Molecular Rearrangements

- Migration of one group from one atom to another within the molecule

- Generally the migrating group never leaves the molecule

- There are five types of skeletal rearrangements:
  1. Electron deficient skeletal rearrangement
  2. Electron rich skeletal rearrangement
  3. Radical rearrangement
  4. Rearrangements on an aromatic ring
  5. Sigmatropic rearrangement
Molecular Rearrangements

Electron Deficient Skeletal Rearrangement

- Generally it involves migration of a group from one atom to an adjacent atom, having six electrons in the valence shell.
- The molecular system may be either a cation or a neutral molecule.

Examples:

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

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{C} \\
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{C} \\
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{N} \\
\text{R} & \quad \text{R} \\
\text{C} & \quad \text{O} \\
\text{R} & \quad \text{R}
\end{align*}
\]
Molecular Rearrangements

Wagner- Meerwin Rearrangement

- Rearrangement of alcohols under acidic condition

![Chemical structure diagram]

- Alkyl migration occurs to give stable carbocation
- This is the driving force for the migration of alkyl, aryl or even hydrogen atom
Molecular Rearrangements

Wagner- Meerwin Rearrangement

\[
\text{Isoborneol} \xrightarrow{H^+} \text{Camphene}
\]

\[
\text{Isoborneol} \xrightarrow{H^+} \text{ Intermediate} \xrightarrow{\text{Cyclization}} \text{Camphene}
\]
Molecular Rearrangements

Ring Expansion

- More stable carbocation will be generated
- Stability of carbocations - 
  $3^\circ > 2^\circ > 1^\circ$

Can we go from $3^\circ$ to $2^\circ$ ??

- Cations can be made more stable if they become less strained

Relief in strain from four to five membered ring is driving force
Molecular Rearrangements

Ring Expansion

Tertiary carbocation migrated to secondary
Molecular Rearrangements
Pinacol-Pinacolone Rearrangement

Pinacol + H$_2$SO$_4$ → Pinacolone

- Carbocation is already tertiary
- There is no ring strain
- Then why should it rearrange?

**Reason:**
The lone pair of electrons on the oxygen is another source to stabilize the carbocation
Molecular Rearrangements

Pinacol-Pinacolone Rearrangement

- Pinacol-Pinacolone rearrangement can be viewed as a push and a pull rearrangement
- The carbocation formed as a result of loss of $H_2O$, pulls the migrating group
- Lone pair on oxygen pushes the migrating group

Preparation of Spiro System:
Molecular Rearrangements

Pinacol-Pinacolone Rearrangement

Epoxides:
Epoxides also undergo pinacol type rearrangement on treatment with acid

- With a Grignard reagent, rearrangement occurs faster than addition to the epoxide
Molecular Rearrangements

Pinacol-Pinacolone Rearrangement

- **Migrating group preference:**
  - It doesn't matter when we have symmetrical diols & epoxides
  - It doesn't matter when we have unsymmetrical epoxides & diols

Only I is formed in quantitative amount because the carbocation is stabilized by two phenyl groups
Molecular Rearrangements
Semipinacol Rearrangement

They are nothing but pinacol rearrangement without choice

Isonopinone

Under normal acidic conditions

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Molecular Rearrangements

Semipinacol Rearrangement

For the required product, the primary hydroxyl group needs to be made as better leaving group

\[
\text{HO} - \text{CH}_3 - \text{OH} \xrightarrow{\text{TsCl, Py}} \text{HO} - \text{CH}_3 - \text{OTs}
\]

\[
\text{CaCO}_3 \quad \text{Weak base} \quad \xrightarrow{} \quad \text{HO} - \text{CH}_3 - \text{OTs} \quad \xrightarrow{} \quad \text{Cyclohexanone}
\]

Corey exploited a similar sequence in the synthesis of longifolene
Molecular Rearrangements

Semipinacol Rearrangement

Leaving group need not be tosylated and it can be anything which can readily leave

Longifolene
Molecular Rearrangements
Semipinacol Rearrangement

\[
\begin{align*}
\text{Ome} & \text{OH} \quad \xrightarrow{H^+} \quad \text{OMe} \quad \xrightarrow{\text{OH}_2} \quad \text{C} \quad \equiv \\
\text{Ome} & \text{OH} \quad \xrightarrow{H^+} \quad \text{OMe} \quad \xrightarrow{\text{OH}_2} \quad \text{C} \quad \equiv 
\end{align*}
\]
Molecular Rearrangements
Diazonium salts

Tiffeneau-Demjanov Rearrangement:

Selectivity:
Molecular Rearrangements
Diazonium salts

Mechanism:

Alkyl group which is anti to the leaving group, will migrate
Molecular Rearrangements

Fragmentation:

Fragmentations always require electron push and electron pull

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Molecular Rearrangements

An Important Method to Make Higher Cycloalkanes:

\[
\begin{align*}
\text{Initial Compound} & \xrightarrow{H^+} \text{Intermediate Compound} & \xrightarrow{H^+} \text{Final Compound} \\
\text{Initial Compound} & \xrightarrow{H^+} \text{Intermediate Compound} & \xrightarrow{H^+} \text{Final Compound}
\end{align*}
\]
Molecular Rearrangements

Base Conditions or Nucleophilic Conditions:

Antiperiplanar bond migrates

10-membered ring
Molecular Rearrangements

Eschenmoser Fragmentation

1) NaOH/H₂O₂

2) TsNHNH₂/PTSA

Base

Ts⁻ + N₂ + CHO

1) NaBH₄

2) PTSA

O₃/Me₂S

Base

1) NaOH/H₂O₂

2) TsNHNH₂/PTSA

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Molecular Rearrangements

Fragmentation of Four-Membered Ring

Other Examples:

- Aldol condensation

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Molecular Rearrangements

Sigmatropic Rearrangements

[3,3]-Sigmatropic Rearrangement

Cope Rearrangement:

It is a [3,3]-sigmatropic rearrangement with only carbon atoms involved in the six membered transition state.

Why is it called [3,3]?

The new $\sigma$ bond formed has 3,3-relationship with the old $\sigma$-bond.
Molecular Rearrangements
Sigmatropic Rearrangements

Mechanism:
It goes via six-membered chair-like transition state

trans

More stable conformer

trans

Less stable conformer

\[\Delta\]

E,E-isomer
Favoured

\[\Delta\]

Z,Z-isomer

\[\Delta\]

E,Z

\[\Delta\]

Z,E

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Molecular Rearrangements
Sigmatropic Rearrangements

1) Cope:

2) Oxy-Cope:
Molecular Rearrangements

3) Anionic-Oxy-Cope:

4) Claisen Rearrangement of Allylvinyl Ethers:
Molecular Rearrangements

Sigmatropic Rearrangements

5) Claisen Rearrangement of Allylphenyl Ethers:

\[
\text{PhO} \xrightarrow{\text{Ph}} \text{Ph} = \text{CH} \xrightarrow{\text{Ph}} \text{PhOH} \]

6) Ortho-Ester Claisen Rearrangement:

\[
\text{RO} \xrightarrow{\text{ROH}} \text{OR} \xrightarrow{\text{Hg(OAc)}_2} \text{OEt} \xrightarrow{\Delta} \text{OEt} \]
Molecular Rearrangements

Sigmatropic Rearrangements

7) O-Allyl-O-TMS-Ketone Acetals:

8) Ester-Enolate Claisen:

9) Ketene Aminals:
Molecular Rearrangements

Sigmatropic Rearrangements

10) Aza-Claisen Rearrangement:

Other Examples:
Molecular Rearrangements

Sigmatropic Rearrangements

**Stereochemistry:**

\[
\begin{align*}
\text{Z-silyl ether} & \quad \rightarrow \quad \text{trans} \\
\text{E-silyl ether} & \quad \rightarrow \quad \text{cis}
\end{align*}
\]
Molecular Rearrangements

1. Allylic Sulfoxides:

2. Allylic Sulfonium Ylides:
3) N-Oxides:

**Sommelet-Hauser Rearrangement**
Molecular Rearrangements

Sigmatropic Rearrangements

Stevens Rearrangement

\[
\text{Stevens Rearrangement:} \quad \text{NaOH} \quad \rightarrow
\]

Wittig Rearrangement

\[
\text{Wittig Rearrangement:} \quad \text{PhLi} \quad \rightarrow
\]

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Molecular Rearrangements

Sigmatropic Rearrangements

Ene Reaction

\[
\text{H} \quad \text{EWG} \quad \rightarrow \quad \text{EWG} \quad \text{H}
\]

\[
\text{CO}_2\text{R} \quad \text{OH}
\]

\[
\text{H} \quad \text{CO}_2\text{R} \quad \rightarrow \quad \text{CO}_2\text{R}
\]

\[
\text{H} \quad \text{CO}_2\text{R} \quad \rightarrow \quad \text{CO}_2\text{R}
\]
Molecular Rearrangements

Cheletropic Elimination

Two bonds are broken at a single atom

\[
\text{Cycloaddition reaction:} \quad \text{SO}_2 + \text{Ph} \rightarrow \text{Ph} + \text{SO}_2
\]
Molecular Rearrangements

Elimination of Carbon monoxide (CO)

\[
\text{Ph} \quad \text{CHO} \quad \text{OEt}
\]

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Molecular Rearrangements

Elimination of Carbon monoxide (CO)

[4+2]-Cycloaddition

- CO₂

- MeOH

Aromatization
Molecular Rearrangements
Dienone-Phenol Rearrangement

- Can be considered as a reversal of pinacol rearrangement
- Pinacol & semipinacol rearrangements are driven by the formation of a carbonyl group
- In dienone-phenol rearrangement protonation of carbonyl group Rearranges to a tertiary carbocation
- The driving force for this reaction is the formation of aromatic rings
Molecular Rearrangements
Dienone-Phenol Rearrangement

Mechanism:
The industrial formation of nylon relies upon the alkaline polymerization of a acyclic amide known as caprolactam.

Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the Beckmann rearrangement.
Molecular Rearrangements

Beckmann Rearrangement

Mechanism:

- Follows the same pattern as pinacol
- Converts the oxime into a good leaving group
- Alkyl/ Aryl group migrates on to nitrogen as water departs
- The product cation is then trapped by water to give an amide
Molecular Rearrangements

Beckmann Rearrangement

- It can also work with acyclic oximes
- \( \text{PCl}_5, \text{SOCl}_2 \) & other acyl or sulfonyl chlorides can be used instead of acid

![Beckmann Rearrangement Diagram]

Migratory Aptitude:

![Migratory Aptitude Diagram]
In case of unsymmetrical ketone:

- There are two groups that could migrate
- There are two possible geometrical isomers of unsymmetrical oxime
- When the mixtures of geometrical isomer of oximes are rearranged, mixtures of products result
- Interestingly, the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials
- The group that has migrated, is trans to the -OH group
Molecular Rearrangements

Beckmann Rearrangement

86 : 14
Steric effect

88 : 12
Molecular Rearrangements

Baeyer Villiger Oxidation

Mechanism:

\[ \text{R} \overset{\text{R''-C-O-OH}}{\rightarrow} \text{R'} \overset{\text{O}}{\rightarrow} \text{R''} \overset{\text{O}}{\rightarrow} \text{R'} \overset{\text{O}}{\rightarrow} \text{R''} \overset{\text{O}}{\rightarrow} \text{R'COOR} \]

Migratory Aptitude:

\( t-\text{Bu} > i-\text{Pr} = \text{Ph} > \text{Et} > \text{Me} \)

L-dopa

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B.V.O. of Unsaturated Ketones:

There are three possibilities

1) Peracids can selectively epoxidize

2) Peracids can selectively carry out B.V.O

3) Can carry out both reactions

It is difficult to predict the outcome & it depends on-

1) Electrophilic nature of the ketone

2) Nucleophilic nature of the alkene
Molecular Rearrangements

Baeyer Villiger Oxidation

- Tertiary group migrates in preference of the secondary group
- The alkene is not as reactive as expected because of steric crowding
Molecular Rearrangements
Baeyer Villiger Oxidation

Small ring ketones will readily undergo B.V.O.

Starting material configuration is retained in the product
The transition state has two more electrons

Generally initiated by basic reagents which remove a group or an atom such as hydrogen

The residual anion then stabilizes itself by rearrangement

In the first step an acid strengthening substituent is necessary to stabilize the ionic center
Molecular Rearrangements
Electron-Rich (Anionic) Skeletal Rearrangements
Stevens Rearrangement

Proton removal is facilitated by the positive charge in the cationic substrate and also by the enolate ion formation.

Migrating groups are generally benzyl or allyl system.
Molecular Rearrangements

Electron-Rich (Anionic) Skeletal Rearrangements

Wittig Rearrangement

- It also follows a similar pathway
- Only difference is substrates are much less acidic than those encountered in Stevens rearrangement
- Powerful basic reagents are required to cause the Wittig Rearrangement

\[
\begin{align*}
H_3C\overset{O}{-}C\overset{C}{-}C_6H_5 & \xrightarrow{\text{PhLi}} H_3C\overset{O}{-}C\overset{\text{H}}{-}C_6H_5 & \xrightarrow{\text{H}_3\text{O}^+} \text{HO-C-C}_6\text{H}_5 \\
H_2C\overset{C}{-}C\overset{C}{-}O\overset{C}{-}C\overset{\text{H}}{-}C\overset{\text{H}}{-}C\overset{\text{H}}{-}C\overset{\text{H}}{-}C\overset{\text{CH}_2}{-} & \xrightarrow{\text{1) PhLi}} H_2C\overset{\text{H}}{-}C\overset{\text{C}}{-}\overset{\text{C}}{-}\overset{\text{OH}}{-}C\overset{\text{H}}{-}C\overset{\text{C}}{-}C\overset{\text{H}}{-}C\overset{\text{CH}_2}{-} & \xrightarrow{\text{2) H}_3\text{O}^+} H_2C\overset{\text{C}}{-}C\overset{\text{C}}{-}\overset{\text{C}}{-}\overset{\text{CH}}{-}C\overset{\text{C}}{-}C\overset{\text{H}}{-}C\overset{\text{H}}{-}C\overset{\text{CH}_2}{-}
\end{align*}
\]
Molecular Rearrangements

Electron-Rich (Anionic) Skeletal Rearrangements

Sommelet-Hauser Rearrangement

Nucleophilic alkylation of the aromatic rings of a benzyltrimethylammonium ion
Rearrangements

Benzilic acid Rearrangement

Mechanism:

Formation of stable carboxylate salt is driving force for the reaction

Application has been limited only to aromatic α-diketones
Rearrangements on an Aromatic Ring

1. Fries Rearrangement
2. Claisen Rearrangement
3. Rearrangements of Derivative of aniline

Rearrangements of Derivatives of Aniline:

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \xrightarrow{\text{Cl}_2} \quad \text{ClN}_2\text{O}_3\text{C}_3\text{CH}_3 & \quad \xrightarrow{\text{HCl}} & \quad \text{NHCOCH}_3 & + & \text{HNCOCH}_3 \\
\text{ClN}_2\text{O}_3\text{C}_3\text{CH}_3 & \quad \xrightarrow{\text{HCl}} & \quad \text{HNCOCH}_3 & + & \text{HNCOCH}_3
\end{align*}
\]
Rearrangements on an Aromatic Ring

Rearrangements of Derivatives of Aniline:

![Chemical structure of diazoamino benzene and its rearrangement to p-amino diazobenzene](image)

It is still not clear whether it involves inter or intramolecular mechanism

Rearrangement of N-Methyl-N-Nitrosoamine:

![Chemical structures showing the rearrangement](image)
Rearrangements on an Aromatic Ring

Rearrangement of N-Phenylhydroxylamine:

\[ \text{NH}_2 \text{OH} + \text{NH}_2 \text{OH} \rightarrow 2 \text{NH}_2 \text{OH} \]

Mechanism:

1. \[ \text{HO-NH} \rightarrow \text{NH}^+ \text{NH} \]
2. \[ \text{NH}^+ \text{NH} \rightarrow 2 \text{NH}^+ \]
3. \[ \text{NH}^+ \text{NH} \rightarrow \text{NH}_2 \text{OH} \]
Rearrangements

Rearrangements on Aromatic Ring

Rearrangement of N,N-Dimethylanilinium chloride:

\[ \text{NHCH}_3 \rightarrow \text{NH} \rightarrow \text{H}_3 \text{C} \rightarrow \text{Cl} \]

\[ \Delta \]

\[ \text{CH}_3 \text{Cl} \rightarrow 275^\circ \text{C} \rightarrow \text{NHCH}_3 \]

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Rearrangements

Rearrangements on Aromatic Ring

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[\text{H}_3\text{O}^+ \quad \text{hydrolysis} \quad \rightarrow \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]

\[\text{H}^+ \quad \rightarrow \quad \text{H}^+ \quad \rightarrow \quad \text{H}^+ \quad \rightarrow \quad \text{H}^+ \]

\[\text{OH} \quad \text{OH} \quad \text{OH} \quad \text{OH} \]

\[\text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]

\[\text{HN} \quad \text{OH} \quad \text{HN} \quad \text{OH} \]

\[\text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]

\[\text{HN} \quad \text{OH} \quad \text{HN} \quad \text{OH} \]

\[\text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]

\[\text{HN} \quad \text{OH} \quad \text{HN} \quad \text{OH} \]

\[\text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]

\[\text{HN} \quad \text{OH} \quad \text{HN} \quad \text{OH} \]

\[\text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \quad \text{H}_3\text{C} \]
Rearrangements on an Aromatic Ring

Rearrangement of PhenylNitramine:

\[
\text{NHNO}_2 \xrightarrow{H^+} \text{H}_2\text{N}^+\text{NO}_2 \xrightarrow{H^+} \text{N}_2\text{H}^+\text{NO}_2 \xrightarrow{H^+} \text{NH}_2\text{NO}_2 + \text{NH}_2
\]

Rearrangement of Phenylsulfamic acid:

\[
\text{NHSO}_3\text{H} \xrightarrow{H^+} \text{H}_2\text{N}^+\text{SO}_3\text{H} \xrightarrow{H^+} \text{NH}_2\text{SO}_3\text{H} \xrightarrow{\Delta} \text{NH}_2\text{SO}_3\text{H}
\]

These reactions involve intramolecular pathway.
Rearrangements
Rearrangements on an Aromatic Ring

Benzidine Rearrangement:

\[
\text{Benzidine Rearrangement:} \quad \begin{array}{c}
\text{NH}_2 \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{NH}_2 \\
\text{H} \\
\text{H}
\end{array} \xrightarrow{2\text{H}^+} \begin{array}{c}
\text{N}^+ \text{H} \\
\text{H} \\
\text{N}^+ \text{H}
\end{array} \xrightarrow{\text{H}_2\text{N}} \begin{array}{c}
\text{N}^+ \text{H} \\
\text{H} \\
\text{N}^+ \text{H}
\end{array} \xrightarrow{\text{H}_2\text{N}} \begin{array}{c}
\text{NH}_2 \\
\text{H} \\
\text{H}
\end{array} \xrightarrow{\text{H}_2\text{N}} \begin{array}{c}
\text{NH}_2 \\
\text{H}
\end{array}
\]
Rearrangements

Some Additional Problems

\[
\text{Cl-}\text{C-}\text{C}^- + 2\text{CaCO}_3 \xrightarrow{\text{NaCN}} \text{Cl-}\text{C-}\text{C-CN} \xrightarrow{\text{H}_3\text{O}^+} \text{Cl-}\text{C}^-\text{CN} \xrightarrow{\text{hydrolysis of acid derivative}} \text{Cl-}\text{CH-}\text{C-O}_2^- \xrightarrow{\text{CaCl}_2 + 2\text{CO}_2 + \text{H}_2\text{O}} \text{dichloro acetic acid}
\]
Rearrangements

Some Additional Problems

\[
\text{methanolic NH}_3 \quad \text{sealed tube heating} \quad \overset{\text{ring opening}}{\longrightarrow} \quad \text{vinylogous substitution}
\]
Rearrangements

Some Additional Problems

\[
\begin{align*}
\text{Rearrangements} & \\
\text{Some Additional Problems} & \\
\end{align*}
\]
Rearrangements

Some Additional Problems
Rearrangements

Some Additional Problems

Acid cat. aldol condensation

[Chemical reactions and structures]

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