Chapter 7
Cyclic Compounds.
Stereochemistry of Reactions

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Chapter 7 Overview

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- 7.8 Reactions that form Stereoisomers
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Monocyclic Compounds

• Compounds containing a single ring (e.g., cyclopentane, cyclohexane)
• Relative stabilities are determined from heats of formation ($\Delta H_f^\circ$)
• All have the same empirical formula: $\text{CH}_2$
• Thus, stabilities can be readily compared on a per carbon basis

7.1 Relative Stabilities of the Monocyclic Alkanes
Cycloalkane Heats of Formation per CH₂

\[(n = \text{number of carbon atoms})\]

<table>
<thead>
<tr>
<th>(\Delta H_f^o / n)</th>
<th>(\Delta H_f^o / n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>Compound</td>
</tr>
<tr>
<td>3</td>
<td>cyclopropane</td>
</tr>
<tr>
<td>4</td>
<td>cyclobutane</td>
</tr>
<tr>
<td>5</td>
<td>cyclopentane</td>
</tr>
<tr>
<td>6</td>
<td>cyclohexane</td>
</tr>
<tr>
<td>7</td>
<td>cycloheptane</td>
</tr>
<tr>
<td>8</td>
<td>cyclooctane</td>
</tr>
</tbody>
</table>

7.1 Relative Stabilities of the Monocyclic Alkanes
Cyclohexane

• Has the *same stability* as a typical unbranched alkane
• Prevalent in many naturally occurring organic compounds
• Its conformation reveals its unique stability
The Chair Conformation

- Cyclohexane adopts a non-planar, puckered conformation
- This avoids angle strain and torsional strain
The Chair Conformation

(a) ball-and-stick model

(b) space-filling model

(c) skeletal structure with hydrogens shown

7.2 Conformations of Cyclohexane
Drawing Chair Conformations

- Note the “V” arrangement

Step 1

Step 2

Step 3

7.2 Conformations of Cyclohexane
Drawing Chair Conformations

• Note the parallel lines

• Identify up and down carbons
Equatorial and Axial Hydrogens

7.2 Conformations of Cyclohexane
Interconversions of Chair Conformations

- Commonly referred to as a *chair flip*

7.2 Conformations of Cyclohexane
7.2 Conformations of Cyclohexane
Boat and Twist Boat Conformations

7.2 Conformations of Cyclohexane
Relative Enthalpies

7.2 Conformations of Cyclohexane
Monosubstituted Cyclohexanes

- Substituents can occupy an axial or equatorial position
Monosubstituted Cyclohexanes

- Represent conformational diastereomers
- *Equatorial* is preferred by larger groups
- Note that the ‘down’ methyl remains down after the chair interconversion
1,3-Diaxial Interactions

(a)

(b)

(c)

7.3 Monosubstituted Cyclohexanes. Conformational Analysis
Methylcyclohexane

- The axial conformation is analogous to gauche butane
tert-Butylcyclohexane

- The conformation placing the bulky t-butyl group equatorial is overwhelmingly favored

\[ \Delta G^\circ = 20 \text{ kJ mol}^{-1} \quad (5 \text{ kcal mol}^{-1}) \]
Cis-Trans Isomers

- **Trans**: the two groups have an *up-down* relationship

- **Cis**: the two groups have a *down-down* relationship
Cis-Trans Isomers

- *Cis* and *trans* specify the *relative* stereochemical configurations
- *Cis* and *trans* says *nothing* about absolute configuration
- For example, there are two enantiomers of *cis*-1-chloro-2-methylcyclohexane:

![Chemical structures of (1S,2R)-1-chloro-2-methylcyclohexane and (1R,2S)-1-chloro-2-methylcyclohexane]
Conformational Analysis

• For disubstituted derivatives, the larger group will preferentially occupy the equatorial position

![Chemical structures showing conformational analysis](image)
Use of Planar Structures

• Although cyclic structures have non-planar conformations, planar representations are still useful

7.4 Disubstituted Cyclohexanes
Stereochemistry and the Chair Conformer

• *Cis*-1,2-dimethylcyclohexane conformers can be shown to be chiral

• ...but a chair interconversion converts one enantiomer into the other:

7.4 *Disubstituted Cyclohexanes*
Stereochemistry and the Chair Conformer

- *Cis*-1,3-dimethylcyclohexane has two asymmetric carbons

  ![Chair interconversion of Cis-1,3-dimethylcyclohexane](diagram1)

  - Yet neither conformer is chiral

  ![Diastereomers and planes of symmetry](diagram2)

*7.4 Disubstituted Cyclohexanes*
Stereochemistry and the Chair Conformer

• Therefore, planar representations can be used to more readily evaluate chirality

\[ \text{cis-1,2-dimethylcyclohexane} \]

\[ \text{cis-1,3-dimethylcyclohexane} \]
Stereochemistry and the Chair Conformer

- *Trans*-1,2-dimethylcyclohexane represents a different situation
- The planar structures reveal it to be chiral

\[
\text{enantiomers of } \textit{trans}-1,2\text{-dimethylcyclohexane}
\]

7.4 *Disubstituted Cyclohexanes*
Stereochemistry and the Chair Conformer

• Hence, each enantiomer can exist independently and can be isolated in optically active form

7.4 Disubstituted Cyclohexanes
Cyclopentane

- Exists in the **envelope conformation**
- Each carbon rapidly alternates as the “point” of the envelope
Cyclobutane

- Suffers from **angle strain**
- Exists in a **puckered** conformation
- Puckering helps relieve some eclipsing
Cyclopropane

- Suffers from **angle strain** and **eclipsing strain**
- Cannot pucker to relieve these strains
- C-C bonds are sometimes referred to as **banana bonds**
- Note that bonding primarily occurs **outside** of the internuclear axis
Classification and Nomenclature

• **Bicylic** compounds: Two rings share two or more common atoms

• **Spiroyclic** compounds: Two rings have a single common atom

![Diagram of bicyclic and spirocyclic compounds]

- bicyclo[4.3.0]nonane
- bicyclo[2.2.1]heptane
- spiro[4.4]nonane

(bicyclic compounds)

(a spirocyclic compound)
Classification and Nomenclature

• **Fused** and **bridged** bicyclic compounds

![Diagram of a fused bicyclic compound with bridgehead carbons (*) at adjacent positions.]

![Diagram of a bridged bicyclic compound with bridgehead carbons (*) not adjacent.]

- One-carbon bridge
- Two-carbon bridge
- Three-carbon bridge

**bicyclo[3.2.1]octane**

(* = bridgehead carbons)
Classification and Nomenclature

• **Polycyclic** compounds
• Possess fascinating molecular architecture commonly with interesting physical properties
• Can be synthetically challenging
Cis and Trans Ring Fusion: Decalin

decalin (bicyclo[4.4.0]decane)

cis-decalin

trans-decalin

7.6 Bicyclic and Polycyclic Compounds
Trans-Decalin

- Ring fusion causes *trans*-decalin to be conformationally locked
Ring Fusion with Small Rings

- Bicyclic compounds with small rings are restricted to cis ring fusion
- *Trans* fusion would incur too much ring strain

\[ \text{bicyclo[1.1.0]butane} \quad \text{bicyclo[3.1.0]hexane} \]
Trans-Cycloalkenes

• Small rings ($\leq 7$) cannot have trans (or $E$) stereochemistry

• \textit{Trans}-cyclooctene has been prepared, but it significantly less stable than the $Z$ isomer

• Larger rings ($\geq 9$) can comfortably exist as either $cis$ or \textit{trans}

• Try building models for these cycloalkenes
Bredt’s Rule

• A double bond cannot be at a **bridgehead** position unless one of the rings has ≥ 8 atoms

![Chemical structures](https://example.com/structures.png)

**bicyclo[2.2.1]hept-1(2)-ene**
- too unstable to isolate

**bicyclo[4.4.1]undec-1(2)-ene**
- stable enough to isolate

7.6 Bicyclic and Polycyclic Compounds
Steroids

cholesterol
(important component of membranes:
principal component of gallstones;
major constituent of atherosclerotic plaques)

cortisone
(anti-inflammatory hormone)

progesterone
(human female sex hormone)

testosterone
(human male sex hormone)

7.6 Bicyclic and Polycyclic Compounds
Steroids

7.6 Bicyclic and Polycyclic Compounds
Relative Reactivities of Enantiomers

- Enantiomers *react at the same rate with an achiral reagent*
- For example, both the $R$ and $S$ enantiomers of the following alkene react at the same rate:

```
\begin{align*}
3 \text{Ph}\text{C} - \text{CH} = \text{CH}_2 + \text{BH}_3 & \quad \text{THF} \\
\text{H} & \quad \text{Ph}\text{C} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{B} \\
\end{align*}
```

(a chiral alkene)
Relative Reactivities of Enantiomers

- Enantiomers *react at the different rates with a chiral reagent*
- Diastereomeric products and transition states have different free energies

(2R,5R)-2,5-dimethylborolane (a chiral borane)
Relative Reactivities of Enantiomers

• Enzymes are enantiomerically pure chiral molecules (reagents)
• They catalyze the reaction of only one enantiomer of a pair
Relative Reactivities of Enantiomers

\[ \text{enzyme} + (S)\text{-substrate} \rightarrow \text{enzyme, (S)-substrate} \xrightarrow{3\text{rd}} \text{products} \]

\[ \text{enzyme} + (R)\text{-substrate} \rightarrow \text{enzyme, (R)-substrate} \xrightarrow{3\text{rd}} \text{products} \]

Enzyme catalyzes the reaction of (S)-malate to give fumarate and water. (R)-Malate does not react with fumarase at 37 °C.

7.7 Relative Reactivities of Stereoisomers
Relative Reactivities of Diastereomers

- Diastereomers generally have *different* reactivities toward *any* reagent (chiral or achiral)
- Both the starting materials and transition states are diastereomeric
- Consequently, their standard free energies of activation, and hence their reaction rates, differ
Reactions That Give Enantiomeric Products

• Consider an achiral compound yielding a chiral product

\[
\begin{align*}
\text{Ph—CH=CH}_2 + \text{HBr} & \rightarrow \text{Ph—CH—CH}_3 \\
\text{styrene} & \quad \text{(1-bromoethyl)benzene}
\end{align*}
\]

7.8 Reactions that form Stereoisomers
Chiral Environments

7.8 Reactions that form Stereoisomers
Reactions That Give Diastereomeric Products

• Some reactions could lead to diastereomeric products

\[
\begin{align*}
\text{CH}_3 & \quad \text{BH}_3 \text{ (THF)} \quad \text{H}_2\text{O}_2 \text{ (OH)} \quad \text{OH} \\
\text{trans isomer (observed)} & \quad \text{cis isomer (not observed)} \\
\text{all products are racemic} & 
\end{align*}
\]

• In general, when diastereomeric products can be formed, they are formed at different rates

• By convention, only one of the enantiomers is normally drawn

7.8 Reactions that form Stereoisomers
Stereochemistry of Addition Reactions

- **Syn-addition:**

\[
\text{cyclohexene} + \text{X} - \text{Y} \rightarrow \text{cyclohexane} + \text{cyclohexane} \\
\text{X and Y add from the top face} \quad \text{X and Y add from the bottom face}
\]

- **Anti-addition:**

\[
\text{cyclohexene} + \text{X} - \text{Y} \rightarrow \text{cyclohexane} + \text{cyclohexane} \\
\text{X adds from top face; Y adds from bottom face} \quad \text{X adds from bottom face; Y adds from top face}
\]
Stereochemistry of Substitution Reactions

• **Retention** of configuration:

\[
\begin{array}{c}
\text{X} \\
\text{Y} \\
\end{array} \xrightarrow{\text{replace X with } X'} \begin{array}{c}
\text{X'} \\
\text{Y} \\
\end{array}
\]

• **Inversion** of configuration:

\[
\begin{array}{c}
\text{X} \\
\text{Y} \\
\end{array} \xrightarrow{\text{replace X with } X'} \begin{array}{c}
\text{X'} \\
\text{Y} \\
\end{array}
\]
Overview

• In order to observe whether retention or inversion has occurred, the carbon undergoing substitution must be a stereocenter
Stereochemistry of Bromine Addition

• Addition of bromine to an alkene is a highly stereoselective reaction

• Three stereoisomers are possible for the following reaction:

\[
\text{cis-2-butene} + \text{Br}_2 \rightarrow \text{2,3-dibromobutane}
\]

\[
\text{cis} \quad \text{trans} \quad \text{racemate} \quad \text{meso}
\]
Stereochemistry of Bromine Addition

7.9 Stereochemistry of Chemical Reactions
Stereospecificity

• Reactions in which different stereoisomers of a starting material give different stereoisomers of a product are called **stereospecific reactions**
Stereochemistry of Hydroboration-Oxidation

• Hydroboration is a stereospecific syn-addition
Stereochemistry of Hydroboration-Oxidation

- The oxidation of organoboranes is a *stereospecific substitution* reaction.

\[ \text{trans-2-methylcyclohexanol} \]
Stereochemistry of Hydroboration-Oxidation

- The two steps of hydroboration-oxidation result in net *syn*-addition of H-OH to the alkene

1-methylcyclohexene \[\xrightarrow{\text{H-Br, } \text{syn-addition}}\] 1-methylcyclohexanol

- Note that the *trans* designation of the name has *nothing* to do with the way H-OH added
Stereochemistry of Hydrogenation

• Catalytic hydrogenation is a stereospecific syn-addition
Stereochemistry of Oxymercurication-Reduction

• Oxymercurication of alkenes is a stereospecific anti-addition

• Recall that this proceeds via a cyclic mercurinium ion

7.9 Stereochemistry of Chemical Reactions
Stereochemistry of Oxymercurcation-Reduction

- The reduction step varies from case to case

- Overall, the oxymercurcation-reduction reaction is not stereospecific

- It is highly regioselective, however