

4.10: Reactions with cyclic transition state

Learning Objectives

- Learn examples of reactions that involve five- or six-member transition state, including cyclonic hemiacetal formation of monosaccharides, Diels-Alder reactions producing six-membered cyclic products, and decarboxylation of β -keto acids.

Intramolecular reactions happen if the two reacting groups are on the same molecule and can come to a bonding distance through a five- or six-member cyclic transition state. Some examples of it are described in the next sections.

Cyclic hemiacetal formation of monosaccharides

Monosaccharides, like glucose, fructose, galactose, etc., have a $C=O$ -group on one C and $-OH$ -group on every other C. $-OH$ -group can add to $C=O$ -group forming a hemiacetal. Monosaccharides exist primarily in a five- or six-membered hemiacetal form because one of their $-OH$ -group can form a five- or six-membered transition state for the reaction, as shown in Figure 4.10.1 for the case of D-glucose and D-fructose.

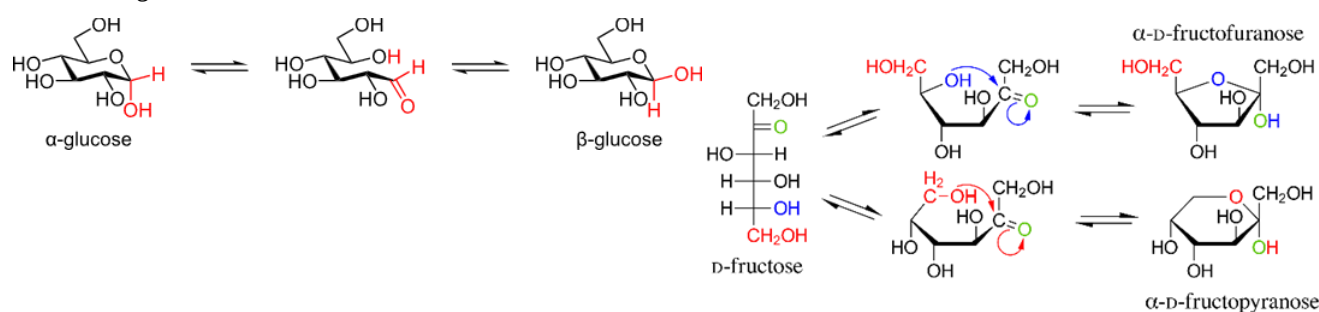


Figure 4.10.1: Illustration of five- or six-member cyclic hemiacetal formation of D-glucose and D-fructose through a cyclic transition state. (Copyright; Glucose: Calvero (talk · contribs), Public domain, via Wikimedia Commons, and Fructose: Vaccinationist, Public domain, via Wikimedia Commons)

Diels-Alder reaction

A conjugated diene, e.g., butadiene, and an alkene, e.g., ethene, make a cyclic six-member transition state. They react by the Diels-Alder reaction mechanism and produce a six-member cyclic product. This reaction can be intermolecular, e.g., between butadiene and then, or intramolecular, e.g., in the biosynthesis of antibiotic lovastatin, illustrated in Figure 4.10.2

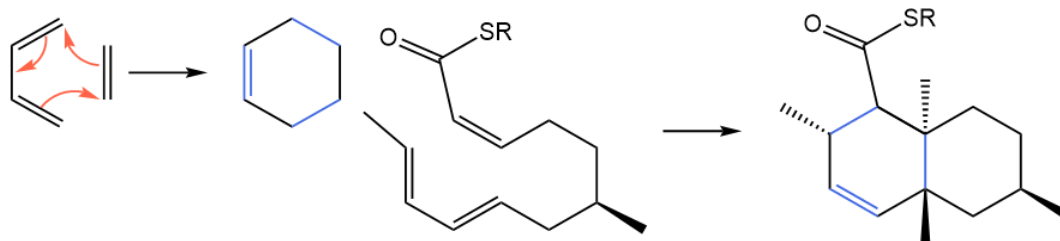
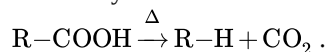


Figure 4.10.2: Mechanism of Diels-Alder reaction illustrated with the example of reaction between butadiene and ethene (left) and biosynthesis of lovastatin (right). Three π -bonds break, and two σ -bonds and one π -bond form, shown in blue. (Copyright: Public domain)

Decarboxylation

Decarboxylation is the removal of carbon dioxide (CO_2) from a carboxylic acid ($R-COOH$), as in this example:



This reaction requires high temperatures, such as in the thermal decomposition process. However, if there is a second carbonyl ($C=O$) group β to the $-COOH$ group, it can easily acquire a six-member transition state and decarboxylate at moderate temperatures, as illustrated in Figure 4.10.3

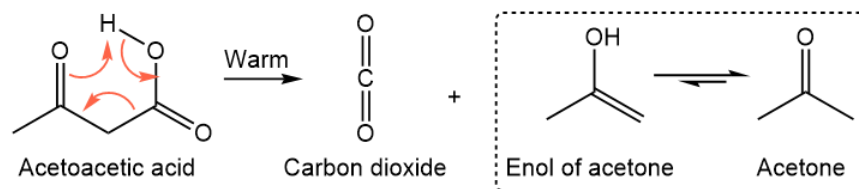
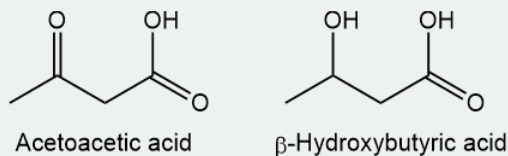


Figure 4.10.3: Decarboxylation mechanism of β -keto carboxylic acids illustrated with the example decarboxylation of acetoacetic acid. (Copyright: Public domain).

📌 Ketone bodies and diabetes mellitus

Acetoacetic acid and its reduced product β -hydroxybutyric acid, shown below, are produced in the liver as a result of the metabolism of fatty acids and some amino acids.



Acetoacetic acid and β -hydroxybutyric acid are called **ketone bodies**. Their concentration in the blood of healthy persons is about 0.01 mmol/L but in persons suffering from starvation or diabetes mellitus may be up to 500 times higher.

Carboxylic acids exist as carboxylate anions under physiological conditions. Decarboxylation of the β -keto carboxylates happens spontaneously under physiological conditions. For example, acetoacetate decarboxylates and produces carbon dioxide and acetone, as illustrated in Figure 4.10.4

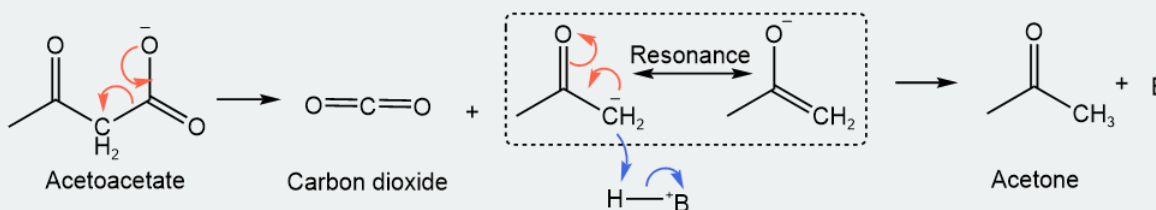


Figure 4.10.4: Illustration of decarboxylation mechanism with the example of acetoacetate converting into carbon dioxide and acetone. (Copyright: Public domain)

Carbon dioxide leaves under moderate conditions in this case because the anion left behind is in resonance with the β -C=O group. The body does not metabolize acetone but exhales through the lungs. Acetone is responsible for its characteristic sweet smell in the breath of people with severe diabetes.

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