

Conformational Analysis

Stereochemistry

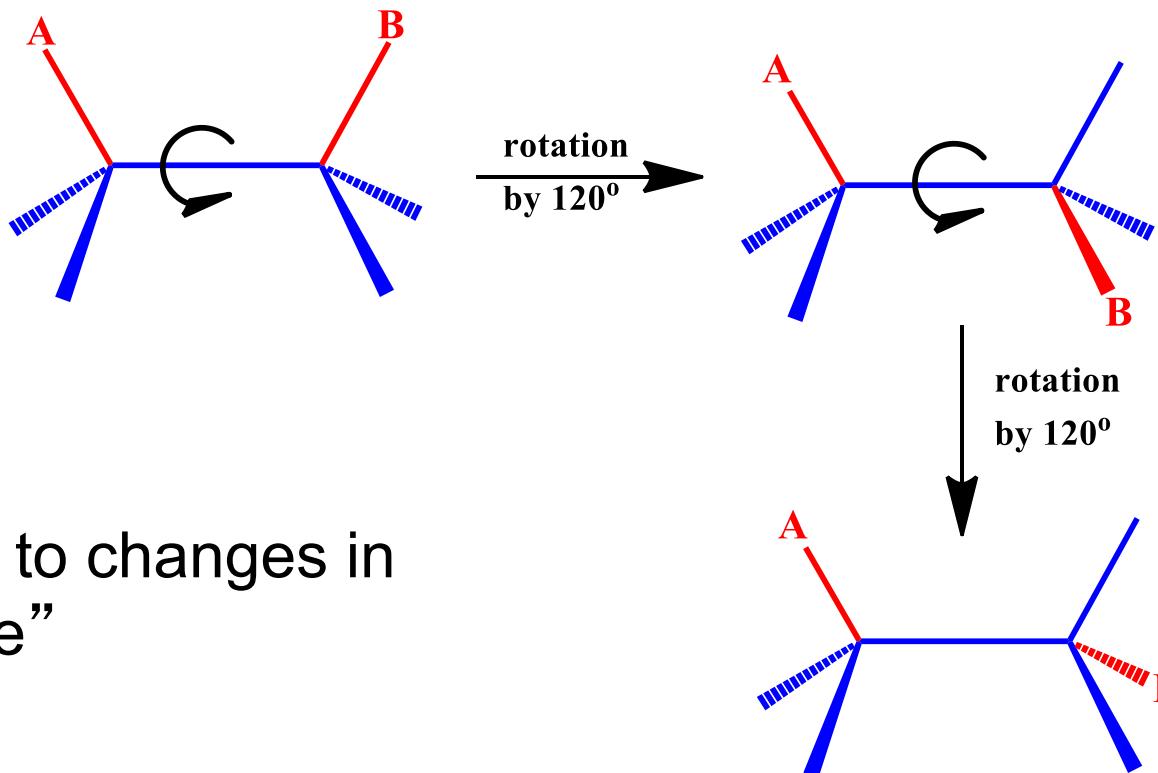
- *Stereochemistry* describes how the atoms of a molecule are arranged in three-dimensional space.
- *Stereoisomers* are molecules that have identical connectivity (constitution) but differ in three-dimensional structure.
- Stereoisomers differ from one another in *configuration* at one or more atoms.
- *Conformations* are the various shapes that are available to molecules by single-bond rotations and other changes that do not involve bond breaking.

Conformational Analysis

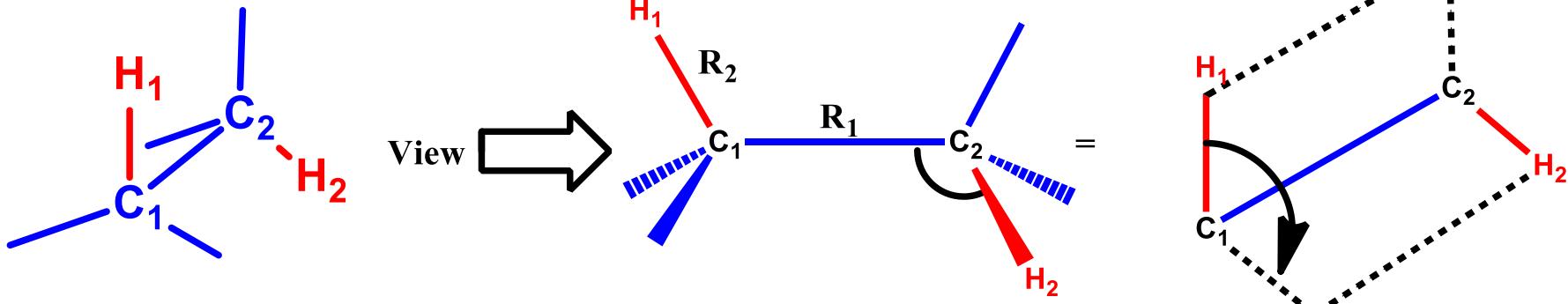
Conformational Analysis is the study of energetics of different conformers

Energy versus torsional angle (dihedral angle)

Conformers arise due to the possible free rotation around single bonds



Internal Coordinates



Bond length

between 2 atoms

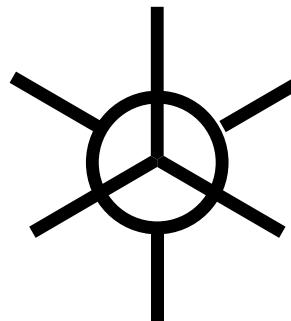
Bond angle

between 3 atoms

Dihedral angle

between 4 atoms

(torsion angle)

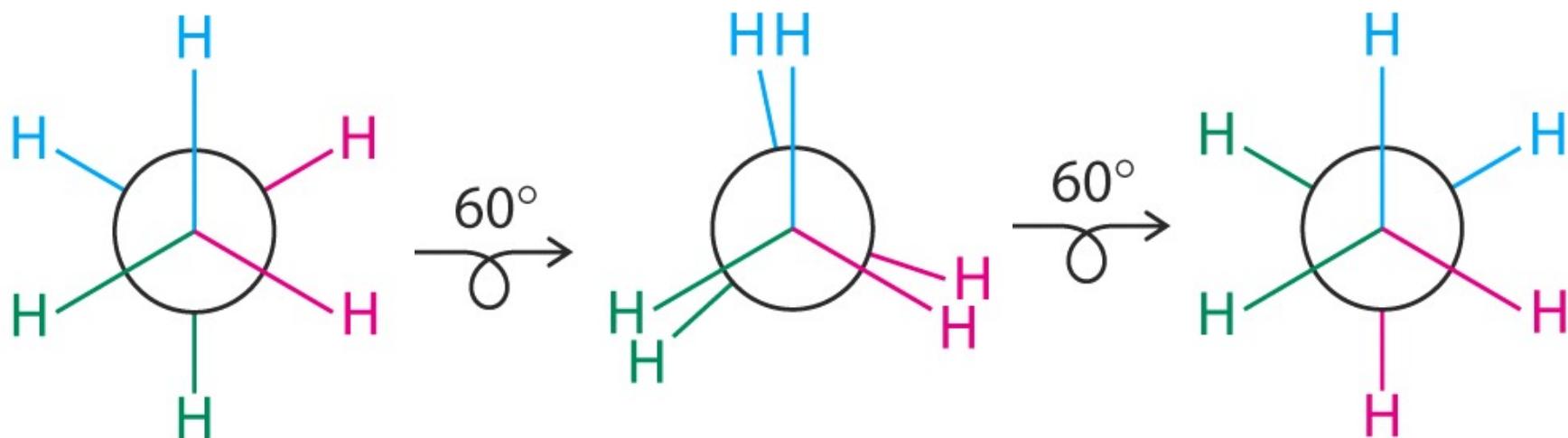


Melvin Newman
1908-1993⁶

Conformational Analysis, Example-1: Ethane

Ethane has two major conformers – **Staggered** and **Eclipsed**

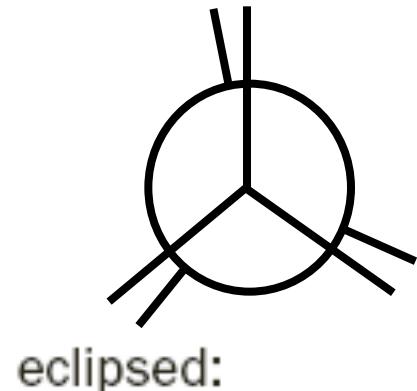
- The eclipsed conformation of ethane is -3 kcal/mol less stable than the staggered conformation. (-1 kcal/mol for each eclipsed H/H pair)



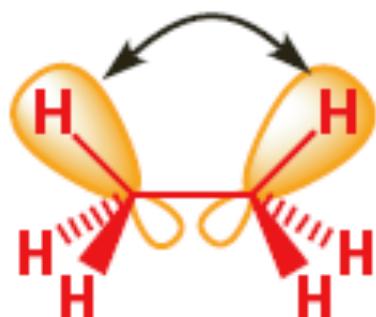
Rotation Around Bonds is Not “Free”: Barriers to Rotation

Ethane has barrier to rotation of ~ 3 kcal mol $^{-1}$. Barrier due to steric and electronic effects

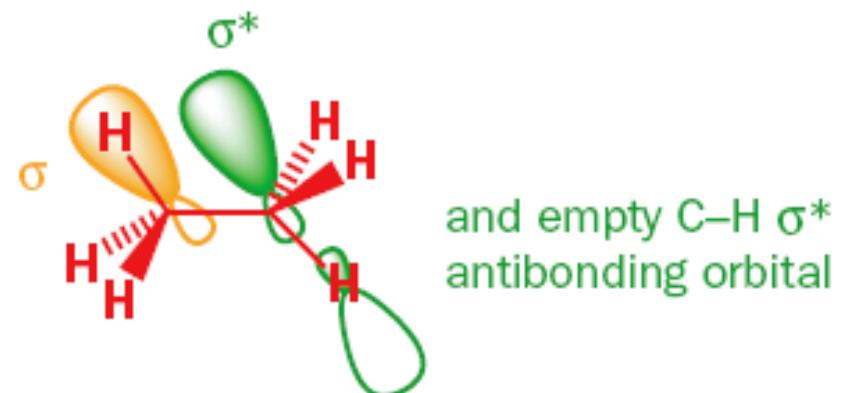
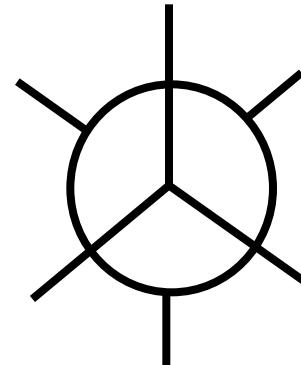
Transition state
is **eclipsed**



filled orbitals repel

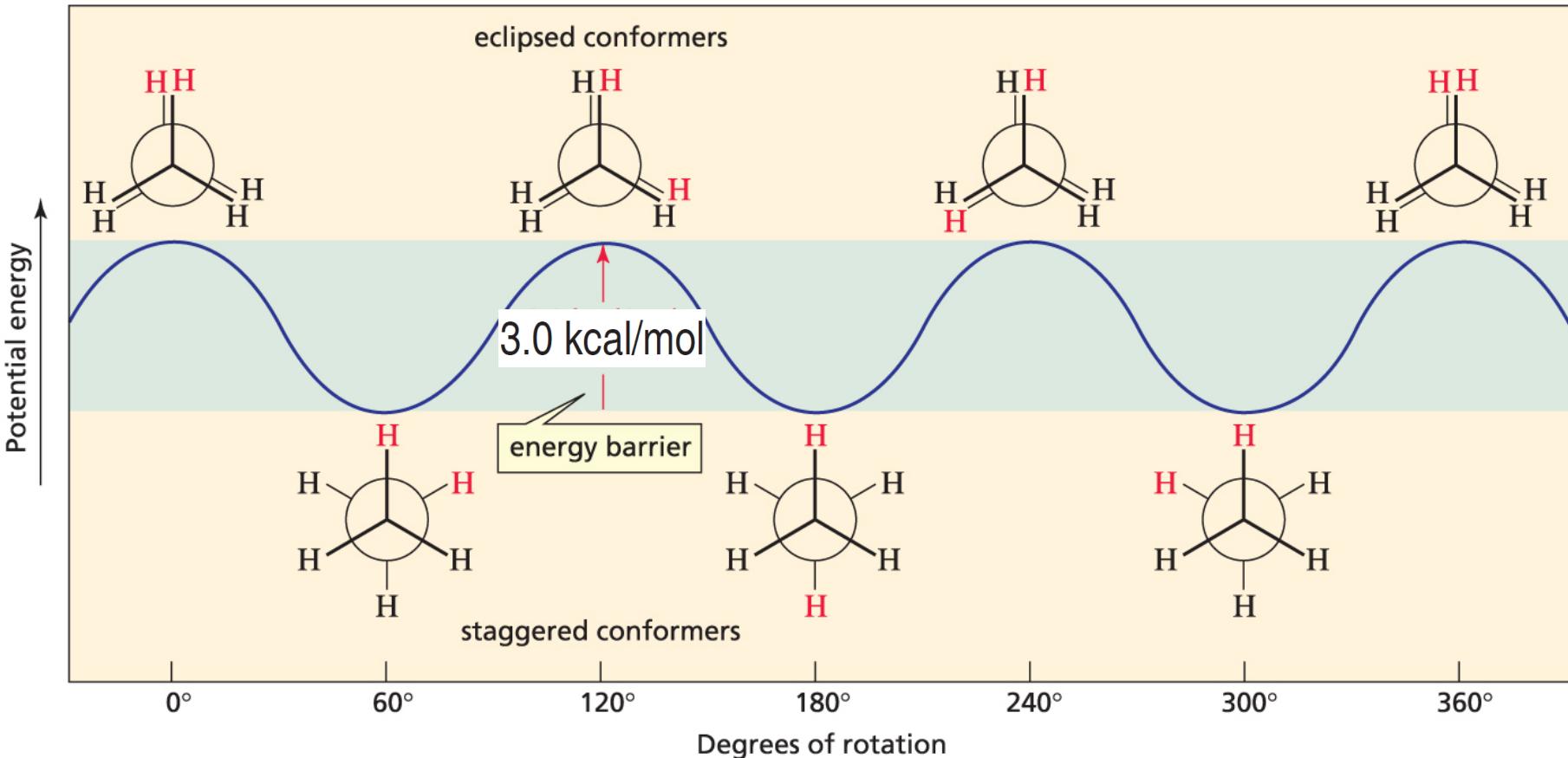
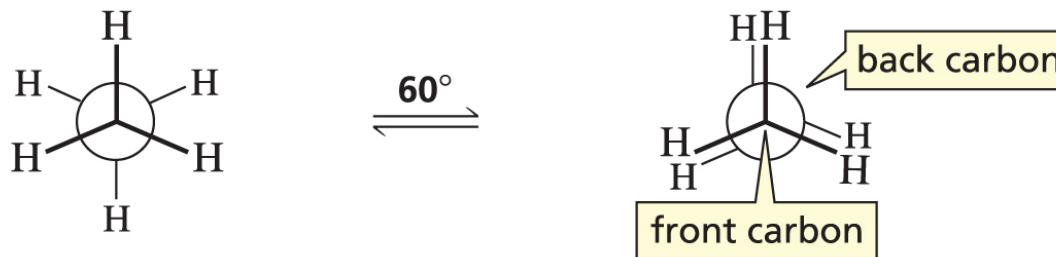


Most **stable** rotamer
is **staggered**



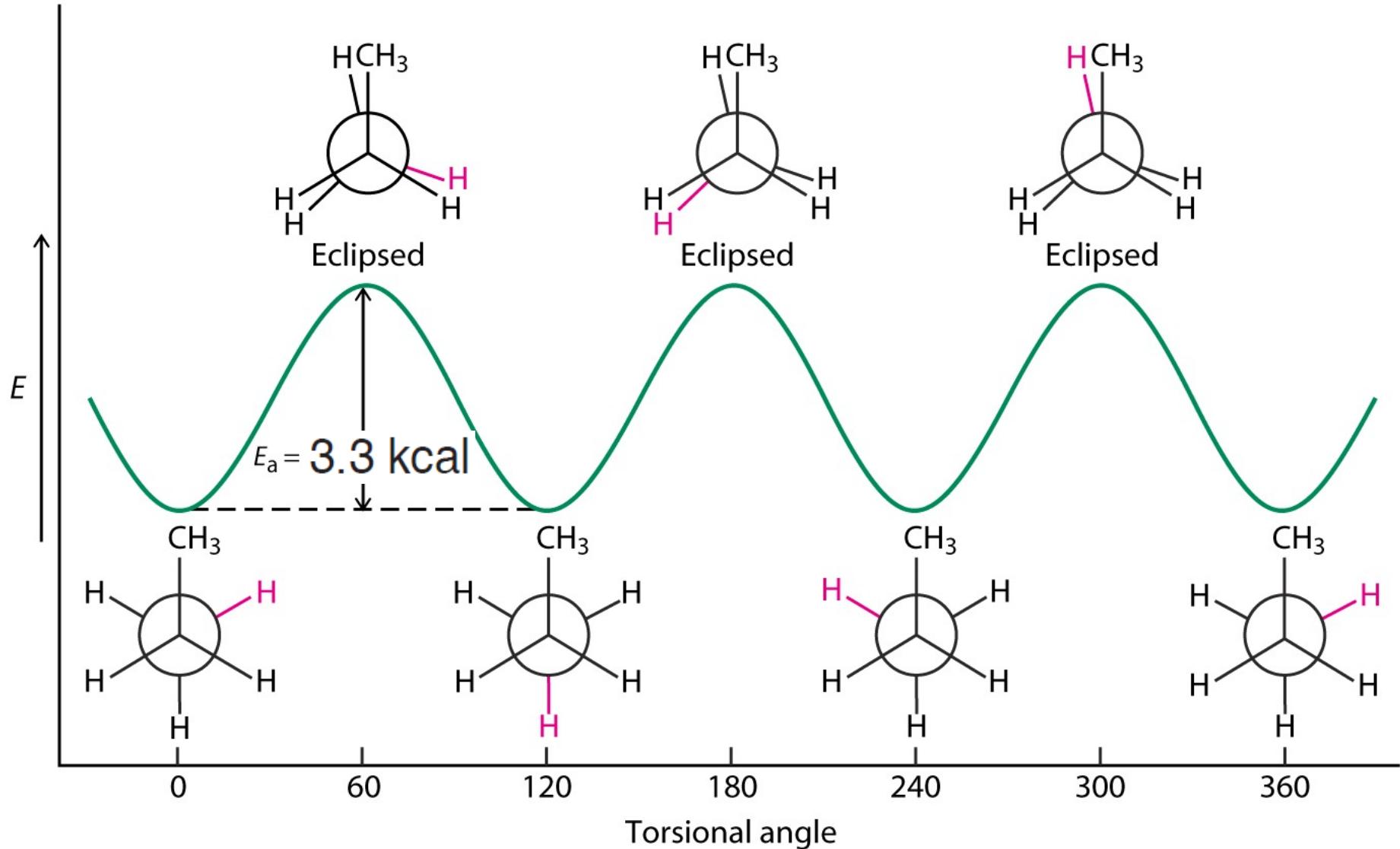
Conformational Analysis, Example-1: Ethane

Eclipsed conformer is 3.0 kcal/mol higher in energy than the staggered conformer: eclipsing interactions H/H (1.0 kcal)

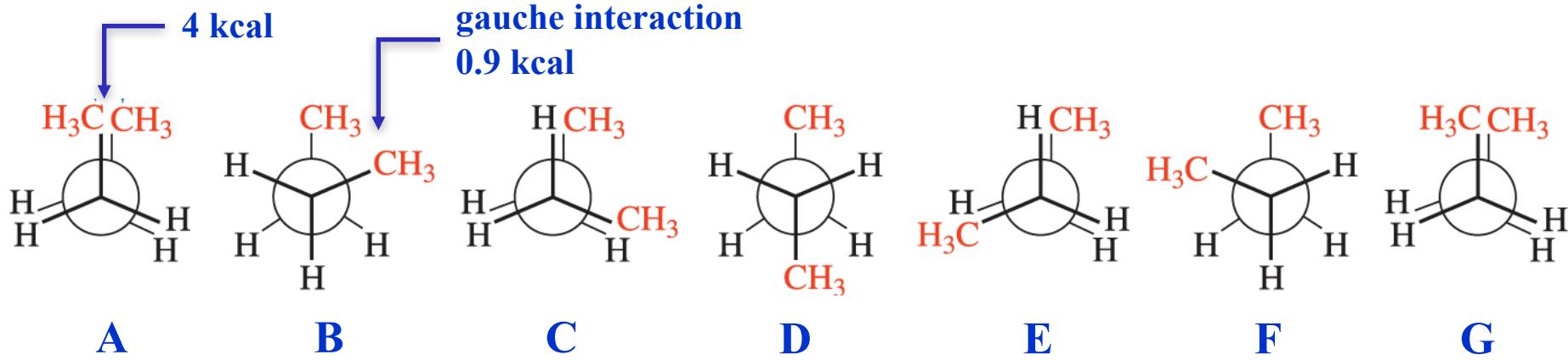
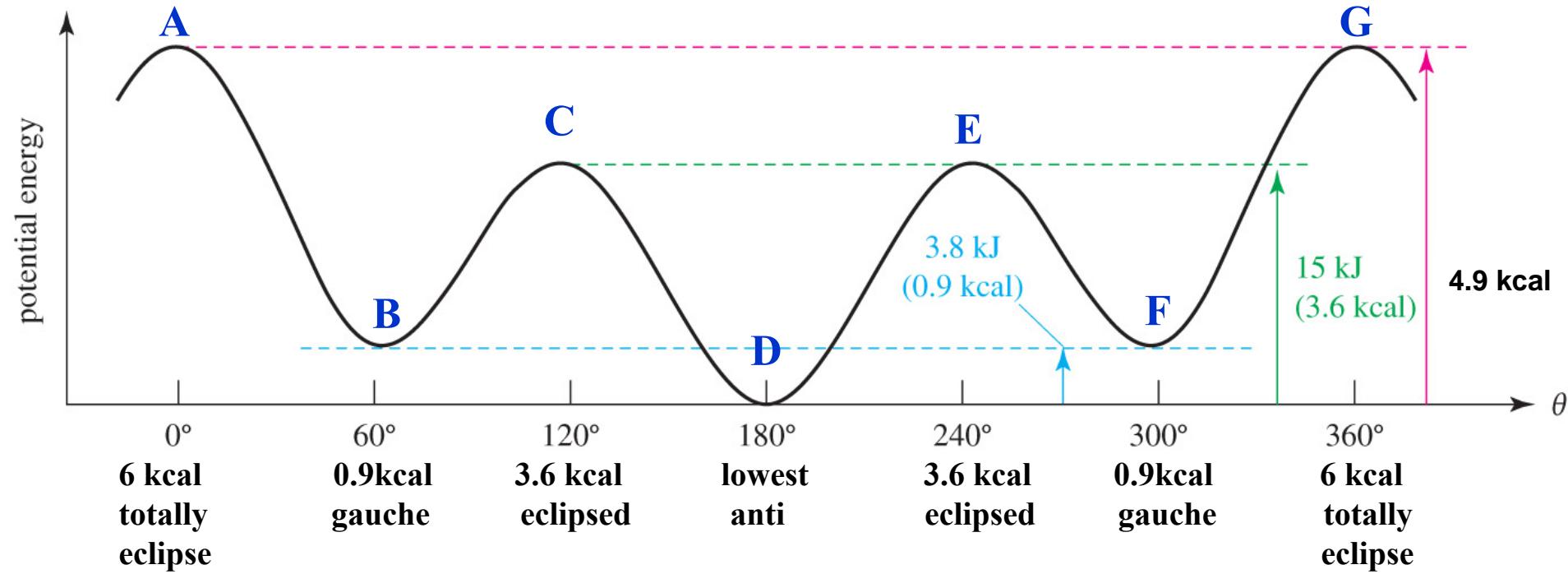


Conformational Analysis, Example-2: Propane

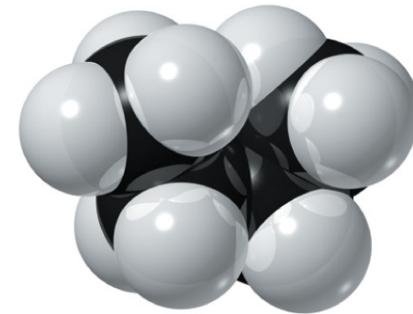
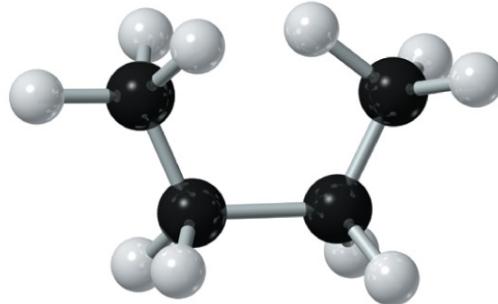
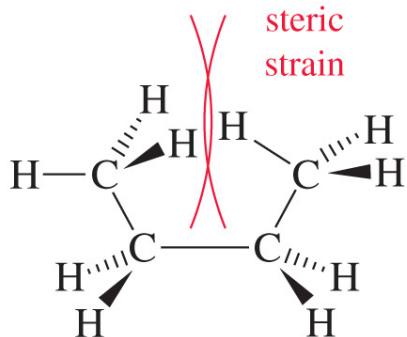
Note: eclipsing interactions H/H (1.0 kcal) and Me/H (1.3 kcal)



Conformational Analysis, Example-3: *n*-Butane



Steric Strain



Totally eclipsed conformation of butane

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- **The totally eclipsed conformation is higher in energy because it forces the two end methyl groups so close together that their electron clouds experience a strong repulsion.**
- **This kind of interference between two bulky groups is called *steric strain* or *steric hindrance*.**

Torsional Barrier for C-C bond rotation

Eclipsing Group	Contribution to Barrier height (kcal/mol)
(CH ₃) ... (CH ₃) <i>gauche</i>	0.9
(C-H) ... (C-H)	1
(C-H) ... (CH ₃)	1.3
(CH ₃) ... (CH ₃)	2.9
(CH ₃) ... (CH ₂ CH ₃)	3.4
(CH ₃) ... (CH(CH ₃) ₂)	3.9
(CH ₃) ... (C(CH ₃) ₃)	4.7

Important Types of Molecular STRAINS

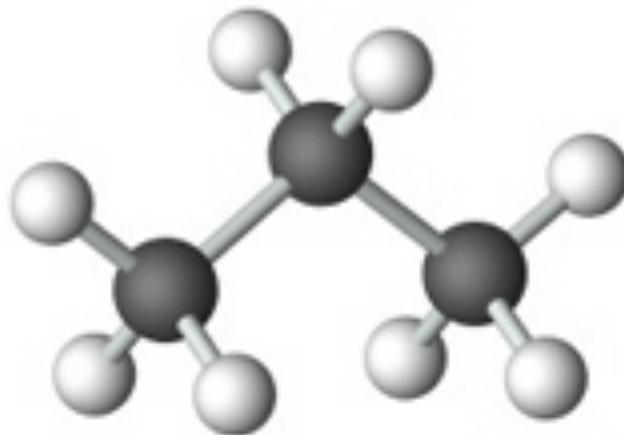
Torsional Strain: Extra energy of eclipsed conformation arising due to the repulsion between bonding electrons of one substituent with that of the other as they pass close to each other

Steric Strain: Strain induced when two atoms or groups in a molecule are too close to each other, arising due to repulsion between electron clouds of interacting atoms/groups

Angle Strain: Strain induced in molecules when the bond angles are different from the desired tetrahedral bond angle of 109.5°

Small Ring Compounds – (1) cyclopropane

Propane



Angle strain : None

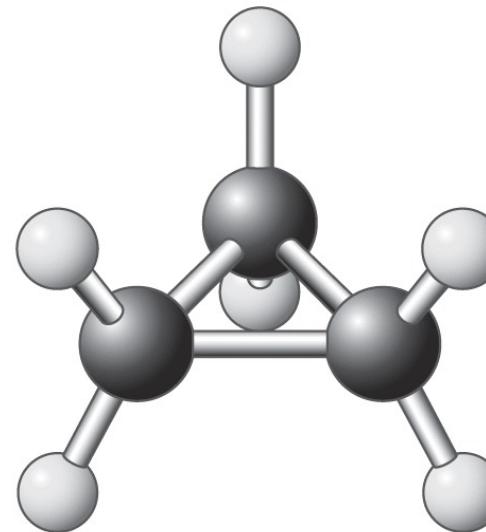
(all angles are nearly tetrahedral)

Steric strain: None

(Fully staggered conformer)

Cyclopropane suffers from angle strain and torsional strain

Cyclopropane



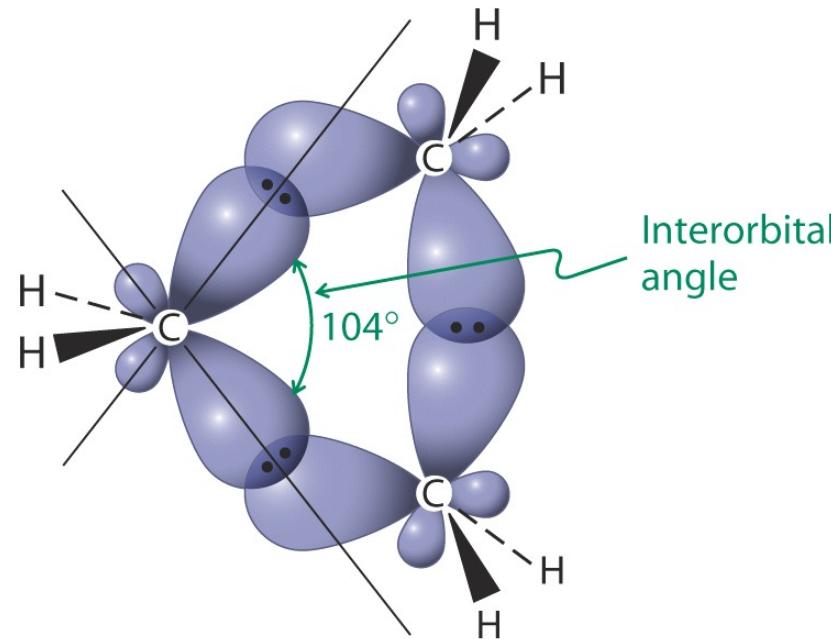
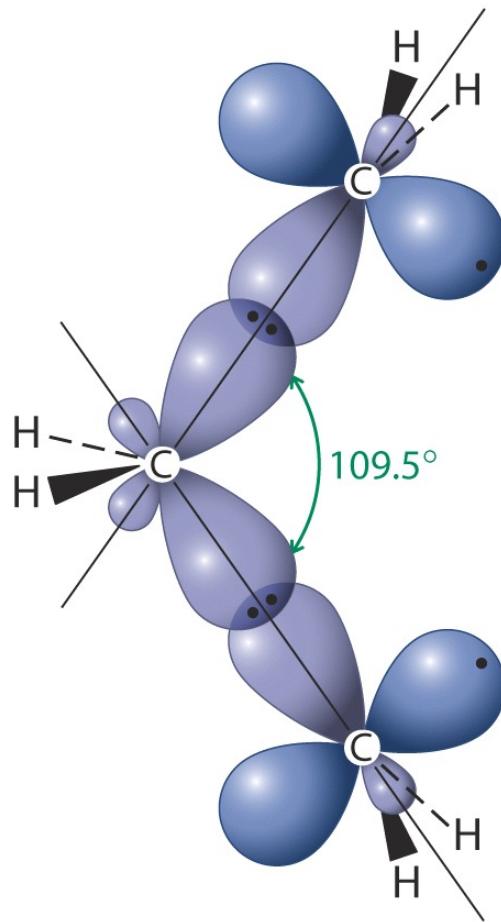
Deviation of 49.5° per carbon

Torsional strain: (C-H) ... (C-H) eclipsing interactions

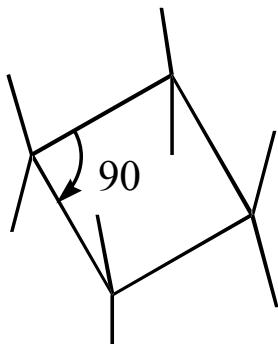
Renders higher reactivity, Weaker C-C and C-H bonds

Small Ring Compounds – (1) cyclopropane

Strain relief through the formation of “banana” bonds

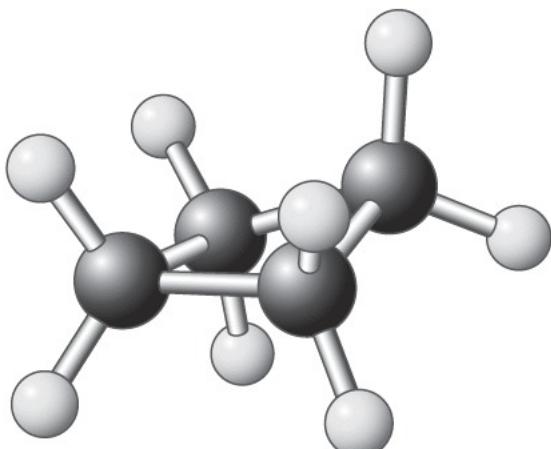


Small Ring Compounds – (2) cyclobutane



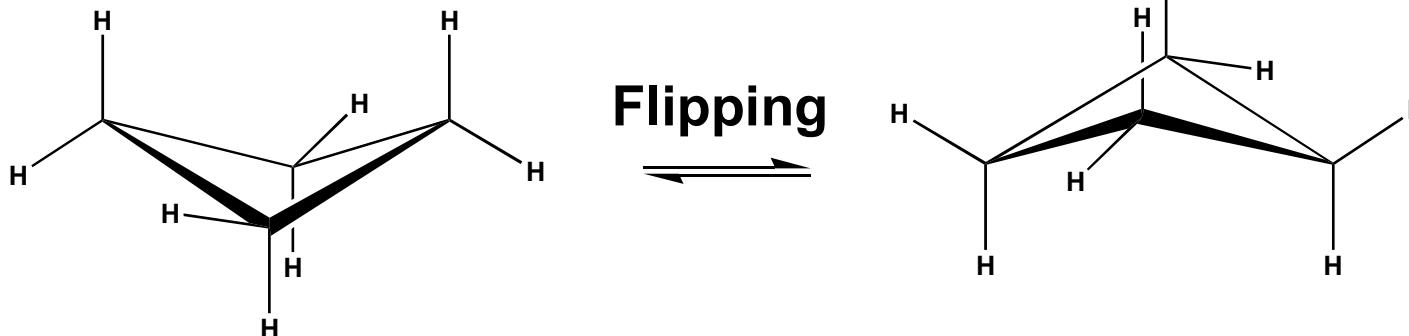
Planar? Problems are: **Angle strain** plus
severe torsional strain

Compromise is



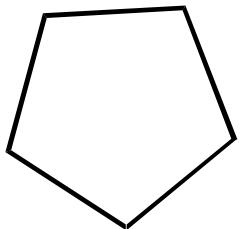
Ring puckering

Relieves eclipsing interactions with only a slight increase in angle strain (90 to 88°)



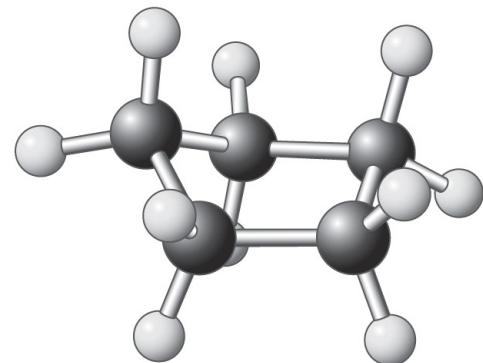
Cyclobutane has a ‘wing shaped’ or ‘puckered’ conformer

Small Ring Compounds – (3) Cyclopentane



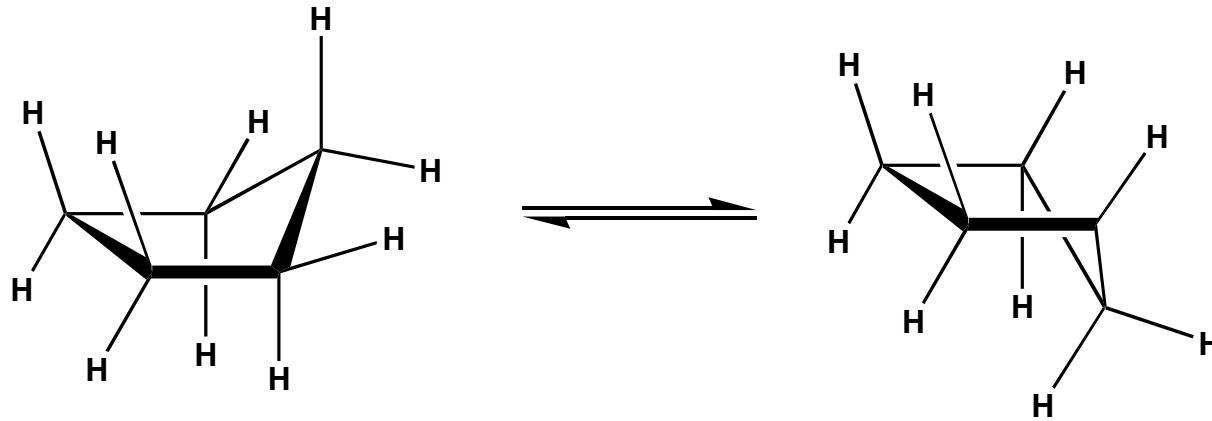
Planar? Though the angle strain is very little, there will be 10 eclipsing interactions!

Ring puckering



Relieves eclipsing interactions with only a slight increase in angle strain

Four coplanar carbon atoms



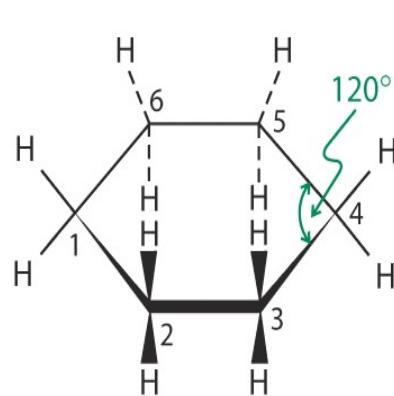
Cyclopentane has an ‘envelope’ conformer

Small Ring Compounds – (4) Cyclohexane

One of the most abundant and important structural units in organic chemistry (and nature!)

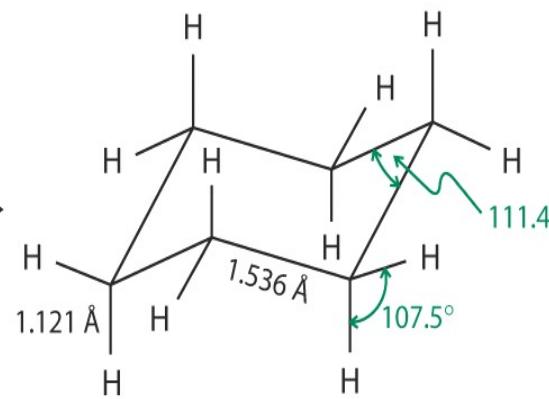
Both angle and torsional (eclipsing interactions) strains can be avoided by **ring puckering**.

Ring puckering leads to “CHAIR” and “BOAT” conformers



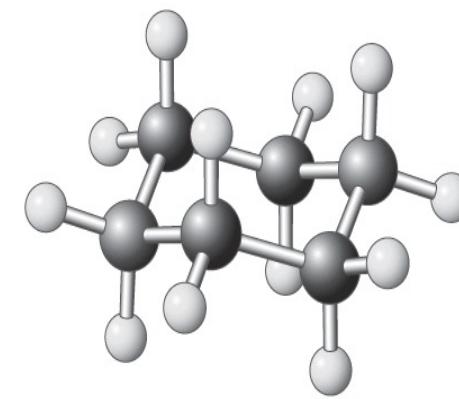
A

Planar cyclohexane
(120° bond angles;
12 eclipsing hydrogens)



B

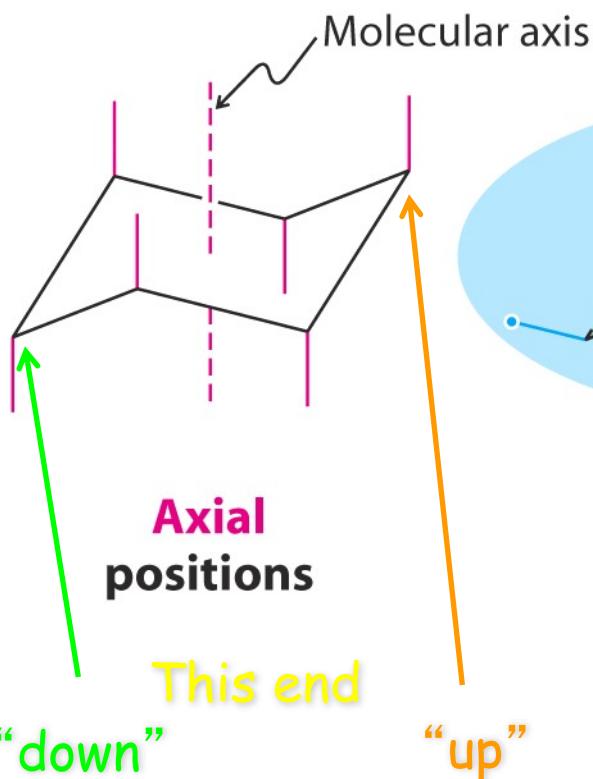
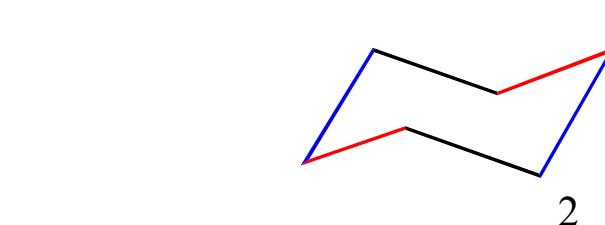
Chair cyclohexane
(Nearly tetrahedral bond angles;
no eclipsing hydrogens)



C



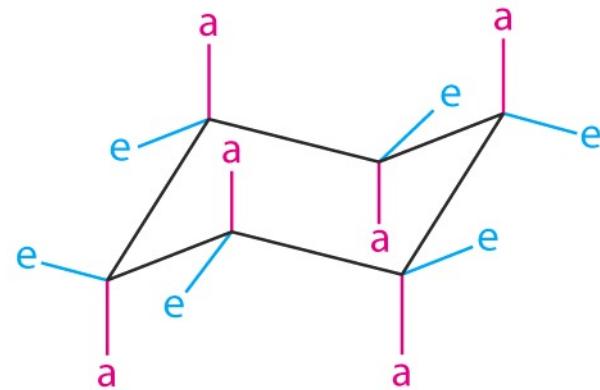
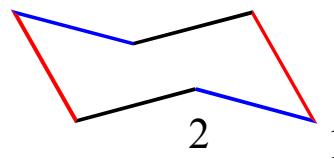
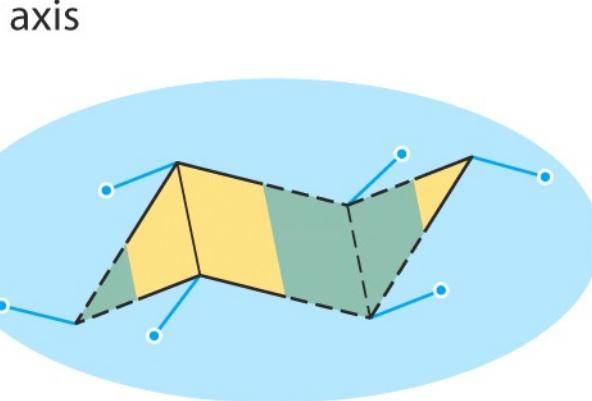
Drawing Cyclohexanes



Look for “W” and “M”

Look for ‘parallel’ bonds

Tips:

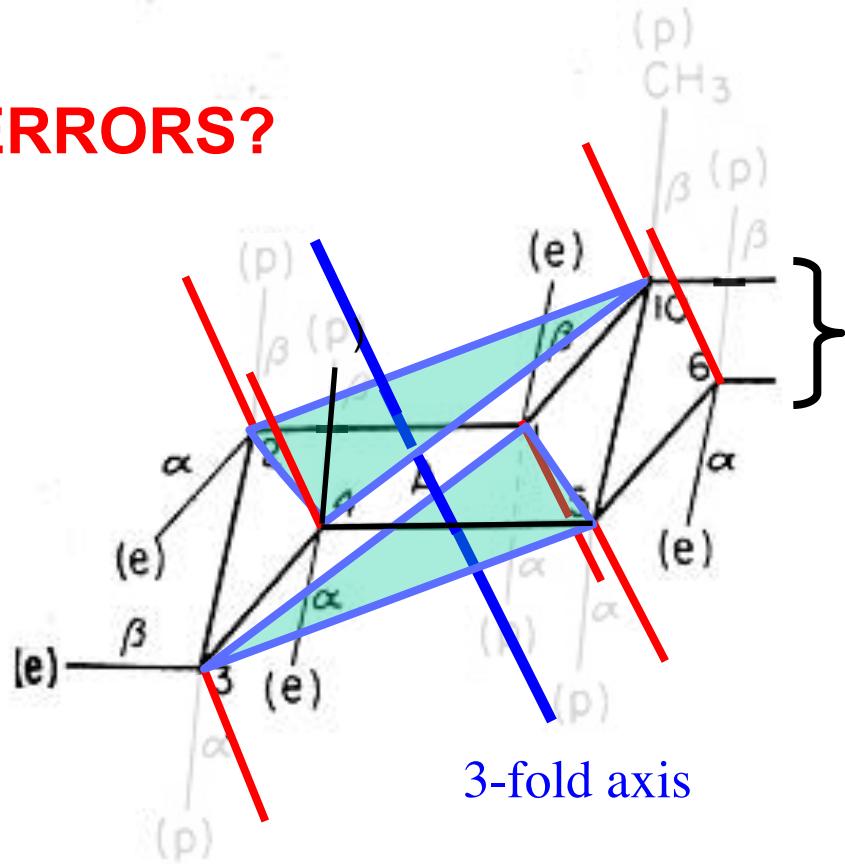


Axial (a) and equatorial (e) positions

Equatorial bonds must be parallel to the C–C bond(s) “one over” [not the attached one(s), but the next one(s)]

D.H.R. Barton Invents Conformational Analysis (1950)

ERRORS?



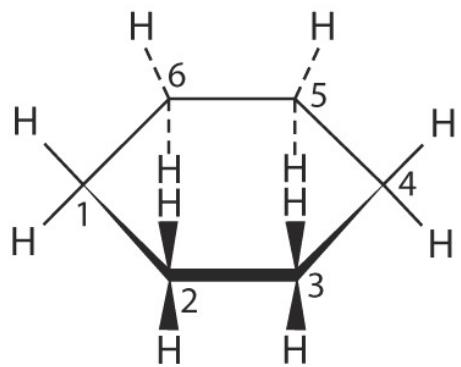
$\beta \Rightarrow$ “up” ; $\alpha \Rightarrow$ “down”
(for molecule in conventional orientation,
old-fashioned configuration notation, like *cis* / *trans*)

(e) “equatorial”

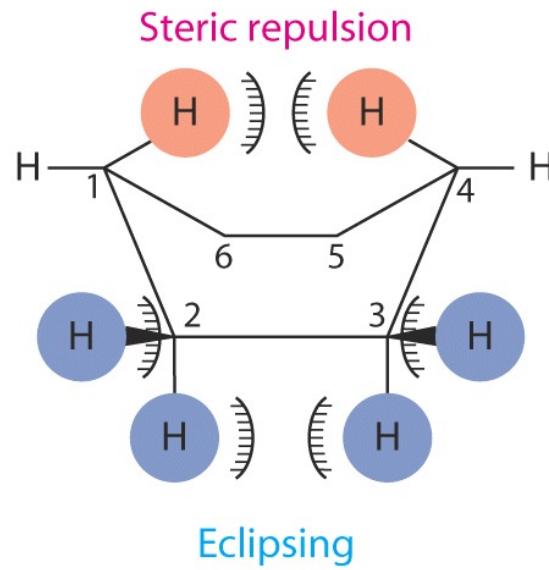
(p) “polar” (now axial)

(Nobel Prize 1969 for “development of the concept of conformation and its application in chemistry”)

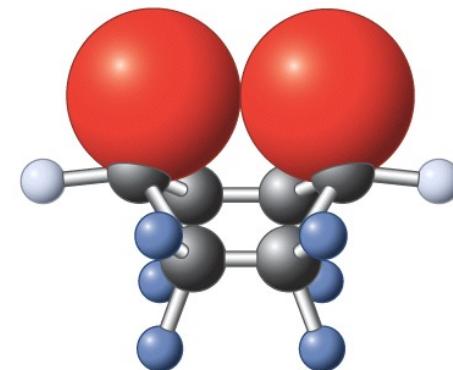
Boat conformer of cyclohexane is strained



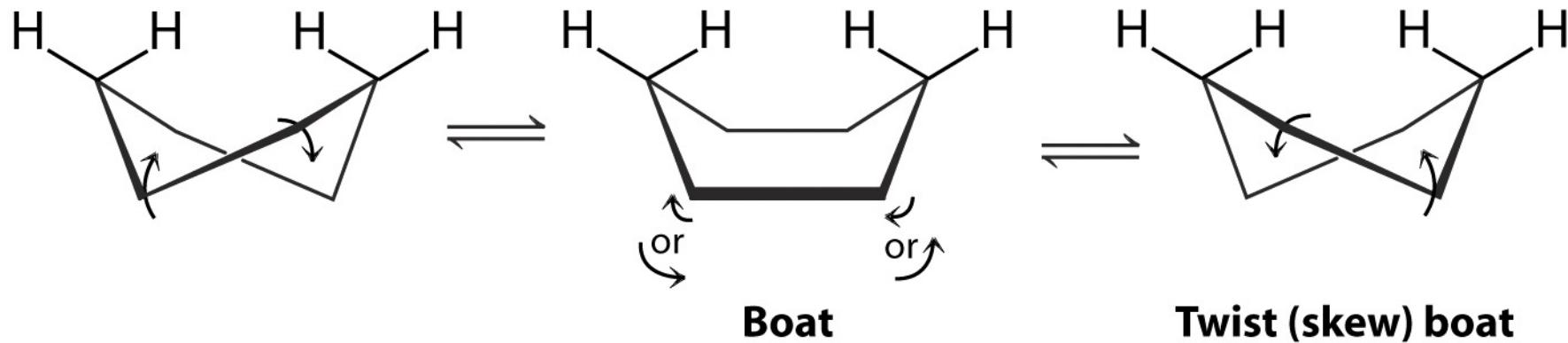
Planar cyclohexane



Boat cyclohexane



So the boat twists

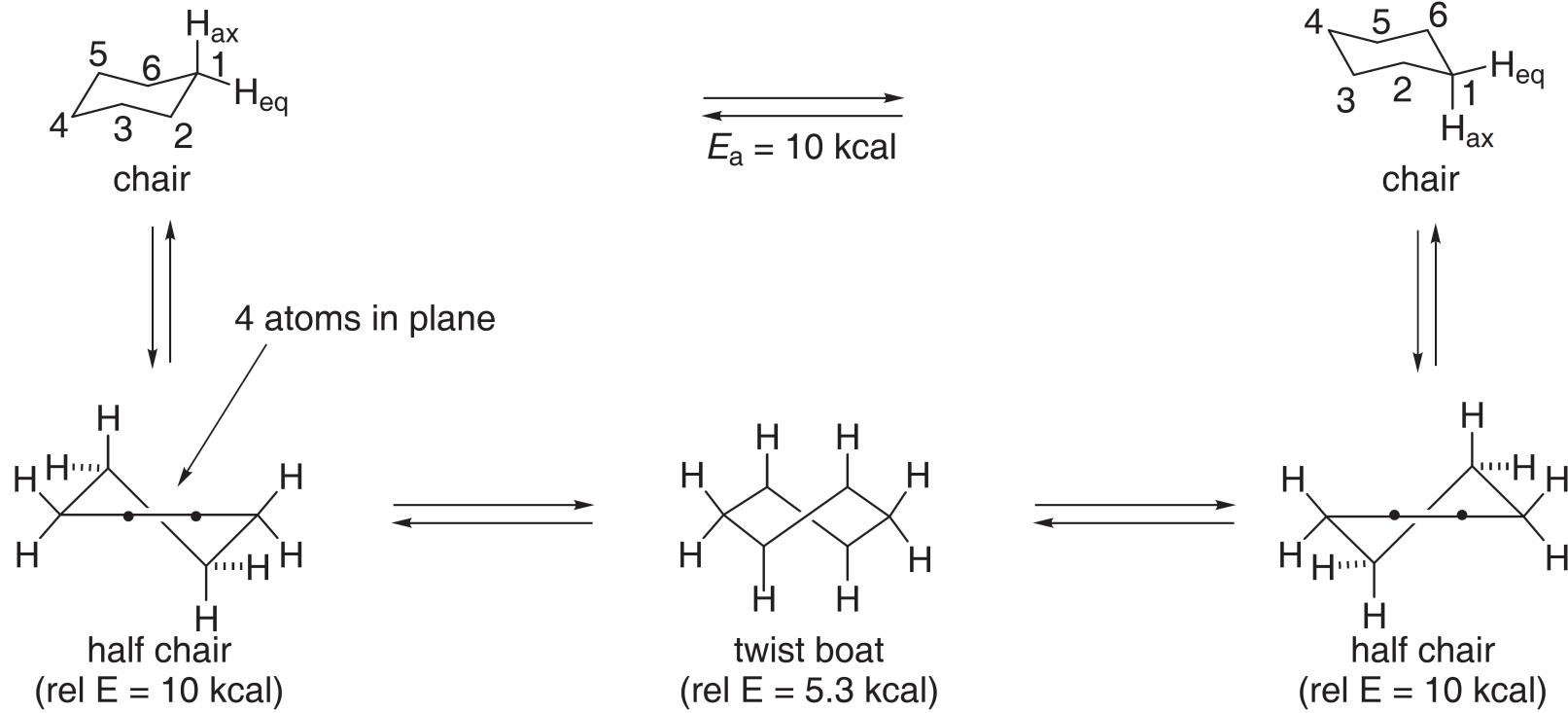


But this is only part of its mobility. The molecule “flips” from one chair to another chair form.

Animations

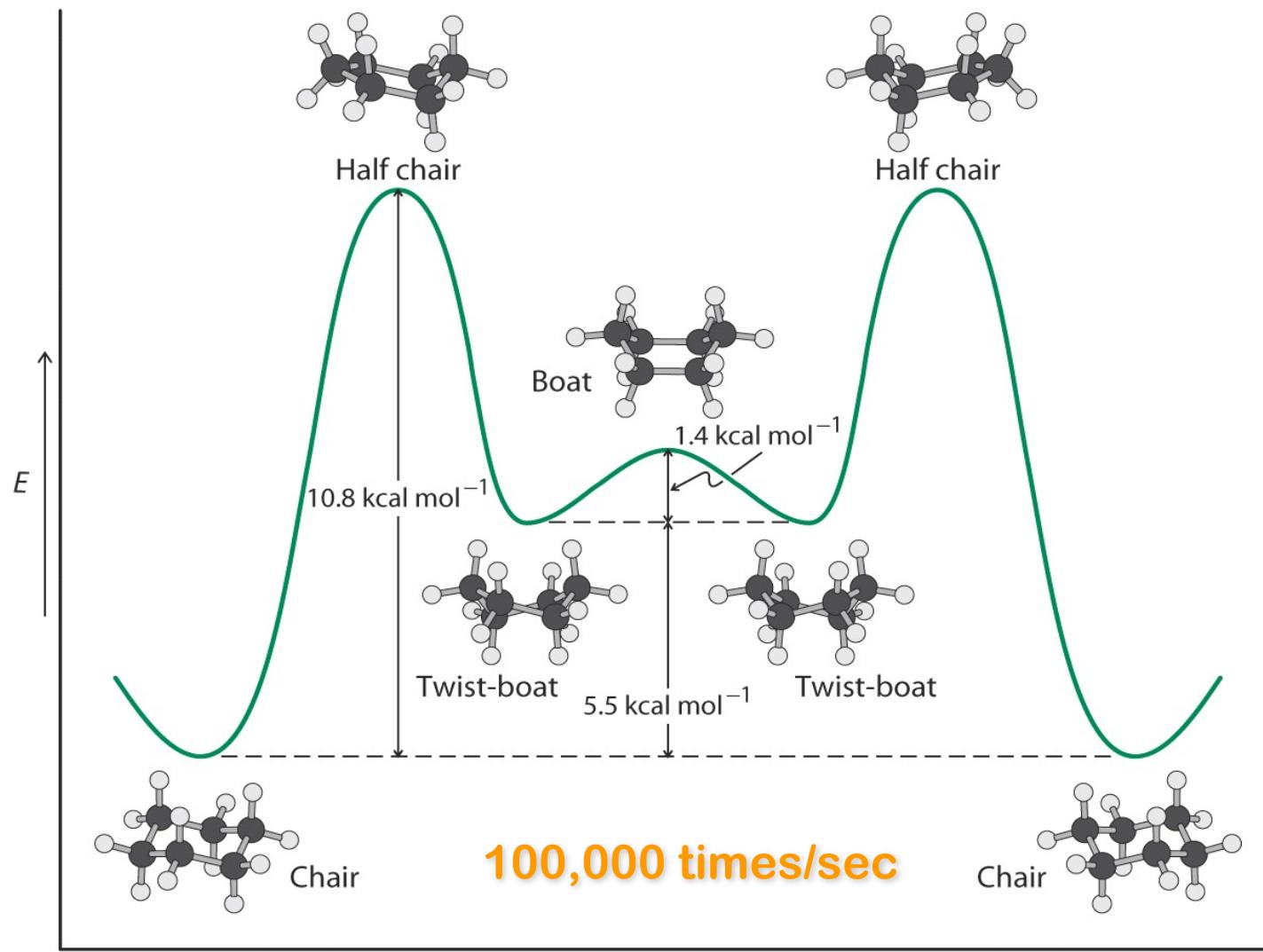
<http://www.chemtube3d.com/>

Ring Inversion or Ring Flipping

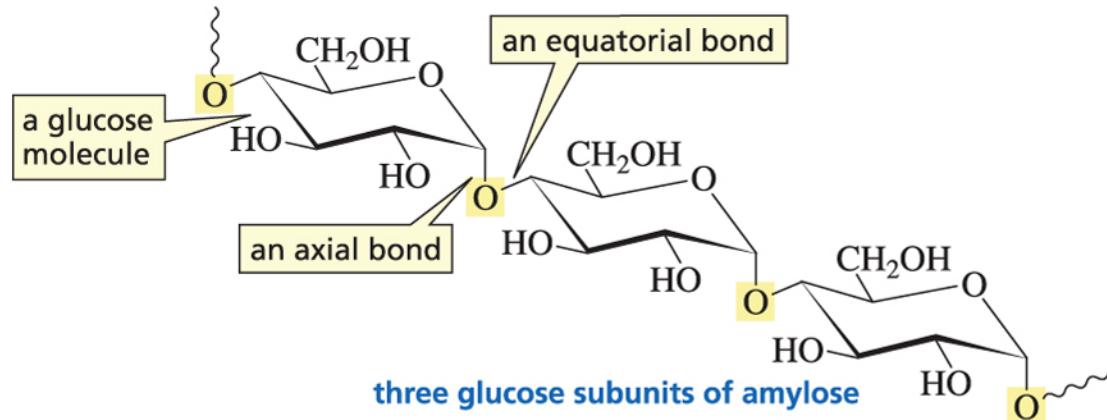


Ring Inversion or Ring Flipping

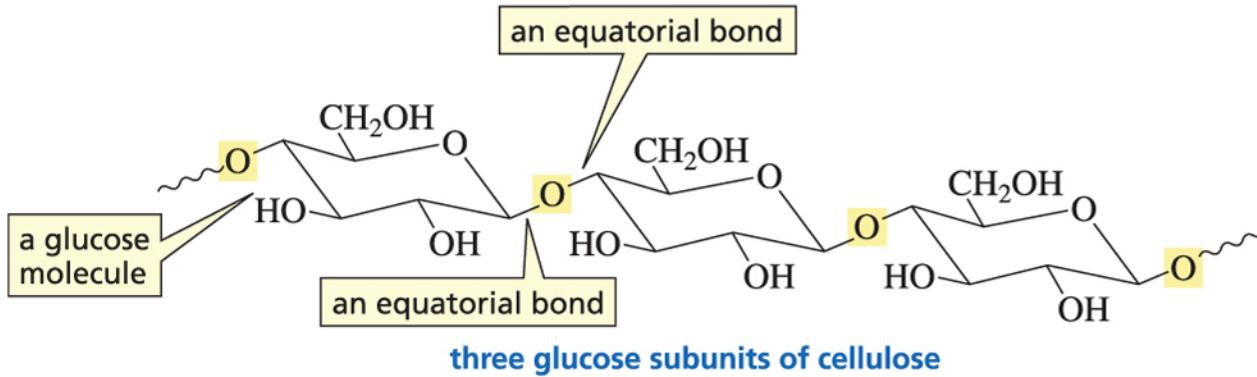
In monosubstituted (small groups) cyclohexanes the ring flipping is of the order of 10^4 to 10^5 inversions/second



The Only Difference Between Starch and Cotton is an Equatorial Bond Versus an Axial Bond

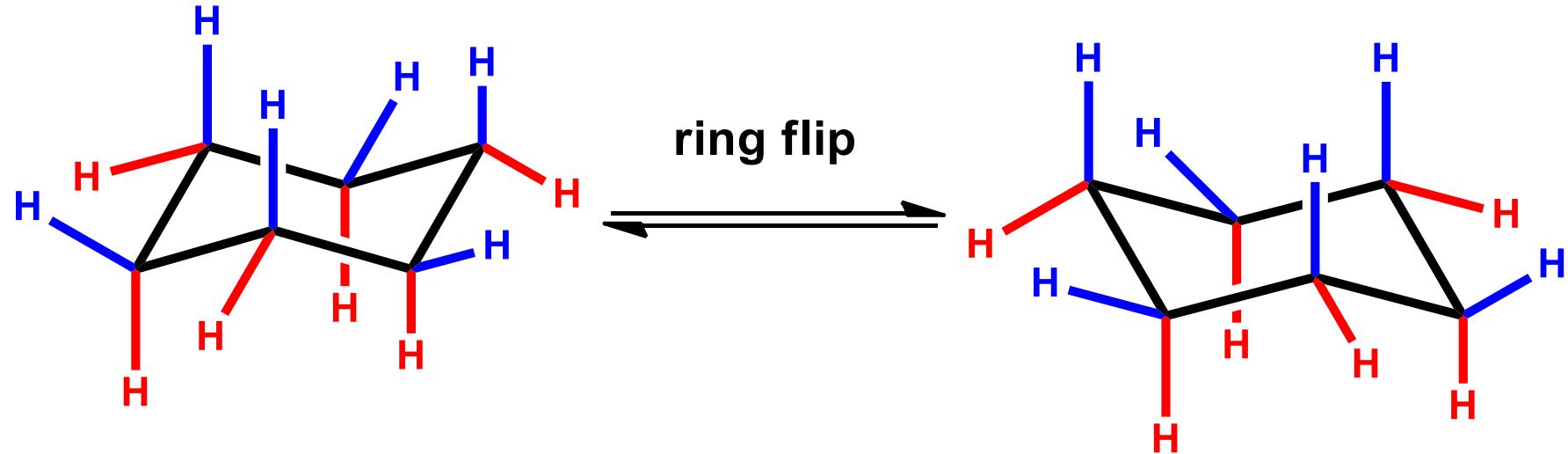


foods rich in starch



cotton plant and cotton towel

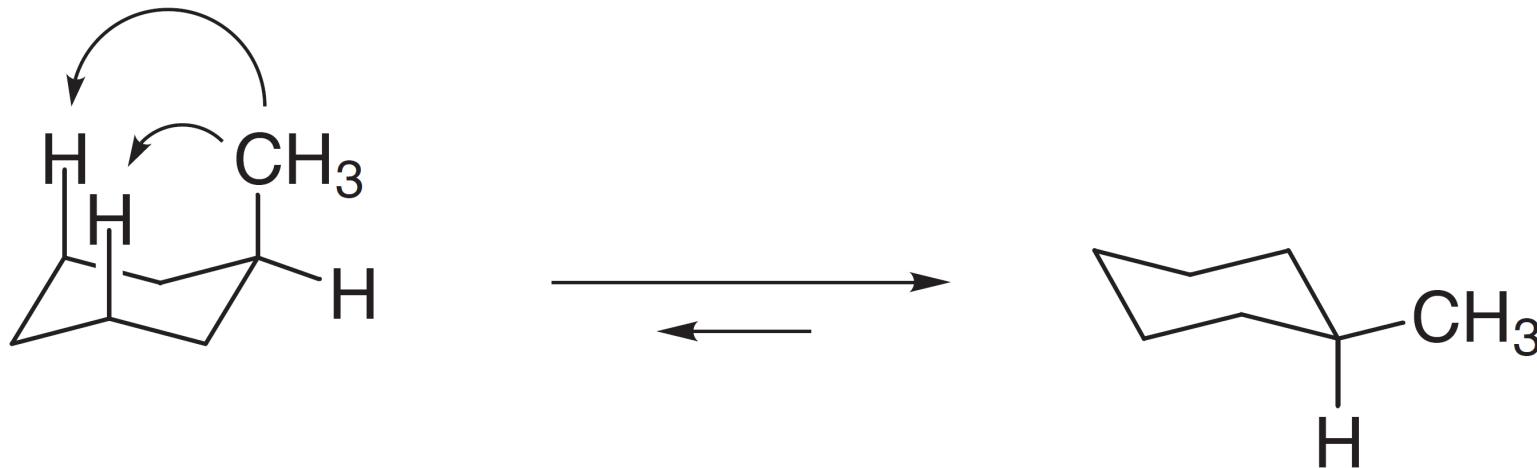
The Chair-Chair Flip Causes Equatorial-Axial Exchange



The two structures are the same. However, what happens in substituted cyclohexanes?

Substituted cyclohexanes: $\Delta G^\circ \neq 0$

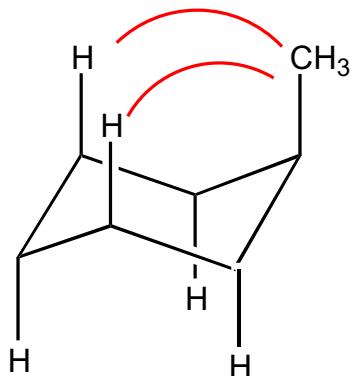
Conformational Analysis: Interplay of energetics of ax-eq substituents. Example: Methylcyclohexane



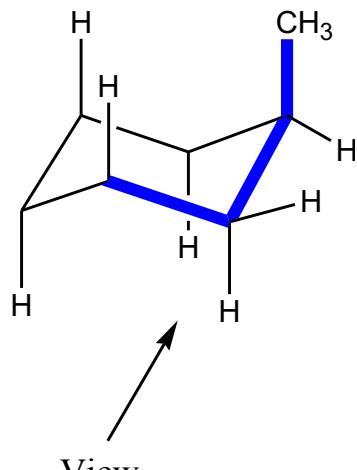
$$\Delta G^\circ = -RT(\ln K)$$
$$\frac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$$

$$K = 21$$

Why Axial –R group is disfavored?

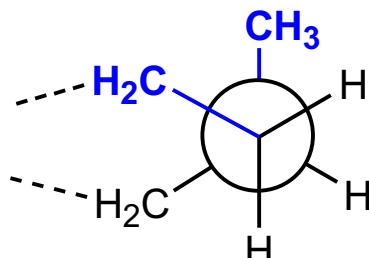


1. van der Waals repulsion between the axial methyl group and the axial hydrogens at C3 and C5 is known as **1,3-diaxial interactions**



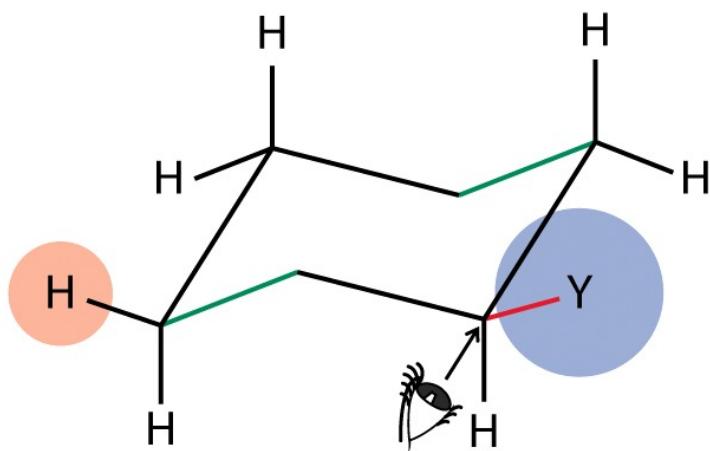
CH_3 is gauche to two C-C bonds

2. ‘gauche-butane’ type interaction in axial position

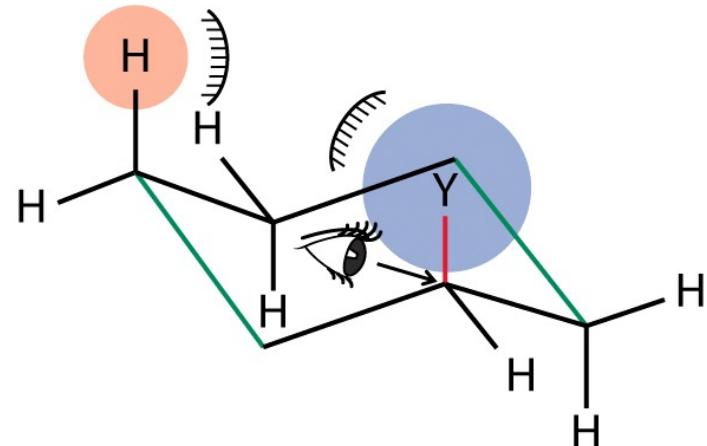


Axial-Equatorial Conformers

Equatorial Y

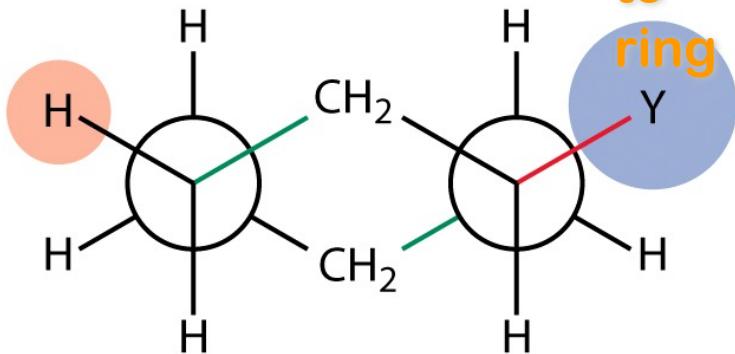


Axial Y

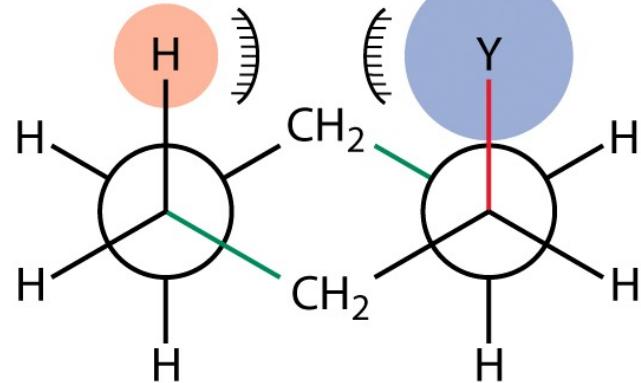


III

Anti
to
ring

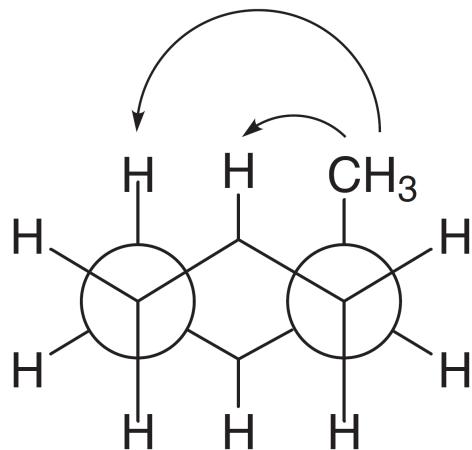


Gauche
to ring

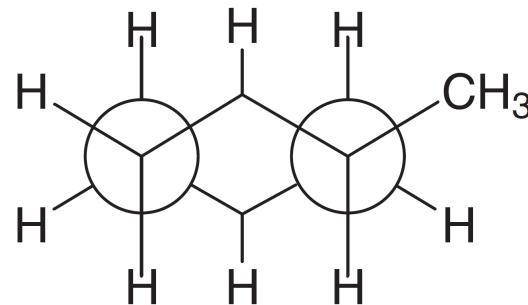


Gauche interactions

- The gauche butane interaction is most often identifiable as 1,3-diaxial interactions.



2 gauche butane interactions
 $2 \times 0.9 \text{ kcal} = 1.8 \text{ kcal}$
(experimental 1.8 kcal)

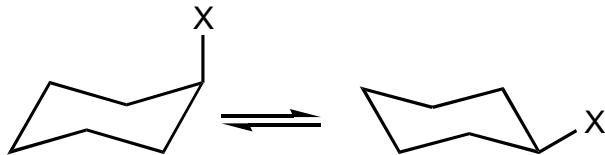


0 gauche butane interactions

A-value for mono substituted cyclohexanes

Free energy difference between axial and equatorial conformers of monosubstituted cyclohexanes are known as **A-values**

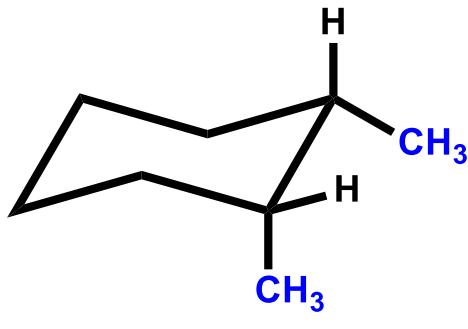
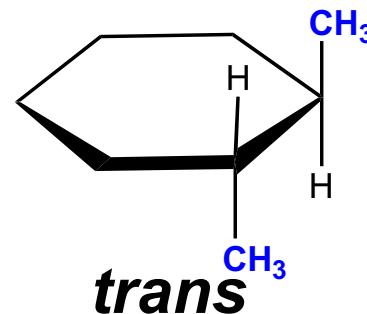
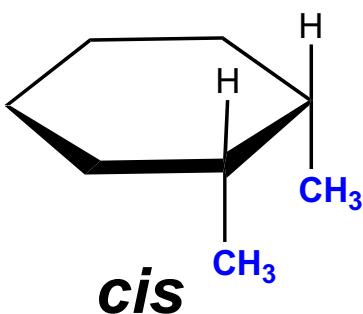
$$\Delta G = G_{\text{ax}} - G_{\text{eq}}$$



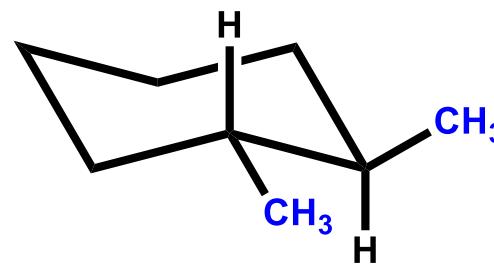
X group	A value (kcal/mol)	K	% eq
H	0	1	50
CH ₃	1.7	19	95
CH(CH ₃) ₂	2.15	42	98
C(CH ₃) ₃	5	3000	99.9

Disubstituted cyclohexanes

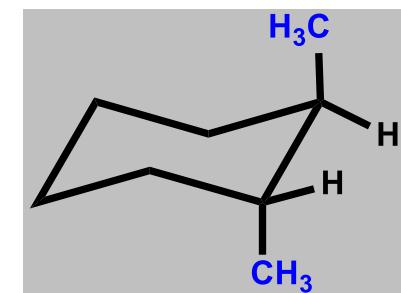
1,2-disubstituted



cis

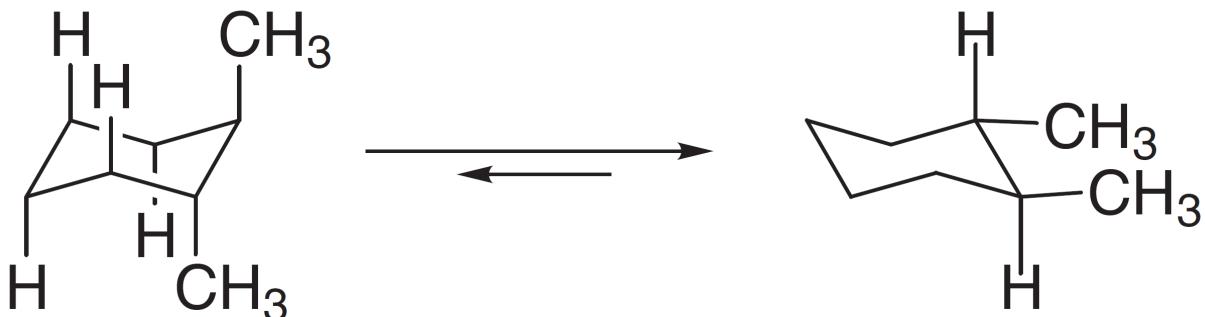


trans

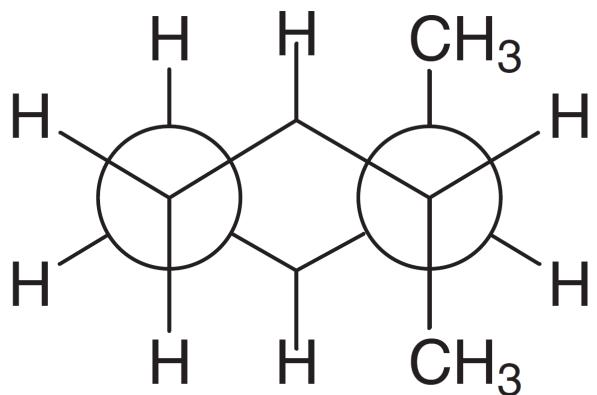


trans

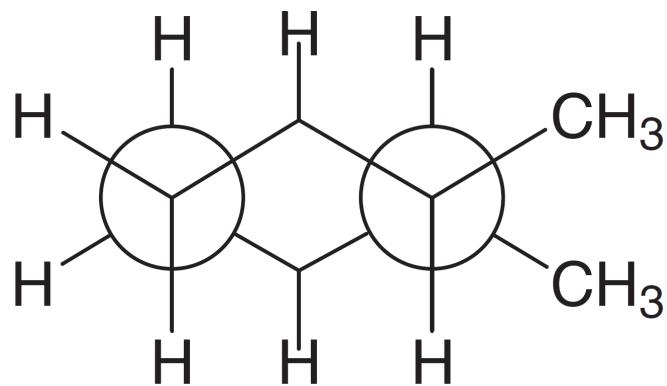
trans-1,2-dimethylcyclohexane



2.7 kcal/mol more stable

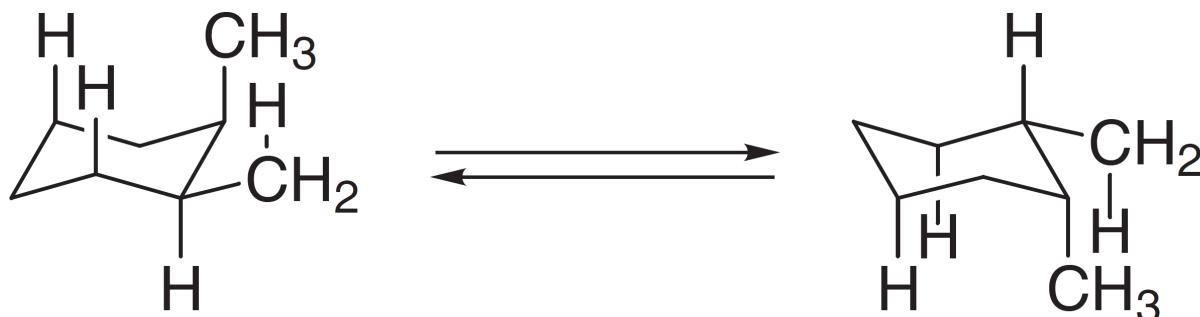


$$4 \times (\text{gauche interaction}) \\ 4 \times (0.9 \text{ kcal}) = 3.6 \text{ kcal}$$

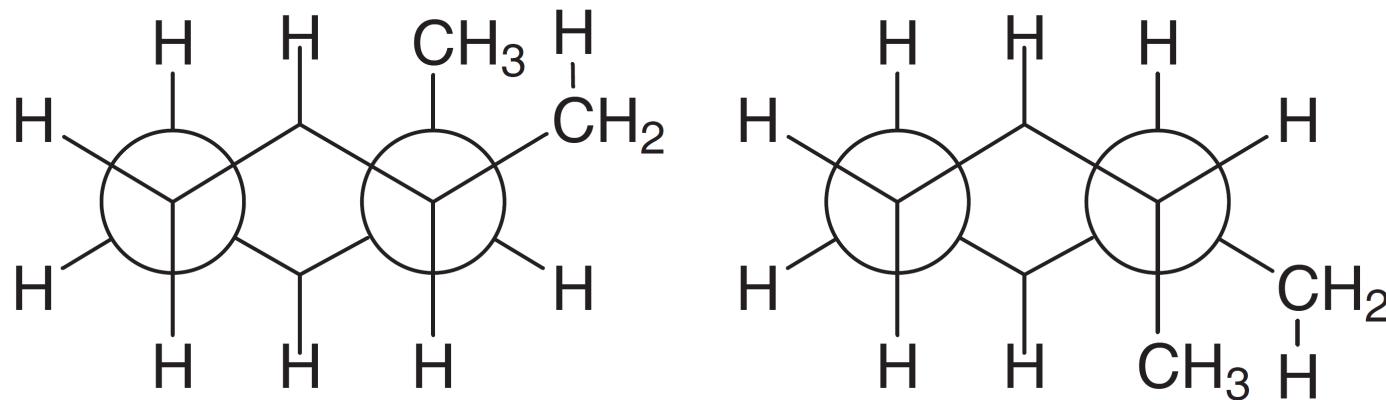


$$1 \times (\text{gauche interaction}) \\ 1 \times (0.9 \text{ kcal}) = 0.9 \text{ kcal}$$

cis-1,2-dimethylcyclohexane



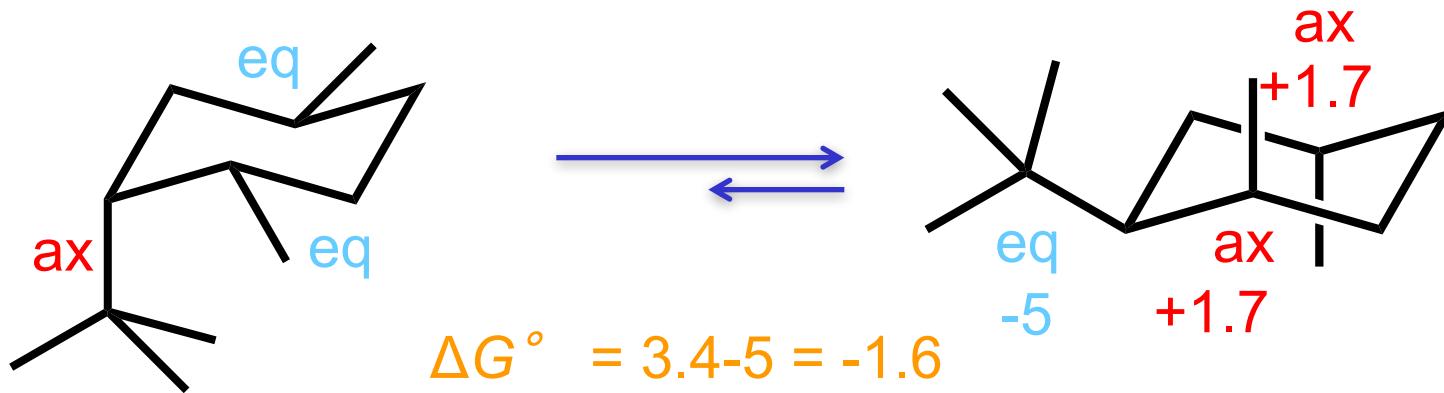
$$\Delta E = 0 \text{ kcal/mol}$$



$$3 \times (\text{gauche interaction}) \\ 3 \times (0.9 \text{ kcal}) = 2.7 \text{ kcal}$$

$$3 \times (\text{gauche interaction}) \\ 3 \times (0.9 \text{ kcal}) = 2.7 \text{ kcal}$$

The largest group often biases one conformation

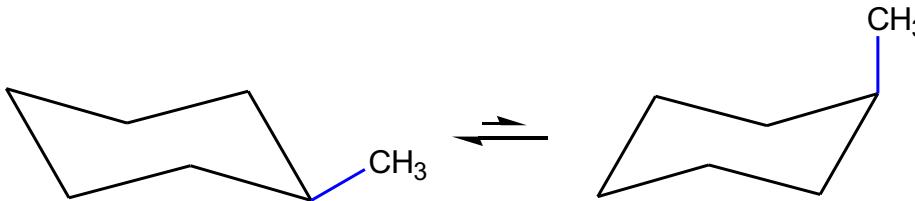


**Conformation of t-butylcyclohexane is said to be
BIASED**

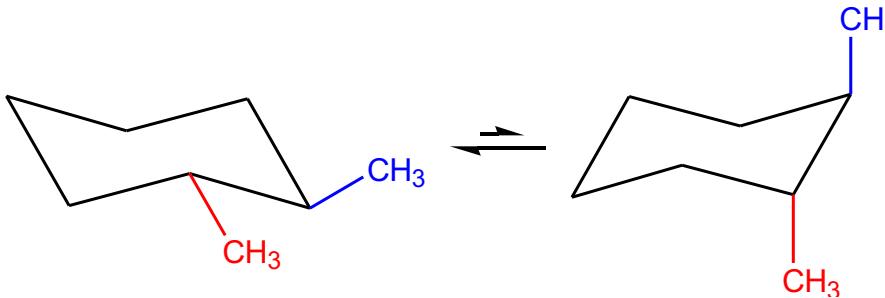
but
NOT LOCKED

Points to remember while ring-inversion is done

(i) Groups which are above the avg. plane would continue to be above the avg. plane even after ring flipping



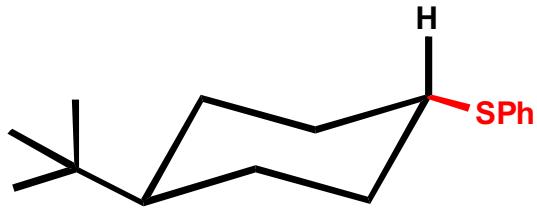
(ii) A *cis*-isomer would remain as *cis*-isomer, so is *trans*



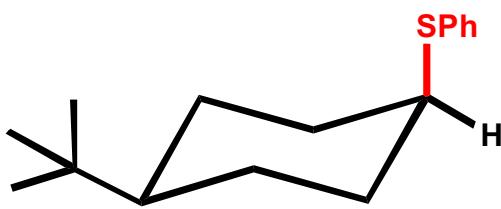
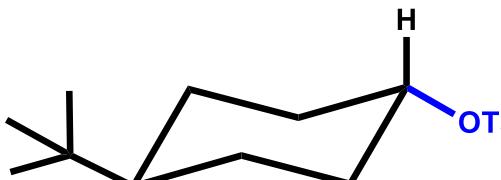
Conformational Features and Chemical Reactivity

Reactions of axial and equatorial substituents could be very different!

cis



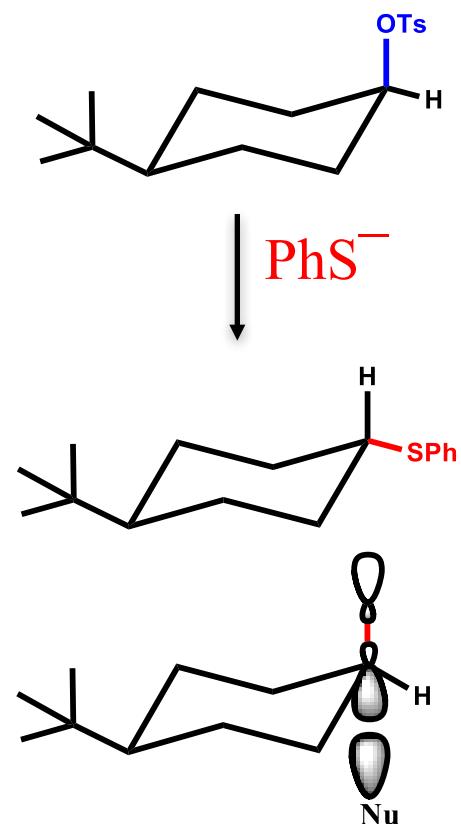
trans



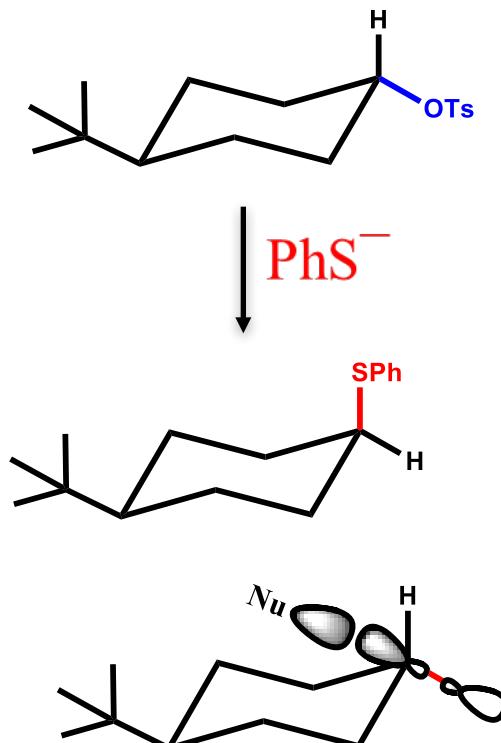
cis-compound reacts 31 times faster!!

Selectivity in nucleophilic substitution reactions

The reaction is due to the interaction between *filled orbital* of the nucleophile with the *unfilled σ^* orbital* of the C-L bond (where L is the leaving group)



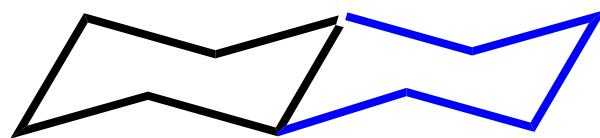
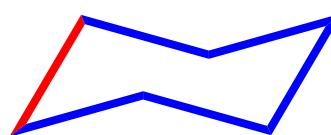
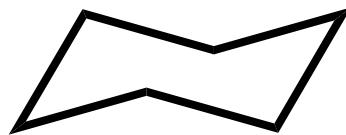
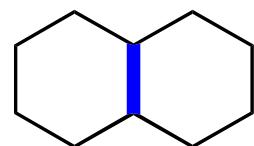
favored attack



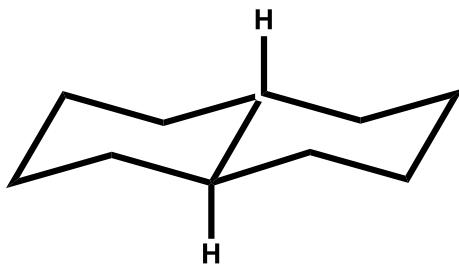
hindered attack

Fused ring compounds - Decalins

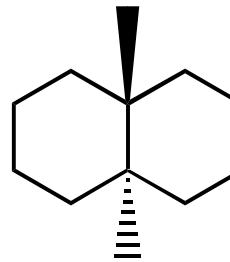
Fused cyclohexane rings which share a common C-C bond



Depending on the orientation of the hydrogen atoms at the ring junction there are two stereoisomers for decalins



***trans*-decalin**

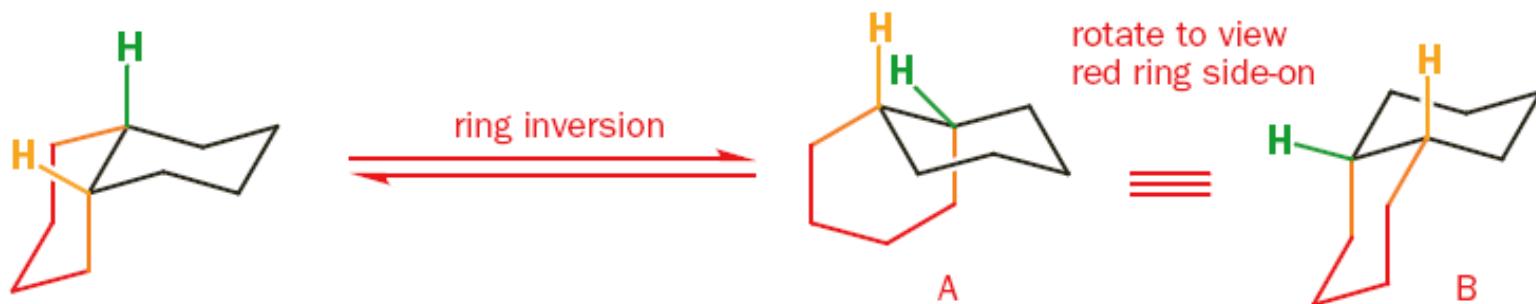


***trans*-decalins are conformationally LOCKED** as they cannot undergo ring flipping.

Cis - Decalins

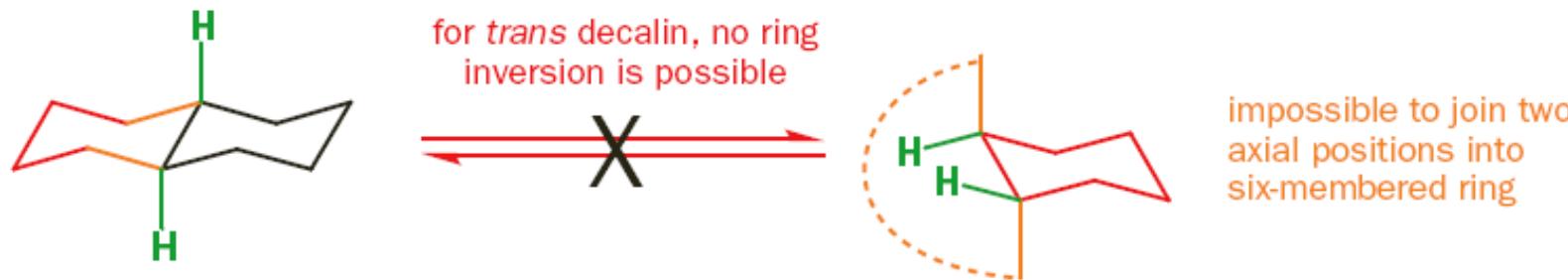
Cis-decalins are **conformationally flexible** and can undergo ring flipping

ring inversion of *cis*-decalin



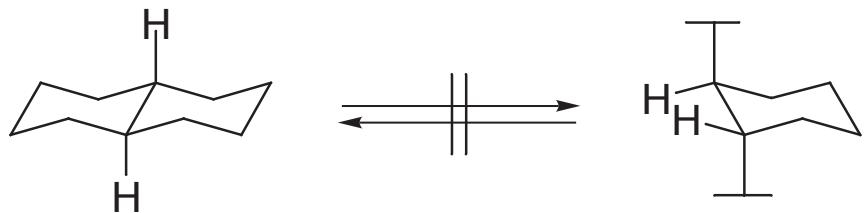
after ring inversion,
green H is equatorial on black ring
yellow H is axial on black ring

no ring inversion in *trans*-decalin

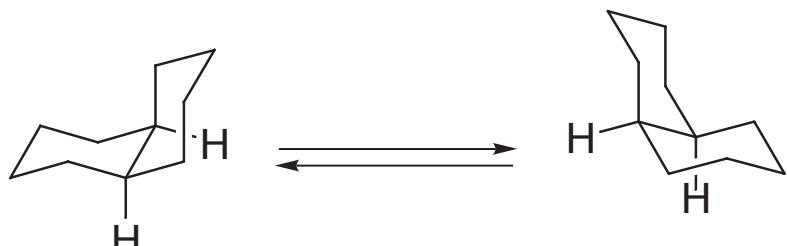


Cis- and trans-Decalins

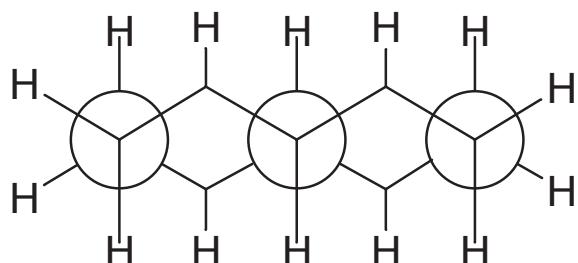
trans-decalin



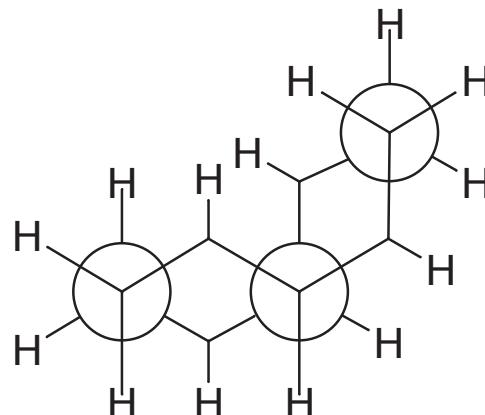
cis-decalin



two conformations equivalent



0.0 kcal



3 gauche interactions
3 × 0.9 kcal = 2.7 kcal

ΔE between *cis*- and *trans*-decalin = 2.7 kcal/mol