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
  - Volcanoes and marine kelp release up 5 million tons of CH3Cl per year
  - Industrial emissions release about 26 tons of Chloroform, bromophenoles and bromoindoles per year (nonnatural pollutants)
Organohalides

- Trichloroethylene (a solvent)
- Halothane (an inhaled anesthetic)
- Dichlorodifluoromethane (a refrigerant)
- Bromomethane (a fumigant)

Epibatidine (from the Ecuadorian frog *Epipedobates tricolor*)

Vancomycin
Why this Chapter?

- We'll begin in this chapter with a look at how to name and prepare alkyl halides, and we'll see several of their 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)

5-Bromo-2,4-dimethylheptane

2-Bromo-4,5-dimethylheptane
If different halogens are present, number all and list them in alphabetical order when writing the name.

1-Bromo-3-chloro-4-methylpentane
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.

2-Bromo-5-methylhexane
(NOT 5-bromo-2-methylhexane)
Many simple alkyl halides are also named by identifying first the alkyl group and then the halogen.

- **Iodomethane** (or methyl iodide)
- **2-Chloropropane** (or isopropyl chloride)
- **Bromocyclohexane** (or cyclohexyl bromide)
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 slight positive on carbon and slight negative on halogen

Table 10.1 | A Comparison of the Halomethanes

<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>

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10.3 Preparing Alkyl Halides from Alkanes: Radical Halogenation

- The reaction of an alkane with Cl\textsubscript{2} or Br\textsubscript{2} through a radical chain-reaction pathway.

\[ \text{Initiation step: } \text{Cl} - \text{Cl} \xrightarrow{h\nu} 2 \text{ Cl}^\cdot \]

\[ \text{Propagation steps (a repeating cycle):} \]

\[ \text{Step 1: } H_3C^-H + \text{Cl}^\cdot \rightarrow H^-\text{Cl} + H_3C^-\text{Cl} \]

\[ \text{Step 2: } H^-\text{Cl} + \text{Cl}^-\text{Cl} \rightarrow \text{Cl}^-\text{Cl} + H_3C^-\text{Cl} \]

\[ \text{Termination steps:} \]

\[ H_3C^-\text{Cl} + \cdot\text{CH}_3 \rightarrow H_3C^-\cdot\text{CH}_3 \]

\[ \text{Cl}^\cdot + \cdot\text{CH}_3 \rightarrow \text{Cl}^-\text{CH}_3 \]

\[ \text{Cl}^\cdot + \cdot\text{Cl} \rightarrow \text{Cl}^-\text{Cl} \]

\[ \text{Overall reaction: } CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \]
10.3 Preparing Alkyl Halides from Alkanes: Radical Halogenation

- Alkane + Cl$_2$ or Br$_2$, 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

\[
\begin{align*}
\text{CH}_4 & + \text{Cl}_2 \xrightarrow{hv} \text{CH}_3\text{Cl} + \text{HCl} \\
\text{CH}_2\text{Cl}_2 & \xrightarrow{\text{Cl}_2} \text{CHCl}_3 + \text{HCl} \\
\text{CHCl}_3 & \xrightarrow{\text{Cl}_2} \text{CCl}_4 + \text{HCl}
\end{align*}
\]
Radical Halogenation of Alkanes

- If there is more than one type of hydrogen in an alkane, reactions favor replacing the hydrogen at the most highly substituted carbons (not absolute).

\[
\text{Butane} + \text{Cl}_2 \xrightarrow{h\nu} \text{1-Chlorobutane} + \text{2-Chlorobutane} \\
\text{2-Methylpropane} + \text{Cl}_2 \xrightarrow{h\nu} \text{2-Chloro-2-methylpropane} + \text{1-Chloro-2-methylpropane}
\]

Dichloro-, trichloro-, tetrachloro-, and so on

30 : 70

35 : 65
Relative Reactivity

- Based on quantitative analysis of reaction products, relative reactivity is expected.
- Order parallels stability of radicals.
- Reaction difference is more selective with bromine than chlorine.
10.4 Preparing Alkyl Halides from Alkenes: Allylic Bromination

There are several methods for preparing alkyl halides from alkenes, including the reaction of HX and X₂ with alkene in electrophilic addition reactions.

- N-bromosuccinimide (NBS) selectively brominates allylic positions
- Requires light for activation
- A source of dilute bromine atoms

\[ \text{Cyclohexene} \rightarrow \text{3-Bromocyclohexene (85\%)} \]
Allylic Stabilization

- Allyl radical is electron delocalized
- More stable than typical alkyl radical by 45 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, useful in synthesis of complex molecules

Cyclohexene \( \xrightarrow{\text{NBS}} \) 3-Bromocyclohexene \( \xrightarrow{\text{KOH}} \) 1,3-Cyclohexadiene
10.5 Stability of the Allyl Radical: Resonance Revisited

- Three electrons are delocalized over three carbons
- Spin density surface shows single electron is dispersed
Allylic bromination of an unsymmetrical alkene often leads to a mixture of products.
What products would you expect from reaction of 4,4-dimethylcyclohexene with NBS?

3-Bromo-4,4-dimethylcyclohexene + 3-Bromo-6,6-dimethylcyclohexene = 3-Bromo-5,5-dimethylcyclohexene
The major product of the reaction of methylenecyclohexane with N-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.
10.6 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
The reaction of HX (HCl or HBr) with a tertiary alcohol

Primary and secondary alcohols are best converted into alkyl halides by treatment with thionyl chloride (SOCl₂) or phosphorus tribromide (PBr₃).
How would you prepare the following alkyl halides from the corresponding alcohols?

(a) \( \text{Cl} \) 
\[ \text{CH}_3\text{CCH}_3 \]
\[ \text{CH}_3 \]

(b) \( \text{Br} \) \( \text{CH}_3 \) 
\[ \text{CH}_3\text{CHCH}_2\text{CHCH}_3 \]

(c) \( \text{CH}_3 \) 
\[ \text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3 \]

(d) \( \text{CH}_3 \) \( \text{Cl} \) 
\[ \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CHCH}_3 \]
10.7 Reactions of Alkyl Halides: Grignard Reagents

- Reaction of RX with Mg in ether or THF
- Product is RMgX – an organometallic compound (alkyl-metal bond)(alkylmagnesium halides) called Grignard reagents
  - R is alkyl 1°, 2°, 3°, aryl, alkenyl
  - X = Cl, Br, I

![Chemical reaction diagram]

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} & \xrightarrow{\text{Mg, Ether}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr} & \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
\]

1-Bromohexane \rightarrow 1-Hexylmagnesium bromide \rightarrow Hexane (85%)
10.8 Organometallic combination Reactions

- Alkylolithium (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. The reaction is useful in Organic synthesis, preparation of larger molecules from smaller ones.
The value of Organometallic Coupling in Synthesis

- Coupling of two organometallic molecules produces larger molecules of defined structure
- Aryl and vinyl organometallics also effective
- Coupling of lithium dialkylcopper molecules proceeds through trialkylcopper intermediate

\[
\begin{align*}
\text{trans-1-Iodo-1-nonene} & \quad + \quad (n-C_4H_9)_2CuLi & \quad \rightarrow & \quad \text{trans-5-Tridecene (71\%)} \\
\text{Iodobenzene} & \quad + \quad (CH_3)_2CuLi & \quad \rightarrow & \quad \text{Toluene (91\%)}
\end{align*}
\]
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.

- Oxidation is a reaction that results in loss of electron density at carbon (as more electronegative atoms replace hydrogen or carbon).

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

- Organic reduction is the opposite of oxidation
- Results in gain of electron density at carbon (replacement of electronegative atoms by hydrogen or carbon)

Reduction: form C-H (or C-C) and break C-O, C-N, C-X
**Ethylene** + **Br**₂ → **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 levels
- Any reaction that converts a compound from a lower level to a higher level is an oxidation.
- Any reaction that converts a compound from higher level to a lower level is a reduction
- Any reaction that doesn't change the level is neither an oxidation nor a reduction.

<table>
<thead>
<tr>
<th>Low oxidation level</th>
<th>H₂C＝CH₂</th>
<th>CH₃OH</th>
<th>CH₃Cl</th>
<th>CH₃NH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HC≡CH</td>
<td>H₂C＝O</td>
<td>H₂C＝N</td>
<td>HC≡N</td>
</tr>
<tr>
<td></td>
<td>HCO₂H</td>
<td>CHCl₃</td>
<td>CHCl₃</td>
<td>CO₂</td>
</tr>
<tr>
<td></td>
<td>CCl₄</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High oxidation level
Comparing oxidation levels of compounds

Rank the following compounds in order of increasing oxidation level:

- a) $CH_3CH=CH_2$, $CH_3CHCH_3$, $CH_3CCH_3$, $CH_3CH_2CH_3$
- b) $CH_3C=CH$, $CH_3C=CH$, $CH_3C=CH$, $CH_3C=CH$
- c) $CH_3CN$, $CH_3CH_2NH_2$, $H_2NCH_2CH_2NH_2$
Tell whether each of the following reaction is an oxidation, a reduction, or neither.

(a) \[ \text{CH}_3\text{CH}_2\text{CH} \quad \overset{\text{NaBH}_4}{\text{H}_2\text{O}} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \]

(b) \[ \text{hexene} \quad \overset{1. \text{BH}_3}{\text{2. NaOH, H}_2\text{O}_2} \quad \rightarrow \quad \text{OH} \]}