Chapter 17: Enols and Enolate Anions as Nucleophiles

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<td>5. R-X alkyl, allyl, &amp; benzyl halides</td>
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(1) Generation of enolates

- Halogen and most of the carbon electrophiles react at the carbanion center.
- The solution structures of carbanions closely resemble the structures of enolates. In addition, the only reason for the acidity of the α-hydrogen is the presence of a C=O group. Therefore, the following mechanism for the deprotonation of the α-hydrogen by a base is recommended:

(i) H₃C-MgBr

Note: A carbanion addition reaction to a C=O is irreversible.
Enolate formation vs carbanion addition (cont'd).

(ii) When \((H_2C)_3C-Li\) or \(H_2CCH_2CHLi(CH_3)\) is used, enolate formation is greatly favored due to the increased steric energy for the addition.

(iii) Commonly used non-nucleophilic bases:

<table>
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<th>Base</th>
<th>Description</th>
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<tr>
<td>(Na^+)</td>
<td>(sodium hydride); Just a base; not a nucleophilic hydride source (i.e., does not reduce a ketone nor aldehyde).</td>
</tr>
<tr>
<td>(K^+)</td>
<td>(O-C(CH_3)_3) (potassium tert-butoxide)</td>
</tr>
<tr>
<td>(Li-)</td>
<td>(C(CH_3)_3) (tert-butyllithium)</td>
</tr>
<tr>
<td>(Li-N[CH(CH_3)]_2)</td>
<td>(lithium diisopropylamide; LDA)</td>
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</table>

Lithium diisopropylamide = LDA

One of the most frequently used, strong base!

**Preparation:**

\[ pH_3C-C\bigg\|C-C=H\bigg\|C\bigg\|C-H + LiBr \rightarrow \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H \]

\[ \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H + 2 Li \]

**Enolate formation:**

\[ pH_3C-C\bigg\|C=H + \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H \rightarrow \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H \]

\[ \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H + \delta^+\delta^-\delta^+\delta^-\delta^+\delta^-H \]
II. Reactions of Enols and Enolates

(1) Reactions of enolates

The transition states for the reactions of enolates with highly reactive electrophiles, e.g., H-X, H₃O⁺, and (H₂C)₃Si-Cl, closely resemble the structures of the starting enolates. In contrast, the reactions with slower-reacting carbon electrophiles, e.g., R-X and R-C(=O)-Z, go through the transition states that have an energetically favorable, strong C=O bond character. This leads to the preferential reactions at the α-carbon.

(2) Reactions with Halogens

(i) Enols:

Even with ketones with the same substitution on α- and α'-carbons, the mono bromide product can be obtained cleanly:
(2) Reactions with Halogens (cont’d)

(ii) Enolates

For this haloform reaction to take place, there have to be three \( \alpha \)-hydrogens (i.e., methyl ketone). With only two halogens attached, no C-C bond cleavage takes place to form the corresponding carbanion.
II. Reaction of Enols and Enolates (cont’d)

(3) Reactions with alkyl, allyl, and benzyl halides – Exclusive C-alkylation

- Enols are not nucleophilic enough to have reactions with these halides.
- Enolates readily undergo reactions on the α-carbons with alkyl, allyl, and benzyl halides.

\[
\text{Enol} + \text{NH}_3 \rightarrow \text{Enolate}
\]

Enolate preformed, then treated with allyl bromide.

III. The Regioselectivity of the Enolate Reactions

(1) Kinetic enolates

**Kinetic enolates:**
- Use of an extremely strong base; non-nucleophilic base in an aprotic solvent, typically in tetrahydrofuran (THF)
- Use of a slight excess of the base at a low temperature (typically at -78°C) to ensure no equilibrium between the two enolates.

\[
\text{H}_3\text{C}=\text{CHCH}_3 \overset{\text{LDA}, \text{Li} (1.1 \text{ mol equiv})}{\longrightarrow} \left[\begin{array}{c}
\text{H}_3\text{C}\text{CH} \\text{CH}_3 \\
\text{H}_3\text{C}\text{CH} \\text{CH}_3 \\
\text{H}_3\text{C}\text{CH} \\text{CH}_3 \\
\text{H}_3\text{C}\text{CH} \\text{CH}_3 \\
\end{array}\right] + \text{H-N(CH}_3\text{)}_2\text{CH}_2
\]

- **major enolate**
- **minor enolate**

\[
\text{Si(CH}_3\text{)}_2\text{Cl} \text{ (reacts at the O}^\text{-})
\]

\[
\text{Br} \text{ (reacts at the C}^\text{-})
\]

\[
\text{diastereomeric mixture}
\]

**99 : 1**

**95 : 5**
III. Enolates (cont’d)

(1) Kinetic enolates
LDA: an extremely strong base and a bulky base; does not add to the C=O carbon.

The bulky LDA approaches from the less-hindered side of the C=O.

More hindered side!                  Less hindered side!

axial α-H on the less-substituted side

More favored for deprotonation       Less favored for deprotonation

(2) Thermodynamic Enolates

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H} & \quad \text{O} & \quad \text{H} \\
\text{Cl-Si(CH}_3\text{)}_3 & \quad \text{+} & \quad \text{N(CH}_3\text{CH}_3\text{)}_3 & \quad \Delta \\
\text{H}_3\text{C} & \quad \text{H} & \quad \text{Si-CH}_3 & \quad \text{Si-CH}_3
\end{align*}
\]

22% + 78% + HCl·N(CH$_3$CH$_3$)$_3$

Mechanism:

pKa 19-20

reaction with Cl-Si(CH$_3$)$_3$

less-stable enolate (kinetic enolate)

more-stable enolate (thermodynamic enolate)

tautomerization

reaction with Cl-Si(CH$_3$)$_3$
(2) Thermodynamic enolates (cont’d)
These conditions allow equilibrium to occur and preferentially produce the more stable “thermodynamic enolate,” i.e., under the “thermodynamic control.”

Highly reactive electrophiles such as H-X, (H₃C)₃Si-X, H₃O⁺ react at the enolate O site.

Thermodynamic enolates can be obtained:
- Normally using a weak base
- High temperatures
- Excess ketone or proton source such as an alcohol.

Note: Even if LDA is used as a base, if less than 1.0 mol equiv of LDA is used at a higher temperature, such as 0 °C or room temperature, the equilibrium between the kinetically generated enolate and the starting ketone could be achieved, thus effectively creating the thermodynamic enolate.

(3) Examples

(i) 

kinetic enolate

```
H₃C\(\text{OCH}_3\)
```

thermodynamic enolate

```
LDA (1.1 mol equiv)
```

```
(1.2-dimethoxy-ethane; solvent)
```

```
0 °C
```

```
H₃C\(-I\)
```

```
cis
76%

trans
```

```
+ enantiomer
```

(ii) 

```
LDA (1.1 mol equiv)
```

```
H₂CCH₂OCH₂CH₃
```

```
- 60 °C
```

```
kinetic enolate
```

```
80%
```

```
+ LiBr
```

```
thermodynamic enolate
```

```
91%
```

```
+ KBr
```

```
O\(\text{CH}_3\)
```

```
```

```
```

Chapter 17: IV. Base-catalyzed Aldol Reactions and Condensation Reactions

The original aldol reaction:

\[
2 \text{H}_2\text{C}=\text{H} \xrightarrow{\text{NaOH, } \text{H}_2\text{O}} 5 \degree \text{C, 1 h}} \xrightarrow{\text{H}_3\text{O}^+ \text{workup}} \sim 50\% 
\]

Aldol products [aldehyde + \text{ol}]

(\beta\text{-hydroxy-aldehyde})

Note these specific reaction conditions.

Often difficult to stop at the stage of a \(\beta\)-hydroxy-aldehyde or ketone.

**Aldol condensation reaction**

\[
\text{phenyl} + \text{CH}_3\text{C}=(\text{CH}_3)_2\xrightarrow{\text{NaOH, 95\% EtOH, rt}} \text{phenyl} + \text{H}_2\text{O} 
\]

In this combination,

this is the only "acidic" \(H\) (pK\(_a\) \sim 18).

Note:

\[
\text{not acidic} \quad \text{base}
\]

The resulting carbanion is not stabilized by the C=O \(\pi\)-electrons.

**Comments:**

1. \(\alpha\)-hydrogens
   \(\text{pK}_a\) of H-OH is 15.7
   (resonance stabilized)

2. Whenever a nucleophilic base (e.g., HO\(^-\), \text{H}_3\text{CO}^-) is used, the base adds to the C=O carbon.

\[
\text{phenyl} \quad \xrightarrow{\text{OH}^-} \quad \text{phenyl} \quad \xrightarrow{\text{OH}^-} \quad \text{phenyl} \quad \xrightarrow{\text{OH}^-} \quad \text{phenyl}
\]

However, these adducted compounds are less stable than the original C=O compounds and do not undergo any other reactions but to go back to the original aldehyde/ketone.
**The reaction mechanism:**

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Comments: (1) The conjugated ketone produced is primarily the more stable trans (or E) isomer. 
(2) The reaction of the ketone enolate with benzaldehyde takes place exclusively at the \(\alpha\)-carbon.

(3) The last dehydration step should go through the ketone enolate intermediate as shown above. The alternative E\(_2\) process should require a higher energy of activation than the pathway that involves the enolate formation by deprotonation (i.e., the faster acid-base reaction).

(4) The last dehydration step is thermodynamically driven, i.e., the formation of the highly stable \(\alpha,\beta\)-unsaturated ketone.

Problems: Provide in the following boxes the structures of appropriate compounds.
V. Acid-catalyzed Aldol Reactions/Condensation Reactions

Acids can catalyze aldol reactions as well.

\[ \text{Acid} + \text{Aldehyde} \rightarrow \text{Aldol Product} \]

**mechanism:**

\[ \text{Base} + \text{Enolate} \rightarrow \text{Enolate Product} \]

Alternatively, may use H - B and B for acid and conjugate base, respectively.

VI. Directed Aldol Reactions

[In this case, the word “directed” refers to the regiochemistry of the enolate formation].

When a weak base such as NaOH and NaOCH\(_3\)CH\(_3\) is used, only a small amount of an enolate is generated. Therefore, the initial aldol (addition) reaction product (i.e., β-hydroxy ketone) is exposed to such a base, thus often resulting in the formation of the aldol condensation product. The only practical way of ensuring the clean formation of the β-hydroxy ketone product is to use 1.0-1.1 mol equiv of a strong base such as LDA. Since the base will be used up completely for the enolate generation, there is no excess base left when the β-alkoxy ketone is formed, thus preventing the further reaction to form the aldol condensation product.

\[ \text{LDA (1.1 mol equiv)} \]

THF, -78 °C
VII. Retro-Aldol Reactions under Basic or Acidic Conditions

The Aldol reactions-condensations are reversible both under basic and acidic conditions.

**Mechanism under basic conditions:**

**Mechanism under acidic conditions:**
Chapter 17: VIII. Reactions of Stabilized Enolate Anions with Alkyl Halides

Enolates of Active Methylene Systems.

(1) Enolates from 1,3-diketone and β-Keto Esters: Hydrogens alpha to both of the carbonyl groups in 1,3-diketones and β-keto esters are highly acidic. Therefore, those Hs could readily be deprotonated by the use of a relatively weak base and the resulting enolates undergo facile alkylations with alkyl halides. These mono-anions are stabilized by resonance with both of the C=O groups.

(2) Dienolates from 1,3-diketone and β-Keto Esters: Mono-enolates (mono-anions) formed from 1,3-diketone and β-keto esters can further be deprotonated by the use of a stronger base (typically n-butyllithium or LDA) to generate di-enolate (dianions).

If these dianionic species is treated with one mol equiv of a carbon electrophile, the C-C bond forming reaction takes place selectively at the second deprotonation site.

(3) An example of the mono-alkylation of a dienolate.
IX. Formation of β-Keto Esters and Their Reactions

(1) Synthesis of β-keto esters from ketone enolates

ketone \[ \rightarrow \text{LDA (1.0 mol equiv) THF, -78 °C} \rightarrow \text{enolate} \rightarrow \beta\text{-keto ester} \]

Mechanism:

(2) Synthesis of β-keto esters from esters

(i) The Claisen Condensation: between two ester compounds; intermolecular reaction

\[ 2 \times \text{ester} + \text{ester} \rightarrow \beta\text{-keto ester} + \text{acid} \]

Reaction end-products before acidic workup.
IX. (2) (ii) The Dieckmann Condensation: an intramolecular version of the Claisen condensation.

Reversible reactions observed for the β-keto ester products lacking an active methylene H.
Chapter 17: IX. Formation of \( \beta \)-Keto Esters and Their Reactions (cont’d)

(3) Decarboxylation of \( \beta \)-keto acid and malonic acid and substituted malonic acid

Carboxylic acids with a C=O group \( \beta \)-to the carboxylic acid C=O are unstable and lose CO\(_2\) gas upon warming/heating. These carboxylic acids include \( \beta \)-keto acid and malonic and substituted malonic acids. These acids can be obtained by the acid catalyzed or base catalyzed hydrolysis followed by acidification of the corresponding esters. The decaboylation is shown to go through a six-membered cyclic transition state. As such, the two carbonyl groups need to be located at the 1,3-positions or the \( \beta \)-position to the carboxylic acid C=O. The resulting enols undergo tautomerization to provide the more stable C=O structures.

Example:

\[
\begin{align*}
\text{OCH}_2\text{CH}_3 & \quad \text{(1 mol equiv)} \\
\text{CO} & \quad \text{(1 mol equiv)} \\
\end{align*}
\]
X. Reactions of Carboxylic Acid Derivatives

(1) Reduction with hydride reagents

\[ \text{NaBH}_4: \text{ typically in a protic solvent that serves as a proton source (e.g., CH}_3\text{OH, and CH}_3\text{CH}_2\text{OH) reduces: aldehydes, ketones, imines, acid halides (to RCH}_2\text{OH), acid anhydrides [RC(=O)]_2\text{O [to RCH}_2\text{OH and RC(=O)O]} \]

But, does not reduce esters, acids, or amides.

\[ \text{LiAlH}_4: \text{ reacts with a protic solvent (i.e., R-O-H); use a non-polar solvent such as diethyl ether and THF; requires acidic workup.} \]

highly reactive; reduces virtually all C=X bonds and cyano group.

(i) esters, carboxylic acid, and lactones

\[ \begin{align*}
\text{ester} & \rightarrow \text{R-CH}_2\text{OH} + \text{HO-R}' \\
\text{carboxylic acid} & \rightarrow \text{R-CH}_2\text{OH}
\end{align*} \]

**mechanism:**

The aldehyde intermediate above can't be isolated as this gets quickly reduced.

\[ + \text{R'}\text{OH} + 2 \text{H}_2 + \text{Al(OH)}_3 + \text{LiOH} \]

\[ \begin{align*}
\text{carboxylic acid} & \rightarrow \text{aldehyde}
\end{align*} \]
X. Reactions of Carboxylic Acid Derivatives

(1) Reduction with hydride reagents: (ii) LiAlH₄ reduction of amides

Unlike an OR group, the N of an NR'R" group is basic and nucleophilic. Thus, it donates its lone-pair electrons to kick out Al-O- species.

(2) Reactions with Organometallic Reagents: Grignard Reagents

(i) esters

Mechanistic interpretation:

*As soon as a small amount of an ester reacts with the Grignard reagent, the adduct immediately produces a ketone, which reacts quite rapidly with the Grignard reagent in solution, thus not accumulating the ketone product.
X. Reactions of Carboxylic Acid Derivatives: (2) Reactions with Organometallic Reagents

(ii) Reaction with carboxylic acids: Grignard reagents react to form carboxylate salts and the resulting salts do not undergo a further reaction with the Grignard reagents at room temperature.

\[
\begin{align*}
\text{PhCO}_2\text{H} + \text{MgBr}_2 & \quad \text{H}_3\text{C} - \text{MgBr} \\
\text{PhCO}_2\text{MgBr} & \quad \text{PhCO}_2^+\text{MgBr} + \uparrow \text{CH}_4 \\
\text{C=O} & \quad \text{too non-electrophilic to reaction with an additional equivalent of a Grignard reagent}
\end{align*}
\]

In contrast, more nucleophilic organolithium reagents can add to the initially produced lithium salt.

\[
\begin{align*}
\text{PhCO}_2\text{H} + 2 \text{H}_3\text{C-Li} & \quad \text{H}_3\text{C-Li} \\
\text{PhCO}_2\text{H} & \quad \text{PhCO}_2\text{OLi} + \uparrow \text{CH}_4 \\
\text{ketone} & \quad \text{acidic workup (pH 1 - 2)} \\
\text{H}_3\text{C-Li} & \quad \text{PhCO}_2\text{OLi} + \text{H}_3\text{O}^+ \\
\text{PhCO}_2\text{H} & \quad \text{PhCO}_2\text{H} + \text{H}_2\text{O} + 2 \text{LiOH}
\end{align*}
\]

(iii) Reactions with amides: In general, amides are not quite reactive with most organometallic reagents (RM), but under forcing conditions, they react similarly as esters.

**N-Methoxy-N-methylamides (Weinreb amides):** special class of amides that react with most RMs and the initially formed addition products exist as stable chelate, thus affording ketones upon acid hydrolysis.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3\text{N(OCH}_3\text{)CH}_3 \\
\text{H}_3\text{C-MgBr} & \quad \text{H}_3\text{C-MgBr} \\
\text{N-methoxy-N-methylamide} & \quad \text{5-membered, stable chelate; does not fragment to a C-O species}
\end{align*}
\]

**mechanism for the hydrolysis:**

Note: Even if excess RM reagents are used, the chelated adduct does not react further with the reagent. This is an extremely convenient method for the synthesis of ketones from carboxylic acids (via Weinreb amides).
Chapter 17 XI: Conjugate Addition to $\alpha,\beta$-Unsaturated Carbonyl Compounds

(1) Conjugate Addition (or 1,4-Addition) – with “weaker” or “softer” nucleophiles

Examples of conjugate addition reactions

1. 

\[
\begin{align*}
\text{H}_2\text{N} & \xrightarrow{0 \degree C} \text{H}_2\text{C} & \text{CH}_3 \\
\text{H}_{\beta} & \alpha \text{CH}_3
\end{align*}
\]

Mechanism:

2. 

\[
\begin{align*}
2 \text{H}_{\beta} & \alpha \text{OCH}_3 + \text{H}_2\text{S} & \xrightarrow{\text{(catalytic)}} \text{H}_3\text{CO}_x \hspace{1cm} \text{OCH}_3 \\
\end{align*}
\]

Mechanism:
Chapter 17 XI: Conjugate (or 1,4-) Addition to \( \alpha,\beta \)-Unsaturated Carbonyl Compounds

(2) 1,2- vs 1,4-Addition reactions

- 1,4-addition products (thermodynamic products): formed with “weaker” or “softer” nucleophiles; those nucleophiles with pKa of the conjugate acids in the range of 8 – 25 generally produce 1,4-adducts (those nucleophiles include RS-, RR’R”N, and ketone/ester enolates); the conjugate addition reactions with enolates are referred to as the Michael reactions.
- 1,2-addition products (kinetic products): formed with strong nucleophiles such as RMgBr and RLi (these addition products are formed irreversibly).

Conjugate-adding organometallic reagents:

- "hypothetical, mildly nucleophilic CH\(_3\) anion"

The most commonly used such mildly nucleophilic reagents are "organocuprates."

- These cuprate reagents are prepared from: \( 2 \text{H}_3\text{C}Li + \text{Cu} \rightarrow (\text{H}_3\text{C})_2\text{CuLi} \)

1. Homocuprates (R = R’): only one of these two groups (R=R’) works as a nucleophile; \( \text{H}_3\text{CCu} \) produced by the reaction is not nucleophilic enough to undergo the reaction.
2. Heterocuprates (R \( \neq \) R’)

- e.g., (NC)RCuLi and \( \text{H}_3\text{CCH}_{2}\text{CH}_{2}C\equiv\text{CCuRLi} \): only R group works as a nucleophile.

The organocuprates undergo: conjugate addition (to, e.g., \( \alpha,\beta \)-unsaturated ketones/esters), \( S_N2 \) reactions (onto, e.g., RCH\(_2\)X and epoxides).

Example:

\[
\begin{align*}
\text{O} & \quad \text{(H}_3\text{CCH}_{2}\text{CH}_{2}\text{CH}_{2})_2\text{CuLi} \\
(1 \text{ mol equiv}) & \quad \text{(tetrahydrofuran=THF; solvent)} \\
-78 \degree C & \quad \text{H}_3\text{CCH}_{2}\text{CH}_{2}\text{CH}_{2}\text{Li}^+ \quad \text{(not reactive)}
\end{align*}
\]

\[
\begin{align*}
\text{1. H}_3\text{C}^- & \text{I} (-30 \degree C) \\
2. \text{aq NH}_4\text{Cl} & \quad \text{+ enantioomer [mostly trans-diastereomer]}
\end{align*}
\]