Published in the Slovak Republic
European Journal of Molecular Biotechnology
Has been issued since 2013.
E-ISSN: 2409-1332
2018, 6(1): 3-15

DOI: 10.13187/ejmb.2018.1.3
www.ejournal8.com

Articles and Statements

An Investigation of the Reason of not Feasibility of Hetero-Diels-Alder Reaction of Isoselenazole with Unsymmetrical Acetylenic Dienophile: A Conceptual DFT Study and Topological Analysis of ELF Function

Abdelilah Benallou [a, *], Habib El Alaoui El Abdallaoui [a], Hocine Garmes [b]

[a] Team of Chemoinformatics Research and Spectroscopy and Quantum Chemistry, Physical and Chemistry Lab, Faculty of Science, University Chouaib Doukkali, El Jadida, Morocco
[b] Laboratory of Bio-organic Chemistry, Department of Chemistry, Faculty of Science, University Chouaib Doukkali, El Jadida, Morocco

Abstract

A detailed mechanistic study by molecular electron density of the Hetero-Diels-Alder (HDA) reaction of isoselenazole with unsymmetrical acetylenic dienophile is carried out. The high activation energy involved in the transition state of both Ortho and Meta cycloadduct implies that this reaction may not possible, even in the presence of solvent toluene. Besides, ELF shows that the not formation of the basin at the N2 nitrogen atom of isoselenazole moiety. Therefore, the negligible charge transfer between reagents and the large electron density attracted by the lone pair at the N2 atom, in addition to the C1SeN2 fragment distortion energy cost, they are not allowing the formation of the radicals (basins) necessary at the most significant atoms, these factors are probably responsible for the highest barrier activation.

Keywords: MED analysis, ELF, HDA, IRC, Conceptual DFT, TST.

1. Introduction

The Hetero-Diels-Alder (HDA) reactions are powerful tools in organic synthetic chemistry, they represent a significant importance, it have allow the construction of six-membered heterocycles with high stereo and regioselectivity of 1,3-butadiene and an ethylene dienophile (Soto-Delgado et al., 2010; Paton et al., 2011; Benallou et al., 2014; Benallou et al., 2014; Domingo, Saez, 2009). Furthermore, the synthetic utility of this reaction does not arise only from the substitution of both diene and dienophile, but also from the modification of one or more carbon atoms of the π systems by a heteroatom, such as Cl, N, O, S, ... etc. However, the substitution diversity of the dienophile or diene moiety breaks the symmetry and thus favors DA reactions by lowering the activation energy (Berski et al., 2006), which was related to the polar character. Interestingly, to analyze the changes in mechanical quantum observable on the reaction path, mainly the reorganization of the electron density throughout the reaction path, the theoretical model of the evolution of the bonding (Krokidis et al., 1998) and the topological analysis of the electrons localization (Krokidis et al., 1999) are combined during this last decade, because these

* Corresponding author
E-mail addresses: abdo_benallou@yahoo.fr (A. Benallou)

latter's are successively verified an appropriate tool for the studies of organic reactions (Mahdieh et al., 2017; Domingo et al., 2013; Mierzwa et al., 2015), that justify the development of the theoretical approach for the DA reactions implying a large number of dienes and dienophiles (Benallou et al., 2016; Benallou et al., 2016; Diels, Alder, 1928; Woodward et al., 1969; Winkler, 1996; Carruthers, 1990; Chen, Trudell, 1996; Finguelli, Tatichi, 2002). In this context, and to understand the reason of the not feasibility of the cycloaddition HDA reaction of isoselenazole 1 with acetylenic dienophile 2 to afford the intermediary cycloadducts and afterwards the subsequent removal of Selenium from this latter to yield the polysubstituted pyridine (Figure 1) (Shimada et al., 2009), a theoretical computational study has been established. However, this HDA reaction was performed in the presence of solvent toluene, although after 24h in reflux, this reaction does not take place (Shimada et al., 2009). Make a note of that, the polysubstituted and fused pyridine cores have been found in a wide variety of naturally occurring polycyclic alkaloid skeletons having biological, pharmaceutical, and agrochemical activities (Shimada et al., 2009).

In order to evaluate the factors responsible of not feasibility of HDA between isoselenazole with acetylenic dienophile, an analysis of the bonding formation along the reaction and a conceptual DFT (CDFT) indices have been performed and then a complete characterization to provide a new insight into the nature of the transition state (TS) and the mechanism processes, equally how do C-C and C-N bonds formation in this HDA reaction is carried out. Effectively, the combination of conceptual DFT, TST and ELF theories have been used to characterize the reaction pathway through optimized geometries for corresponding stationary points on the IRC path. Then the molecular mechanism study of the HDA reaction has been performed. However, ester groups ($COOCH_3$) as electron withdrawing group (EWG) is attached to acetylenic dienophile, so the asymmetric reaction will give two different region-isomers of ortho and meta intermediary poly-substituted pyridines product (Figure 1). The reaction pathway can be established using intrinsic reaction coordinate (IRC) procedure (Gonzalez, Schlegel, 1990) on the potential energy surface.

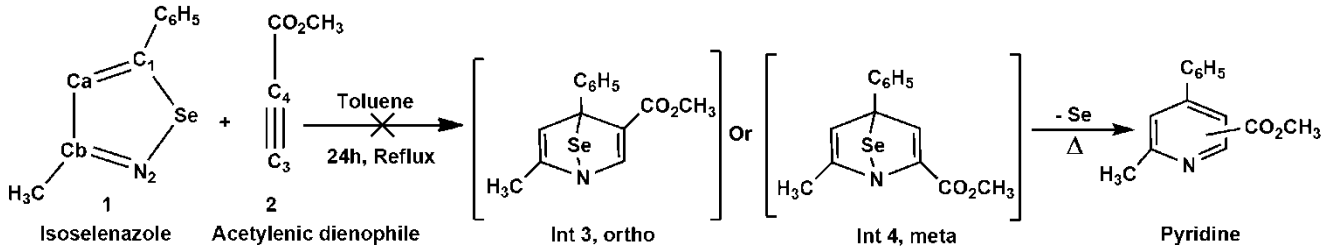

Fig. 1. Not-feasibility of the Hetero-Diels-Alder reactions of isoselenazole with acetylenic dienophile to yield poly-substituted pyridines

2. Computational methods

All DFT computations were carried out using the B3LYP (Lee et al., 1988) exchange–correlation functional, together with the standard 6-311++G(d,p) basis set (Hehre et al., 1986). The optimizations were carried out using the Berny analytical gradient optimization method (Schlegel, 1994). The stationary points were characterized by frequency computations in order to verify that the transition state structure (TS) has one and only one imaginary frequency. The IRC paths (Fukui, 1970) were traced in order to check the energy profiles connecting the TS to the two associated minima of the proposed mechanism using the second order Gonzalez–Schlegel integration method (Gonzalez, Schlegel, 1991). The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method (Reed et al., 1988) and by ELF topological analysis (Krokidis et al., 1999). The ELF study was performed with the Multiwfn program (Tian, Feiwu, 2012) using the corresponding mono determinantal wavefunctions of the selected structures of the IRC at the B3LYP/6-311++G(d,p)basis set. All computations were carried out with the Gaussian 09 suite of programs (Frisch et al., 2009). The global electrophilicity index (Parr et al., 1999), ω, is given by the following expression, $\omega = \mu^2/2\eta$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, e_H and e_L, as $\mu=(e_H+e_L)/2$ and $\eta=(e_L-e_H)$, respectively (Parr, Yang, 1989) then the local electrophilicity for a site or an atom

(k) (Domingo et al., 2002) is given by the equation: $\omega_k=\omega f_k^+$. Domingo et al have proposed a new descriptor, the nucleophilicity index, N (Domingo, Pérez, 2011), based on the HOMO energies obtained within the Kohn–Sham scheme (Kohn et al., 1965), and defined as $N=E_{HOMO(Nu)}-E_{HOMO(TCE)}$. Similarly, the local nucleophilicity index N_k (Perez et al., 2009) defined as the product of global nucleophilic index N and the nucleophilic of the Fukui index $N_k=Nf_k^-$, while the nucleophilicity has referred to tetracyanoethylene (TCE) as a reference. Where f_k^- and f_k^+ are the Fukui functions for nucleophilic and electrophilic attacks, respectively (Contreras et al., 1999).

3. Results and discussion

In order to shed light the mainly factors responsible of the not feasibility of this HDA reactions between isoselenazole (1) and acetylenic dienophile (2), an analysis of the physicochemical parameter to choose the most favorable product based on the CDFT reactivity descriptors will be performed, followed by a potential energy surfaces (PES) study of the reaction to characterize the barrier activation of this reaction in gas phase and in presence of the solvent toluene. To conclude, an ELF bonding analysis along the new probably bond-formation pathway of this reaction will be carried out in order to study properties of electron localization in the processes of the bond formation/breaking.

3.1. Conceptual DFT (CDFT) indices of the reagents

In this paragraph, we will determine the physic-chemical characteristics of isoselenazole (1) and acetylenic dienophile (2) substrates, for this instance the distribution of the global and local electrophilicity and nucleophilicity indices of each molecule, as chemical potential μ and chemical hardness η in order to characterize the reactivity of these compounds, and thus, the CDFT indices of the isoselenazole and acetylenic dienophile are given in Table 1.

Table 1. HOMO and LUMO energies, chemical potential μ, chemical hardness η, global electrophilicity ω and global nucleophilicity N

Parameters	*Isoselenazole*	*Acetylenic dienophile*
HOMO (au)	- 0.23037	-0.24826
LUMO (au)	-0.05229	-0.03791
μ (au)	-0.141	-0.143
η (au)	0.178	0.210
ω (eV)	1.52	1.32
N (eV)	2.87	2.36

In Table 1, we have noted that the chemical potential of isoselenazole is slightly higher to compare with the acetylenic dienophile, in which μ(-0.141)>μ(-0.143), indicates that the global electron density transfer (GEDT) will take place from diene (isoselenazole 1) to dienophile (acetylenic 2). Interestingly, the global electrophilic and nucleophilic indices show that the isoselenazole moiety behaves as nucleophile and electrophile in the same time, such as 1.52eV(1)>1.32eV(2) and 2.87eV(1)>2.36eV(2), and this is not suitable in point of view chemically, and then, to overcome this complicated situation and to correctly predict the electrophilic and/or the nucleophilic character of the diene and dienophile for this HDA reaction, in other words to evaluate the withdrawing and releasing groups, that envisaged us to identify the nature of the reaction mechanism (NRM). For this purpose, we will need to determine the absolute value of the energy difference such as: $E1|\varepsilon_{HOMO(Diene)}-\varepsilon_{LUMO(Dienophile)}|//E2|\varepsilon_{HOMO(Dienophile)}-\varepsilon_{LUMO(Diene)}|$. Note that the reaction is: Normal electronic demand (NED) if E1 < E2, and Inverse electronic demand (IED) if E2 < E1. Herein, we have found that E1(0.192)<E2(0.196), and thus this HDA reaction takes

place as a normal electronic demand (NED) which meant that the diene (isoselenazole) plays the role of electron donor (nucleophile), whereas the dienophile (acetylenic) plays the role of electron attractor (electrophile). Consequently, the charge transfer will take place from the diene to the dienophile, these results will be confirmed next by the charge transfer in the transition states.

In order to predict the selectivity of the HDA reactions (region/chemo), we have used the polar model (Domingo et al., 2008) which states that the formation of the first new σ bond will take place by the most favorable interaction between two sites (the more nucleophilic site is characterized by *the maximum nucleophilic value of local nucleophilicity index* N_k, while the more electrophilic site that possessing *the maximum electrophilic value of local electrophilicity index* ω_k) and Houk rule (Fleming, 1976), in this latter, "small-small" and "large-large" type interactions are more favored by report interactions 'large-small' and 'small-large'. However, this Houk approach is based essentially on the coefficients of orbital molecular HOMO/LUMO for diene and dienophile substrates. The results are given in Figure 2.

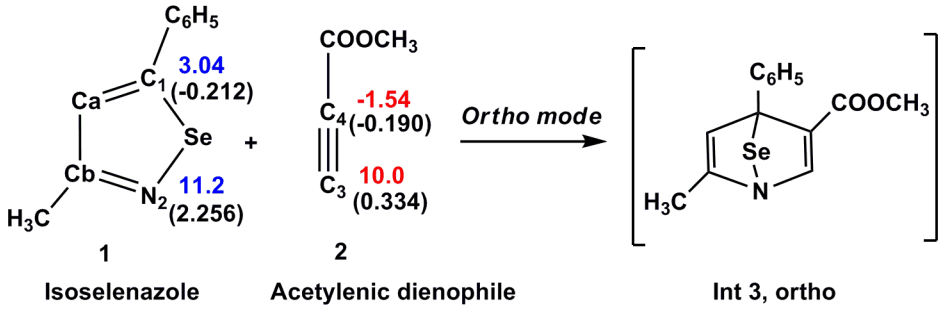

Fig. 2. Predict regioselectivity using the local nucleophilicity N_k (1, in blue) and local electrophilicity ω_k (2, in red) indices (eV) and Houk rule (in parentheses)

According to the results noted in Figure 2, we have established that the most favorable interactions are between N2 atom of the isoselenazole 1 and C3 atom of the acetylenic dienophile 2, so taking into account the polar model we have noted that; the local nucleophilic index *N* of N2 is 11.2eV, it is extremely superior to that of C1 carbon (3.04eV), while the local electrophilic index ω of C3, is 10.0eV, which very higher to compare with C4 atom (-1.54eV), therefore the most favorable interaction will take place between N2 and C3 centers that having the biggest nucleophilic N and electrophilic ω values, respectively. Subsequently, the ortho/endo adduct is the most stable product. Similarly, Houk rule shows that the large values and the small values of the coefficients of orbital molecular HOMO/LUMO are attributed consecutively to the atoms N2 (isoselenazole 1) vs C3(acetylenic dienophile 2) and {C1 vs C4}, respectively. Enabling us to deduce that the interaction is highly appreciated between N2 and C3 atoms, subsequently provide the ortho/endo adduct as majority product.

3.2. PES path study and analysis of the stationary points involved in the two regioisomeric pattern associated with the endo approach of isoselenazole 1 with unsymmetrical acetylenic dienophile 2

In Figure 3 and 4, we have shown that the activation energies of both regioisomeric patterns are generally very higher energy cost, 46(GP) /46 (ST)kcal/mol and 45 (GP) /44 (ST) kcal/mol in gas phase (GP) and in presence of solvent toluene (ST) at 298K of meta and ortho, respectively, similarly, we have remarked that an unappreciable amount of charge transfer in transition states 0.05e and 0.09e (see figure 2), strongly indicates this reaction is a non polar reaction, in good agreement with the chemical potential of both isomers that have a closer values (see Table 1). Thus, none of the reagents will have a tendency to exchange electron density with the other along of the reaction. So these reagents are not have evidently most important interactions, which induce a feeble change of electron density between so-called reagents, therefore the unsymmetrical substitution of the acetylenic dienophile does not has the sufficient effect for improving reactivity, in contrast to many (4+2) cycloaddition reactions. Whereas the calculations of Gibbs free energies ΔG of the reaction in gas phase show that theses mechanism processes are totally endergonic in which ΔG equal 14kcal/mol and 15kcal/mol of meta and ortho region-isomeric, respectively, indicate on the one hand, that these products not have the sufficient stability to compare with the

reagents, on the other hand, these mechanisms processes are not spontaneously possible. Subsequently, despite that the activation energy of ortho regioisomeric channel is somewhat lowest than meta regioisomeric, this reaction cannot occur efficiently because of the highest barrier activation and that can be related; firstly to the energy cost of the C1SeN2 fragment distort and secondly to the energy gain from bond formation (σ)/breaking (pi) processes, it is worthy to note that, a very similar reaction of selenadiazole with dimethyl actelenedicarboxylate (DMAD) is take place in the presence of solvent benzene (Takikawa et al., 1991). Some appealing conclusions can be drawn from this PES study, the closer values of chemical potential and the weak charge transfer of the reagent imply a very higher energy cost reaction. Taking into account these considerable results and furthermore to give a fundamental and basic explanation of not reactivity of such reaction between isoselenazole 1 and the unsymmetrical acetylenic dienophile 2 a complete investigation by molecular electron density (MED) theory will be performed.

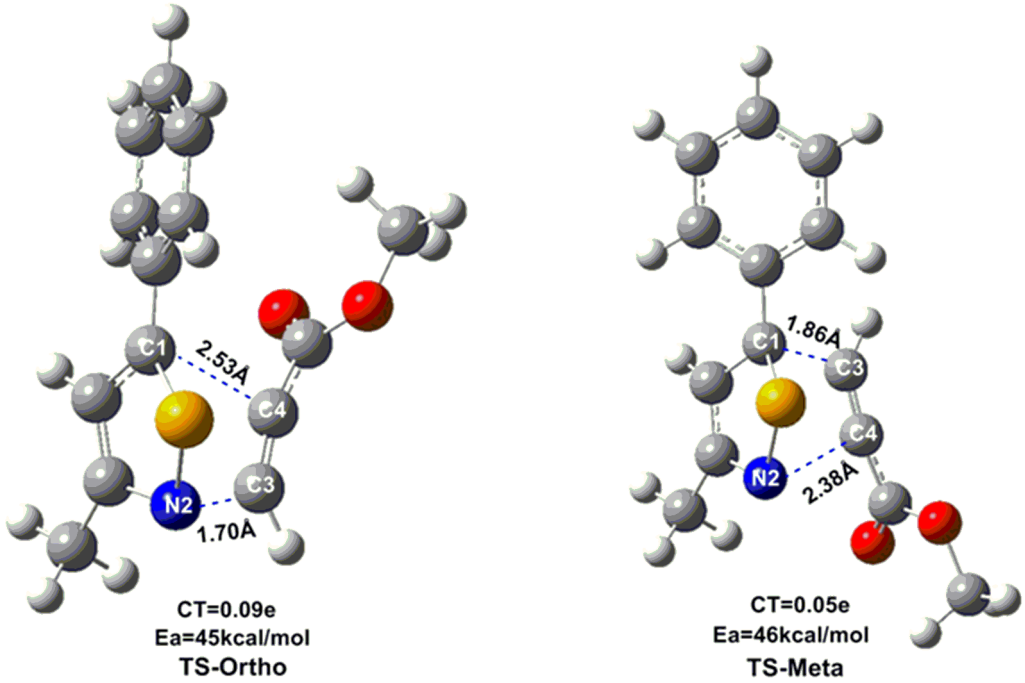

Fig. 3. Bond distances (Å), charge transfer in e and activation energy in kcal/mol of ortho and meta transition structures in the gas phase

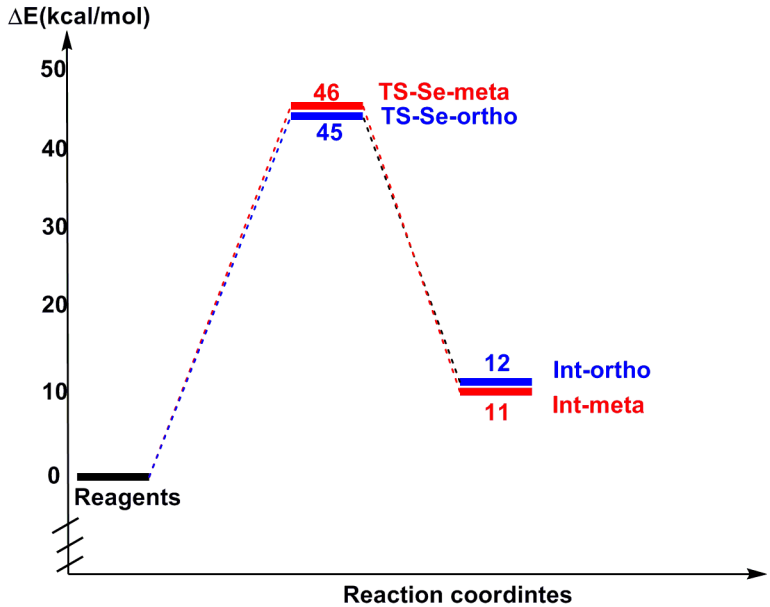

Fig. 4. Profile energetic, in gas phase, of HDA reaction between isoselenazole 1 and the unsymmetrical acetylenic dienophile 2

3.3. Analysis of bonding evolution in the HDA reaction using topological analysis of ELF function

In this study, we have shown previously that this reaction is highly energetic, 45kcal/mol for the most favorable channel, clearly indicates this reaction may not occur efficiently in the noted conditions, in good accordance with the reactivity experimentally observed (Shimada et al., 2009). Thus, a MED study of this HDA reaction will be carried out to interpret and understand the feeble reactivity. At this end, the topological analysis of the ELF along the reaction path associated with a cycloaddition is a valuable tool for understanding the bonding changes along the reaction path (Polo et al., 2004; Berski et al., 2006; Polo et al., 2008) and thus, to characterize the molecular mechanism (Silvi, 2002). Consequently, a topology analysis of the ELF along IRC of the most favorable *endo/ortho* channel associated with the HDA reaction between isoselenazole and acetylenic dienophile was performed to identify the distribution of electron density with the progress of the reaction along of bond breaking/formation. In this context, the total electronic populations of the more relevant ELF valence basins of selected structures along IRC (Figure 5) are listed in Table 2, the attractor positions for the most relevant points associated with the formation of the C1–C4 and N2-C3 single bond, are shown in Figure 5.

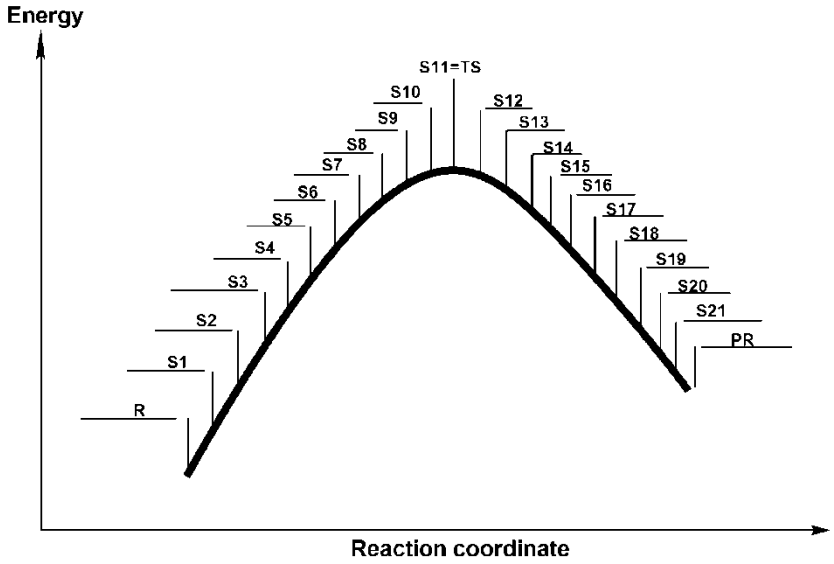

Fig. 5. Several analysis structures along IRC of Hetero-Diels-Alder reaction between isoselenazole with acetylenic dienophile

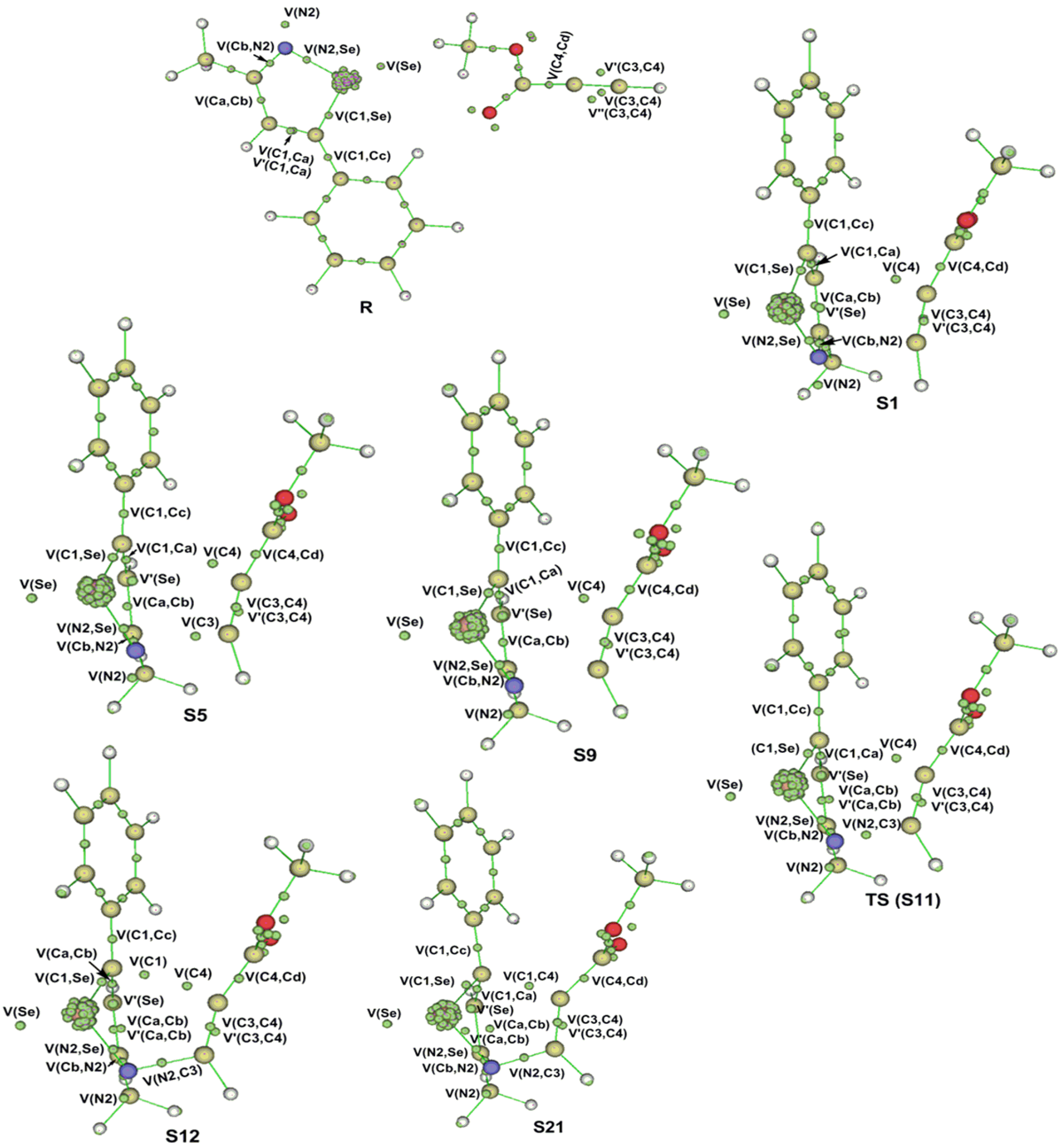

Fig. 6. ELF attractors of some selected points of the IRC associated with the formation of the new C–C and N-C single bond in the HDA reaction of isoselenazole 1 with acetylenic dienophile 2

Table 2. Valence basin populations of the most relevant points calculated from the ELF of HDA reaction of isoselenazole with acetylenic dienophile, associated with the C1–C4 and N2-C3 bonds formation step. Bond order (Wiberg index) and charge transfer in *e* (NBO)

Phase	R	S1	S2	S3	S4	S5	S6	S7	**S8**	**S9**	**S10**	S11 =TS	S12
d(C1-C4)	>2.83	2.83	2.81	2.78	2.76	2.73	2.71	2.68	2.65	2.61	2.57	2.53	2.48
d(N2-C3)	>2.19	2.19	2.13	2.08	2.03	1.98	1.93	1.88	1.83	1.78	1.74	1.70	1.67
V(C1)													0.20

V'(C1)													
V(N2)	3.25	3.19	3.18	3.18	3.18	3.18	3.19	3.19	3.23	3.57	2.71	2.67	2.64
V'(N2)													
V(C3)						0.06	0.14	0.21	0.27				
V(C4)		0.29	0.33	0.37	0.42	0.47	0.50	0.55	0.58	0.63	0.68	0.70	0.74
V(C1,Ca)	3.38	3.12	3.07	3.02	2.98	2.92	2.86	2.79	2.72	2.65	2.60	2.51	2.45
V'(C1,Ca)	3.38												
V(Ca,Cb)	2.43	2.68	2.75	2.81	2.88	2.96	3.05	3.14	3.22	3.27	3.32	3.38	3.41
V'(Ca,Cb)												3.38	3.41
V(Cb,N2)	2.76	2.56	2.51	2.47	2.42	2.36	2.30	2.25	2.18	2.14	2.09	2.05	2.00
V'(Cb,N2)													
V(N2,Se)	1.15	1.22	1.23	1.24	1.25	1.26	1.27	1.28	1.28	1.28	1.28	1.27	1.26
V(C1,Se)	1.81	1.86	1.86	1.87	1.88	1.88	1.89	1.90	1.90	1.93	1.96	2.02	1.85
V(C1,Cc)	2.22	2.27	2.27	2.28	2.28	2.28	2.29	2.30	2.30	2.30	2.30	2.30	2.29
V(C4,Cd)	2.38	2.50	2.51	2.51	2.52	2.52	2.54	2.55	2.56	2.57	2.60	2.57	2.56
V(C1,C4)													
V(N2,C3)											0.94	1.06	1.15
V(C3,C4)	2.75	2.53	2.50	2.48	2.45	2.41	2.38	2.32	2.19	2.20	2.15	2.10	2.07
V'(C3,C4)	2.49	2.46	2.44	2.42	2.41	2.37	2.28	2.23	2.16	2.15	2.12	2.09	2.06
V''(C3,C4)	0.13												
V(Se)	2.35	2.30	2.30	2.32	2.32	2.33	2.33	2.34	2.36	2.37	2.38	2.39	2.41
V'(Se)	2.39	2.46	2.47	2.47	2.46	2.46	2.46	2.47	2.47	2.47	2.47	2.47	2.47

Table 3 (Next)

Phase	S13	S14	S15	S16	S17	S18	S19	S20	S21	PR
d(C1-C4)	2.43	2.38	2.33	2.27	2.22	2.16	2.10	2.05	1.99	1.55
d(N2-C3)	1.64	1.62	1.60	1.58	1.57	1.56	1.55	1.54	1.54	1.48
V(C1)	0.27	0.33	0.44	0.46	0.49	0.53	0.54	0.56		
V'(C1)										
V(N2)	2.62	2.61	2.60	2.60	2.60	2.59	2.59	2.59	2.60	2.65

V'(N2)										
V(C3)										
V(C4)	0.76	0.80	0.85	0.86	0.87	0.89	0.93	0.98		
V(C1,Ca)	2.39	2.35	2.27	2.25	2.24	2.21	2.17	2.14	2.12	2.00
V′(C1,Ca)										
V(Ca,Cb)	3.45	3.48	3.54	3.51	1.83	1.82	1.85	1.87	1.86	1.87
V′(Ca,Cb)	3.45	3.48	3.54	3.51	1.74	1.77	1.77	1.77	1.79	1.88
V(Cb,N2)	1.97	1.95	1.93	1.90	1.88	1.86	1.84	1.83	1.82	1.72
V′(Cb,N2)										
V(N2,Se)	1.25	1.24	1.22	1.22	1.22	1.20	1.19	1.18	1.17	1.03
V(C1,Se)	1.82	1.79	1.74	1.73	1.71	1.70	1.68	1.65	1.63	1.32
V(C1,Cc)	2.28	2.27	2.24	2.25	2.22	2.21	2.18	2.17	2.17	2.15
V(C4,Cd)	2.54	2.52	2.46	2.50	2.44	2.41	2.39	2.37	2.35	2.39
V(C1,C4)									1.59	2.00
V(N2,C3)	1.23	1.28	1.39	1.40	1.42	1.46	1.49	1.52	1.54	1.78
V(C3,C4)	2.03	2.02	1.99	1.99	1.98	1.96	1.94	1.93	1.92	1.85
V'(C3,C4)	2.05	2.01	1.98	1.98	1.97	1.96	1.95	1.95	1.94	1.71
V''(C3,C4)										
V(Se)	2.41	2.43	2.45	2.45	2.45	2.47	2.47	2.47	2.48	2.54
V'(Se)	2.47	2.47	2.47	2.47	2.48	2.48	2.49	2.49	2.49	2.55

In order to explain the not feasibility of the Hetero-Diels-Alder reaction between isoselenazole and acetylenic dienophile we have commented 21 stationary points along IRC, also the structure of reagent and products are discussed. So, taking into account the results noted in table 2, relative to the most attractive centers. For isoselenazole, in distances d(C1-C4)>2.83Å and d(N2-C3)>2.19Å, ELF shows two {V(C1,Ca); V'(C1,Ca)} and only V(Cb,N2) disynaptic basins associated with C1-Ca and Cb-N2 double bonds, whose electronic population integrate 3,38e and 2,76e, respectively, the presence of a single disynaptic basin of Cb-N2 double bond reveals strongly that this bond is poor electronically and a part of electronic population has been absorbed by the lone pair of N2 atom, V(N2) monosynaptic basin, integrating 3.24e. However, in the same reagent the topology of the ELF relative of the Ca-Cb single bond shows an one V(Ca,Cb) disynaptic basin reaching 2.43e. Equally, for acetylenic dienophile, the ELF reveals that the presence of the three pairs V(C3,C4), V'(C3,C4) and V''(C3,C4) disynaptic basins associated with the C3-C4 triple bonds, whose electronic population 2.75e, 2.49e and 0.13e respectively. Therefore, the electronic population of the reagents is in good consistency with the molecular structure.

The bonding change (BC) theory along of the reaction mechanism gives us the opportunity to characterize the reorganization and the distribution of electron density between the reagents, and thus, the investigation of the reason of not feasibility of such reaction leads us to analysis exclusively the most significant attractors such as C1, N2, C3 and C4, because such atoms will react one of the other to yield poly-substituted pyridine. Although, in the most favorable ortho/endo adduct, C1 vs C4, while N2 must interact with C3 atom. In this context, in the structure 1 (S1) (Table 2), we have noted the appears of the first radical monosynaptic basin, V(C4) with an electronic population of 0.29e, this attractor will permit the creation of the new bond between C4 and C1 atoms, equally in this structure we have shown that a depopulation and reduction of the disynaptic basins relative to the C1-Ca, C3-C4 bonds. At this point, regarding the S2, S3, S4 and S5 structures, the second monosynaptic basin V(C3) positioned at C3 is appeared finally, integrates a very small electronic population to be 0.06e, note that these first appeared radicals are belonging to the acetylenic dienophile, whereas V(C1) and V(N2) basins of isoselenazole are not yet localized. In the structures S6 and S7, the noted basins do not have more changes throughout the progress of the reaction, at this long process the new monosynaptic basin of V(C1) and V(N2) are not yet appeared.

The most relevant changes in this reaction analysis take place in the structures S8, S9 and S10, while 2.57Å≤d(C1-C4)≤2.65Å, and 1.74Å≤d(N2-C3)≤1.83Å, herein in S8, we have remarked that V(N2) monosynaptic basin associated with the lone pair positioned at N2 nitrogen atom experience a slight increase to reach 3.23e, however, this basin experiences a feeble reduction from reagent to the structure S7, integrates 3.19e, it has a significant impact towards the reaction processes, equally in the same structure along IRC, the V(C3) monosynaptic basin profit to more electronic population, reaching 0.27e.

In S9, the V(N2) monosynaptic basin related to the lone pair has been increased to achieve a maximum electronic population, 3.57e, while V'(N2) monosynaptic basin is never going to likely take place. Surprisingly, the formation of the new N2-C3 bond is located in S10, and this is worth considering, because the formation of the new bond requires two adjacent pseudo-radicals under N2 and C3 atoms, however this process is not achieved. So in this case the formation of V'(N2) monosynaptic basin at N2 position involves high activation energy to occur efficiently, therefore three reasons should be responsible for the not formation of the N2 pseudoradical; (**1**): the observable amount of electronic density associated with the lone pair of N2 atom in S8 and S9 structures can be responsible for the not appearance of V'(N2) radical, in which an expect electron density presumed at V'(N2) has totally absorbed by the lone pair of the N2 atom, that can be explained by the high electronic population in the structure S9, (**2**): will N2 and C3 atoms near one to the other along IRC a noticeable amount of electron density has been shifted from the monosynaptic basin of V(C3) and V'(N2) to the monosynaptic basin of V(Se) and V(N2), (**3**) a very important energy is necessarily for distort C1SeN2 fragment. Consequently, the formation of the new bond of N2-C3 may not occur as a consequence of the absence of two radicals (basins) at the N2 and C3 atoms.

The analysis of the subsequent structures shows the split of the V(Ca,Cb) disynaptic basin in structure S11 (Transition State) to the pairs of V(Ca,Cb) and V'(Ca,Cb) disynaptic basins to reach 3.38e each one, indicates that this Ca-Cb sequence becomes double bonds, however the new monosynaptic basin of V(C1) has reached the sufficient electronic density to occur in structure S12, reaching 0.20e, and then, the analyses of the succeeding structures do not have any scientific significance considering the obvious reasons of the non reactivity found of this reaction.

Consequently, the feeble charge transfer involved in this reaction, an inequitable distribution of electron density and the huge energy cost to distort C1SeN2 fragment have unhelpfully influenced the reactivity and subsequently generate a great difficulty to form the pseudo-radical at the principle attractor, N2. So, when the reagents near one to the other, the formation of the N2 pseudo-radical has failed and due to the more reason (lone pair of the N2 attractor of electron, Se atom attractor of electron, C1SeN2 sequence distortion), therefore these factors are probably responsible for the high activation energy. However, the change of solvent or the substituent of both substrates of diene and dienophile could improve the reactivity through modifying the reorganization of the electron density and then to make a balance between the bond formation (energy gain)/breaking (energy loss) and the C1SeN2 sequence distortion energy cost within the molecule.

In conclusion, a schematic picture of the bonding changes along the selected points involved in this HDA reaction is given in Figure 7, and then; a clear representation of the not feasibility of this reaction has been depicted in Figure 8.

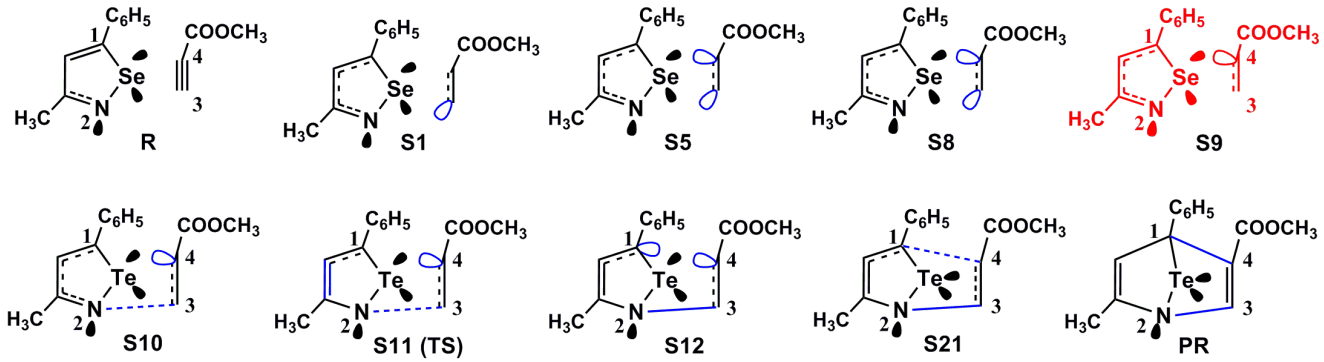

Fig. 7. Schematic picture of the bonding changes at the selected points involved in the HDA reaction of isoselenazole 1 with acetylenic dienophile 2. Lines represent bonding V(M,N) disynaptic basins, and ellipses represent non-bonding V(M) monosynaptic basins. Filled lines (in blue) indicate new V(M,N) disynaptic basins formation

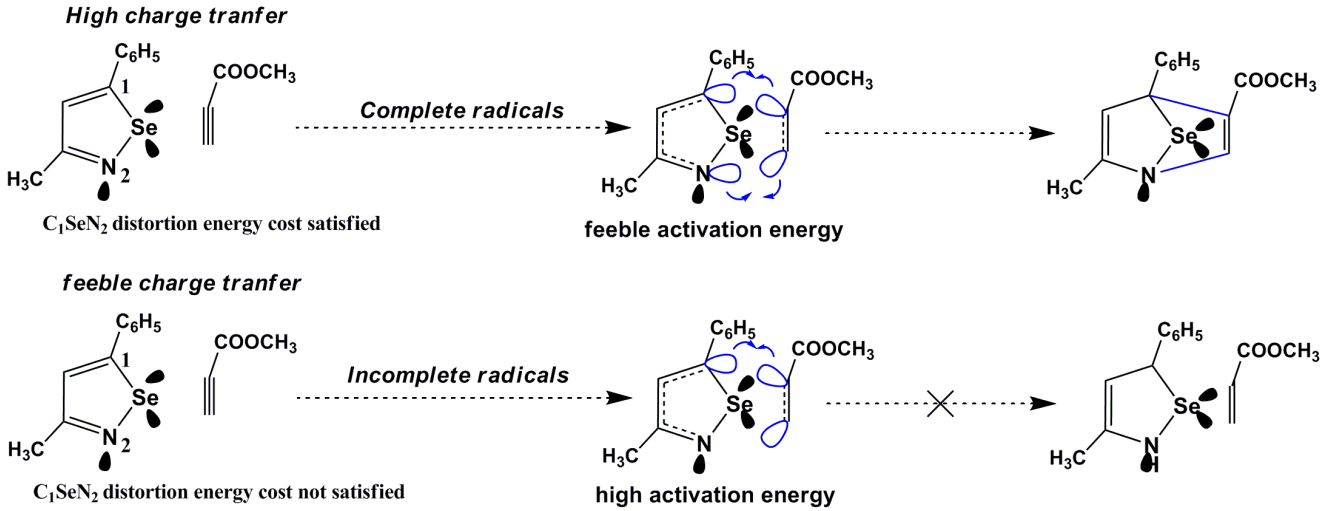

Fig. 8. Demonstration of not formation of the new N–C bond in the Hetero-Diels–Alder reaction of isoselenazole 1 with acetylenic dienophile 2

4. Conclusion

The reason responsible of the not feasibility of Hetero-Diels-Alder (HDA) reaction of isoselenazole with unsymmetrical acetylenic dienophile has been performed in this study using DFT, and ELF topological analysis methods at B3LYP/6-311++g(d,p) basis set level. And thus, this study shows that the formation of both isomers, necessities high activation energy, 45 (44) kcal/mol and 46(46) kcal/mol, in the gas phase and in the presence of the solvent toluene, for ortho and meta regioisomeric respectively. Equally, the ELF study of the most probably endo/ortho cycloadduct predicts that the electron density reorganization of the pseudo-radical centers of the most electrophilic site (C3 carbon) of acetylenic dienophile 2 and the most nucleophilic site (N2 nitrogen) of isoselenazole 1 are not appeared completely by the reason of the feeble charge transfer in the transition state, energy cost for distort C1SeN2 fragment, and electronic attractor of lone pair, they make it impossible the occur of N2 pseudo-radical. Therefore, the formation of the monosynaptic basin at N2 requires high energy contribution. Consequently, the formation of the pseudo-radical at the most attractive atoms is very significant for the formation of the new bond, however that can be solved by the use of another appropriate solvent or by the change of the substituent to make a balance between energy gain/energy loss relative to the bond formation/breaking and geometry reorganization energy cost due to distort of the C1SeN2 fragment.

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