

# **Topic-III**

# **Conformational Analysis**

**Lecture slides are courtesy of:**  
**Prof. Pradeepkumar P. I., IIT Bombay**  
**Prof. Peter Volhardt, UC Berkeley**  
**Prof. J. M McBride, Yale University**  
**Oxford University Press**

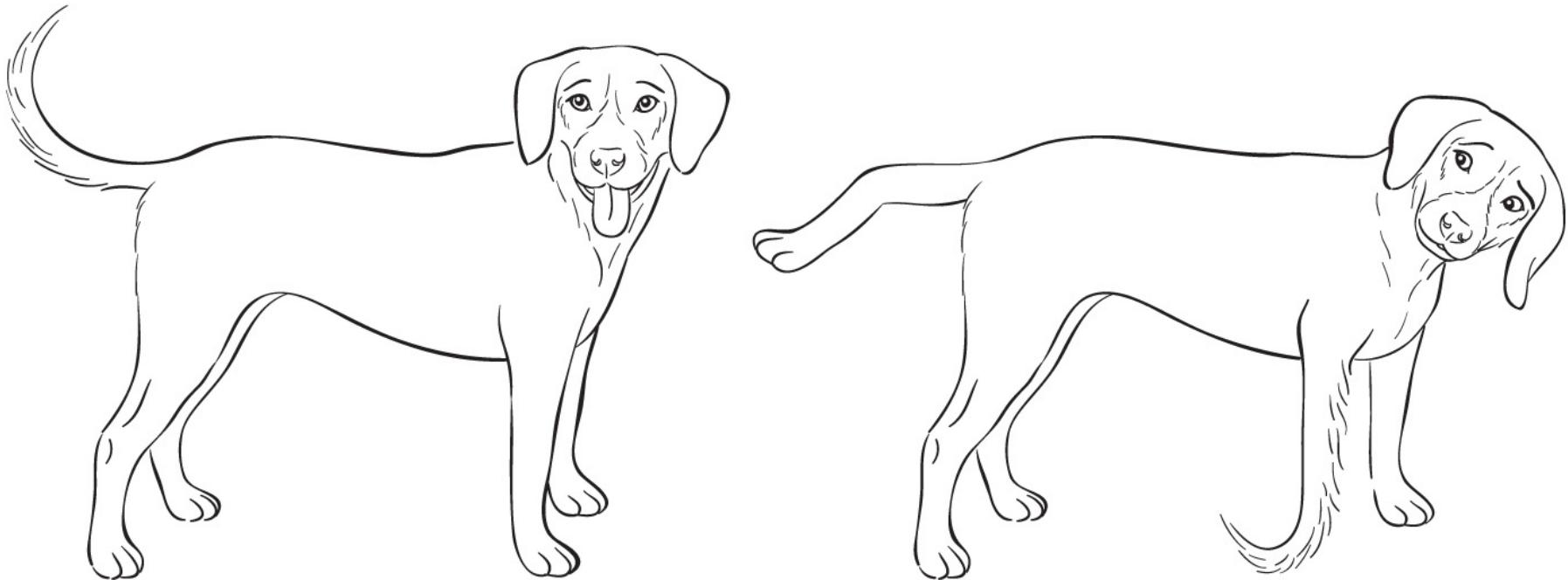
# Stereochemistry

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- *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.

# Different Configurations

## Different Configurations



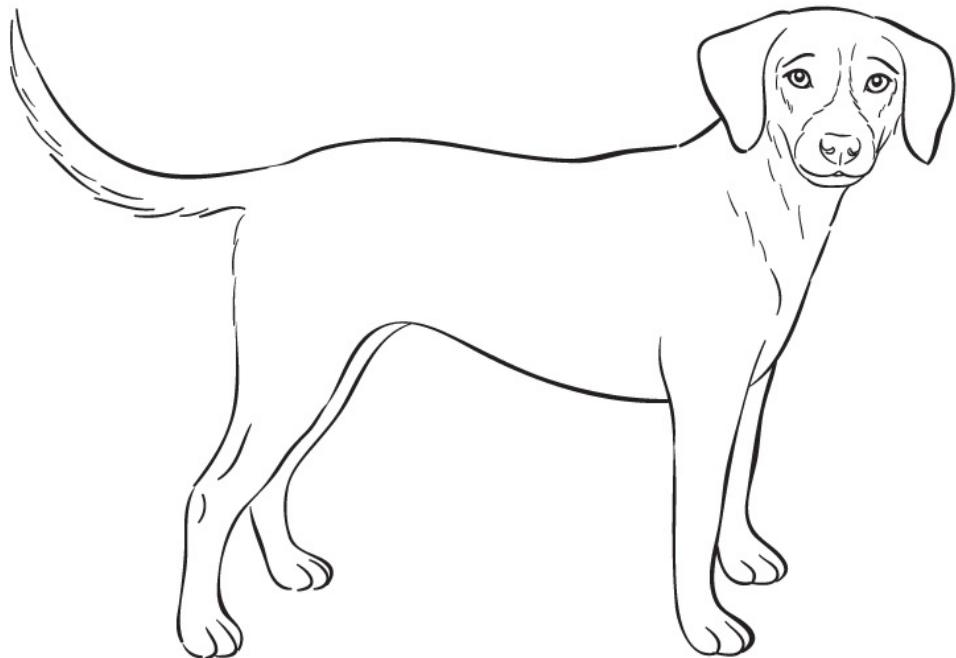
**Compounds with different configurations can be separated.**

**Cis–trans isomers have different configurations.**

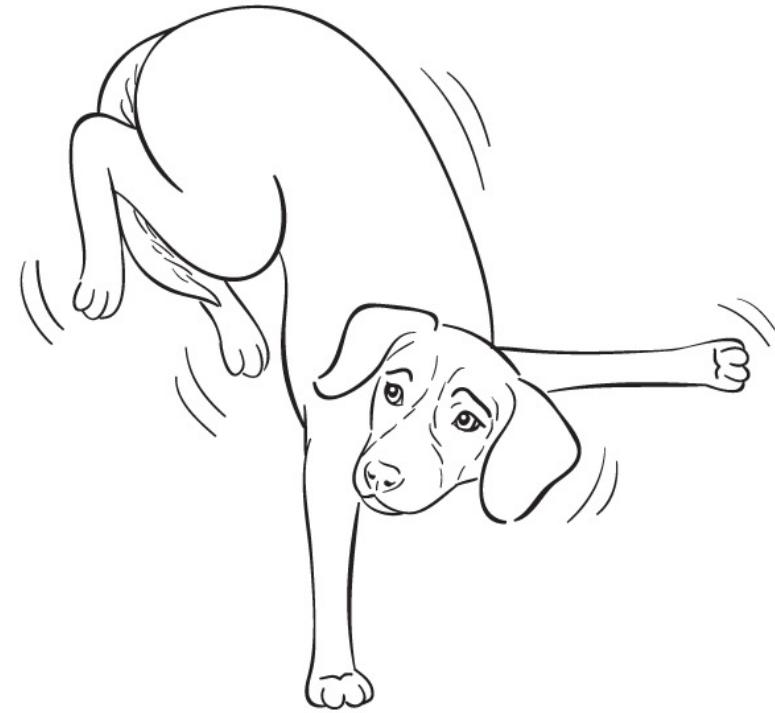
# Different Conformations

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## Different Conformations



**Stable**



**Unstable**

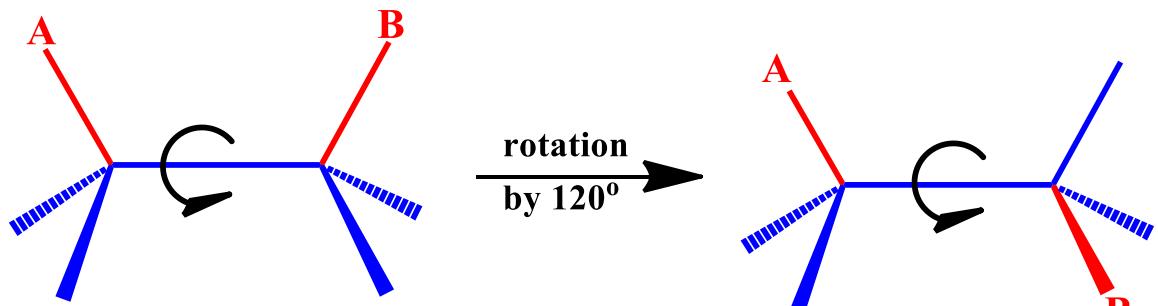
**Compounds with different conformations (conformers) cannot be separated in most cases.**

# Conformational Analysis

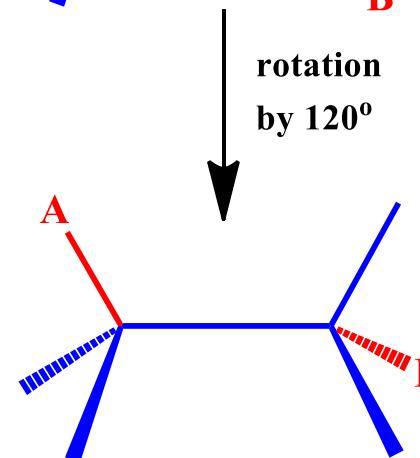
Conformational Analysis is the study of energetics of different conformers

Energy versus torsional angle (dihedral angle)

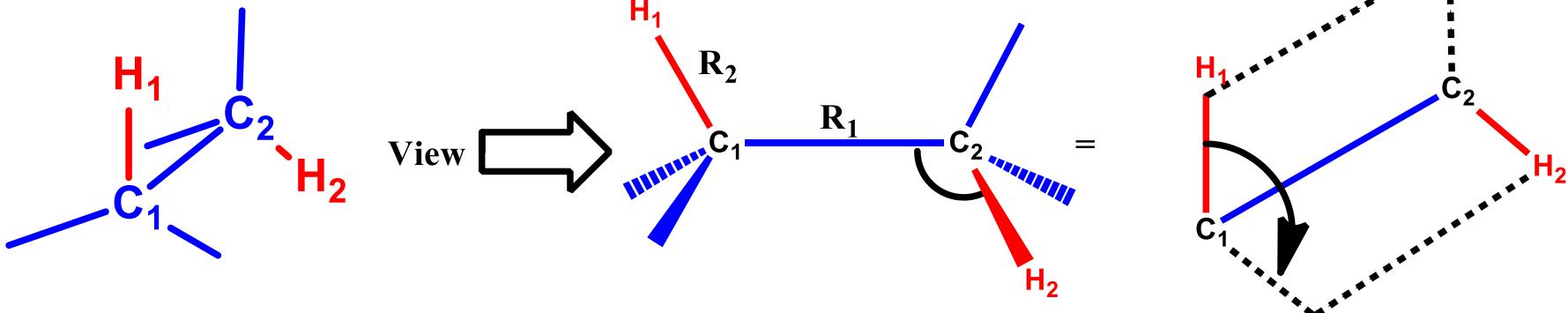
Conformers arise due to the possible free rotation around single bonds



Refers to changes in  
“Shape”



# Internal Coordinates



Bond length

between 2 atoms

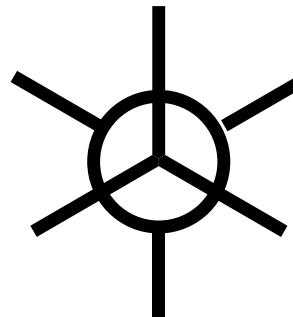
Bond angle

between 3 atoms

Dihedral angle

between 4 atoms

(torsion angle)

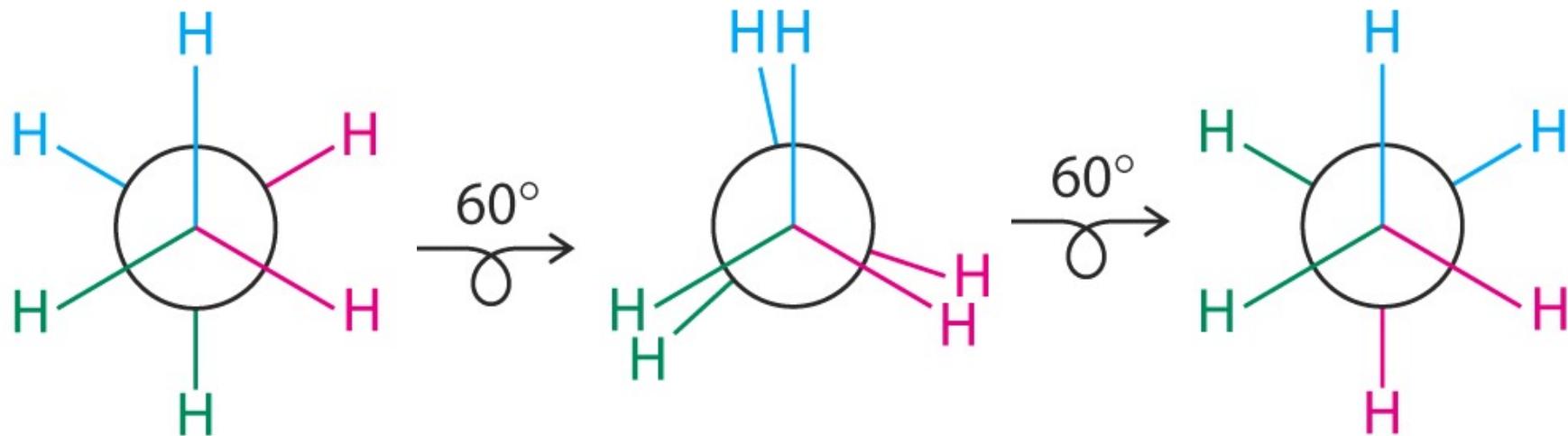


Melvin Newman  
1908-1993<sup>6</sup>

# Conformational Analysis, Example-1: Ethane

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

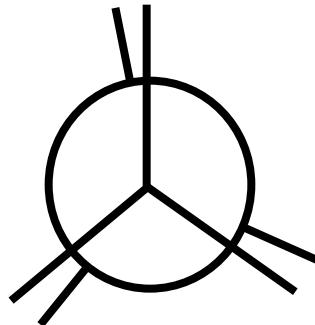
- The eclipsed conformation of ethane is -3 kcal/mol less stable than the staggered conformation. (-1 kcal/mol for each eclipsed H/H pair)



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

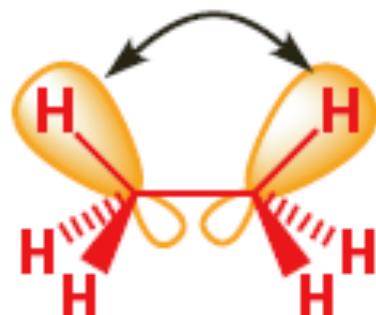
Ethane has barrier to rotation of  $\sim 3$  kcal mol $^{-1}$ . Barrier due to steric and electronic effects

Transition state  
is **eclipsed**

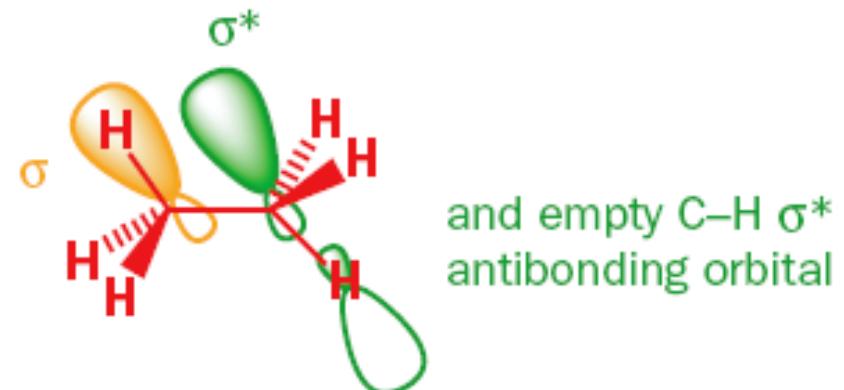
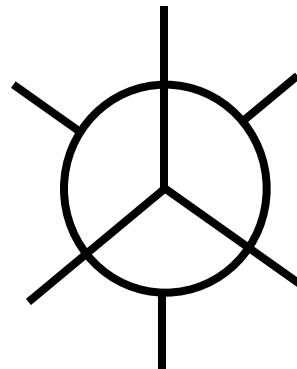


eclipsed:

filled orbitals repel



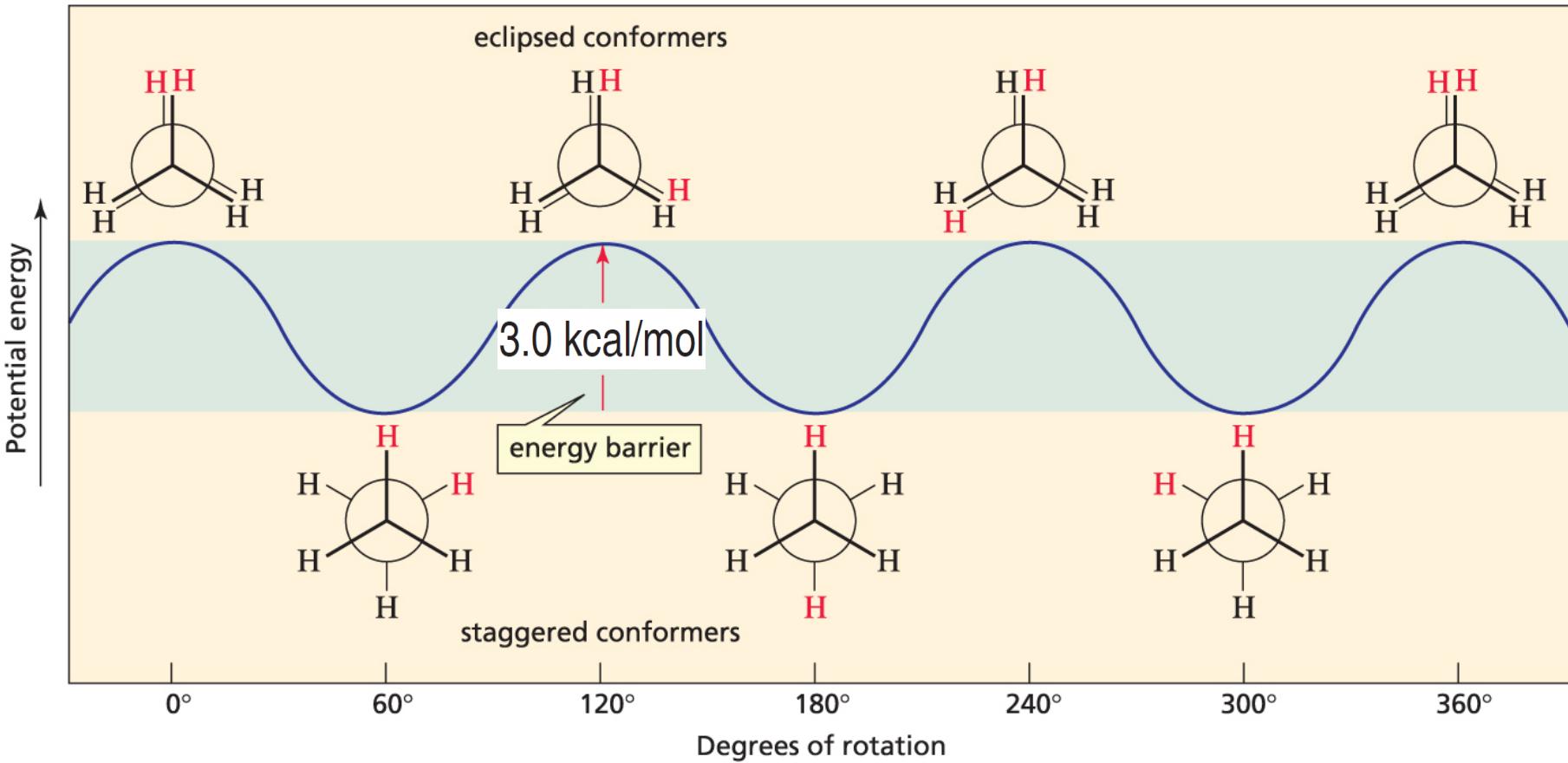
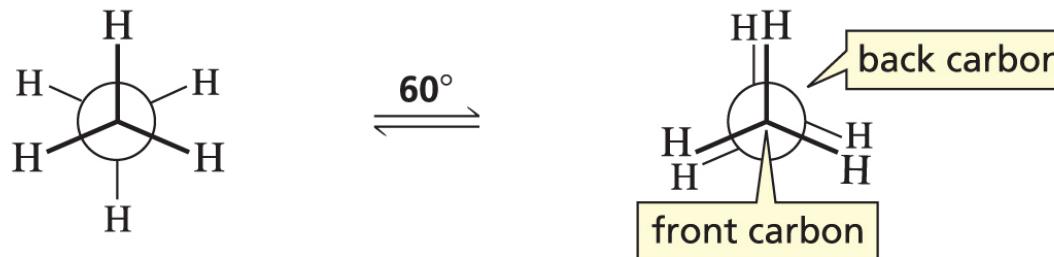
Most **stable** rotamer  
is **staggered**



and empty C–H  $\sigma^*$  antibonding orbital

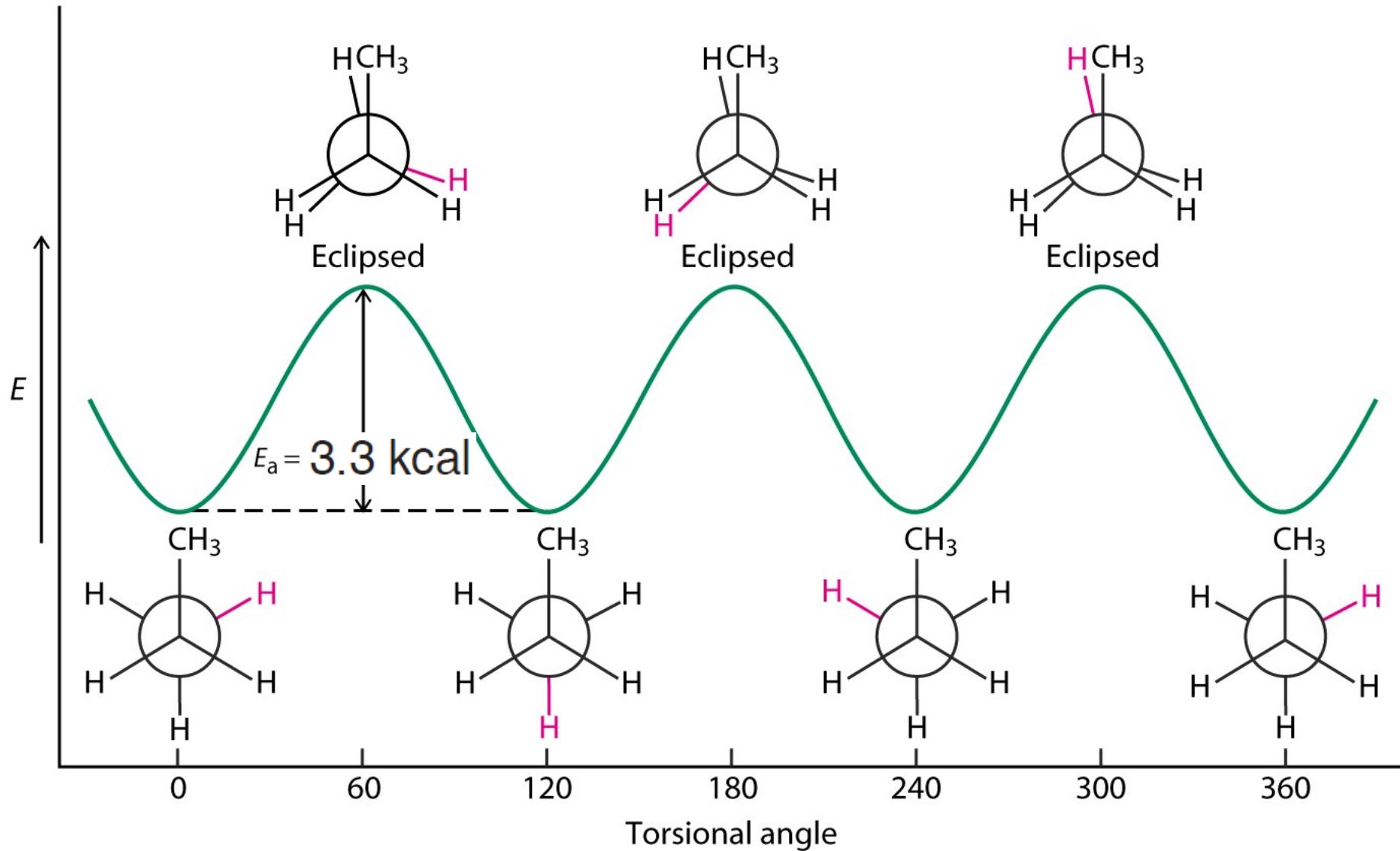
# Conformational Analysis, Example-1: Ethane

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

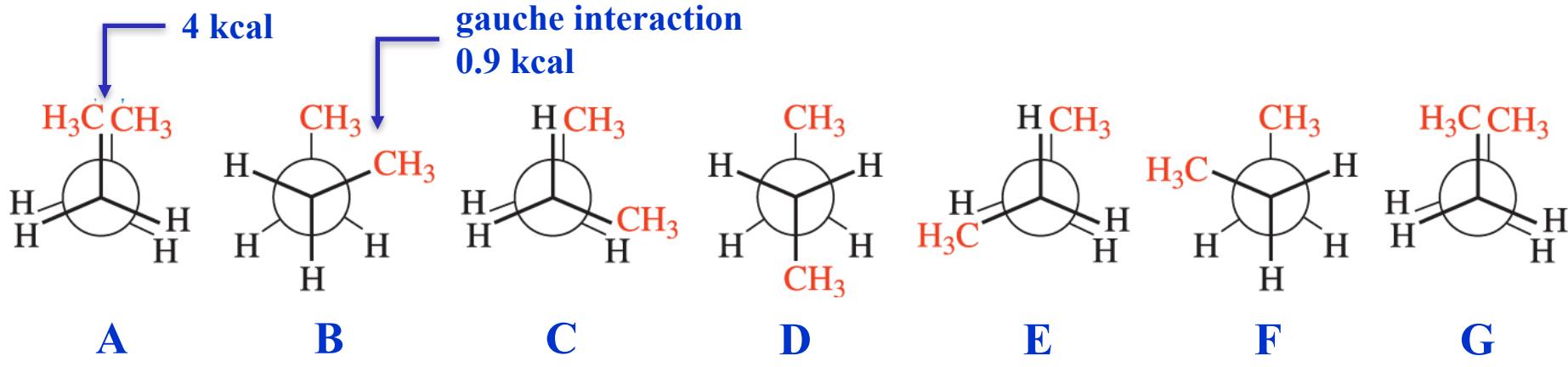
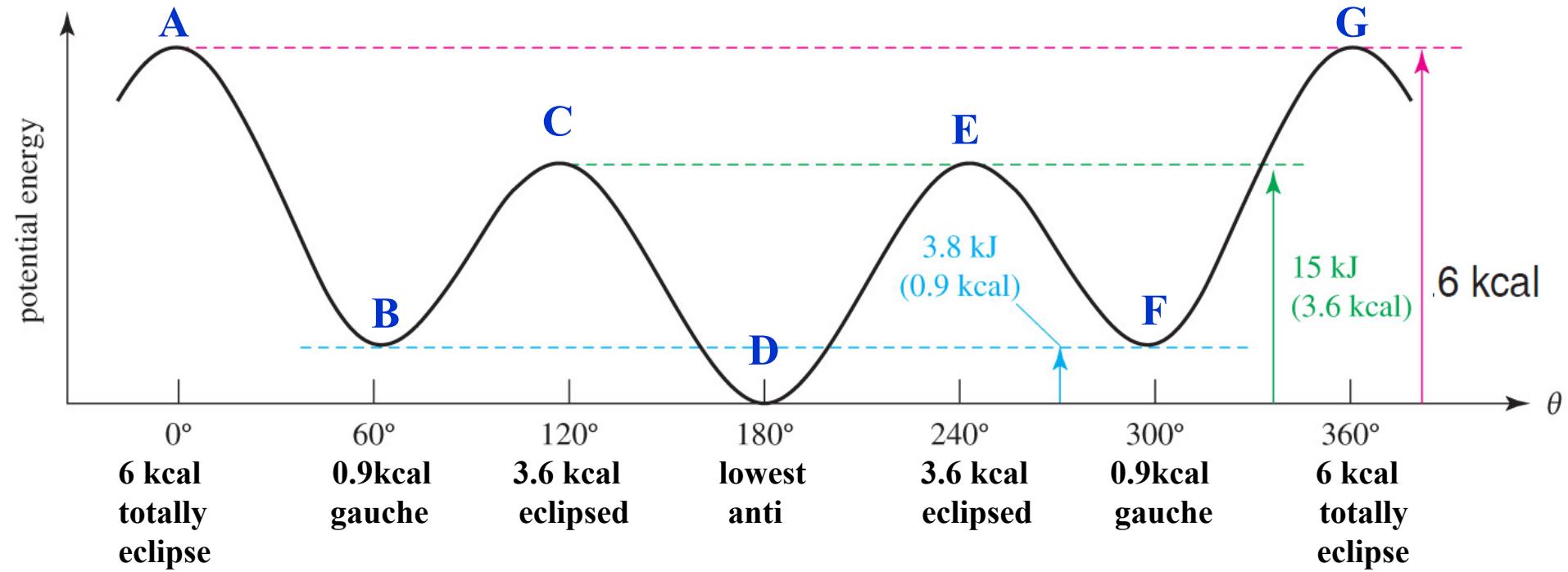


# Conformational Analysis, Example-2: Propane

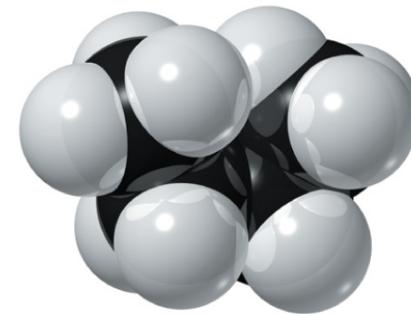
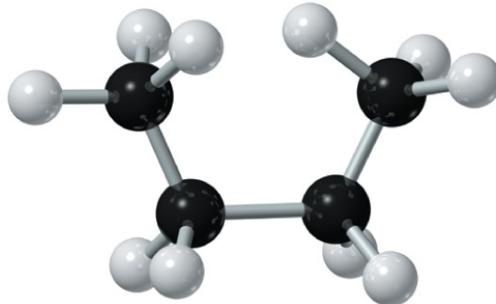
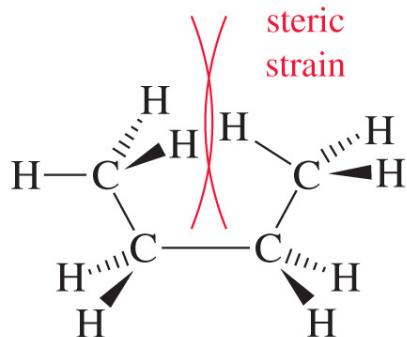
Note: eclipsing interactions H/H (1.0 kcal) and Me/H (1.3 kcal)



# 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 <sub>3</sub> ) ... (CH <sub>3</sub> ) <i>gauche</i>	0.9
(C-H) ... (C-H)	1
(C-H) ... (CH <sub>3</sub> )	1.3
(CH <sub>3</sub> ) ... (CH <sub>3</sub> )	2.9
(CH <sub>3</sub> ) ... (CH <sub>2</sub> CH <sub>3</sub> )	3.4
(CH <sub>3</sub> ) ... (CH(CH <sub>3</sub> ) <sub>2</sub> )	3.9
(CH <sub>3</sub> ) ... (C(CH <sub>3</sub> ) <sub>3</sub> )	4.7

# **Important Types of Molecular STRAINS**

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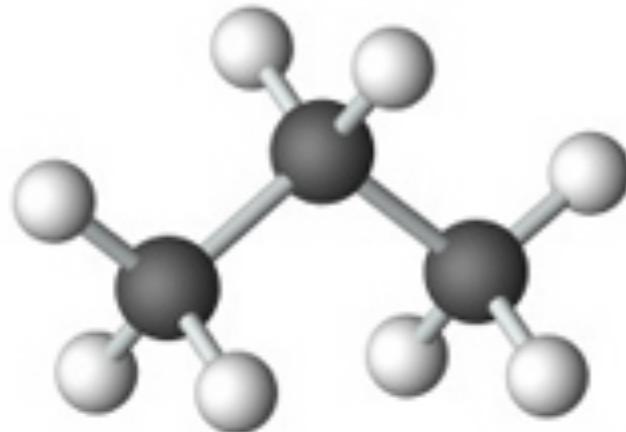
**Torsional Strain:** Extra energy of eclipsed conformation arising due to the repulsion between bonding electrons of one substituent with that of the other as they pass close to each other

**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  $109.5^\circ$

# Small Ring Compounds – (1) cyclopropane

## Propane



Angle strain : None

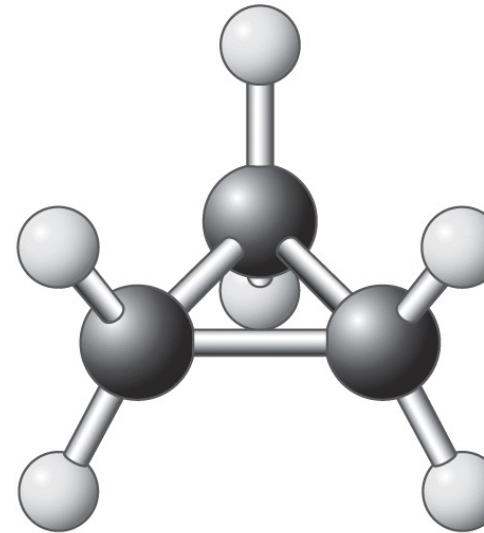
(all angles are nearly tetrahedral)

Steric strain: None

(Fully staggered conformer)

Cyclopropane suffers from angle strain and torsional strain

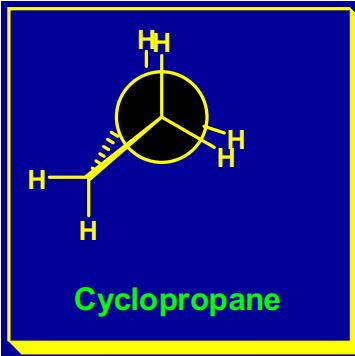
## Cyclopropane



Deviation of  $49.5^\circ$  per carbon

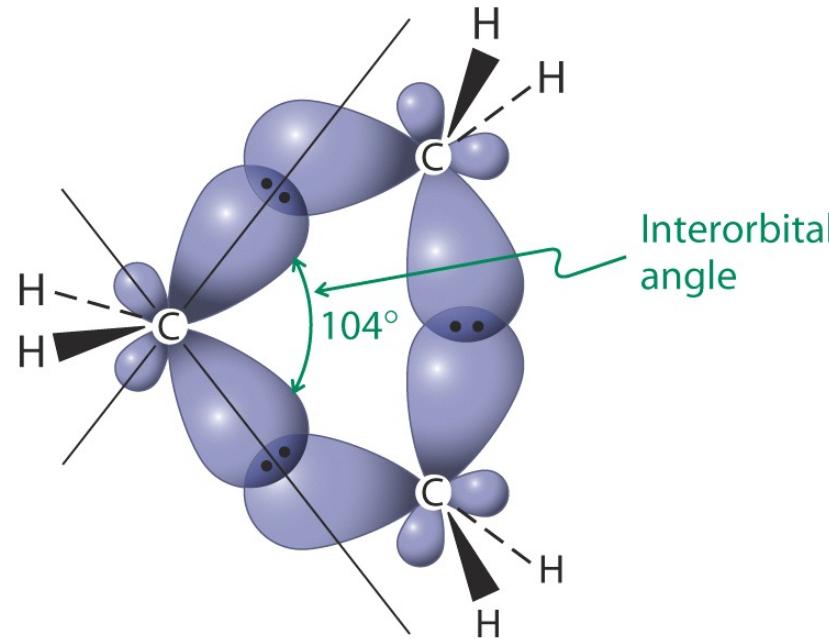
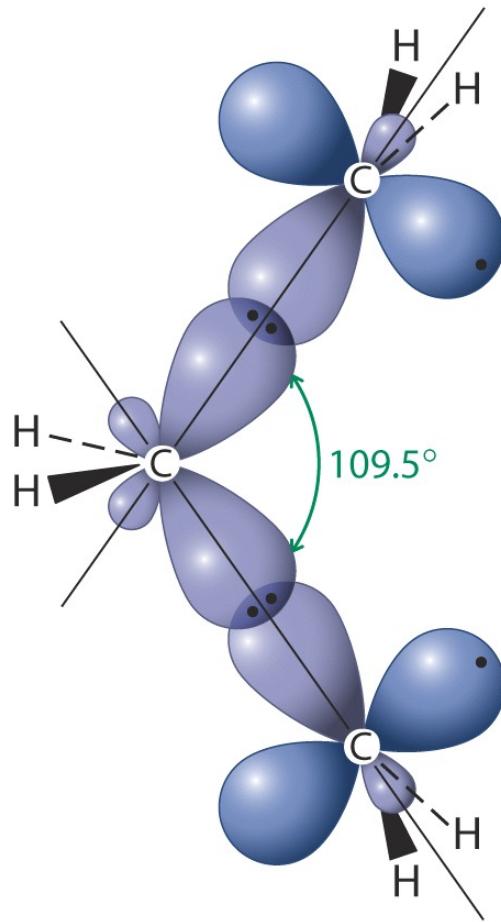
Torsional strain: (C-H) ... (C-H) eclipsing interactions

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

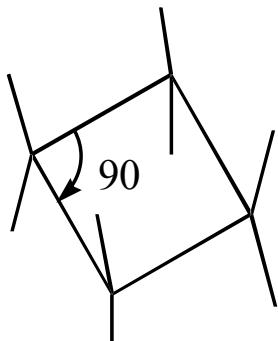


# Small Ring Compounds – (1) cyclopropane

Strain relief through the formation of “banana” bonds

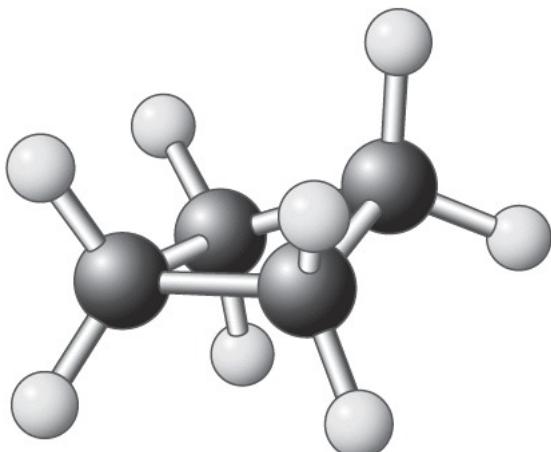


# Small Ring Compounds – (2) cyclobutane



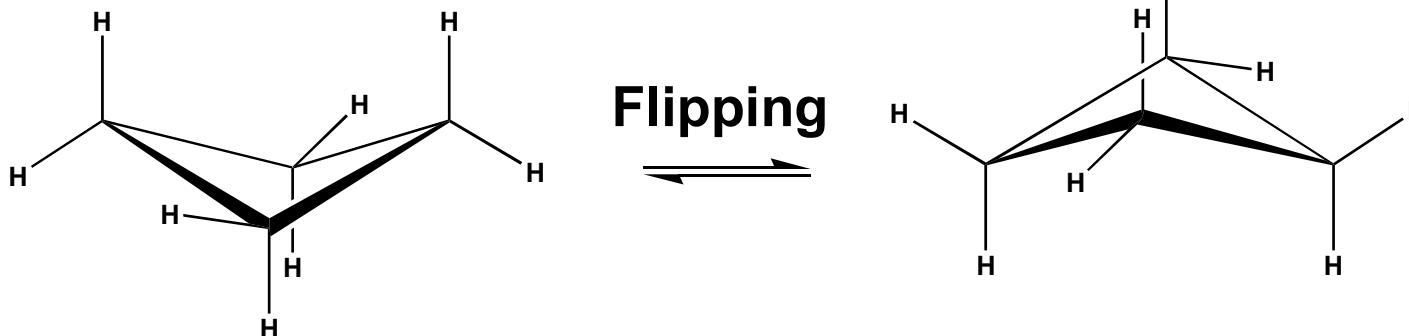
Planar? Problems are: **Angle strain** plus  
severe **torsional strain**

Compromise is



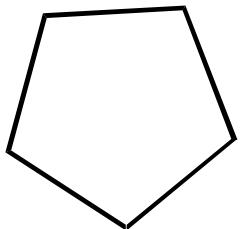
**Ring puckering**

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



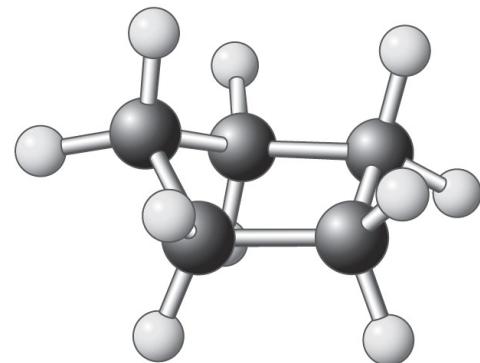
Cyclobutane has a ‘wing shaped’ or ‘puckered’ conformer

# Small Ring Compounds – (3) Cyclopentane



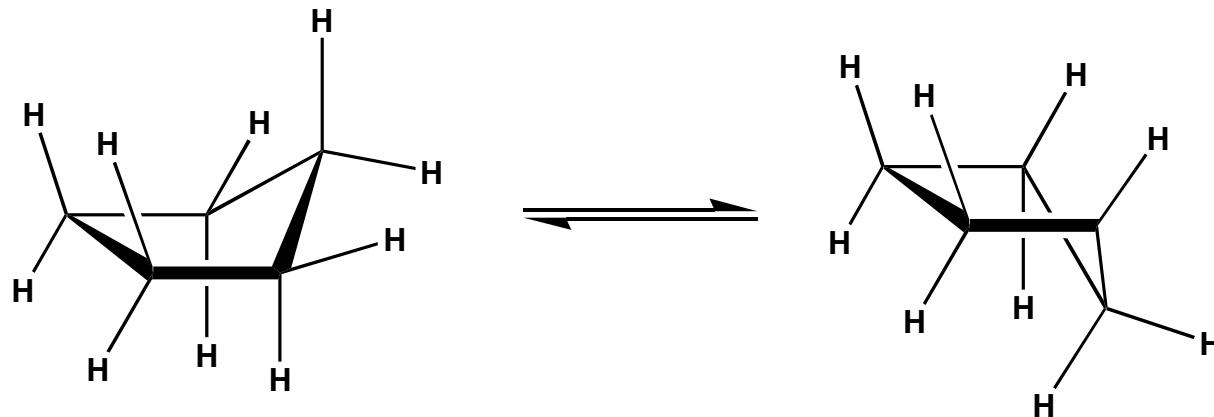
Planar? Though the angle strain is very little, there will be 10 eclipsing interactions!

## Ring puckering



Relieves eclipsing interactions with only a slight increase in angle strain

Four coplanar carbon atoms



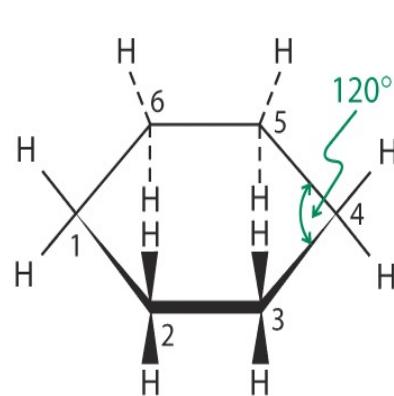
Cyclopentane has an ‘envelope’ conformer

# Small Ring Compounds – (4) Cyclohexane

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

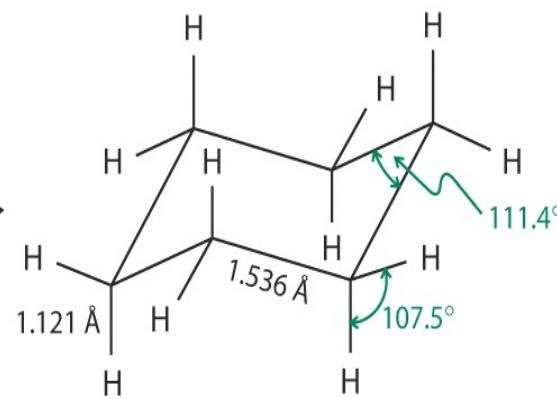
Both angle and torsional (eclipsing interactions) strains can be avoided by **ring puckering**.

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



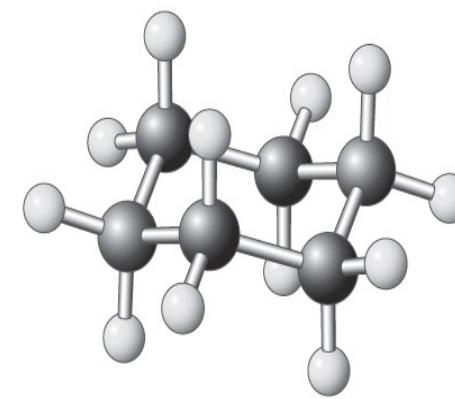
A

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



B

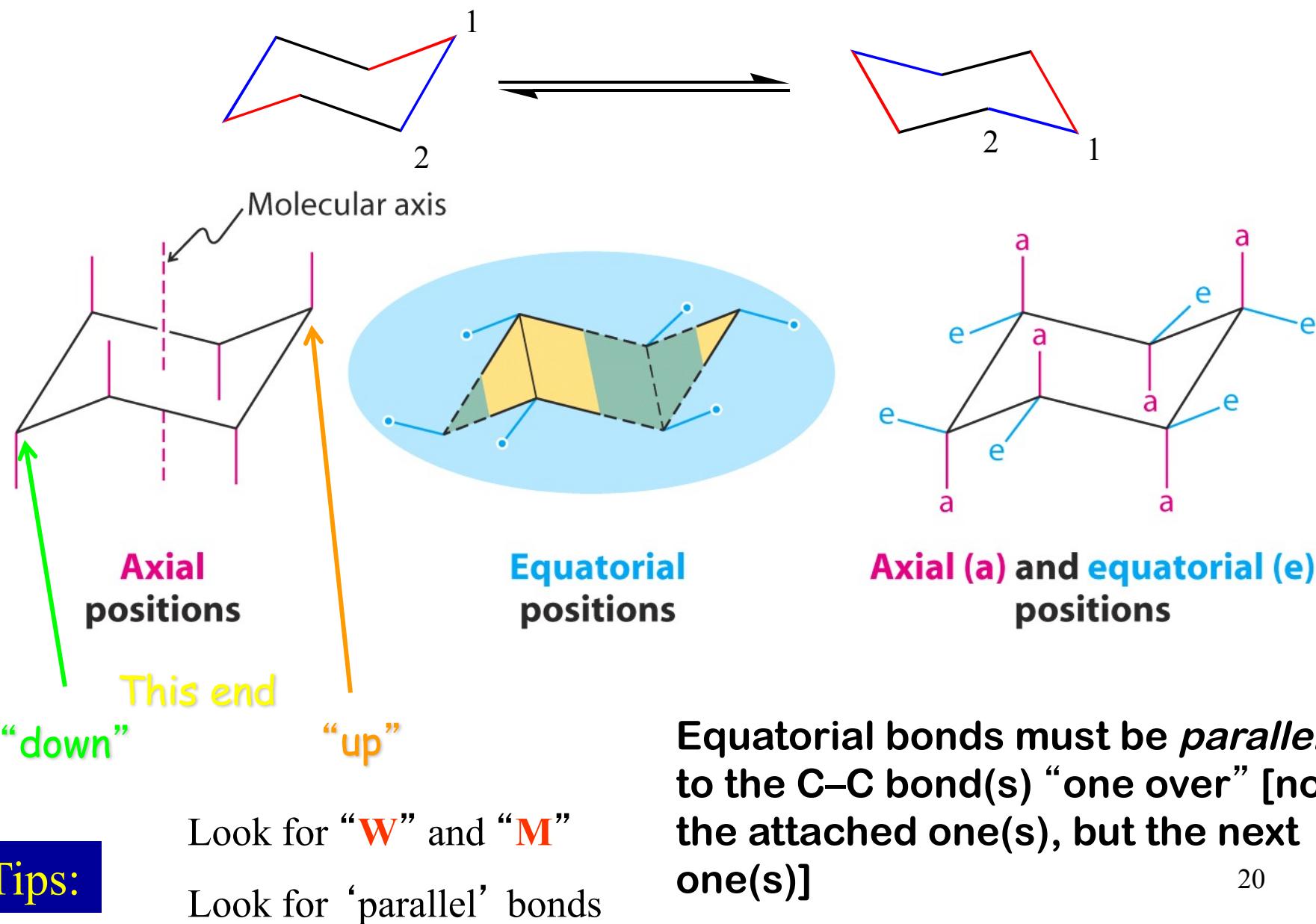
Chair cyclohexane  
(Nearly tetrahedral bond angles;  
no eclipsing hydrogens)



C

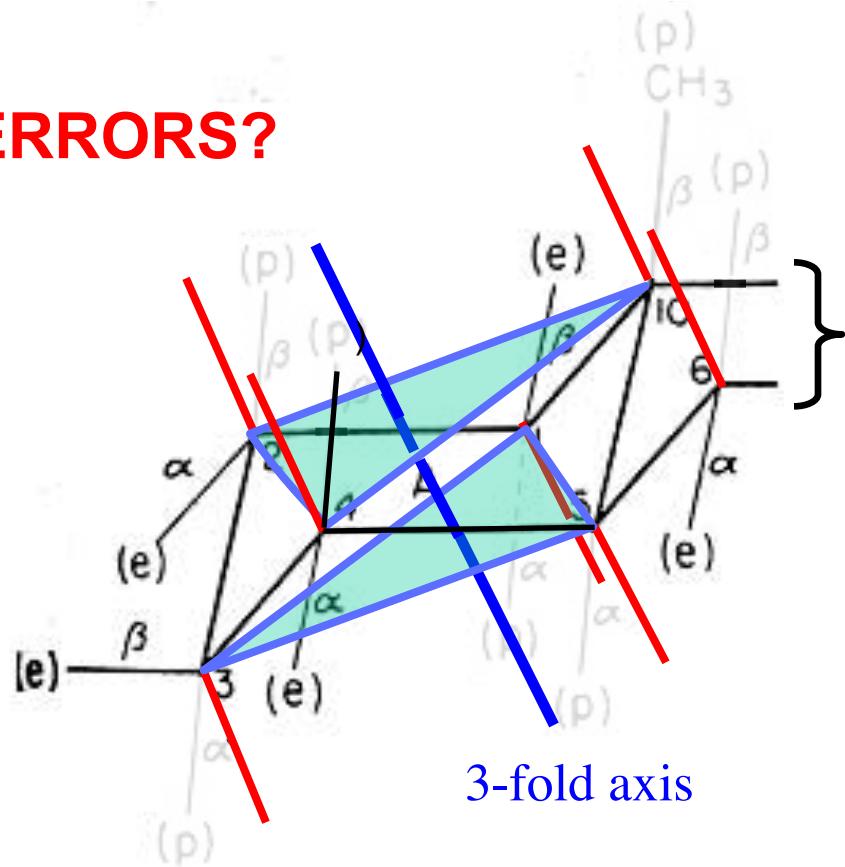


# Drawing Cyclohexanes



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

ERRORS?



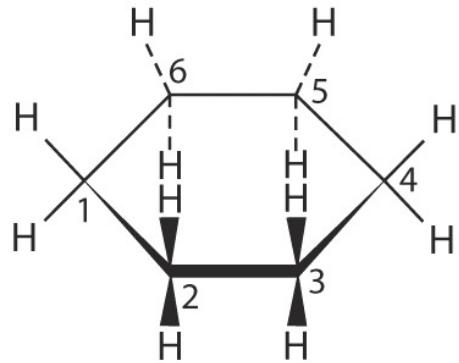
$\beta \Rightarrow$  “up” ;  $\alpha \Rightarrow$  “down”  
(for molecule in conventional orientation,  
old-fashioned configuration notation, like *cis* / *trans*)

(e) “equatorial”

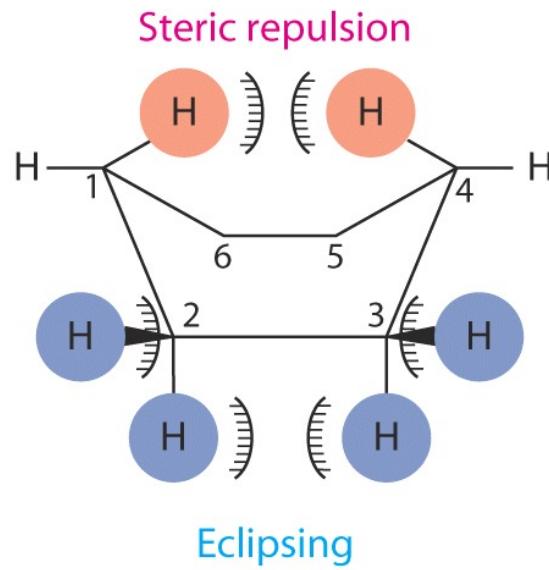
(p) “polar” (now axial)

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

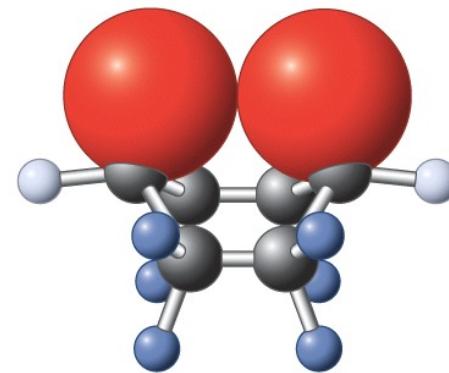
# Boat conformer of cyclohexane is strained



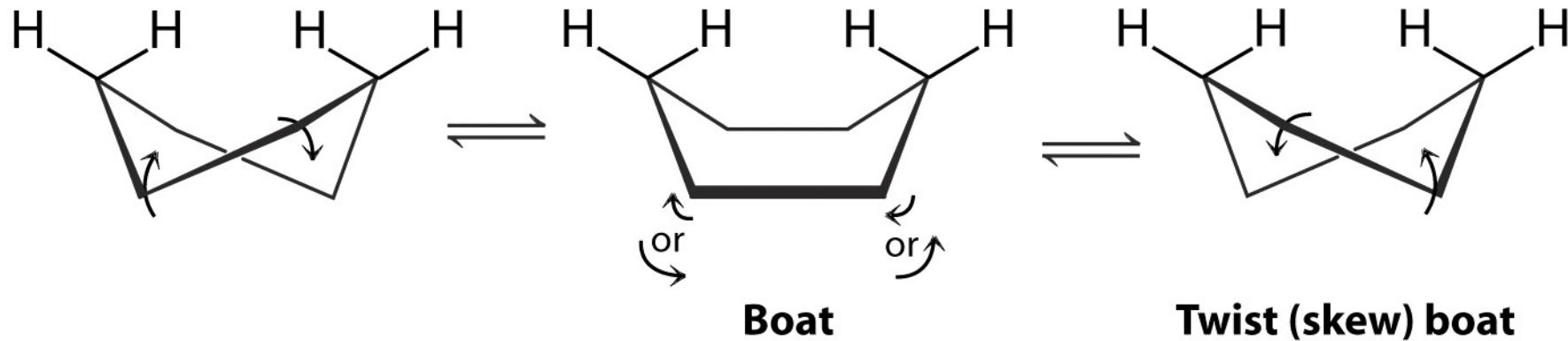
Planar cyclohexane



Boat cyclohexane



# So the boat twists

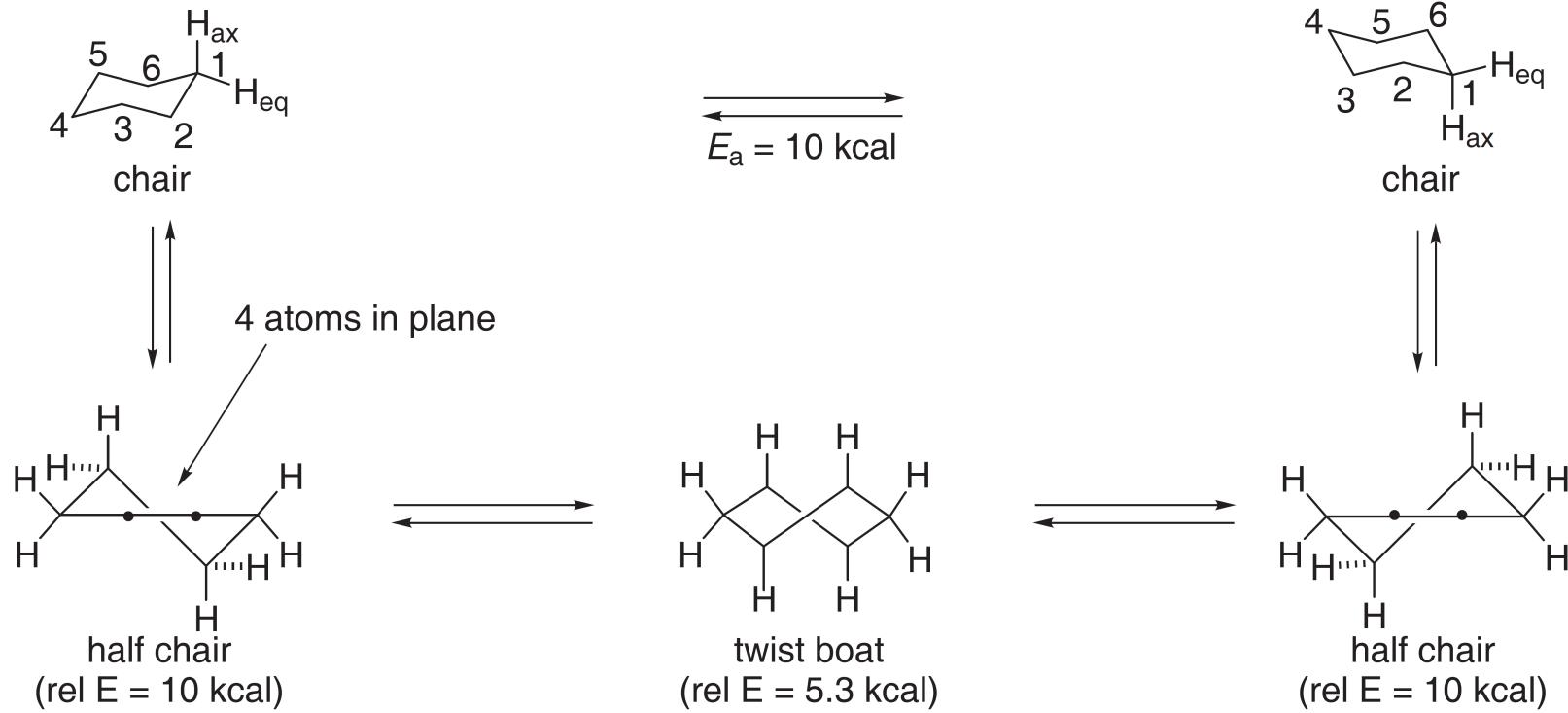


**But this is only part of its mobility. The molecule “flips” from one chair to another chair form.**

Animations

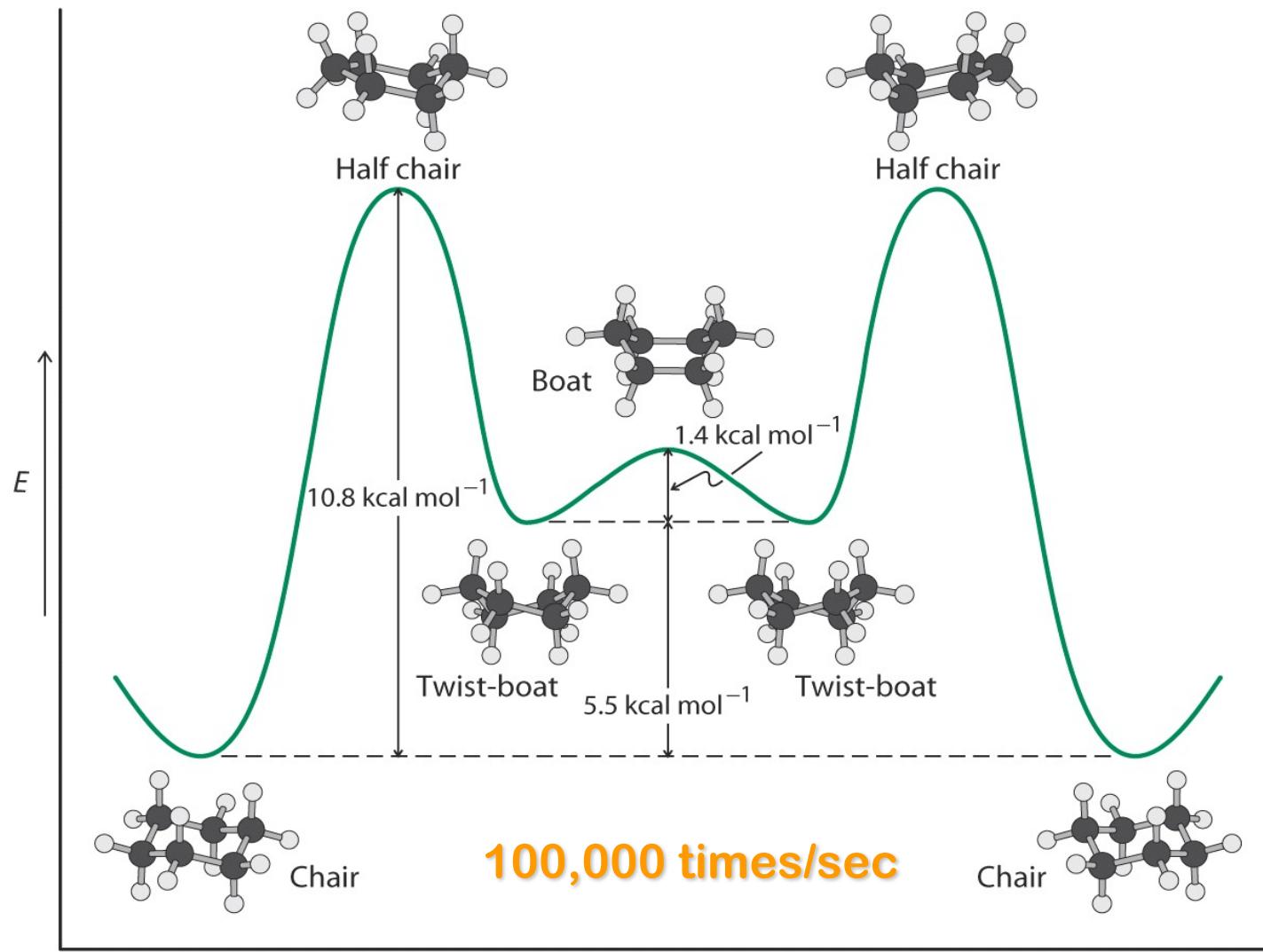
<http://www.chemtube3d.com/>

# 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

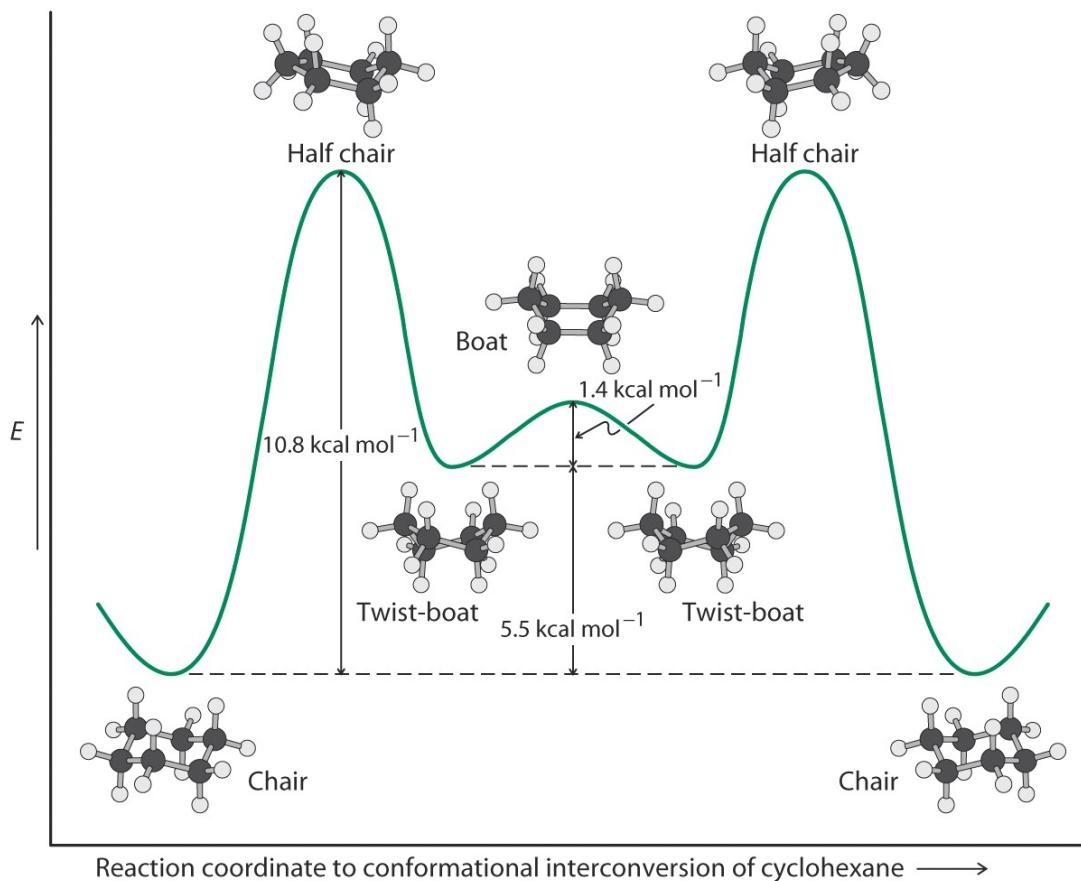


# A grossly approximate comparison

Molecules ‘move around’ on potential energy surfaces



# Ring Inversion or Ring Flipping in Cyclohexane



## Summary

Maxima      (1) Half-chair (2) Boat

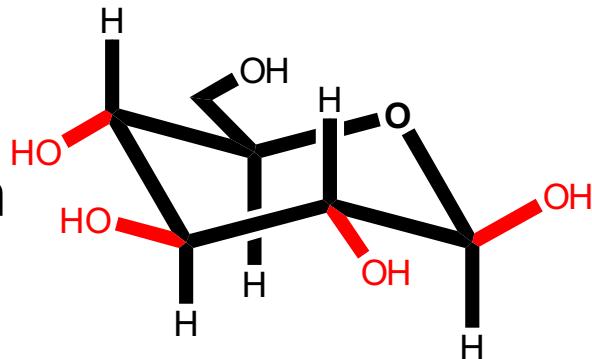
Minima      (1) Chair      (2) Twist-boat

# Examples of chair conformers – (D)-Glucose

## $\beta$ -D-(+)-glucose

Equatorial Region

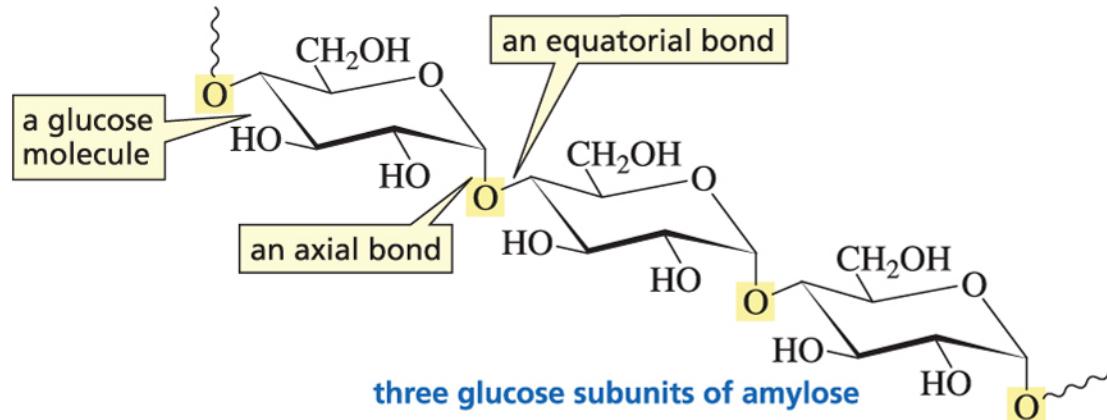
Polar face



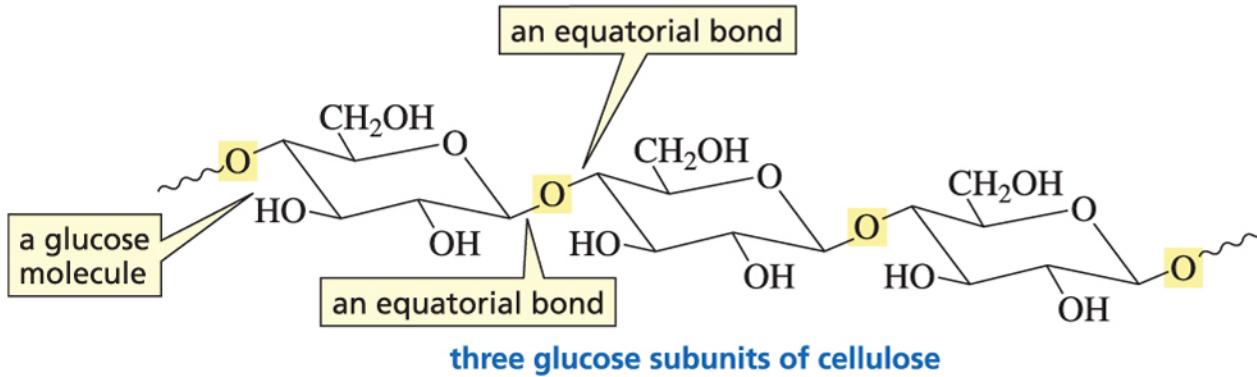
Axial Region

Apolar face

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

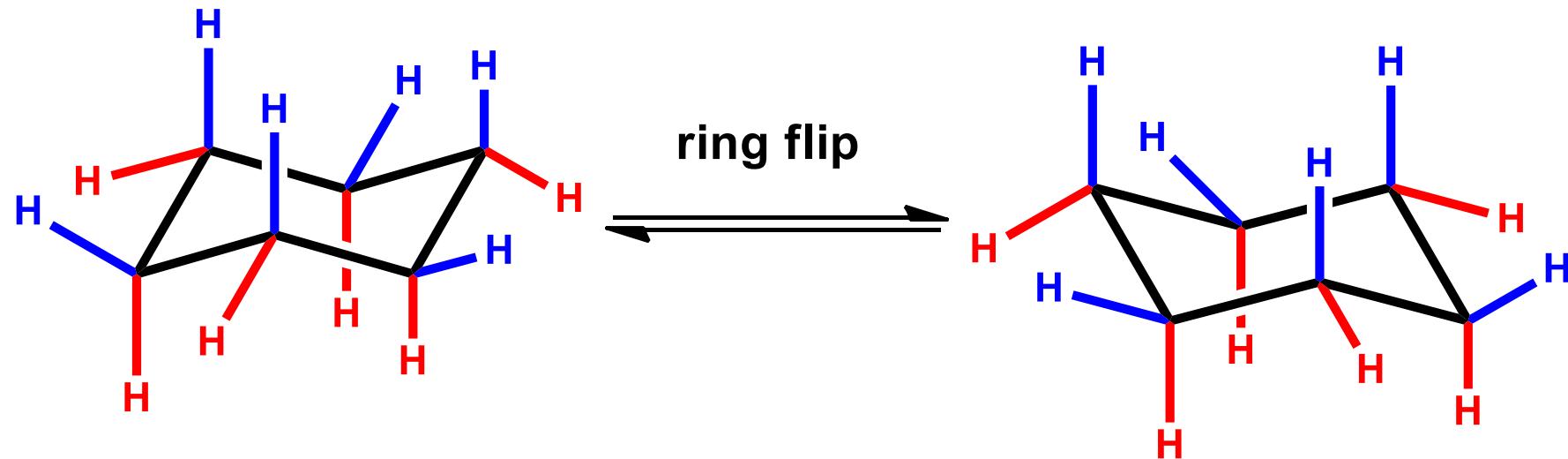


foods rich in starch



cotton plant and cotton towel

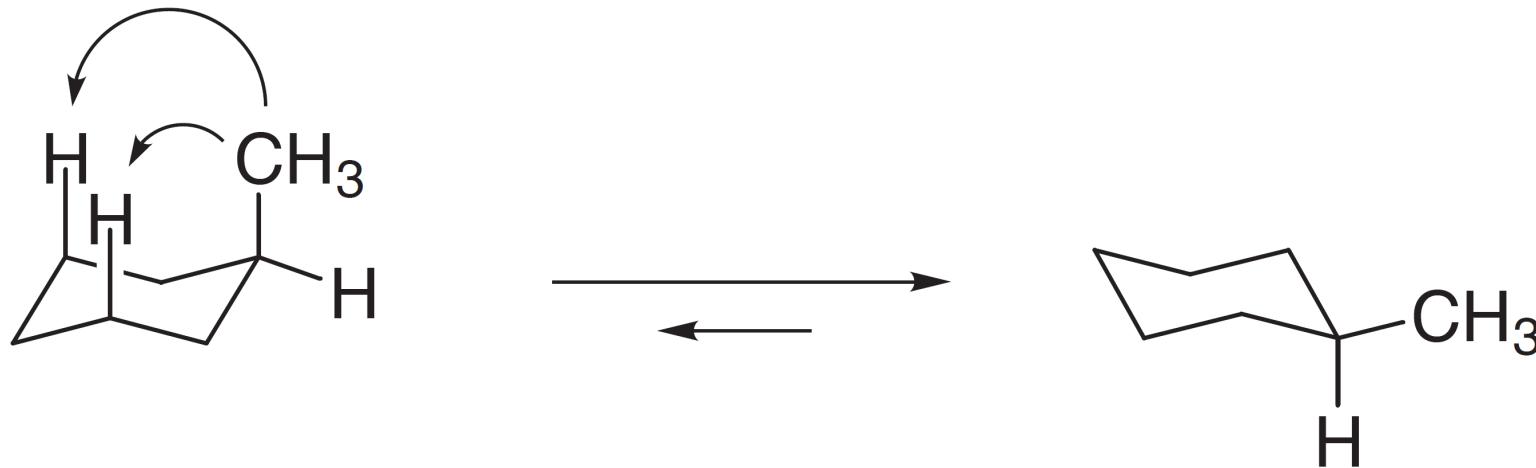
# The Chair-Chair Flip Causes Equatorial-Axial Exchange



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

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

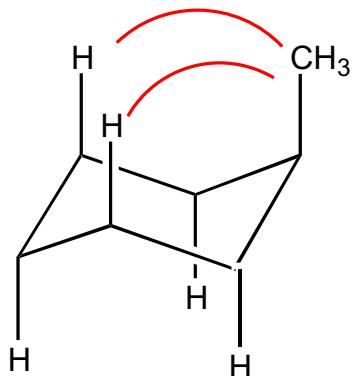
**Conformational Analysis:** Interplay of energetics of ax-eq substituents. Example: Methylcyclohexane



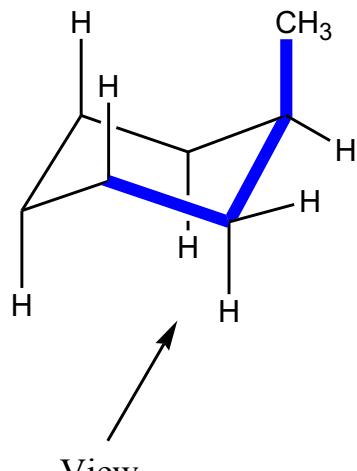
$$\Delta G^\circ = -RT(\ln K)$$
$$\frac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$$

$$K = 21$$

# Why Axial –R group is disfavored?

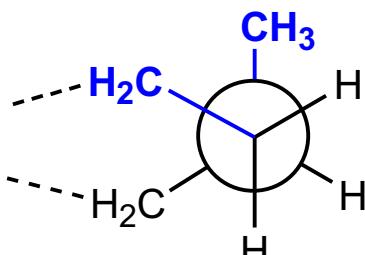


1. van der Waals repulsion between the axial methyl group and the axial hydrogens at C3 and C5 is known as **1,3-diaxial interactions**



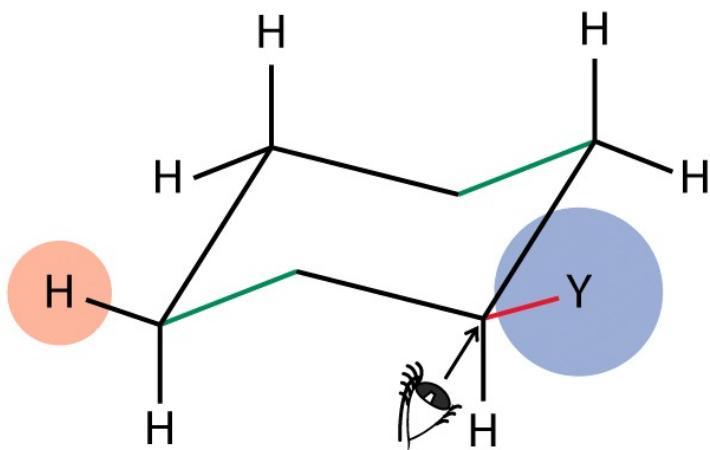
$\text{CH}_3$  is gauche to two C-C bonds

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

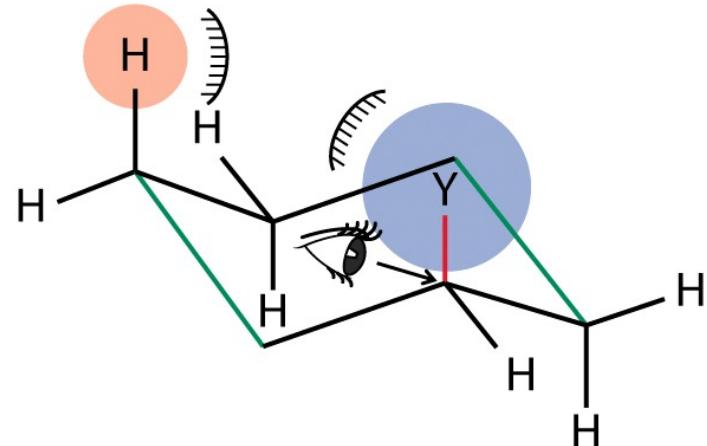


# Axial-Equatorial Conformers

Equatorial Y

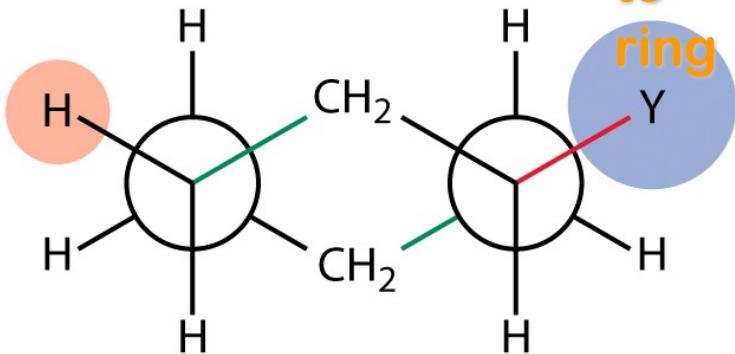


Axial Y

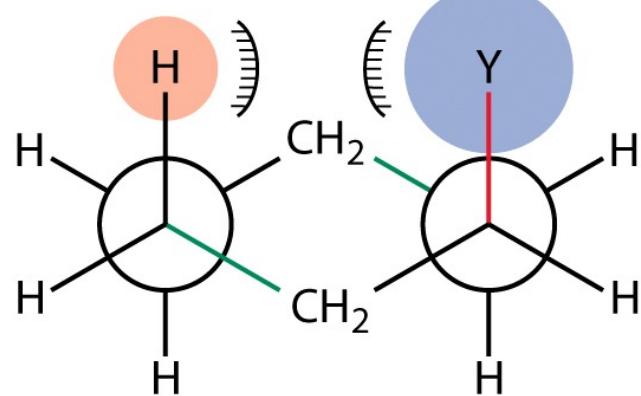


|||

Anti  
to  
ring



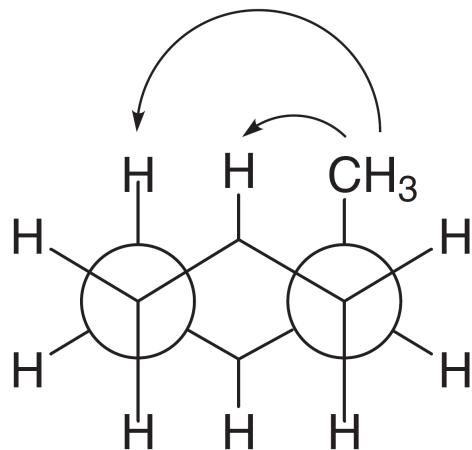
|||  
Gauche  
to ring



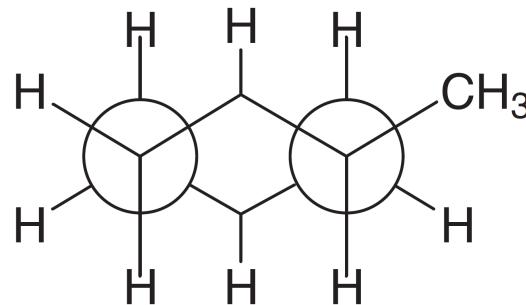
# Gauche interactions

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



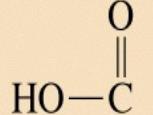
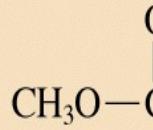
2 gauche butane interactions  
 $2 \times 0.9 \text{ kcal} = 1.8 \text{ kcal}$   
(experimental 1.8 kcal)



0 gauche butane interactions

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	$\Delta G^\circ$ (kcal mol <sup>-1</sup> )	Substituent	$\Delta G^\circ$ (kcal mol <sup>-1</sup> )
H	0	F	0.25
CH <sub>3</sub>	1.70	Cl	0.52
CH <sub>3</sub> CH <sub>2</sub>	1.75	Br	0.55
(CH <sub>3</sub> ) <sub>2</sub> CH	2.20	I	0.46
(CH <sub>3</sub> ) <sub>3</sub> C	≈ 5	HO	0.94
	1.41		0.75
		CH <sub>3</sub> O	
		H <sub>2</sub> N	1.4

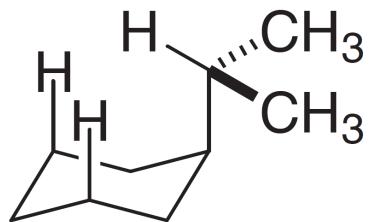
Size  
vs  
bond  
length



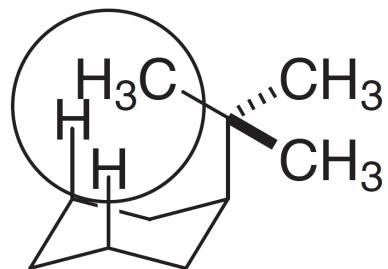
Note: In all examples, the more stable conformer is the one in which the substituent is equatorial.

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

- Note on difference between  $i\text{Pr}$  and  $t\text{Bu}$  A values.



$i\text{Pr}$  group can position H toward "inside,"

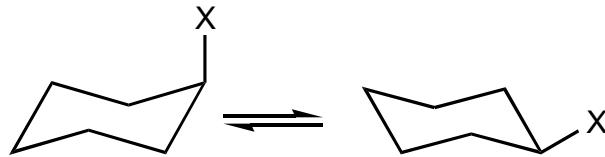


but  $t\text{Bu}$  group cannot.  
Very serious interaction, 7.2 kcal.

# A-value for mono substituted cyclohexanes

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

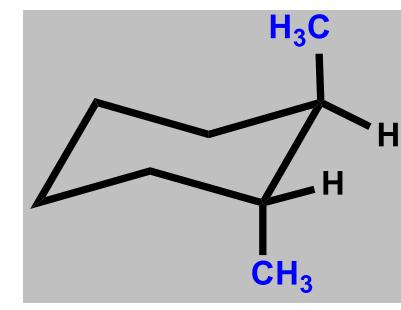
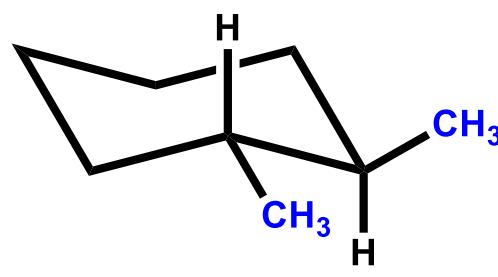
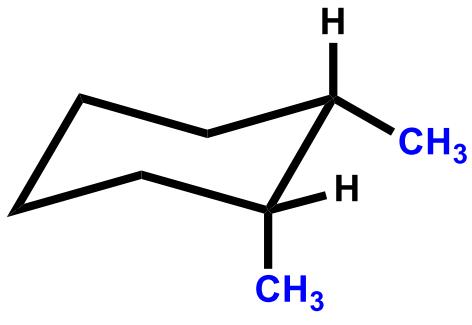
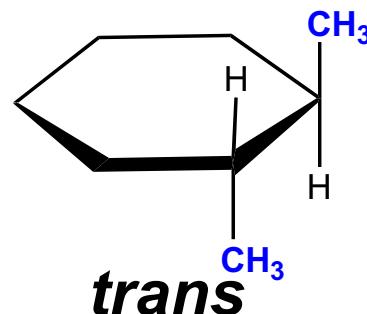
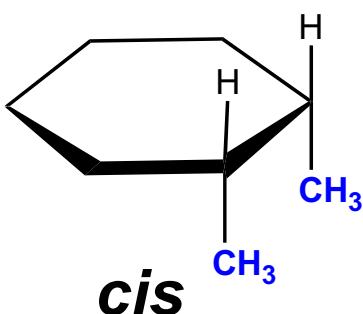
$$\Delta G = G_{\text{ax}} - G_{\text{eq}}$$



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

# Disubstituted cyclohexanes

1,2-disubstituted

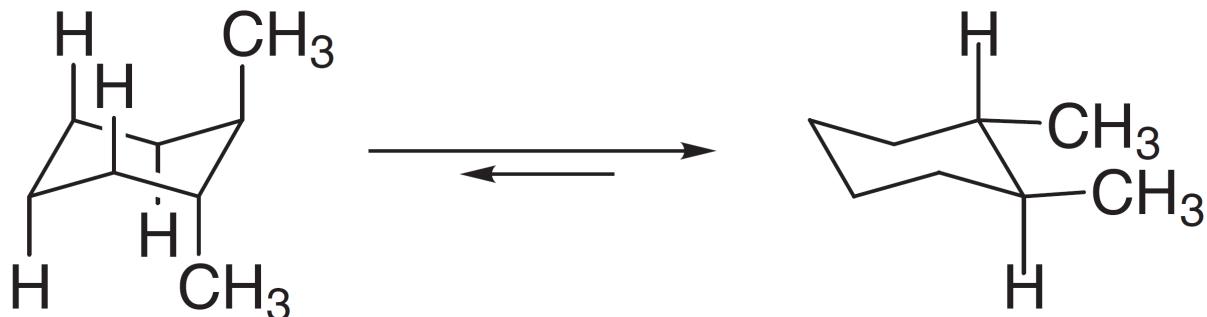


*cis*

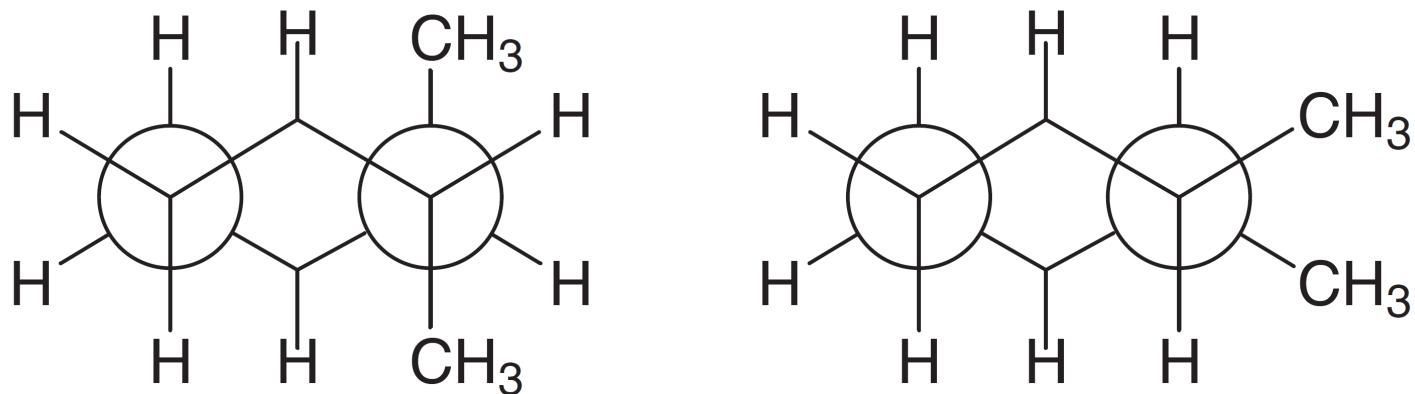
*trans*

*trans*

## *trans*-1,2-dimethylcyclohexane



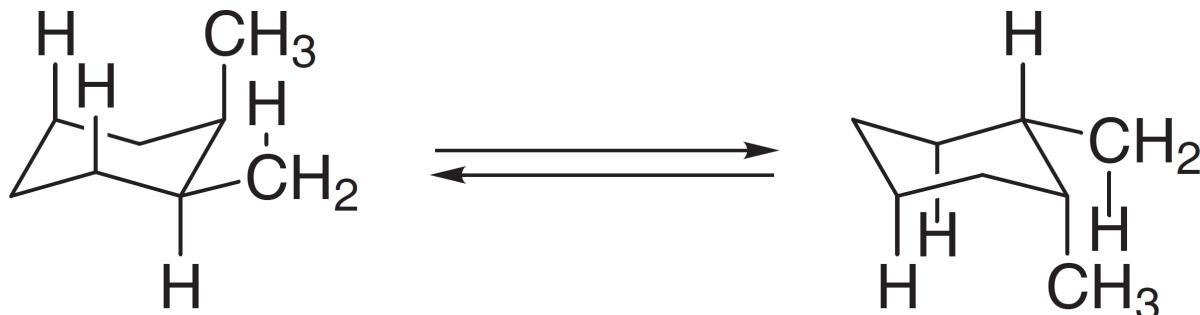
2.7 kcal/mol more stable



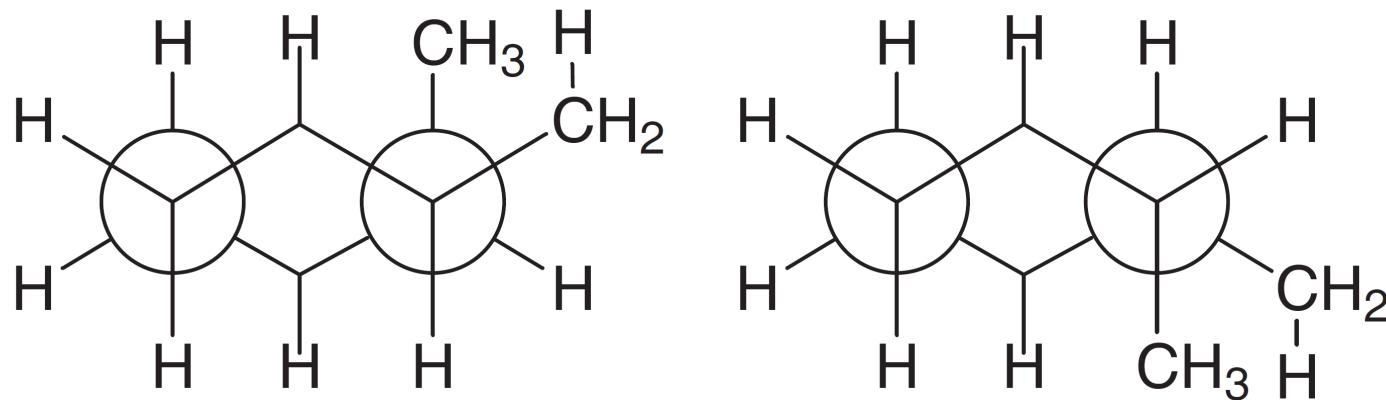
$$4 \times (\text{gauche interaction}) \\ 4 \times (0.9 \text{ kcal}) = 3.6 \text{ kcal}$$

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

## *cis*-1,2-dimethylcyclohexane



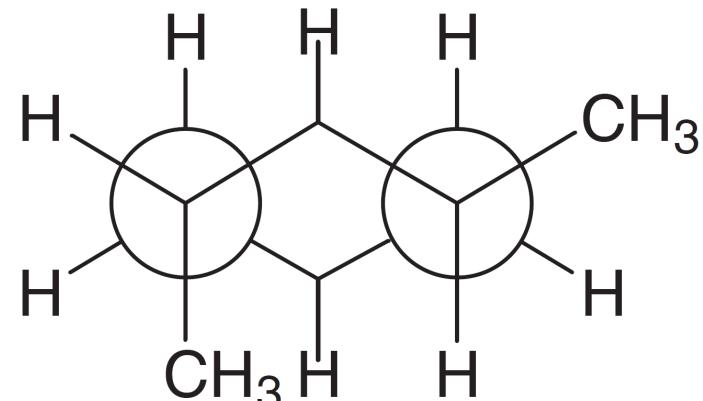
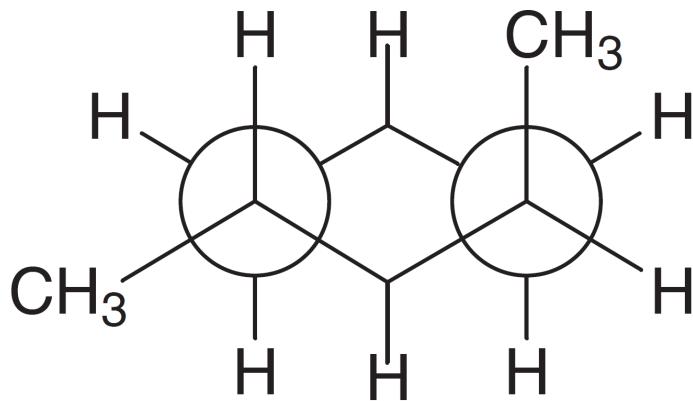
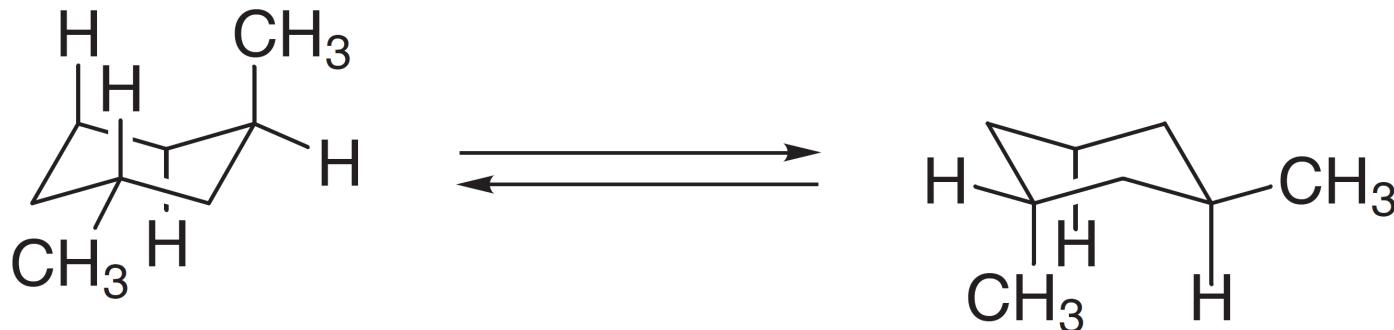
$$\Delta E = 0 \text{ kcal/mol}$$



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

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

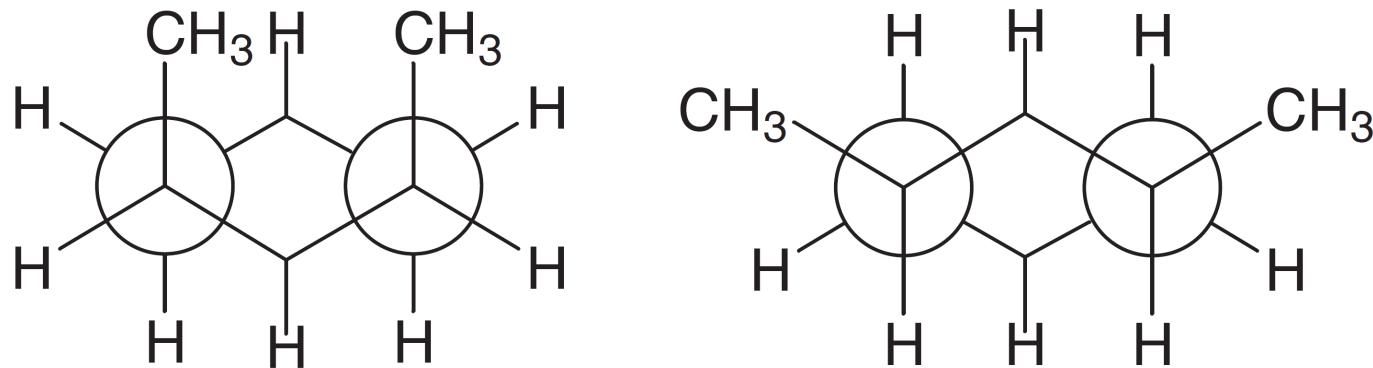
## *trans*-1,3-dimethylcyclohexane



$2 \times (\text{gauche interaction})$   
 $2 \times (0.9 \text{ kcal}) = 1.8 \text{ kcal}$

$2 \times (\text{gauche interaction})$   
 $2 \times (0.9 \text{ kcal}) = 1.8 \text{ kcal}$

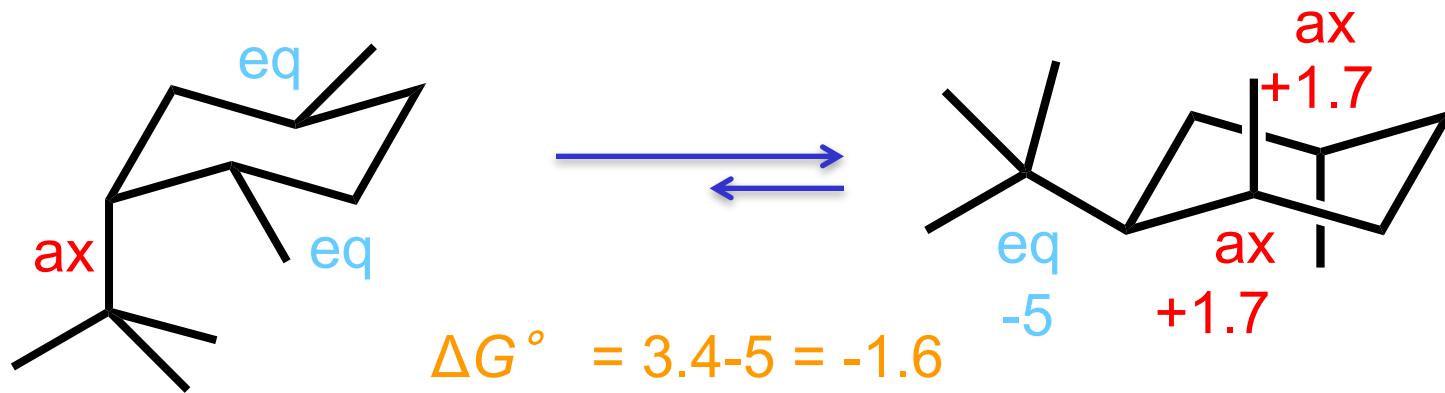
## *cis*-1,3-dimethylcyclohexane



$$\begin{aligned}
 & 2 \times (\text{gauche interaction}) + \\
 & 1 \times (\text{Me-Me 1,3 diaxial int}) \\
 & 2 \times (0.9 \text{ kcal}) + 3.7 \text{ kcal} \\
 & = 5.5 \text{ kcal}
 \end{aligned}$$

$$\begin{aligned}
 & 0 \times (\text{gauche interaction}) \\
 & 0 \times (0.9 \text{ kcal}) = 0 \text{ kcal}
 \end{aligned}$$

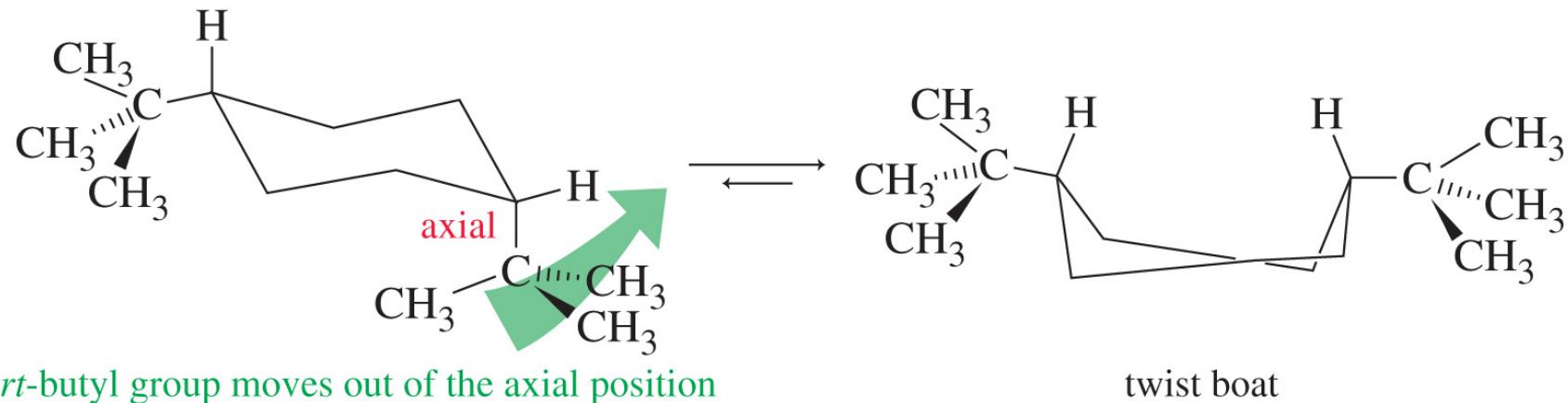
# The largest group often biases one conformation



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

but  
**NOT LOCKED**

# *Cis*-1,4-ditertbutylcyclohexane

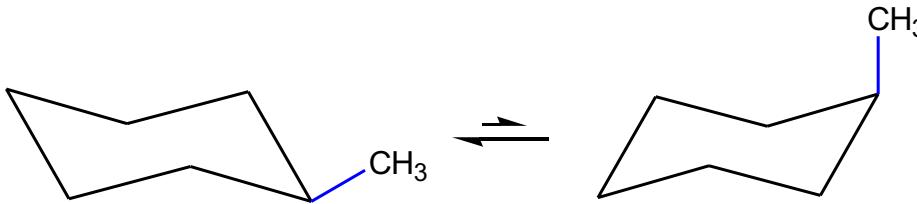


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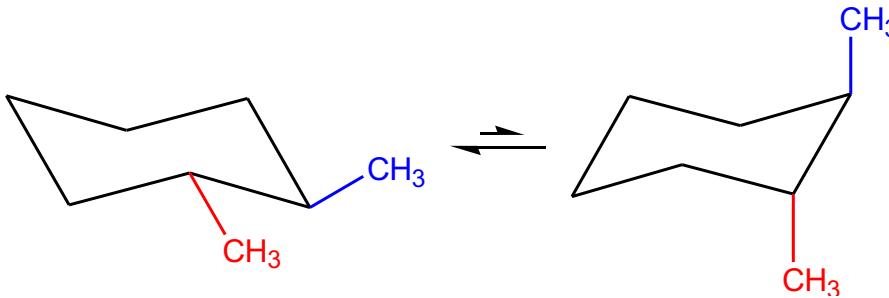
The most stable conformation of *cis*-1,4-di-tertbutylcyclohexane is the twist boat. Both chair conformations require one of the bulky *t*-butyl groups to occupy an axial position.

# 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



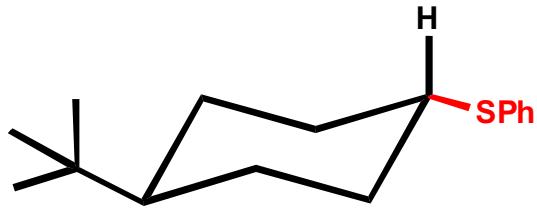
(ii) A *cis*-isomer would remain as *cis*-isomer, so is *trans*



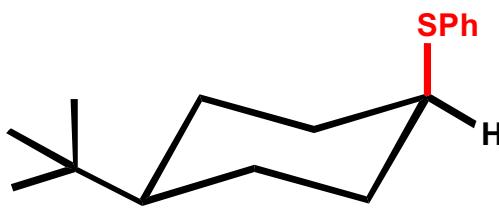
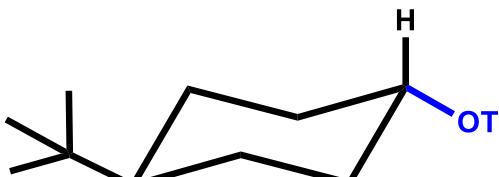
# Conformational Features and Chemical Reactivity

Reactions of axial and equatorial substituents could be very different!

cis



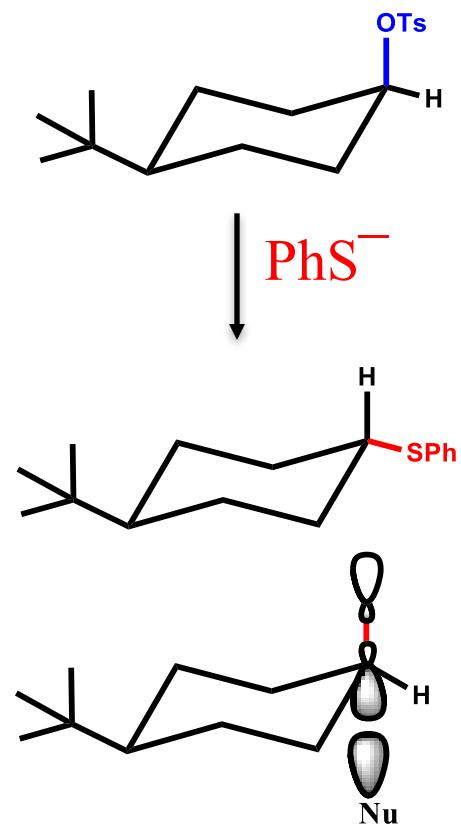
trans



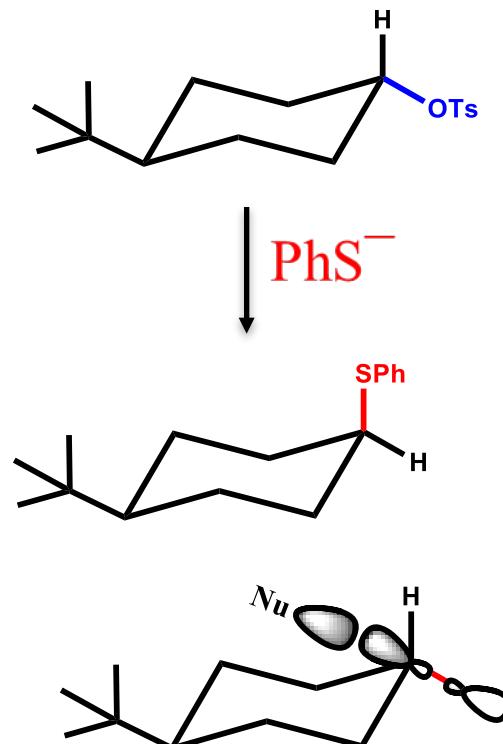
**cis-compound reacts 31 times faster!!**

# Selectivity in nucleophilic substitution reactions

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



favored attack

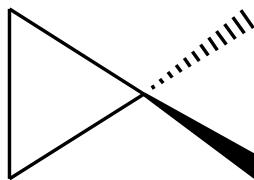


hindered attack

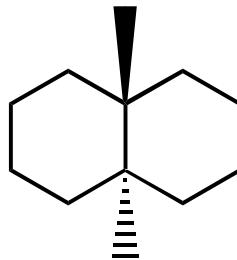
# Polycyclic compounds

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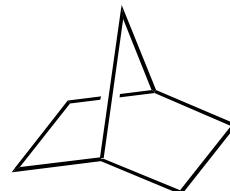
**Spiro cyclic** compounds: Compounds that share one carbon atom between two rings



**Fused ring** compounds: Compounds that share two adjacent carbon atoms

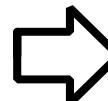
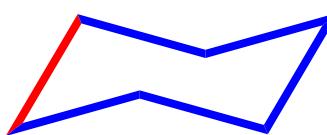
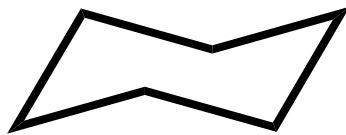
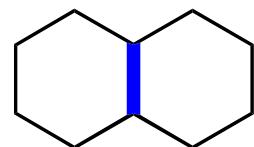


**Bicyclic** ring compounds: Compounds that share two non-adjacent carbon atoms

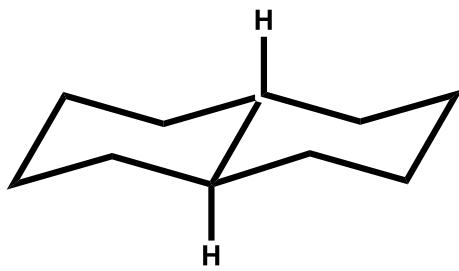


# Fused ring compounds - Decalins

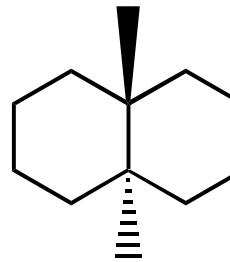
Fused cyclohexane rings which share a common C-C bond



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



**trans-decalin**

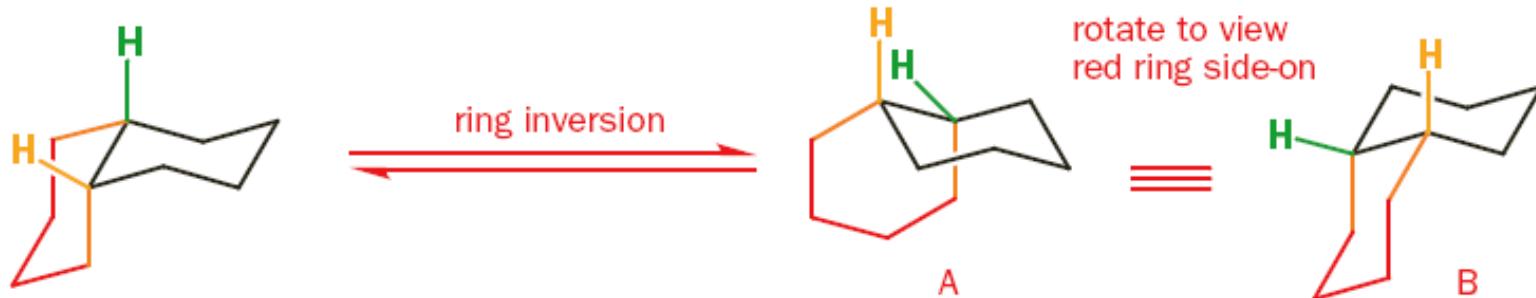


**trans-decalins are conformationally LOCKED** as they cannot undergo ring flipping.

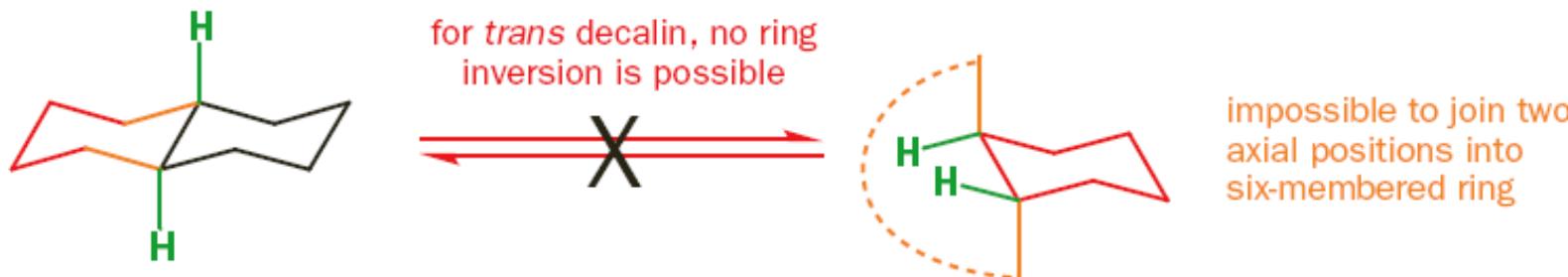
# Cis - Decalins

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

ring inversion of *cis*-decalin

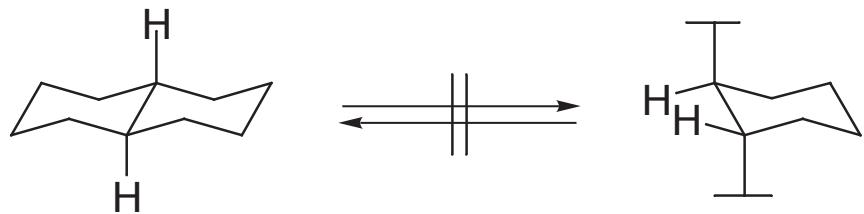


no ring inversion in *trans*-decalin

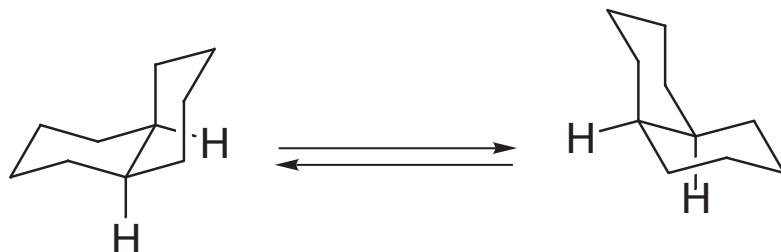


# Cis- and trans-Decalins

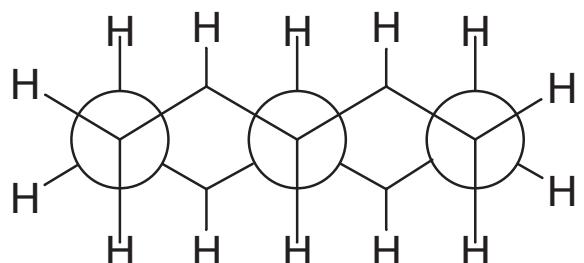
*trans*-decalin



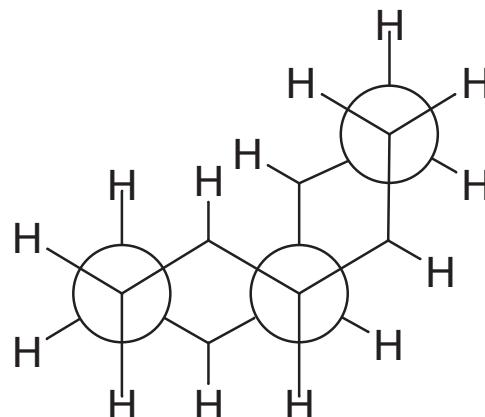
*cis*-decalin



two conformations equivalent



0.0 kcal



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

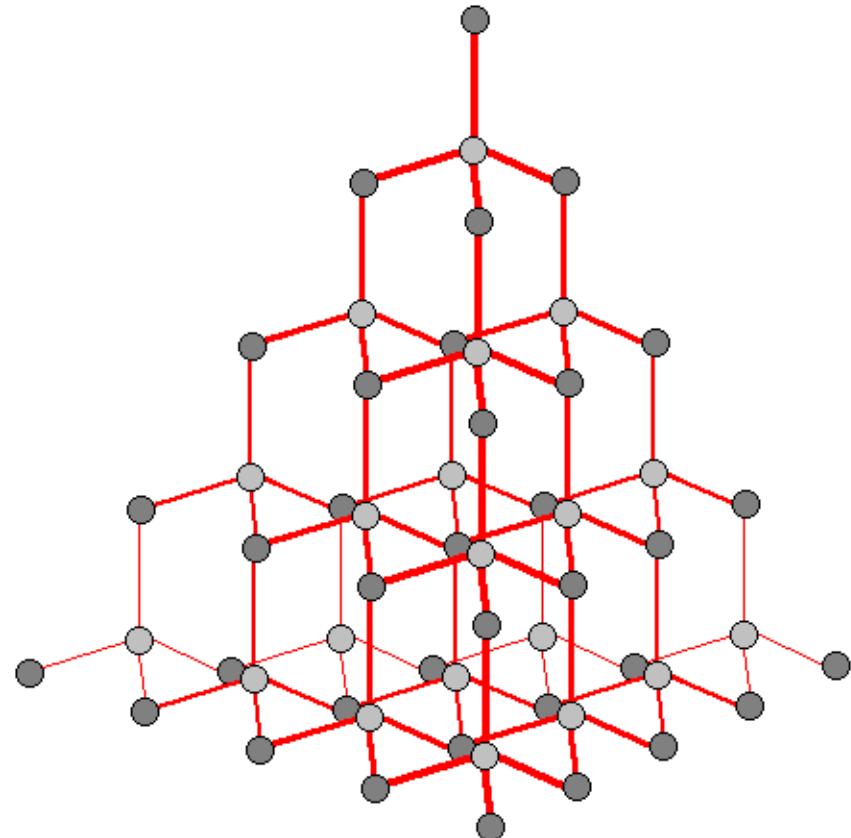
$\Delta E$  between *cis*- and *trans*-decalin = 2.7 kcal/mol

# Stability of trans-ring fusion

---

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

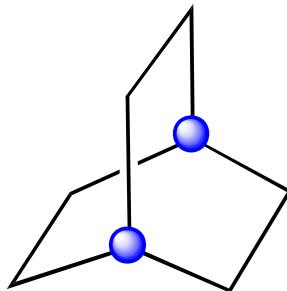
Diamond structure resembles trans-fusion



# Bicyclic compounds

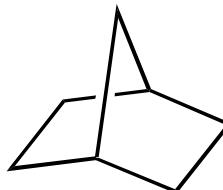
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Compounds sharing two non-adjacent carbon atoms are termed as bicyclic compounds



**Bicyclo[2.2.2]octane**

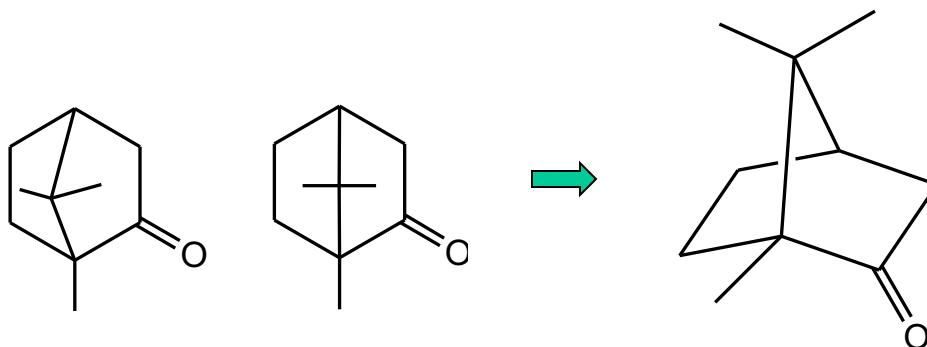
Bridgehead carbons are indicated as blue circles



**Bicyclo[2.2.1]heptane**

# Bicyclic compounds

Camphor skeleton is [2.2.1] system



Sanskrit: *karpoor*  
(Also known as *karpooram*)

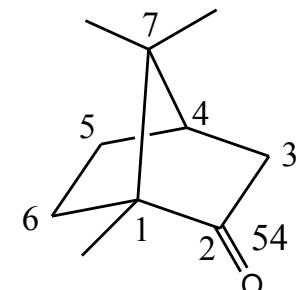
Used as moth repellent,  
antimicrobial, used in medicine

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**

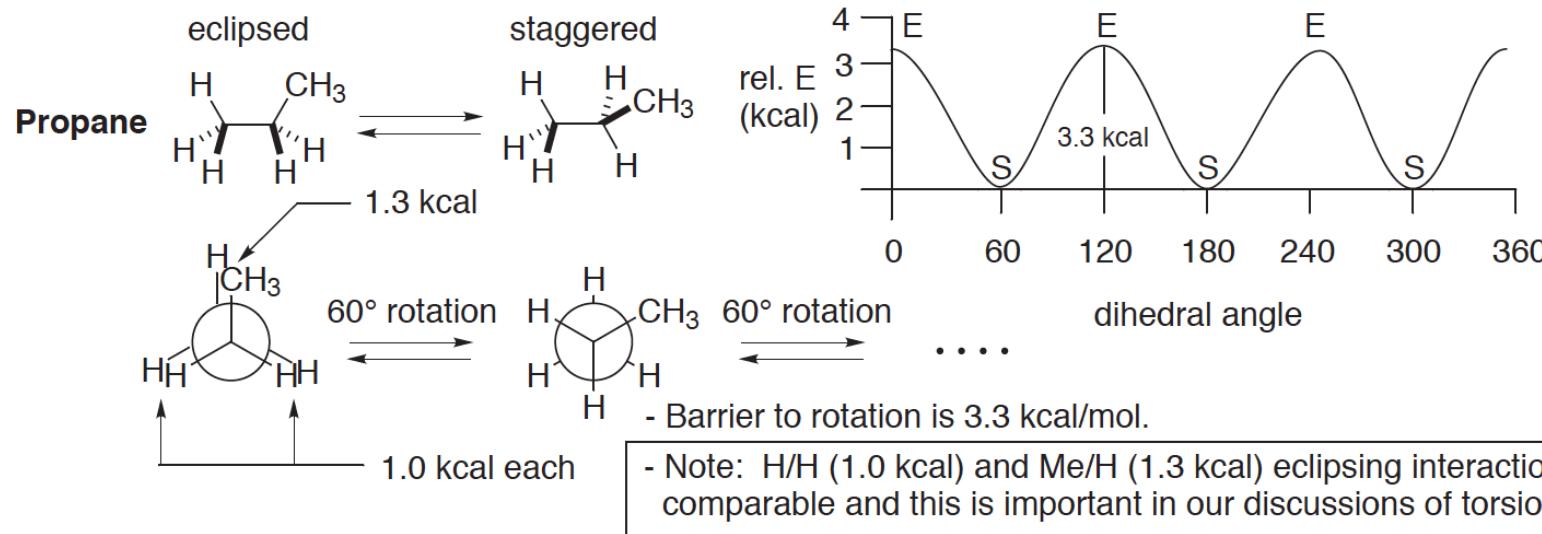
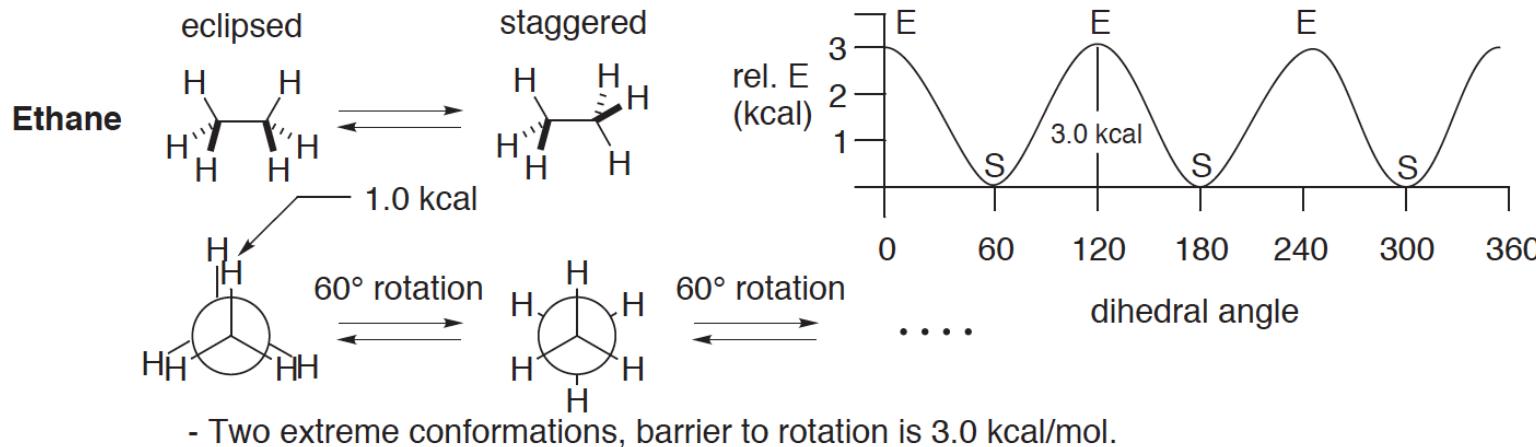


# **THANK YOU**

# 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.

# Conformation of Acyclic Compounds



What is the rationale for barrier or torsional strain?

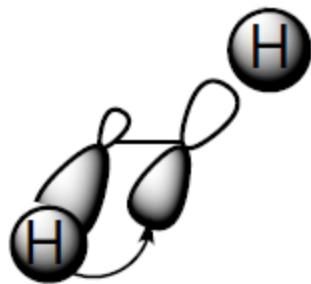
**Electronic argument:** Bond pair repulsion in eclipsed conformation

**Steric argument:** van der Waals repulsion

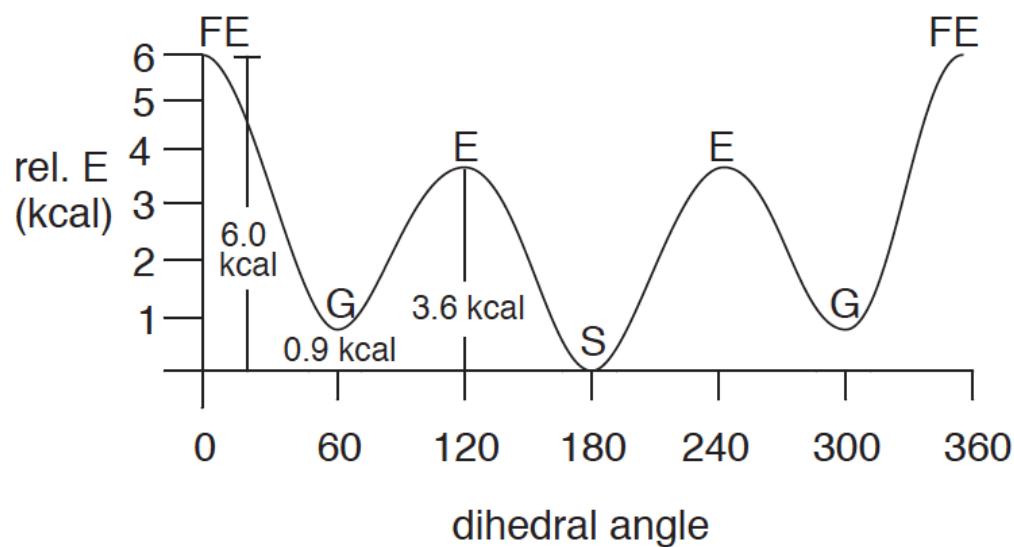
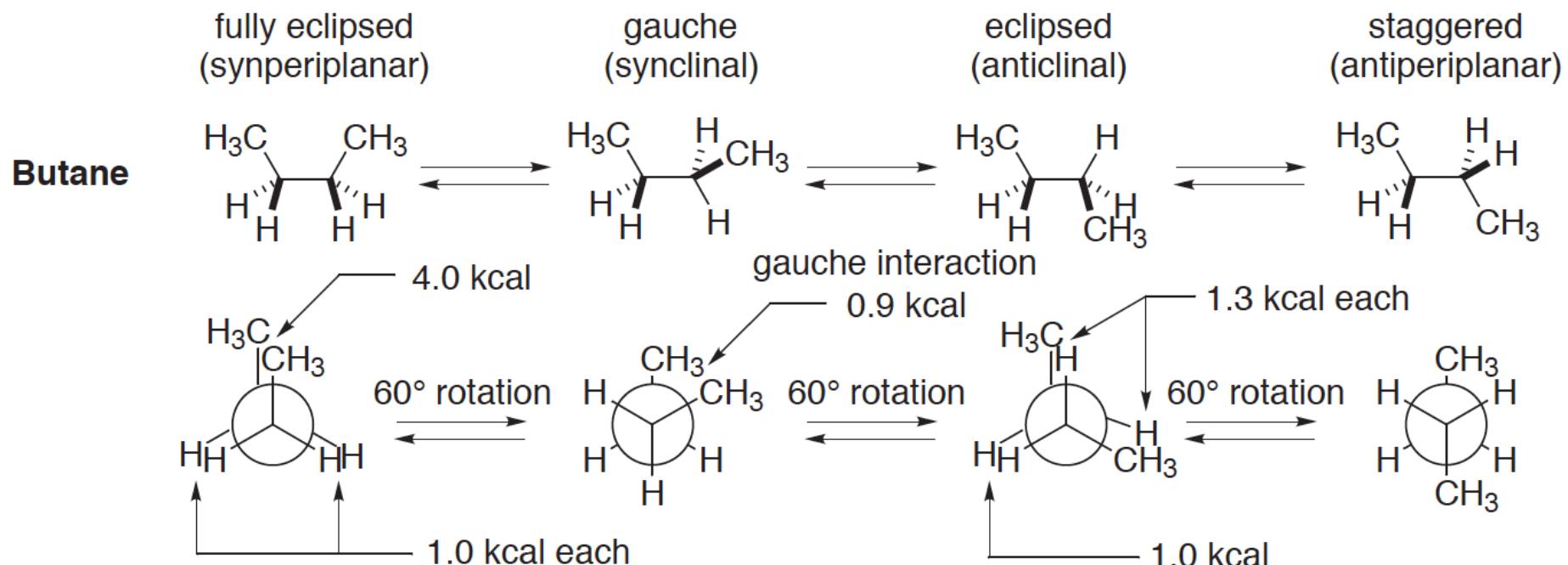
Careful analysis of the van der Waals radii show that the hydrogens do not come close enough to account for the barrier to rotation

The barrier becomes significantly larger only when additional steric components are added, the barrier is intrinsic property of the bond and not directly dependent on substituent size

Currently it is accepted that the main factor responsible for the torsional barrier is  $\sigma-\sigma^*$  delocalization (hyperconjugation), which favors the staggered conformation



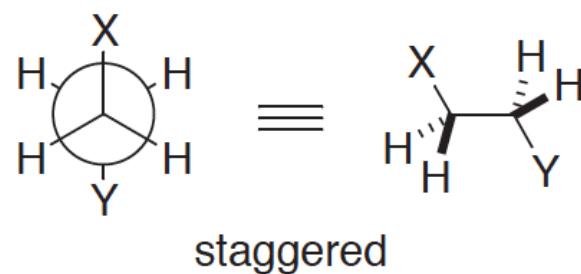
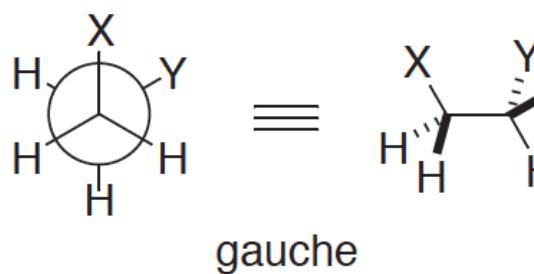
hyperconjugation  
in *anti* conformation



- Note: the gauche butane interaction and its magnitude (0.9 kcal) are very important and we will discuss it frequently.

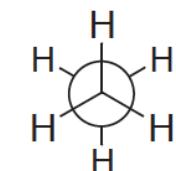
## Substituted Ethanes

- There are some exceptions to the lowest energy conformation. Sometimes, a gauche conformation is preferred over staggered if X,Y are electronegative substituents.  
cf: Kingsbury *J. Chem. Ed.* **1979**, 56, 431.

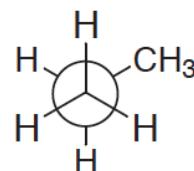


$E_{\text{gauche}} < E_{\text{staggered}}$  if  $X = \text{OH}, \text{OAc}$  and  $Y = \text{Cl}, \text{F}$

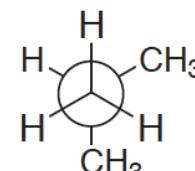
## Rotational Barriers



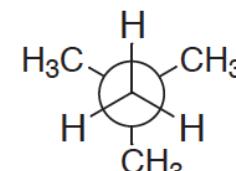
2.88 kcal/mol  
(3.0 kcal/mol)



3.40 kcal/mol  
(3.3 kcal/mol)



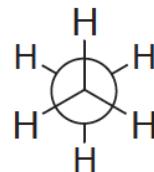
3.90 kcal/mol  
(3.6 kcal/mol)



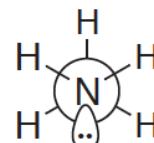
4.70 kcal/mol  
(3.9 kcal/mol)

- Experimental
- Simple prediction

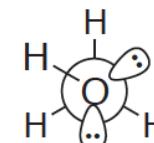
- The rotational barrier increases with the number of CH<sub>3</sub>/H eclipsing interactions.



2.88 kcal/mol  
(3.0 kcal/mol)



1.98 kcal/mol  
(2.0 kcal/mol)



1.07 kcal/mol  
(1.0 kcal/mol)

- Experimental
- Simple prediction

- The rotational barrier increases with the number of H/H eclipsing interactions.

# Important Types of Molecular STRAINS

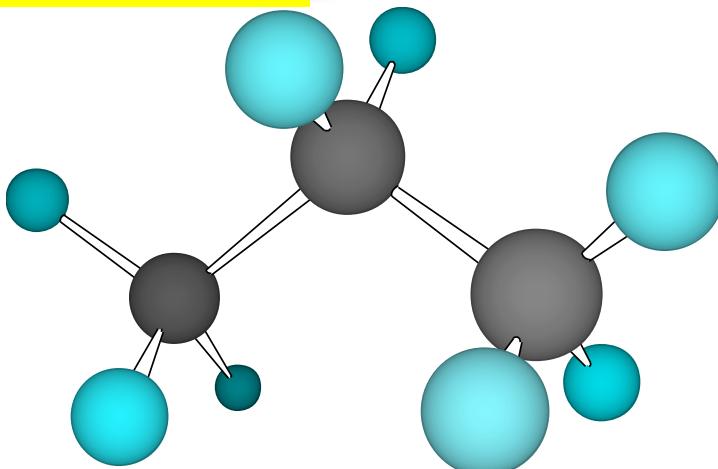
**Torsional Strain:** Extra energy of eclipsed conformation arising due to the repulsion between bonding electrons of one substituent with that of the other as they pass close to each other

**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

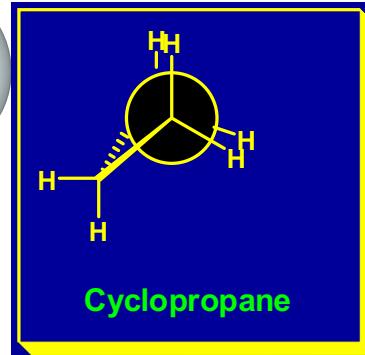
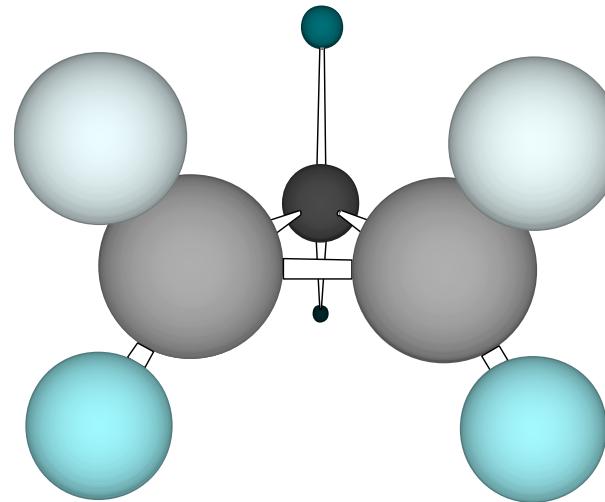
**Angle Strain:** Strain induced in molecules when the bond angles are different from the desired tetrahedral bond angle of  $109.5^\circ$

# Small Ring Compounds – (1) cyclopropane

## Propane



## Cyclopropane



Angle strain : **None**

(all angles are nearly tetrahedral)

Steric strain: **None**

(Fully staggered conformer)

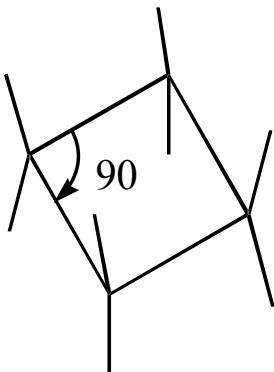
Deviation of **49.5°** per carbon

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

Cyclopropane suffers from angle strain and torsional strain

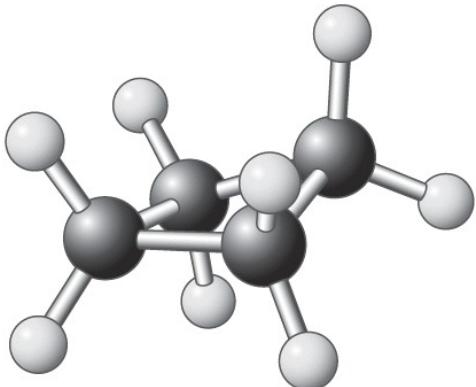
Renders higher reactivity, Weaker C-C and C-H bonds

# Small Ring Compounds – (2) cyclobutane



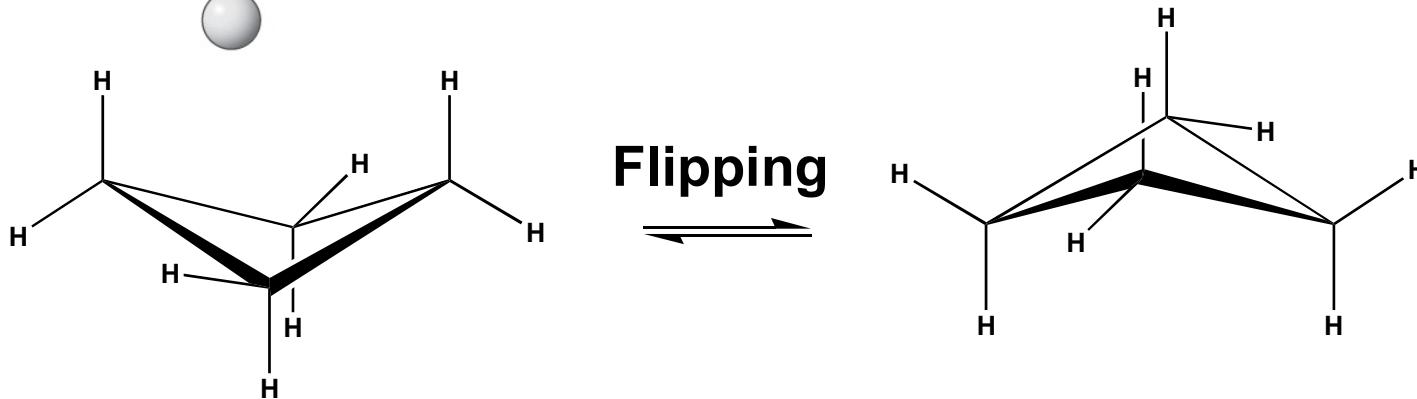
**Planar?** Problems are: **Angle strain** plus severe **torsional strain**

Compromise is



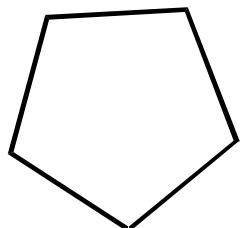
**Ring puckering**

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

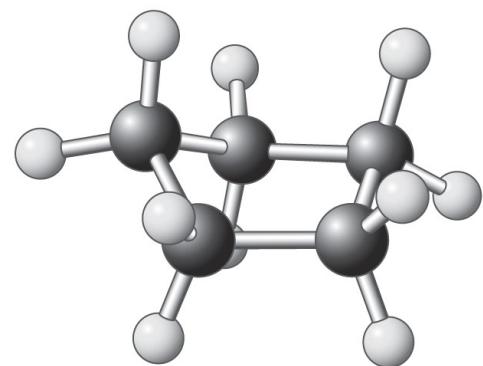


Cyclobutane has a '**wing shaped**' or '**puckered**' conformer

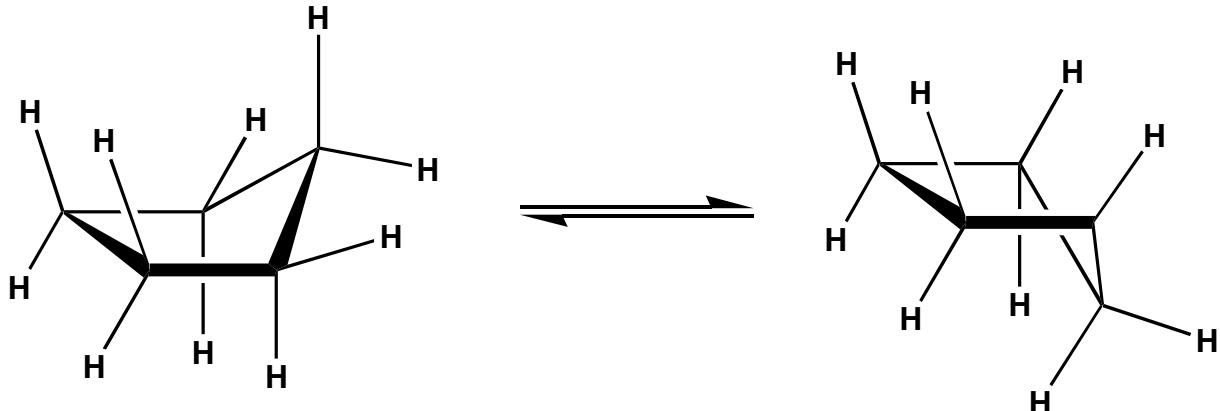
# Small Ring Compounds – (3) Cyclopentane



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



Four coplanar carbon atoms



Cyclopentane has an ‘envelope’ conformer

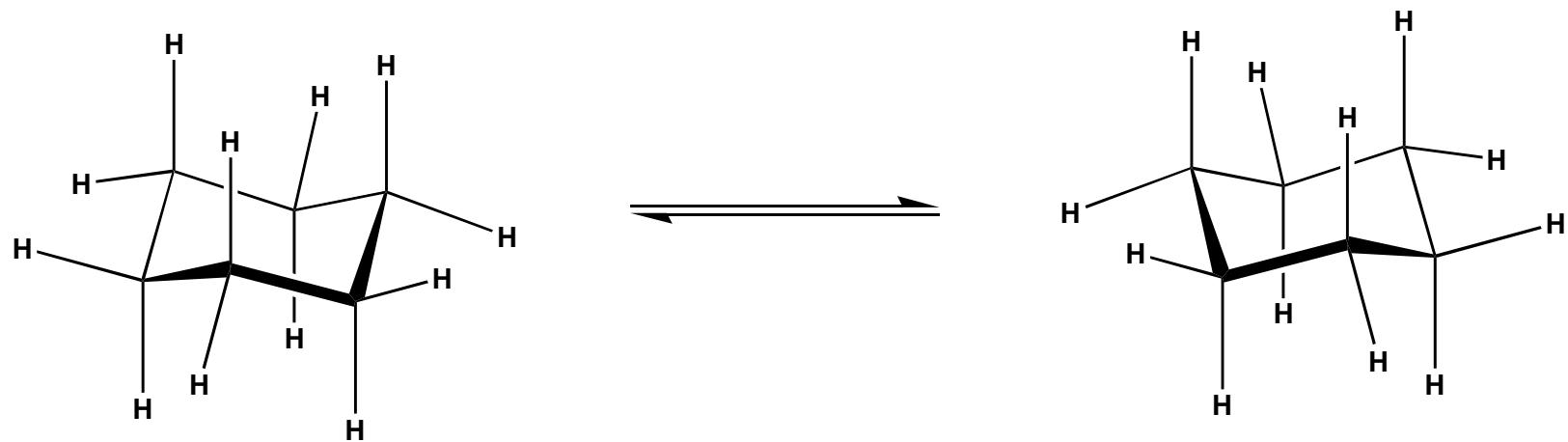
# Small Ring Compounds – (4) Cyclohexane

CH105  
R. B. Sunoj

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

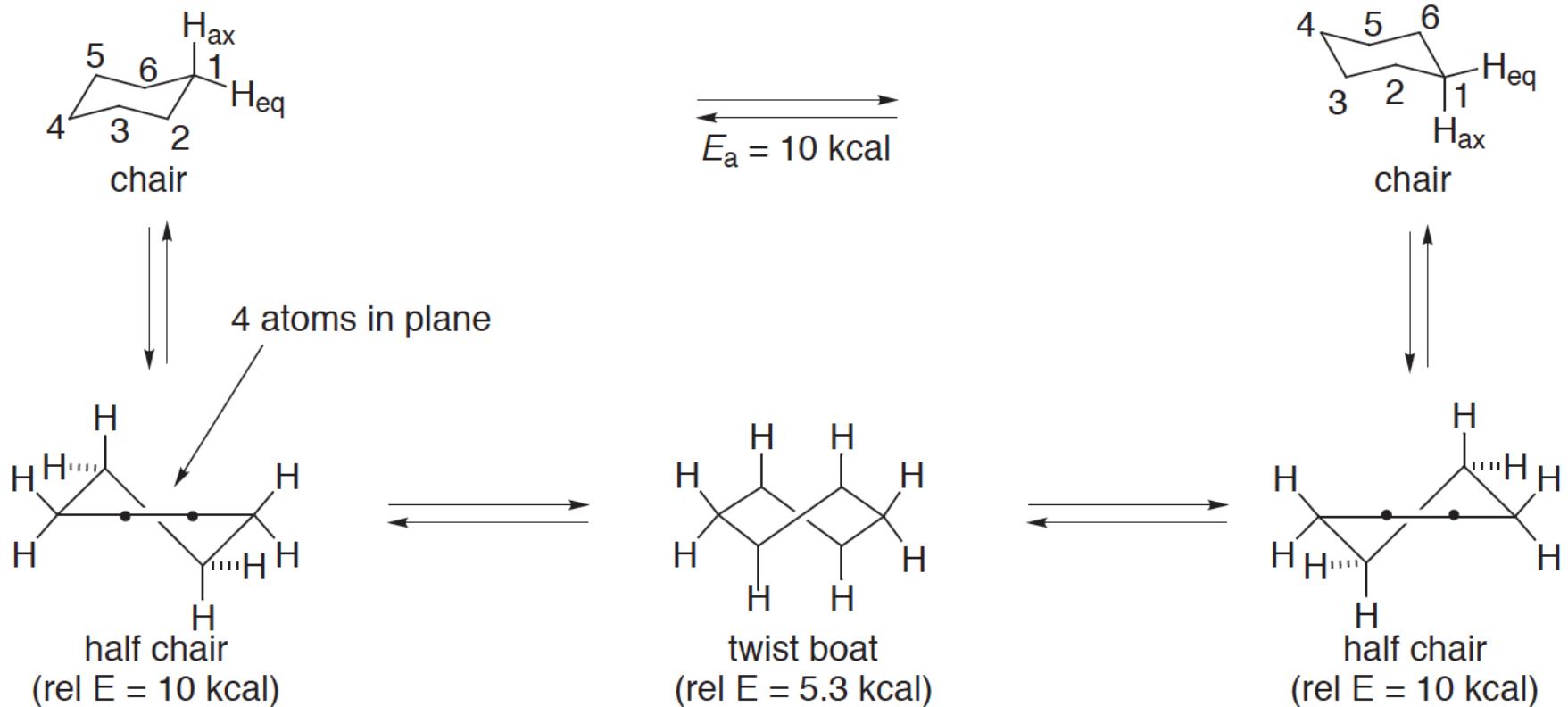
Both angle and torsional (eclipsing interactions) strains can be avoided by **ring puckering**.

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

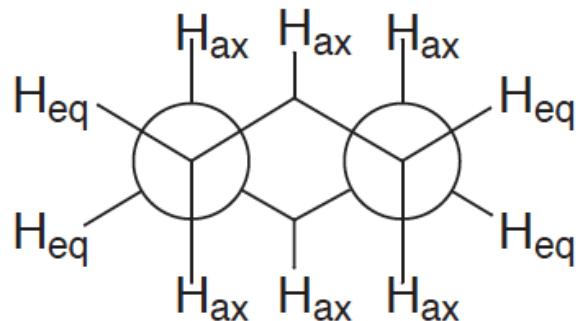


## B. Cyclohexane and Substituted Cyclohexanes, A Values ( $\Delta G^\circ$ )

### 1. Cyclohexane

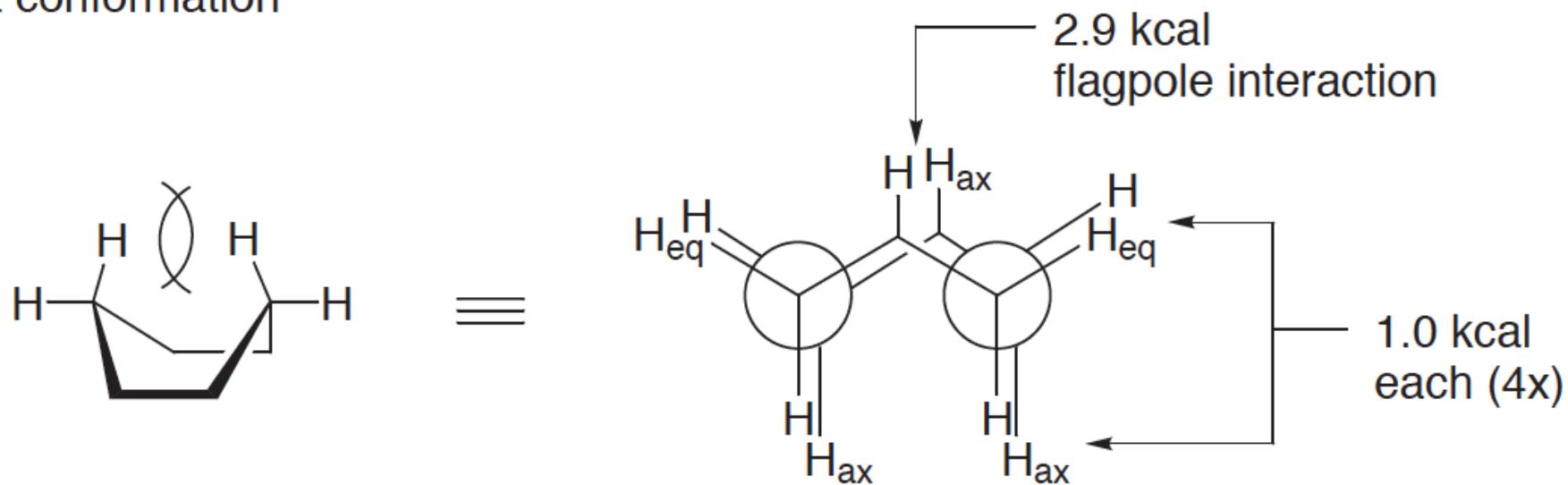


- Chair conformation (all bonds staggered)

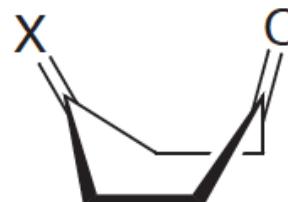


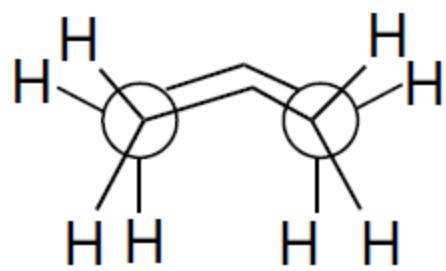
- Rapid interconversion at 25 °C ( $E_a = 10 \text{ kcal/mol}$ , 20 kcal/mol available at 25 °C).
- H<sub>ax</sub> and H<sub>eq</sub> are indistinguishable by  $^1\text{H}$  NMR at 25 °C.
- At temperatures < –70 °C, H<sub>eq</sub> and H<sub>ax</sub> become distinct in  $^1\text{H}$  NMR.

- Boat conformation

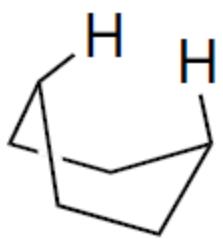


- Rel E = 6.9 kcal, not local minimum on energy surface.
- More stable boat can be obtained by twisting (relieves flagpole interaction somewhat).
- Twist boat conformation (rel E = 5.3 kcal) does represent an energy minimum.
- The boat conformation becomes realistic if flagpole interactions are removed, i.e.

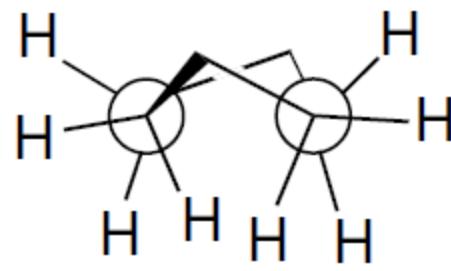




eclipsing in boat  
conformation

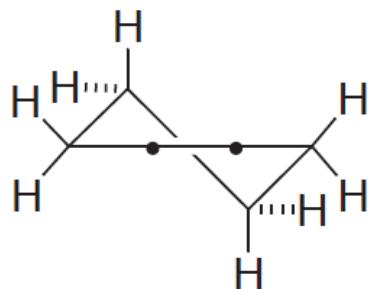


flagpole interaction  
in boat conformation

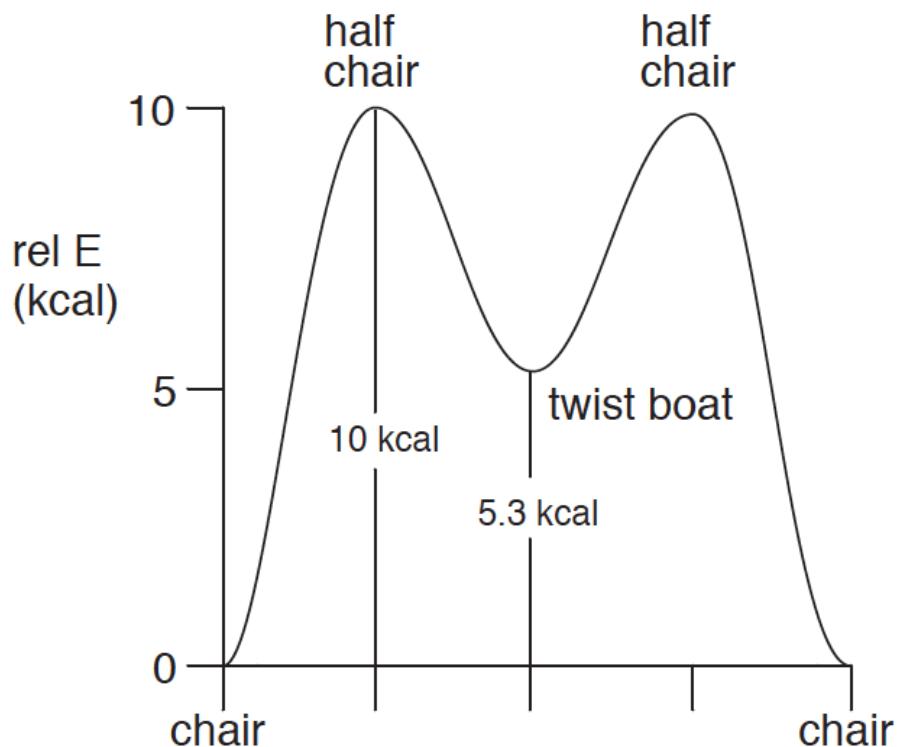


partial relief of eclipsing  
in twist conformation

- Half chair conformation



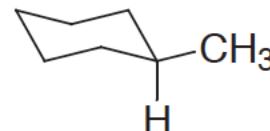
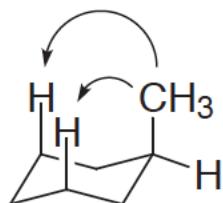
- Energy maximum (rel E = 10.0 kcal)



D.H.R. Barton received the 1969 Nobel Prize in Chemistry for his contributions to conformational analysis, especially as it relates to steroids and six-membered rings.  
Barton *Experientia* **1950**, *6*, 316.

## Substituted Cyclohexanes

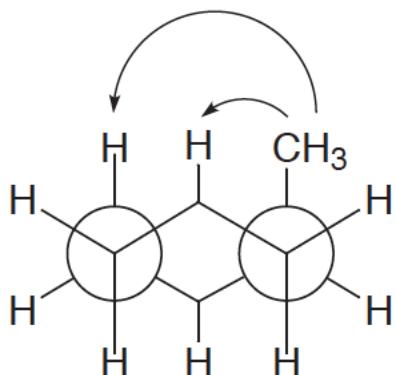
- Methylcyclohexane



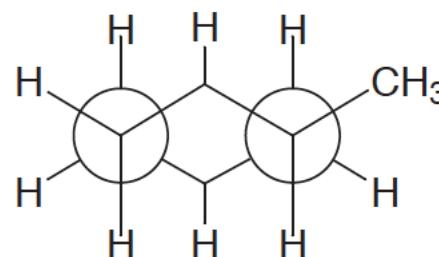
1.8 kcal more stable

$$\Delta G^\circ = -RT(\ln K)$$
$$\frac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$$
$$K = 21$$

- 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)



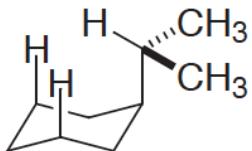
0 gauche butane interactions

- A Value ( $-\Delta G^\circ$ ) = Free energy difference between equatorial and axial substituent on a cyclohexane ring.

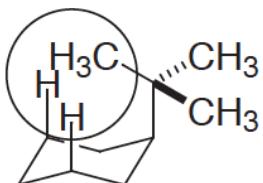
## Typical A Values

R	A Value (kcal/mol)	R	A Value (kcal/mol)
F	0.25	CN	0.2
Cl	0.52	C≡CH	0.41
Br	0.5–0.6	ca. 0.5 kcal	Small, linear
I	0.46	NO <sub>2</sub>	1.1
OH	0.7 (0.9)	CH=CH <sub>2</sub>	1.7
OCH <sub>3</sub>	0.75	CH <sub>3</sub>	1.8
OCOCH <sub>3</sub>	0.71	(2 <sup>nd</sup> atom effect very small)	2 <sup>nd</sup> atom effect very small
NH <sub>2</sub>	1.8 (1.4)	<sup>n</sup> C <sub>3</sub> H <sub>7</sub>	2.1
NR <sub>2</sub>	2.1	<sup>n</sup> C <sub>4</sub> H <sub>9</sub>	2.1
CO <sub>2</sub> H	1.2 (1.4)	CH(CH <sub>3</sub> ) <sub>2</sub>	2.1
CO <sub>2</sub> Na	2.3	C(CH <sub>3</sub> ) <sub>3</sub>	>4.5 (ca. 5.4)
CO <sub>2</sub> Et	1.1	C <sub>6</sub> H <sub>5</sub>	3.1 (2.9)
SO <sub>2</sub> Ph	2.5		

- Note on difference between <sup>i</sup>Pr and <sup>t</sup>Bu A values.

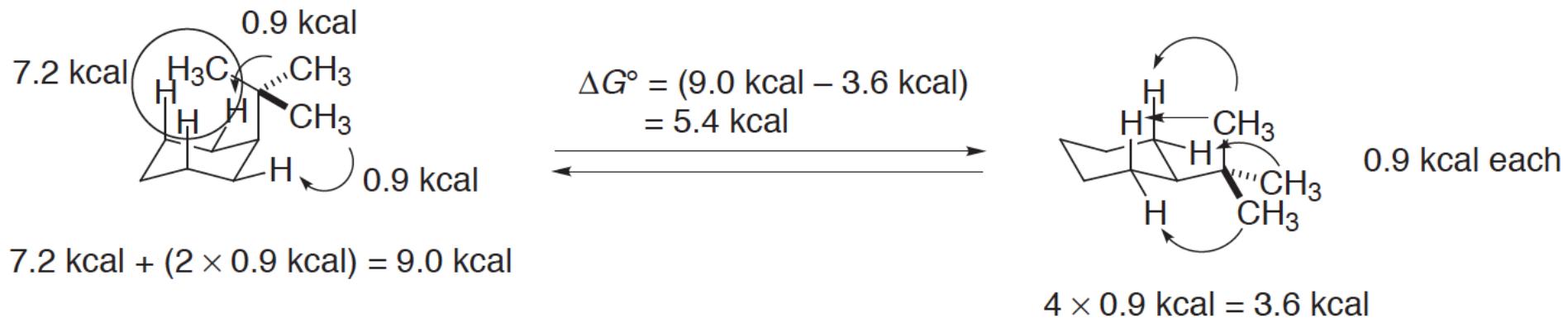


<sup>i</sup>Pr group can position H toward "inside,"

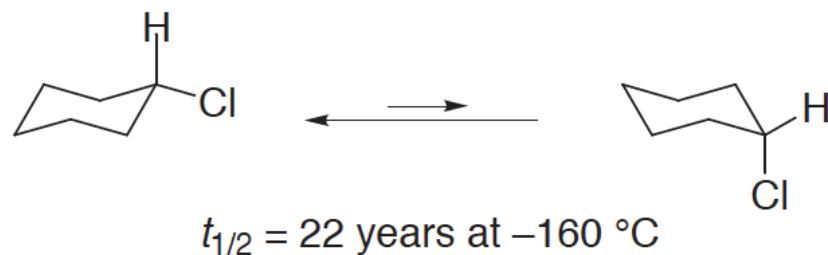


but <sup>t</sup>Bu group cannot.  
Very serious interaction, 7.2 kcal.

- Determination of A value for  $t\text{Bu}$  group.

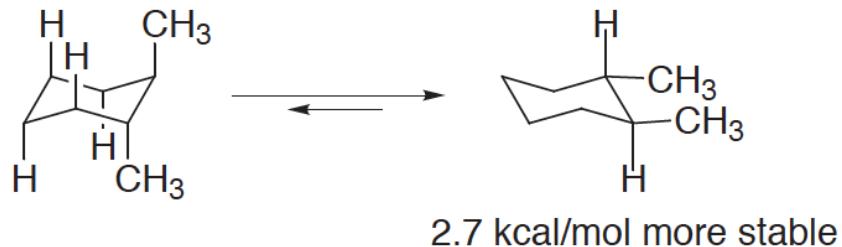


- Note on interconversion between axial and equatorial positions.

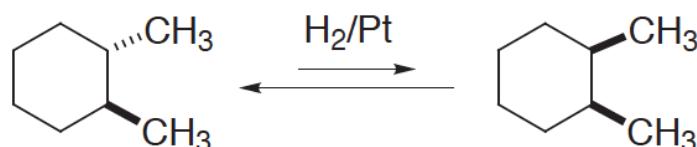
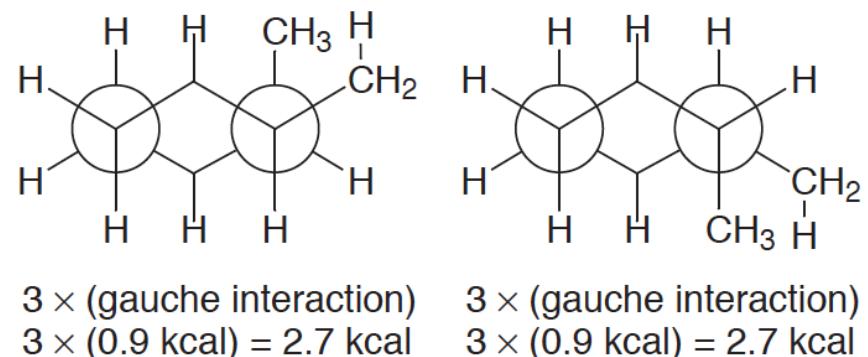
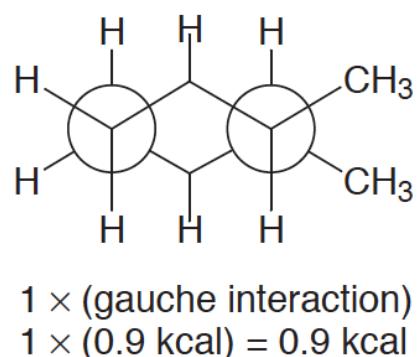
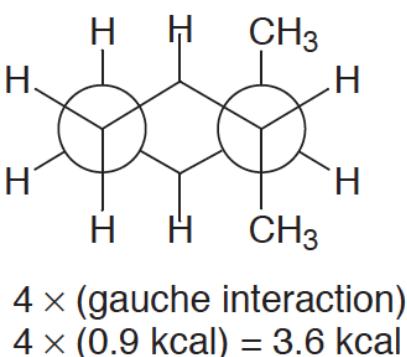
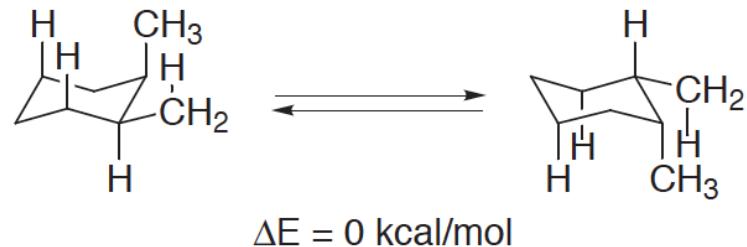


Even though Cl has a small A value (i.e., small  $\Delta G^\circ$  between rings with equatorial and axial Cl group), the  $E_a$  (energy of activation) is high (it must go through half chair conformation).

*trans*-1,2-dimethylcyclohexane

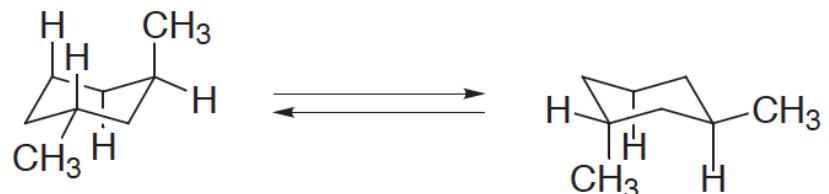


*cis*-1,2-dimethylcyclohexane

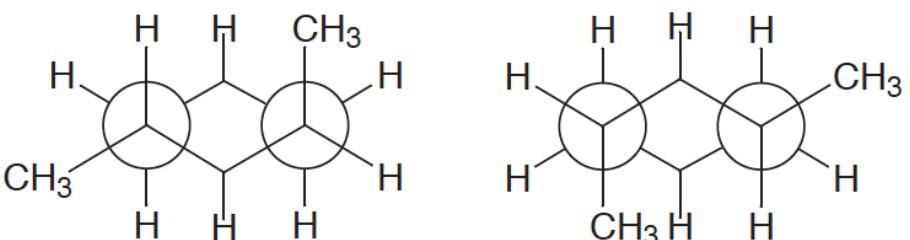
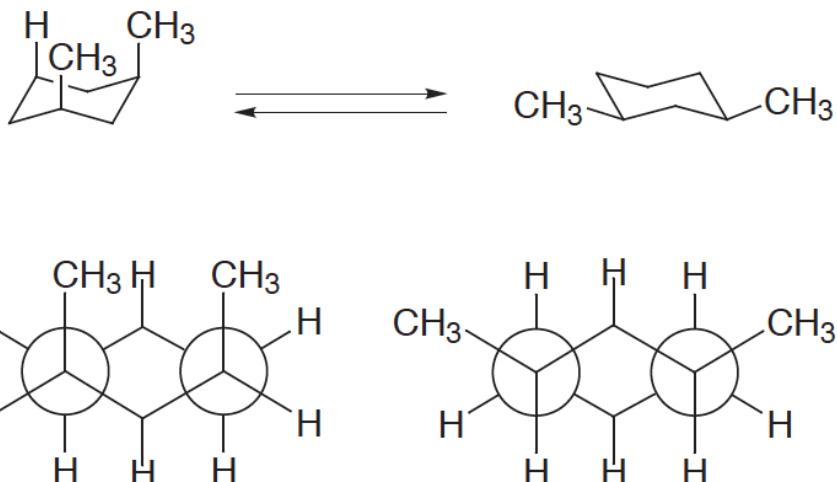


$ΔG = 1.87 \text{ kcal/mol (exp)}$   
 $ΔG = 1.80 \text{ kcal/mol (calcd)}$

*trans*-1,3-dimethylcyclohexane



*cis*-1,3-dimethylcyclohexane

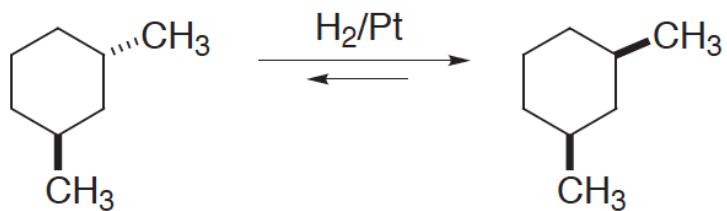


$$2 \times (\text{gauche interaction}) \\ 2 \times (0.9 \text{ kcal}) = 1.8 \text{ kcal}$$

$$2 \times (\text{gauche interaction}) \\ 2 \times (0.9 \text{ kcal}) = 1.8 \text{ kcal}$$

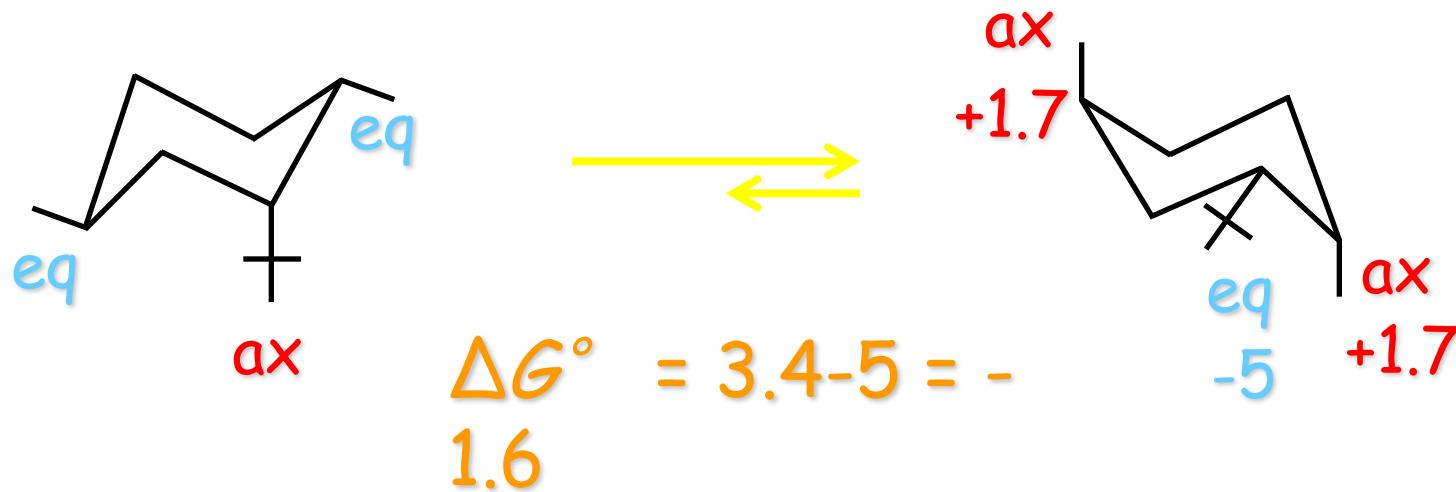
$$2 \times (\text{gauche interaction}) + \\ 1 \times (\text{Me-Me 1,3 diaxial int}) \\ 2 \times (0.9 \text{ kcal}) + 3.7 \text{ kcal} \\ = 5.5 \text{ kcal}$$

$$0 \times (\text{gauche interaction}) \\ 0 \times (0.9 \text{ kcal}) = 0 \text{ kcal}$$



$$\Delta G = 1.80 \text{ kcal/mol (exp and calcd)}$$

# The largest group often biases one conformation

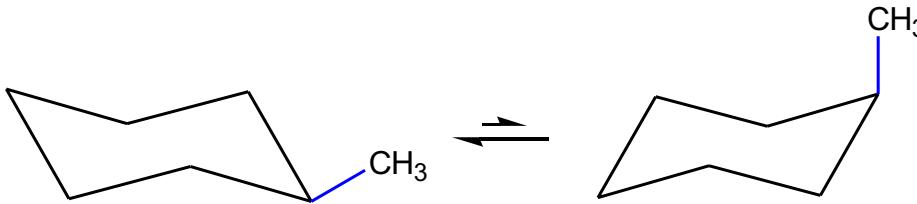


**Conformation of t-butylcyclohexane is said to be  
BIASED**

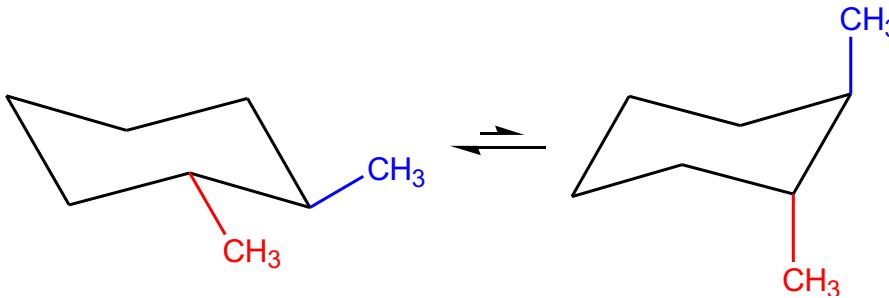
but  
**NOT LOCKED**

# 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

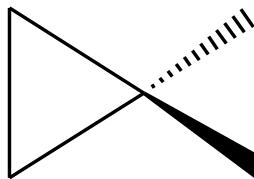


(ii) A *cis*-isomer would remain as *cis*-isomer, so is *trans*

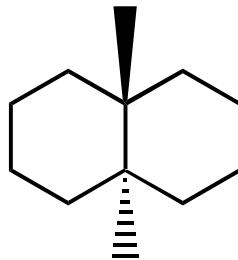


# Polycyclic compounds

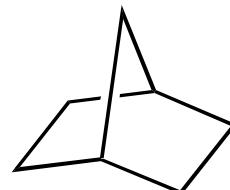
**Spiro cyclic compounds:** Compounds that share one carbon atom between two rings



**Fused ring compounds:** Compounds that share two adjacent carbon atoms

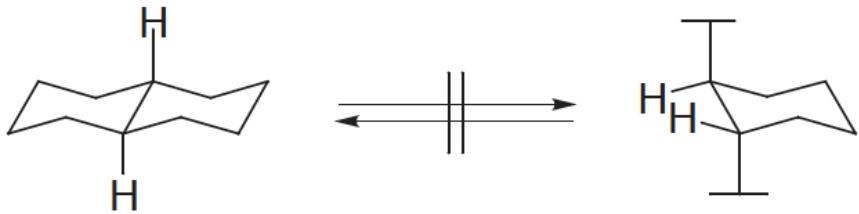


**Bicyclic ring compounds:** Compounds that share two non-adjacent carbon atoms

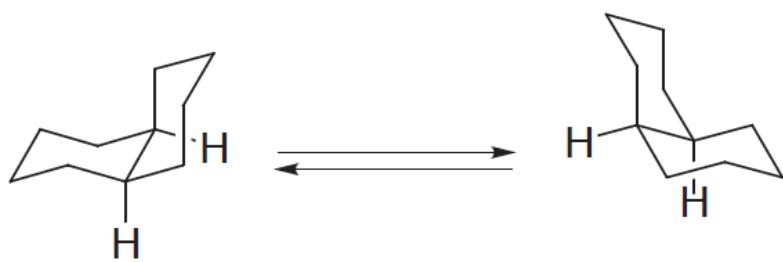


# Decalins

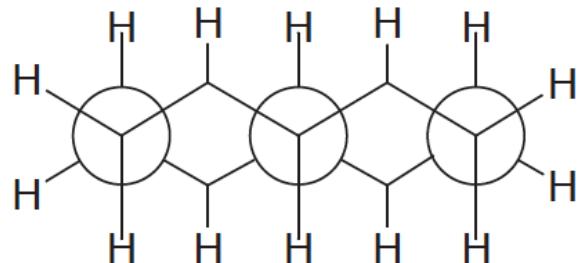
*trans*-decalin



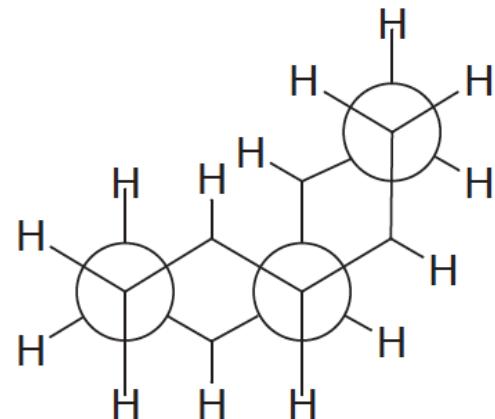
*cis*-decalin



two conformations equivalent



0.0 kcal



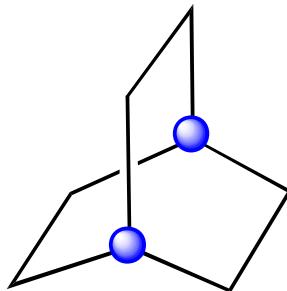
3 gauche interactions  
 $3 \times 0.9 \text{ kcal} = 2.7 \text{ kcal}$

$\Delta E$  between *cis*- and *trans*-decalin = 2.7 kcal/mol

# Bicyclic compounds

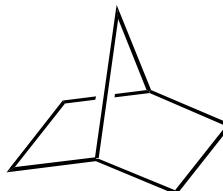
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Compounds sharing two non-adjacent carbon atoms are termed as bicyclic compounds



**Bicyclo[2.2.2]octane**

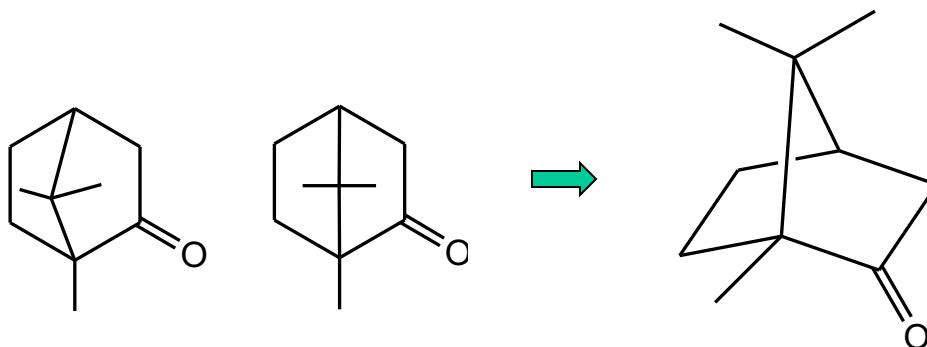
Bridgehead carbons are indicated as blue circles



**Bicyclo[2.2.1]heptane**

# Bicyclic compounds

Camphor skeleton is [2.2.1] system



Sanskrit: *karpoor*

(Also known as *karpooram*)

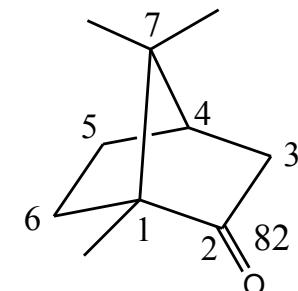
Used as moth repellent,  
antimicrobial, used in medicine

Used along with menthol in Vicks!

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

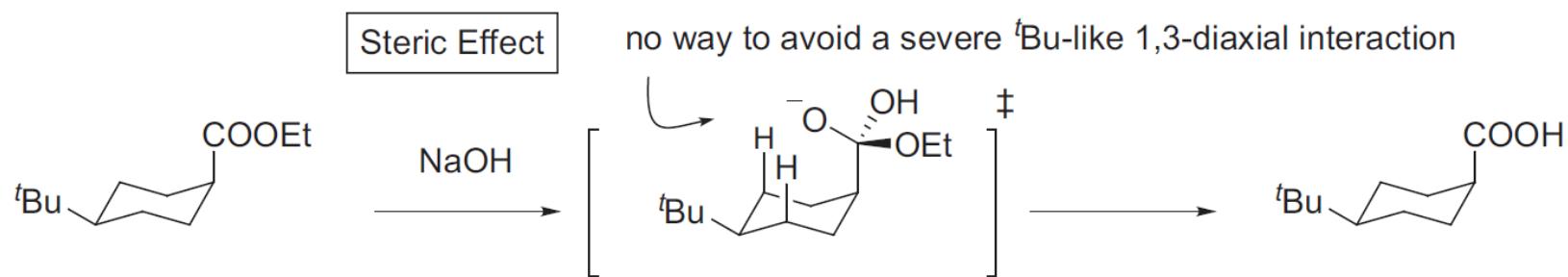
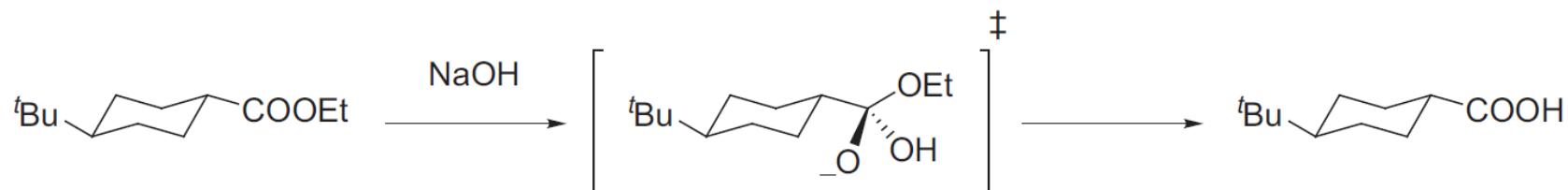
IUPAC

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



# Reaction Mechanisms and Conformational Effects on Reactivity

Kinetics of Ester Hydrolysis (Stereochemistry and Rates of Reactions)



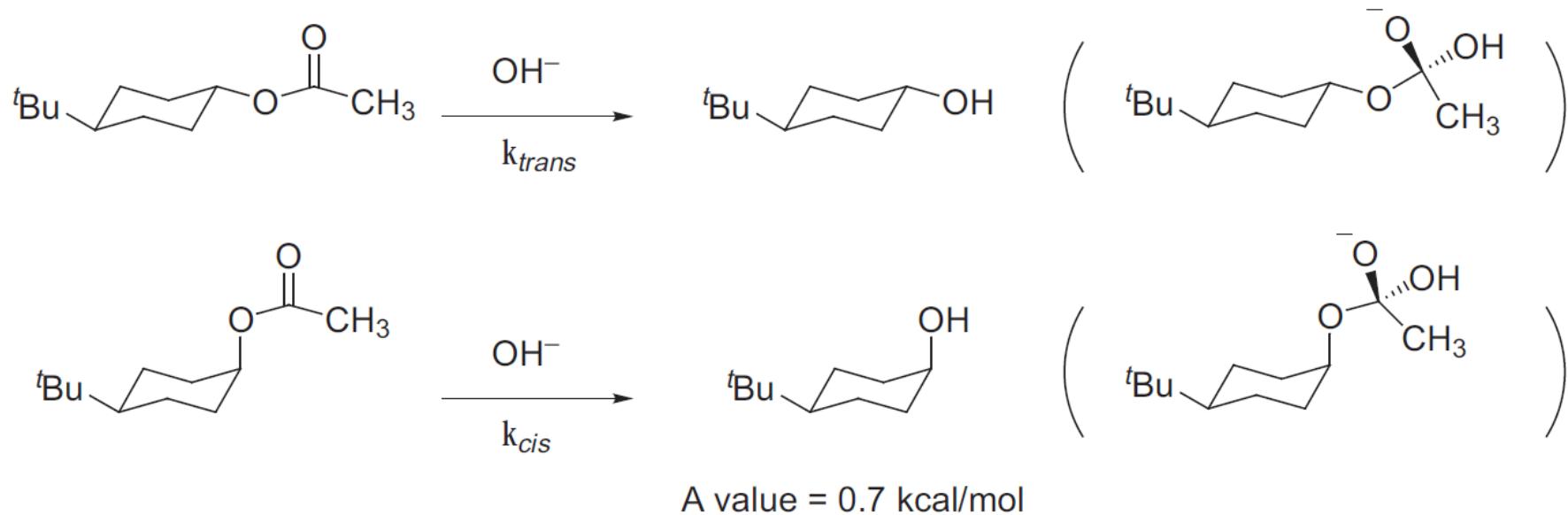
A value = 1.2 kcal

A value = 2.3 kcal

$$\frac{k_{\text{trans}}}{k_{\text{cis}}} = 19.8$$

The rate determining step for ester hydrolysis is the formation of tetrahedral intermediate and the ratio of  $k_{\text{trans}}/k_{\text{cis}} \gg 1$ .

Same effect is observed, but to a lesser extent with acetate hydrolysis



$$\frac{k_{trans}}{k_{cis}} = 6.65$$

effect is smaller because of the more remote distance of the steric interactions

Similarly, the rates of acetylation are  $k_{trans} / k_{cis} = 3.7$

Eliel *J. Am. Chem. Soc.* **1966**, 88, 3334.