Chapter 18

Conformational analysis
three compounds, each shown in two conformations
three pairs of stereoisomers: each member of a pair has a different configuration
Barriers to rotation about different types of bond

- 12 kJ mol\(^{-1}\)
- 30 kJ mol\(^{-1}\)
- 85 kJ mol\(^{-1}\)
- 260 kJ mol\(^{-1}\)
the two extreme conformations of ethane, staggered and eclipsed, each shown from three different viewpoints

staggered:

side view

end-on view

eclipsed:
the staggered conformation of ethane

the eclipsed conformation of ethane
staggered

further C atom

nearer C atom

eclipsed

far C–H bonds stop at edge of circle

near C–H bonds meet at centre
In the eclipsed conformation, \( \theta = 0, 120, \text{or } 240^\circ \)

In the staggered conformation, \( \theta = 60, 180, \text{or } 300^\circ \)
given enough energy the marble will go over the energy maximum and into a different well. You would be very surprised if the marble stuck on the ridge!

when we supply energy by rocking the box, the marble moves but still stays within the well.

with no shaking (no energy), the marble remains in the lowest energy state at the bottom of the well.
space-filling models of the conformations of ethane

eclipsed  staggered
eclipsed:

filled orbitals repel

staggered:

stabilizing interaction between filled C–H σ bond...

and empty C–H σ* antibonding orbital
Hexachloroethane

Compare ethane with hexachloroethane, C₆Cl₆. The chlorine atoms are much larger than hydrogen atoms (van der Waals radius: H, about 130 pm; Cl, about 180 pm) and now they do physically get in the way of each other. This is reflected in the increase in the rotational barrier from 12 kJ mol⁻¹ in C₂H₆ to 45 kJ mol⁻¹ in C₂Cl₆ (although other factors also contribute).
there is greater repulsion between two C–C bonds than between two C–H bonds
the staggered conformation of propane

the eclipsed conformation of propane
conformations of butane

- **Me–Me dihedral angle:**
  - $0^\circ$
  - $60^\circ$
  - $120^\circ$
  - $180^\circ$
  - $240^\circ$
  - $300^\circ$

- **Eclipsed or staggered:**
  - Eclipsed
  - Staggered

- **Name of conformation:**
  - Syn-periplanar
  - Synclinal or gauche
  - Anticinal
  - Anti-periplanar
  - Anticinal
  - Synclinal or gauche
all internal angles 109.5°
The carbon skeleton for cyclohexane

cyclohexane as a "chair"
the boat conformation of cyclohexane
a side-on view of cyclopropane

viewing cyclopropane (almost) along a C–C bond shows that all the C–H bonds are eclipsed
planar cyclobutane (not the real conformation)

side-on view of planar cyclobutane shows eclipsing C–H bonds

the puckered 'wing' conformation of cyclobutane

C–H bonds no longer fully eclipsed
"open envelope" conformation of cyclopentane
A side-on view of the chair conformation of cyclohexane

A view of cyclohexane looking along two of the C–C bonds.

A Newman projection of the same view.
a side-on view of the boat conformation of cyclohexane

view along C–C

a view of the boat conformation looking along two of the C–C bonds

Newman projection of the same view
pushing these two carbon atoms in the direction shown....

...gives a slightly different conformation in which the eclipsing interactions have been reduced: the "twist-boat" conformation

view along C–C

an end-on view of the twist-boat conformation shows how the eclipsing interactions have been reduced
these hydrogens are all 'down' relative to their partners on the same C atom

these hydrogen atoms are all 'up' relative to their partners on the same C carbon
Guidelines for drawing cyclohexane

**The carbon skeleton**

Trying to draw the chair conformation of cyclohexane in one continuous line can lead to some dreadful diagrams. The easiest way to draw a chair conformation is by starting off with one end.

Next draw in two parallel lines of equal length.

At this stage, the top of the new line should be level with the top of the original pair.

Finally, the last two lines should be added. These lines should be parallel to the first pair of lines as shown and the lowest points should also be level.

**Adding the hydrogen atoms**

This is often the trickiest part. Just remember that you are trying to make each of the carbon atoms look tetrahedral. (Note that we don’t normally use wedged and hashed bonds; otherwise things get really messy.)

The axial bonds are relatively easy to draw in. They should all be vertically aligned and alternate up and down all round the ring.
Guidelines for drawing cyclohexane (contd)

The equatorial bonds require a little more care to draw. The thing to remember is that each equatorial bond must be parallel to two C–C bonds.

![Diagram of cyclohexane with parallel C–C bonds.]

In each diagram, all the red bonds are parallel.

Put in all 6 equatorial C–H bonds... notice the 'W' shape here...

... and the 'M' shape here.

The completed diagram with all the hydrogen atoms should look like this.

![Completed cyclohexane diagram.]

Common mistakes

If you follow all the guidelines above, you will soon be drawing good conformational diagrams. However, a few common mistakes have been included to show you what not to do!

How not to draw cyclohexanes...

- The chair has been drawn with the middle bonds horizontal, so the upper points of the chair are not level. This means the axial hydrogens can no longer be drawn vertical.

- The axial hydrogens have been drawn alternating up and down on the wrong carbons. This structure is impossible because none of the carbons can be tetrahedral.

- The red hydrogens have been drawn at the wrong angles - look for the parallel lines and the 'W' and 'M'.
There is only one type of equatorial conformer, and one type of axial conformer. Convince yourself that these drawings are exactly the same conformation just viewed from different vantage points.
substituent equatorial

substituent axial
ring inversion of a monosubstituted cyclohexane
notice that the hydrogen atom shown changes from axial to equatorial
In the **half-chair** conformation of cyclohexane, four adjacent carbon atoms are in one plane with the fifth above this plane and the sixth below it. You will this conformation again later—it represents the energy minimum for cyclohexene, for example.

There are also a number of ways of drawing a twist-boat conformer.

... although it's easier to see why it's called a twist boat from this viewpoint.
conformational changes during the inversion of cyclohexane

<table>
<thead>
<tr>
<th>energy / kJ mol⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

reaction coordinate

chair A

half chair

true boat

twist boat

chair B
this conformation is lower in energy
equatorially substituted cyclohexane:

axially substituted cyclohexane:

the black bonds are anti-periplanar (only one pair shown for clarity)

the black bonds are synclinal (gauche) (only one pair shown for clarity)
The equilibrium constant, $K$, is defined as:

$$K = \frac{\text{concentration of equatorial conformer}}{\text{concentration of axial conformer}}$$

<table>
<thead>
<tr>
<th>X</th>
<th>Equilibrium constant, $K$</th>
<th>Energy difference between axial and equatorial conformers, kJ mol$^{-1}$</th>
<th>% with substituent equatorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Me</td>
<td>19</td>
<td>7.3</td>
<td>95</td>
</tr>
<tr>
<td>Et</td>
<td>20</td>
<td>7.5</td>
<td>95</td>
</tr>
<tr>
<td>iPr</td>
<td>42</td>
<td>9.3</td>
<td>98</td>
</tr>
<tr>
<td>t-Bu</td>
<td>&gt;3000</td>
<td>&gt;20</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>OMe</td>
<td>2.7</td>
<td>2.5</td>
<td>73</td>
</tr>
<tr>
<td>Ph</td>
<td>110</td>
<td>11.7</td>
<td>99</td>
</tr>
</tbody>
</table>
in the axial conformer of methylcyclohexane, there is a direct interaction between the methyl group and the axial hydrogen atoms

in methoxycyclohexane, the methyl group is removed somewhat from the ring

when a methyl, ethyl or \( \alpha \)-propyl group is axial, only a hydrogen atom need lie directly over the ring

the steric requirements for putting a \( \beta \)-butyl group axial are enormous since now there is a severe interaction between a methyl group and the axial protons
Both the OH groups occupy positions on the upper side of the cyclohexane ring.

In trans-1,4-cyclohexanediol, one OH group is above the plane of the ring in either conformation, whereas the other is below, in either conformation.

Conformer with both OHs axial

The more stable conformer with both OHs equatorial
*cis*-1,3-disubstituted cyclohexane

In both conformers, both substituents are 'up'.

*trans*-1,3-disubstituted cyclohexane

In both conformers one substituent is 'up', the other 'down'.

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two substituents equatorial
  two axial
favoured
two substituents equatorial
  two axial (including large phenyl)
**cis-4-\textit{t}-butylcyclohexanol**

- In the *cis* diastereoisomer, the hydroxyl group is forced into an axial position.
- In both compounds, the \textit{t}-butyl group is equatorial.

**trans-4-\textit{t}-butylcyclohexanol**

- In the *trans* diastereoisomer, the hydroxyl group is forced into an equatorial position.
- In both compounds, the \textit{t}-butyl group is equatorial.
**Cis-1,4-di-t-butylcyclohexane**

An axial t-butyl group really is very unfavourable. In *cis*-1,4-di-t-butylcyclohexane, one t-butyl group would be forced axial if the compound existed in a chair conformation. To avoid this, the compound prefers to pucker into a twist boat so that the two large groups can both be in equatorial positions (or ‘pseudoequatorial’, since this is not a chair).

The twist-boat conformer (with both t-butyl groups in pseudoequatorial positions) is lower in energy than the chair conformation.
this bond is an equatorial substituent on the black ring

cis-decalin

decalin

this bond is an axial substituent on the black ring

both green bonds are equatorial substituents on the black ring

trans-decalin
ring inversion of cis-decalin

- green H starts axial on black ring
- yellow H starts equatorial on black ring

- after ring inversion, green H is equatorial on black ring
- yellow H is axial on black ring

no ring inversion in trans-decalin

- for trans decalin, no ring inversion is possible
- impossible to join two axial positions into six-membered ring
the steroid skeleton
trans ring junction

cholestanol

equatorial hydroxyl

axial hydroxyl

coprostanol
cis ring junction
inversion during nucleophilic substitution at saturated carbon

transition state
The image shows a chemical reaction mechanism involving a nucleophile, H, and a leaving group, X. The reaction proceeds through a transition state where the substituent is axial or equatorial, depending on whether it is locked into the axial or equatorial position by the t-butyl group.

- **Substituent is axial:**
  - t-Bu
  - H
  - X
  - 
  - Substituent is axial

- **Substituent is equatorial:**
  - t-Bu
  - H
  - X
  - Nu
  - Transition state

- **Transition state:**
  - t-Bu
  - H
  - X
  - Nu
  - Substituent is equatorial

- **Substituent is equatorial:**
  - t-Bu
  - H
  - X
  - Nu
  - Transition state

- **Substituent is axial:**
  - t-Bu
  - H
  - X
  - Nu
  - Substituent is axial
axial leaving group is substituted 31 times faster than equatorial leaving group
equatorial leaving group

axial leaving group

approach hindered by green axial Hs

less hindered approach
cyclohexyl bromide

substitution faster from axial conformer
epoxide ring-opening reaction

\[ \text{Nu} \rightarrow \text{Nu} \]

epoxide ring-closing reaction

\[ \text{Cl} \rightarrow \text{Cl} \]

Intramolecular S_N2 nucleophilic attack by R0^- on alkyl chloride
trans 2-chloro cyclohexanol

epoxide can't form because oxygen can't reach σ* orbital

with two groups axial, oxygen can attack the C–Cl σ* orbital

ring inversion

neither conformation can form an epoxide

cis 2-chloro cyclohexanol

ing ring inversion
the half-chair conformation of cyclohexene oxide...

...compared with the normal chair conformation of cyclohexane.
this transition state is the same for both formation and ring opening of the epoxide
initial product of ring opening is diaxial
diaxial can flip to diequatorial
ring opening the wrong way would give a twist boat, which is too high in energy to form even though it could ring flip to the stable all-equatorial chair if it got the chance.
methylene cyclohexane

the green parts of the molecules are planar

cyclohexanone

ring inversion
where the hydrogens would be in cyclohexane

C=O bisects this angle

CORRECT

WRONG
don’t try and make the C=O equatorial!
carbon atoms 1, 2, 3, and 4 are all in the same plane
Nu

\[
\begin{align*}
\text{Nu} & \quad \leftrightarrow \quad \text{Nu} \\
\text{OH} & \quad \rightarrow \quad \text{OH}
\end{align*}
\]
axial attack of the nucleophile

equatorial attack of the nucleophile
1. Lis-Bu₃BH
2. H₂O

1. LiAlH₄
2. H₂O

large nucleophile: 96% equatorial attack
small nucleophile: 90% axial attack
norbornane

without the hydrogens  with hydrogens included

the red CH$_2$ bridges across the ring

bridgehead positions

the cyclohexane boat is shown in black
**Nor-**

The *nor-* prefix has a number of meanings in ‘trivial’ organic nomenclature. Here it tells us that this structure is like that of the parent compound but less one or more alkyl groups—that is, *no R* groups. This isn’t the derivation of the word though—historically it comes from the German *Nitrogen ohne Radikal* (‘nitrogen without R-groups’)—it was used first for amines such noradrenaline (also known as norepinephrine) and norephedrine. You met ephedrine in Chapter 16.

- **camphor** (bornane skeleton in red)
- **norbomane**
- **adrenaline**
- **noradrenaline**
The reaction shown in the diagram is the base-catalyzed elimination of Br from 2-bromo-3-methylcyclohexane, leading to 2-methylcyclohexene.
\[
\begin{align*}
8A & \quad \xrightarrow{\text{HO-}OH} \quad 8A\text{ acetal} \\
8B & \quad \xrightarrow{\text{HO-}OH} \quad 8B\text{ acetal}
\end{align*}
\]
12A \xrightarrow{\text{PhCHO}} 12B

12A \xrightarrow{\text{H}^+} 12A