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Theoretical study on the mechanism of the domino reactions of tertiary α-cyano-enamines and dimethyl acetylenedicarboxylate

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Abstract—The mechanisms of the domino reaction between dimethyl acetylenedicarboxylate, **1**, and 2-(*N*,*N*-dimethylamino)acrylonitrile, **2**, and these in presence of acrylonitrile have been theoretically studied using ab initio methods. These domino reactions comprise several pericyclic-type reactions. The geometrical and electronic analysis of the HF/6-31G* transition structures and intermediates allows characterizing the processes that take place along these domino reactions. B3LYP/6-31G* energetic results are in agreement with the experimental outcomes.

1. Introduction

Domino reactions are processes involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reaction results as a consequence of the functionality formed in the previous step.[1,2] These sequential reactions are characterized by their great elegance, frequently high stereoselectivity, and the simple manner in which they may be carried out. They permit complex molecules to be constructed in only a few steps.[1]

Domino cycloadditions play a key role in organic syntheses where construction of complex polycyclic structures with an adequate regio and stereochemical control is needed.[1–4] The interest in this subject is shown by numerous recent reviews.[1,5,6]

Our research program has long maintained an interest in these kind of chemical reactions and the understanding of the characteristic feature of these consecutive processes prompted us to explore further the mechanistic aspects. In previous theoretical works, several [4+2]/[4+2][7] and [4+2]/[3+2][8] domino cycloaddition reactions to give complex polycyclic systems have been studied. Therefore it seemed of interest to extend these studies to domino reactions involving different pericyclic-type reactions which have neither been treated by computational methods and no generally accepted molecular mechanism has emerged.

Recently, B. De Boeck and H. G. Viehe[9,10] have reported the reaction of dimethyl acetylenedicarboxylate (DMAD), **1**, with an α-cyano-enamine, **2**, to give the pyrroline derivative **3** (see **DR1** in Scheme 1). This domino reaction is initialized by a cycloaddition reaction between **1** and **2**, followed by a subsequent electrocyclic ring-opening process on the cyclobutene obtained at the first reaction to give two isomeric butadienamine intermediates. An hydrogen shift on the (*E*)-isomer gives a vinyl azomethine ylide intermediate, which by a subsequent electrocyclic ring-closure process affords the pyrroline derivative **3** (see Scheme 2).

On the other hand, refluxing **1** and **2** in acrylonitrile leads exclusively to the vinylpyrroline **5** (see **DR2** in Scheme 1). This domino process takes place by an 1,3-dipolar cycloaddition of the aforementioned azomethine ylide with acrylonitrile, followed by an HCN elimination to give the vinylpyrroline **5** (see Scheme 3).

In the present paper, an ab initio study for the domino reactions between **1** and **2**, and these in presence of acrylonitrile reported by B. De Boeck and H. G. Viehe[9,10] is carried out (see Scheme 1). Our purpose is to contribute to a better mechanistic understanding of these domino processes, especially by characterization of the stationary points on the reactive potential energy surface (PES).

2. Computing methods

All gas phase calculations were carried out with the

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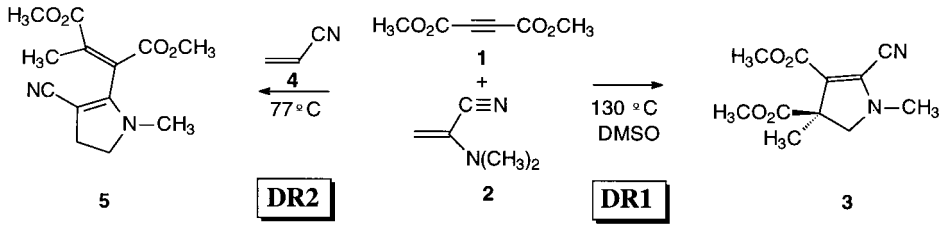
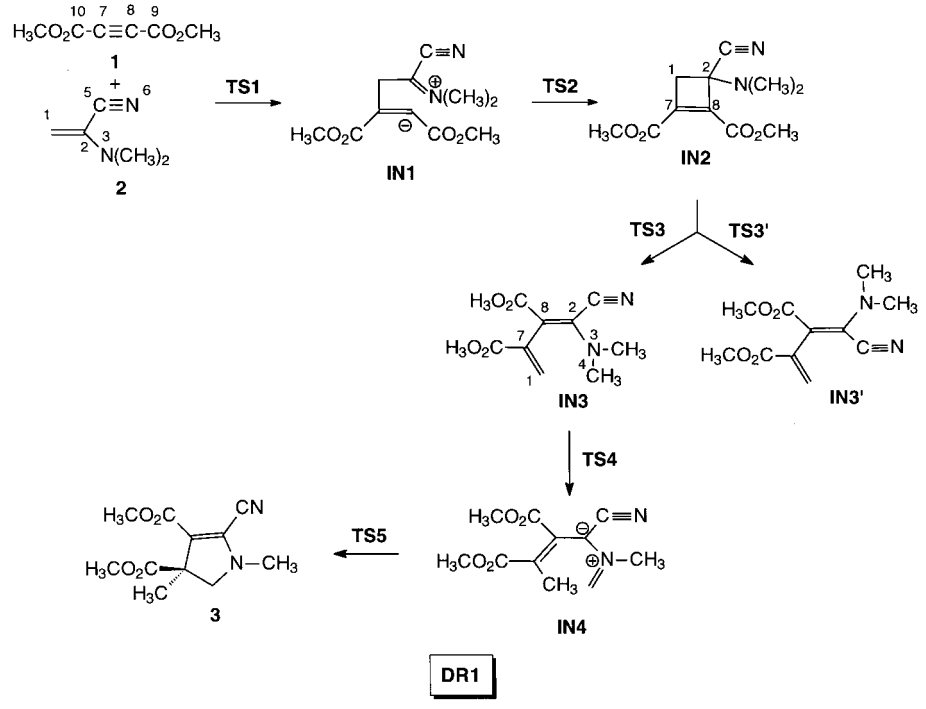


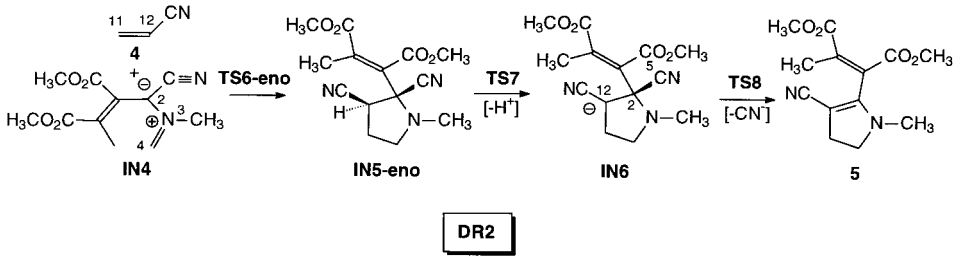
Scheme 1.

Gaussian 98 suite of programs.[11] An extensive characterization of the PES was carried out at HF/3-21G[12] level to ensure that all relevant stationary points were located and properly characterized. 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 HF/3-21G frequencies were used as a starting point in the search of the HF/6-31G*[12] structures. The optimizations were carried out using the Berny analytical gradient optimization method.[13] The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[14] Optimized geometries of all structures are available from the authors.

Previous theoretical studies of cycloadditions and related pericyclic-type reactions have indicated that the activation energies calculated at the HF level are too large, whereas MP2 calculations tend to underestimate them. However, energy calculations for stationary points using MP3/6-31G* are in accord with experimental values.[15] Recently, density functional theory (DFT) calculations using the B3LYP hybrid functional[16] have been shown to be in good agreement with experimental activation energy values,[17] and to give a similar potential energy barrier to that obtained using time-consuming MP3 calculations.[7c,17d,17e] Consequently, B3LYP/6-31G* single point calculation at the HF/6-31G* stationary points were performed in order to calculate the energetic parameters.



Scheme 2.



Scheme 3.

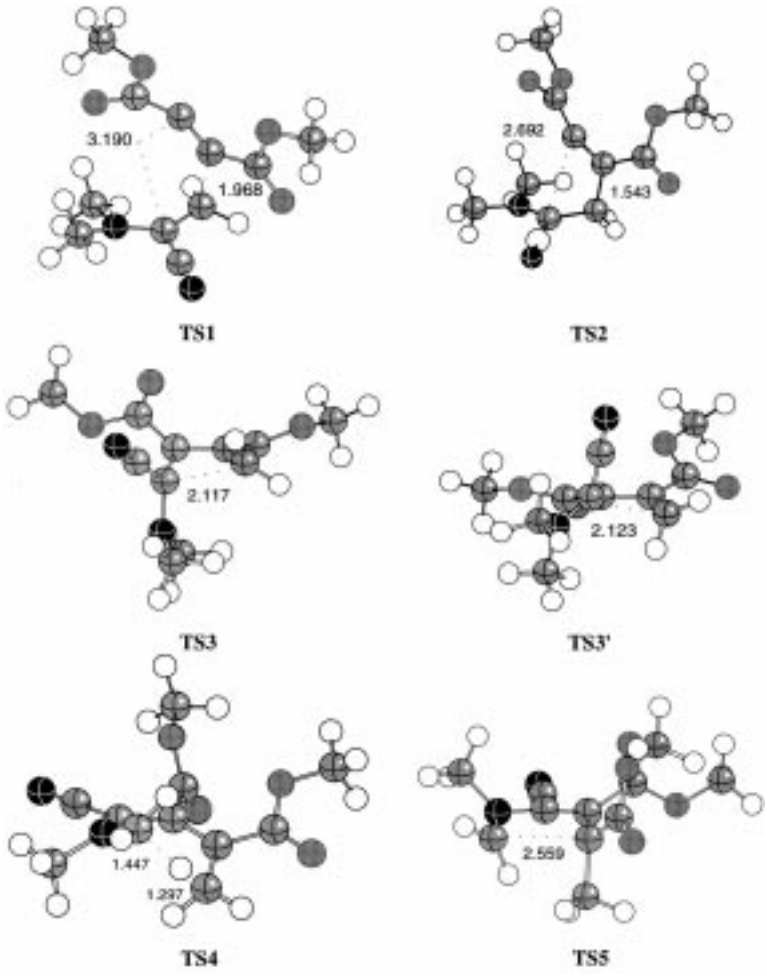


Figure 1. Selected geometrical parameters for the transition structures corresponding to the domino reaction between **1** and **2** (**DR-1**). The lengths of the C–C forming bonds involved in the reaction are given in angstroms.

3. Results and discussions

3.1. Energies

3.1.1. Domino reaction between DMAD and the vinylamine 2. DR1. The domino reaction between DMAD and the vinylamine **2** comprises four consecutive reactions: (i) A formally [2+2] cycloaddition reaction between **1** and **2** to give the cyclobutene intermediate **IN2**; (ii) the ring-opening process of this intermediate to give two isomeric butadienamines; (iii) an hydrogen shift on the (*E*)-isomer to give a vinyl azomethine ylide intermediate **IN4**; and finally (iv) a cyclization of this intermediate to give the final pyrroline derivative **3**.

In Scheme 2 the stationary points corresponding to the domino reaction **DR1** have been presented together with the atom numbering, while the geometries of the TSs are

Table 1. Total energies (in au) for the stationary points along the domino reactions **DR1** and **DR2**

	HF/6-31G*	B3LYP/6-31G*//HF/6-31G*		HF/6-31G*	B3LYP/6-31G*//HF/6-31G*
	DR1			**DR2**	
1	−302.849422	−304.798223	**4**	−169.768015	−170.829062
2	−530.096484	−533.068493	**IN5-eno**	−1002.815726	−1008.798035
IN1	−832.910764	−837.850377	**IN5-exo**	−1002.817622	−1008.799276
IN2	−832.993941	−837.914416	**IN5-enm**	−1002.812554	−1008.796795
IN3	−833.007278	−837.928358	**IN5-exm**	−1002.811996	−1008.796502
IN3′	−833.007108	−837.925881	**IN6**	−1002.211579	−1008.206296
IN4	−832.959640	−837.907445	**TS6-eno**	−1002.691554	−1008.723259
TS1	−832.886199	−837.845162	**TS6-exo**	−1002.687457	−1008.721462
TS2	−832.911299	−837.839967	**TS6-enm**	−1002.696837	−1008.721265
TS3	−832.921102	−837.872878	**TS6-exm**	−1002.695232	−1008.720626
TS3′	−832.935451	−837.884024	**TS7**	−1095.089343	−1101.641487
TS4	−832.924941	−837.893729	**TS8**	−1002.201865	−1008.206510
TS5	−832.925718	−837.884269	**5**	−909.929534	−915.370745
3	−833.047114	−837.970456			

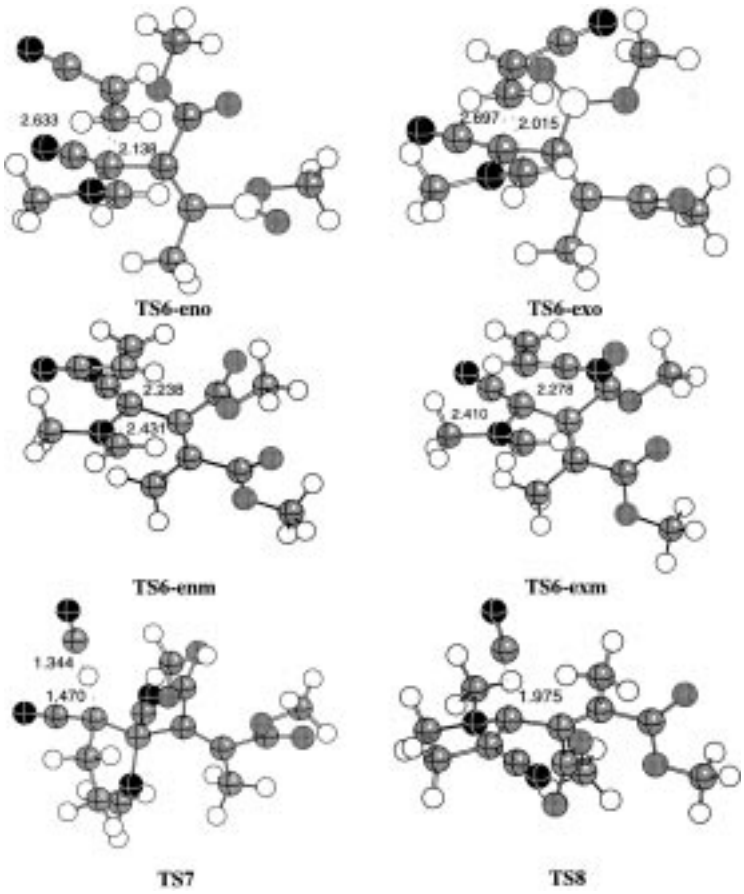


Figure 2. Selected geometrical parameters for the transition structures corresponding to the domino reaction between **1** and **2** in presence of acrylonitrile (**DR-2**). The lengths of the C–C forming bonds involved in the reaction are given in angstroms.

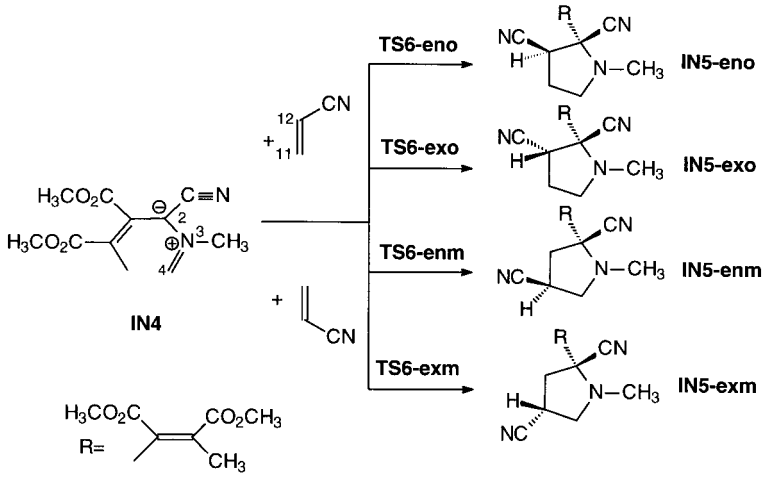
depicted in Fig. 1. The total energies are summarized in Table 1.

The formally [2+2] cycloaddition between DMAD and the vinylamine **2** to give the cyclobutene **IN2** takes place along a stepwise process which is initialized by the nucleophilic attack of electron-rich vinylamine **2** to a conjugate position of the electron-poor acetylenic system of DMAD, to give a zwitterionic intermediate **IN1**. The subsequent ring-closure of this intermediate give the cyclobutene **IN2**. The potential energy barrier (PEB) associated with **TS1** is 13.5 kcal/mol (energetic results correspond to the B3LYP/6-31G*//HF/6-31G* calculations). A comparison of the B3LYP results with those obtained at the HF level, 37.5 kcal/mol, points out that while the HF calculations give a very large barrier, the DFT ones give reasonable value.[18] The zwitterionic intermediate **IN1** is very unstable, 10.3 kcal/mol, and with a low barrier, 6.5 kcal/mol, is converted in the cyclobutene **IN2**. The larger relative energy of **TS2** than **TS1** along this stepwise process does the cyclization process as the rate-determining step of this formally [2+2] cycloaddition; the PEB for the formation of the cyclobutene **IN2** is 16.8 kcal/mol. Formation of **IN2** is thermodynamically very favourable, −29.9 kcal/mol.

The ring-opening process of the cyclobutene **IN2** via a conrotatory electrocyclic process[19] can afford the (*E*)- and (*Z*)-isomeric butadienamines **IN3** or **IN3′**, via **TS3** and **TS3′**, respectively. The PEBs associated with these TSs are: 26.1 kcal/mol (**TS3**) and 19.1 kcal/mol (**TS3′**); both ring-opening processes are exothermic: −8.7 and −7.2 kcal/mol, respectively. Therefore, the formation of **IN3′** corresponds to the reactive channel of the kinetic control, while under thermodynamic control a mixture of **IN3** and **IN3′** can be obtained.[9]

The hydrogen shift[19] on the (*E*)-isomer **IN3**, via **TS4**, gives the vinyl azomethine ylide intermediate **IN4**. The PEB associated with this process is 21.7 kcal/mol; it being very endothermic, 13.1 kcal/mol. In consequence, formation of the azomethine ylide **IN4** is kinetic and thermodynamically very unfavourable.

The subsequent cyclization of **IN4**, via **TS5**, affords the final pyrroline derivative **3**. Although **TS5** presents a large PEB, 27.7 kcal/mol from **IN3**, formation of the final pyrroline derivative **3** is thermodynamically very favourable, −26.4 kcal/mol. These energetic results allow to justify the high temperature demanded at this domino reaction. Moreover, the fact that the barrier corresponding to the conversion of **IN3′** in **IN3**, (**IN3′↔IN2↔IN3**; 33.3 kcal/mol) is closer to that for the cyclization process (**IN3→3**, 27.7 kcal/mol), and lower than that for the retro-formation of **IN3′** (**IN3′→1+2**, 46.7 kcal/mol) open the possibility that the Curtin–Hammett principle[7c,20] can be operative, allowing the conversion of **IN3** and **IN3′** in the pyrroline **3** at the reaction conditions (130°C).[9]



Scheme 4.

3.1.2. Domino reaction between DMAD and the vinylamine 2 in presence of acrylonitrile. DR2. The domino reaction between DMAD and the vinylamine **2** in presence of acrylonitrile to give the vinylpyrroline **5** demands several consecutive reactions: (i) formation of intermediate **IN4** (via **DR1**); (ii) an 1,3-dipolar cycloaddition of the azomethine ylide **IN4** with acrylonitrile to give the cycloadduct **IN5-eno**; and (iii) an HCN elimination on this cycloadduct to yield the final vinylpyrroline **5**.

In Scheme 3 the stationary points corresponding to the domino reaction **DR2** have been presented together with the atom numbering, while the geometries of the TSs are depicted in Fig. 2. The total energies are summarized in Table 1.

The cycloaddition reaction between the azomethine ylide **IN4** and acrylonitrile can take place along four reaction channels corresponding to the *endo* and *exo* approaches of the acrylonitrile in two regioisomeric possibilities, *ortho* and *meta*. We have considered the four possibilities. In Scheme 4 the stationary points corresponding to the four possibilities are depicted. Thus, four TSs have been studies: **TS6-eno** (*endo*/*ortho*), **TS6-exo** (*exo*/*ortho*), **TS6-enm** (*endo*/*meta*) and **TS6-exm** (*exo*/*meta*). The PEBs associated with these 1,3-dipolar cycloadditions are between 8 to 10 kcal/mol; formation of the cycloadducts being very exothermic processes, between −38 to −39 kcal/mol.

DFT calculations give formation of the *endo*/*ortho* cycloadduct **IN5-eno** as the most favourable reactive channel. Formation of **IN5-eno**, via **TS6-eno**, is 1.3 kcal/mol more favourable that formation of the *exo*/*meta* cycloadduct **IN5-exm**, via **TS6-exm**, showing the reaction to be regioselective in agreement with the experimental results; only the *ortho* regioisomers can undergo the subsequent HCN elimination. An opposite regioselectivity is found at the HF level; now formation of the *endo*/*meta* cycloadduct **IN5-enm**, via **TS6-enm**, is the most favourable channel. This trend is similar to that found for a related 1,3-dipolar cycloaddition of a nitrone with acrylonitrile where a poor regioselectivity is predicted at HF level.[21]

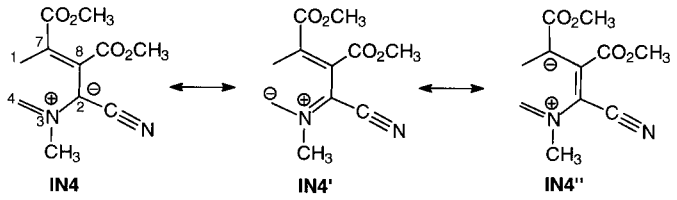
Transformation of the cycloadduct **IN5-eno** in the final vinylpyrroline **5** demands the proton abstraction by a basic specie to give the stabilized carbanion **IN6** followed by the extrusion of cyanide anion. The proton abstraction process has been studied using the cyanide anion as a base since it is generated in the posterior step. The proton abstraction process to give the carbanion intermediate **IN6**, via **TS7**, and the subsequent extrusion of cyanide anion via **TS8** take place with low PEBs. (Presence of charged species in this two-step elimination does very difficult to obtain accurate energies. As an approximation, we have estimated that in gas phase both barriers are lower than 6 kcal/mol). Although the HCN elimination is slightly endothermic, 3.9 kcal/mol, the entropy increase and the high reaction temperature make the process thermodynamically favourable.

The lower barrier found for the 1,3-dipolar cycloaddition of **IN4** with acrylonitrile than that for the cyclization of **IN4**, via **TS5**, together with the thermodynamically favorable HCN elimination allow to explain the formation of the vinylpyrroline **5** instead of the pyrroline derivative **3** along the domino reaction **DR2**.

3.2. Geometries and frequency analysis

For **TS1**, the C1–C7 and C2–C8 distances, 1.968 and 3.190 Å, respectively, indicate that this TS is associated to the C1–C7 bond formation process. Moreover, the large C2–C8 distance together with the C7–C8–C9 bond angle, 148°, and the C2–C1–C7–C8 dihedral angle −80°, indicate that the C2 and C8 atoms are not being bonded in this step. This process corresponds to the nucleophilic attack of the electron-rich vinylamine to one conjugate position of the acetylenic system of DMAD to give the zwitterionic intermediate **IN1**.

The planar arrangement of the substituents present on the N3 nitrogen atom, which agree with a sp^2 hybridization for the nitrogen atom, together with the shortening of C2–N3 bond length at **TS1** relative to that at vinylamine **2** suggest the participation of the N3 lone pair along the C1–C7 bond formation process. Moreover, the C2–C5 bond length, 1.457 Å at **TS1**, which is identical to that at **2**, indicates



Scheme 5.

the non-participation of the nitrile group in the cycloaddition process.

The value of the unique imaginary frequency of **TS1** is 605i cm^{-1}. Analysis of the atomic motions along this vibrational frequency indicates that **TS1** is mainly associated to the motion of the C1 and C7 carbon atoms along the bond formation process.

The C1–C7 bond length at **IN1**, 1.543 Å, indicates that this bond is already formed in this intermediate. The C2–N3 bond length at **IN1**, 1.278 Å, is shorter than that at **TS1** indicating a large participation of the N3 lone pair in the stabilization of the corresponding zwitterionic intermediate.

The C2–C8 bond distance at **TS2** is 2.692 Å. This distance together with the C2–C1–C7–C8 dihedral angle, −42°, indicate that this process is mainly associated to the C2–C8 bond formation, which demands the twist of the C1–C7 single-bond (along the C–C bond-formation process the C2–C1–C7–C8 dihedral angle goes from −56° at **IN1** to −1° at the planar cyclobutene **IN2**).

The value of the unique imaginary frequency of **TS2** is very low, 79 cm^{-1}. Analysis of the atomic motions along this vibrational frequency indicates that **TS2** is mainly associated to the twist of the C1–C7 single bond in order to approach the C2 and C8 carbon atoms.

The C1–C2 bond length at **TS3** and **TS3′** are: 2.117 and 2.123 Å. These data together with the H1–C1–C7–C8 and C5–C2–C8–C7 dihedral angles indicate that this reaction is associated with a ring-opening process of the cyclobutene system of **IN2**, via a conrotatory electrocyclic reaction.[19] The C1–C7–C8–C2 dihedral angles at both TSs show the twist of the C7–C8 bond, which allows a decrease of the strain present in the cyclobutene system. The main structural difference between **TS3** and **TS3′** is the inclock twist of the C1 and C2 carbon atoms at the most favourable **TS3′** which decreases the hindrance between the bulky C2 dimethylamine group and the C1 methylene group that is present in the outclock twist at **TS3** (see Fig. 1).

The values of the imaginary frequency for the TSs corresponding to these electrocyclic processes are: 728i cm^{-1} (**TS3**) and 656i cm^{-1} (**TS3′**). These imaginary frequencies are associated to the C1–C2 breaking-bond together with the twist of the light C1 methylene group.

The lengths of C4–H4 breaking-bond and C1–H4 forming-bond at **TS4** are: 1.447 and 1.297 Å, respectively. The (*E*)-dimethylbutadienamine **IN3** adopts an helicoidal arrangement which allows a favourable proton transfer (see Fig. 1). This arrangement, which is not possible at the intermediate **IN3′** justifies that only the (*E*)-isomer **IN3** undergoes the hydrogen shift process. The C1 and C4 carbon atoms at **TS4** present a piramization as a consequence of change of hybridization from sp^2 to sp^3 and sp^3 to sp^2, respectively.

TS4 has a very high imaginary frequency, 1714i cm^{-1}, which is associated to the motion of the light H4 hydrogen atom from C4 to C1 positions.

At the azomethine ylide **IN4** the C7–C8 and C8–C2 bond lengths, 1.334 and 1.486 Å, respectively, together with the C7–C8–C2–N3 dihedral angle, 130°, indicate that the electronic structure of this intermediate corresponds to a vinyl azomethine ylide **IN4** instead of an 1,5 azomethine ylide **IN4″** (see Scheme 5, and vide infra). The N3–C4 bond length at **IN4**, 1.285 Å, is shorter that the C2–N3 one, 1.375 Å. This dissymmetry is a consequence of the presence of the electron-withdrawing CN substituent at the C2 position which allows a favourable stabilization of the negative charge present at the azomethine system (**IN4** versus **IN4′** in Scheme 5).

For **TS5**, the length of the C4–C7 forming-bond, 2.559 Å, indicates that this TS corresponds to an early process. The piramidalization of the C4 and C7 carbon atoms shows the change of hybridization of these center from sp^2 to sp^3 along the C4–C7 bond formation. Moreover, the arrangement of the carboxylate group present on C7, together with the shorter C7–C10 bond length than the C8–C9 one indicate the participation of the C7 carboxylate group along the cyclization process.

The imaginary frequency associated to **TS5** corresponding to the cyclization process is 343i cm^{-1}. This value is lower than that found for **TS3** corresponding to the electrocyclic ring-opening process.

For **TS6-eno**, corresponding to the most favourable *endo*/*ortho* reactive channel of the 1,3-dipolar cycloaddition between **IN4** and acrylonitrile, the lengths of the C4–C11 and C2–C12 forming-bonds are: 2.138 and 2.633 Å, respectively. These data indicate that this cycloaddition takes place along a very asynchronous process, which can be characterized by the nucleophilic attack of the C4 azomethine carbon atom to the C11 conjugated position of the acrylonitrile.[22] A similar bond formations is found at the *exo*/*ortho* diasteroisomer **TS6-exo**.

The lengths of the two forming-bonds along the more

defavorable *meta* TSs indicate that these processes correspond to asynchronous concerted 1,3-dipolar cycloadditions (see Fig. 2).

The imaginary frequencies for the TSs corresponding to the 1,3-dipolar cycloadditions are: 566i cm^{-1} (for **TS6-eno**), 578i cm^{-1} (for **TS6-exo**), 491i cm^{-1} (for **TS6-enm**) and 488i cm^{-1} (for **TS6-enm**). Analysis of the atomic motions along the vibrational frequency corresponding to **TS6-eno** and **TS6-exo** indicates that these TSs correspond to very asynchronous processes where the C4–C11 bond formation has a large participation than the C2–C12 one.

For **TS7**, corresponding to the proton elimination process, the lengths of the C12–H12 breaking-bond and the H12–C13 forming-bond are: 1.470 and 1.344 Å, respectively; the distance between the C12 donor and the C13 acceptor centers is 2.8 Å. For this step, the C12–H12 breaking-bond is more advanced that the H12–C13 forming-bond. Finally, at **TS8** the length of the C2–C5 breaking-bond is 1.975 Å.

The imaginary frequencies for the TSs corresponding to the HCN elimination are: 1642 cm^{-1} (for **TS7**) and 425 cm^{-1} (for **TS8**). The high imaginary frequency associated to **TS7** agrees with a proton abstraction process.

3.3. Bond order and charge analysis

The extent of bond formation or bond breaking along a reaction pathway is provided by the concept of bond order (BO). This theoretical tool has been used to study the molecular mechanism of chemical reactions.[23] Values of the BO can be used to evaluate the asynchronicity for the bond formation processes. Thus, the Wiberg bond indices[24] have been computed by using the NBO analysis[14] as implemented in GAUSSIAN 98.

For **TS1**, the values of the C1–C7 and C2–C8 BOs are: 0.45 and 0.08, respectively. These data indicate that while the C1–C7 forming-bond is very advanced, the C2 and C8 carbon atoms are not being bonded in this TS.[18,25] The value of the C2–N3 BO, 1.28, shows the participation of the N3 lone pair along the nucleophilic attack of the vinylamine to the DMAD. Finally, the larger C8–C9 BO, 1.14, than the C7–C10 one, 0.99, indicates a larger participation of carboxylate group present at the C8 position along the cycloaddition process. The arrangement of the C8 carboxylate group at **TS1** allows an effective delocalization of the negative charge that is being transferred at DMAD.[18,25] The C1–C7 and C2–C8 BOs at **TS2** are: 1.01 and 0.03, respectively. These data indicate that while the C1–C7 bond is already formed, the formation of the C2–C8 bond is very early along the cyclization process.

The natural population analysis (NPA) allows us to evaluate the charge transferred along the formally [2+2] cycloaddition process. The atomic charges have been shared between the donor vinylamine **2** and the acceptor DMAD. The values of the charge transferred at **TS1**, **IN1**, and **TS2** are: 0.38, 0.80 and 0.69 au, respectively. These values indicate an increase of the charge transferred along the nucleophilic attack of the β-carbon of the vinylamine **2** to a conjugated position of the acetylenic system of **1** up to formation of the zwitterionic intermediate **IN1**.[18,25]

For **TS3** the BO value of the C1–C2 breaking-bond is 0.47. The C1–C7, C7–C8 and C2–C8 BOs, 1.32, 1.51 and 1.16, respectively, indicate that the ring-opening takes place via a concerted process. The low BO value found for the C2–C8 bond at this pericyclic process can be justify by the participation of the N3 nitrogen atom in the ring-opening process; the C2–N3 BO is 1.16.

For **TS4** the BO values corresponding to C4–H4 breaking-bond and C1–H4 forming-bond are: 0.34 and 0.52, respectively. These data indicate that the C4–H4 breaking-bond process is more advanced that the C1–H4 forming-bond process in this TS. The large BO value of the N3–C4 single bond, 1.25, indicates the participation of the N3 nitrogen atom at the C4–H4 breaking-bond process.

For the azomethine intermediate **IN4**, the BO values of the C2–C8 and C7–C8 bonds, 1.03 and 1.78 respectively, indicate that the C7–C8 bond has a large double bond character. Moreover, the BO values of the N3–C4 and C2–N3 bonds, 1.54 and 1.10, respectively, indicate that the structure of the vinyl azomethine ylide corresponds with **IN4** instead of **IN4′** and **IN4″** (see Scheme 5).

For **TS5**, the BO value of the C4–C7 forming-bond is 0.27. This low value indicates that the cyclization process is early. Moreover, the values of the N3–C4, C2–N3, C2–C8 and C7–C8 BOs, 1.41, 1.04, 1.46 and 1.35, respectively, indicate a larger participation of the C2–C8–C7 vinyl anion system on the cyclization.

The NPA for **TS5** shows the presence of a large negative charge at the C7 carbon atom, −0.32 au, while at the C4 carbon atom it is negligible, 0.00 au. Both bond order and charge analysis indicate that the cyclization process can be undertook as a nucleophilic attack of C7 carbon atom belonging to the C2–C8–C7 allyl anion system to the C4 carbon atom of the C4=N3+ iminium system present in the vinyl azomethine framework, instead of an electrocyclic process. This behavior allows us to explain the low imaginary frequency value found at **TS5**, 343i cm^{-1}, relative to that for **TS3′**, 656i cm^{-1}, associated to an electrocyclic ring-opening process.

For the *ortho* 1,3-dipolar cycloadditions between **IN4** and acrylonitrile, the BO values of the C4–C11 and C2–C12 forming-bonds are: 0.39 and 0.22 for **TS6-eno**, and 0.40 and 0.22 for **TS6-exo**, respectively. These values indicate that these cycloadditions correspond to very asynchronous process where the β carbon atom of acrylonitrile participates in a large extension in the bond formation than the α one. The NPA for the **TS6-eno** and **TS6-exo** give a small charge transfer for these cycloaddition processes, being slightly larger for the more favourable *endo* TS (0.18 au) than for the *exo* one (0.15 au). A similar result is found for the 1,3-dipolar cycloaddition of an azomethine ylide with acrylonitrile where a very asynchronous process with a low charge transfer is found.[21]

For the **TS7**, the BO values of the C12–H12 breaking-bond

and the H12–C13 forming-bond are: 0.30 and 0.56, respectively. These data indicate that this TS corresponds to an asynchronous process where the C12–H12 breaking-bond is more advanced than the H12–C13 forming-bond. The presence of the electron-withdrawing –CN substituent at the C12 position favours the breaking-bond process by a stabilization of the negative charge that is developing at the C12 carbon atom. Finally, for the **TS8**, the BO values of the C2–C5 breaking-bond, 0.54, and the C2–C12 bond, 1.27, indicate that the cyanide extrusion process is more advanced than the C2–C12 double bond formation.

4. Conclusions

The mechanisms of the domino reactions between dimethyl acetylenedicarboxylate, **1**, and 2-(*N*,*N*-dimethylamino)acrylonitrile, **2**, in absence and in presence of acrylonitrile has been theoretically studied using ab initio methods. Geometrical and electronic analysis have been carried out at the HF/6-31G* computational level, while the energies have been computed using B3LYP/6-31G* calculations. These approaches give a correct description for these domino reactions.

These domino reactions comprise several pericyclic-type reactions. The process is initialized by a formally [2+2] cycloaddition reaction between **1** and **2** to give a cyclobutene intermediate, which by a subsequent electrocyclic ring-opening process affords two isomeric butadienamines. The cycloaddition reaction takes place along an ionic process initialized by the nucleophilic attack of the β-carbon atom of the enamine to a conjugate position of the substituted acetylenic system to give a zwitterionic intermediate, which by a subsequent ring-closure affords the formally [2+2] cycloadduct. An hydrogen shift on the (*E*)-butadienamine gives an unstable vinyl azomethine ylide intermediate which by a ring-closure process achieved by the nucleophilic attack of the allyl anion system to the carbon atom of the iminium rest of the azomethine framework affords the final pyrroline derivative **3**.

In presence of acrylonitrile, the vinyl azomethine ylide intermediate undergoes an 1,3-dipolar cycloaddition to give a cycloadduct, which by an HCN elimination affords the final vinylpyrroline **5**.

The larger barrier associated with the cyclization of the vinyl azomethine intermediate **IN4** relative to that for the 1,3-dipolar cycloaddition with acrylonitrile justifies the formation of the vinylpyrroline **5** instead of the pyrroline derivative **3**.

The analysis of the HF/6-31G* structures of TSs and intermediates together with B3LYP/6-31G* energetic results allow to understand the processes involved along these domino reactions and to explain the experimental outcomes.

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