UNIT – 4 📚 CARBONYL COMPOUNDS (ALDEHYDES AND KETONES)

POINTS TO BE COVERED IN THIS TOPIC 📝

- ➤ NUCLEOPHILIC ADDITION
- ➤ ELECTROMERIC EFFECT
- ➤ ALDOL CONDENSATION
- ➤ CROSSED ALDOL CONDENSATION
- ➤ CANNIZZARO REACTION
- ➤ CROSSED CANNIZZARO REACTION
- ➤ BENZOIN CONDENSATION
- ➤ PERKIN CONDENSATION
- ➤ QUALITATIVE TESTS
- ➤ STRUCTURE AND USES OF IMPORTANT CARBONYL COMPOUNDS

🧬 INTRODUCTION TO CARBONYL COMPOUNDS

Carbonyl compounds are organic compounds containing the carbonyl group (C=O). This functional group is present in aldehydes and ketones, which are among the most important classes of organic compounds in pharmaceutical chemistry.

Aldehydes contain the carbonyl group attached to at least one hydrogen atom, while **ketones** have the carbonyl group attached to two carbon atoms. The carbonyl carbon is sp^2 hybridized and exhibits electrophilic character due to the electronegativity difference between carbon and oxygen.

⚡ NUCLEOPHILIC ADDITION REACTIONS

Definition and Mechanism

Nucleophilic addition is the characteristic reaction of carbonyl compounds where a nucleophile attacks the electrophilic carbonyl carbon. This reaction occurs due to the polarization of the C=O bond, making the carbon atom electron-deficient and susceptible to nucleophilic attack.

General Mechanism

1. **Step 1**: Nucleophile attacks the carbonyl carbon
2. **Step 2**: Protonation of the oxygen atom
3. **Step 3**: Formation of the final addition product

Important Nucleophilic Addition Reactions

Addition of HCN (Cyanohydrin Formation)

- Aldehydes and ketones react with HCN to form cyanohydrins
- The reaction is catalyzed by small amounts of base (KCN or NaCN)
- Cyanohydrins are important intermediates in organic synthesis

Addition of Bisulfite

- Carbonyl compounds react with sodium bisulfite to form crystalline bisulfite addition compounds
- This reaction is used for purification and identification of carbonyl compounds
- The reaction is reversible and can be used to regenerate the original carbonyl compound

Addition of Alcohols

- **Hemiacetal Formation**: Addition of one molecule of alcohol
- **Acetal Formation**: Addition of two molecules of alcohol with elimination of water
- Acetals are stable under basic conditions but hydrolyze under acidic conditions

Addition of Ammonia and Its Derivatives

- **Ammonia**: Forms imines (Schiff bases)
- **Primary Amines**: Forms substituted imines
- **Hydroxylamine**: Forms oximes
- **Hydrazine**: Forms hydrazones
- **Phenylhydrazine**: Forms phenylhydrazones

🔄 ELECTROMERIC EFFECT

Definition

The electromeric effect is a temporary effect that occurs in organic molecules containing multiple bonds (double or triple bonds) in the presence of an attacking reagent. It involves the complete transfer of a shared pair of π electrons to one of the atoms joined by the multiple bond.

Characteristics of Electromeric Effect

Temporary Nature

- The electromeric effect is observed only in the presence of an attacking reagent
- It disappears as soon as the attacking reagent is removed
- It is different from the inductive effect, which is permanent

Types of Electromeric Effect

+E Effect (Positive Electromeric Effect)

- The π electrons are transferred towards the attacking reagent
- Occurs when the attacking reagent is electrophilic
- Results in the development of positive charge on the carbon atom

-E Effect (Negative Electromeric Effect)

- The π electrons are transferred away from the attacking reagent
- Occurs when the attacking reagent is nucleophilic
- Results in the development of negative charge on the carbon atom

Electromeric Effect in Carbonyl Compounds

In carbonyl compounds, the electromeric effect plays a crucial role during nucleophilic addition reactions. When a nucleophile approaches the carbonyl carbon, the π electrons of the C=O bond shift towards the more electronegative oxygen atom, making the carbon more electrophilic and facilitating nucleophilic attack.

🌟 ALDOL CONDENSATION

Definition and Overview

Aldol condensation is an important carbon-carbon bond forming reaction where aldehydes or ketones containing α-hydrogen atoms undergo condensation in the presence of a base to form β-hydroxy aldehydes or ketones (aldol products).

Mechanism of Aldol Condensation

Step 1: Enolate Ion Formation

- The base abstracts an α-hydrogen from the carbonyl compound
- This leads to the formation of an enolate ion, which is resonance stabilized
- The negative charge is delocalized between the α-carbon and the oxygen atom

Step 2: Nucleophilic Attack

- The enolate ion acts as a nucleophile and attacks the carbonyl carbon of another molecule
- This results in the formation of a new C-C bond
- The product formed is called an aldol (aldehyde + alcohol)

Step 3: Protonation

- The alkoxide ion formed in step 2 is protonated by the solvent
- This gives the final aldol product containing both aldehyde and alcohol functional groups

Conditions for Aldol Condensation

- **Base Catalyst**: Usually dilute NaOH or KOH
- **Temperature**: Moderate temperature (room temperature to 50°C)
- **Solvent**: Protic solvents like water or ethanol
- **Requirement**: At least one α-hydrogen must be present

Dehydration of Aldol Products

Under more vigorous conditions (heat and strong base), the aldol product can undergo dehydration to form α,β-unsaturated carbonyl compounds. This process involves the elimination of a water molecule and the formation of a double bond between the α and β carbon atoms.

🔄 CROSSED ALDOL CONDENSATION

Definition

Crossed aldol condensation occurs between two different carbonyl compounds. This reaction is more complex than simple aldol condensation due to the possibility of multiple products formation.

Successful Crossed Aldol Condensation

Case 1: One Component Lacks α-Hydrogen

- When one carbonyl compound has no α-hydrogen (like formaldehyde, benzaldehyde)
- Only one enolate ion can form, leading to a single major product
- The compound without α-hydrogen acts as the electrophile

Case 2: Mixed Ketone-Aldehyde Systems

- Aldehydes are more reactive than ketones as electrophiles
- Ketones form enolate ions more readily due to less steric hindrance
- This combination often gives good yields of crossed aldol products

Strategies for Controlling Crossed Aldol Condensation

Use of LDA (Lithium Diisopropylamide)

- LDA is a strong, non-nucleophilic base
- It can selectively form kinetic enolates at low temperature
- This allows for better control over product formation

Preformed Enolate Method

- The enolate ion is preformed using a strong base
- The second carbonyl compound is then added
- This method provides better selectivity and higher yields

⚖️ CANNIZZARO REACTION

Definition and Scope

The Cannizzaro reaction is a disproportionation reaction of aldehydes that lack α-hydrogen atoms. In this reaction, two molecules of aldehyde undergo simultaneous oxidation and reduction in the presence of a strong base to form a carboxylic acid salt and a primary alcohol.

Mechanism of Cannizzaro Reaction

Step 1: Nucleophilic Attack by Hydroxide Ion

- Hydroxide ion attacks the carbonyl carbon of the aldehyde
- This forms a tetrahedral intermediate with a negative charge on oxygen

Step 2: Hydride Transfer

- The tetrahedral intermediate transfers a hydride ion to another aldehyde molecule
- This is the rate-determining step of the reaction
- One aldehyde molecule is reduced while the other is oxidized

Step 3: Proton Transfer

- The alkoxide ion formed abstracts a proton from the carboxylic acid
- This gives the final products: carboxylate salt and primary alcohol

Requirements for Cannizzaro Reaction

- **No α-hydrogen**: The aldehyde must not have any hydrogen atoms on the carbon adjacent to the carbonyl group
- **Strong Base**: Concentrated NaOH or KOH is typically used
- **High Temperature**: The reaction usually requires heating

Common Examples

- **Formaldehyde**: Forms methanol and sodium formate
- **Benzaldehyde**: Forms benzyl alcohol and sodium benzoate
- **Furfural**: Forms furfuryl alcohol and sodium furoate

🔀 CROSSED CANNIZZARO REACTION

Definition

Crossed Cannizzaro reaction occurs between two different aldehydes that lack α-hydrogen atoms. This reaction follows the same mechanism as the regular Cannizzaro reaction but involves two different aldehyde molecules.

Selectivity in Crossed Cannizzaro Reaction

Factors Affecting Selectivity

- **Electronic Effects**: Electron-withdrawing groups make the aldehyde more susceptible to reduction
- **Steric Effects**: Bulky groups can hinder the hydride transfer process
- **Relative Reactivity**: More electrophilic aldehydes are preferentially reduced

Predictable Crossed Cannizzaro Reactions

- **Formaldehyde + Aromatic Aldehyde**: Formaldehyde is always oxidized, aromatic aldehyde is reduced
- **Formaldehyde + Aliphatic Aldehyde**: Formaldehyde typically undergoes oxidation

Synthetic Utility

The crossed Cannizzaro reaction is particularly useful when one of the products is more valuable than the other. For instance, the reaction between formaldehyde and benzaldehyde produces benzyl alcohol, which is more synthetically useful than methanol.

💎 BENZOIN CONDENSATION

Definition

Benzoin condensation is a carbon-carbon bond forming reaction between two molecules of aromatic aldehydes in the presence of cyanide ion catalyst. The reaction produces α-hydroxyketones known as benzoins.

Mechanism of Benzoin Condensation

Step 1: Cyanohydrin Formation

- Cyanide ion acts as a nucleophile and attacks the carbonyl carbon
- This forms a cyanohydrin intermediate
- The presence of the cyano group makes the α-hydrogen more acidic

Step 2: Enolate Formation

- Base abstracts the α-hydrogen from the cyanohydrin
- This creates a stabilized enolate ion (carbanion)
- The negative charge is stabilized by the electron-withdrawing cyano group

Step 3: Nucleophilic Attack

- The enolate ion attacks the carbonyl carbon of another aldehyde molecule
- This forms a new C-C bond
- The intermediate formed has both cyano and hydroxyl groups

Step 4: Elimination of Cyanide

- Cyanide ion is eliminated from the intermediate
- This regenerates the catalyst and forms the final benzoin product
- The product contains both ketone and alcohol functional groups

Requirements and Conditions

- **Catalyst**: Sodium cyanide (NaCN) or potassium cyanide (KCN)
- **Solvent**: Ethanol or aqueous ethanol
- **Temperature**: Room temperature to moderate heating
- **Substrate**: Aromatic aldehydes without strong electron-withdrawing groups

Limitations

- The reaction works best with aromatic aldehydes
- Aliphatic aldehydes generally do not undergo benzoin condensation
- Strong electron-withdrawing groups on the benzene ring inhibit the reaction

---

🌸 PERKIN CONDENSATION

Definition

Perkin condensation is a condensation reaction between aromatic aldehydes and acid anhydrides in the presence of the sodium salt of the corresponding acid. The reaction produces α,β-unsaturated carboxylic acids.

Mechanism of Perkin Condensation

Step 1: Enolate Formation

- The sodium salt of the acid acts as a base

- It abstracts a proton from the methyl group of the acid anhydride
- This forms an enolate-type intermediate

Step 2: Aldol-type Addition

- The enolate intermediate attacks the carbonyl carbon of the aromatic aldehyde
- This forms a β-hydroxy acid anhydride intermediate
- The reaction is similar to an aldol condensation

Step 3: Elimination and Hydrolysis

- The intermediate undergoes elimination of water
- Hydrolysis of the anhydride group occurs
- The final product is an α,β-unsaturated carboxylic acid

Classical Perkin Reaction

- **Reactants**: Benzaldehyde + Acetic anhydride
- **Catalyst**: Sodium acetate
- **Product**: Cinnamic acid (phenylacrylic acid)
- **Conditions**: Heating at 180-200°C

Scope and Limitations

Suitable Aldehydes

- Aromatic aldehydes work well
- Electron-donating groups on the benzene ring favor the reaction

- Strong electron-withdrawing groups may inhibit the reaction

Acid Anhydrides

- Acetic anhydride is most commonly used
- Other simple acid anhydrides can also be employed
- The corresponding sodium salt must be present as catalyst

🧪 QUALITATIVE TESTS FOR CARBONYL COMPOUNDS

Test Name	Reagent	Observation	Specificity
2,4-DNP Test	2,4-Dinitrophenylhydrazine	Orange/Yellow precipitate	General test for C=O
Fehling's Test	Fehling's reagent	Red precipitate (Cu_2O)	Aldehydes only
Benedict's Test	Benedict's reagent	Red precipitate	Aldehydes only
Tollens' Test	Tollens' reagent	Silver mirror	Aldehydes only
Schiff's Test	Schiff's reagent	Pink/Magenta color	Aldehydes only
Iodoform Test	I_2 + NaOH	Yellow precipitate	Methyl ketones
Bisulfite Test	Sodium bisulfite	White crystalline precipitate	Aldehydes and methyl ketones

Detailed Description of Important Tests

2,4-Dinitrophenylhydrazine (2,4-DNP) Test

This is a general test for detecting the presence of carbonyl compounds. The reagent reacts with both aldehydes and ketones to form colored precipitates (hydrazones). The color varies from yellow to orange-red depending on the structure of the carbonyl compound.

Procedure: Add a few drops of 2,4-DNP reagent to the test solution. Formation of a colored precipitate confirms the presence of a carbonyl group.

Tollens' Test (Silver Mirror Test)

This test is specific for aldehydes. Tollens' reagent contains silver ammonia complex, which is reduced by aldehydes to metallic silver, forming a characteristic silver mirror on the inner surface of the test tube.

Procedure: Add Tollens' reagent to the test solution and warm gently. Formation of a silver mirror indicates the presence of an aldehyde.

Fehling's Test

This test uses Fehling's reagent (alkaline solution of cupric sulfate and potassium sodium tartrate). Aldehydes reduce the blue cupric ions to red cuprous oxide precipitate.

Procedure: Add Fehling's reagent to the test solution and heat. Formation of a red precipitate indicates the presence of an aldehyde.

Iodoform Test

This test is specific for compounds containing the CH_3CO- group (methyl ketones) or compounds that can be oxidized to form such groups. The reaction produces a yellow precipitate of iodoform (CHI_3).

Procedure: Add iodine solution and sodium hydroxide to the test solution. Formation of a yellow precipitate with a characteristic odor indicates a positive test.

🏗 STRUCTURE AND USES OF IMPORTANT CARBONYL COMPOUNDS

FORMALDEHYDE 🧪

- **Molecular Formula**: HCHO
- **Molecular Weight**: 30.03

Properties

- Formaldehyde is the simplest aldehyde
- It exists as a gas at room temperature
- Highly reactive due to the absence of alkyl groups
- Readily polymerizes to form paraformaldehyde
- Soluble in water, forming hydrates

Structure

Formaldehyde has a planar structure with the carbon atom sp^2 hybridized. The C=O bond length is shorter than a typical C-O single bond due to partial double bond character.

Uses

- **Disinfectant and Preservative**: Used in biological specimen preservation
- **Polymer Industry**: Production of phenol-formaldehyde and urea-formaldehyde resins
- **Textile Industry**: Used in wrinkle-resistant fabric treatments
- **Medical Applications**: Sterilization and preservation of medical equipment
- **Chemical Synthesis**: Raw material for various organic syntheses

---

PARALDEHYDE 🔄

- **Molecular Formula**: $(CH_3CHO)_3$
- **Molecular Weight**: 132.16

Properties

- Paraldehyde is a cyclic trimer of acetaldehyde
- White crystalline solid at room temperature
- Pleasant ethereal odor
- Soluble in organic solvents, slightly soluble in water
- Stable under normal conditions but can depolymerize to acetaldehyde

Structure

Paraldehyde has a six-membered ring structure containing three carbon atoms and three oxygen atoms alternately arranged. Each carbon atom is bonded to a methyl group and participates in the ring formation through C-O bonds.

Uses

- **Pharmaceutical Industry**: Previously used as a sedative and hypnotic drug
- **Chemical Industry**: Source of acetaldehyde when depolymerized
- **Solvent**: Used as a solvent in some specialized applications
- **Laboratory Reagent**: Used in organic synthesis as an acetaldehyde equivalent

---

ACETONE ⚗️

- **Molecular Formula**: CH_3COCH_3
- **Molecular Weight**: 58.08

Properties

- Acetone is the simplest ketone
- Colorless, volatile liquid with a characteristic odor
- Completely miscible with water and most organic solvents
- Low boiling point (56.2°C) makes it highly volatile
- Excellent solvent properties for both polar and nonpolar compounds

Structure

Acetone has a planar structure around the carbonyl carbon, which is sp^2 hybridized. The two methyl groups are attached to the carbonyl carbon, making it a symmetrical molecule.

Uses

- **Industrial Solvent**: Widely used solvent for plastics, synthetic fibers, and resins
- **Chemical Industry**: Raw material for production of methyl methacrylate and other chemicals
- **Pharmaceutical Industry**: Solvent in drug formulations and extraction processes
- **Cosmetic Industry**: Nail polish remover and other cosmetic applications
- **Laboratory Applications**: Common laboratory solvent and cleaning agent

---

CHLORAL HYDRATE 💧

- **Molecular Formula**: $CCl_3CH(OH)_2$
- **Molecular Weight**: 165.40

Properties

- Chloral hydrate is the hydrate form of chloral (CCl_3CHO)
- White crystalline solid with a slightly bitter taste
- Readily soluble in water, ethanol, and ether

- Stable in aqueous solution due to hydrate formation
- The gem-diol structure is stabilized by the electron-withdrawing effect of the CCl_3 group

Structure

Chloral hydrate exists as a gem-diol (1,1-diol) where the carbonyl carbon of chloral is bonded to two hydroxyl groups. This structure is unusual for aldehydes but is stabilized by the strong electron-withdrawing effect of the trichloromethyl group.

Uses

- **Pharmaceutical Applications**: Historically used as a sedative and hypnotic
- **Veterinary Medicine**: Used as an anesthetic and sedative for animals
- **Chemical Synthesis**: Intermediate in the production of other chemicals
- **Research Applications**: Used in laboratory studies and research
- **Industrial Applications**: Limited use in specialized chemical processes

---

HEXAMINE 🔷

- **Molecular Formula**: $(CH_2)_6N_4$
- **Molecular Weight**: 140.19

Properties

- Hexamine (hexamethylenetetramine) is a heterocyclic compound

- White crystalline solid with a fishlike odor
- Highly soluble in water and polar solvents
- Stable under normal conditions but decomposes in acidic media
- Forms salts with acids

Structure

Hexamine has a cage-like structure with four nitrogen atoms and six methylene groups. The structure is highly symmetrical and resembles an adamantane framework with nitrogen atoms replacing four of the carbon atoms.

Uses

- **Medical Applications**: Used as a urinary antiseptic (methenamine)
- **Industrial Applications**: Production of phenolic resins and rubber chemicals
- **Explosives Industry**: Component in solid fuel tablets and explosives
- **Chemical Synthesis**: Source of formaldehyde under acidic conditions
- **Analytical Chemistry**: Used in various analytical procedures

---

BENZALDEHYDE 🌸

- **Molecular Formula**: C_6H_5CHO
- **Molecular Weight**: 106.12

Properties

- Benzaldehyde is the simplest aromatic aldehyde
- Colorless liquid with a characteristic almond-like odor
- Slightly soluble in water, miscible with organic solvents
- Undergoes autoxidation in air to form benzoic acid
- Shows typical aldehyde reactions

Structure

Benzaldehyde consists of a benzene ring directly attached to an aldehyde group. The carbonyl carbon is sp^2 hybridized and lies in the same plane as the benzene ring, allowing for conjugation between the aromatic π-system and the carbonyl group.

Uses

- **Flavoring Industry**: Natural and artificial almond flavoring
- **Perfume Industry**: Used in perfumes and cosmetic products
- **Chemical Synthesis**: Starting material for various organic syntheses
- **Pharmaceutical Industry**: Intermediate in drug synthesis
- **Food Industry**: Food flavoring and preservation

VANILLIN 🍦

- **Molecular Formula**: $C_8H_8O_3$
- **Molecular Weight**: 152.15

Properties

- Vanillin is 4-hydroxy-3-methoxybenzaldehyde
- White crystalline solid with a pleasant vanilla odor
- Soluble in ethanol and ether, slightly soluble in water
- Stable under normal storage conditions
- Shows characteristic reactions of both aldehydes and phenols

Structure

Vanillin has a benzene ring substituted with three functional groups: an aldehyde group at position 1, a hydroxyl group at position 4, and a methoxy group at position 3. This substitution pattern is responsible for its unique properties and biological activity.

Uses

- **Food Industry**: Most widely used flavoring agent (vanilla flavoring)
- **Pharmaceutical Industry**: Flavoring agent in pharmaceutical formulations
- **Perfume Industry**: Component in various fragrances
- **Chemical Industry**: Starting material for synthesis of other vanillin derivatives
- **Research Applications**: Used in biochemical and analytical studies

---

CINNAMALDEHYDE 🌿

- **Molecular Formula**: C_9H_8O
- **Molecular Weight**: 132.16

Properties

- Cinnamaldehyde is 3-phenylprop-2-enal
- Pale yellow viscous liquid with a characteristic cinnamon odor
- Insoluble in water, soluble in organic solvents
- Shows E/Z isomerism due to the presence of a C=C double bond
- Undergoes typical α,β-unsaturated aldehyde reactions

Structure

Cinnamaldehyde contains both a benzene ring and an α,β-unsaturated aldehyde system. The molecule exists primarily in the E-configuration (trans), where the phenyl group and the aldehyde group are on opposite sides of the C=C double bond.

Uses

- **Flavoring Industry**: Natural cinnamon flavoring in foods and beverages
- **Pharmaceutical Industry**: Antimicrobial and antifungal properties
- **Cosmetic Industry**: Fragrance component in perfumes and cosmetics
- **Agricultural Applications**: Natural pesticide and fungicide
- **Chemical Synthesis**: Starting material for various organic compounds

---

📊 COMPARISON TABLE OF CARBONYL COMPOUNDS

Compound	Type	Key Functional Groups	Primary Uses	Special Properties
Formaldehyde	Aldehyde	-CHO	Preservative, Resin production	Highly reactive, polymerizes easily
Paraldehyde	Cyclic trimer	Three -CHO units	Sedative, Acetaldehyde source	Stable cyclic structure
Acetone	Ketone	C=O	Solvent, Chemical intermediate	Excellent solvent properties
Chloral hydrate	Hydrated aldehyde	$-CH(OH)_2$, CCl_3	Sedative, Veterinary medicine	Stable gem-diol structure
Hexamine	Heterocyclic	N atoms, CH_2 groups	Urinary antiseptic, Resin production	Cage-like structure
Benzaldehyde	Aromatic aldehyde	-CHO, Benzene ring	Flavoring, Perfumes	Almond-like odor
Vanillin	Phenolic aldehyde	-CHO, -OH, $-OCH_3$	Vanilla flavoring	Most used flavoring

Compound	Type	Key Functional Groups	Primary Uses	Special Properties
				agent
Cinnamaldehyde	α,β-unsaturated aldehyde	-CHO, C=C, Benzene	Cinnamon flavoring	Antimicrobial properties

---

🎯 SUMMARY

This comprehensive study of carbonyl compounds covers the fundamental reactions and important compounds in pharmaceutical organic chemistry. Understanding nucleophilic addition mechanisms, various condensation reactions, and the properties of specific carbonyl compounds is essential for pharmaceutical applications. The qualitative tests provide practical methods for identification, while the detailed study of individual compounds highlights their pharmaceutical and industrial importance.

The carbonyl group's electrophilic nature makes it a versatile functional group in organic synthesis, and mastering these concepts is crucial for advanced pharmaceutical chemistry studies.