3

IDENTIFYING ACIDIC AND BASIC FUNCTIONAL GROUPS

LEARNING OBJECTIVES

After completing this chapter, students will be able to:

- Identify the following acidic functional groups: carboxylic acids, β-dicarbonyls, imides, sulfonamides, sulfonylureas, tetrazoles, phenols, thiols, phosphates, phosphonates, and sulfates.
- Identify the following basic functional groups: aliphatic amines, alicyclic amines (aka saturated heterocycles), aromatic amines, imines, hydrazines, amidines, guanidines, and nitrogen containing aromatic heterocycles.
- Classify a drug molecule as one of the following: acidic, basic, amphoteric, an electrolyte, or a nonelectrolyte.
- Explain how the acid/base nature of a drug molecule can influence its chemical, pharmaceutical, and therapeutic properties.

Functional groups that are either acidic or basic have the ability to become ionized and as a result become negatively or positively charged, respectively, within the structure of a drug molecule. This ability to ionize increases the overall water solubility of the drug molecule, allows for the formation of specific types of interactions between the drug molecule and its biological target(s), and influences the transport, metabolism, and elimination of the drug molecule. In addition, acidic and basic functional groups can be used to produce water- or lipid-soluble salts for the purpose of providing a specific physicochemical or therapeutic advantage.

This chapter reviews the acidic and basic functional groups that are present within the structures of drug molecules. The discussion of each acidic and basic functional group includes an explanation as to why it is acidic or basic, as well as examples of commercially available drugs that contain the functional group within their structures. When applicable, the relative acid/base strengths among the different functional groups are provided along with an explanation. The chapter ends with a discussion regarding the therapeutic significance of the acid/base nature of a drug molecule.

ACIDIC FUNCTIONAL GROUPS

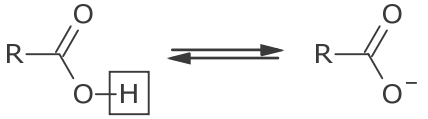
Acidic functional groups are those that can donate (or lose) a proton (H^+). From a very simplistic view, an acid can be represented as:

There are two key features of an acidic functional group: the presence of a hydrogen atom that can dissociate from the group (H^+), and the ability of the remaining atoms to delocalize the resulting negative charge via resonance. As a reminder, *resonance delocalization* refers to the ability of the functional group to spread the charge in a manner that allows it to be shared among two or more atoms.

The pK_a values of these functional groups are used to compare their relative acidity. The most important fact here is that the lower the pK_a value, the stronger the acid. As an example, an acidic functional group with a pK_a of 2.4 is more acidic than one with a pK_a of 3.4. A more extensive discussion of pK_a values and their determination can be found in **Chapter 4**. It is strongly suggested that you focus more on learning the relative acidity and ranges of the groups listed above rather than memorize specific pK_a values for specific drugs. A summary table of pK_a values and ranges is provided later in this chapter.

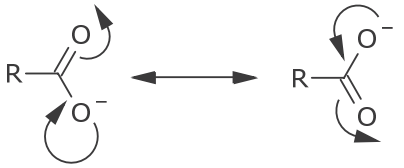
Carboxylic Acids

A carboxylic acid is the most common acidic functional group found in drug molecules. The acidic hydrogen atom has been highlighted with a box below.



Unionized Ionized

The resulting anion (i.e., negatively charged species) is stabilized by resonance delocalization or the sharing of the negative charge between the two oxygen atoms.



The ionized form of a carboxylic acid is known as a *carboxylate*. The pK_a values of carboxylic acids normally range from 2.5 to 5 depending on the electron donating or withdrawing character of adjacent or surrounding groups. Some examples are shown in **Figure 3-1**.