A Brief Description on Pericyclic Reactions

(Student reference)

Pericyclic Reactions

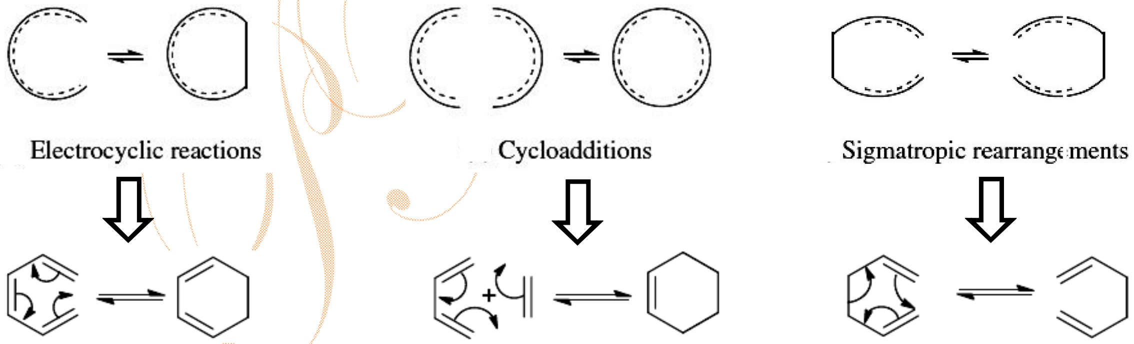
Peri= periphery, around

Cyclic= following a circular path or forming a cycle

Definition: Pericyclic reaction is defined as a thermal or photochemical induced reaction involving a stereospecific, (rather highly stereoselective) ***concerted cyclic shift of the electrons***. The reactant is converted to a product typically by a cyclic conjugated transition state (T.S) either thermally or photochemically.

The first key term ***concerted*** implies to no intermediate since bond breaking and bond making takes place simultaneously. The second key point ***cyclic shift of electrons*** signifies a kind of reaction that occurs around the periphery of a molecule following a typical involvement of π-orbital via a circular pathway. It rules out either homolytic/heterolytic cleavage or radical/ionic pathway.

There are three major classes of pericyclic reactions. Besides, Group transfer reaction is accounted as another class of pericyclic reactions.



Characteristics features of Pericyclic reactions

1. A *concerted pathway via a single cyclic conjugated T.S* where lack of evidence in isolation of intermediate like free radical, carbocation etc. rather the bond breaking and bond making takes place synchronously.

2. *Cyclic shift of electrons* as a result of in general participation of p/π-orbital with some extent to σ-bond: A reorganization of electron pairwise within the close loop of interacting orbitals (***around cyclic***).
3. Usually *unaffected by* acids or bases, *the change of* solvent polarity, catalyst (exception in Diels-Alder cycloaddition reaction accelerated by Lewis acid catalyst) and radical initiator or change in structural motif of the molecule.
4. *No nucleophilic or electrophilic* reagents are required.
5. No such *ionic or radical* pathway.
6. Highly *stereoselective* in nature.
7. Most of the reactions are equilibrium processes in which direction of equilibrium depends on the enthalpy and entropy of the reacting species. *Large decrease in entropy or loss of degree of freedom* illustrates the rigid transition state (e.g D.A reaction $\Delta S^{\neq} = -150$ to $-200\ JK^{-1}mole^{-1}$ and in sigmatropic reaction $\Delta S^{\neq} = -50\ JK^{-1}mole^{-1}$) and with a low enthalpy of activation reflecting the exothermic nature of the reaction.
8. They follow **Woodward-Hoffmann rule of "*Conservation of Orbital Symmetry*"** which states that the orbital symmetry should be maintained through out the reaction i.e before and after the reaction the orbital symmetry of both the reactant and product should be conserved. Thus, it is an **orbital symmetry controlled** reaction. The pericyclic reaction excludes any usual nucleophilic-electrophilic selective transformation of stereoheterotopic faces and ligand discrimination by intramolecular symmetry.

Source/ Influencing factor/Mode of activation

1. Heat or Thermal (Δ)
2. Light or Photochemical (hγ)

Non- Influencing factor

1. Polar/Non polar solvents.

2. Radical initiator or inhibitor.

3. Catalysis (except Diels-Alder cycloaddition reaction).

Criteria for Pericyclic Reaction

1. Mode of activation. (Δ/ hγ)
2. Number of p/π-orbital participatiion [4nπ or (4n+2)π]
3. Stereochemical outcome (stereospecific or stereoselective).

Advantages of Pericyclic Reaction

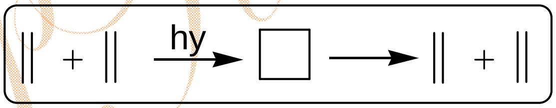
(a) Generation of variety of new *carbon-carbon σ-bond* (due to reorganization of p/π-bond).

(b) Less probabilities of formation of *unwanted side products*. (due to concerted cyclic process and unreacted or unaffected by the influence of solvent or any reagent). So, it is straight forward, non-complicated and anticipated reaction.

(c) The reaction is highly *stereospecific in nature*. (due to concerted orbital symmetry controlled process).

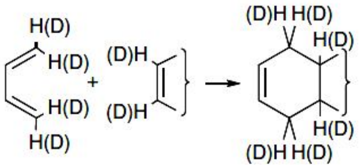
(d) Enormous *application in biosynthesis*.

(e) *Non conventional energy source* e.g. the cycloreversal of cyclobutane to two ethelene molecule is accompanied by liberation of heat.



Evidence for the concertedness of Pericyclic reaction

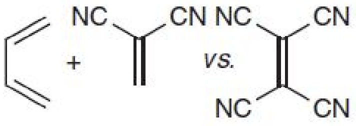
Point 1: Although small, an inverse secondary kinetic isotope effects was observed for the following diene and the dienophile when the deuterium substitution on the four carbon atoms changes from trigonal to tetrahedral as the reaction proceeds. It was experimentally found a geometrically related $(k_D/k_H)^2 = (k_{D2}/k_H)$ [not arithmetically related, $(k_{D2}/k_H) = 2(k_D/k_H) - 1$] to the isotope effects at both deuterated ends indicating both ends are formed simultaneously.



Point 2: Bimolecular reactions account for inherently high negative entropies of activation ($\Delta S^{\neq}$). Exceptionally high negative $\Delta S^{\neq}$ (typically in the range of —150 to —200 J K^{-1} mol^{-1}) for Diels-Alder (D.A) reactions or cycloaddition reactions reveals <u>a favourable alignment with compact transition structure</u> of two components only if both bonds can form at the same time.

Point 3: The rates of D.A reactions are slightly increased by a factor of only 10 upon the change in the polarity of the solvents or with large change in dipole moment from 2.3 to 39 in contrast to several orders of magnitude for stepwise ionic cycloaddition reactions.

Point 4: The dienophile tetracyanoethylene reacts significantly much faster rate with butadiene than 1,1-dicyanoethylene which can't be rationalized by ionic stepwise pathway.

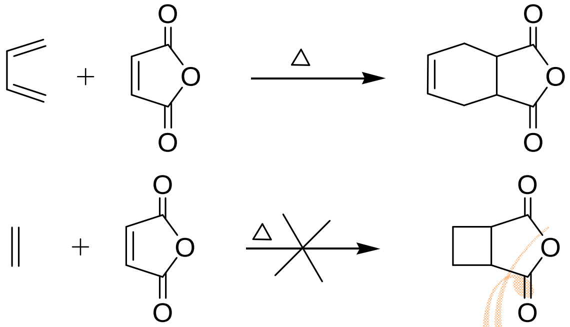


Q. What is the difference between S_N^2 reaction and pericyclic reaction although both literally proceed in stereospecific concerted manner?

S_N^2 reaction constitutes a transition state of non-isolable intermediate that may be linear or cyclic transition state where the HOMO of nucleophilic approach must be exactly opposite to that of LUMO of leaving group. A stereospecific product having inversion of configuration is expected to result in S_N^2 reaction. On the other side, Pericyclic reaction is an orbital symmetry controlled reaction with non-isolable intermediate via cyclic conjugated transition state which demands stereospecific product by virtue of suprafacial or anatarafacial or HOMO-LUMO interaction.

Woodward-Hoffmann Selection Rule

Let us take an example in which maleic anhydride reacts butadiene spontaneously but not with ethelene under thermal condition.



In order to explain the phenomenon, we need to consider the Woodward-Hoffmann selection rule.

In a Pericyclic reaction, the set of in phase atomic orbitals (A.Os) to form molecular orbitals (M.Os) of reactants are transformed into corresponding in phase set of M.Os of the products by conserving the symmetry of the orbitals throughout the reaction in a concerted manner via symmetry allowed low energy transition state. This is called as woodward-Hoffmann rule of "**Conservation of Orbital Symmetry**". This clearly indicates that the orbital symmetry should be maintained through out the reaction i.e before and after the reaction the orbital symmetry of both the reactant and product should be conserved. Hence, Pericyclic reaction can be attributed as orbital symmetry controlled reaction.

Maintaining the principle of conservation of orbital symmetry, a Pericyclic reaction can be visualized as reorganization of electron (pairwise) with in a close loop of interacting orbitals through symmetry allowed concerted process.

Selective transformation of organic reaction is based on

(a) Stereoheterotopic faces

(b) Stereoheterotopic ligand

These are distinguished by intramolecular symmetry or overall symmetry of the molecule. But, the Pericyclic Reaction relies on the interactive molecular orbitals (M.Os), not as a whole molecular symmetry.

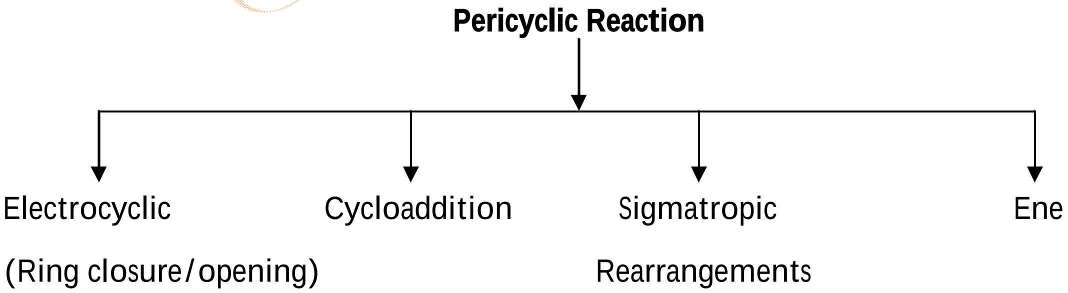
The basic difference between pericyclic chemistry with heterocyclic or alicyclic reaction is that the pericyclic reaction is guided by "Rule of Conservation of Orbital Symmetry" proposed by Woodward and Hoffman. In addition to this, the former involves a cyclic concerted process with the help of p/π-orbital and the mode of activation must be either thermal or photochemical. No other reagents are associated with the pericyclic reaction.

To explain the stereochemistry of the product, three fundamental approaches have to be considered-

1. Correlation of orbitals in relation to symmetry should be preserved (W. H principle).
2. Aromaticity or anti aromaticity of T.S by Hückel Molecular orbital theory.
3. Fronteir Molecular Orbital (FMO) approach: HOMO-LUMO interactions.

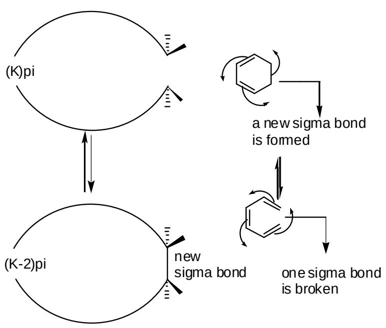
Most of the pericyclic reactions, of course not all, are little influenced by Coulombic forces e.g. the rates of D.A reactions are little affected by polarity of the solvent. We can therefore expect that the major factor influencing the reactivity will be the size of the Frontier orbital interaction represented by energy expression from Klopman and Salem's perturbation of orbital symmetry. Thus, FMO approach among three fundamental approaches is most widely applicable in Pericyclic reaction.

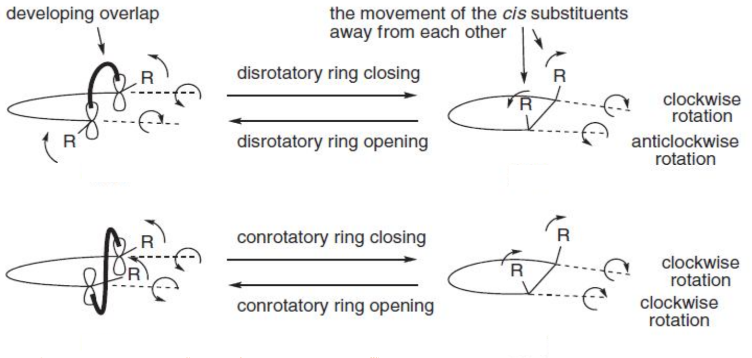
Class of Pericyclic Reactions



Electrocyclic Reaction

An intramolecular pericyclic reaction where reversible concerted cyclic shift of electrons occurs by virtue of ring closing with the formation of new σ-bonds across the ends of conjugated acyclic π-electrons of polyene or breaking of ring to form acyclic analogue from its corresponding cyclic framework, is typically termed as **Electrocyclic reaction**. The reaction can be best way represented by the following diagram;





The reaction is activated either by heat or by UV-light. The reaction follows the principle of microscopic reversibility. The reaction sequence can be explained by three fundamental approaches;

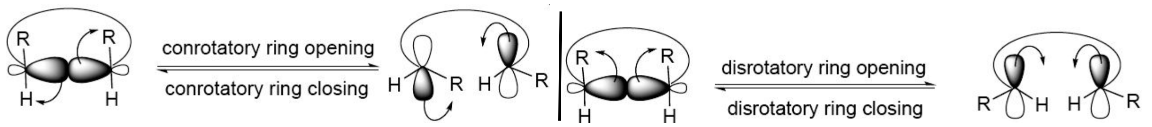
(a) Correlation of orbital symmetry of terminal lobes of interacting orbitals

(b) Perturbation of M.O theory or HMO theory of aromaticity or anti aromaticity in T.S

(c) FMO approach of HOMO-LUMO interactions of orbital energy states.

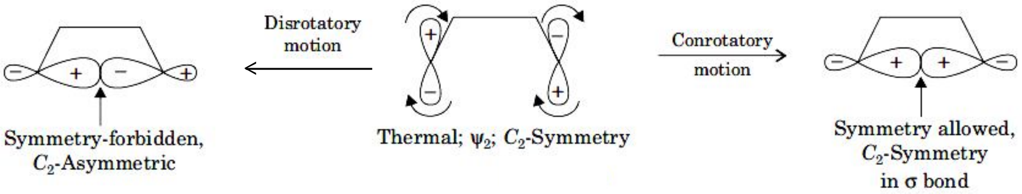
Conditions for Electrocyclic Reaction

1. Symmetry of terminal orbitals in conjugated π-system has to be considered.
2. Terminal p-orbitals form σ-bond by maintaining phase distribution of lobes after rotation.
3. Two possible ways of the rotation of lobes or p-orbitals: (a) Conrotation motion (b) Disrotation motion.

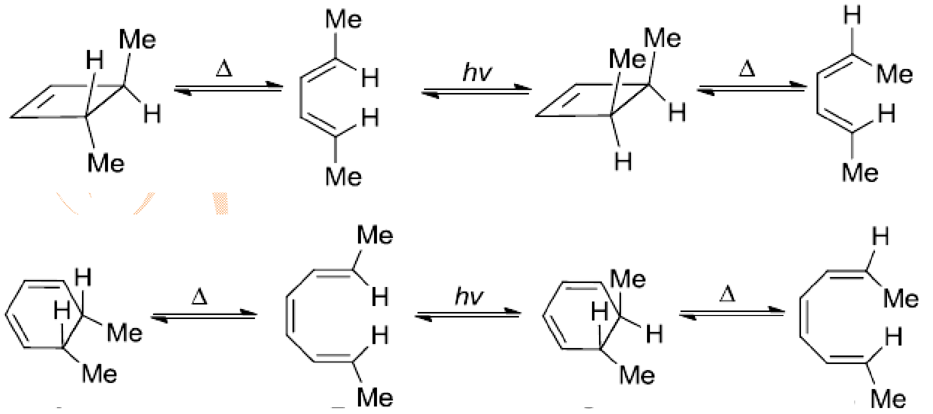


4. Movement of the groups or substituents attached to terminal lobes according to the lobe's movements which bring about the stereochemistry of the resultant product.

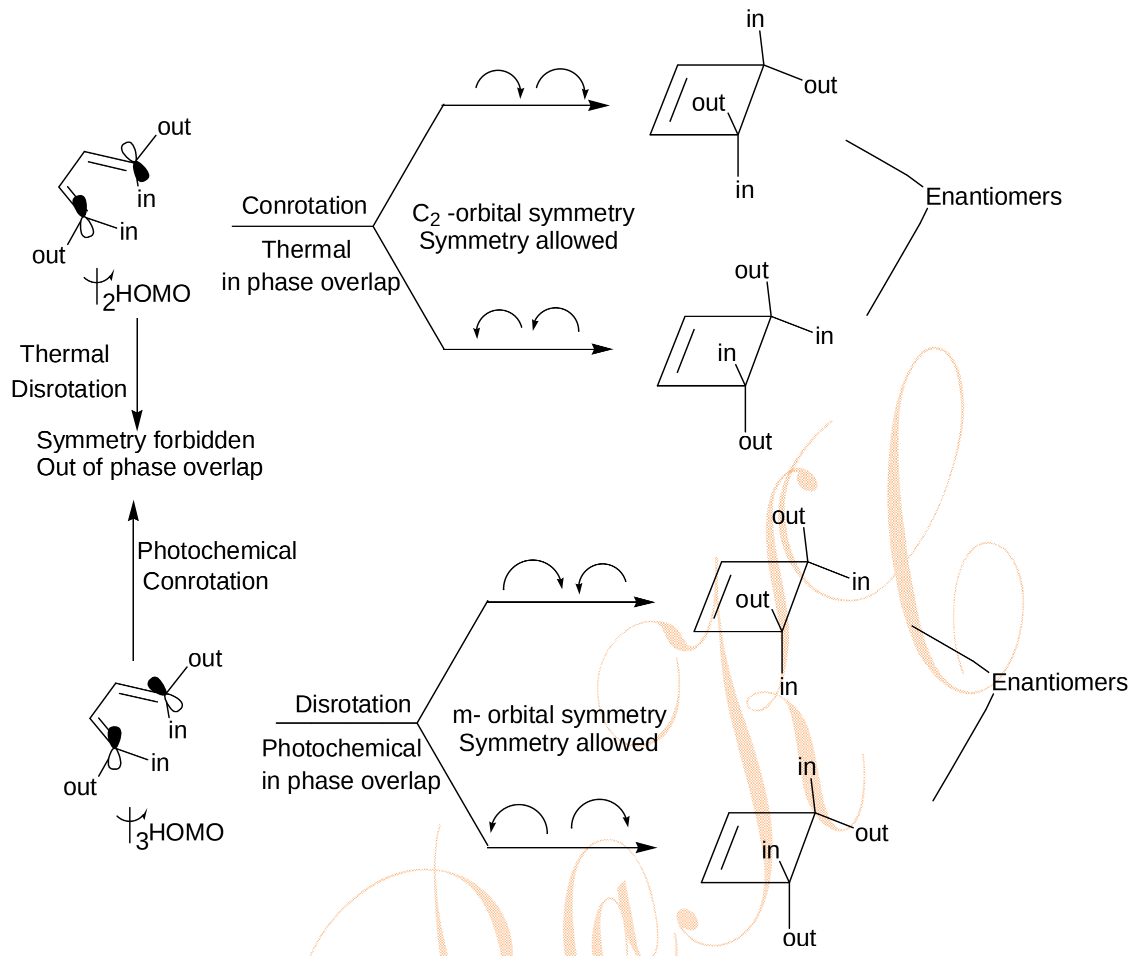
5. Conrotation or disrotation should follow Woodward –Hoffmann principle of orbital symmetry and will be favoured if the process is devoid of any steric crowding and generation of strain in the molecule.



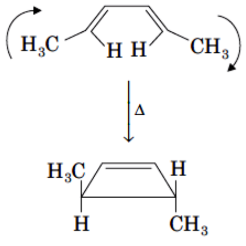
Example of electrocyclic reactions and their stereochemical significance of two modes of ring opening/closing are illustrated through thermal and photochemical transformations of isomeric 3,4-dimethylcyclobutenes and isomeric 5,6-dimethylcyclohexa-1,3-dienes. The stereochemistry of the substituents depends on the mode of activation and the mode of rotation of terminal orbitals

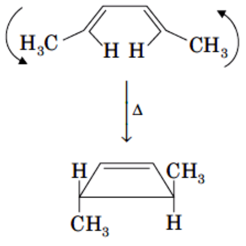


Let us consider a butadiene system ($4n\pi$) as *s-cis* conformation where the terminal groups are considered as 'in' group (concave face of the arc) and 'out' group (convex face of the arc).



If the termini rotates in the *same direction i.e. either both clockwise or both anticlockwise, is called* ***Conrotatary motion***. Here both 'in-in' and 'out-out' groups are in *trans* relationship. If the termini rotates in the *opposite direction i.e. one in clockwise and another in anticlockwise or vice-versa, is called* ***Disrotatary motion***. Here both *'in-in' and 'out-out' groups are in cis relationship.* In both cases the ***enantiomeric*** **mixtures** are formed. Enantiomers have equal energies and hence ***enantiomeric pathways*** have identical energies. The enantiomeric excess depends on the movements of the termini offering the in phase orbital overlap.



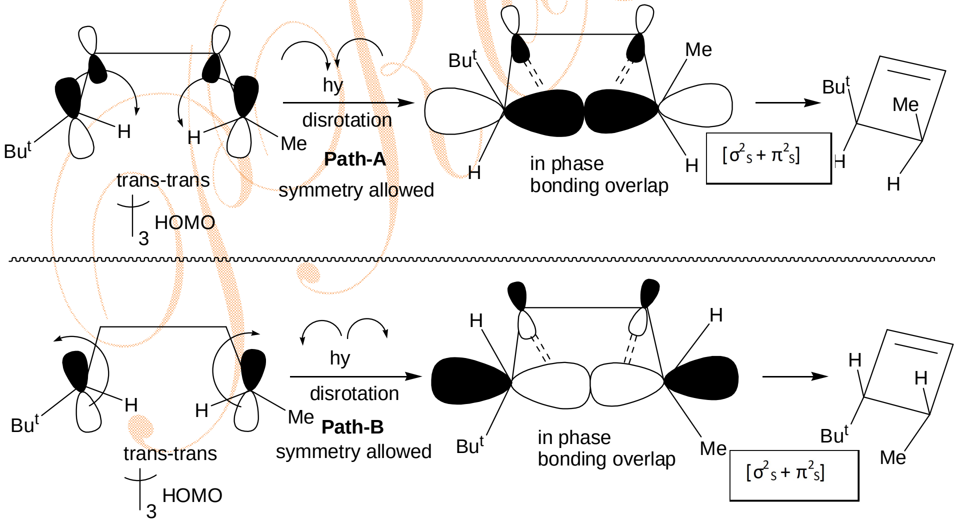


During conrotation C_2 symmetry has been maintained whereas for disrotation mirror plane (m) symmetry has been followed for 4nπ system. But the situation is exactly reversed in case of (4n+2)π system. It should be kept in mind that in both cases HOMO orbitals do participate in the conrotation or disrotation pathway which in turn regulates the stereochemical outcome.

Pictorial Representation: FMO Approach

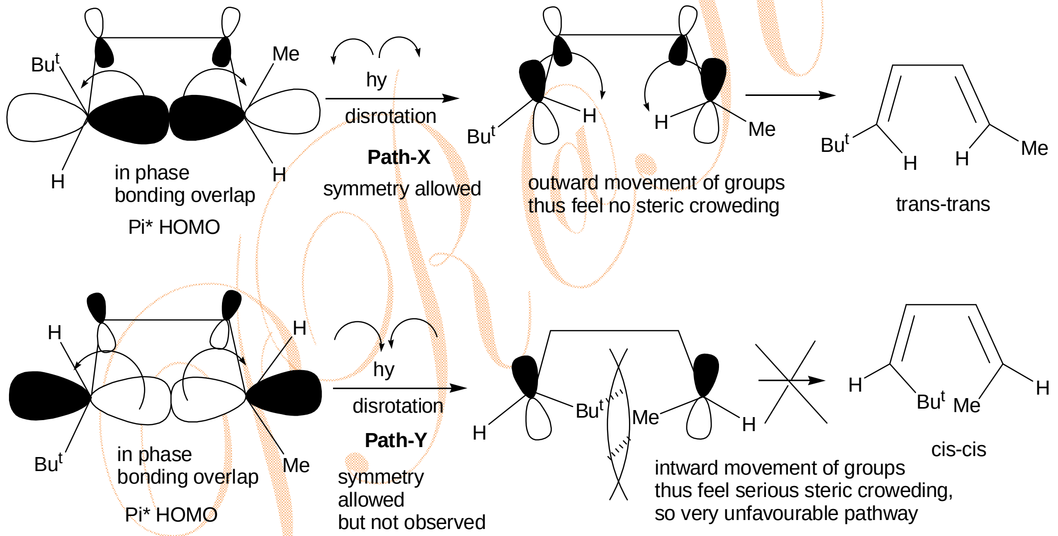
According to Frontier Molecular Orbital approach, the valence π-electrons in the HOMO orbital of polyene system dictates the course of the Pericyclic Reaction. Similarly the valence π-electrons in the HOMO orbital of cyclo-polyene system also regulate the course of the pericyclic reaction. Therefore, combination of above HOMO orbital participation ultimately leads to a bonding interaction. The selection of HOMO participation obviously depends on the mode of activation.

Let us consider a **photochemical electrocyclic ring closure reaction** of 1,3 butadiene to cyclobutene derivative. The pictorial representation is shown below.

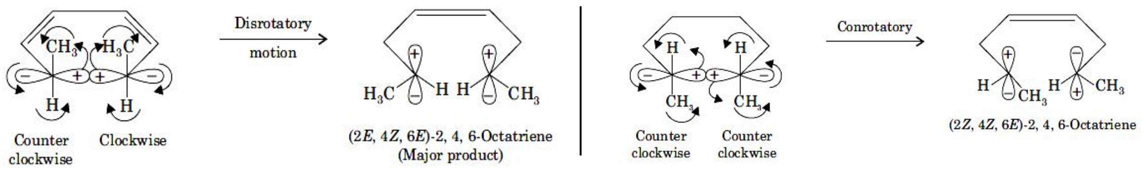


Which pathway is more favourable, Path-A or Path-B?

Both the Path A and Path B are symmetry allowed process and is represented by $[\sigma^2_S + \pi^2_S]$ interaction where 'S' stands for suprafacial interaction. The FMO suggests the both pathways are facilitated by suprafacial in phase bonding interaction leading to symmetry allowed process. Although enantiomeric mixture is formed but the Path-A is slightly enegetically more favourable than Path-B since during T.S the bulky substituents ^{t}Bu and Me groups tend to move towards inward direction in Path-B although both of the pathways results syn conformation. But such impact is even more pronounced while considering reverse reaction i.e. Electrocyclic ring opening. Then it will be observed that inward movements of arrows can be better pathways than outward movements of arrows because the later constitutes a bulk effect as a result of direct confrontation in T.S due to close proximity of ^{t}Bu and Me groups. This makes Path-Y although symmetry allowed process but not observed due to thermodynamically almost impossible situation to take place.

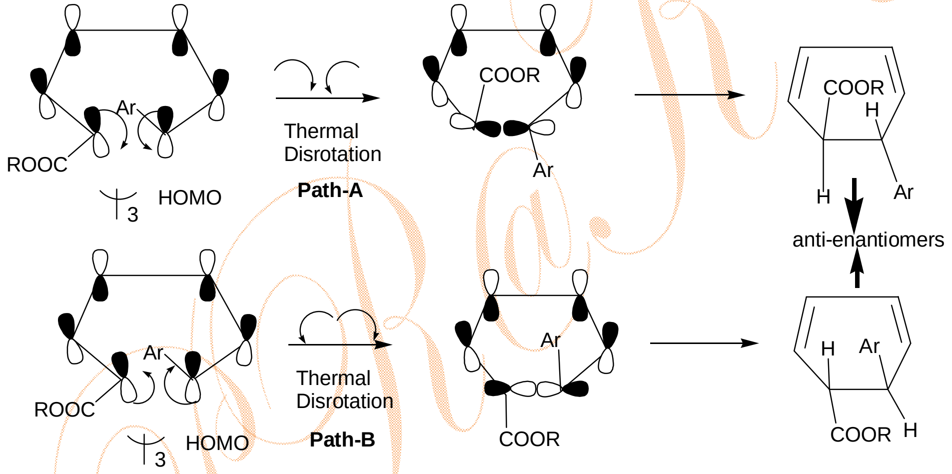


Thermal induced cyclization uses ground state ψ_3 as HOMO which has m-symmetry. So, the mode of thermal cyclisation is disrotatory motion. Photochemical induced cyclization uses excited state ψ_4 as HOMO which has C_2-symmetry. So, conrotatory motion is the mode of photo-induced cyclisation. For ring opening reaction, the similar energy of HOMO orbital, the symmetry element and mode of reaction would be followed.

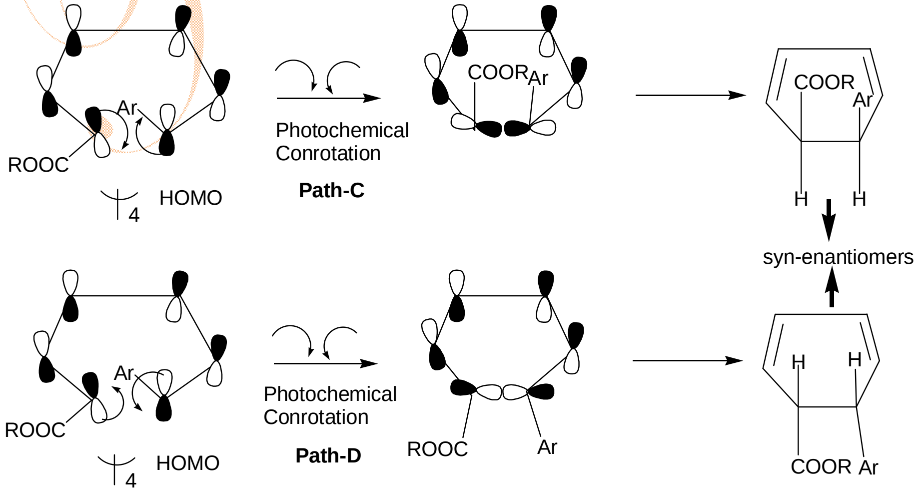


In case of 6π i.e [(4n+2)π] system, the same situation happens as that found in 4π system. Here both Path-A and Path-B have equal probabilities during thermal induced ring closing reaction. Because of similar type of steric interaction may occur at T.S, their formation of either pathway is statistically favourable. However, the photochemical pathway is both kinetically and thermodynamically unfavourable compared to that of thermal process because Path-D clearly shows a bulk atmosphere during the course of the reaction.

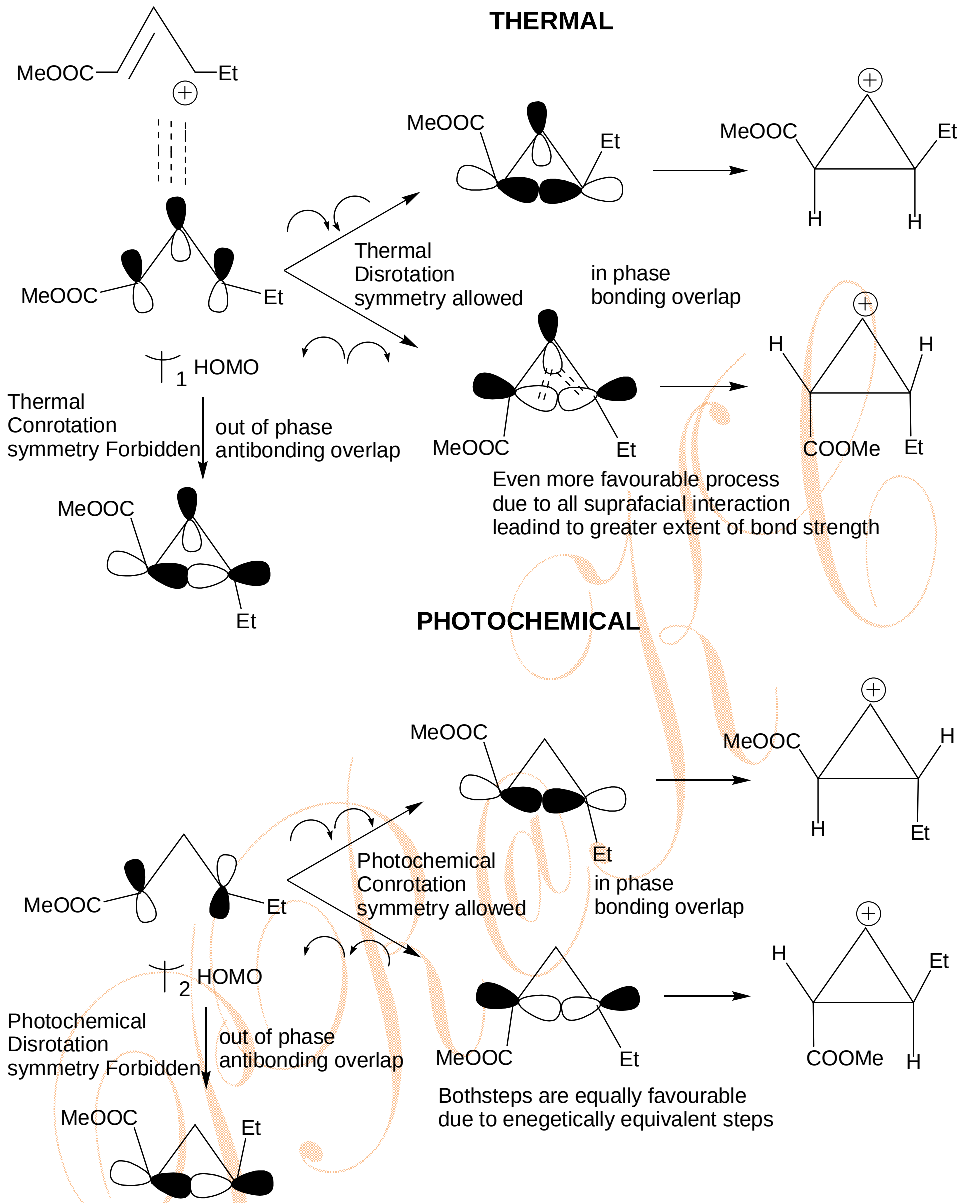
Thermal (4n+2)pi system



Photochemical (4n+2)pi system



Allylic carbocationic system



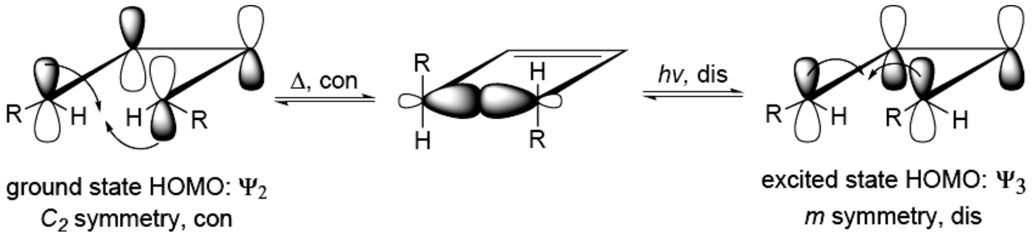
Even more favourable process due to all suprafacial interaction leadind to greater extent of bond strength

Bothsteps are equally favourable due to enegetically equivalent steps

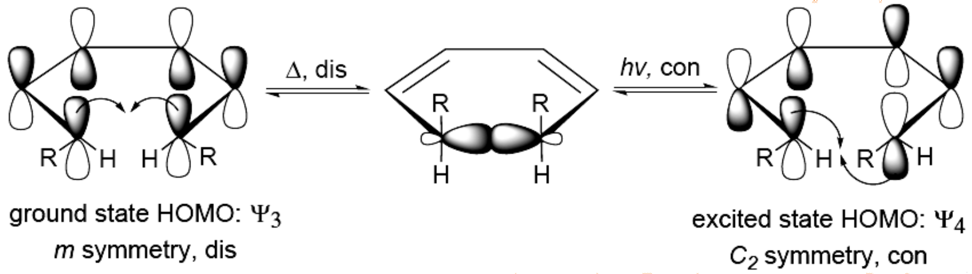
Q. What is the driving force for allylic cation or pentadienyl cation to undergo Electrocyclic Ring closure reaction?

Ans: Generally less conjugated carbocations undergo in Electrocyclic ring closing reaction. The formation of ring from allylic or pentadienayl cation increase the strain in the ring as well as decrease the stabilization of carbocation. In spite of that such reactions undergo due to gain in extra carbon-carbon σ-bond which compensate the destabilization energy.

FMO of butadiene



FMO of hexatriene

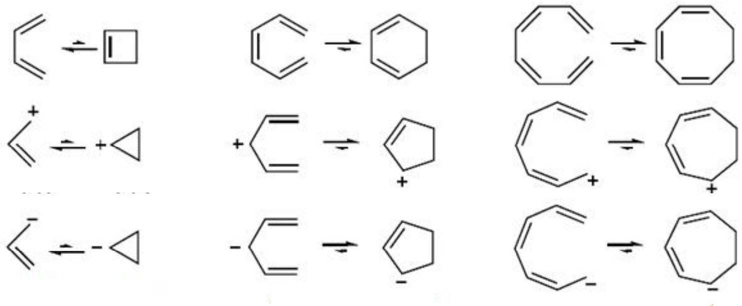


The following table provides a correlation among the entire factors associated with Elecrocyclic Reaction.

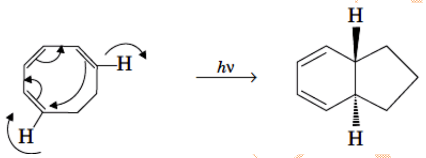
No. of π electrons	Symmetry	Mode of activation	Pathway	Reactants stereochemistry	Product Stereochemistry
$4n\pi$	C_2(s)	Thermal(Δ)	Conrotation	*trans-trans* *cis-cis*	*trans*
				trans-cis	*cis*
$4n\pi$	m(s)	Photochemical (hγ)	Disrotation	*trans-trans* *cis-cis*	*cis*
				trans-cis	*trans*
$(4n+2)\pi$	m(s)	Thermal(Δ)	Disrotation	*trans-trans* *cis-cis*	*cis*
				trans-cis	*trans*
$(4n+2)\pi$	C_2(s)	Photochemical (hγ)	Conrotation	*trans-trans* *cis-cis*	*trans*
				trans-cis	*cis*

Thermal electrocyclic reactions involving a total number of electrons that can be expressed in the form (4nþ2) are disrotatory, and thermal electrocyclic reactions in which the total number of electrons can be expressed in the form (4n) are conrotatory. Some examples of electrocyclic reaction are shown below.

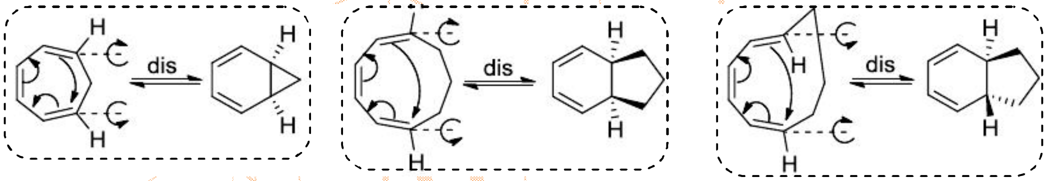
Ex 1: A representative of various types of electrocyclic reactions is illustrated.



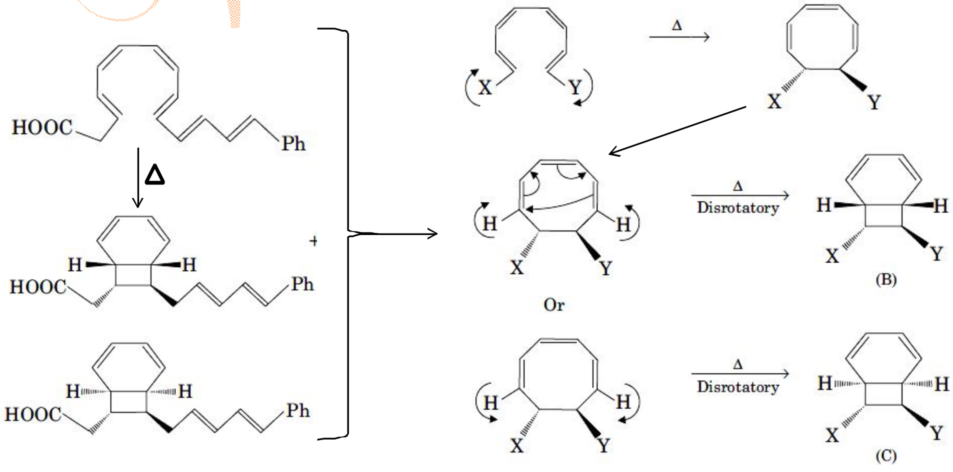
Ex 2: The reaction below is photo-induced conrotatory mode of reaction in which reactant comprises $(4n + 2)\pi$ electrons with ψ_4^* excited HOMO having C_2-symmetry.



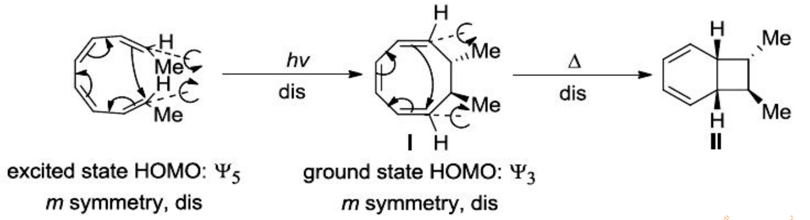
Ex 3: The following disrotatory mode of conversions of hexatriene $[(4n + 2)\pi$ electrons system] are observed in thermal condition.



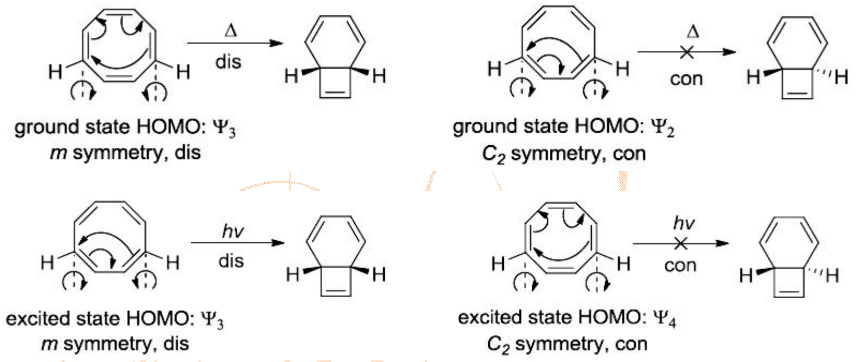
Ex 4: The following reactions represent double electrocyclic ring closure reaction. The first involves $(4n)\pi$ electrons, resulting a conrotatory motion while the second cyclization has $(4n + 2)\pi$ electrons showing disrotatory motion.



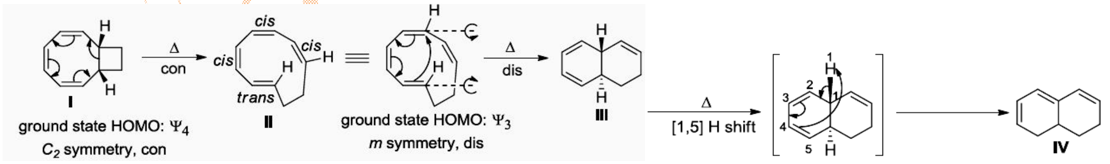
Ex 5: Octatetraene produces 7,8-dimethyl cycloocta-1,3,5-triene upon photochemical disrotatory ring closure followed by thermal disrotatory electrocyclization to yield fused ring.



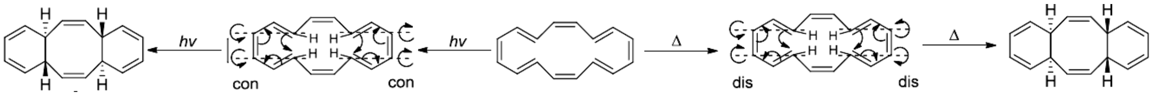
Ex 6: Under thermal conditions, cyclooctatetraene preferentially undergoes a 6π-electron disrotatory electrocyclization whereas under photochemical conditions, cyclooctatetraene preferentially undergoes a 4π-electron disrotatory electrocyclization. However, both form only the *cis*-isomer.



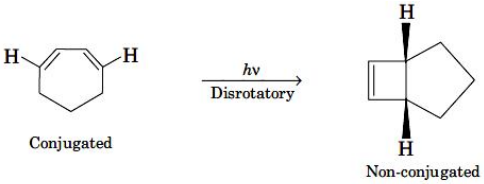
Ex 7: Compound II and III are formed by the ring opening via thermal conrotation and disrotatory electrocyclization respectively. Compound III undergoes [1,5] hydrogen shift to yield IV.



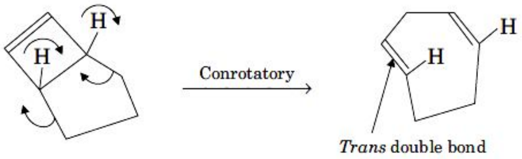
Ex 8: [16]-annulene isomerizes both thermally through two *cis*-fused 6-membered double disrotatory closure and photochemically through two *trans*-fused 6-membered double conrotatory closure.



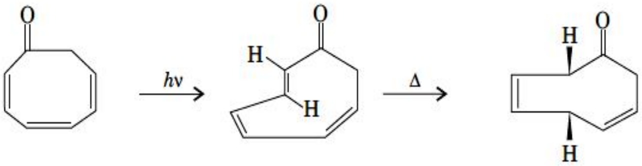
Ex 9: It is usual for a photochemical reaction to favour the less stable isomer of an equilibrium. For instance, the conjugated diene absorbs UV light, but the bicyclic compound does not, hence, the photochemical reaction favours the latter.



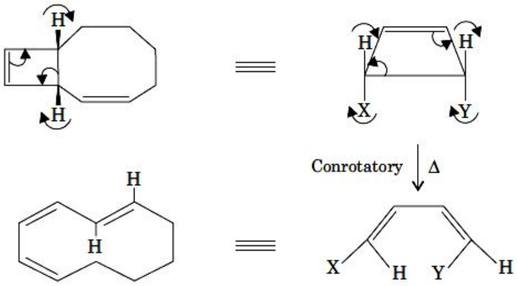
Ex 10: The allowed thermal conrotatory process would give a highly strain molecule containing a *trans* double bond within a small ring.



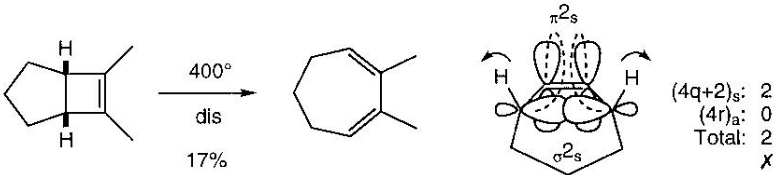
Ex 11: (2Z, 4Z, 6Z)-2, 4, 6-cyclooctatrione first isomerizes photochemically to (2E, 4Z, 6Z)-2, 4, 6-cyclooctatrienone, which then cyclises thermally to cis-bicyclo [4, 2, 0]octa-3, 6-dien-2-one by a conrotatory process.



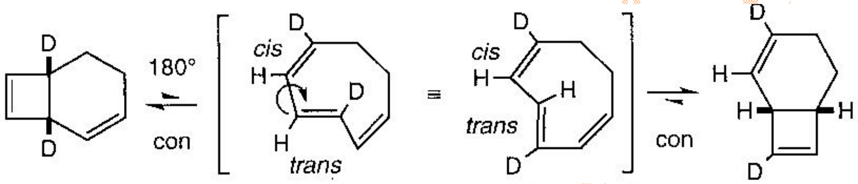
Ex 12: Thermal isomerization of *cis*-bicyclo [6, 2, 0] deca-2, 9-diene gives (1E, 3Z, 5Z)-1, 3, 5-cyclodecatriene.



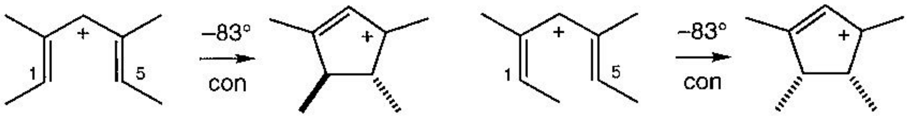
Ex 13: In bicycloheptane, a conrotatory reaction is virtually impossible since it would put *trans* double bond in the seven membered ring. Rather a forbidden disrotatory reaction occurs at high temperature (≈ 400 °C).

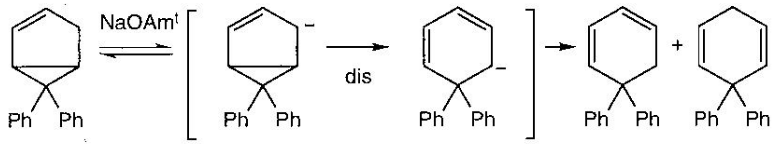


Ex 14: Since the ring fusion as well as double bond within the ring is the low energy *cis* arrangement, a conrotatory ring opening is expected to give strained *trans* double bond within 8-membered ring. It is thermodynamically unfavourable. The reaction thus needs a high temperature to resulting in the formation of another isomer.

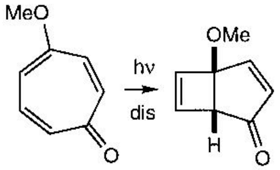


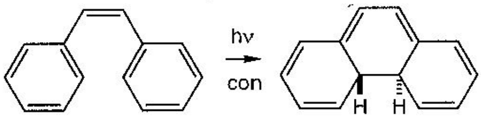
Ex 15: Stereoisomeric pentadienyl cations give stereoiosmeric cyclopentenyl cations in conrotatory reactions. The reactions are fully stereospecific. In contrary, for cyclopentenyl anion that disrotatory opens to allow two H's moving outward.



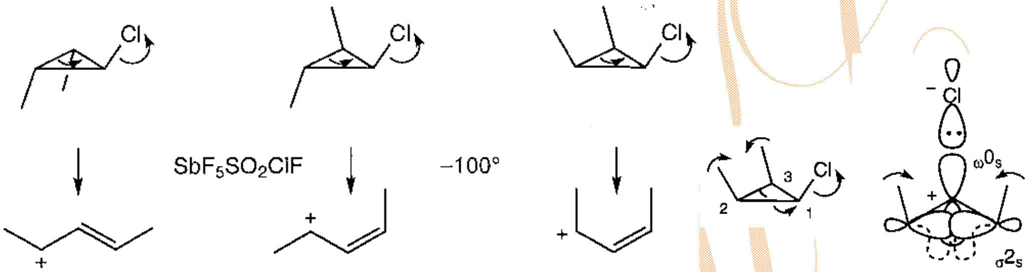


Ex 16: In case of constrained systems, the photochemical reaction can easily lead to a product thermodynamically much higher in energy than the starting material; but nevertheless they are thermally stable. Because the bicyclic ketone (first reaction) lost is not only strained but it lost the partial aromaticity of tropone and similar loss of aromaticity for dihydroanthracene from *cis*-stilbene.

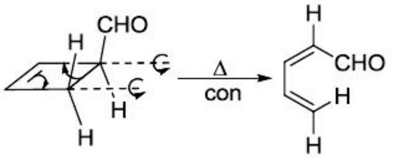




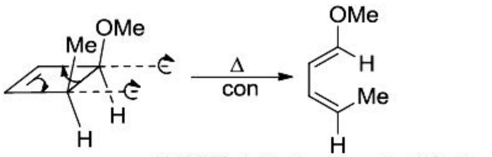
Ex 17: Disrotatory ring opening of various cyclopropyl halide results three different shapes of allyll cations: W-shaped, sickle shape and U-shaped which largely retain their conformation at low temperature as obvious from ^{1}H NMR spectroscopy. These recations demonstrate **torqueoselectivity**. *It defines that the direction of disrotatory ring opening is determined by which side of the ring the halide leaves from as shown from contrast between the products from the cyclopropyl halides*. The former opens the two –CH_3 groups moving outwards as thermodynamically preferred direction. However, later shun thermodynamics to open as U-shaped geometry.



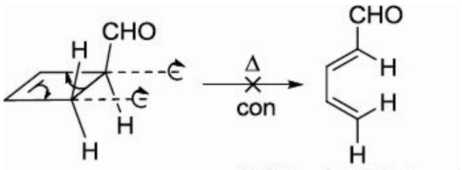
Ex 18: There is another example of Torquoselectivity as the predisposition of a given R substituent for a given conrotatory motion. Steric factors cause a preference for the larger group to move outward. It is observed that π-donor substituents prefer con-out mode whereas π-acceptor substituents prefer con-in mode.



(*Z*)-Penta-2,4-dienal

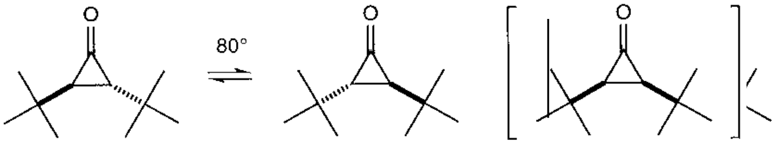


(1*E*,3*Z*)-1-Methoxypenta-1,3-diene

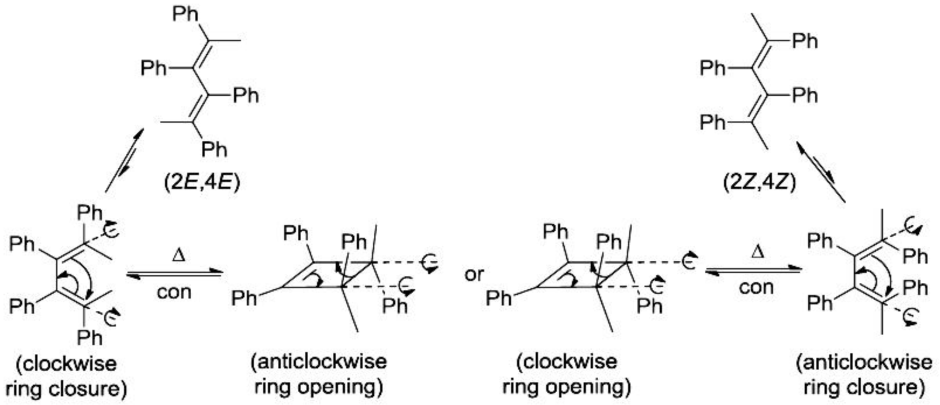


(*E*)-Penta-2,4-dienal
(not formed)

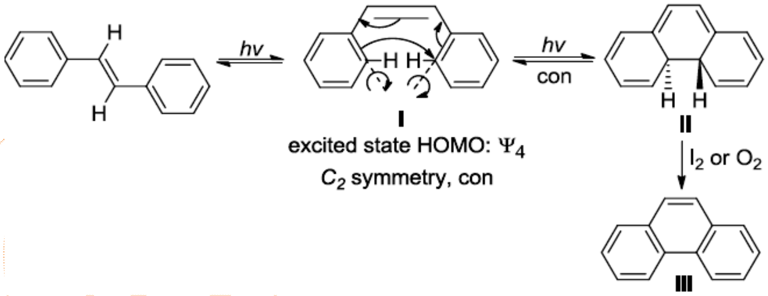
Ex 19: The *trans* isomer of 2,3-ditertiary butyl cyclopropanone readily isomerizes at 80 °C whereas the *cis* isomer does not because the disrotatory ring opening required for isomerization is sterically prevented for *cis* isomer.



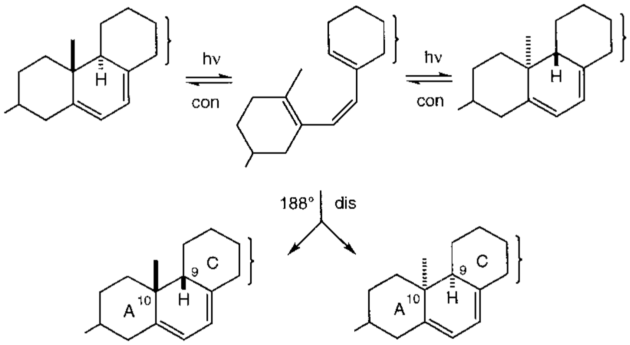
Ex 20: Thermal isomerization of Ph-substituted dienes occurs via cyclobutene intermediate following a thermally allowed conrotatory electrocyclization.



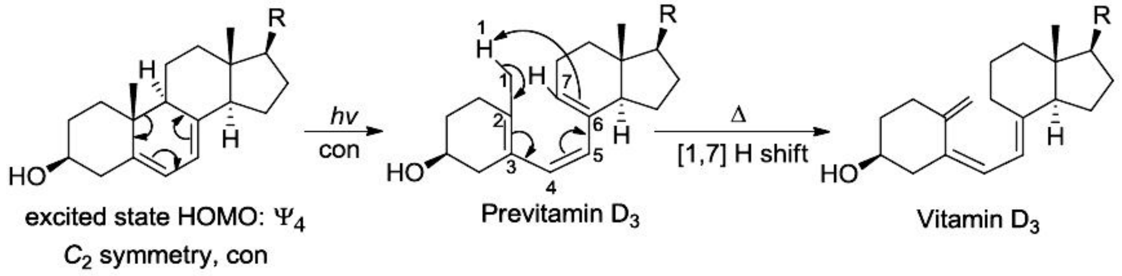
Ex 21: The *trans*-stilbine isomerizes to cis-stilbine (I) under photochemically. On irradiation of *cis*-stilbine provides dihydrophenanthrene (II) by conrotatory cyclization.



Ex 22: A beautiful illustration of the synthesis of ergosterol involves electrocyclic reaction under irradiation by light.



Ex 23: Vitamin D3 (cholecalciferol) is produced through the action of UV irradiation on its precursor 7-dehydrocholesterol.



Typical examples of electrocyclic reactions

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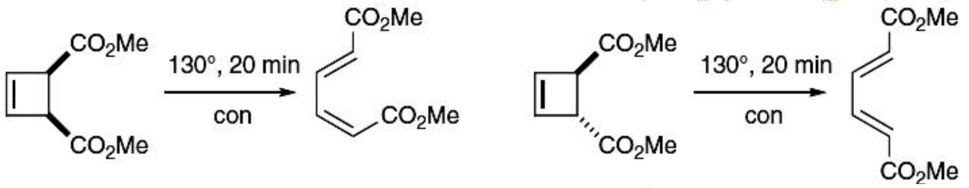

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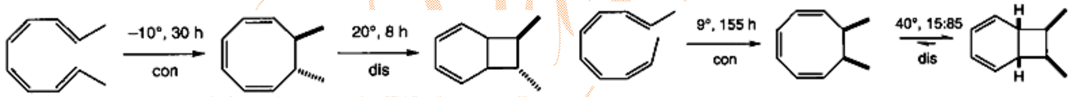

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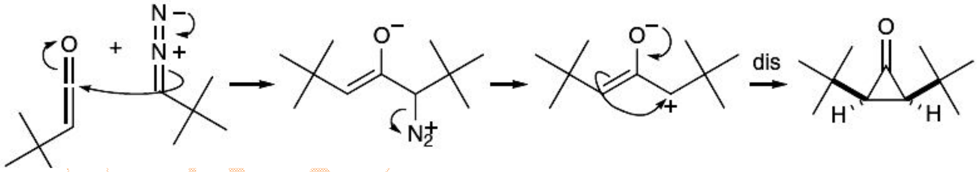

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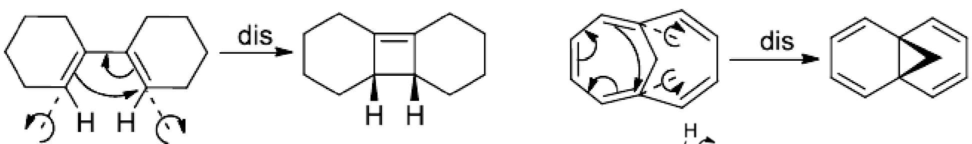

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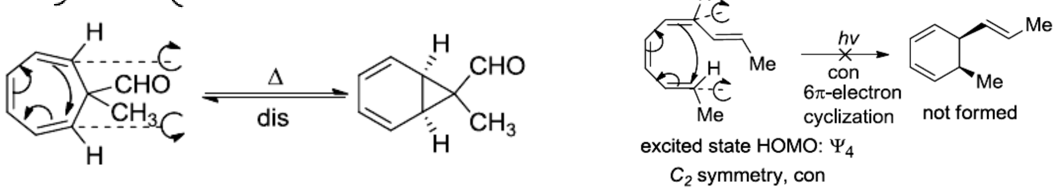

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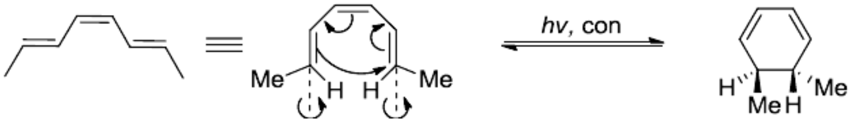

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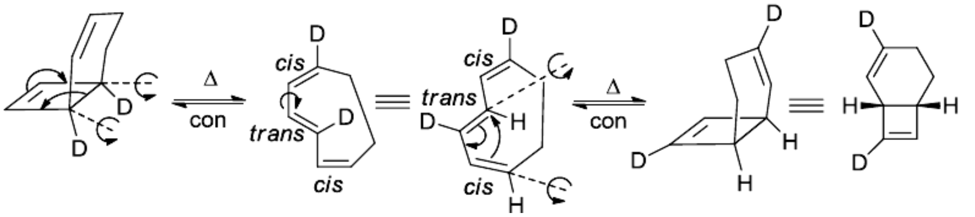

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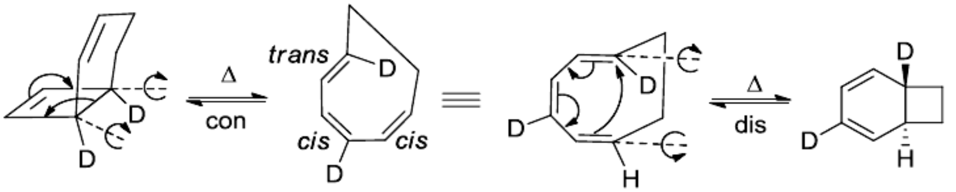

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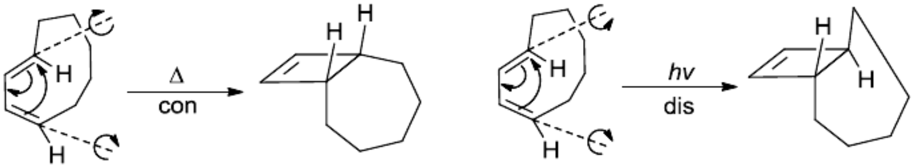

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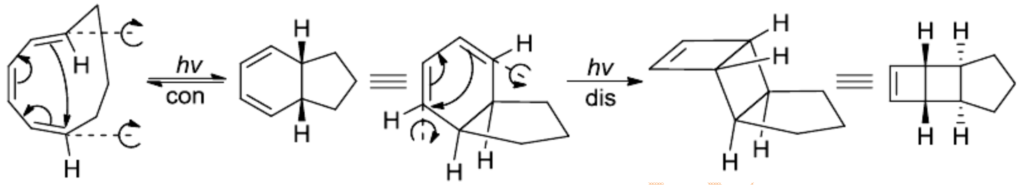

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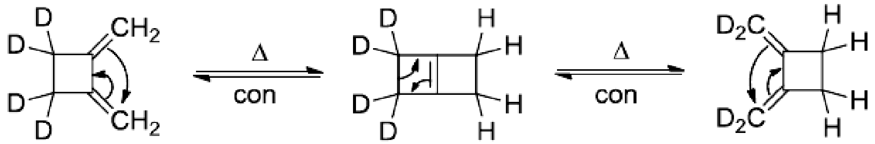
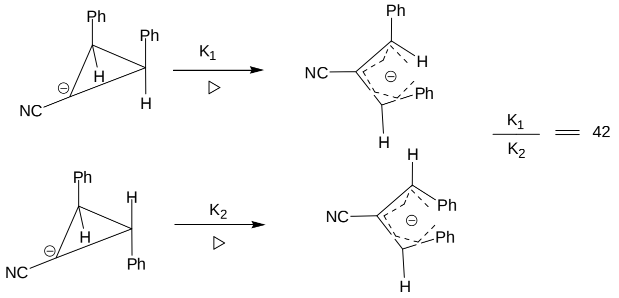


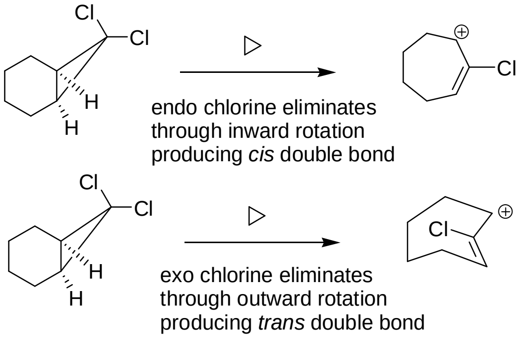
Q.1. Compare to allylic cation, pentadienyl cation undergoes faster rate of electrocyclic ring closure reaction while the situation is completely reversed in case of allylic anion compared to pentadienyl anion. Logically explain the fact.

Q.2. The endo isomer of 7-chloro bicycle [4,1,0] heptane reacts 10,000 times more faster rate than that of its corresponding exo-isomer. Account for the fact.

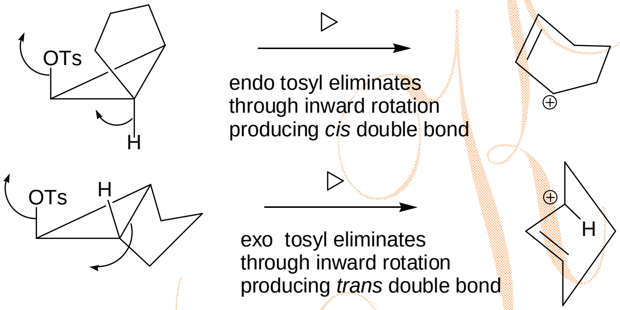
Q.3. Explain the following phenomena with proper mechanistic details.



Q.4. Which one of the following reaction is feasible according to pericyclic rules?



Q.5. Account for the following observation of thermal three membered electrocyclic ring opening reaction.



Q6. The endo isomer of 6-chloro bicycle [3,1,0] hexane undergoes facile reaction to produce 3-chloro hexane upon heating for 3hrs at 125^0C, while the exo-isomer remain unaffected even at drastic condition. Account for the fact.

Q7. The endo isomer of 7-chloro bicycle [4,1,0] heptane reacts 10,000 times more faster rate than that of its corresponding exo-isomer. Account for the fact.

Q8. The rate of solvolysis of endo isomer of 8-bromo bicycle [5,1,0] octane by silver perchlorate in acetone –water mixture produces trans cyclo allylic alcohol. The exo-isomer on same reaction condition results cis cyclo allylic alcohol. Account for the fact.

Q. Cyclobutene to 1,3 butadiene conversion thermally favours in the direction of diene system whereas the reverse occurs at longer wavelength. However, hexatriene to 1,3 cyclohexadiene conversion is both thermally and photochemically favourable compared to its correspondind reverse reaction. But the situation looks completely reversed if the electrocyclic equilibrium of benzocyclobutene is taken into consideration. Explain the above observation.

Ans: Due to small member of carbocycle as well as presence of internal double bond, cyclobutene becomes highly strained and its energy is higher than that of butadiene. Naturally, according to law of themodynamics, cyclobutadiene to butadiene conversion occurs smoothly under thermal condition. The reverse reaction invokes high energy thermal process, rather presence of more conjugation in butadiene absorbs a particular (quantized) light energy at longer wave length to bring about apparently non favourable process.

However, the energy difference between cyclohexadiene and hexatriene is very less as cyclohexadiene does not contain as much strain and also have one more σ-bond. Due to comparatively lower energy of cyclohexadiene, the interconversion to it from hexatriene proceeds spontaneously at thermal condition. Again we know that a photochemical reaction proceeds at much faster rate than thermal condition if there is more and more number of double bond. Therefore, it is clear that such above transformation becomes kinetically faster if allowed under photochemical condition.

The electrocyclic equilibrium shifts towards cyclobutane direction not towards diene system because the benzocyclobutane to butadiene produces a non-aromatic, unstable xylene like compound. Therefore, aromatic to non-aromatic conversion is both kinetically and thermodynamically impossible.

CYCLOADDITION REACTIONS

Definition

A concerted cyclic shift of two separate π-electron systems in which a ring is produced with the formation of two new σ-bonds is termed as **Cycloaddition reaction**. The reaction is activated either by heat or by UV-light. The reaction follows the principle of microscopic reversibility. The reaction sequence can also be explained by three fundamental approaches; (a) correlation of orbital symmetry of terminal lobe of interacting orbitals (b) perturbation of M.O theory or HMO theory of aromaticity or anti aromaticity in T.S (c) FMO approach of HOMO-LUMO interaction of corresponding orbital energy state. The reverse reaction of cycloaddition is called **cycloreversion**.

Conditions for Cycloaddition Reaction

1. The symmetry of those orbitals w.r.t terminal conjugated π-system of two separate polyene system has to be considered.
2. Always the terminal p-orbitals of both polyene which are going to form σ-bond must overlap by maintaining the in phase distribution of of lobes after rotation.
3. The groups or substituent attached to terminal lobes also moves according to the lobe's movements. This brings about the stereochemistry of the resultant product.
4. HOMO of the one polyene interact effectively with LUMO of other polyene forming both endo and exo product where endo product is kinetically more stable.
5. That cycloaddition will be favoured which follows the Woodward –Hoffmann principle of orbital symmetry. The involvement of any steric crowding or generation of strain in the product molecule will avoid the subsequent mechanism.

Source/ Influencing factor/ Mode of activation:

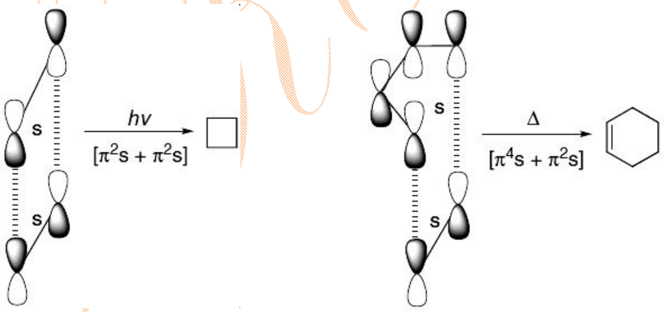
1. Heat or Thermal (Δ)
2. Light or Photochemical (hγ)

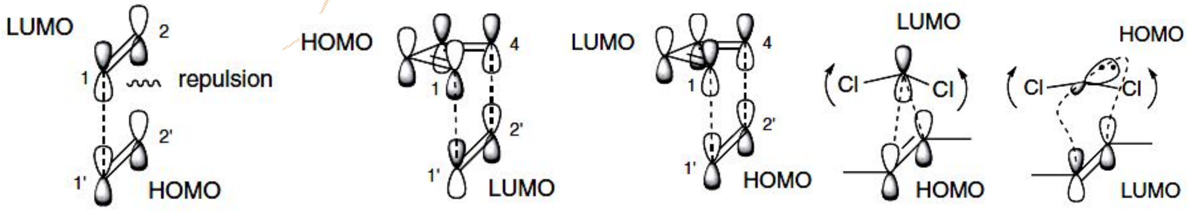
Criteria for Cycloaddition Reaction:

1. Mode of activation. (Δ/ hγ)
2. Number of p/π-orbital participates. [4nπ or (4n+2)π]
3. Stereochemical outcome (wthether stereospecific or stereoselective).
4. The nature of orbitals undergoing change (σ or π).

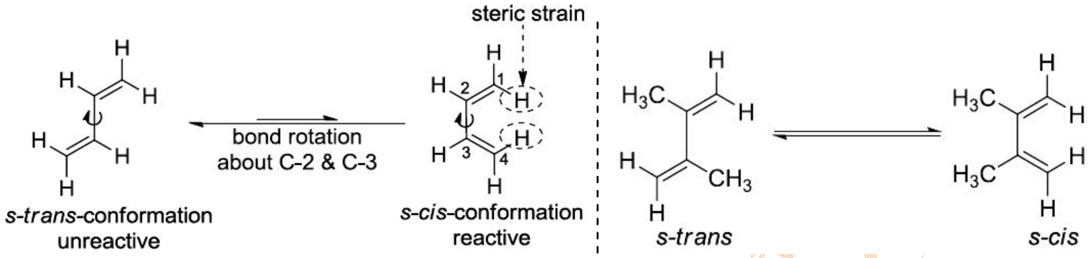
Here Woodward-Hoffmann suggested that if the reaction would take place through same face of a π-system, the reaction is said to be Suprafacial (s) to that of π-system and if the reaction occurs through opposite face of a π-system, the reaction is said to be Antarafacial (a) to that of π-system. For example (supra)-ethylene and (supra) cis-2-butene yields cis-1,2-dimethyl cyclobutane whereas (supra)-ethylene and (antara) cis-2-butene yields trans-1,2-dimethyl cyclobutane.

Pictorial Representation

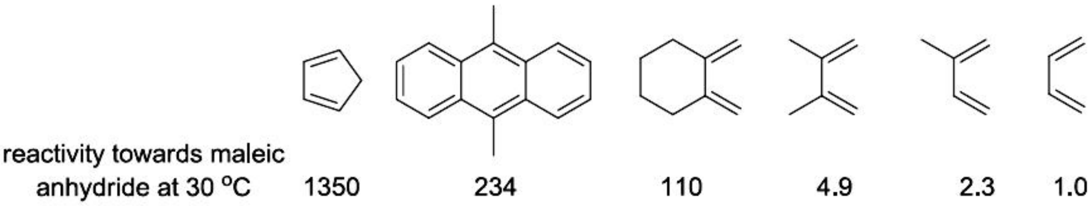




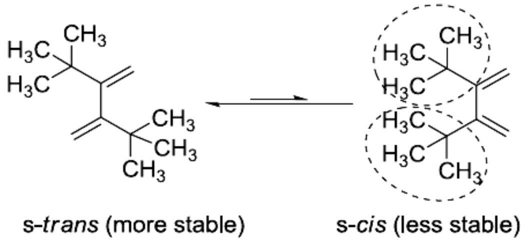
Diene in the s-cis conformation undergoes Diels-Alder reaction because C-1 and C-4 of the diene is close enough to react through a cyclic transition state. In s-*trans* conformation, the T.S would be strain.

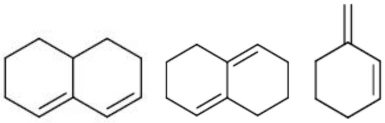


Dienes with an enforced coplanar s-cis conformation are exceptionally reactive in Diels-Alder reaction. The reactivity of diene depends on the rigidity (locked conformation in cyclic form), coplanarity and the concentration of the s-cis conformation in the equilibrium mixture.

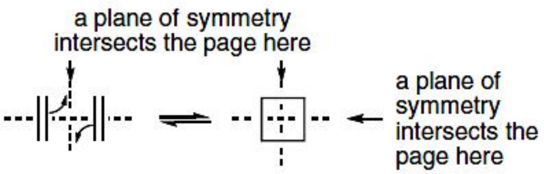


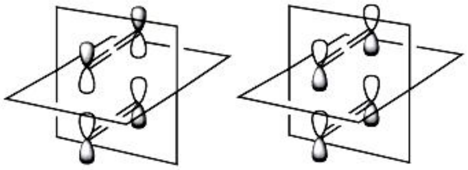
The following acyclic dienes are very unstable in s-cis form owing to severe steric hindrance. Cyclic dienes of permanent s-trans conformation are unable to adopt s-cis conformation and thus will not undergo Diels-Alder reaction.



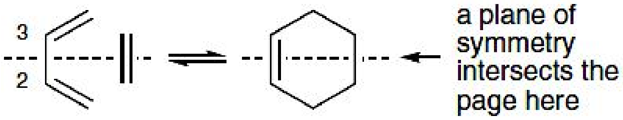


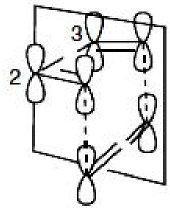
Approaching π—bonds and pair them up in a lower energy symmetric and a higher energy antisymmetric combination can be classified based on symmetry of orbitals w.r.t an imiginary plane.



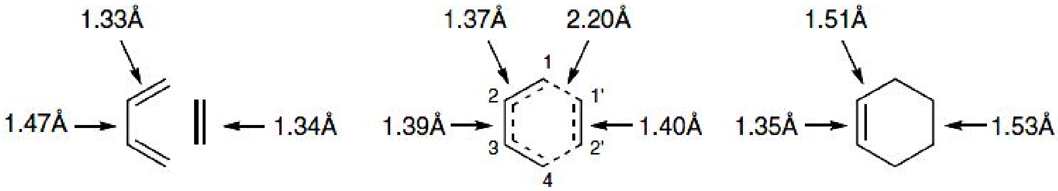


The Diels-Alder reaction which is suprafacial on both components, a plane of symmetry bisects the bond between C-2 and C-3 of the diene and the π bond of the dienophile. If any substituents cause the diene or dienophile unsymmetrical, they do not necessarily disturb the symmetry of the orbitals that are involved directly.

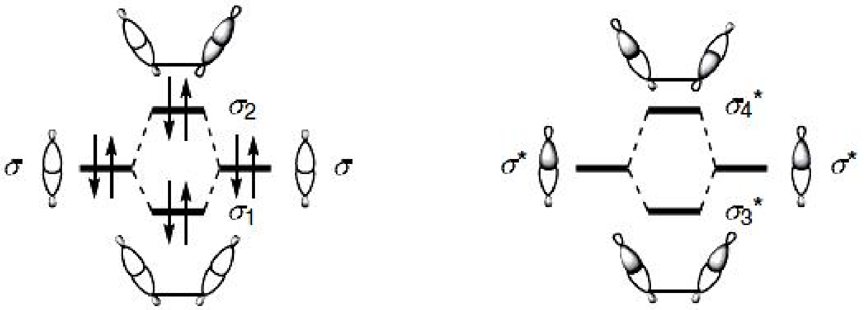




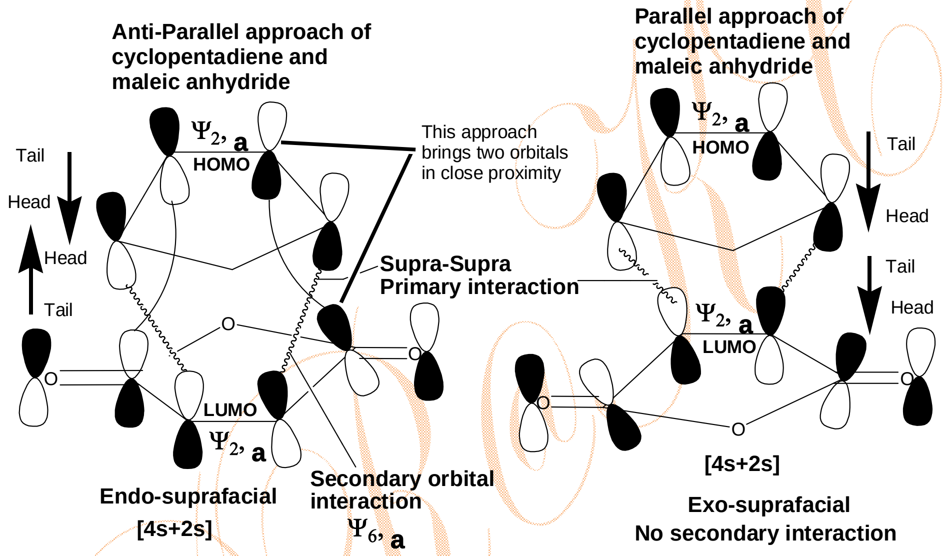
In the transition structure, the π bond between C-2 and C-3 has sharply formed (66%) and likewise, the σ bonds are little formed (22%). The π bonds in the dienophile and the diene seems not so weakened (32% and 22%, respectively). A late transition structure is accounted by the larger changes in the π-bonding in the diene and an early transition structure implies the small changes in the σ bonding and in the π-bonding of the dienophile. This asynchronicity reflects the sum of the HOMO(diene)/HOMO(dienophile) interactions and substantial contributions from both FOIs.



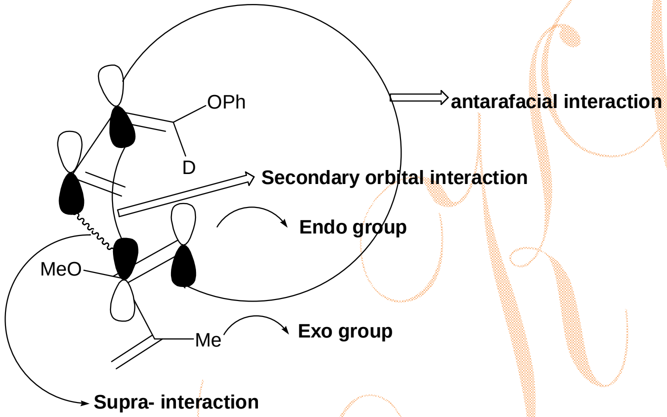
Molecular orbitals from combination of σ orbitals (left) and σ^* (right)



Primary and Secondary Orbital interaction



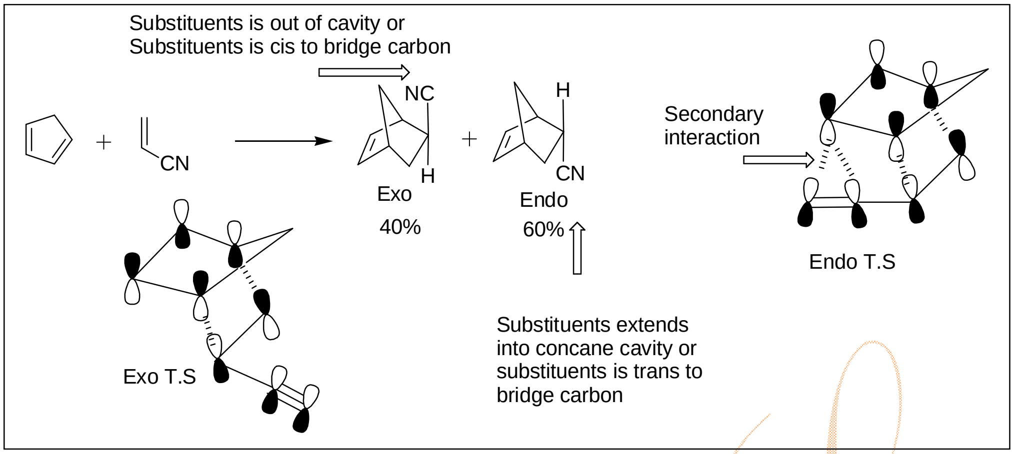
Both the cyclopentadiene and maleic anhydride can interact to each other w.r.t C_2 symmetry orbital under thermal condition. Their approach is either in parallel direction or in anti-parallel direction as shown in the figure. Both the approaches are basically supra-supra addition where in phase bonding overlap takes place. The antiparallel approach leads to *endo* product whereas parallel approach exerts *exo* product. The *endo* product is formed as kinetically controlled product (KCP) which occurs at low temperature while the *exo* addition is produced as thermodynamically controlled product (TCP) at comparatively higher temperature. The reason is that there is an additional orbital interaction between non-terminal lobes of both diene and carbonyl lobes of dienophile which strengthen the net overlap. This interaction enables lowering in activation barrier and faster the reaction rate. Therefore, such interaction which stabilizes the *endo* addition is known as secondary orbital interaction. Since exo product is formed due to parallel approach of two π-systems, so the lobes involving secondary orbital interaction are far apart from each other. Hence, the secondary orbital interaction is virtually absent in *exo* product. The *endo* product can be converted to *exo* product at high temperature (190 ^{0}C) but the reverse can not be possible.



Supra-antara orbital interaction

The above supra-antara interaction leads to a bonding with highly strained system. Hence the reaction is symmetry forbidden reaction.

The *exo* product is more stable than the *endo* product for steric reasons. Since the reaction is concerted, the transition state for *exo* product formation must be less crowded than the transition state for *endo* product formation. In practice, it has been found that the *endo* product is more stable than the expected *exo* product. This clearly confirms that the transition state of *endo* product should be more stable than that of the *exo* product due to some other factors which overwhelms steric consideration. This factor is known as secondary orbital interaction. In *endo* transition state the double bonded carbon of dienophile is directed to the inside of diene ring where the there can be interaction between back diene orbitals and orbitals on the substituents ($C\equiv N$) in dienophile. Such interaction is absent in case of *exo* orientation as dienophile is directed away from the cyclic diene conjugated system.



Point to be noted:

1. For two component system the maximum number of mode of addition=$2^n=2^2=4$. (ss, sa, as, aa).

2. ss mode means parallel approach of orbital whereas sa, as, aa indicates orthogonal approach of orbitals.

3. Terminal group retains its configuration in suprafacial approach while it is inverted in antarafacial approach.

4. Both *endo* and *exo* addition occurs through ss mode depending on the substitution pattern.

5. Favourable as well as facile pathways is shown when $[\pi^4_s + \pi^2_s]$ is greater than $[\pi^4_a + \pi^2_a]$.

6. Always *s-cis* conformation reacts in cycloaddition reaction because in *s-trans* conformation the terminal lobes are anti to each other.

7. Any bulky group or ring at the termini will retard the rate.

8. The rate of cycloaddition reaction depends on the energy difference between HOMO and LUMO orbital. The electron releasing group enhances the HOMO energy of diene and electron withdrawing group lowers the LUMO energy of dienophile except for cycloaddition reaction with reverse electron demand.

Energies of frontier orbitals

C- (extra conjugation)

Raises the energy of the HOMO and lowers the energy of the LUMO.

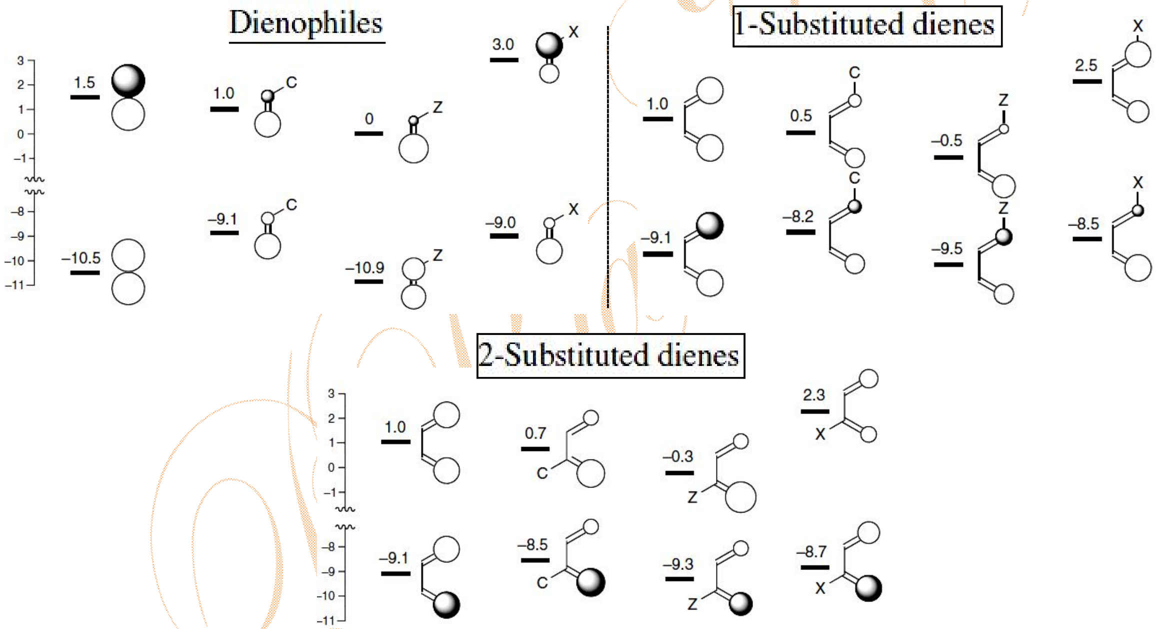
Z- (an electron-withdrawing group)

Slightly lowers the energy of the HOMO and substantially lowers the energy of the LUMO.

X- (an electron-donating group)

Substantially raises the energy of the HOMO and slightly raises the energy of the LUMO.

Frontier orbital energies (eV) of alkenes and dienes (1 eV = 23 kcal = 96.5 kJ).

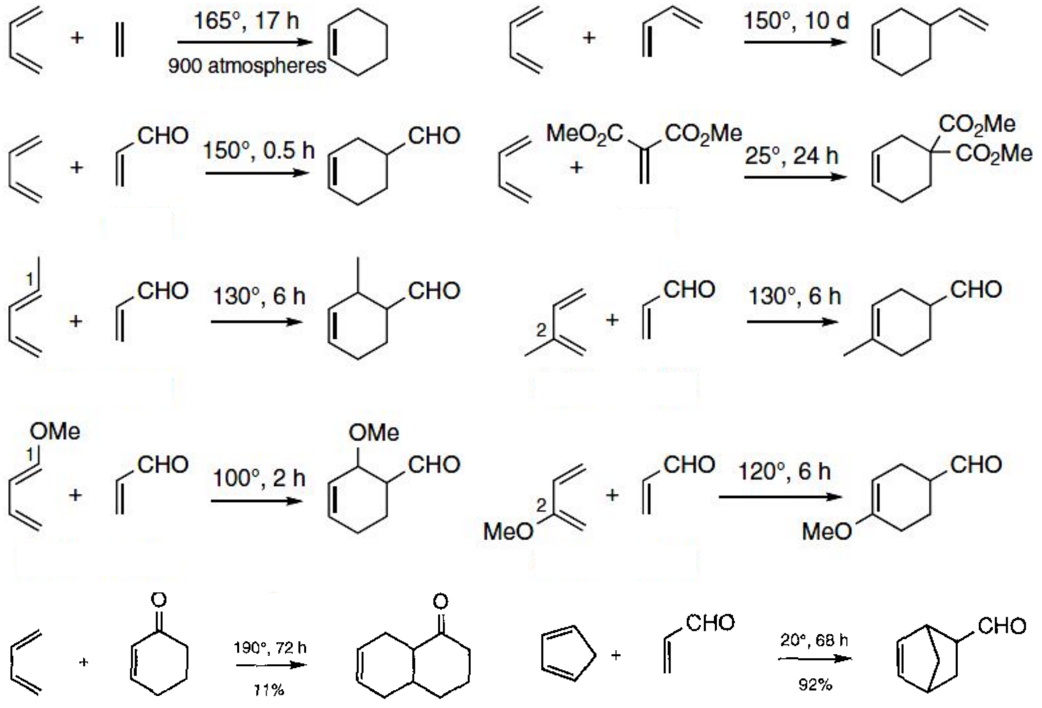


Frontier orbital energies are experimentally measured by photoelectron spectra for the occupied orbitals, and a combination of electron affinity measurements, charge transfer spectra and polarographic reduction potentials for the unoccupied orbitals. Frontier orbital energies provide a clear idea about the **rate of cycloaddition** reactions by considering lower energy difference between HOMO and LUMO. The size of the orbital coefficients seldom influences in the frontier orbitals energies.

Rather the relative sizes of the coefficients are principally used to account for **regioselectivity**.

Butadiene reacts with ethylene at high temperature (165 ^{o}C), high pressure to give a low yield of cyclohexene. The rate becomes little faster with acrolein (at 150 ^{o}C) in terms taking less time at the same temperature. Introducing a second Z-substituent (EWG) such as methylenemalonate or maleic anhydride increases the rate even more that eventually reacts at room temperature.

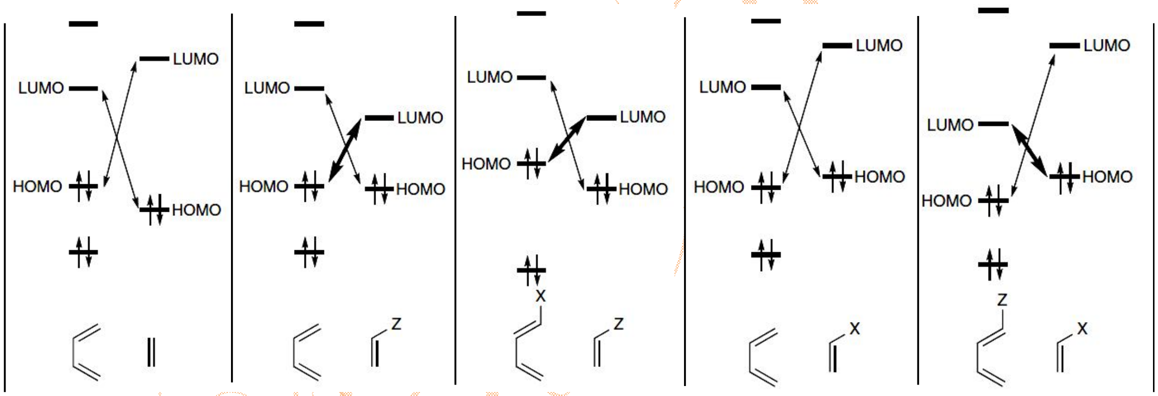
An X-substituent (ERG) diene on C-1 or C-2 such as *trans*-piperylene, isoprene or methoxybutadiene increases the rate further with acrolein at 130 ^{o}C. In contrast to times and temperatures, the yield of the isolated product (here say 80 %) is a reliable way of measuring relative rates.



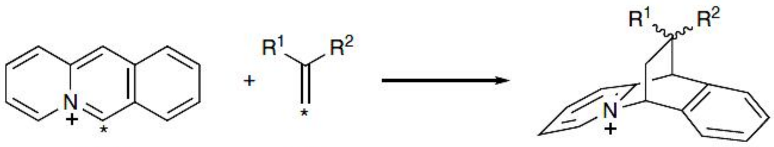
Cause: In order to explain the rat**e** of the reaction, the proper selection of HOMO and LUMO for either of diene or dienophile is essential. Considering two pathways, the direction of the reaction and rate depend on the smaller energy difference between HOMO-LUMO either of diene or dienophile. Normally, a Diels-Alder reaction is characterized by the interaction of HOMO-diene (9.1 eV) and LUMO-dienophile (0 eV) ***with energy difference = 9.1 eV as compared to 11.9 eV*** arising from LUMO-diene (1.0 eV) and HOMO-dienophile (10.9 eV). Thus, a faster reaction is associated with more electron-withdrawing group in dienophile comprising low-lying LUMO such as tetracyanoethylene. This enables smaller the separation of the HOMO-diene and the LUMO-dienophile. The combination of X-substituent HOMO-diene (raising energy) and Z-substituted LUMO-dienophile produces relatively ***lower energy gap of 8.5 eV***.

That is why, in above example, the energy separation between the HOMO of butadiene and the LUMO of a Z-substituted dienophile is less than that between the HOMO of butadiene and the LUMO of ethylene.

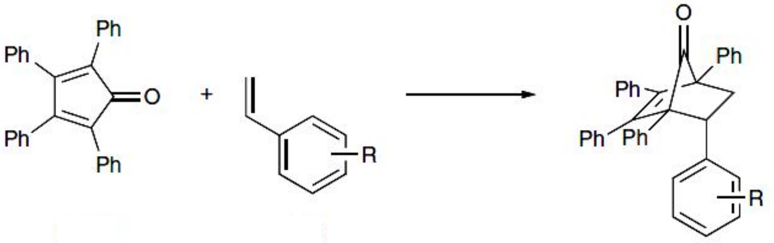
Frontier orbital interactions for Diels-Alder reactions



Diene with electron-withdrawing Z-substituents reacting with dienophiles with electron-donating X-substituents are said to be **<u>Diels-Alder reactions with inverse electron demand</u>**. Following examples represent this idea, although are not common.

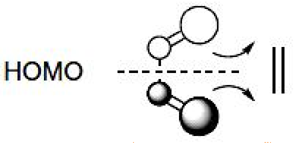


a $R^1=R^2=OEt$ 75% reaction in 4 min at 25 °C
b $R^1=CH_2OH$, $R^2=H$ 75% reaction in 275 min at 100 °C
c $R^1=CN$, $R^2=H$ 75% reaction in 1080 min at 100 °C

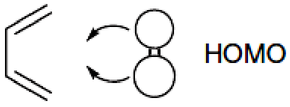


R:	p-NMe$_2$	p-OMe	H	p-Cl	m-NO$_2$	p-NO$_2$
k_2 (10^6 mol^{-1}s^{-1}):	338	102	73	78	79	88

Cause: Suppose the electron density is supplied from from the diene. Since one node is there, the ψ_2 HOMO of diene ensures the flow of electrons that are concentrated at the sides where the σ—bonds are formed in lieu of concentrated in the centre of the diene (left). In case of inverse electron demand, the major supply of electrons comes from the ψ_1 HOMO of dienophile which consists of no node. Consequently, it interacts with ψ_3 diene LUMO even more strongly with lowe activation barrier.



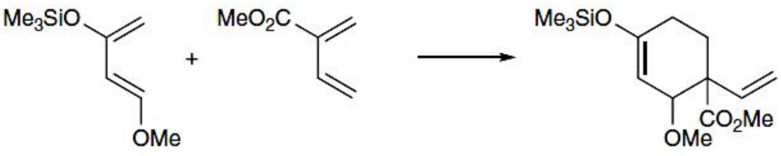
Normal Diels-Alder reaction
HOMO(diene)/LUMO(dienophile)



Inverse electron demand
LUMO(diene)/HOMO(dienophile)

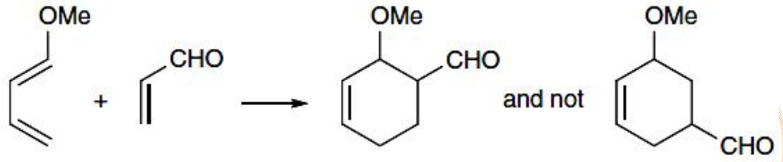
In both examples (above), R = ERG raises the HOMO of dienophile that becomes closer to LUMO of diene containing EWG. It helps strong HOMO-LUMO interactions.

If two dienes one having a EWG and another with ERG are allowed to react, diene with EWG always acts as dienophile while diene with ERG behaves as diene.

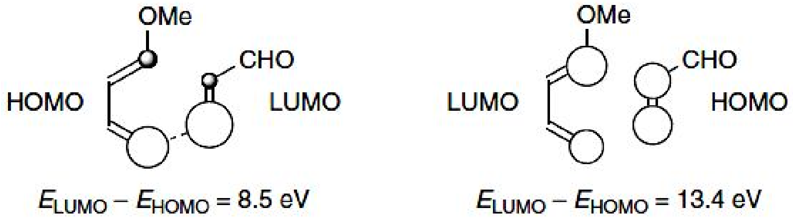


Regioselectivity of Diels-alder reactions

Regioselectivity refers to the orientation of a cycloaddition. Methoxybutadiene reacts with acrolein to give more of the ‘**ortho**’ adduct than of the ‘**meta**’ adduct.

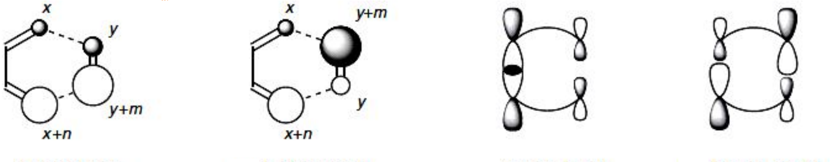


Cause: The coefficients of the atomic orbitals undergoing new σ—bond formation should be the concern of regioselectivity. The combination HOMO-diene and the LUMO-dienophile gives E_{act}, Er –Es = 8.5 eV (left) predominantly, as compared to the reverse where Er – Es = 13.4 eV (right).



Let the square of the terminal coefficients on X be x and (x+n), and let the square of the coefficients on Y be y and (y+m).

Large-large/small-small interaction [xy+(x+n)(y+m)] > Large-small/small-large interactions [x(y+m)+(x+n)y]. substracting gives the value nm. Therefore, former interaction is greater as long as n and m are of the same sign.



Large-large small-small

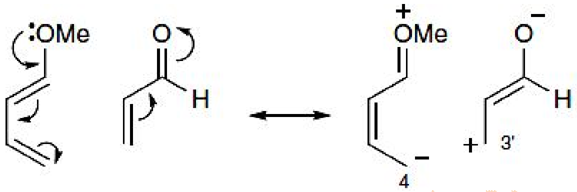
Large-small large-small

Large-large small-small

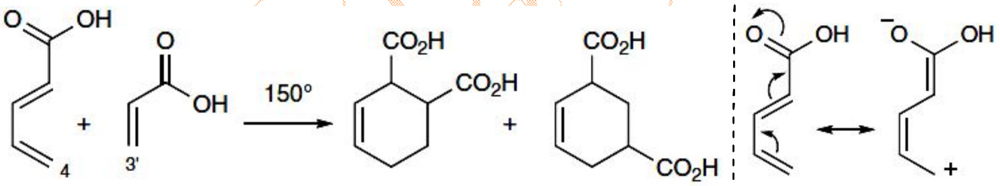
Large-small large-small

It is important to note that the large-large interaction precedes over the small-small interaction (third figure). It indicates that the transition structure of an unsymmetrical Diels-Alder reaction is itself unsymmetrical where two σ bonds are formed to different extents. Despite the fact, the reaction is still concerted, with both bonds forming at the same time, but it is not synchronous.

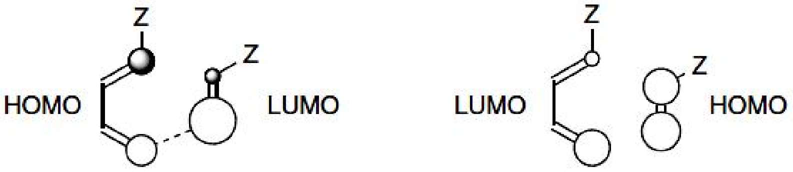
Drawing curly arrows and creating canonical structures to express the logic that C-4 of the diene is a nucleophilic carbon and C-$3^{/}$ of the acrolein an electrophilic carbon works well for the reaction between ERG-diene and EWG of dienophile. However, this is not applicable to all.



Clearly the valence bond argument is not good enough, rather the frontier orbital interactions. For instance, the curly arrows reflect that both C-4 of the diene carboxylic acid and C-$3^{/}$ of acrylic acid are expected to be electrophilic which repels due to partial positive charges. The expected adduct would be the 'meta' adduct. In contrary, the mainly the 'ortho' adduct were isolated.



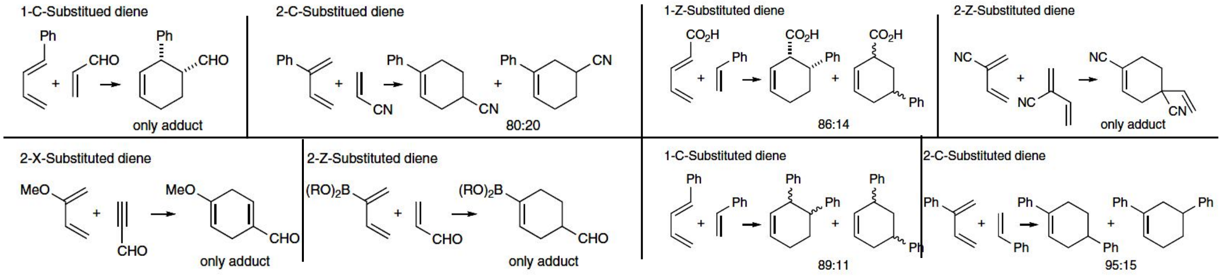
The 'ortho' adduct is also consistent with smaller HOMO-LUMO energy gap. It is assumed that the orbitals are polarized with marginally higher coefficient on C-4 in the diene-HOMO which stems from the hexatriene-like character of the conjugated system. As a result, the counter-intuitive combination with bonding between C-4 and C-$3^{/}$ is achieved.



$E_{LUMO} - E_{HOMO} = 9.5$ eV

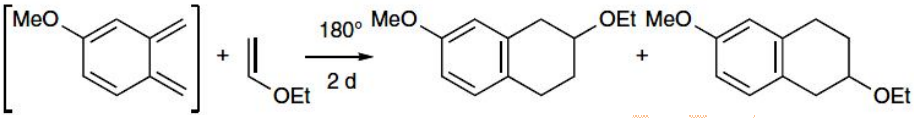
$E_{LUMO} - E_{HOMO} = 10.4$ eV

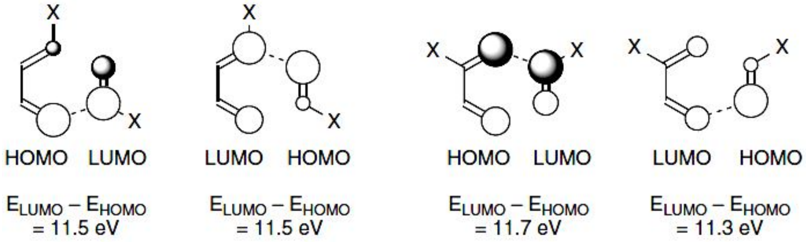
Examples that obey ‘ortho-para’ rule



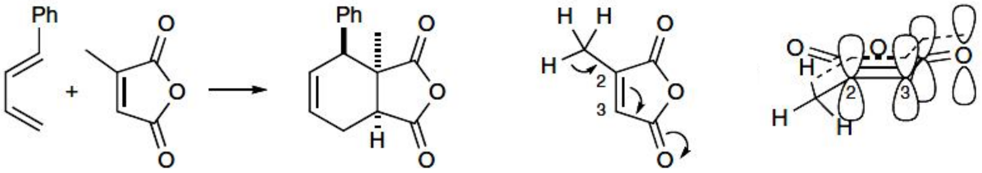
Exception of ‘ortho-para’ rule

The rule breaks when both diene (at C-1 and C-2 position) and dienophile contain ERG (X substituent). It yields a substantial yield of ‘meta’ adduct with reasonable loss of regioselectivity partly because of high temperature reactions.

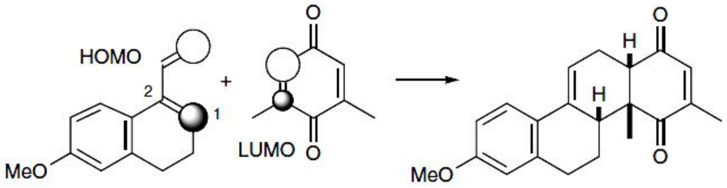




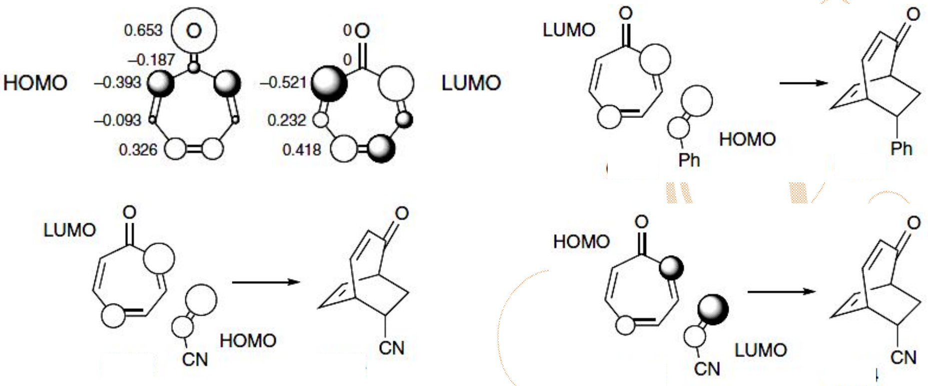
Hyperconjugation of the C-2 methyl group through the double bond with the carbonyl group attached to C-3 can reduce the electron-withdrawing effect of that carbonyl group. The C=C orbital is more polarised by the C-2 carbonyl which is the guiding factor than by the C-3 carbonyl.



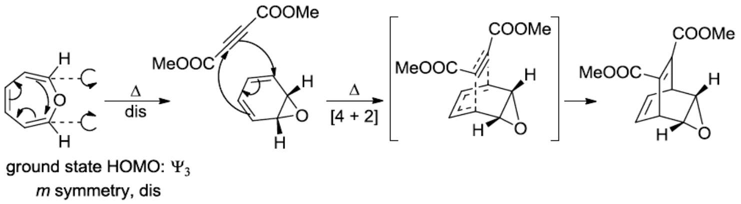
2-aryl substituent is usually less effective in polarising the coefficient at of frontier orbital at C-2 position than that at C-1 which eventually explains the observed regioselectivity.

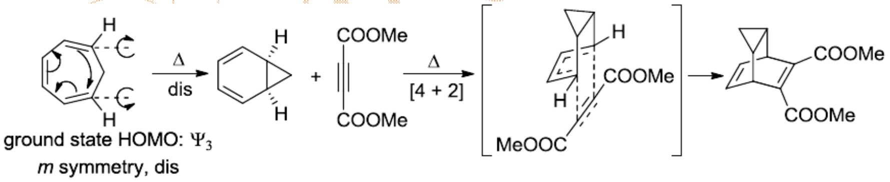


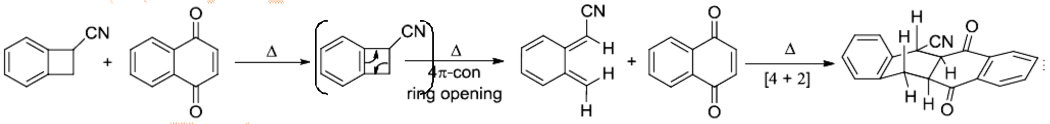
Based on the frontier orbital coefficients of tropone, the regioselectivity arises while reacts to various dienophiles.



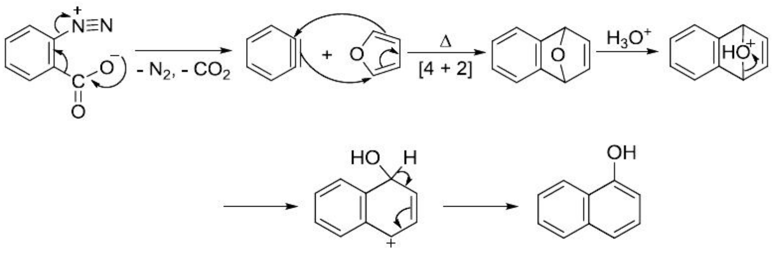
Typical [4+2] cycloadditions occur after electrocyclic ring closure.







A transformation is shown using cycloaddition reaction as intermediate.



The Stereoselectivity of Diels-Alder Reactions

Three stereochemical issues related to product formation for cycloaddition:

1. *cis/trans* product formation w.r.t stereochemistry of starting diene and dienophile
2. *exo/endo* products based on secondary HOMO-LUMO interactions
3. Regioselectivity measured by the relative size of terminal orbital lobes

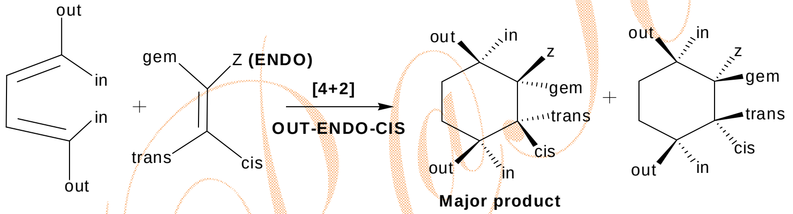
OUT-ENDO-CIS Rule:

out = refers to the orientation of a group on the termini of diene

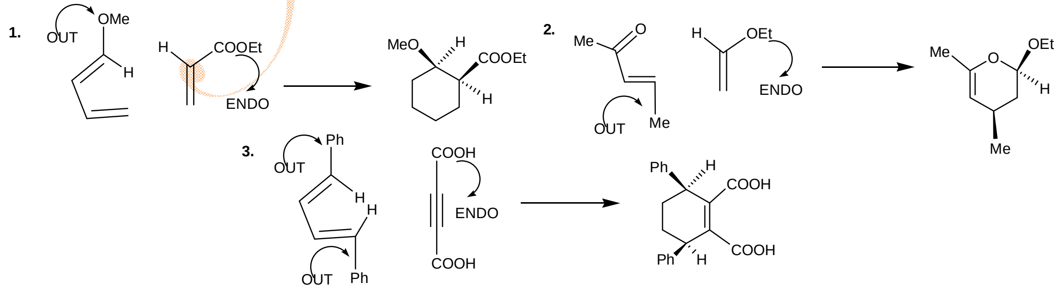
endo = refers to the substituents (usually EWG) on the dienophile

cis = refers to stereochemical relationship of two groups in the product

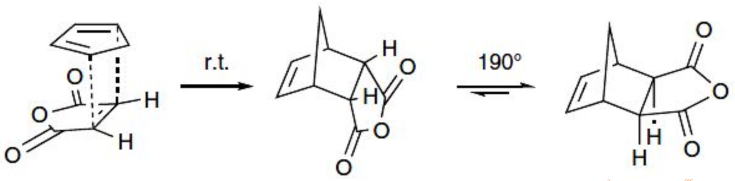
In order to determine product stereochemistry in D.A reaction Out-Endo-Cis rule is applied provided the interaction is *supra-supra*.

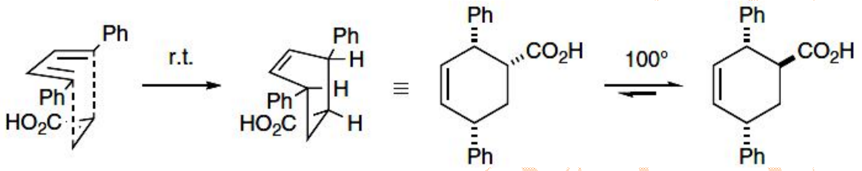


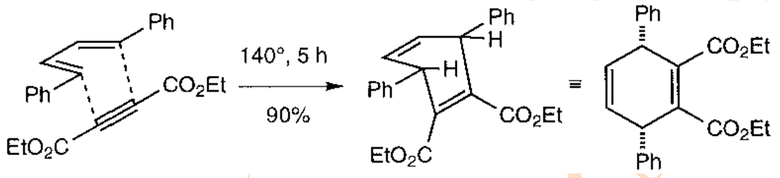
Therefore, out group on diene and endo group in dienophile are in *cis* in the product. Generally most electron withdrawing group in dienophile has been considered as *endo* group. Similarly OUT-EXO-TRANS, IN-ENDO-TRANS, IN-EXO-CIS are also can be applied.

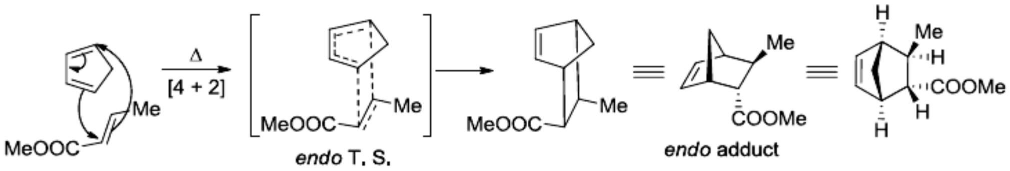


The stereochemical finding for Diels-Alder reactions relies on Alder's endo rule in which the favoured transition structure includes electron-withdrawing substituents in the more hindered environment under the diene unit. This gives kinetically favourable *endo* product at lower temperature with additional secondary orbital interactions. Long heating equilibrates this isomer with the thermodynamically favoured *exo* adduct by a retro-cycloaddition pathway.

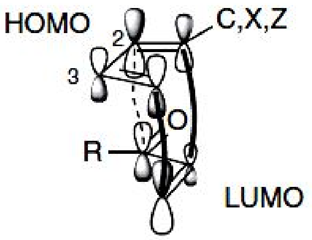




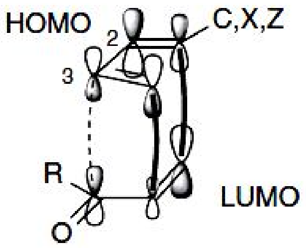




Secondary interactions determines the regioselectivity of a Diels-Alder reaction

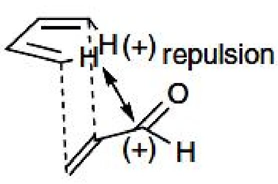


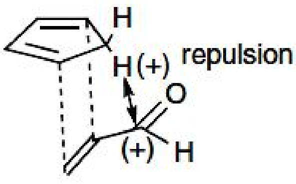
Transition structure for
formation of an 'ortho' adduct

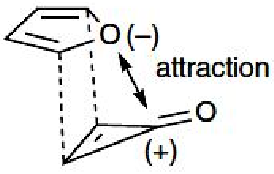


Transition structure for
formation of a 'meta' adduct

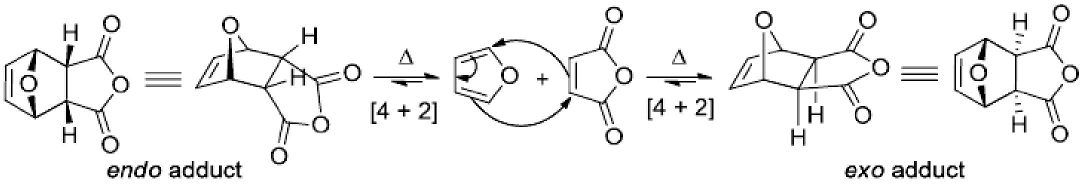
The possibility for an electrostatic or Coulombic repulsive effect occurs in the *exo* transition structure. Such effect, in turn, has the greater propensity for forming the *endo* isomer. A Coulombic attraction favours *exo* attack both kinetically and thermodynamically in case of furan react with cyclopropenone.

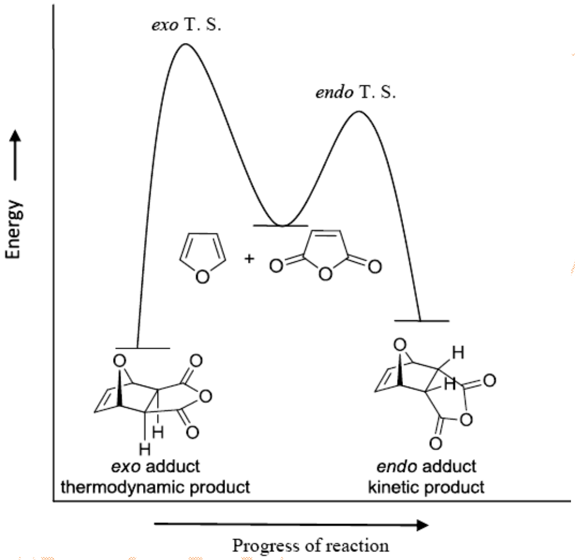






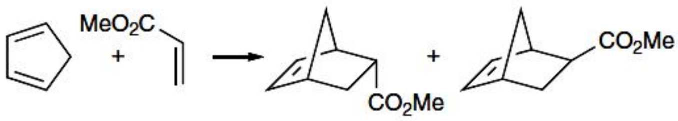
Energy profile diagram



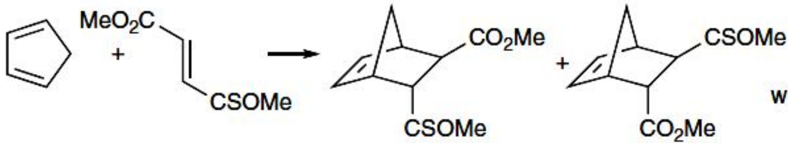


Effect of Lewis Acids on Diels-Alder Reactions

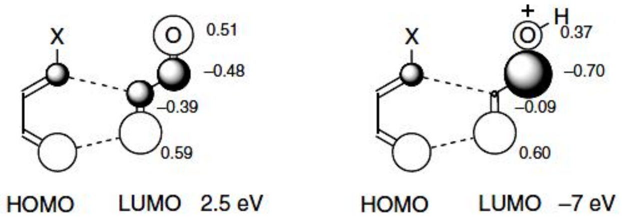
Lewis acids exert a strong catalysing effect in Diels-Alder reactions both as faster reaction rate and stereo/regioselectivity of the reactions.



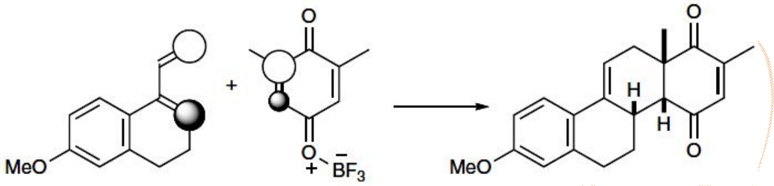
	endo:exo
without $AlCl_3$ at 0 °C	88 : 12
with $AlCl_3$ at 0 °C	96 : 4
with $AlCl_3$ at –80 °C	99 : 1



with BCl_3	4 : 96
with $Cu(OTf)_2$	89:11

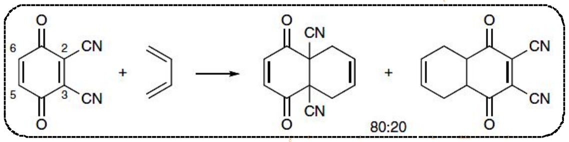


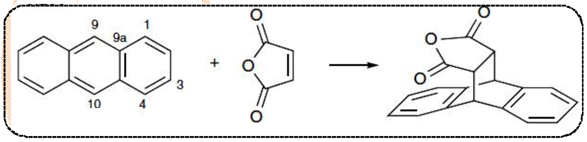
Without acid catalysis With acid catalysis

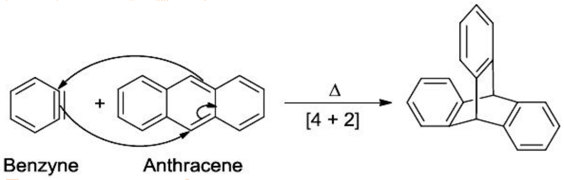


Site selectivity of Diels-Alder Reactions

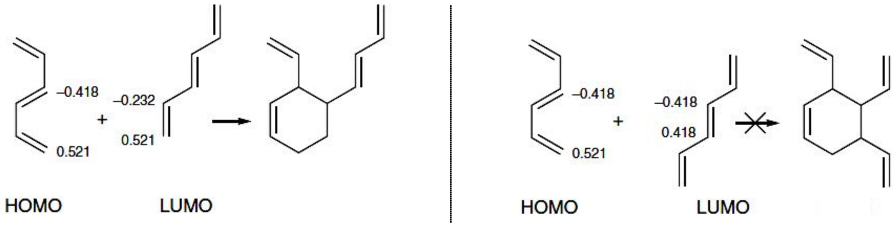
In cycloadditions, site selectivity is a pair of regioselectivity of a polyfunctional molecule having multiple sites in which the counterpart of another molecule reacts. The adduct obtained from anthracene arises due to product stability by achieving two isolated benzene ring and the largest coefficients in the HOMO at the 9,10-positions.

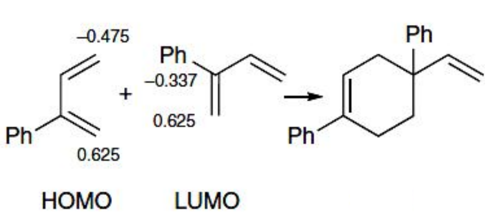


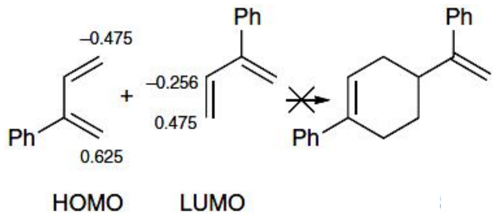


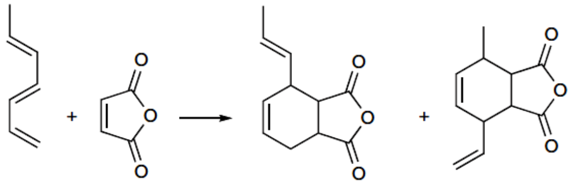


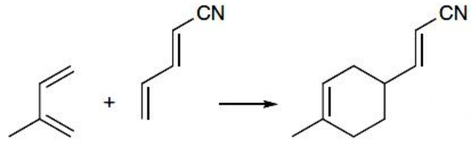
The dimerisation of hexatriene is another example of site selectivity. The former retains a conjugated diene system and is likely to be lower in energy than the latter. The former product is thermodynamically favoured.

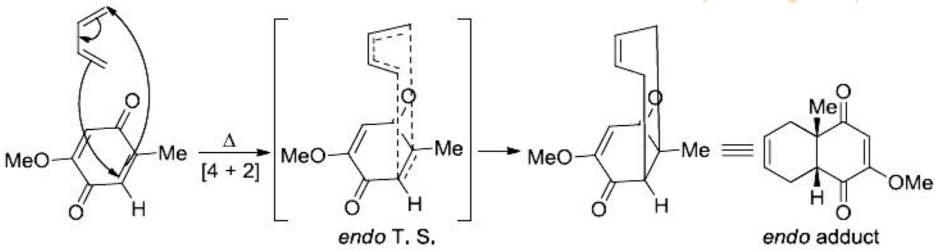


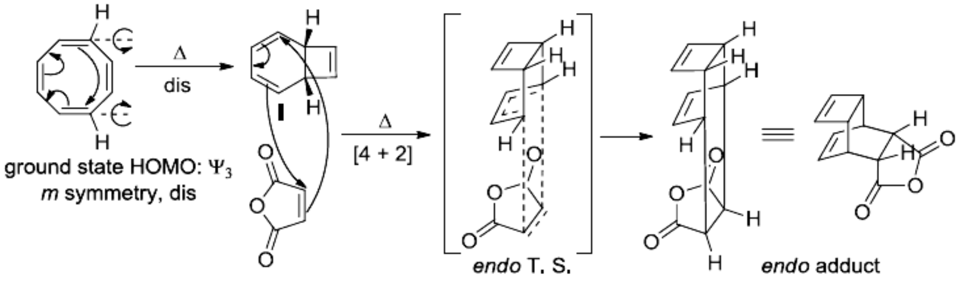




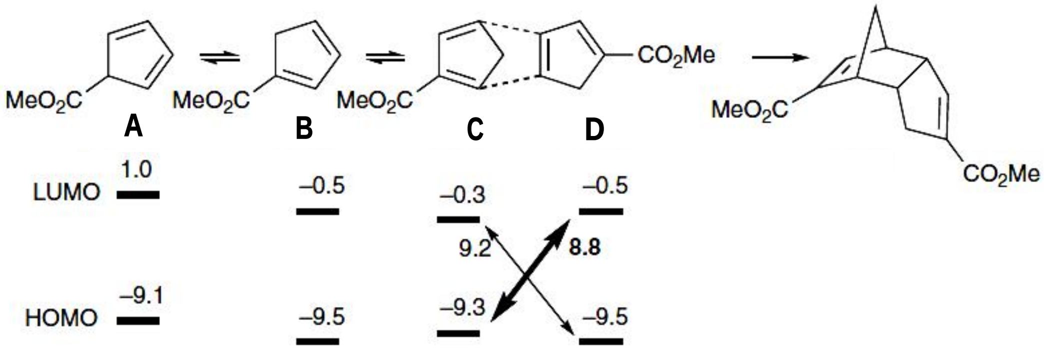






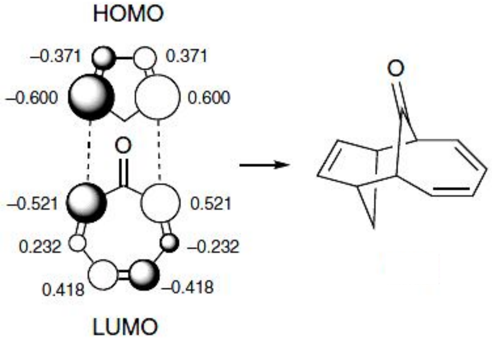


Among the four isomers (A-D), isomer (A) is more reactive for the highest HOMO energy and it remains in equilibrium in very low extent. The smallest energy is between the diene-HOMO of (C) and the dienophile-LUMO of (D). The reverse variation suffers from steric hindrance. The product has always *endo* selectivity.

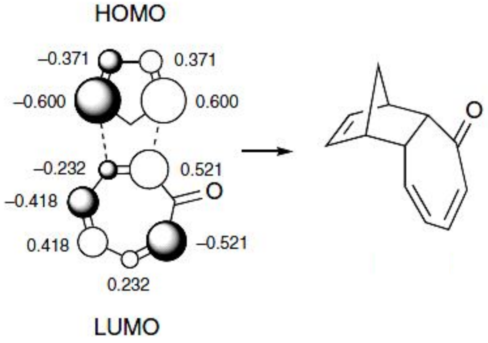


Periselectivity

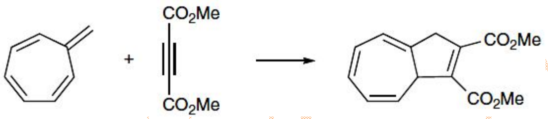
[4+6] favoured path

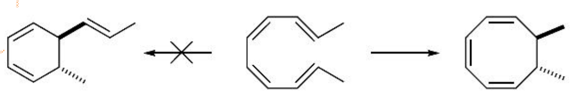


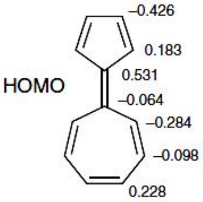
[2+4] Less-favoured path

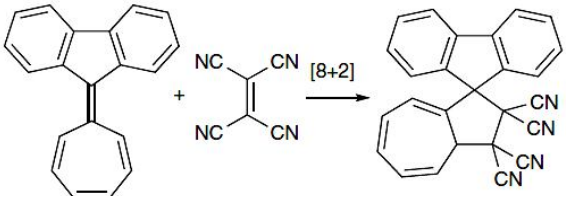


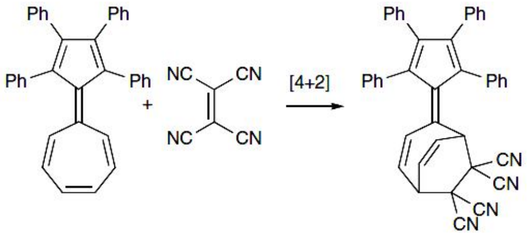
Periselectivity is a special case of site-selectivity which considers whether whole of the conjugated array of electrons or a large part of it, or only a small part of it is involved in pericyclic reaction. Periselectivity decides [4+6] cycloaddition adduct between cyclopentadiene and tropone prefers over [2+4] cycloaddition although both are thermodynamically much different in energy. Rather, the frontier orbitals indicate that the longer conjugated system of the tropone is more reactive than the shorter. The largest coefficients of the LUMO of tropone are at C-2 and C-7. It results the bonding to these sites with lower energy more than bonding to C-2 and C-3.

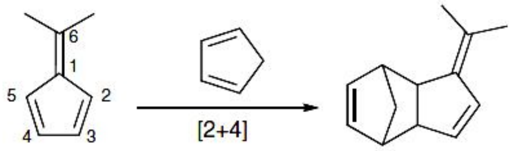






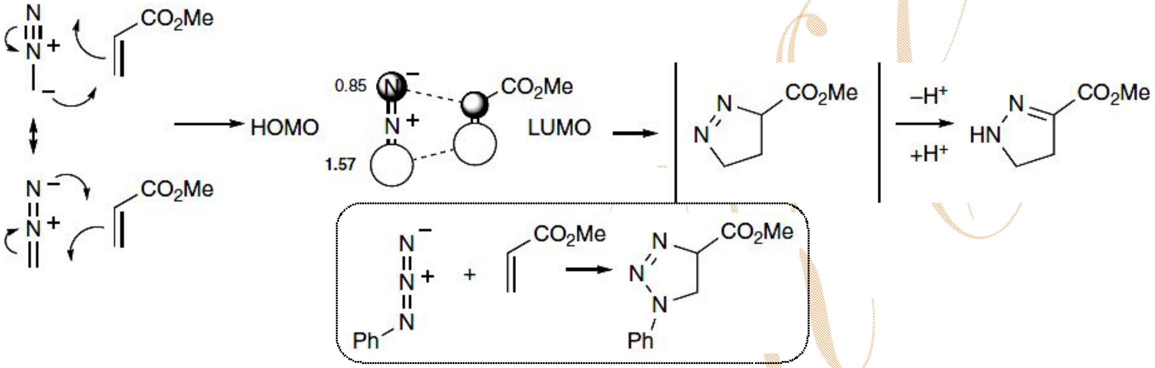




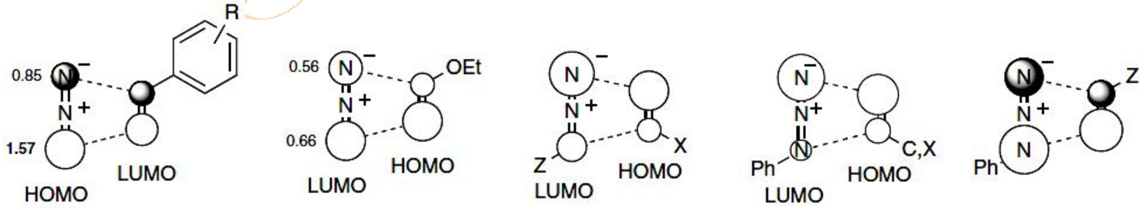


Rates, Regioselectivity and Site selectivity of 1,3-Dipolar Cycloadditions

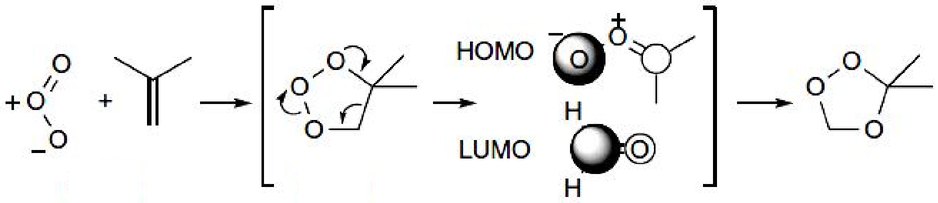
1,3-dipolar cycloaddtions is faster rate of concerted cycloaddition reaction between 1,3-dipole (like diazomethane, nitrone, ozone) with high-energy HOMOs and low energy –LUMO alkenes (dipolarophiles) carrying electron-withdrawing substituents. Frontier orbital interactions resemble this reaction with normal Diels-Alder reactions. The reaction of diazomethane or phenyl azide with methyl acrylate shows the regioselectivity.



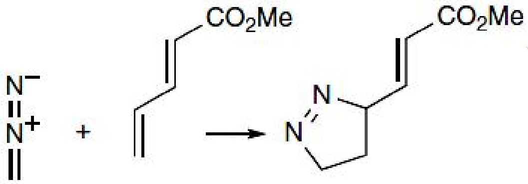
A smaller separation between the HOMO of the dipole and the LUMO of the dipolarophile is called **dipole-HO controlled** and between the LUMO of the dipole and the HOMO of the dipolarophile is called **dipole-LU controlled**. The regioselectivity of of 1,3-dipolar cycloadditions are shown below. The smallest energy separation (7.8 eV) is with X-substituted dipolarophiles implies a dipole-LU-controlled reactions. Conversely, regioselectivity for phenyl azide reacting with a Z-substituted alkene is dipole-HO-controlled regiochemistry with $E_{LUMO} - E_{HOMO} = 9.5$ eV (compared to dipole-LU-controlled regiochemistry $E_{LUMO} - E_{HOMO} = 10.7$ eV).



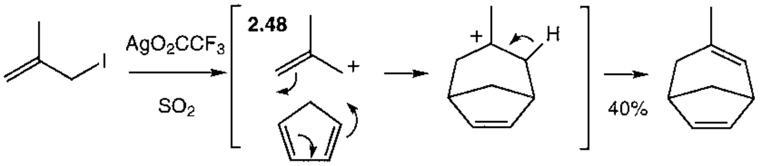
Overall ozonolysis reaction exhibits regioselectivity. The first step has no regiochemistry; the second step is a cycloreversion, but the third stage the cycloaddition of a ketone oxide to a carbonyl group, is highly regioselective.



The site selectivity of 1,3-dipolar cycloadditions is analogous to the Diels-Alder reactions.

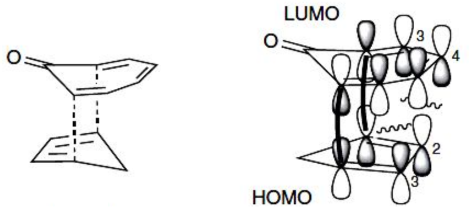


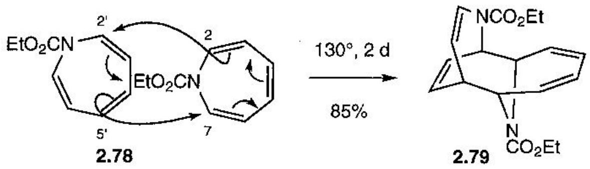
[4+2] cycloaddition of cations



[4+6] Cycloadditions

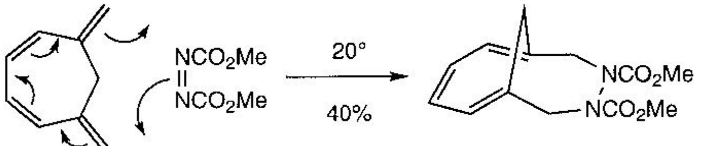
An explanation for the stereochemistry of [4+6] cycloadditions underlies secondary orbital interactions. The reaction between cyclopentadiene and tropone produces thermodynamically favoured exo adduct with favourable *exo* transition structure. Frontier orbitals indicate a repulsive interaction (wavy lines) between C-3, C-4 on the tropone and C-2 on the diene (and between C-5 and C-6 on the tropone and C-3 on the diene) in the endo transition structure.

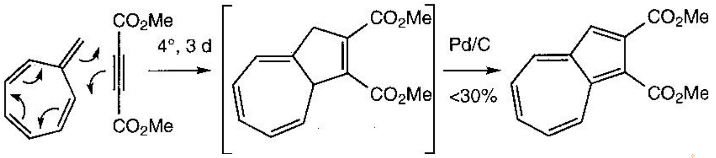


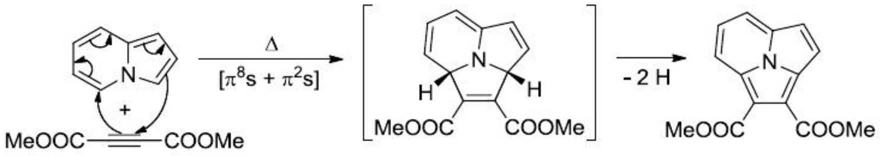


2.78 **2.79**

[8+2] cycloadditions

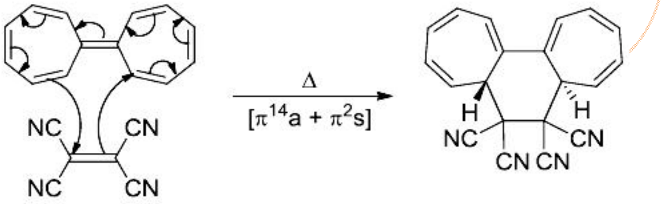


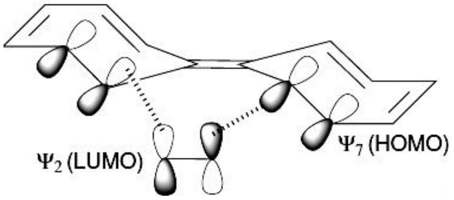




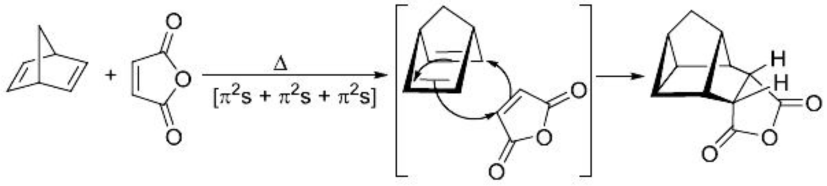
[14+2] Cycloadditions

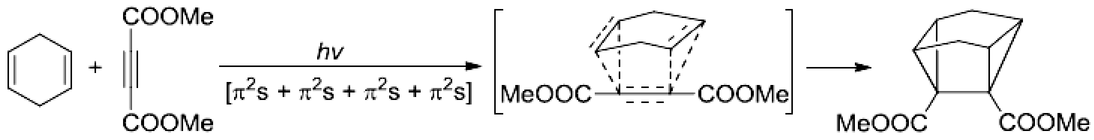
[14+2] Cycloaddition of heptafulvalene (HOMO) with tetracyanoethylene (LUMO) involves an antiaromatic transition state. The reaction is termed as $[\pi_{14}^{a} + \pi_{2}^{s}]$ and is thermally allowed process. This is possible because heptafulvalene is flexible enough not to lose the conjugation through seven double bonds.





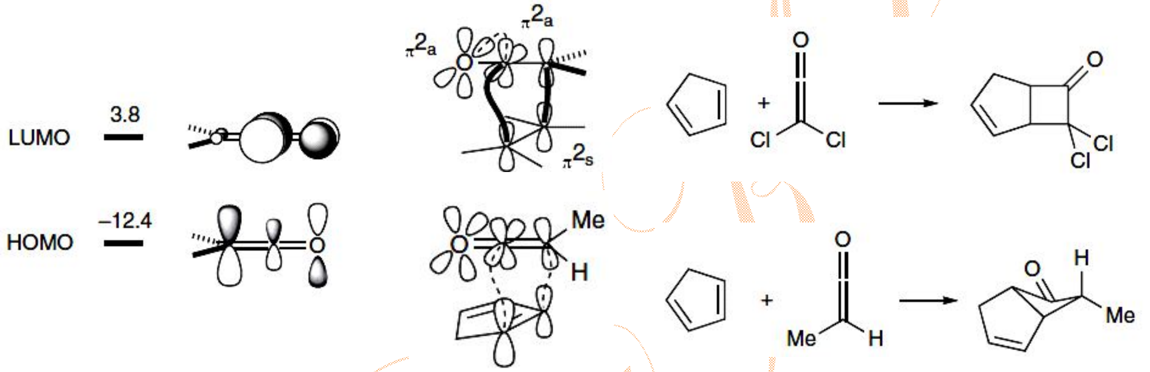
Cycloaddition with multiple components



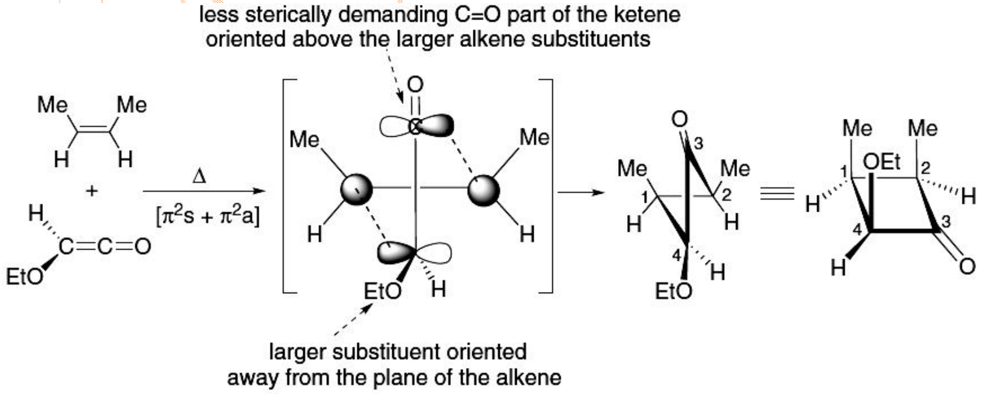


Ketene cycloaddition

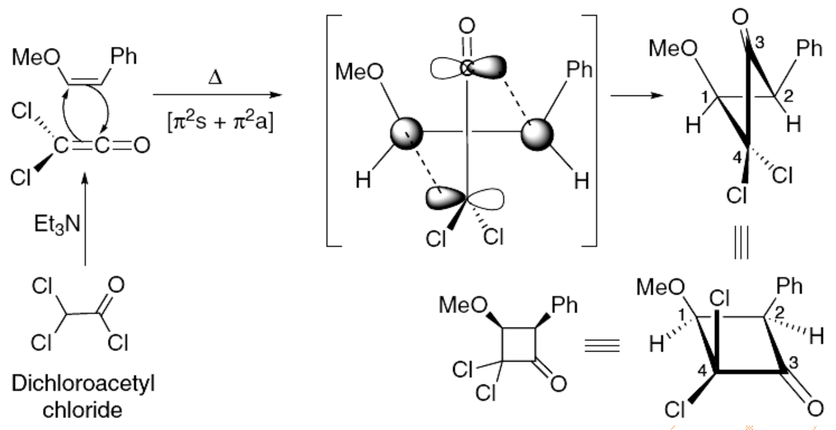
Ketenes undergo faster cycloadditions with double bonds to give cyclobutanones. It uses the interaction between the LUMO of the ketene and the HOMO of the ketenophile. The conjugation of the C—Cl bonds with the carbonyl group of the ketene will lower, by negative hyperconjugation, the energy of the LUMO, which is more or less π^*_{CO}. A C or X substituent on the alkene raises the energy of its HOMO, and the energy separation between the frontier orbitals is reduced.

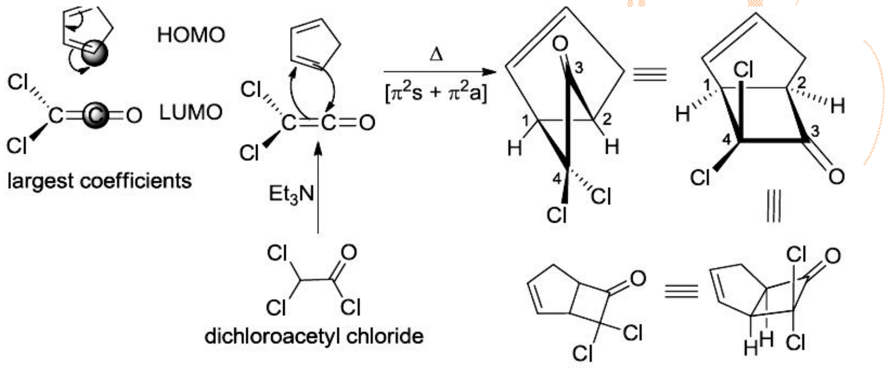


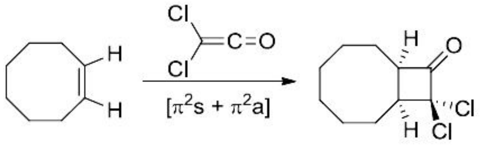
The regioselectivity in the reaction between cyclopentadiene and dichloroketene giving the cyclobutanone is explained by the overlap from the large LUMO coefficient on the central atom of the ketene and the larger coefficient in the HOMO of the diene at C-1.

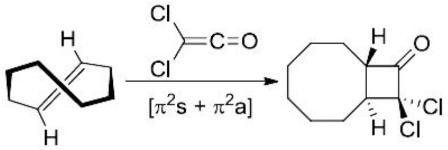

less sterically demanding C=O part of the ketene oriented above the larger alkene substituents

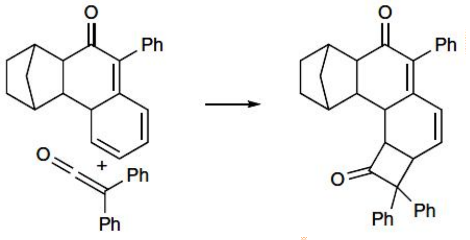
larger substituent oriented away from the plane of the alkene

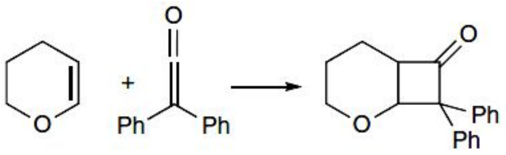




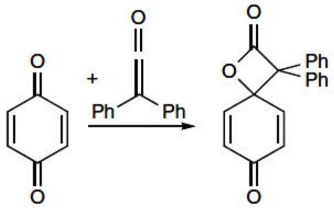


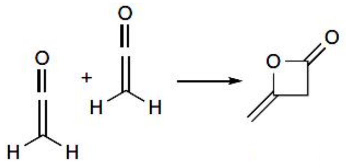


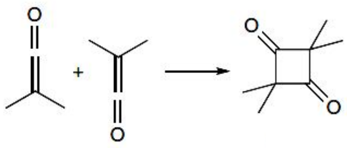




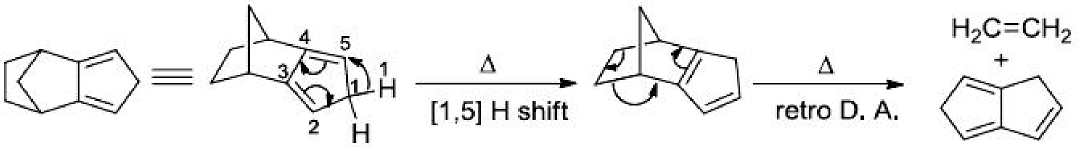
Both HOMO(ketone)/LUMO(ketene) and LUMO(ketone)/HOMO(ketene) interactions lead to the same conclusions about regioselectivity.

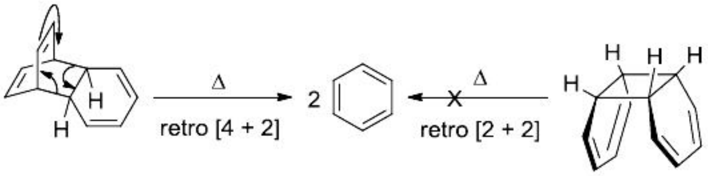


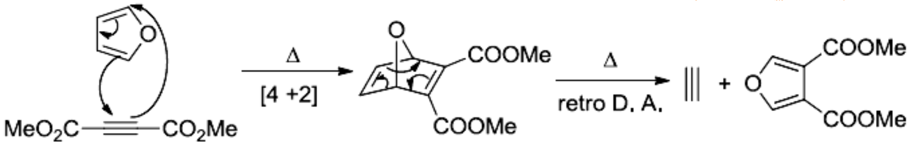




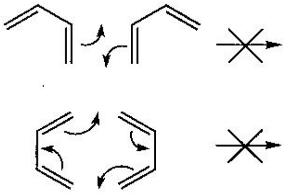
Retro Diels alder reaction

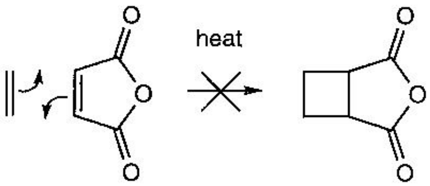






Forbidden reactions



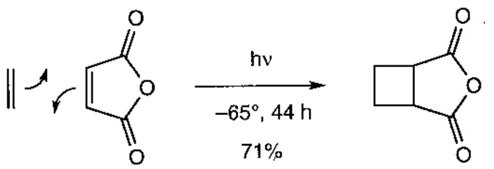


[4+2], [4+6] and [8+2] cycloaddition are commonplace. Burtadiene dimerizes following [4+2] cycloaddition reactions, not by [2+2] or [4+4] pathway. The simplest answer is 6-membered ring is easiest to form energetically than that of 4 or 8 membered ring due to ring starin or little probability to get two ends close. This argument does not apply to the reaction between ethylene and maleic anhydride. To get 4-membered ring with lower energy, a high kinetic barrier has to overcome. Thus, a total number of [4n+2] electron involved in cycloaddition reaction is thermally allowed; but not 4n number of electron system. Thus, the selection rule of orbital symmetry proposed by Woodward Hoffmann is justified. They are accomplished by photochemical means.

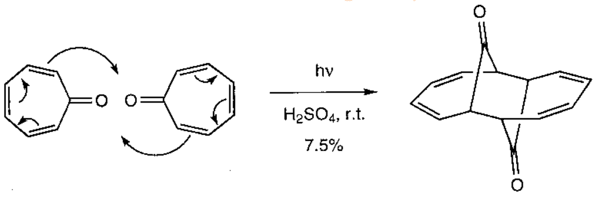
Photochemical cycloadditions

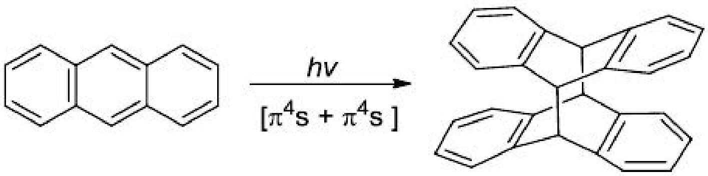
Cycloaddtion by photoactivation considers the first electronically excited state. Since photoactivation puts so much energy into the molecule, many pathways including self and crossdimerization are available in the first electronically excited state. This is accentuated by the observation that photo induced Diels-alder reactions are very rare.

[2+2] Cycloaddition



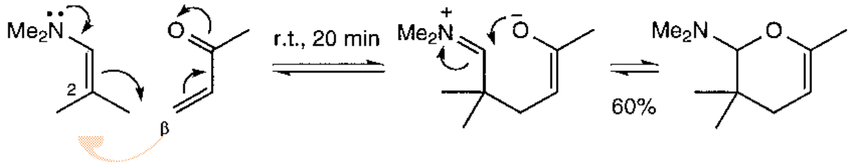
[6+6] cycloaddition

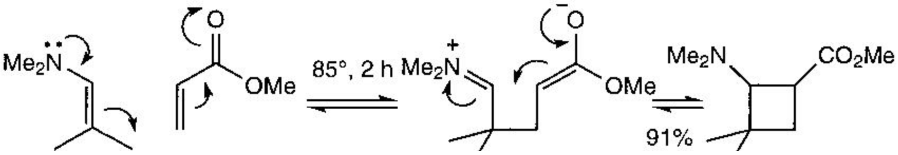




All cycloadditions are not pericyclic

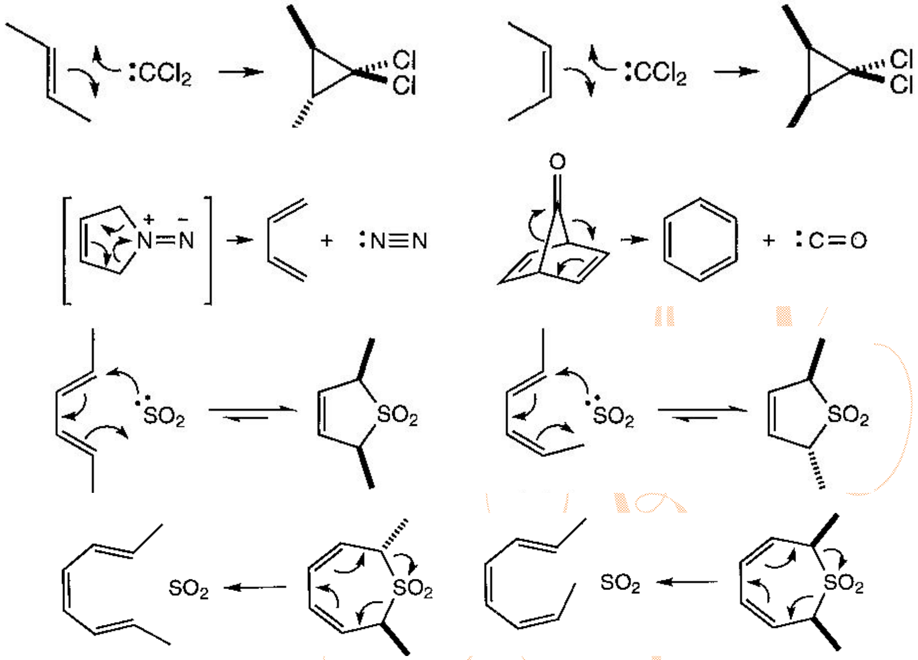
The reaction of enamine with methyl vinyl ketone provides hetero Diels Alder adduct. However, the product is cycloadduct, the reaction is not included in pericyclic because of isolation of zwitter ionic intermediate due to stepwise reaction. Even, the nucleophilic enamine reacts readily with either electrophilic methyl vinyl ketone or methyl acrylate gives different types of adducts.





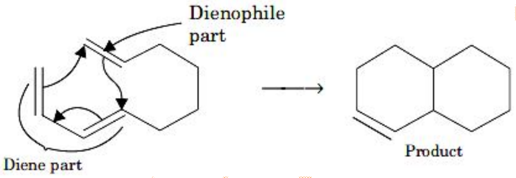
Cheletropic reactions

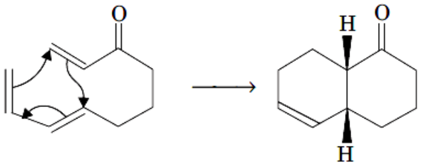
The stereospecific and suprafacial insertion of carbine into double bond (alkene) is known as Cheletropic reaction.



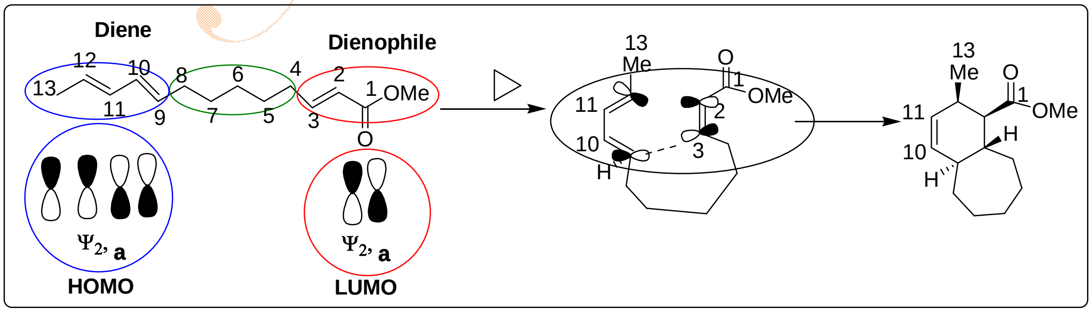
Intramolecular cycloaddition reaction

When diene and the dienophile are part of the same molecule, such type of molecule gives Diels-Alder reaction known as intramolecular Diels-Alder reaction.

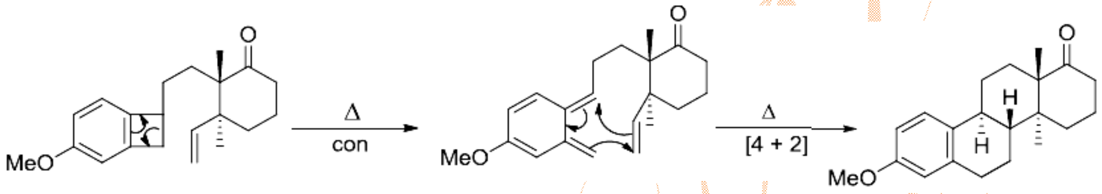




Q. Explain the following.

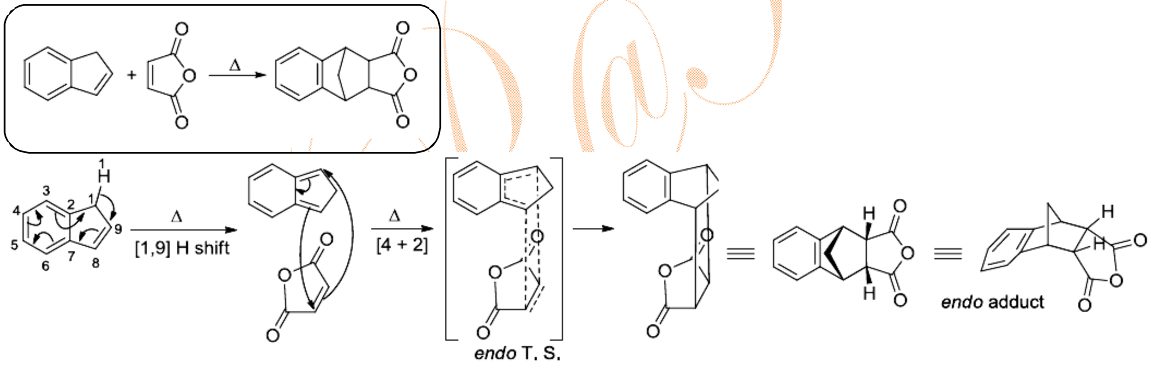


Ans: It is an example of intramolecular cycloaddition reaction or intramolecular Diels-alder reaction which takes places under thermal activation following orbital symmetry rules. The formation of the product follows 'Out-Endo-Cis' rule with supra-supra interaction. The (4n+2)π cycloaddition reaction occurs after adopting a suitable conformation necessary for cycloaddition. The driving force of the product may be the formation of stable 6-fused-7 membered ring with trans trans stereochemistry at the fused junction chiral centre.

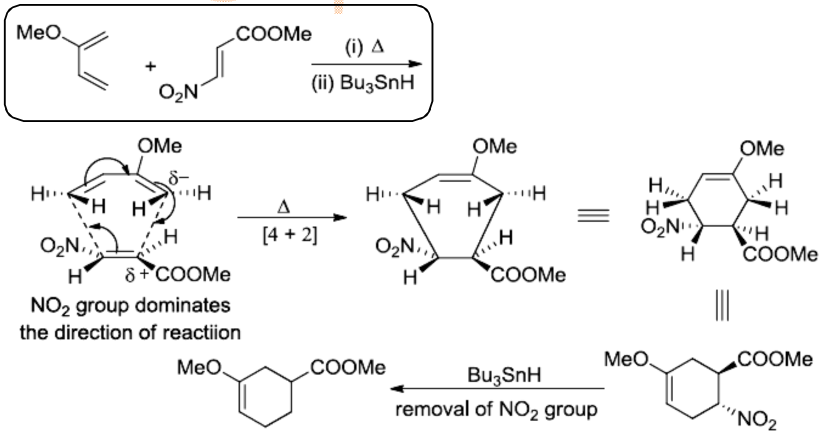


Typical examples on cycloadditions

Examples 1



Examples 2



The following table gives a correlation among the entire factors associated with Cycloaddition Reaction:

No. of total π e^- involved	Symmetry	Mode of activation	Interaction	Feasibility	Reactants stereochemistry	Product Stereochemistry
4nπ	m(s)	Thermal (Δ)	Supra-supra	Symmetry allowed	trans-trans cis-cis	trans
			Supra-antara	Symmetry Forbidden	trans-cis	cis
4nπ	C_2(s)	Photochemical(hγ)	Supra-supra	Symmetry allowed	trans-trans cis-cis	cis
			Supra-antara	Symmetry Forbidden	trans-cis	trans
(4n+2)π	C_2(s)	Thermal (Δ)	Supra-supra	Symmetry allowed	trans-trans cis-cis	cis
			Supra-antara	Symmetry Forbidden	trans-cis	trans
(4n+2)π	m(s)	Photochemical(hγ)	Supra-supra	Symmetry allowed	trans-trans cis-cis	trans
			Supra-antara	Symmetry Forbidden	trans-cis	cis

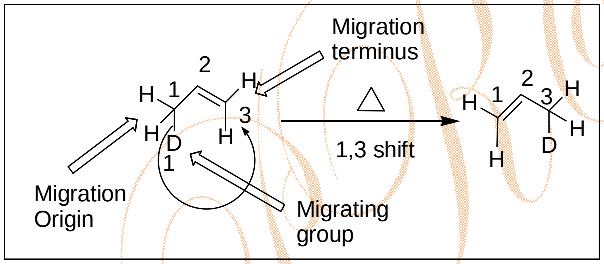
Sigmatropic Rearrangement

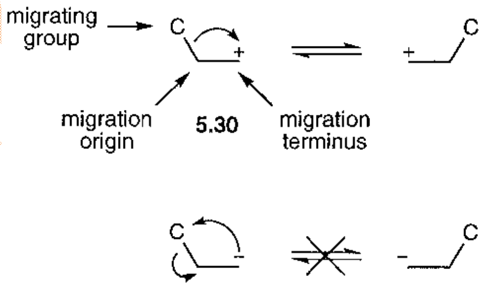
Definition:

Sigmatropic rearrangement is defined as the intramolecular migration of an allylic σ-bond or atom or group or ligand along with an σ-bond from a migration origin to the terminus of a polyene system through reorganization of π-bonds. This process is concerted involving simultaneous breaking of one σ-bond with the formation of new σ-bond and rearrangements of π-bonds. The numbers of π-bonds remain unchanged.

Classification of sigmatropic rearrangement:

The sigmatropic rearrangement can be represented by [i,j] shift where i and j are defined as the centre of migration origin and centre of migration terminus respectively. The difference of sigmatropic rearrangement from electrocyclic and cycloaddition reaction is that the later are classified by the number of π electrons involved in the cyclic transition state without migration of bonds.





Basic Features and Conditions for Sigmatropic rearrangement:

1. The symmetry of migrating orbital which migrates from migratory origin to migratory terminus must be in same phase and suprafacial.

2. Suprafacial in phase interaction of lobes must take place by maintaining a reliable orientation and certain distance between migratory origin and terminus.

3. Depending on the way of migration, stereochemical features would be resulted. If the migratory group is chiral, the configuration of the chiral centre

will depend on the total number of electron involves during the process [4n or (4n+2)].

4. HOMO of either migrating group and LUMO rest of the residue or vice-versa has to be considered in order to get symmetry allowed kinetically and thermodynamically more stable product.

5. That sigmatropic rearrangement will be favoured which follows the Woodward –Hoffmann principle of orbital symmetry. The involvement of any steric crowding or generation of strain in the product molecule will avoid the subsequent mechanism.

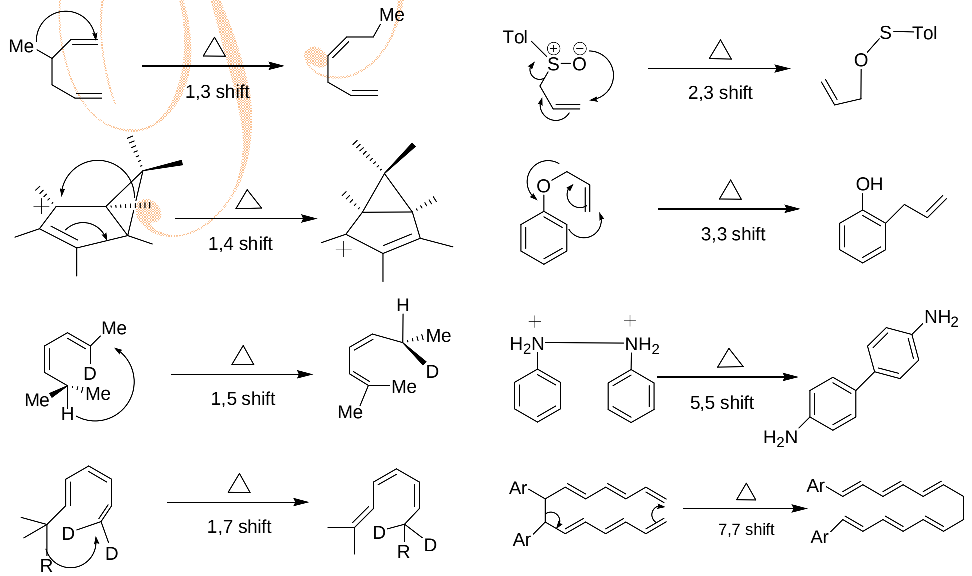
Source/ Influencing factor/ Mode of activation:

1. Heat or Thermal (Δ)
2. Light or Photochemical (hγ)

Criteria for Sigmatropic reaction:

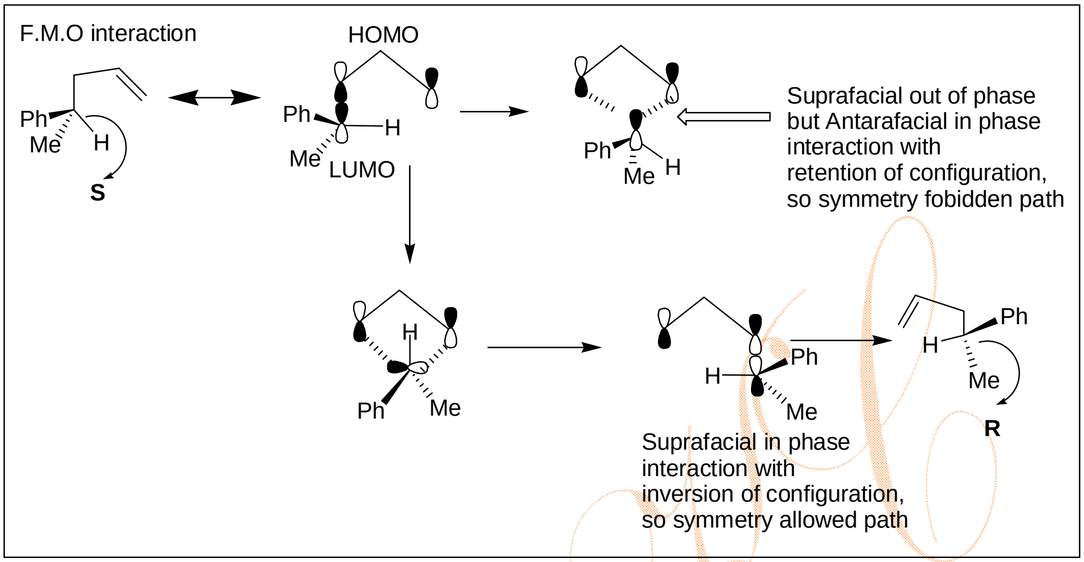
1. Mode of activation. (Δ/ hγ)
2. Total number of electron participates. [4n or (4n+2)]π
3. Stereochemical outcome (stereospecific, stereoselective).
4. The nature of orbitals interacting (σ and π).

Representative examples of various types of sigmatropic rearrangement



Case I: [1,3] Sigmatropic shift

A thermal [1,3] Sigmatropic shift is illustrated below.

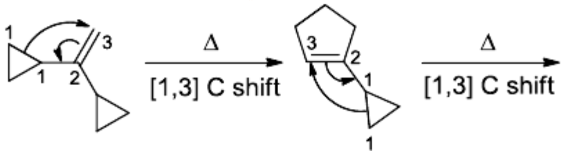


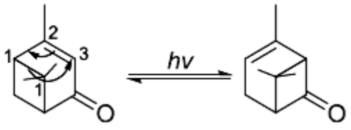
Suprafacial out of phase but Antarafacial in phase interaction with retention of configuration, so symmetry fobidden path

Suprafacial in phase interaction with inversion of configuration, so symmetry allowed path

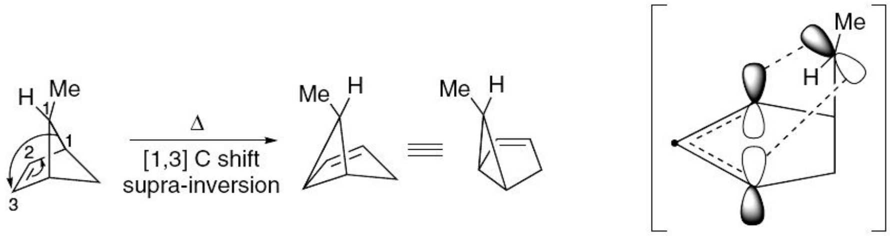
Orbital symmetry considers that the suprafacial path is thermally symmetry forbidden while antarafacial path might be followed; but it is geometrically impossible. Therefore, thermal [1,3] shift is very unlike. The process should be symmetry allowed under photochemical condition. However, the examples for 1,3 shift in photochemical process are rare. Because, when photon is absorbed by the molecule, the LUMO of the ground state will become HOMO of the excited state known as photochemical HOMO. Such situation is very unlikely.

Ex-1: A thermal ring expansion (left) with antarafacial [1,3] shift while a reversible suprafacial [1,3] shift (right) with retention of configuration in the migrating group are observed.

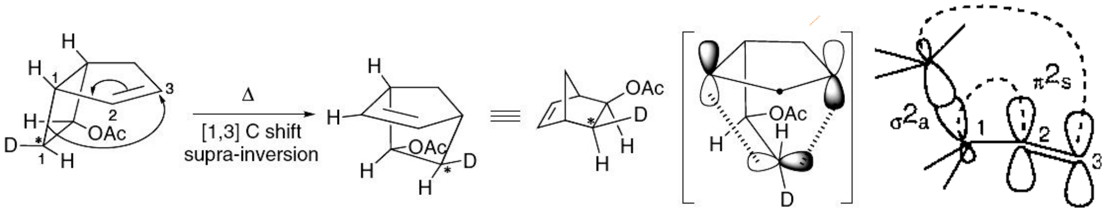




Ex-2: The reaction involves [1,3] sigmatropic shift under thermal conditions which is characterized by suprafacial with inversion at the migrating apical carbon.

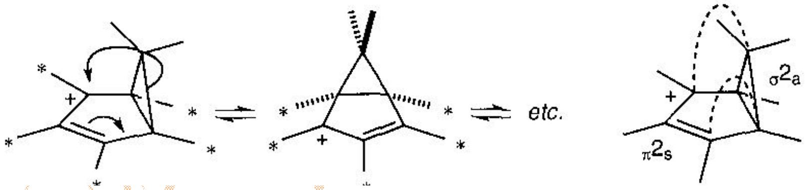


Ex-3: [1,3] suprafacial shift of an alkyl group proceeds with inversion at the migrating center at high temperature (300 °C).



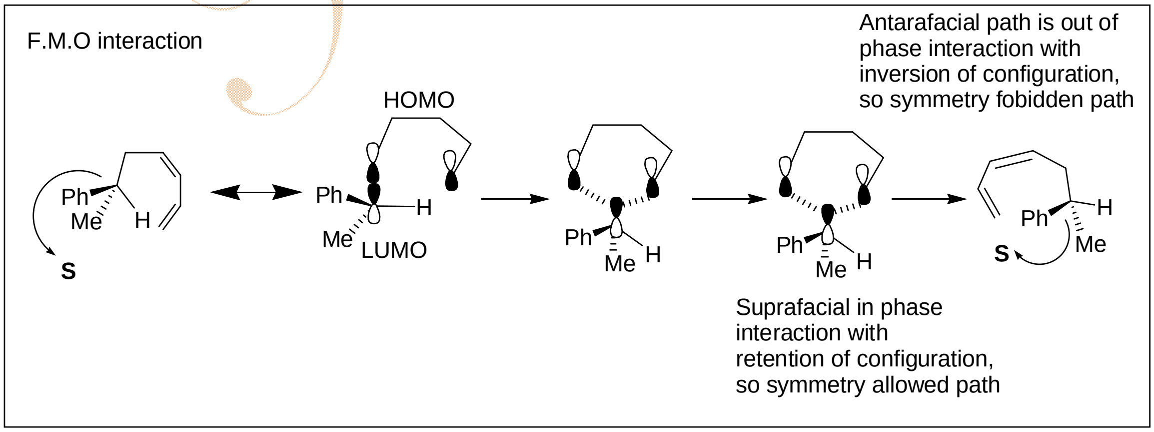
[1,4] Sigmatropic shift

[1,4] Sigmatropic shift involves allylic cation. The example is the degenerate rearrangement of bicyclic cation in which the bridge moves around perimeter of the five membered ring. The *endo* and *exo* —Me-groups remain unaltered from spectroscopic point of view.



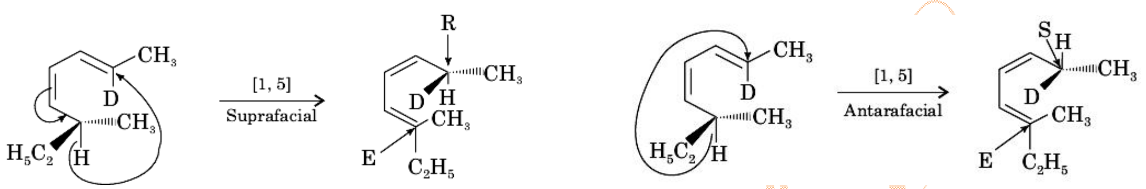
Case II: [1,5] Sigmatropic shift

A thermal [1,5] Sigmatropic shift is illustrated below.



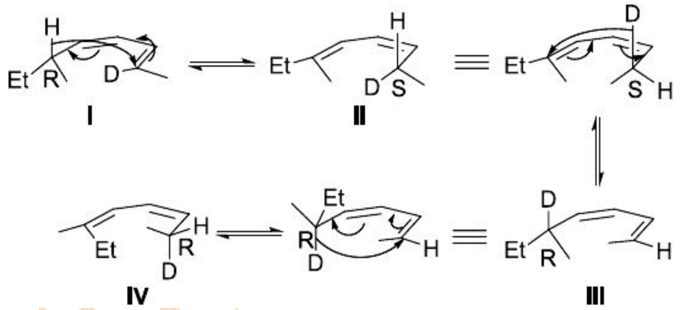
Among all possibilities of sigmatropic migration, always 1,5 shift occurs due both symmetrically and geometrically favourable migration. H's and alkyl groups migration favours suprafacial [1,5] shift. The [1,5] sigmatropic shift results symmetry allowed suprafacial migration with retention of configuration.

Stereochemistry of migration



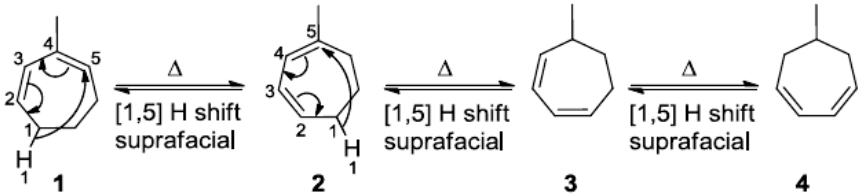
Suprafacial migration renders R-configuration at C-5 and E-configuration at C-1 (left) whereas antarafacial migration yields S-configuration at C-5 and E-configuration at C-2 (right).

Ex-4: The structures of the dienes present in the reaction mixture via sequential thermal [1,5] suprafacial sigmatropic H and D—shifts.

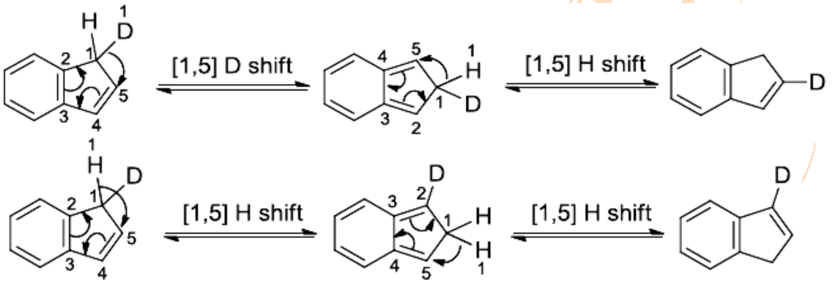


Ex-5: The isomers of monosubstituted cycloheptatriene are interconvertible following successive suprafacial [1,5] 'H shifts. This reaction involving [1,5] 'H shifts is reasonably slower than that of cyclopentadienes. In contrary, photochemically [1,5] 'H shifts occurs only in open chain system where the migration can be antarafacial.

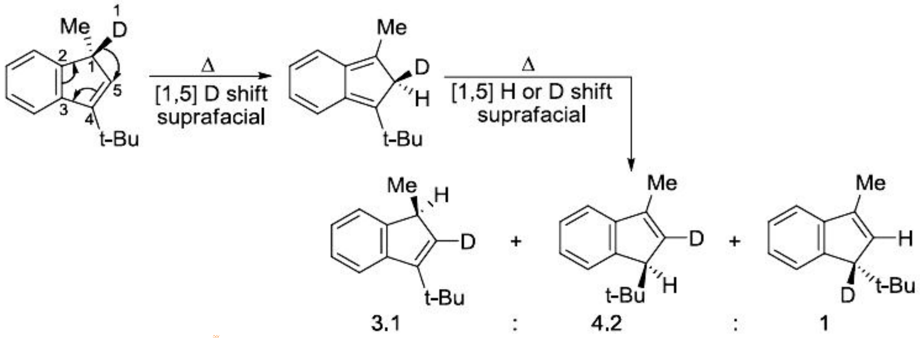
Ex-6: Isomeric methylcycloheptadienes (**1—4**) are in a thermal equilibration as a result of successive [1,5] ‘H shifts.



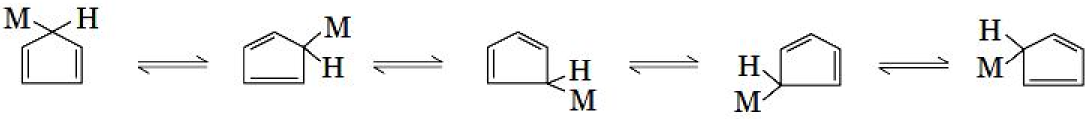
Ex-7: Both thermally allowed [1,5] H and D—shifts shows the scrambling of deuterium label of 1-deuteroindene.



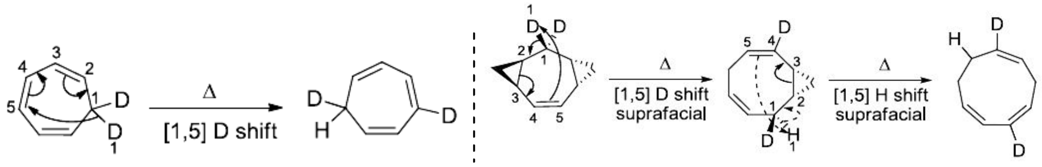
Ex-8: The deuterium labeling is found consistent with thermal suprafacial [1,5] deuterium shift for optically active 1-deuterio-1-methyl-3-tert-butylindene. Three products were obtained as optical active.



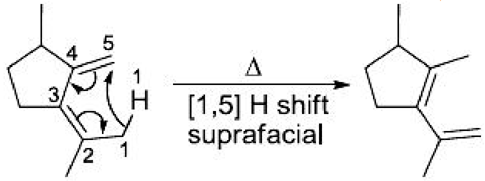
Ex-9: The given molecule represents fluxtionality. The fluxionality of the σ (sigma) bonded atom in cyclopentadienide involves migration.



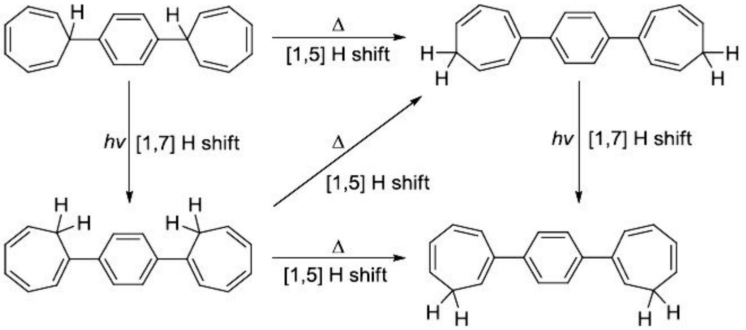
Ex-10: Both reactions involve a suprafacial [1,5] deuterium shift under thermal condition.



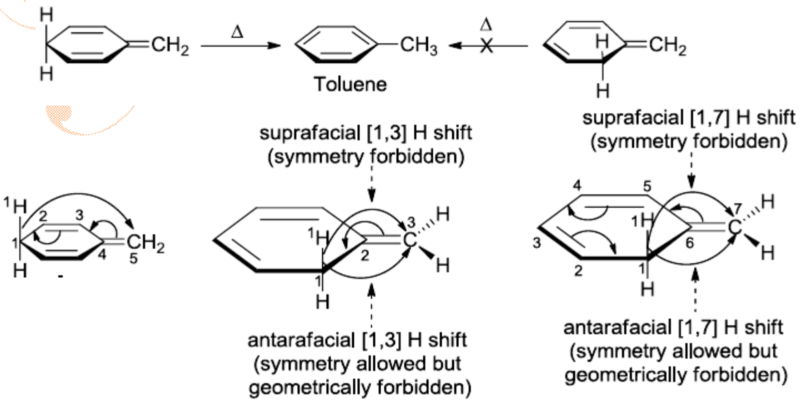
Ex-11: A relatively less stable diene with exocyclic double bonds is switched to a stable diene containing endocyclic double bond by [1,5] H-shift.



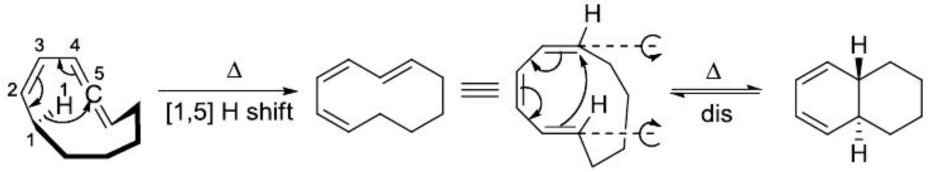
Ex-12: The isomers of 1,4-di(cycloheptatrienyl)benzene are interconverted by thermal [1,5] and photochemical [1,7] suprafacial sigmatropic hydrogen shifts.



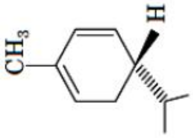
Ex-13: Only suprafacial [1,5] hydrogen shift is thermally allowed for the conversion into toluene.



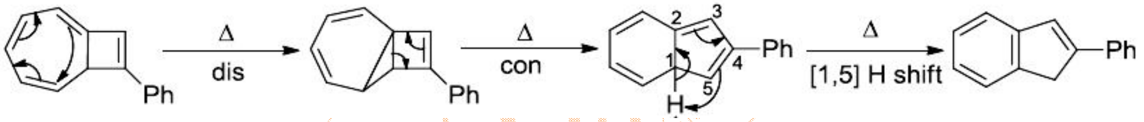
Ex-14: Suprafacial [1,5] H shift of Z-cyclodeca1,2,4 triene followed by an 6π electrocyclic ring closure in disrotatory manner yield bicycle[4,4,0] deca2,4-diene.



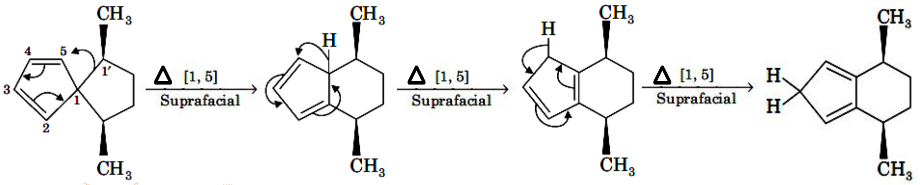
Ex-15: S-(+)-α-phellandrene loses its optical activity on distillation owing to spontaneous and geometrically favourable [1,5] H shift of chiral hydrogen within the molecule.



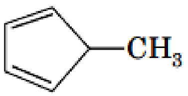
Ex-16: An 6π electrocyclic disrotatory ring closure followed by suprafacial [1,5] H shift results 7-fused-4 to stable 6-fused-5 membered ring.



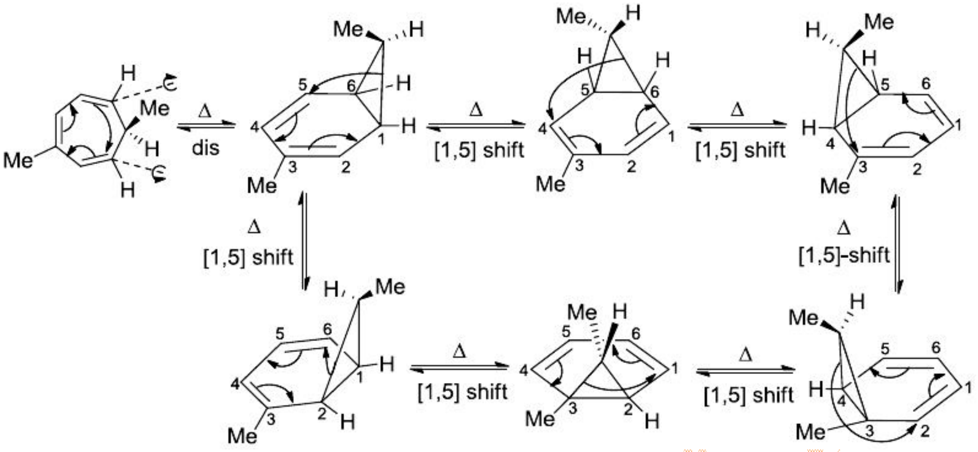
Ex-17: Three successive thermal suprafacial [1,5] sigmatropic shifts including one σ—bond and two hydrogens occurs with retention of configuration.



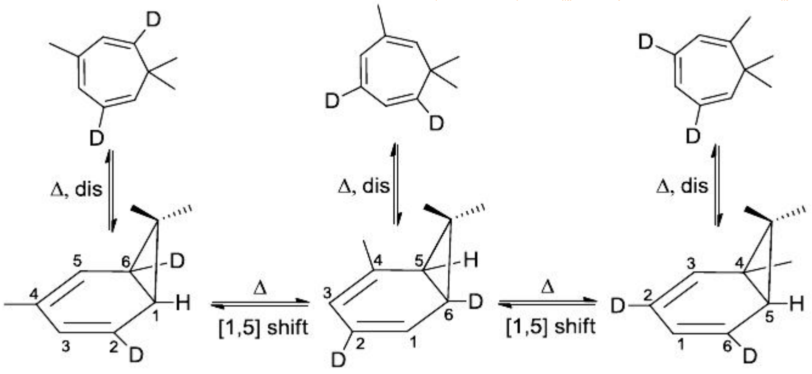
Ex-18: The given compound shows only a singlet for the methyl group in ^{1}H NMR. Because the [1, 5] migration of hydrogen takes place in the preference to the methyl group and the migration is so fast at room temperature that only a singlet is observed for the methyl group.



Ex-19: Walk rearrangement of norcaradiene with [1,5] shifts

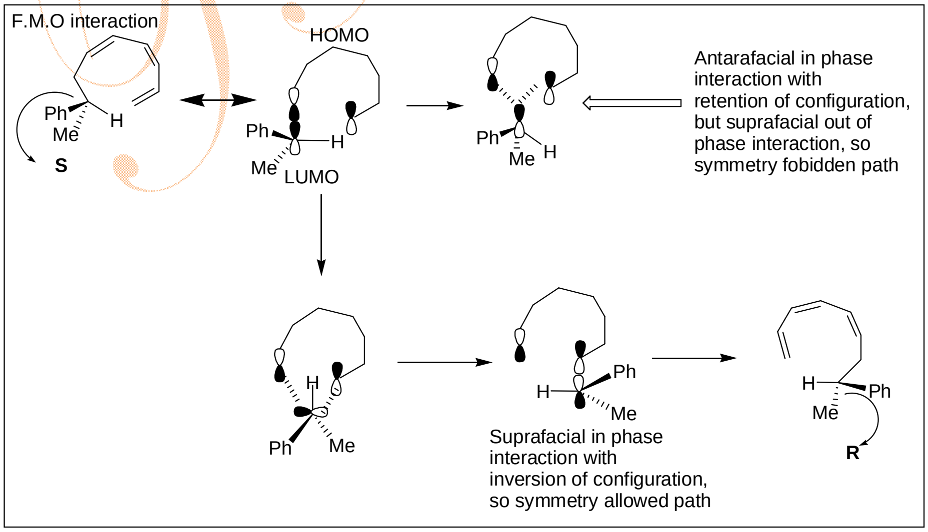


Ex-20: Isomerization of substituted cycloheptatrienes takes place through sequences of [1,5] sigmatropic rearrangements and electrocyclic reactions.



Case III: [1,7] Sigmatropic shift

A thermal [1,7] Sigmatropic shift is illustrated below.

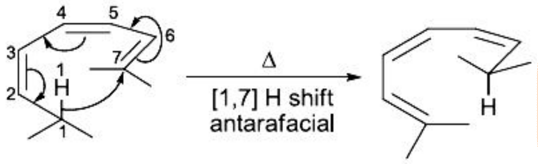


Antarafacial in phase interaction with retention of configuration, but suprafacial out of phase interaction, so symmetry fobidden path

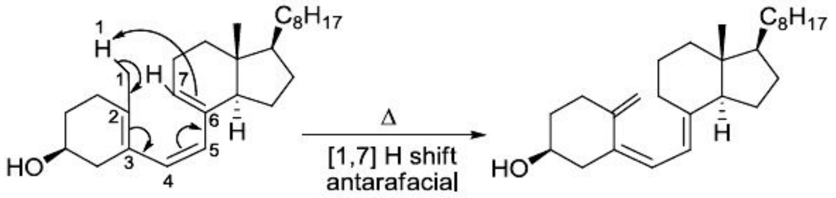
Suprafacial in phase interaction with inversion of configuration, so symmetry allowed path

Thermally [1,7] shift although is suprafacial symmetry forbidden process, it occurs due to achievement of favourable geometry.

Ex-21: Unlike [1,3] shift, antarafacial migration is allowed for [1,7] hydrogen shift since the geometrical restrictions on antarafacial T.S of [1,7] hydrogen shift is not as severe as in the [1,3] shift case due to flexibility of a π-system of seven carbon atoms.



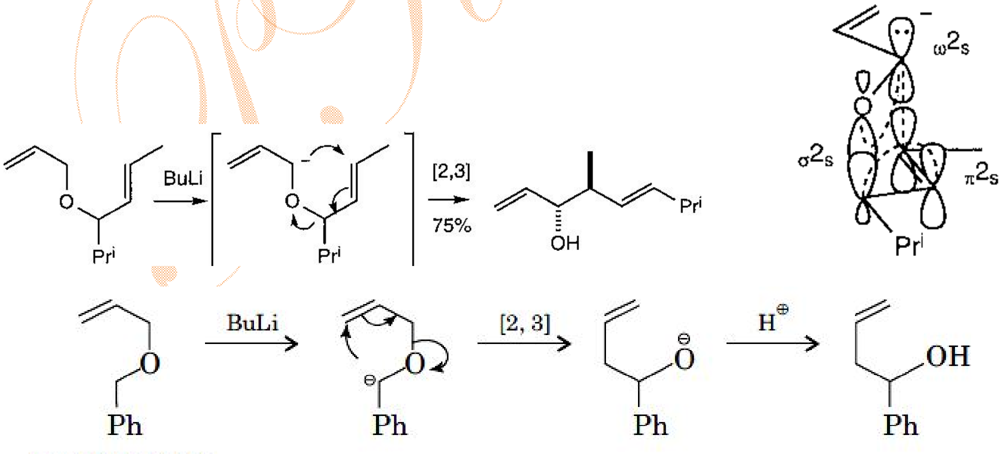
Ex-22: The thermal equilibrium between precalciferol (previtamin D_2) and calciferol (vitamin D_2) is illustrated by [1,7] Hydrogen shift.



Precalciferol

Calciferol

[2,3] Sigmatropic shift: Wittig rearrangement [$\sigma^2{}_s+\omega^2{}_s+\pi^2{}_s$]

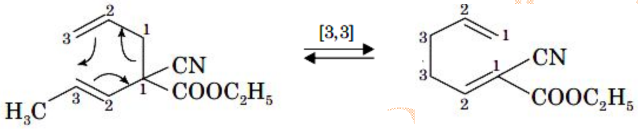


Benzylallyl ether

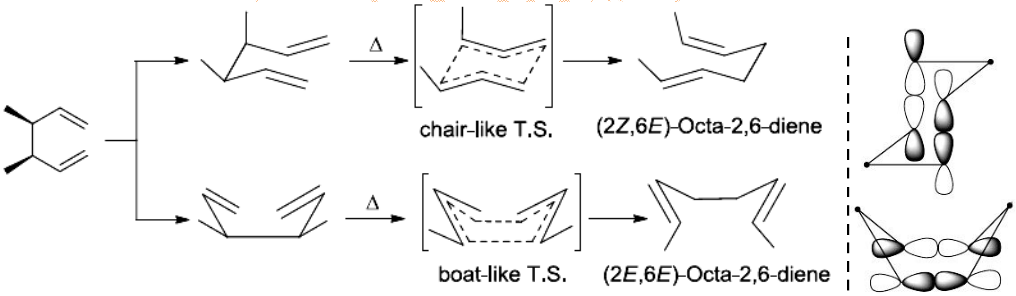
[3,3] Sigmatropic shift

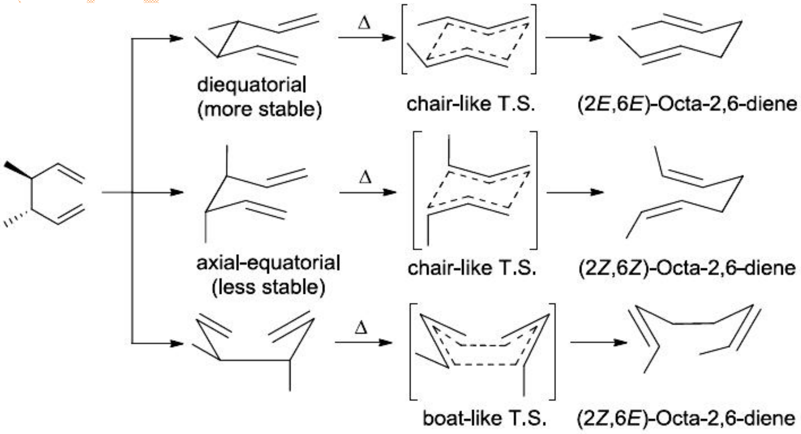
Cope rearrangements

A [3,3] sigmatropic rearrangement of 1,5-dienes under thermal condition is called the **Cope rearrangement**. The reaction proceeds through a 6-membered cyclic T.S. The Cope rearrangement is a reversible process; the equilibrium mixture has a great proportion of the thermodynamically stable isomer. It is an intramolecular process because rearrangement of a mixture of two different hexa-1,5-dienes does not lead to the formation of cross products.

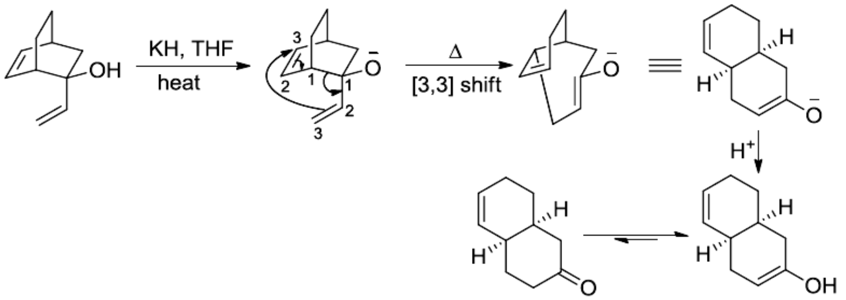


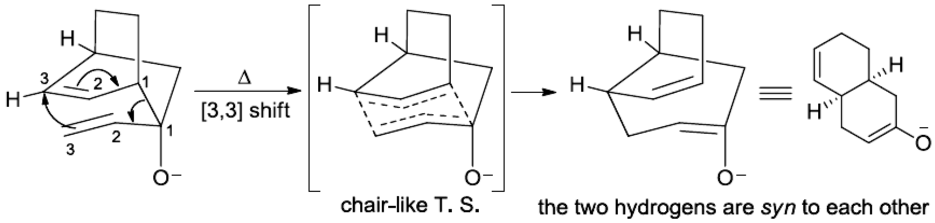
Ex-23: In [3,3] sigmatropic shifts, a chair-like transition state is energetically preferred to a boat-like structure. Rearrangement of the meso diene through such a transition state then would give the cisetrans isomer while in the case of the rearrangement of the racemic mixture the *trans-trans* isomer is the major product

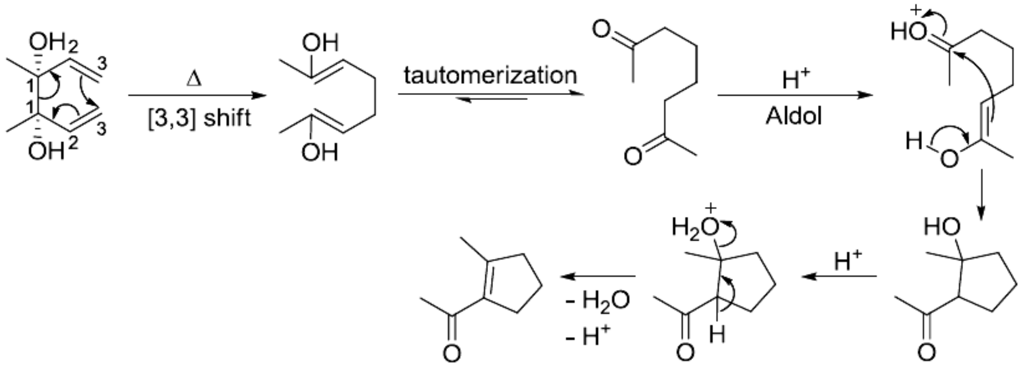


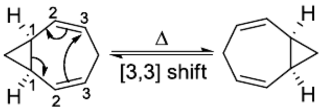


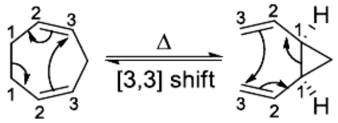
Ex-24: The following examples represent [3,3] shift mostly via a suitable chair conformation.

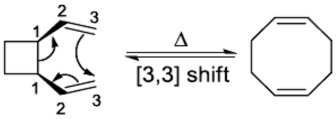


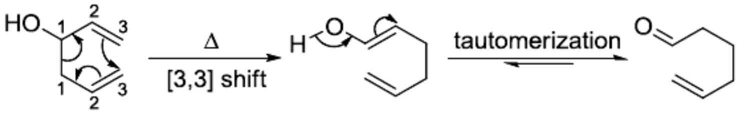


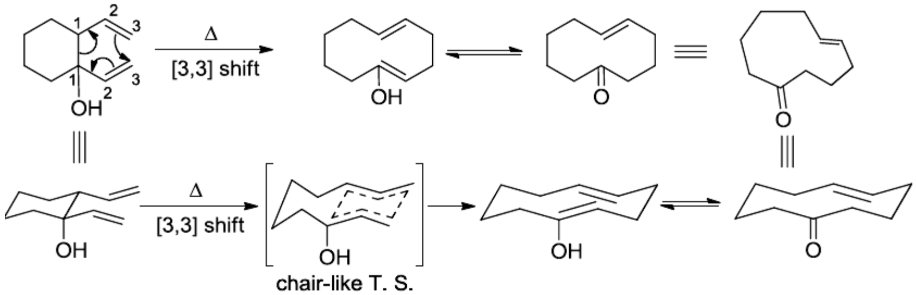




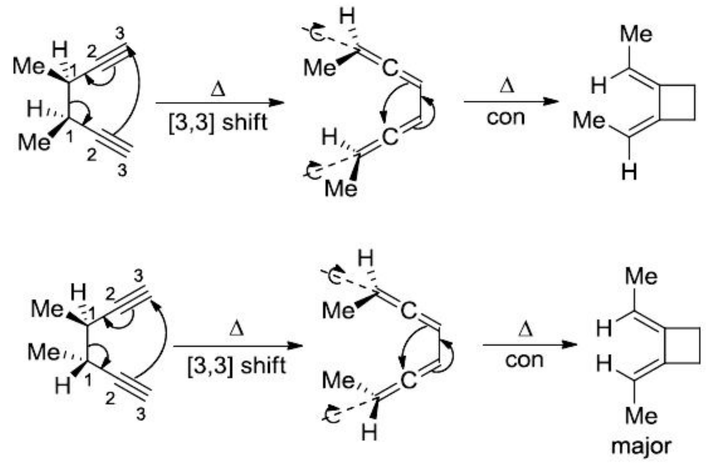






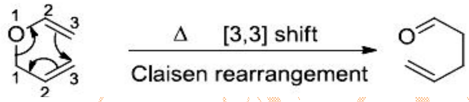


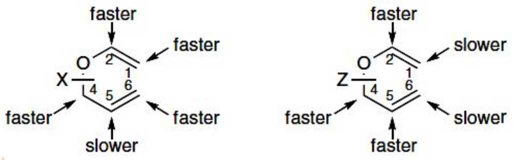
Ex-25: Diyne system can be thermally activated to suprafacial [3,3] sigmatropic shift via reactive allene intermediate which allows thermal electrocyclic ring closing reaction through conrotatory mode to furnish conjugated exocyclic double bond.



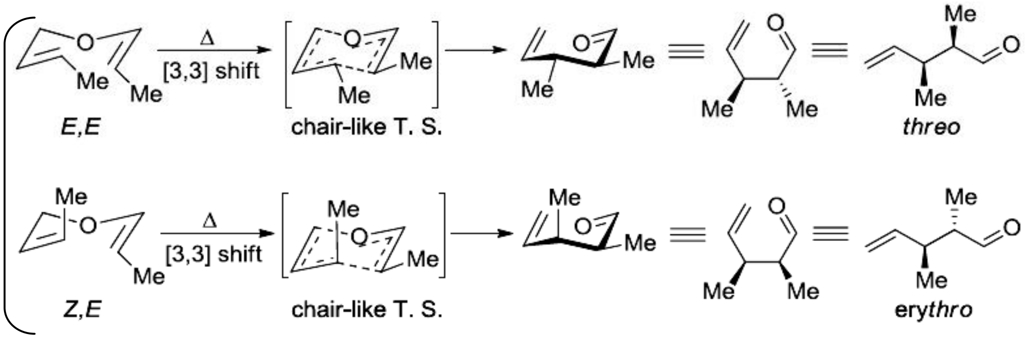
Claisen rearrangement

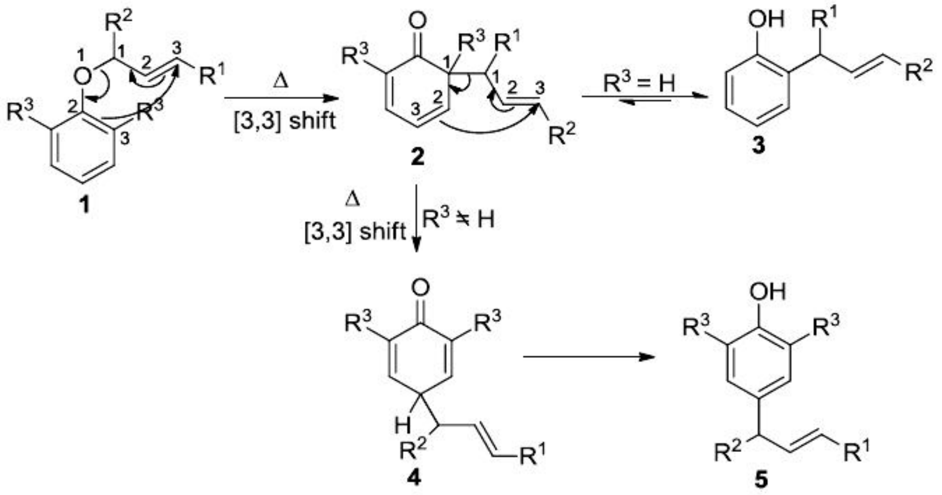
The Claisen rearrangement is an typical example of [3,3] sigmatropic rearrangement; for instance, the conversion of allyl vinyl ether to pent-4-enal or an allyl phenyl ether to an ortho-substituted phenol on heating.

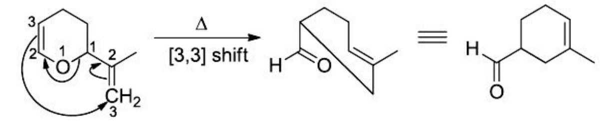


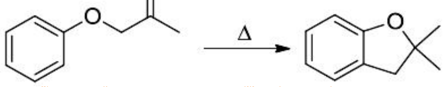


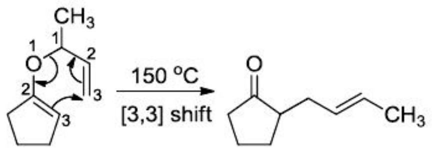
Ex-26: The mechanism of Claisen rearrangement for various isomers is shown in chair like T.S. Most favorable geometry arises in case of two larger methyl substituents in the pseudoequatorial position (E,E) in the transition state. The order of increasing rates toward the Claisen rearrangement is E,E > Z,E ≈ E,Z > Z,Z.

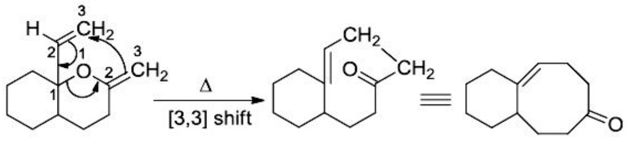




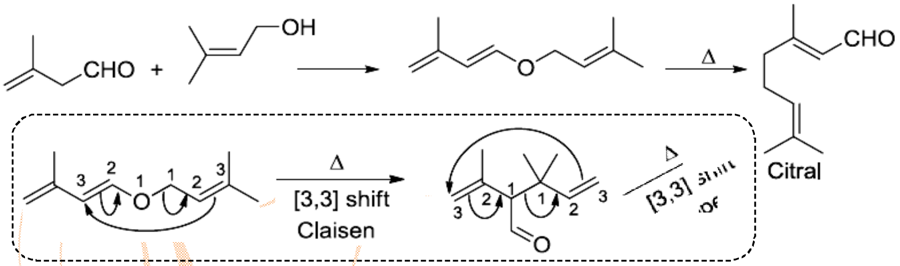




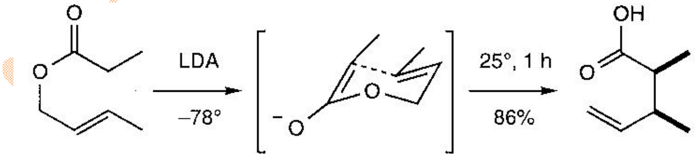




Ex-27: Citral is formed by following [3,3] sigmatropic rearrangement.

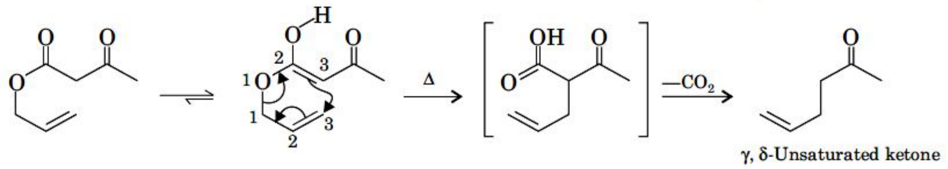


Ex-28: Ireland-Claisen rearrangement

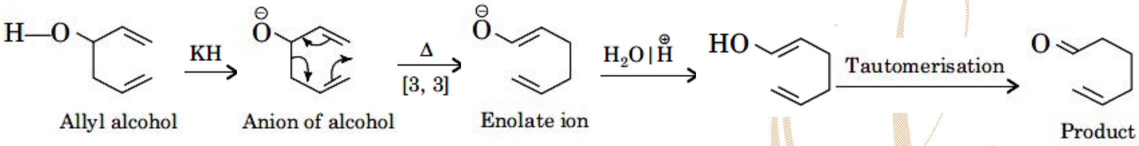


The β-ketoesters can rearrange to β-ketoacids following a [3,3] shift which is decarboxylated to give γ, δ-unsaturated ketone. This rearrangement is known as

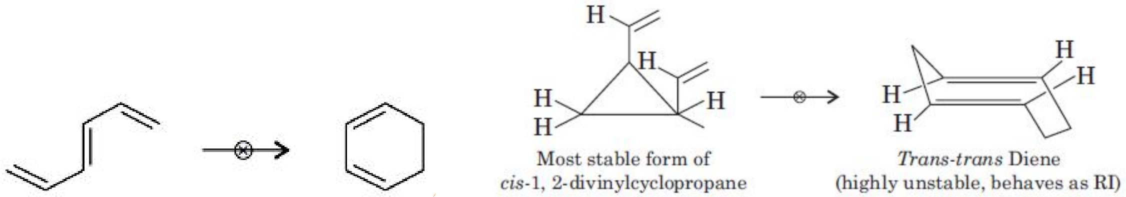
Ex-29: **Kimel-Cope rearrangement**.

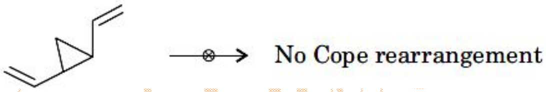


Ex-30: A typical example for anionic oxy-Cope rearrangement is depicted by converting allyl alcohol to anion and then [3,3] shift occurs.



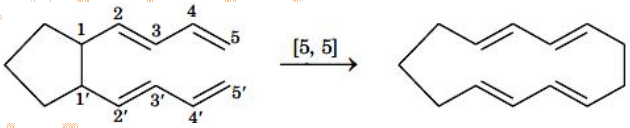
Ex-31: The following molecules do not exhibit Cope rearrangement.

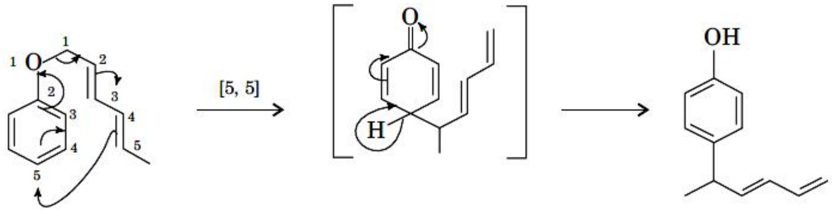




[5,5] Sigmatropic shift

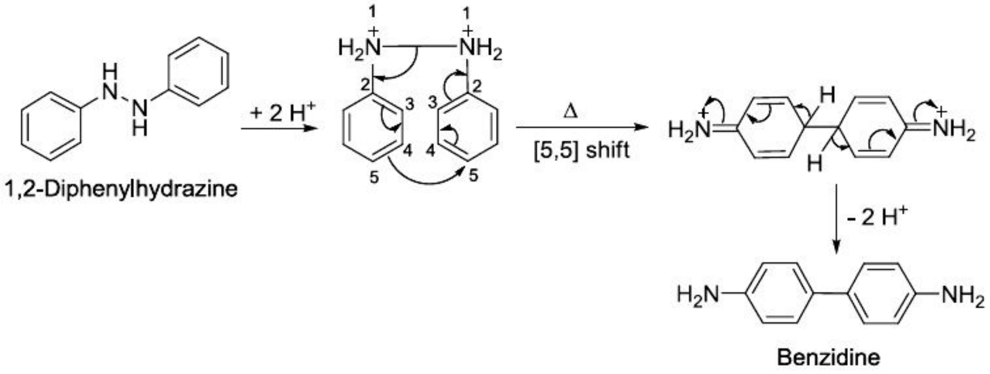
Ex-32:





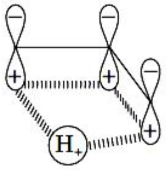
Ex-33:**Benzidine rearrangement**

An acid-catalyzed rearrangement of hydrazobenzenes involving [5,5] sigmatropic shifts proceeds suprafacially through 10-membered T.S.

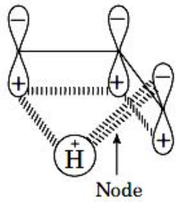


Hückel-Mobius rule in Sigmatropic rearrangements

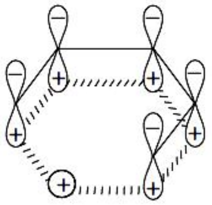
According to Hückel-Mobius rule, a thermal sigmatropic rearrangement take places via aromatic T.S whereas photochemical sigmatropic rearrangement proceeds via antiaromatic T.S.



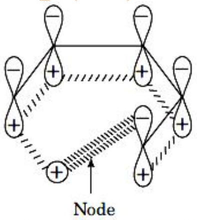
Suprafacial [1, 3], 4 electrons, zero node Hückel system, anti aromatic, hν allowed



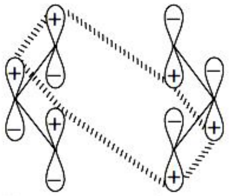
Antarafacial, 4 electrons, 1 node aromatic, mobius system, Δ allowed



6 Electrons, zero node, aromatic, Hückel system, Δ allowed

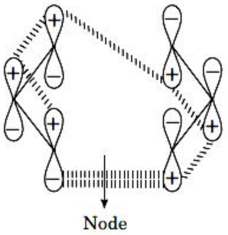


6 Electrons, one node, antiaromatic, mobius system, hν allowed



Supra-Supra

6 Electrons, zero node, aromatic, Hückel system, Δ allowed.



Suprafacial-antara facial

6 Electrons, one node, antiaromatic, mobius system, hν allowed.

No. of allylic πe⁻	Mode of activation	Interaction	Feasibility	Product Stereochemistry
4nπ	Thermal (Δ)	Suprafacial	Symmetry allowed	Retention
		Antarafacial	Symmetry Forbidden	Inversion
4nπ	Photochemical (hγ)	Antarafacial	Symmetry allowed	Inversion
		Suprafacial	Symmetry Forbidden	Retention
(4n+2)π	Thermal (Δ)	Antarafacial	Symmetry allowed	Inversion
		Suprafacial	Symmetry Forbidden	Retention
(4n+2)π	Photochemical (hγ)	Suprafacial	Symmetry allowed	Retention
		Antarafacial	Symmetry Forbidden	Inversion

Q. Why are HOMO-LUMO interactions so significant in order to prove concerted reaction and how the two approaches FMO and Woodward Hoffmann rule are rational in this concern?

Ans: The electrons in HOMO of a molecule are considered to be in the outer shell orbital. The energy required to expel those electrons will be less as they are already in higher energy level. LUMO is the unoccupied lowest energy orbital where electron can be transformed with the expense of least energy. Thus, least energy is expensed to remove electrons from HOMO and subsequent accommodation into LUMO. It makes smallest energy difference between HOMO and LUMO to ensure strong bonding. The Frontier Molecular Orbital (FMO) interactions of HOMO-LUMO must be abided by symmetry allowed process according Woodward-Hoffmann selection rule of orbital symmetry. Thus, a pericyclic reactivity can be understood in terms of FMO theory and the outcome of reactions can be predicted using the Woodward-Hoffmann rules.

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