UNIT – II RETRO SYNTHETIC ANALYSIS

Introduction to Retro Synthetic Analysis

1. Understanding Disconnections

- Definition: Disconnections refer to the breaking of bonds in a target molecule to identify simpler precursor molecules.
- Purpose: It aids in planning the synthesis of complex molecules by working backward from the target.

2. Synthons and Synthetic Equivalents

- Synthons: Hypothetical fragments resulting from the disconnection of bonds in a molecule.
- Synthetic Equivalents: Compounds that can be transformed into synthons through chemical reactions.
- Importance: They provide a strategic framework for designing synthetic routes.

Applications:

- Retrosynthetic analysis of complex molecules using synthons and synthetic equivalents.
- Case studies demonstrating the strategic use of synthons and synthetic equivalents in total synthesis.
- Industrial applications of retro synthetic analysis in pharmaceutical and agrochemical sectors.

3. Synthon Approach

- Methodology: It involves breaking down a complex molecule into simpler synthons, which are then assembled to construct the target molecule.
- Advantages: Offers a systematic and logical approach to synthesis planning.

- Disconnections: Commonly based on functional group interconversions and retrosynthetic disconnections.

Applications of Synthon Approach:

Complex Molecule Synthesis:

- The Synthon Approach allows chemists to plan the synthesis of complex molecules by breaking them down into simpler building blocks.
- It facilitates the synthesis of natural products, pharmaceuticals, and agrochemicals with intricate molecular structures.

Efficient Route Design:

- By identifying key synthons and strategic disconnections, chemists can design more efficient synthetic routes.
- The approach minimizes the number of synthetic steps and improves overall yield.

Diversity-Oriented Synthesis:

- Synthon Approach enables the synthesis of diverse chemical libraries by varying the combination of synthons and reaction conditions.
- This is valuable in drug discovery efforts, where a diverse set of compounds is needed for screening purposes.

Mechanistic Insights:

- Analyzing retrosynthetic pathways provides valuable insights into reaction mechanisms and functional group interconversions.
- Understanding these mechanisms aids in the development of new synthetic methodologies.

4. Electron Donors (Nucleophiles)

- Definition: Nucleophiles are electron-rich species that donate electron pairs in chemical reactions.

Types of Nucleophiles:

Neutral Nucleophiles: Such as amines, alcohols, and ethers.

Anionic Nucleophiles: These carry a negative charge and include species like alkoxides, enolates, and cyanide ions.

Radical Nucleophiles: Free radicals that can donate an unpaired electron to form a bond with an electrophile.

- Examples: Grignard reagents, organolithium compounds, amines, and carbanions.
- Role: Nucleophiles participate in bond-forming reactions, especially in the formation of new carbon-carbon or carbon-heteroatom bonds.

Applications in Retro Synthetic Analysis:

Planning Synthesis Routes: Understanding nucleophilic reactivity helps in designing retrosynthetic pathways for target molecules.

Substitution Reactions: Nucleophiles often participate in substitution reactions, where they displace a leaving group from an electrophilic center.

Addition Reactions: Nucleophiles can add to multiple bonds, such as carbonyl groups, to form new carbon-carbon or carbon-heteroatom bonds.

Nucleophilic Aromatic Substitution: Nucleophiles can also substitute aromatic rings in a process known as nucleophilic aromatic substitution (SNAr)

5. Electron Acceptors (Electrophiles)

- Definition: Electrophiles are electron-deficient species that accept electron pairs in chemical reactions.
- Examples: Carbonyl compounds, alkyl halides, and Lewis acids.
- Role: Electrophiles react with nucleophiles to form new bonds, facilitating key transformations in synthesis.

Applications:

Retrosynthetic analysis of electron acceptors is employed in various organic synthesis endeavors:

- **Designing Synthetic Routes:** It guides the selection of appropriate starting materials and reaction sequences to achieve the target molecule efficiently.

- **Understanding Reaction Mechanisms:** By dissecting the target molecule into simpler precursors, retrosynthesis aids in comprehending the individual steps and the overall mechanism of electrophilic reactions.
- **Developing New Synthetic Methods:** The analysis can inspire the exploration of novel reaction pathways for generating specific electrophilic functionalities.

Introduction of Functional Groups:

1. **Definition:**
    - Functional groups are specific groups of atoms within molecules that are responsible for the characteristic chemical reactions of those molecules.
2. **Types of Functional Groups:**
    - Alcohols
    - Olefins (alkenes)
    - Ketones
    - Acids
3. **Chemical Properties and Reactivity:**
    - Each functional group exhibits unique chemical properties and reactivity.
    - Understanding these properties is crucial for designing synthetic routes in organic chemistry.

Umpolung Reactions:

1. **Definition:**
    - Umpolung reactions involve the reversal of the polarity of functional groups or the reversal of their reactivity patterns.
2. **Mechanism:**
    - Umpolung reactions often involve the use of reagents or conditions that alter the electronic structure of functional groups.
    - Common strategies include the use of reagents such as Nucleophiles, Electrophiles, Radicals, and Carbonyl Compounds.

3. **Examples:**
    - Examples of umpolung reactions include:
        - The Wittig reaction for olefin synthesis.
        - The Grignard reaction for carbon-carbon bond formation.
        - The Michael addition for nucleophilic addition to α,β-unsaturated carbonyl compounds.

One Group Disconnections:

1. **Definition:**
    - One group disconnections involve breaking a single bond to disconnect a specific functional group from the molecule.
2. **Strategic Planning:**
    - One group disconnections are commonly used in retrosynthetic analysis to simplify complex target molecules.
    - They allow chemists to identify key starting materials and plan synthetic routes efficiently.
3. **Applications by Functional Group:**
    - **Alcohols:**
        - One group disconnections involving alcohols often lead to carbonyl compounds through oxidation or elimination reactions.
        - Examples include the conversion of alcohols to ketones or aldehydes through oxidation with reagents like PCC or Jones reagent.
    - **Olefins:**
        - One group disconnections for olefins often involve functional group interconversion, such as the conversion of alkynes to alkenes or vice versa.
        - Examples include the hydrogenation of alkynes to form alkenes using catalytic hydrogenation.
    - **Ketones:**
        - One group disconnections for ketones often involve carbonyl group manipulation to introduce or remove substituents.

- Examples include the reduction of ketones to form alcohols using reducing agents like NaBH4 or LiAlH4.

- **Acids:**
    - One group disconnections for acids often involve transformations such as esterification or decarboxylation.
    - Examples include the conversion of carboxylic acids to esters using acid-catalyzed esterification reactions.

Applications:

- **Drug Synthesis:**
    - Retro synthetic analysis is extensively used in the pharmaceutical industry to design efficient synthetic routes for the production of drug molecules.
    - By identifying key functional groups and strategic disconnections, chemists can streamline the synthesis of complex drug candidates.
- **Natural Product Synthesis:**
    - Retro synthetic analysis is also employed in the synthesis of natural products, such as plant-derived compounds or bioactive molecules.
    - Understanding functional group interconversions and strategic disconnections is crucial for efficiently accessing complex natural product structures.
- **Materials Science:**
    - In materials science, retro synthetic analysis is used to design and synthesize polymers, catalysts, and other functional materials.
    - By strategically disconnecting functional groups, researchers can tailor the properties and functionalities of materials for specific applications.

Two Group Disconnections:

Two-group disconnections involve the simultaneous disconnection of two functional groups from a molecule. This strategic approach allows chemists to break down complex target molecules into simpler building blocks, facilitating the design of efficient synthetic routes.

1. 1,2-Difunctional Compounds:

- **Definition:**
    - 1,2-Difunctional compounds possess two functional groups attached to adjacent carbon atoms within the molecule.
- **Disconnection Strategy:**
    - A common strategy for 1,2-difunctional compounds is to disconnect the molecule into two fragments at the bond connecting the two functional groups.
- **Example:**
    - Ethylene glycol can be disconnected into two fragments: a primary alcohol (CH_2OH) and a halide (X) or a leaving group (LG), such as Cl or Br.
- **Application:**
    - One application is the synthesis of diols, such as ethylene glycol, which serves as a precursor for the production of polyester fibers and antifreeze.

2. 1,3-Difunctional Compounds:

- **Definition:**
    - 1,3-Difunctional compounds possess two functional groups separated by one carbon atom within the molecule.
- **Disconnection Strategy:**
    - The molecule can be disconnected into two fragments by breaking a bond between the central carbon atom and one of the functional groups.
- **Example:**
    - 1,3-Dibromopropane can be disconnected into two fragments: a primary halide (CH_2Br) and a secondary halide ($CHBr_2$).
- **Application:**
    - One application is the synthesis of vicinal dihalides, which are important intermediates in organic synthesis for the preparation of various organic compounds.

3. 1,4-Difunctional Compounds:

- **Definition:**

- 1,4-Difunctional compounds possess two functional groups separated by three carbon atoms within the molecule.

- **Disconnection Strategy:**
  - The molecule can be disconnected into two fragments by breaking a bond between the central carbon atoms, resulting in the formation of two symmetrical fragments.

- **Example:**
  - 1,4-Dibromobutane can be disconnected into two fragments: two secondary halides (CH_2Br).

- **Application:**
  - One application is the synthesis of symmetrically substituted butanes, which are commonly used as building blocks in organic chemistry for the synthesis of various organic compounds.

4. 1,5-Difunctional Compounds:

- **Definition:**
  - 1,5-Difunctional compounds possess two functional groups separated by four carbon atoms within the molecule.

- **Disconnection Strategy:**
  - The molecule can be disconnected into two fragments by breaking a bond between the central carbon atoms, resulting in the formation of two fragments with a greater distance between them.

- **Example:**
  - 1,5-Dibromopentane can be disconnected into two fragments: a primary halide (CH_2Br) and a tertiary halide (CBr_3).

- **Application:**
  - One application is the synthesis of symmetrically substituted pentanes, which are important intermediates in organic synthesis for the preparation of various organic compounds.

Convergent Syntheses:

1. **Definition:**
   - Convergent synthesis is a strategy in organic chemistry wherein complex molecules are synthesized through the assembly of smaller, simpler fragments or intermediates.

- These fragments are synthesized independently and then joined together in a convergent manner to form the final target molecule.

2. **Key Points:**

   - **Modular Approach:** Convergent synthesis employs a modular approach, where different fragments are prepared separately and then coupled together.
   - **Efficiency:** It allows for the efficient synthesis of complex molecules by breaking down the overall synthetic route into smaller, more manageable steps.
   - **Reduction of Complexity:** By dividing the synthesis into smaller subunits, convergent synthesis reduces the complexity of individual synthetic steps and facilitates the optimization of reaction conditions.

Applications:

- **Total Synthesis of Natural Products:** Convergent synthesis is widely used in the total synthesis of complex natural products, such as alkaloids, terpenoids, and polyketides.
- **Medicinal Chemistry:** In drug discovery and development, convergent synthesis enables the efficient assembly of drug candidates with complex structures and diverse functionalities.
- **Materials Science:** Convergent synthesis plays a crucial role in the fabrication of functional materials, including polymers, nanoparticles, and supramolecular assemblies.
- **Biotechnology:** It is utilized in the synthesis of biomolecules, peptides, and proteins, facilitating the construction of molecular scaffolds and bioconjugates.
- **Catalyst Design:** Convergent synthesis is employed in the design and synthesis of catalysts for organic transformations, enabling the incorporation of multiple catalytic functionalities into a single molecule.

Functional Group Interconversion:

1. **Alkene to Alcohol:**

   - Hydroboration-oxidation: Converts alkene to alcohol, anti-Markovnikov addition.
   - Application: Preparation of alcohols as intermediates in drug synthesis and natural product chemistry.

2. **Alkene to Halide:**

   - Halogenation: Addition of halogens like Cl_2 or Br_2 to alkenes.
   - Application: Synthesis of alkyl halides used in pharmaceuticals and agrochemicals.

3. **Alkene to Carbonyl Compound:**
    - Ozonolysis: Cleavage of alkene double bond, forming carbonyl compounds.
    - Application: Preparation of aldehydes and ketones for use in fragrance and flavor synthesis.
4. **Alcohol to Alkene:**
    - Dehydration: Removal of water from alcohol under acidic conditions.
    - Application: Production of alkenes for polymer synthesis and fine chemical manufacturing.
5. **Alcohol to Alkyl Halide:**
    - Substitution reactions with hydrogen halides or thionyl chloride.
    - Application: Preparation of alkyl halides for use in organic synthesis and material science.

Carbon-Heteroatom Bonds in Organic Synthesis:

Introduction: Carbon-heteroatom bonds play a pivotal role in organic chemistry, enabling the formation of diverse molecules with varied properties and functionalities. These bonds involve the connection between carbon atoms and atoms of other elements, such as nitrogen, oxygen, sulfur, and halogens.

Methods for Carbon-Heteroatom Bond Formation:

1. **Nucleophilic Substitution:**
    - Reaction between a nucleophile and a carbon atom bonded to a leaving group.
    - Example: SN1 or SN2 reactions with alkyl halides to form carbon-heteroatom bonds.
    - Application: Synthesis of a wide range of organic compounds, including pharmaceuticals and agrochemicals.
2. **Electrophilic Addition:**
    - Addition of an electrophile to a double or triple bond, resulting in the formation of a carbon-heteroatom bond.
    - Example: Addition of hydrogen halides to alkenes to form alkyl halides.
    - Application: Preparation of alkyl halides, important intermediates in organic synthesis.
3. **Condensation Reactions:**

- Reaction between a carbonyl compound and a compound containing a heteroatom, leading to the formation of a carbon-heteroatom bond.
- Example: Formation of imines or enamines from aldehydes or ketones and amines.
- Application: Synthesis of a variety of nitrogen-containing compounds, including amino acids and peptides.

4. **Metal-Heteroatom Bond Formation:**
    - Transition metal-catalyzed cross-coupling reactions between organometallic reagents and compounds containing heteroatoms.
    - Example: Suzuki-Miyaura cross-coupling reaction between aryl halides and boronic acids.
    - Application: Synthesis of complex organic molecules, including pharmaceuticals and materials.
5. **Oxidation-Reduction Reactions:**
    - Oxidation or reduction of functional groups to introduce or modify carbon-heteroatom bonds.
    - Example: Oxidation of alcohols to carbonyl compounds using oxidizing agents like chromic acid.
    - Application: Functionalization of organic molecules for further elaboration in synthesis.

Applications of Carbon-Heteroatom Bonds:

- Drug Discovery and Development: Carbon-heteroatom bond formation is crucial in the synthesis of pharmaceuticals and medicinal compounds.
- Material Science: Used in the design and synthesis of polymers, catalysts, and functional materials.
- Fine Chemicals Production: Enables the preparation of specialty chemicals, flavors, fragrances, and agrochemicals.

Methods for 3- and 4-Membered Rings:

1. **Ring Expansion:**
    - Cycloaddition reactions involving small ring compounds like cyclopropanes or epoxides can lead to the formation of larger rings.
    - Example: Conversion of cyclopropane to cyclobutane using a metal-catalyzed ring expansion reaction.
    - Application: Synthesis of medium-sized rings with diverse functionality.
2. **Ring Contraction:**

- Ring-opening reactions of strained cyclic compounds can lead to the formation of smaller rings.
- Example: Opening of cyclobutane ring under reducing conditions to form ethylene.
- Application: Preparation of smaller cyclic compounds for further functionalization.

Synthesis of Mono- and Difunctional Open Chain Molecules:

1. **Functional Group Addition Reactions:**
   - Addition of nucleophiles or electrophiles to unsaturated bonds in open chain molecules.
   - Example: Grignard reaction with aldehydes or ketones to form alcohols.
   - Application: Preparation of versatile intermediates with different functional groups for further elaboration.
2. **Reductive Functionalization:**
   - Reduction of functional groups followed by selective introduction of new functional groups.
   - Example: Reduction of a ketone to an alcohol followed by oxidation to form a carboxylic acid.
   - Application: Sequential functionalization of open chain molecules to access complex structures.

Mono- and Bicyclic Molecules with Substituents:

1. **Cyclization Reactions:**
   - Intramolecular cyclization reactions to form mono- or bicyclic structures.
   - Example: Intramolecular Friedel-Crafts acylation to form a benzene ring from a substituted alkyl chain.
   - Application: Synthesis of cyclic compounds with substituents at specific positions.
2. **Ring Expansion/Contraction:**
   - Controlled expansion or contraction of existing rings to introduce substituents.
   - Example: Ring expansion of cyclopentane to cyclohexane under specific conditions to accommodate substituents.

- Application: Modification of ring size to accommodate functional groups or improve stereochemical control.

Applications:

- Medicinal Chemistry: Synthesis of small heterocyclic molecules with pharmacological activity.
- Natural Product Synthesis: Preparation of complex frameworks found in natural products with diverse biological activities.
- Material Science: Functionalization of open chain molecules for the development of novel materials with tailored properties.
- Catalysis: Design of catalysts based on mono- and bicyclic molecules for various organic transformations.