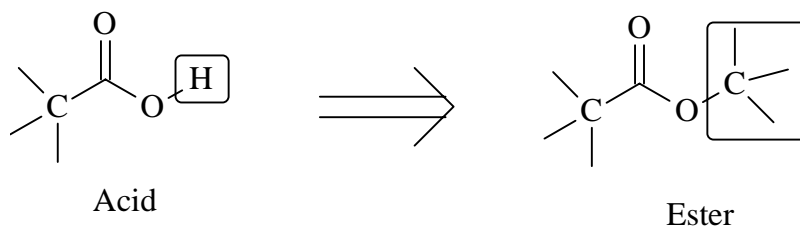


ESTERS AND RELATED CARBOXYLIC ACID DERIVATIVES

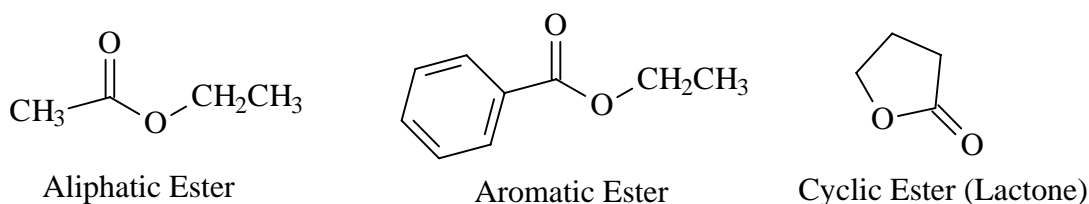
Jack DeRuiter

I. Structure and Preparation

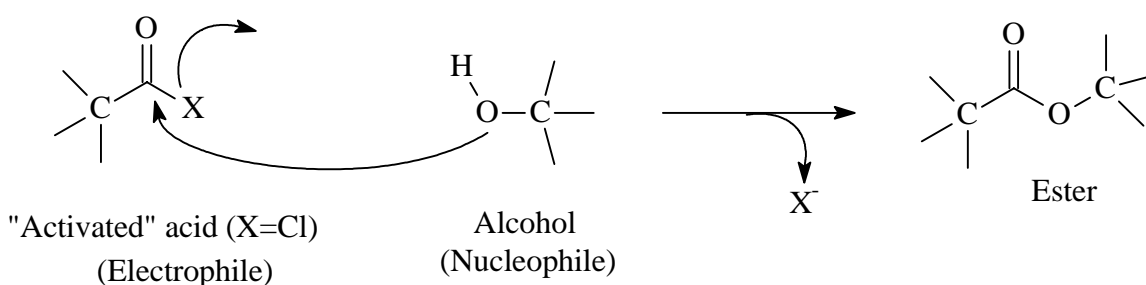
Esters are derivatives of carboxylic acids that arise via replacement of the hydroxyl (OH) portion of the acid COOH function with an "ether" moiety (-OR):



Note that replacement of the acid OH group with an "ether" moiety removes the acidic function from the parent structure (acid) resulting in the formation of non-acidic (neutral, but somewhat polar) compounds (esters). Esters can be sub-classified based on their general structure as aliphatic, aromatic or cyclic (called "lactones") as illustrated by the examples below:



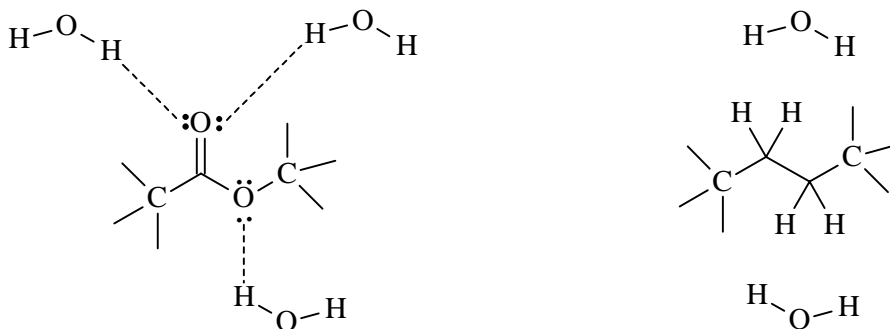
A variety of methods have been developed for the preparation of esters. Most of these methods involve reaction of an alcohol with an "activated carboxylic acid" compound (i.e. acid chloride):



The ester functionality does not introduce a center of asymmetry and thus optical and geometric isomerism does not result from the presence of this functional group. The ester functionality (the carbonyl and ether oxygen) is composed of an sp^2 hybridized carbon so it cannot be chiral, and since there is free rotation about the ether bond geometric isomerism also is not possible at the sp^2 center.

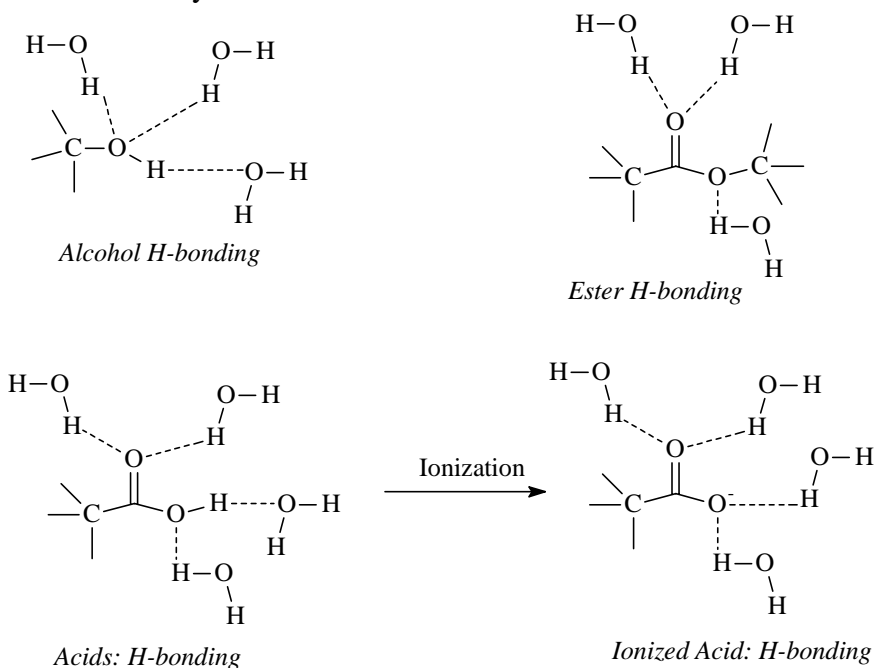
II. Solubility of Esters

Esters contain carbonyl (C=O) and ether (O-C) dipoles arising from covalent bonding between electronegative oxygen atoms and electronically neutral carbon atoms. Because of the π -bonding arrangement of the carbonyl (C=O), this is the stronger of the two dipoles. The presence of these dipoles allows esters to act as hydrogen-bond acceptors. Thus esters can participate in hydrogen bonding with water and other protic solvents; the oxygen atoms can accept hydrogen bonds from water. As a result the water solubility of esters is greater than that of corresponding hydrocarbons as illustrated below:



Ester: Hydrogen bonding and solubility Hydrocarbon: Hydrogen bonding not possible!

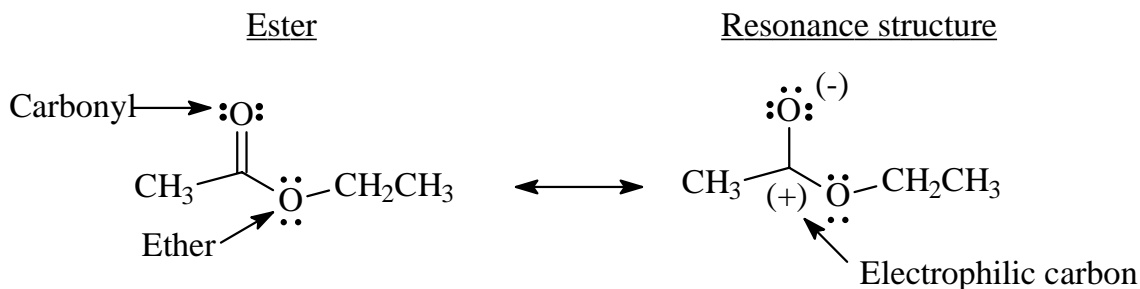
While hydrogen bonding may enhance the water solubility of esters relative to hydrocarbons (alkanes, alkenes, alkynes and aromatic compounds), esters typically are regarded as compounds with relatively low water solubility. They are significantly less water soluble than comparable acids or alcohols due to: 1). Their non-ionic character, 2). the inability to both donate and accept hydrogen bonds from water (they can only be H-bond acceptors) and, 3). the presence of non-polar hydrocarbon functionality. Consider the comparisons above. Alcohols have an OH group that can both accept and donate H-bonds with water. An ester can only accept H-bonds from water. Carboxylic acids can both donate and accept hydrogen bonds, AND can ionize at pHs above their pKas to further enhance solubility:



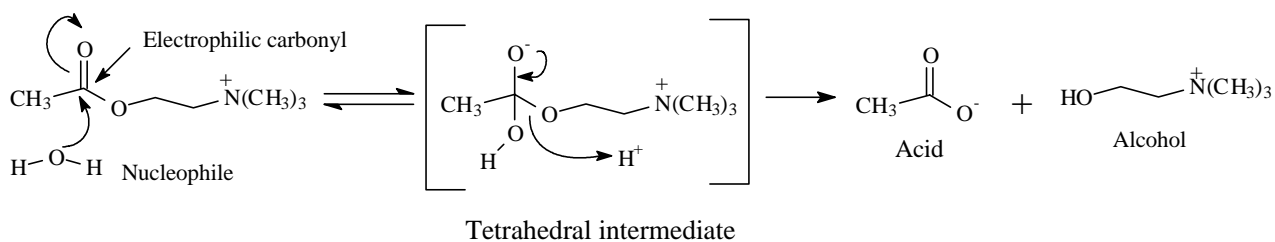
III. Reactivity of Esters

B. Hydrolysis and Nucleophilic Attack at Carbonyl

The presence of a carbonyl (C=O) and ether (O-C) dipole renders the "central" carbonyl carbon of an ester electron deficient; it is an electrophilic carbon atom. This can be illustrated by the resonance structures for an ester drawn below:

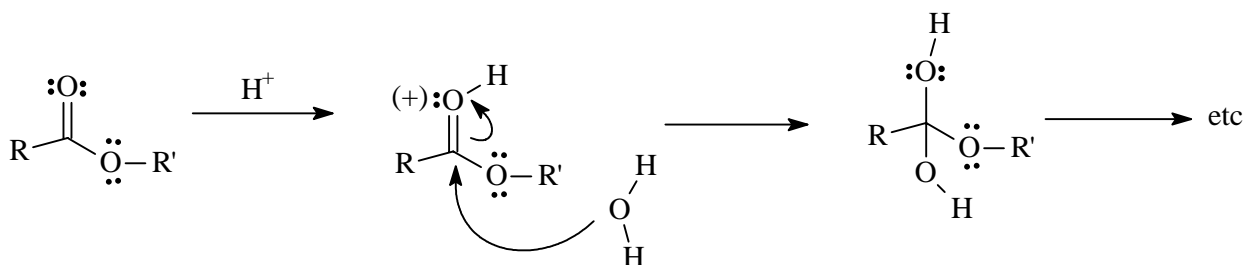


Thus the esters carbonyl carbon is susceptible to "attack" by electron rich atoms (nucleophiles) including the oxygen of water and the nucleophilic residues at the active sites of esterase enzymes. When in the presence of a nucleophile, an ester may undergo reaction leading to cleavage of the carbonyl carbon-ether bond as shown below. Initial nucleophilic attack at the electrophilic carbonyl of an ester results in the formation of a tetrahedral intermediate. This reaction is reversible and may simply revert back to the original reactants, or go forward resulting in ether bond cleavage (hydrolysis) yielding an acid and alcohol product if the nucleophile is water (or an esterase enzyme). The "forward" reaction resulting in hydrolysis is determined by the ability of the "ether" bond (-O-C) to be cleaved and the stability of the alcohol product.

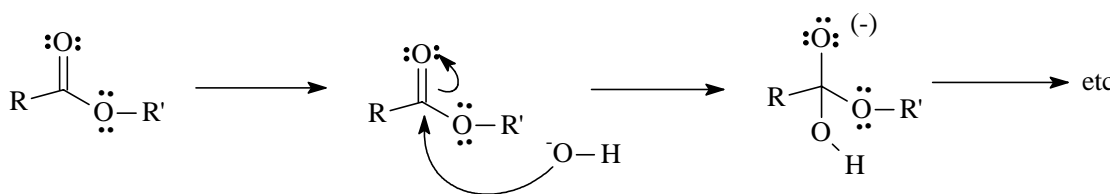


Simple hydrolysis of an ester (with water) may be catalyzed (rate of the reaction increased) by acids, bases or enzymes as illustrated in the examples below:

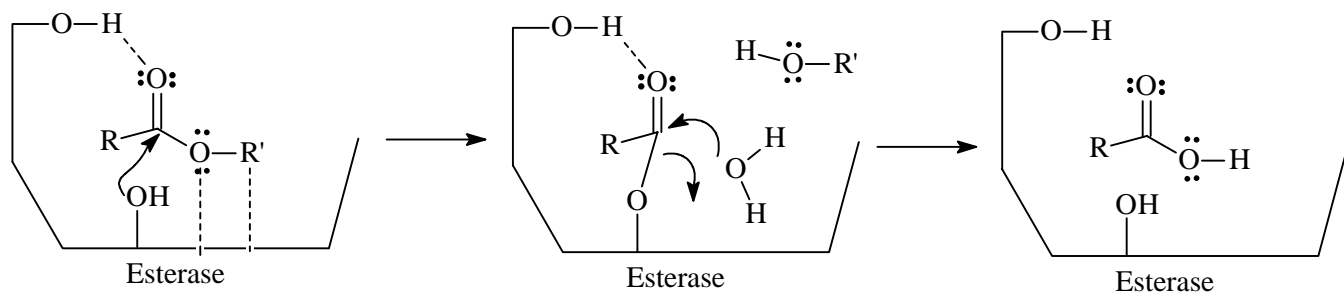
- Acids enhance the reaction by protonation of the carbonyl oxygen as shown below and thereby increasing the electrophilicity of the carbonyl carbon and thus its susceptibility to nucleophilic attack:



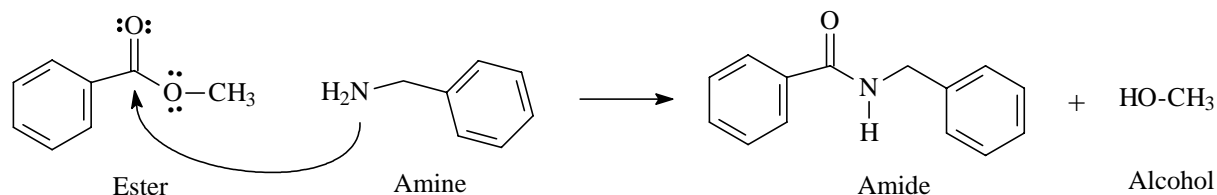
- Basic conditions enhance the rate of ester hydrolysis by increasing the concentration of attacking nucleophile at the reaction site as shown below:



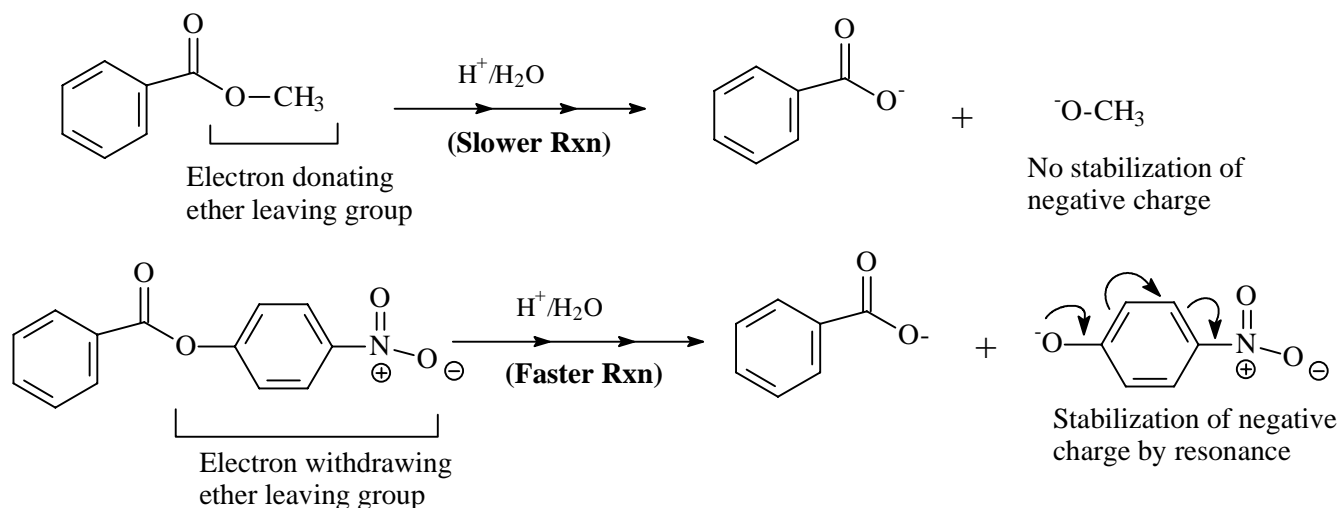
- Enzymes (esterases) catalyze hydrolysis by a variety of mechanisms including entropic factors (binding and locating the ester on the catalytic site of the enzyme) as well as being able to accomplish simultaneous acid and base catalysis with acidic and basic moieties on the surface of the enzyme as shown below:



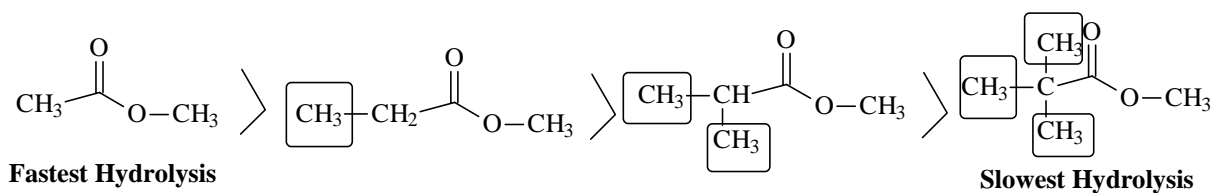
Nucleophiles other than water, such as amines, thiols, etc. can react with esters and form cleavage products. Consider the example below where a primary amine (nucleophile) reacts with the ester to form an amide and alcohol product:



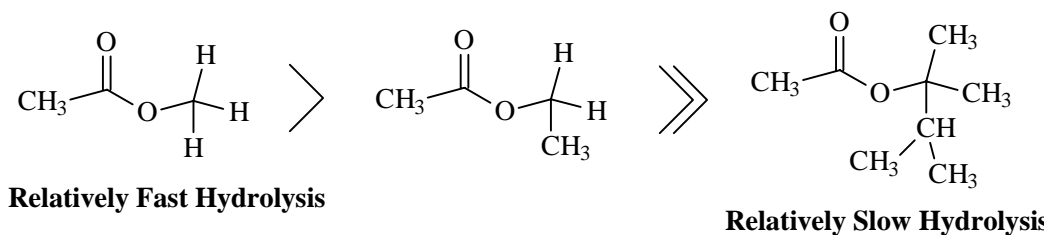
In addition to the electrophilic nature of the ester carbonyl, the electronic nature of the "ether" group (O-C) may influence hydrolysis reactions. For example, esters in which the "ether oxygen" is linked to a strong electron withdrawing group (by resonance or induction) undergo hydrolysis more readily. This is due to stabilization of the developing negative charge in the "ether" (actually "alkoxide") leaving group by the electron withdrawing functionality as illustrated below:



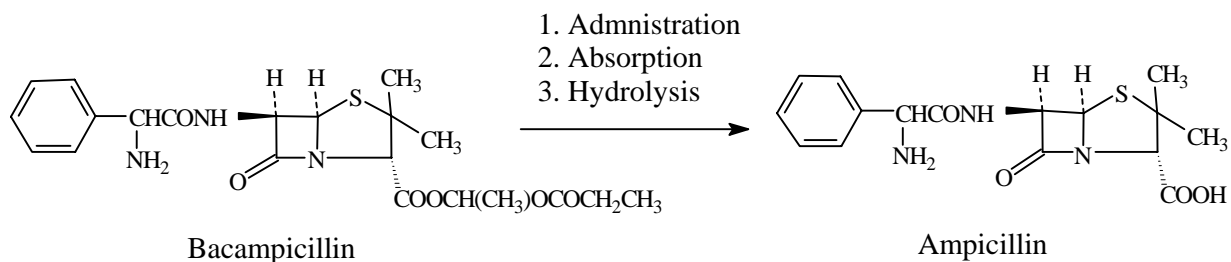
In addition to the electrophilic nature of the ester carbonyl, steric factors also may influence ester hydrolysis reactions. Large or sterically bulky near the reaction site may hinder attack of the nucleophile (i.e. HO^-) at the ester carbonyl and thereby slow down the rate of hydrolysis. Usually the larger the group and the closer it is to the reaction site, the greater "steric inhibition" of hydrolysis. In the example below the effect of increasing steric bulk on the alpha-carbon on hydrolysis is illustrated:



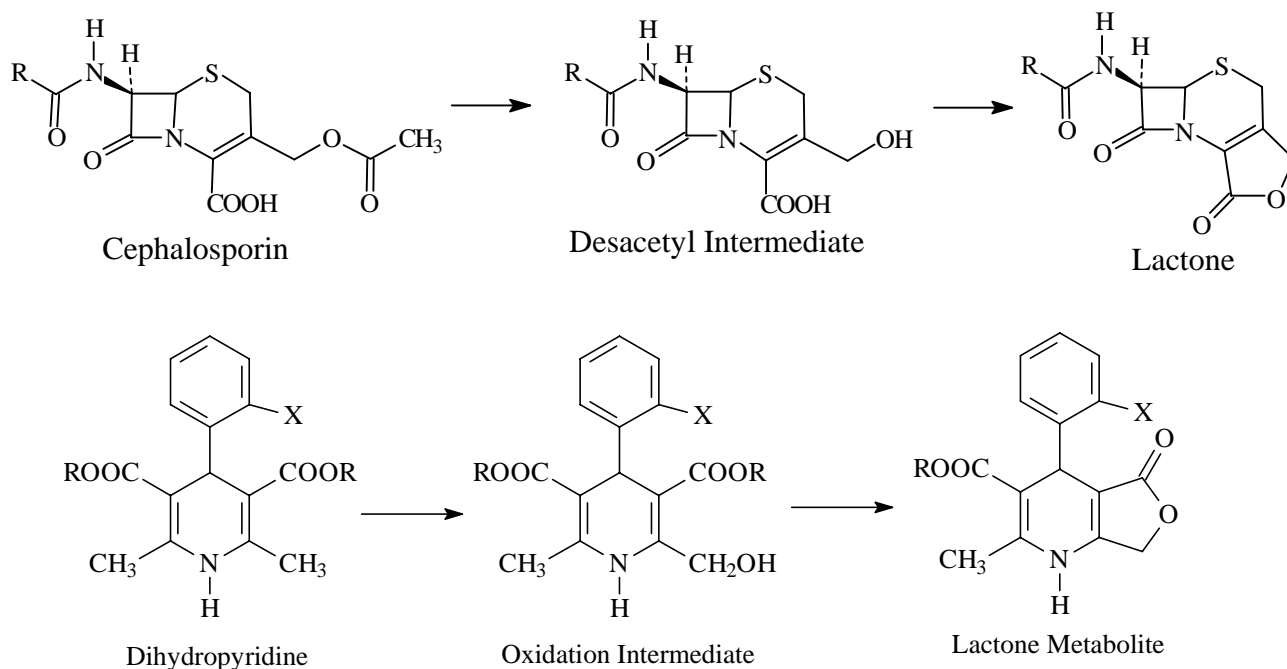
Bulk on the "ether" carbon atoms may also slow the rate of hydrolysis by a similar mechanism. Again, the larger the group and the closer it is to the reaction site, the greater "steric inhibition" of hydrolysis:



In the ester prodrug of the amino acid drug ampicillin, is absorbed far more readily from the GI tract. Once absorbed, it is cleaved by esterases to the parent, active drug:

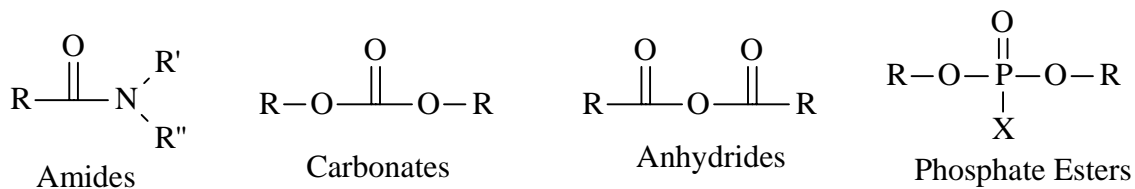


In the introductory portion of this chapter, a general synthetic approach is described for the preparation of esters. Ester derivatives of certain drugs also can be formed as part of normal human metabolic reactions as illustrated for the cephalosporin and dihydropyridine drugs below. Note in these cases that oxidation of a benzylic-type carbon occurs first to yield a nucleophilic hydroxyl group in proximity to an acid functionality or derivative. These two groups can then react to form a cyclic ester or lactone:



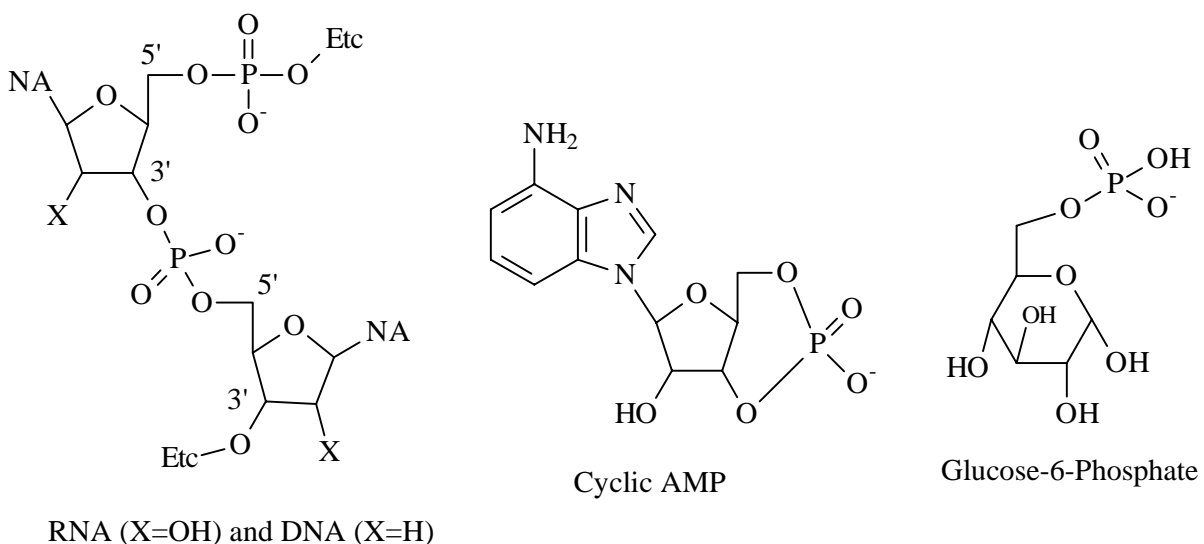
V. Other "Ester-like" Functional Groups

There are a number of other functional groups that are derivatives of traditional esters or "ester-like" including amides and amide derivatives (carbamates, ureas, etc.), carbonates, anhydrides and phosphate esters. The amide and amide derivatives are discussed in a separate chapter:

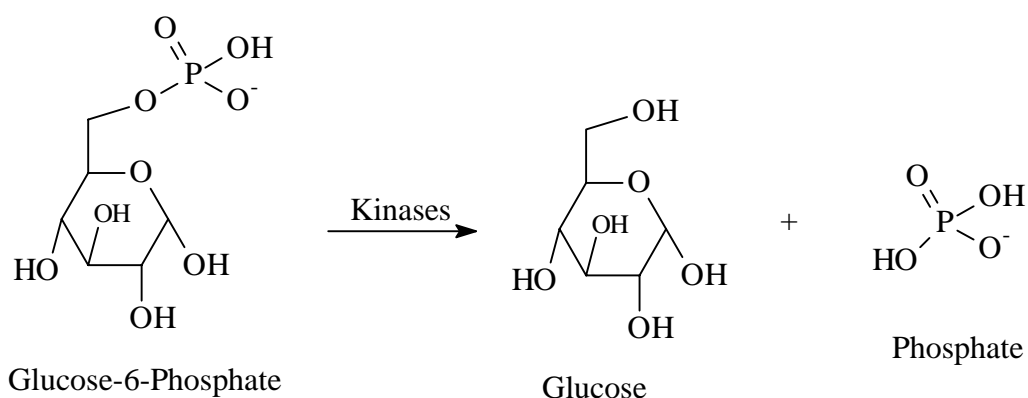


Generally, amides and carbonates are less susceptible than esters to hydrolysis or nucleophilic reactions based on the increased electron donation by resonance by the atoms linked to the central carbonyl group. Anhydrides are more susceptible than esters to hydrolysis or nucleophilic reactions because the second carbonyl creates an electron withdrawing moiety by resonance. Phosphate esters may be more or less reactive than traditional esters, depending on their overall structure.

Phosphate esters are essential components of human biochemistry. They provide the linkage between nucleosides in RNA and DNA (the 3'-5' phosphodiester bond), and the "high energy bonds" of biochemical messengers such as cyclic AMP and intermediates of metabolism such as glucose-6-phosphate:

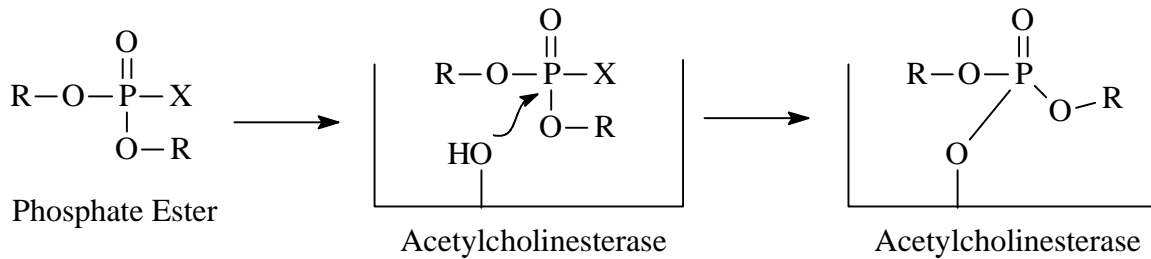


These biochemical substrates undergo hydrolysis reactions *in vivo* catalyzed by kinases and other related enzymes as illustrated for glucose-6-phosphate below:

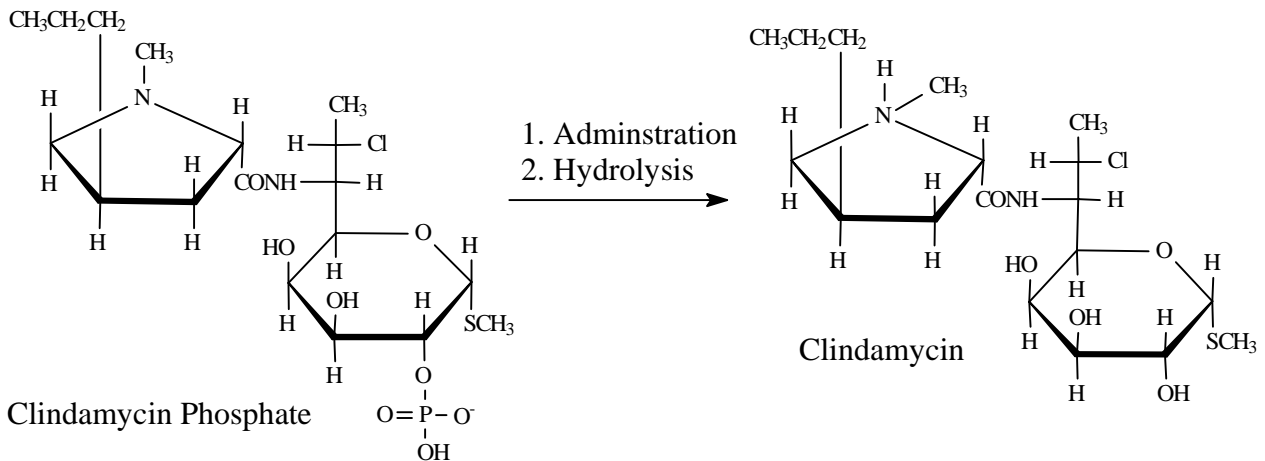


The phosphate ester group also is an essential component of a number of drugs including the organophosphate acetylcholinesterase inhibitors (OP-AChEIs). It also is a common structural component of nerve gases and insecticides, and can be used as a prodrug functionality. The OP-AChEIs consist of a phosphate ester moiety with a good leaving group (X). This structure is

capable of being recognized by the enzyme AChE and chemically reacting with a nucleophile (OH) present on the enzyme as shown below. More details regarding the structure, reactivity and pharmacologic activity of the OP-AChEIs is presented in the Acetylcholine Inhibitor Chapter:

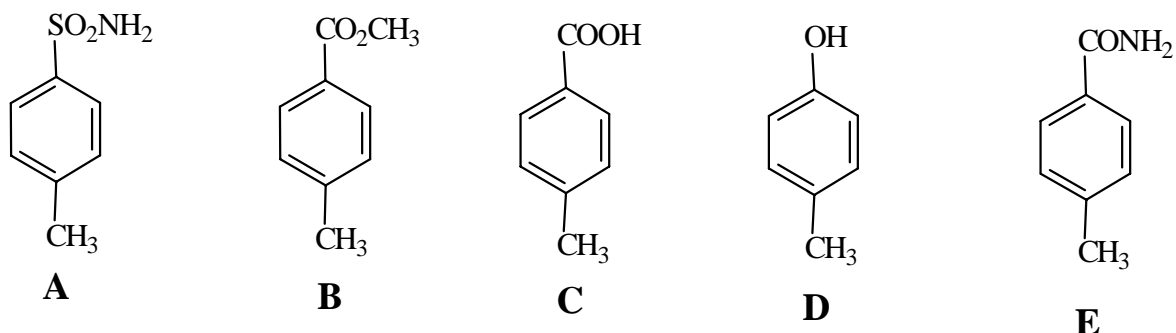


The use of phosphate esters in prodrug design is illustrated by clindamycin phosphate. The parent drug clindamycin is a relatively lipophilic, water insoluble drug. The phosphate prodrug is water soluble and thus can be dissolved in aqueous solutions for parenteral administration. Once administered, the phosphate moiety is rapidly hydrolyzed to yield the parent, active drug in the circulation as shown below:



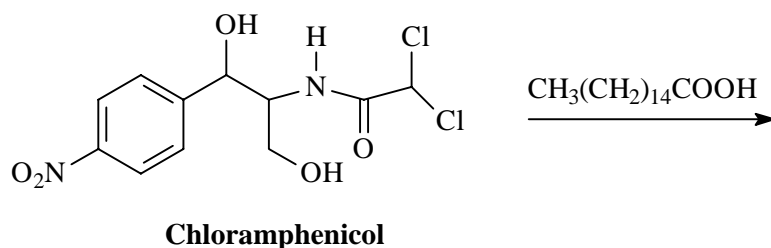
VI. Problems

1. Answer the questions below (a-c) for the follow series of compounds:

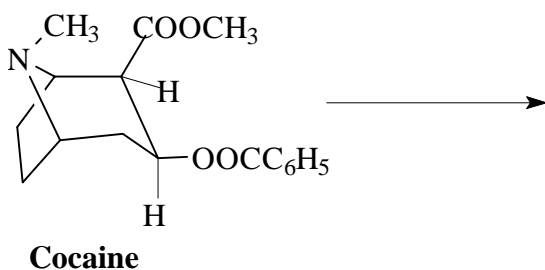


- Which compound above is MOST acidic?
- Which compound above is LEAST acidic?
- Which compound above is MOST susceptible to hydrolysis?
- Which compound would be MOST likely to undergo electrophilic substitution?
- Which compound(s) above would be predominately ionized at physiologic pH?
- Which compound(s) above would yield a salt upon treatment with NaHCO_3 ?
- Which compound would be MOST water soluble at pH 7?

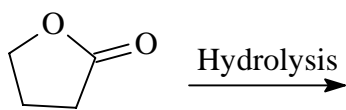
2. The palmitate ester of chloramphenicol is used as a prodrug to mask the unpleasant taste of the chloramphenicol in oral dosage forms. Esterification occurs selectively at the primary alcohol group of chloramphenicol. Show the structure of this ester prodrug and explain why esterification occurs preferentially at the primary alcohol group.



3. A new compound known as Coca ethylene is often found in the plasma and brain tissue of cocaine abusers who also abuse alcohol ($\text{CH}_3\text{CH}_2\text{OH}$). This new substance has all the same pharmacological properties as cocaine, suggest a structure for this new compound.

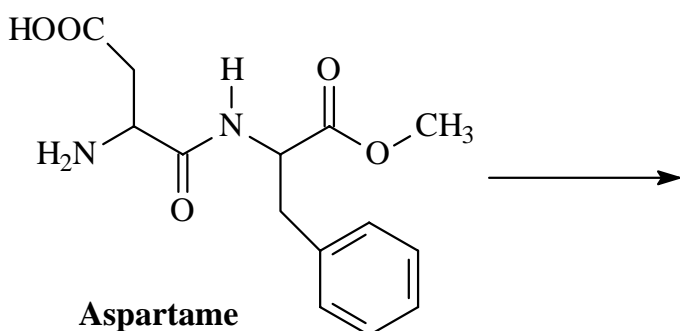


4. The cyclic ester (lactone) below is rapidly hydrolyzed under physiologic conditions to yield the hydroxy-acid product, gamma-hydroxybutyric acid (GHB). Show the structure of GHB:



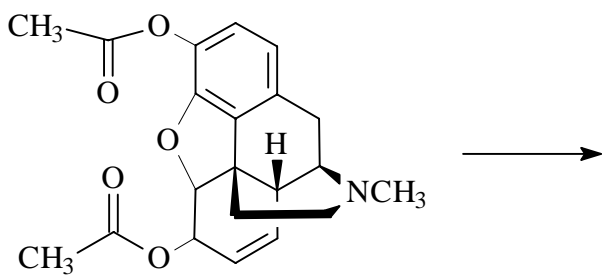
Lactone

5. Aspartame (NutraSweet) is a low calorie sugar substitute used in many food and beverage products. There are some claims (but minimal scientific evidence) that high levels of aspartame use exposes individuals to low but sustained levels of methanol. By what chemical or metabolic process could methanol be formed from aspartame?



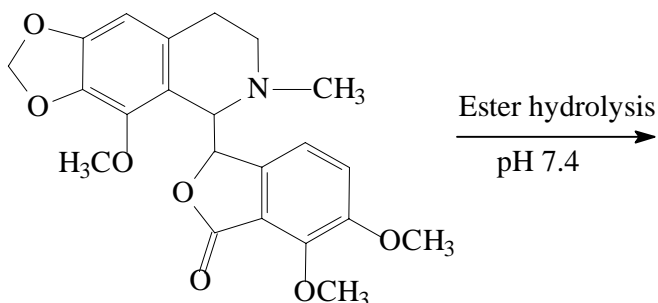
Aspartame

6. Some drug molecules contain multiple ester groups. In the di-ester heroin shown below, relative chemical reactivity allows for the hydrolysis of one ester group at a faster rate to yield one major mono-ester product. Show the product from the hydrolysis of the more labile ester group for heroin.

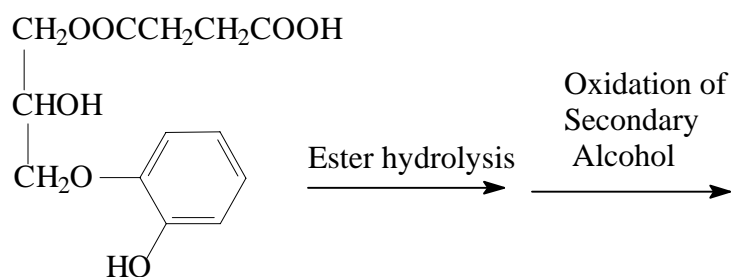


Heroin

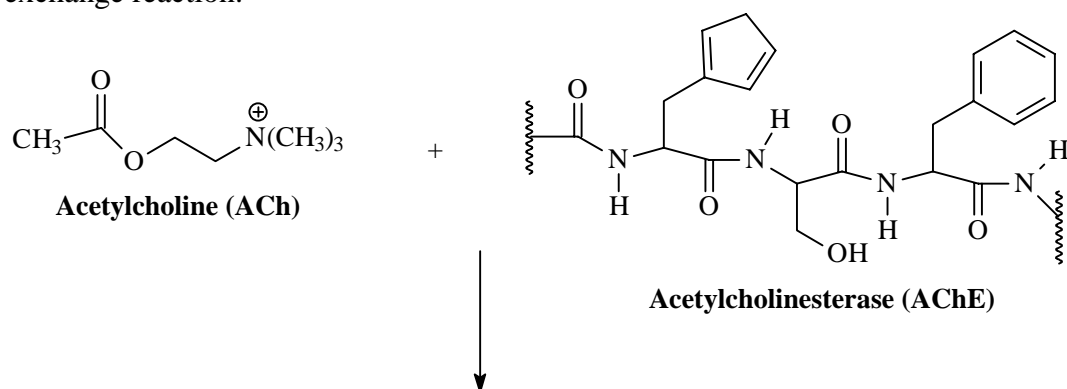
7. Show the structure of the ester hydrolysis products for the following compound, noscapine and the exact structure of this hydrolysis product at pH 7.4.



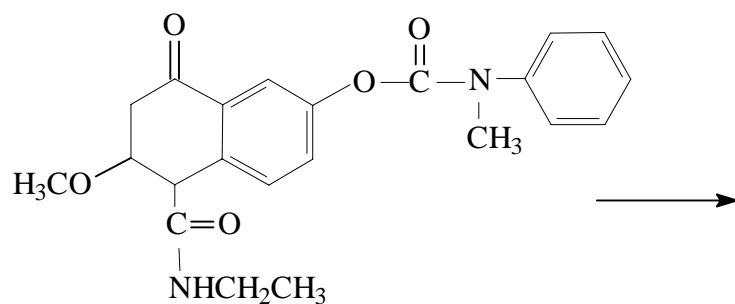
8. Show the structure of the ester hydrolysis products for the following drug. Also, show the product of oxidation of the secondary alcohol group of the hydrolysis product.



9. The major process in the inactivation of the neurotransmitter acetylcholine (ACh) is hydrolysis by the enzyme acetylcholinesterase (AChE). The mechanism of this reaction involves an ester exchange (transesterification) reaction between the primary hydroxyl group of a serine residue present on the active site of AChE and the substrate ACh. Show the product of this ester exchange reaction.



10. Show all the products that form from carbamate hydrolysis of the following molecule.



11. 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. Why does this decarboxylation reaction occur? Also, propose a prodrug derivative of carbenicillin to overcome (or minimize) this problem.

