Toward an Understanding of Molecular Mechanism of Domino Cycloadditions. Density Functional Theory Study of the Reaction between Hexafluorobut-2-yne and *N*,*N*′-Dipyrrolylmethane

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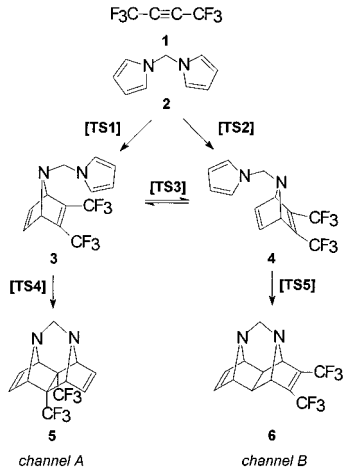
Domino reactions are the stepwise formation of the individual bonds in the target molecule with the advantage that several bonds can be formed in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents.[1] Domino Diels−Alder cycloadditions are powerful methods for the construction of bridged polycyclic systems. These chemical reactions proceed in a highly diastereoselective manner with quantitative yields, occupying a central role in organic synthesis to devise reactions that can form several carbon−carbon bonds in one operation leading to the construction of complex polycyclic structures with the proper regio- and stereochemical control.[2−4]

Despite the obvious potential of this process and the myriad of possible modifications, from a theoretical point of view, this intramolecular form has not received the same amount of attention as its counterpart, the intermolecular Diels−Alder reaction,[5] and the nature by which the reactions follow one another is fundamental to understanding the reaction pathways. This theoretical study was undertaken in order to provide knowledge regarding the nature of the molecular mechanism of the reaction, to gain insight into the origins of the thermodynamic and kinetic controls, and to interpret experimental results. All calculations were performed with Gaussian 94 suite of programs.[6] Previous theoretical studies of Diels−Alder reactions have indicated that the activation energies calculated at the Hartree−Fock level of theory are too large, while the MP2 calculations underestimate it.[7] However, energy calculations for stationary points using the MP3/6-31G*[8] and B3LYP/6-31G*[9] levels are in reasonable agreement with experimental activation energy values. Thus, in the present study, we have used the latter method to obtain accurate barrier heights. An extensive characterization of the potential energy surface (PES) was carried out with the B3LYP/6-31G* functional,[10] which includes dynamic electron correlation. The stationary points were characterized by frequency calculations in order to verify that minimal and transition structures (TS) have zero and one and only one imaginary frequency, respectively. No symmetry constraints have been imposed in the geometrical optimizations of stationary points.

Scheme 1



We chose the domino cycloaddition of hexafluorobut-2-yne (**1**) to *N*,*N*′-dipyrrolylmethane (**2**) to yield bisethenodiazanoradamantane ring systems: the regioisomer cycloadducts **5** or **6** (see Scheme 1) as the calculational model. For this case, extensive experimental data are available.[11]

Figure 1 displays a pictorial representation of PES and the location of the stationary points: reactants **1** + **2**, intermediates **3** and **4**, products **5** and **6**, and the five transition structures **TS1**, **TS2**, **TS3**, **TS4**, and **TS5** along the reactive channels A and B. Figure 2 presents the geometries and selected geometrical parameters for transition structures, while the computed energies are summarized in Table 1.

The domino cycloaddition between **1** and **2** takes place along two reaction pathways, which involve two consecutive Diels−Alder cycloadditions. Pathways A and B are exothermic processes. The first steps are [4 + 2] intermolecular cycloadditions between **1** and **2** with formation of two azanorbornadiene intermediates, **3** and **4**, via the transition structures **TS1** and **TS2**, corresponding to the reactive channels A and B, respectively. The second steps are the [4 + 2] intramolecular cycloaddition of intermediates to yield the regioisomer cycloadducts **5** and **6**, via the corresponding transition structures, **TS4** and **TS5**, respectively.

The first intermolecular cycloaddition is the rate-limiting step for both reaction pathways, representing the corresponding barrier

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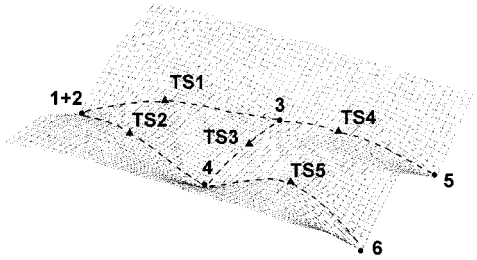

Figure 1. A schematic representation of the potential energy surface for the domino cycloaddition of hexafluorobut-2-yne to *N*,*N*′-dipyrrolylmethane. The location of the stationary points are depicted.

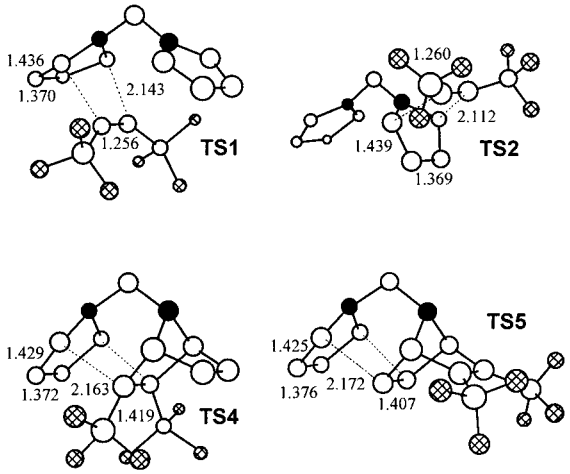

Figure 2. Selected geometrical parameters for the Diels−Alder transition structures corresponding to the domino cycloaddition of hexafluorobut-2-yne to *N*,*N*′-dipyrrolylmethane. The values of the lengths of the C−C bonds directly involved in the cycloaddition obtained at the B3LYP/6-31G* level are given in angstroms.

Table 1. B3LYP/6-31G* Relative Energies[a] (in kcal/mol) for the Stationary Points on the Potential Energy Surface of the Domino Cycloaddition of Hexafluorobut-2-yne to *N*,*N*′-Dipyrrolylmethane

3	**4**	**5**	**6**	**TS1**	**TS2**	**TS3**	**TS4**	**TS5**
−9.8	−8.7	−18.3	−22.2	18.7	25.8	0.3	3.4	9.1

[a] Total energy of hexafluorobut-2-yne plus *N*,*N*′-dipyrrolylmethane is −1209.829416 hartree.

heights of 18.7 and 25.8 kcal/mol for the pathways A and B, respectively. These values indicate that the first step for the intermolecular Diels−Alder cycloaddition is more favorable along channel A. The intermediates formed in the initial stage are unstable, carrying out the intramolecular cycloaddition by surmounting the low second barrier height. Similar to that of the intermolecular Diels−Alder cycloaddition, the barrier height for **TS5** is higher than that corresponding to **TS4** (17.8 and 13.2 kcal/mol, respectively), resulting in the elimination of channel A and the kinetic control of cycloadduct **5** formation in the global process. However, the cycloadduct **6** is more stable (−22.2 kcal/mol) than the cycloadduct **5** (−18.8 kcal/mol).

Rotation of the *N*-pyrrolylmethyl group and the configurational inversion on nitrogen atom of azanorbornadienes **3** and **4** yield a conformational arrangement between both intermediates. We have characterized the transition structure, **TS3**, associated with the transformation **3** → **4** with a barrier height of 10.1 kcal/mol. This fact opens the possibility that the Curtin−Hammett principle[12] can be operative in this reaction. Although only the intermediate **3** is obtained in the first step, the lower value of this barrier height allows the interconversion between intermediates **3** and **4** and the connection of the reaction pathways A and B.

The theoretical results show that by thermolysis the cycloadduct **5** can undergo a retro-Diels−Alder reaction to give the intermediate **3**, the barrier height being 21.7 kcal/mol. In addition, the retro-Diels−Alder reaction from **3** to yield the initial reactants, **1** + **2**, presents a larger value of barrier height (28.5 kcal/mol). Furthermore, the easy interconversion between the azanorbonadiene intermediates **3** and **4** allows that under these condition the cycloadduct **6** (thermodynamic control) can be preferentially formed.

We have computed the values of the difference of enthalpy, entropy, and Gibbs energies corresponding to the thermochemical equilibrium between the cycloadducts **5** and **6** at the B3LYP/6-31G* level along with the RHF/6-31G* harmonic frequencies. These frequencies have been scaled by 0.9,[13] and the enthalpy and entropy changes are calculated from standard statistical thermodynamic formulas.[13] These calculations show that differences of enthalpies and entropies are favorable for the cycloadduct **6** (−2.7 kcal/mol and 12.1 cal/(mol K), respectively), the difference of Gibbs energy being −6.2 and −6.7 kcal/mol, at 25 and 60 °C, respectively. These theoretical results explain the experimental data reported by Visnick and Battiste;[4] at room temperature, only product **5** is obtained, while with heat, product **6** is quantitatively formed.

The **TS1** and **TS2** are stereoisomer structures (see Figure 2). The main difference between **TS1** and **TS2** is the configuration of nitrogen atom of the pyrrole ring involved in the intermolecular [4 + 2] cycloaddition. For **TS1**, the lone pair of this nitrogen atom is located along the opposite direction of the forming bonds while for **TS2**, it is situated along the same direction. Therefore, the repulsive interactions between the lone pair and the forming bonds are responsible for the larger energy for **TS2** relative to that of **TS1**.

The **TS4** and **TS5** are related to a different type of intramolecular [4 + 2] Diels−Alder reaction. In the former, the presence of the two CF_3 groups in the dienophile fragment led to the decrease of the barrier height for **TS4** relative to that of **TS5**. Pathway A is preferred because the electron-rich diene adds to the electron-poor double bond bearing the CF_3 groups. The calculated distances for the forming carbon−carbon bonds are 2.143, 2.112, 2.163, and 2.172 Å for **TS1**, **TS2**, **TS4**, and **TS5** respectively, corresponding with a concerted synchronous process. The presence of the two trifluoromethyl substituents on the dienophile fragment does not substantially modify the geometrical parameters.

The conclusions of this density functional theory study can be summarized as follows: (i) Formation of the two possible regioisomer cycloadducts takes place along a stepwise mechanisms with formation of the two azanorbornadiene intermediates. Due to the low values of the barrier heights for the second steps, these intermediates are unstable. (ii) The rate-limiting steps are the initial [4 + 2] intermolecular cycloadditions for both processes or channel A, the kinetically favorable mode of attack. (iii) The two azanorbonadiene intermediates are connected via a low barrier height associated with the inversion of nitrogen atom. (iv) With thermolysis, the product **5** was quantitatively converted in the most stable thermodynamically product **6**. (v) These findings suggest that thermodynamic and kinetic controls take place in this domino cycloaddition process, helping to explain the experimental data. We are currently investigating the extension of this methodology to other substituted systems.

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