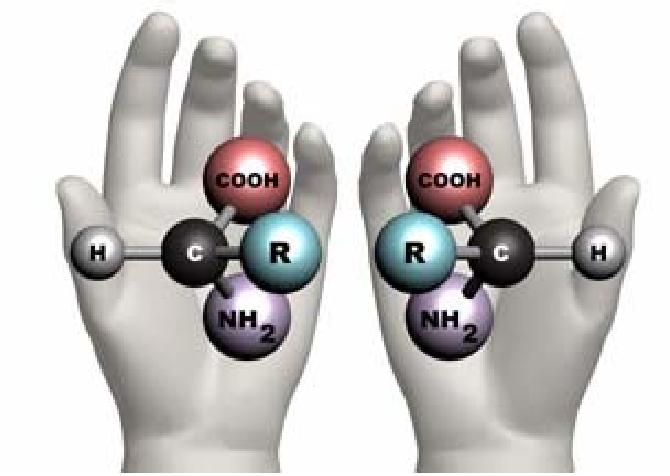
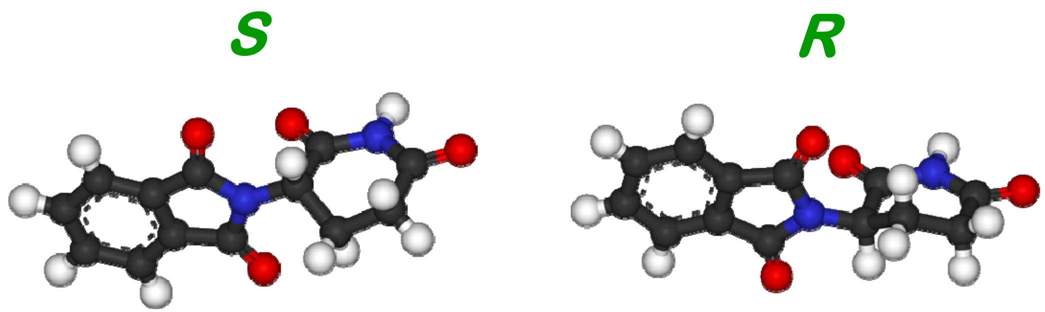

H O H





Stereochemistry:
biological significance of isomerism

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October 17th, 2008
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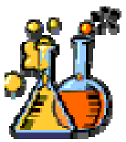
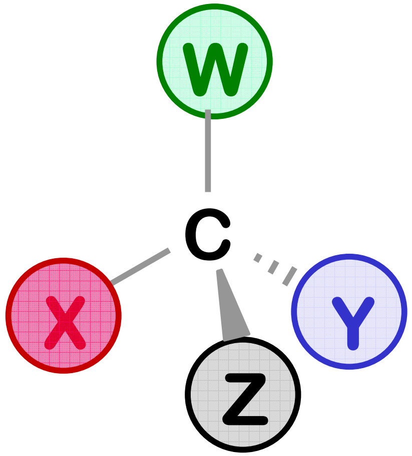
(copies of slides can be downloaded from my homepage)



Learning Objectives

- **Understand concepts of stereochemistry and isomerism**
- **Be able to assign isomer configuration**
- **Rationalize energy-dependence of cyclohexane conformations**
- **Know biological significance of isomerism and optical activity**

Stereochemistry



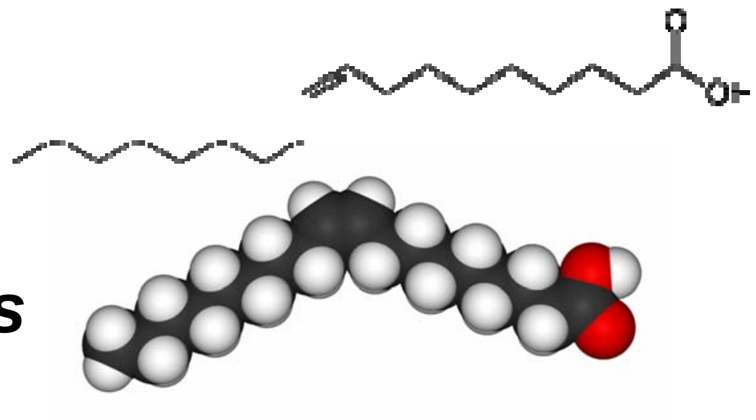
Types of Isomers

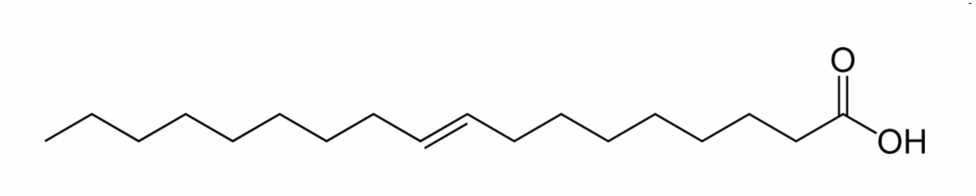
- Structural (constitutional)
  - same molecular formula, different attachment order
- Geometric (*cis* and *trans*, *E* and *Z*)
  - molecular rigidity (alkenes and cyclic systems)
- Conformational (cyclohexane)
  - molecular shape
- Optical (chirality)
  - arrangement ("right- or left-handedness")

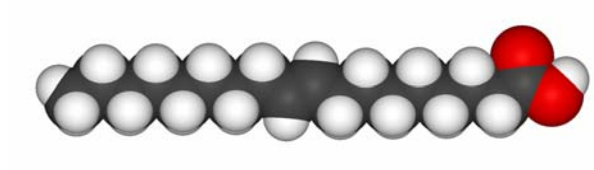
Importance of stereochemistry

- *trans* fat – elevated risk in coronary heart disease

cis



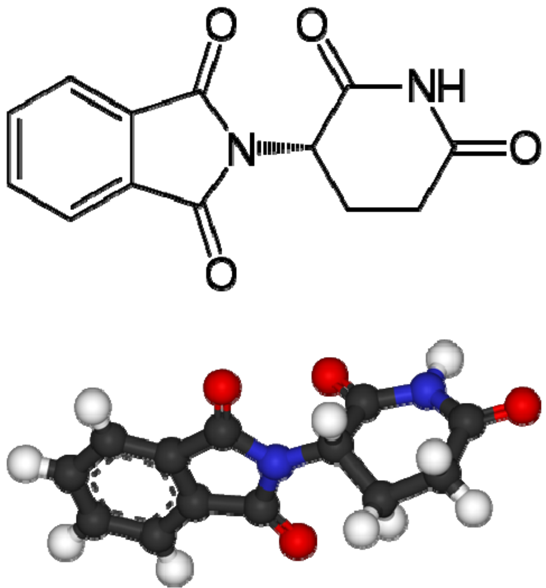




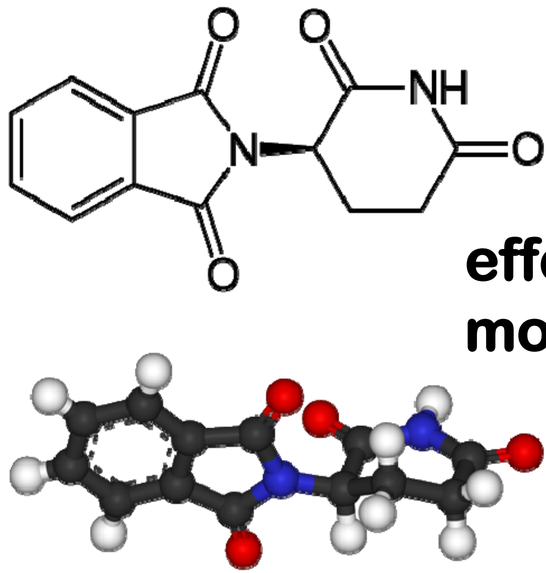
trans

- Thalidomide (Neurosedyn)

S



R



teratogenic and causes birth defects

effective against morning sickness

Geometric Isomers

occurs in only 2 classes of compounds:

1. Alkenes
2. Cyclic systems

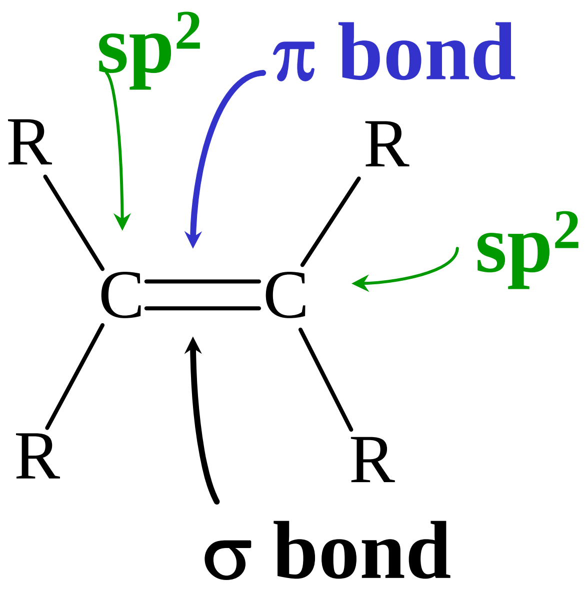
ALKENES

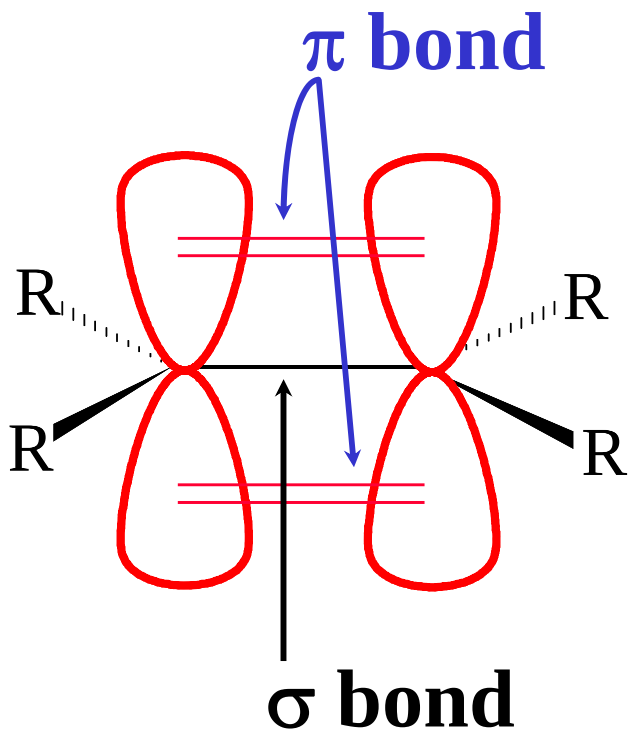
cis and *trans*

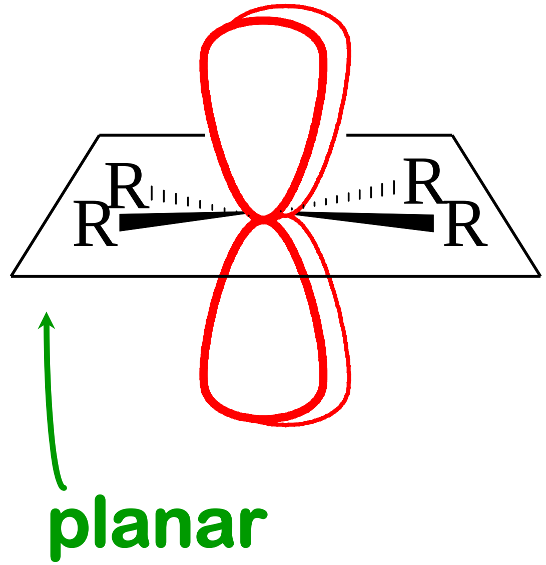
E and *Z*

ALKENE GEOMETRY

A REVIEW





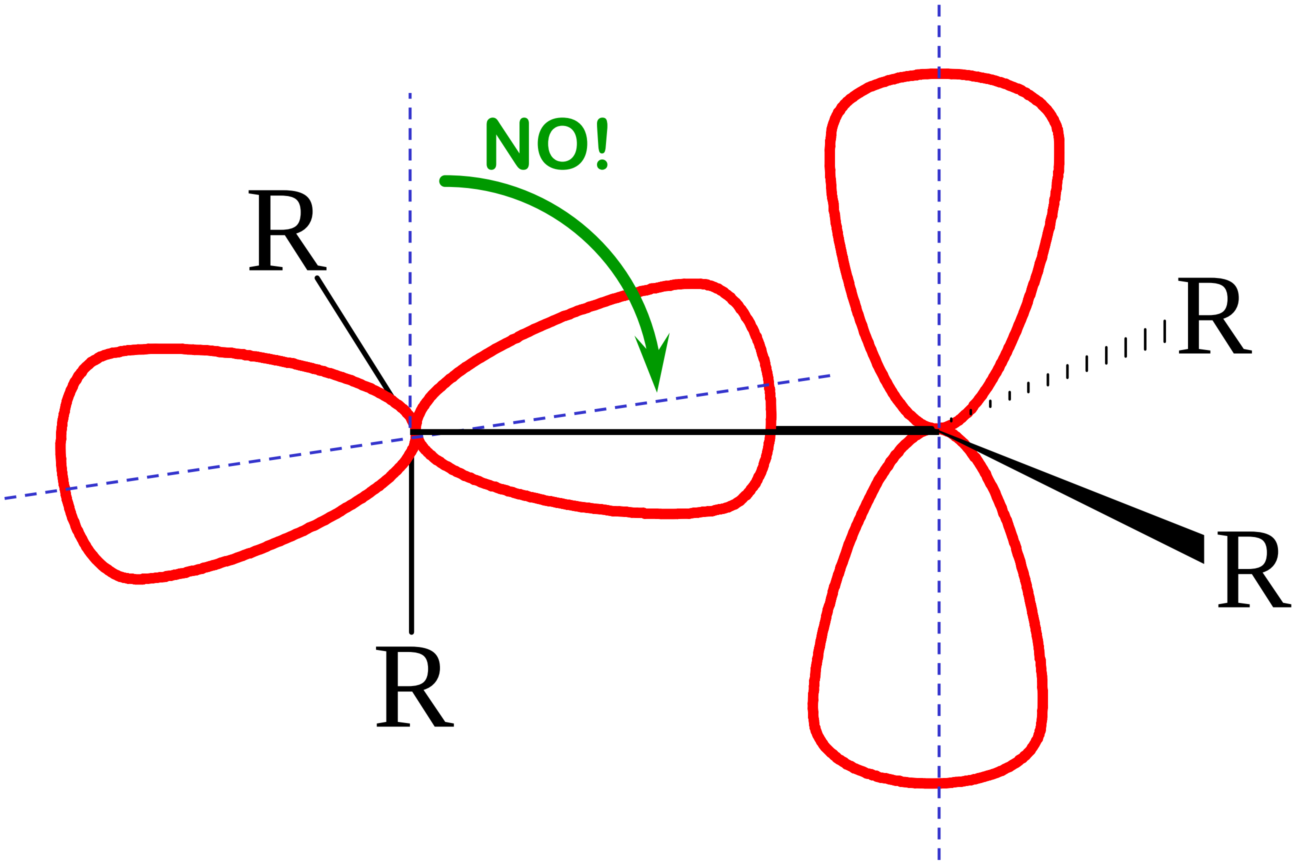


SIDE VIEW

END VIEW

ROTATION BREAKS THE π BOND

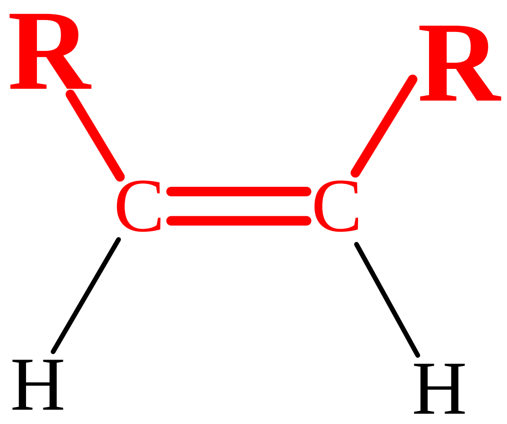
Unlike σ bonds, π bonds do not rotate.



- **requires 50-60 kcal/mole to break the π bond**
- **this does not happen at reasonable temperatures**

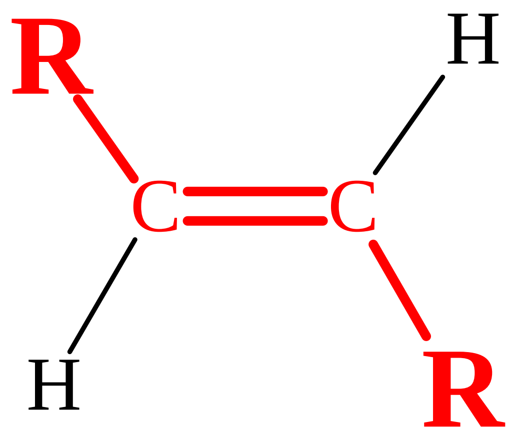
CIS / TRANS ISOMERS

Because there is no rotation about a carbon-carbon bond, isomers are possible



cis

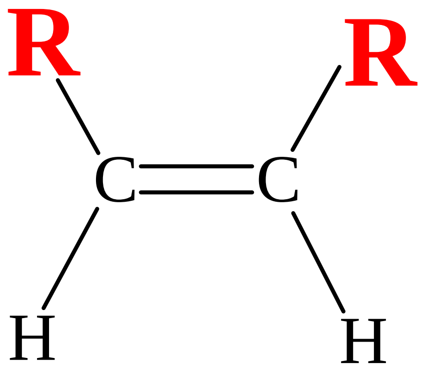
substituents on the same side of main chain

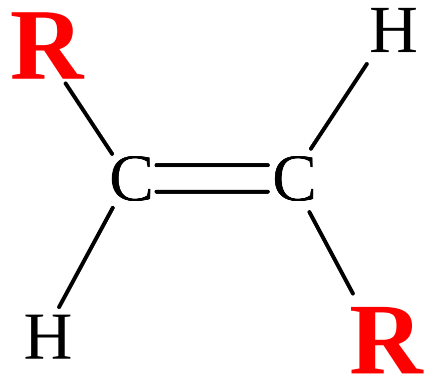


trans

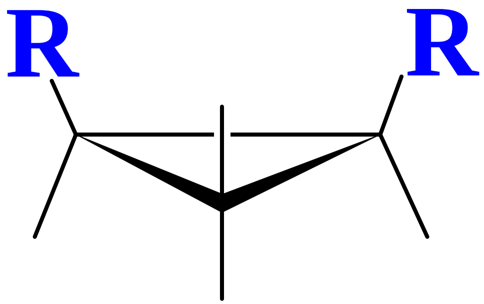
substituents on opposite sides of main chain

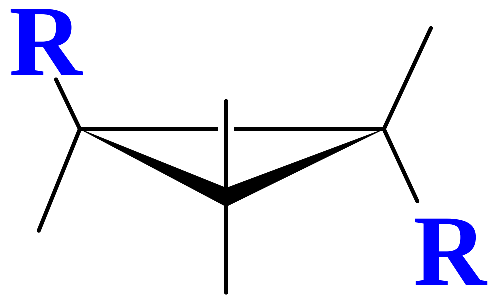
COMPARE *cis / trans* ISOMERS IN RING COMPOUNDS





cis ***trans***

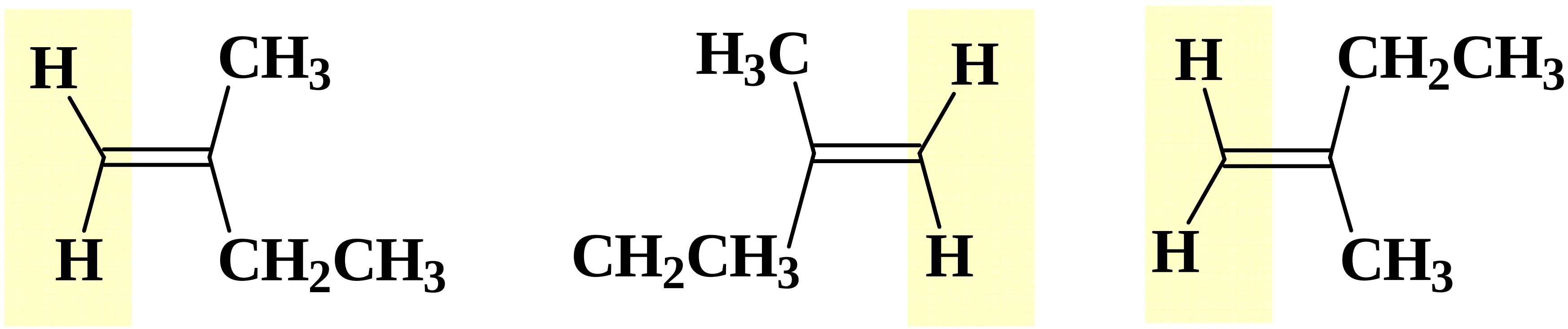




In alkenes *cis / trans* isomers used to be called geometric isomers, a term generally not generally used for cyclic systems (rings)

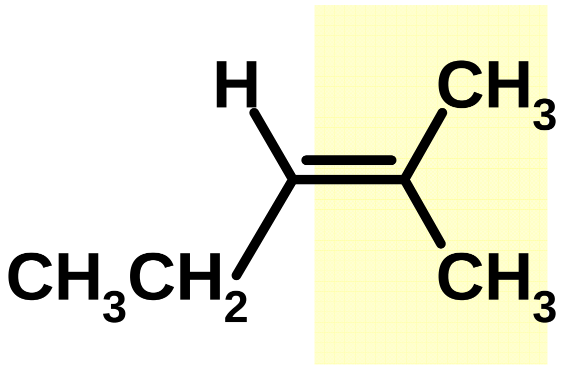
TWO IDENTICAL SUBSTITUENTS

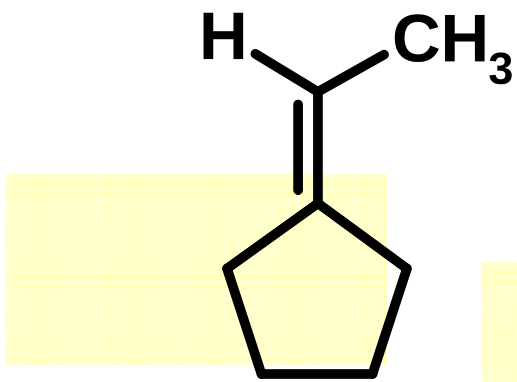
If an alkene has 2 identical substituents on one of the double bond carbons, *cis / trans* (or *E / Z*) isomers are not possible

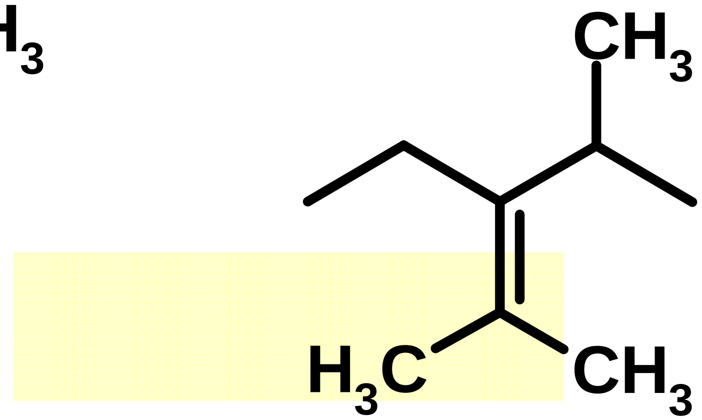


all of these compounds are identical
no *cis / trans* isomers

OTHER COMPOUNDS WITH NO *CIS / TRANS*



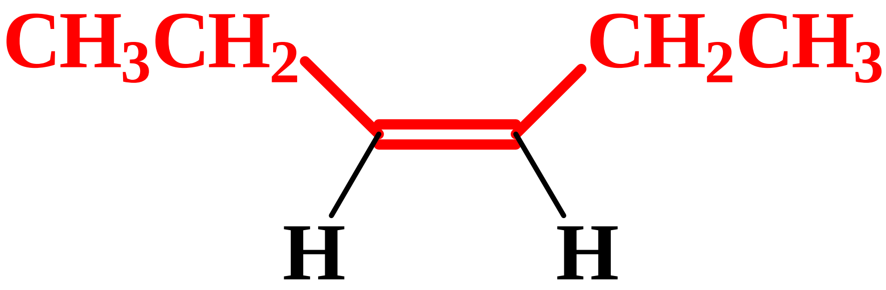




no *cis / trans* isomers

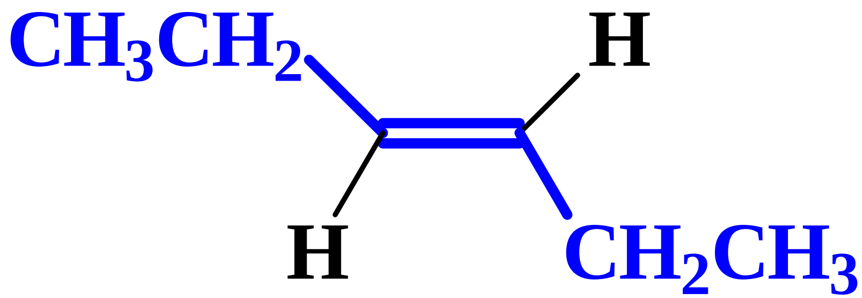
NAMING *cis* / *trans* ISOMERS OF ALKENES

main chain stays on same side of double bond = *cis*



cis-3-hexene

main chain crosses to other side of double bond = *trans*

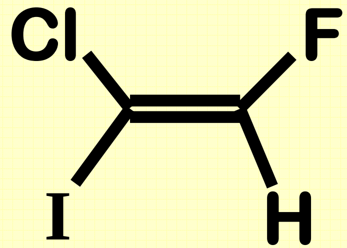


trans-3-hexene

notice that these prefixes are in italics

E / *Z* SYSTEM OF NOMENCLATURE

To avoid the confusion between what the main chain is doing and the relationship of two similar groups ..... the IUPAC invented the *E* / *Z* system



cis ?

trans ?

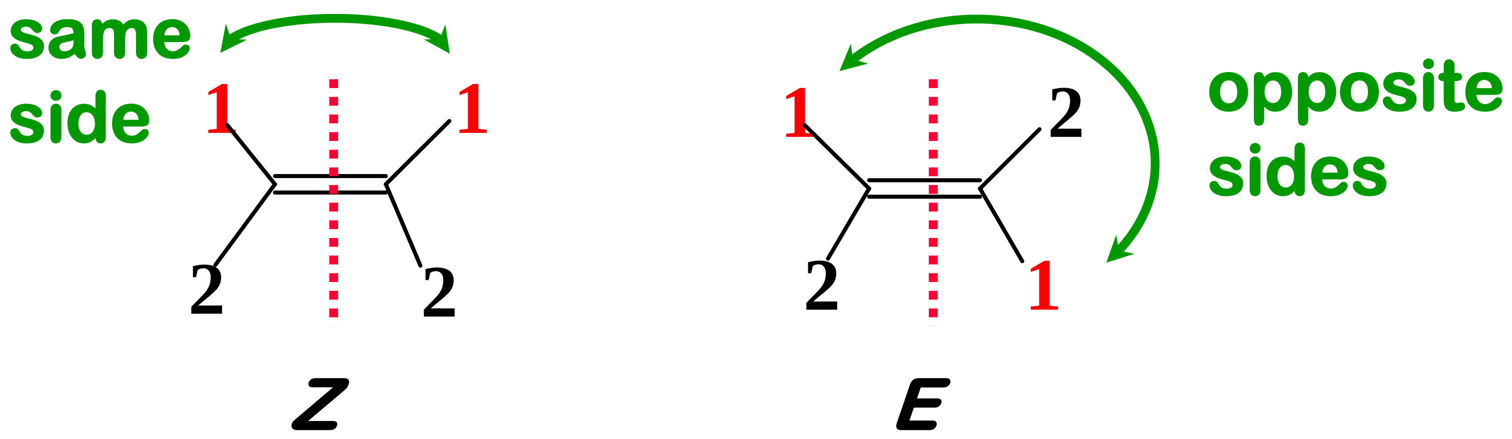
This system also allows alkenes like the one above to be classified .....
an impossibility with *cis* / *trans*

E / *Z* NOMENCLATURE

In this system the two groups attached to each carbon are assigned a priority (1 or 2)

If priority 1 groups are both on same side of double bond:

Z **isomer = zusammen = *together (in German)***



If priority 1 groups on opposite sides of double bond:

E **isomer = entgegen = *opposite (in German)***

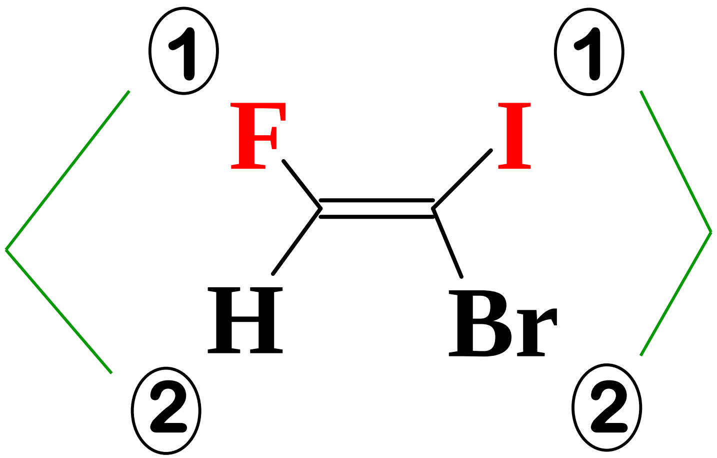
ASSIGNING PRIORITIES
Cahn-Ingold-Prelog System

1. Look at the atoms attached to each carbon of the double bond
2. Atom of higher **atomic number** has higher (1) priority

example

F > H

atomic number 9 > 1



I > Br

53 > 35

bigger is better

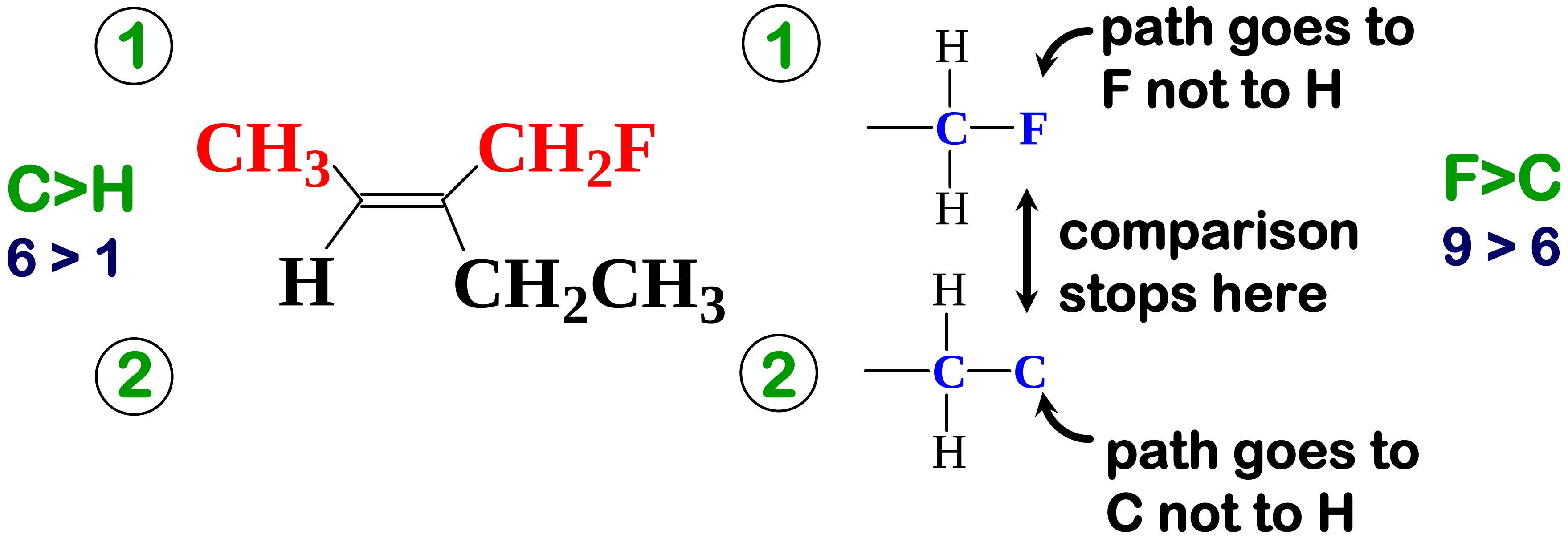
Since the 1's are on the same side, this compound is Z

(*Z*)-1-bromo-2-fluoro-1-iodoethene

notice use of parentheses

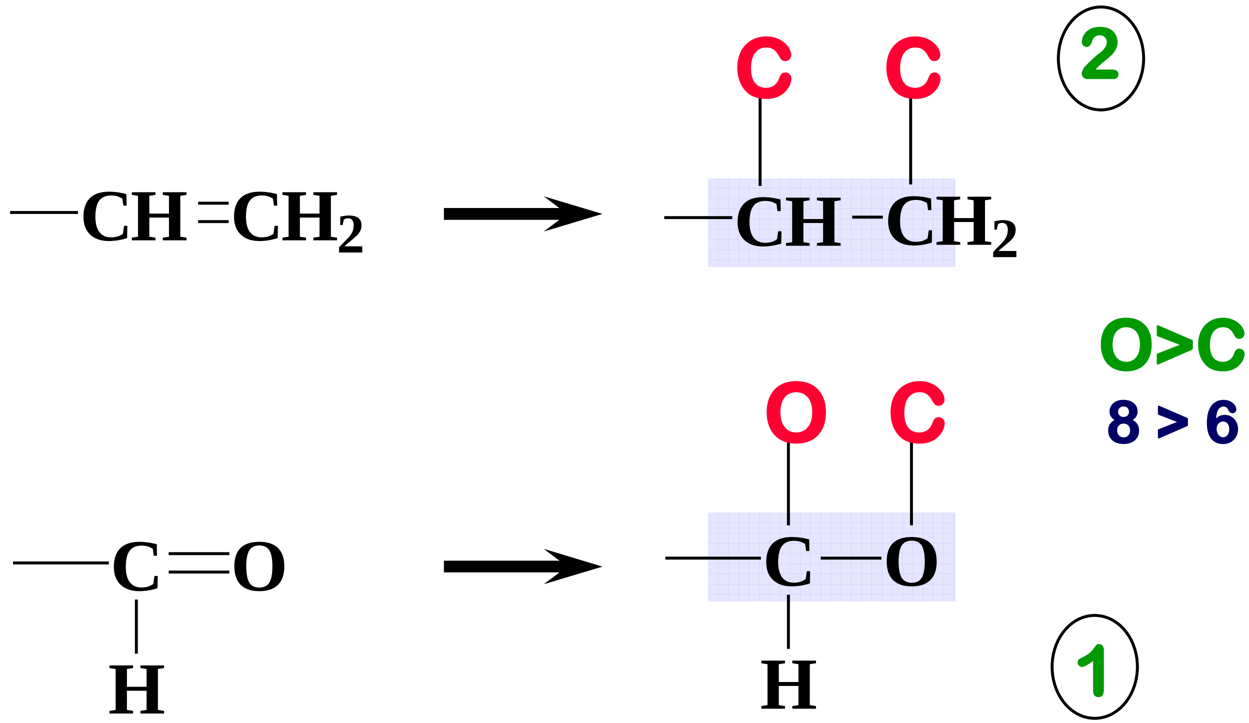
3. If you can't decide using the first atoms attached, go to the next atoms attached. If there are non-equivalent paths, always follow the path with atoms of higher atomic number.

Once you find a difference, you can stop.



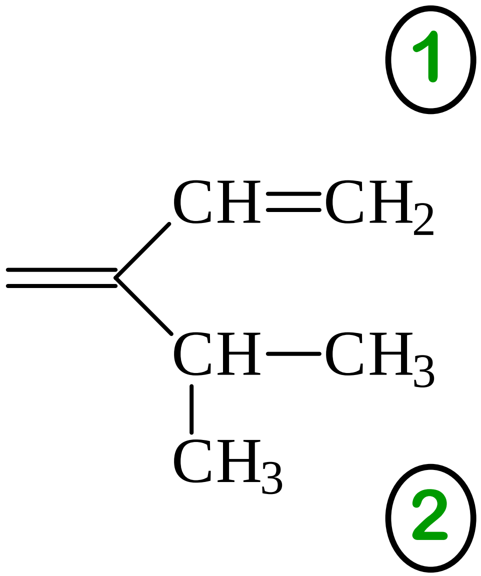
This molecule has *Z* configuration

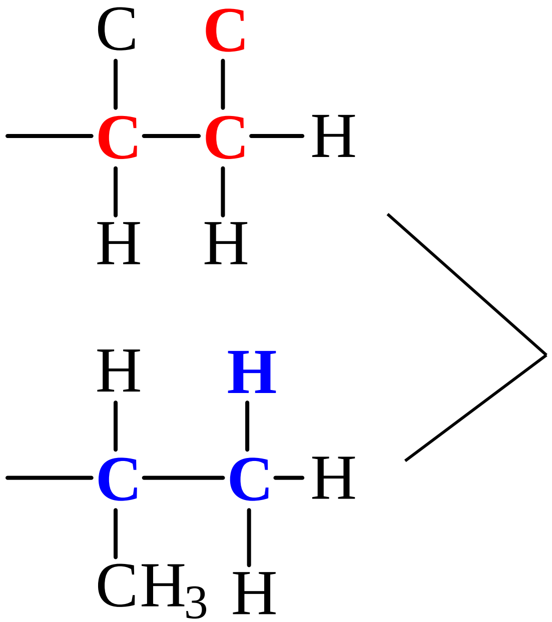
4. The atoms in double bonds are "replicated" at either end of the double bond.



Then, when comparing groups, follow the path of highest priority as before.

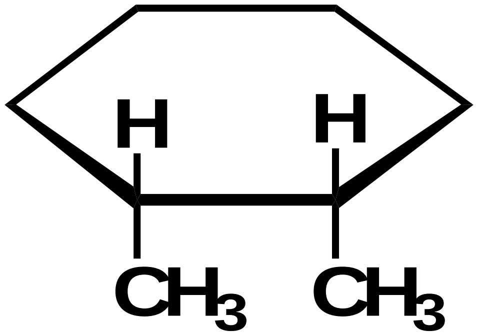
EXAMPLE USING REPLICATION



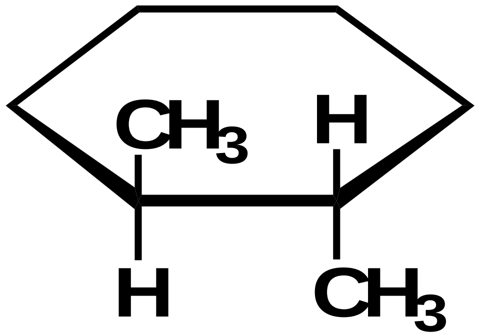


C > H

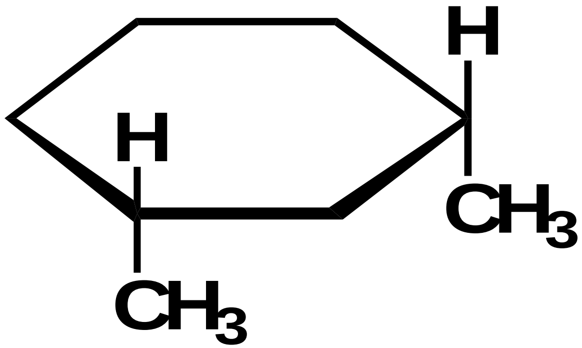
cis / *trans* with rings



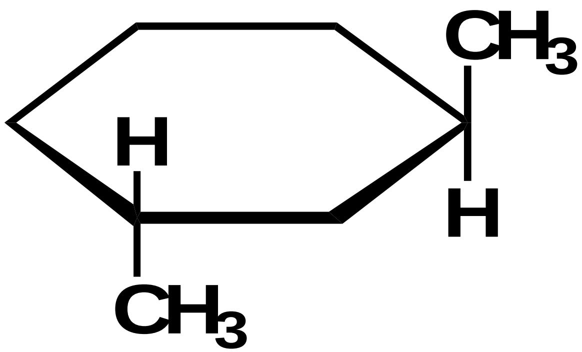
cis-1,2-dimethylcyclohexane



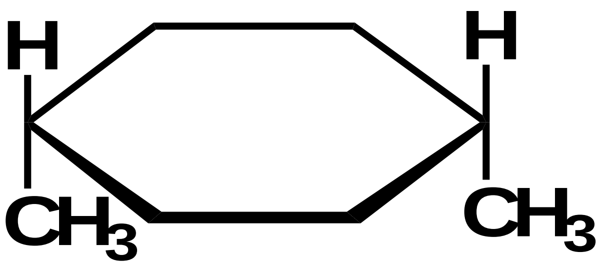
trans-1,2-dimethylcyclohexane



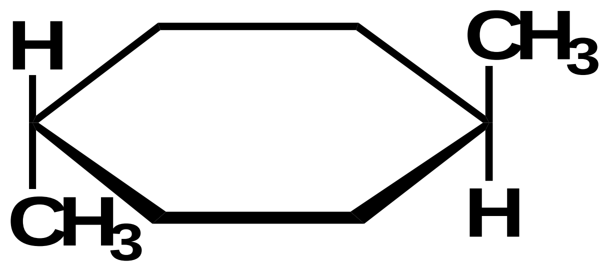
cis-1,3-dimethylcyclohexane



trans-1,3-dimethylcyclohexane



cis-1,4-dimethylcyclohexane



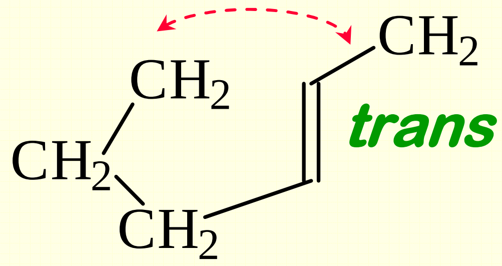
trans-1,4-dimethylcyclohexane

DOUBLE BONDS IN RINGS

RINGS

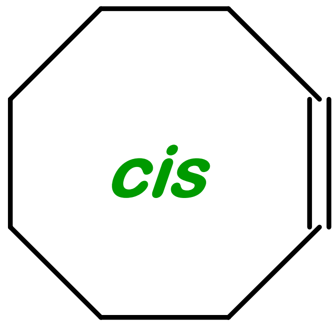
trans double bonds are not possible until the ring has at least eight carbon atoms

if C<8 then the chain is too short to join together

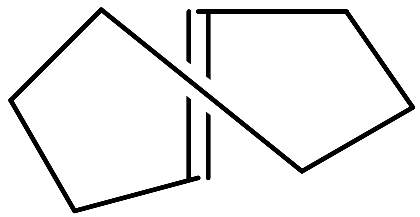


C = 5

C = 6



C = 8

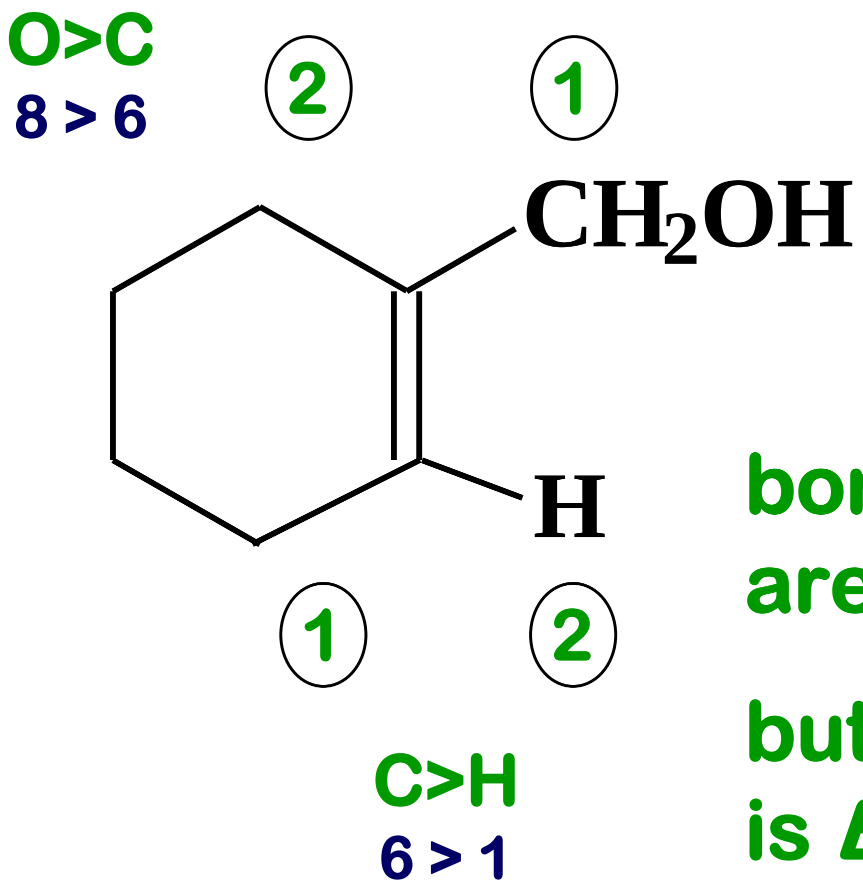


trans

smallest ring that can have a *trans* double bond

Note that <u>both</u> *cis* and *trans* exist for C8

cis and *Z* are not always the same for a given ring

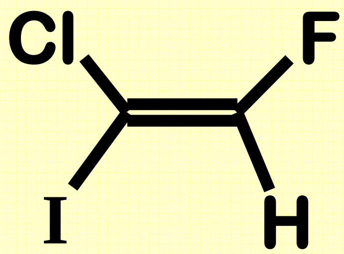


bonds in the ring are *cis*

but this compound is *E*

Applying Cahn-Ingold-Prelog

Is this molecule *cis* or *trans*, *E* or *Z*???



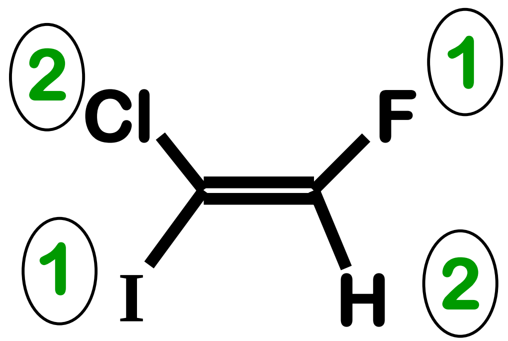
cis? *Z*?

trans? *E*?

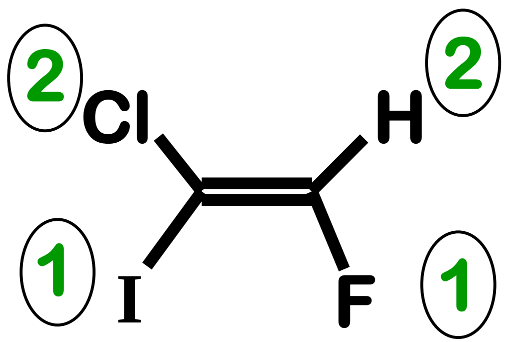
atomic number

1	9	17	35	53
H	F	Cl	Br	I

Increasing priority



E



Z

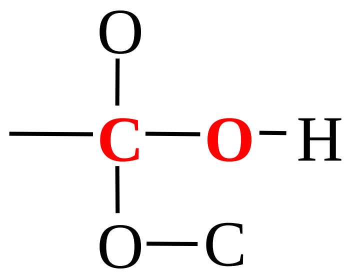
atomic number for N=7

Lets' Practice . . . ..

- **List the following atoms/groups in order of increasing priority**

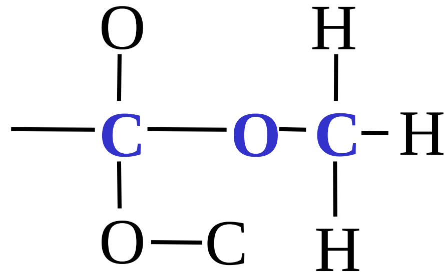
1) $-NH_2$, $-H$, $-CH_3$, $-Cl$

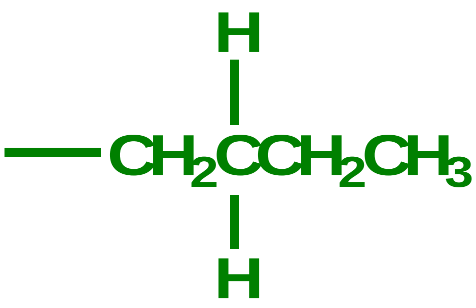
$-H$, $-CH_3$, $-NH_2$, $-Cl$



2) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, $-OH$, $-H$

$-H$, $-CH_2OH$, $-CO_2H$, $-CO_2CH_3$, $- OH$



3) 

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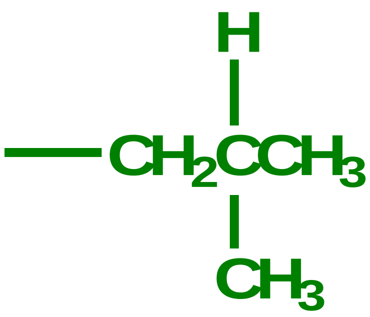
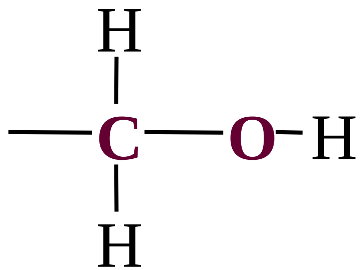
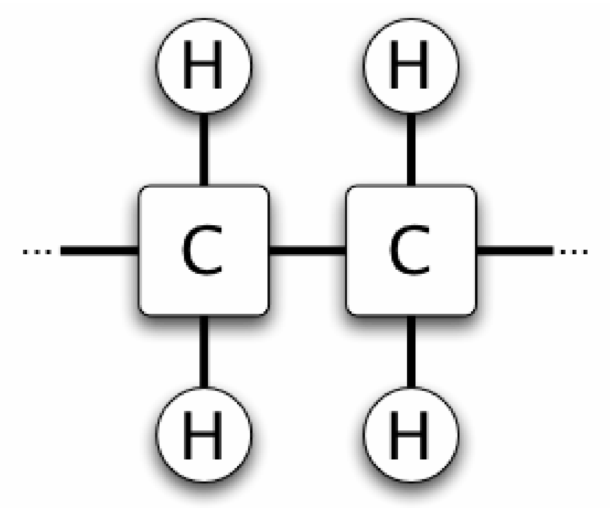


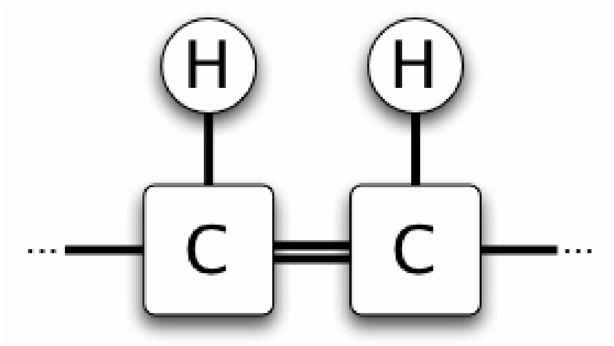
butyl isobutyl

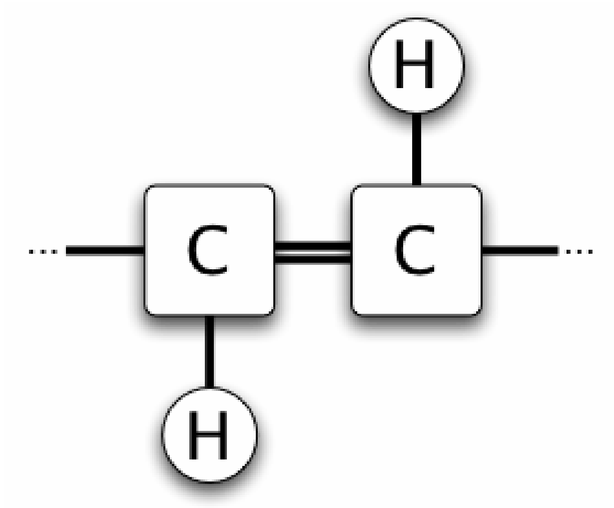


Why do we care about *cis* and *trans*?????

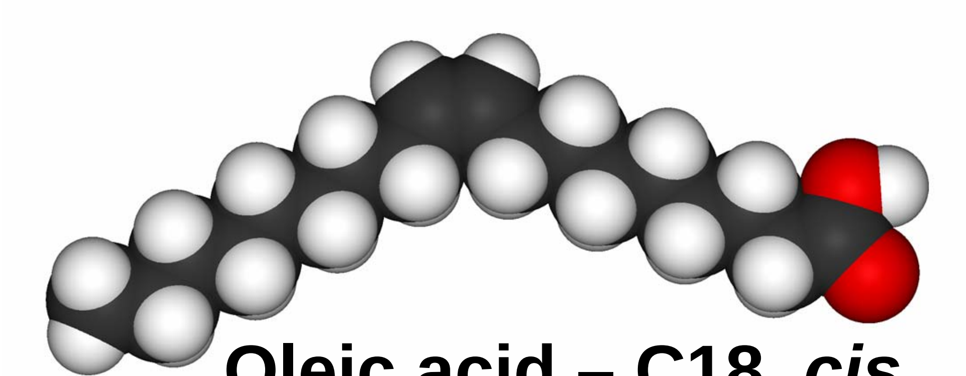
Trans-fat = Geometric isomers contains *trans* vs. *cis* bond



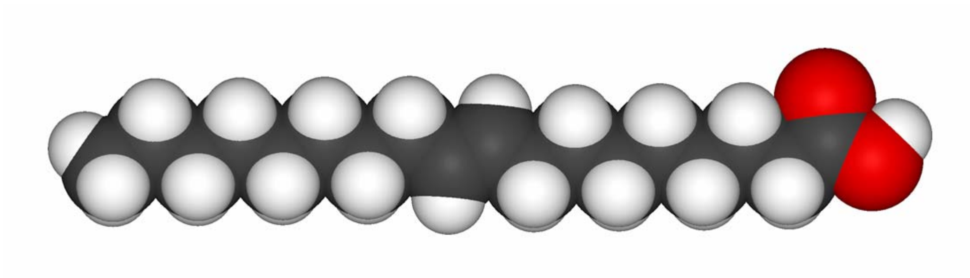




saturated | ***cis*** **double bond** | ***trans*** **double bond**



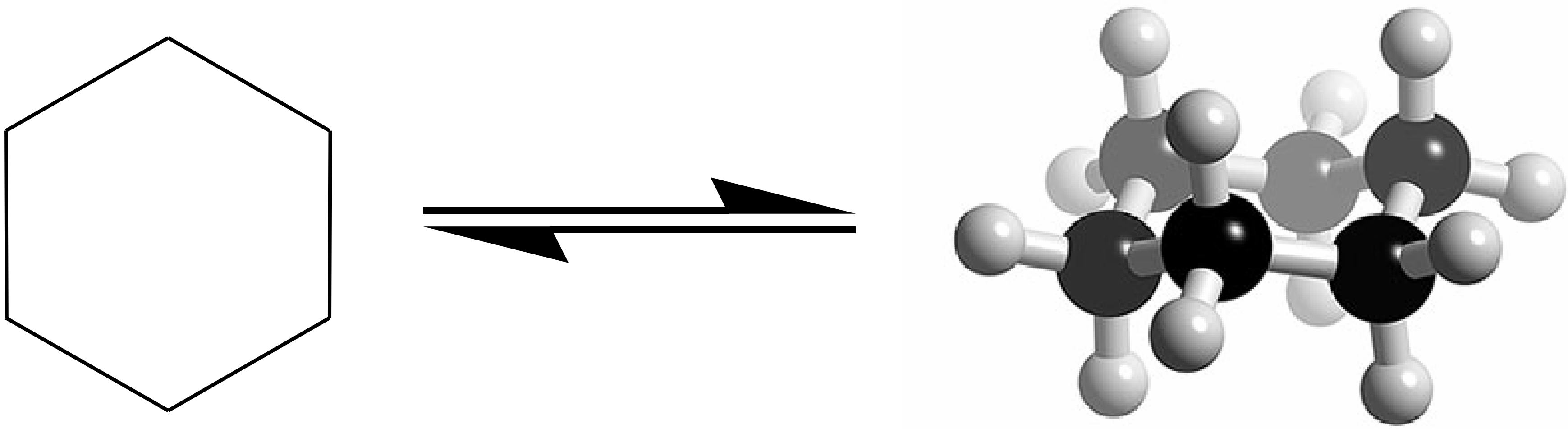
Oleic acid – C18, *cis*
Melting point = 13°C



Elaidic acid – C18, *trans*
Melting point = 45°C

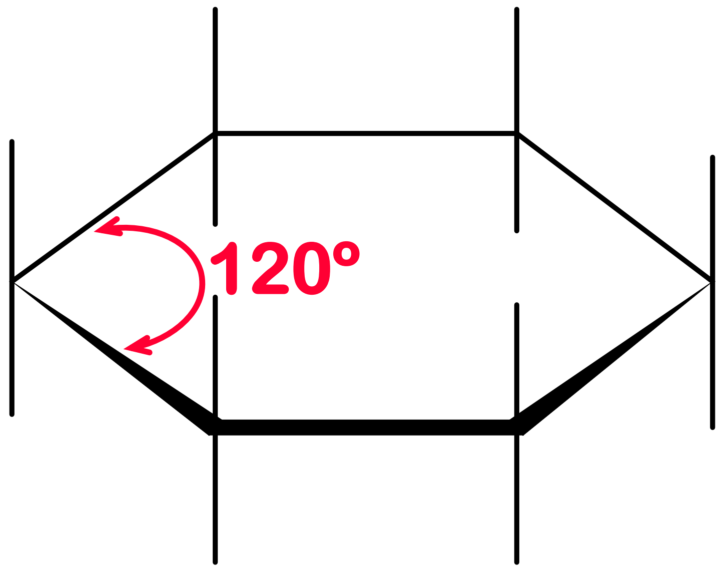
CYCLOHEXANE

Conformational isomers



PLANAR CYCLOHEXANE

(doesn't exist)

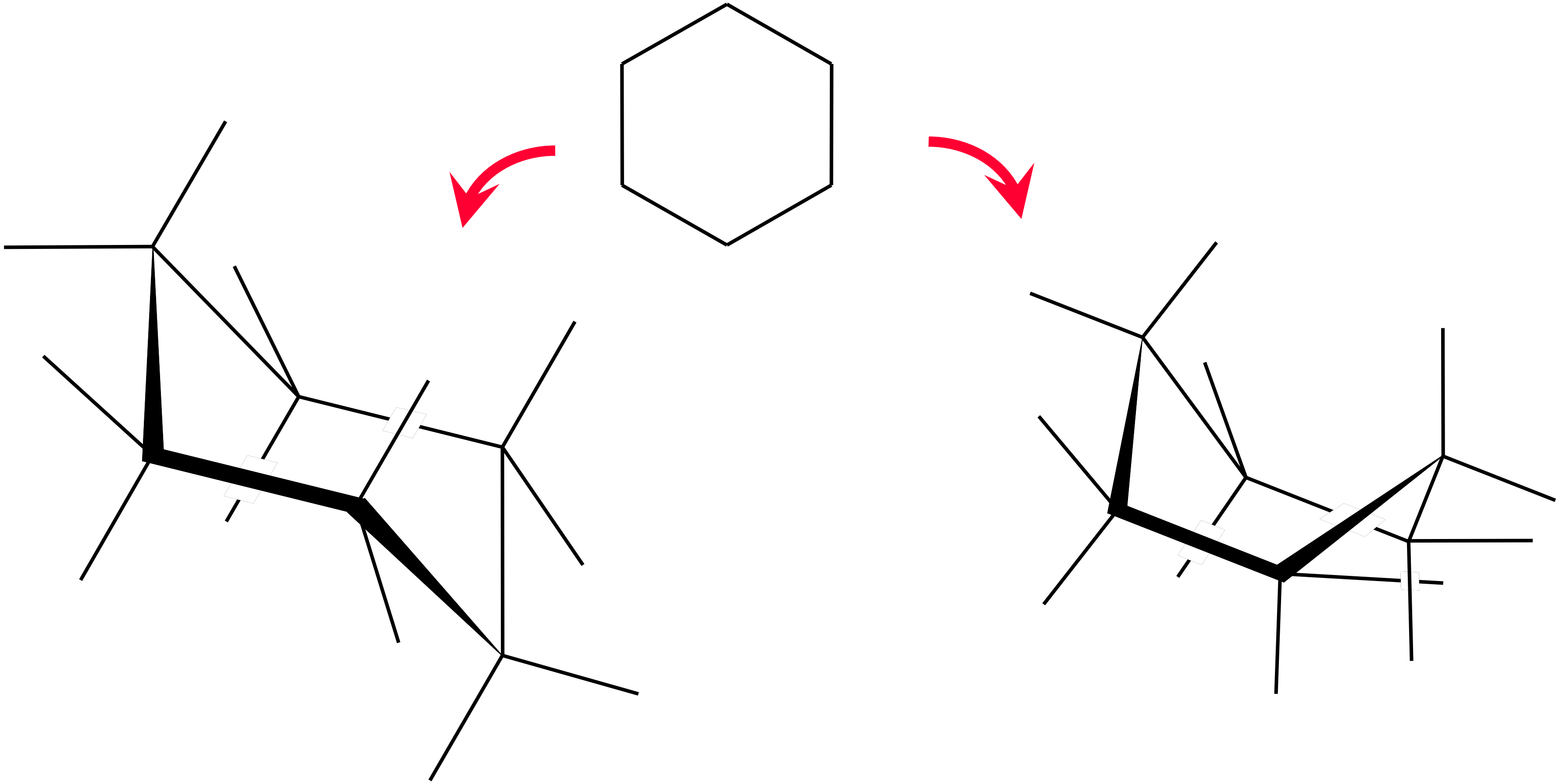


If cyclohexane were planar all of the hydrogens would be eclipsed, resulting in torsional strain.

There would also be angle strain - a hexagon has 120° internal angles.

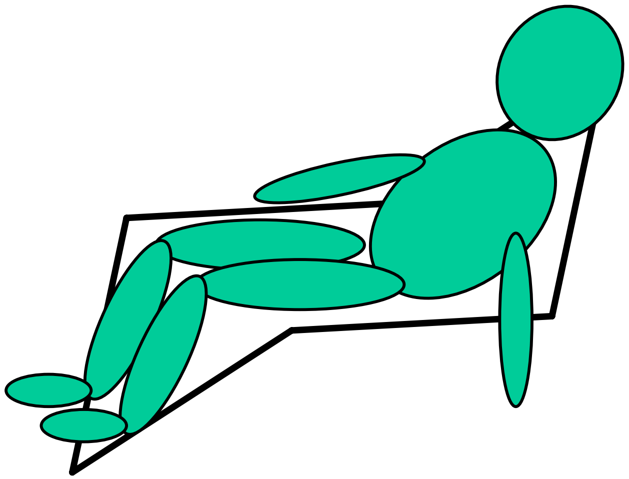
cyclohexane is not planar ...

CYCLOHEXANE CONFORMATIONS

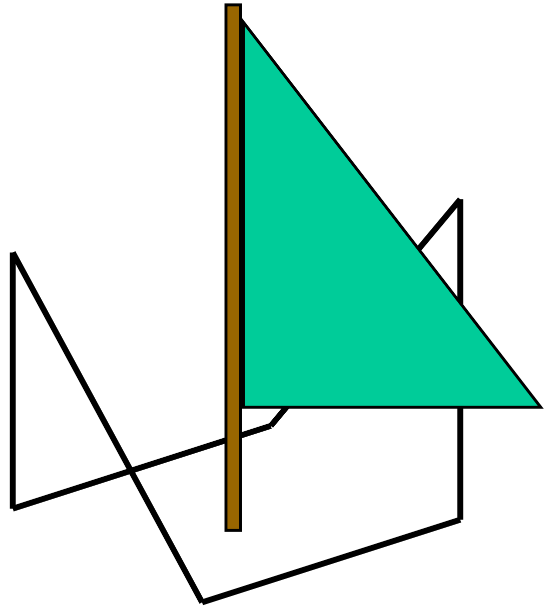


CHAIR

BOAT

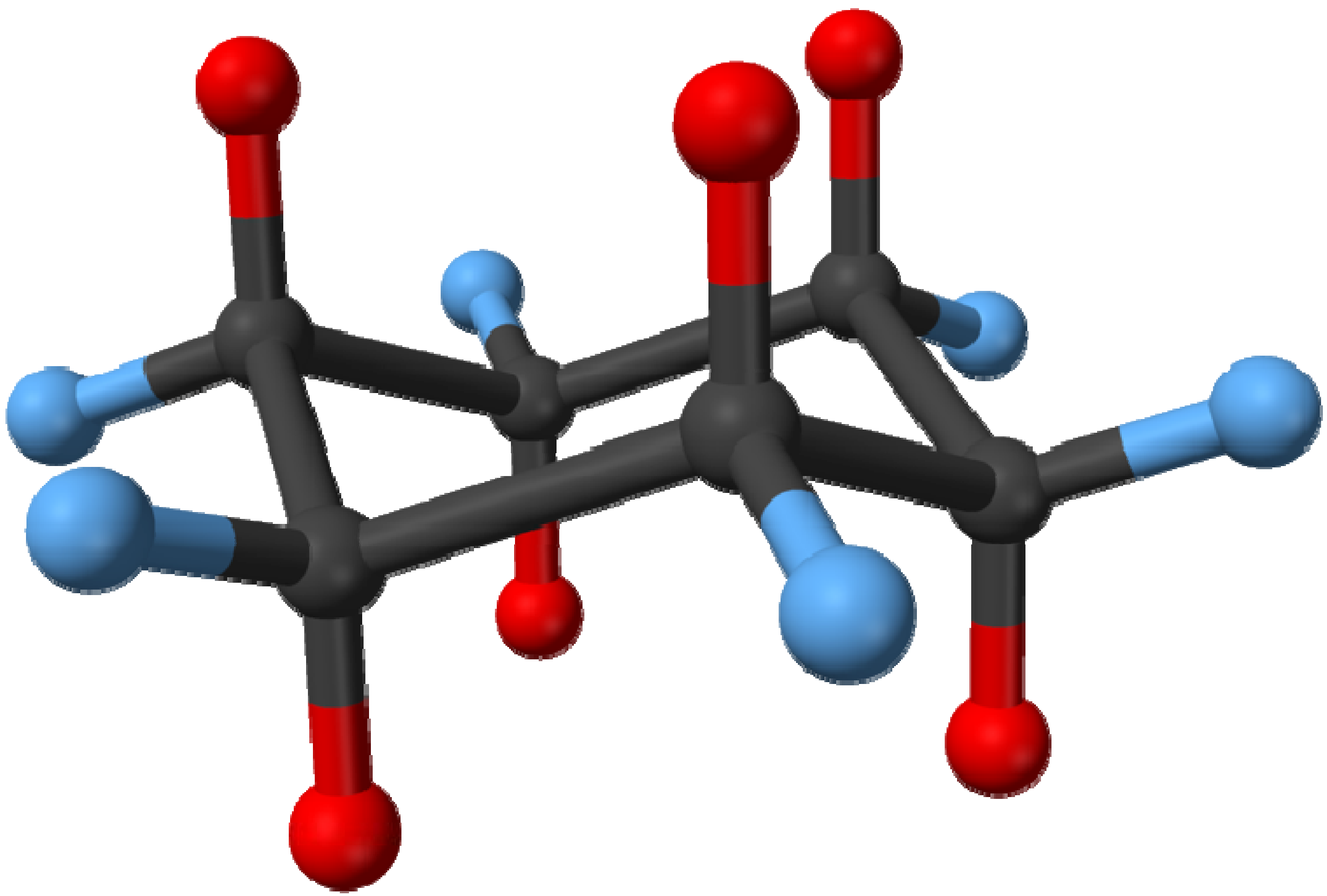


CHAIR



BOAT

CHAIR CONFORMATION



SELECTED DIMENSIONS FOR THE CHAIR

Van der Waal's radius of H = 1.20 Å

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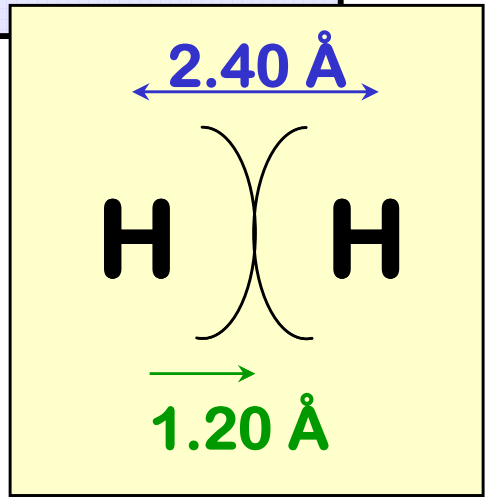
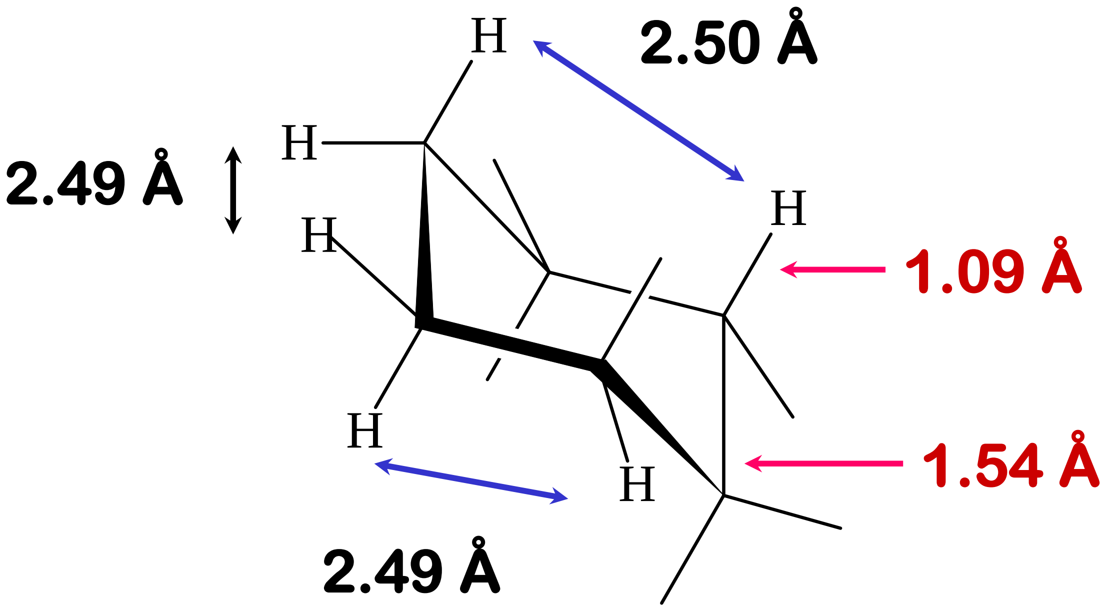
distances greater than 2.40 Å have no steric interaction

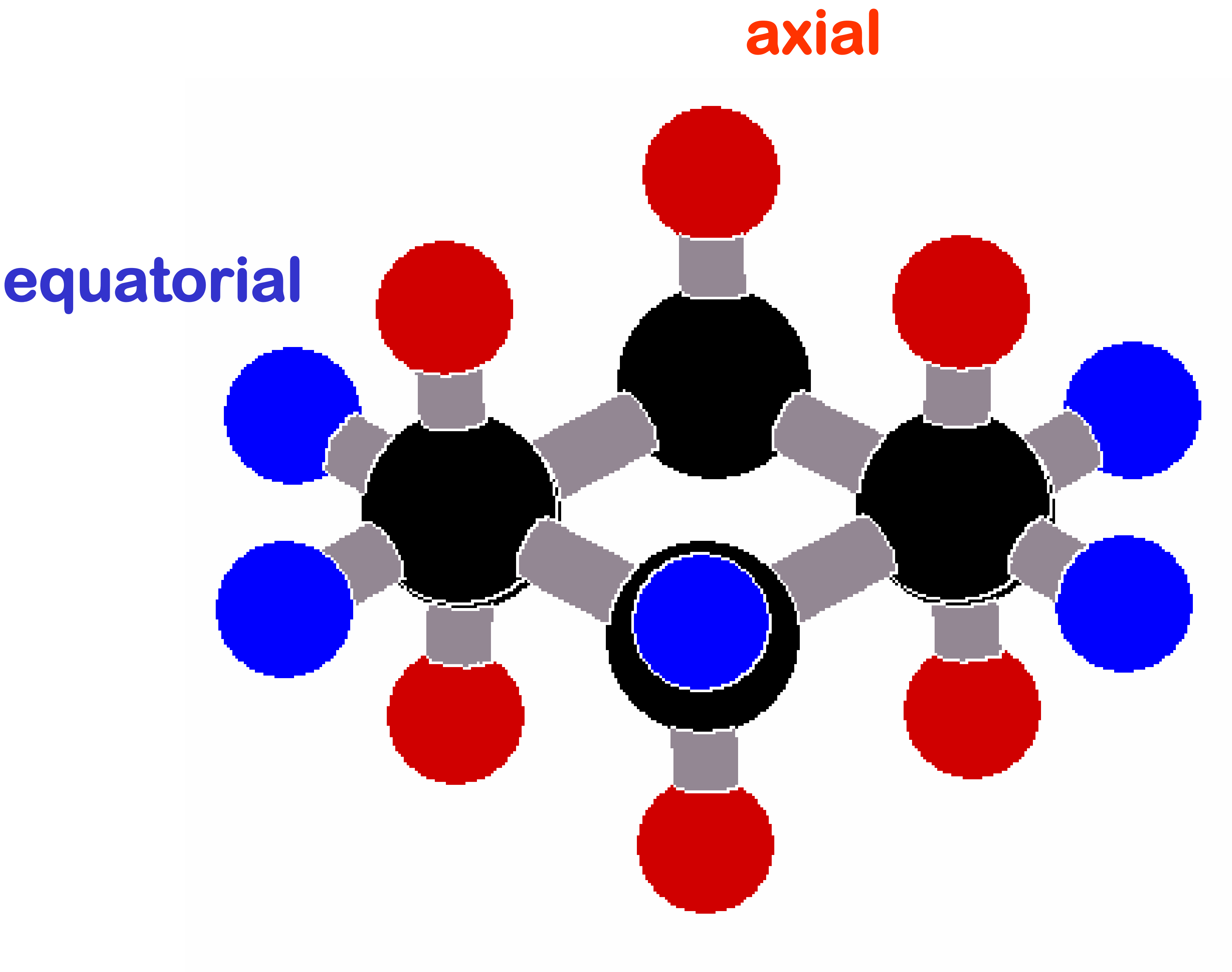




normal C-H and C-C bond lengths

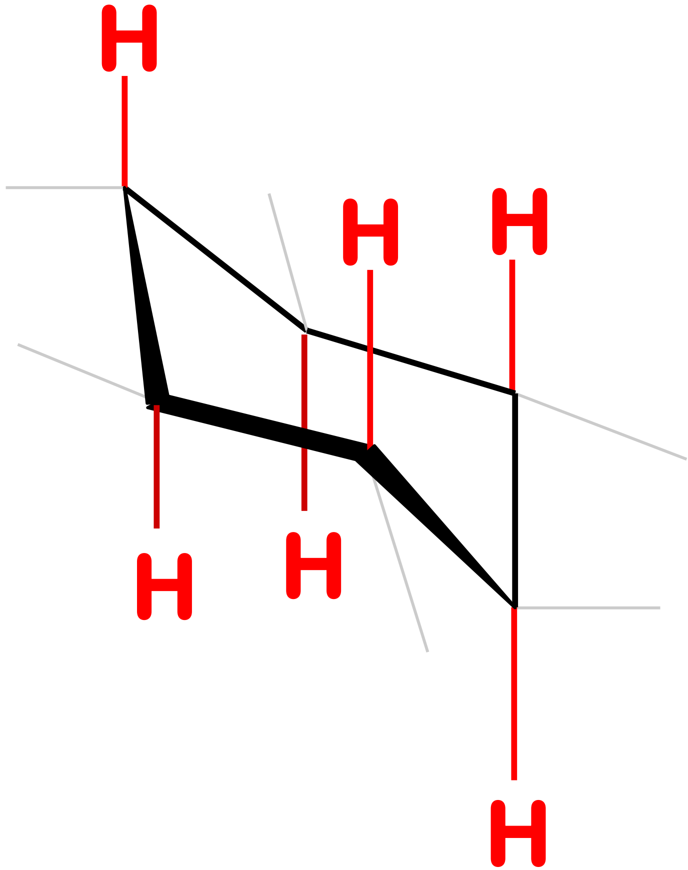
All of the hydrogens are more than 2.40 Å apart.

COMPLETE STAGGERING ABOUT ALL BONDS

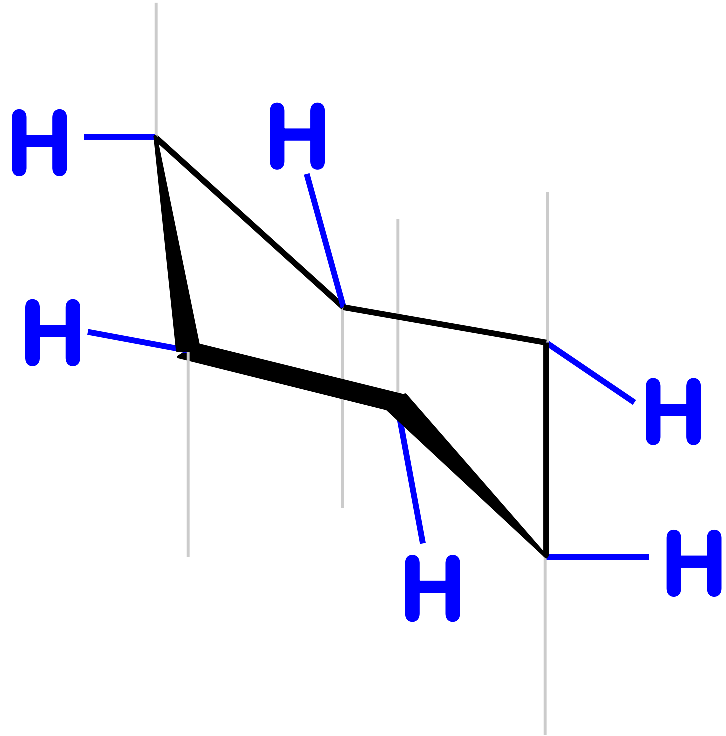


AXIAL AND EQUATORIAL HYDROGENS

Chair conformations

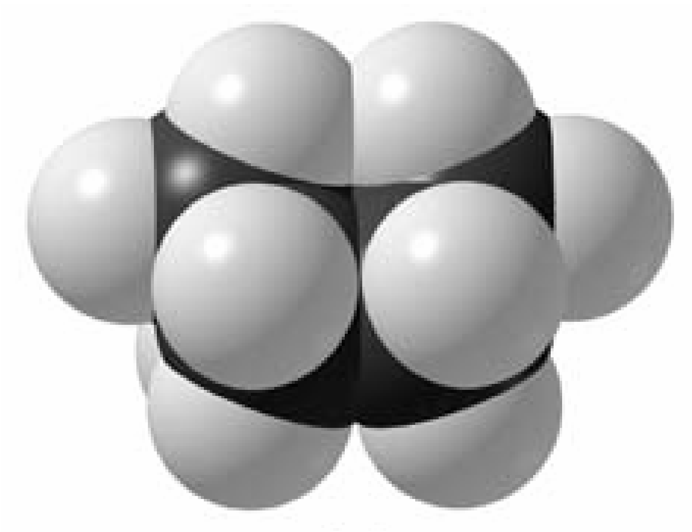


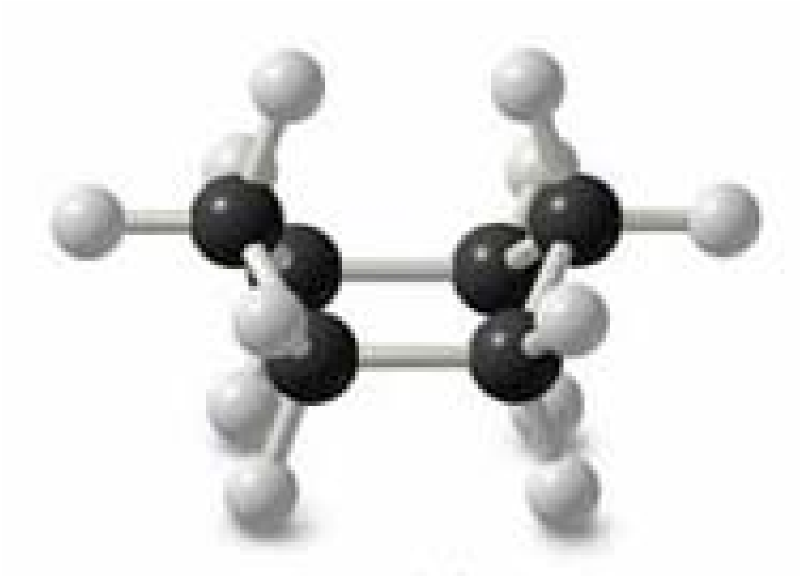
axial



equatorial

BOAT CONFORMATION

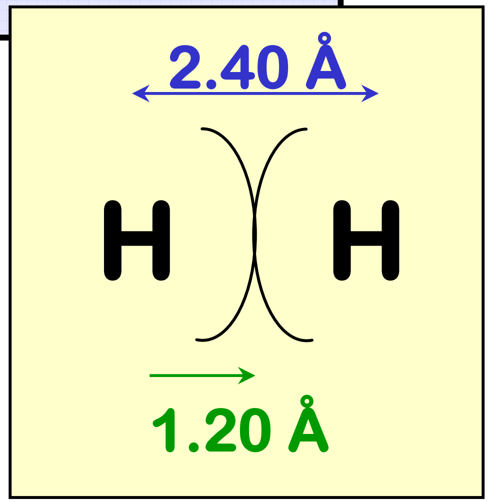


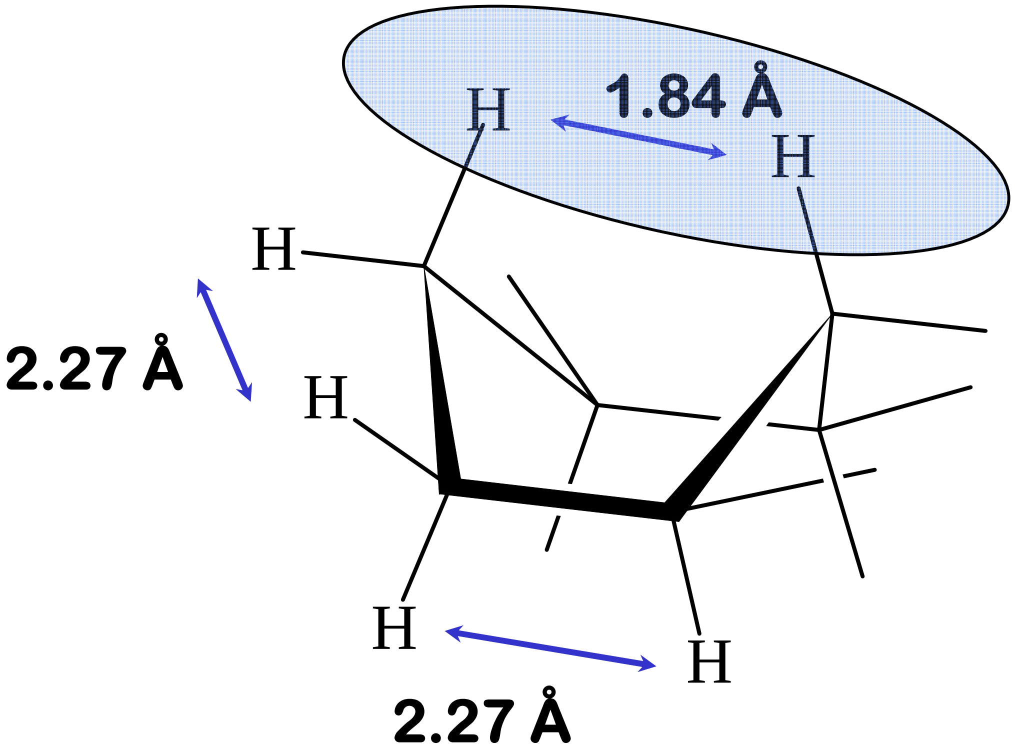


SELECTED DIMENSIONS FOR THE BOAT

Van der Waal's radius of H = 1.20 Å

distances greater than 2.40 Å have no steric interaction

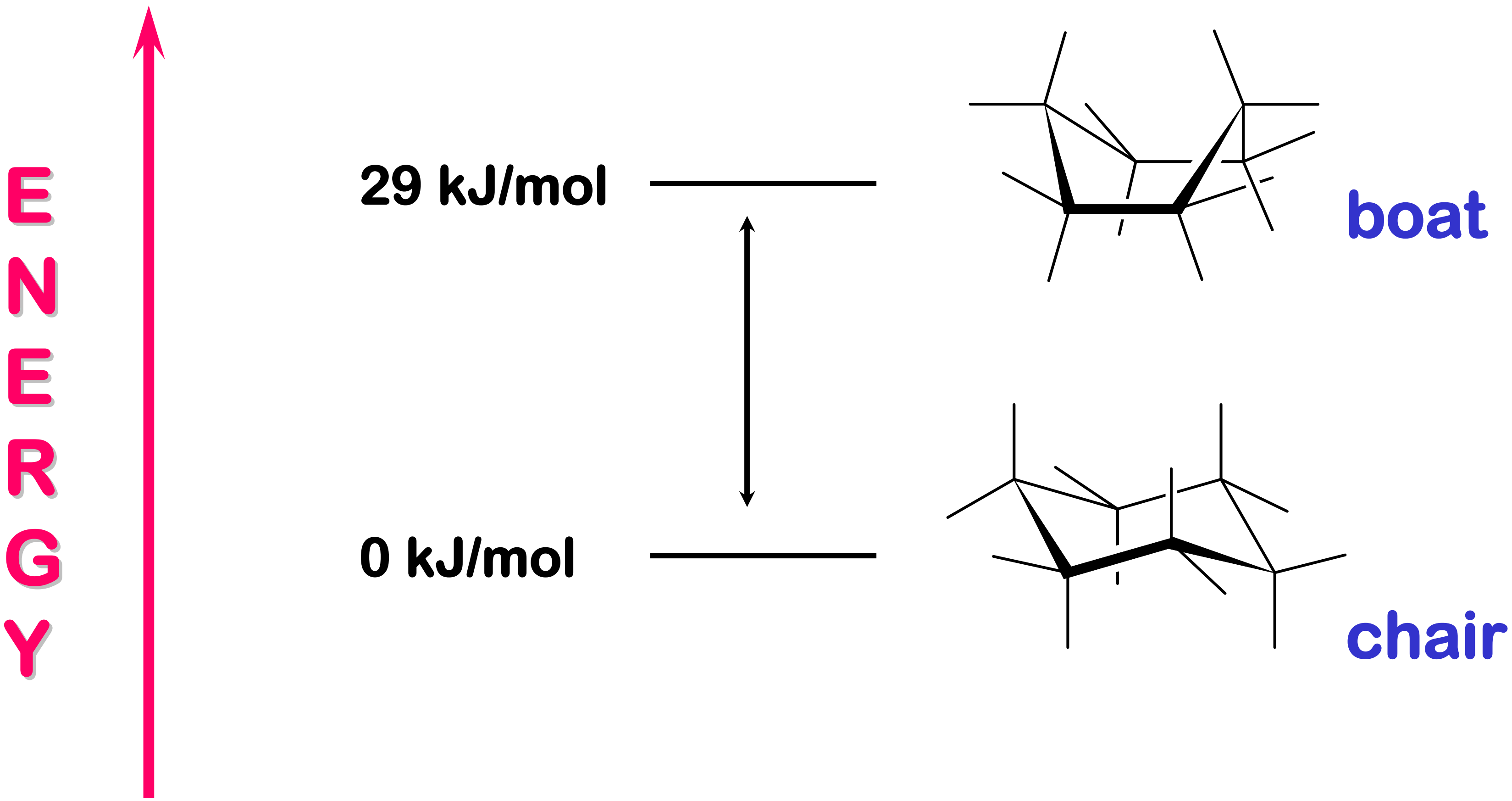




Bond lengths are normal.

A number of pairs of hydrogens are closer than 2.40 Å.

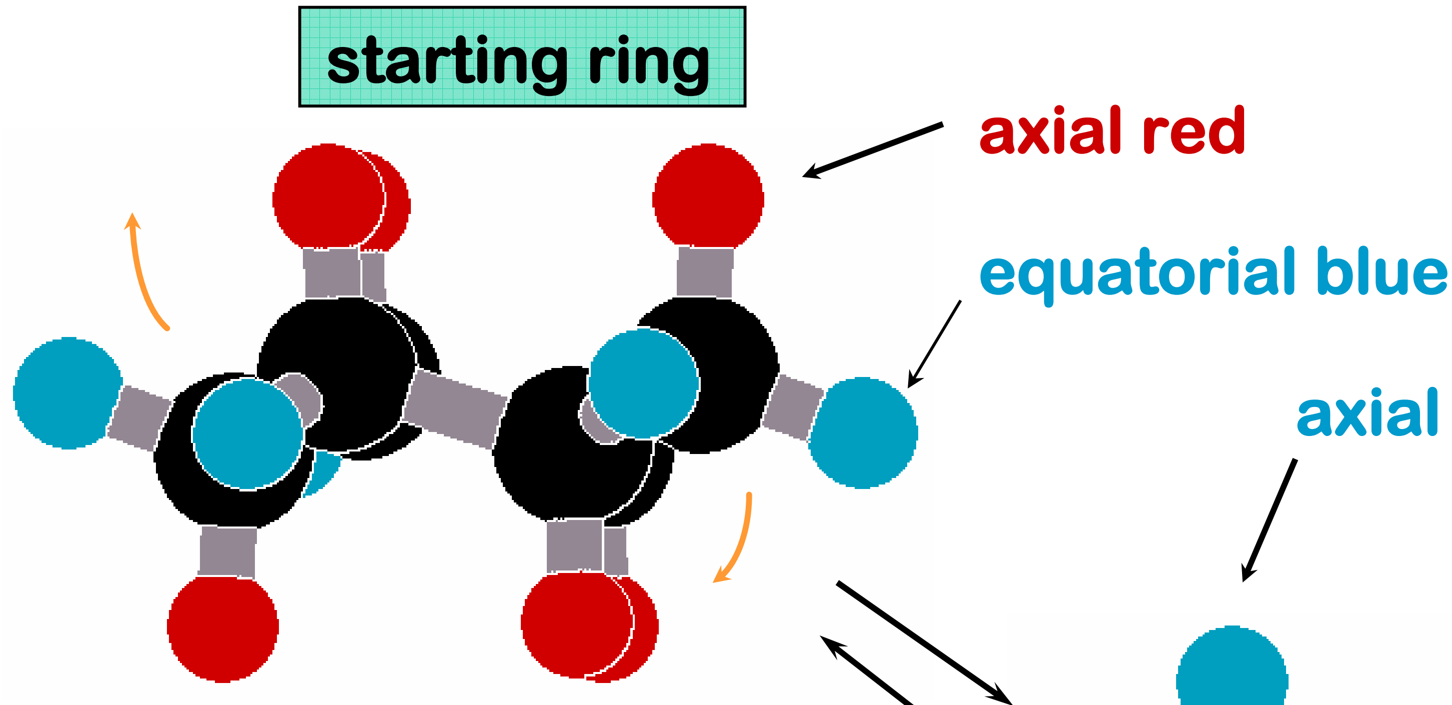
THE CHAIR CONFORMATION HAS LOWER ENERGY THAN THE BOAT

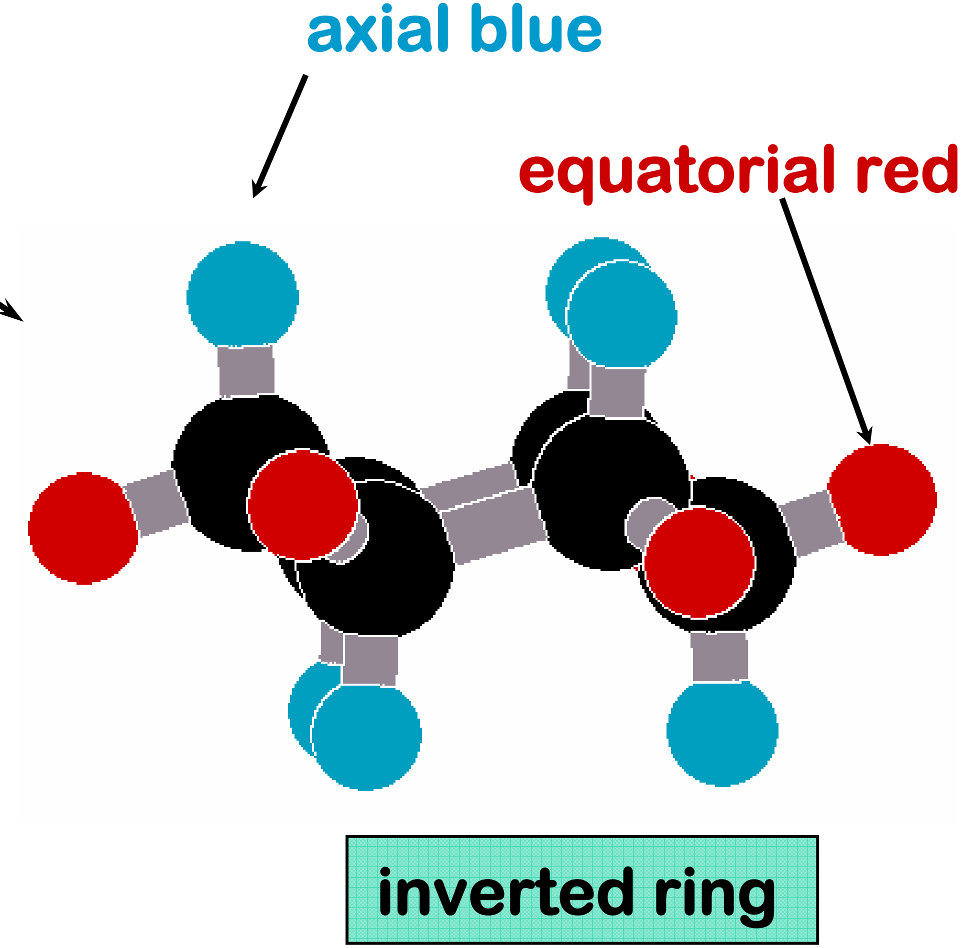


INTERCONVERSIONS

RING INVERSION

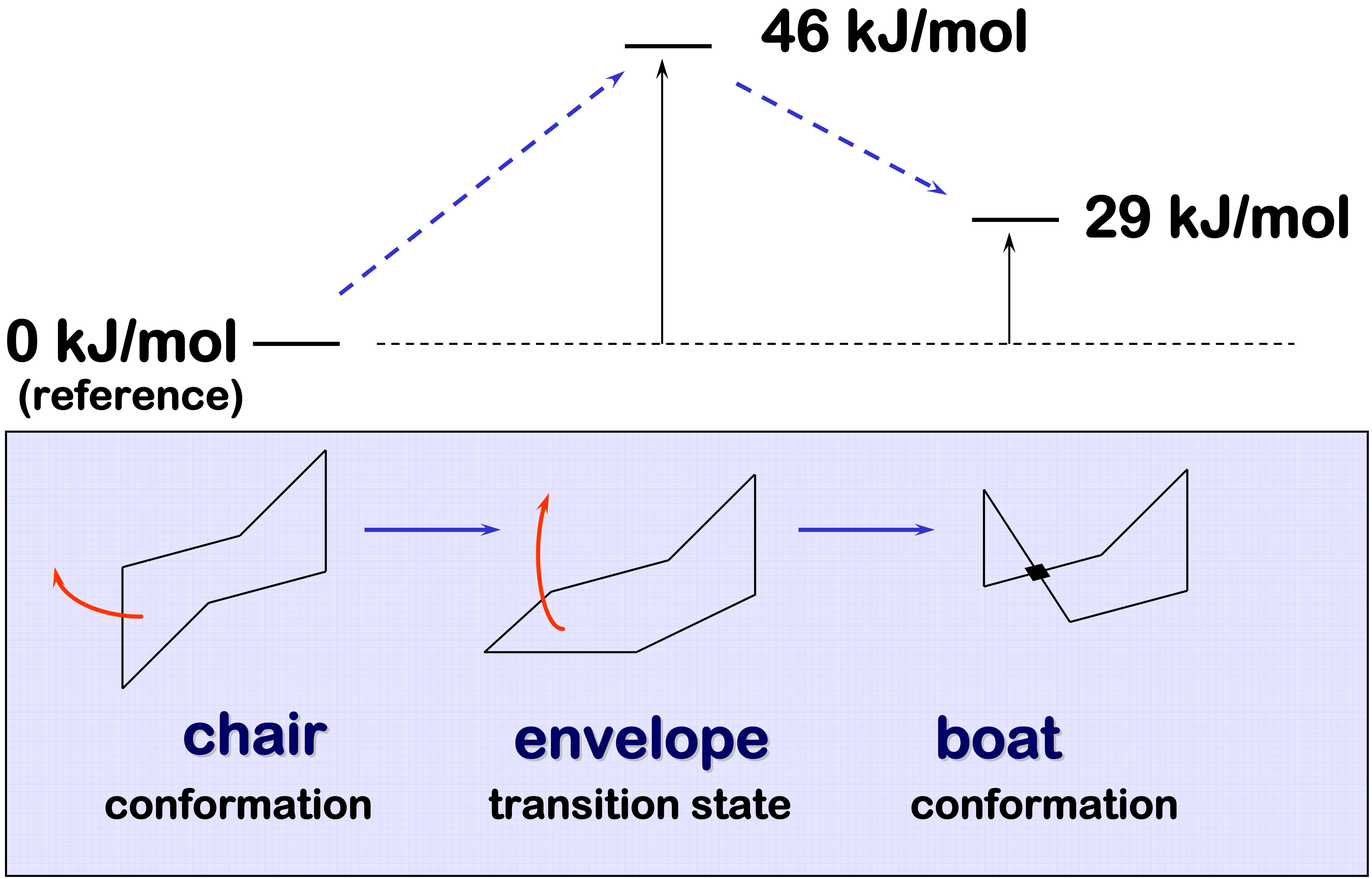
RING INVERSION



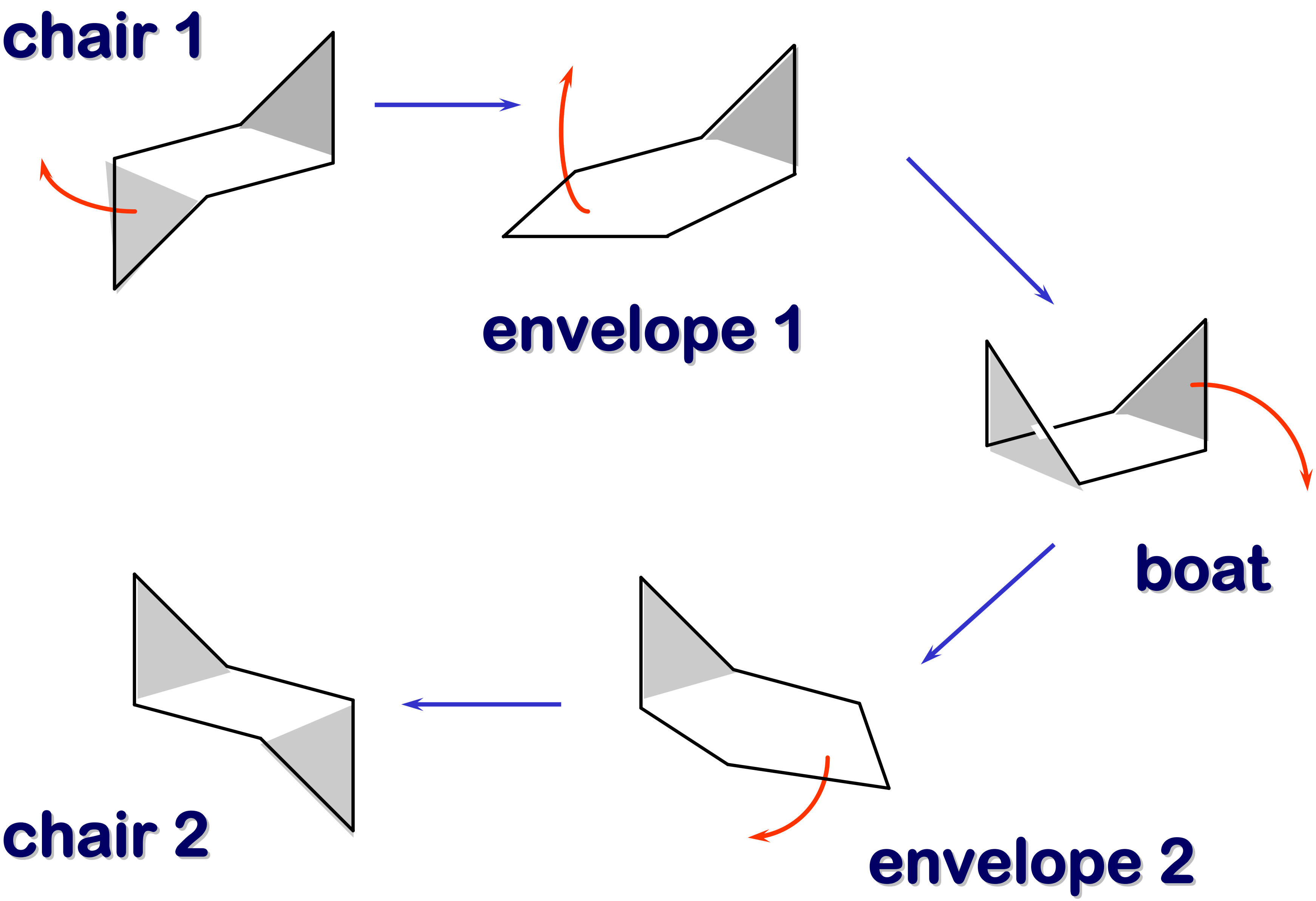


axial and equatorial hydrogens are interchanged when the ring is inverted

CONVERSION OF CHAIR TO BOAT



CYCLOHEXANE RING INVERSION

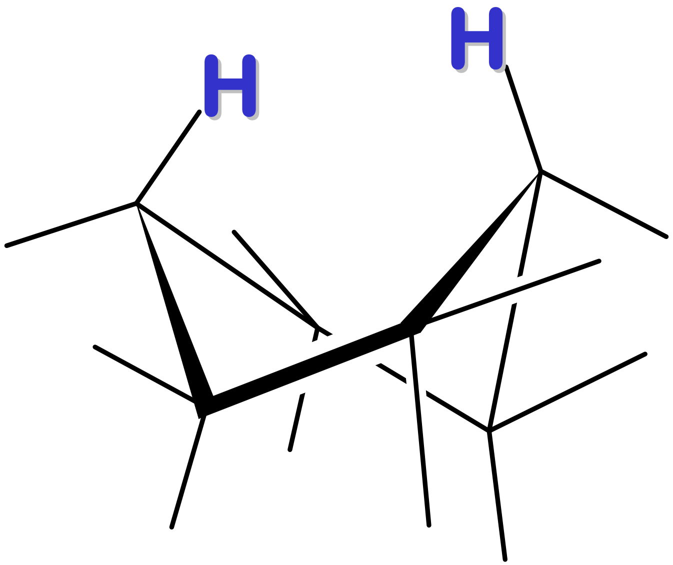


TWIST BOAT

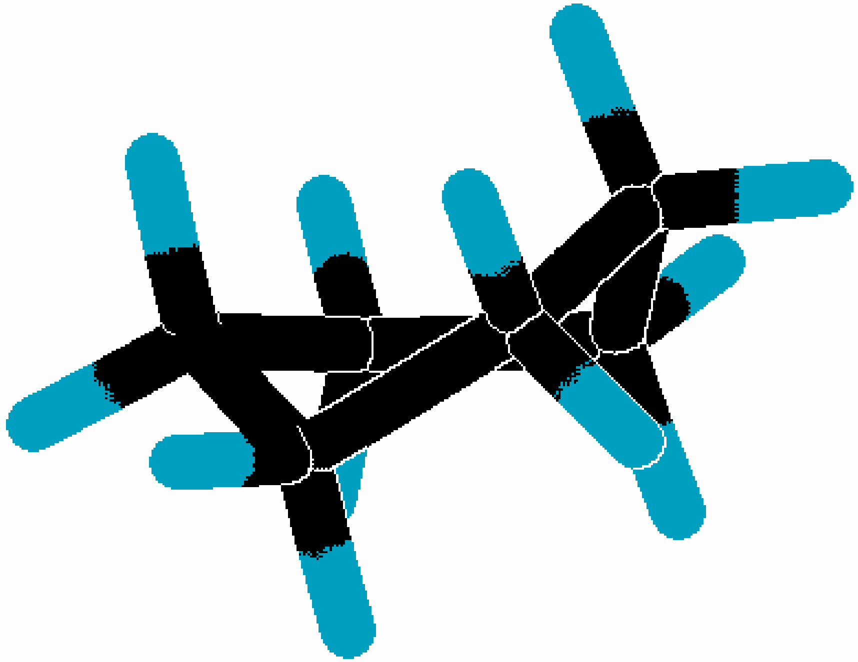
THE BOAT IS A FLEXIBLE CONFORMATION

IT WILL TWIST OR FLEX

twisting relieves the eclipsing
at the bottom of the ring ...

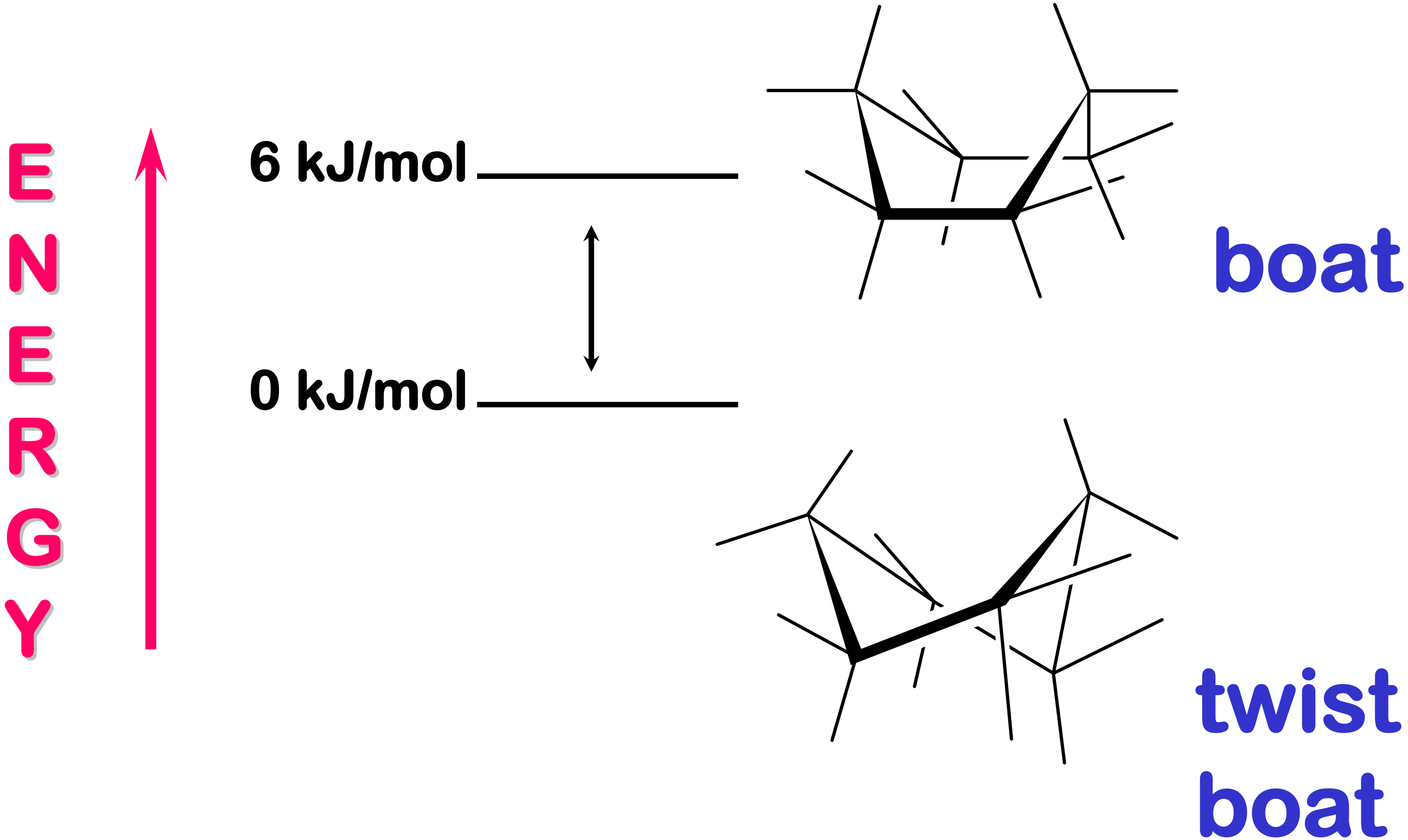


... and the top axial
hydrogens move apart



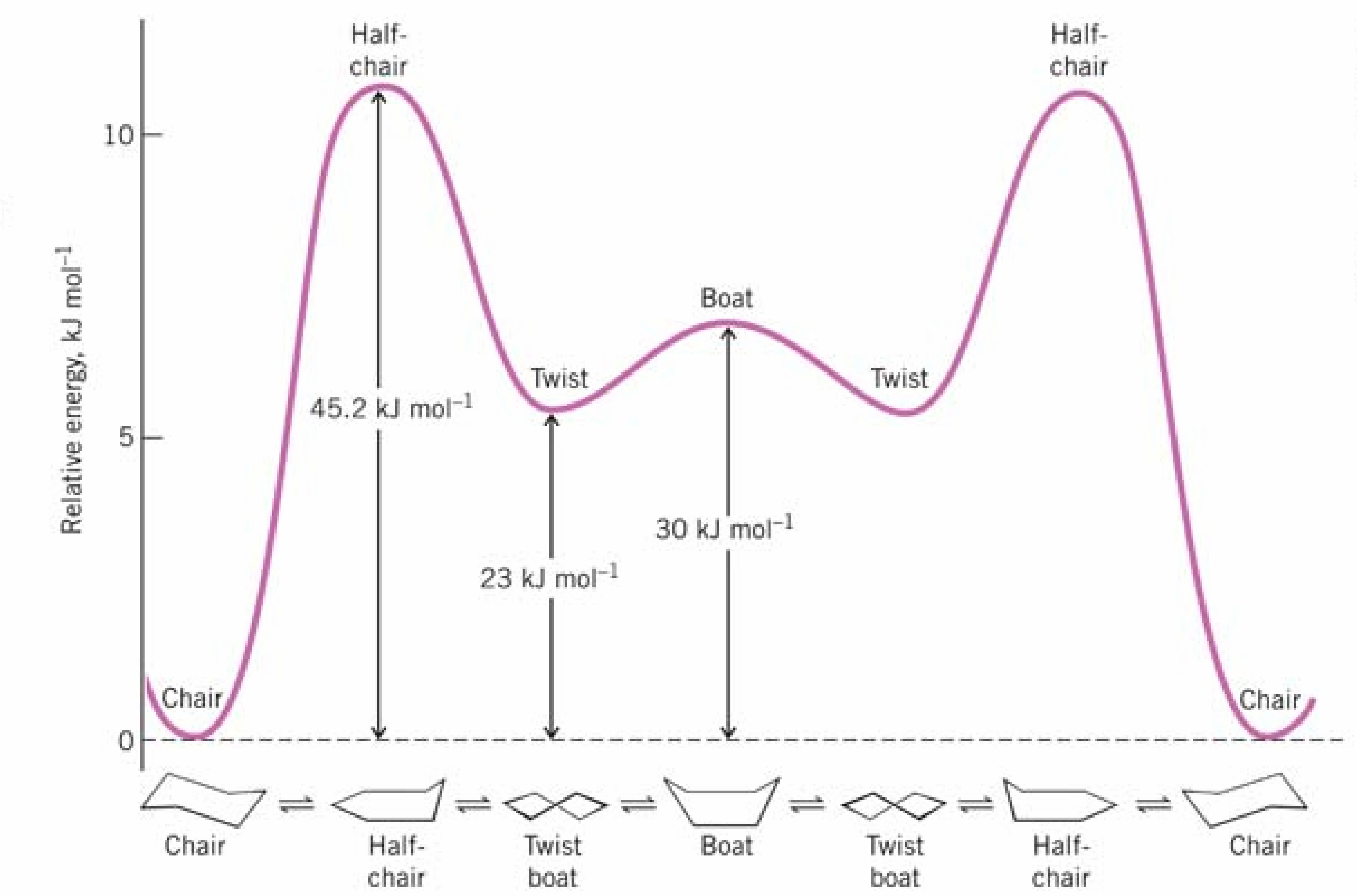
TWIST BOAT
SKEW BOAT

THE TWIST BOAT HAS LOWER ENERGY THAN THE BOAT



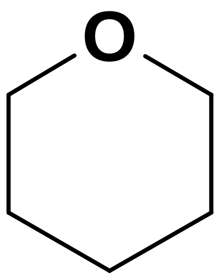
THE COMPLETE PICTURE

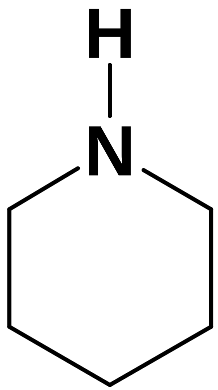
cyclohexane conformation affects the energy state

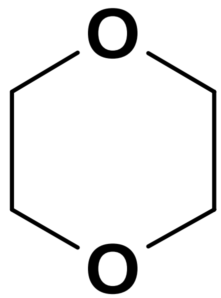


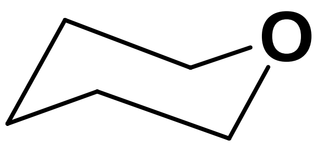
OTHER MOLECULES THAT HAVE CHAIR AND BOAT CONFORMATIONS

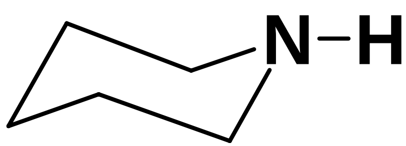
NITROGEN AND OXYGEN HETEROATOMS CAN REPLACE CARBON

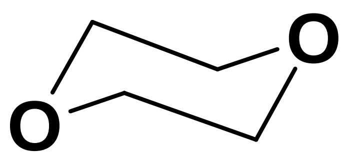








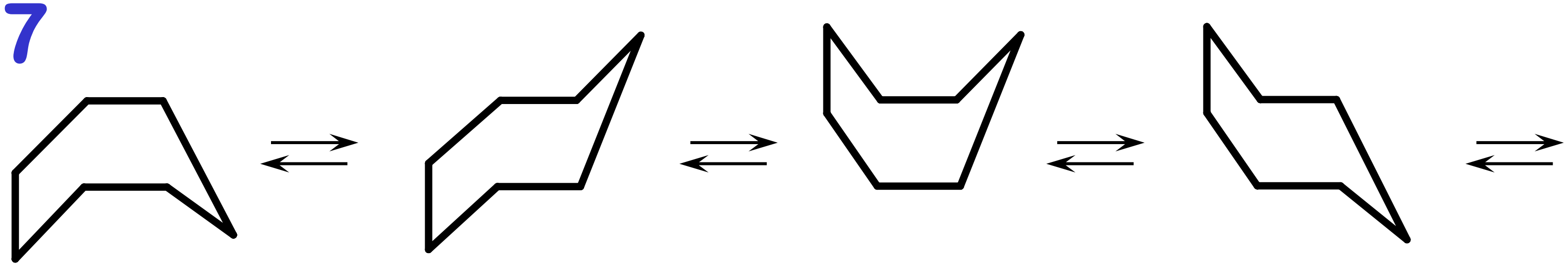




All of these atoms have sp^3 hybridization

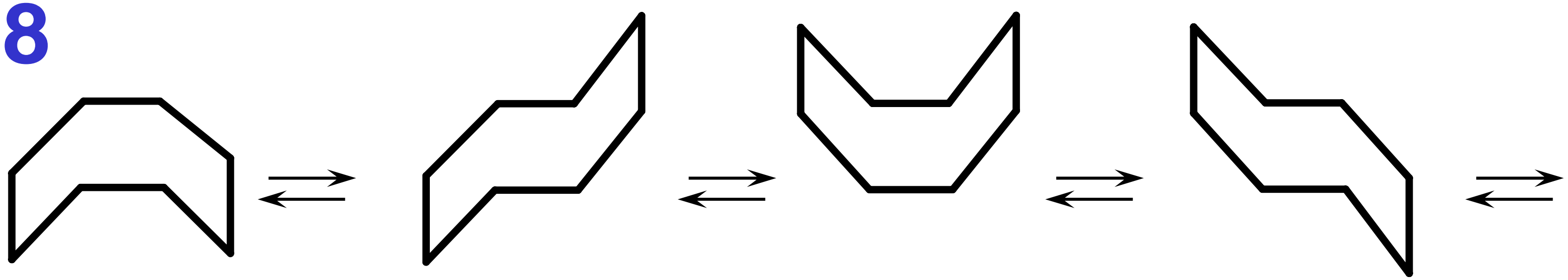
LARGER RINGS HAVE MANY CONFORMATIONS
...... AND THEY ARE MORE FLEXIBLE

C7



etc

C8

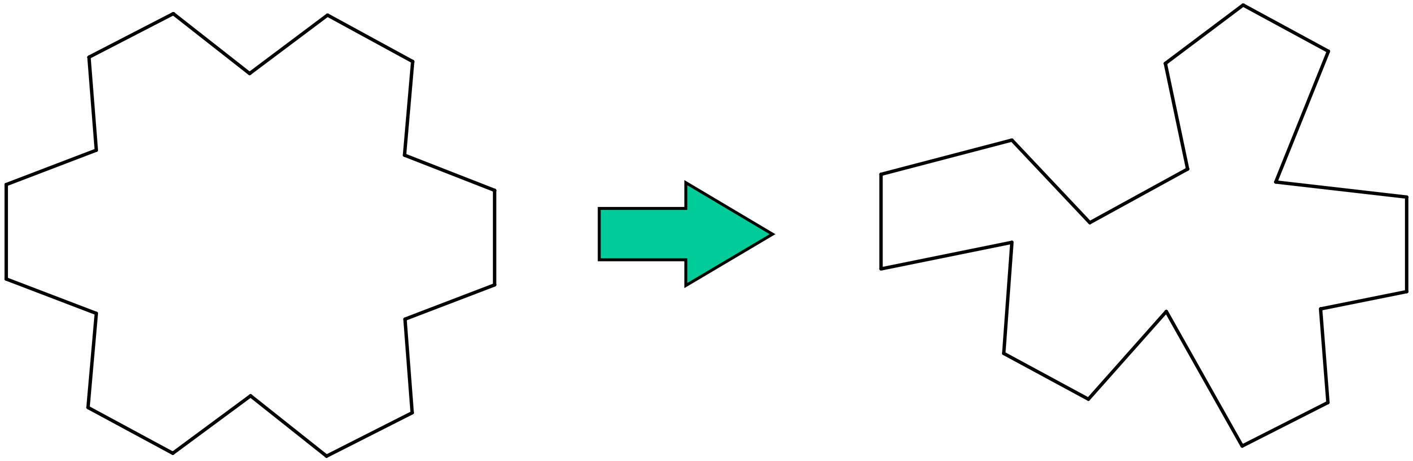


etc

The bigger the ring, the more flexible.

We study cyclobutane, cyclopentane and cyclohexane specifically because the rings are common and they have conformations that are easily defined.

LARGE MOLECULES HAVE MANY POSSIBLE CONFORMATIONS



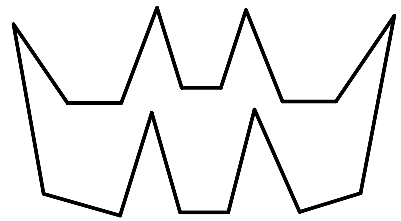
Drawn as a regular figure

One of its many possible conformations involving twisting and rotation

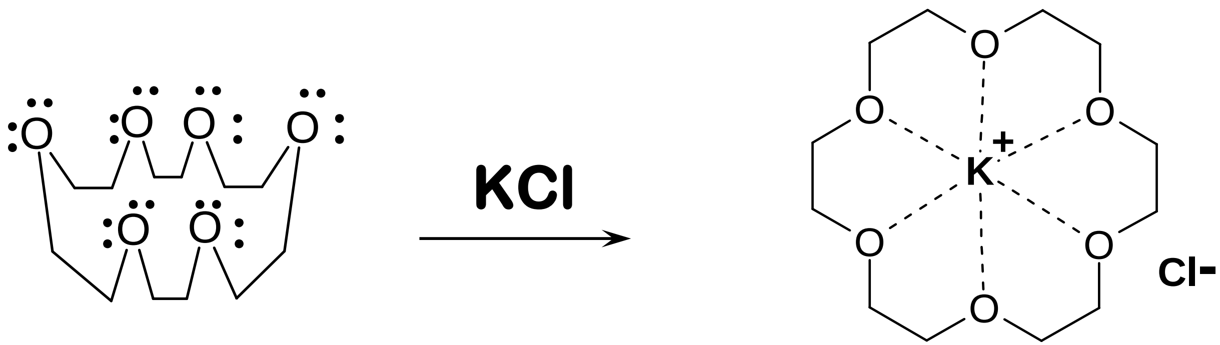
Conformations are not easy to define.

LARGE RINGS CAN FORM A “CROWN”

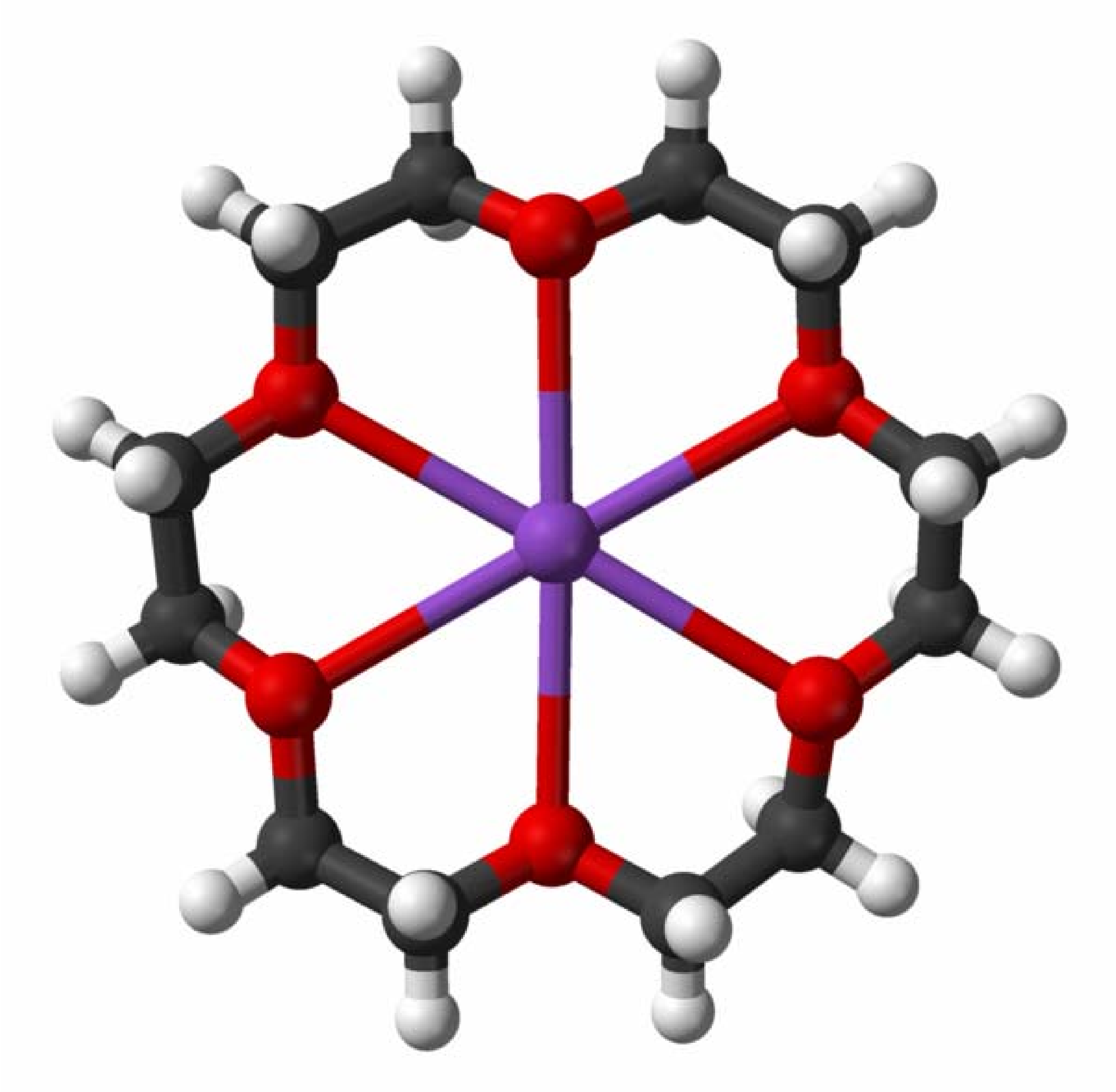
One of the more interesting conformations of large rings is the crown.



If the peak carbons are replaced by oxygens you get a “crown ether”. Crown ethers are good at complexing (dissolving) metal cations.



18-crown-6 coordinating ether



Nobel Prize in Chemistry 1987

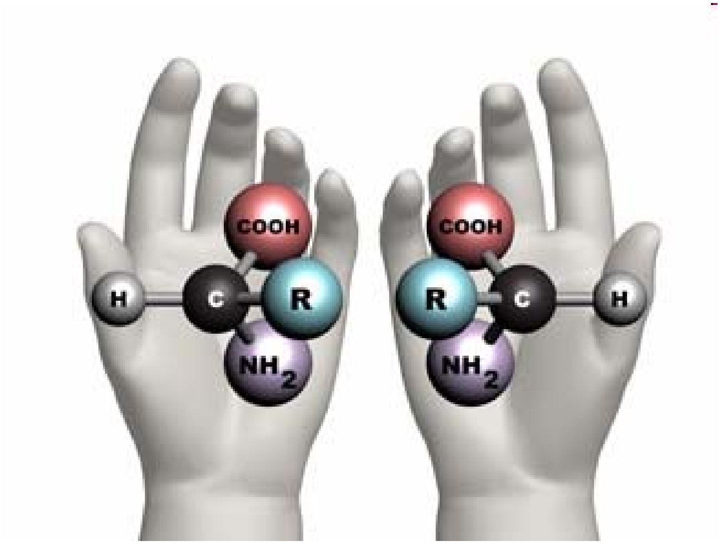
To recapitulate . . .

- geometric isomers
  - alkenes and cyclic systems
- *cis* / *trans* and *E* / *Z*
- use Cahn-Ingold-Prelog priority rules
- cyclohexane has multiple conformations
  - affects substituent interaction & energy states
- stereoisomers can have significant biological effects

What's next ???

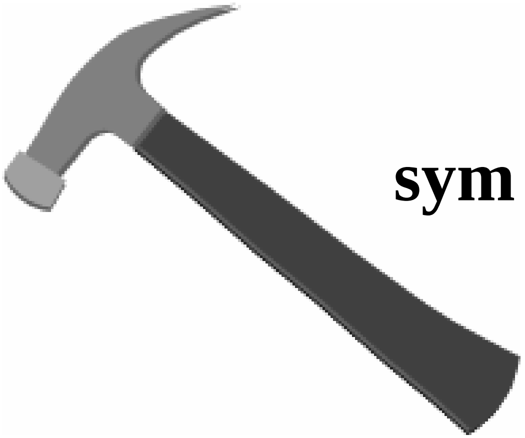
- After the break, we will discuss optical isomers
- Homework assignment for the break

What is symmetry??



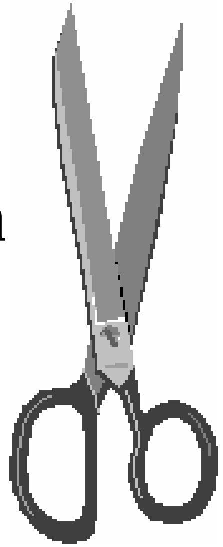
WHICH OBJECTS ARE SYMMETRIC?

(mirror image is identical)

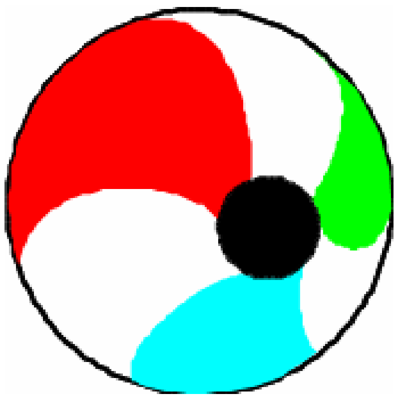


sym

asym

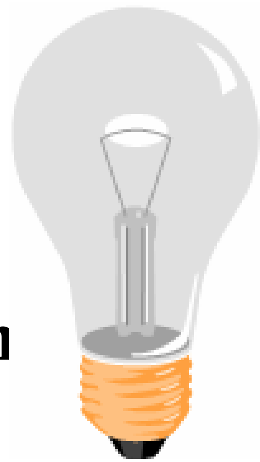


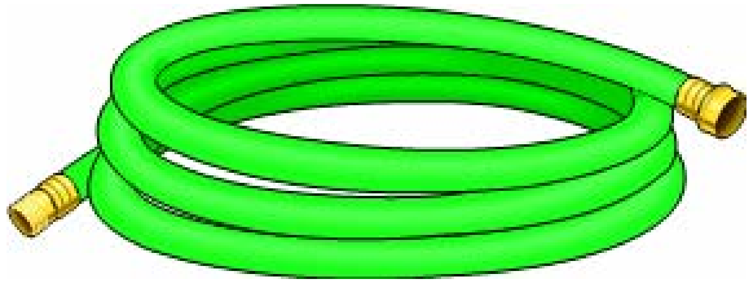
sym



asym **(due to pattern)**

asym





asym