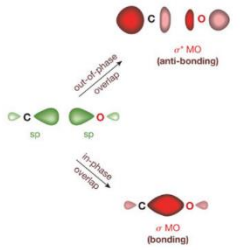
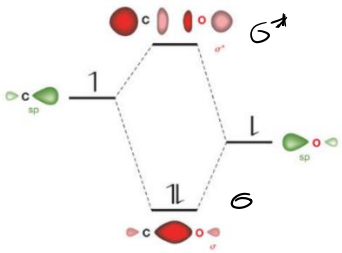
Mid 1:

- Formal charge: (Group #) – (# bonds) – (# bonded electrons)
- Incomplete octet: common with Be, B, Al -- Expanded octet: common with S, P, Xe



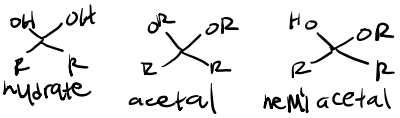
Anti-bonding molecular orbitals (*) result from **out-of-phase overlap**.

Bonding molecular orbitals result from **in-phase overlap**.



Sigma bonding stabilizes a molecule while sigma* (anti-bonding) destabilizes a molecule. 2 e- in sigma orbital & zero in sigma* means there is a net stabilization of the molecule

R—OH Alcohol	R—COOH Carboxylic acid	$NR_3/NR_2H/NRH_2$ Amine
R—O—R Ether	R—COOR Ester	R—NO_2 Nitro group
R—CO—R Ketone	R—CON—$R_2/RH/H_2$ Amide	R—C≡N Nitrile
R—CO—H Aldehyde	R—X (X=halogen) Halide	1=alkane, 2=kene, 3=kyne

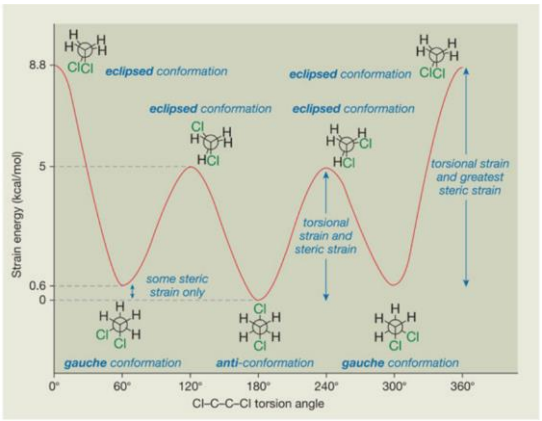


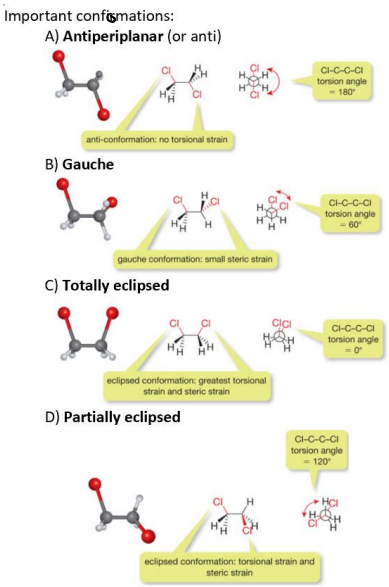
Longer chains = more SA = higher melting and boiling point
Branching of hydrocarbon = less SA = lower melting and boiling point
Ring structure = well packed atoms = increased IMF = higher melting and boiling point

Longer chains = lower solubility
Branched chains = less SA so easier for H_2O hydrogen bonds to remain = increased solubility over unbranched

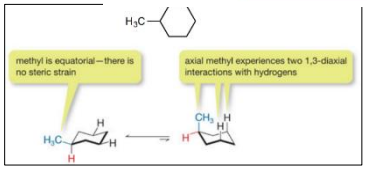
Polar protic: acts as HB donor and are miscible with water (eg. water, methanol, ethanol)
Polar aprotic: strong dipoles, HB acceptors, miscible with water (eg. acetone)
Polar organic: weak dipoles; no HBs (eg. ethyl acetate, $CHCl_3$)
Non-polar: Held by LDFs (eg. hexane, ether, benzene)

Torsional strain: repulsions in bonds on adjacent atoms (almost none in staggered, most in eclipsed)
Steric strain: repulsion from interpenetration of electron clouds – atoms that are close but not directly bonded; increases with size of groups as bigger electron clouds





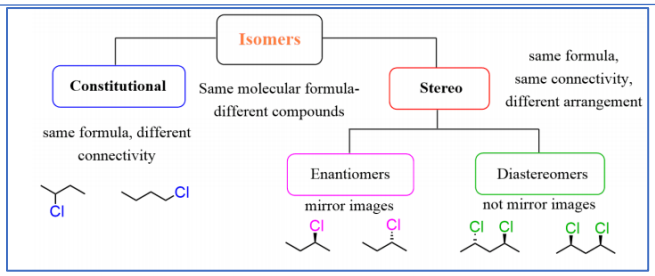
Cyclopropane: great angle strain **and** torsional strain; unstable
Cyclobutane: angle and torsional strain alleviated by **butterfly** conformation
Cyclopropane: little angle strain, torsional strain reduced by **envelope**
Cyclohexane: most stable in **chair** conformation

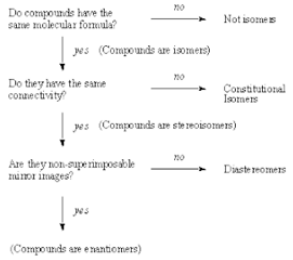


- Chair flip: axial up substituents → equatorial up // axial down substituents → equatorial down
- 1,3-diaxial interactions: steric strain that arises from substituent e- clouds separated by 2 carbon atoms

Cis isomer: two substituents on same face of the ring (both up, both down)
Trans isomer: one substituent bonded to each face of the ring

- Depending on cis/trans isomerization and positions of both substituents (1,2 , 1,4, etc.), both may be axial, equatorial, 1 each, etc.





Meso: molecules with more than one chiral centre and are **superposable** on their mirror image (same molecule)

- Possess internal plane of symmetry

Clockwise = rector = R, Counterclockwise = sinister = S

- If only one stereocenter, configuration indicated by italicized R or S in parenthesises at start of name
- If more than one center, a number indicating location precedes each configuration symbol

Drawing enantiomers: Draw mirror image, or invert chirality centre, or switch any two substituent groups

- If group switching is done **twice**, result is original compound

Estimating number of stereoisomers = 2^n , n=# of chirality centres – actual number can be lower due to meso (need to look at planes of symmetry within the molecules)

Enantiomers = all chirality centres switched, diastereomers = only some switched (diast's have 2+ stereocentres)

Double bond stereoisomers: *E*-name = highest priority groups are **trans**, *Z*-name = highest are **cis**

Melting point of enantiomers separately are higher than a mixture of two enantiomers due to altered packing arrangement

Optical rotation: Enantiomers rotate polarized light by same angle, but opposite directions

- Either **clockwise** (a>0, or d) or **counterclockwise** (a<0, or l)

Specific rotation [α] accounts for these parameters:

$$[\alpha] = \frac{\alpha}{c \cdot l}$$ ↘ λ

[α] = specific rotation
α = optical rotation
c = concentration of the solution in g/mL
λ = length of cell in dm

It is usually reported with temperature and wavelength of light used:

$$[\alpha]_{\lambda}^{T}$$

T = temperature
λ = wavelength

Convention is to use sodium-D line as light source (589 nm).

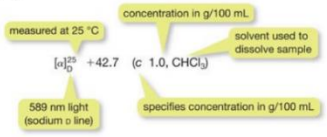
This is represented as $[\alpha]_D$

Most [α] measurements made using concentrations in g/100 mL

To correct for this concentration unit, use the following equation:

$$[\alpha]_{\lambda}^{T} = \frac{100\alpha}{c \cdot l}$$

Reporting [α]:



Solution can be **optically pure** (all molecules have the same configuration (1 enantiomer)), **racemic** (equal mixture of both enantiomers = no rotation), or somewhere in between

- Optical purity = ratio of specific rotation of a sample to the specific rotation of a pure enantiomer

$$\text{optical purity} = \frac{|\text{observed}[\alpha]|}{|[\alpha] \text{ of pure enantiomer}|} \times 100\%$$

$$\%\text{ee} = \frac{\left(\begin{matrix}\text{number of molecules} \\ \text{of isomer in excess}\end{matrix}\right) - \left(\begin{matrix}\text{number of molecules} \\ \text{of other isomer}\end{matrix}\right)}{\text{total number of molecules}} \times 100\%$$

Optical purity and %ee are numerically equivalent (optical purity = %ee). For a sample that is 70% optically pure (−), the remaining 30% is optically inactive. That inactive portion contains equal amounts of the two enantiomers. Thus 15% of the sample is (+) isomer and 85% is (−) isomer (70% excess + half of the inactive portion).

When drawing reaction mechanisms, draw lone pairs on heteroatoms and areas of electron movement

****Electrons generally move from nucleophilic regions to electrophilic regions****

- Nucleophilic: usually negative/lewis bases; Electrophiles: usually positive/lewis acids
- E-s flow from area of high electron density (lone pair or -) to low density (incomplete octet or +)

Resonance:

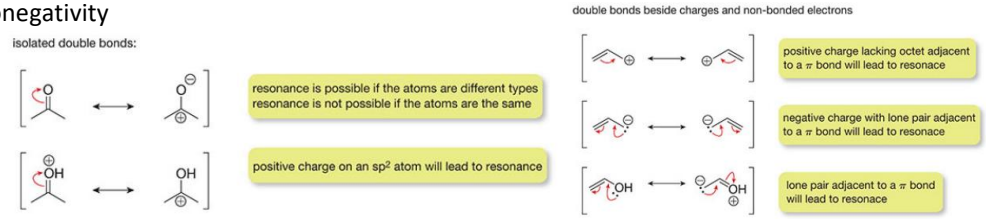
1. Pi bond made up of atoms with different electronegativities
2. Pi bond directly beside either (a) paired/unpaired electrons, (b) atoms with incomplete octets, (c) other pi bonds, (d) charged atoms lacking octets or carrying lone pairs
3. An atom with an incomplete octet adjacent to an atom with a pair of non-bonding electrons

Usually # of resonance structures = # pi bonds or conjugated lone pairs + 1

Highest quality resonance:

1. Most atoms with full octets, 2. Fewest number of formal charges, 3. Negative formal charges on electronegative atoms, positive on electropositive 4. Like charges as separated, opposite charges as close as possible

Insignificant forms: more than 2 formal charges in one group, breaking pi bond flow to atoms with inappropriate electronegativity



- Lower pKa value = greater acidity = more likely to be deprotonated by a base
- Need a stronger base to deprotonate a high pKa value Lewis acid (eg. C—H bond)

- Stronger acid = weaker conjugate base, weaker acid = stronger conjugate base
- Sharing electron density can weaken charge, makes it more stable
- More stable = resonance, delocalization of electrons (shared, free to move)

Estimates of relative acidities (by looking at stability of negative conjugate base)

1. **Electronegativity**: higher EN accommodates negative charge better: conjugate base with more EN atom with negative charge will be more stable; stronger acid
2. **Atomic size**: bigger size spreads out electron density on ion: bases with negative charge on bigger atoms are more stable; stronger acid
3. **Induction**: Electronegative atoms nearby the negative ion that can spread out electron density; depends on # of EN atoms and proximity to the charge, will stabilize base so stronger acid
4. **Hybridization**: atoms with orbitals of higher "s" character (sp>sp2>sp3) will be more stable for negative charge on their conj bases, therefore stronger acids
5. **Charge delocalization** (**resonance**): more resonance= stable – on base = stronger acid

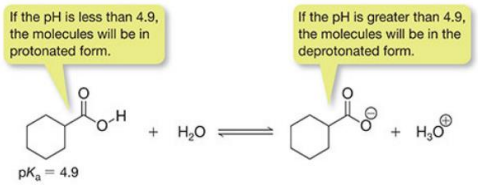
Estimates of relative acidities (by looking at positive acids)

1. **Electronegativity**: higher EN destabilizes positive charge; will be stronger acids
2. **Atomic size**: greater size = greater charge delocalization
    - Stronger acid will be with bigger atom carrying +
3. **Induction**: EN atoms nearby will INCREASE positive charge on cation and destabilize = stronger acid
   Alkyl groups though will STABILIZE positive charges by donating e- density = weaker acids
4. **Charge delocalization**: Less resonance for positive ion will lead to stronger acid

*B^- + **NH4+** ←→ NH3 + HB ---- pKa NH4+= 9.42 / B^- + **NH3** ←→ NH2- + HB ----- pKa NH3 = 41*

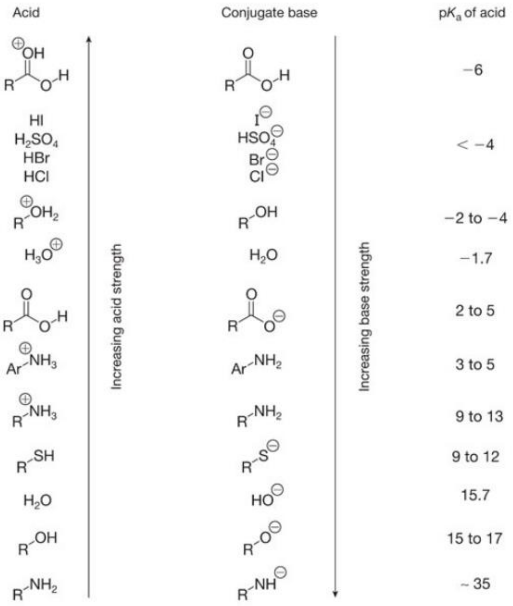
pKa of an acid can predict the protonation state of a particular acid

- Acids are primarily PROTONATED form when pH is less than pKa (COOH)
- Acids are primarily DEPROTONATED form when pH is more than pKa (COO-)



Lewis acid = electron pair acceptor, Lewis base = electron pair donor

- Common lewis acids = BF_3, BBr_3, $AlCl_3$, $FeCl_3$, $ZnCl_2$, $Hg(OAc)_2$



C–H 50
=C 42
≡C 25
N–H 35
O–H 16-18
H–F ~2
H–Cl ~7
H–Br ~9
H–I ~11

Mid 2: atom that replaces another atom in compound is lower in EN = REDUCTION

- Oxidation = loss of electrons [O], Reduction = gain of electrons [H] … accompanied by changes in H #'s

Carbonyl groups: electrophile @ positive carbon

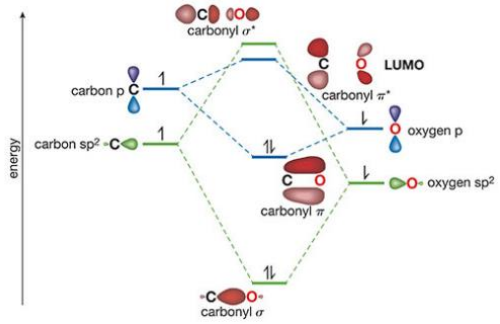
- Cannot add to areas with full octets (ex. Oxocarbenium) so move pi bond electrons up to electronegative atom to reveal unfilled carbon octet

1. **Hydride**: H- is carried by larger reagent ($NaBH_4$, $LiAlH_4$) → addition and reduction process
   - H- to carbonyl, rest of compound binds to negative oxygen; use acid/base with water for work-up
   - Overall: Carbonyl group → alcohol group
2. **Grignard:** bases – R-Mg-Br; formed by reacting R-Br halide and Mg^0 metal in ether (NO H_2O)
   - Carbon on Mg is neg, acts as nucleophile to carbonyl carbon → R group to carbonyl C, MgX+ to O- → workup: get rid of Mg-X on O with acid/water (hydrolysis)
   - Overall: New carbon-carbon bond between R-Mg-Br & carbonyl
3. **Organolithium:** Like Grignard, v strong bases so no water; formed from R-Br + 2Li $-Et_2O\rightarrow$ R-Li + LiBr
   - R to carbonyl C, Li+ beside O-, same workup as (2)
   - Overall: New carbon-carbon bond between R-Li & carbonyl
4. **Acetylides:** C≡C-H deprotonate to C- → formed from alkyne + $NaNH_2$ → Na^+ acetylide$^-$ + NH_3
   - Highly nucleophilic; reacts with carbonyl C (no H2O); then quenched like (2) to protonate O-
   - Overall: New alkyne-carbon-carbon bond using alkyne & strong base & carbonyl
5. **Cyanohydrin:** (CN-R-OH) – Net reaction of HCN across double bond by adding CN- first then strong acid
   - Negative C on CN- to carbonyl, H+ from strong acid (HCl) to O-
   - Can reverse by exposing cyanohydrin to basic conditions; OH deprotonated, O- recreates pi bond, CN- expelled as leaving group (LG =stabilize negative charge well, conjugate base of strong acid)
   - Overall: Creation of cyanohydrin from carbonyl, CN- and strong acid

LG examples (I^- is good LG as H–I is strong acid) → I^-, Br^-, Cl^-, HSO_4^-, H_2O

6. **Hydrate:** replacing C=O with HO-C-OH by addition of water and acid or base catalyst
    - If base: will be nucleophile: OH- to carbonyl C, O- takes H+ from H_2O, leaves hydrate + OH-
    - If acid: will be electrophile: H+ to O → OH^+, pi electrons up to neutralize, positive charge on C is electrophile, attracts water molecules (OH_2^+), H+ then removed by H_2O to restore acid
    - Equilibrium position for carbonyl + H_2O / Hydrate will favour carbonyl EXCEPT when electronegative groups on **R=**CO**=R** (poor resonance forms)
    - Overall: <u>Carbonyl to dihydroxy carbon (hydrate) by water addition and Acid/base catalyst</u>
7. **Hemiacetals:** sp_3 carbon connected to OH group and OR group; acid catalyzed ***alcohol*** addition to aldehyd
    - Acid activates O to OH+, pi bond up, alcohol O to carbocation, H_2O removes H+ to restore acid
    - Can occur intramolecularly with ***hydroxyaldehyde***
    - Overall: <u>Carbonyl to hemiacetal by alcohol addition and acid catalyst</u>

Acid cat: activates electrophile by converting O to O+ and pulling pi e-s
Base cat: activates nucleophile by adding to C and pushing e- to O (O-)
Choosing acid or base: look at pKa of intermediate that is formed; ex. Base addition to imine C forms N-, which is difficult and unstable to form (pKa=35), but acid addition to imine N is more stable & yield same result



Oxygen has more of sigma bond due to electronegativity, carbon has positive character

P orbital of oxygen closer in energy to pi orbital of C-O; electrons in pi orbital more likely found near oxygen

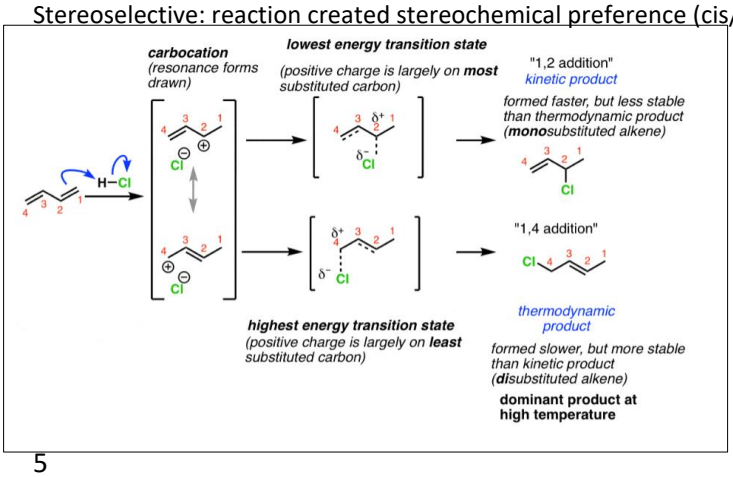
Nucleophile HOMO reacts with LUMO (largest pi*) of electrophile → found on Pi* antibonding orbital of carbon

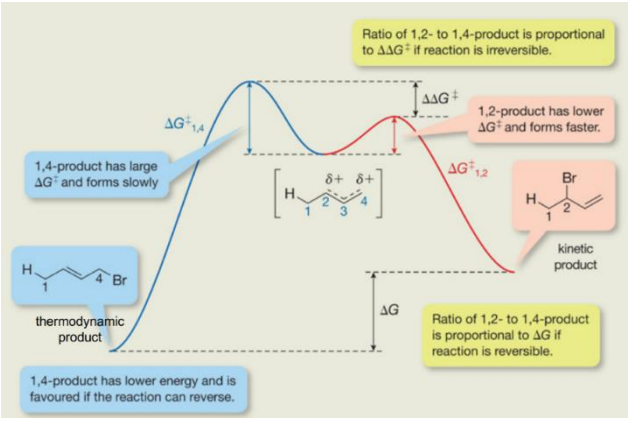
- Carbonyl is planar; add to either face → if carbonyl is asymmetric then enantiomers formed in racemic mixture
    - But, presence of substituent groups can favour addition of one side; if large chain on one side, nucleophile will favour approach from other side due to steric strain

Pi bond nucleophiles
- P orbitals are more reactive, less stable, accessible (alkenes, alkynes, dienes, enols)

Regioselectivity of electrophilic addition is controlled by **carbocation stability**
- Regioisomers form based on regioselectivity (different locations in a molecule) – most stable carbocation will be major regioisomer formed (**markovnikov rule**)
- Stability based on **hyperconjugation** ($3^0>2^0>1^0$ stability), and resonance/electron+charge delocalization)

Regioselective: reaction occurs more likely at a specific region of the molecule
Stereoselective: reaction created stereochemical preference (cis/trans addition)





Carbocation rearrangements: can occur from *hydride shifts* to move positive charge to more substituted C
Hammond postulate:

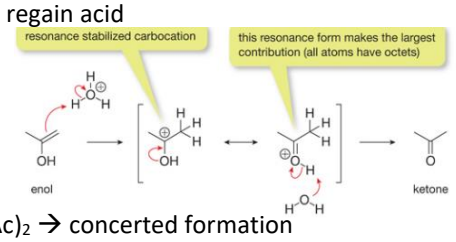
- Structure of transition state resembles the species nearest to it in free energy
- More stable carbocations have lower energy transition states for their formation

Markovnikov additions: (major product is formed from the most stable carbocation)

1. **Addition of haloacids to alkene:** pi bond breaks and bonds to hydrogen of H-X, leaving carbocation and X^- → H on least substituted carbon so most substituted has positive charge
    - X^- will then attach to carbocation
    - Overall: <u>alkene + haloacid = alkyl halide</u>
        - Regioselective (carbocation stability)

    Addition of haloacids to alkyne: requires 2 molecules of haloacid, but net addition of one across triple bond → X- breaks off and adds to more substituted carbon – pushes electrons to other side of bond and attracts H+ of other H-X
    - Overall: <u>alkyne + 2 haloacid = alkyl halide + 1 haloacid (net addition of 1)</u>
        - Regioselective (X- to substituted C)
        - Stereoselective (H and X finish *trans* to each other)
2. **Addition of H_2O to alkene (acid-catalyzed):** needs acid catalyst; H+ from H_3O+ to less substituted site, H_2O to carbocation, then H+ from H_2O+ removed by another H_2O to recover original acid
    - Overall: <u>alkene + water + acid → alcohol + acid</u>
        - Regioselective (Initial H+ to least substituted C so carbocation forms on most stable C)

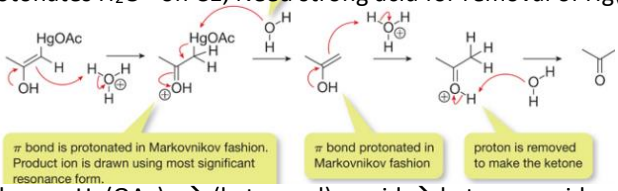
    Addition of H_2O to alkyne (acid-catalyzed): H_2O to more stable C of triple bond, pushes pi e- to other side of double bond, attracts H+ from H_3O+ -- H_2O removes H+ from H_2O+ on C1 to regain acid
    - Forms a **keto-enol** → tautomerization into ketone
    - Overall: <u>alkyne + water + acid → (keto-enol) + acid → ketone + acid</u>
        - Regioselective (H_2O to more substituted C)
        - Stereoselective (H_2O and H trans to each other)



3. **Addition of water to alkenes (oxymercuration-demercuration):** Use of $Hg(OAc)_2$ → concerted formation of mercurinium ion as both sides of double bond bind to Hg; becomes Hg+--OAc, second OAc is LG
    - C-Hg that is more substituted donates e- to the Hg, C becomes C+, H_2O will attach
    - OH_2+ deprotonated by OAc- to leave OH; HgOAc can be removed with **$NaBH_4$ & EtOH**
    - Overall: <u>Alkene + $Hg(OAc)_2$ → Alcohol</u>
        - Regioselective (carbocation forms on more stable carbon; H_2O attacks more subst.)

    Addition of water to alkynes (oxymercuration-demercuration): H_2O to more substituted C → C on other side of bond binds to $Hg(OAc)_2$, OAc^- leaving group
    - OAc- deprotonates H_2O+ on C1, Need strong acid for removal of Hg(OAc) and keto-enol tautom.

no discrete C+ intermed.



    - Overall: <u>Alkyne + $Hg(OAc)_2$ → (keto-enol) + acid → ketone + acid</u>
        - Regioselective (carbocation forms on more stable carbon; H_2O attacks more subst.)
        - Stereoselective: H_2O and $Hg(OAc)_2$ trans addition
4. **Addition of halogens (X_2) to alkene:** dipole induced into diatom, positive dipole halogen concerted bind to both sides of double bond (X+), leaving X- → carbocation forms on most stable carbon and X- bonds to that spot same time
        - Regioselective: X- attacks more substituted carbon as that is where carbocation forms
        - Stereoselective: X+ and X- add to opposite sides of double bond → trans addition

- Overall: Alkene + X_2 → dihalogenated alkane

Addition of hypohalous acid to alkene: same first stem as halogenation, but instead of X^- acting as nucleophile, it will be H_2O → H+ is removed by another H_2O to leave OH

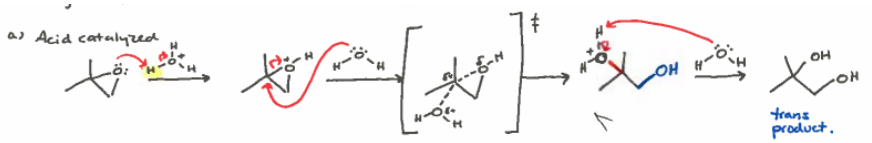
- Overall: Alkene + X_2 + H_2O → halohydrin + X- + H_3O+
  - Same regio/stereoselectivity as halogenation of alkene

Addition of halogens (X_2) to alkynes: 2 X_2 are required, net addition of 1X_2 across double bond

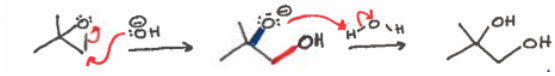
- Negative X- leaves X+, attacks triple bond at more substituted carbon, other carbon attacks X+ of other diatom, X+ separates and X- leaving group
- Overall: Alkyne + 2X_2 → dihalogenated alkene + X_2
  - Regioselective: X- attacks more substituted carbon as that is where carbocation forms
  - Stereoselective: X+ and X- add to opposite sides of triple bond → trans addition

5. **Epoxidation of alkene:** Concerted bond between alkene bonds and oxygen from peracid (mCPBA) to form epoxide and carboxylic acid
   - Stereoselective as C-O bonds both on same side of alkane (triangle)

   Opening of epoxide (acid catalyzed): based on carbocation stability – Nu- to most substituted carbon
   - Regioselective: Nucleophile (H_2O) adds to most substituted carbon
   - Stereoselective: H_2O adds trans to epoxide oxygen



   Opening of epoxide (base catalysed): based on sterics, no electronic preference – Nu- to least substituted
   - Regioselective: Nucleophile (OH-) to least substituted C
   - Stereoselective: Trans addition



   - Overall: Epoxide + H_2O + (acid/base catalyst) → trans-diol

Anti-markovnikov addition: nucleophilic atom on the carbon of the alkene that is less stable carbocation

Hydroboration (BH_3) of alkenes: BH_2 will add to less substituted carbon, H- adds to same face on more substituted carbon → BH_2 converted to OH with H_2O_2/NaOH

- 1 Borane can react 3x for reaction; each time slower
  - Regioselective: BH_2 to less substituted C (sterics), H- to more substituted side (as C-H bond forms slower, so carbocation will be stabilized on more sub't carbon
  - Stereospecific: cis (syn) addition, same face
- Overall: Alkene + BH3 + H_2O_2/NaOH → anti-markovnikov alcohol

Hydroboration ($BHCy_2$) of alkynes: same concept except can't use BH_3 → too reactive

- Syn addition, forms anti-markovnikov keto-enol → tautomerizes into ketone/aldehyde
  - Regioselective (same reasons)
  - Stereospecific (same reasons) technically
- Overall: alkyne + $BHCy_2$ + H_2O_2/NaOH → anti-markovnikov ketone/aldehyde

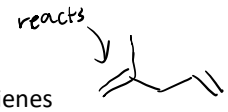
Hydrogenation of double bonds:

- H_2 and Pd (catalyst) added to alkene; cis addition of H_2 across bond = reduced to alkane

Hydrogenation of triple bonds:

- H_2 and Pd (catalyst) added to alkyne; cis addition of H_2 x 2 = reduced to alkane
- H_2 and Lindlar's catalyst added to alkyne; cis addition of H_2 x 1 = reduced to alkene
  - Created cis alkene product

} stereospecific

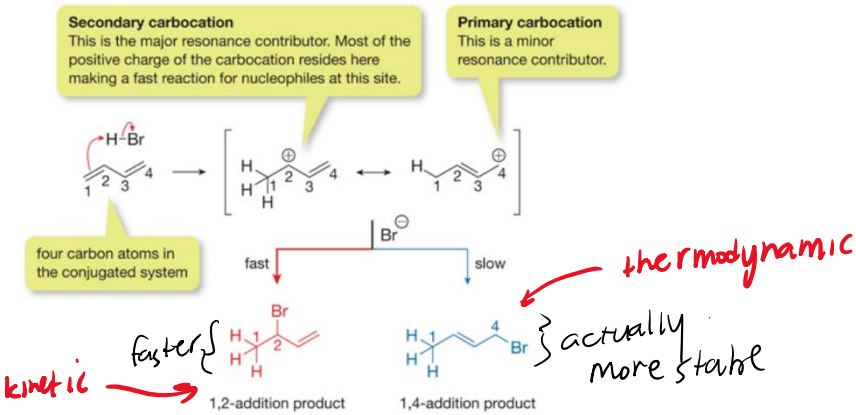


Isolated dienes: alkenes separated by 1+ sp3 atom, no delocalization between dienes

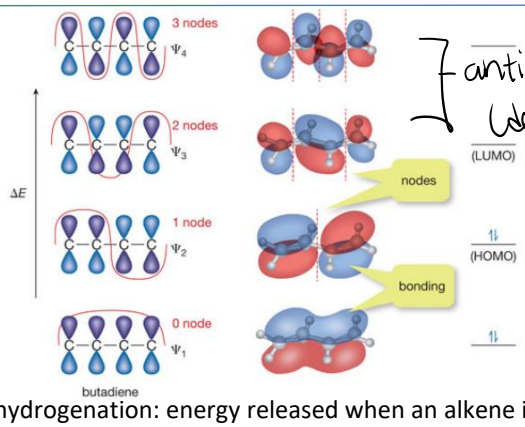
- Addition to dienes: will be fastest on most tertiary, slow on secondary, and very slow on primary carbocation → major product will be whichever forms fastest (most stable)
  - Regioselectivity: (i) more substituted double bond reacts, (ii) more stable reactive intermediate/carbocation forms with breaking of (i)

Conjugated dienes: alkenes not separated; all sp2, delocalization across all 4 carbons

- More substituted double bond reacts and formation of carbocation; can move due to resonance with other double bond
- More stable carbocation (reac. Int.) will react faster and form kinetic product; **BUT,** more stable <u>product</u> will have double bond in the middle, forms thermodynamic product
  - Thermo. Prod. Is actually more stable; let rxn sit and stir to obtain it



Exam:

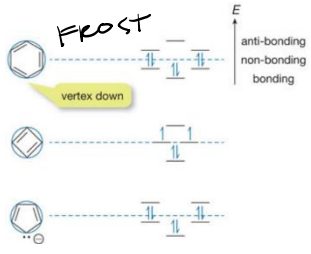


LUMO = Lowest Unoccupied Molecular Orbital
HOMO = Highest Occupied Molecular Orbital

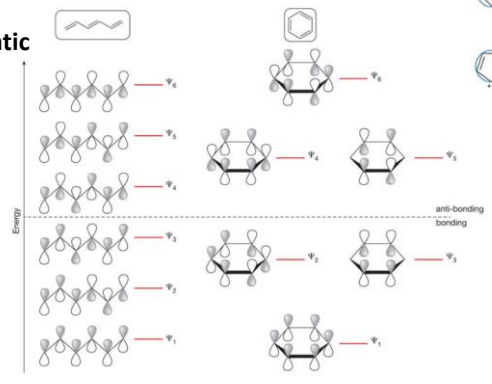
Heat of hydrogenation: energy released when an alkene is saturated to an alkane by hydrogenation

- Lower H_H means increased stability (eg. more conjugated) → aromatics have low H_H compared to alkenes

Criteria for aromaticity: (1) Be cyclic, (2) Have a p orbital on all participating ring atoms (eg. all sp or sp_2 hybridized), (3) Be planar, (4) Have 4n+2 pi electrons delocalizing in the ring, where n is an integer value (Huckels)



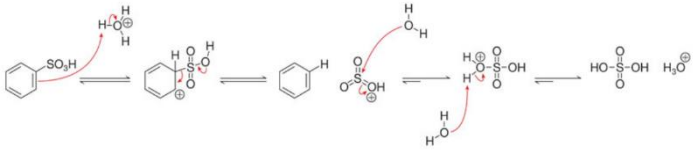
- All properties except (4): **Anti-aromatic**
- All properties except (2) or (3): **Non-aromatic**



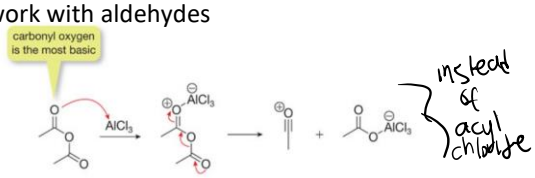
Electrophilic aromatic **substitution**:

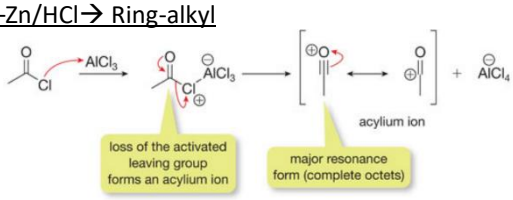
1. Addition of an electrophile using pi electrons, forms carbocation on adjacent carbon
2. Elimination of hydrogen by base, which restores aromaticity

1. **Halogenation**: Ring halogenated with X_2 to form Ring-X + HX → needs halogen-dependent catalyst for reaction to occur
   - F=none, Cl=$FeCl_3$, Br=$FeBr_3$, I=$CuCl_2$, catalyst bonds to X_2, then cat-X act as LG while other X is attacked by electrophilic ring
   - Cat-X will then deprotonate same carbon X is attached to on ring, forming HX & restores aromat.
   - Overall: Ring + X_2 + catalyst → Ring-X + HX + catalyst
2. **Nitration:** nitronium (NO_2^+) first formed by deprotonation of H_2SO_4 by HNO_3, then dehydration of H_2NO_3
   - Pi electrons to N^+ of nitronium, deprotonation of H by H_2O
   - -NO_2 can become -NH_2 with (a) Fe or Sn and (b) HCl
   - Overall: Ring + HNO_3 + H_2SO_4 → Ring-NO_2 + H_3O^+ + HSO_4^-
3. **Sulfonation:** sulfonic acid (HSO_3^+) formed by deprotonation of H_2SO_4 by SO_3 → same process as (2) except base is HSO_4^- in this case
   - Can be reversed by strong acid addition

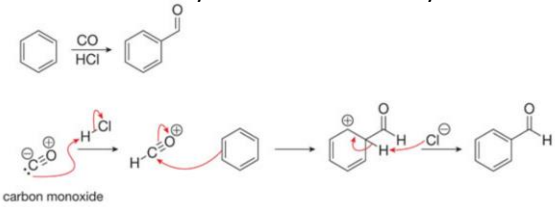


4. **Friedel-Crafts Alkylation**
   - Using R-Cl and $AlCl_3$ to form carbon-carbon bond to ring: R-Cl-$AlCl_3$ complex forms and $AlCl_4$- leaves R+, R+ attacked by pi electrons onto ring, H+ removed by $AlCl_4$- to form HCl and $AlCl_3$
   - Limitations
     - Carbocations not reactive enough to react with deactivated rings (nitrobenzene)
     - Alkyl groups are e-donating so product is usually more reactive than starting reactant, can add alkyl group more than once possibly
     - Carbocations rearrange to stabilize charge (alkyl/hydride shifts) → 1° and 2° to stable 3°
5. **Friedel-Crafts Acylation**
   - Same as (4) but use acyl group instead (ketone) → form acylium ion in same way with $AlCl_3$
   - Use Zn/HCl or NH_2NH_2/KOH to reduce/remove carbonyl group
   - Product of acylation **less reactive** than products, and provide clear route to product
   - Overall: Ring + acyl group-Cl + $AlCl_3$ →Ring-ketone + $AlCl_3$ + HCl –Zn/HCl→ Ring-alkyl
   - Does not work with aldehydes





6. **Gatterman-Koch**: yields aromatic aldehydes



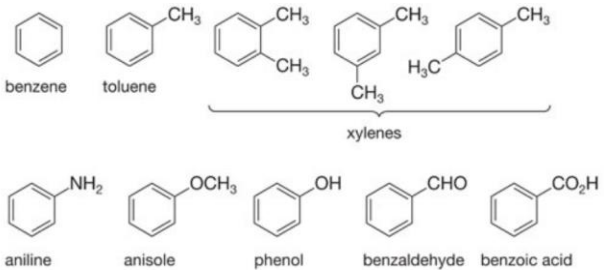


TABLE 10.2 Aromatic Substituents' Effect on the Rate of Reaction and the Regioselectivity of Incoming Groups

Substituent	Features	Reactivity	Direction
NH_2, NHR, NR_2, OH, O^-	Lone pair on heteroatom	Strongly activating	*Ortho/para*
NHCOR, OCOR	Electron-delocalized lone pair on heteroatom	Moderately activating	*Ortho/para*
Alkyl, aryl	Hyperconjugation or weak electron delocalization	Weakly activating	*Ortho/para*
F, Cl, Br, I	Lone pair on electronegative halogen atom	Deactivating	*Ortho/para*
COH(R), CO_2H(R), CONHR, CN	Polar π bond conjugated to ring	Moderately deactivating	*Meta*
NO_2, NR_3^+, CX_3	Strong inductive electron-withdrawing group	Strongly deactivating	*Meta*

cross-conjugation

Directing groups:

- Activating vs deactivating, and ortho/para vs meta

1. **Activ.** Strong ortho-para directors: have lone pair on heteroatoms that delocalize in the ring via resonance
    - Positive charge can only be adjacent to heteroatom if E+ is placed ortho or para
    - Ortho/para: 4 resonance with carbocat. Vs meta: only 3
    - Para is preferred due to sterics of substituent
2. **Activ.** Moderate ortho/para
    - Lone pair heteroatom already delocalized in the substituent group
    - Same principles, but less than (1) due to **cross-conjugation**
3. **Activ.** Weak ortho/para
    - (a) Alkyl groups → hyperconjugation so has weak electron donating character
    - (b) Aromatic ring substituent → very weak O/P
4. **Deactiv.** Ortho/para director
    - Halogens deactivate due to high electronegativity & poor orbital overlap for 2p ring and lone P (3/4/5p for Cl/Br/I)
    - Still act as ortho/para due to weak resonance effect (electron donate in theory)

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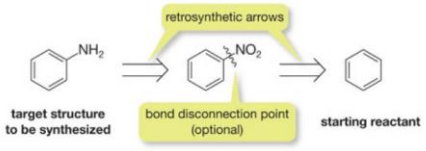
5. **Deactiv.** Moderate meta
    - Polar pi bonds connected to electronegative atoms and conjugated to the ring
    - Meta placement allows EWG to not directly attach adjacent to carbocation, and therefore not become *extra* destabilized → lowest E pathway
    - All have 3 resonance, but meta will be the only one with positive charge next to EWG
6. **Deactiv.** Strong meta
    - Due to strong inductive effects (NO_2, NR_3^+, CX_3)
    - Same principles

- When multiple substituents are present, the **collective** effects of directing groups must be considered (eg. weak vs strong, activating vs deactivating, ortho/para/meta etc.)

Synthesis: Assembling new substances
Retrosynthesis: Planning synthesis (backwards)

- Use disconnection, an imaginary "reverse" arrow



NOTE: Friedel-Crafts Alkyl/Acyl reaction does not occur in deactivated ring