CHEM60001: An Introduction to Reaction Stereoelectronics

LECTURE 6 1,2-Rearrangements & Fragmentations

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Format & scope of lecture 6

• *Ionic 1,2-rearrangements, part 2*
  – Pinacol & semi-pinacol
  – Baeyer-Villiger reaction
  – Beckmann rearrangement

• *Ionic fragmentations*
  – Grob
  – Eschenmoser ring expansion

• *Reflection on Importance of Reaction Stereoelectronics*
[1,2]-Sigmatropic rearrangements

• [1,2]-Sigmatropic rearrangements take place when an electron deficient/cationic centre is formed adjacent to a group capable of migration using a lone or bonding pair of electrons
  – Participation of bonding electrons of aryl, alkyl and hydride groups are of particular importance:
  – 1,2-Aryl-, alkyl- & hydride shifts towards carbenium ions/electron deficient carbon:

\[
\begin{array}{c}
\text{H/R/Ar}^+ \rightarrow \text{H/R/Ar}^+ \\
\text{H/R/Ar}^+ + \text{LG}^+ \rightarrow \text{H/R/Ar}^+ + \text{LG}^-
\end{array}
\]

a range of mechanistic cases from true carbenium ion-mediated to fully concerted rearrangements

– 1,2-Aryl-, alkyl- & hydride shifts towards electron deficient oxygen:

\[
\begin{array}{c}
\text{H/R/Ar}^+ \rightarrow \text{H/R/Ar}^+ \\
\text{H/R/Ar}^+ + \text{LG}^+ \rightarrow \text{H/R/Ar}^+ + \text{LG}^-
\end{array}
\]

oxenium ion too high in energy to exist

– 1,2-Aryl-, alkyl- & hydride shifts towards electron deficient nitrogen:

\[
\begin{array}{c}
\text{H/R/Ar}^+ \rightarrow \text{H/R/Ar}^+ \\
\text{H/R/Ar}^+ + \text{LG}^+ \rightarrow \text{H/R/Ar}^+ + \text{LG}^-
\end{array}
\]
nitrenium ion too high in energy to exist
1,2-Shifts to C⁺ – pinacol rearrangements

- Treatment of the 1,2-diol ‘pinacol’ with acid results in a 1,2-rearrangement to give a ketone ‘pinacolone’:

- The ‘push’ of the lone pair and the ‘pull’ of the carbenium ion provide a low energy kinetic pathway
- The exothermicity of C=O bond formation provides a thermodynamic driving force

- The reaction is a useful method of preparing spirocyclic compounds:

- More generally, any functionality giving rise to a carbenium ion adjacent to an oxygenated carbon can undergo a semi-pinacol rearrangement...
1,2-Shifts to C⁺ – *semi-pinacol rearrangements*

- **Treatment of epoxides with Lewis acids results in semi-pinacol rearrangements:**

  
  ![Chemical structure](image)

  - 1) $\sigma_\text{O} \rightarrow \sigma^*_\text{C-H (app)}$
  - 2) $\sigma_{\text{C-H}} \rightarrow \rho_{\text{vac}}$ (pp, suprafacial)

- **Diazotisation of $\beta$-amino alcohols results in semi-pinacol rearrangements (Tiffaneau-Demyanov):**

  
  ![Chemical structure](image)

  - 1) $\sigma_\text{O} \rightarrow \sigma^*_\text{C-C (app)}$
  - 2) $\sigma_{\text{C-C}} \rightarrow \rho_{\text{vac}}$ (pp)
Semi-pinacol rearrangement - *stereochemistry*

- *The importance of correct orbital alignment* for 1,2-shifts is illustrated by subjecting all four isomers of the following bromohydrin to identical conditions:

  1. **(1S,2S,5S)-bromohydrin**
     - Conformational lock
     - **Semi-pinacol (1,2-alkyl shift)**
     - Deprotonation → Ring-contracted aldehyde

  2. **(1S,2R,5S)-bromohydrin**
     - 1,2-hydride shift
     - Deprotonation → Cyclohexanone

  3. **(1R,2R,5S)-bromohydrin**
     - Epoxide formation
     - Deprotonation → Epoxide

  4. **(1R,2S,5S)-bromohydrin**
     - **Semi-pinacol (1,2-alkyl shift)**
     - Deprotonation → Ring-contracted aldehyde

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1) \(n_O \rightarrow \sigma^*_{C-C} \text{ (app)}\)
2) \(\sigma_{C-C} \rightarrow \sigma^*_{C-Br} \text{ (app)}\)
1,2-Shifts to O\(^+\) – Baeyer-Villiger reaction

- Treatment of ketones & aldehydes with peracids induces a Baeyer-Villiger reaction:

  - use of basic hydrogen peroxide on an electron rich aryl ketone/aldehyde is called the Dakin reaction

- the driving force is the exothermicity of cleavage of a weak O-O bond and formation of a C=O bond
- order of migration generally follows migratory aptitude series presented earlier:
1,2-Shifts to N⁺ – Beckmann rearrangement

- **Hydride, alkyl & aryl groups** also migrate towards **electron deficient nitrogen centres**
  - NB. nitrenium ions themselves are too high in energy to exist (cf. carbenium ions)

- **Oximes** undergo useful 1,2-**rearrangements** in **acidic media** – the Beckmann rearrangement:

  oxime → [*1,2-alkyl shift*] → 1,2-aryl shift (via aronium ion) → hydration → tautomerisation → caprolactam → Nylon 6,6

  - the group **app** to the N-O bond migrates irrespective of migratory aptitude BUT **beware oxime E/Z isomerisation**

  - (E)-oxime → [*1,2-aryl shift (via aronium ion)*] → hydration → tautomerisation → lactam
  - (Z)-oxime → [*1,2-alkyl shift*] → hydration → tautomerisation → lactam

  \[ \sigma_{C-C} \rightarrow \sigma^*_{N-O} \text{ (app)} \]
Ionic fragmentations – characteristics

- Ionic fragmentation reactions are reactions in which C-C bonds are broken in a heterolytic fashion.
- They are relatively rare NOT because C-C bonds are particularly strong:
  - cf. Bond Dissociation Energies:
    - C-C: 339 kJ mol⁻¹ (weakest)
    - C-O: 351 kJ mol⁻¹
    - C-H: 418 kJ mol⁻¹
    - O-H: 460 kJ mol⁻¹ (strongest)
- BUT because C-C bonds are not generally highly polarised/polarisable.
- It follows that fragmentations occur for polarised/polarisable C-C bonds
  - the most common scenario involves an electron source at one end and an electron sink at the other:
    - C-C bond fission
    - 1) nX → σ⁺C-C (app)
    - 2) σC-C → σ⁺C-Y (app)
    - NB. the molecule breaks into three fragments

- This type of fragmentation is sometimes referred to as a Grob fragmentation (=homologous pinacol)
- As with 1,2-rearrangements CORRECT ORBITAL OVERLAP IS CRUCIAL...
Grob-type fragmentations

- There are numerous variants of the Grob fragmentation – in all cases correct conformation & stereoelectronics are crucial for success.
  - Contrast the behaviour of two isomeric tosylates:

  * cis-isomer *

  

  \[
  \text{Me}_2\text{N} = \text{H}_2\text{N} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  Me$_2$NO Ts = Me$_2$NO Ts

  both groups equatorial

  1) \( \eta_N \rightarrow \sigma^*_C-C \) (app)
  2) \( \sigma^*_C-C \rightarrow \sigma^*_C-O \) (app)

  2x severe 1,3-diaxial interactions

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  alkenyl aldehyde
  [64\%, exclusive prod]

  alkenyl aldehyde
  [11\%, minor prod]

  cyclohexenes
  [49\%, mix of regioisomers]

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  2x less severe 1,3-diaxial interactions

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  \[
  \text{Me}_2\text{N} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N}
  \]

  HNMe$_2$

  HNMe$_2$

  HNMe$_2$

  HNMe$_2$

  HNMe$_2$

  E$_2$ elimination
  (MAJOR path)
The Eschenmoser fragmentation

- A particularly spectacular type of fragmentation for ring-expansion was developed in the late 1960s by the Swiss chemist Albert Eschenmoser – the Eschenmoser fragmentation

- the driving force for the fragmentation is enthalpic (formation of toluene sulfinate) & entropic [formation of $N_2$ (g)]
Stereoelectronics - A panacea for rationalisation of conformation & reactivity?

• **NO!**...stereoelectronic analysis is constrained by the limitations of:
  
  – APPROXIMATIONS INVOLVED IN CONSIDERING ONLY LOCALISED MOLECULAR ORBITALS (e.g. NBOs)
  – PERTURBATION THEORY (*i.e.* the Klopman-Salem expression)
  – FRONTIER ORBITAL THEORY

• Moreover, stereoelectronic analysis must, as we have seen, be augmented by consideration of many additional factors which influence chemical reactivity:
  
  – STRAIN: Compressive/tensile: Bayer (=angle)/Pitzer (=torsional)/Prelog (=transannular). All van der Waals in origin
  – STERIC EFFECTS: van der Waals in origin (*e.g.* hydrocarbon conformations; Lennard-Jones potential)
  – ENTROPY EFFECTS: Statistics! [*e.g.* possibly of significance in the ‘Thorpe-Ingold effect’]
  – SOLVENT EFFECTS: electrostatic and dipole interactions with the reaction medium
  – ELECTROSTATIC/DIPOLE EFFECTS: [*e.g.* a factor in the anomeric effect, significant factor in carbonyl addition reactions *cf.* Felkin-Anh]