Lewis Acid Mediated Domino Reaction between 2-Cyclohexenone and Methyl Azide – A DFT Study

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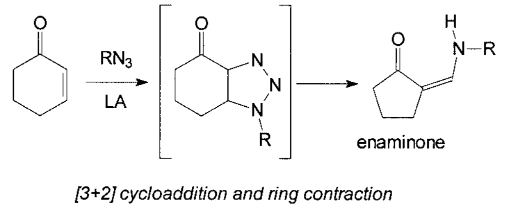
We have studied the Lewis acid mediated domino reaction between 2-cyclohexenone and methyl azide at the B3LYP/6-31G* and B3LYP/6-31+G**//B3LYP/6-31G* levels of theory. A complete survey of the potential energy surface is presented, and the structures of the stationary points and the corresponding molecular mechanism are discussed. The calculations suggest that the product, a cyclopentanone derivative, is formed by means of a domino process that comprises three consecutive reactions. The first and rate-limiting step is a concerted 1,3-dipolar cycloaddition between the Lewis acid coordinated cyclohexenone and methyl azide that yields the corresponding bicyclic 1,2,3-triazoline. The second reaction is a concerted process that includes the extrusion of nitrogen followed by a concomitant skeletal rearrangement to yield the corresponding cyclopentanone derivative. Finally, this cyclopentanone equilibrates to the thermodynamically more stable exocyclic cyclopentanone by means of a stepwise tautomerization of the corresponding iminone. Solvent effects (dichloromethane) were taken into account by using a polarizable continuum model. The results show that no significant changes in the energy profile were found.

Introduction

The appearance of azides in organic synthesis has gained in frequency over the past few decades because they are arguably one of the most versatile organic synthetic intermediates and they present a broad range of chemical reactivity. For instance, they can play the role of either an electrophile or nucleophile, they also appear in radical reactions, and in 1,3-cycloadditions.[1–3] Investigations of new methods for the generation and reaction of azide systems have received significant attention; in particular, groundbreaking efforts of Sharpless et al.[2] and Aube et al.[4,5] allowed the synthesis of a variety of nitrogen-containing heterocycles. Recently, Aube et al.[4b] reported that Lewis acids (LAs) activate the reaction between enones and azide derivatives along a domino reaction path, the first step corresponds to a [3+2] cycloaddition to afford 1,2,3-triazolines, followed by a ring contraction process to obtain the final enaminone product (see Scheme 1). This method also provides an alternative route to the preparation of enaminones that are generally obtained from 1,3-diketones and amines.[6] These compounds are versatile building blocks for the construction of various heterocycles[7] and natural products, and they are often endowed with useful pharmacological properties.



Scheme 1.

In the present work, the LA (BH$_3$) mediated domino reaction between 2-cyclohexenone (**1**) and methyl azide (**2**) that gives the enaminone **5** has been theoretically studied (see Scheme 2); in this case, the Schmidt reaction that yields a ring-expansion product was not observed, and this rearrangement does not proceed when α,β-unsaturated ketones are used.[4] Our aim was to characterize the nature of the molecular mechanism for the ring contraction involved in the formation of the cyclopentanone moiety. Therefore, an effort is made to explain the observed trends from the detailed analysis of the potential energy surface (PES), and the location and characterization of transition structures (TSs) and related minima. This article is structured as follows: the results are discussed on the basis of the analysis of stationary points on the PES. This analysis allows one to rationalize and explain the experimental observations. Finally, in the concluding section, the outcome of the work is summarized. The computational techniques and methodologies adopted are presented in the last section.

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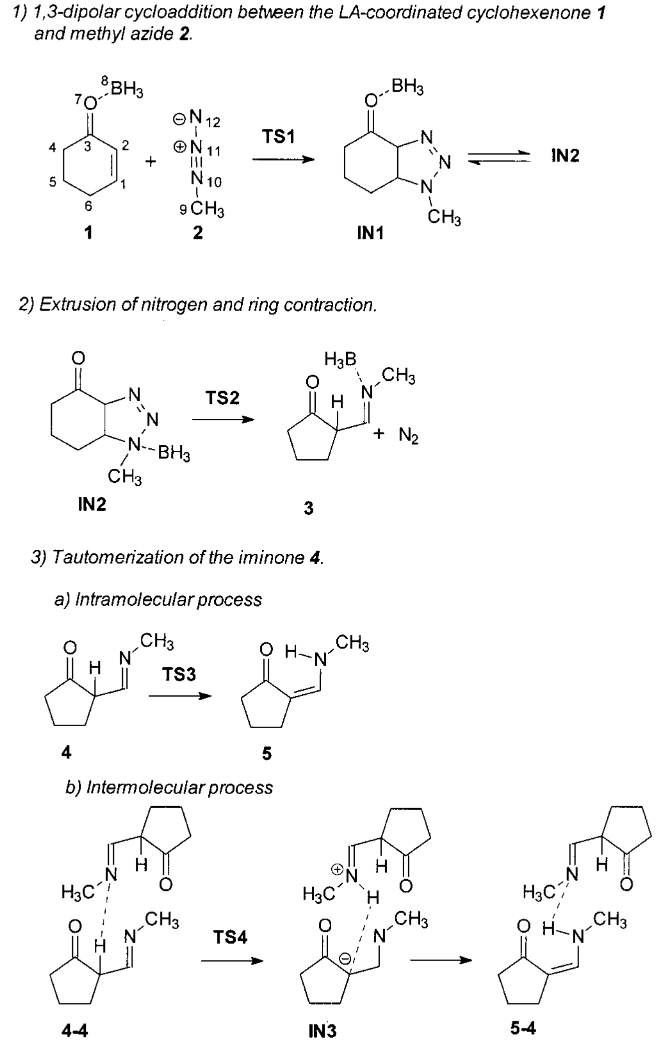

Scheme 2.

Results and Discussion

The stationary points obtained on the PES for the LA-mediated domino reaction between 2-cyclohexenone (**1**) and methyl azide (**2**) to give the enaminone **5** have been depicted in Scheme 2, together with the atom numbering, and the energies are listed in Table 1. The optimized geometries of the TSs are depicted in Figure 1 and Figure 2.

An analysis of the results indicates that this domino process comprises three consecutive reactions (see Scheme 2). The first step is a 1,3-dipolar cycloaddition reaction between the LA-coordinated cyclohexenone **1**, acting as an activated dipolarophile, and methyl azide (**2**), acting as dipole, to yield the corresponding [3+2] cycloadduct **IN1**. The gas-phase activation enthalpy associated with **TS1** is 17.2 kcal/mol. The formation of the triazoline intermediate **IN1** is exothermic by 9.6 kcal/mol. All attempts to locate the TS associated with the nucleophilic attack of the **2** at the C3 carbon atom of the α,β-unsaturated cyclohexenone **1** were unsuccessful, in agreement with the non-observed ring expansion.[4]

Table 1. B3LYP/6-31G* relative enthalpies (ΔH, in kcal/mol), entropies (ΔS, in cal/mol·K) and free energies (ΔG, in kcal/mol) of the stationary points of the Lewis acid mediated reaction between cyclohexenone and methyl azide computed at 298.15 K and 1.0 atm.

		ΔH	ΔS	ΔG
[a]	**1 + 2**	0.0	0.0	0.0
	TS1	17.2	–45.4	30.8
	IN1	–9.6	–45.9	4.1
	IN2	–11.3	–55.9	5.4
	TS2	11.0	–48.8	25.6
	3	–66.0	–29.5	–57.2
[b]	**4**	0.0	0.0	0.0
	TS3	50.4	–2.6	51.2
	5	–9.4	–1.3	–9.0
[c]	**4 + 4**	0.0	0.0	0.0
	4-4	–3.9	–30.7	5.3
	TS4	19.1	–46.0	32.8
	IN3	21.2	–40.0	33.1
	5-4	–10.9	–32.1	–1.4

[a] Relative to **1** and **2**. [b] Relative to **4**. [c] Relative to **4** + **4**.

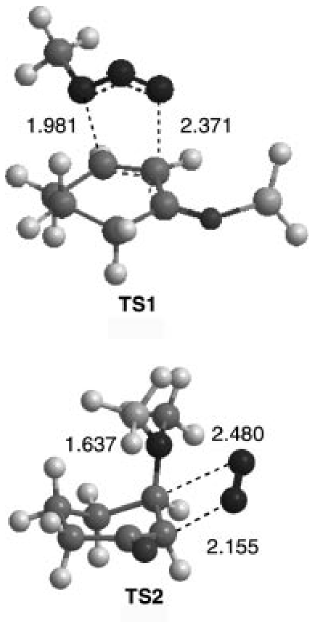

Figure 1. B3LYP/6-31G* geometries of the transition structures **TS1** and **TS2** involved in the LA-mediated domino reaction between cyclohexenone and methyl azide. The bond lengths directly involved in the reaction are given in Å.

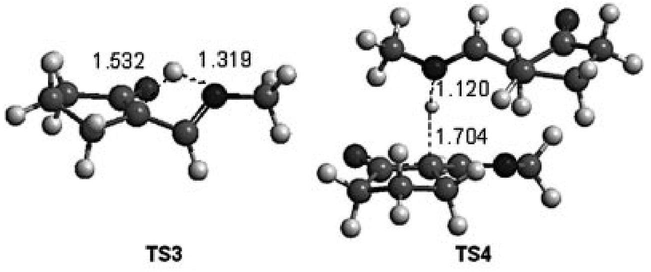

Figure 2. B3LYP/6-31G* geometries of the transition structures involved in the intramolecular, **TS3**, and intermolecular, **TS4**, tautomerization of the imine **4**. The bond lengths directly involved in the reaction are given in Å.

The second reaction that consists of nitrogen extrusion and cyclohexane-ring contraction is a concerted process which yields the corresponding cyclopentanone derivative **3**. All attempts to open the triazoline system starting from **IN1** were unsuccessful; but coordination of BH_3 to the N10 nitrogen atom yields a new LA-coordinated triazoline **IN2** that is 1.7 kcal/mol more stable in energy than **IN1**. This fact can be attributed to the larger basic character of the N10 atom with respect to the carbonyl O7 oxygen atom. From **IN2**, the **TS2** associated mainly with the nitrogen extrusion was found and characterized. The IRC analysis from this TS to the two associated minima, **IN2** and **3**, shows that the nitrogen extrusion and the cyclohexane-ring contraction take place through a concerted process. The activation enthalpy associated with **TS2** is 22.3 kcal/mol, but **TS1** is located 6.2 kcal/mol above **TS2**. As a consequence, the first reaction is the rate-limiting step of this domino process. The formation of iminone **3** is very exothermic, 66.0 kcal/mol; the transformation of cyclohexenone **1** and azide **2** into **3** is an irreversible process.

Finally, in the third reaction of this domino process, iminone **4** (it has the same structure as **3** but without the BH_3 and N_2 molecules) equilibrates to the thermodynamically more stable exocyclic enaminone **5**. The formation of enaminone **5** is exothermic by 9.4 kcal/mol. This equilibrium can take place through two different competitive channels that can involve the direct tautomerization of **4** to **5** by a 1,3-hydrogen shift or the stepwise tautomerization via the enolate **IN3** (see Scheme 2).

The tautomerization of **4** to **5** by a 1,3-hydrogen shift presents a very large activation energy, 50.4 kcal/mol (**TS3**). This unfavourable activation energy is mainly due to the strain associated with the formation of the four-membered ring at the **TS3**. This tautomerization can also be achieved through a stepwise process via the enolate intermediate **IN3**. This process demands the participation of a basic species in order to favour the enolization of **4**. We modelled this process by using a second molecule of imine **4** through its basic N10 nitrogen atom. The model for the stepwise tautomerization process is depicted in Scheme 2. The activation energy associated with the enolization of **4** via **TS4** is 24.0 kcal/mol. In the gas-phase, the formation of the enolate **IN3** is endothermic by 25.1 kcal/mol because of the anionic character of the enolate system in **IN3** and the cationic character of the protonated imine **4**. Finally, the proton transfer from the protonated imine to the nitrogen atom of enolate **IN3** with formation of enone **5** takes place along a process with no barrier. We have explored in detail the corresponding zone of the PES and any attempt to locate the TS was unsuccessful at the B3LYP/6-31G* level.

In order to increase the level of calculations, B3LYP/6-31+G**//B3LYP/6-31G* single-point calculations were computed. The obtained energies are listed in Table S1 of the Supporting Information (see footnote on first page of this article). All values are very similar to those obtained with the 6-31G* basis set, only the structure **4-4** is 6 kcal/mol less stable. In addition, the zwitterionic intermediate **IN3** is now lower in energy than **TS4**. This result does not change the energy profile of the reaction or the nature of the reaction mechanism.

The geometries of the TS are depicted in Figures 1 and 2. At the **TS1**, associated with the 1,3-dipolar cycloaddition, the lengths of the C1–C10 and C2–C12 forming bonds are 1.981 Å and 2.371 Å, respectively. These values suggest that the cycloaddition corresponds to an asynchronous concerted process where the C–N forming bond at the β-position of the α,β-unsaturated ketone is more advanced than that at the α-position. At **TS2**, the lengths of the C1–C11 and C2–C12 breaking bonds are 2.480 Å and 2.155 Å, respectively, whereas the C1–C6 bond length is 1.637 Å. The distances between the transferred hydrogen and the C2 and the N12 atoms at **TS3** are 1.532 Å and 1.319 Å, respectively, whereas in **TS4**, the distances between this hydrogen and the C2 and the N12′ atoms are 1.704 Å and 1.120 Å, respectively. The strain, associated with the C2–C3–N12 bond angle at **TS3** (106.6°), is responsible for the large activation energy associated with the intramolecular process. This angle at iminone **4** is 121.9°.

In summary, four TSs (**TS1**, **TS2**, **TS3**, and **TS4**), three intermediates (**IN1**, **IN2**, and **IN3**) and three products (**3**, **4** and **5**) have been located and characterized on the PES. In order to understand the domino nature of this complex reaction, the free energies of all stationary points involved in this reaction were computed at 25 °C; a schematic representation of the relative free energies are given in Figure 3. The activation free energy for the 1,3-dipolar cycloaddition is calculated from the activation entropy and the activation enthalpy to be 30.8 kcal/mol (see Table 1). The LA-coordinated triazolines **IN1** and **IN2** are 4.1 and 5.4 kcal/mol higher in energy than the reactants, respectively. The activation free energy associated with **TS2** is 20.2 kcal/mol; **TS1** is 5.2 kcal/mol above **TS2**. The extrusion of the nitrogen molecule and accompanying ring contraction is a very exergonic process. As a consequence, as soon as the triazoline **IN2** is formed, it is irreversibly converted into the thermodynamically more stable cyclopentanone **3** (see Figure 3). Finally, the gas-phase activation free energy associated with the tautomerization of **4** to **5** is 35.4 kcal/mol (30.1 kcal/mol from the complex **4-4**).

The bond order (BO)[8] values of the C1–N10 and C2–N12 forming bonds at **TS1** are 0.42 and 0.25, respectively. The value of the unique imaginary frequency for the **TS1** is 401.93i cm^{-1}. At **TS2** the BO values of the C1–N11 and C2–N12 forming bonds are 0.14 and 0.26, respectively, while the N11–N12 and C1–C2 BO values are 2.80 and 0.82, respectively. These values indicate that at **TS2**, the nitrogen extrusion is very advanced with respect to the cleavage of the six-membered ring. The unique imaginary frequency of **TS2**, 201.77i cm^{-1}, is associated mainly with the nitrogen extrusion via the C2–N12 and N10–N11 breaking bonds. Analysis of the IRC from **TS2** to **3** shows that the cyclohexane-ring contraction takes place after the nitrogen extrusion in a concerted fashion.

Solvent effects in this domino reaction have been included using the PCM method. Table 2 reports the relative energies in dichloromethane. When solvent effects are taken

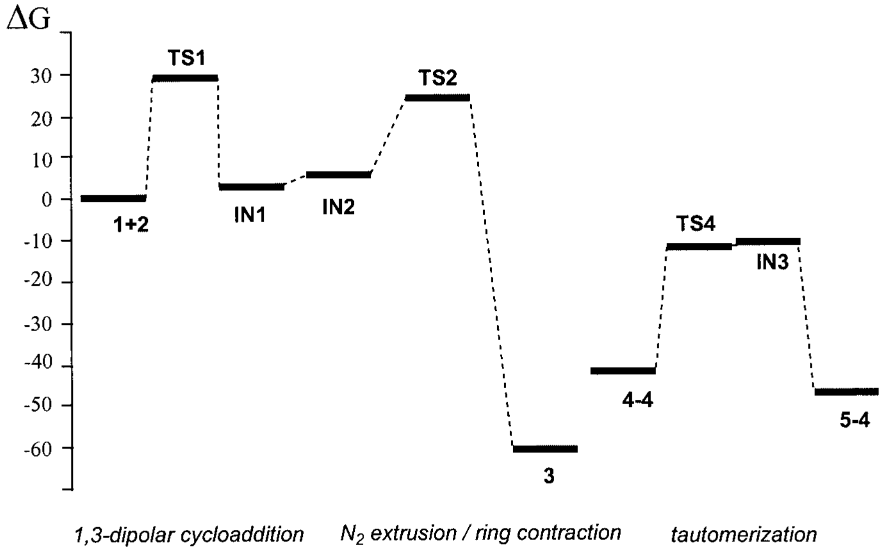

Figure 3. Free energy profile (in kcal/mol) for the LA-mediated domino reaction between cyclohexenone and methyl azide.

into account, the TSs and intermediates are stabilized between 10 and 13 kcal/mol, while the reactants and products are stabilized to a minor extent, between 2 and 10 kcal/mol. The larger stabilization of the former indicates the polar character of these species. However, solvent effects do not have a noticeable change on the energetic barrier of this domino reaction. In dichloromethane, the zwitterionic intermediate **IN3** is lower in energy than **TS4**.

Table 2. PCM B3LYP/6-31G* relative energies[a] (Δ*E*, in kcal/mol) of the stationary points of the Lewis acid mediated reaction between cyclohexenone and methyl azide in dichloromethane.

		Δ*E*
[a]	**1 + 2**	0.0
	TS1	16.1
	IN1	–11.0
	IN2	–13.2
	TS2	12.6
	3	–63.9
[b]	**4 + 4**	0.0
	4-4	–0.8
	TS4	20.3
	IN3	19.6
	5-4	11.8

[a] Relative to **1** and **2**. [b] Relative to **4 + 4**.

Conclusions

We present the complete study of the potential energy surface for the LA-mediated domino reaction between 2-cyclohexenone, an α,β-unsaturated ketone, and methyl azide to give the corresponding ring-contraction product (a cyclopentanone derivative). The main conclusions of the present theoretical study can be summarized as follows: i) this transformation corresponds to a domino process with three well-defined consecutive reactions; ii) the first step of the domino process is an LA-catalyzed 1,3-dipolar cycloaddition between the LA-coordinated 2-cyclohexenone and methyl azide to give a triazoline intermediate; iii) in the second step the LA is coordinated to the more basic nitrogen atom of the triazoline ring in order to assist the subsequent decomposition process. The LA promotes the nitrogen extrusion and the subsequent ring contraction via a skeleton rearrangement; iv) finally, equilibration converts the cyclopentanone-imine into the corresponding thermodynamically more stable enaminone through a stepwise process; v) the inclusion of solvent effects through the continuum model does not significantly change the energy profile.

Computing Method

Density functional theory (DFT) calculations were carried out using the B3LYP[9] exchange-correlation functional, together with the standard 6-31G* and 6-31+G** basis sets,[10] as well as single-point calculations at the B3LYP/6-31+G**//B3LYP/6-31G* level. The PES was explored in detail to ensure that all relevant stationary points were located and properly characterized. Berny analytical gradient optimization routines[11] were used for optimization. The stationary points were characterized by frequency calculations in order to verify that the TSs had one imaginary frequency. The intrinsic reaction coordinate (IRC)[12] path was traced to obtain and check the energy profiles connecting each TSs to the two associated minima of the proposed mechanism by using the second-order Gónzalez–Schlegel integration method.[13] Relative enthalpies, Δ*H*, entropies, Δ*S*, and free energies, Δ*G*, were calculated with the standard statistical thermodynamics[10] at 298.15 K. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[14]

The solvent effects, modelled as a continuum medium, were considered by performing single-point B3LYP/6-31G* calculations using the self-consistent reaction field (SCRF)[15] based on the polarizable continuum model (PCM) of Tomasi's group.[16] Dichloromethane was used as solvent (in the experimental work, $\varepsilon = 8.93$). All calculations were carried out with the GAUSSIAN03 suite of programs.[17]

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