

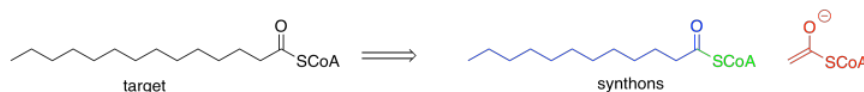
10.2: Transformations in Fatty Acid Synthesis

When we looked earlier at [the citric acid cycle](#), we saw that acetyl coenzyme A, or AcCoA, was a key link between that process and [glycolysis](#). This two-carbon remnant of glucose metabolism undergoes additional metabolic steps that harness energy in the form of ATP. But that's not the only purpose of AcCoA; it also serves as a building block for other compounds that are necessary for the survival of the cell or the organism.

Take myristic acid as an example, and think about how simple building blocks like AcCoA might be used to make it. AcCoA is a thioester, much like an ester but with a sulfur in place of one of the oxygen atoms. If we need to build myristic acid up from smaller pieces, we are going to need carbon-carbon bond-forming steps or *homologation* steps. You may not realise it, but there aren't an awful lot of those; their number just doesn't compare to the number of reactions that will simply switch out one heteroatom for another, such as an oxygen for a nitrogen. So, there may be a couple of choices, but not many.

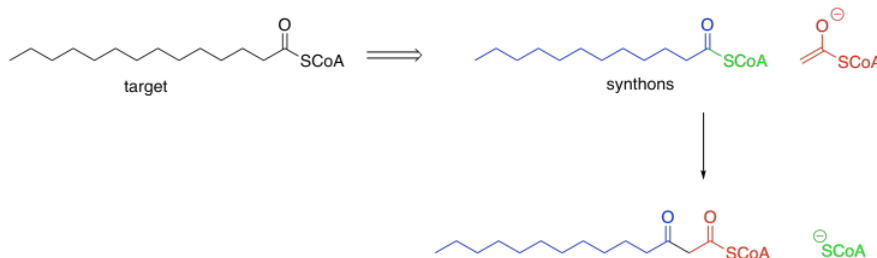
The obvious carbon-carbon bond-forming reaction to perform with an ester is a [Claisen condensation](#). In a Claisen condensation, the leaving group attached to the carbonyl is replaced by an enolate nucleophile. If the enolate nucleophile comes from AcCoA, then two more carbons will be added to the structure of the electrophile. So, if we were going to add two carbons to something in order to get myristic acid, it should be something with twelve carbons, like lauric acid.

Remember, the open arrow (below) means "comes from", so this picture means the target compound, myristic acid thioester, could come from the two synthons on the right.



This isn't exactly how it happens in the cell, but there are a couple of complications in the actual biosynthesis and we will work our way up to them.

Retrosynthetically, we could think of myristic acid (or the corresponding thioester, easily hydrolysed to give the free fatty acid) as potentially being made from two simpler synthetic precursors: lauric acid (or its thioester) and the enolate ion of AcCoA. The AcCoA would add another two carbons to the chain of the lauric acid, making a fourteen-carbon chain.



? Exercise 10.2.1

Show the product of a Claisen condensation between the enolate anion of acetyl CoA and another molecule of acetyl CoA.

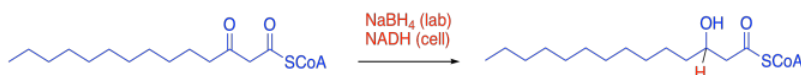
Answer



Where would the lauric acid come from? We will need to look further into that question, but you may already have thought of another problem that we need to solve, first: Although a Claisen condensation of lauric acid thioester and AcCoA enolate would result in a two-carbon chain extension, it would also bring an unwanted oxygen into the structure. There is a missing link between this structure and myristic acid. That oxygen needs to be replaced by a pair of hydrogens.



We can certainly get started by replacing one of the C=O bonds with a C-H bond. That should bring to mind a familiar [carbonyl reaction](#). In the lab, we could use a hydride reagent, such as sodium borohydride (although we would have to worry about whether that thioester might react, too). In the cell, the equivalent reagent would be another hydride donor such as [NADH](#).



That gets us part of the way there. How do we get rid of the other bond to oxygen? How do we add a second hydrogen? The first question might be answered by thinking about something else that might be familiar: [an aldol addition](#). The reason that might be relevant is that the compound now contains a beta-hydroxy carbonyl. We see something similar in an aldol addition. Aldol additions frequently result in beta-hydroxy carbonyl units. However, they sometimes proceed through a subsequent elimination reaction, the loss of water to give an enone ("een-own"). That variation is sometimes called an aldol condensation to distinguish the two outcomes, although the two terms are used loosely.



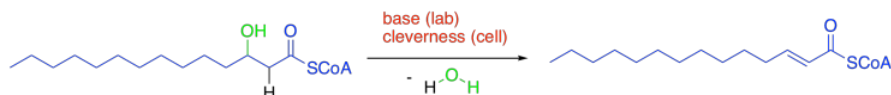
? Exercise 10.2.2

What is the driving force for the dehydration reaction (loss of water) after the initial aldol addition?

Answer

The product becomes conjugated. In general, the more conjugation there is in the product of an aldol addition, the more likely is a subsequent condensation (elimination or dehydration). However, other conditions can lead to the loss of water.

In laboratory chemistry, that condensation often results in the presence of strong base and high heat -- conditions that might be a little hard on a cell. We'll find that the reaction conditions are much milder in the cell.



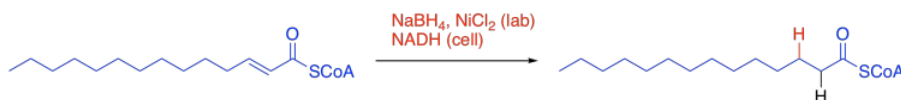
? Exercise 10.2.3

What thermodynamic factor leads increased heat to promote the dehydration reaction?

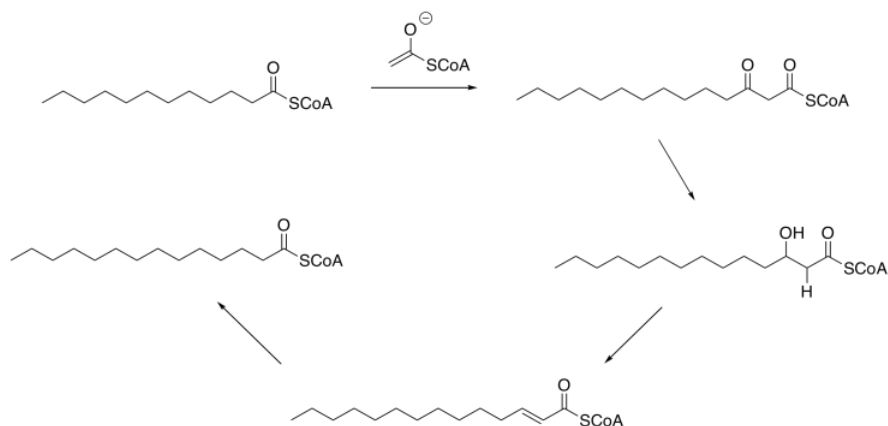
Answer

Entropy. The dehydration or elimination takes one molecule (the beta-hydroxy thioester) and converts it into two molecules (the water and the alpha,beta-unsaturated thioester). That change represents an increase in internal entropy. Because the entropy term in free energy is weighted by temperature ($\Delta G = \Delta H - T\Delta S$), it predominates as the temperature rises.

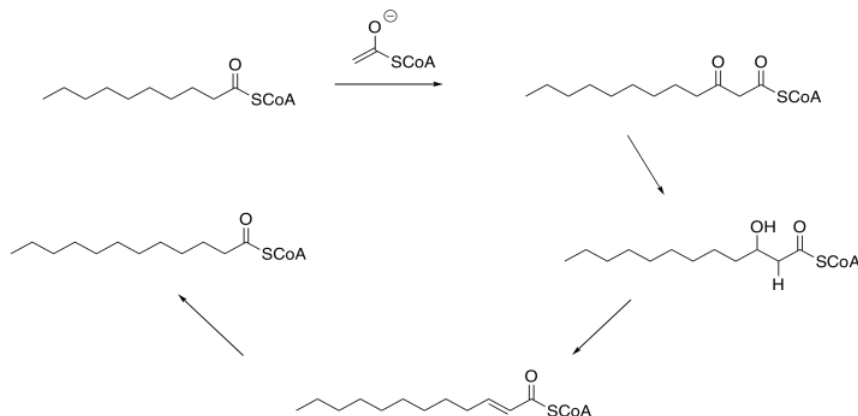
Now the problem of replacing that extra oxygen with two hydrogens is almost solved. The first hydrogen was added as a hydride, and that would work for the second one, too. This time, we need a 1,4-addition rather than a regular 1,2-addition. In the lab, that might be helped by adding a Lewis acid under the right conditions. In the cell, it might be aided by positioning of the hydride reducing agent in the right place in the enzyme, so that it delivers the hydride to the right place.



If we put all of those steps together, we can get from lauric acid thioester to myristic acid thioester in just a few steps.



Hold onto that thought, because we can use it again to make lauric acid from one that is two carbons shorter. In fact, we can keep repeating this cycle over and over until we work our way back to acetyl coenzyme A. Two molecules of AcCoA, one acting as the electrophile and the other as the enolate, could be used to make a four-carbon thioester. Adding another AcCoA would make a six-carbon thioester, and so on.



This dependence on a two-carbon building block is the reason for the vast preponderance of even-numbered carbon chains in natural fatty acids.

Next, we will take a look at how the cell actually shepherds these molecules through these kinds of reactions.

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