Stereochemistry – The Chemistry of Shape

a) **Constitutional isomers**: order of bond attachment is different

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

b) **Stereoisomers**: non-identical compound of identical connectivity

1) **Configurational isomers**: stereoisomers which are interconvertible by interchanging groups attached to the same (carbon) atom

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

2) **Conformational isomers**: isomers which are interconvertible by rotation about single bonds

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

when such a rotation requires high energy (> 20 kcal/mol) the isomers are known as **atropisomers**

ex.

3) **Enantiomers**: configurational or conformational isomers which have a non-superimposable mirror-image relationship

\[ \text{CH}_3 \quad \text{H} \quad \text{Cl} \quad \text{F} \quad \text{vs.} \quad \text{H} \quad \text{Cl} \quad \text{F} \quad \text{vs.} \quad \text{H} \quad \text{Cl} \quad \text{F} \quad \text{vs.} \quad \text{H} \quad \text{Cl} \quad \text{F} \]

or

\[ \text{vs.} \quad \text{vs.} \]
4) **Diastereomers:** any set of configurational or conformational isomers which do not have a non-superimposable mirror-image relationship

5) **Epimers:** diastereomers that differ at one center

Diastereomers behave as different chemical entities (different solubility, reactivity, spectra, etc.); Enantiomers behave identically except when exposed to a chiral reagent or polarized light.

**Optical activity** (reported as $\alpha_{D}^{20} = x.xxx$° $c = y.yy$)

$\alpha_{D}^{20} = \text{specific rotation of Na D line (589.3nm)}$

$= [\text{observed rotation (degrees)}] / [\text{Length (dm)} \times \text{g/cc}]$

$c = \text{concentration in g / 100mL}$

**ORD:** optical rotatory dispersion

measurement of rotation as a function of wavelength

enantiomers give mirror image curves

**Chiral:** a stereoisomer non-superimposable on its mirror image

**Achiral:** a stereoisomer superimposable on its mirror image due to a plane of symmetry
Reevaluation of Stereochemistry: The Mislow Approach

(JACS 1984, 3319)

- Stereochemistry and chirality have nothing to do with one another. “Chirality and achirality are purely geometric attributes that are in no way dependent on models of bonding.” (Mislow & Siegel)

**stereogenicity:** a property of tetrahedral atoms, in which all four ligands are different; exchange of any two ligands results in a different isomer. Such (stereogenic) atoms can be assigned an $R$ or $S$ designation using the Cahn-Ingold-Prelog system.

**chirotopicity:** a term applied to any atom that exists in a chiral environment; in general, non-chirotopic atoms lie on a plane or point of symmetry

**Note:** The term "stereogenic center" is now preferred to "chiral center" or "asymmetric center".

Ex:

Mislow also points out that the term "stereoisomer" is impossible to define in purely geometric terms and can be abandoned if one attaches no stereochemical significance to bonding. In addition, if we discard the term "stereoisomer," then "diastereomer" becomes a meaningless term.

**Flow charts for the classification of symmetry relationships among molecules and topic relationships among sets of atoms**
**Topicity**

Stereochemical relationships between individual atoms or groups within a single molecule can be defined in terms of *topicity*. Thus, two atoms equated by a mirror reflection of the molecule are **enantiotopic** and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are **homotopic**. Two protons placed in diastereomeric positions by a mirror reflection are in **diastereotopic** environments.
Cahn-Ingold-Prelog Rules for Assignment of Stereogenicity

1) Assign each substituent on the stereogenic atom a priority based on the following considerations:
   a) Atomic number (higher atomic numbers get higher priority)
   b) In the event of a tie, look at the substituents attached to each substituent:
      c) The higher priority goes to the atom with the highest priority substituent
      d) In the event of a tie, give a higher priority to the atom with the greater number of
         higher priority substituents (count multiple bonds as multiple substituents)
      e) In the event of a tie, repeat step b) until a difference is encountered

2) Once priorities have been assigned, view the molecule from the perspective in which
   the lowest priority substituent is directly behind the stereogenic atom. If the remaining
   three substituents are arranged such that traveling from highest to lowest priority occurs
   in a clockwise direction, the stereogenic atom is assigned the (R) designation; if traveling
   from highest to lowest occurs in a counterclockwise direction, the stereogenic atom is
   assigned the (S) designation.

\[
\begin{align*}
\text{O} & \text{C(H)(CH[CCC])}_2 \text{C(H)(CH}_3)\text{2} > \text{C(H)}\text{2(C)}
\end{align*}
\]

Note: If two substituents differ only in their stereogenicity, we give a higher priority to
the (R) configuration and assign \(r\) and \(s\) designations to the stereogenic center.

Prochirality (Stereotopicity) of sp\(^2\) Atoms

Any sp\(^2\) atom attached to three different ligands is considered prochiral and the faces of the
multiple bond are either enantiotopic or diastereotopic. The two faces can be
designated as \(si\) or \(re\) using a variation of the Cahn-Ingold-Prelog convention: the face in
which the travel is clockwise is designated \(re\); the face in which the travel is
counterclockwise is given the \(si\) designation.

\[
\begin{align*}
\text{pyruvate reductase} & \quad \text{H}_3\text{C CO}_2\text{H} \\
\text{(si facial selectivity)} & \quad \text{H}_3\text{C CO}_2\text{H (S)}
\end{align*}
\]
**Symmetry Operations:** operations which convert an object into itself  
  a) Rotation ($C_n$) rotation of $360^\circ/n$ about an axis gives the original species  
  b) Reflection ($\sigma$) reflection in a plane gives the original species  
  c) Rotation-reflection ($S_n$) rotation of $360^\circ/n$ about an axis followed by  
      reflection in a plane perpendicular to the axis of rotation gives the original species

**Relationship Between Chirality and Symmetry Groups**

<table>
<thead>
<tr>
<th>Chiral without stereogenic carbons</th>
<th>Chiral with stereogenic carbons</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Achiral without stereogenic carbons</td>
<td>Achiral with stereogenic carbons</td>
</tr>
</tbody>
</table>

**Class I**

optically active  
no stereogenic carbons *but* chiral
Class II

non-superimposable mirror images, no plane of symmetry
(lots of molecules in this class)

Class III

superimposable mirror images
plane of symmetry - C₁, C₂, C₃, C₄, OH plane
(lots of molecules in this class)

Class IV

meso compound, 2 stereogenic centers but a plane of symmetry running through the molecule
**Cycloalkanes:**

Draw the possible stereoisomers of 1,2-dimethylcyclobutane

```
CH₃   CH₃
H     H
```

meso

```
CH₃   H   CH₃
H     H   H
```

enantiomers

Draw the possible stereoisomers of 1,3-dimethylcyclobutane

```
CH₃
H
CH₃
```

achiral

```
CH₃
H
CH₃
```

achiral

one plane of symmetry    two planes of symmetry

**Diastereomers:**

```
CH₃
H
OH
```

D-erythrose

```
CH₃
H
```

L-erythrose

```
CH₃
H
```

D-threose

```
CH₃
H
```

L-threose
Stereochemistry of Transition States

Like ground state molecules, transition states also have stereochemical properties:

- enantiomers
  - same energies, so equally populated

- diastereomers
  - different energies, so differentially populated
Conformation

a) Ethane

Staggered Ethane Conformation

H C H  
\[ \text{HCCH dihedral angle} = 60^\circ \]

staggered form = (S)
(rear H's bisect front H's)

Eclipsed Ethane Conformation

H C H  
\[ \text{HCCH dihedral angle} = 0^\circ \]

eclipsed form = (E)
(rear H's behind front H's)

3 Kcal/mol
b) Butane

1. Fully eclipsed (one eclipsed CH₃-CH₃; and two eclipsed H-H)

2. Gauche (offset CH₃-CH₃ and offset H-H)

3. Partly eclipsed (two eclipsed CH₃-H; and one eclipsed H-H)

4. Anti (CH₃’s 180° apart and H-H offset)

Angle of rotation, degrees.
Alkane Steric Interactions

Gauche butane    =    0.9 Kcal/mol
Eclipsed H...H   =    1 Kcal/mol
Eclipsed H...CH₃ =    1.5 Kcal/mol
Eclipsed CH₃...CH₃=    4 Kcal/mol

Substituted Butane

\[ Y \quad X \quad \rightarrow \quad X, Y = \text{OR, Cl, F (electronegative groups)} \]

\[ E_{\text{gauche}} < E_{\text{anti}} \]

“gauche effect” ascribed to a dipole / dipole interaction

c) Pentane

\[ H \quad H \quad H \quad H \quad H \quad \rightarrow \quad 1,7 \text{ interaction} \]

very bad steric interaction ( > 5 kcal/mol )

d) Butadiene

\[ s\text{-trans} \quad \rightarrow \quad s\text{-cis} \]

e) acrolein

\[ s\text{-trans} \quad \rightarrow \quad s\text{-cis (less stable } \approx 0.5 - 1.0 \text{ kcal/mol)} \]
f) alkenes

\[ \begin{align*}
\text{R}_1 \text{ eclipses C=Y to allow } \text{R}_2 & \text{ & } \text{R}_3 \text{ to hyperconjugate} \\
(\text{allows overlap with } \pi^*) \\
- \text{contributes electron density to electron deficient } \pi^*
\end{align*} \]

(esp. when Y = N, O and R_{2,3} = H > C > N > O > X)

- C-H hyperconjugates better than C-C > C-O (C-N)

\[ \begin{align*}
\therefore \text{ the more electropositive } \text{R}_2 & \text{ & } \text{R}_3 \text{ the better} \\
\text{Topics in Stereochem, 1971, 5, 167}
\end{align*} \]

\[ \begin{align*}
\text{ex} \\
\text{H}_3\text{C} & \text{O} > \text{H}_3\text{C} & \text{O} \\
\text{by } & \approx 1 \text{ kcal/mol}
\end{align*} \]

\[ \begin{align*}
\text{Exception!} \\
\text{dipole / dipole repulsion} \\
\text{true for carbonyls} \\
\text{not true for olefins (due to sterics)}
\end{align*} \]

\[ \begin{align*}
\text{1,6 interaction} & \approx 1 \text{ kcal/mol} \\
\text{bisected} & \approx 2 \text{ kcal/mol} \\
\text{lowest E} & 0 \text{ kcal/mol}
\end{align*} \]

2 kcal/mol energy difference is typical for not eclipsing a bond
\[ (E_{\text{bisected}} - E_{\text{eclipsed}} \approx 2 \text{ kcal/mol}) \]
substituted sp<sup>2</sup> - sp<sup>2</sup>

\[ \begin{align*}
\text{perpendicular} & \quad +0 \text{ kcal/mol} \\
\text{bisected} & \quad +0.5 \text{ kcal/mol} \\
\text{eclipsed} & \quad +0.6 \text{ kcal/mol} \\
\text{eclipsed} & \quad +4 \text{ kcal/mol} \\
\text{bisected} & \quad +5 \text{ kcal/mol} \\
\end{align*} \]

\[ \begin{align*}
\text{α - CH}_3 & \text{ destabilized s-cis} \\
\Delta G & \approx 0.5 \text{ kcal/mol} \\
\text{β - CH}_3 & \text{ destabilized s-trans} \\
\end{align*} \]
\[ \Delta G^\dagger \approx 10 \text{ kcal/mol} \]

\[ \Delta G^\dagger = 15 \text{ kcal/mol} \]

\[ \Delta G^\dagger = 12 \text{ kcal/mol} \]

for \( R_2 \) larger than \( R_3 \)

Dale, *Stereochemistry & Conformational Analysis* (Verlag Chemie)
g) Cyclohexane

3 representations

a dot denotes a non-visible bond (H$_{eq}$ on C-1) toward the observer.

an open circle denotes an invisible bond (H$_{eq}$ on C-4) away from the observer.
interconversion of cyclohexane conformers

Chair 1

Hax Hax Hax Hax
Hex Hex Hex Hex
Hax Hax Hax Hax

Chair 2

Hax Hax Hax Hax
Hex Hex Hex Hex
Hax Hax Hax Hax

Note that the ring flip interchanges axial and equatorial protons

Bring C2,1,6,5 all into same plane while keeping C3,4 unchanged

Half-Chair 1

The eight hydrogens shown are all eclipsed

Half-Chair 2

In the **twist-boat** form, the two flagpole hydrogens are "offset" so they do not directly run into each other as in the **boat** form.

Twist-boat (two views)

"Flagpole Hydrogens"

Boat (three views)
energetics of the cyclohexane interconversion process

Substituted Cyclohexanes

a) Methylcyclohexane
The equatorial methyl group is in an anti-butane conformation; no destabilizing interactions.

The axial methyl group is in a gauche butane conformation with the two axial protons on C-1 and C-3; a total of (1.8 Kcal/mol) destabilization.

The amount of energy necessary to convert from an equatorial form to an axial form is called the A-value for a given substituent.

**Typical “A” Values For Monosubstituted Cyclohexanes**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>(Kcal / mol)</th>
<th>Substituent</th>
<th>(Kcal / mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.25</td>
<td>CH$_3$</td>
<td>1.80</td>
</tr>
<tr>
<td>Cl, Br, I</td>
<td>0.50</td>
<td>C$_2$H$_5$</td>
<td>1.90</td>
</tr>
<tr>
<td>OH</td>
<td>0.70</td>
<td>n-C$_3$H$_7$</td>
<td>2.10</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>0.70</td>
<td>i-C$_3$H$_7$</td>
<td>2.10</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>1.80</td>
<td>t-C$_4$H$_9$</td>
<td>5.60</td>
</tr>
<tr>
<td>NR$_2$</td>
<td>2.10</td>
<td>C$_9$H$_5$</td>
<td>3.10</td>
</tr>
<tr>
<td>CO$_2$H</td>
<td>1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
b) \textit{trans-1,2-dimethylcyclohexane}

The diequatorial dimethyl cyclohexane has one gauche butane type interaction... this results in a destabilization of the diequatorial isomer by 0.9 Kcal/mol.

The two axial methyl groups (on C_{5,6}) are each in a gauche butane conformation with two axial protons on C-1 and C-3, and C-2 and C-4 respectively; this results in a total of four destabilizations, each worth 0.9 Kcal/mol... Total = 3.6 Kcal/mol.

The difference in energy between the two forms favors the diequatorial conformer by 2.7 Kcal/mol, this means that this form will represent 99% of the equilibrium mixture.
c) *cis*-1,2-dimethylcyclohexane

Each of these isomers will be present in equilibrium in **equal amounts**, (50% : 50%) since they are of **equal energy**.

The monoaxial, monoequatorial dimethylcyclohexane has three **gauche** butane type interactions; this results in a destabilization of this isomer by a total of 2.7 Kcal/mole.

Same for this form.

---

d) *cis*-1,3-dimethylcyclohexane

Chair 1 has no destabilizing steric interactions; the two equatorial methyl groups are both anti-butane type.

Chair 2 has two gauche butane interactions (0.9 kcal/mole each; dotted arrows), in addition to the 3.7 Kcal/mol (solid arrows) for a total of 5.5 Kcal/mole!
e) Various mono-substituted cyclohexanes

= H coming out of page
= H going into page
dot = H<sub>d</sub> dot = H<sub>e</sub>

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Equatorial</th>
<th>Axial</th>
<th>Energy Diff. (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>none</td>
<td>(2) g.b.</td>
<td>1.8</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>(2) g.b.</td>
<td>(2) 1,3-diax.</td>
<td>5.6</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>(1) g.b.</td>
<td>(3) g.b.</td>
<td>1.8</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>(1) g.b.</td>
<td>(3) g.b.</td>
<td>1.8</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>(3) g.b.</td>
<td>(1) g.b. plus</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) 1,3-diax.</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>(2) g.b.</td>
<td>(4) g.b.</td>
<td>1.8</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>(3) g.b.</td>
<td>(1) g.b. plus</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) 1,3-diax.</td>
<td></td>
</tr>
</tbody>
</table>

f) 6-member ring heterocycles

favored $\Delta G^\circ \approx -$2 kcal/mol

Why?
g) Other rings

5:

\[ \begin{array}{c}
\text{envelope}
\end{array} \rightleftharpoons \begin{array}{c}
\text{half-chair} \quad (2 \text{ of them})
\end{array} \]

8:

\[ \begin{array}{c}
\text{boat-chair}
\end{array} = \begin{array}{c}
\text{chair-chair} \quad \text{or} \quad \text{crown}
\end{array} \]

10:

\[ \begin{array}{c}
\text{boat-chair-boat}
\end{array} \]

\[ \begin{array}{c}
cyclohexene:
\end{array} \]
h) Bicycles

decalin:

\[
\begin{align*}
\text{trans} & \quad \equiv \quad \text{cis} \\
\text{ring-flip} & \\
\end{align*}
\]

(3) 1,6-interactions = 3 (0.87 kcal/mol) = 2.61 kcal/mol

methyldecalin:

\[
\begin{align*}
\text{4 gauche} & \quad \Delta E = 0.9 \text{ kcal/mol} \\
\end{align*}
\]
Stereochemistry and Chemical Reactions

Increasingly important topic: the FDA has mandated that all new drugs be sold as single enantiomers! Much effort is now put in to the development of enantioselective reactions and asymmetric catalysis.

A) Achiral compounds.

Achiral compounds react with achiral reagents to produce achiral products.

1) Addition of an achiral reagent to an achiral substrate
   a) bromination of an achiral olefin

       Formation of bromonium ion intermediate from either face of the olefin generates the same symmetrical (achiral) species

       ![Bromination Reaction Diagram]

   b) osmylation of an achiral olefin

       ![Osmylation Reaction Diagram]
B) Prochiral compounds.

Prochiral compounds are an important subclass of achiral compounds (those containing no preexisting chiral centers). Prochiral materials bear at least one sp\(^2\) atom which becomes a stereogenic center in the course of a chemical reaction.

Prochiral compounds react with achiral reagents to produce racemic products (enantiomers have exactly equal free energy and therefore will be formed in equal amounts when produced from achiral reagents). **Optical activity never arises spontaneously in the reactions of prochiral compounds.**

![Prochiral center (becomes a chiral center in the product)](image)

Formation of bromonium ion intermediate is equally likely from either face of the olefin.

c) bromination of a prochiral olefin

d) osmylation of a symmetrical trans-olefin

![Anti addition (to give the meso compound from a symmetrical trans-olefin)](image)

These enantiomers will be produced in equal amounts since OsO\(_4\) is an achiral reagent and access to either face of the olefin is equally likely.

Anti addition (to give the meso compound from a symmetrical trans-olefin) is not observed since OsO\(_4\) adds via a concerted syn addition mechanism!
C) Chiral compounds.

1) Pure enantiomers
   a) bromination of a single enantiomer of a prochiral olefin

   The two transition states have different energies; therefore the two diastereomeric products will be formed in unequal amounts.

When reactions can produce a mixture of diastereomers, the products will always be formed at different rates; thereby producing unequal amounts of the diastereomers. The ratio of the diastereomers can be either almost 50/50 or may range up to >99.9999 to .0001 but, in principle, one expects that diastereomers should be formed in differing amounts since they have different free energies.
**Stereospecificity:**  The product (or mixture of products) from the reaction of two (or more) isomeric starting materials under the same reaction conditions are different.

\[
\text{烯烃} + \text{Br}_2 \rightarrow \text{烯烃} + \text{Br}^- \rightarrow \text{烯烃} + \text{Br}^- \text{ erythro}
\]

\[
\text{烯烃} + \text{Br}_2 \rightarrow \text{烯烃} + \text{Br}^- \rightarrow \text{烯烃} + \text{Br}^- \text{ threo}
\]

**Stereoselectivity:**  given a particular starting material and a particular set of reaction conditions, one of the possible diastereomers / enantiomers is formed in excess.

\[
\text{苯甲酸} \xrightarrow{\text{MeMgBr}} \text{苯乙醇}
\]

\[
\text{烯烃} \xrightarrow{\text{H}_n\text{BuOOH} \atop \text{Ti(O\text{OiPr})}_4} \text{烯烃}
\]
2) Racemic mixtures

When the starting material of a chemical reaction is a racemic mixture (a 50:50 mixture of one enantiomer and its mirror image) the creation of a new chiral center again results in the formation of diastereomers. However in this case, each of the diastereomers is accompanied by equal amounts of its mirror image so a racemic mixture of diastereomeric products is formed.

a) bromination of a racemic prochiral olefin

The (S,R/R,S) racemic stereoisomers are diastereomeric to the (R,R/S,S) racemic stereoisomers.
3) Resolutions of racemic mixtures.

An analogous situation occurs when we consider the reaction of enantiomers with a **chiral reagent**. This also results in the formation of a pair of diastereomers; once again, since diastereomers have different energies, they should be formed in unequal amounts. This allows us to perform **resolutions** (chemical separations of enantiomers).

**Classical resolution:**

![Diagram of classical resolution](image)

- **Single enantiomer** (1.0 equivalent)
- **R,S** (a racemic dl pair; 1:1 mixture of enantiomers)

If this reaction is run until the total amount of the slow-reacting component has been completely consumed, it will produce a 50:50 mixture of two diastereomers which can be separated. If we then perform chemistry on the diastereomers to regenerate the two component parts, we would have achieved a **classical resolution** by forming (and then cleaving) the diastereomeric derivatives.

**Kinetic resolution:**

Consider the limiting case where the slow reaction is about 100 times slower than the fast reaction, and we use only 1/2 the stoichiometric quantity of our optically active reagent $R^*$; this will provide the following mixture:

![Diagram of kinetic resolution](image)

- **Single enantiomer** (0.5 equivalent)
- **R,S** (a racemic dl pair; 1:1 mixture of enantiomers)

Easily separated; each in essentially optically pure form.
D) Asymmetric induction.

Reaction of achiral compounds with optically active chiral reagents allows the stereogenic center of the reagent to take an active part in the creation of a new stereogenic center on the substrate (a diastereomeric process). To the extent that these two reaction pathways differ in energy, absolute stereochemistry will be induced in the product; a process referred to as asymmetric induction. We measure the effectiveness of such a process in terms of enantiomeric excess (ee).

The optically active borane is unsymmetrical. There are two different orientations (transition states) from which the hydrogen from the borane can be delivered to the carbonyl group of the ketone. The (Pro-S) transition state has smaller through-space interactions between the methyl group on the borane and the methyl group of the ketone and is therefore preferred.
Stereochemistry of Reactions (cont.'d))

1) Cram’s Rule

To explain the selectivity seen in nucleophilic addition to carbonyls

Cram proposed the following rule (where S, M, L denote the size of the substituent)

\[ \text{JACS 1952, 74, 5828} \]
\[ \text{JACS 1959, 81, 2748} \]

According to Cram, the nucleophile should attack from the side of the smallest substituent.
- assumes a reactive conformer when L eclipses R
- problem: when M = Cl the wrong product is predicted
2) Karabatsos model

![Diagram of Karabatsos model]

- assumes a reactant-like transition state
- Nucleophile approaches from side of S.
- model breaks down when S ≠ H

*JACS* 1965, 87, 1367

*JACS* 1969, 91, 1124, 3572 & 3577

3) Felkin-Ahn model

![Diagram of Felkin-Ahn model]

- observation
- previous models suffer from torsional strain
- assumptions:
  a) reactant-like transition state
  b) incoming nucleophile avoids L
  c) incoming nucleophile will approach *anti* to most electroneg. atom

Which to use?

a) as M or R increase in size, B is favored over A
b) if an electronegative atom (-O, -N, -X) is present, make it L and make the larger of the two remaining substituents M.
c) does not work well for cyclic systems
\[
\text{syn / anti } > 98:2 \\
\text{Cram / anti-Cram } 6:1
\]

4) Cieplak Hypothesis

Cieplak proposed “that the carbonyl group has undergone extensive pyramidalization in the transition state, and the outcome is primarily a consequence of interactions between the vicinal occupied \( \sigma \) orbital and \( \sigma^* \) orbital of the incipient bond between the nucleophile and the carbonyl group.”

\[
\begin{align*}
\text{O} & \xrightarrow{\text{NaBH}_4, \text{\textit{i-PrOH}}} \text{HO} \\
\text{X} & \xrightarrow{\text{RCO}_3\text{H}} \text{O} \\
\text{H} & \xrightarrow{\text{RCO}_3\text{H}} \text{O} \\
\end{align*}
\]

**X** | **E / Z**
--- | ---
Cl | 59:41
p-Cl-C\(_6\)H\(_5\) | 60:40
C\(_6\)H\(_5\) | 58:42
p-HO-C\(_6\)H\(_5\) | 44:56
p-H\(_2\)N-C\(_6\)H\(_5\) | 34:66

see: *JACS* 1981, *103*, 4540
*JACS* 1989, *111*, 8447
*JACS* 1986, *108*, 1598
5) Bürgi - Dunitz Angle

Angle of nucleophilic attack to an sp² hybridized carbon should be ~110°!

\[ \text{Nuc} \sim 110° \]

This was proved by the following crystallographic data

<table>
<thead>
<tr>
<th>Compound</th>
<th>C=O Length (Å)</th>
<th>N⋯C Distance (Å)</th>
<th>N-C-O Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>methadone</td>
<td>1.214</td>
<td>2.910</td>
<td>105.0</td>
</tr>
<tr>
<td>cryptopine</td>
<td>1.209</td>
<td>2.581</td>
<td>102.2</td>
</tr>
<tr>
<td>protopine</td>
<td>1.218</td>
<td>2.555</td>
<td>101.6</td>
</tr>
<tr>
<td>clivorine</td>
<td>1.258</td>
<td>1.993</td>
<td>110.2</td>
</tr>
<tr>
<td>retusamine</td>
<td>1.38</td>
<td>1.64</td>
<td>110.9</td>
</tr>
<tr>
<td>N-brosylmitomycin A</td>
<td>1.37</td>
<td>1.49</td>
<td>113.7</td>
</tr>
</tbody>
</table>

*JACS 1973, 95, 5065*  
*JACS 1974, 96, 1956*

- **Exo**
  - 3 to 7-Exo-Tet are all favored processes with many literature precedents
  - 5 to 6-Exo-Tet are disfavored

- **Endo**

- **Why?**

**Diagram:**

6-Exo-Tet

5-Exo-Tet

4-Exo-Tet

3-Exo-Tet

5-Endo-Tet

6-Endo-Tet

7-Exo-Tet

5-Endo-Tet

6-Endo-Tet
b) Trigonal systems

1) 3 to 7-Exo-Trig are all favored processes with many literature precedents
2) 3 to 5-Endo-Trig are disfavored, 6 to 7-Endo-Trig are favored

\[ \begin{array}{c}
\text{3-Exo-Trig} & \text{4-Exo-Trig} & \text{5-Exo-Trig} & \text{6-Exo-Trig} & \text{7-Exo-Trig} \\
\text{3-Endo-Trig} & \text{4-Endo-Trig} & \text{5-Endo-Trig} & \text{6-Endo-Trig} & \text{7-Endo-Trig}
\end{array} \]

\[ \alpha = 109^\circ \]

\[ \alpha = 120^\circ \]

c) Digonal Systems

1) 3 to 4-Exo-Dig are disfavored processes, 5 to 7-Exo-Dig are favored
2) 3 to 7-Endo-Dig are favored processes
7) **Anomeric Effect**

A polar group on a carbon $\alpha$ to a heteroatom prefers the axial position. One set of lone pair electrons on the polar atom connected to the carbon atom can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom.

$X=\text{electron negative atom}$
• Kinetic anomeric effect:

8) Stereoelectronic Control

look at the transition state:
9) Macrocyclic Stereocontrol

Tetrahedron 1981, 37, 3981

works for rings ≥ 9 members
approaches from exterior of the ring
See, for ex. *JACS* 1984, 106, 1148

10) Acyclic Stereocontrol

The stereochemistry of the molecule near the reaction site determines / influences the stereochemistry of the reaction product.

for a general review: *Tetrahedron* 1980, 36, 3
Example – Diastereoselective reduction of β-hydroxyketones:

\[
\begin{align*}
\text{OH} & \quad \text{NaBH}_4 \\ \text{Zn(BH}_4)_2 \quad \text{OH} & \quad \text{Zn(BH}_4)_2 \\ \text{NH}_4^+ \cdot \text{BH(OAc)}_3 \quad \text{OH} & \quad \text{NH}_4^+ \cdot \text{BH(OAc)}_3
\end{align*}
\]