Reactions of Alkyl Halides

- Aside from Grignard reactions and organocuprate coupling reactions, alkyl halides take part in substitution and elimination reactions.
- Substitution reactions allow the halide to be displaced with another group.
- Elimination reactions allow the formation of C=C bonds.

Substitution

\[
\text{Nu}^- + CH_X + \rightarrow \text{Nu}^- \text{Nu}_X
\]

Elimination

\[
\text{H} + \text{CH}_X \rightarrow \text{C} + \text{Nu}^- \text{X}^-
\]

Second Order Nucleophilic Substitution, \( \text{Sn}_2 \)

- Reaction follows the following general mechanism:

\[
\text{Nu}^- \rightarrow \text{Nu}^- + \text{X}^-
\]

- In the above equation, \( \text{Nu}^- \) is the nucleophile and \( \text{X}^- \) is the leaving group.
- The driving force for this reaction is the polarized bond between \( \text{C} \) and \( \text{X} \).
- Factors that influence the rate of this reaction:
  - Substrate steric effects
  - Nucleophile: negatively charged species are capable of electron donation.
  - Leaving group: species that are able to stabilize a negative charge.
  - Solvent: solvent affects the strength of the nucleophile.

Energy Diagram for \( \text{Sn}_2 \)

- Substitution, Nucleophilic, Bimolecular.
- Reaction is a one step, concerted reaction.
- Bond breaking and bond formation occur at the same time.
- Direct displacement.
- Rate = \( k \) [Alkyl halide] \( \text{Nu}^- \).
- Second-order.
Steric Effects on the Alkyl Halide

- The alkyl halide is involved in the transition state of the reaction
- The rate-determining step is the attack on the alkyl halide by the nucleophile
- Anything that hinders this attack will slow down the rate of the reaction
- Bulky alkyl groups on the alkyl halide cause steric hinderance
- The more sterically hindered the alkyl halide, the higher in energy the transition state

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Rate Constant</th>
<th>Rate Factor</th>
<th>Energy</th>
<th>ΔE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃Cl</td>
<td>1.0</td>
<td>1</td>
<td>150.0 kcal/mol</td>
<td>12.9 kcal/mol</td>
</tr>
<tr>
<td>CH₃Br</td>
<td>0.1</td>
<td>0.1</td>
<td>175.0 kcal/mol</td>
<td>15.8 kcal/mol</td>
</tr>
<tr>
<td>CH₃I</td>
<td>0.01</td>
<td>0.01</td>
<td>190.0 kcal/mol</td>
<td>17.8 kcal/mol</td>
</tr>
<tr>
<td>CH₃Cl</td>
<td>1.0</td>
<td>1</td>
<td>150.0 kcal/mol</td>
<td>12.9 kcal/mol</td>
</tr>
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<td>17.8 kcal/mol</td>
</tr>
</tbody>
</table>

Steric Effects on the Alkyl Halide

- The alkyl halide is involved in the transition state of the reaction
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- Anything that hinders this attack will slow down the rate of the reaction
- Bulky alkyl groups on the alkyl halide cause steric hinderance
- The more sterically hindered the alkyl halide, the higher in energy the transition state
Steric Effects on the Alkyl Halide

Besides 3° alkyl halides, Vinyl and Aryl halides are also quite unreactive toward S_N2 reaction conditions.

The pi system creates steric hinderance, and prevents backside attack by the Nu^-.

S_N2 favored with methyl and primary halides, some secondary halides.

Nucleophile Strength

- The strength of the nucleophile affects the rate of the reaction
  - Nucleophile in rate law
  - In general, a species with a negative charge is a better nucleophile than a neutral species
  - Nucleophilicity roughly parallels basicity, but this is not a good indicator of nucleophilicity
- Basicity is defined by an equilibrium constant

B^- + HA ⇌ B-H + A^-  \[ K_{eq} \]

- Nucleophilicity is defined by the rate of attack on an electrophilic carbon atom

Comparing Nucleophilicity to pKa

- Consider the reaction \( \text{CH}_3\text{Br} + \text{Nu}^- \rightarrow \text{CH}_3\text{Nu} + \text{Br}^- \)
- Compare relative rate of reaction to pKa of the conjugate acid of Nu^-.

<table>
<thead>
<tr>
<th>Nu^-</th>
<th>HS^-</th>
<th>CN^-</th>
<th>F^-</th>
<th>CH_3CO^-</th>
<th>HO^-</th>
<th>CT^-</th>
<th>NH_2^-</th>
<th>H_2O^-</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>7.7</td>
<td>9.3</td>
<td>-10.7</td>
<td>15.7</td>
<td>15.7</td>
<td>-5.7</td>
<td>9.25</td>
<td>-1.7</td>
<td>125,000</td>
</tr>
<tr>
<td></td>
<td>125,000</td>
<td>100,000</td>
<td>25,000</td>
<td>16,000</td>
<td>1,000</td>
<td>700</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- However, if you compare bases with the same attacking atom, then nucleophilicity parallels basicity.

<table>
<thead>
<tr>
<th>Nu^-</th>
<th>CH_3CO^-</th>
<th>HO^-</th>
<th>CH_3CO_2^-</th>
<th>H_2O^-</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>15.7</td>
<td>15.7</td>
<td>4.7</td>
<td>-1.7</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.3</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Trends in Nucleophilicity**

- A species with a negative charge is a stronger nucleophile than a neutral species.
- A base is a better nucleophile than its neutral conjugate acid: $\text{OH}^- > \text{H}_2\text{O}$, $\text{SH}^- > \text{H}_2\text{S}$, $\text{NH}_2^- > \text{NH}_3$.
- Nucleophilicity decreases from left to right across the periodic chart, as electronegativity increases.
- More electronegative atoms hold electrons more tightly, less likely to share: $\text{OH}^- > \text{F}^-$, $\text{NH}_3 > \text{H}_2\text{O}$, $(\text{CH}_3\text{CH}_2)_3\text{P} > (\text{CH}_3\text{CH}_2)_2\text{S}$.
- Nucleophilicity increases down a column in the periodic chart.
  - Atoms get bigger, charge is more polarizable: $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$, $\text{SeH}^- > \text{SH}^- > \text{OH}^-$.

**Polarizability and Nucleophilicity**

- The mechanism of $\text{Sn}_2$ reactions call for the nucleophile to approach the alkyl halide from the backside.
- Anytthing that hinders this approach, slows down the reaction.
- Compare $t$-Butoxide to Ethoxide:
  - $t$-Butoxide is a better base but a poorer nucleophile.
  - The $\text{CH}_3$ groups make the anion too bulky to approach an alkyl halide.
  - This phenomenon is called **steric hinderance**.
Leaving Group and $\text{S}_2$ Reactions

- Since the leaving group is involved in the transition state of the reaction, it must have the following properties:
  - Very electron-withdrawing making that carbon atom as electropositive possible
  - Very stable, able to hold a negative charge or neutral
  - Very polarizable
- Halogens, oxygen, nitrogen, and sulfur all form very polarized bonds with carbon
- Weak bases, which are the conjugate bases of strong acids, make good leaving groups
- Large, easily polarized atoms are good nucleophiles and good leaving groups
- Small, neutral molecules make very good leaving groups

Examples of Good Leaving Groups

<table>
<thead>
<tr>
<th>Ion</th>
<th>Halogen</th>
<th>Sulfate</th>
<th>Nitrate</th>
<th>Phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral molecules:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{H}^+$</td>
<td>$\text{O}^-_\text{H}$</td>
<td>$\text{O}^-_\text{R}$</td>
<td>$\text{N}^-_\text{R}$</td>
<td>$\text{P}^-_\text{R}$</td>
</tr>
<tr>
<td>$\text{R} - \text{X}$</td>
<td>$\text{Nu}^-_1$</td>
<td>$\text{R} - \text{Nu}^-_1$</td>
<td>$\text{X}^-_1$</td>
<td>$\text{P}^-_\text{R}$</td>
</tr>
</tbody>
</table>

Where $\text{X} = \text{Cl, Br, I, O}^2-$
$\text{Nu} = A$ nucleophile

Poor leaving Groups

$\text{R} - \text{F} \quad \text{R} - \text{OH} \quad \text{R} - \text{OR} \quad \text{R} - \text{NII}_2$

These compounds do not undergo $\text{S}_2$ reactions.
Protic Polar Solvent and Nucleophilicity

- A protic polar solvent is one that has an "acidic" hydrogen
- Common examples are CH$_3$OH and CH$_3$CH$_2$OH
- Protic solvents are the worst for Sn$_2$ reactions
- Protic solvents decrease the rate of reaction by clustering around the Nu$-$ and lowering its energy
- This phenomenon is called solvation
- The solvent molecules form a cage around the nucleophile, stabilizing the charge

\[
\text{RO-H} \quad \text{Nu}^{-} \quad \text{H-OR}
\]

Aprotic Polar Solvent and Nucleophilicity

- An aprotic polar solvent is one that does not contain O-H or N-H bonds
- These are good solvents for Sn$_2$ reactions
- They dissolve ionic compounds, which are often used for nucleophiles
- They also tend to solvate cations well which leaves the anion bare
- Non-solvated anions tend to have greater nucleophilicity
- These are some of the more common aprotic solvents

\[
\text{CH}_3\text{CN (Acetonitrile)} \quad \text{CH}_3\text{C} = \text{N}(\text{O})\text{CH}_3 (\text{Dimethyl sulfoxide}) \quad \text{CH}_3\text{C} = \text{N}(\text{CH}_3)\text{CH}_3 (\text{Dimethyl formamide}) \quad \text{CH}_3\text{P} = \text{N}(\text{CH}_3)\text{CH}_3 (\text{Hexamethylphosphoramide})
\]

Stereochemistry of Sn$_2$

- Because the nucleophile attacks the alkyl halide from the back, if the carbon involved in this step is chiral, the configuration is inverted
- The Sn$_2$ reaction is a good example of a stereospecific reaction
- The fact that the stereochemistry becomes inverted, supports the one step mechanism proposed for these reactions
Problem
When (S)-1-bromo-1-fluoroethane reacts with CH₃O⁻, pure (S)-1-fluoro-1-methoxyethane is formed.
Why is Br replaced in preference to F?
Is this result consistent with the mechanism?

CH₃CHBrF + CH₃O⁻ → CH₃CHFOCH₃ + NaBr

Summary of Sn₂ Reactions
• Steric hinderance in the alkyl halide raises the energy of the transition state, increasing Eₐ and decreasing the reaction rate
• The Sn₂ reaction works best for methyl and 1o alkyl halides
• More reactive nucleophiles are higher in energy, decreasing Eₐ and increasing the reaction rate
• Good leaving groups, better able to stabilize a negative charge, lower the energy of the transition state, decreasing Eₐ and increasing the reaction rate
• Polar protic solvents form hydrogen bonds to the nucleophile, lowering the energy of the nucleophile, increasing Eₐ, slowing reaction rate
• Polar aprotic solvents interact with cations, causing the nucleophile to be bare, raising the energy of the nucleophile, lowering Eₐ, and increasing reaction rate
First Order Nucleophilic Substitution, $\text{Sn}_1$

- Consider the following reaction:

$$\text{H}_2\text{O} + \text{CH}_3\text{Br} \rightarrow \text{CH}_3\text{OH} + \text{HBr}$$

- From $\text{Sn}_2$ reactions we learned that protic polar solvents slow down the reaction rate
- But this reaction is very rapid
- In fact, 3° alkyl halides react \textbf{1 million} times faster with water than CH₃Br
- The rate of this reaction depends only on the alkyl halide concentration
  - Rate = $k \cdot [\text{Alkyl halide}]$ - first order

Mechanism of $\text{Sn}_1$

- Unlike $\text{Sn}_2$, this reaction is a two step mechanism
- Rate determining step is \textit{unimolecular}

**Step 1, Rate determining step**

$$\begin{align*}
\text{H}_2\text{O} + \text{CH}_3\text{Br} & \rightleftharpoons \text{CH}_3\text{Br}^+ + \text{Br}^- \\
\text{H}_2\text{O} + \text{CH}_3\text{Br}^+ & \rightarrow \text{CH}_3\text{OH} + \text{HBr}
\end{align*}$$

**Step 2, Fast step**

$$\begin{align*}
\text{H}_2\text{O} + \text{CH}_3\text{OH} & \rightarrow \text{CH}_3\text{OH} + \text{H}_2\text{O}
\end{align*}$$
Effect of the Alkyl halide on $\text{Sn}_1$

- The transition state for step 1 comes late and therefore resembles the intermediate.
- According to the Hammond Postulate, anything that lowers the energy of the transition state, increases the rate of reaction.
- The intermediate in this reaction is a carbocation.
- The rate of this reaction follows this trend, and is opposite the trend for $\text{Sn}_2$.

Carbocation Stability

- We saw in Chapter 6 that alkyl groups stabilize a positive charge by donating electron density through the single bonds, **inductive effect**.
- Electron density is also donated by overlap between filled sp³ orbitals and the empty unhybridized p orbital, **hyperconjugation**.
Problem
Account for the following relative rates of reaction under Sn1 conditions

(CH3)3CBr
relative rate 1 1 x 10^-7 1 x 10^-12

Allylic Cations and Sn1 Reactions
• Consider the following reaction

• Even though the alkyl halide in this reaction is 1°, it reacts as fast as a 3°
• The reason for this is the resonance stabilized cation

Benzylic Cations and Sn1
• Consider the following reaction

• Again, this a 1° alkyl halide, yet this reaction goes as fast as with 3°
• The cation formed is a benzylic cation and is resonance stabilized
Problem

• Predict the product(s) of the following Sn₂ reactions

\[ \text{Problem} \]

Solution

\[ \text{Solution} \]
Effect of Leaving Group on Sn1

- In the first transition state, the bond is breaking between the carbon and the leaving group.
- A good leaving group is necessary since this is the rate determining step.
- A good leaving group should be polarizable.
- A good leaving group should be a weak base and able to stabilize a negative charge.

<table>
<thead>
<tr>
<th>Axle</th>
<th>Reaction</th>
<th>Substrate</th>
<th>Product</th>
<th>Oxidation Oxidation</th>
<th>Polarizability</th>
<th>Base Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
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<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
<td>H2O</td>
</tr>
</tbody>
</table>

Effect of Nucleophile on Sn1

- The nucleophile does not participate in the rate determining step.
- Therefore, the strength of the nucleophile doesn’t matter as much.
- Consider the following Sn1 reaction:

\[
\text{CH}_3\text{CH}_2\text{OH} + \text{HX} \rightarrow \text{CH}_3\text{CH}_2\text{X} + \text{H}_2\text{O}
\]

- The rate of reaction is the same for X = Cl, Br, or I.

Effect of Solvent on Sn1

- Polar protic solvents make Sn1 go faster.
- Polar protic solvents tend to solvate the cation intermediate.
- A solvated cation is more stable and lower in energy.
- Solvents with a high dielectric constant (\(\varepsilon\)) increase the rate.
- Consider the following reaction:

\[
\text{H}_2\text{O} + \text{CH}_3\text{Cl} + \text{ROH} \rightarrow \text{H}_2\text{O} + \text{CH}_3\text{OH} + \text{HCl}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Relative Rate</th>
<th>ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2O</td>
<td>100,000</td>
<td>80.4</td>
</tr>
<tr>
<td>80% H2O/Ethanol</td>
<td>14,000</td>
<td>42.3</td>
</tr>
<tr>
<td>40% H2O/Ethanol</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>
Stereochemistry and Sn₁ Reactions
Because Sn₁ reactions proceed through a cation intermediate, we might expect a 50/50 mixture of enantiomers or complete racemization.

Reality and Sn₁ Stereochemistry
- The above reaction leads to 80% R,S and 20% S
- This implies that there is more than a simple cation intermediate

Tight Ion Pairs
- This side opens to attack
- This side subtracts from attack
- Inversion
- Racemization
Summary of Sn₁ vs Sn₂

- **Effect of Nucleophile**
  - Sn₂: Nucleophile involved in RDS, strong nucleophile needed
  - Sn₁: Nucleophile not involved in RDS, strength unimportant

- **Effect of Alkyl halide**
  - Sn₂: Allylic, benzylic, 3° > 2° (1° and CH₃ unlikely)
  - Sn₁: Benzylic, allylic, CH₂X > 3° > 2° (3° unlikely)

- **Effect of Solvent**
  - Sn₂: Polar aprotic solvents work better, tend to increase nucleophile strength
  - Sn₁: Polar protic solvent, since they stabilize the cation

- **Stereochemistry**
  - Sn₂: Complete inversion
  - Sn₁: Partial Racemization

- **Rearrangements**
  - Sn₂: No charged intermediate, no rearrangements
  - Sn₁: Cation intermediate formed, rearrangement possible

Biological Application

- CH₃Br is relatively easy and inexpensive to make
- It finds use as a fumigant to eradicate insect infestations
- Its high toxicity is coupled to its Sn₂ reactivity
- It acts as an alkylating agent toward biological molecules which contain ~SH and ~NH₂ groups

\[ \text{RS}^- + \text{CH}_3\text{Br} \rightarrow \text{RSCH}_3 + \text{HBr} \]

Second Order Elimination, E₂

- Occurs when an alkyl halide is treated with a strong base like OH⁻ or RO⁻
- Like Sn₂, E₂ takes place in one step without an charged intermediate
- Like Sn₂, the rate equation for E₂ depends on the alkyl halide concentration and base concentration
- Rate = k[RX][Base]
Stereochemistry and E₂

- E₂ like the Sn₂ mechanism is concerted, bond breaking and bond formation occur simultaneously.
- In order for this to happen, overlap between the orbitals involved must be very good.
- For E₂, this requires that the hydrogen which is being abstracted by the base, the two carbons, and the leaving group all lie in the same plane periplanar or coplanar.
- Two possible geometries are possible for the hydrogen and the leaving group:
  - Anti-coplanar
  - Syn-coplanar

Transition States for E₂

**E₂ Reactions with Diastereomers**
Mechanism of E₂ for R,R or S,S

Mechanism of E₂ for S,R and R,S

Cyclohexanes and E₂

- In order for E₂ to occur, the hydrogen and the leaving group must be anti-coplanar.
- In a cyclohexane ring this means that the H and the leaving group must be trans diaxial.
- Even if this is not the most stable conformation, the cyclohexane must ring flip.

In order for E₂ to occur, the hydrogen and the leaving group must be anti-coplanar.
In a cyclohexane ring this means that the H and the leaving group must be trans diaxial.
Even if this is not the most stable conformation, the cyclohexane must ring flip.
Cyclohexanes and E₂

Neomenthyl chloride vs. Menthyl Chloride

Neomenthyl chloride vs. Menthyl Chloride
Competition $\text{Sn}_2$ vs. $E_2$

- **Primary Alkyl halide**
  - Mostly substitution, unless steric hinderance in either the alkyl halide or nucleophile
- **Secondary Alkyl halide**
  - Both substitution and elimination can occur
  - Stronger, bulkier base favors elimination
- **Tertiary Alkyl halide**
  - Only elimination

First Order Elimination, $E_1$

- Like $\text{Sn}_2$, $E_1$ is a two step mechanism where the first step is the rate determining step
- The intermediate is a carbocation
- The rate equation is $\text{rate} = k [RX]$
  
  Step 1, rate determining

  \[
  \text{H}_2\text{C} \quad \text{H}_3\text{C} \quad \text{H}_2\text{O} \quad \text{H}_2\text{C} \quad \text{H}_3\text{C} \quad + \quad \text{Cl}^- \quad \text{H}_2\text{C} \quad \text{H}_3\text{C} \quad + \quad \text{H}_3\text{O}^+ \]

  Step 2, fast step

  What other mechanism contains this exact step?

Energy Diagram for $E_1$

- $E_1$ rate = $k_2[R - X]$
Competition Between $\text{Sn}_1$ and $\text{E}_1$

- $\text{E}_1$ is always in competition with $\text{Sn}_1$.
- Whenever a cation is formed under $\text{Sn}_1$ or $\text{E}_1$ conditions, either substitution or elimination can occur.
- Consider the previous example:

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \text{H}_2\text{O} \rightarrow \text{H}_3\text{C}\text{CH} = \text{CH}_2 + \text{H}_3\text{O}^+ + \text{Cl}^-$$

Stereochemistry and $\text{E}_1$

- $\text{E}_1$ occurs through a cation intermediate.
- Because a proton can be removed from either the same face or opposite face as the cation, two possible geometries are possible for the alkene products.
- However, the more stable alkene will usually predominate.

Competition $\text{Sn}_1$ vs. $\text{E}_1$

- Primary Alkyl halide
  - Cannot undergo $\text{Sn}_1/\text{E}_1$ mechanism.
- Secondary Alkyl halide
  - Both substitution and elimination can occur.
- Tertiary Alkyl halide
  - Both substitution and elimination can occur.
Zaitsev’s Rule

• Most alkyl halides can eliminate in more than one way
• This gives rise to a mixture of alkene products
• How do we predict which one is the favored product?
• We apply Zaitsev’s Rule: the most highly substituted double bond is favored
• This rule applies to both E₁ and E₂ reactions
• For both E₁ and E₂ the reactivity of alkyl halides is \( 3º > 2º > 1º \)
• \( R_2C=CR_1 > R_2C=CHR > RHC=CHR \) and \( R_2C=CH_2 > RCH=CH_2 \)

Example of Zaitsev’s Rule

• Consider the reaction below


Less substituted, minor product

More substituted, major product

Exceptions to Zaitsev Rule

Hoffman Product

• In E₂ reactions, the base and substrate must approach each other in the rate determining step.
• Bulky bases will not be able to approach the most substituted carbon.
• They abstract the proton from the less substituted carbon forming the least-substituted alkene
Multistep Synthesis

- Using any of the reactions you have learned to date, perform the following syntheses:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{CH}_3\text{CH}_2\text{CCH}_3
\]

\[
\text{CH}_3\text{CH}_2\text{CCH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{Br}
\]