Scientific paper

Theoretical Analysis of the Mechanism and Regioselectivity of the 1,3-dipolar Cycloaddition of \( E-3\)-(dimethylamino)-1-(10\( H \)-phenothiazin-2-yl) prop-2-en-1-one with Some Nitrilimines Using DFT and the Distortion/interaction Model

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Abstract

The regiochemistry of 1,3-dipolar cycloaddition reactions of \( E-3\)-(dimethylamino)-1-(10\( H \)-phenothiazin-2-yl) prop-2-en-1-one with some nitrilimines were investigated using density functional theory (DFT) -based reactivity indexes, activation energy calculations and the distortion/interaction model at B3LYP/6-311G(d,p) level of theory. Analysis of the geometries and bond orders (BOs) at the TS structures associated with the different reaction pathways shows that these 1,3-dipolar cycloaddition reactions occur via an asynchronous concerted mechanism.

**Keywords:** Regioselectivity; cycloaddition; DFT calculations; distortion/interaction model

1. Introduction

The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring.\(^1\) These reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. Current understanding of the underlying principle in the Diels–Alder reactions and the 1,3-dipolar cycloadditions (1,3-DC) has grown from valuable interaction between theory and experiment.\(^2\)\(^-\)\(^4\) The 1,3-DC reactions possess several interesting characteristics, in particular, regioselectivity. Although transition state theory remains the most widely used and the exact approach for the study of the mechanism and the regiochemistry of these reactions, the localization of transition states is not always easy. Furthermore, transition-state calculations are often very time-consuming when bulky substituents are present in reactive systems. Reactivity descriptors based on the density functional theory (DFT), such as Fukui indexes, local softnesses and local electrophilicity, have been extensively used for the prediction of the regiochemistry. For instance, several treatments of 1,3-DC reactions of nitrilimines with various dipolarophiles can be found in the literature.\(^5\)\(^-\)\(^7\) The 1,3-DC reactions of nitrilimines with alkenes is an important method for preparing pyrazoles and pyrazolidines in a regioselective and stereoselective manner.\(^8\) Experimentally; it has been found that the cycloaddition reactions of nitrilimines \(1a-c\) with \(E-3\)-(dimethylamino)-1-(10\( H \)-phenothiazin-2-yl) prop-2-en-1-one \(2\) give preferentially the cycloadducts \(3a\), \(3b\) and \(3c\) respectively, shown in Scheme 1.\(^9\) In continuation of our studies on the mechanism and regioselectivity of the 1,3-DC reactions,\(^10\)\(^-\)\(^18\) we became interested in the above mentioned reactions based on activation energy calculations, the distortion/interaction model and DFT-based reactivity indexes.

2. Computational Details

All calculations were carried out with GAUSSIAN03 program suite.\(^19\) Geometry optimization of the reactants was carried out using DFT methods at the B3LYP/6-311G (d,p) level of theory.\(^20\) The transition sta-
tes (TSs) for the 1,3-DC reactions have been localized at the B3LYP/6-311G(d,p) level of theory. Frequency calculations characterized the stationary points to verify that the TSs had one imaginary frequency. The intrinsic reaction coordinates (IRC)\textsuperscript{21} calculation was performed in forward and backward path to identify that each saddle point connects to the two associated minima using the second-order González–Schlegel integration method.\textsuperscript{22,23} The atomic electronic populations were evaluated according to Merz–Kollman scheme (MK option).\textsuperscript{24,25} The electronic chemical potential $\mu$ was evaluated in terms of the one electron energies of the HOMO and LUMO, using Eq. (1):\textsuperscript{26}

$$\mu = \epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}}/2$$

The global electrophilicity $\epsilon$ for dipoles and dipolarophile was evaluated using Eq. (2):\textsuperscript{27}

$$\omega = \mu^2/2(\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})$$

As usual, local indexes are computed in atomic condensed form.\textsuperscript{28} The well-known Fukui function \textsuperscript{29,30} for electrophilic ($f^-_k$) and nucleophilic attack ($f^+_k$) can be written as

$$f^-_k = [q_k(N) - q_k(N - 1)]$$
$$f^+_k = [q_k(N + 1) - q_k(N)]$$

Where $q_k(N)$, $q_k(N - 1)$ and $q_k(N + 1)$ are the electronic population of the site k in neutral, cationic, and anionic systems, respectively. The local electrophilicity index, $\omega_k$, condensed to atom k is easily obtained by projecting the global quantity onto any atomic centre k in the molecule by using the electrophilic Fukui function (e.g. the Fukui function for nucleophilic attack, $f^+_k$)\textsuperscript{31}

$$\omega = \omega f^+_k$$

Domingo et al. has introduced an empirical (relative) nucleophilicity index, $N$,\textsuperscript{32} based on the HOMO energies obtained within the Kohn–Sham scheme,\textsuperscript{26} and defined as:

$$N = \epsilon_{\text{HOMO}}(\text{Nu}) - \epsilon_{\text{HOMO}}(\text{TCE})$$

This nucleophilicity scale is referred to tetracyanoethylene (TCE) taken as a reference. Local nucleophilicity index, $N_k$, was evaluated using the following equation:

$$N_k = N f^-_k$$

Where $f^-_k$ is the Fukui function for an electrophilic attack.\textsuperscript{29,30}

### 3. Results and Discussion

#### 3.1. Activation Energy Calculations

The transition states have been localized for both cyclization modes. The corresponding activation energies and structures are given in Table 1 and Figure 1, respectively. Analysis of the geometries at the TS structures given in Figure 1 shows that they correspond to asynchronous bond formation processes. The extent of bond formation along a reaction pathway is provided by the concept of bond order (BO).\textsuperscript{34} The BO (Wiberg indexes) values of the N–C and C–C forming bonds at TS-
s are shown in brackets in Figure 1. These values are within the range of 0.03 to 0.37. The BO analysis shows that these TSs correspond to asynchronous concerted processes.

In the gas phase, the results show that the TS3a is more asynchronous than the TS4a, the TS3b is more asynchronous than the TS4b and the TS3c is more asynchronous than the TS4c. In general, the asynchronicity shown by the geometrical data is accounted by the BO values. All reactions are exothermic with large ΔE (# (relative energies between products and reactants) energy values. According to Hammond’s postulate, the TSs should then be closer to the reactants and can also be interpreted in terms of the position of the transition state along the reaction coordinate, n_T, as defined by Agmon:35

\[ n_T = \frac{1}{2 - (\Delta G/#/\Delta G^*)} \]  \tag{8}  

Where ΔG# and ΔG are the relative Gibbs free energy change between the reactants and their corresponding transition states and relative Gibbs free energy change between products and reactants respectively.

The extent of n_T shows the degree of similarity between the transition state and the product. According to the equation 8, the situation of the transition state along the reaction coordinate is determined exclusively by ΔG (# (a thermodynamic quantity) and ΔG^# (a kinetic quantity). If n_T < 0.5, the transition state is similar to reactants (early TS) and if n_T > 0.5, the transition state is similar to products (late TS).35 The values of n_T for these 1,3-DCs are 0.2604 (for 1a + 2 → 3a), 0.2953 (for 1a + 2 → 4a), 0.2545 (for 1b + 2 → 3b), 0.2924 (for 1b + 2 → 4b), 0.2562 (for 1c + 2 → 3c), and 0.2942 (for 1c + 2 → 4c). Therefore, we can conclude that TSs in all these reactions should be closer to the reactants. As it can be seen in Table 1, TS3a is located 13.7 kcal below TS4a, TS3b is located 13.5 kcal below TS4b and TS3c is located 14.0 kcal below TS4c. Thus, regioisomers 3a–c are kinetically more favored than regioisomers 4a–c. Furthermore, the presence of the CF₃ group in nitrilimine 1c slightly increases the barrier.

The comparison of the results presented in Table 1 with above mentioned BO values reveals a relationship between the activation energy of the TS structures and the asynchronicity of the reactions. Less energetic transition states TS3a–c are more asynchronous than TS4a–c. This findings are in line with the empirical rule that holds for a variety of [4 + 2] cycloaddition reactions that “as for asymmetrically substituted dienophiles, the more asynchronous TS has the lower energy”.36–38

The evaluation of the electronic nature of these 1,3-DC reactions showed that the atomic charges in the transition state were shared between the dipoles DC reactions showed that the atomic charges in the transition state, which fluxes from the dipolarophile to the polar nature of the 1,3-DC reactions. The comparison of the results presented in Table 1 with above mentioned BO values reveals a relationship between the activation energy of the TS structures and the asynchronicity of the reactions. Less energetic transition states TS3a–c are more asynchronous than TS4a–c. This findings are in line with the empirical rule that holds for a variety of [4 + 2] cycloaddition reactions that “as for asymmetrically substituted dienophiles, the more asynchronous TS has the lower energy”.36–38

The evaluation of the electronic nature of these 1,3-DC reactions showed that the atomic charges in the transition state were shared between the dipoles. IRC calculations were carried out for all studied reactions, and presented only for the reaction between 1a and 2 at the pathway leading to 3a (Figure 2). This figure shows saddle point clearly, and demonstrates that the TS

| Reaction | System | E (a.u.) | ΔE₀ # | ΔG # | ΔE₀ # | ΔG # |
|----------|--------|---------|-------|------|-------|------|
| 1a + 2   | 1a     | −532.5441 |       |      |       |      |
|          | 2      | −1240.5913 |       |      |       |      |
|          | TS 3a  | −1773.1240 | 7.19  | 21.45| −44.53| −39.46|
|          | TS 4a  | −1773.1022 | 20.86 | 35.26| −44.53| −39.46|
|          | 3a     | −1773.1949 |       |      |       |      |
|          | 4a     | −1773.1881 |       |      |       |      |
| 1b + 2   | 1b     | −571.8718  |       |      |       |      |
|          | 2      | −1240.5913 |       |      |       |      |
|          | TS 3b  | −1812.4513 | 7.37  | 20.44| −44.50| −39.43|
|          | TS 4b  | −1812.4298 | 20.83 | 34.27| −44.50| −39.43|
|          | 3b     | −1812.5222 |       |      |       |      |
|          | 4b     | −1812.5153 |       |      |       |      |
| 1c + 2   | 1c     | −869.6831  |       |      |       |      |
|          | 2      | −1240.5913 |       |      |       |      |
|          | TS 3c  | −2110.2641 | 6.46  | 20.53| −44.59| −39.06|
|          | TS 4c  | −2110.2418 | 20.45 | 35.05| −44.59| −39.06|
|          | 3c     | −2110.3351 |       |      |       |      |
|          | 4c     | −2110.3280 |       |      |       |      |

# Relative to the reactants.
(ΔE^+_{1}, as shown in Eq. (9):

\[ \Delta E^+ = \Delta E^+_{d} + \Delta E^+_{i} \] (9)

Where ΔE^+_{d} and ΔE^+_{i} are the energies required to distort the reactants from their initial geometries to their transition state geometries and the binding energy between the deformed reactants in the transition state respectively.\(^{31}\)

In Figure 3 are shown the values computed for ΔE^+_{d}, ΔE^+_{i} and dissected as the sum of the 1,3-dipole distortion energy (ΔE^+_{d-dipole}) and the dipolarophile distortion

connect to the associated minima of the concerted mechanism.

3.2. Distortion/interaction Model

Bickelhaupt (activation/strain model),\(^{39}\) and Houk (distortion/interaction model),\(^{40}\) independently developed an useful model to understand different issues such as reactivity trends and TS geometries. According to this model, the activation energy (ΔE^+) is decomposed into two main components: the distortion energy (ΔE^+_{d}, also known as the strain energy) and the interaction energy

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Figure 2. B3LYP/6-311G (d,p) IRC plot for the pathway of 1,3-DC reaction between 1a and 2 leading to 3a.

Figure 3. Values of $\Delta E^1$ (black line), $\Delta E^1_{d-dipole}$ (green line), $\Delta E^1_{d-dipolarophile}$ (red line) and $\Delta E^2$ (blue line) for the studied 1,3-DCs.
energy ($\Delta E_d^{\ddagger}$, dipolarophile).

Ess and Houk reported that “the energy to distort the 1, 3-dipole and dipolarophile to the transition state geometry is the major factor controlling the reactivity differences of 1,3-dipoles. Interaction energies between the 1, 3-dipole and the dipolarophile differentiate reactivity for a series of substituted alkenes when the distortion energies are nearly constant." As shown in Figure 3, the $\Delta E_d^{\ddagger}$ value for 3a–c formation is smaller than that for 4a–c. The later transition state means that greater geometrical deformation of reactants requires more distortion energy. Therefore, we can conclude that the distortion energy values favor the formation of the cycloadducts 3a–c against their regioisomers 4a–c respectively. Furthermore, Sarotti showed that highly asynchronous TS is predicted to be considerably less distorted than more synchronous one. According to this finding, as shown in Figure 3 and discussed in section 3.1, the TS3a–c are more asynchronous than TS4a–c. In general, the asynchronicity shown by the geometrical data in section 3.1 agrees with the reactivity trends experimentally observed and predicted by distortion energies.

3.3. DFT-based Reactivity Indexes

As it can be seen in Table 2, the electronic chemical potential ($\mu$) of dipolarophile 2 (–0.1216) is greater than those of dipoles 1a (–0.1246), 1b (–0.1479) and 1c (–0.1665), thereby suggesting that the net charge-transfer will take place from the dipolarophile 2 to dipoles 1a–1c. This indicates that dipoles 1a–c will more likely behave as electron acceptor species (i.e. as electrophile). These results are in agreement with CT calculations at the TSs.

The difference in electrophilicity for the dipole/dipolarophile pair, $\Delta \omega$, was found to be a measure of the high- or low-polar character of the cycloaddition. The small $\Delta \omega$ between 1a and 2 (0.98 eV), and 0.82 eV for 1b + 2, shows a low-polar character for these 1,3-DC reactions, but the presence of CF$_3$ group (an electron-withdrawing group) on phenyl ring in dipole 1c, not only increases $\Delta \omega$ (1.35) but also, in comparison to the dipoles 1a and 1b, enhances electrophilicity ($\omega$) and reduces nucleophilicity (N).

Table 2. HOMO and LUMO energies in a.u., electronic chemical potential ($\mu$ in a.u.), chemical hardness ($\eta$ in a.u.), global electrophilicity ($\omega$), in eV and global nucleophilicity (N, in eV) for reactants 1a–c and 2.

| Reactants | $\varepsilon_{\text{HOMO}}$ | $\varepsilon_{\text{LUMO}}$ | $\mu$ | $\eta$ | $\omega$ | N$^*$ |
|-----------|----------------|----------------|--------|--------|---------|-------|
| 1a        | –0.2248        | –0.0244        | –0.1246 | 0.2004 | 1.05    | 3.00  |
| 1b        | –0.2192        | –0.0766        | –0.1479 | 0.1426 | 2.09    | 3.16  |
| 1c        | –0.2387        | –0.0944        | –0.1665 | 0.1443 | 2.61    | 2.63  |
| 2         | –0.1888        | –0.0545        | –0.1216 | 0.1343 | 1.49    | 3.98  |

$^*$ The HOMO energy of tetracyanoethylene is –0.3351 a.u. at the same level of theory.

The Fukui indexes for the atoms N1 and C3 of the dipoles (1a–c) and for the atoms C4 and C5 of the dipolarophile 2 are given in Table 3 (see Figure 4 for atom numbering). Computed Fukui functions are based on the MK electronic population.

Table 3. Fukui indexes for N1 and C3 atoms of the dipoles 1a–c and for atoms C4 and C5 of the dipolarophile 2.

| Reactants | Atom number | $f^–_k$ | $f^+_k$ |
|-----------|-------------|---------|---------|
| 1a        | N1          | 0.0792  |
| C3        | 0.1053      |
| 1b        | N1          | 0.0788  |
| C3        | 0.1045      |
| 1c        | N1          | 0.0660  |
| C3        | 0.0981      |
| 2         | C4          | 0.0252  |
| C5        | 0.0211      |

In Figure 4 are reported values of local electrophilicities $\omega$ for atoms N1 and C3 of the dipoles 1a–c and local electrophilicities N for atoms C4 and C5 of the dipolarophile 2. According to the Domingo’s model, in a polar cycloaddition reaction between unsymmetrical reagents, the more favorable two-centre interaction will take place between the more electrophilic center, characterized by the highest value of the local electrophilicity index $\omega$ at the electrophile, and the more nucleophilic center characterized by the highest value of the local nucleophilicity index N$^*$ at the nucleophile. These results show that the two-center polar model, based on electrostatic charges, correctly predicts experimental regioselectivity.

4. Conclusion

Mechanism of the 1,3-dipolar cycloaddition reactions of E-3-(dimethylamino)-1-(10H-phenothiazin-2-yl) prop-2-en-1-ones 1a–c with nitrilimine 2 has been investigated using activation energy calculations, distortion/interaction model and DFT-based reactivity indexes at the B3LYP/6-311G (d,p) level of theory. The results of this work clearly support the experimentally observed regiochemistry.
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6. References

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Povzetek

V prispevku je opisana raziskava regiokemijskega poteka 1,3-cikoadicijskih reakcij E-3-(dimetilamino)-1-(10H-fenotiazin-2-il) prop-2-en-1-ona z nekaterimi nitrilimini, ki je bila narejena z uporabo reaktivnostnih indeksov, izračunom aktivacijske energije in modelom popačenja/interakcije na osnovi teorije gostotnega funkcionala (DFT) in uporabe B3LYP/6-311G(d,p) funkcij. Analiza geometrij prehodnih stanj in reda vezi struktur, ki so povezane z različnimi reakcijskimi potmi, kaže na to, da te 1,3-dipolarne cikloadicijske reakcije potekajo preko asinhronega koncertiranega mehanizma.

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