

Week 8

Nucleophilic Substitutions

8.1 Nucleophilic Substitutions

11/18:

- Philosophy of learning mechanisms (the most difficult and important part of organic chemistry to understand):
 - The origin is the structure, which determines the reactivity of the reagent, which determines the mechanism.
- In this chapter, we consider **haloalkanes** or **alkyl halides**.
 - Alkyl halides have polar bonds.
 - The electropositive carbon center is key for attracting electrons from nucleophiles or other things.
- Nucleophilic substitution.
- General form.



- The nucleophile (Nu^-) attacks the electrophile (R-X), generating the product (Nu-R) and leaving group or LG (X^-).
- Motivation: Stability — X^- is more stable than Nu^- .
- We can use this to perform a wide variety of coupling reactions (coupling R to Nu^-) given a good leaving group.
 - For example, generating methanol from hydroxide and bromomethane.
- Mechanisms.

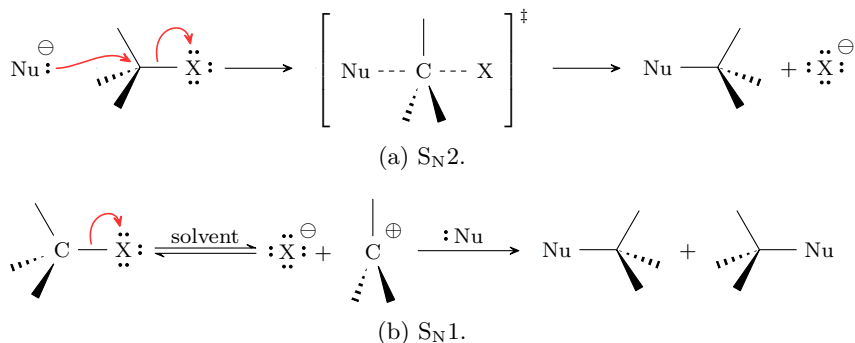
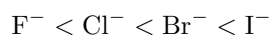
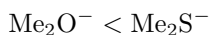
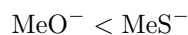


Figure 8.1: Nucleophilic substitution mechanisms.

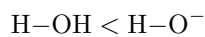
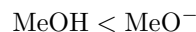
- **S_N2**: Bimolecular nucleophilic substitution. *Also known as backside attack.*
 - Bimolecular refers to the number of reactants in the rate-determining step.
 - Compare to the opening of the bromonium ion (see Figure 6.3b).
 - The backside attack breaks the carbon-halogen bond by pumping electron density into the large lobe of the σ^* antibonding orbital on the back side of the carbon.
 - Mechanism type.
 - Concerted, as per the energy diagram.
 - Rate law.
$$r = k[\text{Nu}^-][\text{RX}]$$
 - First-order dependence on both the nucleophile and alkyl halide.
 - Stereochemistry.
 - Flips.
 - Stereoinversion (as opposed to stereoretention).
- **S_N1**: Unimolecular nucleophilic substitution.
 - Unimolecular refers to the number of reactants in the rate-determining step.
 - Initiated by a **sloppy electrophile**.
 - Since it still take a lot of energy to break the C–X bond, the first step is the RDS.
 - Gives a racemic mixture of products since the nucleophile can attack the carbocation intermediate from either face.
 - Mechanism type.
 - Stepwise, as per the energy diagram.
 - Rate law.
$$r = k[\text{RX}]$$
 - Zeroth-order dependence on the nucleophile; first-order dependence on the alkyl halide.
 - Stereochemistry.
 - Racemic.
- **Sloppy electrophile**: An electrophile that can undergo a self-ionization reaction.
- Key requirement: Predict whether a reaction proceeds through an S_N1 or S_N2 mechanism.
 - Experimentally, we can do...
 - Kinetic/rate law studies.
 - Stereochemical analyses.
 - For the exam, we need to be able to predict based off of the reactants and conditions.
- Choosing between the mechanisms.
- The general form has four variables/parameters.
 1. Structure of the nucleophile.
 - A good nucleophile has electron pairs that are “held loosely.”
 - Trend:
 - Nucleophilicity of elements in the same period.



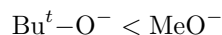
- Nucleophilicity of elements in the same group.



- Nucleophilicity of the same element.



- Nucleophilicity of species with differently sized ligands.



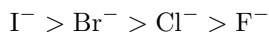
- Basically, elements that are more positive, less electronegative, and larger (i.e., more basic) hold electron pairs more loosely. Sterically hindered bases are also less nucleophilic because they're too bulky to attack (linear nucleophiles are often the best).
- Take-home message: A good nucleophile favors $\text{S}_{\text{N}}2$.

2. Structure of the R group.

- Tertiary alkyl halides.
 - Backside is blocked.
 - Carbocation is stable.
 - $\text{S}_{\text{N}}1$ is favored.
- Primary alkyl halides.
 - Backside is wide open.
 - Carbocation is unstable.
 - $\text{S}_{\text{N}}2$ is favored.
- For $\text{S}_{\text{N}}2$ reactions, sterics matter (affect the rate) a lot.
 - Neopentyl alkyl halides block $\text{S}_{\text{N}}2$ reactions.
- Secondary alkyl halides.
 - Case-by-case analysis.

3. Leaving group.

- Important for both $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ reactions.
- Good leaving groups are stable, weak bases.



- These raise the reaction rate.