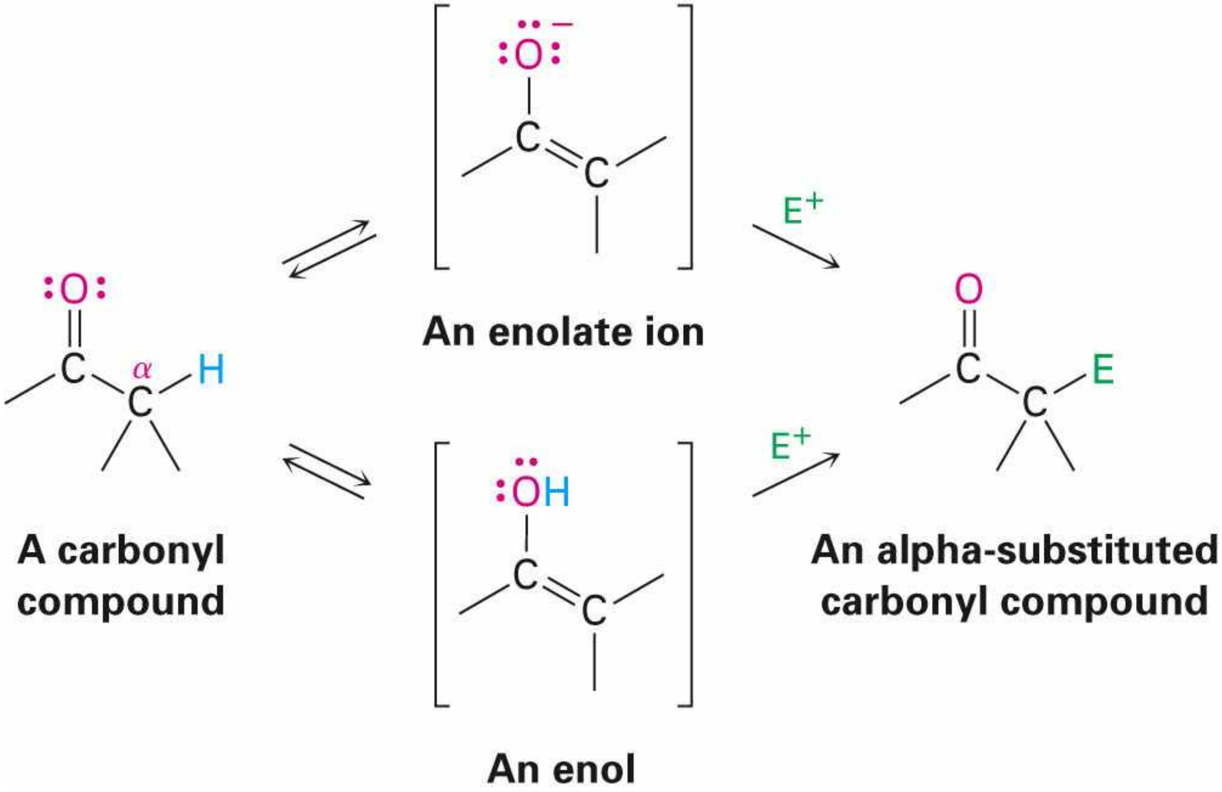
여덟째주

Carbonyl Alpha-Substitution Reactions (1)

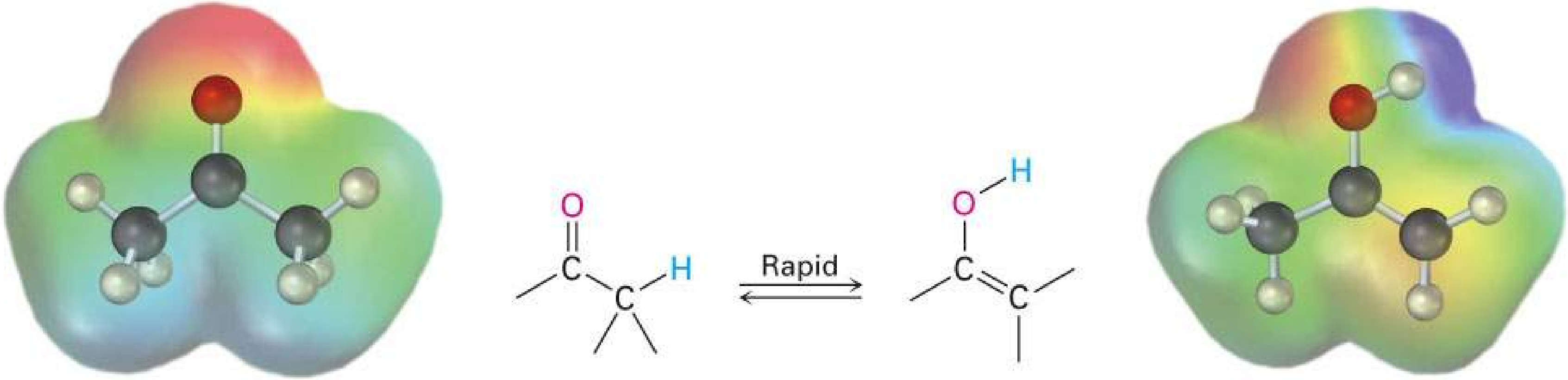
The α Position

- The carbon next to the carbonyl group is designated as being in the α position
- Electrophilic substitution occurs at this position through either an *enol* or *enolate ion*



Keto–Enol Tautomerism

- A carbonyl compound with a hydrogen atom on its a carbon rapidly equilibrates with its corresponding enol
- Compounds that differ only by the position of a moveable proton are called tautomers

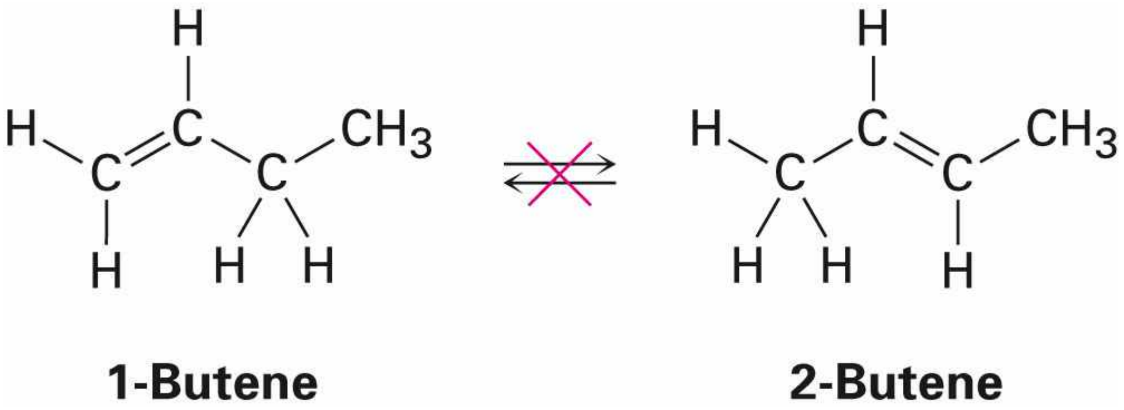


Keto tautomer

Enol tautomer

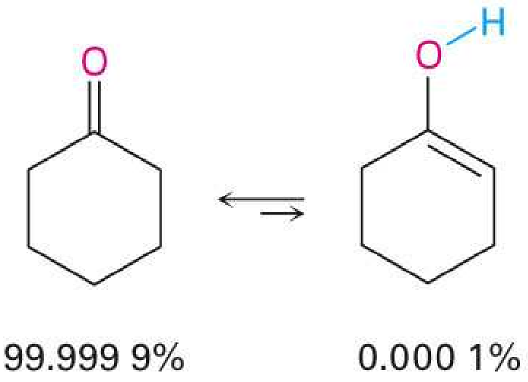
Tautomers Are Not Resonance Forms

- Tautomers are structural isomers
- Resonance forms are representations of contributors to a single structure
- Tautomers interconvert rapidly while ordinary isomers do not

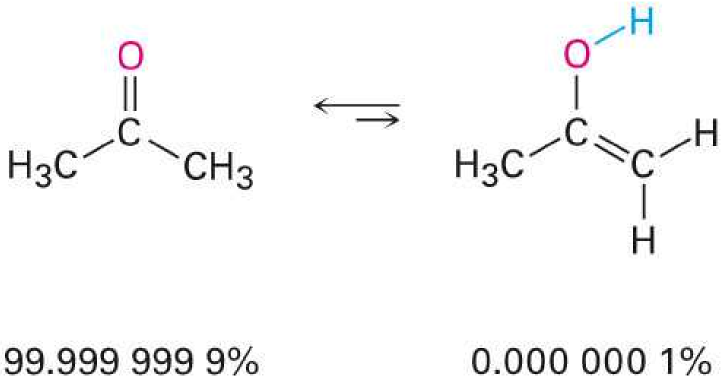


Enols

- The enol tautomer is usually present to a very small extent and cannot be isolated
- However, since it is formed rapidly, it can serve as a reaction intermediate



Cyclohexanone

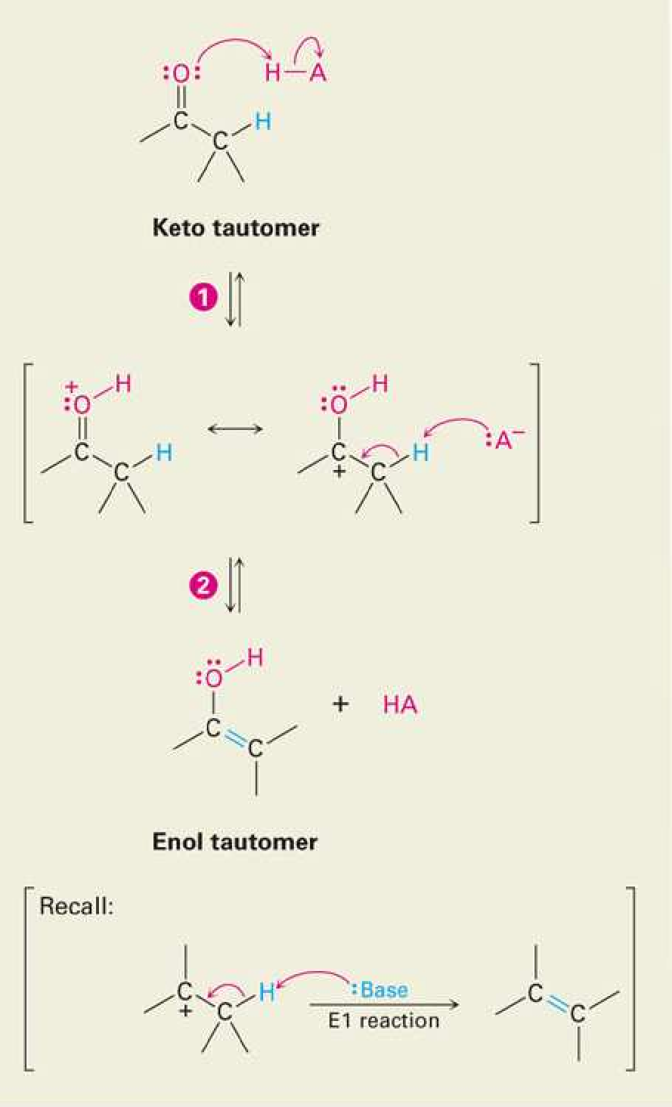


Acetone

Acid Catalysis of Enolization

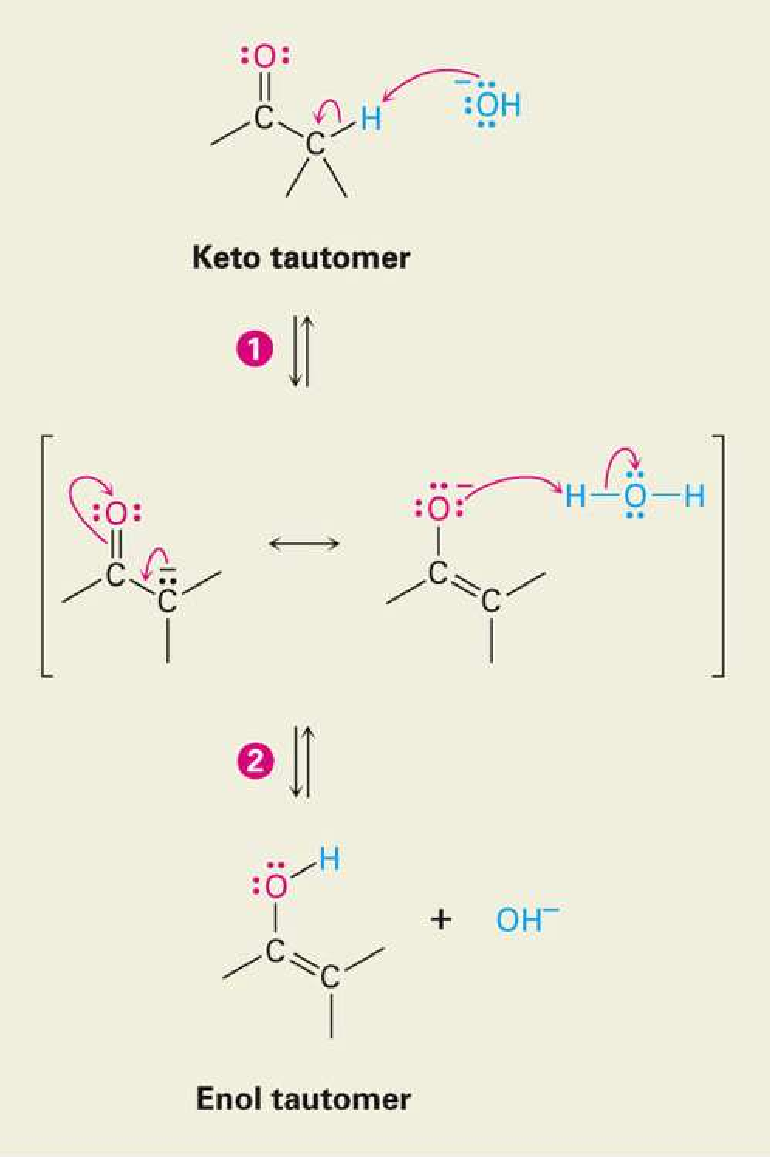
- Brønsted acids catalyze keto-enol tautomerization by protonating the carbonyl and activating the α protons

1. Protonation of the carbonyl oxygen atom by an acid catalyst HA yields a cation that can be represented by two resonance structures
2. Loss of H+ from the position by reaction with a base A- then yields the enol tautomer and regenerates HA catalyst



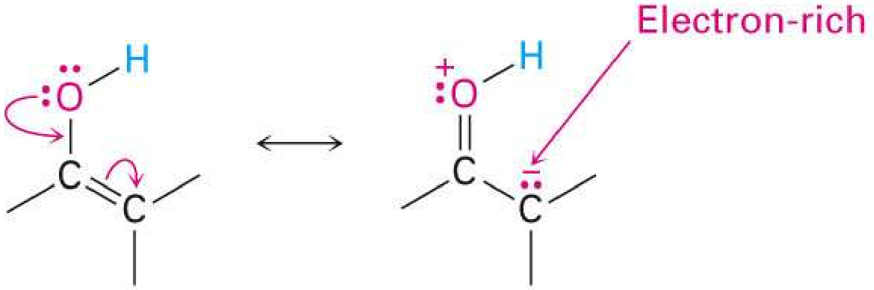
Base Catalysis of Enolization

- Brønsted bases catalyze keto-enol tautomerization
- The hydrogens on the α carbon are weakly acidic and transfer to water is slow
- In the reverse direction there is also a barrier to the addition of the proton from water to enolate carbon

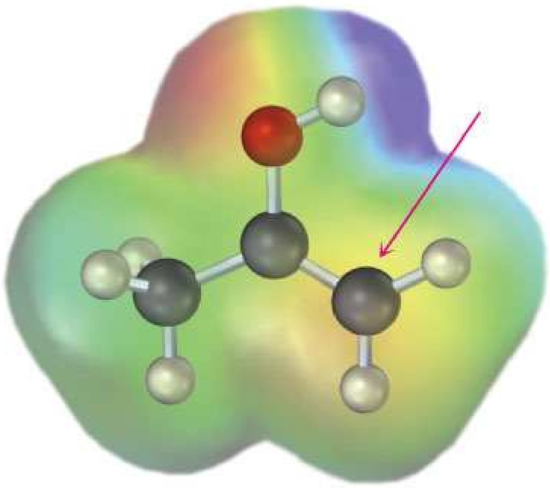


Mechanism of Alpha-Substitution Reactions

- Enols behave as nucleophiles and react with electrophiles because the double bonds are electron-rich compared to alkenes

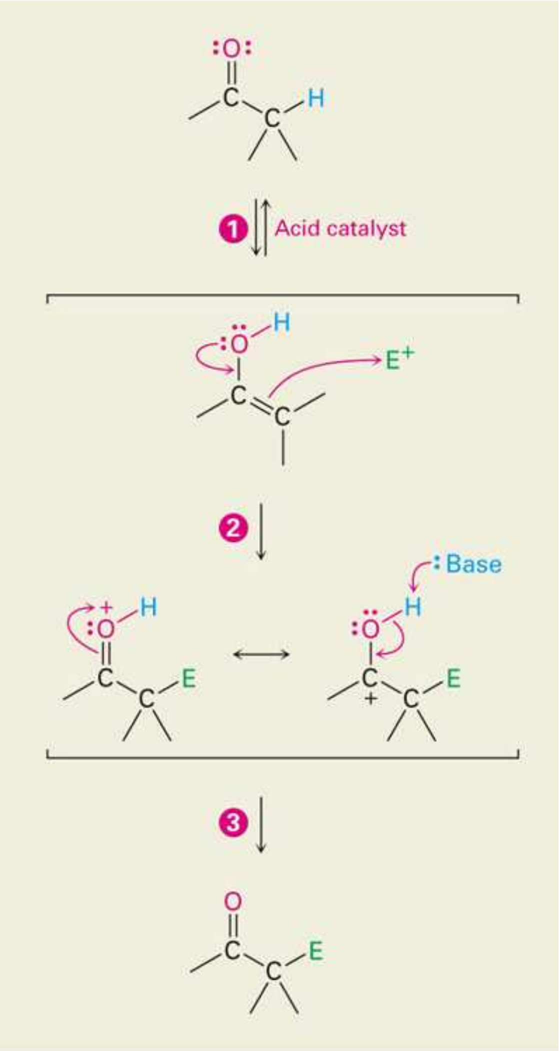


Enol tautomer



General Mechanism of Addition to Enols

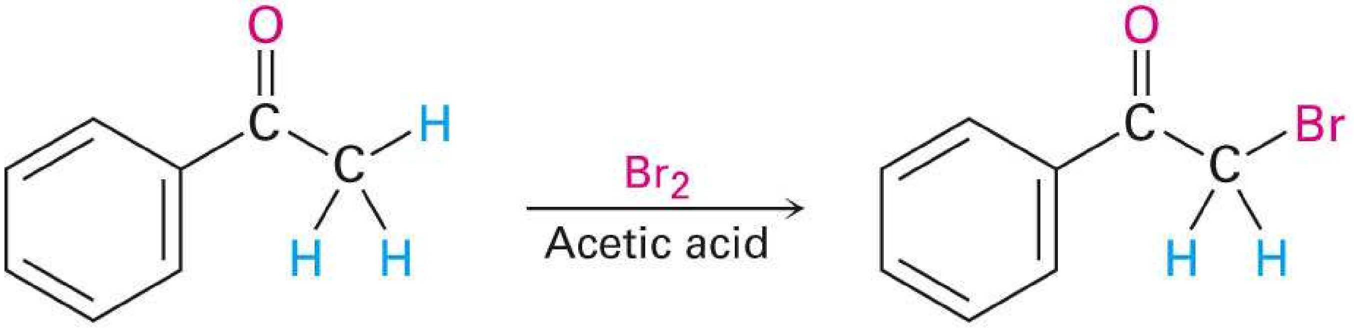
- When an *enol* reacts with an electrophile the intermediate cation immediate loses the —OH proton to give a substituted carbonyl compound



1. Acid-catalyzed enol formation occurs by the usual mechanism.
2. An electron pair from the enol oxygen attacks an electrophile (E+), forming a new bond and leaving a cation intermediate that is stabilized by resonance between two forms.
3. Loss of a proton from oxygen yields the neutral alpha-substitution product as a new C=O bond is formed.

Alpha Halogenation of Aldehydes and Ketones

- Aldehydes and ketones can be halogenated at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution



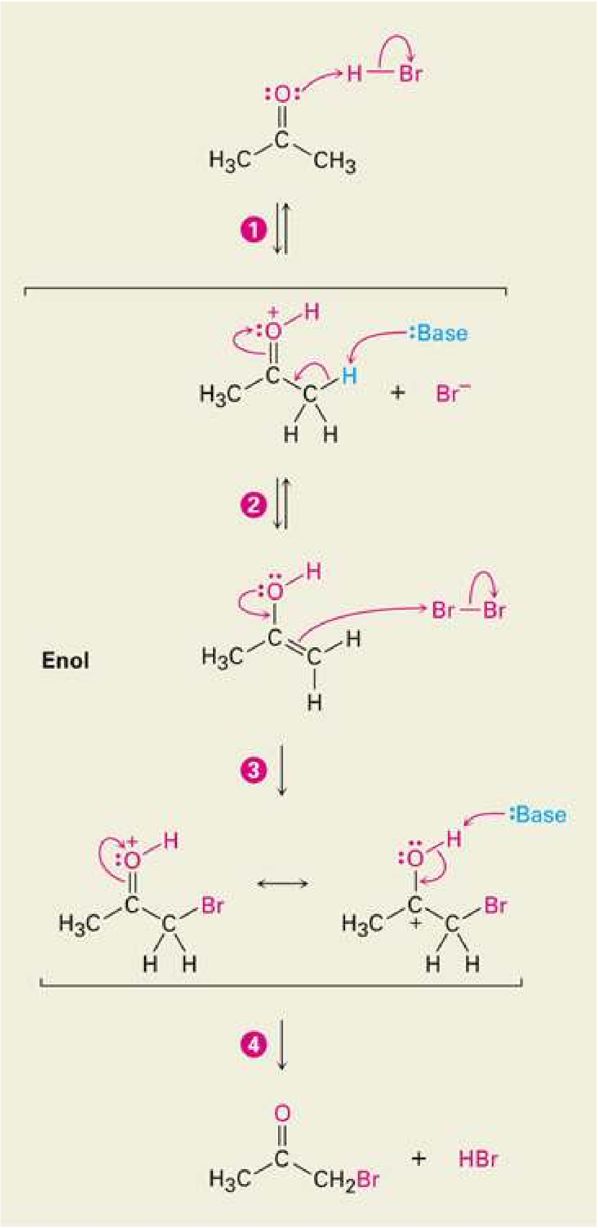
Acetophenone

α-Bromoacetophenone (72%)

Mechanism of Acid-Catalyzed Bromination

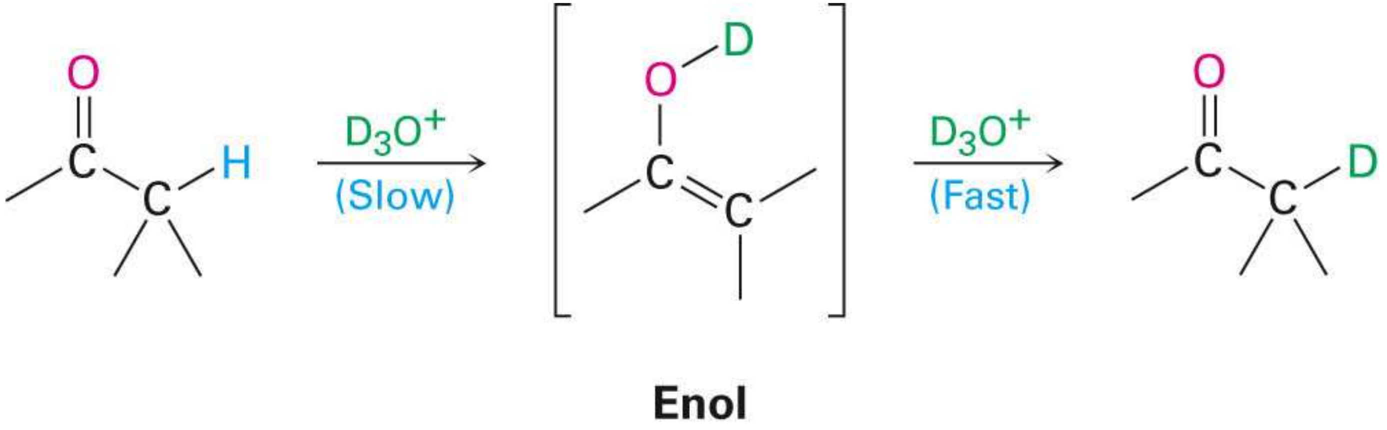
- The enol tautomer reacts with an electrophile
- The keto tautomer loses a proton

1. The carbonyl oxygen atom is protonated by acid catalyst.
2. Loss of an acidic proton from the alpha carbon takes place in the normal way to yield an enol intermediate
3. An electron pair form the enol attacks bromine, giving an intermediate cation that is stabilized by resonance between two forms.
4. Loss of the –OH proton then gives the alpha-halogenated product and generates more acid catalyst.



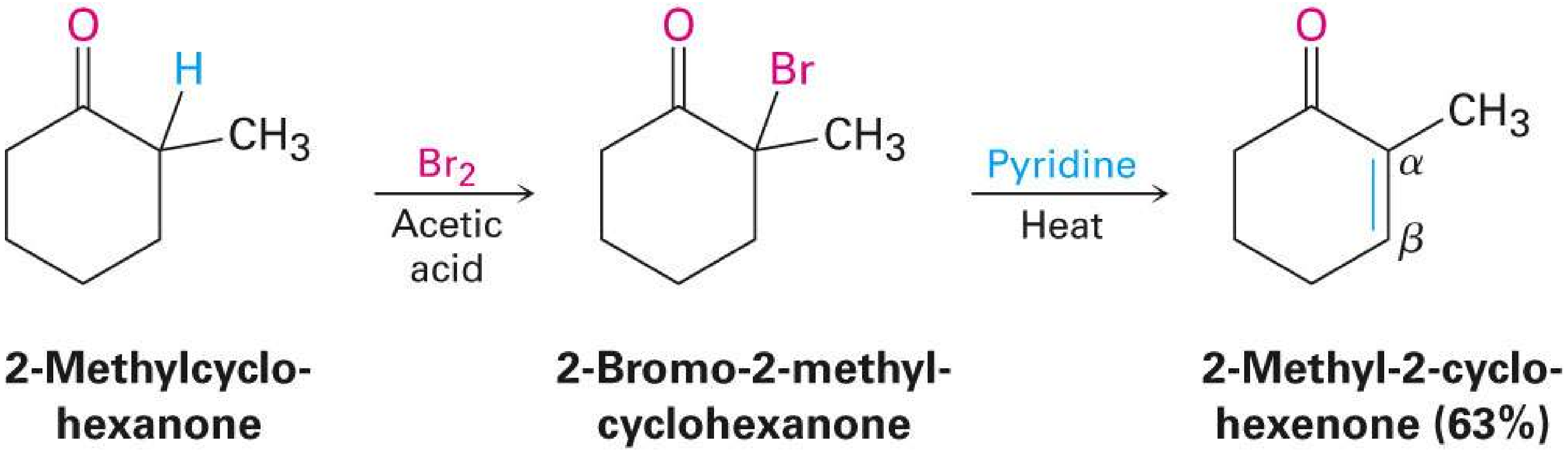
Evidence for the Rate-Limiting Enol Formation

- The rate of halogenation is independent of the halogen's identity and concentration
- In D_3O^+ the α H's are replaced by D's at the same rate as halogenation
- This is because the barrier to formation of the enol goes through the highest energy transition state in the mechanism



Elimination Reactions of α-Bromoketones

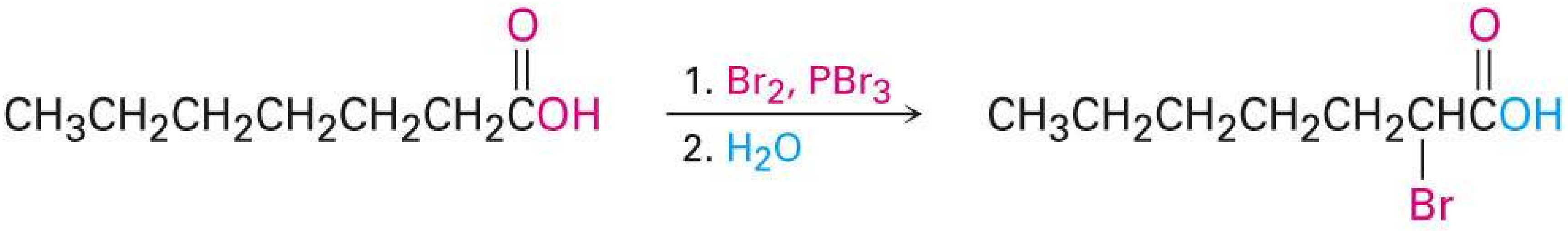
- α-Bromo ketones can be dehydrobrominated by base treatment to yield α,b-unsaturated ketones



Alpha Bromination of Carboxylic Acids

Hell–Volhard–Zelinskii Reaction

- Carboxylic acids do not react with Br_2 (unlike aldehydes and ketones)
- They are brominated by a mixture of Br_2 and PBr_3 (Hell–Volhard–Zelinskii reaction)



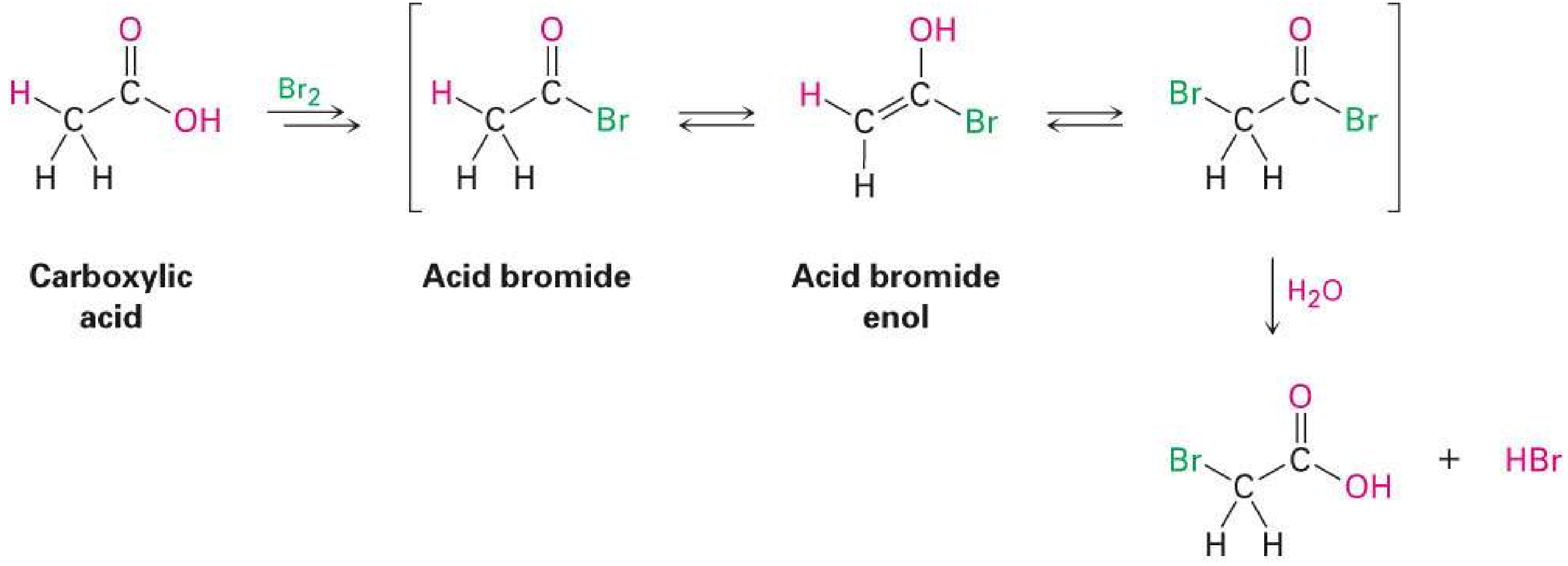
$$CH_3CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ H_2O]{1.\ Br_2,\ PBr_3} CH_3CH_2CH_2CH_2CH_2\underset{Br}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}OH$$

Heptanoic acid

2-Bromoheptanoic acid (90%)

Mechanism of Bromination

- PBr_3 converts -COOH to –COBr, which can enolize and add Br_2



Carboxylic acid

Acid bromide

Acid bromide enol