Tetrahedron 72 (2016) 8261–8273

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Mechanistic studies on Diels-Alder [4 + 2] cycloaddition reactions of α,β-substituted cyclobutenones: Role of substituents in regio- and stereoselectivity

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ARTICLE INFO

Article history:
Received 17 August 2016
Received in revised form
11 October 2016
Accepted 24 October 2016
Available online 3 November 2016

Keywords:
Diels-Alder cycloaddition
Mechanism
Regioselectivity
Stereoselectivity
Dane's diene
Cyclobutenone

ABSTRACT

Diels-Alder reactions of substituted cyclobutenones with 6-methoxy-1-vinyl-3,4-dihydronaphthalene and methoxy-substituted-1,3-butadiene have been studied with DFT. In the reactions of 6-methoxy-1-vinyl-3,4-dihydronaphthalene with cyclobutenone and α-bromocyclobutenone, the formation of the *meta* and *ortho* isomers have the same barriers, indicating that the two isomers might be formed in equal proportions, contrary to earlier reports. The regiochemistry of the reaction is mainly controlled by the ketone functionality at C1 on the dienophiles. In the reactions of methoxy-substituted-1,3-butadiene with cyclobutenone and α, β-substituted cyclobutenones the *ortho/endo* and *para/endo* stereo-isomeric pathways are the most favorable pathways, changing to *exo* selectivity when OH, Br, CH_3 are placed on the β-carbon of the cyclobutenone, but still with *ortho* and *para* regioselectivity. The stereoselectivity is independent of the bulkiness of substituents. The stability of substituted cycloadducts are lower compared to unsubstituted adducts and this explains why the α-cyanoketones and α-bromoketone products readily undergo *trans*-methylation and angular-alkylation as electrophiles.

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1. Introduction

The mechanism of the Diels-Alder reaction, a [4π + 2π] cycloaddition reaction between a molecule with a conjugated π-system (diene) and another with at least one π-bond (dienophile) to form cyclohexene derivatives, has been the subject of the most heated and interesting controversies. Woodward and Hoffmann defined the concept of a pericyclic reaction, of which the Diels-Alder reaction is an example, as a concerted reaction in which all bonds are made or broken around a circle. Although the Woodward-Hoffmann rules declare what may and may not happen, the rules served not to settle mechanistic questions but to raise the stakes on what was already lively controversies.[1]

The Diels-Alder reaction is one of the most important reactions in organic chemistry, and has both enabled and shaped the art and science of total synthesis over the last few decades to an extent which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire. With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and programmed cascade sequences facilitating complex molecule construction, the Diels-Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by Nature in the form of natural products, and has proved a reliable method for forming six-membered systems with good control over regio and stereochemical properties.[2,3]

The Diels-Alder reaction was expanded recently through the discovery by Li and Danishefsky that cyclobutenone is an unusually reactive dienophile and that, more importantly, the cycloadducts formed can undergo subsequent regioselective ring expansion to form lactones, lactams and cyclopentanones which are difficult to obtain in the direct Diels-Alder reactions.[4] It was reported that experimental outcomes indicated that cyclobutenone was more reactive than classical 2-cyclopentenone or 2-cyclohexenone dienophiles.

Diels-Alder reactions of silyloxydienes, silylated dienes with cyclic or acyclic α, β unsaturated ketones, as dienophiles were reported to have the *endo*/*exo* stereochemical outcome which is strongly influenced by the substitution pattern of the reactants.[5,6] Asymmetric Diels-Alder reaction of halogenated cyclic enones has

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http://dx.doi.org/10.1016/j.tet.2016.10.063
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been an attractive approach for the stereoselective formation of halogenated quaternary stereogenic centers. However, adducts derived from α-bromo or α-cyano cyclic ketones could also be converted into transfused bicyclic systems by reductive alkylation involving an inversion of the stereochemistry.[7–10] Diels-Alder reaction of 2-cycloalkenones and 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene) and its derivatives with α,β-enones were demonstrated to be catalyzed by Lewis acid with profound effects on the ratio of *exo* and *endo* addition products.[11]

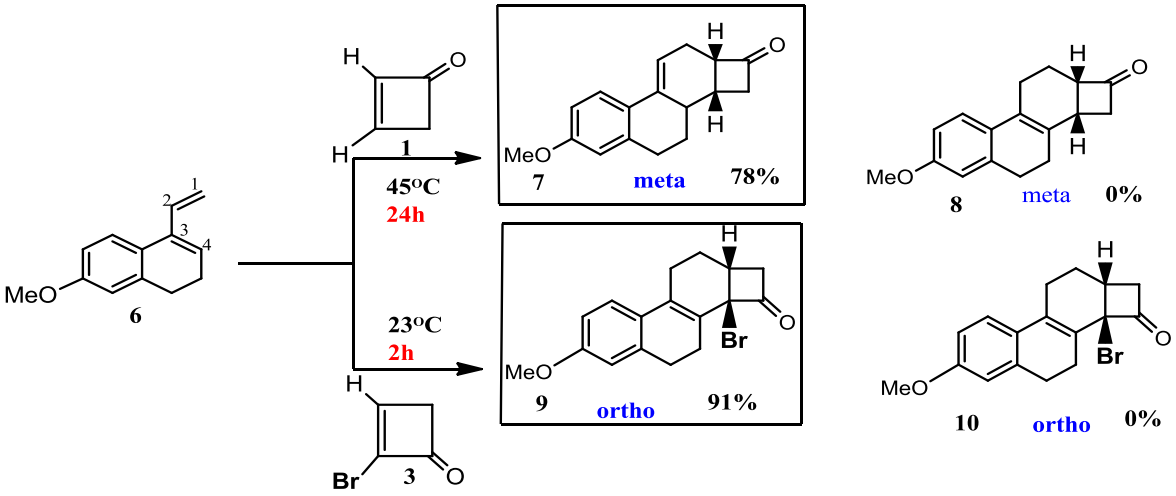
Further studies by Ross et al.[12] on reactions of halo-cycloenones as dienophiles in inter- and intra-molecular Diels-Alder cycloaddition reaction shows 2-bromocyclobutenone to be far more reactive as compared to the corresponding higher cycloenones without any catalyst. They also reported that reactions of α-bromocyclobutenone with Dane's diene gives one *meta* regioisomer with intramolecular isomerization of the olefinic bond from the newly formed ring C to a more substituted inner ring to form a steroid derivative (Scheme 1). It was hypothesized that because these particular dienophiles are exceptionally electrophilic "Michael–type" DA acceptors, they have greater asynchronicity in a Diels-Alder transition state, perhaps approaching, in the extreme, a formal stepwise reaction.

Paul et al.[13] performed a computational and experimental study to elucidate the effect of halogen substitution on furan diene and vinyl ethylene dienophile for the intramolecular furan Diels–Alder (IMDAF) reactions. The halogen substitution on the dienophile was reported to have a significant effect, making the reactions slower and less thermodynamically favorable. Therefore, a choice of position on the furan for halogenation could be used to overcome problems with dienophile halogen substitution, leading to highly functionalized cycloadducts. Spanevello et al.[14] conducted experimental and computational studies to evaluate the effect of chlorine and bromine substitution in Diels–Alder reactions involving chiral α-halo enones as dienophiles. An important rate enhancement was reported to be observed in the case of acyclic dienes, while the use of cyclic dienes led to prolonged reaction times and lower yields. It was reported that DFT calculations suggest that these reactions are governed by finely balanced geometric and electronic features at the transition states. Paton et al.[15] studied the reactions of pent-3-en-2-one, cyclohex-2-enone, cyclopent-2-enone, cyclobutenone and cyclopropenone with cyclopentadiene, 1,3-cyclohexadiene and 1,3-cycloheptadiene at the M06-2X/6-31G(d) level of theory and found that cyclobutenone has consistently lower activation barriers, and accordingly higher rate constants, than corresponding enones. The high reactivity of strained cycloalkenones was attributed to an ease in out of- plane distortion, noting that there is a weak correlation between the activation energy of the reactions and their reaction energies but a strong correlation between activation energies and reactant distortion energies, and that the difficulty of out-of-plane distortion parallels increased ring size. The same observations were reported when cycloalkenes were also used as dienophiles.[16] This behavior was reported to arise from the larger s character in the C–H bond and the fact that the smaller internal angle in the small rings is more appropriate for the pyramidal transition state.

Tia et al.[17] performed a computational study on the reactions of maleic anhydride and cyclobutenone at the MP2/6-31G* level of theory and found maleic anhydride to be a far better dienophile than cyclobutenone, concluding that for cyclic dienophiles ring strain is not the dominant factor controlling the kinetics of the Diels-Alder reaction. The reactions of substituted cyclobutenones were all found to follow an asynchronous concerted reaction pathway. In the reactions of the 1,3-butadiene and cyclopentadiene with the parent (unsubstituted) cyclobutenone, the *endo* pathway was the most preferred kinetically. The regio-and stereoselectivity of Diels–Alder reactions between electron-rich 1,3-butadiene derivatives and 2-substituted cyclobutenones were studied using density functional theory (DFT). Four possible reaction pathways, which leads to the formation of bicyclo[4.2.0]3,7-octenones were proposed and it was reported that the larger activation energy prevents the formation of *meta* products.[17,18]

Theoretical investigations of intramolecular Diels-Alder reactions of cycloalkenones and terminal dienes in which geometry optimizations were conducted in the gas phase using the M06-2X hybrid *meta*-GGA density functional theory have been reported. The reactions were reported to be highly *endo* stereoselective for both thermal and Lewis-acid conditions and it was shown that steric repulsion and tether conformation governed the selectivity of the cycloadducts, and incorporation of either BF_3 or α-halogenation increases the rate of cycloadditions.[19]

Some computational studies have been performed to determine the origin of the special reactivity of cyclobutenone, the effect of substituents on the reactivity as well as regio- and stereoselectivity of the Diels-Alder reaction of cyclobutenone. However, to the best of our knowledge no systematic studies have been conducted to assess the most favorable pathway (*ortho* or *meta*) that leads to the experimentally-observed isomerization adduct in the reaction of 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene) with



Scheme 1. Diels-Alder reactions of Dane's diene (**6**) with cyclobutenone (**1**) and α-bromocyclobutenone (**3**).

cyclobutenone and halo-cyclobutenones as dienophiles. Also, the exact key roles of substituents on the reactions leading to the formation of bicyclo[4.2.0]-3,7-octenones have not been conducted yet. Therefore, by means of quantum chemical calculations at the M06/6-31G* level of theory, this work aims at investigating the *endo*/*exo*, *ortho*/*meta* and *para*/*meta* regio-and stereoselectivity of Diels-Alder reactions of substituted cyclobutenones with Dane's diene and methoxy substituted 1,3-butadiene.

2. Details of calculations

All calculations were performed with the Spartan'08 V1.2.0 and Spartan '10 V1.1.0 Molecular Modeling programs[28] at the DFT M06/6-31G* levels of theory.[29]

Spartan uses a graphical model builder for input preparation. Molecules were constructed and minimized interactively using an appropriate molecular mechanics force field. All structural optimizations were done without symmetry restrictions. Normal mode analysis was performed to verify the nature of the stationary points located. Minima, representing reactants, intermediates and products were shown to have no imaginary frequencies.

Guess structures for transition state calculations were obtained by first constraining specific bonds along the reaction coordinates at fixed lengths while the remaining internal coordinates were fully optimized. This procedure gives an approximate transition state guess which is then submitted for transition state calculation using the standard transition state optimization procedure in Spartan. All transition state structures were subjected to full normal mode analyses to ensure that they have a Hessian matrix with a single negative eigen-value, characterized by an imaginary vibrational frequency along the reaction coordinate. An intrinsic reaction coordinate (IRC) calculation was carried out to ensure that transition states smoothly connect reactants and products.

3. Results and discussion

3.1. Regio- and stereoselectivity of Diels-Alder cycloaddition reactions of cyclobutenone, α-bromocyclobutenone with 6-substituted-1-vinyl-3, 4-dihydronaphthalene

Fig. 1 shows the optimized geometries and Gibbs free energetics of the transition states and adducts in the Diels-Alder reaction of the unsubstituted cyclobutenone with 6-methoxy-1-vinyl-3,4-dihyhronaphthalene (Dane's diene). Dane's diene is an exocyclic diene in which the C_3–C_4 fragment forms part of a 3,4-dihyhronaphthalene ring with free C_1–C_2 end which makes it flexible to adopt the *cis* and *trans* conformations at the free end. The *cis* form of this diene was considered throughout in the calculations in which the C_1–C_2 and C_3–C_4 bond lengths were calculated to be 1.35 Å while the C_2–C_3 bond length is 1.47 Å.

The cycloaddition reaction of Dane's diene with cyclobutenone goes through the *endo*/*exo* transition state in which the new C_1–C_α

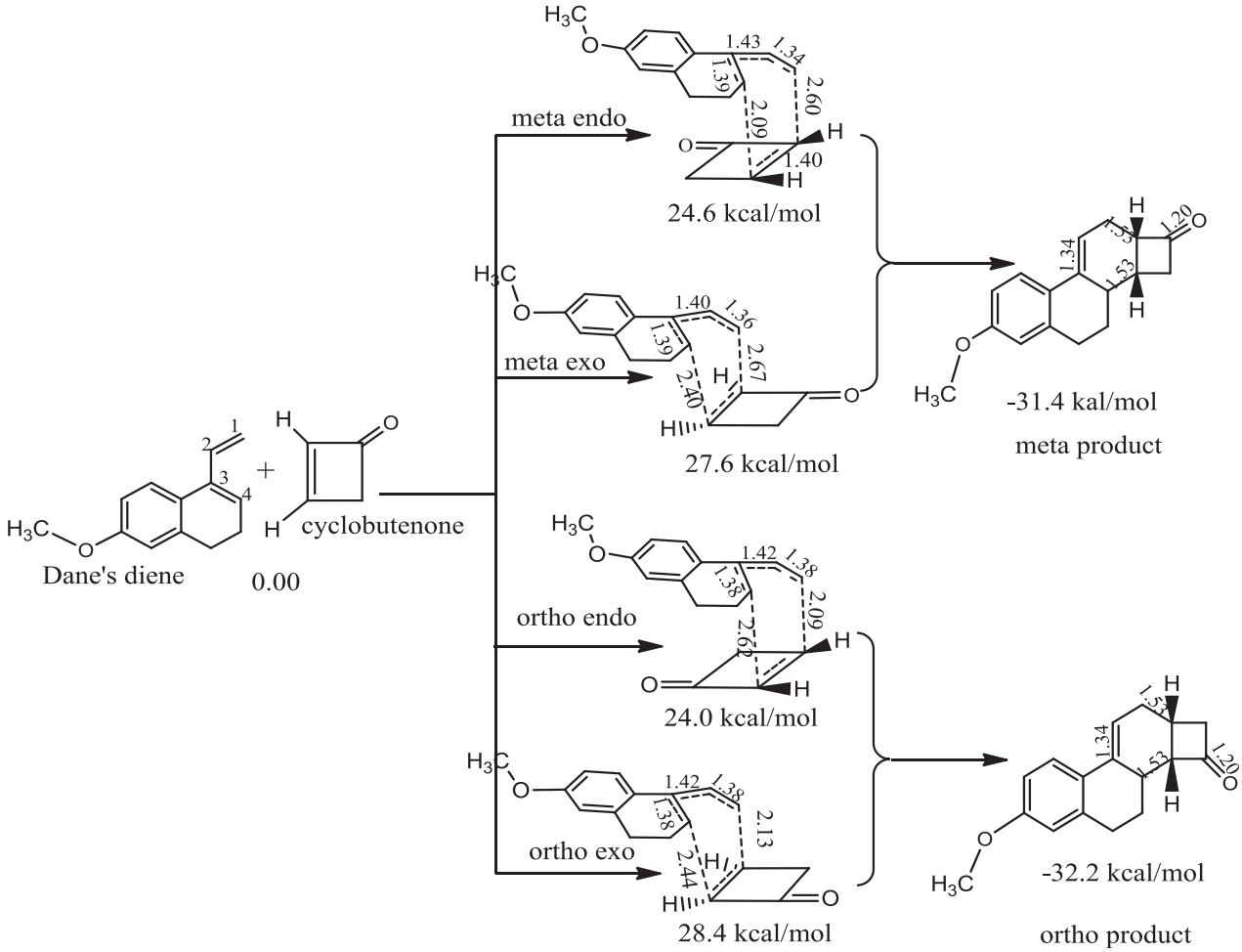


Fig. 1. Optimized geometries, Gibbs free energies of the transition states and products of Dane's diene with parent cyclobutenone. All the calculated bond lengths are measured in Å units and energies in kcal/mol.

and C_4—C_β forming bonds lengths are 2.65 Å and 2.09 Å for the *endo* transition state and 2.44 Å and 2.13 Å for the *exo* transition state. The normal mode analysis shows that the reactions follow a synchronous concerted pathway. The energy barrier through the *meta endo* transition state is 24.6 kcal/mol while that through the *meta exo* transition state is 27.6 kcal/mol, making the *endo* kinetically favorable over the *exo* by 2.9 kcal/mol. The reaction is exergonic with a reaction energy of ?31.4 kcal/mol. Since Dane's diene is an asymmetrical diene with the C_3—C_4 portion locked in the 3,4-dihyhronaphthalene ring, flipping the orientation of approach of the cyclobutenone gives another *ortho endo*/*exo* isomeric channel. The energy barrier via the *ortho endo* is 24.0 kcal/mol whereas the *ortho exo* transition state energy is 28.3 kcal/mol making the *ortho endo* pathway also the most favored pathway.

Thermodynamically, the reaction is also exergonic with a reaction energy of ?32.3 kcal/mol. Comparing the two isomeric pathways, the *ortho endo* pathway is kinetically more favorable than the *meta endo* pathway, albeit only marginally by just 0.6 kcal/mol. The closeness of the energy barriers of the two pathways shows that the two isomers should be formed in equal quantities. Even though the work of Townsend et.[12] indicates that the *meta endo* adduct is the only observed product, this study reveals that the unobserved *ortho endo* isomer is most likely present in equal amount. Obviously, the *ortho* cycloadduct is more favored over the *meta* cycloadduct if the reaction is thermodynamically controlled. These observations from the calculations are not unanticipated because the locking of C3—C4 in the six membered ring of the 3,4-dihydronaphthalene means that there are two alkyl substituents on C-3 and C-4 and these alkyl substituents contribute to the closeness of the energies between *meta* and *ortho* isomers.

It has been reported[12] that substitution of bromine atom on α-carbon (C2) of the cyclobutenone improves the reactivity of the cyclobutenone with Dane's diene and that the product could undergo intramolecular isomerization to form tetra-substituted steroidal *meta* products. To study the effects of bromine on the reactivity and the reaction pathways only the most favorable *endo* isomeric pathways were considered. The substitution of hydrogen with bromine atom on the α-carbon reduces the energy barriers by about 3.2 kcal/mol (Fig. 2). The energy difference between the *meta endo* and the *ortho endo* transition states remains the same (0.6 kcal/mol), demonstrating that the halogen is able to enhance the dienophilicity of the cyclobutenone in terms of reactivity but not its preferential regioselectivity. The bromine does not make the *meta* isomer more regioselectively favored over the *ortho* isomer either kinetically or thermodynamically as claimed by some experiments. The study of the intramolecular isomerization shows that about 96.5 kcal/mol energy is needed to overcome the second energy barrier which is about four times the initial energy barrier (21.8 and 21.2 for *meta* and *ortho* respectively). This shows clearly that the isomerized product observed in experiment did not arise

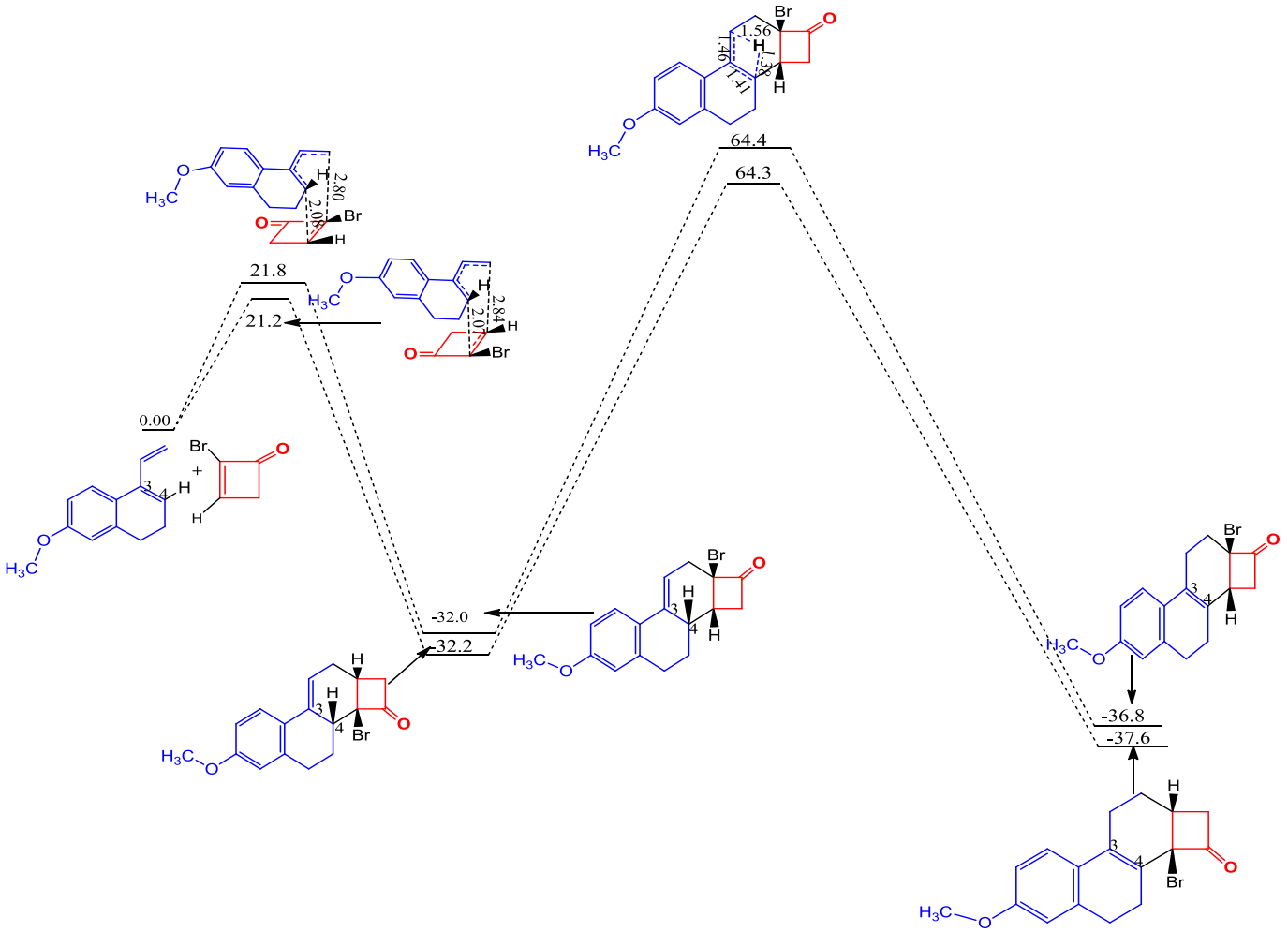


Fig. 2. Optimized geometries, Gibbs free energies of the transition states and products of Dane's diene with α-bromocyclobutenone. All the calculated bond lengths are measured in Å units and energies in kcal/mol.

Table 1
Energetics of the reactions of cyclobutenone with substituents at position 6 of 1-vinyl-3,4-dihyhronaphthalene (derivatives of Dane's diene)/kcalmol^{-1}.

Substituent	Ortho T. S	Meta T. S	Ortho Product	Meta product
−H	24.3	24.7	−32.5	−31.9
−OH	24.3	24.6	−32.4	−31.8
$-CH_3$	24.5	24.7	−32.4	−31.7
−Br	24.5	25.2	−32.4	−31.6
−CN	24.6	25.4	−32.5	−31.7

from the primary Diels-Alder [4 + 2] cycloaddition pathway.

Table 1 presents both activation and reaction energies of the reactions of cyclobutenone with derivatives of Dane's diene in which the methoxy ($-OCH_3$) substituent at the position 6 is replaced with −H, −OH, $-CH_3$, −Br and −CN substituents to study the effects on the *ortho* and *meta* pathways. The change of $-OCH_3$ substituent to −H, −OH, $-CH_3$, −Br and −CN substituents do not have any significant effects on the new forming bond lengths. The mechanism of the reactions is seen to follow a synchronous concerted one for all these substituents which is the same as the original Dane's diene.

Table 1 shows that the activation barriers along the *ortho* pathway do not change upon changing the substituent on position 6 of 1-vinyl-3,4-dihyhronaphthalene; the same is true along the *meta* pathway. It is also seen that the *ortho*/*meta* selectivity is the same as that of the original methoxy substitution at the 6 position of 1-vinyl-3,4-dihyhronaphthalene. The Br and CN which are negative electron withdrawing groups at the position 6 increase the activation energy by about 1.0 kcal/mol for the *meta* isomeric pathway while that of the *ortho* pathway still remains unchanged. The *ortho* isomeric pathway is more favored both kinetically and thermodynamically for Br and CN substitutions at the 6 position over the *meta* isomeric pathways. Energetically, the two pathways are found to be the same for −H, −OH, and $-CH_3$ substituents if the reactions are kinetically controlled but thermodynamically the *ortho* isomeric pathway is more favored for all the substituents studied at the 6 position. To make either *ortho* or *meta* isomer favored over the other then there should be an electron withdrawing group at sixth position of the 1-vinyl-3,4-dihyhronaphthalene as in the case of Br and CN.

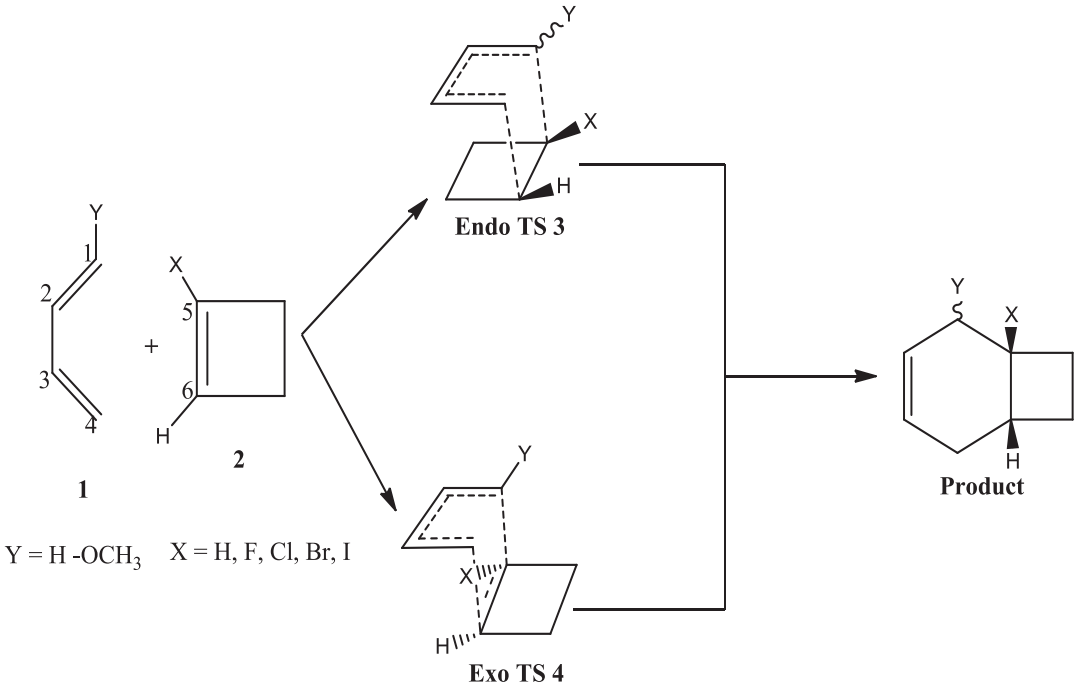
3.2. Diels-Alder reaction of halogen substitutions of cyclobutene as dienophile with 1,3-butadiene and 1-methoxy-1,3-butadiene

Generally, halogens (−F, −Cl, −Br −I) as substituents are known to exhibit negative electron withdrawing effects while donating them through resonance when they are attached to double bonds. These halogens are known to accelerate the rates of cycloaddition reactions of cycloakenenones.[27] The most important feature of these halogens is that, they can be replaced easily by other groups because of the electronegativity differences they usually display. However, no study has been conducted to ascertain the exact effects of the halogens on the ring without the ketone functionality. In order to explore the relationship between halogen substitutions of cyclobutenone moieties on the reactivity and selectivity in Diels-Alder reactions, halogens substitutions on cyclobutene are studied to understand the exact effects they exhibit on cyclic dienophiles.

Scheme 2 shows the proposed pathways and Table 2 summarizes the calculated results of substituted 1, 3- butadiene and halogens substitution of cyclobutene as dienophile. The *cis* form of the 1,3-butadiene is considered where the C_1-C_2 and C_3-C_4 bond lengths are 1.33 Å and 1.46 Å respectively whereas the bond length between C_5-C_6 of the dienophile is 1.34 Å. At the transition state the C_1-C_5 and C_4-C_6 bond lengths are the same which is 2.28 Å.

The reactions are found to proceed by *endo* and *exo* addition pathways which eventually lead to a product for the parent reactants. The reaction follows a synchronous concerted mechanism with activation energy of 29.1 kcal/mol through the *endo* transition state **TS3** and 29.5 kcal/molthrough the *exo* transition state **TS4** for parent compounds (when X=Y=H). Thus, kinetically the *endo* route has almost the same barrier as the *exo*. Thermodynamically, the reaction is exergonic with reaction energy of ?36.1 kcal/mol.

When hydrogen (substitution of H in Scheme 2) is replaced by



Scheme 2. Proposed pathways for the reactions of cyclobutene with 1,3-butadiene.

Table 2
Energetics of the Diels-Alder cycloaddition reactions of butadiene,1- methoxy-1,3-butadiene and substituted cyclobutenes as dienophile.

Substituents	Activation Energy (ΔG^*)/kcal/mol		Reaction energy (ΔG_{rxn})/kcal/mol	
	Endo	*Exo*	*Endo*	*Exo*
Y=H; X=H	29.1	29.5	−36.1[a]	
Y=H; X=F	30.6	31.8	−39.1	
Y=H; X=Cl	30.2	31.9	−37.9	
Y=H; X=Br	30.2	31.7	−37.6	
Y=H; X=I	29.9	31.5	−36.7	
Y=OCH_3; X=F	36.7	38.4	−35.5	- 32.3
Y=OCH_3; X=Cl	36.2	38.7	−33.9	−31.4
Y=OCH_3; X=Br	36.1	38.5	−33.3	−31.3
Y=OCH_3; X=I	35.1	38.5	−32.4	−30.7

[a] When Y=H and X=H, F, Cl, Br, I, there are no endo/exo stereo-isomers for the adducts formed.

halogens on compound **2** the activation barriers are observed to increase for all compared to the parent compounds but decrease as the size of the halogens increases down the group (Table 2). The halogenated adducts are also found to be more stable relative to the parent adduct. Therefore, if the reaction is kinetically controlled iodine is the most reactive in the group and fluorine is the least reactive but if the reaction is thermodynamically controlled the reversed order is true. Pieniazek and Houk[21] reported that halogens substitution of hydrogen on the furan diene decrease activation barriers by 2–3 kcal/mol and increase reaction exothermicities by 4–9 kcal/mol and that halogen substitution of hydrogen on hydrocarbon dienes have the same effects as that of furan with the activation barriers decreasing by 0–2 kcal/mol and reaction exothermicities increasing by 0–4 kcal/mol at B3LYP/6-31G(d). However, in this work the activation barriers of the reaction of halogen-substituted cyclobutene with 1,3-butadiene are seen to increase by 0.8–1.6 kcal/mol while the reaction energy trend agrees with their results. This suggests that the effect of halogens substitution on dienes (in terms of reactivity) is not the same as when it is on the dienophiles for kinetics studies of cycloaddition reactions. The rates of the reactions increase as halogens are being substituted in the reaction center of cyclobutene dienophiles.

The idea of inverse electron demand in Diels-Alder reactions is taken into consideration whereby methoxy ($-OCH_3$) group is placed on C1 (Y in Scheme 2) of 1,3-butadiene and the halogens are maintained at the reaction center of the dienophile to study the electronic effects. It is seen that when $-OCH_3$ replaces H on the butadiene (Y in Scheme 2), the activation barriers increase significantly compared to unsubstituted 1,3-butadiene energies and the reaction energies increase substantially towards positive values indicating that halogens on the cyclic dienophiles do not display any withdrawal effects to cause any polarity in the dienophile and this could be attributed to either the ring or the back donating ability of the halogens.

3.3. Regio- and stereoselectivity of Diels-Alder cycloaddition reactions of parent cyclobutenone and substituted cyclobutenone with 1-methoxy-1, 3-butadiene

The Diels-Alder reaction of 1,3-butadiene **1** and planar cyclobutenone **5a** (Fig. 3) is also studied. The bond length of the reacting center ($^{\alpha,\ \beta}$) of **5a** has been calculated to be 1.35 Å. The reaction proceeds through two possible transition states (*endo* **T S6** and *exo* **TS7**). The normal mode analysis of the transition state structures shows that the reactions follow synchronous concerted reaction mechanisms. The new σ bond between the α-carbon of the dienophile and C-1 of the diene is 2.46 Å and that between the β-carbon and C-4 of the diene is 2.10 Å. The *endo* transition state is lower in energy than the *exo* transition state by 1.9 kcal/mol and the reaction is observed to be exergonic with an energy of ?34.4 kcal/mol.

Although at the transition state there are direct σ bonds forming between α, β-carbons of **5a** and C1 and C4 of **1**, the distances between C_2–C_3 of the diene and Cγ-carbonyl of the dienophile is 3.2 Å which is within the range through which van der Waals forces of attraction between carbon atoms exist which means that this additional effect might be exerted on the molecules to attain those

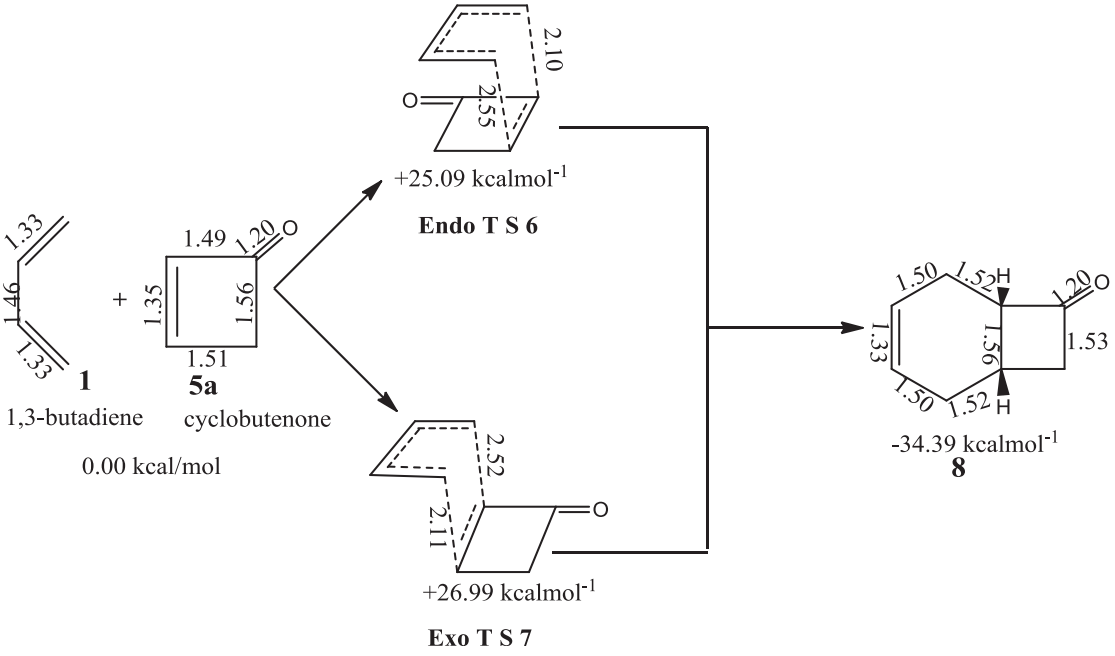
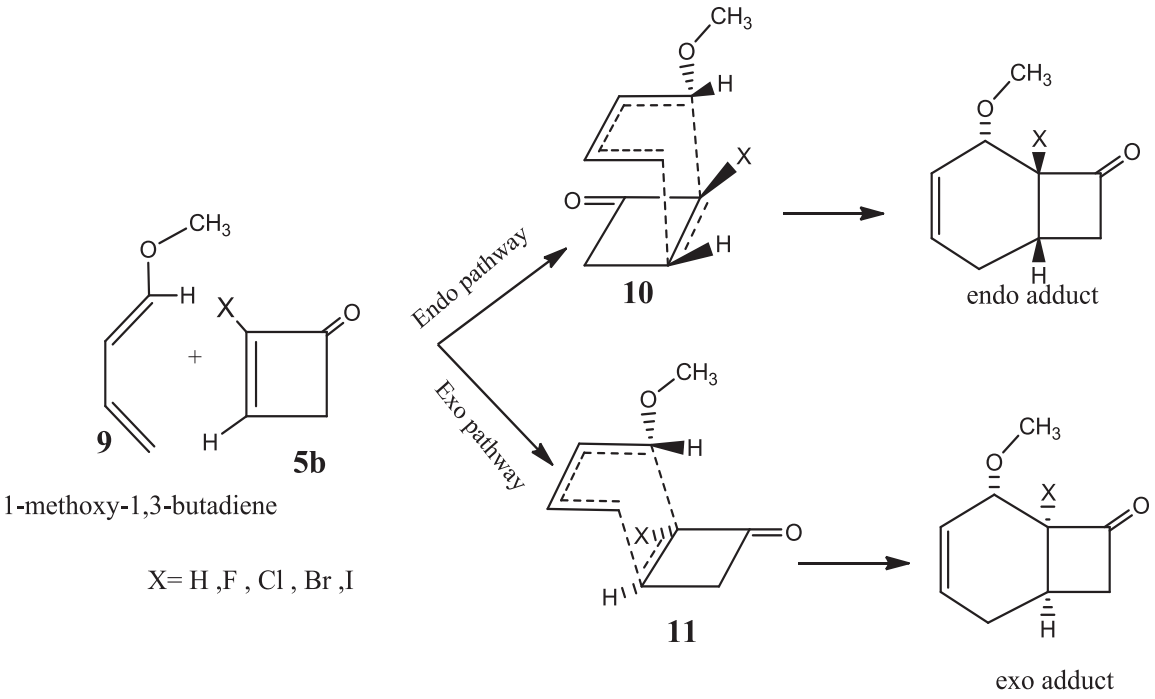


Fig. 3. The optimized geometries of the reactants, transition states and the products of Diels-Alder reaction of cyclobutenone and butadiene. All the calculated bond lengths are measured in Å units and energies in kcal/mol.



Scheme 3. Proposed pathways for the reactions of halogens substitution of cyclobutenone with 1-methoxy-1,3-butadiene.

structural conformations at the *endo* transition states since the approach from the two reactants is not planar. It should be noted that the same observation were made when cyclobutene was used as dienophile. The lack of these atomic interactions in the *exo* transition states might account for the high energies of the *exo* transition state. These facial selectivity has been studied both experimentally and computationally whereby secondary orbital interaction, frontier molecular orbital interaction, CH … π and more recently the activation strain model of Houk and workers to explain this selectivity but no explicit conclusions have been drawn on this selectivity.

Scheme 3 shows the proposed pathways involved in the reaction of α-halogen substituted of **5b** with **9** and Table 3 presents the Gibbs free activation and reaction energies. The methoxy group on the C-1 does not change the bond lengths of 1,3-butadiene significantly and the halogens substitution on α-carbon of **5b** has only a small effect on the bond length depending on the size of the halogens. The forming-bond lengths in the transition state for C_{α}-C_1 are in the range of 2.64–2.82 Å while those of C_{β}-C_4 are also in the range of 2.08–2.12 Å. The substantial change in new forming bond lengths of halogens substituted on **5b** is due to the electronic characteristics of the halogens. The reaction mechanism changes from synchronous concerted mechanism to asynchronous concerted mechanism when methoxy (−OCH_3) substituent is placed at C-1 of the 1,3-butadiene.

The −OCH_3 on the 1,3-butadiene has the potential of reducing the *endo* energy barrier by 4.3 kcal/mol but it has no or very little effect on the *exo* energy barrier which in turns reduces the stability of the product. The Cl, Br and I α-substitution of **5b** with **9** are very close in energies (both activation and reaction energies). The activation energies decrease down the series as observed for halocyclobutene reactions (Table 2) and the *endo* isomeric pathways are preferentially regio- and stereoselective over the *exo* pathways (energetics in Table 3). The activation energies of the halogen substitutions have also been observed to increase with increasing electron- withdrawing power of the halogens in the order of F > Cl=Br > I. The lower activation energy of α-halo-cyclobutenones as dienophiles could be attributed to the electronic effects of the halogens.

Emamian[19] has reported that the bulky bromine atom on α-carbon of cyclobutenone destabilizes the *exo* transition state making the *endo* stereo-isomers predominate at the transition state. However, these calculations show that none of the halogenated *endo/exo* activation energy difference exceeds the *endo/exo* energy difference of the parent which suggests that the dominance of *endo* isomers over the *exo* isomers does not come about as a result of atomic size at the reaction center of cyclobutenone (**5b**). It is of interest to note that unlike in the cyclobutene where the halogenated adduct energies increase compared to those of the parent products, here the energies of the halogenated adducts of compound **5b** rather decrease appreciably for both *endo* and *exo* stereoisomers. The decrease in products energies explains the readiness of the halogenated products to undergo *trans* alkylation reactions with other reagents such as alkyl lithium or methyl iodide as observed in experiments.[17,18,20,21]

To understand the exact driving force of the regio- and stereoselectivity when other substituents are placed on α, β-carbons of cyclobutenone **5a** with 1-methoxy-1,3-butadiene **9** as diene, the energetics of **5a** and **9** were computed as shown in Fig. 4. The methoxy (−OCH_3) group on C-1 serves as electron donating

Table 3
The free energies of the Diels-Alder cycloaddition reactions of methoxy-1,3-butadiene and substituted cyclobutenone as dienophile.

Substituent	Activation Energy (ΔG^*)/kcal/mol		Reaction energy (ΔG_{rxn})/kcal/mol	
X	*Endo*	*Exo*	*Endo*	*Exo*
H	20.8	26.4	−31.1	−28.2
F	18.6	22.7	−29.1	−29.1
Cl	16.5	20.2	−29.4	−28.9
Br	16.5	20.1	−29.5	−29.0
I	16.0	19.9	−29.3	−28.5

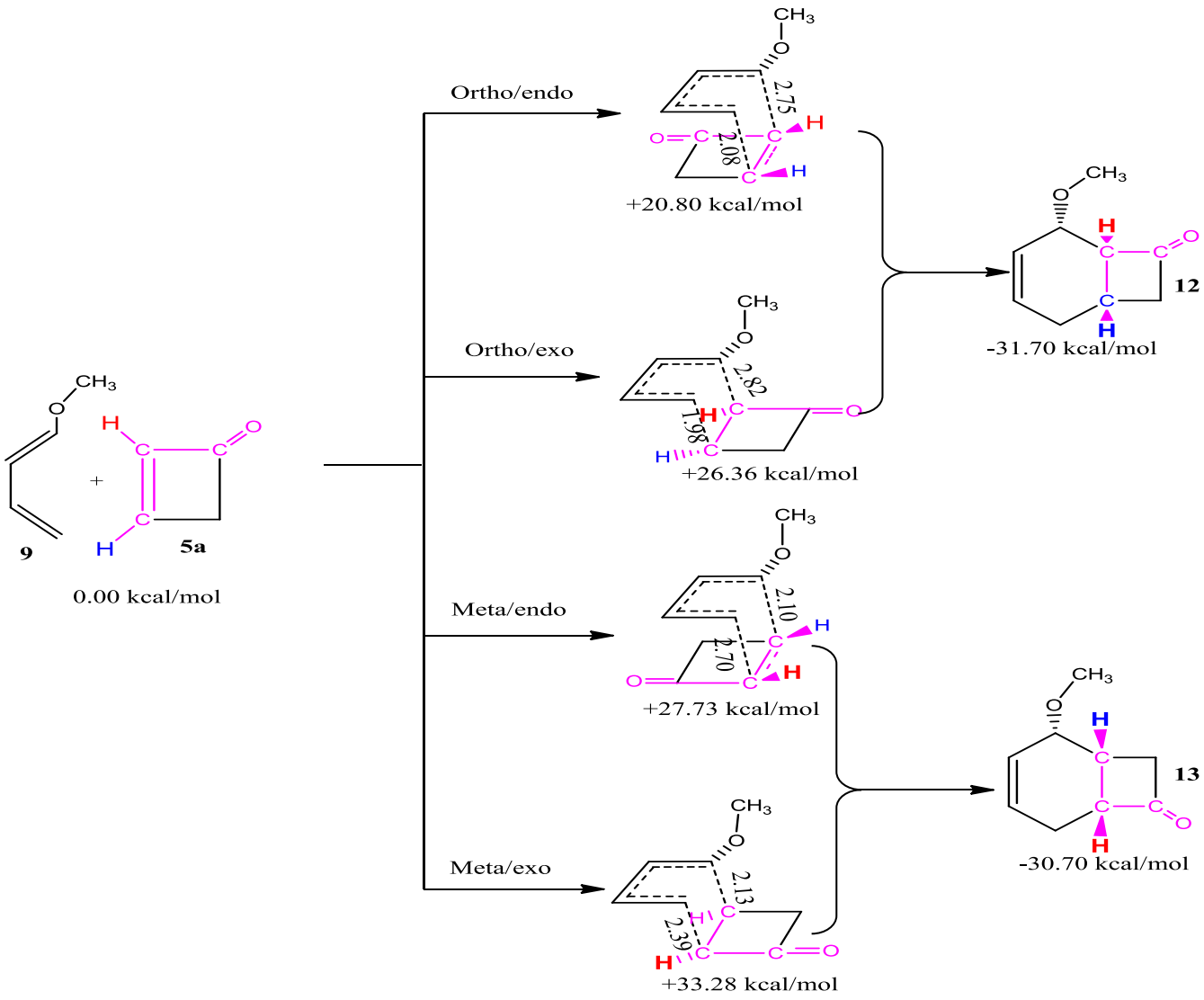


Fig. 4. Optimized geometries and Gibbs free energies of the transition states and products of Diels-Alder reaction of 1-methoxy-1,3-butadiene with cyclobutenone **5a**. All the calculated bond lengths are measured in Å units and energies in kcal/mol.

substituent which increases the electron density on the diene. It is known from previous works[24] that when substituents such as −CHO, CH_3−NO_2, −CO_2H, −CN etc are placed on ethylene they act as electron withdrawing groups which increase the reactivity of the dienophile. Nonetheless, the carbonyl (C═O) functionality which forms part of the ring could be assumed to act as a substituent on the vinylic carbon. The Diels-Alder cycloaddition reactions of **9** with **5a** produces four regio-isomers through *endo* and *exo* transition states (structures in Fig. 4) with the −OCH_3 in either 1, 2 (*ortho*) or 1, 3 (*meta*) position to the carbonyl (C═O) functionality. The transition states structures follow the same asynchronous concerted reaction mechanism with the C_α–C_1 bond length longer than C_β-C_4 by about 0.6 Å and that outlines the polar nature of the dienophile.

The formation of the *ortho* or *meta* transition states are achieved based on the position of the carbonyl group on the dienophile **5a** as shown by adducts **12** and **13** in Fig. 4. The formation of the *ortho endo* and *exo* regio-isomers have activation energies of 20.8 kcal/mol and 26.4 kcal/mol respectively which show that the *endo* pathway is favored over the *exo* if the reaction is kinetically controlled. The two transition states lead to a single product with free energy of reaction of ?31.2 kcal/mol. The *meta* isomeric pathways are also seen to have the same selectivity with the energy barrier difference of 5.5 kcal/mol between the *endo* and *exo* isomers. Comparatively the formation of the *ortho* oriented isomers have lower energy barriers and form more stable products than the *meta* isomers, implying that the reactions will not proceed via the unfavorable *meta* pathways which is in agreement with the experimental results of Danishefsky and co-workers.[5,12,23] The transition state structural conformations of regio-isomers signify that the carbonyl (C═O) group bonded to the α-carbon of **5a** indeed acts as a substituent on the vinylic carbon and that controls the regio-selectivity of the reactions. However, the ring does not prevent the 1,2 preference on the cyclohexene even though the C═O group is locked in position.

Table 4 shows the effects of substituents on the energies of the transition states and products for all the reactions shown in Fig. 4.

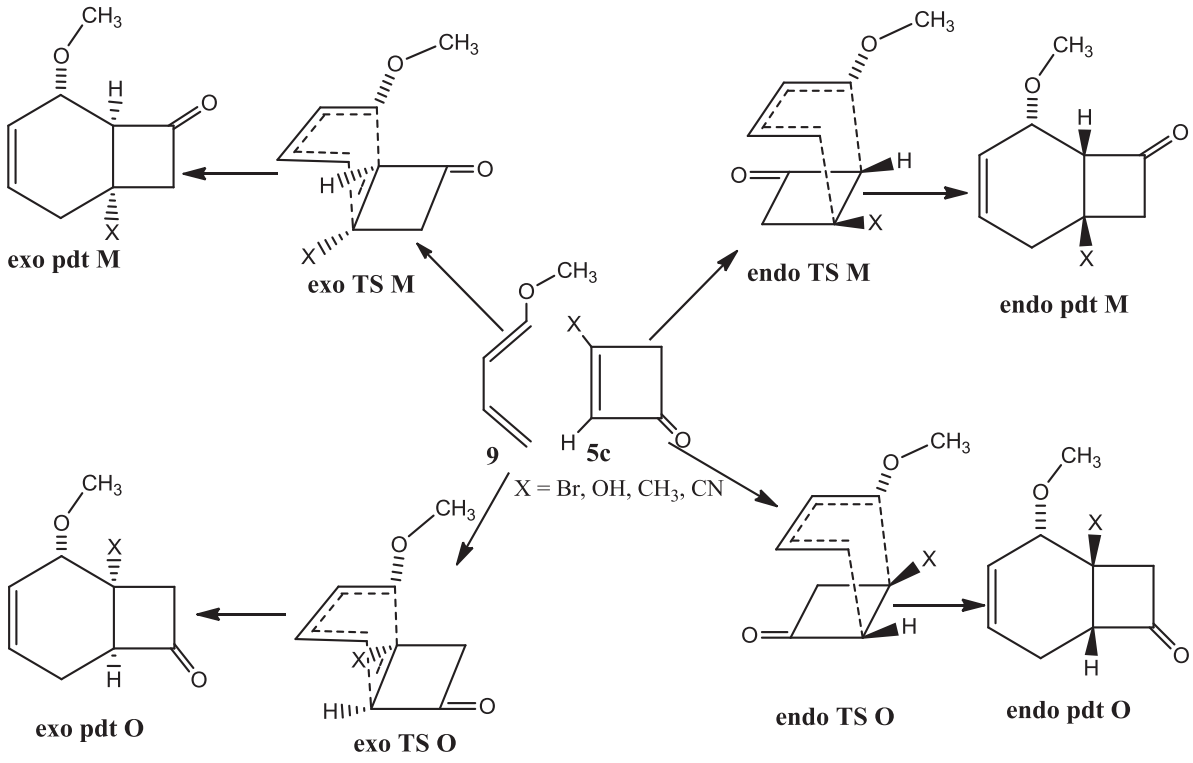
In order to study the kinetically and thermodynamically preferred adducts and the stability of the favorable substituted adducts according to the *ortho*/*meta* rule, four substituents with different inductive and mesomeric effects (CN, Br, OH, CH_3) were selected and the choice for these substituents is based on their flexibility to be transformed into *trans* and different adducts.[20,22]

Table 4
Energetics of the reactions of 1-methoxy-1,3-butadiene with α substitutions of cyclobutenones.

Substituent	Activation Energy (ΔG^*)/kcal/mol				Reaction energy (ΔG_{rxn})/kcal/mol			
X	*ortho-endo*	*ortho-exo*	*meta-endo*	*meta-exo*	*ortho-endo*	*ortho-exo*	*meta-endo*	*meta-exo*
$-CH_3$	22.7	25.9	28.9	355	−27.5	−25.6	−26.2	−25.8
−OH	22.1	25.5	28.9	32.4	−28.6	−25.3	−25.0	−23.1
−Br	16.5	20.1	27.7	33.7	−29.5	−29.4	−29.0	−29.0
−CN	15.3	18.4	24.4	29.7	−28.1	−27.3	−27.0	−26.5

The −CN and −Br substituents are electron-withdrawing, $-CH_3$ is electron-donating and −OH is electron-withdrawing by inductive effect and electron-donating through resonance effect. With these substituents, reactions including the case with electron-donating substituent on diene and electron-withdrawing substituent on the dienophile (normal type) and neutral type in which both diene and dieneophile have electron donating substituents have been studied. All the reactions are found to follow an asynchronous concerted reaction mechanism with the CN substitutions forming the most asynchronous transition state followed by −Br, −OH, $-CH_3$ in that order. The forming bond lengths differ depending on the electron-withdrawing or donating effects of the substituents on the α-carbon and this is in the range of 2.65–2.83 Å for the C_α-C_1 whereas those of C_β-C_4 are in the range of 2.01–2.25 Å. The calculations point out that these substituents do not change the preference of the *ortho* isomeric pathways over the *meta* ones, with −Br and −CN substitutions further decreasing the energy barriers whereas the −OH and $-CH_3$ increase them. Moreover the *endo* isomeric channels are still the preferred pathways both kinetically and thermodynamically which is in agreement with experimental results. The stability of these substituted products also decreases substantially in the order of $-CH_3$ < −OH < −CN < −Br. It is also seen that the unfavorable *exo* isomeric pathway is independent of the size of these substituents on the α-carbon of cyclobutenone because all of these groups have atom(s) with atomic radius larger than hydrogen and yet hydrogen substitutions have higher *exo* activation energies.

All the substituents (CN, Br, OH, CH_3) that were studied in the α-substitution of cyclobutenone **5c** reactions were also considered for β-substitutions of cyclobutenone with structure **9**. In these reactions there are partial formations of two new different σ bonds in the various transition states. The reaction mechanism is seen to be a synchronous concerted one. It produces four possible transition state structures, *endo* and *exo* **TS M,** ($-OCH_3$ is 1,2 position to C═O i.e *ortho* but1,3 position to the selected substituents i.e *meta*), *endo* and *exo* **TS O** ($-OCH_3$ is at 1,2 position to the selected substituents i.e *ortho* but 1,3 position to C═O i.e *meta*), as shown in the proposed Scheme 4. Along the 1,3 or *meta* $-OCH_3$ substitutions to the selected substituents **TS M** ($-OCH_3$ *ortho* to C═O) has lower energy barriers relative to 1,2 or *ortho* $-OCH_3$ substitutions to selected substituents **TS O** ($-OCH_3$ *meta* to C═O) which is an indication that $-OCH_3$ to carbonyl *ortho* substitutions are preferentially regioselective over substituents to $-OCH_3$ *ortho* regioselectivity. The preferred *endo* stereochemistry observed for α substitutions change from the favorable *endo* to *exo* both kinetically and thermodynamically for all the substituents on the β carbon except CN substituent where the *endo* is still the preferred pathway (energetics in Table 5). Tia et al.[17] reported the same changes in stereoselectivity



Scheme 4. The four modes of addition of cyclobutenone β-substituted cyclobutenone and 1-methoxy-1,3-butadiene.

Table 5
Energetics of the reactions of 1-methoxy-1,3-butadiene with β-substitutions of cyclobutenones (**5c**).

Substituent	Activation energy (ΔG*)/kcal/mol				Reaction energy (ΔG_{rxn}) kcal/mol			
X	*Endo* M	*Exo* M	*Endo* O	*Exo* O	*Endo* pdt M	*Exo* pdt M	*Endo* pdt	*Exo* pdt Ob
CH_3	29.8	25.9	31.5	31.7	−24.9	−26.5	−26.2	−24.7
OH	24.5	22.3	27.7	29.8	−25.0	−29.9	−26.5	−30.9
Br	24.5	20.5	30.1	29.9	−30.8	−29.05	−31.2	−29.3
CN	19.7	25.1	20.7	20.6	−29.4	−26.8	−30.3	−29.4

when 4-mono and 4-disubtituted cyclobutenones were studied at MP2/6-31G* level of theory. This suggests that apart from the α-position on the cyclobutenone dienophile, placing a substituent anywhere else brings about a change in stereochemistry from *endo* to *exo*. The reaction with the lowest activation barrier is that of the −Br-substituted cyclobutenone through the *exo* **TS M** pathway followed by −OH and CH_3 respectively.

Fig. 5 shows a Diels-Alder reaction where the $-OCH_3$ substituent is placed on the C2 of compound **14.** The C_2-C_3 bond lengths of the diene increase by just 0.01 Å in relation to the unsubstituted 1,3-butadiene. The forming C_α-C_1 bond lengths at the transition states for either the *para* or *meta* isomeric adducts are in the range of 2.40–2.82 Å while that of the C_β-C_4 is also in the range 2.00–2.10 Å. The reactions of 2-methoxy-1,3-butadiene **14** with **5a** follows a synchronous concerted reaction mechanisms which is different from the case of $-OCH_3$ substitution at C-1 of butadiene. This suggests that whether the reaction follows a synchronous or asynchronous mechanism also depends on where the substituent on the diene is placed. The calculations reveal that the *para* oriented isomeric channels have lower activation energies than the

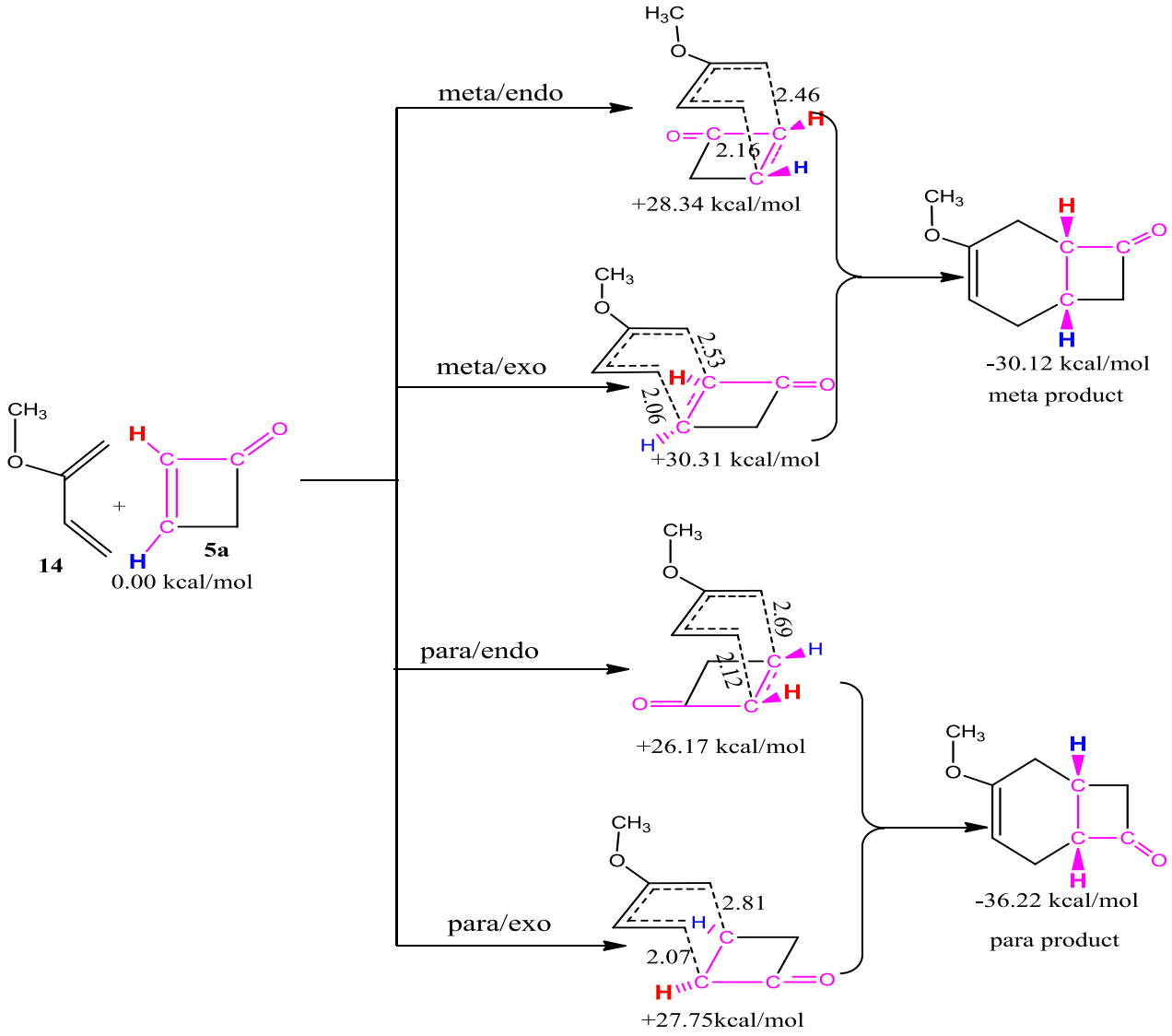


Fig. 5. Optimized geometries, energies of the transition states and products of 2-methoxy-1,3-butadiene (**14**) with substituted-cyclobutenone. All the calculated bond lengths are measured in Å units and energies in kcal/mol.

Table 6
Energetics of the reactions of 2-methoxy-1,3-butadiene with substituted cyclobutenones.

Substituent	Activation energy (ΔG^*)/kcal/mol				Reaction energy (ΔG_{rxn}) kcal/mol			
X	*para-endo*	*para-exo*	*meta-endo*	*meta-exo*	*para-endo*	*para-exo*	*meta-endo*	*meta-exo*
$-CH_3$	27.1	29.7	29.8	30.2	−33.1	−30.9	−26.0	−25.7
−OH	26.3	27.1	27.1	27.4	−32.9	−30.9	−22.2	−22.6
−Br	23.0	25.5	28.0	28.1	−36.8	−34.2	−28.6	−28.5
−CN	19.6	19.7	23.5	23.7	−34.2	−31.8	−31.8	−26.6

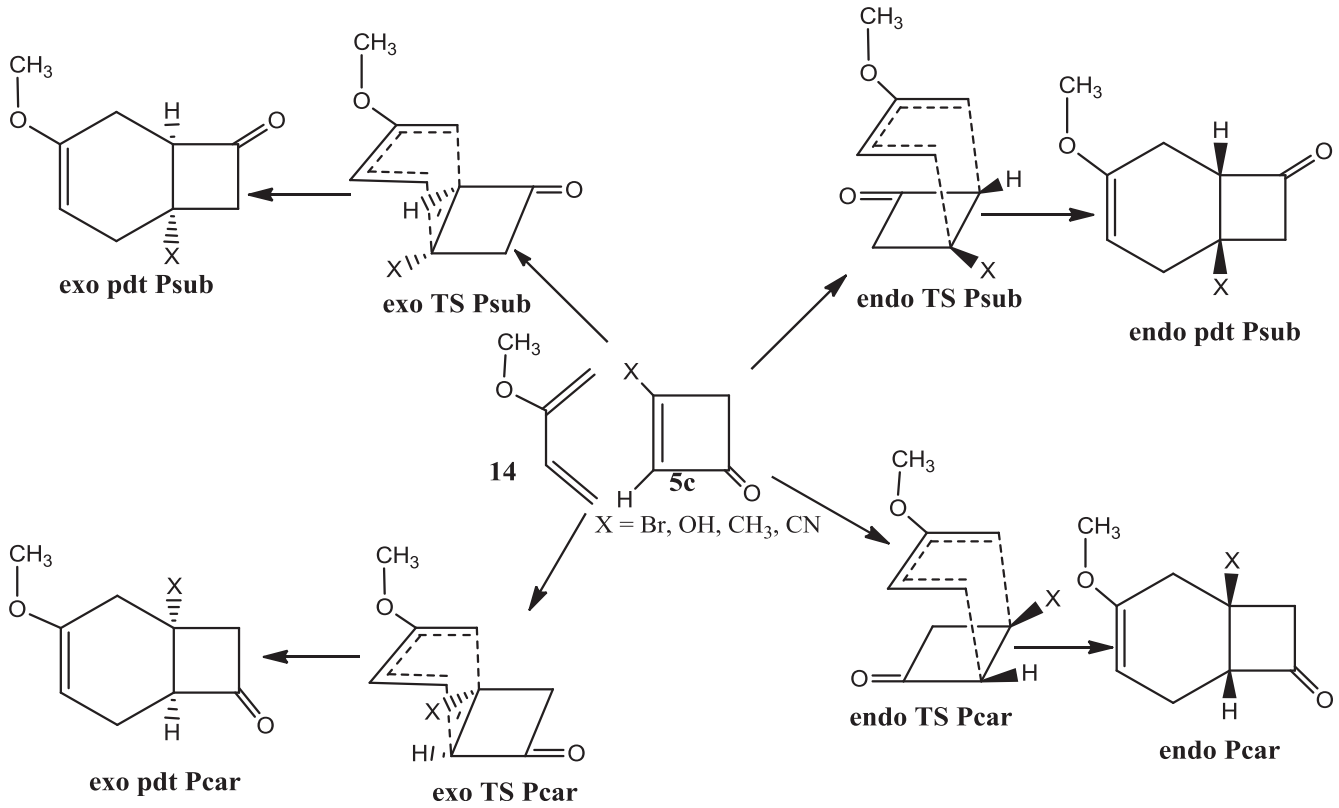
meta conformations and the *endo* isomers are still the most favored both kinetically and thermodynamically.

Aside from the *para endo* isomeric pathways having lower energy barriers, the *para* adduct is thermodynamically more stable than the *meta* product by 6.1 kcal/mol which means that the *para* product should be the predominant product from a kinetic perspective as well as from thermodynamics consideration which is in agreement with experimental results.

Haghdadi et al.[25] predicted the same *para endo* regio-selectivity using acyclic enone as dienophile with 1-(4-methoxy-phenyl)-2-methylene-but-3-en-1-ol and t-butyl-dimethyl-(2-methylene-1-phenyl-but-3-enyl)-silane as dienes in density functional theory calculations at the B3LYP/cc-pVDZ level of theory. This suggests that the acyclic and cyclic enone dienophiles have the same effect in terms of regioselectivity and therefore the ring does not seem to affect the regioselectivity in any noticeable way.

Table 6 summarizes the effects of $-CH_3$, −OH, −Br and CN substituents on the α carbon of cyclobutenone **5a** with 2-methoxy-1,3-butadiene **14** (structures in Fig. 5). The $C\alpha$-C_4 forming bond lengths increase by 0.32 Å while the change in C_β-C_4 is insignificant. The reactions of the substituted dienes show that the *meta* isomeric pathways are still the unfavored pathways over the *para* isomeric channels both kinetically and thermodynamically. Only the $-CH_3$ substituent has activation energies higher than the unsubstituted derivatives. The −Br and −CN substitutions of hydrogen on **5a** farther decrease the favorable *para endo* activation energy by 6.8 kcal/mol. In all the substituents studied, −CN has the lowest activation energy either *para* or *meta* whereas the −Br substituted cycloadducts are the most stable products. Although all the reactions are exergonic, the stability of the adducts decrease compared to the parent cyclobutenone adduct in the order of Br > CN > CN > CH_3. Mina et al.[26] performed theoretical study of 2-substituted cyclobut-2-enones with 1-methoxy-3-(*tert* butyldimethylsilyl)-1, 3-butadiene using DFT at the B3LYP/cc-pVDZ level of theory. It was reported that the pathways leading to the *ortho* isomers were the most favorable but in the course of our studies, it is seen that when a substituent is placed at position one and three at the same time on the diene, the selectivity towards either the *ortho* and *para* isomer disappears.

Scheme 5 shows the four modes of addition of β-substituted cyclobutenones and 2-methoxy-1,3-butadiene and Table 6 presents the activation and the reactions energies. The bond lengths of the β-substituted cyclobutenones change slightly from those of the α-substituted cyclobutenones in that the β substitutions decreases



Scheme 5. The four modes of addition of β substituted cyclobutenone and 1- methoxy-1,3-butadiene.

Table 7
Energetics of the reactions of 2-methoxy-1,3-butadiene with β-substituted cyclobutenones.

Substituent	Activation Energy (ΔG*)/kcal/mol				Reaction energy (ΔG_{rxn})/kcal/mol			
X	*Endo Psub*	*Exo Psub*	*Endo Pcar*	*Exo Pcar*	*Pdt Psub*	*Exo Psub*	*Pdt Pcar*	*exo Pcar*
−CH3	35.1	33.6	31.6	32.2	−26.6	−26.2	−31.7	−30.5
−OH	33.6	31.8	30.0	29.6	−29.6	−29.5	−27.5	−30.9
−Br	32.9	32.2	30.3	26.0	−30.4	−29.2	−36.4	−33.8
−CN	25.7	25.1	25.9	26.3	−29.4	−28.4	−35.5	−33.9

the C_1-Cα bond lengths which are in the range of 2.52−2.83 but the change in C_4-C_β bond lengths are found to be insignificant.

The reaction of β-substituted cyclobutenones with 2-methoxy-1,3-butadiene is also seen to be a concerted one with partial formation of two new different σ bonds in the transition state. The reaction mechanism is observed to be a synchronous concerted one. This substitutions produce four possible transition state structures, *endo* and *exo* **TS Pcar,** (where $-OCH_3$ is 1,4 position to the C═O i.e *para* but1,3 position to the selected substituents i.e *meta*), *endo* and *exo* **TS Psub** (where $-OCH_3$ is at 1,4 position to the selected substituents i.e *para* but 1,3 position to C═O i.e *meta*), as shown in the proposed Scheme 5. Along the 1,4 or *para* methoxy ($-OCH_3$) substitutions to the carbonyl **TS Pcar** ($-OCH_3$ *para* to C═O) has lower energy barriers relative to 1,4 or *para* $-OCH_3$ substitutions to selected substituents **TS Psub (**$-OCH_3$ *meta* to C═O**)** which is an indication that $-OCH_3$ and carbonyl *para* substitutions are preferentially regioselective to substituents *para* regioselectivity. Even though the $-OCH_3$ *para* substitutions to the substituents are unfavorable, the *endo* stereochemistry observed for α substitutions change from the favorable *endo* to *exo* both kinetically and thermodynamically for all the substituents on the β carbon. In the most favorable $-OCH_3$ to carbonyl *para* substitutions only OH and Br are seen to have *exo* stereo-isomeric pathways being the most favorable both kinetically and thermodynamically whereas CN and CH_3 substituents still maintain the *endo* as the most preferred pathway (energetics in Table 7). The β-substituted products are also less stable compared to unsubstituted ones except Br where the product stability is almost the same as the unsubstituted adducts for the most preferred *para* isomer.

4. Conclusions

The following conclusions can be drawn from the results discussed;

1. In the reactions of Dane's diene with cyclobutenone and α-bromocyclobutenone, the formation of the ortho and *meta* isomers have similar activation barriers and the adducts formed have similar stabilities. Therefore, the two must be formed in equal amounts.
2. The reactions of α-bromocyclobutenone and Dane's diene reveals that Br atom on cyclobutenone only enhances the reactivity of the dienophile by lowering the activation energy but it does not make the *meta* isomers preferentially selective over the *ortho* isomers.
3. The reactions of −H, −OH, and $-CH_3$ substitutions at position 6 of 1-vinyl-3,4-dihyhronaphthalene (derivatives of Dane's diene) have the same reactivity both kinetically and thermodynamically whereas the Br and CN substitutions at position 6 of 1-vinyl-3,4-dihyhronaphthalene make the *ortho* isomers preferentially regio-selective over the *meta* isomers.
4. The inductive electron withdrawing power of the halogens is not observed in the reactions studied; it is the donating ability that is observed to dominate.
5. The stability of all the halogen-substituted cyclobutenones cycloadducts decrease compared to the unsubstituted adducts in the order of Br > Cl > I > F.
6. Using cyclobutenone and α,β-substituted cyclobutenone with C1 or C2 methoxy substituted 1,3-butadiene reveal that the regioselectivity is mainly controlled by the ketone functionality.
7. The study shows that α substitutions only enhance the reactivity of the cyclobutenone dienophiles while those of β decrease its reactivity.
8. All the *meta* (orth/*meta* and *para*/*meta*) isomeric channels are unfavorable pathways both kinetically and thermodynamically.
9. The *endo-exo* selectivity is independent of the bulkiness of the atom (s) at the reaction center of the cyclobutenone dienophiles. Therefore sterics do not seem to play a role in the *endo* selectivity of the reactions studied.
10. In α substituted cyclobutenones the most preferred pathways are the *endo* pathways for all the substituents whereas the β substitutions of cyclobutenone the *exo* pathways are the most preferred pathway both kinetically and thermodynamically for all the substituents studied except CN where the *endo* is still the most preferred pathway.
11. The stability of the substituted adducts decreases relative to unsubstituted products for all the substituents studied in the order of Br > CN > OH > CH_3.
12. The reaction mechanisms are seen to be asynchronous concerted when the methoxy substituent is placed on C1 of the butadiene with Br, CN, OH and CH_3 found on the α-carbon of the cyclobutenone but when the methoxy is placed on C2 of the 1,3-butadiene with Br, CN, OH and CH_3 on the β carbon of the cyclobutenone dienophiles, all the reaction mechanisms is found to be synchronous concerted ones.

Acknowledgements

The authors gratefully acknowledge the funding support of the National Council for Tertiary Education, Republic of Ghana, for a research grant under the Teaching and Learning Innovation Fund (TALIF/KNUST/3/0008/2005).

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