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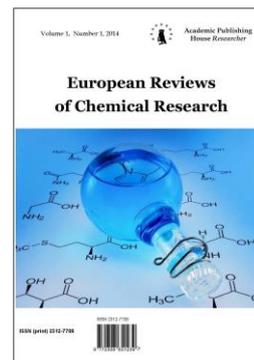
Articles and Statements

A Quantum Chemical Topological Analysis of the C-O Bond Formation in the 32CA Reaction Involving Zwitterionic Specie Type

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Abstract

The mechanism nature of the 32CA reaction involving zwitterionic species has been performed; and thus, the changes of electron density associated with the O-C and C-C bond formation along IRC are characterized. Conceptual DFT analyses of the most favorable adduct, Endo-mode α; shows that the electronic flux will takes place from nitrone to methacrylonitrile moiety. Furthermore, ELF topological analysis based on the electron density predicts that C-C bond is formed by the coupling of two pseudoradical centers generated at the most significant atoms of the molecules, while O-C bond is formed by the donation of the some electron density given by the lone pair. Two-stage one-step is the most probably mechanism of this reaction, the first stage aims for the formation of C2-C3 σ bond while the second stage aims for the formation of O1-C1 σ bond. In general, the observed asynchronicity of this 32CA reaction can be related mainly to the asymmetric reorganization of the electron density at the most attractive centers.

Keywords: 32CA, DFT, Cycloaddition, ELF, Nitrone.

1. Introduction

Organic compounds of small cycles are of great interest in medicinal chemistry (De Luca, 2006), and are swiftly prepared from a [3+2] cycloaddition (32CA) reaction between a Three Atom- Component (TAC) and an ethylene derivative (see Fig. 1). While TACs are species including four electrons delocalized among three continuous atoms. The 32CA reactions have proven to be a powerful synthetic tool in the construction of five-membered heterocyclic compounds (Padwa et al., 2002). Since the introduction of the chemical bond concept has been explored at the beginning of the 20th century by G. N. Lewis (Irvin, 1938), a lot of theoretical models have been developed to understand the structure and chemical reactivity of the subject. Quantum chemical tools based on the valence bond theory, molecular orbital theory, and the most recent density functional theory (DFT) have proven to be useful to improve the study of structure and reactivity (Confalone et al., 1988; Benallou et al., 2016; Benallou et al., 2016; Benallou et al., 2017; Benallou et al., 2016; Benallou et al., 2017). One appealing procedure that provides a more straightforward connection between the electron density distribution and the chemical structure is the quantum chemical

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topological (QCT) analysis of the electron density based on the electron localization function (ELF) (Brandi et al., 2009; Benallou et al., 2018; Benallou et al., 2018). In this sense, Silvi and Savin presented the ELF in a very chemical manner, using their topological analysis as an appealing model of chemical bonding (Malinina et al., 2014). Moreover, the characterization of the electron density reorganization to evidence the bonding changes along a reaction path is the most attractive method to analyze a reaction mechanism. A number of the Molecular Electron Density Theory (MEDT) (Domingo, 2016) devoted to the study of the reactivity and mechanism of three-atom-components (TACs), however their contribution in the 32CA reactions have permitted establishing a useful classification of this class of cycloaddition reactions, in which associate to the electronic structure and behavior of the TAC into *pseudodiradical*-type (*pr-type*, typically an azomethine ylide), zwitterionic-type (*zw-type*, typically a nitrone) reactions (Figure 2) (Domingo, Emamian, 2014). Usually, nitrones are good nucleophiles that react with electron-deficient alkenes (Domingo et al., 2014).
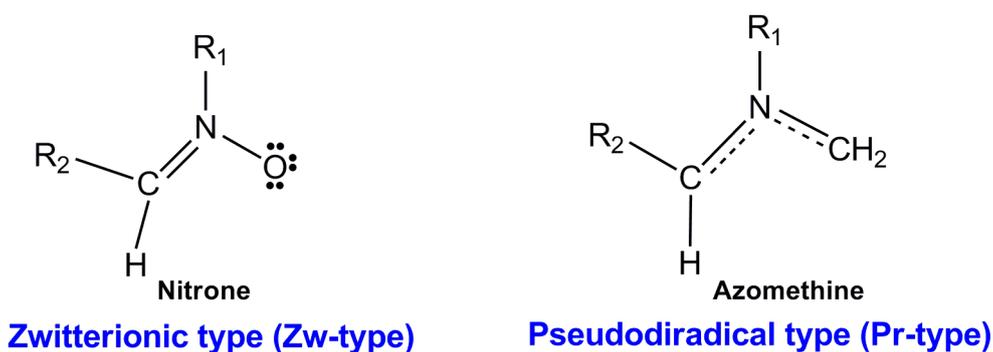

Fig. 1. Electronic structure of TACs and the proposed reactivity zwitterionic and pseudodiradical types in 32CA reactions

In this letter, the 32CA reactions of nitrone with electronic deficient methacrylonitrile derivative (Carmona et al., 2016), are studied within the MEDT through DFT calculations at the B3LYP/6-31G(d) computational level. This study is dedicated to the most favorable adduct, *endo α*, the preference of the region-specific Endo is confirmed by Parr functions and is strengthen by the thermodynamically evaluation (Figure 2). A quantum chemical topological analysis of the C-C and O-C single bond formation in organic reactions involving cationic species along these 32CA reactions is performed in order to characterize the molecular mechanisms of this cycloaddition reaction.
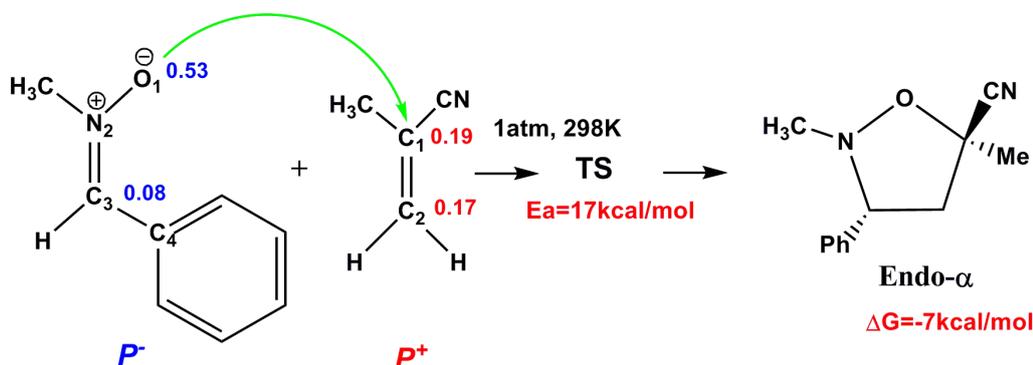

Fig. 2. 32CA reaction of nitrone (left side) with methacrylonitrile, nucleophilic P^- and electrophilic P^+ Parr functions

2. Computational methods

DFT computations were carried out using the B3LYP exchange–correlation functional (Lee et al., 1988; Becke, 1993), the equilibrium geometries have been optimized at the 6-31G(d) basis set level on Gaussian 09 (Frisch et al., 2009), using Berny's algorithm (Schlegel, 1981). Atomic

electronic populations and reactivity indices were calculated using natural population (NPA). The global electrophilicity index ω (Parr et al., 1999), was given by the following expression $\omega = \mu^2 / \eta$, in terms of the electronic chemical potential μ=e$_{HOMO}$+e$_{LUMO}$/2 and the chemical hardness η=e$_{LUMO}$-e$_{HOMO}$. Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, and as and, respectively. The empirical nucleophilicity index N (Domingo et al., 2011), N=(N$_{(HOMO-reagent)}$-N$_{(HOMO-TCE)}$) based on the HOMO energies obtained within the Kohn-Sham (Kohn, Sham, 1965), and defined as the nucleophilicity was referred to tetracyanoethylene (TCE). Electrophylic P_k^+ nucleophilic P_k^- Parr functions (Domingo et al., 2013) were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents.

The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method (Reed et al., 1988) and by ELF topological analysis (Savin et al., 1996). The ELF study was performed with the Multiwfn program (Tian, Feiwu, 2012) using the corresponding mono determinantal wave-functions of the selected structures of the IRC.

3. Results and discussions

In order to obtain a greater understanding of the bonding formation in the 32CA reaction, the present study has been divided into three parts: (i) in the first one, an analysis of the CDFT reactivity indices at the ground state (GS) of the reagents involved in the 32CA reaction of nitrone with methacrylonitrile is performed; (ii) then, an ELF topological analysis of the electronic structure associated with the 32CA reaction of nitrone and methacrylonitrile are explored and characterized; (iii) in the third part, a topological analysis of the ELF of the nitrone and methacrylonitrile is performed in order to characterize their electronic structures, the C-O bond formation and mechanism nature.

3.1. Analysis of the CDFT reactivity indices of nitrone and methacrylonitrile

An analysis of the CDFT reactivity indices computed in gas phase at the 298K of nitrone with methacrylonitrile was performed to predict their reactivity in 32CA reactions. The global indices, namely, the electronic chemical potential, μ, chemical hardness, η, electrophilicity, ω, and nucleophilicity, N, at the ground state (GS) of the reagents involved in these 32CA reactions are given in Table 1.

Table 1. B3LYP/6-31G(d) electronic chemical potential (μ), chemical hardness (η), electrophilicity (ω) and nucleophilicity (N), in eV, of nitrone and methacrylonitrile

Reagent	HOMO(au)	LUMO(au)	μ(eV)	η(eV)	ω(eV)	N(eV)
Nitrone	-0.20231	-0.04651	-2.1	4.2	0.5	3.6
Methacrylonitrile	-0.27715	-0.04511	-3.1	6.3	0.8	1.6

The electronic chemical potential of nitrone μ=-2.1eV, is higher to that of methacrylonitrile, μ=-3.1eV. Thus, the nitrone moiety has a tendency to exchange electron density with methacrylonitrile along this 32CA reaction, so the electro, flow will take place from nitrone to methacrylonitrile. So, methacrylonitrile presents an electrophilicity ω index of 0.8eV, being classified as a feeble electrophile and as a moderate nucleophile, 1.6eV. At this time, nitrone behaves as a great nucleophile which the nucleophilicity N index equal 3.6eV according to the nucleophilicity scales. The electrophilicity of methacrylonitrile is close to that of nitrone 0.5eV, indicates strongly this reaction is moderately polar. Therefore, in this 32CA reaction, nitrone and methacrylonitrile moieties behave as nucleophile and electrophile, respectively.

3.2. ELF topological analysis of the electronic structure of nitrone and methacrylonitrile

The reactivity of nitrone can be correlated with their electronic structure. Therefore, an ELF topological analysis of the nitrone and methacrylonitrile was performed in order to characterize the electronic structure of this TAC. The representation and attractor positions of ELF valence basins, as well as ELF electron populations, arising from the ELF topological analysis are shown in Figure 3.
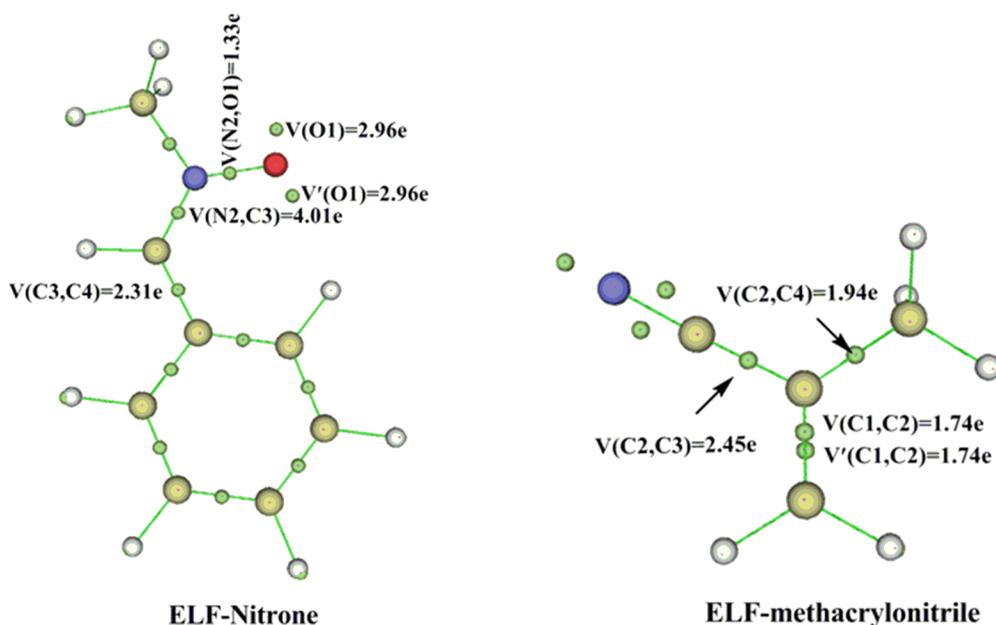
Fig. 3. ELF valence basins populations, in e, of nitrone and methacrylonitrile

ELF topology of the nitrone permits establishing the electronic structure distribution on this TAC (see Figure 3). However, nitrone presents two V(O1) and V'(O1) monosynaptic basins, integrating 2.96e each one (total 5.92e≈ 6e), and one V(O1,N2) disynaptic basin with a population of 1.33e. This behavior suggests that the O1-N2 bonding region is strongly polarized towards the O1 oxygen atom. Additionally, the presence of one V(N2,C3) disynaptic basin integrating 4.01e indicates that the N2-C3 bonding region has a strong double bond character. Consequently, ELF topology of the nitrone clearly indicates that this TAC is able to participate only in zw-type 32CA reactions, as it neither presents a pseudodiradical (Domingo et al., 2010) electronic structure, and thus, ELF topological allows establishing the proposed Lewis structure given in Figure 4. On the other hand, the ELF topology of methacrylonitrile shows the presence of two V(C1,C2) and V'(C1,C2) disynaptic basins integrating a total electronic density of 3.48e indicates that the C1-C2 bonding region has a strong double bond character, furthermore C2-C3 and C2-C4 frameworks represent 2.45e and 1.94e respectively, they can be considered single bonds. Consequently, both reagents have the tendency to exchange electron density between them and provide high reactivity.
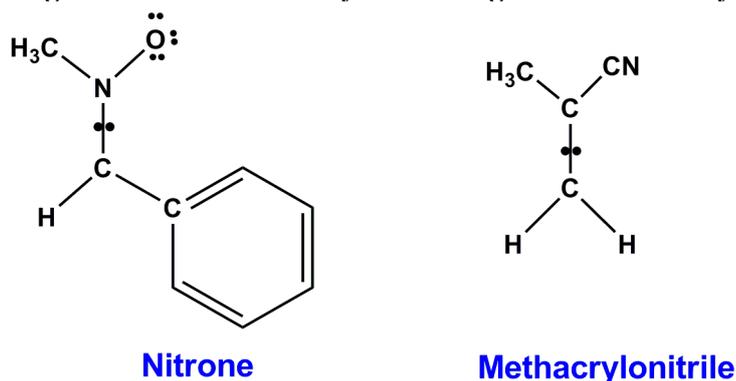

Nitrone   **Methacrylonitrile**

Fig. 4. Representation of Lewis structures for nitrone and methacrylonitrile obtained from ELF topological analysis in Zwitterionic specie type

3.3. BET/ELF Characterizations of the molecular mechanism of the zw-type 32CA reaction between nitrone and methacrylonitrile.

In order to better understanding the bonding changes in organic chemical reactions, the so-called bonding evolution theory (BET) has proved to be a very useful methodological tool (Krokidis et al., 1997). Several theoretical studies have shown that the topological analysis of the ELF derived

from BET offers a suitable framework for the study of the changes of electron density. This methodological approach is used as a valuable tool to understand the bonding changes along the reaction path, and consequently, to establish the nature of the electronic rearrangement associated with a given molecular mechanism.

In this latter decade, an ELF study of the bonding changes along the zw-type 32CA reactions was carried out in order to understand the bond formation processes and to know the molecular mechanism of this zw-type 32CA process (Ríos-Gutiérrez et al., 2015). An ELF study of the most favorable reaction channel along IRC (Figure 5) associated with the 32CA reaction is performed with the aim of characterizing the molecular mechanism of 32CA reactions involving zwitterionic species. The electronic populations of the most relevant ELF valence basins of selected structures along IRC of this 32CA reaction are listed in Table 2, while the attractor positions for the most relevant points associated with the formation of the O1−C1 and C2-C3 single bonds, are shown in Figure 5.
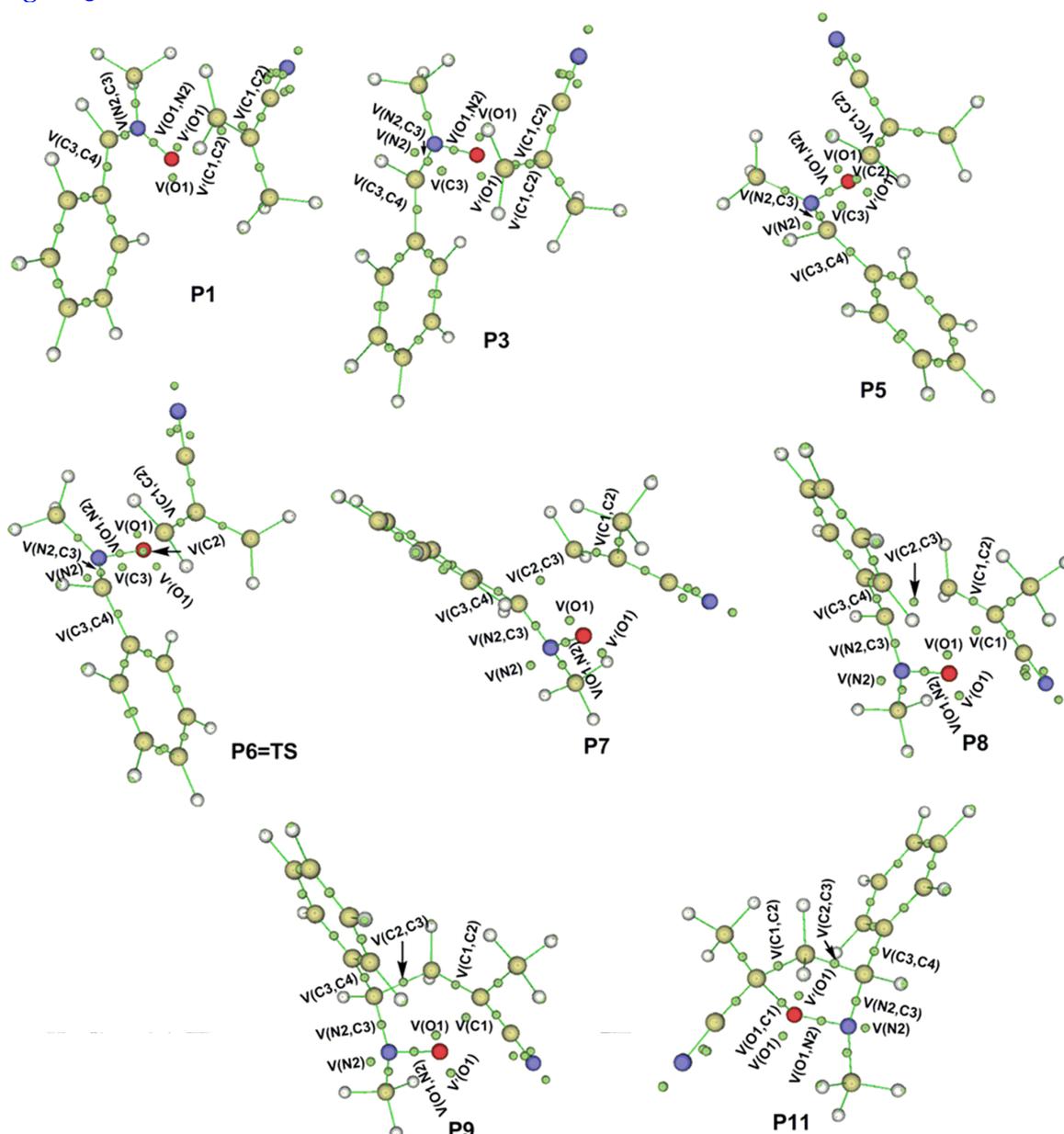

Fig. 5. ELF attractors of some selected points of the IRC associated with the formation of the new O−C and C-C single bond in the 32CA reaction of nitrone with methacrylonitrile

Table 2. Valence basin populations of the most relevant points calculated from the ELF of 32CA reaction of nitrone with methacrylonitrile, associated with the O1−C1 and C2-C3 bonds formation step

Points	P1	P2	P3	P4	P5	P6=TS	P7	P8	P9	P10	P11
d(O1-C1)	2.70	2.47	2.37	2.27	2.24	2.21	2.11	2.08	1.91	1.85	1.57
d(C2-C3)	2.81	2.51	2.35	2.19	2.13	2.08	1.92	1.86	1.69	1.66	1.58
V(O1)	2.89	2.89	2.88	2.87	2.86	2.87	2.85	2.86	2.89	2.88	2.67
V'(O1)	3.03	3.00	2.99	2.97	2.95	2.95	2.92	2.92	2.87	2.86	2.73
V(C1)								0.22	0.35	0.35	
V(C2)					0.28	0.39					
V(C3)				0.43	0.49	0.55					
V(N2)			0.86	1.20	1.32	1.41	1.69	1.77	2.02	2.13	2.25
V(O1,C1)											0.87
V(C2,C3)							1.30	1.39	1.65	1.65	1.79
V(O1,N2)	1.31	1.29	1.25	1.21	1.18	1.17	1.13	1.11	1.04	0.97	0.91
V(N2,C3)	3.91	3.94	2.90	2.56	2.45	2.37	2.15	2.09	1.93	1.90	1.88
V(C3,C4)	2.33	2.33	2.32	2.26	2.23	2.20	2.13	2.11	2.06	2.05	2.04
V(C1,C2)	2.30	2.32	3.32	3.28	3.00	2.89	2.67	2.40	2.15	2.07	2.00
V'(C1,C2)	1.70	1.62	3.32	3.28							

Some appealing conclusions can be pointed from this ELF study: the IRC associated with the 32CA reaction of nitrone with methacrylonitrile is divided in eleven differentiated points. A behavior that clearly indicates that the bonding changes along this one-step mechanism are non-concerted; the formation of the first C2-C3 single bond takes place at a C-C distance of 1.92Å, by the coupling of the pseudo-diradical of the monosynaptic basin of V(C2) and V(C3) in point P7, with an electronic population of 1.30e. (see Table 2, and the V(C2,C3) disynaptic basin in P7 in Figure 6); in which demand an asymmetric depopulation of the C1-C2 bonding region of methacrylonitrile. At this stage, the second O1-C1 single bond is not yet started. Furthermore this first stage is characterized by the absence of the monosynaptic basin of lone pair V(N2) in P1 and P2 due principally to their contribution to enriching N2-C3 double bond region. The formation of the second O1-C1 single bond takes place at a O-C distance of 1.57Å at the end of the reaction in P11 by the donation of some of the electron density of the O1 oxygen lone pairs to the C1 pseudoradical center of the methacrylonitrile framework (see Table 2, and the V(C1,O1) disynaptic basin in P11 in Figure 6). Note that the O1 oxygen is the most nucleophilic center of nitrone and the C1 carbon corresponds to the most electrophilic center of methacrylonitrile. This carbon participates with an appreciable electron density of 0.35e in the formation of the C1-O1 single bond. Subsequently, this 32CA reaction follows a two-stage one-step mechanism in which the formation of the second O1-C1 bond begins when the first C2-C3 single bond is practically already formed. Moreover, the formation of these bonds is totally different and high asynchrounous (O-C and C-C bond distances, Table 2); strongly indicates that this reaction is a non-concerted mechanism processes. The depopulation of C1-C2 bonds and the donation of electron density by lone pairs of O1 atom, which revealed by this BET/ELF study can be related to the zwitterionic-type 32CA reaction between nitrone and methacrylonitrile. A summarized picture illustrates the bonding changes along the selected points involved in this 32CA reaction is presented in Figure 5, while a representation of the relative position of the selected points along IRC with respect to the energy profile along two-stage one-step mechanism of the 32CA reaction between nitrone and methacrylonitrile is given in Figure 7.
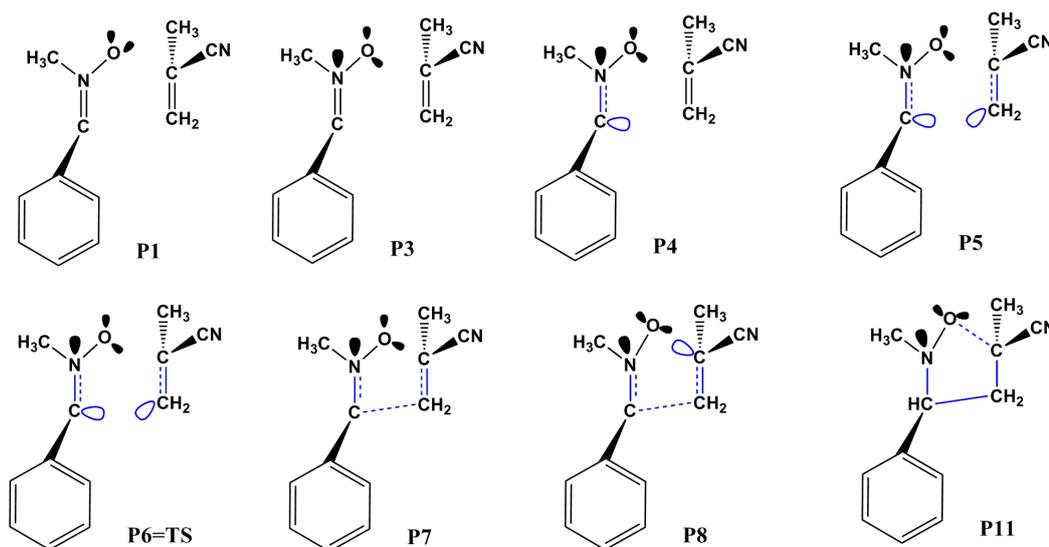
Fig. 6. The bonding changes at the selected points involved in the 32CA reaction of nitrone with methacrylonitrile
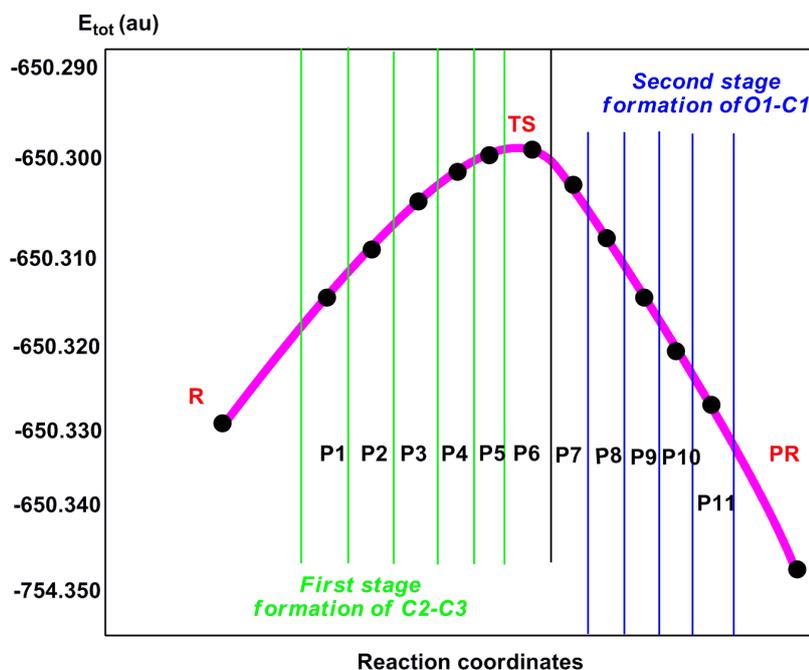

Fig. 6. Energy profile, in atomic units (au), along two-stage one-step mechanism associated with the formation of the O1–C1 and C2–C3 single bonds of the 32CA reaction of nitrone with methacrylonitrile

4. Conclusion

The 32CA reaction involving zwitterionic species to give small heterocyclic compounds has been studied within MEDT at the DFT B3LYP/6-31G(d) computational level in order to explain the mechanism process and the C-O bonding formation between the rich and the deficient electron atom. The study has been effectuated to the most favorable adduct; the Endo in mode α. Interestingly, this 32CA reaction can takes place along two-stages one-step process; the first stage aims for the formation of the C-C between the weak nucleophilic and electrophilc by coupling of the pseudoradical center as a result of the charge transfer and the depopulation of C-C double bonds. Since, the second stage is located after TS location between the most significant centers to achieve O-C bond in the end of the reaction, by the donation of the some electron density is a part of lone

pair associated with the O atom, which explains that the Zwitterionic character of Nitrone moiety. What means that this reaction is not concerted process. So, the asymmetric reorganization of electron density can be responsible of the observed asynchronicity of this reaction.

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