**Alkyl Halides and Nucleophilic Substitution**

**Introduction to Alkyl Halides:**

- **Alkyl halides** are organic molecules containing a halogen atom bonded to an $sp^3$ hybridized carbon atom.

- Alkyl halides are 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.

- The halogen atom in halides is often denoted by the symbol “$X$”.
Physical Properties:

- Alkyl halides are weak polar molecules. They exhibit dipole-dipole interactions because of their polar C—X bond, but because the rest of the molecule contains only C—C and C—H bonds, they are incapable of intermolecular hydrogen bonding.

Dipole–dipole interactions

Opposite ends of the dipoles interact.
The Polar Carbon-Halogen Bond

- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient.

Electrostatic potential maps of four halomethanes (CH₃X)
Nucleophile (Nucleophile = “seeks a nucleus”   Nucleus = + charge)

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.

Nucleophilic substitution and elimination reactions Generally speaking, there are two things that can happen when a nucleophile ("Nu:-") encounters an alkyl halide:
The replacement of one of the groups (leaving group, ) bonded to a carbon, by a electron-rich reagent, nucleophile, such as I- or HO-
An electron-rich reagent, Nu, bonds to an H as HX is removed in a elimination reaction. Nucleophile can act as a base, inducing "dehydrohalogenation" of the alkyl halide and producing an alkene.

- Alkyl halides undergo substitution reactions with nucleophiles.

- Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.
Alkyl Halides and Nucleophilic Substitution

The Nucleophile:

- Nucleophiles and bases are structurally similar: both have a lone pair or a $\pi$ bond. They differ in what they attack.
- Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).
The Leaving Group (a review of basicity):

- There are periodic trends in leaving group ability:
  - Left-to-right across a row of the periodic table, basicity decreases so leaving group ability increases.
  
  With second-row elements:
  
  Increasing basicity
  
  :NH₃  H₂Ō⁺  
  
  Increasing leaving group ability
  
  better leaving group

- Down a column of the periodic table, basicity decreases so leaving group ability increases.
  
  Increasing basicity
  
  F⁻  Cl⁻  Br⁻  I⁻  
  
  Increasing leaving group ability
  
  weakest base best leaving group
The Leaving Group:

### Poor leaving groups for Nucleophilic Substitution

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Leaving group</th>
<th>Conjugate acid</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>R−F</td>
<td>F⁻</td>
<td>HF</td>
<td>3.2</td>
</tr>
<tr>
<td>R−OH</td>
<td>OH⁻</td>
<td>H₂O</td>
<td>15.7</td>
</tr>
<tr>
<td>R−NH₂</td>
<td>NH₂⁻</td>
<td>NH₃</td>
<td>38</td>
</tr>
<tr>
<td>R−H</td>
<td>H⁻</td>
<td>H₂</td>
<td>35</td>
</tr>
<tr>
<td>R−R</td>
<td>R⁻</td>
<td>RH</td>
<td>50</td>
</tr>
</tbody>
</table>

These molecules do not undergo nucleophilic substitution.

Strong bases
The Leaving Group

**Good leaving groups for Nucleophilic Substitution**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Leaving group</th>
<th>Conjugate acid</th>
<th>pK$_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>R−Cl</td>
<td>Cl$^-$</td>
<td>HCl</td>
<td>−7</td>
</tr>
<tr>
<td>R−Br</td>
<td>Br$^-$</td>
<td>HBr</td>
<td>−9</td>
</tr>
<tr>
<td>R−I</td>
<td>I$^-$</td>
<td>HI</td>
<td>−10</td>
</tr>
<tr>
<td>R−OH$_2^+$</td>
<td>H$_2$O</td>
<td>H$_3$O$^+$</td>
<td>−1.7</td>
</tr>
</tbody>
</table>

These molecules undergo nucleophilic substitution.

**good leaving groups**

Weak bases
General Features of Nucleophilic Substitution:

- Negatively charged nucleophiles like $\text{HO}^-$ and $\text{HS}^-$ are used as salts with $\text{Li}^+$, $\text{Na}^+$, or $\text{K}^+$ counterions to balance the charge. Since the identity of the counterion is usually inconsequential, it is often omitted from the chemical equation.

- When a neutral nucleophile is used, the substitution product bears a positive charge.
The Nucleophile:

• Nucleophilicity parallels basicity in three instances:

  1. For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile.
     The relative nucleophilicity of HO\(^-\) and CH\(_3\)COO\(^-\), two oxygen nucleophiles, is determined by comparing the p\(K_a\) values of their conjugate acids (H\(_2\)O = 15.7, and CH\(_3\)COOH = 4.8). HO\(^-\) is a stronger base and stronger nucleophile than CH\(_3\)COO\(^-\).

  2. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid.
     HO\(^-\) is a stronger base and stronger nucleophile than H\(_2\)O.

  3. Right-to-left-across a row of the periodic table, nucleophilicity increases as basicity increases:
Common Nucleophiles:

<table>
<thead>
<tr>
<th></th>
<th>Negatively charged nucleophiles</th>
<th>Neutral nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>−OH</td>
<td>H₂O</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>N₃⁻</td>
<td>NH₃</td>
</tr>
<tr>
<td>Carbon</td>
<td>−CN</td>
<td>H₂S</td>
</tr>
<tr>
<td>Halogen</td>
<td>Cl⁻</td>
<td>H₂S</td>
</tr>
<tr>
<td>Sulfur</td>
<td>HS⁻</td>
<td>H₂S</td>
</tr>
</tbody>
</table>

In the left box, all are strong nucleophiles except chloride and acetate which are medium.

In the right box, HOH and ROH are weak, the others medium.
Solvent effect on the Nucleophile:

**Polar protic** solvent has a hydrogen atom attached to a strongly electronegative element (e.g. oxygen) that forms hydrogen bonds. **-Polar protic** solvent solvate cations and anions effectively while **aprotic solvents** do not solvate anions to any appreciable extend.

- **Polar protic** solvents are more suitable for $S_N1$ reactions, while **aprotic solvents** are used for $S_N2$ reactions

**Example of polar protic solvents**

$H_2O$ \hspace{1cm} $CH_3OH$ \hspace{1cm} $CH_3CH_2OH$ \hspace{1cm} $(CH_3)_3COH$ \hspace{1cm} $CH_3COOH$

methanol \hspace{1cm} ethanol \hspace{1cm} \hspace{1cm} tert-butanol \hspace{1cm} acetic acid
• Polar aprotic solvents are those solvents whose molecules do not have a hydrogen atom that's attached to an atom of an electronegative element. **Polar aprotic solvents** also exhibit dipole—dipole interactions, but they have no O—H or N—H bonds. Thus, they are incapable of hydrogen bonding.

**Examples of polar aprotic solvents**

- acetone
- acetonitrile
- tetrahydrofuran (THF)
- dimethyl sulfoxide (DMSO)
- dimethylformamide (DMF)
- hexamethylphosphoramide (HMPA)
• In polar aprotic solvents, nucleophilicity parallels basicity, and the stronger base is the stronger nucleophile.
• Because basicity decreases as size increases down a column, nucleophilicity decreases as well. \[ \text{F highest nucleophilicity and I lowest} \]
The Nucleophile:

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- **Steric hindrance** is a decrease in reactivity resulting from the presence of bulky groups at the site of a reaction.
- Steric hindrance decreases nucleophilicity but not basicity.
- Sterically hindered bases that are poor nucleophiles are called **nonnucleophilic bases**.
Mechanisms of Nucleophilic Substitution:

In a nucleophilic substitution:

But what is the order of bond making and bond breaking? In theory, there are three possibilities.

[1] Bond making and bond breaking occur at the same time.

In this scenario, the mechanism is comprised of one step. In such a bimolecular reaction, the rate depends upon the concentration of both reactants, that is, the rate equation is second order.
Mechanisms of Nucleophilic Substitution:


In this scenario, the mechanism has two steps and a carbocation is formed as an intermediate. Because the first step is rate-determining, the rate depends on the concentration of RX only; that is, the rate equation is first order.
This mechanism has an inherent problem. The intermediate generated in the first step has 10 electrons around carbon, violating the octet rule. Because two other mechanistic possibilities do not violate a fundamental rule, this last possibility can be disregarded.
$S^{N1}/E1$

$S^{N1}$ and E1 have identical rate determining steps, so they generally occur simultaneously and have the same properties.

$S^{N2}$

E2
Kinetics

- If two molecules must come together in order for a reaction to take place, then the rate at which that reaction occurs will depend on the concentrations of both of these species. If this reaction is the slowest step (i.e., the "rate-determining step") in a series of steps leading to an overall transformation, or if it is the only step in the reaction, then that reaction will exhibit "bimolecular" or "second-order" kinetics.

- Both the $S_N2$ and $E2$ reactions exhibit bimolecular kinetics. That is, these reactions have "rate laws" that show the direct dependence of the reaction rate on the concentrations of both the alkyl halide and the nucleophile:
  - rate = $k[RX][Nu:\cdot]$  

- $S_N1$ and $E1$ reactions exhibit "unimolecular" kinetics, for which the rate depends only on the concentration of the alkyl halide, and not at all on the nucleophile. The different rate law for these reactions implies that they proceed by a different mechanism.
Kinetic data show that the rate of reaction depends on the concentration of both reactants, which suggests a bimolecular reaction with a one-step mechanism. This is an example of an $S_N2$ (substitution nucleophilic bimolecular) mechanism.
examples of $S_N2$ inversion of configuration: The Walden Inversion.

- The bond to the nucleophile in the product is always on the opposite side relative to the bond to the leaving group in the starting material.
An energy diagram for the $S_N2$ reaction:

$$\text{CH}_3\text{Br} + \text{CH}_3\text{COO}^- \rightarrow \text{CH}_3\text{COOCH}_3 + \text{Br}^-$$

- In the transition state, the C–Br bond is partially broken, the C–O bond is partially formed, and both the attacking nucleophile and the departing leaving group bear a partial negative charge.
• The higher the $E_a$, the slower the reaction rate. Thus, any factor that increases $E_a$ decreases the reaction rate.

Two energy diagrams depicting the effect of steric hindrance in $S_{N2}$ reactions
Mechanisms of Nucleophilic Substitution:

- As the number of R groups on the carbon with the leaving group increases, the rate of an $S_N2$ reaction decreases.

<table>
<thead>
<tr>
<th>CH$_3$–X</th>
<th>RCH$_2$–X</th>
<th>R$_2$CH–X</th>
<th>R$_3$C–X</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>1°</td>
<td>2°</td>
<td>3°</td>
</tr>
</tbody>
</table>

Increasing rate of an $S_N2$ reaction

- Methyl and 1° alkyl halides undergo $S_N2$ reactions with ease.
- 2° Alkyl halides react more slowly.
- 3° Alkyl halides do not undergo $S_N2$ reactions. This order of reactivity can be explained by steric effects. Steric hindrance caused by bulky R groups makes nucleophilic attack from the backside more difficult, slowing the reaction rate.
All $S_N2$ reactions proceed with backside attack of the nucleophile, resulting in inversion of configuration at a stereogenic center.

**Stereochemistry of the $S_N2$ reaction**

:nu$^-$ and Br$^-$ are 180° away from each other, on either side of a plane containing R, H, and D.
Factors influencing the rate of $S_{N2}$ reactions

There are four factors that influence the rate of $S_{N2}$ reactions:

1. the substrate (alkyl halide) structure
2. the nucleophile
3. the leaving group
4. the solvent
## Characteristics of $S_N2$ reactions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics</td>
<td>- Second-order kinetics; rate $= k[RX][\text{Nu}^-]$</td>
</tr>
<tr>
<td>Mechanism</td>
<td>- One step</td>
</tr>
<tr>
<td>Stereochemistry</td>
<td>- Backside attack of the nucleophile</td>
</tr>
<tr>
<td></td>
<td>- Inversion of configuration at a stereogenic center</td>
</tr>
<tr>
<td>Identity of R</td>
<td>- Unhindered halides react fastest.</td>
</tr>
<tr>
<td></td>
<td>- Rate: $\text{CH}_3\text{X} &gt; \text{RCH}_2\text{X} &gt; \text{R}_2\text{CHX} &gt; \text{R}_3\text{CX}$</td>
</tr>
</tbody>
</table>
Kinetic data show that the rate of reaction [2] depends on the concentration of only the alkyl halide. This suggests a two-step mechanism in which the rate-determining step involves the alkyl halide only. This is an example of an S_N1 (substitution nucleophilic unimolecular) mechanism.

- mechanism SN1 indicates a substitution, nucleophilic, unimolecular reaction, described by the expression rate = k [R-LG]. This implies that the rate determining step of the mechanism depends on the decomposition of a single molecular species.

- This pathway is a multi-step process with the following characteristics:
  
  step 1: slow loss of the leaving group, LG, to generate a carbocation intermediate,
The mechanism of an $S_N1$ reaction would be drawn as follows: Note the curved arrow formalism that is used to show the flow of electrons.

Key features of the $S_N1$ mechanism are that it has two steps, and carbocations are formed as reactive intermediates.
Multi-step reactions have intermediates and several transition states (TS). In an SN1 there is loss of the leaving group generates an intermediate carbocation which is then undergoes a rapid reaction with the nucleophile.
An energy diagram for the $S_N1$ reaction:

$\text{(CH}_3\text{)}_3\text{CBr} + \text{CH}_3\text{COO}^- \rightarrow \text{(CH}_3\text{)}_3\text{COCOCH}_3 + \text{Br}^-$

- Since the $S_N1$ mechanism has two steps, there are two energy barriers.
- In each step only one bond is broken or formed, so the transition state for each step has one partial bond.
- The reaction is drawn with $\Delta H^\circ_{\text{overall}}$ as a negative value, since the products are lower in energy than the starting materials.
In multistep reactions, the rate of the slowest step will be the rate of the entire reaction. This is called the rate determining step. In the case to the right, $k_1 \ll k_2$ or $k_3$ and the first step is rate determining.
SN1 MECHANISM FOR REACTION OF ALCOHOLS WITH HBr

Step 1:
An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.

Step 2:
Cleavage of the C-O bond allows the loss of the good leaving group, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic).

Step 3:
Attack of the nucleophilic bromide ion on the electrophilic carbocation creates the alkyl bromide.
To understand the stereochemistry of the $S_N1$ reaction, we must examine the geometry of the carbocation intermediate.

A trigonal planar carbocation

- A carbocation (with three groups around C) is $sp^2$ hybridized and trigonal planar, and contains a vacant $p$ orbital extending above and below the plane.

The more highly substituted a carbocation is, the more stable it is.
The more stable a carbocation is, the easier it is to form.

$3^0 > 2^0 > 1^0 >$ methyl
• Loss of the leaving group in Step [1] generates a planar carbocation that is achiral. In Step [2], attack of the nucleophile can occur on either side to afford two products which are a pair of enantiomers.
• Because there is no preference for nucleophilic attack from either direction, an equal amount of the two enantiomers is formed called a racemic mixture. We say that racemization has occurred.

(transformation of of optically active compound to a racemic mixture)
components of the reaction influence the reaction pathway:

- **R-** Reactivity order: (CH$_3$)$_3$C- > (CH$_3$)$_2$CH- > CH$_3$CH$_2$- > CH$_3$-

In an SN1 reaction, the rate determining step is the loss of the leaving group to form the intermediate carbocation. The more stable the carbocation is, the easier it is to form, and the faster the SN1 reaction will be. Since a carbocation intermediate is formed, there is the possibility of rearrangements (*e.g.* 1,2-hydride or 1,2-alkyl shifts) to generate a more **stable carbocation**. This is usually indicated by a change in the position of the substituent or a change in the carbon skeleton of the product when compared to the starting material.

- **LG**

  The only event in the rate determining step of the SN1 is breaking the C-LG bond. Therefore, there is a very strong dependence on the nature of the leaving group, the better the leaving, the faster the SN1 reaction will be.

- **Nu**

  Since the nucleophile is not involved in the rate determining step, the nature of the nucleophile is unimportant in an SN1 reaction. However, the more reactive the nucleophile, the more likely an SN2 reaction becomes.
Carbocation Stability:

• The order of carbocation stability can be rationalized through inductive effects and hyperconjugation.

• Inductive effects are electronic effects that occur through $\sigma$ bonds. Specifically, the inductive effect is the pull of electron density through $\sigma$ bonds caused by electronegativity differences between atoms.

• Alkyl groups are electron donating groups that stabilize a positive charge. Since an alkyl group has several $\sigma$ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.

• In general, the greater the number of alkyl groups attached to a carbon with a positive charge, the more stable will be the cation.
Carbocation Stability:

- The order of carbocation stability is also a consequence of hyperconjugation.

- **Hyperconjugation** is the spreading out of charge by the overlap of an empty $p$ orbital with an adjacent $\sigma$ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.

- **Example:** $\text{CH}_3^+$ cannot be stabilized by hyperconjugation, but $(\text{CH}_3)_2\text{CH}^+$ can.
Carbocation Stability:

- The effect of the type of alkyl halide on $S_N 1$ reaction rates can be explained by considering carbocation stability.
- Carbocations are classified as primary ($1^\circ$), secondary ($2^\circ$), or tertiary ($3^\circ$), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.
Carbocation Stability:

- The rate of an $S_{N1}$ reaction increases as the number of R groups on the carbon with the leaving group increases.
- The stability of a carbocation increases as the number of R groups on the positively charged carbon increases.

![Increasing rate of the $S_{N1}$ reaction](image)

![Increasing carbocation stability](image)
Characteristics of $S_{N1}$ reactions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetics</td>
<td>• First-order kinetics; rate = $k[RX]$</td>
</tr>
<tr>
<td>Mechanism</td>
<td>• Two steps</td>
</tr>
<tr>
<td>Stereochemistry</td>
<td>• Trigonal planar carbocation intermediate</td>
</tr>
<tr>
<td></td>
<td>• Racemization at a single stereogenic center</td>
</tr>
<tr>
<td>Identity of $R$</td>
<td>• More substituted halides react fastest.</td>
</tr>
<tr>
<td></td>
<td>• Rate: $R_3CX &gt; R_2CHX &gt; RCH_2X &gt; CH_3X$</td>
</tr>
</tbody>
</table>
Substrate in predicting SN1 vs SN2 mechanisms:

- Four factors are relevant in predicting whether a given reaction is likely to proceed by an $S_N 1$ or an $S_N 2$ mechanism: The most important is the structure of the alkyl halide.

- Increasing alkyl substitution favors $S_N 1$.
- Decreasing alkyl substitution favors $S_N 2$.

### Increasing rate of the $S_N 1$ reaction

- Methyl and $1^\circ$ halides (CH$_3$X and RCH$_2$X) undergo $S_N 2$ reactions only.
- $3^\circ$ Alkyl halides (R$_3$CX) undergo $S_N 1$ reactions only.
- $2^\circ$ Alkyl halides (R$_2$CHX) undergo both $S_N 1$ and $S_N 2$ reactions. Other factors determine the mechanism.
Nucleophile in predicting SN1 vs SN2 mechanisms:

- The strong nucleophile favors an $S_N2$ mechanism.

- The weak nucleophile favors an $S_N1$ mechanism.

The nucleophile attacks from **above** and **below**.

Two products are formed.
Leaving Group in predicting SN1 vs SN2 mechanisms:

- The leaving group is the third factor. A better leaving group increases the rate of both $S_N1$ and $S_N2$ reactions.
Solvent in predicting SN1 vs SN2 mechanisms:

- **The nature of the solvent is a fourth factor.**
- Polar protic solvents like H$_2$O and ROH favor $S_{N1}$ reactions because the ionic intermediates (both cations and anions) are stabilized by solvation.
- Polar aprotic solvents favor $S_{N2}$ reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.
Factors in predicting SN1 vs SN2 mechanisms:

Nucleophile:
- **SN1**  Nucleophilic strength not important
- **SN2**  Needs a strong nucleophile

Substrate:
- **SN1**  $3^\circ > 2^\circ$
- **SN2**  $\text{CH}_3 > 1^\circ > 2^\circ$

Solvent:
- **SN1**  Enhanced by more polar solvent
- **SN2**  Enhanced by less polar solvent

Leaving Group:
- **SN1**  Good LG important to form $\text{C}^+$
- **SN2**  Not as important but enhances reaction
Results of SN1 vs SN2 mechanisms:

**Kinetics:**
- SN1: rate = k[RX]
- SN2: rate = k[RX][Nu:]

**Stereochemistry:**
- SN1: both inversion and retention (racemic)
- SN2: inversion only

**Rearrangements:**
- SN1: rearrangements common
- SN2: rearrangements not possible
Factors in predicting SN1 vs SN2 mechanisms:

<table>
<thead>
<tr>
<th>Alkyl halide</th>
<th>Mechanism</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃X</td>
<td>S₉²</td>
<td>Favored by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- strong nucleophiles (usually a net negative charge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- polar aprotic solvents</td>
</tr>
<tr>
<td>RCH₂X (1°)</td>
<td>S₉¹</td>
<td>Favored by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- weak nucleophiles (usually neutral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- polar protic solvents</td>
</tr>
<tr>
<td>R₃CX (3°)</td>
<td>S₉¹</td>
<td>The mechanism depends on the conditions.</td>
</tr>
<tr>
<td>R₂CHX (2°)</td>
<td>S₉¹ or S₉²</td>
<td>Strong nucleophiles favor the S₉² mechanism over the S₉¹ mechanism. For example, RO⁻ is a stronger nucleophile than ROH, so RO⁻ favors the S₉² reaction and ROH favors the S₉¹ reaction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protic solvents favor the S₉¹ mechanism and aprotic solvents favor the S₉² mechanism. For example, H₂O and CH₃OH are polar protic solvents that favor the S₉¹ mechanism, whereas acetone [(CH₃)₂C=O] and DMSO [(CH₃)₂S=O] are polar aprotic solvents that favor the S₉² mechanism.</td>
</tr>
</tbody>
</table>
## Correlation of Structure and Reactivity for Substitution and Elimination Reactions

<table>
<thead>
<tr>
<th>Halide Type</th>
<th>$S_{N}1$</th>
<th>$S_{N}2$</th>
<th>E1</th>
<th>E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH$_2$X (primary)</td>
<td>Does not occur</td>
<td>Highly favored</td>
<td>Does not occur</td>
<td>Occurs when strong bases are used</td>
</tr>
<tr>
<td>R$_2$CHX (secondary)</td>
<td>Can occur with benzylic and allylic halides</td>
<td>Occurs in competition with E2 reaction</td>
<td>Can occur with benzylic and allylic halides</td>
<td>Favored when strong bases are used</td>
</tr>
<tr>
<td>R$_3$CX (tertiary)</td>
<td>Favored in hydroxylic solvents</td>
<td>Does not occur</td>
<td>Occurs in competition with $S_{N}2$ reaction</td>
<td>Favored when bases are used</td>
</tr>
</tbody>
</table>
(as a function of RX Structure)

In general, substrates react in the following way:

- $\text{RCH}_2\text{X}$ (primary): Mostly $S_N^2$ substitution
- $\text{R}_2\text{CHX}$ (primary): $S_N^2$ substitution with nonbasic nucleophiles, E2 elimination with strong bases
- $\text{R}_3\text{CX}$ (primary): Mostly E2 elimination, ($S_N^1$ substitution and E1 elimination in nonbasic solvents)
So what you need to take home is, that if it's a strong base (such as H$_2$N-, R-O-, or OH-) the reaction will most likely be elimination. If the reactant is a good nucleophile, but a poor base then substitution is a safe bet.

Protic, highly polar solvents favor $S_N$1 and E1, while aprotic, polar solvents will be found in $S_N$2 reactions. Following these simple tips will get you through the vast majority of nucleophilic substitution and beta elimination reactions.
Molecules synthesized from R-X by the **SN2** reaction

<table>
<thead>
<tr>
<th>Nucleophile ((\text{Nu}^-))</th>
<th>Product</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-\text{OH})</td>
<td>R-\text{OH}</td>
<td>alcohol</td>
</tr>
<tr>
<td>(-\text{OR}')</td>
<td>R-\text{OR}'</td>
<td>ether</td>
</tr>
<tr>
<td>(\text{CO}_2\text{H})</td>
<td></td>
<td>ester</td>
</tr>
<tr>
<td><strong>Carbon compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-\text{CN})</td>
<td>R-\text{CN}</td>
<td>nitrile</td>
</tr>
<tr>
<td>(\text{R}^\equiv\text{C}=\text{H})</td>
<td>R-\text{C}≡\text{C}=\text{H}</td>
<td>alkyne</td>
</tr>
<tr>
<td><strong>Nitrogen compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{N}_3^-)</td>
<td>R-\text{N}_3</td>
<td>azide</td>
</tr>
<tr>
<td>(\text{NH}_3)</td>
<td>R-\text{NH}_2</td>
<td>amine</td>
</tr>
<tr>
<td><strong>Sulfur compounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-\text{SH})</td>
<td>R-\text{SH}</td>
<td>thiol</td>
</tr>
<tr>
<td>(-\text{SR}')</td>
<td>R-\text{SR}'</td>
<td>sulfide</td>
</tr>
</tbody>
</table>

**products of nucleophilic substitution**