Theoretical Elucidation of the Mechanism and Regio-Stereoselectivity of the Cycloaddition between Nitrone Ylides and Electron-Deficient Methacrylonitrile

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Abstract

The [3+2] cycloaddition (32CA) reaction of nitrone with methacrylonitrile, has been studied within Electron localization function (ELF) at the DFT B3LYP/6-31G(d) computational level. This feeble-polar 32CA reaction, which takes place via an asynchronous mechanism, proceeds with a moderate activation energy of 17 kcal/mol, for the most favourable adduct; endo-α, and presents low stereo- and regioselectivities due to the existence of various competitive channels (exo(α,β) and endo((α,β). The Conceptual DFT is in good consistency with the thermodynamically results. ELF analysis shows that 1,3 dipolarophile O1 and C3 atom of nitrone are extensively higher in reactivity.

Keywords: Nitrone; 32Cycloaddition; ELF; DFT; Regio-stereoselectivity.

1. Introduction

The first examples of 1,3 dipolar cycloaddition is gathered by Irvin in 1938 (Irvin, 1938), demonstrating that nitrones are capable of undergoing 1,3-additions, the [3+2] cycloaddition (32CA) reaction of nitrones with alkenes (Confalone, Huie, 1988) has been widely used as a key step for the synthesis of heterocycles and natural products (Martin, Jones, 2002). The ready availability and ease of use of nitrones (Merino, 2010), the tendency of the reaction by using chiral Lewis acids (Kanemasa et al., 2002) and the high efficiency of this transformation (Rück-Braun et al., 2005) combine to make this reaction a powerful method for heterocyclic synthesis (Brandi et al., 1997). The asymmetric 1,3-dipolar cycloaddition reactions provide efficient and reliable access to enantiomerically enriched five membered heterocyclic systems (Hassana, Müller, 2015). In particular, the 1,3-dipolar cycloaddition of nitrones to electron-deficient alkenes or alkynes afford one powerful method for the construction of highly substituted isoxazolidine rings (Sibi et al., 2003), which is usually the core framework of many biologically active compounds and readily converted into b- or g-amino alcohols and others. The greatest challenge for the dipolar cycloaddition reactions of nitrones with alkenes (methacrylonitrile) is to control the region and stereoselectivity of the 32CA reactions.

In latest years, computational chemistry has become a principal instrument for chemists and a well-accepted instrument for experimental chemistry. Herein, in order to understand the molecular mechanism and the region-streoselectivity of the 32CA reaction between nitrone and electron-deficient methacrylonitrile (Figure 1), a theoretical characterization of the molecular mechanism of this reaction is carried out within the computational methods. We examine analyses of the reactivity indices of the reagents, Parr and Fukui functions are performed and also ELF

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analysis using density functional theory (DFT) methods with 6-31G(d) basis set. Our aim is to explicate the mechanism and stereo -regioselectivity of such reaction (Figure 1).
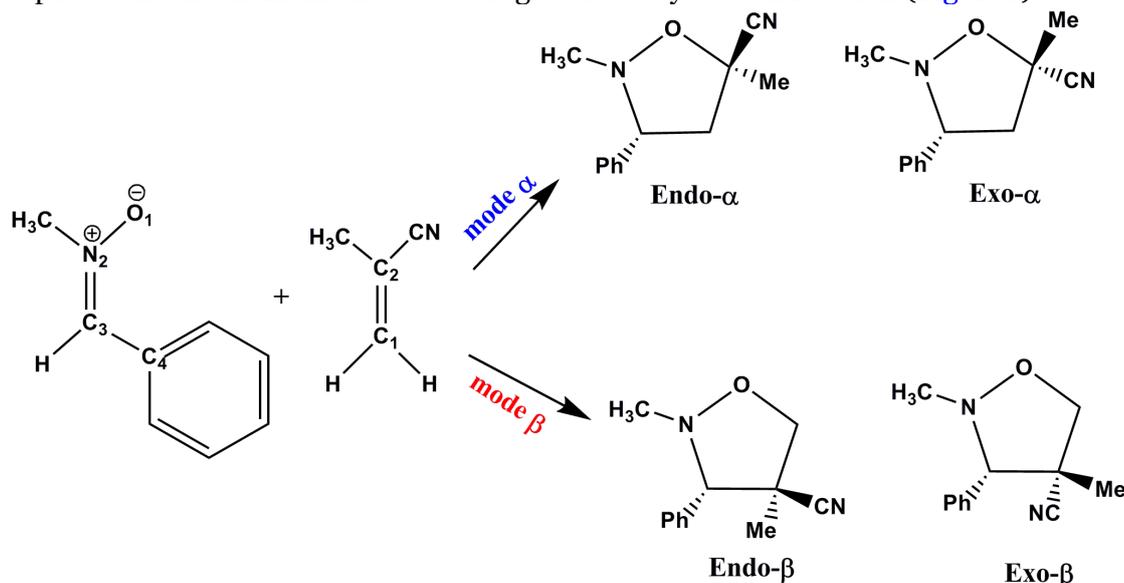
Fig. 1. Stereo-regioselectivity of the 32CA reaction of nitrone with methacrylonitrile

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, 1982). 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, Pérez, 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). Electrophilic P_k^+ and nucleophilic P_k^- Parr functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. The condensed form of the functions of Fukui in a molecule with N electrons was proposed (Chattaraj et al., 2012; Benallou et al., 2016; Benallou et al., 2016):

$f_k^+ = [q_k(N+1) - q_k(N)]$ for nucleophilic attack
$f_k^- = [q_k(N) - q_k(N-1)]$ for electrophilic attack

q$_k$(N): Electronic population of the atom k in the neutral molecule.
q$_k$(N+1): Electronic population of the atom k in the anionic molecule.
q$_k$(N-1): Electronic population of the atom k in the cationic molecule.

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; Benallou et al., 2018; Benallou et al., 2018; Benallou, 2018). 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

In order to obtain a greater understanding of the 32CA reaction, the present study has been divided into four 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 reactions of nitrone with methacrylonitrile is performed; (ii) then, the reaction paths associated the 32CA reaction of nitrone with methacrylonitrile are explored and characterized; (iii) in the third part, a topological analysis of the ELF of the simplest allene and methacrylonitrile is performed in order to characterize their

electronic structures. Finally, a characterization of the reaction paths associated with the 32CA reaction of nitrone and methacrylonitrile is carried out.

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	LUMO	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 practically 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. 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 presents a nucleophilicity N index about 3.6eV according to the nucleophilicity scales. The electrophilivity of methacrylonitrile is close to that of nitrone 0.5eV, indicates strongly this reaction is moderately polar. Therefore, at this 32CA reaction, Nitrone and methacrylonitrile moieties behaves as nucleophile and electrophile, respectively.

3.2. An analysis of the reactivity by estimating the local indices of the reagents

By approaching a non-symmetric electrophilic/nucleophilic pair along an organic reaction process, the most favourable reactive channel is that associated with the initial two-center interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. Recently, Domingo proposed the nucleophilic P_k^- and P_k^+ electrophilic Parr functions, derived from the changes of spin electron-density. Accordingly, the nucleophilic and electrophilic Parr functions centers and Fukui indices of the reagents involved in this 32CA reaction are portrayed in Figure 2.
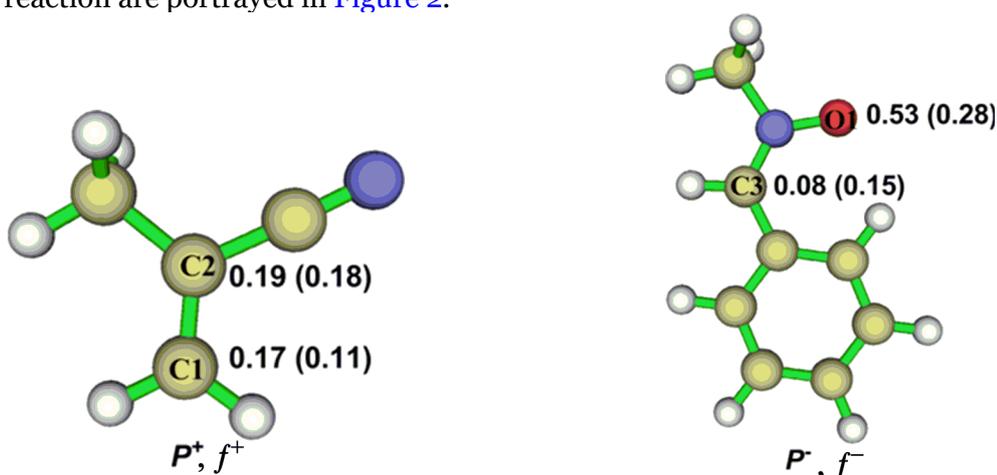
Fig. 2. The nucleophilic P_k^- and electrophilic P_k^+ Parr functions and Fukui indices (in parentheses)

It is worth mentioning that the most favourable electrophile–nucleophile interaction along the 32CA reaction between nitrone (right side) and methacrylonitrile in moderate polar process will take place between the most nucleophilic center of nitrone, the O1 oxygen atom, and the most

electrophilic center of methacrylonitrile, the C2 carbon atom. In which the greater value of nucleophilic and electrophilic Parr and Fukui functions are attributed consecutively to the O1 and C1 atoms, respectively (Figure 2), and then, O1 atom is very rich electronically, it has considered as an electron donor. So, α- mode is eventually the most favourable pattern channel in this 32CA reaction.

3.3. ELF analysis of electron density involved at the centers reactive associated with 32CA reaction

One appealing procedure that provides a straightforward connection between the electron density distribution and the chemical structure is the quantum chemical analysis of the Becke and Edgecombe's Electron Localization Function (ELF). An ELF topological analysis of the electronic structure of nitrone and methacrylonitrile make it possible to explain the reactivity of these reagents. The ELF of nitrone shows the presence of two monosynaptic basins, V(O1) and V'(O1), associated with the lone pairs integrating 2.96e each one (see Fig. 3). This electronic characteristic of nitrone allowed associating its reactivity to that of a high reactive pseudo-diradical species. While methacrylonitrile presents two disynaptic basins, V(C1,C2) and V'(C1,C2), associated with double bonds of C1-C2, integrating 1.74e each one. So, Nitrone represents high reactivity by their electron density established in O1 atom, allowing high performance with both centers reactive of methacrylonitrile, C1 and C2 atom.
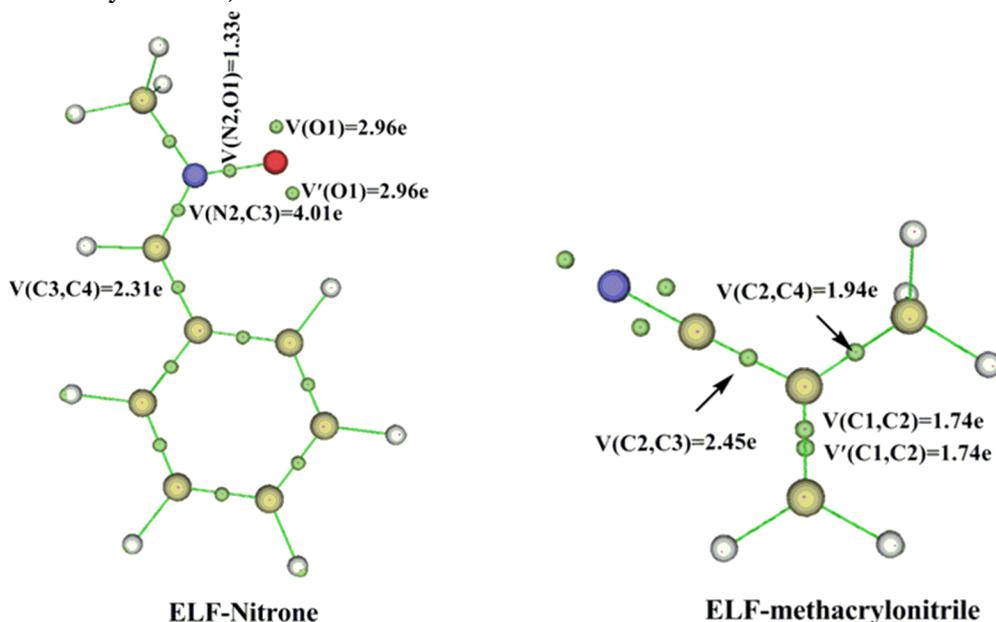
Fig. 3. Some significant valence ELF basins of Nitrone and Methcrylonitrile. The non-bonding V(M) and bonding V(M,N) monosynaptic basins are represented in green circle

3.4. Study of the reaction paths associated with the 32CA reaction of nitrone and methacrylonitrile

Due to the non-symmetry of the two reagents, the (3+2) cycloaddition reaction of nitrone with methacrylonitrile can take place along four isomeric channels: one pair of stereoisomeric exo channels of both mode and one pair of regioisomeric endo channels of both α and β mode (Figure 4). In this part we want to study the stereoselectivity and regioselectivity through evaluating the barrier activation.
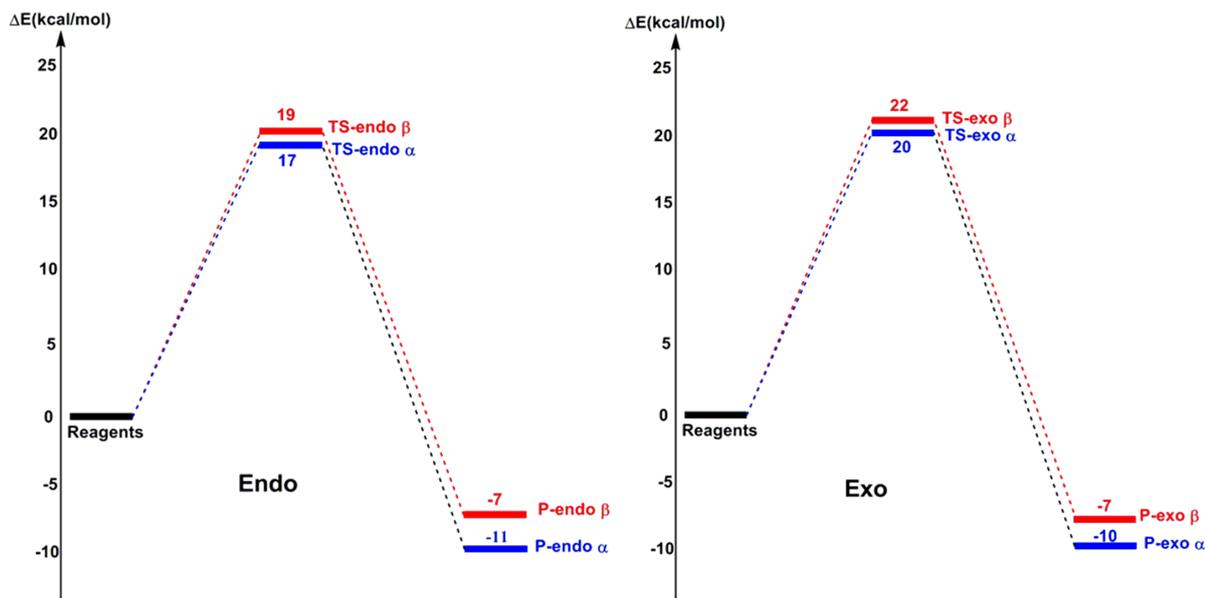
Fig. 4. The competitive reactive channels associated with the 32CA reaction of nitrone with methacrylonitrile. B3LYP/6-31G(d) relative energies, are given in kcal/mol.

The activation energies associated with the competitive channels are 17 (TS-endo α), 19 (TS-endo β), 20 (TS-exo α), 22 (TS-exo β), kcal mol⁻¹. So, Endo, in α mode is the most favourable competitive channel of this reaction. Some appealing conclusions can be drawn from these relative energies: the activation energy associated with the 32CA reaction via TS-endo α is 17kcal mol⁻¹ lower in energy than remaining regio-specific channels (TS-endo β), (TS-exo α) and (TS-exo β), indicating that the formation of the product P-endo α is kinetically very favored.

These 32CA reactions are exergonic by -7.2, -2.7, -6.5 and -3.2 kcal mol⁻¹ for P-endo α, P-endo β, P-exo α and P-exo β, respectively. Note that the most favourable reactive channel associated with the 32CA reaction involving is extremely exergonic, the formation of the product P-endo in mode α is enormously exothermic by -13 kcal mol⁻¹ to compare with other product, and therefore this channel process is completely irreversible. Consequently, the product P-endo-α is kinetically and thermodynamically favored.

Optimized TSs involved in the 32CA reactions between nitrone and metacrylonitrile, including some selected distances, are given in Figure 5.
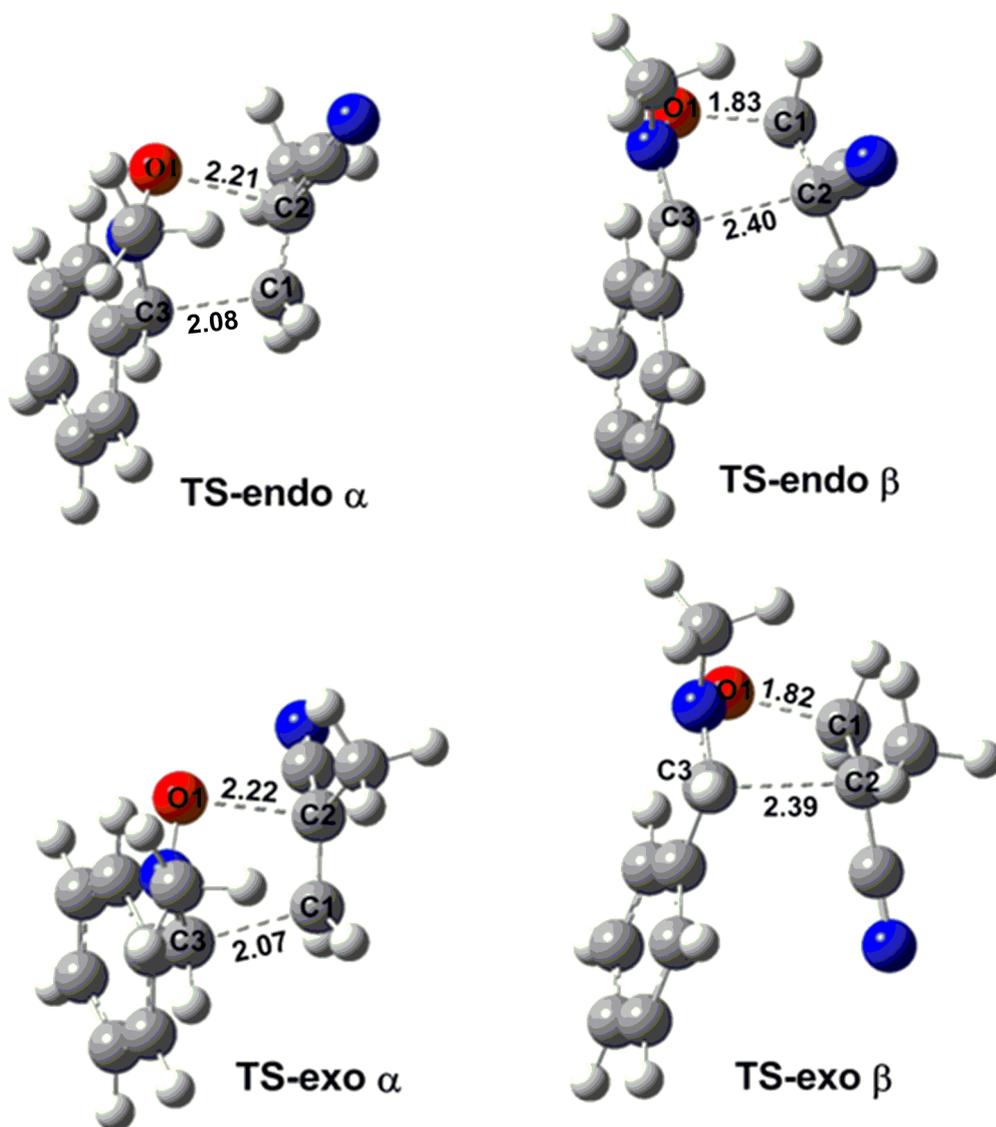
Fig.5. B3LYP/6-31G(d) optimized geometries of the TSs involved in the 32CA reactions between nitrone and methacrylonitrile. Distances are given in Angstroms

At the TSs associated with the 32CA reaction, the distances between the atoms involved in the formation of the C–C and C–O single bonds for both region-stereoselective channels are: 2.21Å, 2.22Å (C2–O1) and 2.08, 2.07Å (C1-C3) at TS-endo,exo α respectively, equally 1.83, 1.82Å (C1–O1) and 2.40 , 2.39Å (C2-C3) at TS-endo,exo β, respectively.

In α-mode, C1-C3 will be eventually formed first, while in β-mode, O1-C1 bond is formed before C2-C3, regarding the shortest distances involved in these bonds. Therefore, this mechanism process is an asynchronous. In which the integrated C1 atom bonding will be formed early. Consequently, the products Endo, in both α and β mode are favored.

4. Conclusion

In order to understand the mechanism and regio- and stereospecificity, this reaction has been theoretically studied using DFT methods at the B3LYP/6−31G(d) level of theory. The reactive channels corresponded to the regioselective and stereoselective approach modes have been explored and characterized. We can summarize the results of the present study in the following points:

Analysis of the computed Parr and Fukui functions of the nucleophilic and electrrophilic centers between nitrone and methacrylonitrile, as well as thermodynamic calculations at gas phase justifying the preference region- and stereo-selective of Endo in both α and β mode.

The relatively moderate activation energies found for both modes of this reaction and the high electron density revealed by ELF topological are explained by the high nucleophilic nature of O1 centers atom of nitrone, and the moderate electrophilic nature of C1 and C2 atom of methacrylonitriles, giving a good explanation of the activation barrier.

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