1.24: Nucleophilic Substitution, SN2, SN1

Recall Nucleophilic Substitution Examples

Today's topic takes us back to an important organic reaction mechanism. We've studied a few reactions which proceed by this mechanism. Now it's time to examine it in detail.

Let's begin by recalling a couple of reactions which occur with alkyl halides, but only work well when the alkyl halide is primary (the halogen is bonded to a carbon which is directly bonded to only one other carbon.) One such reaction involved cyanide ion and resulted in a nitrile which was then converted to a carboxylic acid:
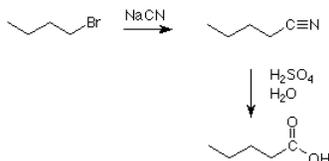
Another similar reaction used an alkoxide (the conjugate base of an alcohol) and resulted in an ether. You may recall this as the Williamson ether synthesis:

$$RO\colon^{\ominus} + R'CH_2Br \longrightarrow ROCH_2R' + Br^{\ominus}$$

In both of these examples the bond between the carbon and the halogen (usually bromine or chlorine) has broken and its pair of electrons has remained with the halide. If we compare what happens here with what happened with the chlorine in an acyl chloride, we recognize that in both situations the halide has behaved as a leaving group.
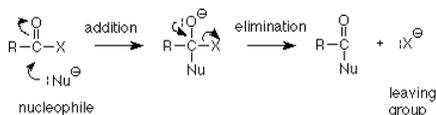
Similarly, we can focus our attention on the new bond that is being made. The electrons which form this bond in the product have come from the attacking reagent -- the cyanide in making a nitrile and the alkoxide in the Williamson ether synthesis. We recognize this behavior as that of a nucleophile, an atom or group which supplies a pair of electrons to form a new covalent bond. We've seen nucleophiles add to carbonyl carbons in both ketones and aldehydes and in carboxylic acid derivatives.

These reactions are known as *Nucleophilic Substitution Reactions*, substitution reactions because one atom or group has been substituted for another, and nucleophilic because the substituting atom or group has supplied the electrons for the new bond.

Possible Mechanisms

The typical reactions of carboxylic acid derivatives are also nucleophilic substitution reactions, but these are different. Remember that in the reactions of carboxylic acid derivatives there was first an addition to a the carbonyl group in which the carbon-oxygen pi bond was broken. This step was followed by one in which the leaving group departed and the carbon-oxygen pi bond was re-formed:

In alkyl halides this mechanism is not available since there is no carbon-oxygen pi bond to break and reform. This leaves us with two possibilities:

1. The bond between the carbon atom and the leaving group breaks first. The carbon is left with six bonding electrons, an empty orbital, and a positive charge.
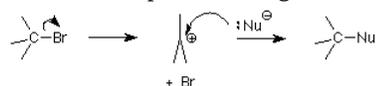
2.

   In a second step, the nucleophile reacts to form a bond, much like the pattern which we saw in the acid catalyzed reactions of carbonyl groups. We'll study these reactions next time.

3. The bond between the carbon atom and the leaving group breaks at the same time as the bond between the nucleophile and the carbon atom is formed.

4.
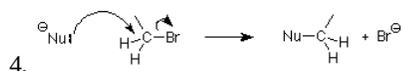
There is only one step and it requires the nucleophile and the alkyl halide (also called the substrate) to collide for it to take place.

(A third possibility, that the nucleophile attacks first to form an intermediate which later loses the leaving group, is not possible because the carbon in the intermediate would have ten bonding electrons and five bonds -- a very high energy situation.)

Today we'll consider the second of these possibilities. This mechanism is called an S_N2 mechanism; S for substitution, N for nucleophilic and 2 because two molecules collide at the critical point in the reaction.

S_N2 Mechanism

First, let's look at what happens in a little more detail. This is a one step reaction. In order for it to take place, the nucleophile must come close enough for bonding to begin to happen, but this also means that the carbon-halogen bond must begin to break. Both of these actions increase the energy of the combination - bond breaking requires energy as does overcoming the repulsion which results from moving the nucleophile's electron pair into close contact with the electrons in the carbon's bonding shell.
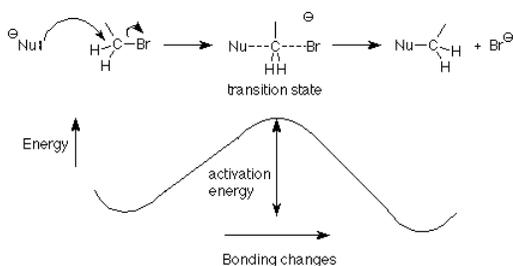
As the reaction process goes forward, the energy increases until a significant bonding begins to occur between the nucleophile and the carbon. This releases enough energy to balance the energy required to break the carbon-halogen bond. At this point. called a transition state, the energy is at a maximum. There is roughly a half bond between the nucleophile and the carbon and a half bond between the carbon and the halogen. Since the energy is at a maximum, any slight movement will cause it to decrease, either to go back to reactants or to go on to products. This picture of the transition state is the key to understanding the characteristics of the S_N2 mechanism.

The energy required to boost the nucleophile and the alkyl halide to the transition state energy level is called the activation energy. It comes from the energy with which the molecules collide. If the activation energy is low, many collisions will provide enough energy and the reaction will be fast. If the activation energy is high, few collisions will provide enough energy and the reaction will be slow. Another way to say this is that slow reactions have high activation energies (and high energy transition states) and fast reactions have low activation energies (and low energy transition states). In order to understand what makes a reaction go slow or go fast, we examine the transition state to see what changes will increase or decrease its energy.

Effect of Alkyl Halide Structure

With this background, we can look back at the restriction that our examples of S_N2 reactions (nitrile and ether synthesis) only work well on primary alkyl halides. In the structure of the S_N2 transition state, there are 90° bond angles between the breaking bond to the leaving group and the three bonds which remain connected to the carbon as well as between the bond being made to the nucleophile and those same three bonds.
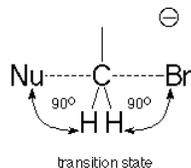
As long as the two of the groups attached to the carbon being attacked are small hydrogens, the repulsions which happen do not require much energy. If the groups attached to the carbon are larger, though, like methyl groups, the transition state energy increases, the activation energy increases, and the reaction becomes much slower.
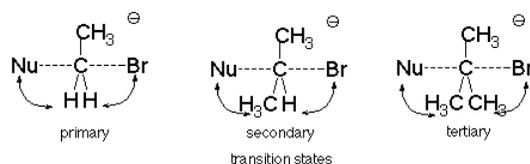
This means that the reactivity order for alkyl halides in S_N2 reactions is:

methyl > primary > secondary > tertiary
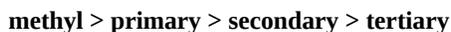
The practical outcome of this is that S_N2 reactions are generally reliable only when the alkyl halide is primary.

Stereochemical Inversion

The structural picture of the S_N2 transition state also accounts for another characteristic of S_N2 reactions. Notice that the nucleophile is bringing its bond-forming electrons into the transition state on the side of the carbon opposite to the position of the leaving group. We can understand this if we remember that the nucleophile and the leaving group are both electron rich atoms. We would expect them to repel each other and stay as far apart as possible while remaining connected by their half bonds to the central carbon atom.

The result of this is that the carbon atom is **inverted**. If we examine a three-dimensional picture of this, we can see that the three groups which remain connected to the carbon throughout the reaction move away from the entering nucleophile and towards the position occupied by the departing leaving group.
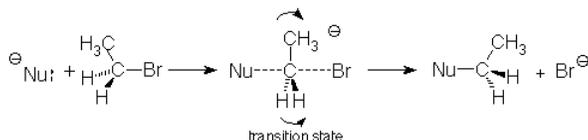
If the nucleophile and the leaving group are both high in the *R/S* priority order, this means that an *R* alkyl halide gives an *S* product, and *vice-versa.* The term for this is *inversion of configuration* and it is an inherent and consistent characteristic of the S_N2 mechanism. If we know the configuration of the alkyl halide before reaction, we know that the configuration of the product will be the opposite. Conversely, if we determine that a nucleophilic substitution reaction proceeds with inversion of configuration, we conclude that its mechanism is S_N2.

Our picture of this reaction starts with a tetrahedral sp^3 carbon in the alkyl halide and ends with a tetrahedral sp^3 in the product. In the transition state the three bonds to carbon which don't react are approximately flat, it makes sense to regard the carbon atom as sp^2 hybridized at this point. One consequence of this is that the S_N2 mechanism is restricted to halides which are sp^3 hybridized at the reactive carbon. Carbons which are sp^2 hybridized at the halogen-bearing carbon do not react by this mechanism.

Kinetics, Alkyl Halide and Nucleophile Effects

Earlier we saw that the energy required to reach the transition state comes from the energy with which the nucleophile and the alkyl halide collide. The requirement for a collision also means that the frequency with which the nucleophile and the alkyl halide collide is important. This frequency is primarily controlled by concentration.

If the concentration of the alkyl halide is high, then there will be many opportunities for a nucleophile to collide with an alkyl halide molecule. The rate of the reaction will increase proportionately as the alkyl halide concentration is made higher. When this is the case the reaction is said to be first order in alkyl halide. Similarly an increase in the nucleophile concentration will result in a proportionate increase in the rate, so the reaction is also first order in nucleophile. Overall, the reaction is said to be second order. This can be summarized in the *rate equation.*

$$\text{Rate} = k[\text{RBr}][\text{Nu}^-]$$

It is the second order behavior (requirement for two molecules to collide in the critical transition state) which is designated by the "2" in S_N2

Since the bond between the carbon and the leaving group is being broken in the transition state, the weaker this bond is the lower the activation energy and the faster the reaction. This leads to the following reactivity order for alkyl halides

RI > RBr > RCl > RF
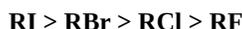
Practically, alkyl fluorides are not used for S_N2 reactions because the C-F bond is too strong. Often alkyl iodides are reactive enough to be difficult to store, so the the common choices for reactions are alkyl chlorides and alkyl bromides.

If we remember that the function of the nucleophile is to provide an electron pair to make a new bond, we can see a similarity between a nucleophile and a base. A Lewis base makes a new bond, typically to hydrogen, using its own electron pair. A nucleophile makes a new bond to carbon, using its own electron pair. As this suggests, good nucleophiles are typically strong bases. There are are other factors, but this is a good starting place and it reminds us to review base strengths, perhaps by reviewing Table 2.1 on p p 43 of Brown. Keep in mind that high pK_a numbers mean weak acids which have strong conjugate bases.

Next time we'll take a look at the other mechanism for nucleophilic substitution, the S_N1 mechanism. We'll also see how elimination reactions fit into this picture.

This page titled 1.24: Nucleophilic Substitution, SN2, SN1 is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Kirk McMichael.