

# 1, 3-Dipolar cycloaddition reactions of selected 1,3-dipoles with 7-isopropylidenenorbornadiene and follow-up thermolytic cleavage: A computational study

Grace Arhin, Anita Houston Adams, Ernest Opoku, Richard Tia\*, Evans Adei

Theoretical and Computational Chemistry Laboratory, Department of Chemistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

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## ABSTRACT

The mechanism, regio-, stereo-, and enantio-selectivities of the 1,3-dipolar cycloaddition reactions of 7-isopropylidenenorbornadiene (DENBD) with nitrones and azides to form pharmaceutically relevant isoxazolidine and triazole analogues have been studied computationally at the M06/6-31G(d), 6-31G(d,p), 6-311G(d,p), 6-311++G(d,p) and M06-2X/6-31G(d) levels of theory. In the reactions of DENBD with phenyl nitrones, the cycloaddition steps have low activation barriers, with the highest being 16 kcal/mol; and the Diels-Alder cycloreversion steps have generally high barriers, with the lowest being 20 kcal/mol, suggesting that the isolable products in these reactions are the bicyclic isoxazolidine cycloadducts and not the thermolytic products. This is in contrast to the reactions of DENBD with phenyl azide where the isolable products are predicted to be the thermolytic products since the Diels-Alder cycloreversion steps had relatively lower activation barriers. Electron-donating substituents on the dipolarophile substrate favour attack of the nitron on the least hindered side of the DENBD substrate while electron-withdrawing substituents on the dipolarophile substrate favour attack on the more hindered side of the DENBD, indicating that site-selectivity is affected by nature of substituents. Global reactivity indices calculations are in good agreement with the activation barriers obtained. Analysis of the electrophilic ( $P_K^+$ ) and nucleophilic ( $P_K^-$ ) Parr functions at the reactive centres reveal that the cycloaddition occurs between atoms with the largest Mulliken and NBO atomic spin densities which agrees well with the energetic trends and the experimental product outcomes.

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## 1. Introduction

1,3 dipolar cycloaddition reactions have become a well-known approach to the construction of variety of heterocyclic molecular structures. A highlight of its power in synthesis is its use to construct five-membered rings such as isoxazolidines, pyrrolines, triazoles and pyrrolidines [1–4]. 1,3 dipolar cycloaddition (1,3 DC) of nitrones and azides with alkenes in particular has received considerable attention in organic synthesis due to their numerous importance [5]. Among the reasons for the successful synthetic applications of nitrones and azides is that, unlike the majority of other 1,3 dipoles, nitrones and azides are stable compounds, readily

available and easy to handle [6,7]. Also, adducts obtained from the reaction of these dipoles and olefins are privileged scaffolds in organic chemistry and natural product synthesis [1].

The use of norbornadiene and its derivatives as dipolarophiles in (3 + 2) cycloaddition with these selected dipoles permits the synthesis of important cycloadducts under mild conditions. These cycloadducts formed can undergo Diels-Alder cycloreversion reactions to form five membered heterocycles such as isoxazolidines, triazoles and carbocycles such as dimethyl fulvenes [6]. In view of the usefulness of these heterocycles, several attempts are still ongoing in the advancement of efficient methods [2,3,5,8,9] towards the chemical transformation of readily available chemical feedstocks to isoxazolidines and triazoles. A detailed search of the chemical literature revealed several applications of isoxazolidines [10–12] ranging from anti-biological properties to environmental remediation [13].

In light of the title reaction, Cristina et al. [6] reacted norbornadiene derivatives with some selected 1,3-dipoles. In this reaction,

\* Corresponding author.

E-mail addresses: [arhingrace@yahoo.com](mailto:arhingrace@yahoo.com) (G. Arhin), [anita.adams2015@gmail.com](mailto:anita.adams2015@gmail.com) (A.H. Adams), [ernopoku@gmail.com](mailto:ernopoku@gmail.com) (E. Opoku), [richtiagh@yahoo.com](mailto:richtiagh@yahoo.com), [richardtia.cos@knust.edu.gh](mailto:richardtia.cos@knust.edu.gh) (R. Tia), [eadei@yahoo.com](mailto:eadei@yahoo.com) (E. Adei).

regio- and stereo-selectivities occurred as a result of the different reactivity of the two double bonds in the 7-isopropylideneborbornadiene (Scheme 1). Particularly when an acyclic nitron (N-methyl-C-phenylnitron) was employed, the reaction was 100% regioselective with respect to attack on the highly hindered side of the dipolarophile.

Prior to this work, Michelle et al. [15] had also reported the *syn* and *anti* selectivities of polychloronorbornadienes by reacting it with various 1,3 dipoles. It is important to note that whereas the former work focused on the regio- and enantio-selectivity of this reaction, the latter was focused on the stereoselectivity.

Numerous theoretical studies have been devoted to the reactions of nitrones to ethylene derivatives since they lead to the effective synthesis of important scaffolds [16–19]. Quite recently, Domingo et al. [20] reported a theoretical study of the reactions of C, N dialkyl nitrones with ethylene derivatives and the impact of varying substituents on the ethylene substrate of the reaction. Their study has provided an insightful rationalization of the general selectivities of nitrones with ethylene derivatives in (3 + 2) cycloadditions (32CA) reactions, making a huge contribution to the theoretical, as well as experimental understanding of dipolar cycloaddition chemistry.

Although the products from Cristina and her co-workers [14] study are known, the mechanistic rationale for the outcome in their experimental study is still lacking. Computational chemistry tools are continuously being applied in the rationalization and prediction of reactivity patterns in order to provide theoretical guidance for correlative experiments. As part of an ongoing studies on selected 1,3-dipolar cycloaddition reactions in our group [21,22], we extend our arms to carry out investigations into the mechanism of the titled reaction.

The aim of this present study is to perform a detailed theoretical study on the reactivity and selectivities in the reaction of 7-isopropylideneborbornadiene with N-methyl-C-phenylnitron and phenyl azide by examining the energetics of the various elementary steps involved in the productive reactive channels as well as various routes leading to minor addends. The impact of different substituents on the energetics and selectivities of the reaction are also investigated. Subsequent thermolytic cleavage (Diels-Alder cycloreversion) of the initial adducts are also explored. In addition, the effects of temperature and solvent on the reaction pathways are computed to enhance chemical insights. The study is based on Schemes 2–4 which depict the various regio-, stereo- and enantio-selectivities investigated.

## 2. Computational details and methodology

All the quantum chemical calculations were carried with the

Spartan'14 [23] and Gaussian 09 [24] computational chemistry software suites at the M06/6-31G(d), M06-2X/6-31G(d), M06/6-31G(d,p), M06/6-311G(d,p) M06/6-311++G(d,p) levels of theory. The Minnesota functionals (M06 and M06-2X) which originates from Zhao and Truhlar [25] are hybrid meta-generalized gradient approximations (meta-GGA) that have been shown to be effective at geometry optimizations and computing thermochemical and kinetic parameters of chemical reactions [26–28].

Using the polarizable continuum model (PCM), benzene was employed to compute solvation effects in the reactions [29].

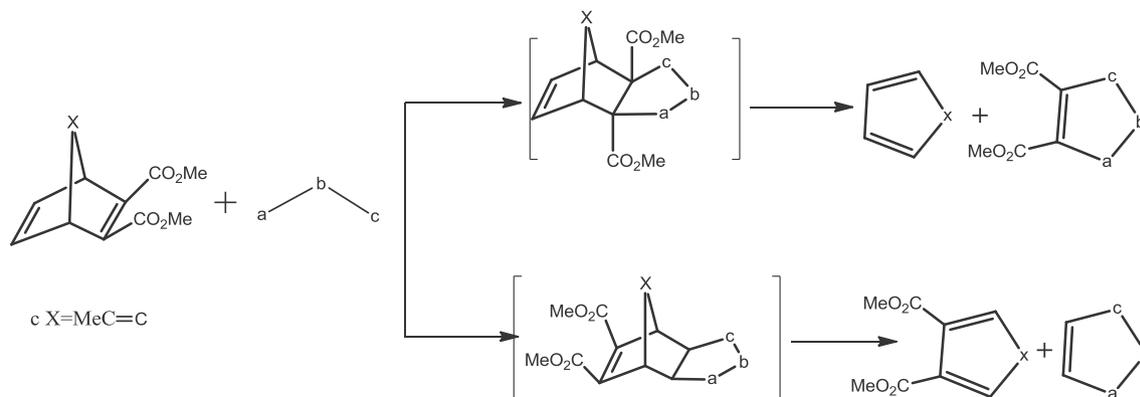
The guess geometries of the molecules were constructed with the Spartan's graphical model builder and minimized interactively using the sybyl force field [30]. Transition state structures were computed by first obtaining guess input structures. This was achieved by constraining specific internal coordinates of the molecules (bond lengths, bond angles, dihedral angles) while fully optimizing the remaining internal coordinates. This procedure gives appropriate guess transition state input geometries which are then submitted for full transition state calculations without any geometry or symmetry constraints.

Full harmonic vibrational frequency calculations were carried out to verify that each transition state structure had a Hessian matrix with only a single negative eigen value, characterized by an imaginary vibrational frequency along the respective reaction coordinates. The default self-consistency field (SCF) convergence criteria (SCF=Tight) within the Gaussian 09 molecular modeling package was used [31,32]. Intrinsic reaction coordinate calculations [32–34] were then performed to ensure that each transition state smoothly connects the reactants and products along the reaction coordinate [35–37].

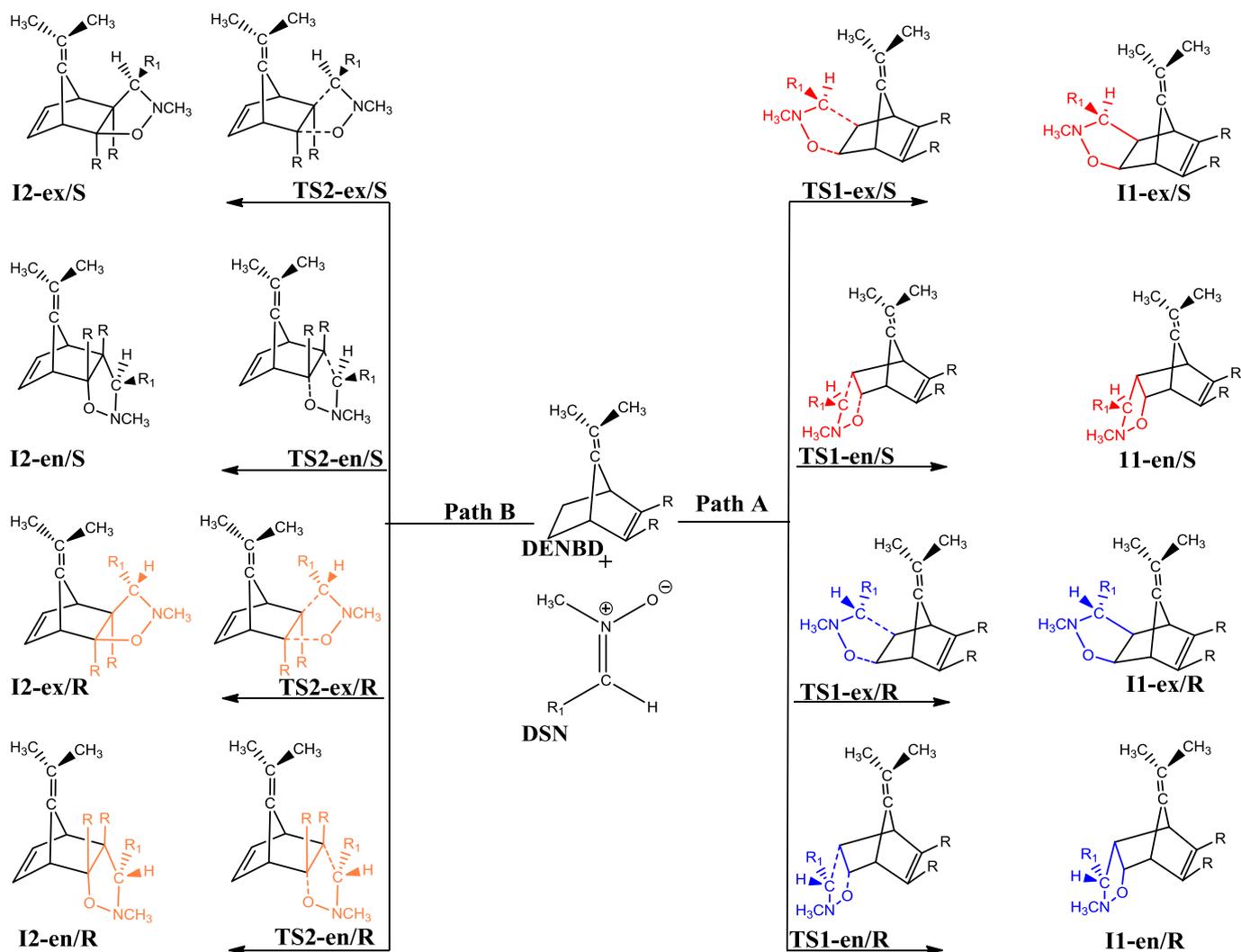
The global electrophilicities ( $\omega$ ) and maximum electronic charge ( $\Delta N_{\max}$ ) of the various 7-isopropylideneborbornadiene and the nitron derivatives were calculated using equations (1) and (2). The electrophilicity index measures the ability of a reaction substrate to accept electrons [38] and it has been found to be a function of the electronic chemical potential,  $\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2$  and chemical hardness,  $\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})$  as defined by Pearson's acid-base concept [39]. Hence, species with large electrophilicity values are more reactive towards nucleophiles. These equations are based on the Koopmans theory [40] originally established for calculating ionization energies from closed-shell Hartree–Fock wavefunctions, but have since been adopted as acceptable approximations for computing electronic chemical potential and chemical hardness.

$$\omega = \mu^2/2\eta \quad (1)$$

$$\Delta N_{\max} = -\mu/\eta \quad (2)$$



Scheme 1. Cycloadditions of Selected dipoles to 7-isopropylideneborbornadiene derivatives [14].



**Scheme 2.** 32CA Reactions of C, N-Disubstituted Nitrones with 7-isopropylidenenorbornadiene (DENBD) derivatives to form isoxazolidine cycloadducts.

The maximum electronic charge transfer ( $\Delta N_{\max}$ ) measures the maximum electronic charge that the electrophile may accept. Thus, species with large  $\Delta N_{\max}$  index would be best electrophile given a series of compounds.

The global electrophilic ( $P_K^+$ ) and nucleophilic ( $P_K^-$ ) Parr functions were obtained through the analysis of the Mulliken and Natural Bond Orbital (NBO) atomic spin densities (ASD) of the radical anion and the radical cation by single-point energy calculations over the optimised neutral geometries using the unrestricted UM06 formalism for the radical species [41].

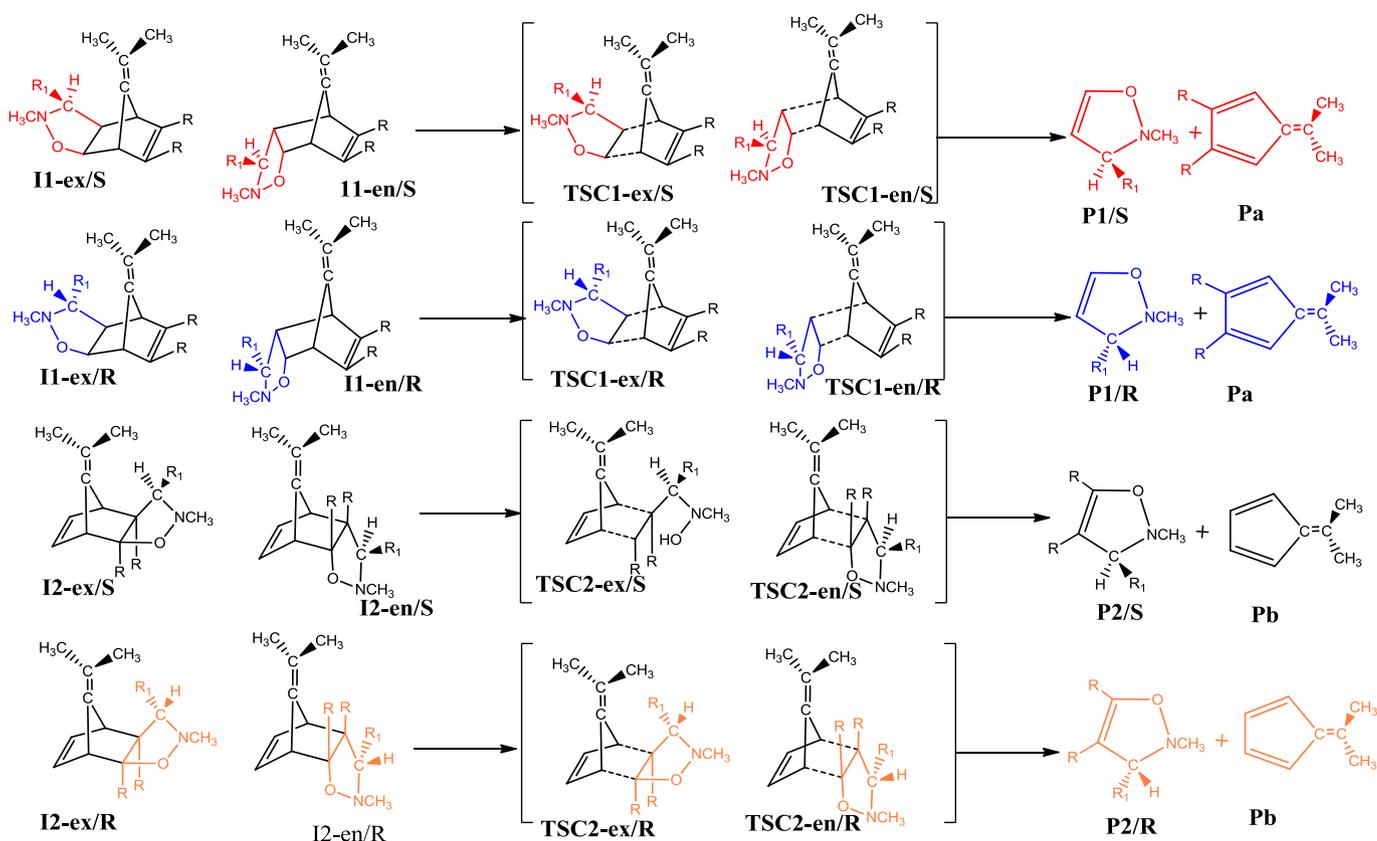
### 3. Results and discussion

Based on Schemes 2 and 3, the 1,3-dipolar cycloaddition reaction of the C,N disubstituted nitrones (DSN) with 7-isopropylidenenorbornadiene derivatives (DENBD) has been predicted to take place along eight possible reaction channels corresponding to the regioselectivity arising from whether the approach on the dipolarophile by the dipole is on the disubstituted double bond (path A) or the tetrasubstituted double bond (path B), the stereoselectivity arising from whether the incoming group is *syn* or *anti* to the bridging atom, and the enantioselectivity arising from whether the  $R_1$  group on the nitron adopts the 'S' or the 'R' configuration. The transition states **TS1-ex/S**, **TS1-ex/R**, **TS1-en/S**,

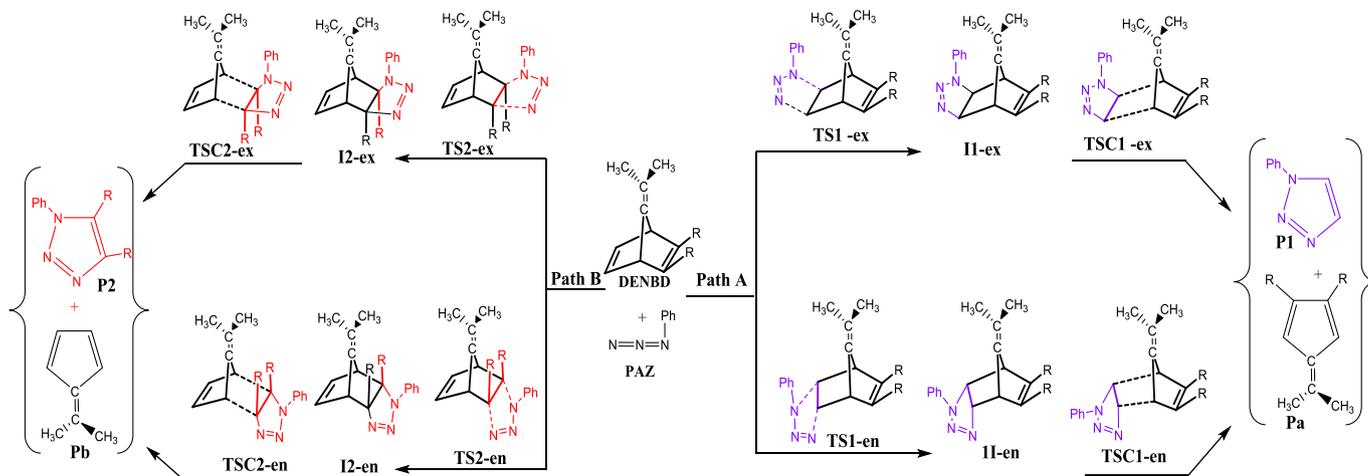
**TS1-en/R**, **TS2-ex/S**, **TS2-ex/R**, **TS2-en/S** and **TS2-en/R** have thus been studied. Eight cycloadducts **I1-ex/S**, **I1-ex/R**, **I1-en/S**, **I1-en/R**, **I2-ex/S**, **I2-ex/R**, **I2-en/S** and **I2-en/R** which can then undergo Diels-Alder cycloreversion through transition states **TSC1-ex/S**, **TSC1-ex/R**, **TSC1-en/S**, **TSC1-en/R**, **TSC2-ex/S**, **TSC2-ex/R**, **TSC2-en/S** and **TSC2-en/R** to form the five-membered heterocycles isoxazolidines and carbocycle dimethyl fulvene **P1/S** + **Pa**, **P1/R** + **Pa**, **P2/S** + **Pb**, **P2/R** + **Pb** have also been studied. All the energies reported herein are Gibbs free energy with zero point energy corrections.

#### 3.1. The reaction of C-Phenyl, N-methyl nitron ester-substituted 7-isopropylidenenorbornadiene derivatives (DENBD)

The energy profiles corresponding to the eight pathways at the DFT M06/6-31G(d) levels are displayed in Fig. 1. The analysis of the relative energies reveals the following: the formation of the transition state of the *R* enantiomer **TS2-ex/R** is more favored over the corresponding *S* enantiomer transition state **TS2-ex/S** by 7.1 kcal/mol. As shown in Fig. S1, the phenyl substituent on the nitron and ethylene substituent on the DENBD are too close to each other leading to unfavourable interactions between these groups. The transition state **TS2-ex/R** corresponding to attack on the highly substituted double bond in the *exo* manner is more favored over the corresponding regio isomer (**TS1-ex/R**) by 12.1 kcal/mol and



**Scheme 3.** Diels-Alder cycloreversion of the (3 + 2) cycloadducts to form five-membered rings (isoxazolines and dimethyl fulvene).



**Scheme 4.** 32CA Reactions of phenyl azide with 7-isopropylidenenorbornadiene (DENBD) derivatives and cycloreversion of cycloadducts to form dimethyl fulvene and triazoles.

more stable than the corresponding stereoisomer in the endo fashion (**TS2-en/R**) by 10.7 kcal/mol. The regio-, stereo- and enantio-selectivities found for the 32CA reaction involving the nitrene with the dipolarophile DENBD derivative is in complete agreement with the yields experimentally found by Cristina et al. [14]. The activation energies of transition states **TSC1-ex/S** to **TSC2-en/R** arising from the Diels-Alder cycloreversion of the cycloadducts in both gas phase and solvent (benzene) are given in Table 1. Quantum-chemical calculations using benzene in the PCM method showed that in the reaction of phenyl nitrene with ester-

substituted norbornadiene, the activation energies changes insignificantly within 3 kcal/mol, but practically do not modify the regio-, stereo- and enantio-selectivities computed in the gas phase.

The geometries of the transition states involved in the 32CA reactions of C-phenyl, N-methyl nitrene with ester-substituted DENBD including the bond distances between the carbon and oxygen nuclei involved in the formation of the C–O bond and the bond distances between the carbon and carbon nuclei involved in the formation of the C–C bond are displayed in Fig. S1 in the supplementary information.

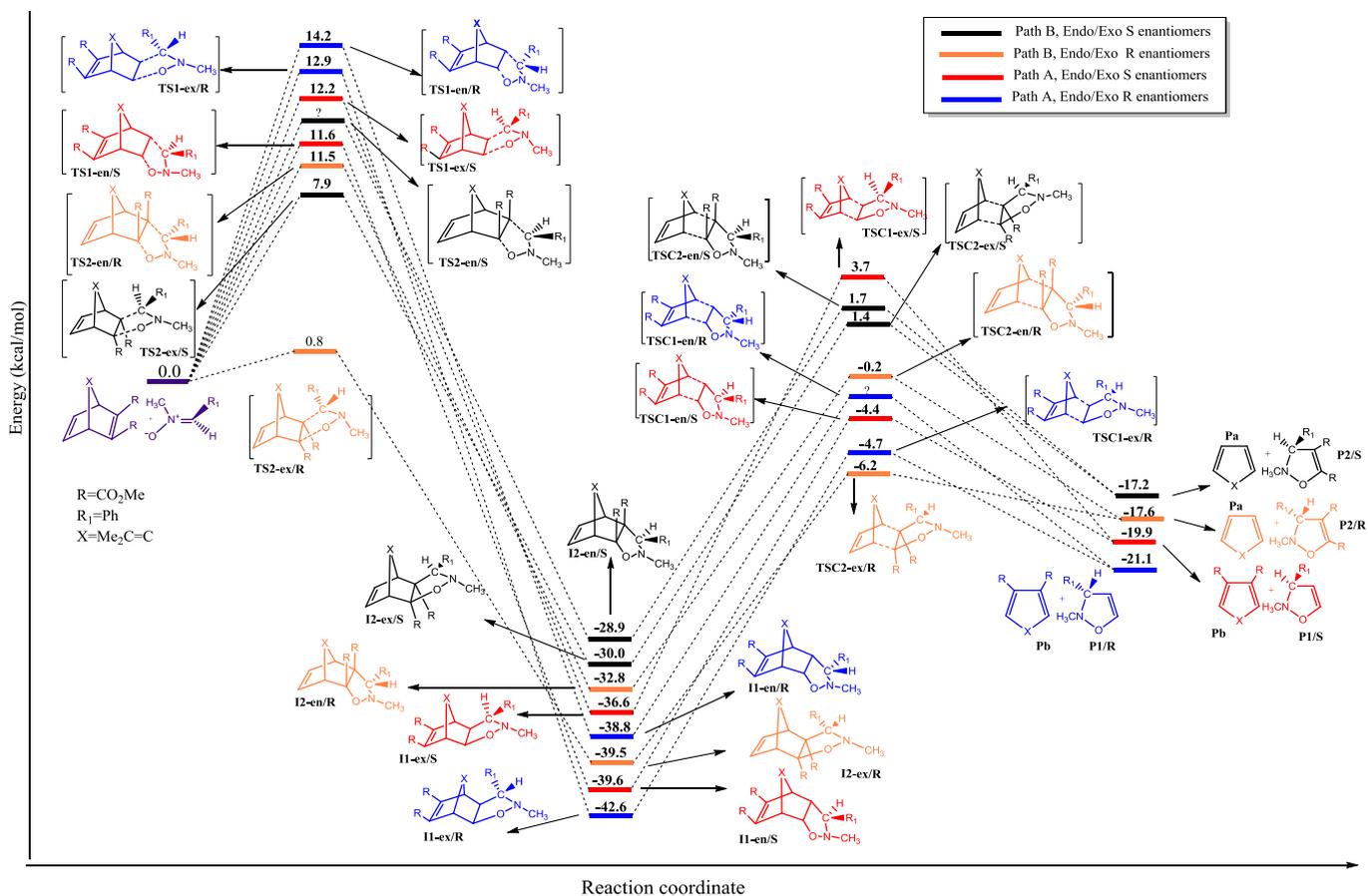


Fig. 1. Free energy profile for the (3 + 2) addition of ester substituted DENBD to phenyl nitrene. Relative energies in kcal/mol.

Table 1

Activation energies (kcal/mol) in the gas phase and in solvent, for the species involved in the 32CA reactions of phenyl nitrene with ester-substituted norbornadiene at the M06/6-31G(d) level of theory.

| Specie   | Gas phase | Benzene | Specie    | Gas phase | Benzene |
|----------|-----------|---------|-----------|-----------|---------|
| TS1-ex/S | 12.2      | 13.4    | TSC1-ex/S | 40.3      | 39.9    |
| TS1-ex/R | 12.9      | 13.8    | TSC1-ex/R | 37.8      | 36.9    |
| TS1-en/S | 11.6      | —       | TSC1-en/S | 35.2      | 35.9    |
| TS1-en/R | 14.2      | 16.2    | TSC1-en/R | —         | —       |
| TS2-ex/S | 7.9       | 10.1    | TSC2-ex/S | 31.5      | 30.9    |
| TS2-ex/R | 0.8       | —       | TSC2-ex/R | 33.3      | 32.5    |
| TS2-en/S | —         | —       | TSC2-en/S | 30.8      | 31.1    |
| TS2-en/R | 11.6      | 12.8    | TSC2-en/R | 32.6      | 32.3    |

### 3.2. The effects of substituents on the reactions

#### 3.2.1. The reaction of C-phenyl, N-methyl nitrene with methyl-substituted DENBD

The energy profiles corresponding to the eight pathways as shown in Schemes 2 and 3 at the DFT M06/6-31G(d) levels are displayed in Fig. 2. Replacing the ester groups on the DENBD substrate of the reaction with methyl groups generally favors attack of nitrene via path A. However, the reaction is only slightly regioselective in that TS1-ex/R becomes 2 kcal/mol lower in energy than TS2-ex/R. It is however highly stereoselective in that TS1-ex/R is 7.7 kcal/mol lower in energy than the corresponding TS1-en/R, and fairly enantioselective with TS1-ex/R being 2.7 kcal/mol lower in energy than the corresponding TS1-ex/S. The possibility of a smaller R<sub>1</sub> such as CH<sub>3</sub> group altering the enantioselectivities of the

reaction was studied and the results are shown in Fig. 2 and Table 2.

The activation energies associated with the 32CA reaction of phenyl nitrene to methyl substituted 7-isopropylidenenorbornadiene substrate range from 9.8 kcal/mol to 17.5 kcal/mol while those associated with the 32CA reaction of methyl nitrene with methyl substituted 7-isopropylidenenorbornadiene range from 3.2 kcal/mol to 12.2 kcal/mol. The activation energies associated with the Diels-Alder cycloreversion of the cycloadducts to form the corresponding isoxazolidines and dimethyl fulvene for phenyl nitrene and methyl nitrene range from 35.9 kcal/mol to 46.3 kcal/mol and 45.9 kcal/mol to 36.2 kcal/mol. Analysis of the activation energies given in Table 5 allows drawing the following conclusions: the trends in the activation associated with the 32CA reactions of C-phenyl, N-methyl nitrene with the methyl substituted 7-isopropylidenenorbornadiene are similar to those associated with the 32CA reactions involving methyl nitrene, thus supporting methyl nitrene as a reduced model for the experimental phenyl nitrene.

#### 3.2.2. Substituent effects on the reactions of DENBD to C, N-dimethyl nitrenes

The effects of various substituents on the reactivity and selectivities of different substituted 7-isopropylidenenorbornadiene have been investigated to gain insight into the various factors that control the selectivities of the eight different reaction channels. The reactivity and selectivities were studied from determination of the mechanistic routes of the reaction of various substituted norbornadiene with C, N-dimethyl nitrene.

The goal of this section of the study is to predict the type of

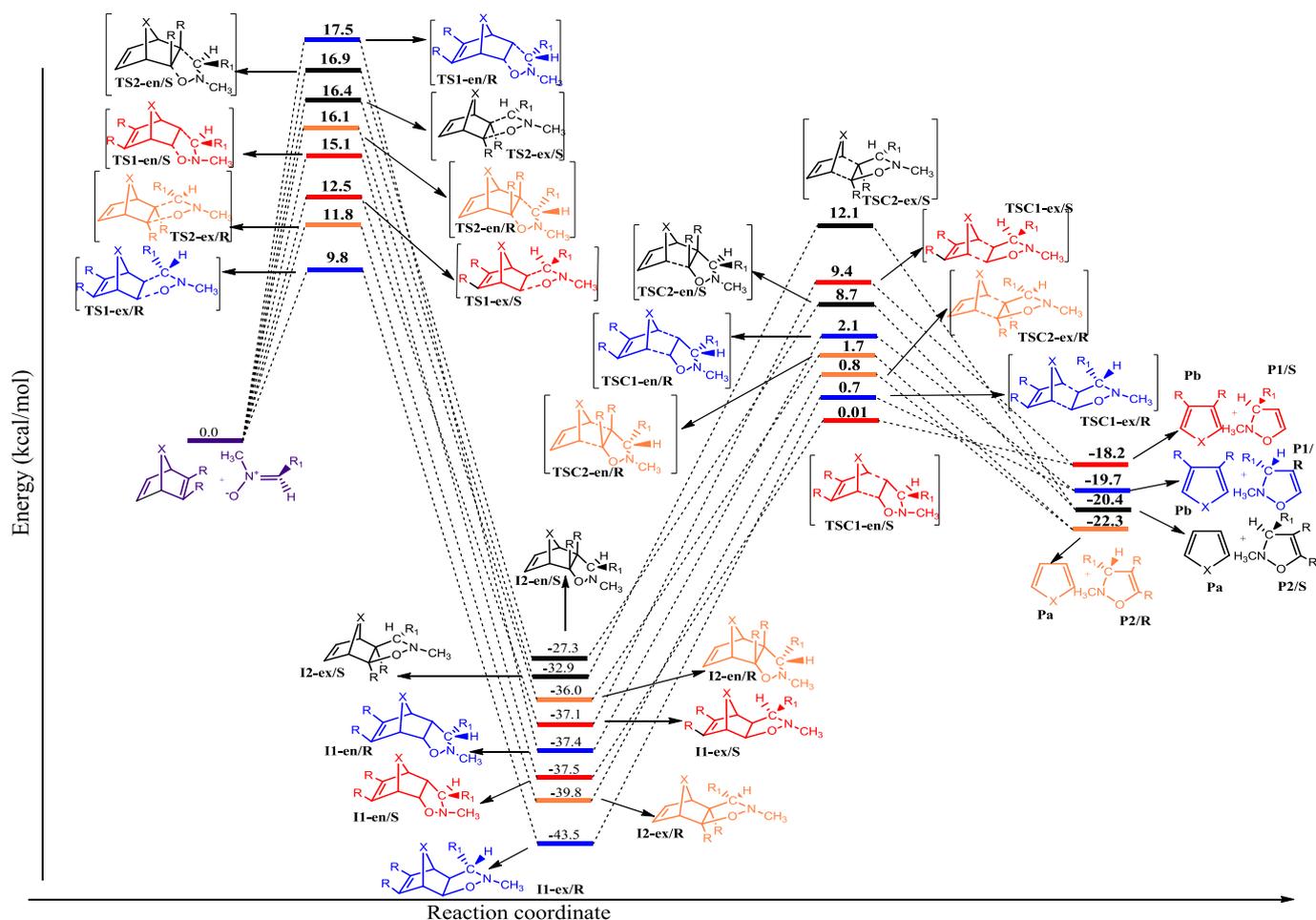


Fig. 2. Free energy profile for the (3 + 2) addition of methyl substituted 7-isopropylidenenorbornadiene to phenyl nitrene. Relative energies in kcal/mol.

**Table 2**  
Activation energies (kcal/mol) for the species involved in the 32CA Reactions of phenyl nitrene and methyl nitrene with methyl substituted norbornadiene at the M06/6-31G(d) level of theory.

| Specie   | Phenyl nitrene | Methyl nitrene | Specie    | Phenyl nitrene | Methyl nitrene |
|----------|----------------|----------------|-----------|----------------|----------------|
| TS1-ex/S | 12.5           | 8.5            | TSC1-ex/S | 46.5           | 45.9           |
| TS1-ex/R | 9.8            | 3.2            | TSC1-ex/R | 44.2           | 43.7           |
| TS1-en/S | 15.1           | 10.0           | TSC1-en/S | 37.5           | 39.0           |
| TS1-en/R | 17.5           | 8.9            | TSC1-en/R | 39.5           | 38.5           |
| TS2-ex/S | 16.4           | 12.2           | TSC2-ex/S | 44.9           | 41.8           |
| TS2-ex/R | 11.8           | 5.8            | TSC2-ex/R | 40.6           | 40.2           |
| TS2-en/S | 16.9           | 9.9            | TSC2-en/S | 35.9           | 36.2           |
| TS2-en/R | 16.1           | 10.0           | TSC2-en/R | 37.8           | 37.6           |

**Table 3**  
Activation energies of transition states and reaction energies (in kcal/mol) of intermediates for the cycloaddition of CH<sub>3</sub>, NH<sub>2</sub>, OMe, and OH-substituted 7-isopropylidenenorbornadiene to C, N-dimethyl nitrene.

| Substituents | TS1-ex/S | TS1-en/R | TS1-en/S | TS1-en/R | TS2-ex/S | TS2-ex/R | TS2-en/S | TS2-en/R | I1-ex/S | I1-ex/R | I1-en/S | I1-en/R | I2-ex/S | I2-ex/R | I2-en/S | I2-en/R |
|--------------|----------|----------|----------|----------|----------|----------|----------|----------|---------|---------|---------|---------|---------|---------|---------|---------|
| Amine        | 7.5      | 2.3      | 7.5      | 7.4      | 10.2     | 4.0      | 9.8      | 6.7      | -47.4   | -51.8   | -45.9   | -47.0   | -46.7   | -51.6   | -44.4   | -47.9   |
| Methyl       | 8.5      | 3.2      | 10.0     | 8.9      | 12.2     | 5.8      | 9.9      | 10.0     | -45.4   | -49.8   | -45.4   | -45.5   | -40.9   | -45.6   | -40.1   | -43.2   |
| Hydroxy      | 7.3      | 2.6      | 5.2      | 3.9      | 7.3      | -0.03    | 6.3      | 4.0      | -46.8   | -51.4   | -48.9   | -51.2   | -55.6   | -60.1   | -54.5   | -55.0   |
| Methoxy      | 10.7     | 3.3      | 6.9      | 9.5      | 9.3      | 5.8      | 16.9     | 14.0     | -45.3   | -50.1   | -47.0   | -49.2   | -43.2   | -51.8   | -44.1   | -43.6   |

**Table 4**

Activation and reaction energies (kcal/mol) of transition states and products for cycloreversion of CH<sub>3</sub>, NH<sub>2</sub>, OMe, and OH-substituted cycloadduct to isoxazolidines and dimethyl fulvene.

| Substituents | TSC1-ex/S | TSC1-ex/R | TSC1-en/S | TSC1-en/R | TSC2-ex/S | TSC2-ex/R | TSC2-en/S | TSC2-en/R | P1/S +Pa | P1/R +Pa | P1/S +Pa | P1/R +Pa | P2/S +Pb | P2/R +Pb | P2/S +Pb | P2/R +Pb |
|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Amine        | 41.8      | 40.4      | 37.8      | 37.9      | 44.5      | 40.2      | 35.7      | 37.9      | 18.6     | 20.0     | 17.1     | 15.4     | 18.3     | 20.8     | 15.9     | 17.2     |
| Methyl       | 45.9      | 43.7      | 39.0      | 38.5      | 41.8      | 40.2      | 36.2      | 37.6      | 20.0     | 21.6     | 19.9     | 17.2     | 13.7     | 15.8     | 12.8     | 13.5     |
| Hydroxy      | 42.2      | 40.8      | 37.8      | 37.7      | 51.5      | 50.4      | 47.6      | 47.5      | 15.8     | 17.4     | 17.8     | 17.2     | 31.6     | 33.6     | 30.6     | 28.5     |
| Methoxy      | 43.7      | 42.1      | 37.5      | 37.8      | 43.9      | 45.2      | 41.3      | 43.8      | 16.9     | 18.8     | 18.6     | 17.9     | 19.8     | 25.8     | 20.8     | 17.6     |

**Table 5**

Activation energies (kcal/mol) for the species involved in the 32CA Reactions of phenyl nitron and methyl nitron with cyano-substituted DENBD at the M06/6-31G(d) level of theory.

| Specie          | Phenyl nitron | Methyl nitron | Specie           | Phenyl nitron | Methyl nitron |
|-----------------|---------------|---------------|------------------|---------------|---------------|
| <b>TS1-ex/S</b> | 11.3          | 6.7           | <b>TSC1-ex/S</b> | 42.9          | 36.7          |
| <b>TS1-ex/R</b> | 8.5           | 1.8           | <b>TSC1-ex/R</b> | 37.6          | 36.7          |
| <b>TS1-en/S</b> | 13.7          | 7.8           | <b>TSC1-en/S</b> | 33.5          | 33.8          |
| <b>TS1-en/R</b> | 14.7          | 6.6           | <b>TSC1-en/R</b> | 35.7          | 34.9          |
| <b>TS2-ex/S</b> | 8.1           | 3.4           | <b>TSC2-ex/S</b> | 36.7          | 34.7          |
| <b>TS2-ex/R</b> | 4.1           | -3.7          | <b>TSC2-ex/R</b> | 34.3          | 33.1          |
| <b>TS2-en/S</b> | 10.7          | 0.1           | <b>TSC2-en/S</b> |               | 29.9          |
| <b>TS2-en/R</b> | 14.2          | 6.9           | <b>TSC2-en/R</b> | 28.5          | 27.7          |

substituents that these substrates must contain to influence particular product outcomes.

### 3.2.3. Effects of electron-donating groups on the reaction

The effects of electron-donating groups CH<sub>3</sub>, NH<sub>2</sub>, OMe, and OH on the 7-isopropylidenenorbornadiene by reaction with C, N-dimethyl nitron were also carried out.

Intermediates, products and transition states corresponding to all the eight channels of the proposed mechanisms depicted in Schemes 2 and 3 were located. The transition-states structures and the relative energies for the reaction pathways are detailed in Fig. 3. Replacing the methyl groups on the 7-isopropylidenenorbornadiene substrate of the reaction with OCH<sub>3</sub> favors attack of the nitron via path A just as was observed in methyl substituted 7-isopropylidenenorbornadiene. The transition state with the least activation energy was found to be **TS1-ex/R** with a barrier of 3.3 kcal/mol. Again, the reaction was found to be slightly regioselective with **TS1-ex/R** being 2.5 kcal/mol lower than its corresponding **TS2-ex/R**, fairly enantioselective with **TS1-ex/R** being 6.2 kcal/mol lower in energy than the corresponding enantiomer, and highly *exo* stereoselective with the transition state for the *exo* stereoisomer being 7.4 kcal/mol lower in energy than that for the *endo* stereoisomer. Intermediates and products from these reactions are slightly more stable compared to those for the methyl substituted NBD. Replacing the methoxy groups on the NBD substrate with NH<sub>2</sub> produces the same trends. However, the barriers are relatively lower, intermediates are relatively stable and the barriers for the cycloreversion steps are slightly higher with products that are slightly more stable compared to when methyl and methoxy groups were on the dipolarophile.

Analysis of the transition states of the reaction of methyl nitron with OH substituted 7-isopropylidenenorbornadiene shows that the nitron attack will be along path A. However, the trends in the stereo- and enantioselectivities remains the same as observed for the other substituents.

The geometries of the products arising from the Diels-Alder cycloreversion of the various cycloadducts formed from reactions of C, N-dimethyl nitron with methoxy substituted 7-isopropylidenenorbornadiene are displayed in Fig. S2.

Tables 3 and 4 give the activation and reaction energies of the various electron donating substituents considered in this study.

### 3.2.4. Effects of electron-withdrawing groups on the reaction

The effects of electron-withdrawing groups CHO, NO<sub>2</sub>, Br, and CN on the 7-isopropylidenenorbornadiene were carried out. Generally, the electron-withdrawing groups on the dipolarophile substrate favors nitron attack on the dipolarophile via path B. To investigate the effects of different **R**<sub>1</sub> groups on the selectivities of the reaction, the reactions of C-Phenyl, N-methyl nitron and C, N-dimethyl nitron to CN-substituted DENBD were studied.

The energy profiles corresponding to the eight pathways for the reaction of C-Phenyl, N-methyl nitron to CN-substituted DENBD at the DFT M06/6-31G(d) are displayed in Fig. 4.

Replacing the ester groups on the 7-isopropylidenenorbornadiene substrate of the reaction with cyano groups also favors attack of nitron via path B. The transition states **TS1-ex/S**, **TS1-ex/R**, **TS1-en/S**, **TS1-en/R**, **TS2-ex/S**, **TS2-ex/R**, **TS2-en/S** and **TS2-en/R** have been computed at the M06/6-31G(d) level of theory. The calculated activation energies suggest that the **TS2-ex/R** leading to the formation of the cycloadduct **I2-ex/R** is energetically favoured by 4.4 kcal/mol compared to the corresponding **TS1-ex/R** and highly stereoselective in that, **TS2-ex/R** is 10.1 kcal/mol lower in energy than the corresponding **TS2-en/R**, and slightly enantioselective with **TS2-ex/R** being 4.0 kcal/mol lower in energy than the corresponding **TS2-ex/S**. Again, the possibility of a smaller **R**<sub>1</sub> group altering the enantioselectivities of the reaction was explored by replacing the phenyl group on the nitron with a methyl group. Analysis of the energetics showed that this group does not modify the enantioselectivities; however, slight changes are observed in the stereoselectivities of the reactions. It has been observed that the activation energies for the formation of the *endo* cycloadducts are relatively lower than those for the formation of the *exo* cycloadducts.

### 3.2.5. The reaction of methyl nitron with CHO-, Br-, NO<sub>2</sub>-substituted DENBD

The reaction and activation energies corresponding to eight reaction channels of the 1,3-dipolar cycloaddition reactions between C, N-dimethyl nitron and DENBD derivatives calculated at the M06/6-31G(d) level of theory are displayed in Tables 6 and 7. At first sight it is clear that the most favourable pathway for the reaction is through channel **TS2-ex/R** in all cases. However, it is worth noting that the activation energies are negative. These transition states have thus been examined and re-located with M06/6-31G(d),

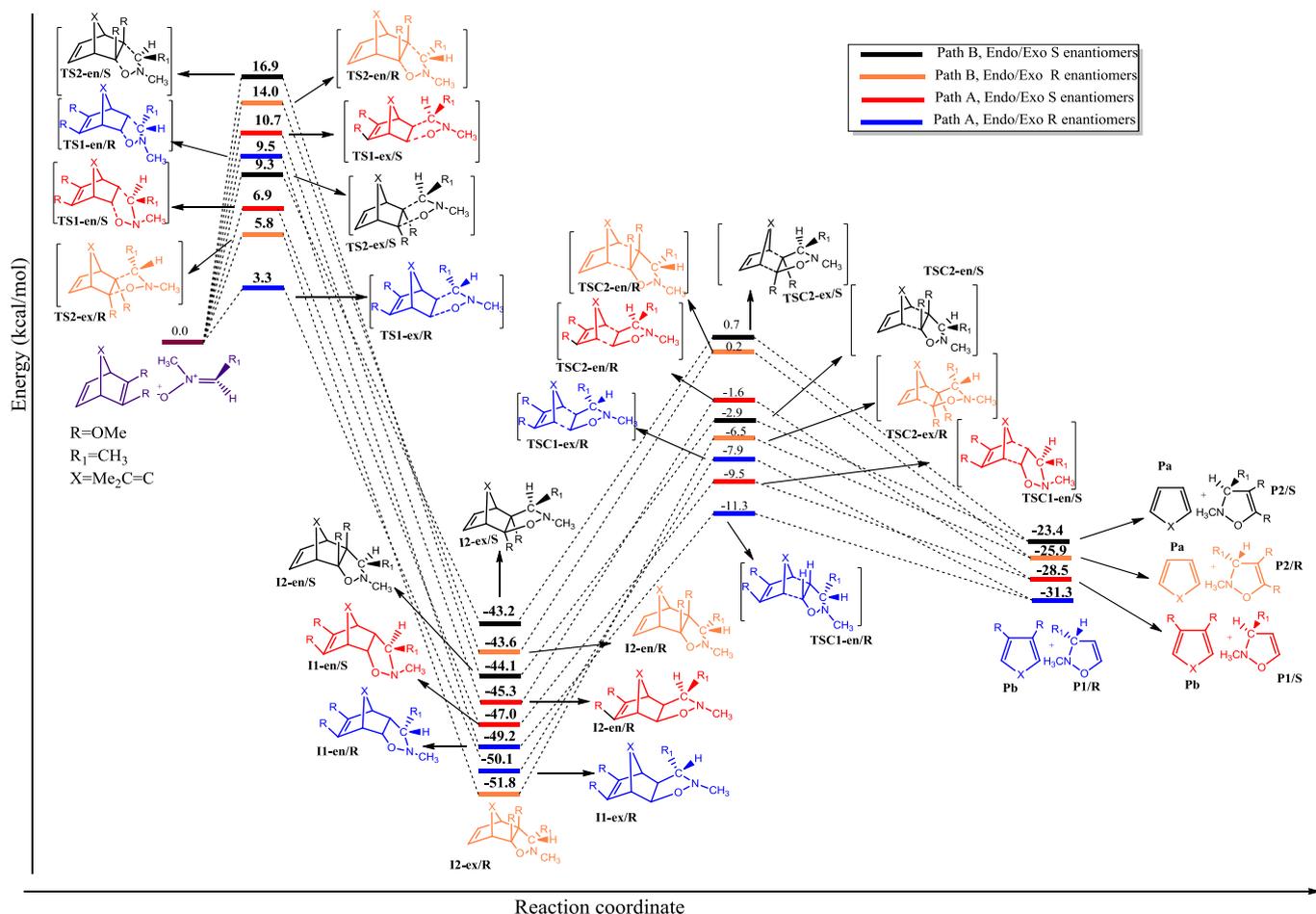


Fig. 3. Free energy profile for the (3 + 2) addition of OMe substituted 7-isopropylidenebornadiene to methyl nitrone. Relative energies in kcal/mol.

p), M06/6-311G (d, p) M06-2x/6-31G(d) and M06/6-311++G (d, p) levels of theory and the results are shown in Table S1. The calculated energies suggest that higher basis sets generally raised some of the barriers above zero. Hence, the initial negative activation barriers observed with the M06/6-31G(d) could be attributed to basis set superposition errors.

### 3.3. The effects of temperature on the Diels-Alder cycloreversion reaction

The geometries of the transition states involved in the Diels-Alder cycloreversion of the various cycloadducts formed from reactions of C-phenyl N-methyl nitrone with methyl substituted 7-isopropylidenebornadiene including the bond distances between the two carbon and carbon nuclei involved the Diels-Alder cycloreversion reaction are displayed in Fig. 5.

While the factors that influence the rate of the Diels-Alder reactions are rather well established, there remains little predictive ability in knowing at what temperature a retro-Diels-Alder reaction will occur [42]. In principle, it becomes thermodynamically favorable for the DA reactions to proceed in the reverse direction if the temperature is high enough. In practice however, this reaction generally proceeds at temperatures of synthetic relevance. Even though the cycloadducts in these reactions were formed by 32CA reactions, Cristina et al. [14] had proposed that these thermally labile cycloadducts formed from the 32CA reactions of various 1,3 dipoles with norbornadiene derivatives would undergo Diels-Alder

cycloreversion to yield the various five-membered rings. However, in the case of the nitrone, they had isolated the intermediates rather than the five membered rings. Analysis of the transition states involved in the cycloreversion step of the reaction shows that, the energy barriers are far too high and the products are far less stable than the cycloadducts, suggesting that the isolable products are the isoxazolidine cycloadducts and not the thermolysis products. The effects of varying temperatures on the reaction was studied at temperatures of 298K, 398K, 423K, 473K and 673K. In general, it is observed that temperature has negligible effects on the energetics of the reaction as shown in Table S2.

### 3.4. Normal versus inverse electron demand cycloadditions

From literature, the dipolar cycloaddition reaction of some dipoles such as nitrones, nitrile imines and carbonyl oxides with dipolarophiles can proceed in two ways: the HOMO of the dipole can pair with LUMO of the dipolarophile (normal electron demand additions); alternatively, the HOMO of the dipolarophile can pair with LUMO of the dipole (inverse electron demand additions). This two-way interaction arises because the energy gap in either direction is similar; however, any substituent on the dipolarophile would accelerate the reaction by raising or lowering the energy gap between the two interacting orbitals. The calculated HOMO and LUMO energy for the dipole are  $-5.85$  eV and  $-1.12$  eV respectively and that for the dipolarophile are  $-6.21$  eV and  $-1.57$  eV respectively (Fig. 6). The dominant pathway is the one which possesses

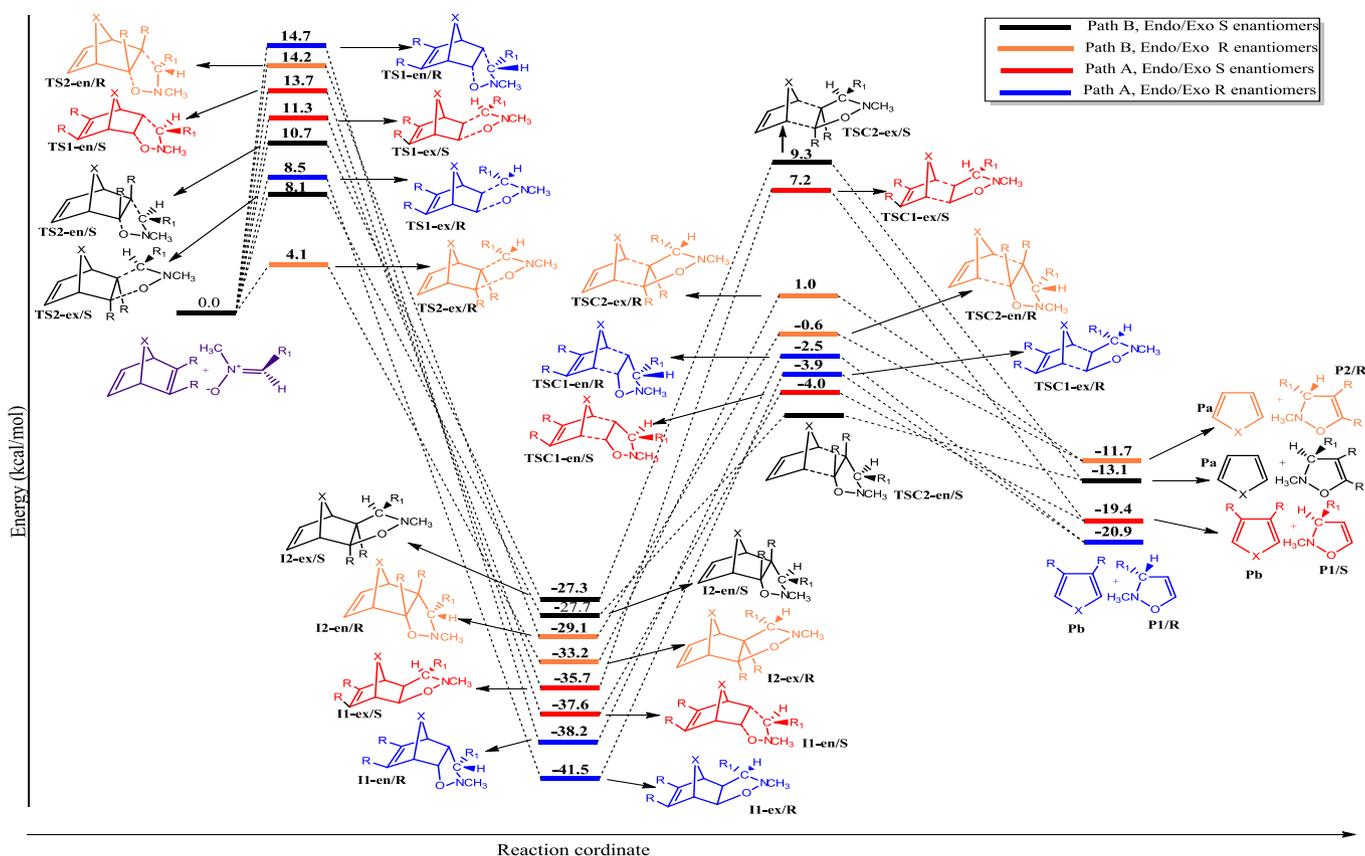


Fig. 4. Gibbs free energy profile for the (3 + 2) addition of cyano-substituted DENBD to phenyl nitrone. Relative energies in kcal/mol.

Table 6

Reaction and activation energies (kcal/mol) of transition state and intermediates for the cycloaddition of 7-isopropylidenenorbornadiene to dimethyl nitrone.

| Substituents | TS1-ex/S | TS2-en/R | TS3-en/S | TS4-en/R | TS5-ex/S | TS6-ex/R | TS7-en/S | TS8-en/R | I1-ex/S | I1-ex/R | I1-en/S | I1-en/R | I2-ex/S | I2-ex/R | I2-en/S | I2-en/R |
|--------------|----------|----------|----------|----------|----------|----------|----------|----------|---------|---------|---------|---------|---------|---------|---------|---------|
| Carbonyl     | 7.4      | 2.7      | 7.1      | 4.9      | 0.9      | -6.3     | -0.03    | 2.2      | -44.1   | -48.8   | -46.7   | -47.1   | -32.7   | -37.2   | -36.3   | -35.5   |
| Bromo        | 7.0      | 2.1      | 5.8      | 4.1      | 2.8      | -3.6     | 1.8      | 5.4      | -44.6   | -49.7   | -48.6   | -47.9   | -48.6   | -56.6   | -53.8   | -53.2   |
| Nitro        | 6.1      | 1.2      | 6.3      | 4.7      | -        | -        | -        | -        | -44.6   | -49.7   | -48.6   | -47.9   | -48.6   | -56.6   | -53.8   | -53.2   |

Table 7

Reaction and activation energies (Kcal/mol) of transition states and products for cycloreversion of cycloadduct to isoxazolidines and dimethyl fulvene.

| Substituents | TSC1-ex/S | TSC2-ex/R | TSC3-en/S | TSC4-en/R | TSC5-ex/S | TSC6-ex/R | TSC7-en/S | TSC8-en/R | P1/S +Pa | P1/R +Pa | P1/S +Pa | P1/R +Pa | P2/S +Pb | P2/R +Pb | P2/S +Pb | P2/R +Pb |
|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Carbonyl     | 34.9      | 33.7      | 33.5      | 34.7      | 23.7      | 23.4      | 21.0      | 20.8      | 16.3     | 18.1     | 18.9     | 16.6     | 9.3      | 11.3     | 12.8     | 9.2      |
| Bromo        | 41.6      | 40.6      | 38.3      | 38.8      | 46.6      | 46.9      | 42.9      | 41.6      | 25.1     | 22.6     | 27.0     | 20.2     | 28.2     | 31.6     | 32.4     | 27.8     |
| Nitro        | 29.3      | 29.2      | 29.6      | 30.9      | 30.6      | 43.4      | 38.8      | 32.5      | 14.9     | 17.1     | 18.9     | 15.4     | 29.3     | 33.9     | 34.1     | 30.5     |

the smallest HOMO-LUMO energy gap. In the case of the ester-substituted DENBD, the gap between the LUMO of the dipole (phenyl nitrone) and the HOMO of the dipolarophile is calculated to be 5.09 eV meanwhile the gap between the HOMO of the dipole and the LUMO of the dipolarophile is 4.28 eV, suggesting that this reaction is a normal electron demand cycloaddition.

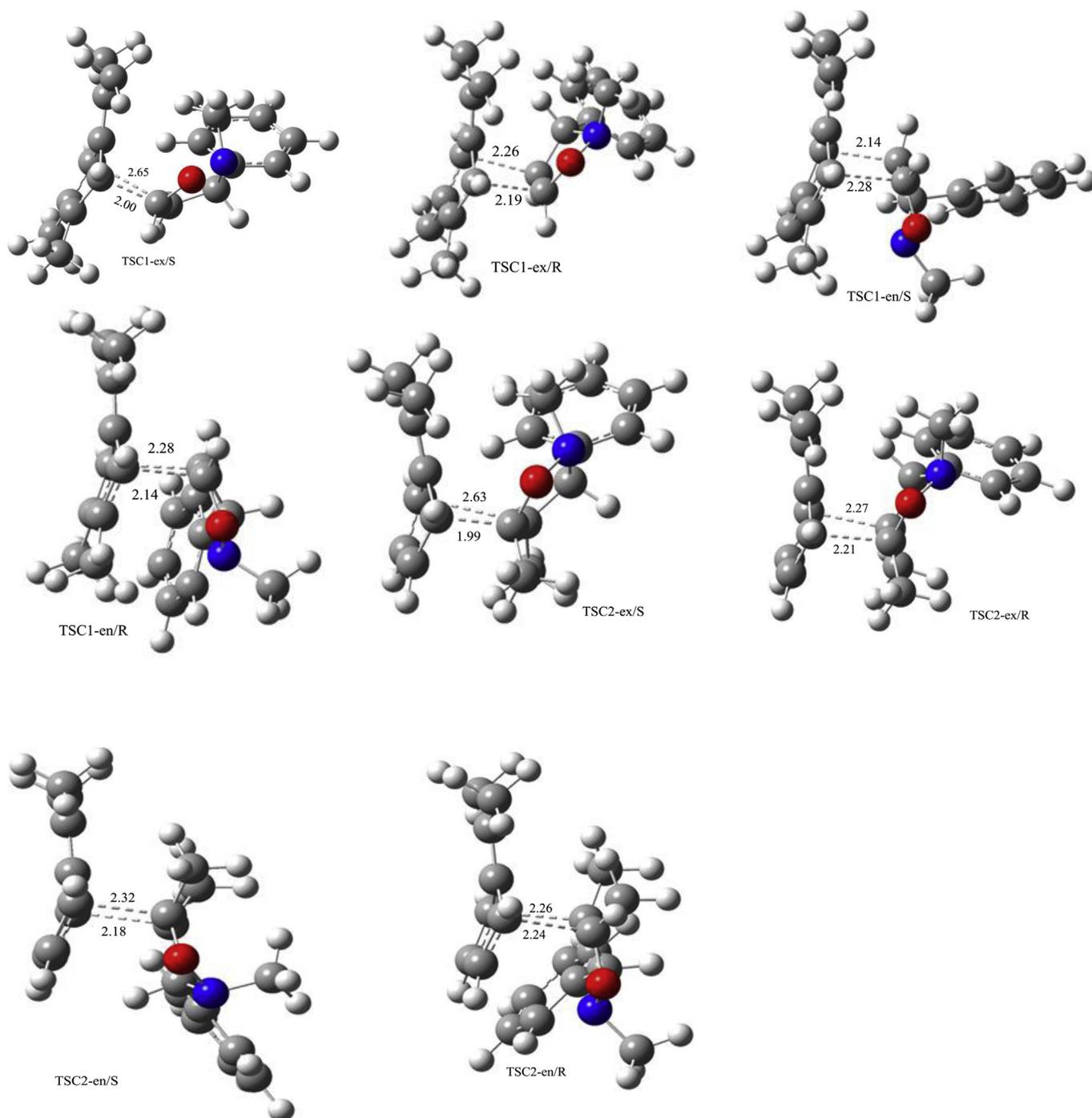
### 3.5. Analysis of the global reactivity indices

The electrophilicity index ( $\omega$ ) is used as a parameter for the analysis of the chemical reactivity of molecules. The compound with the largest electrophilicity index value will be the best electrophile given in a series of molecules.

Species with large electrophilicity values ( $\omega$ ) are more reactive

towards nucleophiles. From Table 8, the electrophilicities of the various DENBD derivatives is given in the order  $\text{NO}_2 > \text{CHO} > \text{CN} > \text{CO}_2\text{Me} > \text{Br} > \text{NH}_3 > \text{OH} > \text{CH}_3 > \text{OCH}_3$ , making the nitro-substituted DENBD the most electrophilic and hence the most reactive towards the nucleophilic nitrone, and the methoxy-substituted DENBD is the least electrophilic. Indeed, trends in the activation energies agree well with the electrophilicity index values as shown above.

On the other hand,  $\Delta N_{\text{max}}$  measures the electronic charge that the electrophile may accept during chemical transformation. Similar observations are also made for the computed  $\Delta N_{\text{max}}$  values, where substrates with small  $\Delta N_{\text{max}}$  values are found to have lower activation energies. The local electrophilicities, the electronic chemical potential and the chemical hardness are given in Table 8.



**Fig. 5.** Gas phase optimized geometries of the reactants and TSs involved in the Diels-Alder cycloreversion of cycloadducts formed from the 32CA of phenyl nitron with methyl-substituted DENBD. Distances are given in Å.

### 3.6. Analysis of selectivities with the parr functions

The Mulliken and NBO atomic spin densities (ASD) at the cycloaddition centers give a quantitative measure of their electron density. Therefore, atomic centers with the largest Mulliken and NBO spin densities in a given molecule will be the most favored point of attack during the cycloaddition reaction. In this study, Ester substituted DENBD and C-Phenyl, N-methyl nitron were arbitrary selected to investigate their selectivity. Results obtained from the Mulliken and NBO spin densities calculations are summarized in [Table S3](#).

Analysis of two olefinic centers of the dipolarophile (ester-substituted DENBD) in the results show that, for the electrophilic Mulliken spin densities,  $C_6 = -0.051$ ,  $C_7 = -0.061$ ,  $C_9 = 0.089$  and  $C_{10} = 0.096$ . Therefore, it is predicted that in the course of the cycloadditions, the most favorable nucleophilic/electrophilic interactions will occur between the  $O_5$  and  $C_{16}$  of the dipole and the  $C_9$  and  $C_{10}$  double bond of the dipolarophile which is well consistent with the energetic trends and experimental product outcomes.

Similarly, analysis of the electrophilic NBO spin densities reveal that  $C_6 = -0.082$ ,  $C_7 = -0.095$ ,  $C_9 = -0.071$  and  $C_{10} = -0.036$ . Again, based on the results, it is expected that in the course of the

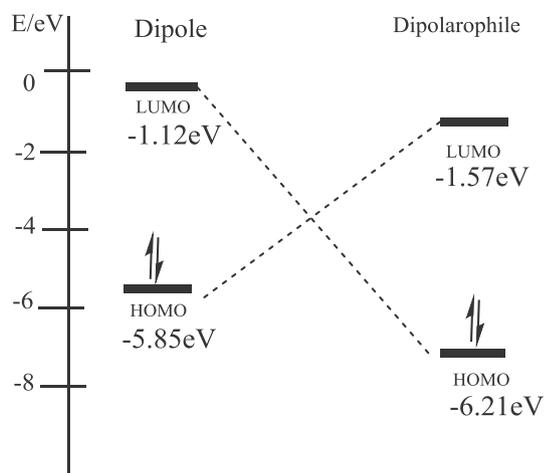


Fig. 6. Graphical depiction of the HOMOs and LUMOs of the phenyl nitrene and DENBD.

Table 8

Global electrophilicities for various-substituted DENBD. Orbital energies are in electron volts (eV).

| Substituent    | HOMO  | LUMO  | $\mu$ | $\eta$ | $\omega$ | $\Delta N_{max}$ |
|----------------|-------|-------|-------|--------|----------|------------------|
| Amine          | -4.45 | 0.75  | -1.85 | 5.20   | 0.32     | 0.36             |
| Bromo          | -6.01 | -0.47 | -3.24 | 5.54   | 0.95     | 0.58             |
| CHO            | -6.46 | -2.63 | -4.54 | 3.83   | 2.69     | 1.19             |
| CN             | -6.80 | -2.39 | -4.59 | 4.41   | 2.39     | 1.04             |
| OMe            | -5.17 | 0.44  | -2.37 | 5.62   | 0.50     | 0.42             |
| Ester          | -6.16 | -1.56 | -3.86 | 4.60   | 1.62     | 0.84             |
| Methyl         | -5.48 | 0.44  | -2.52 | 5.92   | 0.54     | 0.43             |
| Nitro          | -6.94 | -3.13 | -5.04 | 3.81   | 3.33     | 1.32             |
| OH             | -5.11 | 0.45  | -2.33 | 5.56   | 0.49     | 0.42             |
| Methyl nitrene | -5.91 | -0.22 | -3.06 | 5.69   | 0.82     | 0.54             |
| Phenyl nitrene | -5.81 | -1.11 | -3.46 | 4.69   | 1.28     | 0.74             |

cycloaddition reaction, the nitrene will preferentially add across carbons C<sub>9</sub> and C<sub>10</sub> which is well consistent with the energetic trends and experimental product outcomes. The atomic labels present in the ester substituted DENBD and the C-Phenyl, N-methyl nitrene are shown in Fig. 7 for clarity sake.

### 3.7. The reaction of DENBD with phenyl azide

This present work has been extended to rationalize the

reactivity and selectivity of phenyl azide as a dipole in these cycloadditions.

The 1,3 dipolar cycloaddition reaction of phenyl azide with 7-isopropylidenenorbornadiene can proceed along four possible reaction as displayed in Scheme 4. The energy profiles corresponding to the four reaction channels calculated at the M06/6-31G(d) level of theory are displayed in Fig. 8. Analysis of the relative energies shows that **TS2-ex** regioisomeric transition state is again predicted to be favored in the gas phase by 1.6 kcal/mol. However, this reaction can be said to be slightly regioselective, in that the difference in energy between this **TS2-ex** and its corresponding regioisomer **TS1-ex** is about 1.6 kcal/mol. These transition states lead to the formation of cycloadducts **I1-ex** and **I2-ex**. These reactions however are highly stereoselective in that the barriers for the formation of the endo products are relatively higher compared to that for the exo products. Unlike the nitrenes that favored the formation of the intermediates over the products, analysis of the transition states involved in the Diels-Alder cycloreversion shows that **I1-ex** and **I2-ex** cleaves to form their respective products with relatively smaller activation energies. In this step, formation of **P1 + Pa** is favored because the barrier for that step is quite lower and the products formed are quite stable. It is important to note that, at the cycloreversion step, the stereoselectivity of the reaction is lost, ergo both **I1-ex** and **I1-en** would form the same products (**P1 + Pa**), likewise **I2-ex** and **I2-en** form **P2 + Pb**.

## 4. Conclusion

The results of the study show that in the 1,3-dipolar (3 + 2) cycloaddition reaction between C, N-disubstituted nitrenes with norbornadiene derivatives, the reaction proceeds via path A (addition across the least substituted double bond of the DENBD substrate) when the substituent R is an electron-donating group and path B (addition across the highly substituted double bond of the DENBD substrate) when R is an electron-withdrawing group. The formation of the *R* enantiomer is favoured over the *S* and this could be due to steric interactions between the R<sub>1</sub> group and the ethylene substituent on the norbornadiene derivative. Generally, the barrier for the formation of the *exo* products is much lower compared to that of the *endo* products.

Temperature has no significant effects on the energetic trends of the reaction. Solvent (benzene) is seen to increase the activation energies by up to 3 kcal/mol but practically does not modify the selectivities observed in the gas phase. The Diels-Alder cycloreversion steps have generally high barriers, with the lowest being 20 kcal/mol, suggesting that the isolable products are the

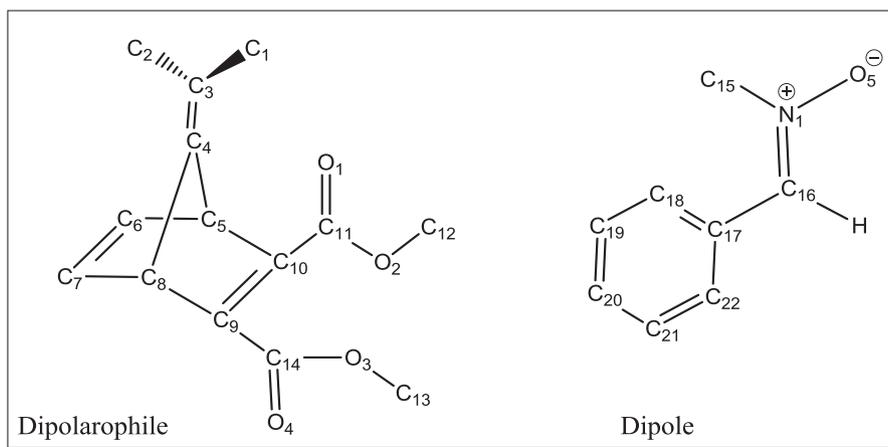


Fig. 7. Atomic labels of the dipolarophile and the dipole.

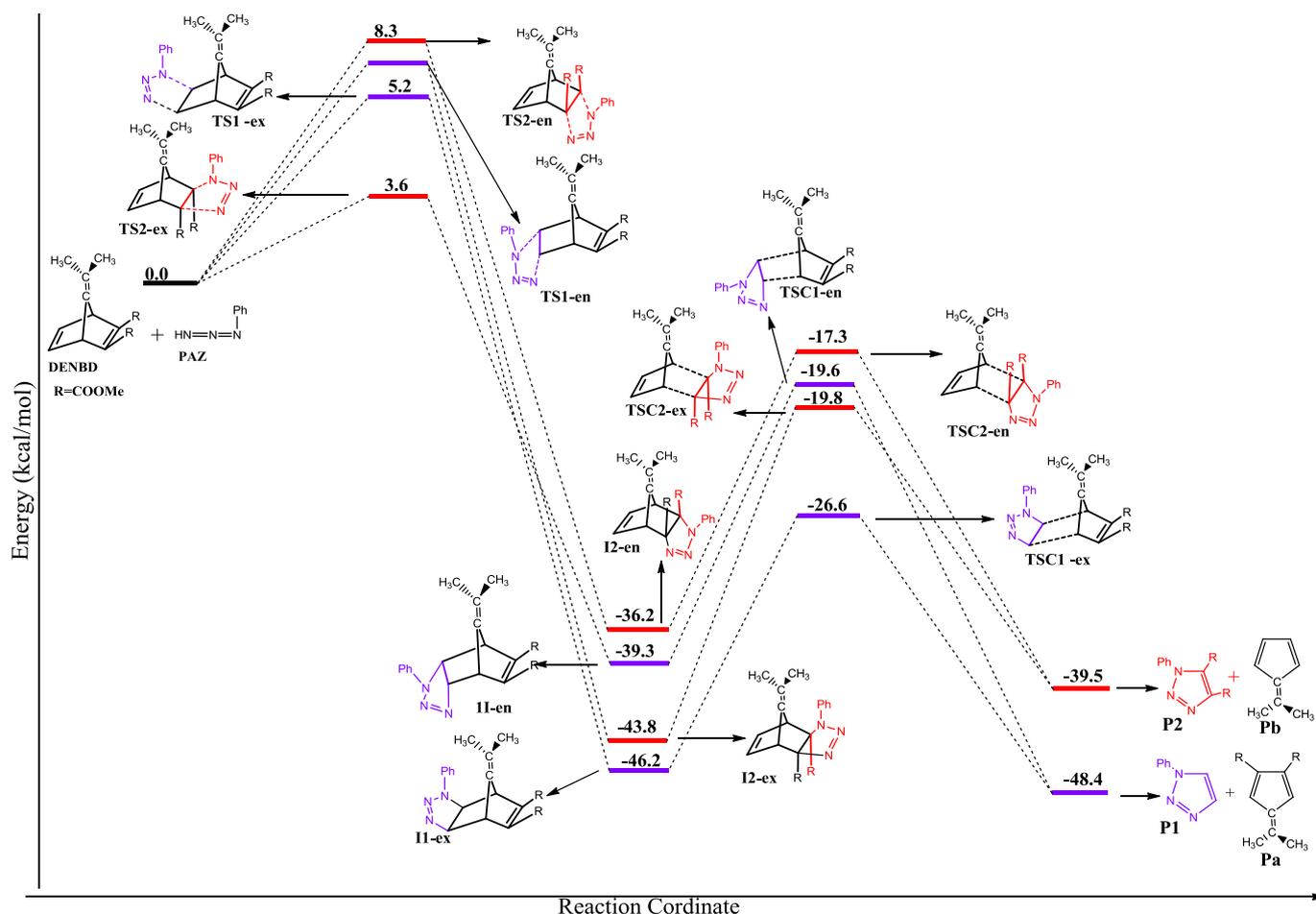


Fig. 8. Gibbs free energy profile for the (3 + 2) addition of ester-substituted DENBD to phenyl azide. Relative energies in kcal/mol.

isoxazolidine cycloadducts and not the thermolytic products (five membered rings isoxazolidine and dimethyl fulvene).

Results from the global reactivity indices (global electrophilicities and maximum electronic charge transfer) calculations gave the same energetic patterns as that dictated by the activation energies. Also, results obtained from the Parr functions revealed that the cycloaddition occurs between atomic centres with the largest Mullikan and NBO atomic spin densities.

In the reaction of phenyl azide with DENBD, ratio of varying selectivities were observed. These energetic trends reported are in complete agreements with the experimental product outcomes. The Diels-Alder cycloreversion step has relatively lower activation barriers with the highest being 24 kcal/mol and so the isolable products in this reaction are the phenyl triazoles and the dimethyl fulvene.

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#### Conflicts of interest

The authors declare that they have no conflict of interest whatsoever regarding this manuscript.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmgm.2019.08.004>.

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