Chapter *3*

Bases and Nucleophiles

In the previous chapter, the concept of acidity was introduced and discussed as related to organic molecules. Additionally, various functional groups were presented along with the concepts of resonance effects and inductive effects. Moving forward, resonance effects and inductive effects were applied to rationalize variations in pK_a values that exist among compounds bearing similar functional groups. All of these factors were described using arrow pushing.

While relative acidities are extremely important to our abilities to accurately predict the mechanistic courses of organic reactions, we must recognize that in addition to acids, most heterolytic reactions involve bases as well. Furthermore, as will soon be discussed, in organic chemistry, bases generally are able to function as nucleophiles. Therefore, this chapter will serve as an introduction to the types of bases and nucleophiles that drive mechanistic organic chemistry.

3.1   WHAT ARE BASES?

The most general definition of a base is a molecule that has an affinity for protons. For example, if we consider a molecule, B, or an anion, B$^-$, these species are said to be bases if they react with an acid, HA, as shown in Scheme 3.1. As with the dissociation of acids, discussed in Chapter 2, the reaction of bases with acids is an equilibrium process that produces an anionic species, A$^-$, and, depending on the charged nature of the base, either a cationic or a neutral species. Furthermore, considering the species formed when a base reacts with an acid, the anionic component, A$^-$, is said to be the **conjugate base** of the starting acid, HA. Likewise, the cationic or neutral species formed, BH$^+$ or BH, is said to be the **conjugate acid** of the starting base, B$^-$ or B.
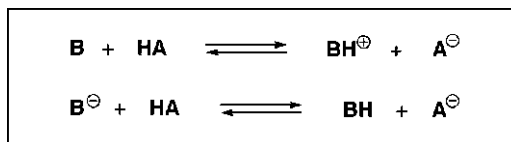
Scheme 3.1   *General representation of bases reacting with acids.*

Common base classes and examples of bases used in organic chemistry are shown in Figure 3.1 along with their conjugate acids and associated pK_a values.

In looking at the conjugate acid pK_a values listed in Figure 3.1, we realize that in order for the reactions represented in Scheme 3.1 to occur, the conjugate acid of a given base must have a pK_a value that is higher than the pK_a value associated with a proton of interest. For example, as shown in Scheme 3.2, we would not expect triethylamine to effectively deprotonate methyl acetate because the pK_a of methyl acetate is 15 pK_a units higher than the pK_a
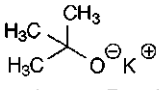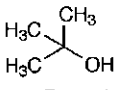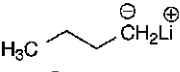

Figure 3.1   *Common bases used in organic chemistry.*
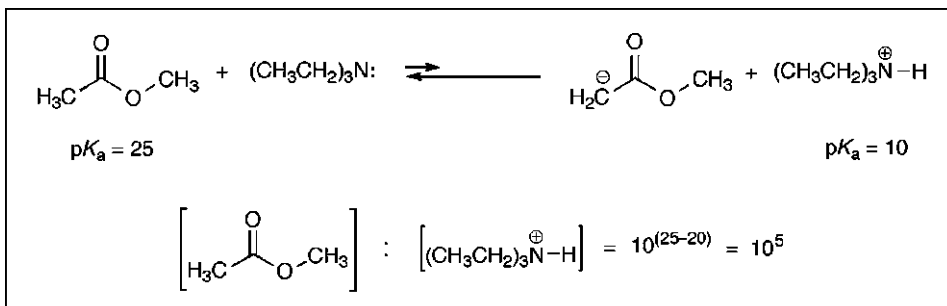
Scheme 3.2 Equilibrium between methyl acetate and triethylamine.
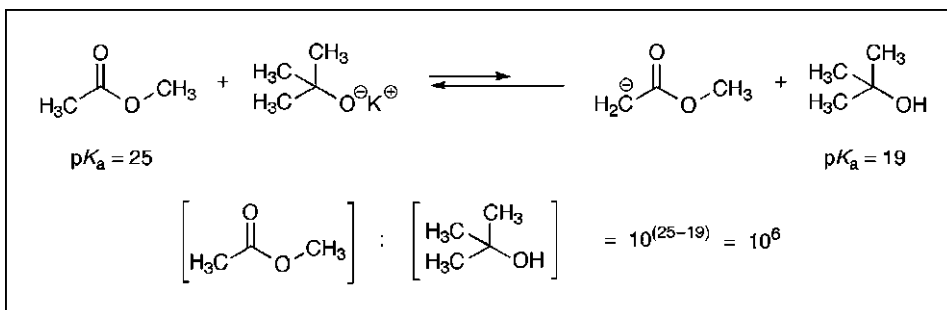
Scheme 3.3 Equilibrium between methyl acetate and potassium tert-butoxide.

of the triethylammonium cation. Since each pK_a unit represents a factor of 10 (see the definition of pK_a described in Chapter 2), this differential indicates that for each 10^{15} molecules of methyl acetate, only one will be deprotonated. As shown in Scheme 3.3, the more basic potassium *tert*-butoxide will have a greater effect on this equilibrium because the pK_a differential between that of methyl acetate and that of *tert*-butanol is 6. By comparison, for every 10^6 molecules of methyl acetate, one will be deprotonated. Finally, in the absence of reactions other than deprotonation, Scheme 3.4 illustrates that very strong bases such as phenyllithium will effect essentially complete deprotonation. This is due to the pK_a differential between methyl acetate and benzene being at least -15, indicating
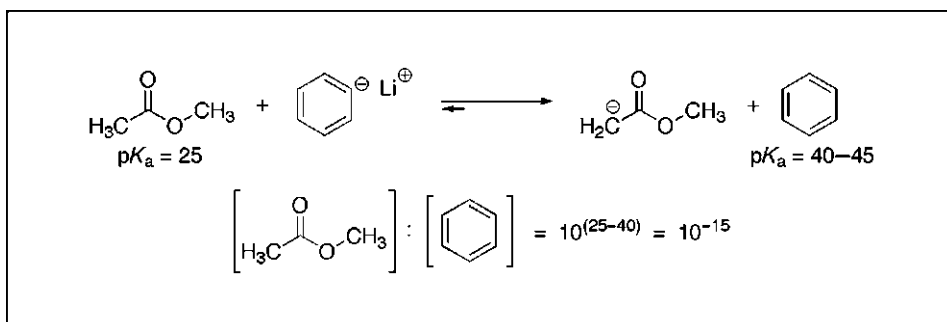
Scheme 3.4 Equilibrium between methyl acetate and phenyllithium.
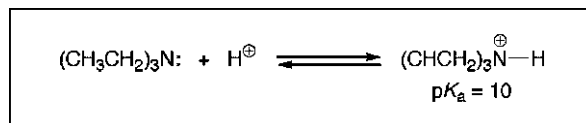
Scheme 3.5   Amine basicity is related to the nitrogen lone pair.
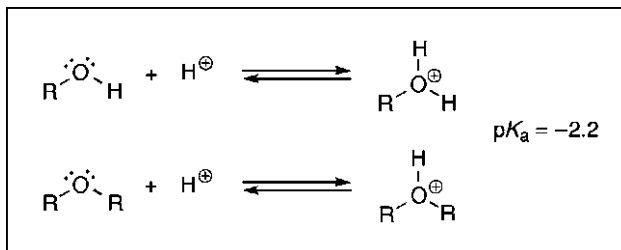
Scheme 3.6   Alcohol and ether oxygens can be protonated.

that for every molecule of methyl acetate, there will be 10^{15} molecules of benzene. Thus, it is important to understand the relative acidities of all components involved in organic reactions in order to predict the direction and outcome from a mechanistic perspective.

Again referring to the bases listed in Figure 3.1, triethylamine stands out because it is the only base listed that does not rely on a negative charge to impose basicity. In fact, the basicity of amines such as triethylamine is attributable to the lone pair associated with nitrogen (Scheme 3.5). Expanding upon the ability of lone pairs to act as bases and attract protons, we can expect that atoms and functional groups that possess lone pairs will also have measurable basicity and that their corresponding conjugate acids will have measurable pK_a values.

Moving beyond amines in our discussion of the acidity of conjugate acids of neutral bases, let us now consider alcohols and ethers. The protonation of these functional groups, illustrated in Scheme 3.6, results in positively charged trivalent oxygen atoms referred to as **oxonium ions**. While this protonation is possible due to oxygen possessing two **lone pairs** of electrons, it is not surprising that oxygen is far less basic than nitrogen due to its increased electronegativity. Consequently, oxonium ions are far more acidic than their corresponding **ammonium ions** and exhibit pK_a values around -2.2.

Extending beyond alcohols and ethers, conjugate acids of carbonyl-based functional groups are known. Specifically referring to carboxylic acids and esters, the corresponding conjugate acids, illustrated in Scheme 3.7, have pK_a values around -6. Furthermore, **protonated aldehydes and ketones**, illustrated in Scheme 3.8, have pK_a values ranging from -7 to -9.

While not practical as bases, as demonstrated by pK_a values, the protonation of carbonyl-based functional groups is important. As previously discussed, carbonyl compounds possess partial positive charges and partial negative charges and, consequently, are capable of delocalizing adjacent charges through resonance. Scheme 3.9 illustrates this fact as applied to an ester. However, if we consider a protonated carbonyl compound, the resulting positive charge residing on the carbonyl oxygen is delocalized to the
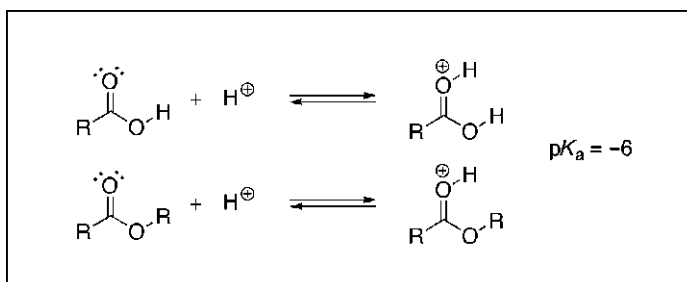
Scheme 3.7 *Carboxylic acids and esters can be protonated.*
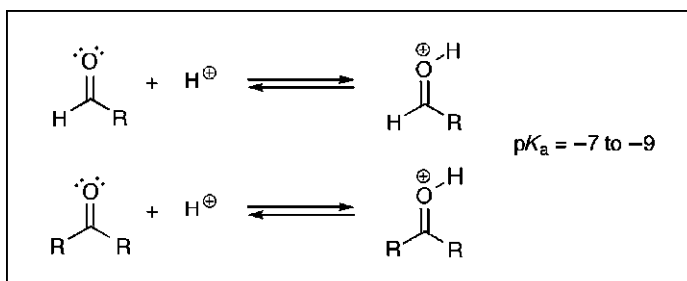
Scheme 3.8 *Aldehydes and ketones can be protonated.*
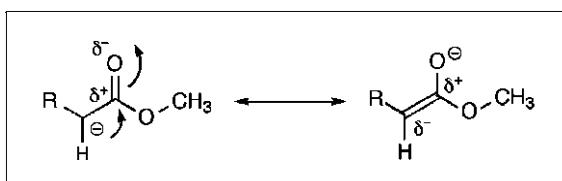
Scheme 3.9 *Carbonyl-based functional groups delocalize charges through resonance.*

Scheme 3.10 *Protonated carbonyl-based functional groups delocalize their positive charges.*

Scheme 3.11 *Protonated carbonyl-based functional groups are susceptible to reaction with nucleophiles.*

associated carbon atom (Scheme 3.10). The net result renders the carbon atom highly susceptible to reaction with nucleophiles (Scheme 3.11).
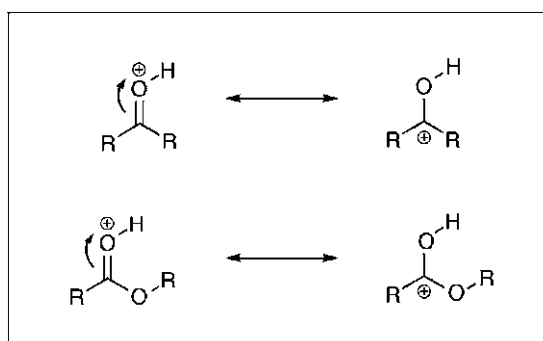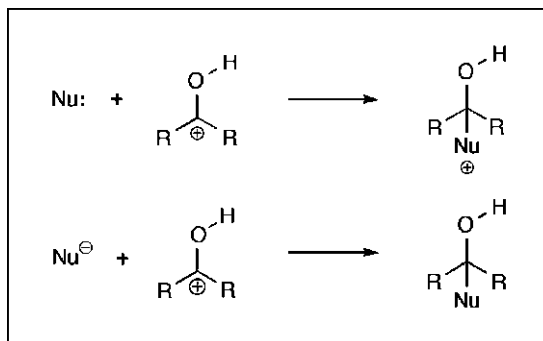
3.2   WHAT ARE NUCLEOPHILES?

As alluded to in Section 1.3 and in the previous section, heterolytic reactions generally involve species known as nucleophiles and complementary species known as electrophiles. By definition, a nucleophile is a compound that has an affinity for a positive charge. By analogy, an electrophile is a compound that has an affinity for a negative charge. Nucleophiles generally present themselves as either neutral species bearing available lone pairs of electrons or as anions (negatively charged ions). When a nucleophile is an anion, the anion is generally the conjugate base of an acid. Figure 3.2 lists common conjugate bases used as nucleophiles along with their parent acids and associated pK_a values.

In considering the information presented in Figure 3.2, it is important to become familiar with the general trends that influence the degree of **nucleophilicity** associated with the conjugate bases of various acids. From our discussions of acids, we know that as the pK_a increases, acidity decreases. Furthermore, as acidity decreases, the basicity associated with conjugate bases increases. Since, by definition, bases attract protons and since protons are, by definition, positively charged, we can translate this relationship to infer that bases exhibit affinities for positive charges. Since nucleophiles are defined as substances that have affinities for positive charges, we can understand the statement from the previous paragraph equating nucleophiles with conjugate bases of acids. Taking this discussion to the next level, the weaker the acid (higher pK_a), the stronger the conjugate base. Furthermore, the stronger the conjugate base, the stronger the nucleophile.

While the general trend relating **basicity** and nucleophilicity stands, we cannot simply rely on the pK_a values listed in Figure 3.2 as a guide for these trends. In fact, with respect to overall nucleophilicity, there are relevant factors other than basicity. Among these are **polarizability** of the nucleophilic atom, electronegativity of the nucleophilic atom, **steric factors**, and solvent effects. For our purposes, solvent effects will be discussed in the context of polarizability.
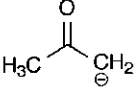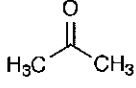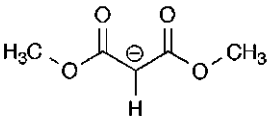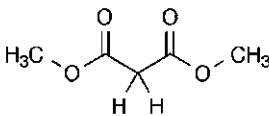
Nucleophile/ Conjugate base	Acid	pK_a
$F^\ominus$ Fluoride Anion	HF Hydrofluoric Acid	3.18
$Cl^\ominus$ Chloride Anion	HCl Hydrochloric Acid	−2.2
$Br^\ominus$ Bromide Anion	HBr Hydrobromic Acid	−4.7
$I^\ominus$ Iodide Anion	HI Hydroiodic Acid	−10
$N{\equiv}C^\ominus$ Cyanide Anion	H−CN Hydrocyanic Acid	9.3
$^\ominus N{=}\overset{\oplus}{N}{=}N^\ominus$ Azide Anion	H−N₃ Hydrazoic Acid	4.6
$H_3C{-}O^\ominus$ Methoxide Anion	$H_3C{-}OH$ Methyl Alcohol	15
$H_3C{-}\overset{\ominus}{N}H$ Methylamide Anion	$H_3C{-}NH_2$ Methylamine	35
$N{\equiv}C{-}\overset{\ominus}{C}H_2$ Acetonitrile Anion	$N{\equiv}C{-}CH_3$ Acetonitrile	25
Acetone Anion	Acetone	20
Dimethyl Malonate Anion	Dimethyl Malonate	13
$H_3C^\ominus$ Methyl Anion	CH_4 Methane	50–75

Figure 3.2 *Representative nucleophiles and their corresponding acid forms.*

Figure 3.3 *Relationship between nucleophilicity, electronegativity, and basicity as illustrated using first-row elements.*

Electronegativity, discussed in Chapter 1, is a measure of an atom's affinity for electrons. Thus, as electronegativity increases, affinity for electrons increases. Furthermore, as affinity for electrons increases, so does acidity. This is reflected in the decreasing pK_a values moving from methane to methylamine to methanol to hydrofluoric acid (Fig. 3.3). In this sequence, the trend relating increasing basicity of conjugate bases to increasing nucleophilicity holds true. Furthermore, this relationship holds true for each row in the periodic table of the elements moving from left to right.

Polarizability refers to the ability of an atom to become polarized in the presence of external influences such as solvent effects. In general, polarizability increases as electronegativity decreases. Another way of looking at this relationship involves atomic size. Essentially, the larger an atom, the more diffuse its outer shell of electrons. As this electron shell becomes more diffuse, it also becomes more susceptible to polarizing influences. Furthermore, these polarizing influences can dramatically impact the order of nucleophilicity among atoms represented in any given column of the periodic table of the elements. In fact, polarizability can override the relationship between nucleophilicity and pK_a. This effect is illustrated using the relative nucleophilicities of Cl^-, Br^-, and I^-. If we refer to the pK_a values listed in Figure 3.2, we would expect the order of nucleophilicity among these halide ions to be $Cl^- > Br^- > I^-$. This is, in fact, the case in the presence of **polar aprotic solvents** (solvents not possessing a dissociable proton) such as dimethylformamide. However, in the presence of **polar protic solvents** (solvents possessing a dissociable proton) such as water or alcohols the order of nucleophilicity is $I^- > Br^- > Cl^-$. This effect, shown in Figure 3.4, illustrates that relative nucleophilicities are not absolute.

Another factor influencing nucleophilicity and related to polarizability is the **hardness** or **softness** of the nucleophilic base. Specifically, a **hard base** is high in electronegativity and low in polarizability. Alternatively, a **soft base** is low in electronegativity and high in polarizability. Using these definitions, F^- is considered a hard base because it is high in electronegativity, small in size and holds its electrons very tightly. On the other hand, I^- is considered a soft base because its large size causes it to hold its electrons loosely and renders it highly **polarizable**.

The relationship between hard bases and soft bases now relates back to solvent effects. if we consider a hard base in a polar solvent, we find that the concentrated electron density
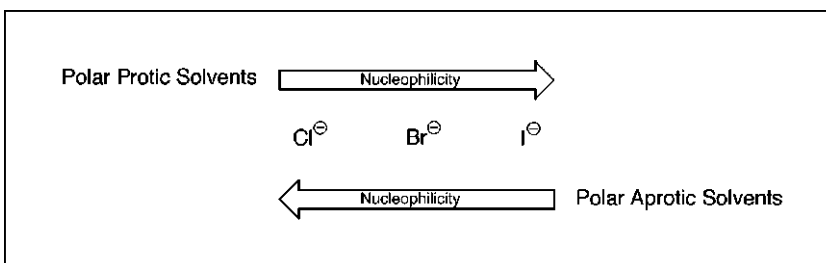
Figure 3.4   *Order of increasing nucleophilicity of halide ions is influenced by polarizing influences such as solvent effects.*

associated with a hard base attracts a tight shell of solvent surrounding it. This solvent shell blocks the hard base from reacting as a nucleophile. On the other hand, this solvent effect is minimized for a soft base due to its large size and diffuse electron concentration. The absence of a solvent shell around a soft base enhances its ability to react as a nucleophile. This effect is illustrated in Figure 3.5. Thus, while solvent effects can influence the order of nucleophilicity observed for halide ions, the general rule of thumb is that nucleophilicity increases as we move from the top to the bottom of any given column in the periodic table of the elements.

Of the factors influencing nucleophilicity, **steric effects** have perhaps the greatest influence. Steric effects occur when groups attached to a nucleophilic atom are too large
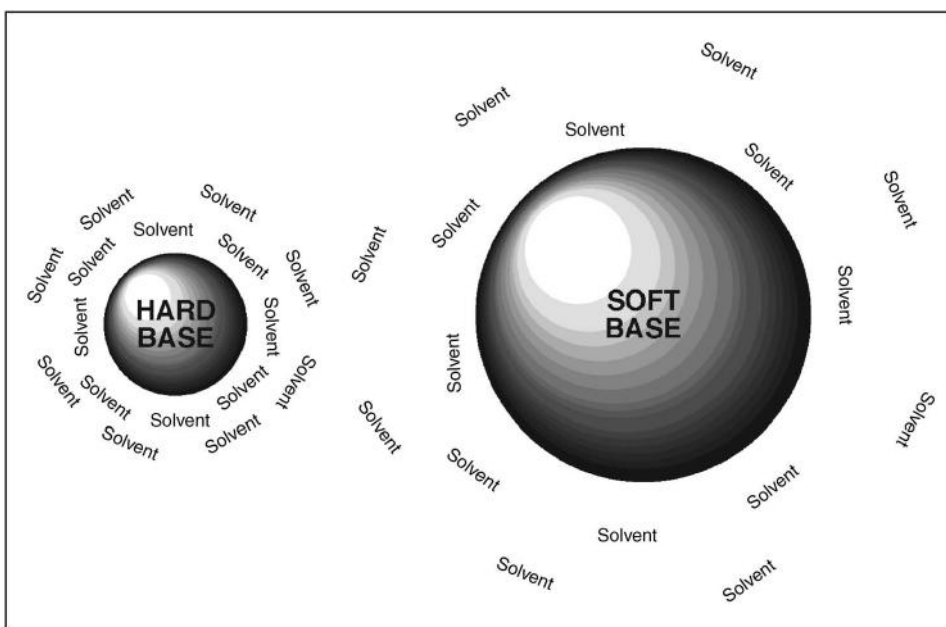

**Figure 3.5**   *Solvent shells surround hard bases rendering them less reactive nucleophiles than soft bases.*

Figure 3.6 *Steric effects can override the influence of* pK_a *values on nucleophilicity.*

to allow the nucleophile to react. In fact, it is this effect that can differentiate between a reactive nucleophile and a true base. Consider the alkoxide ions illustrated in Figure 3.6. If we take into account only the pK_a values listed, we may expect that nucleophilicity would increase as we move from methoxide to ethoxide to isopropoxide to *tert*-butoxide. However, if we look at these conjugate bases not as a function of their corresponding pK_a values but as a function of their overall **structure**, we find a very different story. Specifically, a methyl group is small compared to an ethyl group. Furthermore, an ethyl group is small compared to an isopropyl group. Finally, an isopropyl group is small compared to a *tert*-butyl group. Therefore, if we consider that increasing **molecular volume** around a nucleophilic atom results in decreasing nucleophilicity, it is easy to reconcile the trend illustrated in Figure 3.6. Furthermore, when a nucleophilic atom becomes sterically blocked from acting as a nucleophile, the basic characteristics of this atom becomes manifested. In fact, *tert*-butoxide anions are commonly used as bases in organic chemistry due to the diminished nucleophilicity surrounding the oxygen. Finally, it is important to remember that this effect is generally applicable to all nucleophiles regardless of the atoms involved.

3.3 LEAVING GROUPS

No discussion of nucleophiles would be complete without addressing leaving groups. As mentioned in Chapter 1 and illustrated in Scheme 3.12, leaving groups are important components in nucleophilic reactions because they represent the molecular fragment that
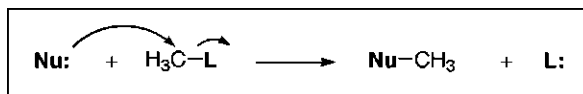
Scheme 3.12 *Example of a nucleophilic reaction.*

detaches from the parent molecule during the course of the reaction. Specifically, a nucleophile, Nu, approaches an organic molecule and displaces the leaving group, L. This type of reaction raises the question of what relationship links nucleophiles to leaving groups. The answer to this question begins with pK_a values.
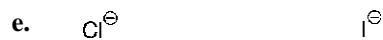
As previously discussed, relative acidities are important with respect to our ability to predict which proton will be removed first. Furthermore, relative acidity brings our attention to the relative stability of conjugate bases. Specifically, the more stable the conjugate base, the higher the acidity and, in general, the lower the nucleophilicity. This trend, as discussed in the previous section holds true when comparing nucleophiles from the same row in the periodic table of the elements. Keeping this trend in mind, we can argue that since a leaving group is essentially the opposite of a nucleophile, the trend regarding nucleophilicity should roughly reverse when considering trends regarding the efficiency of leaving groups. This is, in fact, the case and, as we will see as discussions progress through this book, the acid forms of leaving groups will generally exhibit higher pK_a values than the acid forms of competing nucleophiles.
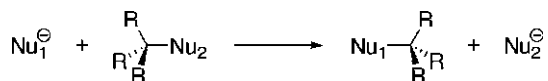
3.4 SUMMARY

In this chapter, the concepts of organic bases and basicity were presented. These discussions were expanded to define nucleophiles and nucleophilicity. Trends associated with conjugate bases of acids and nucleophilicity were presented and translated to define the concept of leaving groups. As discussions continue, all of these concepts will play important roles in the various organic reaction mechanistic types presented in the following chapters.

PROBLEMS

1. In each case, circle the better nucleophile. Explain your answers.

   a. H_3C-OH H_3C-NH_2

   b. $H_3C-O^{\ominus}$ $H_3C-\overset{\ominus}{N}H$

   c. $H_3C-O^{\ominus}$ H_3C-NH_2

   d. H_3C-OH $H_3C-\overset{\ominus}{N}H$

   e. $Cl^{\ominus}$ $I^{\ominus}$

   f. $N\equiv C^{\ominus}$ $HC\equiv C^{\ominus}$

   g. $H_3C^{\ominus}$ $N\equiv C-\overset{\ominus}{C}H_2$

   h.

2. Nucleophiles often participate in nucleophilic substitution reactions. The general form of these reactions may be represented by the following equation where Nu_1^- and Nu_2^- are nucleophiles:

$$Nu_1^{\ominus} \quad + \quad \underset{R}{\overset{R}{\underset{R}{\diagup}}}\!\!-Nu_2 \quad \longrightarrow \quad Nu_1\!-\!\underset{R}{\overset{R}{\diagup}}\!\!R \quad + \quad Nu_2^{\ominus}$$

a. Explain what type of relationship between Nu_1^- and Nu_2^- is necessary in order for this reaction to be favored.

b. What does this say about the relative basicities of Nu_1^- and Nu_2^-?

c. Which nucleophile has the larger pK_a?

d. What generalization can be concluded about the relationship between bases and nucleophiles?

3. How can pK_a values be used to describe basicity?

4. As electron-donating and electron-withdrawing substituents will affect the acidity of organic molecules, so will they affect the basicity. How will the following substituents affect (raise, lower, or no change) the pK_a of aniline (aminobenzene)? Explain using partial charges to illustrate inductive effects. Remember, *o* refers to *ortho* positions, *m* refers to *meta* positions and *p* refers to the *para* position. *In addressing these problems, assume that the acidity of the amine is influenced solely by the partial charges induced by additional ring substituents.*

   a. *o*-NO$_2$

   b. *p*-NO$_2$

c. *m*-NO$_2$

d. *p*-NH$_2$

e. *m*-CH$_3$
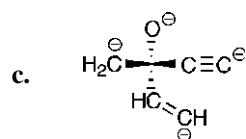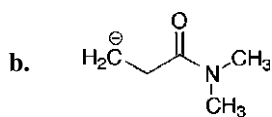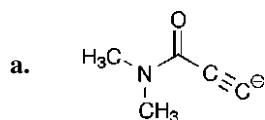
f. *p*-CH$_3$

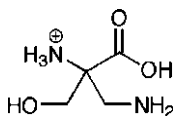**g.** *p*-OCH$_3$

h. *p*-Cl

i. *m*-Cl

5. Arrange the following groups of molecules in order of increasing basicity. Explain your results using partial charges and inductive effects.
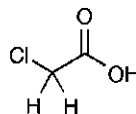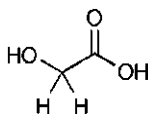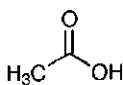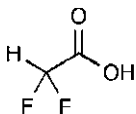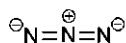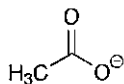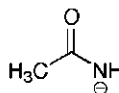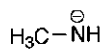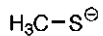
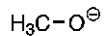**6.** Predict the order of protonation of the basic sites on the following molecules. Support your answers with pK_a values.
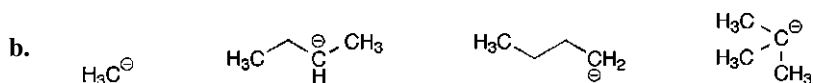
a.

b.

c.

d.
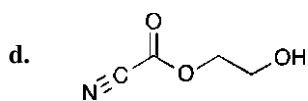
7. Which proton is the least acidic? Explain your answer.

8. Separate the following group of bases into a group of hard bases and a group of soft bases. Rationalize your answers based on electronegativity and polarizability.

9. Arrange the following structures in order of increasing nucleophilicity:

a.

b.
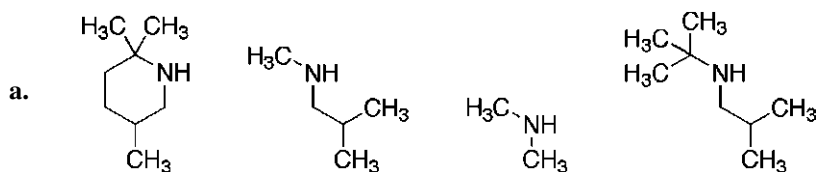
10. For the following pairs of structures, circle the better leaving group.

a. $Cl^{\ominus}$ $I^{\ominus}$

b. $H_3C-O^{\ominus}$ $H_3C-\overset{\ominus}{N}H$

c. $CH_3CH_2-O^{\ominus}$ $CF_3CH_2-O^{\ominus}$

d. $H_3C-S^{\ominus}$ $H_3C-O^{\ominus}$

e.   F$^{\ominus}$ Br$^{\ominus}$

f.   H$_3$C $-$ $\overset{\ominus}{\text{N}}$H   H$_3C-S^{\ominus}$

g.   Br$^{\ominus}$ H$_3$C$-$O$^{\ominus}$

h.   F$_3$C $-\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{S}}}}-O^{\ominus}$ H$_3$C$-\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{S}}}}-O^{\ominus}$