**Supporting Information for**

**On the outside looking in: rethinking the molecular mechanism of 1,3-dipolar cycloadditions from the perspective of bonding evolution theory. The reaction between cyclic nitrones and ethyl acrylate**

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**Table 1S:** Lengths (Å) of the C-C and C-O forming bonds at the indicated TSs, at the corresponding level of calculation.

| | B3LYP/6-31G(d) | | M06-2X/6-311++G** | |
|---|---|---|---|---|
| | C☐☐ | C☐☐ | C-C | C-O |
| **TS1oen** | 2.023 | 2.281 | 2.007 | 2.158 |
| **TS1oex** | 2.044 | 2.268 | 2.042 | 2.144 |
| **TS1men** | 2.312 | 1.867 | 2.352 | 1.838 |
| **TS1mex** | 2.309 | 1.898 | 2.334 | 1.896 |
| **TS2oen** | 2.006 | 2.246 | 2.001 | 2.116 |
| **TS2oex** | 2.006 | 2.265 | 2.015 | 1.141 |
| **TS2men** | 2.350 | 1.792 | 2.411 | 1.761 |
| **TS2mex** | 2.309 | 1.846 | 2.341 | 1.843 |

*Charge Transfer (CT) at the transition structures*

The low-polar nature of these 1,3 dipolar cycloaddition reactions can be evaluated by charge transfer analysis at the transition state. The atomic charges calculated using NBO have been shared between the nitrones and ethyl acrylate. For reaction 1, the charges transferred from nitrone **1** to ethyl acrylate are 0.12 e at **TS1oen**, 0.10 e at **TS1oex**, 0.11 e at **TS1men**, and 0.11 e at **TS1mex**. For reaction 2, the charges transferred from nitrone **2** to ethyl acrylate are 0.09 e at **TS2oen**, 0.09 e at **TS2oex**, 0.08 e at **TS2men**, and 0.12 e at **TS2mex**. These computed (at the B3LYP/6-31G(d) level) CTs indicate that the electron flux will occur from nitrones to ethyl acrylate, and these results are in agreement with the DFT reactivity indices derived from CDT (see below). Moreover, the low values of the CTs suggest the low-polar nature of these 1,3-DC reactions.

Conceptual DFT provides different indices to rationalize and understand chemical structure and reactivity.[1] The global electrophilicity index, $\omega$, is given by the following expression in terms of the electronic chemical potential $\mu$ and the chemical hardness $\eta$[2-3]

$$\omega = (\mu^2/2\eta) \tag{1}$$

$\mu$ and $\eta$ quantities may be approached in terms of the one-electron energies of the frontier molecular orbitals HOMO and LUMO, $\varepsilon_H$ and $\varepsilon_L$, given respectively by equations 2 and 3.

$$\mu = (\varepsilon_H + \varepsilon_L)/2 \tag{2}$$

$$\eta = (\varepsilon_L - \varepsilon_H) \tag{3}$$

The global nucleophilicity index, N, based on the HOMO energies obtained within the Kohn–Sham scheme[4] is defined as:

$$N = \varepsilon_{HOMO}(Nu) - \varepsilon_{HOMO}(TCE) \tag{4}$$

Where tetracyanoethylene (TCE) is the reference because it presents the lowest HOMO energy in a long series of molecules already investigated in the context of polar organic reactions[5]. This choice allows handling conveniently a nucleophilicity scale of positive values. The local electrophilicity ($\omega_k$) condensed to atom k was calculated by projecting the index $\omega$ onto any reaction center k of the molecule by using the Fukui function $f_k^+$.

$$\omega_k = \omega f_k^+ \tag{5}$$

The local nucleophilicity $(N_k)$[6] condensed to atom k was been calculated using the global nucleophilicity N and the Fukui function $f_k^-$ according to the formula:

$$N_k = N f_k^- \tag{6}$$

For an atom k in a molecule, depending upon the type of electron transfer, we have the following condensed Fukui function of the atom k.[6,7]

$$f_k^+ = \rho_k(N+1) - \rho_k(N) \quad \text{(for nucleophilic attack)}, \tag{7}$$

$$f_k^- = \rho_k(N) - \rho_k(N-1) \quad \text{(for electrophilic attack)}, \tag{8}$$

$$f_k^O = [\rho_k(N+1) - \rho_k(N-1)]/2 \quad \text{(for radical attack)}, \tag{9}$$

Where $\rho_k(N+1)$, $\rho_k(N)$ and $\rho_k(N-1)$ are defined as the gross electronic populations of the site k in the anionic, neutral and cationic species, respectively.

### DFT reactivity indexes analysis.

The global indexes namely, electronic chemical potential $\mu$, chemical hardness $\eta$, global electrophilicity $\omega$, and global nucleophilicity $N$ and HOMO, LUMO energies of nitrones **1** and **2** and ethyl acrylate are given in Table 2S.

**Table 2S**: a) Reactivity descriptors for nitrones and ethyl acrylate at the B3LYP/6-31G(d) level.

| Reactants | $\varepsilon_{HOMO}$ (a.u.) | $\varepsilon_{LUMO}$ (a.u.) | $\mu$(eV) | $\eta$(eV) | $\omega$ (eV) | N(eV) |
|---|---|---|---|---|---|---|
| Nitrone **1** | -0.20715 | -0.00622 | -2.903 | 5.468 | 0.7707 | 3.484 |
| Nitrone **2** | -0.20119 | -0.00678 | -2.830 | 5.290 | 0.7568 | 3.646 |
| Ethyl acrylate | -0.27124 | -0.04309 | -4.277 | 6.208 | 1.4731 | 1.740 |

b) Reactivity descriptors at the M06-2X/6-311++G** level.

| Reactants | $\varepsilon_{HOMO}$ (a.u.) | $\varepsilon_{LUMO}$ (a.u.) | $\mu$(eV) | $\eta$(eV) | $\omega$ (eV) | N(eV) |
|---|---|---|---|---|---|---|
| Nitrone **1** | -0.27485 | -0.00976 | -3.872 | 7.214 | 1.0394 | 3.425 |
| Nitrone **2** | -0.26964 | -0.01138 | -3.824 | 7.028 | 1.0401 | 3.567 |
| Ethyl acrylate | -0.34974 | -0.01838 | -5.009 | 9.017 | 1.3911 | 1.387 |

From the Table 2S, we can see that the electronic chemical potential ($\mu$) of ethyl acrylate (-4.277 eV at B3LYP or -5.009 eV at M06 theoretical level) is lower than those of nitrone **1** (-2.903 eV or -3.872 eV) and nitrone **2** (-2.830 eV or -3.824 eV), which suggests that along the polar reaction the charge transfer will take place from nitrones to ethyl acrylate. According to the electrophilicity values, nitrones will act as nucleophiles

and ethyl acrylate as electrophile. The global electrophilicity difference $\Delta\omega$ (0.70 eV or 0.35 eV) between nitrone **1** and ethyl acrylate indicates a lower polar (CT< 0.15e) character for this cycloaddition.

The analysis of the local electrophilicity index $\omega_k$, and the nucleophilic index $N_k$ of reagents in most studies of cycloaddition reactions allows explaining the observed regioselectivity. In order to determinate the most electrophilic and nucleophilic centers for the reagents, the values of the Fukui indices have been calculated and reported in Table 3S. The analysis show that the largest electrophilic center of ethyl acrylate is the C5 carbon atom with $\omega_k$ = 0.402 eV (0.500 at M06 level). The nitrones **1** and **2** have the largest nucleophilic centers at the O1 oxygen atom with respectively $N_k$=1.428 (or 1.602) and 1.542 (or 1.733) eV. Thus, the most nucleophilic center of nitrones (O1 oxygen atom) and the most electrophilic center of the dipolarophile (C5 atom) will allow the nucleophilic attack of nitrones on ethyl acrylate. This nucleophilic attack allows explaining the formation of the *meta*-regioisomers.

**Table 3S:** a) Values of the Fukui indices of pyrroline-1-oxide, 2,3,4,5 tetrahydropyridine-1-oxyde and ethyl acrylate calculated at the B3LYP/6-31 G (d) level.

| Reactants | Sites | $\rho(N)$ | $\rho(N+1)$ | $\rho(N-1)$ | $f_k^+$ | $f_k^-$ | $\omega_k$ | $N_k$ |
|---|---|---|---|---|---|---|---|---|
| Nitrone **1** | $O_1$ | -0.509 | -0.714 | -0.099 | 0.205 | 0.410 | 0.158 | 1.428 |
| | $C_4$ | -0.036 | -0.353 | 0.290 | 0.317 | 0.326 | 0.244 | 1.135 |
| Nitrone **2** | $O_1$ | -0.532 | -0.722 | -0.109 | 0.190 | 0.423 | 0.144 | 1.542 |
| | $C_4$ | -0.023 | -0.320 | 0.289 | 0.297 | 0.312 | 0.225 | 1.137 |
| Ethyl acrylate | $C_5$ | -0.338 | -0.611 | -0.160 | 0.273 | 0.178 | 0.402 | 0.309 |
| | $C_6$ | -0.342 | -0.459 | -0.248 | 0.116 | 0.095 | 0.171 | 0.165 |

b) Values of the Fukui indices of pyrroline-1-oxide, 2,3,4,5 tetrahydropyridine-1-oxyde and ethyl acrylate calculated at the M06-2X/6-311++G** level.

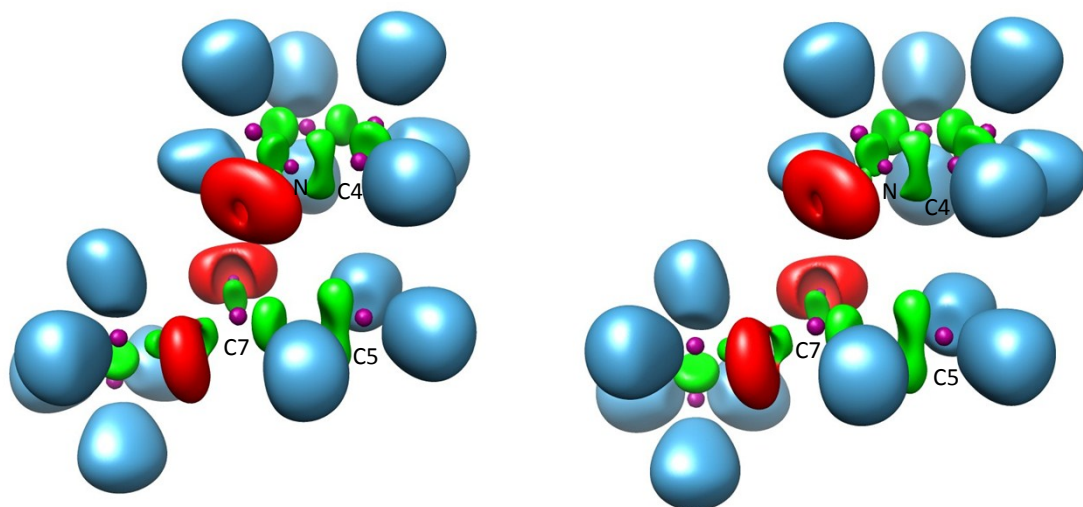| Reactants | Sites | $\rho(N)$ | $\rho(N+1)$ | $\rho(N-1)$ | $f_k^+$ | $f_k^-$ | $\omega_k$ | $N_k$ |
|---|---|---|---|---|---|---|---|---|
| Nitrone **1** | $O_1$ | -0.561 | -0.601 | -0.093 | 0.041 | 0.468 | 0.043 | 1.602 |
| | $C_4$ | 0.009 | 0.029 | 0.357 | -0.019 | 0.347 | -0.020 | 1.190 |
| Nitrone **2** | $O_1$ | -0.586 | -0.627 | -0.100 | 0.041 | 0.486 | 0.042 | 1.733 |
| | $C_4$ | 0.033 | 0.040 | 0.361 | -0.006 | 0.328 | -0.007 | 1.170 |
| Ethyl acrylate | $C_5$ | -0.283 | -0.643 | -0.159 | 0.360 | 0.124 | 0.500 | 0.171 |
| | $C_6$ | -0.310 | -0.435 | -0.317 | 0.125 | -0.007 | 0.173 | -0.009 |

Figure 1S. Pictorial representation of the ELF localization (η=0.82 isosurface) domains for the reactants pyrroline-1-oxide and ethyl acrylate. Left, calculated at M06-2X/6-311++G** level. Right, calculated at B3LYP/6-31G(d) level. The color code is as follows: green: disynaptic basins; red: monosynaptic basins; blue: hydrogenated basins; and purple: core basins. The numbering of some atoms is shown.
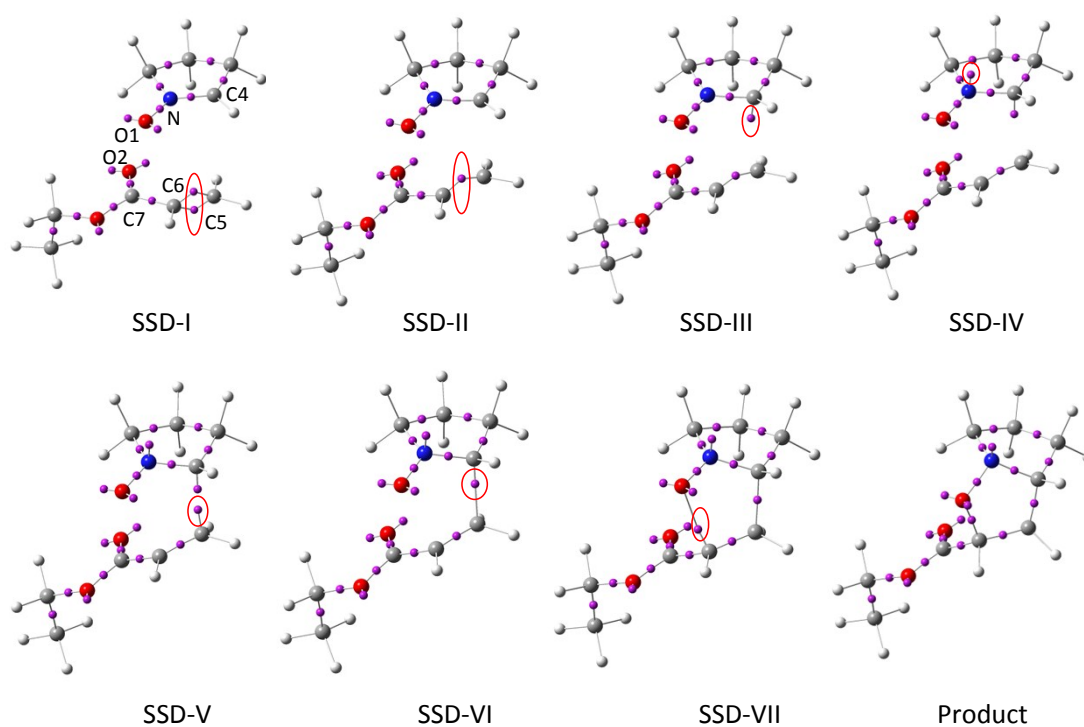
Figure 2S. ELF attractor positions for selected points that are representative of each of the SSDs found along the IRC associated with **TS1oen**, as well as for the reaction product, obtained at the B3LYP/6-31G(d) level. The numbering used for some atoms is also shown, and a red ellipse has been used to highlight the topological changes encountered.
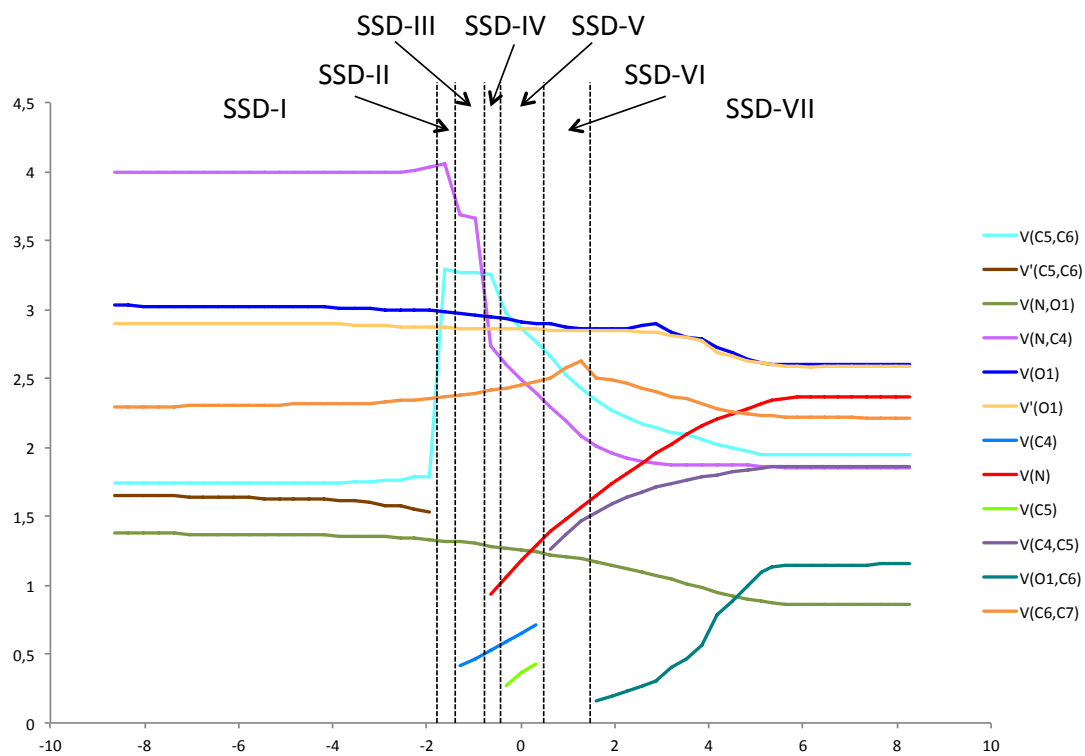
Figure 3S. Population (in electrons) evolution of selected basins along the IRC associated with **TS1oen** as a function of the IRC coordinate (in $\text{amu}^{1/2} \cdot \text{bohr}$) as obtained at the B3LYP/6-31G(d) level. The separate reactants are located on the left, while the product of the cycloaddition is on the right. Dashed lines indicate the frontiers between the SSDs found.
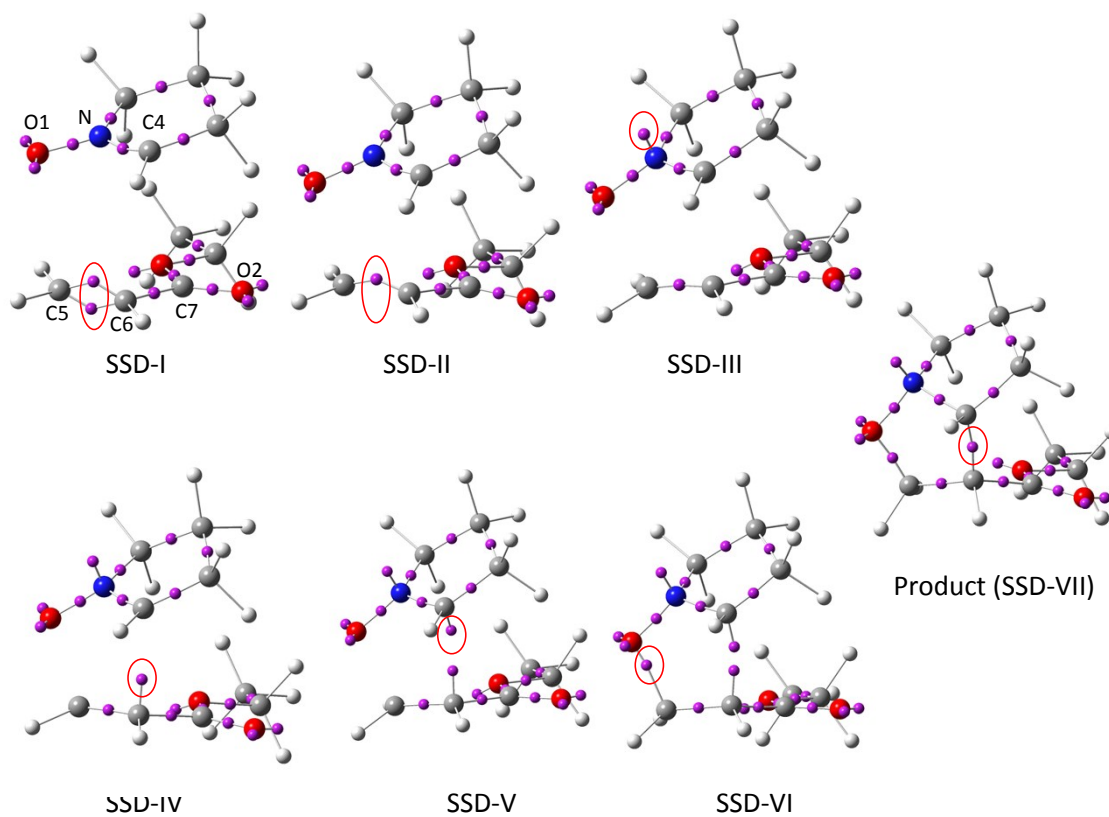
Figure 4S. ELF attractor positions for selected points that are representative of each of the SSDs found along the IRC associated with **TS1men**, as well as for the reaction product, obtained at the B3LYP/6-31G(d) level. The numbering used for some atoms is also shown, and a red ellipse has been used to highlight the topological changes encountered.
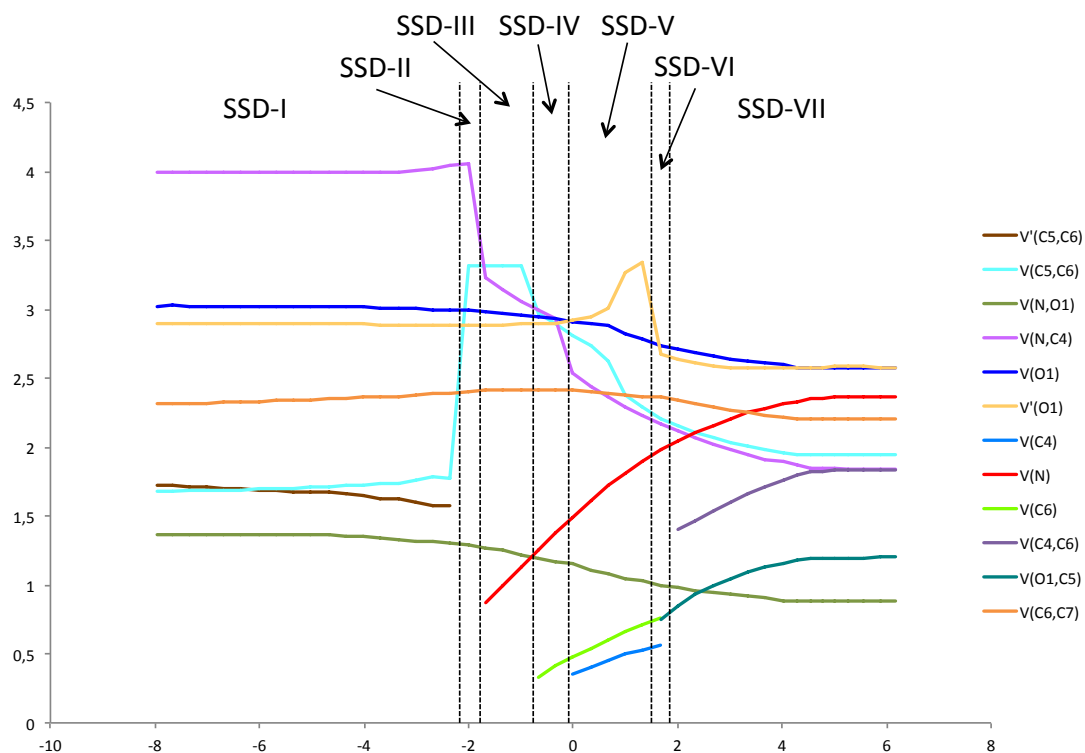
Figure 5S. Population (in electrons) evolution of selected basins along the IRC associated with **TS1men** as a function of the IRC coordinate (in $amu^{1/2} \cdot bohr$) as obtained at the B3LYP/6-31G(d) level. The separate reactants are located on the left, while the product of the cycloaddition is on the right. Dashed lines indicate the frontiers between the SSDs found.

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