CHEM60001: An Introduction to Reaction Stereoelectronics

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

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College London

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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):
      - Rearrangements occur when the participating group ends up bonded to a different atom...

\[
\text{RELATIVE RATE } 1 : 600
\]
NGP with rearrangement

- **Payne rearrangements:**

\[
\text{BnO} -\text{O} -\text{OH} \xrightarrow{\text{NaOH, } H_2O} \text{BnO} -\text{O} -\text{O}^- \xrightarrow{\text{inversion}} \text{BnO} -\text{OH} -\text{O}^- \xrightarrow{\text{Et}_2\text{N}^+, \text{H}_2\text{O}} \text{BnO} -\text{OH} -\text{S}^\text{Bu}^- \xrightarrow{\text{iBuS}^-} \text{BnO} -\text{OH} -\text{S}^\text{Bu}^- \]

- **aza-Payne rearrangements:**

\[
\text{Et}_2\text{N} -\text{Cl} -\text{Me} \xrightarrow{\text{NaOH, } H_2O} \text{Et}_2\text{N} -\text{N} -\text{Me} \xrightarrow{\text{inversion}} \text{Et}_2\text{N} -\text{Me} -\text{OH} \xrightarrow{\text{H}^-} \text{Et}_2\text{N} -\text{Me} \]

- **Bromonium ion rearrangements:**

- **anti** (single enantiomer)

\[
\begin{align*}
\text{Br} & \quad \text{Me} \\
\text{Me} & \quad \text{OH} \\
\text{H}^- & \quad \text{Me}
\end{align*}
\]

**diastereoisomers**

- **syn** (single enantiomer)

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Br} & \quad \text{Me} \\
\text{H}^- & \quad \text{Me}
\end{align*}
\]

**C₃-symmetric bromonium ion**

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

\[\xrightarrow{\text{H-Br, } H_2O} \text{Me} \quad \text{Me} \quad \text{Br} \quad \text{Me} \quad \text{Br} \]

*rearranged product*

\[1 : 1\]

*achiral (meso) [without ^13C label]*

\[\text{Me} \quad \text{Me} \quad \text{Br} \quad \text{Me} \quad \text{Br} + \text{Me} \quad \text{Me} \quad \text{Br} \quad \text{Me} \quad \text{Br} \]

*rearranged product*

\[1 : 1\]

*racemate*
NGP with rearrangement – *involvement of π & σ bonds*:

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

  ![Diagram](attachment:image.png)

  - *anti* (single enantiomer)
  - *syn* (single enantiomer)

  - *C₇-symmetric phenonium ion* → rearranged product (1:1, single enantiomer without ¹³C label)
  - *meso phenonium ion (achiral)* → rearranged product (1:1, racemate without ¹³C 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](https://doi.org/10.1126/science.1234567)

- 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**:

\[
\text{H/R/Ar}^+ + \text{LG} \rightarrow \text{H/R/Ar}^+ \quad \text{H/R/Ar}^+ + \text{LG}^- \quad \text{a range of mechanistic cases from true carbenium ion-mediated to fully concerted rearrangements}
\]

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

\[
\text{H/R/Ar}^+ + \text{O} \rightarrow \text{H/R/Ar}^+ \quad \text{H/R/Ar}^+ + \text{O}^- \\
\text{oxenium ion too high in energy to exist}
\]

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

\[
\text{H/R/Ar}^+ + \text{N} \rightarrow \text{H/R/Ar}^+ \quad \text{H/R/Ar}^+ + \text{N}^- \\
\text{nitrenium ion too high in energy to exist}
\]
Mechanistic variations

- 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 possible for 1,3 and higher sigmatropic rearrangements (see ‘Pericyclic reactions’ lectures), but loss of stereochemical integrity at this centre is never observed

*loss of stereochemical integrity at cationic centres*

*inversion of stereochemistry at migration origin and/or terminus*

"onium ions" are usually intermediates for heteroatom migrations & Ar but usually transition states for R & H
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:

- 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:

- 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)

  - e.g. rearrangement during substitution at a neopentyl centre:

    \[
    \text{neopentyl iodide} \xrightarrow{\text{AgNO₃, H₂O}} \text{MeMeMeMeI} \xrightarrow{\text{Ag⁺}} \text{MeMeMeMeMe} \xrightarrow{\sigma_{C-C} \rightarrow \sigma^*_{C-I} (app)} \text{MeMeMeMeMe} + \text{MeMeMe} \]

    - 1,2-Me shift

    \[
    \text{OH} \quad \xrightarrow{\#} \quad \text{MeMeMeMeMe} \quad \xrightarrow{\text{OH₂, H⁺}} \text{MeMeMeMeMe} \quad \xrightarrow{\text{OH₂, H⁺}} \text{MeMeMeMeMe} \]

    - 1,2-hydride shift

    \[
    \text{MeMeMe} \xrightarrow{\sigma_{C-H} \rightarrow \text{Pvac (pp)}} \text{MeMeMeMeMe} \]

    - 1,2-hydride shift

  - e.g. rearrangement during Friedel-Crafts alkylation:

    \[
    \text{MeCl} \xrightarrow{\text{AlCl₃ cat., benzene}} \text{MeMeMeMeMe} \quad \xrightarrow{\sigma_{C-H} \rightarrow \text{Pvac (pp)}} \text{MeMeMe} \]

    - 1,2-hydride shift

    \[
    \xrightarrow{\#} \quad \text{MeMeMeMeMe} \quad \xrightarrow{\text{OH₂, H⁺}} \text{MeMeMeMeMe} \quad \xrightarrow{\text{OH₂, H⁺}} \text{MeMeMeMeMe} \]

    - 1,2-hydride shift

    \[
    \text{MeMeMe} \xrightarrow{\sigma_{C-H} \rightarrow \text{Pvac (pp)}} \text{MeMeMeMeMe} \]

    - 1,2-hydride shift

    \[
    \approx 1:1 \text{ mix as both cations precursors are secondary} \]

    - Rearranged substituted product

    \[
    \text{MeMeMeMeMe} \xrightarrow{\text{OH₂, H⁺}} \text{MeMeMeMeMe} \]

    - Rearranged substituted product

    \[
    \text{MeMeMe} + \text{MeMeMe} \]
Wagner-Meerwein rearrangements - *isomerisations*

- *Synthetically useful Wagner-Meerwein rearrangements*

  - *e.g. isomerisation of alkyl halides:*

    ![Chemical Reaction](image)

    - A remarkable synthesis of adamantane (C\(_{10}H_{16}\)):
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

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\[
\begin{align*}
\text{2,3-oxidosqualene} & \quad \text{1) epoxide opening} \quad \text{2) 2x Markovnikov ring-closures (6-memb rings)} \\
\text{lanosterol} & \quad \text{Markovnikov ring-closure (5-memb ring)} \\
\text{protosterol cation} & \quad \text{1,2-alkyl shift} \quad \text{ring expansion (5 \to 6)}
\end{align*}
\]
```

- “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:

  - NB. $H_2SO_4/\text{Ac}_2O$ is a weak sulfonylating mixture (cf. oleum) for $S_{E}Ar$: