

Four Factors In Nucleophilic R_NU.S

Factor	S _N 1 (usually occurs together with E ₁)	S _N 2 (1° or 2° if used strong base & normal 2°)	E ₁ (usually occurs together with S _N 1)	E ₂ (often occurs with S _N 2)
Substrate	Cation stability is what matters because of carbocation intermediate. more highly substituted is better.	Steric Hindrance won't let highly substituted substrates react. The less hindered the better.	Cation stability most important. same intermediate as S _N 1. The more highly substituted the better.	Must be able to get H & leaving group in same plane. Anti-periplanar Best.
Nucleophile or Base	Does not affect S _N 1 R _N U.S because not in rate-limiting step	The better the nucleophile the faster the reaction (less stable (- charged) & highly basic favored.)	Does not affect E ₁ same as in S _N 1.	This reaction is favored whenever strong bases are used. Usually KOH or NaOH or sterically hindered bases like (CH ₃) ₃ CO ⁻ K ⁺
Leaving Group	good leaving groups (more stable anion, or more acidic) favored for S _N 1	good leaving groups favored for S _N 2 just like S _N 1	good leaving groups favored as in S _N 1	Best if it can be anti-periplanar. Must be planar with an H.
Solvent	Polar solvents favored. Can be protic or aprotic unlike S _N 2	Should be polar & aprotic (no H ₂). Protic solvents solvate nucleophile	Not very important. Use ^{opposite} ethanol.	Not very important. Use ethanol

3° or stable 2°

1° or 2° if used strong base & normal 2°

3° or stable 2°

1°, 2°, or 3° whenever if strong base

How to tell which nucleophilic mechanism takes place

1. Look at carbon substrate & determine how substituted it is. i.e. is it 1°, 2°, or 3°

- Be careful to keep these straight. They are different from just carbons, you are labeling alkyl halides.

For example

P. 78: naming alkyls: $\begin{array}{c} \text{H} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{H} \end{array}$ is 1° & $\begin{array}{c} \text{R} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{H} \end{array}$ is 2°

labeling alkyl halides:

$\begin{array}{c} \text{X} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{H} \end{array}$ is 1°, $\begin{array}{c} \text{X} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{R} \end{array}$ is 2°, & $\begin{array}{c} \text{R} \\ | \\ \text{R}-\text{C}-\text{X} \\ | \\ \text{R} \end{array}$ is 3°

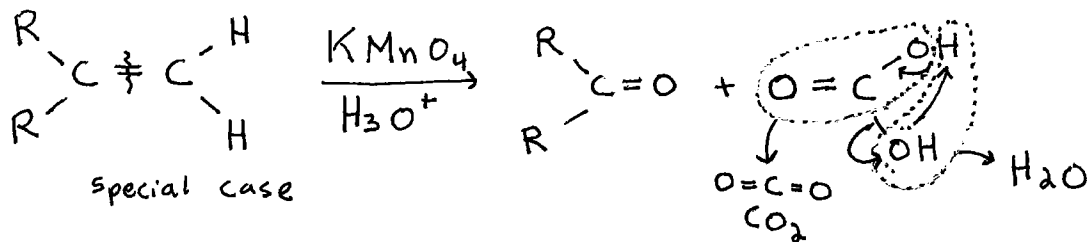
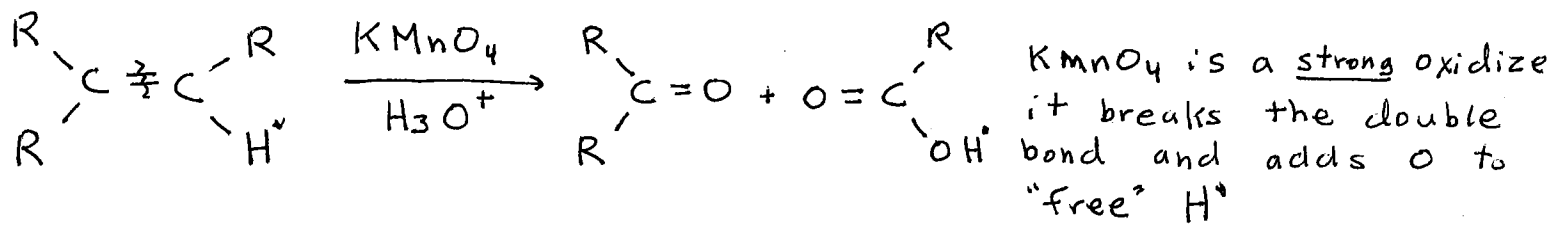
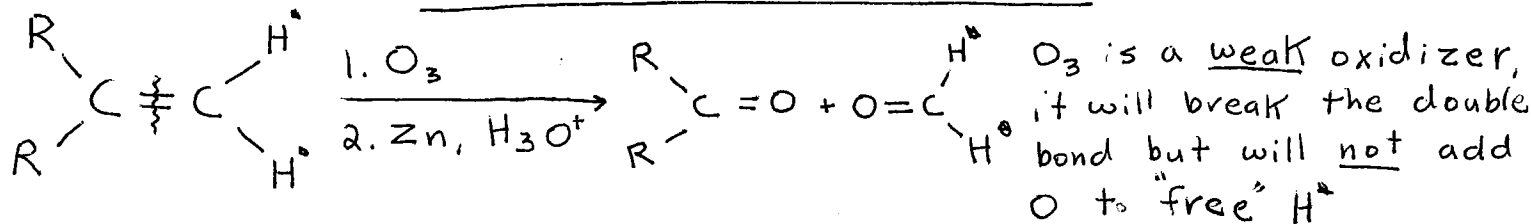
2. Look at conditions:

- If 1° ($\begin{array}{c} \text{X} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{H} \end{array}$): This will be either SN2 or E2. It will be SN2 unless a strong, sterically hindered base is used.

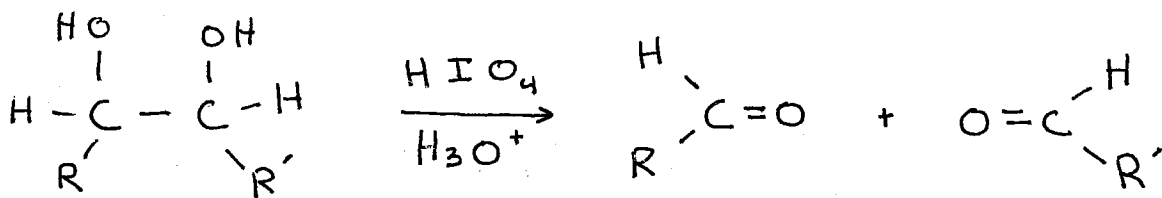
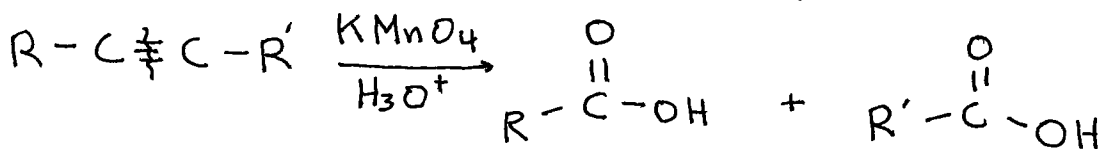
- If 2° ($\begin{array}{c} \text{X} \\ | \\ \text{R}-\text{C}-\text{H} \\ | \\ \text{R} \end{array}$): This will be SN2 or E2 unless C is allylic ($\text{C}=\text{C}-\begin{array}{c} \text{X} \\ | \\ \text{C}-\text{H} \\ | \\ \text{R} \end{array}$) or benzylic ($\text{C}_6\text{H}_5-\begin{array}{c} \text{X} \\ | \\ \text{C}-\text{H} \\ | \\ \text{R} \end{array}$) & protic solvents are used; then it will be both SN1 & E1. If those conditions are not met it is SN2 & E2: if weakly basic nucleophile in polar aprotic solvent it is SN2; if strong base is used it is E2. strong bases: $\text{CH}_3\text{CH}_2\text{O}^-$, OH^- , NH_2^- , KOH , NaOH .

- If 3° ($\begin{array}{c} \text{R} \\ | \\ \text{R}-\text{C}-\text{X} \\ | \\ \text{R} \end{array}$): This will be SN1 & E1 unless a strong base is used it will be E2. Weak base, Ethanol & heat (mild conditions) make both SN1 & E1 reactions

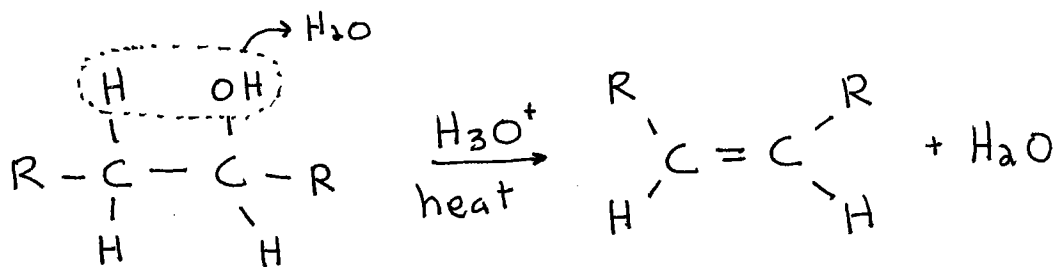
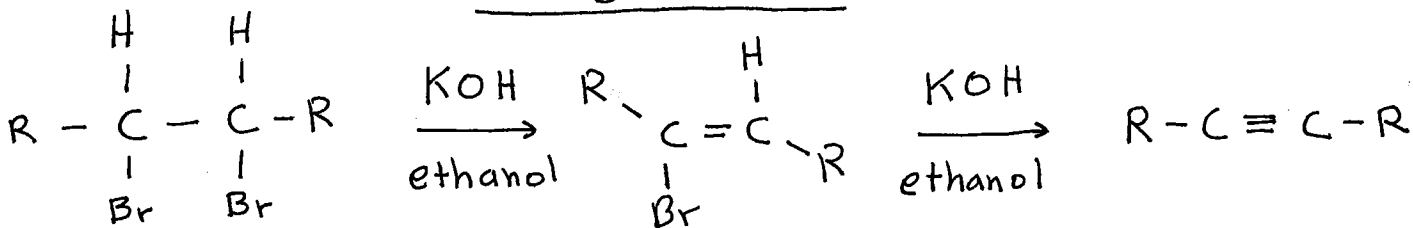
Cleavage Reactions



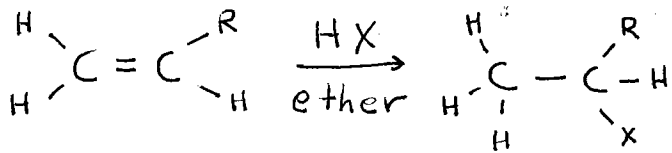
This is how the book gets CO_2 , they don't show this so it is often confusing.



Dehydration (forming double/triple bonds)



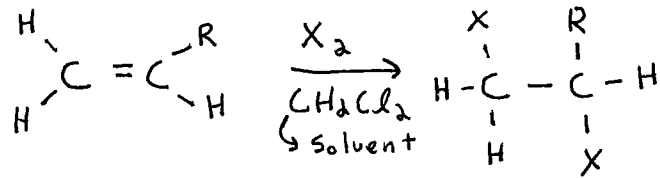
Adding Halogens



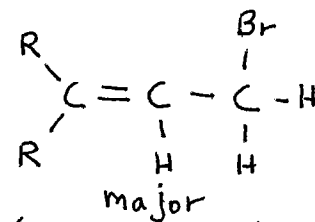
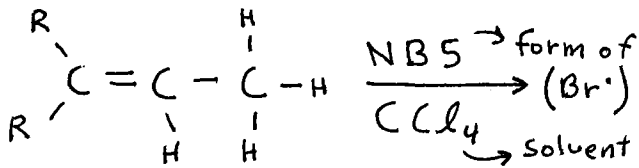
$x = \text{Cl, Br, F or I}$

Markovnikov addition of x
X adds more substituted

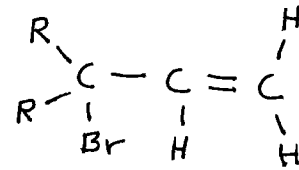
same for alkynes
but reaction can happen twice



anti-addition



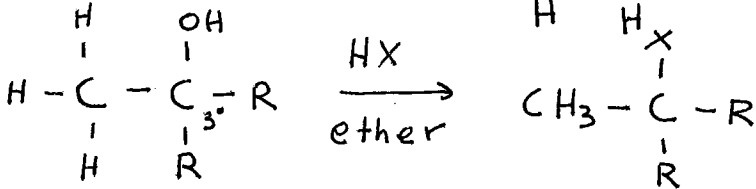
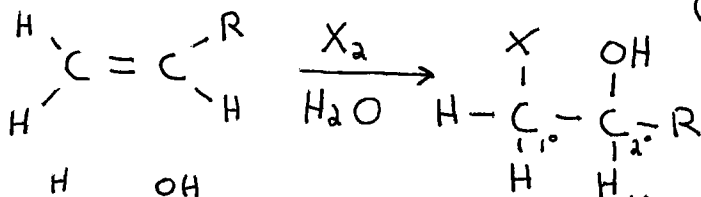
major
(more substituted double bond)



minor
(less substituted double bond)

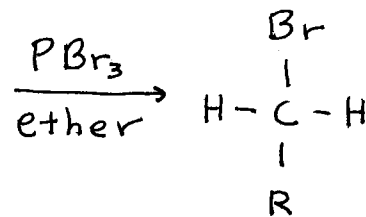
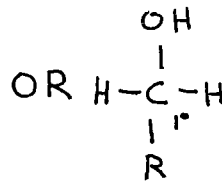
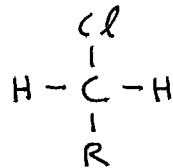
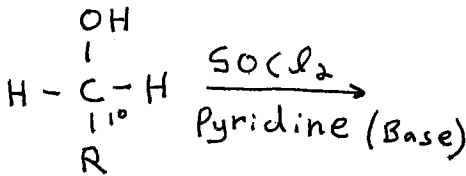
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The OH follows Markovnikov rules

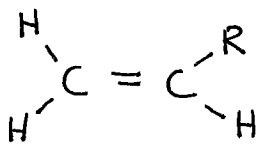


$3^\circ > 2^\circ > 1^\circ$ only works well with 3° because there is a carbocation intermediate

for 1° and 2° alcohols use the following:

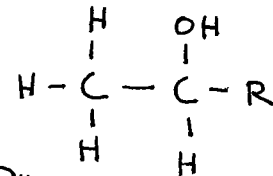


Adding -OH

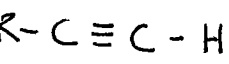


1. $\text{Hg}(\text{OAc})_2, \text{H}_2\text{O}, \text{THF}$

2. $\text{NaBH}_4 \rightarrow$ source of (H^-)

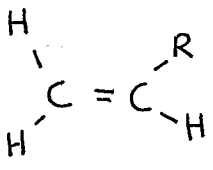
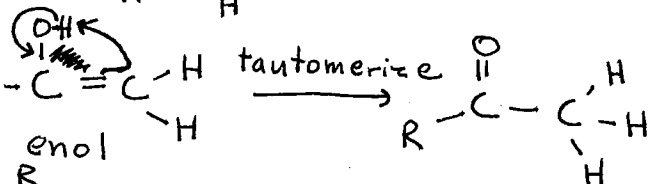


Markovnikov and -OH more sub



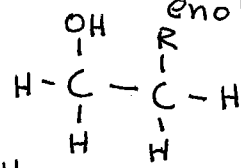
H_2SO_4 (acid), H_2O

HgSO_4 (similar to $\text{Hg}(\text{OAc})_2$)

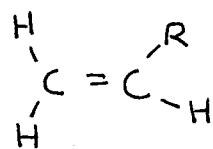


1. BH_3, THF

2. $\text{H}_2\text{O}_2, \text{H}_2\text{O}$

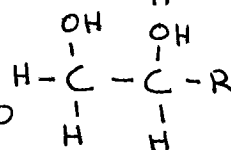


non-markovnikov -OH less sub
2nd step of reaction replaces BH_2 with OH

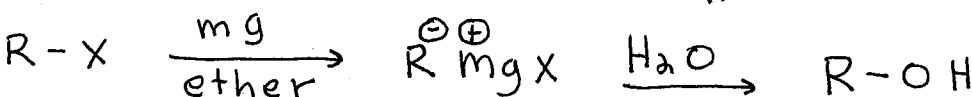


1. OsO_4

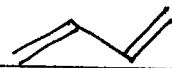
2. $\text{Na}^\oplus \text{HSO}_3^\ominus, \text{H}_2\text{O}$



Syn (same side addition)



Conjugated Dienes (CH 14)

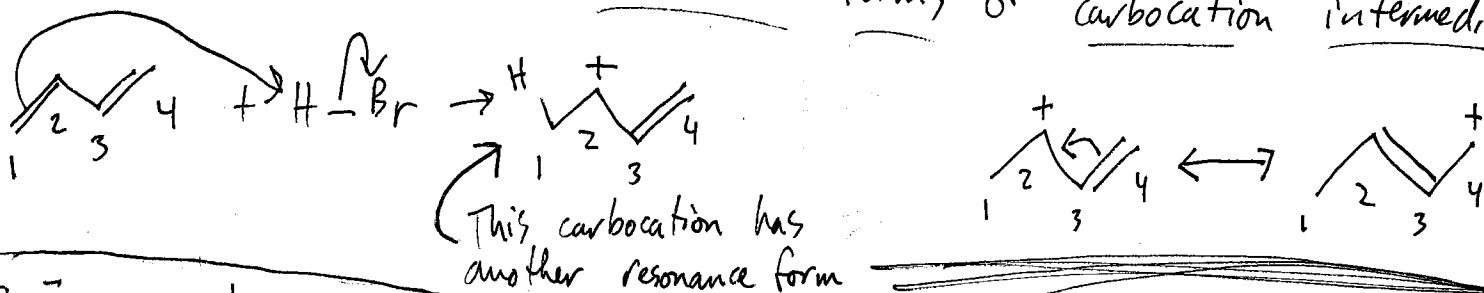


In Addition Rxns conjugated dienes () give 2 products per double bond. These are "1,2 Addition" & "1,4 Addition" products.

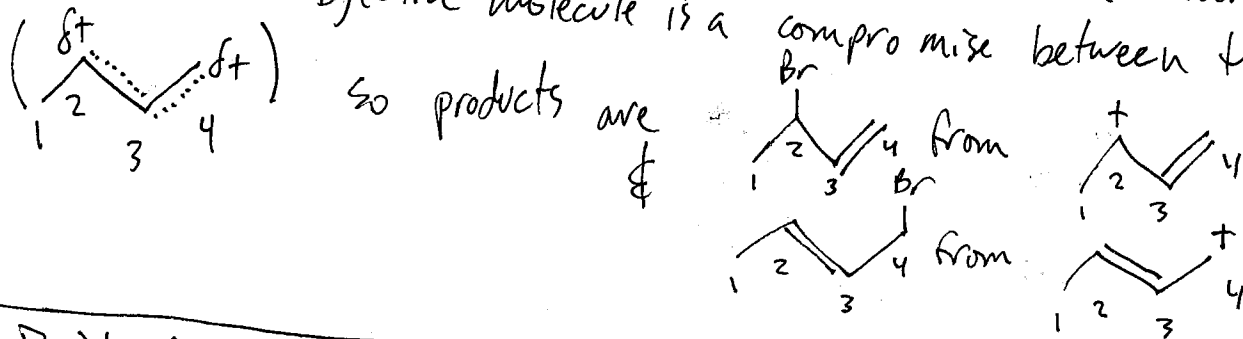
1,2 Addition product \rightarrow b/c H is on C₁ & Br is on C₂

1,4 Addition product \rightarrow notice now double bond is between C₂ & C₃

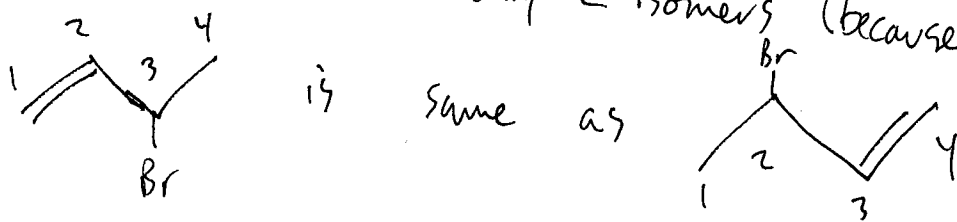
This is because of resonance Forms of carbocation intermediate



Br⁻ can then add to either of the resonance variations because the actual objective molecule is a compromise between the two

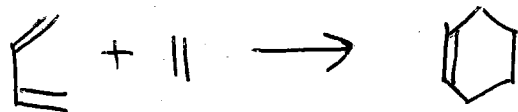


Don't forget you can get up to four isomers from 2 double bonds because you get 2 isomers per double bond. A similar rxn. occurs with addition to double bond between C₃ & C₄. Be careful! Some "isomers" may actually be the same molecule, for example for molecule above there are only 2 isomers (because of symmetry).

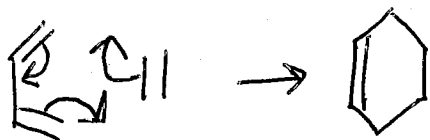


Conjugated Dienes p. 2 (CH 14)

Diels-Alder Rxn.

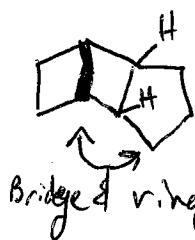


Notice there are 3 Xtra bonds in reactants (3 double bonds) & 2 new bonds in product with just 1 double. The # of bonds stays the same because the new bonds come from the double bonds.



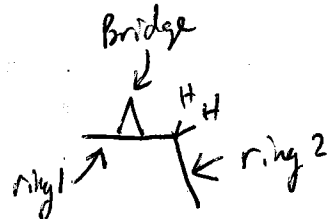
Things To Know About Diels-Alder

- The diene must be able to have this conformation or rxn. can't happen for example C1=CC=CC1 is a conjugated diene but can't undergo Diels-Alder
- If X alkene piece is alkyne \equiv then results in double bond
- If reactants are both rings product is Endo



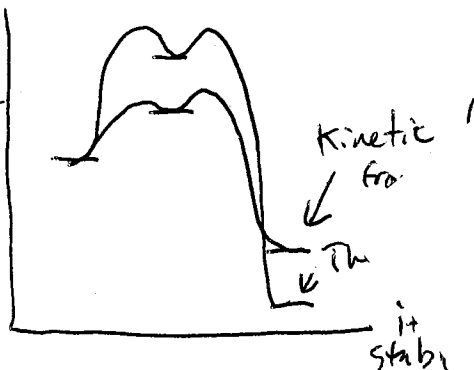
Bridgehead rings are "trans-like"

seen from side would look like



Kinetic vs. Thermodynamic Control

The main difference between kinetic & Thermodynamic Control is that in Kinetic Control (0°C) the rxn. is one-way $A + B \rightarrow C$ & in Thermodynamic Control (40°C) the rxn. is reversible $A + B \rightleftharpoons C$. The result of this is that under Kinetic Control the product from the more stable intermediate predominates. Under thermodynamic Control the more stable product predominates.



Aromaticity (CH 15)

- Aromatic compounds are extremely stable
- A compound is aromatic if it is:
 1. planar
 2. cyclic
 3. Follow's Huckel's $4n+2$ rule (This only directly applies to monocyclic compounds)

• Huckel's rule is an aromatic compound must have $4n+2$ π electrons, n has nothing to do with the compound itself, but rather is any positive integer. It is just a formal way of saying a compound must have 2, 6, 10, 14, 18, 22, 26... etc. π electrons

Because of added stability compounds will do anything to become aromatic including showing abnormal orbital character.

For Example:



is unusually acidic because



is planar w/ $6\pi e^-$ & therefore Aromatic

In



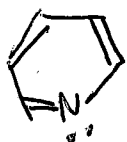
N is sp^3 hybridized & tetrahedral

In



N is sp^2 hybridized making it planar & putting the lone pair into a p-orbital giving the compound $6\pi e^-$ & making it Aromatic

In



However lone pair is in sp^2 orbital & does not contribute to conjugated system

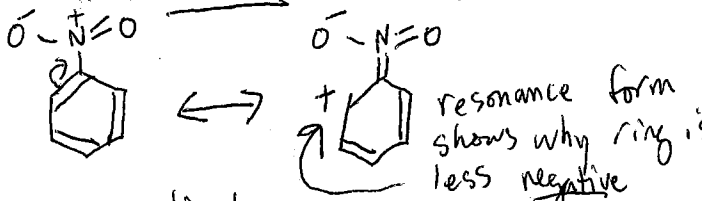
← This is because it already has $6e^-$ in conjugated system

Benzene (CH 16)

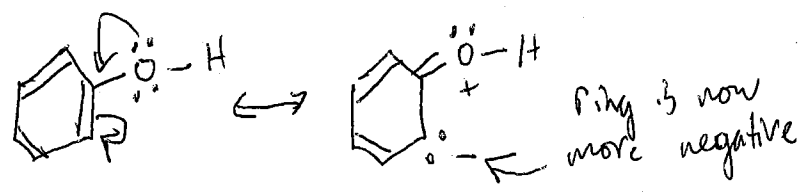
• What makes a substituent "activating" or "deactivating"?

This usually refers to Electrophilic (E⁺) substitution: since E⁺ is positive, it reacts with negative charge in ring from all the double bonds. Therefore anything which makes ring more negative will be considered an activator

For Example -NO₂ is a deactivator because it is an electron withdrawing group (EWG)



-O-H is an activator because it is an electron donating group (EDG)

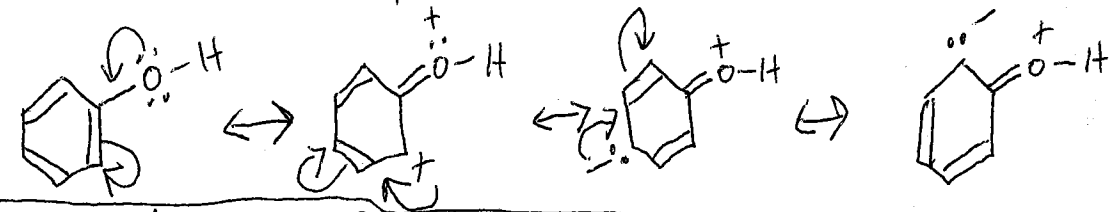


This is why Electrophilic-activators are Nucleophilic-deactivators

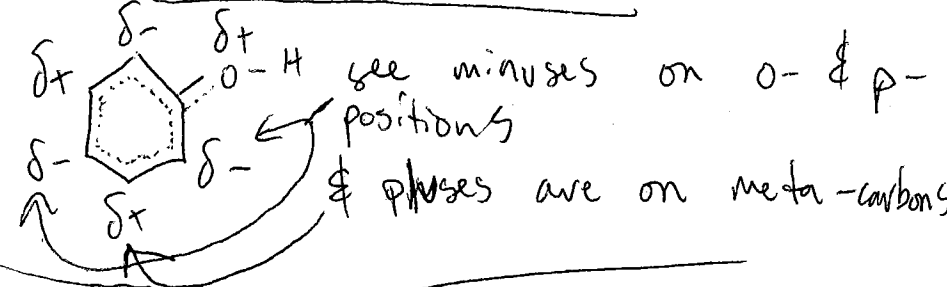
• Why meta- or ortho-, para-directors?

The real reason has to do with stability of carbocation intermediate forms: product is result of more stable intermediate (see p. 545-548)

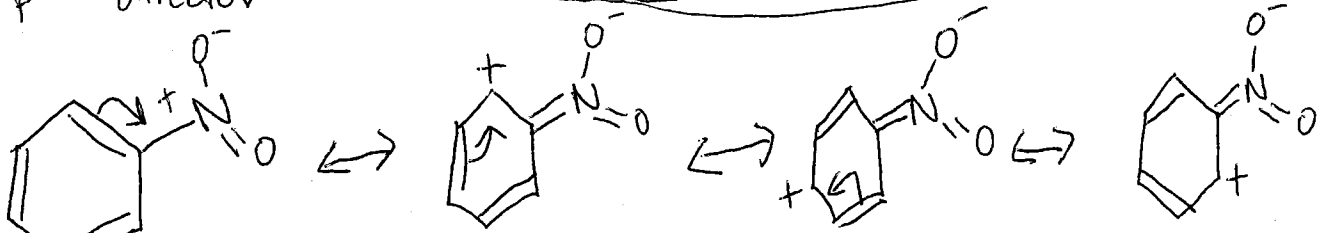
But... there is an easier way to remember without drawing all intermediates. Keep in mind this is not why it happens but a helpful way to remember. If you look at resonance forms they show similar behavior for meta director



remember real form is hybrid...



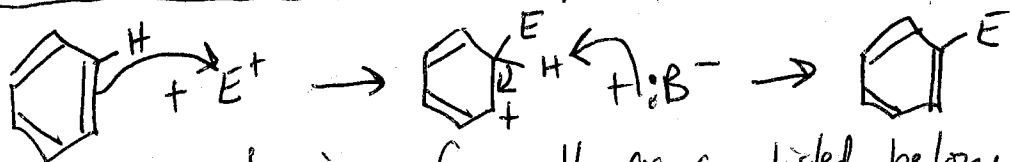
for o-, p- director



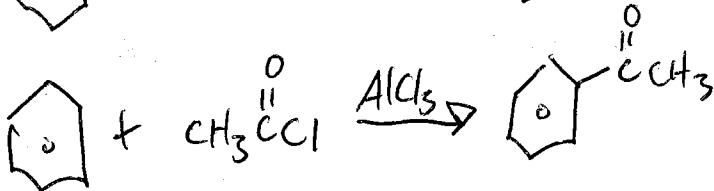
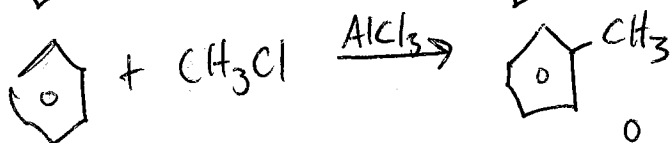
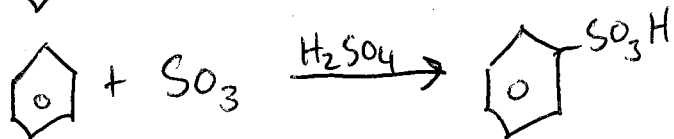
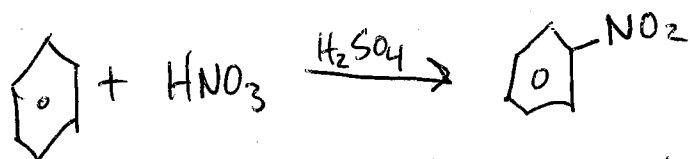
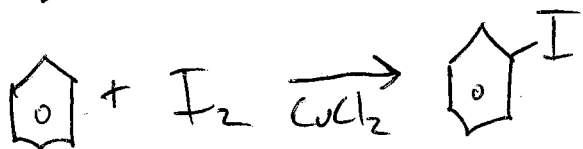
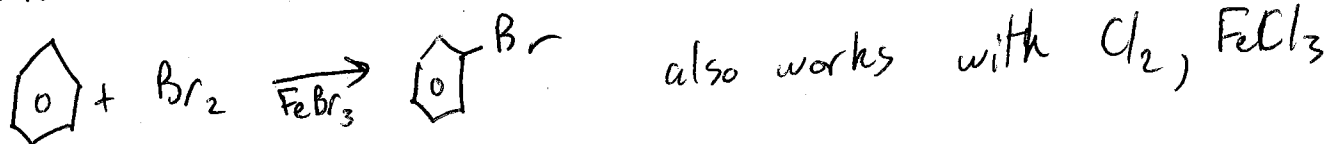
Notice carbocation is on ortho- & para- carbons

Benzene p. 2 (CH 16)

General Benzene Electrophilic Substitution Mechanism



This is mechanism for all rxns listed below in this section



• Deactivated rings don't react
• Be careful; carbocation intermediate may show rearrangement

• This can then be treated with H_2/Pd to give alkane side group $\frac{1}{2} CH_2CH_3$

Other important rxns

