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Trapping of 1,2-cyclohexadiene: A DFT mechanistic study on the reaction of 1,2-cyclohexadiene with olefins and nitrones

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ABSTRACT

The mechanistic aspects of cycloaddition reactions of 1,2-cyclohexadiene with olefins and nitrones have been investigated with DFT calculations. The results show that the cycloaddition reactions of 1,2-cyclohexadiene with olefins do not go through a concerted pathway (one-step mechanism) but rather a stepwise one involving the formation of a biradical intermediate which then closes to form final cycloadduct. Electron-withdrawing substituents on the 1,2-cyclohexadiene decrease the activation barrier of the biradical-forming step but increase the barrier of the product-forming step and product stability, while electron-donating substituents on the 1,2-cyclohexadiene increase the barriers for both the biradical-forming step and the product-forming step but decrease the product stability. In the reaction of 1,2-cyclohexadiene with nitrones, the four pathways investigated have activation barriers within 1 kcal/mol of one another, the lowest being 10.45 kcal/mol and the highest 11.04 kcal/mol, indicating that these reactions are very unselective. Electron-withdrawing groups on the nitrone increase the stability of the resulting products whereas electron-donating group on the nitrone decrease the stability of the resulting products. The [3 + 2] cycloadduct proceeds to the formation of a more stable formal [5 + 2] cycloadduct if a phenyl substituent is present on the nitrogen of the nitrone.

1. Introduction

1,2-Cyclohexadiene, a cyclic allene, is a highly strained reactive intermediate that usually serves as a useful synthetic building block in chemical synthesis [1–18]. Being highly reactive and unstable, 1,2-cyclohexadiene is usually generated *in situ* and trapped for subsequent conversion to useful products, to prevent it from undergoing dimerization or cyclization. 1,2-cyclohexadiene reacts with nitrones and olefins in trapping reactions to yield isoxazolidines and bicyclo (4.2.0) oct-1-enes respectively, which are useful synthetic building blocks and have been shown to have medicinal applications [1].

The existence of 1,2-cyclohexadiene was not discovered until 1966, which is due to its high reactivity as a result of its rapid dimerization at low temperatures and cyclization at high temperatures [2]. The dimerization and cyclization of the 1,2-cyclohexadiene are seen to proceed via two steps, first the formation of a diallylene which either dimerizes or cyclizes to an unwanted product depending on the temperature [3]. This finding underscored the need to appropriately trap 1,2-cyclohexadiene to allow its use as a building block in chemical synthesis.

1,2-cyclohexadiene is known to undergo a number of reactions. It was observed by Wittig et al. [2] to react with 1,3-diphenylisobenzofuran in a [4 + 2] fashion to produce two stereo-adducts – the *endo* being the major and the *exo* the minor in a combined yield of 37%. Reaction of 1,2-cyclohexadiene with styrene has been found [3] to be mostly a [2 + 2] cycloaddition which yields two stereoisomers (exo-major isomer and endo-minor isomer in a ratio of 2.2:1) indicating the stereo-selectivity of the 1,2-cyclohexadiene intermediates. However, it could not be settled conclusively whether the reaction proceeds by a stepwise or concerted pathway as some experimental results [2–4] suggest a concerted [4 + 2] cycloaddition and others [3,4] suggest a stepwise [2 + 2] cycloaddition with conjugated dienes and styrenes. Even though concerted thermal [2 + 2] cycloaddition reactions are orbital forbidden, the strain imposed on cyclic reactive intermediates such as ketene and 1,2-cyclohexadiene makes it possible for them to undergo the concerted thermal [2 + 2] cycloaddition reaction. It was therefore initially proposed [3] that the reaction could proceed through both concerted and stepwise

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pathways but because the mode of dimerization of the 1,2-cyclohexadiene suggests a stepwise reaction pathway [3,8], it has been envisaged that the [2 + 2] cycloaddition reaction of the 1,2-cyclohexadiene will proceed through only stepwise reaction pathway with the formation of biradical intermediate which closes up to form product [3].

Even though strong evidence is lacking for the mechanism of the [4 + 2] cycloaddition of 1,2-cyclohexadiene, because of the high degree of regioselectivity in the reaction of the 1,2-cyclohexadiene with furan, a stepwise [4 + 2] cycloaddition reaction mechanism was proposed [2,4].

A density functional theory (B3LYP/6-31G*) study to investigate the mechanism of [3 + 2] cycloaddition reaction of 1,2-cyclohexadiene with nitrones suggest a competition of both stepwise and concerted pathways [5]. The [3 + 2] cycloaddition reaction mechanism is as a result of the experimentally-observed bond formation between the weak nucleophilic central carbon atom of the cyclic allene and an electrophilic carbon terminus of the nitrone (1,3-dipole) [6]. It was found from the calculations that, the reaction leads to the formation of an *endo* major product and an *exo* minor product for the stepwise pathway while the concerted pathway was postulated to give only an *endo* major product since no concerted *exo* transition state could be located [5].

Although it has been established that the [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with olefins proceeds via a stepwise reaction pathway to yield bicyclo (4.2.0) oct-1-ene [3,8,9], the mechanistic details have not been clearly elucidated. Moreover, computational studies done so far on the subject have investigated only the [3 + 2] cycloaddition reaction of 1,2-cyclohexadiene with nitrones [5], but the functional groups in the reactants point to the possibility of other cycloaddition modes in addition to the [3 + 2] mode. The nature of 1,2-cyclohexadiene and nitrone makes it possible for various reaction pathways - [2 + 2], [3 + 3] and formal [5 + 2] to be considered in addition to the [3 + 2] reaction pathway. The effects of substituents and temperatures have also not been investigated. This work therefore aims at studying computationally the [2 + 2], [3 + 2], [3 + 3] and formal [5 + 2] cycloaddition reactions of 1,2-cyclohexadiene with olefins and nitrones at the DFT M06/6-31G* level of theory to investigate the kinetically and thermodynamically preferred pathways as well as the effect of substituents and temperature on the energetics of the reactions. The optimized geometries and the relative energies of the reactants, transition states, intermediates and products along the proposed pathways (Schemes 1–4) are computed to provide molecular-level understanding into the plausible mechanistic channels of the reactions.

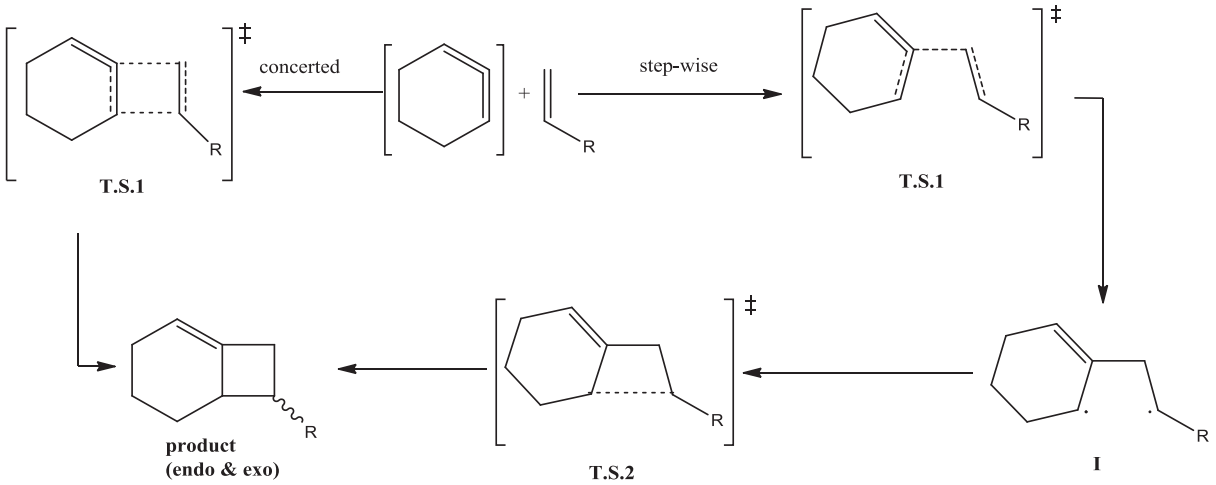
2. Computational details and methodology

All calculations were carried out with the Spartan '14 Molecular Modeling program [19] at the DFT M06/6-31G* level of theory. The selection of hybrid density functional theory method was based on efficiency and accuracy. The M06 functional is the most versatile of the Minnesota 06 functionals of Donald Truhlar, and the work of Ken Houk on the applications of these functionals on organic reactions has shown that these functionals have comparable accuracies to higher levels of theory [20–22]. The starting geometries of the molecular systems were constructed using Spartan's graphical model builder and minimized interactively using the MMFF force field. All geometries were fully optimized without any symmetry constraints. The optimized geometries were subjected to full frequency calculations to verify the nature of the stationary points. Equilibrium geometries were characterized by the absence of imaginary frequencies. The transition state structures were located by a series of constrained geometry optimizations in which the forming-bonds and breaking-bonds were fixed at various lengths while the remaining internal coordinates were optimized. The approximate stationary points located from such a procedure were then fully optimized using the standard transition state optimization procedure in Spartan. All first-order saddle-points were shown to have a Hessian matrix with a single negative eigenvalue, characterized by an imaginary vibrational frequency along the reaction coordinate. Intrinsic reaction coordinate (IRC) calculations were carried out to ensure that transition states smoothly connect reactants and products. The reported energies are Gibbs free energies with zero-point energy corrections.

3. Results and discussion

3.1. The reaction of 1,2-cyclohexadiene with olefins

Attempts to optimize transition states corresponding to the concerted (one-step) [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with ethylene, styrene and vinyl chloride resulted in structures shown in Fig. 1. The transition states bond lengths across C_1 and C_7 are 3.06, 3.18 and 3.57 Å for the reaction of 1,2-



Scheme 1. Proposed scheme for the [2 + 2] cycloaddion reaction of 1,2-cyclohexadiene with olefins [3].

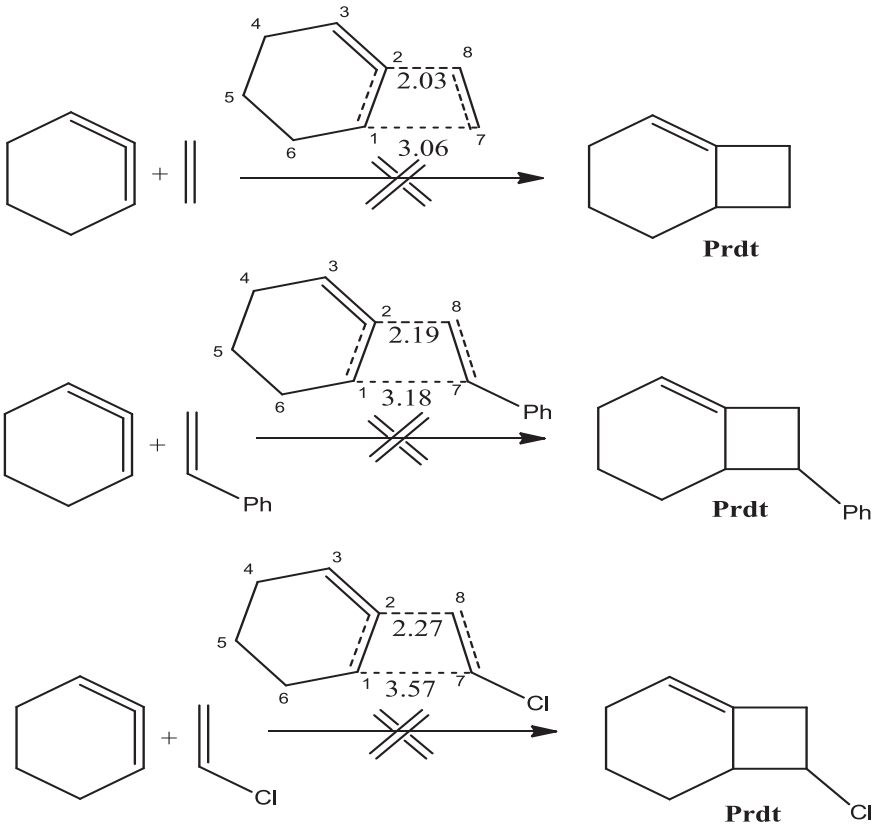


Fig. 1. Concerted [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with ethylene, styrene and vinyl chloride. All bond distances are measured in Å.

cyclohexadiene with ethylene, styrene and vinyl chloride respectively. Since these bond distances are greater than a normal carbon-carbon forming transition state bond distances and all attempts to obtain transition states for a concerted (one-step) addition failed, the implication is that there is likely no concerted addition pathway (one-step mechanism) and that the reaction involves the formation of a biradical intermediate first which then closes up to form the products. This is in agreement with the work of Jasinski [23] which showed that [2 + 2] cycloadditions of these type proceed via biradical or zwitterionic intermediates.

Based on this results, a stepwise [2 + 2] pathway was explored for the reaction of 1,2-cyclohexadiene with olefins, the energetics of which is shown in Fig. 2.

The formal [2 + 2] cycloaddition of the C=C bond of ethylene across the C_1 - C_2 bond of the 1,2-cyclohexadiene through transition state **TS1** leads to biradical intermediate **I** which closes up through **TS2** to product **Prdt** (Fig. 2). The activation barriers of the first and second steps of the reaction are 25.5 kcal/mol and 7.9 kcal/mol respectively and the formation of biradical intermediate **I** and product **Prdt** are 11.2 kcal/mol and 41.7 kcal/mol exergonic respectively.

To investigate the effects of substituents on the energetics of the reactions, a series of reactions involving electron-donating (CH_3, Ph, OH^-) and electron-withdrawing (Cl^-, NO_2 and CN^-) groups on both the 1,2-cyclohexadiene and the olefin were studied and the energetics reported in Tables 1 and 2.

All the electron-donating groups have higher activation barriers compared to the parent (ethylene) for both steps with the exception of phenyl substituted substrate which has lower activation barrier for the biradical-forming step (Table 1). All the substituted olefins give less stable products compared to the parent (ethylene), implying that the reaction of 1,2-cyclohexadiene with substituted olefins (electron-donating groups) is less feasible thermodynamically and kinetically compared to the reaction of 1,2-cyclohexadiene with the parent (ethylene).

All the electron-withdrawing groups have higher activation barriers compared to the parent (ethylene) with the exception of cyano and nitro substitution on the 1,2-cyclohexadiene substrate which has lower activation barrier for the biradical-forming step (Tables 1 and 2). All the electron-withdrawing groups give less stable products compared to the parent (ethylene) with the exception of cyano and nitro substitution on the 1,2-cyclohexadiene (Tables 1 and 2). This implies that, with all the electron withdrawing groups considered in this work, the reaction of cyano and nitro substituted 1,2-cyclohexadiene substrate with ethylene is favoured thermodynamically and kinetically compared to the reaction of 1,2-cyclohexadiene with the parent (ethylene). This is because the cyano and nitro groups are strong electron-withdrawing groups, and strongly deactivate the 1,2-cyclohexadiene which makes it less electron-rich, thereby making it more reactive towards the nucleophilic olefin.

It is important to note that the differences in the energetics are very marginal and may well be within the margin of error.

3.2. Effect of substituents on regioselectivity

The stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with substituted olefins leads to two regioisomers, a 7-substituted bicyclo (4.2.0) oct-1-ene or 8-substituted bicyclo (4.2.0) oct-ene depending on the position of the substituent (Scheme 2). As Table 3 shows, the barriers for the radical-forming step for the two pathways are close except for the cyano

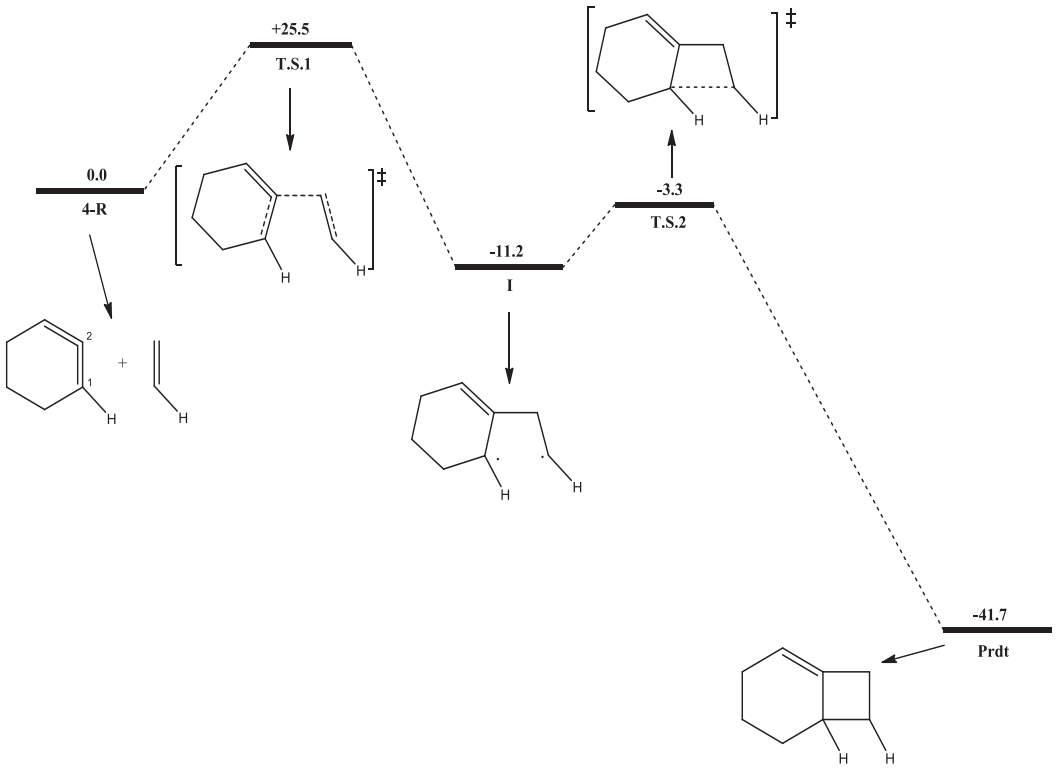


Fig. 2. Free energy profile for the stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with ethylene. Relative energies in kcal/mol.

Table 1
Gibbs free activation barriers and reaction energies of reaction of the stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with substituted olefins (H, CH_3, Ph, OH^-, Cl^-, CN, NO_2). Relative energies in kcal/mol.

Olefin/Substituent	Activation barrier (T.S.1)	I ΔG_1	Activation barrier (T.S.2)	Prdt ΔG_2
Ethylene	+25.5	−11.2	+7.9	−41.7
Propene	+27.2	−10.6	+7.4	−39.6
Styrene	+2.4	−41.2	+20.9	−29.2
Vinyl alcohol	+26.9	−8.4	+9.6	−39.3
Vinyl chloride	+26.0	−12.5	+8.8	−41.1
Acrylonitrile	+62.3	−18.2	+9.6	−32.4
Nitro ethylene	+56.8	−16.7	+14.2	−35.3

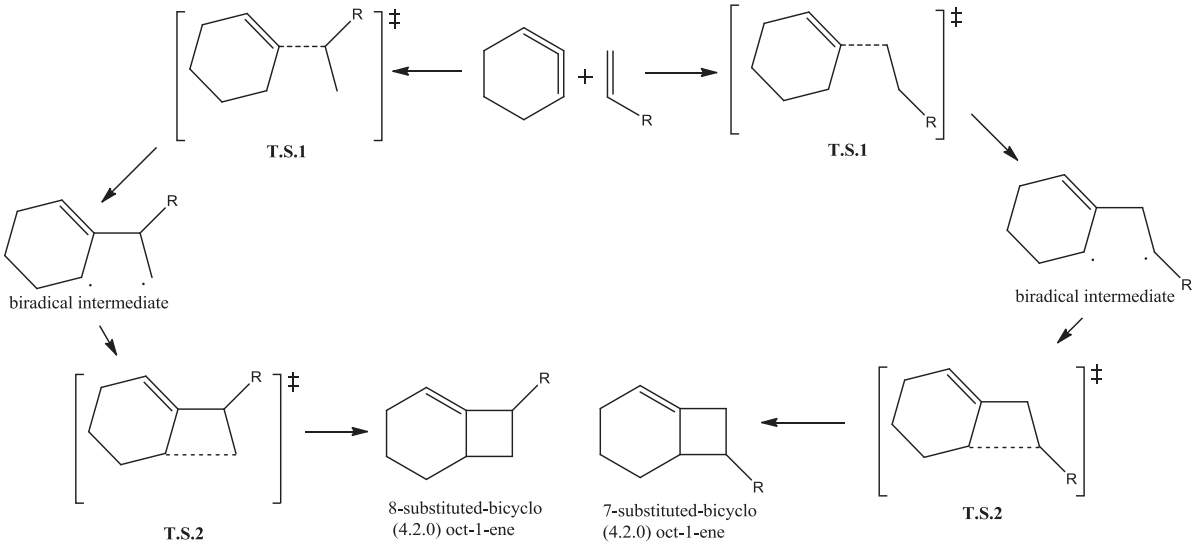
Table 2
Activation barriers and free energies of the stepwise formal [2 + 2] cycloaddition reaction of substituted 1,2-cyclohexadiene with ethylene (H, CH_3, OH^-, CN, NO_2). Relative energies in kcal/mol.

1,2-cyclohexadiene/substituent	Activation barrier (T.S.1)	I ΔG_1	Activation barrier (T.S.2)	Prdt ΔG_2
1,2-cyclohexadiene	+25.5	−11.2	+7.9	−41.7
1-Methyl-1,2-cyclohexadiene	+26.2	−10.6	+10.2	−39.1
1-Hydroxy-1,2-cylohexadiene	+26.1	−12.3	+16.6	−37.1
1-Cyano-1,2-cyclohexadiene	+21.6	−16.4	+11.8	−41.3
1-Nitro-1,2-cyclohexadiene	+22.1	−13.5	+15.3	−42.2

and nitro substituents. In the product-forming step, the barriers for the formation of the 8-isomer are less than those for the 7-isomer, except in the reaction of the methyl-substituted olefin where the reverse is true. Thus in the reaction of the cyano- and nitro-substituted olefins, the formation of the 8-substituted bicyclo (4.2.0) oct-ene is clearly favoured; in the reaction of the phenyl-substituted olefin, if the radical-forming step is reversible then the 8-isomer product will dominate but if it is not reversible then both the 7- and 8-isomers will be formed. In the reaction of the hydroxy- and chloro-substituted olefins, both the 7- and 8-isomers are expected to form.

3.3. Effect of substituents on stereoselectivity

The stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with substituted olefins results in the formation of stereo-isomers, an *exo* product and *endo* product (Scheme 1). The TS1 to the formation of the *endo* and *exo* products is the same as the



Scheme 2. Proposed scheme for the formation of regioisomers of the reaction of 1,2-cyclohexadiene with olefins [8].

Table 3
Activation barriers and free energies of the stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with substituted olefins for regioselectivity (CH_3, Ph, OH^-, Cl^-, CN, NO_2). Relative energies in kcal/mol.

Substituents	7-substituted-bicyclo (4.2.0) oct-1-ene				8-substituted-bicyclo (4.2.0) oct-1-ene			
	T.S.1	ΔG_1	T.S.2	ΔG_2	T.S.1	ΔG_1	T.S.2	ΔG_2
Methyl	+27.2	−10.6	+7.4	−39.6	+28.4	−13.6	+14.1	−36.6
Phenyl	+2.4	−41.2	+20.6	−29.2	+5.4	−3.2	+10.9	−43.1
Hydroxy	+26.9	−8.4	+9.6	−39.3	+28.4	−4.5	+6.2	−43.5
Chloro	+26.0	−12.5	+8.8	−41.1	+28.8	−11.6	+7.7	−41.6
Cyano	+62.3	−18.2	+9.6	−32.4	+26.7	−5.7	+6.2	−44.5
Nitro	+56.8	−16.7	+14.2	−36.0	+24.9	−10.4	+9.1	−42.6

TS1 of the 7-substituted-bicyclo (4.2.0) oct-1-ene but the stereoselectivity is effected for the product-forming step. The *endo* product is formed as a result of closure of the biradical intermediate without sterical reorientation of the groups in space whereas the *exo* product is obtained via rearrangement of the biradical intermediate to assume a more preferable sterical conformation [3]. For all the substituents considered in this work (phenyl, methyl, cyano and nitro), formation of the endo isomers are kinetically more preferred over the formation of the exo isomers (Table 4).

3.4. Effect of temperature on energetics of reactions

Temperature effects is considered in this study to determine how varying temperature affects the energetics of the [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with olefins. In the reaction of unsubstituted 1,2-cyclohexadiene with ethylene, an increase in temperature generally increases the activation barriers and decrease the stability of the intermediate and the stability of the product, implying that the reaction is less feasible kinetically and thermodynamically at high temperatures (Table 5). The reaction of 1,2-cyclohexadiene with substituted olefins has two stereochemical outcomes - the formation of an exo and endo-product. In the reaction of 1,2-cyclohexadiene with styrene and acrylonitrile, an increase in temperature has no effect on the activation barriers for both the exo and endo product-forming steps and also has no appreciable effect on the stability of the products (Table 6). This implies that temperature has no effect on stereoselectivity of these reactions. The reaction of 1,2-cyclohexadiene with substituted olefins results in the formation of 7-substituted and 8-substituted products. In the reaction of 1,2-cyclohexadiene with propene and acrylonitrile, an increase in temperature increases the activation barriers for the biradical-forming step and the product-forming step but decreases the stability of the biradical and the stability of the products for both the 7-substituted and 8-substituted products (Tables 7 and 8). This implies that temperature has no effect on regioselectivity (see Table 9).

Table 4
Activation barriers and free energies of the stepwise formal [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with substituted olefins for stereoselectivity (CH_3, Ph, CN, NO_2). Relative energies in kcal/mol.

Substituents	Exo-isomer		Endo-isomer	
	T.S.2	ΔG_2	T.S.2	ΔG_2
Methyl	+19.4	−29.2	+20.9	−28.2
Phenyl	+7.4	−39.6	+7.8	−39.6
Cyano	+9.6	−32.4	+10.6	−32.4
Nitro	+14.2	−37.0	+17.4	−35.3

3.5. The cycloaddition of 1,2-cyclohexadiene with nitrones

Structurally, nitrones are 1,3-dipoles and have shown a great potency in recent years for the trapping of 1,2-cyclohexadienes. This section looks at trapping the transient 1,2-cyclohexadiene with nitrones.

3.5.1. The cycloaddition of 1,2-cyclohexadiene with parent nitrones ($R_1 = R_2 = R_3 = H$)

The addition of the C − N and C − N − O bonds of nitrone B across the C = C bonds of 1,2-cyclohexadiene A results in [2 + 2] and [3 + 2] cycloaddition respectively while the addition of the C − N − O bonds of nitrone B across the C = C = C bonds of the 1,2-cylohexadiene A results in [3 + 3] cycloaddition. The energetics of these reactions along the concerted and stepwise reaction pathways are shown in Fig. 3.

The concerted [2 + 2] cycloaddition of the C-N bond of the parent nitrone **B** across the C=C bond of the 1,2-cyclohexadiene **A** through transition state **TSG** leads to the formation of product **F**

Table 5
Effect of temperature changes on the parent (unsubstituted) 1,2-cyclohexadiene with ethylene. Relative energies in kcal/mol.

Temperature/C	Activation barrier (T.S.1)/kcalmol^{-}	ΔG_1/kcalmol^{-}	Activation barrier (T.S.2)/kcalmol^{-}	ΔG_2/kcalmol^{-}
0	+24.5	−12.2	+7.9	−41.7
50	+26.5	−10.1	+7.9	−41.6
100	+28.6	−7.9	+8.0	−41.5
150	+30.8	−5.7	+8.1	−41.3
200	+33.0	−3.5	+8.3	−41.1

Table 6
Effect of temperature changes on stereoselectivity. Relative energies in kcal/mol.

Substituent	Phenyl				Cyano			
Temperature/C	Exo-isomer		Endo-isomer		Exo-isomer		Endo-isomer	
	T.S.2	ΔG_2	T.S.2	ΔG_2	T.S.2	ΔG_2	T.S.2	ΔG_2
0	+20.9	−29.4	+21.9	−28.0	+9.6	−31.8	+10.6	−32.4
50	+20.9	−29.4	+21.9	−27.9	+9.6	−31.7	+10.6	−32.3
100	+20.9	−29.3	+21.9	−27.8	+9.6	−31.6	+10.6	−32.2
150	+20.9	−29.2	+21.9	−27.7	+9.7	−31.5	+10.8	−32.1
200	+20.9	−29.1	+21.9	−27.6	+9.8	−31.3	+10.8	−31.9

Table 7
Effect of temperature changes on regioselectivity for methyl-subtituted group. Relative energies in kcal/mol.

Substituent	Methyl							
Temperature/C	7-substituted-bicyclo (4.2.0) oct-1-ene				8-substituted-bicyclo (4.2.0) oct-1-ene			
	T.S.1	ΔG_1	T.S.2	ΔG_2	T.S.1	ΔG_1	T.S.2	ΔG_2
0	+26.1	−11.8	+7.3	−39.7	+27.3	−14.8	+14.1	−36.8
50	+28.4	−9.3	+7.4	−39.6	+29.7	−12.5	+14.2	−36.5
100	+30.8	−6.9	+7.5	−39.5	+32.0	−10.1	+14.3	−36.3
150	+33.4	−4.4	+7.6	−39.3	+34.6	−7.6	+14.4	−36.2
200	+36.0	−1.7	+7.6	−39.2	+37.2	−5.0	+14.5	−36.0

Table 8
Effect of temperature changes on regioselectivity for cyano-subtituted group. Relative energies in kcal/mol.

Substituent	Cyano							
Temperature/C	7-substituted-bicyclo (4.2.0) oct-ene				8-substituted-bicyclo (4.2.0) oct-1-ene			
	T.S.1	ΔG_1	T.S.2	ΔG_2	T.S.1	ΔG_1	T.S.2	ΔG_2
0	+61.1	−19.4	+9.6	−32.4	+25.5	−6.9	+6.2	−44.5
50	+63.5	−16.9	+9.6	−32.3	+27.9	−4.4	+6.2	−44.4
100	+65.9	−14.4	+9.6	−32.2	+30.4	−1.9	+6.3	−44.2
150	+68.5	−11.8	+9.7	−32.1	+33.0	+0.7	+6.4	−44.1
200	+71.2	−9.1	+9.8	−31.9	+35.7	+3.3	+6.5	−44.0

(Fig. 3) with an activation barrier of +10.52 kcal/mol, leading to a [2 + 2] product **F** which is −25.44 kcal/mol below the reactants, indicating an exergonic reaction. The stepwise formal [2 + 2] cycloaddition reaction of the parent nitrone **B** with the 1,2-cyclohexadiene **A** leading to product **F** first involves the formation of a C-C bond through transition state **TSC** with activation barrier +10.45 kcal/mol to form intermediate **D** of relative energy −25.25 kcal/mol and then the formation of a C-N bond through transition state **TSE** to form the four-membered ring, which has an activation energy barrier +17.07 kcal/mol. The concerted [3 + 2] cycloaddition of C-N-O bond of the parent nitrone **B** across the C=C bond of the 1,2-cyclohexadiene **A** through transition state **TS H** leads to the formation of [3 + 2] product **I** with a barrier of +10.51 kcal/mol; the final [3 + 2] product **I** is −58.00 kcal/mol below the reactants, indicating a very exergonic reaction. The stepwise formal [3 + 2] cycloaddition reaction of the parent nitrone **B** with the 1,2-cyclohexadiene **A** first involves the formation of a C-C bond through transition state **TSL** with activation barrier +11.04 kcal/mol to form intermediate **K** of energy −58.01 kcal/mol below the reactants. Intermediate **K** then undergoes C-N ring-closing bond formation through transition state **TSJ** with activation barrier +59.00 kcal/mol to form the [3 + 2] product **I** of energy −58.00 kcal/mol below the reactants. The concerted [3 + 3] cycloaddition of C-N-O bonds of the parent nitrone **B** across the C=C=C functionality of the 1,2-cyclohexadiene **A** through transition state **TSN** leads to the formation of [3 + 3] product **M** with a barrier of 12.37 kcal/mol and reaction energy of +11.63 kcal/mol, indicating an endergonic reaction.

The [3 + 2] concerted pathway is found to be thermodynamically and kinetically more feasible compared to the [2 + 2] and [3 + 3] concerted reaction pathway. Along the stepwise formal reaction pathway, the [2 + 2] is found to be kinetically more feasible compared to the [3 + 2]. The [3 + 3] adduct is found to have a very unstable product and thus will break back easily if the reaction is reversible.

The energetics displayed in Fig. 3 shows that these reactions are very unselective. The activation barriers of the first step of all five reaction pathways studied are within 1 kcal/mol of each other. Thermodynamics dictates that with longer reaction times, the concerted addition product **I** will be dominant followed by the concerted addition product **F**. Since intermediate **K** is very stable and the barrier for its conversion to product **I** is high (59.00 kcal/mol), it is expected that intermediate **K** will also be available in the reaction mixture for isolation. There is also expected to be a small amount of intermediate **D** since the activation barrier for the formation of product **F** is 17.07 kcal/mol.

3.5.2. The cycloaddition of 1,2-cyclohexadiene with chloro - substituted nitrones ($R_1 = R_3 = Cl$)

The concerted [2 + 2] addition pathway is 1.16 kcal/mol more

Table 9
The cycloaddition of 1,2-cyclohexadiene with chloro - substituted nitrones ($R_1 = R_3 = Cl$) against parent nitrones in kcal/mol.

	Parent nitrone ($R_1 = R_2 = R_3 = H$)					Chloro-substituted nitrone ($R_1 = R_3 = Cl$)				
	E_a	E_a 1	Int	E_a 2	Prdt	E_a	E_a 1	Int	E_a 2	Prdt
[2 + 2]	10.45	17.07	−25.25	10.52	−25.44	11.98	39.11	−41.83	14.55	−43.61
[3 + 2]	11.04	59.00	−58.01	10.51	−58.00	13.14	12.24	−58.64	43.02	−58.63
[3 + 3]				12.37	11.63	15.25				14.90

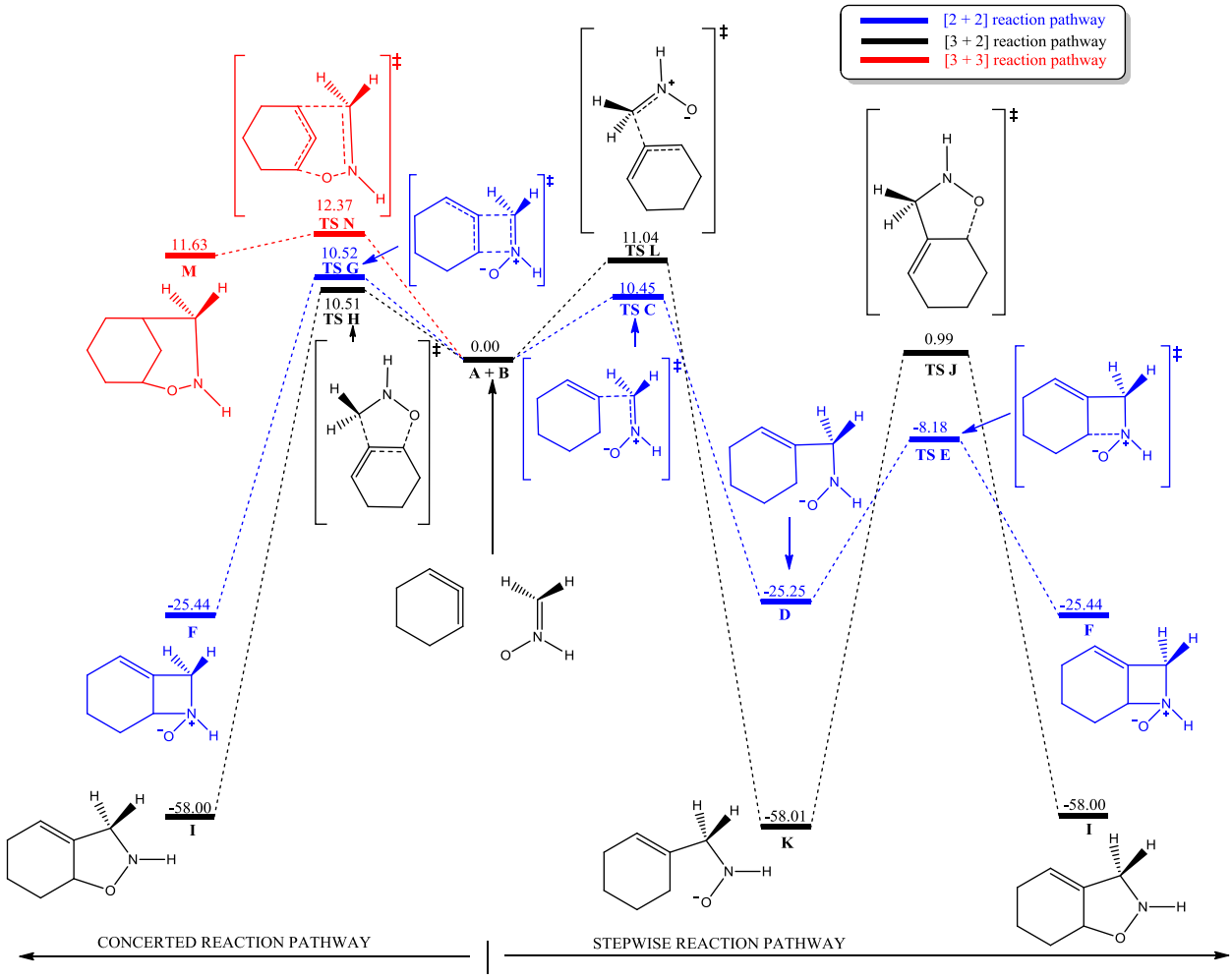


Fig. 3. Relative Free Energy Profile for the [2 + 2], [3 + 2] and [3 + 3] reaction pathways for the concerted and stepwise mechanisms in kcal/mol ($R_1 = R_2 = R_3 = H$) at 25 °C.

feasible kinetically than the [3 + 2] pathway but thermodynamically the [3 + 2] concerted pathway is found to be more feasible compared to the [2 + 2] and [3 + 3] concerted reaction pathways whereas along the stepwise reaction pathway, the formal [2 + 2] pathway is found to be kinetically more feasible compared to the formal [3 + 2] pathway. The [3 + 3] adduct is found to have very unstable.

The activation barriers of the various elementary steps in the concerted addition pathways in chloro-substituted nitrone are marginally smaller (within 1–2 kcal/mol) than those of the parent nitrone. Along the stepwise pathways, the activation barrier of the chloro-substituted nitrone in the second step of the formal [3 + 2] addition is 16 kcal/mol lower than that of the parent while the barrier of the first step of the formal [2 + 2] addition of the chloro-substituted nitrone is 29 kcal/mol higher than that of the parent nitrone. The relative energies, the [2 + 2] and [3 + 2] products of the chloro-substituted nitrone are more stable compared to the [2 + 2] and [3 + 2] products of the parent nitrone.

3.5.3. *The cycloaddition of 1,2-cyclohexadiene with methyl- and ethyl-substituted nitrones ($R_1 = CH_3$, $R_3 = CH_2CH_3$)*

It is observed that the [2 + 2] concerted pathway is kinetically feasible over the [3 + 2], and the [3 + 2] concerted pathway is thermodynamically more feasible compared to the [2 + 2] and [3 + 3] concerted reaction pathway whereas along the stepwise formal reaction pathway, the [2 + 2] is kinetically more feasible compared to [3 + 2]. The [3 + 3] adduct is very unstable and thus will break back easily if the reaction is reversible.

The relative energies depict that [2 + 2] and [3 + 2] products of the methyl-ethyl substituted nitrone are less stable compared to the [2 + 2] and [3 + 2] products of the parent nitrone.

In the reactions of the substituted nitrones, just as in the case of the parent nitrone, thermodynamics dictates that with longer reaction time, the concerted product **I** will be dominant followed by the concerted **F**. Since intermediate **K** is very stable and the barrier for its conversion to product **I** is high, it is expected that intermediate **K** will also be available in the reaction mixture for isolation. There is also expected to be a small amount of intermediate **D**(see Table 10).

Table 10
The cycloaddition of 1,2-cyclohexadiene with methyl- and – ethyl-substituted nitrones ($R_1 = CH_3$ $R_3 = CH_2CH_3$).

	E_a	E_a 1	Intermediate	E_a 2	Product
[2 + 2]	11.73	12.44	−22.39	27.95	−16.86
[3 + 2]	11.85	12.12	−54.93	55.54	−54.91
[3 + 3]	14.70				13.92

3.5.4. Effects of temperature changes on the cycloaddition of 1,2-cyclohexadiene with parent nitrones ($R_1 = R_2 = R_3 = H$)

Effect of temperature on the energetics of the cycloaddition of 1,2-cyclohexadiene with the parent nitrone **B** was investigated and the results are shown in Table 11 below.

The effects of temperature variation on the energetics and the selectivity of the reactions have been studied. The activation energy barriers for the [2 + 2], [3 + 2] and [3 + 3] reaction pathways generally increase as temperature increases from 0 °C to 100 °C along the concerted reaction pathway, but along the stepwise formal reaction pathway the second activation barrier for the [3 + 2] pathway decreases from 59.05 to 58.79 from 0 °C to 100 °C and the [2 + 2] pathway decreases from 17.15 to 16.95 from 0 °C to 100 °C as temperature increases. The change in activation energies with changing temperature is within 2 kcal/mol, thus temperature does not seem to have a marked effect on the energetics of the reaction. As for the selectivity of the reactions towards the [2 + 2], [3 + 2] and [3 + 3] pathways, there is no effect since the barriers increase and decrease by the same margin and thus the preference for the pathways do not change with change in temperature over the range studied.

3.5.5. Formal [5 + 2] cycloaddition reaction of 1,2-cyclohexadiene with nitrones ($R_1 = R_2 = H$, $R_3 = Ph$)

A formal [5 + 2] cycloaddition involving a nitrone substituted with one phenyl group at R_3 has been investigated (Fig. 4). The formal [5 + 2] addition pathway involves first a [3 + 2] cycloaddition followed by N-O bond cleavage, oxygen migration, hydrogen exchange and rearomatization. The concerted and the stepwise reaction pathways have been considered.

The concerted [3 + 2] cycloaddition involves a synchronous bond formation of the weak nucleophilic carbon C_2 (Scheme 3) and the oxygen of the nitrone with the electrophilic terminal carbon of the nitrone (C_o) and carbon C_1 respectively through transition state **TS3** to the formation of the five-membered heterocyclic intermediate **F**. The activation barrier for the formation of the intermediate **F** through transition state **TS3** is 9.8 kcalmol^{-1}. The reaction is exergonic by 62.5 kcalmol^{-1}.

The stepwise addition mechanism involves a stepwise bond formation between the nucleophilic carbon C_2 of the 1,2-cyclohexadiene and the electrophilic terminal carbon C_o of the nitrone through transition state **TS1** to the formation of intermediate **O**. The activation barrier for this step is 10.2 kcalmol^{-1} and the reaction energy is −17.0 kcalmol^{-1}. The cyclization process is completed by a bond formation between the oxygen atom in intermediate **O** and carbon C_1 through a proposed transition state **TS2** leading to the formation of intermediate **F**. However, attempts to compute **TS2** always resulted in a structure with an elongated C_3-O bond; thus the transition state **TS2** could not be computed.

Intermediate **F** from either the concerted or stepwise [3 + 2] cycloaddition undergoes an N-O bond cleavage followed by oxygen migration through transition state **TS4** with activation barrier of 57.1 kcalmol^{-1} to form intermediate **P** with relative energy of −68.8kcalmol^{-1}. This is the rate-determining step for this kinetically favoured reaction pathway. This very high barrier may be due to resonance stabilization of the phenyl group on the nitrogen of the nitrone making intermediate **F** less susceptible to undergo reaction with the oxygen as indicated in Fig. 4.

Intermediate **P** then undergoes a hydrogen exchange via two pathways − through transition states **TS5** or **TS7** as indicated in Fig. 4. Intermediate **P** undergoing a hydrogen exchange between the two carbon atoms (Scheme 4) requires an activation barrier of 34.7 kcalmol^{-1} through transition state **TS5** to the formation of the intermediate **Q** of relative energy −70.0 kcalmol^{-1}. Intermediate **Q** then undergoes a hydrogen exchange followed by rearomitization through transition state **TS6** with activation barrier of 43.1 kcalmol^{-1} to the formation of the seven-membered heterocyclic product **R** of relative energy −99.0 kcalmol^{-1}.

The other hydrogen exchange reaction of intermediate **P** involving two different electronic environments of the carbon and nitrogen proceeds via transition state **TS7** with activation barrier of 67.8 kcalmol^{-1} leading to the formation of the seven-membered heterocyclic product **R** of relative energy −99.0 kcalmol^{-1} as indicated in Fig. 4.

For the elementary steps, increase in temperature increases the activation barriers for the concerted [3 + 2] cycloaddition along **A + B-F** as well as along the stepwise addition mechanism via **A + B-O** from 0 °C−200 °C. However, this increase in temperature has no significant effect on the activation barriers on the N-O bond cleavage, oxygen migration, hydrogen exchange and rearomitization mechanism of the formal [5 + 2] cycloaddition as the activation barriers remain fairly constant as indicated in Table 12.

3.5.6. The reaction of 1,2-cycohexadiene with a diphenyl-substituted nitrone ($R_1 = R_3 = Ph$, $R_2 = H$) of the formal [5 + 2] pathway

The reaction of 1,2-cyclohexadiene with this phenyl-substituted nitrone ($R_1 = R_3 = Ph$, $R_2 = H$) leads to the formation of two stereochemically complex cycloadducts; *endo* and *exo* isomers. These isomers are formed as a result of the attachment of the oxygen of the nitrone to the carbon C_1 (Scheme 3) of the 1,2-cyclohexadiene from either the back or front. Products or intermediates arrangement in which the hydrogen of C_1 is in the same direction as the phenyl substitute ($R_1 = Ph$) is considered the *endo* adducts (Fig. 5) whereas when the hydrogen is in the opposite direction to this phenyl, it becomes the *exo* adduct. The phenyl substituent at position R_1 of the nitrone is demonstrated by dashes at its point of attachment (Fig. 5) and hence the point of attachment of the C_1 hydrogen is represented by dashes when in the same direction (*endo*) and wedges when in the opposite direction (*exo*) to the phenyl substitute.

The synchronous cycloaddition of the nitrone across the double bond of C_2-C_1 (Scheme 3) of the 1,2-cyclohexadiene via transition state **TS3a** and **TS3b** has an activation barrier of 17.4 kcalmol^{-1} and

Table 11
Effects of temperature changes on the activation energies of the parent nitrone ($R_1 = R_2 = R_3 = H$).

Reaction Pathways (Activation Energy) Concerted	0 °C	25 °C	50 °C	100 °C
[3 + 2] E_a	9.35	10.51	11.69	14.14
[2 + 2] E_a	9.36	10.52	11.69	14.14
[3 + 3] E_a	11.19	12.37	13.54	15.95
STEPWISE				
[3 + 2] E_a 1	9.85	11.04	12.23	14.66
[2 + 2] E_a 1	9.29	10.45	11.63	14.08
[3 + 2] E_a 2	59.05	59.00	58.93	58.79
[2 + 2] E_a 2	17.15	17.07	17.00	16.95

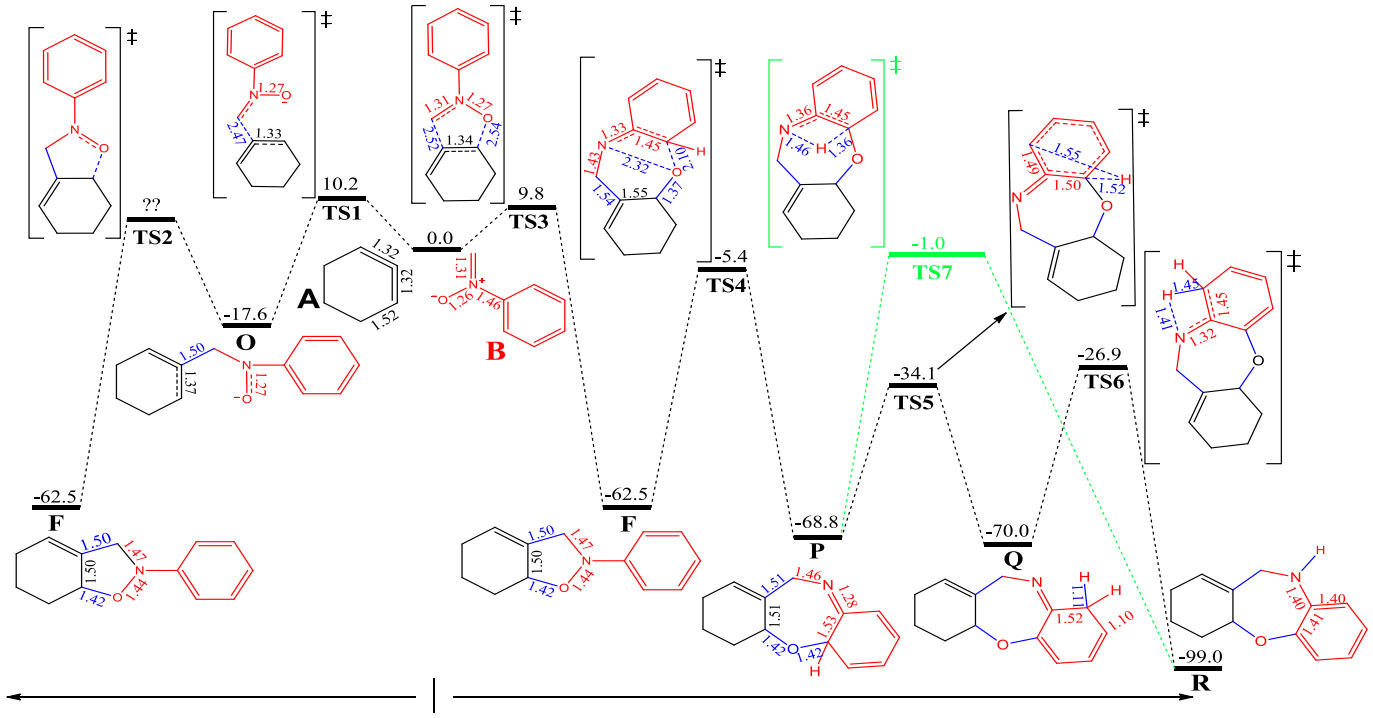


Fig. 4. Energy profile for the formal [5 + 2] cycloaddition reaction between 1,2-cyclohexadiene and nitrone ($R_1 = R_2 = H$, $R_3 = Ph$). Relative Energies in kcalmol^{-1}. All bond distances are measured in Å.

12.1 kcalmol^{-1} for the *endo* and *exo* intermediate **F** respectively. The resulting *endo* and *exo* intermediate **F** formed has a relative energy of −55.2 kcalmol^{-1} and -56.5 kcalmol^{-1} respectively.

The C_2-C_o bond formation in the stepwise addition proceeds via transition state **TS1** with activation barrier of 16.6 kcalmol^{-1}. Intermediate **O** for this transformation is found to be.

−5.9 kcalmol^{-1}. The transition state **TS2** for the cyclization process of intermediate **O** to the formation of the five-membered heterocyclic *endo* and *exo* isomer could not be computed as a result of C_1-O bond elongation. An activation barrier of 62.7 kcalmol^{-1} and -56.0 kcalmol^{-1} were found respectively for the transformation of intermediate **F** from either the concerted or stepwise [3 + 2] cycloaddition to the formation of the *endo* and *exo* intermediate **P** of relative energy −58.1 kcalmol^{-1} and -47.3 kcalmol^{-} through **TS4a** and **TS4b**. This is regarded as the rate-determining step for the indicated kinetically favoured pathway (Fig. 5).

The kinetically favoured pathway of the two hydrogen exchange pathways for the transformation of intermediate **P** has an activation barrier of 32.8 kcalmol^{-1} and 25.9 kcalmol^{-1} for the formation of the *endo* and *exo* intermediate **Q** of relative energy −60.2 kcalmol^{-1} and -60.7 kcalmol^{-1} respectively through transition state **TS5a** and **TS5b**. Intermediate **Q** then undergoes hydrogen exchange and rearomitization through transition state **TS6a** and **TS6b** with activation barrier of 46.7 kcalmol^{-1} and 46.9 kcalmol^{-1} to the formation of the final *endo* and *exo* product **R** of relative energy −90.1 kcalmol^{-1} and -86.2 kcalmol^{-1} respectively.

The direct formation of the final *endo* and *exo* product **R** from the intermediate **P** by the direct hydrogen exchange proceeds via an activation barrier of 65.8 kcalmol^{-1} and 51.5 kcalmol^{-1} through transition state **TS7a** and **TS7b** respectively.

From the results obtained, the concerted pathway for the formation of the *exo* intermediate **F** is kinetically and thermodynamically favoured over the *endo* intermediate **F**. However, the final *endo* product **R** is thermodynamically favoured over the *exo* product indicating a higher yield of the *endo* over the *exo* final product.

3.5.7. Reaction of 1,2-cyclohexadiene with diphenyl-substituted nitrone ($R_1 = H$, $R_2 = R_3 = Ph$) of the formal [5 + 2] pathway

The reaction of 1,2-cyclohexadiene with a phenyl-substituted nitrone ($R_1 = H$, $R_2 = R_3 = Ph$) also leads to the formation of two stereo-chemically complex cycloadducts; the *endo* and *exo* isomers as described in 3.5.6 above. The phenyl substituent at position R_2 of the nitrone represented by wedge lines however make these *endo* and *exo* products regio-isomers to the *endo* and *exo* of the phenyl at position R_1 (Fig. 5) of the nitrone respectively. The *endo* here is represented by wedge at the point of attachment of the C_1 hydrogen (Fig. 6) while the *exo* is represented by dashes at the C_1 hydrogen.

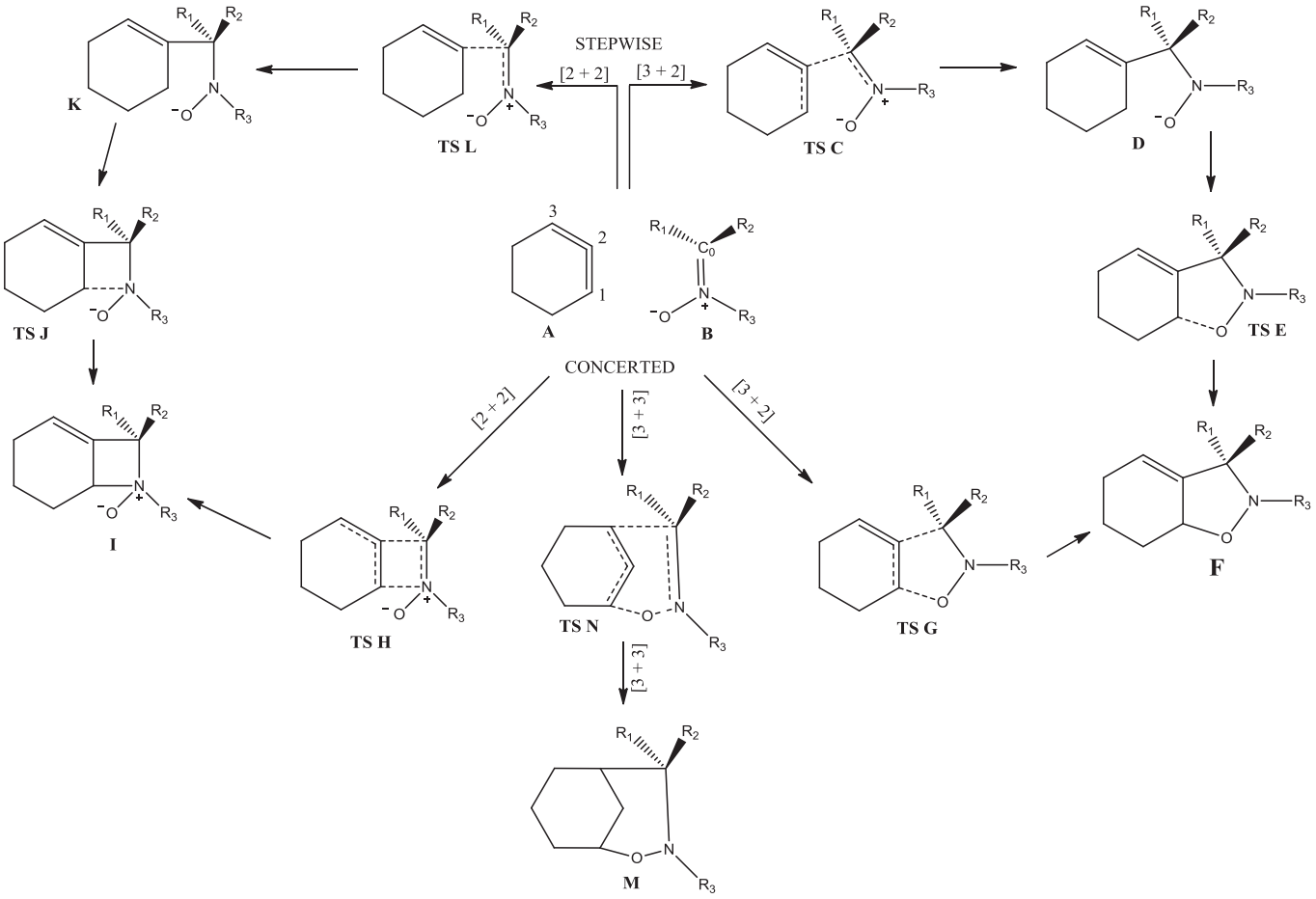
For the formation of the *endo* and *exo* cycloadduct of this compound ($R_1 = H$, $R_2 = Ph$), the concerted [3 + 2] cycloaddition of the reaction mechanism require activation barrier of 9.7 kcalmol^{-1} and 5.5 kcalmol^{-1} through transition state **TS3a** and **TS3b**. These transition lead to the formation of the *endo* and *exo* intermediate **F** of relative energy −62.2 kcalmol^{-1} and -63.3 kcalmol^{-1} respectively.

The stepwise formation mechanism proceeds via transition state **TS1** with an activation barrier of 5.2 kcalmol^{-1} to the formation of intermediate **O** of relative energy −13.3 kcalmol^{-1}.

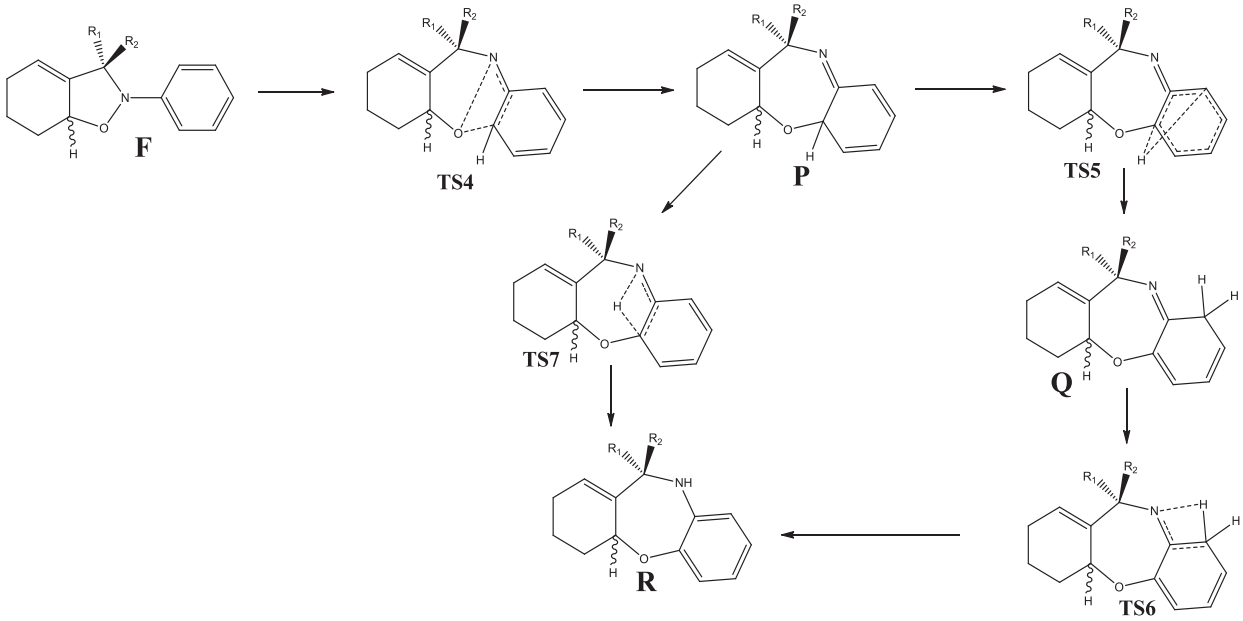
The transition state **TS2** for the cyclization of intermediate **O** leading to the five-membered heterocyclic *endo* isomer could not be determined as a result of C_1-O bond elongation.

The *endo* and *exo* intermediate **F** proceed to the formation of their respective intermediate **P** of relative energies −63.2 kcalmol^{-1} and -64.2 kcalmol^{-1} via activation barrier of 59.7 kcalmol^{-1} and 59.3 kcalmol^{-1} respectively.

For the two hydrogen exchange pathways, the transformation of both the *endo* and *exo* intermediate **P** which are kinetically favoured proceed with activation barriers of 34 kcalmol^{-1} and 33.5 kcalmol^{-1} to the formation of intermediate **Q** of relative energies −69.2 kcalmol^{-1} and 72.4 kcalmol^{-1} respectively through transition state **TS5a** and **TS5b**. The seven-membered heterocyclic *endo* and *exo* product **R** are formed by a hydrogen exchange and



Scheme 3. Proposed scheme for the reaction of 1,2-cyclohexadiene with nitrones [5].



Scheme 4. Proposed scheme for the formal [5 + 2] cycloaddition of 1,2-cyclohexadiene with nitrones [7].

Table 12
Temperature effects on the activation barriers of the reaction ($R_1 = R_2 = H$, $R_3 = Ph$). Activation barriers in kcalmol^{-1}.

STEPS	0 °C	25 °C	150 °C	200 °C
Concerted [3 + 2]				
A + B-F	8.5	9.8	16.7	19.7
Stepwise [3 + 2]				
A + B-O	8.9	10.2	17.2	20.1
Formal [5 + 2]				
F-P	57.1	57.1	57.0	56.9
P-Q	34.8	34.7	34.6	34.6
Q-R	43.0	43.1	43.0	43.0
P-R	67.9	67.8	67.9	67.9

rearomitization mechanism of the respective *endo* and *exo* intermediate **Q** via activation barriers of 49.9 kcalmol^{-1} and 50.0 kcalmol^{-1} respectively. The transformation of the *endo* and *exo* intermediate **P** to the final *endo* and *exo* products **R** by the direct hydrogen exchange (transfer) mechanism occurred via activation barriers of −61.3 kcalmol^{-1} and 63.7 kcalmol^{-1} respectively through transition state **TS7a** and **TS7b**.

Fig. 6 implies that the concerted pathway for the formation of *exo* intermediate **F** is kinetically and thermodynamically favoured over the corresponding *endo* adduct **F.** The relative energies of intermediates suggest a thermodynamic dominancy of the *exo* adducts over the *endo* adducts except for the final step of formation of the product **R** in which the *endo* dominates over the *exo*. This implies that for the final product **R**, the *endo* exist in higher amount than that of the *exo* cycloadduct.

4. Summary and conclusions

The [2 + 2] cycloaddition reaction of 1,2-cyclohexadiene with olefins all follow a stepwise reaction pathway via a biradical intermediate whereas the [3 + 3] cycloaddition of the 1,2-cyclohexadiene with nitrones follows a concerted pathway. With the [3 + 3], [2 + 2] and the formal [5 + 2] cycloaddition of the 1,2-cyclohexadiene with the nitrones, the concerted and stepwise mechanism are seen to be in competition.

The [3 + 2] cycloadduct of the 1,2-cyclohexadiene with the nitrone can proceed to the formation of a more stable formal [5 + 2] cycloadduct if the nitrone bears a phenyl substiuent at its nitrogen, implying that 1,2-cyclohexadiene can be trapped with nitrones in a [3 + 2] fashion and converted to a formal [5 + 2] cycloadduct.

The reaction of 1,2-cyclohexadiene with substituted olefins and nitrones can form *endo* and *exo* stereo-isomers but the reactions are found to be stereoselective towards the formation of the *exo* product as this product is favoured kinetically and thermodynamically over the *endo* product for the reaction with substituted olefins. However, the formal [5 + 2] cycloaddition of the 1,2-cyclohexadiene with phenyl-substituted nitrones exhibit a thermodynamic favourability towards the *exo* adducts over the *endo* adducts but the final *endo* products dominate over the final *exo* products of the reaction as a results of its negatively higher relative energy.

In the concerted reactions between 1,2-cyclohexadiene and nitrones, the [3 + 2] addition pathway is kinetically and thermodynamically more feasible compared to the [2 + 2] and [3 + 3] addition pathways. However, in the stepwise reactions, the [2 + 2] addition pathway is kinetically more feasible but

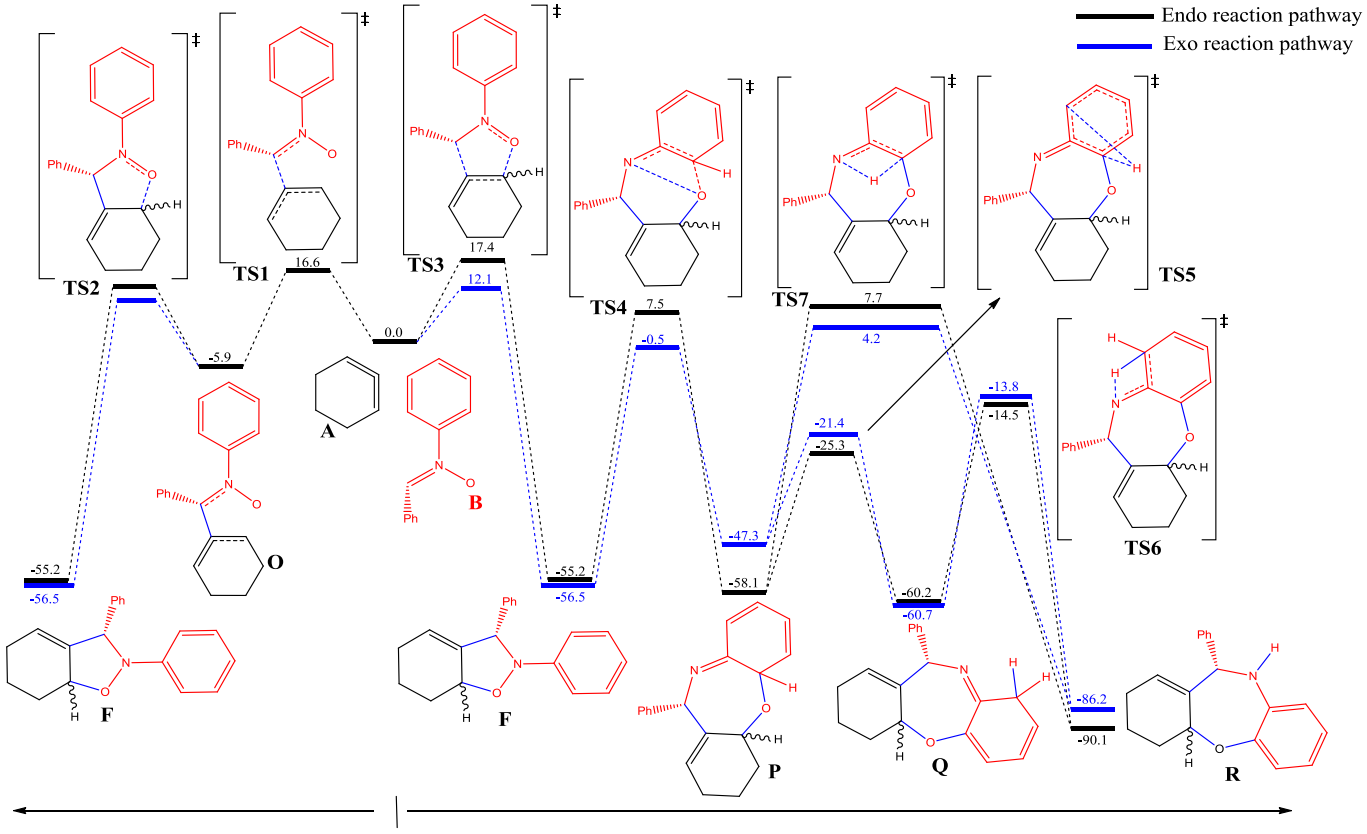


Fig. 5. Energy profile for the formal [5 + 2] cycloaddition reaction between 1,2-cyclohexadiene and diphenyl substituted nitrone ($R_1 = R_3 = Ph$, $R_2 = H$). Relative Energies in kcalmol^{-1}.

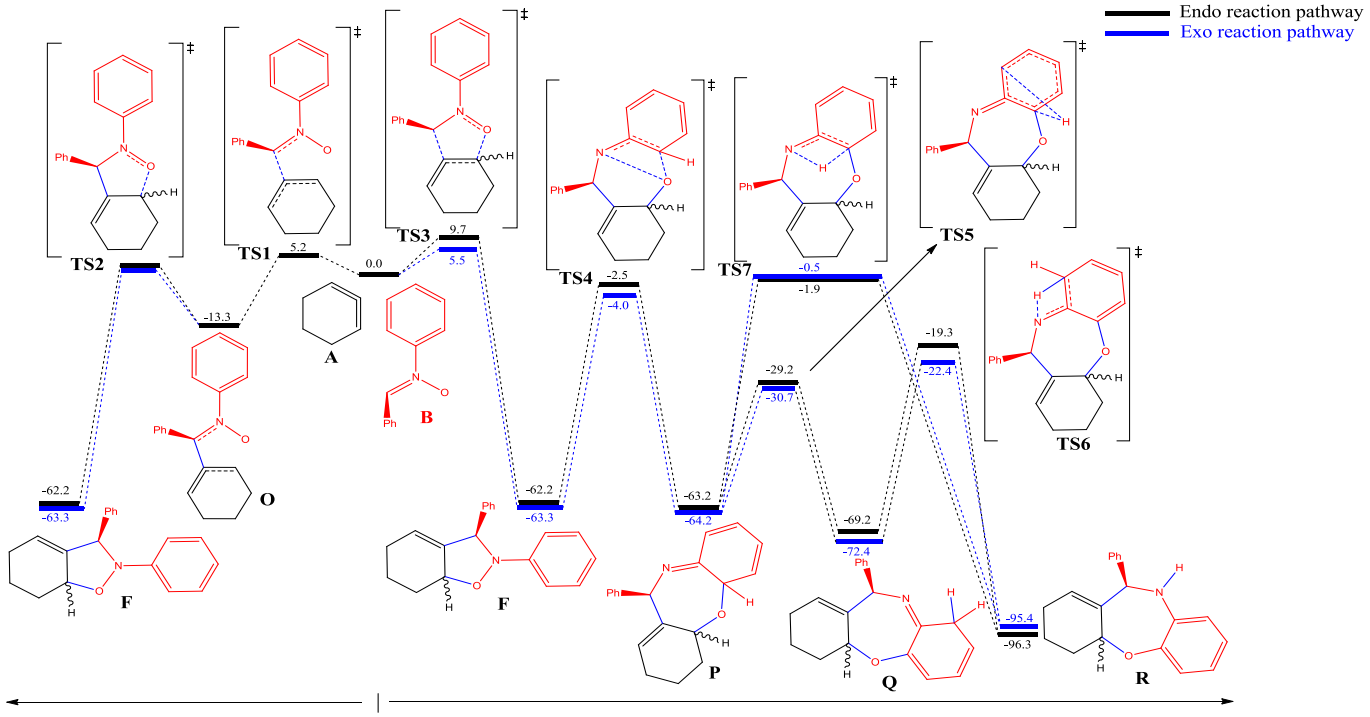


Fig. 6. Energy profile for the formal [5 + 2] cycloaddition reaction between 1,2-cyclohexadiene and diphenyl substituted nitrone ($R_1 = H$, $R_2 = R_3 = Ph$). Relative Energies in kcalmol^{-1}.

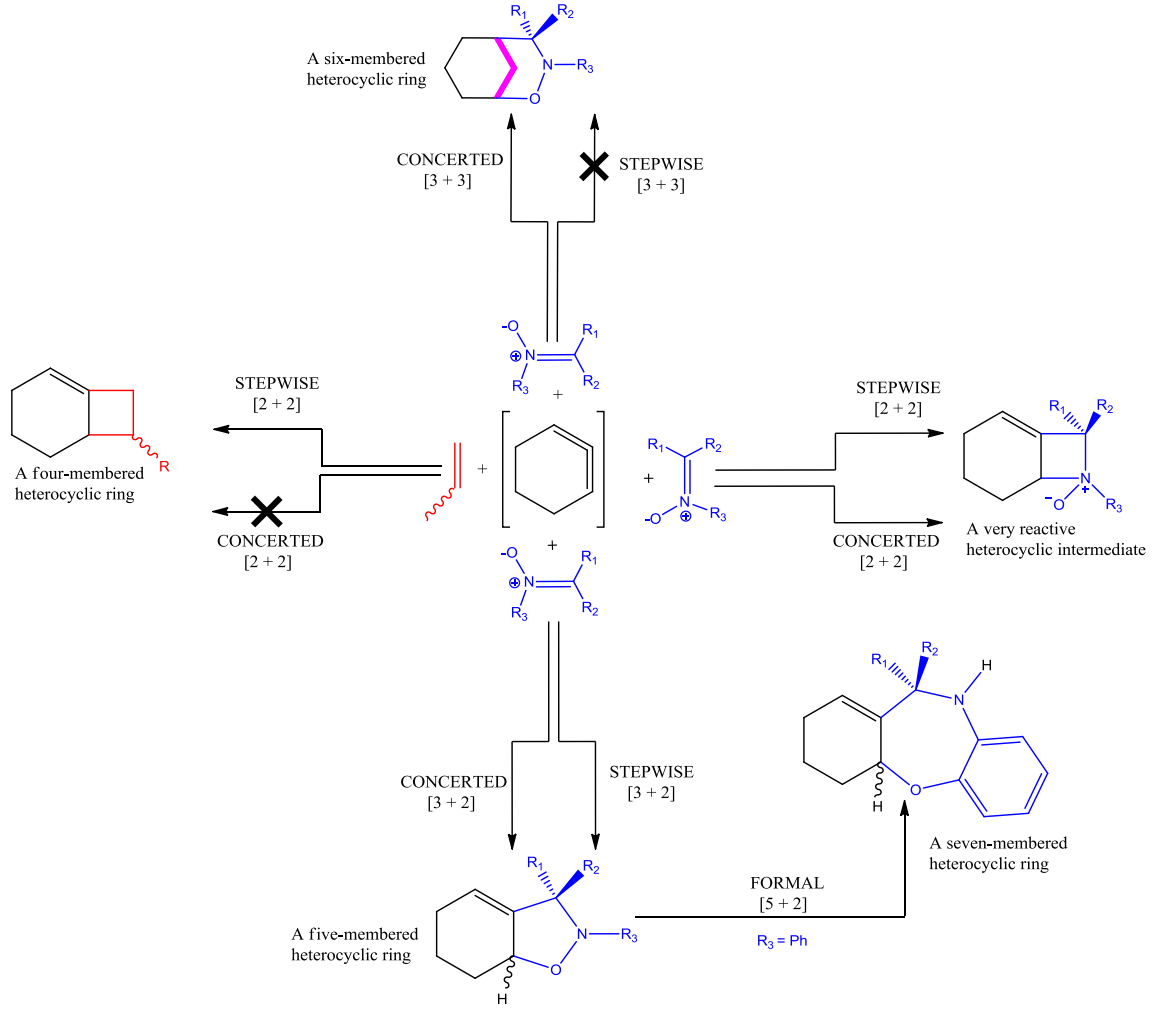


Fig. 7. Summary of the pathways for the reactions of 1,2-cyclohexadiene with nitrones and olefins.

thermodynamically less feasible compared to the [3 + 2] reaction pathway.

The cycloadducts of the [3 + 3] reaction addition are highly unstable and thus are very good precursors for subsequent reactions.

The reaction of 1,2-cyclohexadiene with substituted olefins could form two regioisomers 7-substituted bicyclo (4.2.0) oct-1-ene and 8-substituted bicyclo (4.2.0) oct-1-ene but the reactions are found to be regioselective towards the 8-substituted bicyclo (4.2.0) oct-1-ene product as it is favoured kinetically and thermodynamically over the 7-substituted bicyclo (4.2.0) oct-1-ene product, with the exception of substitution with methyl group.

Temperature does not seem to have an effect on the reaction pathway except for the reaction of un-substituted 1,2-cyclohexadiene with ethylene in which there is a recorded increase in the activation barriers and decrease in the stabilities of the product, implying that the reaction is less feasible kinetically and thermodynamically at high temperatures. Also with the phenyl substituted nitrone, there are slight temperature effects on only the [3 + 2] cycloaddition mechanism.

Fig. 7 is a summary of the pathways for the reactions of 1,2-cyclohexadiene with olefins and nitrones that have been studied in this work.

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