Topics
Acidity of alpha-H
Enols and enolates
Alpha-H substitution reactions
Alkylation reactions

Connections

\[
\begin{align*}
RCH_3O & \rightarrow RCH_3Br \\
\text{H}_3C\text{O} & \rightarrow \text{Br}\text{O} \\
RCH_3O & \rightarrow RCH_3O^- + \text{CH}_3X \\
\text{RO} & \text{OR} \rightarrow \text{RO} \text{OH} \\
\text{H}_3C\text{O} & \text{OR} \rightarrow \text{CH}_3\text{C} \text{H}_3 \\
\text{CO} & \rightarrow \text{CO} \text{R} \\
\text{H}_3\text{C} & \text{O} \text{CH}_3 & \rightarrow \text{R} \text{O} \text{CH}_3
\end{align*}
\]
**Alpha Hydrogen and a new perspective**

Review of C-H acidities:

- $R_3C\text{--H}$, $pK_a=40-50$
- $R\equiv\equiv\text{H}$, $pK_a=25$
- $\text{CH}_3\text{C--H}$, $pK_a=20$

Starting from the C=O, what is the position that the alpha-H is in? Why is the alpha H so much more acidic? Draw the Acid Dissociation reaction of acetone:

![Acetone dissociation reaction]

Acetone $\text{proton} + \text{enolate}$

The anion from above should look like the one below. The anion is stabilized by resonance. Draw a resonance form for it:

![Resonance form of acetone anion]

The above anions are called enolates. What is the root of enolate?

We have to distinguish enolate from enol. If we protonate the enolate of acetone then we get an enol. Draw that enol:

![Enol molecule]

Enolate $\text{proton} + \text{enol}$

OK. Does enol have a resonance structure? Yes or No? If so, show it.

How does this resonance structure compare to the enolate form?

Well there is a form that we learned was associated with enol. It is a ketone. Draw this ketone:

![Ketone structure]

What is the relationship between the ketone and the enol? Why are they not resonance?

Now, let’s review the keto-enol tautomerism mechanism:

What is the role of acid in this reaction? Why is the hydroxyl-alkene so reactive towards traces of acid?
Which is more acidic the enol proton or the alpha proton? How could you tell? In the reaction above which is the direction and what is the magnitude of the eq constant? Assume enol has a pKa like alcohol ~ 16. How do you know that the alcohols are more acidic?

**Reaction Overview of Enols and Enolates:** Reactions of enols and enolates: In general, we have reactions that go through acid catalysis and they involve the _______ form and those that go through base and these involve the ____________ form.

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Acid</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>α – C=O compound</td>
<td>Enol</td>
<td>Enolate</td>
</tr>
<tr>
<td>Catalysts</td>
<td>H⁺</td>
<td>OH⁻ or RO⁻</td>
</tr>
</tbody>
</table>

There are two reactions for acidic conditions which involve enols.
1. Alpha-Bromination.
2. HVZ reaction—(alpha-bromination of carboxylic acids).

**Alpha-Bromination:** The general reaction mechanism is elimination + addition = ________.

First let’s look at the bromination of the enol. Below is the reaction of Br⁺ from Br₂.

Fill in the arrows. What is the role of acid?

This reaction is important because base can take off the Beta H by elimination making alpha-beta unsaturated ketones:

**Review:** What are two reactions that can occur at the Beta-C of an alpha-Beta conjugated ketone.

1. 

2. 

**HVZ Reaction:** When this reaction happens to carboxylic acids, it is called the HVZ reaction named after three chemists.

The first step is the PBr₃ dehydration of the carboxylic acid to make the acyl bromide.

Next the acyl bromide equilibrates to the the acyl bromo enol which adds Br⁺ as above. The acyl bromide is hydrolyzed back to the acid.
Overall reaction:

**Application**  
Synthesis of amino acids: Go through the retrosynthetic steps of an amino acid: 
Phenylalanine from a carboxylic acid:

What is the stereochemistry of this phenylalanine? 
The amino acid has two forms. Which form is favored by equilibrium? 

In a little while, you will see how addition of halogens in basic conditions leads to different type products. 

**enol—acidic conditions** (above this line)  
**enolate—basic conditions** (below this line) 

**Enolate formation:**  The enol is the ______ form and the enolate is the ______ form. 
We can try to force the formation of the enolate by reacting the ketone with a base. Let’s predict the following reactions:

Well what base will work? 
We don’t usually use NH$_2$ because it blows up and it is too wild. We hinder it with alkyl groups?  Meet LDA  
LDA =  
LDA is made from Diisopropylamine and nBuLi: 
What are the products of this reaction?
Formation of stable enolates
Predict the stable enolate from the reaction of cyclohexanone with LDA?

\[
\text{Cyclohexanone} + \text{LDA} \rightarrow \text{Enolate}
\]

How about 2-methylcyclohexanone?

\[
\text{2-Methylcyclohexanone} + \text{LDA} \rightarrow \text{Enolate}
\]

Here there are two types of alpha-H. Pick the enolate that is thermodynamically stabilized and pick the enolate that is more kinetically stabilized.

The Kinetic enolate is formed by ____________.

The Thermodynamic enolate is formed under conditions of ____________.

These are stable enolates. They can be stored or made just-in-time. Why are enols not compatible with enolates?

On to the alpha-H in basic conditions
HVZ occurs under acidic or basic conditions. This is a weird reaction because the equilibrium to get started is quite bad, but once it gets started it cannot be stopped until it makes haloform. Thus, it is named the haloform reaction because the product always involves the formation of CX₃H (X=Cl=Chloroform, X=Br=Bromoform, X=I=Iodoform).

**Haloform Reaction:** Base enolate formation of haloform and a carboxylic acid:

(1) The bad equilibrium. How bad is this equilibrium? \( K_{eq} = ____ \)

\[
\begin{array}{c}
\text{H} + :\text{OH}^- \rightleftharpoons \text{H}_2\text{O} + \text{Enolate}^- \\
pKa=20 & pKa=16
\end{array}
\]

(2) Now we add Br₂ to the enolate and here we go:

Why does the reaction, slow to start, go on to the end?
Why does the reaction only react on a CH₃ end?
Why does the more halogens added to the molecule make the molecule more reactive?

How does this reaction compare to HVZ?

Overall, the reaction is butanone + NaOH/Br₂ → Bromoform + propanoate
So be on the lookout for a ketone + X₂ in basic solution. It will lead to an unusual result.

**Alpha-keto anions as nucleophiles: Direct Alkylation**

The enolate can act like any nucleophile reacting in an \( S_N2 \) fashion. This process is called alkylation.

\[
\begin{array}{c}
\text{O} \\
\text{RCH}_2\text{Br} \\
\text{O} \\
\text{CH}_2\text{R} \\
\end{array}
\]

Any good LG works fine: Tosylate > I > Br > Cl

What kind of carbon substrates work best?

The enolate can react with an alkyl halide in a regular \( S_N2 \) fashion as shown below:

Let's step back and examine this reaction. First we have to make the enolate. What is the best base?

Here is a possible sequence:

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{LDA} \\
\text{Li}^+ \\
\text{+ (iPr)₂NH} \\
\end{array}
\]

What is the magnitude of the above reaction constant: \( K_{eq} = \)

The three cases, in which direct alkylation is effective is for esters, nitriles and ketones. Aldehydes can be easily deprotonated to make enolates, but the enolates then react immediately with the aldehyde C=O rather than R-Br.

An example of the ester direct alkylation:

What's a cyclic ester called?

We can see the same reaction with nitriles:
What's the product?

Compare all this to Beta substitution. Recall how to make alpha methyl cyclohexanone:

To make Beta-methyl cyclohexanone, we need a methyl nucleophile, Me₂CuLi and an alpha-beta unsaturated ketone:

To make an alcohol from the C=O, we need a Grignard.

On to even more acidic Alpha-H!
There are even more acidic ketone forms than the ones we have just seen. Take for example the Beta keto carbonyl compound. For 2,4-pentanedione, there are two type of alpha H's. Circle them. Why might you have circled 3 regions, but only two types?
Below are the acid dissociation equilibria of the two types of alpha-H. The top one is pKa=20, the bottom is pKa=10.

For the single carbonyl acid like acetone, we needed what base to pull the proton completely off? 

Let's consider a simpler base for the above Beta-diketo case: What would be the complete reaction for 2,4-pentanedione and hydroxide to go to water and the 2,4-pentanedione enolate? Predict the Keq from the pKas.
**Malonic Ester Synthesis**

Based on malonic ester, a beta-diester, has acidic protons (pKa=13) that are removed one at a time by Na alkoxide solutions. The enolate will add one or two alkyl halides in S_N2 manner. Then, the malonic ester is heated in dilute aqueous acid, the esters are hydrolyzed and one of the acids loses CO_2. The final product is an alpha substituted acid.

![Malonic Ester Synthesis Diagram]

The substitution can happen a second time if there is enough alkyl halide: Nu: is more hindered.

![Second Substitution Diagram]

Now for decabonylation:

![Decabonylation Diagram]

Why do we use Na^+ Ethoxide and not hydroxide?

Reaction summary:

- Malonic ester + R-Br (NaOEt/HOEt) → R-CH_2CO_2H
- Malonic ester + 2 moles R-Br (NaOEt/HOEt) → R_2CHCO_2H

**AcetoAcetic Ester Synthesis**

Like malonic ester, except acetoacetic ester gives alpha-substituted acetones.

![AcetoAcetic Ester Synthesis Diagram]

The substitution can happen a second time if there is enough alkyl halide: Nu: is more hindered.

![Second Substitution Diagram for AcetoAcetic Ester]

Now for decabonylation:

![Decabonylation Diagram for AcetoAcetic Ester]
Reaction summary:
Acetoacetic ester + R-Br (NaOEt/HOEt) $\rightarrow$ R-CH$_2$COCH$_3$

Acetoacetic ester + 2 moles R-Br (NaOEt/HOEt) $\rightarrow$ R$_2$CHCOCH$_3$

Why do you think people are interested in these syntheses? What are other alkylation reactions?

What is the main difference between the malonic ester type synthesis and the alpha-C alkylation using LDA and an alkyl bromide?

**Application – Synthesis of Sibutramine**

The synthesis of the antidepressant Sibutramine is made according to the scheme below. Jeffery, James E.; Kerrigan, Frank; Miller, Thomas K.; Smith, Graham J.; Tometzki, Gerald B.; J.Chem.Soc.Perkin Trans.1; EN; 21; 1996; 2583-2590.

A synthesis for sibutramine is provided below

http://www.ch.ic.ac.uk/local/projects/rowlands/index.html
Note in compound 4, what is a more facile reaction:
Alpha-bromination or aromatic bromination?

The last step comes from Chapter 23. We will revisit this step then.

Isobuteryl groups can be used as a surrogate for a CH₂COCH₃ group, enabling a three-step annulation from a ketone to a cyclopentenone. McMurry used this approach in his synthesis of Aphidicolin. JACS, 1979, 101, 1330-1332.