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# 1 Big Chapter

## First Section

Various points

Various points

## First Section

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## First Section

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## $S_N1$ Mechanism

- ▷ **Solvolysis:** when an alkyl halide undergoes ionization in a polar solvent (hydrogen connects to electronegative atom), and the solvent functions as a **nucleophile** which attacks the intermediate carbocation, resulting in a two-step substitution.
  - The concentration of the **alkyl halide** acts as the **rate-determining** step, since the loss of the leaving group, and the formation of the carbocation, represents the highest energy transition state of the multi-step process.
    - Loss of leaving group (formation of carbocation) → nucleophilic attack
- ▷ If the nucleophile is uncharged, which is often the case for  $S_N1$  reactions, then there will be an additional step at the end of the mechanism in which the extra proton is removed by a solvent molecule.

## E1 Mechanism

- ▷ When a 3° alkyl halide undergoes ionization in a polar solvent and can function as a **base** and deprotonate the intermediate carbocation, resulting in an two-step elimination.
  - The **loss of the leaving group** also is the **rate-determining** step for eliminations.
- ▷ Often the second rate-limiting step is either the substitution or elimination.
  - Usually substitution is favored due to the lower energy transition state requirement.
  - Elimination is favored when potential energy is high enough for the more stable product of elimination to have greater determining effect.
    - E.g, when the resulting alkene is tri- or Tetrasubstituted; more stability in the end product is favored.
  - This is why a mixture of products is often observed.

## Solvent and Substrate Effects on Ionization Rates

- ▷ Ionization process occurs most readily in **protic solvents**, since both ionization products are well solvated in protic solvents.
  - Carbocations are stabilized by interacting with lone pairs of the oxygen atoms.
  - Chloride ions are stabilized via hydrogen bonds.
  - Aprotic cannot stabilize both equally, as there is little free hydrogen, thus unfavorable for solvolysis reactions.
- ▷ To contrast,  $S_N2$  reactions are enhanced by the **strength of the nucleophile**, which allows them to overcome activation energy of the reaction.
  - Lack of stabilization increases energy of nucleophiles.
- ▷ Protic solvents stabilize the ionic intermediates and transition states, allowing for smaller activation energy barrier due to loss of leaving group being the rate-limiting step.
- ▷ **Effect of Substrate**
  - Alkyl iodides are the most reactive, while fluorides are the least.
    - $I^- > Br^- > Cl^- > F^-$

## Predicting Products: Substitution vs Elimination

- ▷ Often elimination and substitution are in competition with each other, with sometimes one product dominating, or reactions resulting in multiple products.
- ▷ Main steps in determining products:
  - Determine the function of the reagent.
  - Analyze the substrate and determine the expected mechanism(s).
  - Consider any relevant regiochemical and stereochemical requirements.

## Determining the Function of the Reagent

- To recap: substitution occurs when the reagent functions as a nucleophile, while an elimination reaction occurs when the reagent functions as a base.
- Major factors (not all) that Determine nucleophilicity: presence of high electron density and polarizability, while basicity is determined by base stability.
  - Strong acids have weaker conjugate bases. The weaker the base, then the more stability the molecule has, and the less likely to act as base rather than nucleophile.
  - Often bases bear negative charges, allowing them to also function as nucleophiles.
  - Small size often decreases polarizability, which makes some weak bases unable to be nucleophiles.
- Common reagents can be classified into four categories, with two-dimensions based on base and nucleophile strength.
  - **Strong base, weak nucleophile:** NaH, DBN, DBU
    - Strong tendency to give up hydrogens leads reagents functioning almost exclusively as bases, leading to the elimination reaction.
  - **Strong base, strong nucleophile:**  $\text{HO}^-$ ,  $\text{MeO}^-$ ,  $\text{EtO}^-$ 
    - Can act as both, often producing mixture of products.
    - Such reagents are generally used for biomolecular processes.
  - **Weak base, strong nucleophile:**  $\text{I}^-$ ,  $\text{Br}^-$ ,  $\text{Cl}^-$ ,  $\text{RS}^-$ ,  $\text{HS}^-$ , RSH,  $\text{H}_2\text{S}$ 
    - Reagents mainly function as nucleophiles due to high polarizability, despite being weak bases, leading to substitution reactions.
  - **Weak base, weak nucleophile:**  $\text{H}_2\text{O}$ , MeOH, EtOH
    - Can act as both a nucleophile and base.
    - Mainly used in unimolecular reactions.

|    | Expected Mechanism(s)      |                              |                            |                          |
|----|----------------------------|------------------------------|----------------------------|--------------------------|
|    | Strong Base<br>Weak Nucleo | Strong Base<br>Strong Nucleo | Weak Base<br>Strong Nucleo | Weak Base<br>Weak Nucleo |
| 1° | E2                         | $E2, S_N2$                   | $S_N2$                     | —                        |
| 2° | E2                         | $E2, S_N2$                   | $S_N2$                     | —                        |
| 3° | E2                         | E2                           | $S_N1$                     | E1, $S_N1$               |

### Determining the Expected Mechanism(s)

- After determining categories, then the next step is to identify likely mechanisms, which is done by analyzing the substrate (3°, 2°, 1°).
- The identify of the substrate plays a vital role in determining reactions when the reagent is a strong nucleophile and a strong base.
  - If both are weak, then substitution and elimination can only occur in 3° due the need of carbocation intermediate (some rare exceptions with 2° allylic and benzylic compounds).
- Elimination is not hindered by steric interactions, so generally it will prevail long as substitution isn't favored.
  - Except in unimolecular, where E1 is favored when the products is tri- or tetrasubstituted, and  $S_N1$  with mono- and disubstituted.

### Considering Regiochemical and Stereochemical Outcomes

- Much of follow information was already discussed, but will be recapped here.
- $S_N2$ :
  - Regiochemical: the nucleophile attacks the  $\alpha$  position where the leaving group is connected.
  - Stereochemical: the nucleophile replaces the leaving group with inversion of configuration.
- E2:
  - Regiochemistry: The Zaitsev product (more hydrogen-dense) is generally favored over Hofmann product (less hydrogen-dense), unless sterically hindered, then Hofmann will be favored.
  - Stereochemical: stereoselective, with preference for *trans* over *cis* in disubstituted alkene.

- Also stereospecific: when the  $\beta$  position has only one proton, then the stereoisomeric alkene resulting from the anti-periplanar elimination will be obtained.
- $S_N1$ :
  - Regiochemical: nucleophile attacks the carbocation, which is where leaving group is originally connected, unless carbocation rearrangement took place.
  - Stereochemical: nucleophile replaces the leaving group, giving a nearly racemic mixture of inverted and retained configurations.
    - Often though there is slight preference on inversion as a result of the ion pairs effect.
- $E1$ :
  - Regiochemical: Zaitsev product will always be favored over the Hofmann product.
  - Stereochemical: Stereoselective, with the *trans* disubstituted alkene often being favored.



## 2 Colors

### Colors

▷ Yes