Topic-III

Conformational Analysis

Lecture slides are courtesy of : Prof. R.B Sunoj, IIT Bombay
Prof. Peter Volhardt, UC Berkeley
Prof. J. M McBride, Yale University
Oxford University Press

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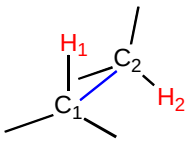
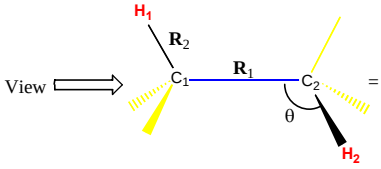
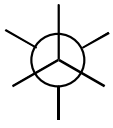
Internal Coordinates





Bond length	between 2 atoms
Bond angle	between 3 atoms
Dihedral angle (torsion angle)	between 4 atoms



Melvin Newman
1908-1993

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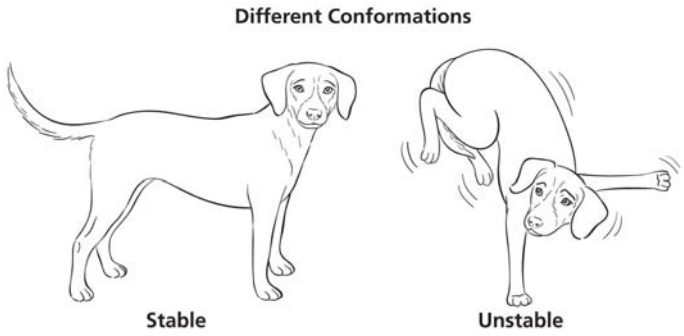
Different Conformations



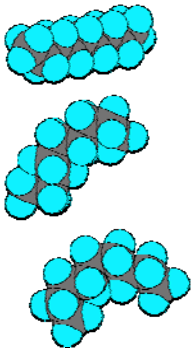
Compounds with different conformations (conformers) cannot be separated in most cases.

Conformational Analysis

Conformational Analysis is the study of energetics of different conformers

Energy versus tortional angle (dihedral angle)

Conformers arise due to the possible free rotation around single bonds



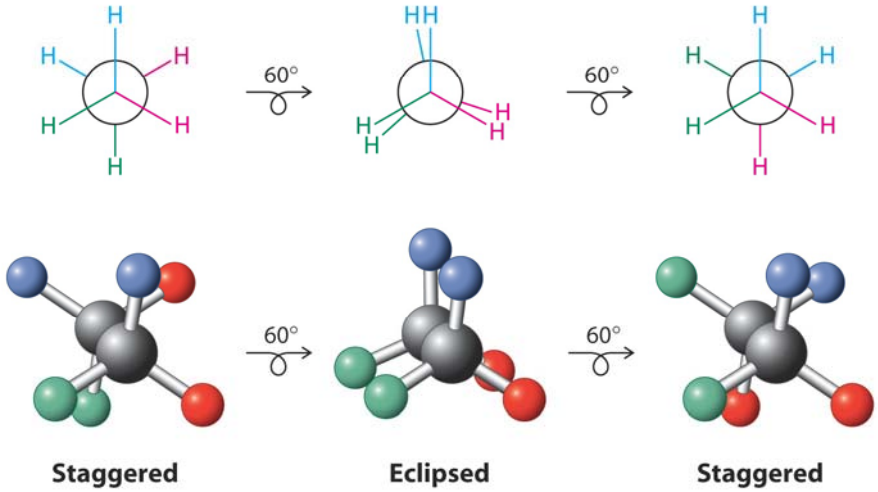
n-octane

Refers to changes in "Shape"

4

Conformational Analysis, Example-1: Ethane

Ethane has two major conformers – Staggered and Eclipsed



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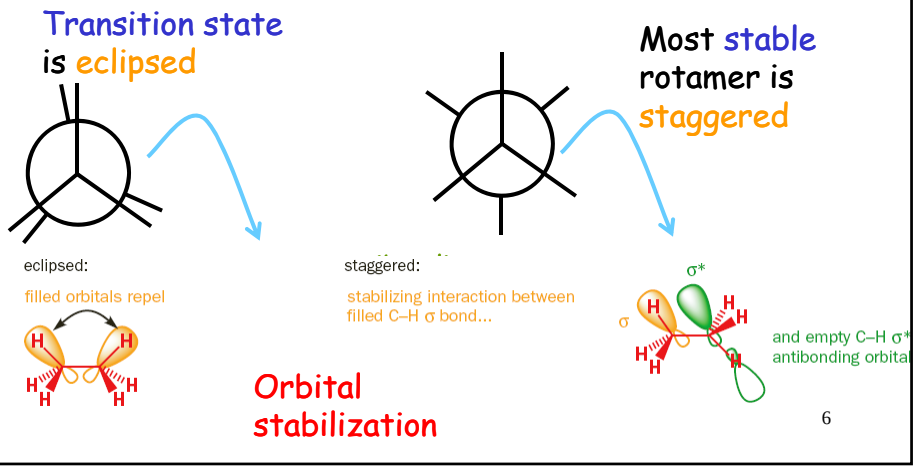
Rotation Around Bonds is Not "Free": Barriers to Rotation

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



6

addition, possible effects of contamination of MgB_2 with other elements, such as from the cladding metal, is of interest and needs to b

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cond-mat/0103563 at ⟨xxx.lanl.gov⟩ (2001).

Hyperconjugation not steric repulsion leads to the staggered structure of ethane

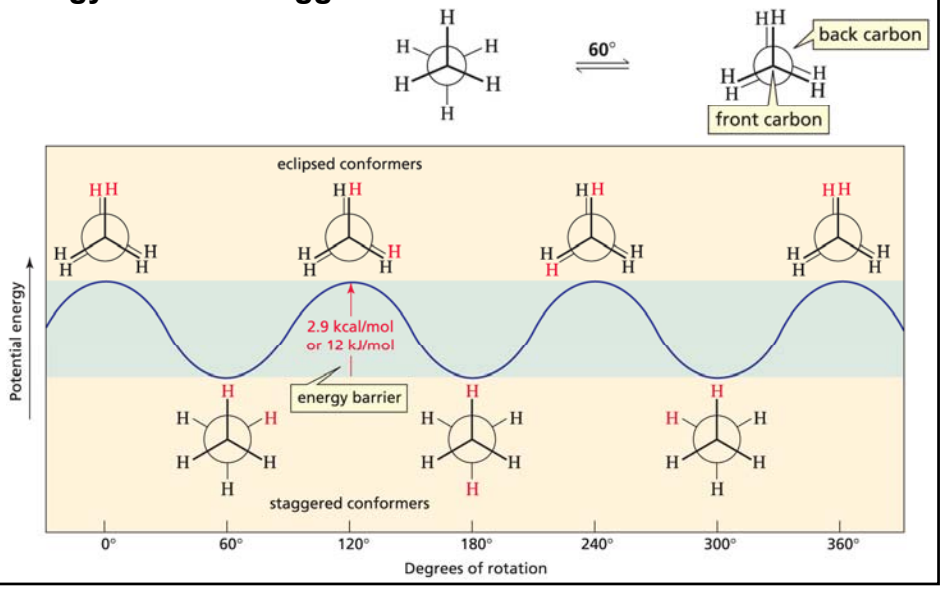
Vojislava Pophristic & Lionel Goodman

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 (CH_3) 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 bond[10] and hyperconjugation[11,12] has been considered to be

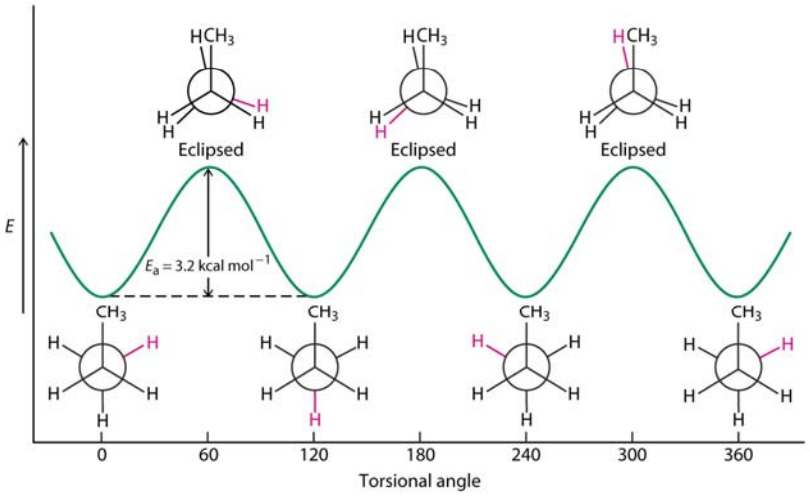
Conformational Analysis, Example-1: Ethane

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



Conformational Analysis, Example-2: Propane

Methyl group increases the barrier



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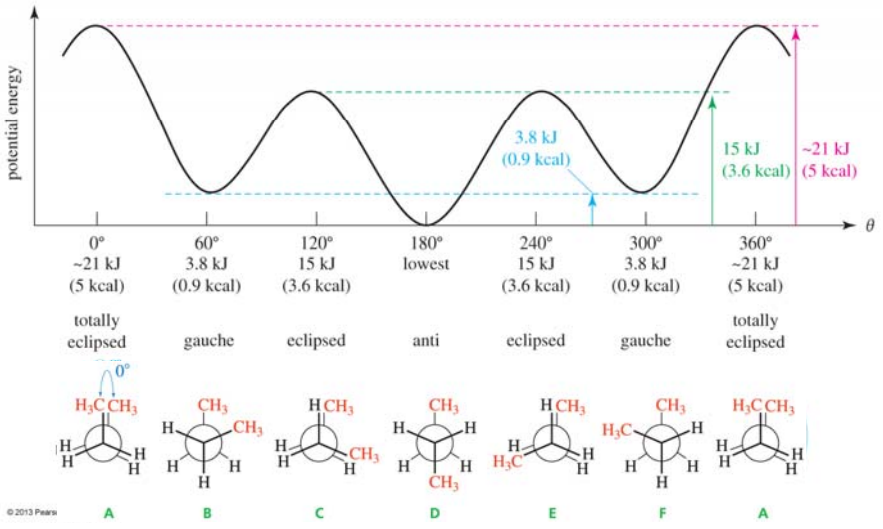
Conformational Analysis, Example-3: *n*-Butane



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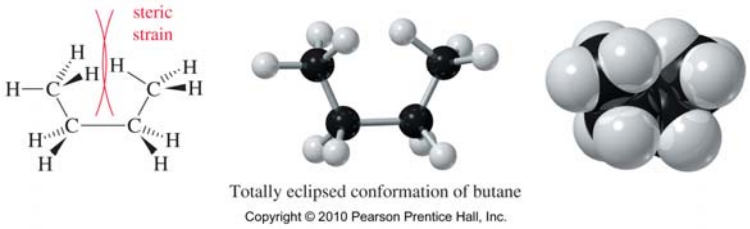
Steric Strain



Totally eclipsed conformation of butane

- **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*.**

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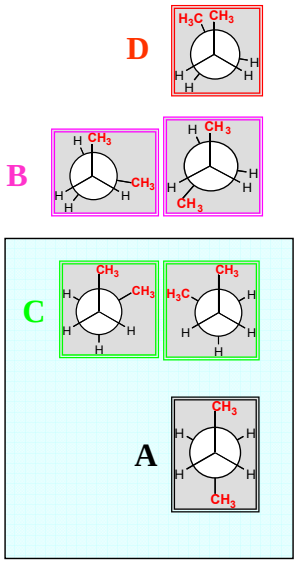
Conformers and Conformations



4.9

3.6

0.9

0.0

<u>Conformations</u>: Can take any value of θ, includes maxima as well

Infinite number of conformations!
Can not be isolated

<u>Conformers</u>: Minima on the Potential Energy Curve

Could be isolated

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Torsional Barrier for C-C bond rotation

Eclipsing Group	Contribution to Barrier height (kcal/mol)
(CH_3) … (CH_3) *gauche*	0.9
(C-H) … (C-H)	1
(C-H) … (CH_3)	1.3
(CH_3) … (CH_3)	2.9
(CH_3) … (CH_2CH_3)	3.4
(CH_3) … $(CH(CH_3)_2)$	3.9
(CH_3) … $(C(CH_3)_3)$	4.7

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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°**

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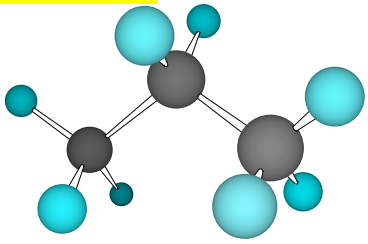
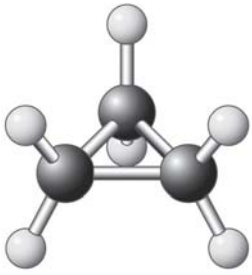
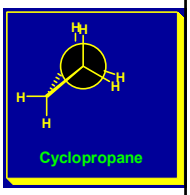
Small Ring Compounds – (1) cyclopropane

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

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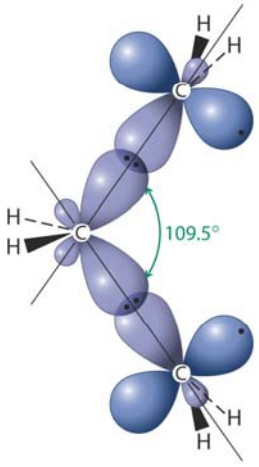
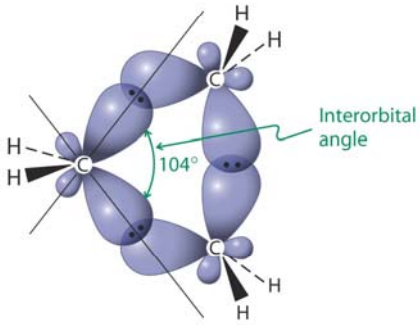
Small Ring Compounds – (1) cyclopropane

Strain relief through the formation of "banana" bonds





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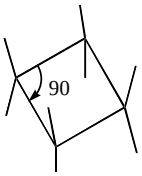
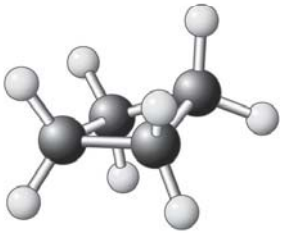
Small Ring Compounds – (2) cyclobutane



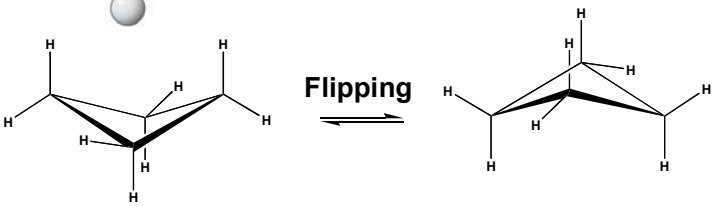
Planar? Problems are: Angle strain plus severe torsional strain

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

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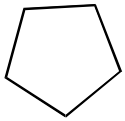
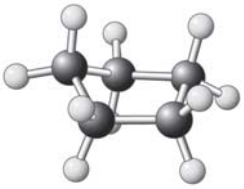
Small Ring Compounds – (3) Cyclopentane



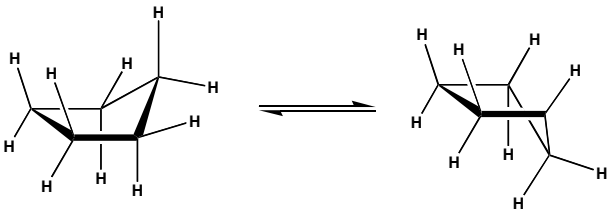
Planar? Though the angle strain is very little, there will be 10 eclipsing interactions!

Ring puckering



Relieves eclipsing interactions with only a slight increase in angle strain

Four coplanar carbon atoms



Cyclopentane has an 'envelope' conformer

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Help Session for those who signed up and those have serious doubts on topics/ tutorial problems/those who are shy to ask questions
(mostly in English)

When: 7th August Wednesday

Time: 9.30 AM to 10.50 AM

Venue: IC 04 (S.J. Mehta School of Management Building)

People who really need help are requested to show up (room size is small)

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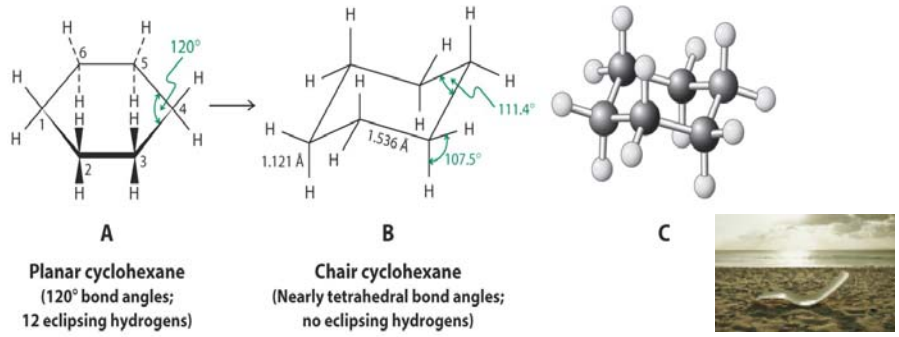
Small Ring Compounds – (4) Cyclohexane

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

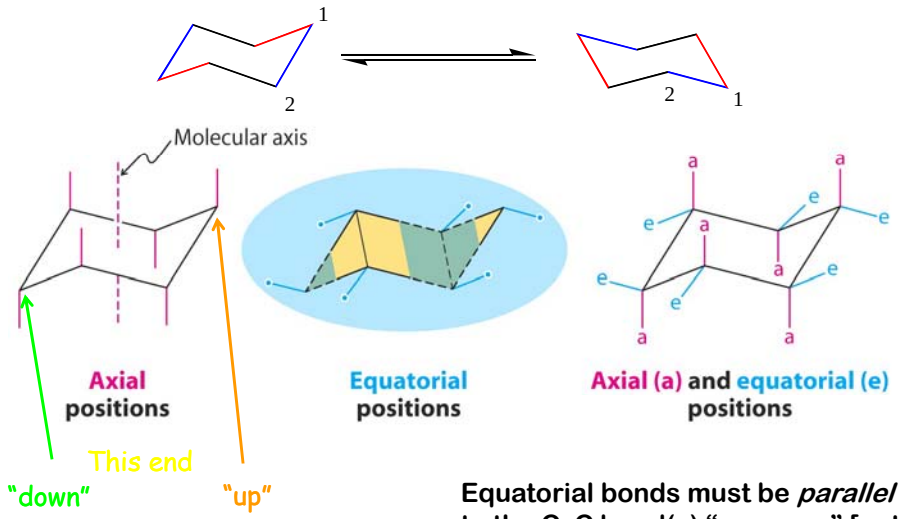


A
Planar cyclohexane
(120° bond angles;
12 eclipsing hydrogens)

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

C

Drawing Cyclohexanes



Tips:

Look for "W" and "M"

Look for 'parallel' bonds

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

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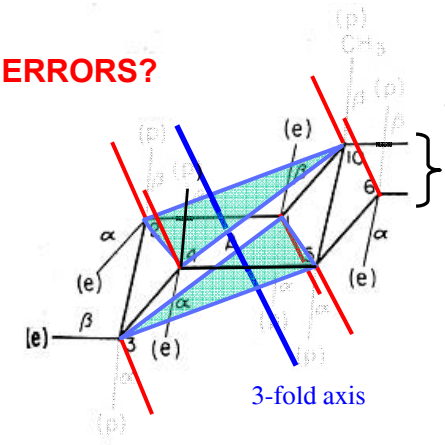
D.H.R. Barton Invents *Conformational Analysis* (1950)

ERRORS?



β ⇒ "up" ; α ⇒ "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")

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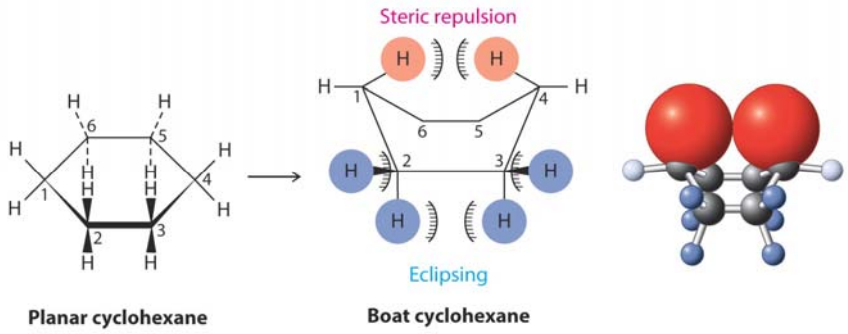
Boat conformer of cyclohexane is strained



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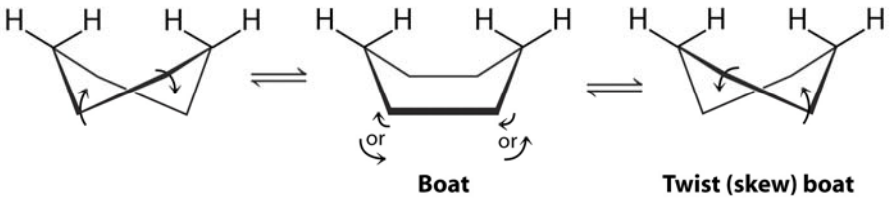
So the boat twists



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

Animations
http://www.chemtube3d.com/

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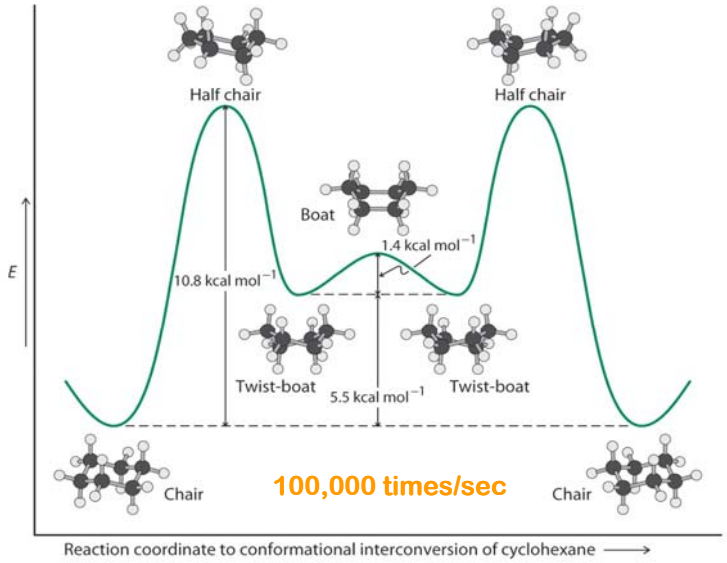
Ring Inversion or Ring Flipping

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



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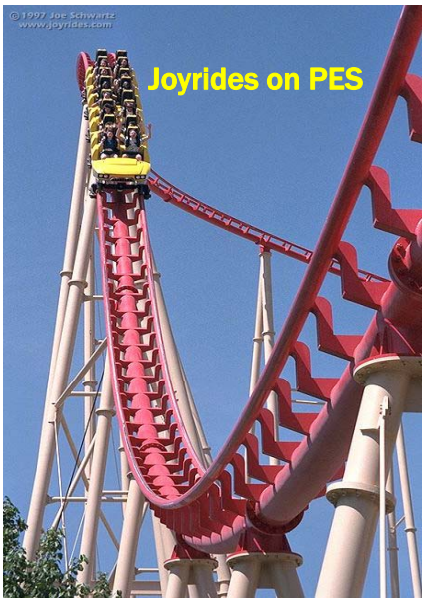
A grossly approximate comparison

Molecules 'move around' on potential energy surfaces



Picture courtesy: http://www.joyrides.com

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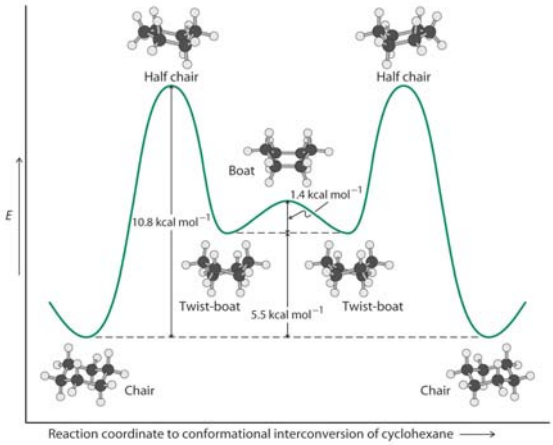
Ring Inversion or Ring Flipping in Cyclohexane



Summary

Maxima (1) Half-chair (2) Boat

Minima (1) Chair (2) Twist-boat

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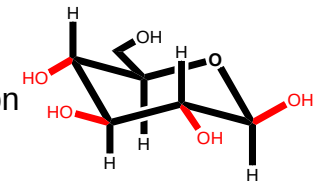
Examples of chair conformers – (D)-Glucose

β-D-(+)-glucose



Equatorial Region

Polar face

Axial Region

Apolar face

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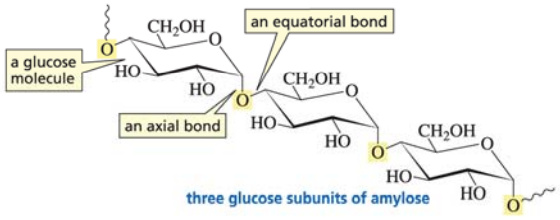
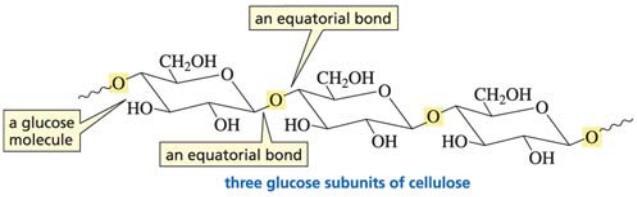
The Only Difference Between Starch and Cotton is an Equatorial Bond Versus an Axial Bond

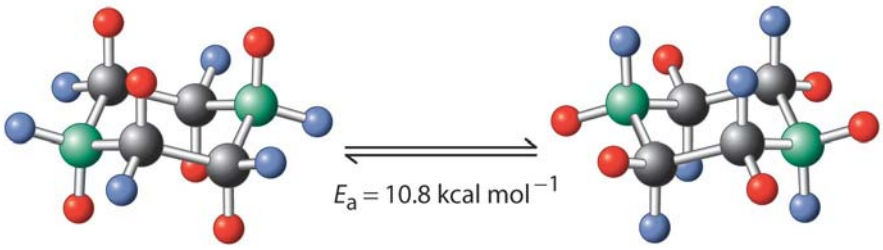


foods rich in starch



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?

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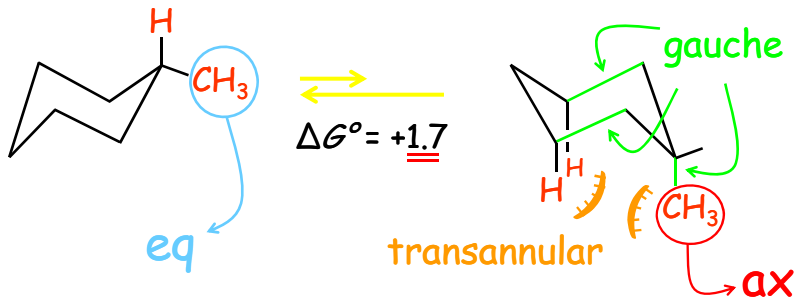
Substituted cyclohexanes: $\Delta G° \neq 0$

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



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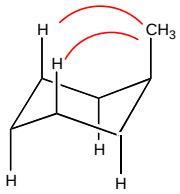
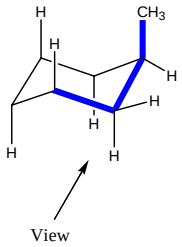
Why Axial –R group is disfavored?

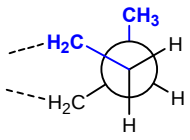


1. van der Waals repulsion between the axial methyl group and the axial hydrogens at C3 and C5 is known as 1,3-diaxial interactions



CH_3 is gauche to two C-C bonds

2. 'gauche-butane' type interaction in axial position



32

Axial-Equatorial Conformers

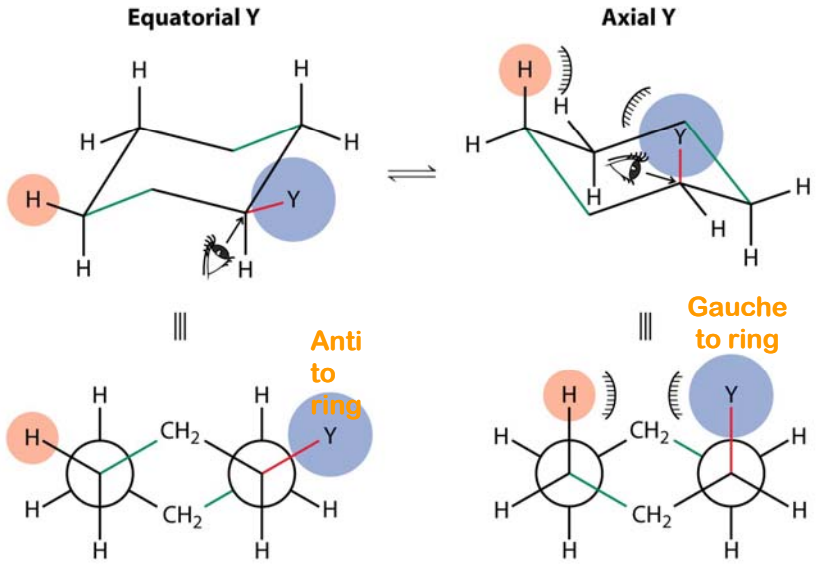


TABLE 4-3 Change in Free Energy on Flipping from the Cyclohexane Conformer with the Indicated Substituent Equatorial to the Conformer with the Substituent Axial

Substituent	ΔG° (kcal mol^{-1})	Substituent	ΔG° (kcal mol^{-1})
H	0	F	0.25
CH_3	1.70	Cl	0.52
CH_3CH_2	1.75	Br	0.55
$(CH_3)_2CH$	2.20	I	0.46
$(CH_3)_3C$	≈ 5	HO	0.94
HO—C(=O)	1.41	CH_3O	0.75
CH_3O—C(=O)	1.29	H_2N	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.

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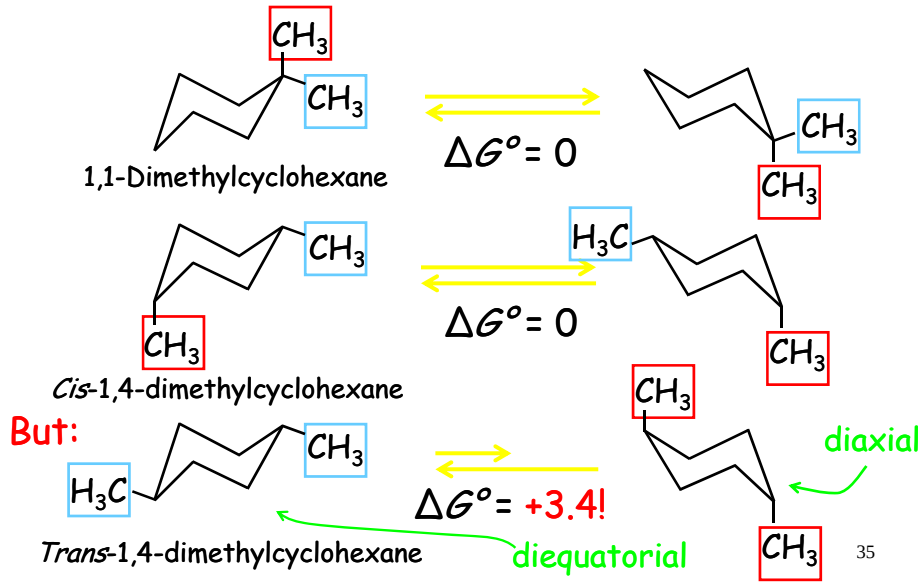
The power of conformational analysis: ΔG° may be additive. Consider the dimethylcyclohexanes:

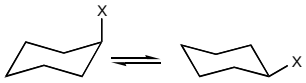


35

A-value for mono substituted cyclohexanes

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

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



X group	A value (kcal/mol)	K	% eq
H	0	1	50
CH_3	1.7	19	95
$CH(CH_3)_2$	2.15	42	98
$C(CH_3)_3$	5	3000	99.9

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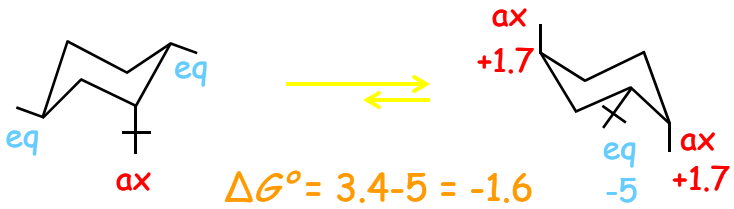
The largest group often biases one conformation



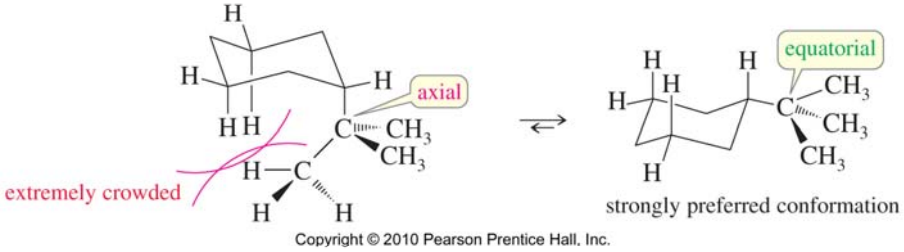
Conformation of t-butylcyclohexane is said to be BIASED

but

NOT LOCKED

37

Tert-butylcyclohexane



Substituents are less crowded in the equatorial positions

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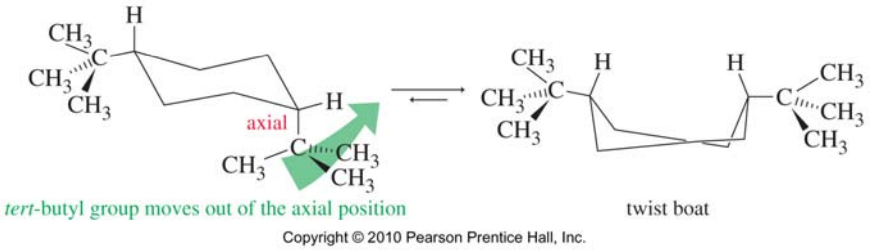
Cis-1,4-ditertbutylcyclohexane



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.

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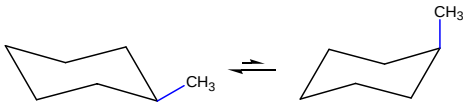
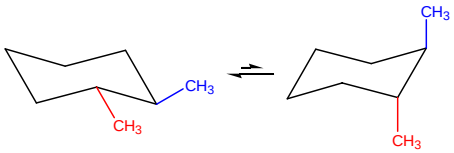
Points to remember while ring-inversion is done

(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*



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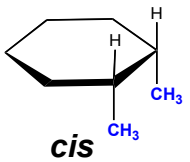
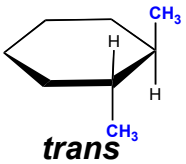
Disubstituted cyclohexanes

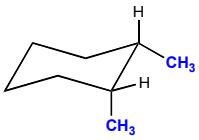
1,2-disubstituted



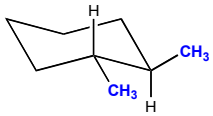
cis



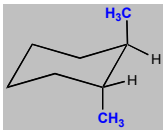
trans



cis



trans



trans

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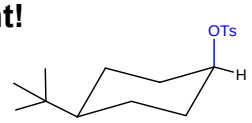
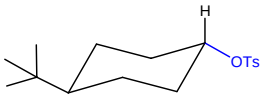
Conformational Features and Chemical Reactivity

Reactions of axial and equatorial substituents could be very different!

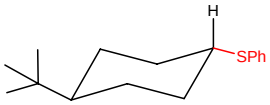
cis

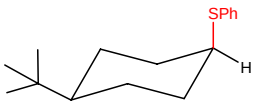




trans

PhS^- PhS^-





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

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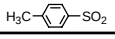
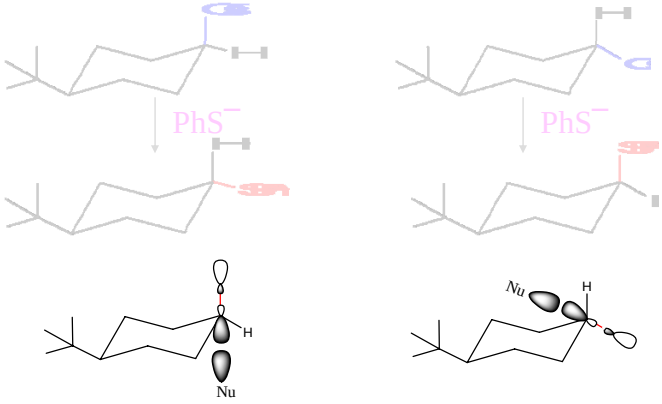
Ts = *p*-toulene sulphonyl 

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**

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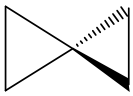
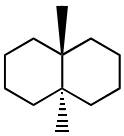
Polycyclic compounds

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

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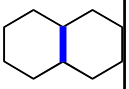
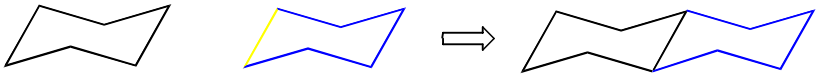
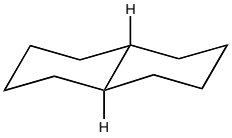
Fused ring compounds - Decalins

Fused cyclohexane rings which share a common C-C bond

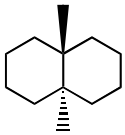




Depending on the orientation of the hydrogen atoms at the ring junction there are two stereoisomers for decalins



***trans*-decalin**



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

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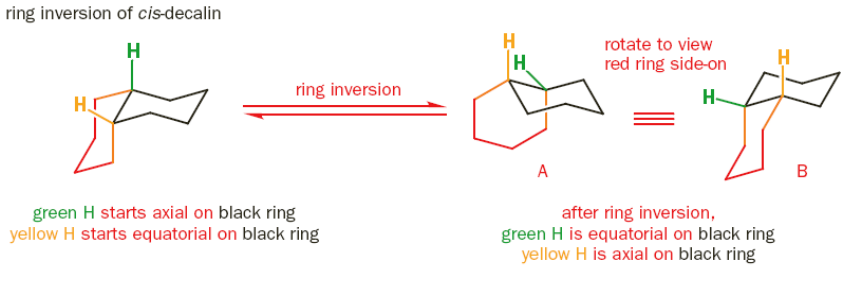
Cis - Decalins

Cis-decalins are conformationally flexible and can undergo ring flipping



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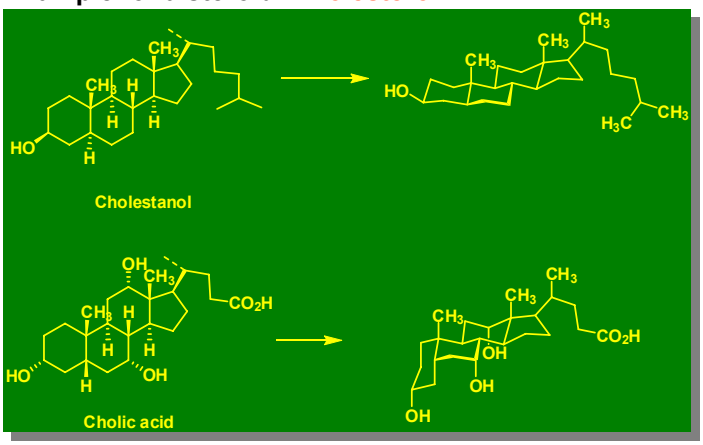
trans – Decalins in Nature

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 10^9 years old from sediments!

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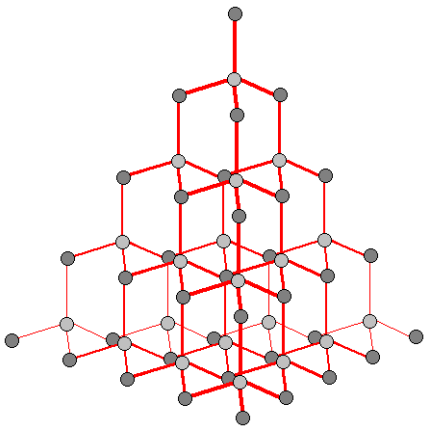
Stability of trans-ring fusion

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

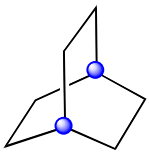
Diamond structure resembles trans-fusion



Picture courtesy: University of Wiscosin-Green Bay

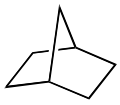
Bicylic compounds

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

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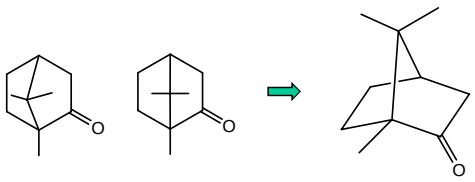
Bicylic compounds

Camphor skeleton is [2.2.1] system



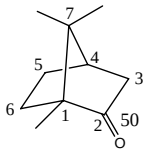
Sanskrit: *karpoor*

(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