Objectives

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid-catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base-catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

Study Notes

Keto-enol tautomerism was first introduced in Section 9.4, in the discussion of the hydration of alkynes. The subject was raised again in the chapter entitled A Preview of Carbonyl Compounds, during the brief overview of the alpha-substitution reactions of carbonyl compounds. You may wish to review these sections before proceeding.

Often, the position of carbon atoms near a carbonyl group are designated by Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α Hydrogens are bonded to α carbons and β hydrogens are bonded to β carbons etc.

The presence of α hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and Chapter 23. Because of this, the ability to identify α hydrogens is an important skill. As shown below, pentanal has two α hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are referred to simply as an aldehyde hydrogen.
Indicate any α hydrogens contained in the following molecules:

Solution

4 α-Hydrogens          0 α-Hydrogens

4 α-Hydrogens          6 α-Hydrogens
α hydrogens, which are directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the stabilizing C=O is seen when comparing the pKₐ for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

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Keto-enol Tautomerization

Because of the acidity of α hydrogens, many carbonyl containing molecules undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms they are distinctly different than resonance forms, which only differ in the position of pi bonds and lone pair electrons. This discussion will focus on carbonyl group with alpha hydrogen, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group.

The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.99% keto tautomer). The keto tautomer is preferred because it is usually more stable the the enol tautomer by about 45–60 kJ/mol, mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611 kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. Propanal is 1000 times more likely to be in its enol tautomer than acetone.
Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones have two or more. The preferred enol tautomer form can be predicted by considering effects which stabilize alkenes, such as conjugation and alkyl group substitution.
1,3-Dicarbonyls

In certain cases additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 2,4-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.

Another effect which can stabilize an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.

Mechanism for Catalyzed Keto-Enol Tautomerization

The enol tautomer has valuable nucleophilic characteristics. In neutral media, tautomerization is slow but it can be speed up by catalysis with acids or bases. Both pathways involve two separate proton transfer steps. Because enols are a key reactive intermediate, these mechanistic steps will be used repeatedly in later reactions. The following mechanistic steps represent the continuous interconversion between the keto and enol tautomers.
Overall Process

Acidic Conditions

Keto Tautomer → Enol Tautomer

In the first step, the carbonyl oxygen is protonated by an acid to form an intermediate oxonium compound. A base removes an α-hydrogen during the second step forming a double bond by an E2 type reaction. This causes the pi electrons of the protonated cabonyl to move to the oxygen forming the hydroxyl group of the enol product and regenerating the acid catalyst.

1) Protonation of the carbonyl to form an oxonium compound

2) Deprotonation of an α hydrogen to form an enol

Enol Tautomer → Keto Tautomer

First, pi bond electrons from the carbon in the alpha position attack the electrophilic H⁺ provided by acid catalyst causing one of the lone pairs of electrons on the oxygen to form a pi bond to carbon generating a carbonyl. This produces an oxonium intermediate with is subsequently deprotonated to form the neutral ketone and regenerates the acid catalyst.

1) Protonation at the alpha carbon
Under Basic Conditions

**Keto Tautomer → Enol Tautomer**

In the first step, a base removes an α hydrogen to form an alkene by an E2 type process. This causes the π electrons of the carbonyl to move onto the oxygen forming an enolate anion. The oxygen of the enolate anion is protonated in the second step to create a neutral enol and regenerate the base catalyst.

1) **Deprotonation** α to the carbonyl to form an enolate ion

2) **Protonation** the enolate ion to form an enol

**Enol Tautomer → Keto Tautomer**

The mechanistic return to the keto tautomer begins with deprotonnation of the hydroxyl hydrogen producing an enolate. Then lone pair electrons from the enolate anion attack an electrophilic $H^+$ through conjugation with the double
bond. This simultaneously forms the carbonyl double bond, adds an alpha hydrogen, and regenerates the base catalyst.

1)  

\[
\begin{align*}
\text{Enolate} & \quad \text{Enol Tautomer} \\
\text{Keto Tautomer} & \quad + \quad \text{H} - \text{B}
\end{align*}
\]

2)  

\[
\begin{align*}
\text{Enolate} & \quad \text{Enol Tautomer} \\
\text{Keto Tautomer} & \quad + \quad \text{H} - \text{B}
\end{align*}
\]

**Biological Enol Forming Reactions**

**Carbonyl Isomerization**

One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose in a process called carbonyl isomerization (recall that the terms ketose and aldose refer to sugar molecules containing ketone and aldehyde groups, respectively).

\[
\begin{align*}
\text{ketose} & \quad \text{aldose}
\end{align*}
\]

**Mechanism**

Carbonyl isomerization can only occur if there is an OH group adjacent to the carbonyl. This forms an ene-diol intermediate which has both OH hydrogens available to be removed to reform the carbonyl. If the hydrogen from the original OH group is removed a new carbonyl bond is formed.
Carbonyl isomerization is involved in the metabolism of carbohydrates (starches and sugars) to their eventual conversion to CO₂ and H₂O. First, starches are broken down into glucose in the digestive tract. In the cells, the first step of the glycolysis pathway involves an enzyme converting glucose to glucose-6-phosphate. This is followed by the enzyme-catalyzed tautomerization of glucose-6-phosphate (an aldose) to fructose-6-phosphate (a ketose) through an enediol intermediate. Notice how the carbonyl has moved from the 1-carbon (terminal) to the 2-carbon.

Exercises

1) Draw the enol forms of the following molecules
   a. 4-methylcyclohexanone
   b. Ethyl thioacetate
   c. Methyl acetate
   d. Butanal
   e. 1-phenyl-2-butanone

2) How many α hydrogens do each of the molecules from the previous question have? Label them.

3) Draw all of the monoenol forms for the following molecule. Which ones are most stable? Why?
4) Under normal conditions cyclohexanone exists in the enol tautomer in a much higher percentage than acetone. Explain.

**Solutions**

1)

(a)

(b)

(c)

(d)

(e)
3) Additional resonance forms stabilizes this enol.

This enol has fewer resonance forms and is therefore less stable.

4) The enol tautomer of cyclohexanone has more alky substituents than the enol tautomer of acetone. This makes the double bond of the enol double bond of cyclohexanone more stable and easier to form.

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