Lecture 17

8.1 Types of Rearrangements

Rearrangements are divided into intramolecular and intermolecular processes. In intramolecular process, the group that migrates is not completely detached from the system in which rearrangement is taking place. In contrast, in intermolecular process, the migrating group is first detached and later re-attached at another site.

8.2 Rearrangement to Electron Deficient Carbon

These reactions are classified according to the nature of group that migrates.

8.2.1 Carbon Migration

8.2.1.1 Wagner-Meerwein Rearrangement

It is one of the simplest systems where an alkyl group migrates, with its bonding pair, to an electron-deficient carbon atom.

The driving force for the rearrangement resides in the greater stability of a tertiary carbocation compared to that of primary carbocation.
The classical and non-classical carbocation controversy concerned the Wagner-Meerwein rearrangement of norbornyl systems:

![Classical and Non-Classical Carbocation Diagram]

Cl undergoes solvolysis reaction significantly greater than the endo isomer

**Features of this migration**

- The carbocation may be produced by a variety of ways.
- Hydrogen can also migrate in this system.

![Migration Reaction Diagram]

- Aryl groups have a greater migratory aptitude than alkyl group or hydrogen due to the formation of lower-energy bridged phenonium ion.

![Aryl Group Migration Diagram]

- Rearrangements in bicyclic systems are common.
- The rearrangement is stereosepecific
- Two or more rearrangements may take place simultaneously.

**Examples:**

- [Chemical structure of β-Amyrin](#)
  - [Chemical structure of enol of Freidelin](#)


- [Chemical structure of another compound](#)
  - [Chemical structure of another compound](#)

8.2.1.2 Pinacol Rearrangement

Treatment of 1,2-diols (pinacol) with acid lead to rearrangement to give ketone. Although this rearrangement fundamentally is similar to the above described Wagner-Meerwein rearrangement, but differs in that the rearranged ion, the conjugate acid of ketone, is relatively more stable than the rearranged carbocation formed in Wagner-Meerwein rearrangement. Thus, the driving force for pinacol is greater compared to Wagner-Meerwein rearrangement. However, the characteristics of the Wagner-Meerwein apply to the pinacol rearrangement.

Mechanism
Examples:

**Effect of Temperature**

\[
\begin{align*}
\text{Conc. H}_2\text{SO}_4 & \quad 0 \degree \text{C} & \quad \text{major} & \quad \text{minor} \\
\text{Conc. H}_2\text{SO}_4 & \quad 97 \degree \text{C} & \quad \text{minor} & \quad \text{major}
\end{align*}
\]


**Effect of Concentration**

\[
\begin{align*}
\text{Conc H}_2\text{SO}_4 & \quad 0 \degree \text{C} & \quad 0 & \quad 5 & \quad 95 \\
25\% \text{Conc. H}_2\text{SO}_4 & \quad 0 \degree \text{C} & \quad 30 & \quad 1 & \quad 69
\end{align*}
\]


8.2.1.3 Benzilic Acid Rearrangement

1,2-Diketones that have no \( \beta \)-hydrogen react with hydroxide ion to give \( \beta \)-hydroxyacid. The best known example is the rearrangement of benzil to benzilic acid. The driving force for the reaction lies in the removal of the product by ionization of carbonyl group.

**Mechanism**

\[
\begin{align*}
\text{R} = \text{aromatic, group without \( \alpha \)-hydrogen}
\end{align*}
\]
Examples:


8.2.1.3 Arndt-Eistert Homologation Reaction

The reaction of acid chloride with diazomethane gives a diazoketone which is in the presence of silver oxide under heating proceeds the Wolff rearrangement to yield a ketene that is directly converted into an acid in the presence of water.
Mechanism

Elimination of nitrogen yield a carbene followed by migration of the R group

The rearrangement of diazoketone is called the Wolff Rearrangement

Examples:


8.2.2 Halogen, Oxygen, Sulfur, and Nitrogen Migration

In the system \( X\text{-C-C-Y} \), an atom \( X \) with an unshared pair of electrons can assist the heterolysis of the \( C\text{-Y} \) bond. In case of unsymmetrical system, nucleophilic attack predominates at the less substituted carbon of the bridged ion that leads to rearranged skeleton.

Some examples follow:

`Rupe Rearrangement`

The bridged cation may be produced via protonation of an unsaturated bond as in the `Rupe rearrangement` of \( \alpha \)-acetylenic alcohols.
Mechanism

Examples:


In case of a neighbouring acetoxy group, the solvolysis is assisted via a five-membered acetoxonium ion.

![Diagram of acetoxonium ion solvolysis]

**Problems:**

A. Predict the major products in the following reactions with mechanism.

1. ![Chemical structure](image1)

2. ![Chemical structure](image2)

3. ![Chemical structure](image3)

4. ![Chemical structure](image4)

5. ![Chemical structure](image5)

6. ![Chemical structure](image6)

7. ![Chemical structure](image7)

B. Solvolysis of *trans*-2-acetoxycyclohexyl tosylate in acetic acid about 100 times faster than its *cis*-isomer. Explain.
Text Books:


Lecture 18

8.3 Rearrangement to Electron Deficient Nitrogen

8.3.1 Hofmann Rearrangement

This rearrangement provides an effective method for the synthesis of primary aliphatic and aromatic amines from primary amides (Scheme 1).

![Scheme 1](image-url)
Mechanism

Treatment of amide with sodium hypobromite gives $N$-bromo-amide which reacts with base to afford a conjugate base within which rearrangement takes place to give isocyanate. The formed isocyanate may be isolated in anhydrous conditions or it can be converted into amine by aqueous workup (Scheme 2).

![Scheme 2](image)

The workup can also be with alcohol or amine to give urethane or urea, respectively (Scheme 3).

![Scheme 3](image)

Examples:

\[ \text{OH} \quad \text{O} \quad \text{PhI(OAc)\textsubscript{2}} \quad \text{KOH, iPrOH} \quad \text{OH} \quad \text{NH}_2 \]


\[ \text{OH} \quad \text{O} \quad \text{AgOAc, NBS} \quad \text{DMF} \quad 77\% \quad \text{OH} \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{R} \quad \text{H}_2\text{O} \quad \text{R}'\text{OH} \quad \text{R}'\text{NH}_2 \]


### 8.3.2 Curtius Rearrangement

This rearrangement describes the transformation of acyl azide into isocyanate by decomposition on heating and its application for the synthesis of primary amines, urethanes and ureas as presented in Hofmann rearrangement.
Mechanism

![Mechanism Diagram]

Examples

![Examples Diagram]

8.3.3 Schmidt Rearrangement

Carboxylic acid reacts with hydrazoic acid in the presence of conc. \( \text{H}_2\text{SO}_4 \) to give acid azide which is present in the form of conjugate acid eliminates nitrogen to afford isocyanate that could be converted into amine as reported in Hofmann rearrangement.
The reaction is also effective with aldehydes, ketones, tertiary alcohols and substituted alkenes.

Mechanism
Examples:

\[
\begin{align*}
\text{MeCO}_2\text{Et} & \xrightarrow{\text{NaN}_3, \text{MeSO}_3\text{H}} \text{MeNCO}_2\text{Et} \\
& \quad \text{(55\%)}
\end{align*}
\]


\[
\begin{align*}
\text{PhCO}_2\text{Et} & \xrightarrow{\text{HN}_3, \text{H}_2\text{SO}_4} \text{HN} & \quad \text{HNCO}_2\text{Et} & \quad \text{PhCO}_2\text{Et} \\
& \quad \text{66\%} & \quad + & \quad \text{66\%} & \quad \text{36\%}
\end{align*}
\]


### 8.3.4 Lossen Rearrangement

Ester of hydroxamic acid reacts with base to give isocyanate that could be converted into amine as shown in Hofmann rearrangement.

Mechanism
Examples:

All these four rearrangements have common intermediate isocyanate forming from different substrate precursors. Among the all, the Hofmann rearrangement is more convenient providing that other functional group do not react under the conditions.

### 8.3.4 Beckmann Rearrangement

Oximes rearranges in acidic conditions to give amides. The reaction is intramolecular and stereospecific: the substituent trans to the leaving groups migrates.

An interesting application of this method is the synthesis caprolactam from cyclohexanone oxime. Caprolactam is the substrate precursor for nylon preparation.
Mechanism

The rearrangement of amidoximes lead to the formation of urea derivatives which is called the **Tiemann Rearrangement**
Problems:

What products would you expect from the following reactions? Explain with mechanisms.

1. \[
\begin{array}{c}
O \\
\text{Br}_2-\text{KOH}
\end{array}
\]

2. \[
\begin{array}{c}
O \\
\text{OH}
\end{array}
\]

3. \[
\begin{array}{c}
\text{Me}
\end{array}
\]

4. \[
\begin{array}{c}
\text{OH}
\end{array}
\]

5. \[
\begin{array}{c}
\text{HCl-} \text{EtOH}
\end{array}
\]

6. \[
\begin{array}{c}
\text{Me}_3\text{Al}
\end{array}
\]

Text Books:


Lecture 19

8.4 Rearrangement to Electron Deficient Oxygen

8.4.1 Baeyer Villiger Reaction

Treatment of ketones with peroxycacid gives ester. The reaction is effective with acid or base and the mechanism is closely related to pinacol rearrangement: nucleophilic attack by the peroxycacid on the carbonyl group gives an intermediate that rearranges with the expulsion of the anion of the acid.

Mechanisms

**Acid Catalysed Reaction**

**Base Catalysed Reaction**

*Migratory Aptitude: 3° > 2° > PhCH₂ > Ph > 1° > Me > H.*
Examples:

\[
\begin{align*}
\text{MeMe} & \quad \xrightarrow{\text{MCPBA}} \quad \text{MeMe} \\
\text{MeMe} & \quad \xrightarrow{\text{MCPBA}} \quad \text{MeMe} \\
\end{align*}
\]


**8.4.2 Hydroperoxide Rearrangement**

Tertiary hydroperoxide with acid undergoes rearrangement to give ketone and alcohol or phenol. The mechanism is similar to that of Baeyer-Villiger reaction. For example, cumene forms hydroperoxide by autoxidation which rearranges in the presence of an acid to give phenol and acetone.
8.4.2 Dakin Reaction

Benzaldehyde or acetophenone bearing hydroxyl substituent in the ortho or para position proceed rearrangement to give catechol or quinol, respectively. The reaction is performed in the presence of alkaline hydrogen peroxide and the mechanism is similar to that of Baeyer-Villiger reaction.

**Proposed Mechanism**

**Examples:**


8.5 Rearrangement to Electron-Rich Carbon

This group of reaction has been less explored, and is less of synthetic importance compared to the rearrangements to electron deficient carbons. The rearrangements to electron deficient hetero atom may be generally explained as:

\[ R_X C \xrightarrow{\Theta} R_X C \quad X = N, S, O \]

8.5.1 Stevens Rearrangement

Quaternary ammonium salt which has β-hydrogen proceeds E₂ (Hofmann) elimination with base.

In case of quaternary ammonium salts containing β-ketone or ester or aryl group, an α-hydrogen is removed by base to give an ylide and then the rearrangement occurs.

\[ \text{Mechanism} \]

Migratory Aptitude \( R = \text{propargyl} > \text{allyl} > \text{benzyl} > \text{alkyl} \)

Solvent Cage
Examples:


8.5.2 Sommelet-Hauser Rearrangement

In the absence of β-carbonyl group, the α-hydrogen is too weakly acidic for hydroxide ion induced rearrangement. Thus, a strong base, such as amide ion in liquid ammonia, is to be used, when the rearrangement takes a different course: instead of [1,2] shift (Steven’s rearrangement), a [3,2]-sigmatropic rearrangement takes place which is called Sommelet-Hauser rearrangement.
Mechanism

There can be competition between Stevens and Sommelet-Hauser rearrangement mechanisms.

Examples:


8.5.3 Wittig Rearrangement

Ethers undergo [1,2]-sigmatropic rearrangement in the presence of strong base such as amide ion or phenyllithium to give more stable oxyanion. The mechanism is analogous to that of Stevens rearrangement.

\[
\begin{align*}
\text{RO} & \quad \text{H} \\
R' & \quad \text{RO} \\
& \quad \text{Li} \\
\text{R} & \quad \text{O} \\
& \quad \text{Li} \\
& \quad \text{H} \\
\text{R'} & \quad \text{RO} \\
& \quad \text{Li} \\
& \quad \text{H} \\
& \quad \text{R'} \\
& \quad \text{RO} \\
& \quad \text{Li} \\
\end{align*}
\]

**Mechanism**

\[
\begin{align*}
\text{R'Li} & \quad \text{R'} \quad \text{Li} \\
\text{R} & \quad \text{O} \\
& \quad \text{Li} \\
& \quad \text{H} \\
\text{R'} & \quad \text{RO} \\
& \quad \text{Li} \\
& \quad \text{H} \\
& \quad \text{R'} \\
& \quad \text{RO} \\
& \quad \text{Li} \\
\end{align*}
\]

**Examples:**

8.5.4 Favorskii Rearrangement

$\alpha$-Haloketones with base afford enolates which rearrange to give esters via cyclopropanones.

Mechanism

The direction of ring opening of cyclopropanone is determined by the more stable carbanion, formed in the reaction.
Examples:

\[
\begin{align*}
\text{Me} & \quad \text{Br} & \quad \text{Me} \\
\text{O} & \quad \text{O} & \quad \text{Me} \\
\text{Et}_2\text{N}, \text{CF}_3\text{CH}_2\text{OH} & \quad \rightarrow & \quad \text{Me} \quad \overset{\ominus}{\text{O}} \\
\text{OMe} & \quad \rightarrow & \quad \text{Me} \quad \overset{\ominus}{\text{O}} \\
\text{OMe} & \quad \rightarrow & \quad \text{OMe} \quad \overset{\ominus}{\text{O}} \\
\text{O} & \quad \text{O} & \quad \text{OMe} \\
\end{align*}
\]


\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{Et} & \quad \text{Br} \\
\text{O} & \quad \text{N} & \quad \text{CO}_2\text{Et} \\
\text{MeO} & \quad \rightarrow & \quad \text{MeO} \\
\text{DME} & \quad \rightarrow & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

Problems:

A. Formulate mechanisms for the following reactions.

1. \[
\begin{align*}
\text{Br} & \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \text{Br} \\
\text{O} & \quad \text{CMe} \\
\end{align*}
\]

\[\overset{\Theta}{\text{MeO, MeOH}}\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Et} \\
\text{MeO}_2\text{C} & \quad \\
\end{align*}
\]

2. \[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \\
\end{align*}
\]

\[\text{n-BuLi, THF}\]

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Ph} & \quad \\
\end{align*}
\]

3. \[
\begin{align*}
\text{OH} & \quad \text{CHO} \\
\text{Cl} & \quad \text{C} \\
\text{Cl} & \quad \text{H} \\
\end{align*}
\]

\[\text{Sodium percarbonate}\]

\[\text{THF, DMF, H}_2\text{O}\]

B. Complete the following reactions.

1. \[
\begin{align*}
\text{O} & \quad \\
\end{align*}
\]

\[\text{mCPBA}\]

2. \[
\begin{align*}
\text{O} & \quad \text{Br} \\
\end{align*}
\]

\[\overset{\Theta}{\text{OH}}\]

3. \[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{Me} \\
\text{Bu}_3\text{Sn} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \\
\end{align*}
\]

\[\text{n-BuLi}\]

4. \[
\begin{align*}
\text{Bu}_3\text{Sn} & \quad \text{Me} \\
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \\
\end{align*}
\]

\[\text{n-BuLi}\]

5. \[
\begin{align*}
\text{Cl} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[\text{MeLi}\]
Text Books:


Lecture 20

8.6 Aromatic Rearrangements

A number of rearrangements occur in aromatic compounds of the type:

\[
\begin{align*}
X \equiv Y & \quad \text{XH} \quad \text{Y} \\
\text{benzene} & \quad \text{XH} \\
\text{Y} & \quad \text{XH} \\
\end{align*}
\]

X is usually nitrogen or oxygen. Both intermolecular and intramolecular migrations are known.

8.6.1 Intermolecular Migration from Nitrogen to Carbon

Aniline derivatives readily proceed rearrangement on treatment with acid. First, the formation of conjugate acid of the amine takes place which then eliminates the electrophilic species that reacts at the activated ortho or para position of the aromatic ring.
8.6.1.1 N-Haloanilides (Orton Rearrangement)

Treatment of $N$-chloroacetanilide with hydrochloric acid affords a mixture of ortho and para-chloracetanilides in the same proportions as in the direct chlorination of acetanilide.

Mechanism

8.6.1.2 N-Alkyl-N-nitrosoanilines (Fisher-Hepp Rearrangement)

The conjugate acid of the amine releases nitrosonium ion which reacts at para-position to give the $p$-nitroso product.
Mechanism

![Mechanism Diagram]

8.6.1.3 N-Arylazoanilines

N-Arylazoanilines undergo rearrangement in presence of an acid to produce 4-(2-aryldiazenyl)aniline. On treatment with acid, aryldiazonium ion is formed from the conjugate acid of amine, which migrates to the para position almost selectively.

![8.6.1.3 N-Arylazoanilines Diagram]

8.6.1.4 N-Alkylanilines (Hofmann-Martius Rearrangement)

The mechanism of this rearrangement is same as described above, except the requirement of higher temperature (250-300 °C).

![8.6.1.4 N-Alkylanilines Diagram]
Mechanism

8.6.1.5 N-Arylhydroxylamines (Bamberger Rearrangement)

Arylhydroxyamines with acid undergoes rearrangement to give aminophenols. Mechanism of this reaction is different from those described above. In this rearrangement, the conjugate acid of the hydroxylamine undergoes nucleophilic attack by the solvent.
Examples:

\[
\begin{align*}
\text{Cl} & \quad \text{NOH} & \quad \text{R. E. Harman, Org. Synth. CV4, 148.} \\
\text{H} & \quad \text{HOAc, H}_2\text{SO}_4 & \quad \text{H}_2\text{O, Et}_2\text{O} & \quad \text{Cl} \\
\text{NH} & \quad \text{O} & \quad \text{HOAc, H}_2\text{SO}_4 & \quad \text{H}_2\text{O, Et}_2\text{O} & \quad \text{Cl} \\
\text{R. E. Harman, Org. Synth. CV4, 148.} \\
\text{O} & \quad \text{NOH} & \quad \text{HCl, EtOH} & \quad \text{H}_2\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{Et} & \quad \text{O} \\
\end{align*}
\]

8.6.2 Fries Rearrangement

Aryl esters with Lewis acid undergo rearrangement to give phenols having keto substituent at \textit{ortho} and \textit{para} positions. The complex between the ester and Lewis acid gives an acylium ion which reacts at the \textit{ortho} and \textit{para} positions as in Friedel-Crafts acylation.
**Mechanism**

In general, low temperature favors the formation of *para*-product (kinetic control) and high temperature lead to the formation *ortho*-product (thermodynamic control).

![Chemical Reaction Diagram]

**Examples:**

```
OAc  Cu(OTf)₂  MeSO₃H
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

90%


```

```
Me  OAc  ZrCl₄  CH₂Cl₂
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

47%  32%

```
8.6.3 Intramolecular Migration from Nitrogen to Carbon

The mechanisms of these reactions are not fully understood.

8.6.3.1 PhenylNitramines

These compounds on heating with acid rearrange to give mainly the o-nitro-derivative.

For example,

8.6.3.2 Phenylsulfamic Acids

These compounds rearrange on heating to give o-sulfonic acid derivative that further rearranges at high temperature to afford p-sulfonic acid derivatives. For example,

8.6.3.3 Hydrazobenzenes

These compounds undergo [5,5]-sigmatropic rearrangement in the presence of acid to give benzidines.
Mechanism

![Mechanism diagram]

Examples:

![Examples diagram]

8.6.4 Claisen Rearrangement

Aryl allyl ethers undergo [3,3]-sigmatropic rearrangement on being heating to allylphenols.
Mechanism

If the ortho position is blocked, rearrangement continues to give para-product.

Examples:


Problems:

A. Complete the following reactions with major products and mechanism.

1. 

2. 

3. 

4. 

5. 

B. Write mechanism for the following conversion.
Text Books:

