Faculty of Science

Unit 6: Mechanisms and Organic Reactions

CHEM 1503
Chemical Bonding and Organic Chemistry

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Overview

In this unit, you will study several mechanisms of organic reactions. The term **mechanism** refers to the events that occur during a chemical reaction. A **reaction** may take place in one step or in several; the mechanism is what happens at each step.

Or, rather, a mechanism is *what chemists think happens*. Because they cannot directly observe the movement of electrons as bonds form or break, chemists cannot be absolutely sure that a particular mechanism describes actual events at the atomic and molecular levels. Although a proposed mechanism is shown to be wrong if it does not fit experimental results, one that does fit those results is not necessarily right. A subsequent experiment may prove it to be incorrect. In this unit, we won't be going into all the details of experiments that are performed to verify reaction mechanisms.

You may be wondering why it is important to know how a reaction occurs. Why should we worry whether a reaction takes place in three steps or one? Why should we worry whether one atom shares its lone pair of electrons with another atom to form a bond? In addition to natural curiosity and a desire to understand why molecules behave the way they do, there are some very practical reasons for studying reaction mechanisms.

If you know how and why a reaction occurs, you can control the reaction conditions to get a better yield of the desired product. In the chemical industry, a small change in reaction temperature or in the solvent used might lead to significant savings by causing the quantity of product to jump dramatically.

In addition, if you know the mechanism of a particular reaction, you can often predict how a similar reaction might work and what its reaction products might be. Although they have not always been right, chemists have been able to predict with remarkable accuracy the rate, product, and percent yield of many reactions.

An understanding of reaction mechanisms is especially important in pharmaceutical chemistry. If you know which biochemical reactions an antibiotic or antiviral agent disrupts, you can determine why it has therapeutic properties. You can then try to synthesize a compound with the same properties but with fewer side effects.

For example, sulpha drugs inhibit the growth of certain types of bacteria. These bacteria require a substance called ***p*-aminobenzoic acid** (PABA, the compound used in sunscreen agents) in order to produce folic acid for growth. **Sulphanilamide** has a structure very similar to that of *p*-aminobenzoic acid, as you can see in Figure 6.1 in this unit. Because of this, bacterial enzymes mistake sulphanilamide for *p*-aminobenzoic acid and bind to the sulpha drug. As a result, they cannot produce folic acid (shown in Figure 6.2 in this unit).

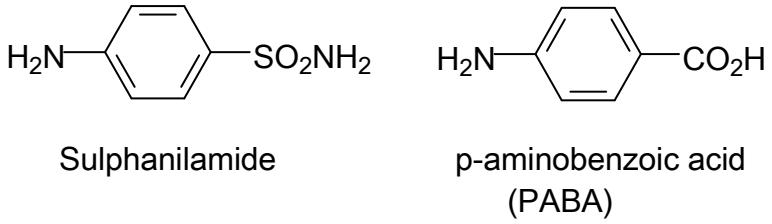


Figure 6.1: Structure of sulphanilamide and *p*-aminobenzoic acid

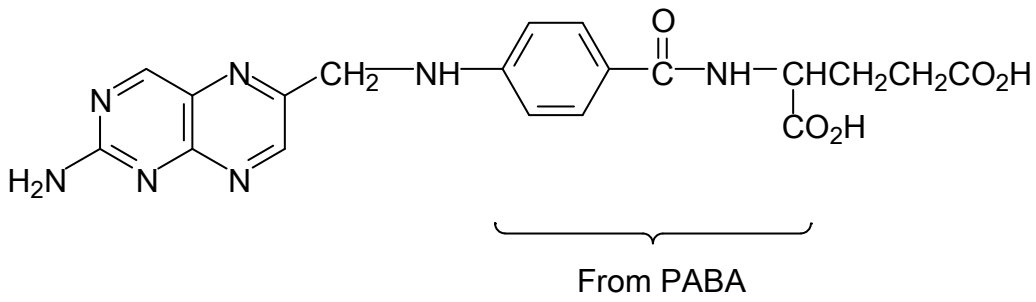


Figure 6.2: Folic acid

Sulpha drugs are not effective against all bacterial strains because not all bacteria use PABA in this manner. Neither do sulpha drugs rob humans of folic acid. We consume this *vitamin* as part of our diet since we do not have the biochemical machinery to synthesize it ourselves. Sulphanilamide is too toxic for general use. Knowing how it worked, however, chemists were able to make compounds similar in structure that were just as effective but less toxic.

An understanding of reaction mechanisms also helps in the fight against cancer. When scientists know how a chemotherapeutic agent works, they can try to synthesize similar compounds in the hope that some will be more effective against cancer cells and less toxic to normal cells.

In this unit, we shall first cover Chapter 3 and then Chapters 6 and 7 of your *Organic Chemistry* supplement. It is logical to study the free radical reactions (Chapter 3) in the same unit as the first ionic ones you will be introduced to (Chapters 6 and 7).

Learning Outcomes

When you are finished this unit, you should be able to:

- Draw, using curved arrows correctly, mechanisms for S_N1 and S_N2 reactions and for free radical halogenation.
- Identify leaving groups, substrates, and nucleophiles.
- Determine the order of a reaction from kinetic data.
- Explain the effect of structure, solvent, and nucleophile on substitution reactions.
- Distinguish between protic and aprotic solvents, good and poor nucleophiles, and good and poor leaving groups.
- Explain the stereochemistry involved in S_N1 and S_N2 reactions with chiral molecules and during free radical halogenation.
- Predict substitution products under a variety of reaction conditions.
- Synthesize simple organic compounds using radical halogenation and substitution reactions.

How Bonds Break

When a bond breaks during a chemical reaction, each atom involved in the bond may get one of the bond electrons. This type of bond breaking is called **homolysis**. It results in the formation of **free radicals**, species with unpaired electrons.

A bond may also break by **heterolysis**. One of the atoms involved in the bond gets both bond electrons and becomes negatively charged; the other atom gets none and becomes positively charged. Thus, heterolysis leads to the formation of charged particles, or **ions**.

Study Section 3-1 of your *Organic Chemistry* supplement, which describes these processes of bond cleavage. Make sure you understand the following terms:

- Bond-dissociation energy
- Bond strength
- Homolytic cleavage
- Heterolytic cleavage
- Radicals
- Stability of alkyl radicals

Do Exercises 3-1 and 3-3 in the supplement.

Free Radical Halogenation

When bonds break by **homolysis**, **free radicals** are produced. These are species with unpaired electrons. Halogen free radicals, not ions, are involved in reactions where a halogen replaces a hydrogen on an alkane. In the process, very reactive alkyl free radicals are also formed as intermediates.

Turn now to Chapter 3 of your *Organic Chemistry* supplement, and study Sections 3-2 and 3-4. Section 3-2 discusses the principal reason for why a carbon free radical can be stable, and Section 3-4 describes in detail the mechanism of the chlorination of methane. The mechanism of the chlorination of methane is the same reaction mechanism for all the halogenations of alkanes that you will encounter in this chapter.

Free radical halogenations are **chain reactions**. They can be divided into **chain-initiating**, **chain-propagating**, and **chain-terminating** steps.

In the chain-initiating step, halogen radicals are produced when halogen molecules are subjected to heat or to irradiation with ultraviolet light. In the chain-propagating steps, halogen radicals react with alkane molecules to produce alkyl radicals, and alkyl radicals react with halogen molecules to produce more halogen radicals. Theoretically, once a chain reaction is started, it can continue until all the starting materials are used up.

Chain-terminating steps prevent this from happening, however. In such steps, free radicals combine with each other to form molecules. As the radicals disappear, the reaction comes to a halt. To keep it going, you have to constantly produce halogen radicals by irradiating the reaction mixture. The longer you do this, the more substitution you get in your reaction products. Thus, by controlling the irradiation period and the light intensity, you can control the kind of products you end up with. In most cases, we are interested in only replacing one hydrogen in an alkane structure with a halogen. Replacing just one hydrogen in an alkane structure with a halogen atom is called a **monohalogenation** reaction.

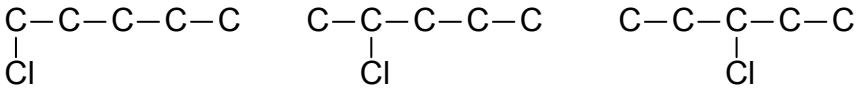
Do Exercises 3-4, and 3-5 in your *Organic Chemistry* supplement.

Read Sections 3-5 and 3-6 in your *Organic Chemistry* supplement. Section 3-5 discusses the nature of other halogenations of methane, namely fluorination, bromination, and iodination. Section 3-6 describes the chlorination of other alkanes in addition to methane and how the **selectivity** of different hydrogens (primary versus secondary versus tertiary) for replacement by chlorine is different. In your reading of Section 3-5, take note of the facts that: (a) an iodine radical is too unreactive and thus iodination is not practical, and (b) a fluorine radical is so reactive that fluorination will replace every hydrogen on an alkane with a fluorine atom. In Section 3-6, take note of the difference between the **statistical product ratios** that would be expected for the chlorination of primary, secondary, and tertiary hydrogens as compared to the actual **selectivity** for these hydrogens. Make sure you understand the following terms:

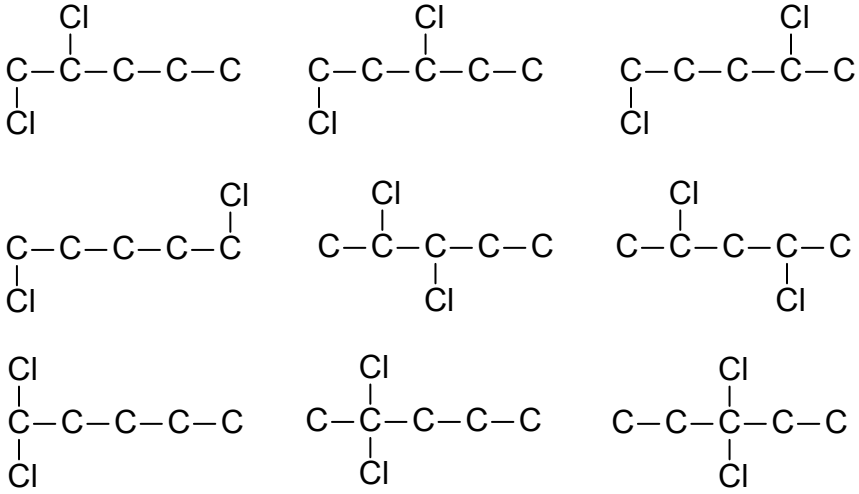
- Relative reactivity
- Early transition state
- Late transition state
- Hammond postulate
- Statistical product ratio
- Selectivity

Do Exercises 3-7, 3-8, and 3-9 in the supplement.

The more carbon atoms there are in an alkane, the more possible products there are. The number of monohalogenated and polyhalogenated isomers can become very large. For example, n-pentane has three monochlorinated isomers:



and nine dichlorinated isomers:



It also has fifteen trichlorinated isomers—and at this point we'll stop counting! In a case like this, it is not worth using a free radical chlorination of an alkane to prepare one particular isomer. It can be done, but separating the products from each other would be difficult and tedious.

Bromination might be more feasible. Bromine is less reactive than chlorine and hence more selective in its substitution site. Because of this, bromination may yield one major product in a reaction where chlorination might yield a mixture of many products. Fluorine is extremely—sometimes explosively—reactive. It is used only in special cases. Iodine, on the other hand, is unreactive toward alkanes. Hence, when chemists talk about free radical halogenation, they really mean free radical chlorination or bromination.

Study Section 3-7 in your *Organic Chemistry* supplement. Section 3-7 describes the selectivity of bromine compared to chlorine and fluorine in radical halogenation reactions.

For this course, you don't need to do problems similar to the calculation of energy changes shown in Section 3-5 of the *Organic Chemistry* supplement. Neither will you be asked for the actual percentages of products given in the examples in Section 3-6. You should, however, be able to predict the major product or products from the monochlorination and monobromination of alkanes, based on the reactivity of different types of hydrogen atoms (3° > 2° > 1°).

Now do Exercise 3-9 in your *Organic Chemistry* supplement.

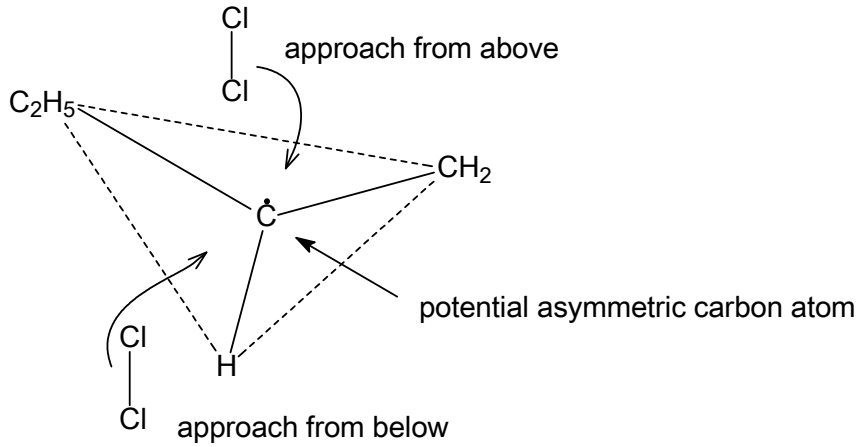
Radical halogenation is your entry point in organic chemistry for learning the art of **organic synthesis**, the synthesis of larger or more complex organic compounds from smaller ones. Radical halogenation allows us to convert simple alkanes to haloalkanes. The carbon-halogen bond (C—Br or C—Cl) in an organic molecule can be converted to other functional groups by other reactions that you will learn about in later in this unit. Section 3-8 of your *Organic Chemistry* supplement describes which radical halogenations are **synthetically useful**.

Study Section 3-8 in your *Organic Chemistry* supplement and then do Exercise 3-11.

Stereochemistry of Free Radical Reactions

Alkyl radicals are trigonal planar about the carbon atom with the unpaired electron. This carbon is considered to be sp^2-hybridized with the radical electron located in the remaining *p* orbital. If it were attached to three different alkyl groups or to two different alkyl groups and a hydrogen atom, it would become an asymmetric carbon atom when a halogen atom is added to it.

Because the halogen can approach from either the front or the back of the planar alkyl radical, both (*R*) and (*S*) enantiomers have *equal chances* of forming, resulting in a racemate.



Read Section 5-7 in your *Organic Chemistry* supplement. Don't worry about all the details regarding the creation of a second stereogenic carbon during free radical halogenation. It is only necessary that you can explain why the products of such a halogenation would be diastereomers.

Now do Exercise 5-25 in the supplement.

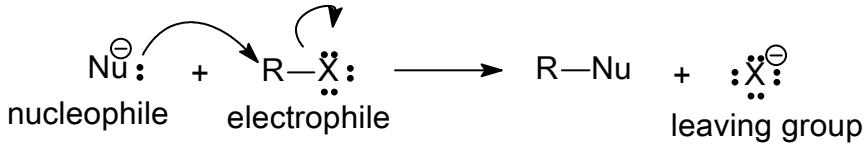
Also study Section 3-3 in your *Organic Chemistry* supplement, on conversion of petroleum; Section 3-9 on synthetic chlorine compounds and depletion of the Earth's ozone layer; and Section 3-10 on the combustion of alkanes. These topics are especially appropriate today, as scientists and the general public become increasingly concerned about the way ozone depletion is changing the Earth's climate and the limitations of fossil fuels as an energy source. Review the Chapter 3 summary from your supplement, do some of the Chapter Integration Problems and review the Important Concepts section.

Nucleophilic Substitution Reactions

As the name implies, a **substitution reaction** involves the substitution of one group for another. In a **nucleophilic substitution reaction**, the substituting species is a **nucleophile** ("nucleus loving"). A nucleophile is a species that has an atom in its structure with a concentration of electron density in the form of a lone pair. As a result of this electron density, the nucleophile seeks to use the lone pair of electrons to make a bond to a positively polarized centre (usually a carbon atom).

The positively polarized centre to which the nucleophile is attracted is called the **electrophile** ("electron loving"). The nucleophile must have a lone pair of electrons on an atom in its structure. The lone pair may or may not be associated with an actual negative charge.

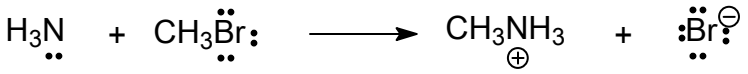
In a typical nucleophilic substitution, the nucleophile uses its lone pair to form a bond to an atom in an electrophile by displacing some other group, called the **leaving group**, from the **electrophilic centre**. The displacement of the leaving group makes room for the new bond between the electrophile and the nucleophile because the leaving group leaves with the pair of electrons it was using in its bond to the electrophile. This reaction concept is illustrated as follows:



Substitution reactions are extremely common in organic chemistry and can be utilized to make many different compounds.

Study Sections 6-1 and 6-2 in your *Organic Chemistry* supplement. A number of reaction equations are given in Table 6-3; make sure you can identify the nucleophile, the substrate, the leaving group, and the product in these reactions.

Note also the conservation of charge in these reaction equations. If the left side of an equation has an overall negative charge, so does the right side. If one side has no charged species but the other does, the charges cancel each other, as in the following example:



After studying Sections 6-1 and 6-2 in the supplement, work on Exercises 6-1, 6-2 and 6-3. The point of the exercises is for you to remember that a nucleophile always has at least one unshared electron pair (lone pair).

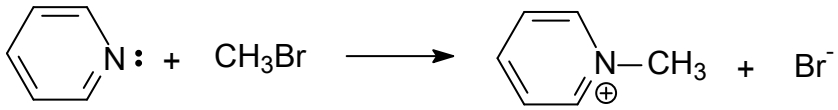
Now try this example:

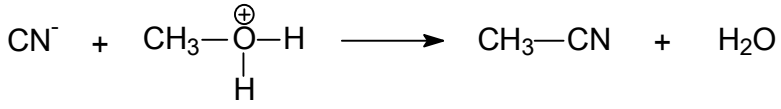
Example

Label the nucleophile and substrate, and circle the leaving group in each of the following reaction equations.

a) $C_2H_5O^- + C_2H_5Cl \longrightarrow C_2H_5{-}O{-}C_2H_5 + Cl^-$

b) $C_6H_{12}I + CH_3S^- \longrightarrow C_6H_{12}{-}S{-}CH_3 + I^-$

c) 

d) 

Answer

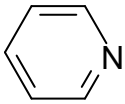
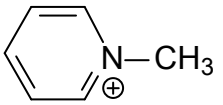
Note that the nucleophile does not have to be written first in a reaction equation, although your textbook normally does it that way. Note also the conservation of charge in each equation.

a) $C_2H_5O^-$ + C_2H_5Cl ⟶ $C_2H_5—O—C_2H_5$ + Cl^-

nucleophile substrate

b) $C_6H_{12}I$ + CH_3S^- ⟶ $C_6H_{12}—S—CH_3$ + I^-

substrate nucleophile

c)  + CH_3Br ⟶  + Br^-

nucleophile substrate

d) CN^- + $CH_3—\overset{\oplus}{O}(H)—H$ ⟶ $CH_3—CN$ + H_2O

nucleophile substrate

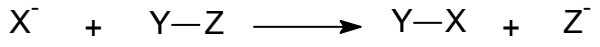
Now read Section 6-3 in your *Organic Chemistry* supplement. This section reinforces the methods by which organic chemists represent reaction mechanisms in drawings. It is important that you understand clearly the "electron-pushing" arrows concept. Then do Exercises 6-4 to 6-8.

Kinetics

The subject of **kinetics**, or reaction rates, is important in a study of the mechanisms of chemical reactions. The dependence of rate on reactant concentration often indicates how the reaction occurs.

You may have studied kinetics in previous chemistry courses. We will not go into much detail here, but you might need to keep in mind the relationship between kinetics and reaction mechanisms. In particular, chemical reactions occur when molecules collide with each other with favourable orientations and sufficient energy. Therefore, it follows that increasing the temperature of a reaction should increase the number of collisions possible, increase the energy available to overcome any barriers to the reaction, and increase the rate of the reaction.

If we were to do a kinetic study for the general reaction



we might obtain the following data for the initial concentrations of the reactants and the rate of formation of the product:

Experiment Number	Initial Concentration X^- (mole/L)	Initial Concentration Y-Z (mole/L)	Initial Rate of formation of X-Y (mole/L/second)
1	1.00	0.500	0.125
2	1.00	1.00	0.250
3	2.00	0.500	0.125

Note that in Experiment 2, when the concentration of Y—Z was doubled and that of X^- held constant, the rate of product formation doubled. We conclude that the reaction rate is proportional to the concentration of Y—Z. In Experiment 3, when the concentration of Y—Z was held constant while that of X^- was doubled, the reaction rate remained constant.

These data tell us that the reaction rate is independent of the concentration of X^- but dependent on that of Y—Z. A reaction with a rate that depends on the concentration of only one species of reactant is said to be **first order**. If the rate depends on the concentration of two species of reactant, the reaction is said to be **second order**. Any mechanism proposed for a particular reaction must explain the reaction's order.

There is good evidence that molecules must collide with each other in order for a chemical reaction to occur. Mere collision is not sufficient, however. The collisions must be frequent enough, and the colliding species must be favourably oriented toward each other. In addition, the kinetic energy of the particles must be large enough to overcome a barrier called the **energy of activation**. The greater the collision frequency and the lower the energy of activation, the faster the rate of a reaction will be. Figure 2-1 in your *Organic Chemistry* supplement shows an example of a potential energy diagram for a combustion reaction.

The influence of temperature on the rate of a reaction is shown in Figure 6.3 in this unit, a Boltzmann (or Maxwell-Boltzmann) distribution curve. You may have seen such a diagram in an introductory chemistry course. At higher temperatures (T_2), the curve flattens out and more molecules have enough energy to overcome the barrier posed by the energy of activation. In addition to having more energy, the molecules will be moving faster and thus colliding more often.

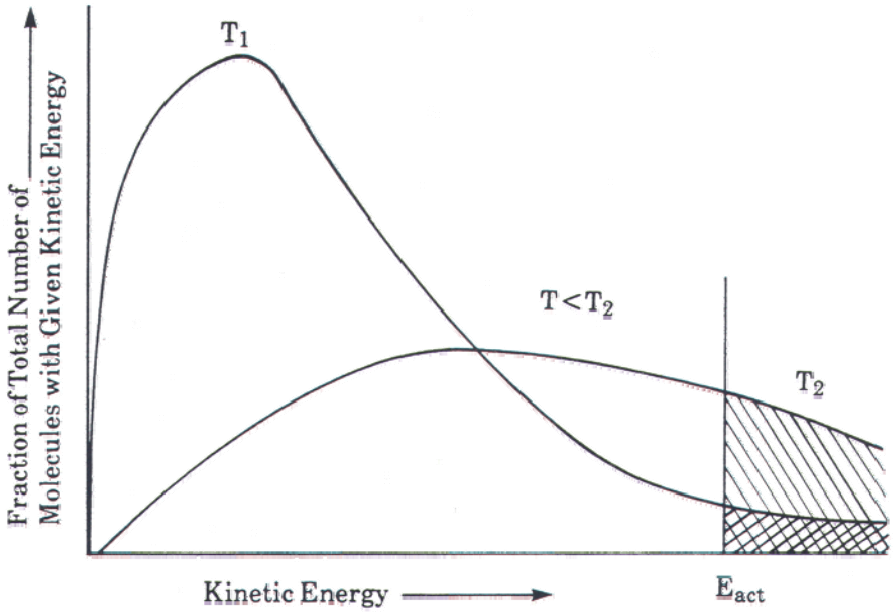


Figure 6.3: Boltzmann distribution curve for molecular kinetic energies

Now study Section 6-4 in your *Organic Chemistry* supplement.

The S_N2 Mechanism

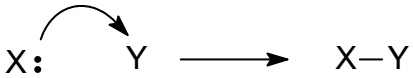
Section 6-3 in your *Organic Chemistry* supplement reviewed the **curved arrow** concept for illustrating reaction mechanisms. Before we look at the S_N2 mechanism, let's spend some time on these arrows and find out exactly what they mean by introducing some additional examples.

A curved arrow represents the movement of a *pair of electrons*. This is a critical point, and you must understand it in order to interpret and use curved arrows correctly. If you think they show how atoms move, you won't be able to follow a mechanism!

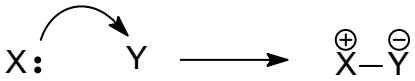
Here are three examples showing different ways electrons can move:

1. A lone pair can become a bond pair:

Note that the arrow starts at the lone pair on atom X and curves toward atom Y. This electron pair movement results in a new bond between X and Y, which you can represent as

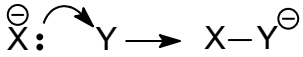


Here you can visualize atom X donating one electron to atom Y and then sharing that electron in the covalent bond between X and Y. You could add charges in order to complete the electronic bookkeeping for this example, and write the equation as

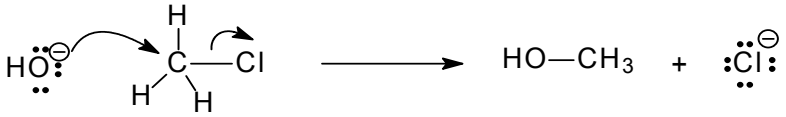


There is still a conservation of charge, but now the equation shows that atom X lost an electron and atom Y gained one.

If atom X originally had a negative charge, the complete equation would be



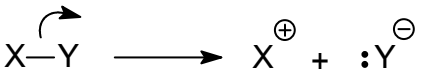
Here $X:^-$ has lost an electron and thus shows up on the right side with no charge. The neutral atom Y, on the other hand, has gained an electron, which is now part of the new bond pair. In the new molecule, the negative charge rests on Y. An actual example showing this type of electron movement is the first part of the replacement of a halide atom in an alkyl halide with an alcohol group:



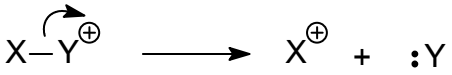
The second part of this mechanism is described in example 2 below.

2. A bond pair can become a lone pair:

Note that the arrow starts at the bond between X and Y and curves toward atom Y. One of the electrons in the bond pair came from X and the other came from Y. The curved arrow indicates that both electrons now "belong" to Y. Overall, X has lost an electron and Y has gained one. The complete equation is:

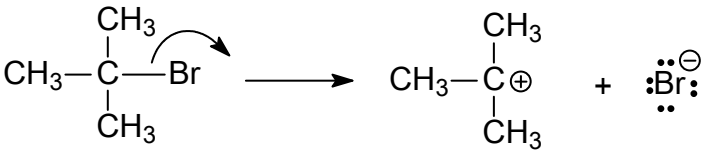


with the charges shown to reflect the electronic bookkeeping. If the bond-pair-to-lone-pair step occurs where there is already a positive charge



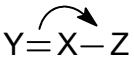
there is still a conservation of charge.

An actual example showing the bond-pair-to-lone-pair type of electron movement is the formation of an alkyl cation intermediate (called a **carbocation**):

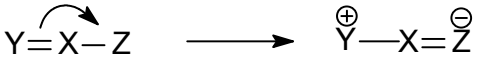


Here the electrons of the carbon-bromine bond are shown moving to bromine. Because one of these bond electrons originally came from the carbon atom and one from the bromine, overall carbon loses an electron and becomes positively charged. Bromine gains this electron and becomes negatively charged.

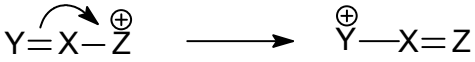
3. A bond pair can become a different bond pair:



The arrow starts at one bond pair and goes toward an adjacent bond pair. The complete step is



If the initial molecular species is charged, the electron movement both shifts the site of the charge and rearranges the bond positions:



Go over these three types of electron pair movements and make sure you can describe where the electrons move from and where they move to. These can be thought of simply as the movement of electrons: (1) from an atom to a bond, (2) from a bond to an atom, and (3) from a bond to a bond. You should also be able to explain why the charges in the various equations appear where they do.

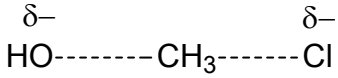
Keep in mind that certain things do not happen:

- An electron pair (lone or bond) does not move toward a negative charge.
- A lone pair does not become another lone pair.

Now that you have seen these basic rules for mechanisms, review Section 6-4 in your *Organic Chemistry* supplement. Write out the mechanism for yourself and, as you draw the curved arrows, try to imagine where the electrons are going.

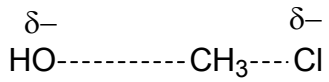
Do Exercises 6-9 and 6-11 in the supplement.

Before you move on to the stereochemistry of the S_N2 reaction, look again at Figure 6-2 in your *Organic Chemistry* supplement. This diagram shows the **transition state** for the methyl chloride-hydroxide ion reaction as

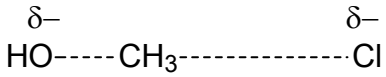


The transition state is the species at the point of highest energy along the reaction pathway. Despite the way the structure is drawn, we cannot be sure that in the transition state the bond between the hydroxide ion and carbon is half-formed and the bond between carbon and chlorine is half-broken. Neither is there any way of

knowing whether the hydroxide-carbon bond has barely started forming and the carbon-chlorine bond has barely started breaking



or whether the hydroxide-carbon bond is almost complete and the carbon-chlorine bond is almost broken



An S_N2 reaction takes place in a single step. It is bimolecular, and its rate depends on the concentration of both nucleophile and substrate. The S_N2 mechanism you have just studied accounts for these experimental observations. Unless future studies prove otherwise, we can assume it to be correct.

Stereochemistry of the S_N2 Mechanism

Because the nucleophile is presumed to attack the target carbon atom in a substrate from the side opposite to that of the leaving group, we would expect S_N2 reactions to always lead to an inversion of configuration at that carbon atom. There is evidence for this in the reactions of some cyclic compounds, as explained in your *Organic Chemistry* supplement, and in reactions at a stereogenic carbon atom. If the reaction takes place at a stereogenic carbon atom, an (*R*) enantiomer would be converted into a product for which the configuration is (*S*), and vice versa, *unless the entering group changes the priority order*.

Remember from Unit 5 that whether an enantiomer is (+) or (–) does not depend on its (*R*)-(*S*) configuration. An inversion of configuration may change a (+) reactant into a (–) product, or it may not. In this discussion, however, we are mainly interested in the absolute configuration—the actual arrangement of groups around the stereogenic carbon.

Study Sections 6-5 and 6-6 in your *Organic Chemistry* supplement, which describe the stereochemistry of S_N2 reactions. Make models of (*R*)-2-bromooctane, (*S*)-2-octanethiol, (*S*)-2-iodooctane, and (*R*)-2-octanethiol as you work through the examples in Section 6-6. Note that the entering group, the sulphide or iodide ion, does not change the priority order of groups around the stereogenic carbon atom.

Do Exercises 6-12 to 6-17 in the supplement.

Factors Affecting Rates of S_N2 Reactions

To more completely understand the nature of the S_N2 reaction, you must consider the role of several factors, among them the leaving group, the nucleophile, the solvent, and the substrate.

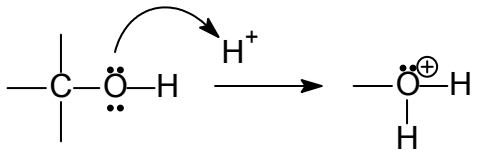
The Leaving Group

Read Section 6-7 in your *Organic Chemistry* supplement.

In general, ions or molecules that are **weak bases** *are the best leaving groups* because they are very stable once they have left the substrate. Among the halogens, I^- is the conjugate base of the strongest acid, HI, and is therefore the weakest base and the best leaving group. F^-, on the other hand, is the conjugate base of the weak acid, HF, and so is a fairly strong base and a poor leaving group.

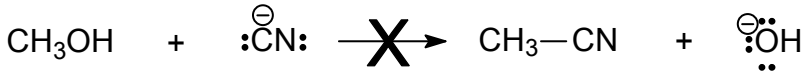
The methyl sulphate and three sulphonate ions are described Section 6-7 of the *Organic Chemistry* supplement. All three are good leaving groups because they are very stable ions. The stability of these anions is the result of the delocalization of the negative charge by resonance with the S=O oxygens.

The OH^- ion is highly basic and is another example of a poor leaving group. In the presence of a strong acid, however, an alcohol group can become protonated



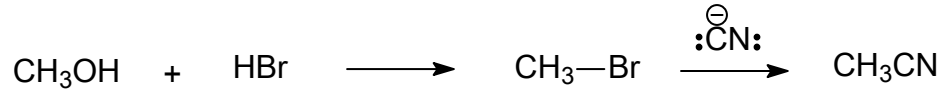
and easily leave as a weakly basic H_2O molecule. Thus, the protonated alcohol group is a good leaving group. The following example illustrates these points.

These two reactions do not occur:



In both cases, —OH is such a poor leaving group that the substitution does not take place. HCN is a weak acid and does not protonate the alcohol OH group to any noticeable degree. A strong acid such as HBr, however, can protonate the alcohol group and allow H_2O to leave as a bromine nucleophile enters. Br^- is a good leaving group and

CN^- can easily substitute for it:



Review Section 6-7 in your *Organic Chemistry* supplement and then do Exercises 6-18 to 6-20.

The Nucleophile and the Solvent

Read Section 6-8 in your *Organic Chemistry* supplement.

Note that the rates of S_N2 reactions depend on the concentrations of both substrate and nucleophile. Section 6-8 contains highlighted statement titles in bold that you should be able to explain. Nucleophiles can be classified as either strong or weak. Remember that a negatively charged nucleophile is always stronger than its conjugate acid. This means that it reacts more rapidly with a given substrate. Also, among compounds with the same nucleophilic atom or among compounds where the nucleophilic atom is in the same row of the periodic table, the more basic a compound, the stronger a nucleophile it is.

Don't worry about memorizing the order of nucleophilicities. You can always figure out which of two compounds is the stronger nucleophile. For example, which is a stronger nucleophile in an S_N2 reaction, NH_2^- or OH^-? In both, the nucleophilic atoms are in the second row of the periodic table, so the more basic species is also the better nucleophile.

Which species is more basic? The conjugate acid of NH_2^- is NH_3, and the conjugate acid of OH^- is H_2O. According to Table 2-2 in your *Organic Chemistry* supplement, H_2O is a stronger acid than NH_3. In Unit 4, you learned that the stronger the acid, the weaker its conjugate base and vice versa. Thus OH^-, the conjugate base of H_2O, is a weaker base than NH_2^-, the conjugate base of NH_3. NH_2^- is therefore the stronger nucleophile.

Now review Section 6-8 in your *Organic Chemistry* supplement.

The middle portion of Section 6-8 covers the effects of solvents on the nucleophile. In Unit 4, you learned the differences between polar and non-polar solvents. Polar solvents can be further subdivided into **protic** and **aprotic** solvents, depending on whether or not they have a hydrogen attached to their electronegative atom.

Protic and aprotic solvents affect nucleophiles in different ways. Protic solvents form hydrogen bonds with anions, especially small anions. In such solvents, small nucleophiles become highly solvated and are less likely to undergo S_N2 reactions than large nucleophiles. This explains why the fluoride ion is a weaker nucleophile in water than the larger chloride ion.

Aprotic solvents, on the other hand, do not solvate anions. During an S_N2 reaction, small anions can approach the target carbon in a substrate more easily than large anions can. Thus, in aprotic solvents, small nucleophiles are stronger than large ones. Table 6-6 in your *Organic Chemistry* supplement shows the effect of different solvents on the chloride ion as a nucleophile.

You don't need to learn the names and structures of the aprotic solvents DMF, DMSO, and HMPA given in the supplement. You can always look up this information if you need to.

In S_N2 reactions, the solvent's most important effect is on the nucleophile.

Note that increasing polarizability improves nucleophilic power, as described on in your *Organic Chemistry* supplement. The sterically hindered nucleophiles (also called "hindered bases") are generally poor nucleophiles because of the *steric hindrance*.

After you are through studying Section 6-8, do Exercises 6-21 to 6-25 in your *Organic Chemistry* supplement.

The Substrate Structure

In an S_N2 reaction, the order of decreasing reactivity among alkyl halides is methyl > primary > secondary > tertiary. This is caused by **steric hindrance**. Steric hindrance does not make methyl and primary substrates react faster. Rather, it prevents or drastically slows down a nucleophilic attack on the back side of tertiary and most secondary substrates. The bulky groups surrounding the target carbon atom get in the way of the nucleophile. Figure 6-8 in your *Organic Chemistry* supplement illustrates this very well. If you are not convinced of how difficult it is for a nucleophile to attack a hindered electrophile, take out your model kit and build a model of 2-chloro-2-methylpropane (*tert*-butyl chloride) that includes all the

carbon-to-hydrogen bonds and all the hydrogen atoms. You will see how little space there is for a nucleophile approaching from the direction opposite to the chlorine atom's departure.

Methyl and primary alkyl halides undergo S_N2 reactions easily. What about secondary halides and tertiary halides? Secondary halides do react via the S_N2 mechanism, but usually very slowly. Primary halides that have branching groups next to the primary electrophilic carbon also can be very slow in S_N2 reactions. This is described in Section 6-9 in your supplement. Both secondary and tertiary halides can undergo a second type of nucleophilic substitution known as an S_N1 reaction. The S_N1 reaction is described in the next section.

Now study Section 6-9 in your *Organic Chemistry* supplement. Do Exercises 6-27 and 6-28.

The S_N1 Mechanism

Not all alkyl halide substitution reactions have second-order kinetics. An example is the rate of the reaction of 2-chloro-2-methylpropane (*tert*-butyl chloride) with the hydroxide ion, which depends solely on the concentration of *tert*-butyl chloride. You can run this reaction with twice or a hundred times as many hydroxide ions, but if you keep the concentration of *tert*-butyl chloride constant, the reaction rate does not change. Any mechanism proposed for this reaction must thus explain its first-order kinetics. It must also account for experimental observations that the reaction occurs in more than one step.

The mechanism that does so is known as the **S_N1 mechanism** (Substitution, Nucleophilic, Unimolecular). Remember what the "1" and "2" refer to in the names S_N1 and S_N2. They do not refer to the number of steps, since an S_N1 reaction has two or more and an S_N2 reaction has only one. Rather, they refer to the number of species in the rate-determining step or in the transition state: one species in an S_N1 reaction and two species in an S_N2 reaction.

Study Sections 7-1 and 7-2 in your *Organic Chemistry* supplement. Be sure you can define the terms **solvolysis** and **hydrolysis,** which are described in Section 7-1. Hydrolysis and **methanolysis** are examples of **solvolysis**. What solvent do you think is used in a reaction classified as methanolysis? Draw the S_N1 mechanism for yourself, and imagine where the electrons are going as you draw the curved arrows. To get an even better feel for the S_N1 mechanism, build models of the compounds and intermediates illustrated in Section 7-2 of the supplement.

Now consider Figure 6.4 in this unit. Figure 6.4 describes the potential energy diagram for the solvolysis reaction of *tert*-butyl chloride with water. This reaction involves three steps with three transition states and two intermediates. Note how the first transition state for the leaving of the chlorine group and the formation of the carbocation intermediate has the highest energy of activation. That makes this step the rate-controlling (slowest) step. The second step involves the nucleophilic attack of the water molecule on the carbocation to form an intermediate protonated alcohol. The third step, with the lowest energy of activation, is the deprotonation of the protonated alcohol to give the alcohol product.

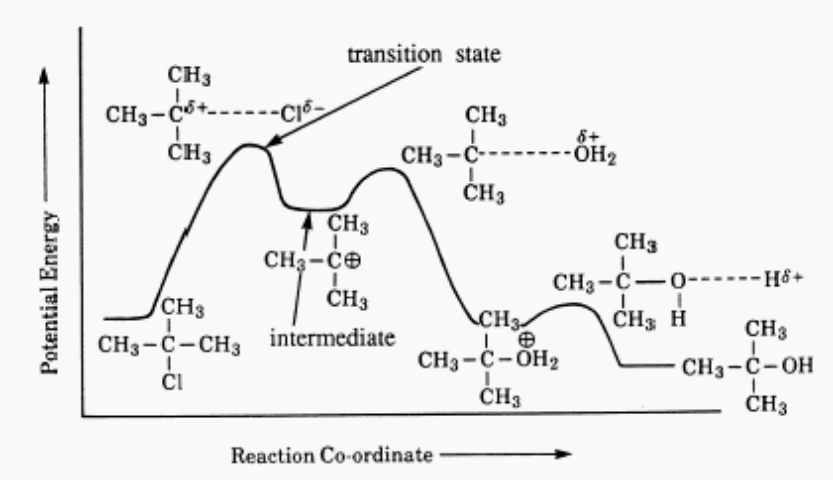


Figure 6.4: Potential energy diagram showing structures of intermediates and possible transition state structures

Do Exercises 7-1 and 7-2 in the *Organic Chemistry* supplement.

Carbocations

When a reaction intermediate is an alkyl cation, it is known as a **carbocation**. Although these are usually very transient, there is good evidence that they exist, and some have even been isolated. If you continue on with organic chemistry, you will encounter them throughout your subsequent courses.

Carbocations have a trigonal planar structure, and the carbon atom bearing the positive charge is sp^2-hybridized. There are several different types of carbocations. In a **tertiary (3°) carbocation**, the carbon with the positive charge is attached to three other carbon atoms. In a **secondary (2°) carbocation**, it is attached to two other carbons, and in a **primary (1°) carbocation**, it is attached to only one. The **methyl carbocation** is H_3C^+.

The number of alkyl groups attached to the positively charged carbon determines how stable a carbocation is. The overall order of stability is 3° > 2° > 1° > methyl.

You will see shortly that the more stable a carbocation, the greater its chances of participating in an S_N1 reaction. Conversely, the less stable the carbocation, the less likely it is to be involved in such a reaction.

Students often find it useful to recognize that, when an organic chemistry question starts with "Explain why . . .," the correct answer probably has to do with either electronegativity differences, resonance stabilization, or carbocation stability. This should tell you how important it is to know and understand the order of stability.

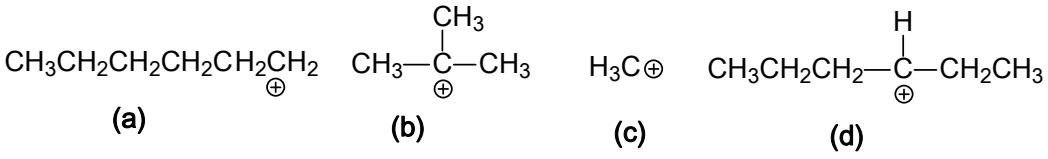
Study Section 7-5 of your *Organic Chemistry* supplement. Section 7-5 explains why a tertiary carbocation and the methyl carbocation are the most and least stable, respectively.

As you study this section, make a model of the *tert*-butyl carbocation. You don't have to include all the carbon-hydrogen bonds, just the carbon-carbon ones. You should end up with a model containing a trigonal planar carbon atom. Keep it handy, as you will use it later in this unit.

Now work on the following example:

Example

Arrange the following carbocations in order of increasing stability.



Answer

First determine what type each carbocation is: (a) is 1°, (b) is 3°, (c) is methyl, and (d) is 2°. Therefore, the order of increasing stability is **(c) < (a) < (d) < (b).**

Stereochemistry of the S_N1 Mechanism

You should now have a good idea of how S_N1 and S_N2 mechanisms work. The stereochemical consequences of the S_N1 mechanism are different from those of the S_N2 mechanism because the intermediate carbocation in an S_N1 mechanism is planar and achiral. The nucleophile in an S_N1 mechanism can attack with equal probability from either side of the planar carbocation and, as a result, if the reaction creates an asymmetric carbon, the product will be a racemic mixture of the two possible enantiomers.

Study Section 7-3 in your *Organic Chemistry* supplement. This section describes the stereochemical consequences of the S_N1 reaction. Build a model of the planar carbocation shown in Figure 7-3 of the supplement so that you can better visualize how the approach of the nucleophile is equally as probable from either side of the carbocation.

Work now on Exercises 7-3, 7-4 and 7-5 in the supplement. Make sure you can write out the mechanisms of the reactions described in these exercises by first forming a planar carbocation intermediate in each case.

Try to do the following problems. Close all your books, including this unit, before you begin.

Example

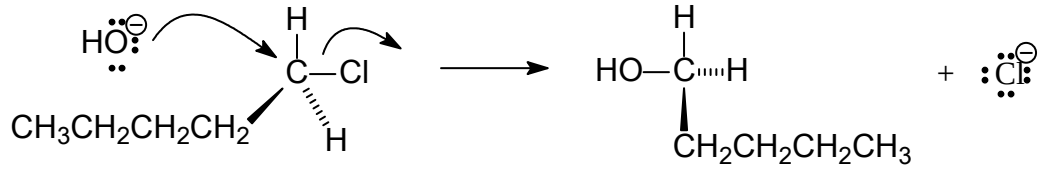
Write out the mechanism for

a. The S_N2 reaction of OH^- with 1-chloropentane

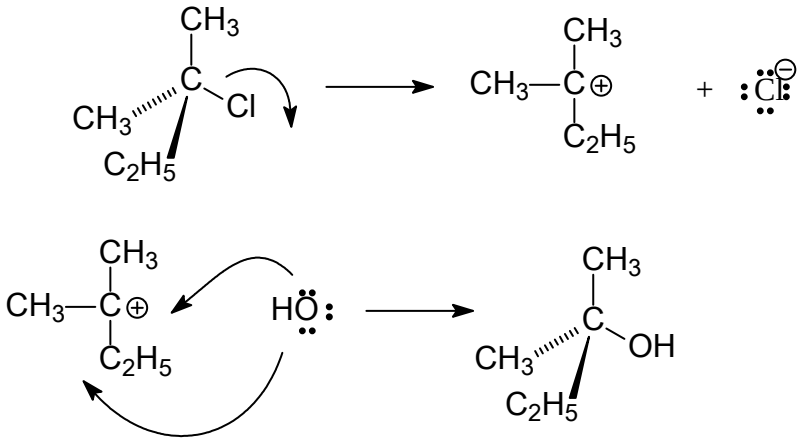
b. The S_N1 reaction of OH^- with 2-chloro-2-methylbutane

Answer

c. This is a one-step reaction where OH^- attacks from the rear as Cl^- leaves from the front



d. This is a two-step reaction. The first involves the production of the carbocation, and the second involves the attack from either side by the OH^- nucleophile. There is no third step, since the nucleophile is negatively charged and is joining a positively charged carbocation.



Factors Affecting Rates of S_N1 Reactions

As with an S_N2 reaction, varying the solvent, leaving group, and nucleophile will have a strong influence on the S_N1 reaction. In general, polar solvents, such as water or an alcohol, accelerate the S_N1 reaction because they stabilize the leaving group anion and the carbocation that form in the first transition state by **solvation**. Because the rate-controlling step in an S_N1 reaction is the loss of the leaving group, it is not surprising that the S_N1 reaction speeds up with better leaving groups. The reaction rate of an S_N1 does not depend on the strength of the nucleophile, but if you have two competing nucleophiles, the product distribution will favour the stronger nucleophile.

Study Section 7-4 in your *Organic Chemistry* supplement, and then do Exercise 7-6.

Review Section 7-5 in the supplement. Table 7-2 is an excellent summary of the conditions required for S_N1 versus S_N2 reactions. Take particular note of the reactivity of secondary leaving groups, since whether they go by an S_N1 or an S_N2 reaction is highly dependant on the conditions.

You have now almost finished Unit 6. After working on some of the following supplementary and practice exercises and the final assignment, you will have completed CHEM 1503—except for writing the final exam. You have learned quite a bit about atoms, molecules, bonding, and organic chemistry, and should be proud of your accomplishment!

Self-Assessment

By the time you complete Unit 6, you should be able to:

- Draw, using curved arrows correctly, mechanisms for S_N1 and S_N2 reactions and for free radical halogenation.
- Identify leaving groups, substrates, and nucleophiles.
- Determine the order of a reaction from kinetic data.
- Explain the effect of structure, solvent, and nucleophile on substitution reactions.
- Distinguish between protic and aprotic solvents, good and poor nucleophiles, and good and poor leaving groups.
- Explain the stereochemistry involved in S_N1 and S_N2 reactions with chiral molecules and during free radical halogenation.
- Predict substitution products under a variety of reaction conditions.
- Synthesize simple organic compounds using radical halogenation and substitution reactions.

Practice Exercise 6

Because the following problems integrate concepts and information from all of Unit 6, finish working through the unit before attempting to do them. The exercise is found listed under the Practice Exercises section of course. The solutions to these problems will be provided once you have completed this practice exercise.

If you would like a little more practice first, you may do other appropriate problems from Chapters 3, 6, and 7 of your *Organic Chemistry* supplement. These are listed on the last page of this unit under Suggested Supplementary Exercises. It is a good idea to do as many of these as possible. These additional problems will give you an excellent indication of the depth you will need to complete Assignment 6 and to pass the final exam.

Once you feel you have a good grasp of the topics covered in this unit, work on the practice exercises. Make a serious attempt to do them by yourself, using as a guide similar examples from the textbook and this unit. Spend as much time as you need to understand these problems and their solutions. This will help you do the unit assignment.

Suggested Supplementary Exercises

At the end of each chapter in your *Organic Chemistry* supplement are further exercises on the material covered. We suggest that you do as many of these exercises as necessary. Doing such problems helps you understand and apply the principles involved in the concepts discussed.

From the Problems at the end of Chapter 3:
15, 16, 20, 22, 27, 30, 35, 46, and 48.

From the Problems at the end of Chapter 6:
31–42, 44–48, 54, 55, 59, 63, and 65.

From the Problems at the end of Chapter 7:
25–35, 37, 62, and 64–66.

Assignment 6

Now refer to your *Assignments* and complete Assignment 6. Consult your Course Guide for the week this assignment is due.

You may send the assignment to your Open Learning Faculty Member using the assignment tool in Blackboard or by mail with a Marked Assignment Form.

Be sure to keep a copy of the assignment—it will be useful if you wish to discuss your work with your Open Learning Faculty Member.