PERICYCLIC REACTIONS

(PHARMACEUTICAL. CHEMISTRY)

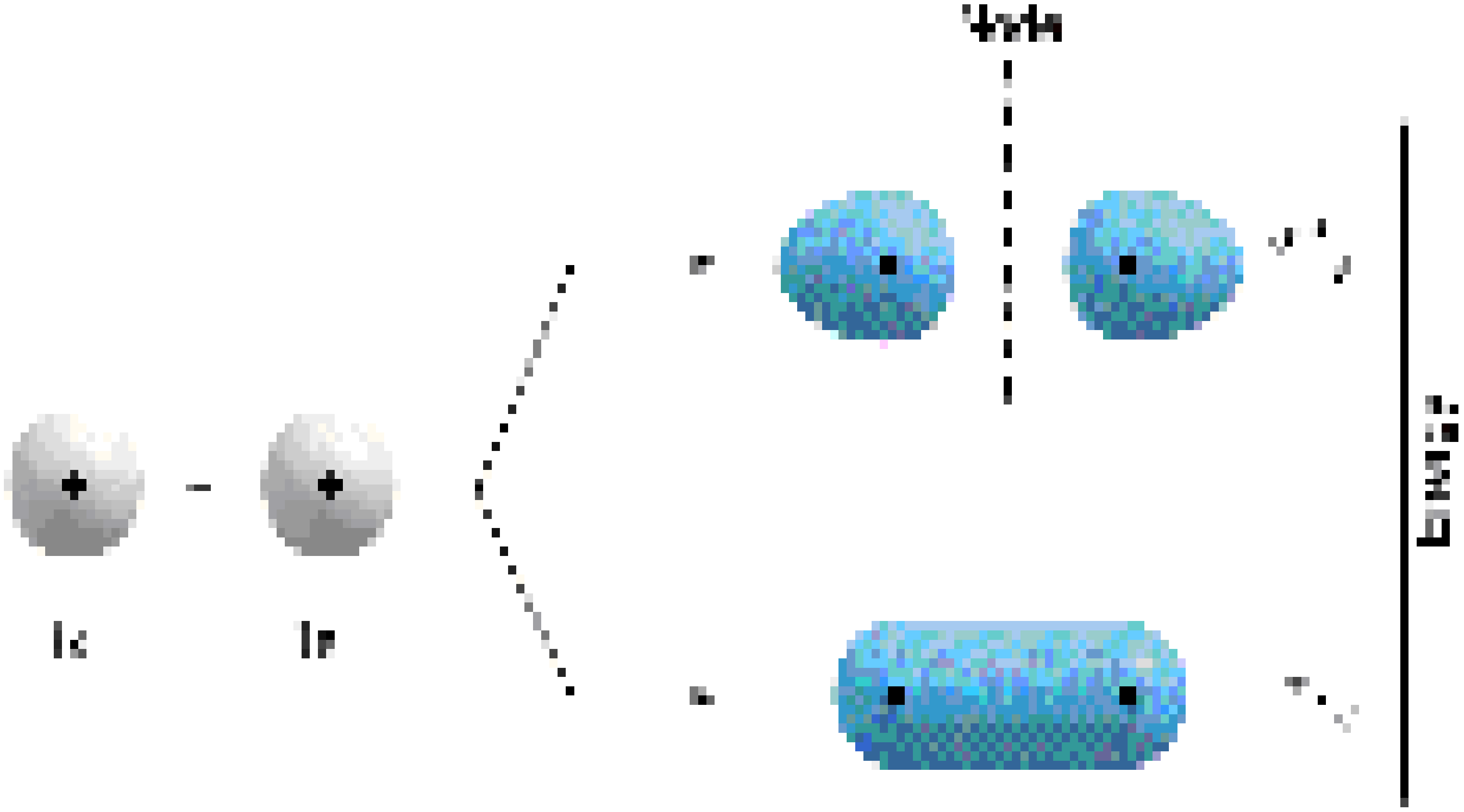
CONTENTS

Introduction

- Pericyclic reactions are the reactions that occur by cyclic shift of electrons.
- These reactions are stereospecific and stereo selective.
- The energy of activation is supplied by heat(thermal method) or by UV light(photo induction)

Molecular Orbitals (LCAO Method)

- Quantum mechanics shows that linear combination of a 2 atomic orbitals gives not one, but two combination and hence two molecular orbitals.
- A bonding orbital more stable than the component atomic orbitals.
- Anti bonding orbital less stable than the component atomic orbitals.
- In addition, orbitals of a third kind non bonding orbitals; electrons in these orbitals- unshared pairs.



H Atomic orbitals

H_2 Molecular orbitals

FMO METHOD

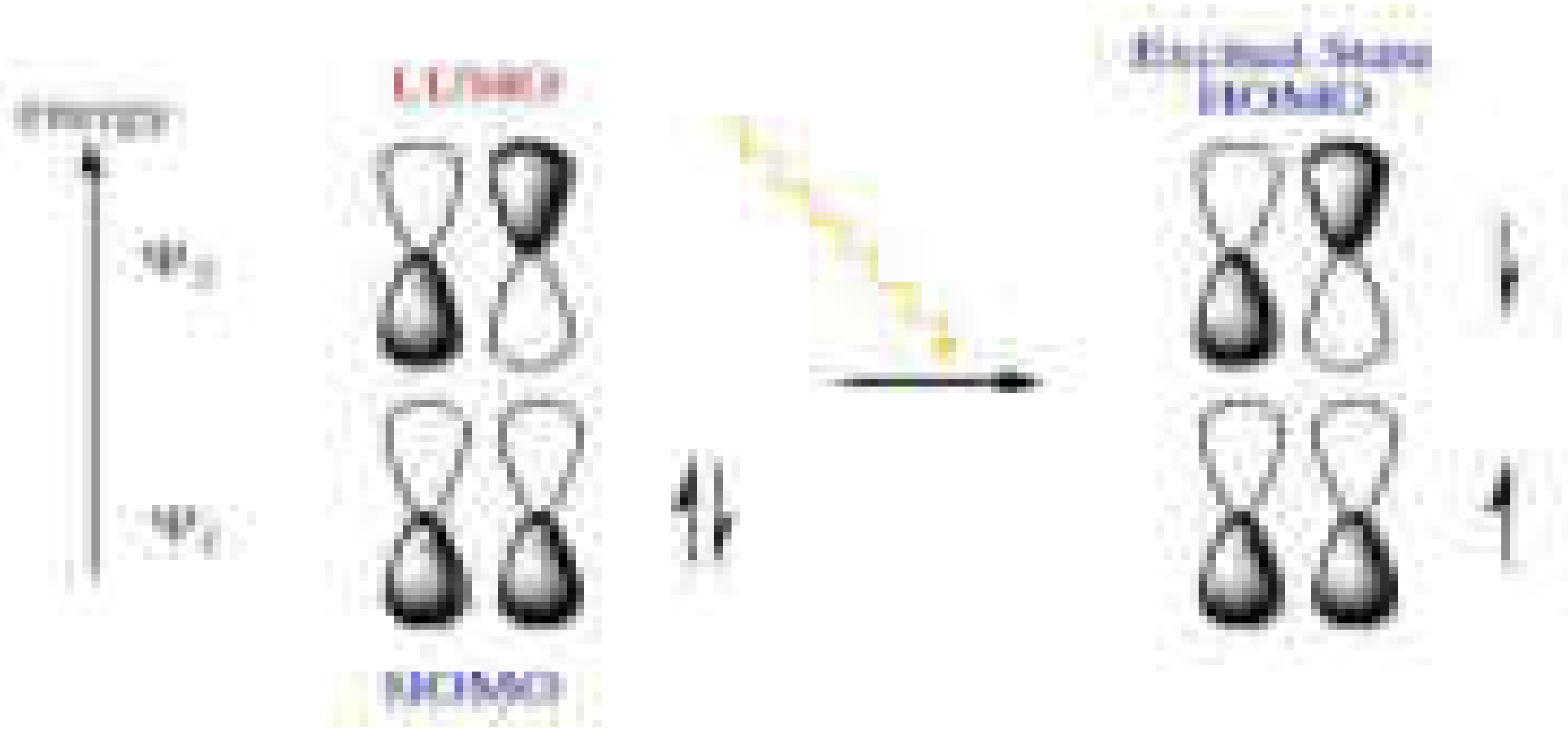
- *Principle of the conservation of the orbital symmetry in the concerted reactions.*

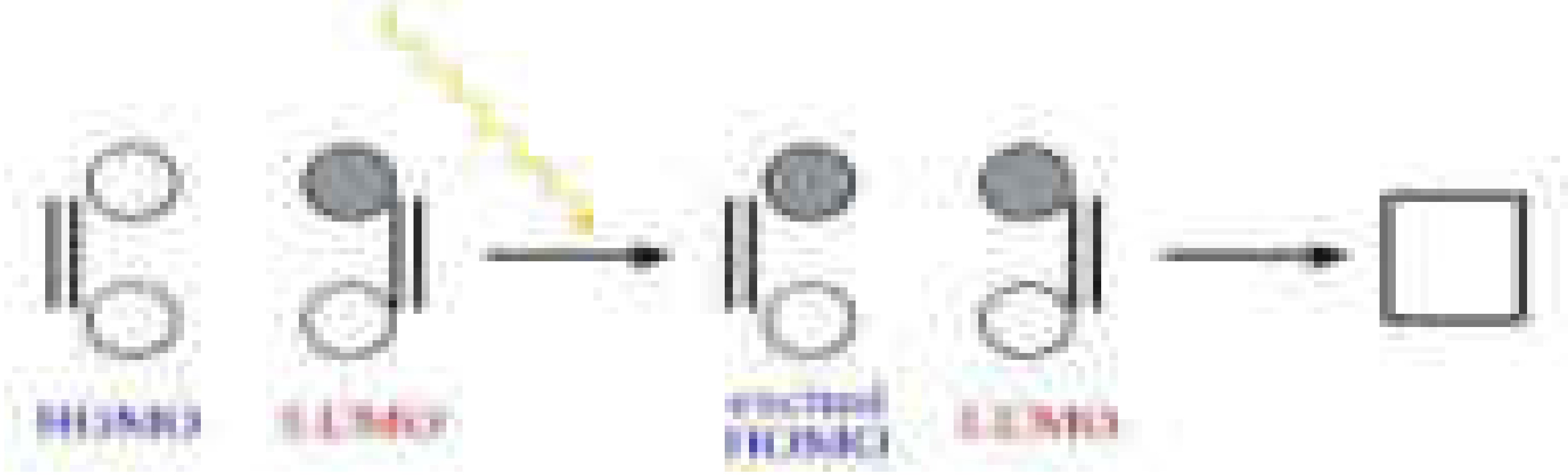
- Symmetry allowed process
- Symmetry forbidden process.

- The energy of transition state of symmetry allowed process is lower than the symmetry forbidden process

INTERACTION BETWEEN MOLECULAR ORBITALS

- Reaction takes place when the highest molecular orbital of one reactant interacts with the lowest energy molecular orbitals of other reactant.
- The orbitals that interact are called **frontier molecular orbitals** for reaction


energy
LUMO
Excited State HOMO
Ψ_2
Ψ_1
HOMO


HOMO
LUMO
excited HOMO
LUMO

HUCKLE MOBIUS METHOD

- ***Huckle system:*** i.e.,In the absence of node.

  (4n+2)pi electrons : aromatic; stable in ground state.

  (4n) pi electrons : anti aromatic; unstable in ground state.

- ***Mobius system:*** i.e., In the presence of node.

  (4n)pi electrons :aromatic; stable in ground state.

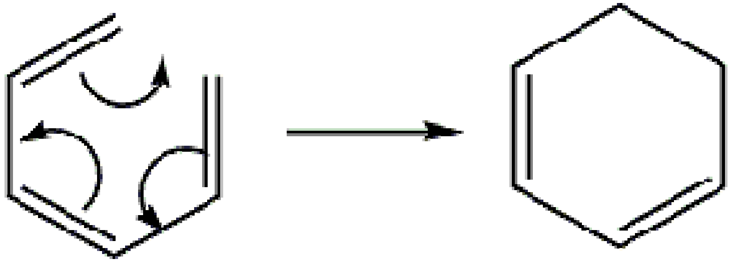
  (4n+2) pi electrons: anti aromatic; unstable in ground state.

Types of pericyclic reactions

- Electrocyclic reactions
- Cyclo addition reactions
- Sigmatropic reactions

ELECTROCYCLIC REACTIONS

- Under the influence of heat or light, the conjugated polyene undergoes isomerisation to form a cyclic compound with a single bond between terminal carbons of original conjugated system.

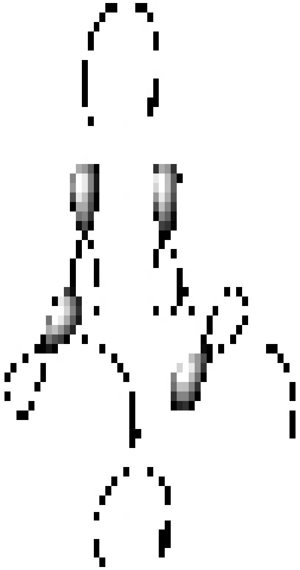


- Such interconversions are called **electrocyclic reactions.**

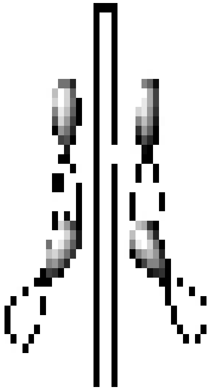
STEREOCHEMISTRY

- These reactions are stereospecific and stereochemistry of products depends if reaction is thermal or photochemical.

- *Two types of rotation*.
  - Conrotatory motion
  - Disrotatory motion



In a conrotatory process symmetry about the C_2 axis of rotation is maintained throughout the reaction.



In a disrotatory process symmetry about the σ_v reflection plane is maintained throughout the reaction.

CYCLISATION OF 4n SYSTEM

- **1,3 butadiene:** the cyclisation can be thermal as well as photo chemical reaction.

- ***Thermal reaction:***

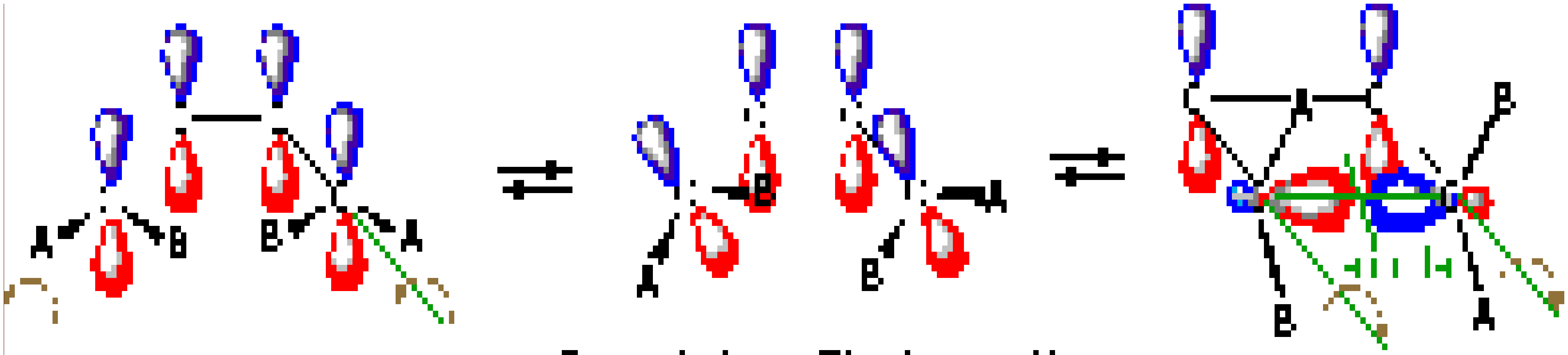
- HOMO of conjugated diene is Ψ_2. Bond formation requires overlap.
- In these case,overlap of lobes C_1 and C_4 of diene.
- Thus for a new sigma bond to form rotation must be conrotatory.

Photo induced cyclisation

- On absorption of light, butadiene is converted into the excited state in which one electron from Ψ_2 has been raised to Ψ_3 .

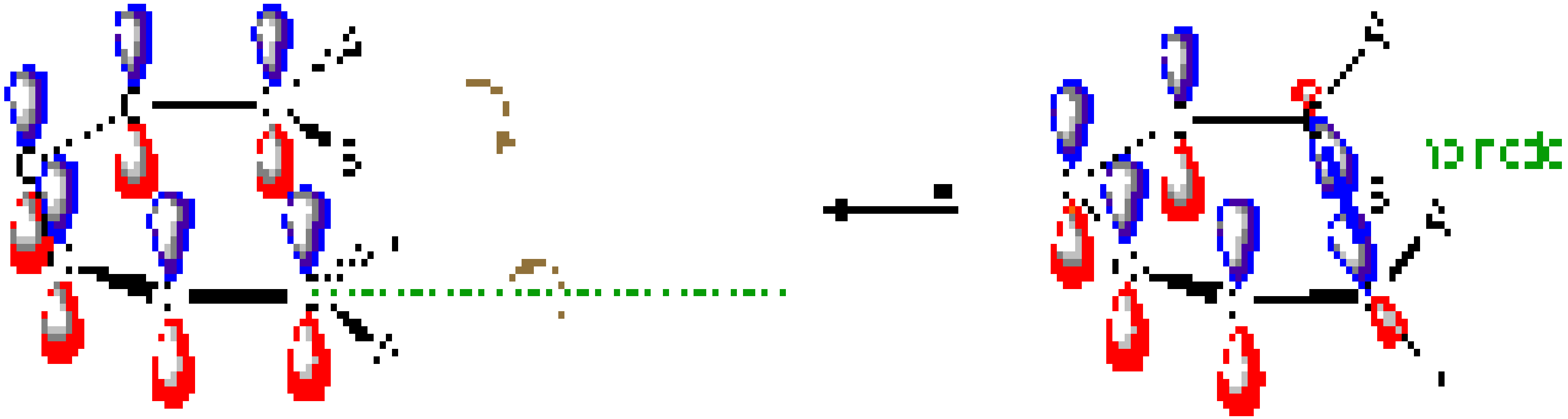
- So, disrotatory motion brings lobes of same phase together and stereochemistry is reversed.

- Where as conrotatory motion brings orbitals of opposite phase together. Interaction is ***antibonding***



Conrotatory Electrocyclic
ring closing & opening

4 electrons



Disrotatory Electrocyclic
ring closed & opened

6 electrons

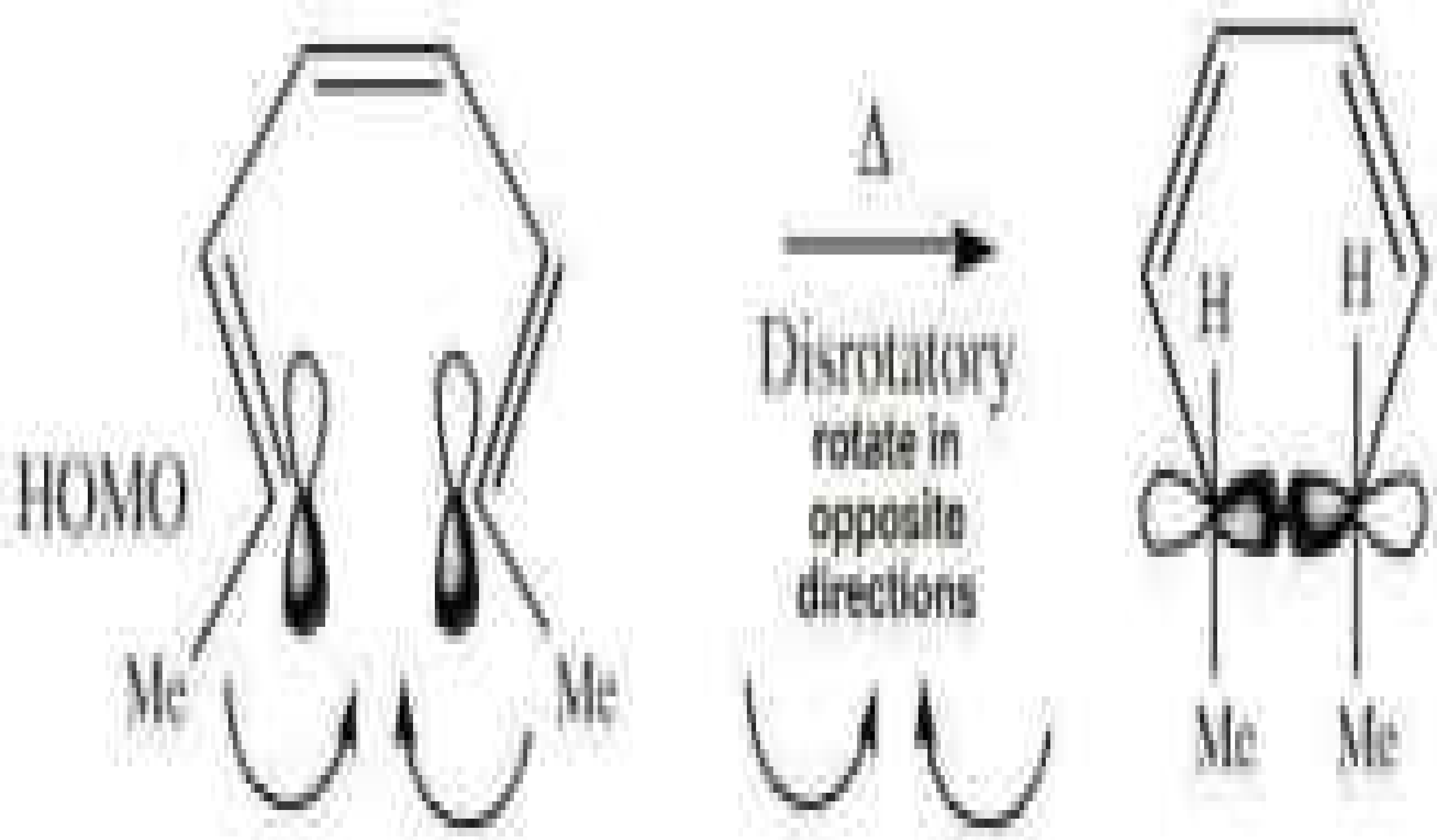
Cyclisation of (4n+2)π system

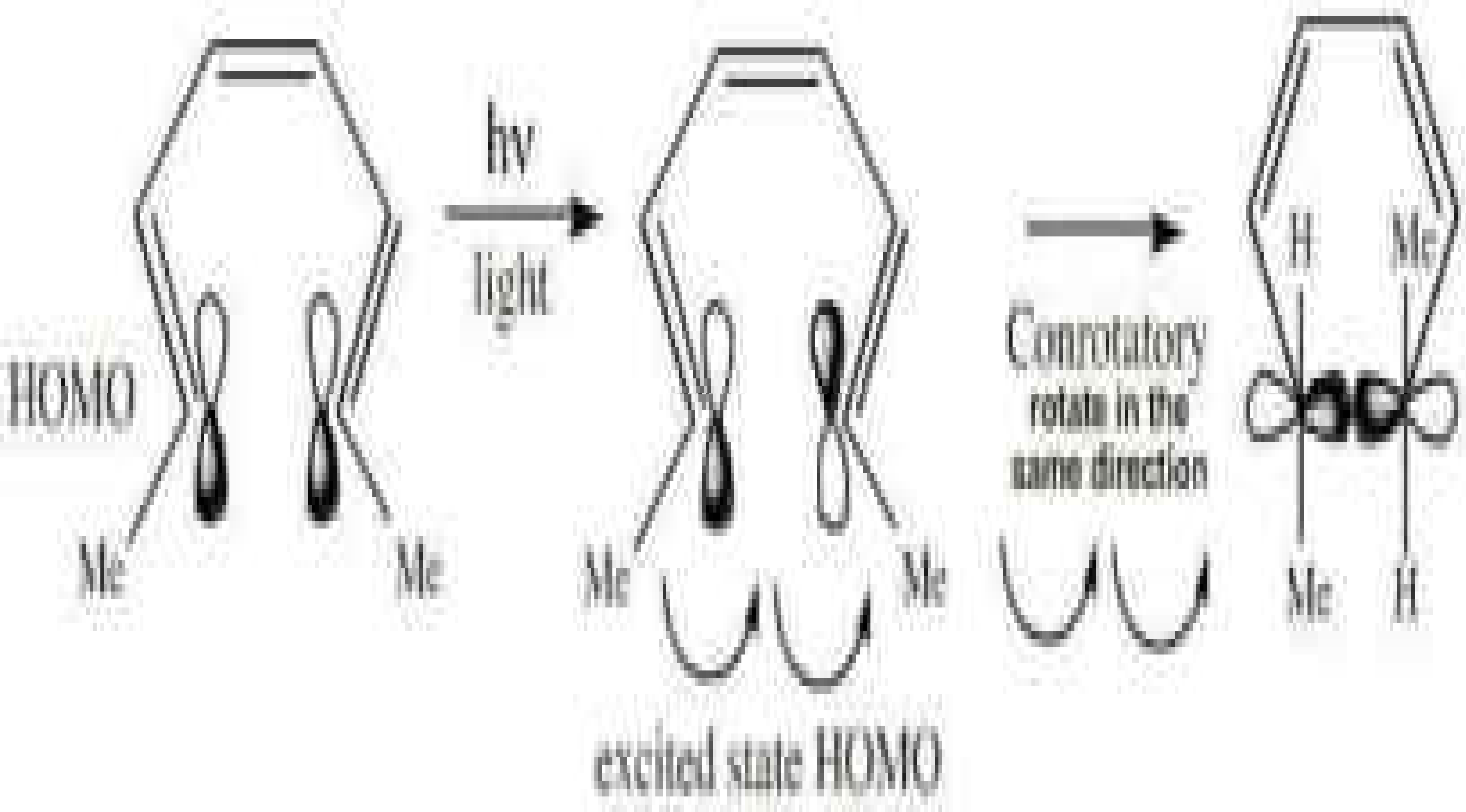
- ***Thermal induced :***

  1,3,5 hexatriene is a (4n+2)π system and Ψ_3 is homo in ground state which has m- symmetry.

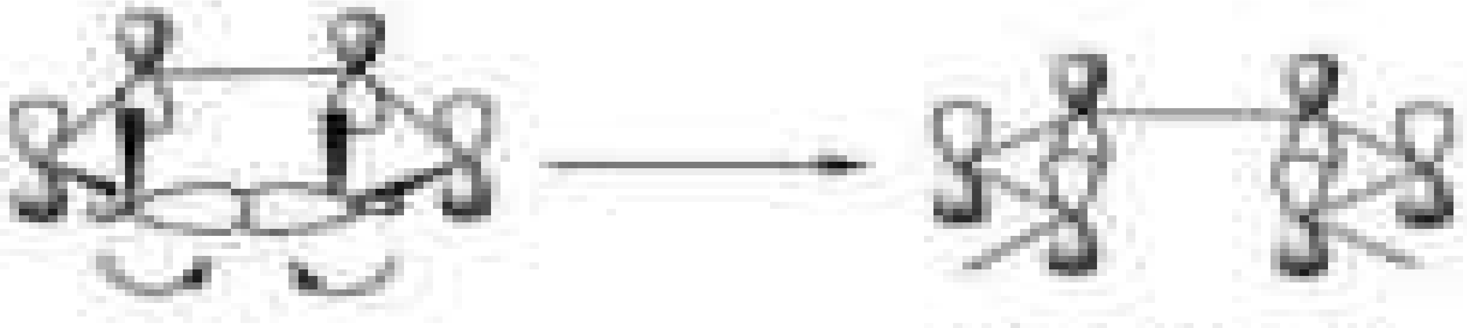
- ***Photochemical induced :***

  when an electron of 1,3,5 hexatriene is promoted by absorption of light, Ψ_4 becomes the excited HOMO of C_2 system. Thus the p-orbitals are out of phase.


HOMO
Me
Me
Δ
Disrotatory
rotate in
opposite
directions
H
H
Me
Me


HOMO
Me
Me
hν
light
Me
Me
excited state HOMO
Conrotatory
rotate in the
same direction
H
Me
Me
H

RING OPENING



HOMO of hexatriene

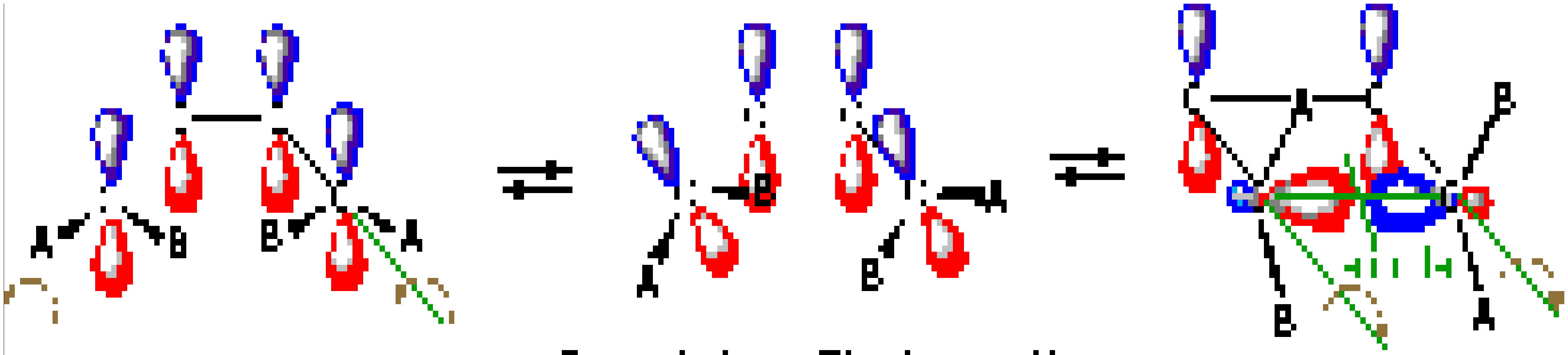
HOMO of butadiene

SELECTION RULE FOR ELECTROCYCLIC REACTIONS

No. of electrons	***Mode of activation***	***Symmetry allowed motion***
4n	Thermal photochemical	Conrotatory disrotatory
4n+2	Thermal photochemical	Disrotatory conrotatory

HUCKEL MOBIUS METHOD

No.of electrons	*No. of nodes*	*Aromaticity*	*Thermally allowed*	*hv allowed*
4n	zero	Anti aromatic	-	Disrotatory
4n	one	aromatic	conrotatory	-
4n+2	zero	Aromatic	Disrotatory	-
4n+2	One	Anti aromatic	-	conrotatory



Conrotatory Electrocyclic
Ring Closing & Opening

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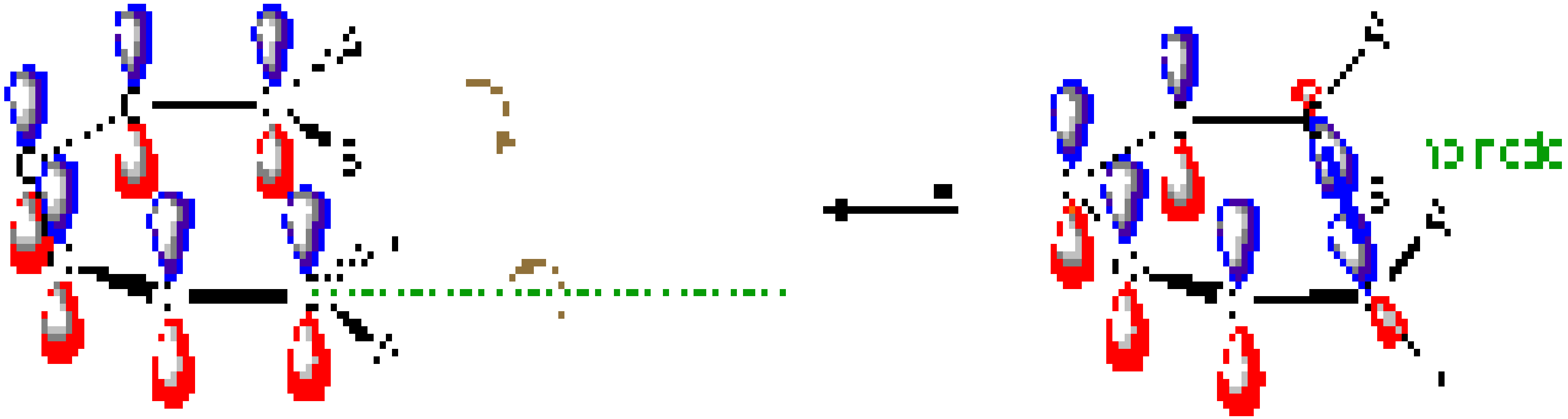

Disrotatory Electrocyclic
Ring Closed & Opened

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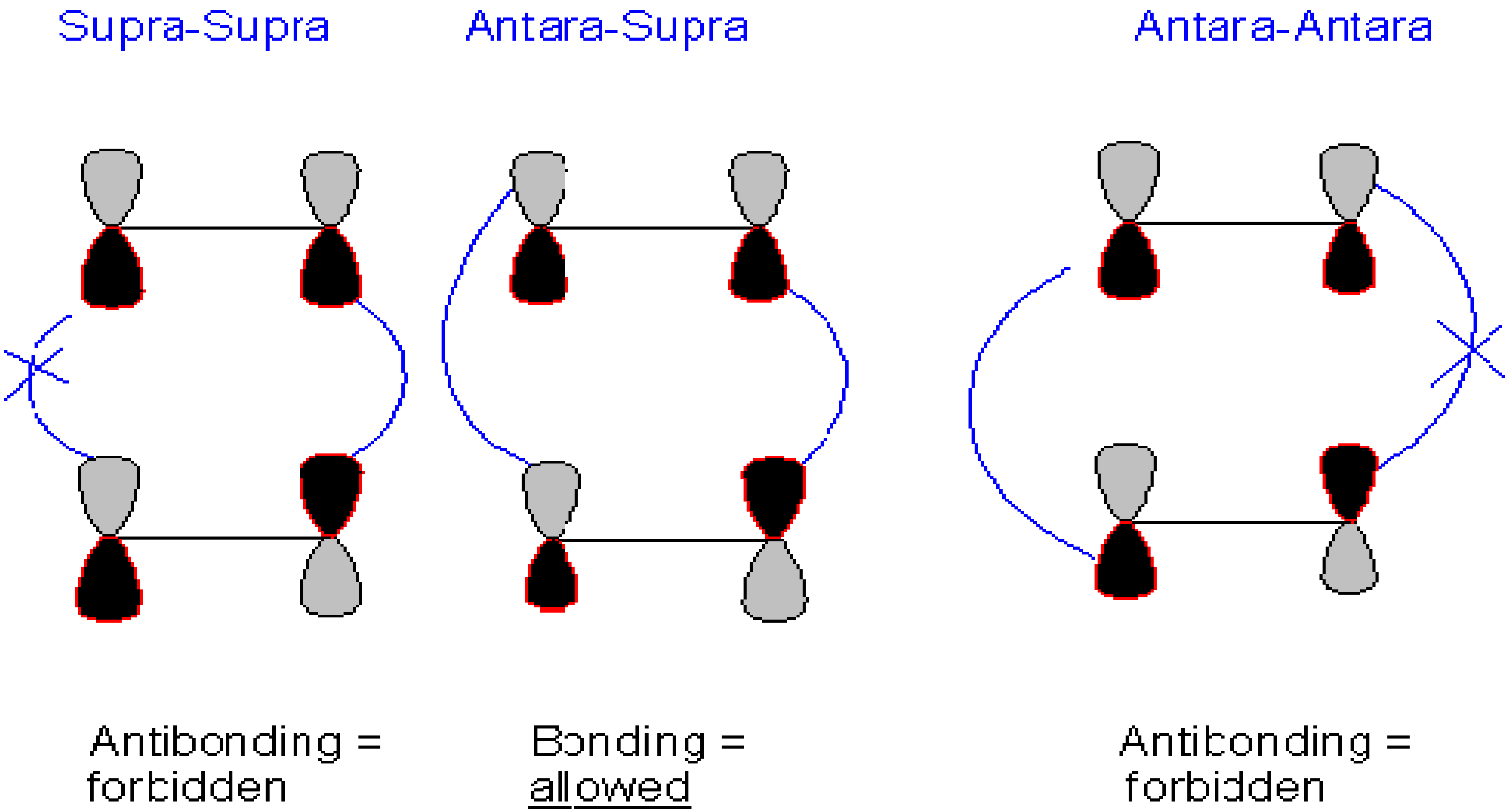
CYCLO ADDITION REACTIONS

- It is a reaction in which two unsaturated molecules combine to form a cyclic compound,with pi electrons being used to form two new sigma bonds.
- The Diel’s-Alder Reaction is a (4+2) cyclo addition reaction,since it involves a system of 4 π electrons and a 2 π electrons.

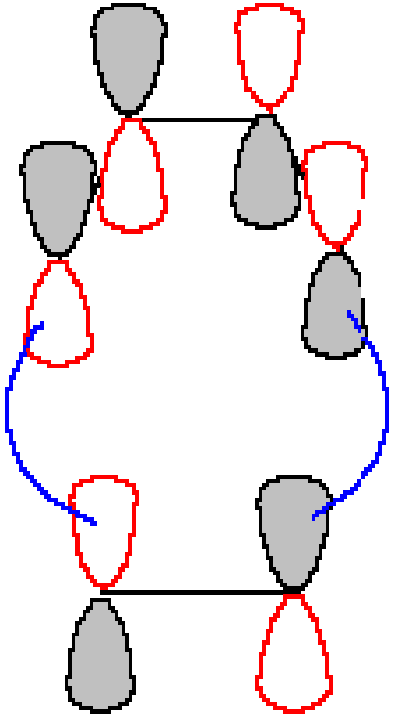
STEREOCHEMISTRY OF DIEL'S ALDER REACTION

- The diene must be in cisoid conformation.
- The dienophile addition is ***syn***; thus the reaction is a concerted one, i.e., both new bonds are formed in the same transition state.
- Takes place in ***endo***, rather than ***exo.***

- Supra facial addition
- Anthra facial addition

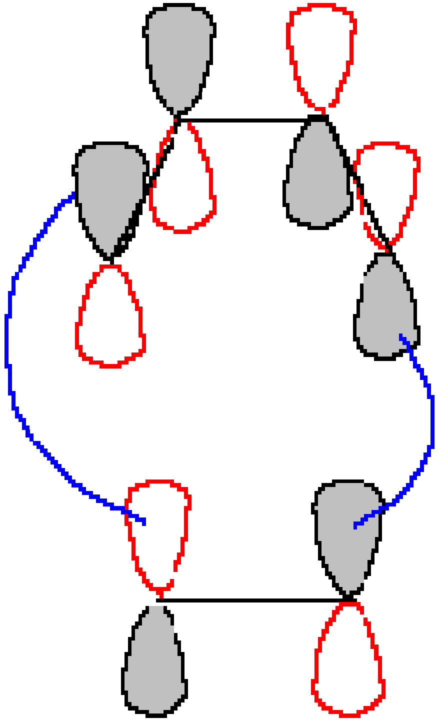


Supra-Supra



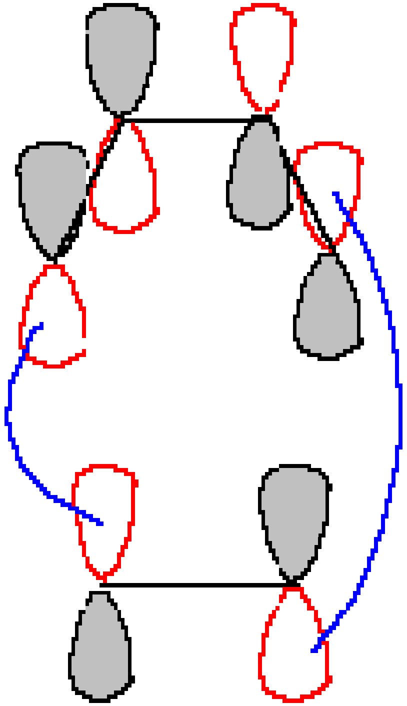
Bonding =
Allowed

Antara-Supra



Antibonding =
forbidden

Antara-Antara



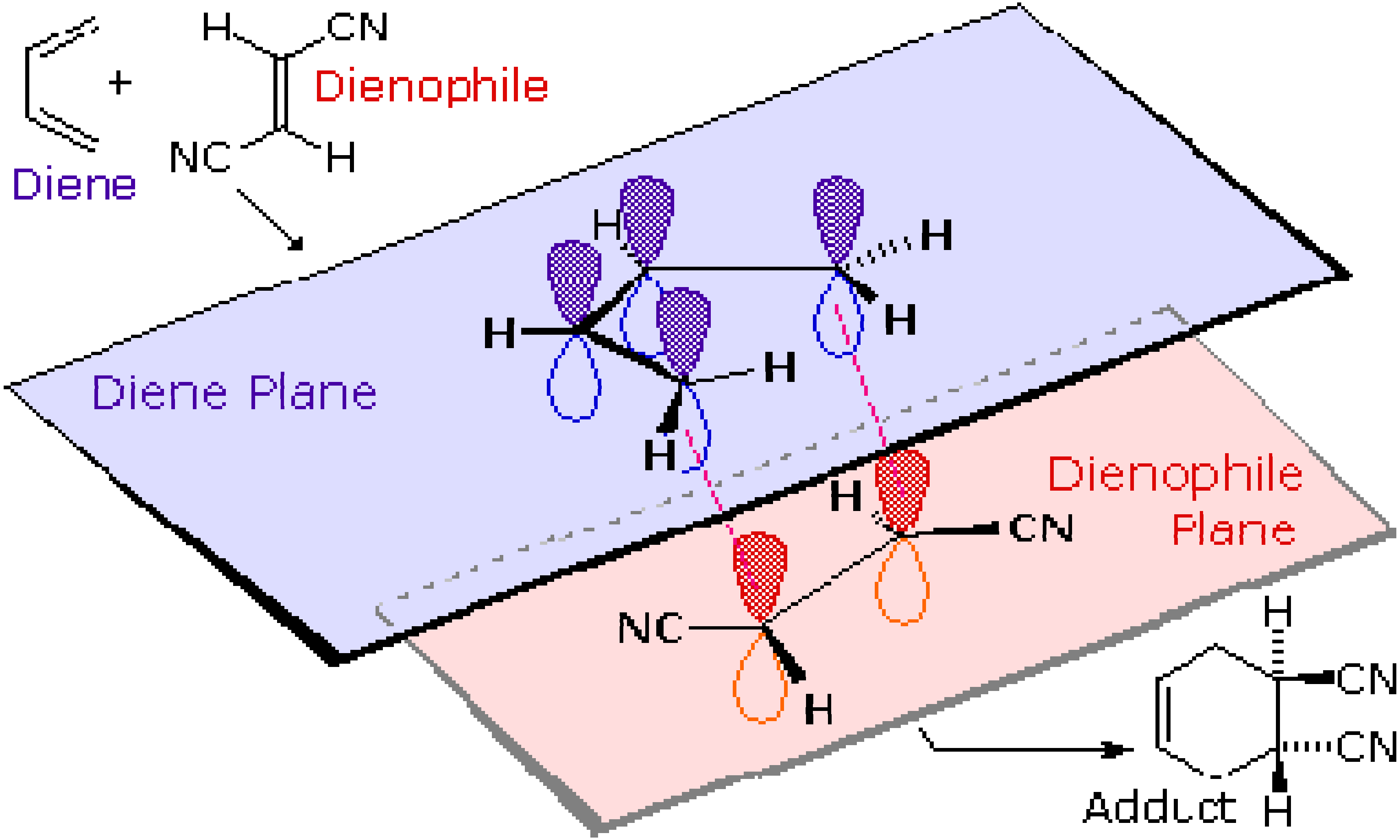
Bonding =
Allowed

Thermal induced:

***(4+2)cycloaddition**:*

eg: 1,3butadiene and ethylene.

- There are two combinations i.e., overlap of HOMO of butadiene (Ψ_2) with LUMO of ethylene(π^*).
- And overlap of HUMO of ethylene(π) with the LUMO of butadiene (Ψ_3).


Diene
+
H
CN
NC
H
Dienophile
Diene Plane
H
H
H
H
H
H
H
Dienophile
Plane
H
CN
NC
H
H
CN
CN
H
Adduct

(2+2) CYCLO ADDITION REACTIONS

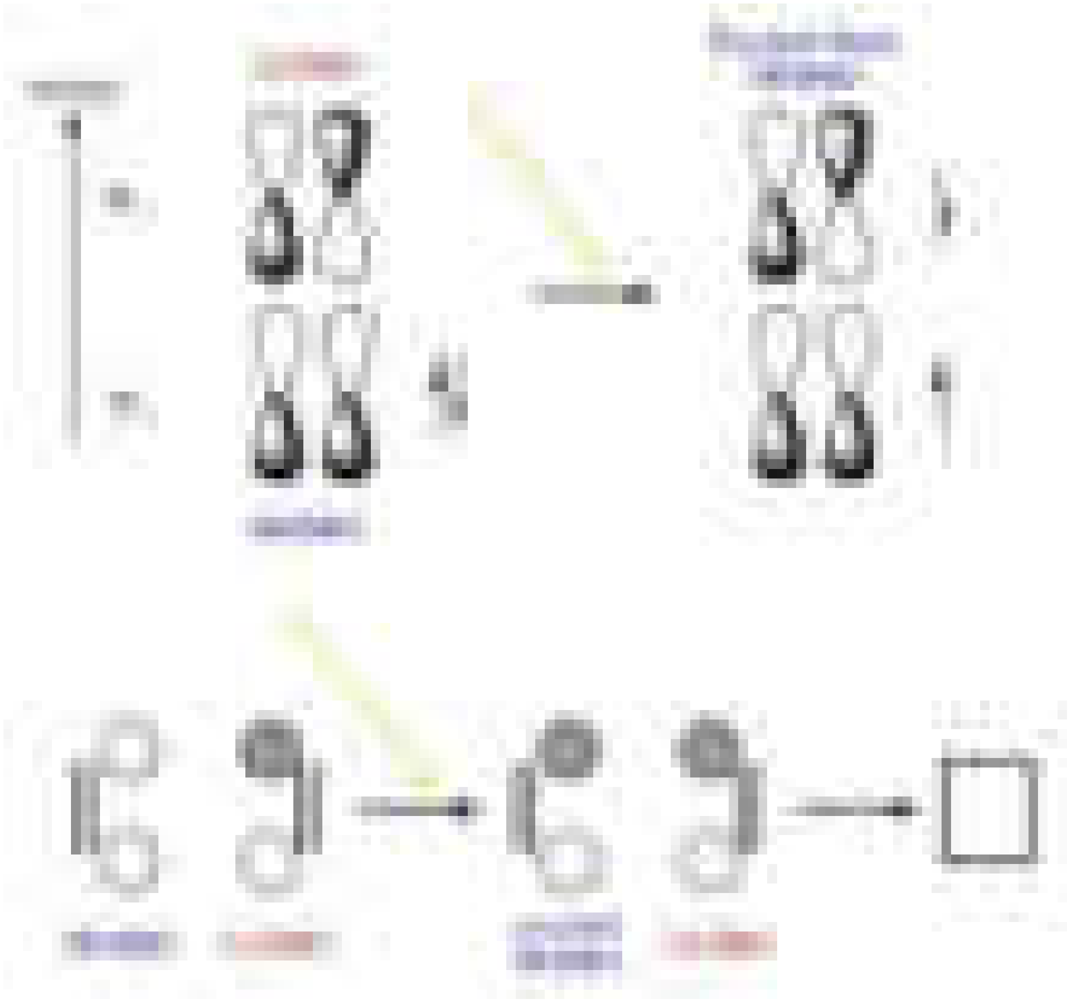
- Dimerisation of ethylene.
- This involves the overlap of HOMO π of one molecule with LUMO π* of other.
- Interaction is antibonding and concerted reaction does not occur.

PHOTOCHEMICAL INDUCED

- ***(2+2) CYCLO ADDITION***
  - These are symmetry allowed process.
  - Overlap of the HOMO(π*) of an exited molecule with the LUMO (π*) of a ground state molecule

- ***(4+2) CYCLO ADDITION***
  - These are ***symmetry forbidden*** process.

  In these HOMO is Ψ_3,which has m symmetry and this molecular orbitals cannot overlap with overlap of LUMO of ethylene which has C_2 symmetry.

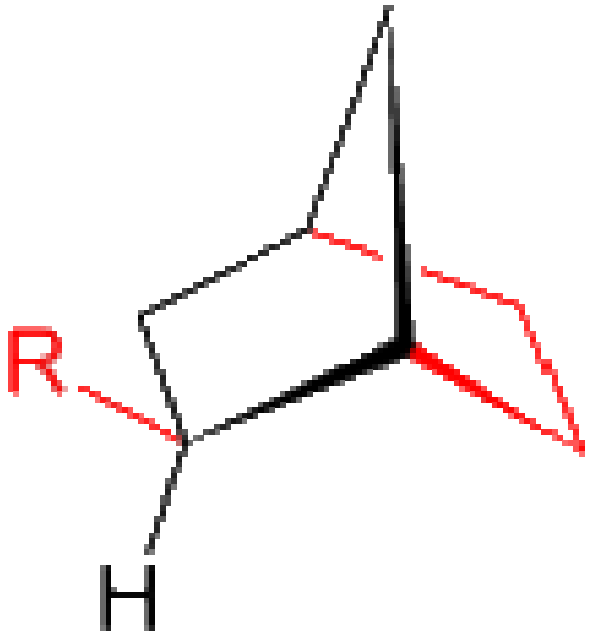


SELECTION RULE FOR CYCLOADDITION REACTIONS

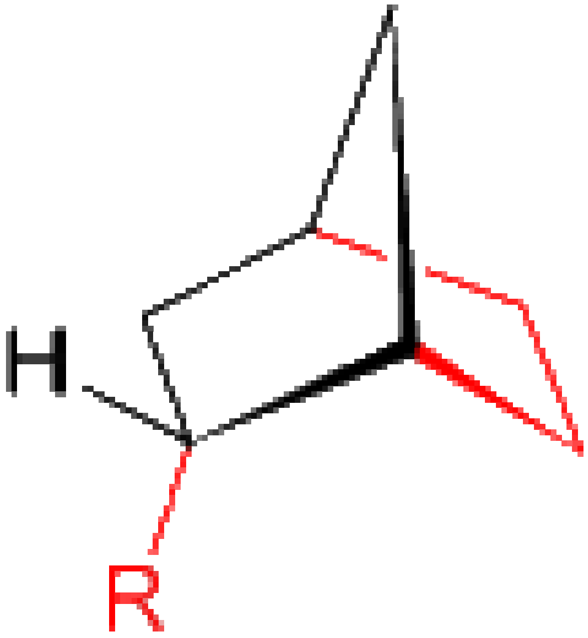
No. of electrons	Mode of activation	Allowed stereochemistry
4n	photochemical	Supra-supra
4n+2	thermal	supra-supra

ENDO-EXO STEREOCHEMISTRY

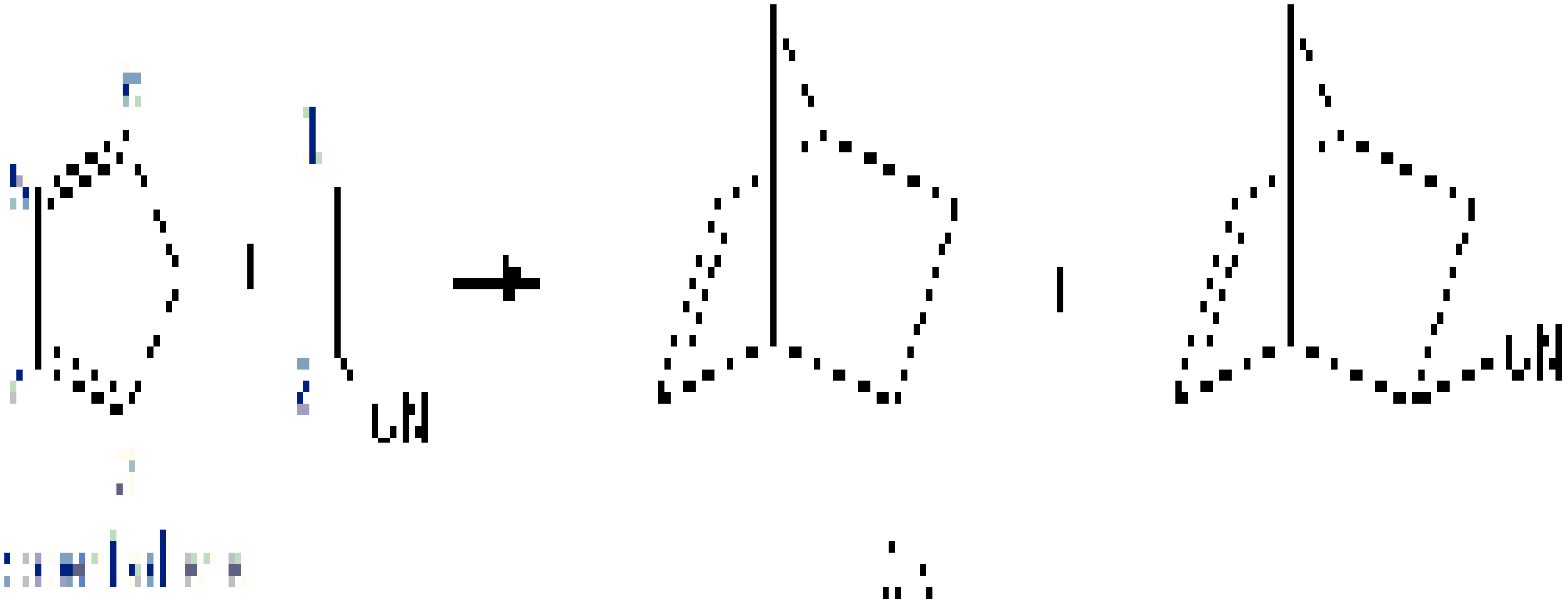
- Cyclic dienes are reactive in Diel's-Alder reaction because the two double bonds are held in ***cis*** conformation in 5 or 6 membered rings.
- *Endo orientation* : substituents project in to the cavity.
- *Exo orientation*: substituents project out of the cavity.
- Endo product is more stable than the exo product.



Exo



Endo



cyclopentadiene

endo product

exo product

not formed

HUCKLE MOBIUS METHOD

No.of electrons	No. of modes	Aromaticity	Thermally allowed	hv allowed
4n	zero	Anti aromatic	-	s-s a-a
4n	one	Aromatic	s-a a-s	-
4n+2	zero	Aromatic	s-s a-a	-
4n+2	one	Anti aromatic	-	s-a a-s

SIGMATROPIC REARRANGEMENT

- It is a concerted type of reaction, in which a group migrates with its sigma bond within a pi framework an ene (or) polyene.

- The migration is accompanied by a shift in pi bonds.

- ***Numbering of alkenyl chain..***

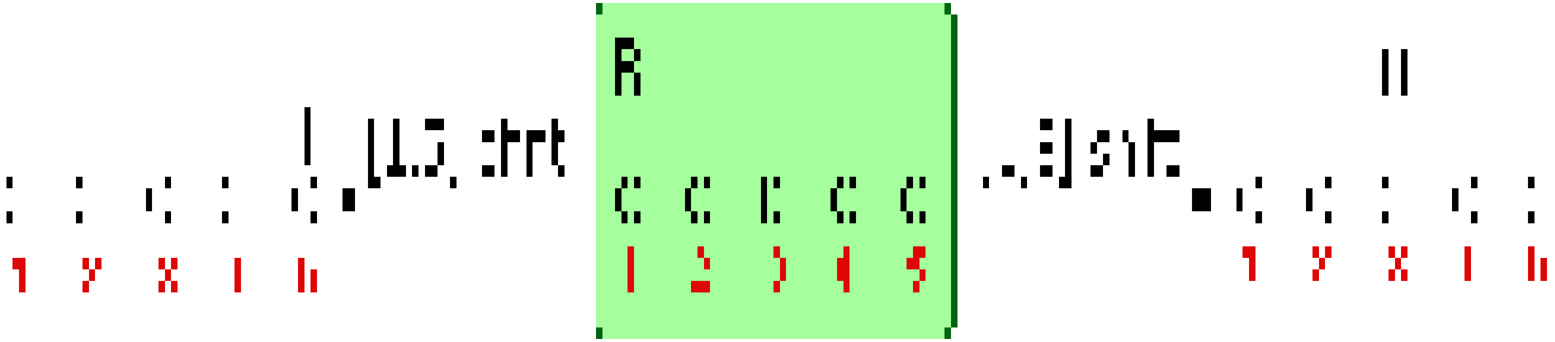
- ***Numbering of migrating group***

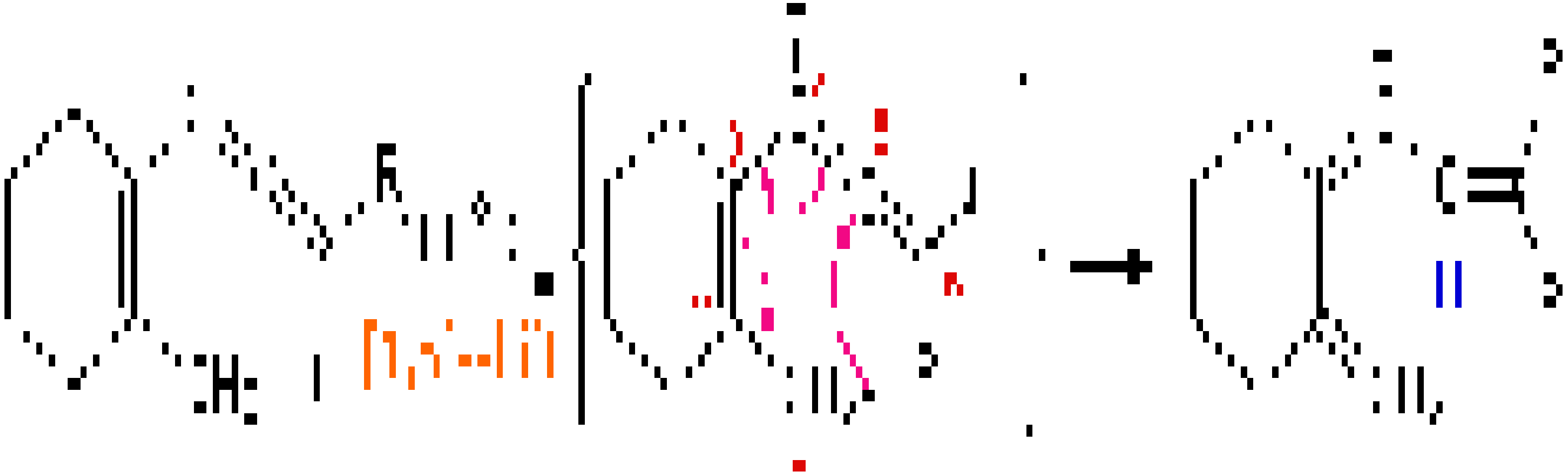
Name of rearrangement

- For e.g; 1,3 sigmatropic rearrangement.

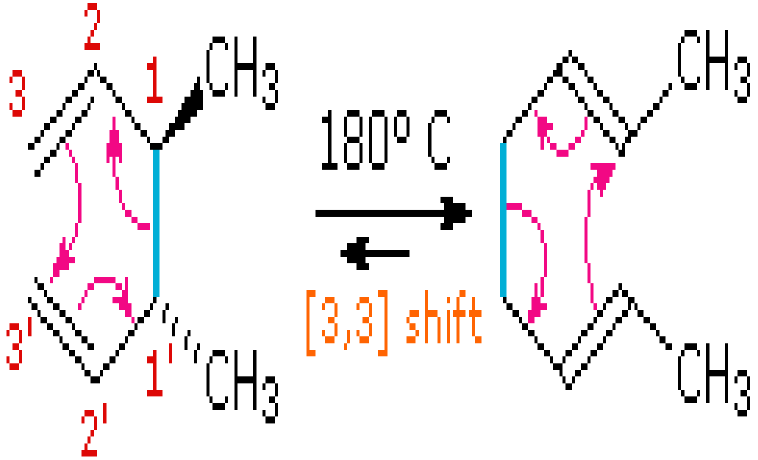
  In these 1 indicates position of atom in the migrating group and 3 indicates position of atom in alkenyl chain.

Similarly 1,7 and 3,3 sigmatropic rearrangement.

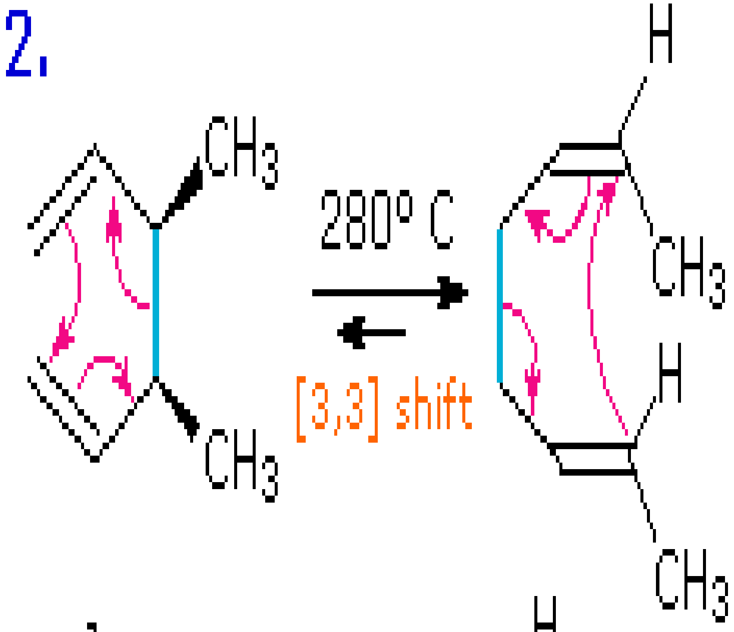




1.


2
3
1
CH3
180° C
[3,3] shift
CH3
3'
1'
CH3
2'
CH3

2.


CH3
280° C
[3,3] shift
H
CH3
H
CH3
CH3

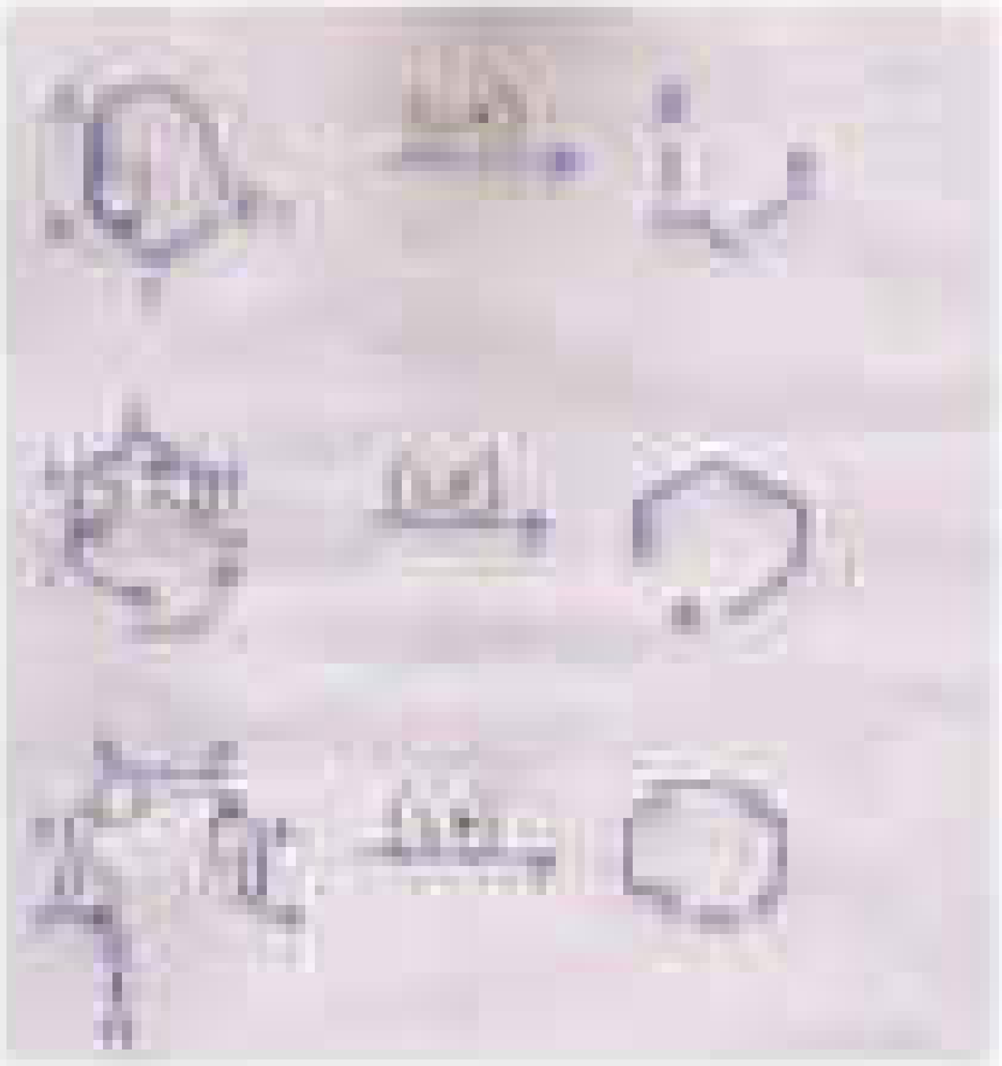
3.


2
1'
3'
3
1
2'
OH
OH
H
O

Sigmatropic Rearrangements are divided into two classes.

- Migrating group is bonded through the same atom in both reactant and product.

- Migrating group is bonded through different atoms in reactant and in product.



MECHANISIM

- In the transition state, bonding arises from overlap between an orbital(HOMO) of an atom (or) free radical(G) and an orbital(HOMO) of an allylic free radical (pi framework).

- HOMO of an allylic radical depends on the no. of carbons in pi frame work.The migrating group is passed from one end of allylic radical to the other.

MIGRATION OF HYDROGEN

- Stereochemically, this shift can be supra (or) antra facial.

- In the transition state, 3- centered bond is required and must involve the overlap between S orbital of H and lobe of P orbitals of 2 terminal carbons.

- It depends not only on symmetry but also on geometry of system.

Supra Facial

Antara Facial

Symmetry Allowed
migration of H

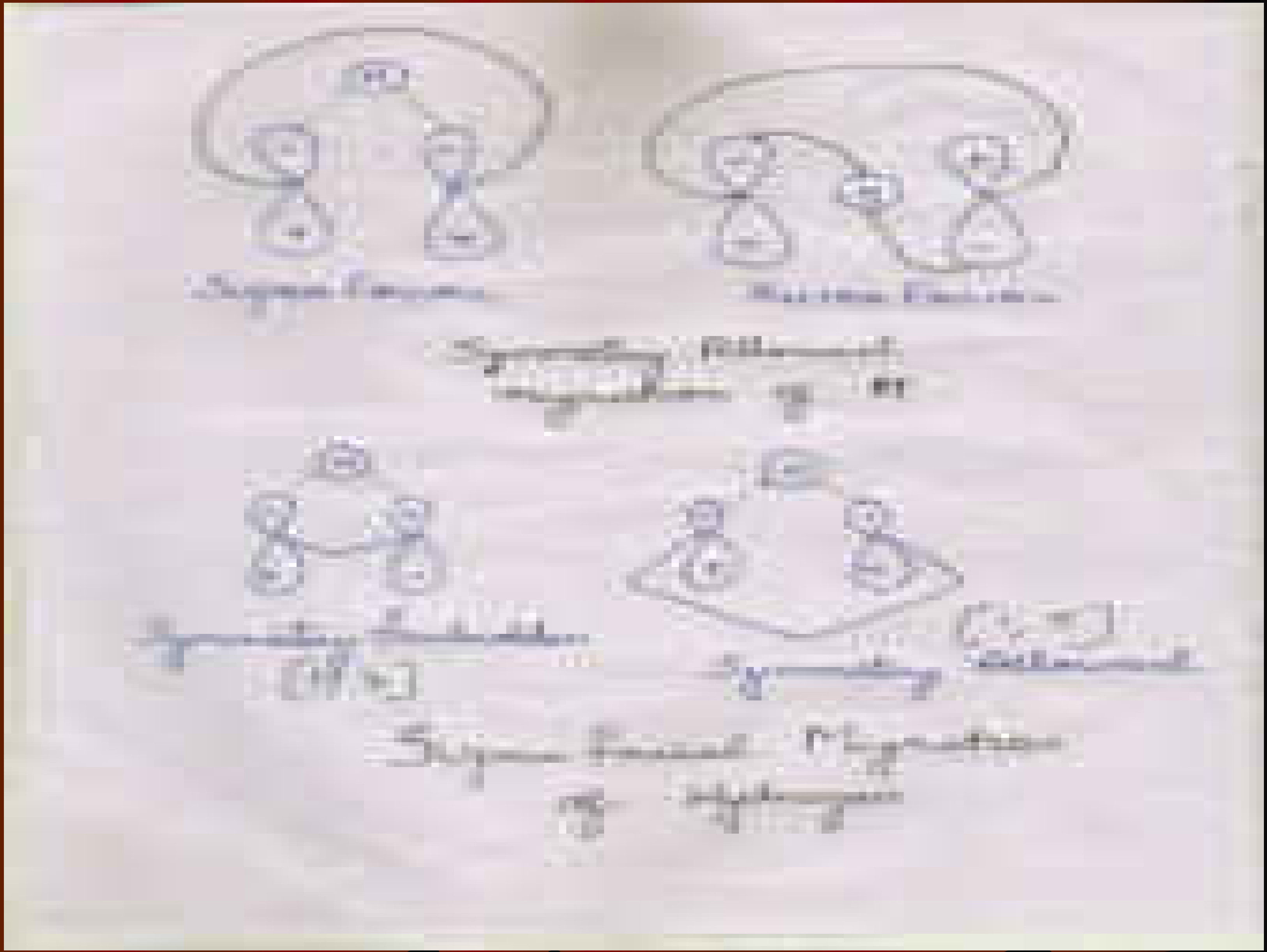
Symmetry Forbidden
[1,3]

[1,5]
Symmetry Allowed

Suprafacial Migration
of Hydrogen

MIGRATION OF CARBON

- Stereochemistry in migrating group…
- Bonding through same lobe on carbon means attachement to same face of atom i.e.,***retention of configuration in G***
- And if bonding to 2 ends of pi framework through different lobes of P orbital. These lobes are on opposite faces of C.i.e., ***inversion of configuration in G***



SELECTION RULES (G=H)

No. of electrons	Thermally allowed	Photochemically allowed
4n	anthra	supra
4n+2	supra	anthra

SELECTION RULES (G=C)

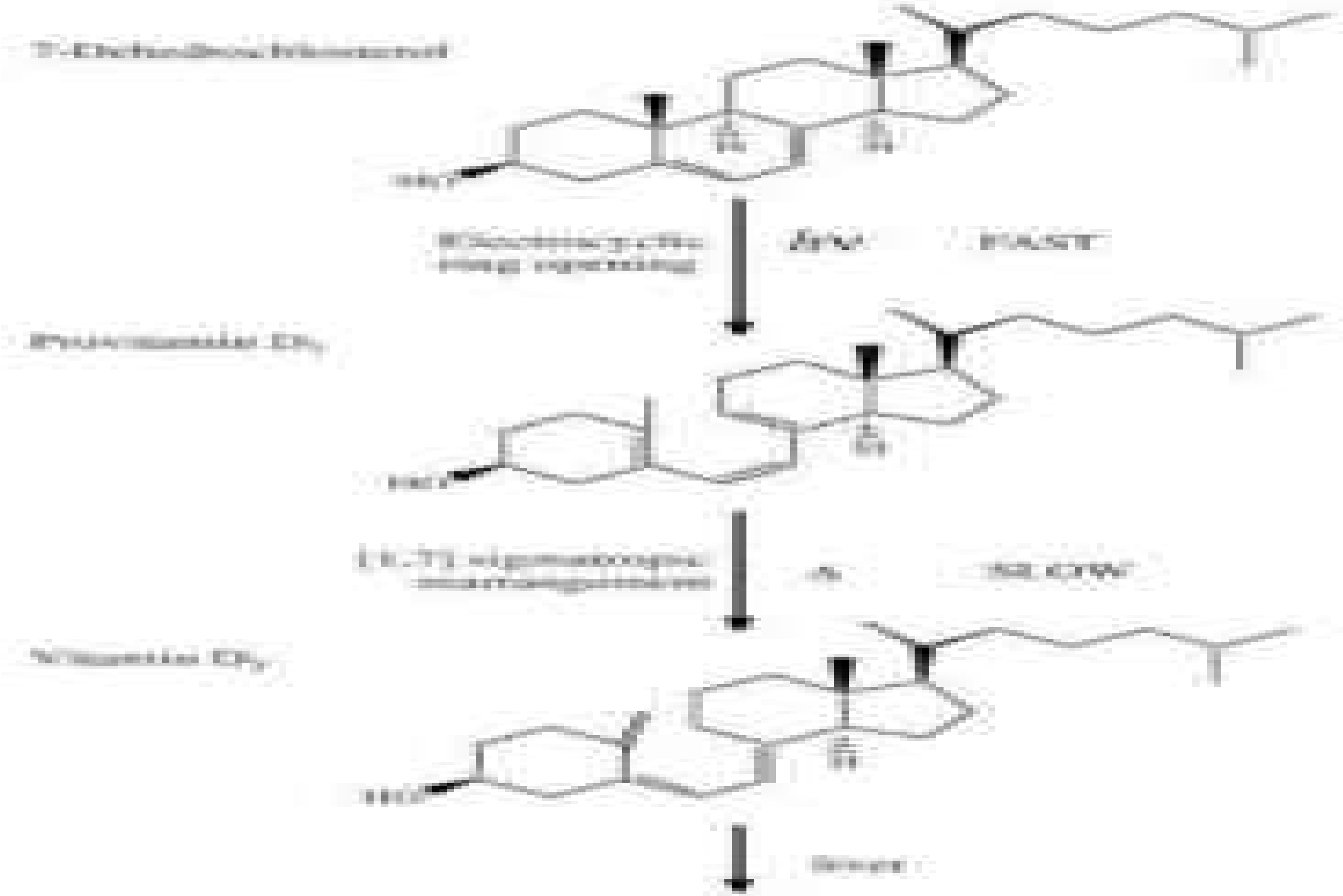
No. of electrons	Thermally allowed	Photochemically allowed
4n	Anthra-retention Supra-inversion	Supra-retention anthra-inversion
4n+2	supra-retention Anthra-inversion	Anthra-retention Supra-inversion

HUCKLE MOBIUS METHOD

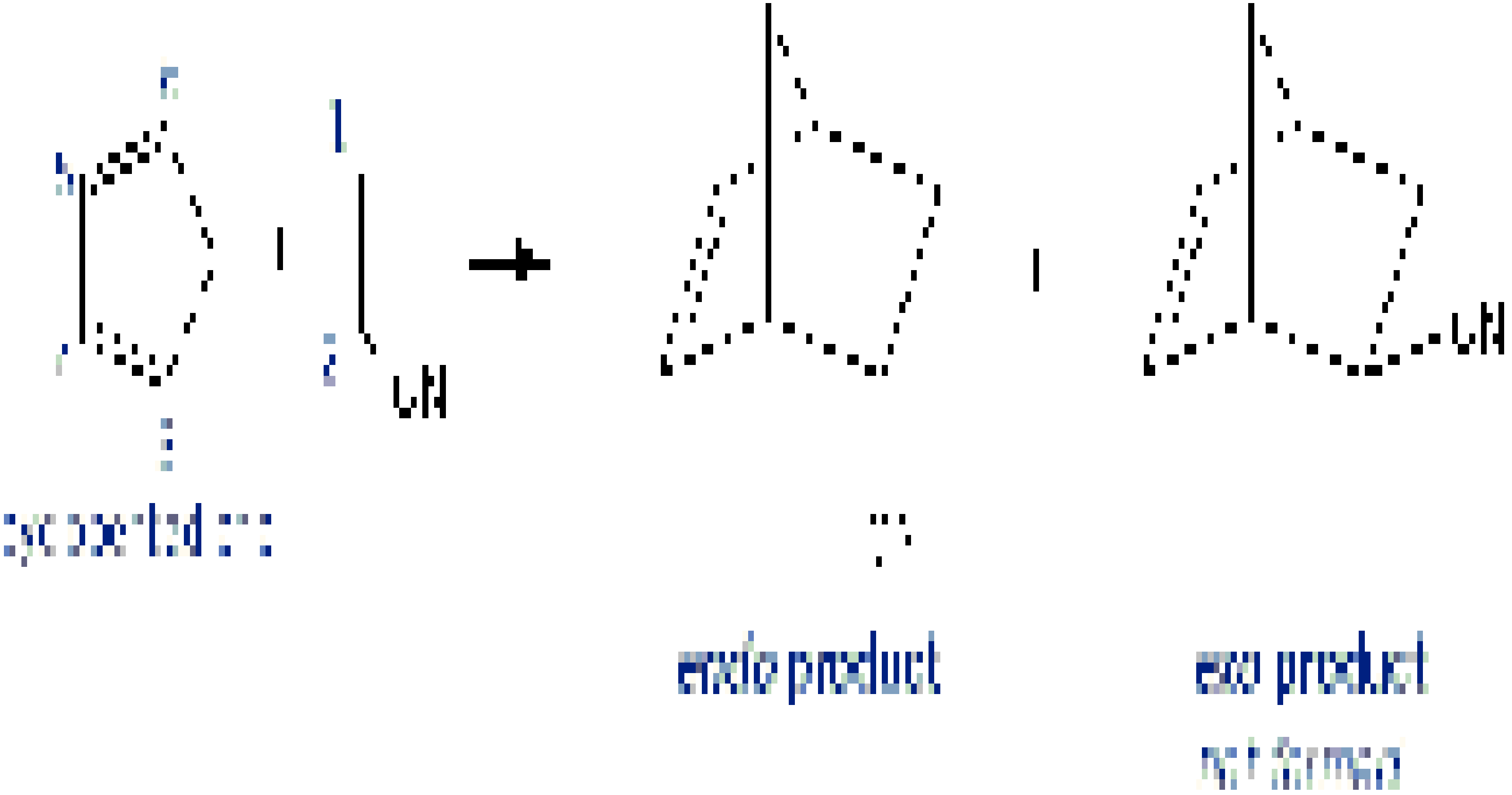
No. of electrons	No. of nodes	Aromaticity	Thermally allowed	hv allowed
4n	zero	Anti aromatic	-	supra
	one	Aromatic	anthra	-
4n+2	zero	Aromatic	supra	-
	one	Anti aromatic	-	anthra

APPLICATIONS

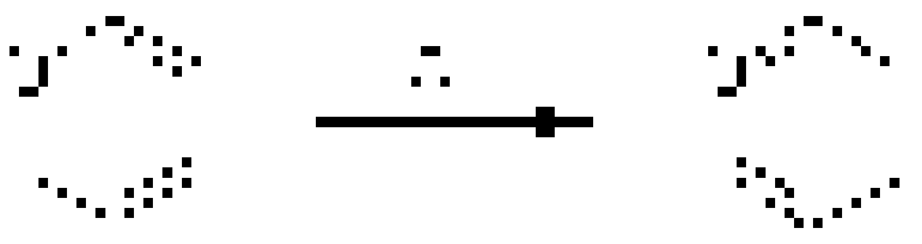
Vitamin D Biosynthesis



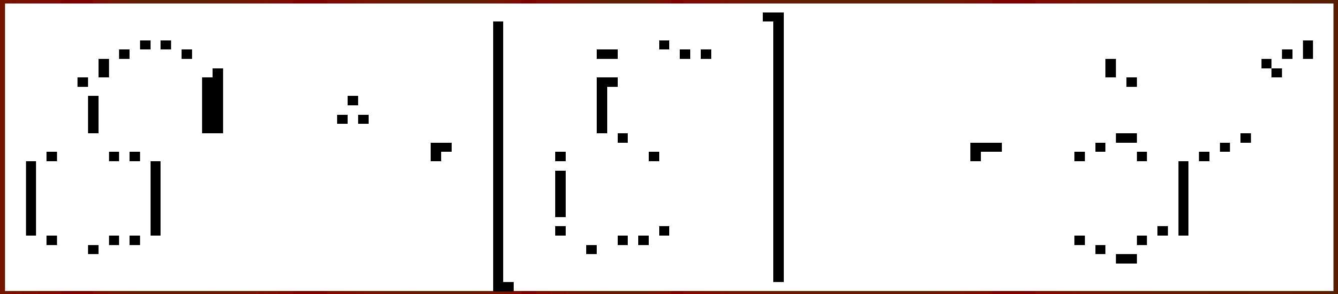
DIEL’S ALDER REACTION



CLAISEN REARRANGEMENT

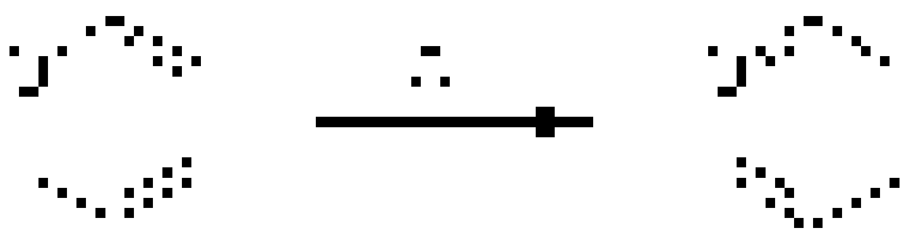


- The aliphatic Claisen Rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to an unsaturated carbonyl compound.
- The aromatic Claisen Rearrangement is accompanied by a rearomatization



- Rearrangement under thermal conditions makes possible an extension of the carbon chain of the molecule.

CLAISEN REARRANGEMENT



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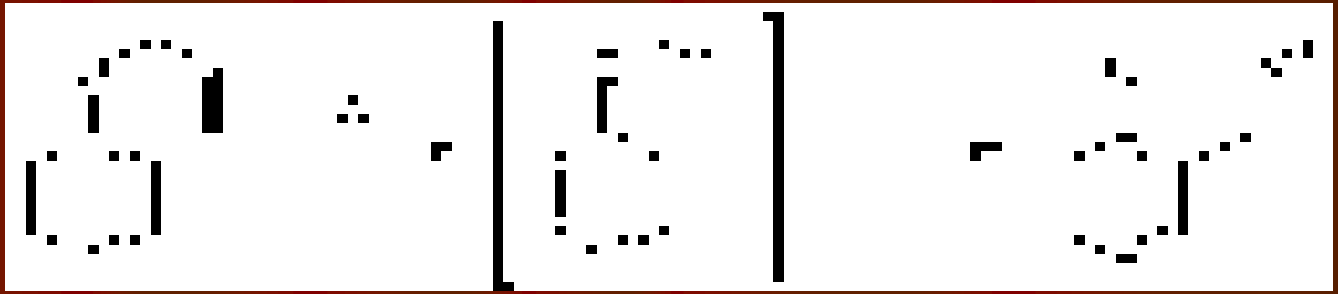
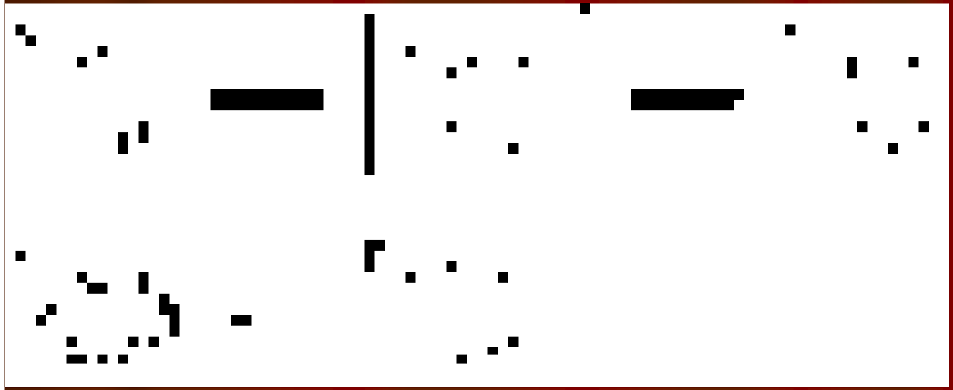
- The aromatic Claisen Rearrangement is accompanied by a rearomatization



- Rearrangement under thermal conditions makes possible an extension of the carbon chain of the molecule.

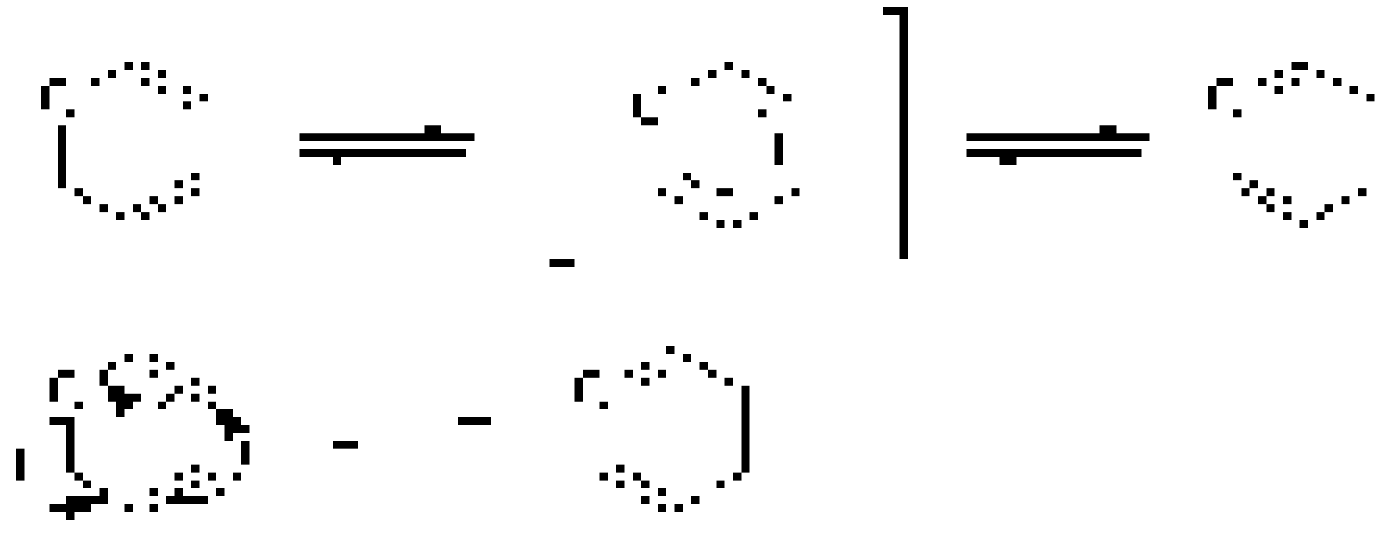
Mechanism of the Claisen Rearrangement:

The Claisen Rearrangement may be viewed as the oxa-variant of the Cope Rearrangement:



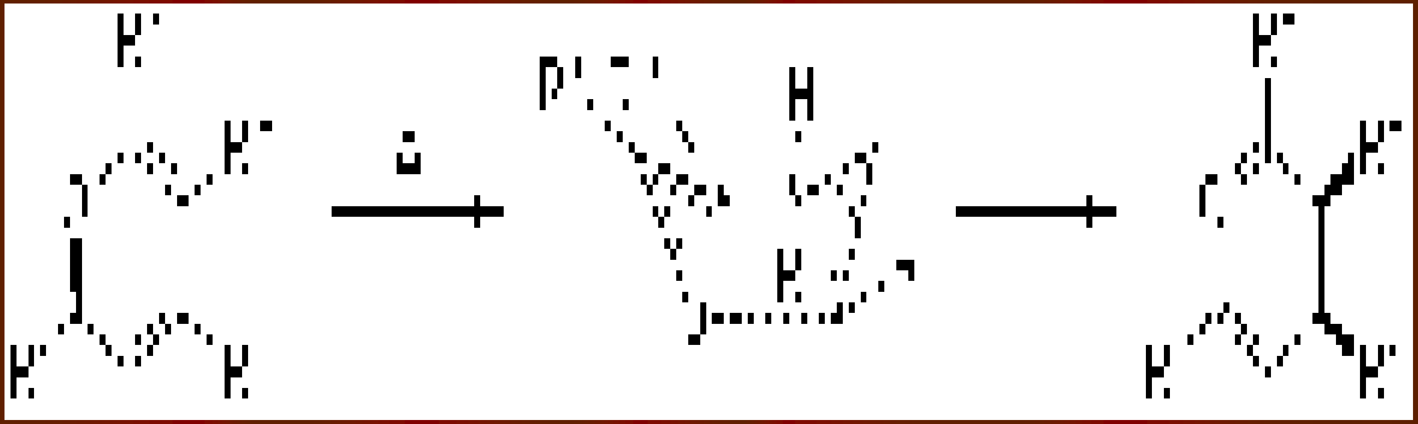
Mechanism of cope Rearrangement

Mechanism of the ClaisenRearrangement

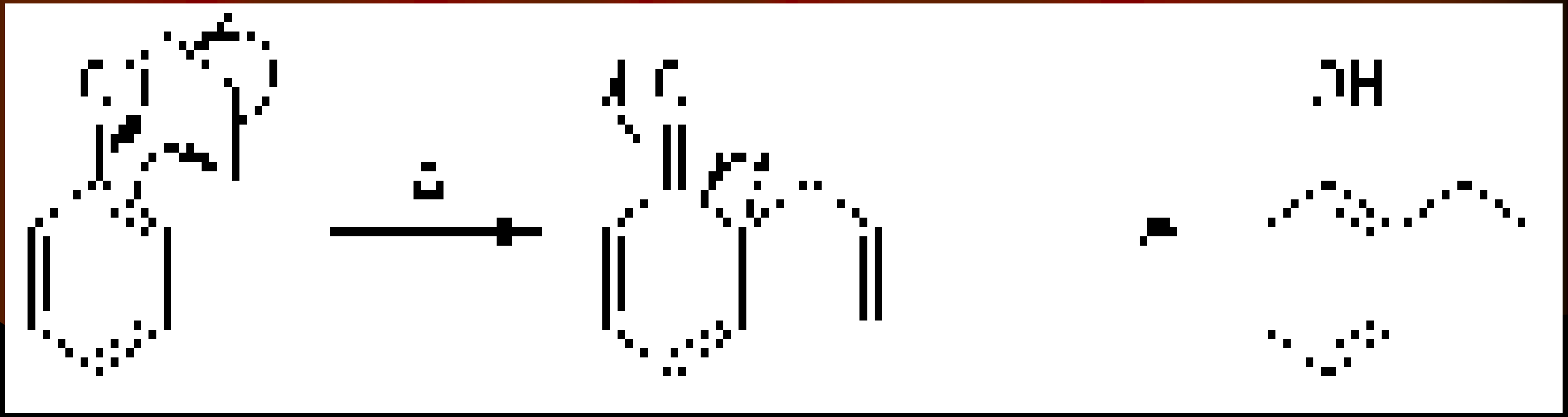


The reaction proceeds preferably *via* a chair transition state. Chiral, enantiomerically enriched starting materials give products of high optical purity.

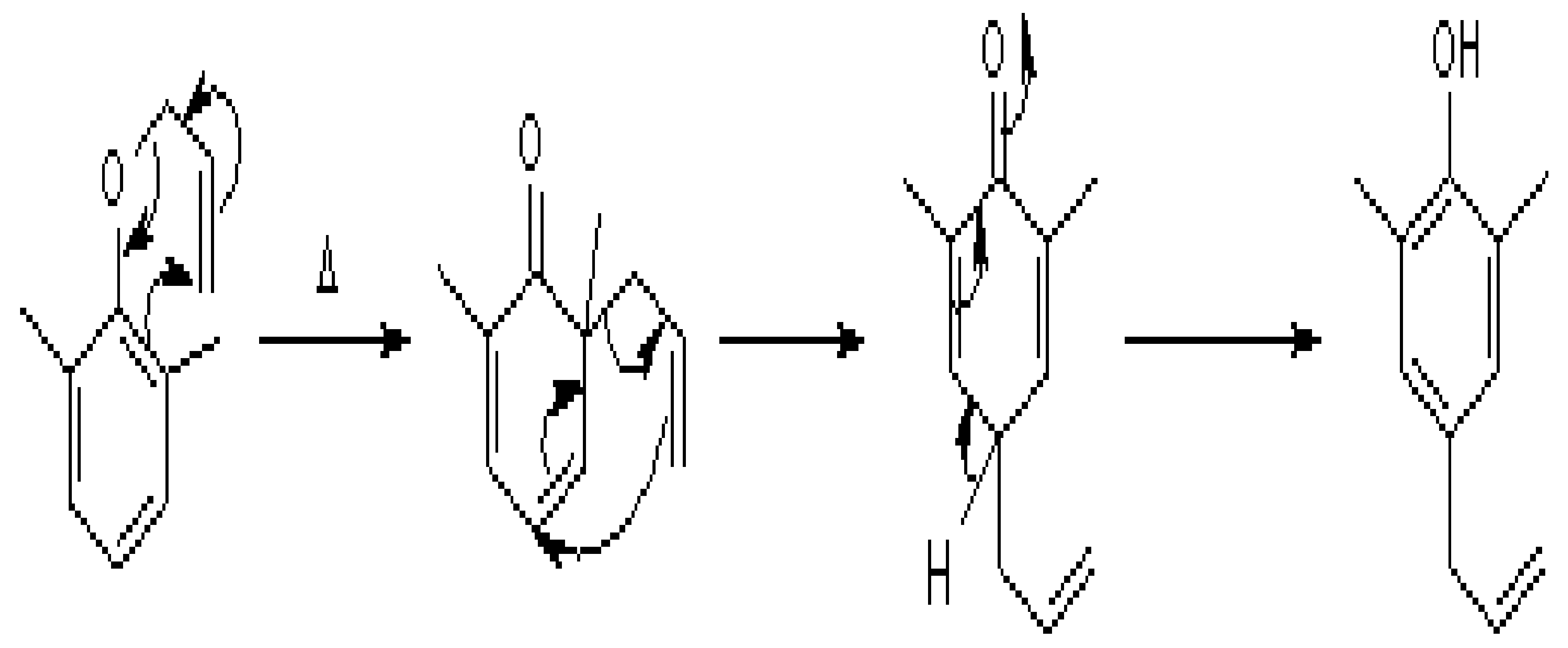
A boat transition state is also possible, and can lead to side products:



The aromatic Claisen Rearrangement is followed by a rearomatization:



When the *ortho*-position is substituted, re-aromatization cannot take place. The allyl group must first undergo a Cope Rearrangement to the *para*-position before tautomerization is possible.



CONCLUSION

- Pericyclic reactions are reactions in which the bond-making and bond-breaking is a concerted one-step process.They donot involve any ionic or radical intermediates,remain unaffected by solvent polarity,and take place only thermally or photochemically.

- The stereochemical course of pericyclic reactions has been explained by the principle of conversion of orbital symmetry.An alternative simpler approach namely FMO. If the orbital symmetry permits bonding interaction between them the reaction is symmetry allowed otherwise it is symmetry forbidden.

- Well ordered transition states of these reactions they are highly sometimes even totally diastereoselective. Several other types of selectivity such as regio, site, and periselectivity are also observed.

- In sigmatropic rearrangements transfer of chirality from one end of a pi-system to the other takes place with high efficiency.

REFERENCES

- Organic chemistry by Morrison and Boyd.
- Stereochemistry of organic compounds by D.Nasipuri.
- Advanced Organic chemistry by Jagadamba Singh & L.D.S Yadav.
- Organic chemistry by SEYHAN EGE (second edition).

THANK YOU