Chemistry II (Organic): Introduction to Stereoelectronics

LECTURE 4 Stereoelectronics of Transition States – Reactivity of Carbonyls

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Mar 2007
Format & scope of lecture 4

• **Thermodynamically vs. kinetically controlled reactions**
  – Stereoelectronics of products vs. transition states
  – Thermodynamic control: Ley spiroacetal formation
  – Kinetic control: enamine alkylation & the Curtin-Hammett principle

• **Reactions of the carbonyl Group**
  – Nucleophilic addition to carbonyls (Bürgi-Dunitz angle)
  – Deprotonation $\alpha$ to carbonyls – 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:*

  ![Diagram showing thermodynamic control with ΔG and SM, prod A, prod B, TS_B, and ΔG°.](image)

– **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):

  ![Diagram showing kinetic control with ΔG and SM, prod A, prod B, TS_A, TS_B, and ΔG°.](image)

**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)

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

Thermodynamic control – e.g. enamine formation

- e.g. Condensation of **2-methyl cyclohexanone** with **pyrrolidine** – giving an equilibrating mixture of three isomeric products

![Diagram of enamine formation](image_url)
Kinetic control – e.g. enamine alkylation

- **The Curtin-Hammet principle**: ‘major conformer in starting material may not be most reactive’
  - Alkylation of 2-Me cyclohexanone/pyrrolidine enamine with MeI - the experimental result:

  \[
  \begin{align*}
  A + B + C & \quad 10 : 1 \ : 89 \\
  \text{equilibrated mixture as in previous slide} & \quad 1) \text{Mel} \\
  & \quad 2) \text{H}_2\text{O}, \text{H}^{\ominus} (\text{cat.})
  \end{align*}
  \]

  - The rationale - axial alkylation of conformer B (the minor conformer in the mixture):

    - cf. equatorial alkylation, which leads to a high energy twist chair 'intermediate':

  - NB. axial alkylation of C (which would lead to cis product) is disfavored due to a developing syn pentane interaction between the incoming Me group and the existing Me substituent. Equatorial alkylation of C (which would lead to trans product) is disfavored because, as for B, it leads to a twist chair intermediate. Axial or equatorial alkylation of A is sterically disfavored.
The Curtin-Hammet principle - energetics

- Alkylation of 2-Me cyclohexanone/pyrrolidine enamine with MeI – energetic situation:

\[ \Delta G \]

\[ \Delta G_{\text{eq}} \]

\[ \Delta G_{\text{ax}} \]

\[ \text{trans-product (MAJOR)} \]

\[ \text{cis-product} \]

\[ \text{rapidly equilibrating enamine mixture} \]
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**.
Enolisation of carbonyl functions

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

- **Evidence:**
  - Deprotonation of norcamphor at the exo-hydrogen is favoured over that at the endo-hydrogen by a factor of $>700$:
Stereoselective enolate formation - \((E)\) vs \((Z)\) enolates

- **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 through lithium amide bases with THF at -78°C. The structure depicts two chair-like transition states with \(A^{1,2}\) strain and 1,3-diaxial interactions, favoring the \((Z)\)-enolate with large \(X\) and small \(L\) and the \((E)\)-enolate with small \(X\) and large \(L\).]
(E)-Selective enolisation

- **(E)-Lithium enolates of esters & ketones** *(via closed TS# with small R group):*
  - Lithium amide bases used in enolisation generally have bulky substituents (*e.g.* 2 × iPr groups in the case of LDA) – 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 **A¹,²-strain** for enolisation of standard esters & ketones.
  - This leads to the predominant formation of **(E)-enolates** when using LDA in THF at -78°C:

![Chemical diagram showing enolisation reaction](image)
(Z)-Selective enolisation

- **(Z)-Lithium enolates of esters & ketones** [via closed TS* with large R group or via open TS*]:

  - Substrates containing very **bulky X groups** (e.g. \(X = \text{tBu}\)) 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 & hexamethyldiphosphoroustriamide (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 factor:

\[
\begin{align*}
\text{R} &= \text{ bulky group} \\
\text{THF/HMPA} &\text{ at } -78^\circ\text{C} \\
\text{iPr}_2\text{NLi} &\rightarrow \text{Me} \quad \text{OR} \\
\end{align*}
\]

\[
\begin{align*}
\text{(Z)-enolate} &\quad \text{MAJOR} \\
\text{(E)-enolate} &\quad \text{MINOR} \\
\text{ratio} &\quad 81 : 19
\end{align*}
\]