Chapter 6
Alkyl Halides: Nucleophilic Substitution and Elimination

Classes of Halides
- Alkyl: Halogen, X, is directly bonded to \( sp^3 \) carbon.
- Vinyl: X is bonded to \( sp^2 \) carbon of alkene.
- Aryl: X is bonded to \( sp^2 \) carbon on benzene ring.

Examples:

\[
\text{alkyl halide: } H-C-C-Br
\]
\[
\text{vinyl halide: } H=CH-C=Br
\]
\[
\text{aryl halide: } \text{Ph} - I
\]

Polarity and Reactivity
- Halogens are more electronegative than C.
- Carbon-halogen bond is polar, so carbon has partial positive charge.
- Carbon can be attacked by a nucleophile.
- Halogen can leave with the electron pair.

\[
\text{alkyl halide: } H-C-C-Br
\]

Classes of Alkyl Halides
- Methyl halides: only one C, \( \text{CH}_3X \)
- Primary: C to which X is bonded has only one C-C bond.
- Secondary: C to which X is bonded has two C-C bonds.
- Tertiary: C to which X is bonded has three C-C bonds.

Classify These:

- \( \text{CH}_3-\text{CH}-\text{CH}_3 \)
- \( \text{CH}_3\text{CH}_2\text{F} \)
- \( (\text{CH}_3)_3\text{CBr} \)
- \( \text{CH}_3\text{I} \)

Dihalides
- Geminal dihalide: two halogen atoms are bonded to the same carbon
- Vicinal dihalide: two halogen atoms are bonded to adjacent carbons.
IUPAC Nomenclature

- Name as haloalkane.
- Choose the longest carbon chain, even if the halogen is not bonded to any of those C's.
- Use lowest possible numbers for position.

\[ \text{CH}_3\text{CH}(-\text{Cl})\text{CH}_2\text{CH}_3 \quad \text{2-chlorobutane} \]

\[ \text{CH}_3\text{CH}_2\text{CH}(-\text{Cl})\text{CH}_2\text{CH}_3 \quad \text{4-(2-bromoethyl)heptane} \]

Systematic Common Names

- Name as alkyl halide.
- Useful only for small alkyl groups.
- Name these:

\[ \text{CH}_3\text{CH}(-\text{Cl})\text{CH}_2\text{CH}_3 \quad \text{(CH}_3\text{)}_2\text{CBr} \]

\[ \text{CH}_3\text{CH}(-\text{Cl})\text{CH}(-\text{Br})\text{CH}_3 \quad \text{CH}_3\text{CH}(-\text{Br})\text{CH}_2\text{CH}_3 \]

“Trivial” Names

- \text{CH}_2\text{X}_2 \text{ called methylene halide.}
- \text{CHX}_3 \text{ is a haloform.}
- \text{CX}_4 \text{ is carbon tetrahalide.}
- Examples:
  - \text{CH}_2\text{Cl}_2 \text{ is methylene chloride}
  - \text{CHCl}_3 \text{ is chloroform}
  - \text{CCl}_4 \text{ is carbon tetrachloride.}

Uses of Alkyl Halides

- Solvents - degreasers and dry cleaning fluid
- Reagents for synthesis of other compounds
- Anesthetic: Halothane is \text{CF}_3\text{CHClBr}
- Freons, chlorofluorocarbons or CFC’s
  - Freon 12, \text{CF}_2\text{Cl}_2, \text{now replaced with Freon 22, CF}_3\text{CHCl}, \text{not as harmful to ozone layer.}
- Pesticides - DDT banned in U.S.

Dipole Moments

- \( \mu = 4.8 \times \delta \times d \), where \( \delta \) is the charge (proportional to \( \Delta EN \)) and \( d \) is the distance (bond length) in Angstroms.
- Electronegativities: \( F > Cl > Br > I \)
- Bond lengths: \( C-F < C-Cl < C-Br < C-I \)
- Bond dipoles: \( C-Cl > C-F > C-Br > C-I \)
  - 1.56 D  1.51 D  1.48 D  1.29 D
- Molecular dipoles depend on shape, too!

Boiling Points

- Greater intermolecular forces, higher b.p.
  - dipole-dipole attractions not significantly different for different halides
  - London forces greater for larger atoms
- Greater mass, higher b.p.
- Spherical shape decreases b.p.
  - \( \text{CH}_3\text{Br} \) 73°C  \( \text{CH}_3\text{(CH}_2\text{)}_2\text{Br} \) 102°C
Densities

- Alkyl fluorides and chlorides less dense than water.
- Alkyl dichlorides, bromides, and iodides more dense than water.

Preparation of RX

- Free radical halogenation (Chapter 4)
  - produces mixtures, not good lab synthesis
  - unless: all H's are equivalent, or
  - halogenation is highly selective.
- Free radical allylic halogenation
  - produces alkyl halide with double bond on the neighboring carbon.

Halogenation of Alkanes

- All H's equivalent. Restrict amount of halogen to prevent di- or trihalide formation
- Highly selective: bromination of 3°C

\[
\begin{align*}
\text{CH}_3\text{CH} = \text{CH}_2 + \text{Br}_2 & \xrightarrow{hv} \text{CH}_3\text{CH} = \text{CH}\text{Br} + \text{HBr} \\
\end{align*}
\]

Allylic Halogenation

- Allylic radical is resonance stabilized.
- Bromination occurs with good yield at the allylic position (sp³ C next to C=C).
- Avoid a large excess of Br₂ by using N-bromosuccinimide (NBS) to generate Br₂ as product HBr is formed.

\[
\begin{align*}
\text{N-Br} + \text{HBr} & \rightarrow \text{N-H} + \text{Br}_2 \\
\end{align*}
\]

Reaction Mechanism

Free radical chain reaction
- initiation, propagation, termination.

\[
\begin{align*}
\text{Br}_2 & \xrightarrow{hv} 2 \text{Br}^- \\
\end{align*}
\]

Substitution Reactions

- The halogen atom on the alkyl halide is replaced with another group.
- Since the halogen is more electronegative than carbon, the C-X bond breaks heterolytically and X⁻ leaves.
- The group replacing X⁻ is a nucleophile.
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Elimination Reactions

\[ \text{H} - \text{S} - \text{Hal} + \text{B}^- \rightarrow \text{C} = \text{C}^- + \text{Hal}^- + \text{HB} \]

- The alkyl halide loses halogen as a halide ion, and also loses H⁺ on the adjacent carbon to a base.
- A pi bond is formed. Product is alkene.
- Also called dehydrohalogenation (-HX).

SN₂ Mechanism

- Bimolecular nucleophilic substitution.
- Concerted reaction: new bond forming and old bond breaking at same time.
- Rate is first order in each reactant.
- Walden inversion.

SN₂ Energy Diagram

- One-step reaction.
- Transition state is highest in energy.

Uses for SN₂ Reactions

- Synthesis of other classes of compounds.
- Halogen exchange reaction.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>Class of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-X + I⁻</td>
<td>R-I</td>
<td>alkyl halide</td>
</tr>
<tr>
<td>R-X + OH⁻</td>
<td>R-OH</td>
<td>alcohol</td>
</tr>
<tr>
<td>R-X + Br⁻</td>
<td>R-Br</td>
<td>thiol</td>
</tr>
<tr>
<td>R-X + NH₃</td>
<td>R-NH₂⁺</td>
<td>amine salt</td>
</tr>
<tr>
<td>R-X + N₃⁻</td>
<td>R-N₃</td>
<td>azide</td>
</tr>
<tr>
<td>R-X + C≡C⁻</td>
<td>R-C≡C⁻</td>
<td>alkyne</td>
</tr>
<tr>
<td>R-X + C≡N</td>
<td>R-C≡N</td>
<td>nitrile</td>
</tr>
<tr>
<td>R-X + R-COO⁻</td>
<td>R-COO⁻</td>
<td>ester</td>
</tr>
</tbody>
</table>

SN₂: Nucleophilic Strength

- Stronger nucleophiles react faster.
- Strong bases are strong nucleophiles, but not all strong nucleophiles are basic.

Trends in Nuc. Strength

- Of a conjugate acid-base pair, the base is stronger: \( \text{OH}^- > \text{H}_2\text{O} \), \( \text{NH}_2^- > \text{NH}_3 \)
- Decreases left to right on Periodic Table. More electronegative atoms less likely to form new bond: \( \text{OH}^- > \text{F}^- \), \( \text{NH}_3 > \text{H}_2\text{O} \)
- Increases down Periodic Table, as size and polarizability increase: \( \text{I}^- > \text{Br}^- > \text{Cl}^- \)
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Polarizability Effect

Sterically hindered for attack on carbon, so weaker nucleophiles.

CH₃CH₂O⁻ (unhindered) weaker base, but stronger nucleophile

C

CH₃

O

t-butoxide (hindered) stronger base, but weaker nucleophile

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Bulky Nucleophiles

Sterically hindered for attack on carbon, so weaker nucleophiles.

CH₃—CH₂—O⁻

ethoxide (unhindered)

weaker base, but stronger nucleophile

CH₃

H₃C—C—O⁻

CH₃

CH₃

CH₃

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Solvent Effects (1)

Polar protic solvents (O-H or N-H) reduce the strength of the nucleophile. Hydrogen bonds must be broken before nucleophile can attack the carbon.

CH₃CN

acetone

dimethylformamide (DMF)

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Solvent Effects (2)

• Polar aprotic solvents (no O-H or N-H) do not form hydrogen bonds with nucleophile

• Examples:

CH₃—C≡N

acetonitrile

O

K⁺

18-crown-6

CH₂Cl

KF, (18-crown-6)

CH₃CN

CH₂F

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Crown Ethers

• Solvate the cation, so nucleophilic strength of the anion increases.

• Fluoride becomes a good nucleophile.

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S_N2: Reactivity of Substrate

• Carbon must be partially positive.

• Must have a good leaving group

• Carbon must not be sterically hindered.
Leaving Group Ability

• Electron-withdrawing
• Stable once it has left (*not* a strong base)
• Polarizable to stabilize the transition state.

<table>
<thead>
<tr>
<th>Base</th>
<th>Halide</th>
<th>3°</th>
<th>2°</th>
<th>1°</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>0.7</td>
<td>1.2</td>
<td>1.5</td>
<td>2.4</td>
</tr>
<tr>
<td>alcohol</td>
<td>2.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>amines</td>
<td>3.9</td>
<td>2.0</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>phosphines</td>
<td>4.6</td>
<td>3.9</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Structure of Substrate

• Relative rates for $S_N^2$:
  $CH_3X > 1° > 2° >> 3°$

• Tertiary halides do not react via the $S_N^2$ mechanism, due to steric hindrance.

Stereochemistry of $S_N^2$

Walden inversion

SN1 Reaction

• Unimolecular nucleophilic substitution.
• Two step reaction with carbocation intermediate.
• Rate is first order in the alkyl halide, zero order in the nucleophile.
• Racemization occurs.

SN1 Mechanism (1)

Formation of carbocation (slow)

$\text{(CH}_3\text{)}_3\text{CBr} \rightleftharpoons \text{(CH}_3\text{)}_3\text{C}^+ + \text{Br}^-$

SN1 Mechanism (2)

• Nucleophilic attack
  $\text{(CH}_3\text{)}_3\text{C}^+ + \text{H}_2\text{O} \rightarrow \text{(CH}_3\text{)}_3\text{C}^\ominus + \text{H}_3\text{O}^+$

• Loss of $H^+$ (if needed)
  $\text{(CH}_3\text{)}_3\text{C}^\ominus + \text{H}_2\text{O} \rightarrow \text{(CH}_3\text{)}_3\text{C}^\ominus + \text{H}_3\text{O}^+$
**S_N1 Energy Diagram**

- Forming the carbocation is endothermic
- Carbocation intermediate is in an energy well.

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**Rates of S_N1 Reactions**

- \(3^\circ > 2^\circ > 1^\circ \gg \text{CH}_3\text{X}\)
  - Order follows stability of carbocations (opposite to \(S_N2\))
  - More stable ion requires less energy to form
- Better leaving group, faster reaction (like \(S_N2\))
- Polar protic solvent best: It solvates ions strongly with hydrogen bonding.

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**Stereochemistry of S_N1**

Racemization: inversion and retention

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**Rearrangements**

- Carbocations can rearrange to form a more stable carbocation.
- Hydride shift: \(\text{H}^+\) on adjacent carbon bonds with \(\text{C}^+\).
- Methyl shift: \(\text{CH}_3\) moves from adjacent carbon if no \(\text{H}\)'s are available.

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**Hydride Shift**

![Hydride Shift Diagram]

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**Methyl Shift**

![Methyl Shift Diagram]
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**SN2 or SN1?**

- Primary or methyl
- Strong nucleophile
- Polar aprotic solvent
- Rate = $k[\text{halide}][\text{Nuc}]$
- Inversion at chiral carbon
- No rearrangements

**E1 Reaction**

- Unimolecular elimination
- Two groups lost (usually $X^-$ and $H^+$)
- Nucleophile acts as base
- Also have $SN_1$ products (mixture)

**E1 Mechanism**

- Halide ion leaves, forming carbocation.
- Base removes $H^+$ from adjacent carbon.
- Pi bond forms.

**E1 Energy Diagram**

- Note: first step is same as $SN_1$

**E2 Reaction**

- Bimolecular elimination
- Requires a strong base
- Halide leaving and proton abstraction happens simultaneously - no intermediate.
E2 Mechanism

\[ \text{H}_2\text{O} + \text{Br}^- \rightarrow \text{H} = \text{C} = \text{C} - \text{CH}_3 + \text{H} = \text{C} = \text{CH}_3 \]

Saytzeff’s Rule
- If more than one elimination product is possible, the most-substituted alkene is the major product (most stable).
- \( R_4\text{C} = \text{CR}_2 > R_3\text{C} = \text{CHR} > R_2\text{C} = \text{CHR} > R\text{C} = \text{CHR} \)
i.e., tetra > tri > di > mono

E2 Stereochemistry
- Tertiary > Secondary
- Weak base
- Good ionizing solvent
- Rate = \( k[\text{halide}] \)
- Saytzeff product
- No required geometry
- Rearranged products

E1 or E2?
- Tertiary > Secondary
- Strong base required
- Solvent polarity not important
- Rate = \( k[\text{halide}][\text{base}] \)
- Saytzeff product
- Coplanar leaving groups (usually anti)
- No rearrangements

Substitution or Elimination?
- Strength of the nucleophile determines order: Strong nuc. will go \( S_N2 \) or E2.
- Primary halide usually \( S_N2 \).
- Tertiary halide mixture of \( S_N1 \), E1 or E2
- High temperature favors elimination.
- Bulky bases favor elimination.
- Good nucleophiles, but weak bases, favor substitution.

Secondary Halides?
Mixtures of products are common.
End of Chapter 6