I. Basic Principles

IA. Conformational Analysis

Boger Notes: p. 1 - 16 (Chapter I)


- Explain the stereoselectivity
- Draw two chair conformations of 3; vicinal 1H J-analysis indicates that the SPh substituent is equatorial; is this supported by an analysis of the relative energies of the two chair conformers?

• Configuration: defines the orientation of atoms in space. Compounds with the same constitution and connectivity, but different orientation of atoms in space, are configurational isomers = stereoisomers. Only chiral molecules have enantiomers; chiral compounds are not superimposable on their mirror image and have only different physical and chemical properties within a chiral environment; chiral molecules don't have α, i, or S4 elements of symmetry
**Definitions**

*Constitution:* defines the connectivity of atoms in a molecule of a given composition. E.g. $\text{C}_2\text{H}_5\text{O}$ and $\text{C}_2\text{H}_6\text{O}$ have different composition; $\text{CH}_3\text{CH}_2\text{OH}$ and $\text{CH}_3\text{O}-\text{CH}_3$: have the same number and kind of atoms, but different connectivity - they are **constitutional isomers**.

Constitutional isomers have different physical and chemical properties.

Special cases: **tautomers** (rapidly equilibrating constitutional isomers)
valence tautomerism:

![Diagram of valence tautomerism](image1)

with R = H; degenerate structures, at rt 10 peaks are observed in $^1$H NMR; bond migration is fast at 100 °C: 1 (single) peak in $^{13}$C NMR. For a review of bullvalenes, see: Angew. Chem. Int. Ed. Engl. 1967, 6, 414.

Note: the difference between valence tautomerism and resonance (the positions of the nuclei is not the same in valence tautomers).

![Diagram of resonance and valence tautomers](image2)

- Examples:

  ![Diagram of diastereomers and enantiomers](image3)

  $(R)$-configuration (clockwise) according to CIP (Cahn-Ingold-Prelog)

  ...more challenging
**Relative Stereochemistry:**

- cis or syn
  - or
  - vs.
  - or
- 2,3-dimethyltetrahydropyran

**Absolute Configuration**

- (2S,3S)-dimethyltetrahydropyran

More or less commonly used descriptors are: cis/trans; threo/erythro, exo/endo; li/di, and syn/anti for the description of the relative stereochemistry of two or more stereocenters.

More specifically, threo/erythro are ambiguous, because there are at least two different definitions that have been used for aldol reactions. The most appropriate definition stems from the carbohydrate literature and uses the requirements of Fischer projections (threose/erythrose).
However, a definition referring to the more familiar zigzag backbone has also been used and, unfortunately but quite obviously, results in the reversed assignment. For a documentation of this nomenclature chaos, see: Seebach, D.; Prelog, V. *ACE* 1982, 21, 654. This paper also discusses the *Ikeda* nomenclature.

**carbohydrate convention:**

![Diagram of carbohydrate convention]

- *threo*
- *erythro*

but:

![Diagram of OH, CO2Et, and R]

- a *threo* aldol product (?!)

---

Partially to avoid this problem, Masamune has introduced the *syn/anti* nomenclature for substituents that are on the same/opposite side along a *zigzag* conformation.

**Masamune convention:**

![Diagram of Masamune convention]

- *syn*
- *anti*

The biggest problems with *syn/anti* and *threo/erythro* nomenclature is the ambiguous distinction between backbone and substituents. Additionally, models with more than two stereocenters create new problems. We will generally use the *syn/anti* description, but a picture naturally tells more than a thousand words.
Stereochemistry: More Definitions

- **Chirality**: If a molecule is not superimposable on its mirror image, it is chiral.

If a molecule is achiral, but nonetheless contains asymmetric carbons, it is called a *meso* compound.

$$\text{meso 1,3-dibromocyclohexane:} \quad \begin{array}{c}
\text{Br} \\
(S) \\
\text{Br}
\end{array} \quad \text{=} \quad \begin{array}{c}
\text{Br} \\
(R) \\
\text{Br}
\end{array}$$

A 1:1 mixture of enantiomers is called a *racemic mixture*. Mixtures that are enriched in one enantiomer over another are called *scilemic*. Enantiomers rotate the plane of polarized light in equal amounts but in opposite directions. The **specific rotation** is the degree that the plane of polarization of the light is rotated after passing through a solution of an enantiomer.

$$\left[ \frac{\alpha}{100}^D \right] = \frac{\text{specific rotation}}{c \cdot l}$$

$D$: sodium-D-line (589 nm); $\alpha$: observed rotation angle; $c$: concentration in g/mL; $l$: length of cell in dm.

There is no obvious (cf. the Rosenfeld equation) correlation between the configuration of enantiomers and the sign (+, or -) or the value of their specific rotation. However, the rotation of a *scilemic* mixture can be used to assess their degree of **optical purity** (ratio of enantiomers) if the $[\alpha]^D_0$ of a pure enantiomer is known. For two enantiomers $A$ and $A'$:

$$\% \text{ optical purity} = \% \text{ enantiomer excess} (\text{ee}) = \frac{[A]-[A']}{[A]+[A']} \times 100 = \frac{[\alpha]^\text{obs}_{\text{percent}}}{[\alpha]^D_0} \times 100$$

The ratio of enantiomers $\frac{[A]}{[A']}$ can be calculated accordingly:

$$\frac{[A]}{[A']} = \frac{100 + \% \text{ee}}{100 - \% \text{ee}}$$

The process of separating enantiomers is called **resolution**. Generally, chemical resolution is performed by the reversible conversion of a racemic mixture to diastereomers, which can be separated according to their different physical properties.
Structure Analysis by Computational Methods: ORD Calculations

- L/R circ. pol. light see Δ index
- rotation of polarization
- rotation angle \( \beta = \frac{\omega^2 I N}{2c^2 s_0} \)

Key Challenge: Link Molecular Structure to \( \beta \) via Q. M.

Schrödinger: The Equation - 1926/27
Rosenfeld: The quantum equation for \( \beta \): 1928 (!) [Z. Physik 1928, 52, 161]

\[
H^{(0)} \Psi^{(0)} = E^{(0)} \Psi^{(0)}
\]
\[
H^{(1)}(t) = - \mu \cdot E - m \cdot \vec{B}
\]
\[
\Psi(t) = \Psi^{(0)} + \Psi^{(1)}
\]
\[
P(t) \propto \langle \Psi | \hat{\tau} | \Psi \rangle
\]

Molecular S. E.
Time-dep. Pert.
Perturbed W. F.
Induced Polarization

\[
\beta_D \propto \sum \text{Im}_{\text{ex}} \text{Im}_{\text{sts.}} \frac{\langle \Psi^{(0)}_g | \hat{r} | \Psi^{(0)}_{ex} \rangle \cdot \langle \Psi^{(0)}_{ex} | \hat{r} \times \hat{p} | \Psi^{(0)}_g \rangle}{\omega^{(0)}_{ex} - \omega^{(0)}_D}
\]

Stereogenic/Chirotopic:

\[
\begin{align*}
\text{OMe} & \quad \text{CO}_2\text{Me} \\
\text{OMe} & \quad \text{H} \\
\text{CO}_2\text{Me} & \quad \text{OMe} \\
\text{O} & \quad \text{Bn} \\
\end{align*}
\]

1. \( \text{H}_2, \text{Pd(OH)}_2 \)
2. \( \text{PPTs, 65\%, 25\% SM} \)

* chirotopic, nonstereogenic

Chirotopic describes any point in a molecule (including an atom) that resides in a local chiral environment, even if the molecule as a whole is not chiral. A point or atom located on a plane or at a center of symmetry is achirotopic.

Stereogenic is largely equivalent to chiral, with the exception of a cis/trans isomerization in an alkene, where the sp2 carbon is stereogenic but of course not chiral. A stereogenic element in a molecule accordingly is a focus of stereoisomerism (stereogenic center, axis, or plane) such that interchange of two ligands attached to an atom in such a molecule leads to a stereoisomer.
What are chiral molecules?
Conformational analysis allows us to predict the shape of molecules and the spatial orientation of functional groups and substituents. The architecture of molecules determines its reactivity and selectivity in organic reactions as well as its biological properties.

acyclic conformations:

- **Staggered**
- **Eclipsed**

Newman projections

---

ethane

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>staggered</td>
<td>0</td>
</tr>
<tr>
<td>eclipsed</td>
<td>2.8</td>
</tr>
</tbody>
</table>

butane

<table>
<thead>
<tr>
<th>Conformation</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>staggered</td>
<td>0</td>
</tr>
<tr>
<td>eclipsed</td>
<td>0.9</td>
</tr>
<tr>
<td>antiperiplanar</td>
<td>3.6</td>
</tr>
<tr>
<td>gauche</td>
<td>6.3</td>
</tr>
</tbody>
</table>

The preference for the staggered conformation of ethane appears to be mostly due to hyperconjugative stabilization, and not to steric (e.g. Coulombic) repulsion (cf. *Nature*, 2001, 411, 565).
In cycloalkanes, angle strain (derivation from the ideal tetrahedral bond angle of 109.5°) and torsional strain (eclipsing interactions) determine the overall ring strain. Total ring strain decreases from cyclopropane (27.6 kcal/mol) to cyclohexane (0 kcal/mol) and increases again for the higher cycloalkanes.

![Graph showing total strain energy per CH₂ group versus ring atoms.]

In cyclohexane, the chair conformation is about 6 and 5.1 kcal/mol lower in energy than boat and twist-boat conformations, respectively.

![Diagram showing chair, boat, and twist conformations with energy differences.]

chair 0  
boat + 6 kcal/mol (eclipsing interactions)  
twist +5.1 kcal/mol
A chair ring flip converts axial substituents into equatorial positions and vice versa.

The relative stability of the two chair conformations is determined by the 1,3-diaxial interactions of the substituents on the ring. A-Values (≡ diff. in kcal/mol of the energy of the axial vs. the equatorial conformational isomers) allow us to predict the most stable conformations. For determination of A-values, see: Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. J. Org. Chem. 1999, 64, 2085.

\[
\Delta G^\ddagger = 10 \text{ kcal/mol}
\]

\[
A = - (\Delta G^{\circ}_{eq} - \Delta G^{\circ}_{ax})
\]

<table>
<thead>
<tr>
<th>Substituent</th>
<th>A-Value [kcal/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>1.80</td>
</tr>
<tr>
<td>CH(CH₃)₂</td>
<td>1.9</td>
</tr>
<tr>
<td>Ph</td>
<td>2.2</td>
</tr>
<tr>
<td>CO₂CH₃</td>
<td>1.3</td>
</tr>
<tr>
<td>OCH₃</td>
<td>0.60</td>
</tr>
<tr>
<td>OH</td>
<td>0.9 - 0.54</td>
</tr>
<tr>
<td>SH</td>
<td>0.9</td>
</tr>
<tr>
<td>CN</td>
<td>0.2</td>
</tr>
<tr>
<td>N(CH₃)₂</td>
<td>2.1</td>
</tr>
<tr>
<td>Cl, Br, I</td>
<td>0.4</td>
</tr>
</tbody>
</table>

A values are larger in:

- shorter bond distance
- much larger steric interactions
Effective Size of Substituents

a) Effective size of substituents according to A-values (free-energy differences between equatorial and axial substituents on a cyclohexane ring [kcal/mol]):

<table>
<thead>
<tr>
<th>Substituent</th>
<th>A-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgCl</td>
<td>-0.25</td>
</tr>
<tr>
<td>HgBr</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>0.008</td>
</tr>
<tr>
<td>CN</td>
<td>0.17</td>
</tr>
<tr>
<td>F</td>
<td>0.25</td>
</tr>
<tr>
<td>Br</td>
<td>0.4</td>
</tr>
<tr>
<td>C=C</td>
<td>0.41</td>
</tr>
<tr>
<td>I</td>
<td>0.46</td>
</tr>
<tr>
<td>OTs</td>
<td>0.5</td>
</tr>
<tr>
<td>Cl</td>
<td>0.52</td>
</tr>
<tr>
<td>OAc</td>
<td>0.7</td>
</tr>
<tr>
<td>OMe</td>
<td>0.75</td>
</tr>
<tr>
<td>SH</td>
<td>0.9</td>
</tr>
<tr>
<td>OH</td>
<td>0.52-0.95</td>
</tr>
<tr>
<td>NO₂</td>
<td>1.1</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>1.15</td>
</tr>
<tr>
<td>COCH₃</td>
<td>1.2</td>
</tr>
<tr>
<td>COCl</td>
<td>1.25</td>
</tr>
<tr>
<td>COOH</td>
<td>1.4</td>
</tr>
<tr>
<td>NH₂</td>
<td>1.4-1.6</td>
</tr>
<tr>
<td>CH=CH₂</td>
<td>1.7</td>
</tr>
<tr>
<td>CH₃</td>
<td>1.74</td>
</tr>
<tr>
<td>CH₂CH₃</td>
<td>1.75</td>
</tr>
<tr>
<td>COO⁻</td>
<td>1.9</td>
</tr>
<tr>
<td>NMe₂</td>
<td>2.1</td>
</tr>
<tr>
<td>iPr</td>
<td>2.15</td>
</tr>
<tr>
<td>c-C₃H₁₁</td>
<td>2.15</td>
</tr>
<tr>
<td>TMS</td>
<td>2.5</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>2.7</td>
</tr>
<tr>
<td>t-Bu</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Effective Size of Substituents

a) Effective van der Waals radii (Å) derived from the rotational barriers in 6-aryl-1,1,5-trimethylylindane (Bott, G.; Fled, L. D.; Stemhelt, S. J. Am. Chem. Soc. 1980, 102, 5618)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>X</th>
<th>van der Waals radius (Bonds)²</th>
<th>effective radius (Charlton)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.97 ± 0.06</td>
<td>1.98</td>
<td>1.97</td>
</tr>
<tr>
<td>Br</td>
<td>1.96 ± 0.04</td>
<td>1.83</td>
<td>1.85</td>
</tr>
<tr>
<td>Cl</td>
<td>1.73 ± 0.03</td>
<td>1.75</td>
<td>1.73</td>
</tr>
<tr>
<td>F</td>
<td>1.47 ± 0.01</td>
<td>1.47</td>
<td>1.47</td>
</tr>
<tr>
<td>OMe</td>
<td>1.52 ± 0.03</td>
<td>1.52 (O)</td>
<td>1.56</td>
</tr>
<tr>
<td>OH</td>
<td>1.53 ± 0.03</td>
<td>1.52</td>
<td>1.52</td>
</tr>
<tr>
<td>OAc</td>
<td>1.56 ± 0.03</td>
<td>1.80 (S)</td>
<td>1.84</td>
</tr>
<tr>
<td>SH</td>
<td>1.80 ± 0.03</td>
<td>1.80</td>
<td>1.80</td>
</tr>
<tr>
<td>CH₃</td>
<td>1.80 ± 0.03</td>
<td>2.0</td>
<td>1.72, 2.23b</td>
</tr>
<tr>
<td>CH₂</td>
<td>2.2 ± 0.13</td>
<td>2.11, 2.74b</td>
<td>1.73</td>
</tr>
<tr>
<td>CH₂(OAc)</td>
<td>1.84 ± 0.05</td>
<td>1.96</td>
<td>2.4, 3.2b</td>
</tr>
<tr>
<td>CH₂(C₂H₅)</td>
<td>2.2 ± 0.12</td>
<td>2.4, 3.2b</td>
<td>1.96</td>
</tr>
<tr>
<td>t-Bu</td>
<td>3.6 ± 0.5</td>
<td>2.4, 3.2b</td>
<td>1.96</td>
</tr>
<tr>
<td>COOMe</td>
<td>1.62 ± 0.03</td>
<td>1.56 ± 0.04</td>
<td>1.77</td>
</tr>
<tr>
<td>Ph</td>
<td>1.62 ± 0.03</td>
<td>1.77</td>
<td>1.77</td>
</tr>
<tr>
<td>CN</td>
<td>1.51 ± 0.03</td>
<td>1.78</td>
<td>1.60</td>
</tr>
<tr>
<td>NMe₂</td>
<td>1.61 ± 0.02</td>
<td>1.55 (N)</td>
<td>1.63</td>
</tr>
<tr>
<td>NH₂</td>
<td>1.91 ± 0.05</td>
<td>1.79</td>
<td>1.63</td>
</tr>
<tr>
<td>NH₃</td>
<td>1.79 ± 0.03</td>
<td>1.79</td>
<td>1.79</td>
</tr>
<tr>
<td>NMe₃</td>
<td>&gt;2.27</td>
<td>2.42, 3.11b</td>
<td>2.42, 3.11b</td>
</tr>
<tr>
<td>NO₂</td>
<td>1.58 ± 0.03</td>
<td>1.58 ± 0.04</td>
<td>1.79</td>
</tr>
<tr>
<td>HgCl</td>
<td>1.63 ± 0.01</td>
<td>1.5-1.65 (Hg)</td>
<td>2.6, 3.99b</td>
</tr>
<tr>
<td>SMMe₂</td>
<td>2.01 ± 0.08</td>
<td>2.1</td>
<td>2.6, 3.99b</td>
</tr>
</tbody>
</table>
I. Basic Principles
IA. Conformational Analysis - Continued


- Propose relative configurations for 2-6
- What is the name of the conversion of 4 to 6 via 5?
- What is the name of the natural product that contains the decalin 6 as a substructure? What is it used for, and who discovered it?

Chair-chair interconversion of silyloxy-cyclohexanes. Conformational equilibrium in CDCl₃ solution at about 200 K. The same trend is seen for toluene solutions but with a greater population of the axial conformation:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Percentage Axial Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>3.6</td>
</tr>
<tr>
<td>1b</td>
<td>Et</td>
<td>Et</td>
<td>Et</td>
<td>4.0</td>
</tr>
<tr>
<td>1c</td>
<td>Me</td>
<td>Me</td>
<td>i-Pr</td>
<td>6.5</td>
</tr>
<tr>
<td>1d</td>
<td>i-Pr</td>
<td>i-Pr</td>
<td>i-Pr</td>
<td>8.6</td>
</tr>
<tr>
<td>1e</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>14.3</td>
</tr>
<tr>
<td>1f</td>
<td>Ph</td>
<td>Ph</td>
<td>i-Bu</td>
<td>19.6</td>
</tr>
</tbody>
</table>

The anomeric effect

The anomeric effect is an $n \rightarrow \sigma^*$ phenomenon. The presence of good donor orbitals vicinal and antiperiplanar to the C-O bond results in a strong response of the C-OR distance to the electron demand of OR. This reflects increased stabilization of the cation part of the valence bond form C$^+$-OR.

Hyperconjugation (or $\sigma-\pi$ conjugation) is a particularly important type of donor-acceptor interaction between a filled $\sigma$-bonding orbital and an electron deficient orbital such as a carbocation p-orbital.

A related effect can be attributed to silicon groups, double bonds, and cyclopropanes ($\sigma \rightarrow \sigma^*$ interaction).

Cram and related Stereoechemical Rules

It is a capital mistake to theorise before one has data. Insensibly, one begins to twist facts to suit theories, instead of theories to suit facts.
(Sherlock Holmes, A Scandal in Bohemia)

Substituents are usually ordered according to their effective size if steric hindrance is the selectivity-determining factor. For electronic effects, consider:

Anh-Eisenstein: The strongest e-withdrawing group favors the anti position, $\alpha \rightarrow \alpha^*$
Felkin/Karabatsos/Houk: Torsional strain
Klein/Burgess-Liotta: Orbital distortion
Cleplak: The most powerful e-donating group favors the anti position, $\alpha \rightarrow \alpha$
Padovan-Row/Houk: Electrostatic effects

Cram’s Rule


In this model, Cram proposed that complexation of the metal to the carbonyl oxygen rendered it the bulkiest group in the molecule, thus forcing it in between the two least bulky substituents at the $\alpha$-carbon. Attack would occur from the side of the smallest substituent.
This model correctly predicted the major diastereomer of most asymmetric additions, with the notable exception of Grignard additions to α-chloro ketones. Cornforth proposed a model where the halogen plays the role of the large substituent, so that the C=O and C-Cl dipoles are opposed.

The predictive value of Cram’s rule notwithstanding, the rationale was speculative, and as spectroscopic methods developed, it was called into question.

In 1968, Felkin noted that the Cram as well as the Karabatsos models failed to account for the outcome of nucleophilic additions to cyclohexanones, and do not explain the effect of the R substituent on the selectivity (Tetrahedron Lett. 1968, 2199).

Effects of substituents at ketone carbonyl:

\[
\begin{array}{cccc}
R = \text{Me} & \text{Et} & \text{Pr} & \text{Bu} \\
\text{Ph} & 74 & 76 & 83 & 98 \\
\text{Cyclohexyl} & 62 & 66 & 80 & 62 \\
\end{array}
\]

\% major isomer for LAH reduction

preferred for Ph; steep potential
preferred for CH; shallow potential

To explain these results, Felkin proposed that the incoming nucleophile attacks the carbonyl from a direction that is antiperiplanar to the large substituent. This model has major weaknesses, e.g. it assumes that intramolecular interactions in the substrate are responsible for the selectivity of a bimolecular reaction (most distances are identical in both transition states); it is also hard to accept that R=H is more sterically demanding than oxygen as would be required for aldehydes.
In 1977, Ahn used ab initio methods to evaluate the energies for all postulated transition state structures. This clearly showed that Felkin’s transition states were the lowest energy conformers for attack on either face of the carbonyl, including metal ion coordinated carbonyl groups. Ahn and Eisenstein found that the energy difference between the two Felkin transition states was amplified when the angle of nucleophilic attack was adjusted to 100°. Thus, the Felkin model was revised to include the Bürgi-Dunitz trajectory. This established the first sound theoretical basis for the transition states in nucleophilic carbonyl additions.

**Felkin-Ahn Model**

- **Bürgi-Dunitz trajectory:**

Anh and Eisenstein also addressed the issue which substituent would assume the role of the large group anti to the incoming nucleophile. A simple rule was offered (Nouv. J. Chim. 1977, 1, 61): the substituents should be ordered according to the energies of the antibonding \( \sigma^* \) orbitals. The preferred anti substituent will be that one having the lowest lying \( \sigma^* \) orbital. This rule also explains the \( \alpha \)-chloro ketone anomaly, since the \( \sigma^* \) for the carbon-chlorine bond is lower than a carbon-carbon bond.

**Anh-Eisenstein (polar Felkin model)**

- → attack is anti to a substituent with a low \( \sigma^* \) (\( \sigma \rightarrow \sigma^* \) donation)}
In 1987, Heathcock tested this hypothesis, and concluded that the rule is only partially correct (J. Am. Chem. Soc. 1987, 109, 3353).

\[
\text{X} \quad \text{R = Me} \quad \text{Et} \quad \text{2-Pr} \quad \text{t-Bu} \quad \text{Ph}
\]

\begin{tabular}{c|c|c|c|c|c}
 & OMe & 58\% & 76\% & 93\% & 93\% & 83\% \\
 & Ph & 78\% & 86\% & 70\% & -63\% & - \\
\end{tabular}

According to the Anh-Eisenstein α+ hypothesis, one would expect a gradual increase in the selectivity as the bulk of the remaining substituent R increases. However, this is clearly not the case!

→ both steric and electronic effects determine the favored anti substituent

In a 1959 analysis, Cram considered cases with α-hydroxy and amino carbonyl compounds.

→ chelation increases rate of reaction
Cram-Chelate

Nucleophilic additions to cyclohexanones

*small* Nu (LAH, NaBH₄)

*bulky* Nu (L-selectride)

The question, put simply, is: What forces determine whether the attack is from above or below, and are they stereoelectronic or purely steric?

\[
\text{Nu} \quad \text{vs.} \quad \text{Nu}
\]

\[
\text{OH} \quad + \quad \text{OH}
\]

| JACS 1970, 92, 709 | LAH | 17 | 83 |
| JACS 1956, 78, 2579 | NaBH₄ | 25 | 75 |
| JACS 1972, 94, 7159 | L-selectride | 90 | 10 |
| JACS 1988, 110, 3508 | MAD:Bu/MgCl | 8 | 92 |


Stabilizing interaction between C-H \( \sigma \)-orbital and \( \sigma^* \)

\( \alpha^* \)-orbital forming in transition state

One of the disagreements regarding Cieplak’s interpretation is as to the better electron-donor capacity of C-H bonds compared to C-C bonds. This model succeeds in rationalizing adamantanone addition chemistry, though.
Application of the concept to adamantanes (Le Noble):

Quantum chemical calculations do not agree with the Cieplak interpretation of this phenomena, though. For a review, see: Gung, B. W. *Tetrahedron* 1996, 52, 5263.

Electrostatic (dipole) effects are also important:

Calculation of the component of the molecular dipole moment parallel to the π-plane, \( \mu_\perp \), by fast semiempirical MO methods results in a straightforward linear relationship with the logarithm of the experimental ratio of \( \alpha \)- and \( \beta \)-attack of organometallic reagents. This correlation allows the quantitative prediction of experimental 1,4-diastereoselectivities. Our conclusion is that electrostatic effects determine the face-selectivity of nucleophilic carbonyl additions in sterically unhindered cyclohexadienones and naphthoquinones.

Percentage of axial attack in nucleophilic additions to 3-substituted cyclohexanones:

\[
\begin{align*}
\text{MeLi} & \quad \begin{array}{c}
\text{R} \\
\text{H}
\end{array} \\
\text{OH} & \quad \\
\text{R} & \quad \begin{array}{c}
\text{H} \\
\text{Ph}
\end{array}
\end{align*}
\]

- \( \text{R} = \text{TMS} \): 15%
- \( \text{R} = \text{H} \): 21%
- \( \text{R} = \text{Ph} \): 25%
- \( \text{R} = \text{CF}_3 \): 34%
- \( \text{R} = \text{CF}_3 \): 50%

These results can be explained by electrostatic or the Cieplak model.

This result can be explained by either the electrostatic or the Cieplak model (J. Am. Chem. Soc. 1981, 103, 4540). However, Gung et al. (TH 1996, 52, 5263) showed that it was most likely simply a steric effect.
Consequences of substitution by oxygen and sulfur:

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Equatorial attack [%]</th>
<th>Axial attack [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>MeMgl</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>EtMgl</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Me2CHMgl</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

Nucleophile | Equatorial attack [%] | Axial attack [%] |
-------------|-----------------------|-----------------|
LAH          | 6                     | 94              |
MeMgl        | 0.3                   | 99.7            |
EtMgl        | 2                     | 98              |
Me2CHMgl     | 4                     | 96              |

Nucleophile | Equatorial attack [%] | Axial attack [%] |
-------------|-----------------------|-----------------|
LAH          | 85                    | 15              |
MeMgl        | 93                    | 7               |
EtMgl        | 89                    | 11              |
Me2CHMgl     | 91                    | 9               |

Explanations?
The results can be explained in terms of Felkin’s torsional strain model plus steric interactions (for cyclohexanone).