10. Organohalides

Based on McMurry’s *Organic Chemistry, 7th edition*
What Is an Alkyl Halide

- An organic compound containing at least one carbon-halogen bond (C-X)
  - X (F, Cl, Br, I) replaces H
- Can contain many C-X bonds
- Properties and some uses
  - Fire-resistant solvents
  - Refrigerants
  - Pharmaceuticals and precursors

Trichloroethylene (a solvent)  Halothane (an inhaled anesthetic)  Dichlorodifluoromethane (a refrigerant)  Bromomethane (a fumigant)
Why this Chapter?

- Reactions involving organohalides are less frequently encountered than other organic compounds, but reactions such as nucleophilic substitutions/eliminations that they undergo will be encountered frequently.

- Alkyl halide chemistry is model for mechanistically similar but more complex reactions.
10.1 Naming Alkyl Halides

- Find longest chain, name it as parent chain
- (Contains double or triple bond if present)
- Number from end nearest any substituent (alkyl or halogen)

\[
\text{CH}_3\text{CHCH}_2\text{CHCHCH}_2\text{CH}_3 \quad \text{Br} \\
1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7
\]

5-Bromo-2,4-dimethylheptane

\[
\text{CH}_3\text{CHCH}_2\text{CHCHCH}_2\text{CH}_3 \quad \text{Br} \\
1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7
\]

2-Bromo-4,5-dimethylheptane

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Naming if Two Halides or Alkyl Are Equally Distant from Ends of Chain

- Begin at the end nearer the substituent whose name comes first in the alphabet

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CHCH}_3 \\
6 \quad 5 \quad 4 \quad 3 \quad 2 \quad 1
\end{array}
\]

2-Bromo-5-methylhexane

*(NOT 5-bromo-2-methylhexane)*
10.2 Structure of Alkyl Halides

- C-X bond is longer as you go down periodic table
- C-X bond is weaker as you go down periodic table
- C-X bond is polarized with partial positive charge on carbon and partial negative charge on halogen

<table>
<thead>
<tr>
<th>Halomethane</th>
<th>Bond length (pm)</th>
<th>Bond strength (kJ/mol)</th>
<th>Bond strength (kcal/mol)</th>
<th>Dipole moment (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃F</td>
<td>139</td>
<td>452</td>
<td>108</td>
<td>1.85</td>
</tr>
<tr>
<td>CH₃Cl</td>
<td>178</td>
<td>351</td>
<td>84</td>
<td>1.87</td>
</tr>
<tr>
<td>CH₃Br</td>
<td>193</td>
<td>293</td>
<td>70</td>
<td>1.81</td>
</tr>
<tr>
<td>CH₃I</td>
<td>214</td>
<td>234</td>
<td>56</td>
<td>1.62</td>
</tr>
</tbody>
</table>
Preparing Alkyl Halides from Alkenes

- Alkyl halide from addition of HCl, HBr, HI to alkenes to give Markovnikov product (see Alkenes chapter)

- Alkyl dihalide from *anti* addition of bromine or chlorine
Preparing Alkyl Halides from Alkanes: Radical Halogenation

- Alkane + Cl<sub>2</sub> or Br<sub>2</sub>, heat or light replaces C-H with C-X but gives mixtures
  - Hard to control
  - Via free radical mechanism
- It is usually not a good idea to plan a synthesis that uses this method—multiple products
Radical Chain Mechanism

Initiation step

\[
\begin{align*}
\text{Cl} & \rightarrow \text{Cl} \quad \xrightarrow{h\nu} \quad 2 \text{Cl} \cdot \\
\end{align*}
\]

Propagation steps (a repeating cycle)

\[
\begin{align*}
\text{H}_3\text{C} & \cdot \quad + \quad \text{Cl} \cdot \\
\text{H}_3\text{C} & \cdot \quad + \quad \text{H}_3\text{C} \cdot \\
\text{H}_3\text{C} & \cdot \quad + \quad \text{Cl} \cdot \\
\end{align*}
\]

Step 1

\[
\begin{align*}
\text{H} & \cdot \quad + \quad \text{Cl} \cdot \\
\text{H}_3\text{C} & \cdot \quad + \quad \text{Cl} \cdot \\
\end{align*}
\]

Step 2

\[
\begin{align*}
\end{align*}
\]

Termination steps

\[
\begin{align*}
\text{H}_3\text{C} & \cdot \quad + \quad \cdot\text{CH}_3 \quad \rightarrow \quad \text{H}_3\text{C} \cdot \cdot\text{CH}_3 \\
\text{Cl} & \cdot \quad + \quad \cdot\text{CH}_3 \quad \rightarrow \quad \text{Cl} \cdot \cdot\text{CH}_3 \\
\text{Cl} & \cdot \quad + \quad \cdot\text{Cl} \quad \rightarrow \quad \cdot\text{Cl} \cdot \cdot\text{Cl} \\
\end{align*}
\]

Overall reaction

\[
\begin{align*}
\text{CH}_4 & \quad + \quad \text{Cl}_2 \quad \rightarrow \quad \text{CH}_3\text{Cl} \quad + \quad \text{HCl}
\end{align*}
\]
Radical Halogenation: Selectivity

If there is more than one type of hydrogen in an alkane, reactions favor replacing the hydrogen at the most highly substituted carbons.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{Cl}_2 & \xrightarrow{h\nu} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{CHCH}_3 \\
\text{Butane} & \quad \text{1-Chlorobutane} \quad \text{2-Chlorobutane} \\
30\% \text{ (1°) Product} & = 5\% \text{ per (1°) H} \\
6 \text{ (1°) H's} & \\
70\% \text{ (2°) Product} & = 17.5\% \text{ per (2°) H} \\
4 \text{ (2°) H's} & \\
\frac{17.5\% \text{ per (2°) H}}{5\% \text{ per (1°) H}} & = 3.5 : 1 \text{ relative reactivity} \\
\frac{65\% \text{ (1°) Product}}{9 \text{ (1°) H's}} & = 7.2\% \text{ per (1°) H} \\
35\% \text{ (3°) Product} & = 35\% \text{ per (3°) H} \\
\frac{1 \text{ (1°) H's}}{} & \\
\frac{35\% \text{ per (3°) H}}{7.2\% \text{ per (1°) H}} & = 5 : 1 \text{ relative reactivity}
\end{align*}
\]
Relative Reactivity

Based on quantitative analysis of reaction products, relative reactivity is estimated for Cl₂: (5:3.5:1 for 3°:2°:1°)

- Order parallels stability of radicals
- Reaction distinction is more selective with bromine than chlorine (1700:80:1 for 3°:2°:1°)
Allylic Bromination

- N-bromosuccinimide (NBS) selectively brominates allylic positions (Allylic = next to a double bond)
- Requires light for activation—just like radical halogenation
- NBS is just a source of dilute bromine radicals (Br▪)

![Chemical Reaction Diagram]

Cyclohexene + NBS (NBS) → 3-Bromocyclohexene (85%) + N-H

Allylic 360 kJ/mol (87 kcal/mol)

Alkyl 400 kJ/mol (96 kcal/mol)

Vinylic 445 kJ/mol (106 kcal/mol)
Allylic Stabilization

- Allyl radical is delocalized—radical is shared over 2 carbons
- More stable than typical alkyl radical by 40 kJ/mol (9 kcal/mol)
- Allylic radical is more stable than tertiary alkyl radical
Use of Allylic Bromination

Allylic bromination with NBS creates an allylic bromide

Reaction of an allylic bromide with base produces a conjugated diene (by elimination), useful in synthesis of complex molecules.

Why this Major Product?
1. Less Hindered Radical Gives Major Product
2. More substituted alkene is more stable
Preparing Alkyl Halides from Alcohols

- Reaction of tertiary C-OH with HX is fast and effective
  - Add HCl or HBr gas into ether solution of tertiary alcohol

- Primary and secondary alcohols react very slowly and often rearrange, so alternative methods are used: SOCl₂ or PBr₃
- Mechanisms of all of these reactions in next chapter
Reactions of Alkyl Halides: Grignard Reagents

- Reaction of RX with Mg in ether or THF
- Product is RMgX – an organometallic compound (alkyl-metal bond)

Carbanions ($\text{CH}_3^-$ $\text{MgX}^+$) are very strong bases
Deprotonate water, alcohols, carboxylic acids, etc…

Iodomethane → Methylmagnesium iodide

CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$Br $\xrightarrow{\text{Mg, Ether}}$ CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$MgBr $\xrightarrow{\text{H}_2\text{O}}$ CH$_3$CH$_2$CH$_2$CH$_2$CH$_3$

1-Bromohexane → 1-Hexylmagnesium bromide → Hexane (85%)
Organometallic Coupling Reactions

- Alkyllithium (RLi) forms from RBr and Li metal
- RLi reacts with copper iodide to give lithium dialkylcopper (Gilman reagents)
- Lithium dialkylcopper reagents react with alkyl halides to give alkanes

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{2 \text{ Li}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} + \text{LiBr} \]

\[ 2 \text{ CH}_3\text{Li} + \text{CuI} \xrightarrow{\text{Ether}} (\text{CH}_3)_2\text{Cu}^-\text{Li}^+ + \text{LiI} \]

\[ (\text{CH}_3)_2\text{CuLi} + \text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{I} \xrightarrow{0 \degree C, \text{Ether}} \text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{CH}_3 + \text{LiI} + \text{CH}_3\text{Cu} \]
Utility of Organometallic Coupling in Synthesis

- Coupling of two organometallic molecules produces larger molecules of defined structure
- Aryl and vinyl organometallics also effective

\[ n-C_7H_{15} + (n-C_4H_9)_2CuLi \rightarrow n-C_7H_{15} + n-C_4H_9Cu + LiI \]

**trans-1-Iodo-1-nonene**

\[ \text{Iodobenzene} + (CH_3)_2CuLi \rightarrow \text{Toluene (91%)} + CH_3Cu + LiI \]

**trans-5-Tridecane (71%)**

Coupling of lithium dialkylcopper molecules proceeds through trialkylcopper intermediate
Oxidation and Reduction in Organic Chemistry

- In organic chemistry, we say that **oxidation** occurs when a carbon or hydrogen that is connected to a carbon atom in a structure is replaced by oxygen, nitrogen, or halogen.
  - Not defined as loss of electrons by an atom as in inorganic chemistry.
- Oxidation is a reaction that results in loss of electron density at carbon (as more electronegative atoms replace hydrogen or carbon).
- Organic reduction is the opposite of oxidation.
  - Results in gain of electron density at carbon (replacement of electronegative atoms by hydrogen or carbon).

**Oxidation**: *break C-H (or C-C) and form C-O, C-N, C-X*

**Reduction**: *form C-H (or C-C) and break C-O, C-N, C-X*
**Oxidation and Reduction Reactions**

**Methane** + **Cl₂** → **Chloromethane**

**Oxidation**: C–H bond broken and C–Cl bond formed

**Chloromethane** → **Methane**

**Reduction**: C–Cl bond broken and C–H bond formed

**Ethylene** + **Br₂** → **1,2-Dibromoethane**

**Oxidation**: Two new bonds formed between carbon and a more electronegative element

**Ethylene** + **HBr** → **Bromoethane**

**Neither oxidation nor reduction**: One new C–H bond and one new C–Br bond formed
Oxidation Levels

- Functional groups are associated with specific oxidation levels.

\[
\text{Level} = (\# \text{ of C-O, C-N, C-X bonds}) - (\# \text{ of C-H bonds})
\]

Ex. 10.12

(a) 
- \(0-12 = -12\)
- \(0-6 = -6\)
- \(2-10 = -8\)
- \(1-9 = -8\)

(b) 
- \(\text{CH}_3\text{CN} \quad 3-0 = 0\)
- \(\text{CH}_3\text{CH}_2\text{NH}_2 \quad 1-5 = -4\)
- \(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2 \quad 2-4 = -2\)
Let’s Work a Problem

How would you carry out the following syntheses?

Cyclohexene → ? → ?
Cyclohexanol → ?
Cyclohexane → ? → ?
Answer

The dialkylcopper reagent should be used (di-butylCuLi) that can be added to cyclohexylBr after cyclohexene is treated with HBr.
11. Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

Based on McMurry’s *Organic Chemistry, 7th edition*
Alkyl Halides React with Nucleophiles and Bases

- Alkyl halides are polarized at the carbon-halide bond, making the carbon electrophilic.
- Nucleophiles will replace the halide in C-X bonds of many alkyl halides (reaction as Lewis base).
- Nucleophiles that are Brønsted bases produce elimination.

Substitution:

\[
\begin{align*}
\text{C-Br} + \text{OH}^- & \rightarrow \text{C-OH} + \text{Br}^- \\
\end{align*}
\]

Elimination:

\[
\begin{align*}
\text{C-Br} + \text{OH}^- & \rightarrow \text{C=C} + \text{H}_2\text{O} + \text{Br}^- \\
\end{align*}
\]
Why this Chapter?

- Nucleophilic substitution, base induced elimination are among most widely occurring and versatile reaction types in organic chemistry
- Reactions will be examined closely to see:
  - How they occur
  - What their characteristics are
  - How they can be used
11.1 The Discovery of Nucleophilic Substitution Reactions—Walden

- The reactions alter the array at the chirality center.
- The reactions involve substitution at that center.
- Therefore, nucleophilic substitution can invert the configuration at a chirality center.
- The presence of carboxyl groups in malic acid led to some dispute as to the nature of the reactions in Walden’s cycle.

\[
\begin{align*}
\text{HOCH}_2\text{CHCOH} & \quad \text{PCl}_5, \text{Ether} \quad \text{HOCH}_2\text{CHCOOH} \\
(-)-\text{Malic acid} & \quad \alpha_D = -2.3 \\
\text{Ag}_2\text{O}, \text{H}_2\text{O} & \quad \downarrow \quad \text{Ag}_2\text{O}, \text{H}_2\text{O} \\
\text{HOCH}_2\text{CHCOCl} & \quad \text{HOCH}_2\text{CHCOH} \\
(-)-\text{Chlorosuccinic acid} & \quad \alpha_D = +2.3
\end{align*}
\]
11.2 The $S_{N2}$ Reaction

- Reaction is with inversion at reacting center (substrate)
- Follows second order reaction kinetics
- Ingold nomenclature to describe characteristic step:
  - $S$ = substitution
  - $N$ (subscript) = nucleophilic
  - $2$ = both nucleophile and substrate in characteristic step (bimolecular)
Reaction Kinetics

- The study of rates of reactions is called *kinetics*
- Rates decrease as concentrations decrease but the rate constant does not
- Rate units: [concentration]/time such as L/(mol x s)
- The *rate law* is a result of the mechanism
- The *order* of a reaction is sum of the exponents of the concentrations in the rate law

A + B -----→ C + D

- Experimentally determine the effect of increasing A/B
- First Order: rate = k[A] (only depends on [A], not [B])
- Second Order: rate = k[A][B] (depends on both [A],[B])
- Third order: rate = k[A]^2[B]
$S_{N2}$ Process

- The reaction involves a transition state in which both reactants are together
- Rate = $k[\text{ROTs}][\text{OAc}]$
**S\textsubscript{N}2 Transition State**

- The transition state of an S\textsubscript{N}2 reaction has a planar arrangement of the carbon atom and the remaining three groups.
11.3 Characteristics of the $S_{N}2$ Reaction

- Occurs with inversion of chiral center
- Sensitive to steric effects
- Methyl halides are most reactive
- Primary are next most reactive
- Secondary might react
- Tertiary are unreactive by this path
- No reaction at C=C (vinyl halides)
Steric Effects on $S_N2$ Reactions

The carbon atom in (a) bromomethane is readily accessible resulting in a fast $S_N2$ reaction. The carbon atoms in (b) bromoethane (primary), (c) 2-bromopropane (secondary), and (d) 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower $S_N2$ reactions.
Order of Reactivity in $S_N2$

- The more alkyl groups connected to the reacting carbon, the slower the reaction.

![Reaction diagram]

**Relative reactivity**
- Tertiary: $< 1$
- Neopentyl: 1
- Secondary: 500
- Primary: 40,000
- Methyl: 2,000,000

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The Nucleophile

- Neutral or negatively charged Lewis base
- Reaction increases coordination at nucleophile
  - Neutral nucleophile acquires positive charge
  - Anionic nucleophile becomes neutral

Negatively charged nucleophile

\[
\text{Nu}^- + \text{R}^- \rightarrow \text{R}^-\text{Nu} + \text{Y}^- \\
\text{Nu} + \text{R}^- \rightarrow \text{R}^-\text{Nu}^+ + \text{Y}^- \\
\text{Neutral nucleophile} \quad \text{Neutral product} \quad \text{Positively charged product}
\]
Relative Reactivity of Nucleophiles

- Depends on reaction and conditions
- More basic nucleophiles react faster
- Better nucleophiles are lower in a column of the periodic table
- Anions are usually more reactive than neutrals

Table 11.1  Some $S_N2$ Reactions with Bromomethane

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Formula</th>
<th>Name</th>
<th>Product</th>
<th>Relative rate of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O</td>
<td>H$_2$O</td>
<td>Water</td>
<td>CH$_3$OH$_2^+$</td>
<td>1</td>
</tr>
<tr>
<td>CH$_3$CO$_2^-$</td>
<td>CH$_3$CO$_2$CH$_3$</td>
<td>Acetate</td>
<td>Methyl acetate</td>
<td>500</td>
</tr>
<tr>
<td>NH$_3$</td>
<td>NH$_3$</td>
<td>Ammonia</td>
<td>CH$_3$NH$_3^+$</td>
<td>700</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>Cl$^-$</td>
<td>Chloride</td>
<td>CH$_3$Cl</td>
<td>1,000</td>
</tr>
<tr>
<td>HO$_2^-$</td>
<td>HO$_2^-$</td>
<td>Hydroxide</td>
<td>CH$_3$OH</td>
<td>10,000</td>
</tr>
<tr>
<td>CH$_3$O$^-$</td>
<td>CH$_3$O$^-$</td>
<td>Methoxide</td>
<td>CH$_3$OCH$_3$</td>
<td>25,000</td>
</tr>
<tr>
<td>I$^-$</td>
<td>I$^-$</td>
<td>Iodide</td>
<td>CH$_3$I</td>
<td>100,000</td>
</tr>
<tr>
<td>CN$^-$</td>
<td>CN$^-$</td>
<td>Cyanide</td>
<td>CH$_3$CN</td>
<td>125,000</td>
</tr>
<tr>
<td>HS$^-$</td>
<td>HS$^-$</td>
<td>Hydrosulfide</td>
<td>CH$_3$SH</td>
<td>125,000</td>
</tr>
</tbody>
</table>
The Leaving Group

- A good leaving group reduces the barrier to a reaction
- Stable anions that are weak bases are usually excellent leaving groups and can delocalize charge

<table>
<thead>
<tr>
<th>Relative reactivity</th>
<th>$\text{OH}^-$, $\text{NH}_2^-$, $\text{OR}^-$</th>
<th>$\text{F}^-$</th>
<th>$\text{Cl}^-$</th>
<th>$\text{Br}^-$</th>
<th>$\text{I}^-$</th>
<th>$\text{TosO}^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;$1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td>60,000</td>
<td></td>
</tr>
</tbody>
</table>
Poor Leaving Groups

- If a group is very basic or very small, it prevents reaction.

<table>
<thead>
<tr>
<th>Relative reactivity</th>
<th>OH(^{-}), NH(_2)^{-}, OR(^{-})</th>
<th>F(^{-})</th>
<th>Cl(^{-})</th>
<th>Br(^{-})</th>
<th>I(^{-})</th>
<th>TosO(^{-})</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;&lt;1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td>60,000</td>
<td></td>
</tr>
</tbody>
</table>

- Alkyl fluorides, alcohols, ethers, and amines do not typically undergo S\(_\text{N}\)2 reactions.
- Poor Leaving groups can be made into good leaving groups

A 1° or 2° alcohol  
"Tosyl chloride"  
A tosylate
The Solvent

- Solvents that can donate hydrogen bonds (-OH or –NH) slow $S_N$2 reactions by associating with reactants.
- Energy is required to break interactions between reactant and solvent.
- Polar aprotic solvents (no NH, OH, SH) form weaker interactions with substrate and permit faster reaction.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{N}_3^- \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}_3 + \text{Br}^-
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>CH(_3)OH</th>
<th>H(_2)O</th>
<th>DMSO</th>
<th>DMF</th>
<th>CH(_3)CN</th>
<th>HMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative reactivity</td>
<td>1</td>
<td>7</td>
<td>1300</td>
<td>2800</td>
<td>5000</td>
<td>200,000</td>
</tr>
</tbody>
</table>

- DMSO (Dimethyl Sulfoxide)
- HMPA (Hexamethylphosphoramide)
- DMF (Dimethylformamide)
- Acetone
11.4 The $S_N 1$ Reaction

- Tertiary alkyl halides react rapidly in protic solvents by a mechanism that involves departure of the leaving group prior to addition of the nucleophile.
- Called an $S_N 1$ reaction – occurs in two distinct steps while $S_N 2$ occurs with both events in same step.
- If nucleophile is present in reasonable concentration (or it is the solvent), then ionization is the slowest step.

![Chemical reaction and chain reactivity chart](image-url)
$S_N1$ Energy Diagram and Mechanism

- Rate-determining step is formation of carbocation
- Rate $= k[RX]$
Stereochemistry of $S_N1$ Reaction

- The planar intermediate leads to loss of chirality
  - A free carbocation is achiral
- Product is racemic or has some inversion
$S_N 1$ in Reality

- Carbocation is biased to react on side opposite leaving group
- Suggests reaction occurs with carbocation loosely associated with leaving group during nucleophilic addition (Ion Pair)
- Alternative that $S_N 2$ is also occurring is unlikely

![Chemical reaction diagram with text annotations](attachment:chemical_diagram.png)

(R)-6-Chloro-2,6-dimethyloctane

\[ \text{H}_3\text{C} \quad \text{CH}_2\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \quad \text{H}_2\text{O}^+ \quad \text{Ethanol} \]

\[ \rightarrow \quad \text{CH}_3 \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \quad \text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \quad \text{CH}_3 \]

60% $S$ (inversion)

40% $R$ (retention)
11.5 Characteristics of the $S_N1$ Reaction

**Substrate**
- Tertiary alkyl halide is most reactive by this mechanism

- Controlled by stability of carbocation
- Remember Hammond postulate, "Any factor that stabilizes a high-energy intermediate stabilizes transition state leading to that intermediate"

![Carbocation stability diagram]

- Allylic and benzylic intermediates stabilized by delocalization of charge
- Primary allylic and benzylic are also more reactive in the $S_N2$ mechanism

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Carbocation Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>Primary &lt; Allylic ≈ Benzylic ≈ Secondary &lt; Tertiary</td>
</tr>
<tr>
<td>CH$_3$CH$_2$Cl</td>
<td>338 kJ/mol (81 kcal/mol)</td>
</tr>
<tr>
<td>H$_2$C=CHCH$_2$Cl</td>
<td>289 kJ/mol (69 kcal/mol)</td>
</tr>
<tr>
<td>CH$_2$Cl-Ph</td>
<td>293 kJ/mol (70 kcal/mol)</td>
</tr>
</tbody>
</table>
Effect of Leaving Group on $S_N 1$

- Critically dependent on leaving group
  - Reactivity: the larger halides ions are better leaving groups
- In acid, OH of an alcohol is protonated and leaving group is $H_2O$, which is still less reactive than halide
- p-Toluensulfonate ($TosO^-$) is excellent leaving group

$HO^- < Cl^- < Br^- < I^- \approx TosO^- \approx H_2O$
Nucleophiles in $S_N1$

- Since nucleophilic addition occurs \textit{after} formation of carbocation, reaction rate is not normally affected by nature or concentration of nucleophile.

\[
\begin{array}{c}
\text{CH}_3\text{C}^-\text{OH} + \text{HX} \rightarrow \text{CH}_3\text{C}^-\text{X} + \text{H}_2\text{O}
\end{array}
\]

\textit{2-Methyl-2-propanol}  
(Same rate for $X = \text{Cl, Br, I}$)

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Solvent in $S_{N}1$

- Stabilizing carbocation also stabilizes associated transition state and controls rate
- Protic solvents favoring the $S_{N}1$ reaction are due largely to stabilization of the transition state
- Protic solvents disfavor the $S_{N}2$ reaction by stabilizing the ground state
- Polar, protic and unreactive Lewis base solvents facilitate formation of $R^+$

\[
\text{CH}_3\text{C-Cl} + \text{ROH} \rightarrow \text{CH}_3\text{C-OR} + \text{HCl}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Relative Reactivity</th>
<th>40% Water/60% Ethanol</th>
<th>80% Water/20% Ethanol</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>1</td>
<td>100</td>
<td>14,000</td>
<td>100,000</td>
</tr>
</tbody>
</table>

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11.7 Elimination Reactions of Alkyl Halides: Zaitsev’s Rule

- Elimination is an alternative pathway to substitution
- Opposite of addition
- Generates an alkene
- Can compete with substitution and decrease yield, especially for $S_N 1$ processes
Zaitsev’s Rule for Elimination Reactions

In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

Mechanisms of Elimination Reactions

- **E1**: X⁻ leaves first to generate a carbocation
  - a base abstracts a proton from the carbocation
- **E2**: Concerted transfer of a proton to a base and departure of leaving group
11.8 The E2 Reaction

- A proton is transferred to base as leaving group begins to depart
- Transition state combines leaving of X and transfer of H
- Product alkene forms stereospecifically
- Rate = \( k[RX][B] \)
Geometry of Elimination – E2

- Syn arrangement requires eclipsed conformation = disfavored
- Anti arrangement allows orbital overlap and minimizes steric interactions
- Overlap of the developing $\pi$ orbital in the transition state requires periplanar geometry, anti arrangement
Predicting Product

- E2 is stereospecific
- Meso-1,2-dibromo-1,2-diphenylethane with base gives cis-1,2-diphenyl

RR or SS 1,2-dibromo-1,2-diphenylethane gives trans 1,2-diphenyl
E2 Reactions and Cyclohexene Formation

- Abstracted proton and leaving group should align trans-diaxial to be anti periplanar (\textit{app}) in approaching transition state

- Equatorial groups are not in proper alignment

**Axial chlorine: H and Cl are anti periplanar**

**Equatorial chlorine: H and Cl are not anti periplanar**

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Neomenthyl chloride

Menthyl chloride

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11.10 The E1 Reaction

- Competes with $S_{N1}$ and E2 at 3° centers
- Rarely have “clean” $S_{N2}$ or E1 single products
- Rate = $k [RX]$, same as $S_{N1}$

\[ \text{CH}_3 - \text{C} - \text{CH}_3 \]

\[ \text{Cl} \]

\[ \text{CH}_3 \]

1 Rate-limiting

\[ \text{H}_3\text{C} - \text{C} - \text{H} \]

\[ \text{+ Base} \]

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

2 Fast

\[ \text{CH}_3 - \text{C} = \text{C} - \text{H} \]

\[ \text{CH}_3 \]

\[ \text{H}_3\text{C} - \text{C} - \text{Cl} \quad \text{H}_2\text{O, ethanol} \quad 65 \degree \text{C} \]

\[ \text{H}_3\text{C} - \text{C} - \text{OH} \quad \text{H}_3\text{C} - \text{C} = \text{H} \]

2-Chloro-2-methylpropane

2-Methyl-2-propanol (64%)

2-Methylpropene (36%)

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Comparing E1 and E2

- Strong base is needed for E2 but not for E1
- E2 is stereospecific, E1 is not
- E1 gives Zaitsev orientation
E1cB Reaction

- Takes place through a carbanion intermediate
- Common with very poor leaving group (OH-)
- HO-C-C=O fragment often involved

**E1cB Reaction:** C–H bond breaks first, giving a carbanion intermediate that loses $X^-$ to form the alkene.
Summary of Reactivity: $S_N2$, $S_N1$, E1, E2

- Alkyl halides undergo different reactions in competition, depending on the reacting molecule and the conditions.
- Based on patterns, we can predict likely outcomes.

**Primary Haloalkanes**
- $S_N2$ with any fairly good nucleophile
- E2 only if Bulky, strong base

**Secondary Haloalkanes**
- $S_N2$ with good nucleophiles, weak base, Polar Aprotic Solvent
- $S_N1$/E1 with good LG, weak Nu, Polar Protic Solvent
- E2 with strong base

**Tertiary Haloalkane**
- $S_N1$/E1 with good LG, no base (solvolysis)
- E2 with strong base

Good L.G.
2° alkyl halide
Poor Nucleophile
Polar Protic Solvent
$S_N1$ and E1 products