CHEM60001: An Introduction to Reaction Stereoelectronics

LECTURE 3 Stereoelectronics of Transition States – Kinetic vs Thermodynamic Control

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Nov 2016
Format & scope of lecture 3

- *Thermodynamically vs. Kinetically Controlled Reactions*
  - Stereoelectronics of products vs. transition states
  - Thermodynamic control: Ley spiroacetal formation
  - Kinetic control: 1,2-diaxial processes

- *Steric/Strain vs. Stereoelectronic Control of Reactivity*
  - Affect of 1,3-diaxial compression on reactivity

- *Ring-closure Reactions*
  - Baldwin’s rules
  - The Thorpe-Ingold Effect
Themodynamic vs. kinetic reaction control

- **Thermodynamic control:**
  - the reaction is *reversible* under the conditions & so *equilibrium* is attained between starting materials & products.
  - the *most stable product predominates*:

- **Kinetic control:**
  - the reaction is *irreversible* under the conditions & so the transition state represents a ‘point of no return’
  - the *most rapidly formed product predominates* (*i.e.* that reached via the lowest energy transition state):

**Hammond’s Postulate:**

the starting material, intermediate or product CLOSEST IN ENERGY to the transition state of interest will be most similar in structure
Thermodynamic control – e.g. Ley ‘dispoke’ protection

- Reaction of 1,2-Diols with a bis-enol ether to give dispiroketalts
  - The dispiroketal forms as a single diastereomer as the result of its formation being under thermodynamic control. The product is stabilised by multiple anomeric effects (Deslongchamps theory)

\[
\text{HO-CH}_2\text{OH} + \begin{array}{c}
\text{CSA (cat.), toluene,} \\
110^\circ\text{C}
\end{array} \rightarrow \text{I} \xrightleftharpoons{73\%} \begin{array}{c}
\text{II} \\
\text{III}
\end{array}
\]

- used e.g. for selective protection of di-equatorial 1,2-diols (over 1,3-, 1,2-di-axial & 1,2-axial/equatorial diols)

\[
\text{OH} + \begin{array}{c}
\text{CSA (cat.), toluene,} \\
110^\circ\text{C}
\end{array} \rightarrow \text{IV} \xrightleftharpoons{73\%} \begin{array}{c}
\text{V} \\
\text{VI}
\end{array}
\]

Kinetic Control – 1,2-diaxial processes

- **Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted cyclohexanes:**
  - *epoxide formation*: e.g. in A-ring of steroids (*NB. No-ring flipping possible – rigid framework*)
  - *epoxide ring-opening*: e.g. in A-ring of steroids
    - Diaxial ring-opening ('Fürst-Plattner' rule) controls regioselectivity of nucleophilic attack
Kinetic control – 1,2-diaxial processes

- **Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted cyclohexanes:**
  - **HOBr addition:** e.g. in A-ring of steroids

    ![Reaction diagram showing HOBr addition](image1)

  - **E2 elimination:** e.g. in A-ring of steroids

    ![Reaction diagram showing E2 elimination](image2)

- **[90%]**
- **[1%]**

- **via twist-chair TS**
Steric/strain effects - 1,3-diaxial compression

- The steric requirement of a rate-determining Transition State involving a cyclohexane substituent can have important consequences for reactivity. There are two cases:
  - The Transition State (TS#) is MORE crowded than the Starting Material (SM)
    - e.g. base hydrolysis of esters:
      \[
      \text{R-OCOR} \xrightarrow{\text{rds}} \left[ \text{R-O\textcolor{red}{\text{OH}}} \right]_{\#} \xrightarrow{\text{tetrahedral intermediate}} \text{R-OCOR} \xrightarrow{\ominus \text{OR}} \text{HO}.
      \]
    - For axial and equatorial positions on cyclohexanes:
**Steric/strain effects - 1,3-diaxial compression cont.**

- The Transition State (TS#) is **LESS** crowded than the Starting Material (SM)
  - e.g. Oxidation of alcohols:

```
R               CrO3
\H\O\ OH \ H\O\Cr\O\ OH\ R\ R'  \ H\O\Cr\O\ OH\ R\ R'  \ H\O\Cr\O\ OH\ R\ R'  \ H\O\Cr\O\ OH\ R\ R'  \ H\O\Cr\O\ OH\ R\ R'
\ R'\     \ rds\     \ R'\ CrO(H)2\     \ R'\ CrO(H)2\     \ R'\ CrO(H)2\     \ R'\ CrO(H)2
  \ 'big'
  \ 'small'
```

- For axial and equatorial positions on cyclohexanes:

```
\[\text{TS}^\#_{ax} \text{ and } \text{TS}^\#_{eq}\]
\[\Delta G^\#_{ax} \text{ and } \Delta G^\#_{eq}\]
\[1,3\text{-diaxial compression (LESS severe for TS}\#\text{s than SMs)}\]
```

- For a recent discussion of this 'strain-release CH activation' see: Eschenmoser & Baran *Angew. Chem. Int. Ed* 2009, 48, 9705 [DOI]
Baldwin’s Rules for Ring Closure

- **For kinetically controlled ring closures:**
  - For a review see: Gilmore *Chem. Rev.* **2011**, 111, 6513 [DOI]
  - the relative facility of ring-closure depends critically on the ring size, the hybridisation of the reacting centres & the mode of ring-closure (*exo* or *endo*)

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<tr>
<th><strong>nomenclature</strong></th>
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<tr>
<td><strong>Exo</strong> - the bond being broken in the ring closure is exocyclic <em>i.e.</em> outside the ring</td>
</tr>
<tr>
<td><strong>Endo</strong> - the bond being broken in the ring closure is endocyclic <em>i.e.</em> inside the ring</td>
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<tr>
<td><strong>Tet</strong> - electrophilic centre has sp³ hybridisation</td>
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<tr>
<td><strong>Trig</strong> - electrophilic centre has sp² hybridisation</td>
</tr>
<tr>
<td><strong>Dig</strong> - electrophilic centre has sp hybridisation</td>
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**E.g.**

- **tetrahedral systems:**
  - 3 to 7-*exo-tet* are all favoured processes
  - 5 to 6-*endo-tet* are disfavoured

- **trigonal systems:**
  - 3 to 7-*exo-trig* are all favoured processes
  - 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured

- **digonal systems:**
  - 3 to 4-*exo-dig* are disfavoured processes; 5 to 7-*exo-dig* are favoured
  - 3 to 7-*endo-dig* are favoured
Baldwin’s Rules for Ring Closure cont.

- **Baldwin’s rules were formulated following analysis of transition state geometries:**

  - **Tet** - electrophilic centre has sp³ hybridisation - $S_N2$ reaction

```
\[ \text{X}^\ominus \overset{\bullet}{\longrightarrow} \text{Y} \rightarrow \text{X}^\ominus \overset{\bullet}{Y} \rightarrow \text{X}^\ominus + \text{Y}^\ominus \]
```

  - **Trig** - electrophilic centre has sp² hybridisation - Nucleophilic addition to carbonyl/imine

```
\[ \text{X}^\ominus \overset{\bullet}{\longrightarrow} \text{O} \rightarrow \text{X}^\ominus \overset{\bullet}{\text{O}} \rightarrow \text{X}^\ominus + \text{O}^\ominus \]
```

  - **Dig** - electrophilic centre has sp hybridisation - Nucleophilic addition to nitrile/alkyne

```
\[ \text{X}^\ominus \overset{\bullet}{\longrightarrow} \text{C} \equiv \text{N}\overset{\bullet}{\longrightarrow} \text{X}^\ominus \overset{\bullet}{\text{N}} \rightarrow \text{X}^\ominus + \text{N}^\ominus \]
```
The Thorpe-Ingold Effect

- **The gem-dialkyl (Thorpe-Ingold effect) refers to the relative ease with which ring-closure can be achieved for small & medium rings when such a group is present in the tethering chain**
  - The effect is generally considered to be a *kinetic* phenomenon which has been attributed to:
    1. The *gem*-substituents compressing the angle between the two substituents bearing the reactive end groups thereby bringing them closer together
    2. The *gem*-substituents increasing the solution population of *gauche* conformers in which the reactive ends are close together
    3. The *gem*-substituents hindering solvation of the reactive centre (*e.g.* In epoxide formation, see below)
  - *Thermodynamic* factors (*e.g.* entropy) have also been invoked but recent evidence suggests that this is usually a negligible component (see: Bachrach *J. Org. Chem.* 2008, 73, 2466 [DOI])
  - *e.g.* For hydroxide-catalysed epoxide formation (see: Jorgensen *J. Am. Chem. Soc.* 2010, 132, 8766 [DOI])

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<tr>
<th>relative rate</th>
<th>1</th>
<th>5.5</th>
<th>21</th>
<th>248</th>
<th>252</th>
<th>1,360</th>
<th>2,040</th>
<th>11,600</th>
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- Synthetically, the following (non-alkyl) groups are also useful for promoting cyclisation in the same manner: