

## Objective 6

Draw conformational isomers of chains (staggered, eclipsed) and rings (chair – axial/equatorial, boat, cis/trans) using

- skeletal structures,
- Newman projections,
- wedge-dash,
- sawhorse.

Identify most stable conformer.

## ***Molecules Are NOT Static Structures!***

Molecular dynamics simulation of a drug entering into the binding site of a target protein

([http://www.youtube.com/watch?v=ckTqh50r\\_2w](http://www.youtube.com/watch?v=ckTqh50r_2w))

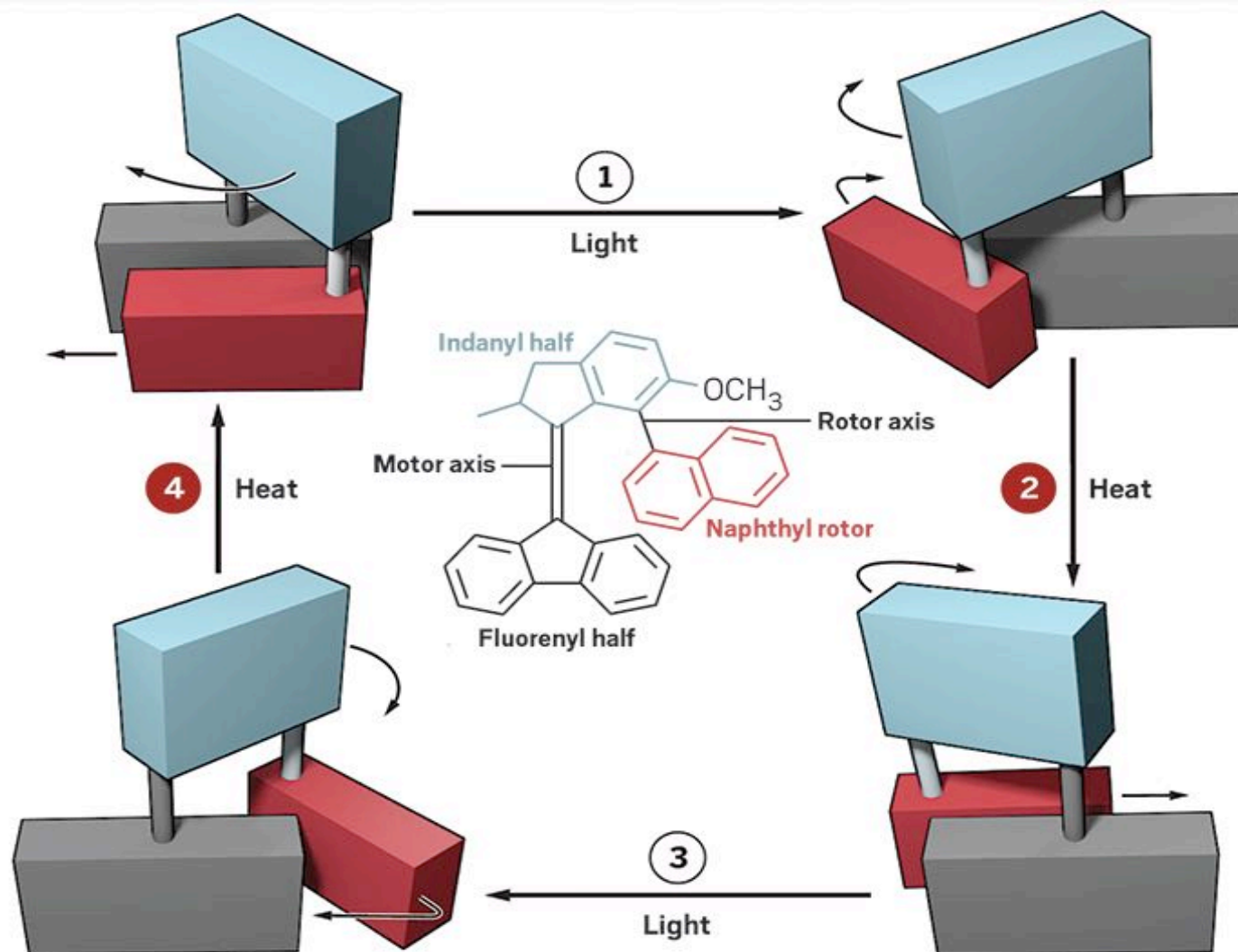
First Spontaneous Ligand Binding Simulated

(<http://www.youtube.com/watch?v=8xQtaWEroWM>)

# Molecules Are NOT Static Structures!

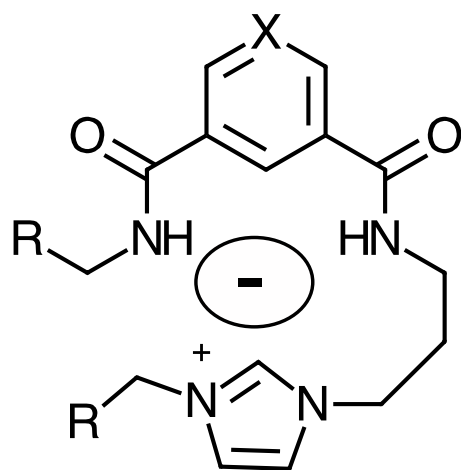
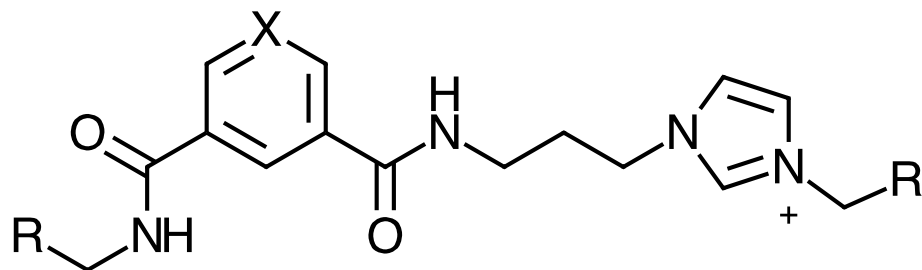
## Molecular motor turns rotor

<http://cen.acs.org/articles/95/i23/Molecular-motor-turns-rotor.html>

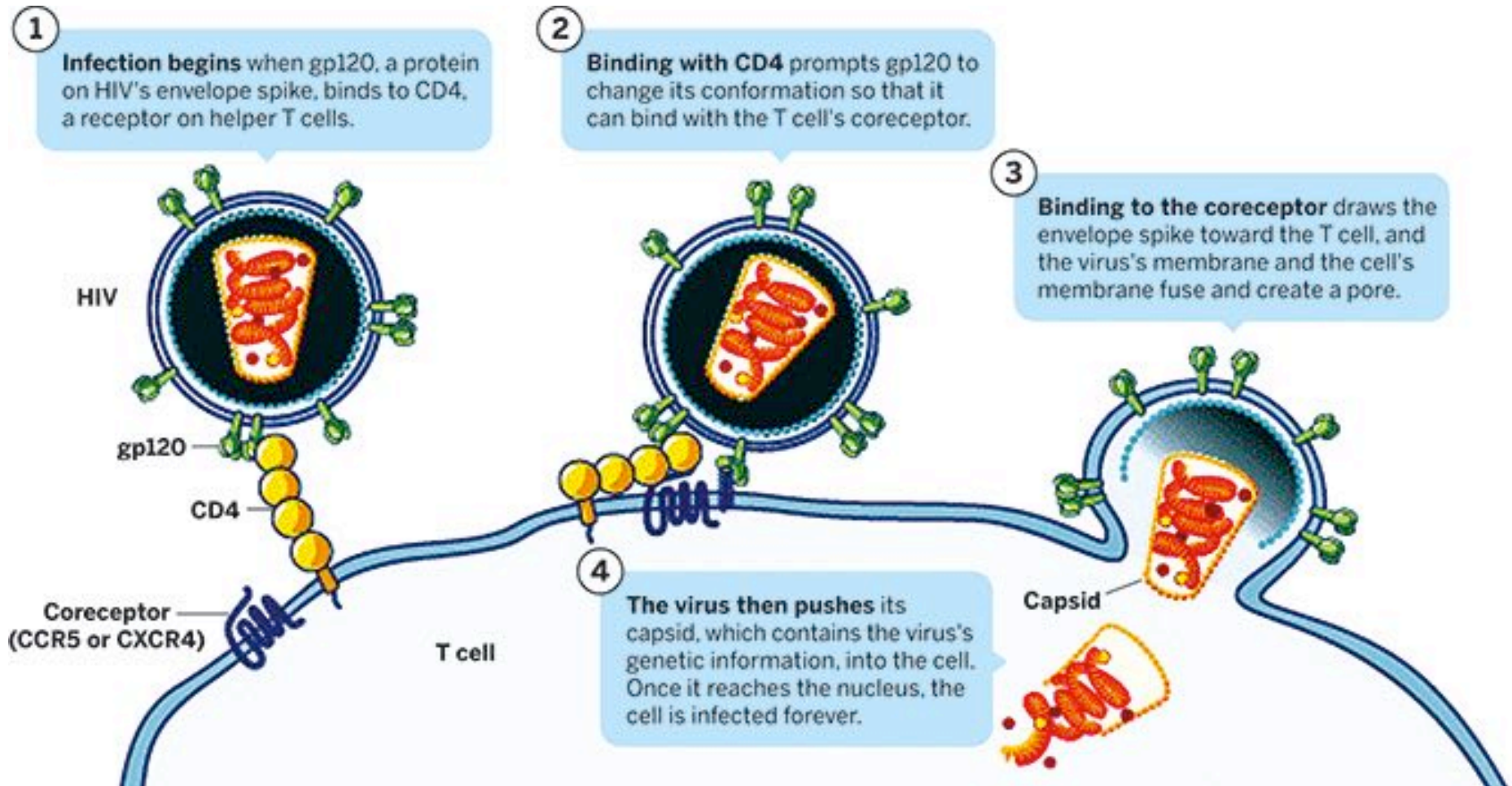


# Molecular Switches involve conformational change

<https://www.youtube.com/watch?v=loaqlqKCmog>



# How is Stereochemistry Involved?



<http://cen.acs.org/articles/92/i35/Aiming-HIVs-Weak-Spot.html>

# A Structure Looks Static But A Molecule Is Dynamic

**Conformational Analysis** - bonds vibrate (stretch and bend).  
Repulsion of electrons (lp/bp) distorts (*strains*) a molecule from ideal shape/angle --> Destabilizes molecule.

**Steric**: through space.    **Inductive**: through bonds

**Steric** strain consists of angle, torsional, and Van der Waals strain.

Angle strain: distortion of a bond angle from ideal angle

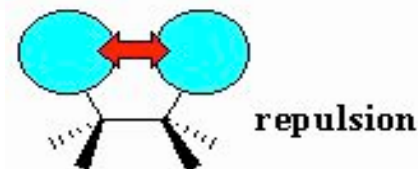


Torsional Strain: repulsion between pairs of bonds caused by the electrostatic repulsion of the electrons in the bonds.



Van der Waals strain: repulsion

between electron clouds in atoms or groups

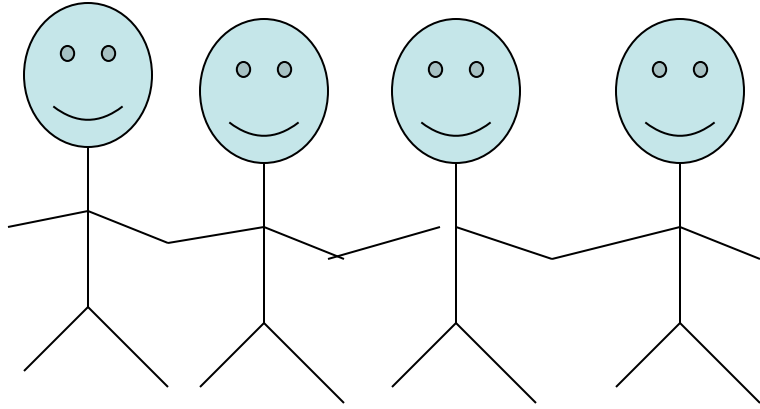


Ring Strain: ring is less stable than chain due to angle and torsional strains.

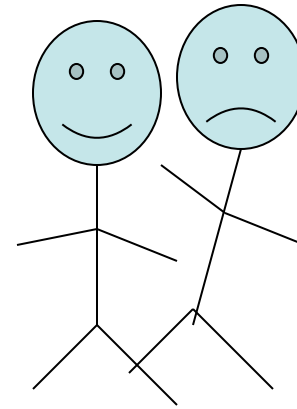
The extra energy released when a ring is broken.

# ***Inductive vs. Steric***

Which one is like a steric effect?



“Don’ t pull too hard!”



“too close - get out of my face!”

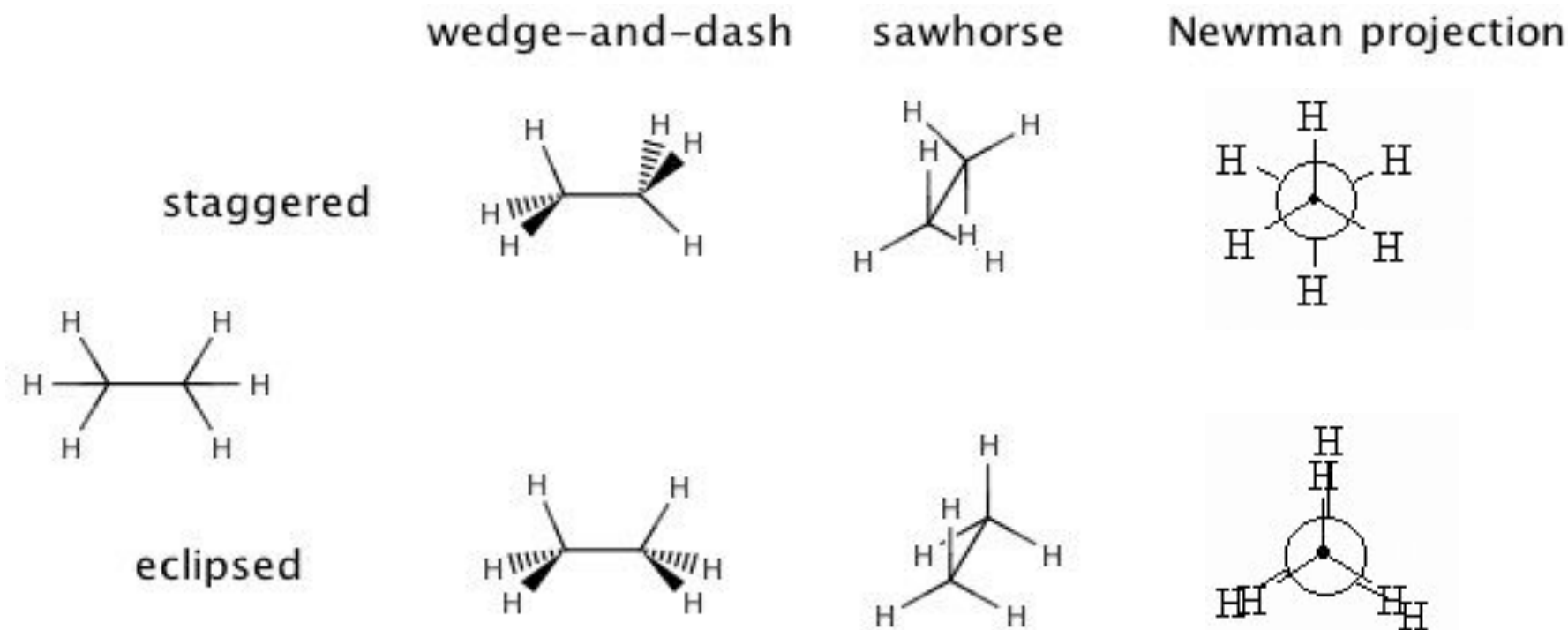
## Alkane Chains: **Staggered Conformer is More Stable**

Steric Strain within Molecule Causes Rotation about the C-C  $\sigma$  Bond

Conformational Isomers (Conformers) have different stabilities.

Conformer types: staggered/anti/gauche (more stable) and eclipsed/syn (less stable) <http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch03/ch3-03.html>

Conformers are represented by:

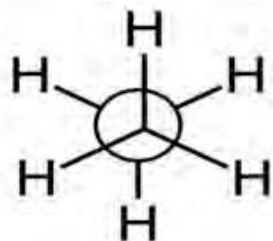


Which atoms are causing the strain?

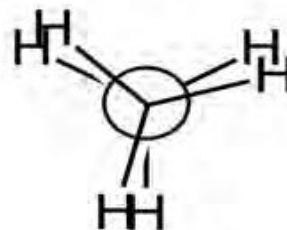


**Objective:** identify the most stable conformer  
Which conformational isomer is the most stable?

Ethane:

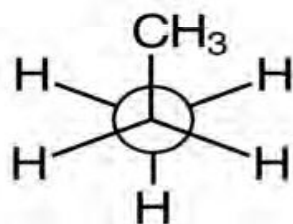


a

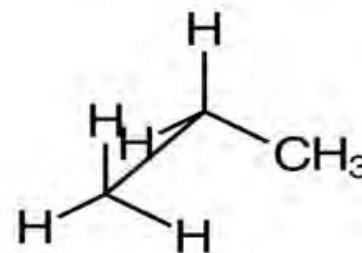


b

Propane



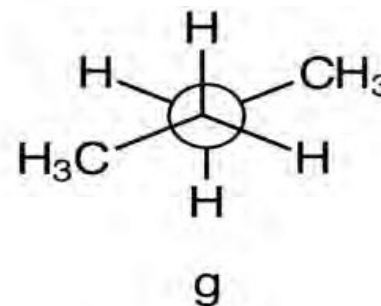
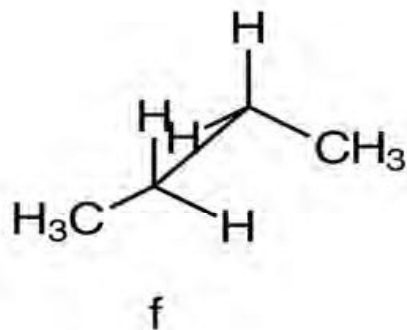
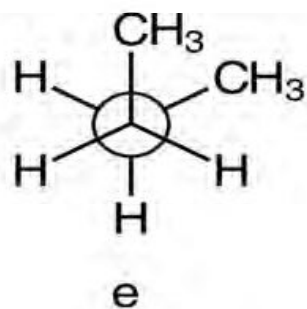
c



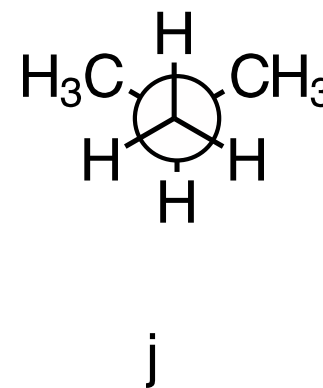
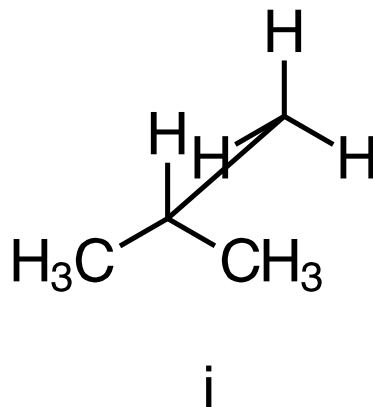
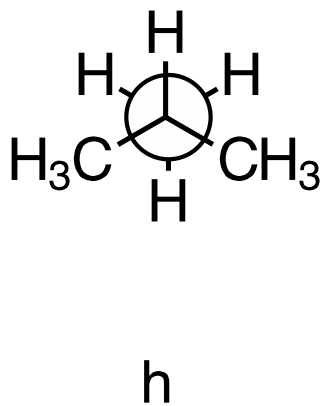
d

**Objective:** identify the most stable conformer  
Which conformational isomer is the most stable?

## Butane



## Isobutane



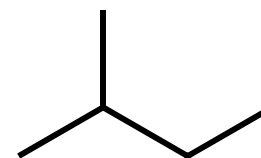
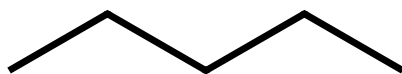
Objective: draw Newman, wedge-and-dash, sawhorse representations

Draw the wedge-and-dash, sawhorse, and Newman projection of the conformers of  $n\text{-C}_5\text{H}_{12}$  and 2-methylbutane. Identify the most stable isomer.

Staggered - anti and gauche

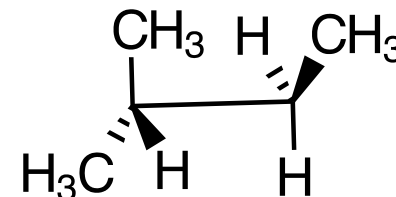
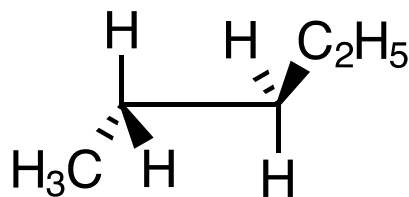
Eclipsed - syn

Draw the wedge-and-dash, sawhorse, and Newman projection of the conformers of n-C<sub>5</sub>H<sub>12</sub> and 2-methylbutane. Identify the most stable isomer.

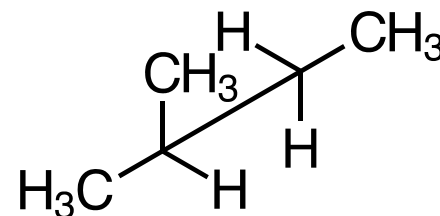
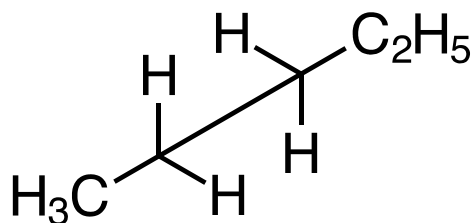


Sight along a specific C-C bond, e.g., C2-C3

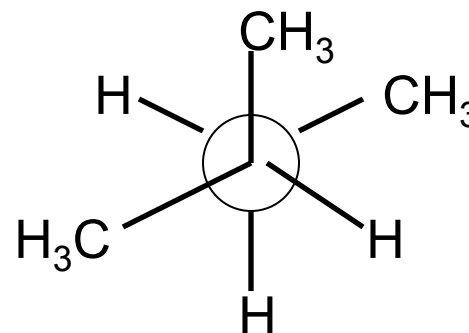
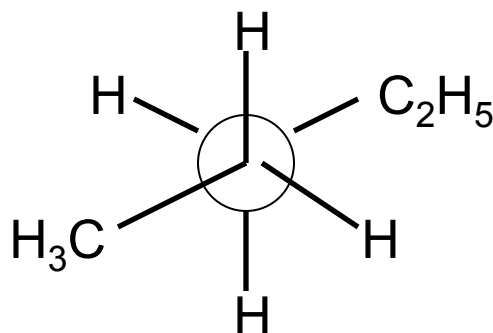
Wedge-and-dash



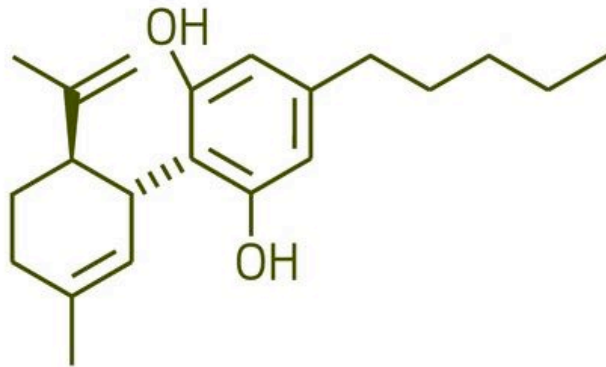
Sawhorse



Newman projection



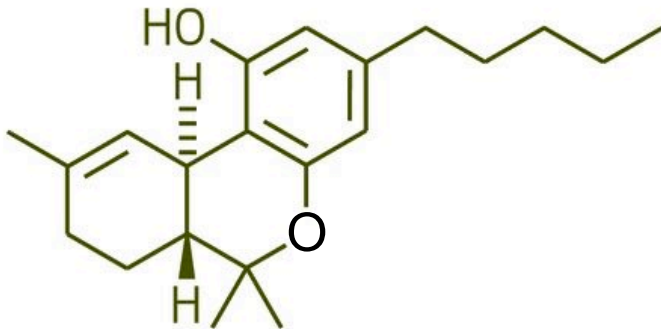
CANNABIDIOL (CBD)



CBD – no psychogenic effects  
Possible medicinal: analgesic, anti-inflammatory, antianxiety properties

Which bond rotates in CBD to form THC?

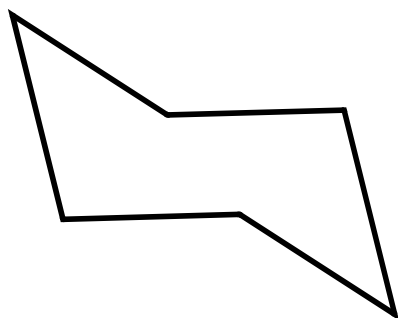
TETRAHYDROCANNABINOL (THC)



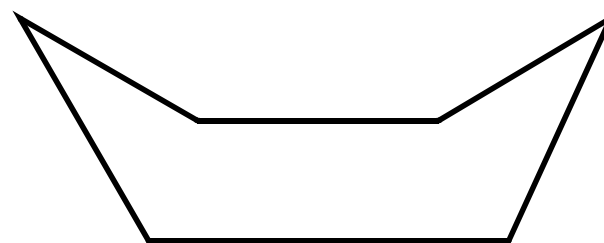
THC– intense psychogenic effects

Objective: Which conformer is more stable?

cyclohexane



a



b

Hint: draw in the H's.  
Which H's are closest (repulsion)?

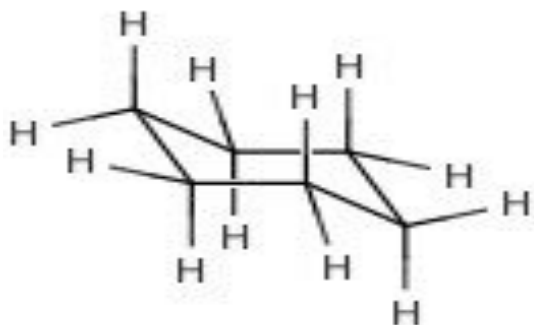
Alkane Rings: ***Chair Conformer is More Stable***  
Steric Strain Leads to Different Ring Conformers

Conformers for cyclohexane: chair and boat (and twist boat)

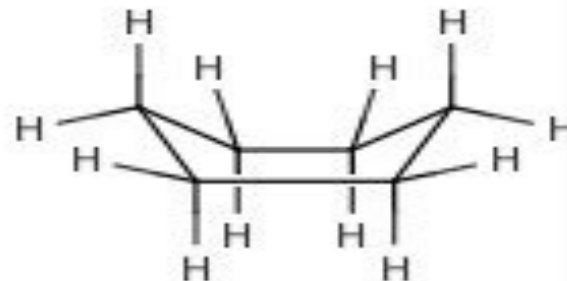
Substituents: axial and equatorial

Which conformer is more stable? Why?

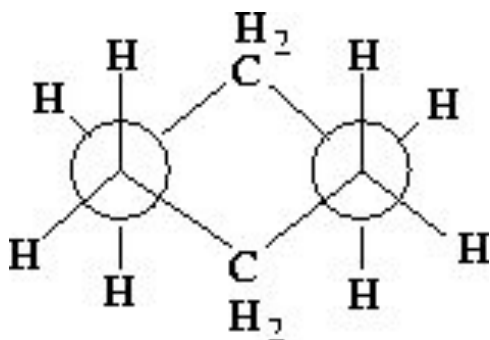
Which atoms are causing the strain?



chair



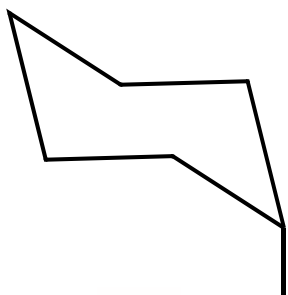
boat



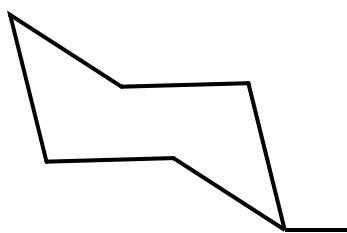
Draw the Newman projection of the boat conformer.

Objective: Which conformer is more stable?

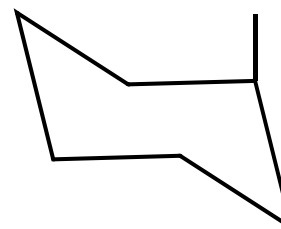
Methylcyclohexane



c



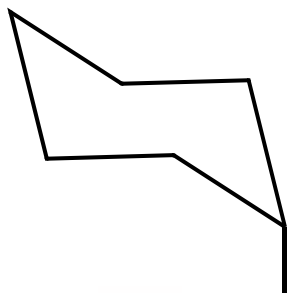
d



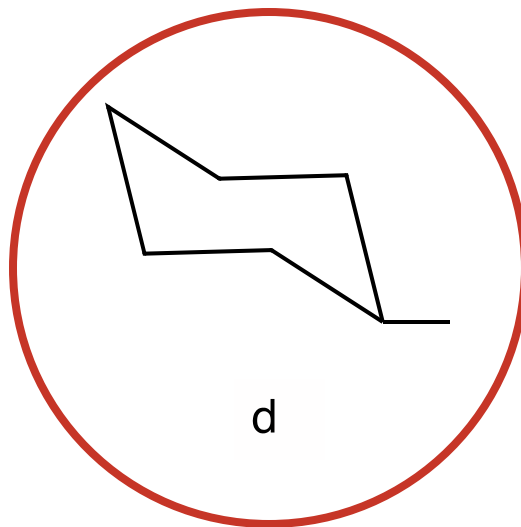
e



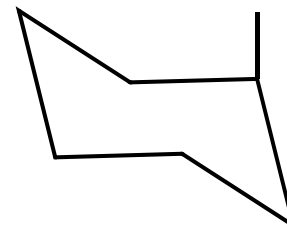
Substituted cycloalkane rings (Klein, 1st ed., p. 172) “*the equilibrium between the two chair conformations will generally favor the conformation with the equatorial substituent.*”



c



d



e

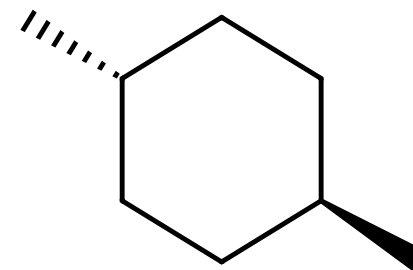
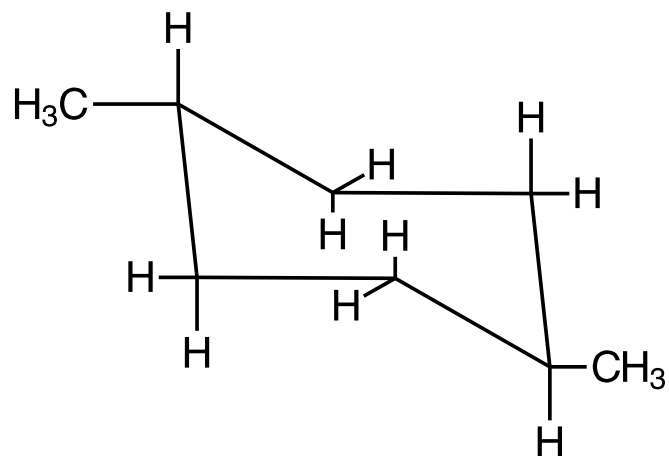
## Di (or poly) Substituted cycloalkane rings: **Cis** and **Trans**

**Wedges** - up (above the ring)  
the ring)

2 substituents: **Cis** - same side of ring  
of ring

**Dashes** - down (below  
the ring)

**Trans** - opposite sides  
of ring



Which methyl group is above the ring?  
Which methyl group is below the ring?

**Trans-1,4-dimethyl  
cyclohexane**

## Di-Substituted cycloalkane rings: **Cis** and **Trans**

**Wedges** - up (above the ring)

**Dashes** - down (below the ring)

2 substituents: **Cis** - same side of ring

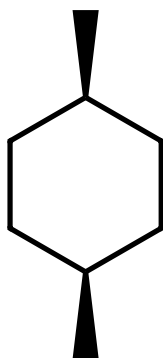
**Trans** - opposite sides of ring

1,4-dimethylcyclohexane is shown below.

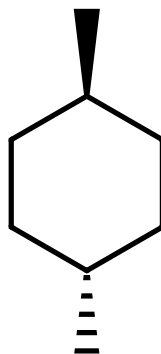
Which structures are trans? Draw the chair conformer to confirm.

Which are isomers?

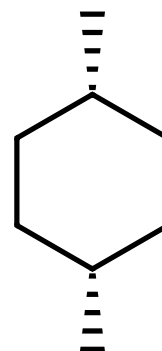
Which are the same?



(i)

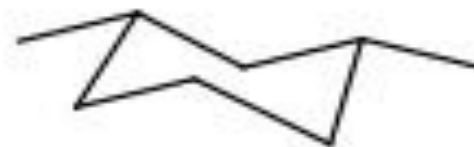


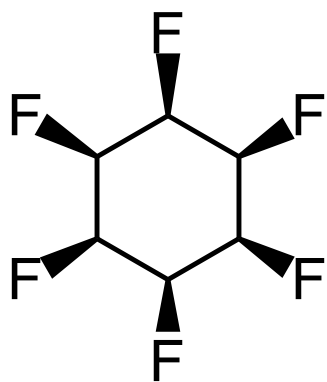
(ii)



(iii)

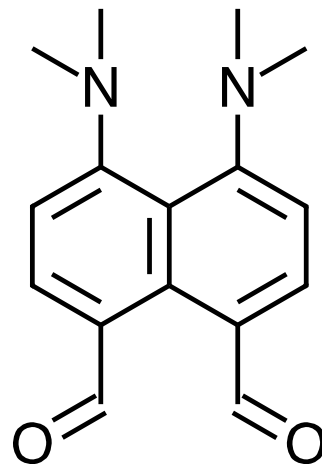
Select the compounds in each group that are isomers and specify whether they are constitutional isomers or stereoisomers.





3/30/15, CEN, p. 5 “**Most polar**  
non-ionic compound”  
All-cis hexafluorocyclohexane  
Dipole moment = 6.2 Debyes  
*Draw the chair conformer.*

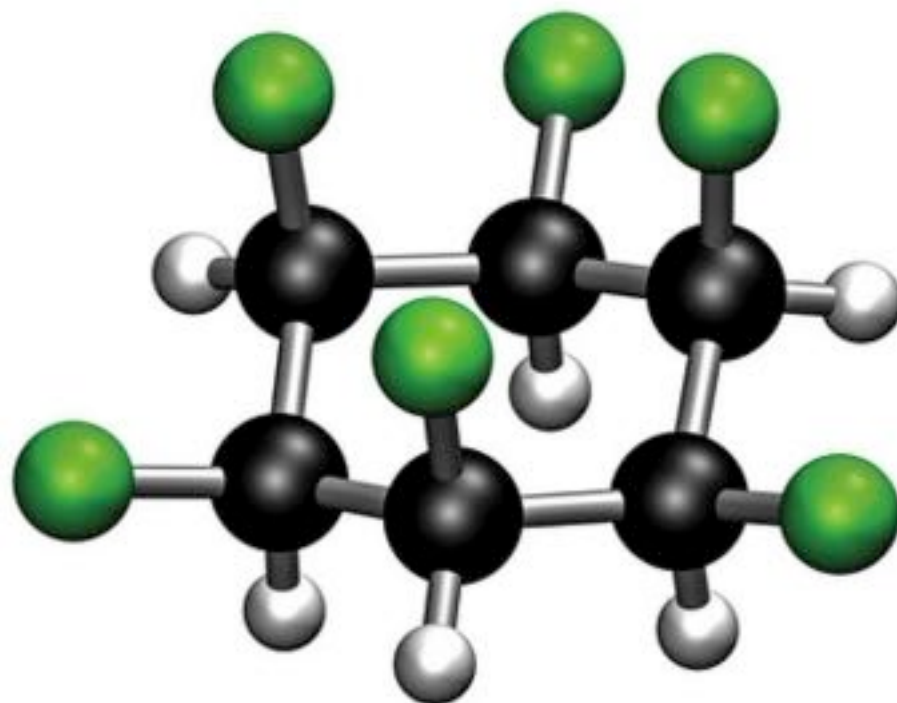
7/27/15, CEN, p. 4 Letters:  
“Debating **Most Polar**”  
Dipole moment = 9.2 Debyes  
Effective conjugation of 2 pairs of  
dimethylamino and aldehyde groups



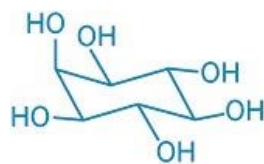
<http://cen.acs.org/articles/93/i13/Molecule-Claims-Polar-Title.html>

Is the ring in the **chair** or **boat** conformer?

Is this molecule **polar** or **non-polar**?

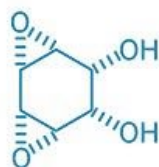


**All-cis hexafluorocyclohexane**



**Inositol**

Six steps

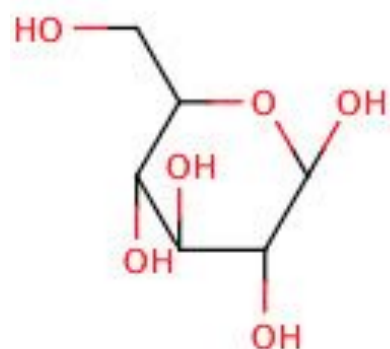


Six steps

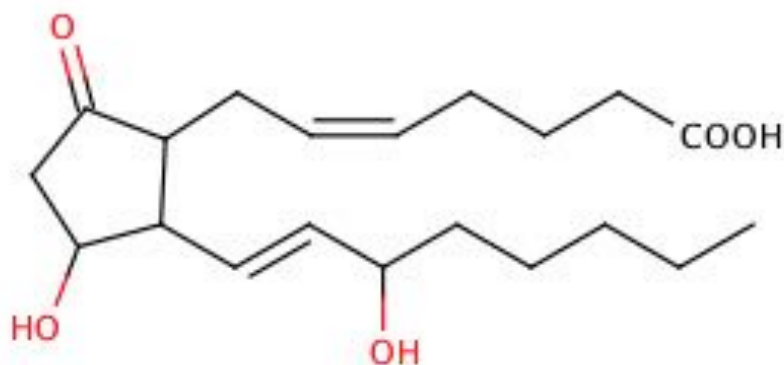


**All-cis hexafluorocyclohexane**

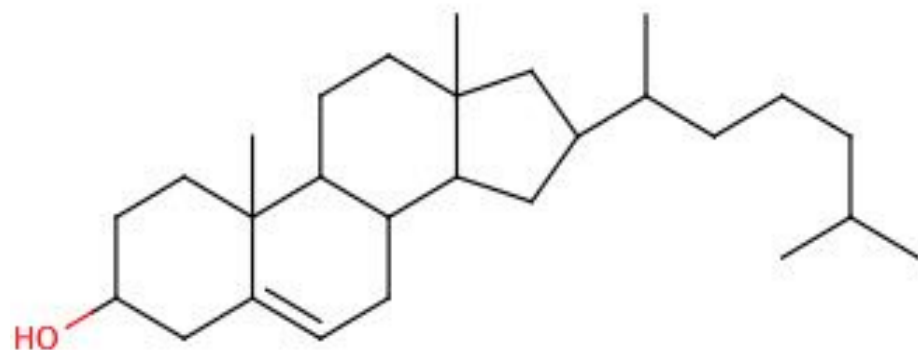
Biomolecules Contain Rings: What is the most stable conformer of each compound?



D-glucose



prostaglandin (PGE<sub>2</sub>)  
from arachidonic acid

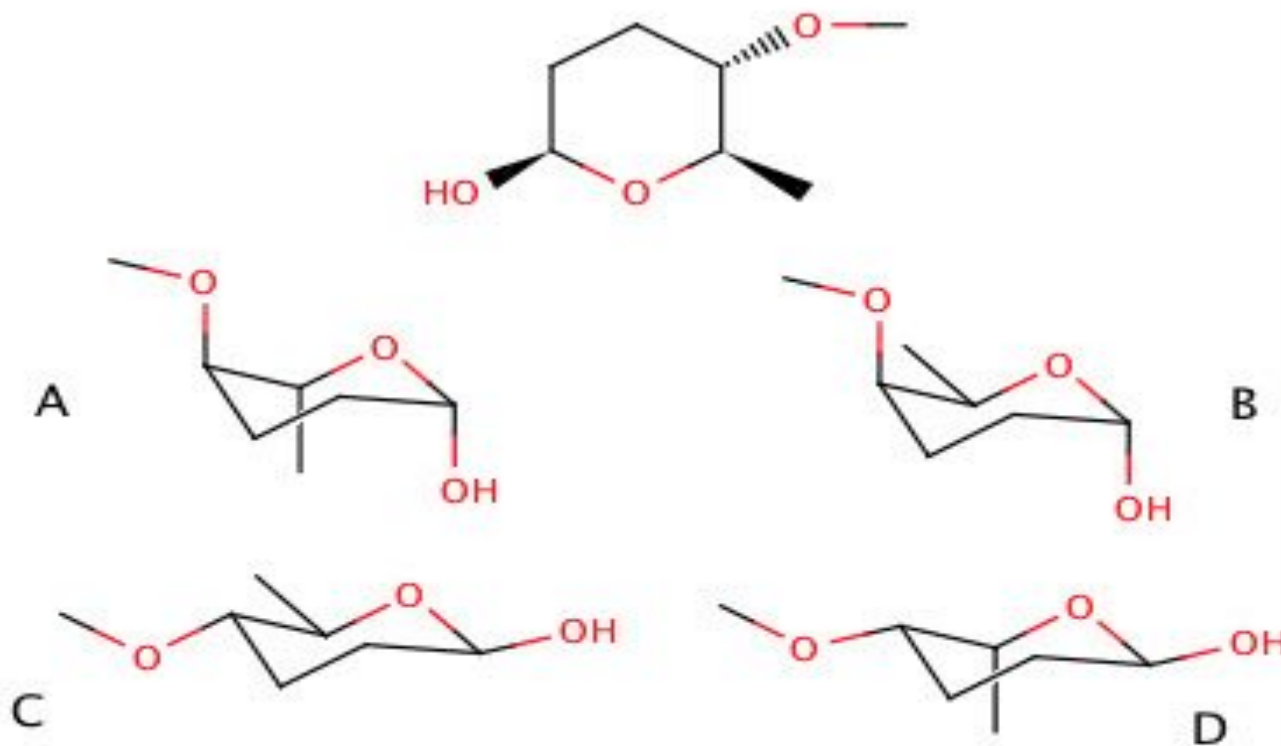


cholesterol from  
squalene

Also, see <http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch03/ch3-10.html>

The carbohydrate shown here is a component of a drug used in veterinary medicine.

Which is the most stable pyranose conformation?





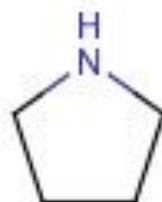
Heterocyclic compounds: rings than contain atoms besides C



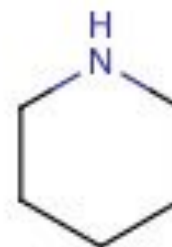
ethylene  
oxide



tetrahydrofuran



pyrrolidine



piperidine

Do these heterocyclic compounds have conformers? If so, which conformer is the most stable?

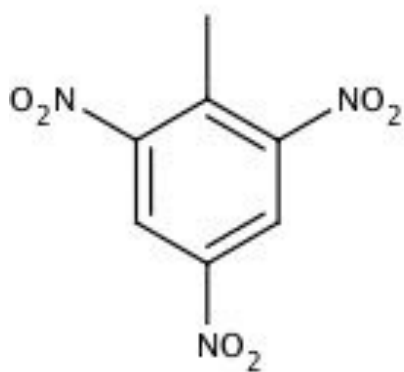
## “Examining Explosives”, C&EN, 7/18/11, p. 32

Energetic material: combination of oxidizer and fuel. E.g., in TNT, O in nitro groups = oxidizer, C = fuel

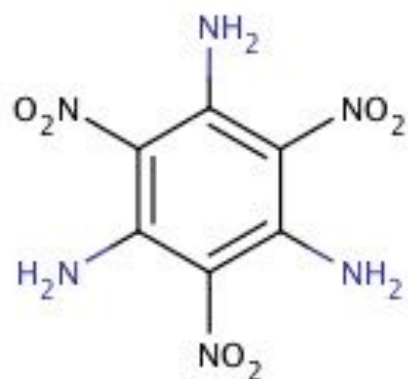
“Low” explosives propagate energy relatively slowly by burning. E.g., gunpowder and fireworks.

“High” explosives detonate through a shock front that propagates at 5-10 km/sec. E.g., TNT, peroxides

HMX has 2 crystal forms: chair  $\beta$  form at r.t. and boat  $\delta$  form at 165°C.  $\delta$  form explodes more violently than  $\beta$  form.

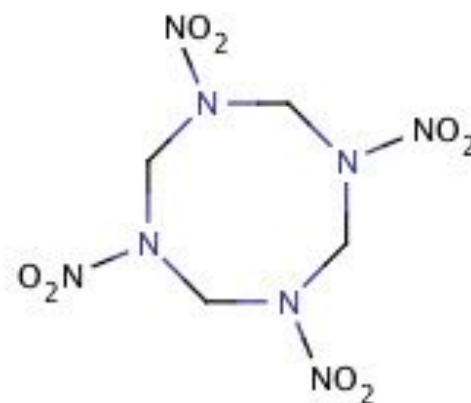


TNT



TATB

Insensitive to impact and friction. Rings line up parallel so layers slide past each other to dissipate friction energy



HMX

Heat sensitive. Herringbone-like crystal structure so friction can tear up molecules and set off explosion

# Cubane is studied as a Fuel and Explosive

(Carey, 8<sup>th</sup> ed., p. 134, 3.37)

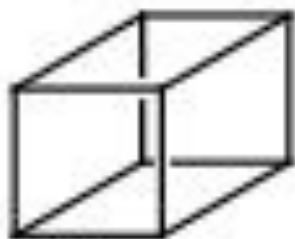
What is the chemical formula of cubane?

Does cubane have conformers? If so, what is the most stable conformer?

What type of strain is involved in cubane?

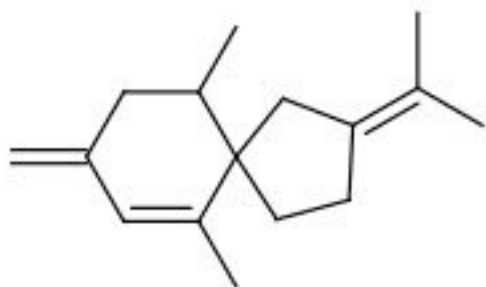
Why do you think cubane is a fuel and explosive?

How many rings are in cubane? (see Carey, 8th ed., p. 124)



Cubane synthesis (<http://en.wikipedia.org/wiki/Cubane>) involves Diels-Alder reaction (see conjugated dienes, Ch. 10.15)

## Polycyclic Rings Are Found in Natural Products



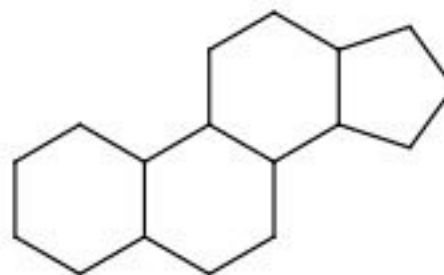
vetivone

**spiro** – one atom  
common to two rings



camphene (pine oil)

**bridged** – two atoms  
common to two  
rings



steroid

**fused rings** – rings  
that share a common side  
but are classified and named  
as bridged

Do these compounds have conformers? If so, which conformer is the most stable?

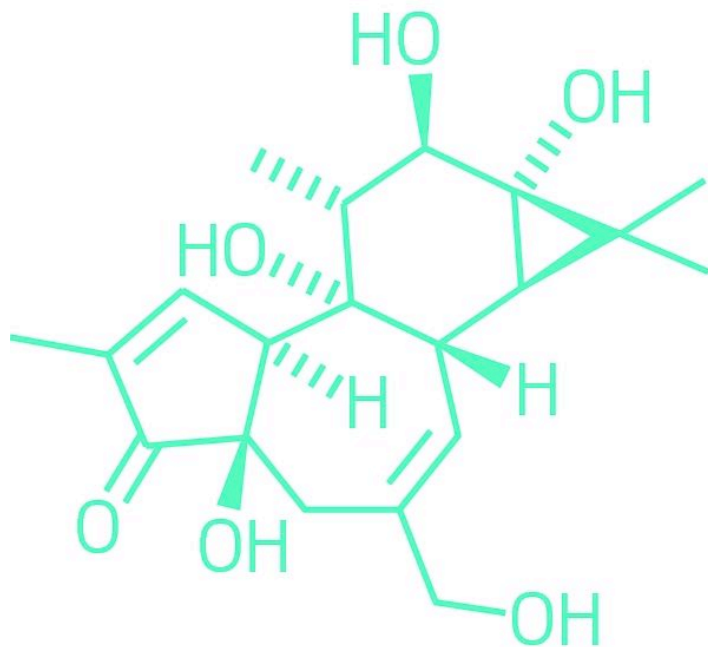
Are any of these compounds planar?

## Polycyclic Rings Are Found in Natural Products

(+)-Phorbol is found in the sap of the manchineel tree. The sap can cause skin to blister on contact.

Phorbol esters encourage tumors to grow rapidly.

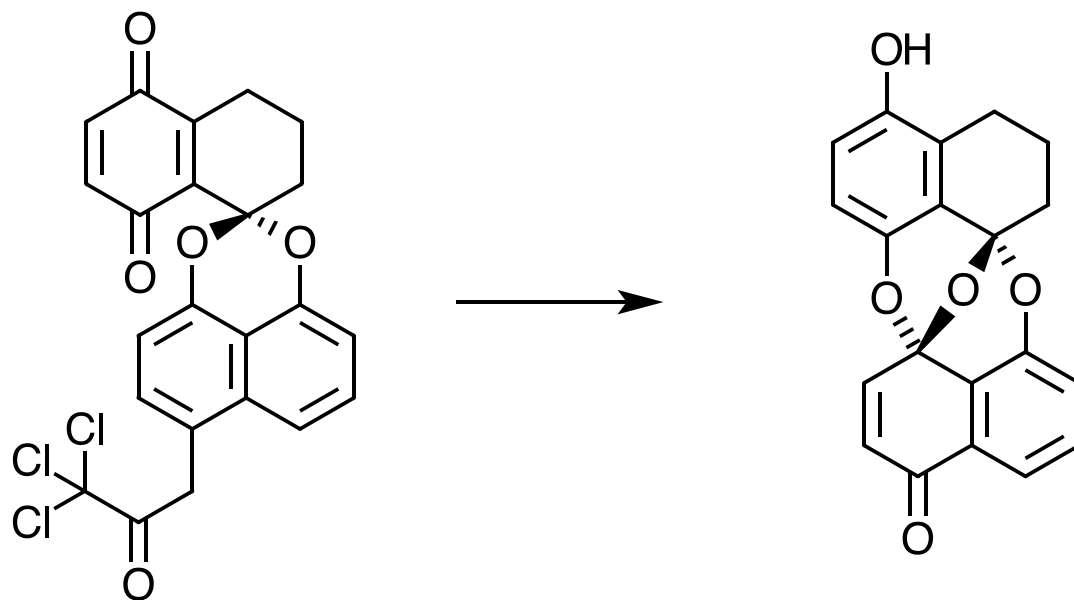
Phorbol compounds show promise as immune-modulating, antiviral, anticancer therapies.



**(+)-Phorbol**

How many rings?  
Which ring(s) have conformers?

Preussomerins are a novel class of fungal metabolites that share a stable bis-spiroacetal ring system and are related to naphthalenediol-derived spiroacetals that show a wide range of biological activities. (CEN, 5/24/99, p. 30)



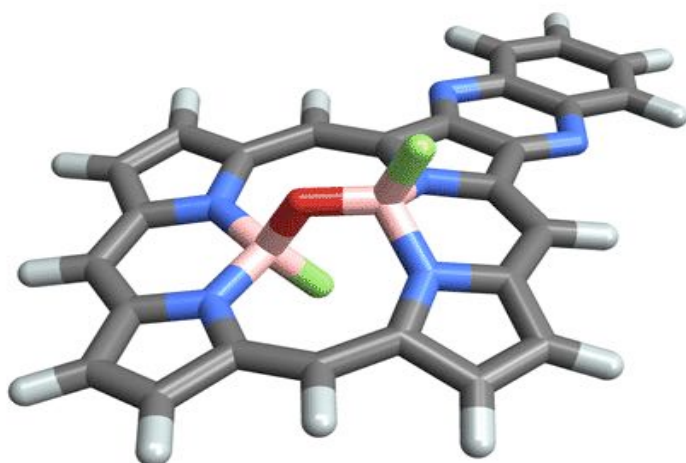
Are the four rings in the same plane?

<https://cen.acs.org/physical-chemistry/chemical-bonding/Chemists-claim-ve-defined-first/96/i22>

## New class of stereoisomers?

*Akamptisomers* – bond angle inversion in which the central atom in a bent, singly bonded trio of different atoms flexes in the opposite direction.

B=pink  
O=red  
Porphyrin  
ring



For other isomer, see

<https://cen.acs.org/is/content//content/dam/cen/96/22/09622-scicon3-inversion.gif>

Possible applications: drug molecules, molecular switches