Synthesis of Aspirin

Synthesis

Purification

Characterization

Aspirin: some background

- Patented by Bayer in 1893
- One of the oldest drugs
- One of the most consumed drugs (Production in the US is 10 million Kg/year)

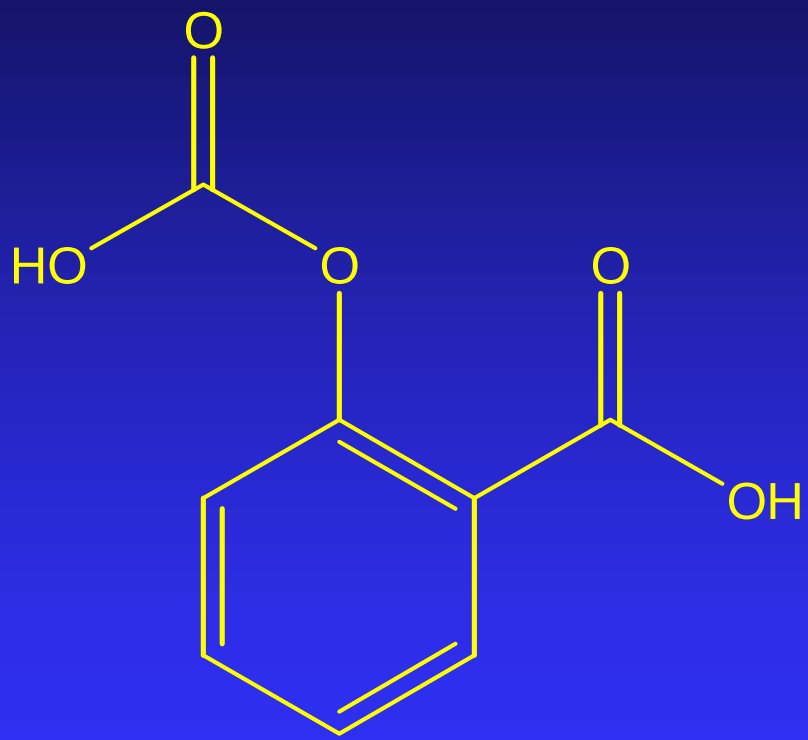
Aspirin: Biological activity

- Analgesic (painkiller)
- Antipyretic (fever reducer)
- Anti-inflammatory (inhibition of the synthesis of prostaglandins)

- Side effects: gastric irritation, bleeding

  Apparition of new analgesics (Tylenol)

Aspirin: The Molecule



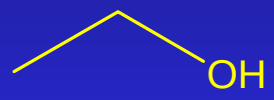
acetyl salicylic acid (aspirin)

Organic background
Alcohols

- Alcohols 

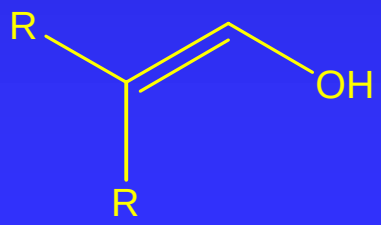
- Aliphatic alcohols: Hydroxyl derivatives of saturated hydrocarbons

methanol

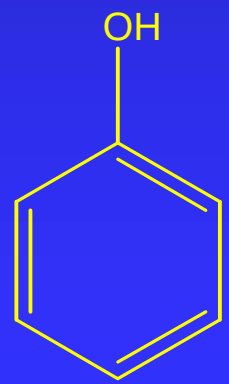


ethanol

- Enols: Hydroxyl derivatives of unsaturated hydrocarbons

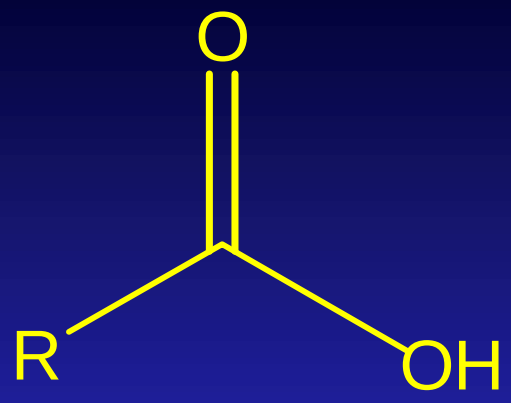


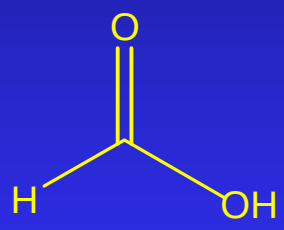
enol



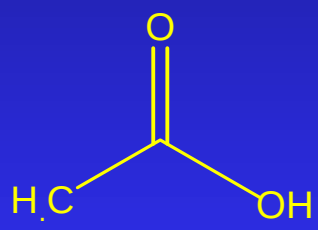
phenol

Organic background
Carboxylic acids

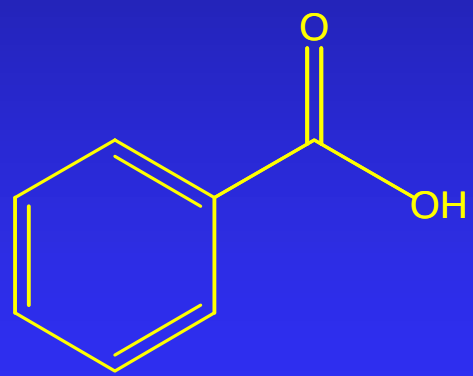




formic acid



acetic acid



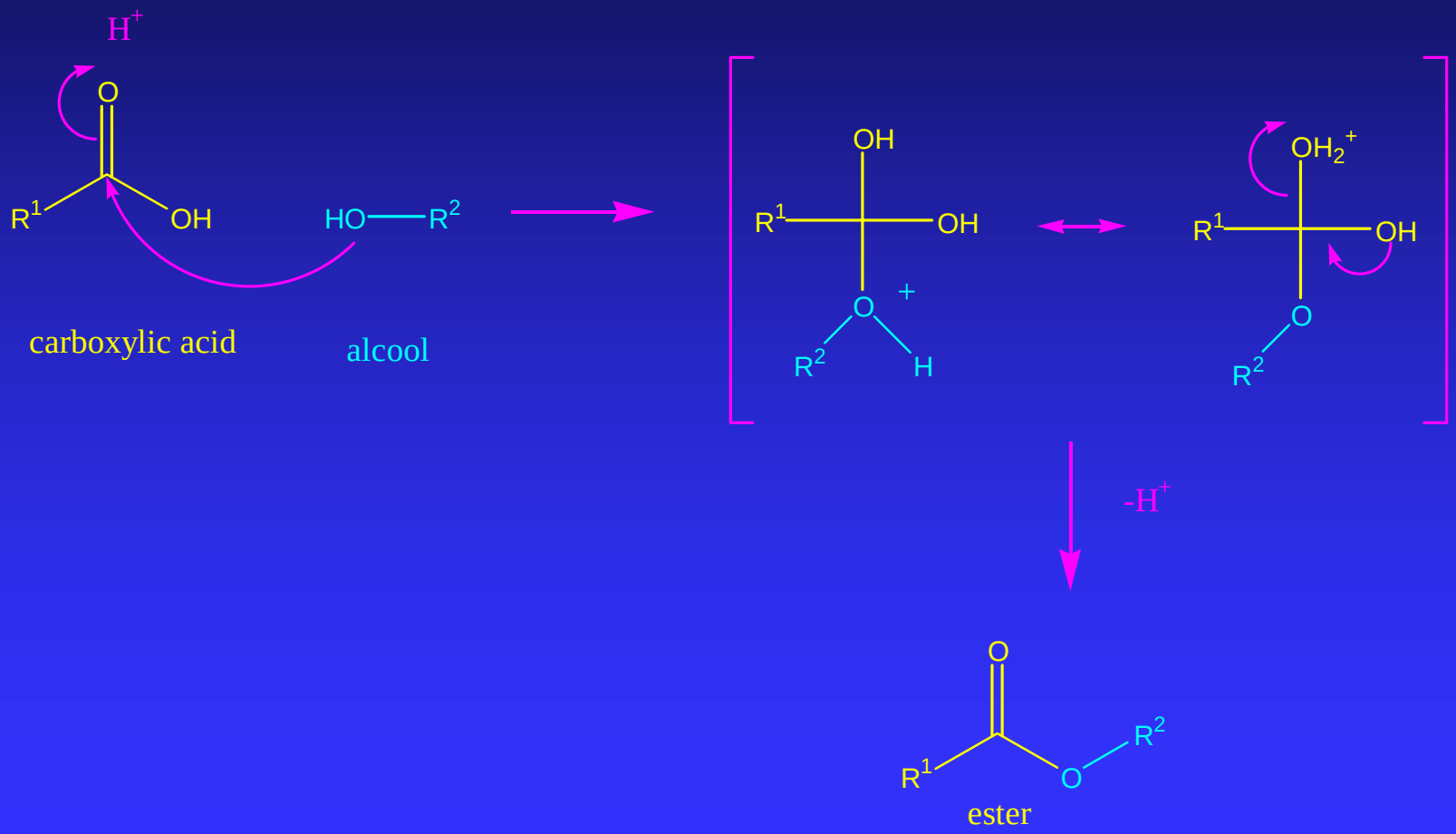
benzoic acid

Organic background
Esterification

carboxylic acid alcool ester

This is an equilibrium!

Organic background
Esterification mechanism



Organic background
Acidity: a review

- Bronsted-Lowry acid

Substance that can donate a proton

- Lewis acid

Substance that accepts lone-pair electrons

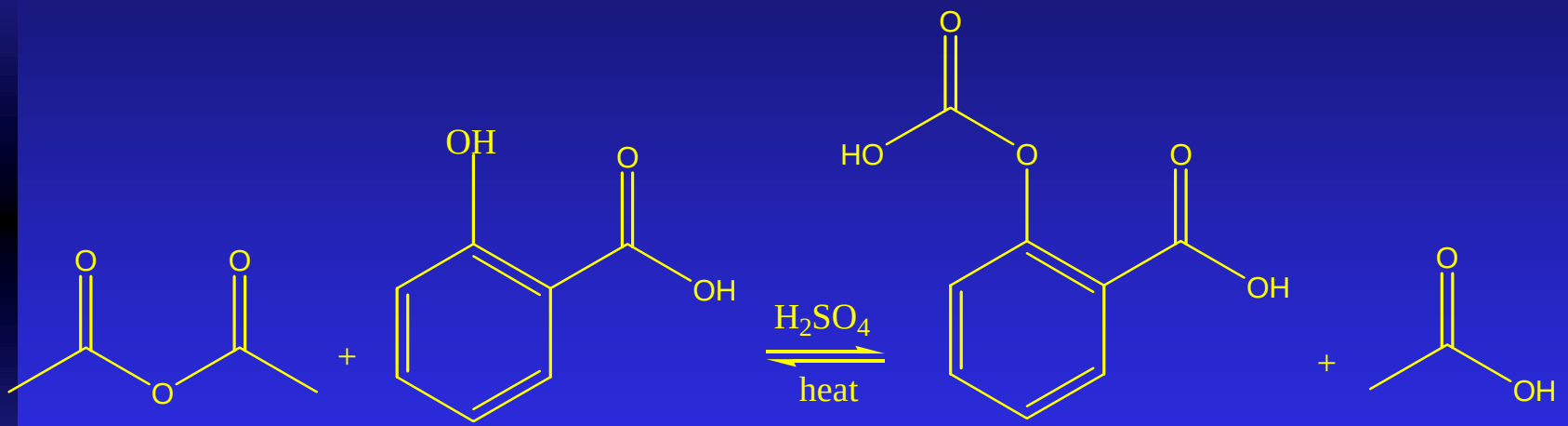
- $AH + H_2O \rightarrow A^- + H_3O^+$

  $K_a = [H_3O^+][A^-] / [AH]$

  $pK_a = -\text{Log } K_a$

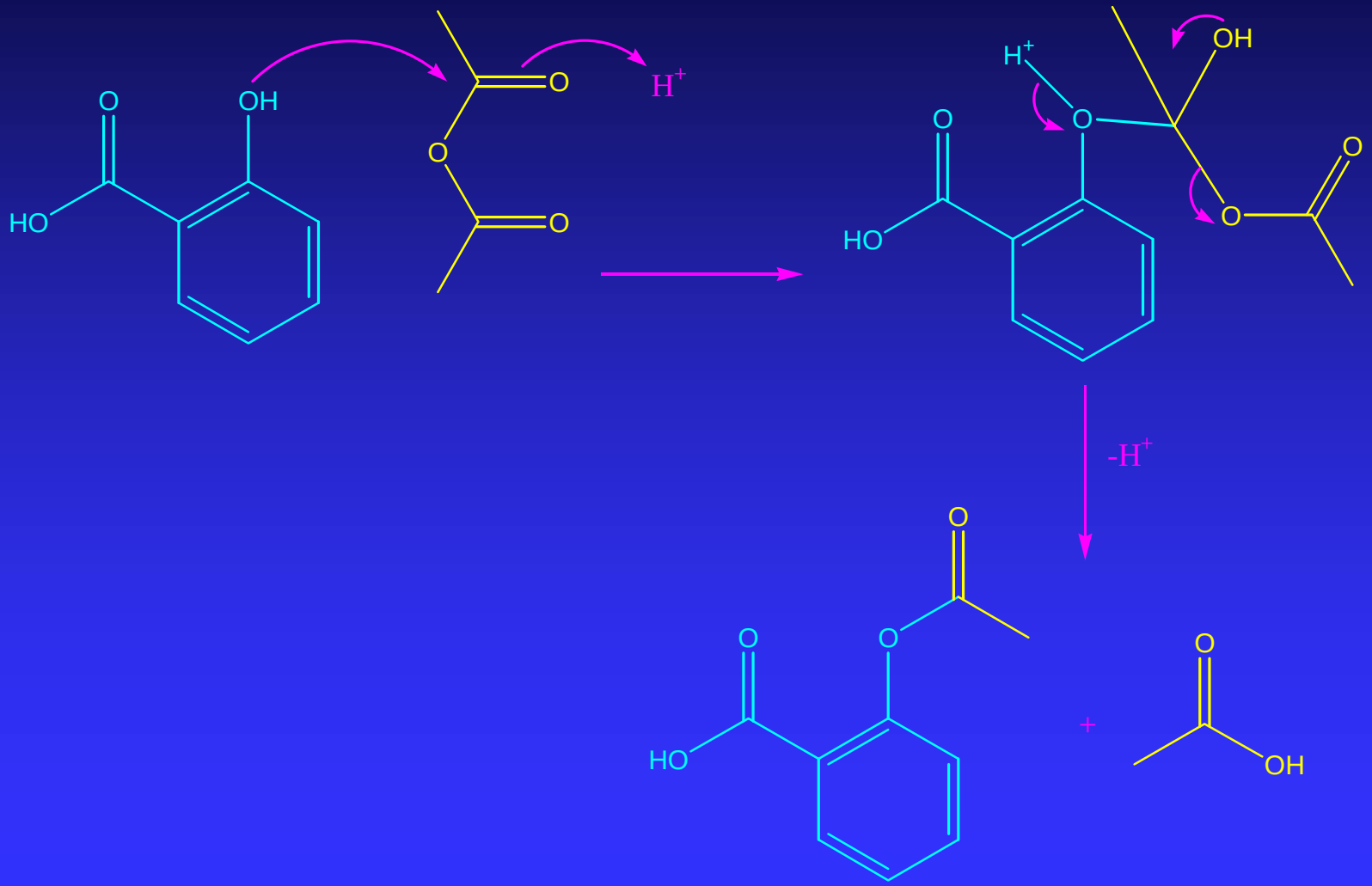
Acid	pK_a
water	14.0
Acetic acid	4.75
Benzoic acid	4.19
Formic acid	3.75
Sulfuric acid	1

Reaction



acetic anhydride salicylic acid acetyl salicylic acid (aspirin) acetic acid

Reaction mechanism



Safety

- Consult MSDS for safety information on all the chemicals you plan to use.
- MSDS are available from the 2507 webpage.

Synthesis procedure

- Mix salicylic acid (solid) with acetic anhydride (liquid) and a catalytic amount of H_2SO_4.
- Heat for 10 min at 90^0C.
- Cool down to room temperature and add water (crystallization solvent).
- Induce crystallization.
- Filter the crystals.

Purification by Recrystallization

WHAT IS RECRYSTALLIZATION?

- Rapid and convenient way of purifying a solid organic compound
- The material to be purified is dissolved in the hot appropriate solvent
- As the solvent cools, the solution become saturated with respect to the substance, which then crystallize
- Impurities stay in solution

METHOD

- Choose the solvent
- Dissolve the solute
- (Filter suspended solids)
- Crystallize the solute
- Collect and wash the crystals
- Dry the crystals

Assessment of purity: Looking for properties

Physical properties

- Physical appearance
- Solubility
- Melting point
- Infrared spectra

Chemical properties

- Percent yield
- Potentiometric titration
- Phenol test

Assessment of purity: Physical appearance

- Physical state (solid? liquid? ..)
- Color
- Odor
- Texture
- Homogeneity in composition

Assessment of purity: Solubility

- In a test tube, transfer a small amount of your product (end of a spatula)
- Add ~1/2mL of solvent
- Determine solubility at room temperature
- If not, gently heat and determine solubility at higher temperature
- Test several organic solvents and compare with litterature

Assessment of purity: Melting point

- Melting point characterize the compound
- Range of the melting point indicate the purity of the compound

- Method: scanning of the temperature until melting occurs. Determine start and end temperature of melting.
- Don't heat too fast!! ($<1^0$C / min)

Assessment of purity: Infrared Spectra

- Dissolve the product in chloroform and obtain the IR spectrum.
- Assign the peaks
- Do you see impurities?
- Compare with the reference spectrum.

Assessment of purity: Percent yield

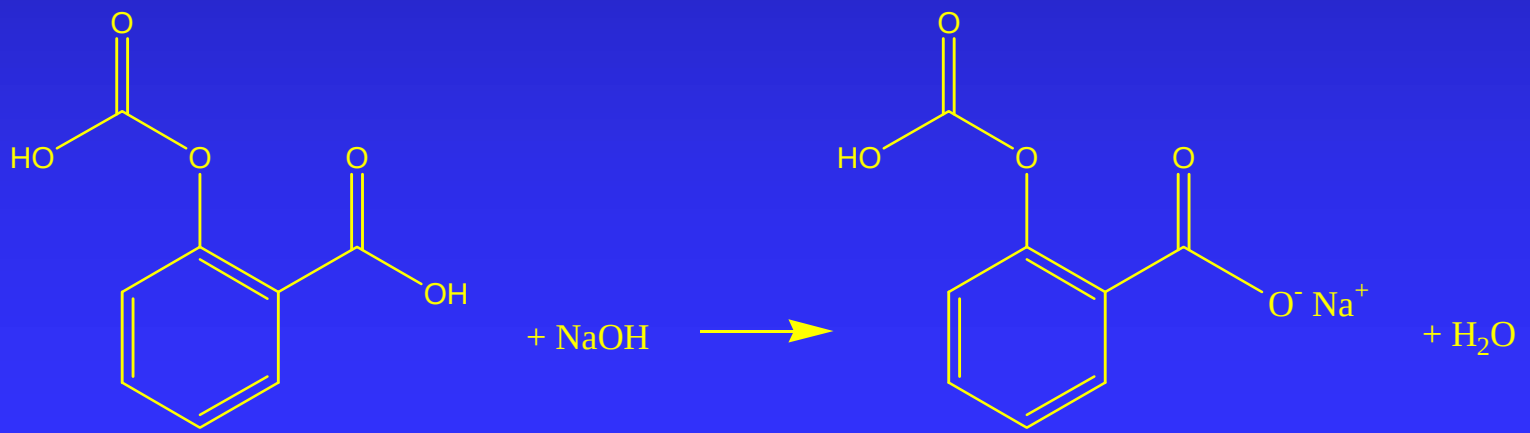
- Definition: %Yield = n_{exp}/n_{th}

- Write down the reaction with the correct stoechiometry. Ex: A+B → C
- Prepare a chart like below and calculate yield.

m_A (g) or V_A (mL)	n_A (mol)	m_B (g) or V_B (mL)	n_B (mol)	m_C (g) theoretical	n_C (mol) theoretical	m_c (g) experimental	n_C (mol) experimental

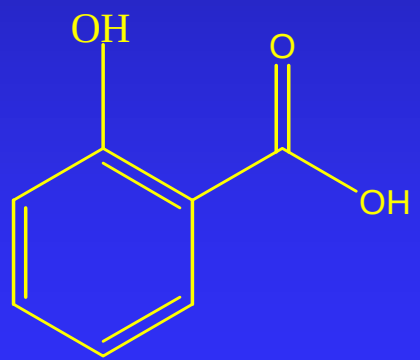
Assessment of purity: potentiometric titration

- Objective: Determine the pKa at the half equivalence point.
- Procedure: Titrate potentiometrically the acetylsalicylic **acid** with a **strong base** and find pKa



Assessment of purity: Phenol test and visible spectroscopy

- Phenol react with $FeCl_3$ (aq) to give a deep purple complex.
- Phenol is not present in the product but in one of the reactant.
- This test indicate the presence of **unreacted starting material** (quantitative analysis possible via visible spectroscopy).



salicylic acid

+ Fe^{3+} → Deep purple complex