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Principal Investigator		Co- Principal Investigator and Technical Coordinator
Prof A.K.Bakhshi Sir Shankar Lal Professor, Department of Chemistry University of Delhi		**Dr Vimal Rarh** Deputy Director, Centre for e-Learning and Assistant Professor, Department of Chemistry, SGTB Khalsa College, University of Delhi *Specialised in : e-Learning and Educational Technologies*
Paper Coordinator	**Content Writer**	**Reviewer**
Prof. J M Khurana Professor Department of Chemistry University of Delhi	**Dr. Vimal Rarh** Assistant Professor Department of Chemistry, SGTB Khalsa College, University of Delhi **Dr. Kanika Malik** Department of Chemistry University of Delhi	**Dr. V K Sharma** Associate Professor Department of Chemistry Hindu College University of Delhi
Anchor Institute : SGTB Khalsa College, University of Delhi		

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1. Learning Outcomes

After studying this module you shall be able to:

- Know about tautomerism and its causes.
- Learn about acidic protons being the root cause of tautomerism and other facets of the same.
- Understand details of keto-enol tautomerism and evidences in favour for it.
- Know what factors affect the different forms of tautomers.
- Learn about some modern theories of tautomerism with suitable examples.

2. Introduction

Tautomers are isomers of a compound, which differ only in the position of the protons and electrons. The carbon skeleton of the compound is unchanged but functional groups are different. A reaction which involves simple proton transfer in an intramolecular fashion is called a tautomerism. Keto-enol tautomerism is a very common process, and is acid or base catalysed. Typically the 'keto' form of the compound is more stable, but in some instances the 'enol' form can be the more stable.

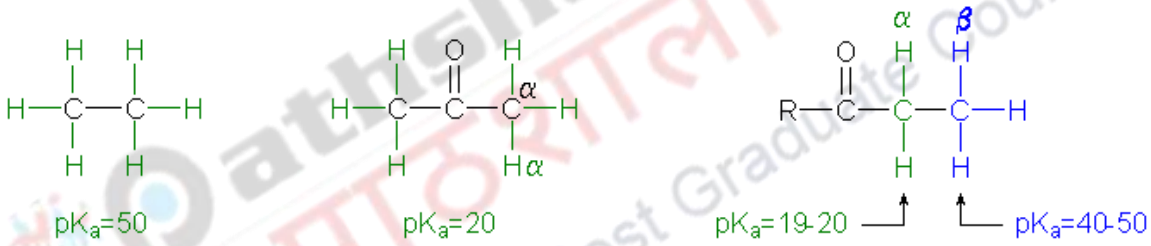
There are many types of tautomerism. Let us try to understand tautomerism with the help of keto-enol tautomerism and later extend to other types. It is also important to understand the acidity of alpha hydrogen atoms to understand why tautomerism takes place.

a.) Cause of Tautomerism: Acidity of alpha hydrogens

Aldehydes and ketones are weak acids and have abnormally low pKa values (between 15 and 20). Therefore, they can behave as a Bronsted acid in an acid-base reaction with a strong base.

But, aldehydes and ketones are much stronger acids than alkanes.

As there is hardly any electronegativity difference between hydrogen and carbon, C-H bonds in alkanes are almost not polarized. Therefore, hydrogens in alkanes are not acidic. The values of pKa of alkanes are nearly 50.



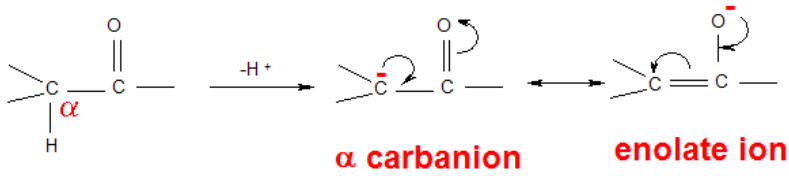
But the α-hydrogens of aldehydes and ketones are quite acidic as compared to the hydrogens of alkanes. The acidity of α -hydrogens of aldehydes and ketones is although much less than carboxylic acids, which have pK_a values around 3 to 4.

b.) Reasons for acidity

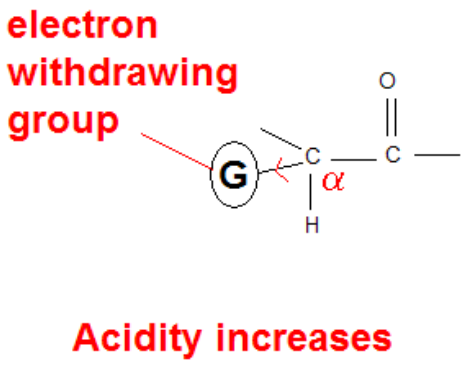
The α- hydrogen of carbonyl compounds is acidic, as it is connected with the α-carbon that is directly bound to the electron withdrawing carbonyl group. The high acidity of carbonyl compounds as compared to alkanes can be explained by the resonance stabilization of the conjugate base by the carbonyl group, or in other words anion's stabilization by deprotonation. The anion is known as enolate anion.

Due to resonance, the negative charge is mostly dispersed between the α-carbon and the carbonyl oxygen, by resonance, which leads to the stabilization of the otherwise highly energized carbanion.

The negative charge and the nucleophilic qualities are hence distributed at the carbon (in carbanion) and at the oxygen (in enolate anion). As a result, the α-carbon and the carbonyl oxygen are the two nucleophilic and basic centres of enolate anions.

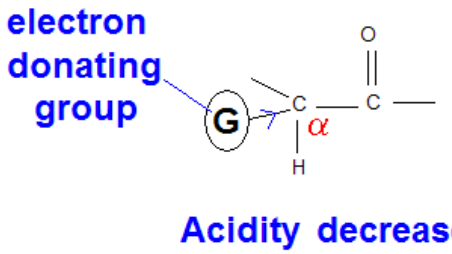


Variation of acidity: The acidities of these α-hydrogen atoms is enhanced if an electron withdrawing group is attached to the α-carbon atom.



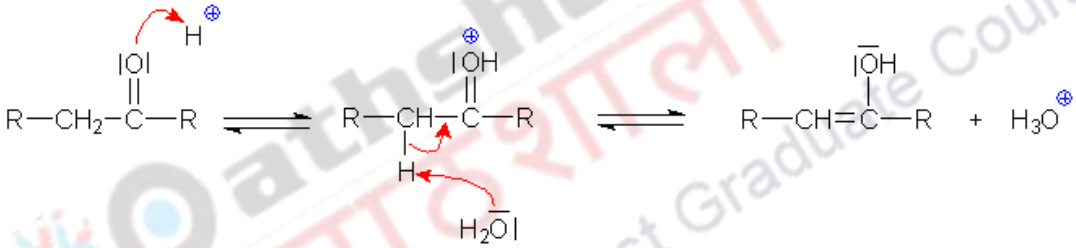
Acidity increases

On the other hand, the acidity of the α-hydrogen atoms decreases if an electro-donating group is attached to the α□carbon atom.



3. Keto-enol tautomerism Types

The keto form and enolic form are in equilibrium called as **keto-enol tautomerism**.



The establishment of equilibrium may be catalyzed by both acids and bases. Through suitable means, such as by fractional crystallization or careful distillation in the absence of any acid and any base, the keto and the enolic form may be separated from each other. The keto and enolic form of a carbonyl compound are constitutional isomers.

The separation should take place in the absence of all acids and bases, as the equilibrium reaction would otherwise proceed too rapidly. Therefore, the separated, pure keto and enolic form would immediately be "contaminated" at least to some degree by the other form again.

a.) Equilibrium Position in keto-enol Tautomerism

The position of the keto-enol equilibrium is influenced by the temperature and the solvent (if present). In simple aldehydes and ketones, the keto form usually exceeds the enolic form to a considerable degree.

For example, acetone contains only 1.5×10^{-4} % of the enolic form.

Ketones are usually not enolized to such a degree as aldehydes are. However, **β-dicarbonyl compounds** are significantly much more enolized, as the double bond of a monoenolized β-dicarbonyl compound is additionally stabilized through resonance with the second carbonyl group. As a result, the α- hydrogen between the two carbonyl groups of β-dicarbonyl compounds is much more acidic.

On the other extreme, the classic example of a compound that is virtually completely enolized is phenol. The equilibrium constant of keto-enol tautomerism equilibrium of phenol amounts to roughly 10^{10}. It follows that the enolic form of phenol predominates to over 99.99 %. The enolic form of phenol (aromatic) is much more stable than the non-aromatic keto form (cyclohexadienone) due to the strikingly high resonance stabilization of the aromatic system.

Also, phenol's enolate is much more stable than non-aromatic enolates are, as its negative charge is stabilized through resonance with the aromatic system. As a result, phenol is considerably more acidic than other enols or alcohols. The pK_a value of is 9.95.

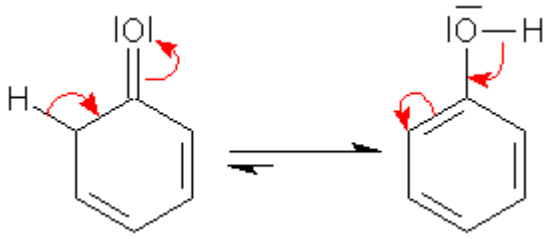
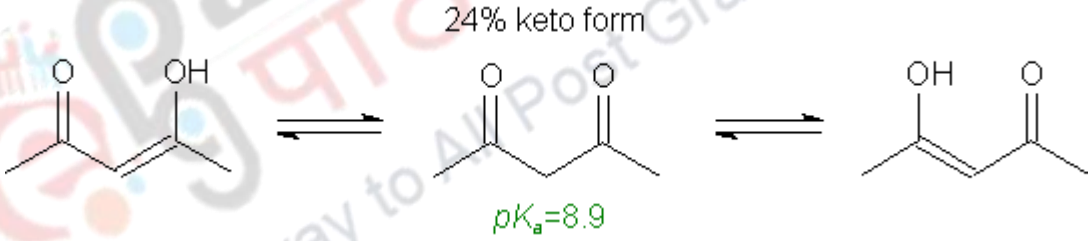


Fig: keto and enol form of phenol

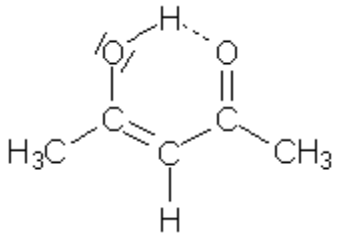
b.) Acidity of β-dicarbonyl compounds

The acidity of β-dicarbonyl compounds is considerably higher than that of monocarbonyl compounds and other dicarbonyl compounds. In keto-enol equilibrium of β-dicarbonyl compounds, the (mono)enolic form usually exceeds the keto form.

For example, 2,4-Pentadione consists of about 76 % enolic form.



The reason for this is the noticeably higher stabilization of the enol in comparison to other carbonyl compounds. On the one hand, a β-dicarbonyl compound's enol is additionally stabilized through resonance of the enol's carbon-carbon double bond with the second carbonyl group. On the other hand, the enol's hydroxyl hydrogen is connected to the carbonyl oxygen by an intramolecular **hydrogen bond**. The formation of this hydrogen bond is further facilitated by the six membered planar structure of the enol-carbonyl resonance system.



c.) **Keto-enol tautomerism of ethyl acetoacetate**

Acetic ester or **ethyl acetoacetate** is the ethyl ester of acetoacetic acid $CH_3 \cdot CO \cdot CH_2 \cdot CO_2H$, a β-ketonic acid.

Acetoacetic ester was first discovered by **Geuther** (1863), who prepared it by the action of sodium on ethyl acetate, and gave the formula as $CH_3 \cdot C(OH) : CH \cdot CO_2C_2H_5$ (β-hydroxycrotonic ester).

In 1865, **Frankland and Duppa**, also prepared acetoacetic ester by the action of sodium on ethyl acetate,but they proposed a different formula $CH_3 \cdot CO \cdot CH_2 \cdot CO_2C_2H_5$ (β-ketobutyric ester).

a.) Which of these is correct?

Evidence in favour of the Geuther formula (*reactions of an unsaturated alcohol*),
(i) When acetoacetic ester is treated **with sodium**, hydrogen is evolved and the sodium derivative is formed. This showed the presence of a hydroxyl group.

(ii) When acetoacetic ester is treated with an ethanolic solution of **bromine,** it readily decolourises. This indicates the presence of an olefinic double bond.

(iii) When acetoacetic ester is treated with **ferric chloride**, a reddish-violet colour is produced. This is characteristic of compounds containing the enolic group (-C(OH)=C<) like phenols.

Evidence in favour of the Frankland-Duppa formula (*reactions of a ketone*).
(i) With **sodium hydrogen sulphite,** acetoacetic ester forms a bisulphate derivative.

(ii) With **hydrogen cyanide**, acetoacetic ester forms a cyanohydrin.

Thus, evidence for both the structure were there. The controversy continued until about 1910, when chemists came to the conclusion that both formula were correct, and that the two compounds existed together in equilibrium in solution (or in the liquid state):

$$CH_3 \cdot CO \cdot CH_2 \cdot CO_2C_2H_5 \rightleftharpoons CH_3 \cdot \overset{\overset{OH}{|}}{C} = CH \cdot CO_2C_2H_5$$

When a reagent which reacts with ketones is added to acetoacetic ester, the ketone form is removed. This upsets the equilibrium, and in order to restore the equilibrium mixture, the hydroxyl form of acetoacetic ester changes into the ketone form. Thus provided insufficient reagent is added, acetoacetic ester reacts completely as the ketone form.

Similarly, when a reagent which reacts with olefins or with hydroxy-compounds is added in sufficient quantity, acetoacetic ester reacts completely as the hydroxyl form.

Knorr(1911) succeeded in isolating both forms.

1. Ketone form:

On cooling a solution of acetoacetic ester in light petrol to –78°, he obtained crystals which melted at –39°. This substance gave no coloration with ferric chloride and did not combine with bromine, and was therefore, the pure ketone form corresponding to the Frankland-Duppa formula.

2. Hydroxyl form:

By suspending the sodium derivative of acetoacetic ester in light petrol cooled to –78°C, and treating this suspension with just enough HCl to decompose the sodium salt, he obtained a glassy solid when cooled. This substance gave an intense coloration with ferric chloride, and was therefore the pure hydroxyl form corresponding to the Geuther formula.

Thus acetoacetic ester is a substance that does the duty of two structural isomers, each isomer being capable of changing rapidly into the other when the equilibrium is distributed, e.g., by the addition of certain reagents.

This is a case of ***dynamic isomerism,*** and the name ***tautomersim*** (Greek: *same parts*) was given to this phenomenon by Laar (1885).

The two forms are known as *tautomers* or *tautomerides*, the phenomenon being called the ***keto-enol* tautomerism**.

Note that the term "*enol"* is a combination of *-en* for double bond and *-ol* for hydroxyl.

4. Stability of Tautomers

When one tautomer is more stable than the other under ordinary conditions, the former is known as the stable form, and the latter as the labile form.

It is generally difficult to say which is the labile form, since very often a slight change in the conditions, e.g., temperature, solvent, shifts the equilibrium from keto to enol or vice versa.

Tautomerism in the **solid state** is rare, and hence, in the solid state, one or other tautomer is normally stable, but in the liquid or gaseous state, or in solution, the two forms usually exist as an **equilibrium mixture.**

It has been found that the *enol form is more volatile than the keto*. The *change from enol to keto* is extremely sensitive to catalysts like acid or bases.

Experiments **using deuterium exchange reactions** have also shown the presence of keto-enol mixtures.

Table showing % of enol content

Compound	% enol (in ethanol)
$CH_3 . CO . CH_2 . CO_2CH_3$	4.8
$CH_3 . CO . CH_2 . CO_2C_2H_5$	7.5
$CH_3 . CO . CH_2 . CO . CH_3$	76
$CH_3 . CO . CH(CH_3) . CO . CH_3$	31

$C_6H_5 . CO . CH_2 . CO . C_6H_5$	96
$CH_2(CO_2C_2H_5)_2$	trace
Aldehydes of type $R . CH_2 . CHO$	trace
Ketones of type $R . CH_2 . CO . CH_2 . R$	trace

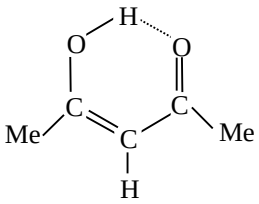
4.1 Factors affecting the enol Content

1. **Ring strain**

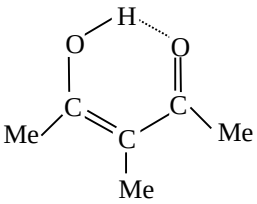
If the enol form is intra-molecularly hydrogen bonded, it is more stable and would lead to a higher enol content. Cyclic monoketones contain more enol than the corresponding acyclic 2-one. In the cyclic ketones, change from keto to enol involves a relatively small change in strain in the ring due to the introduction of a double bond. For acyclic ketones, the introduction of the double bond has a much greater effect on the freedom to take up different conformations.

2. Steric factor

The enol content of acetylacetone is higher than α-methylacetylacetone (in gas phase). In the later compound, there is much greater steric repulsion due to the presence of the □-methyl group. Thus, the α-methyl enol form has greater internal strain than the enol form of acetylacetone.



91 – 93%



43.5 – 44.5%

3. Nature of solvent:

Any solvent that can form hydrogen bonds with the carbonyl group of the keto form will stabilize this form (by solvation). The enol form, however, since it forms an intramolecular bond, will be largely prevented from forming hydrogen bonds with the solvent i.e., solvation will be less.

Thus the keto form is stabilized with respect to the enol form e.g., solvents such as water, methanol, acetic acid, etc. tend to reduce the enol content. On the other hand, in solvents such as hexane, benzene etc. the enol content will be larger, e.g., the enol content of acetylacetone in hexane is 92 per cent.

5. Modern Theories of Tautomerism

Ingold (1927) suggested the names

a. ***Cationotropy*** for all those cases of tautomerism which involve the separation of a *cation*

Lowry (1923) suggested the name ***prototropy*** for those cases in which a proton separates, and called such systems *prototropic* systems. It can be seen that prototropy is a special case of cationotropy.

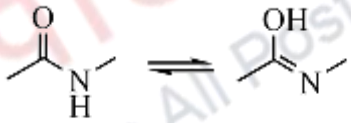
b. ***Anionotropy*** for those cases which involve the separation of an *anion.*

Braude and Jones (1944) proposed the term ***oxotropy*** for aniontropic rearrangements involving only the migration of *hydroxyl* group.

Let us consider some examples involving prototropy and anionotropy and some other types of Tautomerism:

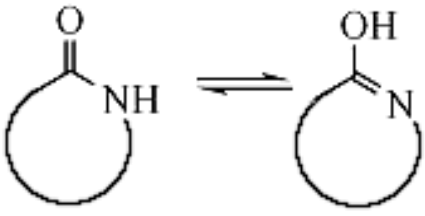
Analogous to keto-enol tautomerism the following are some other types of tautomerism involving other functional groups. Notice that here also, an acidic hydrogen shifts its position giving rise to the other functional groups and they are in dynamic equilibrium.

- **Amide-Iminol (amide-imidic acid) tautomerism**



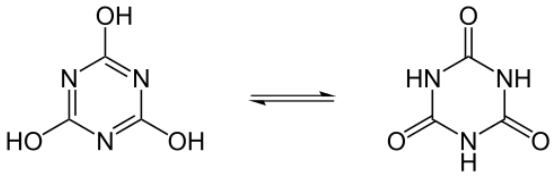
Amide form Iminol form

- **Lactam - Lactim tautomerism**

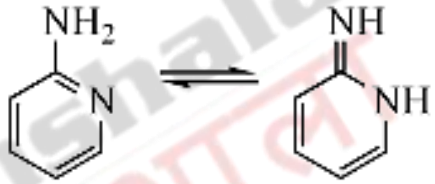


Lactam form Lactim form

e.g.,



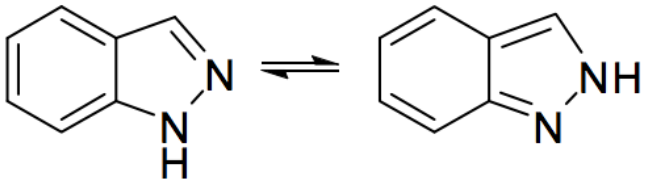
- **Amine-Imine tautomerism**



Amine form Imine form

- **Annular tautomerism**

This is a special case of prototropic tautomerism, where a hydrogen atom can occupy two or more possible locations in a heterocyclic system, e.g. indazole, which can have 1H and 2H tautomers.



1H and 2H tautomers of indazole.

- **Valence tautomerism**

Valence tautomerism is a type of tautomerism in which single and/or double bonds are rapidly formed and ruptured, without migration of atoms or groups.

It is different from prototropic tautomerism or prototropy, and involves processes with rapid reorganisation of bonding electrons. It is also referred to as fluxional tautomerism.

e.g.,

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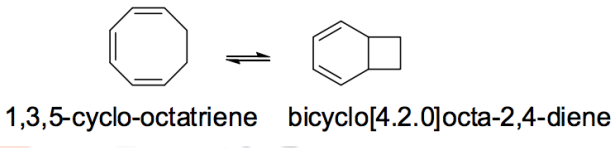
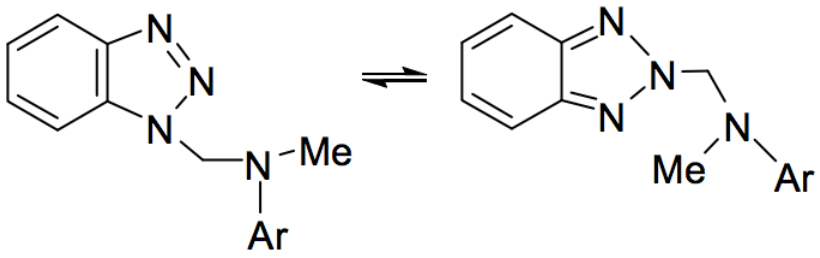
- 

- **Non-prototropic tautomerism**

It involves the relocation of a substituent other than H.

e.g. the tautomerism of 1- and 2-(N,N-disubstituted aminomethyl)benzotriazoles (Fig. 4)



Other forms of non-prototropic tautomerism include acylotropism (transfer of acyl group), methylotropism (transfer of a Me group) and arylotropism (transfer of an Ar group), transfer of N groups and elementotropism (transfer of halogens and metals).

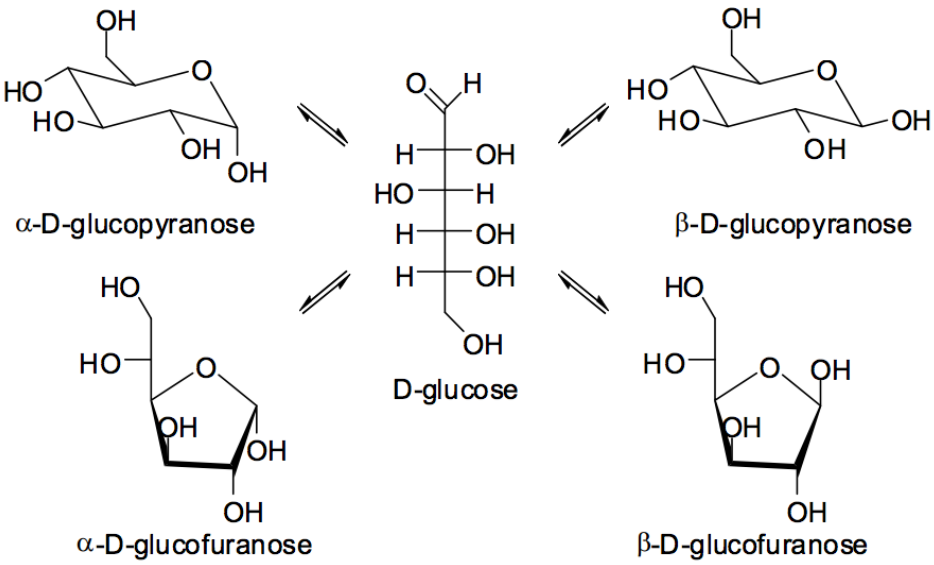
Elementotropism includes chlorotropism (transfer of a Cl), and metallotropism (transfer of a metal atom or a metal-containing group)

- **Ring-chain tautomerism**

In ring-chain tautomerism, a structural change occurs between an open-chain form and a

ring form through a H-shift. This is an important process for monosaccharides such as sugars.

e.g., Glucose can exist in five different tautomeric forms in solution as shown below.



6. Summary

- *Tautomers* are isomers of a compound, which differ only in the position of the protons and electrons. The carbon skeleton of the compound is unchanged but functional groups are different.
- The α- hydrogen of carbonyl compounds is acidic, as it is connected with the α-carbon that is directly bound to the electron withdrawing carbonyl group. This is the main reason for the tautomerism to occur.
- The acidities of these α-hydrogen atoms is enhanced if an electron withdrawing group is attached to the α-carbon atom.
- The establishment of equilibrium may be catalyzed by both acids and bases. Through suitable means, such as by fractional crystallization or careful distillation in the absence of any acid and any base, the keto and the enolic form may be separated from each other.

- It is generally difficult to say which is the labile form, since very often a slight change in the conditions, e.g., temperature, solvent, shifts the equilibrium from keto to enol or vice versa.
- Many scientists have suggested various forms and theories of tautomerism and this module discusses an exhaustive list of some different types of tautomerism.