Carboxylic Acid Structure and Chemistry: Part 2

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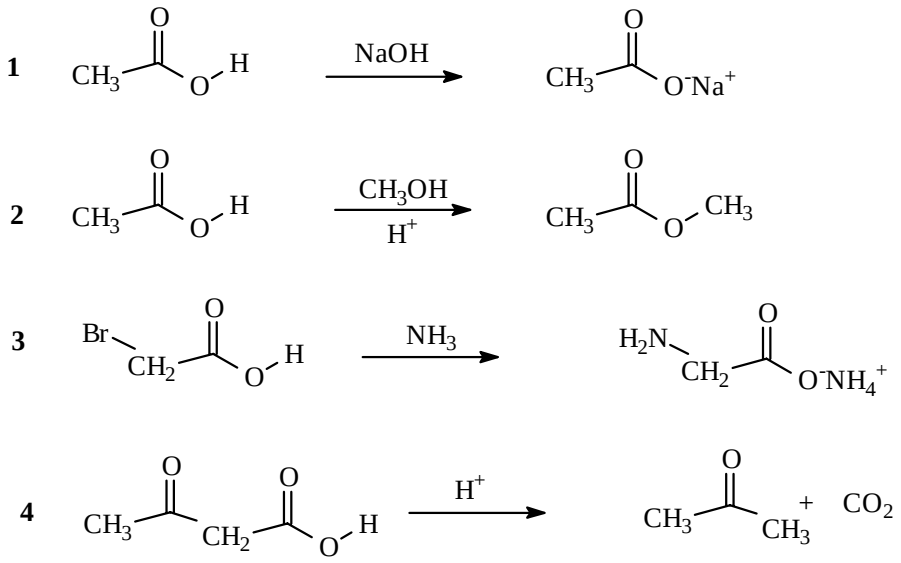
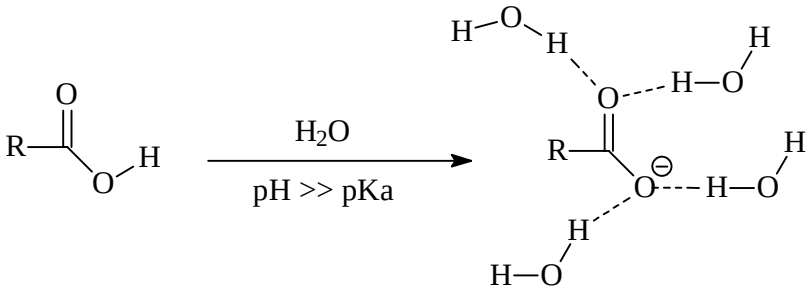
IV. Reactions of the Carboxylic Acid Reactions

Depending on their overall structure, carboxylic acids may participate in a variety of reactions including (1) ionization and salt formation, (2) nucleophilic attack at the carbonyl carbon or (3) adjacent (α) carbon, and (4) decarboxylation. These reactions are summarized below and discussed in detail in the sections that follow:



A. Ionization and Salt Formation

As a result of their relatively acidic nature, carboxylic acids will ionize if placed in an environment of adequate basicity. Thus carboxylic acids (typical pKa values in the range of 3-5) in aqueous media of pH>7, such as aqueous sodium hydroxide or sodium bicarbonate solutions, will exist primarily in the ionized, conjugate base form. Furthermore, this ionization enhances water solubility by providing an anionic center that can participate in energetically favorable ion-dipole interactions with water. Thus the water solubility of carboxylic acids is "optimized" in aqueous environments where they exist primarily in their ionized, conjugate base form (when pH >> pKa) as shown below:



Carboxylate Base:
H-Bonding and
Ion-Dipole Bonding

As discussed on previous chemistry coursework, the extent of ionization of a carboxylic acid (or any weak acid) of known pKa can be determined at any pH using the Henderson Hasselbalch equation. This equation is derived from the equilibrium reaction as follows:

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

$$Ka = \frac{[H^+][RCOO^-]}{[RCOOH]}$$

$$[H^+] = Ka \frac{[RCOOH]}{[RCOO^-]}$$

$$-\log [H^+] = -\log Ka - \log \frac{[RCOOH]}{[RCOO^-]}$$

$$\boxed{pH = pKa + \log \frac{[RCOO^-]}{[RCOOH]}}$$

Henderson-Hasselbalch Equation

Consider a carboxylic acid (RCOOH) with a pKa of 4 at physiologic pH (assume pH of 7). Substituting these values, the log ratio of ionized to non-ionized acid is 3:1, for an actual ratio of ionized to non-ionized compound being 1000:1. When expressed as a percent, this means that the acid is 99.90% ionized at this pH.

$$7 = 4 + \log \frac{[RCOO^-]}{[RCOOH]}$$

$$\log \frac{[RCOO^-]}{[RCOOH]} = 3$$

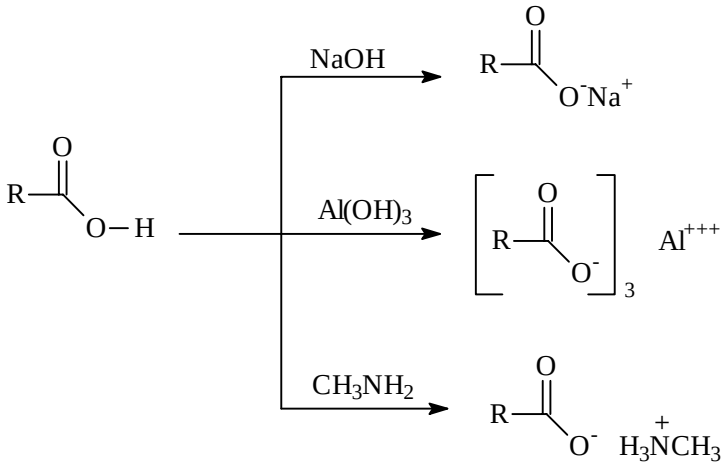
$$\frac{[RCOO^-]}{[RCOOH]} = \frac{1000}{1}$$

Percent ionized (RCOO-) = (1000/1001) X 100 = 99.90%

Based on the Henderson-Hasselbalch equation, the ratio of ionized and non-ionized acid is 1 when the pH equals the pKa (50% ionized, 50% non-ionized). Also, each pH unit above the pKa of an acid results in a 10-fold increase in the ratio of ionized to non-ionized compound. Thus at a pH value of 9, the ratio of ionized to non-ionized acid

would be 100,000 to 1 (or 5 log units). Conversely each pH unit <u>below</u> the pKa of an acid results in a 10-fold increase in the ratio of non-ionized to ionized compound!

Because of their acidity, carboxylic acids react with either inorganic bases (NaOH, $NaHCO_3$, etc.) or organic bases to form salts:



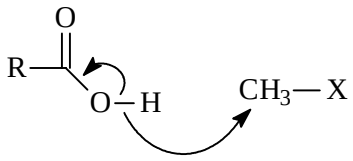
Sodium (Na) and potassium (K) salts have significantly greater H_2O solubility than the parent carboxylic acids because of their ionic nature and ability to participate in energy favorable ion-dipole interactions with water. These principles are illustrated by comparison of the water solubilities of benzoic acid and its sodium salt:

Water Solubility: 0.34 g/100 mL 55.5 g/100 mL

Dissolution of sodium and potassium salts of carboxylic acids in water yields an alkaline medium (salt of a strong base and a weak acid). Salts of carboxylic acids formed with heavy metal ions such as Ca^{+2}, Mg^{+2}, Zn^{+2}, Al^{+3} tend to be relatively water insoluble. Similarly, carboxyl salts with lipophilic amines will also be relatively insoluble in H_2O.

<u>B. Electrophilic/Nucleophilic Reactions at the Acid Carboxyl Group</u>

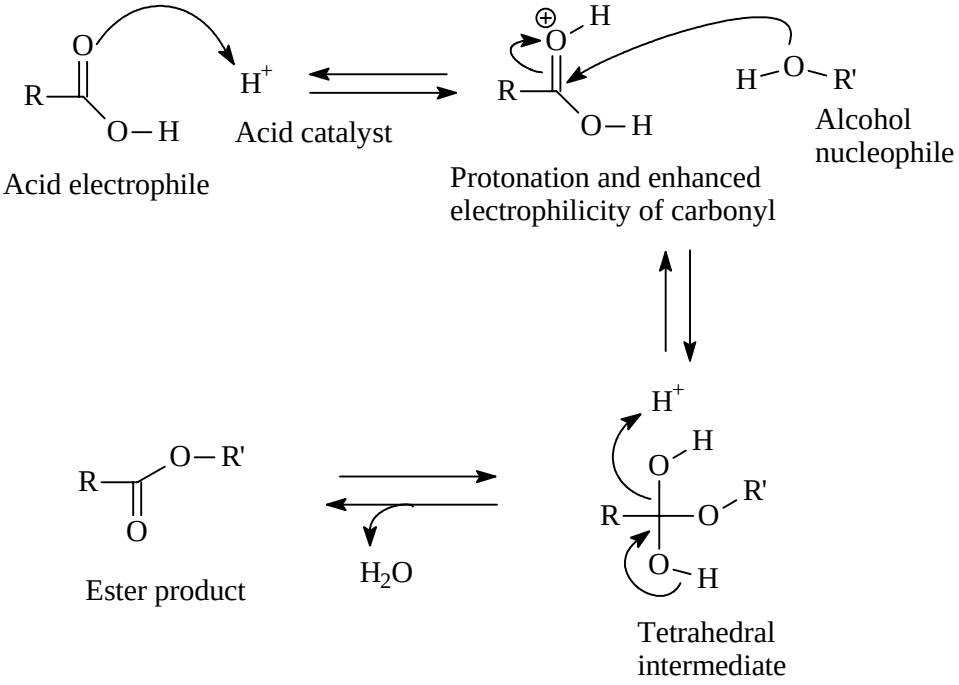
Carboxylic acids contain electron rich oxygen atoms, but are relatively 'weak" nucleophiles since oxygen is relatively electronegative and the electron density is distributed by resonance throughout the carboxyl system as illustrated below. Thus the carboxyl group is less likely to share its NBEs in a displacement reaction than amines or



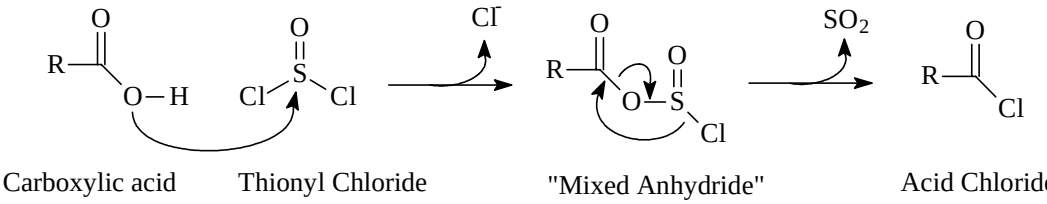
even alcohols:

Acids: Weak nucleophiles

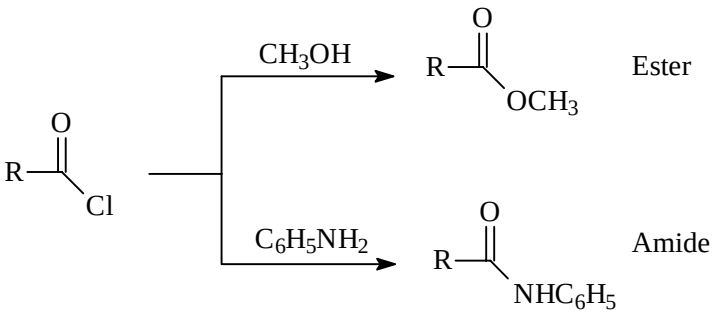
Carboxylic acids, however, are capable of functioning as electrophiles under the appropriate conditions, due to the presence of the carbonyl moiety. Under "dehydrating conditions" nucleophiles can attack the acids carbonyl and displace the acid OH as water, or another good leaving group. Such is the case in esterification reactions performed under acidic conditions. In these reactions an acid is treated with an alcohol which serves as the nucleophile, and an acid which serves as a catalyst. The acid catalyzes the reaction by 1). Further polarizing the carbonyl moiety through partial protonation, and 2). Providing a proton source for a hydroxyl leaving group (which "leaves" as water). This reaction and the role of the acid and alcohol nucleophile are illustrated in the following reaction scheme and mechanism:



While the esterification reaction above can be used effectively to prepare esters from acids, it can be a relatively inefficient reaction due to its reversibility and the sluggish nature of the dehydration step. Esterification, as well as amide formation, may be accomplished much more efficiently in the laboratory by first converting the carboxylic acid to a more reactive electrophilic species, such as an "acid chloride", and then allowing the acid chloride to react with an alcohol or amine nucleophile to form an ester or amide product. Acid chlorides can be formed readily with strong "dehydrating reagents" such as thionyl chloride. Treatment of an acid with thionyl chloride results in formation of a very reactive "mixed anhydride" intermediate as shown below. This intermediate is attacked by Cl^- generated in the reaction, eliminating SO_2 and yielding the acid chloride. This reaction is essentially irreversible since the carboxylic acid OH leaves as SO_2 which is a gas and is eliminated form the reaction mixture.

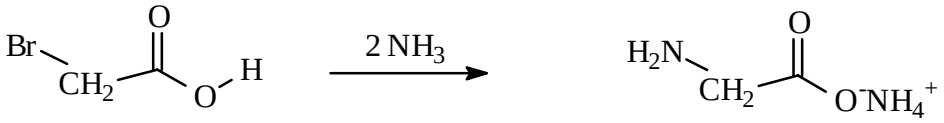


Replacement of the carboxylic acid OH with a halogen as in acid chlorides (and other acid halides) greatly enhances the electrophilicity of the carbonyl dipole. Thus it reacts more readily than a carboxylic acid carbonyl with nucleophiles such as acids and amines, yielding ester or amide products, respectively:



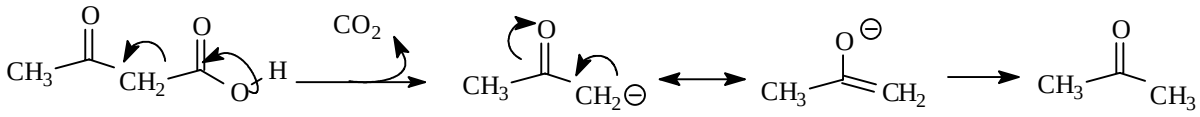
C. Nucleophilic Reactions at the Alpha-Carbon

Carboxylic acids containing a "good leaving" group at the carbon atom adjacent to the carbonyl (the α-carbon) may be substrates for nucleophilic displacement reactions. The α-carbon atoms in these systems are electron deficient due to their positioning next to an electron withdrawing carbonyl moiety. Thus the α-carbon contains a leaving group, such as a halogen, it is subject to displacement. It is important to note that if the nucleophile in such a reaction is also basic, two equivalents must be added to complete the reaction since one will be consumed in an acid-base reaction with the acidic carboxyl group:



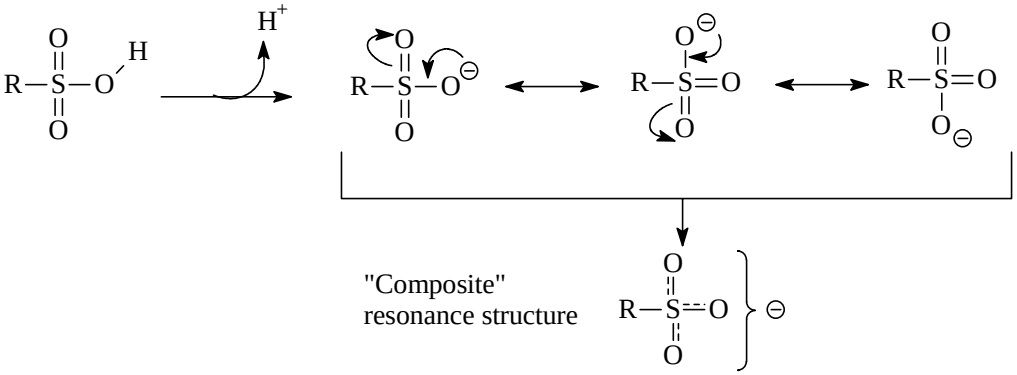
D. Decarboxylation Reactions

Carboxylic acids and other carbonyl-containing compounds with an additional carboxyl group located on the α-carbon are subject to decarboxylation reactions. In these cases the carboxyl group is lost as carbon dioxide and this reaction can occur because the remaining carbonyl can readily accept the electron pair left in the reaction. Again, this reaction occurs because the charge formed by decarboxylation is stabilized by resonance through the carbonyl system as shown below:

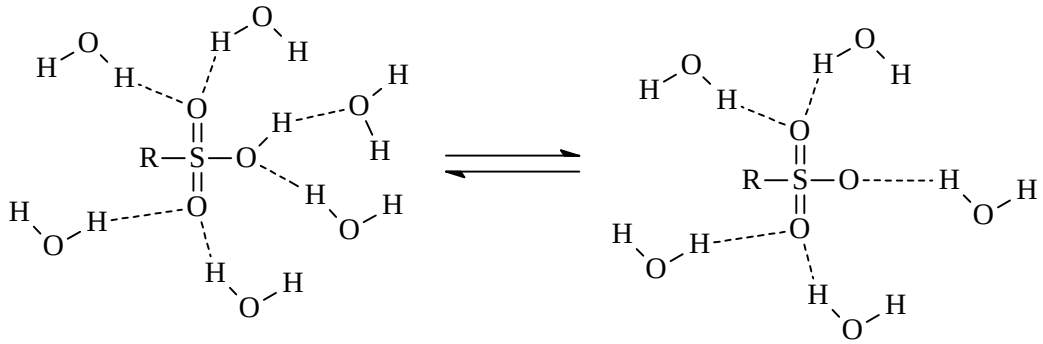


V. Sulfonic Acids and Sulfonamides

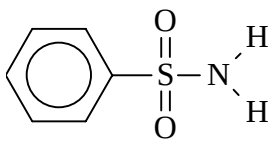
Sulfonic acids (R-SO_3H) are "isosteres" of carboxylic acids. As a result, they share many properties in common with carboxylic acids, as described in the preceding sections. It is important to note that sulfonic acids are more acidic than carboxylic acids and this enhanced acidity results primarily from the presence of the additional oxygen atom which provides BOTH a greater negative inductive effect to enhance ionization and additional resonance stabilizaition of the resultant conjugate base anion as shown below:



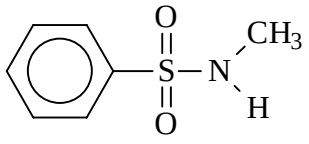
The presence of the -SO_3H group increases H_2O solubility due to its ability to act as both a H-bond donor and acceptor. In addition, these compounds easily ionize at physiological pH and this greatly increases the H_2O solubility of these compounds. Also, Sulfonic acids undergo the same reactions as carboxylic acids.



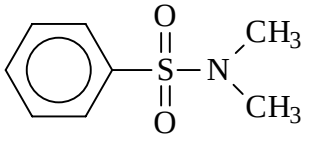
Sulfonamides can be considered to be acid analogs in which the carbonyl moiety is replaced with an isosteric SO_2 group, and the hydroxyl replaced with a nitrogen group. Because they contain a nitrogen atom which may have three substituents, sulfonamides may be classified as primary, secondary or tertiary depending on the degree of substitution on the sulfonamide nitrogen:



Primary Sulfonamide



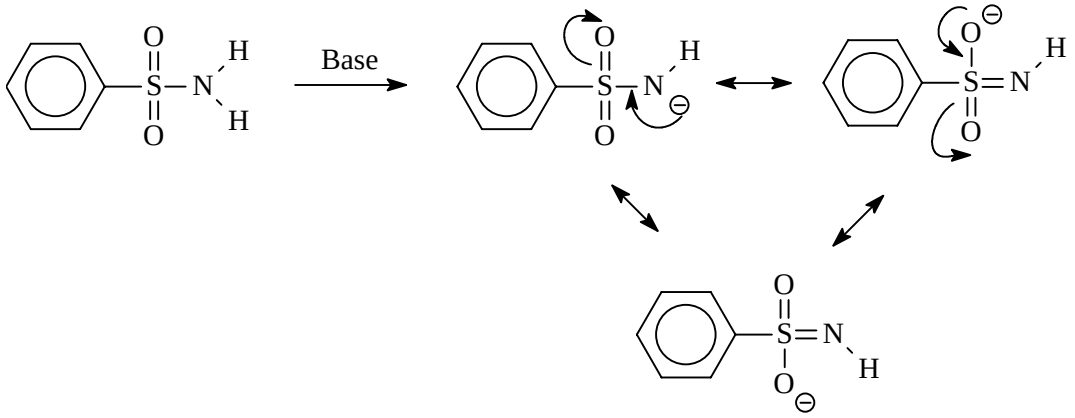
Secondary Sulfonamide



Tertiary Sulfonamide

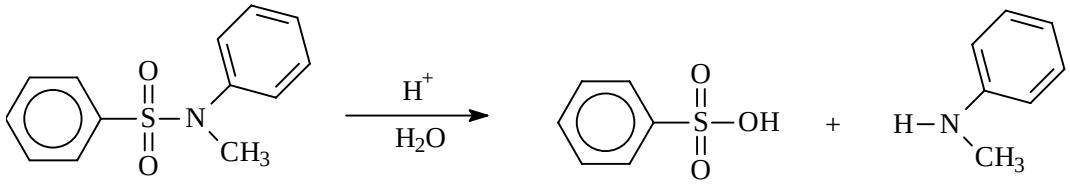
There are a number of drug classes containing the sulfonamide group including the sulfonamide antibacterials, some diuretics and the sulfonylurea hypoglycemics (more on these below and in the Antidiabetic Drug Tutorial).

Primary sulfonamides contain two hydrogen atoms on the sulfonyl group and secondary sulfonamides contain one hydrogen atom. These hydrogens are relatively acidic, again because the charge formed in the conjugate base can be stabilized by resonance. Sulfonamides are less acidic than carboxylic acids, due to the formation of a negative charge on a less electronegative nitrogen atom. However, they display greater acidity than amides because the negative charge formed in the conjugate base can be stabilized over more electronegative atoms as shown by the following resonance structures (also see Amide Tutorial):

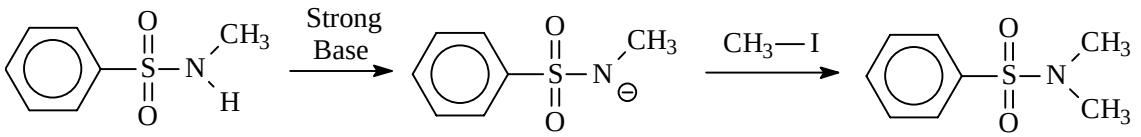


Again it is important to realize that tertiary sulfonamides are NOT acidic because they do not contain an "ionizable" proton.

Generally sulfonamides are relatively unreactive compounds. They can be hydrolyzed under relatively extreme conditions to the corresponding sulfonic acid and amine as shown below:



Also, although relatively unreactive as nucleophiles, similar to amides, primary and secondary sulfonamides can be converted to more nucleophilic anions upon treatment with strong bases, and these nucleophiles can participate in displacement reactions similar to ionized amides as shown below:



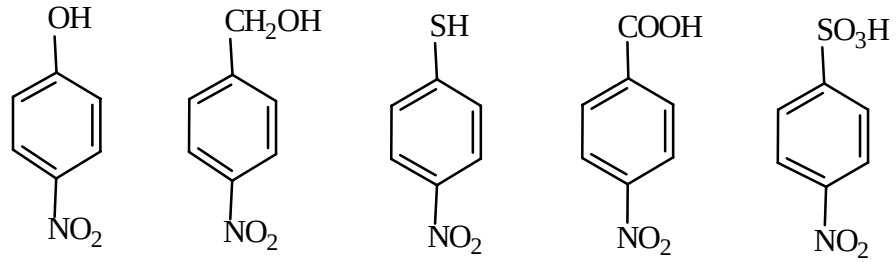
VI. Problems

1. Why is butyric acid more water soluble than butyrylaldehyde?

$CH_3CH_2CH_2COOH$ **Butyric acid**

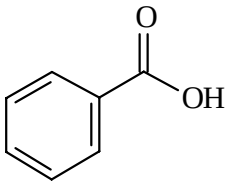
$CH_3CH_2CH_2CHO$ **Butyrylaldehyde**

2. Rank the following set of compounds in terms of relative acidity (1 = most, 5 = least):

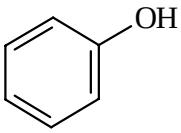


A **B** **C** **D** **E**

3. You have a mixture of benzoic acid and phenol you wish to separate by extraction using benzene and water. How would you accomplish this taking advantage of the differences in the pKas of these two compounds?

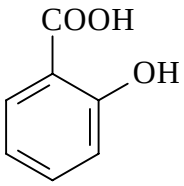


Benzoic acid



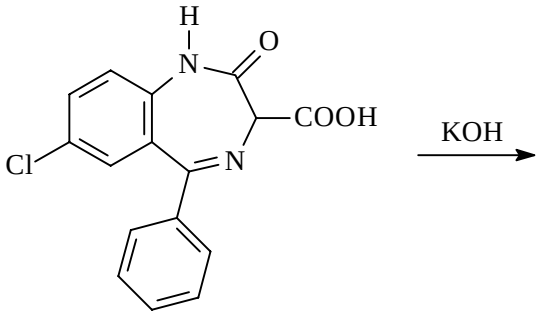
Phenol

4. Explain why the phenolic group of salicylic acid has such a high pKa value (13.4)?

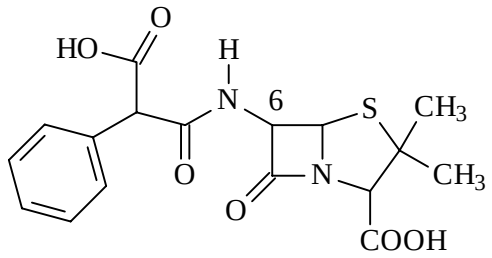


Salicylic Acid

5. Clorazepate is a benzodiazepine tranquilizer administered as the dipotassium salt. Propose a structure for the dipotassium salt.

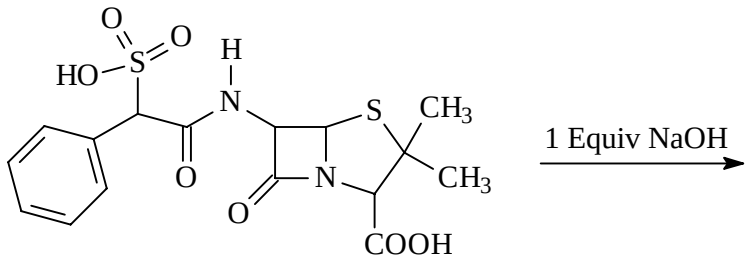


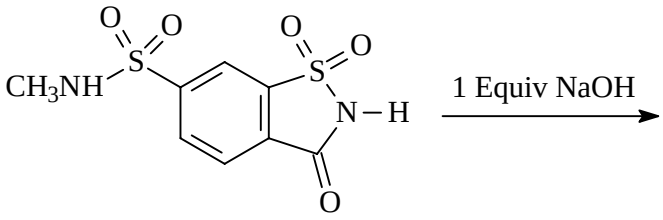
6. Carbenicillin is an acid unstable penicillin and thus cannot be administered orally. The initial acid-catalyzed decomposition reaction this compound undergoes in the stomach is decarboxylation in the 6-acylamino side chain. Show the product of this reaction and explain why it occurs. Also, propose a prodrug derivative of carbenicillin to overcome (or minimize) this problem.



Carbenicillin

7. Show the product formed from the following reactions:





8. Show the structure of the predominate form of the following molecules at physiological pH 7.4.