



Abstract: We have elucidated the electron density rearrangements that govern the formation of C–C and O–C bonds along the 32CA reaction between (E)-2-butenol and benzonitrile oxide, using both Bonding Evolution Theory (BET) and Quantum Theory of Atoms in Molecules (QTAIM) at the M06-2X/6-311+G(d,p) level of theory. Before analyzing that, the analysis of potential energy surface reveals that this 32CA reaction proceeds via *ortho* and *meta*-path, with activation barriers of 27.1 and 29.8 kcal/mol, respectively. The analysis of the two new forming bonds (C–C and C–O) at the transition states (TSs) shows that the C–C bond is shorter than the C–O one. Regarding their formation, the BET analysis indicates that the process occurs in five steps. The first three steps involve the depopulation of the N–C and C–C bonds, leading to the creation of V(N2), V(C3), and V(C4)/V(C5) monosynaptic basins. The final two steps correspond to the formation of the disynaptic basins V(C,C) and V(O,C), which represent the C–C and O–C bonds, respectively. When analyzed with QTAIM, the number of steps for each bond formation decreases to three. Specifically, the initial three steps merge into one, illustrating the transformation of the N–C triple bond into a double bond, accompanied by a decrease in its Laplacian from 1.00 a.u. to -0.03 a.u. The final two steps then correspond to the formation of the C–C and O–C bonds, which occur through a negative Laplacian. These Laplacian values decrease before stabilizing at a constant value along each reaction pathway.

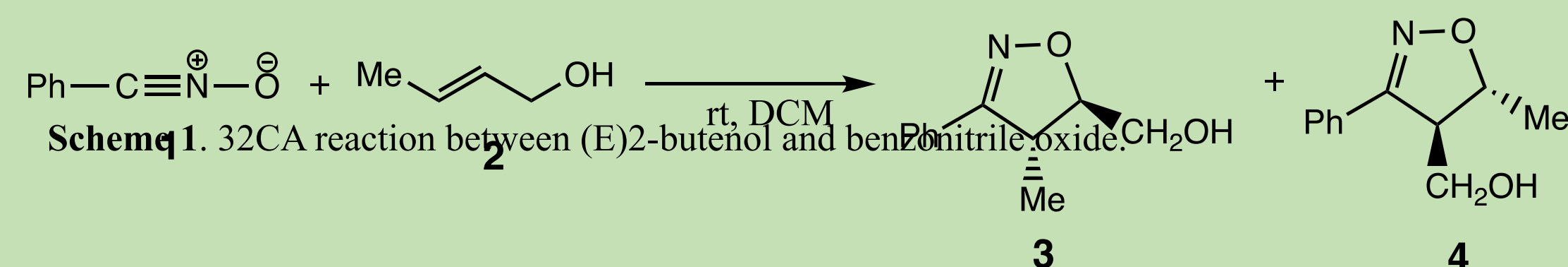
1.Introduction

A central goal of chemistry is to explain and understand the fundamental features of the formation and cleavage of chemical bonds along the reaction mechanism of a given chemical rearrangement. Following this goal, Krokidis et al. [1] have proposed the bond evolution theory (BET) which combines the electronic localization function (ELF) and Thom's catastrophe theory (CT) to unravel reaction mechanisms. While the quantum theory of atoms-in-molecules (QTAIM) inspired by the methodology known as Bader's theory is a topological approach which helps to characterize the nature of bond from the electron density and its Laplacian at the bond critical points (BCP) [2].

However, well known as a five-membered heterocyclic compound, 2-isoxazolines are commonly used for the development of pharmacological active molecules. Occurring via the 32 CA reaction (known as Huisgen reaction) [3] between nitrile oxides and alkenes, 2-isoxazolines are valuable intermediates in synthetic organic chemistry [4]. In fact, they are useful precursors for the synthesis of β -hydroxy ketones, β -amino alcohols, 1,3-diols, and a range of other 1,3-disubstituted compounds [5]. The application of 32CA reactions for synthesis of 2-Isloxazolines is an interesting research field in synthetic chemistry which continues to attract the attention of experimental and theoretical chemists over the decades [6]. For that, Rispens et al.[7], have performed the kinetics of the 32CA.

Concerning the bond formation of new C-C and C-O bonds along the 32CA leading to 2-isoxazolines, a BET (Bonding Evolution Theory) has become a detailed topological analysis for their better understanding when a chemical reaction takes place [8]. But, a deeper understanding of this reaction mechanism remains a big preoccupation for chemists.

The present study aims to combine BET with QTAIM analysis in the framework of density functional theory (M06-2X/6-311+G(d,p) computation method) to deeper decipher the electron rearrangement involved in the formation of C-C and C-O bonds along the *ortho*- and *meta*-path of the 32CA reaction between benzonitrile oxide and (E)2-butenol (see, Scheme 1). This joint-used of BET with QTAIM will offer us a detailed molecular perspective on the reaction mechanism by tracking the evolution of electron density and by visualizing the topological changes that occur during bond formation and breaking.



1.Computational method

The geometries of the reactants, products, and transition states (TS) involved in this 32CA reaction were optimized at the density functional theory (DFT) using Gaussian 16 program at the M06-2X/6-311+G(d,p) level of theory. The nature of stationary points was characterized by frequency calculations in presence of dichloromethane (DCM) along the potential energy surface (PES). The implicit solvent effects of DCM were taken into consideration via the polarizable continuum model (PCM) implemented in Gaussian 16. The IRC paths [40] were traced using the second order González-Schlegel integration method [41,42]

The global electron density transfer (GEDT) [43] computed as the sum of the natural atomic charges (q) of the atoms belonging to each framework (f) at the TSs via the natural population analysis (NPA). Hence, GEDT values are calculated using the following equation Eq 1. . To perform a topological analysis of the C–C and C–O bond formation within the framework of BET and QTAIM theory, the wave function was computed at each point along the IRC curves. The Electron Localization Function (ELF) analysis was then carried out using the TopMod package [44], and the positions of the ELF basins were visualized with the DrawProfile tool [45]. The bonding properties and nature of the newly forming C–C and C–O bonds during this 32CA reaction were examined through QTAIM analysis at the bond critical points (BCPs) using the AIMALL program [46]. The nature of the chemical bond is characterized by coupling the total electron density and Laplacian at the BCPs, Especially the sign of Laplacian ($\nabla^2\rho(r) < 0$ and $\nabla^2\rho(r) > 0$) coupled with electron density $\rho(r)$ values highlight the nature of bond involved [3].

Conclusion

The 32CA reaction mechanism between (E)-2-butenol and benzonitrile oxide has been investigated using BET and QTAIM analyses at the M06-2X/6-311+G(d,p) level. This study provides a detailed description of the bond-breaking and bond-forming events occurring along the potential energy surface. The reaction proceeds through two distinct exothermic pathways, *ortho* and *meta*, yielding adducts 3 and 4. At the transition states (TS-*o* and TS-*m*), QTAIM results reveal a positive Laplacian of electron density at the C–C and C–O interactions. This indicates that the new bonds are not yet fully established at these critical stages. ELF analysis supports this observation by highlighting the emergence of a new monosynaptic basin V(N2). This basin, with a population of about 2.07 e, reflects the restoration of the lone pair on the nitrogen atom. Simultaneously, the C≡N triple bond undergoes conversion into a C=N double bond. BET analysis provides a comprehensive view of the electron density redistribution during the reaction. The mechanism can be divided into five sequential stages, each marked by specific electronic reorganizations. The first stages involve the depopulation of the V(N2,C3) basin, leading to the appearance of monosynaptic basins V(N2) and V(C3). Subsequent stages involve the depopulation of the V(C4,C5) basin and the emergence of V(C4)(C5). These newly formed basins ultimately merge to generate disynaptic basins associated with C–C and C–O bond formation. Altogether, the combined BET, QTAIM, and ELF analyses demonstrate that the 32CA process is stepwise, involving intricate electron redistribution before the final stabilization of the adducts.

3. Results

3.1. BET Analysis.

-BET (1)-ELF (2) analysis along the *ortho*-path.

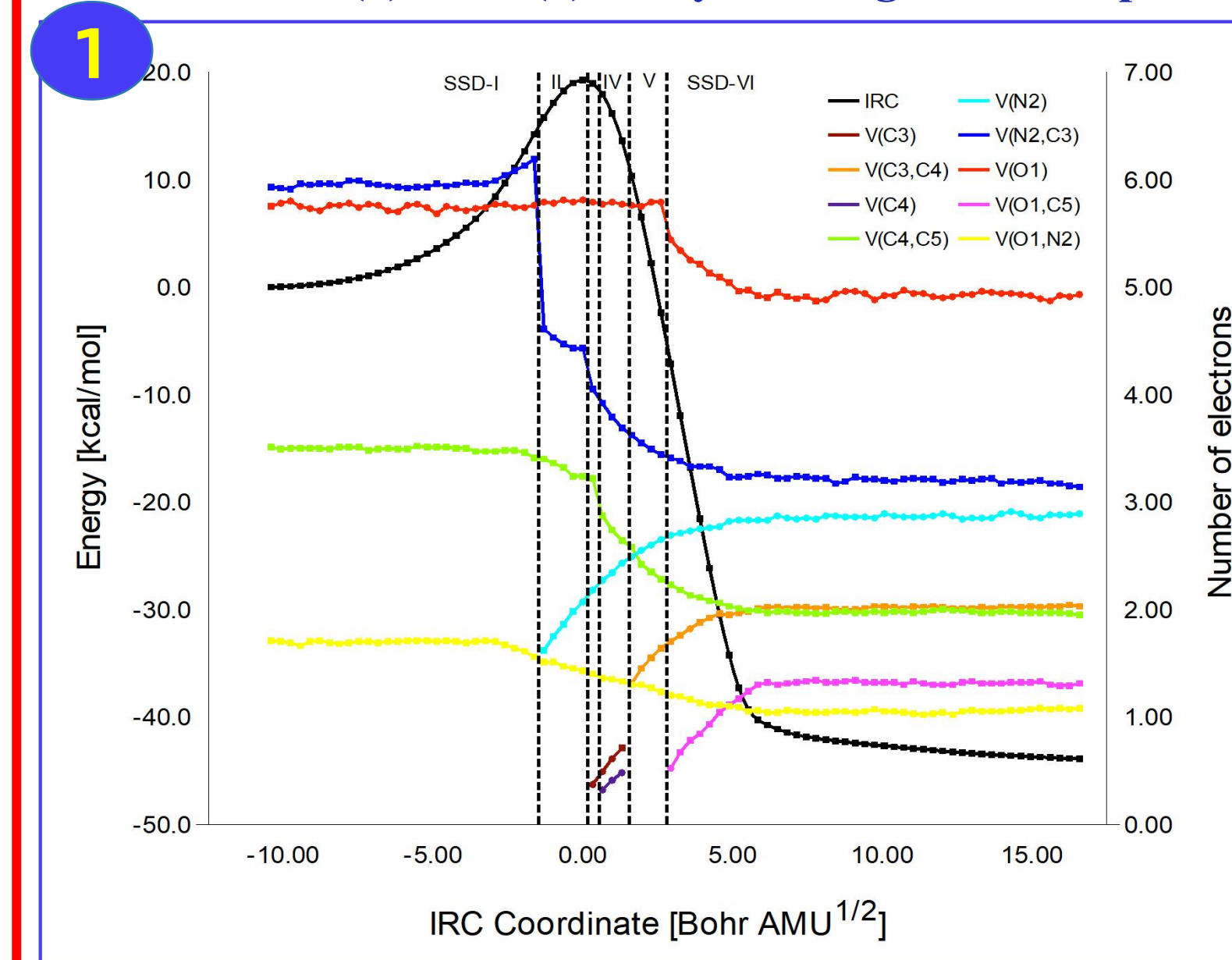


Fig. 1. BET Population evolution (in e) of selected basins along the IRC associated with TS-*o* together with the relative potential energy surface (black dot curve).

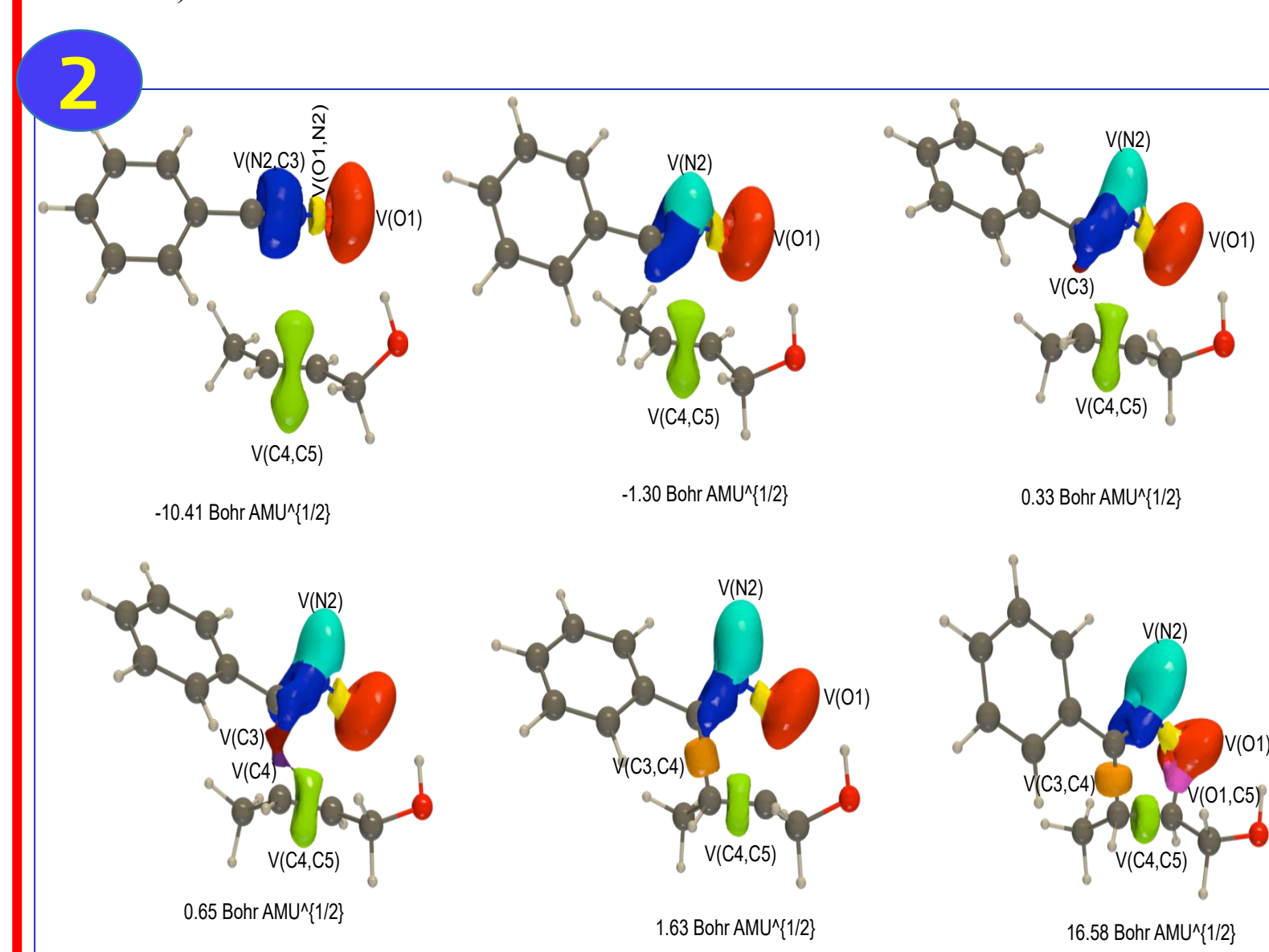


Fig. 2. ELF basin isosurfaces ($\eta=0.72$) of each of the SSDs found along the IRC corresponding to TS-*o*.

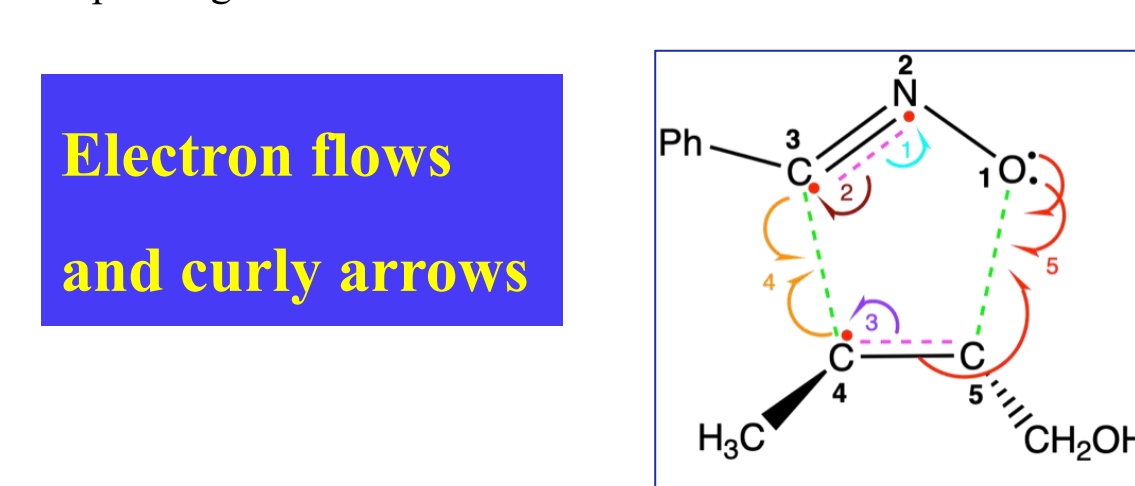


Fig. 3. Electrons flow along *o*-path.

Magenta dashed lines represent disynaptic basins that disappear while the green ones correspond for disynaptic basins appearing. The red dots represent the monosynaptic basins appearing along the processes.

3.2. QTAIM analysis

QTAIM analysis along the *ortho*-path

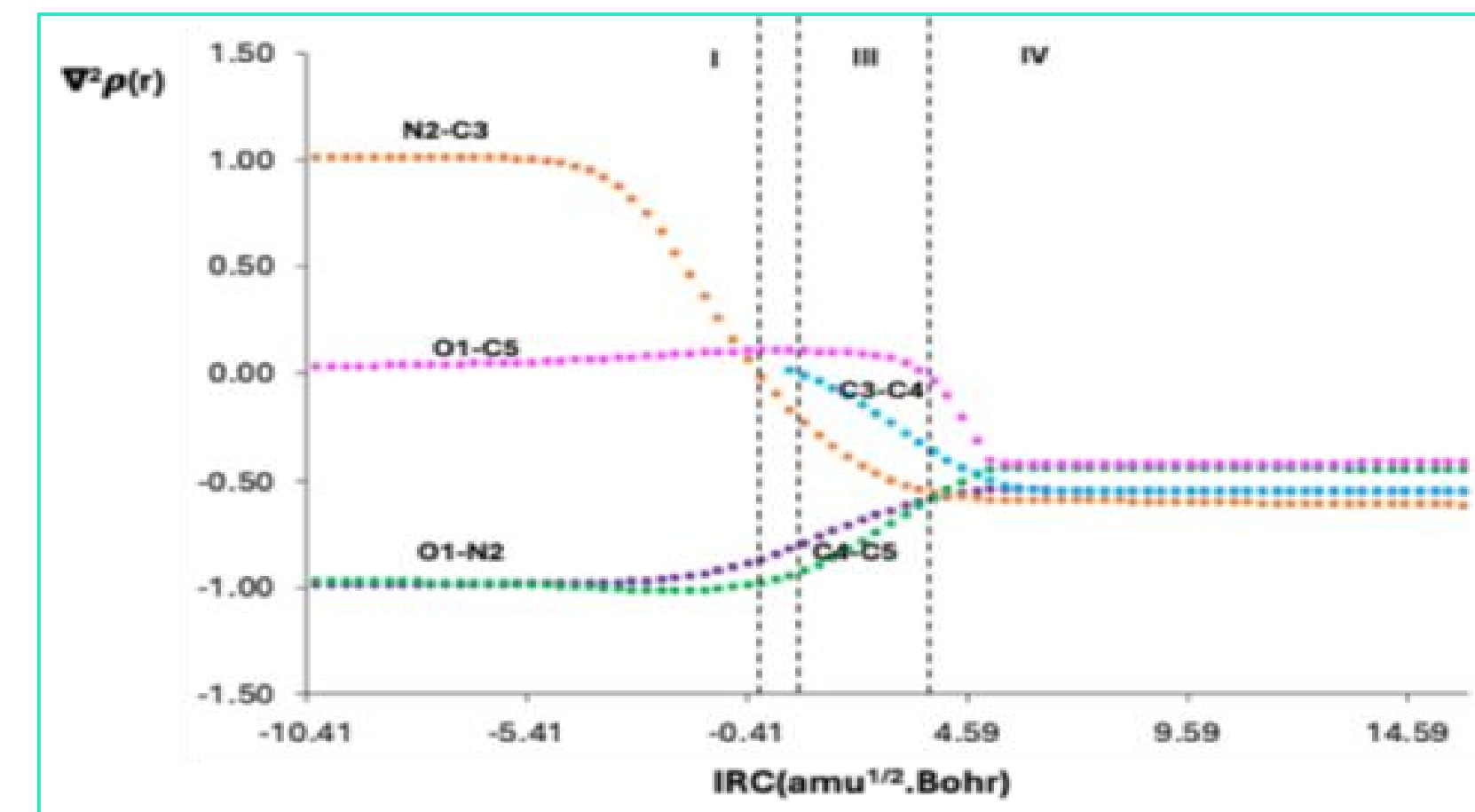


Fig. 4. Variation of the Laplacian of bonds (N2–C3, C4–C5, C3–C5, and O1–C4) along the *ortho*-path.

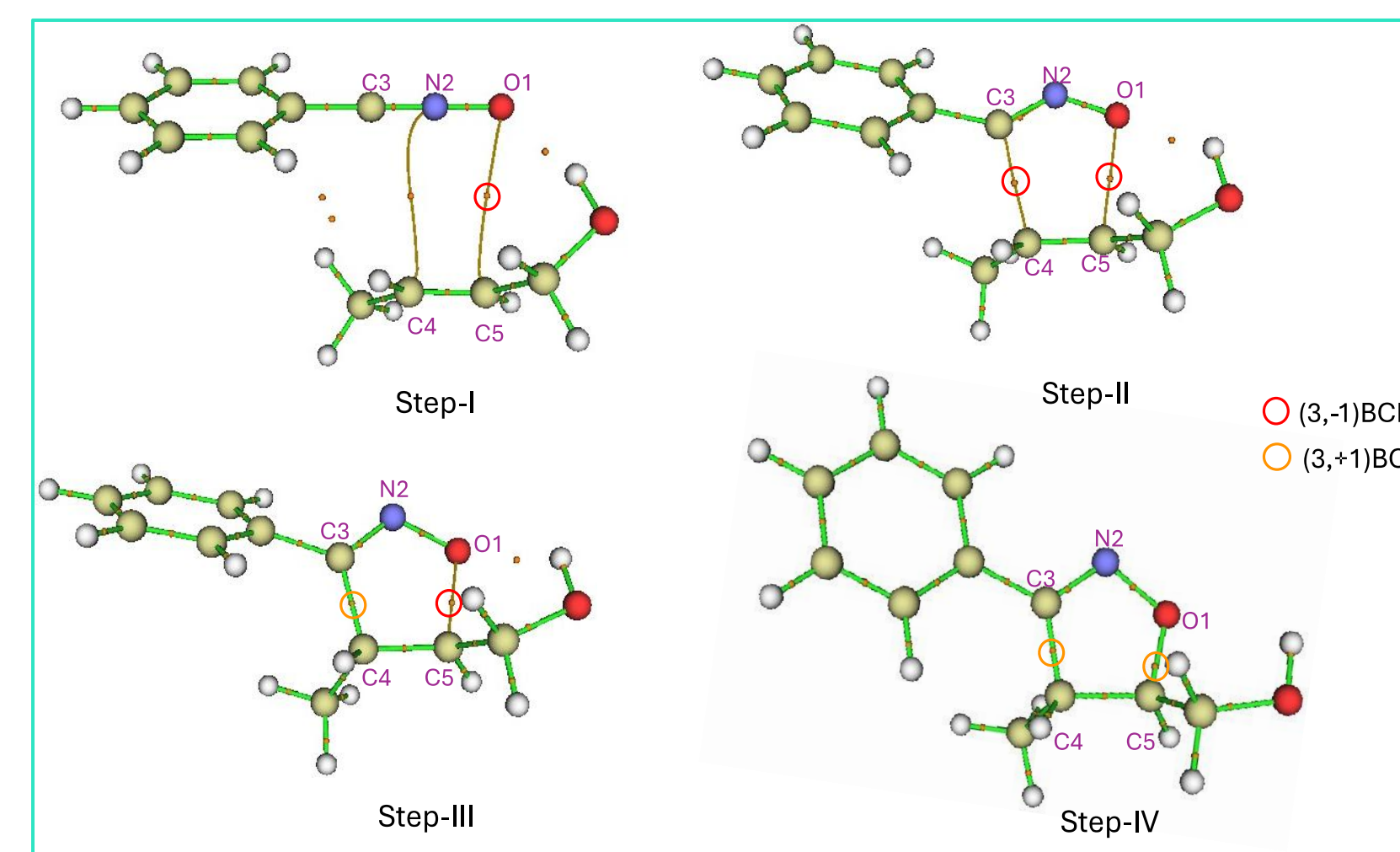


Fig. 5. AIM snapshots along the *ortho*-path.

Orange and red ellipses highlight the BCP of new forming bonds. The numbers in grape indicate different atoms (carbon, nitrogen, and oxygen) involved in the formation of these new bonds along the path.

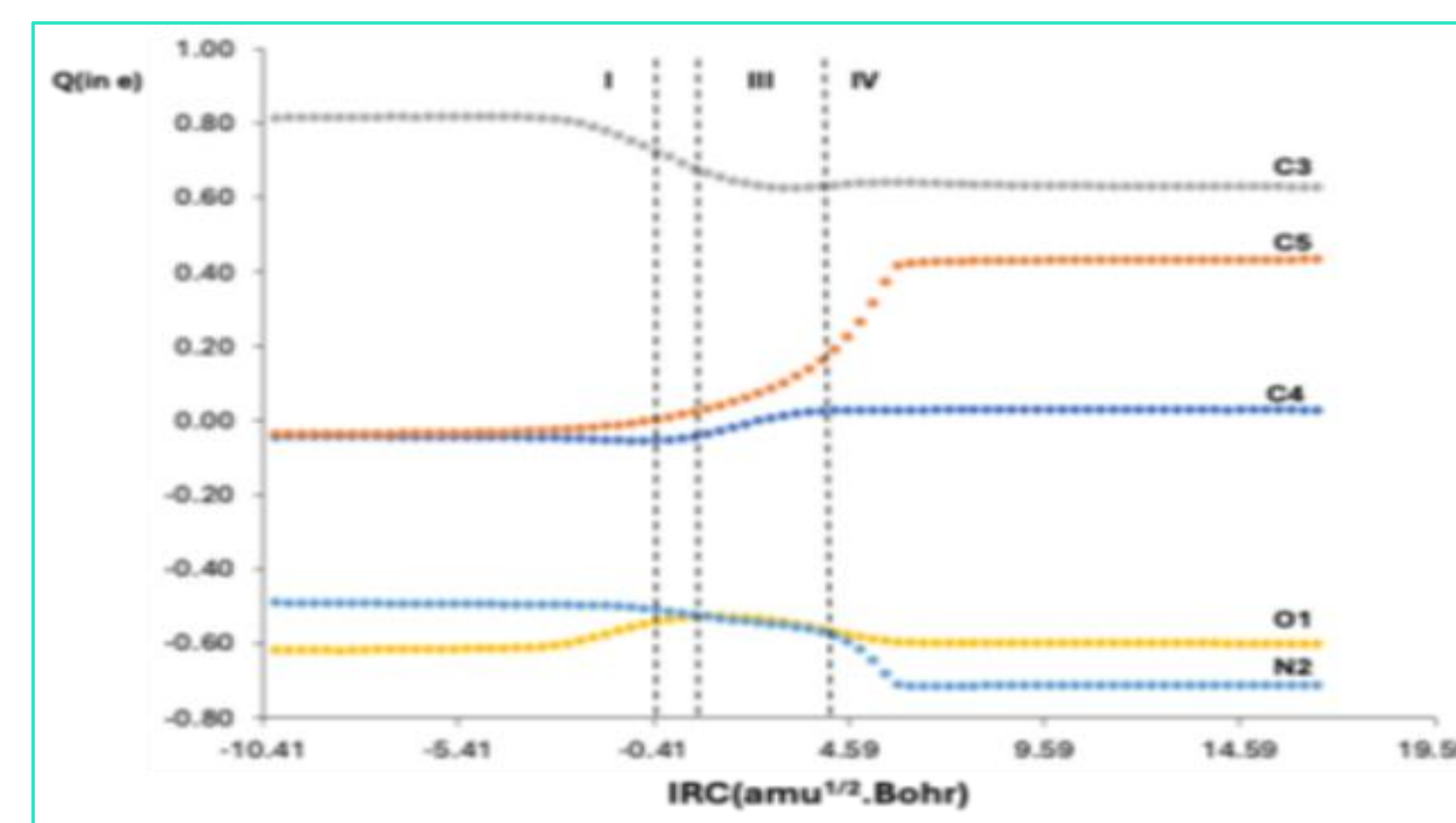


Fig. 6. Variation of the charges(Q) of O1, N2, C3, C4, and C5 atoms along *meta*-path.

3.3. BET Analysis.

BET (1)-ELF (2) analysis along the *meta*-path.

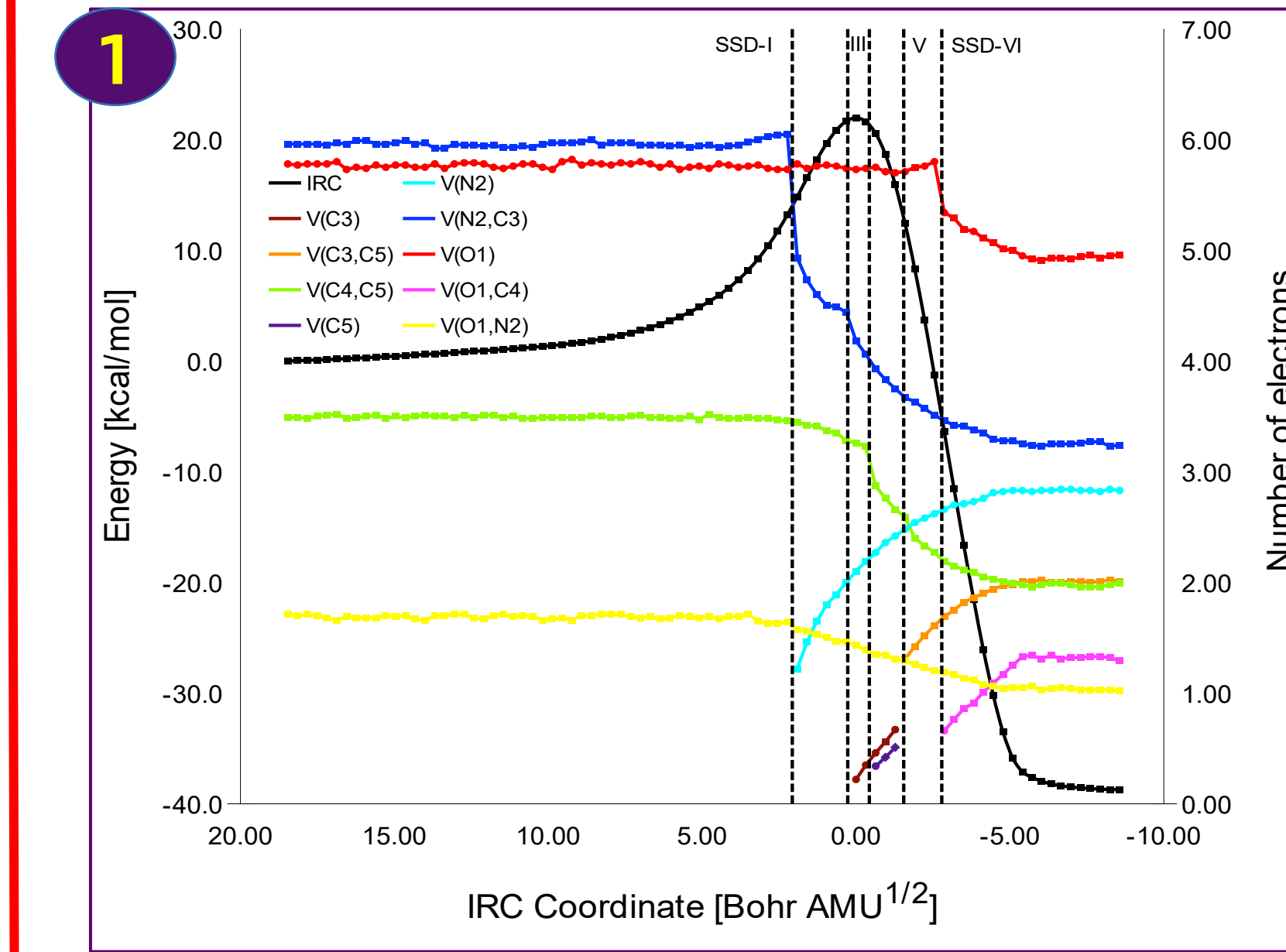


Fig. 7 BET Population evolution (in e) of selected basins along the IRC associated with TS-*m* together with the relative potential energy surface (black dot curve).

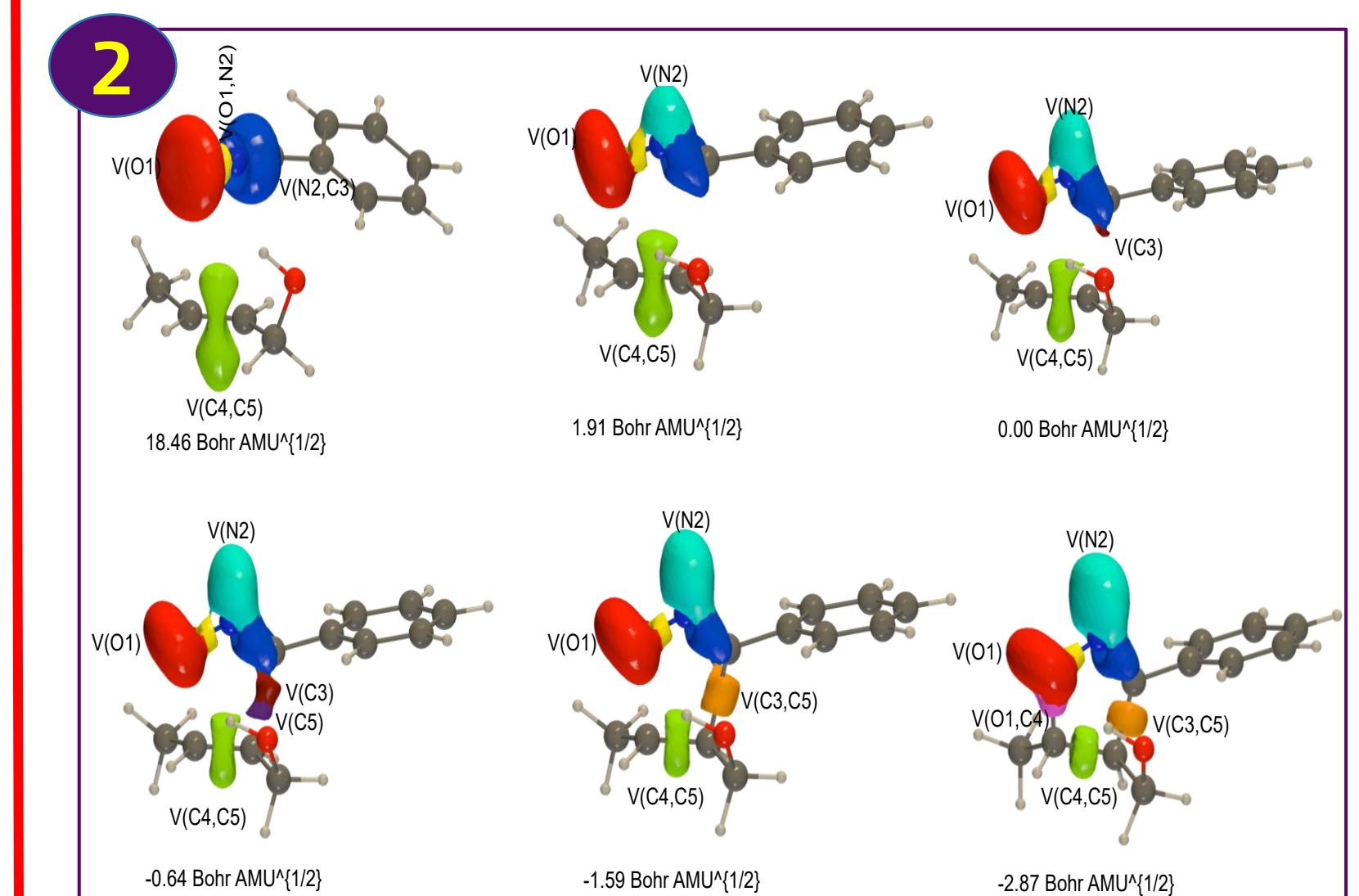


Fig. 8. ELF basin isosurfaces ($\eta=0.72$) of each of the SSDs found along the IRC corresponding to TS-*m*

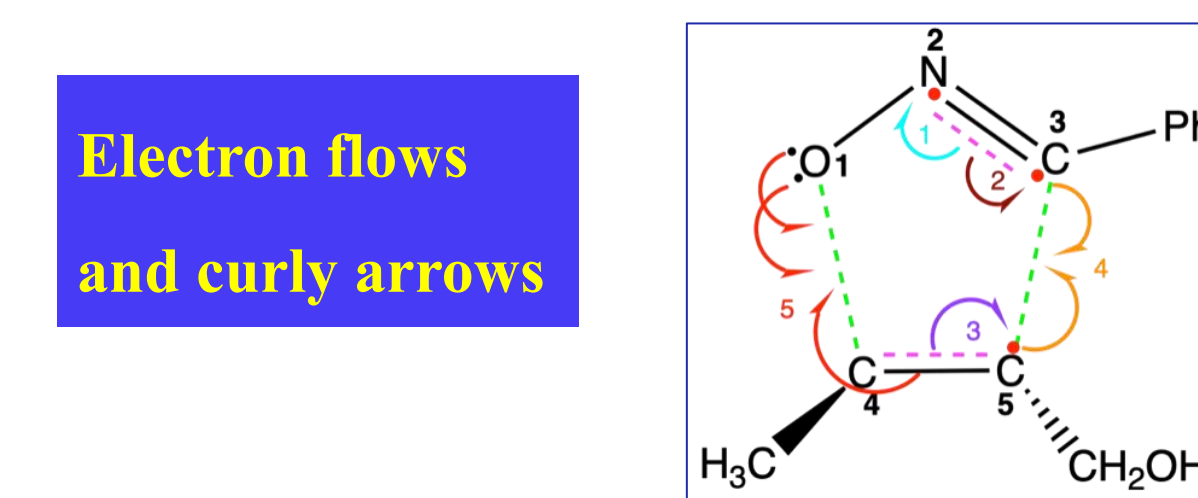


Fig. 9. Electrons flow along *meta*-path.

Magenta dashed lines represent disynaptic basins that disappear while the green ones correspond for disynaptic basins appearing. The red dots represent the monosynaptic basins appearing along the processes.

3.4. QTAIM analysis

QTAIM analysis along the *meta*-path

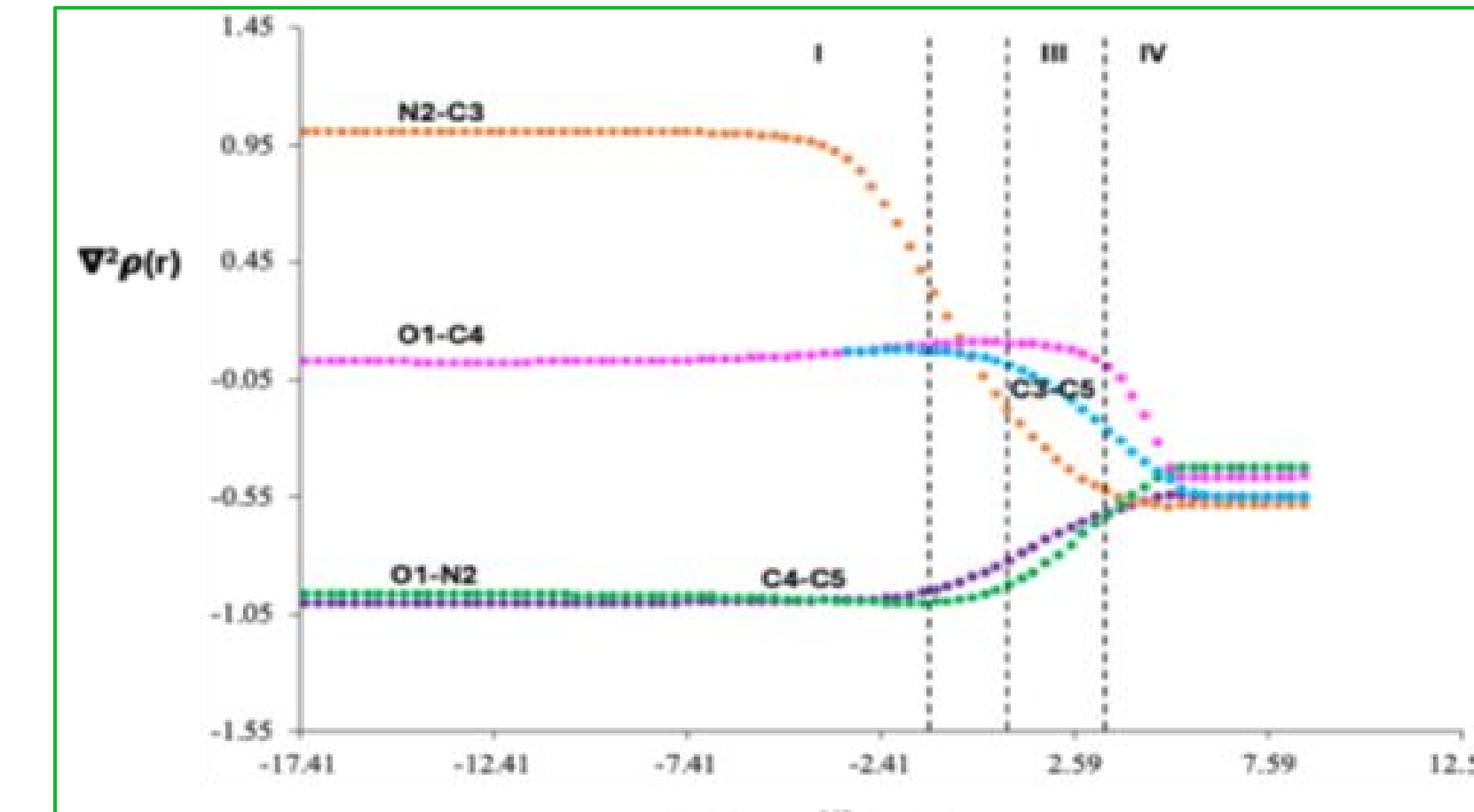


Fig. 10. Variation of the Laplacian of bonds (N2–C3, C4–C5, C3–C5, and O1–C4) along the *meta*-path.

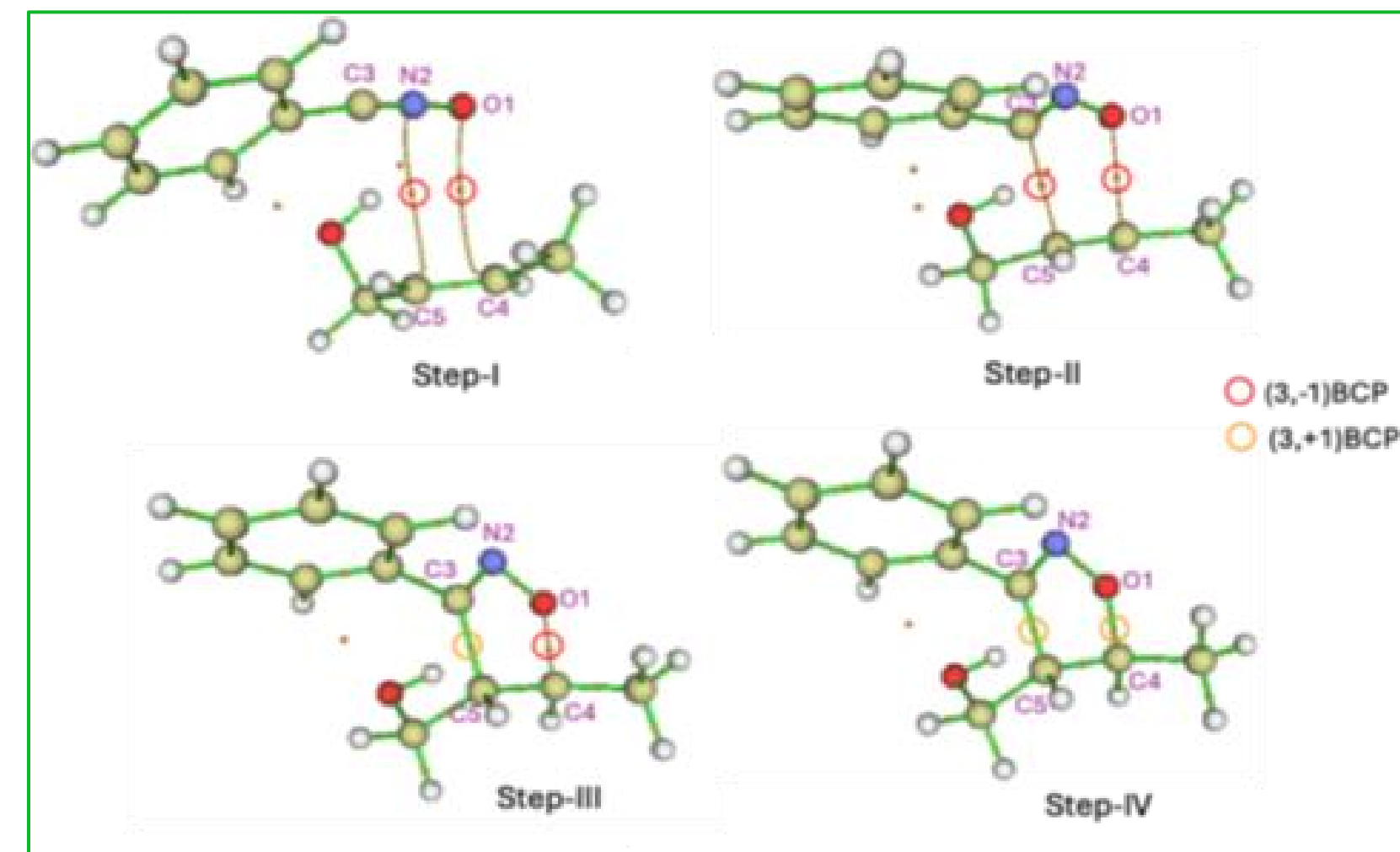


Fig. 11. AIM snapshots along the *meta*-path.

Orange and red ellipses highlight the BCP of new forming bonds. The numbers in grape indicate different atoms (carbon, nitrogen, and oxygen) involved in the formation of these new bonds along the path.

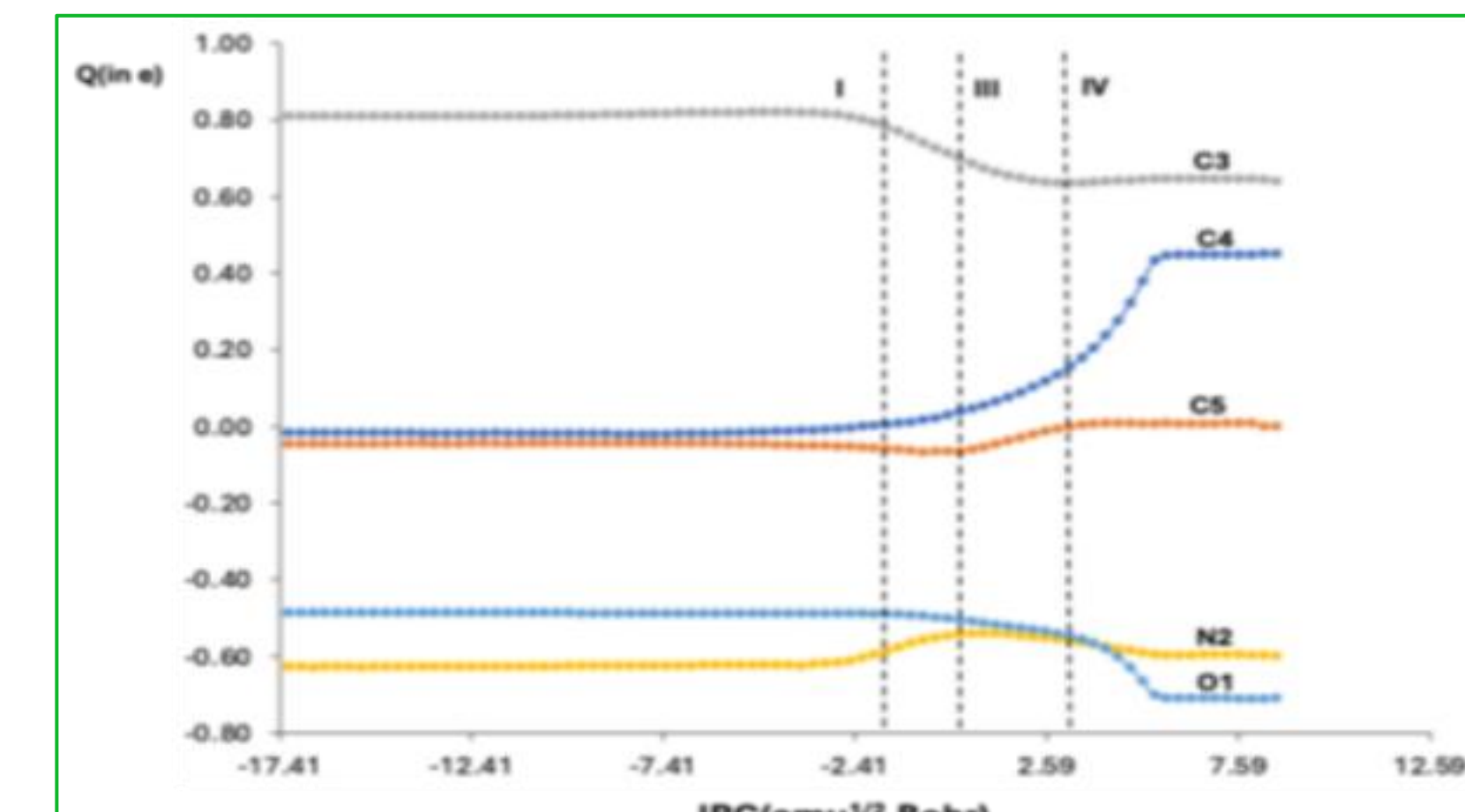


Fig. 12. Variation of the charges(Q) of O1, N2, C3, C4, and C5 atoms along *meta*-path.

References

- [1] X. Krokidis, S. Noury, B. et al.; *J. Phys. Chem. A*, **1997**, *101*, 7277–7282/ [2] R. F. W. Bader, Atoms in Molecules: A Quantum Theory, Clarendon Press, Oxford 1994./ [3] R. Huisgen; *Angew. Chem., Int. Ed.* **1963**, *2*, 633–645./ [4] J. T. Sharp; *John Wiley & Sons, New York 2002*./ [5] J. N. Martin, R. C. F. Jones; *Wiley, Chichester, United Kingdom 2002*./ [6] G. McArthur, S. Abel, G. et al.; *Eur. J. Org. Chem.* **2022**, e202200947./ [7] T. Rispens, and J.B.F.N. Engberts; *J. Phys. Org. Chem.*, **2005**, *18*, 908./ [8] A.I. Adjieufack, *; J.O. Moto Ongagna et al.; *Organometallics*, **2022**, *41*, 3809.