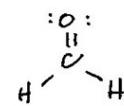
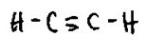
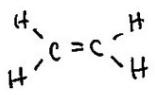
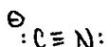
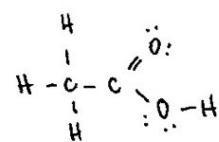
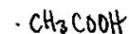
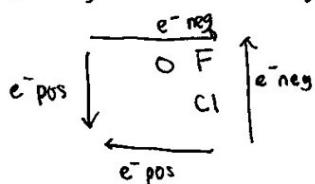


1 Oct 2020

ch 1 Chemical Bonding & Structure

CHEM 237

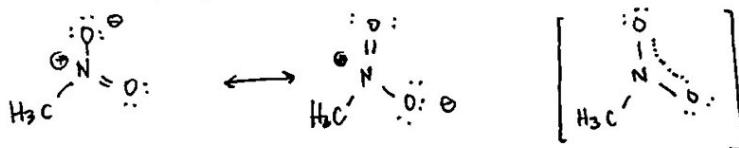
<< Lewis Dot Structure

<< e⁻negativity & Bond Polarity

- bond polarity: $\text{H-O} > \text{H-Cl} > \text{H-S} > \text{H-C}$

- polar bond: $\text{H}_2\text{O} > \text{HCl} > \text{CN}^- > \text{O}_2$

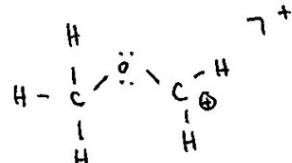
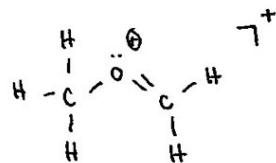
<< Resonance Structure



- same bond length

- trigonal planar

<< Determining Structures



- filled octet

- small formal charge

- carbocation: incomplete octet on \oplus formal charge OK

<< Molecular Geometry

→ Bond Length (BL)

- size of atom (within family) \uparrow , BL \uparrow

- bond order \uparrow , BL \downarrow

- size of atom (within period) \uparrow , BL \downarrow

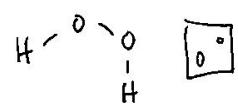
- hybridization

- sp^2 shorter orbital, BL \downarrow

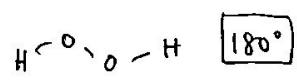
→ VSEPR

	# of domain	e ⁻ geometry	Molecular shape	bond angle
AX_2	2	X-A-X	linear	180°
AX_3	3	X-A-X	trigonal planar	120°
AX_2E	3	X-A-E	bent	$<120^\circ$
AX_4	4	X-A-X	tetrahedral	109.5°
AX_3E	4	X-A-X	trigonal pyramidal	$<109.5^\circ$
AX_2E_2	4	X-A-X	bent	$<109.5^\circ$

→ Dihedral angle



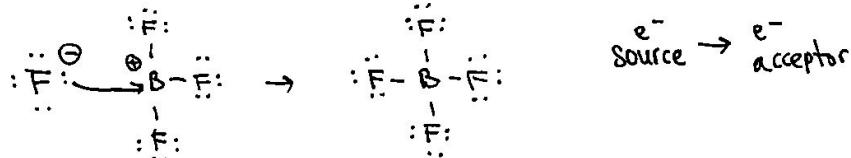
$$0^\circ$$



$$180^\circ$$

<< Lewis Acid & Base

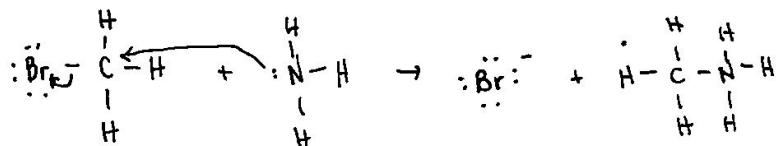
- > e^- -deficient compound - short of an octet by 1⁽⁺⁾ e^- pairs
 - have tendency to complete valence shell octet
- > Lewis acid - accept e^- pair
- > Lewis base - donate e^- pair
- > Lewis acid-base association rxn - Lewis acid + base \rightarrow one product
- > Lewis acid-base dissociation rxn - one reactant \rightarrow Lewis acid + base
- Curved-arrow notation



- total charge conserved

<< e^- pair Displacement Rxn

- > one e^- pair is displaced from an atom by the donation of another e^- pair from another atom

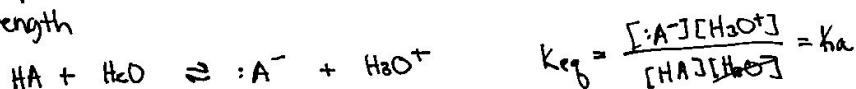


- > nucleophile - donate e^- pair to form new bond
- > nucleophilic center - atom actually donating e^- pair
- > electrophile - accepts e^- pair from nucleophile
- > electrophilic center - atom actually accepting e^- pair
- > leaving group - group accepts e^- from breaking bond
- resonance structure: e^- goes to more e^- neg. atom

<< Bronsted-Lowry Acid & Base

- > Bronsted acid - donate H^+
- > Bronsted base - accept H^+
 - conjugate acid-base pair
 - amphoteric - can be acid & base

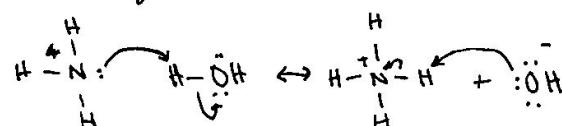
→ Strength



- $K_a \uparrow$, acid strong \uparrow , $pK_a \downarrow$, conjugate base weak \downarrow

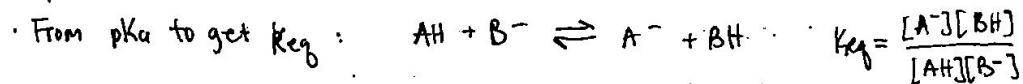
- $pK_a = -\log K_a$

- $pK_a + pK_b = 14 = pK_w$



<< Acid-Base Equilibrium

- equilibrium favors weaker acid & base

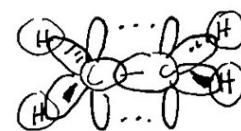


$$\log K_{eq} = pK_{BH} - pK_{AH}$$

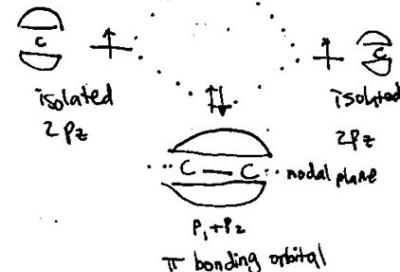
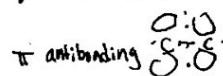
$$K_{eq} = 10^{(pK_{BH} - pK_{AH})}$$

<< Structure & Bonding in Alkene

- > alkene - hydrocarbon with $\text{1}^{\text{+}}$ double bonding $\text{C}=\text{C}$
- > unsaturated hydrocarbon - compound with multiple bonds
- > saturated hydrocarbon - alkane



- sp^2 , 120° , trigonal planar, shorter bond length of double bond & single bonds attached
- π -bond formed by overlapping 2p_z orbitals
- π bonding MO has lower energy
 - 1 nodal plane
 - π^* antibonding MO has higher energy
 - 2 nodal planes
 - unoccupied
- πe^- has higher energy (less stable) than σe^-
- π bond is weaker than σ bond

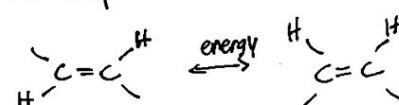


→ Stereoisomers

- Constitutional isomers - diff location of $\text{C}=\text{C}$

- > stereoisomer - identical connectivity, diff arrangement in space

- interconversion breaks $\text{C}=\text{C}$
- no random rotation internally
- energy needed



- > cis-trans isomer (E, Z) - compounds related by 180° internal rotation about $\text{C}=\text{C}$

- > stereocenter - interchange of two bonded groups gives stereoisomers (chiral center)

→ Nomenclature

- replace -ane by -ene
- $\text{C}=\text{C}$ receives smallest number
- principle chain has most $\text{C}=\text{C}$
- more $\text{C}=\text{C}$ receives numerical prefix (eg. diene, triene)
- substituents numbered from point of attachment



→ E,Z double bond stereoisomer

- Z - high priority same side
- E - high priority diff side

Rules of Higher Priority

1. higher atomic number (diff atom); higher atomic mass (isotope)

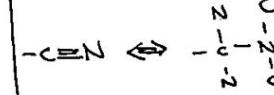
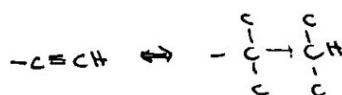
divide along
 $\text{C}=\text{C}$

2. arrange level-2 atom in decreasing mass, then apply rule 1

3. identify level-3 atom by choosing atom w/ highest priority in level 2

- 3a. repeat for lower priority level 2

* multiple bond convention: $-\text{CH}=\text{CH}_2 \leftrightarrow -\underset{\text{C}}{\text{CH}}-\underset{\text{C}}{\text{CH}}_2$



<< Unsaturation Number

- cycloalkane & alkene has 2 H less than linear alkane
- > unsaturation number (degree of unsat.) = # of rings & multiple bonds

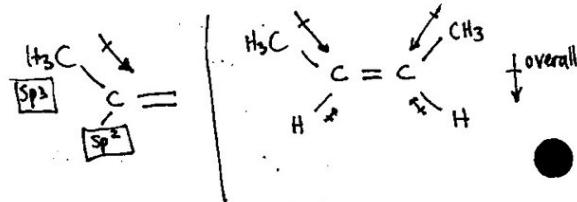
$$\text{unsat. \#} = \frac{2C + 2 - H}{2} = \# \text{ rings} + \# \text{ multiple bond}$$

$2C + 2$ is # H
in linear alkene

$$\text{unsat. \#} = \frac{2C + 2 + N - H - X}{2}$$

<< Physical Properties of Alkenes

- similar to alkanes: flammable, nonpolar, less dense than H_2O , insoluble in H_2O
- lower melting pt
- some dipole moment
- sp^2 C more e⁻ neg than sp^3 C
- $2p_z$ e⁻ cannot screen nucleus from e⁻ in xy plane
- electron-withdrawing polar effect



<< Relative Stability of Alkene Isomers

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

$$\Delta G^\circ = -2.3RT \log(k_{eq})$$

→ Heats of Formation ΔH_f°

> heat change when compound formed from its natural state @ 1 atm, 25°C

$$\Delta H^\circ_{rxn} = \Delta H^\circ_{prod} - \Delta H^\circ_{reactant}$$

• exothermic $\Delta H^\circ < 0$

• endothermic $\Delta H^\circ > 0$

• more negative ΔH_f° , more stable

• $|\Delta H_f^\circ| \uparrow$, stability \uparrow

• smaller heat of combustion magnitude, more stable

• $|\Delta H_{comb}| \downarrow$, stability \uparrow

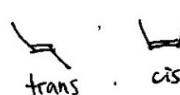
• reason: $\Delta H_f^\circ(CO_2, H_2O)$ is constant /locked in

→ Stability of Alkene Isomers

→ cis-trans

• trans = stability \uparrow

• avoid van der Waals repulsion

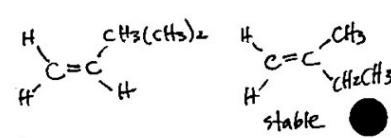
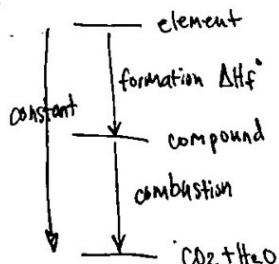


→ Alkyl groups

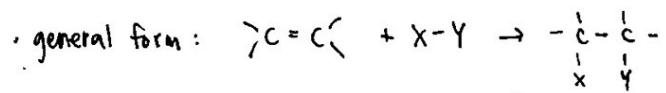
• # alkyl substituent of double bond \uparrow , stability \uparrow

• s character \uparrow , stability \uparrow

• sp^2-sp^3 C-C bond favored



Alkene Addition Reactions



→ Addition of hydrogen halide (H-X) Markov

→ Regioselectivity

> regioselective reaction - product of a rm can consist of constitutional isomers and one of them is formed in excess over another

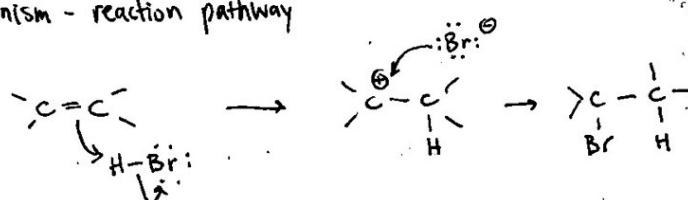
• Markovnikov's Rule - halogen bond to C with double bond that has most alkyl substituents; hydrogen bond to C with least alkyl sub.

→ Carbocation Intermediate

> carbocation - positively charged, e⁻-deficient carbon

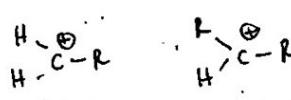
> mechanism - reaction pathway

HBr reacts with Markov
regioselectivity /
mechanism of reaction

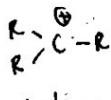


→ Stability of Carbocation

• carbocation classified by alkyl sub.



primary



tertiary

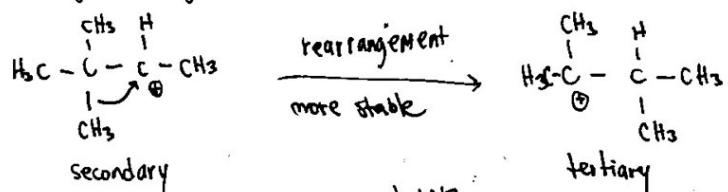
• alkyl sub. stabilize carbocation
tertiary > secondary > primary

stability

/ hyperconjugation
R groups can donate e⁻ to empty p_z orbital in sp² C.

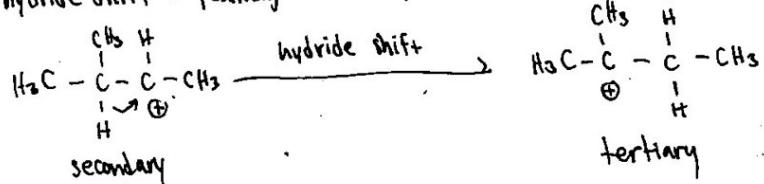
→ carbocation rearrangement

> rearrangement - group in reactant moved to diff position in product



• rearrangement favors increase stability

> hydride shift - rearrangement of H with its two bonding e⁻



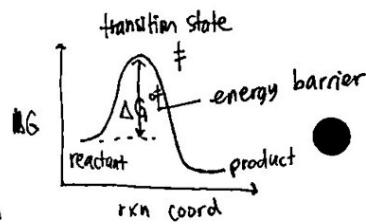
• hydride shift → alkyl shift

<< Reaction Rates

→ Transition State

- > rate = # reactant converted to product in given time
- > transition state = unstable state of max free energy
- > standard free energy of activation (ΔG^\ddagger) = diff of G° of transition state & reactant

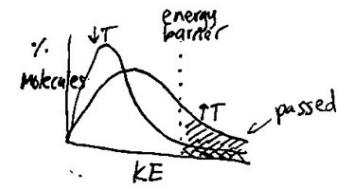
• barrier ↑ ; $\Delta G^\ddagger \uparrow$, rate ↓



→ Energy Barrier

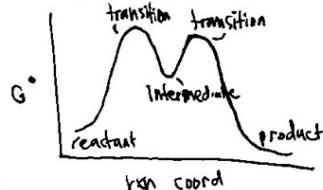
- > rxn rate very sensitive to G° : $\log\left(\frac{k_A}{k_B}\right) = \frac{\Delta G_B^\ddagger - \Delta G_A^\ddagger}{2.3 RT}$
- > Maxwell-Boltzmann distribution provides KE of molecules

• $T \uparrow$, rate ↑



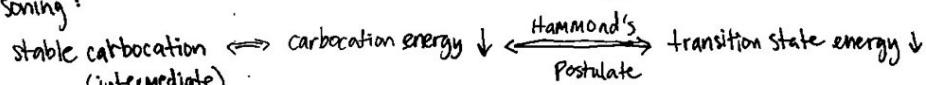
→ Multistep Rxn & Rate-limiting Step

- > rate of overall rxn is the rate of rate-limiting step
 - > rate limiting = $\Delta G^\ddagger \uparrow$

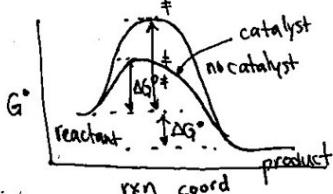


→ Hammond's Postulate

- > structure & energy of transition state can be approximated by that of intermediate if reactant & product have lower energy.
- > transition state energy → don't know ; intermediate energy (carbocation) → know !
- > reasoning :



$\Leftrightarrow \text{energy barrier } \Delta G^\ddagger \downarrow \Leftrightarrow \text{rxn rate} \uparrow$



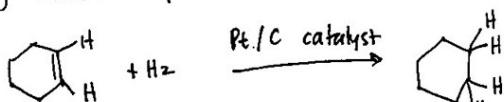
<< Catalysis

- > catalyst - substance increase rxn rate but not consumed
- > increase rxn rate \Leftrightarrow lower ΔG^\ddagger energy barrier
- > not consumed
- > does not change ΔG° ($\Delta G^\circ \neq \Delta G^\ddagger$) \Leftrightarrow no change in log
- > accelerate both fwd and reverse rxn

> heterogeneous - catalyst & reactant diff phase

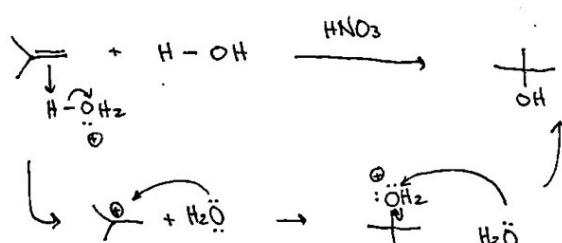
> homogeneous - catalyst & reactant same phase

→ Hydrogenation (catalytic)



• benzene can't

→ Hydration (catalytic) Markov



When H_3O^+ acts as acid,
 H_2O acts as base.

(Markov)

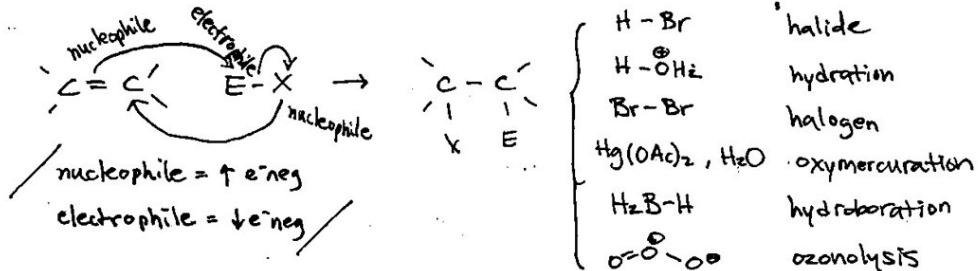
4 Nov 2020

ch5a Addition Reaction of Alkene

CHEM 237

<< Overview of Electrophilic Addition Rxn

- less e⁻ neg group → C w/ fewer alkyl sub
- More e⁻ neg group → C with more alkyl sub
- first step of rxn is C=C donate e⁻ pair to less e⁻ neg group : nucleophilic \rightarrow electrophilic
- electrophilic addition - begins with donation of e⁻ pair from π bond to an electrophilic atom.

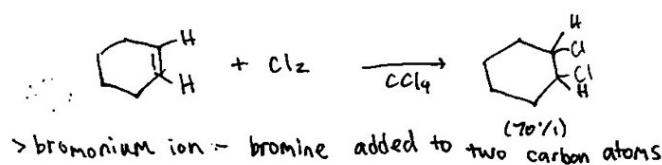


<< Reactions of Alkenes with Halogens

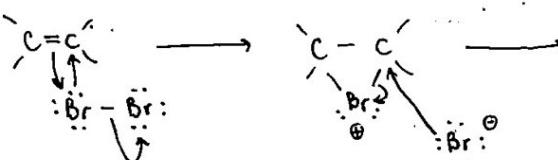
→ Addition of Br₂, Cl₂ + bromonium

> vicinal dihalide - compounds with halide on adjacent carbons

- product of Br₂, Cl₂ addition



Br₂ reacts with alkene so fast that it acts as test for existence of alkene.
(change of color)

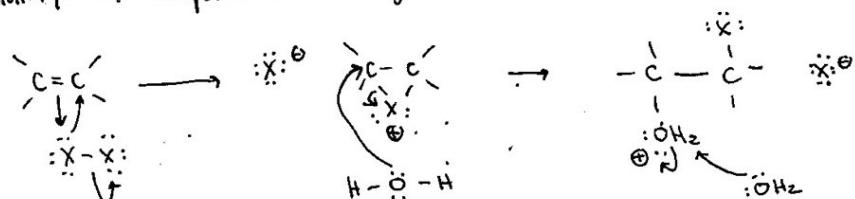


- no rearrangement
- no carbocation → bromonium ion instead
- bromonium more stable: more covalent bond; all has octet

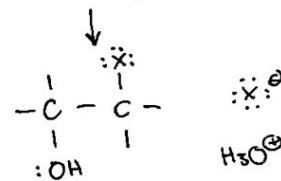
→ Halohydrins ~~to it~~ × bromonium

- nucleophilic solvent attack bromonium ion

> halohydrin - compound with halogen and -OH group.



- OH add to C with more alkyl since it is more e⁻ neg.
- regioselectivity: -OH add to More alkyl

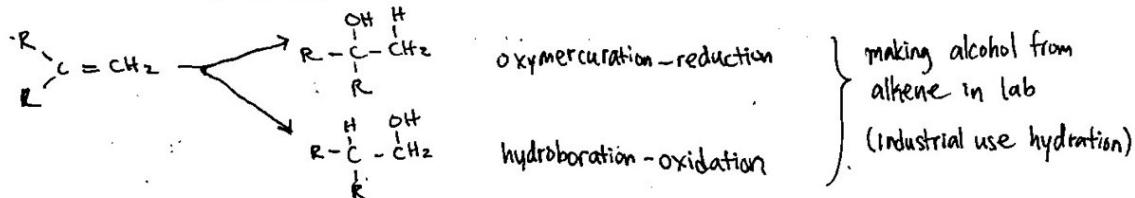


<< Writing Organic Reactions

- complete, balanced
- solvent below arrow, catalyst above arrow
- sometimes: organic starting material → major organic product

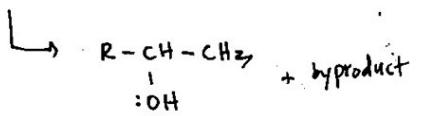
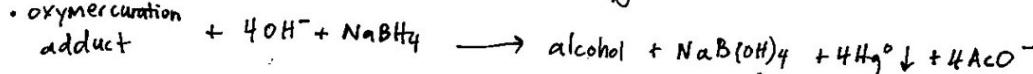
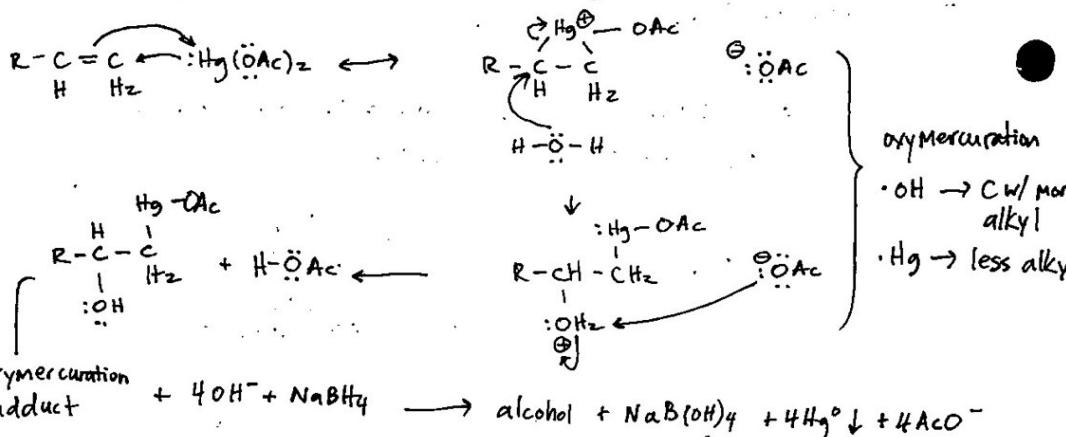
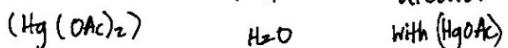
reactant $\xrightarrow[\text{catalyst}]{\text{solvent}}$ product
(%, yield)

<< Conversion of Alkenes to Alcohol

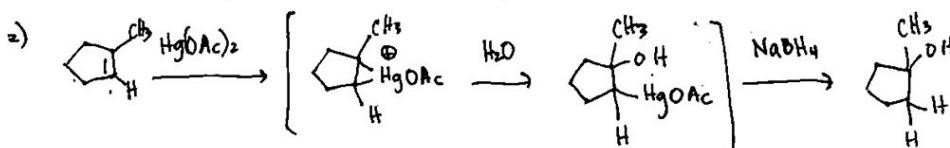
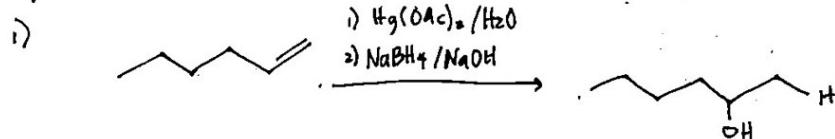


→ Oxymercuration-Reduction of Alkene Markovnikov

- alkene + Mercuric acetate + water → alcohol + acetic acid



- CONCLUSION: net addition of H and OH to alkene, H → less alkyl
- no rearrangement worries
- examples:

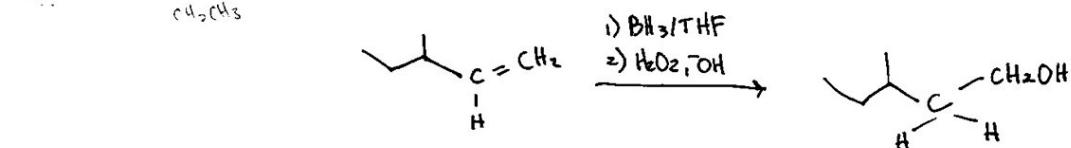
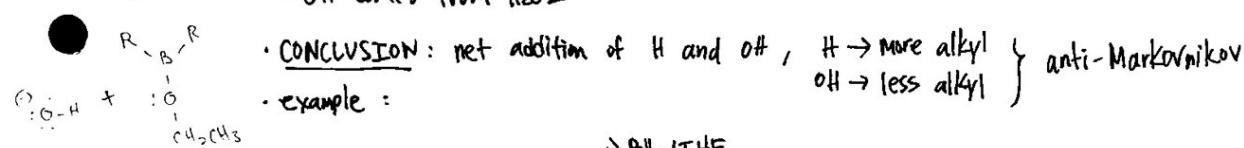
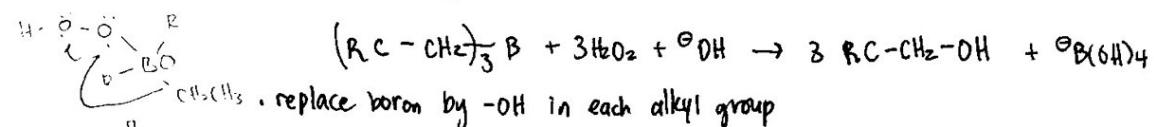
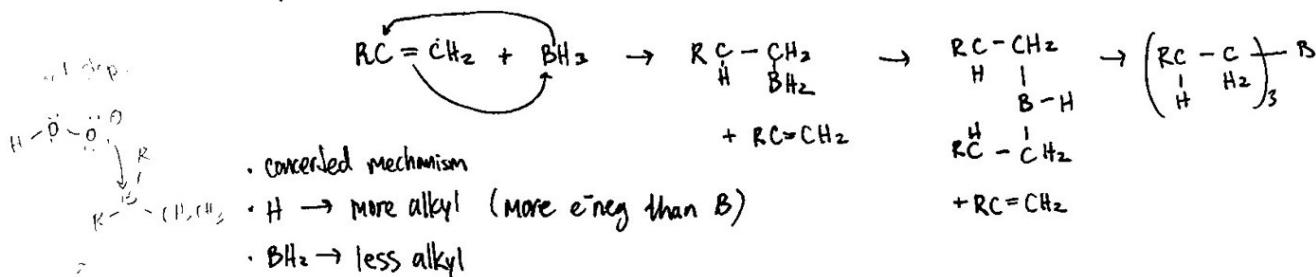


OH → more alkyl
Markovnikov

<< Conversion of Alkenes to Alcohol

→ Hydroboration - Oxidation of Alkenes Anti-Markovnikov

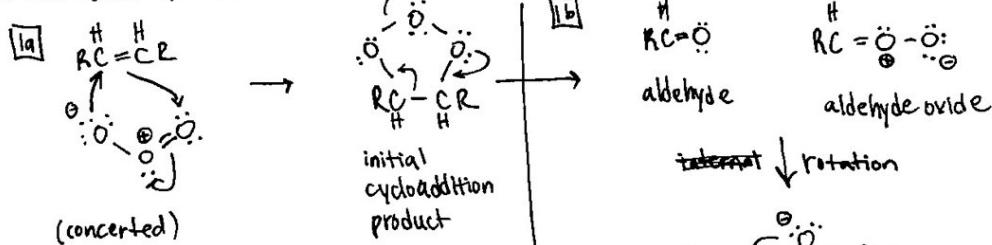
> hydroboration - addition of BH_3 to individual alkenes



- no rearrangement
- benzene ring doesn't react

<< Ozonolysis of Alkenes

→ Formation of Ozonide



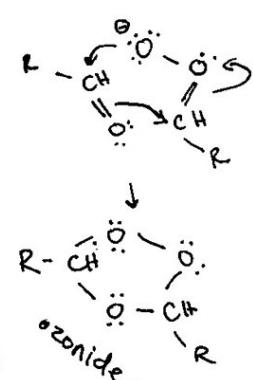
□ ozonide treated with diff chemicals result in diff products: $\text{>} \text{C}=\text{O} \rightarrow \text{>} \text{C=O}$ $\text{>} \text{C}=\text{O} \rightarrow \text{HO}-\text{C=O}$

initial alkene	(i) O_3 ; (ii) $(\text{CH}_3)_2\text{S}$ reductive (DMS)	(i) O_3 ; (ii) $\text{H}_2\text{O}_2/\text{H}_2\text{O}$ oxidative
----------------	--	--

$\text{R}-\text{C}=\text{}$	$\text{R}-\text{C}= \text{O}$ ketone	$\text{R}-\text{C}= \text{O}$ Ketone
-----------------------------	---	---

$\text{R}-\text{C}=\text{}$	$\text{H}-\text{C}= \text{O}$ aldehyde	$\text{H}-\text{C}= \text{O}$ carboxylic acid
-----------------------------	---	--

$\text{H}-\text{C}=\text{}$	$\text{H}-\text{C}= \text{O}$ formaldehyde	$\text{H}-\text{C}= \text{O}$ formic acid
-----------------------------	---	--



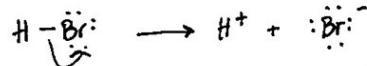
«« Free Radical Addition of HBr to Alkenes

→ Peroxide Effect

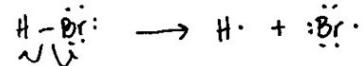
- HBr addition to alkene with peroxide ($R-O-O-R$) present has anti-Markovnikov regioselectivity : H → more alkyl ; Br → less alkyl
- light promotes peroxide effect
- only HBr has peroxide effect, not HCl, HI

→ Free Radicals & "Fish-Hook" Notation

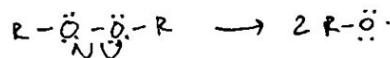
→ heterolysis - bond-breaking process where e⁻ move in pairs



→ homolysis - bond-breaking process where e⁻ move unpaired (individually)



• peroxide has weak O-O bond:



→ free radical - species with 1⁽⁺⁾ unpaired e⁻

→ Free Radical Chain Rxn

- free radical chain rxn - involves free radical intermediate
 - undergo initiation, propagation, termination

→ Initiation

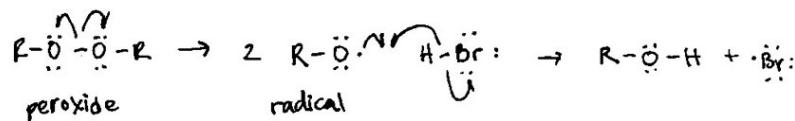
→ free-radical initiator - molecule that undergo homolysis with ease

• source of free radical

• e.g. peroxides (but not H₂O₂), azoisobutyronitrile (AIBN)

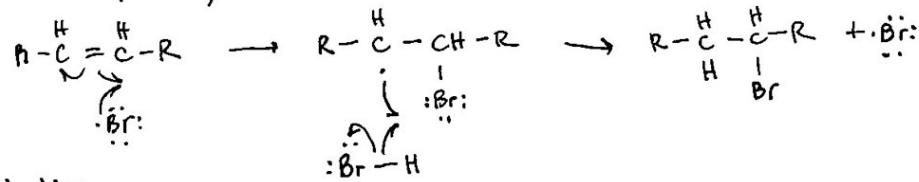
→ atom abstraction - free radical remove an atom from another molecule, forming a new free radical

can have initial radical to start initiation.



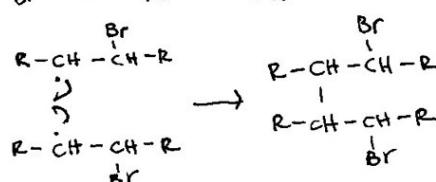
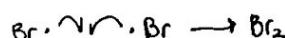
→ Propagation

- no net formation / destruction of free radicals
- occurs repeatedly



→ Termination

- radical recombination rxn - exothermic $\Leftrightarrow \Delta H^\circ \downarrow \Leftrightarrow$ favorable $\Leftrightarrow \Delta G^\circ + \downarrow$ very negative



- free radicals don't immediately recombine due to high conc. of other reactants.
- HCl, HI addition rare due to endothermic propagation steps (not favored!)

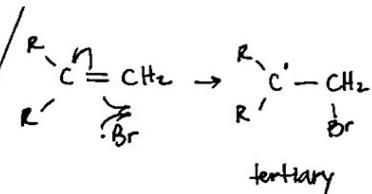
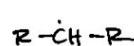
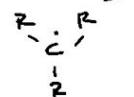
« Free Radical Addition of HBr to Alkenes (cont.)

→ Explanation of Peroxide Effect Anti-Markov

• peroxide effect - under presence of peroxide, HBr add to alkene with anti-Markovnikov

• stability of free radical

tertiary > secondary > primary



• steric effect - Br on alkyl has VDW repulsion

• lower heat of formation ΔH_f° for more substituted

• almost sp^2 geometry for primary radical

{ • electrophilic addition - H adds first to less alkyl \leftrightarrow tertiary stable carbocation

• radical addition - Br adds first to less alkyl \leftrightarrow tertiary stable radical

→ Bond Dissociation Energy (BDE)

• bond dissociation energy - standard enthalpy of rxn ΔH_{rxn}°

• always break bond by homolysis : $X\sim Y \rightarrow X\cdot + Y\cdot$

• measures intrinsic strength of bond

• $\Delta H_{rxn}^\circ \leftrightarrow T \downarrow$ to break bond

• $\Delta H_{rxn}^\circ = BDE(\text{broken}) - BDE(\text{formed})$

• HCl and HI cannot have peroxide effect due to high ΔH_{rxn}° , being endothermic

<< Enantiomers, Chirality, Symmetry

> stereoisomer - compounds have same atomic connectivity but diff spacial arrangement

> stereochemistry - study of stereoisomers and chemical effects of stereoisomerism

→ Enantiomers & chirality

> congruent - all atoms & bonds can be superimposed w/ mirror image (via rotation)

> enantiomers - stereoisomers that has noncongruent mirror images

> chiral - molecules that exist as enantiomers

> achiral - not chiral

→ Asymmetric Carbons & Stereocenters

> asymmetric carbon atom - carbon with 4 diff groups bound

- molecule with only one asymmetric carbon is chiral

- not condition for chirality (asymmetric C \nleftrightarrow chiral)

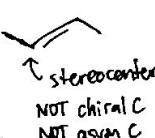
> asymmetric center - the asymmetric atom

> stereocenter - atom which the interchange of two groups gives stereoisomer

- not all are asymmetric carbon (stereocenter \nleftrightarrow asymmetric carbon/atom)

asymmetric atom \rightarrow stereocenter

\neq Stereocenter \neq
chiral center

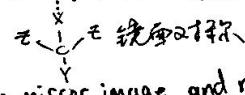


→ Chirality & Symmetry

> symmetry elements - how lines, points, planes relate to equivalent parts of an object

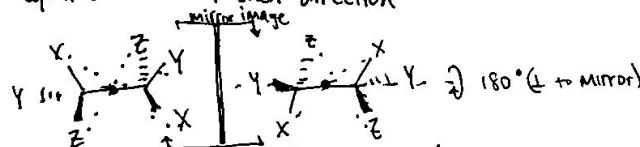
> plane of symmetry (internal mirror plane) - planes divides object into exact mirror images

- plane of symmetry $\checkmark \rightarrow$ achiral



> center of symmetry (point of symmetry) - same if form mirror image and rotate 180°

- has a point that lines thru it contact exactly equivalent part of object at equal distance in each direction



NOTE:
E/Z system is for
alkene cis-trans

<< Enantiomer Nomenclature: R/S system

. stereochanical configuration:

- Identify asymmetric carbon (4 diff groups!)

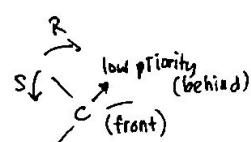
- Assign priority (Cahn-Ingold-Prelog priority in alkene E/Z)

- View molecule along bond from asym. carbon $\xrightarrow{\text{(front)}}$ group of lowest priority $\xrightarrow{\text{(behind)}}$

- the remaining group big \rightarrow small (high prior \rightarrow low prior)

- clockwise (R) rectus - proper - right

- counterclockwise (S) sinister - left



* IMPORTANT: HIGH \rightarrow LOW

<< Optical Activity of Enantiomers

- Same: melting pt, boiling pt, density, ΔH_f° , ΔG° , ...
- Diff: effect on polarized light

→ Polarized light

- ordinary light - electric field oscillates in all planes

> plane-polarized light - light that electric field oscillate in only one plane

- obtained by passing ordinary light thru Nicol prism

> if polarized light subjected to a polarizer with perpendicular axis of polarization, no light passes thru

→ Optical Activity



- > optically active - substance that rotates plane of polarized light

> individual enantiomers of chiral structure \Leftrightarrow optically active

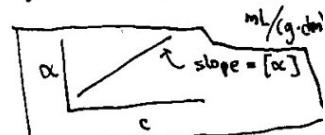
> polarimeter - device measuring optical activity

> optical rotation - angle analyzer has to turn to reestablish dark field

> dextrorotatory - clockwise rotation, positive, right (D) (+)

> levorotatory - counter-clockwise, negative, left (L) (-)

$$\alpha = [\alpha] c l \quad \left\{ \begin{array}{l} [\alpha] \text{ specific rotation - observed rotation @ } 1g/mL, 1dm \quad [\alpha] = \text{deg.} \\ c \text{ concentration } [c] = g/mL \\ l \text{ length } [l] = \text{dm} \end{array} \right.$$



→ Optical Activity of Enantiomers

> enantiomers rotate plane of polarized light by equal amounts in opposite directions.

> optical rotation \Leftrightarrow R/S config

> measured experimentally

<< Mixtures of Enantiomers

→ Enantiomeric excess

> enantiomerically pure - one enantiomer of chiral compound is contaminated by the other

> enantiomeric excess (EE) = % Major - % Minor $\quad (\% \text{ Major} + \% \text{ Minor} = 100\%)$

$$\text{(optical purity)} = \frac{[\alpha]_{\text{mix}}}{[\alpha]_{\text{pure major}}} \times 100\%$$

/racemization : 80%S/20%R \rightarrow 50%/50%

/enantiomeric resolution : 50%/50% \rightarrow 100%/0/00%

$$\cdot \% \text{ Major} = \frac{\text{EE} + 100\%}{2}$$

→ Racemate

> racemate/racemic mixture - mixture with equal amount two enantiomers

> optical rotation = 0 ; EE = 0

> diff physical property: melting pt, ...

> enantiomeric resolution - separation of a pair of enantiomers

<< Stereochemical Correlation

> absolute configuration - actual 3D arrangement of atom

• X-ray crystallography

> stereochemical correlation - chem reactions to correlate compounds with other compounds of known abs config.

• asymmetric atom should be unaffected by rxn

<< Diastereomers

• For a pair of chiral molecules with 1+ asymmetric C to be enantiomer, they must have opposite config at every asymmetric C

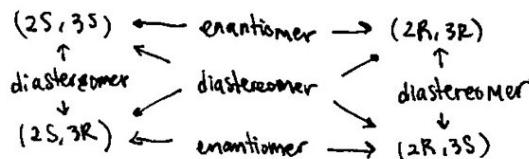
• eg. $(2S, 3S) \leftarrow$ enantiomer $\rightarrow (2R, 3R)$

• $(2S, 3R) \leftarrow$ enantiomer $\rightarrow (2R, 3S)$ can be E/Z alkenes

> diastereomer - stereoisomers that are not enantiomers (same connectivity, not mirror imgs)

• diastereomers has diff physical properties

• if optically active, may have specific rotation that are not the same



molecular formula?
same ✓ no ↴
isomer
connectivity?

no ↴
constitutional isomer
noncongruent mirror img?
✓ same stereoisomer
enantiomer ↴
diastereomer

↳ (2R, 3S) can meso (2S, 3R)

(2R, 3R) can't meso (2S, 3S)

↑ ↴
not opposite

<< Meso Compound

> meso compound - achiral compound that has chiral diastereomers

• optical inactive

• 2⁽⁺⁾ asym. C, achiral (operational definition)

• can be divided into halves with same connectivity, with opposite stereochem config

• one molecule

• usually have internal mirror plane

<< Enantioselective Resolution (Separation)

> enantioselective resolution - separation of two enantiomers

• take advantage of diff property of diastereomers

• interact with an enantioselectively pure chiral agent

→ Methods

• chiral chromatography

• diastereomeric salt formation

• selective crystallization

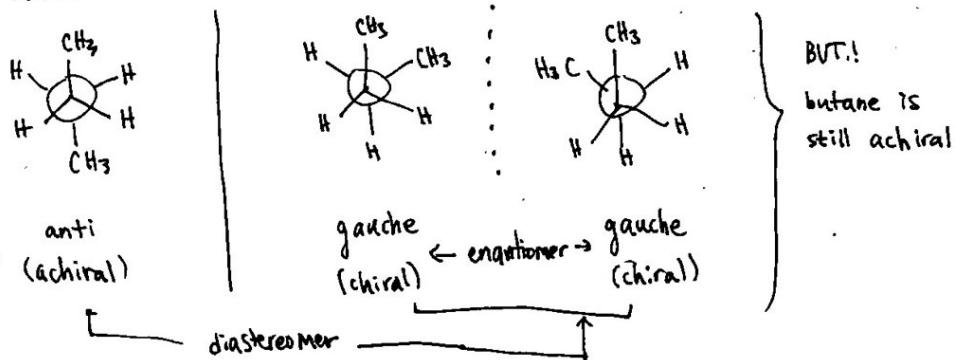
<< Rapidly Interconverting Stereoisomers

→ Internal Rotations

> conformational enantiomer - enantiomers interconverted by internal rotation

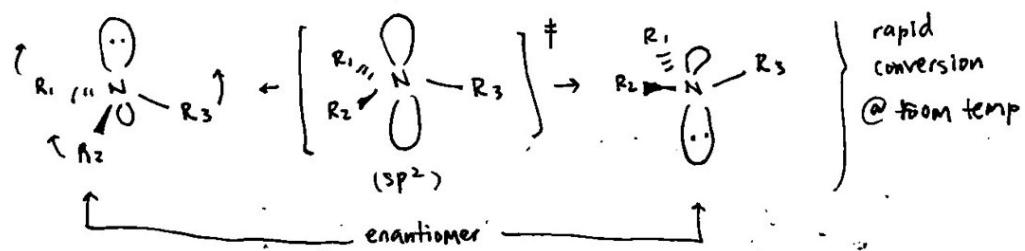
> conformational diastereomer - diastereomer interconverted by internal conrotatory rotation

e.g. butane

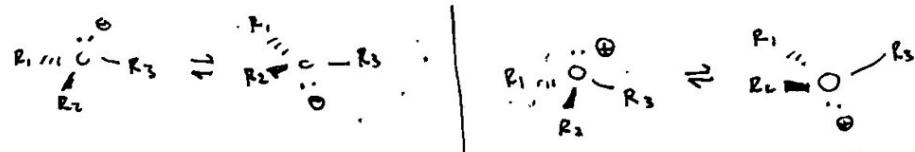


• a molecule is said to be achiral when it consists of rapidly equilibrating enantiomeric conformations that cannot be separated on any reasonable time scale.

→ Amine Inversion



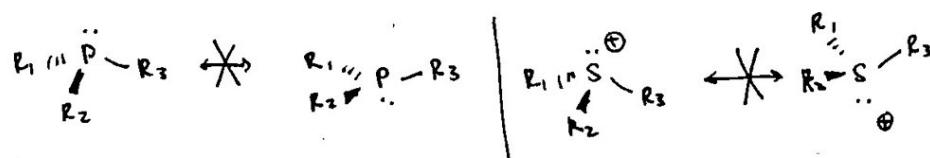
• inversion also works with carbon anion, oxonium ion (all with a lone pair)



• the rapid inversion is fast in room temp, making them achiral

* phosphine, sulfonium ion are chiral since inversion doesn't occur

• higher s character



Conclusion:

achiral	chiral
amine (N^+)	phosphine (P^-)
carbon anion (C^-)	sulfonium ion (S^+)
oxonium ion (O^+)	

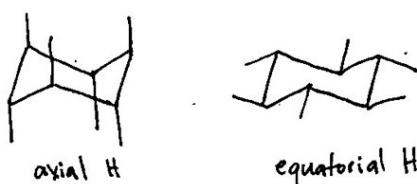
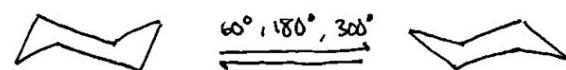
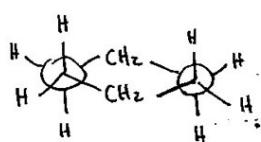
<< Monocyclic Alkanes

- > monocyclic compound - a compound with a single ring
- compare stability by ΔH_f° of empirical formula C_6H_{12}
- cyclohexane (6C) is most stable
- cyclohexane (6C) has same stability as typical unbranched alkane.

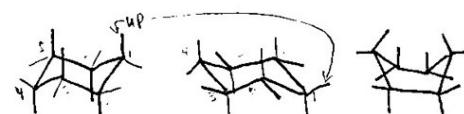
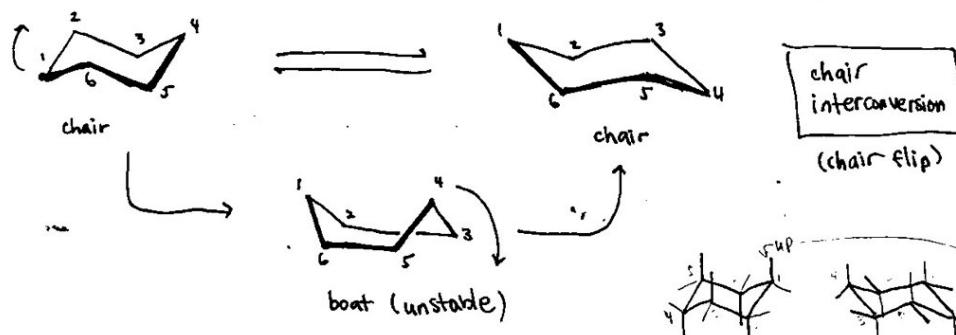
<< Conformations of Cyclohexane

→ Chair Conformation

- carbon 1,4 in page
- carbon 2,3 in front of page
- carbon 5,6 behind page
- mirror images can be obtained by rotating $60^\circ, 180^\circ, 300^\circ$
- > axial hydrogen - point away
- > equatorial hydrogen
- all bonds staggered (low E)



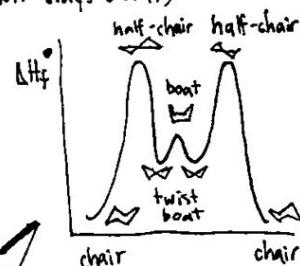
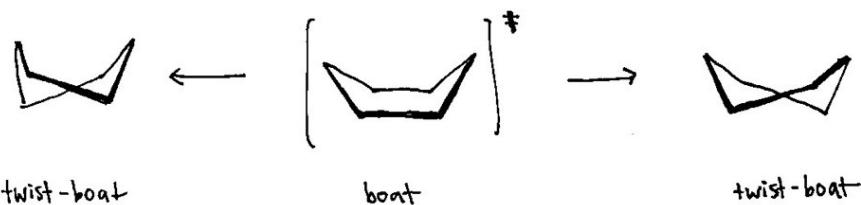
→ Interconversion of Chair Conformation



- equatorial H \rightleftharpoons axial H
- up C \Rightarrow down C (but note, for hydrogen, up stays up, down stays down)

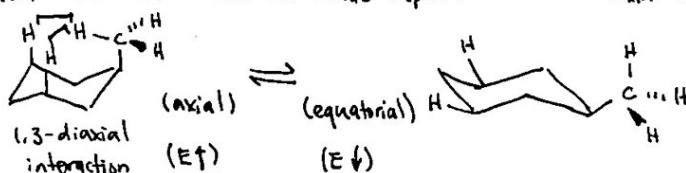
→ Boat & Twist Boat Conformation

- boat unstable { & eclipsed conformation
flagpole hydrogen repulsion (steric clash)



<< Monosubstituted Cyclohexane

- chair interconversion { equatorial H \leftrightarrow axial H
H position up H remains up H ; down H remains down H
- equatorial conformation of substituted cyclohexane is more stable than axial
- > 1,3-diaxial interaction - van der Waals repulsion between axial H and axial substituent.



- axial E > equatorial E

axial stability < equatorial stability

- 1,3-diaxial interaction \leftrightarrow gauche-butane interactions
- > conformational analysis - investigation of molecular conformation & energy

<< Disubstituted Cyclohexanes

\rightarrow Cis-trans Isomerism

- planar-ring structure



flip orientation

- cis - sub. has same rel orientation



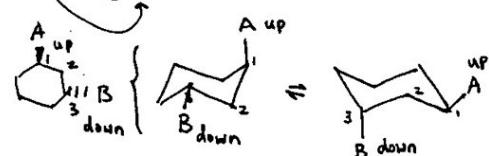
- trans - sub. has diff rel orientation



- plane-ring structure { ① config (R,S)cistrans)

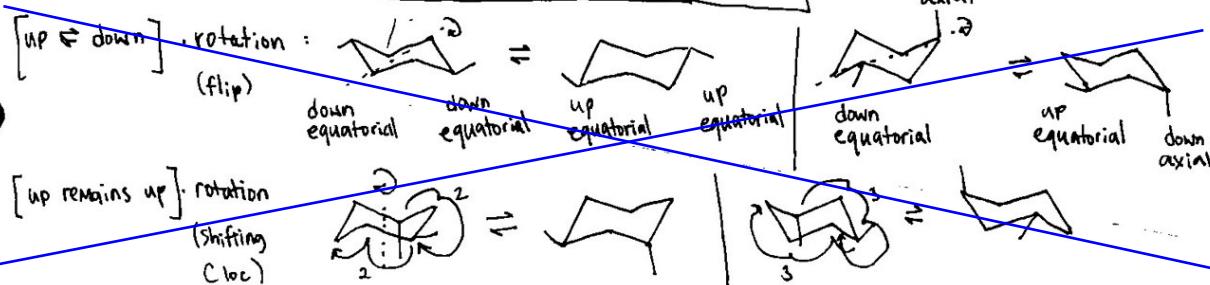
- ② conformation (two chairs)

- cis trans \rightleftharpoons R,S



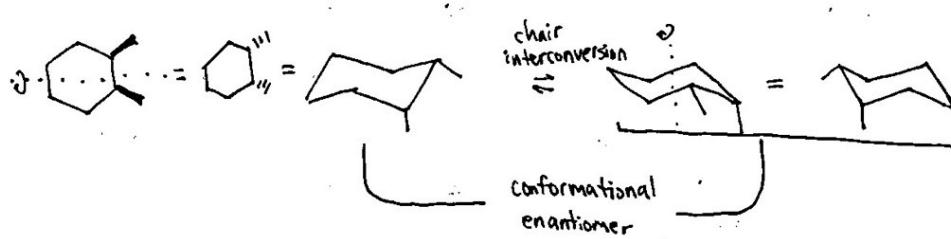
		\rightleftharpoons		(S,R)	same
cis		\rightleftharpoons		(R,S)	same
		\rightleftharpoons		(R,R)	diff
trans		\rightleftharpoons		(S,S)	diff
	same molecule			(Br,Cl)	hedge-dash

- choose Cl at edge
- up remains up! down remains down!

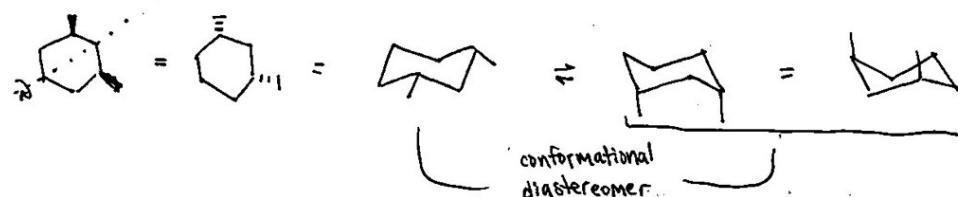


<< Disubstituted Cyclohexanes (cont.)

→ meso Compound



• due to rapid chair conversion, it is meso.



• due to rapid chair conversion, it is meso.

→ conformational analysis

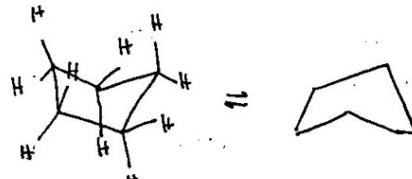
- for less E, more stability
- put more substituent at equatorial
- put bulky group at equatorial

<< Other Cycloalkanes

→ cyclopentane □

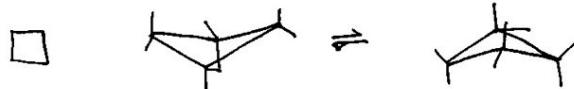
• envelope conformation

• higher energy than C_5
due to eclipsing H



→ cyclobutane □ & cyclopropane △

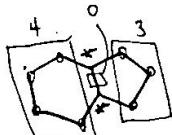
> angle strain - excess energy caused by low bond angle



"bent", "banana" bond that's not on
straight line

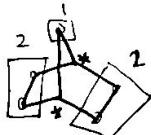
<< Bicyclic & Polycyclic Compounds

- > bicyclic compound - two rings share 2⁽⁺⁾ common atoms
- > spirocyclic compound - two rings share a single common atom
- > bridge-head carbon - atoms at which two rings join in bicyclic compound
 - fused bicyclic compound - adjacent bridge-head carbon
 - bridged bicyclic compound - non-adjacent bridge-head carbon



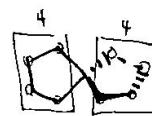
bicyclo[4.3.0]nonane

fused bicyclic compound



bicyclo[2.2.1]heptane

bridged bicyclic compound



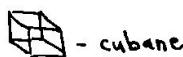
spiro[4.4]nonane

spirocyclic compound

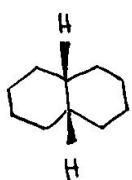
• nomenclature

1. bicyclo / spiro
2. [#, #, #] / [#, #] # is amount of carbon at each side divided by bridge-head carbon from high to low
4. [num]ane num = total amount of carbon as prefix.

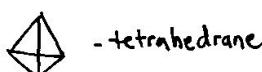
> polycyclic compound - contain many rings joined at common atoms



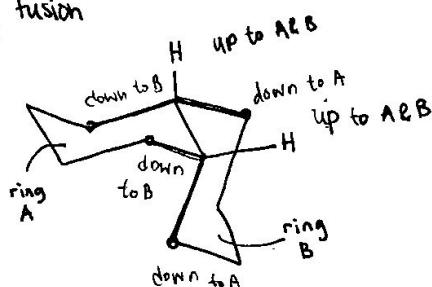
→ cis & trans ring fusion



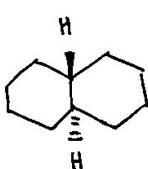
cis-decalin



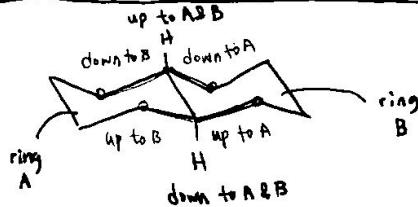
• can have chair interconversion



• both change at same time

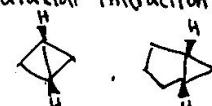


trans-decalin

• no chair interconversion
due to ring strain:

• trans-decalin > cis-decalin (less diaxial interaction)

• but! some small rings has only cis : (trans ↑ ring strain)



<< Bicyclic & Polycyclic Compounds (cont.)

→ trans-cycloalkanes & Bredt's Rule

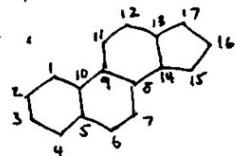
- only cis-cycloalkene observed
- no trans-cycloalkene due to strain or twisting molecule about double bond

> Bredt's rule - in bicyclic compound, a bridgehead atom contained solely within small rings (≤ 7 atoms) cannot be a part of double bond.

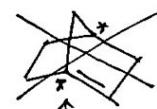
- twisting \Rightarrow double bond, $\uparrow E$

→ Steroid

steroid - compound derived from the tetracyclic ring system below



- α face behind page
- β face in front of page



does NOT happen

- six member ring
- double bond

- naturally occurring steroid structure
 - 1. all trans ring fusion (no chair interconversion)
 - 2. angular methyl at C10, C13

<< Reactions Involving Stereoisomers

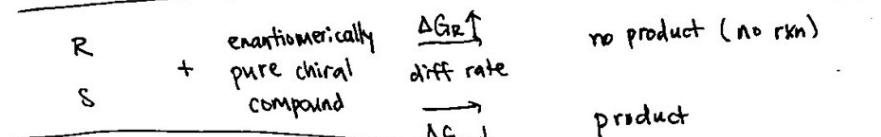
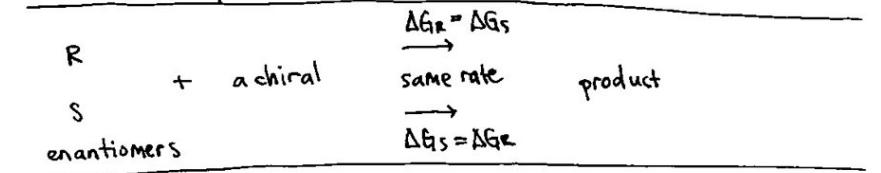
→ Reactions Involving Enantiomers

- Enantiomers react at identical rates with an achiral reagent
- Enantiomers have same free energy \Leftrightarrow same rate
- Enantiomers reacting with enantiomerically pure compound produces diastereomers
 - diastereomers have diff $\Delta G \Leftrightarrow$ diff rate (even occurrence of rxn)

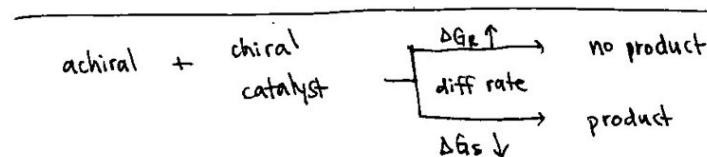
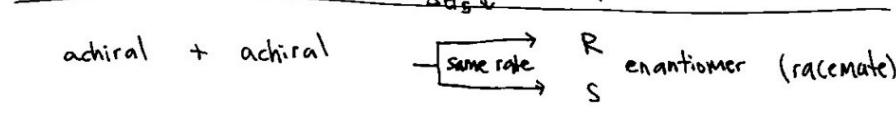
enantiomer
→ achiral molecule

- When chiral products are formed from achiral reactant, both enantiomers of a pair are always formed at identical rates \Leftrightarrow racemate forms
- optical activity never arises spontaneously in rxns of achiral compounds
- Enantiomers are formed at diff rate from achiral starting materials in presence of chiral catalyst

achiral molecule
→ enantiomer



* random example of R/S, May Vary by case



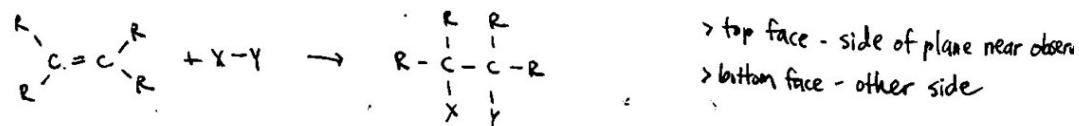
<< Reactions Involving Stereoisomers (cont.)

→ Reactions Involving Diastereomers

- diastereomers have diff reactivity with dk any reagent
 - diff ΔG
 - diastereomers are formed by diff amount & rate
 - diastereomeric transition state \leftrightarrow diff $\Delta G \leftrightarrow$ diff rate & amount

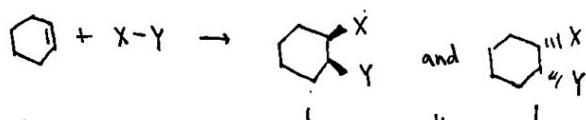
<< Stereochemistry of Reactions

→ Addition Reactions



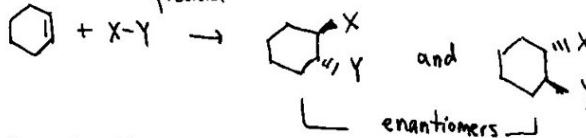
> Syn-addition - two groups add to a double bond from same face

- #### • enantiomeric product



→ anti-addition - two groups add to a double bond from diff. face

- enantiomeric product

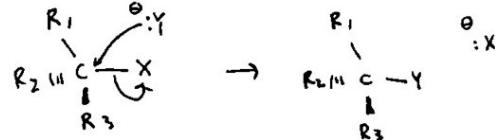


- Stereochem of addition can be determined only when stereochemically diff Mode of addition give raise to stereochemically diff products

- syn- and anti-addition give diff products only when both carbons of double bond become carbon stereocenter in product.

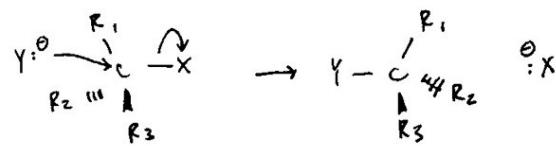
→ Substitution Reactions

> retention of configuration - old & new sub. have same priority, no R/S change.



> inversion of configuration - new group replace from opposite side from old group.

- have RIs change



- Same product is formed if the substitution site will is not stereocenter

➢ stereoselective reaction - reaction which particular stereoisomer product is formed more than others.

<< Stereochemistry of Reactions

→ Bromine Addition anti

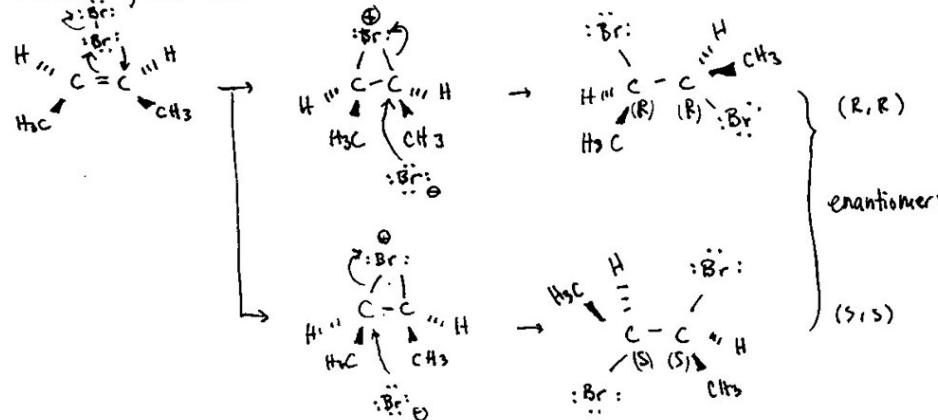
> stereospecific reaction - diff stereoisomers of a starting material give diff stereoisomer product.

stereoselective
stereospecific

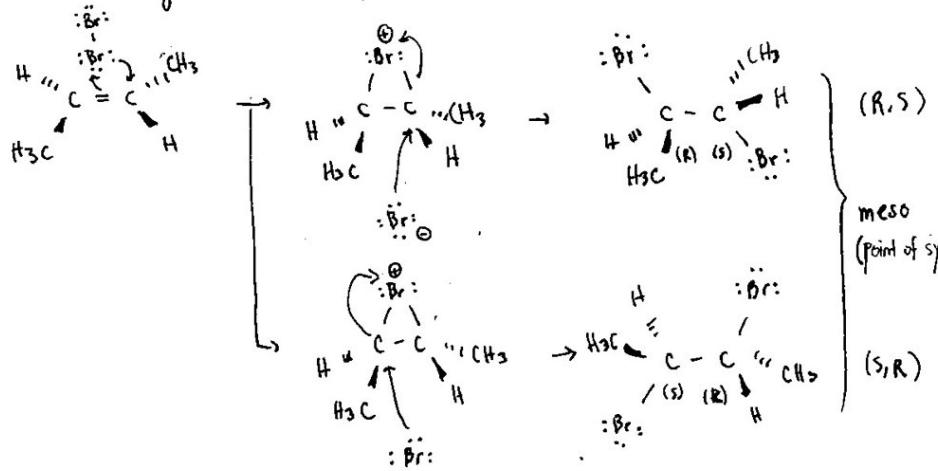
> opposite-side substitution - new sub. attack from opposite face from the broken bond
must occur with inversion of ~~stereo~~ configuration.

Ex. 2-butene + bromine (anti addition)

cis-2-butene gives racemic mixture



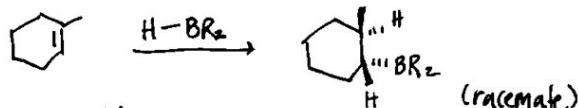
trans-2-butene gives meso compound



<< Reactions Involving Stereoisomers (cont.)

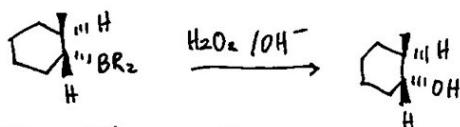
→ Hydroboration - Oxidation syn (Anti-Markov)

- hydroboration is a stereospecific syn-addition (concerted)

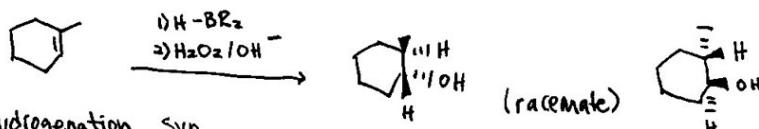


- concerted anti-addition not possible

- Oxidation is stereospecific substitution with retention of stereochemical configuration

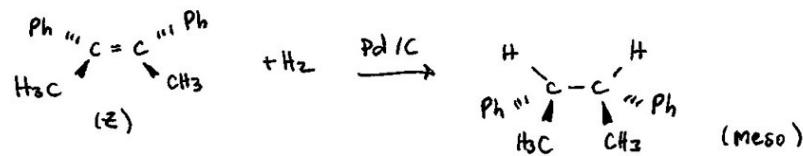
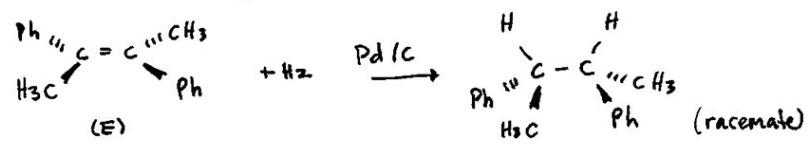


- Conclusion : net syn-addition of H-OH to double bond



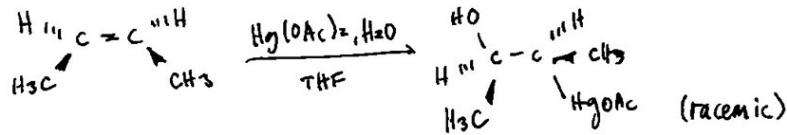
→ Catalytic Hydrogenation syn

- syn-addition, stereospecific



→ Oxymercuration-Reduction (Markov)

- anti-addition, stereospecific oxymercuration anti / none *



- Overall: not stereoselective, but regioselective (Markov.)

→ Reactions with Carbocation Intermediate none

- not reg stereoselective - all stereochem lost when sp²-hybridized carbocation formed

<< Heterogeneous Intermolecular Interactions: Solutions

→ Solution Definition & Energetics

> Solute - small amount

> solvent - large amount

> insoluble - solute & solvent persist as separate phases even in contact

> solution - solute & solvent form single liquid phase

> soluble - solute & solvent form solution

> solvent shell - solvent that are in direct contact of solute

> free energy of soln - free energy change of dissolving solute in 1L of solvent

$$\Delta G_s = G(\text{soln}) - [G(\text{pure solute}) + G(\text{pure solvent})]$$

• $\Delta G_s < 0$ favorable• $\Delta G_s > 0$ unfavorable

> entropy of mixing - probability of soln formation that is completely independent of any intermolecular interactions

• ΔS_{mixing} , statistical driving force for formation of solvent, regardless IMF• $\Delta S > 0$ • less probable → more probable

$$\Delta S_{\text{mixing}} = -2.3 R (n_1 \log x_1 + n_2 \log x_2) \quad \begin{array}{l} \xrightarrow{n \text{ # moles}} \\ \times \text{ Mole fraction in soln} \end{array}$$

$$\Delta G_s = \Delta G_{\text{interaction}} - T \Delta S_{\text{mixing}}$$

→ Classification of Solvents

{> protic - can act as H-bond donor (H_2O , alcohol, carboxylic acid)}

{> aprotic - cannot act as H-bond donor (hexane)}

{> dipolar - have significant dipole moment ($\mu > 1D$) (property of one molecule)}

{> non-polar - doesn't have dipole moment}

{> polar - have high dielectric constant ($\epsilon \geq 15$) (property of many molecules) (water, formic acid, methanol)}{> apolar - have low dielectric constant ($\epsilon < 15$) (property of many molecules) (hexane, ether, acetic acid)}> dielectric constant (ϵ) - $E = k \frac{q_1 q_2}{\epsilon r}$ • $\uparrow \epsilon$, $\downarrow E$ of interaction, \downarrow weak attraction & repulsion, \uparrow shielding• $\downarrow \epsilon$, $\uparrow E$ of interaction, \uparrow strong attraction & repulsion, \downarrow shielding

• polar solvent effectively separates/shields ions from one another

• polar → dipolar

• polar $\not\leftrightarrow$ dipolar{> donor - have N, O to donate unshared e^- pair (Lewis base) (ether, THF, methanol) (H bond acceptor)}{> nondonor - cannot donate e^- pair (not Lewis base) (pentane, benzene) (not H bond acceptor)}

\leftrightarrow Solubility of Covalent Compounds

- like dissolves like
- > miscible - mixable, form solution when mixed in any proportion
- when attraction between solvent & solute is similar to that between pure solvent,
 $\Delta G_{\text{attraction}} \rightarrow 0$, $\Delta G_s = \Delta S_{\text{mixing}} T < 0$, favorable mixing

<< Overview

→ Nucleophilic Substitution Rxn

> nucleophile donates e⁻ pair to electrophile to displace a leaving group

> alkoxide - conjugate bases of alcohol

> Spectator ion - ion has no role in overall rxn

> net ionic equation - only reacting ionic component are shown; spectator ion omitted

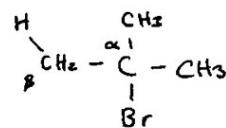
→ β-elimination Rxn

> two or more groups are lost from the same molecule

> α-carbon - C with halogen

> β-carbon - adjacent carbon to α-C

> β-elimination - loss of 2 groups from adjacent C to form double bond
• (reverse of alkene addition)



<< Equilibria in Nucleophilic Substitution Rxn

• equilibrium favors weaker base product (more stable product)
(nucleophile)

<< Reaction Rates

• equilibrium ≠ rate (reactivity)

→ Definition of Rxn Rate

$$\text{rxn rate} = \frac{\Delta [\text{product}]}{\Delta t} = - \frac{\Delta [\text{reactant}]}{\Delta t} \quad [\text{rate}] = \text{M/s}$$

• Rate Law

• experimentally determined (e.g. rate = k[A][B])

> rate constant - rate which the reactants are at 1M [k] - dependent on rate law

• ↑ rate constant, ↑ rate (same conc.)

> overall kinetic order - sum of power of all conc. in rate law

→ k and ΔG°‡ (standard free energy of activation)

• ΔG°‡ ↑, energy barrier ↑, rate ↓

• ΔG°‡ ↓, energy barrier ↓, rate ↑

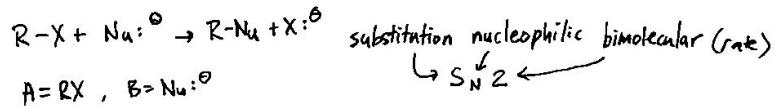
> relative rate - ratio of two rates

$$\cdot \text{rel rate} = \frac{\text{rate}_A}{\text{rate}_B} = \frac{k_A}{k_B} = 10^{\frac{(\Delta G_B^{\ddagger} - \Delta G_A^{\ddagger})}{2.3RT}}$$

$$\cdot \log(\text{rel rate}) = \log\left(\frac{k_A}{k_B}\right) = \frac{\Delta G_B^{\ddagger} - \Delta G_A^{\ddagger}}{2.3RT}$$

\leftrightarrow S_N2 Rxn nucleophile direction

→ Rate Law & Mechanism



substitution nucleophilic bimolecular (rate)
 ↴ S_N2 ↵

- rate = $k[A][B]$
- second order rxn with first order for each reactant
- rate law indicate which species are present in transition state of rate-limiting step.
- S_N2 mechanism - e⁻ pair donation by nucleophile to electrophile displaces leaving group from the electrophile in concerted manner

➢ S_N2 rxn - rxn occur by S_N2 mechanism

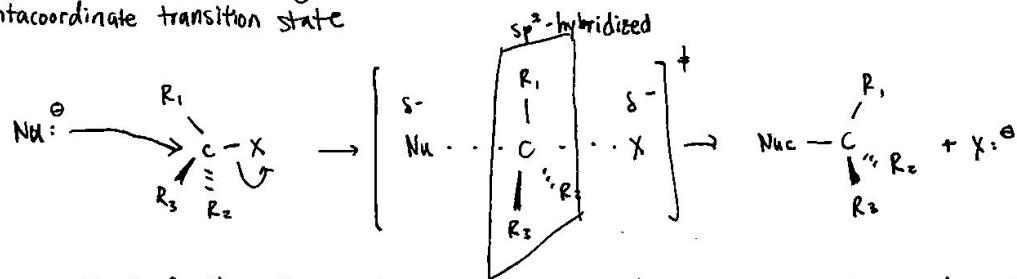
- no rxn intermediate (concerted, only transition state)
- Simplest mechanism consistent with the rate law is adopted.
- rate law says nothing about molecular arrangement → need more experiment.

→ Relative Rate of S_N2 Rxn & Acid-Base Rxn

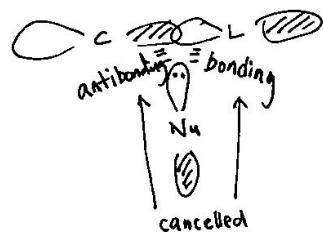
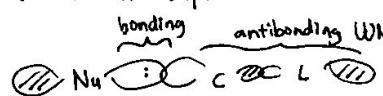
- acid-base rxn much faster than S_N2 rxn (Bronsted)
- proton small, easy to react
- Bronsted acid reacts with Bronsted base over alkyl halide

→ Stereochemistry of S_N2

- inversion of stereochemistry → opposite side substitution
- pentacoordinate transition state



- e⁻ pair of Nu: first interact with LUMO (lowest unoccupied Molecular orbital)
- only antibonding left for alkyl halide
- Opposite side provides bonding overlap
- same side ~~also~~ has both bonding & antibonding interactions → cancelled



→ Factors affecting S_N2 rate

- sterics of electrophile
 - ↑ sterics, ↓ rate
- nucleophilicity
 - ↑ strong nucleophile, ↑ rate
- leaving group ability
 - ↑ leaving group ability, ↑ rate

\Leftarrow Factors Affecting SN2 Rxn Rate

→ Steric Effects (on electrophile)

- \uparrow alkyl sub at β/α -C, \uparrow steric hindrance, \downarrow rate

• van der Waals repulsion makes rxn unfavorable

→ Nucleophilicity

→ Basicity & Solvent Effect

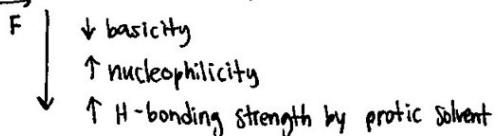
- \uparrow base, \downarrow acid, \uparrow nucleophilicity, \uparrow rate

- solvent
 - protic, react with nucleophile by H-bonding, \downarrow rate
 - aprotic, no H-bonding, \uparrow rate

- aprotic
 - (E) More expensive
 - hard to remove from mixture (\uparrow boiling pt)
 - Won't dissolve salts

- combination: polar, protic solvent \Rightarrow basicity considerations

$$\text{basicity} \approx \text{nucleophilicity} \quad (\text{similar H-bonding strength})$$

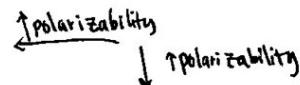


- \uparrow steric bulk, \downarrow nucleophilicity, \downarrow rate

→ Polarizability

- weak base can be good nucleophile if polarizable

- \uparrow polarizability, \uparrow nucleophilicity, \uparrow rate



→ Distinguish Nucleophilicity & Basicity

- nucleophilicity have bond formation with atoms other than H
- basicity have bond formation with H

- nucleophilicity measured with rel. rate. (kinetics)

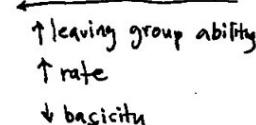
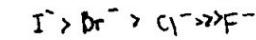
- basicity measured with pKa (equilibrium)

- polarizability have effect on nucleophilicity rather than basicity

→ leaving Group Effect (on electrophile)

- weak conj. base, strong acid, \uparrow ability to stabilize neg charge, \uparrow leaving group ability, \uparrow rate

- halides are better leaving group than hydroxide etc. (base!)



<< E2 Rxn Ligand base addition

→ Rate Law & Mechanism

$$\text{rate} = k[A][B] \quad A = RX, B = B^-$$

second order rxn with first order for each reactant

E2 mechanism - concerted removal of β -proton by a base and loss of halide ion

E2 rxn - rxn occur by E2 mechanism (β -elimination)

→ Stereochemistry of E2

syn-elimination - H & X at same side (dihedral angle = 0°)

anti-elimination - H & X at opposite side (dihedral angle = 180°)

E2 has anti-elimination.

- staggered transition state

- avoided steric interference at same side

- opposite side e^- displacement ($\downarrow E$ by MO theory)

→ Regiochemistry of E2

- major product is more stable alkene

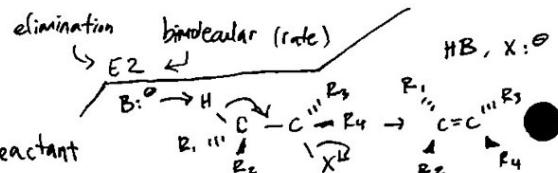
- Marcov. rule - alkyl group, \uparrow stability

Zaitsev's rule - elimination rxn forms predominantly most stable alkene

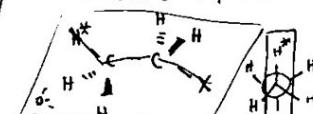
- not driven by equilibrium, but rate

- major product, \downarrow energy barrier, \uparrow rate

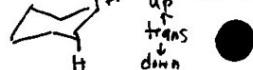
- minor product, \uparrow energy barrier, \downarrow rate



"antiperiplanar" -
 180° and same plane



leaving group trans to
C-H bond at axial position
(not necessary)



(to have anti-config
instead of gauche)



+ remember check
cis/trans if no
stereochem given

<< Factors Affecting E2 Rxn Rate

→ Leaving Group Effect

- \uparrow leaving group stability, \uparrow rate

- weak conj. base, strong acid, \uparrow ability to stabilize neg charge

- R-I \rightarrow R-Br $>$ R-Cl

→ Deuterium Kinetic Isotope Effect

primary deuterium kinetic isotope effect - replacing H with D in the E2 rxn will

- used to confirm rxn mechanism Slow its rate

- D-C is stronger than H-C, need more E to break, \downarrow rate

<< Competition Between S_N2 & E2 Rxn

→ Sterics of Alkyl Halide

- \uparrow alkyl sub. @ α -/ β -carbon, \uparrow steric bulk, \downarrow S_N2 rate, \uparrow E2 rate

- alkyl halide w/o β -hydrogen has no E2, only S_N2.

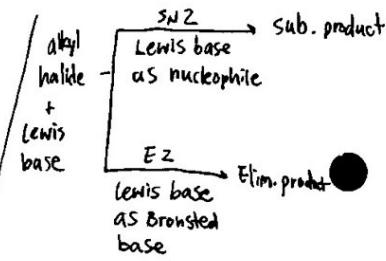
→ Structure of Base

- alkyl sub., \uparrow steric bulk, \uparrow E2 rate, \downarrow S_N2 rate

- Weak base but strong nucleophiles (eg. I⁻) - \uparrow S_N2 rate

- S_N2 nucleophilic-promoted

- E2 bronsted-base-promoted



⇒ S_N1 & E_I Rxn

⇒ solvolysis - rxn of alkyl halide with a solvent without other base/nucleophile

→ Rate Law & Mechanism

- rate = $k[A]$ A = RX

- first-order rate law

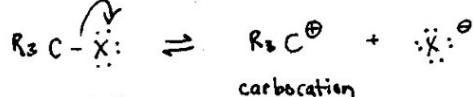
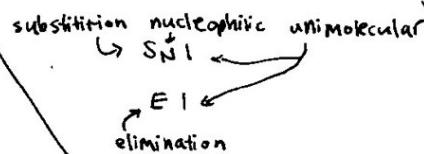
- polar, protic, donor solvent, ↑ solvation, ↑ rate

→ Common first step

- Lewis-acid-base dissociation to form carbocation.

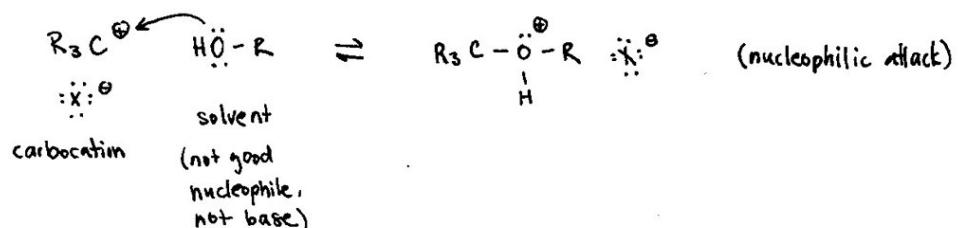
- rate limiting

- S_N1 and E_I competes

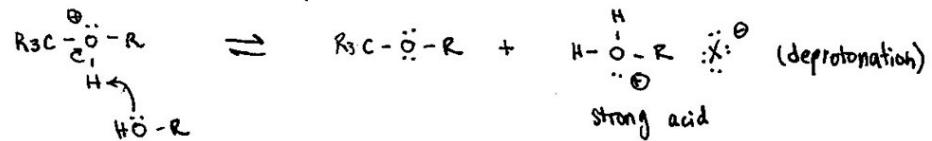


→ S_N1 Rxn

- Lewis acid-base association of carbocation and solvent

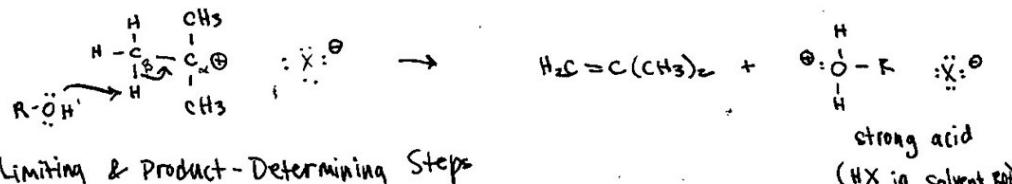


- Bronsted acid-base reaction deprotonates the ion to solvent



→ E_I Rxn

- solvent deprotonate β-carbon (R = CH₃)

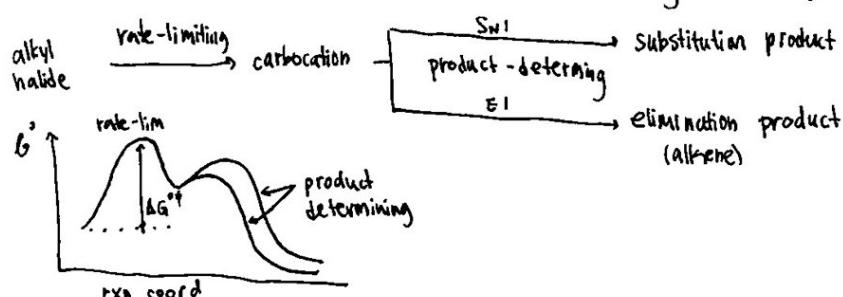


→ Rate-Limiting & Product-Determining Steps

- product-determining step - rate of steps determine ratio of products

- common first step is rate limiting

- individual steps of S_N1 and E_I are product determining (competing)



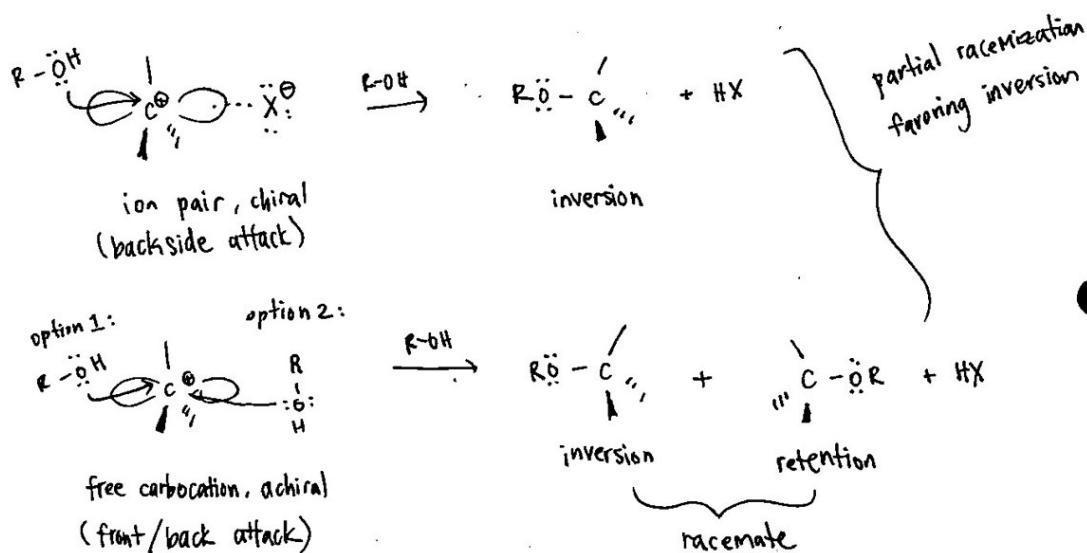
<< S_N1 & E_I Rxn (Cont.)

→ Reactivity & Product Distribution

- reactivity: tertiary > secondary > primary in alkyl halide
 - highly sub = stability of carbocation
- reactivity: I > Br > Cl > F in alkyl halide
 - leaving group ability ↑, stability ↑, rate ↑
- ↑ rate in polar, protic, donor solvent
 - accommodate charges
- ↑ alkyl sub in alkene, ↑ alkene stability, ↑ E_I rate
 - > 2 alkyl sub, ↑ E_I rate, ↓ S_N1 rate (but still occurs)
- rearrangement occurs

→ Stereochemistry of S_N1 Rxn

- partial racemate form due to achiral carbocation intermediate
 - carbocation could be attacked from both sides → racemate
 - carbocation could form ion pair with X⁻, blocking front attack
 - only back attack possible → inversion of stereochemistry
 - Overall, ↑ inversion, ↓ retention of stereochem
 - EE of inversion

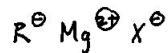


<< Organometallic Compound

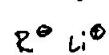
> organometallic compound - compound with C-M (carbon-metal) bond

→ Grignard Reagent & Organo lithium Reagent

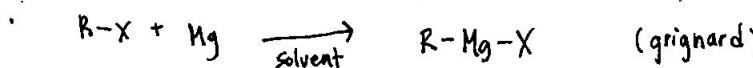
> Grignard Reagent - $R-Mg-X$ ($X = Br, Cl, I$)



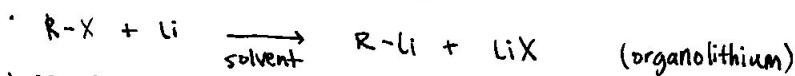
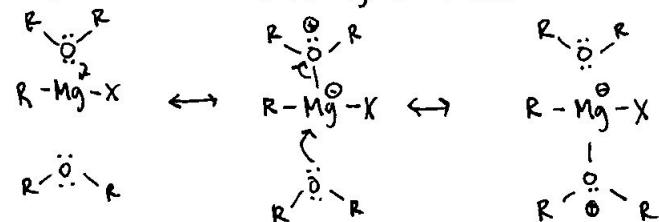
> Organo lithium reagent - $R-Li$ > strong base!



→ Formation of Grignard & Organo lithium Reagent



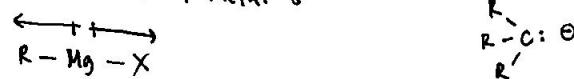
- Grignard reagent solvates in solvent by Lewis-acid-base interaction



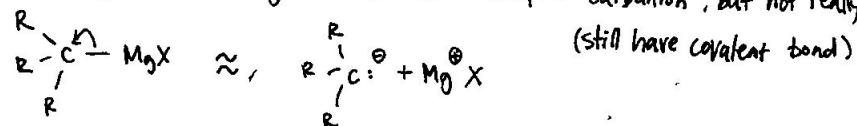
→ Protonysis of Grignard & Organo lithium Reagent

> carbonian - carbon with three bonds and an unshared e^- pair

- carbon has δ^- ; metal δ^+



- Grignard & organolithium reagent react as if they're carbonian, but not really

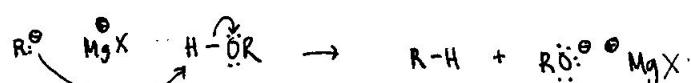


> protonysis - rxn with proton of an acid that breaks chemical bond

- Grignard & organolithium are strong base, reacting with weak acids (H_2O , alcohol).



as if...



- Grignard & organolithium cannot be prepared in moisture

- a way to prepare hydrocarbon from alkyl halide

<< Carbenes & Carbenoids

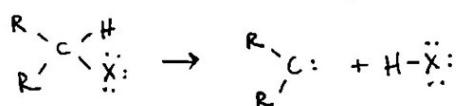
→ α -elimination rxn

> carbene - neutral species with divalent carbon atom

- zero formal charge, six valence e⁻ (2 short from octet)

- very reactive

> α -elimination - elimination of two groups from same atom



- β -elimination > α -elimination when possible

- alkene product from β more stable than carbene from α .

- carbene is e⁻-deficient, strong electrophile

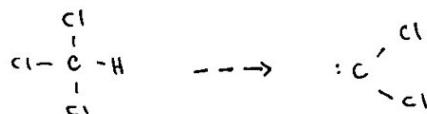
- carbene has unshared e⁻ pair, strong nucleophile

→ Cyclopropane Formation

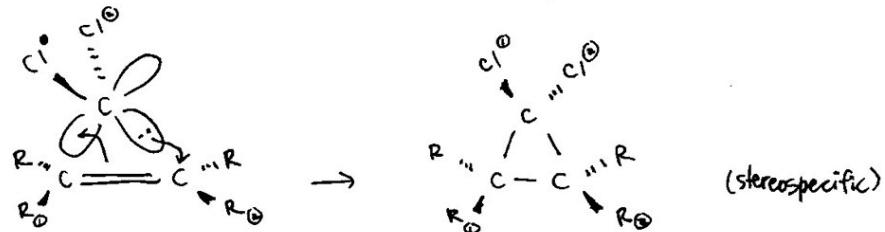
- carbene react with alkene both as nucleo- and electro-philic in alkene to yield cyclopropane.

- stereospecific syn-addition at step ②

① chloroform → dichloromethylene (carbene)



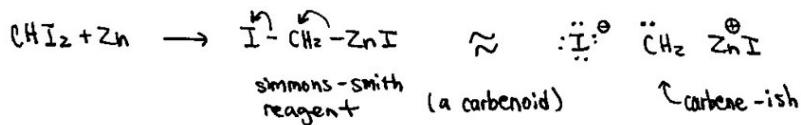
② carbene attack alkene → cyclopropane



<< Simmons-Smith Rxn

> cyclopropane formation without halogen: alkene + CH₂I₂ $\xrightarrow{\text{Zn-Cu}}$ cycloalkane.

> carbenoid - reagent that's not free carbene but has carbenelike reactivity



• overall: stereospecific syn-addition (as in cyclopropane formation) (carbenoid act like carbene)

