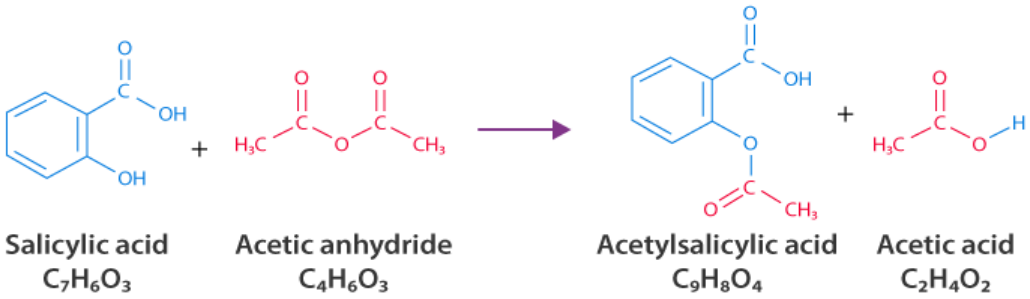
5.D) CASE STUDY: SYNTHESIS OF ASPIRIN (ACETYLSALICYLIC ACID)

Aspirin (acetylsalicylic acid) is one of the most widely used pharmaceutical drugs, synthesized through an esterification reaction between salicylic acid and acetic anhydride**,** catalysed by an acid.

Reaction Mechanism

The synthesis follows an acid-catalyzed esterification mechanism:

$$C_7H_6O_3 + (CH_3CO)_2O \xrightarrow{H_2SO_4} C_9H_8O_4 + CH_3COOH$$



- Reactants:
  - Salicylic acid ($C_7H_6O_3$) – Provides the hydroxyl (-OH) group.
  - Acetic anhydride $(CH_3CO)_2O$ – Acetylates the salicylic acid.
  - Catalyst: Sulfuric acid (H_2SO_4) or Phosphoric acid (H_3PO_4) – Speeds up the reaction by donating protons.
- Products:
  - Aspirin ($C_9H_8O_4$, acetylsalicylic acid**)** – The desired pharmaceutical compound.
  - Acetic acid (CH_3COOH) – A byproduct.

Steps in the Synthesis

1. Activation of Acetic Anhydride
   - The catalyst (H_2SO_4 or H_3PO_4) protonates acetic anhydride, making it more electrophilic.
2. Nucleophilic Attack
   - The hydroxyl (-OH) group of salicylic acid attacks the carbonyl carbon of acetic anhydride, leading to the formation of an ester bond.
3. Elimination of Acetic Acid
   - The reaction results in the formation of aspirin and acetic acid as a byproduct.
4. Purification
   - The reaction mixture is cooled to precipitate aspirin.
   - The crude product is filtered and washed with cold water to remove unreacted acetic acid.
   - Recrystallization in ethanol or water improves purity.

Role of the Catalyst

- Sulfuric acid (H_2SO_4) or Phosphoric acid (H_3PO_4) acts as a homogeneous catalyst, increasing reaction rate by:
    - Protonating the carbonyl oxygen of acetic anhydride, enhancing its reactivity.
    - Stabilizing the transition state, lowering activation energy.
    - Being regenerated at the end, making it reusable.

Industrial and Laboratory Applications

- Laboratory Scale: Small-scale synthesis uses phosphoric acid for safety.
- Industrial Scale: Large-scale production optimizes conditions for high yield and purity. Sulfuric acid is commonly used, followed by purification steps like crystallization and filtration.

Factors Affecting the Reaction

- Temperature: Heating (50–70°C) speeds up the reaction but prevents unwanted side reactions.
- Catalyst Choice: Phosphoric acid is milder than sulfuric acid, preventing unwanted side reactions.
- Purification Methods: Recrystallization ensures pharmaceutical-grade purity.

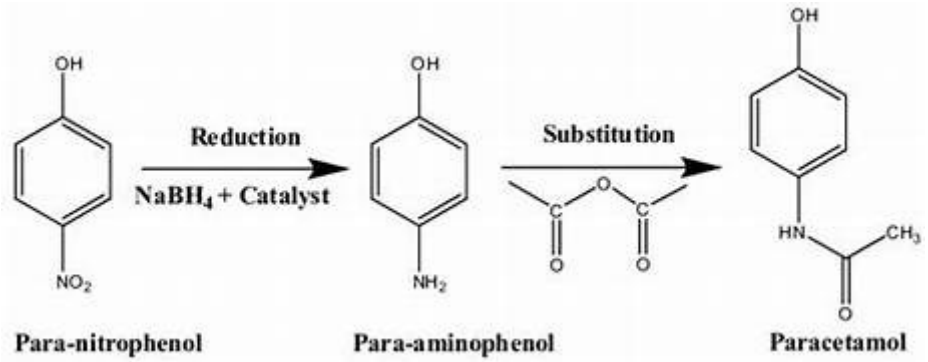
5.E) CASE STUDY: SYNTHESIS OF PARACETAMOL (ACETAMINOPHEN)

Paracetamol (also known as acetaminophen) is a widely used analgesic and antipyretic drug. Its synthesis involves an acetylation reaction**,** where a hydroxyl group is acetylated using an amide formation process.

Reaction Mechanism

The synthesis of paracetamol ($C_8H_9NO_2$) from p-aminophenol (C_6H_7NO) and acetic anhydride ($C_4H_6O_3$) follows an amide formation reaction**:**

$$C_6H_7NO + (CH_3CO)_2O \rightarrow C_8H_9NO_2 + CH_3COOH$$



- Reactants:
  - p-Aminophenol (C_6H_7NO) **–** Provides the amine ($-NH_2$) functional group.
  - Acetic anhydride ($C_4H_6O_3$) **–** Acetylates the amine group.
- Product:
  - Paracetamol ($C_8H_9NO_2$, acetaminophen) – The desired pharmaceutical compound.
  - Acetic acid (CH_3COOH) – A byproduct.

Steps in the Synthesis

(a) Acetylation Reaction

1. Nucleophilic Attack:
   - The amine ($-NH_2$) group of p-aminophenol acts as a nucleophile and attacks the carbonyl carbon of acetic anhydride.
2. Formation of Paracetamol:
   - This reaction results in an amide bond ($-NHCOCH_3$)**,** converting p-aminophenol into paracetamol.
   - Acetic acid (CH_3COOH) is released as a byproduct.

(b) Purification of Paracetamol

3. Cooling and Precipitation:
   - The reaction mixture is cooled, and paracetamol precipitates out.
4. Filtration and Washing:
   - The solid product is filtered and washed to remove impurities.
5. Recrystallization:

- The crude product is purified by recrystallization, typically using hot water or ethanol.

Role of the Catalyst

- No strong acid catalyst is required because the reaction involves direct nucleophilic attack of the amine ($-NH_2$) on the carbonyl carbon.
- In some cases, a mild acid catalyst (HCl or acetic acid) is used to increase reaction efficiency by making the carbonyl group more electrophilic.

Industrial and Laboratory Applications

- Laboratory Scale: Small-scale synthesis involves direct acetylation using acetic anhydride or acetyl chloride.
- Industrial Scale: Large-scale manufacturing uses cost-effective, high-purity reactants with optimized reaction conditions to maximize yield (~90–95%) and minimize impurities.

Factors Affecting the Reaction

- Temperature: Mild heating (~50–70°C) improves reaction efficiency without decomposing the product.
- Solvent Choice**:** Water, ethanol, or methanol is used for recrystallization.
- Purification Methods: Multiple filtration and recrystallization steps ensure pharmaceutical-grade purity.