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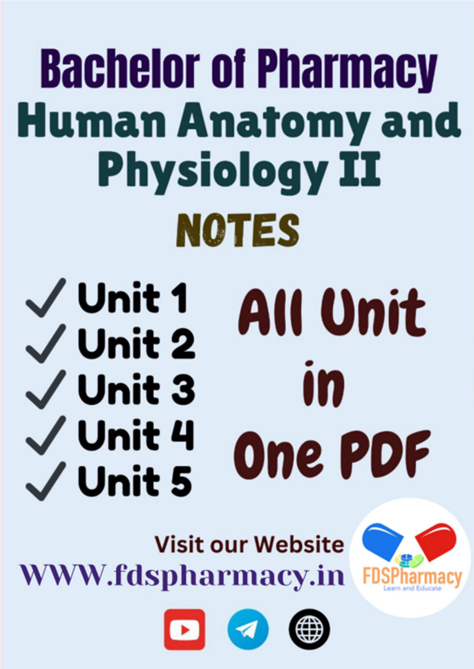
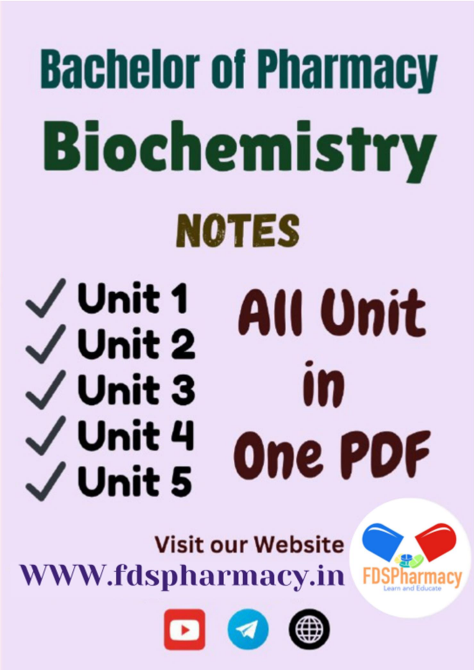




PHARMACEUTICAL ORGANIC CHEMISTRY – I

UNIT 3

TOPIC :

- **Alkylhalides***

  SN1 and SN2 reactions- kinetics, order of reactivity of alkyl halides, stereochemistry and rearrangement of carbocations.

  SN1versus SN2 reactions, Factors affecting SN1 and SN2 reactions

  Structure and uses of ethylchloride, Chloroform, trichloroethylene, tetrachloroethylene, dichloromethane, tetrachloromethane and iodoform.

Alkyl Halides

→ SN1 & SN2 reactions are nothing but simply a type of Nucleophilic Substitution Reaction.

→ A Nucleophilic substitution reaction is a type of organic reaction in which an atom or group of an atom is replaced from substrate by a nucleophile.

→ The substitution can be occur either in one or two step.

→ The two step mechanism is known as SN1 Reactions while the one step mechanism is known as SN2 Reactions.

→ Nucleophilic substitution reaction mainly occurs in Alkyl Halides and Alcohols.

→ Types of Nucleophilic substitution Reaction

- SN1 Reaction
- SN2 Reaction

SN1 Reaction

SN1 stands for Substitution Nucleophilic Unimolecular.

- It follows a two-step mechanism.
- In the first step, the leaving group leaves forming a carbocation.
- In the second step, the nucleophile attacks the carbocation.
- The reaction rate depends only on the concentration of substrate.
- It generally occurs in tertiary alkyl halides.
- SN1 reaction gives racemic mixture due to carbocation formation.
- It occurs in polar protic solvents (e.g., water, alcohol).

Kinetics

- Follows first-order kinetics:

$$\text{Rate} = k[\text{substrate}]$$

- Depends only on the concentration of the alkyl halide (substrate).
- Nucleophile does not participate in the rate-determining step.

Mechanism

1. **Step 1 : Slow, rate-determining step**
    - The leaving group (LG) departs, forming a **carbocation.**

$$R - LG \rightarrow R^{+} + LG^{-}$$

2. **Step 2 : Fast step**

- The nucleophile attacks the **planar carbocation**, forming the product

$$R^{+} + Nu^{-} \rightarrow R - Nu$$

Order of Reactivity of Alkyl Halides

Depends on carbocation stability:

$$3^{o} > 2^{o} \gg 1^{o}$$

- Tertiary halides form stable carbocations, so they react faster.
- Primary halides usually do not undergo SN1 due to unstable carbocations.

Stereochemistry

- The intermediate carbocation is planar.
- Nucleophile can attack from either side, leading to a racemic mixture (equal amounts of R and S enantiomers).
- Thus, SN1 results in racemization of chiral centers.

Carbocation Rearrangement

- Since a **carbocation intermediate** is formed, **rearrangements are common**:
    - **Hydride shift**
    - **Alkyl shift**
- Rearrangement leads to a **more stable carbocation**.

SN2 Reaction

→ SN2 stands for Substitution Nucleophilic Bimolecular.
→ It follows a single-step mechanism.
→ The nucleophile attacks from the backside while the leaving group leaves.
→ The reaction rate depends on both substrate and nucleophile concentration.
→ It mostly occurs in primary alkyl halides.
→ SN2 causes inversion of configuration (Walden inversion).
→ It occurs in polar aprotic solvents (e.g., DMSO, acetone).

Kinetics

- Follows second-order kinetics:

$$\text{Rate} = k[\text{substrate}][\text{nucleophile}]$$

- The rate depends on both the alkyl halide and nucleophile.

Mechanism

→ A one-step mechanism: concerted.
→ The nucleophile attacks the carbon from the opposite side as the leaving group, pushing the leaving group out simultaneously.

$$Nu^{-} + R - LG \rightarrow [\text{Transition State}] \rightarrow R - Nu + LG^{-}$$

Order of Reactivity of Alkyl Halides

Depends on steric hindrance:

$1^{o} > 2^{o} \gg 3^{o}$

- Tertiary halides are too hindered to allow backside attack.
- Methyl and primary halides react fastest.

Stereochemistry

- SN2 reactions cause inversion of configuration (also called Walden inversion).
- If the substrate is chiral, the product will have opposite configuration (R to S or S to R).

Carbocation Rearrangement

- No carbocation intermediate is formed.
- No rearrangement occurs in SN2 reactions.

SN1 Reaction vs SN2 Reaction

Feature	SN1 Reaction	SN2 Reaction
Full Form	Substitution Nucleophilic Unimolecular	Substitution Nucleophilic Bimolecular
Mechanism	Two-step (Carbocation formed)	One-step (Backside attack, no carbocation)
Rate Law	Rate = k [Substrate]	Rate = k [Substrate][Nucleophile]
Order of Reaction	First order	Second order
Intermediate Formed	Carbocation	No intermediate, forms a transition state
Substrate Preference	Tertiary > Secondary > Primary	Primary > Secondary > Tertiary
Nucleophile Strength	Can be weak (e.g., H_2O, ROH)	Requires strong nucleophile (e.g., OH^-, CN^-)
Solvent Used	Polar protic solvents (e.g., H_2O, alcohol)	Polar aprotic solvents (e.g., DMSO, acetone, DMF)
Stereochemistry	Racemization (mixture of enantiomers)	Inversion of configuration (Walden inversion)
Possibility of Rearrangement	Yes, due to carbocation stability	No, no carbocation formed
Type of Product	Often mixture of stereoisomers	Always inverted product
Example Substrate	$(CH_3)_3C–Br$ (tert-butyl bromide)	CH_3CH_2Br (ethyl bromide)
Common in	Tertiary alkyl halides and allylic/benzylic halides	Primary alkyl halides

Factors Affecting SN1 Reaction

1. **Nature of Substrate:**
   - More stable carbocation → faster SN1.
   - Order of reactivity:
     Tertiary (3°) > Secondary (2°) > Primary (1°)
     (Primary rarely undergoes SN1 due to unstable carbocation.)
2. **Nature of Nucleophile:**
   - Nucleophile is **not involved** in the rate-determining step.
   - **Weak nucleophiles** can participate.
     Examples: H_2O, ROH, NH_3
3. **Nature of Leaving Group:**
   - A **good leaving group** is essential.
   - Best leaving groups:
     $\mathbf{I^- > Br^- > Cl^- >> F^-}$
4. **Nature of Solvent:**
   - SN1 occurs faster in **polar protic solvents.**
   - These solvents stabilize the **carbocation** and **leaving group.**
     Examples: H_2O, alcohols
5. **Carbocation Stability:**
   - **Resonance and hyperconjugation** stabilize carbocations.
   - Allylic and benzylic halides undergo SN1 easily.

Factors Affecting SN2 Reaction

1. **Nature of Substrate:**
   - Less bulky substrate → faster SN2.
   - Order of reactivity:
     Primary (1°) > Secondary (2°) > Tertiary (3°)
2. **Nature of Nucleophile:**
   - SN2 is **nucleophile-dependent.**
   - Requires **strong nucleophiles.**
     Examples: OH^-, CN^-, NH_2^-, I^-
3. **Nature of Leaving Group:**

    - A **good leaving group** speeds up SN2.
    - Same order as SN1:
      $\mathrm{I^-} > \mathrm{Br^-} > \mathrm{Cl^-} >> \mathrm{F^-}$

4. **Nature of Solvent:**
    - SN2 is favored by **polar aprotic solvents.**
    - These solvents do not solvate the nucleophile, so it stays reactive.
      Examples: DMSO, DMF, acetone
5. **Steric Hindrance:**
    - **Highly sensitive** to bulky groups near the reaction center.
    - Bulky groups **slow down** or **prevent** SN2 reaction.

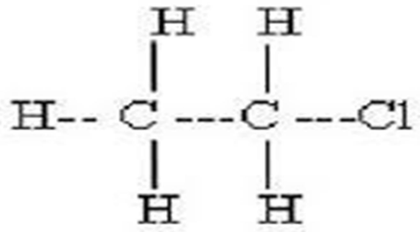
Ethyl Chloride (C2H5Cl)

→ IUPAC Name: Chloroethane

→ Molecular Formula: C_2H_5Cl or CH_3CH_2Cl

→ Molecular Weight: 64.51 g/mol

Structure:



→ It consists of an ethyl group (CH_3CH_2–) attached to a chlorine atom.

→ The molecule is linear and saturated, containing only single bonds.

→ The C–Cl bond is polar covalent, making the molecule slightly reactive.

Uses of Ethyl Chloride

→ Ethyl chloride is mainly used for medicinal, industrial, and chemical purposes:

Medicinal Uses

→ **Local Anesthetic (Cooling Spray):**

- Used in topical anesthesia by rapid evaporation on the skin.
- Causes skin cooling and numbness, used during minor surgical procedures (e.g., injections, removal of splinters).

→ **Pain Relief:**

- Used to temporarily relieve muscle pain, strains, and bruises.

Industrial Uses

→ **Intermediate in Synthesis:**

- Acts as an intermediate in the production of tetraethyl lead (TEL) — an old anti-knocking agent for petrol (now banned in most countries).

→ **Ethylating Agent:**

- Used in organic synthesis to introduce ethyl groups (C_2H_5–) into other molecules.

→ **Refrigerant (historical):**

- Previously used as a refrigerant gas before modern alternatives like Freon.

Other Uses

→ **Solvent:**

- Occasionally used as a solvent in chemical processes.

→ **In Laboratory:**

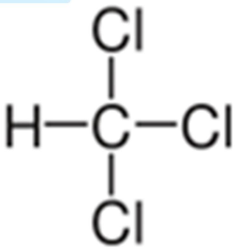
- Used in Grignard reagent formation where ethylmagnesium chloride is required.

Chloroform

→ IUPAC Name: Trichloromethane
→ Common Name: Chloroform
→ Chemical Formula: $CHCl_3$
→ Molecular Weight: 119.38 g/mol

Structure of Chloroform

→ Chloroform has a tetrahedral geometry like methane, with three chlorine atoms and one hydrogen atom attached to a central carbon atom.



- It contains:
    - **Three polar C–Cl bonds**
    - **One non-polar C–H bond**
- Due to the high electronegativity of chlorine, it is **moderately polar**.

Uses of Chloroform

Medicinal Uses (Earlier Use)

→ **General Anesthetic (Historic Use):**

- Formerly used as an inhalation anesthetic during surgeries.
- It induced unconsciousness by depressing the central nervous system (CNS).
- Now banned in many countries due to hepatotoxicity and risk of cardiac arrhythmia.

→ **Pharmaceutical Solvent:**

- Used as a solvent for alkaloids, fats, oils, and other pharmaceuticals.
- Present in chloroform water, a mild carminative and flavoring agent (use now discontinued in many formulations).

Industrial and Laboratory Uses

→ **Solvent:**

- Commonly used in the laboratory and industry to dissolve fats, rubber, resins, waxes, and alkaloids.

→ **Reagent in Organic Synthesis:**

- Used in the preparation of chlorinated compounds like:
  - Chloropicrin (a pesticide)
  - Trichloroacetic acid
  - Fluorocarbon refrigerants (via further reactions)

→ **Intermediate in Freon Production:**

- Used in the manufacture of refrigerant gases such as Freon-22 ($CHClF_2$).

Miscellaneous Uses

→ **Preservative:**

- Acts as a preservative in some pharmaceutical preparations by preventing microbial growth.

→ **Microscopy and Histology:**

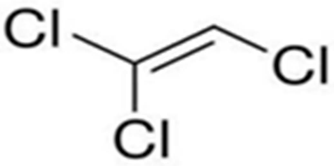
- Used for clearing tissues during slide preparation.

Trichloroethylene (TCE)

→ IUPAC Name: Trichloroethene
→ Common Name: Trichloroethylene (TCE)
→ Molecular Formula: C_2HCl_3
→ Molecular Weight: 131.39 g/mol

Structure of Trichloroethylene

→ It is a halogenated alkene, meaning it contains a carbon-carbon double bond (C=C) and three chlorine atoms attached.



It consists of:

- **C=C double bond**
- **Three chlorine atoms** attached (two on one carbon and one on the other)
- **One hydrogen atom**

Uses of Trichloroethylene

Industrial Uses

→ **Solvent for Degreasing Metals:**

- Widely used in cleaning and degreasing metal parts in automotive and aerospace industries.

→ **Dry Cleaning (Historic Use):**

- Previously used as a dry-cleaning solvent, now replaced due to toxicity concerns.

→ **Extraction Solvent:**

- Used to extract fats, oils, waxes, and resins.

→ **Intermediate in Synthesis:**

- Used to manufacture fluorocarbons (e.g., hydrofluorocarbons like HFC-134a).
- Also used in synthesis of other chlorinated compounds.

Medicinal and Laboratory Uses

→ **Anesthetic (Historic Use):**

- Once used as an inhalation anesthetic, but discontinued due to toxicity and better alternatives.

→ **Laboratory Reagent:**

- Acts as a nonpolar solvent in laboratory settings for reactions and extractions.

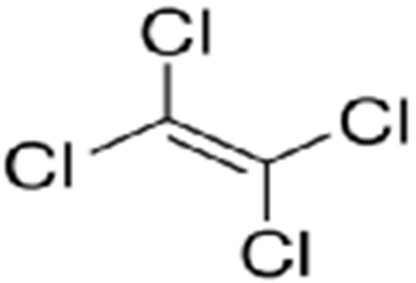
Tetrachloroethylene

→ IUPAC Name: Tetrachloroethene
→ Common Name: Perchloroethylene (PCE)
→ Molecular Formula: C_2Cl_4
→ Molecular Weight: 165.83 g/mol

Structure of Tetrachloroethylene

→ Tetrachloroethylene is a halogenated alkene with a carbon-carbon double bond (C=C).

→ Each carbon of the double bond is bonded to two chlorine atoms.



→ It is a symmetric molecule.

→ Contains 4 chlorine atoms and 1 carbon-carbon double bond.

→ Non-polar due to symmetrical distribution of Cl atoms, despite polar C–Cl bonds.

Uses of Tetrachloroethylene

Industrial Uses

→ **Dry Cleaning Solvent:**

- Most widely used solvent in dry cleaning of fabrics.
- Preferred due to its non-flammable, effective degreasing properties.

→ **Degreasing Agent:**

- Used to clean metal parts in the automotive and aerospace industries.
- Removes oils, greases, waxes.

→ **Solvent in Organic Chemistry:**

- Used in the laboratory and industry as a nonpolar solvent for extractions and reactions.

→ **Intermediate in Chemical Synthesis:**

- Used to synthesize fluorinated hydrocarbons and other chlorinated compounds.

Minor and Historical Uses

→ **Textile and Leather Processing:**

- Used to remove oils and waxes in textile finishing.

→ **Anesthetic Use (Historical):**

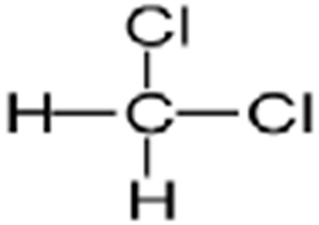
- Occasionally used in early medicine, but discontinued due to toxicity.

Dichloromethane (DCM)

→ IUPAC Name: Dichloromethane
→ Common Name: Methylene chloride
→ Chemical Formula: CH_2Cl_2
→ Molecular Weight: 84.93 g/mol

Structure of Dichloromethane

- Dichloromethane is a **halogenated methane** derivative**.**
- It has a **central carbon atom** bonded to:
  - Two **hydrogen atoms**
  - Two **chlorine atoms**



- Tetrahedral geometry around carbon atom
- Contains polar C–Cl bonds, making it moderately polar.
- Despite polarity, it's immiscible with water.

Uses of Dichloromethane

Industrial and Laboratory Uses

→ **Solvent:**

- Widely used as a solvent in laboratories and industries for:
- Paint strippers
- Degreasing agents
- Adhesive removers
- Extraction processes

→ **Pharmaceutical Manufacturing:**

- Acts as a solvent in drug formulation and tablet coating.

→ **Reaction Medium:**

- Used as a reaction solvent in organic synthesis, especially for halogenation, acylation, and nitration.

Medical and Cosmetic Uses

→ **Aerosol Propellant:**

- Used in inhalers and sprays in non-flammable aerosol formulations (now limited due to toxicity concerns).

→ **Decaffeination of Coffee/Tea:**

- Used in some solvent-based decaffeination processes (trace amounts only).

Other Applications

→ **Plastic and Polymer Industry:**

- Used in the production and cleaning of plastics.

→ **Foam Blowing Agent:**

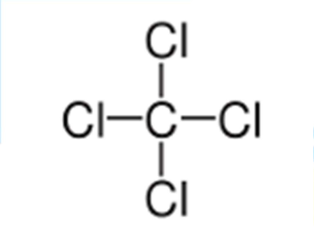
- Used in the production of polyurethane foams.

Tetrachloromethane (Carbon Tetrachloride)

→ IUPAC Name: Tetrachloromethane
→ Common Name: Carbon tetrachloride
→ Chemical Formula: CCl_4
→ Molecular Weight: 153.82 g/mol

Structure of Tetrachloromethane

- It is a **halogenated methane** derivative where all four hydrogen atoms of methane are replaced by **chlorine atoms**.



- The carbon atom is at the center of a **tetrahedral structure.**
- All C–Cl bonds are **polar**, but the molecule is **symmetrical**, so **overall it is non-polar.**

Uses of Tetrachloromethane

Industrial Uses

→ **Solvent:**

- Used as a solvent for oils, fats, resins, rubber, waxes, and other non-polar substances.
- Preferred in laboratories and industries for organic extractions.

→ **Fire Extinguishers (Historical Use):**

  - Once widely used in fire extinguishers, especially for electrical fires.
  - Replaced now due to toxic fumes and health risks.

→ **Refrigerant Production:**

  - Used as a precursor for chlorofluorocarbons (CFCs) like Freon (now largely banned due to ozone depletion).

→ **Cleaning Agent:**

  - Historically used as a metal degreasing and dry cleaning agent (now replaced due to toxicity).

Laboratory Use

→ **Reaction Medium:**

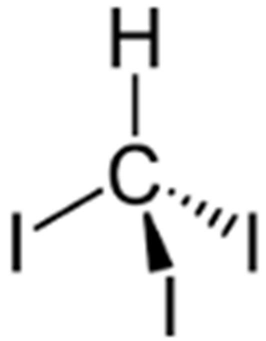
  - Acts as an inert, nonpolar solvent for chemical reactions, especially halogenations.

Iodoform

→ IUPAC Name: Triiodomethane
→ Common Name: Iodoform
→ Chemical Formula: CHI_3
→ Molecular Weight: 393.73 g/mol

Structure of Iodoform

- Iodoform is a **halogenated methane derivative**, where three iodine atoms are attached to a single carbon atom, along with one hydrogen atom.



Tetrahedral geometry around the carbon atom.

Contains:

- One **C–H bond**
- Three **C–I bonds** (very heavy due to iodine atoms)

It is a **yellow crystalline solid** with a **distinct antiseptic odor**.

Uses of Iodoform

Medicinal Uses

→ **Antiseptic and Disinfectant:**

- Traditionally used as a topical antiseptic for wounds, cuts, and ulcers.
- Its antiseptic action is due to the release of iodine, which kills bacteria.

→ **Dental Applications:**

- Used in root canal filling materials and as an antibacterial dressing in dentistry.

→ **Healing Agent:**

- Promotes the healing of chronic wounds and post-surgical dressings.

Laboratory Use

→ **Iodoform Test:**

- Used to test for methyl ketones and secondary alcohols with a methyl group.
- Formation of yellow precipitate of iodoform confirms presence of such compounds.

Veterinary Use

→ **Disinfectant Powder:**

- Used in veterinary medicine as a wound-healing powder or ointment base.