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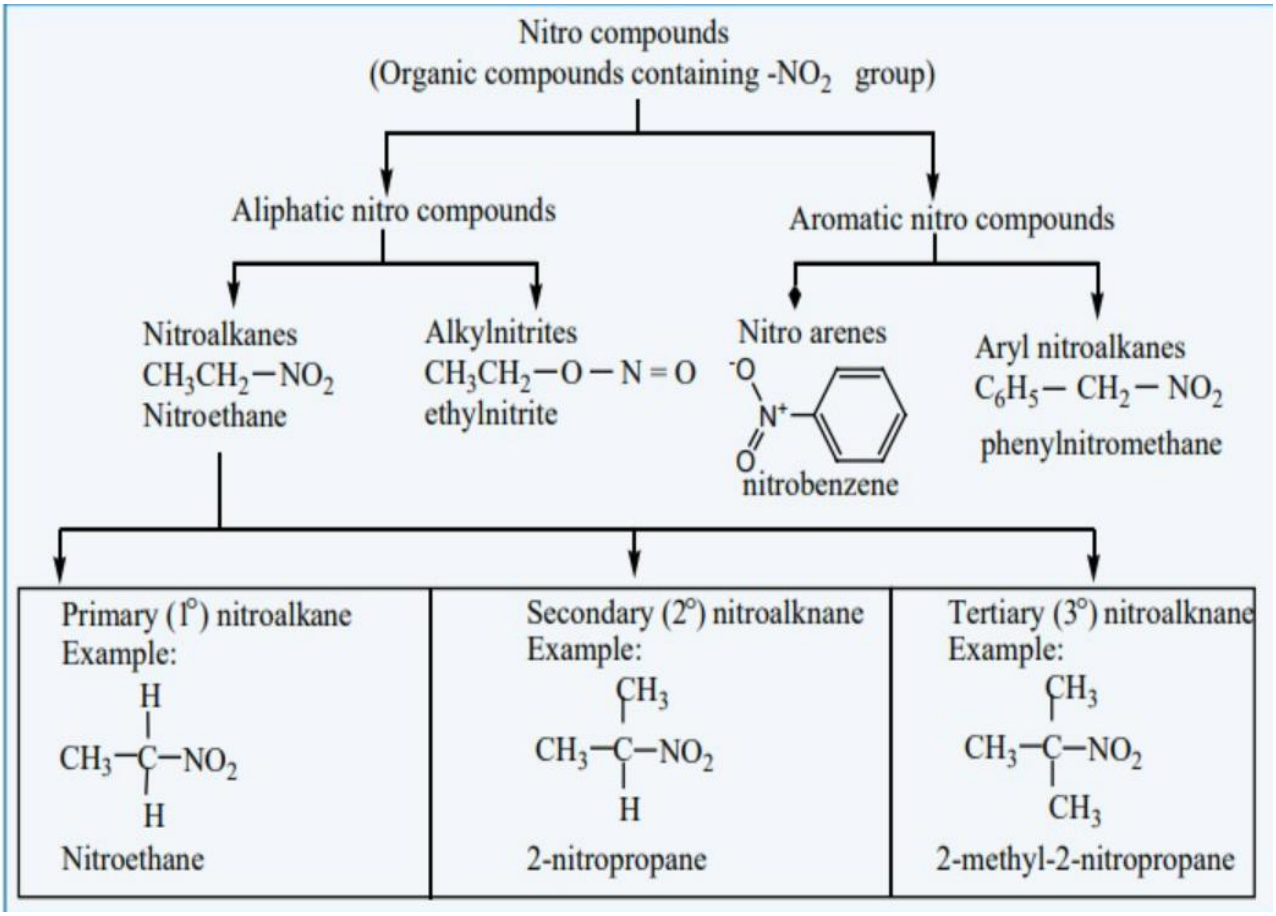
Lecture 7: Nitro compounds

Nitro compounds are organic molecules containing the **nitro functional group (–NO_2)** attached to a carbon atom.

Classification of nitro compound



Properties

- **High Polarity:** The strong electron-withdrawing nature of the -NO_2 group makes the α-hydrogens (in aliphatic types) acidic and deactivates aromatic rings toward electrophilic substitution.
- **Boiling Points:** Higher than comparable hydrocarbons due to polarity and dipole-dipole interactions.
- **Color:** Most simple aliphatic nitro compounds are colorless liquids. Many aromatic nitro compounds are pale yellow liquids or solids.
- **Explosive Nature:** Compounds with multiple nitro groups (especially on an aromatic ring, like TNT, picric acid) are highly explosive. The -NO_2

groups provide a dense source of oxygen for rapid combustion/oxidation of the carbon and hydrogen atoms.

Preparation of Aliphatic Nitro Compounds

Aliphatic nitro compounds have the general formula **R-NO_2,** where R is an alkyl group.

1. Nitration of Alkanes

Direct substitution of a hydrogen with a nitro group using nitric acid at high temperature

$$\text{R-H} + \text{HNO}_3 \xrightarrow[400\text{-}450^\circ\text{C}]{\text{Vapor Phase}} \text{R-NO}_2 + \text{H}_2\text{O}$$

2. Nucleophilic Substitution (Williamson Nitro Synthesis)

A primary or secondary alkyl halide reacts with a metal nitrite (usually silver nitrite, $AgNO_2$).

$$\text{R-X} + \text{AgNO}_2 \rightarrow \text{R-NO}_2 + \text{AgX}$$

3. Oxidation of Amines and Oximes

Oxidation of primary amines can be oxidized with peroxy acids (e.g., trifluoroperacetic acid) or potassium permanganate.

$$\text{R–NH}_2 \xrightarrow[\text{O}]{} \text{R–NO}_2$$

4. Nitroaldol (Henry) Reaction - For β-Nitro Alcohols

While not a direct synthesis of simple R-NO_2, it's a crucial method for making nitro compounds with additional functionality. It involves the base-catalyzed condensation of a nitroalkane with an aldehyde/ketone.

$$\text{R-CH}_2\text{-NO}_2 + \text{R'CHO} \xrightarrow{\text{Base}} \text{R-CH(OH)-CH(R')-NO}_2$$

Preparation of Aromatic Nitro Compounds

Aromatic nitro compounds have the general formula **Ar-NO_2.** The primary and most important method is **Electrophilic Aromatic Nitration**.

Electrophilic Aromatic Nitration

This is the standard, large-scale industrial method for introducing a nitro group onto an aromatic ring.

A mixture of **concentrated nitric acid (HNO_3) and concentrated sulfuric acid (H_2SO_4)**. This mixture is called **"mixed acid"** or **"nitrating mixture"**.

The sulfuric acid protonates nitric acid, which then loses water to form the **true electrophile: the nitronium ion (NO_2^+)**.

1. Generation of Electrophile:

$$HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$$

2. Electrophilic Attack (Standard EAS):

$$Ar\text{-}H + NO_2^+ \rightarrow Ar\text{-}NO_2 + H^+$$

Metabolism of nitro compounds

Metabolism of nitro compounds primarily involves **reduction reactions**, catalyzed by a variety of enzymes. The general progression is:

Nitro compound (R-NO_2) → Nitroso (R-NO) → Hydroxylamine (R-NHOH) → Amine (R-NH_2)

1. Enzymatic Reduction (The Major Pathway)

This occurs mainly in **liver microsomes** and **mitochondria**, and also in gut bacteria.

- **Cytochrome P450 (CYP) Enzymes:** Particularly CYP2E1 and others under low oxygen conditions can reduce nitro groups.
- **NADPH-Quinone Oxidoreductase:** A key two-electron reductase that directly reduces nitro compounds to hydroxylamines, bypassing the more reactive nitroso intermediate, which can be less toxic.

- **Xanthine Oxidase, Aldehyde Oxidase:** Molybdenum-containing enzymes that contribute to nitro reduction.
- **Bacterial Nitroreductases (in gut flora):** Anaerobic bacteria in the intestine extensively reduce nitro compounds. This is critical for drugs like **nitrofurantoin** (activated in the bladder) and for the toxicity of compounds like **TNT**.

Why Reduction Matters:

- **Activation to Toxic Species:** The partially reduced intermediates (**nitroso** and **hydroxylamine**) are highly reactive. They can:
    - Bind to proteins, causing cytotoxicity (e.g., methemoglobinemia).
    - **Generate DNA adducts** and cause oxidative stress (via redox cycling), leading to **mutagenesis and carcinogenesis**.
- **Detoxification:** Complete reduction to the inert **amine** is often a detoxification step.
- **Therapeutic Action:** Antibiotics like **metronidazole** are activated by bacterial nitroreductases. The reduced products damage bacterial DNA, making them selectively toxic to anaerobic bacteria.

2. Conjugation (Detoxification)

Reactive hydroxylamine intermediates can be detoxified by conjugation:

- **Glucuronidation:** UDP-glucuronosyltransferases (UGTs) add glucuronic acid to hydroxylamines, making them water-soluble for excretion.
- **Acetylation:** *N*-acetyltransferases (NATs) can acetylate the amine product.

3. Redox Cycling (A Source of Oxidative Stress)

This is a critical toxic mechanism. Partially reduced nitro radicals (e.g., the nitro anion radical, $R\text{-}NO_2^{\bullet -}$) can spontaneously re-oxidize in the presence of oxygen, regenerating the parent nitro compound and producing **superoxide anion ($O_2^{\bullet -}$)**.

- **Cycle:** Nitro compound → One-electron reduction → Nitro radical → + O_2 → Parent compound + Superoxide.
- **Result:** This futile cycle consumes cellular reducing equivalents (NADPH) and generates **reactive oxygen species (ROS)**, leading to oxidative stress, lipid peroxidation, and DNA damage.

Toxicological & Medical Implications

- **Methemoglobinemia:** Nitroso metabolites oxidize iron in hemoglobin from Fe^{2+} to Fe^{3+}, reducing oxygen-carrying capacity (classic "blue-baby syndrome" from nitrates/nitrites, but nitro compounds also cause it).
- **Carcinogenicity:** Many nitroarenes (e.g., nitropyrenes) are potent mutagens. Metabolic activation to hydroxylamines that form DNA adducts is a key mechanism.
- **Organ Toxicity:** Liver (hepatotoxicity) and lung (pneumonitis) are common targets due to metabolic activation and oxidative stress.
- **Drug Design:** Understanding nitro-reduction is key for designing **prodrugs** activated in hypoxic environments (e.g., **hypoxia-activated prodrugs for cancer therapy**, targeting the low-oxygen tumor microenvironment where nitroreduction is favored).
- **Bioremediation:** Certain bacteria and fungi use nitroreductases to degrade environmental nitro pollutants (e.g., TNT in contaminated soil).