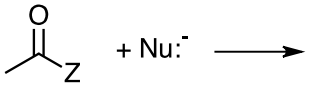
12. Apply nucleophilic addition and elimination concepts to nucleophilic acyl substution reactions of acids and derivatives (focus on esters and amides)

In Class problems:
1. The reactive site of aldehydes, ketones, acids, and acid derivatives, such as esters, is the carbonyl carbon. (Note: the acidic H in an acid is also a reactive site.) The carbonyl carbon is an electrophile.



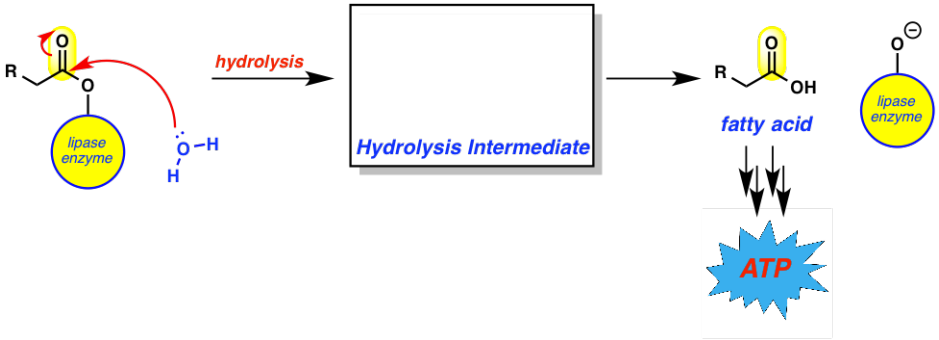
a. Use curved arrows to show how the above reaction forms a tetrahedral intermediate.
b. For an aldehyde, Z = H. H is a very poor leaving group (LG). It cannot be made into a better LG.
Fill in the table:

Functional Group	Z	Can Z be Made into a Better LG?	How to Make Z a Better LG?	$Nu:^-$ Addition or $Nu:^-$ Acyl Substitution?
Aldehyde	H	no	Can't	$Nu:^-$ Addition
Ketone				
Acid				
Ester				
Acid chloride				
Anhydride				
Amide				

c. Compare the acid, ester, acid chloride, anhydride, and amide. The carbonyl carbon in an acid chloride is the most reactive and the amide is the least reactive. Briefly explain this reactivity trend.

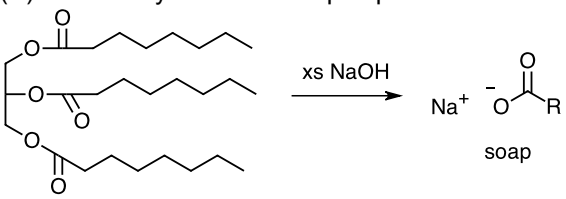
2. An acid reacts with an alcohol to form an ester. E.g., acetic acid reacts with ethanol to form ethyl acetate, which is the solvent in non-acetone finger nail polish remover, and water. In this reaction, ethanol is the $Nu:^-$ and acetic acid is the E^+.
a. Identify the two electrophilic atoms in acetic acid. Which atom is the better E^+? (Partial answer: carbonyl carbon.)
b. Ethanol is not a strong enough $Nu:^-$ to react with the best E^+ in acetic acid because _____. (Hint: see pK_a table.)
c. Acetic acid reacts slowly with ethanol so this reaction needs help. Acetic acid reacts with NaOH to form Compound 1. Compound 1 reacts with ethylbromide to form ethyl acetate. Use curved arrows to show how Compound 1 and ethyl acetate form. What is the reaction type?
d. Acetic acid reacts slowly with ethanol so this reaction needs help.
(i) Acetic acid reacts with H_2SO_4 to form Compound A. (Hint: see carbonyl O.) Draw a resonance strucure of Compound A. Explain why an acid catalyst makes the carbonyl carbon a better electrophile.
(ii) Compound A reacts with ethanol to form Compound B (a tetrahedral intermediate). Why does ethanol react at the carbonyl carbon instead of one of the acidic H's? (Hint: compare resonance structures.)
(iii) Compound B reacts with ____ to form ethyl acetate. Use curved arrows to show how Compound B forms ethyl acetate.
(iv) In Compound B, circle the group bonded to the carbon (which was the carbonyl carbon) that behaves like a leaving group. Is this group a good leaving group?
(v) Identify the bonds that broke in the reactants and the bonds that formed in the products. (So if you are given the structure of an ester, you can predict the structures of the acid and alcohol.)
e. Compare Compound B to a tetrahedral intermediate that forms from an aldehyde or ketone. Does the tetrahedral intermediate that formed from an aldehyde or ketone have a leaving group?
f. How does this explain why aldehydes and ketones undergo nucleophilic addition whereas acids and acid derivatives undergo nucleophilic acyl substitution?

3. Esters undergo hydrolysis (usually with a base catalyst) to form an acid and alcohol.
a. (From LearnBacon.com) Predict the structure of the intermediate formed initially after attack of the water onto the enzyme bound ester.

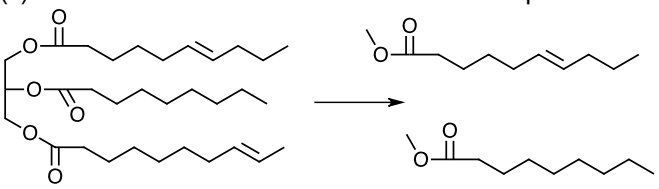


b. Use curved arrows to show how reactants form products. In the tetrahedral intermediate, which group is the leaving group?

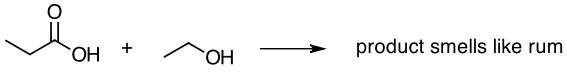
c. The ester hydrolysis reaction is used to make soap. This is called a saponification reaction.
(i) Use curved arrows to show the triglyceride (fat) reacts with excess NaOH to make soap.
(ii) Draw the structure of the R group in soap for this reaction.
(iii) How many moles of soap is produced from one mole of fat?

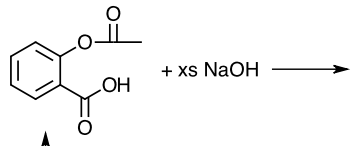


d. Biodiesel and transesterification. The triester (triglyceride = fat) reacts under basic conditions, e.g., NaOH, and methanol to form three esters. Two esters are shown.
(i) Draw the structure of the third ester. Use curved arrows to show how this ester is formed.
(ii) How is this reaction different than the soap reaction in part c?

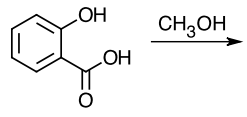


4. Predict the product of the following reactions. For (c), determine the reaction conditions.

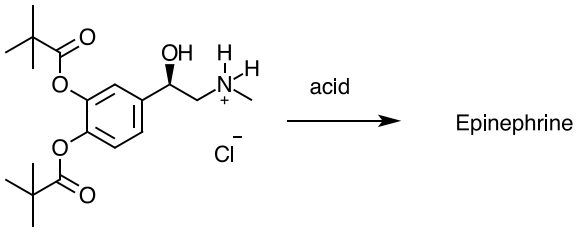
a. 

b. 

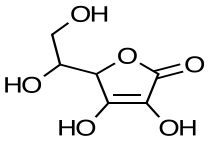
c.

d. 

5. Ester groups are often found in biomolecules and drugs. One way our body metabolizes chemicals is by hydrolysis of the ester group to form an alcohol and acid.
a. Prodrugs: inactive form of a drug that makes the active form in the body. E.g., epinephrine is used in the treatment of glaucoma. What is the structure of epinephrine?

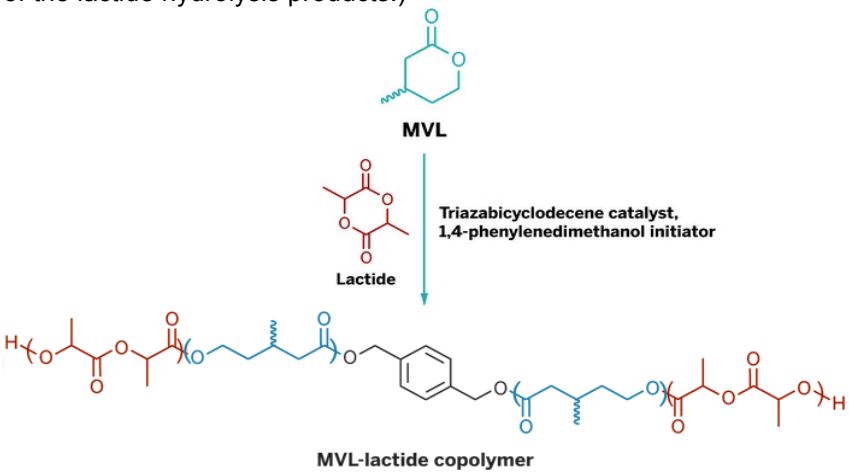


b. Vitamin C is a lactone. Draw the structures of the metabolic products of Vitamin C. In other words, draw the structure of the acid and alcohol that makes Vitamin C.

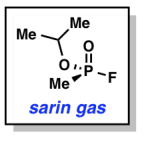


Vitamin C

6. Poly(lactide) is a rigid aliphatic polyester used in compostable drinking cups and in medical devices BUT it's brittle. The ratio of MVL (β-methyl-δ-valerolactone) to lactide determines copolymer properties: soft, stretchy (shoe soles) to stiff, tough (cars). (C&EN, 6/2/14, p. 7 (http://cen.acs.org/articles/92/i22/Building-Biobased-Copolymers.html))
Use curved arrows to show how MVL reacts with lactide to form the MVL-lactide copolymer.
(Hint: MVL undergoes hydrolysis to form _____ and ____ functional groups. Lactide undergoes hydrolysis to form _____ and ____ functional groups. Then, the ____ group from one of the MVL hydrolysis products with the ____ group from one of the lactide hydrolysis products.)



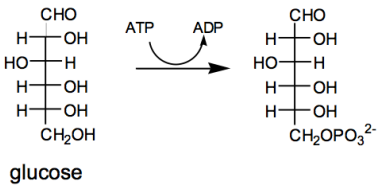
7. Biology and nucleophillic acyl substitution reactions. A phosphate or phosphate ester reacts like an acid or acid derivative. Treat the phosphorus atom in phosphate or a phosphate ester like a carbonyl carbon.
a. (From LearnBacon.com) Chemical warfare and esters. The phosphate ester (contains P atom in place of the carbony C) is found in our body. A Phosphate ester is found in sarin nerve gas. How does it work? The phosphate ester of sarin gas can be attacked by AChE enzyme and disables the AChE enzyme and prevents the necessary metabolism of acetylcholine in our body. Without muscle control in breathing, asphyxia occurs --> death.



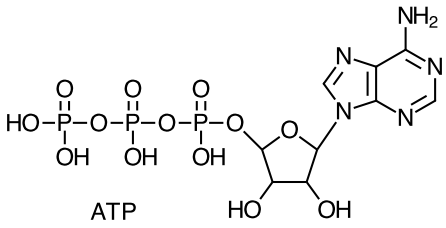
Use curved arrows to show how sarin reacts with the AChE enzyme. What is the leaving group?

b. The first step of glycolysis is shown below.

Glycolysis 1st step: phosphoryl transfer



glucose



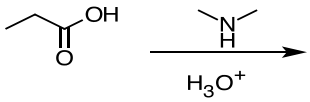
ATP

Use curved arrows to show how glucose reacts with ATP to form glucose-6-phosphate. What is the leaving group?

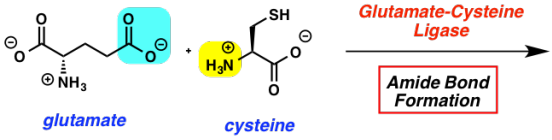
In Class problems:

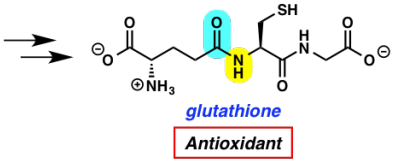
1. An acid reacts with an amine in the presence of an acid catalyst to form an amide.

a. For the reaction below, use curved arrows to show how the amide product forms. What is the leaving group? This reaction is reversible which means an amide undergoes hydrolysis to form an acid and amine. What bond forms? What bond breaks? This will help you on Question 2.



b. (From LearnBacon.com) Glutathione (antioxidant found in plants, animals, and fungi) synthesis.
Predict the structure of the amide product γ–glutamylcysteine that is formed after coupling of glutamate and cysteine.

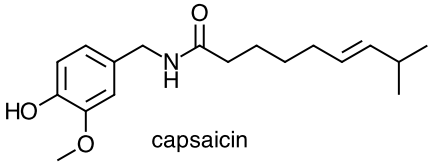




2. One way our body metabolizes chemicals is by hydrolysis of the amide group.

a. Capsaicin is found in chili peppers and is hot and spicy. It is also an anti-viral and is being investigated as a cancer drug.

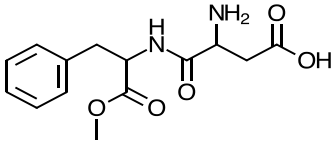
(i) Draw the structure(s) of the metabolic (hydrolysis) product(s).



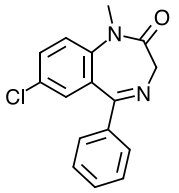
capsaicin

(ii) Milk or an adult beverage, like tequila, works better than water for relieving the burning sensation on your tongue. Explain why.

b. Aspartame is an artificial sweetener (Nutrasweet). In the body, aspartame is hydrolyzed to form methanol, aspartic acid, and phenylalanine. Draw the structures of aspartic acid and phenylalanine.

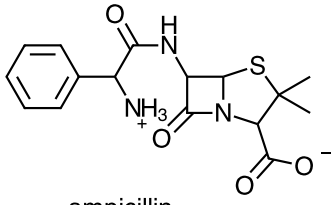


c. Valium is an anti-anxiety drug. Draw the structure of a metabolic (hydrolysis) products of this compound.



Diazapam (Valium)

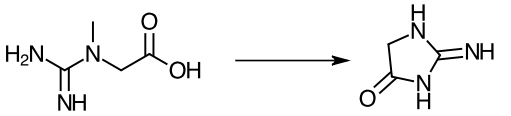
3. Ampicillin is a beta-lactam (a beta-lactam is an amide group in a four sided ring) antibiotic. Beta-lactam antibiotics disrupt cell wall biosynthesis in bacteria by inactivating a transpeptidase enzyme. Assume this enzyme is ROH.



ampicillin

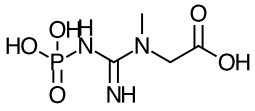
a. Ampicillin has two amide groups and an acid group. The amide group in the ring is the most reactive because _____.
b. Use curved arrows to show how ROH reacts with ampillicin. Draw the structure of the product.

4. Creatine is found in vertebrates (mainly in skeletall muscle) and facilitates recycling of ATP. Creatine supplements are used by athletes to gain muscle mass. Creatine breaks down to creatinine.
Use curved arrows to show how creatine forms creatinine.

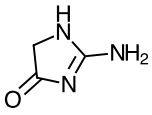


creatine

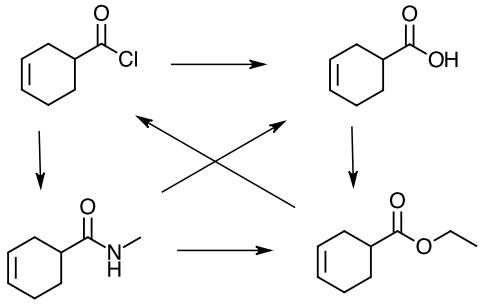
creatinine



phosphocreatine

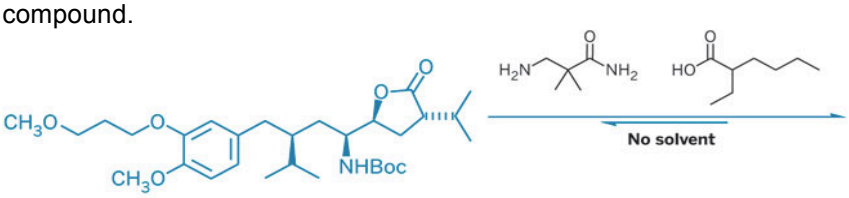


5. Functional group conversions.
a. For each compound, identify the $Nu:^-$ and E^+. If there is more than one $Nu:^-$ or E^+., identify the strongest $Nu:^-$ or E^+.
b. Determine the reaction conditions for each reaction. Which reaction needs an acid catalyst? Why?
If a reaction does not need an acid catalyst, make sure the $Nu:^-$ is strong enough to react at the carbonyl C.
c. Draw the tetrahedral intermediate for each reaction. Circle the leaving group in each tetrahedra intermediate.

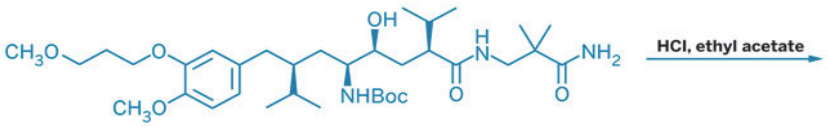


d. You want to form a C-C bond using CH_3MgBr. Which compound will <u>not</u> react with CH_3MgBr at the carbonyl C? Why?
e. Hydride, $H:^-$, (from $LiAlH_4$ or $NaBH_4$) is a good $Nu:^-$. Use curved arrows to show how hydride reacts with each compound. Draw the structure of each product.

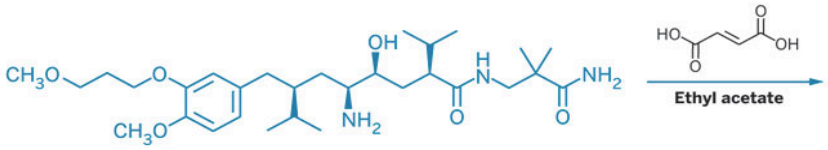
6. Aliskiren hemifumarate is an active pharmaceutical ingredient (API) to make Tekturna, a cardiovascular drug. The process is shown below (http://cen.acs.org/articles/92/i21/EndEnd-Chemistry.html).
The first compound is a lactone. Use curved arrows to show how the lactone undergoes aminolysis to form the second compound.



Lactone aminolysis



Deprotection



Crystallization to final product

Boc = *tert*-butyloxycarbonyl