Rings (Cycloalkanes)

Due to the ring in cycloalkanes, the $\sigma$ bonds cannot rotate 360° as in alkanes. Do not have the same conformational analysis as with other alkanes.

Due to requirement that rings be connected in a cyclic manner and the lack of ability to rotate 360° about the bonds, leads to two main causes of strain in rings—angle strain and torsional strain.

The amount of strain, and the relationship between these two types of strain, is different for different ring sizes.

Therefore rings adopt a certain preferred geometry.
Rings Strain for Simple Cycloalkanes

<table>
<thead>
<tr>
<th>Ring Size</th>
<th>Cycloalkane</th>
<th>Total Ring Strain (Kcal/mol)</th>
<th>Ring Strain per CH₂ (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>cyclopropane</td>
<td>27.4</td>
<td>9.1</td>
</tr>
<tr>
<td>4</td>
<td>cyclobutane</td>
<td>26.4</td>
<td>6.6</td>
</tr>
<tr>
<td>5</td>
<td>cyclopentane</td>
<td>5.8</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>cyclohexane</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>cycloheptane</td>
<td>6.0</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>cyclooctane</td>
<td>9.5</td>
<td>1.2</td>
</tr>
<tr>
<td>10</td>
<td>cyclodecane</td>
<td>12.1</td>
<td>1.2</td>
</tr>
<tr>
<td>12</td>
<td>cyclododecane</td>
<td>3.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Small rings have large strain

Ring strain reaches a minimum at a 6-membered ring and then increases until rings become very large

What is special about a 6-membered ring?
Conformation of Cyclopropane

All three carbon atoms must be coplanar

This geometry causes strain due to both small bond angles and torsional strain

The $\langle$C-C-C bond angle has the most strain (fixed at 60° in space) compared to 109.5° for a unstrained sp$^3$ hybridized carbon

Due to all three carbons forced in a plane, must have eclipsed conformations for every substituent
Conformation of Cyclobutane

Cyclobutane adopts a “puckered” conformation in order to lower torsional strain
Still have high bond angle strain
Substituents are no longer totally eclipsed, thus the torsional strain is lower per substituent compared to cyclopropane
Conformation of Cyclopentane

The ring forms a preferred geometry to lower torsional strain

The conformation is called the “envelope” due to its similarity to a mailing envelope

Angle strain is lower for cyclopentane, but still have some torsional strain due to the inability to reach a fully staggered conformation
Conformation of Cyclohexane

Cyclohexane has the least amount of ring strain

The reason is the ability of the ring to form a stable conformation

Planar cyclohexane
(120° <C-C-C, All hydrogens eclipsed)

Chair cyclohexane
(nearly tetrahedral <C-C-C, no hydrogens eclipsed)
Names for Various Conformers of Cyclohexane

Remove hydrogens

Chair conformation
Twist-boat conformation
Boat conformation
Newman Projection for Chair Conformation

The chair conformation has a low torsional strain as seen in a Newman projection.

Nearly perfect staggered alignment

Still have some gauche interactions, but energy is low for this conformation.
Key point – there are two distinct chair conformations for a cyclohexane that can interconvert

The energy of activation for the interconversion is 10.8 Kcal/mol
6-Membered Rings are Observed Frequently in Biological Molecules

D-glucose

Steroid ring structure

cholesterol

Simvastatin (Zocor)

Many drugs also contain six-membered rings
The 12 substituents in a chair (12 hydrogens for cyclohexane) occur in two distinct types of positions.

In flat conformation, all hydrogens are identical.

In chair conformation, 2 sterically different positions occur.

Axial hydrogens in white, Equatorial hydrogens in yellow.

Space filling model.
Chair-Chair Interconversion with Cyclohexane

In initial chair, yellow substituents are equatorial and white are axial
In final chair, yellow substituents are axial and white are equatorial

This motion proceeds through the various cyclohexane conformations (chair – half-chair – twist boat – boat) and eventually to the other chair conformation
The Axial and Equatorial Positions have Different Spatial Requirements

There are two chair conformations, a substituent moves from equatorial to axial in a chair-chair interconversion.

Bigger Y substituent has more steric interactions in an axial position than equatorial.

The chair conformation which has the Y group equatorial is therefore more stable.
Axial Strain in Monosubstituted Cyclohexanes

Due to the difference in energy between placing a substituent in the axial versus equatorial position, the two chair conformations are no longer equal in energy.

\[ \Delta G \text{ (ax/eq) (Kcal/mol)} = 1.74 \] for a methyl group

\[ \Delta G \text{ will be larger as the size of the substituent increases} \]

Can therefore determine the exact equilibrium between the two conformers using Gibb’s

\[ \Delta G = -RT \ln K \]

The equilibrium thus is 19.5 at room temperature, favoring the equatorial position for the methyl group.

An easy approximation for equilibrium and rate:

(Without needing to calculate using exact formula at room temperature)

\[ K \approx 10^{(3/4)\Delta G} \quad \text{Would yield } K = 20.1 \]

\[ k \approx 10^{(13-3/4)\Delta G^4} \]
Axial Strain with t-Butyl Substituted Cyclohexanes

As the substituent is increased in size to a tertButyl group, the large substituent has a very large $\Delta G(\text{ax/eq})$ of 5.5 Kcal/mol

Due to the large steric strain of substituent interacting with the axial 1,3 substituents

Large $\Delta G$ results in an equilibrium of $\sim13,000$ (using approximation)

In essence, with t-Butyl substituent only the conformer with the t-Butyl group equatorial is present regardless of other substituents
Multiple Substituents Have Cumulative Effect

If there are two substituents they will compete for the equatorial position.

An ethyl group is bigger than a methyl so therefore this compound would prefer the left conformation.

If both substituents can be in the equatorial position then this conformer will be heavily favored.

If there are more substituents, need to compare the cumulative steric for all substituents to predict which chair is more stable.
Don’t confuse Equatorial/Axial with Cis/Trans

A cis/trans ring junction refers to whether both substituents are on the same side or opposite sides of a flat ring.

Methyl group is axial, ethyl group is equatorial

Methyl group is equatorial, ethyl group is equatorial

This compound is trans-1-ethyl-3-methylcyclohexane

This compound is cis-1-ethyl-3-methylcyclohexane
Bicyclic Compounds

Depending upon the number of atoms connected in both rings, bicyclic compounds have a variety of names

Spiro bicyclic
When the two rings share only 1 carbon the compounds are named Spiro

Due to the sp\(^3\) hybridized carbon connecting the two rings, spiro compounds have the rings orthogonal to each other

Bicyclo[4.4.0]decane
Fused bicyclic
Fused rings share two atoms for both rings

Bicyclo[2.2.1]heptane
Bridged bicyclic
Bridged rings share more than two atoms for both rings

The naming for the bicyclic rings counts the total number of carbons to reach the root name and then adds the number of carbons fused in each ring and places these numbers in [brackets]
The fused carbons (in blue \(^*\)) are included in counting total carbons but not included in size of bridges (either red \(^*\), green \(^*\) or purple \(^*\))

To number, a fused carbon is 1 and count towards the first substituent for lowest number
Decalin Compounds

Small fused bicyclics must have the bridged carbons cis to each other, but with larger rings could have either cis or trans ring junctions.

See a variety of fused rings with the “Decalin” framework:

- **trans-Decalin**
- **cis-Decalin**

The “trans” and “cis” designations refer to the attachment of the substituents.

A major consequence of the fused rings is that conformational freedom has been limited (cannot do chair-chair interconversions).
Each Decalin (trans or cis) is “locked” into that conformation.