UNIT – 4 💎 POLYNUCLEAR HYDROCARBONS

B. PHARMACY - 3RD SEMESTER

POINTS TO BE COVERED IN THIS TOPIC

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🧪 INTRODUCTION TO POLYNUCLEAR HYDROCARBONS

DEFINITION

Polynuclear hydrocarbons, also known as polycyclic aromatic hydrocarbons or fused ring aromatic compounds, are organic compounds consisting of two or more benzene rings fused together in a linear, angular, or clustered arrangement. These compounds share two or more carbon atoms between adjacent rings, forming a continuous conjugated system of pi electrons.

The term "polynuclear" refers to the presence of multiple aromatic nuclei or ring systems. These compounds exhibit enhanced stability due to the extensive

delocalization of electrons across the fused ring system. Polynuclear hydrocarbons are important in both natural and synthetic chemistry, serving as starting materials for numerous pharmaceuticals, dyes, and other industrially significant compounds.

CLASSIFICATION

Polynuclear hydrocarbons can be classified based on the arrangement of their aromatic rings:

Based on Ring Fusion:

Linearly Fused Systems: In these compounds, the benzene rings are fused in a linear or straight-line arrangement. Each ring shares one edge with the adjacent ring, creating an extended conjugated system.

Angularly Fused Systems: These compounds have benzene rings fused at an angle to each other, creating a bent or angular molecular structure. The rings share edges but not in a straight-line arrangement.

Clustered Systems: In these systems, three or more rings are fused around a central point, creating a more compact, branched structure.

Based on Number of Rings:

Bicyclic Compounds: Contain two fused aromatic rings.

Tricyclic Compounds: Contain three fused aromatic rings.

Polycyclic Compounds: Contain four or more fused aromatic rings.

GENERAL PROPERTIES

Physical Properties: Polynuclear hydrocarbons are generally colorless or pale yellow crystalline solids with characteristic odors. As the number of fused rings increases, the melting point, boiling point, and molecular weight increase. These compounds are generally insoluble in water but soluble in organic solvents such as benzene, toluene, and chloroform. The increased molecular size and extended conjugation lead to higher stability and lower volatility compared to benzene.

Chemical Properties: Polynuclear hydrocarbons undergo electrophilic aromatic substitution reactions, though their reactivity patterns differ from benzene due to the presence of multiple rings. The position of substitution depends on the electronic distribution within the molecule. Some positions are more reactive than others due to differences in electron density and resonance stabilization. These compounds are generally less reactive than benzene toward electrophilic substitution but show increased reactivity at certain positions.

OCCURRENCE AND SOURCES

Polynuclear hydrocarbons occur naturally in coal tar, petroleum, and as products of incomplete combustion of organic materials. They are found in tobacco smoke, automobile exhaust, and grilled foods. Some are produced industrially for use as intermediates in the synthesis of dyes, pharmaceuticals, plastics, and other chemicals. The study of these compounds is important in pharmaceutical chemistry as many drugs and biologically active molecules contain polynuclear aromatic systems.

🔷 NAPHTHALENE

STRUCTURE AND NOMENCLATURE

Naphthalene is the simplest polynuclear aromatic hydrocarbon, consisting of two benzene rings fused together in a linear arrangement. It has the molecular formula $C_{10}H_8$ and molecular weight of 128.17. The structure contains ten carbon atoms and eight hydrogen atoms arranged in a planar configuration.

Numbering System: The carbon atoms in naphthalene are numbered in a specific pattern. The numbering starts from one of the carbons adjacent to the ring junction and proceeds around the first ring, then continues to the second ring. Positions 1, 4, 5, and 8 are called alpha positions, while positions 2, 3, 6, and 7 are called beta positions. The two rings share two carbon atoms, which are referred to as the ring junction carbons.

Electronic Structure: Naphthalene has ten pi electrons delocalized over the entire molecular framework, contributing to its aromatic stability. The molecule exhibits resonance, with the double bonds not being localized but spread over the entire ring system. This delocalization provides extra stability compared to isolated benzene rings.

SYNTHESIS OF NAPHTHALENE

1. Industrial Production from Coal Tar: Naphthalene is obtained on a large scale from coal tar, which is a by-product of coal carbonization. Coal tar contains approximately seven to twelve percent naphthalene. The crude coal tar is subjected to fractional distillation, and naphthalene is collected in the middle oil fraction that distills between 170°C and 230°C. The crude naphthalene is further purified by recrystallization, washing with dilute alkali to remove phenolic impurities, and final crystallization from alcohol or by sublimation.

2. Haworth Synthesis: This is an important synthetic method for preparing naphthalene and its derivatives. The process involves the following steps:

- Benzene is first acylated with succinic anhydride in the presence of anhydrous aluminum chloride through a Friedel-Crafts acylation reaction to form gamma-benzoylbutyric acid.
- The acid is then reduced using zinc amalgam and hydrochloric acid through the Clemmensen reduction to form gamma-phenylbutyric acid.
- Cyclization is achieved by heating with concentrated sulfuric acid or polyphosphoric acid, forming alpha-tetralone.
- Finally, the ketone is reduced to tetralin, which is then dehydrogenated using a catalyst such as palladium or selenium at high temperature to yield naphthalene.

3. Dehydrogenation of Tetralin: Tetralin (1,2,3,4-tetrahydronaphthalene) can be dehydrogenated to naphthalene by heating with sulfur or selenium, or by passing the vapor over a heated catalyst such as palladium on charcoal at 300-400°C. This method is useful for producing naphthalene from partially hydrogenated derivatives.

4. Elbs Reaction: Ortho-methylbenzophenone, when heated with sodium or potassium hydroxide at high temperature, undergoes intramolecular condensation followed by dehydration to form naphthalene derivatives.

REACTIONS OF NAPHTHALENE

Naphthalene undergoes various chemical reactions, primarily electrophilic aromatic substitution reactions. The alpha positions (1, 4, 5, 8) are generally

more reactive than the beta positions (2, 3, 6, 7) toward electrophilic attack due to better resonance stabilization of the intermediate carbocation.

1. Halogenation: Naphthalene reacts with halogens in the presence or absence of a catalyst. When treated with chlorine or bromine without a catalyst, substitution occurs preferentially at the alpha position, forming alpha-chloronaphthalene or alpha-bromonaphthalene. In the presence of a Lewis acid catalyst such as ferric chloride or aluminum chloride, the reaction proceeds more rapidly, but the product distribution remains predominantly alpha-substituted. With excess halogen and prolonged reaction time, polysubstituted products can be formed.

$C_{10}H_8 + Cl_2 \rightarrow C_{10}H_7Cl + HCl$

2. Nitration: Naphthalene undergoes nitration when treated with a mixture of concentrated nitric acid and concentrated sulfuric acid. The nitration occurs preferentially at the alpha position, yielding alpha-nitronaphthalene as the major product. The reaction conditions can be controlled to produce mono-nitro or di-nitro derivatives. At higher temperatures or with excess nitrating mixture, 1,5-dinitronaphthalene or 1,8-dinitronaphthalene can be formed.

$C_{10}H_8 + HNO_3 \rightarrow C_{10}H_7NO_2 + H_2O$

3. Sulfonation: Sulfonation of naphthalene shows interesting temperature-dependent regioselectivity. When naphthalene is treated with concentrated sulfuric acid at temperatures below 80°C, the kinetically favored alpha-naphthalenesulfonic acid is formed predominantly. However, when the reaction is carried out at temperatures above 160°C, the thermodynamically more stable beta-naphthalenesulfonic acid becomes the major product. This temperature-

dependent isomerization is reversible, allowing for the conversion of alpha to beta isomer under appropriate conditions.

$C_{10}H_8 + H_2SO_4 \rightarrow C_{10}H_7SO_3H + H_2O$

4. Friedel-Crafts Alkylation: Naphthalene undergoes Friedel-Crafts alkylation in the presence of aluminum chloride as a catalyst. Alkyl halides react with naphthalene to introduce alkyl groups, predominantly at the alpha position. The reaction follows the mechanism of electrophilic aromatic substitution with the formation of a carbocation intermediate.

5. Friedel-Crafts Acylation: Similar to alkylation, naphthalene undergoes acylation with acyl halides or acid anhydrides in the presence of aluminum chloride. The acyl group enters predominantly at the alpha position, forming alpha-acylnaphthalene derivatives. This reaction is important in the synthesis of various naphthalene-based compounds.

6. Oxidation: Naphthalene is relatively resistant to oxidation but can be oxidized under vigorous conditions. When treated with strong oxidizing agents such as alkaline potassium permanganate or hot chromic acid, naphthalene is oxidized to phthalic acid. The oxidation proceeds through the cleavage of one of the aromatic rings. Under milder conditions, specific oxidation of side chains or partial oxidation of the ring system can be achieved.

$C_{10}H_8 + [O] \rightarrow C_6H_4(COOH)_2$ (Phthalic acid)

7. Reduction: Naphthalene can be reduced to various extent depending on the conditions:

- Partial reduction with sodium and alcohol in liquid ammonia yields 1,2,3,4-tetrahydronaphthalene (tetralin).

- Complete reduction with hydrogen in the presence of a metal catalyst at high pressure yields decahydronaphthalene (decalin), which exists as cis and trans isomers.
- The reduction proceeds stepwise, with one ring being reduced before the other.

8. Hydroxylation: Naphthalene can be hydroxylated to form naphthols. Fusion with sodium hydroxide at high temperature converts naphthalene to sodium naphtholate, which upon acidification yields naphthols. Alpha-naphthol and beta-naphthol are important derivatives used in dye synthesis and pharmaceutical applications.

MEDICINAL USES OF NAPHTHALENE

Antiseptic and Disinfectant: Naphthalene derivatives, particularly chlorinated and hydroxylated compounds, possess antiseptic and disinfectant properties. They are used in topical formulations for treating skin infections and as preservatives in pharmaceutical preparations.

Moth Repellent: Pure naphthalene is widely used as a moth repellent and insecticide. Mothballs are made from naphthalene, which slowly sublimes at room temperature, releasing vapors that repel moths and other insects. This application protects woolens and other fabrics from insect damage.

Precursor for Drug Synthesis: Naphthalene serves as a starting material for the synthesis of numerous pharmaceutical compounds. Naphthol derivatives are used in the preparation of various drugs including antimalarials, anthelmintics, and analgesics. Naphthalene-based structures are found in several cardiovascular drugs and anti-inflammatory agents.

Industrial Applications: In pharmaceutical manufacturing, naphthalene derivatives are used as intermediates in the synthesis of dyes used in biological staining and diagnostic procedures. Naphthalene sulfonates are used as solubilizing agents and dispersants in pharmaceutical formulations.

PHENANTHRENE

STRUCTURE AND NOMENCLATURE

Phenanthrene is a tricyclic aromatic hydrocarbon consisting of three benzene rings fused together in an angular arrangement. It has the molecular formula $C_{14}H_{10}$ and molecular weight of 178.23. Unlike naphthalene's linear structure, phenanthrene has a bent or angular configuration, with the three rings arranged in a distinctive pattern.

Structural Features: Phenanthrene contains fourteen carbon atoms and ten hydrogen atoms. The three benzene rings share edges, with the middle ring sharing one edge with each of the outer rings. The central ring is often referred to as the "bay" region, and this structural feature significantly influences the chemical reactivity and biological properties of phenanthrene and its derivatives.

Numbering System: The carbon atoms in phenanthrene are numbered systematically, starting from one corner and proceeding around the molecule. Positions 9 and 10 are located at the central ring junction and are particularly reactive. These positions are often called the meso positions and exhibit unique reactivity compared to other positions in the molecule.

Electronic Structure: Phenanthrene has fourteen pi electrons delocalized across the three rings, providing aromatic stability. However, the angular arrangement creates regions of varying electron density, making certain positions more reactive than others. The molecule can be represented by multiple resonance structures, contributing to its overall stability.

SYNTHESIS OF PHENANTHRENE

1. Haworth Synthesis: This method is specifically designed for the synthesis of phenanthrene and involves multiple steps:

- Naphthalene is first acylated with succinic anhydride in the presence of aluminum chloride to form a keto acid.
- The keto group is reduced to a methylene group using Clemmensen reduction or Wolff-Kishner reduction.
- The resulting acid is cyclized by heating with polyphosphoric acid or concentrated sulfuric acid.
- The cyclized product undergoes dehydrogenation with selenium or sulfur at high temperature to yield phenanthrene.

2. Pschorr Synthesis: This method involves the coupling of aromatic diazonium salts:

- An appropriately substituted biphenyl derivative is prepared with an amino group and a carboxylic acid group in suitable positions.
- The amino group is converted to a diazonium salt by treatment with sodium nitrite and acid.

- The diazonium compound undergoes intramolecular cyclization in the presence of copper powder, forming a new carbon-carbon bond.
- Aromatization and further modifications yield phenanthrene.

3. Oxidative Coupling: Biphenyl derivatives can undergo oxidative coupling reactions in the presence of strong oxidizing agents and Lewis acids to form phenanthrene. This method involves the formation of a new carbon-carbon bond between the two aromatic rings through dehydrogenative coupling.

REACTIONS OF PHENANTHRENE

1. Halogenation: Phenanthrene undergoes halogenation, with bromine and chlorine reacting at the 9 and 10 positions preferentially. When treated with bromine in carbon disulfide at room temperature, 9-bromophenanthrene is formed as the major product. The high reactivity of the 9,10-positions is due to the fact that substitution at these positions preserves two complete benzene rings in the product, maintaining aromatic stability.

2. Nitration: Nitration of phenanthrene occurs predominantly at the 9-position when treated with dilute nitric acid. With concentrated nitric acid and sulfuric acid mixture, multiple nitro groups can be introduced. The orientation of nitration is controlled by the electron density distribution in the molecule.

3. Sulfonation: Phenanthrene undergoes sulfonation at various positions depending on temperature and reaction conditions. At lower temperatures, kinetic products are formed, while higher temperatures favor thermodynamically stable isomers.

4. Oxidation: Phenanthrene is particularly susceptible to oxidation at the 9,10-positions due to the higher reactivity of these positions. When oxidized with

chromic acid or potassium permanganate, phenanthrene forms phenanthraquinone (9,10-phenanthrenedione). Further vigorous oxidation can cleave the ring system to form diphenyl dicarboxylic acid.

$C_{14}H_{10} + [O] \rightarrow C_{14}H_8O_2$ (Phenanthraquinone)

5. Addition Reactions: Unlike benzene and naphthalene, phenanthrene can undergo addition reactions at the 9,10-positions. When treated with bromine in the absence of a catalyst, phenanthrene forms 9,10-dibromo-9,10-dihydrophenanthrene. This addition occurs because the resulting product still retains two intact benzene rings, maintaining significant aromatic character.

6. Reduction: Phenanthrene can be reduced to 9,10-dihydrophenanthrene by treatment with sodium and alcohol or by catalytic hydrogenation. Further reduction can yield tetrahydro and octahydro derivatives, eventually producing perhydrophenanthrene under vigorous conditions.

MEDICINAL USES OF PHENANTHRENE

Steroid Structure: The most significant pharmaceutical importance of phenanthrene lies in its structural relationship to steroids. The steroid nucleus, found in numerous biologically important compounds including cholesterol, sex hormones, corticosteroids, and bile acids, is essentially a perhydrophenanthrene system (phenanthrene with fully saturated rings) fused to a cyclopentane ring. Understanding phenanthrene chemistry is crucial for comprehending steroid chemistry and the synthesis of steroidal drugs.

Morphine and Alkaloids: Several important alkaloids, including morphine and related analgesics, contain a phenanthrene-based structure. These compounds are powerful pain relievers and are extensively used in medicine.

The phenanthrene moiety contributes to the binding affinity of these molecules to opioid receptors.

Pharmaceutical Intermediates: Phenanthrene derivatives serve as intermediates in the synthesis of various pharmaceutical compounds. They are used in preparing drugs with analgesic, anti-inflammatory, and anticancer properties. The rigid, planar structure of phenanthrene makes it useful as a scaffold for designing molecules with specific biological activities.

Fluorescent Probes: Phenanthrene-based compounds exhibit fluorescence and are used in developing fluorescent probes and markers for biological and pharmaceutical research. These applications include drug delivery monitoring, cellular imaging, and diagnostic procedures.

◆ ANTHRACENE

STRUCTURE AND NOMENCLATURE

Anthracene is a tricyclic aromatic hydrocarbon consisting of three benzene rings fused together in a linear arrangement. It has the molecular formula $C_{14}H_{10}$ and molecular weight of 178.23. Anthracene is an isomer of phenanthrene but differs significantly in structure and properties due to its linear fusion pattern.

Structural Features: Anthracene has a linear, symmetrical structure with three benzene rings arranged in a straight line. The central ring shares edges with the two outer rings. The molecule is planar with fourteen carbon atoms and ten hydrogen atoms. The central ring positions (9 and 10) are particularly reactive due to the electronic distribution in the molecule.

Numbering System: Carbon atoms in anthracene are numbered systematically. The numbering starts at one corner and proceeds around the molecule. Positions 9 and 10 are the meso positions located in the central ring and exhibit the highest reactivity. Positions 1, 4, 5, and 8 are alpha positions, while positions 2, 3, 6, and 7 are beta positions.

Electronic Structure: Anthracene has fourteen pi electrons distributed over the three rings. However, the linear arrangement results in the central ring having less aromatic character compared to the outer rings. Resonance structures show that certain bonds have more double bond character than others, making the 9,10-positions particularly reactive.

SYNTHESIS OF ANTHRACENE

1. Friedel-Crafts Synthesis: Anthracene can be synthesized through a multi-step Friedel-Crafts approach:

- Benzene is acylated with phthalic anhydride in the presence of aluminum chloride to form ortho-benzoylbenzoic acid.
- The acid is cyclized by heating with sulfuric acid or phosphorus pentoxide to form anthraquinone.
- Anthraquinone is reduced to anthracene using zinc dust and sodium hydroxide solution, or by reduction with tin and hydrochloric acid followed by treatment with base.

2. Diels-Alder Approach: Anthracene and its derivatives can be synthesized using Diels-Alder cycloaddition reactions followed by dehydrogenation. This method is particularly useful for preparing substituted anthracenes.

3. Haworth Synthesis: Similar to naphthalene and phenanthrene, anthracene can be prepared by the Haworth synthesis involving acylation of benzene derivatives, reduction, cyclization, and dehydrogenation steps, appropriately modified for the linear three-ring system.

4. Industrial Production: Commercially, anthracene is obtained from coal tar. The heavy oil fraction of coal tar, which distills above 270°C, contains anthracene. It is separated and purified by fractional crystallization, utilizing the differential solubility of anthracene and its associated compounds in various solvents.

REACTIONS OF ANTHRACENE

Anthracene is more reactive than benzene, naphthalene, and phenanthrene, particularly at the 9,10-positions. This enhanced reactivity is due to the fact that reactions at these positions convert the central ring to a non-aromatic state while preserving two complete benzene rings, resulting in a thermodynamically favorable transformation.

1. Halogenation: Anthracene reacts readily with halogens. When treated with bromine in the presence of sunlight or a catalyst, addition occurs at the 9,10-positions to form 9,10-dibromoanthracene. This is an addition reaction rather than substitution, which is unusual for aromatic compounds. The product retains two intact benzene rings, accounting for the favorable energetics. Under forcing conditions, substitution products can also be obtained.

$C_{14}H_{10} + Br_2 \rightarrow C_{14}H_{10}Br_2$

2. Oxidation: Anthracene is readily oxidized at the 9,10-positions. When treated with oxidizing agents such as chromic acid, potassium dichromate, or sodium dichromate in acetic acid, anthracene is converted to anthraquinone

(9,10-anthraquinone). This oxidation is commercially important as anthraquinone is a valuable intermediate for dye synthesis.

$C_{14}H_{10} + [O] \rightarrow C_{14}H_8O_2$ (Anthraquinone)

3. Addition Reactions: Anthracene undergoes Diels-Alder reactions, acting as a diene. The central ring participates as a diene with dienophiles such as maleic anhydride. The reaction occurs readily at moderate temperatures, forming bridged adducts. This reaction is useful in organic synthesis and demonstrates the reduced aromatic character of the central ring.

4. Reduction: Anthracene can be reduced to 9,10-dihydroanthracene by treatment with sodium and alcohol or by catalytic hydrogenation. Further reduction yields tetrahydro, octahydro, and eventually perhydroanthracene derivatives. The reduction typically begins at the central ring.

5. Photochemical Dimerization: When exposed to ultraviolet light in solution or in the solid state, anthracene undergoes photodimerization. Two anthracene molecules combine through cycloaddition at the 9,10-positions to form a dimer. This reaction is reversible upon heating, regenerating anthracene. This photochemical behavior is utilized in photochromic materials and optical data storage.

6. Substitution Reactions: Under appropriate conditions, anthracene can undergo substitution reactions. Nitration with dilute nitric acid produces 9-nitroanthracene. Sulfonation occurs at the alpha positions or at the 9-position depending on conditions. Friedel-Crafts acylation and alkylation can also be performed, though they are less common than addition reactions.

MEDICINAL USES OF ANTHRACENE

Laxative Properties: Anthracene derivatives, particularly anthraquinone glycosides, are found in several natural laxatives. Compounds such as sennosides (from senna), aloin (from aloe), and cascara compounds are anthraquinone derivatives that act as stimulant laxatives. These compounds are widely used in treating constipation and are found in many over-the-counter laxative preparations.

Anticancer Activity: Several anthracene derivatives, particularly anthracyclines such as doxorubicin and daunorubicin, are important anticancer drugs. These compounds intercalate into DNA and inhibit topoisomerase enzymes, preventing DNA replication and leading to cell death. They are used in chemotherapy for various cancers including leukemias, lymphomas, and solid tumors.

Dye Intermediates: Anthraquinone, derived from anthracene oxidation, is a crucial intermediate in the synthesis of dyes used in pharmaceutical and biological applications. These dyes are used in histological staining, diagnostic procedures, and as markers in pharmaceutical research.

Photosensitizers: Anthracene derivatives are being investigated as photosensitizers in photodynamic therapy for cancer treatment. These compounds absorb light and generate reactive oxygen species that can destroy cancer cells.

Antimicrobial Agents: Some anthracene derivatives exhibit antimicrobial properties and are used in topical antiseptic formulations. They inhibit bacterial and fungal growth and are incorporated into dermatological preparations.

🔹 DIPHENYLMETHANE

STRUCTURE AND NOMENCLATURE

Diphenylmethane is a polynuclear aromatic compound consisting of two benzene rings connected by a methylene (–CH_2–) group. It has the molecular formula $C_{13}H_{12}$ and molecular weight of 168.23. Unlike naphthalene, phenanthrene, and anthracene where rings are fused, in diphenylmethane the benzene rings are linked through a single carbon bridge.

Structural Features: The structure consists of two phenyl groups attached to a central methylene carbon. The two benzene rings are not in the same plane due to steric factors and can rotate relatively freely around the carbon-carbon single bonds connecting them to the central methylene group. This flexibility distinguishes diphenylmethane from rigid fused-ring systems.

Electronic Structure: Each benzene ring retains its full aromatic character since there is no direct fusion. The methylene bridge does not participate in aromatic delocalization but can influence the reactivity of the benzene rings through inductive effects and can itself be reactive due to the activating influence of the two phenyl groups.

SYNTHESIS OF DIPHENYLMETHANE

1. Friedel-Crafts Alkylation: The most common method for preparing diphenylmethane involves the Friedel-Crafts alkylation of benzene with methylene chloride (dichloromethane) in the presence of aluminum chloride as a catalyst:

- Methylene chloride reacts with aluminum chloride to generate a carbocation or a similar electrophilic species.

- This electrophile attacks benzene, introducing the first phenyl group.
- The resulting chloride undergoes a second Friedel-Crafts reaction with another molecule of benzene, forming diphenylmethane.

$2C_6H_6 + CH_2Cl_2 \rightarrow C_6H_5–CH_2–C_6H_5 + 2HCl$

2. Reduction of Benzophenone: Diphenylmethane can be prepared by the reduction of benzophenone (diphenyl ketone) using strong reducing agents:

- Clemmensen reduction: Benzophenone is reduced with zinc amalgam and concentrated hydrochloric acid.
- Wolff-Kishner reduction: Benzophenone is treated with hydrazine and strong base at elevated temperature.
- Catalytic hydrogenation: Benzophenone is reduced with hydrogen in the presence of a metal catalyst.

$C_6H_5–CO–C_6H_5 + 4[H] \rightarrow C_6H_5–CH_2–C_6H_5 + H_2O$

3. Grignard Reaction: Benzyl chloride can react with phenylmagnesium bromide (a Grignard reagent) to form diphenylmethane after hydrolysis. This method provides good yields under controlled conditions.

REACTIONS OF DIPHENYLMETHANE

1. Oxidation: The methylene group in diphenylmethane is readily oxidized due to the activating effect of the two phenyl groups. When treated with oxidizing agents such as chromic acid, potassium permanganate, or nitric acid, diphenylmethane is oxidized to benzophenone.

$C_6H_5–CH_2–C_6H_5 + [O] \rightarrow C_6H_5–CO–C_6H_5$

2. Halogenation: The methylene hydrogen atoms in diphenylmethane are more acidic and reactive than typical aliphatic hydrogens due to the activation by both phenyl groups. Halogenation can occur at the methylene group or on the benzene rings:

- At the methylene group: Treatment with halogens in the presence of light or heat leads to substitution at the methylene carbon, forming benzhydryl halides (diphenylmethyl halides).
- On the aromatic rings: In the presence of Lewis acid catalysts, halogenation occurs on the benzene rings, predominantly at the para positions.

3. Nitration: Nitration of diphenylmethane with nitric acid and sulfuric acid mixture introduces nitro groups onto the benzene rings. The methylene group is electron-donating by hyperconjugation, making the rings more reactive toward electrophilic substitution. The nitration occurs predominantly at the para positions of the benzene rings.

4. Sulfonation: When treated with concentrated sulfuric acid or fuming sulfuric acid, diphenylmethane undergoes sulfonation on the aromatic rings. The sulfonic acid groups enter predominantly at the para positions.

5. Formation of Diphenylmethyl Cation: Under strongly acidic conditions, diphenylmethane can lose a hydride ion from the methylene group to form the diphenylmethyl cation (benzhydryl cation). This carbocation is relatively stable due to resonance delocalization of the positive charge into both benzene rings. This cation can be trapped by nucleophiles, leading to substitution reactions.

6. Dehydrogenation: At high temperatures in the presence of catalysts, diphenylmethane can undergo dehydrogenation, eventually forming fluorene

(dibenzocyclopentadiene) through cyclization and loss of hydrogen.

MEDICINAL USES OF DIPHENYLMETHANE DERIVATIVES

Antihistamines: Many important antihistamine drugs contain the diphenylmethane structure. Diphenhydramine, a widely used antihistamine, contains the diphenylmethane moiety linked to an aminoethyl side chain. These compounds are used to treat allergic conditions, motion sickness, and as sleep aids. The diphenylmethane structure provides the appropriate spatial arrangement for binding to histamine receptors.

Antitussives: Several cough suppressants are based on diphenylmethane structures with modifications. These compounds act on the cough center in the brain to reduce cough reflex.

Antimicrobial Agents: Certain diphenylmethane derivatives possess antimicrobial properties. Triclosan and related compounds contain modified diphenylmethane structures and are used as antiseptics and disinfectants in healthcare and consumer products.

Pharmaceutical Intermediates: Diphenylmethane serves as an intermediate in the synthesis of various drugs. Its ease of functionalization at both the methylene position and the aromatic rings makes it a versatile building block in medicinal chemistry.

TRIPHENYLMETHANE

STRUCTURE AND NOMENCLATURE

Triphenylmethane is a polynuclear aromatic compound consisting of three

benzene rings attached to a central carbon atom. It has the molecular formula $C_{19}H_{16}$ and molecular weight of 244.33. The structure features a quaternary carbon (the central carbon) bonded to three phenyl groups and one hydrogen atom.

Structural Features: The three phenyl groups are arranged around the central carbon in a propeller-like configuration due to steric crowding. The phenyl rings are not coplanar but are twisted relative to each other. This three-dimensional arrangement has important consequences for the chemical and physical properties of triphenylmethane and its derivatives.

Electronic Structure: Each benzene ring maintains its aromatic character. The central carbon can develop carbocationic character under appropriate conditions, and this carbocation is highly stabilized by resonance delocalization into all three phenyl rings. This exceptional stability of the triphenylmethyl cation is a defining feature of triphenylmethane chemistry and is crucial to understanding the properties of triphenylmethane dyes.

SYNTHESIS OF TRIPHENYLMETHANE

1. Friedel-Crafts Alkylation: The most common laboratory synthesis of triphenylmethane involves the Friedel-Crafts alkylation of benzene with chloroform in the presence of aluminum chloride as a catalyst:

- Chloroform reacts with aluminum chloride to generate an electrophilic species.
- This electrophile undergoes successive substitution reactions with benzene molecules.

- Three phenyl groups become attached to the central carbon, forming triphenylmethane.

$3C_6H_6 + CHCl_3 \rightarrow (C_6H_5)_3CH + 3HCl$

2. Grignard Synthesis: Triphenylmethane can be prepared by the reaction of phenylmagnesium bromide (Grignard reagent) with benzophenone or with ethyl benzoate:

- Phenylmagnesium bromide adds to the carbonyl group of benzophenone.
- The resulting alkoxide intermediate is hydrolyzed to form triphenylmethanol.
- Triphenylmethanol is then reduced to triphenylmethane using reducing agents such as hydriodic acid and red phosphorus, or by catalytic hydrogenation.

$C_6H_5MgBr + (C_6H_5)_2CO \rightarrow (C_6H_5)_3COH \rightarrow (C_6H_5)_3CH$

3. Reduction of Triphenylmethanol: Triphenylmethanol can be directly reduced to triphenylmethane using various reducing systems including zinc dust in acetic acid, hydriodic acid with red phosphorus, or catalytic hydrogenation.

REACTIONS OF TRIPHENYLMETHANE

1. Oxidation: Triphenylmethane is readily oxidized at the central carbon atom. When treated with oxidizing agents such as chromic acid, nitric acid, or potassium permanganate, triphenylmethane is converted to triphenylmethanol, and further oxidation can yield triphenylcarbinol derivatives or benzophenone.

$(C_6H_5)_3CH + [O] \rightarrow (C_6H_5)_3COH$

2. Formation of Triphenylmethyl Cation: Under strongly acidic conditions, triphenylmethane can lose a hydride ion to form the triphenylmethyl cation (trityl cation). This carbocation is exceptionally stable due to extensive resonance delocalization of the positive charge over all three benzene rings. The stability of this cation is so great that salts of the trityl cation can be isolated and characterized. This carbocation is central to the chemistry of triphenylmethane dyes.

$(C_6H_5)_3CH + H^+ \rightarrow (C_6H_5)_3C^+ + H_2$

3. Formation of Triphenylmethyl Radical: When triphenylmethane derivatives are treated with certain reagents or exposed to light, the triphenylmethyl free radical can be formed. This radical is also stabilized by resonance delocalization into the three phenyl rings and has historical importance as one of the first stable free radicals to be characterized.

4. Electrophilic Substitution on Aromatic Rings: The benzene rings in triphenylmethane can undergo electrophilic aromatic substitution reactions such as nitration, halogenation, and sulfonation. The central carbon has an electron-withdrawing effect, making the rings slightly less reactive than benzene, but substitution can still occur under appropriate conditions, typically at the para positions of the phenyl groups.

5. Chloromethylation: Triphenylmethane can undergo chloromethylation reactions on the aromatic rings, introducing chloromethyl groups that can serve as reactive sites for further modifications.

TRIPHENYLMETHANE DYES

The most important derivatives of triphenylmethane are the triphenylmethane

dyes, a large class of synthetic dyes with intense colors. These dyes are characterized by their triphenylmethane skeleton with various substituents that create extended conjugation and intense coloration.

Structure and Color: The color of triphenylmethane dyes arises from the formation of the triphenylmethyl cation with electron-donating groups (such as amino or hydroxyl groups) in the para positions of the phenyl rings. These substituents participate in resonance with the central positive charge, creating an extended conjugated system that absorbs visible light, producing intense colors.

Classification of Triphenylmethane Dyes:

1. Amino Triphenylmethane Dyes: These contain amino groups in the para positions of the phenyl rings.

Malachite Green: Structure: Contains two para-dimethylamino groups on two of the phenyl rings. Uses: Used as a biological stain, antiseptic, and antifungal agent. It is used in aquaculture to treat fungal infections in fish and fish eggs. In histology, it is used to stain bacteria and as a counterstain.

Crystal Violet (Gentian Violet): Structure: Contains three para-dimethylamino groups, one on each phenyl ring. Uses: Widely used as a topical antiseptic and antifungal agent. It is used in Gram staining procedures in microbiology to identify bacteria. It has applications in treating fungal skin infections and oral thrush. Used as a biological stain in histology and cytology.

2. Hydroxy Triphenylmethane Dyes: These contain hydroxyl groups in the para positions.

Phenolphthalein: Structure: Contains two para-hydroxyphenyl groups with a lactone ring. Uses: Widely used as a pH indicator in acid-base titrations. Changes from colorless in acidic solution to pink in alkaline solution. Historically used as a laxative, though this use has been discontinued in many countries due to safety concerns.

3. Mixed Amino-Hydroxy Dyes: These contain both amino and hydroxyl substituents.

Fuchsin (Rosaniline): Structure: Contains amino and hydroxyl groups on the phenyl rings. Uses: Used as a biological stain, particularly in the Ziehl-Neelsen stain for acid-fast bacteria such as Mycobacterium tuberculosis. Used in various histological staining procedures.

MEDICINAL USES OF TRIPHENYLMETHANE DERIVATIVES

Antiseptic and Antimicrobial Agents: Crystal violet and malachite green are used as topical antiseptics and antifungal agents. They are effective against gram-positive bacteria and various fungi. Crystal violet is used to treat skin infections, burns, and oral candidiasis. These compounds disrupt bacterial cell walls and interfere with cellular processes.

Diagnostic Stains: Triphenylmethane dyes are extensively used in medical diagnostics. Crystal violet is an essential component of Gram staining, one of the most important differential staining techniques in microbiology. Fuchsin is used in the Ziehl-Neelsen stain for detecting acid-fast bacteria. These staining techniques are crucial for identifying pathogens and diagnosing infectious diseases.

pH Indicators: Phenolphthalein and related compounds are used as pH indicators in pharmaceutical analysis and quality control. They are used in titrations and in monitoring pH in various pharmaceutical processes.

Anthelmintic Activity: Some triphenylmethane derivatives exhibit anthelmintic properties and are investigated for treating parasitic worm infections.

Research Tools: Triphenylmethane dyes are used as fluorescent probes and markers in pharmaceutical research, cell biology, and drug development. They help in visualizing cellular structures and tracking drug distribution.

📊 COMPARISON TABLES

Table 1: Structural Comparison of Polynuclear Hydrocarbons

Compound	Molecular Formula	Number of Rings	Ring Arrangement	Key Structural Feature	Molecula Weight
Naphthalene	$C_{10}H_8$	2	Linear fusion	Two fused benzene rings	128.17
Anthracene	$C_{14}H_{10}$	3	Linear fusion	Three linearly fused rings, reactive	178.23

Compound	Molecular Formula	Number of Rings	Ring Arrangement	Key Structural Feature 9,10-positions	Molecula Weight
Phenanthrene	$C_{14}H_{10}$	3	Angular fusion	Three angularly fused rings, bay region	178.23
Diphenylmethane	$C_{13}H_{12}$	2	Methylene bridge	Two benzene rings linked by $–CH_2–$	168.23
Triphenylmethane	$C_{19}H_{16}$	3	Single carbon bridge	Three benzene rings attached to one carbon	244.33

Table 2: Reactivity Comparison

Compound	Most Reactive Position	Addition vs Substitution	Oxidation Product	Special Reactions
Naphthalene	Alpha	Primarily	Phthalic acid	Temperature-

Compound	Most Reactive Position (1,4,5,8) positions	Addition vs Substitution substitution	Oxidation Product	Special Reactions dependent sulfonation
Anthracene	9,10-positions	Both addition and substitution	Anthraquinone	Diels-Alder reactions, photodimerizat
Phenanthrene	9,10-positions	Primarily substitution	Phenanthraquinone	Addition at 9,1 positions possi
Diphenylmethane	Methylene group and para positions	Substitution	Benzophenone	Stable carbocation formation
Triphenylmethane	Central carbon and para positions	Substitution	Triphenylmethanol	Highly stable carbocation (tr cation)

Table 3: Medicinal and Pharmaceutical Applications

Compound	Derivative/Application	Medicinal Use	Mechanism/Property
Naphthalene	Naphthols, substituted naphthalenes	Drug intermediates, antiseptics	Antimicrobial activity

Compound	Derivative/Application	Medicinal Use	Mechanism/Property
Anthracene	Anthraquinone glycosides	Laxatives	Stimulant laxative action
Anthracene	Anthracyclines (doxorubicin)	Anticancer agents	DNA intercalation, topoisomerase inhibition
Phenanthrene	Steroid-related compounds	Hormone replacement, anti-inflammatory	Receptor binding
Phenanthrene	Morphine alkaloids	Analgesics	Opioid receptor agonist
Diphenylmethane	Diphenhydramine	Antihistamine	H_1-receptor antagonist
Triphenylmethane	Crystal violet, malachite green	Antiseptic, antifungal	Cell wall disruption
Triphenylmethane	Fuchsin	Diagnostic stain	Selective bacterial staining

Table 4: Important Reactions and Products

Starting Compound	Reaction Type	Reagents/Conditions	Major Product	Ap
Naphthalene	Sulfonation (80°C)	Concentrated H_2SO_4	α-Naphthalenesulfonic acid	Dy inte
Naphthalene	Sulfonation (160°C)	Concentrated H_2SO_4	β-Naphthalenesulfonic acid	Dy inte
Naphthalene	Oxidation	$KMnO_4$, heat	Phthalic acid	Pla resi
Anthracene	Oxidation	Chromic acid	Anthraquinone	Dy syn
Anthracene	Diels-Alder	Maleic anhydride	Bridged adduct	Syr inte
Phenanthrene	Oxidation	$KMnO_4$	Phenanthraquinone	Che inte
Diphenylmethane	Oxidation	Chromic acid	Benzophenone	Per pol add
Triphenylmethane	Acid treatment	Concentrated H_2SO_4	Triphenylmethyl cation	Dy for

STRUCTURE-ACTIVITY RELATIONSHIPS

Influence of Ring Fusion on Properties

The manner in which aromatic rings are fused or connected significantly influences the physical and chemical properties of polynuclear hydrocarbons:

Linear Fusion (Naphthalene, Anthracene): Linear fusion results in elongated molecules with increased conjugation along the molecular axis. These compounds exhibit:

- Progressive increase in melting point with additional rings
- Enhanced reactivity at terminal positions
- Greater tendency toward addition reactions at central positions in larger systems
- Increased absorption of longer wavelength light

Angular Fusion (Phenanthrene): Angular fusion creates bent molecules with:

- Different reactivity patterns compared to linear isomers
- Relationship to important biological structures (steroids)
- Unique bay region chemistry
- Different packing in crystalline state

Bridge Connection (Diphenylmethane, Triphenylmethane): Non-fused systems connected by saturated carbon bridges show:

- Greater conformational flexibility
- Reactivity of the bridging carbon

- Ability to form stable carbocations
- Less extended conjugation unless ionized

Electronic Effects and Reactivity

Electron Density Distribution: In fused ring systems, electron density is not uniform. Positions with higher electron density are more susceptible to electrophilic attack. The distribution of electron density determines the orientation and rate of electrophilic substitution reactions.

Carbocation Stability: The ability to form stable carbocations increases in the order: benzyl < diphenylmethyl < triphenylmethyl. This increasing stability is due to greater resonance delocalization of the positive charge over multiple aromatic rings. This stability is exploited in dye chemistry and various synthetic applications.

Aromatic Character: In fused ring systems like anthracene, not all rings have equal aromatic character. The central ring in anthracene has reduced aromatic character compared to the terminal rings, explaining its propensity for addition reactions at the 9,10-positions.

Color and Conjugation

Chromophore Development: The color of compounds is related to the extent of conjugation. Simple polynuclear hydrocarbons are colorless or pale yellow. However, when extended conjugation is introduced through substituents or ionization (as in triphenylmethane dyes), intense colors develop due to absorption of visible light.

Auxochromes: Electron-donating groups (amino, hydroxyl) act as auxochromes, extending conjugation when attached to aromatic systems. In triphenylmethane dyes, amino groups in para positions participate in resonance with the central carbocation, creating extended conjugation and intense coloration.

🔬 PHARMACEUTICAL SIGNIFICANCE

Drug Design Considerations

Rigid vs Flexible Structures: Fused ring systems like naphthalene, anthracene, and phenanthrene provide rigid, planar scaffolds useful for designing drugs that need to fit precisely into receptor binding sites. The rigidity ensures consistent spatial orientation of substituents. In contrast, diphenylmethane and triphenylmethane offer more conformational flexibility, which can be advantageous for drugs that need to adapt to different receptor conformations.

Lipophilicity: Polynuclear aromatic systems are highly lipophilic, affecting drug absorption, distribution, and metabolism. This property must be balanced with appropriate polar groups to achieve optimal pharmacokinetic properties.

Metabolic Stability: Aromatic rings are generally resistant to metabolic degradation. However, positions of high electron density may undergo oxidation by cytochrome P450 enzymes. Understanding the reactivity patterns of these compounds helps predict metabolic pathways and design metabolically stable drugs.

Toxicological Considerations

Carcinogenicity: Some polynuclear aromatic hydrocarbons, particularly those with four or more rings, exhibit carcinogenic properties. Metabolic activation to reactive epoxides can lead to DNA damage. This is particularly relevant for compounds related to anthracene and larger systems. Pharmaceutical development must consider these structural alerts.

Photosensitivity: Certain polynuclear aromatic compounds can absorb light and transfer energy to oxygen, producing reactive oxygen species. This photosensitivity can cause phototoxic reactions in patients. Drugs containing these structures require careful evaluation for photosafety.

Drug-Drug Interactions: The planar aromatic structures can intercalate into DNA, affecting the activity of other drugs that also interact with DNA. This is relevant for anthracycline anticancer drugs and must be considered in combination therapies.

💊 MODERN APPLICATIONS AND DEVELOPMENTS

Advanced Drug Delivery

Fluorescent Markers: Polynuclear aromatic compounds, particularly anthracene and phenanthrene derivatives, exhibit fluorescence useful for:

- Tracking drug distribution in tissues
- Monitoring drug release from delivery systems
- Imaging in diagnostic procedures

- Development of theranostic agents (combined therapy and diagnostics)

Nanoparticle Formulations: The lipophilic nature of polynuclear aromatics makes them suitable for incorporation into lipid-based nanoparticles, improving drug delivery to specific tissues.

Biosensors and Diagnostics

Molecular Probes: Triphenylmethane dyes and other polynuclear aromatic compounds are used in developing biosensors for detecting:

- Specific biomolecules
- pH changes in microenvironments
- Cellular processes
- Pathogenic organisms

Smart Indicators: pH-sensitive triphenylmethane derivatives are incorporated into intelligent packaging and diagnostic devices that provide visual feedback on product quality or patient status.

Environmental and Safety Considerations

Green Chemistry: Modern synthetic approaches focus on:

- Using safer reagents and catalysts
- Reducing hazardous waste
- Improving atom economy
- Developing sustainable sources of polynuclear aromatics

Biodegradation: Understanding the environmental fate of these compounds is crucial. Research focuses on microbial degradation pathways and designing derivatives that are more readily biodegradable while maintaining pharmaceutical efficacy.

📋 SUMMARY

This unit comprehensively covered polynuclear hydrocarbons, a class of organic compounds containing multiple aromatic rings either fused together or connected through carbon bridges. The major compounds studied include naphthalene, phenanthrene, anthracene, diphenylmethane, and triphenylmethane, each with distinct structural features, chemical reactivity, and pharmaceutical applications.

Key Structural Concepts: Naphthalene represents the simplest fused bicyclic aromatic system with two benzene rings. Anthracene and phenanthrene are tricyclic isomers differing in linear versus angular ring fusion, leading to dramatically different reactivity patterns. Diphenylmethane and triphenylmethane feature benzene rings connected through saturated carbon bridges rather than direct fusion.

Synthetic Methods: Multiple synthetic approaches were covered including Friedel-Crafts reactions, Haworth synthesis, reduction methods, Grignard reactions, and oxidative cyclization. Industrial production from coal tar remains important for naphthalene and anthracene.

Chemical Reactivity: These compounds undergo electrophilic aromatic substitution reactions with position-dependent reactivity determined by electronic distribution. Anthracene uniquely undergoes addition reactions at the

9,10-positions. Oxidation patterns vary with structure, producing phthalic acid from naphthalene, anthraquinone from anthracene, and phenanthraquinone from phenanthrene. Diphenylmethane and triphenylmethane form exceptionally stable carbocations crucial to dye chemistry.

Pharmaceutical Applications: Naphthalene derivatives serve as drug intermediates and antiseptics. Phenanthrene's relationship to steroids and morphine alkaloids makes it fundamental to medicinal chemistry. Anthracene derivatives include important laxatives and anticancer agents like doxorubicin. Diphenylmethane structures appear in antihistamines like diphenhydramine. Triphenylmethane dyes including crystal violet and malachite green function as antiseptics and diagnostic stains.

Modern Relevance: These compounds remain important in pharmaceutical development, serving as scaffolds for drug design, fluorescent probes for drug delivery research, and diagnostic agents. Understanding their synthesis, reactivity, and biological properties is essential for pharmaceutical scientists involved in drug discovery, development, and quality control.

The study of polynuclear hydrocarbons bridges organic chemistry and pharmaceutical sciences, providing fundamental knowledge applicable to drug synthesis, medicinal chemistry, pharmaceutical analysis, and understanding drug-receptor interactions.

END OF UNIT 4 📚