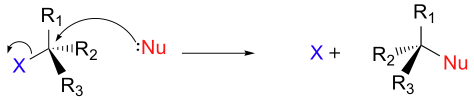
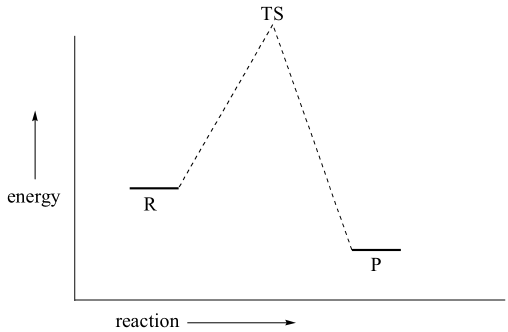
7.11: The S N 2 SN2 Mechanism

The S_N2 mechanism

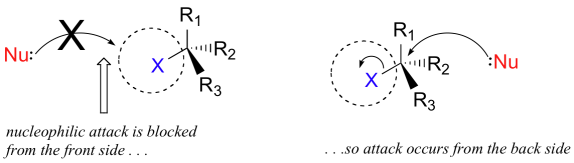
There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution. In the first picture, the reaction takes place in a single step, and bond-forming and bond-breaking occur simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



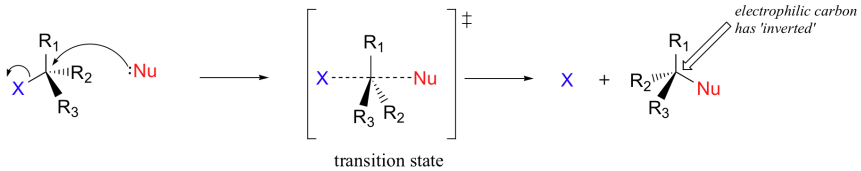
This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



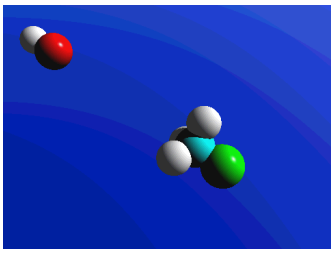
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side 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 *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.

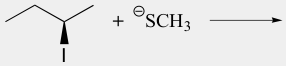


What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



Exercise

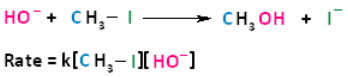
Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



We will be contrasting about two types of nucleophilic substitution reactions. One type is referred to as **unimolecular nucleophilic substitution (S_N1)**, whereby the rate determining step is unimolecular and **bimolecular nucleophilic substitution (S_N2)**, whereby the rate determining step is bimolecular. We will begin our discussion with S_N2 reactions, and discuss S_N1 reactions elsewhere.

Biomolecular Nucleophilic Substitution Reactions and Kinetics

In the term S_N2, the S stands for substitution, the N stands for nucleophilic, and the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



$$\text{Rate} = k[CH_3{-}I][HO^-]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 2k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 2\,\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$\text{Rate}_1 = k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 4k[CH_3{-}I][HO^-]$$
$$\text{Rate}_2 = 4\,\text{Rate}_1$$

The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

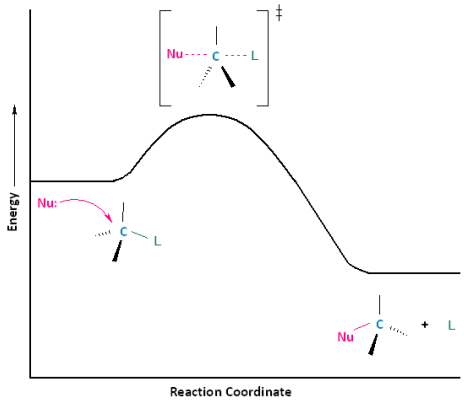
- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

Bimolecular Nucleophilic Substitution Reactions Are Concerted

Bimolecular nucleophilic substitution (SN_2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the

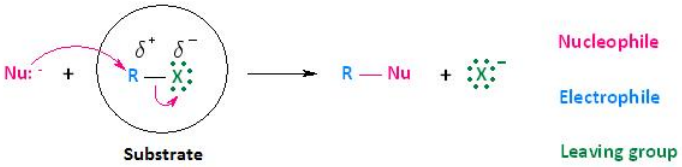
nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electophilic carbon and the halogen.

The potential energy diagram for an SN_2 reaction is shown below. Upon nucleophilic attack, a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. Again, this is a single-step, concerted process with the occurrence of a single transition state.

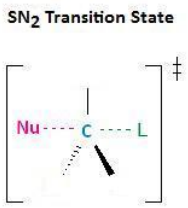


Sterrically Hindered Substrates Will Reduce the S_N2 Reaction Rate

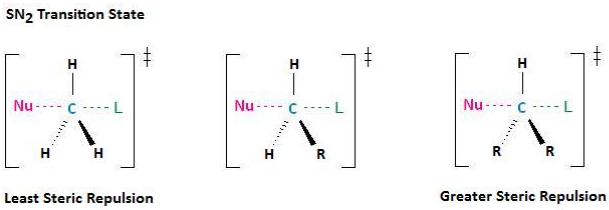
Now that we have discussed the effects that the leaving group, nucleophile, and solvent have on biomolecular nucleophilic substitution (S_N2) reactions, it's time to turn our attention to how the substrate affects the reaction. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below, we will be paying particular attention to the alkyl portion of the substrate. In other words, we are most interested in the electrophilic center that bears the leaving group.



In the section Kinetics of Nucleophilic Substitution Reactions, we learned that the SN_2 transition state is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

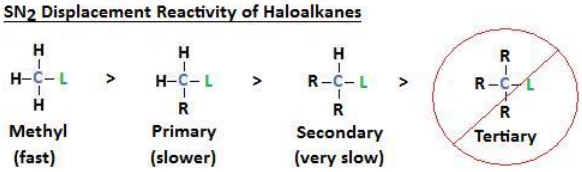


If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the SN_2 reaction to occur, the nucleophile must be able to attack the electrophilic center, resulting in the expulsion of the leaving group. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.



How does steric hindrance affect the rate at which an SN_2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. This is because the addition of one or two R groups shields the backside of the electrophilic carbon, impeding nucleophilic attack.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.



Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.

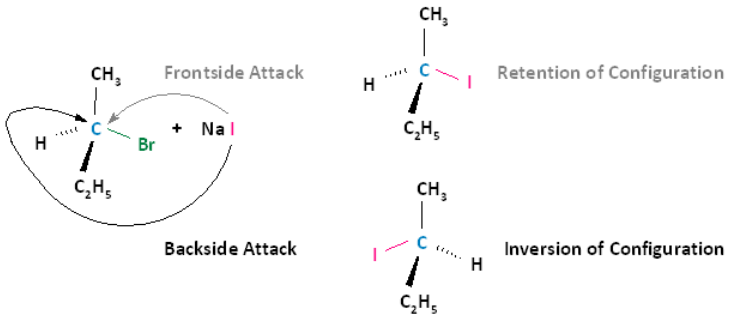
If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

Frontside vs. Backside Attacks

A biomolecular nucleophilic substitution (S_N2) reaction is a type of nucleophilic substitution whereby a lone pair of electrons on a nucleophile attacks an electron deficient electrophilic center and bonds to it, resulting in the expulsion of a leaving group. It is possible for the nucleophile to attack the electrophilic center in two ways.

- **Frontside Attack:** In a frontside attack, the nucleophile attacks the electrophilic center on the same side as the leaving group. When a frontside attack occurs, the stereochemistry of the product remains the same; that is, we have retention of configuration.
- **Backside Attack:** In a backside attack, the nucleophile attacks the electrophilic center on the side that is opposite to the leaving group. When a backside attack occurs, the stereochemistry of the product does not stay the same. There is inversion of configuration.

The following diagram illustrates these two types of nucleophilic attacks, where the frontside attack results in retention of configuration; that is, the product has the same configuration as the substrate. The backside attack results in inversion of configuration, where the product's configuration is opposite that of the substrate.

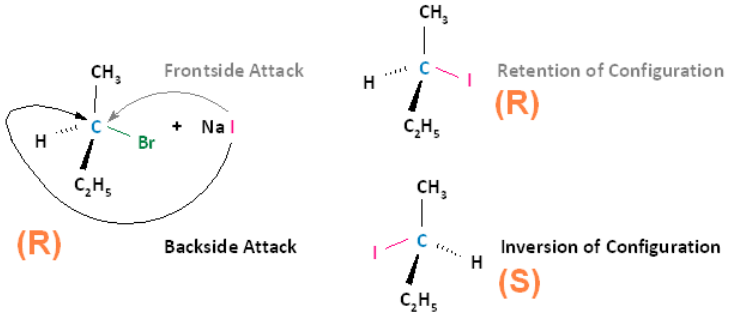


Experimental Observation: All S_N2 Reactions Proceed With Nucleophilic Backside Attacks

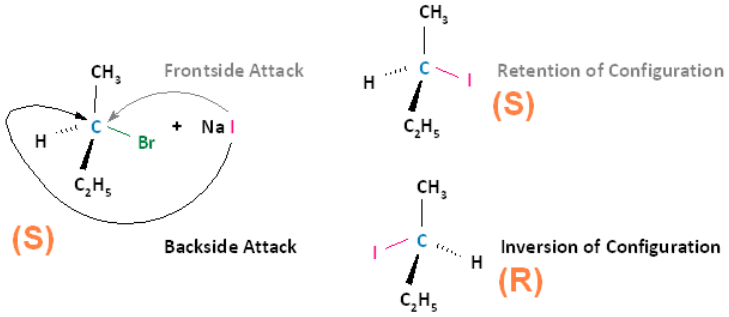
Experimental observation shows that all S_N2 reactions proceed with inversion of configuration; that is, the nucleophile will always attack from the backside in all S_N2 reactions. To think about why this might be true, remember that the nucleophile has a lone pair of electrons to be shared with the electrophilic center, and the leaving group is going to take a lone pair of electrons with it upon leaving. Because like charges repel each other, the nucleophile will always proceed by a backside displacement mechanism.

S_N2 Reactions Are Stereospecific

The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an R enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the S enantiomer.



Conversely, if the substrate is an S enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the S enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the R enantiomer.



In conclusion, S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

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