ALKYL HALIDES

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LEARNING OBJECTIVES

Students will be able to learn;

- Method of Preparations
- SN2 Reactions & SN1 Reactions
**INTRODUCTION:**

Alkyl halides: Organic molecules containing a halogen atom bonded to an $sp^3$ hybridized carbon atom.

Alkyl halides: Classified as primary ($1^\circ$), secondary ($2^\circ$), or tertiary ($3^\circ$), depending on the number of carbons bonded to the carbon with the halogen atom.
Common Name: Alkyl halide (chloride, bromide, iodide, fluoride)

IUPAC Name: As rules of Alkane
halogen write as halo like chloro, bromo, iodo, fluoro

CH₃CH₂CH₂CH₂-Br

n-butyl bromide
1-bromobutane

Uses: Pesticides
Refrigerants (freons)
Solvents
Synthetic intermediates
SYNTHESIS OF ALKYL HALIDE

1. From alcohols

a) $\text{HX}$

$$\text{R-OH} + \text{HX} \rightarrow \text{R-X} + \text{H}_2\text{O}$$

$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{-OH} + \text{NaBr, H}_2\text{SO}_4, \text{heat} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{-Br}$

$n$-Butyl alcohol (HBr) $n$-Butyl bromide

[1-Butanol] [1-Bromobutane]

b) $\text{PX}_3$

$\text{PX}_3 = \text{PCl}_3, \text{PBr}_3, \text{P} + \text{I}_2$

$$\text{CH}_3\text{CH}_2\text{-OH} + \text{P, I}_2 \rightarrow \text{CH}_3\text{CH}_2\text{-I}$$

Ethyl alcohol Ethyl iodide

Ethanol Iodoethane
2. Halogenation of certain hydrocarbons

\[ R-H + X_2, \Delta \text{ or } h\nu \rightarrow R-X + HX \]

\[
\begin{align*}
\text{CH}_3 \\
\text{CH}_3\cdot\text{C}-\text{CH}_3 + \text{Cl}_2, \text{heat} & \rightarrow \text{CH}_3\cdot\text{C}-\text{CH}_2-\text{Cl} \\
\text{CH}_3 \\
\text{Neopentane} & \rightarrow \text{Neopentyl chloride} \\
\text{2,2-Dimethylpropane} & \rightarrow \text{1-Chloro-2,2-dimethylpropane}
\end{align*}
\]

3. Halide exchange for iodide

\[ R-X + \text{NaI, acetone} \rightarrow R-I + \text{NaX} \downarrow \]

**R-X = R-Cl or R-Br**

\[ \text{CH}_3\text{CH}_2\text{CH}_2-\text{Br} + \text{NaI, acetone} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2-\text{I} \]

\[ n\text{-Propyl bromide} \rightarrow n\text{-Propyl idodide} \]
REACTIONS OF ALKYL HALIDE

1. Nucleophilic substitution reactions (SN1 and SN2)

\[ R-X + :Z^- \rightarrow R-Z + :X^- \]

2. Elimination reactions (E1 and E2)

2. Preparation of Grignard Reagent

\[ R-X + Mg \rightarrow RMgX \]

3. Reduction

\[ R-X + Mg \rightarrow RMgX + H_2O \rightarrow R-H \]

\[ R-X + Sn, HCl \rightarrow R-H \]
Alkyl Halides and Nucleophilic Substitution

Lewis Bases – any species that has a lone pair of electrons.

The electrons can be used to make a new bond to an electron deficient species.

- Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. **They differ in what they attack.**

- Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).
Nucleophillic substitution

R-W + :Z^- \rightarrow R-Z + :W^-

**Substrate** \hspace{1cm} **Nucleophile**  \hspace{1cm} **Substitution product** \hspace{1cm} **Leaving group**

- **Good nucleophile** ≈ strong base
- **Good leaving group** ≈ weak base
Substitution reactions are ionic reactions.

There are two possible ionic mechanisms for nucleophilic substitution:

**SN1 and SN2**

S – Substitution and N – Nucleophilic;

1 – Unimolecular (the rate determining, r.d.s., step entails one molecule);

2 – Bimolecular (the rate determining step entails two species).
When a **nucleophile** (electron donor, e.g., OH\(^-\)) reacts with an alkyl halide, the halogen leaves as a halide.

\[
\text{Nu}^- + \text{C} \quad \rightarrow \quad \text{Nu} - \quad + \quad \text{C} \quad + \quad \text{Halogen} \quad (\text{Hal})^-
\]

There are **two competing reactions** of alkyl halides with nucleophiles....

1) **Substitution**

\[
\text{Nu}^- + \text{C} \quad \rightarrow \quad \text{Nu} - \quad + \quad \text{C} \quad + \quad \text{Halogen} \quad (\text{Hal})^-
\]

**Nu**: replaces the halogen on the alpha-carbon

2) **Elimination**

\[
\text{Nu}^- + \text{C} \quad \rightarrow \quad \text{Nu} - \quad + \quad \text{C} \quad + \quad \text{Halogen} \quad (\text{Hal})^-
\]

**Nu**: removes an H\(^+\) from a b-carbon & the halogen leaves forming an alkene
Bimolecular SN2 Reactions

- The nucleophile and the alkyl halide combine to form a transition state.

- The dotted lines indicate partially formed or partially broken covalent bonds.

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

- The transition state dissociates to form the product, Nu-R, and the halide ion (the leaving group).
- Bimolecular (or 2nd order) means that the rate of an SN2 reaction is directly proportional to the molar concentration of **two reacting molecules**, the alkyl halide ‘substrate’ and the nucleophile.

\[ \text{Rate} = k \ [RX] \ [Nu:] \]

- Note that the nucleophile must hit the back side of the alpha-carbon.
- The nucleophile to C bond forms as the C to X bond breaks.
- No C+ intermediate forms.
2nd Order Nucleophilic Substitution Reactions, i.e., $S_N^2$ reactions

Inversion of Configuration (Walden inversion)
Why backside attack?

To ensure **maximum overlapping leading to stability of T.S.**

- Inversion of configuration does not mean R going to S or vice versa.
- It means that bond formation takes place opposite to that of bond breaking, which leads to the inversion.
- It is like inversion of umbrella in a storm.

![Diagram showing backside attack with Y, C, X atoms and bond formation and breaking processes](image-url)
One-step reaction.
Transition state is highest in energy.
One more example

The nucleophile $\text{-OH}$ 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 $\text{C–OH}$ bond and a partially broken $\text{C–Br}$ bond.

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

\[
\text{(S)-2-Bromobutane} \quad \xrightarrow{\text{HO\textsuperscript{-}}} \quad \left[\begin{array}{c}
\text{H} \\
\text{CH\textsubscript{3}}
\end{array}\right] \quad \xrightarrow{\text{\textsuperscript{\Large{$\ddagger$}}}} \quad \left[\begin{array}{c}
\delta^- \\
\text{HO} \\
\text{CH\textsubscript{2}CH\textsubscript{3}}
\end{array}\right] \quad \xrightarrow{\text{\textsuperscript{\Large{$\ddagger$}}}} \quad \text{(R)-2-Butanol}
\]

\[
\text{Transition state}
\]

\[
\text{HO–C–H} \quad + \quad \text{Br}^- \\
\text{CH\textsubscript{2}CH\textsubscript{3}}
\]
The rate of an $S_N2$ reaction depends upon 4 factors:

1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

1. **Consider the nature of the substrate:**
   - Unhindered alkyl halides, those in which the back side of the alpha-carbon is not blocked, will react fastest in $S_N2$ reactions, that is:

   \[
   \text{Me}^\circ \quad >> \quad 1^\circ \quad >> \quad 2^\circ \quad >> \quad 3
   \]

   While a methyl halides reacts quickly in $S_N2$ reactions, a $3^\circ$ does not react. The back side of an alpha-carbon in a $3^\circ$ alkyl halide is completely blocked.

   - Crowding of the transition state in $S_N2$ reaction by bulky alkyl groups increases the energy of the transition state and lowers the reaction rate.
Effect of nature of substrate on rate of $S_N2$ reactions:

- $\text{Me} - \text{Br}$ (methyl bromide)
- $\text{H}_3\text{C} - \text{CH}_2 - \text{Br}$ (ethyl bromide)
- $\text{H}_3\text{C} - \text{CH} - \text{Br}$ (isopropyl bromide)
- $\text{H}_3\text{C} - \text{CH} - \text{Br}$ (t-butyl bromide)

Space filling models show actual shapes and relative sizes.

- Back side of $\alpha$-C of a methyl halide is unhindered.
- Back side of $\alpha$-C of a $1^\circ$ alkyl halide is slightly hindered.
- Back side of $\alpha$-C of a $2^\circ$ alkyl halide is mostly hindered.
- Back side of $\alpha$-C of a $3^\circ$ alkyl halide is completely blocked.

Decreasing rate of $S_N2$ reactions:

The more alkyl groups connected to the reacting carbon, the slower the reaction.
**Steric Hindrance in an SN2 Reaction Raises Transition State Energy and Slows Reaction**

How Varying the Reactant and Transition-state Energy Levels Effects the Reaction Rates

Higher reactant energy level (red curve) = faster reaction (*smaller* $\Delta G^\ddagger$).

Higher transition-state energy level (red curve) = slower reaction (*larger* $\Delta G^\ddagger$).

Steric effects destabilize transition states.
2. **Consider the power of the nucleophile:**

- The better the nucleophile, the faster the rate of SN2 reactions.
- The table below shows the relative power of various nucleophiles.
- The best nucleophiles are the best electron donors.

<table>
<thead>
<tr>
<th>Reactivity</th>
<th>Nu:^-</th>
<th>Relative Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>very weak</td>
<td>HSO\textsubscript{4}^-, H\textsubscript{2}PO\textsubscript{4}^-, RCOOH</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>weak</td>
<td>ROH</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>HOH, NO\textsubscript{3}^-</td>
<td>100</td>
</tr>
<tr>
<td>fair</td>
<td>F^-</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Cl\textsuperscript{-}, RCOO\textsuperscript{-}</td>
<td>20 \times 10\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>NH\textsubscript{3}, CH\textsubscript{3}SCH\textsubscript{3}</td>
<td>300 \times 10\textsuperscript{3}</td>
</tr>
<tr>
<td>good</td>
<td>N\textsubscript{3}^-, Br\textsuperscript{-}</td>
<td>600 \times 10\textsuperscript{3}</td>
</tr>
<tr>
<td></td>
<td>OH\textsuperscript{-}, CH\textsubscript{3}O\textsuperscript{-}</td>
<td>2 \times 10\textsuperscript{6}</td>
</tr>
<tr>
<td>very good</td>
<td>CN\textsuperscript{-}, HS\textsuperscript{-}, RS\textsuperscript{-}, (CH\textsubscript{3})\textsubscript{3}P\textsuperscript{-}, NH\textsubscript{2}^- ,RMgX, I, H\textsuperscript{-}</td>
<td>&gt; 100 \times 10\textsuperscript{6}</td>
</tr>
</tbody>
</table>
3. **Consider the nature of the leaving group:**

The leaving group usually has a negative charge

- Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.

- Weak bases are readily identified. They have high pKb values.

<table>
<thead>
<tr>
<th>pKb = 23</th>
<th>pKb = 22</th>
<th>pKb = 21</th>
<th>pKb = 11</th>
<th>pKb = -1.7</th>
<th>pKb = -2</th>
<th>pKb = -21</th>
</tr>
</thead>
<tbody>
<tr>
<td>I^-</td>
<td>Br^-</td>
<td>Cl^-</td>
<td>F^-</td>
<td>HO^-</td>
<td>RO^-</td>
<td>H2N^-</td>
</tr>
<tr>
<td>30,000</td>
<td>10,000</td>
<td>200</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Increasing leaving ability*

- Iodine (-I) is a good leaving group because iodide (I^-) is non basic.
- The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH^-) is a strong base.
4. **Consider the nature of the solvent:**

There are 3 classes of organic solvents:

- **Protic solvents**, which contain –OH or –NH₂ groups. Protic solvents slow down SN2 reactions.
- **Polar aprotic solvents** like acetone, which contain strong dipoles but no –OH or –NH₂ groups. Polar aprotic solvents speed up SN2 reactions.
- **Non polar solvents**, e.g., hydrocarbons. SN2 reactions are relatively slow in non polar solvents.

Protic solvents (e.g., H₂O, MeOH, EtOH, CH₃COOH, etc.) cluster around the Nu:- (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.

Are capable of hydrogen bonding to the nucleophile, lowering the energy of the reactant, and consequently increasing the activation energy barrier, decreasing the reaction rate.
The best SN2 solvents are those that are incapable of hydrogen bonding and yet are sufficiently polar to dissolve the polar nucleophilic reagent.

**Polar Aprotic Solvents:** solvate the cation counterion of the nucleophile but not the nucleophile.

Examples include acetonitrile (CH$_3$CN), acetone (CH$_3$COCH$_3$), dimethylformamide (DMF) [(CH$_3$)$_2$NC=OH], dimethyl sulfoxide, DMSO [(CH$_3$)$_2$SO], hexamethylphosphoramide, HMPA {[(CH$_3$)$_2$N]$_3$PO} and dimethylacetamide (DMA).

Non polar solvents (benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles.

SN2 reactions are relatively slow in non polar solvents similar to that in protic solvents.
THE EFFECTS OF
A) SUBSTRATE, B) NUCLEOPHILE, C) LEAVING GROUP AND D) SOLVENT
ARE INDICATED BY THE FOLLOWING

(a)
(b)
(c)
(d)

SN2 Reaction
- SN1 = Substitution, Nucleophilic, 1st order (Unimolecular)
- SN1 reactions obey 1st order kinetics

\[ \text{Rate} = k [RX] \]

- The rate depends upon the concentration of only 1 reactant, the alkyl halide - **not** the nucleophile

- The order of reactivity of substrates for S_N1 reactions is the reverse of S_N2

\[ 3^\circ > 2^\circ > 1^\circ > \text{vinyl} > \text{phenyl} > \text{Me}^\circ \]
The mechanism of an $S_N1$ reaction occurs in 2 steps:

1. The slower, rate-limiting dissociation of the alkyl halide forming a C+ intermediate

2. A rapid nucleophilic attack on the C+

Note that the nucleophile is not involved in the slower, rate-limiting step.
**FACTORS affecting THE RATE of S<sub>N</sub>1 reactions**

The rate of an S<sub>N</sub>1 reaction depends upon 3 factors:

1. The nature of the substrate (the alkyl halide)
2. The ability of the leaving group to leave
3. The nature of the solvent

1. **Consider the nature of the substrate:**
   Highly substituted alkyl halides (substrates) form a more stable C+.

![Increasing rate of S<sub>N</sub>1 reactions]

<table>
<thead>
<tr>
<th>more stable</th>
<th>less stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;C—C&lt;sup&gt;+&lt;/sup&gt;</td>
<td>H—C&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
</tr>
<tr>
<td>tertiary 3º</td>
<td>secondary 2º</td>
</tr>
</tbody>
</table>

Increasing rate of S<sub>N</sub>1 reactions
2. **Consider the nature of the leaving group:**

- The nature of the leaving group has the same effect on both SN1 and SN2 reactions.
- The better the leaving group, the faster a C+ can form and hence the faster will be the SN1 reaction.
- The leaving group usually has a negative charge.
- Groups which best stabilize a negative charge are the best leaving groups, i.e., the **weakest bases** are **stable as anions** and are the **best leaving groups**.
- Weak bases are readily identified. They have high pKb values.

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</tr>
</thead>
<tbody>
<tr>
<td>I⁻</td>
<td>Br⁻</td>
<td>Cl⁻</td>
<td>F⁻</td>
<td>HO⁻</td>
<td>RO⁻</td>
<td>H₂N⁻</td>
</tr>
<tr>
<td>30,000</td>
<td>10,000</td>
<td>200</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Iodine (-I) is a good leaving group because iodide (I⁻) is non basic.
- The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH⁻) is a strong base.
3. Consider the nature of the solvent:

- For SN1 reactions, the solvent affects the rate only if it influences the stability of the charged transition state, i.e., the C+.
- Polar solvents, both Protic and Aprotic, will solvate and stabilize the charged transition state (C+ intermediate), lowering the activation energy and accelerating SN1 reactions.
- Nonpolar solvents do not lower the activation energy and thus make SN1 reactions relatively slower.

The relative rates of an $S_N1$ reaction due to solvent effects are given:

$$(\text{CH}_3)_3\text{C-Cl} + \text{ROH} \rightarrow (\text{CH}_3)_3\text{C-OR} + \text{HCl}$$

<table>
<thead>
<tr>
<th>Solvent</th>
<th>100,000</th>
<th>20% EtOH (aq)</th>
<th>40% EtOH (aq)</th>
<th>EtOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{O}$</td>
<td>100,000</td>
<td>14,000</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

reaction rate increases with polarity of solvent
### Differences between SN\(^1\) and SN\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>SN(^1)</th>
<th>SN(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="R(_1)R(_2)R(_3)C-Cl" /> → aq. KOH ➔ <img src="image" alt="R(_1)R(_2)R(_3)C-OH" /> + <img src="image" alt="HO-C-R(_2)" /></td>
<td><img src="image" alt="H(_\cdot\cdot\cdot)C-Cl" /> ➔ <img src="image" alt="HO-C-H" /></td>
</tr>
<tr>
<td>chiral-3(^\circ) alkyl halide</td>
<td><img src="image" alt="50% enantiomers" /> <img src="image" alt="50% racemic mixture" /></td>
<td><img src="image" alt="100% inversion of configuration" /></td>
</tr>
<tr>
<td>1.</td>
<td>Takes place in 3(^\circ) alkyl halides</td>
<td>Takes place in 1(^\circ) alkyl halide</td>
</tr>
<tr>
<td>2.</td>
<td>Two steps</td>
<td>Only one step</td>
</tr>
<tr>
<td>3.</td>
<td>1(^{st}) step is slow and rate determining</td>
<td>Only one step</td>
</tr>
<tr>
<td>4.</td>
<td>Rate is (\alpha) to conc. of alkyl halide</td>
<td>Rate is (\alpha) to conc. of alkyl halide and alkali</td>
</tr>
<tr>
<td>5.</td>
<td>Unimolecular</td>
<td>Bimolecular</td>
</tr>
<tr>
<td>6.</td>
<td>Non-concerted</td>
<td>Concerted</td>
</tr>
<tr>
<td>7.</td>
<td>Independent of concentration of alkali</td>
<td>Dependent on concentration of both</td>
</tr>
<tr>
<td>8.</td>
<td>Carbo-cation intermediate is formed</td>
<td>Takes place via only transition state</td>
</tr>
<tr>
<td>9.</td>
<td>Racemic mixture is formed</td>
<td>Walden inversion takes place</td>
</tr>
<tr>
<td>10.</td>
<td>Favorable in protic solvents (H(_2)O, HCOOH)</td>
<td>Aprotic solvents DMSO, DMF, etc.</td>
</tr>
<tr>
<td>11.</td>
<td>Order of reactivity: 3(^\circ) &gt; 2(^\circ) &gt; 1(^\circ)</td>
<td>Order of reactivity: 1(^\circ) &gt; 2(^\circ) &gt; 3(^\circ)</td>
</tr>
<tr>
<td>12.</td>
<td>Rearrangement may take place</td>
<td>No rearrangement takes place</td>
</tr>
</tbody>
</table>
THANK YOU