Chapter 2
Stereochemical Considerations in Planning Synthesis

• 2.1 Conformational Analysis

Molecules that differ from each other by rotation about single bonds are called conformational isomers or conformers.

(Derek H. R. Barton (1918-98; Nobel Prize in 1969)
Propane: steric strain, the repulsion between nonbonded atoms or groups

3.4 kcal/mol

0 kcal/mol

Types of interactions:
• eclipsed H—CH₃ = 1.4 kcal/mol
• 2 eclipsed H—H = 2 kcal/mol
Butane; at room temperature, n-butane is a mixture of 70% anti and 30% gauche conformation. To separate these two species, one would have to slow down the interconversion by working at -230°C.

Ring system: in addition to torsional strain (eclipsing interaction) and steric strain (nonbonded interaction), angle strain exists.

6 kcal/mol torsional strain + angle strain

Total strain: 27 kcal/mol
The poor overlap in cyclopropane allows for C-C bond cleavage under conditions where typical C$_{sp^3}$-C$_{sp^3}$ bonds are stable.

**Hydrogenolysis**

\[
\text{H}_2, \text{ cat.} \text{PtO}_2 \quad \xrightarrow{\text{HOAc, rt}} \quad \text{C}_2\text{H}_4 + \text{CO}_2 \text{CH}_3 \quad 93\% \ (97:3 \text{ mixture})
\]

**Cleaved by nucleophile**

\[
\text{CO}_2\text{Et} \quad \xrightarrow{\text{PhS}^- \text{Na}^+} \quad \text{resonance-stabilized anion}
\]

\[
\text{H}_2\text{O} \quad \text{workup} \quad \text{PhS}^- \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

**Cyclobutane: slightly bent (puckered)**

One carbon lies about 25° above the plane of the other three. Torsional strain is less than 8 kcal/mol.

\[
\text{Total strain: } 26 \text{ kcal/mol}
\]
Cyclopentane

Not static but is in constant motion in such a way that each carbon alternates as the point of the envelope. Total strain is 6 kcal/mol.

Cyclohexane

Cyclohexane is a dynamic structure, and the chair conformation rapidly flips. At room temperature, $^1$H NMR displays a broad singlet at $\delta 1.43$ ppm. At -106°C, it resolves into absorption at $\delta 1.20$ (axial H's) and at $\delta 1.66$ (equatorial H's) ppm.

The interconversion of two conformations has an enthalpy of activation of 10.8 kcal/mol.
2.2 Evaluation of nonbonded interactions

Two gauche butane-type interactions:
\( C(1) - CH_3 \parallel C(3) - H_{ax} \) and \( C(1) - CH_3 \parallel C(9) - H_{ax} \)

Two gauche interactions: \textit{1,3-diaxial interaction}

\[ \Delta G^\circ = -(2 \times 0.9) = -1.8 \text{ kcal/mol} \]

\[ \Delta G^\circ = -RT \ln K_{eq} \]

1800 cal/mol = \(-RT \ln K_{eq}\)

\( K_{eq} = 21: \) % equatorial = 21/22 = 95%, axial = 5%

\textit{trans}-1,2-Dimethylcyclohexane

four 1,3-diaxial CH3—H interactions = \( 4 \times 0.9 = 3.6 \text{ kcal/mol} \)

one gauche CH3—CH3 interaction = \( 1 \times 0.9 = 0.9 \text{ kcal/mol} \)

\[ \Delta G^\circ = -(3.6 - 0.9) = -2.7 \text{ kcal/mol} \]
cis-1,2-Dimethylcyclohexane

\[
\begin{align*}
\text{two 1,3-diaxial CH}_3\text{—H interactions} & \quad \text{two 1,3-diaxial CH}_3\text{—H interactions} \\
\text{one gauche CH}_3\text{—CH}_3\text{ interaction} & \quad \text{one gauche CH}_3\text{—CH}_3\text{ interaction} \\
1.8 + 0.9 &= 2.7 \text{ kcal/mol} & 1.8 + 0.9 &= 2.7 \text{ kcal/mol} \\
\Delta G^\circ = 0 \\
\end{align*}
\]

\[
\begin{align*}
\text{two 1,3-diaxial CH}_3\text{—H interactions} & \quad \text{no 1,3-diaxial interactions} \\
\text{one 1,3-diaxial CH}_3\text{—CH}_3\text{ interaction} & \quad \text{no gauche interactions} \\
1.8 + 3.6 &= 5.4 \text{ kcal/mol} & \text{no gauche interactions} \\
\Delta G^\circ = -5.4 \text{ kcal/mol} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>1,2-Diequatorial</th>
<th>1,3-Diaxial</th>
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</thead>
<tbody>
<tr>
<td>-Cl</td>
<td>-Cl</td>
<td>0.7–1.5</td>
<td>5.5</td>
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<tr>
<td>-CH₃</td>
<td>-CH₃</td>
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<td>-CH₂</td>
<td>-OH</td>
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<td>-CH₃</td>
<td>CO₂Et</td>
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<td>2.8–3.2</td>
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</table>

The interaction of a pair of cis-1,3-diaxial substitution (1,3-diaxial interaction)
Evaluation of Destabilization Energies ($E_D$)

Corey and Feiner have developed a computer program (LHSA) for conformational analysis and for determining the destabilization energies ($E_D$) in substituted cyclohexane derivatives.

![Chemical structure](image)

### An $A_R$ value for $R\cdot H$ 1,3-diaxial interactions
### A $G_R$ value for gauche $R\cdot R'$ 1,2-diequatorial interactions
### An $U_R$ value for $R\cdot R'$ 1,3-diaxial interactions.

<table>
<thead>
<tr>
<th>$R$ or $R'$</th>
<th>$A$</th>
<th>$G$</th>
<th>$U$</th>
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<tbody>
<tr>
<td>F</td>
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<td>0</td>
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<tr>
<td>Cl</td>
<td>0.4</td>
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</tr>
<tr>
<td>Br</td>
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<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>I</td>
<td>0.4</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>OH, OR</td>
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<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
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<td>0.3</td>
<td>1.3</td>
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<tr>
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<td>2.1</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>N=</td>
<td>0.5</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>N≡</td>
<td>0.2</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>C=</td>
<td>1.3</td>
<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Aryl</td>
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<td>1.1</td>
</tr>
<tr>
<td>C3H</td>
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<td>0</td>
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</tr>
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<td>CH=O</td>
<td>0.8</td>
<td>0.3</td>
<td>0.8</td>
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<td>CH₂R</td>
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<td>0.4</td>
<td>1.8</td>
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<tr>
<td>CH₂R₂</td>
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<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>CR₃</td>
<td>6.0</td>
<td>2.5</td>
<td>6.0</td>
</tr>
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</table>
**Evaluation of Destabilization Energies ($E_D$)**

\[ E_D = U_{Me} + U_{OH} + G_{OMe} + G_{Cl} + 1/2(A_{Me} + A_{OH}) \]

\[ = 1.8 + 0.9 + 0.2 + 0.5 + 0.9 + 0.45 \]

\[ = 4.75 \text{ kcal/mol} \]

\[ E_D = A_{OMe} + A_{Cl} \]

\[ = 0.9 + 0.4 \]

\[ = 1.3 \text{ kcal/mol} \]

**Atypical Disubstituted Cyclohexanes**

**Dipole-Dipole Interactions**

Favored conformation in methanol (polar solvent, solvation of Cl and C=O)

Favored conformation in octane (nonpolar solvent, smaller dipole moment)

**Hydrogen Bonding**

Intramolecular hydrogen bonding

Nonpolar solvent favors this conformation
2.3 six-membered heterocyclic system

No interaction between axial substituent and b-substituted heteroatom

\[ E_D = \frac{1}{2} A_R \]

\[ E_D = A_R \]

**1,3-dioxane**

Anomeric Effect: refers to the tendency of a group X at C(1) of a pyranose ring to assume the axial rather than the equatorial position. This phenomenon is important in carbohydrate chemistry.

Stabilizing interaction between the axial lone pair of electrons on the ring oxygen atom and the antiperiplanar, antibonding \( s^* \) orbital of the C-X bond. This leads to a shortening of the bond between the ring oxygen and the anomeric carbon and a lengthening of the C-X bond.

\[ \Delta E_D \sim 2.1 \text{ kcal/mol} \]

Oxygen lone pair interacts with C—X \( s^* \) orbital

No stabilization

Nonrepulsive

Repulsive

dipole-dipole interactions
The anomeric effect is solvent and substituent dependent and
decreases in the following order: Cl> OAc > OMe > OH

Reference : Table p41

Hydrindane: C/D rings of steroid

Cis isomer is more stable than the trans because the cis isomer
has fewer 1,3-diaxial interactions.
Decalin-Bicyclo[4.4.0]decane

Trans-decalin is rigid conformation while cis one is mobile. These two are stereoisomers, not the conformers.

Trans-decalin is more stable than cis-decalin about 2.7 kcal/mol
E_D = 2.7 + 1.0 - 4.5 kcal/mol
E_U = 2.7 kcal/mol

\[ \Delta E_D = 4.5 - 2.7 = 1.8 \text{ kcal/mol} \]

**Bridged Bicyclic Systems**

*Norbornane*

`bicyclo[2.2.1]heptane`

`bicyclo[2.2.2]octane`

Bredt’s rule: qualitative generalization that bicyclic ring system cannot have a double bond at the bridgehead.

**Fused**

Double bond to the bridgehead is stable (independent of \( n \)).

**Bridged**

Double bond to the bridgehead is highly strained when \( n < 3 \).

Bredt’s rule violation
2.5 Cyclohexyl system with sp2-hybridized atoms

**Cyclohexanones**

One anticipated that $E_D$ should be reduced by half. But conformational studies have revealed varied values.

\[
\Delta E_D = 0.2 \text{ kcal/mol}
\]

\[E_D = 1.8 \text{ kcal/mol}
\]

\[E_D = \frac{2}{3} (3.0) = 2.0 \text{ kcal/mol}
\]

Value of two-thirds $A_H$

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**Cyclohexenes**

For half-chair cyclohexenes, three types of destabilization interactions:
1. 1,3-axial-pseudoaxial, 2. 1,2-equatorial-pseudoequatorial
3. 1,2-diequatorial

\[\text{ax} = \text{axial}\]
\[\text{ax'} = \text{pseudoaxial}\]
\[\text{eq} = \text{equatorial}\]
\[\text{eq'} = \text{pseudoequatorial}\]

half-chair form

---
Allylic Strain

1,2-equatorial-pseudoequatorial

\[ E_D = G_R + G_{R'} \]

1,2-diequatorial

\[ E_D = G_R + G_{R'} \]

1,3-axial-pseudoaxial

\[ E_D = \frac{1}{2} A_R \]

\[ E_D = U_R + U_{R'} \]

Allylic Strain

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

- at 25 °C
- 30:70 mixture

\[ A^{1,3} \text{ strain} \]

favored
A\textsuperscript{1,3} strain in acyclic system

\[ \text{rel. energies} \quad 0.73 \quad 0 \quad > 2 \text{ kcal/mol} \]

\[ \text{rel. energies} \quad 3.4 \quad 0 \quad > 4 \text{ kcal/mol} \]

2.6 Significant Energy Difference

The stereochemical course of the reaction at three-, four-, and five membered rings can be reliably predicted by assuming the relative congestion of the two faces. As the ring size increases above six, uncertainty prevails.

For six membered ring system, a significant energy difference for a conformer is considered to be 1.8 kcal/mol. This corresponds to roughly 95% preponderance of one conformer at room temperature. Thus conformational homogeneity would be predicted for 2-methylcyclohexanone (\( \Delta E_D = 1.8 \text{ kcal/mol} \))
2.8 Reactivity and Product determination as a function of conformation

Two extreme situations

1. Curtin-Hammett principle states that the rate of reaction of a molecule is a function not only of the concentration of any reacting conformation but also of its transition state energy.

2. Conformation barrier (A $\leftrightarrow$ B) is substantially higher than the reaction barriers TSA and TSB. This case is known as the conformational equilibrium control, where the ratio of products is equal to the ratio of the population of the starting states.

Hammond Postulate

Stereoelectronic Effect

Terminology of Selectivity
Esterification and Saponification

The rate of esterification and the rate of saponification will depend on \( \Delta G^\ddagger \) for the rate determining step (RDS).

Equatorial isomers B and D will react faster than the corresponding axial isomers A and C. Note that the conformational energies of sp\(^3\) groups are generally greater than those of sp\(^2\) groups.
**S\textsubscript{N}2-type reactions**

Steric hindrance to the approaching nucleophile plays an important role in these reactions.

Cis isomer A proceeds 60 times faster than with the equatorial trans isomer B.

**Two effects are reinforced.**

- **A**
  - cis isomer
  - Less stable (0.4 kcal/mol) than B

- **B**
  - trans isomer

Much less stable than A\textsuperscript{‡}

**S\textsubscript{N}2’ reaction with cyclohexenyl systems generally proceeds via an anti addition of the nucleophile to the double bond (best overlap of participating orbitals)**

- **CH\textsubscript{3}(CN)CuLi (2.5 eq)**
- **anti-S\textsubscript{N}2’ addition**
- **main product**

- **Me**
  - a. n-Bu\textsubscript{2}CuLi
  - b. H\textsuperscript{+}, H\textsubscript{2}O

...
Michael-Type Addition

The stereochemistry of nucleophilic 1,4-additions to enone is controlled by stereo electronic factors.

Without steric effects, the nucleophile approaches the β-carbon of the enone antiparallel to the neighboring (γ) pseudoaxial substituent (circled H).

E2 Elimination Reactions

For stereo electronic reason (overlap of reacting orbitals), the two reacting groups, H and X, must be either antiperiplanar or synperiplanar.

Leaving groups to be eliminated should be antiperiplanar.

synperiplanar
Neomenthyl chloride reacts 200 times faster with sodium ethoxide than does menthyl chloride.
Addition Reactions to Double Bonds

Under kinetic control, the predominant product formed is via pathe b resulting from diaxial addition of Br₂ to the double bond.

Antiperiplanar (S₂,2 type), antiparalled opening
Addition of Br$^+$ to the less hindered $\alpha$-face

Octanin (octahydronaphthalene)

Antiplanar or antiparallel opening

Diaxial product
1) anti-Markovnikov addition of the B-H bond
2) cis addition of the B-H bond
3) Addition of the B-H bond from the less hindered double bond
4) Oxidation with retention of configuration

Oxidation of Alcohol

R\text{O} + \text{H}_2\text{CrO}_4 \rightarrow \text{RCOOH}

E2-type elimination

RDS

2 \text{Cr(VI)} \rightarrow \text{Cr(III) green}
A large portion of the conformational free energy of the diaxial interactions of the sp\(^3\) hybridized chromate ester in the trans isomer is relieved as the reaction proceeds toward the sp\(^2\) hybridized keto group. Thus more strained trans alcohol is more reactive (relief of steric strain). Another one is the greater accessibility of the equatorial hydrogen for removal by the base in the rate determining step.

Trans is much faster for oxidation

Thank you