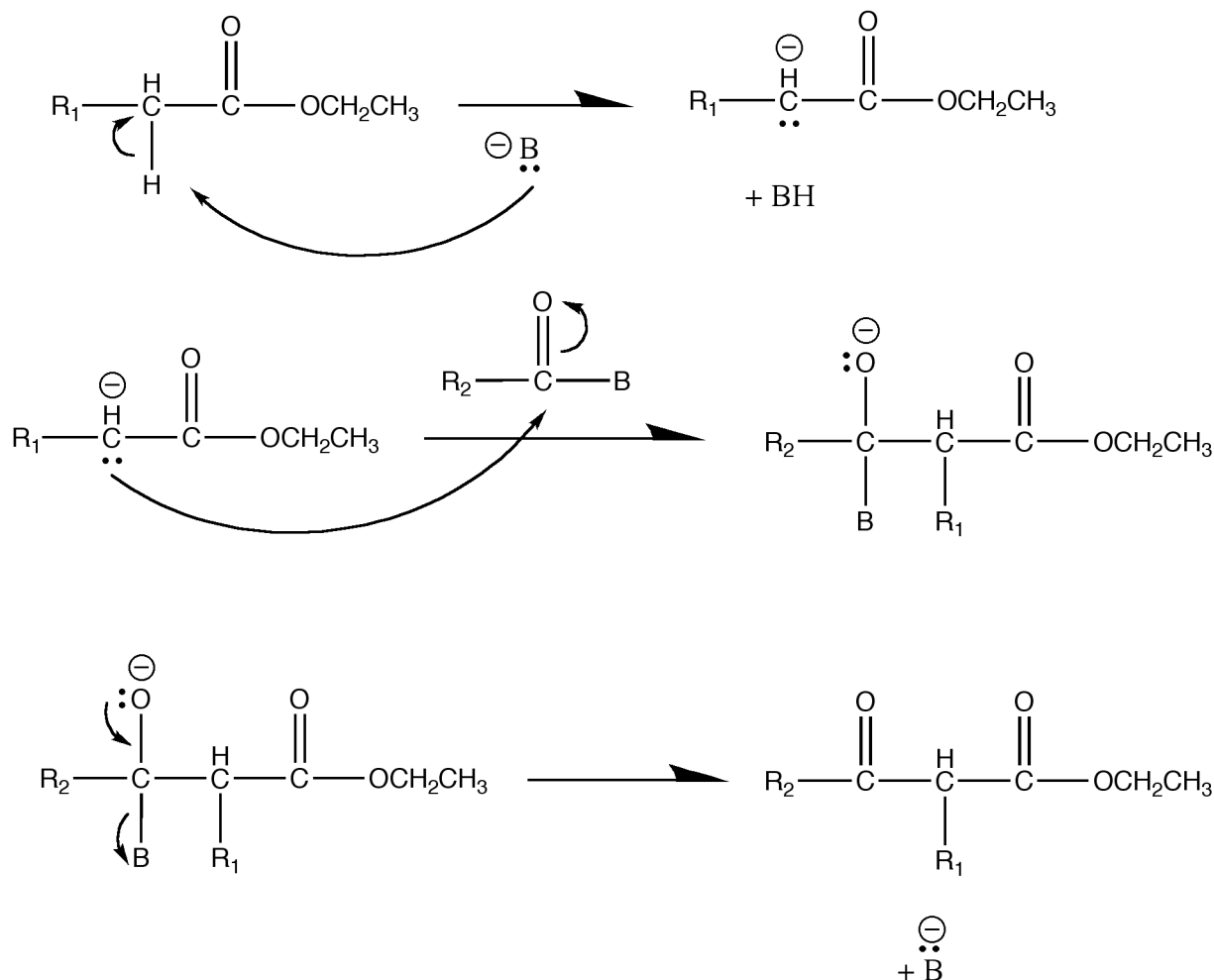


Exercise 3: The Claisen condensation-related mechanisms of lipids

1. As mentioned in the text on page 689, the thiolase reaction, which is the fourth step in the β -oxidation of a fatty acid, is a Claisen ester cleavage, which is “the reverse of a Claisen condensation”. Let’s test the text’s assertion.

Here is the Claisen condensation mechanism (B = any base of the form $-OR$):



In the fourth step of the β -oxidation of a fatty acid, a β -ketoacyl-CoA molecule is cleaved (with the aid of a CoA-SH) into a fatty acyl-CoA and an acetyl-CoA. Assuming that the initial β -ketoacyl-CoA is of the form:

$R-C(=O)-CH_2-C(=O)-SCoA$, show the mechanism of the fourth step that is consistent with the text’s assertion. Hint: figure 20-14 on the same page might be helpful; you may use notation for the enzyme’s structure like the text does (i.e., with an “S” and a “BH”).

2. On page 699 of the text, the formation of ketone bodies, specifically acetoacetate, involve some of these same mechanisms.

a. In the first step of acetoacetate formation, “two molecules of acetyl-CoA are condensed to acetoacetyl-CoA by thiolase...working in the reverse direction from the way it does in the final step of β -oxidation [which is the fourth step seen in question 1].” Propose a mechanism for this reaction; as in the last question, use a truncated enzyme structure notation. Is this similar to a Claisen condensation, a Claisen ester cleavage or neither?

b. In the second step of acetoacetate formation, “condensation of the acetoacetyl-CoA with a third acetyl-CoA by HMG-CoA synthase forms β -hydroxy- β -methylglutaryl-CoA (HMG-CoA). The mechanism of this reaction resembles the reverse of the thiolase reaction...” You do not need to propose a mechanism for this reaction, but is this reaction similar to a Claisen condensation, a Claisen ester cleavage or neither? Note: I am not having you propose a mechanism here because this is the reaction where the “mystery oxygen” from lecture shows up!

c. In the third step of acetoacetate formation, “HMG-CoA is degraded to acetoacetate and acetyl-CoA in a mixed aldol-Claisen ester cleavage by HMG-CoA lyase.” Propose a mechanism for this reaction. Why is this called a “mixed” mechanism? Hint: You may wish to look up “aldol additions” in an organic chemistry textbook.