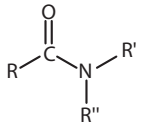
Carboxylic Acid Derivatives

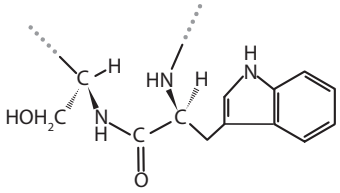
Answers and Explanations

1. D

The peptide bond is an amide linkage. Amides are carboxylic acid derivatives with the general structure below, where R, R', and R" represent organic groups or hydrogen atoms. The peptide bond is a 2˚ amide (R" is a hydrogen).

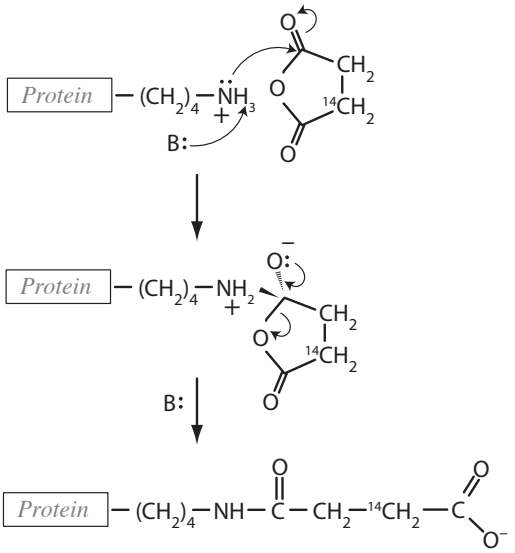


The figure below depicts the peptide bond between serine and tryptophan residues within a polypeptide:



2. C

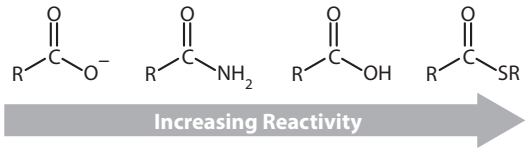
Aminolysis of an anhydride is a type of nucleophilic acyle substitution reaction. In this type of reaction, a nucleophile – such as an alcohol, amine, or enolate – displaces the leaving group of an acyl derivative – such as an acid halide, anhydride, or ester. In the resulting product, the nucleophile has taken the place of the leaving group present in the original acyl derivative. In the mechanism, the nucleophile attacks the carbonyl carbon, forming a tetrahedral intermediate. The tetrahedral intermediate of an acyl compound contains a substituent attached to the central carbon that can act as a leaving group. After the tetrahedral intermediate forms, it collapses, recreating the carbonyl C=O bond and ejecting the leaving group in an elimination reaction.



3. B

Among the choices, thioesters are the most reactive towards nucleophiles, followed by esters and carboxylic acids. Carboxylate ions are essentially unreactive towards nucleophilic substitution, since they possess no leaving group.

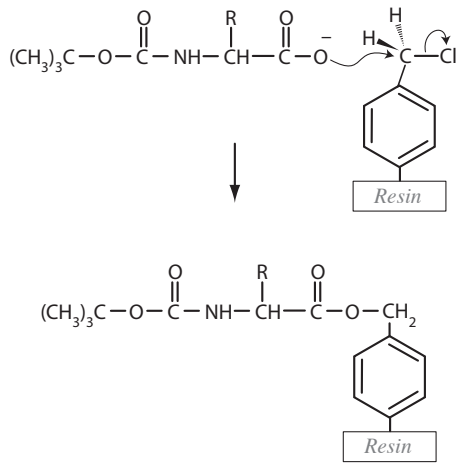
A major factor in determining the reactivity of acyl derivatives is leaving group ability, which is related to basicity. This is a thumbnail heuristic for comparing the reactivity of various carboxylic acid derivatives. Weak bases are better leaving groups than strong bases. Thiolate will be a better leaving group than amide or hydroxide. Therefore, thioesters are more reactive than esters or carboxylic acids.



The reactivity of thioesters (and phosphate anhydrides) towards nucleophilic acyl substitution is a *major* theme in biochemistry. For example, the role of coenzyme A as a carrier of 'activated' acyl groups depends on the reactivity of thioesters for nucleophilic acyl substitution. Thioesters are involved in the synthesis of many biomolecules including triglycerides, fatty acids, sterols, terpenes, porphyrins, and others.

4. A

The deprotonating agent triethylamine (Et_3N) transforms the α-carboxyl of the amino acid into its carboxylate form. The carboxylate anion then serves as a nucleophile in an SN2 reaction upon the chloromethyl substituent to form an ester.

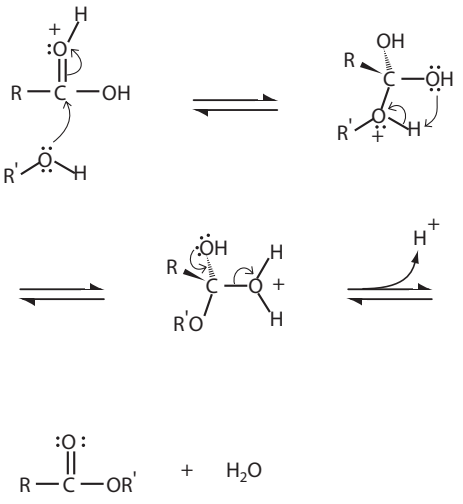


5. B

Lactones are cyclic esters. (Lactams are cyclic amides.)The Greek letter prefixes indicate the size of the ring: α-lactone = 3-membered ring, β-lactone = 4-membered, γ-lactone = 5-membered, and δ-lactone = 6-membered.

6. C

Fischer esterification is, basically, acid catalyzed nucleophilic acyl substitution. The acid catalyst protonates the carbonyl group to increasing its electron withdrawing character. In the mechanism, the alcohol nucleophile attacks the carbonyl carbon, forming a tetrahedral intermediate. The tetrahedral intermediate then collapses, recreating the carbonyl C=O bond and ejecting the water leaving group in an elimination reaction.



To keep track of the ^{18}O label, it's important to understand that *the two carboxyl group oxygens are equivalent*. Acidic protons come and go many thousands of time per second. Even under acidic conditions, the identity of the protonated oxygen changes frequently, so it will be a 50% chance whether the water leaving group carries the ^{18}O label, so there will be label present in the water, the ethyl caprylate product, as well as the unreacted caprylic acid (also some of the caprylate reformed at equilibrium through the reverse reaction).

7. B

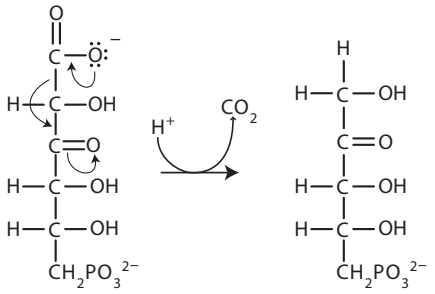
$NaBH_4$ is not powerful enough to reduce carboxylic acids but will reduce phosphate anhydrides (acyl phosphates). The presence of the alcohol product of reduction, homoserine, confirms the presence of phosphorylated aspartate residues in the enzyme being tested.

8. A

Transthioesterification is the process of exchanging the organic group SR″ of an thioester with the organic group SR′ of a thiol. The reaction is nucleophilic acyl substitution with $\Delta G \sim 0$. The reaction is driven forward by mass action as the acetyl CoA product is removed for citric acid cycle in the mitochondrion or shuttled to the cytosol for fatty acid synthesis.

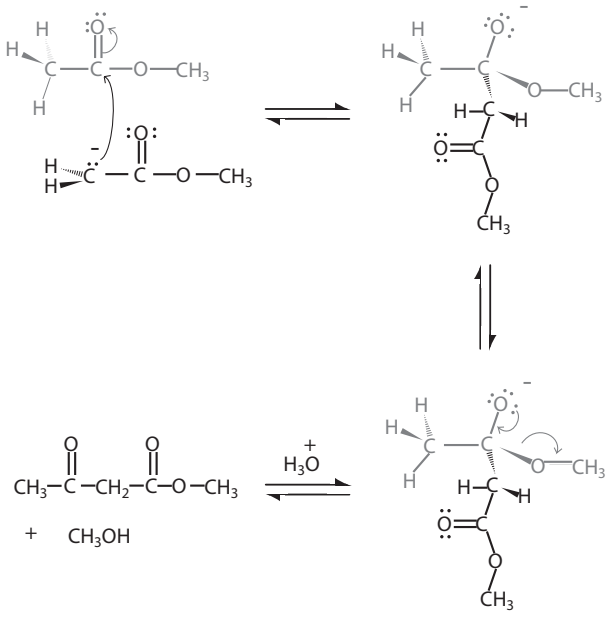
9. C

6-phospho-2-dehydro-D-gluconate is a β-keto acid, a molecule in containing a carbonyl group on the β-carbon of a carboxylic acid. β-Keto acids are very unstable and readily undergo decarboxylation with elimination of carbon dioxide under mild conditions.



10. A

Claisen condensation is like aldol addition for the world of esters. Instead of the nucleophilic addition pattern you see with aldehydes and ketones, the reaction follows the pattern of nucleophilic acyl substitution.



There are a number of reactions that appear frequently in biochemistry that did not appear on the AAMC MCAT topic outline. Familiarity with these is a figure of merit for the exam. These reactions include E1 & E2 elimination, Michael addition, and Claisen condensation. There may be others. The appearance of things like this in an MCAT passage from outside the scope is part of the exam. Prior knowledge is better, but the test won't necessarilly expect it.

11. C

Thioesters are among the more reactive carboxylic acid derivatives. Hydrolysis of a thioester is thermodynamically favorable. To see thioesters (and phosphate anhydrides) as a form of metabolic energy is a big theme in biochemistry.

12. D

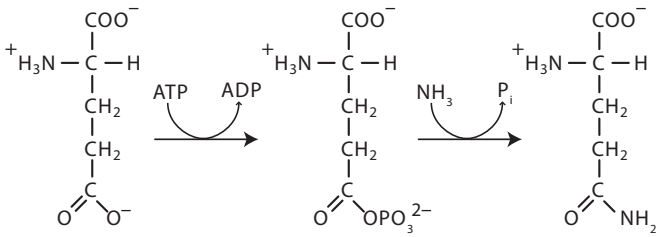
Assign oxidation numbers by deciding which atom has 'control' of the electrons in the bonds. Control goes to the more electronegative atom.

In redox accounting, the thioester carbon at the start has lost two electrons to the double bond to oxygen and an additional electron to sulfur, which is slightly more electronegative than carbon (2.6 vs. 2.5). Therefore, the oxidation state of the thioester carbon in HMG-CoA is +3. This is the univeral oxidation state of the carboxylic acid derivatives.

After the reaction, the carbon will now have one electron invested in a bond with oxygen while it gained two from the bonds to hydrogens, so carbon's oxidation state in mevalonate has become −1.

13. D

Both steps have a negative standard free energy change (ΔG°). Phosphorylation of glutamate is powered by ATP cleavage. The second step, aminolysis of phosphate anhydride, transforms a higher energy carboxylic acid derivative into a lower energy carboxylic acid derivative. This is one of the most basic functions of ATP, activating a carboxylate for nucleophilic acyl substitution by first transforming it into a phosphate anhydride.



14. A

After the reaction the ^{18}O label will be on the polypeptide. This type of question, which tests understanding of the nucleophilic acyl substitution mechanism, is a long-standing tradition with AAMC.