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Research Article

Theoretical Analysis of the Mechanism of the 1,3-Dipolar Cycloaddition of Benzodiazepine with N-Aryl-C-ethoxycarbonylnitrilimine

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In this work, the mechanism and regio- and no-periselectivity of the 1,3-dipolar cycloaddition reaction of 2,4-dimethyl-3H-1,5-benzodiazepine with N-aryl-C-ethoxycarbonylnitrilimine have been studied using the DFT method at the B3LYP/6-31G(d) level of theory. IRC calculations and activation energies show that this reaction follows an asynchronous concerted mechanism. The two C=N sites of 2,4-dimethyl-3H-1,5-benzodiazepine are easily reached by the dipole, and the energy barrier between the reagents and the transition states is too weak. The secondary barriers are traversed by the heat released in the reaction medium after the crossing of the first TS, which facilitates the addition reaction and does not require high energy. The obtained results of this study are in good agreement with experimental outcomes.

1. Introduction

Since the introduction of the 1,3-dipole concept established by Huisgen [1, 2], cycloaddition reactions have been developed considerably. In 1963, Huisgen had proposed a concerted mechanism different from the radical interpretation put forward by Firestone [3–5] and adopted for longtime. Currently, the concerted mechanism seems to be well established as a result of numerous experimental and theoretical studies [6–8]. The Huisgen cycloaddition is the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5-membered (hetero) cycles. Examples of such dipolarophiles are alkenes, alkynes, isothiocyanates, enamines, nitriles, and imines.

Over the last several decades, the extensive and detailed studies of 1,3-dipolar cycloaddition (1,3-DC) methodologies have provided organic chemists with indispensable tools to synthesize a wide array of heterocyclic products from natural products synthesis, materials science, and polymer chemistry to chemical biology [1, 6, 9–27]. For example, 1,3-dipolar cycloadditions of nitrilimines with different kinds of triple and double bonds have been extensively used in the last few decades for the synthesis of numerous five-membered N-heterocycles of effective biological importance [28–33]. Literature offers many examples of regioselectivity of 1,3-dipolar cycloadditions (1,3-DCs) that were successfully explained using quantum chemistry- (QC-) based reactivity indices [34–41].

Although transition state (TS) theory remains the most widely used and the most rigorous approach for the study of the reactional mechanisms, the localization of TSs is not always easy. Furthermore, TS calculations are often very time-consuming when bulky substituents make parts of the studied systems.

On the other hand, the nitrilimines are characterized by their high reactivity with dipolarophiles in 1,3-dipolar cycloaddition reactions. We have attempted to prepare the nitrilimine from the corresponding precursor in the presence of triethylamine.

We performed the cycloaddition reaction of 2,4-dimethyl-3H-1,5-benzodiazepine **1** [42] with N-aryl-C-ethoxycarbonylnitrilimine **2**. This latter is, experimentally,

generated in situ from ethyl N-arylhydrazono-bromoglyoxylate [43] with the excess triethylamine in anhydrous benzene as solvent. It was performed at room temperature by simple agitation for 48 hours. After the usual treatment of the reaction mixture, only one product **4** was isolated (Scheme 1). Based on the experimental results [44], a first reaction mechanism is proposed.

Whatever the amount of dipole used, monocycloadduct **3** has not been isolated. On the other hand, the spectroscopic analyses show the presence of compound **4**, and a double or triple bond in dipolarophiles leads, a priori, to two **trans** or **cis** isomers (Figure 1). However, the objective of the current study is to explain the mechanism of such reaction, to determine the no-periselectivity of the reaction as well as the most favored isomer, and to make a comparison with experimental data and theoretical ones obtained in this study.

2. Computational Details

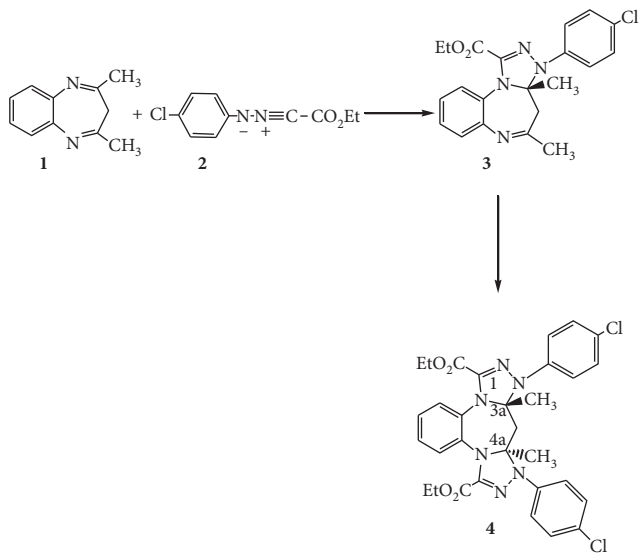
Equilibrium geometries were optimized using the density functional theory (DFT). The computations were performed using Becke's three-parameter exchange functional with the Lee–Yang–Parr (LYP) [45–49] correlation functional and the 6-31G(d) basis set [50–52]. The Gaussian 09W [53] program series were used to perform full geometry optimizations. To check the computation level, we have performed a high-level B3LYP/6-31+G(d,p) on the reagents and the first TS and noted that the activation barrier is almost the same. So we generalized the B3LYP/6-31G(d) to localize all the extrema of the total potential surface (PES). Minima and TSs have been characterized by diagonalizing the Hessian matrix (all force constants are positive for minima and only one is negative for TSs). Moreover, intrinsic reaction coordinate (IRC) calculations were performed to check the topology of the TS environment or confirm the right (TS) connectivity to the right minima (reagents and product) [54, 55].

3. Results and Discussion

Even though the total potential energy surface (PES), without any geometrical restriction, of this 1,3-DC reaction was meticulously explored, only two stereoisomers have been localized. These later differ of each other by both methyl groups on C2 and C10 position leading to **trans** or **cis** (Figure 1).

Thermodynamically, the results show that the formation of **trans** product **4 (4-trans)** is energetically favored since it is lower than the **cis** one (**4-cis**) by 12 kcal/mol (Table 1). This is in perfect agreement with the experimental results [44] where only the **trans** one has been isolated and well characterized.

As the use of reliable ab initio methods for a reaction path treatment is too heavy for large systems, we have primarily processed our study by models. However, the 2,4-dimethyl-3H-1,5-benzodiazepines **1** molecule was modeled by R1 model (Scheme 2). The total PES exploration of both approaches on C=N bond shows that, for both cis and trans isomers, the reaction implies an unstable reactional



Scheme 1: Reaction of 2,4-dimethyl-3H-1,5-benzodiazepine **1** with N-aryl-C-ethoxycarbonylnitrilimine **2**.

intermediate located between two TSs before reaching the products.

We reported in Table 2 the energetic data of all extrema (reagents, TSs (TS1 and TS2), intermediates, and products).

In approach 1, the first energy barrier TS1 is only about 3 Kcal/mol (Figure 2) above the reagent's level. The intermediate **Int1** and the **TS2** are so close in structure and energy that the crossing of the second barrier is done easily thanks to the released heat in the reactional medium by the transformation TS1-Int1. Figure 3 shows that the first transition corresponds to the C(dipole)-N(reagents) bond formation and the second one corresponds to the five-membered cycle closing by the N(dipole)-C(reagent) bond formation. Approach 2 corresponds to the attack of the second dipole **D1** on the monocycloadduct product **P1**. The reaction is like the first one with a first activation energy of 2 kcal/mol (Figure 2).

The vibrational normal mode and the IRC analysis of both approaches show that there are no other intermediates nor TSs on the total PES and these later correspond to the formation of the cyclic C(dipole)-N(reagents) and N (dipole)-C (reagents) bonds. The weak activation energies suggest that the addition occurs easily and seems the reason why the intermediate states **Int1** and **Int2** and the monocycloadduct product P1 cannot be isolated. The energetic profiles extracted from the total PES show that the reaction is exothermic, and the released energy is about 56 Kcal/mol. We have depicted in Figure 3 all the optimized structures involved in the study.

Now let us analyze the mechanism on the real molecules and rationalize the regioselectivity of the cycloaddition reaction (Scheme 1). To compute the extrema corresponding to the reaction sketched in Scheme 1, we have performed DFT calculations, as detailed in the Computational Details section, on the species reported in Figure 4. This figure represents the reagents, intermediates, transition states, and products along the proposed reaction pathway leading from

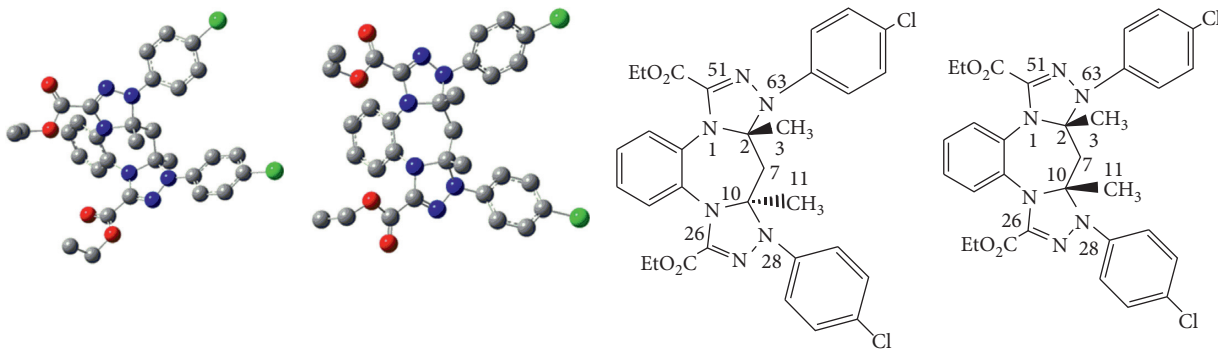
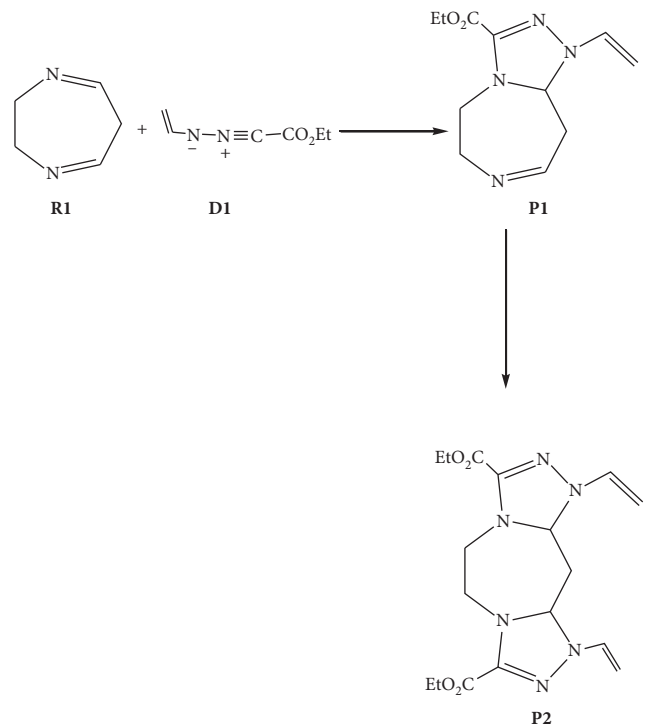


Figure 1: The lowest lying isomers (**4-trans** and **4-cis**) on the total PES of the bis-cycloaddition. (a) **4-Trans** (0.00 kcal/mol), (b) **4-cis** (12.00 kcal/mol), (c) **4-Trans**, and (d) **4-cis**.

Table 1: Relative energies[a] (kcal/mol), binding lengths (Å), and dihedral angle (°) of the low-lying isomers of the bis-cycloaddition.

	4-Trans	4-Cis
ΔE (kcal/mol)	00	12
C51-N1	1.413	1.430
N63-C2	1.502	1.521
C10-N28	1.489	1.521
C26-N15	1.385	1.429
C7-C2	1.536	1.537
C7-C10	1.552	1.537
N63-N62	1.367	1.374
N63-C64	1.407	1.420
N28-N27	1.379	1.374
N28-C29	1.397	1.420
C73-Cl50	1.759	1.758
C38-Cl39	1.759	1.758
C3-C2-C7-C10	54.84	67.20
C11-C10-C7-C2	162.13	−67.42
N63-C2-C7-C10	0.30	−170.16
N28-C10-C7-C2	−70.01	170.00

[a]Calculated according to **4-trans** whose E is −2749.107545 ua at B3LYP/6-31G(d).



Scheme 2: Reaction of diazepine **R1** with nitrilimine **D1.**

1 and **2** to **4**. The energies of the TSs, TS1 and TS2, and the obtained cycloadduct **4** are reported in Table 3 and Figure 5. In both reaction profiles of Figure 5, the starting reagents (compounds 1-D1 and 3-D1) consist of a bimolecular system corresponding to an energy minimum in the potential energy surface (PES), stabilized by weak intermolecular interactions.

Both reaction profiles involve two transition states and one intermediate. Intermediates **1-D1-Int1** and **3-D1-Int2** of both mono- and bis-1,3-DC, respectively, present only a single covalent bond between one of the two nitrogen atoms of **1** and carbon atom of **2** (Scheme 1). In detail, the first transition state of both the mono- and the bis-cycloaddition is characterized by an activation energy lower than 3 kJ/mol. The activation energy of the second transition state of the mono-cycloaddition is lower than 4 kJ/mol for **1-D1-Int1–3** (Approach 1). The second transition state of the bis-cycloaddition has an activation energy lower than 3 kJ/mol for **3-D1-Int2–4** (Approach 2). This value indicates that the formation of the intermediate states **1-D1-Int1** and **3-D1-Int2** and the monocycloadduct product **3** is very easy to be obtained and cannot be isolated.

Intermediate **1-D1-Int1** can rotate its **C51-N1** bond (Figure 1) to form another complex **1-D1-TS2** (Figure 4). For the second dipole attack on the second double bond, our calculations show a similar path to that of the first approach (Figure 5) with an activation energy of about 2.4 kcal/mol to cross the first TS.

Comcerning the periselectivity of the reaction, as both C=N sites are easily reached by the dipole and the energetic barrier between reagents and TSs are too weak (less than 4 Kcal/mol) on one hand, and on another hand the second barriers are crossed by the heat released in the reactional medium after crossing the first TSs, making the addition

Table 2: Relative energies[a] (ΔE) for DC reactions of reagents R**1** and dipole **D1** at B3LYP/6-31G(d).

Approach 1		Approach 2	
	ΔE (kcal/mol)		ΔE (kcal/mol)
R1-D1	0.00	P1-D1	0.00
R1-D1-TS1	3.00	P1-D1-TS1	2.00
R1-D1-Int1	−13.50	P1-D1-Int2	−31.00
R1-D1-TS2	−13.10	P1-D1-TS2	−30.60
P1	−40.20	P2	−56.30

[a]Calculated according to R1 whose E is −796,88897 ua and to P1-D1 whose E is -1290,24796 ua at B3LYP/6-31G(d).

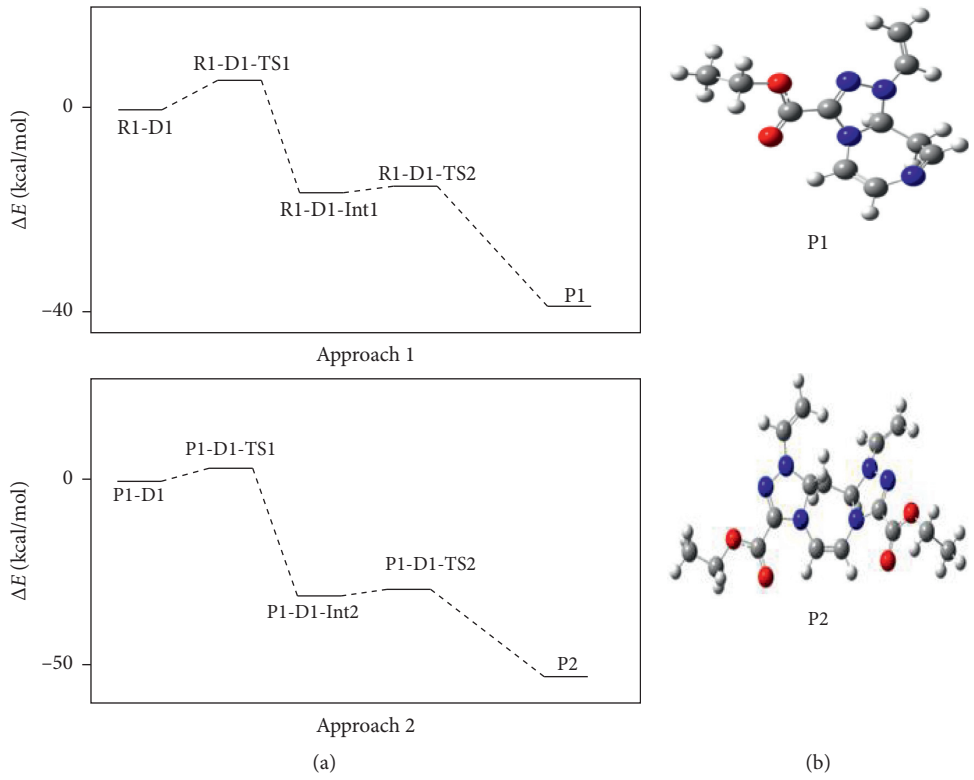


Figure 2: Energetic profile of both approaches at B3LYP/6-31G(d) level (a) and the lowest lying isomers of P1 and P2 products (b).

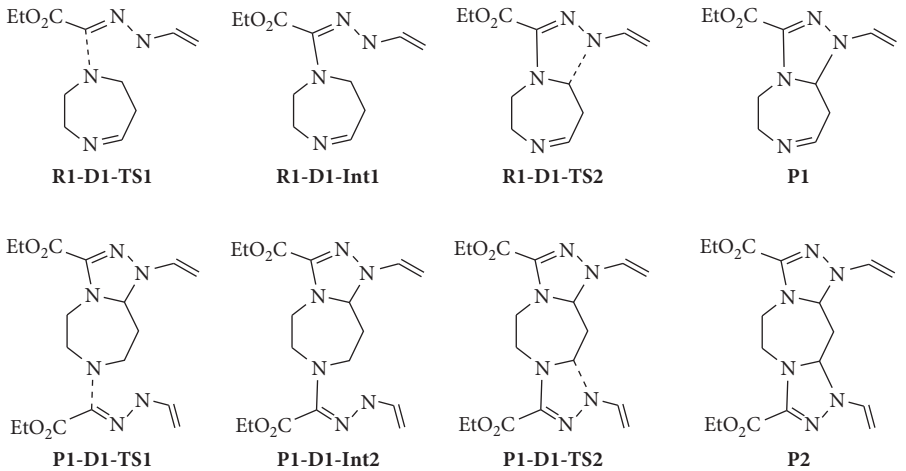


Figure 3: Species involved in the cycloaddition reaction (see Scheme 2 and Table 1).

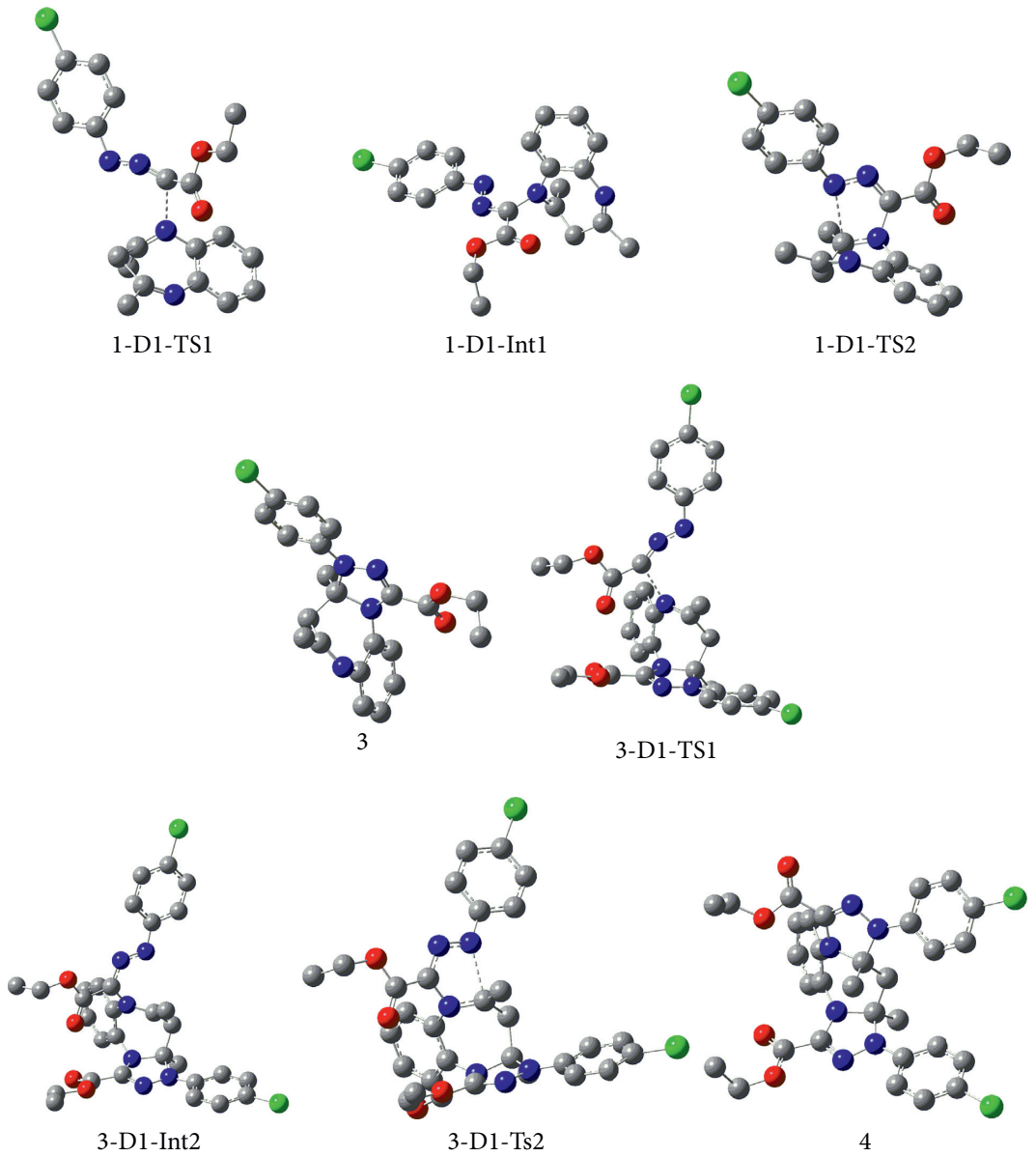


Figure 4: Selected optimized geometries of intermediates and TSs computed at B3LYP/6-31G(d) level of theory for DAC of 2,4-dimethyl-3H-1,5-benzodiazepine **1** with N-aryl-C-ethoxycarbonylnitrilimine **2** (hydrogen atoms have been omitted for clarity).

Table 3: Relative energies[a] (ΔE) of the low-lying isomers for 1,3-DC of benzodiazepine **1** and dipole **D1** at B3LYP/6-31G(d) level.

Approach 1		Approach 2	
	ΔE (kcal/mol)		ΔE (kcal/mol)
1-D1	0.00	**3**-D1	0.00
1-D1-TS1	1.60	**3**-D1-TS1	2.40
1-D1-Int1	−55.44	**3**-D1-Int2	−20.50
1-D1-TS2	−52.17	**3**-D1-TS2	−18.50
3	−76.40	**4**	−34.70

[a]Calculated according to 1-D1 whose E is −1642,38099 ua and to 3-D1 whose E is −2749,05229 ua at B3LYP/6-31G(d).

reaction easy and not requiring high energy. The second barriers are crossed by the heat released in the reactional medium after crossing the first TSs, making the addition reaction easy and not requiring high energy. This is also due to the attractive group CO_2ET. However, we can conclude that (i) the reaction is exothermic with a released heat of −76,40 kcal/mol for **3** and the formation of the two bis-cycloaddition **4** is exothermic by −34.70 kJ/mol; (ii) the addition on the C=N bond is characterized by an asynchronous mechanism; (iii) the 1,3-DC of 2,4-dimethyl-3H-1,5-

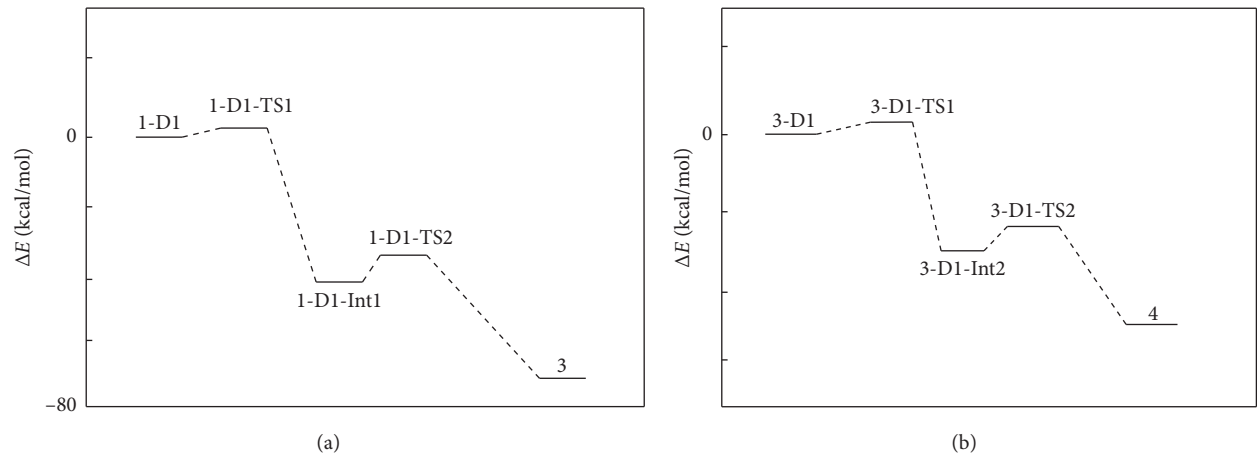


Figure 5: Proposed mechanisms for the DC reaction of benzodiazepine **1** and dipole **D1**. (a) Approach 1. (b) Approach 2.

benzodiazepine **1** and with N-aryl-C-ethoxycarbonylnitrilimine **2** is not periselective. Finally, the energetic values obtained from this theoretical study allow us to generalize that this type of reaction is kinetically easier and thermodynamically more favorable. This is consistent with our experimental results [44].

4. Conclusion

The mechanism of the 1,3-dipolar cycloaddition reaction of 2,4-dimethyl-3H-1,5-benzodiazepine with N-aryl-C-ethoxycarbonylnitrilimine was investigated using the DFT method at the B3LYP/6-31G(d) level of theory. The computation allowed us to conclude that

(i) The attack of the dipole on benzodiazepine **1** takes palace only in one direction, which supports that the reaction is regioselective.

(ii) The low activation energy values are consistent with the intermediate states instability since it was not observed in the spectroscopic analysis at room temperature.

(iii) The favored cycling path and the experimental regioselectivity and no-periselectivity of this cycloaddition have been rationalized by the energetic analysis. Finally, this cycloaddition follows an asynchronous mechanism.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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