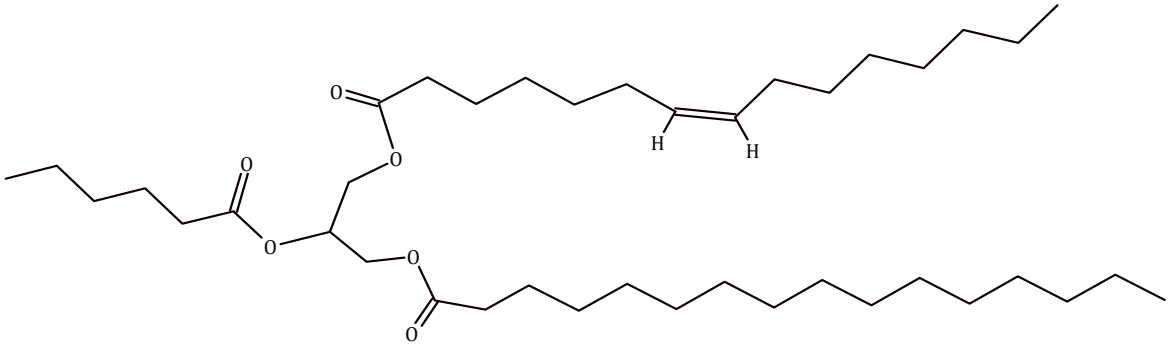
Chemistry 5.07
Problem Set 9 2013

1. The triacylglycerol drawn below acts as an energy source when administered by way of the diet to an organism. You may assume that it is delivered by chylomicrons to the target cell intact and that lipoprotein lipase fully hydrolyses the compound to its constituents, which are absorbed into the cell efficiently.



a. Showing your reasoning, calculate the maximum amount of ATP that could be generated by the full oxidation of the compound.

b. One of the arms has the same number of carbons as glucose. Compare the maximum yield of ATP achievable from full oxidation of that fatty acid, as compared to the ATP yield from glucose.

2. After adding the lipid in Problem 1 to a mammalian cellular extract, you note that the rate of evolution of CO_2 from glucose increases (note that I wrote "glucose"). You speculate that some kind of "catalyst" has been added to the system to cause this enhanced rate of CO_2 evolution.

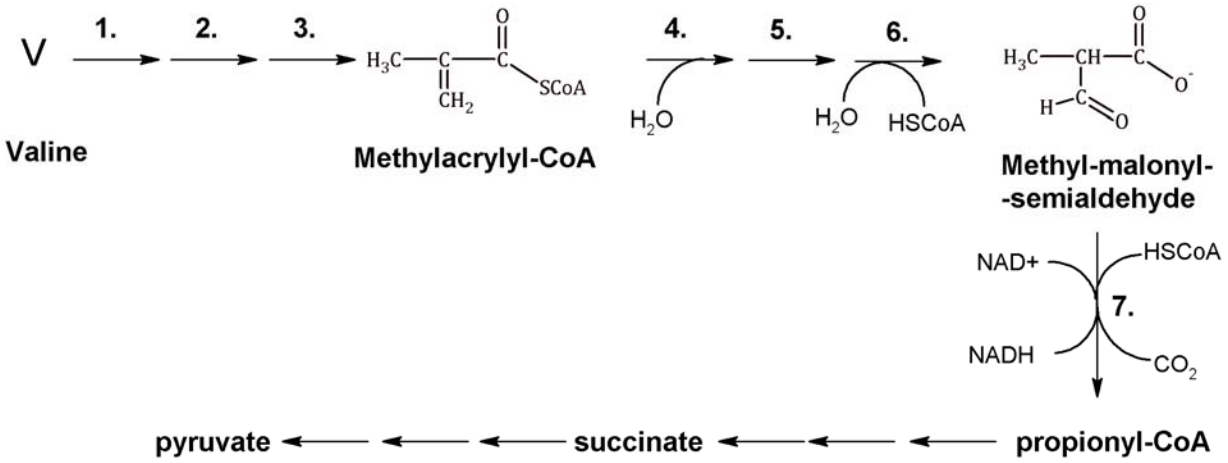
- A friend who aced 5.07 tells you that she thinks you can probe the effect by making one of the fatty acids in the lipid radioactive, putting the radioactive fatty acid into a metabolic extract and then looking over short intervals of time at the labeling pattern in TCA cycle intermediates. Show each molecule of the TCA cycle and its anticipated labeling pattern through one turn of the cycle. Note that you need to design the compound you need to test your hypothesis. Imagine that you have the capability to synthesize any part of the molecule in Problem 1 with a ^{14}C label exactly where you want to put it.

- Another friend suggests that you use Pfizer's biotin carboxylase inhibitor, which knocks out the "catalytic effect."

Put together a pathway showing how the lipid in Problem 1 causes the catalytic enhancement of the TCA cycle. Draw out the chemical reactions in reasonable detail along the way. Use all of the data in the bullet points above.

3. Amino acid catabolism is an important group of biochemical pathways that allows the use of amino acids as fuels. These pathways can convert any amino acids into intermediates of primary metabolism. These processes are very important in conditions of extreme starvation, when proteins are broken down into amino acids, which then can be metabolized to generate energy.

Degradation of branched chain amino acids occurs by reactions analogous to many of those you have seen in primary metabolism. The pathway for valine (one of the branched-chain amino acids) is sketched below.



a. The first step in degradation of almost any amino acids involves a transamination reaction. Indicate the cofactor required and write the mechanism.

b. Step 2 is the decarboxylation of an α-keto acid and involves a multienzyme complex that includes 3 proteins and 5 co-factors. This complex is very similar to the reaction discussed in class that connects glycolysis to the TCA cycle. Write a detailed mechanism for this transformation. Show the role of all cofactors.

c. Steps 3-5 are very similar to the steps in β-oxidation of fatty acids. Write the mechanism for these steps, indicating all cofactors required.

d. Step 6 hydrolyzes the SCoA group to generate methylmalonyl-semialdehyde. This compound is then oxidized and decarboxylated in step 7 by an enzyme called methylmalonyl-semialdehyde dehydrogenase (MSDH) to generate propionylCoA. MSDH has an active site cysteine and uses a mechanism similar to GAPDH. Propose a mechanism for this transformation.

e. To generate energy, propionyl-CoA is converted to pyruvate and fed into the TCA cycle. Write out the metabolic steps that accomplish this transformation. You do not need to show the mechanisms. Just draw each intermediate and indicate what cofactors are required.

f. Some of the steps in the conversion of propionylCoA to pyruvate take place outside the mitochondria. Indicate which ones and briefly explain why.

g. How much ATP can we generate by completely metabolizing valine to CO_2 ? (Assume each NADH generate gives 3 ATP, each $FADH_2$ gives 2 ATP).

h. Is valine a glucogenic or ketogenic amino acid? Briefly explain your answer.

i. If valine were ^{14}C labeled at both α and β positions, indicate the metabolic steps in which $^{14}CO_2$ will be released.

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