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 success fully 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-bromo- 
glyoxylate [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 ex- 
pperimental 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 opti- 
mizations. To check the computation level, we have per- 
fomed 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 co- 
ordinate (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 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 models by DFT. 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 
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 inter- 
mediate 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 latter 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 mono-
cycloadduct 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 re- 
action (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 

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

Concerning the peri-selectivity 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 (ΔE) for DC reactions of reagents R1 and dipole D1 at B3LYP/6-31G(d).

|                      | Approach 1 | ΔE (kcal/mol) | Approach 2 | 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 a.u. and to P1-D1 whose E is -1290,24796 a.u. 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).
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$_2$ET. 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 bicycloaddition 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-

**Table 3:** Relative energies ($\Delta E$) 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 |          |
|-------|------------|----------|------------|----------|
|       | $\Delta E$ (kcal/mol) |          | $\Delta E$ (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).
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 place 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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