calculations were carried out using the B3LYP[18] exchange-correlation functional, together with the standard 6-31G(d) basis set.[19] The optimizations were carried out using the Berny analytical gradient optimization method.[20] All calculations were carried out with the Gaussian 03 suite of programs.[21] Structures were optimized by the step by step calculations starting with the semiempirical calculation using the MOPAC program,[22] then moving to the B3LYP/6-31G(d) calculations. The stationary points were characterized by frequency calculations. The vibration associated with the imaginary frequency was checked to the consistency with the formation of C–C and C–O bonds. The electronic structures of stationary points and bond orders (Wiberg indexes[23]) were analyzed by the natural bond orbital (NBO) method.[24] The solvent effects were treated by B3LYP/6-31G(d) single-point calculations at the gas-phase stationary points involved in the reaction using a relatively simple self-consistent reaction field[25] (SCRF) based on the polarizable continuum model (PCM) of Tomasi's group.[26] Since the solvent used is usually dichloromethane, we used the dielectric constant at 298.0 K of ω=8.93.

The global indexes defined in the context of the DFT, the electronic chemical potential, μ, chemical hardness,[27] η, and electrophilicity power,[28] ω, values were approximated in terms of the one electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO, ε_H and ε_L, using the expressions $\mu \approx (\varepsilon_H+\varepsilon_L)/2$, $\eta \approx (\varepsilon_L-\varepsilon_H)$ and $\omega=\mu^2/2\eta$, respectively, at the ground state of the molecules.

Besides the global electrophilicity index, it is possible to define its local (or regional) counterpart condensed to atoms. The local electrophilicity,[29] ω_k, condensed to atom k is easily obtained by projecting the global quantity onto any atomic center k in the molecule by using the electrophilic Fukui function, f_k^+:[30] $\omega_k = \omega f_k^+$.

3. Results and discussion

3.1. Global and local electrophilicity analysis

The 13DC reactions under investigation have been analyzed using global indexes defined in the context of conceptual DFT.[31] Recent studies devoted to the Diels–Alder[32] and

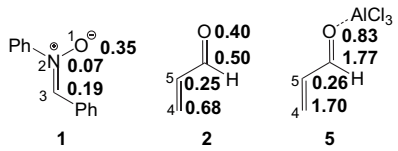
Table 1. Electronic chemical potential (μ, in au), chemical hardness (η, in au), and global electrophilicity (ω, in eV) of nitrone, acrolein, and three Lewis acid coordinated acroleins (LA=Al(OPh)$_3$, AlCl$_3$, Al(OMe)$_3$)

	μ (au)	η (au)	ω (eV)
Acrolein–Al(OPh)$_3$	−0.1687	0.0640	6.06
Acrolein–AlCl$_3$ (**5**)	−0.2189	0.1413	4.62
Acrolein–Al(OMe)$_3$	−0.1740	0.1133	3.63
Acrolein (**2**)	−0.1611	0.1921	1.84
Nitrone (**1**)	−0.1312	0.1405	1.67
Simplest nitrone	−0.1260	0.2038	1.06

13DC[15] reactions have shown that the global indexes are a powerful tool to understand the behavior of polar cycloadditions. Thus, the difference in global electrophilicity power between the reagent pair, $\Delta\omega$, can be used to predict the polar character of the process.[32] On the other hand, the analysis of the global electrophilicity for a series of LA coordinated nitroethenes has been used to choose the more appropriate computational model for LA catalyzed cycloadditions involving large molecules.[33] In Table 1, we report the static global properties, namely, electronic chemical potential μ, chemical hardness η, and global electrophilicity ω, for the nitrone **1** and the simplest (i.e., phenyl groups replaced by hydrogen atoms) nitrone, acrolein **2**, and for the three LA coordinated acrolein (LA=Al(OPh)$_3$, Al(OMe)$_3$, AlCl$_3$).

The electronic chemical potential of the nitrone **1** (μ=−0.1312 au) is higher than the electronic chemical potential of acrolein **2**, μ=−0.1611 au, and the LA coordinated acroleins (μ=−0.1687 to −0.2189 au), thereby indicating that along these 13DC reactions, the net charge transfer (CT) will take place from nitrone **1** toward these acrolein derivatives, in clear agreement with the CT analysis performed at the transition states (see later).

The electrophilicity power of the simplest nitrone is 1.06 eV, a value that falls in the range of moderate electrophiles within the ω scale.[15] Inclusion of the two phenyl groups on the nitrone increases the electrophilicity of simplest nitrone to 1.67 eV, as a consequence of the electron-withdrawing effect of the phenyl groups. Acrolein **2** has an electrophilicity power of 1.84 eV, being classified as a strong electrophile.[15] The low $\Delta\omega$ value for the nitrone **1**/acrolein **2** reaction, 0.17 eV, indicates that the reaction will have a low polar character (see later). Coordination of the aluminum metal of these LA catalysts to the oxygen atom of acrolein increases notably the electrophilicity of the corresponding complex (see Table 1). This fact allows the participation of these activated dipolarophiles in 13DC reactions with a large polar character. Thus, the Al(OPh)$_3$–acrolein complex, as a model of the experimental molecule, has an electrophilicity value of 6.06 eV. This large value indicates that these species will participate in cycloaddition with a large polar character. Note that the $\Delta\omega$ value for the nitrone/Al(OPh)$_3$–acrolein complex reaction presents a large value, 4.39 eV, indicating that this reaction will have a large polar character. On the other hand, substitution of the three phenyl groups for three methyl ones decreases the electrophilicity of the corresponding complex to 3.63 eV, as a consequence of the electron-releasing character of the methyl group. Finally, the AlCl$_3$–acrolein complex **5** has an electrophilicity value of 4.62 eV. This large value allows us to assert



1 2 5

Figure 1. The nucleophilic Fukui functions, f_k^-, at the nitrone **1**, and the local electrophilicity values, ω_k, at acrolein **2** and the AlCl$_3$–acrolein complex **5**.

the use of the AlCl$_3$–acrolein complex **5** as a reduced model of the experimental one. The use of AlCl$_3$ model (four atoms) permits to diminish the computational cost caused by the big encumbrance of the ATPH LA catalyst (97 atoms).

Recent studies devoted to cycloaddition reactions with a large polar character have shown that the analysis of the local electrophilicity ω_k[29] at the electrophilic reagent and the nucleophilic Fukui function f_k^-[30] at the nucleophilic one allows to explain the regioselectivity that is experimentally observed.[34] The values of the nucleophilic Fukui functions at nitrone **1** and the local electrophilicity at the acrolein **2** and the complex **5** are summarized in Figure 1.

N-Benzylideneaniline *N*-oxide **1** has the largest value of f_k^- at the oxygen O1 atom, 0.35; consequently this is the more reactive site for a nucleophilic attack. Note that the f_k^- value at O1 is twice this value at the C3 position, 0.19. Consequently along a polar interaction the nitrone oxygen O1 atom will be the preferment position for a nucleophilic attack.

The analysis of the local electrophilicity at acrolein **2** indicates that the β-conjugated C4 position is the more electrophilic center of the molecule, ω_{C4}=0.68 eV. Note that the carbonyl carbon atom has also a large electrophilic activation, $\omega_{C=O}$=0.50 eV. Coordination of AlCl$_3$ to acrolein **1** increases the local electrophilicity at the C4 position of the corresponding complex **5** to 1.70 eV. The carbonyl carbon atom is the more activated center with the coordination; however, the nucleophilic attack of the nitrone **1** at this position, which does not allows the formation of any [3+2] cycloadducts, can be reversible, and consequently the attack at the C4 favors the formation of the regioisomer that is experimentally observed.[17]

3.2. Study of the 13DC reaction between *N*-benzylideneaniline *N*-oxide 1 and acrolein 2

Due to the asymmetry of the dipole **1** and the dipolarophile **2**, for the 13DC reaction between the nitrone **1** and acrolein **2**, several reactive channels are feasible. They are mainly related to the *endo* and *exo* approach modes of the carbonyl group present in the dipolarophile **2** relative to the nitrogen atom of nitrone **1**, and the two regioisomeric approach modes of the oxygen atom of **1** relative to the β-conjugated position of the acrolein **2**, named as *ortho* and *meta*. Only the two regioisomeric possibilities associated with the *endo* approaches are studied in this work.

An analysis of stationary points found along the two reactive channels (see Fig. 2a) indicates that this 13DC reaction take place along a concerted mechanism. Thus two TSs, **TS1** and

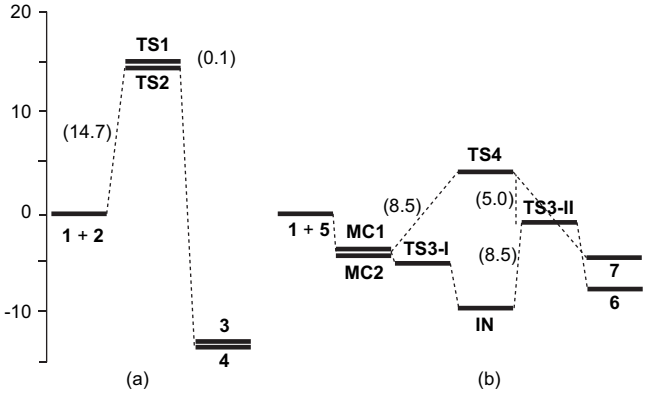


Figure 2. Energy profiles, in dichloromethane and in kcal/mol, for the uncatalyzed (a) and $AlCl_3$ catalyzed (b) 13DC reactions between **1** and **2**. Relative energies are given in parenthesis.

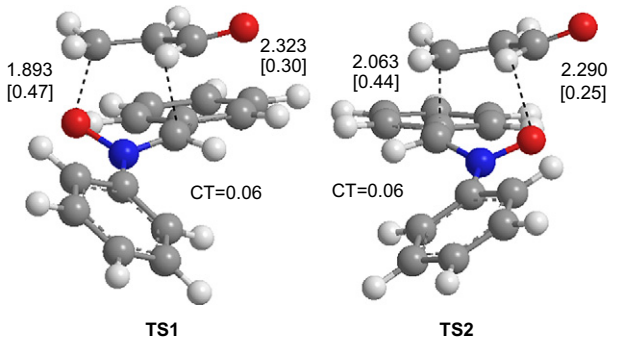


Figure 3. B3LYP/6-31G(d) structures of TSs involved in the *endo* regioisomeric pathways of the 13DC reaction between the nitrone **1** and acrolein **2**. The distances are given in Å. The bond orders are given in brackets. The charge transfer, CT, is given in e.

TS2, and two cycloadducts, **3** and **4**, associated to the *endo* approach mode of the nitrone **1** to acrolein **2** along the *meta* and *ortho* reactive channels, respectively, have been located and characterized (see Scheme 2).

The activation energies associated with the two regioisomeric 13DC reactions are: 12.8 (**TS1**) and 13.5 (**TS2**) kcal/mol (see Table 2). The gas-phase calculations give an inverted regioselectivity yielding the favored formation of the *meta* cycloadduct **3**. Formation of the cycloadducts **3** and **4** is exothermic by −16.0 and −17.3 kcal/mol, respectively.

The geometries of the TSs are given in Figure 3. The lengths of the O–C and C–C forming bonds at the regioisomeric TSs are: 1.893 (O1–C4) and 2.323 (C3–C5) Å at **TS1**, and 2.290 (O1–C5) and 2.063 (C3–C4) Å at **TS2**. Therefore, these TSs correspond to concerted bond-formation processes. The symmetry of the process is broken by the electron-deficient dipolarophile, acrolein **2**. Note that the lengths of the forming bond at the β-conjugated position of acrolein, the C4, are shorter than those at the C5.[34]

Table 2. B3LYP/6-31G(d) Total (*E*, in au) and relative[a] (Δ*E*, kcal/mol) energies, in gas phase and in dichloromethane, of the stationary points involved in the *endo* regioisomeric pathways of the 13DC reaction between the nitrone **1** and acrolein **2**, in absence and in presence of the LA

	In gas phase		In dichloromethane	
	E	Δ*E*	*E*	Δ*E*
1	−631.915868		−631.928298	
2	−191.911974		−191.918799	
TS1	−823.807404	12.8	−823.823545	14.8
TS2	−823.806256	13.5	−823.823646	14.7
3	−823.853341	−16.0	−823.867455	−12.8
4	−823.855358	−17.3	−823.868655	−13.5
5	−1815.198008		−1815.216250	
MC1	−2447.131448	−11.0	−2447.150690	−3.9
TS3-I	−2447.130801	−10.6	−2447.152581	−5.0
IN	−2447.132172	−11.5	−2447.159318	−9.3
TS3-II	−2447.124362	−6.6	−2447.145829	−0.8
6	−2447.137160	−14.6	−2447.156655	−7.6
MC2	−2447.125017	−7.0	−2447.151418	−4.3
TS4	−2447.108077	3.6	−2447.137885	4.2
7	−2447.132701	−11.8	−2447.151421	−4.3

[a] Relative to reagents.

The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO).[23] The BO values of the O–C and C–C forming bonds at the TSs are: 0.47 (O1–C4) and 0.30 (C3–C5) at **TS1** and 0.25 (O1–C5) and 0.44 (C3–C4) at **TS2**. These data show that in both cases, the bond formation at the β-conjugated position of acrolein is more advanced.[34] The less energetic **TS1** is slightly more advanced but less asynchronous than **TS2**.

The natural population analysis (NPA)[24a] allows us to evaluate the CT along these 13DC reactions. The resulting values are reported in Figure 3. The natural charges at the TSs appear shared between the nitrone **1** and acrolein **2**. The CT from **1** to **2** at the TSs is 0.06e in both cases. These low values indicate that these TSs have a low polar character, in agreement with the low $\Delta\omega$ computed to this cycloaddition. In addition, the CT fluxes from **1** to **2** in clear agreement with the lower electronic chemical potential of acrolein **2** than nitrone **1**, and with the larger electrophilic character of **2**.

As this 13DC reaction is carried out in a polar solvent (dichloromethane) and it can have some incidence on the energies, they have been considered by single-point calculations on the gas-phase geometry using the PCM model. In dichloromethane, all structures are stabilized between 4.3 and 10.9 kcal/mol. The reactants, **1**+**2**, are ca. 2 kcal more solvated than the TSs, and consequently the activation energies rise to 14.7 kcal/mol (see Table 2). The more relevant feature with the inclusion of the solvent effects is that **TS2** is 0.8 kcal/mol more stabilized than **TS1**, in clear agreement with the large dipole moment of the former: 3.07 debye (**TS1**) and 5.95 debye (**TS2**) (see Fig. 2a). Consequently in dichloromethane there is an inversion in the relative energy of the TSs, in clear agreement with the regioselectivity that is experimentally observed.

3.3. Study of the 13DC reaction between *N*-benzylideneaniline *N*-oxide 1 and the $AlCl_3$–acrolein complex 5

An early analysis for the lowest energy structure of $AlCl_3$–acrolein complex **5** indicates that it corresponds to the *s-trans* conformation of acrolein, with the LA in the *anti* disposition. The *syn* conformation of the LA coordinated acrolein is higher in energy by 2.0 kcal/mol. Consequently, only the *s-trans*/*anti* conformation of $AlCl_3$–acrolein complex **5** was considered in the catalyzed reaction. Likewise

for the case of the 13DC reaction between **1** and **2**, we studied only the effects of the LA catalyst along the two regioisomeric possibilities associated with the *endo* approach modes.

An analysis of stationary points found along these reactive channels (see Fig. 2b) indicates that the LA has different behavior along the two regioisomeric channels; thus, while the *meta* channel has a stepwise mechanism, two TSs, **TS3-I** and **TS3-II**, and one intermediate, **IN**, have been located and characterized, the *ortho* channel is concerted and only one TS being found, **TS4** (see Scheme 3).

At the beginning of the two reaction channels, it is also feasible to find two molecular complexes, **MC1** and **MC2**, associated with a very earlier step of the reaction, in which the two reactant molecules are interacting in gas phase. **MC1** and **MC2** are located 11.0 and 7.0 kcal/mol, respectively, below the reagents **1** and **5**. **TS3-I** is located only 0.4 kcal/mol above **MC1**, whereas the corresponding intermediate **IN** is located 0.5 kcal/mol below it (see Table 2). Therefore, formation of the zwitterionic intermediate **IN** does not present any appreciable barrier. The activation energy associated with the ring closure at the intermediate **IN** with formation of the cycloadduct **6** is 4.9 kcal/mol; this step corresponds to the rate-determining step of the stepwise process. Along the *ortho* reactive channel, **TS4** is located 10.6 kcal/mol above **MC2**. Formation of the cycloadducts **6** and **7** is exothermic by −14.6 and −11.8 kcal/mol, respectively.

These energy results indicate that the presence of the LA coordinated to acrolein **2** decreases markedly the activation energies associated with both reactive channels. However, the LA has not the same incidence along the two regioisomeric channels, being clearly favored the attack along the *meta* approach. Now, **TS3-II** is located 10.2 kcal/mol below **TS4**. This fact can be explained through a favorable two-center interaction that appears at the *meta* channel between the more nucleophilic center of the nitrone **2**, the oxygen O1 atom, and one of the more electrophilic centers of the LA coordinated acrolein **5**, the β-conjugated position C4, a Michael-type addition. This large energy difference justifies the only formation of the cycloadduct **6** through the stepwise mechanism.[17]

B3LYP calculations give a very flat surface at the first step of the stepwise pathway, **MC1**, **TS3-I**, and **IN**, and they point out that the second step is the rate-determining step of this stepwise process. Several studies devoted to Diels–Alder reactions have shown that while HF overestimates the activation energies, MP2 underestimates them,[35] being necessary to perform MP3 calculations to obtain reasonable activation energies.[36] Therefore, in order to test the B3LYP results, single-point calculations at the MP3/6-31G* level over the DFT optimized geometries were performed. A comparison of the relative energies obtained at the two computational levels (see Table 3) allows us to redraw some interesting conclusions. (i) The relative energies of **MC1** and **TS3-I** are similar at the two computational levels. These results indicate that after formation of **MC1**, the nucleophilic attack of the nitrone **1** at the complex **5** does not have any appreciable barrier. (ii) The large discrepancy is found in the relative energies of **IN**, **TS3-II**, and **6**. This behavior is a consequence of B3LYP calculations, which underestimate the energies of the C–C bond formation.[37] However, the activation barriers obtained for the ring closure are similar at the two computational levels: 4.9 (B3LYP) and 6.1 (MP3) kcal/mol. (iii) Although the MP3 calculations give a larger stabilization for **MC2** than the B3LYP ones, 3.4 kcal/mol, the activation energies for the concerted process are closer at the two levels, 10.3 (B3LYP) and 11.4 (MP3) kcal/mol. (iv) Finally, MP3 gives a similar regioselectivity than that obtained at the B3LYP level, to locate **TS3-II** 14.2 kcal/mol below **TS4**. The flat region given by the B3LYP calculations around **MC1**, **TS3-I**, and **IN** is broken at the MP3 level to yield **IN** 6.5 kcal/mol below **MC1**. The MP3 energies indicate that along the *meta* channel the reagents collapse to the formation of the intermediate **IN**, being the ring closure via **TS3-II** the rate-determining step of the process.

Table 3. B3LYP/6-31G(d) and MP3/6-31G(d) relative energies[a] (kcal/mol) of the stationary points involved in the *endo* regioisomeric pathways of the LA catalyzed 13DC reaction between the nitrone **1** and acrolein **2**

	B3LYP	MP3
MC1	−11.0	−12.5
TS3-I	−10.6	−12.5
IN	−11.5	−19.0
TS3-II	−6.6	−12.9
6	−14.6	−30.1
MC2	−6.7	−10.1
TS4	3.6	1.3
7	−11.8	−28.4

[a] Relative to reagents.

The geometries of the TSs and the intermediate involved in the two regioisomeric channels are given in Figure 4. At the

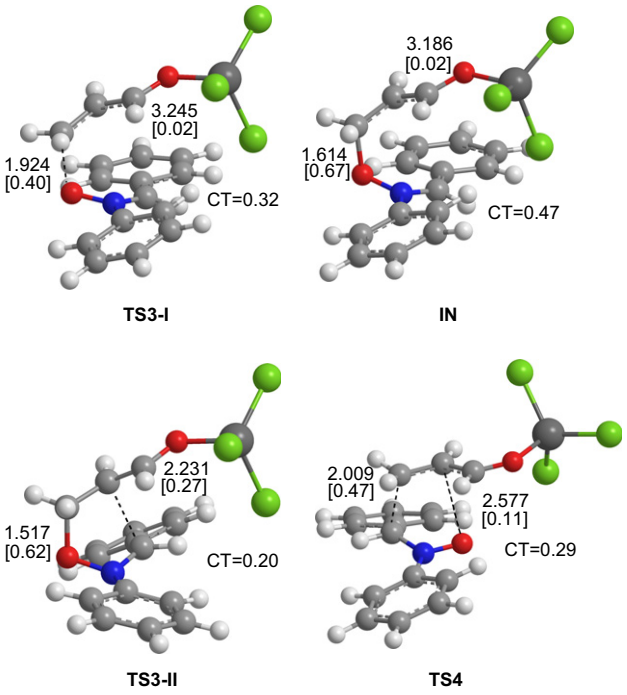


Figure 4. B3LYP/6-31G(d) structures of TSs and intermediate involved in the *endo* regioisomeric pathways of the 13DC reaction between the nitrone **1** and the $AlCl_3$–acrolein complex **5**. The distances are given in Å. The bond orders are given in brackets. The charge transfer, CT, is given in e.

TS associated with the nucleophilic attack of the nitrone oxygen atom of **1** at the β-conjugated position of **5**, **TS3-I**, the length of the O1–C4 forming bond is 1.924 Å, while the distance between the C3 and C5 carbon atoms becomes 3.245 Å. The O1–C4 bond length of the corresponding intermediate **IN** is 1.614 Å while the C3–C5 distance remains as 3.186 Å. Finally, at the **TS3-II** associated with ring-closure process, the length of the C3–C5 forming bond is 2.231 Å. The lengths of the C3–C4 and O1–C5 forming bonds at the concerted **TS4** are 2.009 and 2.577 Å. These lengths indicate that this TS corresponds to a high asynchronous bond-formation process where the C3–C4 bond formation at the β-conjugated position of **5** is more advanced than O1–C5 one. The asynchronicity at this concerted TS is larger than that at **TS2**.

The O1–C4 BO value at **TS3-I** is 0.40, while the C3–C5 BO value is 0.02. At the intermediate **IN**, the O1–C4 BO value is 0.67. The BO values of the C3–C4 and O1–C5 forming bonds at the concerted **TS4** are 0.47 and 0.11, respectively. These BO values indicate the highly asynchronous character of this TS.

The atomic charges have been partitioned between the donor nitrone **1** and the acceptor complex **5**. The resulting values are reported in Figure 4. Along the two regioisomeric channels, the CT flows from the dipole to the dipolarophile. The CT along the nucleophilic attack of the nitrone **2** at the LA coordinated acrolein **5** is: 0.19e at **MC1**, 0.32e at **TS3-I**, 0.16e at **MC2**, and 0.29e at **TS4**. At the stepwise process, going from **TS3-I** to **IN**, the CT increases from 0.32e to 0.47e. These large values indicate the zwitterionic character of these species. The large CT obtained at **MC1** and **MC2** points to a large electronic interaction between both the reagents, justifying the large stabilization found with the formation of these molecular complexes. The large polar character of this cycloaddition, compared with the uncatalyzed process, is in clear agreement with the large increase in the electrophilicity of acrolein with the coordination to the LA. This coordination leads to the increase of the $\Delta\omega$ for the catalyzed process, after which it becomes a more polar process.

Because of the large zwitterionic character of the TSs and intermediate involved in this LA catalyzed 13DC reaction, it is expected that solvent effect has a large incidence on the energies. Solvent effects stabilize all species between 8 and 19 kcal/mol. In dichloromethane, **MC1** and **MC2** present similar energies as a consequence of a larger solvation of the later. Now, **TS3-II** is located only 0.8 kcal/mol below reagents, while **TS4** is located 4.2 kcal above them (see Table 2). With the inclusion of solvent effects, **TS3-II** is located 5.0 kcal/mol below **TS4**. This energy result is in reasonable agreement with the large regioselectivity that is experimentally observed.[17] Note that this difference in gas phase is 10.2 kcal/mol. In spite of the large incidence of the solvent effect on the relative energies, there are some behaviors that remain invariant: (i) coordination of the LA to acrolein accelerates considerably the reaction by a strong reduction of the activation energies associated to this cycloaddition; (ii) along the more favorable stepwise *meta* channel, the second step associated with the ring closure is the rate-determining step; and (iii) the larger acceleration along the *meta* reactive channel than the *ortho* one makes this LA catalyzed 13DC reaction to be remarkably regioselective.

4. Conclusions

The mechanisms of the 13DC reactions of *N*-benzylideneaniline *N*-oxide with acrolein in the absence and in the presence of an aluminum based LA catalyst, $AlCl_3$, have been studied using DFT method at the B3LYP/6-31G(d) computational level. For these cycloaddition reactions, two regioisomeric reactive channels were studied. In the absence of a LA catalyst, the 13DC reaction takes place through an asynchronous concerted mechanism with a very low polar character. The two reactive channels present similar activation energies, being necessary to include solvent effects to reproduce the trend of the regioselectivity observed experimentally.

Coordination of the $AlCl_3$ to acrolein produces relevant changes in this 13DC reaction as a consequence of the large enhancement in the electrophilicity of the corresponding $AlCl_3$–acrolein complex. Formation of the experimentally observed isoxazolidine-4-carboxaldehyde cycloadduct takes place through a stepwise mechanism with formation of a zwitterionic intermediate. The formation of this intermediate is achieved by the nucleophilic attack of the oxygen atom of the nitrone at the β-conjugated position of the $AlCl_3$–acrolein complex. This step that can be classified as a Michael-type addition does not present appreciable activation energy, being the ring-closure step the rate-determining step of this stepwise cycloaddition. Although the presence of the LA catalyst accelerates also the formation of the other regioisomeric cycloadduct, the difference in the activation energy associated with the two regioisomeric channels justifies the large regioselectivity that is experimentally observed at this LA catalyzed 13DC reaction.

Analysis of the global and local electrophilicity allows to explain correctly the behaviors of the LA catalyzed cycloaddition. Coordination of the LA to acrolein changes the mechanism from a concerted cycloaddition to a polar Michael addition followed by a ring closure, as a consequence of the large electrophilic character of the $AlCl_3$–acrolein complex. Analysis of the local indexes allows to characterize the more nucleophilic center of the nitrone, the oxygen atom, and one of the more electrophilic centers of the $AlCl_3$–acrolein complex, the β-conjugated position of acrolein. Regioselectivity is correctly explained by means of the favorable two-center interaction that takes place along the *meta* reactive channel.

Although $AlCl_3$ is a very reduced model of the ATPH used by the experimentalist and does not reproduce the steric congestion of the latter, our results indicate that $AlCl_3$ reproduces well the electronic behavior responsible for the complete regioselectivity as well as the large acceleration that is experimentally observed. The steric congestion caused by ATPH can increase the activation energy for the ring-closure step, which corresponds to the rate-determining step of the LA catalyzed cycloaddition, but their unfavorable effects cannot be larger than that of the favorable catalytic effect caused by the aluminum based ATPH catalyst.

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