

Chapter 2

Acids

As mentioned at the end of Chapter 1, an understanding of heterolytic reaction mechanisms must be accompanied by an understanding of the properties of organic acids and bases. Through this understanding, an ability to predict the reactive species in organic reactions and the reactive sites in organic molecules will evolve. Therefore, this chapter focuses on the properties of acids, dissociation constants, and the relative acidities observed for protons in different environments.

2.1 WHAT ARE ACIDS?

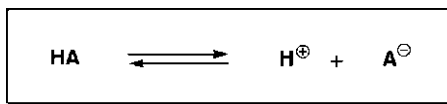
The most general description of an **acid** is a molecule that liberates **hydrogen ions**. Therefore, if we consider a molecule, HA, this molecule is said to be an acid if it dissociates as shown in Scheme 2.1. It is important to note that any **acid dissociation** is an **equilibrium process**. Through this equilibrium process, two species, a **proton** (hydrogen **cation**) and an **anion**, are liberated. Furthermore, because this dissociation results in the formation of two ionic (charged) species, it is important to consider why this would be favorable as compared to the neutral state of undissociated HA. The answer to this question lies in the stability of the anion, A^- , itself.

Regarding **anionic stability**, there are many relevant factors. Among these are external influences such as **solvent effects** (Fig. 2.1). Specifically, a **polar solvent** has the ability to **stabilize** ionic species through **charge–charge interactions** or **charge–heteroatom interactions**. Conversely, a **nonpolar solvent** generally **inhibits** formation of charged species because it cannot interact with the ions. Figure 2.2 lists common polar and nonpolar organic solvents. While solvent polarity is an important factor in the progression and rate of reactions, its role applied to arrow pushing relates more to mechanistic determination

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.

By Daniel E. Levy

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Scheme 2.1 General representation of acid dissociation.

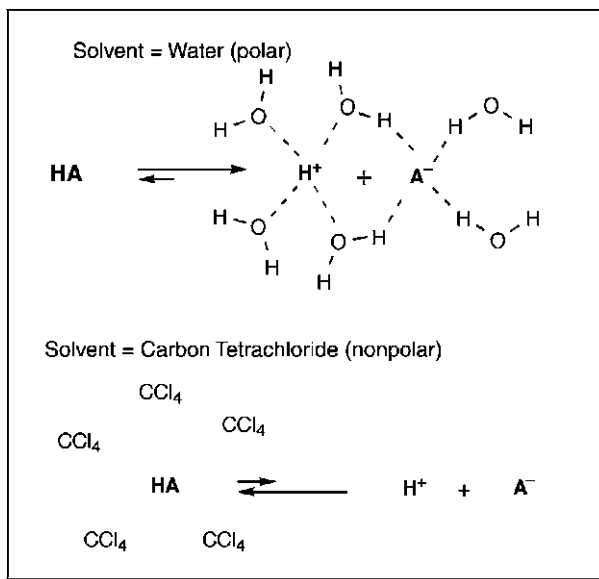


Figure 2.1 Solvent effects on acid dissociation.

than to how electrons move. Therefore, solvent polarity will not be addressed further in this chapter and will be revisited in the context of various mechanistic types.

In addition to external factors such as solvent effects, there are internal factors that influence anionic stability. Among these are **inductive effects** (how do electron-donating or electron-withdrawing substituents affect a molecule?), and **resonance effects** (is the charge localized or delocalized?). As inductive effects generally work in concert with resonance effects, our primary focus will be on the resonance effects themselves.

2.2 WHAT IS RESONANCE?

When a given molecule or ion can exist with multiple configurations of double/triple bonds or multiple sites bearing positive/negative charges, the molecule or ion is said to possess **resonance** forms. These resonance forms can be represented by drawings where the changes in electronic configuration are rationalized using arrow pushing. Furthermore, these changes in electronic configuration occur with no alterations to the connectivity of the individual atoms. For example, as shown in Scheme 2.2, a **carboxylic acid** dissociates into a **proton** and a **carboxylate anion**. As shown in Scheme 2.3, this carboxylate anion possesses two resonance structures. These resonance structures, illustrated using a

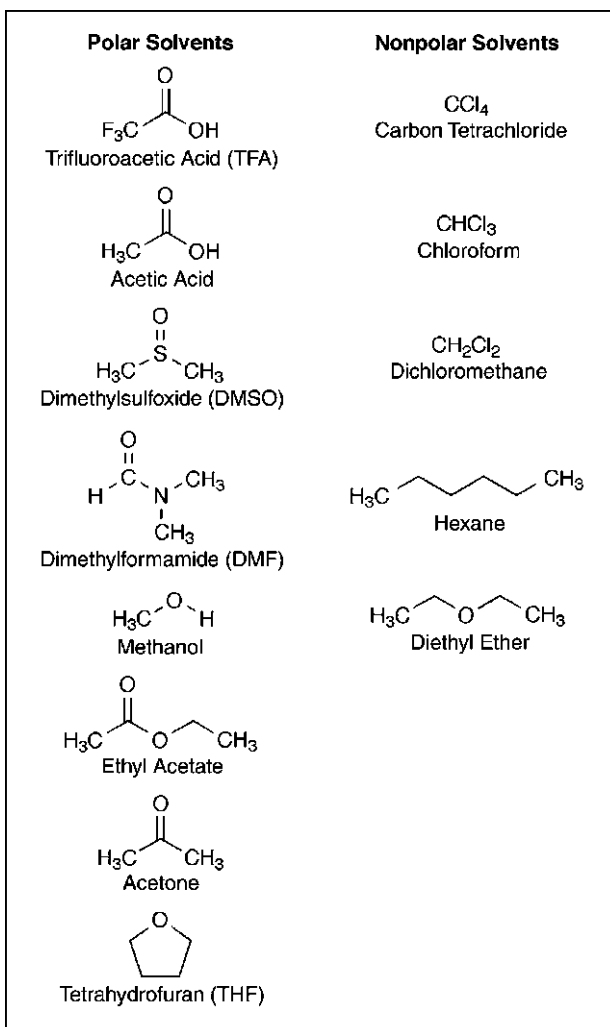
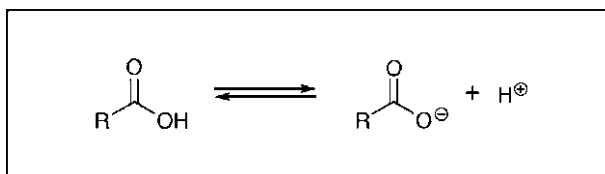


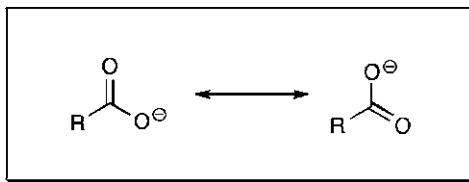
Figure 2.2 Common polar and nonpolar organic solvents.

double-headed arrow, are easily explained using arrow pushing to move the electrons associated with the negative charge from one oxygen atom to the other (Scheme 2.4).

Although carboxylic acids exist in **equilibrium** with their resonance-stabilized carboxylate anions, it is important to understand that resonance stabilization alone will

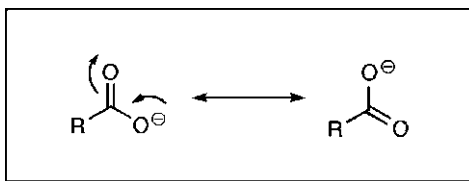


Scheme 2.2 Dissociation of a carboxylic acid forming a proton and a carboxylate anion.

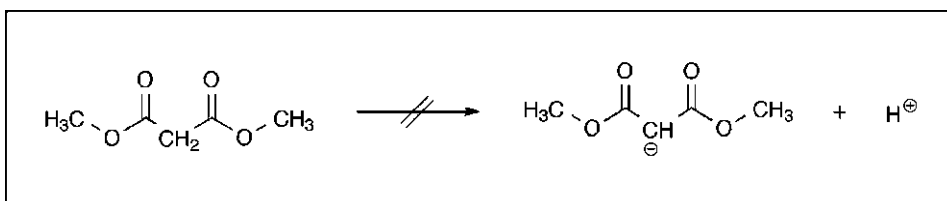


Scheme 2.3 Resonance forms of the carboxylate anion.

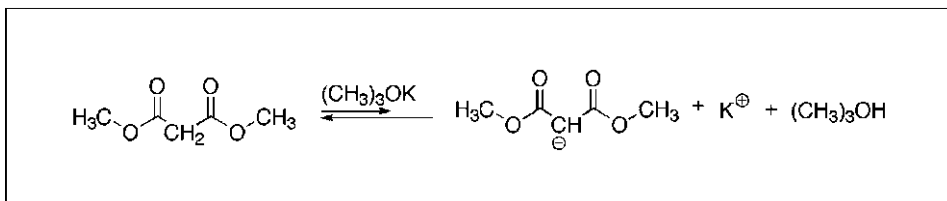
not induce carboxylate anions to form. In fact, when resonance stabilization is not enough to induce formation of a carboxylate anion, addition of a base generally will accomplish this task. For example, considering **dimethyl malonate**, there is no **dissociation** of any protons liberating **malonate anions** (Scheme 2.5). The equilibrium lies entirely in favor of neutral dimethyl malonate. However, with addition of a **base** such as **potassium *tert*-butoxide**, a proton is readily extracted, generating malonate anions, potassium cations, and *tert*-butyl alcohol (Scheme 2.6). The three resonance forms of the malonate anion, described using arrow pushing, are illustrated in Scheme 2.7. While **deprotonation** under these conditions does not proceed to completion, the equilibrium is such that malonate anions are available in sufficient quantities to react as required.



Scheme 2.4 Rationalization of the carboxylate anion resonance forms using arrow pushing.



Scheme 2.5 Dimethyl malonate does not spontaneously liberate malonate anions.



Scheme 2.6 Potassium *tert*-butoxide partially deprotonates dimethyl malonate.

Again referring to general chemistry coursework, the degree of acidity of a solution is measured according to the concentration of hydrogen ions present. The **pH** of a solution is defined as the negative logarithm of the hydrogen ion concentration (Fig. 2.5). Similarly, if K_a is converted to its negative logarithm, we calculate the **pK_a** (Fig. 2.6). It is, in fact, the pK_a that is used to represent the **acidity** associated with the various hydrogen atoms present in organic molecules.

When calculating the pK_a of a given hydrogen atom, it is important to remember that the pK_a is related to the pH of the solution. This relationship is represented in Figure 2.7. As illustrated, the pH value can be mathematically separated from the negative logarithm of the ratio of the anion concentration to the concentration of the undissociated acid. Taking this relationship to its final derivation, we find the **Henderson–Hasselbach equation** (Fig. 2.8), which provides us with the key to determining pK_a values and relative acidities. An important result derived from the Henderson–Hasselbach equation is that in a **perfect equilibrium** (a system where there is an equal amount of dissociated and undissociated acid), the pK_a is equal to the pH. This arises from the fact that in a perfect equilibrium, the concentration of HA is equal to the concentration of A⁻, making the ratio of [A⁻] to [HA] equal to 1. Since the log of 1 is 0, this term drops out of the equation (Fig. 2.9).

$$K_{\text{eq}} = \frac{[\text{H}^{\oplus}][\text{A}^{\ominus}]}{[\text{HA}]} = K_a$$

Figure 2.4 K_a is the K_{eq} specifically related to dissociation of acids.

$$\text{pH} = -\log[\text{H}^{\oplus}]$$

Figure 2.5 Definition of pH.

$$\text{p}K_a = -\log K_a$$

Figure 2.6 Definition of pK_a.

$$\text{p}K_a = -\log K_a = -\log \left\{ \frac{[\text{H}^{\oplus}][\text{A}^{\ominus}]}{[\text{HA}]} \right\} = -\log [\text{H}^{\oplus}] + \left\{ -\log \frac{[\text{A}^{\ominus}]}{[\text{HA}]} \right\} = \text{pH} + \left\{ -\log \frac{[\text{A}^{\ominus}]}{[\text{HA}]} \right\}$$

Figure 2.7 pK_a values are related to pH.

$$pK_a = \text{pH} - \log \left\{ \frac{[A^\ominus]}{[HA]} \right\}$$

Figure 2.8 Henderson–Hasselbach equation.

$$\text{When } [A^\ominus] = [HA],$$

$$pK_a = \text{pH} - \log \left\{ \frac{[A^\ominus]}{[HA]} \right\} = \text{pH} - \log 1 = \text{pH} - 0 = \text{pH}$$

Figure 2.9 In a perfect equilibrium, $pK_a = \text{pH}$.

2.4 RELATIVE ACIDITIES

Having explored the relationships between solution pH and pK_a values, we can now explore the **relative acidities** of various hydrogen atoms and how these values are influenced by neighboring functional groups and heteroatoms. In this arena, it is important to remember that how a reaction proceeds is largely dependent upon the relative acidities of protons (hydrogen atoms) compared to one another and not on the **absolute acidity** of a given proton.

Considering a compound that produces a solution pH greater than 7, that compound is generally referred to as **basic**. However, a proton of interest (proton A) on this compound may be considered **acidic** compared to another proton (proton B) if the pK_a of proton A is lower than the pK_a of proton B. In other words, the lower the pK_a for a given proton, the more acidic that proton is. Consequently, in order to predict the mechanistic course of a given organic reaction, it is *extremely* important to be able to recognize the *most acidic proton* in a given molecule.

As previously stated, acidities of various protons are dependent upon their associated functional groups and nearby heteroatoms. Furthermore, these protons may be either components of relevant functional groups or adjacent to relevant functional groups. Figure 2.10 illustrates examples of compounds possessing acidic protons associated with representative functional groups, and Figure 2.11 illustrates examples of compounds possessing acidic protons adjacent to representative functional groups. In both figures, the acidic protons are highlighted in bold.

In studying the relationships between functional groups and proton acidities, we will first look at carboxylic acids. As illustrated in Scheme 2.2, carboxylic acids dissociate to form protons and carboxylate anions. Furthermore, as shown in Scheme 2.3, the carboxylate anion is stabilized through two resonance forms. It is this **resonance stabilization** that serves as the primary driving force behind the acidic nature of carboxylic acids. Further evidence of the relationship between resonance stabilization of anions and acidity can be seen when comparing the pK_a values of carboxylic acids to the pK_a values of **alcohols**.

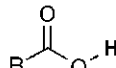
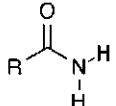


Functional Group	pK_a
 Carboxylic Acid	4–6
 Primary Amide	15–17
 Alcohol	15–19
 Amine	33–38

Figure 2.10 Representative functional groups with associated acidic protons.

As shown in Figure 2.10, carboxylic acids (compounds that dissociate into resonance-stabilized carboxylate anions) have pK_a values ranging from 4 to 6. However, alcohols (compounds that dissociate into alkoxide anions possessing no resonance stabilization) have pK_a values ranging from 15 to 19. A comparison of the resonance capabilities of carboxylic acids compared to alcohols is illustrated in Scheme 2.8. As shown, the resonance capabilities of the carboxylate anion are due to the presence of a **carbonyl** group adjacent to the OH. This carbonyl group imparts additional partial charges that attract the negative charge and distribute it over **multiple centers**. In the case of an alcohol, the deprotonated **alkoxide anion** has no place to distribute its charge and the charge remains entirely on the oxygen. Because alcohols have no resonance capabilities, their pK_a values are higher than those of carboxylic acids. Nevertheless, both carboxylic acids and alcohols are considered organic acids.

Having illustrated how resonance effects influence the relative acidities of different functional groups, it is important to understand why the same functional groups in different compounds can possess different acidities. In order to address this, we must move from the general representation of compounds presented above to a treatment of specific compounds. For example, the carboxylic acid represented in Scheme 2.2 possesses an “R” group. In organic chemistry, R groups are commonly used to represent regions of compounds that are variable. To illustrate this point, Figure 2.12 lists several common carboxylic acids and their respective pK_a values.

As illustrated in Figure 2.12, **formic acid** ($R = H$) has a pK_a of 3.75. However, if R is changed to an electron-withdrawing group such as CF_3 , the anion resulting from dissociation becomes more stabilized resulting in a lower pK_a compared to formic acid. Alternately, if R is changed to an electron-donating group such as CH_3 , the anion resulting

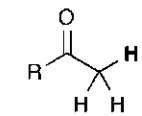
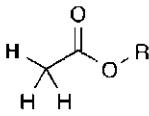
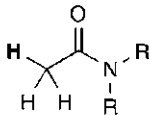
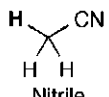
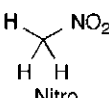
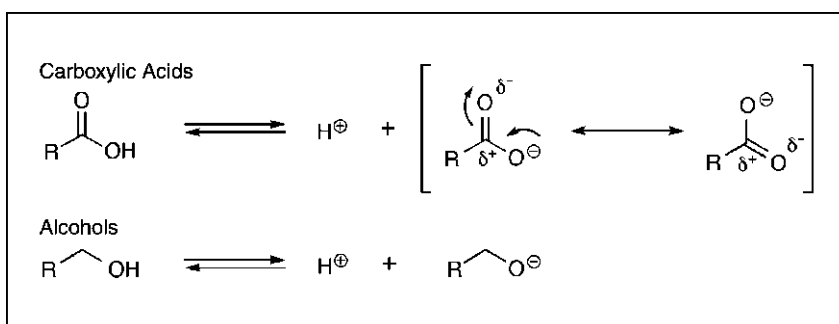
Functional Group	pK_a
 Aldehyde / Ketone	20–25
 Ester	25–30
 Tertiary Amide	30–35
 Nitrile	20–25
 Nitro	10–15

Figure 2.11 Representative functional groups with adjacent acidic protons.

from dissociation becomes less stable as illustrated by a higher pK_a compared to that of formic acid.

The changes in the pK_a values associated with different carboxylic acids are the result of inductive effects. Inductive effects occur when electronegative groups pull electron density away from acidic centers, rendering these centers more acidic. Conversely, inductive effects



Scheme 2.8 Resonance capabilities of carboxylic acids compared to alcohols.

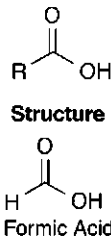
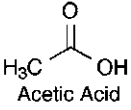
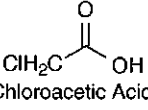
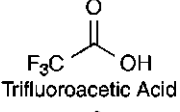
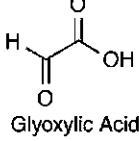
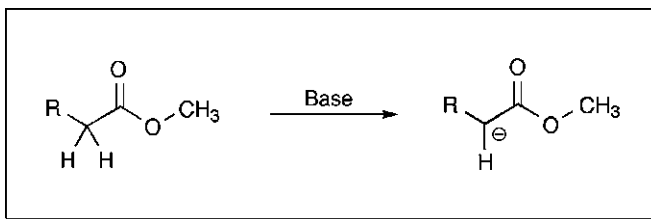
R	Structure	pK _a
H	 Formic Acid	3.75
CH ₃	 Acetic Acid	4.75
CH ₂ Cl	 Chloroacetic Acid	2.85
CF ₃	 Trifluoroacetic Acid	0.30
CHO	 Glyoxylic Acid	3.18

Figure 2.12 Common carboxylic acids and their respective pK_a values.

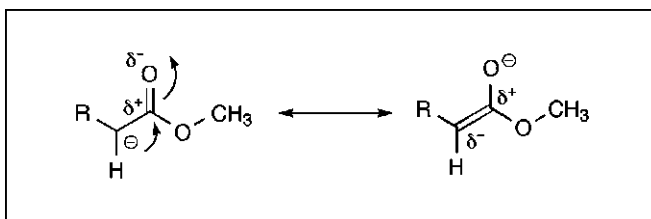
also occur when **electropositive** groups push electron density toward acidic centers, rendering these centers less acidic. The concept of electronegativity was introduced in Section 1.2 and referred to the periodic table of the elements as a resource for calibration. In comparing formic acid to **acetic acid**, the CH₃ group of acetic acid is electron-donating while the H of formic acid is not. This means that there is greater electron density present in the carboxylate anion of acetic acid than in the carboxylate anion of formic acid. An *increase* in electron density associated with a carboxylate anion *lowers* the **stability** of the anion and raises the pK_a. Thus, as mentioned at the end of Section 2.1, these observations demonstrate that inductive effects work in concert with resonance effects to alter pK_a values.

While carboxylic acids are among the most acidic of all organic compounds, we are more frequently interested in removing protons that are not directly associated with the carboxylic acid functional group. Additionally, reliance upon removal of protons from molecules containing functional groups other than carboxylic acids is common. In this context, **esters** represent the next functional group we will study.

Esters, as functional groups, are simply oxygen-alkylated carboxylic acids (see Fig. 1.3). As such, we cannot remove a proton from the oxygen as we are able to do with carboxylic acids. However, as shown in Scheme 2.9, the proton in the position α (adjacent) to the ester



Scheme 2.9 Esters can be deprotonated α to ester carbonyls.



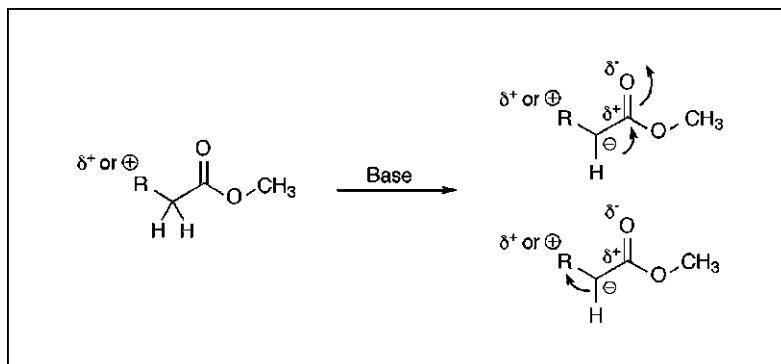
Scheme 2.10 Rationalization of the acidity of protons α to ester carbonyls.

carbonyl can be removed under basic conditions. Furthermore, the rationalization of the **acidity** of this proton is represented in Scheme 2.10 using arrow pushing and the placement of partial charges. The pK_a is approximately 25 for the illustrated ester when R is hydrogen.

As with carboxylic acids, pK_a values associated with esters will change accordingly when the molecule is changed. Specifically, the associated pK_a values are subject to the influence of inductive effects. An excellent example brings us back to dimethyl malonate illustrated in Schemes 2.6 and 2.7. If we consider the second ester group in dimethyl malonate as an electron-withdrawing group as illustrated by the additional resonance forms of the anion, we can understand that, compared to simple esters, the malonate diester will be more acidic. In fact, the pK_a associated with deprotonation of dimethyl malonate is approximately 12. Thus, considering inductive effects of neighboring groups, we can predict relative acidities for most organic compounds.

2.5 INDUCTIVE EFFECTS

Having introduced the concept of inductive effects using carboxylic acids and esters as examples, we will now explore these effects in greater detail. As alluded to through the pK_a values of the selected carboxylic acids shown in Figure 2.12, inductive effects can be either electron donating or electron withdrawing. Specifically, an electron-donating inductive effect will result from incorporation of an **electron-donating group**. Similarly, an electron-withdrawing inductive effect will result from incorporation of an **electron-withdrawing group**. When an electron-donating group is incorporated adjacent to an acidic proton, the acidity decreases and the pK_a increases. Similarly, when an electron-withdrawing group is incorporated adjacent to an acidic proton, the acidity increases and the pK_a decreases. Thus, it is imperative for those studying organic chemistry to fully understand what constitutes electron-donating groups and electron-withdrawing groups.

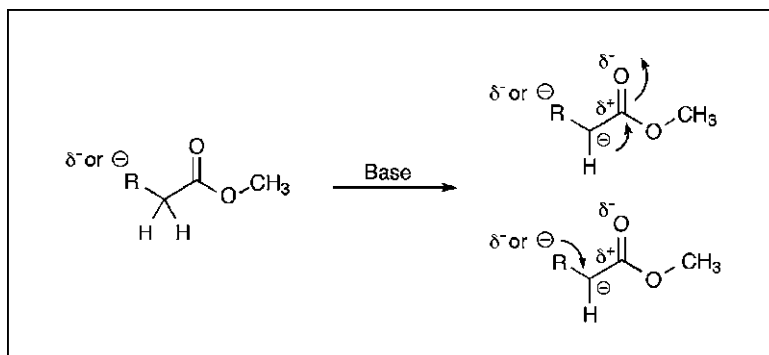


Scheme 2.11 Electron-withdrawing groups increase acidity by increasing anionic stability.

As illustrated in Scheme 2.11, electron-withdrawing groups are readily recognized when the group places either a partial or formal positive charge adjacent to an acidic center. This placement of a partial positive charge allows greater **delocalization** of the negative charge that develops when the acidic proton is removed. Through this increased delocalization of the developing negative charge, the stability of the developing anion increases, thus increasing the acidity of the target proton.

As illustrated in Scheme 2.12, electron-donating groups are readily recognized when the group places either a partial or formal negative charge adjacent to an acidic center. This placement of a negative charge forces destabilization of the negative charge that develops when the acidic proton is removed. To illustrate, imagine trying to force two magnets to meet at their negative poles. As the negative poles get closer, the repulsive forces between the magnets increase. As with magnets, two negative charges on adjacent atoms result in a destabilizing situation. By decreasing the stability of a developing negative charge, the stability of a developing anion decreases, thus decreasing the acidity of the target proton.

Functional groups were defined and discussed in Chapter 1 (Section 1.2). In that discussion, the concept was presented that functional groups can be either electron-withdrawing groups or electron-donating groups. In fact, all inductive effects result from the introduction of functional groups to organic molecules. Furthermore, through an understanding of the characteristics of the various functional groups, one can predict



Scheme 2.12 Electron-donating groups decrease acidity by decreasing anionic stability.

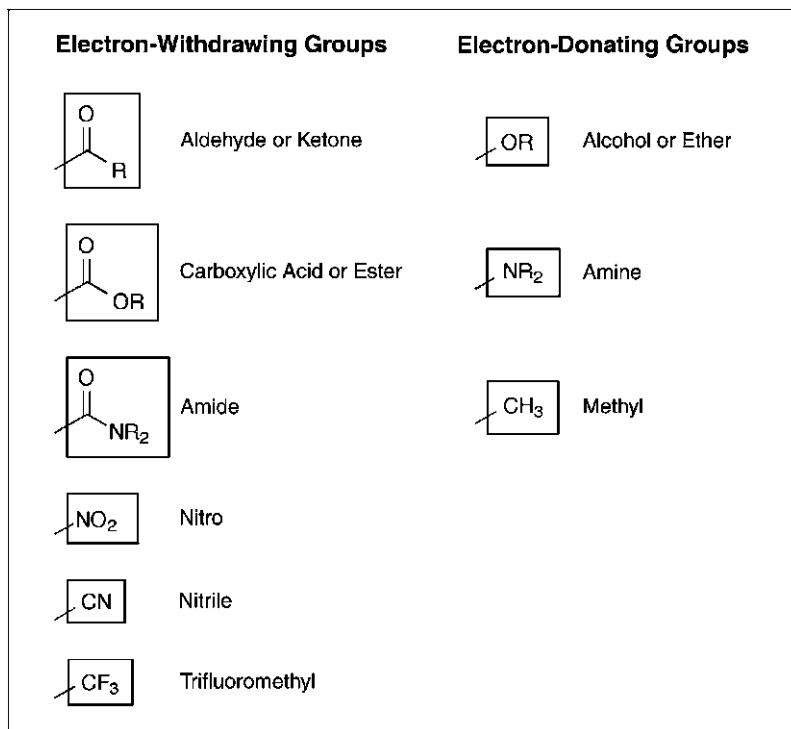


Figure 2.13 Common electron-withdrawing groups and electron-donating groups.

whether these functional groups are electron-donating groups or electron-withdrawing groups. In general, if a functional group is capable of absorbing electron density through delocalization, it will act as an electron-withdrawing group. Such groups include carbonyl-based groups, nitro groups, and nitriles. On the other hand, if a functional group possesses free lone pairs of electrons, this functional group will act as an electron-donating group regardless of the electronegativity of the specific atom involved. Such groups include alcohols, ethers, amines, and halogens. From the group of halogens, fluorine is the exception and serves as an electron-withdrawing group due to its high electronegativity. Finally, while inductive effects thus far have been tied to heteroatoms, it is important to note that alkyl groups are weak electron-donating groups and will impact pK_a values as we will soon discuss. Common electron-donating groups and electron-withdrawing groups are listed in Figure 2.13.

2.6 INDUCTIVE EFFECTS AND RELATIVE ACIDITIES

In Section 2.4, the concept of relative acidities was presented without fully defining the concept of inductive effects. In Section 2.5, the concept of inductive effects was defined and linked to functional groups. In this section, the concept of relative acidities is presented in conjunction with discussions of associated functional groups and their respective inductive effects. Since a treatment of this subject was already introduced in Section 2.4 as applied to carboxylic acids and esters, this section focuses on

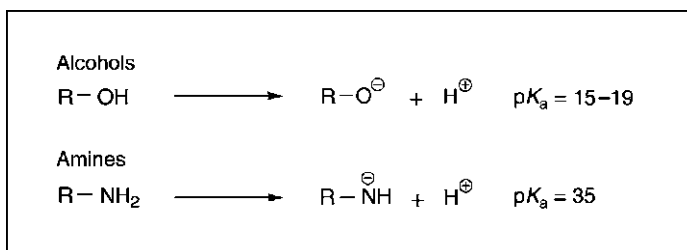
oxygen- and nitrogen-containing functional groups lacking carbonyl components. Specifically, the relative acidities of alcohols and amines are discussed.

Beginning with alcohols, the simplest is methanol with a pK_a of 15. As illustrated in Figure 2.14, as **branching** of the alkyl group increases, so does the pK_a . This observation is a direct result of the inductive effect associated with **alkyl groups** such as methyl (CH_3). As mentioned in the previous section, the inductive effects of **methyl groups** result in donation of electron density. This increase in electron density in the vicinity of the oxygen atom destabilizes the anion resulting from deprotonation, thus increasing the pK_a . The more methyl groups adjacent to the OH, the greater the effect as illustrated in the case of *tert*-butanol with a pK_a of 18–19.

While our discussion of how inductive effects alter alcohol pK_a values has focused primarily on electron-donating groups, we cannot ignore the effect resulting from incorporation of electron-withdrawing groups. As one would expect, if electron-donating groups adjacent to alcohol functional groups increase pK_a values through destabilization of anions resulting from deprotonation, the opposite effect should be observed when electron-withdrawing groups are used. This is in fact the case as supported by the entry for 2,2,2-trifluoroethanol in Figure 2.14. The electron-withdrawing nature of the trifluoromethyl group adds stabilization to the anion resulting from deprotonation and reduces the pK_a compared to ethanol.

Alcohol	pK_a
$\text{H}_3\text{C}-\text{O}-\text{H}$ Methanol	15
$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{C}-\text{O}-\text{H} \\ \quad \\ \text{H} \quad \text{H} \end{array}$ Ethanol	15–16
$\begin{array}{c} \text{F}_3\text{C} \\ \\ \text{C}-\text{O}-\text{H} \\ \quad \\ \text{H} \quad \text{H} \end{array}$ 2,2,2-Trifluoroethanol	11–12
$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{C}-\text{O}-\text{H} \\ \quad \\ \text{H}_3\text{C} \quad \text{H} \end{array}$ Isopropanol	16–17
$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{C}-\text{O}-\text{H} \\ \quad \\ \text{H}_3\text{C} \quad \text{CH}_3 \end{array}$ <i>tert</i> -Butanol	18–19

Figure 2.14 pK_a values associated with alcohols increase as alkyl branching increases.

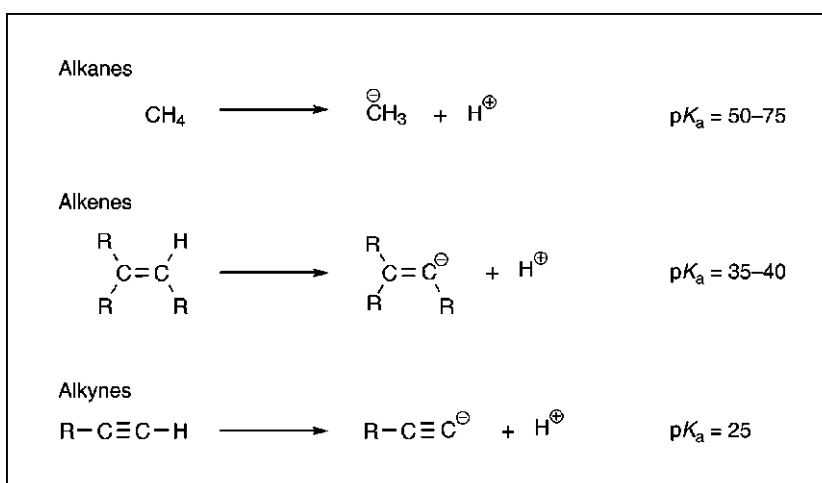


Scheme 2.13 Amines and alcohols can both be deprotonated.

Amines are similar to alcohols in that they can be deprotonated under basic conditions to generate anions (Scheme 2.13). However, because nitrogen is less electronegative than oxygen, considerably stronger bases are required to effect these deprotonations. This is further supported by the significantly higher pK_a values measured for amines as compared to alcohols (Scheme 2.13). These observations should not indicate in any way that the rules regarding inductive effects are different. In fact, they are exactly the same, and amines possessing electron-donating groups will exhibit higher pK_a values while amines possessing electron-withdrawing groups will exhibit lower pK_a values.

2.7 RELATIVE ACIDITIES OF HYDROCARBONS

Any discussion surrounding pK_a values would not be complete without addressing the deprotonation of hydrocarbons. Since hydrocarbons generally refer to organic molecules made up only of hydrogen and carbon, inductive effects resulting from introduction of functional groups is not relevant and we do not usually consider these compounds to be acidic. However, pK_a values of various protons associated with hydrocarbons have been measured. As illustrated in Scheme 2.14, saturated hydrocarbons are the least acidic while olefinic and



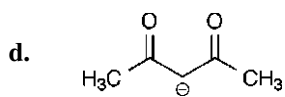
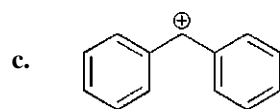
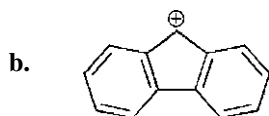
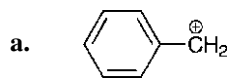
Scheme 2.14 Hydrocarbons can be deprotonated and have measurable pK_a values.

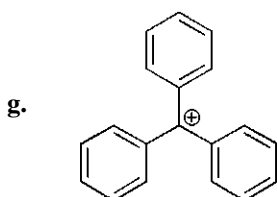
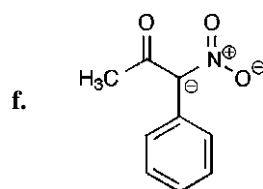
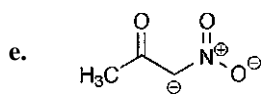
acetylenic protons have acidities on the same order of magnitude as those associated with esters and amines.

2.8 SUMMARY

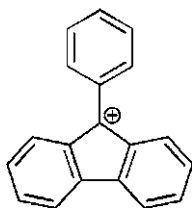
This chapter focused on the definition of acids as applied to **organic molecules**. Furthermore, the impacts of electronegativities and functional groups on the acidities of various types of protons were rationalized in the context of inductive effects. As discussions advance throughout this book and through organic chemistry coursework, a clear understanding of the various pK_a values associated with different environments and how they relate to one another will be beneficial. Consequently, a complete familiarization of the pK_a values presented in this chapter is essential. For convenience, all the pK_a values discussed in this chapter are listed in Appendix 1, and *their general magnitudes with respect to one another should be committed to memory*. This is the only recommended memorization task associated with this treatment of arrow pushing and will greatly facilitate the development of skills enabling the prediction of the mechanistic progression of organic reactions.

3. Draw the resonance structures of the following charged molecules:





h.



4. Which cation from Problem 3 is more stable, 3(g) or 3(h)? Explain using partial charges.

5. How will the following substituents affect the pK_a of benzoic acid (raise, lower, or no change)? 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 carboxylic acid is influenced solely by the partial charges induced by additional ring substituents.

a. *o*-NO₂

b. *p*-NO₂

c. *m*-NO₂

d. *p*-OH

e. *m*-OH

f. *p*-NH₂

g. *m*-CH₃

h. *p*-CH₃

i. *m*-CHO

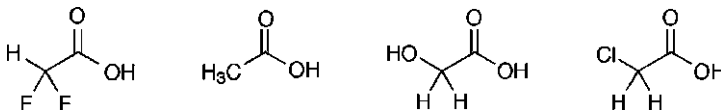
j. *p*-OCH₃

k. *o*-NO

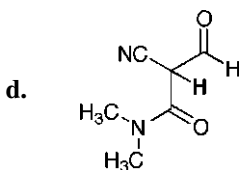
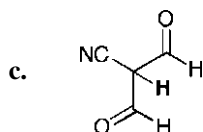
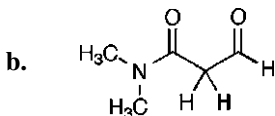
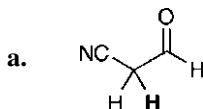
l. *p*-Cl

m. *m*-Cl

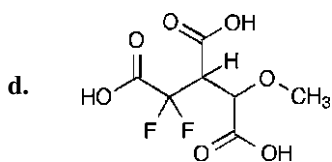
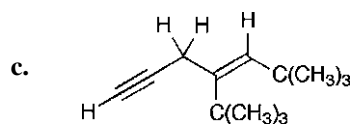
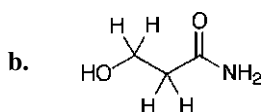
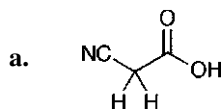
6. Arrange the following groups of molecules in order of increasing acidity. Explain your results using partial charges and inductive effects.



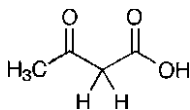
7. Predict pK_a values for the protons shown in boldface in the following molecules. Rationalize your answers.



8. Predict the order of deprotonation of the various protons in the following molecules. Back up your answers with appropriate pK_a values.



9. Which proton is the most acidic? Rationalize your answer.



10. Using the pK_a values given in Appendix 1, calculate the equilibrium constants for the following reactions:

