

## Enhancing Reactivity of Carbonyl Compounds via Hydrogen-Bond Formation. A DFT Study of the Hetero-Diels–Alder Reaction between Butadiene Derivative and Acetone in Chloroform

Luis R. Domingo<sup>\*,†</sup> and Juan Andrés<sup>‡</sup>

*Instituto de Ciencia Molecular, Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain, and Departament de Ciències Experimentals, Universitat Jaume I, Apartat 224, 12080, Castelló, Spain*

domingo@utopia.uv.es

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To examine how hydrogen-bond (HB) formation involving chloroform solvent molecules influences the chemical reactivity of ketones, the hetero-Diels–Alder reaction of *N,N*-dimethyl-1-amino-3-methoxy-1,3-butadiene and acetone has been studied by using density functional theory (DFT) at the B3LYP/6-31G\* level. The effects of the chloroform on the activation energies have been modeled by means of discrete-continuum models. In the gas phase, the formation of specific HB between acetone and one and two chloroform molecules decreases the activation barriers from 19.3 to 13.6 and 8.5 kcal/mol, respectively. Inclusion of solvent effects by means of combined discrete and polarizable continuum models yields a change of molecular mechanism from a concerted to a two-step mechanism, and the first nucleophilic step is the rate-limiting step. The corresponding values of activation barriers in chloroform are 18.6 kcal/mol (no HB), 13.5 kcal/mol (one HB), and 9.6 kcal/mol (two HBs). These theoretical results account for the experimental observation that chloroform accelerates the reaction more markedly than more polar aprotic solvent such as acetonitrile. A DFT analysis of the global electrophilicity power of the reagents provides a sound explanation about the catalytic effects of chloroform.

### Introduction

The hetero-Diels–Alder (HDA) reaction between general dienes and carbonyl derivatives, acting as dienophiles, provides one of the most direct methods for the construction of six-membered oxo heterocycles. Although these HDA reactions have been studied extensively<sup>1,2</sup> due to the prevalence and biological importance of the oxygen heterocycles,<sup>3</sup> their use in organic synthesis has been of limited scope because the normally unreactive dienophile generally requires some special reaction conditions.<sup>1</sup>

HDA reactions have been reported with aldehydes as dienophiles, and usually they need long reaction times, high temperatures, and sometimes high pressure, restricting the practical synthetic utility of this chemistry. This hindrance can also be overcome with the use of electron-withdrawing substituents on the dienophile, very reactive dienes, or Lewis acid catalysis.<sup>2,4</sup> Alternatively, in aqueous media, these reactions can proceed

under milder conditions with simple protonation of the dienophile being the most convenient approach.<sup>5</sup>

The HDA reaction involving oxygen atom has been comparatively less studied from a theoretical point of view than the Diels–Alder one. Several theoretical works devoted to the study of oxa-Diels–Alder reactions, oxadienes,<sup>6</sup> formaldehyde,<sup>7</sup> acetaldehyde,<sup>8</sup> and glyoxylate,<sup>9</sup> have been reported in the literature.

As the C=O double bond of the ketones is less reactive than that in aldehydes, there are very few reports of HDA reactions using simple ketones.<sup>1,2,10</sup> Very recently, Huang

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<sup>†</sup> Universidad de Valencia.

<sup>‡</sup> Universitat Jaume I.

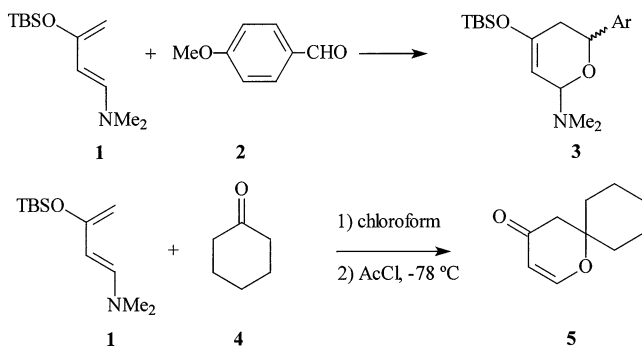
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## SCHEME 1



and Rawal<sup>11</sup> have reported the hydrogen-bond (HB) promoted HDA reactions of unactivated ketones. Thus, for the reaction between the 1-amino-3-silyloxy-1,3-butadiene **1** and *p*-anisaldehyde (**2**) (see Scheme 1) they found that solvent effects produce a significant higher reaction rate in chloroform than in other aprotic organic solvents. The relative rate coefficients for the cycloaddition using different solvents show that those do not correlate with the solvent dielectric constants: for instance, the reaction in chloroform was 10 times faster than that in the more polar solvent acetonitrile. These authors conclude that the increased reaction rate in chloroform could arise from a C–H···O=C interaction, which would render the carbonyl group a stronger heterodienophile. This HB involves the solvent and the activation is sufficient that even simple ketones, generally considered as unreactive, undergo HDA reactions. Thus, when cyclohexanone **4** was treated with the butadiene derivative **1** in chloroform the spiro-fused dihydropyran **5** was obtained by elimination of the amino group (see Scheme 1).

The effects of the HB formation involving water molecules on the Diels–Alder (DA) transition states were studied by Blake et al.<sup>12</sup> using HF/6-31G\* ab initio methods. They found that the values of interaction energies are 1.5–2.0 kcal/mol more favorable for the HB to the oxygen atom in the transition state than in the ground state. Evanseck et al.<sup>13</sup> studied the rate acceleration and the endo/exo selectivity of the butadiene and acrolein DA reaction in the aqueous phase using B3LYP/6-31G\* calculations. The experimental acceleration and enhanced endo/exo selectivity are reproduced only when solvation forces are approximated by a discrete-continuum model. The gas-phase activation energy is lowered to 11.5 kcal/mol, in excellent agreement with the experiments. Recently, Jorgensen et al.<sup>14</sup> have used QM/MM simulations to study the free energy profiles for DA reactions in water. The free energy for the cycloaddition between methyl vinyl ketone and butadiene is reduced on going from gas phase to water by 2.8 kcal/mol. These authors conclude that the rate increase in water arises in part from hydrophobic association of the reactants but predominately from enhanced HB between water molecules and the polarized transition state.

For a long time we have been interested in understanding the molecular mechanism of DA reactions. Studies on the polarity of the substituents, the role of Lewis acid catalysts, and the solvent effects suggest that the feasibility of the cycloaddition reaction can be related to the charge transfer on the bond-formation process, i.e., the polar character of the cycloaddition.<sup>15,16</sup> Thus, the increase of the electron-rich character of the diene (the nucleophilicity) together with the increase of the electron-poor character of the ethylene derivative (the electrophilicity), or vice versa, results in an increase in the charge transfer and a decreasing of the activation barrier.<sup>15</sup>

Recently, we have reported the use of the global electrophilicity index proposed by Parr et al.,<sup>17</sup>  $\omega$ , defined within of the density functional theory<sup>18</sup> (DFT), to classify the global electrophilicity of a series of dienes and dienophiles currently present in DA reactions.<sup>19</sup> The difference in electrophilicity for the diene/dienophile pair,  $\Delta\omega$ , was found to be a measure of the less or more polar character of the cycloaddition. Coordination of a Lewis acid to the diene or dienophile increases markedly the electrophilicity of the DA reagent, and the reduction of the activation energy associated with the catalyzed process can be explained as an increase of the polar character of the DA reaction measured by  $\Delta\omega$ .<sup>16,19</sup> Later, the local electrophilicity index<sup>20</sup> was proposed as a valuable tool to study the regioselectivity in polar Diels–Alder reactions. This model together with the Fukui functions<sup>21</sup> for nucleophilic attack,  $f_k^+$ , and for electrophilic attack,  $f_k^-$ , allows the identification of the most electrophilic and nucleophilic centers in the reactants.<sup>16</sup>

Although it is well-known from experimental and computational data that dienophile power is highly enhanced by HB, the foregoing aspect has not yet been subject of any computational investigation. Now, we present the first DFT study to address and explain the enhancing reactivity of carbonyl compounds in the HDA reaction via HB formation involving chloroform solvent molecules. To perform this analysis, we chosen as a working molecule *N,N*-dimethyl-1-amino-3-methoxy-1,3-butadiene, **6**, as a model of **1**. Both the exploration of the potential energy surface (PES) for the HDA reaction between **6** and acetone (**7**) (see Scheme 2), in the absence and presence of one and two explicit chloroform molecules in the gas phase and condensed phase, and the analysis of the reactivity index defined on the DFT are used to explain the catalytic effects of chloroform found recently for Huang and Rawal.<sup>11</sup>

**Computational Methods and Models.** An extensive exploration of the PES for these cycloadditions was first carried out at the HF/3-21G and HF/6-31G\* computational level.<sup>22</sup> Previous theoretical studies on Diels–Alder reactions and related pericyclic reactions indicated that

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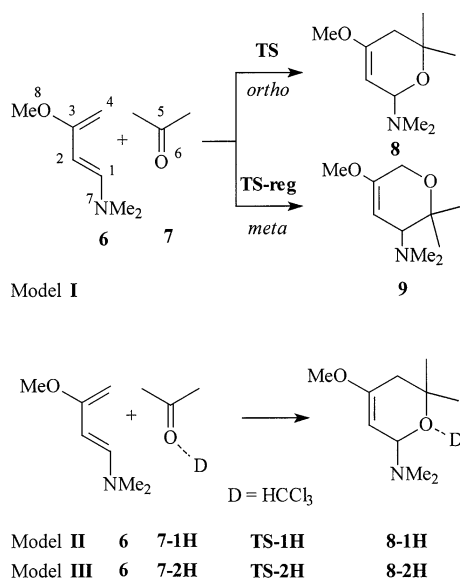
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## SCHEME 2



the activation energies calculated at the HF level are too large, while DFT calculations using the B3LYP hybrid functional<sup>23</sup> have been shown to be in good agreement with experimental values.<sup>24</sup> Therefore, the HF stationary points were optimized and characterized at the B3LYP/6-31G\* level.

The optimizations were carried out using the Berny analytical gradient optimization method.<sup>25</sup> The stationary points were characterized by frequency calculations in order to verify that the transition structures (TSs) have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)<sup>26</sup> path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method.<sup>27</sup> The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.<sup>28</sup> All calculations were carried out with the Gaussian 98 suite of programs.<sup>29</sup>

The values of the relative energies,  $\Delta E$ , have been calculated on the basis of the total energies of stationary points. Relative enthalpies,  $\Delta H$ ; entropies,  $\Delta S$ ; and free energies,  $\Delta G$ , were calculated with the standard statistical thermodynamics<sup>22</sup> at 298.15 K. The thermal contributions to the vibrational energy and entropy have been scaled by 0.96.<sup>30</sup>

The solvent effects modeled as a continuum model have been considered by B3LYP/6-31G\* geometrical optimization using a self-consistent reaction field (SCRF)<sup>31</sup> based on the polarizable continuum model (PCM) of the Tomasi's group.<sup>32</sup> The solvents used in the experimental work were chloroform and acetonitrile. Therefore, we have used the dielectric constants at 298.15 K,  $\epsilon = 4.9$  and 36.64, respectively. In this continuum model, the values of  $\Delta E$  have been calculated.

The global electrophilicity index  $\omega$ , which measures the stabilization in energy when the system acquires an additional electronic charge  $\Delta N$  from the environment, has been given by the following simple expression,<sup>17</sup>  $\omega = \mu^2/2\eta$ , in terms of the electronic chemical potential ( $\mu$ ) and the chemical hardness ( $\eta$ ). Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO,  $\epsilon_H$  and  $\epsilon_L$ , as  $\mu \approx (\epsilon_H + \epsilon_L)/2$  and  $\eta \approx \epsilon_L - \epsilon_H$ , respectively.<sup>18</sup> Electrophilic and nucleophilic Fukui functions<sup>21</sup> condensed to atoms have been evaluated from single point calculations performed at the ground state of molecules at the same level of theory, using a method described elsewhere.<sup>33</sup> This method evaluates Fukui functions using the coefficients of the frontier molecular orbitals involved in the reaction and the overlap matrix.

For the present study three computational models have been selected (see Scheme 2): model I corresponds with the HDA reaction between the substituted butadiene **6** and acetone (**7**). Then, the influence of the HB between acetone and the aprotic chloroform in the cycloaddition process has been studied by means of model II and III, including one and two chloroform molecules, respectively. Finally, the solvent effects modeled by a continuum approach on the three models have been considered.

## Results and Discussion

First, energetic aspects, geometrical parameters of TSs, and their electronic structure in terms of bond orders and natural charges for the three cycloaddition models in the gas phase will be analyzed. Then, the energetic and geometrical results including solvent effects as a continuum model will be discussed. Finally, a DFT analysis based on the reactivity indexes of the reactants involved in these cycloadditions will be performed.

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**TABLE 1.** Relative<sup>a</sup> Energies ( $\Delta E$ ), Enthalpies ( $\Delta H$ ), Entropies ( $\Delta S$ ), and Free Energies ( $\Delta G$ ) Computed at 298.15 K of the Stationary Points Corresponding to the Cycloaddition Reaction between the Substituted butadiene **6** and Acetone **7**, in the Absence and Presence of One and Two Chloroform Molecules

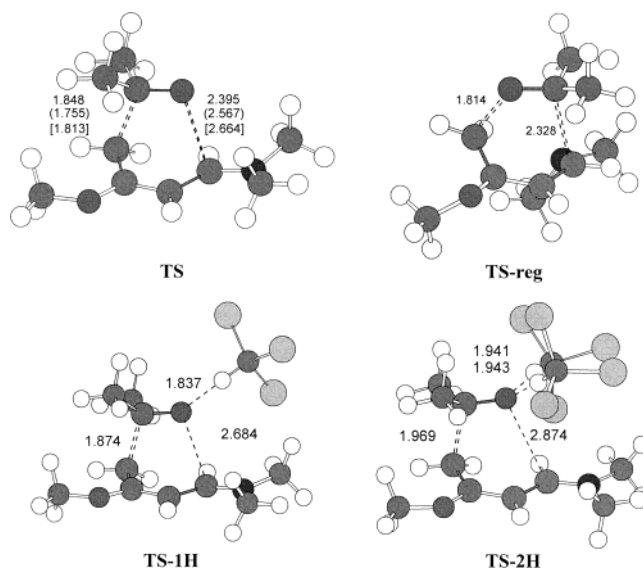
	$\Delta E^b$	$\Delta H^b$	$\Delta S^c$	$\Delta G^b$		$\Delta E^b$	$\Delta H^b$	$\Delta S^c$	$\Delta G^b$
<b>TS</b>	19.3	20.5	-49.7	35.3	<b>TS-1H</b>	13.6	14.6	-53.3	30.5
<b>8</b>	-6.5	-3.5	-55.1	12.9	<b>8-1H</b>	-5.5	-2.6	-58.4	14.8
<b>TS-reg</b>	52.1	52.5	-51.4	67.9	<b>TS-2H</b>	8.5	9.7	-61.1	27.9
<b>9</b>	2.7	5.7	-57.1	22.7	<b>8-2H</b>	-2.7	0.2	-62.1	18.7

<sup>a</sup> Relative to the separated reagents. <sup>b</sup> In kcal/mol. <sup>c</sup> In cal/mol K.

**(a) Study of the Cycloaddition Reaction between the Substituted Butadiene **6** and Acetone **7** in the Absence and Presence of Chloroform Molecules.** The cycloaddition reaction between the substituted butadiene **6** and acetone (**7**) can take place along two regioisomeric channels: the ortho and the meta (see Scheme 2). The ortho channel corresponds to the C1–O6 and C4–C5 bond forming process, whereas the meta channel corresponds to the C1–C5 and C4–O6 one. For the model **I** the two regioisomeric channels have been considered. Experimentally, only the ortho regioisomeric cycloadduct is formed.<sup>11</sup>

An analysis of the gas-phase results indicates that these cycloadditions take place along a concerted mechanism. Thus, one TS and the corresponding cycloadduct were found and characterized. They are named as **TS** and **8** (ortho channel) and **TS-reg** and **9** (meta channel), respectively, for the cycloaddition between **6** and **7** (model **I**), and **TS-1H** and **8-1H**, and **TS-2H** and **8-2H**, for the models **II** and **III** (ortho channels), respectively. The different stationary points of these cycloadditions have been depicted in Scheme 2 together with the atom numbering, while the energetic results are listed in Table 1. The total energies are given in Table 1S (see Supporting Information). The geometries of the TSs are presented in Figure 1.

The activation enthalpy for the cycloaddition between the substituted butadiene **6** and acetone (**7**) along the ortho and meta channels are 20.5 and 52.5 kcal/mol, respectively. Therefore, there is a pronounced ortho regioselectivity for this HDA reaction; **TS-reg** is 32.0 kcal/mol higher in energy than **TS**. These energetic results allow us to discard the study of the meta channels associated with the cycloaddition models **II** and **III**. In addition, the large activation energy associated with the more favorable ortho channel, which is closer to that computed for the reaction between 1,3-butadiene and ethylene (24.1 kcal/mol), accounts for the low reactivity of the double bond C=O of a ketone as dienophile in a HDA reaction. However, formation of one or two HBs between the hydrogen atom of chloroform and the O6 oxygen atom of acetone decreases markedly the activation enthalpy 5.9 and 10.8 kcal/mol for models **II** and **III**, respectively. Thus, the values of the activation enthalpy for **TS-1H** and **TS-2H** are 14.6 and 9.7 kcal/mol, respectively. This decreasing is similar to that found for the DA reaction between butadiene and acrolein in water.<sup>13</sup> The activation entropies associated with **TS**, **TS-reg**, **TS-1H**, and **TS-2H** are -49.7, -51.4, -53.3, and -61.1 cal/mol K. From these negative entropies arise the



**FIGURE 1.** Transition structures corresponding to ortho (**TS**) and meta (**TS-reg**) channels of the cycloaddition between the substituted butadiene **6** and acetone (**7**). Transition structures corresponding to ortho channels of the cycloaddition between the **6** and **7** in the presence of one and two chloroform molecules. The bond lengths directly involved in the reaction are given in angstroms. The values obtained using the PCM approach to simulate chloroform and acetonitrile are given in parentheses and brackets, respectively.

activation free energies for the cycloadditions: 35.3, 67.9, 30.5 and 27.9 kcal/mol, respectively (see Table 1).

To explain the reduction of the activation energy, the enthalpies of formation of the HB to acetone (**7**) and **TS** were calculated. Formation of one and two HBs at **7** stabilizes the ground state in 4.3 (**7-1H**) and 7.3 (**7-2H**) kcal/mol, respectively. However, a large stabilization was found at the corresponding TSs, 10.1 (**TS-1H**) and 18.0 (**TS-2H**) kcal/mol, respectively, as a consequence of the large charge transfer that takes place along these polar HDA reactions (see later).

The lengths of the C1–O6 and C4–C5 forming bonds at the TSs associated with the ortho channels are 2.395 and 1.848 Å at **TS**, 2.684 and 1.874 Å at **TS-1H**, and 2.874 and 1.969 Å at **TS-2H**, respectively, while the lengths of the C1–C5 and C4–O6 forming bonds at the TS associated with the meta channel, **TS-reg**, are 2.328 and 1.814 Å, respectively. Formation of the HB at the TSs has two main effects: (i) the corresponding TS is earlier, and the C4–C5 distance increases with the HB formation; and (ii) the C1–O6 distance increases more markedly due to a decrease of the interaction between the ends of diene and dienophile fragments.

The values of the HB lengths decrease on going from acetone to TS: 2.076 Å at **7-1H**, and 1.834 Å at **TS-1H**, 2.155 and 2.150 Å at **7-2H**, and 1.943 and 1.941 Å at **TS-2H**. This decreasing is a consequence of stronger HB formation at the corresponding polar TSs with respect separated reactants.

The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO).<sup>34</sup> The BO values of the C4–C5 and C1–O6 forming bonds at the TSs associated with the ortho channels are 0.62 and 0.16

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**TABLE 2.** Relative Energies<sup>a</sup> ( $\Delta E$ ) of the Stationary Points Corresponding to the Cycloaddition Reaction between the Substituted Butadiene **6** and Acetone (**7**), in the Absence and Presence of One and Two Chloroform Molecules, in Chloroform

	$\Delta E^b$			$\Delta E^b$	
<b>TS-s</b>	18.6		<b>8-1H-s</b>	-4.0	
<b>8-s</b>	-4.8		<b>TS1-2H-s</b>	9.6	
<b>TS1-1H-s</b>	13.5		<b>IN-2H-s</b>	7.2	
<b>IN-1H-s</b>	11.9		<b>TS2-2H-s</b>	9.5	
<b>TS2-1H-s</b>	12.0		<b>8-2H-s</b>	0.9	

<sup>a</sup> Relative to the separated reagents. <sup>b</sup> In kcal/mol.

at **TS**, 0.59 and 0.08 at **TS-1H**, and 0.51 and 0.05 at **TS-2H**, respectively, while the BO values of the C1–C5 and C4–O6 forming bonds at the TS associated with the meta channel, **TS-reg**, are 0.36 and 0.49, respectively.

The BO values of the C1–N7 and C3–O8 bonds are 1.26 and 1.04 at **TS** and 1.30 and 1.06 at both HB TSs **TS-1H** and **TS-2H**. These BO values indicate a large  $\pi$  character for the C1–N7 single bond as a consequence of the delocalization of the N7 lone pair on the 1,3-butadiene system.

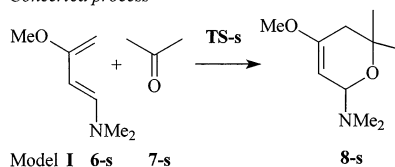
Finally, the natural population analysis (NPA)<sup>28a</sup> allows us to evaluate the charge transfer. The B3LYP/6-31G\* atomic charges at the TSs have been shared between the donor-substituted butadiene **6** and the acceptor acetone (**7**), **7-1H**, and **7-2H**. The values of the charge transferred from **6** to corresponding acetone system along the ortho channels are 0.40 e (**TS**), 0.46 e (**TS-1H**), and 0.44 e (**TS-2H**), while the value of the charge transferred from **6** to **7** along the meta channel is 0.18 e (**TS-reg**). These data indicate that the nature of these TSs may have some zwitterionic character. For the cycloaddition between **6** and **7**, the TS associated with the more favorable ortho reactive channel, **TS**, is more asynchronous and has a larger zwitterionic character than that associated with the meta one, **TS-reg**. Formation of the HBs at the carbonyl oxygen atom increases slightly the charge transfer of the process. The larger stabilization of the TSs than reactants with the HB can be undertook as the large stabilization of the negative charge that is developing at the carbonyl O6 oxygen atom along the nucleophilic attack.

**(b) Solvent Effects Modeled by a Polarizable Continuum Model.** Solvent effects of chloroform and acetonitrile have been modeled using the PCM method by means of geometrical optimizations of the stationary points. Table 2 reports the relative energies,  $\Delta E$ , while their corresponding geometries are given in Figures 1 and 2.

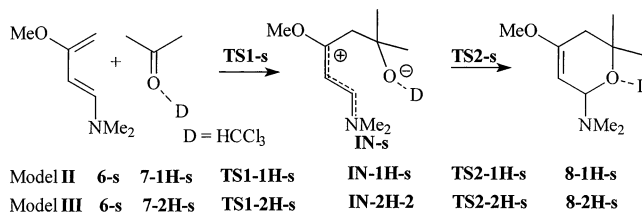
The more noticeable effect with the inclusion of solvent by the PCM approach is the change of the nature for the molecular mechanism of the cycloadditions. For models **II** and **III**, a stepwise mechanism emerges. The first and rate-limiting step corresponds to the nucleophilic attack of the activated diene **6** to the HB acetone, via **TS1-H-s** and **TS1-2H-s**, to form the corresponding zwitterionic intermediate, **IN-1H-s** and **IN-2H-s**, and the second step corresponds to a cyclization process along **TS2-1H-s** and **TS2-2H-s**, respectively (see Scheme 3 and Figure 2). The present results point out that a combined strategy of discrete-continuum models affords a stepwise mechanism

### SCHEME 3

Concerted process



Stepwise processes

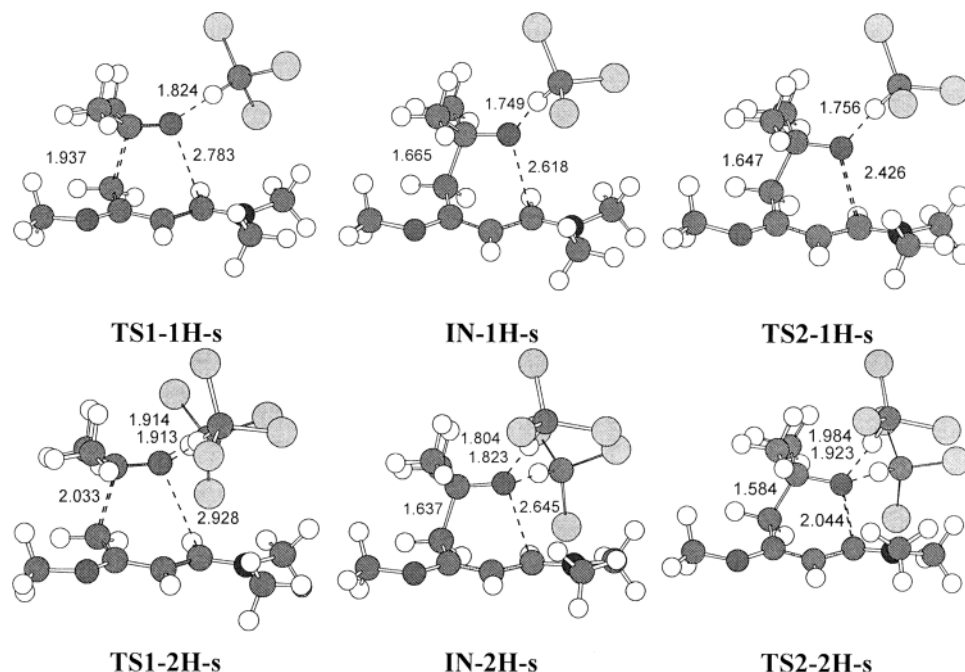


as a consequence of the larger stabilization of the corresponding zwitterionic intermediate.

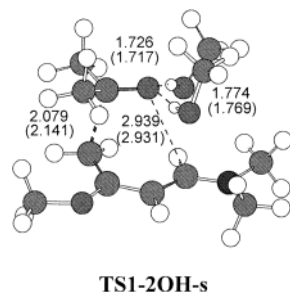
Inclusion of chloroform by the PCM method decreases the activation energy in model **I**, from 19.3 to 18.6 kcal/mol, and in model **II**, from 13.6 to 13.5 kcal/mol, while it increases in model **III**, from 8.5 to 9.6 kcal/mol. The variation of the activation energy values via the inclusion of solvent effects by the PCM is lower than the reduction found in the gas phase with the inclusion of explicit chloroform molecules, 5.7 and 10.8 kcal/mol for **TS-1H** and **TS-2H**, respectively.

Huang and Rawal<sup>11</sup> found that chloroform produces a more significant rate acceleration than in other aprotic organic solvents with a larger dielectric constants: for instance, the reaction in chloroform was 10 times faster than that in the more polar solvent acetonitrile. To probe this finding, the relative energy associated with **TS** in acetonitrile was computed using the PCM method. As was expected, the barrier for **TS-s** in acetonitrile ( $\epsilon = 36.64$ ) is 0.9 kcal/mol lower than that in chloroform ( $\epsilon = 4.9$ ). However, the barrier computed with the combined discrete-continuum models remains 4.3 (model **II**) and 9.9 (model **III**) kcal/mol lower than that in acetonitrile. These cycloadditions were carried out also in *tert*-butyl and isopropyl alcohol.<sup>11</sup> In these polar protic solvents the reaction is very fast.<sup>11</sup> Therefore, it is expected that the strong HB formation between the acidic hydrogen of the alcohols and the carbonyl oxygen of acetone can be responsible for the large rate acceleration. To test this possibility, the nucleophilic attack of the substituted butadiene **6** to acetone (**7**) coordinated to two discrete methanol molecules in a continuum model of methanol ( $\epsilon = 32.62$ ) was analyzed. The geometry of the optimized TS, **TS1-2OH-s**, is given in Figure 3. The corresponding barrier height is 7.4 kcal/mol, 2.2 kcal/mol lower than that for **TS1-2H-s** in chloroform, in agreement with the larger capability for HB formation of the acidic hydrogen of methanol than chloroform toward the oxygen carbonyl of **7**. In summary, the solvent effect on the rate acceleration modeled by discrete-continuum models increases in the following order: acetonitrile (model **I**) < chloroform (model **II**) < methanol (model **II**), in good agreement with the experiments.<sup>11</sup>

A comparison of the geometrical parameters of **TS** in gas phase and in chloroform and acetonitrile given in Figures 1 and 2 shows that with the inclusion of solvent



**FIGURE 2.** Transition structures and intermediates corresponding to the discrete-continuum models for the cycloaddition between the substituted butadiene **6** and acetone (**7**), in the presence of one and two chloroform molecules. The bond lengths directly involved in the reaction are given in angstroms.



**FIGURE 3.** Transition structure corresponding to the nucleophilic attack the substituted butadiene **6** to acetone (**7**) hydrogen bonded to two methanol molecules. The bond lengths directly involved in the reaction are given in angstroms. The values obtained using the PCM approach to simulate methanol are given in parentheses.

effects there is an increase of the asynchronicity on the bond-formation process that can be related with the polarity of the solvent,  $\Delta r = 0.55$  (gas-phase), 0.81 ( $\epsilon = 4.9$ , chloroform), and 0.85 ( $\epsilon = 36.64$ , acetonitrile). Thus, the stabilization of the zwitterionic **TS** by the environment produces a reduction of the Coulombic interactions at the ends of these TSs, increasing the C1–O6 distance. Finally a comparison of the geometrical parameters between **TS1-2H-s** (see Figure 2) and **TS1-2OH-s** (see Figures 3) shows a similar bond-formation process. The values of the HB lengths at **TS1-2OH-s**, 1.720 and 1.770 Å, are shorter than those at **TS1-2H-s**, 1.913 and 1.914 Å, as a consequence of the stronger HB formation on the former, in agreement with the lowering of activation energy.

**(c) Global and Local Electrophilicity/Nucleophilicity Analysis.** These cycloaddition reactions have been also analyzed using the global and local indexes defined in the context of the DFT.<sup>18</sup> Recent studies carried out on cycloaddition reactions with a polar character have

**TABLE 3.** Global Properties<sup>a</sup> and Global Electrophilicity of the Substituted butadiene **6**, Acetone (**7**), and Acetone Hydrogen-Bonded to One and Two Discrete Chloroforms

molecule	$\mu$	$\eta$	$\omega$
<b>7-BH<sub>3</sub></b>	−0.1669	0.1962	1.93
<b>7-2H</b>	−0.1655	0.2362	1.58
<b>7-1H</b>	−0.1503	0.2325	1.32
acetaldehyde	−0.1385	0.2334	1.12
acetone <b>7</b>	−0.1277	0.2330	0.95
butadiene <b>1</b>	−0.0832	0.1858	0.51
butadiene <b>6</b>	−0.0823	0.1899	0.48

<sup>a</sup> Electronic chemical potential ( $\mu$ ) and chemical hardness ( $\eta$ ) in atomic units; global electrophilicity ( $\omega$ ) in eV. See the text for definitions.

**TABLE 4.** Values of the Fukui Functions for the Electrophilic ( $f^+$ ) and Nucleophilic ( $f^-$ ) Attack between the Substituted butadiene **6** and Acetone (**7**)

$f^+$ for <b>6</b>				$f^-$ for <b>7</b>	
C1	C2	C3	C4	C5	O6
0.01	0.24	0.05	0.30	0.53	0.30

shown that these indexes are powerful tools to study both reactivity<sup>19</sup> and regioselectivity.<sup>20</sup> In Table 3 the static global properties, electronic chemical potential ( $\mu$ ), chemical hardness ( $\eta$ ), and global electrophilicity ( $\omega$ ) for the substituted butadienes **1** and **6** and acetone (**7**) in the absence and presence of chloroform molecules are displayed, while the local properties are presented in Table 4.

The electronic chemical potential of acetone (**7**) and acetaldehyde, −0.1277 and −0.1385 au, respectively, are less than the electronic chemical potential of the substituted butadienes **1** and **6** ( $\mu = -0.0832$  and  $-0.0823$  au), thereby indicating that the net charge transfer will take



place from **1** and **6** toward these carbonyl compounds, in agreement with the charge-transfer analysis.

The substituted butadienes **1** and **6** present similar global properties (see Table 3). Both systems have a very low electrophilicity values,  $\omega = 0.51$  and  $0.48$  eV, respectively. Therefore, they are classified as strong nucleophiles in a polar DA reactions.<sup>19</sup> In addition, the values of chemical reactivity indexes of both substituted butadienes allow us to assert that **6** is a reasonable computational model of **1**.

The electrophilicity of acetone,  $0.95$  eV, is lower than that for acetaldehyde,  $1.12$  eV, in agreement with the large reactivity of the later as electrophile. Coordination of the oxygen atom of acetone to the Lewis acid modeled by  $\text{BH}_3$  enhances the electrophilicity of the acetone to  $1.93$  eV. On the other hand, explicit solvation of acetone, **7-1H** and **7-2H**, enhances the electrophilicity to  $1.32$  and  $1.58$  eV, respectively. In both cases, the solvated acetones have a larger electrophilicity power than acetaldehyde. Therefore, a larger reactivity is expected toward a nucleophile.

The difference in electrophilicity,  $\Delta\omega$ , for the 1,3-butadiene/ethylene<sup>19</sup> and the substituted butadiene **6**/acetone DA reactions are  $0.32$  and  $0.47$  eV, respectively. These low values of  $\Delta\omega$  point out a poor reactivity pattern,<sup>35</sup> in agreement with the large activation energy found for these cycloadditions. A different behavior is found for the reaction between the substituted butadiene **6** and the ketones **7-1H** and **7-2H**. The  $\Delta\omega$  for the **6/7-1H** and **6/7-2H** HDA reactions arise to  $0.84$  and  $1.10$  eV, respectively. Note that  $\Delta\omega$  the for the Lewis acid-catalyzed reaction modeled by the **6/7-BH<sub>3</sub>** cycloaddition is  $1.45$  eV. Therefore, the role of chloroform can be considered comparable to that produced by a Lewis acid catalyst; they increase the electrophilicity of the electron-acceptor reagent. It is noteworthy that the feasibility for these HDA reactions is not only a consequence of the increase of the electrophilicity of the acetone by the explicit solvation but also by the strong nucleophilic character of the substituted butadiene **1**. Both factors contribute to the enhancement of the  $\Delta\omega$  for these cycloaddition reactions and, in consequence, the feasibility of the HDA reaction.<sup>19</sup>

Recent studies devoted to cycloaddition reactions with a large polar character have shown that the analysis of the electrophilic and nucleophilic Fukui functions<sup>21</sup> at the corresponding reactants allows one to explain the regioselectivity experimentally observed.<sup>20</sup> The values of the Fukui functions for the substituted butadiene **6** and acetone (**7**) are summarized in Table 4.

The substituted butadiene **6** has the largest value of  $f_k^-$ ,  $0.30$ , at the C4 position and, in consequence, this is the more reactive site for a nucleophilic attack. The presence of the two electron-releasing groups at the C1 and C3 atoms of the substituted butadiene **6** activate the C4 center.<sup>20</sup> On the other hand, acetone (**7**) has the largest value of  $f_k^+$ ,  $0.53$ , at the C5 center. In consequence, the most favorable nucleophile/electrophile interaction will take place between the C4 carbon atom of

**6** and the C5 carbon atom of acetone (**7**), in agreement with the regioselectivity experimentally observed.<sup>11</sup> This analysis is in complete agreement with the larger charge-transfer found at the ortho channel compared with the meta one and with the lower activation energy found at the former.

## Conclusions

DFT calculations, at the B3LYP/6-31G\* level, have been used to study how HB formation influences the chemical reactivity of ketones. The HDA reaction of *N,N*-dimethyl-1-amino-3-methoxy-1,3-butadiene and acetone have been studied by means of three model systems. The effect of the chloroform on the activation energies have been modeled by means of discrete-continuum models. Explicit HB formation to chloroform lowers the gas-phase activation barrier. The inclusion of solvent effects via the continuum approach changes the nature of the molecular mechanism, from a concerted process (discrete model) to a two-step mechanism (discrete-continuum models), the first nucleophilic attack being the rate-limiting step. The joint use of discrete-continuum models allows us to rationalize the experimental observation that chloroform accelerates the reaction more markedly than a more polar aprotic solvent such as acetonitrile. A DFT analysis of the global electrophilicity power of the reagents provides a sound explanation about the catalytic effects of chloroform. This analysis shows that the feasibility of these cycloadditions is not only a consequence of the increase of the electrophilicity of the ketone by the explicit solvation but also by the strong nucleophilic character of these substituted butadienes. Both factors contribute to the increase of the  $\Delta\omega$  and, finally, an analysis of the Fukui functions on the reactants allows us to explain the regioselectivity observed in these polar cycloadditions. We think that the present study based on the characterization of TSs and reactivity indexes may have a more general applicability in the HDA reactions that may go beyond the particular reactions of acetone and can involve carbonyl compounds such aldehydes or ketones.

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**Supporting Information Available:** Table with the total energies, enthalpies, entropies, and free energies for the stationary points corresponding to the cycloaddition reaction of the substituted butadiene **6** and acetone (**7**), in the absence and presence of one and two chloroform molecules; SRCF total energies for the stationary points corresponding to the cycloaddition reaction of the substituted butadiene **6** and acetone (**7**), in the absence and presence of one and two chloroform molecules, in chloroform, and in acetonitrile; total energies, imaginary frequencies, and Cartesian coordinates for the optimized stationary points, in the gas phase and in chloroform. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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