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Computational Studies of the Reactivity, Regio-Selectivity and Stereo-Selectivity of Pericyclic Diels-Alder Reactions of Substituted Cyclobutenones

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Abstract

The power of the Diels-Alder reaction was expanded recently through the discovery by Li and Danishefsky that cyclobutenone is an unusually reactive dienophile and that the adducts formed can be converted to products that are formally the Diels-Alder adducts of unreactive dienophiles. However, the effects of substituents on the reactivity as well as the region - and stereo-selectivity of the Diels-Alder reactions of cyclobutenone have not been clearly elucidated yet. This paper reports the results of a computational study at the MP2/6-31G* level of theory into the effects of substituents on the reactivity, regio-selectivity and stereo-selectivity of the Diels-Alder reactions of some substituted cyclobutenones with cyclic and acyclic dienes. It was found that the Diels-Alder reaction of maleic anhydride is far more feasible kinetically than the reaction of cyclobutenone, the activation barrier of the former being more than thrice that of the latter, indicating that maleic anhydride is a far better dienophile than cyclobutenone, which in turn implies that for cyclic dienophiles ring strain is not the dominant factor controlling the kinetics of the Diels-Alder reaction as has been suggested elsewhere. The Diels - Alder reactions of cyclobutenones were all found to follow an asynchronous concerted reaction pathway. In the reactions of the parent (unsubstituted) cyclobutenone with 1,3-butadiene and cyclopentadiene, the *endo* pathway is the most preferred kinetically, by 2.24 and 1.64 kcal/mol respectively. However, in the reactions of the 4,4-disubstituted cyclobutenones the *exo* pathway becomes the most preferred in the reactions with both 1,3-buadiene and cyclopentadiene, except for the CN-substituted cyclobutenone where the *endo* pathway is still the most preferred pathway. In the reactions of the 4-monosubstituted cyclobutenone with 1,3-butadiene, the anti-positions are preferred over the *syn* positions. The *endo-anti* position gives the most reactive dienophile kinetically. In the reactions of trans-piperylene with substituted cyclobutenones, the *meta-endo* position is the most preferred kinetically. In the reactions of isoprene with substituted cyclobutenones, the *para-endo* substitution gives the lowest activation barriers and therefore the most favorable reaction kinetics. In all the reactions considered in this work, the CN-substituted species have the lowest activation barriers and the most stable products. In the reactions of 4,4-disubstituted cyclobutenones with 1,3-butadiene and cyclopentadiene, the order of activation barriers is CN < OH < Cl < CH_3 and the stability of the products decrease in the order CN>OH>Cl>CH_3.

Keywords: Diels-Alder; Cycloaddition; Regio-selectivity; Stereo-selectivity; Cyclobutenone

Introduction

The Diels-Alder reaction, a [4 + 2] cycloaddition reaction in which a molecule with a conjugated π-system (a diene) and another with at least one π-bond (a dienophile) react to form a cyclohexene derivative (Scheme 1), is a powerful tool for the synthesis of six-membered ring systems. This reaction involves the breaking of three π-bonds to form two new σ-bonds that form a ring and the generation of a new π-bond in a cyclohexene derivative. A simplest prototype is the reaction of 1,3-butadiene and ethylene (Scheme 1).

The Diels-Alder reaction 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 stereo-chemical properties [1-6].

The control of stereo- and regio- chemistry plays an important role in the world of synthetic organic chemistry. In the case of the pharmaceutical industry, some drugs such as thalidomide, the dextrorotary enantiomer of the drug has the desired sedative properties while the levorotatory enantiomer is teratogenic. Stereo- and regio-selectivity of the Diels - Alder reaction is of most paramount concern because it is a crucial element for a successful synthesis [7]. Theoretically investigated the Diels-Alder reaction between 2-phenylcyclopentadiene and α-(methylthio) acrylonitrile (Scheme 2) in which geometry optimizations were performed with RHF/3-21G, RHF/3-21G*, and RHF/6-31G* calculations while the correlation energy was calculated at the MP2 and MP3 levels of theory. The reaction produced four asynchronous transition structures corresponding to the formation of different stereo- and regio-isomers associated with the four reaction channels. The theoretical results pointed out that the regioselectivity is controlled by the presence of phenyl group on C_2 carbon atom of the diene system while the stereoselectivity is controlled by a favorable

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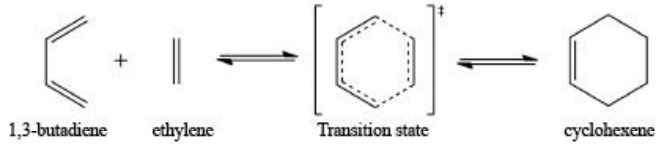
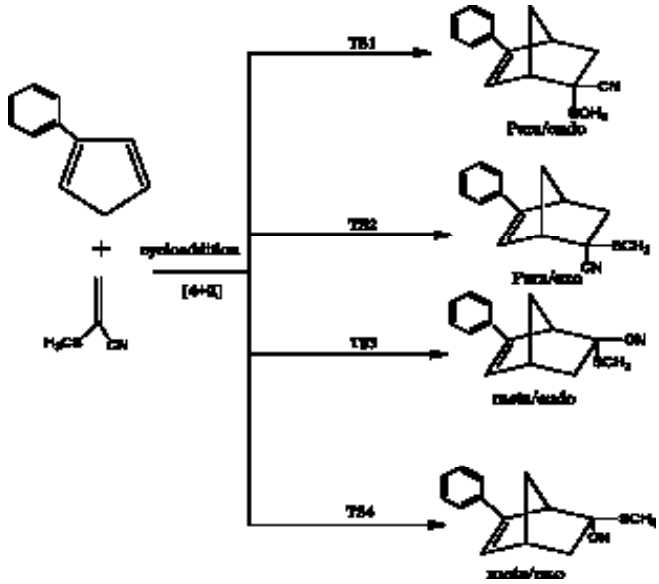


Scheme 1: The Diels-Alder reaction of 1,3-butadiene and ethylene.



Scheme 2: The Diels-Alder reaction of 2-phenylcyclopentadiene and alpha-(methylthio) acrylonitrile

secondary orbital overlap between the lone pair of the sulphur atom located in the dienophile fragment and the π-system of the diene at the *endo* transition structures.

The issues of facial selectivity of the Diels-Alder reaction was first addressed by Williamson et al. [8] who argued that the reaction would occur on the face that when colliding with a dienophile exhibited the lesser amount of Van der Waals repulsion. The predominantly syn addition of $CpCl_5H$ to some dienophiles was attributed to attractive van der Waals and London-dispersion forces. The preference for syn addition was reported to be greater for more polar dienophiles, indicating a dipole-dipole interaction.

Cieplak [9] suggested that in the Diels-Alder reaction the better σ-donor should lie antiperiplanar to the incipient bond, thus stabilizing the forming σ^* anti-bond. Macaulary and Fallis [10] extended this concept, stating that the dienophile preferred to attack the face opposite the one bearing the better σ-donating substituent. However, Werstiuk and Ma [11] in their work found no significant evidence of Fallis' Cieplak effect. They concluded that facial selectivity in the Diels-Alder reaction of substituted cyclopentadiene with maleic anhydride was thermodynamically controlled. However, the work of Werstiuk and Ma was done at the AM1 level, which is probably too low to arrive at a reliable conclusion. Most Diels-Alder reactions are known to give kinetic products through early transition states [12].

Substituents play an important role in the facial selectivity. Substituent type can be used to predict the facial selectivity (anti-syn) of the Diels-Alder reaction. Generally, as the substituent is on the face opposite to the diene or dienophile, the anti-mode is favored because of its lowest possibility of steric interaction [13]. However, syn addition in Diels-Alder reactions has been observed [14].

Cieplak effect, Fukui orbital mixing rules, orbital tilting arguments and substituent effects continue to be used to explain the facial selectivity of the Diels-Alder reaction. Though they may have little predictive power, they have been used to rationalize observed facial selectivity.

Frontier molecular orbital (FMO) theory was earlier used for the determination/prediction of regioselectivity of the Diels-Alder reaction. However, in recent times, research has shown that frontier molecular orbital theory is not useful for larger systems.

In the light of Pearson's hard and soft acid and base (HSAB) principle [15], Gazquèz and Mendez provided a local HSAB principle [16]. Recently, Damoun et al. [17] theoretically investigated HSAB to explain the observed regioselectivities of the Diels-Alder reactions. They claimed that two chemical species should react through atoms showing equal softness and this rationalized the regioselectivity of normal electron demand Diels-Alder reactions between terminally monosubstituted 1,3-butadiene and monosubstituted dienes. Cong et al. [18] in the light of the local HSAB principle, theoretically investigated the Diels-Alder reaction through the local softness of both the reaction center atoms and π - bonds based upon the local HSAB principle and the result was in accordance with experimental and theoretical results. Theoretical work by Hirao and Ohwada [19] claimed that their reactive hybrid orbital (RHO) method provides a superior means to obtaining the correct experimental regioselectivities for a series of Diels-Alder reaction. The RHO is essentially a single reactive orbital that is localized at the reaction site and according to Hirao and Ohwada, provides a better picture of orbital interaction in the transition state structure than the frontier molecular orbital (FMO).

Wang et al. [20] theoretically studied the hetero Diels-Alder reactions between phosphonodithioformate and butadiene and indicated that the BF_3 catalyst not only catalyzed the reaction but also promoted the regioselectivity of the reaction. The high regioselectivity could be attributed to the blue shifting C - H --- F hydrogen bond interaction in some transition states.

The global electrophilicity index proposed by Parr et al. [21] has been used to classify dienes and dienophiles, currently used in Diels-Alder reactions within a unique scale of electrophilicity. They found that there is a good correlation between the difference in electrophilicity of the diene and dienophile pair and the feasibility of the cycloaddition. These have been found to be a useful tool that correctly explains the regioselectivity of the polar Diels-Alder reaction. Boulanouar et al. [22] studied the local electrophilicity and local nucleophilicity index proposed by Domingo et al. [23] to rationalize the regioselectivities of the polar Diels-Alder reactions involving thiophene-1,1-dioxides. Domingo et al. [24] proposed two new electrophilic P_k^+ and nucleophilic, P_k^- Parr functions based on the spin density distribution at the radical anion and at the radical cation of a neutral molecule.

These local functions allow for the characterization of the most electrophilic and nucleophilic centres of a molecule and for the establishment of the regio- and chemo-selectivity in the polar Diels-Alder reactions. Maihami [25] theoretically studied the regioselectivity for a series of Diels-Alder reactions using hardness, polarizability and electrophilicity of the corresponding products as global reactivity indices. It was shown that the maximum hardness and minimum polarizability principle (MHP and MPP) could not predict the major region-isomer of a Diels-Alder reaction whereas the analysis of a local

electrophilicity of the products showed that the major product of the reaction has always the less electrophilicity values.

Alder and Stein [26] were the first to explain the *endo* selectivity of the Diels-Alder reactions. They attributed the preference for *endo* addition to a favorable "maximum accumulation of double bonds". Woodward and Hoffman [27] later extended the theory by providing the *endo* rule in the quantum mechanical foundation using FMO theory. The *endo* preference could be attributed to significant favorable overlap of the secondary orbitals in the *endo* transition state structure, which is not present in the *exo* transition state structure.

Saeed et al. [28] theoretically studied the hetero Diels - Alder reaction of thiazole and isothiazole with thiophene - 2,5- dione and showed that the reactions follow normal electron demand. They rationalized the *endo*/*exo* stereoselectivity results by the use of the secondary molecular orbital interactions and molecular orbitals (MO) structures. However, it has been stated recently that secondary orbital interaction may not be a significant factor that determine the stereoselectivity but there are other factors that play very important roles in stereoselectivity. Garcia et al. [29] concluded that factors such as steric interaction, electrostatic effect and solvent effect lead to *endo* selectivity. However, Dirhoussi et al. [30] studied the reaction of the beta-ionone with maleic anhydride and concluded that the *exo*-transition state structure is more stable than the *endo* transition state structure. They attributed this to the steric repulsion between the diene and dienophile and concluded that the inclusion of solvent effect produced a significant increase of *exo* selectivity hence the combined effect of Lewis acid catalyst and solvent decrease the *endo*/*exo* selectivity. Luiz et al. [31] stated that the role of the Lewis acid is to produce an extra lowering of the LUMO energy of the dienophile, increasing secondary orbital interaction and rendering the molecule more susceptible to the nucleophilic attack. These result in the lowering of the activation energy, hence an enhancement of stereo- and regio- selectivity. They also concluded that $NbCl_5$ is more effective compared to other Lewis acids, giving higher stereoselectivity, good yields and requiring lower reaction time and temperature.

The deformation energy also plays an important role in stereoselectivity as indicated by Cristiana et al. [32] who rationalized the high *endo* selectivity based on solvent effect and reactant deformations.

Calvo-Losada and Suarez [33]. Theoretically studied the Diels-Alder reaction of furan with maleic anhydride and found that the *endo* transition state had ΔG values of about 0.56 and 0.25 kcal/mol lower than the *exo* transition state structure in gas phase and acetonitrile solution respectively. They concluded that the factors governing the stereochemistry of the reaction are the dispersion interaction, which stabilizes the *endo* orientation through π-π secondary contacts and the solvent effect that favors the *exo* addition.

In the theoretical work of Wheeler et al. [34] computations on model systems demonstrated that the stereo selectivity in the reaction was mediated by differential π-stack interactions in competing transition states. This allowed relative stacking free energies of substituted and unsubstituted sandwich complexes to be derived from measured product distribution.

The power of the Diels-Alder reaction was expanded recently through the discovery by Li and Danishefsky that cyclobutenone is an unusually reactive dienophile and that the adducts formed can be converted to products that are formally the Diels-Alder adducts of unreactive dienophiles [35]. Experimental outcomes indicated cyclobutenone to be more reactive than either cyclopentenone or cyclohexonone.

Adducts bearing a strained cyclobutenone moiety were able to undergo regioslective ring expansions to produce corresponding cyclopentanones, lactams, and lactones, which are otherwise difficult to obtain by direct Diels-Alder reactions [36,37]. Li and Danishefsky have attributed the high reactivity of cyclobutenone to its high ring strain which enhances its dienophilicity relative to corresponding cyclopentenones or cyclohexenones. Patton, et al. [38] 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 MO6-2X/6-31G(d) level of theory and found that cyclobuteone has consistently lower activation barriers, and accordingly higher rate constants, than pent-3-en-2-one, cyclohex-2-enone and cyclopent-2-enone. They attributed the high reactivity of strained cycloalkenones in part 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. They asserted that this behavior arises 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. Belluš and Ernst [39] stated that the chemical reactivity of cyclobutanones and cyclobutenones was considerably different from that of cyclic ketones with larger rings because of their ring strain of ca 25 kcal/mol.

Even though Paton et al. have performed some computational studies to determine the origin of the special reactivity of cyclobutenone, a systematic study of the effect of substituents on the reactivity, stereoselectivity and regioselectivity of the Diels-Alder reaction of cyclobutenone has not yet been carried out. Therefore, by means of quantum chemical calculations at the MP2/6-31G* level of theory, this work aims at investigating the reactivity, the *endo*/*exo* and *syn*/*anti* stereo-selectivity, and the *meta*/*para* and *ortho*/*para* regio-selectivity of the Diela-Alder reactions of 4-monosubstituted and 4,4-disubstituted cyclobutenones with 1,3-butadiene, cyclopentadiene, trans-piperylene and isoprene (Schemes 3, 4, 5 and 6).

Details of calculations

All the calculations were carried out with the Spartan '08 V 1.2.0 and Spartan '10 V 1.1.0 Molecular Modelling Programs at the second order Møller Plesset Perturbation Theory (MP2) with the 6 -31G* basis set.

The starting geometries of the molecular systems were constructed using Spartan's graphical model builder and minimized interactively using the sybyl force field. All geometries were fully optimized at the MP2/6-31G* levels of theory 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- 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 fully optimized using the standard transition state optimization procedure in Spartan.

All the 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.

Results and Discussion

Comparison of ethylene, maleic anhydride and cyclobutenone as dienophiles

Figure 1 and Table 1 show a comparison of the optimized geometries of the stationary points and energetics respectively for the Diels-Alder reactions of ethylene, maleic anhydride and cyclobutenone as dienophiles with 1,3-butadiene as diene. It is seen that the reactions of ethylene and maleic anhydride are synchronous whereas the reaction of cyclobutenone is asynchronous. The energetics show that the reaction of cyclobutenone is kinetically and thermodynamically favored over the reaction of ethylene by 7.84 and 0.97 kcal/mol respectively, and thus cyclobutenone is a far better dienophile than ethylene, in conformity with the findings of Li and Danishefsky. However, it is also seen that the reaction of maleic anhydride with 1,3-butadiene is far more feasible kinetically than the reaction of cyclobutenone, the activation barrier of the former being about thrice that of the latter, but the thermodynamic stability of the maleic anhydride product is less than that of the two others. Thus, of the three dienophiles, maleic anhydride is the best by a great margin if the reaction is kinetically controlled but the worst if it thermodynamically controlled. Cyclobutenone is the best dienophile if the reaction is thermodynamically controlled. Therefore, for cyclic dienophiles, ring strain does not appear to be the dominant factor controlling the kinetics of the Diels-Alder reaction, as has been suggested elsewhere [35-37].

The Diels-Alder reactions of cyclobutenone with 1,3-butadiene and cyclopentadiene

Figure 2 and Table 2 show the optimized geometries and relative energies respectively of the reactants, transition states and products in the Diels-Alder reaction of the parent unsubstituted cyclobutenone with 1,3-butadiene and cyclopentadiene. The 1,3-butadiene is in the

Dienophile	Activation Energy, kcal/mol	Reaction Energy, kcal/mol
Ethylene	+15.29	-55.18
Maleic anhydride	+2.18	-53.12
Cyclobutenone	+7.45	-56.15

Table 1: Energetics of the Diels-Alder reactions of ethylene, maleic anhydride and cyclobutenone with 1,3-butadiene.

	Activation energies, Ea (kcal/mol)		Enthalpy change, ΔH (kcal/mol)	
	Endo	*Exo*	*Endo*	*Exo*
1,3-butadiene	+7.45	+9.69	-56.15	-56.15
cyclopentadiene	+4.69	+6.33	-37.85	-39.87

Table 2: Energetics of the Diels-Alder reactions of cyclobutenone with 1,3-butadiene and cyclopentadiene (parent reactions).

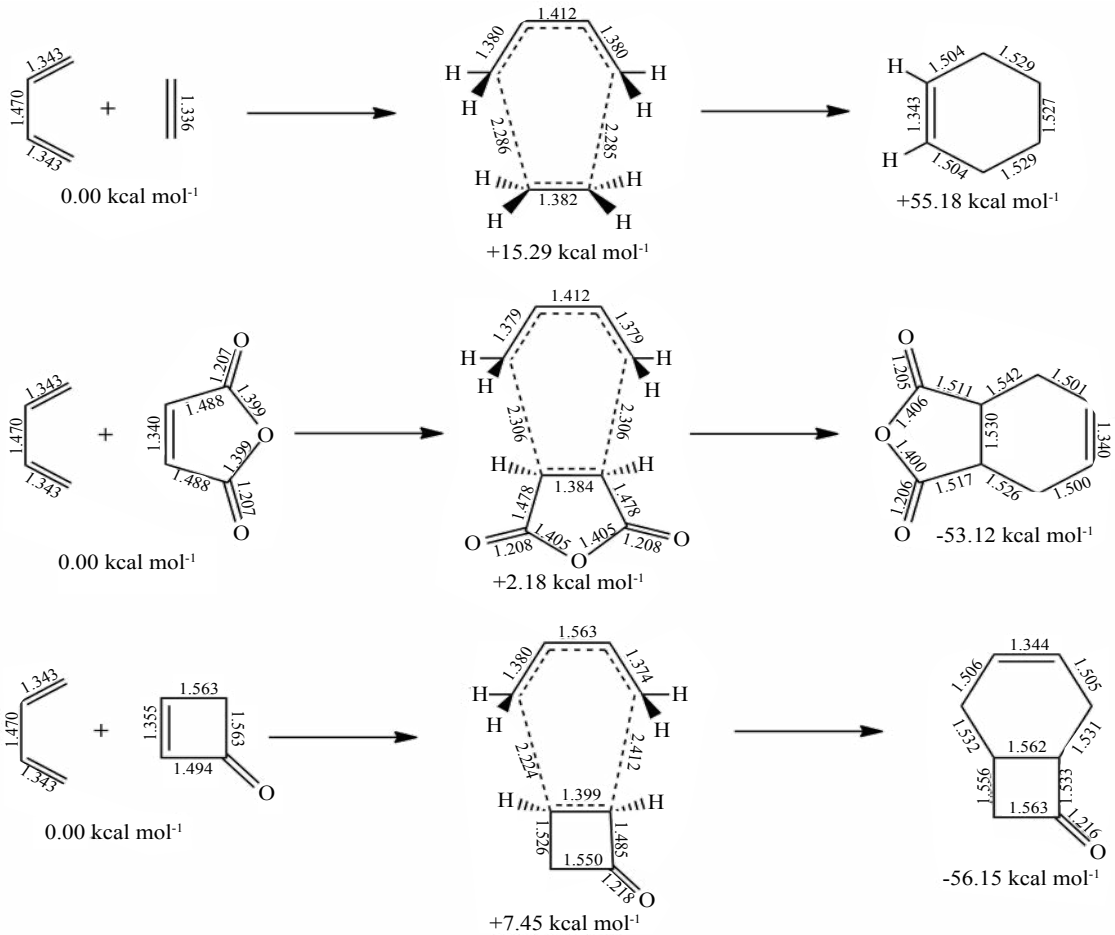


Figure 1: Optimized geometries and relative energies of the reactants, transition states and products in the Diels-Alder reaction of ethylene, maleic anhydride and cyclobutenone with butadiene.

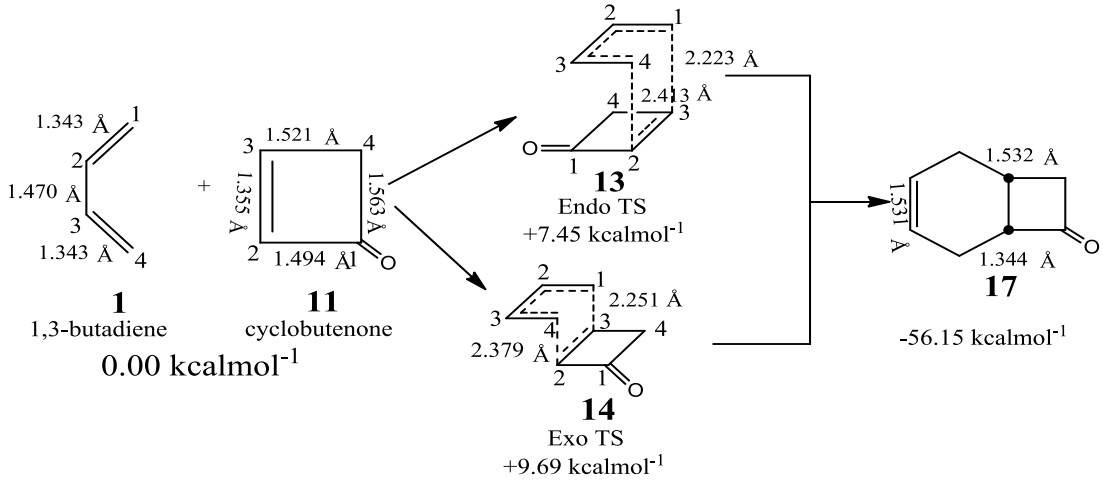


Figure 2: The optimized geometries of the reactants, intermediates and products in the reaction of cyclobutenone with 1,3-butadiene and cyclopentadiene.

cis geometry and has a C_2 - C_3 bond length of 1.470 Å and C_1 - C_2 and C_3 - C_4 bond lengths of 1.343 Å. The geometry of cyclobutenone is planar and the reactive center of C_2 - C_3 is at 1.355 Å. The reaction of 1,3-butadiene and cyclobutenone produces two possible transition state structures, *viz* an *endo* transition state 13 and an *exo* transition state 14. The C_1 - C_3 and C_4 - C_2 forming bond lengths are 2.223 Å and 2.413 Å for the *endo* transition state and 2.251 Å and 2.379 Å for the *exo* transition state respectively. The reaction is asynchronous, with the *endo* transition state being more asynchronous than the *exo* transition state. The activation energy of the reaction through the *endo* transition state is 7.45 kcal/mol while that through the *exo* transition state is 9.69 kcal/mol. Thus, kinetically the *endo* route is more favored over the *exo* route. Thermodynamically, the reaction is *exo*thermic, with reaction energy of -56.15 kcal/mol.

The cyclopentadiene has a fixed cis geometry with C_1 - C_2 and C_3 - C_4 bond lengths of 1.354 Å, C_2 - C_3 bond length of 1.465 Å, and C_1 – C_5 and C_4 – C_5 bond lengths of 1.501 Å. The reaction of cyclopentadiene and cyclobutenone produces transition state structures 15 (*exo*) and 16 (*endo*). The C_1 – C_3 and C_4 – C_2 forming bonds are 2.227 Å and 2.357 Å long for the *endo* transition state and 2.206 Å and 2.412 Å for the *exo* transition state. The *exo* transition state is more asynchronous than the *endo* transition state, which is opposite to what was observed in the reaction of cyclobutenone with 1,3-butadiene. The activation energy through the *endo* transition state is 4.69 kcal/mol while that through the *exo* transition state is 6.33 kcal/mol, making the *endo* kinetically favored over the *exo* by 1.64 kcal/mol. The reaction produces two products with reaction energies of -37.85 kcal/mol for the *endo* product and -39.87 kcal/mol for the *exo* product. Paton et al. [38] reported activation barriers of 9.8 and 11.0 kcal/mol respectively at the MO6-2X/6-31G (d) level of theory, which are higher than the values reported here but with similar *endo-exo* selectivity. For the maleic anhydride and furan reaction, Calvo-Losada and Suarez [33] found the activation barrier of the *exo* stereo-isomer to be 0.36 kcal/mol higher than that of the *endo* stereo-isomer and the *exo* adduct to be 2.54 kcal/mol more stable than the *endo* adduct at the MP2/6-31G*. The corresponding values at the MP4/6-31G*//MP2/6-3G* levels were found to be 0.22 and 3.24 kcal/mol respectively.

Facial Selectivity of the reaction of 4-monosubstituted cyclobutenone with 1, 3-butadiene

Figure 3 shows the optimized geometries of the main stationary points involved in the reaction of 4-monosubstituted cyclobutenone with 1,3-butadiene (Scheme 3) and Table 3 presents the activation energies and enthalpy changes of the reactions. The substituents considered in this work are -CH_3, -OH, -CN and -Cl. The -CN and -Cl substituents are electron withdrawing, -CH_3 is electron-donating and -OH is electron withdrawing by inductive effect and electron donating through resonance effect.

The bond lengths in the substituted cyclobutenones do not change significantly from those of the unsubstituted cyclobutenones.

The reaction of 4-monosubstituted cyclobutenone with 1,3-butadiene (Scheme 5) is a concerted one with partial formation of two new different σ bonds in the single transition state. The reaction mechanism is seen to be an asynchronous concerted one. It produces four possible transition state structures, *exo-syn* 3, *exo*-anti 4, *endo-syn* 5, and *endo-anti* 6 transition state structures (Scheme 5). The -CN substituted transition states in all the four pathways have the most asynchronous transition states (3c, 4c, 5c, and 6c in Figure 3) while –OH produces the most asynchronous transition state in the *endo-anti* pathway (6b in Figure 3).

Along the *endo-syn* pathway, substitution with -CH_3 (through transition state 5a), -OH(through transition state 5b) and -Cl (through transition state 5d) increase the activation barrier by 4.77, 1.08 and 1.29 kcal/mol respectively relative to the parent (unsubstituted) cyclobutenone, while substitution with -CN (through transition state 5c) decreases the activation barrier by 1.22 kcal/mol. Along the *endo*-anti pathway, substitution with -OH (through transition state 6b), -CH_3 (through 6a), -CN (through 6c) and -Cl (through 6d) decrease the activation barrier by 0.06, 0.045, 2.35 and 0.77 kcal/mol respectively relative to the parent. Along the *exo-syn* pathway, substitution with -CH_3 (through 3a) increases the activation barrier by 2.34 kcal/mol while substitution with -OH (through 3b), -CN (through 3c) and -Cl (through 3d) decreases the activation barrier by 2.35, 2.41 and 1.39 kcal/mol respectively. Along the *exo*-anti pathway, substitution with -CH_3 (through 4a), -OH (through 4b), -CN(through 4c) and -Cl (through 4d) decrease the activation barrier by 0.47, 0.49, 1.78 and

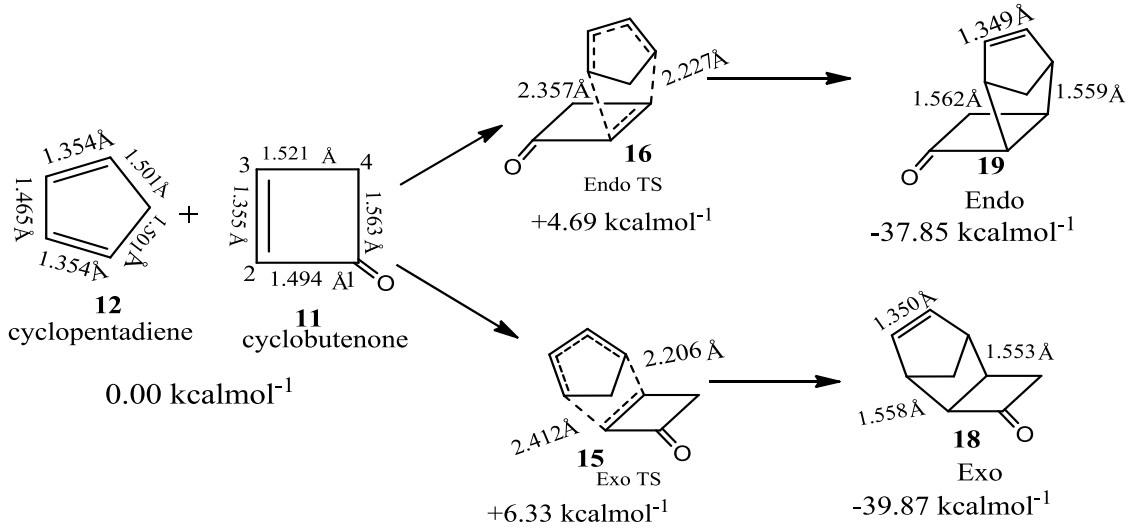
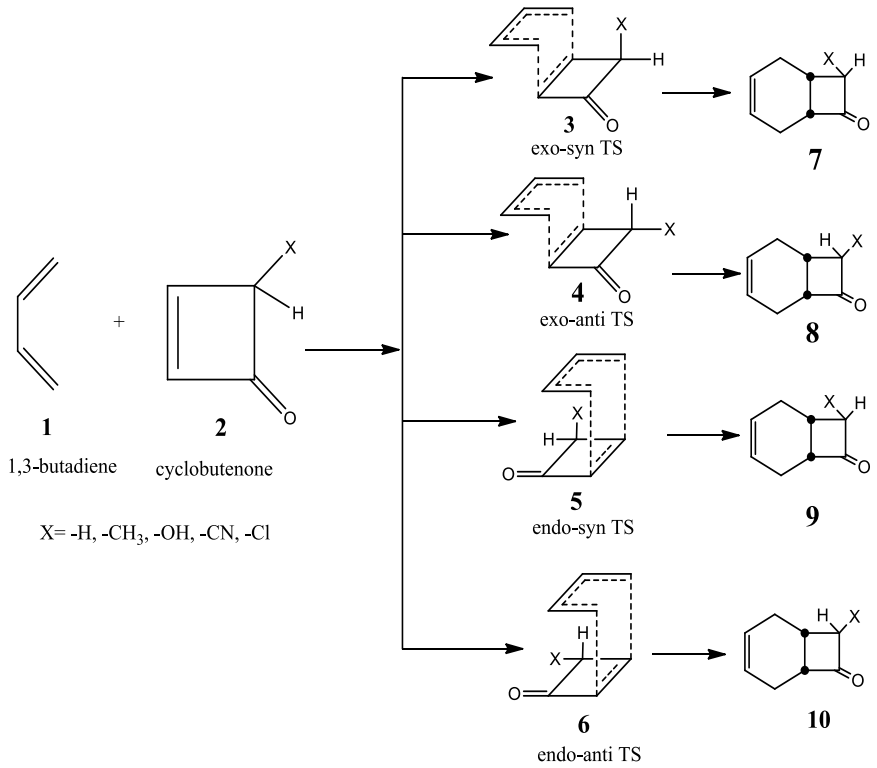


Figure 3: The optimized transition state geometries of the reaction of 4-monosubstituted cyclobutenone 2 with 1,3-butadiene 1. All bond lengths are measured in Å.



Scheme 3: The four modes of addition of the Diels-Alder reaction of 1,3-butadiene and 4-substituted cyclobutenone.

substituent	Activation energies, ΔEact (kcal/mol)				Enthalpy change, ΔH (kcal/mol)			
	Syn		*Anti*		*Syn*		*Anti*	
	endo	*exo*	*endo*	*exo*	*endo*	*exo*	*endo*	*exo*
$-CH_3$	+12.22	+12.03	+7.00	+9.22	-55.84	-55.94	-55.94	-55.84
-OH	+8.53	+7.34	+7.39	+9.20	-54.89	-56.17	-56.98	-54.90
-CN	+6.23	+7.28	+5.10	+7.91	-57.36	-58.00	-58.00	-57.36
-Cl	+8.74	+8.30	+6.68	+8.77	-55.84	-56.33	-56.33	-55.84

Table 3: Energetics of the reaction of 4-monsubstituted cyclobutenones and 1,3-butadiene.

0.92 kcal/mol respectively relative to the parent. The reaction with the lowest activation barrier is that of the -CN-substituted cyclobutenone along the *endo–anti* pathway. Thermodynamically, the reactions are all-*exo*thermic, with the -CN-substituted reactant giving the highest *exo*thermicity of -57.36 kcal/mol for the *endo*-syn and *exo*-anti products and -58.00 kcal/mol for *exo-syn* and *endo*-anti products. Hence, the reaction of the -CN-substituted reactant along the *endo*-syn and *endo*-anti pathways are the most favored in the reaction. The least favored is seen in the reaction of the -CH_3-substituted reactant along the *endo*-syn pathway which is -54.84 kcal/mol.

In all the regio- and stereo-isomers, the -CN-substituted systems have the lowest activation barriers and the most stable products.

Reactions of the 4,4-disubstituted cyclobutenone with 1,3-butadiene and cyclopentadiene

Figure 4, Tables 4 and 5 respectively give the optimized geometries and energetics of the reaction of 4,4-disubsituted cyclobutenone with 1,3-butadiene and cyclopentadiene (Scheme 4).

The effect of the substituents on the C=C bond lengths is insignificant. The reaction of 4,4-disubstiuted cyclobutenone with 1,3-butadiene and cyclopentadiene gives two possible transition state structures; *endo* 13 and *exo* 14 transition state structures shown in Scheme 6. The reaction follows an asynchronous concerted pathway and the forming bond distances are in the range of 2.200 Å-2.400 Å.

The double substitution of all the substituents give asynchronous transition states with the most asynchronicity occurring in the -CN-substituted transition states (13c and 16c) while the least asynchronicity occur in the -CH_3-substituted transition states (13a and 16a) along the *endo* pathway and the -Cl-substituted transition state (14d) along the *exo* pathway.

For the reaction of 4,4-disubstituted cyclobutenone with 1,3-butadiene along the *endo* pathway, double substitution with -CH_3 and -Cl increase the activation barrier by 4.81 and 1.15 kcal/mol through transition states 13a and 13d respectively relative to the parent while substitution with -OH and -CN decrease the barriers by 0.15 and 3.11 kcal/mol through transition states 13b and 13c respectively. Along the *exo* pathway, double substitution with -CH_3 (through 14a) increases the activation barrier by 2.18 kcal/mol while substitution with -OH (through 14b), -CN (through 14c), and -Cl (through 14d) decreases the activation barriers by 3.21, 4.53 and 1.81 kcal/mol respectively relative to the parent cyclobutenone. Thus, kinetically the reaction of the -CN-substituted derivative is the most favored reaction along the *endo* pathway. Thermodynamically, the most stable product is the one with the -CN substituent while the least stable product is the one with

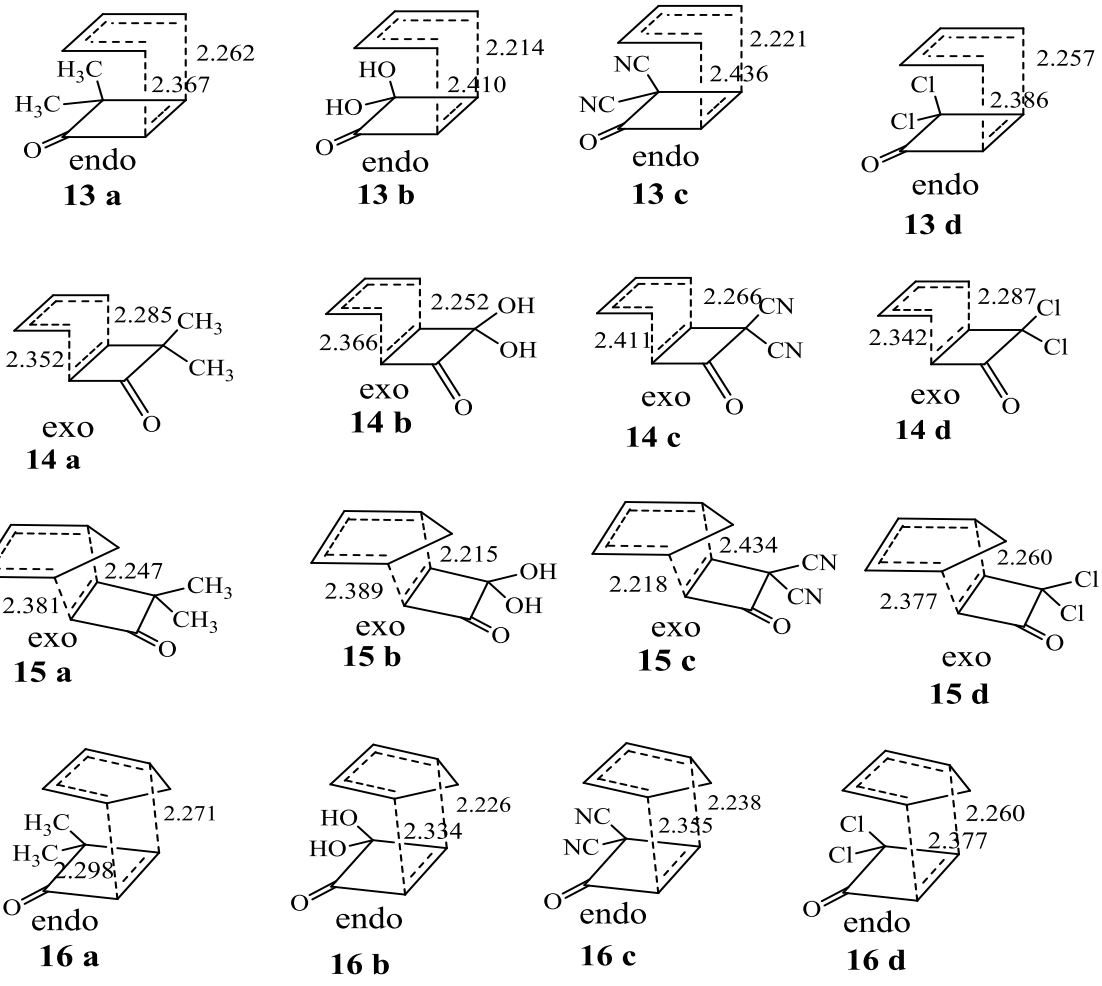
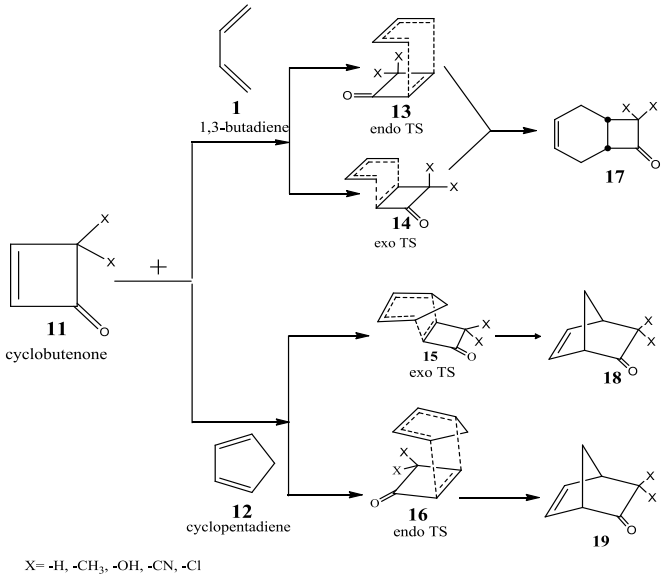


Figure 4: The optimized transition state geometries for the reactions of the 4,4-disubstituted cyclobutenone with 1,3-butadiene and cyclopentadiene. All bond lengths are measured in Å.



Scheme 4: The modes of addition of 4,4-disubstituted cyclobutenones with 1,3-butadiene and cyclopentadiene.

Substituents	Activation energies, E_a (kcal/mol)		Enthalpy changes, ΔH (kcal/mol)	
	Endo	*Exo*	*Endo*	*Exo*
$-CH_3$	+12.26	+11.87	-55.54	-55.54
-OH	+7.30	+6.48	-56.93	-56.97
-CN	+4.34	+5.16	-58.75	-58.75
-Cl	+8.60	+7.88	-56.30	-56.30

Table 4: Energetics of the reactions of 4,4-disubstituted cyclobutenone with 1,3-butadiene.

Substituents	Activation energies, E_a (kcal/mol)		Enthalpy changes, ΔH (kcal/mol)	
	Endo	*Exo*	*Endo*	*Exo*
$-CH_3$	+9.82	+9.25	-38.49	-35.30
-OH	+3.85	+3.31	-40.57	-38.25
-CN	+0.42	+0.55	-42.19	-40.20
-Cl	+4.62	+3.99	-39.81	-37.21

Table 5: Energetics of the reactions of 4,4-disubstituted cyclobutenones with cyclopentadiene.

the $-CH_3$ substituent.

The reaction of cyclobutenone with cyclopentadiene (Scheme 4) is *exo*thermic. The most stable product occurs with the double substitution of -CN along the *endo* pathway, which has reaction energy of -42.19 kcal/ mol. The reaction with $-CH_3$ along the *exo* route gives the least stable product with the reaction energy of -35.30 kcal/mol. Along the *endo* pathway, double substitution with $-CH_3$ (through 16a) increases the activation barrier by 5.13 kcal/mol relative to the parent reaction while double substitution with -OH (through 16b), -CN (through 16c) and -Cl (through 16d) decrease the activation barrier by 0.84, 4.27 and 0.07 kcal/mol respectively. Along the *exo* pathway, double substitution with $-CH_3$ (through 15a) increases the barrier by 2.92 kcal/mol while with -OH (through 15b), -CN(through 15c) and -Cl(through 15d) decrease the activation barrier by 3.02, 5.78 and 2.34 kcal/mol respectively relative to the parent. Thus, the most favored reaction is that of the -CN-substituted reactant along the *endo* pathway.

In the reactions of 4,4-disubstituted cyclobutenones with 1,3-butadiene and cyclopentadiene, the order of activation barriers is CN<OH<Cl<CH_3 and the stability of the products decrease in the order CN > OH > Cl >CH_3.

The Diels-Alder reaction of trans-piperylene with substituted cyclobutenone

Figure 5 and Table 6 respectively give the optimized geometries and relative energies of the stationary points involved in the reaction of trans-piperylene with subsituted cyclobutenones (Scheme 5).

Trans-piperylene has $-CH_3$ on the first carbon of 1,3-butadiene. The difference between the C=C and C-C bond lengths in trans-piperylene and 1,3-butadiene is insignificant.

The presence of substituents lengthens or shortens the reaction center of cyclobutenone depending on the electronic effects of the substituents. The reaction center, C=C, lengthens in the range of 1.356 Å - 1.362 Å with all substituents with the exception of -Cl on the y-position which shortens by 0.001 Å.

The Diels -Alder reaction of trans-piperylene with substituted cyclobutenones (Scheme 7) is an asynchronous concerted reaction. The forming bond lengths are in the ranges of 2.259 Å - 2.447 Å and 2.207 Å - 2.298 Å for *ortho* substitution and 2.146 Å - 2.226 Å and 2.423 Å - 2.580 Å for Meta substitution.

For all the substituents, *meta/endo* substitutions present the

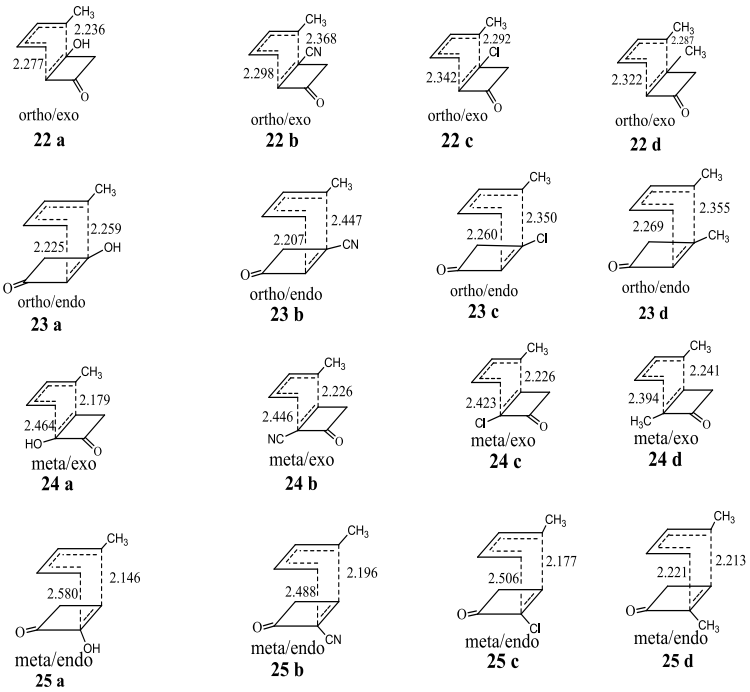
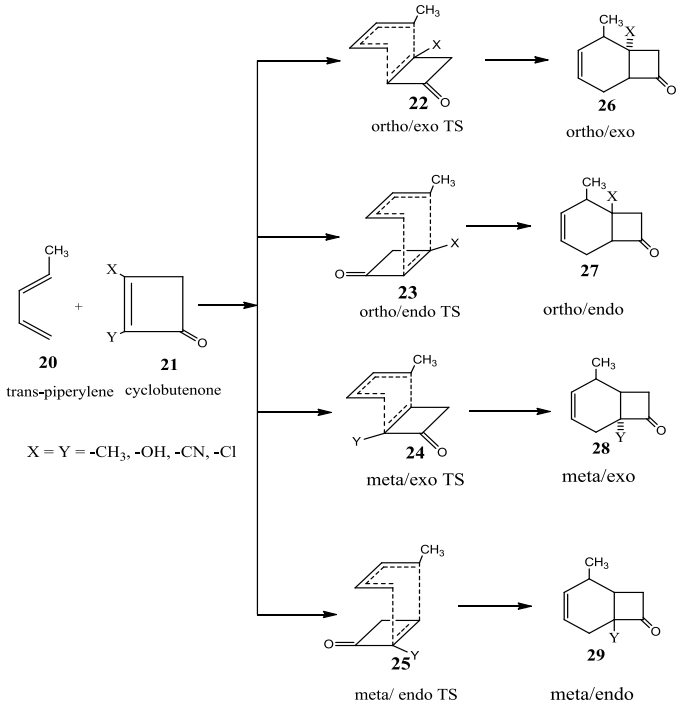


Figure 5: The optimized transition state structures for the reaction of trans-piperylene with substituted cyclobutenone. All bond lengths are measured in Å.

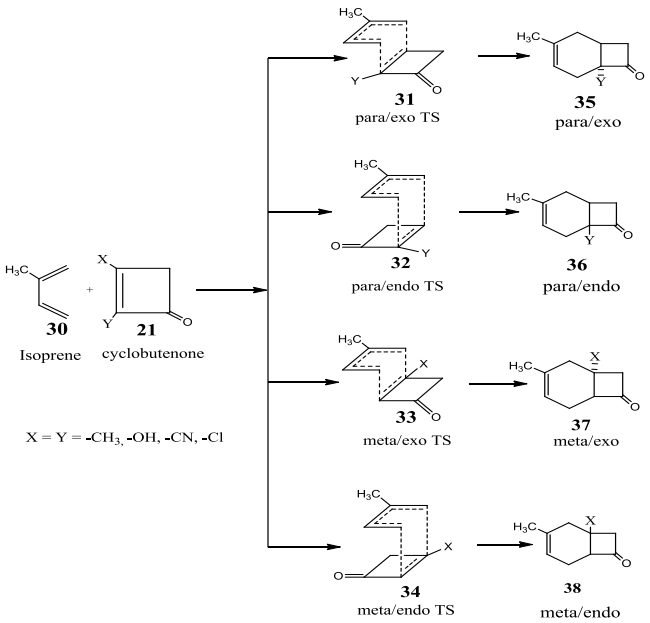
substituents	Activation energies, ΔEact (kcal/mol)				Enthalpy changes, ΔH (kcal/mol)			
	Ortho-endo	*Ortho-exo*	*Meta-endo*	*Meta-exo*	*Ortho-endo*	*Ortho-oxo*	*Meta-endo*	*Meta-exo*
-CH3	+11.80	+11.42	+7.18	+9.32	-50.85	-49.93	-52.95	-50.68
-OH	+15.56	+14.71	+3.76	+10.37	-47.82	-47.82	-52.31	-49.47
-CN	+2.66	+4.05	+2.81	+4.68	-56.08	-55.34	-55.44	-55.16
-Cl	+10.65	+10.70	+4.91	+8.40	-55.70	-54.30	-56.19	-55.73

Table 6: Energetics of the reactions of trans-piperylene with substituted cyclobutenones.



Scheme 5: The modes of addition of trans-piperylene with substituted cyclobutenone.

most asynchronous transition states (ie 25a, 25b and 25c), with the substitution of -OH (25a) being the most asynchronous in the reaction. The lowest activation barriers and most stable products occur in the -CN-substituted cyclobutenones in all the regio- and stereo-isomers, the *ortho-endo* being the most preferred both in terms of kinetics and thermodynamics. The highest activation barriers and least stable products occur in the -OH-substituted cyclobutenones in all the regio- and stereo-isomers, except in the *meta-endo* situation where



Scheme 6: The modes of addition of isoprene with substituted cyclobutenone.

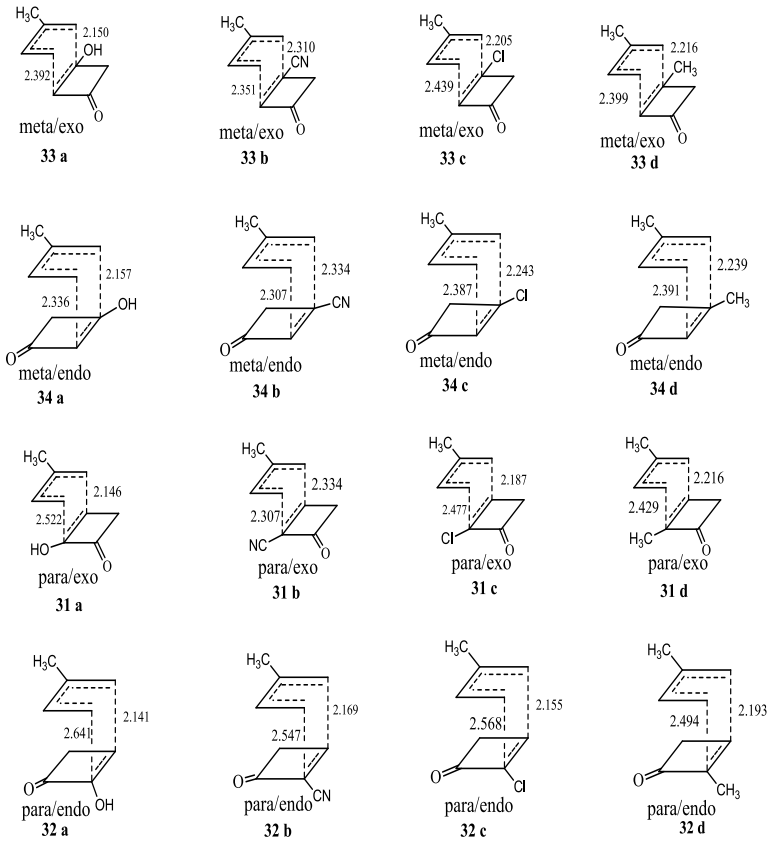


Figure 6: The optimized transition state geometries for the reaction of isoprene with substituted cyclobutenone. All bond lengths are measured in Å.

substituents	Activation energies, ΔEact (kcal/mol)				Enthalpy changes, ΔH (kcal/mol)			
	Para-endo	*Para-exo*	*Meta-endo*	*Meta-exo*	*Para-endo*	*Para-exo*	*Meta-endo*	*Meta-exo*
$-CH_3$	+7.63	+10.07	+11.20	+12.18	-55.18	-52.62	-54.00	-52.84
-OH	+3.97	+11.06	+17.11	+16.21	-54.45	-52.11	-49.93	-50.08
-CN	+3.27	+5.06	+4.50	+5.02	-57.85	-57.85	-57.94	-57.94
-Cl	+5.30	+8.78	+11.25	+11.50	-58.48	-58.48	-58.08	-58.08

Table 7: Energetics of the reactions of isoprene and substituted cyclobutenones.

the -OH-substituted species has a lower barrier than the $-CH_3$ and -Cl-substituted species. The *endo* pathways are more favorable by 0.05-6.67 kcal/mol than the *exo* pathways. The *ortho* rule stipulates that the *ortho* position is more preferred than the meta in the Diels-Alder reactions but this is not observed to be the case in the reaction with cyclobutenone substituted with -OH and -Cl. The activation energies for the meta-substituted –OH and -Cl (3.76 and 4.91 kcal/mol respectively) are less than the activation energies for the corresponding *ortho* substituted. The *meta-endo* is preferred in all cases, kinetically and thermodynamically.

The Diels-Alder reaction of isoprene with substituted cyclobutenone

The main stationary points of the reactions of isoprene with substituted cyclobutenones (Scheme 6) are shown in Figure 6 and the energetics is reported in Table 7. The presence of $-CH_3$ at the second carbon increases the C - C bond lengths by 0.005 Å and the C=C bond lengths by 1.342 Å and 1.345 Å.

The forming-bond lengths in the transition states for the *para*-substituted derivatives (ie 31, 32) are in the ranges of 2.141 Å-2.188 Å and 2.477 Å - 2.641 Å while the forming-bond lengths for the meta-substituted derivatives (ie 33, 34) are in the ranges of 2.150 Å - 2.334 Å and 2.307 Å - 2.439 Å. The most asynchronous is the *para/endo* substitution with -OH (i.e. 32a).

The lowest activation barriers occur in the -CN-substituted cyclobutenones in all the regio- and stereo-isomers; while the highest activation barriers occur in the -OH-substituted cyclobutenones except for the *para-endo* in which it is the lower than the $-CH_3$-substituted cyclobutenones. The most stable products occur in the -Cl-substituted cyclobutenones while the least stable products occur in the –OH-substituted systems. The *para-endo* is preferred in all cases, kinetically and thermodynamically. For the reaction of 2-phenylcyclopentadiene and α-(methyl) acrylonitrile system, Domingo et al. [7] obtained activation barriers of 12.21, 12.83, 13.38 and 13.86 for the *para-endo*, para-*exo*, *meta-endo* and meta-*exo* regio- and stereo-isomers at the MP2/3-21G*//HF/6-31G* level of theory, indicating that just like in our work the para-*endo* is the most preferred on kinetic grounds.

Conclusions

From the results discussed, the following conclusions are drawn:

1. The Diels-Alder reaction of maleic anhydride is far more feasible kinetically than the reaction of cyclobutenones, indicating that maleic anhydride is a better dienophile than cyclobutenone, which in turn implies that for cyclic dienophiles ring strain is not the dominant factor controlling the kinetics of the Diels-Alder reaction.

2. The Diels – Alder reactions of cyclobutenones all follow an asynchronous concerted reaction pathway.

3. In the reactions of the parent substituted cyclobutenone with 1,3-butadiene and cyclopentadiene, the *endo* pathway is the most preferred kinetically. However, in the reactions of the 4,4-disubstituted cyclobutenones the *exo* pathway becomes the most preferred in the reactions with both 1,3-buadiene and cyclopentadiene, except for the CN-substituted cyclobutenone where the *endo* pathway is still the most preferred pathway.

4. In the reactions of the 4-monosubstituted cyclobutenone with 1,3-butadiene, the *anti*-positions are preferred over the syn positions. The *endo-anti* position gives the most reactive dienophile kinetically.

5. In the reactions of trans-piperylene with substituted cyclobutenones, the *meta-endo* position is the most preferred kinetically.

6. In the reactions of isoprene with substituted cyclobutenones, the *para-endo* substitution gives the lowest activation barriers and therefore the most favorable reaction kinetics.

7. In all the reactions considered in this work, the CN-substituted species have the lowest activation barriers and the most stable products. In the reactions of 4,4-disubstituted cyclobutenones with 1,3-butadiene and cyclopentadiene, the order of activation barriers is CN<OH<Cl<CH_3 and the stability of the products decrease in the order CN>OH>Cl >CH_3.

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