Substitution Reactions

Substitution reactions are reactions in which a nucleophile displaces an atom or group of atoms (the leaving group) from a tetrahedral carbon atom.

Consider the following general substitution reaction:

\[
\text{Nu} + \text{R-LG} \rightarrow \text{R-Nu} + \text{LG}
\]

How might this reaction proceed?

We can imagine three different mechanisms:

- the nucleophile Nu-R bond forms first then the R-LG bond breaks.
- the Nu-R bond forms at the same time as the R-LG bond breaks.
- the R-LG bond breaks first then the Nu-R bond forms.

Are all these mechanisms reasonable?
The two mechanisms that are operative in substitution reactions are the $S_{N}1$ and $S_{N}2$ reactions.

- Reactions in which the leaving group leaves before the attack of the nucleophile are referred to as $S_{N}1$ reactions.
- Reactions in which the nucleophile attacks at the same time as the leaving group leaves are referred to as $S_{N}2$ reactions.

Consider the two different mechanisms for a substitution reaction. What factors would favour one pathway over the other?
Substitution Reactions of Alkyl Halides

All of these reactions:
- involve displacement of a heteroatom from carbon -- the "leaving group"
- have a leaving group that is more EN than carbon making the carbon electrophilic
- have an electrophilic carbon that is sp$^3$ hybridized
- have a nucleophile present, which is either -ve or δ-

Remember: Good leaving groups are weak bases!
Alkyl halides and alcohols $S_N 1$ or $S_N 2$?

- $3^\circ$, benzylic and allylic substrates undergo $S_N 1$ reactions because THEY FORM RELATIVELY STABLE CARBOCATIONS.

- $1^\circ$, substrates undergo $S_N 2$ reactions because they DO NOT FORM STABLE CARBOCATIONS and THE REACTION SITE IS STERICALLY ACCESSIBLE.

- $2^\circ$, substrates can undergo both types of reaction, but do so slowly.

**The $S_N 1$ Reaction**

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \ldots \text{C} \ldots \text{C} \ldots \text{Br} \\
\text{H}_3\text{C} \\
\end{array}
\quad \xrightarrow{\text{H}_2\text{O}} \quad
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \ldots \text{C} \ldots \text{C} \ldots \text{OH} \\
\text{H}_3\text{C} \\
\end{array} + \text{HBr}
\]

- $S_N 1$ reactions in which the solvent participates as a nucleophile are called solvolysis reactions.
Substitution Reactions – $S_N1$

Sketch a reaction profile diagram for the following reaction:

$$
: \text{I} {-} : + (\text{H}_3\text{C})_3\text{C} — \text{Br} : \rightarrow \text{I} — \text{C(CH}_3)_3 : + \text{Br} :$$
Substitution Reactions – $S_N1$

$S_N1$ reactions predominate when:
  - A relatively stable carbocation is formed.
  - The solvent is polar and protic.
  - Weak nucleophile (e.g. a neutral molecule such as $H_2O$, ROH, etc.).

Carbocation Stability

Carbocation stability is dependent on:
  - Coulombic stabilization
  - Inductive stabilization
  - Delocalization (resonance)
  - Hyperconjugation.
Since $S_N1$ reactions involve carbocation intermediates, only those species that form reasonable carbocations will undergo this reaction in a timely fashion (this lifetime).
Aryl and vinyl carbocations cannot be stabilized by resonance. The empty orbital is orthogonal to the $\pi$-system and as such cannot be delocalized:
- Alkyl carbocations are also stabilized by electron donation from adjacent C–H bonds. This phenomenon is known as hyperconjugation.

![Diagram of alkyl carbocation stabilization](image)

- Recall that inductive and field arguments suggest carbocation stability is:

\[ 3° > 2° > 1° \]

- Vinyl and aryl carbocations CANNOT be stabilized by resonance.

![Diagram of vinyl and aryl carbocation](image)

Thus, the order of carbonium ion stability is:

Benzylic ~ allylic > 3° > 2° > 1° > CH₃ > vinyl ~ aryl

- Usually, S_N1 reactions are practical for benzylic allylic and 3° substrates.
One consequence of reactions proceeding via carbocation intermediates is the occurrence of **rearrangement** side reactions. Consider the following reaction:

\[
\text{H}_3\text{C}\text{Br} + \text{OH} \rightarrow \text{H}_3\text{C}\text{CH}_3 + \text{H}^+ + \text{Br}^-
\]

The substitution product is a constitutional isomer of the product expected. Propose a mechanism for the above reaction:
It is worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion. In either case, you will always be forming a more stable carbocation.

Pay close attention to the way curly arrows are drawn when proposing a hydride or methyl shift. We should be able to tell if you are proposing a hydride shift or generation of a pi bond.
The S$_\text{N}1$ Reaction - Kinetics.

\[ \text{I}^- + (\text{CH}_3)_3\text{CBr} \rightarrow (\text{CH}_3)_3\text{Cl} + \text{Br}^- \]

Consider:

• What happens to the rate of production of (CH$_3$)$_3$Cl if the concentration of I$^-$ is held constant and the concentration of (CH$_3$)$_3$CBr is increased?

• What happens to the rate of production of (CH$_3$)$_3$Cl if the concentration of (CH$_3$)$_3$CBr is held constant and the concentration of I$^-$ is increased?
The Stereochemistry of the $S_N1$ reaction

- The nature of the intermediate is such that the nucleophile can attack from either side with equal likelihood.

- Reactions in which the configuration of a chiral centre is scrambled are said to occur with RACEMIZATION.
The Stereochemistry of the $S_N1$ reaction

Sometimes (depending on conditions) reactions occur with only partial racemization.
**S\textsubscript{N}1 reactions – Solvent Effects**

- \( S\textsubscript{N}1 \) reactions are typically done in **polar protic** solvents. Polar protic solvents are used because they help stabilize the transition state during the process of forming the carbocation intermediate. The more stabilized the transition state, the faster the carbocation will form.

Some common **polar protic** solvents:

- Acetic Acid (**AcOH**)
- t-Butanol (**t-BuOH**)
- Isopropanol (**iPrOH**)
- Ethanol (**EtOH**)
- Methanol (**MeOH**)
- Water
The $S_N2$ Reaction.

The $S_N2$ reaction is favoured for $1^\circ$ and methyl substrates.

\[ \text{I}^- + \text{H}_3\text{C} - \text{Br} \rightarrow \text{I} - \text{CH}_3 + \text{Br}^- \]

Sketch a reaction profile diagram for the above reaction.
The $S_N2$ Reaction - Kinetics.

Consider:

• What happens to the rate of production of CH$_3$I if the concentration of CH$_3$Br is held constant and the concentration of I$^-$ is increased?

• What happens to the rate of production of CH$_3$I if the concentration of I$^-$ is held constant and the concentration of CH$_3$Br is increased?
The Stereochemistry of the $S_N2$ reaction

The reaction geometry is such that the collision must occur with the nucleophile attacking the back side of the C—LG bond.

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

When attack occurs at an asymmetric carbon, the reaction occurs **exclusively** with inversion of the absolute stereochemistry.

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

Stereospecific: A reaction in which the mechanism dictates that different stereoisomeric reactants give different stereoisomeric products.
The Stereochemistry of the $S_N2$ reaction

Why backside attack?
### $S_N2$ reactions - Reactivity

Substrate dependance:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{Br}$</td>
<td>100</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{Br}$</td>
<td>1.31</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$</td>
<td>0.81</td>
</tr>
<tr>
<td>$\text{H}_3\text{C} - \text{CH}_2\text{Br}$</td>
<td>0.015</td>
</tr>
<tr>
<td>$\text{H}_3\text{C} - \text{CH}_3\text{Br}$</td>
<td>0.004</td>
</tr>
</tbody>
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</tr>
<tr>
<td>$\text{H}_3\text{C} - \text{CH}_3\text{Br}$</td>
<td>0.004</td>
</tr>
<tr>
<td>$\text{H}_3\text{C} - \text{CH}_3\text{Br}$</td>
<td>0.000001</td>
</tr>
</tbody>
</table>
$S_N2$ reactions – Solvent Effects

$S_N2$ reactions are typically done in **polar aprotic** solvents. These solvents are polar enough to solubilize the nucleophile but do not stabilize the nucleophiles enough to prevent reaction.

Some common **polar aprotic** solvents:

- Acetone
- Acetonitrile (MeCN)
- Dimethoxyethane (DME)
- Dimethylformamide (DMF)
- Dimethyl sulfoxide (DMSO)
- Ethyl ether (Et$_2$O)
- Pyridine (Pyr)
- Tetrahydrofuran (THF)
**SN2 reactions - Reactivity**

When evaluating SN2 reactions, you have to consider everything involved in the reaction. This includes the substrate, the nucleophile, the leaving group and the solvent.

For each set of reactions, draw the SN2 products. Then indicate which reaction should proceed faster and why.

**A**

\[
\begin{align*}
\text{SH} + \text{H}_3\text{C-Cl} & \rightarrow \\
\text{SH} + \text{H}_3\text{C-I} & \rightarrow 
\end{align*}
\]

**B**

\[
\begin{align*}
\text{SH} + \text{H}_3\text{C-Br} & \rightarrow \\
\text{OH} + \text{H}_3\text{C-Br} & \rightarrow 
\end{align*}
\]
For each set of reactions, draw the $S_{N2}$ products. Then indicate which reaction should proceed faster and why.

C

$\text{SH} + \text{Br}$

$\text{SH} \rightarrow \text{Br}$
### SN1 vs. SN2 reactions – Comparison

<table>
<thead>
<tr>
<th></th>
<th>SN2</th>
<th>SN1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction Order</strong></td>
<td>second order reaction</td>
<td>first order reaction</td>
</tr>
<tr>
<td><strong>Minimum # Steps</strong></td>
<td>1 or more steps</td>
<td>2 or more steps</td>
</tr>
<tr>
<td><strong>Intermediates?</strong></td>
<td>No</td>
<td>carbocation</td>
</tr>
<tr>
<td><strong>Stereochemical</strong></td>
<td>stereospecific inversion of configuration at electrophilic site</td>
<td>racemization (full or partial) at electrophilic site</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>very important; no reaction for weak nucleophiles like H₂O</td>
<td>unimportant</td>
</tr>
<tr>
<td><strong>Importance of</strong></td>
<td>very important; no reaction for weak leaving groups like HO⁻</td>
<td>very important; no reaction for weak leaving groups like HO⁻</td>
</tr>
<tr>
<td><strong>Nucleophile Strength</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Importance of</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leaving Group</strong></td>
<td>avoid steric hindrance; CH₃ &gt; 1° &gt; 2° (slow) &gt; 3° (no); no reaction for aryl/vinyl</td>
<td>need carbocation stabilization; 3° &gt; 2° (slow) &gt; 1° (no); resonance stabilization helps; no reaction for aryl/vinyl</td>
</tr>
<tr>
<td><strong>Substrate Structure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dependence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solvent</strong></td>
<td>polar aprotic</td>
<td>polar protic</td>
</tr>
<tr>
<td><strong>Competing Reactions</strong></td>
<td>E2</td>
<td>E1, E2, rearrangement</td>
</tr>
</tbody>
</table>
Would you expect the following reactions to proceed via $S_N\text{1}$, $S_N\text{2}$, both, or neither? Draw the expected product(s) for each reaction.

1. 
   \[
   \text{CH}_3\text{CH}(_2\text{CH}_2\text{CH}_2\text{Cl}) + \text{NaI} \rightarrow \text{acetone}
   \]

2. 
   \[
   \text{CH}_3\text{CH}(_2\text{CH}_2\text{Cl}) + \text{NaI} \rightarrow \text{acetone}
   \]

3. 
   \[
   \text{Br}^- + \text{ArCH}_2\text{Cl} \rightarrow
   \]

4. 
   \[
   \text{H}_2\text{O} + \text{ArCH}_2\text{Cl} \rightarrow
   \]