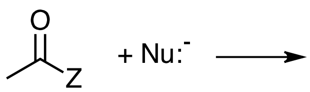
Objective 12a. Apply nucleophilic addition and elimination concepts to nucleophilic acyl substution reactions of acids and derivatives (focus on esters)
<u>Skills</u>: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu^- and E^+, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.
Key ideas: Compare to Nu addn. Both have Td intermediate. No LG in Nu addn vs. LG in acyl sub.

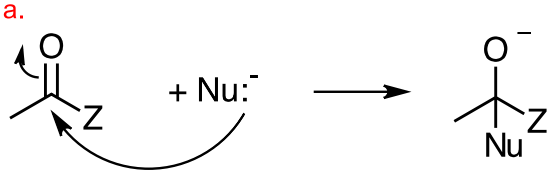
Practice problems solutions:
1. The reactive site of aldehydes, ketones, acids, and acid derivatives, such as esters, is the carbonyl carbon. (Note: the acidic H in an acid is also a reactive site.) The carbonyl carbon is an electrophile.



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.
Answers:
a.

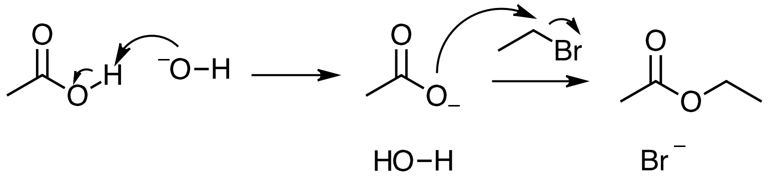


b.

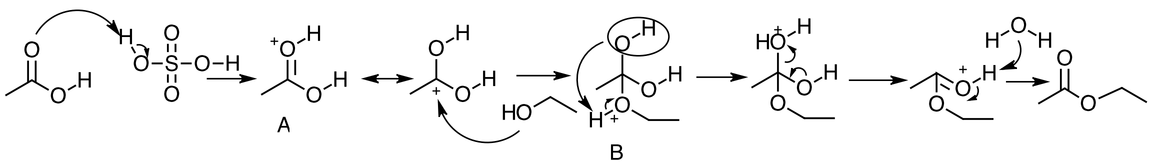
Functional Group	Z	Can Z be Made into a Better LG?	How to Make Z a Better LG?	$Nu:^-$ Addition or $Nu:^-$ Acyl Substitution?
Aldehyde	H	no	Can't	$Nu:^-$ Addition
Ketone	R	no	Can't	$Nu:^-$ Addition
Acid	OH	yes	Use acid to protonate Z	$Nu:^-$ Acyl Substitution
Ester	OR	yes	Use acid to protonate Z	$Nu:^-$ Acyl Substitution
Acid chloride	Cl	yes	Use acid to protonate Z	$Nu:^-$ Acyl Substitution
Anhydride	OCOR	yes	Use acid to protonate Z	$Nu:^-$ Acyl Substitution
Amide	NHR	yes	Use acid to protonate Z	$Nu:^-$ Acyl Substitution

c. Acid chloride is the most reactive because the electronegative Cl withdraws electron density (inductive effect) from the carbonyl carbon (carbonyl carbon has a larger partial positive charge) and makes the carbonyl carbon a better electrophile ==> most reactive.
Amide is the least reactive because the N is less electronegative than Cl and O and does not withdraw as much electron density from the carbonyl carbon (carbonyl carbon has a smaller partial positive charge) ==> least reactive.

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?
Answers:
a. acetic acid electrophiles are the acidic H in the acid group and the carbonyl carbon. The acidic H in the acid group is the better electrophile. See Reactivity Principles and Trends.
b. Ethanol is not a strong enough Nu:$^-$ to react with the best E$^+$ in acetic acid because ethanol is not a strong enough base to react with acetic acid. (pK_a of conjugate acid of ethanol = -2, pK_a of acetic acid = 5.)
c. Acetic acid + NaOH ---> water + Na$^+$ + acetate ion (Compound 1) acid-base reaction
acetate ion + ethylbromide ---> ethyl acetate + Br$^-$. substitution reaction

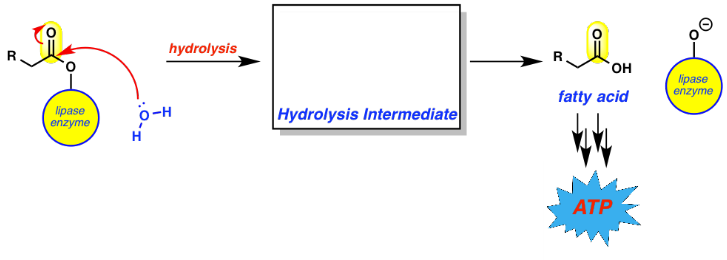


d.

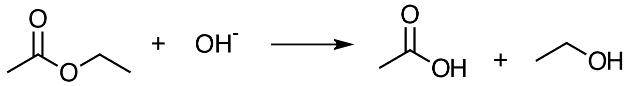


(i) Explain why an acid catalyst makes the carbonyl carbon a better electrophile. See carbocation on resonance structure.
(ii) Why does ethanol react at the carbonyl carbon instead of one of the acidic H's? Carbocation is a better E than acidic H.
(iv) OH group is not a good leaving group.
(v) Identify the bonds that broke in the reactants and the bonds that formed in the products.
Overall reaction: acetic acid + ethanol --> ethyl acetate + water
Reactants: carbony C-O single bond breaks in acetic acid, O-H bond breaks in ethanol.
Products: C-O bond forms to make ester, O-H bond forms to make water.
e. The tetrahedral intermediate that formed from an aldehyde or ketone does NOT have a leaving group.
f. The tetrahedral intermediate that formed from an acid (or ester or acyl cloride or amide) does have a leaving group. The leaving group leaves so new group can substitute for it.
The nucleophilic acyl substitution reaction is similar to the formation of an imine (aldehyde/ketone + 1^o amine).

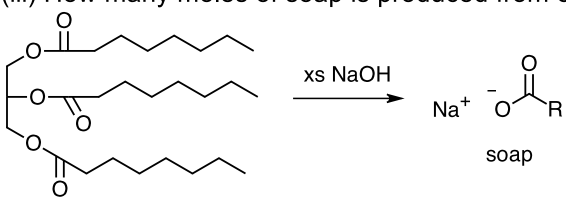
3. Esters undergo hydrolysis (usually with a base catalyst) to form an acid and alcohol.
a. (From LearnBacon.com) Predict the structure of the intermediate formed initially after attack of the water onto the enzyme bound ester.



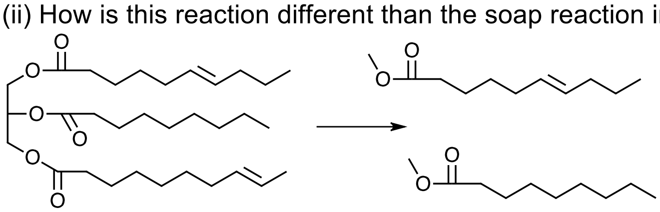
b. Use curved arrows to show how reactants form products. In the tetrahedral intermediate, which group is the leaving group?



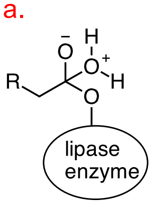
c. The ester hydrolysis reaction is used to make soap. This is called a saponification reaction.
(i) Use curved arrows to show the triglyceride (fat) reacts with excess NaOH to make soap.
(ii) Draw the structure of the R group in soap for this reaction.
(iii) How many moles of soap is produced from one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



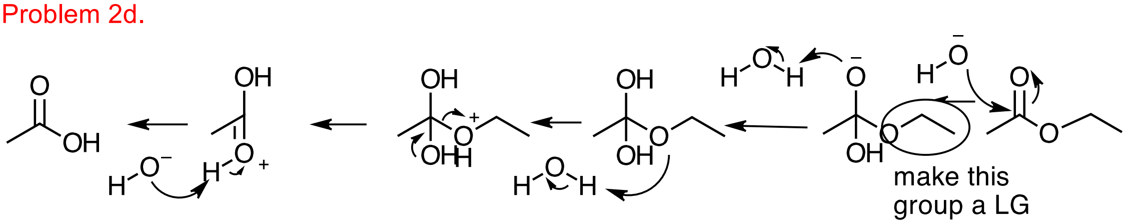
d. Biodiesel and transesterification. The triester (triglyceride = fat) reacts under basic conditions, e.g., NaOH, and methanol to form three esters. Two esters are shown.
(i) Draw the structure of the third ester. Use curved arrows to show how this ester is formed.
(ii) How is this reaction different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



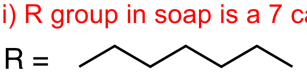
Answers:
a.



b. Nucleophilic acyl substitution reactions are equilibrium reactions. Reverse the acetic acid + ethanol reaction from Problem 2d.

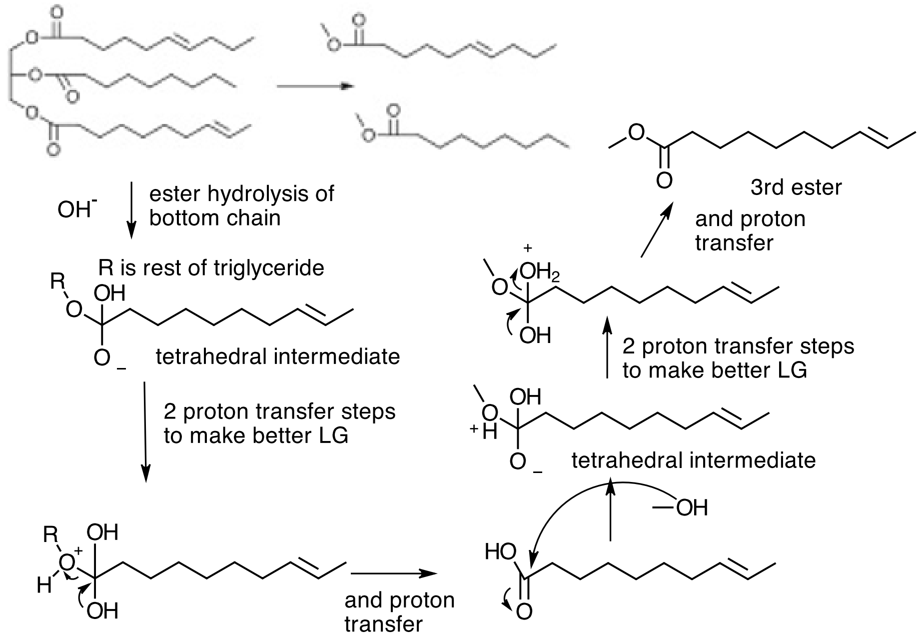


c. (i) A triglyceride (fat) has an ester group. The ester group reacts with excess NaOH with the same mechanism as Problem 3b. There is one more step: the acidic H in the acid group reacts with OH^- to form the conjugate base of the acid.
(ii) R group in soap is a 7 carbon alkyl group.



(iii) 3 moles of soap is produced from one mole of fat.

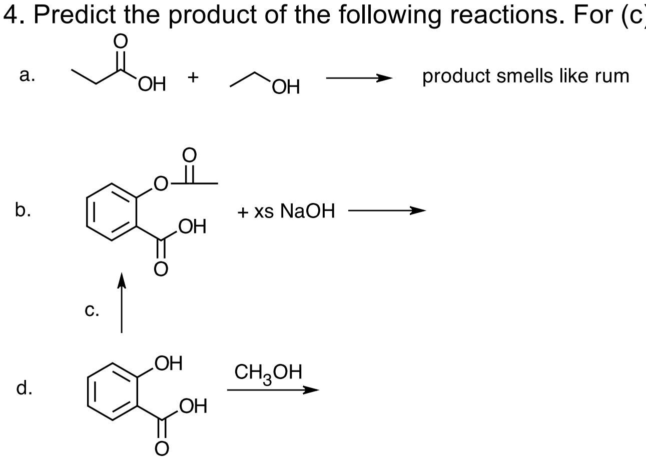
d. (i) 3rd ester



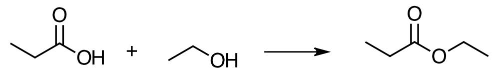
(ii) In the transesterification reaction and soap (saponification) reaction, NaOH reacts with an ester. Each each reaction, an acid forms (-OR group in ester leaves, -OH group replaces it). Once the acid forms in the transesterification reaction, it reacts with methanol to form an ester.

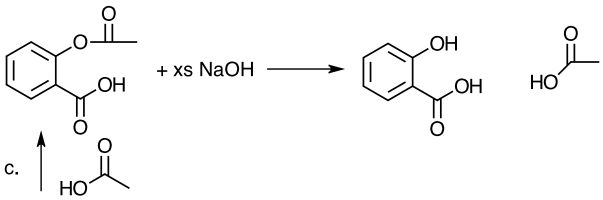
Another way to look at the transesterification reaction: NaOH reacts with methanol (CH_3OH) to form CH_3O^-. The CH_3O^- reacts with the carbonyl C in the ester and replaces the –OR group with the $–OCH_3$ group.

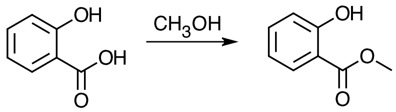
4. Predict the product of the following reactions. For (c), determine the reaction conditions.



Answers:

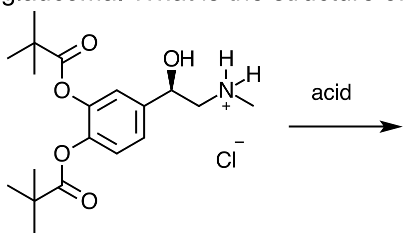
a.  product smells like rum

b. 

d. 

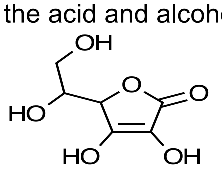
5. Ester groups are often found in biomolecules and drugs. One way our body metabolizes chemicals is by hydrolysis of the ester group to form an alcohol and acid.

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?



Epinephrine

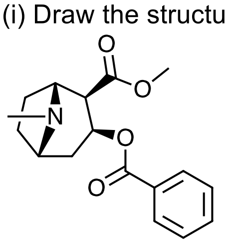
b. Vitamin C is a lactone. Draw the structures of the metabolic products of Vitamin C. In other words, draw the structure of the acid and alcohol that makes Vitamin C.



Vitamin C

c. Cocaine is an illicit drug. This compound is metabolized in a person's body by ester hydrolysis.

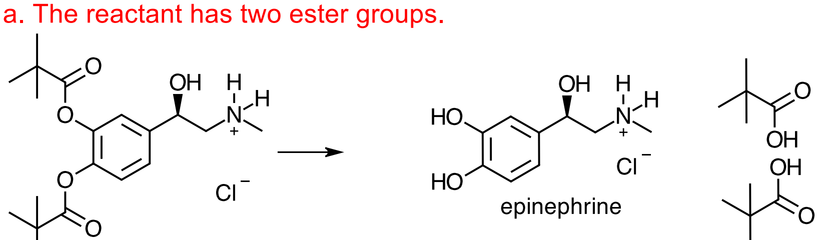
(i) Draw the structure of the metabolic products (3 products).



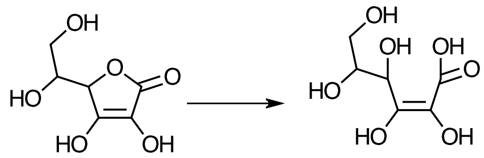
(ii) If a person undergoes drug testing, e.g., with a urine sample, what compound would the testing lab look for to identify cocaine?

Answers: Identify the ester group in each compound. The ester group reacts with water (hydrolysis) to form an alcohol and acid.

a. The reactant has two ester groups.

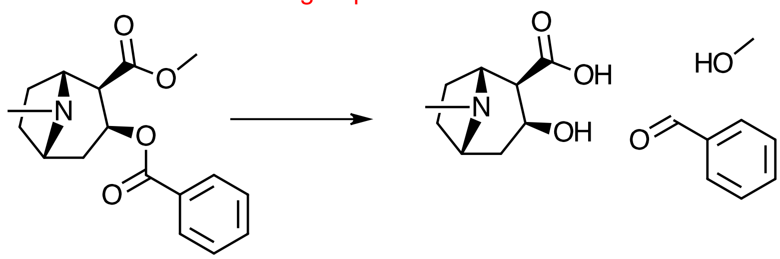


b. Vitamin C has one ester group.

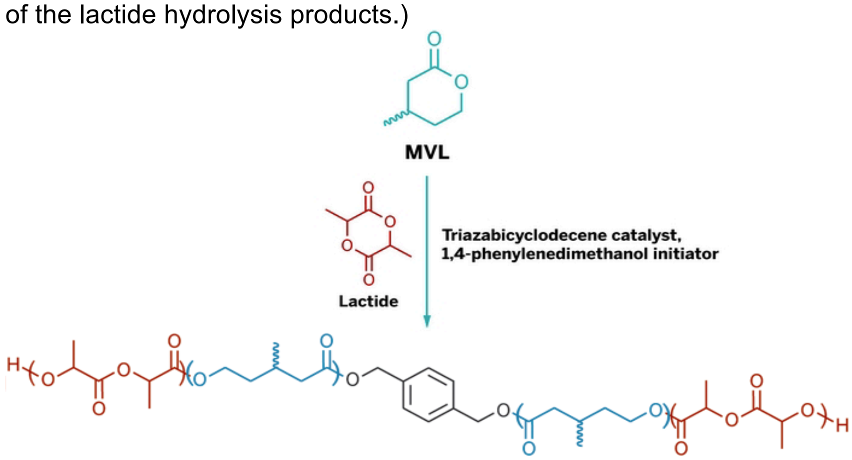


Vitamin C

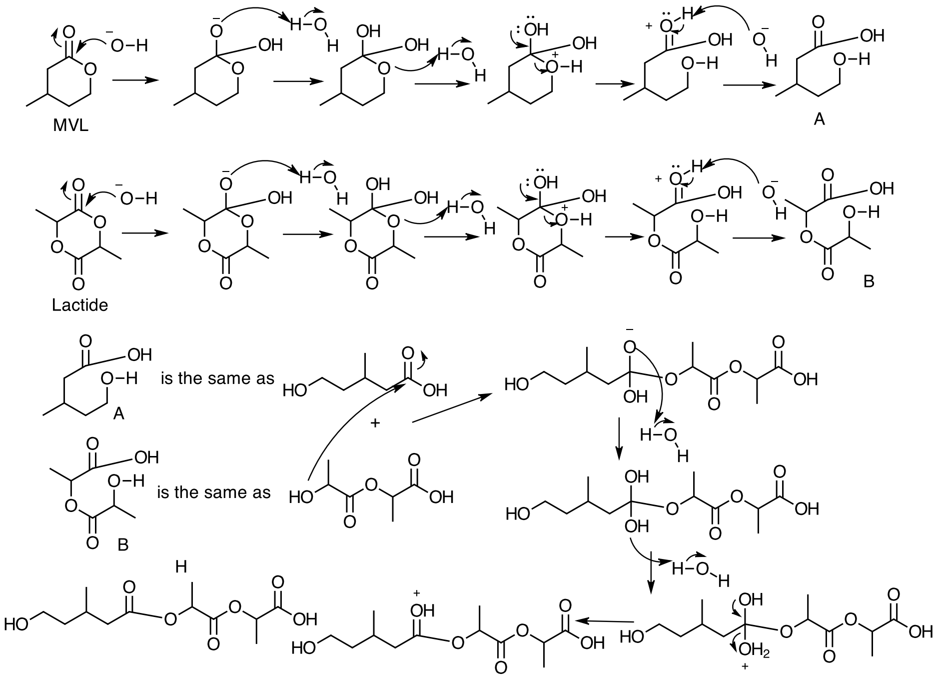
c. Cocaine has two ester groups.



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.)

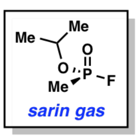


Answers: MVL undergoes hydrolysis to form acid and alcohol functional groups. Lactide undergoes hydrolysis to form acid and alcohol functional groups. Then, the alcohol group from one of the MVL hydrolysis products with the acid group from one of the lactide hydrolysis products.)



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.

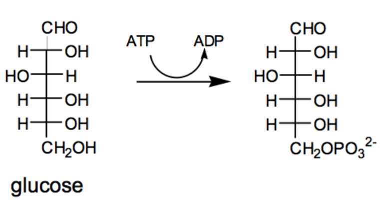
a. (From LearnBacon.com) Chemical warfare and esters. The phosphate ester (contains P atom in place of the carbony C) is found in our body. A Phosphate ester is found in sarin nerve gas. How does it work? The phosphate ester of sarin gas can be attacked by AChE enzyme and disables the AChE enzyme and prevents the necessary metabolism of acetylcholine in our body. Without muscle control in breathing, asphyxia occurs --> death.

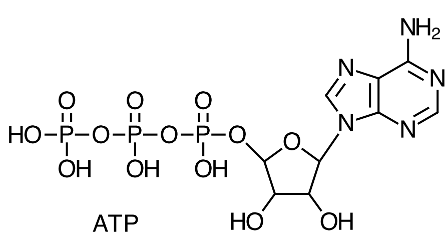


Use curved arrows to show how sarin reacts with the AChE enzyme. What is the leaving group?

b. The first step of glycolysis is shown below.

Glycolysis 1st step: phosphoryl transfer

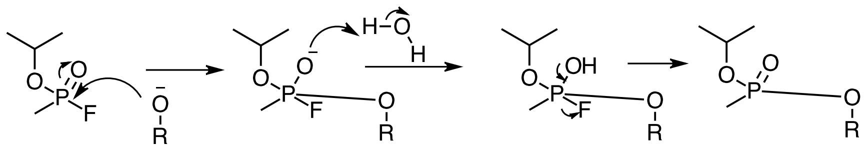




Use curved arrows to show how glucose reacts with ATP to form glucose-6-phosphate. What is the leaving group?

Answers:

a. The leaving group is F. R is the AChE enzyme.



b. The leaving group is ADP. P in ATP behaves like a carbonyl carbon.