CHEM95002: Orbitals in Organic Chemistry - Stereoelectronics

LECTURE 4 Neighbouring Group Participation (NGP), Rearrangements & Fragmentations

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

Imperial College
London

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Format & scope of lecture 4

- **Neighbouring Group Participation (NGP)**
- **Non-classical carbocations**
- **1,2-rearrangements/shifts/migrations**
  - Wagner-Meerwein methyl and hydride shifts
  - Pinacol & semi-pinacol
  - Baeyer-Villiger reaction
  - Beckmann rearrangement
- **Fragmentations**
  - Grob
  - Eschenmoser ring expansion
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

\[
\text{RELATIVE RATE } 1 : 600
\]

- retention of stereochemistry (via double inversion):

\[\text{ α-amino acid} \rightarrow \text{ α-hydroxy acid}\]

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

- **Payne rearrangements:**

  \[
  \text{BnO} \xrightarrow{\text{NaOH, H}_2\text{O}} \xrightarrow{\text{inversion}} \xrightarrow{\text{BnO}} \xrightarrow{\text{BuS}^-} \text{BnO}
  \]

- **aza-Payne rearrangements:**

  \[
  \text{Et}_2\text{N} \xrightarrow{\text{NaOH, H}_2\text{O}} \xrightarrow{\text{regioselective ring-opening (sterics)}} \text{Et}_2\text{N}
  \]

- **Bromonium ion rearrangements:**

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

  \[
  \text{Br} \xrightarrow{\text{H-Br}} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{\text{C}_2\text{-symmetric bromonium ion}} \xrightarrow{\text{rearranged product}} \
  \]

  \[
  \text{Br} \xrightarrow{\text{H-Br}} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{\text{meso bromonium ion (achiral)}} \xrightarrow{\text{rearranged product}}
  \]

  achiral (meso) [without $^{13}$C label]

  1:1 racemate
NGP with rearrangement – *involvement of* $\pi$ *& $\sigma$* bonds

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

  ![Diagram of anti and syn rearrangements](image)

  - Crystal structure of this carbocation finally obtained in 2013! See: Scholz Science, 2013, 341, 62 [DOI]

- **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]

  ![Diagram of non-classical rearrangement](image)

- The rearranged products of the above “NGP” processes can also be regarded as having undergone rearrangements/shifts/migrations...
1,2-Rearrangements/Shifts/Migrations

• **1,2-Rearrangements/shifts/migrations** 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*:

```
H/R/Ar^+ → H/R/Ar^+ = H/R/Ar/LG^+ + 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*:

```
H/R/Ar^+ → H/R/Ar^+ = H/R/Ar−LG/O^− + LG^−
```

*oxenium ion too high in energy to exist*

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

```
H/R/Ar^+ → H/R/Ar^+ = H/R/Ar−LG/N^− + LG^−
```

*nitrenium ion too high in energy to exist*
**Mechanistic variations**

- The overall mechanisms of 1,2-migrations vary from **stepwise** to **concerted** (cf. \(S_N1 \leftrightarrow S_N2\)) wrt the adjacent centres from and to which the migrating group moves:

  - The migrating centre however **always retains** its configuration during the actual migration step
    - This process is necessarily concerted and can be considered a [1,2]-sigmatropic shift (see Pericyclic lectures)
    - The migrating centre retains an octet of electrons, e.g. 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, but loss of stereochemical integrity at this centre is never observed (see Pericyclic lectures).
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-Rearrangements/shifts/migrations 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:

\[
\begin{array}{c}
\text{neopentyl iodide} \quad \text{AgNO}_3 \quad \text{H}_2\text{O} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{I} \quad \rightarrow \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Ag} \quad \text{OH} \\
\end{array}
\]

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

1,2-Me shift

direct substitution product NOT observed

\[\text{rearranged substituted product} \]

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

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \quad \text{Cl} \quad \text{AlCl}_3 \text{ cat.} \quad \text{phenyl} \\
\end{array}
\]

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

1,2-hydride shift

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

- “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”
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*:

  ![Reaction Diagram](image)

  - 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

- More generally, any functionality giving rise to a carbenium ion adjacent to an oxygenated carbon can undergo a semi-pinacol rearrangement...
  - Treatment of epoxides with Lewis acids results in semi-pinacol rearrangements:

  ![Reaction Diagram](image)
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. **Semi-pinacol rearrangement (1,2-alkyl shift)**
   - **Conformational lock**: The orientation of the hydroxyl group and the bromine atom facilitates the 1,2-alkyl shift.
   - **Reagents**: Ag$_2$O
   - **Products**: Ring-contracted aldehyde

2. **1,2-hydride shift**
   - **Reagents**: Ag$_2$O
   - **Products**: Cyclohexanone

3. **Epoxide formation**
   - **Reagents**: Ag$_2$O
   - **Products**: Epoxide

These processes highlight the critical role of orbital alignment in controlling the stereochemical outcome of semi-pinacol rearrangements.
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:

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

• Ionic fragmentation reactions are reactions in which a molecule breaks into 3 (or more) fragments.
• Typically, at least one C-C bonds is broken in a heterolytic fashion
• They are relatively rare NOT because C-C bonds are particularly strong:
  – cf. Bond Dissociation Energies:
    - C-C 339 kJmol\(^{-1}\) weakest
    - C-O 351 kJmol\(^{-1}\)
    - C-H 418 kJmol\(^{-1}\)
    - O-H 460 kJmol\(^{-1}\) 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:

  1) \(n_X \rightarrow \sigma^*_{C-C}\) (app)
  2) \(\sigma_{C-C} \rightarrow \sigma^*_{C-Y}\) (app)

  - 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:
    - NB. NMe₂ group is ‘bigger’ than OTs group (i.e. has greater A-value) so occupies equatorial position preferentially

\[
\text{Me}_2\text{N} + \text{OTs} \rightarrow \text{Me}_2\text{N} - \text{Me} \quad \text{both groups equatorial}
\]

1) \( n_N \rightarrow \sigma^*_{C-C} \) (app)
2) \( \sigma_{C-C} \rightarrow \sigma^*_{C-O} \) (app)

- 2x severe 1,3-diaxial interactions

\[
\begin{align*}
\text{Me}_2\text{N} & \rightarrow \text{Me}_2\text{N} \\
\text{TsOH} & \rightarrow \text{TsOH}
\end{align*}
\]

- MAJOR
  - \( E_2 \) elimination (MAJOR path)
  - \( \sigma_{C-H} \rightarrow \sigma^*_{C-O} \) (app)

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

\[
\begin{align*}
\text{Me}_2\text{N} & \rightarrow \text{Me}_2\text{N} \\
\text{Et}_3\text{N} & \rightarrow \text{Et}_3\text{N}
\end{align*}
\]

- MINOR
  - fragmentation (MINOR path)

\[
\begin{align*}
\text{Me}_2\text{N} & \rightarrow \text{Me}_2\text{N} \\
\text{EtOH, H}_2\text{O} & \rightarrow \text{EtOH, H}_2\text{O}
\end{align*}
\]

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

- alkenyl aldehyde [64%, exclusive prod]
- alkenyl aldehyde [11%, minor prod]
- cyclohexenes [49%, mix of regioisomers]

- \( n_N \rightarrow \sigma^*_{C-C} \) (app)
- \( \sigma_{C-C} \rightarrow \sigma^*_{C-O} \) (app)
- \( \sigma_{C-H} \rightarrow \sigma^*_{C-O} \) (app)
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**

\[
\text{enone} \xrightarrow{\text{epoxidation}} \text{epoxide} \xrightarrow{\text{hydrazone formation}} \text{hydrazone} \xrightarrow{\text{elimination}} \text{ketone}
\]

- The driving force for the fragmentation is enthalpic (formation of toluene sulfinate) & entropic (formation of \(N_2\))

- For a minireview on fragmentation for the synthesis of medium-rings, see: Clarke Chem. Sci. 2020, 11, 2876 [DOI]

\[
\text{12,5-fused bicycle} \xrightarrow{\text{epoxidation}} \text{epoxide} \xrightarrow{\text{hydrazine formation}} \text{hydrazine} \xrightarrow{\text{elimination}} \text{ketone}
\]

\[
\text{muscone} \xrightarrow{\text{hydrogenation}} \text{15-membered ring fragrance ketone}
\]