Chapter 7. Alkyl Halides

Organohalides are valuable as industrial solvents, inhaled anesthetics in medicine, refrigerants, and pesticides. Trichloroethylene is used for cleaning semiconductor chip and other components.

7.1 Naming Alkyl Halides

Alkyl halides are named in the same way as alkanes, by considering the halogen as a substituent on the parent alkane chain.

**Step 1. Find the longest chain, and name it as the parent.** If a multiple bond is present, the parent chain must contain it.

**Step 2. Number the carbons of the parent chain beginning at the end nearer the first substituent, regardless of whether it is alkyl or halo** (following alphabetic priority rule).

**Step 3. Write the name.** List all substituents in alphabetical order.

In addition to their systematic names, alkyl halides are named by identifying first the alkyl group and then halogen.

7.2 Preparing Alkyl Halides

- The addition reactions of HX and X₂ with alkenes.
- The reaction of an alkane with Cl₂.
The most general method for preparing alkyl halides is to make them from alcohols—a reaction carried out simply by treating the alcohol with halogen halide, HX.

\[
\begin{align*}
\text{OH} \quad & \quad \text{HCl (gas)} \quad \text{Cl} \quad \text{OH} \\
\text{Cl} \quad & \quad \text{H}_2\text{O} \\
\text{Cl} \quad & \quad \text{H}_2\text{O} \\
\text{Cl} \quad & \quad \text{H}_2\text{O} \\
\text{OH} \quad & \quad \text{H}_2\text{O} \\
\text{OH} \quad & \quad \text{H}_2\text{O} \\
\text{OH} \quad & \quad \text{H}_2\text{O} \\
\end{align*}
\]

(The reaction works best with tertiary alcohols. Primary and secondary alcohols react much more slowly.)

**Primary and secondary** alcohols are best converted into alkyl halides by treatment with SOCl₂ or PBr₃.

\[
\begin{align*}
\text{OH} \quad & \quad \text{SOCl}_2 \\
\text{Cl} \quad & \quad \text{SO}_2 + \text{HCl} \\
\text{Br} \quad & \quad \text{P(OH)}_3 \\
\end{align*}
\]

7.3 Reactions of Alkyl Halides: Grignard Reagents

Alkyl halides react with magnesium metal in ether solvent to yield **organomagnesium halides**, called **Grignard reagents**. Grignard reagents contain a carbon-metal bond and are thus **organometallic** compounds.

\[
\begin{align*}
\text{R–X} + \text{Mg} \rightarrow \text{R–MgX} \\
\text{R} = \text{alkyl, aryl, alkenyl} \quad \text{X} = \text{Cl, Br, I} \\
\end{align*}
\]

A carbon-magnesium bond is strongly polarized, making the organic part both **nucleophilic** and **basic**. A Grignard reagent reacts with acids and electrophiles. The overall sequence, \( \text{R–X} \rightarrow \text{R–MgX} \rightarrow \text{R–H} \), is a useful method for converting an organic halide into a hydrocarbon.
7.4 Nucleophilic Substitution Reactions

1869, Paul Walden discovered that (+)- and (−)-malic acids could be interconverted by a series of simple substitution reactions,

\[
\text{HO} \quad \text{OH} \\
\text{O} \quad \text{OH} \\
\text{O} \\
\text{HO} \quad \text{OH} \\
\text{OH} \quad \text{OH}
\]

(−)-Malic acid \[\alpha_D = -2.3^\circ\]

\[
\text{HO} \quad \text{Cl} \\
\text{O} \quad \text{OH} \\
\text{HO} \quad \text{OH} \\
\text{OH} \quad \text{OH}
\]

(−)-Chlorosuccinic acid

\[
\text{HO} \quad \text{Cl} \\
\text{O} \quad \text{OH} \\
\text{HO} \quad \text{OH} \\
\text{OH} \quad \text{OH}
\]

(−)-Chlorosuccinic acid

\[
\text{HO} \quad \text{Cl} \\
\text{O} \quad \text{OH} \\
\text{HO} \quad \text{OH} \\
\text{OH} \quad \text{OH}
\]

(+)-Malic acid \[\alpha_D = +2.3^\circ\]

Some reactions in the cycle must have occurred with an inversion of the configuration at the stereocenter through nucleophilic substitution reactions.

**Nucleophilic substitution reaction (SN):** A nucleophile (Nu or Nu\(^{-}\)) reacts with a substrate R–X and substitutes for a leaving group X\(^{-}\) to yield the product R–Nu.

Neutral Nu\(^{+}\): \[\text{Nu}^{+} + \text{R–X} \rightarrow \text{R–Nu}^{+} + \text{X}^{-}\]

Negatively charged Nu\(^{-}\): \[\text{Nu}^{-} + \text{R–X} \rightarrow \text{R–Nu}^{-} + \text{X}^{-}\]
\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{Cl} & \quad + \quad \text{HO}^- \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{OH} & \quad + \quad \text{Cl}^- & \quad \text{an alcohol} \\
\text{CH}_3\text{CH}_2\text{Br} & \quad + \quad \text{HS}^- \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{SH} & \quad + \quad \text{Br}^- & \quad \text{a thiol} \\
\text{CH}_3\text{CH}_2\text{I} & \quad + \quad \text{RO}^- \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{OR} & \quad + \quad \text{I}^- & \quad \text{an ether} \\
\text{CH}_3\text{CH}_2\text{Br} & \quad + \quad \text{RS}^- \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{SR} & \quad + \quad \text{Br}^- & \quad \text{a thioether} \\
\text{CH}_3\text{CH}_2\text{Cl} & \quad + \quad \text{NH}_2^- \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{NH}_2 & \quad + \quad \text{Cl}^- & \quad \text{a primary amine} \\
\text{CH}_3\text{CH}_2\text{Br} & \quad + \quad \text{C}≡\text{CR} \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{C}≡\text{CR} & \quad + \quad \text{Br}^- & \quad \text{an alkyne} \\
\text{CH}_3\text{CH}_2\text{I} & \quad + \quad \text{C}≡\text{N} \quad \longrightarrow \quad \text{CH}_3\text{CH}_2\text{C}≡\text{N} & \quad + \quad \text{I}^- & \quad \text{a nitrile}
\end{align*}
\]
7.5 The S_N2 Reaction

**S_N2 – substitution, nucleophilic, bimolecular**

An S_N2 reaction takes place in a **single step without intermediates** when the entering nucleophile attacks the substrate from a direction 180° away from the leaving group.

**Mechanism**

![Chemical reaction image]

The nucleophile HO\(^-\) uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a **transition state** with a partially formed C–OH bond and a partially broken C–Br bond.

The **stereochemistry** at carbon is inverted as the C–OH bond forms fully and the bromide ion departs with the electron pair from the former C–Br bond.

**Evidence and Chemical Consequences of the above mechanism**

1. **Rates of S_N2 Reactions**

   *The determination of reaction rates and of how those rates depend on reactant concentrations is a powerful tool for probing mechanism.*

   The rate of the reaction depends on the concentrations of two substrates.

   **Rate = [HO\(^-\)][CH\(_3\)–Br]**
2. Stereochemistry of S_N2 Reactions
An inversion of configuration occurs through a planar transition state.

3. Steric Effects in S_N2 Reactions
The ease with which a nucleophile can approach a substrate to carry out an S_N2 reaction depends on spatial accessibility. Bulky substrates, in which the halide-bearing carbon atom is difficult to approach (steric hindrance), react much more slowly than those in which the carbon is more accessible.
No $S_N2$ reaction for vinylic ($R_2C=CRX$) and aryl halides ($Ar-\cdot X$).
4. The Leaving Group in $S_N2$ Reactions

The best leaving groups are those that give the most stable anions (anions of strong acids).

A halide ion (I$^-$, Br$^-$, or Cl$^-$) is the most common leaving group. Anions such as F$^-$, OH$^-$, OR$^-$, and NH$_2^-$ are rarely found as leaving groups.

Relative Reactivity

<table>
<thead>
<tr>
<th>OH$^-$</th>
<th>NH$_2^-$</th>
<th>OR$^-$</th>
<th>F$^-$</th>
<th>Cl$^-$</th>
<th>Br$^-$</th>
<th>I$^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>≪ 1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

less reactive → more reactive
7.6 The S\textsubscript{N}1 Reaction

\textbf{S\textsubscript{N}1 – substitution, nucleophilic, unimolecular}

S\textsubscript{N}1 reactions take place on tertiary substrates and under neutral or acidic conditions in a hydroxylic solvent such as water or alcohol. S\textsubscript{N}1 reaction occurs by spontaneous loss of the leaving group before the incoming nucleophile approaches, producing a carbocation intermediate, which then reacts with nucleophile in a second step to yield the substitution product.

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (a) at (0,0) {\textbf{tert-butyl bromide}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (b) at (2,0) {\textbf{tert-butyl alcohol}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (c) at (0,-1) {\textbf{CH}_3\text{--C--Br}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (d) at (2,-1) {\textbf{CH}_3\text{--C--OH}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (e) at (4,-1) {\textbf{CH}_3\text{--C--OH} \ + \ \textbf{HBr}};
  \draw (a) -- (b);
  \draw (c) -- (d) node[midway,above] {\textbf{CH}_3\text{--C--OH}};
  \draw (d) -- (e) node[midway,above] {\textbf{HBr}};
\end{tikzpicture}
\end{center}

\textbf{mechanism of the S\textsubscript{N}1 reaction}

\begin{center}
\begin{tikzpicture}
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (a) at (0,0) {\textbf{CH}_3\text{--C--Br}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (b) at (2,0) {\textbf{CH}_3\text{--C--OH} \ + \ \textbf{HBr}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (c) at (0,-1) {\textbf{CH}_3\text{--C--Br}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (d) at (2,-1) {\textbf{CH}_3\text{--C--OH}};
  \node[draw,shape=rectangle,minimum width=2cm,minimum height=2cm,align=center] (e) at (4,-1) {\textbf{CH}_3\text{--C--OH} \ + \ \textbf{H^+}};
  \draw (a) -- (b) node[midway,above] {\textbf{CH}_3\text{--C--OH}};
  \draw (c) -- (d) node[midway,above] {\textbf{CH}_3\text{--C--OH}};
  \draw (d) -- (e) node[midway,above] {\textbf{H^+}};
\end{tikzpicture}
\end{center}

\textbf{Step 1.} Spontaneous dissociation of the C–Br bond occurs in a slow, rate-limiting step to yield a carbocation intermediate.

\textbf{Step 2.} The carbocation intermediate reacts with water in a fast step to yield the alkyloxonium ion intermediate.

\textbf{Step 3.} Dissociation of proton from the alkyloxonium ion intermediate in a fast step produces the neutral substitution product.

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1. Rates of $S_N1$ Reactions
The rate of an $S_N1$ reaction depends only on the concentration of the substrate and is independent of the nucleophile concentration. The substrate must undergo a spontaneous reaction to produce a carbocation intermediate without involvement of the nucleophile. Thus, the reactivity order of substrates is the same as the stability order of carbocations.

<table>
<thead>
<tr>
<th>Alkyl bromide</th>
<th>Class of alkyl bromide</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3$</td>
<td>primary $\text{Br}$</td>
<td>1.00*</td>
</tr>
<tr>
<td>$\text{C(H)} - \text{Br}$</td>
<td>secondary $\text{CH}_3$</td>
<td>11.6</td>
</tr>
<tr>
<td>$\text{C(H)} - \text{Br}$</td>
<td>tertiary $\text{CH}_3$</td>
<td>1,200,000</td>
</tr>
<tr>
<td>$\text{C(H)} - \text{Br}$</td>
<td>methyl $\text{CH}_3$</td>
<td>1.05*</td>
</tr>
</tbody>
</table>

*Although the rate of the $S_N1$ reaction of this compound with water is 0, a small rate is observed as a result of an $S_N2$ reaction.

2. Stereochemistry of $S_N1$ Reactions
Carbocations are planar and $sp^2$-hybridized, and they are achiral. The positively charged carbon can therefore react with a nucleophile equally well from either top or bottom face, leading to a racemic mixture of enantiomers.
3. The Leaving Group in $S_N1$ Reactions

The best leaving groups in $S_N1$ reactions are those that give the most stable anions, just as in $S_N2$ reactions.

$$F^- << Cl^- = H_2O < Br^- < I^-$$

Worse leaving group $\rightarrow$ Better leaving group

7.7 Eliminations: The $E_2$ Reaction

Nucleophile ($Nu^-$) vs. Base ($B^-$)

The nucleophile can substitute for the leaving group in an $S_N1$ or $S_N2$ reaction, and the base can cause elimination of HX, leading to formation of an alkene.

**Substitution**

$$\text{BrCH}_2\text{CH}_3 + \text{OH}^- \rightarrow \text{HOCH}_2\text{CH}_3 + \text{Br}^-$$

**Elimination**

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

Elimination reactions almost always give mixtures of alkene products.

**1875, Zaitsev's rule:** Base-induced elimination reactions generally give the more highly substituted alkene product – that is, the alkene with the larger number of substituents on the double bond.
E2 reaction – elimination, bimolecular

E2 reaction takes place in one step without intermediates, through a transition state in which the double bond begins to form at the same time the H and X groups are leaving. The process takes place when an alkyl halide is treated with a strong base (HO\(^-\)).
7.8 Eliminations: The E₁ Reaction

**E₁ reaction – elimination, unimolecular**

E₁ eliminations begin with the same unimolecular dissociation as the one in S₁N₁ reaction, but the dissociation is followed by loss of H⁺ from the intermediate carbocation rather than by substitution.

\[
\begin{align*}
\text{CH}_3\text{C–CH}_3 \quad + \quad \text{H}_2\text{O} \quad &\rightarrow \quad \text{CH}_2=\text{C–CH}_3 \quad + \quad \text{H}_3\text{O}^+ \quad + \quad \text{Br}^- \\
\text{tert-butyl bromide} &
\end{align*}
\]

**mechanism of the E₁ reaction**

**Step 1.** Spontaneous dissociation of the tertiary alkyl bromide yields an intermediate carbocation in a slow, rate-limiting step.

**Step 2.** Loss of neighboring H⁺ in a fast step yields the neutral alkene product. The electron pair from the C–H bond goes to form the alkene π bond.
E1 and S_N1 reactions may occur in competition.

\[
\text{CH}_3\text{C} - \text{C} - \text{Cl} \xrightarrow{\text{H}_2\text{O}, \text{ethanol}} \text{65 °C} \rightarrow \text{CH}_3\text{C} - \text{C} - \text{OH} + \text{H}_3\text{C} = \text{C} = \text{H} \\
\text{64%} \quad \text{36%}
\]

7.9 A Summary of Reactivity: S_N1, S_N2, E1, E2

How to predict what will take place in any given case (Substitution – Elimination, Unimolecular – Bimolecular).

**a primary alkyl halide**

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_3\text{O}^- \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 + \text{CH}_3\text{CH} = \text{CH}_2 + \text{CH}_3\text{OH} + \text{Br}^- \\
\text{propyl bromide} \quad \text{methyl propyl ether} \quad \text{90%} \quad \text{propene} \quad \text{10%}
\]

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**a secondary alkyl halide**

\[
\text{CH}_3\text{CHCH}_3 + \text{CH}_3\text{O}^- \xrightarrow{\text{CH}_3\text{OH}} \text{OCH}_2\text{CH}_3 + \text{CH}_3\text{CHCH}_3 + \text{CH}_3\text{CH} = \text{CH}_2 + \text{CH}_3\text{OH} + \text{Cl}^- \\
\text{2-chloropropane} \quad \text{ethyl isopropyl ether} \quad \text{25%} \quad \text{propene} \quad \text{75%}
\]

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A primary substrate reacts by an **S\text{N}2** pathway if a good nucleophile such as I\text{−}, Br\text{−}, RS\text{−}, NH_3\text{−}, or CN\text{−}, is used. Some reaction by an E2 pathway may accompany the S\text{N}2 reaction if a strong base such as HO\text{−} or RO\text{−} is used.

- A secondary substrate reacts by both S\text{N}2 and E2 pathways to give a mixture of substitution and elimination products.

A tertiary substrate reacts by an **E2** pathway if a strong base is used or by a mixture of S\text{N}1 and E1 pathways under neutral or acidic conditions.

Chap_07_SN1,2-E1,2.ppt
**Saytzeff** rule: more highly substituted alkene

E1 elimination, base induced elimination of alkyl halides and aryl sulfonates

\[ \text{HO} \quad \xrightarrow{\text{PCl}_5} \quad \text{Br} \quad \xrightarrow{\text{NaOEt}} \quad \text{EtOH} \]

\[ \text{81\%} \quad + \quad \text{19\%} \]

**Hofmann** rule: less substituted alkene

base induced elimination of quaternary ammonium salts or sulfonium salts

\[ \xrightarrow{\text{NaOEt}} \quad \text{EtOH} \]

\[ \text{26\%} \quad + \quad \text{74\%} \]

\[ \xrightarrow{\text{H}_2\text{O, KOH}} \quad 130 \degree\text{C} \]

\[ \text{98\%} \quad + \quad \text{2\%} \]