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Unveiling the Unexpected Reactivity of Electrophilic Diazoalkanes in [3+2] Cycloaddition Reactions within Molecular Electron Density Theory

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Abstract

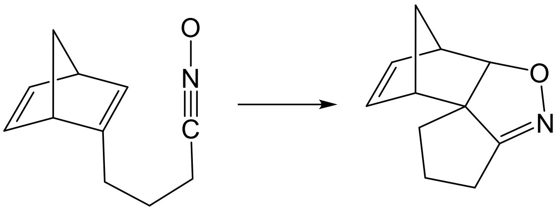
The [3+2] cycloaddition (32CA) reactions of strongly nucleophilic norbornadiene (NBD) with simplest diazoalkane (DAA) and three DAAs of increased electrophilicity have been studied within the Molecular Electron Density Theory (MEDT) at the MPWB1K/6-311G(d,p) computational level. These *pmr-type* 32CA reactions follow an asynchronous one-step mechanism with activation enthalpies ranging from 17.7 to 27.9 kcal·mol^{-1} in acetonitrile. The high exergonic character of these reactions makes them irreversible. The presence of electron-withdrawing (EW) substituents in the DAA increases the activation enthalpies, in complete agreement with the experimental slowing-down of the reactions, but contrary to the Conceptual DFT prediction. Despite the nucleophilic and electrophilic character of the reagents, the global electron density transfer at the TSs indicates rather non-polar 32CA reactions. The present MEDT study allows establishing that the depopulation of the N–N–C core in this series of DAAs with the increase of the EW character of the substituents present at the carbon center is responsible for the experimentally found deceleration.

Keywords

Molecular Electron Density Theory, Norbornadiene, Diazoalkanes, Conceptual DFT, Electron Localization Function.

1. Introduction

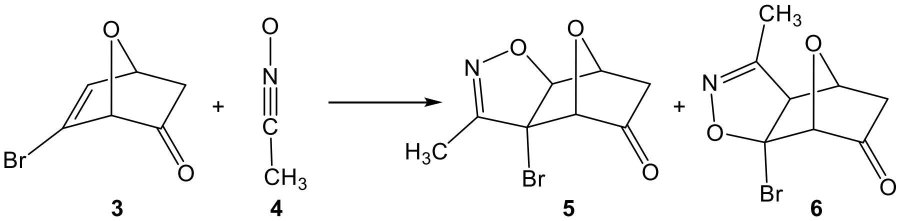
Norbornadiene (NBD) (bicyclo [2.2.1] hepta-2,5-diene), norbornene (bicyclo [2.2.1] hept-2-ene) and related compounds serve as key intermediates in natural product synthesis [1-3] and polymer chemistry [1,4] owing to their angularly strained unusual geometry and high reactivity. Recently, NBD has also found applications in molecular photoswitches to absorb solar radiation [5] and, by 2018, more than 30 thousand publications and patents had reported their production and applications in various fields [1]. The behavior of NBD derivatives in the Wagner-Meerwin rearrangement [6,7], photochemical di-π methane rearrangement [8], Diels Alder reactions [9], catalytic reactions with alkynes [10] and several other instances [1] have established their uniqueness as organic reagents and fostered their wide synthetic applications in [3+2] cycloaddition (32CA) reactions to form isoxazolidines, triazoles, carbocycles and other heterocycles of biological and environmental relevance [11-15]. In 2001, Tam and coworkers [16,17] reported the highly regio- and stereoselective intramolecular 32CA reactions of NBD-tethered nitrones and nitrile oxides (Scheme 1).



1 **2**

Scheme 1. Intramolecular 32CA reaction of NBD-tethered nitrile oxide **1**.

The 32CA reactions of 7-oxanorbonadiene with nitrile oxides were theoretically studied by Tajabadi et al. [18] in 2015, concluding their *anti* and *exo*-stereoselective one-step mechanism. In 2017, Domingo et al. [19] reported the complete *syn* facial stereoselectivity in the 32CA reactions of acetonitrile oxide and 7-oxanorborn-5-en-2-ones as an outcome of the unfavorable steric interactions along the *anti* approach (see Scheme 2).

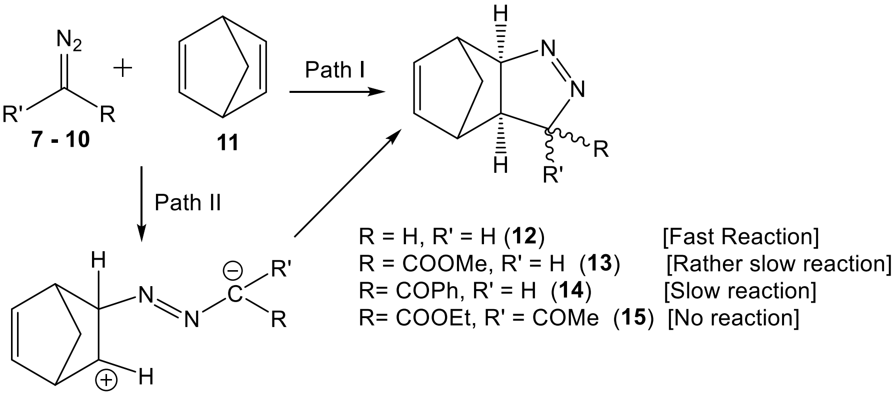


3 **4** **5** **6**

Scheme 2. 32CA reaction of 7-oxanorborn-5-en-2-one **3** with acetonitrile oxide **4**.

Very recently, two different studies [20,21] have addressed the regio-, stereo- and enantioselectivities of the 32CA reactions of 7-isopropylidenenorbornadiene and oxonorbornadiene with nitrones, azides and nitrileimines.

The substituent effects on the rates of the 32CA reactions between NBD and diazoalkanes (DAAs) were experimentally evidenced by Huisgen in 1963 to establish the accountability of the one-step mechanism for 32CA reactions. [22] Considering the 32CA reactions of substituted DAAs **7-10** with NBD **11**, (Scheme 3) Huisgen compared the one-step mechanism (Path I, Scheme 3) and the two-step addition (Path II, Scheme 3) possibilities in 32CA reactions [22].



Scheme 3. 32CA reactions of substituted DAAs **7-10** with NBD **11**

The addition tendency of simplest DAA **7** with NBD **11** was maximum along this series, while the 32CA reaction slowed down by introducing electron-withdrawing (EW) carbonyl substituents at the carbon of the DAA in **8** and **9**, and finally, DAA **10**, with two carbonyl substituents, was completely inactive. Since the nucleophilic additions of NBD to the terminal nitrogen of DAAs are well known [23], it was expected that DAAs act as an electrophilic species and NBD **11**, with two electron rich C–C double bonds, as the nucleophilic one. Hence, EW substituents in DAA should enhance the addition tendency. However, this behavior was contrary to the experimental observation (Scheme 3) and, consequently, it demands a detailed explanation for the bond formation process and a rationalization of the decrease in reaction rate experimentally observed.

The underlying theory adopted for explaining 32CA reactions was based on the Frontier Molecular Orbital [24] (FMO) concept since last 50 years, until in 2016, Domingo proposed the Molecular Electron Density Theory [25,26] (MEDT) to recognize the decisive role of the changes in electron density on the molecular reactivity. The MEDT concept, which rejects any analysis based on molecular orbitals, has allowed explaining the experimental outcome of 32CA reactions, for example, the strain promotion [27,28], selectivities [29,30], substituent effects [31-33], catalysis [34,35] etc.

Within the MEDT framework, the three-atom-components (TACs) participating in 32CA reactions are classified in four types [36], which answers their reactivity in 32CA reactions. TACs with two *pseudoradical* centres participate in *pdr-type* 32CA reactions [37] which take place very easily. TACs with one *pseudoradical* centre participate in *pmr-type* 32CA reactions [38], while TACs with a carbenoid centre participate in *cb-type* 32CA reactions [39]. TACs showing the absence of *pseudoradical* or carbenoid centres are classified as zwitterionic type and participate in *zw-type* 32CA reactions [29] associated with high energy barrier demanding overcome through appropriate electrophilic-nucleophilic interactions [29]. Recent studies devoted to the participation of DAAs in 32CA reactions have evidenced that DAAs have a *pseudoradical* structure, thus participating in *pmr-type* 32CA reactions.[28,40]

Herein, an MEDT study for the 32CA reactions of substituted DAAs **7-10** with NBD **11**, experimentally studied by Huisgen[22] (Scheme 3), is performed at the MPWB1K/6-311G(d,p) computational level in order to explain the unexpected reactivity of these electrophilic DAAs. This MEDT report is shaped into eight sections: i) in section 3.1, a topological analysis of the electron localization function (ELF) [41,42] at the ground state electronic structures of the reagents is performed to structurally classify the DAAs and determine their reactivity; ii) in section 3.2, the global reactivity indices defined within the conceptual density functional theory [43,44] (CDFT) are discussed; iii) in section 3.3, the energy profiles of the feasible reaction paths and some of the properties of the corresponding stationary points are analyzed; iv) in section 3.4, a topological analysis of non-covalent interactions is performed in order to understand the origin of the stereoselectivity; v) in section 3.5, the molecular mechanisms of the 32CA reactions of DAAs **7** and **10** with NBD **11** are analyzed through a bonding evolution theory (BET) [45] study of the most favorable reaction paths; vi) in section 3.6, the topology of the ELF at the TSs is analyzed; vii) in section 3.7, the nature of bonding at the interatomic bonding regions is assessed through the Quantum Theory of Atoms in Molecules [46,47] (QTAIM) parameters proposed by Bader and coworkers; and finally, viii) in section 3.8, the origin of the deceleration with the EW substitution is analyzed.

2. Computational methods

Optimization of the reactants, TSs and products was done using Berny analytical gradient optimization method [48] at MPWB1K [49]/6-311G(d,p) [50]. This computational level has been recently used in the study of 32CA reactions.[27,28,30-32] Frequency calculations were performed at the located stationary points to ensure that the TSs have one and only one imaginary frequency and all positive frequencies exist for the local minimum. The intrinsic reaction coordinate [51] (IRC) calculations using González-Schlegel integration method [52,53] verified the minimum energy reaction pathway connecting the reactants and the products. Solvent effects were studied by modelling the solvent acetonitrile using the polarizable continuum model [54,55] (PCM) with the self-consistent reaction field [56-58] (SCRF) method and the stationary points were optimized at MPWB1K (PCM)/6-311G(d,p) level of theory. The thermodynamic parameters, i.e. the enthalpies, entropies and Gibbs free energies were calculated at 298.15 K and 1 atm in acetonitrile using the standard statistical thermodynamics.

Equations reviewed in reference 44 are used to calculate the CDFT indices, while the global electron density transfer [59] (GEDT) at the TSs was computed from the summation of charges at each fragment derived from natural population analysis [60,61] (NPA) using the equation GEDT (f)=$\sum_{q\in f} q$, where q denotes the natural atomic charges. The topological analysis of the ELF [41] and QTAIM [46,47] was performed using Multiwfn software [62]. The ELF localization domains (isovalue of 0.75 au) are represented from Paraview visualization software [63,64]. The calculations are performed using Gaussian 03 package [65]. NCI analysis [66] was performed with the NCIPLOT4 program.[67]

*3.1. Analysis of the ELF topology at the ground state electronic structures of DAAs **7-10** and NBD **11***

ELF [41,42] topology allows a quantitative characterization of chemical regions of a molecule, being used to classify the TACs, and then, to correlate their electronic structure with their molecular reactivity within the MEDT framework. Proposed by Domingo in 2019 [36], this standard classification of TACs into *pseudodiradical*, *pseudo(mono)radical,* carbenoid or zwitterionic type has allowed characterizing 32CA reactions into *pmr-type*, *pdr-type*, *cb-type* and *zw-type*, respectively, based on the respective TAC participation [36]. Herein, the ELF topology of DAAs **7-10** and NBD **11** is studied to assess their electronic structures. The ELF valence basin populations are given in Table 1, while the ELF basin attractor positions are shown in Figure 1.

Table 1. ELF valence basin populations at the MPWB1K/6-311G(d,p) optimized structures of DAAs **7-10** and NBD **11**.

	7	**8**	**9**	**10**	**11**
V(N1)	1.89	3.61	3.58	3.47	
V'(N1)	1.89				
V(N1,N2)	1.87	1.99	2.05	2.05	
V'(N1,N2)	1.87	1.89	1.85	1.92	
V(C3,N2)	3.01	2.90	2.88	2.82	
V(C3)	0.46	0.46	0.39	0.49	
V'(C3)	0.46	0.46	0.49	0.49	
V(C4,C5)					1.74
V'(C4,C5)					1.74
V(C6,C7)					1.74
V'(C6,C7)					1.74

The ELF topological analysis of DAAs **7-10** shows the presence of two monosynaptic basins, V(N1) and V'(N1), in **7** and one V(N1) monosynaptic basin in **8-10**, integrating a total population of 3.78 e (**7**), 3.61 e (**8**), 3.58 e (**9**) and 3.47 e (**10**), associated with the non-bonding electron density on N1 nitrogen; two disynaptic basins, V(N1,N2) and V'(N1, N2), integrating 3.74 e (**7**), 3.88 e (**8**), 3.90 e (**9**) and 3.97 e (**10**), associated with the N1–N2 double bond; and one V(C3,N2) disynaptic basin, integrating 3.01 e (**7**), 2.90 e (**9**), 2.88 e (**9**) and 2.82 e (**10**), associated with the C3–N2 overpopulated single bond, which shows the influence of substitution on the electronic distribution of the N1–N2–C3 moiety of these DAAs. Finally, the presence of two monosynaptic basins, V(C3) and V'(C3), integrating a total of 0.92 e (**7**), 0.92 e (**8**), 0.88 e (**9**) and 0.98 e (**10**), associated with a *pseudoradical* centre at C3, allows the classification of DAAs **7-10** as *pseudo(mono)radical* TACs, thus suggesting their participation in *pmr-type* 32CA reactions [36].

ELF topology of NBD **11** shows the presence of two pairs of disynaptic basins, V(C4,C5) and V'(C4,C5), and V(C6,C7) and V'(C6,C7), integrating a total population of 3.48 e each pair, associated with the C4–C5 and C6–C7 double bonds of NBD **11**.

The proposed Lewis-like structures together with the natural atomic charges of compounds **7-11** are represented in Figure 1. The *pseudoradical* C3 carbon is negatively charged by −0.47 e (**7**), −0.34 e (**8**), −0.34 e (**9**) and −0.25 e (**10**), suggesting the influence of the EW substitution. The N1 and N2 nitrogen nuclei show negligible charges in simplest

DAA **7**, while the N2 nitrogen shows a charge slightly greater than 0.10 e at DAAs **8**, **9** and **10**. The charge distribution pattern in the DAAs **7-10** does not follow the commonly accepted 1,2-zwitterionic concept for DAAs.

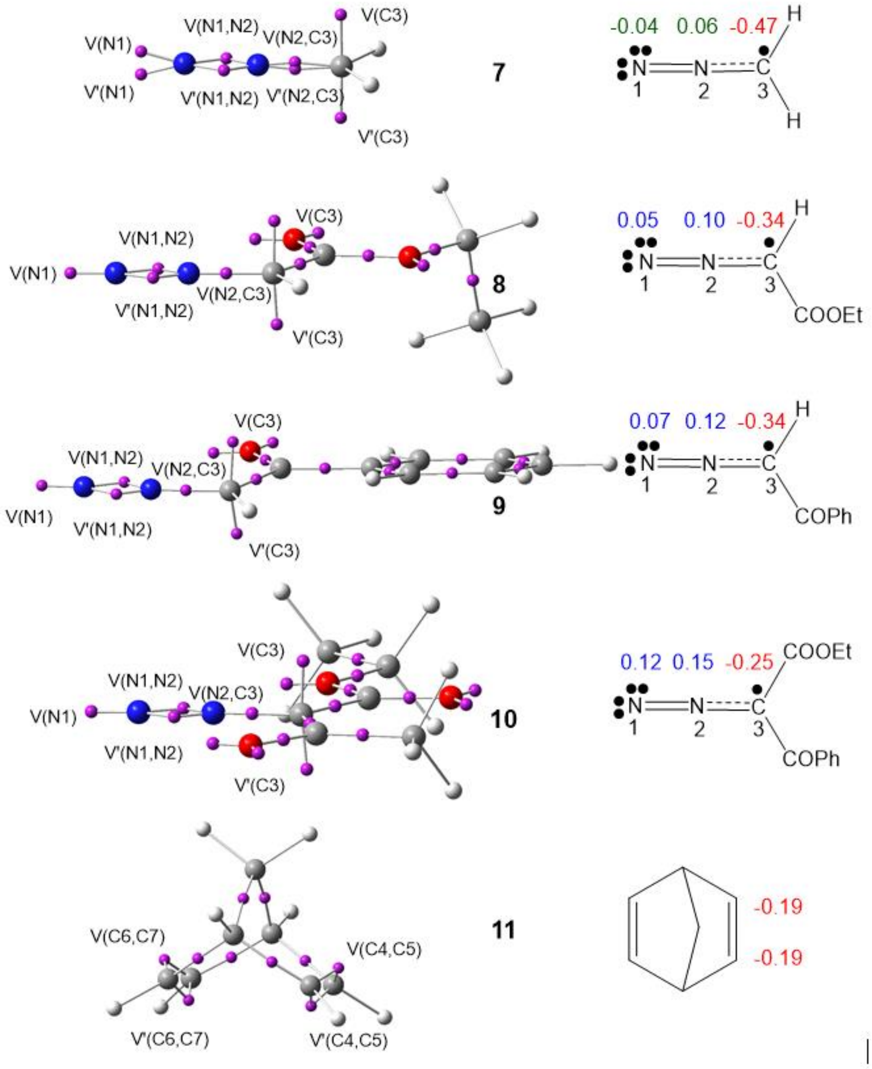


Figure 1. MPWB1K/6-311G(d,p) ELF basin attractor positions of DAAs **7-10** and NBD **11** and the proposed Lewis-like structures together with the natural atomic charges in average number of electrons e. Negative, negligible and positive charges are shown in red, green and blue colours, respectively.

*3.2. Analysis of the CDFT indices of DAAs **7-10** and NBD **11***

The analysis of the reactivity indices based on CDFT[43,44] has become a useful tool for the study of reactivity in polar reactions [43]. Therefore, an analysis of CDFT reactivity indices was performed in order to predict the reactivity of the reagents in these 32CA reactions. The CDFT indices were calculated at the B3LYP/6-31G(d) computational level since it was used to define the electrophilicity and nucleophilicity scales [43,68,69]. The electronic chemical potential μ, chemical hardness η, electrophilicity ω and nucleophilicity N indices of compounds **7-11** are gathered in Table 2.

The electronic chemical potentials μ of DAAs **7-10**, μ = −3.63 (**7**), −4.27 (**8**), −4.20 (**9**), and −4.58 (**10**) eV, are lower than that of NBD **11**, μ = −2.94 eV, suggesting that along a polar process the electron density will flux from NBD **11** to DAAs **7-10** via reverse electron density flux (REDF) reactions.[70]

Table 2. B3LYP/6-31G(d) electronic chemical potential μ, chemical hardness η, electrophilicity ω and nucleophilicity N indices of DAAs **7-10** and NBD **11**.

	μ	η	ω	*N*
DAA**10**	-4.58	4.87	2.15	2.09
DAA **8**	-4.27	4.79	1.90	2.45
DAA **9**	-4.20	4.76	1.85	2.53
DAA **7**	-3.63	4.70	1.40	3.13
NBD **11**	-2.94	5.88	0.74	3.23
ethylene **26**	-3.37	7.77	0.73	1.87

The chemical hardness η of DAAs **7-10**, ranging from 4.70 to 4.87 eV, is also lower than that of NBD **11**, 5.88 eV, which means that the DAAs are more prone to electron density deformation than NBD **11**, i.e. they are softer. Interestingly, DAA **10**, having more EW substituents, is chemically harder than the simplest DAA **7**.

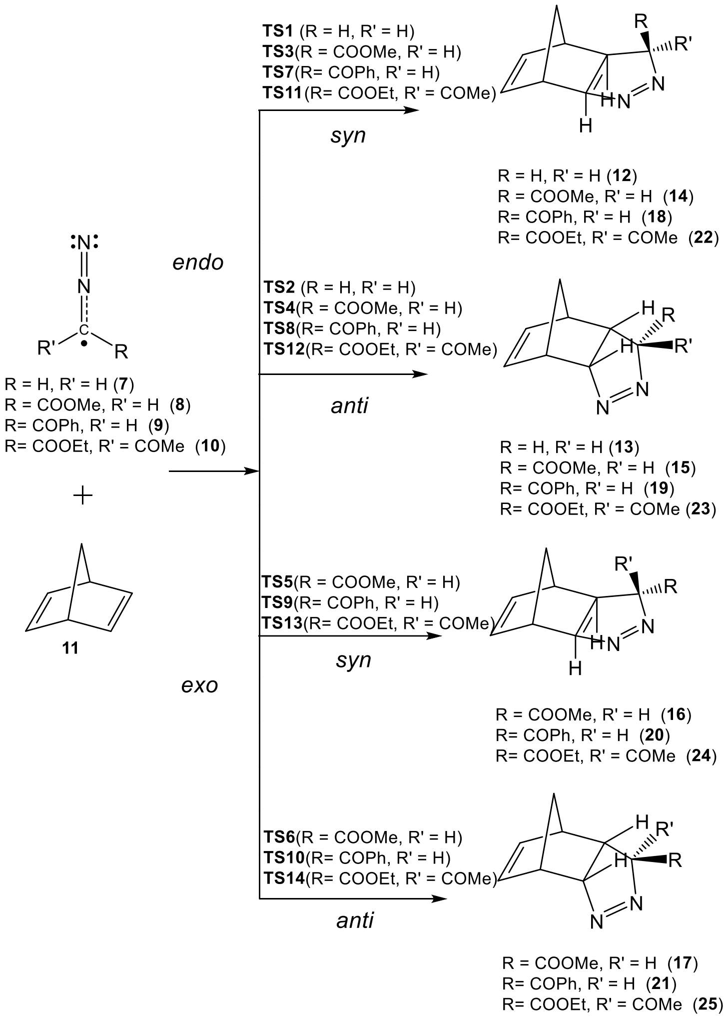
Within the electrophilicity scale [68], simplest DAA **7**, ω = 1.40 eV, is classified as a moderate electrophile, while DAAs **8-10**, ω > 1.85 eV, are classified as strong electrophiles. However, it is worth noting that among the strongly electrophilic DAAs, only DAA **10** would be enough electrophilically activated to work well experimentally, which is against the experimental findings. On the other hand, within the nucleophilicity scale [69], simplest DAA **7**, N = 3.13 eV, is classified as a strong nucleophile, while DAAs **8-10**, N < 2.53 eV, are classified as moderate nucleophiles. As expected, the inclusion of electron-withdrawing groups at the C3 carbon of simplest DAA **7** increases the electrophilicity ω index and decreases the nucleophilicity N index of the DAA derivatives.

NBD **11** is classified as a marginal electrophile, ω = 0.74 eV, and a strong nucleophile, N = 3.23 eV. Both, the strain caused by the bicyclic system and the presence of two C–C double bonds considerably increase the nucleophilicity N index of **11** with respect to that of ethylene **26**, N = 1.87 eV.

The analysis of the CDFT indices predicts that along a polar process, DAAs **7-10** will behave as electrophilic species while NBD **11** as the nucleophilic one. However, the experimental outcome [22] revealed that the EW substitution in the DAA decreases its reactivity towards NBD **11**. Along this series, the fastest 32CA reaction was that involving simplest DAA **7**, while strongly electrophilic DAA **10** having two EW –COOMe and –COPh groups was completely inactive. In addition, except the reaction involving DAA **10**, CDFT predicts the other reactions to have low-polar character as the DAAs are not sufficiently electrophilically activated. Thus, this CDFT analysis does not agree with the experimental results of this series of reactions.

*3.3. Analysis of the reaction paths associated with the 32CA reactions between DAAs **7-10** and NBD **11***

Due to the molecular symmetry of simplest DAA **7** and NBD **11**, two competitive stereoisomeric reaction paths are feasible for this 32CA reaction. They are related to the two approach modes of DAA **7** with respect to the two stereoisomeric faces of the C–C double bonds of NBD **11**. These reaction paths are called *syn* and *anti*. For DAAs **8-10**, which present a different substitution at the C3 carbon, two additional stereoisomeric reaction paths are feasible, the *endo* and the *exo* ones. Consequently, for the 32CA reactions involving DAAs **8-10**, four competitive reaction path were considered (see Scheme 4). For the 32CA reaction of simplest DAA **7**, the *syn* and *anti* reaction paths leads to two diastereoisomeric pyrazolines **12** and **13**, respectively, *via* **TS1** and **TS2**. For the 32CA reactions involving substituted DAAs **8-10**, four diastereoisomeric pyrazolines **14-17**, **18-21** and **22-25** can be formed *via* **TS3-TS6**, **TS7-TS10** and **TS11-TS14**, respectively (Scheme 4). The four 32CA reactions follow a *one-step* mechanism. Relative electronic energies, enthalpies, entropies and Gibbs free energies of the TSs and adducts are given in Table 3.



Scheme 4. Studied reaction paths for the 32CA reactions of DAAs **7-10** with NBD **11**.

From the energy results given in Table 3 a series of appealing conclusions can be obtained: i) the gas phase activation energies associated with the energetically most favorable reaction paths of these 32CA reactions are found between 15.9 (**TS1**) and 23.3 (**TS11**) kcal·mol^{-1}; ii) the increase of the activation energies in the order **TS1** (**7**) < **TS3** (**8**) < **TS10** (**9**) < **TS11** (**10**) is in complete agreement with the experimental outcomes [22]; iii) these reactions are strongly exothermic by more than 30 kcal·mol^{-1}; iv) inclusion of solvent effects increases the activation energies by between 0.3 (**TS11**) and 1.9 (**TS7**) kcal·mol^{-1}, and increases the exothermic character of the reactions by between 2.0 (**12**) and 4.1 (**22**) kcal·mol^{-1}. Formation of **18** is disfavored by 1.2 kcal·mol^{-1}; v) inclusion of the thermal corrections increases the activations enthalpies in acetonitrile by between 0.8 (**TS3**) and 1.1 (**TS11**) kcal·mol^{-1} and decreases the reaction enthalpies by between 3.6 (**22**) and 4.8 (**12**) kcal·mol^{-1}; vi) inclusion of entropies to enthalpies rises the activation Gibbs free energies in acetonitrile between 29.9 (**TS1**) and 43.0 (**TS14**) kcal·mol^{-1}, and decreases the reaction Gibbs free energies between -16.2 (**22**) and -37.1 (**12**) kcal·mol^{-1}; vii) the strong exergonic character of these 32CA reactions makes them irreversible and consequently, the products are obtained by kinetic control; viii) the *syn*/*anti* facial stereoselectivity ranges from 0.7 (**7**) to 3.1 (**8**) kcal·mol^{-1}. While DAAs **7**, **8** and **10** prefer the *syn* attack, DAA **9** prefers the *anti* one; and ix) these 32CA reactions present a low *endo*/*exo* stereoselectivity; lower than 0.8 kcal·mol^{-1}. While the 32CA reactions of DAAs **7**, **8** and **10** are *endo* selective, that of DAA **9** is *exo* selective.

Table 3. MPWB1K/6-311G(d,p) relative energies (ΔE), enthalpies (ΔH), entropies (ΔS), Gibbs free energies (ΔG) and GEDT (in average number of electrons e) of TSs and pyrazolines for the 32CA reactions of DAAs **7-10** with NBD **11** (superscript 'a' refers to FEDF (forward electron density transfer) and superscript 'b'refers to REDF (reverse electron density transfer)).

	gas phase					*acetonitrile*				
	ΔE	ΔH	ΔS	ΔG	GEDT	ΔE	ΔH	ΔS	ΔG	GEDT
TS1	15.9	16.8	-42.3	29.4	0.10[a]	16.7	17.7	-40.8	29.9	0.10
12	-53.6	-49	-47.3	-34.8		-55.6	-50.8	-46	-37.1	
TS2	16.6	17.4	-42.9	30.2	0.12[a]	17.6	18.5	-41.6	30.9	0.12
13	-52.9	-48.3	-47.5	-34.1		-55.2	-50.4	-46.1	-36.7	
TS3	18.9	19.4	-42.3	32	0.04	20.0	20.8	-42.5	33.5	0.03
14	-44	-40.3	-46.5	-26.4		-46.3	-42.1	-48.2	-27.7	
TS4	22.0	22.6	-44.1	35.7	0.04	23.3	24.1	-44	37.2	0.02
15	-42.1	-38.2	-49.2	-23.6		-45.3	-41.2	-49.2	-26.5	
TS5	19.5	20.1	-42.5	32.8	0.04	20.9	21.8	-44.1	35	0.03
16	-45.3	-41.4	-47.4	-27.3		-46.3	-42.1	-46.4	-28.3	
TS6	20.4	20.8	-41.4	33.2	0.06	21.9	22.5	-42.4	35.1	0.04
17	-44.1	-40.4	-43.5	-27.4		-45.9	-41.8	-45.8	-28.2	
TS7	21.4	22	-45.9	35.7	0.02	23.3	24.1	-47	38.1	0.01
18	-40.3	-37.2	-55	-20.8		-39.1	-35	-42.4	-22.4	
TS8	22.3	23.1	-48.3	37.5	0.05	24.0	24.7	-46.3	38.5	0.02
13	-39.5	-35.5	-52.2	-20		-42.4	-38	-52.2	-22.5	
TS9	21.7	22.5	-47	36.5	0.04	24	24.9	-46.8	38.8	0.02
20	-41.3	-37.3	-50.5	-22.2		-41.2	-37.1	-49.5	-22.3	
TS10	20.6	21.1	-46	34.8	0.05	22.8	23.5	-45.9	37.2	0.02
21	-44.6	-40.8	-51.1	-25.5		-43.8	-39.8	-50.1	-24.8	
TS11	23.3	24.2	-47.7	38.5	0.04	23.6	24.7	-47.8	38.9	0.08[b]
22	-30.1	-26.8	-48	-12.5		-34.2	-30.6	-48.3	-16.2	
TS12	26.2	27	-48.5	41.4	0.04	26.7	27.6	-47.9	41.9	0.08[b]
23	-35.1	-31.8	-49.9	-16.9		-36.3	-32.9	-51.2	-17.6	
TS13	23.9	24.2	-46	37.9	0.04	23.9	24.8	-46.1	38.6	0.08[b]

24	-34.0	-30.8	-43.1	-18		-36.1	-32.6	-48.6	-18.1	
TS14	26.5	27.2	-49.5	41.9	0.03	26.9	27.9	-50.6	43.0	0.08[b]
25	-31.5	-28.2	-50.6	-13.1		-34.4	-30.9	-49.2	-16.2	

The gas phase optimized geometries of the more favorable TSs are given in Figure 2, while the distances between the C–C and C–N interacting nuclei are given in Table 4. Some appealing conclusions can be drawn for these geometrical parameters: i) considering that C–C bond formation begins slightly earlier than the C–N one,[36] these distances at **TS1-TS10** indicate that, from a geometrical point of view, they correspond to hardly asynchronous TSs; ii) a comparison of these distances at **TS11-TS14** with respect to those at the other TSs shows that the TSs involving DAA **10** are clearly more asynchronous. At **TS11** - **TS14**, the C–N distances are shorter, while the C–C ones are longer, suggesting more delayed C–C bond formation but more advanced C–N bond formation; i.e. more asynchronous processes; iii) as all these distances are greater than 2.0 Å in gas phase and acetonitrile, and considering that the C–C and C–N single bond formation take place at the short range of 2.0-1.9 and 1.9-1.8 Å, respectively, [36] they indicate that formation of the new C–C and C–N single bonds has not started yet at any TS (see Section 3.6); iv) inclusion of solvent effects in the optimizations does not considerably modify the gas phase geometries. Note that for the 32CA reactions of DAAs **7-9**, these differences are lower than 0.02 Å.

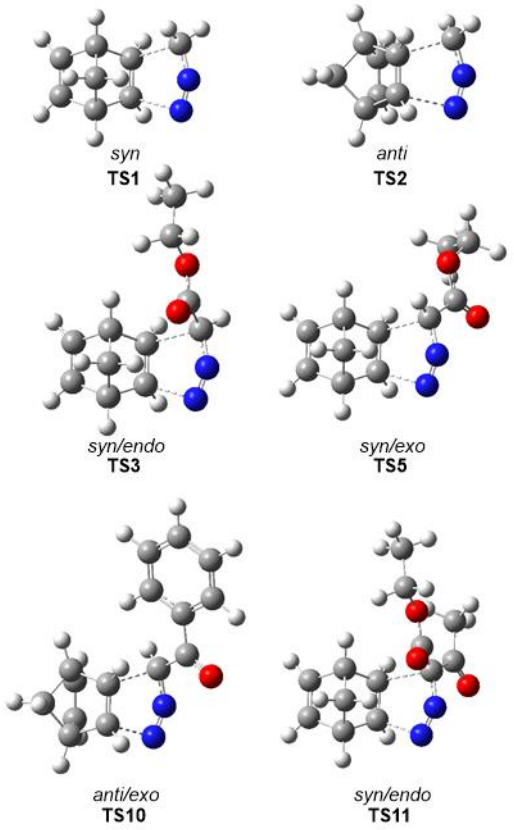


Figure 2. MPWB1K/6-311G(d,p) optimized geometries of some selected TSs associated with the 32CA reactions of DAAs **7-10** with NBD **11**

Table 4. C–C and C–N distances, in angstroms Å, at the TSs involved in the 32CA reactions of DAAs **7-10** with NBD **11**, in gas phase and in acetonitrile.

	C–C	C–N	C–C	C–N
	gas phase		*acetonitrile*	
TS1	2.245	2.333	2.230	2.357
TS2	2.208	2.311	2.196	2.338
TS3	2.250	2.236	2.251	2.247
TS4	2.231	2.201	2.242	2.206
TS5	2.246	2.220	2.253	2.229
TS6	2.218	2.203	2.231	2.204
TS7	2.255	2.227	2.251	2.214
TS8	2.237	2.173	2.247	2.185
TS9	2.230	2.239	2.244	2.226
TS10	2.233	2.163	2.261	2.155
TS11	2.296	2.080	2.337	2.087
TS12	2.289	2.052	2.331	2.062
TS13	2.291	2.088	2.338	2.084
TS14	2.289	2.052	2.330	2.057

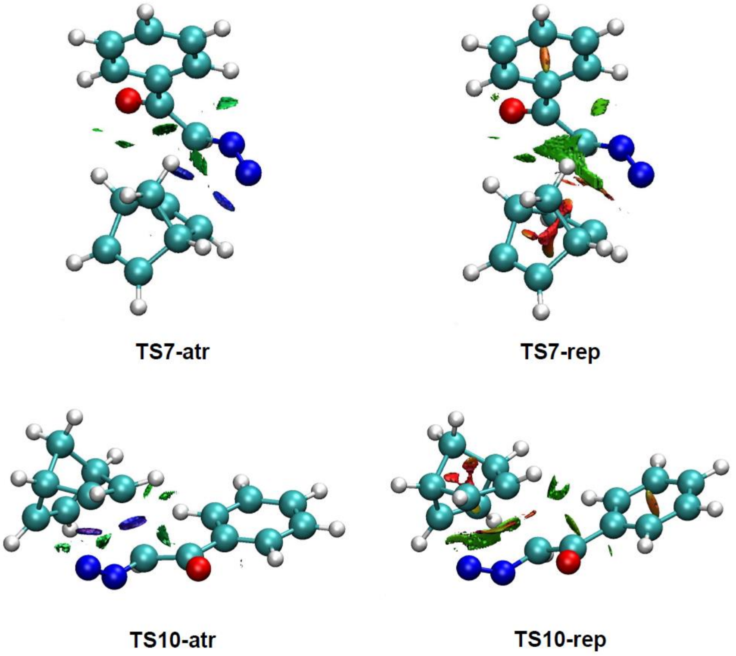
Finally, the GEDT at the TSs was calculated to assess the polarity of these 32CA reactions, and is given in Table 3. Reactions with GEDT values lower than 0.05 e correspond to non-polar processes, while values higher than 0.20 e correspond to polar processes. The 32CA reaction between simplest DAA **7** and NBD **11**, with GEDT of 0.10 e (**TS1**) and 0.12 (**TS2**), in gas phase and in acetonitrile, is predicted as a 32CA reaction with some polar character, with the electron density fluxing from DAA **7** to NBD **11**. This GEDT analysis suggests that this 32CA reaction is classified as a forward electron density flux (FEDF) reaction [70]. Interestingly, this finding is against the analysis of the electronic chemical potential μ, electrophilicity ω and nucleophilicity *N* indices of DAA **7** and NBD **11**, which predict that the reaction would not work experimentally but, if so, it should be a reaction of reverse electron density flux (REDF) [70] (see Table 2 and section 3.2).

For the 32CA reactions of DAAs **8-10** with NBD **11**, the GEDT values are found between 0.02 - 0.05 e, predicting non-polar 32CA reactions, thus, being classified as reactions of null electron density flux (NEDF).[71] This decrease in polarity is consistent with the increase in energy barrier of the corresponding 32CA reactions. For the 32CA reaction of DAA **10** with NBD **11** in acetonitrile, which does not take place experimentally, the GEDT at the TSs is 0.08 e, showing a very low polar character. At this TS, the low electron density that fluxes from the NBD framework to the DAA ones, might permit to classify this 32CA reaction as a reaction of REDF.[70] However, note that this 32CA does not take place experimentally.

Interestingly, the 32CA reaction of simplest DAA **7**, the least electrophilic DAA of the series, with NBD **11** presents the highest GEDT. In addition, the electron density fluxes from DAA **7** to NBD **11**, against the analysis of the CDFT indices (see Section 3.2). A similar behavior was found along the *pdr-type* 32CA reaction between the simplest azomethine ylide and ethylene **26**, GEDT = 0.10 e,[37] which was expected to be a reaction of NEDT. Note that neither NBD **11** nor ethylene **26** have any tendency to act as electrophiles. It seems that the presence of a non-bonding electron density at the ends of these TACs, which accounts for their high nucleophilic character, is responsible for the local electron density transfer (LEDT) taking place from these terminal carbon and nitrogen atoms to the double bonds of NBD **11** and ethylene **26**, a local phenomenon that cannot be anticipated by the analysis of the global electronic chemical potential μ of the reagents.

3.4. NCI analysis of the preferred anti/exo stereoselectivity in the 32CA reaction of DAA ***9*** *with NBD* ***11***

In order to understand the origin of the *anti/exo* stereoselectivity in the 32CA reaction of DAA **9** with NBD **11**, a comparative topological analysis of the attractive and repulsive NCIs taking place at *syn/endo* **TS7** and *anti/exo* **TS10** was performed by means of the NCI approach. Note that the *syn/endo* stereoselectivity is preferred in every 32CA reaction except that involving DAA **9**. The corresponding isosurfaces are represented in Figure 3, while the plots of the reduced density gradient *s* vs sign(λ_2)ρ(r) are given in Figure 4. A continuous color-coding scheme based on the second eigenvalue of the Hessian is used, where strong attractive interactions are represented in blue, weak interactions in green, and strong repulsive interactions in red.

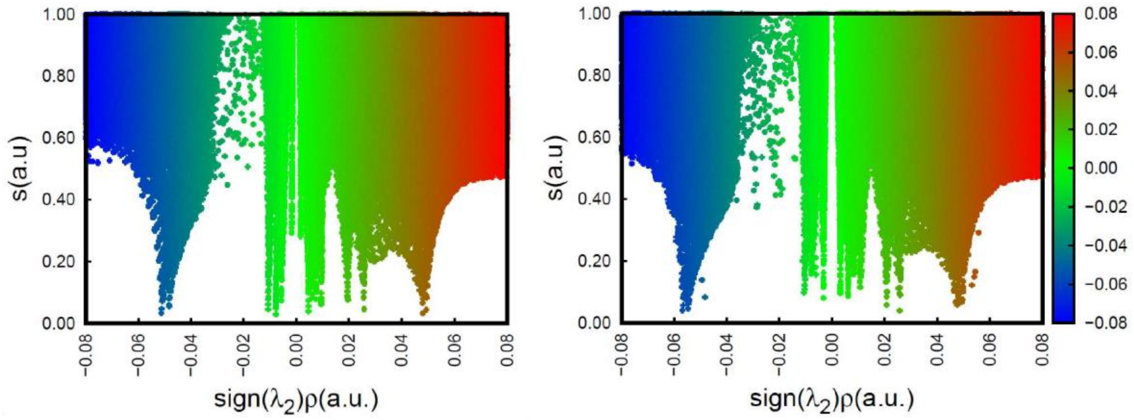

TS7-atr TS7-rep

TS10-atr TS10-rep

Figure 3. NCI isosurfaces associated with the attractive and repulsive density overlap at **TS7** and **TS10**. An isosurface value of 0.5 and a blue-green-red color scale from $-0.05 < \text{sign}(\lambda_2)\rho(r) < 0.05$ a.u. were used.

As can be observed in Figure 3, the surfaces associated with repulsive density overlap are greater than those associated with attractive interactions. This suggests that the repulsive interactions have a greater role than the attractive ones in the preference for the *anti/exo* approach. A closer look reveals that, considering only the surfaces associated with intermolecular interactions and skipping those associated with bond formation, the repulsive overlap spreads wider at **TS7** than at **TS10**.

The plots of the reduced density gradient *s* vs sign(λ_2)ρ show that there are no qualitative differences between the density characteristics of the interactions (see Figure 4). The only noticeable change is that the peaks associated with the weak NCIs, both the attractive and the repulsive ones, reach higher values of *s* at **TS10** than at **TS7**. This feature only indicates that these interactions are not associated with critical points in the electron density, [72] thus being only different in strength. Consequently, this analysis suggests that the weaker unfavorable interactions present at **TS10** are responsible for the *anti/exo* stereoselectivity in the 32CA reaction between DAA **9** and NBD **11**.



TS7 **TS10**

Figure 4. Plot of the reduced density gradient *s* vs sign(λ_2)ρ for **TS7** and **TS10**.

*3.5. BET study for the 32CA reactions of DAAs **7** and **10** with NBD **11***

The BET has allowed establishing the molecular mechanism of a great number of organic reactions by means of the analysis of the bonding changes along the reaction path, which is possible due to the straightforward connection between the electron density distribution and the chemical structure.[42] The detailed BET studies of the 32CA reactions of DAAs **7** and **10** with NBD **11** are given in the Supplementary Material in Sections 1 and 2. Herein, only the most relevant conclusions are analyzed and compared. The ELF basin attractor positions of the structures involved in the bond formation are shown in Figure 5.

The BET study of the 32CA reaction of simplest DAA **7** with NBD **11** allows concluding some significant mechanistic aspects: i) this 32CA reaction can be topologically divided into nine phases starting from structure **S0-I** and ending in pyrazoline **12**; ii) *Phases I* and *II* are characterized by the depopulation of the N1–N2, N2–C3 and C4–C5 bonding regions. These changes in electron density demand an energy cost (EC) of 15.4 kcal mol^{-1}, which accounts for 97% of the activation energy needed to reach **TS1**, found in *Phase III*; iii) the depopulation of these bonding regions allows the creation of the N2 nitrogen non-bonding electron density at structure **S1-I**, and the C4 and C5 *pseudoradical* centres at **S3-I** and **S4-I**, respectively (see **S4-I** in Figure 5); v) formation of the first C3–C4 single bond takes place at **S5-I**, by the C-to-C coupling of the two C3 and C4 *pseudoradical* centres present in **S4-I**, at a C–C distance of 2.05 Å and with an initial population of 1.36 e (see **S5-I** in Figure 5); vii) formation of the second N1–C5 single bond takes place at **S8-I**, by sharing part of the non-bonding electron density of the N1 nitrogen and that of the C5 *pseudoradical* centre present in **S7-I**, at a C–N distance of 1.84 Å and with an initial population of 1.51 e (see **S8-I** in Figure 5); vii) the formation of the second N1–C5 single bond begins when the first C3–C4 single bond formation has been completed by up to 93%, suggesting a *two-stage one-step* mechanism.[73]

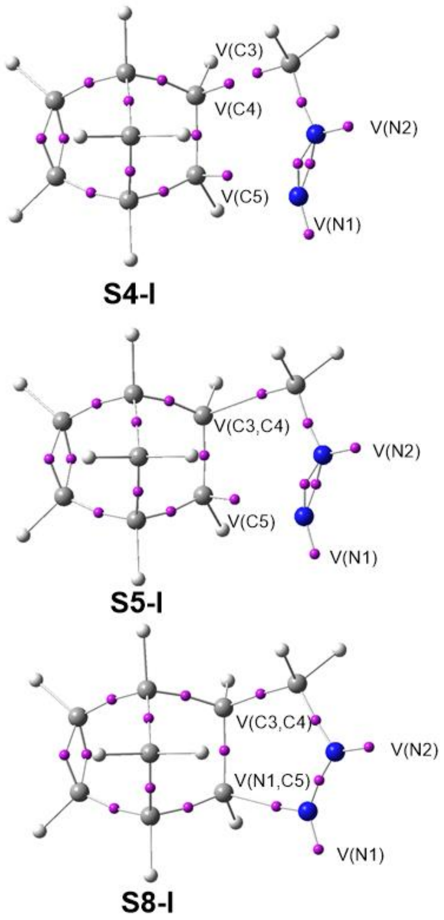


Figure 5. ELF basin attractor positions of **S4-I**, **S5-I** and **S8-I**, involved in the formation of the C3–C4 and N1–C5 single bonds.

The BET study of the 32CA reaction of DAA **10** with NBD **11** allows drawing some significant mechanistic conclusions: i) this 32CA reaction can be divided into seven topological phases starting from **S0-II** and ending in pyrazoline **22**; ii) *Phases I - III* are characterized by the depopulation of the N1–N2, N2–C3 and C4–C5 bonding regions. These changes in electron density demand an EC of 20.9 kcal mol^{-1}. This accounts for 90% of the activation energy needed to reach **TS11**, which is found in *Phase IV*; iv) the depopulation of N1–N2 and N2–C3 bonding regions along *Phase I* allows the creation of the non-bonding electron density at N2 nitrogen at **S1-II**, while the depopulation of the C4–C5 bonding region along *Phases I - III* allows the creation of the C4 and C5 *pseudoradical* centres; v) formation of the first C3–C4 single bond takes place at **S5-II**, by the C-to-C coupling of the two C3 and C4 *pseudoradical* centres present in **S4-II**, at a C–C distance of 2.11 Å, and with an initial population of 1.25 e; vii) formation of the second N1–C5 single bond takes place at **S6-II**, by sharing part of the non-bonding electron density of the N1 nitrogen and that of the C5 *pseudoradical* center present in **S5-I**, at a C–N distance of 1.82 Å, and with an initial population of 1.38 e; vii) the formation of second N1–C5 single bond begins when the first C3–C4 single bond formation has been completed by up to 70%, suggesting an asynchronous one-step mechanism.

A comparative analysis of the two BET studies allows concluding the following: i) these 32CA reactions follow an asynchronous one-step mechanism, the highest asynchronicity in bond formation being observed for the most favorable 32CA reaction of simplest DAA **7** with NBD **11**, which takes place via a *two-stage one-step* mechanism.[73] This finding confirms that any analysis based on the geometries of TSs, such as bond orders, is not suitable to assess the asynchronicity of a reaction; ii) the initial phases of both 32CA reactions are related to the rupture of the N1–N2, N2–C3 and C4–C5 double bonds, demanded for the formation of the N1, C3 and C5 non-bonding electron densities ; iii) while at the 32CA reaction involving simplest DAA **7** these bonding changes demand an EC of 15.4 kcal mol^{-1} with a GEDT of 0.10 e, at the 32CA involving DAA **10** these changes demand an EC of 20.9 kcal mol^{-1} with a GEDT of 0.01 e; and finally, iv) formation of the C3–C4 single bond takes place before the N1–C5 bond formation, by coupling of two C3 and C4 *pseudoradical* centres. While the former is already present at the reagents, the latter is created along the reaction path. This behavior confirms the *pmr-type* mechanism.[36]

*3.6. ELF study at the TSs associated with the 32CA reactions of DAAs **7-10** with NBD **11***

A comparative topological analysis of the ELF of the TSs involved in the 32CA reactions of DAAs **7-10** with NBD **11** was performed. The ELF valence basin populations at **TS1-TS14** associated with the 32CA reactions of DAAs **7-10** with NBD **11** are given in Table 5, while the ELF basin attractor positions of the *syn/endo* TSs, **TS1**, **TS3**, **TS7** and **TS11**, are represented in Figure 6.

Table 5. ELF valence basin populations at the MPWB1K/6-311G(d,p) optimized at the TSs associated with the 32CA reactions of DAAs **7-10** with NBD **11**

	V(N1)	V(N1,N2)	V'(N1,N2)	V(N2)	V(C3,N2)	V(C3)	V(C4,C5)
TS1	3.64	1.57	1.58	1.74	2.04	0.87	3.32
TS2	3.63	1.57	1.59	1.76	2.03	0.87	3.29
TS3	3.56	1.64	1.48	1.83	2.04	0.81	3.26
TS4	3.55	1.73	1.35	1.90	2.00	0.88	3.22
TS5	3.56	1.64	1.47	1.84	2.04	0.80	3.26
TS6	3.56	3.10		1.85	2.04	0.81	3.25
TS7	3.59	1.68	1.41	1.87	2.03	0.73	3.25
TS8	3.53	1.64	1.46	1.88	1.99	0.88	3.24
TS9	3.58	1.61	1.47	1.86	2.05	0.81	3.28
TS10	3.53	1.69	1.40	1.88	2.04	0.78	3.23
TS11	3.47	1.76	1.30	1.96	2.01	0.74	3.18
TS12	3.48	3.01		2.01	2.00	0.78	3.16
TS13	3.47	1.65	1.42	1.94	2.01	0.71	3.18
TS14	3.48	1.74	1.30	1.99	1.99	0.77	3.17

TS1-TS14 show the presence of a V(N2) monosynaptic basin integrating between 1.74 and 2.01 e, which is absent at the ground state electronic structures of the DAAs **7-10**. The V(N1,N2) and V'(N1,N2) disynaptic basins are depopulated from 3.74 e at DAA **7** to 3.15 e at **TS1** and 3.16 e at **TS2**, from 3.88 e at DAA **8** to 3.08-3.12 e at **TS3-TS6**, from 3.90 e at DAA **9** to 3.08-3.10 e at **TS7-TS10,** and from 3.97 e at DAA **10** to 3.01-3.07 e at **TS11-TS14**. On the other hand, the V(C3,N2) disynaptic basin integrating 3.01 e at DAA **7** is depopulated to 2.04 e at **TS1** and 2.03 e at **TS2**, from 2.90 e at **8** to 2.00-2.04 e at **TS3-TS6**, from 2.88 e at **9** to 1.99-2.05 e at **TS7-TS10**, and from 2.82 e at **10** to 1.99-2.01 e at **TS11-TS14**. Thus, the N1–N2 and C3–N2 bonding regions are depopulated at the TSs to create the V(N2) monosynaptic basin associated with the N2 non-bonding electron density.

The V(C4,C5) and V'(C4,C5) disynaptic basins, integrating 3.48 e at NBD **11**, are merged into one V(C4,C5) disynaptic basin, integrating 3.16-3.32 e at the TSs, as a consequence of the depopulation of that region.

As shown in the Figure 6, the four TSs, **TS1**, **TS3**, **TS7** and **TS11**, present an identical electronic structure. Only small differences in the basin populations are observed as a consequence of the different substitution at the DAA framework (see Table 5).

The activation energies of the TSs is therefore associated with the EC for the formation of the N2 non-bonding electron density and the rupture of C4–C5 double bond of NBD **11**. The TSs do not involve formation of the new C3–C4 and N1–C5 single bonds, indicated by the absence of any V(C3,C4) and V(N1,C5) disynaptic basin. This is consistent with the distances between the C–C and N–C interacting centres, which are greater than 2 Å (see Figure 2) and the positive Laplacian of electron density at the bond critical points of the interatomic bonding regions at the TSs, discussed in section 3.7.

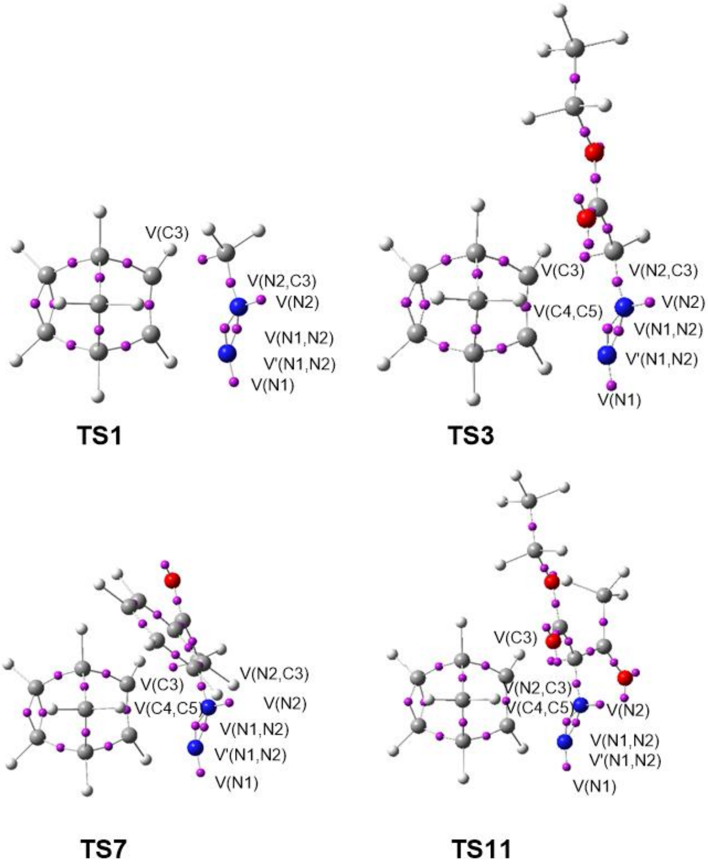


Figure 6. ELF basin attractor positions at the most favorable *endo*/*syn* TSs, **TS1**, **TS3**, **TS7** and **TS11**.

3.7. Analysis of QTAIM parameters at the TSs associated with the 32CA reactions of DAAs ***7-10*** *with NBD* ***11***

Bader and coworkers [46,47] proposed the QTAIM concept to reveal the nature of interatomic interactions. Accordingly, the total electron density ρ and the Laplacian of electron density $\nabla^2\rho(r_c)$ are calculated at the bond critical points (BCPs) **CP1** and **CP2** at the C3–C4 and N1–C5 bonding regions, respectively, and are given in Table 6. The total electron density accumulated at the BCPs is less than 0.1 a.u. and the Laplacian of electron density $\nabla^2\rho(r_c)$ shows small positive values in **TS1-TS14**, suggesting rather non-covalent interactions. Thus, the formation of the new C–C and N–C covalent bonds has not started yet at the TSs, which is in agreement with the topological analysis of the ELF (see section 3.6).

Table 6. Total electron density, ρ and Laplacian of electron density $\nabla^2\rho(r_c)$ at the BCPs **CP1** (C3–C4) and **CP2** (N1–C5) of the interatomic bonding regions in **TS1-TS14**.

	CP1 (C3–C4)		**CP2** (N1–C5)	
	ρ	$\nabla^2\rho(r_c)$	ρ	$\nabla^2\rho(r_c)$
TS1	0.056	0.049	0.043	0.079
TS2	0.060	0.047	0.044	0.082
TS3	0.056	0.048	0.052	0.085
TS4	0.057	0.049	0.055	0.087
TS5	0.057	0.047	0.053	0.086
TS6	0.059	0.045	0.055	0.088
TS7	0.054	0.049	0.053	0.085
TS8	0.057	0.046	0.058	0.089
TS9	0.058	0.046	0.052	0.084
TS10	0.058	0.045	0.059	0.089
TS11	0.052	0.048	0.070	0.087
TS12	0.052	0.048	0.073	0.088
TS13	0.052	0.048	0.069	0.087
TS14	0.053	0.047	0.073	0.088

3.8. Analysis of the origin of the deceleration of these 32CA reactions with the increase of the EW character of the substituents present in these DAA

Many MEDT studies of cycloaddition reactions have shown that the activation energies of non-polar and polar reactions are mainly associated with the EC demanded for the depopulation, i.e. rupture, of the X–Y double bond regions involved in the reaction.[36] In polar reactions, this EC is decreased by the GEDT taking place along the reaction path.[74] The very low GEDT found at the TSs associated with the 32CA reactions of DAA **8-10**, lower than 0.05e (see Table 3), indicates that they have non-polar character. Consequently, the corresponding activation energies can mainly be associated with the changes of electron density in the N1–N2–C3 and C4–C5 bonding regions. Analysis of the total population of the V(N1), V'(N1), V(N1,N2), V'(N1,N2) and V(C3,N2) valence basins of DAAs **7-10**, 3.01e **7**, 2.90e **8**, 2.88e **9**, and 2.82e **10**, shows a continuous depopulation of the N1–N2–C3 bonding region of these TACs with the increase of the EW character of the substituents present at the C3 carbon (see Table 1). Interestingly, as Figure 7 shows , a very good correlation between the total populations of the V(N1), V'(N1), V(N1,N2), V'(N1,N2) and V(C3,N2) valence basins and the activation energies of these 32CA reactions can be established (R^2 = 0.98).

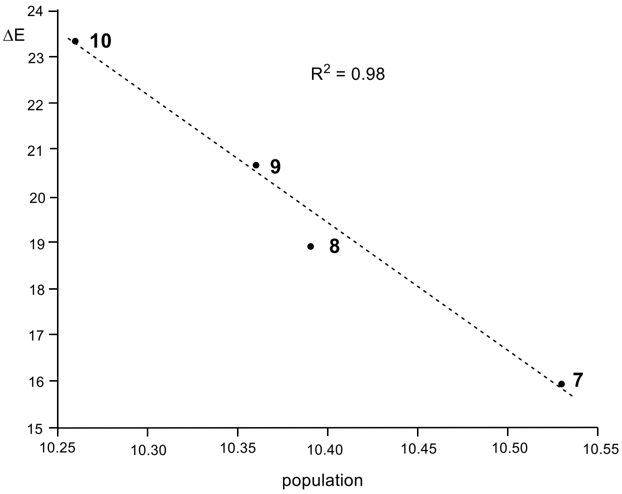


Figure 7. Plot of the activation energies of the 32CA reactions between DAA **7** – **10** and NBD **11**, ΔE_{act}, in kcal·mol^{-1}, vs the total electron density population of the N1–N2–C3 bonding region of DAA **7 - 10**, in average number of e..

As can be seen, the activation energies of this series of 32CA reactions linearly increase with the depopulation of the N1–N2–C3 bonding region, which could be understood as a drawback to the use of the electron density needed for the formation of the new bonds. Consequently, the lowest population found at the disusbtituted DAA **10** provokes that the corresponding 32CA reaction present the highest EC for the bonding changes, thus presenting the highest activation energy (see Section 3.3). Note that the chemical hardness of **10** is the highest (see Table 1). This finding justifies the observation that the 32CA reaction involving the most electrophilic species of this series does not take place experimentally.

Conclusion

The 32CA reactions of NBD **11** with simplest DAA **7** and three substituted DAAs **8-10** of increased electrophilic character, experimentally reported by Huisgen,[22] have been studied at MPWB1K/6-311G(d,p) level of theory within the MEDT framework.

Topological analysis of the ELF at the ground state electronic structures of DAAs **7-10** characterizes these TACS as *pseudo(mono)radical* ones, participating in *pmr-type* 32CA reactions.

Analysis of the CDFT indices predicts the strong nucleophilicity of NBD **11**, while DAAs **7-10** are predicted to be electrophilic reagents. Contrary to the CDFT analysis, these

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pmr-type 32CA reactions experimentally show a decrease in reactivity with the introduction of EW substituents, the most electrophilic DAA **10** being completely inactive towards NBD **11**.

These 32CA reactions are exergonic. The calculated activation enthalpies are found from 17.7 to 27.9 kcal mol^{-1} in acetonitrile. The 32CA reaction of simplest DAA **7**, predicted as the least electrophilic DAA, with NBD **11** shows the lowest activation enthalpy, while the activation parameters increase progressively from the 32CA reaction with DAA **7** to that with DAA **10**, in complete agreement with the experimental outcomes. The *syn/endo* attack is preferred over the *anti/exo* one in every case except DAA **9**. An NCI analysis suggested that the weaker unfavorable interactions taking place at the corresponding *anti/exo* approach than at the *syn/endo* are responsible for that preference. Interestingly, the highest GEDT is found for the fastest 32CA reaction between DAA **7** and NBD **11**, indicating a low polar FEDF process with electron density flux from DAA **7** to NBD **11**, while the reaction with DAA **10**, the most electrophilic species, is characterized as a NEDF process, contrary to the CDFT prediction.

BET study shows that the activation energies of the 32CA reactions of DAAs **7** and **10** with NBD **11** are mainly due to the rupture of the C4–C5 double bond of NBD **11** and the formation of non-bonding electron density at the N2 of the DAAs The topological analysis of the ELF at the TSs and QTAIM parameters indicate that the formation of C3–C4 and N1–C5 covalent bonds has not started yet at any TS.

This MEDT study allows concluding that for the series of 32CA reactions of NBD **11** with substituted DAAs **7**-**10** of increased electrophilic character, the analysis based on CDFT indices does not account for the experimental outcomes. A good linear correlation between the populations of the N–N–C core of these DAAs and the activation energies associated with the corresponding *pmr-type* 32CA reactions is established, indicating that the depopulation of the N–N–C framework of the DAAs, considered an obstacle to bond formation, is responsible for the experimentally found deceleration.

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