Decarboxylation refers to the loss of carbon dioxide from a molecule. This event generally happens upon heating certain carboxylic acids. It can't be just any compound; most commonly, there must be a carbonyl group β- to the carboxylic acid functional group.

The presence of the second carbonyl in that position is crucial in stabilizing the transition state of the reaction. If we try to follow the reaction using curved arrows, we can see something similar to what we have already observed in pericyclic reactions such as the Cope rearrangement. Three pairs of electrons in a six-membered ring are responsible for the reaction.

The loss of carbon dioxide from β-keto acids and esters is a key event in some important processes. Some typical synthetic methods include the acetoacetic ester synthesis and the malonic ester synthesis. These are two methods of α-alkylation. In these approaches, the presence of a carbonyl β- to a second carbonyl makes it much easier to remove the α-proton in between. That means simple bases such as sodium ethoxide are good enough to remove the proton efficiently and allow an alkylation reaction. However, once it is no longer needed for this activating effect, one of the ester groups can then be removed via decarboxylation.

The Knoevenagel reaction is a third, related example of a synthetic transformation that relies on decarboxylation. It differs from the other two in that it involves a carbonyl condensation rather than an alkylation. Once again, the reaction is followed by decarboxylation.
Decarboxylations are also common in biochemistry. For example, loss of CO$_2$ from isocitrate provides α-ketoglutarate. This step is one of several exergonic events in the citric acid cycle.

![Chemical structure of isocitrate and α-ketoglutarate](image)

Exercise (PageIndex{1})

Provide a mechanism for the conversion of isocitrate to α-ketoglutarate.

Many reactions in biochemistry involve decarboxylations, even without a stabilizing group in the β-position. For example, in the entry point to the citric acid cycle, pyruvate is decarboxylated during the formation of acetyl coenzyme A.

![Chemical structure of pyruvate and acetyl coenzyme A](image)

However, a closer look at the mechanistic pathways of these reactions reveals there is something more going on. Intermediate steps involve the introduction of these stabilizing groups, which are later removed again. In the case of pyruvate decarboxylation, the compound must be activated by the addition of a thiamine ylide. The iminium group in the resulting intermediate plays the same role as that of the β-keto group in the decarboxylations we have already seen.

![Mechanistic pathways of pyruvate decarboxylation](image)

Subsequent steps result in the loss of the thiamine group and its replacement with a thioester linkage.

Exercise (PageIndex{2})

Provide products for each of the following reactions.
Exercise \PageIndex{3})

Carbonyls are not the only groups that can promote decarboxylation. Provide a mechanism for each of the following reactions.
Exercise 4

Provide a mechanism for the Carroll Reaction, which involves the initial formation of an enol intermediate.
Answer

Attribution

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