The origin of exo/anti selectivity in the 1,3-dipolar cycloaddition of nitrile oxides with C1-substituted 7-oxabenzonbornadienes have been investigated theoretically.
The origin of regio- and stereoselectivity in 1,3-dipolar cycloaddition of nitrile oxides with C1-substituted 7-oxabenzonorbornadienes, A DFT study

M. Bakavoli, M. Gholizadeh, H. Eshghi, M. Izadyar and J. Tajabadi*

In this computational study, density functional theory (DFT) calculations were performed in order to achieve a deep understanding of the regio- and stereoselectivity of 1,3-dipolar cycloadditions (1,3-DC) of C1-substituted 7-oxabenzonorbornadienes (OBNDs) (2a-2d) with acetonitrile oxide (1a) and benzonitrile oxide (1b). The potential energy surface analysis, Wiberg bond orders (BOs) and global electron density transfer (GEDT) at the transition states (TSs) show that these cycloadditions take place through a low asynchronous one-step mechanism with none polar character. Mechanism studies display these reactions are exo-stereoselective and anti-regioselective (3X) and classified as (pseudodiradical) pr-type 1,3-DC reactions. These results are in excellent agreement with the experimental observations. Distortion-interaction model has been used successfully for understanding of regio- and stereoselectivity in these reactions.

Keywords: regioselectivity, stereoselectivity, 1,3-dipolar cycloaddition, 7-oxabenzonorbornadienes, nitrile oxides, distortion-interaction model.

1. Introduction

2-Isoxazolines (4,5-dihydroisoxazoles)1 are the building blocks of numerous fused heterocyclic compounds exhibiting various biological activities, such as antimicrobial and antifungal,2 anti-inflammatory,3 herbicide and insecticide4 as well as anticancer activity.5 The reductive cleavage of N-O bond in the isoxazoline ring can lead to stereoselective construction of many synthetically important compounds, such as β-hydroxy ketones, 1,3-amino alcohols, or 1,3-diols.6 A paramount synthetic strategy for one step synthesis of isoxazolines is the cycloaddition of alkenes with nitrile oxides.7 Bicyclic and hetero bicyclic alkenes serve as valuable precursors for the creation of highly substituted cyclic and acyclic systems because of their unusual geometry and high reactivity.8

In the past decades, the understanding of the underlying principles in cycloaddition reactions has grown from a fruitful interplay between theory and experiment and continues to present a real challenge. One of frequently studied phenomena in the 1,3-dipolar cycloaddition (1,3-DC) reactions with activated double bond of strained bicyclic systems is their remarkable stereoselectivity and indeed, with norbornene and norbornadiene derivatives proceeds on the exo face (with respect to the methylene bridge).9 In the 1,3-DC reactions of oxabicycle [2,2,1] heptadiene systems also, exo-rule prevails.10 Moreover, unsymmetrically substituted norbornenes and norbornadienes have been reported to undergo cycloaddition reactions with complete stereoselectively.11 The desired exo-isomers are the one in which oxygen of the dipole is attached to the more substituted center of the dipolarophiles. It should be noted the violation of the exo-rule in 1,3-DC reactions of bicycle [2,2,1] alkenes has been observed in some cases.12 Recently, William Tam et al. reported the synthesis of novel oxabicycle fused isoxazolines via 1,3-DC reactions of acetonitrile oxide (1a) and benzonitrile oxide (1b) with unsymmetrical C1-substituted 7-oxabenzonorbornadienes (OBNDs) (2a-2d).13 They concluded that the formed isoxazolines show complete exo-stereoselectivity and major preference for positioning of the nitrile oxide R’ moiety anti to the C1-substituent, resulting from the different atomic charge densities at C2 and C3 atoms of OBNDs (Scheme 1).

A literature survey revealed that there is no report on any theoretical calculations concerning the origin of regio- and stereoselectivity of 1,3-DC reactions of OBNDs with nitrile oxides. Intrigued by these findings and due to our interest in applying the theoretical methods to study of the 1,3-DC reactions,14 a theoretical study on the above reactions was performed, in order to achieve a deeper insight to regio- and stereoselectivity of these 1,3-DC reactions. In this paper, potential energy surface analysis, conceptual density functional theory (DFT) indices and distortion/interaction model are applied and we wish to report our findings pertaining the origin of regio- and stereoselectivity of OBNDs with nitrile oxides using DFT/B3LYP/6-31G(d) calculations.
performed on the TSs to determine the connectivity of the TS structure to the corresponding product and reactant using the Natural bond orbital (NBO) analysis was performed on the electronic structures of the stationary points according to Reed electrostatic, polarization, and orbital (covalent) effects on allowing interaction between the addends. This involves bond stretching, angle decrease or increase, dihedral changes, optimized with more expensive hybrid meta-GGA functionals.

Scheme 1. Stereo- and regioisomeric channels associated with the 1,3-DC reactions of OBNDs 2a-2d with nitrile oxides 1a-1b.

2. Computational details

All computations were carried out with the Gaussian 09 program suite. Geometry optimization of all stationary points was carried out using DFT methods at the B3LYP/6-31G(d) level of theory. This economical method predicts barriers within a mean absolute deviation of 1.5 kcal mol\(^{-1}\) compared to CBS-QB3. Simon and Goodman suggested geometry optimization and frequency calculation by hybrid GGA functionals, (e.g. B3LYP), followed by a single-point calculation using a hybrid meta-GGA functional (e.g. M05-2X), which gives reasonably good results compared with transition states (TSs) which optimized with more expensive hybrid meta-GGA functionals. Therefore, we carried out a single-point calculation using M05-2X(UF)/6-31+G(2d,2p) (integral = grid = ultrafine) on the B3LYP/6-31G(d) geometries.

In all calculations, the ideal gas approximation, at the standard conditions was assumed. Reactants and products were characterized by frequency computations and have positive definite Hessian matrices. The TSs had only one negative eigenvalue in their diagonalized force constant matrices. The vibrational mode was assigned appropriately by means of visual inspection and animation using the GaussView 5 program. The intrinsic reaction coordinate (IRC) calculations were performed on the TSs to determine the connectivity of the TS structure to the corresponding product and reactant using the second-order González–Schlegel integration method. The population of regioisomers was calculated by taking into account the Gibbs energies using the Boltzmann distribution under the experimental conditions. Variational and tunneling effects were neglected in these calculations.

The distortion/interaction model developed by Ess and Houk provides a highly insightful method for understanding reactivity and activation barriers in cycloadditions. Decomposition of the activation energy (\(\Delta E^a\)) for bimolecular reactions into the distortion energy (\(\Delta E^d\)) and the energy of interaction (\(\Delta E^i\)) between distorted fragments, yields valuable insight into the difference between the activation energies of the endo and exo pathways. The distortion energy (\(\Delta E^d\)) is the energy required to geometric and electronic change to deform the reactants into the geometries they possess at the TSs without allowing interaction between the addends. This involves bond stretching, angle decrease or increase, dihedral changes, rehybridization, etc. The interaction energy is comprised of repulsive exchange-repulsions (Pauli repulsions) and stabilizing electrostatic, polarization, and orbital (covalent) effects on the TS structure. The activation barrier is the sum of these two terms, according to eq. 1

\[
\Delta E^a = \Delta E^d + \Delta E^i \quad \text{(eq. 1)}
\]

where \(E\) can be electronic, enthalpic or Gibbs energy.

Natural bond orbital (NBO) analysis was performed on the electronic structures of the stationary points according to Reed et al.

The conceptual DFT indices are used as a powerful tool to predict the chemical reactivity. The electron transfer process can be characterized by the electrophilicity index proposed by Parr et al., which measures the capacity of the molecule to undergo partial electron transfer. The global electrophilicity index is given by the following simple formula: \(\omega = \mu^2/2\eta\). This index is expressed in terms of the electronic chemical potential \(\mu\) and the chemical hardness \(\eta\). Both quantities may be obtained in terms of the electron energies of the frontier molecular orbital, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), \(\epsilon_{HOMO}\) and \(\epsilon_{LUMO}\), as \(\mu = (\epsilon_{HOMO} + \epsilon_{LUMO})/2\) and \(\eta = (\epsilon_{HOMO} - \epsilon_{LUMO})\), respectively. The empirical (relative) nucleophilicity index, \(N\), has been introduced by Domingo. It is based on the HOMO energies of nucleophile (Nu) and tetracyanoethylene (TCE), taken as a reference and defined as \(N = \epsilon_{H(Nu)} - \epsilon_{H(TCE)}\).

3. Results and discussion

The obtained results are divided into three parts. In the first part, an analysis of the DFT reactivity indices at the ground state of the reagents is given. In the second part, we have elaborated on the energetic and structural aspects of the TSs. Finally, an account on the origin of regio- and stereoselectivity of reactions of unsymmetrical OBNDs with nitrile oxides are given.

3.1. Analysis of the DFT reactivity indices of reactants
The global DFT reactivity indices of the reactants are provided in Table S1. The electronic chemical potentials of acetonitrile oxide (1a) and benzonitrile oxide (1b) are slightly higher and lower than that of the OBND dipolarophiles, respectively. This low difference between the electronic chemical potential of dipole/dipolarophile pairs (0.28-0.66 eV) indicates that in these reactions, the electron flux along the cycloadditions is very low, hence, these 1,3-DC reactions have a non-polar character. According to the absolute scale of electrophilicity and nucleophilicity based on \( \omega \) and \( N \) index, acetonitrile oxide (1a) and benzonitrile oxide (1b) can be classified as marginal and moderate electrophiles with \( \omega \) indices of 0.55 (1a) and 1.46 (1b) eV respectively. However, both compounds with moderate nucleophilic \( N \) indices, 2.39 (1a) and 2.78 (1b) eV, are classified as moderate nucleophiles. On the other hand, OBNDs can be classified as moderate electrophiles and strong nucleophiles. The inclusion of electron withdrawing group (COMe) on the \( C_1 \) carbon of OBND, lowers the HOMO and LUMO energy levels, therefore, increases the electrophilicity and decreases nucleophilicity indices, slightly. Electron releasing groups (Me and SiMe\(_3\)) show different behavior. Electrophilicity difference of dipole/dipolarophile pair is a useful tool to describe the electronic pattern expected for the TS structures in 1,3-DC reactions, describing non-polar (\( \Delta \omega \) small) or polar (\( \Delta \omega \) big) mechanisms. Since this index is small for studied reactions (0.38-0.53 eV), the reactions of 1a and 1b nitrile oxides with 2a-2d OBNDs are non-polar, in agreement with the electronic chemical potentials.

Finally, the non-polar character of these 1,3-DC reactions was evaluated by computing the global electron density transfer (GEDT) at the corresponding TSs. The natural atomic charges at the TSs, obtained through the NBO analysis, are shared between the nitrile oxides and the oxabicyclic frameworks. The GEDT values at the TSs are shown in Table 1. Negligible GEDT values (0.00-0.02 e) at all TSs indicate that these reactions are non-polar because of the low electrophilic character of the OBNDs.

A useful classification of 1,3-DC reactions into pseudodiradical-type (pr-type) and zwitterionic-type (zw-type) reactions has been proposed. pr-type reactions take place easily through an earlier TS with non-polar character, and zw-type reactions, taking place through polar TSs. It can be concluded our investigated reactions participate in pr-type reactions.

Recently, Domingo proposed the new local reactivity, Parr functions, in polar organic reactions. In the present study, OBNDs are not electrophilically activated, hence, these 1,3-DC reactions are non-polar. Therefore, Parr functions cannot give information about the regioselectivity in these non-polar 1,3-DC reactions. He claimed that the Fukui functions based on finite charge differentiations lead to some severe errors, because the electrophilic/nucleophilic behavior of these reactions are not correspond to changes in charge distribution, as proposed by these Fukui functions. So, the Fukui functions also could not be used for prediction of regioselectivity in these non-polar reactions.

3.2. Analysis of the energetic and structural aspects of the TSs

The stationary points on the 1,3-DC reactions of acetonitrile oxide (1a) and benzonitrile oxide (1b) with unsymmetrical C?-substituted OBNDs (2a-2d) are shown in Scheme 1. The potential energy diagram (PED), corresponding to these reactions is illustrated in Figure 1. For each of these cycloadditions, the nitrile oxide dipole could theoretically approach from either the exo face or the endo face of the bicyclic substrates. As a result, two stereoisomeric outcomes for the cycloadducts (CAs) could be envisioned. Moreover, except for symmetric OBND (2a), all its singly substituted OBNDs react with dipoles on two different regioisomeric pathways. Therefore, in theory, four distinct types of CAs could arise due to the possibility of the nitrile oxide R' group orienting anti (3) or syn (4) to the C1-substituent of the OBNDs, in addition to the five-membered ring situating stereochemically exo (X) or endo (N).

![Figure 1](image.jpg)

**Figure 1.** Potential energy diagrams for reactions of nitrile oxides (1a, 1b) and OBNDs (2a-2d): violet for 1a+2a, orange for 1b+2a, blue for 1a+2b, pink for 1b+2b, green for 1a+2c and red for 1a+2d. Solid and dotted lines indicate anti and syn regioisomeric channels, respectively.

For understanding the nature of the formed CA(s), at first, the structures of twenty TSs and related products as well as six reactants were fully optimized at B3LYP/6-31G(d) level of theory. IRC calculations were carried out for all studied reactions, and presented only for the reaction pathways leading to 3X (ba) and 3N (ba) in Figure S1. These calculations...
point calculations have been computed for B3LYP/6-31G(d) optimized reactants and TSs at the M05-2X(UF) /6-31++G(2d,2p) level of theory, as have been suggested by Simon and Goodman for the calculation of the activation energies in organic reactions (Table S3). Hereafter, the energies at B3LYP/6-31G(d) level are reported, unless otherwise noted.

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<th>$H_{d}$alkene</th>
<th>$G_{d}$total</th>
<th>$H_{d}$total</th>
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<th>$\Delta H^\ddagger$</th>
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<td>12.7</td>
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$\Delta G^\ddagger = G(\text{dipolarophile}) - G(\text{dipole}) - G(\text{alkene})$

$\Delta G^\ddagger = G(\text{product}) - G(\text{alkene})$

$\Delta G_{\text{dipole}}$, $\Delta G_{\text{dipolarophile}}$, and $\Delta G_{\text{alkene}}$ are distortion energy of nitrile oxides, distortion energy of OBNDs and total distortion energy, respectively. $\Delta E_i$ indicates interaction energy between distorted fragments.

Calculated activation and thermodynamic parameters have been presented in Table 1 which indicates that all these 1,3-DC reactions are very exothermic, ranging from -33.1 to -38.2 kcal mol$^{-1}$ and the exo products are thermodynamically more stable than endo stereoisomers. In addition, a comparison of the activation energies also indicates that in all cases the exo stereoisomers are the major products. The activation Gibbs energy differences between exo and endo forms in these 1,3-DCs are greater than 4.2 kcal mol$^{-1}$, demonstrate that the nitrile oxide dipoles prefer to approach the bicyclic framework from the exo face. Theoretical results for complete exo-stereoselectivity in these reactions are in agreement with experiment.

Computation of activation energies associated with the most favorable reactive channel of these 1,3-DC reactions are in the range of 9.5-10.7 kcal mol$^{-1}$, in the gas phase, while the activation Gibbs energies are in the range of 22.4-23.6 kcal mol$^{-1}$. This behavior is mainly due to the bimolecular character of these cycloadditions, which present unfavorable activation entropy. The different substitution patterns render relatively small energy differences ($\Delta \Delta G^\ddagger \leq 1.2$ kcal mol$^{-1}$), therefore, it can be concluded that the substituents effect at the carbon atom of dipole and C1 atom of dipolarophiles is low on the energy barriers of these 1,3-DC reactions. However, these substituents cause to be produced different ratio of regioisomeric CAs. The relative amount of the two possible CAs is proportional to the relative energies of the two the corresponding TSs. Based on the Gibbs energy activation of the TSs at 298 K, the Boltzmann distribution ratio has been calculated and reported in Table 2.

<table>
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<tr>
<th>Structures</th>
<th>$\Delta G_{\text{dipole}}$</th>
<th>$\Delta G_{\text{dipolarophile}}$</th>
<th>$\Delta G_{\text{alkene}}$</th>
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<th>$\Delta H_{\text{alkene}}$</th>
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<td>3X (bb)/4X (bb)</td>
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<td>100.0</td>
<td>100.0</td>
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<tr>
<td>3X (ba)/4X (ba)</td>
<td>86.14</td>
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<td>100.0</td>
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<td>30.70</td>
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<tr>
<td>3X (ca)/4X (ca)</td>
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Calculated ratios are in harmony with the experimental results. B3LYP/6-31G(d) level of theory produces better results than M05-2X/6-311+G(2d,2p)/B3LYP/6-31G(d) level. The analysis of the regioselectivity of these 1,3-DC reactions measured as the difference of activation Gibbs energies ($\Delta \Delta G^\ddagger$) between the two regioisomeric pathways shows that while, only one regioisomer is formed with bulky SiMe$^3$ substituent at the C1 atom of OBND (2c), the mixture of regioisomeric CAs are obtained with other substituents (Table 2). For all reactions, formation of the anti-regioisomer CAs is preferred over the syn-regioisomer which is in agreement with the experimental outcome. Based on the energies, obtained from single point calculations at the M05-2X(UP)/6-311++G(2d,2p) level of theory for optimized reactants and TSs, the composition of regioisomers are not changed considerably, while for the regioisomeric mixture of 3X (da) and 4X (da) contradictory results are observed. At the B3LYP and M05-2X functionals, the activation energy of the anti-regioisomer path is 0.2 and 0.5 kcal mol$^{-1}$ lower and higher than syn-regioisomeric path, respectively. To analyze this contradiction, TSXA (da) and TSXS (da)
were fully optimized at the M05-2X(UF)/6-311++G(2d,2p) level, but the same results were obtained. For validation of the results obtained experimentally and in continuation of our recently studies on elucidation of regioselectivity by GIAO $^{13}$C NMR calculations, GIAO $^{13}$C chemical shifts for $3X$ (da) and $4X$ (da) are computed by Sarotti and Pellegrinet method.$^{14}$ Experimental and unscaled GIAO $^{13}$C chemical shift values of these two regioisomers calculated at mPW1PW91/6-31G(d)/B3LYP/6-31G(d) level of theory in the gas phase using multi-standard (MSTD) approach$^{15}$ are shown in Table 3. The experimental chemical shifts between the major and minor regioisomers are mostly different for C$_1$ atom (|$\Delta \delta$| = 3.3 ppm) and C$_4$ atom (|$\Delta \delta$| = 5.8 ppm). A comparison of the calculated chemical shifts of C$_1$ and C$_4$ atoms of the two regioisomers with their experimental data shows that $3X$ (da) is the major regioisomer. Therefore, prediction of the regioselectivity of these 1,3-DC reactions by the B3LYP hybrid functional is more reliable than those obtained from M05-2X hybrid meta functional.

Table 3. Experimental and unscaled GIAO $^{13}$C chemical shift values, in ppm, of $3X$ (da) and $4X$ (da) (atom numbering is according to Figure 2)

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<td>144.6</td>
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<td>4X (da) (Exp.)</td>
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</table>

Figure 2. Optimized structure of $3X$ (da) with atom numbering

The geometries of the TSs, the lengths of the C-C and C-O forming bonds and their Wiberg bond order (BO) values at the TSs are shown in Figure 3. Analysis of the lengths of the two forming bonds at the TSs shows that they are not formed to the same extent. Although in all products, C-O bond length is shorter than C-C one (1.44 Å versus 1.51 Å), their values are inverse at the TSs. This suggests that the C-C bond formations at the TSs are more advanced than the C-O bond formations. As a measure of asynchronicity, the parameter $\Delta d_{TS/P}$, defined as the difference between the ratios of the forming bond lengths at the TS and the corresponding bond lengths in the product, was proposed.$^{15}$ Their values range from 0.10 to 0.20 for exo and anti-channels (Table 1) suggest that the reactions are low asynchronous. An observable general trend is that the exo/anti TSs are consistently more asynchronous than the exo/syn TSs with $\Delta d_{TS}$ values range from 0.04 to 0.09 in the gas phase, indicating the latters are almost synchronous. Note that in the exo TSs, the C-C and C-O forming bonds are longer than the endo ones, indicating earlier TSs. The extent of the bond formation can also be provided by the BO analysis$^{16}$ at the TS. Hence, the BO values for all forming bonds are calculated and given in Figure 3. These BO values are in the range of 0.24 to 0.28 for C-C bonds and 0.18 to 0.21 for C-O bonds. These BOs clearly indicate that the bond-formation of C-C are slightly more advanced than C-O bonds.
Figure 3. Geometries of TSs of the 1,3-DC reactions between nitrile oxides (1a, 1b) and OBNDs (2a-2d). The imaginary frequencies are given in cm$^{-1}$ and bond distances in Å units. BO values are given in parenthesis.
3.3. The origin of regio- and stereoselectivity

The distortion/interaction model which is an approach to dissect the activation barriers into distortion energy and interaction energy has been used recently in explaining of the stereoselectivity of norbornene in hetero Diels–Alder and Azide Cycloaddition reactions. This model is also used in order to gain a deeper insight into anti and exo selectivity of C1-substituted OBNDs with nitrile oxides. The distortion of OBNDs and 1,3-dipoles in the transition structures has been taken into account by comparing their structure prior to the cycloaddition to the one in the TSs. The computed activation barriers ($\Delta G^\ddagger$, $\Delta H^\ddagger$, $\Delta E^\ddagger$), distortion ($\Delta E_d^\ddagger$) and interaction ($\Delta E_i^\ddagger$) energies in each transition structure are reported in Table 1. The activation energies ($\Delta E^\ddagger$), interaction and distortion energies are in a range of 9.2-16.4, 6.4–10.4 and 17.0-23.1, in kcal mol$^{-1}$, respectively. This shows that the activation energy is governed mainly by the distortion energy. Figure 4 shows a plot of $\Delta E^\ddagger$ versus $\Delta E_d^\ddagger$ for the studied reactions. There is a fair linear correlation ($r^2 = 0.89$) between the reactant distortion energies and activation energies, because of the existence of two outliers, TSXS (da) and TSNS (da). An excellent linear correlation is observed ($r^2 = 0.98$) when the mentioned two outliers are omitted. The activation barriers for these cases deviate because their interaction energy in their TSs is greater than the other TSs (Table 1).

$$\Delta E^\ddagger = 0.9809 \Delta E_d^\ddagger - 7.0482$$

$$R^2 = 0.89$$

![Figure 4](image_url)

**Figure 4.** Theoretical correlation of the activation energies and distortion energies, in kcal mol$^{-1}$, at the B3LYP/6-31G(d) level

The range of OBND distortion energies (3–7.2 kcal mol$^{-1}$) is larger than that of distortion energies of nitrile oxides (13.9–16.2 kcal mol$^{-1}$), although the latter are generally larger than the former. It was previously shown with 1,3-DC of acetylene and ethylene with many dipoles, the distortion of the 1,3-dipole is about 80% of the distortion energy. In the nitrile oxide cycloaddition studied here, dipole distortion energies comprise 75-82% of the total distortion energies in the exo transition structures. In the case of endo, dipole distortion energy makes up 70% of the total distortion energy. Nitrile oxides in the exo and endo transition structures have $\angle$CNO = 145° and 143°, respectively, hence distortion energies of dipoles are almost similar in all reactions.

On the other hand, the distortion of dipolarophiles comprises ~20% of the total distortion energy in theexo transition structures while it makes up ~30% of the total distortion energy in the endo ones. This portion of the distortion energy is the energy required to distort OBNDs from their equilibrium structures, indicating that in the endo transition structures, dipolarophiles are 1.5 fold more distorted than the exo transition structures.

For understanding the origin of OBNDs distortion energy differences in exo and endo TSs, and in the light of the large distortion which is mostly associated with C–H bonds bending out of plane in OBNDs, six dihedral angles that are changed more along the reaction have been monitored. $\theta_1$ (C1C2C3H26), $\theta_2$ (C2C3C4H26), $\theta_3$ (O1C1C2H26), $\theta_4$ (O1C4C3H26), $\theta_5$...
(H₂₅C₂₂C₇R) and θ₆ (H₂₆C₃₂C₇H₇) (for atom numbering see Figure 2). These dihedral angle values in the optimized reactants and TSs are shown in Table S4. θ₁ and θ₂ values from reactants to the TSs change in a range of 11.2-22.3°; however, these changes are almost the same for exo and endo pathways for each reaction (0-3.8°). On the other hand, not only changes of θ₁, θ₆, θ₅ and θ₆ are large (12.2-32.8° for θ₁ and θ₅ as well as 11.8-31.8° for θ₆ and θ₆), but are also different for two stereoisomers (8.5-13.2° for θ₁ and θ₅ as well as 6.8-11.6° for θ₆ and θ₆). As shown in Table S4, these dihedral angles in endo TSs change more than exo ones. There is not any correlation between ΔEₐₙkene and the sum of the θ₁ and θ₂ dihedral angles, but a good linear correlation is observed (r² = 0.97) for ΔEₐₙkene and Σθₖθₖ (Figure 5). Moreover, the exo stereoselectivity seen in these reactions also results from different torsional effects in exo and endo TSs. Figure 6 shows Newman projections along the C₁-C₂ and C₃-C₄ bonds in the TSXA (ba) and TSNA (ba). While the former is almost in the staggered conformation about these bonds, the latter shows a nearly perfect eclipsing.

![Figure 5](image-url)

**Figure 5.** Linear correlate of the distortion energy of OBNDs, in kcal mol⁻¹ versus \( \sum \theta_i \), in deg.

\[
y = 0.0825x - 2.0427 \\
R^2 = 0.97
\]
Figure 6. Newman projections for TSXA (ba) (left) and TSNA (ba) (right).

Distortion/interaction model is also able to explain regioselectivity in these reactions. The lower distortion energy of anti regioisomers than syn regioisomers (1.2-2.8 kcal mol$^{-1}$), together with their higher stabilizing interactions (0.2-1.1 kcal mol$^{-1}$), except for TSXA (da) (Table 1) make the anti regioisomers more stable and appears to be the major regioisomer. Distortion energy differences of two regioisomeric channels are equal in the reaction of 2b and 2d with nitrile oxides; however, Gibbs energy differences are different. Stabilizing interactions energy at TSXS (da) is 0.9 kcal mol$^{-1}$ more than TSXA (da), hence their Gibbs energy difference is only reduced to 0.2 kcal mol$^{-1}$.

4. Conclusion

The 1,3-DC reactions of some C$_1$-substituted OBNDs (2a-2d) with nitrile oxides (1a-1b) has been investigated theoretically for each plausible type of approach of 1,3-dipoles to OBNDs. It is found that exo CAs are preferred because of the lower distortion of strained dipolarophiles and the lower torsional effects, present in the related TSs. Among the exo TSs, anti regioisomers are more stable than syn ones because of the lower distortion and more favorable interactions. The calculated population of products, based on the Gibbs energy of TSs, reflects the experimental findings. GIAO/$^{13}$C NMR calculations were used for elucidation of regioselectivity in these reactions. Our calculations show these cycloadditions take place through a low asynchronous one-step mechanism with a none polar character and classified as (pseudodiradical) pr-type 1,3-DC reactions. In most cases, the B3LYP and M05-2X results were consistent with experiments. However, in a few cases, under the assumption of the conventional transition state theory, the B3LYP method seemed to give more reasonable results.

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Notes and references

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