Stereoselective Organic Synthesis
(CH30128: Topics in Organic Chemistry I)

Lecture 3 – Diastereocontrol in Acyclic Systems

Dr Alex Cresswell
a.j.cresswell@bath.ac.uk
The **molecular orbitals** for the $\pi$-bond of formaldehyde are depicted below. Notice that the $\rho$ orbital lobes within the antibonding $\pi^*$ orbital are bent outwards – this has stereoelectronic implications for the chemistry of the C=O bond:

![Molecular orbitals](image)

For example, the **lowest energy ('ground state') conformation** of acetaldehyde is one in which a C–H bond eclipses the C=O group, because this gives the best orbital alignment for two stabilising $\sigma_{C-H} \rightarrow \pi^*_{C=O}$ interactions:

![Conformation](image)

This $\sigma_{C-H} \rightarrow \pi^*_{C=O}$ hyperconjugative interaction is also part of the reason that ketones are less reactive than aldehydes, as there are more of these interactions present to stabilise the C=O group.

The approach trajectory of nucleophiles to C=O bonds is called the Bürgi-Dunitz (BD) angle (~107±2°). It was originally based on crystallographic measurements for intramolecular amine-carbonyl interactions in the solid state, but computational estimates (SCF-LCAO-MO calculations) for the approach of a hydride anion (H⁻) to formaldehyde (H₂C=O) give a BD angle value of 107°:

*Stereochemistry of reaction paths at carbonyl centres* Tetrahedron 1974, 30, 1563

Detailed calculations have shown that the conformation of acetaldehyde undergoing nucleophilic attack is not the same as its 'ground state', lowest energy conformation – a **staggered** reactive conformation is adopted. This enables a σ⁺C–H→π⁺C–O LUMO-lowering interaction which makes the C=O bond a better acceptor of electron density:

"Theory and modeling of stereoselective organic reactions" Science 1986, 231, 1108
The most widely accepted model for the addition of nucleophiles to \( \alpha \)-chiral aldehydes/ketones – first proposed by Felkin and later refined by Anh & Eisenstein – is the **Felkin-Anh (F-A) model** [see CH20149 lectures and ‘Clayden’, chapter 33].

The original (and simplest) version of the model pertains to systems in which the \( \alpha \)-substituents are electronically-similar (C or H) but are differentiated by size (L = large, M = medium, S = small). Note that F-A model ‘TSs’ are simplifications of real (i.e. calculated) TSs (c.f. Houk’s ‘staggered’ TS on previous slide and below right).

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The F-A model is built on a number of assumptions:

- TSs are ‘reactant-like’ (early) rather than ‘product-like’ (late).
- Reaction occurs via the most reactive conformation of the carbonyl compound (with a \( \sigma^* \) orbital perpendicular to the C=O bond), not the lowest energy (‘ground state’) conformer. This is a manifestation of the **Curtin-Hammett Principle**.
- The **largest group (L)** is placed perpendicular to C=O to minimise steric interaction with the incoming nucleophile.
- The nucleophile approaches along the **Bürgi-Dunitz trajectory** (~107°).
- The nucleophile approaches **antiperiplanar to the C–L bond** to give the best stereoelectronic interaction between \( \sigma \)-donor (\( \sigma_{Nu\cdot C} \)) and \( \sigma \)-acceptor (\( \sigma^*_{C-L} \)) orbitals (see ‘Houk’s calculated F-A TS’, above).*
- The nucleophile prefers to attack alongside the smaller group (S) than the medium group (M) for steric reasons.

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For aldehydes/ketones with **heteroatom** (X) \( \alpha \)-**substituents** (e.g. O, N, S, Hal), the most reactive conformation is the one where the C–X bond is perpendicular to the \( C=O \) group [see CH20149 lectures and ‘Clayden’, chapter 33].

C–X bonds are generally **better \( \sigma \)-acceptors** than C–H or C–C bonds (i.e. lower energy \( \sigma^*_{C-X} \) orbitals) and offer greater hyperconjugative stabilisation of the transition state:

\[ \text{Me} - \text{O} - \text{Ph} \xrightarrow{\text{LiAlH}_4} \text{Me} - \text{Cl} - \text{Ph} \]

\[ \text{polar F-A model} \]

\[ \xrightarrow{\downarrow} \text{Me} - \text{Cl} - \text{OH} \]

75:25 dr

“**The acceptor ability of \( \sigma \) bonds [...] increases when going to the end of a period and down the group. Enhancement of the acceptor ability of \( \sigma \) bonds within periods parallels the increase in electronegativity of X, whereas augmentation of acceptor ability in groups is opposite to the changes in electronegativity of X and is a consequence of the lowering of energy of \( \sigma^*_{C-X} \) orbitals.”**

The "Syn" or "Anti" Designation is Product-, Not Mechanism-, Dependent

Consider the following addition of a generalised nucleophile (Nu) to an α-chloro carbonyl compound (where identity of R will determine if aldehyde or ketone).

The *mechanism-dependent* stereochemistry resulting from this addition, according to the polar F-A model, is shown in the box.

Sometimes chemists use the stereodescriptors "syn" or "anti" to describe the product. However, unlike R and S descriptors (which are assigned based on rigorous and inflexible rules), these are 'soft' descriptors: the assignment depends on how the chemist chooses to define the 'main' carbon chain.* Thus, these descriptors are *product-, not mechanism-, dependent*:

The Cram chelate model is used when aldehydes/ketones bear an \( \alpha \)-heteroatom substituent capable of chelation to a metal ion [see Clayden pg 862-864].

The \( \alpha \)-heteroatom substituent is almost invariably an alkyl ether (-OR) group, but chelation can also occur with other Lewis basic moieties (e.g. -OH, -SR, -NR\(_2\)).

Trialkylsilyl ethers (-OSiR\(_3\)) tend to chelate very poorly (e.g. -OSiEt\(_3\), -OSiMe\(_2\)-t-Bu) or not at all [e.g. -OSi(i-Pr)\(_3\)] (as ever, there are always some exceptions).

Mg\(^{2+}\), Zn\(^{2+}\), Cu\(^{2+}\), Al\(^{3+}\), Ce\(^{3+}\), Ti\(^{4+}\) are all excellent chelators, and Li\(^+\) (with a high charge density) can often chelate too. Na\(^+\) and K\(^+\) are generally poor at chelating, due to their low charge density.

Note that the Cram chelate model predicts the opposite diastereomer to the polar F-A model.

For Cram’s original articles, see: *J. Am. Chem. Soc.* 1959, 81, 2748; *J. Am. Chem. Soc.* 1963, 85, 1245

For a review on chelation-control in carbonyl additions, see: *Acc. Chem. Res.* 1993, 26, 462
The partitioning between Cram chelate and polar F-A pathways is dependent on the **O-protecting group** and the **solvent**:

<table>
<thead>
<tr>
<th>Solute</th>
<th>Solvent</th>
<th>Cram Chelate Pathway</th>
<th>Polar F-A Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bn</td>
<td>Et₂O</td>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>TBDPS</td>
<td>THF</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>MOM</td>
<td>THF</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>MOM</td>
<td>Et₂O</td>
<td>98</td>
<td>2</td>
</tr>
</tbody>
</table>

Kishi has cleverly employed Cram chelate control in his second-generation (formal) synthesis of the polyether antibiotic **lasalocid A**. This example demonstrates the utility of chelation even in a very complex setting:

![Lasalocid A structure](image)


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**Cram chelate control**

Yoshito Kishi
The Fráter-Seebach alkylation of β-hydroxy esters involves diastereoselective alkylation of the chelated dianion.

As is common with enolate alkylations, steric effects override torsional effects [see lecture 1], such that reaction occurs on the opposite face to the Me group (even though the TS will have a small amount of twist-boat character):

Schreiber has exploited this reaction in his total synthesis of FK506 (an immuno-suppressive drug):

A stereogenic centre at the \( \beta \)-position can also strongly influence diastereoselectivity in C=O additions, but only when the stereocentre bears an electronegative substituent (almost invariably -OH or -OR).

Two general models have been developed to account for the diastereoselectivity:

- **Chelation control**
  - half-chair conformation
  - avoid 'twist-boat' TS [lecture 1]

- **Dipole control**
  - zig-zag conformation of main chain
  - dipole minimisation

Unlike the 1,2-induction models (F-A and Cram chelate), both of these scenarios **predict the same diastereomer**, so it is not always clear which pathway is actually in operation.

Remember that the descriptors "syn" and "anti" are **product-dependent**, and not intrinsically linked to the mechanism (i.e. it's a consequence of how the 'main' carbon chain in the product is defined, and this depends on whether the nucleophile is organometallic or hydride based).

Thus, a 1,3-chelation mechanism with an **aldehyde + an organometallic nucleophile** will give a **1,3-anti** product:

![Diagrams showing 1,3-chelation with an aldehyde and an organometallic nucleophile]

**But a 1,3-chelation mechanism with a ketone + a hydride nucleophile will give a **1,3-syn** product (see Narasaka-Prasad reduction):**

![Diagrams showing 1,3-chelation with a ketone and a hydride nucleophile]

Look for the zig-zag of the 'main' chain.
It is sometimes difficult to know which model to apply, but the **nature of the Lewis acid** and the identity of the **O-protecting group** will dictate whether or not chelation is possible [see Cram chelate model].

Boron Lewis acids like BF$_3$ are monodentate and incapable of chelation (as this would require 5 bonds around B) so the ‘dipole control’ model is more suitable, but Lewis acids based on heavier elements (e.g. Ti, Sn) can expand their coordination sphere more readily, so the chelation model is viable:

In contrast to 1,2-induction (simple F-A model), **steric effects** appear to play only a minor role in 1,3-induction:
One classic method where chelation is thought to be operative is the **Narasaka-Prasad reduction**, which involves the diastereoselective reduction of β-hydroxy ketones to **syn-1,3-diols**.

The reaction is thought to occur via a chelate formed upon exchange of the methoxy substituent on boron by the substrate alcohol, followed by **intermolecular delivery of hydride** from NaBH₄. [Note that chelation with B can occur provided that ligand exchange first occurs with the substrate].

Remember that the facial selectivity of hydride attack is governed by formation of a ‘chair-like’, as opposed to a ‘twist boat-like’ TS [see lecture 1]:

![Narasaka-Prasad reduction mechanism](image)


This method is often used in combination with the aldol reaction to provide a convenient access to 1,3-diol or **skipped polyol** motifs, which occur frequently in **polyketide natural products**:

*Biochemical synthesis of skipped polyols*

![Biochemical synthesis diagram](image)
A complementary reduction process to access \textit{anti-1,3-diols} from \(\beta\)-hydroxy ketones is the \textbf{Evans-Saksena reduction}, which uses \(\text{Me}_4\text{N}^-\text{BH(OAc)}_3^-\) as the reducing agent (in another example of a substrate-directed reaction):

Shortly after, Evans developed a related reaction called the \textbf{Evans-Tishchenko reduction}, which uses an aldehyde as the reducing agent and \(\text{SmI}_2\) as a Lewis acid catalyst (mechanistically very similar to the Meerwein-Ponndorf-Verley reduction – see lecture 1).

The power of this reaction is the ability to \textbf{differentiate between the two resulting hydroxyl groups}, as one of them is selectively protected in the process:
Schreiber has cleverly used the Evans-Tishchenko reduction to achieve a fragment coupling in his total synthesis of \textit{rapamycin}.

Although the stereocentre generated is later destroyed (by oxidation), this does serve to illustrate the complexity of molecules which can be utilised in these types of 1,3-induction processes:

\[ \textit{rapamycin} \]

\[ \text{J. Am. Chem. Soc. 1993, 115, 7906} \]
The Keck allylation reaction involves the Lewis acid-promoted addition of an allyl stannane to an aldehyde or ketone to give a homoallylic alcohol. Account for the following observations (Cy = cyclohexyl):

\[
\begin{align*}
\text{Cy} & \quad \text{OR} \\
\text{H} & \quad \text{SnBu}_3 \\
\text{MgBr}_2 & \\
\text{R} = \text{TBDMS} & : 21 \\
\text{R} = \text{Bn} & : >250
\end{align*}
\]

Using any reagents of your choice, provide a synthetic route to compound B from compound A. Provide justification for the stereochemistry within the target molecule and draw it in its lowest energy conformation: