CHEM 221 section 52

LECTURE #07 Thurs., Feb.14, 2008

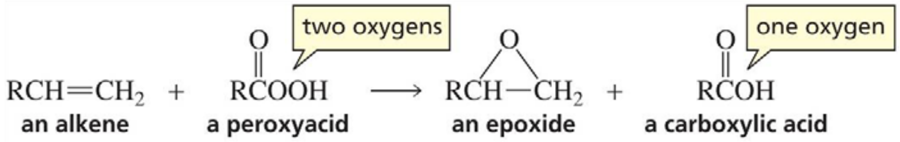
ASSIGNED READINGS:

TODAY'S CLASS:

4.6, 4.7	**in last day's notes actually…**
4.8-4.11	**Alkene reactions with different mechanisms** adding RCOOOH: to make epoxide adding HOH/R: oxymercuration, hydroboration adding hydrogen: to make alkanes adding HBr via radical mechanism
4.12	**Introduction to synthesis**

Midterm exam: Thurs. Feb.28th 6:00-7:15pm
lecture afterwards
covers everything so far to end of Ch.4
see samples on website

4.9 Addition of a peroxyacid to an alkene:
route to "epoxides" = reactive 3-memb. ring ethers

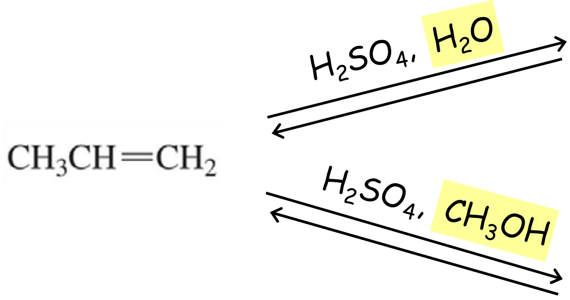


- **Mechanism:** CONCERTED…

Now: let's compare a few ways to make alcohols…

Recall 4.5: Acid-catalyzed addition of H_2O or ROH

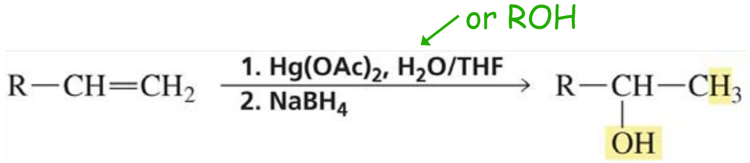
Markovnikov addition: occurs in acid; electrophile = H^+



- C+ int. ⇨ rearrangements possible

4.8 Oxymercuration-reduction:

another Markovnikov way to add HOH / ROH to an alkene



$$R{-}CH{=}CH_2 \xrightarrow[\text{2. NaBH}_4]{\text{1. Hg(OAc)}_2\text{, H}_2\text{O/THF}} R{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3$$

- **Mechanism: (complex)** rxn 1: via cyclic C–Hg^+–C int. similar to halonium ion
  rxn 2: required to replace Hg with H…
- **Markovnikov addition:** H goes where more H's are

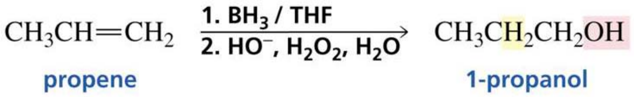
Advantages: gentle conditions & controllable results

1. does not use acidic conditions ⇨ safer for many other funct'l groups
2. does not proceed via C+ int. ⇨ no rearrangements

Why know another route?
Small-scale: can spend $ on rgts & disposal ⇨ oxymercuration-redn used
Industrial: need cheap reagents & disposal ⇨ H^+-cat additions used

4.10 Addition of borane: hydroboration-oxidation

anti-Markovnikov addition of water



Anti-Markovnikov addition

ANTI-MARKOVNIKOV ADDITIONS: H adds where fewer H's were

- **occurs because B acts as the electrophile in the 1^{st} step!**

B—H bond adds across the C=C

↖ open-shell, more electrophilic than H…

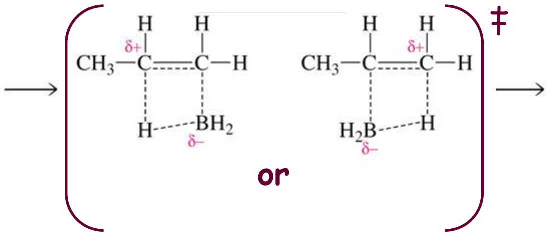
MECHANISM OF HYDROBORATION

Step 1: C=C bond attacks δ^+ B at same time as δ^- H attacks sp^2 C

- a concerted (1-step) process
- thus: H & B on same side of C=C ⇨ syn addition

REGIO: Electrophile adds to the less highly-substituted C

- WHY?



"Syn" addition!

an alkyl borane

Steps 2 &…: complicated oxidation by H_2O_2, OH^-, H_2O

removes boron group & replaces with OH

(you are not responsible for the details here)

MORE DETAILS: 1st steps = formation of alkyl boranes

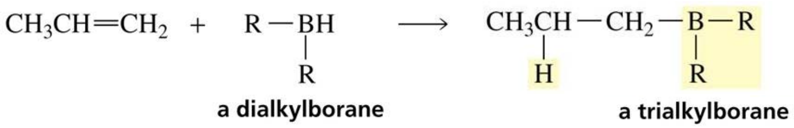
In hydroboration, 1 BH_3 actually reacts with 3 alkene molecules:

First: $CH_3CH{=}CH_2 + H{-}BH_2 \longrightarrow R{-}BH_2$ an alkylborane

Second:

$CH_3CH{=}CH_2 + R{-}BH_2$ (an alkylborane) $\longrightarrow CH_3CH(H){-}CH_2{-}BH{-}R$ (a dialkylborane)

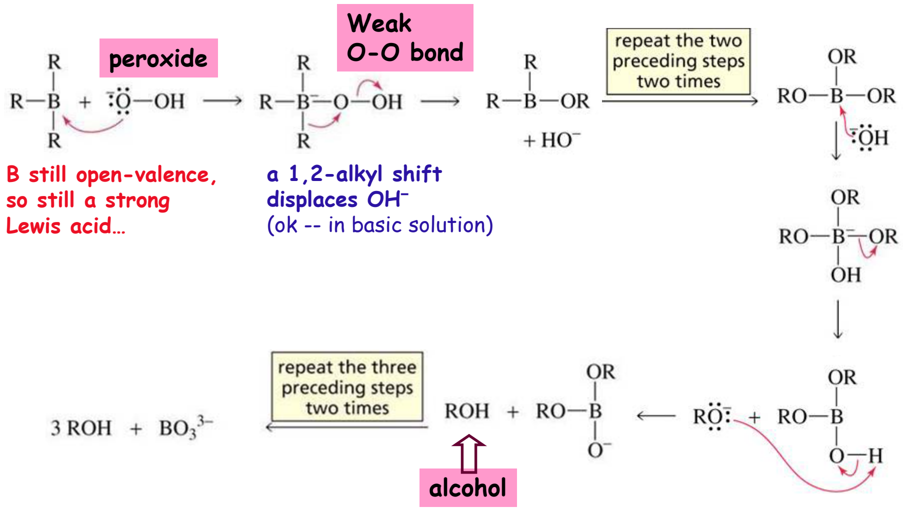
Third:



$CH_3CH{=}CH_2 + R{-}BH(R)$ (a dialkylborane) $\longrightarrow CH_3CH(H){-}CH_2{-}B(R){-}R$ (a trialkylborane)

You are not responsible for reproducing this…
…but seeing the full mechanism will help you understand the rxn

& Next: Oxidation steps (↑ bonds to O): OH replaces B…



peroxide

Weak O-O bond

B still open-valence, so still a strong Lewis acid…

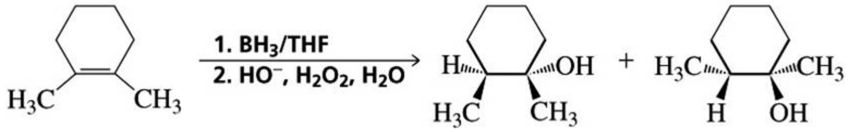
a 1,2-alkyl shift displaces OH⁻
(ok -- in basic solution)

⇧ **alcohol**

You are not responsible for reproducing this…
…but seeing the full mechanism will help you understand the rxn

Stereochemistry of Hydroboration–Oxidation

i.e., relative **orientation of groups in the products** (see more in Ch.5)



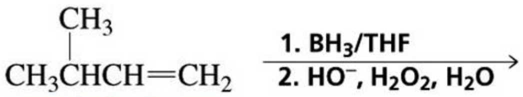
- Always **syn addition:** **H & B add to same face of π-bond**
  because this add'n is concerted, not step-wise
- In addition step: H-B can add to either side of C=C initially,
  so get <u>both</u> possible syn products
- Oxidation steps: do not change the orientation of the groups
  thus: stereochemistry dictated by addition step

Coming soon in Ch.5:
- How do we describe this type of isomer?
- What is different about them?
- What about the other rxns seen so far?

Key synthetically useful features of hydroboration:

1.) adds H-OH with anti-Markovnikov regiochemistry
2.) avoids rearrangements of molecule (no carbocation int.)

⇨ **predictable, clean regiochemistry (good product control)**



$CH_3CH(CH_3)CH{=}CH_2$

3-methyl-1-butene

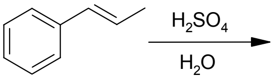
Acid-catalyzed hydration would involve 2° carbocation
⇨ would rearrange

THUS:
major product would be
2-methyl-2-butanol

…3-methyl-2-butanol
as a minor product

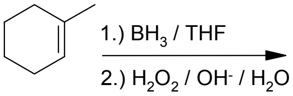
Hydroboration product
⇨ no rearrangement
⇨ anti-Markovnikov
⇨ syn addition of H & OH
(syn not noticeable here since rxn did not generate stereochemistry)

What products would these reaction conditions yield?



aromatic ring
will remain

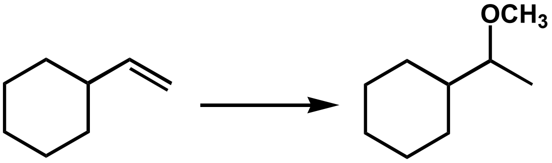
- E = ?
- C+ ?
- Nu = ?



- E = ?
- C+ ?
- Nu = ?

4.5 -
4.10

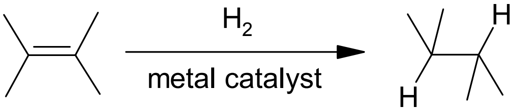
Which set of reagents would be the *best* choice to accomplish the transformation shown below?



a) H_2SO_4, CH_3OH
b) CH_3OH, cat. H^+
c) 1. $Hg(OAc)_2$, CH_3OH 2. $NaBH_4$
d) 1. BH_3, CH_3OH, 2. H_2O_2, CH_3O^-
e) either A or B

4.11 Relative stabilities of alkenes → determined from rates of rxn with H_2

HYDROGENATION:



Common catalysts:
nickel (Ni), Pt/C, Pd/C
= platinum or palladium-impregnated graphite
"platinum on carbon", "palladium on carbon"

Exact **Mechanism of hydrogenation** not known, but is roughly like this:

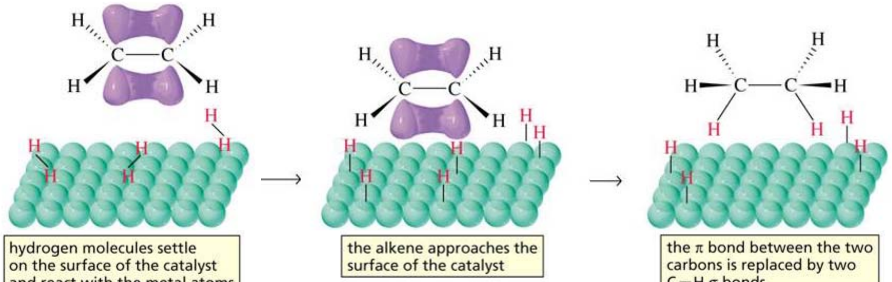


Fig. 4.5

Heats of hydrogenation (ΔH_{rxn} for alkene + H_2 / cat) provide a measure of relative E of alkene isomers

three isomers:
3-methylbutene
2-methylbutene
2-methyl-2-butene

$\xrightarrow[\text{Pt/C}]{H_2}$

All yield same product:
2-methylbutane + HEAT

More heat released MUST mean original alkene was less stable…

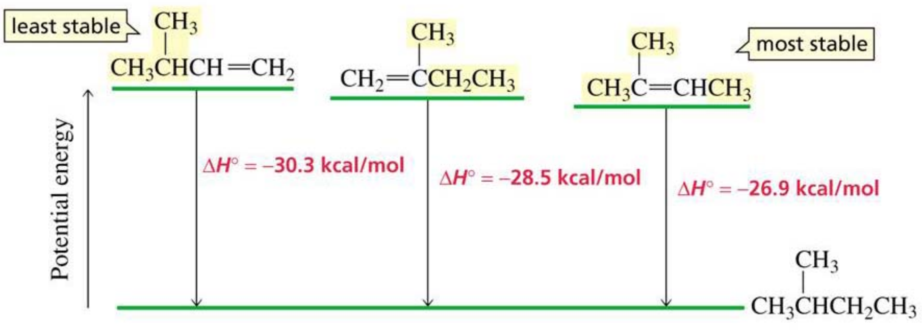
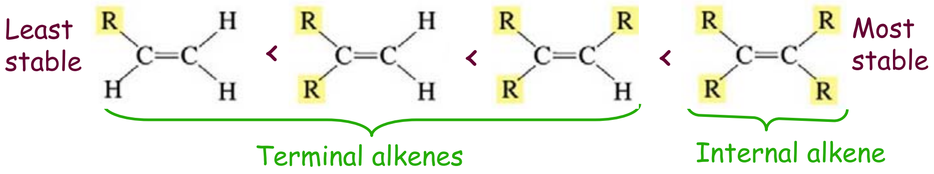


Fig. 4.6

The result: stability varies with substituent # & location

- More highly substituted alkenes are generally more stable: $\Delta H_{H_{2}n}$ data



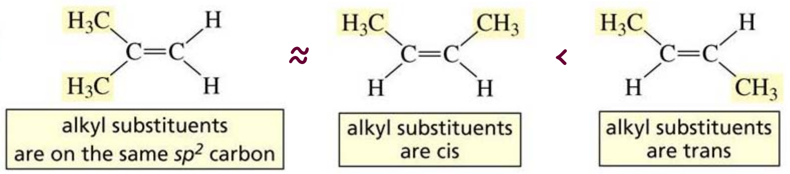
Least stable

Most stable

Terminal alkenes

Internal alkene

- Terminal alkenes *less stable* than isomeric internal alkenes: sterics…



alkyl substituents are on the same sp^2 carbon

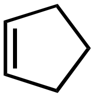
alkyl substituents are cis

alkyl substituents are trans

- And remember: <u>extended</u> π-systems are REALLY stable (delocalized…)

Relevance? *Predicting regiochemistry of rxns that form alkenes: Ch.9*
major product is usually the more-stable alkene

4.11 **Rank the following compounds in order of decreasing stability** (from *most* stable to least stable).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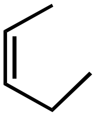
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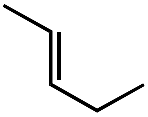
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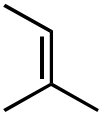
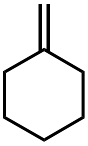

4

a) 1 > 2 > 3 > 4
b) 1 > 2 > 4 > 3
c) 4 > 1 > 2 > 3
d) 4 > 3 > 2 > 1
e) 2 > 4 > 1 > 3

4.4,
4.11

Which of the following compounds will react most readily (*i.e.*, fastest) with HCl?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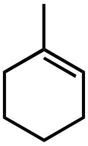
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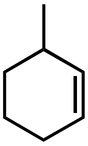
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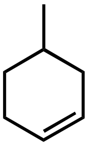
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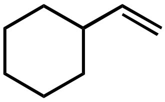
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11.3, 11.6 Addition of Radicals to Alkenes: *Anti-Markovnikov addition of H-Br*

Normal hydrobromination:

$CH_3CH_2CH{=}CH_2 + HBr \longrightarrow$

1-butene

Markovnikov addition product

RADICAL HYDROBROMINATION: opposite regiochemistry

$CH_3CH_2CH{=}CH_2 + HBr \xrightarrow[h\nu \text{ or } \Delta]{\text{peroxide}}$

1-butene

Anti-Markovnikov addition!

Choose rxn conditions that yield desired regiochemistry:

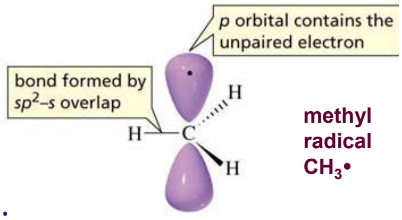
a) HBr at RT in the dark ⇨ Markovnikov addition
b) HBr with heat *or* light ⇨ anti-Markovnikov addition
(+peroxide)

Note: this trick only works with HBr (no regio. change for HCl or HI)

Hydrobromination with peroxide:

proceeds via a radical intermediate

- stability: 3° > 2° > 1° >> methyl
- C• centre is sp^2-hybridized (like C+)



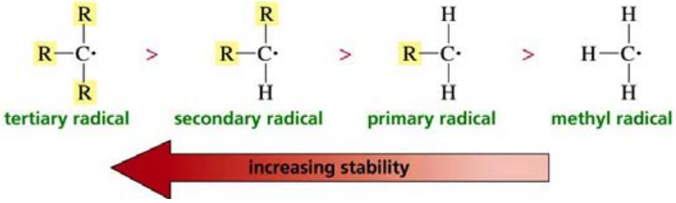
methyl radical CH_3•

IMPLICATIONS of radical intermediate:

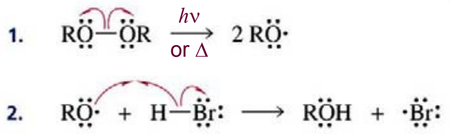
1. regiochemistry: radical centre (& later H) will be on **more subst'd C**
2. stereochemistry: racemization (if chiral) ⇨ *see this in Ch.5*

Relative stabilities of alkyl radicals:

same trend as C+s
for same reason



Mechanism: Addition of radicals to alkenes

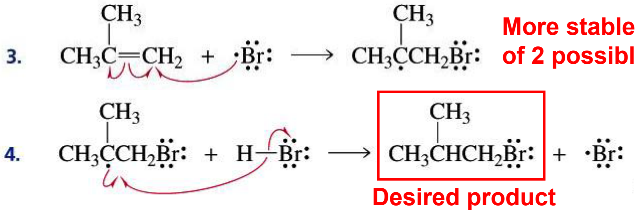


$$\text{1.}\quad \text{RÖ–ÖR} \xrightarrow[\text{or } \Delta]{h\nu} 2\,\text{RÖ·}$$

$$\text{2.}\quad \text{RÖ·} + \text{H–Br:} \longrightarrow \text{RÖH} + \text{·Br:}$$

initiation steps

- Form the 1st reactant radicals
- Good radical initiators
  = organic peroxides (ROOR)
  weak O-O bond homolytically cleaves under heat or light



$$\text{3.}\quad CH_3\overset{CH_3}{C}{=}CH_2 + \text{·Br:} \longrightarrow CH_3\overset{CH_3}{\dot{C}}CH_2\text{Br:}$$

$$\text{4.}\quad CH_3\overset{CH_3}{\dot{C}}CH_2\text{Br:} + \text{H–Br:} \longrightarrow \boxed{CH_3\overset{CH_3}{C}HCH_2\text{Br:}} + \text{·Br:}$$

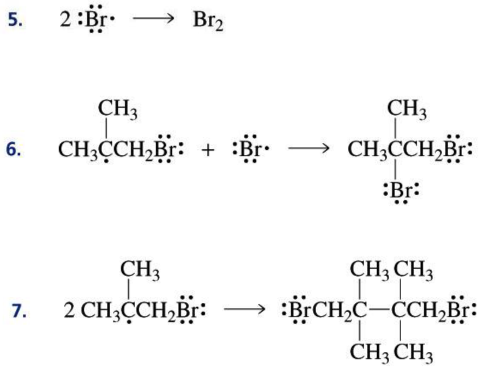
More stable of 2 possible

Desired product

propagation steps

Form radical intermediates that propagate radical chain rxn

…Mechanism: Addition of radicals to alkenes



Side product: dihalide

Side product: dimer (*i.e.*, 2 units coupled)

termination steps

Radical-coupling rxns
→ do not generate
new radicals

Summary: Radical hydrobromination

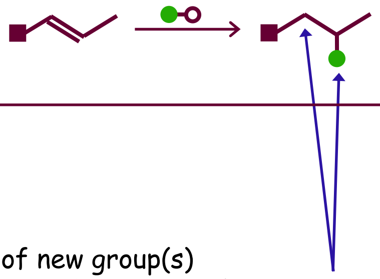
- **anti-Markovnikov HBr addition:** via more stable radical intermediate
- **use dilute solution:** to minimize dimerization of radical intermediates
- **use an inert solvent:** usually CCl_4 or benzene; never a "protic" solvent!

And after Ch.5, you'll see…

- **racemized alkyl halide product:** if chiral centre created…

4.12 Reactions and synthesis

Addition rxns:
use π-bond to add a
new functional group

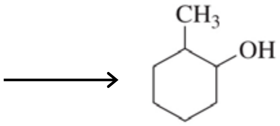


We've seen how to control:

- **functionality:** identity of new group(s)
  whether attach 1 group only *vs* 1 each side
- **regiochemistry:** which site new group attaches at
- **stereochemistry:** relative 3D orientation of groups *(Ch.5…)*

How could this compound be synthesized from an alkene?

PROBLEM 34



PROBLEM 35◆

Why should 3-methylcyclohexene NOT be used as a starting material to make the above compound?

Summary of alkene rxns: what can we make starting from here?

STARTING WITH AN ALKENE

- **Can add electrophiles**

$RCH{=}CH_2 + H_2 \xrightarrow[\text{or Ni}]{\text{Pd/C, Pt/C}} RCH_2CH_3$ **ALKANES**

MARKOVNIKOV ADDITIONS **ANTI-MARKOVNIKOV ADDITIONS**

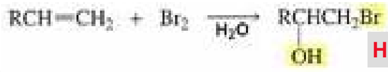
$RCH{=}CH_2 + HX \longrightarrow \underset{\displaystyle X}{RCHCH_3}$

ALKYL HALIDES

$RCH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} RCH_2CH_2Br$

$RCH{=}CH_2 + Br_2 \xrightarrow[CH_2Cl_2]{} \underset{\displaystyle Br}{RCHCH_2Br}$

VICINAL DIHALIDES



$RCH{=}CH_2 + Br_2 \xrightarrow[H_2O]{} \underset{\displaystyle OH}{RCHCH_2Br}$

HALOHYDRINS

$RCH{=}CH_2 + H_2O \overset{H^+}{\rightleftharpoons} \underset{\displaystyle OH}{RCHCH_3}$

ALCOHOLS

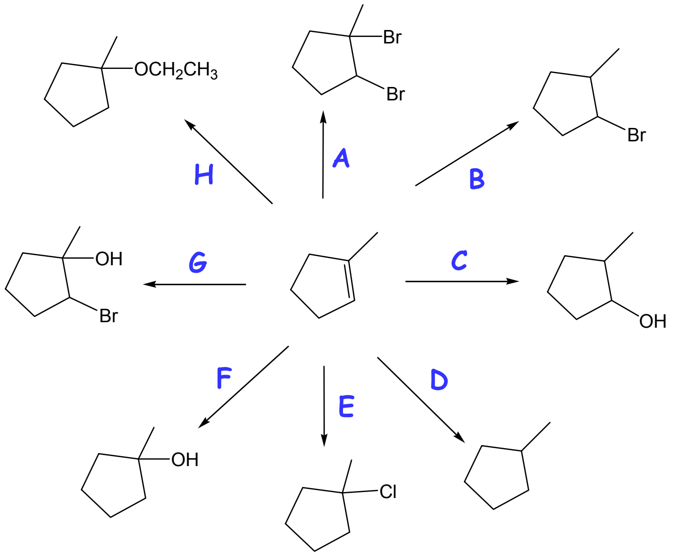
$RCH{=}CH_2 \xrightarrow[\text{2. } HO^-,\ H_2O_2,\ H_2O]{\text{1. } BH_3/THF} RCH_2CH_2OH$

$RCH{=}CH_2 + CH_3OH \overset{H^+}{\rightleftharpoons} \underset{\displaystyle OCH_3}{RCHCH_3}$

ETHERS

EPOXIDES

What reagents should we use to perform the following synthetic transformations?



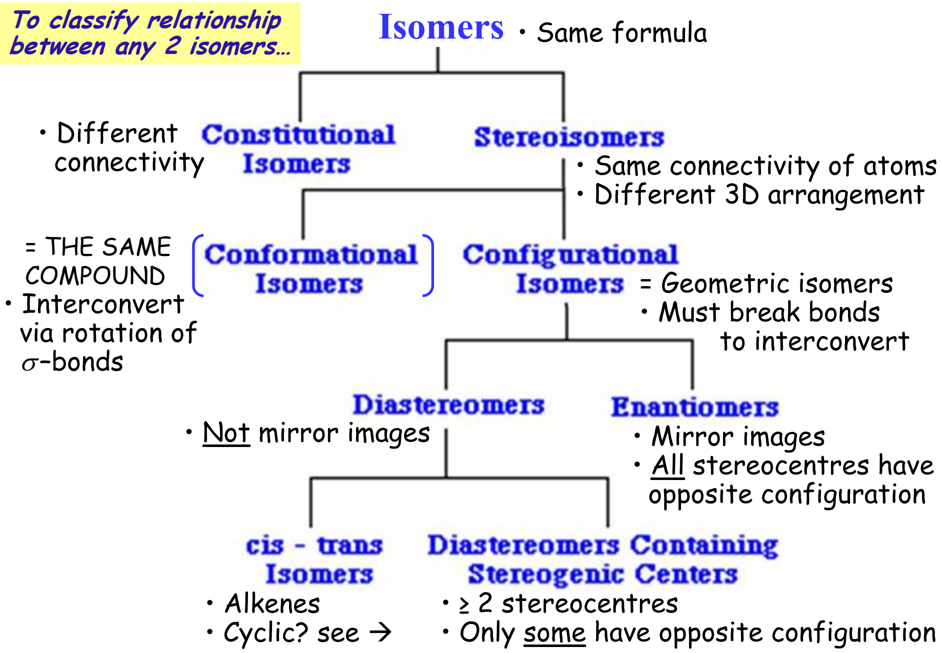
Chapter 5: Stereochemistry

<u>Chapter Goals</u>: *To understand the importance of permanent differences in the spatial arrangement of atoms in molecules.*

- Learn to identify different types of isomers.
- Understand symmetry and chirality, and their implications.
- Understand stereochemistry of reactions.

5.1	Cis-trans isomers
5.2	Chirality
5.3, 5.5	Asymmetric carbons, chirality centres, and stereocentres
5.4	Isomers with one asymmetric carbon
5.6-5.7	Drawing & naming enantiomers
5.8-5.10	Optical activity, optical purity & enantiomeric excess
5.11-5.13	Isomers with more than on asymmetric carbon
5.14	Rxns of compounds that contain an asymmetric carbon
5.15	Absolute configuration
5.16	Separating enantiomers: in the lab, & biologically
5.17-5.18	*covered in more advanced courses*
5.19	Stereochemistry of electrophilic addition rxns of alkenes
5.20-5.21	Stereochemistry of enzyme-catalyzed reactions

To classify relationship between any 2 isomers…



Isomers
- Same formula

Constitutional Isomers
- Different connectivity

Stereoisomers
- Same connectivity of atoms
- Different 3D arrangement

Conformational Isomers

= THE SAME COMPOUND
- Interconvert via rotation of σ-bonds

Configurational Isomers = Geometric isomers
- Must break bonds to interconvert

Diastereomers
- Not mirror images

Enantiomers
- Mirror images
- All stereocentres have opposite configuration

cis - trans Isomers
- Alkenes
- Cyclic? see →

Diastereomers Containing Stereogenic Centers
- ≥ 2 stereocentres
- Only some have opposite configuration

Classification of Isomers

1. Constitutional isomers: different connectivity

e.g. 1-butane and methylpropane (*i.e.* isobutane)

SUBTYPES:

(a) Positional isomers: different position of functional groups

e.g. 1,2-dichlorobenzene & 1,3-dichlorobenzene

(mp 183 °C) (mp 172 °C)

(b) Functional isomers: different functional groups

same bulk formulas but very different properties

e.g.

2. Stereoisomers: same connectivity, but different arrangement of atoms in space
(permanently different 3D orientation)

"Configurational isomers"

- actually different compounds (definitely isolable)
- to interconvert them: must BREAK covalent bonds

a) cis/trans isomers: arrangement around C=C
or relative orientations on a ring

b) Isomers that contain asymmetric atoms: next…

Isomers are NON-identical…

TECHNICALLY SPEAKING: conformers are isomers

IN PRACTICE: Usually non-isolable (cannot isolate them)…

THEREFORE: conformers not usually considered isomers:
treat them as IDENTICAL

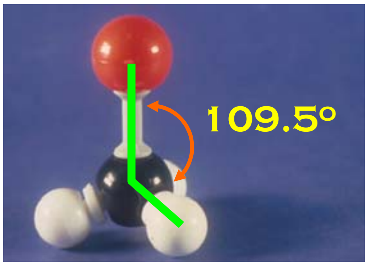
To be isomers, molecules must not be identical.
- check: are they just different conformations?

The test for "identicality": can they be superimposed??

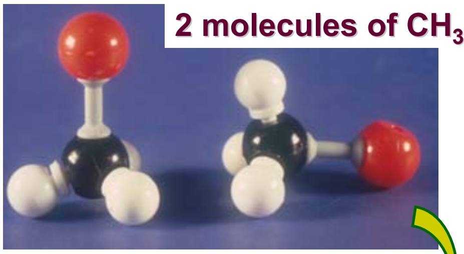
Carbon is tetrahedral: Consequences…

EXAMPLE #1:

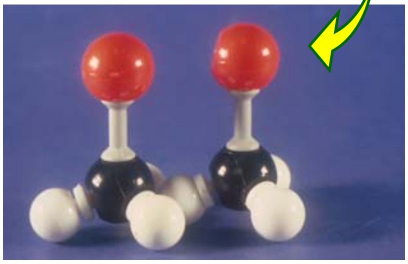
Td C with one substituent (CH_3X)



2 molecules of CH_3X



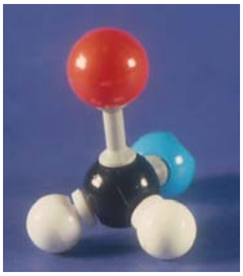
Identical molecules! (can be superimposed…)



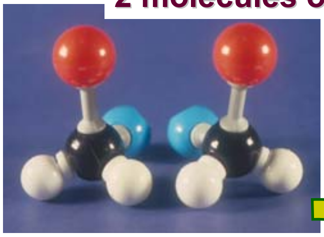
Carbons with two different substituents still have two substituents that are the same… ∴ symmetric

EXAMPLE #2:

Td C with TWO substituents (CH_2XY)



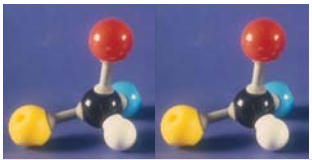
2 molecules of CH_2XY



Identical molecules! (can be superimposed…)

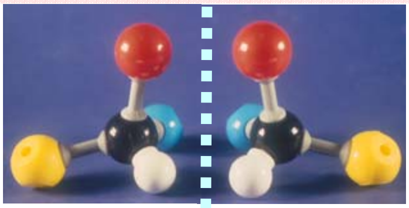
Carbons with 4 <u>different</u> groups are "asymmetric"

Sometimes 2 CHXYs ARE superimposable (∴ identical)



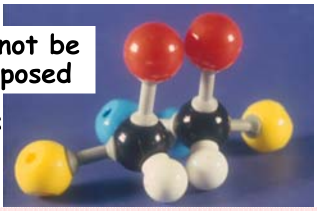
Td C with THREE substituents (CHXYZ)

NOT all CHXYs are identical
(non-identical if non-superimposable)



They are mirror images

AND cannot be superimposed



THEREFORE: <u>different</u> compounds

If two molecules are **non-superimposable mirror-images** of each other: they have **opposite "configuration"**

The two molecules are called **"ENANTIOMERS"** **(Greek *enantion* = opposite)**

These molecules are described as being **"handed"** or **"CHIRAL"** **(Greek *cheir* = hand)**

5.2 Chirality: "Chiral" things are asymmetric

Why does your right hand not fit properly in your left glove?

ANS: because hands are <u>chiral</u>.

- Right and left hands are mirror images.
- They are not superimposable

} they have **opposite configuration**!

- To convert your right hand into your left hand, you would need to:
  remove your thumb & move it to other side of palm
  (and your fingers too actually)

Anything with a non-superimposable mirror image is CHIRAL.

- HINT: all chiral objects are inherently asymmetric
  e.g., hands, feet

Anything with a superimposable mirror image is ACHIRAL.

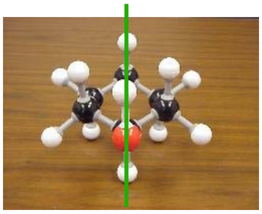
- HINT: look for internal planes of symmetry
  - any object (or molecule) with a mirror plane <u>within</u> it can be superimposed onto its own mirror image
    ⇨is symmetric, ∴ achiral
    e.g., human body (as viewed from the outside)

Two ways to evaluate a molecule, or any object, as being <u>ACHIRAL</u> *…if it's not achiral, it's chiral…*

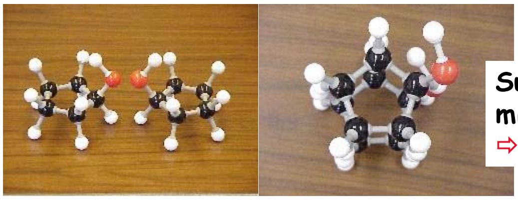
1.) Does it have a plane of symmetry? If YES ⇨ achiral

2.) Does it have a superimposable mirror image?
If YES ⇨ achiral

Cyclohexanol



Plane of symmetry
⇨ achiral!



Superimposable mirror image
⇨ achiral!

Key stereochemical terms: CHIRALITY

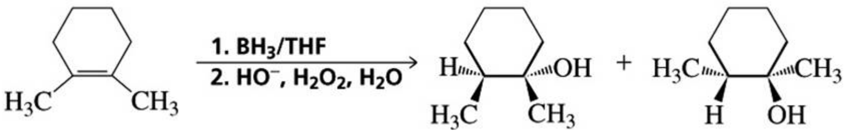
"Chiral" describes objects that are not superposable on their mirror image, *i.e.*, objects that have "handedness"

Achiral is thus used to described the lack of chirality

A plane of symmetry is an imaginary plane passing trough an object, dividing it so that one half is the mirror image of the other one

A centre of symmetry is a point so situated that identical components of an object are located on opposite sides and equidistant from that point along any axis passing through it

Are the two products of this reaction… chiral?
different?



Learn soon how to describe they way they are related.

ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read: rest of Ch.4 & 11.3, 11.6

Practice: predicting products for given reactants
identifying reactants for desired products
writing full mechanisms (arrow pushing!)
including C+ rearrangements…

Midterm exam: Thurs. Feb.28th 6:00-7:15pm
lecture afterwards
covers everything so far to end of Ch.4
see samples on website