M.Sc. (Pharmaceutical Chemistry)
Sem IV (Elective)
Study Material
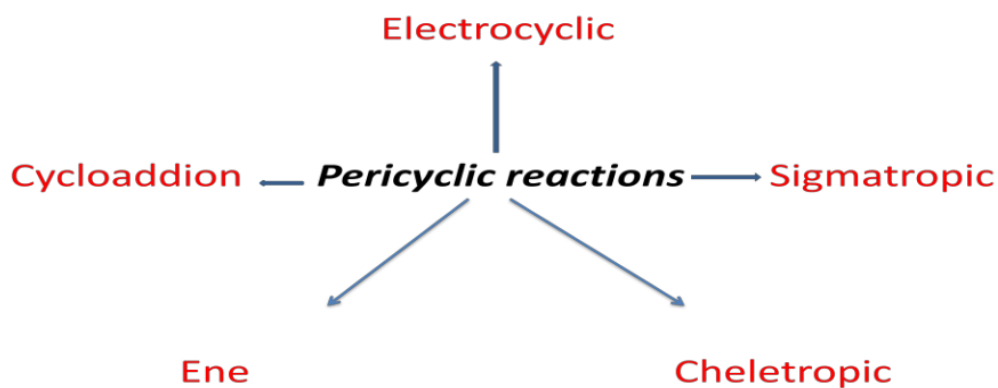
Pericyclic Reactions

Concerted reaction

Transition state

Energy

starting material

product

reaction co-ordinate

Multistep reaction

Transition states

Energy

starting material

inter-mediate

inter-mediate

product

reaction co-ordinate
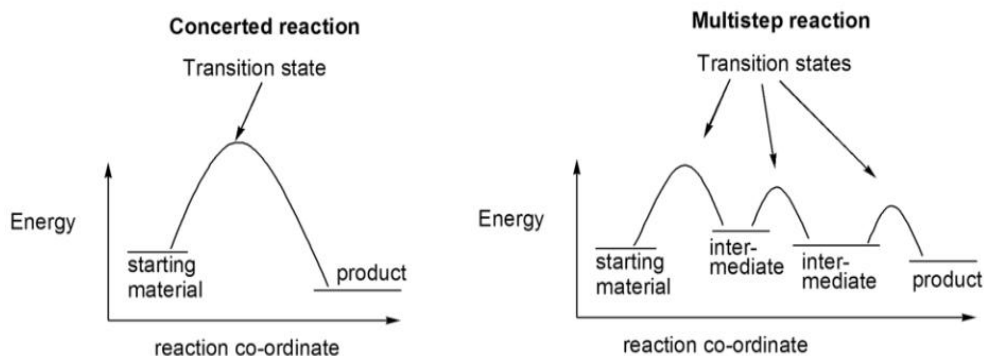
Pericyclic reactions are defined as the reactions that

occur by a concerted cyclic shift of electrons.

- In concerted reaction, reactant bonds are broken and product bonds are formed at the same time, without intermediates.
- The word pericyclic means around the circle.
- Pericyclic word comes from cyclic shift of electrons.
- Pericyclic reactions thus are characterised by a cyclic transition state involving the π bonds.
- key points that characterise a pericyclic reaction
- (a) Little, if any, solvent effect.
- (b) No nucleophiles or electrophiles involved.
- (c) Not generally catalysed by Lewis acids.
- (d) The energy of activation of pericyclic reactions is supplied either
    - by heat (Thermal Induction),
        or
    - by UV light (Photo Induction).

- (f) Pericyclic reactions are stereospecific and it is not uncommon that the two modes of induction yield products of opposite stereochemistry.

Electrocyclic

Cycloaddion ── *Pericyclic reactions* ──→ Sigmatropic

Ene   Cheletropic

- *electrocyclic reaction*: a reaction in which a ring is closed (or opened) at the expense of a conjugated double (or triple bond) bond.

New σ bond closes a ring

Loss of one π bond and
gain of one σ bond
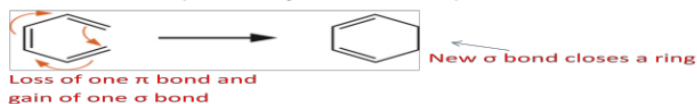
1,3-cyclohexadiene formation

- *cycloaddition reaction*: a reaction in which two or more π electron systems react to form a ring at the expense of one π bond in each of the reacting partners.

New σ bonds

.CN

CN

CN
CN
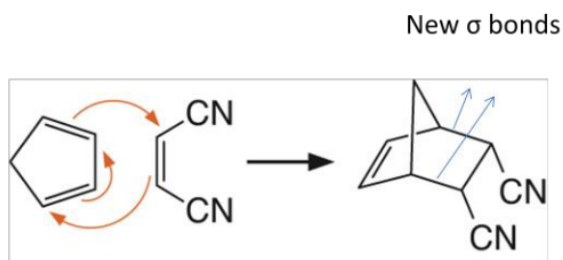
Diels-Alder Reaction

- In this reaction formation of two new *sigma bonds* takes place which close a ring.
- *Overall* there is loss of two *pi bonds in reactants* and *gain of two sigma bonds in a product.*

- *sigmatropic rearrangement (or reaction): a reaction in which a sigma bond formally migrates from one end to the other end of pi electron system and the net number of π bonds remains the same.*


Cope rearrangement

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Cheletropic reactions(variant of cycloaddition):

Reactions in which two sigma bonds are formed on the same atom or two sigma bonds are broken on the same atom.

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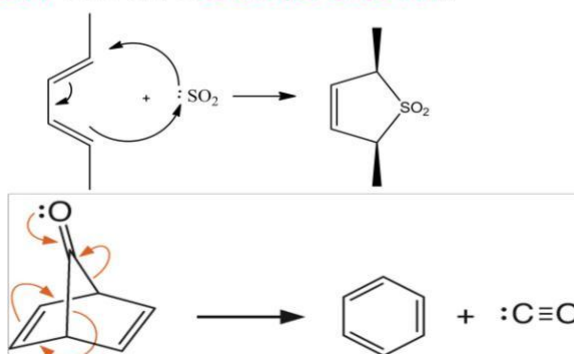
Ene Reaction: involves the transfer of one or more group or atoms from one molecule to another.

- involves the thermal reaction of alkene having an allylic hydrogen (called ene) with compound having multiple bond (x=y ,x triple bond y) , called enophile.

Ene: alkene, alkyne, allene, arene, C-heteroatom bond

Enophile: C=C, C=O, C=N, C=S, O=O, N=N, C≡C

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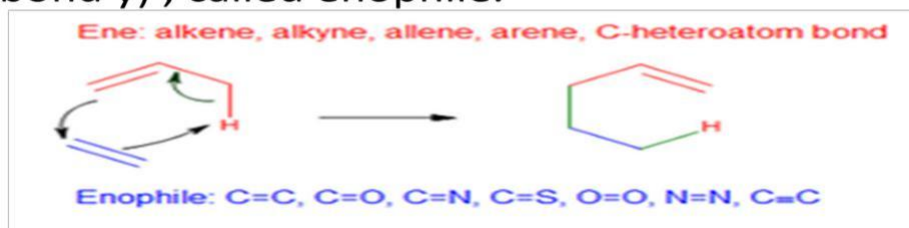
- Several theories have been developed to rationalise the pericyclic reactions.
- R.B. Woodward and R. Hoffmann have proposed explanation based upon the symmetry of the molecular orbitals of the reactants and products. The theory proposed is known as Conservation of Orbital Symmetry.
- K. Fukuii proposed another explanation based upon the frontier molecular orbitals. The theory proposed is known as Frontier Molecular Orbital (FMO) method.
- The Woodward-Hoffmann rule and Hückel-Mobius (H-M) methods are also used for the explanation of pericyclic reactions. These fours theories make the same predictions for pericyclic reactions.
- These four are the alternate ways for looking at the same reaction.

FRONTIER MOLECULAR ORBITALS

- occupied molecular orbital of highest energy, known as highest occupied molecular orbital (HOMO).
- unoccupied molecular orbital of lowest energy known as lowest unoccupied molecular orbital (LUMO).
- HOMO and LUMO of any given compound have opposite symmetries.
- HOMO and LUMO are referred to as frontier molecular orbitals.

molecular orbitals of 1,3-butadiene

molecular orbitals of 1,3,5 hexatriene
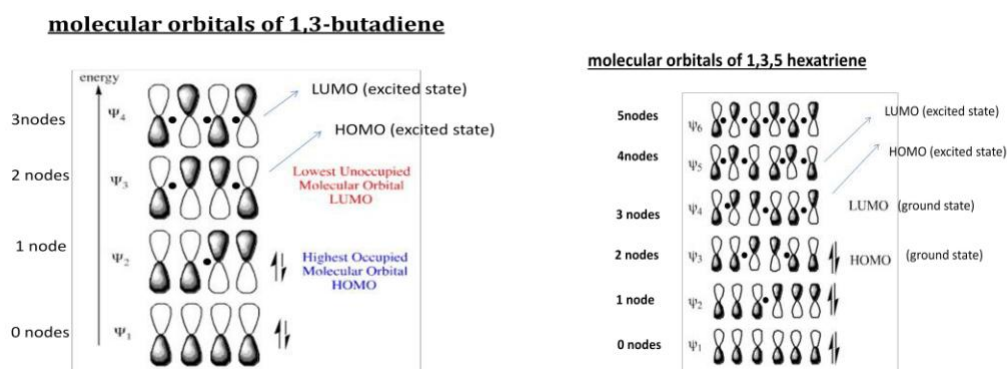
Woodward-Hoffmann theory for prediction of the stereochemistry of Pericyclic reactions: Electrocyclisations.

- explains the stereochemical outcome of pericyclic reactions by considering the symmetry of the 'frontier orbitals' which are involved in the reaction.
- These are the orbitals which actually contribute to the bond making and breaking process. They are also the 'outermost' orbitals (of highest energy) in a structure, hence the term 'frontier'.
- To form the new s bond in the electrocyclic reaction, the p orbitals at the end of the conjugated system must overlap head-to-head.
- **Conrotation:**

Clockwise   Clockwise
© 2004 Thomson/Brooks Cole
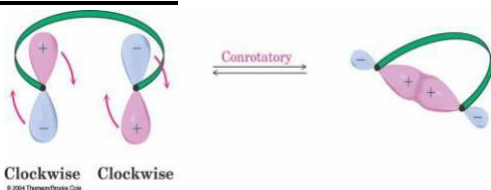
- If lobes of like sign are on opposite sides of the molecule: both orbitals must rotate in the same direction, clockwise or counterclockwise .

- **Disrotarion**
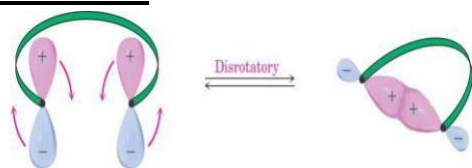
Clockwise Counterclockwise
© 2004 Thomson/Brooks Cole

- If two lobes of like sign are on the same side of the molecule, the two orbitals must rotate in opposite directions—one clockwise, and one counterclockwise.
- Only the symmetry of the HOMO is important in determining the course of the reaction.

HOMO is symmetric

HOMO is asymmetric

## Woodward-Hoffmann theory applied to cyclobutene formation under thermal conditions:

- In order form the new sigma bond, to be formed between the newly-connected carbon atoms, the ends of the molecule have to 'rotate' in a very specific way.

- We only need to consider the highest-energy molecular orbital (HOMO)


$\psi 2$
(HOMO)

Orbitals of same sign form a bond

overall: heat
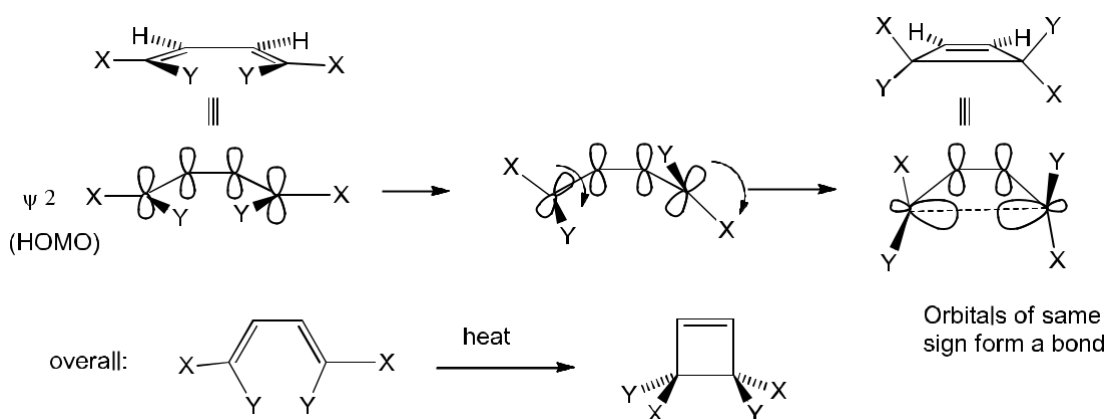
The result is that the 'X' groups end up trans to each other, as do the 'Y' groups. Because this involves a concerted rotation of each end of the diene in the same direction (clockwise, although anticlockwise would give same result) this is referred to as a 'conrotatory' process.

## Woodward-Hoffmann theory applied to cyclobutene formation under photochemical conditions:

- Under photochemical conditions, the orbitals are not changed in structure, but an electron is excited by one level. As a result, a new HOMO (Ψ_3).

- In the new HOMO, the 'ends' of the orbitals with the same sign are on the same face of the diene.

- In order for these to 'join up' to form a bond, the ends of the alkene have to rotate in opposite directions. This process is described as 'disrotation'.

Orbitals of same sign form a σ–bond

overall:
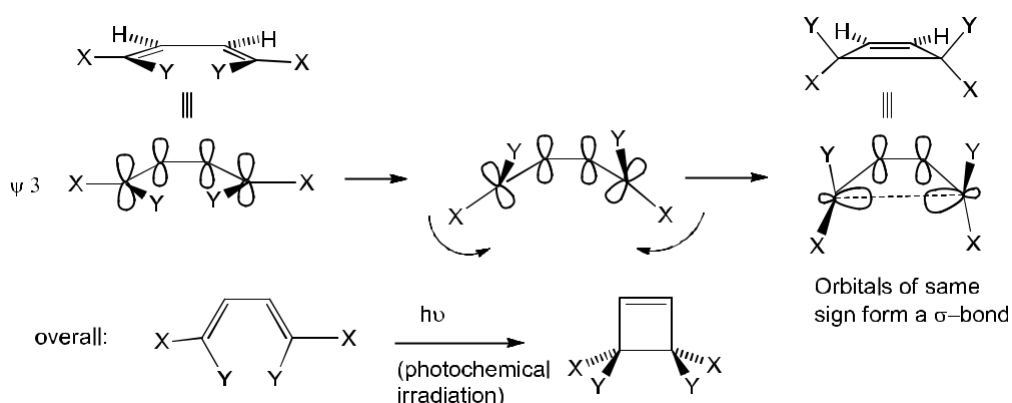
- **If the termini of the HOMO is superimposed upon the triene system**, it can be seen that the end groups must rotate in a disrotatory manner (twist in opposite directions, when viewed front-on) to form the bond
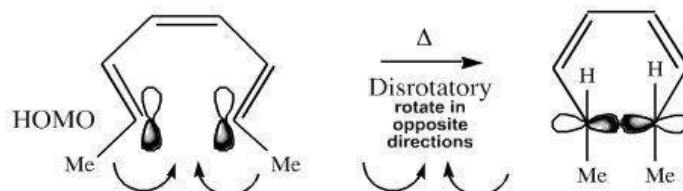
-
- Electrocyclic reactions can also occur photochemically. When photoactivated, an electron moves from the HOMO to the next orbital, the LUMO. (Now this orbital contains an electron it is no longer unoccupied, it is either a SOMO or an excited state HOMO).

- The photo excited system will ring close in the opposite manner to the thermal system and the groups conrotate (twist the same way) to form the sigma bond:
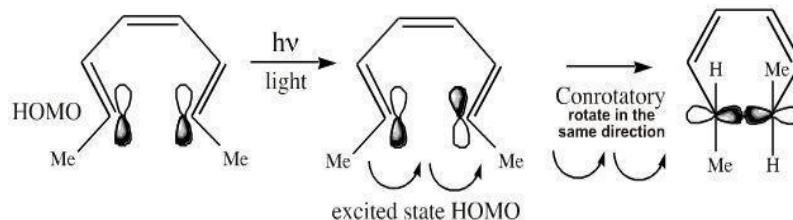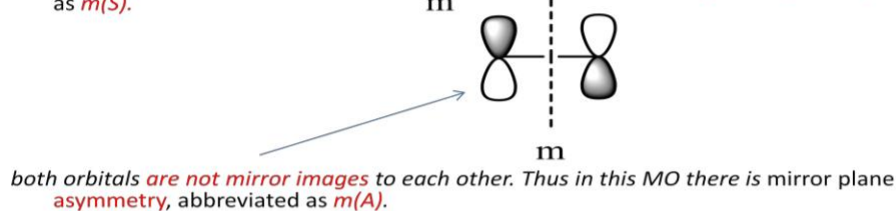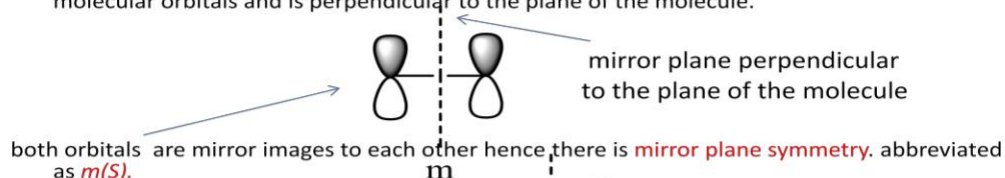

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- The two products have different stereochemistry and are diastereomers.

Woodward-Hoffmann rule

- Conservation of orbital symmetry requires the transformation of the MO of reactants into those of products, by following a reaction path along which the symmetry of these orbitals remains unchanged.

SYMMETRY IN π MOLECULAR ORBITAL

- A π molecular orbital possesses either mirror plane symmetry or centre of symmetry.
- Both symmetries are not present together in a given π molecular orbital.
- **m-Symmetry:**
- *Some molecular orbitals have the symmetry about the mirror plane (m) which bisects the molecular orbitals and is perpendicular to the plane of the molecule.*

mirror plane perpendicular to the plane of the molecule

both orbitals are mirror images to each other hence there is mirror plane symmetry. abbreviated as *m(S)*.

m

m

both orbitals are not mirror images to each other. Thus in this MO there is mirror plane asymmetry, abbreviated as *m(A)*.

- **C₂-Symmetry:**
- *The centre of symmetry is a point in the molecular axis from which if* lines are drawn on one side and extended an equal distance on the other side, will meet the same phases of the orbitals.
- both orbitals are symmetrical with respect to centre of the molecular axis.
- Thus in this MO there is centre of symmetry, abbreviated as *C₂(S)*.

Centre of the molecular axis
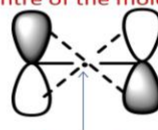
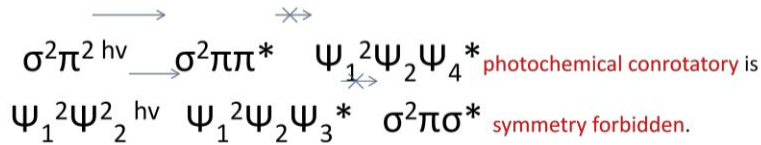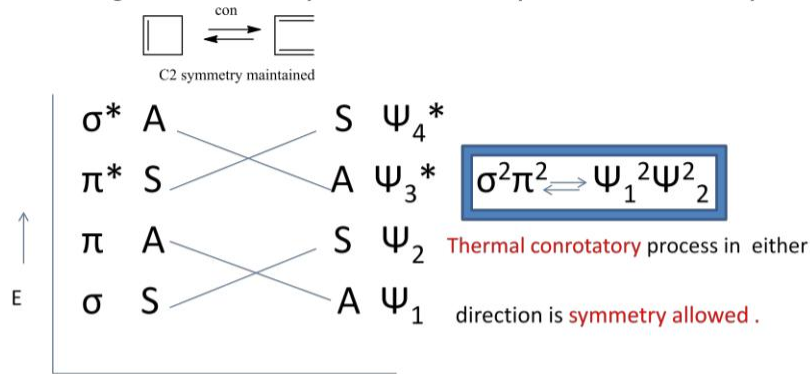both orbitals are asymmetrical with respect to centre of molecular axis. Thus they are *C₂(A)*.

C₂(A)
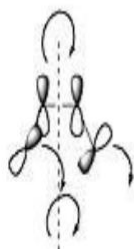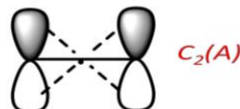
In a conrotatory process symmetry about the C₂ axis of rotation is maintained throughout the reaction.
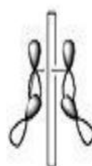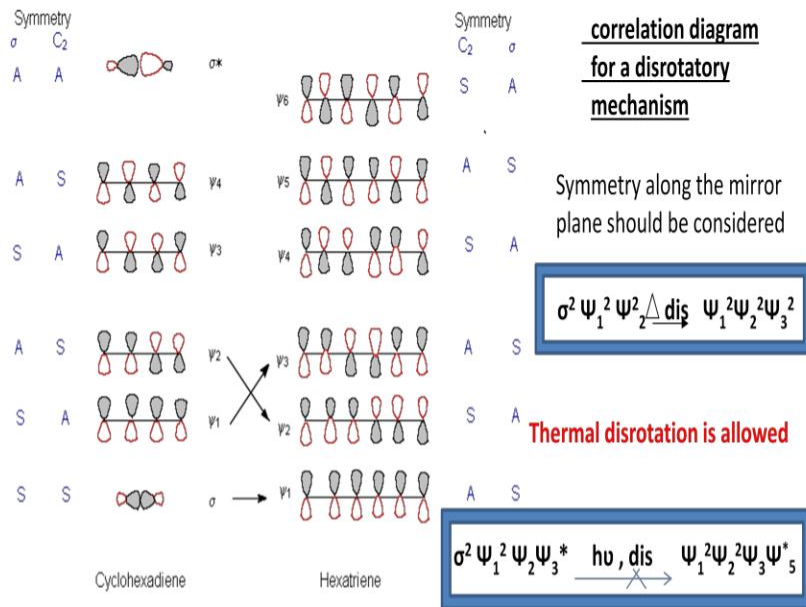
In a disrotatory process symmetry about the σᵥ reflection plane is maintained throughout the reaction.

-

Correlation diagram for conrotatory interconversion of cyclobutene-butadiene system

con

C2 symmetry maintained

E ↑

σ^*	A		S	Ψ_4^*
π^*	S		A	Ψ_3^*
π	A		S	Ψ_2
σ	S		A	Ψ_1

$$\boxed{\sigma^2\pi^2 \rightleftharpoons \Psi_1^2\Psi_2^2}$$

Thermal conrotatory process in either

direction is symmetry allowed .

$$\sigma^2\pi^2 \xrightarrow{hv} \sigma^2\pi\pi^* \quad \Psi_1^2\Psi_2\Psi_4^* \text{ photochemical conrotatory is}$$

$$\Psi_1^2\Psi_2^2 \xrightarrow{hv} \Psi_1^2\Psi_2\Psi_3^* \quad \sigma^2\pi\sigma^* \text{ symmetry forbidden.}$$

hexatriene - cyclohexadiene interconversion

Symmetry					Symmetry	
σ	C_2				C_2	σ
A	A	σ^*		Ψ_6	S	A
A	S	Ψ_4		Ψ_5	A	S
S	A	Ψ_3		Ψ_4	S	A
A	S	Ψ_2		Ψ_3	A	S
S	A	Ψ_1		Ψ_2	S	A
S	S	σ		Ψ_1	A	S

Cyclohexadiene   Hexatriene

correlation diagram for a disrotatory mechanism

Symmetry along the mirror plane should be considered

$$\boxed{\sigma^2 \Psi_1^2 \Psi_2^2 \xrightarrow{\triangle \text{ dis}} \Psi_1^2\Psi_2^2\Psi_3^2}$$

Thermal disrotation is allowed

$$\boxed{\sigma^2 \Psi_1^2 \Psi_2\Psi_3^* \xrightarrow{hv \text{ , dis}} \Psi_1^2\Psi_2^2\Psi_3\Psi_5^*}$$

The correlation of two σ-symmetric and one σ-antisymmetric orbitals for the disrotatory process follows from the same kind of analysis. Here the conrotatory opening is forbidden and the disrotatory is allowed.

$$\boxed{\sigma^2 \Psi_1^2 \Psi_2\Psi_3^* \xrightarrow{\text{con , hv}} \Psi_1^2\Psi_2^2\Psi_3\Psi_4^*}$$

photochemical conrotation is allowed
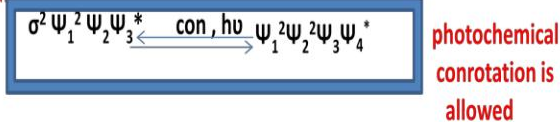
Application of PMO method to pericyclic reactions- Developed by M.J.S. Dewar.

 Huckel's rule of aromaticity states that a monocyclic planar conjugated system with 4n+2 pi e⁻ is aromatic & consequently stable in the G.S. A sys with 4n pi e⁻ is unstable & is reffered to as antiaromatic.

These rules are reversed in pre of a node in the array of atomic orbitals. Thus a sys with 4n+2 pi e⁻ & a node is antiaromatic. While a sys with 4n pi e⁻ & a node is aromatic, hence stable in G.S.

Thermal reactions take place via aromatic T.S.

Photochemical reactions take place via antiaromatic T.S.

consider a cyclic array of atomic orbitals representing those orbitals which undergo change in the T.S. and assign signs to the wave functions in the best manner to overlap.
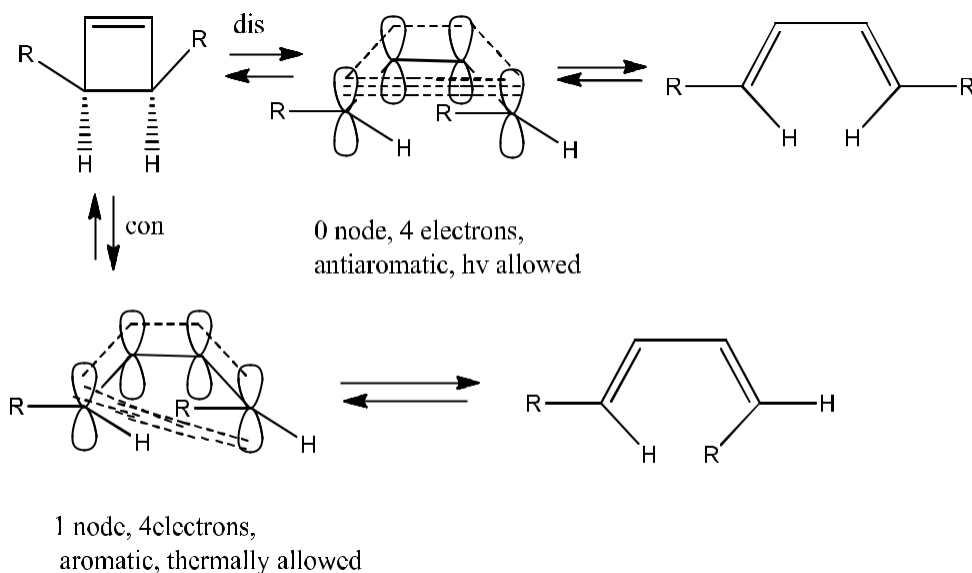
Then the no. of nodes in the array and the no. of e- involved are counted.

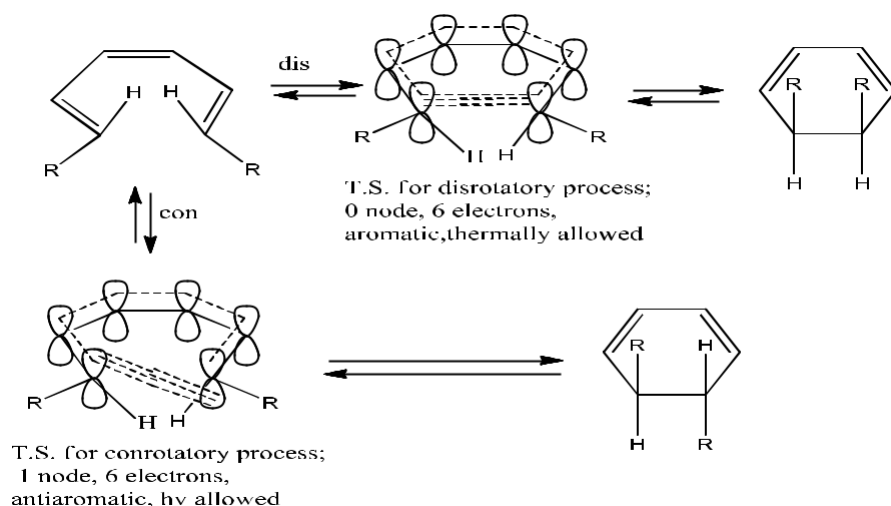Next draw a line to connect the reactant orbitals: by conrotatory and disrotatory processes.

The transition state for butadiene is:

Conrotatory Connection   Disrotatory Connection

One Node = Mobius   No Nodes = Huckel
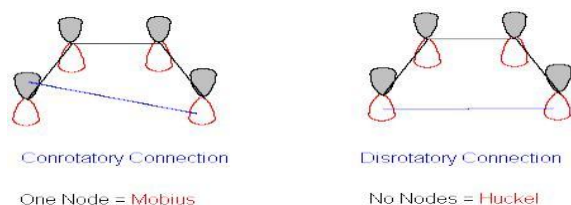
conrotatory and disrotatory processes for cyclobutadiene ⇌ 1,3-butadiene system

0 node, 4 electrons,
antiaromatic, hv allowed

1 node, 4electrons,
aromatic, thermally allowed

conrotatory and disrotatory processes for cis-1,3,5-hexatriene ⇄ cyclohexadiene

**T.S. for disrotatory process;
0 node, 6 electrons,
aromatic, thermally allowed**

**T.S. for conrotatory process;
1 node, 6 electrons,
antiaromatic, hv allowed**

Claisen rearrangement

Discovered in 1912 by Rainer Ludwig Claisen. the Claisen rearrangement is the first recorded example of a [3,3]-sigmatropic rearrangement.This rearrangement is a useful carbon-carbon bond-forming reaction. An example of Claisen rearrangement is the [3,3] rearrangement of an allyl vinyl ether, which upon heating yields a γ,δ-unsaturated carbonyl. The formation of a carbonyl group makes this reaction, unlike other sigmatropic rearrangements, inherently irreversible.

Claisen Rearrangement
of Allyl Vinyl Ether
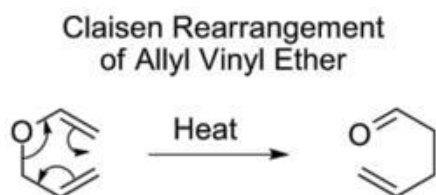
Aromatic Claisen rearrangement

The **ortho-Claisen rearrangement** involves the [3,3] shift of an allyl phenyl ether to an intermediate which quickly tautomerizes to an ortho-substituted phenol.

Aromatic Claisen Rearrangement
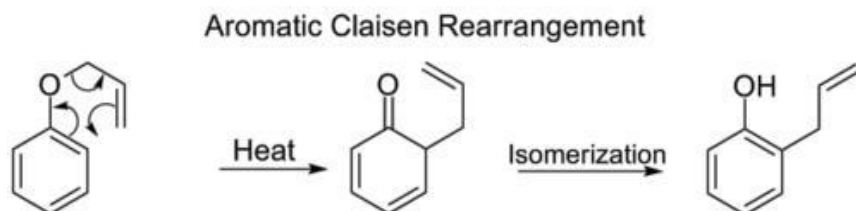
When both the ortho positions on the benzene ring are blocked, a second ortho-Claisen rearrangement will occur. This **para-Claisen rearrangement** ends with the tautomerization
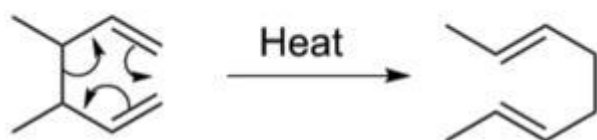
to a tri-substituted phenol.

Para-Claisen Rearrangement
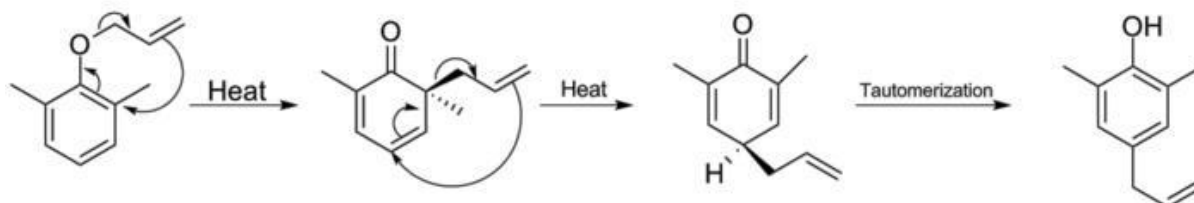
Cope rearrangement

The **Cope rearrangement** is an extensively studied organic reaction involving the [3,3] sigmatropic rearrangement of 1,5-dienes.[13][14][15] It was developed by Arthur C. Cope. For example, 3,4-dimethyl-1,5-hexadiene heated to 300 °C yields 2,6-octadiene.
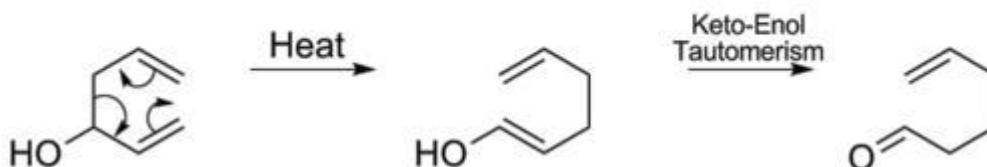
Cope Rearrangement

Oxy-Cope rearrangement

In the **Oxy-Cope rearrangement**, a hydroxyl group is added at C3 forming an enal or enone after Keto-enol tautomerism of the intermediate enol

Oxy-Cope Rearrangement


Mislow–Evans rearrangement

It is named after Kurt Mislow and David A. Evans who discovered this reaction in 1971. The reaction allows the formation of allylic alcohols from allylic sulfoxides in a 2,3-sigmatropic rearrangement.

The reaction is a powerful way to create particular stereoisomers of the alcohol since it is highly diastereoselective and the chirality at the sulphur atom can be transmitted to the carbon next to the oxygen in the product.
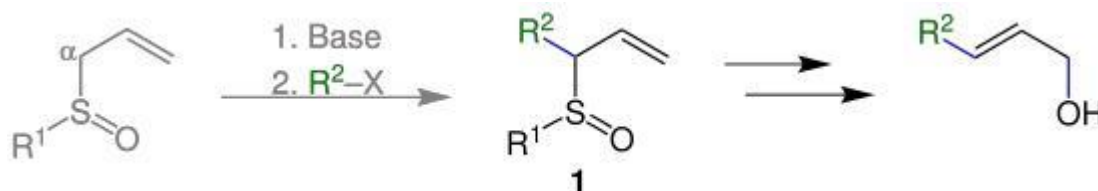
The sulfoxide **1** reagent can be generated easily and enantioselectively from the corresponding sulfide by an oxidation reaction. In this reaction various organic groups can be used, R^1 = alkyl, allyl and R^2 = alkyl, aryl or benzyl
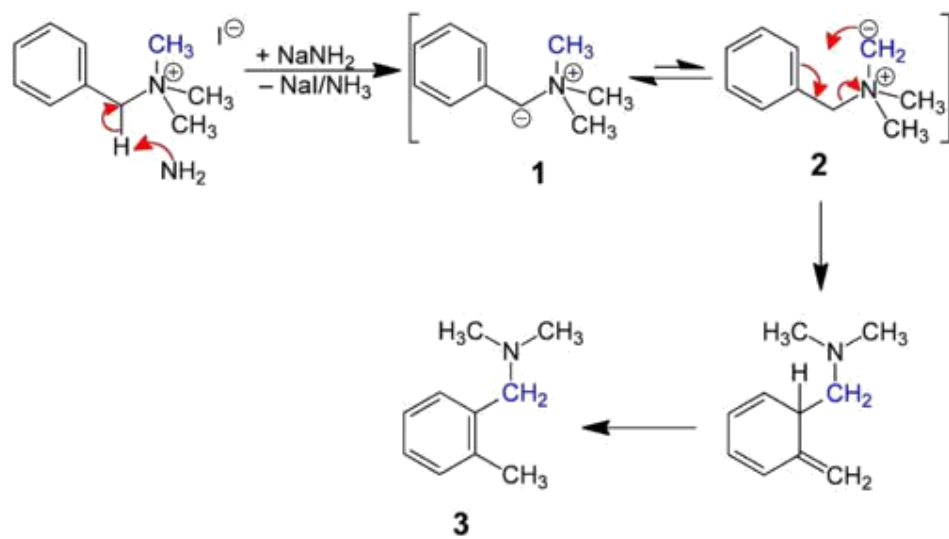
Mechanism
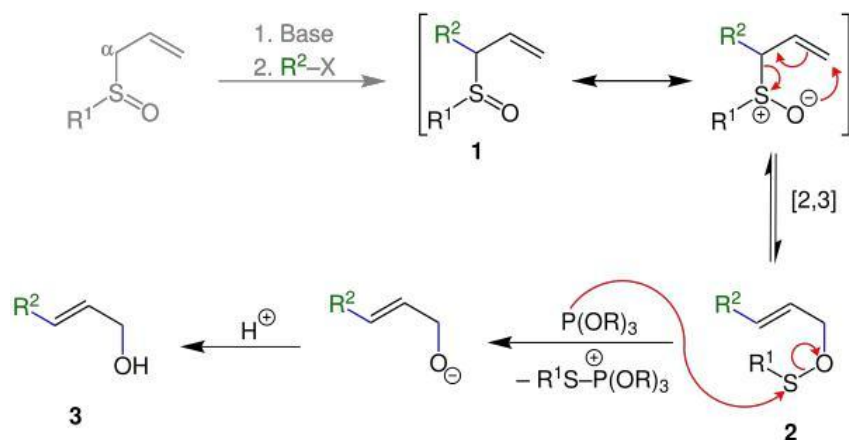
The mechanism starts with an allylic sulfoxide **1** which rearranges under heat to a sulfenate ester **2**. This can be cleaved using a thiophile, which leaves the allylic alcohol **3** as the product.

Sommelet–Hauser rearrangement

is a rearrangement   reaction of certain benzyl quaternary ammonium salts.The reagent is sodium amide or   another alkali metal amide and   the reaction   product a N,N-dialkylbenzylamine with a new alkyl group in the aromatic ortho position. For example, benzyltrimethylammonium iodide, $[(C_6H_5CH_2)N(CH_3)_3]I$,   rearranges in the   presence of sodium amide to yield the o-methyl derivative of N,N-dimethylbenzylamine
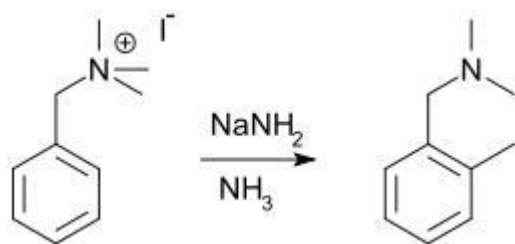
The benzylic methylene proton is acidic and deprotonation takes place to produce the benzylic ylide (**1**). This ylide is in equilibrium with a second ylide that is formed by deprotonation of one of the ammonium methyl groups (**2**). Though the second ylide is present in much smaller amounts, it undergoes a 2,3-sigmatropic rearrangement and subsequent aromatization to form the final product (**3**).