The S\textsubscript{N}2 mechanism

There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution. In the first picture, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).

This is called an 'S\textsubscript{N}2' mechanism. In the term S\textsubscript{N}2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a \textbf{bimolecular reaction}: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.

If you look carefully at the progress of the S\textsubscript{N}2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the \textit{back side} relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.

The result of this backside attack is that the stereochemical configuration at the central carbon \textit{inverts} as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.
What this means is that SN$_2$ reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the SN$_2$ reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.

![SN$_2$ Reaction Animation](image)

**Exercise**

Predict the structure of the product in this SN$_2$ reaction. Be sure to specify stereochemistry.

```
\[
\text{\text{CH}_3-CH}_2-CH}_2-\text{I} + \overset{\Theta}{\text{SCH}_3} \rightarrow 
\]
```

**Influence of the solvent in an SN$_2$ reaction**

The rate of an SN$_2$ reaction is significantly influenced by the solvent in which the reaction takes place. The use of protic solvents (those, such as water or alcohols, with hydrogen-bond donating capability) decreases the power of the nucleophile, because of strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. A less powerful nucleophile in turn means a slower SN$_2$ reaction. SN$_2$ reactions are faster in polar, aprotic solvents: those that lack hydrogen-bond donating capability. Below are several polar aprotic solvents that are commonly used in the laboratory:
These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic effects on the rate at which a nucleophilic substitution reaction can occur. For example, if we consider the reaction between bromoethane and potassium iodide, the reaction occurs 500 times faster in acetone than in methanol.

The **S\textsubscript{N}1** mechanism

A second model for a nucleophilic substitution reaction is called the 'dissociative', or 'S\textsubscript{N}1' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:

This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge
of +1. Recall that a carbocation should be pictured as $sp^2$ hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three $sp^2$ hybrid orbitals is an empty, unhybridized $p$ orbital.

![Image of a carbocation with an empty p orbital](image)

In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' $p$ orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.

![Image of a nucleophilic substitution reaction](image)

We saw that $S_N2$ reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of $S_N1$ reactions? In the model $S_N1$ reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, $sp^2$-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, racemization has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of $R$ and $S$ alcohols after an $S_N1$ reaction with water as the incoming nucleophile.

![Image of a racemic racemization](image)

**Exercise**

Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

The $S_N1$ reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity. Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the $S_N1$ reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an $S_N1$ reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.
Exercise

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher than that for the second step. Also recall that an S_N1 reaction has first order kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding.

Exercise

Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

\[
\text{A: } \text{CH}_3\text{I} + \text{CH}_3\text{S}^\ominus \xrightarrow{S_N2} \\
\text{B: } (\text{CH}_3)_3\text{CBr} + \text{CH}_3\text{SH} \xrightarrow{S_N1}
\]

Influence of the solvent in an SN1 reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an SN2, but it does not affect an SN1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because
the large dipole moment of the solvent helps to stabilize the transition state. The highly positive and highly negative parts interact with the substrate to lower the energy of the transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction. Sometimes in an SN1 reaction the solvent acts as the nucleophile. This is called a solvolysis reaction. The SN1 reaction of allyl bromide in methanol is an example of what we would call methanolysis, while if water is the solvent the reaction would be called hydrolysis:

\[
\text{Br} \quad \xrightarrow{\text{CH}_3\text{OH}} \quad \text{OCH}_3 + \text{HBr} \quad \text{methanolysis}
\]

\[
\text{Br} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{OH} + \text{HBr} \quad \text{hydrolysis}
\]

The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for the solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of SN1 reactions, the faster the rate.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CO₂H</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>H₂O</td>
<td>78</td>
<td>150,000</td>
</tr>
</tbody>
</table>

Below is the same reaction conducted in two different solvents and the relative rate that corresponds with it.

\[
\text{Relative Rate: 150,000}
\]

\[
\text{Relative Rate: 4}
\]

Exercise

Draw a complete curved-arrow mechanism for the methanolysis reaction of allyl bromide shown above.

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp³-hybridized carbons, and not where the leaving group is attached to an sp²-hybridized carbon.
Bonds on sp²-hybridized carbons are inherently shorter and stronger than bonds on sp³-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable (we’ll discuss the relative stability of carbocation intermediates in a later section of this module).

Before we look at some real-life nucleophilic substitution reactions in the next chapter, we will spend some time in the remainder of this module focusing more closely on the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group.

Practice Problems