

A density functional theory study of the region selectivity of the Diels –Aldercyclo addition of 2 methyl- substituted diene with selected dienophiles

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ABSTRACT

In the present work, the regioselectivity for a series of Diels–Alder reactions (4 reactions) has been studied using hardness, electrophilicity and polarizability of products. Furthermore, thermodynamic and kinetic calculations have been done. In all results predicted para regioisomer is more favorable regioisomer in these investigated reactions. All calculations have been done at the DFT-B3LYP/6-31G (d) level of theory.

Keywords: Diels–Alder reaction; Density functional theory; Regioselectivity; Global indexes; Thermodynamic study; Kinetic study

INTRODUCTION

The Diels–Alder (DA) reaction is the reaction of a diene, with a dienophile compound which is an valuable method for the preparation of six-membered ring systems [1-5]. The reaction of butadiene with ethylene is the simplest example of a DA reaction. The region selectivity in this reaction is observed with using unsymmetrically substituted reagents. For 1 or 2-substituted dienes two regioisomers are expected. For 1-substituted diene, head-to-head and head-to-tail interaction produce ortho and meta region isomer

respectively and for 2-substituted diene, produce meta and para region isomer respectively [6]. According to the maximum hardness principle (MHP) and based on a rule of nature, it is expected that molecules arrange themselves to be as hard as possible which was announced by Pearson [7-12]. It means that the more stable structure has the largest HOMO–LUMO energy gap [12-16]. Also, because of inverse relation between hardness(η) and polarizability(α) [17] the minimum polarizability (MPP) principle was

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introduced by Chattaraj and Sengupta which expresses that the natural evolution of any system is toward a state of minimum polarizability [18]. Both of the MHP and MEP principles were investigated and their validity has been confirmed, in various cases such as in the study of different types of chemical reactions [19-24]. Furthermore, since any system is towards a state of minimum electrophilicity, it seems that there is a tendency in atoms to arrange themselves in a way that the obtained molecule reaches the minimum electrophilicity. This rule is called the minimum electrophilicity principle (MEP) [24].

The DA reaction of α,β -unsaturated ketones with dienes is a useful method for the production of substituted cyclohexenes [25-27]. So in the present work, the region selectivity of DA reaction between 2-methyl-1,3-butadiene with several α -cyano α,β -unsaturated ketones was investigated using several parameters such as hardness, electrophilicity and polarizability. Furthermore thermodynamic and kinetic of these reactions are studied to predict more favorable region isomer. It is notable that some of these reactions have been studied experimentally [28].

METHODOLOGY

In this work, the density functional theory (DFT) [29-30] calculations were done for geometry optimization of all structures and vibrational frequency analysis using Gaussian 98 series of programs [31] at B3LYP/6-31G (d) level of theory in the gas phase at 298.15 K. All structures were characterized by the number of imaginary frequencies [32-34]. The global electrophilicity index, ω , for products was calculated using [35]:

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

The electronic chemical potential, μ ,

and chemical hardness, η , were calculated as follows [30, 36]:

$$\mu = \frac{1}{2}(\epsilon_{HOMO} + \epsilon_{LUMO}) \quad (2)$$

$$\eta = (\epsilon_{LUMO} - \epsilon_{HOMO}) \quad (3)$$

where ϵ_{HOMO} and ϵ_{LUMO} are the highest occupied and lowest unoccupied molecular orbital energies, respectively. Noorizadeh and Maihami [37] revealed that the major product of a Diels-Alder reaction has always less electrophilicity than the minor product.

The electric dipole polarizability, α , is another global property that the isotropic average polarizability was calculated as follow [38, 39]:

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (4)$$

Furthermore, thermodynamic and kinetic parameters were investigated. Kinetic parameters such as activation energy, E_a , was computed using Equations (2) which are derived from the TS theory [40, 41]:

$$E_a = \Delta H_{(T)}^\ddagger + 2RT \quad (5)$$

Kinetic and thermodynamic parameters were also calculated at 298.15K and 1.0 atm.

RESULTS AND DISCUSSION

In the present work, the cycloaddition reactions between 2-methyl-1, 3-butadiene with several α -cyano α,β -unsaturated ketones (4 reactions) were investigated (Fig.1). Two region isomers are the main products of these reactions, Para and Meta region isomers, which are shown in Table 1. Global indexes such as hardness (η), electrophilicity (ω) and polarizability (α) values for products and also thermodynamic and kinetic parameters are used to predict the region selectivity in these reactions. Table 2 and Fig.2 show the optimized structures of the reactant, TSs and product of investigated reactions at the B3LYP/6-31G* level.

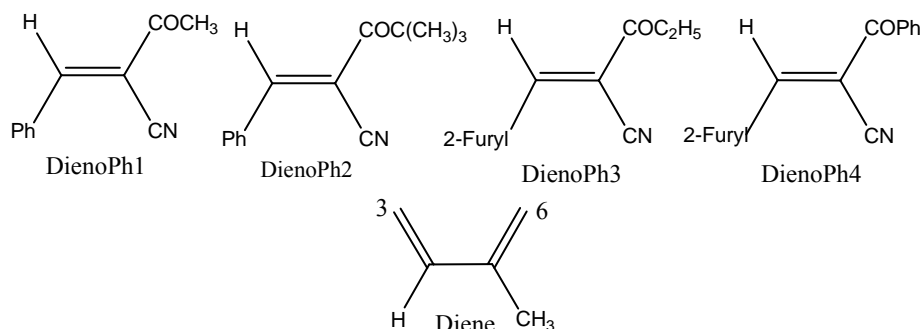


Fig. 1. Reactants of investigated DA reactions (2-methyl-1,3-butadiene =Diene and Dienophile1-4).

Table1. Two products (regioisomers Para and Meta) of investigated DA reaction (2-methyl-1, 3-butadiene =Diene and Dienophile1-4)*

| Reaction 1 (Diene+DienoPh1) | | Reaction 2 (Diene+DienoPh2) | |
|-----------------------------|------|-----------------------------|------|
| Para | Meta | Para | Meta |
| | | | |
| Reaction 3 (Diene+DienoPh3) | | Reaction 4 (Diene+DienoPh4) | |
| Para | Meta | Para | Meta |
| | | | |

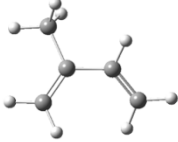
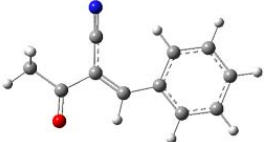
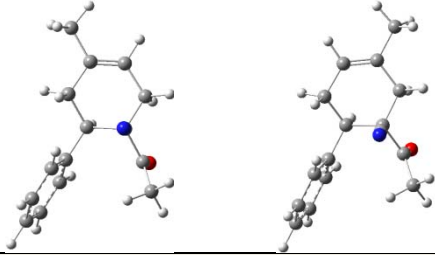
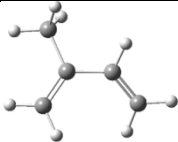
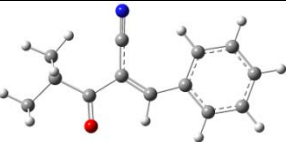
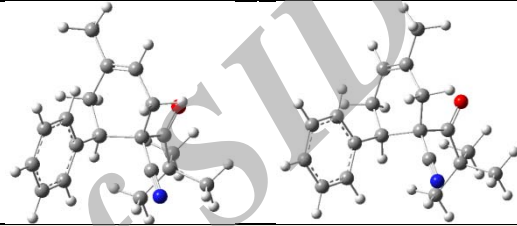
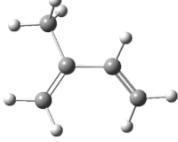
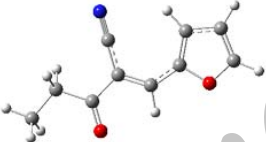
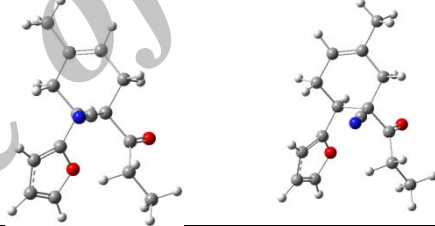
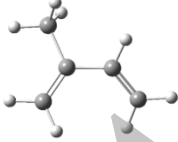
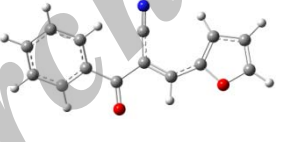
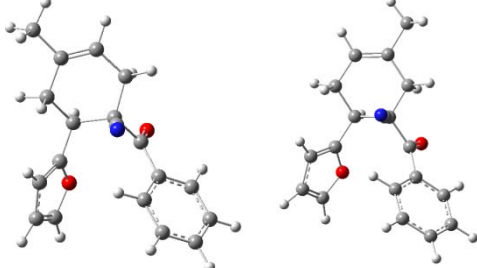
*See Fig 1 for details.

Global reactivity descriptors indexes

In many cases, the validity of MHP and MPP rules are confirmed and these rules are in agreement with the experimental documents [42–44]. But it is found that more reactions should be studied. So, in this work, we wanted to examine these rules to predict region selectivity for some selected DA reactions. Also, MEP rules which was introduced by Noorzadeh *et al.* was used [24]. Based on the para rule, the para region isomer is expected to be the major product of these reactions. The HOMO and LUMO energy and related parameters such as hardness (η),

electrophilicity (ω) and polarizability (α) values for products are listed in Table 3. As expected the MHP, MEP and MPP rules correctly predicted the para region isomer is the major product of all these reactions. Afterwards, with computing and comprising of the global electrophilicity, ω , of dienophiles with different R1 groups (Table 3), the order increase of electrophilicity for dienophiles with R2=phenyl and different R1 groups (first group reactions) was determined as t-Bu>methyl and for dienophiles with R2=2-furyl and different R1 groups (second group reactions) was determined as phenyl>ethyl

Table 2 Optimized structure of reactants (2-methyl-1,3-butadiene with Dienophile1-4) and products (Para and Meta regioisomers) of investigated DA reactions (see fig 1 for details)

| Reaction 1 | | |
|---|---|--|
| Diene | DienoPh 1 | Meta Regioisomer |
|  |  |  |
| Reaction 2 | | |
| Diene | DienoPh 2 | Meta Regioisomer |
|  |  |  |
| Reaction 3 | | |
| Diene | DienoPh 3 | Meta Regioisomer |
|  |  |  |
| Reaction 4 | | |
| Diene | DienoPh 4 | Meta Regioisomer |
|  |  |  |

(see Fig. 1). It is obvious that phenyl group has the most electrophilicity in the above series. At last, presence of an electron-releasing (ER) group on dienophiles decreases both frontier orbital energies, thus ER groups make it more electrophile in global terms.

Thermodynamic and Kinetic parameters

The thermodynamic parameters for the

investigated reactions include: sum of electronic and thermal Gibbs free energies (G), sum of electronic and thermal enthalpies (H), and entropies (S) for the ground state of reactants, products and for TSs from the thermochemistry calculations. Also, the standard Gibbs free energy change (ΔG°), standard enthalpy change (ΔH°) and standard entropy change (ΔS°) of two pathways of reactions are obtained

and reported in Table 5. Thermodynamic results show that all pathways are exothermic ($\Delta H_r^\circ < 0$) by 18.51 -24.91 kcal/mol. It is found that the reaction with the largest exothermicity is related to para region isomer of reaction 1 (see Table 1). Computed standard Gibbs free energy change of reactions (Gibbs free energy difference, ΔG°) show that all reactions are spontaneous processes ($\Delta G^\circ < 0$) and indicate little difference between production pathway of two regioisomers but it can be said that the pathway with meta product is thermodynamically a little more favorable by 2.47-6.57 kcal/mol (except reaction 1). Also, in the reactions including dienophiles with R2= phenyl and different R1 groups (first group reactions) $\Delta G_{r,R1=t-Bu}^0 < \Delta G_{r,R1=methyl}^0$ and in the reactions including dienophiles with R2=2-furyl and different R1 groups (second group reactions) $\Delta H_{r,R1=phenyl}^0 < \Delta H_{r,R1=ethyl}^0$ for para and meta products. This suggests that the use of R1 = t - Bu in first reactions and R1 = phenyl in second reactions is thermodynamically

more favorable than use of R1 = methyl and R1 = ethyl in first and second group reactions respectively. The entropy changes during these DA reactions are positive. As can be seen, all reactions are entropically unflavored.

Kinetic parameters such as activation energies, E_a , and subsequently rate constants, k , for the eight transition states which are shown in Fig.2, are calculated and reported in Table 5. For all reactions, para pathways show lower activation energy and higher rate constant. Para pathway in the reaction of **1** shows the lowest activation energy, 20.63 kcal mol⁻¹. Reactions with lower activation energies should proceed easily. The activation energies of investigated energy reactions are 20.63-23.94 kcal mol⁻¹ which means that these reactions would be possible under mild conditions.

In kinetic results, similar behaviors are seen about R1 rate constants of para and meta products for first and second group reactions, which is $k_{R1=t-Bu} > k_{R1=methyl}$ and $k_{R1=R1=phenyl} > k_{R1=ethyl}$.

Table 3. Calculated frontier molecular orbital energies (ϵ_H and ϵ_L), hardness values (η), global electro philicity indexes (ω) and polarizabilities (α) with 6-31G* basis set for the products of five selected Diels–Alder reactions

| Reaction | Regioisomer | ϵ_H | ϵ_L | η | ω | α |
|----------|-------------|--------------|--------------|----------------|-----------------|---------------|
| 1 | Para | -0.24051 | -0.33080 | 0.20743 | 0.045106 | 160.58 |
| | Meta | -0.24055 | -0.03327 | 0.20728 | 0.045215 | 161.00 |
| 2 | Para | -0.23305 | -0.03818 | 0.19487 | 0.047189 | 193.25 |
| | Meta | -0.23311 | -0.03924 | 0.19386 | 0.047825 | 215.16 |
| 3 | Para | -0.22903 | -0.03031 | 0.19872 | 0.042307 | 153.13 |
| | Meta | -0.22878 | -0.03062 | 0.19816 | 0.042446 | 153.35 |
| 4 | Para | -0.23557 | -0.02995 | 0.16407 | 0.064308 | 192.78 |
| | Meta | -0.23511 | -0.23511 | 0.16364 | 0.064597 | 192.89 |

Table 4. FMO energies (a.u.), electronic chemical potential (a.u.), chemical hardness (a.u.), chemical softness (a.u.⁻¹) and electro philicity index (a.u.) for reactants

| | HOMO | LUMO | μ | η | ω |
|------------|---------|---------|---------|--------|----------|
| DienoPhil1 | -0.2491 | -0.0963 | -0.1727 | 0.1528 | 0.0976 |
| DienoPhil2 | -0.2474 | -0.0944 | -0.1709 | 0.1530 | 0.0954 |
| DienoPhil3 | -0.2363 | -0.0957 | -0.1660 | 0.1406 | 0.0980 |
| DienoPhil4 | -0.2344 | -0.0974 | -0.1659 | 0.1370 | 0.1004 |

In fact, the electron-releasing groups raise both frontier orbital energies, and electron withdrawing groups lower these energies. The presence of electron-releasing groups in the diene and electron-withdrawing in the dienophile can increase rate of reactions. Based on the order increase of electrophilicity which was explained, the methyl and ethyl groups have the least electrophilicity in the first and second group reactions respectively. So, as we

expected, the results showed that the presence of a weaker electron-releasing group on dienophile increases rate of reactions.

CONCLUSION

Density functional theory calculations at the BLYP/6-31G* level was performed to investigate regioselectivity of DA reaction between 2-methyl-1,3-butadiene with selected α -cyano α,β -unsaturated ketones

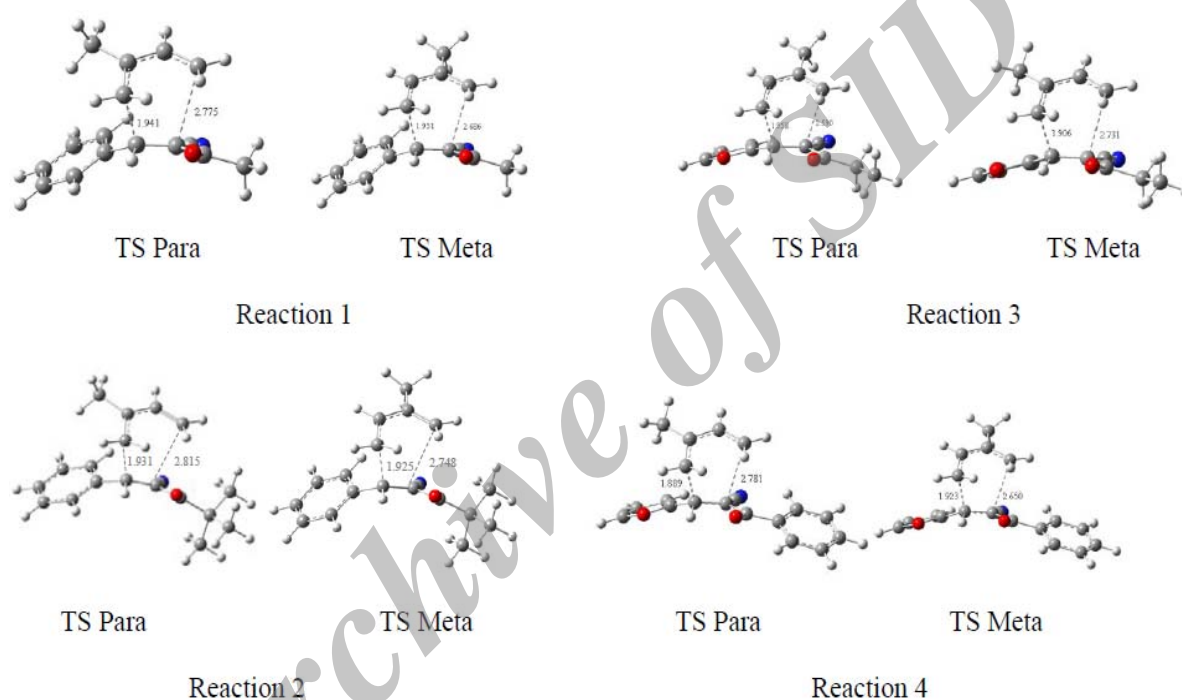


Fig.2. B3LYP/6-31G* transition structures for the DA reaction of reaction of 2-methyl-1,3-butadiene with Dienophile 1-4 (see fig 1 for details). The values of the bond lengths are given in Å.

Table 5. Calculated thermodynamic and kinetic parameters at 298.15 K and 1.0 atm for investigated DA reactions in the gas

| Reaction | Regioisomer | ΔG^0 | ΔS^0 | ΔH^0 | E_a | k |
|----------|-------------|--------------|--------------|--------------|----------|----------|
| | | kcal/mol | cal/mol | kcal/mol | kcal/mol | |
| 1 | Para | -9.08 | -53.104 | -24.915 | 20.63 | 7.30E-11 |
| | Meta | -9.07 | -52.894 | -24.846 | 22.05 | 6.63E-12 |
| 2 | Para | -2.17 | -54.791 | -18.513 | 20.84 | 2.04E-11 |
| | Meta | -2.47 | -54.976 | -18.866 | 22.24 | 1.32E-12 |
| 3 | Para | -6.54 | -51.629 | -21.943 | 21.93 | 6.72E-12 |
| | Meta | -6.57 | -51.481 | -21.928 | 23.86 | 3.29E-13 |
| 4 | Para | -5.41 | -52.061 | -20.941 | 21.77 | 5.76E-12 |
| | Meta | -5.44 | -52.064 | -20.963 | 23.94 | 2.85E-13 |

using several parameters such as the hardness, electrophilicity and polarisability of products. Furthermore thermodynamic and kinetic of these reactions are studied to predict more favorable region isomer. The the MHP, MEP and MPP rules indicated that the pararegioisomer is the major product in all these reactions. Thermodynamic results revealed that all pathways are exothermic and spontaneous. For all reactions para pathways showed lower activation energy and higher rate constant.

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