Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Fischer-Hepp rearrangement

Transformation of an N-nitroso derivative of a secondary aromatic amine to the corresponding p-nitroso derivative, under the influence of acid.

Background information:

Nitrosation of secondary aromatic amines like N-methylaniline gives a mixture of N-nitroso and C-nitroso derivatives. (compare acylation of phenol, as seen in Fries)

When the N-nitroso derivative is heated with aq. HCl, it is converted to the C-nitroso product. This is the Fischer-Hepp rearrangement.

Mechanism: Intramolecular migration of nitrosonium:

Proof of intramolecularity:

When the rearrangement is carried out in presence of $^{15}$N-enriched NaNO$_2$, there is no incorporation of radiolabelled N into the end-product.

This proves that the migrating nitrosonium does not get detached from the starting material at any time and NO$^+$ from outside cannot enter.

Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Hofmann-Martius rearrangement

Transformation of an N-alkyl derivative of an aromatic amine to the corresponding C-alkyl derivative, under the influence of acid. Alkyl group migrates to the o-/p-positions w.r.t. the N.

Mechanism: Intermolecular migration of alkyl

\[
\begin{align*}
\text{N-methylaniline} & \xrightarrow{\text{aq. HCl, heat or ZnCl}_2} \text{p-toluidine} + \text{o-toluidine} \\
\text{N-methylaniline} & \xrightarrow{H^+} \text{NH}_2\text{Me} \xrightarrow{\text{Cl}^-} \text{+NH}_2\text{Me} \xrightarrow{\text{Sn}_2} \text{H}^+\text{NH}_2\text{Me} \xrightarrow{\text{Me-Cl}} \text{H}^+\text{NH}_2\text{Me} \xrightarrow{\text{Me-Cl}}
\end{align*}
\]

When a Lewis acid is used instead of a protic acid, the rearrangement is called Riley-Hickinbottom rearrangement; a variation of the Hofmann-Martius.

Proof:

1. Intermolecular nature proved by following experiment:

\[
\begin{align*}
\text{H}^+\text{N}^+\text{Me} & \xrightarrow{\text{heat}} \text{NH}_2\text{Me} + \text{o-toluidine} + \text{p-toluidine} + \text{di-and trimethylated anilines}
\end{align*}
\]

2. The \textit{in situ} generated alkyl chlorides has been recovered from the medium, thereby proving their formation.

\[
\begin{align*}
\text{H}^+\text{N}^+\text{Me} & \xrightarrow{\text{heat}} \text{aniline} + \text{Me-Cl} \\
\text{H}^+\text{N}^+\text{Me} & \xrightarrow{\text{heat}} \text{aniline} + \text{Me-Cl}
\end{align*}
\]

3. Bromide, chloride and iodide gave \textit{different} o-/p- ratio under same reaction condition which proves that the halide ions are involved in the reaction, as per the mechanism proposed.
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Hofmann-Martius rearrangement

Proof:
4. The recovered primary organohalides do not show any rearranged structure but once incorporated in the ring, they are most frequently rearranged; i.e.

The rearrangement of the alkyl chain during S$_{E}$Ar is reminiscent of the same seen for Friedel-Crafts alkylation.

Synthetic utility:

Synthesis of 2,4,6-trimethylaniline

This is done by a series of Hofmann-Murtius rearrangements:

The reaction proceeds in a stepwise manner, one by one methyls migrate:
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Orton rearrangement

Migration of halogen atom of N-haloanilides to the aromatic ring from the amide side chain on treatment with HX.

Synthesis of the N-haloanilide:

\[
\text{Me} \quad \overset{\text{Base, Cl}_2}{\rightarrow} \quad \text{Me} \quad \overset{\text{Ar-N-H}}{\rightarrow}
\]

Recall Hofmann degradation/rearrangement.

Synthetic utility of Orton rearrangement:
2'- or 4'-haloacetanilides are sources of 2- and 4-haloanilines, recall than monohalogenation of aniline is a challenge via SEAr

Mechanism:

![Mechanism Diagram]

Alternative mechanistic proposal:

![Alternative Mechanism Diagram]
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Orton rearrangement

Proof:

1. Molecular chlorine has been recovered from reaction medium, thereby proving its in situ generation, and intermolecular nature of the reaction.

2. In presence of halogen captors, cross-halogenation take place - again proving that that halide is detached from the N-haloanilide, i.e. reaction is intermolecular.

3. Anisole is more reactive than 2,6-dichloroacetanilide towards SEAr. The acetamido group in the anilide is forced out of the ring plane due to steric crowding with the two ortho-chlorines and thus it cannot stabilize the α-complex by conjugation. This results in selective chlorination of anisole.

The α/β- ratio of this reaction is exactly the same obtained from Orton rearrangement of N-chloroacetanilide. This concurs with the mechanism proposed where this SEAr is the endgame.

Effect of presence of other halides: When done in the presence of other HX acids (X = Br, I), Orton rearrangement of N-chloroacetanilides under hydrochloric acid afford the corresponding bromo- or iodo-derivatives.

X is the electrophilic end when X = Br, I
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement

Rearrangement of \(N\)-phenylhydroxylamine to 4-aminophenol under aq. acidic condition.

Mechanism:

\[
\begin{align*}
\text{HN} & \text{OH} \\
\text{H}^+ & \text{+} \\
& \text{H}_2\text{O} \text{, slow} \\
\text{N} & \text{H} \\
\text{H}_2\text{N} & \text{OH}
\end{align*}
\]

Nitrenium ion like benzylic cation - but less stable
N has only 6 electrons around it

The reason behind exclusive \(p\)-attack is not well-known

Yield improves on heating the reaction mixture.

Proof:

1. Kinetic studies reveal that the mechanism is \(S_N1\) and not \(S_N2\) as the rate is independent of the concentration of added nucleophiles.

2. The rearrangement is intermolecular in nature as proved by following experiments:

a) \[
\begin{align*}
\text{HN} & \text{OH} \\
\text{H}^+ & \text{HO}^* \\
& \text{[} \text{=} ^{18}\text{O} \text{]} \\
\text{N} & \text{H} \\
\text{H}_2\text{N} & \text{OH}
\end{align*}
\]

\[^{18}\text{O} \text{ incorporated}\]

b) \[
\begin{align*}
\text{HN} & \text{OH} \\
\text{H}_2\text{O} & \text{HCl} \\
\text{N} & \text{H} \\
\text{Cl}
\end{align*}
\]

\[\text{chloride incorporated}\]

c) \[
\begin{align*}
\text{Et} & \text{N} \text{OH} \\
\text{H}^+ & \text{HO}^* \\
& \text{H}_2\text{O} \text{, MeOH} \\
\text{Et} & \text{N} \text{H}
\end{align*}
\]

\[\text{MeOH incorporated}\]

The nitrenium cation can be captured by external nucleophiles such as methanol or chloride or radiolabeled water. Concurrent with the mechanism outlined.
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement

Proof (contd.):

3. 

\[ \text{Et-N=O} \xrightarrow{H_2O^+} \text{H}_2\text{O} \]

\[ k_1 \]

\[ \text{Et-N=O} \xrightarrow{H_2O^+} \text{H}_2\text{O} \]

\[ k_2 \approx 100 k_1 \]

The developing positive charge in the TS is mostly localised on C4 and not on N.

The product from the 4-methyl derivative:

\[ \text{NO}_2 \xrightarrow{\text{Zn, NH}_4\text{Cl, aq. alcohol}} \text{Me} \xrightarrow{\text{H}^+} \text{Me} \xrightarrow{\text{H}_2\text{O}} \text{Me} \xrightarrow{\text{MeOH, slow}} \text{Me} \xrightarrow{\text{MeOH}} \text{Me} \]

4-nitrotoluene

Recall,

\[ \text{O} \xrightarrow{\text{HO}_3\text{SO}_3\text{OH, MeOH}} \text{Me} \xrightarrow{[1,2]-shift} \text{Me} \xrightarrow{-\text{H}^+} \text{Me} \xrightarrow{2\text{-methylquinol}} \]

\[ \text{OH} \]

\[ \text{4-nitrotoluene} \]

\[ \text{2-methylquinol} \]

Thus, we are forced to say that C4 carries bulk of the charge - nucleophile attacks that position.

the substrate for dienone-phenol rearrangement that leads to 2-methylquinol.

Therefore, combining the two rearrangements, we can carry out the following conversion:
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement

Synthetic utility:

Synthesis of arylhydroxylamine from nitroaromatics and subsequent functionalisation of the ring. Conventional method for hydroxylamine synthesis is reducing the nitro compound with $\text{Zn-NH}_4\text{Cl}$, in aq. ethanol. But many other methods have been explored:

Nitroaromatic can directly be converted to the aminophenol or its deriv. by modifying the reaction conditions so that reduction to hydroxylamine and Bamberger rearrangement proceed consecutively:

\[
\text{NO}_2^+ \xrightarrow{\text{Pt, H}_2, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{NH}_2 \xrightarrow{\text{DMSO, heat}} \text{OH} \quad \text{via in situ formation of 4-aminophenol}
\]

inhibits nitrobenzene's complete reduction to aniline

Similarly,

\[
\text{NO}_2^+ \xrightarrow{\text{H}_2\text{SO}_4, \text{MeOH}} \text{NH}_2 \xrightarrow{\text{hydrogenation in presence of H}_2\text{SO}_4, \text{MeOH}} \text{OMe} \quad \text{via in situ formation of 4-methoxy-2-methylaniline}
\]

A good source of 4-haloanilines is the reduction of nitrobenzene in presence of HX:

\[
\text{NO}_2^+ \xrightarrow{\text{H}_2, \text{PtO}_2, \text{anh. HF}} \text{NH}_2 \quad \text{4-fluoroaniline}
\]

\[
\text{NO}_2^+ \xrightarrow{\text{H}_2, \text{Pt, conc. HCl}} \text{Cl} \quad \text{via in situ formation of 4-chloroaniline}
\]

Clearly, the halide nucleophile captures the nitrenium int. (at C4) that is formed during Bamberger rearrangement.
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Benzidine rearrangement (aka Zinin benzidine rearrangement):
acid-catalysed conversions of hydrazoarenes into diaminobiaryls and amino diarylamines. These rearrangements are usually carried out in aqueous or ethanolic solutions of HCl or H₂SO₄.

\[
\begin{align*}
\text{1,2-diphenylhydrazine} & \xrightarrow{\text{HCl, heat}} \text{benzidine} + \text{diphenylamine} + \text{o-benzidine} + \text{o-semidine} + \text{p-semidine} \\
(\text{obtained by reduction of nitrobenzene under alkaline condition}) & \quad \text{(almost 70%)} \quad \text{(almost 30%)}
\end{align*}
\]

Observations:
1. Rate of the reaction = \( k [\text{PhNHNNPhH}] [\text{H}^+]^2 \)  First order w.r.t. 1,2-diphephenylhydrazine, second order w.r.t. acid
   However, as the reactivity of the hydrazobenzene increases, rate dependence on acid concentration decreases.

2. With \( \text{PhNHNNPhH} * \text{N} \) where * = \(^{15}\text{N}\), we have PKIE, meaning that the N-N bond breaks in RDS
   but with \( \text{PhNHNNPhH} \) we have no PKIE meaning that the C-D bond does not break in RDS

3. there are no cross products in crossover experiments, meaning intramolecular nature of the reaction:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad HCl, heat \quad \text{Me} \\
& \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
& \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad HCl, heat \quad \text{OMe} \\
& \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \\
\end{align*}
\]

Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Benzidine rearrangement (aka Zinin benzidine rearrangement):

Mechanism:

However, this mechanism has been challenged by the following observation:

So the mechanism has been revised:
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: \( N \)-azo to \( C \)-azo rearrangement:

Diazoization of aniline affords the benzenediazonium salt:

\[
\begin{align*}
\text{NH}_2 & \quad \xrightarrow{\text{NaNO}_2, \text{HCl}} \quad \text{N}^+\text{Cl}^- \\
\end{align*}
\]

via:

\[
\begin{align*}
\text{HO-NO} & \quad \xrightarrow{\text{H}^+} \quad \text{H}_2\text{O-NO} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{H}_2\text{O} + \text{NO} \\
\end{align*}
\]

\[
\begin{align*}
\text{NO}_2^- & \quad \xrightarrow{\text{NO}_2^-} \quad \text{O}\text{N}=\text{O} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{O}\text{N}=\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar-\text{NH}_2} & \quad \xrightarrow{\text{H}_2\text{O-NO or NO}} \quad \text{Ar-\text{N}_2\text{O}} \quad \xrightarrow{\text{fast}} \quad \text{Ar-\text{N}} \quad \text{N}_2\text{O}_2 \quad \xrightarrow{\text{fast}} \quad \text{Ar-\text{N}} \quad \text{N}_2\text{O}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar-\text{N}} \quad \text{N}_2\text{O}_2 & \quad \xrightarrow{\text{fast}} \quad \text{Ar-\text{N}} \quad \text{OH}_2 \quad \xrightarrow{\text{fast}} \quad \text{Ar-\text{N}} \quad \text{OH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar-\text{N}} \quad \text{OH}_2 & \quad \xrightarrow{\text{fast}} \quad \text{Ar-\text{N}} \quad \text{N}_2\text{O}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
N\text{-nitrosation is driven by kinetic control} \\
\end{align*}
\]

The diazonium salts undergo diazocoupling reactions when reacted with aromatic substrates carrying rings activated towards \( S_{E2} \text{Ar} \):

\[
\begin{align*}
\text{Ph-\text{NH}_2} & \quad \xrightarrow{\text{aq. NaNO}_2, \text{HCl}} \quad \text{Ph-\text{N}_2\text{N}} \quad \text{dropped in aqueous alkaline solution of phenol, 0-5 \text{ ^\circ C}}} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph-\text{NH}_2} & \quad \xrightarrow{\text{aq. NaNO}_2, \text{HCl}} \quad \text{Ph-\text{N}_2\text{N}} \quad \text{dropped in aqueous alkaline solution of 2-naphthol, 0-5 \text{ ^\circ C}}} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph-\text{NH}_2} & \quad \xrightarrow{\text{aq. NaNO}_2, \text{HCl}} \quad \text{Ph-\text{N}_2\text{N}} \quad \text{added to the solution of} \quad \text{N,\text{N}-dimethylaniline in AcOH containing NaOAc, 0-5 \text{ ^\circ C}}} \\
\end{align*}
\]
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: $N$-azo to $C$-azo rearrangement:

The benzenediazonium salt can couple with primary aromatic amines as well. In that case a $N$-$N$ coupling is seen:

\[
\begin{align*}
&\text{NH}_2 \quad \text{NaNO}_2 (0.5 \text{ equiv.}) \quad \text{dil. HCl} \\
&\quad \quad \quad \quad (0.5 \text{ equiv.}) \quad \text{NaOAc} \quad \text{forms faster than C-azo} \\
&\quad \quad \quad \quad \text{Enough NaNO}_2 \text{ to diazotize} \\
&\quad \quad \quad \quad \text{only half of the aniline} \\
&\text{N}_2\text{Cl}^\ominus \quad \text{N}_3\text{H}_3\text{Cl}^\ominus \\
&\text{NH}_2 \quad \text{Cl}^\ominus \quad \text{H}^\ominus \\
\end{align*}
\]

Reaction proceeds via:

\[
\text{AcO}^\ominus \quad \text{N}_2\text{H}_2 \quad \text{N}_3\text{N}_2\text{C}_6\text{H}_4\text{H}_2 \quad \text{forms faster than C-azo as its formation does not disrupt aromaticity}
\]

This $N$-azo compound, on heating with acid gets converted to the corresponding $C$-azo compound:

The $C$-azo is more stable than the $N$-azo, as it is conjugated and free of weaker $N$-$N$ bond (i.p.-l.p.repulsions).

This is a rearrangement where the migrating group (Ph-$N=\equiv N$) migrates from $N$ to the ring - just like the series of rearrangements we've seen.

This conversion is akin to transforming the KCP into the TCP.

If the $p$-position of the anilino group is already occupied then the rearrangement is slower and the migrating group ends up at the $o$-position.

Note on nomenclature: $X\text{N}_3\text{N}_2\text{Ar}$ (X = heteroatom) $\text{ArN}_3\text{N}_2\text{Ar}$

Diazo compound

Azo compound

Rearrangements in organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: N-azo to C-azo rearrangement:

The diazoaminobenzene to aminoazobenzene conversion can also be carried out, and more efficiently, by heating the N-azo compound with anilinium hydrochloride.

Mechanism:
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings:

<table>
<thead>
<tr>
<th>Name</th>
<th>Reaction</th>
<th>Migrating group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofmann-Martius</td>
<td>[Reaction image]</td>
<td>Alkyl groups like methyl</td>
</tr>
<tr>
<td>Fischer-Hepp</td>
<td>[Reaction image]</td>
<td>nitroso (NO)</td>
</tr>
<tr>
<td>Orton</td>
<td>[Reaction image]</td>
<td>chlorine</td>
</tr>
<tr>
<td>Bamberger</td>
<td>[Reaction image]</td>
<td>hydroxyl</td>
</tr>
<tr>
<td>Zinin Benzidine</td>
<td>[Reaction image]</td>
<td>N-N σ-bond</td>
</tr>
<tr>
<td>Diazooamino to aminoazo</td>
<td>[Reaction image]</td>
<td>phenyldiazo</td>
</tr>
</tbody>
</table>
Rearrangements in organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings: Sommelet-Hauser rearrangement

A base-mediated aromatic [2,3] sigmatropic rearrangement of a nitrogen ylide generated from a quaternary ammonium salt possessing a benzyl substituent:

\[
\begin{align*}
\text{Ph} & \quad \text{N-Me} \quad \text{HO}^- \\
\text{heat or sunlight} & \quad \rightarrow \\
\text{Ph} & \quad \text{Me} \quad \text{N-Me}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N-Me} \\
\text{NaNH}_2, \text{NH}_3(\text{l}) & \quad \rightarrow \\
\text{Ph} & \quad \text{Me} \quad \text{N-Me}
\end{align*}
\]

Synthesis of quaternary ammonium salt:
by alkylation the corresponding tertiary amines:

\[
\begin{align*}
\text{Ph} & \quad \text{N-Me} \\
\text{Me} & \quad \rightarrow \\
\text{Ph} & \quad \text{Me} \quad \text{N-Me}
\end{align*}
\]

**Mechanism:**

\[
\begin{align*}
\text{Ph} & \quad \text{N-R} \quad \text{X}^- \\
\text{NH}_2 & \quad \rightarrow \\
\text{Ph} & \quad \text{Me} \quad \text{N-R} \quad \text{X}^- \\
\end{align*}
\]

- \text{NH}_3, \text{-X}

**Important limitations:**

1. S.-H. rearrangement can take place on substrates containing a substituted benzene ring, but if the initial benzylic carbanion is significantly stabilized due to the presence of any EWG (e.g., CN, NO₂, Cl, Br) on the ring, then ylide required for [2,3]-shift may not form at all, and the reaction may not occur then.

\[
\begin{align*}
\text{Ph} & \quad \text{N-Me} \\
\text{NaNH}_2, \text{NH}_3(\text{l}) & \quad \rightarrow \\
\text{Ph} & \quad \text{Me} \quad \text{N-Me}
\end{align*}
\]

2. When the alkyl groups attached to the nitrogen contain a hydrogen atom at their \(\beta\)-position, the Hofmann elimination may compete.

Rearrangements in organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings: Sommelet-Hauser rearrangement

Important limitations (contd.):

3. Depending on the substrate and reaction conditions, the S.-H. rearrangement competes with the 1,2-Stevens rearrangement.

In the given example, the ylide is generated by fluoride-induced desilylation:

![Chemical Reaction Diagram]

In systems where both the Stevens- and S.-H. rearrangements are possible, the choice of reaction conditions allow control over which of these competing processes dominate; 9) low temperatures and polar solvents (e.g., NH₃, DMSO, HMPA) usually favor the S.-H. rearrangement, whereas higher temperatures and nonpolar solvents (e.g., hexanes, ether) facilitate the Stevens rearrangement;

Utility of S.-H. rearrangement:

1. At the expense of a C-N bond we get a C-C bond in this reaction, at the α-position w.r.t. the original benzylic substituent. Used en route synthesis of complex organic targets (discussion beyond our scope).

2. Cyclic quaternary ammonium salts react by ring-expansion:

![Chemical Reaction Diagram]