The Beckmann Rearrangement

The Mona Lisa of Rearrangements

Jeremy Henle, 11/19/2013
Outline

- Introduction
  - Oximes
  - Reactions of Oximes

- Discovery

- 100 years of the Beckmann Rearrangement
  - Mechanism Determination

- Organocatalyzed Beckmann Rearrangement

- Summary
Oximes

- Known to exist in isomeric forms (as of 1890, Hantzsch and Werner)
- Many are crystalline, air stable compounds
- Generally more stable to hydrolysis than hydrazones (2-3 times as stable)
- Preparation

\[
\text{R}^1\text{C}=\text{N}+\text{R}^1\text{OH} \xrightarrow{\text{base}} \text{R}^1\text{C}=\text{N}+\text{R}^1\text{OH}
\]
Reactions of Oximes

- **Neber Rearrangement**
  
  ![Neber Rearrangement Reaction](image)

- **Beckmann Fragmentation**
  
  ![Beckmann Fragmentation Reaction](image)

- **Beckmann Rearrangement** - 1886 to present
  
  ![Beckmann Rearrangement Reaction](image)

Most widely used industrial process for lactam formation
Significance of the Beckmann Rearrangement

- Industrial Significance
  
  ![Beckmann Rearrangement Reaction]

  \[
  \begin{align*}
  \text{OH} & \quad \text{H}_2\text{SO}_4 \quad \text{HN} \\
  \text{N} & \quad \text{O} \quad \text{HN} \\
  \text{caprolactam} & 
  \end{align*}
  \]

- Academic Significance
  - Mechanism still uncertain
  - Illustrated in numerous natural product syntheses

  
  Half of all produced cyclohexanone is converted to the oxime for this process. Precursor to nylon-6

Beckmann Rearrangement Publications

[Graph showing years 1896 to 2010 with publication counts for each year]
Ernst Beckmann

- Attempting to find a novel method of distinguishing aldehydes and ketones from their corresponding aldoximes/ketoximes

- Ketoximes gave unexpected products identified by hydrolysis

- Reaction could be catalyzed by PCl$_5$, SbCl$_5$, other metal chlorides
- Strong mineral acids could be used, catalytically if necessary
  - Beckmann solution: acetic acid, HCl, and acetic anhydride
- Alkali metal hydroxides did not catalyze the reaction

Beckmann expected the mechanism to be quite complex with many different intermediates due to generality and possible reagents

Initial Mechanistic Assumptions

- Initial hypothesis that the reaction was formally an exchange of a “hydroxy radical” and “carbon radical” (Hantzsch, 1891)
- Isomeric oximes were shown to give different constitutional products
  - *Cis* shift assumed because the groups are closer in space

\[
\begin{align*}
\text{NOH} & \quad \text{cis shift} \quad \begin{bmatrix} \text{NR}^2 \\ \text{R}^1 \end{bmatrix} \quad \rightarrow \\
\text{R}^1 & \quad \text{R}^2 \\
\text{OH} & \quad \text{NH}^2 \\
\end{align*}
\]

- Mechanism unquestioned due to “inherent reasonableness”
  - Pfieffer (1904) and Bucherer (1914) suggested a *trans* shift
- Reagents were simple catalysts of this process
- Until 1921, the *cis* shift assumption remained popular opinion
  - Used to identify the configuration of many ketoximes

Hantzsch, *Ber.* **1891**, 24, 13, 51
Controversy in Configuration

- In 1921, Meisenheimer constructed a BKR-independent method of determining oxime configuration

\[
\text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{Ph} \quad \text{O} \quad \text{Ph} \quad \text{Ph} \quad \text{Meisenheimer product}
\]

Beckmann had assigned the oximes based on the BKR

The BKR must proceed through a \textit{trans} shift!

Benzoylation of \(\beta\)-oxime gave the Meisenheimer product

\[
\text{Ph} \quad \text{N} \quad \text{O} \quad \text{Ph}
\]

\[
\text{Ph} \quad \text{N} \quad \text{O} \quad \text{Ph} \quad \text{Carboxylic acid}
\]

Meisenheimer was able to generate the oxime directly from an ozonolysis

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

m.p. corresponds to \(\beta\)-oxime

Meisenheimer, \textit{Ber.} \textbf{1921}, 54, 3206.
Further Examples of Stereospecificity

Kinetics and Mechanism (1933)

- Wallach

- Disproven with aromatic substrate

Wallach, *Ann.*, 1899, 309, 3
Wallach, *Ann.*, 1900, 312, 187
Kinetics and Mechanism (1933)

- Sluiter kinetic data
  - BKR of acetophenone oximes is first order in oxime
  - Large temperature coefficient

- No supporting evidence for mechanism other than order of the reaction

“Univalent Nitrogen”
Stieglitz

- **Hoffmann**
  \[
  \text{R}^+\text{C}=\text{NH}_2 \xrightarrow{\text{Br}_2, \text{NaOH}} \text{R}^+\text{C}=\text{NBr} \xrightarrow{-\text{HBr}} \text{R}^+\text{C}=\text{NO} \xrightarrow{\text{H}_2\text{O}} \text{R}^+\text{NH}_2
  \]

- **Curtius**
  \[
  \text{R}^+\text{C}=\text{NO} \xrightarrow{\text{N}_2} \text{R}^+\text{C}=\text{NO}
  \]

- **Beckmann**
  \[
  \text{R}^+\text{C}=\text{NH}_2 \xrightarrow{\text{HCl}} \text{R}^+\text{C}=\text{NCl} \xrightarrow{-\text{H}_2\text{O}} \text{R}^+\text{NH}_R
  \]

**Stereospecificity would not arise from this mechanism!**

Oxime Ester Studies
Kuhara

- Postulated that acyl derivatives of oximes undergo rearrangement, not the original oximes

\[
\text{\begin{align*}
\text{Oxime} & \quad \text{Ester} \\
R^1 & \quad R^2
\end{align*}}
\]

- Careful synthesis of a variety of ester-like oxime compounds showed competency in the reaction
  - Spontaneous
  \[
  \text{Ph} \quad \text{Ph} \quad \text{NH} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph}
  \]
  \[
  \text{HN} \quad \text{Ph}
  \]

- Acid catalyzed

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

Kinetics of Oxime Ester Rearrangement

- Oximes treated with acetyl chloride undergo rearrangement

![Chemical Structures]

- Kinetic trends
  - Addition/Inc. HCl conc, inc. rate
  - Inc. “negativity” of acetyl group (lower pKa of conjugate acid), inc. rate.
  - Sulfonyl esters rearrange without acid.

<table>
<thead>
<tr>
<th>Time</th>
<th>CH₃COCl</th>
<th>CICH₂COCl</th>
<th>C₆H₅SO₂Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.0%</td>
<td>61.0%</td>
<td>93.2%</td>
</tr>
<tr>
<td>60</td>
<td>26.9%</td>
<td>70.7%</td>
<td>-</td>
</tr>
<tr>
<td>120</td>
<td>43.9%</td>
<td>76.9%</td>
<td>-</td>
</tr>
</tbody>
</table>

Summary

- Kuhara conclusions
  - If the “acid group” is sufficiently electron withdrawing, rearrangement will occur spontaneously. If not, salt formation is required to drive rearrangement.
  - Esters of oximes are capable of spontaneous rearrangement

- Problems:
  - Did not account for acid catalyzed BKR (without ester-like precursors)
  - Sulfonyl ester BKR products were oils that could not be purified or separated from sulfonic acids

Oxime Picryl Ethers

- Chapman began to study the picryl ethers of oximes
  - Highly crystalline
  - Easy to isolate and purify

- Undergo spontaneous BKR upon heating to isolable products

- Chapman suggests that sulfonyl esters go through similar process to the $N$-phenylsulfone

Picryl Oxime Ethers Provide First Accurate Kinetics

First order with respect to substrate
- Unimolecular

BKR of Benzophenone Oxime Picryl Ether
(50 °C, chloroform)

\[ y = 32.375 \ln(x) - 88.155 \]
\[ R^2 = 0.9905 \]

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>( k_{\text{obs}} \times 10^3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.5</td>
<td>4.2</td>
</tr>
<tr>
<td>60</td>
<td>3.8</td>
</tr>
<tr>
<td>90</td>
<td>3.95</td>
</tr>
<tr>
<td>120</td>
<td>3.9</td>
</tr>
<tr>
<td>180</td>
<td>4.15</td>
</tr>
<tr>
<td>240</td>
<td>4.1</td>
</tr>
<tr>
<td>Avg</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Substituent Effects

- $k_{rel}$

EWG retard reaction rate, while EWG accelerates. Effect is greater on the migrating group.

Intramolecular or Intermolecular?

- Is the migrating carbon group kinetically “free”?  
  - Entry of the migrating group into a separate molecule has never been observed
- Large ring expansion

Unlikely that the ring opened as closure would be prohibitive

- Retention of stereochemistry

Solvent Effects  
Picryl Oxime Ethers

- Rate increases with increasing dielectric constant
  - $\text{C}_2\text{H}_4\text{Cl}_2 > \text{CHCl}_3 > \text{CCl}_4$
- Rate increases with increased concentration within solvent – first order kinetics
  - Discrepancy between energy of activation calculations and observed rates suggests catalytic activity of other solutes, and that their activity must be essentially equal.
    - Suggests oxime ether functions as a catalyst
  - Further experimentation showed significant discrepancy from observed rate and calculated $E_a$ based on substrate concentration/temp. rate data alone indicating catalytic effect of other solute/solvent molecules

- If correct, it should stand to reason that the addition of “foreign polar molecules” should increase rearrangement rate

Solvent Effects
Polar Solvents as Catalysts

- Carbon tetrachloride as solvent doped with other solvents
  - Benzophenone oxime picryl ether rearrangement

Stereospecificity Explained

1944

Proposed as a concerted exchange

The strength of the dipole dictates the energy required to force the rearrangement

Nature of isomerization unclear

Jones, Chem. Rev. 1944, 335
Addition of EWG on the oxime oxygen polarizes the LUMO contributions
The Problem of Acid-Promoted BKR

- How do mineral acids promote the rearrangement?

- $N$-chloroimines shown to be unable to rearrange

Acid Catalysis
HCl Kinetics

- **Curve I** (approx 0.4 eq HCl used)
  
  \[
  \text{Ph} \equiv \text{N}^+ \text{H}^- \text{Cl}^- + \text{Ph} \equiv \text{N}^- \text{Ph} + \text{HCl}
  \]

- **Curve II**
  
  \[
  \text{Ph} \equiv \text{N}^- \text{Ph} + \text{Ph} \equiv \text{N}^- \text{Ph} + \text{HCl}
  \]

- **Curve III**
  
  \[
  \text{Ph} \equiv \text{N}^- \text{Ph} + \text{HCl} + \text{Ph} \equiv \text{N}^- \text{Ph} + 0.002 \text{ equiv}
  \]

- **Curve IV**
  
  \[
  \text{Ph} \equiv \text{N}^- \text{Ph} + \text{Ph} \equiv \text{N}^- \text{Ph} + 0.002 \text{ equiv}
  \]

Intermediate A was synthesized stoichiometrically and treated with aq HCl, and shown to convert quantitatively to product.
Recap

- While many reagents catalyze the BKR, the mechanism likely requires the intermediate formation of an ester-like compound.
- No evidence of dissociation of free ions in the mechanism.
  - Migrating carbon is never kinetically free.
- “…more needs to be discovered before the mechanism of this Mona Lisa of molecular rearrangements is fully understood” – Jones, 1944.
Introduction of Nitrilium Ion Intermediate

- Jones (Nature, 1946)
  - Recent reports had indicated $^{18}$O incorporation into amides following PCl$_5$ catalyzed BKR – may arise from ionic intermediates

- If ionic intermediate is formed, it must be through a concerted process to preserve stereospecificity

Evidence of Nitrilium Intermediate

- Matsumoto (1955)

- Generated a potential kinetic equation for these steps, which condensed to a relationship between log k and the Hammett acidity property

- Derived eqn:

\[
\log k = \log a_{H_2SO_4} - \log a_{H_2O} + H_0 + \text{const}
\]

\[
H_0 = pK_a + \log \left( \frac{c_B}{c_{BH^+}} \right)
\]

- Observed data appear to support the derived relationship


[Diagram of the reaction pathway involving Nitrilium Intermediate and associated equations]
Initial Evidence of Cationic Intermediate

- Huisgen (1957)
  - $\rho = -4.1$
  - Build up of positive charge in the RDS transition state

- Review of RDS proposals
  - Kuhara – no dissociation
  - Chapman – no dissociation following isomerization
  - Jones – direct isomerization/ionization

\[ \text{Huisgen, Helv. Chim. Acta. 1957, 191} \]
Isolation of a Competent Intermediate

- First isolation of a “nitrilium salt” by Grob

- Authors state competency in reaction precludes other intermediate structures
  - Recall: $N$-chloroimines do not undergo acid catalyzed BKR

- Further kinetic studies indicate isomerization followed by ionization may be a stepwise course to the nitrilium cation

Further Support
Carbenium Ion Trapping and Observation

- $R = \text{EWG}$, fragmentation less favorable (stability of benzylic cation)
- $o$-methylacetophenone oxime
  - “More similar to anilinium than phenonium, and concluded to be nitrilium ion.”

Nelson, JOC., 1969, 1230
Concerted or Stepwise?

- Acetone oxime model $\text{H}^+(\text{AcOH})_3$ (Beckman Solution)

Concerted reaction to the nitrilium cation
Concerted or Stepwise?

- Acetophenone Model $H^+ (\text{AcOH})_3$ (Beckman Solution)
  - Stepwise through pi-complex to nitrilium ion (sigma-complex)

Concerted or Stepwise

- Cyclohexanone model $H^+ (\text{AcOH})_3$ (Beckman Solution)

Concerted directly to protonated caprolactam due to relief of ring strain

Classic BKR

Summary

- Rearrangement is a stereospecific trans shift
- Rearrangement occurs through an ester-like oxime intermediate (either EWG reagent or autocatalysis)
- The migrating carbon group is never kinetically free
  - Migration of chiral group does not decrease ee
- The migration step involves an isomerization followed by ionization to a nitrilium ion intermediate
  - Stabilization of this intermediate enhances rate (solvent, R properties)
- The isomerization/ionization step is a spectrum of step-wise and concerted processes
Organocatalyzed BKR

- First example, advertised as a milder method

\[
\begin{align*}
\text{Proposed mechanism} \\
\text{Meisenheimer Complex}
\end{align*}
\]

- 5a requires addition of acid to act as a catalyst

Ishihara, JACS, 2005, 127, 11240
Other Organocatalysts Lead To Mechanistic Questions
Cyclopropenium Promoted

- **Stoichiometric**

  ![Stoichiometric reaction diagram]

  

- **Catalytic**

  ![Catalytic reaction diagram]

In situ generation prior to addition of oxime

Lambert, *Chem. Sci.* 2010, 1, 705
Catalytic Mechanism

Competition exp. shows cyclopropenone not nucleophilically competitive with oximes

Essentially same rate for these catalysts
Recall: This is the catalytic species
Chapman proposed (1935)

Lambert, Chem. Sci. 2010, 1, 705
Investigation of TsCl Catalysis

- Initially reported in 2009

\[
\text{N-NOH} \xrightarrow{\text{TsCl (2 mol%)}} \text{TsCl} \xrightarrow{\text{ZnCl}_2 (2 mol%) \text{ MeCN, reflux}} \text{R}^1\text{N=CR}^2
\]

- Major limitation

- Required 30 mol% loading of TsCl
- Similar results seen with BOP-Cl, cyanuric chloride

Reinvestigation of TsCl

Authors also state an $^{18}$O experiment that disproves the Meisenheimer complex Mechanism proposed by Ishihara, though it is unpublished.
Proposed Mechanism: TsCl

Cycle I the more favorable pathway

Deng, JOC, 2013 78 4297
Proposed Mechanism: HCl

Deng, JOC, 2013 78 4297
Organocatalyzed Cyclohexanone Oxime BKR

Sequestration of nitrilium ion leads to poor conversion
Generality of Self-Propagation Mechanism

CNC
TAPC
BOP-Cl
TsCl
CPI-Cl

Deng, JOC, 2013 78,6782
Organocatalyzed BKR
Summary

- BKR is a general, stereospecific reaction of oximes that proceeds through an activated ester-like intermediate.
- A Nitrilium ion is the common intermediate.
  - To both the BKR and the BK fragmentation.
- Catalyzed reactions appear increasingly likely to go through a self-propagation/promotion mechanism to regenerate the nitrilium ion.
- Even a 127 year old reaction can introduce new mechanistic insights.
Rearrangement Step
Concerted or Stepwise?

Acetophenone: Three step process
Concerted or Stepwise

Cyclohexanone: Concerted, one step process iminiu

\[
\text{20A} \quad [0 \text{ kcal/mol}]
\]

\[
\text{21A (TS1)} \quad [+10.8 \text{ kcal/mol}]
\]

\[
\text{22A} \quad [-54.2 \text{ kcal/mol}]
\]

\[
\text{+ \text{(AcOH)}_3}
\]