Lipid Metabolism

CHEM-643 Intermediary Metabolism
Written by Harold B. White

www1.cs.columbia.edu/~sedwards/photos/Bahamas

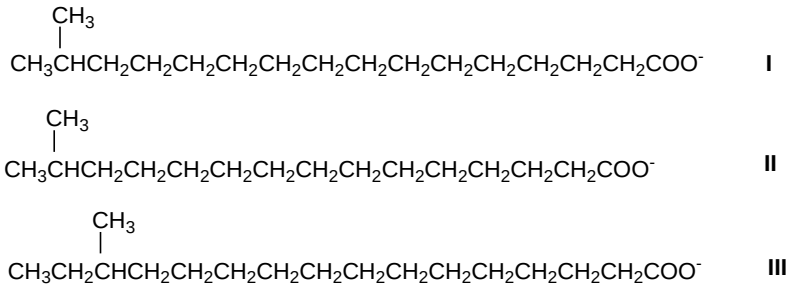
www.starberri.co.uk/assets/images/Eider.jpg

NOTE: It is **not** intended that you will have to go to the original research literature to answer the questions in this problem set. Literature citations are provided in case you wish to check your answers or need assistance. This assignment is meant for you to sharpen your ability to recognize molecular patterns and interpret them in terms of biosynthetic constraints. ***Consequently, it is important that you can demonstrate your understanding with meaningful structures***.

1. The waxes on the feathers of water birds are somewhat unusual (there are no commercial suppliers). When such birds are washed with detergents as was necessary after an oil spill on the nearby Delaware River, the natural waxes are removed along with the oil. It takes at least several days for the uropygial (preen) glands to replenish the natural waxes which are quite distinctive for each species. Hydrolysis of these waxes usually yields fatty acids containing methyl groups on even-numbered carbon atoms [Acct.Chem. Res. 4, 121 (1971)]. The dipper duck, for instance, produces two related waxes, n-hexadecyl 2,4,6-trimethyl nonanoate (76%) and n-octadecyl 2,4,6-trimethyl nonanoate (24%) [Chemica Scripta 8, 5 (1975)].

   Based on analogy with the synthesis of straight chain fatty acids, predict the biosynthesis pathway of 2,4,6-trimethyl nonanoate from simple precursors? Nonanoate contains nine carbon atoms. [Biochemistry 14, 1768 & 1774 (1975)].

2. Biological membranes maintain their liquid crystalline properties over a range of environmental temperatures. At lower temperatures there is an increase in the proportion of unsaturated fatty acids which have lower melting points. Rather than produce unsaturated fatty acids to keep their membranes "flexible," *Bacillus subtilus* achieves the same end by producing fatty acids with a single branch methyl group [Compounds **I**, Eur. J. Biochem. 12, 496 (1970), **II**, Biochemistry 10, 340 (1971), and **III**, J. Biol. Chem. 246, 5264 (1971)]

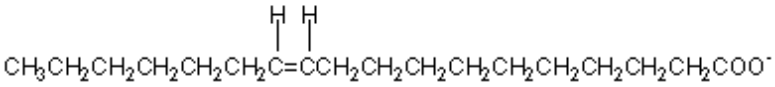


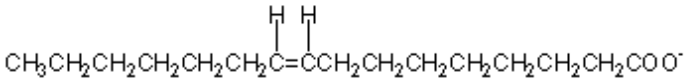
   What is the specific "initiator" molecule for each of these branched chain fatty acids in *B. subtilus*? (e.g. Acetyl CoA is the initiator of straight chain fatty acids). What common compounds are closely related to these unusual initiators? Show the structural similarity.

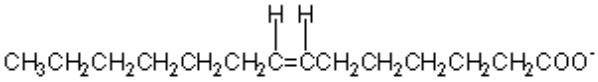
3. An in vitro system containing mitochondria and soluble cytoplasmic enzymes is capable of synthesizing fatty acids from 2-^{14}C-pyruvate. Fatty acid synthesis in this system can also be measured by the incorporation of ^{3}H from $^{3}H_2O$. It was observed that when unlabeled citrate was added to the system, the amount of ^{14}C-labeled fatty acid formed decreased while the amount of ^{3}H-fatty acid formed increased under the same conditions. **Explain.** [J. Biol. Chem 245, 5993 (1970)]. **Fatty acid synthetase is a cytoplasmic enzyme. Show which reactions and chemically how ^{3}H from water gets incorporated into fatty acids?**

4. Bacteria such as *E. coli* synthesize monounsaturated fatty acids via an anaerobic pathway while animals and yeast synthesize monounsaturated fatty acids via an aerobic pathway. Below are several unsaturated fatty acids isolated from *E. coli* and mammalian liver. **What can be concluded about the formation of the double bond in the two different pathways from structures given? What are the pathways in each case?**

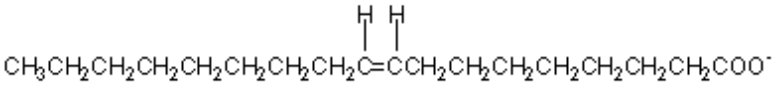
E. coli

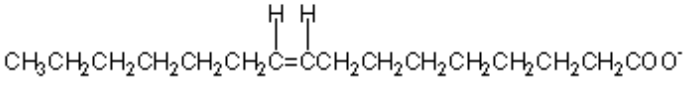

delta 11,12 $C_{18:1}$

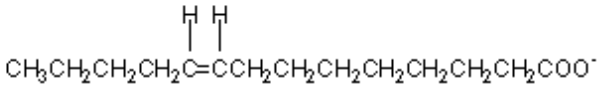

delta 9,10 $C_{16:1}$


delta 7,8 $C_{14:1}$

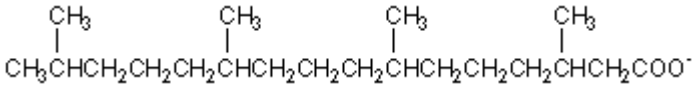
Mammalian liver


delta 9,10 $C_{18:1}$


delta 9,10 $C_{16:1}$


delta 9,10 $C_{14:1}$

5. Beta-oxidation of saturated fatty acids is an essential catabolic pathway in man. There are in addition several enzymes which permit the oxidation of $\Delta^{9,10}$ *cis* unsaturated fatty acids and branched chain fattyacids. Phytanic acid (derived from the phytol side chain of chlorophyll) cannot be metabolized in people with Refsum's disease [J. Inherit. Metab. Dis. 21, 697 (1998)]. It creates another degradative problem. It is thought that these people lack the capacity for α-oxidation. **Show why phytanic acid can't be degraded entirely by beta-oxidation. Show the pathway for the *complete* degradation of phytanic acids to CO_2 and H_2O in your body. Phytanic acid belongs to what class of compounds? (It is a branched-chain fatty acid, but that is not a class that would be biochemically informative given its structure below.)**



This assignment has several purposes:

1. To give you practice seeing patterns in structures that relate to the modular assembly of fatty acids.
2. To provide examples of the importance of lipid in different biological contexts.
3. To provide you with access to the primary literature on lipid metabolism.

This assignment will be evaluated on the following elements:

1. Clear and logical explanations.
2. Appropriate use of chemical structures to illustrate important points.
3. Turned in on time.

Revised 10/09/2009