Chapter 11: Nucleophilic Substitution and Elimination

Walden Inversion

\[
\text{(S)-(-) Malic acid} \quad [\Delta]_D = -2.3^\circ \\
\rightarrow \quad \text{PCl}_5 \\
\text{(S)-(-) Malic acid} \quad [\Delta]_D = +2.3^\circ
\]

The displacement of a leaving group in a nucleophilic substitution reaction has a defined stereochemistry.

Stereochemistry of nucleophilic substitution

p-toluenesulfonate ester (tosylate): converts an alcohol into a leaving group; tosylate are excellent leaving groups. abbreviates as Tos

\[
\begin{align*}
\text{Nu} & : \quad \text{C}=\text{O} \quad \text{X} \\
\text{X} & : \quad \text{Cl, Br, I} \\
\text{C}=\text{O} & : \quad \text{Nu} \quad \text{C} \quad \text{Nu}
\end{align*}
\]

\[
\begin{align*}
\text{Nu} & : \quad \text{C}=\text{O} \quad \text{S}=\text{O} \quad \text{O} \quad \text{C} \quad \text{H}_3 \\
\text{C}=\text{O} & : \quad \text{Nu} \quad \text{C} \quad \text{Nu}
\end{align*}
\]
The nucleophilic substitution reaction “inverts” the Stereochemistry of the carbon (electrophile)- Walden inversion

**Kinetics of nucleophilic substitution**

Reaction rate: how fast (or slow) reactants are converted into product (kinetics)

Reaction rates are dependent upon the concentration of the reactants. (reactions rely on molecular collisions)

Consider:

At a given temperature:
- If [OH\textsuperscript{-}] is doubled, then the reaction rate may be doubled
- If [CH\textsubscript{3}-Br] is doubled, then the reaction rate may be doubled

A linear dependence of rate on the concentration of two reactants is called a second-order reaction (molecularity)
Reaction rates (kinetic) can be expressed mathematically:
reaction rate = disappearance of reactants (or appearance of products)

For the disappearance of reactants:
rate = $k \ [CH_3Br] \ [OH^-]$

$[CH_3Br] = CH_3Br$ concentration
$[OH^-] = OH^-$ concentration
$k = $ constant (rate constant) \(\frac{L}{mol\cdot sec}\)

For the reaction above, product formation involves a collision between both reactants, thus the rate of the reaction is dependent upon the concentration of both.

Nucleophilic Substitution comes in two reaction types:

**$S_N2$**

- S= substitution
- N= nucleophilic
- 2= biomolecular
- rate = $k \ [R-X] \ [Nu:]$

**$S_N1$**

- S= substitution
- N= nucleophilic
- 1= unimolecular
- rate = $k \ [R-X]$
The $S_N2$ Reaction: Mechanism

The nucleophile $-OH$ 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 $C-OH$ bond and a partially broken $C-Br$ bond.

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

Steric effects in the $S_N2$ reaction:
• For an $S_N2$ reaction, the nucleophile approaches the electrophilic carbon at an angle of 180° from the leaving group (backside attack)
• the rate of the $S_N2$ reaction decreases as the steric hindrance (substitution) of the electrophile increases.
### Increasing reactivity in the $S_N2$ reaction

<table>
<thead>
<tr>
<th>R</th>
<th>H_3C-Br</th>
<th>H_3C-C-CH_3-Br</th>
<th>H_3C-C-CH_3-Br</th>
<th>H_3C-C-Br</th>
<th>H-C-Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivity</td>
<td>tertiary</td>
<td>neopentyl</td>
<td>secondary</td>
<td>primary</td>
<td>methyl</td>
</tr>
<tr>
<td>relative</td>
<td>&lt;&lt; 1</td>
<td>1</td>
<td>500</td>
<td>40,000</td>
<td>2,000,000</td>
</tr>
</tbody>
</table>

Vinyl and aryl halides do not react in nucleophile substitution reactions:

The nature of the nucleophile in the $S_N2$ Reaction:

The measure of nucleophilicity is imprecise.

<table>
<thead>
<tr>
<th>Nu</th>
<th>Relative Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H_2O</td>
<td>1</td>
</tr>
<tr>
<td>CH_3CO_2^-</td>
<td>500</td>
</tr>
<tr>
<td>NH_3</td>
<td>700</td>
</tr>
<tr>
<td>Cl^-</td>
<td>1,000</td>
</tr>
<tr>
<td>HO^-</td>
<td>16,000</td>
</tr>
<tr>
<td>CH_3O^-</td>
<td>25,000</td>
</tr>
<tr>
<td>I^-</td>
<td>100,000</td>
</tr>
<tr>
<td>N≡C^-</td>
<td>125,000</td>
</tr>
<tr>
<td>HS^-</td>
<td>125,000</td>
</tr>
</tbody>
</table>
Nucleophiles are Lewis bases

Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same attacking atom

<table>
<thead>
<tr>
<th>Nu:</th>
<th>CH₃O⁻</th>
<th>HO⁻</th>
<th>CH₃CO₂⁻</th>
<th>H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>relative reactivity:</td>
<td>25,000</td>
<td>16,000</td>
<td>500</td>
<td>1</td>
</tr>
<tr>
<td>pKa of the conj. acid:</td>
<td>15.5</td>
<td>15.7</td>
<td>4.7</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

Nucleophilicity usually increases going down a column of the periodic chart. Thus, sulfur nucleophiles are more reactive than oxygen nucleophiles. I⁻ > Br⁻ > Cl⁻.

Negatively charges nucleophiles are usually more reactive than neutral nucleophiles.

The role of the leaving group in $S_N2$ reactions:

The leaving group is usually displaced with a negative charge

The best leaving groups are those with atoms or groups that can best stabilize a negative charge.

Good leaving groups are the conjugate bases of strong acids

\[ H\text{-}X \xrightarrow{\text{Nu}^-} H^+ + X^- \]

the lower the pKa of H-X, the stronger the acid.
**Increasing reactivity in the S_N2 reaction**

<table>
<thead>
<tr>
<th>LG:</th>
<th>HO^-, H_2N^-, RO^-</th>
<th>F^-</th>
<th>Cl^-</th>
<th>Br^-</th>
<th>I^-</th>
<th>TosO^-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Reactivity:</td>
<td>&lt;&lt;1</td>
<td>1</td>
<td>200</td>
<td>10,000</td>
<td>30,000</td>
<td>60,000</td>
</tr>
<tr>
<td>pKa:</td>
<td>&gt;15</td>
<td>3.45</td>
<td>-7.0</td>
<td>-8.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Charged Leaving Groups: conversion of a poor leaving group to a good one

**The role of the solvent in S_N2 reactions:**

Descriptor 1:
- polar: “high” dipole moment
  - water
  - alcohols
  - DMSO
- non-polar: low dipole moment (hexanes)

Descriptor 2:
- protic: acidic hydrogens that can form hydrogen bonds
  - water, alcohols
- aprotic: no acidic hydrogens

- hexamethylphosphoramide (HMPA)
- DMSO
- acetonitrile
- dimethylformamide (DMF)
**Solvation:** solvent molecules form “shells” around reactants and dramatically influence their reactivity.

**Polar protic solvents** stabilize the nucleophile, thereby lowering its energy. This will raise the activation energy of the reactions. $S_{N}2$ reactions are not favored by polar protic solvents.

**Polar aprotic solvents** selectively solvate cations. This raises the energy of the anion (nucleophile), thus making it more reactive. $S_{N}2$ reactions are favored by polar aprotic solvents.

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

<table>
<thead>
<tr>
<th>Solvent</th>
<th>CH$_3$OH</th>
<th>H$_2$O</th>
<th>DMSO</th>
<th>DMF</th>
<th>CH$_3$CN</th>
<th>HMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>relative reactivity:</td>
<td>1</td>
<td>7</td>
<td>1,300</td>
<td>2,800</td>
<td>5,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>

©2011 Brooks/Cole—Thomson Learning  Reaction progress
The **S\textsubscript{N}1 Reaction:**

kinetics: first order reaction (unimolecular)

\[
\text{rate} = k \ [R-X]
\]

[R-X] = alkyl halide conc.

The nucleophile does not appear in the rate expression—changing the nucleophile concentration does not affect the rate of the reaction!

Must be a two-step reaction

The overall rate of a reaction is dependent upon the slowest step: rate-limiting step

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**The Mechanism of the S\textsubscript{N}1 Reaction**

Spontaneous dissociation of the alkyl bromide occurs in a slow, rate-limiting step to generate a carbenium ion plus bromide ion.

The carbenium intermediate reacts with water as nucleophile in a fast step to yield protonated alcohol as product.

Loss of a proton from the protonated alcohol intermediate then gives the neutral alcohol product.
Reactivity of the Alkyl Halide in the $S_N1$ Reaction:

Formation of the carbocation intermediate is rate-limiting. Thus, carbocation stability greatly influence the reactivity.

The order of reactivity of the alkyl halide in the $S_N1$ reaction exactly parallels the carbocation stability.
Allylic and benzylic carbocations are stabilized by resonance.

Stereochemistry of the $S_N1$ Reaction: it is actually a complicated issue. For the purpose of Chem 220a, sect. 2 the stereochemistry of the $S_N1$ reaction gives racemization. A chiral alkyl halide will undergo $S_N1$ substitution to give a racemic product.
The role of the leaving group in S_N1 reactions:

same as for the S_N2 reaction

\[ \text{TosO}^- > \text{I}^- > \text{Br}^- > \text{Cl}^- \approx \text{H}_2\text{O} \]

Charged Leaving Groups: conversion of a poor leaving group to a good one

The role of the nucleophile in S_N1 reactions: None

Involvement of the nucleophile in the S_N1 reaction is after the rate-limiting step. Thus, the nucleophile does not appear in the rate expression. The nature of the nucleophile plays no role in the rate of the S_N1 reaction.

The role of the solvent in S_N1 reactions:

polar solvents are favored over non-polar for the S_N1 reaction
protic solvents are favored over aprotic for the S_N1 reaction

Solvent polarity is measured by dielectric constant (\( \varepsilon \))

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( \varepsilon )</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>1.9</td>
<td>nonpolar</td>
</tr>
<tr>
<td>(CH_3CH_2)_2O</td>
<td>4.3</td>
<td>nonpolar</td>
</tr>
<tr>
<td>HMPA</td>
<td>30</td>
<td>aprotic</td>
</tr>
<tr>
<td>DMF</td>
<td>38</td>
<td>aprotic</td>
</tr>
<tr>
<td>DMSO</td>
<td>48</td>
<td>aprotic</td>
</tr>
<tr>
<td>CH_3CH_2OH</td>
<td>24</td>
<td>polar</td>
</tr>
<tr>
<td>CH_3OH</td>
<td>34</td>
<td>protic</td>
</tr>
<tr>
<td>H_2O</td>
<td>80</td>
<td>protic</td>
</tr>
</tbody>
</table>
\[ \text{CH}_3\text{C}^\text{Cl}\text{CH}_3 + \text{ROH} \rightarrow \text{CH}_3\text{C}^\text{OR}\text{CH}_3 + \text{HCl} \]

Solvent: Ethanol 40% H\text{2O} 80% H\text{2O} H\text{2O}

40% H\text{2O} 80% H\text{2O} H\text{2O}

60% Ethanol 20% Ethanol

Rel. reactivity: 1 100 14,000 100,000

**Increasing reactivity in the S\text{N}1 reaction**

Solvent stabilization of the transition state

Solvent stabilization of the intermediates

Stabilization of the intermediate carbocation and the transition state by polar protic solvents in the S\text{N}1 reaction
Elimination Reactions: Nucleophiles are Lewis bases. In the reaction with alkyl halides, they can also promote elimination reactions rather than substitution.

Elimination is a competitive reaction with nucleophilic substitution.

Zaitsev’s Rule: When more than one alkene product is possible from the base induced elimination of an alkyl halide, the most highly substituted (most stable) alkene is usually the major product.
The E2 Elimination:

rate = k [R-X] [Base]

Base (B⁻) attacks a neighboring hydrogen and begins to remove the H at the same time as the alkene double bond starts to form and the X group starts to leave.

Neutral alkene is produced when the C–H bond is fully broken and the X group has departed with the C–X bond electron pair.

Stereochemistry of the E2 Elimination:

The H being abstracted and the leaving group must be in the same plane.

Syn periplanar: the H and X are eclipsed dihedral angle = 0 °

Anti periplanar: the H and X are anti staggered dihedral angle = 180 °

Generally, the anti periplanar geometry is energetically preferred (staggered conformation vs eclipsed)
In the periplanar conformation, the orbitals are already aligned for \( \pi \)-bond formation.

The E2 elimination has a defined geometric (stereochemical) outcome:

Anti periplanar geometry is usually preferred for E2 elimination.
E2 elimination with halocyclohexane reactants

**Equatorial chlorine: H and Cl are not anti periplanar**

![Equatorial chlorine reaction](image)

Base, No reaction from this conformation

**Axial chlorine: H and Cl are anti periplanar**

![Axial chlorine reaction](image)

Base, E2 reaction, + HCl

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**Neomenthyl chloride**

H<sub>3}C<sub>CH(CH<sub>3)<sub>2</sub> = H<sub>2}C<sub>CH(CH<sub>3)<sub>2</sub> (Fast Na<sup>+</sup> + OCH<sub>3</sub>H<sub>2</sub>, ethanol)

3-Menthene

**Menthylic chloride**

H<sub>3}C<sub>CH(CH<sub>3)<sub>2</sub> = H<sub>2}C<sub>CH(CH<sub>3)<sub>2</sub> (Ring flip)

2-Menthene
The E1 Elimination:
rate = k [R-X]

Spontaneous dissociation of the tertiary alkyl chloride yields an intermediate carbocation in a slow, rate-limiting step.

Carbocation

Loss of a neighboring H⁺ in a fast step yields the neutral alkene product. The electron pair from the C–H bond goes to form the alkene π bond.

No geometric requirements for E1 elimination. Usually follows Zaitsev’s Rule
**S<sub>N</sub>2 vs E2**

For primary alkyl halides S<sub>N</sub>2 is favored with most nucleophiles.

E2 is favored with “bulky” bases (t-butoxide)

- t-butoxide is too bulky to undergo S<sub>N</sub>2

**Secondary halides:** E2 is competitive with S<sub>N</sub>2 and often gives a mixture of substitution and elimination products.

**Tertiary Halides:**
- E2 elimination occurs with strong bases such as HO⁻, RO⁻, H₂N⁻ (strongly basic conditions)
- E1 elimination occurs with heat and weak bases such as H₂O or ROH. (neutral conditions)
- The E1 elimination product is often a minor product with the major product arising from S<sub>N</sub>1 reaction.

S<sub>N</sub>2 reaction does not occur with 3° halides.