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PHARMACEUTICAL ORGANIC CHEMISTRY – I

UNIT 4

TOPIC :

- **Carbonyl compounds* (Aldehydes and ketones)**

  Nucleophilic addition, Electromeric effect, aldol condensation, Crossed Aldol condensation, Cannizzaro reaction, Crossed Cannizzaro reaction, Benzoin condensation, Perkin condensation, qualitative tests, Structure and uses of Formaldehyde, Paraldehyde, Acetone, Chloral hydrate, Hexamine, Benzaldehyde, Vanilin, Cinnamaldehyde.

Carbonyl Compounds (Aldehydes and Ketones)

- Carbonyl compounds are organic compounds that contain a carbonyl group (C=O) as the functional group. The carbonyl group consists of a carbon atom double bonded to an oxygen atom. This group is highly reactive and forms the basis of a large number of organic reactions.
- Carbonyl compounds are a class of organic compounds characterized by the presence of a carbonyl group (C=O).
- The two main types are:
    - Aldehydes – in which the carbonyl group is bonded to at least one hydrogen atom.
    - Ketones – in which the carbonyl group is bonded to two carbon atoms (alkyl or aryl groups).

General Formula

- **Aldehydes**: R–CHO
  (where R = H, alkyl, or aryl group)
- **Ketones**: R–CO–R′
  (where R and R′ = alkyl or aryl groups)

Nucleophilic Addition Reactions

→ Nucleophilic addition reaction is a type of organic reaction in which a nucleophile adds to the electrophilic carbon of a carbonyl group (C=O), forming a new single-bonded product.

→ These reactions are characteristic of aldehydes and ketones due to the polar nature of the carbonyl group.

General Reaction

$$R\text{–}C(=O)\text{–}R' + Nu^- \rightarrow R\text{–}C(OH)Nu\text{–}R'$$

Where

- R = alkyl or H
- Nu^- = nucleophile
- Electrophilic carbon is attacked by Nu^-

Mechanism

Step 1 : Nucleophilic Attack

- Nucleophile attacks the **electrophilic carbon** of the carbonyl group.
- The double bond breaks, pushing electrons to the oxygen.

Step 2 : Protonation

- The oxygen (now negatively charged) **accepts a proton** from water or acid to form a hydroxyl group (–OH).

Examples of Nucleophilic Addition Reactions:

1. *Addition of Hydrogen Cyanide (HCN)*

Reaction :

$$\text{Aldehyde/Ketone} + HCN \rightarrow \text{Cyanohydrin}$$

Example :

$$CH_3CHO + HCN \rightarrow CH_3CH(OH)CN$$

Product is a **cyanohydrin**.

Electromeric Effect (E Effect)

- The Electromeric Effect is a temporary effect in organic molecules in which a pair of π-electrons is completely transferred from one atom to another within a multiple bond (like C=C, C=O, etc.) under the influence of an attacking reagent.
- It occurs only in the presence of an attacking reagent (like electrophile or nucleophile) and disappears when the reagent is removed.

Types of Electromeric Effect:

1. *+E Effect (Positive Electromeric Effect):*

- The π-electrons shift **towards the attacking reagent.**
- Usually occurs when the attacking species is an **electrophile (E^+).**
- Example: Addition of H^+ to ethene.

2. *–E Effect (Negative Electromeric Effect):*

- The π-electrons shift **away from the attacking reagent.**
- Usually occurs when the attacking species is a **nucleophile (Nu^-).**
- Example: Attack of CN^- on carbonyl compound.

Example : –E Effect in Carbonyl Group

When a **nucleophile (like CN^-)** attacks acetaldehyde:

$$CH_3{-}CHO + CN^- \rightarrow CH_3{-}CH(OH){-}CN$$

The π-electrons in the C=O bond shift toward oxygen to make it more negative and receptive to the nucleophile.

Aldol Condensation

→ Aldol condensation is an organic reaction in which two molecules of aldehydes or ketones, having at least one α-hydrogen, combine in the presence of a dilute base or acid to form a β-hydroxy aldehyde (aldol) or β-hydroxy ketone, which then dehydrates to form an α,β-unsaturated compound.

Mechanism (Base-Catalyzed):

Step 1: Formation of Enolate Ion

The base abstracts an α-H to form an **enolate ion**:

$$CH_3CHO + OH^- \rightarrow CH_2^-CHO + H_2O$$

Step 2: Nucleophilic Attack

Enolate ion attacks another carbonyl molecule:

$$CH_2^-CHO + CH_3CHO \rightarrow CH_3CH(OH)CH_2CHO$$

This intermediate is called an **aldol** (β-hydroxy aldehyde).

Step 3: Dehydration

On heating, the aldol loses water:

$$CH_3CH(OH)CH_2CHO \rightarrow CH_3CH = CHCHO + H_2O$$

Crossed Aldol Condensation

→ Crossed aldol condensation (also called mixed aldol condensation) is a type of aldol condensation where two different aldehydes or ketones (at least one with an α-hydrogen) react together in the presence of a base or acid to form a β-hydroxy aldehyde/ketone, which further undergoes dehydration to give an α,β-unsaturated compound.

Requirements:

- Two different carbonyl compounds (at least one must have α-hydrogens).
- Dilute base or acid as a catalyst (commonly NaOH or HCl).
- Heating to promote dehydration.

Example : Acetone + Benzaldehyde

Step 1: Formation of Enolate Ion

Acetone (with α-H) forms enolate:

$$CH_3COCH_3 + OH^- \rightarrow CH_2^-COCH_3 + H_2O$$

Step 2: Nucleophilic Attack

Enolate attacks benzaldehyde:

$$CH_2^-COCH_3 + C_6H_5CHO \rightarrow C_6H_5CH(OH)CH_2COCH_3$$

β-hydroxy ketone

Step 3: Dehydration

$$C_6H_5CH(OH)CH_2COCH_3 \xrightarrow{heat} C_6H_5CH=CHCOCH_3 + H_2O$$

Product : α,β-unsaturated ketone (Cinnamyl methyl ketone)

Cannizzaro Reaction

- Cannizzaro Reaction is a redox reaction in which two molecules of an aldehyde (that does not have an α-hydrogen) react in the presence of a strong base (e.g., NaOH or KOH) to form:
  - One molecule of alcohol (reduction)
  - One molecule of carboxylic acid salt (oxidation)

Mechanism of Cannizzaro Reaction (Base-Catalyzed)

Step 1 : Nucleophilic attack by OH^-

The hydroxide ion attacks the carbonyl carbon of one aldehyde:

$$R\text{-}CHO + OH^- \rightarrow R\text{-}C(OH)O^-$$

→ **Tetrahedral intermediate** (alkoxide ion)

Step 2 : Hydride Transfer

This alkoxide ion **transfers a hydride ion (H^-)** to another aldehyde molecule:

$$R\text{-}C(OH)O^- + R\text{-}CHO \rightarrow R\text{-}COO^- + R\text{-}CH_2O^-$$

- One molecule is **oxidized** to carboxylic acid salt.
- The second is **reduced** to alkoxide.

Step 3: Protonation

The alkoxide ion gets protonated by water:

$$R\text{-}CH_2O^- + H_2O \rightarrow R\text{-}CH_2OH + OH^-$$

Final Products:

- **$R\text{–}CH_2OH$ (Alcohol)**
- **$R\text{–}COO^-$ (Carboxylate salt)**

Crossed Cannizzaro Reaction

- Crossed Cannizzaro reaction is a type of Cannizzaro reaction in which two different aldehydes (both without α-hydrogens) react in the presence of a concentrated strong base (like NaOH or KOH), and only one gets oxidized while the other is reduced selectively.
- It is a redox (disproportionation) reaction involving two different non-enolizable aldehydes.

Mechanism

1. **Nucleophilic Attack:**
   - OH^- attacks formaldehyde → forms alkoxide.
2. **Hydride Transfer:**
   - Hydride ion (H^-) from formaldehyde is transferred to benzaldehyde.
3. **Product Formation:**
   - Formaldehyde becomes formate ion.
   - Benzaldehyde becomes benzyl alkoxide → protonated to benzyl alcohol.

Example : Formaldehyde + Benzaldehyde

$$C_6H_5CHO + HCHO \xrightarrow{NaOH} C_6H_5CH_2OH + HCOONa$$

- Formaldehyde gets oxidized to sodium formate.
- Benzaldehyde gets reduced to benzyl alcohol.

Benzoin Condensation

- Benzoin condensation is a reaction in which two molecules of aromatic aldehyde (like benzaldehyde), having no α-hydrogen, combine in the presence of a cyanide ion (CN^-) as a nucleophilic catalyst to form benzoin — an α-hydroxy ketone.

Mechanism of Benzoin Condensation:

Step 1: Formation of Cyanohydrin Intermediate

- CN^- attacks the carbonyl carbon of benzaldehyde → forms **cyanohydrin intermediate.**

Step 2: Carbanion Formation

- A proton is removed from the α-carbon of cyanohydrin → forms a **carbanion** stabilized by the CN group.

Step 3: Nucleophilic Attack

- The carbanion **attacks a second molecule of benzaldehyde**, forming a new C–C bond.

Step 4: Protonation and Rearrangement

- The oxygen of the newly formed compound is protonated.
- CN^- is **eliminated,** and the product **benzoin** is formed.

Final Product:

$$C_6H_5CH(OH)COC_6H_5 \quad \text{(Benzoin)}$$

Contains both **hydroxy (–OH)** and **ketone (C=O)** functional groups.

Perkin Condensation

- Perkin condensation is an organic reaction in which an aromatic aldehyde (like benzaldehyde) reacts with an acid anhydride (like acetic anhydride) in the presence of a base (typically a sodium or potassium salt of the acid used) to form an α,β-unsaturated carboxylic acid.

Mechanism of Perkin Condensation:

Step 1 :
Base (acetate ion) abstracts α-hydrogen from the acid anhydride to form a **carbanion.**

$$(CH_3CO)_2O + CH_3COO^- \rightarrow CH_2^-CO\text{-}O\text{-}COCH_3$$

Step 2 :
The carbanion attacks the carbonyl carbon of the **aromatic aldehyde**.

$$CH_2^-CO\text{-}O\text{-}COCH_3 + C_6H_5CHO \rightarrow Intermediate$$

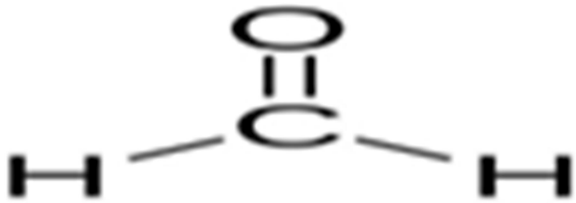
Step 3 :
Elimination of acetic acid (CH_3COOH) from the intermediate gives the final **α,β-unsaturated acid.**

$$\text{Intermediate} \xrightarrow{-CH_3COOH} C_6H_5CH = CHCOOH$$

Cinnamic acid is the main product.

Formaldehyde

→ Molecular formula: HCHO
→ IUPAC name: Methanal
→ Structure:



Structure of Formaldehyde

- Contains a carbonyl group (C=O) bonded to two hydrogen atoms.
- It is the simplest aldehyde.
- The carbon is sp^2 hybridized → planar structure.
- It has a trigonal planar geometry with bond angles of approximately 120°.

Uses of Formaldehyde:

✓ As a disinfectant and preservative:
  - Used in formalin solution to preserve biological specimens.
  - Acts as a powerful disinfectant and tissue hardener.

✓ In textile and paper industries:
  - Used as a finishing agent to make crease-resistant fabrics.
  - Used to treat paper and wood for water resistance.

✓ In the production of other chemicals:
  - Used to synthesize formic acid, hexamine (urotropine), pentaerythritol, and 1,4-dioxane.
  - Acts as a starting material for various organic synthesis reactions.

✓ In agriculture:
  - Used to preserve seeds and sterilize soil.
  - Used in fungicides and pesticide production.

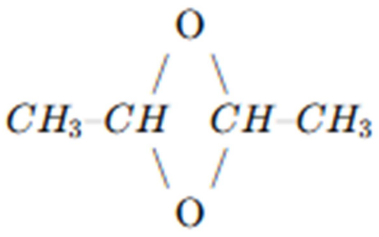
✓ In medicine:
  - Formalin is used in vaccine preparation and embalming.

Paraldehyde

→ Chemical Formula: $C_6H_{12}O_3$
→ IUPAC Name: 2,4,6-Trimethyl-1,3,5-trioxane
→ Type: Cyclic trimer of acetaldehyde (CH_3CHO)

Structure of Paraldehyde:

- Paraldehyde is a six-membered ring compound made up of three acetaldehyde molecules joined by acetal (–C–O–C–) linkages:



- Each corner has a CH_3–CH group, and every oxygen is bonded to two carbons — forming a 1,3,5-trioxane ring.

Uses of Paraldehyde:

✓ Sedative and Hypnotic (CNS depressant):
  - Used to induce sleep in insomnia and seizures.
  - Acts as a CNS depressant similar to barbiturates.
  - Used especially in emergency treatment of status epilepticus.

✓ Anticonvulsant:
  - Effective in controlling convulsions in epilepsy.
  - Was used before modern antiepileptic drugs.

✓ Emergency anesthesia (historical):
  - Sometimes used by inhalation for short-term anesthesia, though now obsolete due to better agents.

✓ Antiseptic and preservative:
  - Has mild antiseptic properties, sometimes used in veterinary or minor applications.

Acetone

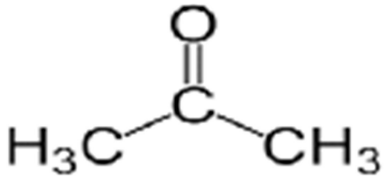
→ Molecular Formula: C_3H_6O

→ IUPAC Name: Propan-2-one

→ Common Name: Acetone

→ Functional Group: Ketone (C=O group)

Structure of Acetone :



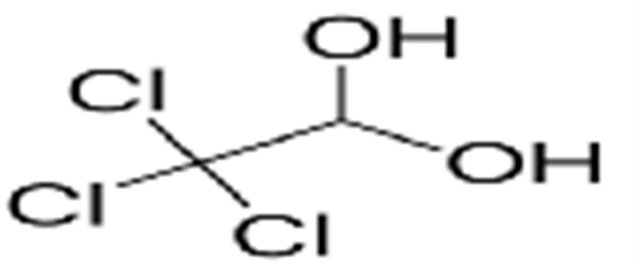
Uses of Acetone:

- ✓ As an Industrial Solvent:
  - Widely used to dissolve plastics, fibers, resins, cellulose acetate, and nitrocellulose.
  - Used in paint thinners, nail polish removers, and varnishes.
- ✓ In Pharmaceuticals:
  - Used as a solvent in the production of medicines and cosmetic preparations.
  - Helps in the crystallization and purification of drugs.
- ✓ In Laboratory Applications:
  - Used as a cleaning agent for lab equipment due to its rapid evaporation.
  - Common solvent for organic synthesis reactions.
- ✓ In the Manufacture of Chemicals:
  - Precursor for the production of:
    - Methyl methacrylate (used in Plexiglas)
- ✓ As a Drying Agent:
  - Used in removing water from laboratory samples due to its hygroscopic nature.
- ✓ In Cosmetics and Personal Care:
  - Main ingredient in nail polish remover.
  - Used in skin cleaning products.

Chloral Hydrate

→ Chemical Formula: $C_2H_3Cl_3O_2$
→ IUPAC Name: 2,2,2-Trichloro-1,1-ethanediol
→ Common Name: Chloral Hydrate
→ It is the gem-diol hydrate of chloral (trichloroacetaldehyde)

Structure of Chloral Hydrate



- Contains:
  - One central carbon bonded to three chlorine atoms ($Cl_3C–$)
  - Two hydroxyl groups (–OH) on the same carbon (gem-diol)
- Formed by the addition of water to chloral ($Cl_3C–CHO$)

Uses of Chloral Hydrate:

✓ Sedative and Hypnotic:
- Acts as a central nervous system depressant
- Used to treat insomnia (induces sleep)
- Effective in mild sedation before surgery

✓ Pediatric Sedative:
- Commonly used in children as a pre-anesthetic sedative or during diagnostic tests like EEG

✓ Treatment of Alcohol Withdrawal (Delirium Tremens):
- Sometimes used in managing agitation and insomnia in alcohol detoxification

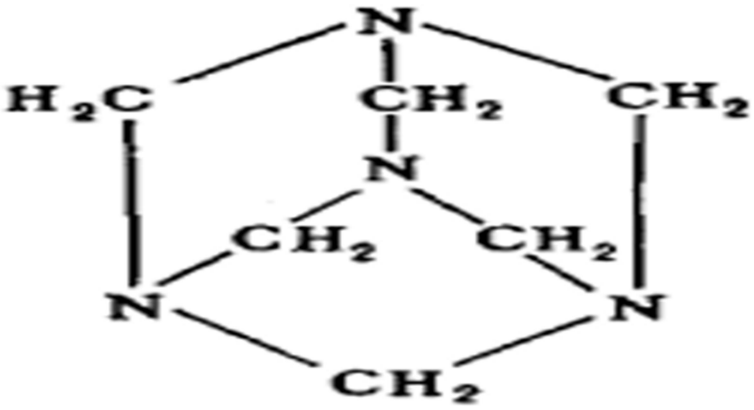
✓ As a Preservative in Microscopy:
- Used as a preservative and mounting medium for biological specimens in microscopy

✓ Chemical Intermediate:
- Used in the synthesis of chloral, DDT (insecticide), and other organic compounds

Hexamine

→ Chemical Formula: $C_6H_{12}N_4$
→ IUPAC Name: Hexamethylenetetramine
→ Other names: Methenamine, Urotropine

Structure of Hexamine



- It has a tetrahedral cage-like structure where:
  - Four nitrogen atoms are present at the corners.
  - Six methylene bridges ($–CH_2–$) connect the nitrogen atoms.

Uses of Hexamine :

✓ Urinary Antiseptic:
- Used as a urinary tract antiseptic.
- In acidic urine, hexamine hydrolyzes to formaldehyde, which is bactericidal.
- Often used in combination with acidifiers (like mandelic acid).

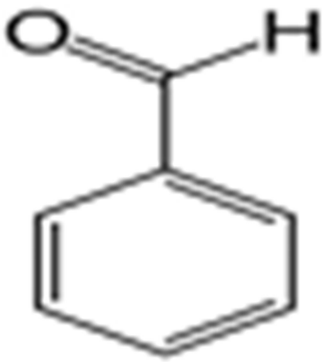
✓ Treatment of Urinary Tract Infections (UTIs):
- Especially used in chronic and recurrent UTIs.
- Marketed as methenamine hippurate or methenamine mandelate.

✓ Explosives Industry:

- Used in the manufacture of RDX (Cyclonite) — a powerful explosive.
- Acts as a starting material for various nitro-compounds.

Benzaldehyde

→ Chemical Formula: C_6H_5CHO
→ IUPAC Name: Benzaldehyde
→ Common Name: Benzaldehyde
→ Functional Group: Aldehyde (–CHO)



Structure of Benzaldehyde :

- Contains a benzene ring (C_6H_5–) directly attached to an aldehyde group (–CHO).
- It is the simplest aromatic aldehyde.
- The carbonyl carbon (C=O) is sp^2 hybridized → planar structure.
- No α-hydrogen present → undergoes Cannizzaro reaction, not Aldol.

Uses of Benzaldehyde:

✓ Flavoring Agent:
  - Used to impart almond flavor in foods, soft drinks, and candies.
  - Approved as a food additive (in very small amounts).

✓ Perfume Industry:
  - Used in making fragrances and cosmetic formulations due to its sweet aroma.

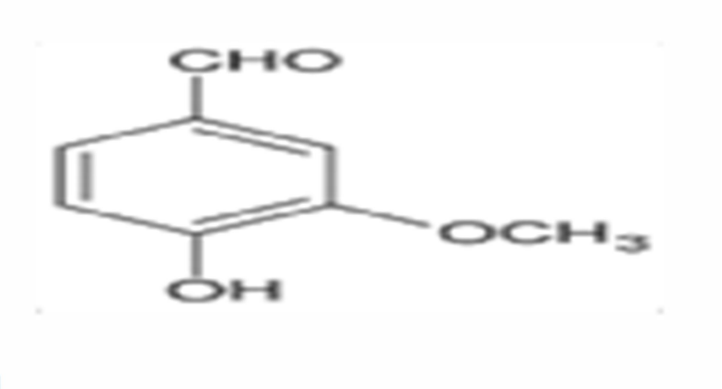
✓ Intermediate in Organic Synthesis:
  - Starting material for the synthesis of:
    - Cinnamic acid (via Perkin reaction)
    - Benzoin (via benzoin condensation)
    - Benzyl alcohol
    - Benzoic acid

✓ Pharmaceutical Industry:
  - Used in the manufacture of dyes, drugs, and intermediates.

Vanillin

→ Chemical Formula: $C_8H_8O_3$
→ IUPAC Name: 4-Hydroxy-3-methoxybenzaldehyde
→ Common Name: Vanillin
→ Functional Groups:
- Aldehyde (–CHO)
- Hydroxyl (–OH)
- Methoxy ($–OCH_3$)

Structure of Vanillin :



Uses of Vanillin:

✓ Flavoring Agent:
- Most widely used vanilla flavor compound in the food and beverage industry
- Used in ice creams, cakes, chocolates, and soft drinks

✓ Fragrance Industry:
- Used in perfumes, cosmetics, and air fresheners
- Provides a sweet and creamy scent

✓ Pharmaceutical Industry:
- Used as a flavoring agent in syrups and tablets
- Acts as a masking agent to hide bitter tastes

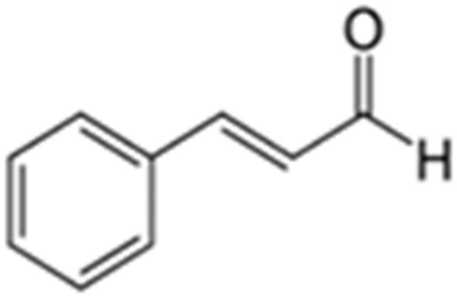
✓ Intermediate in Organic Synthesis:
- Used to synthesize:
  - Vanillic acid
  - Guaiacol
  - Various drugs and dyes

✓ Antioxidant and Preservative:
- Exhibits antioxidant properties

Cinnamaldehyde

→ Chemical Formula: C_9H_8O
→ IUPAC Name: 3-Phenylprop-2-enal
→ Common Name: Cinnamaldehyde
→ Functional Groups:
- Aldehyde group (–CHO)
- Conjugated double bond (C=C)
- Aromatic ring (benzene)

Structure of Cinnamaldehyde :



Uses of Cinnamaldehyde:

✓ Flavoring Agent:
- Main compound in cinnamon oil (from Cinnamomum species)
- Used to flavor candies, gums, desserts, and beverages

✓ Fragrance Industry:
- Used in perfumes, soaps, and cosmetics for its warm, spicy aroma

✓ Pharmaceutical and Medicinal Uses:
- Exhibits antibacterial, antifungal, and anti-inflammatory properties
- Studied for potential use in diabetes control and anticancer activity

✓ Insect Repellent:
- Effective against mosquitoes, ants, and other pests

✓ Preservative and Antioxidant:
- Acts as a natural food preservative