CHEM60001: An Introduction to Reaction Stereoelectronnics

LECTURE 5 Neighbouring Group Participation, Non-classical Carbocations & Wagner-Meerwein 1,2-Shifts

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Format & scope of lecture 5

- *Neighbouring Group Participation (NGP)*
- *Non-classical carbocations*
- *Ionic 1,2-rearrangements, part 1*
  - Wagner-Meerwein methyl and hydride shifts
Neighboring group participation (NGP)

- Groups remote from a reaction centre can participate in substitution reactions – **Neighboring Group Participation (NGP)** (or **anchimeric assistance**):
  - lone pairs of electrons, typically on N, O, S or Hal atoms interact with **electron deficient/cationic centres**
  - NGP is characterised by:
    - rate acceleration
    - retention of stereochemistry (via double inversion):

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<table>
<thead>
<tr>
<th>α-amino acid</th>
<th>NaNO₂, H₂SO₄</th>
<th>H₂O</th>
<th>α-hydroxy acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td></td>
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</tr>
</tbody>
</table>
```

- **Rearrangements** occur when the participating group ends up bonded to a different atom...
NGP with rearrangement

- **Payne rearrangements:**

\[
\text{BnO} - \text{Cl} - \text{Me} \quad \text{NaOH, H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

- **aza-Payne rearrangements:**

\[
\text{Et}_2\text{N} - \text{Cl} - \text{Me} \quad \text{NaOH, H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

- **Bromonium ion rearrangements:**

- **anti** (single enantiomer)

\[
\text{Me} - \text{Br} - \text{Me} \quad \text{H-Br} \quad \text{H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

- **diastereoisomers**

\[
\text{Me} - \text{Br} - \text{Me} \quad \text{H-Br} \quad \text{H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

- **syn** (single enantiomer)

\[
\text{Me} - \text{Br} - \text{Me} \quad \text{H-Br} \quad \text{H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

**C\text{\textunderscore}2-symmetric bromonium ion**

\[
\text{Me} - \text{Br} - \text{Me} \quad \text{H-Br} \quad \text{H}_2\text{O} \quad \text{Et}_2\text{N}^+ \quad \text{Br}^- \quad \text{HO}^- \\
\]

**rearranged product**

- 1:1

**achiral (meso) [without \text{\textsuperscript{13}C} label]**

**rearranged product**

- 1:1

**racemate**
NGP with rearrangement – *involvement of* \( \pi \) & \( \sigma \) *bonds*:

- **NGP by aryl groups** (\& alkenes) results in related rearrangements via *phenonium/arenium ions*:

  ![Chemical structures](image)

  **anti** (single enantiomer) → *C\(_2\)*-symmetric *phenonium ion* → single enantiomer (without \(^{13}\)C label)

  **syn** (single enantiomer) → *meso phenonium ion (achiral)* → racemate (without \(^{13}\)C label)

- **NGP by alkyl groups can also proceed via non-classical cations:**
  - Crystal structure of this carbocation finally obtained in 2013! See: Scholz *Science*, 2013, 341, 62 [DOI]

![Chemical structures](image)

- The rearranged products of the above “NGP” processes can also be regarded as having undergone \([1,2]-\)sigmatropic rearrangements...
[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:

\[
\text{H/R/Ar}^+ \xrightarrow{\text{+ LG}} \text{H/R/Ar}^+ + \text{LG}^-
\]

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

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

\[
\text{H/R/Ar}^+ \xrightarrow{\text{O}} \text{H/R/Ar}^+ + \text{LG}^-
\]

- Oxenium ion too high in energy to exist

- Group exhibiting oxenium ion character

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

\[
\text{H/R/Ar}^+ \xrightarrow{\text{N}} \text{H/R/Ar}^+ + \text{LG}^-
\]

- Nitrenium ion too high in energy to exist

- Group exhibiting nitrenium ion character
Mechanistic variations

- The mechanism of 1,2-migrations vary from stepwise to concerted (cf. $S_N1 \leftrightarrow S_N2$):

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    $\begin{align*}
    &\text{H/R/Ar}^+ \quad \text{H/R/Ar}^+ \\
    \text{H/R/Ar}^{-} \quad \text{H/R/Ar}^{-} \\
    \text{LG}^- \quad \text{LG}^- \\
    \text{Nu}^- \quad \text{Nu}^- \\
    \end{align*}$

    - The mechanism of 1,2-migrations vary from stepwise to concerted (cf. $S_N1 \leftrightarrow S_N2$):

      - The migrating centre however always retains* its configuration as it retains an octet of electrons:
        - Consider the case of a 1,2-alkyl shift:
          - Inversion of configuration at the migrating centre is also possible for 1,3 and higher sigmatropic rearrangements (see ‘Pericyclic reactions’ lectures), but loss of stereochemical integrity at this centre is never observed

- The **migrating centre** however always retains* its configuration as it retains an octet of electrons:
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Migratory Aptitudes

• The ease with which carbon-based groups migrate vary according to the particular reaction & the conditions

• However, an approximate ranking is possible:
  – Data has been accrued from relative rate data and from competition experiments on various rearrangements
  – In general, the group best able to stabilise positive charge (in the transition state/intermediate) migrates:

  ![Diagram showing migratory aptitudes]

  – The position of HYDRIDE in this series is highly unpredictable – often migrates very readily!
  – Care is required in interpreting results as other factors may dominate:
    • e.g. a pinacol rearrangement where cation stability is the determining factor:

  ![Diagram showing pinacol rearrangement]

  – However, CORRECT ORBITAL OVERLAP IS CRUCIAL in the transition state and so (by Hammond’s postulate) the orbital alignment in the substrate must be appropriate for migration...
1,2-Shifts to C⁺ - Wagner-Meerwein rearrangements

- [1,2]-Sigmatropic shifts of hydride & alkyl groups towards carbenium ions are referred to as Wagner-Meerwein shifts (a Me group 1,2-shift is specifically known as a Nametkin rearrangement)

  - rearrangement during substitution at a neopentyl centre:

    \[
    \text{Me}_2\text{CH} - \text{I} \xrightarrow{\text{AgNO}_3, \text{H}_2\text{O}} \text{Me}_2\text{CH}^+ + \text{Ag}^+ \quad \text{direct substitution product NOT observed}
    \]

    1,2-Me shift

    Me Me
    Me Me
    Me Me
    Me Me Ag

    \[\sigma_{C-C} \rightarrow \sigma^*_{C-I} \text{ (app)}\]

    1,2-Me shift

  - rearrangement during Friedel-Crafts alkylation:

    \[
    \text{Me}_2\text{CH} - \text{Cl} \xrightarrow{\text{AlCl}_3 \text{cat.}, \text{C}_6\text{H}_5} \text{Me}_2\text{CH}^+ + \text{Me}_2\text{CH}_2\text{H} \quad \text{1,2-hydride shift}
    \]

    \[\sigma_{C-H} \rightarrow p_{\text{vac}} \text{ (pp)}\]

    1,2-hydride shift

    ~1:1 mix as both cations precursors are secondary
Wagner-Meerwein rearrangements - isomerisations

- Synthetically useful Wagner-Meerwein rearrangements
  - isomerisation of alkyl halides:

  ![Chemical diagram]

  - A remarkable synthesis of adamantane (C\textsubscript{10}H\textsubscript{16}):
Wagner-Meerwein rearrangements - *biosynthesis*

- **Wagner-Meerwein rearrangements** are prevalent in the *biosynthesis of terpenoids* such as **lanosterol** (precursor to *cholesterol* & the human sex hormones)
  - **lanosterol** is formed by the polycyclisation of 2,3-oxidosqualene by the enzyme **OxidoSqualene Cyclase** (OSC)
  - the **conformation** enforced by the enzyme is _chair-boat-chair_, the process is **NOT concerted**, discrete **cationic intermediates** are involved & **stereoelectronics dictate** the **regio- & stereoselectivity**

```
\begin{align*}
\text{2,3-oxidosqualene} & \xrightarrow{1) \text{ epoxide opening}} \text{lanosterol} \\
\text{lanosterol} & \xrightarrow{2) \text{ 2x Markovnikov ring-closures (6-memb rings)}} \text{protosterol cation}
\end{align*}
```

- “The enzyme’s role is most likely to shield intermediate carbocations… thereby allowing the hydride and methyl group migrations to proceed down a thermodynamically favorable and kinetically facile cascade”
Wagner-Meerwein rearrangements - *monoterpenes*

- **Wagner-Meerwein rearrangements** occur widely during the biosynthesis of terpenes (isoprenoids) and are also synthetically useful for the functionalisation of these metabolites:
  - e.g. synthesis of camphor sulfonic acid from camphor:

  ![Diagram of Wagner-Meerwein rearrangements](image)

  - NB. H$_2$SO$_4$/Ac$_2$O is a weak sulfonylating mixture (cf. oleum) for $S_{E}$Ar:

    ![Diagram of weak sulfonylating mixture](image)