1,3-Elimination: Decarboxylation

- Elimination can also occur when an acidic hydrogen and a leaving group are separated by three atoms, in what is termed 1,3-elimination.
- When a carboxyl carbon is β to a π-bond (a carbonyl, alkene or aryl) the acidic hydrogen of the acid can be transferred to the oxygen of the carbonyl (or to the sp² carbon of alkenes or aryls) via a six-center transition state. This requires a syn-orientation of the carbonyl oxygen and the carboxyl hydrogen.
- This 1,3-elimination process is called **decarboxylation** and is a common reaction of β-keto-acids, β-carboxyl esters, and 1,3-diacids (malonic acid derivatives). A simple example is the elimination of carbon dioxide from 3-oxopentanoic acid (290) to give **an enol, which tautomerizes to 2-butanone**.
- Decarboxylation begins with an internal acid-base reaction, where the acid is the O-H unit of the carboxylic acid, and the base is the oxygen of the carbonyl β to the acid moiety. Decarboxylation is assisted by loss of a neutral leaving group carbon dioxide.

![Diagram](image-url)
1,3-Elimination: Krapcho decarboxylation

- Krapcho and co-workers developed a mild decarboxylation procedure of esters.
- In a synthesis of deacetoxyalcyonin acetate by Molander and co-workers, \( \beta \)-keto methyl ester 295 (drawn in its enol form) was heated with LiCl in aqueous DMSO to give decarboxylation and a good yield of 296.
- This mild procedure is referred to as Krapcho decarboxylation.
- An alternative procedure has been reported. In a synthesis of (\( \leftarrow \))-gilbertine by Blechert and Jiricek, heating 297 with DABCO, in toluene and water, gave 298 in 66% yield.
1,3-Elimination: Grob Fragmentation

- Prelog first observed this reaction in work that solved the structure of quinine and other Cinchona alkaloids. This work involved degradation studies that included treatment of 304 with KOH and silver nitrate.
- Silver ion reacted with the bromide to give a carbocation (305). Subsequently, the nitrogen lone pair induced a 1,3-elimination ring-opening reaction, as shown, to give iminium salt 306.
- In the presence of aqueous hydroxide in the reaction medium, addition to the iminium salt led to loss of formaldehyde and formation of the final product, 307.
- Transfer of the nitrogen lone electron pair toward the leaving group (or the carbocation center) required the N-C bond and the C-C\(^+\) bond to have an anti relationship.
- This anti relationship is taken from Prelog's proposed synchronous mechanism for the 1,3-elimination, and can be generalized to say that "both the C\(_a\)-X bond and the orbital of the nitrogen lone pair be antiperiplanar to the C\(_b\)-C\(_g\) bond".

![Chemical reaction diagram](image-url)
1,3-Elimination: Grob Fragmentation

- Elimination of the 5\textsubscript{b}-isomer (308) gave the (E)-isomer (309), whereas elimination of the 5\textsubscript{a}-isomer gave the (Z)-isomer (311), along with 311.
- The stereochemistry of the products is best explained if the pertinent orbitals are antiparallel in the transition state leading to the elimination.
- The 5\textsubscript{a}-isomer (310) reacted much slower and gave a mixture of the substitution product (311) in addition to the elimination product (312).
- Although the reaction was discovered by Prelog, Grob's contributions to this reaction led to its bearing his name, the Grob fragmentation.
1,3-Elimination: Grob Fragmentation

\[
\text{MeO}_2\text{SO} \xrightarrow{t-\text{BuO}^-} \text{Me} \xrightarrow{\text{Me}^+} \text{Me} \xrightarrow{\text{OCH}_2\text{Ph}} 316 \xrightarrow{t-\text{BuO}^-} 317 \xrightarrow{\text{Me}^+} \text{Me} \xrightarrow{\text{OCH}_2\text{Ph}} 318
\]

\[
\text{OMs} \xrightarrow{\text{KH} \text{MDS}} 319 \xrightarrow{0^\circ \text{C}} 320 \xrightarrow{\text{OMs}} 321
\]
Functional Group Change by Rearrangement: Beckmann Rearrangement

- When oximes are treated with sulfuric acid, PCl$_5$ and related reagents, rearrangement occurs to give substituted amides in what is called the **Beckmann rearrangement**.
- The group that migrates is generally the one anti to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, the syn group may migrate in some oximes, especially where R and R' are both alkyl.
- In most cases the oxime can undergo isomerization under the reaction conditions *before* migration takes place.
- It is possible to get mixtures of the two different amides from oximes derives from unsymmetrical ketones. **Note that hydrogen seldom migrates**, and most alkyl groups are compatible with the reaction. In alkyl aryl ketones, the aryl group generally migrates preferentially.
- The oximes of cyclic ketones such as 384 give ring enlargement under these conditions, with formation of a lactam (385).
- Beckmann rearrangements have also been carried out photochemically.
Functional Group Change by Rearrangement:
Beckmann Rearrangement

\[ \text{386} \xrightarrow{\text{H}_2\text{N}-\text{OSO}_3\text{H}} \xrightarrow{\text{HCOOH}} \text{387} \xrightarrow{} \text{388} \]

\[ \text{389} \xrightarrow{\text{TsCl, NaHCO}_3} \xrightarrow{\text{aq acetone}} \text{70\%} \xrightarrow{} \text{390} \]
Functional Group Change by Rearrangement: Schmidt Rearrangement

- The addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes leads to an amide in what is called the **Schmidt reaction**.
- The reaction with carboxylic acids is probably the most common, involving initial formation of an acyl azide ($\text{391}$), which rearrangements with loss of nitrogen to give a transient isocyanate ($\text{392}$).
- Subsequent reaction with water gives $\text{393}$, which decarboxylates to give the amine product.
- Sulfuric acid and many Lewis acids can be used as catalysts in this reaction.
- Under normal reaction conditions, the isocyanate is not isolated. **When hydrazoic acid reacts with a ketone, the product of the rearrangement is an amide ($\text{394}$).**
- Dialkyl ketones and cyclic ketones tend to react faster than alkyl aryl ketones, and these faster than diaryl ketones.
Functional Group Change by Rearrangement:
Schmidt Rearrangement

- Regioselectivity can be a problem when unsymmetrical cyclic ketones are converted to the lactam, but the reaction often proceeds with good regioselectivity.
- When 2-methyl-cyclohexanone reacted with sodium azide in the presence of polyphosphoric acid, for example, the two lactam products were 7-methylhexahydroazepin-2-one (397) in 54% yield and 398 in 10% yield.
- A useful variation of the Schmidt reaction involves reaction of a silyl enol ether of a cyclic ketone with TMSN$_3$, followed by photolysis of the product with UV light to give a lactam.
Without the aqueous conditions, the thermal rearrangement of acyl azides to isocyanates ($\text{391} \rightarrow \text{392}$) is known as the **Curtius rearrangement**. Subsequent reaction with water, alcohols or amines lead to amines, carbamates, or acylureas.

In general, acyl azides are prepared by treatment of acylhydrazines (hydrazides) with nitrous acid. Lewis acids can catalyze the Curtius rearrangement, but they are not required.

When an amide is treated with sodium hypobromite ($\text{NaOBr}$; $\text{NaOH}$ and $\text{Br}_2$) an isocyanate is formed, and subsequent hydrolysis liberates an amine with one less carbon that the starting amide, in what is known as the **Hofmann rearrangement**.

Ureas and acylureas are sometimes formed in this reaction. $N$-Acyl derivatives of hydroxamic acids give isocyanates when treated with base, or upon heating, in the **Lossen rearrangement**. Similarly, aromatic acyl halides are converted to amines when treated with hydroxylamine-$O$-sulfonic acid.
Hückel's rule states that for planar, monocyclic hydrocarbons containing completely conjugated sp\(^2\) hybridized atoms, the presence of \((4n+2)\) \(\pi\)-electrons leads to aromaticity (\(n\) is an integer in the series 0, 1, 2, 3, etc.).

Compounds such as these are termed annulenes (completely conjugated aromatic hydrocarbons) and this becomes part of the name. Benzene could be named [6]-annulene, 111 is named [14]-annulene, and 112 is [18]-annulene.
Aromaticity: Intermediates

Base-mediated alkylation of cyclopentadiene is facile. That for cycloheptatriene is very difficult.
Benzene is a Weak Base

the $\pi$-bond acts as a base

$\text{2} \xrightarrow{\text{H-Br}} \text{4}$

$\text{3} \xrightarrow{\text{H-Br}} \text{6}$

benzene is not basic enough to react with HBr

$\text{1} \xrightarrow{\text{H-Br}} \text{No Reaction}$
Benzene is a Weak Base

\[ \text{Benzene} + \text{Br}_2 \rightarrow \text{No Reaction} \]

\[ \text{Benzene} + \text{Br}_2, \text{FeBr}_3 \rightarrow \text{Benzene} \]

\[ \begin{align*}
\text{Br} & \quad \text{Br}_2 \\
\text{H} & \quad \text{H} \\
\text{Br} & \quad \text{Br} \\
\text{H} & \quad \text{H} \\
\text{Br} & \quad \text{Br}
\end{align*} \]

- Carbocation, 40 is a high energy intermediate called a Wheland intermediate, named after George Willard Wheland (1907-1976; USA).

- Such intermediates have also been called Meisenheimer adducts (named after Jakob Meisenheimer, 1876-1934; German).

- The more name is a \(\sigma\)-adduct or an arenium ion.
Nitration

Which is the acid and which is the base?

\[
\begin{align*}
&\text{base} & \text{acid} \\
&\text{Nitration reaction}
\end{align*}
\]

\[
\begin{align*}
&\text{H}_2\text{SO}_4/\text{SO}_3 \text{ gives benzenesulfonic acid} \\
&\text{Cl}_2/\text{LA} \text{ gives chlorobenzene; Br}_2/\text{LA} \text{ gives bromobenzene} \\
&\text{HNO}_3/\text{H}_2\text{SO}_4 \text{ gives nitrobenzene}
\end{align*}
\]
Bromine reacts in a manner identical to chlorine, producing $\text{Br}^+$ as a reactive intermediate (in the charge-transfer complex).

- Reaction of bromine, benzene, and aluminum chloride gives bromobenzene.
- Typical Lewis acid catalysts for this reaction are $\text{AlCl}_3$, $\text{SbCl}_3$, $\text{PCl}_3$, $\text{PCl}_5$, and $\text{SnCl}_4$.
- When benzene is treated with a mixture of nitric and sulfuric acids, nitrobenzene is the product, via a nitronium ion ($\text{NO}_2^+$).
- Benzene also reacts with sulfuric acid [or sulfuric acid saturated with sulfur trioxide ($\text{SO}_3$), which is known as fuming sulfuric] to give benzenesulfonic acid.
- Benzenesulfonic acid is also formed by reaction of benzene with chlorosulfonic acid ($\text{ClSO}_3\text{H}$) or fluorosulfonic acid ($\text{FSO}_3\text{H}$).
Selectivity

\[ \text{Cl}_2, \text{AlCl}_3 \]

122 \[\rightarrow\] 126

\[ \text{Cl}^+ \]

122 \[\rightarrow\] 127A, 127B, 127C, 127D, 127E

intact benzene rings (2 Kekule structures for each)

\[ \text{Cl}^+ \]

122 \[\rightarrow\] 128A, 128B, 128C, 128D, 128E

intact benzene ring (2 Kekule structures)