D.N.R.COLLEGE (AUTONOMOUS): BHIMAVARM

DEPARTMENT OF PG CHEMISTRY

ORGANIC REACTION MECHANISM–I&PERICYCLIC REACTIONS

III SEMESTER

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SEMESTER-III

ORGANIC REACTION MECHANISM-I&PERICYCLIC REACTIONS

UNIT-I

A)ALIPHATIC NUCLEOPHILIC SUBSTITUTION:

Neighbouring Group Participation (NGP) by bromine:

Neighbouring Group Participation (NGP) by bromine is an important concept in organic chemistry, particularly in understanding reaction mechanisms and stereochemical outcomes. Here are some detailed notes on the topic:

Neighbouring Group Participation (NGP) Overview

- **Definition**: Neighbouring Group Participation (NGP) refers to the interaction of a neighboring atom or group within a molecule with a reaction center, leading to a different reaction pathway and often influencing the rate and stereochemistry of the reaction.
- **Importance**: NGP can stabilize reaction intermediates, usually cations, and can accelerate reactions by providing an alternative, lower-energy pathway.

Mechanism of NGP by Bromine

- **Role of Bromine**: Bromine can participate as a neighboring group due to its lone pairs of electrons. Bromine is less commonly seen in NGP compared to other groups like oxygen or nitrogen, but it can still play a significant role in certain contexts.
- **Stabilization of Carbocations**: Bromine can stabilize carbocations formed during reactions through its lone pairs. The lone pairs on bromine can donate electron density to an adjacent carbocationic center, leading to stabilization of the intermediate.

Examples of Reactions Involving NGP by Bromine

1. SN1 Reactions

- In SN1 reactions, the rate-determining step is the formation of a carbocation intermediate.
- **NGP Effect**: If a bromine atom is present on the carbon adjacent to the leaving group, its lone pairs can interact with the developing positive charge, stabilizing the carbocation and potentially accelerating the reaction.

- **Example**: In a tertiary alkyl halide where the leaving group departs, forming a carbocation, a bromine atom on the adjacent carbon can participate and stabilize the intermediate.

2. Rearrangements

- **Hydride or Alkyl Shifts**: Bromine can facilitate rearrangements involving hydride or alkyl shifts by stabilizing the carbocationic intermediate during the rearrangement.
- **Example**: In the case of an allylic halide, the presence of a bromine atom can stabilize the allylic cation intermediate, leading to rearrangement and formation of a more stable product.

Stereochemical Implications

- **Retention or Inversion of Configuration**: The stereochemical outcome of a reaction involving NGP by bromine depends on the specific mechanism and the nature of the intermediate. For example, if a bromine atom stabilizes a carbocation intermediate, the reaction might proceed through a planar intermediate, leading to racemization.
- **Cyclization and Intramolecular Reactions**: Bromine participation can lead to intramolecular reactions where the reaction pathway involves the formation of a cyclic intermediate. This can result in products with distinct stereochemistry compared to the original molecule.

Kinetic Effects

- **Acceleration of Reaction Rates**: NGP by bromine can lead to significant acceleration of reaction rates due to the stabilization of transition states and intermediates. This is particularly evident in reactions where the formation of a carbocation is a slow step.
- **Comparison with Other Groups**: While bromine is not as strong a neighboring group participant as groups like OH or OR (which have stronger donating abilities), its participation is still notable and can be the deciding factor in the mechanism and outcome of certain reactions.

Neighbouring Group Participation (NGP) by a phenyl group:

Neighbouring Group Participation (NGP) by a phenyl group is another crucial concept in organic chemistry, particularly for understanding reaction mechanisms and the influence of aromatic systems on reaction pathways. The phenyl group can stabilize carbocations and other intermediates through resonance effects. Here are detailed notes and some example equations illustrating NGP by a phenyl group.

Neighbouring Group Participation (NGP) by Phenyl Group

Mechanism of NGP by Phenyl Group

- **Resonance Stabilization**: The phenyl group can stabilize adjacent carbocations through resonance. The delocalized π-electrons of the aromatic ring can interact with the positive charge on an adjacent carbon, distributing the charge over a larger area and thus stabilizing the intermediate.
- **Rate Acceleration**: Due to this stabilization, the phenyl group can accelerate certain reactions, particularly those that proceed via carbocation intermediates, such as SN1 and certain rearrangement reactions.

Examples of Reactions Involving NGP by Phenyl Group

1. SN1 Reaction

- **Example**: The solvolysis of benzylic halides.
- **Mechanism**: The leaving group departs, forming a benzylic carbocation, which is stabilized by resonance with the phenyl group.

Reaction Equation: $Ph\text{-}CH_2-Cl \rightarrow Ph\text{-}CH_2-OH + HCl$

Mechanism Steps:

Formation of benzylic carbocation: $Ph\text{-}CH_2-Cl \rightarrow Ph\text{-}CH_2^{+} + Cl^{-}$

Nucleophilic attack by water: $Ph\text{-}CH_2^{+} + H_2O \rightarrow Ph\text{-}CH_2-OH_2^{+}$

Deprotonation: $Ph\text{-}CH_2-OH_2^{+} \rightarrow Ph\text{-}CH_2-OH + H^{+}$

Ambident Nucleophiles

Ambident nucleophiles are nucleophiles that have two or more reactive atoms or sites where they can donate a pair of electrons to form a bond with an electrophile. This characteristic allows ambident nucleophiles to react at different sites, leading to different products depending on the conditions and the nature of the electrophile. Here are detailed notes on ambident nucleophiles:

Definition

- **Ambident Nucleophiles**: Nucleophiles that can attack through two different atoms, each having lone pairs of electrons that can be donated to an electrophile.

Examples and Reactivity

1. **Cyanide Ion (CN^-)**
    - **Nucleophilic Sites**: Carbon and Nitrogen.
    - **Reactivity**:
        - **Carbon Attack**: Forms alkyl cyanides (R-CN).
        - **Nitrogen Attack**: Forms isocyanides (R-NC).
    - **Example**: Reaction with alkyl halides.
        - R-X+CN−→R-CN (Carbon attack)
        - R-X+CN−→R-NC (Nitrogen attack, less common)
2. **Nitrite Ion (NO_2^-)**
    - **Nucleophilic Sites**: Oxygen and Nitrogen.
    - **Reactivity**:
        - **Oxygen Attack**: Forms alkyl nitrites (R-ONO).
        - **Nitrogen Attack**: Forms nitro compounds (R-NO_2).
    - **Example**: Reaction with alkyl halides.
        - R-X+NO2−→R-ONO (Oxygen attack)
        - R-X+NO2−→R-NO2 (Nitrogen attack)
3. **Enolate Ions**
    - **Nucleophilic Sites**: Alpha carbon and oxygen.
    - **Reactivity**:
        - **Alpha Carbon Attack**: Leads to alkylation at the alpha position.
        - **Oxygen Attack**: Forms O-alkylated products.
    - **Example**: Reaction with alkyl halides.
        - R-CH2−CO−+R'X→R-CH(R')-CO^- (Alpha carbon attack)
        - R-CH2−CO−+R'X→R-CH2−COR' (Oxygen attack)
4. **Thiocyanate Ion (SCN^-)**
    - **Nucleophilic Sites**: Sulfur and Nitrogen.
    - **Reactivity**:
        - **Sulfur Attack**: Forms alkyl thiocyanates (R-SCN).
        - **Nitrogen Attack**: Forms alkyl isothiocyanates (R-NCS).
    - **Example**: Reaction with alkyl halides.
        - R-X+SCN−→R-SCN (Sulfur attack)
        - R-X+SCN−→R-NCS (Nitrogen attack, less common)

Factors Influencing Site of Attack

1. **Nature of Electrophile**: Hard electrophiles (such as R+) tend to react with the harder nucleophilic site, while soft electrophiles prefer the softer site.
2. **Solvent Effects**: Protic solvents can stabilize certain transition states or intermediates, influencing the preferred site of attack.

3. **Steric Effects**: Bulky groups near the electrophilic center can hinder attack at one site, favoring the other.
4. **Electronic Effects**: The electronic environment around the nucleophile and electrophile can dictate the preferred site of attack.

Examples in Organic Synthesis

1. **Kolbe Nitrile Synthesis**:
    - Utilizes the ambident nature of the cyanide ion to form nitriles.

$$R\text{-}X + KCN \rightarrow R\text{-}CN$$

Meyer synthesis of aldehydes

The Meyer synthesis of aldehydes, also known as the Meyer-Schuster rearrangement, is a useful method for converting propargylic alcohols into α,β-unsaturated aldehydes. This reaction involves the rearrangement of a propargylic alcohol (an alcohol with a hydroxyl group attached to a carbon atom that is triple-bonded to another carbon) in the presence of an acid catalyst.

Mechanism of Meyer-Schuster Rearrangement

1. **Protonation**: The hydroxyl group of the propargylic alcohol is protonated by the acid catalyst, making it a better leaving group.
2. **Formation of a Carbocation**: Loss of water generates a resonance-stabilized carbocation (allylic cation).
3. **1,2-Shift**: A 1,2-shift of the alkyne to the carbocation forms a vinyl cation.
4. **Deprotonation**: The vinyl cation is deprotonated to yield the α,β-unsaturated aldehyde.

Reaction Equation

$$R\text{-}C{\equiv}C\text{-}CH(OH)\text{-}R' \rightarrow R\text{-}CH{=}CH\text{-}CHO \text{(in presence of acid)}$$

Example Reaction

Consider the synthesis of cinnamaldehyde from propargylic alcohol:

$$Ph\text{-}C{\equiv}C\text{-}CH(OH)\text{-}CH_3 \rightarrow Ph\text{-}CH{=}CH\text{-}CHO \text{(in presence of acid)}$$

Steps in the Reaction Mechanism

1. **Protonation**: $Ph\text{-}C{\equiv}C\text{-}CH(OH)\text{-}CH_3 + H^+ \rightarrow Ph\text{-}C{\equiv}C\text{-}CH(OH_2)\text{-}CH_3$
2. **Loss of Water**: $Ph\text{-}C{\equiv}C\text{-}CH(OH_2)\text{-}CH_3 \rightarrow Ph\text{-}C{\equiv}C\text{-}CH^{+-}CH_3 + H_2O$

3. **1,2-Shift**: Ph-C≡C-CH+-CH3→Ph-C+=C=CH2
4. **Deprotonation**: Ph-C+=C=CH2→Ph-CH=CH-CHO+H^+
5. **Conditions and Catalysts**

- **Acid Catalysts**: Common acids used in this reaction include sulfuric acid (H_2SO_4), phosphoric acid (H_3PO_4), and p-toluenesulfonic acid (TsOH).
- **Solvent**: The reaction is often performed in an organic solvent such as dichloromethane (CH_2Cl_2) or toluene.

Applications

The α,β-unsaturated aldehydes produced via the Meyer-Schuster rearrangement can be used in various applications, including:

- **Synthesis of Fragrances and Flavors**: Compounds like cinnamaldehyde are key ingredients in the fragrance and flavor industries.
- **Pharmaceutical Intermediates**: These aldehydes are also useful intermediates in the synthesis of pharmaceuticals.
- **Precursor to Other Functional Groups**: The α,β-unsaturated aldehydes can be further transformed into other functional groups, such as alcohols, acids, and amines.

Mitsunobu reaction:

The Mitsunobu reaction is a valuable and versatile transformation in organic chemistry, widely used for converting alcohols into a variety of other functional groups under mild conditions. Here are detailed notes on the Mitsunobu reaction:

Mitsunobu Reaction Overview

- **Definition**: The Mitsunobu reaction involves the conversion of an alcohol into a different functional group via nucleophilic substitution, facilitated by a combination of a phosphine (typically triphenylphosphine, PPh_3) and an azodicarboxylate (commonly diethyl azodicarboxylate, DEAD).
- **Key Reagents**:
    - Alcohol (the starting material)
    - Triphenylphosphine (PPh_3)
    - Diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD)
    - Nucleophile (e.g., carboxylic acids, phenols, thiols, amines)

General Reaction Scheme

$$R\text{-}OH+NuH+PPh3+DEAD \rightarrow R\text{-}Nu+Ph3P{=}O+DEAD\text{-}H2$$

Where:

- R-OH is the alcohol.
- NuH is the nucleophile.
- DEAD-H_2 is the hydrazine byproduct.

Mechanism

1. **Formation of the Phosphonium Intermediate**: The alcohol reacts with triphenylphosphine to form an alkoxyphosphonium ion

$$R\text{-}OH+PPh3 \rightarrow R\text{-}OPPh3^{+}$$

2. **Activation by Azodicarboxylate**: The alkoxyphosphonium ion is activated by DEAD, forming a more reactive complex.

$$R\text{-}OPPh3^{+}+DEAD \rightarrow R\text{-}OPPh3{-}DEAD$$

3. **Nucleophilic Attack**: The nucleophile (NuH) attacks the activated complex, resulting in the substitution product.

$$R\text{-}OPPh3{-}DEAD+NuH \rightarrow R\text{-}Nu+Ph3P{=}O+DEAD\text{-}H2$$

Applications

1. **Inversion of Stereochemistry**: The Mitsunobu reaction proceeds with inversion of configuration, making it useful for synthesizing compounds with desired stereochemistry.
2. **Example**: Conversion of an alcohol to an ester with inversion:

$$R\text{-}OH+R'\text{-}COOH \rightarrow R\text{-}O\text{-}CO\text{-}R'$$

3. **Formation of Ethers**: Reaction with phenols or other alcohols can form ethers.
    - **Example**: $R\text{-}OH+Ph\text{-}OH \rightarrow R\text{-}O\text{-}Ph$

Limitations

- **Functional Group Compatibility**: Sensitive to the presence of certain functional groups that can react with the reagents (e.g., primary amines can react with DEAD).

- **Byproduct Formation**: Generates stoichiometric amounts of byproducts such as triphenylphosphine oxide ($Ph_3P=O$) and hydrazine derivatives from DEAD.
- **Air Sensitivity**: Reagents like triphenylphosphine and DEAD are sensitive to air and moisture, requiring careful handling.

B)ALIPHATIC ELECTROPHILIC SUBSTITUTION:

In organic chemistry, electrophilic substitution reactions are classified based on their mechanisms, much like nucleophilic substitution reactions. The main types of electrophilic substitution reactions are SE2 (second-order electrophilic substitution), SE1 (first-order electrophilic substitution), and SEi (intramolecular electrophilic substitution). Here are detailed notes on each of these mechanisms:

SE2 (Second-Order Electrophilic Substitution)

Mechanism

- **Bimolecular**: The SE2 mechanism involves two molecules in the rate-determining step, the substrate and the electrophile.
- **Concerted Process**: The reaction typically proceeds through a single, concerted step where the electrophile attacks the substrate and the leaving group departs simultaneously.
- **Stereochemistry**: This mechanism often leads to retention of configuration at the reaction center, although inversion can also occur depending on the nature of the electrophile and the substrate.

Example

- **Electrophilic Halogenation**:
    - Halogenation of an alkene where the electrophile (Br_2) adds to the double bond. R-CH=CH2+Br2→R-CH(Br)-CH2Br

SE1 (First-Order Electrophilic Substitution)

Mechanism

- **Unimolecular**: The SE1 mechanism involves one molecule in the rate-determining step, typically the formation of a carbocation intermediate.
- **Stepwise Process**: The reaction proceeds in two steps. First, the leaving group departs, forming a carbocation. Then, the electrophile attacks the carbocation.

- **Rearrangements**: The formation of a carbocation intermediate can lead to rearrangements, resulting in a different product distribution.

Example

- **Aromatic Nitration**:
  - The nitration of benzene using nitric acid and sulfuric acid. $C6H6+NO2+→C6H5NO2+H+$

SEi (Intramolecular Electrophilic Substitution)

Mechanism

- **Intramolecular**: The SEi mechanism involves an electrophile and a nucleophile within the same molecule, leading to substitution.
- **Formation of Cyclic Intermediates**: This reaction often proceeds through the formation of cyclic intermediates or transition states.
- **Stereochemistry**: The stereochemical outcome depends on the ring size and the specific structure of the intermediate.

Example

- **Cyclization Reactions**:

Formation of cyclic compounds via intramolecular electrophilic substitution, such as the formation of lactones or lactams from suitable precursors.

$$R\text{-}CH(OH)\text{-}CH2{-}COOH→R\text{-}CH{-}O{-}C(OH){-}CH2R$$

Detailed Examples and Mechanisms

SE2 Example: Electrophilic Addition to Alkenes

Reaction: $R\text{-}CH=CH2+Br2→R\text{-}CH(Br)\text{-}CH2Br$

Mechanism:

Formation of Bromonium Ion: $R\text{-}CH=CH2+Br2→R\text{-}CH(Br)\text{-}CH2+Br{-}$

Nucleophilic Attack: $R\text{-}CH(Br)\text{-}CH2++Br{-}→R\text{-}CH(Br)\text{-}CH2Br$

SE1 Example: Aromatic Nitration

Reaction: $C6H6+NO2+ \rightarrow C6H5NO2+H+$

Mechanism:

1. **Generation of Electrophile**: $HNO3+H2SO4 \rightarrow NO2++HSO4^{-}+H2O$
2. **Formation of Arenium Ion**: $C6H6+NO2+ \rightarrow C6H5NO2+$
3. **Deprotonation**: $C6H5NO2+ \rightarrow C6H5NO2+H+$
4. **SEi Example: Intramolecular Cyclization**

Reaction: $R\text{-}CH(OH)\text{-}CH2-COOH \rightarrow R\text{-}CH-O-C(OH)-CH2R$

Mechanism:

1. **Formation of Cyclic Intermediate**: $R\text{-}CH(OH)\text{-}CH2-COOH \rightarrow R\text{-}CH(OH)\text{-}CH2-C(OH)-R$
2. **Cyclization**: $R\text{-}CH(OH)\text{-}CH2-C(OH)-R \rightarrow R\text{-}CH-O-C(OH)-CH2R$

HVZ REACTION:

The **Hell-Volhard-Zelinsky (HVZ) reaction** is a classic organic chemistry reaction used to halogenate the alpha position of carboxylic acids. This reaction involves the substitution of an alpha hydrogen atom of a carboxylic acid with a halogen atom, typically bromine or chlorine. The HVZ reaction is particularly useful because it allows for the selective functionalization of the alpha position, which can then be used for further chemical transformations.

Mechanism of the HVZ Reaction

The HVZ reaction proceeds via the following general steps:

1. **Formation of the Acyl Halide**: The carboxylic acid reacts with a halogenating agent, typically PBr_3 or PCl_3, to form an acyl halide intermediate.
2. **Enolization**: The acyl halide undergoes tautomerization to form the enol.
3. **Halogenation**: The enol reacts with the halogen to introduce a halogen atom at the alpha position.
4. **Hydrolysis**: The acyl halide is hydrolyzed back to the carboxylic acid, now bearing a halogen atom at the alpha position.

Detailed Steps and Equations

1. **Formation of the Acyl Halide**:

   $R\text{-}CH_2COOH + PBr_3 \rightarrow R\text{-}CH_2COBr + HBr$

2. **Enolization**: $R\text{-}CH_2COBr \leftrightarrow R\text{-}CH=C(OH)Br$
3. **Halogenation**: $R\text{-}CH=C(OH)Br + Br_2 \rightarrow R\text{-}CBr=CHBr$
4. **Hydrolysis**: $R\text{-}CHBr\text{-}COBr + H_2O \rightarrow R\text{-}CHBr\text{-}COOH + HBr$

Example Reaction

Consider the bromination of acetic acid:

1. **Formation of Acetyl Bromide**: $CH_3COOH + PBr_3 \rightarrow CH_3COBr + HBr$
2. **Enolization**: $CH_3COBr \leftrightarrow CH_2=C(OH)Br$
3. **Halogenation**: $R\text{-}CH=C(OH)Br + Br_2 \rightarrow R\text{-}CBr=CHBr$

$$R\text{-}CBr=CHBr \rightarrow R\text{-}CHBr\text{-}COBr$$

4. **Hydrolysis**: $R\ CHBr\text{-}COBr + H_2O \rightarrow RCHBr\text{-}COOH + HBr$

Applications

1. **Synthesis of Alpha-Halocarboxylic Acids**: The HVZ reaction is a key method for synthesizing alpha-halocarboxylic acids, which are valuable intermediates in organic synthesis.
2. **Further Functionalization**: The alpha-halocarboxylic acids can be further transformed into a variety of other functional groups, including amines, alcohols, and more complex molecules.
3. **Preparation of Pharmaceuticals**: The HVZ reaction is useful in the synthesis of pharmaceuticals and natural products where alpha-halo acids are required intermediates.

Aliphatic Diazo Coupling Reaction

1. **Formation of the Diazonium Salt**: Typically, the diazonium salt is generated from a primary amine through diazotization.
2. **Coupling with Aliphatic Nucleophile**: The diazonium ion then reacts with an aliphatic nucleophile (like an enolate) to form a new carbon-carbon bond.

Mechanism

1. **Formation of the Diazonium Salt**:

- A primary amine is treated with nitrous acid (generated in situ from sodium nitrite and hydrochloric acid) to form the diazonium salt.

$$R\text{-}NH_2 + HNO_2 + HCl \rightarrow R\text{-}N_2^+Cl^- + 2H_2O$$

Enolate Formation:

- A carbonyl compound (e.g., a ketone or an aldehyde) is deprotonated to form an enolate ion.

$$R\text{-}CO\text{-}CH_3 + Base \rightarrow R\text{-}CO\text{-}CH_2^- + HB^+$$

Coupling Reaction:

- The diazonium salt reacts with the enolate ion, resulting in the formation of the coupled product.

$$R\text{-}CO\text{-}CH_2^- + R'\text{-}N_2^+Cl^- \rightarrow R\text{-}CO\text{-}CH_2R' + N_2 + Cl^-$$

Example Reaction

Consider the coupling of ethyl acetoacetate with a diazonium salt derived from ethylamine:

1. **Formation of Ethyl Diazonium Salt**:

   $$CH_3CH_2NH_2 + HNO_2 + HCl \rightarrow CH_3CH_2N_2^+Cl^- + 2H_2O$$

   Formation of the Enolate Ion:

   $$CH_3CO\text{-}CH_2COOEt + Base \rightarrow CH_3CO\text{-}CH^-COOEt + HB^+$$

2. **Coupling Reaction**:

   $$CH_3CO\text{-}CH^-COOEt + CH_3CH_2N_2^+Cl^- \rightarrow$$

   $$CH_3CO\text{-}CH(N_2CH_3CH_2)COOEt + N_2 + Cl^-$$

Applications

1. **Synthesis of α-Diazo Ketones and Esters**: Aliphatic diazo coupling reactions are useful for synthesizing α-diazo ketones and esters, which can serve as intermediates in further chemical transformations.

2. **Introduction of Diazo Groups**: These reactions allow the introduction of diazo groups into aliphatic chains, enabling further transformations via Wolff rearrangement or diazo decomposition.
3. **Creation of Carbenes**: The resulting diazo compounds can be used to generate carbenes, which are highly reactive species that can participate in cyclopropanation, insertion, and addition reactions.

Dakin-West reaction:

The **Dakin-West reaction** is a chemical reaction used to synthesize α,β-unsaturated ketones from α-amino acids. This reaction involves the conversion of an α-amino acid into an α-keto acid, which then undergoes further transformation to yield the α,β-unsaturated ketone. This reaction is particularly useful in the preparation of complex ketones and is named after the chemists Henry Drysdale Dakin and Ralph Alexander Raphael West, who discovered it.

Mechanism of the Dakin-West Reaction

1. **Activation of the Carboxyl Group**: The α-amino acid reacts with an acylating agent (usually acetic anhydride) to form an intermediate mixed anhydride.
2. **Formation of the Enolate Intermediate**: The mixed anhydride undergoes deprotonation to form an enolate intermediate.
3. **Intramolecular Acylation**: The enolate attacks the carbonyl carbon of the acyl group, leading to the formation of an oxazolone intermediate.
4. **Decarboxylation and Rearrangement**: The oxazolone undergoes decarboxylation and rearrangement to yield the final α,β-unsaturated ketone.

Detailed Steps and Equations

1. **Activation of the Carboxyl Group**:
    - The α-amino acid reacts with acetic anhydride to form an intermediate mixed anhydride.

$$R\text{-}CH(NH2)\text{-}COOH + (CH3CO)2O \rightarrow R\text{-}CH(NH2)\text{-}CO\text{-}O\text{-}COCH3$$

Formation of the Enolate Intermediate:

- The mixed anhydride undergoes deprotonation by a base to form the enolate intermediate.

$$R\text{-}CH(NH2)\text{-}CO\text{-}O\text{-}COCH3 \rightarrow R\text{-}C(NH2)\text{-}COCH3$$

Intramolecular Acylation:

- The enolate intermediate undergoes intramolecular acylation to form the oxazolone intermediate.

$$R\text{-}C(NH_2)\text{-}COCH_3 \rightarrow \text{Oxazolone intermediate}$$

Decarboxylation and Rearrangement:

- The oxazolone intermediate undergoes decarboxylation and rearrangement to yield the final α,β-unsaturated ketone.

$$\text{Oxazolone intermediate} \rightarrow R\text{-}CH{=}CH\text{-}COCH_3$$

Example Reaction

Consider the synthesis of 3-phenyl-2-butanone from phenylalanine:

1. **Activation of the Carboxyl Group**:

   $$Ph\text{-}CH_2CH(NH_2)\text{-}COOH + (CH_3CO)_2O \rightarrow$$

   $$Ph\text{-}CH_2CH(NH_2)\text{-}CO\text{-}O\text{-}COCH_3$$

   Formation of the Enolate Intermediate:

   $$Ph\text{-}CH_2CH(NH_2)\text{-}CO\text{-}O\text{-}COCH_3 \rightarrow Ph\text{-}CH_2C(NH_2)\text{-}COCH_3$$

   Intramolecular Acylation:

   $$Ph\text{-}CH_2C(NH_2)\text{-}COCH_3 \rightarrow \text{Oxazolone intermediate}$$

2. **Decarboxylation and Rearrangement**:

   $$\text{Oxazolone intermediate} \rightarrow Ph\text{-}CH_2CH{=}CH\text{-}COCH_3$$

Applications

1. **Synthesis of α,β-Unsaturated Ketones**: The Dakin-West reaction is particularly useful for synthesizing α,β-unsaturated ketones, which are valuable intermediates in organic synthesis.
2. **Preparation of Complex Molecules**: This reaction can be used in the synthesis of complex natural products and pharmaceuticals.

3. **Versatility**: The reaction can be applied to a wide variety of α-amino acids, making it a versatile method for introducing the α,β-unsaturated ketone functionality.

Considerations and Limitations

- **Reactivity of Amino Acids**: The reaction works best with α-amino acids that can form stable enolate intermediates.
- **Reaction Conditions**: The reaction typically requires anhydrous conditions and careful control of temperature to avoid side reactions.
- **Use of Acetic Anhydride**: The use of acetic anhydride is essential for the formation of the mixed anhydride intermediate.

Haller-Bauer reaction:

The Haller-Bauer reaction is an organic transformation that involves the cleavage of ketones or aldehydes into amides and smaller carbonyl compounds under the influence of strong bases such as sodium amide ($NaNH_2$) or lithium diisopropylamide (LDA). This reaction is particularly useful for breaking carbon-carbon bonds adjacent to carbonyl groups, leading to the formation of valuable amide intermediates.

Mechanism of the Haller-Bauer Reaction

1. **Base Attack**: The strong base deprotonates the carbonyl compound to form an enolate.
2. **Nucleophilic Addition**: The enolate attacks another molecule of the base, forming a dianion intermediate.
3. **Cleavage and Formation of Amide**: The intermediate undergoes cleavage to yield an amide and a smaller carbonyl compound.

Detailed Steps and Equations

1. **Base Attack and Enolate Formation**:

   $$R\text{-}CO\text{-}R' + NaNH2 \rightarrow R\text{-}CO\text{-}C(R')NH2^{-} + Na+$$

   Here, the base ($NaNH_2$) deprotonates the ketone to form an enolate ion.

2. **Nucleophilic Addition**:

   $$R\text{-}CO\text{-}C(R')NH2^{-} + NaNH2 \rightarrow R\text{-}CO\text{-}C(R')(NH2)2^{2-} + Na+$$

The enolate further reacts with another molecule of $NaNH_2$ to form a dianion intermediate.

3. **Cleavage and Formation of Amide**:

$$R\text{-}CO\text{-}C(R')(NH2)22^{-} \rightarrow R\text{-}CONH2 + R'\text{-}CO^{-} + Na+$$

The intermediate undergoes cleavage, resulting in the formation of an amide and a smaller carbonyl compound (such as an aldehyde or ketone).

Example Reaction

Consider the cleavage of acetophenone (a simple ketone) using sodium amide:

1. **Base Attack and Enolate Formation**:

$$Ph\text{-}CO\text{-}CH3 + NaNH2 \rightarrow Ph\text{-}CO\text{-}CH2^{-} + Na+$$

2.Nucleophilic Addition:

$$Ph\text{-}CO\text{-}CH2^{-} + NaNH2 \rightarrow Ph\text{-}CO\text{-}CH2NH2^{-} + Na+$$

3.Cleavage and Formation of Amide:

$$Ph\text{-}CO\text{-}CH2NH2^{-} \rightarrow Ph\text{-}CONH2 + CH3CHO$$

This results in the formation of benzamide ($Ph\text{-}CONH_2$) and acetaldehyde (CH_3CHO).

Applications

1. **Synthesis of Amides**: The Haller-Bauer reaction provides a method for synthesizing amides from ketones and aldehydes.
2. **Functional Group Transformations**: The reaction can be used to introduce amide functionality into molecules, which can then undergo further transformations.
3. **Structural Elucidation**: The reaction can be applied in structural elucidation by cleaving complex molecules into simpler fragments.

Considerations and Limitations

- **Strong Bases Required**: The reaction requires the use of strong bases such as $NaNH_2$ or LDA, which can limit its applicability to base-sensitive substrates.

- **Side Reactions**: The presence of other functional groups can lead to side reactions, reducing the overall yield of the desired product.
- **Substrate Scope**: The reaction is typically more successful with ketones and aldehydes that can form stable enolate intermediates.

UNIT-II

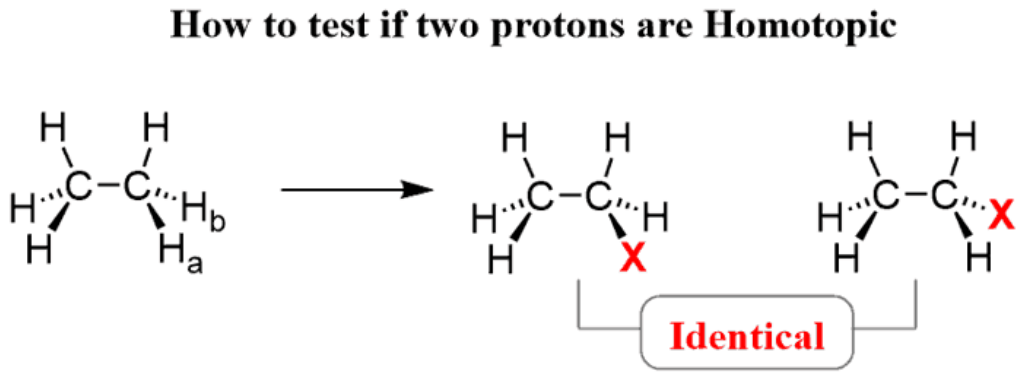
PRINCIPLES OF ASYMMETRIC SYNTHESIS

Topicity refers to the spatial and symmetry-related aspects of atoms or groups within a molecule. It is an important concept in stereochemistry, which is the study of the spatial arrangement of atoms in molecules and their impact on the physical and chemical properties of those molecules.

Topicity helps to describe and predict the behavior of molecules in chemical reactions and interactions, particularly in chiral environments.

The main types of topicity include homotopic, enantiotopic, diastereotopic, and heterotopic. Here's a brief overview of each:

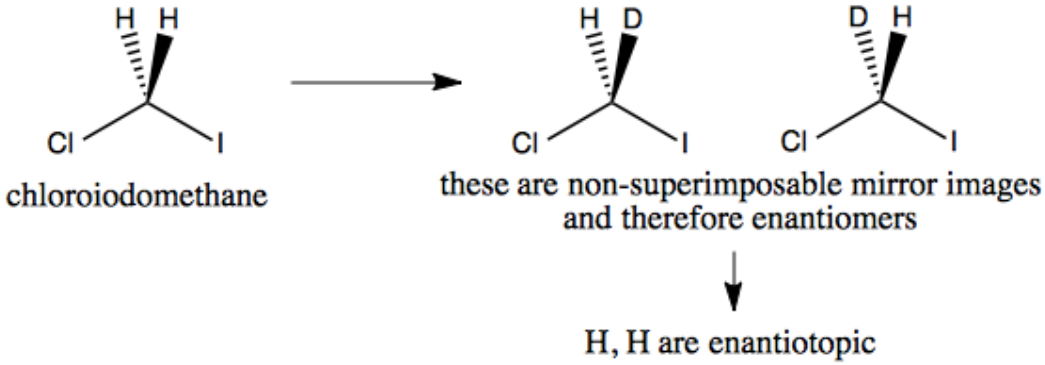
1. **Homotopic**:
   - **Definition**: Atoms or groups in a molecule are homotopic if they are identical and interchangeable by any symmetry operation of the molecule.
   - **Example**: The three hydrogen atoms in a methane (CH_4) molecule are homotopic because rotating the molecule does not change the positions or environments of the hydrogen atoms.



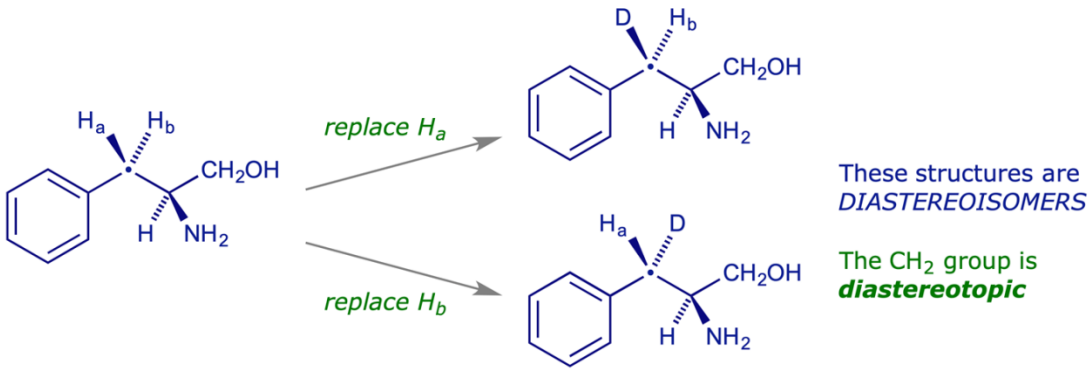
The two molecules are identical (rotate 120º around the C-C bond). Replacing any other H's will result in the same molecule as well - they are all ***homotopic.***

2. **Enantiotopic**:
   - **Definition**: Atoms or groups are enantiotopic if they are related by a symmetry operation that, if applied, would convert one into the mirror image of the other. Replacing one of the enantiotopic groups with a different group results in enantiomers.

- **Example**: In ethanol (CH_3CH_2OH), the two hydrogen atoms on the methylene carbon (CH_2) are enantiotopic. Replacing one of these hydrogens with a different group (e.g., a deuterium) would yield a pair of enantiomers.



3. **Diastereotopic**:
   - **Definition**: Atoms or groups are diastereotopic if they are not related by any symmetry operation, and their replacement leads to diastereomers (non-mirror image stereoisomers).
   - **Example**: In 2-butanol ($CH_3CH(OH)CH_2CH_3$), the two hydrogen atoms on the CH_2 group are diastereotopic. Replacing one of these hydrogens with a different group creates diastereomers.



4. **Heterotopic**:
   - **Definition**: Atoms or groups are heterotopic if they are in different chemical environments, which cannot be converted into one another by any symmetry operation. These atoms or groups are distinct and non-equivalent.
   - **Example**: The hydrogen atoms in propanal (CH_3CH_2CHO) are heterotopic because the chemical environment of the hydrogens in the CH_3 group is different from those in the CH_2 group.

Understanding topicity is essential for analyzing NMR spectra, predicting the outcome of chemical reactions, and designing chiral drugs and catalysts.

It allows chemists to recognize and manipulate the three-dimensional arrangement of atoms in molecules to achieve desired properties

TECHNIQUES FOR DETERMINATION OF ENANTIOMERIC EXCESS

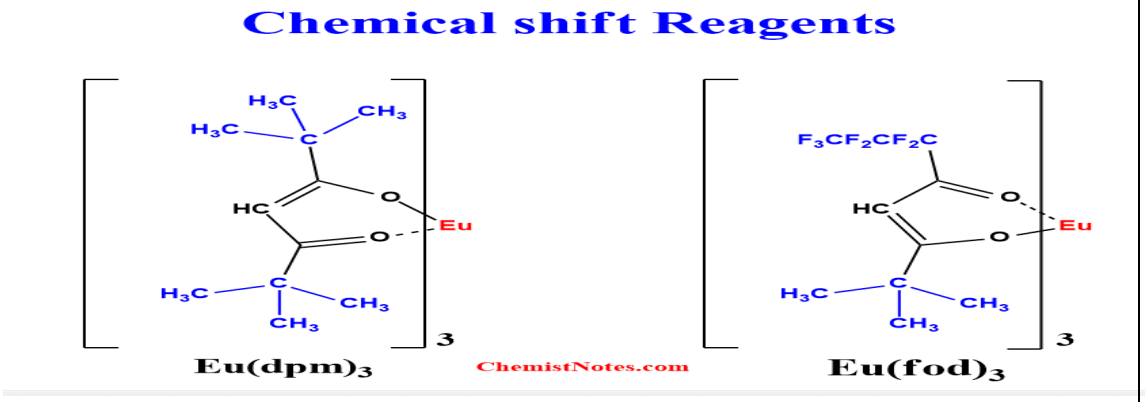
Chiral NMR (Nuclear Magnetic Resonance) spectroscopy is a powerful tool used to study chiral molecules and their environments.

In a chiral environment, enantiomers (non-superimposable mirror images) exhibit distinct NMR spectra, allowing for the differentiation and analysis of these stereoisomers.

This ability to distinguish enantiomers and diastereomers is crucial in the field of stereochemistry and has significant applications in drug development, synthesis of chiral compounds, and asymmetric catalysis. Here's an overview of how chiral NMR works and its key components:

Basic Principles

1. **Chiral Shift Reagents**:
    - **Usage**: Chiral shift reagents are used to induce different chemical shifts in enantiomers, making them distinguishable in NMR spectra.
    - **Example**: Lanthanide-based shift reagents like $Eu(hfc)_3$ (tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato] europium(III)) can be used to induce distinct shifts for enantiomers.



2. **Solvent Effects**:
    - **Chiral Solvents**: Using chiral solvents can create an environment where enantiomers interact differently with the solvent, leading to distinguishable NMR spectra.
    - **Example**: Solvents like (R)- or (S)-2,2,2-trifluoro-1-(9-anthryl)ethanol can be used to achieve this effect.
3. **Chiral Auxiliaries**:
    - **Formation of Diastereomers**: Attaching a chiral auxiliary to a prochiral or achiral molecule converts it into diastereomers, which have different NMR spectra.
    - **Example**: Using (R)- or (S)-Mosher's acid chloride to form diastereomeric esters or amides.

Practical Applications

1. **Determining Enantiomeric Excess (ee)**:
    - **Definition**: Enantiomeric excess is a measure of the purity of an enantiomer in a mixture.
    - **NMR Method**: By integrating the distinct peaks of enantiomers in the presence of a chiral shift reagent, the ratio of enantiomers can be determined, allowing for the calculation of enantiomeric excess.
2. **Stereochemical Assignments**:
    - **Relative Configuration**: Chiral NMR can help determine the relative configuration of stereocenters within a molecule by comparing the chemical shifts and coupling constants in different chiral environments.
    - **Absolute Configuration**: Sometimes, with the help of chiral shift reagents or derivatizing agents, the absolute configuration of stereocenters can be assigned.
3. **Studying Chiral Interactions**:
    - **Host-Guest Chemistry**: Chiral NMR is used to study interactions between chiral hosts and guests, providing insights into molecular recognition and binding.
    - **Example**: Investigating the binding of chiral drugs to protein targets or chiral catalysts.

Techniques in Chiral NMR

1. **1H NMR and 13C NMR**:
    - **Proton NMR (1H NMR)**: Often used to observe the chemical shifts of hydrogen atoms in a chiral environment.
    - **Carbon NMR (13C NMR)**: Useful for observing the shifts of carbon atoms in chiral centers and adjacent carbons.

2. **NOESY and ROESY**:
    - **Nuclear Overhauser Effect Spectroscopy (NOESY)**: Provides information about spatial proximity of nuclei, useful for elucidating 3D structures in chiral molecules.
    - **Rotating-frame Overhauser Effect Spectroscopy (ROESY)**: Similar to NOESY, but often used for larger molecules or those with slow molecular motion.
3. **2D NMR Techniques**:
    - **Heteronuclear Single Quantum Coherence (HSQC)**: Correlates 1H and 13C chemical shifts, aiding in the identification of chiral centers.

PROCHIRALITY

Definition of Prochirality

- **Prochirality** refers to the property of an achiral molecule (or a part of a molecule) that can be converted into a chiral molecule by a single substitution or reaction.
- A molecule is prochiral if it has two identical substituents that, when one is replaced with a different substituent, can form a chiral center.

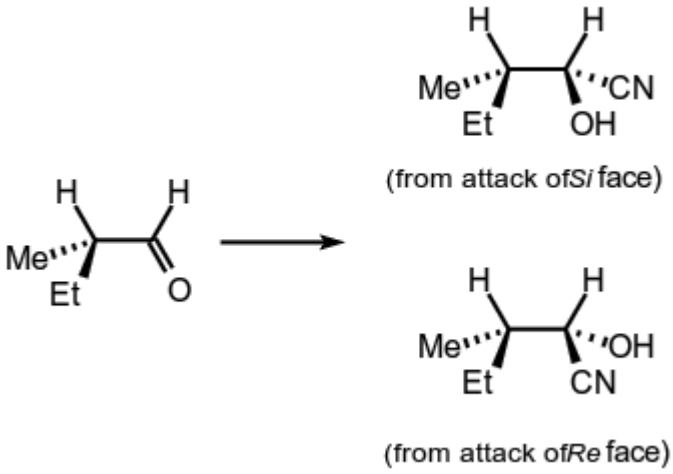
Types of Prochirality

1. **Prochiral Centers**:
    - A carbon atom with two identical groups and two different groups.
    - Example: In 2-butanone, the carbonyl carbon is prochiral because replacing one of the methyl groups with a different substituent would create a chiral center.
2. **Prochiral Faces**:
    - Refers to planar or trigonal molecules where the two faces of the plane are different.
    - Example: The faces of the carbonyl group in aldehydes and ketones are prochiral.

Identifying Prochirality

1. **Re/Si Nomenclature**:
    - Used to describe the faces of trigonal planar molecules.
    - **Re face**: When the substituents are arranged in a clockwise manner in the priority order.
    - **Si face**: When the substituents are arranged in a counterclockwise manner in the priority order.

- Example: In acetophenone, the face that has a clockwise arrangement of substituents (phenyl group, methyl group, hydrogen) is the Re face, and the opposite face is the Si face.



2. **Pro-R/Pro-S Nomenclature**:

1.Identify the stereoheterotopic ligands in a molecule at prochiral center.

2.Give priority fornthe attached groups according to R,S nomenclature rules.

3.While giving the priority assume one of the heterotpic ligand has top priority ligand and the other gets lower priority.

4.After giving priority,keep least priority group away from observer.

5.If priority direction is clock-wise it is Pro-R for highest priority ligand,and Pro-S for lowest priority ligand.

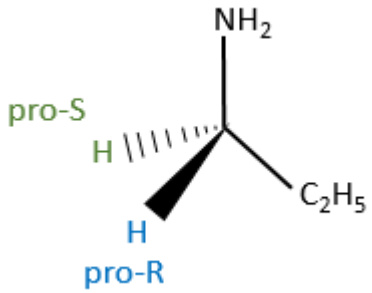
6.If priority direction is anti-clockwise it is Pro-S for highest priority ligand,Pro-R for lowest priority ligand.

7.Used for tetrahedral centers with two identical groups.

8.Pro-R: The replacement of a group leading to an R configuration.

9.Pro-S: The replacement of a group leading to an S configuration.

10.Example: In ethanol (CH3CH2OH), replacing one of the hydrogens on the carbon bearing the hydroxyl group can lead to a chiral center. If replacing one hydrogen results in the R configuration, it is termed Pro-R; if S, then Pro-S.



Examples and Applications

1. **Biochemical Examples**:
   - Enzymatic reactions often involve prochiral substrates, where the enzyme differentiates between prochiral centers or faces.
   - Example: Citrate in the citric acid cycle is a prochiral molecule, where aconitase acts on the pro-R hydrogen of the prochiral center.
2. **Synthesis and Catalysis**:
   - Prochirality is important in asymmetric synthesis, where catalysts or reagents are used to selectively produce one enantiomer from a prochiral substrate.
   - Example: Hydrogenation of prochiral alkenes using chiral catalysts can produce enantiomerically enriched products.
3. **Pharmaceuticals**:
   - Many drugs are developed from prochiral substrates to ensure that only the active enantiomer is produced.
   - Example: The synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease, involves the selective transformation of a prochiral intermediate.

SPECIFIC ROTATION:

In asymmetric synthesis, specific rotation is an important property used to characterize chiral compounds and assess the enantiomeric purity of a product. Specific rotation is defined as the observed angle of rotation of plane-polarized light by a chiral compound under standardized conditions, and it is given by the equation:

$[\alpha] = \alpha / l \cdot c\alpha$

where:

- $[\alpha]$ is the specific rotation.

- α is the observed rotation (in degrees).
- l is the path length of the sample cell (in decimeters).
- c is the concentration of the sample (in grams per milliliter).

Role of Specific Rotation in Asymmetric Synthesis:

1. **Determining Enantiomeric Excess (ee)**: Enantiomeric excess is a measure of the purity of an enantiomeric mixture. It is calculated using the specific rotation values of the mixture and the pure enantiomers.

   e.e=[α]mixture/[α]pure|×100%

   Here,[α]mixture is the specific rotation of the mixture, and [α]pure is the specific rotation of the pure enantiomer.

2. **Monitoring Reaction Progress**: During an asymmetric synthesis, measuring the specific rotation of the reaction mixture at different stages can provide insight into the formation and accumulation of the desired chiral product.
3. **Quality Control**: Specific rotation is used to ensure the consistency and quality of chiral compounds in industrial processes. It helps in verifying the enantiomeric purity of the final product.
4. **Comparison with Literature Values**: The specific rotation of synthesized chiral compounds can be compared with literature values to confirm the identity and purity of the product. Discrepancies might indicate the presence of impurities or incorrect stereochemistry.

Example:

Consider the synthesis of (R)-2-butanol, which has a known specific rotation [α]D20=+13.52∘. Suppose an asymmetric synthesis of (R)-2-butanol yields a product with a specific rotation of [α]D20=+10.14∘. To determine the enantiomeric excess:

$$ee=|10.14/13.52|\times 100\%=75\%$$

This indicates that the product is 75% enantiomerically pure, meaning it contains 75% (R)-2-butanol and 25% of the racemic mixture (equal parts of R and S).

Practical Considerations:

- **Temperature and Wavelength**: Specific rotation is dependent on temperature and the wavelength of light used (typically the sodium D-line, 589 nm). Standard conditions should be specified, such as [α]D20, where D indicates the wavelength and 20 indicates the temperature in Celsius.
- **Solvent Effects**: The solvent can affect the specific rotation. Therefore, the solvent should be specified when reporting specific rotation values.

UNIT-III

PERICYCLIC REACTIONS-I

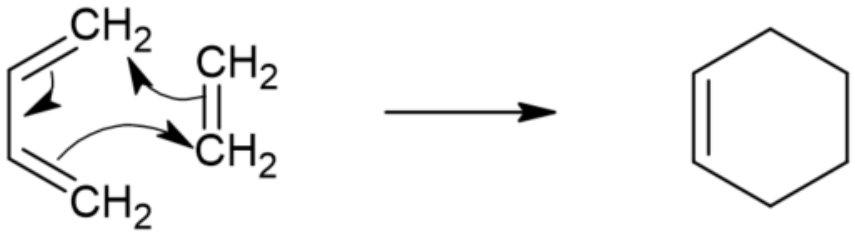
Pericyclic reactions are a class of organic reactions that proceed through a concerted, cyclic transition state, where the electron redistribution occurs in a synchronized manner without the formation of intermediates. These reactions are typically categorized by the nature of the cyclic electron movement and the types of molecular orbitals involved. Here's a comprehensive overview of pericyclic reactions, their types, mechanisms, and key features:

General Characteristics of Pericyclic Reactions

1. **Concerted Mechanism**: The reaction occurs in a single step through a cyclic transition state without intermediates.
2. **Cyclic Transition State**: Electrons move in a loop, maintaining a cyclic array during the transition state.
3. **Orbital Symmetry**: Governed by the conservation of orbital symmetry, described by Woodward-Hoffmann rules.
4. **Thermal vs. Photochemical Activation**: Reactions can be driven by heat (thermal) or light (photochemical), leading to different symmetry requirements.

Types of Pericyclic Reactions

1. **Cycloaddition Reactions**:
    - **Definition**: Two or more π-systems combine to form a cyclic product.
    - **Example**: The Diels-Alder reaction, where a conjugated diene reacts with a dienophile to form a six-membered ring.
    - **Woodward-Hoffmann Rules**: $(4n + 2)$ π-electrons are thermally allowed (Hückel), while $4n$ π-electrons are photochemically allowed (Möbius).



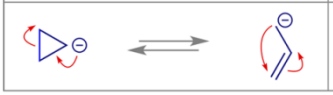
CYCLOADDITIONS

e⁻ in transition state	Activation	Symmetry allowed	Example
4n (even number of curved arrows)	heat	supra/antara	[π2s + π2a]
	light	supra/supra	[π2s + π2s]
4n + 2 (odd number of curved arrows)	heat	supra/supra	[π4s + π2s]
	light	supra/antara	[π4s + π2a]

2.Electrocyclic Reactions:

- **Definition**: A single π-system rearranges to form a ring, changing the number of π and σ bonds.
- **Example**: The thermal ring opening of cyclobutene to 1,3-butadiene.
- **Woodward-Hoffmann Rules**: For thermal reactions, (4n + 2) π-electrons proceed via conrotatory motion, and 4n π-electrons proceed via disrotatory motion. The opposite is true for photochemical reactions.

ELECTROCYCLIC REACTIONS

Reaction	Electrons		Thermal	Photochemical	Examples
	4	*4n*	conrotation	disrotation	005, 006, 025
	6	*4n+2*	disrotation	conrotation	004, 016, 026
	8	*4n*	conrotation	disrotation	017
	4	*4n*	conrotation	disrotation	
	6	*4n+2*	disrotation	conrotation	
	2	*4n+2*	disrotation	conrotation	033
	4	*4n*	conrotation	disrotation	

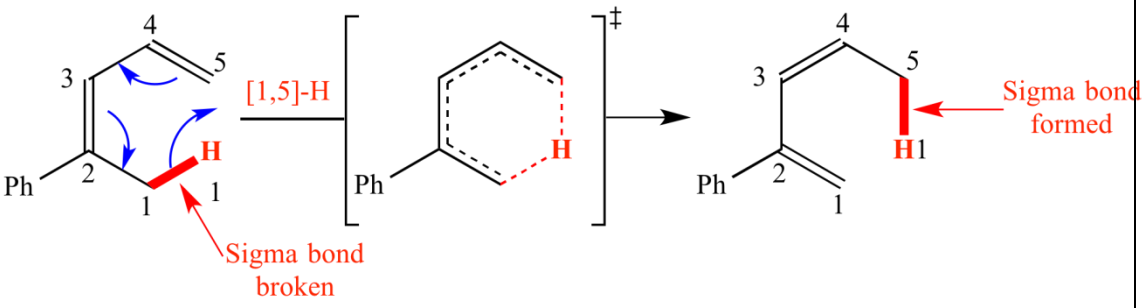
3.Sigmatropic Rearrangements:

- **Definition**: A σ-bonded atom/group migrates across a π-system, with concurrent shift in π-electrons.
- **Example**: The Cope rearrangement, a [3,3]-sigmatropic shift.
- **Woodward-Hoffmann Rules**: The [i,j]-sigmatropic shifts are allowed if (i + j) = 4n + 2 for suprafacial migration and 4n for antarafacial migration.

SIGMATROPIC REARRANGEMENTS

Electrons in TS	Activation	Symmetry allowed
4n (even number of curved arrows)	heat	antara*
	light	supra
4n + 2 (odd number of curved arrows)	heat	supra
	light	antara*

** In most cases restrictions imposed by molecular geometry prevent antarafacial reactions.*



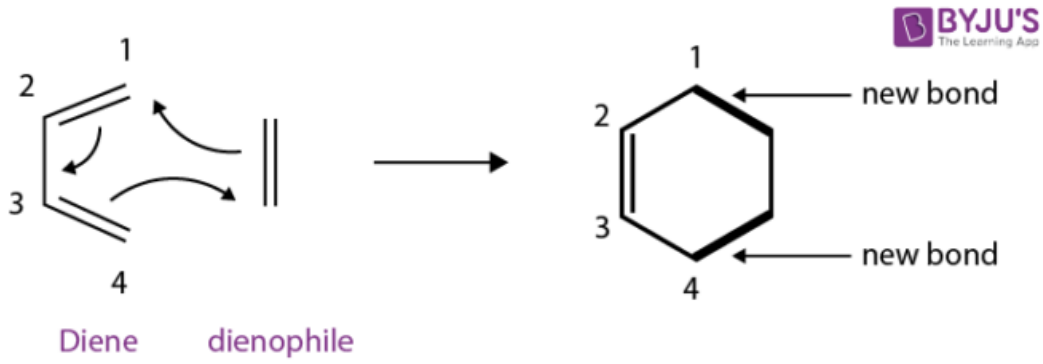
2. **Group Transfer Reactions**:
   - **Definition**: Groups transfer with cyclic electron movement but do not fit neatly into the other categories.
   - **Example**: Ene reactions, where an alkene and a hydrogen atom interact to form a new σ-bond and a new π-bond.

Mechanistic Details and Examples

1. **Cycloaddition Example: Diels-Alder Reaction**:

   Two new σ-bonds are formed at the same time during a Diels-Alder reaction. Therefore two filled p-orbitals and two empty p-orbitals have to be available. Expressed in FMOs this means the interaction between the HOMO of the diene and the LUMO of the dienophile (or vice versa). It is important to note that in cycloadditions the two molecules approach each other.

   - **Reactants**: Conjugated diene (electron-rich) and a dienophile (electron-poor).
   - **Product**: Cyclohexene derivative.
   - **Stereochemistry**: The reaction is stereospecific, retaining the cis/trans configuration of substituents.

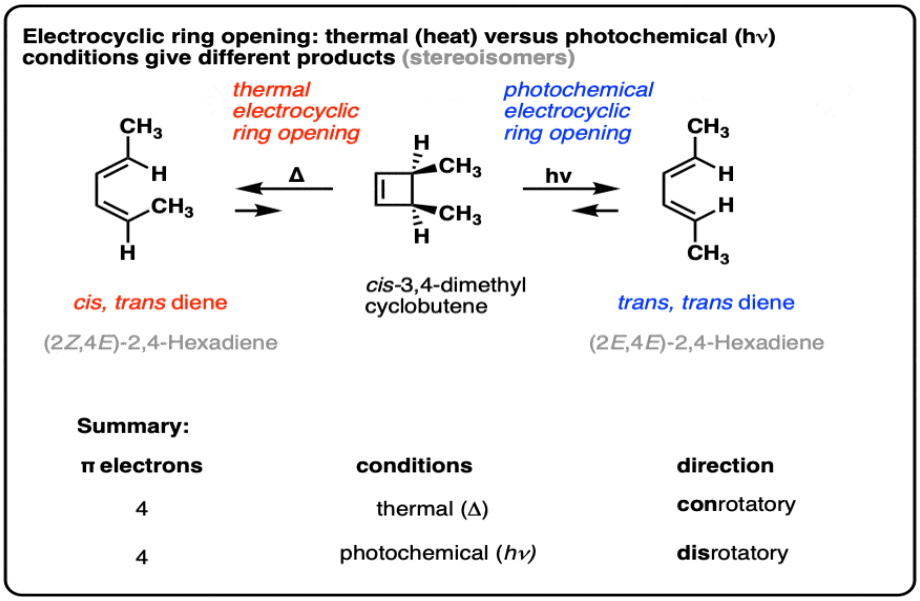


2. **Electrocyclic Example: Ring Opening of Cyclobutene**:
   - **Reactants**: Cyclobutene.
   - **Product**: 1,3-Butadiene.

When performing an electrocyclic reaction, it is often desirable to predict the cis/trans geometry of the reaction's product. The first step in this process is to determine whether a reaction proceeds through conrotation or disrotation.

Stereospecificity of electrocyclic reactions System Thermally induced (ground state) Photochemically induced (excited state) Even of conjugation Conrotatory Disrotatory Odd of conjugation Disrotatory Conrotatory

After determining the type of rotation, whether the product will be cis or trans can be determined by examining the starting molecule. In the example below, the disrotation causes both methyls to point upwards, causing the product to be cis-dimethylcyclohexadiene. In addition, the torquoselectivity in an electrocyclic reaction refers to the direction of rotation. For example, a reaction that is conrotatory can still rotate in two directions, producing enantiomeric products.



3. **Sigmatropic Example: Cope Rearrangement**:
    - **Reactants**: 1,5-Hexadiene.
    - **Product**: Another 1,5-Hexadiene (often isomerized).
    - **Concerted Shift**: All bonds break and form simultaneously in a cyclic transition state.
4. **Ene Reaction Example**:
    - **Reactants**: Alkene and allylic hydrogen.
    - **Product**: Allylic product with new σ-bond and π-bond.
    - **Mechanism**: Concerted transfer of hydrogen atom with migration of double bonds.

Woodward-Hoffmann Rules

These rules are fundamental for predicting the feasibility and stereochemistry of pericyclic reactions. They rely on the conservation of orbital symmetry:

1. **Hückel Systems (4n + 2 π-electrons)**:

   1) Count the contributing p-orbitals. Total = n.

   2) Count the electrons held in these orbitals; two for each double bond, two for a carbanion or lone pair, one for an unpaired electron, zero for a carbocation. Total = m

   3) For n contributing p-orbitals there will be n molecular orbitals.

   4) Draw n horizontal lines stacked on top of each other to represent the molecular orbitals and feed in the m electrons two at a time from the bottom (lowest energy) up (highest energy).

   5) Identify the HOMO, the LUMO, and, for radicals, the SOMO. These are the Frontier Molecular Orbitals (FMOs).

   6.Aromatic Transition State All thermally induced pericyclic reactions have transition structures involving a total of 4n+2 electrons. This explanation in terms of an aromatic transition state can be extended to cover all situations (including those involving antarafacial thermal reactions) using Frontier Orbitals. Frontier Molecular Orbitals These are the HOMO of one component and LUMO of the other

   Möbius Systems (4n π-electrons):

   - Thermally allowed reactions proceed via antarafacial pathways.
   - Photochemically allowed reactions proceed via suprafacial pathways.

Applications of Pericyclic Reactions

1. **Synthesis of Complex Molecules**: Pericyclic reactions are used to synthesize complex natural products and pharmaceuticals.
2. **Asymmetric Synthesis**: Enantioselective pericyclic reactions can be used to produce chiral molecules with high stereocontrol.
3. **Material Science**: These reactions are utilized in the synthesis of polymers and advanced materials with specific properties.

Frontier Molecular Orbitals (FMOs)

Introduction to Frontier Molecular Orbitals

- **Frontier Molecular Orbitals (FMOs)** are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in a molecule.
- These orbitals play a critical role in determining the chemical reactivity and properties of molecules.
- The concept of FMOs is central to the molecular orbital theory and provides insights into reaction mechanisms and electronic transitions.

HOMO and LUMO

1. **HOMO (Highest Occupied Molecular Orbital)**:
    - The molecular orbital that contains the highest energy electrons that are still bound to the molecule.
    - Acts as an electron donor in chemical reactions.
    - Example: In ethylene (C_2H_4), the π-bonding orbital is the HOMO.
2. **LUMO (Lowest Unoccupied Molecular Orbital)**:
    - The molecular orbital that is empty and has the lowest energy among the unoccupied orbitals.
    - Acts as an electron acceptor in chemical reactions.
    - Example: In ethylene (C_2H_4), the π* anti-bonding orbital is the LUMO.

Importance of FMOs

1. **Chemical Reactivity**:
    - FMOs determine how molecules interact with each other.
    - Reactions often occur between the HOMO of one molecule and the LUMO of another.
    - Example: In a Diels-Alder reaction, the HOMO of the diene interacts with the LUMO of the dienophile.
2. **Orbital Interactions**:
    - FMOs dictate the course of orbital overlap and the strength of interactions.
    - Good overlap between HOMO and LUMO results in more effective bonding interactions.
3. **Electrophiles and Nucleophiles**:
    - Electrophiles (electron acceptors) interact with the HOMO of nucleophiles (electron donors).
    - Example: In a nucleophilic substitution reaction, the nucleophile's HOMO donates electrons to the electrophile's LUMO.

Applications in Chemistry

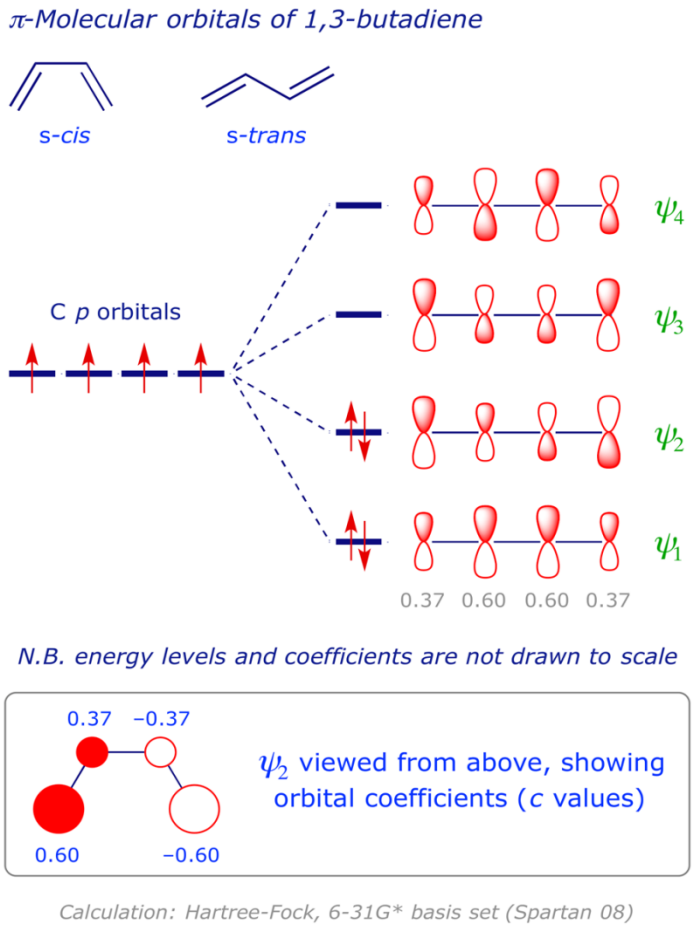
1. **Pericyclic Reactions**:
    - FMOs explain the selectivity and outcomes of pericyclic reactions.
    - Example: Woodward-Hoffmann rules use FMOs to predict the stereochemistry of electrocyclic reactions, cycloadditions, and sigmatropic rearrangements.
2. **Photochemistry**:
    - Electronic transitions involve excitation from HOMO to LUMO.
    - Example: UV-visible spectroscopy analyzes transitions between FMOs to provide information about molecular structure and conjugation.
3. **Catalysis**:
    - Homogeneous and heterogeneous catalysis often rely on the interaction of FMOs between the substrate and the catalyst.
    - Example: Transition metal complexes facilitate reactions by aligning their FMOs with those of the reactants.
4. **Molecular Orbital Diagrams**:
    - Used to visualize and compare the energy levels of FMOs in different molecules.
    - Example: Molecular orbital diagrams of diatomic molecules like O_2 and N_2 illustrate their bonding and antibonding interactions.

Examples of FMO Theory in Practice

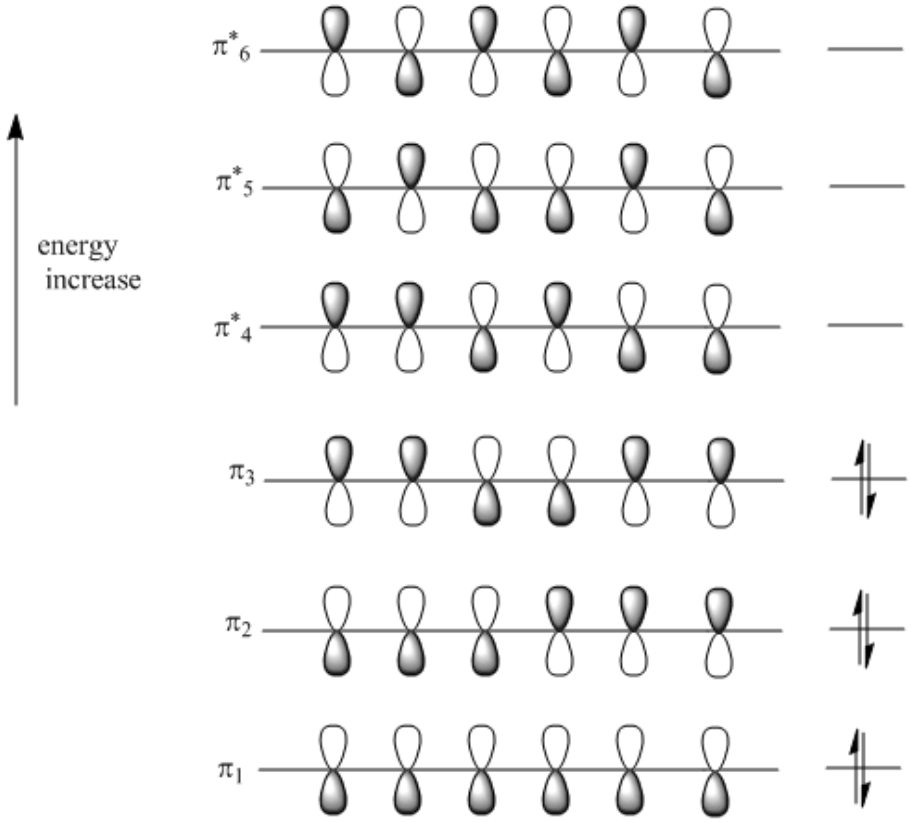
1. **Diels-Alder Reaction**:
    - The HOMO of the diene (with π electrons) interacts with the LUMO of the dienophile (with π* electrons) to form a new cyclic compound.
    - Orbital symmetry considerations are crucial for predicting the reaction pathway and stereochemistry.
2. **Electrophilic Addition to Alkenes**:
    - The π electrons in the alkene's HOMO interact with the electrophile's LUMO, leading to bond formation.
    - Example: In the addition of HBr to ethylene, the HOMO of ethylene donates electrons to the empty orbital of H^+.
3. **Charge Transfer Complexes**:
    - Involves interactions between the HOMO of a donor molecule and the LUMO of an acceptor molecule.
    - Example: Complexes formed between electron-rich aromatic rings and electron-deficient species.
    - **Frontier molecular orbitals of 1,3-Butadiene:** The number of nodes increases by one on going to the next higher MO and, in

general, the number of nodes within a particular MO (ψk) is k-1. In a linear π-system if the number of nodes is Even then the terminal orbital coefficients will be of Equal sign (i.e. both positive or both negative); if the number of nodes is Odd the terminal

	No.of nodes	**σ**	**C2**	**Electron distribution**	
Ψ4	**3**	**A**	**S**	-	LUMO
Ψ3	**2**	**S**	**A**	LUMO	**1e-**HOMO
Ψ2	**1**	**A**	**S**	**2e-**HOMO	**1e-**
Ψ1	**0**	**S**	**A**	**2e-**	**2e-**



- **1,3,5,Hexatriene:**



	No.of nodes	ϭ	C2	Electron distribution	
Ψ6	**5**	**A**	**S**	**G.S**	**E.S**
Ψ5	**4**	**S**	**A**		LUMO
Ψ4	**3**	**A**	**S**	LUMO	**1e-**HOMO
Ψ3	**2**	**S**	**A**	**2e-**HOMO	**1e-**
Ψ2	**1**	**A**	**S**	**2e-**	**2e-**
Ψ1	**0**	**S**	**A**	**2e-**	**2e-**

UNIT-IV
PERICYCLIC REACTIONS-II

Sigmatropic rearrangements are a class of pericyclic reactions where a σ-bonded atom or group migrates across a π-system, resulting in the concurrent shift of π-electrons. These rearrangements are characterized by the migration of atoms or groups along the framework of a molecule, leading to a new structural arrangement without breaking the molecular backbone. The key feature of sigmatropic rearrangements is that they proceed through a cyclic transition state, ensuring a concerted mechanism. Here's a detailed overview of sigmatropic rearrangements:

General Characteristics

1. **Concerted Mechanism**: The migration of the σ-bonded group and the shifting of π-electrons occur simultaneously in a single step.
2. **Cyclic Transition State**: The reaction proceeds through a cyclic transition state, preserving the overall connectivity of the molecule.
3. **Thermal and Photochemical Activation**: These reactions can be driven by heat (thermal) or light (photochemical), which affects the allowed pathways based on orbital symmetry.

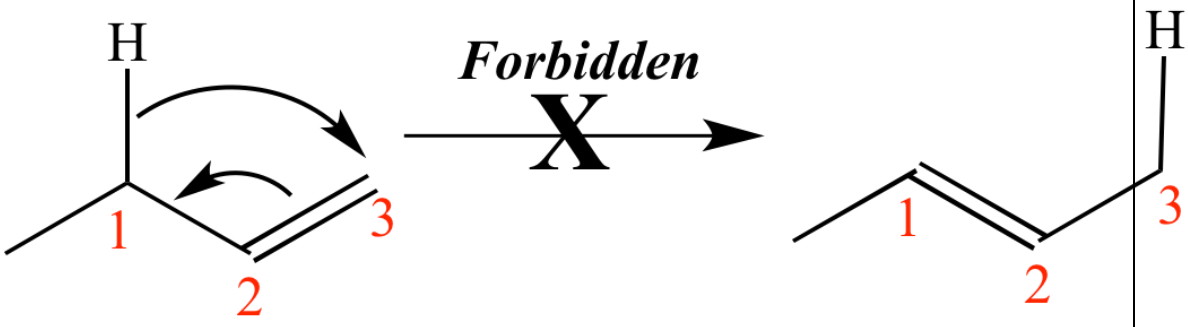
Nomenclature

Sigmatropic rearrangements are denoted by [i,j] notation, where:

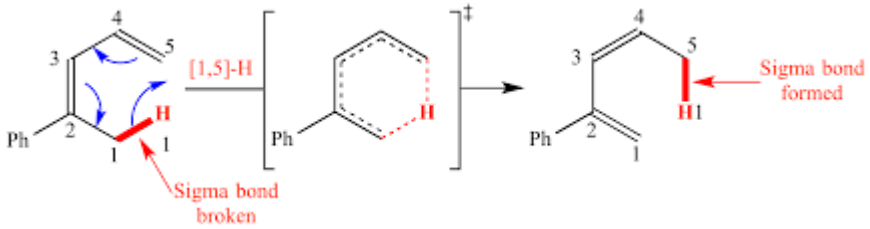
- **i**: The position from which the group migrates.
- **j**: The position to which the group migrates. For example, a [1,5]-sigmatropic shift indicates that a group moves from position 1 to position 5 of the molecular framework.

Types of Sigmatropic Rearrangements

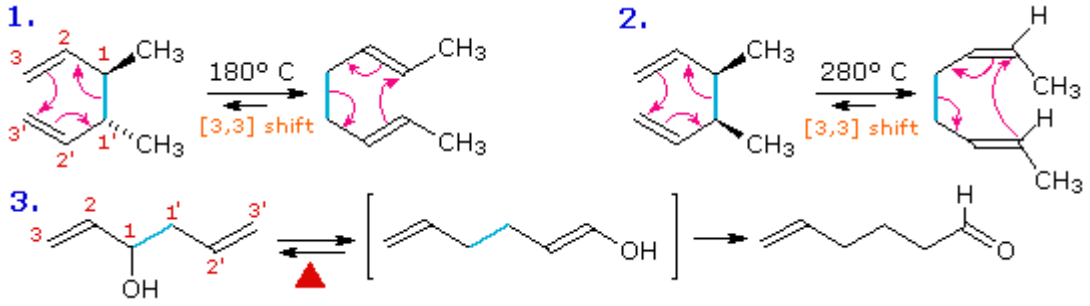
1. **[1,3]-Sigmatropic Shift**:
    - **Example**: Hydrogen shift in allylic systems.
    - **Mechanism**: A hydrogen atom migrates from one position to another across a conjugated π-system.
    - **Example Reaction**: Allyl vinyl ether rearrangement to acrolein.



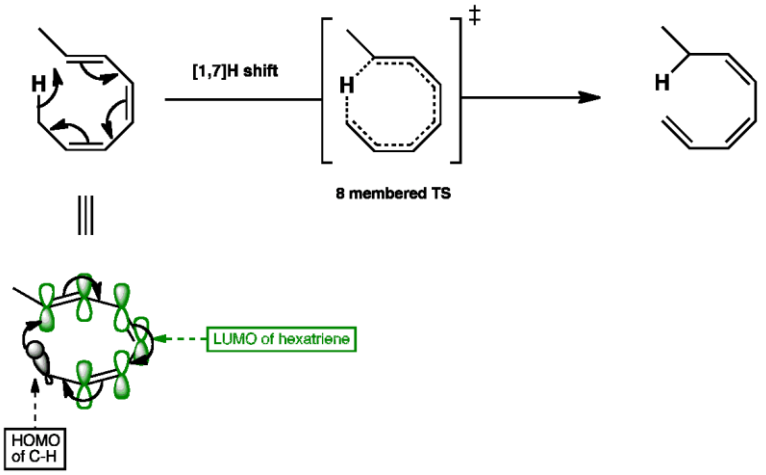
2. **[1,5]-Sigmatropic Shift**:
   - **Example**: Hydrogen or alkyl group migration in pentadiene systems.
   - **Mechanism**: A hydrogen or an alkyl group moves from one end of a conjugated system to another.
   - **Example Reaction**: The Cope rearrangement of 1,5-hexadiene.



3. **[3,3]-Sigmatropic Shift**:
   - **Example**: The rearrangement of allylic and propargylic groups.
   - **Mechanism**: A group moves from the third position of a π-system to another third position.
   - **Example Reaction**: The Claisen rearrangement, where an allyl vinyl ether rearranges to a γ,δ-unsaturated carbonyl compound.



4. **[1,7]-Sigmatropic Shift**:
   - **Example**: Hydrogen migration in heptadiene systems.
   - **Mechanism**: A hydrogen atom migrates from one position to another across a longer conjugated π-system.
   - **Example Reaction**: Sigmatropic shift in polyenes and polydienes.



Mechanistic Details and Examples

1. **Cope Rearrangement ([3,3]-Sigmatropic Shift)**:
    - **Reactants**: 1,5-Hexadiene.
    - **Product**: Another 1,5-Hexadiene (often isomerized).
    - **Transition State**: A six-membered cyclic transition state where bonds are broken and formed simultaneously.
    - **Conditions**: Typically thermally activated

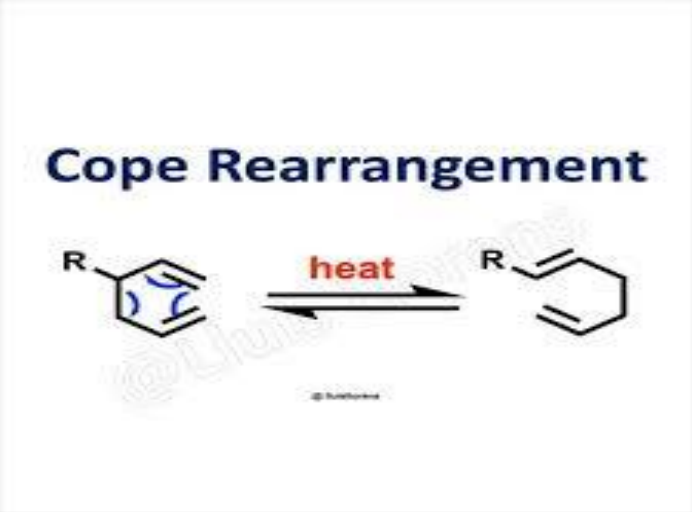
It is classified as a [3,3]-sigmatropic rearrangement with the Woodward-Hoffmann symbol [π2s+σ2s+π2s] and is therefore thermally allowed.

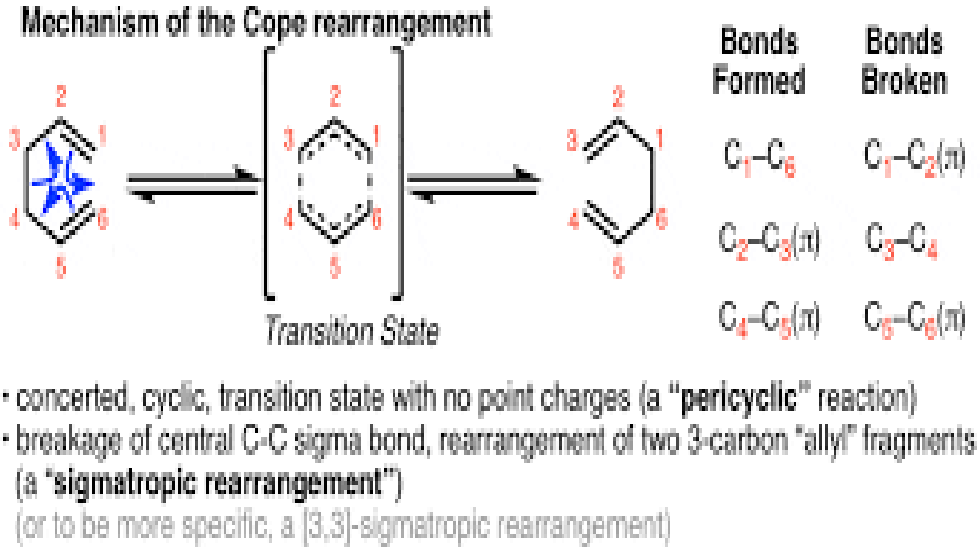
It is sometimes useful to think of it as going through a transition state energetically and structurally equivalent to a diradical, although the diradical is not usually a true intermediate (potential energy minimum).

The chair transition state illustrated here is preferred in open-chain systems (as shown by the Doering-Roth experiments).

However, conformationally constrained systems like cis-1,2-divinylcyclopropanes can undergo the rearrangement in the boat conformation.

It is currently generally accepted that most Cope rearrangements follows an allowed concerted route through a Hückel aromatic transition state and a diradical intermediate is not formed.





2.Claisen Rearrangement ([3,3]-Sigmatropic Shift):

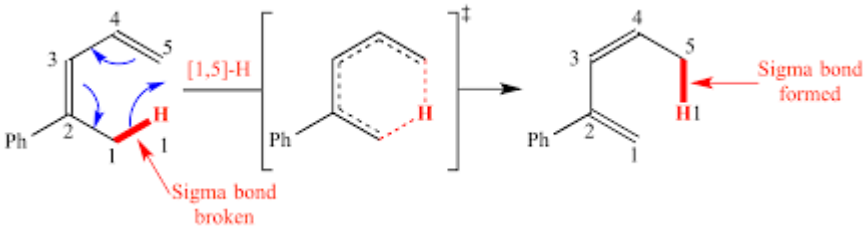
Claisen rearrangement is an organic chemical reaction that offers a *powerful method of the formation of carbon-carbon bonds***. The reactant of this reaction is allyl vinyl ether, is converted into a gamma, delta-unsaturated carbonyl compound when subjected to heat or a Lewis acid This reaction belongs to the *"sigmatropic rearrangement"* category of reactions wherein the mechanism of the reaction is concerted (i.e. all the bonds break and form simultaneously).**

An interesting fact about this reaction is that it was the first ever recorded example of a [3,3]- sigmatropic rearrangement reaction.

An example of the Claisen rearrangement reaction of an allyl vinyl ether is given below.

- **Reactants**: Allyl vinyl ether.
- **Product**: γ,δ-Unsaturated carbonyl compound.
- **Transition State**: A six-membered cyclic transition state with concerted movement of electrons

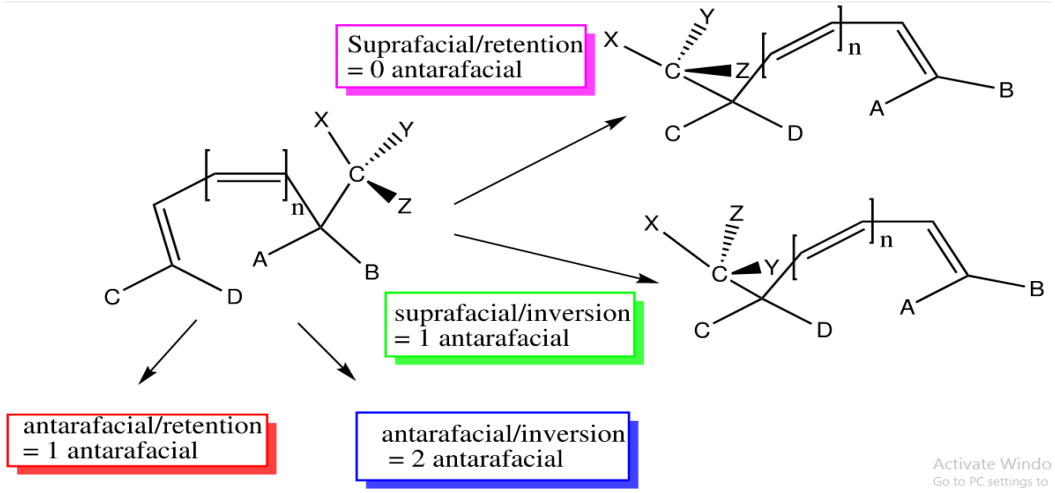
2. **Ene Reaction ([1,5]-Sigmatropic Shift)**:
   - **Reactants**: An alkene and an allylic hydrogen.
   - **Product**: A new alkene and a shifted hydrogen.
   - **Mechanism**: The hydrogen atom migrates from an allylic position to a new position, forming a new double bond.



Woodward-Hoffmann Rules for Sigmatropic Rearrangements

These rules help predict the feasibility and stereochemistry of sigmatropic shifts:

1. **Suprafacial vs. Antarafacial Shifts**:
   - **Suprafacial**: The migrating group and the π-electrons move on the same face of the π-system.
   - **Antarafacial**: The migrating group and the π-electrons move on opposite faces of the π-system.



2. **Thermal Conditions**:
   - **4n + 2 π-electrons**: Suprafacial shifts are allowed.
   - **4n π-electrons**: Antarafacial shifts are allowed.
3. **Photochemical Conditions**:
   - **4n + 2 π-electrons**: Antarafacial shifts are allowed.
   - **4n π-electrons**: Suprafacial shifts are allowed.

Applications of Sigmatropic Rearrangements

1. **Synthesis of Natural Products**: Used in the construction of complex natural products with intricate carbon skeletons.
2. **Asymmetric Synthesis**: Utilized in enantioselective synthesis to produce chiral molecules.
3. **Polymer Chemistry**: Applied in the design and synthesis of polymers with specific properties.
4. **Drug Development**: Essential in the synthesis of pharmaceuticals with precise stereochemical configurations.
