CHEM95002: Orbitals in Organic Chemistry - Stereoelectronics

LECTURE 3 Stereoelectronics of Transition States – Familiar Reactions under Kinetic Control

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Feb 2020
Format & scope of lecture 3

• **Thermodynamic vs. Kinetic Control**
  – Stereoelectronics of products vs. transition states
  – Thermodynamic control: Ley spiroacetal formation
  – Kinetic control: 1,2-diaxial processes

• **Ring-closure Reactions**
  – Baldwin’s rules

• **Reactions of the Carbonyl Group**
  – Nucleophilic addition to carbonyls (Bürgi-Dunitz angle)
  – Deprotonation $\alpha$ to carbonyls – enolate formation
    • Stereoselective lithium enolate formation
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):*

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**HAMMOND’S POSTULATE:**

- the starting material, intermediate or product CLOSEST IN ENERGY to the transition state of interest will be most similar in structure.
- *SM closest in energy -> early TS#*
- *Prod closest in energy -> late TS#*
Thermodynamic control – *e.g.* Ley ‘dispoke’ protection

- **Reaction of 1,2-Diols with a bis-enol ether to give dispiroketal**
  - 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)

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

  
  
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)

  ![Chemical structures](image)

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

**nomenclature**

*Exo* - the bond being broken in the ring closure is exocyclic *i.e.* outside the ring  
*Endo* - the bond being broken in the ring closure is endocyclic *i.e.* inside the ring  
*Tet* - electrophilic centre has sp³ hybridisation  
*Trig* - electrophilic centre has sp² hybridisation  
*Dig* - electrophilic centre has sp hybridisation

- **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 - \( S_N^2 \) reaction

  ![Tetrahedral Transition State]

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

  ![Triangular Transition State]

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

  ![Digonal Transition State]
Nucleophilic attack on carbonyl functions

- **What orbitals are involved?**
  - A donor orbital on the nucleophile [typically a lone pair ($n$)] and the $\pi^*_{\text{C=O}}$ orbital of the carbonyl group
  - Recall the orbital co-efficient situation for a $\pi^*_{\text{C=O}}$ orbital:

$$
\begin{align*}
\text{[Donor orbital]} & \quad \text{[\(\pi^*_{\text{C=O}}\) orbital]} \\
\cdots & \quad \cdots
\end{align*}
$$

- **The Bürgi-Dunitz trajectory**
  - It follows that, at close range, a nucleophile will attack the carbonyl carbon along a trajectory that maximises overlap – the so-called Bürgi-Dunitz trajectory (Bürgi J. Am. Chem. Soc. 1973, 95, 5065 [DOI] & Tetrahedron 1974, 30, 1563 [DOI])
Enolisation of carbonyl functions

- **Enolisation is under stereoelectronic control**
  - This was first proposed in 1956 as ‘CH-π overlap effect’: Corey *J. Am. Chem. Soc.* **1956**, *78*, 6269 [DOI]
  - The essential requirement is that the σ_C-H bond α to the carbonyl must adopt a conformation *perpendicular* to the plane of the carbonyl for deprotonation to occur [i.e. to allow \( σ_{C-H} \rightarrow π^*_C=O \) (pp)]

- **Evidence:**
  - Deprotonation of norcamphor at the *exo*-hydrogen is favoured over that at the *endo*-hydrogen by a factor of >700: Houk *J. Org. Chem.* **2000**, *65*, 8970 [DOI]
Stereoselective Li enolate formation - (E) vs (Z) stereochemistry

- **Lithium enolates of esters & ketones:**
  
  - When an enolate is formed there are often two different stereoisomers that can be formed depending on which α proton is removed: the (E)- or trans enolate and the (Z)- or cis enolate.
  
  - For the formation of lithium enolates using lithium amide bases (e.g. lithium diisopropylamide, LDA) in THF, a six-membered chair-like ‘closed’ TS for deprotonation is expected and two competing factors dictate enolate geometry: A¹,²-strain and 1,3-diaxial interactions:
(E)-Selective Li-enolate formation

- **(E)-Lithium enolates of esters & ketones** *(via closed TS# with small X group)*:

  - Lithium amide bases used in enolisation generally have bulky substituents *(e.g. 2 × i-Pr groups in the case of LDA; 2 × TMS groups in the case of LiHMDS)* – this, and performing the reaction at low temperature, ensures that the reagent acts as a **base** and NOT as a **nucleophile**
  
  - Consequently, the **1,3-diaxial interactions** *(which involve these substituents)* generally override the **$A^{1,2}$-strain** for enolisation of standard esters & ketones *(e.g. $X = \text{Me or OMe}$)*.
  
  - This leads to the predominant formation of **(E)-enolates** when using LDA in THF at -78°C:

- **Diagram**:

  - **BAD 1,3-diaxial interaction**

  - **'Closed' (cyclic) TS#'s**

  - **'LESS BAD' $A^{1,2}$ strain**

  - **(Z)-enolate MINOR**

  - **(E)-enolate MAJOR**

  - **e.g.** $X = \text{Me}$

  - **Ratio** 9 : 91
(Z)-Selective Li enolate formation

- **(Z)-Lithium enolates of esters & ketones** [via closed TS# with large X group OR via open TS#]:
  - Substrates containing very bulky X groups (e.g. X = t-Bu or an Evans oxazolidinone) will lead to predominant formation of (Z)-enolates when using LDA in THF at -78°C because the $A^{1,2}$-strain now overrides the 1,3-diaxial interactions in the ‘closed’ TS.
  - However, when using LDA at -78°C in a **mixed solvent system** of THF & hexamethylphosphoroustriamide (HMPA) even standard esters & ketones give predominant formation of (Z)-enolates because the HMPA strongly co-ordinates to the lithium cation breaking up the ‘closed’ TS and leading to an ‘open’ TS.
  - This removes the 1,3-diaxial interaction leaving the $A^{1,2}$ strain as the dominant/only factor:

\[
\begin{align*}
\text{Me} & \quad \text{CO} & \text{X} \\
& \xrightarrow{i\text{Pr}_2\text{NLi}} \quad \text{THF/HMPA} & -78^\circ \text{C} \\
\text{Me} & \quad \text{O} & \text{X} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Li}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]

**e.g.** $X = \text{O}$

**ratio** 81 : 19

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{O} & \text{Li} \\
& \quad \begin{array}{c}
\text{Me} \\
\text{X}
\end{array}
\end{align*}
\]