CHEM60001: An Introduction to Reaction Stereoelectronics

LECTURE 4 Chemistry of the Carbonyl Group

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Nov 2016
Format & scope of lecture 3

- **Reactions of the Carbonyl Group**
  - Nucleophilic addition to carbonyls (Bürgi-Dunitz angle)
  - Felkin-Anh model for diastereoselective addition to \( \alpha \)-chiral carbonyl compounds
  - Deprotonation \( \alpha \) to carbonyls – enolate formation
    - Stereoselective lithium enolate formation
Nucleophilic attack on carbonyl functions

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

- **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])

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*Note:* The images and diagrams in the document are not fully visible, but the text provides the necessary information to understand the content. The diagrams illustrate the concepts of nucleophilic attack and the Bürgi-Dunitz trajectory.
Diastereoselective addition to $\alpha$-chiral carbonyls

**The Felkin-Anh Model:**

**Features:**
1) $R_L/X$ perpendicular to carbonyl
2) $Nu$ approaches over $Rs$ at Burgi-Dunitz angle
3) $Rs$ distal to carbonyl irrespective of size of $R$ (even $R = H$) to facilitate approach of $Nu$

- Applicable to:

$X = \text{EWG}$

Best acceptor $\sigma^*$ orbital perpendicular to C=O

$\pi_C = O \rightarrow \sigma^*_{C-X}$

See separate handout for details
Diastereoselective addition to $\alpha$-chiral carbonyls

- **The Cram Chelate Model:**
  - Cram J. Am. Chem. Soc. 1959, 81, 2748 [DOI]

- Applicable to:

- Example:

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

- Evidence:
  – Deprotonation of norcamphor at the \textit{exo}-hydrogen is favoured over that at the \textit{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 $\alpha$ 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: $A^{1,2}$-strain and 1,3-diaxial interactions:

![Diagram showing the formation of (E) and (Z) enolates with A1,2-strain and 1,3-diaxial interaction](attachment:image.png)
(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 × iPr 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:

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

- **\(i^\text{Pr}_2\text{NLi in THF at -78°C}\)**

\[\text{e.g. } X = \text{O} \quad \text{ratio } 9 : 91\]
(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 R groups (e.g. X = tBu or an Evans oxazolidinone) will lead to predominant formation of (Z)-enolates when using LDA in THF at -78°C because the A1,2-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 A1,2 strain as the dominant factor:

\[
\text{Me} \quad \text{O} \quad X
\]

\[
\xrightarrow{i\text{Pr}_2\text{NLi}}
\]

\[
\text{THF/HMPA}
\]

\[
\text{-78°C}
\]

\[
\xrightarrow{(\text{acyclic}) \text{ TS}^\#s}
\]

\[
\begin{align*}
\text{(Z)-enolate MAJOR} & \quad \text{Me} \quad \text{OLi} \\
\text{(E)-enolate MINOR} & \quad \text{Me} \quad \text{OLi}
\end{align*}
\]

\[
\text{BAD} \quad A^{1,2} \text{ strain}
\]

\[
e.g. \quad X = \quad \text{ratio} \quad 81 : \quad 19
\]