I. Introduction to Alkyl Halides

Alkyl halides are organic molecules containing a halogen atom X bonded to an sp\(^2\) or sp\(^3\) hybridized carbon atom.

\[
\begin{align*}
\text{X bonded to sp}^3\text{--C} \\
\text{examples:} \\
\text{H} & \text{C--X} & \text{H} & \text{C--X} & \text{H} & \text{C--X} & \text{R} & \text{C--X} & \text{R} & \text{C--X} \\
\text{H} & & \text{H} & & \text{H} & & \text{R} & & \text{R} &
\end{align*}
\]

\[
\begin{align*}
\text{X bonded to sp}^2\text{--C} \\
\text{examples:} \\
\text{H} & \text{C--X} & \text{H} & \text{C--X} & \text{H} & \text{C--X} & \text{R} & \text{C--X} & \text{R} & \text{C--X} \\
\text{H} & & \text{H} & & \text{H} & & \text{R} & & \text{R} &
\end{align*}
\]

A. Nomenclature of Alkyl Halides

**Common name:** Alkyl Halide  
**IUPAC:** Haloalkane (fluoro-, chloro-, bromo-, iodo-)

The rules are the same as with alkanes, except there are halogens present. Halides are given prefixes of chloro-, fluoro-, bromo-, and iodo-.
II. Reactions of Alkyl Halides

Alkyl halides contain a polar carbon-halogen bond, and an electrophilic carbon:

\[
\begin{array}{c}
\text{C} \\
\text{X}
\end{array}
\]

- The characteristic reactions of alkyl halides are nucleophilic substitution and elimination.

A. Nucleophilic Substitution Reactions

When a methyl halide or a primary alkyl halide reacts with a nucleophile such as sodium ethoxide, a reaction occurs in which the nucleophile replaces the halogen, which is expelled as a halide ion.

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

Common nucleophilic reagents for creating new bonds to carbon:

<table>
<thead>
<tr>
<th>C-O Bonds</th>
<th>C-S Bonds</th>
<th>C-N Bonds</th>
<th>C-C Bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO(^-)</td>
<td>HS(^-)</td>
<td>NH(_3)</td>
<td>(\text{C} \equiv \text{N})</td>
</tr>
<tr>
<td>RO(^-)</td>
<td>RS(^-)</td>
<td>RN(_2)</td>
<td>RC(\equiv)C(^-)</td>
</tr>
<tr>
<td>PhO(^-)</td>
<td>PhS(^-)</td>
<td>N(_3)(^-)</td>
<td>CH(_3)C(_2)O(\equiv)C(\equiv)OCH(_2)CH(_3)</td>
</tr>
</tbody>
</table>

** Nucleophilic substitution reactions can be used to transform alkyl halides into a variety of other functional groups!
Examples:

![Chemical structures]

- Substitution is more complicated than it looks!

As we’ve seen, when a 1° or methyl halide reacts with ethoxide ion, substitution takes place. When the nucleophile is changed to ethanol, no reaction occurs. But when ethanol reacts with a tertiary alkyl halide, substitution does occur.

\[
\text{CH}_3\text{CH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \\
(\text{CH}_3)_2\text{CBr} + \text{CH}_3\text{CH}_2\text{OH}
\]

Reacting a tertiary alkyl halide with ethoxide ion, on the other hand, results in a completely different reaction, elimination:

\[
(\text{CH}_3)_2\text{CBr} + \text{CH}_3\text{CH}_2\text{O}^- \rightarrow 
\]

To complicate things further, a methoxymethyl alkyl halide, an allyl halide, and a benzyl halide react with both ethanol and ethoxide ion to form substitution product!

\[
\text{CH}_3\text{OCH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{O}^- \rightarrow \\
\text{CH}_3\text{CH}_2\text{OH}
\]

What’s going on???

There are actually two mechanisms for nucleophilic substitution, and these two mechanisms are in competition with each other!
III. Substitution, Nucleophilic, Bimolecular: The $S_N2$ Reaction

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

The rate law for a reaction often gives clues to the mechanism for a reaction.

**Kinetics:** If we measure the rate of the reaction as a function of varying initial concentrations of reactants we find that:

\[
\text{rate} \propto [\text{CH}_3\text{I}][\text{CH}_3\text{CH}_2\text{O}^-] \]

We can conclude that:

- the reaction is second order
- the reaction is bimolecular
- We call this an $S_N2$ reaction: (Substitution, Nucleophilic, Bimolecular)

The following mechanism is consistent with the rate law:

\[
\text{H} - \text{C} - \text{I} \quad \text{EtO} \quad \text{H} - \text{C} - \text{I} \quad \rightarrow \quad \text{EtO} - \text{C} - \text{H} \]

Although the rate law indicates what atoms are present in the transition state, it provides no information about how they are arranged!
In order to decide how the atoms are arranged in the transition state we have to look at the stereochemistry of the reaction.

**There are three possibilities:**

**#1: If** frontside attack:

\[
\begin{array}{c}
\text{R}^1 \quad \text{C} - X \\
\text{R}^2 \quad \text{Nuc} \\
\text{R}^3
\end{array}
\xrightarrow{\text{‡}}

\begin{array}{c}
\text{R}^1 \quad \text{C} \\
\text{R}^2 \quad \text{Nuc} \\
\text{R}^3
\end{array}
\]

\[
\text{R}^1 \quad \text{C} - \text{Nuc} + \text{X}^-
\]

**#2: If** backside attack:

\[
\begin{array}{c}
\text{Nuc} \quad \text{‡} \\
\text{R}^1 \quad \text{C} - X \\
\text{R}^2 \quad \text{R}^3
\end{array}
\]

\[
\text{Nuc} \quad \text{‡} \\
\text{C} \\
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\]

\[
\text{Nuc} \quad \text{C} \quad \text{R}^1 + \text{X}^-
\]

**#3: If** both attacks occur at equal rates you will get both inversion & retention of configuration!

*What are the experimental results?*

**Example 1** (using a chiral alkyl bromide):

\[
\begin{array}{c}
\text{CH}_2\text{CH}_3 \\
\text{H}_3\text{C} \quad \text{Br}
\end{array}
\xrightarrow{\text{‡}}

\begin{array}{c}
\text{HS} \\
\text{H}_3\text{C}
\end{array}
\]

\[
\text{+} \quad \text{Br}^-
\]

**Example 2:**

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{Cl} \\
\text{H} \quad \text{H} \quad \text{H}
\end{array}
\xrightarrow{\text{S}_2\text{N}}

\begin{array}{c}
\text{N}_3 \\
\text{‡}
\end{array}
\]

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

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Conclusion:

Why is backside attack favored?

Look @ the energy diagram:

Backside attack results in an inversion of the carbon atom's tetrahedron, like the inversion of an umbrella caught by the wind.

Why is backside attack favored?
IV. Factors that Affect the Rate of the \( S_N^2 \) Reaction

We know:

\[
\text{rate} \propto [\text{alkyl halide}][\text{Nuc}]
\]

**Transition State:**

\[
\begin{array}{c}
\text{Nuc} : \text{C} \\
\text{H} \quad \text{H} \\
\text{H} \\
\end{array}
\]

- The bond to the nucleophile forms while the bond to the leaving group breaks.
- The transition state involves five groups around carbon.

**Predict:**

The factors that affect the rates of \( S_N^2 \) reactions:

A. The structure of the substrate
B. The concentration and reactivity of the nucleophile
C. The effect of the solvent
D. The nature of the leaving group

**A. The Structure of the Substrate**

Look @ the relative rates of \( S_N^2 \) reactions for various alkyl bromides:
In the S<sub>N</sub>2 reaction, the rate of the reaction is slowed by bulky groups near the reaction center due to steric hindrance.

<table>
<thead>
<tr>
<th>Alkyl Bromide</th>
<th>Type</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;—Br</td>
<td>methyl</td>
<td>1200</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>primary</td>
<td>40</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>primary</td>
<td>16</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH—Br</td>
<td>secondary</td>
<td>1</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH—Br</td>
<td>secondary</td>
<td>1</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;C—Br</td>
<td>tertiary</td>
<td>negligible</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CHCH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>primary hindered</td>
<td>0.6</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>primary hindered</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
crowding in the T.S. raises the activation energy and slows the reaction.

Look at the energy diagram for a $1^\circ$ and $3^\circ$ alkyl bromide:

![Energy Diagram](image)

**B. The Effect of the Concentration and Strength of the Nucleophile**

The strength & the concentration of the nucleophile greatly effects the rate of an $S_N2$ reaction.

Q. **How do we determine nucleophilic strength?**

A. **By measuring the rates of substitution reactions**

Look at the relative rates of reaction of various nucleophiles with iodomethane (next page):

Nucleophilicity depends on a variety of factors: concentration of charge, solvent, polarizability and the nature of the substituents.

**Best Nucleophiles:**

- have high concentration of negative charge
- are highly polarizable
- are less solvated
- are not too hindered
**Relative Rates of S\textsubscript{N}2 Reaction of Various Nucleophiles with Iodomethane in Methanol:**

\[
\begin{align*}
\text{H} & \quad \text{H} \quad \text{C} & \quad \text{I} & \quad \text{Nu} \\
\hline
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{Nu} \quad \text{C} & \quad \text{H} & \quad \text{H} & \quad \text{Nu} \quad \text{C} & \quad \text{H} & \quad \text{H} & \quad \text{I} & \quad \text{Nu}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>H\textsubscript{2}O</td>
<td>1</td>
</tr>
<tr>
<td>CH\textsubscript{3}OH</td>
<td>1</td>
</tr>
<tr>
<td>F\textsuperscript{-}</td>
<td>500</td>
</tr>
<tr>
<td>O\textsuperscript{-}</td>
<td>20,000</td>
</tr>
<tr>
<td>CH\textsubscript{3}CO\textsuperscript{-}</td>
<td>23,500</td>
</tr>
<tr>
<td>Cl\textsuperscript{-}</td>
<td>316,000</td>
</tr>
<tr>
<td>NH\textsubscript{3}</td>
<td>630,000</td>
</tr>
<tr>
<td>PhO\textsuperscript{-}</td>
<td>630,000</td>
</tr>
<tr>
<td>N\textsubscript{3}\textsuperscript{-}</td>
<td>630,000</td>
</tr>
<tr>
<td>Br\textsuperscript{-}</td>
<td>630,000</td>
</tr>
<tr>
<td>CH\textsubscript{3}O\textsuperscript{-}</td>
<td>1,995,000</td>
</tr>
<tr>
<td>HO\textsuperscript{-}</td>
<td>3,163,000</td>
</tr>
<tr>
<td>(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{3}N</td>
<td>5,010,000</td>
</tr>
<tr>
<td>CN\textsuperscript{-}</td>
<td>5,010,000</td>
</tr>
<tr>
<td>I\textsuperscript{-}</td>
<td>25,100,000</td>
</tr>
<tr>
<td>(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{3}P</td>
<td>501,000,000</td>
</tr>
<tr>
<td>HS\textsuperscript{-}</td>
<td>1,000,000,000</td>
</tr>
<tr>
<td>PhS\textsuperscript{-}</td>
<td>7,943,000,000</td>
</tr>
<tr>
<td>PhSe\textsuperscript{-}</td>
<td>50,000,000,000</td>
</tr>
</tbody>
</table>

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Trends:

1. Increasing negative charge increases nucleophilicity.

\[
\begin{align*}
\text{H—O}^{-} & \quad \text{vs.} \quad \text{H}_{2}\text{O} \\
\text{H—N}^{-} & \quad \text{vs.} \quad \text{H—N}^{-}
\end{align*}
\]

2. Nucleophilicity decreases to the right in the periodic table (this correlates with basicity).

\[
\begin{align*}
\text{R—C}^{-} & \quad \text{R—N}^{-} & \quad \text{R—O}^{-} & \quad \text{F}^{-} \\
\text{R—N}^{-} & \quad \text{R—O}^{-} & \quad \text{Cl}^{-} & \quad \text{Br}^{-} \\
\text{H}_{2}\text{Se} & \quad \text{PhSe} & \quad \text{I}^{-}
\end{align*}
\]

3. Nucleophilicity increases as you go down a row in the periodic table (this does not correlate with basicity!!)
Q. Why doesn’t nucleophilicity always correlate with basicity?
A. Basicity is a thermodynamic property, measured by an equilibrium constant.

\[
\begin{align*}
\text{H-A} & \quad + \quad \text{H}_2\text{O} & \xrightarrow{K} & \quad \text{A}^\ominus & \quad + \quad \text{H}_3\text{O}^+ \\
K &= \text{equilibrium constant}
\end{align*}
\]

In contrast, nucleophilicity is a kinetic phenomenon, measured by comparing rates of reaction.

\[
\begin{align*}
\text{R}^{-} \text{X} & \quad + \quad \text{Nu}^\ominus & \xrightarrow{k} & \quad \text{R} \quad \text{Nu} & \quad + \quad \text{X}^\ominus \\
k &= \text{rate constant}
\end{align*}
\]

As we go down a row in the periodic table, two things happen:

1. **The atoms get larger and the charge becomes less concentrated.** Smaller anions are more tightly solvated than larger atoms because their charge is more concentrated, so \( \text{F}^- \) is more heavily solvated than \( \text{I}^- \).

- **Solvation weakens a nucleophile because it impedes its ability to attack an electrophile!**

2. **Polarizability increases.** Larger elements have larger, more diffuse, and more polarizable electron clouds. These electron clouds allow for more effective orbital overlap in the \( \text{S}_\text{N}2 \) transition state.
C. The Effect of Solvent on the Rate of Reaction

The rates of many $S_N2$ reactions are strongly affected by the solvent used. Why? Look @ the effect of solvent on the $S_N2$ rxn. of methyl iodide with chloride ion:

\[
\text{CH}_3\text{I} + \text{Cl}^- \xrightarrow{\text{solvent}} \text{CH}_3\text{Cl} + \text{I}^- \\
\]

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>Classification</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$OH</td>
<td>methanol</td>
<td>protic</td>
<td>1</td>
</tr>
<tr>
<td>H(\text{C}^-\text{NH}_2)</td>
<td>formamide</td>
<td>protic</td>
<td>12.5</td>
</tr>
<tr>
<td>H(\text{C}^-\text{NHCH}_3)</td>
<td>$N$-methylformamide</td>
<td>protic</td>
<td>45.3</td>
</tr>
<tr>
<td>H(\text{C}^-\text{N(CH}_3)_2)</td>
<td>$N$,$N$-dimethylformamide</td>
<td>aprotic</td>
<td>1,200,000</td>
</tr>
</tbody>
</table>

Other common polar aprotic solvents:

\[
\text{CH}_3\text{O} \\
\text{CH}_3\text{C} \xrightarrow{\text{acetone}} \text{CH}_3\text{CH}_3 \\
\text{CH}_3\text{S} \\
\text{CH}_3\text{C} \xrightarrow{\text{dimethylsulfoxide}} \text{CH}_3\text{C} \]
Compare solvation of Cl\(^{-}\) in a polar aprotic solvent, vs. a polar protic solvent (DMSO):

- Polar aprotic solvents solvate anions relatively weakly because they cannot hydrogen bond, and the positive part of the solvent is in the center of the molecule! On the other hand, polar aprotic solvents solvate cations very well.

Result:
- Anions are freer to react because they are unencumbered by solvent molecules.
- Rates of \(S_N2\) reactions are greatly enhanced in polar aprotic solvents!

\textit{The reactivity order as we descend a row in the periodic table is reversed when we switch to a polar aprotic solvent!!}
**In protic solvents** (e.g. \( \text{H}_2\text{O}, \text{alcohol} \)): \( \Gamma^- > \text{Br}^- > \text{Cl}^- > \text{F}^- \)

**In polar aprotic solvent:** \( \text{F}^- > \text{Cl}^- > \text{Br}^- > \Gamma^- \)

In polar aprotic solvents, nucleophilicity more closely approximates basicity.

Summarizing *Periodic Trends* for nucleophile strength in polar and aprotic solvents:

---

**D. The Nature of the Leaving Group**

**Good leaving groups are weak bases.** The same factors that make a species a weak base also make it a good leaving group.

(Look for conjugate bases of strong acids in the top half of the pKa table with pKa values less than *about 8*.)

\[ \text{—I > —Br > —Cl > —F} \]

*Never* Leaving Groups in Nucleophilic Substitution!
V. The Reversibility of an \( S_{N2} \) Reaction

Many different kinds of nucleophiles can react with alkyl halides, and a wide variety of organic compounds can be synthesized by means of \( S_{N2} \) reactions:

**Examples:**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{Cl} & + \text{HO}^- \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} & + & \text{Cl}^- \\
\text{CH}_3\text{CH}_2\text{Br} & + \text{HS}^- \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{SH} & + & \text{Br}^- \\
\text{CH}_3\text{CH}_2\text{Cl} & + \text{H}_2\text{N}^- \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{NH}_2 & + & \text{Cl}^- \\
\text{CH}_3\text{CH}_2\text{I} & + \equiv\text{C} \equiv \text{N} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{C} \equiv \text{N} & + & \text{I}^{-}
\end{align*}
\]

**Q:** Can the reverse reaction occur by nucleophilic substitution?

**A:**

Look at the TS for the \( S_{N2} \) reaction:

- The reverse reaction cannot occur because hydroxide ion is a terrible leaving group! The reaction is only reversible if the two possible leaving groups have similar leaving group abilities (*i.e.* they have similar basicities)

**Example of reversible \( S_{N2} \) reaction:**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{Br} & + \text{I}^- \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{I} & + & \text{Br}^- 
\end{align*}
\]

- The equilibrium can be driven to favor the desired products by using Le Châtelier’s principle (*if an equilibrium is disturbed, the system will adjust to offset the disturbance.*)
VI. Substitution, Nucleophilic, Unimolecular: The $S_N1$ Reaction

When a primary alkyl halide is dissolved in an alcohol solvent with no added base, no reaction takes place. When a tertiary alkyl halide is subjected to the same conditions, substitution occurs.

This is a solvolysis, a nucleophilic substitution where the nucleophile is the solvent.

A. Rate Law and Mechanism of $S_N1$ Reaction

**Kinetics:** If we measure the rate of the reaction as a function of varying initial concentrations of reactants we find that:

\[
\text{rate} \propto [\text{tert-BuBr}]
\]

We can conclude:

- The reaction is 1st order.
- Any involvement of solvent in the reaction cannot be detected in the rate law because the concentration of the solvent is essentially constant. *However the nature of the solvent does play a critical role in this reaction.*
- Reaction is $S_N1$: (Substitution, Nucleophilic, Unimolecular)

**Mechanism:**
B. The Stereochemistry of the $S_N1$ reaction:

Look at the solvolysis of (S)-3-Bromo-3-methylhexane:

\[
\text{Pr} \\
\text{CH}_3\text{C}^\text{Br} \\
\text{Et}
\]
VII. Factors that Affect the Rate of the $S_N1$ Reaction

*We know:*

$$\text{rate} \propto [\text{tert-BuBr}]$$

*Transition state for the rate determining step:*

\[
\begin{array}{c}
\text{CH}_3 \\
\text{C} \\
\text{Br} \\
\text{CH}_3 \quad \text{CH}_3
\end{array}
\]

- The bond to the leaving group breaks, as a carbocation forms.
- A carbocation is a high energy intermediate

*Predict:*

The factors that affect the rates of $S_N1$ reactions:

- A. The structure of the substrate
- B. The effect of the solvent
- C. The nature of the leaving group

A. The Structure of the Substrate

*Look* @ the relative rates of $S_N1$ reactions for various alkyl chlorides:
Notice:
• As the number of R groups on the carbon with the leaving group increases, the rate of the S\textsubscript{N}1 reaction increases.
• Alkyl halides that form resonance stabilized carbocations have a faster rate of reaction.

☛ The rates of S\textsubscript{N}1 reactions correspond to the stability of the corresponding carbocations!

Stability of carbocations:

- CH\textsubscript{3}C–CH\textsubscript{3} > CH\textsubscript{3}C–H > CH\textsubscript{3}H–H > H–H

• the more alkyl groups bonded to the positively charged carbon, the more stable the carbocation. Why?
Hyperconjugation: Partial overlapping of the sigma bonding orbital of an adjacent C-H or C-C bond with the vacant 2p orbital of the cationic carbon.

![Hyperconjugation Diagram]

- Delocalization of the charge through hyperconjugation stabilizes the (+)-charge on the carbocation.
- Can also think of this as an inductive effect:

What does the stability of the carbocation intermediate have to do with the rate of the $S_{N}1$ reaction? We know the rate of a reaction depends on the magnitude of $E_a$, not on the stability of the reactants, products or intermediates. The magnitude of $E_a$ depends on the energy of the transition state.

Q: How can we estimate the energy of a transition state?

A:

1. The Structure of the Transition State: Hammond’s Postulate

We know that the structure of a transition state lies between the structure of the reactants and the structure of the products. It does not necessarily mean that the structure is halfway in between. The transition state can resemble products more closely than reactants, or reactants more closely than products:
According to Hammond’s postulate, the transition state of a reaction resembles the structure of the species (reactant or product) to which it is closer in energy.

Since the rate-determining step in an $S_N1$ reaction is formation of a carbocation intermediate, an endothermic process, the transition state will resemble the product of this step, a carbocation, more than the reactants.

Look at the structure of the transition state for the rate-determining step in an $S_N1$ reaction of tert-butyl bromide:
This transition state more closely resembles the carbocation intermediate, since the carbocation intermediate is closest in energy. The major factor contributing to the instability of this transition state are the same ones that make the carbocation unstable: development of an electron deficient site.

Compare energy diagrams for formation of methyl and 3° carbocations in the $S_N^1$ reaction:

> The relative rates of formation of the two carbocations is determined by the relative free energies of the transition states for carbocation formation.

> Since $\text{CH}_3^+$ is less stable than $(\text{CH}_3)_3\text{C}^+$, and the transition states resemble these two carbocations, then $E_a[2] > E_a[1]$, and reaction 2 is slower.
B. The Effect of Solvent on the Rate of Reaction

**Polar protic solvents** greatly enhance the rate of ionization of an alkyl halide in an $S_N1$ reaction.

*WHY?* Solvation stabilizes the transition state leading to the carbocation. This lowers $E_a$.

\[
\begin{align*}
\text{CH}_3\text{CBr} & \quad \text{CH}_3\text{C}^+ \quad \text{Br}^- \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

- The higher the **dielectric constant**, the better a solvent’s ability to solvate ions.

*Look at* the ionization of tert-butyl chloride in various solvents:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>dielectric constant</th>
<th>$K_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>80</td>
<td>8000</td>
</tr>
<tr>
<td>methanol</td>
<td>33</td>
<td>1000</td>
</tr>
<tr>
<td>ethanol</td>
<td>24</td>
<td>200</td>
</tr>
<tr>
<td>acetone</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>hexane</td>
<td>2.0</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Best:*

**Alcohol:*

C. The Nature of the Leaping Group

Good leaving groups are also important in the $S_N1$ reaction!
VIII. Benzylic Halides, Allylic Halides, Methoxymethyl Halides, Vinylic Halides, and Aryl Halides

Benzylic, allylic, and methoxymethyl halides readily undergo $S_N2$ reactions unless they are tertiary, and they also undergo $S_N1$ reactions even if they are primary, because they form stable carbocations.

If the resonance contributors of the allylic carbocation intermediate have different groups bonded to their $sp^2$ carbons, two substitution products will be obtained under $S_N1$ conditions:

Q: To avoid this happening what do you do?

A:

\[
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{O}^\ominus \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH}
\]

\[
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{CH}_3\text{CH} = \text{CHBr} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH}
\]
Vinylic and Aryl Halides do not undergo $S_{N1}$ or $S_{N2}$ reactions! Why?

There is no $S_{N2}$ because as the nucleophile approaches on the backside of the sp$^2$ carbon, it is repelled by the $\pi$-electron cloud of the double bond or the aromatic ring.

![Vinylic and Aryl Halides](image)

There is no $S_{N1}$ because vinylic and aryl carbocations are extremely unstable, and the bond between an sp$^3$-carbon and a halogen is much stronger, and therefore harder to break:

![Vinylic and Aryl Halides](image)

---

IX. Competing Mechanisms for Nucleophilic Substitution

*The $S_{N1}$ reaction is in competition with the $S_{N2}$ reaction!*

Q. Why does methyl chloride react by an $S_{N2}$ mechanism and tert-butyl chloride react by an $S_{N1}$ reaction?

A. The relative rates of the possible reactions dictate the outcome of the reaction.

*i.e.* The rate of an $S_{N2}$ reaction for methyl chloride is exceedingly faster than the rate of an $S_{N1}$ reaction for methyl chloride.
Remember the order of reactivity:

$S_N2$ reaction: methyl $> 1^\circ > 2^\circ > 3^\circ$

$S_N1$ reaction: $3^\circ > 2^\circ > 1^\circ >$ methyl

Compare energy diagrams for $S_N1$ & $S_N2$ reaction of a $1^\circ$ & $3^\circ$ alkyl halide:

*For $2^\circ$ alkyl halides the rates of $S_N1$ vs. $S_N2$ are much more competitive!*

- $2^\circ$ alkyl halides react with good nucleophiles by $S_N2$ reactions.
- If a $2^\circ$ alkyl halide is in a good ionizing solvent and no good nucleophile is present, $S_N1$ reactions will predominate.

X. Organic Synthesis

In organic chemistry, you have to predict products that are formed when reagents react, and you also have to be able look at a compound and see how you can synthesize it using reactions that you have learned.
Predict the product:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \text{CHCH}_2 \text{Br} \quad + \quad \text{OH} \\
\text{CH}_3 & \quad \text{CH}_3 \text{CHCH}_2 \text{OH}
\end{align*}
\]

Show how to synthesize the following compound (what starting material and reagent are needed to make it?):

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \text{CHCH}_2 \quad \text{OH}
\end{align*}
\]

Example of a synthesis problem:

Starting with an alkyl halide, show how the following compound can be synthesized:

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} \equiv \text{N}
\end{align*}
\]