ORGANIC CHEMISTRY

Isomerism

Organic compounds possess a unique property known as **isomerism**, which contributes to their vast diversity in nature.

- **Definition:**
  Isomerism is the phenomenon in which compounds with the **same molecular formula** exist in different forms due to variations in the arrangement of atoms.
  - Compounds that exhibit this phenomenon are called **isomers**.
- **Types of Isomerism:**
  Isomerism is broadly classified into two main categories:
  1. **Constitutional (Structural) Isomerism**
     - Arises due to different connectivity of atoms in a molecule.
     - These isomers can usually be interconverted by rotation about single covalent bonds without breaking bonds.
  2. **Stereoisomerism (Configurational Isomerism)**
     - Occurs due to different three-dimensional arrangements of atoms or groups in space.
     - Conversion between stereoisomers requires breaking and reforming bonds.

Note: In previous classes, both structural and stereoisomerism have been introduced. In this chapter, we will focus on **stereoisomerism** in detail.

Stereoisomerism

- **Definition:**
  Stereoisomers are molecules that have the **same molecular formula** and **same structural formula**, but differ in the **spatial arrangement of atoms**. The phenomenon is called **stereoisomerism**.
- **Biological Importance:**
  - Most biochemical reactions involve molecules with specific stereochemistry.
  - Enzymes act as catalysts and interact only with stereoisomers that fit correctly into their active sites.
  - Side effects of drugs often arise from the presence of the wrong stereoisomer, which does not fit properly in the enzyme's active site.
- **Subtypes of Stereoisomerism:**
  1. **Geometric Isomerism**
  2. (Another type—optical isomerism—will be discussed later in the chapter).

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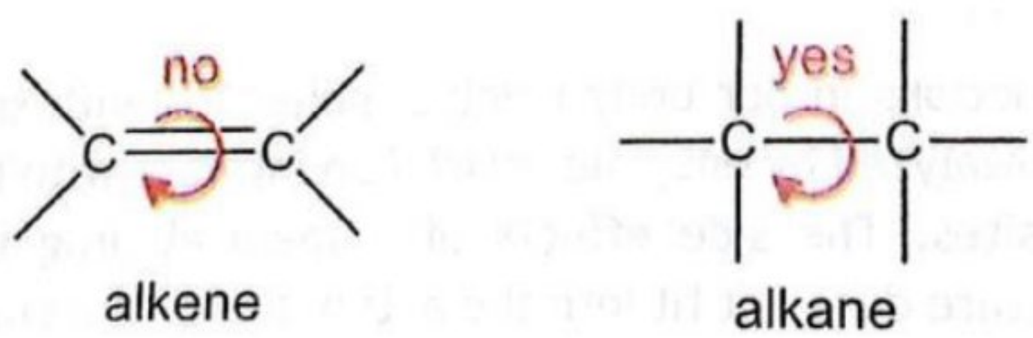
Geometric Isomerism

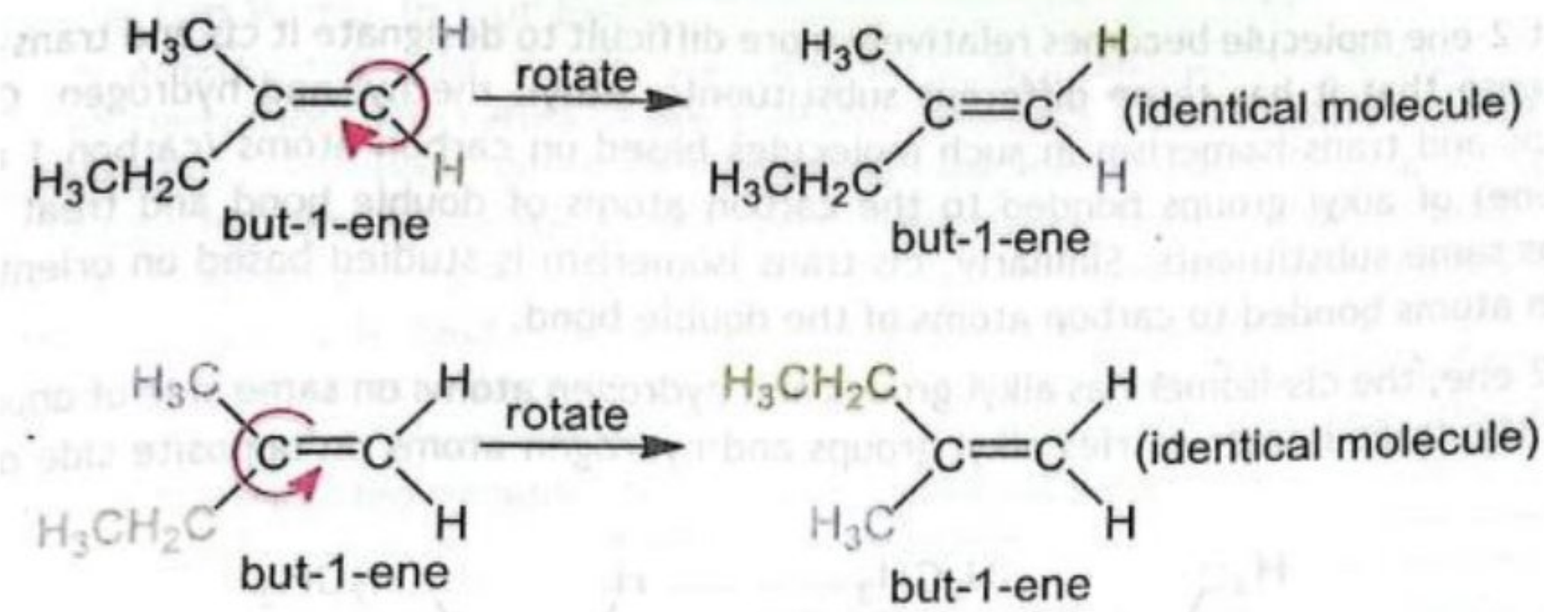
- **Definition:**
  Some organic compounds, especially alkenes, have the same connectivity of atoms and the same structural formula, but differ in the arrangement of atoms or groups around the double bond.
  - Such molecules are called geometric isomers.
  - This phenomenon is called geometric isomerism.
- **Reason for Geometric Isomerism:**
  - Each carbon atom in a double bond is **sp² hybridized**.
  - A double bond consists of:
    - **One sigma (σ) bond** → formed by head-on overlap of sp² orbitals.
    - **One pi (π) bond** → formed by sidewise overlap of unhybridized p orbitals.



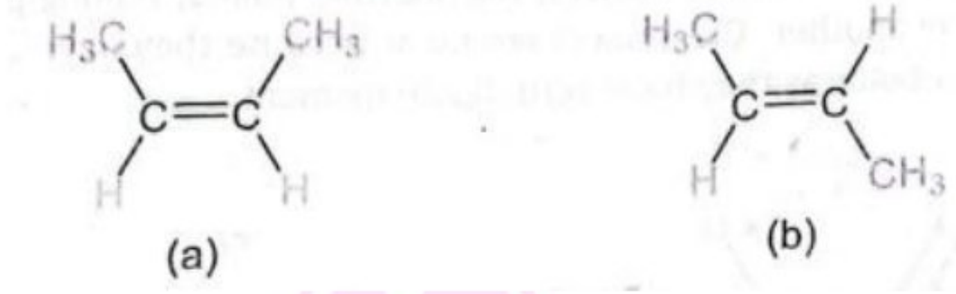
  - The **π bond restricts rotation** around the double bond at room temperature.
    - To rotate, the π bond must be broken, which requires about **264 kJ/mol** (in ethene).
    - In contrast, rotation about a single C–C bond requires only ~**12 kJ/mol** (in ethane), which is easily available at room temperature.
  - Thus, **alkenes show geometric isomerism**, while **alkanes do not**.
- **Example:**
  - In **but-2-ene**, substituents around the C=C bond can be arranged differently, giving rise to distinct molecules.
  - These cannot be converted into each other simply by twisting the double bond because of the restricted rotation caused by the π bond.
- **Nomenclature of Geometric Isomers:**
  - To distinguish between different arrangements of atoms/groups around the double bond, IUPAC recommends specific **designations** (explained later in the chapter, e.g., *cis-trans* or *E-Z* system).

Conditions for Geometric Isomerism in Alkenes

- **When geometric isomerism is not possible:**
  Alkenes in which the **same atoms or groups** are attached to the **same carbon atom** of the double bond **cannot** show geometric isomerism.
  - Reason: Even if the π bond is broken and the molecule is rotated across the carbon–carbon double bond, the resulting structure is **identical** to the original.
  - Example: If one carbon of the double bond is bonded to two hydrogens, no geometric isomers can exist.



- **When geometric isomerism is possible:**
  Alkenes in which **each carbon atom** of the double bond is bonded to **two different substituents** can exist as two distinct molecules.
  - Example: In **but-2-ene**, the physical properties depend on the orientation of substituents around the double bond.
  - Different arrangements of substituents around the C=C bond give rise to **different molecules (isomers)**.



- **Restricted rotation:**
  - Molecule (a) cannot be converted into molecule (b) by simply twisting one carbon atom of the double bond with respect to the other.
  - This is because the ***π* bond restricts free rotation** around the double bond.
- **IUPAC Nomenclature:**
  To distinguish between geometric isomers based on the orientation of substituents around the double bond, the IUPAC system recommends two types of designations:
  - The **cis–trans system**
  - The **E–Z system**

Cis-Trans Isomerism

Definition

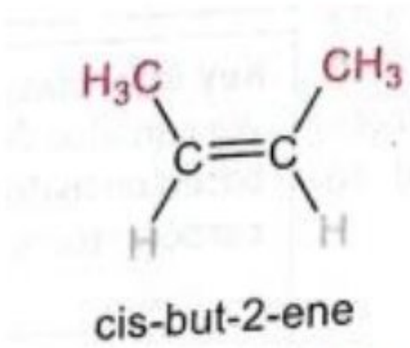
Cis-trans isomerism (also called geometrical isomerism) is a type of stereoisomerism shown mainly by alkenes. It arises due to the restricted rotation around the carbon–carbon double bond. When the same substituents are arranged on the same side of the double bond, the isomer is called a **cis-isomer**, while when they are on opposite sides, the isomer is called a **trans-isomer**.

The word *cis* is derived from Latin meaning "same side," whereas *trans* means "opposite." In this system, the arrangement of atoms or groups around the carbon–carbon double bond determines whether the molecule is cis or trans.

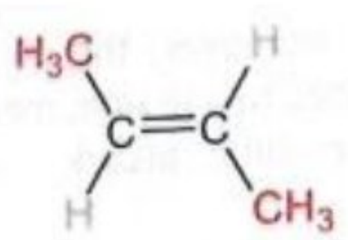
Explanation with Examples

1. But-2-ene

- **Cis-but-2-ene**: The two methyl groups (on carbon 1 and carbon 4 of the chain) are on the **same side** of the double bond.
- **Trans-but-2-ene**: The two methyl groups are on **opposite sides** of the double bond.



cis-but-2-ene



trans-but-2-ene

This is the simplest example that clearly shows cis-trans isomerism.

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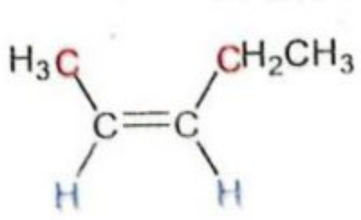
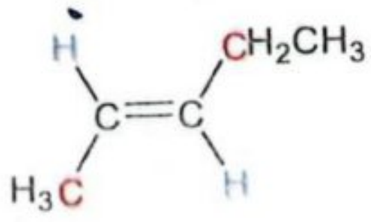
2. Pent-2-ene

- Pent-2-ene is more difficult to classify because it contains **three different substituents**: ethyl, methyl, and hydrogen.
- Chemists determine cis/trans isomerism in such cases by:
  - Comparing alkyl groups (carbon 1 and carbon 4 of the chain) as if they were the same substituents.
  - Or by considering the orientation of hydrogen atoms bonded to the double-bonded carbons.
- **Cis-pent-2-ene**: Alkyl groups and hydrogen atoms are on the **same side** of the double bond.
- **Trans-pent-2-ene**: Alkyl groups and hydrogen atoms are on **opposite sides** of the double bond.



cis-pent-2-ene



trans-pent-2-ene

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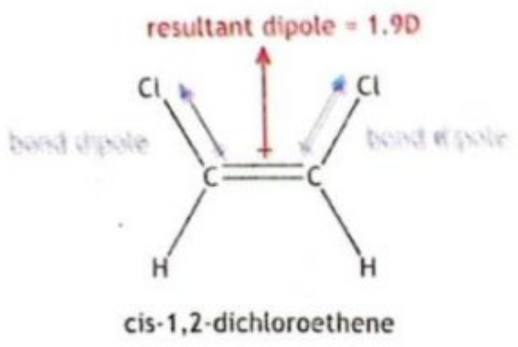
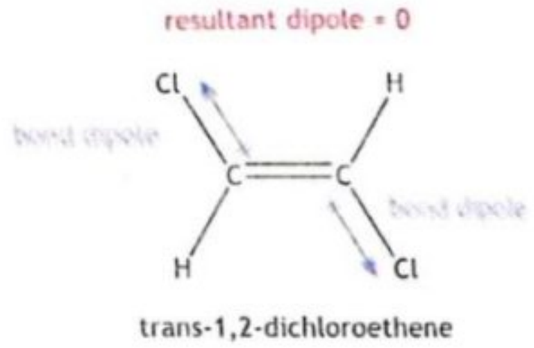
Physical Properties

- **Cis-isomers**:
  - Have a dipole moment → **polar**.
  - Show different melting points, boiling points, and solubility compared to trans-isomers.
- **Trans-isomers**:
  - The dipoles cancel out → **non-polar**.
  - Often have higher symmetry and distinct physical properties.



cis-1,2-dichloroethene



trans-1,2-dichloroethene

Chemical Properties

- Both cis- and trans-isomers contain the same functional groups, so their chemical properties are generally **similar but not identical**.
- **Cis-isomers** are usually **more reactive** than trans-isomers because:
  - Bulky groups are close together, causing **steric hindrance** and lowering stability.
  - The electron cloud is shifted to one side, making it more exposed to **electrophilic attack**.
- **Trans-isomers** are more stable due to the separation of bulky groups and even distribution of electron density.

Biological Importance

- In biological systems, cis- and trans-isomers behave very differently due to their distinct **shapes and arrangements in space**.

Optical Isomerism

1. Concept of Chirality

The easiest way to understand **optical isomerism** is by comparing it to our hands. The right hand is the mirror image of the left hand, but they cannot be placed exactly on top of one another. Such objects are called **nonsuperimposable mirror images**.

Example: A right-handed glove does not fit on the left hand.

Objects that are nonsuperimposable on their mirror images are called **chiral** (from the Greek word *"cheir"* meaning *hand*). Chiral objects show **handedness (chirality)**. Everyday examples include scissors, keyboards, and cars.

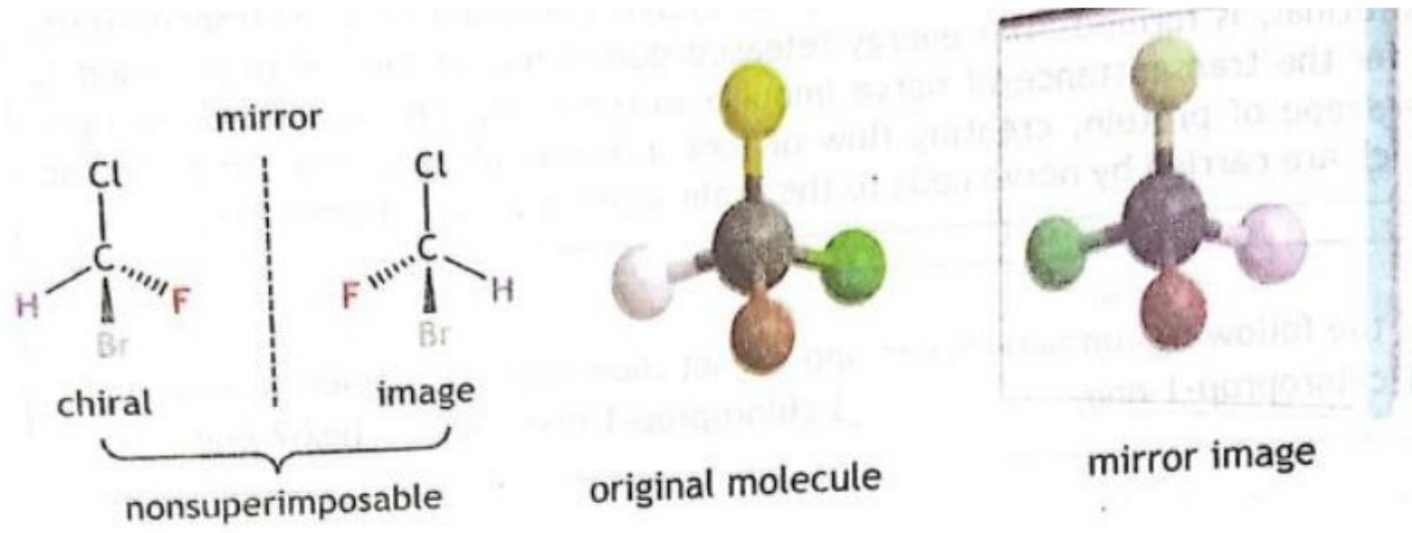
2. Chirality in Molecules

In chemistry, many organic molecules exist as pairs of nonsuperimposable mirror images. Such molecules usually contain a **chiral carbon** (also called an asymmetric carbon)—a carbon atom bonded to four different atoms or groups. Molecules with such a carbon are known as **chiral molecules**.

On the other hand, **achiral molecules** have a central carbon bonded to two or more identical groups, making their mirror images superimposable and identical**.**

Example:

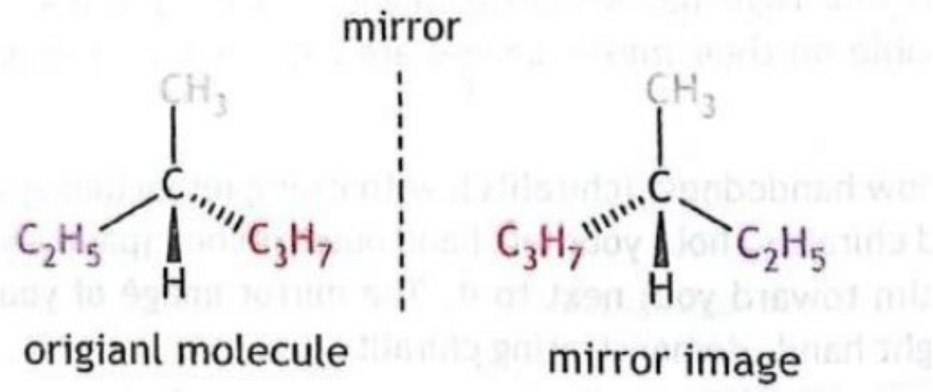
- **Chiral molecule**: Bromochlorofluoromethane (non-superimposable mirror image).
- **Achiral molecule**: Molecules with identical groups around the central carbon.



3. Enantiomers and Enantiomerism

The pair of stereoisomers that are **nonsuperimposable mirror images** of one another—just like our right and left hands—are called **enantiomers**. The phenomenon of their existence is known as **enantiomerism**.

- The word *enantiomer* comes from the Greek word *"enantion"*, meaning **opposite**.
- Example: Consider **3-methylhexane**, which can exist in forms that are mirror images but not superimposable.



4. Optical Activity and Plane Polarized Light

- Ordinary light has waves oscillating in all planes perpendicular to its direction of travel.
- When passed through a polarizing filter (e.g., calcite or Polaroid), only waves vibrating in a **single plane** pass through. This is called plane polarized light.

Optical Activity

- Molecules that can rotate the plane of polarized light are called **optical isomers**.
- This property is known as **optical isomerism**.
- Optical isomers exist as **pairs**:
  - **Enantiomers** (non-superimposable mirror images).
  - **Diastereomers** (stereoisomers that are not mirror images).

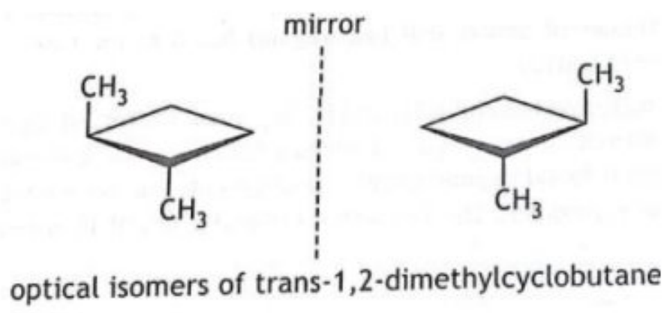
Effect on Polarized Light

- A solution of one enantiomer rotates the plane of polarized light in the **clockwise direction** → called **dextrorotatory (+)**.
- A solution of the other enantiomer rotates it in the **anticlockwise direction** → called **laevorotatory (–)**.

5. Racemic Mixture

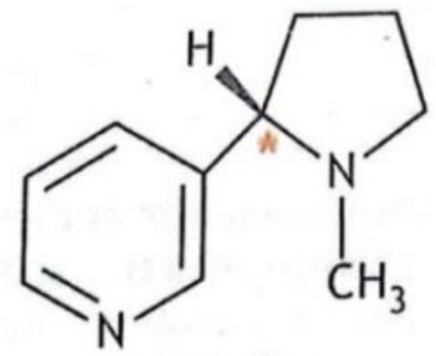
- A **racemic mixture** contains an **equal (50:50) mixture** of the two enantiomers.
- It has:
  - **50% dextrorotatory isomer** (*Latin: "dexter" = right*) → rotates light clockwise.
  - **50% levorotatory isomer** (*Latin: "laevus" = left*) → rotates light anticlockwise.
- Since the rotations cancel out, the mixture shows **no net optical activity**.
- Symbols:
  - Older: **"d"** (dextro), **"l"** (levo) → now obsolete.
  - IUPAC: **"+"** for dextrorotatory, **"–"** for laevorotatory.

Example: The **trans-isomer of 1,2-dimethylcyclobutane** shows **optical isomerism**.



optical isomers of trans-1,2-dimethylcyclobutane

Similarly, nicotine molecules naturally synthesized by tobacco plant are chiral showing optical isomerism. Note the red star shows chiral carbon in nicotine molecule.



nicotine

6. Optical Inactivity of Racemic Mixture

- A **racemic mixture** is **optically inactive**.
- Reason:
  - One isomer rotates plane-polarized light in the **clockwise direction**.
  - The other rotates it in the **anticlockwise direction**.
  - Their effects are **equal but opposite**, so they **cancel each other out**.
- Result: No net rotation of polarized light.

Properties of Optical Isomers

1. Physical and Chemical Properties

- Optical isomers (enantiomers) of the same compound have **similar physical and chemical properties**.
  - Same **density**
  - Same **melting point**
  - Same **boiling point**

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2. Optical Activity

- They differ only in their ability to **rotate the plane of plane-polarized light**:
  - One isomer rotates the plane **to the right (clockwise, + / dextrorotatory)**
  - The other rotates it **to the left (anticlockwise, – / levorotatory)**

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3. Biological & Physiological Differences

- Optical isomers may have **different physiological effects** because the human body can distinguish between their **molecular shapes**.
  - Example:

- One enantiomer of **asparagine** tastes **bitter**.
- The other enantiomer tastes **sweet**.

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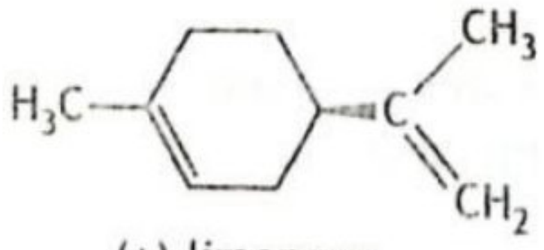
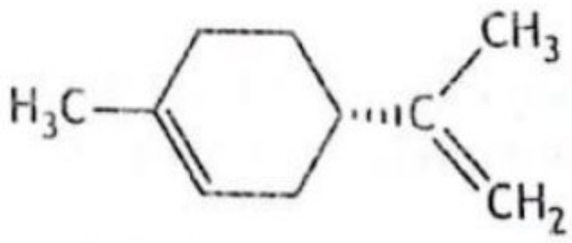
4. Case Study – Limonene

- **Limonene** is a chiral molecule that occurs in nature in two enantiomeric forms:
  - **(+)-Limonene** → Found in lemons and oranges; gives a **citrus smell**.
  - **(–)-Limonene** → Found in pine needles, peppermint, and spearmint; gives a **different smell/taste** compared to the (+) isomer.

Thus, although they have identical structures (except chirality), their **biological perception (taste/smell)** is different.



(+)-limonene



(–)-limonene

Separation of Racemic Mixture of Thalidomide

1. Racemic Mixtures in Drugs

- Many chiral drugs exist as **racemic mixtures** (50% (+) enantiomer, 50% (–) enantiomer).
- Problem:
  - One enantiomer → **therapeutically active** and beneficial.
  - Other enantiomer → may be **inactive, less effective, or harmful**.
- Example: **Thalidomide**
  - One isomer has therapeutic effects.
  - The other causes **severe harmful effects** (e.g., birth defects in history).

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2. Methods of Separation

To make thalidomide safe, two main methods are used:

(a) Optical Resolution

- Separates racemic mixture into two enantiomers.
- Removes harmful (–)-thalidomide.
- Techniques:
  - **High-Performance Liquid Chromatography (HPLC)**
  - **Crystallization**

- **Enzyme-based methods**

(b) Chiral (Asymmetric) Synthesis

- Produces only the **desired enantiomer** (e.g., (+)-thalidomide).
- Prevents formation of harmful isomer.
- Uses **chiral catalysts** such as **BINOL (1,1-bi-2-naphthol) with palladium/rhodium**.
- Reaction: **Selective hydrogenation** of double bond in thalidomide in presence of chiral catalyst → only the desired isomer forms.

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3. Significance

- Ensures **safe and reliable** drug formulation.
- Minimizes risks of harmful effects from (–)-thalidomide.
- Provides intended **therapeutic benefits** only.

For More Information:

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