Section 3 General Self Assessment Answers

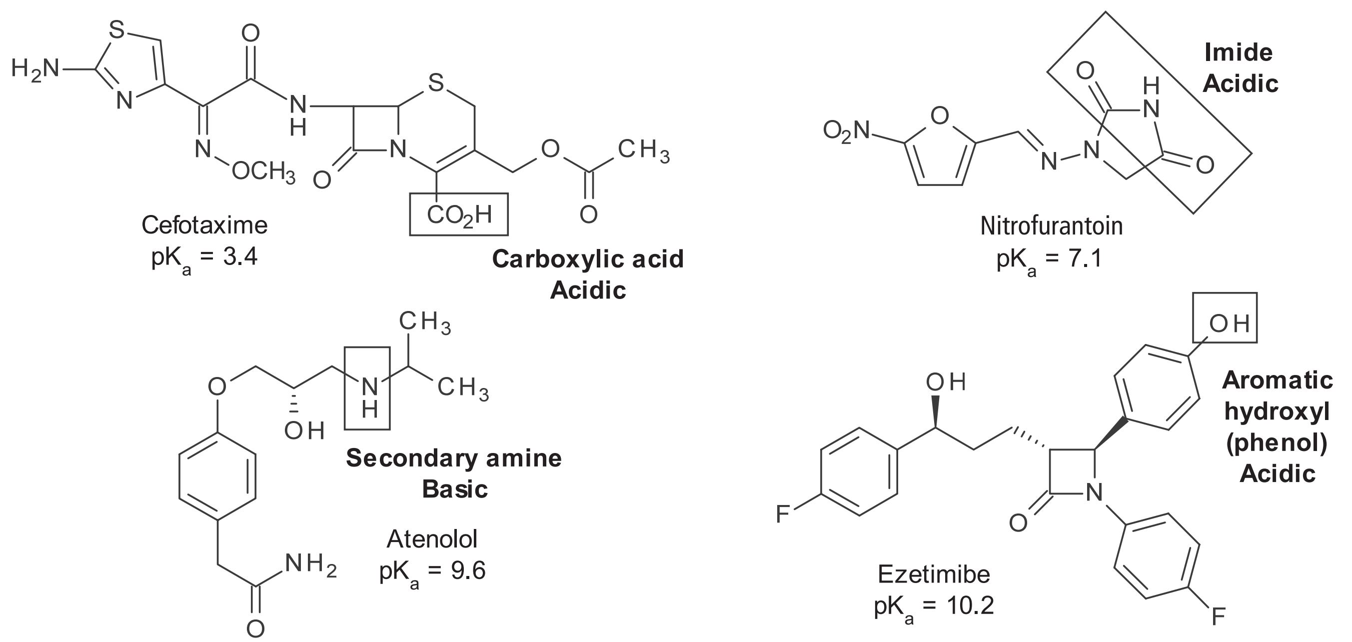
2.3 Solving pH/pK_a Problems

1. Shown below are the structures of cefotaxime, nitrofurantoin, atenolol, and ezetimibe. Each of these drug molecules contains one ionizable functional group. The pK_a values have been provided.

   a. Match the pK_a values provided with the appropriate functional groups. For each functional group, identify the name of the group and whether it is ***acidic*** or ***basic***.

   b. For each functional group indicate whether it would be ***primarily ionized*** or ***primarily unionized*** at a stomach pH = 1.8, a urinary pH = 6.1, or a plasma pH = 7.4. Provide an explanation for your responses for cefotaxime at a plasma pH = 7.4, nitrofurantoin at a urinary pH = 6.1, and atenolol at a stomach pH = 1.8.

   Answer:



Cefotaxime contains an ***acidic*** carboxylic acid. At a plasma pH = 7.4, the environment (i.e., the pH) is more basic than the functional group (i.e., the pH > pK_a). An acidic functional group will be primarily ionized in a basic environment.

Nitrofurantoin contains an ***acidic*** imide group. At a urinary pH = 6.1, the environment (i.e., the pH) is more acidic than the functional group (i.e., the pH < pK_a). An acidic functional group will be primarily unionized in an acidic environment.

Atenolol contains a ***basic*** secondary amine. At a stomach pH = 1.8, the environment (i.e., the pH) is more acidic than the functional group (i.e., the pH < pK_a). A basic functional group will be primarily ionized in an acidic environment.

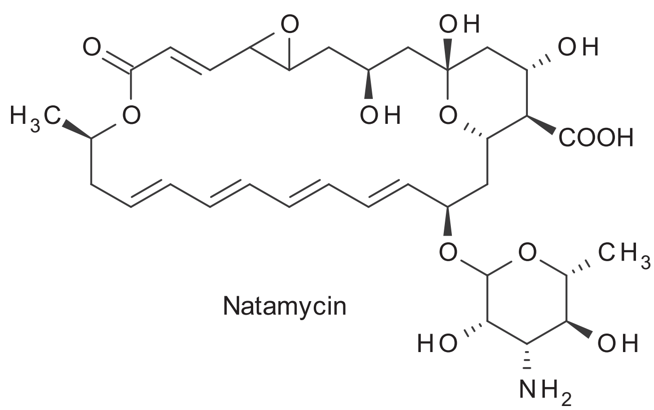
Drug (pK_a Value)	Stomach (pH = 1.8)	Urine (pH = 6.1)	Plasma (pH = 7.4)
Cefotaxime (3.4)	Primarily unionized	Primarily ionized	Primarily ionized
Nitrofurantoin (7.1)	Primarily unionized	Primarily unionized	Primarily ionized
Atenolol (9.6)	Primarily ionized	Primarily ionized	Primarily ionized
Ezetimibe (10.2)	Primarily unionized	Primarily unionized	Primarily unionized

2. In the previous question, we examined four pK_a values in three different environments for a total of 12 different scenarios. Which of these 12 scenarios allow you to use the Rule of Nines to calculate the percent of ionization of the functional group in the specific environment? Identify the specific scenarios and use the Rule of Nines to calculate the percent of the functional group that would be ionized.

   Answer:

   To use the Rule of Nines, the difference between the pH and the pK_a must be an integer (i.e., 1, 2, 3). In evaluating the above 12 scenarios, there are only two scenarios that meet this criterion, cefotaxime (pK_a = 3.4) in a plasma pH = 7.4 and nitrofurantoin (pK_a = 7.1) in a urinary pH = 6.1. For cefotaxime, $|pH - pK_a|$ is equal to 4; thus, there is a 99.99:0.01 ratio. Because the carboxylic acid (pK_a = 3.4) would be primarily ionized in a basic environment (pH = 7.4), we can use this ratio to determine that it would be 99.99% ionized. For nitrofurantoin, $|pH - pK_a|$ is equal to 1; thus, there is a 90:10 ratio. The imide (pK_a = 7.1) functional group is acidic, so it would be primarily unionized in an acidic environment (pH = 6.1). We can use this information to predict that it would be 10% ionized.

3. Shown below is the structure of natamycin. It contains two functional groups that could be potentially ionized. The pK_a values for natamycin are 4.6 and 8.4.



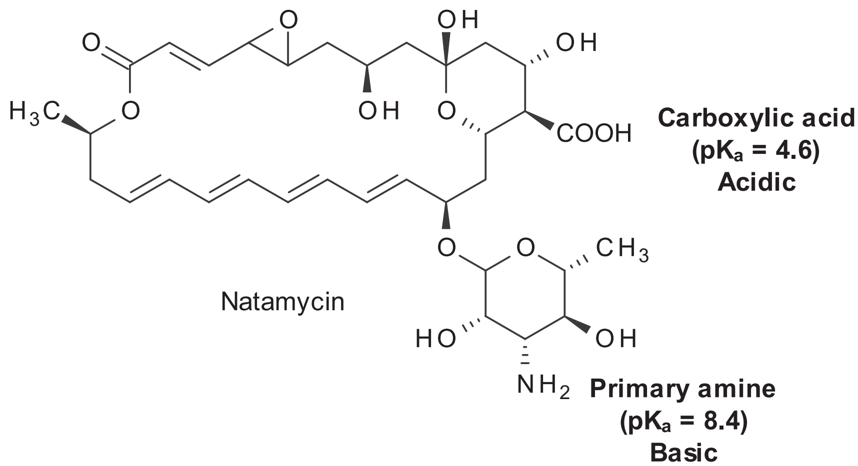
Natamycin

   a. Match the pK_a values provided to the appropriate functional groups and identify if the functional group is ***acidic*** or ***basic***.

   b. Using the Henderson-Hasselbalch equation, calculate the percent ionization that occurs for each of these functional groups at an intestinal pH = 6.2.

Answer:

a.



b. For the carboxylic acid, the pK_a = 4.6 and the pH = 6.2. Using the Henderson-Hasselbalch equation gives the following:

$$6.2 = 4.6 + \log\frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

Solving the equation provides a ratio of [Base Form]/[Acid Form].

$$1.6 = \log\frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$39.8 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{39.8}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

For every molecule that contains this functional group in the acid form, there are 39.8 molecules that contain this functional group in the base form. Because the functional group is ***acidic***, the base form is equal to the ionized form, and the acid form is equal to the unionized form.

39.8 molecules in base form + 1.0 molecule in acid form = 40.8 Total Molecules

Base Form = Ionized Form, and Acid Form = Unionized Form for This Functional Group

$$\text{Percent in Ionized Form} = \frac{\text{39.8 Molecules in Ionized Form}}{\text{40.8 Total Molecules}} \text{ x } 100\%$$

Percent in Ionized Form= 97.5%

For the primary amine, the pK_a = 8.4 and the pH = 6.2. Using the Henderson-Hasselbalch equation gives the following:

$$6.2 = 8.4 + \log\frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

Solving the equation provides a ratio of [Base Form]/[Acid Form].

$$-2.2 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.0063 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.0063}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

For every molecule that contains this functional group in the acid form, there are 0.0063 molecules that contain this functional group in the base form. Because the functional group is ***basic***, the base form is equal to the unionized form, and the acid form is equal to the ionized form.

0.0063 molecules in base form + 1.0 molecule in acid form = 1.0063 Total Molecules

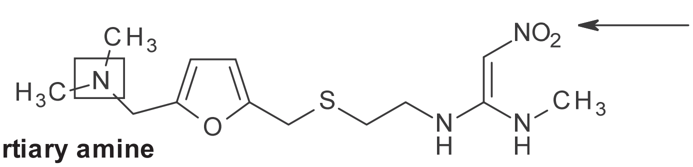
Base Form = Unionized Form, and Acid Form = Ionized Form for This Functional Group

$$\text{Percent in Ionized Form} = \frac{1 \text{ Molecule in Ionized Form}}{1.0063 \text{ Total Molecules}} \times 100\%$$

$$\text{Percent in Ionized Form} = 99.4\%$$

4. The most basic functional group present within the structure of ranitidine has a pK_a value of 8.2. Identify this functional group and calculate the pH that is necessary for this functional group to be 70% ionized.

Answer:



The electron withdrawing property of the nitro group greatly decreases the pK_a value for the adjacent nitrogen-containing group.

Tertiary amine
pK_a = 8.2

Ranitidine

We can use the Henderson-Hasselbalch equation to solve this problem. Because the ionized form of a basic functional group can also be designated as its protonated form or its conjugate acid form, either of the following equations can be used.

$$\text{pH} = \text{p}K_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$\text{or pH} = \text{p}K_a + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

Therefore, if 70% of this functional group is ionized:

$$\text{pH} = 8.2 + \log \frac{[30]}{[70]}$$

$$\text{pH} = 8.2 + \log \frac{[30]}{[70]} = 8.2 + (-0.37) = 7.83$$

Because a pH = 7.83 does not exist physiologically, this percent ionization could only occur in an exogenously prepared solution.