Reaction Mechanisms

1. Base-catalyzed hydrolysis

2. Nucleophilic addition

3. Special nucleophilic addition: Michael Addition (α,β-unsaturated carbonyl)

4. Base-catalyzed elimination
Acid/Base Chemistry

1. Which compound is more acidic? Why?

In which case would the \( \text{C}^+ \) be most delocalized. This is the most acidic compound.

\(-\text{N}((\text{CH}_3)_2)\) is \(\varepsilon\)-donating and the \(\text{F}^-\) on the carboxyl group would be less delocalized.

2. Which compound is more basic? Why?

- lone e-pair tied up in aromaticity
- \(pK_a = 0.5\)

\[\text{H} \quad \text{N} \quad \text{H} \]

- free lone e-pair to accept \(\text{H}^+\), better base
- \(pK_a = 9\)

Given the structure below, answer the following questions.

Indomethacin

1. What is the approximate \(pK_a\) of this acid?

\(4-5\)

2. Draw the structure of the sodium salt of indomethacin.

\[\text{CH}_3\text{O} \quad \text{N} \quad \text{Cl} \quad \text{Na}^+ \]
3. What are the advantages of administering the salt form of this drug? The salt form will dissolve more rapidly/completely from its oral dosage form into physiological fluids, resulting in increased rate of drug absorption thereby decreasing intersubject variability.

4. Using the Henderson-Hasselbach equation, calculate the ionized/unionized ratio of the drug at pH 5. Will indomethacin be excreted faster at a urinary pH 5 or 8? Explain.

\[
\text{pH} = 10^{\text{pH} - \text{pK}_a} = 10^{5-4} = 10^1 = \frac{[\text{unprotonated}]}{[\text{protonated}]} = \frac{[\text{ionized}]}{[\text{unionized}]}
\]

\[
\text{pH} 8: 10^{\text{pH} - \text{pK}_a} = 10^8-4 = 10^4 = \frac{[\text{unprotonated}]}{[\text{protonated}]} = \frac{[\text{ionized}]}{[\text{unionized}]}
\]

At pH 8, more of this drug will be in its ionized form compared to pH 5. Therefore, at pH 8 this compound will be more soluble in the urine which results in less reabsorption and faster excretion (shorter duration of action).

**Stereochemistry**

![Dexfenfluramine](image)

1. Dexfenfluramine exists as the S-isomer. Draw this configuration.
2. What kind of isomers are the following?

a. positional
b. enantiomers
c. diastereomers
d. geometric

```
OH     OH
\(\text{Br} \quad \text{Br}\)
\(\text{N} \quad \text{N}\)
\(\text{H} \quad \text{H}\)

\text{diastereomers}
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```
\text{OH}
\text{OH}
\text{N}
\text{H}

\text{positionai}
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\text{H}_3\text{C} \text{---C---COOH}
\text{NH}_2

\text{COOH}
\text{Hancer}_{\text{CH}_3}

\text{enantiomers}
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