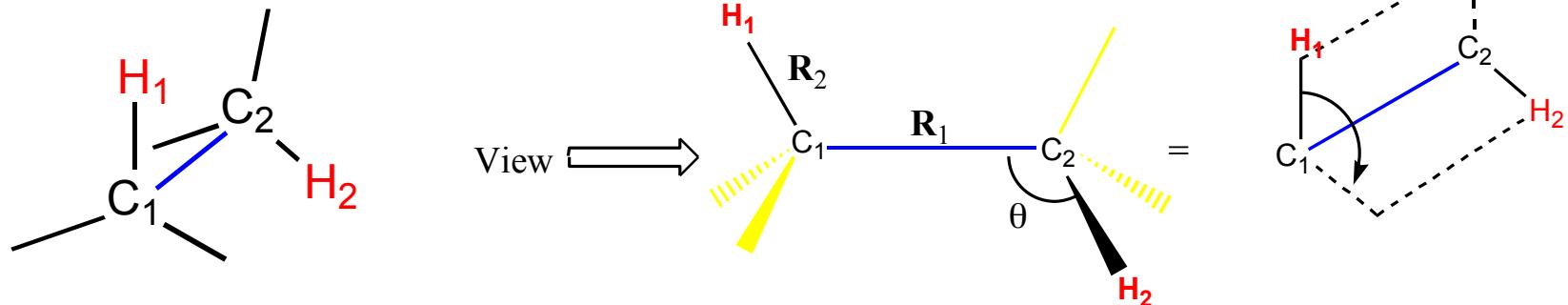


Conformational Analysis

Suvarn S. Kulkarni

Internal Coordinates



Bond length

between 2 atoms

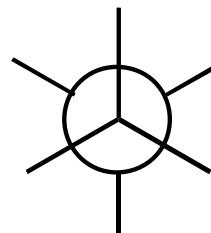
Bond angle

between 3 atoms

Dihedral angle

between 4 atoms

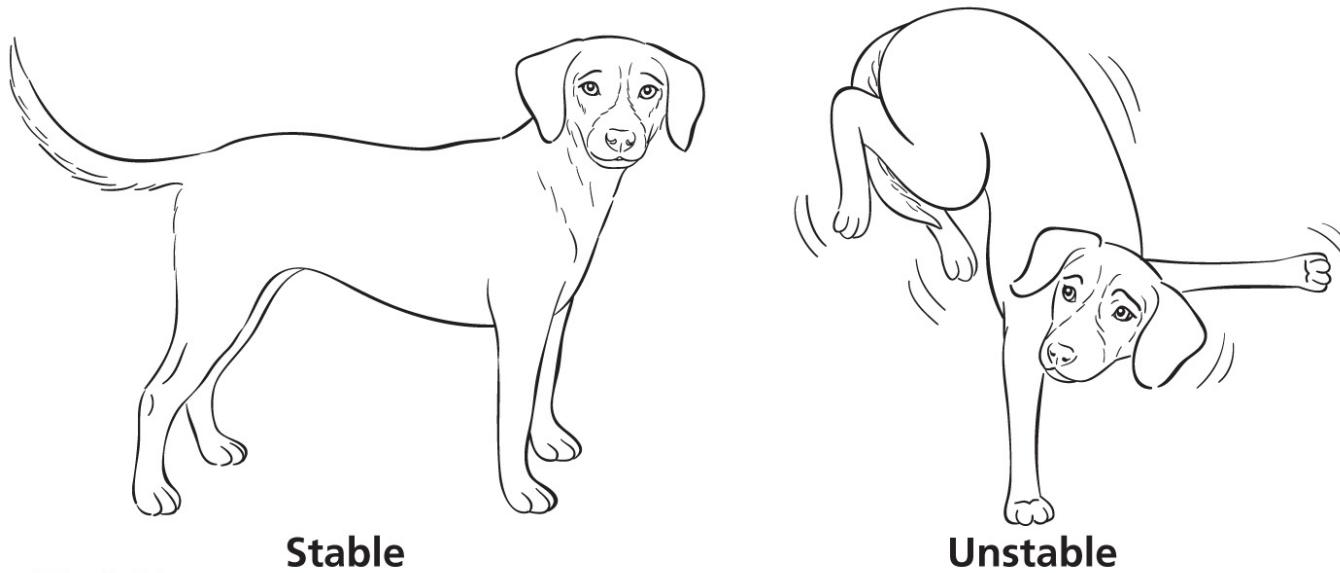
(torsion angle)



Melvin Newman
1908-1993²

Different Conformations

Different Conformations



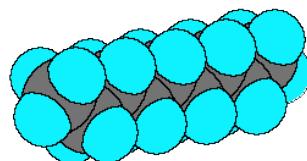
Compounds with different conformations (conformers) cannot be separated in most cases.

Conformational Analysis

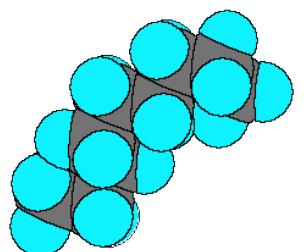
Conformational Analysis is the study of energetics of different conformers

Energy versus torsional angle (dihedral angle)

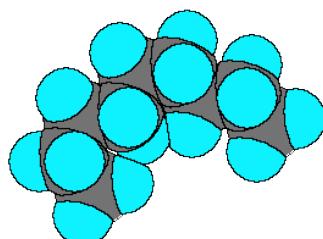
Conformers arise due to the possible free rotation around single bonds



n-octane



Refers to changes in
“Shape”

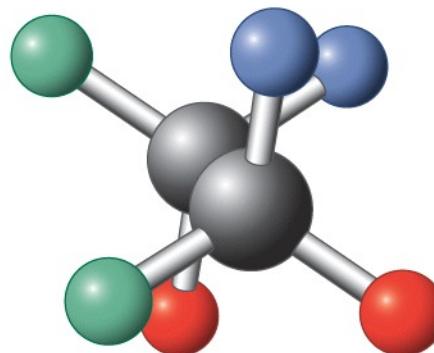
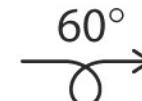
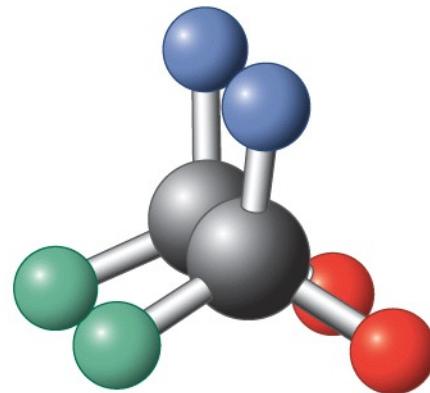
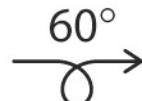
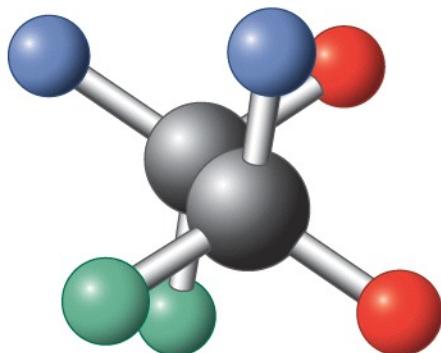
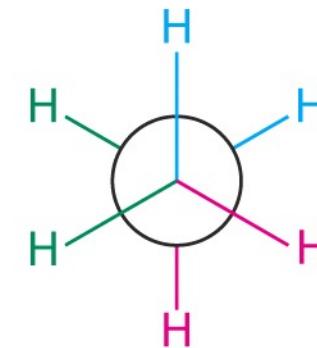
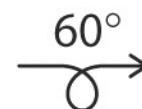
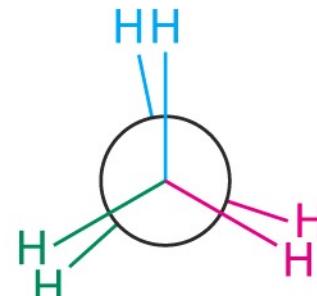
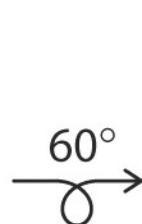
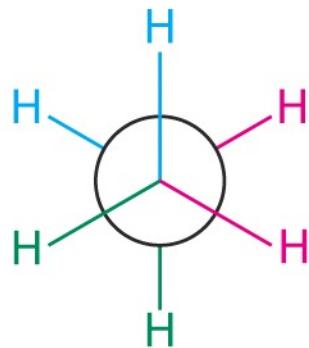


Conformational Analysis

- **Conformations** are the different shapes that a molecule can attain without breaking any covalent bonds.
- They differ from one another as the result of rotation at one or more single bond
- *Conformational analysis* is the process of relating conformation to the properties and reactivity of molecules.

Conformational Analysis, Example-1: Ethane

Ethane has two major conformers – Staggered and Eclipsed



Staggered

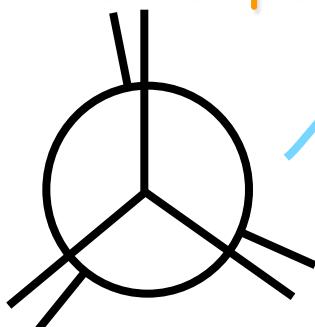
Eclipsed

Staggered

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

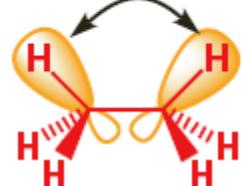
Ethane has barrier to rotation of ~ 3 kcal mol $^{-1}$. Barrier due to steric and electronic effects

Transition state
is eclipsed



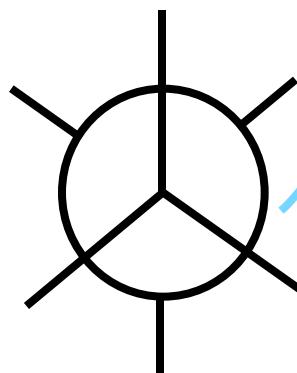
eclipsed:

filled orbitals repel



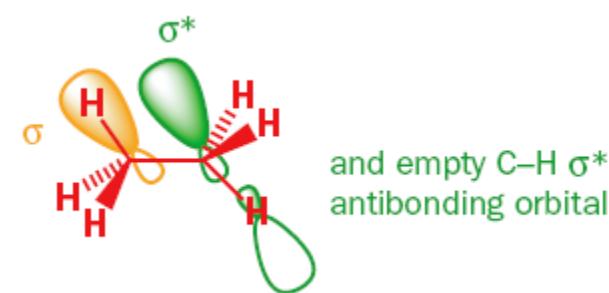
Orbital
stabilization

Most stable
rotamer is
staggered



staggered:

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



and empty C-H σ^*
antibonding orbital

dislocations, grain boundaries, and so on may be attempted. In addition, possible effects of contamination of MgB₂ with other elements, such as from the cladding metal, is of interest and needs to

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Rece
1. N
2. I
3. P
4. C
5. F
6. J
7. S
8. G

YOUNGER
FOR LONGER
How dietary restriction throws
the longevity switch

OCEAN BOXING
Hurricanes making waves
ANIMAL PERSONALITIES
Evolution of individuality
MATHEMATICAL ABILITY
The brain at work

NATURE
Research highlights
cond-mat/0103563 at xxx.lanl.gov (2001).

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4 (2001).
conductor
¹⁰B₂. *Phys.*
5 (2001).
conducting
03 (1987).
self-field.
Preprint

Hyperconjugation not steric repulsion leads to the staggered structure of ethane

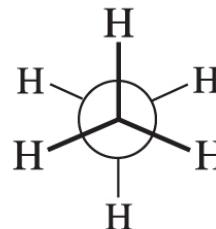
Vojislava Popovska & Lionel Goodman

Wright and Rieman Chemistry Laboratories, Rutgers University, New Brunswick, New Jersey 08903, USA

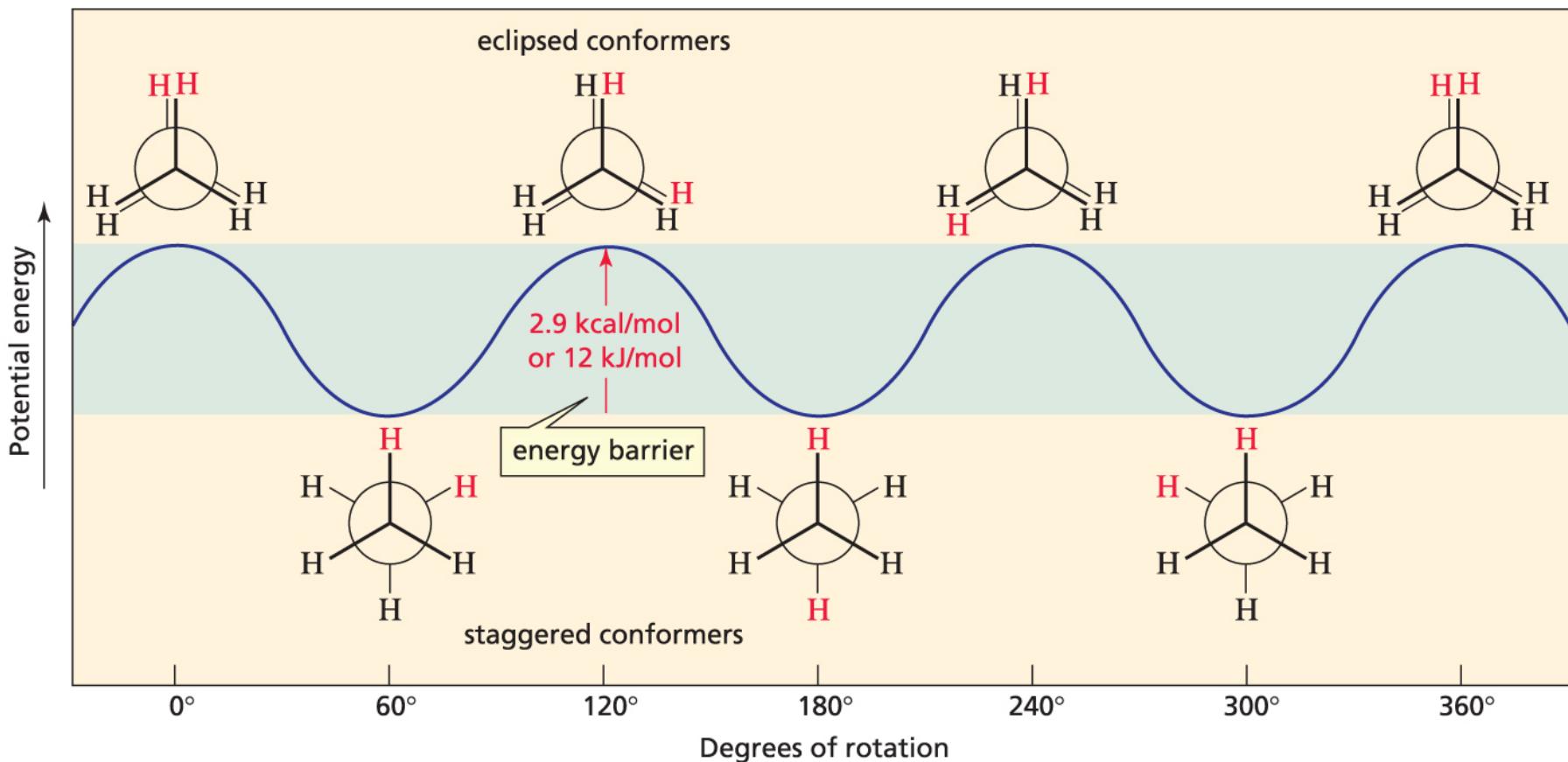
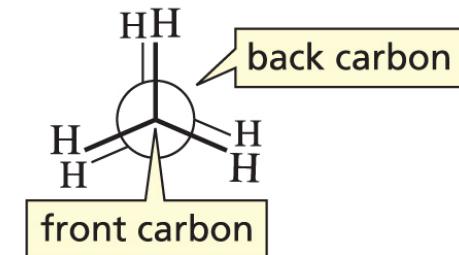
Many molecules can rotate internally around one or more of their bonds so that during a full 360° rotation, they will change between unstable and relatively stable conformations. Ethane is the textbook example of a molecule exhibiting such behaviour: as one of its two methyl (CH₃) groups rotates once around the central carbon–carbon bond, the molecule will alternate three times between an unstable eclipsed conformation and the preferred staggered conformation. This structural preference is usually attributed to steric effects^{1–7}; that is, while ethane rotates towards an eclipsed structure, the electrons in C–H bonds on the different C atoms are drawing closer to each other and therefore experience increased repulsion, introducing a rotation barrier that destabilizes the eclipsed structure^{8,9}. Stabilization of the staggered structure through rotation-induced weakening of the central C–C bond¹⁰ and hyperconjugation^{11,12} has been considered to be

Conformational Analysis, Example-1: Ethane

The Eclipsed conformer is 2.9 kcal/mol higher in energy than the staggered conformer

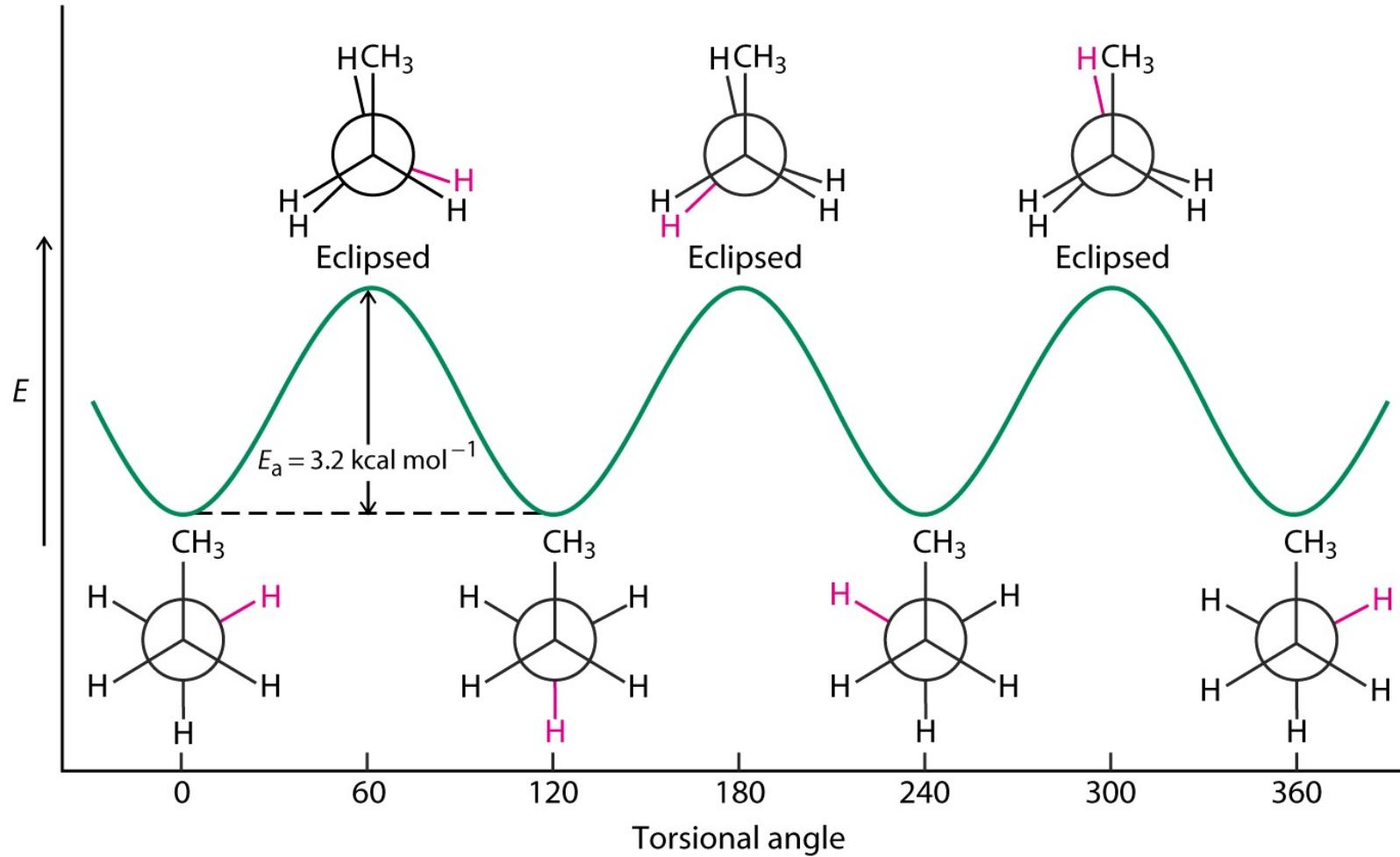


60°

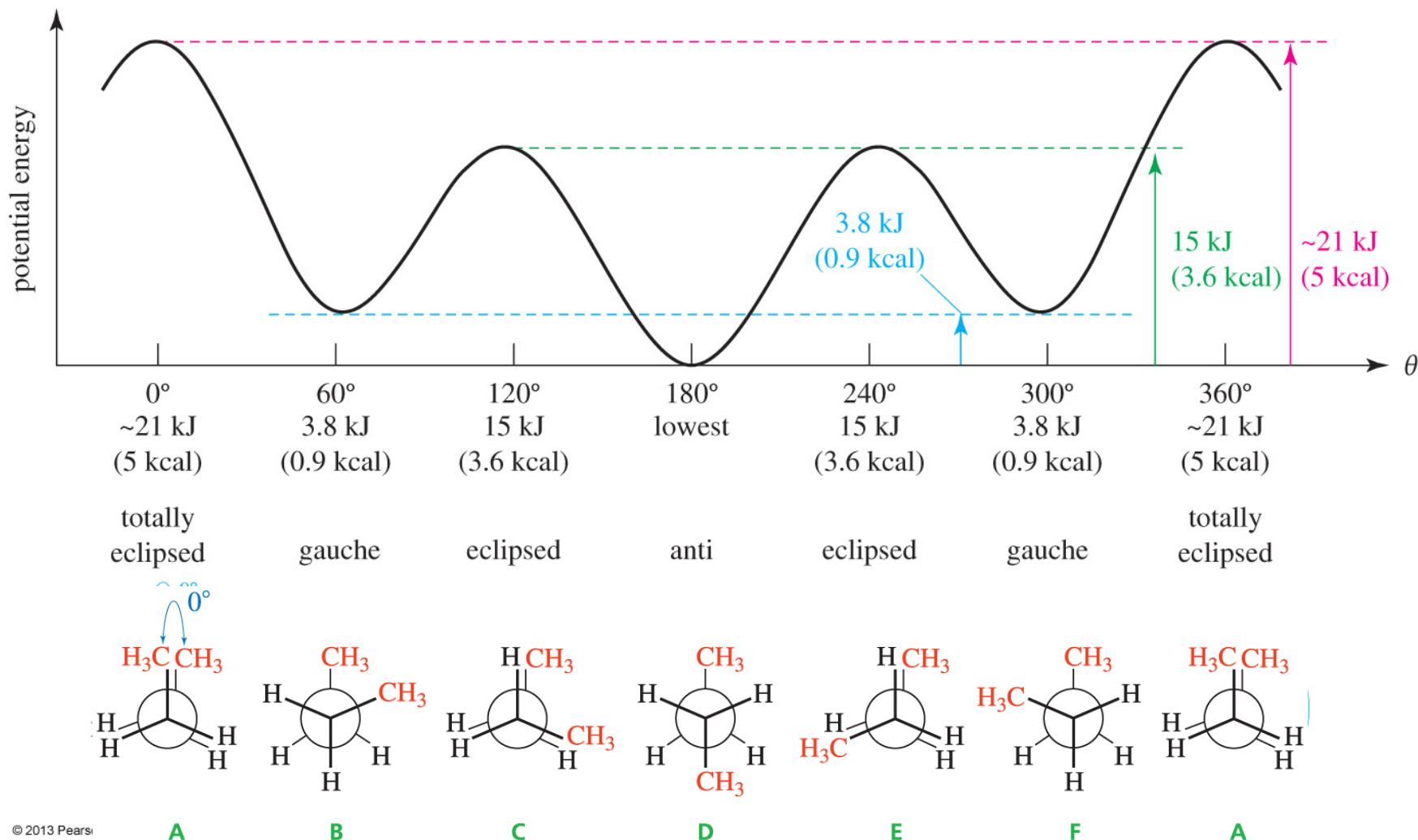


Conformational Analysis, Example-2: Propane

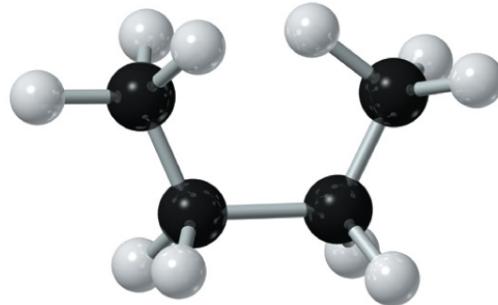
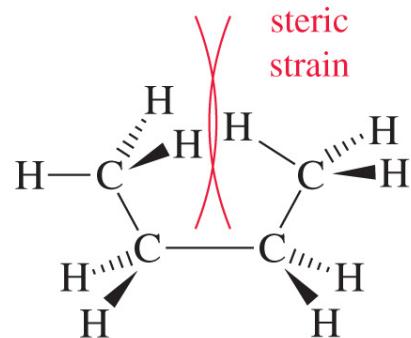
Methyl group increases the barrier



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



Steric Strain



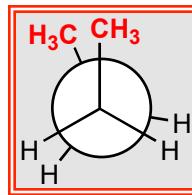
Totally eclipsed conformation of butane

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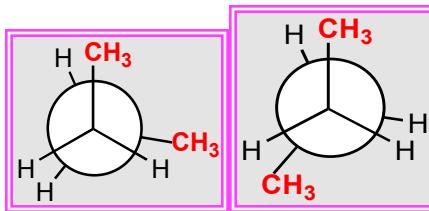
- The totally eclipsed conformation is higher in energy because it forces the two end methyl groups so close together that their electron clouds experience a strong repulsion.
- This kind of interference between two bulky groups is called *steric strain* or *steric hindrance*.

Conformers and Conformations

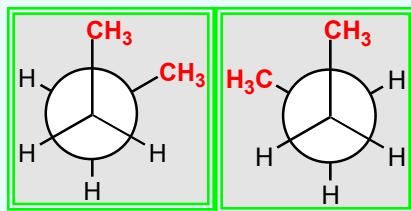
D



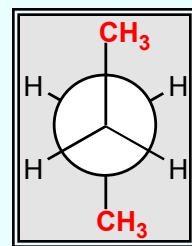
B



C



A



4.9

Conformations: Can take any value of θ , includes maxima as well

3.6

Infinite number of conformations!
Can not be isolated

0.9

Conformers: Minima on the Potential Energy Curve

0.0

Could be isolated

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

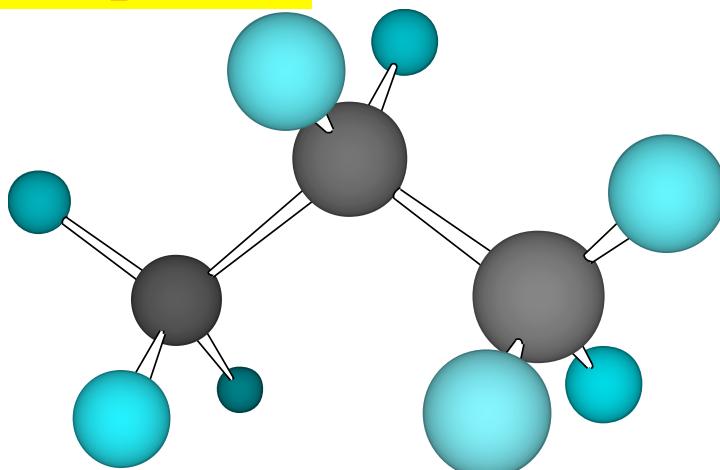
Torsional Strain: Extra energy of eclipsed conformation arising due to the repulsion between bonding electrons of one substituent with that of the other as they pass close to each other

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

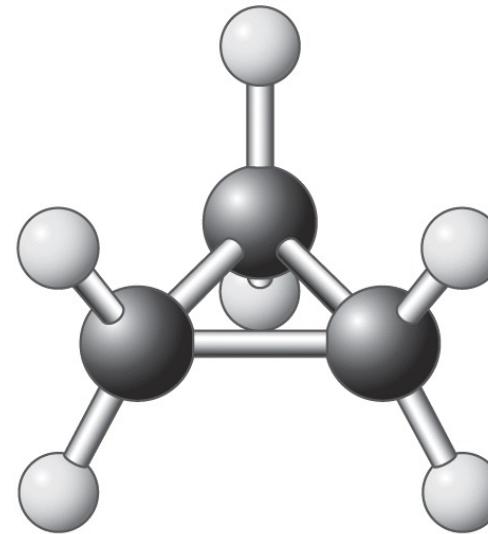
(all angles are nearly tetrahedral)

Steric strain: None

(Fully staggered conformer)

Cyclopropane suffers from angle strain and torsional strain

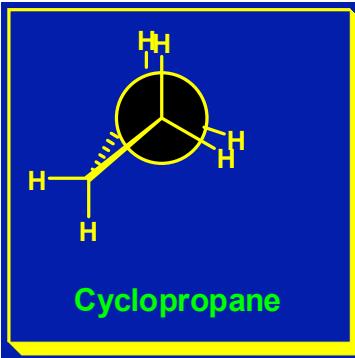
Cyclopropane



Deviation of 49.5° per carbon

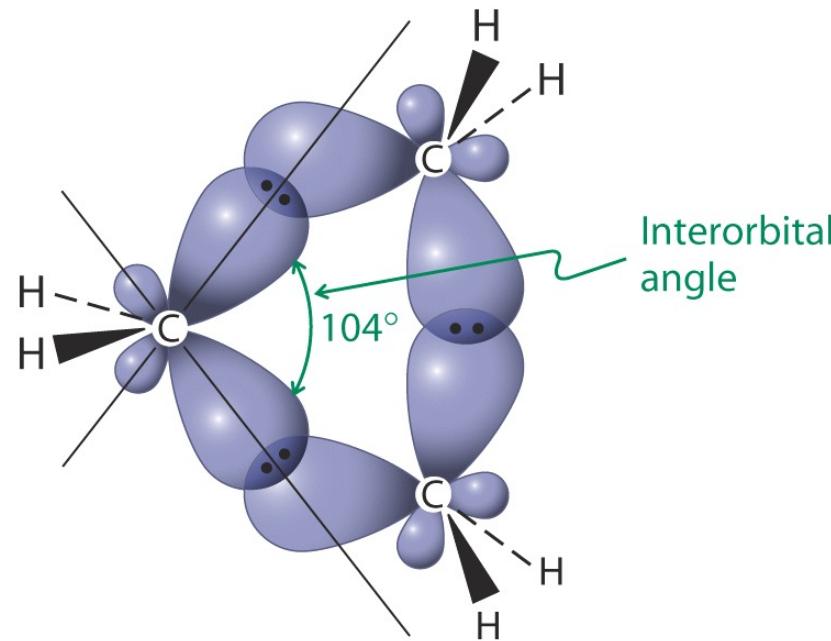
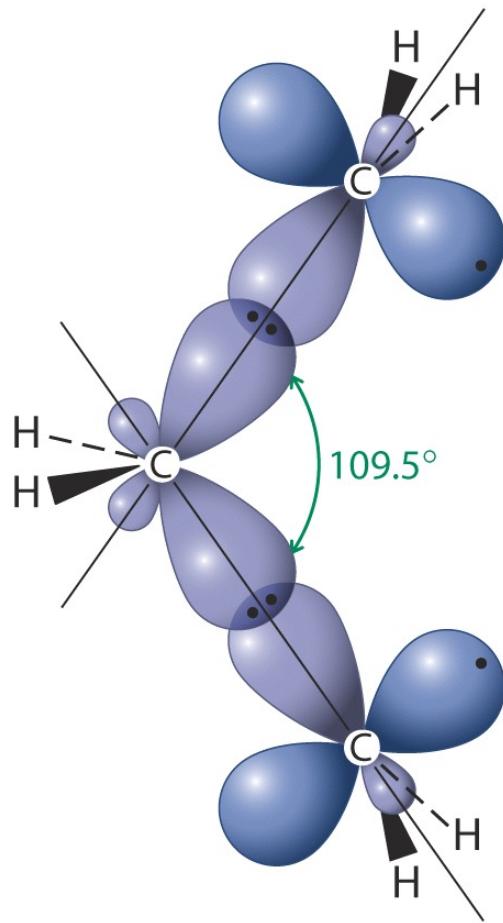
Torsional strain: (C-H) ... (C-H) eclipsing interactions

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

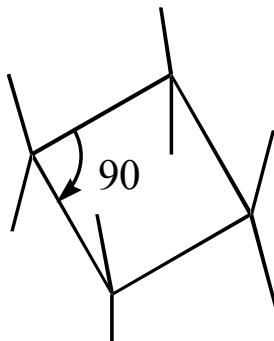


Small Ring Compounds – (1) cyclopropane

Strain relief through the formation of “banana” bonds

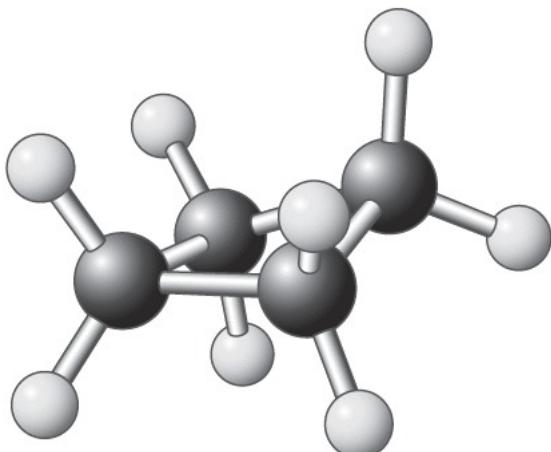


Small Ring Compounds – (2) cyclobutane



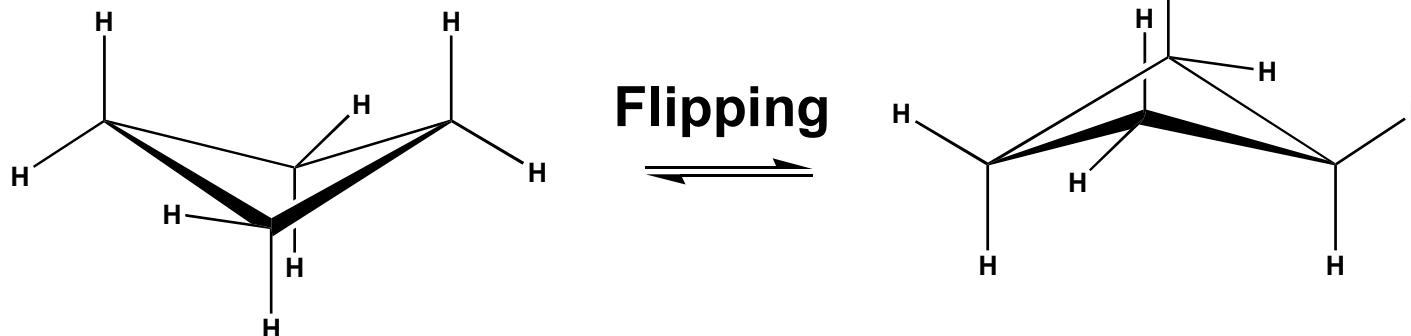
Planar? Problems are: **Angle strain** plus
severe **torsional strain**

Compromise is



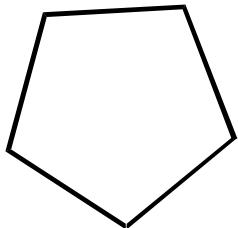
Ring puckering

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



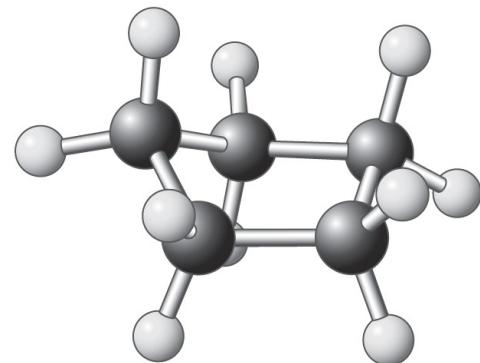
Cyclobutane has a '**wing shaped**' or '**puckered**' conformer

Small Ring Compounds – (3) Cyclopentane



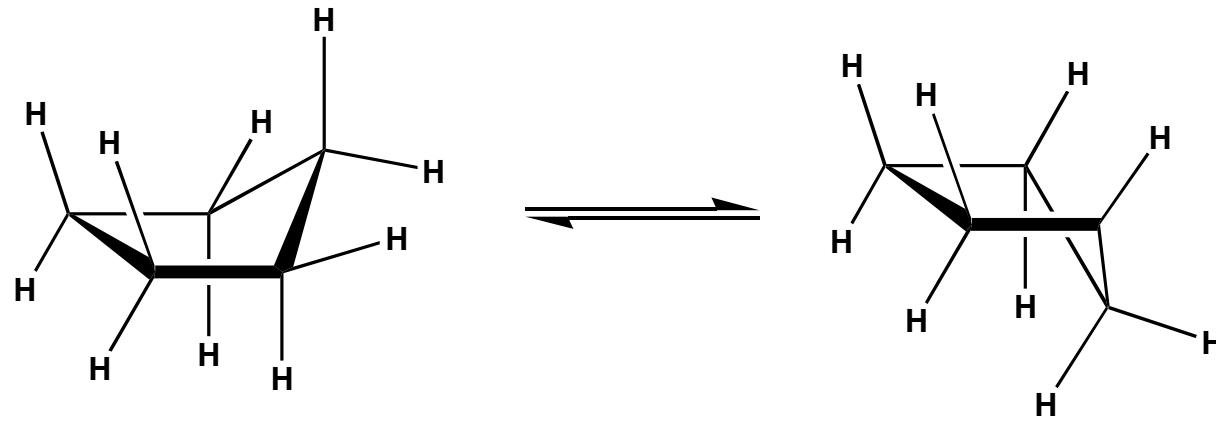
Planar? Though the angle strain is very little, there will be 10 eclipsing interactions!

Ring puckering



Relieves eclipsing interactions with only a slight increase in angle strain

Four coplanar carbon atoms



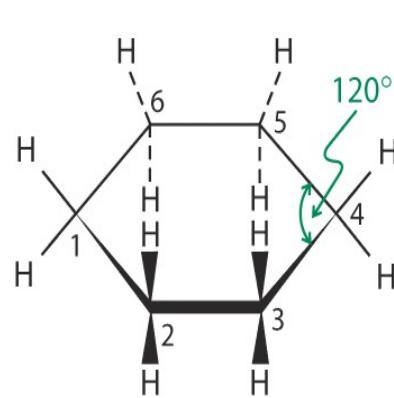
Cyclopentane has an ‘envelope’ conformer

Small Ring Compounds – (4) Cyclohexane

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

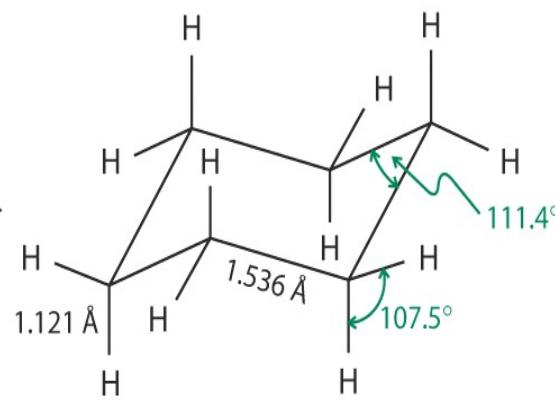
Both angle and torsional (eclipsing interactions) strains can be avoided by **ring puckering**.

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



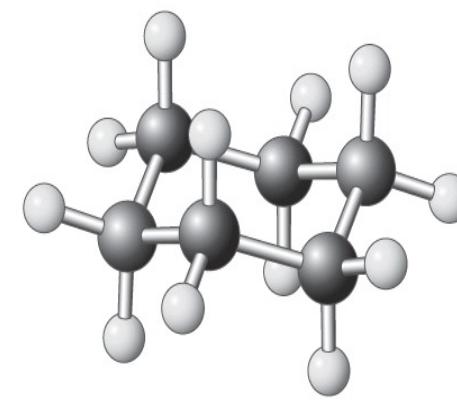
A

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



B

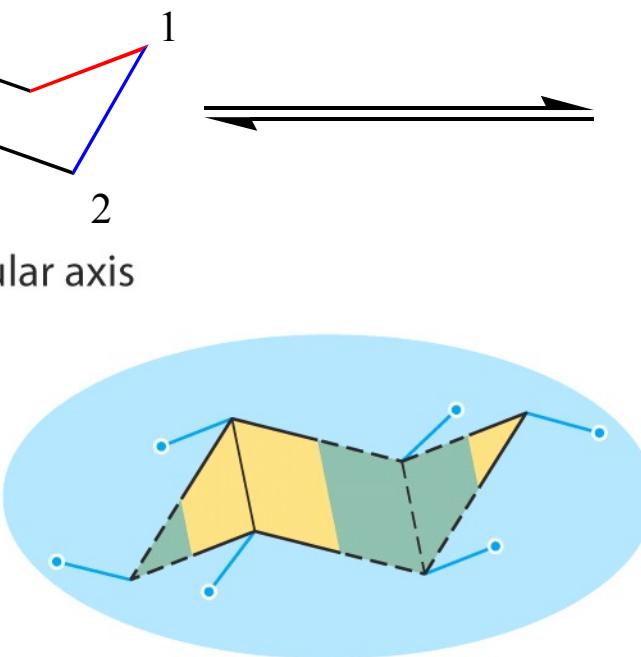
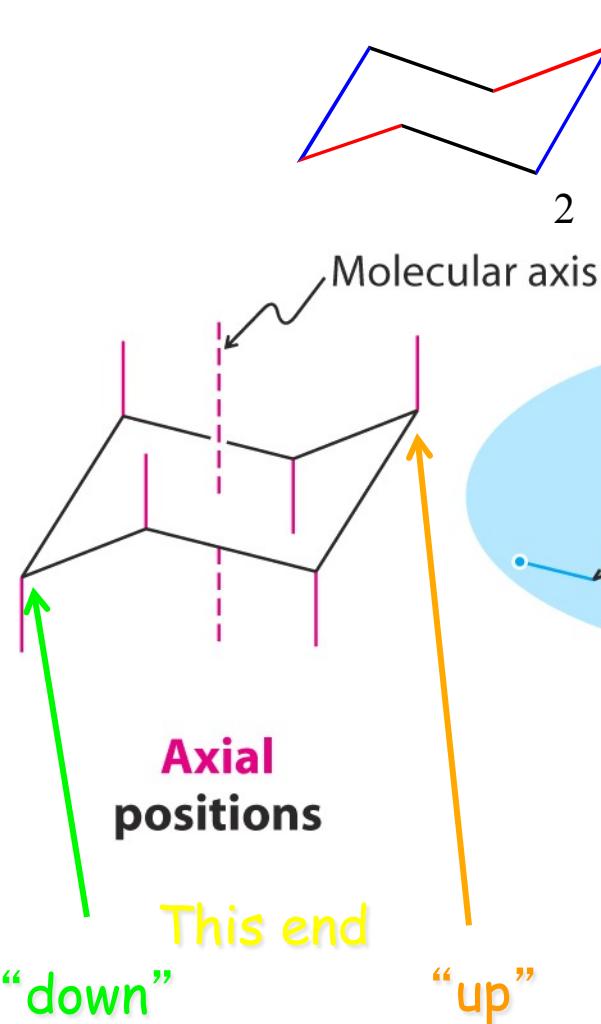
Chair cyclohexane
(Nearly tetrahedral bond angles;
no eclipsing hydrogens)



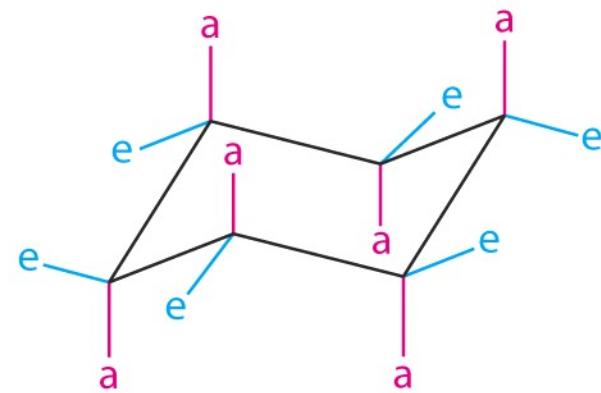
C



Drawing Cyclohexanes



Equatorial positions



Axial (a) and equatorial (e) positions

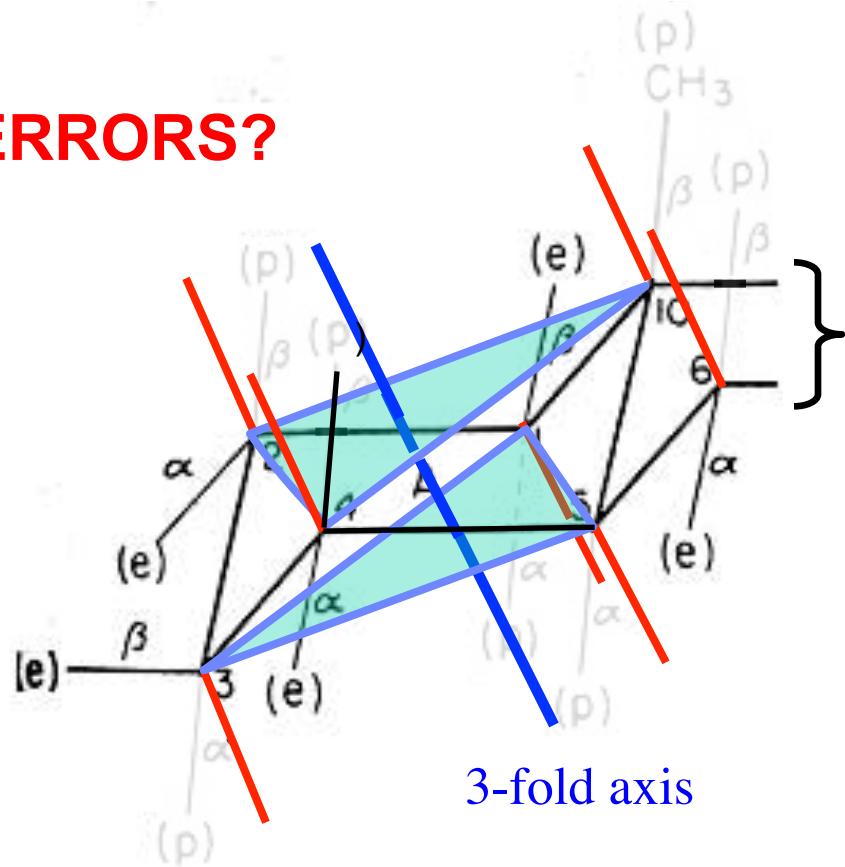
Tips:

Look for ‘parallel’ bonds
Every alternate bond

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?



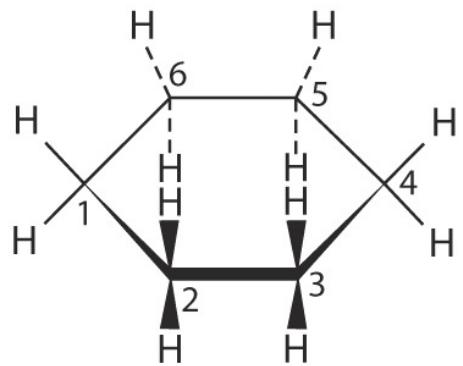
$\beta \Rightarrow$ “up” ; $\alpha \Rightarrow$ “down”
(for molecule in conventional orientation,
old-fashioned configuration notation, like *cis* / *trans*)

(e) “equatorial”

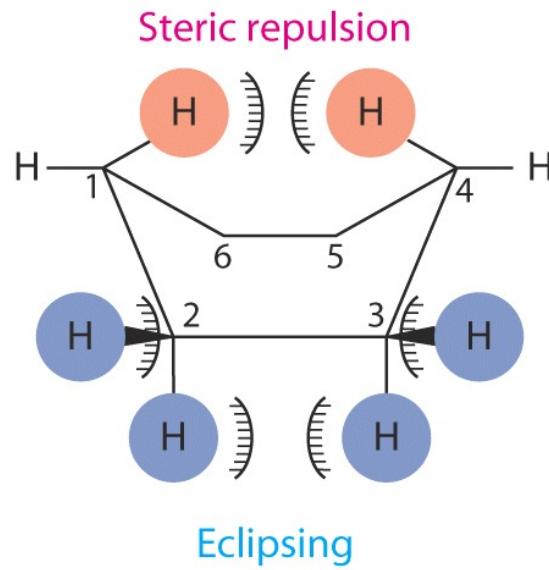
(p) “polar” (now axial)

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

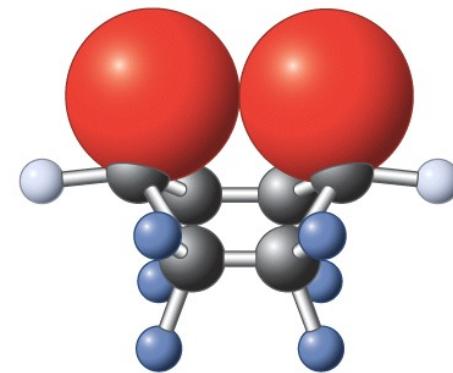
Boat conformer of cyclohexane is strained



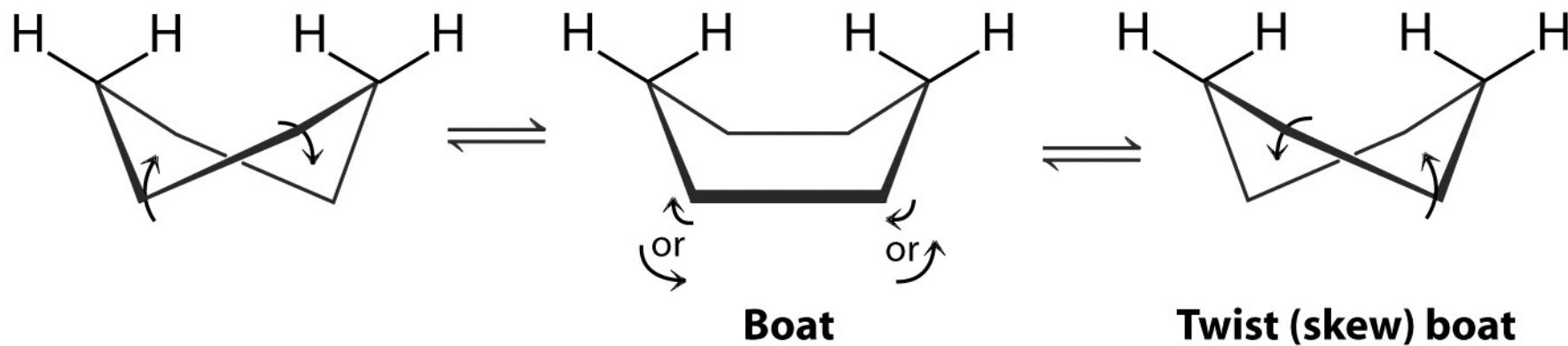
Planar cyclohexane



Boat cyclohexane



So the boat twists



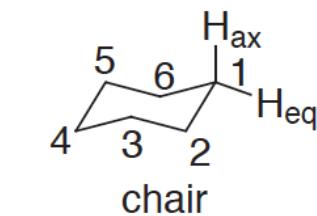
But this is only part of its mobility. The molecule “flips” from one chair to another chair form.

Animations

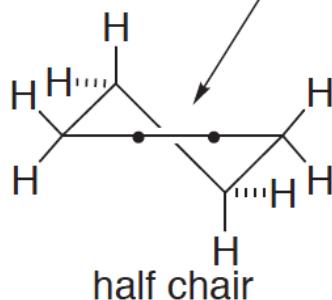
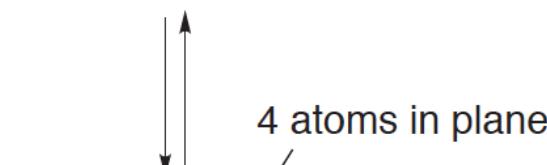
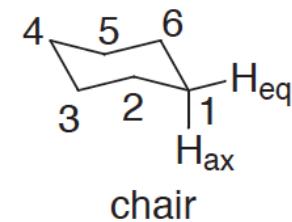
<http://www.chemtube3d.com/>

B. Cyclohexane and Substituted Cyclohexanes, A Values (ΔG°)

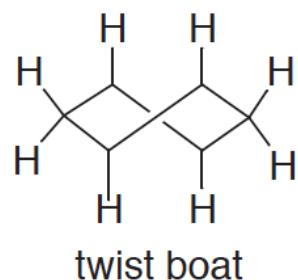
1. Cyclohexane



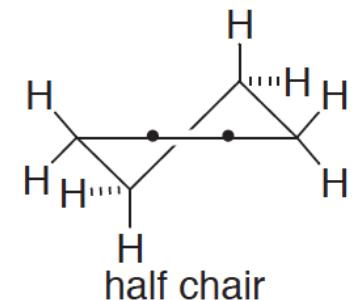
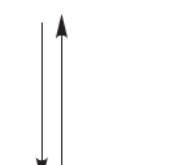
$$E_a = 10.8 \text{ Kcal/mol}$$



$$\text{rel E} = 10.8 \text{ Kcal/mol}$$

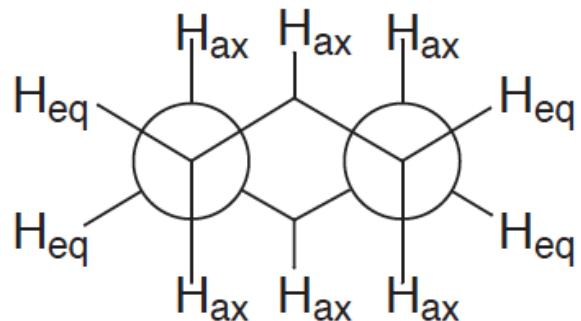


$$\text{Rel E} = 5.5 \text{ Kcal/mol}$$



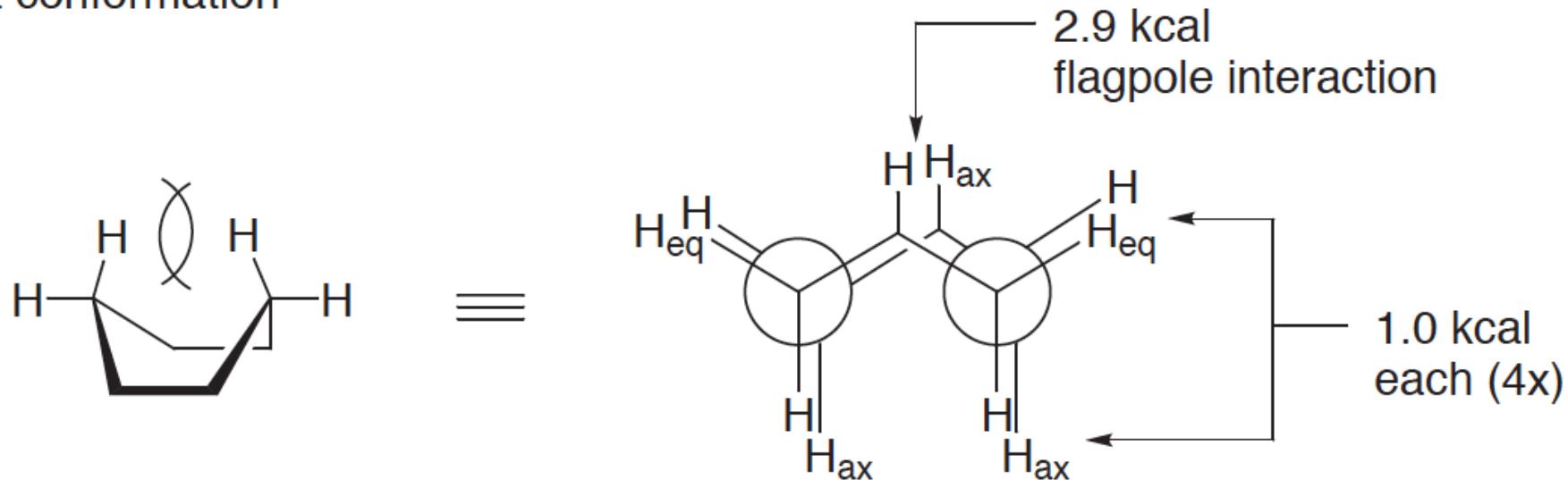
$$\text{rel E} = 10.8 \text{ Kcal/mol}$$

- Chair conformation (all bonds staggered)



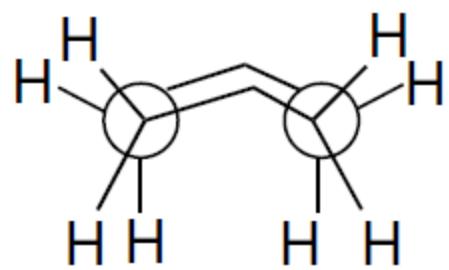
- Rapid interconversion at 25 °C ($E_a = 10 \text{ kcal/mol}$, 20 kcal/mol available at 25 °C).
- H_{ax} and H_{eq} are indistinguishable by ^1H NMR at 25 °C.
- At temperatures < –70 °C, H_{eq} and H_{ax} become distinct in ^1H NMR.

- Boat conformation

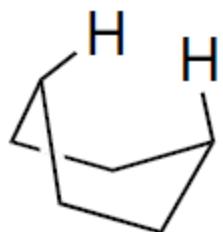


- Rel E = 6.9 kcal, not local minimum on energy surface.
- More stable boat can be obtained by twisting (relieves flagpole interaction somewhat).
- Twist boat conformation (rel E = 5.5 kcal) does represent an energy minimum.
- The boat conformation becomes realistic if flagpole interactions are removed, i.e.

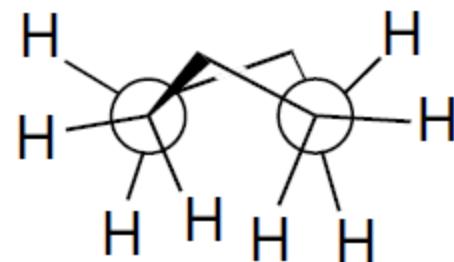




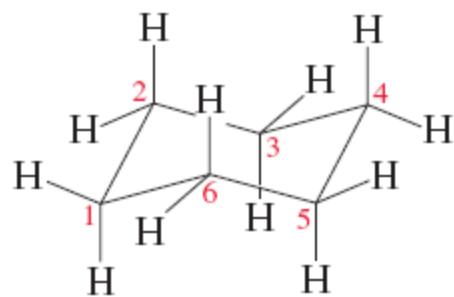
eclipsing in boat conformation



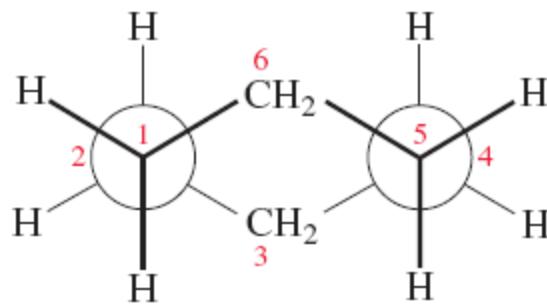
flagpole interaction in boat conformation



partial relief of eclipsing in twist conformation



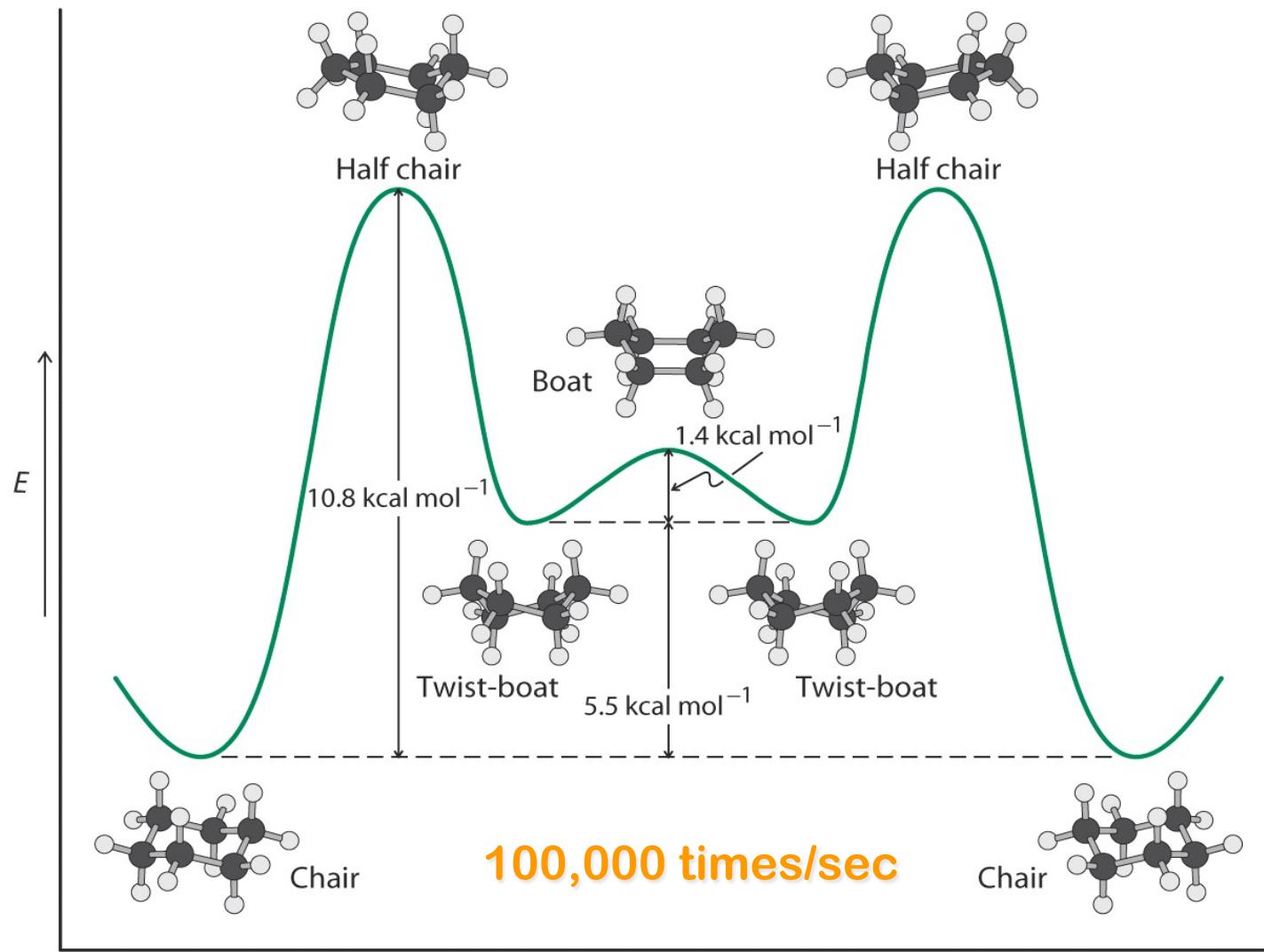
chair conformer of cyclohexane



Newman projection of the chair conformation

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

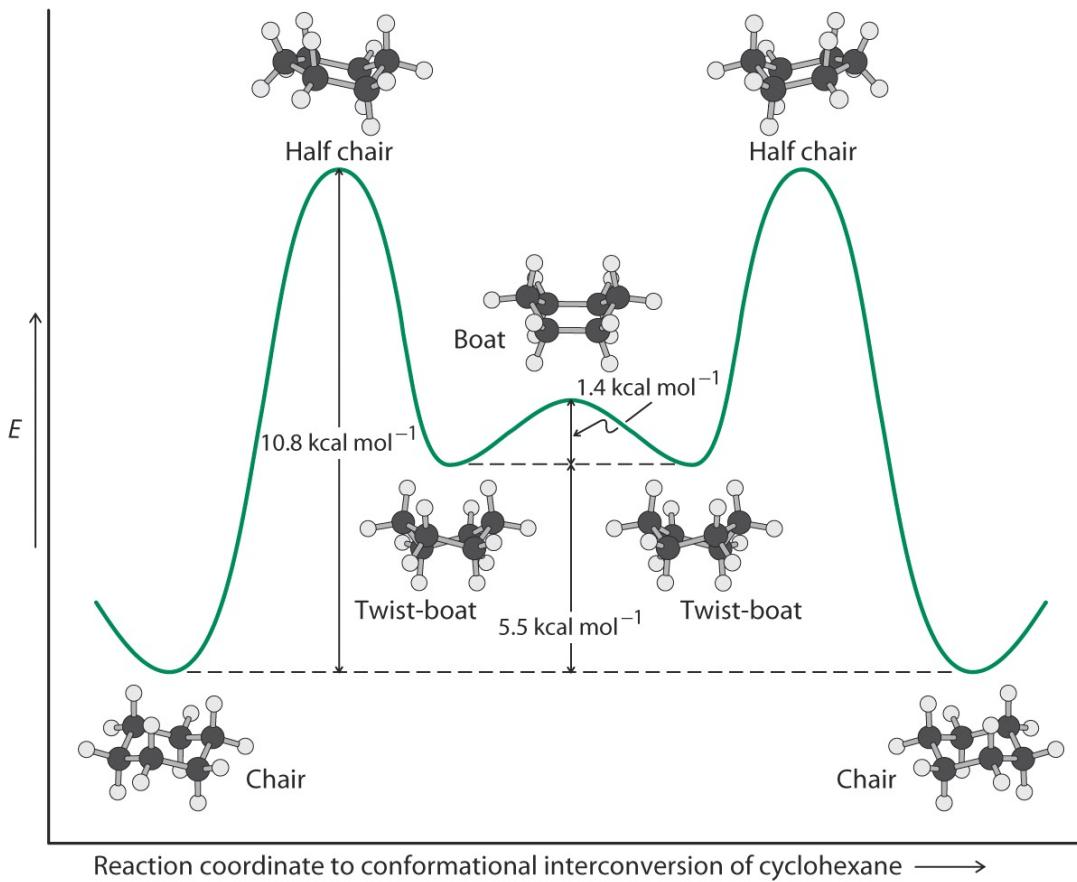


A grossly approximate comparison

Molecules ‘move around’ on potential energy surfaces



Ring Inversion or Ring Flipping in Cyclohexane



Summary

Maxima (1) Half-chair (2) Boat

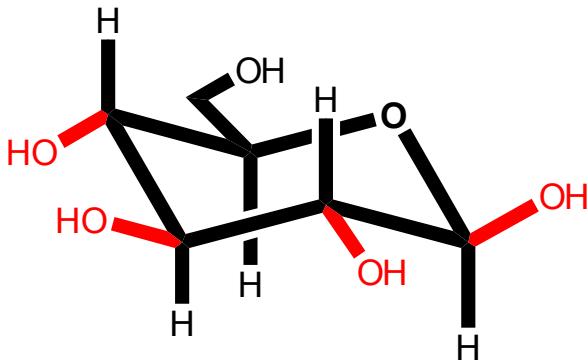
Minima (1) Chair (2) Twist-boat

Examples of chair conformers – (D)-Glucose

β -D-(+)-glucose

Equatorial Region

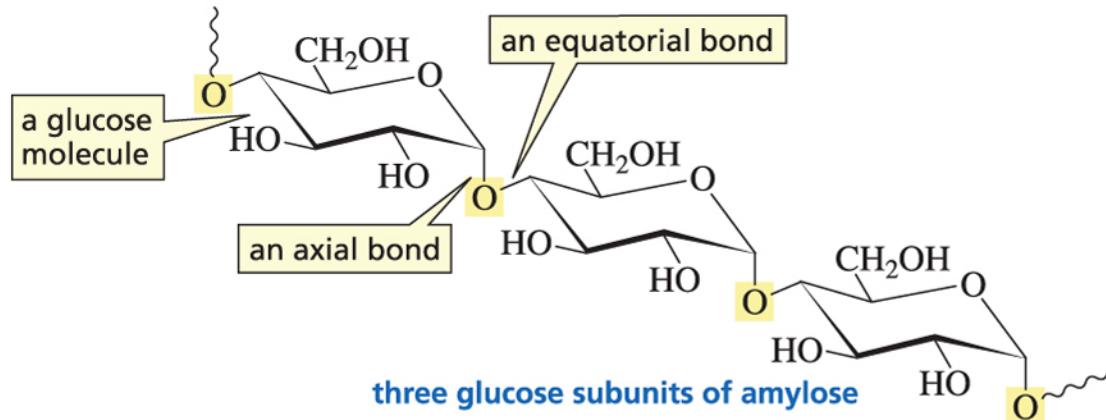
Polar face



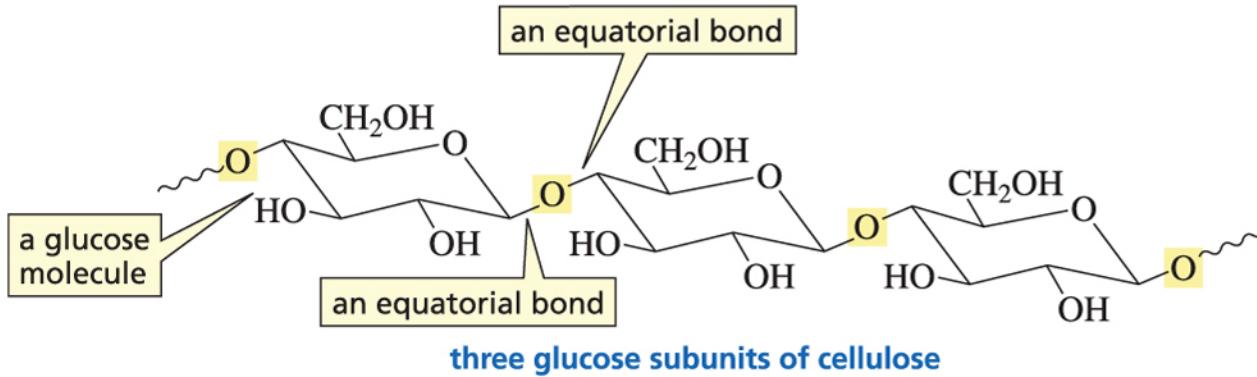
Axial Region

Apolar face

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

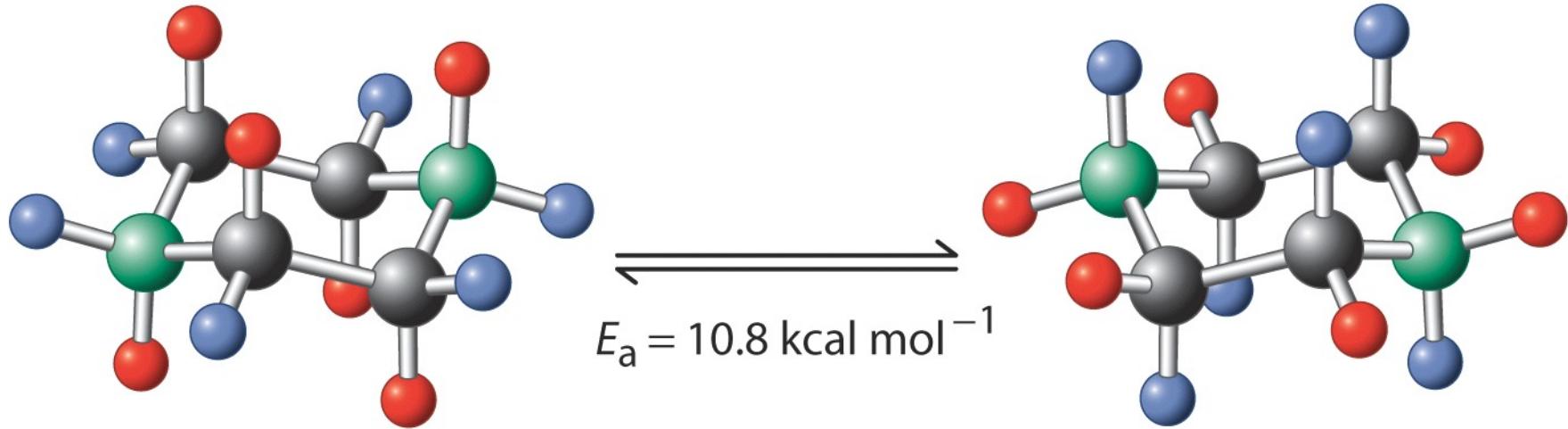


foods rich in starch



cotton plant and cotton towel

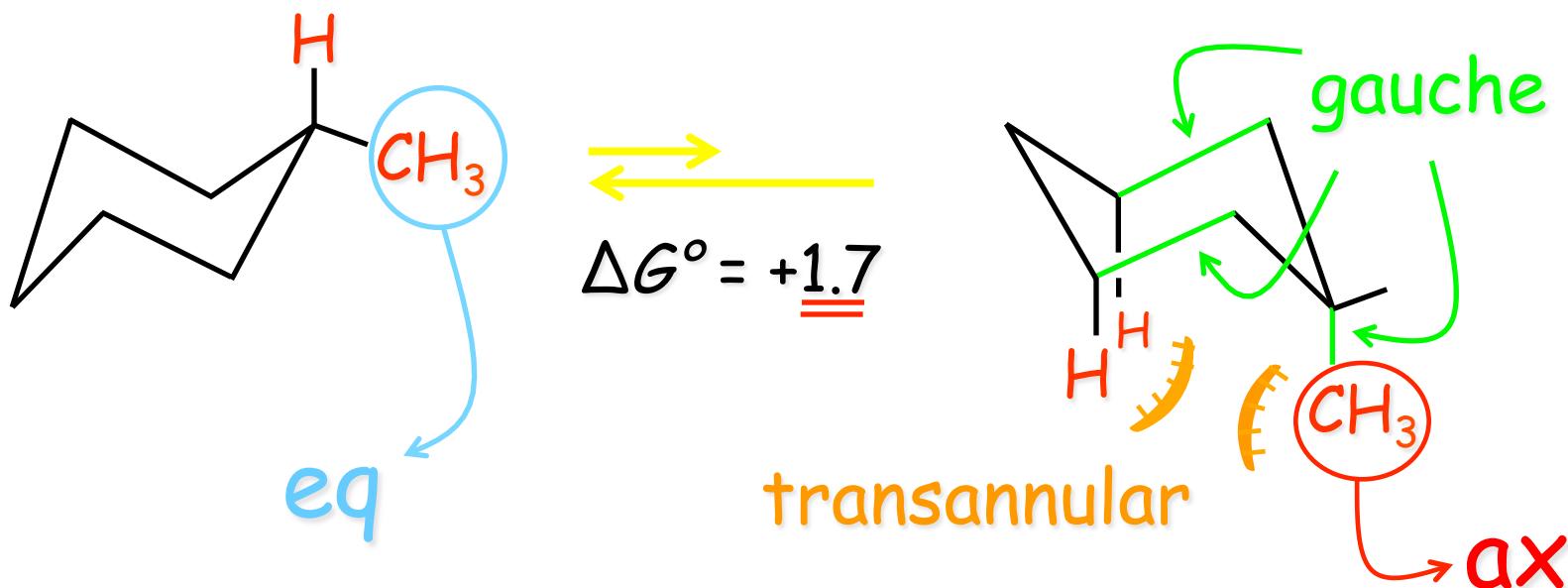
The Chair-Chair Flip Causes Equatorial-Axial Exchange



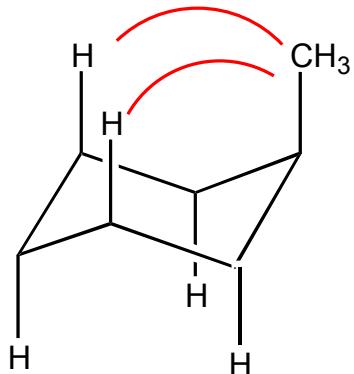
The two structures are the same. However, what happens in substituted cyclohexanes?

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

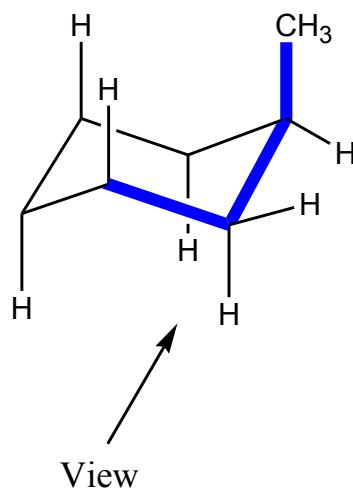
Conformational Analysis: Interplay of energetics of ax-eq substituents. Example: Methylcyclohexane



Why Axial –R group is disfavored?

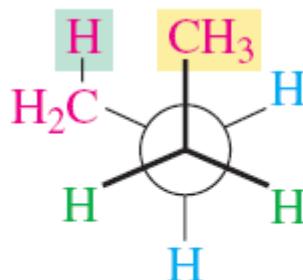
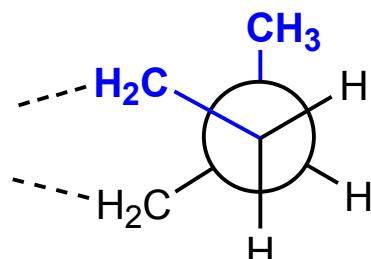


1. van der Waals repulsion between the axial methyl group and the axial hydrogens at C3 and C5 is known as **1,3-diaxial interactions**

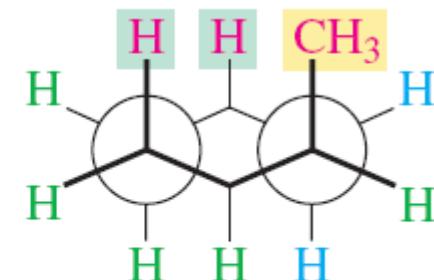


CH_3 is gauche to two C-C bonds

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



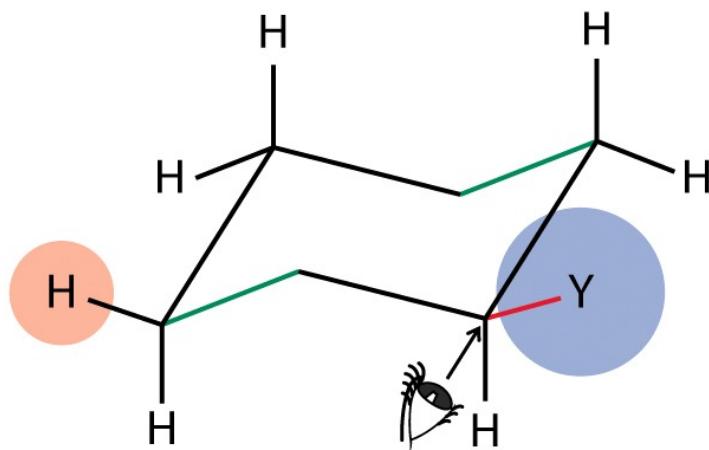
gauche butane



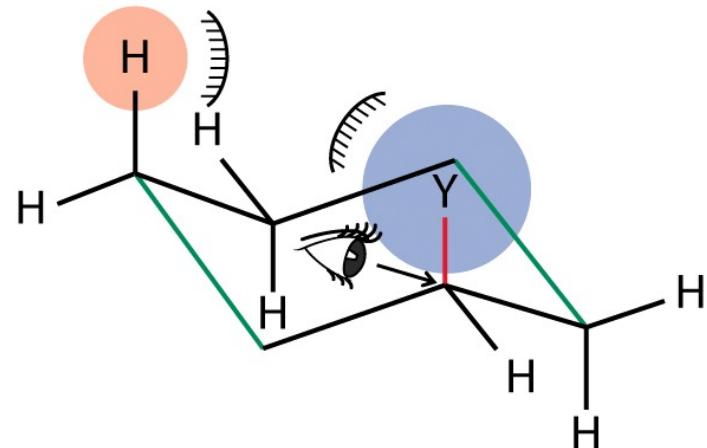
axial
methylcyclohexane

Axial-Equatorial Conformers

Equatorial Y

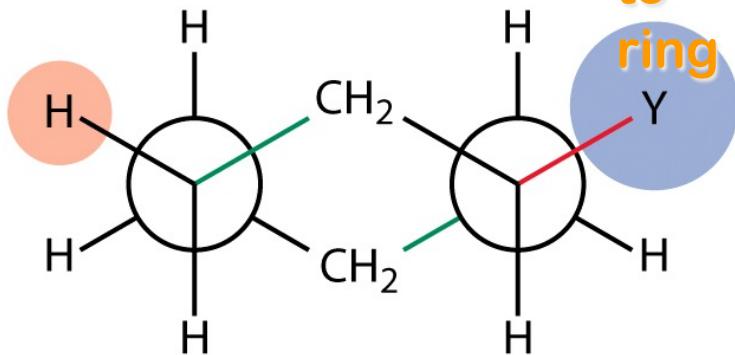


Axial Y

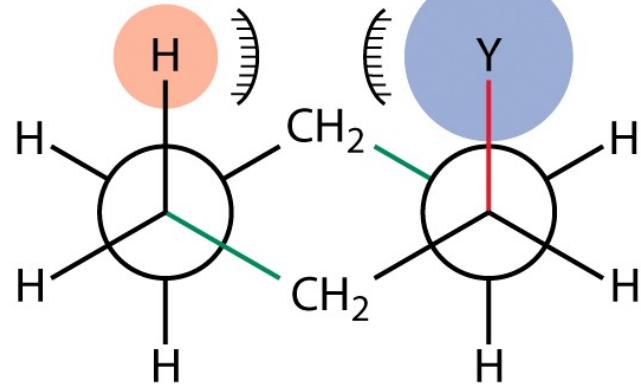


|||

Anti
to
ring



|||
Gauche
to ring



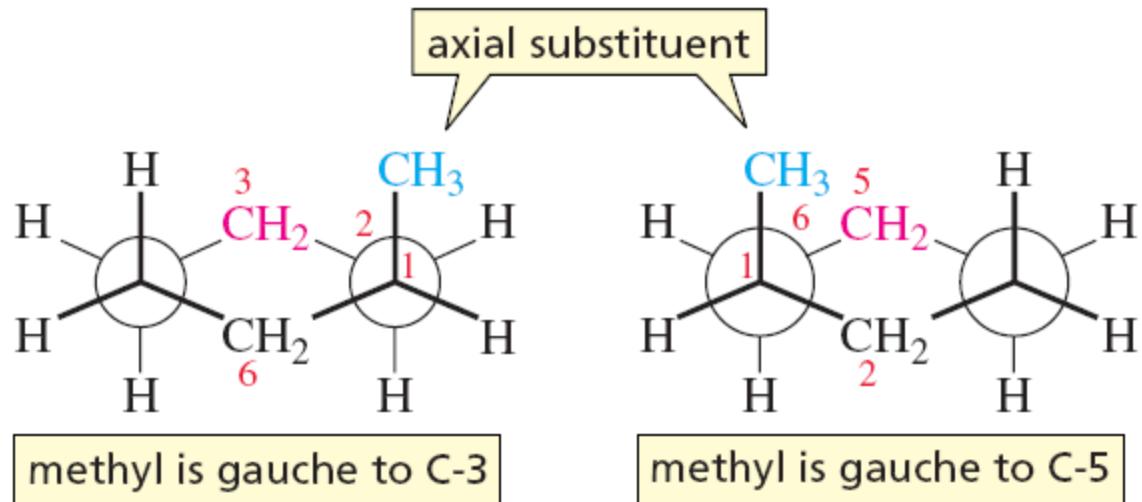
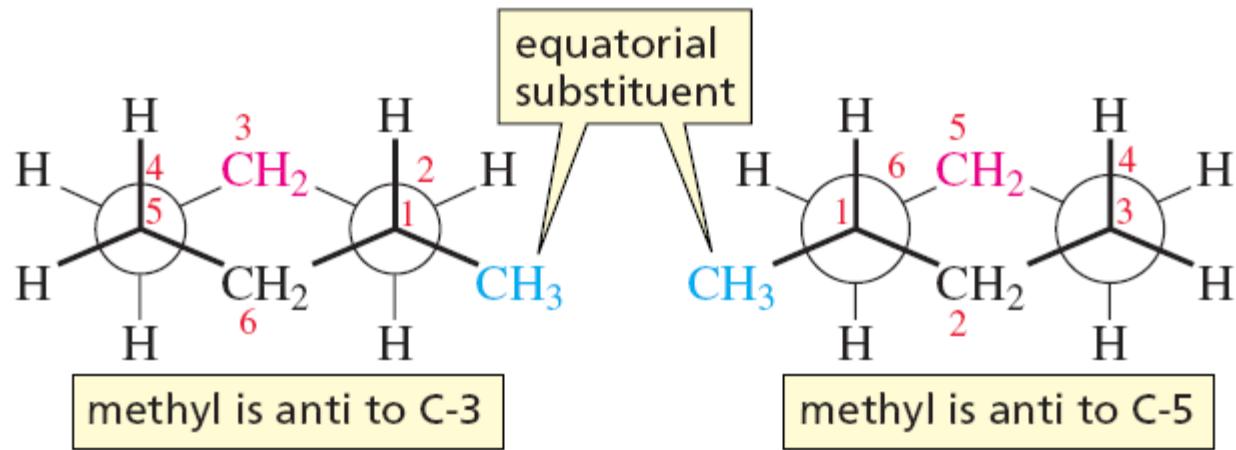
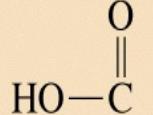
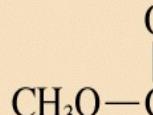


TABLE 4-3

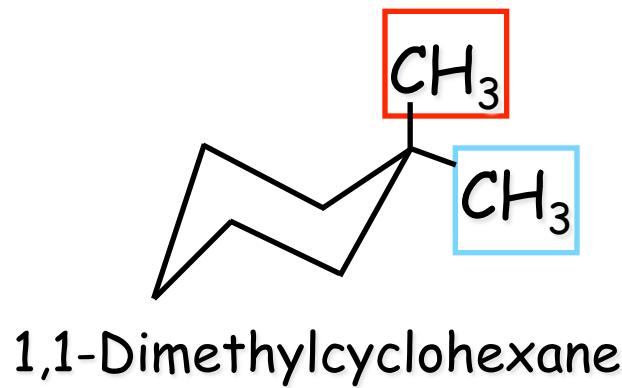
Change in Free Energy on Flipping from the Cyclohexane Conformer with the Indicated Substituent Equatorial to the Conformer with the Substituent Axial

Substituent	ΔG° (kcal mol ⁻¹)	Substituent	ΔG° (kcal mol ⁻¹)
H	0	F	0.25
CH ₃	1.70	Cl	0.52
CH ₃ CH ₂	1.75	Br	0.55
(CH ₃) ₂ CH	2.20	I	0.46
(CH ₃) ₃ C	≈ 5	HO	0.94
	1.41		0.75
		CH ₃ O	
		H ₂ N	1.4

Note: In all examples, the more stable conformer is the one in which the substituent is equatorial.

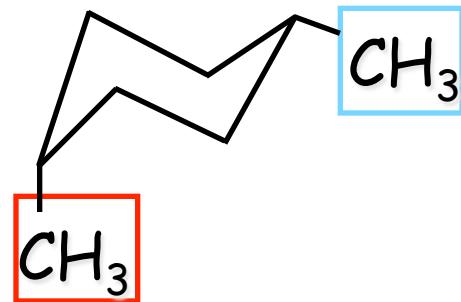
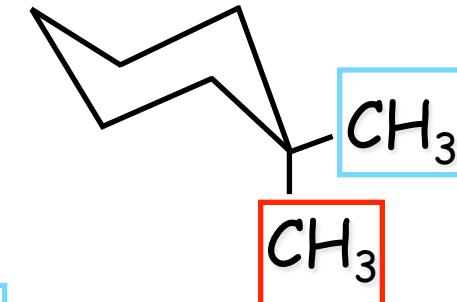
Note: These numbers do not reflect absolute size, but size with respect to transannular and gauche interactions in cyclohexane.

The power of conformational analysis: ΔG° may be additive. Consider the dimethylcyclohexanes:



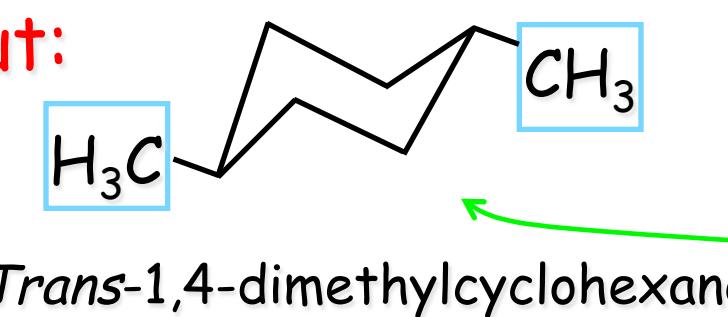
1,1-Dimethylcyclohexane

$$\xrightleftharpoons{\hspace{1cm}} \Delta G^\circ = 0$$



Cis-1,4-dimethylcyclohexane

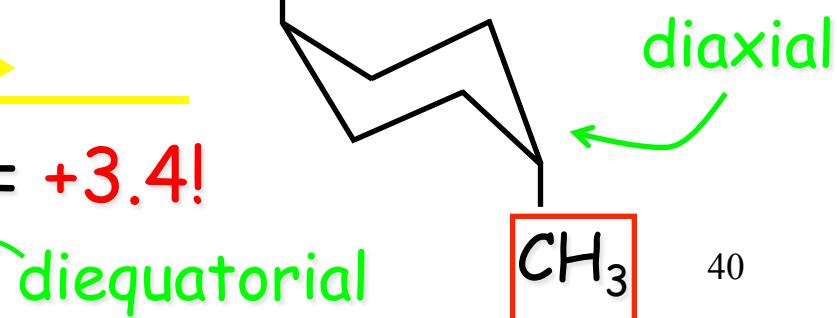
$$\xrightleftharpoons{\hspace{1cm}} \Delta G^\circ = 0$$



Trans-1,4-dimethylcyclohexane

$$\xrightleftharpoons{\hspace{1cm}} \Delta G^\circ = +3.4!$$

diequatorial

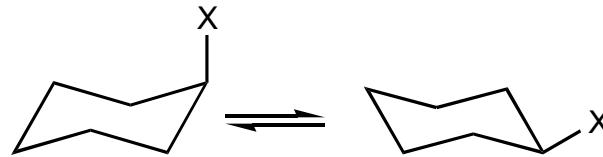


diaxial

A-value for mono substituted cyclohexanes

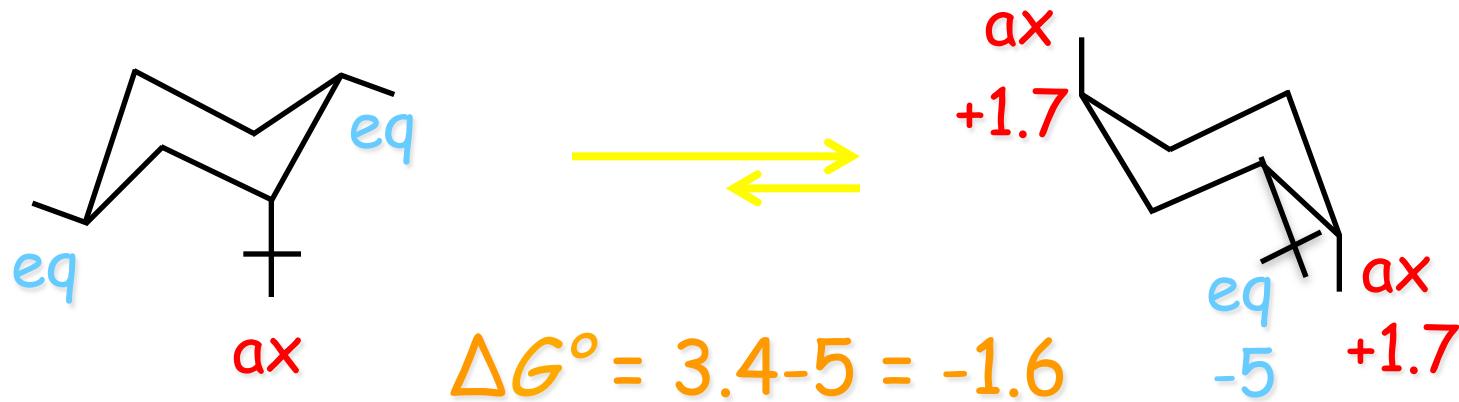
Free energy difference between axial and equatorial conformers of monosubstituted cyclohexanes are known as **A-values**

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



X group	A value (kcal/mol)	K	% eq
H	0	1	50
CH ₃	1.7	19	95
CH(CH ₃) ₂	2.2	42	98
C(CH ₃) ₃	5	3000	99.9

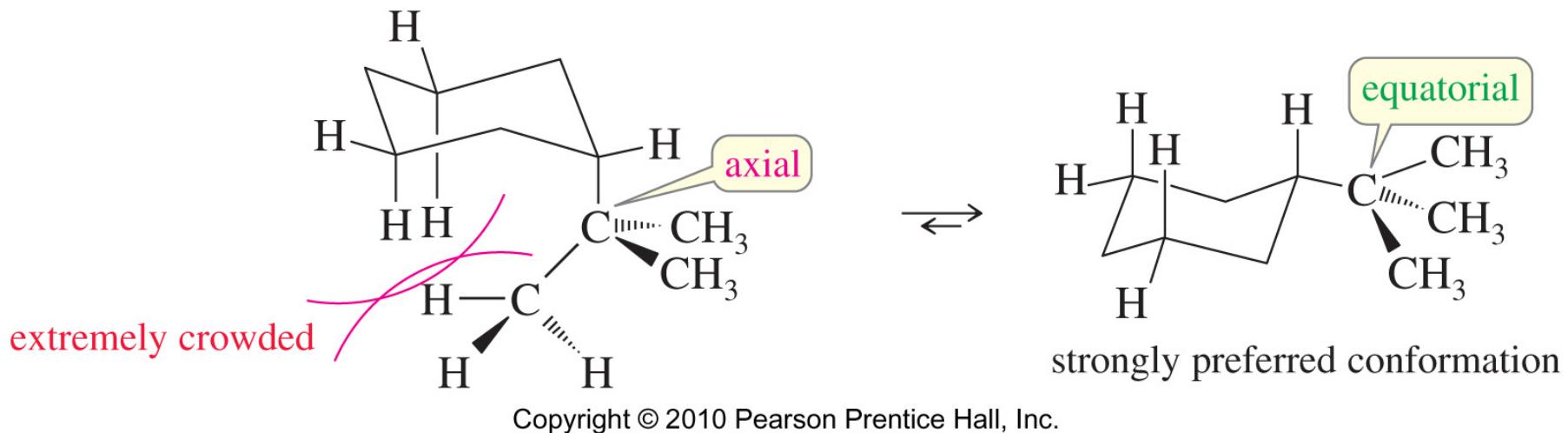
The largest group often biases one conformation



Conformation of t-butylcyclohexane is said to be
BIASED

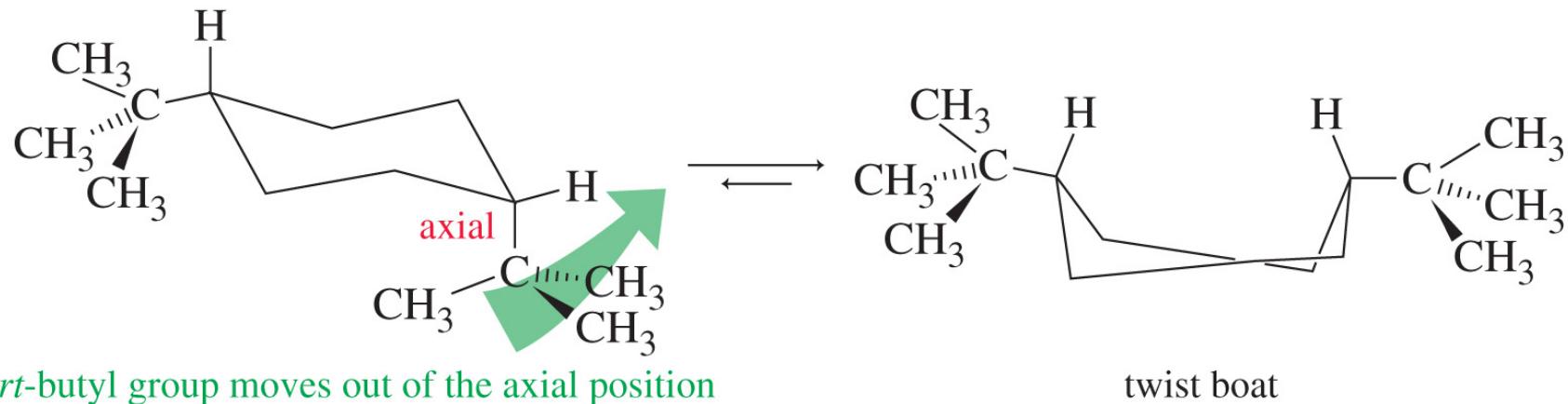
but
NOT LOCKED

Tert-butylcyclohexane



Substituents are less crowded in the equatorial positions

Cis-1,4-ditertbutylcyclohexane

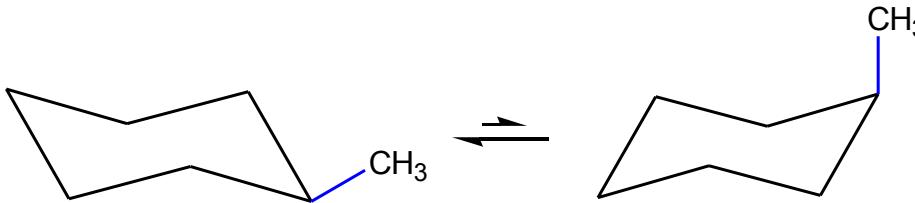


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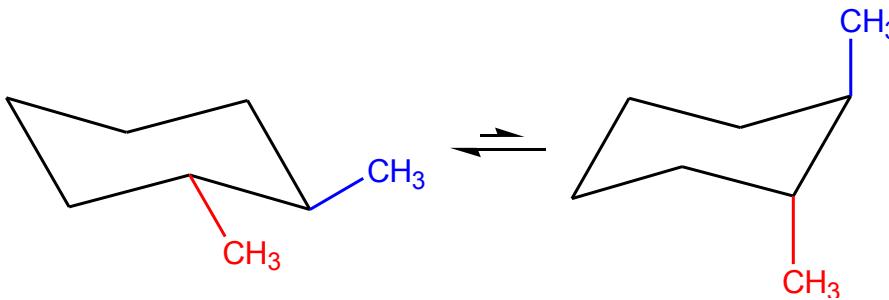
The most stable conformation of *cis*-1,4-di-tertbutylcyclohexane is the twist boat. Both chair conformations require one of the bulky *t*-butyl groups to occupy an axial position.

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

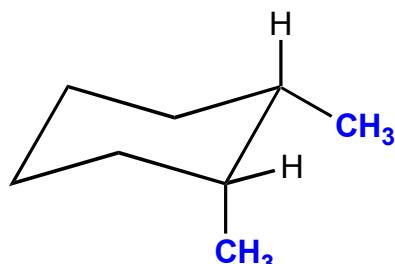
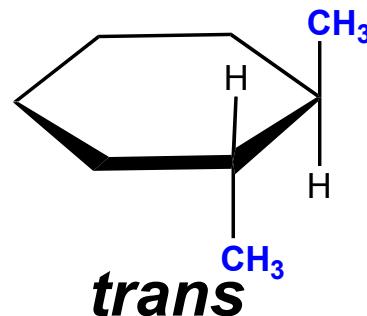
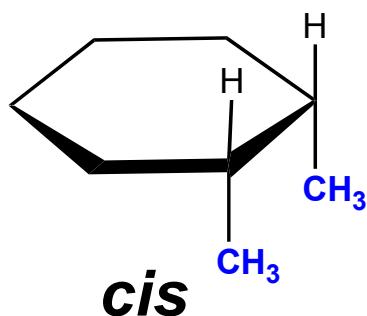


(ii) A *cis*-isomer would remain as *cis*-isomer, so is *trans*

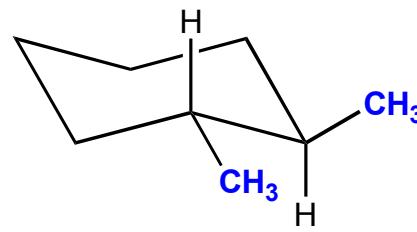


Disubstituted cyclohexanes

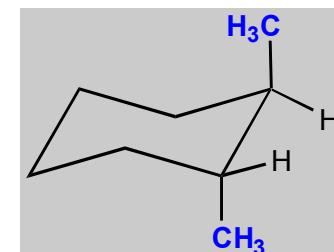
1,2-disubstituted



cis



trans

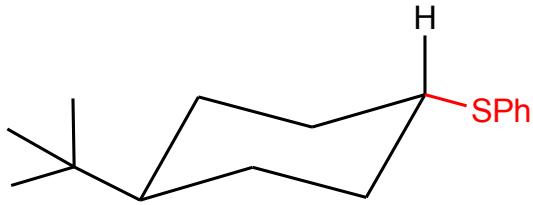
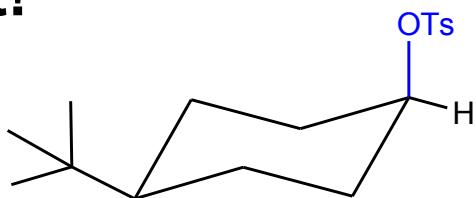


trans

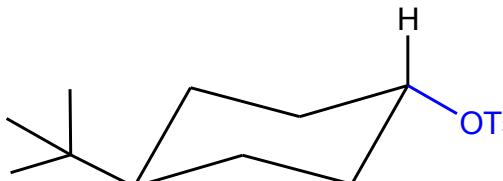
Conformational Features and Chemical Reactivity

Reactions of axial and equatorial substituents could be very different!

cis



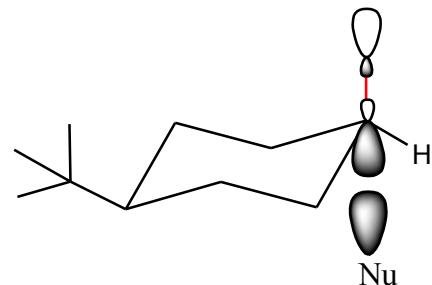
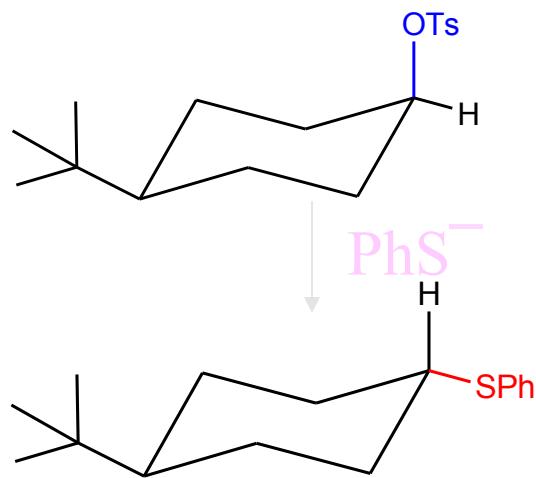
trans



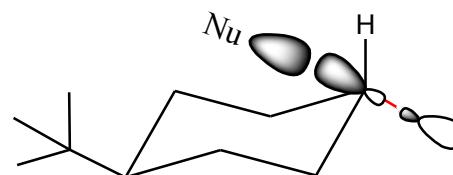
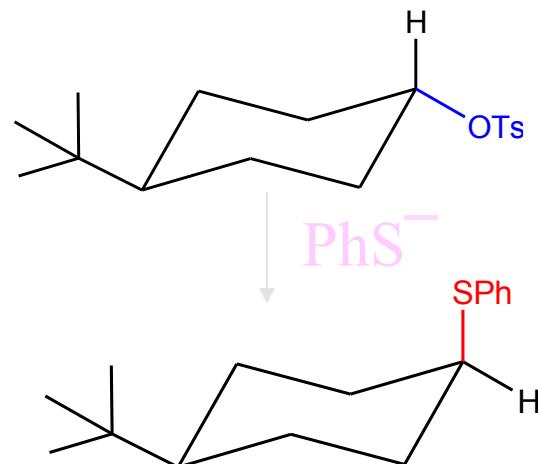
cis-compound reacts 31 times faster!!

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)



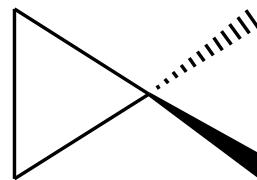
favored attack



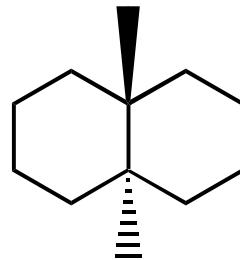
hindered attack

Polycyclic compounds

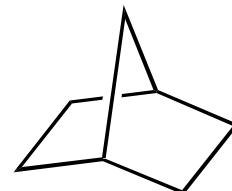
Spiro cyclic compounds: Compounds that share one carbon atom between two rings



Fused ring compounds: Compounds that share two adjacent carbon atoms

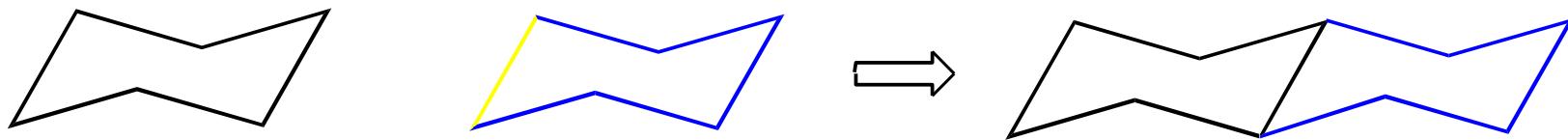
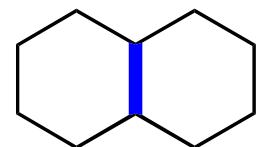


Bicyclic ring compounds: Compounds that share two non-adjacent carbon atoms

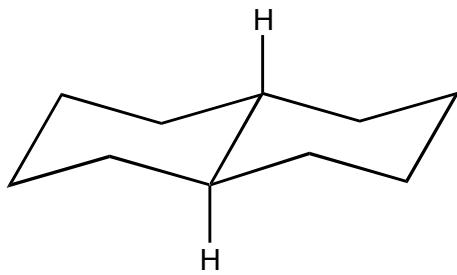


Fused ring compounds - Decalins

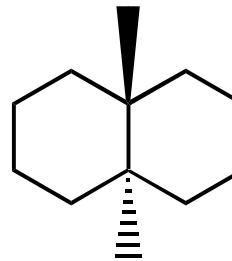
Fused cyclohexane rings which share a common C-C bond



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



***trans*-decalin**

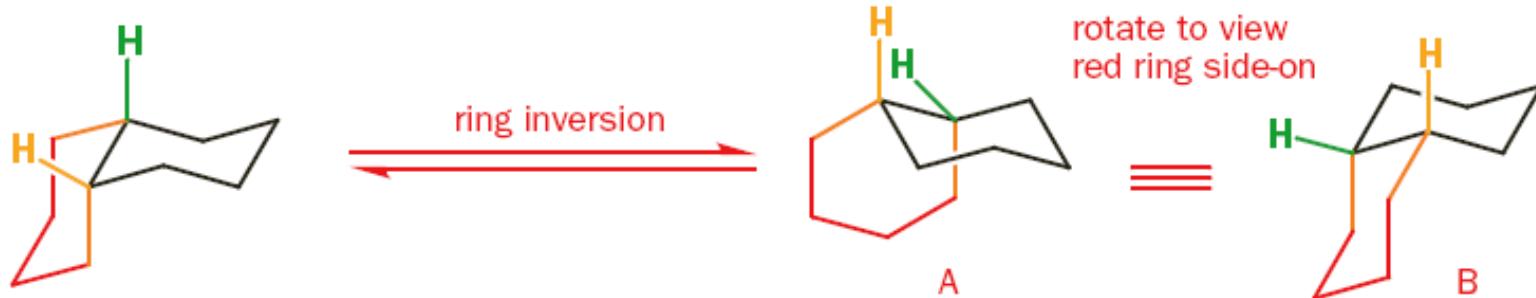


***trans*-decalins are conformationally LOCKED** as they cannot undergo ring flipping.

Cis - Decalins

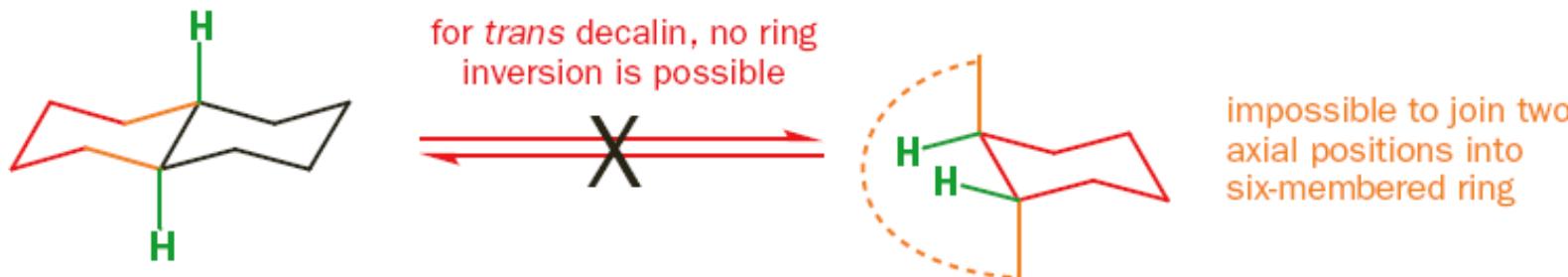
Cis-decalins are **conformationally flexible** and can undergo ring flipping

ring inversion of *cis*-decalin



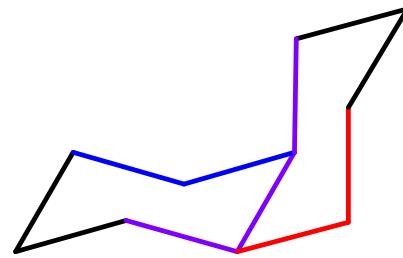
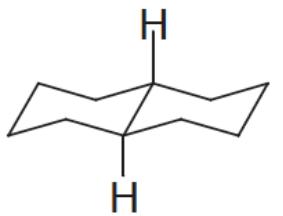
after ring inversion,
green H is equatorial on black ring
yellow H is axial on black ring

no ring inversion in *trans*-decalin

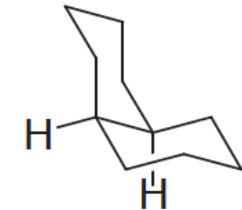
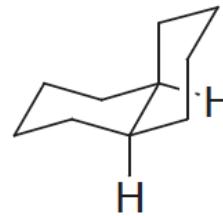


Decalins

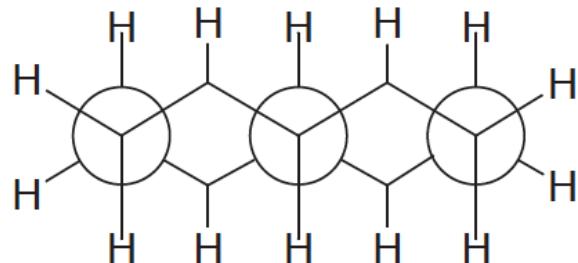
trans-decalin



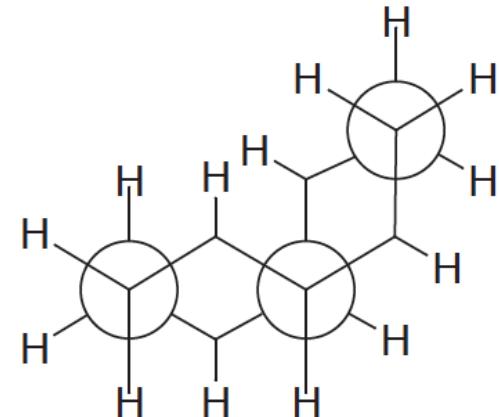
cis-decalin



two conformations equivalent



0.0 kcal



3 gauche interactions
 $3 \times 0.9 \text{ kcal} = 2.7 \text{ kcal}$

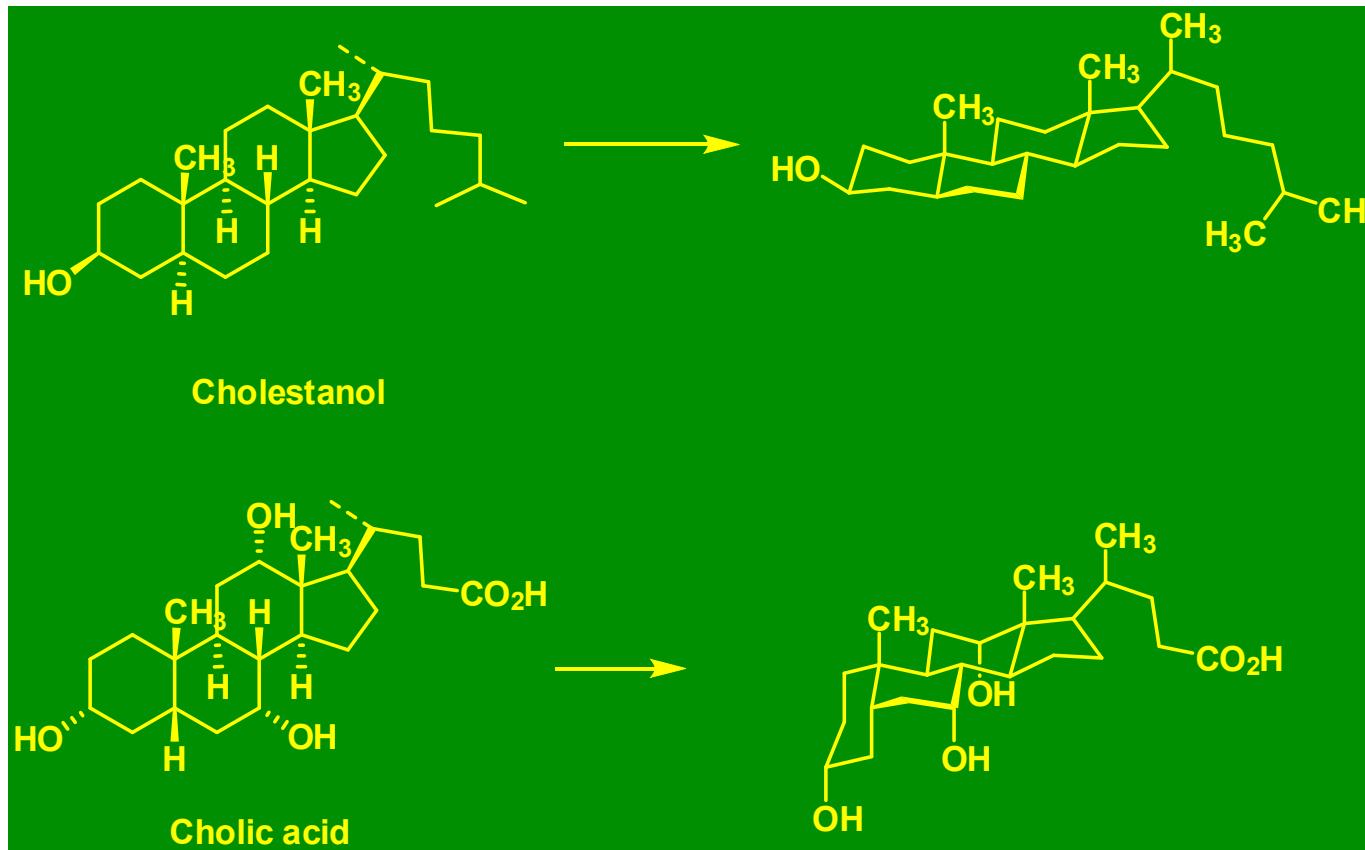
ΔE between *cis*- and *trans*-decalin = 2.7 kcal/mol

trans – Decalins in Nature

Nature uses *trans*-decalins for clever design of steroids!

Steroids generally have all *trans* ring junctions and possesses high stability

Example for a steroid: **Cholesterol**

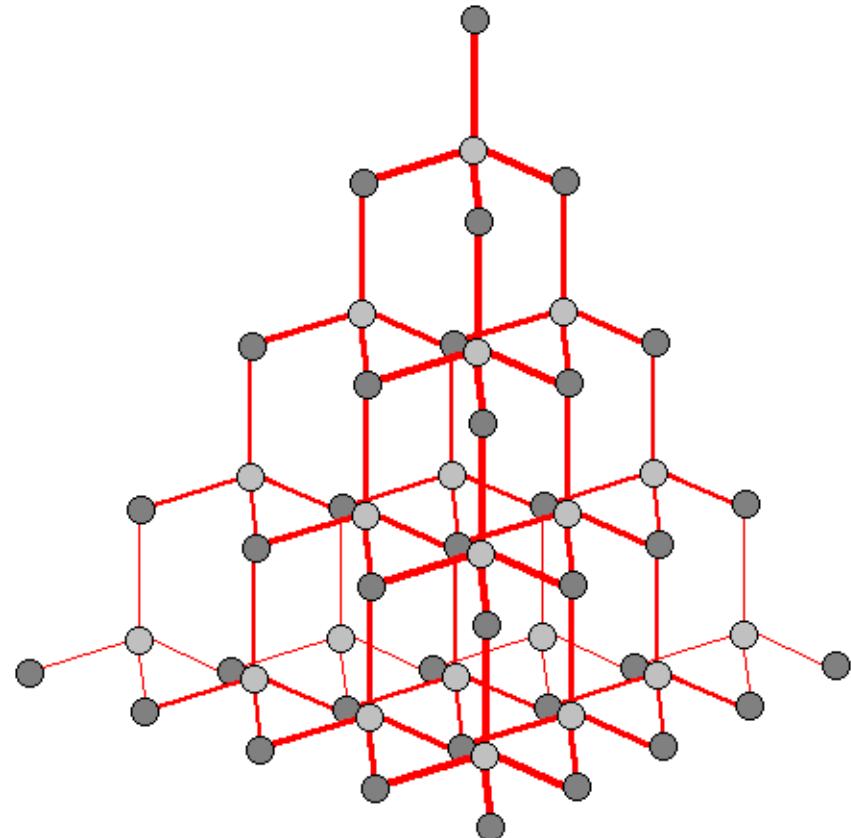


Archeologist have isolated steroids which are **10⁹ years** old from sediments!

Stability of trans-ring fusion

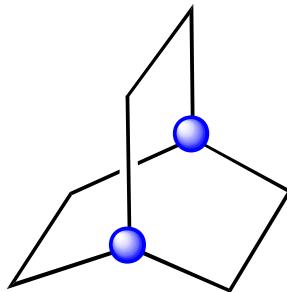
Cyclic six-membered carbon rings fused in trans-fashion is very stable:

Diamond structure resembles trans-fusion



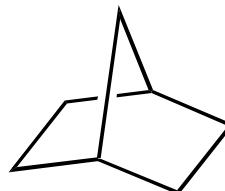
Bicyclic compounds

Compounds sharing two non-adjacent carbon atoms are termed as bicyclic compounds



Bicyclo[2.2.2]octane

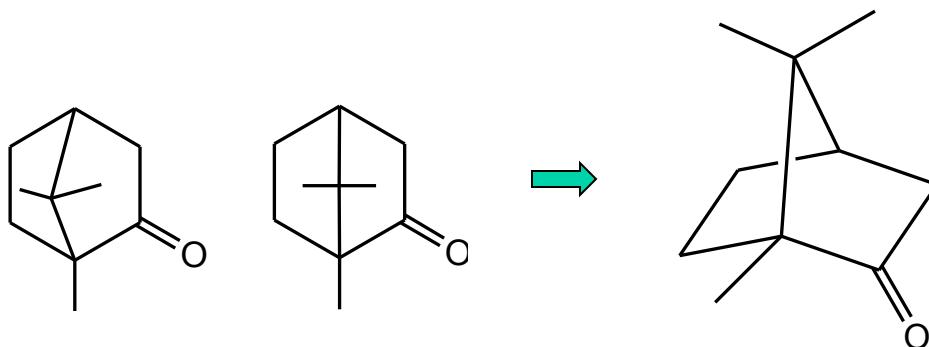
Bridgehead carbons are indicated as blue circles



Bicyclo[2.2.1]heptane

Bicyclic compounds

Camphor skeleton is [2.2.1] system



Sanskrit: *karpoor*

(Also known as *karpooram*)

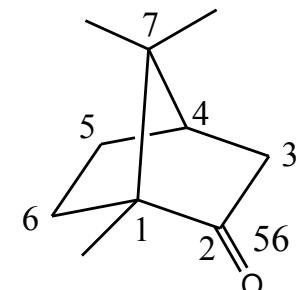
Used as moth repellent,
antimicrobial, used in medicine

Used along with menthol in Vicks!

Camphor is a **bicyclo[2.2.1]heptanone** system

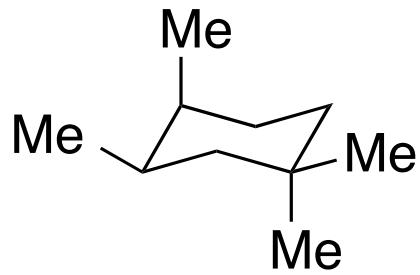
IUPAC

1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

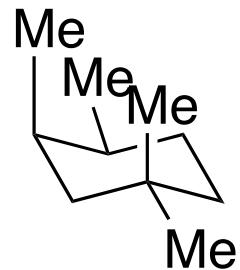


Conformer A is 2 kcal/mol lower in energy than conformer B.

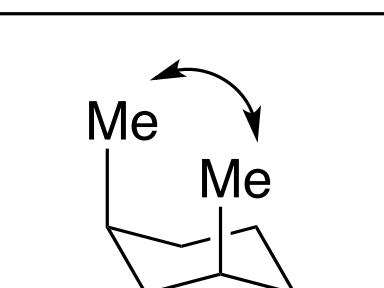
Calculate the energy of 1,3-diaxial interaction between two methyl groups as shown in the box. You must show stepwise calculations.



A



B



$$2 = (2.7+x) - 4.5. \text{ So } 6.5 - 2.7 = x = 3.8 \text{ kcal/mol}$$

THANK YOU