

Organic Reaction Mechanism Review

Lecture 1
Biofuels and Bioproducts

Bronx Community College - 2017
*Chemistry and BioEnergy Technology for Sustainability NSF ATE
1601636*

The CBETS Program

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NSF Award Description:

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Tumblr page for lecture notes:

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Outline

- Structure and Stability of Organic Compounds
 - Drawing Lewis Structures
 - Resonance
 - Molecular Shape and Hybrid Orbitals
 - Aromaticity
- Brønsted Acidity and Basicity
 - pKa values
 - Tautomers
- Kinetics and Thermodynamics
- Drawing Reasonable Reaction Mechanisms
- Classes of Transformations and Mechanisms
 - Polar Mechanisms
 - Free Radical Mechanisms
 - Pericyclic Mechanisms
 - Transition-Metal-Catalyzed/Mediated Mechanisms

The Language of Organic Chemistry

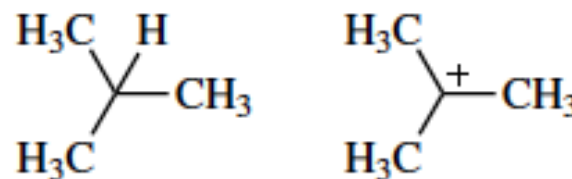
- Lewis Structures = Vocabulary
- Reaction Mechanisms = Plot
- Hard Rules
 - Always draw all bonds and H atoms near reactive center
 - Learn functional group abbreviations, or draw functional group
- Organic chemistry “slang” or dialects
 - e.g. dashes and wedges (Europe vs. U.S.)

Draw H atoms (and, if necessary) lone pairs and CH₃ groups near reactive centers

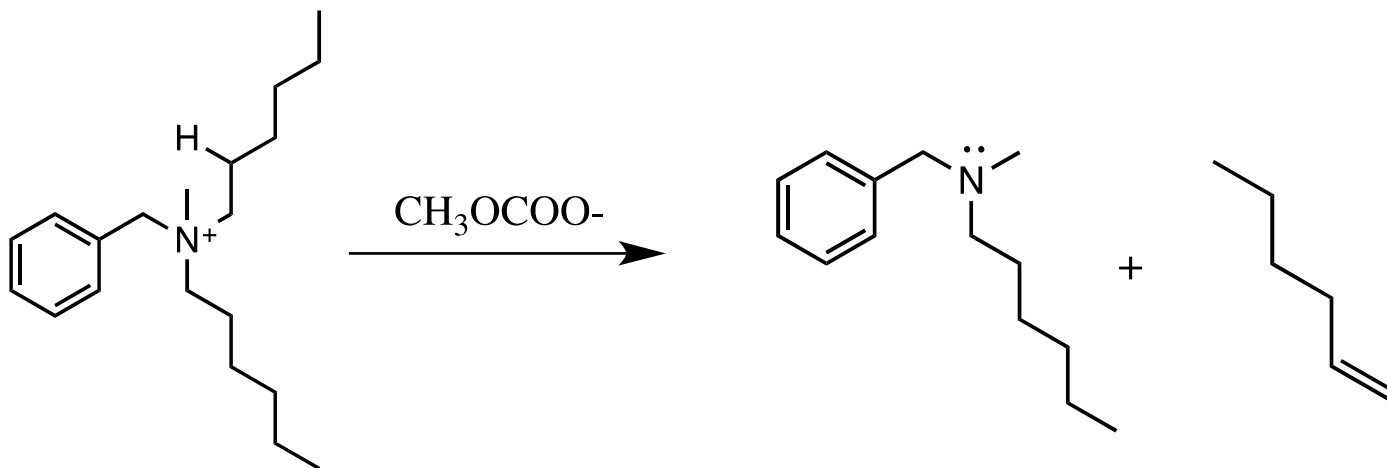
It's easy to confuse these structures ...



... but it's much more difficult to confuse these!



Hoffman elimination (β elimination) – can you propose a mechanism?



Functional Group Abbreviations

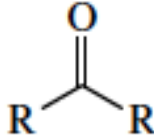
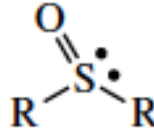
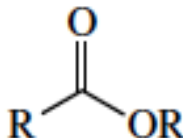
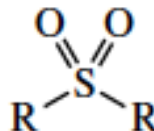
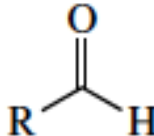
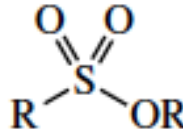
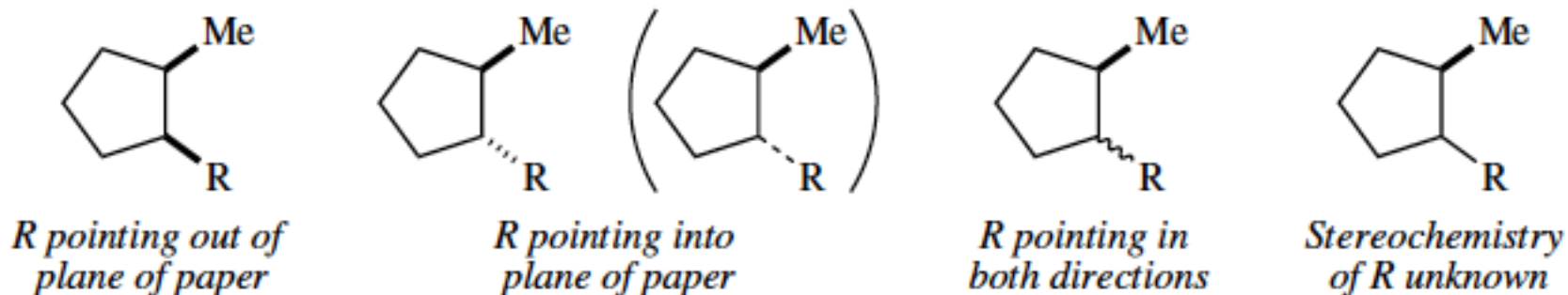
RCOR	ketone		RSOR	sulfoxide	
RCO ₂ R	ester		RSO ₂ R	sulfone	
RCHO	aldehyde		RSO ₃ R	sulfonate ester	

TABLE 1.1. Common abbreviations for organic substructures

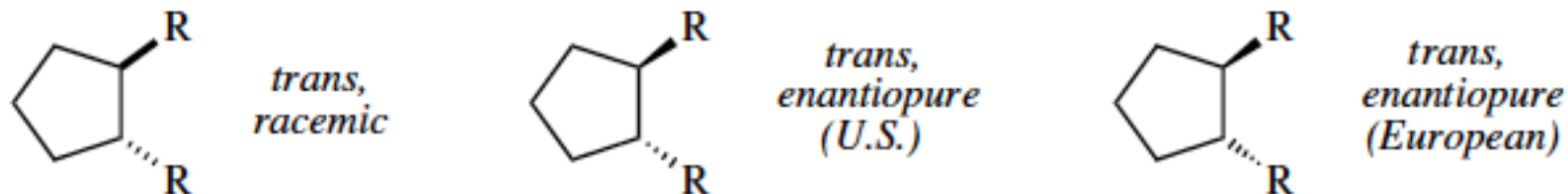
Me	methyl	CH ₃ –	Ph	phenyl	C ₆ H ₅ –
Et	ethyl	CH ₃ CH ₂ –	Ar	aryl	(<i>see text</i>)
Pr	propyl	CH ₃ CH ₂ CH ₂ –	Ac	acetyl	CH ₃ C(=O)–
<i>i</i> -Pr	isopropyl	Me ₂ CH–	Bz	benzoyl	PhC(=O)–
Bu, <i>n</i> -Bu	butyl	CH ₃ CH ₂ CH ₂ CH ₂ –	Bn	benzyl	PhCH ₂ –
<i>i</i> -Bu	isobutyl	Me ₂ CHCH ₂ –	Ts	tosyl	4-Me(C ₆ H ₄)SO ₂ –
<i>s</i> -Bu	<i>sec</i> -butyl	(Et)(Me)CH–	Ms	mesyl	CH ₃ SO ₂ –
<i>t</i> -Bu	<i>tert</i> -butyl	Me ₃ C–	Tf	triflyl	CF ₃ SO ₂ –

Conventions for Stereochemistry

- *Relative configurations (non-tapered)*



- *Absolute configurations (tapered)*

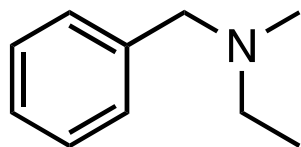


Lewis Structures and Formal Charges

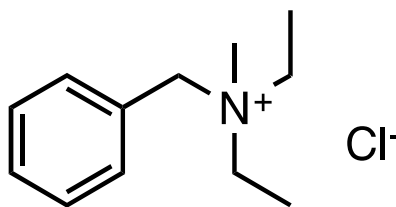
- Formal charge (FC) on any atom in a molecule can always be calculated:

$$\text{formal charge} = (\text{valence electrons of element}) \\ - (\text{number of } \pi \text{ and } \sigma \text{ bonds}) \\ - (\text{number of unshared valence electrons})$$

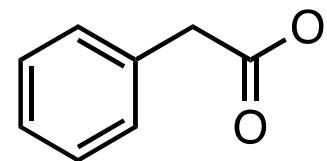
– Examples:



Charge on *methylene* C in *Bn* group?



Charge on *ammonium* N?



Charge oxygen atoms of 2-phenyl acetate?

Common FCs

Even-electron atoms

Atom	1 Bond	2 Bonds	3 Bonds	4 Bonds
C		0*	+1 (no lp) [§] -1 (one lp)	0
N, P	0 [†]	-1	0	+1
O, S	-1	0	+1	0 or +2 [‡]
Halogen	0	+1		
B, Al			0 [§]	-1

Note: lp = lone pair

*Carbene

[†]Nitrene

[‡]See extract following Table 1.2 for discussion of S.

[§]Has an empty orbital

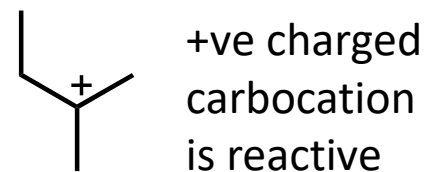
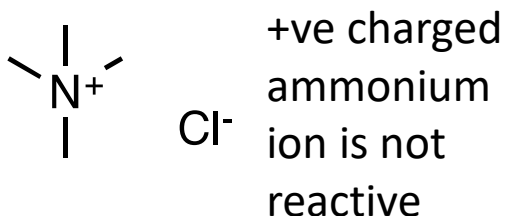
Odd-electron atoms

Atom	0 Bonds	1 Bond	2 Bonds	3 Bonds
C				0
N, P			0	+1
O, S		0	+1	
Hal	0	+1		

Uses of Formal Charge

- Formal charges *ARE* used in “accounting” for electrons in a reaction (to ensure electrons are not gained or lost)

- Formal charges *ARE NOT* used to gauge reactivity



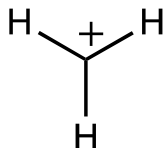
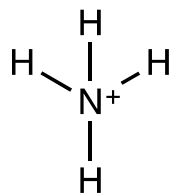
- Electronegative atoms can have positive formal charges (e.g. NH_4^+ , H_3O^+ , $\text{MeO}^+=\text{CH}_2$)

Properties of Chemical Reactivity

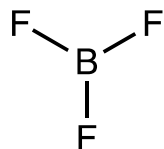
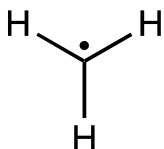
- *Electronegativity/Electropositivity (EN/EP)*– an elemental property, independent of the bonding pattern of an element
- *Electron deficiency (ED)* – lacking an octet in valence shell (or duet for H)
- *Electrophilicity (EPH)*– An atom with an empty, low energy orbital

These properties, including Formal Charge (FC), operate independently of one another

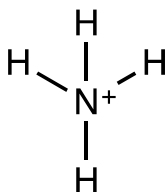
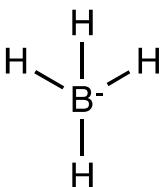
Differences between chemical properties and reactivity



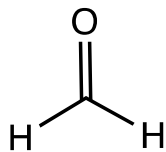
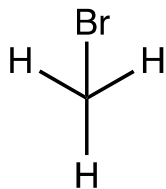
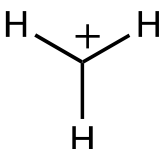
N and C atoms both have +ve FC, but N not ED while C is ED



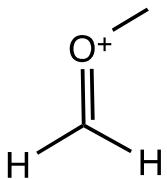
C and B atoms both ED, but neither have FC



B is EP and N is EN, but both ions are stable, have FCs and neither are not ED



C atoms are all EPH, but only the C in CH₃⁺ is ED

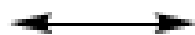
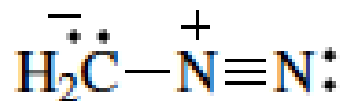


The O atom bears the FC, but the the C atoms are EPH (not the O)

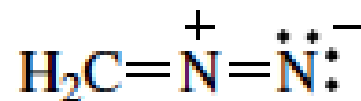
Resonance

- Different arrangements of π electrons and lone pairs for a given σ bond pattern
- The true compound is a “weighted” average of all resonance structures (resonance hybrid)
- Resonance is depicted with double-headed arrows (equilibria is depicted using two opposing arrows)
- *The least dominant resonance forms are often the most reactive resonance forms*

Diazomethane is neither this:



nor this:



but a weighted average of the two structures.

Hierarchy of Resonance Form Rules

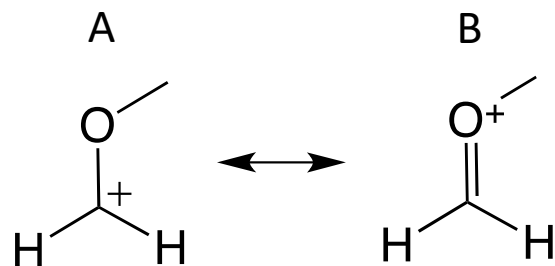
Rule 1: The octet rule *is sacred* for B, C, N, O; *less sacred* for P, S; and *not sacred* for transition metals

Rule 2: Resonance forms with full octets are lower energy (less reactive) than resonance forms where one or more atoms are ED. If there are ED atoms, they should be EP (B, C) not EN (N, O, halogen)

Rule 3: Resonance forms with charge separation are usually higher energy (more reactive) than forms where charges can be neutralized

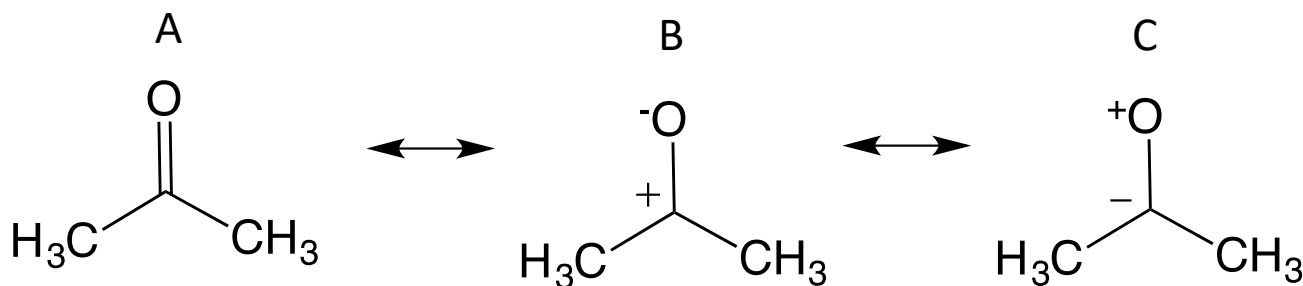
Rule 4: If charge separation is necessary, EN atoms should bear the -ve FC and EP atoms should bear the +ve FC

Some examples of resonance and the importance of resonance contribution



Which structure is a more accurate depiction of the Ground State? **B**

Why? The fact that more atoms have a full octet (Rule 1, form B) is more important than the more EP atom (C, not O) bear the +ve FC

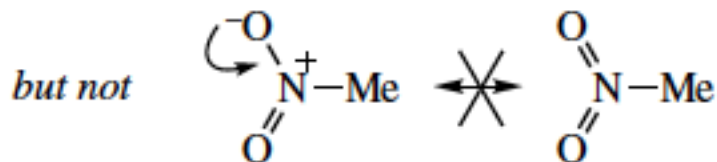


Which structure is a more accurate depiction of the Excited State? **B**

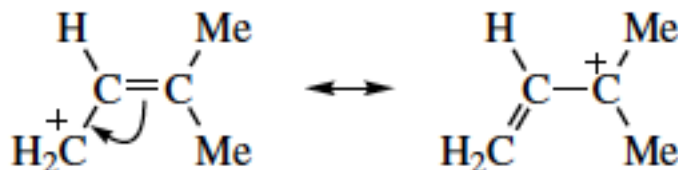
Why? First of all, the 3rd structure is not a valid resonance form (EN atom, O, is made ED). Form B is an important, but higher energy resonance form because it has charge separation (Rule 3) and an EP ED atom (C, Rule 2).

How to spot potential resonance forms?

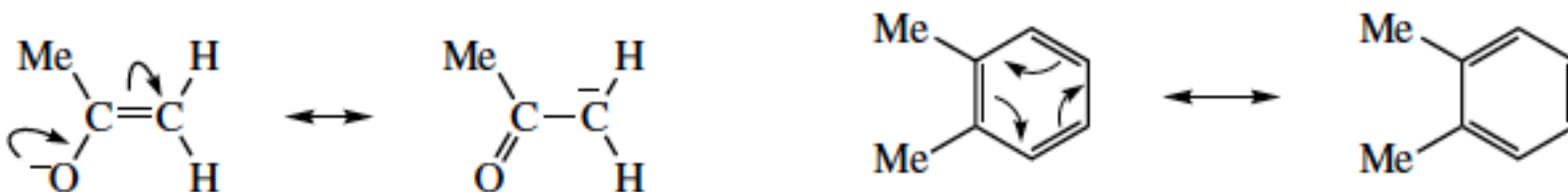
- ED atoms next to LP-bearing atoms make new π bonds:



- Break a π bond to make a more stable carbocation (and serve an ED atom):

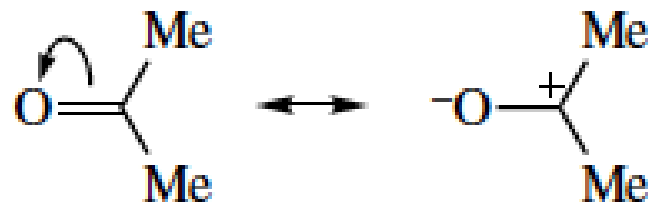


- Move a lone pair adjacent to a π bond; or move π bonds in aromatic rings:

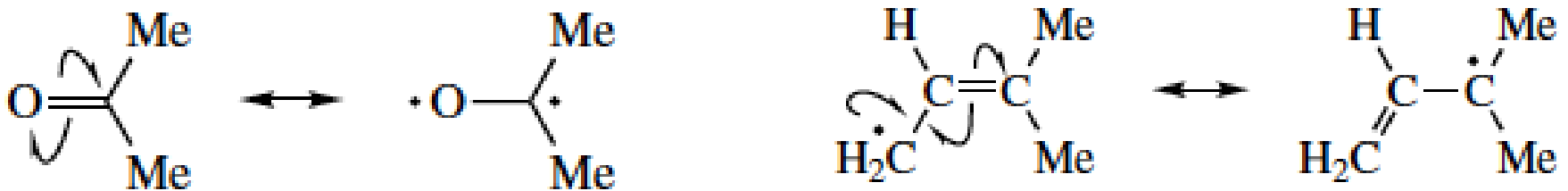


Homolytic vs. Heterolytic Bond Cleavage

- Heterolytic cleavage = 2 electron movement, double-headed arrows

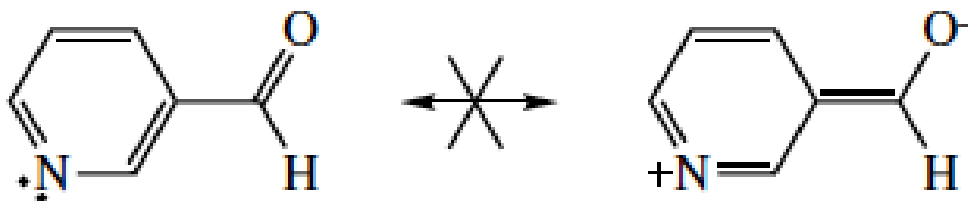


- Homolytic cleavage = 1 electron (radical) movement, single-headed arrows



Additional Rules of Resonance

- LPs or empty orbitals cannot interact with a π bond that is perpendicular (orthogonal)



- Two resonance structures must have the same number of electrons, atoms and FCs
- Tetravalent C or N atoms do not have LPs or π bonds and therefore do not participate in resonance

O and N atoms are like banks with money

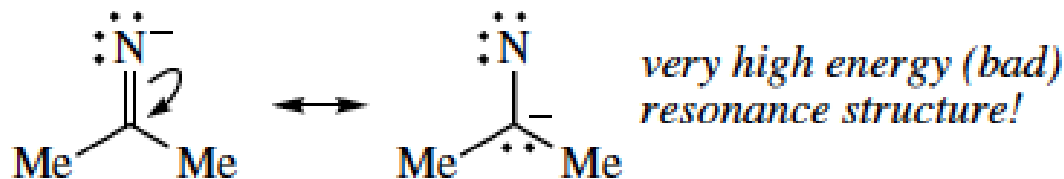
- They are willing to *loan* their electrons, but cannot easily be *robbed* of electrons.

An electronegative atom is happy to share its electrons, even if it gains a formal positive charge ...

... and it can give up a pair of electrons if it gets another pair from another source ...



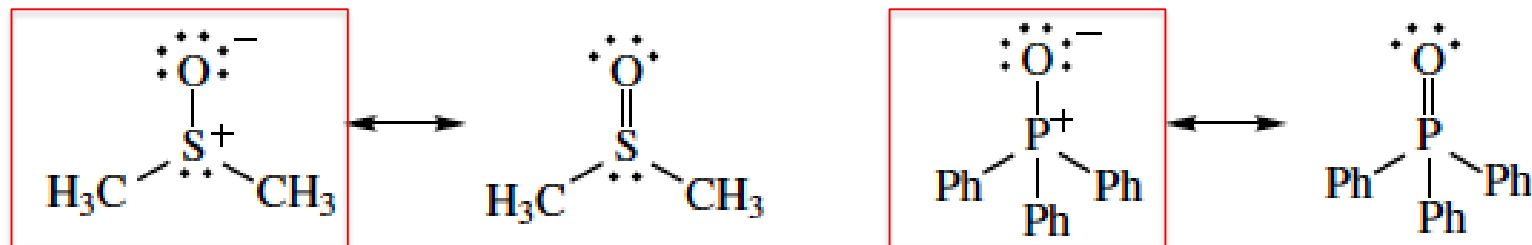
... but it will not give up a pair of electrons entirely, because then it would become electron-deficient.



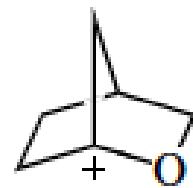
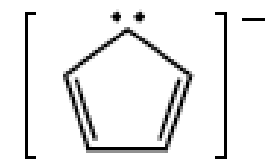
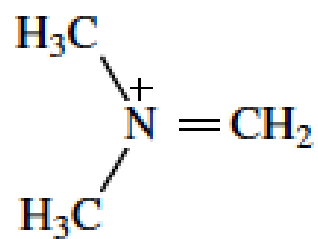
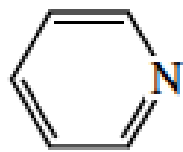
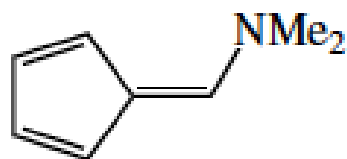
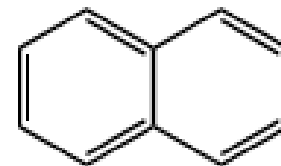
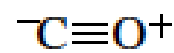
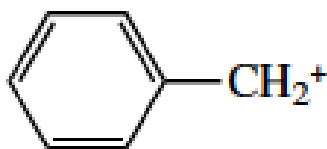
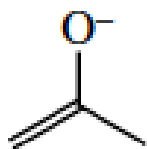
- This rule does not change whether the O or N atoms have a +ve FC or not

Resonance in compounds with S and P

- The dipolar resonance forms are a *better* description of the ground state of DMSO and TPPO
- These are not conventional π bonds because valence shell is extended beyond the octet



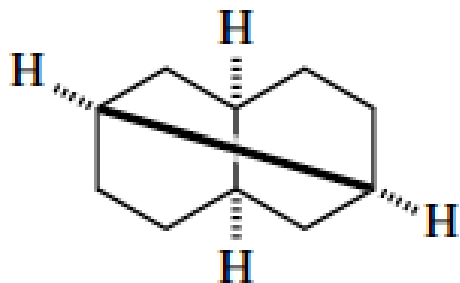
Practice Problems: Draw as many resonance forms for each compound as possible



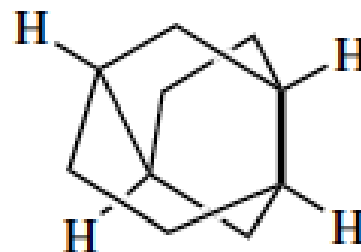
Molecular Shape

- Molecules are 3D objects and thus have shape

This tricyclic compound looks horribly strained ...



... until you look at its three-dimensional structure!



- It is important to realize that molecules (and reaction mechanisms) appear differently when represented in 2D vs. 3D
- To organic chemists, molecular structure is based on *hybrid orbital theory*, a combination of valence bond theory and molecular orbital theory

Atomic Orbitals (AOs)

- Atomic Orbitals are mathematical functions representing the probability of finding an electron in a given space.
- C, N and O each have 4 valence AOs; 1s and 3p.
- Each AO can hold 0, 1 or 2 electrons.
- The s orbital is spherical

s orbital



*spherical distribution of
electron density;
uniform arithmetical sign*

p orbitals

- p orbitals have two lobes and each has opposite arithmetical signs (***not to be confused with charge***)

p orbital

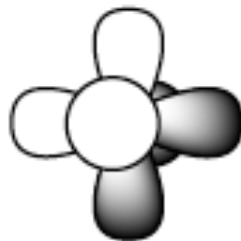


Top lobe: solution to the wave function > 0

Bottom lobe: solution to the wave function < 0

- When p orbitals are squared and added together, a spherical electron probability distribution is obtained

Three mutually perpendicular p orbitals ...

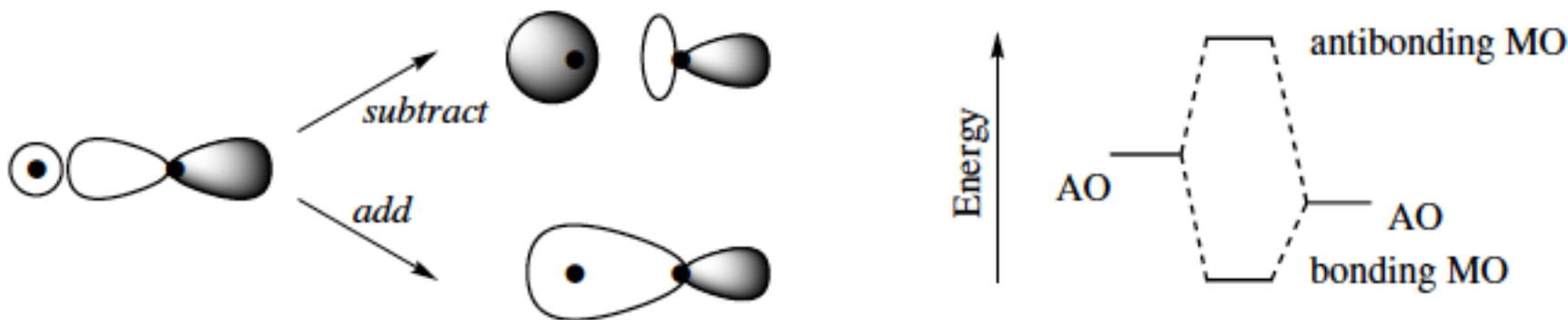


... squared and added together give a spherical probability distribution



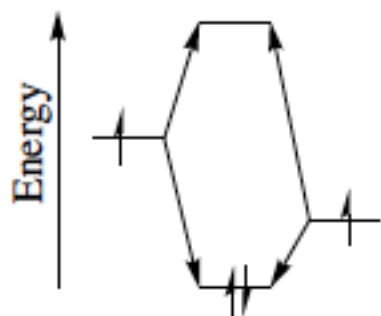
Molecular Orbitals (MOs)

- When two atoms approach each other in space, the probability distribution of their electrons change due to presence of the other nuclei. This effect can be additive (bonding MO) or subtractive (antibonding MO):



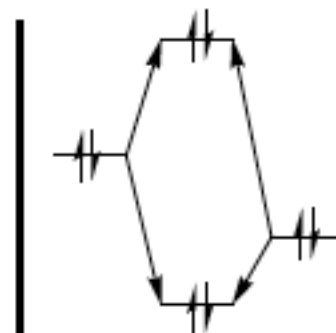
Bond Formation (or not)

- The formation of a bond is dependent upon how much orbital space is available during the atomic interaction



Both electrons decrease in energy upon mixing of AOs to form bonding MO.

Bond formed between two nuclei, each lending an AO with a single electron



Two electrons decrease in energy, two increase. Overall there is an increase in the energy of the electrons.

Bond **not** formed between two nuclei, because each AO has two electrons

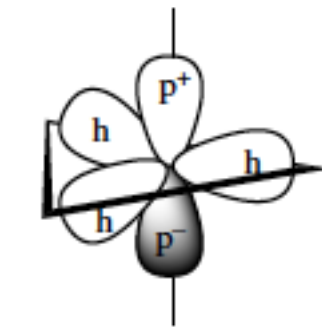
Hybrid AOs

- C, N and O can form *hybrid atomic orbitals* by “averaging” the energy of s and p electrons
- The type and geometry of the hybrid orbitals dictate how the bond reacts:
 - sp³ hybrid orbital (25% s-character, 109° bond angle)
 - sp² hybrid orbital (33% s-character, 120° bond angle)
 - sp hybrid orbital (50% s-character, 180° bond angle)

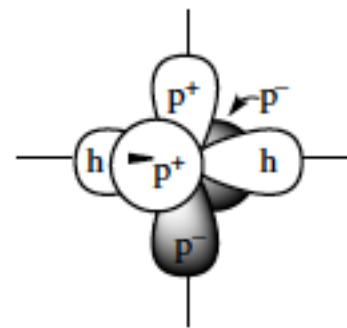
Hybrid and p orbitals

- Hybrid orbitals are used to make σ bonds and hold LPs **not** used in resonance

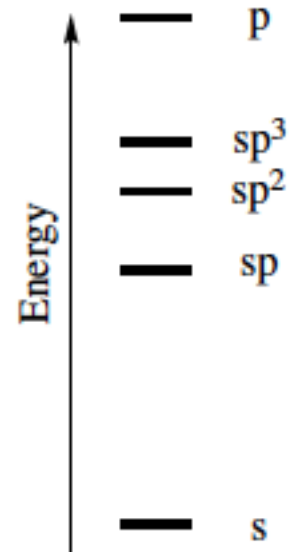
h = hybrid orbital.
p⁺ and p⁻ = lobes of p orbitals.
Back lobes of hybrid orbitals omitted for clarity.



sp² hybridization



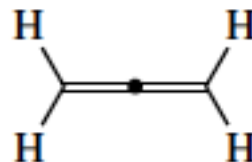
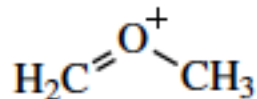
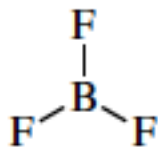
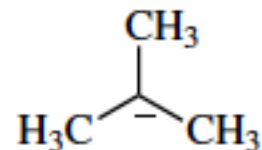
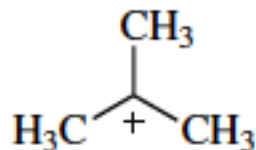
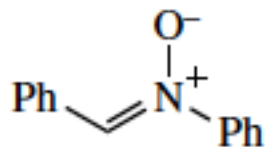
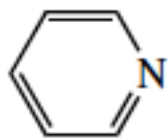
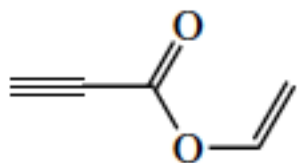
sp hybridization



- p orbitals are used to make p bonds, and hold LPs used in resonance (e.g. a carbanion)
- p orbitals can also be empty (e.g. a carbocation)

Practice Problems

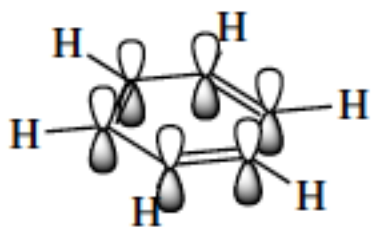
- To determine the hybridization of an atom, add the number of LPs **not** used in resonance to the number of σ bonds
 - If the sum is 4 then it's sp^3 , 3 then sp^2 , 2 then sp
 - Determine the hybridization of C, N and O in each of the following compounds:



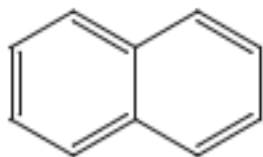
Aromatic and Anti-Aromatic Compounds

- Compounds with a ***cyclic*** array of continuously overlapping p orbitals and are either *stabilized* (aromatic) or *destabilized* (anti-aromatic)
- If there's an ***odd number*** of electron pairs the compound is aromatic
- If an ***even number*** of electron pair the compound is anti-aromatic
- The term aromatic is not to be confused with the term volatile

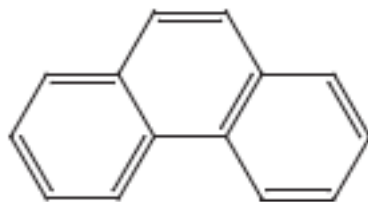
Some aromatic hydrocarbons



benzene



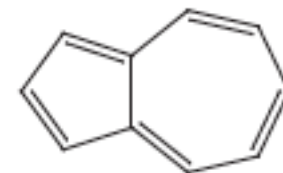
naphthalene



phenanthrene



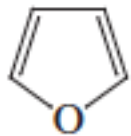
benzo[a]pyrene



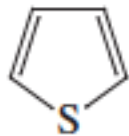
azulene

Aromatic Heterocycles

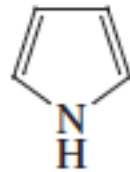
- You ***must*** consider LP contributions, heteroatom hybridization and geometry to make an accurate determination of the aromaticity of a heterocyclic compound



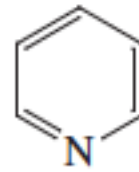
furan



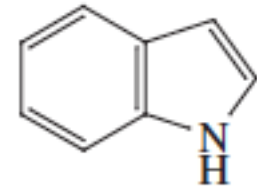
thiophene



pyrrole



pyridine



indole

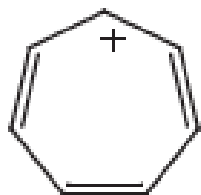
Each heteroatom (O, S, N) contributes a single lone pair (2 electrons) to the aromatic system, making the total number of electron pairs odd.

In pyridine, the N atom is sp^2 hybridized and the LP resides in a p orbital that is orthogonal to the aromatic system

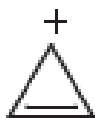
The LP is therefore more reactive

Aromatic ions and anti-aromatic compounds

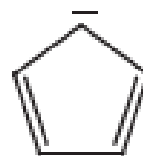
- Aromatic ions:



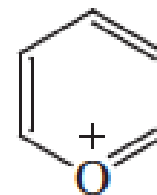
tropylium



cyclopropenium

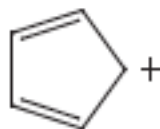
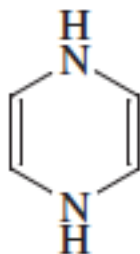


cyclopentadienide



pyrylium

- Anti-aromatic compounds:



Brønsted Acidity and Basicity

- Bases are anionic or neutral, acids are cationic or neutral
- The acid-base reaction is always an equilibrium reaction
- There is both an acid and a base on both sides of the equilibrium
- Proton transfers occur very fast, esp. when transferring from one heteroatom to another
- Proton \neq hydrogen atom \neq hydride anion

pKa and pKb

- pKa = a measure of acidity of a compound.
The lower the pKa, the stronger the acid

$$pK_a = -\log \left(\frac{[H^+][X^-]}{[HX]} \right)$$

- pKb = a measure of basicity of a compound.
In organic chemistry we define pKb of a base as the pKa of its conjugate acid

pKa tables are very helpful

$\text{CCl}_3\text{CO}_2\text{H}$	0	EtOH	*17
$\text{CH}_3\text{CO}_2\text{H}$	*4.7	CH_3CONH_2	17
pyrH^+	*5	$t\text{-BuOH}$	19
PhNH_3^+	5	CH_3COCH_3	*20
$\text{HC}\equiv\text{N}$	9	$\text{CH}_3\text{SO}_2\text{CH}_3$	23
$\text{N}\equiv\text{CCH}_2\text{CO}_2\text{Et}$	9	$\text{HC}\equiv\text{CH}$	*25
Et_3NH^+	*10	$\text{CH}_3\text{CO}_2\text{Et}$	*25
PhOH	10	CH_3CN	26
CH_3NO_2	10	CH_3SOCH_3	31
EtSH	11	NH_3	*35
$\text{MeCOCH}_2\text{CO}_2\text{Et}$	11	$\text{C}_6\text{H}_6, \text{H}_2\text{C}=\text{CH}_2$	*37
$\text{EtO}_2\text{CCH}_2\text{CO}_2\text{Et}$	*14	$\text{CH}_3\text{CH}=\text{CH}_2$	37
HOH	*15	alkanes	*40–44
cyclopentadiene	*15		

Note: pyr = pyridine.

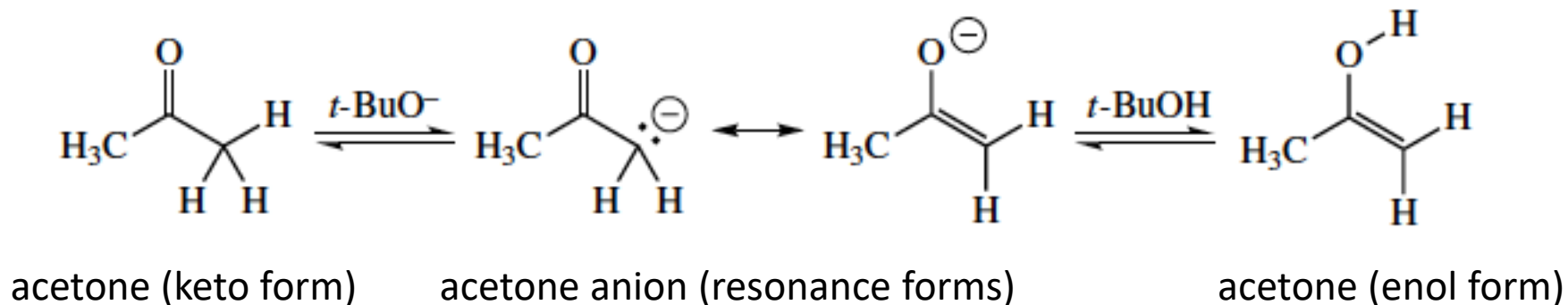
- Usually referenced with water as the solvent
- pKa is also effected by many other chemical factors (e.g. resonance, hybridization, steric bulk, periodicity). When in doubt, use a table!

A more comprehensive pKa table can be found at:

http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf

Tautomers

- Tautomers are not resonance structures, they are isomers with different σ bond networks
- Tautomerization is a rapid equilibrium that can occur in acid or basic conditions. Resonance is not an equilibrium

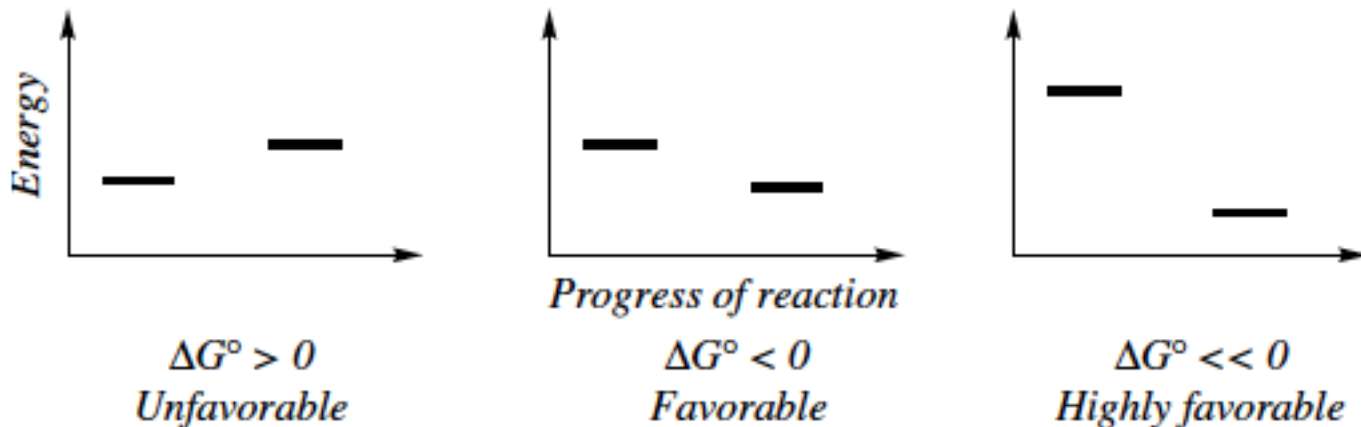


Kinetics and Thermodynamics

- A reaction will occur if it has a negative ΔG°

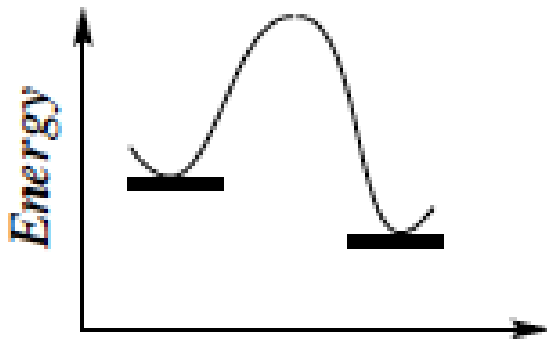
$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

- Enthalpies are typically used to determine if a reaction will occur or not, because they are easier to measure and $T\Delta S$ is small compared to ΔH for reactions run at temperatures $< 100^\circ\text{C}$



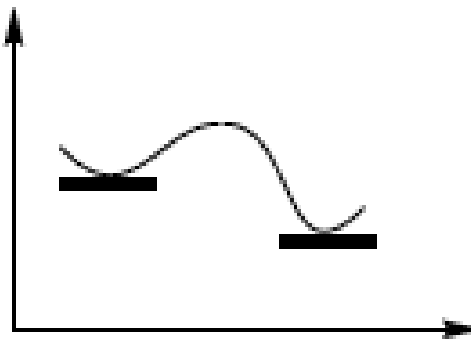
The Activation Energy Barrier

- The **rate** of reaction is dependent upon the size of the activation barrier (ΔG^\ddagger) **not** the energy difference between SM and P (ΔG)



*Large ΔG^\ddagger , $\Delta G^\circ < 0$
slow and favorable*

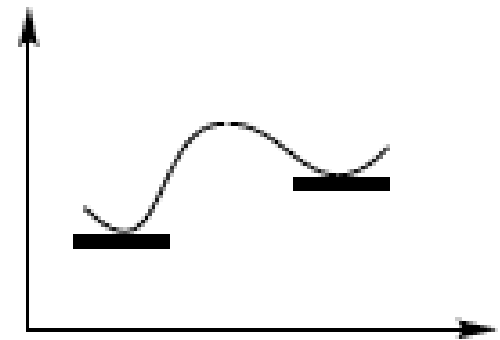
Example: Combustion of gasoline with O_2 to give CO_2 and H_2O at room temperature...



Progress of reaction

*Small ΔG^\ddagger , $\Delta G^\circ < 0$
fast and favorable*

Example: Combustion of biodiesel fuel with O_2 to give CO_2 and H_2O at $200^\circ C$ and 2000 psi!

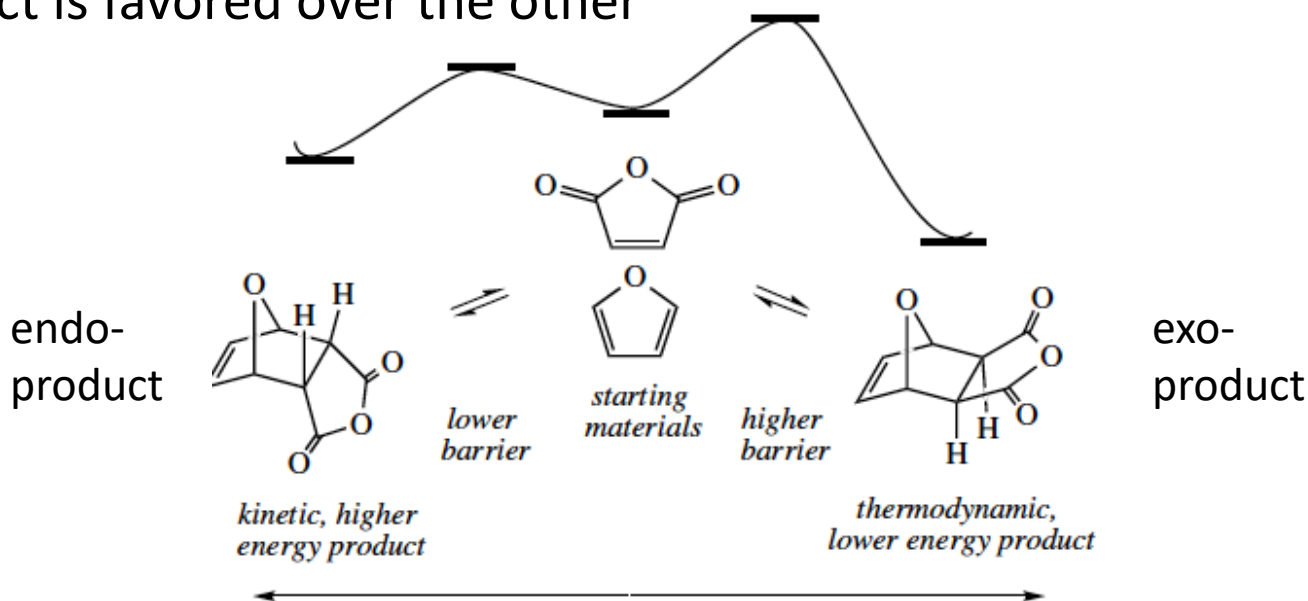


*Small ΔG^\ddagger , $\Delta G^\circ > 0$
fast and unfavorable*

Example: Addition of H_2O across the π bond of acetone

Kinetic vs. Thermodynamic Products

- If a reaction can give two products, that which is obtained most quickly (kinetic product) is not necessarily the product of lowest energy
- If an equilibrium is established, the kinetic product disappears over time
- Many times there is no equilibrium (and thermodynamic product), and many times the thermodynamic product is formed quickly
- A chemist designs conditions (temp, pressure, time) in which one product is favored over the other



All Chemical Transformation are Classified into Four Basic Types

- 1. Addition** – two reactants come together and no atoms are wasted. Usually a π bond of the SM is replaced by two new σ bonds. “e.g. good atom economy”
- 2. Elimination** – essentially the opposite as an addition reaction whereby reactant splits into two products. Usually two σ bonds in SM form a new π bond in the product
- 3. Substitution** – an atom of group that is σ bound to the rest of the SM is replaced by another σ bound atom or group
- 4. Rearrangement** – one SM gives one P with a different structure

Classes of Mechanisms

- **Polar reactions** – movement of *pairs* of electrons from a nucleophilic source (filled orbitals) to an electrophilic sink (empty orbitals)
 - Occur under acid or basic conditions
- **Free-radical reactions** – movement of *single* electrons. New bonds often formed using an electron from a half-filled orbital and another electron from a filled orbital
 - Can occur via a chain reaction, but not always
- **Pericyclic reactions** – movement of electrons in a cyclic formation
- **Metal mediated/catalyzed reactions** – require a transition metal, a transition metal complex (e.g. TiCl_4 or FeCl_3) acting as a Lewis Acid, or (e.g. TiCl_3 or SmI_2) acting as a one-electron reducing agent.
 - Can be classified as polar acidic, pericyclic or free-radical

All bond making and breaking is classified in two ways:

1. Homolytic (symmetrical bond breaking/making)

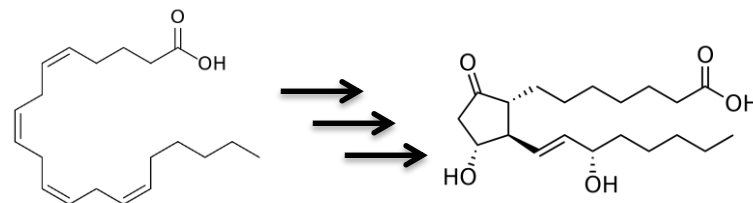
– aka radical mechanisms or **one-electron chemistry**

2. Heterolytic (asymmetric bond breaking/making)

- aka polar mechanisms or **two-electron chemistry**

Homolytic (Radical) mechanisms

- Radicals “live fast and die young” – they are *highly reactive* and thus *short lived*
- Bond cleavage and bond formation are *both* possible
- Mechanistically represented by *single-headed arrows*
- Arrows represent movement of *one electron* (a radical or “free” radical)
- Molecules containing radicals are *neutral*
- Radicals are *unpaired electrons* in an orbital
- Biological occurrences include biosynthesis of prostaglandins and anti-oxidant activity (e.g. resveratrol from red wine)
- Polymer synthesis (polystyrene, polypropylene, PVC, surfactants, elastomers, carbon nanotubes, transparent PTMA solar cells)

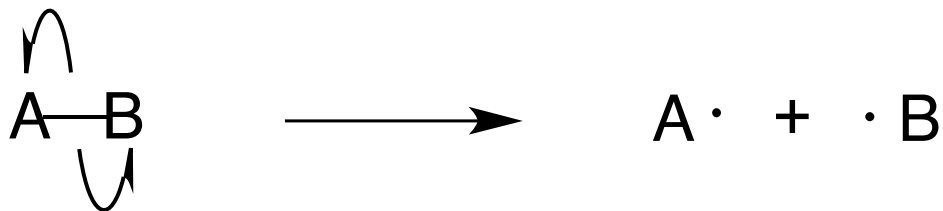


Prostaglandin biosynthesis



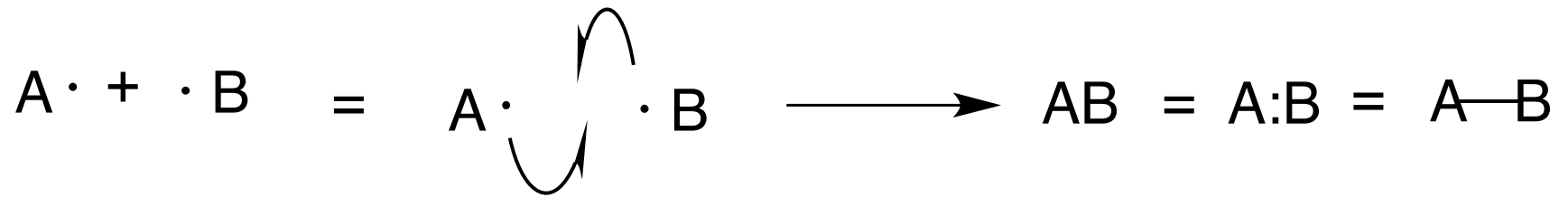
Polypropylene chairs

Homolytic Bond *Cleavage*



- Mechanistically represented by single-headed arrows
- One bonding e- stays with each product (bond cleavage)
- Radicals are neutral species
- Carbon atoms left with an odd number of e-s (7)
- Results in unpaired e-s in an orbital
- Radicals are highly reactive

Homolytic Bond *Formation*

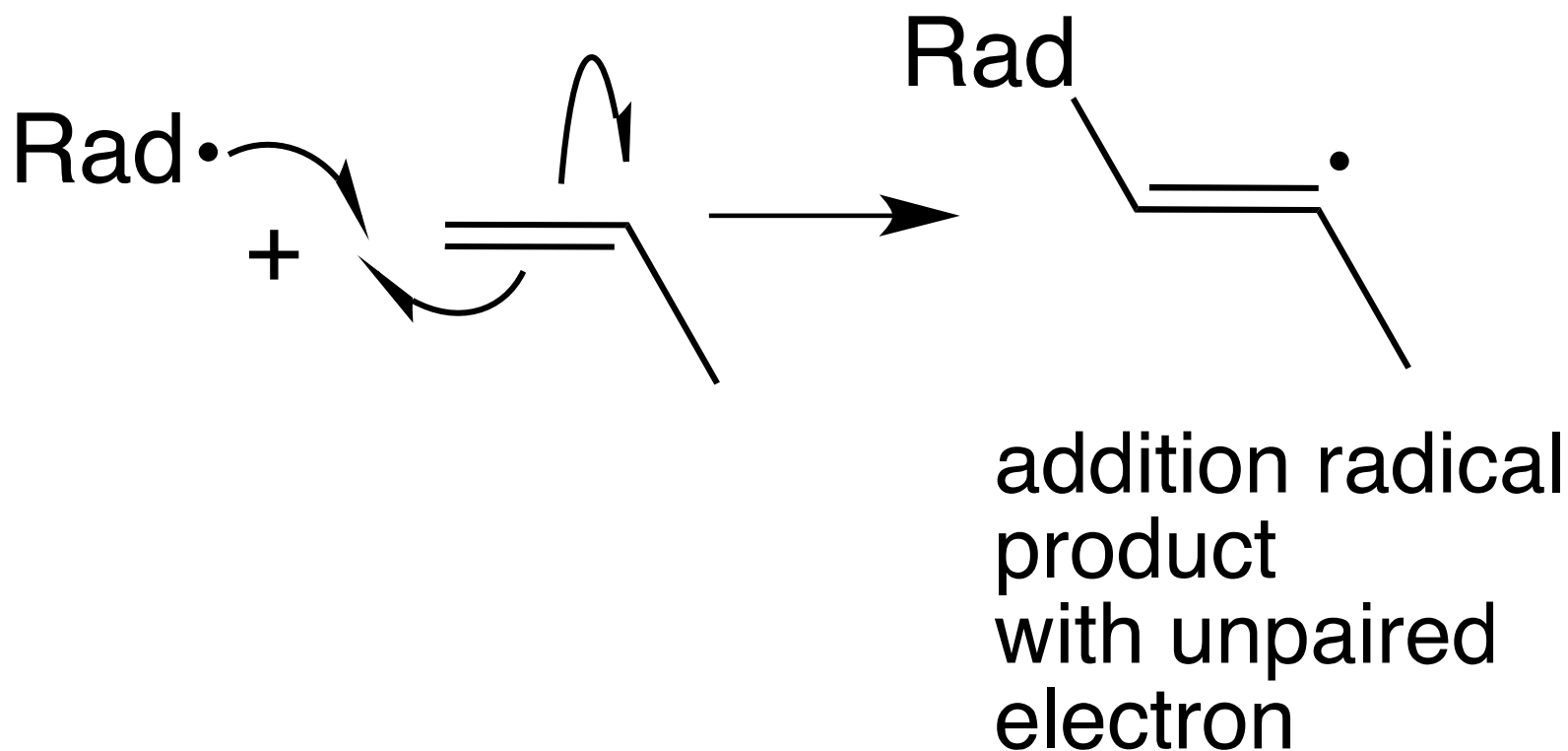


- One bonding electron derived from each reactant
- Result = formation of a new bond

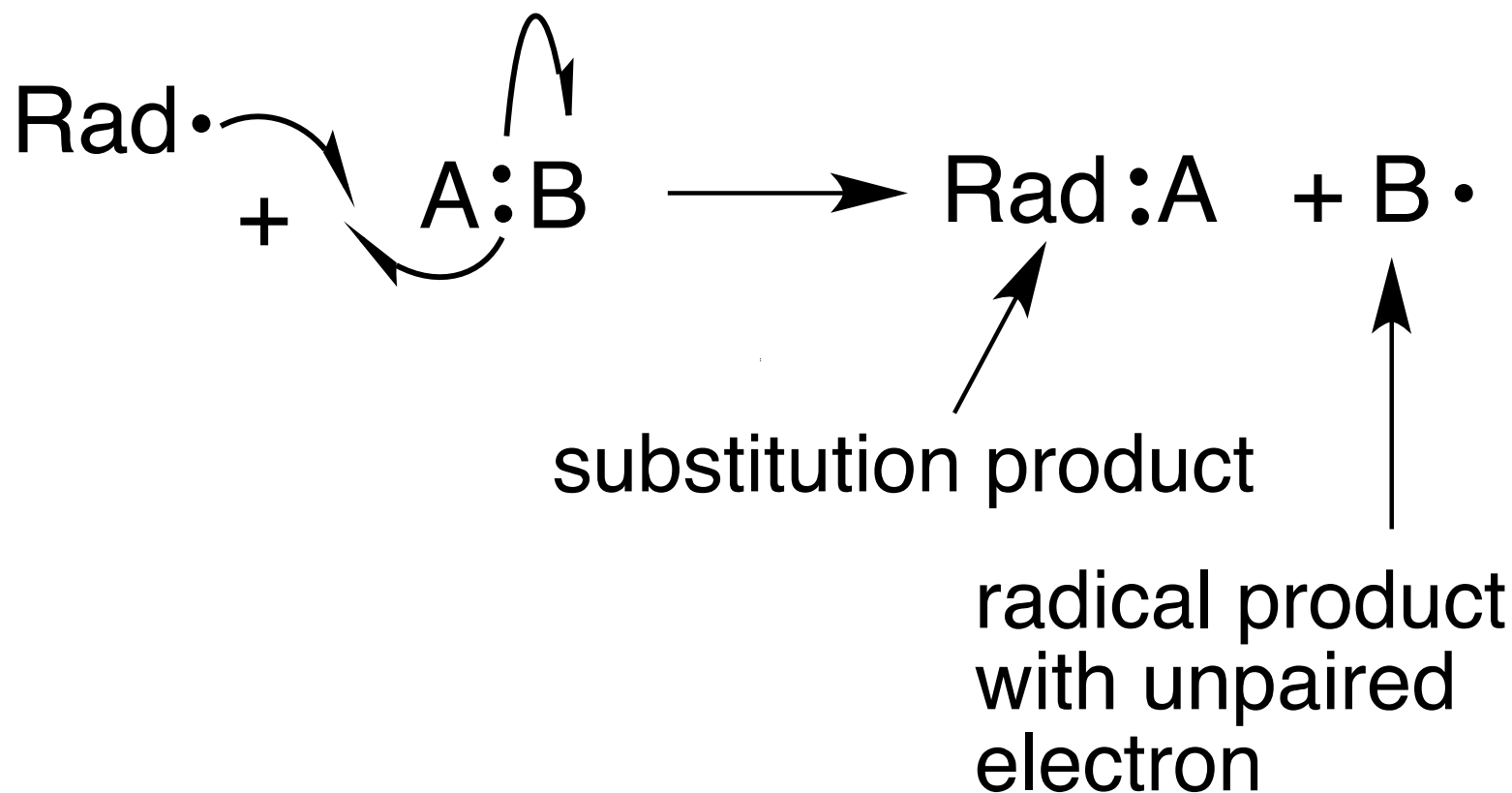
Types of Homolytic Reactions

- Addition Reactions
- Substitution Reactions
- Chain Reactions

Radical *Addition*: General Reaction Mechanism



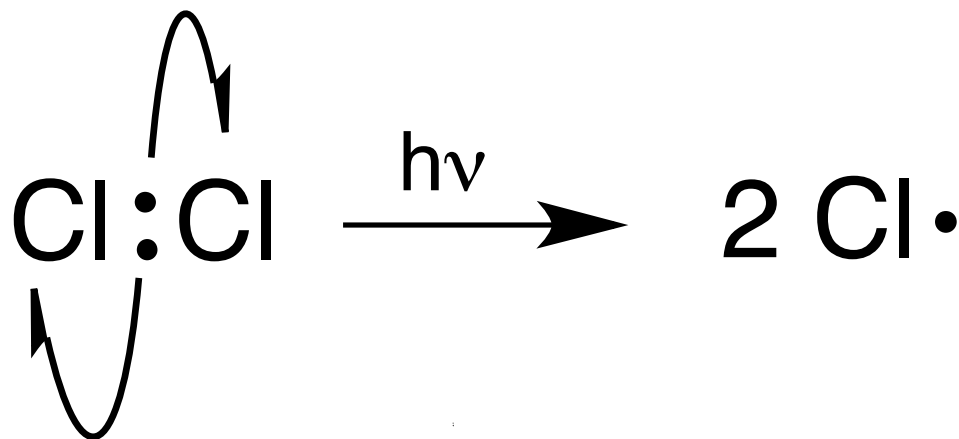
Radical *Substitution*: General reaction mechanism



Chain Reactions

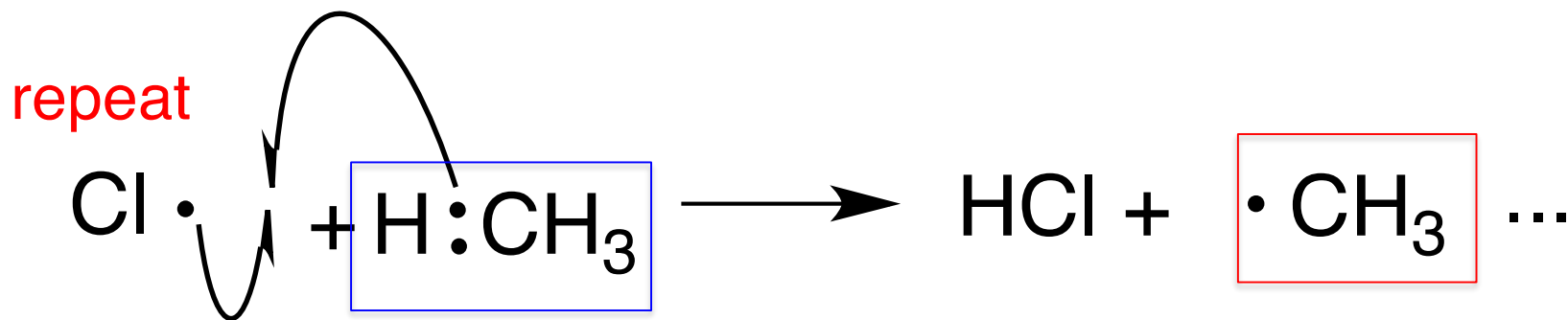
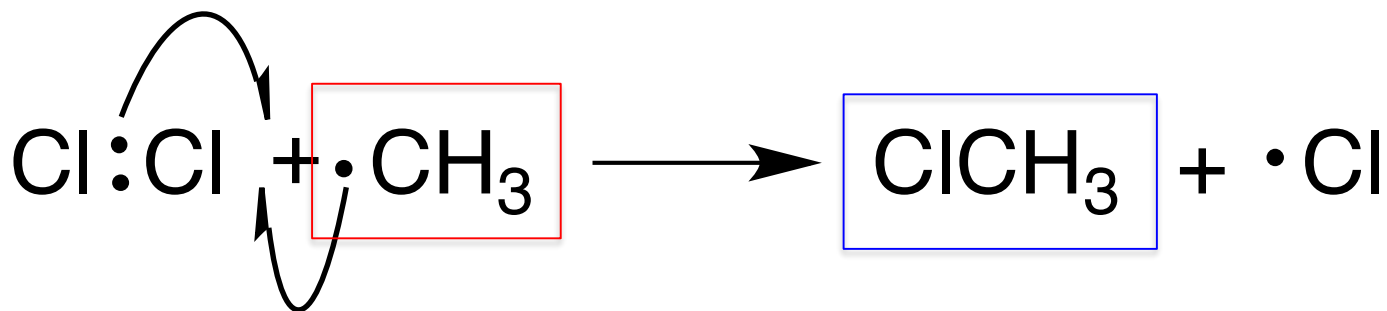
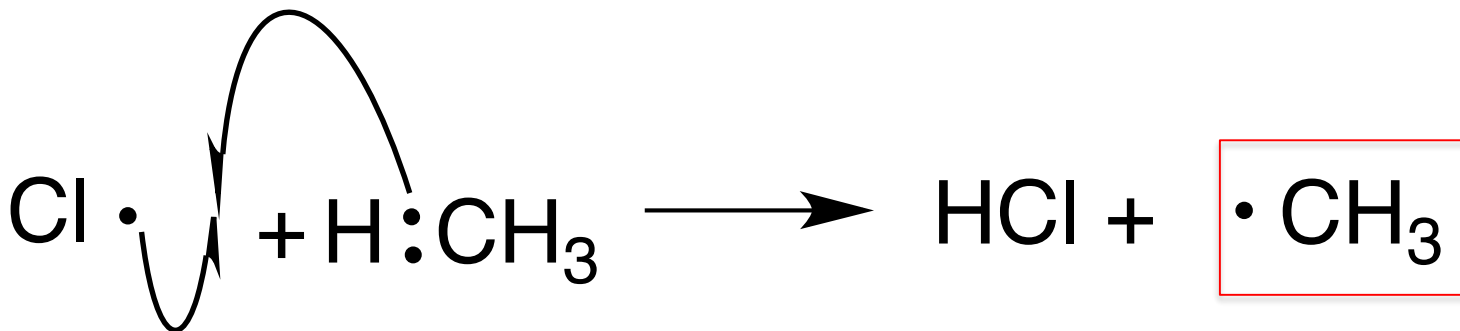
- Three steps: *initiation*, *propagation*, *termination*
- Used to produce *solvents* (e.g. DCM, chloroform) and *polymers* (polyethylene grocery bags, polystyrene foams, surfboards!, PVC pipes, etc.)

Radical Chain Reaction: Part 1: Initiation

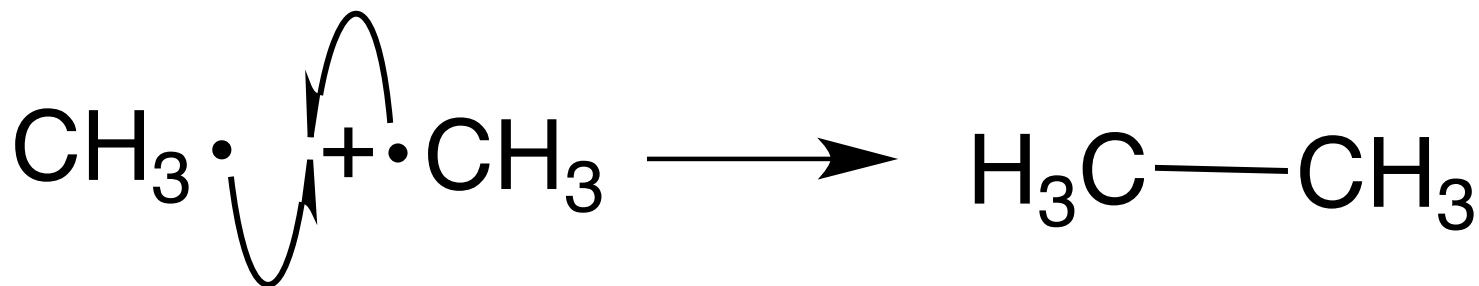
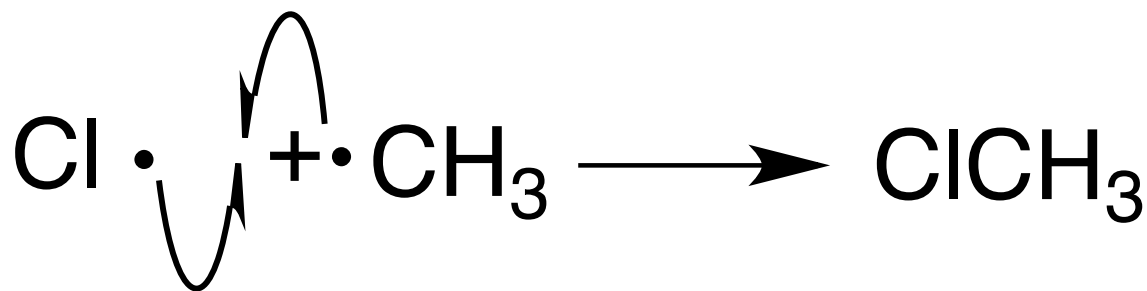
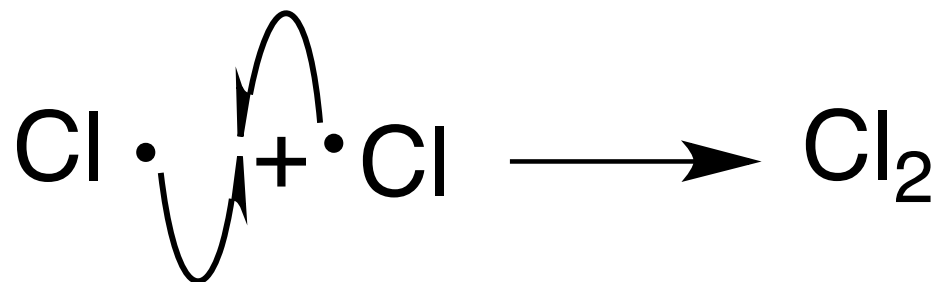


- Weak Cl-Cl bond (243 kJ/mol) is broken by irradiation at < 495 nm
- Only a small number of Cl_2 molecules / radicals actually form in this process, yet the process is still industrially efficient
- Other initiators used for other applications (e.g. peroxides, persulfates, azo compounds)

Radical Chain Reaction: Part 2: Propagation



Radical Chain Reaction: Part 3: Termination



In all cases, two radicals combine to form a stable product

Heterolytic (Polar) Reactions Mechanisms

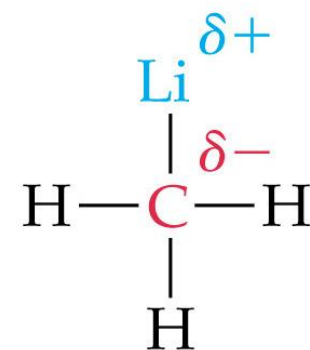
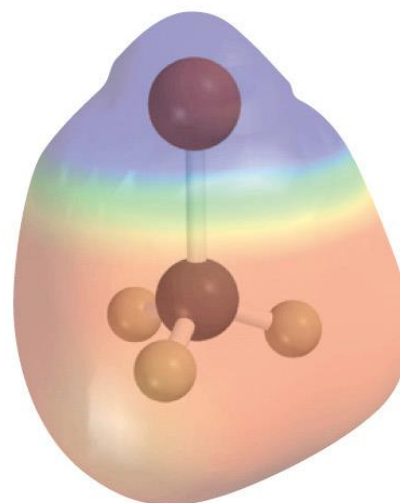
- Represented by double headed arrows
- Two electron chemistry
- Much more common
- Unsymmetrical bond breakage or formation
- Results in polar species bearing (+) and (-) charges
- When two bonding e-s stay with product = -ve charge
- When two bonding e-s migrate = +ve charge
- Leads to even number of electrons in carbon orbitals (carbocations = 6, and carbanions = 8)

Polar Reactions

- Neutrally charged organic compounds often have “polarized” electron density

Often due to *Electronegativity Difference* between atoms:

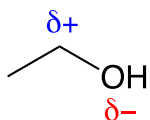
- N, O, Halogen = more electronegative than C
- Metals = less electronegative than C



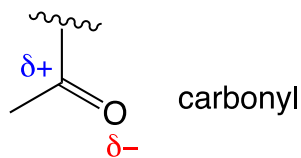
Methyl lithium has an electron rich carbon atom with a partial negative charge (δ^-) known as a “nucleophile”

The lithium atom has a partial positive charge (δ^+)

Polarity Patterns in Common Functional Groups



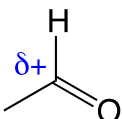
alcohol



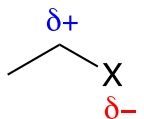
carbonyl



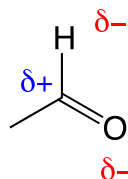
alkene
(symmetrical, non-polar)



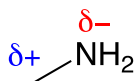
aldehyde



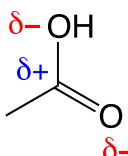
alkyl halide



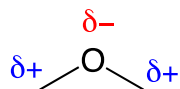
ketone



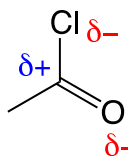
amine



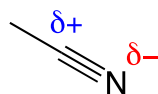
carboxylic acid



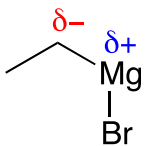
ether



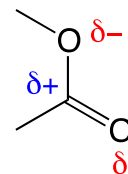
carboxylic acid
chloride



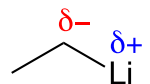
nitrile



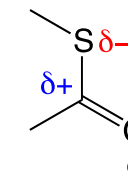
Grignard reagent



ester



Alkyllithium



thioester

TM_+ = electrophilic site
= electron acceptor site
= Lewis acidic site

TM_- = nucleophilic site
= electron donor site
= Lewis basic site

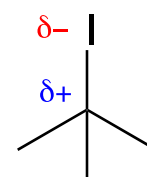
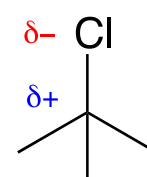
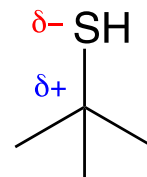
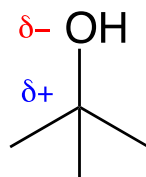
Polarizability

- Different than a polar bond; it is a dynamic quality of a specific atom
- Measure of the *response* of a atom in a molecule to an external electric field
- *Influenced* by interactions between solvent or polar molecules nearby
- e- distribution around the atom and (by extension) the molecule *changes*
- **Larger atoms with more loosely held e-'s are more "polarizable"**
- **Smaller atoms with fewer, tightly held e-'s are less "polarizable"**

For example:

C, S and I all have same Pauling electronegativity (2.5) so we would expect non-polar C-S and C-I bonds

However, because S and I are larger and polarizable than carbon, polar bonds result and $\delta+$ carbon atom becomes "**electrophilic**"



Electronegativity

C = 2.5

O = 3.5

S = 2.5

Cl = 3.0

I = 2.5

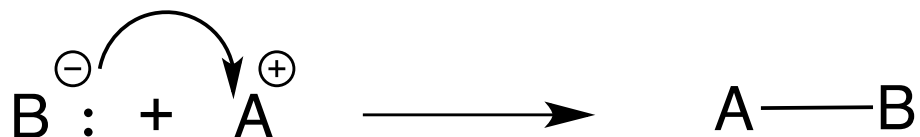
Why is this important for heterolytic reactions?

- Fundamental characteristic of heterolytic organic reactions is that e- rich sites react with e- poor sites
- ***Bond making***: an e- rich atom donates an e- pair to an e- poor atom
- ***Bond breaking***: when one atom leaves with both e-s from the former bond

(Nu:) Nucleophiles vs. Electrophiles (E)

- “Nucleus loving” (The nucleus is +vely charged)
 - Has a negatively polarized, e- rich atom
 - Forms new bonds by donating e-s
 - Can either be neutral or negatively charged
 - Neutral nucleophiles (ammonia NH_3 , water H_2O) have lone pairs
 - Negatively charged nucleophiles (hydroxide ion OH^- , chloride ion Cl^-) have lone pairs
 - Typically Lewis bases (e- donors)
- “Electron loving”
 - Positively charged, electron poor atom
 - Forms bonds by accepting e-s from nucleophile
 - Can be neutral or positively charged
 - Neutral electrophiles (carbonyl compounds, alkyl halides)
 - Positively charged electrophiles (hydronium ion, carbocations)
 - Typically Lewis acids (e-

Interaction between nucleophiles and electrophiles



nucleophile
(electron rich)

electrophile
(electron poor)

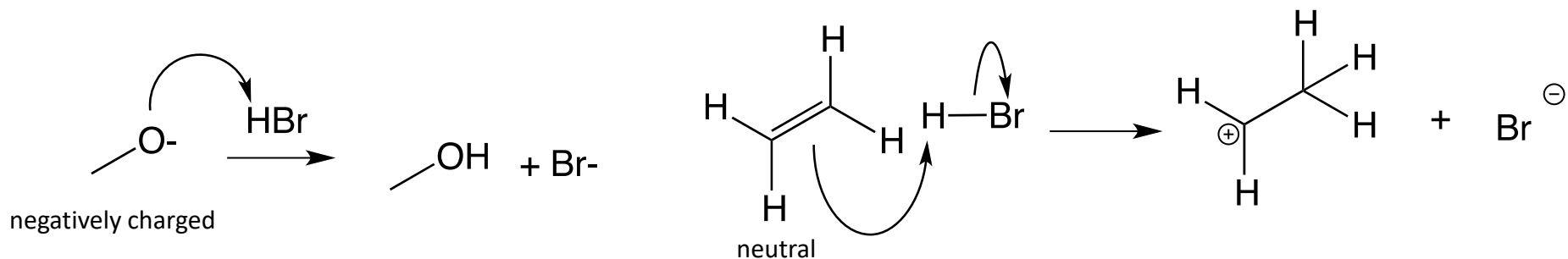
electrons that moved from B^{\ominus} to A^{\oplus}
are now located in *new covalent bond*

* Note direction of electron movement (arrow pointing) from rich to poor

The Nucleophile can be negatively charged or neutral

if negatively charged, it becomes neutral

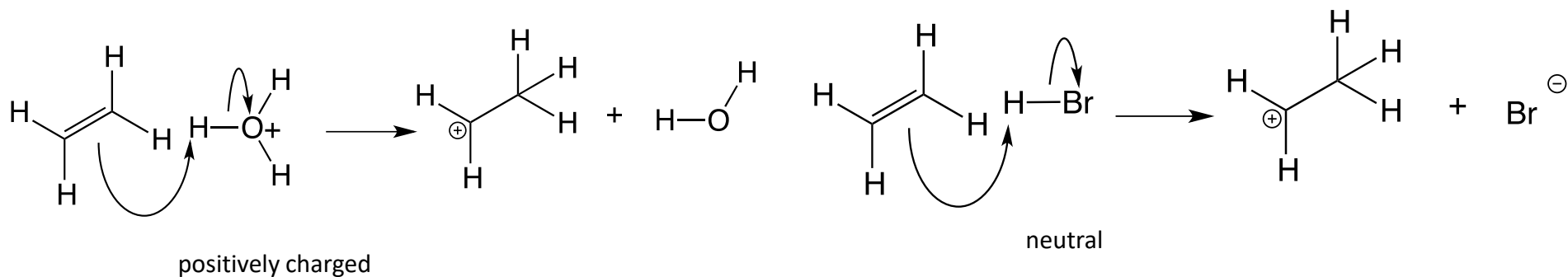
if neutral, it becomes positively charged



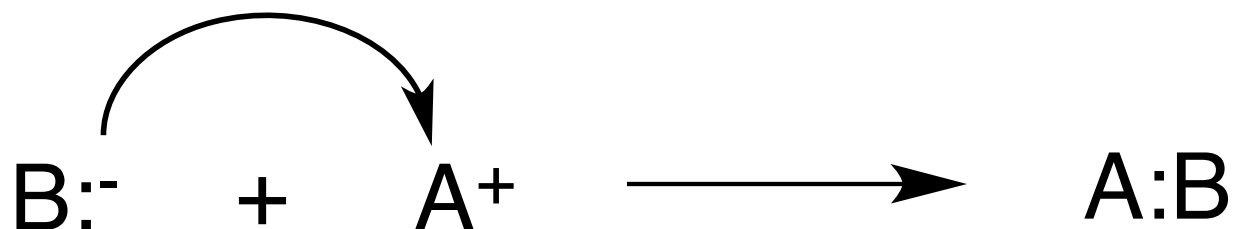
The Electrophile can be positively charged or neutral

if positively charged, it becomes neutral

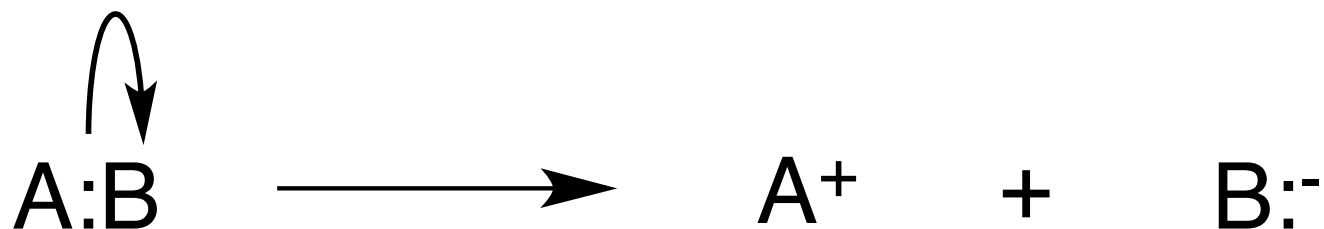
if neutral, it becomes negatively charged



Heterolytic mechanisms



Heterolytic bond formation

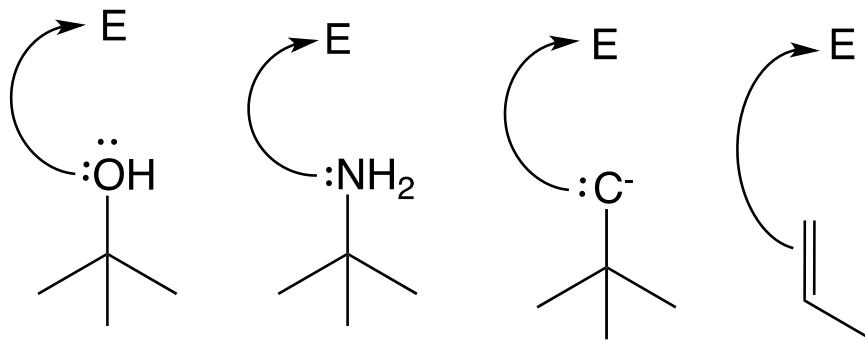


Heterolytic bond cleavage

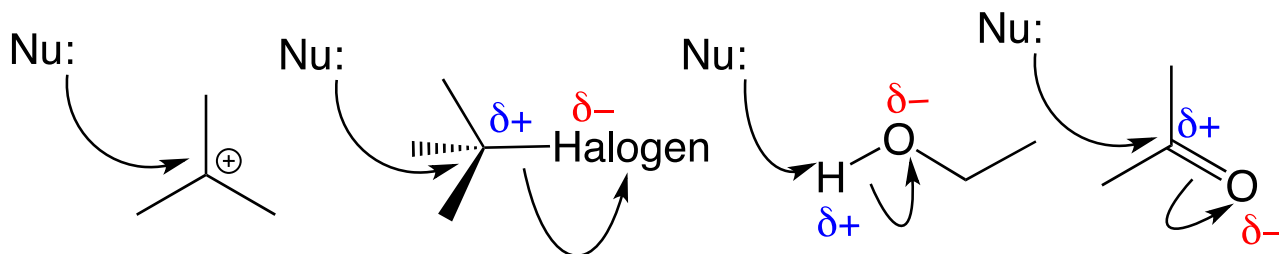
Tips for “arrow pushing” in Polar Reactions

Electrons must move from a nucleophilic source (Nu:) to an electrophilic sink (E)

Nucleophilic source must have electron pair available as a lone pair or in a multiple bond



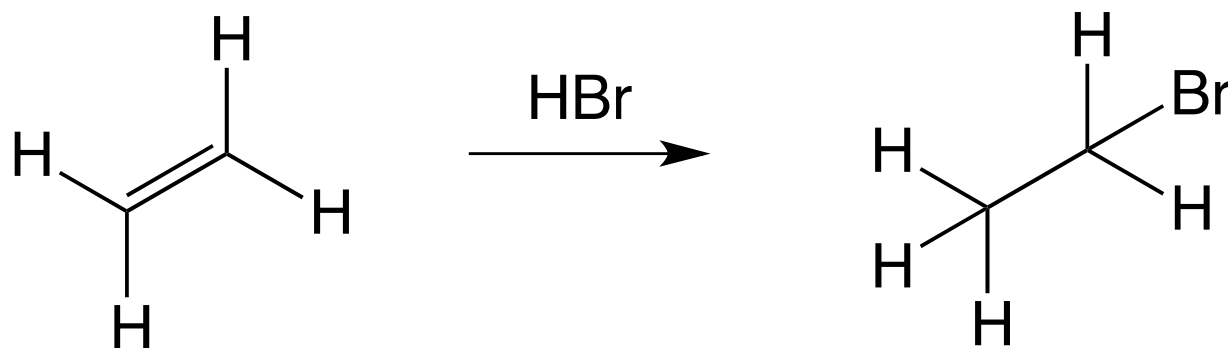
Electrophilic sink must have be able to accept a pair or electrons, either on a positively charged atom or an atom with partial positive charge (polarized bond)



Follow the octet rule

- Moving electrons must be done so all atoms are left with 8 electrons (or 2 electrons for H), or appropriate + or – charges (i.e. protons, carbocations, carbanions)
- No second row atom (C, N, O) can be left with 10 electrons (or 4 for H)
- If an electron pair moves to an atom that already has an octet (or 2 electrons if H) then another electron pair must move simultaneously away from that atom to maintain the octet

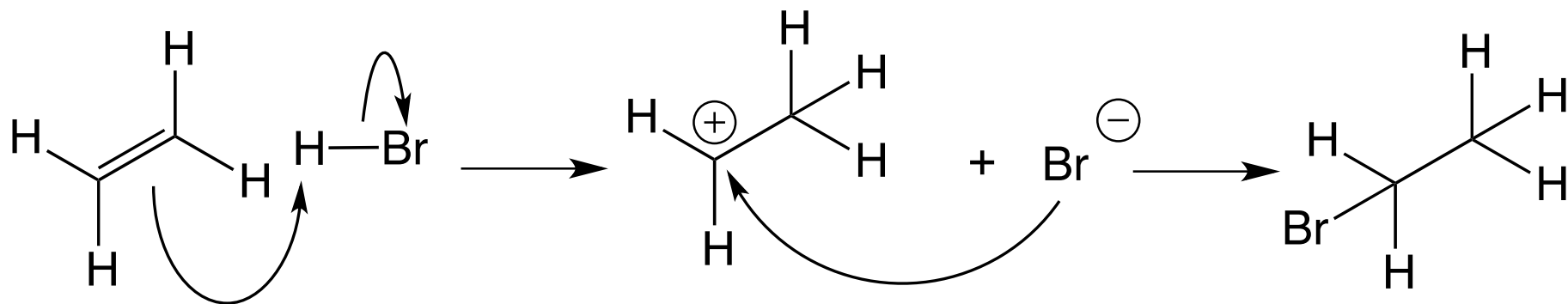
Addition reactions



- Good “atom economy” – 2nd Principal of Green Chemistry
- Atom economy asks “what atoms of the reactants are incorporated into the final desired product(s) and what atoms are wasted?”¹
- The opposite of elimination reactions

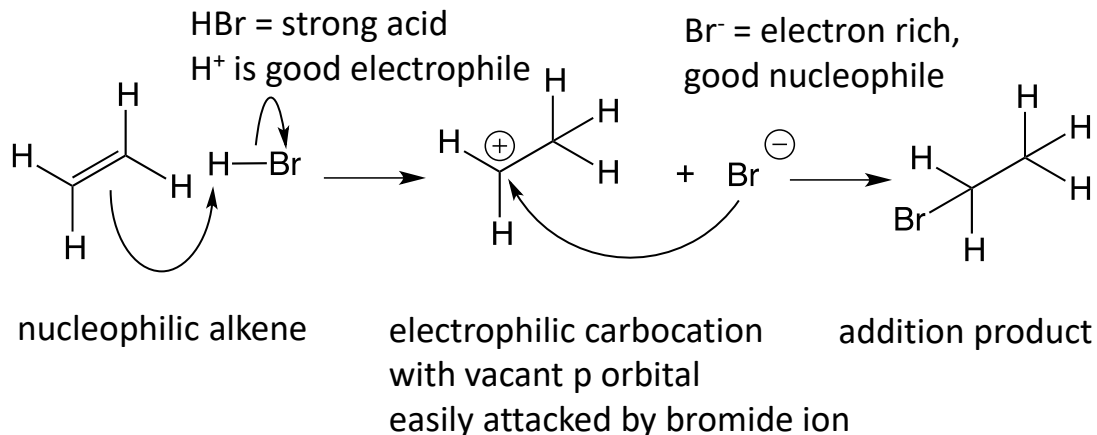
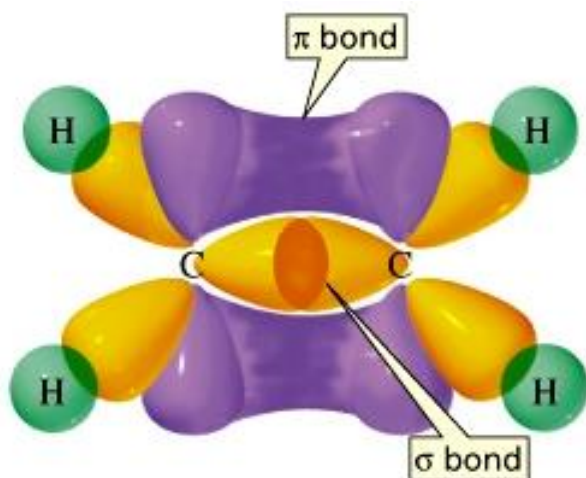
¹The Atom Economy-A Search for Synthetic Efficiency; Barry M. Trost; *Science* 1991, (254), pp 1471-1477.

Electrophilic addition of HBr to ethylene



- Ethylene is nucleophile
- HBr is electrophile
- Two electrons move onto bromine giving bromide ion
- Ethane carbocation has a vacant p-orbital
- Bromide “attacks” carbocation
- Addition product

Electrophilic addition reaction of ethylene and HBr

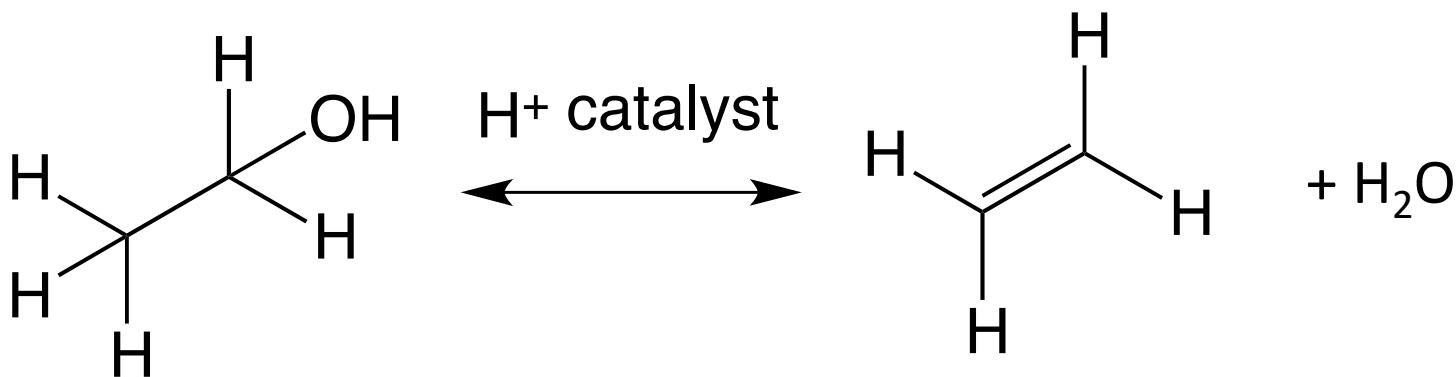


Alkane (C-C and C-H single bonds) electrons in sigma bonds, close to nucleus, non-polar, inert

Alkenes (C=C double bonds) have greater e⁻ density (4 instead of 2 e⁻s), are accessible (i.e. pi bond located above and below plane of sp², trigonal planar molecule), and are further from nucleus.

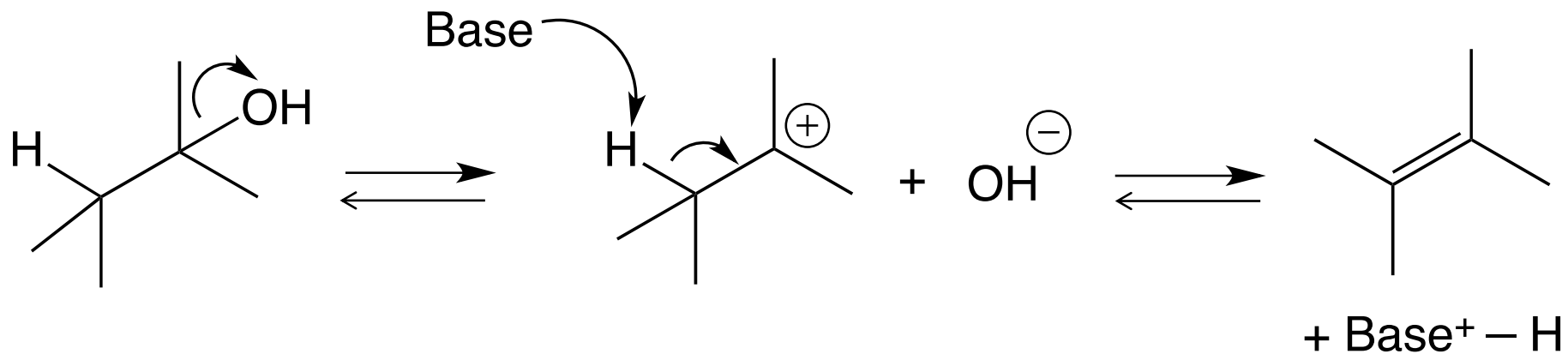
Therefore, alkene double bonds can react as nucleophiles

Elimination Reactions



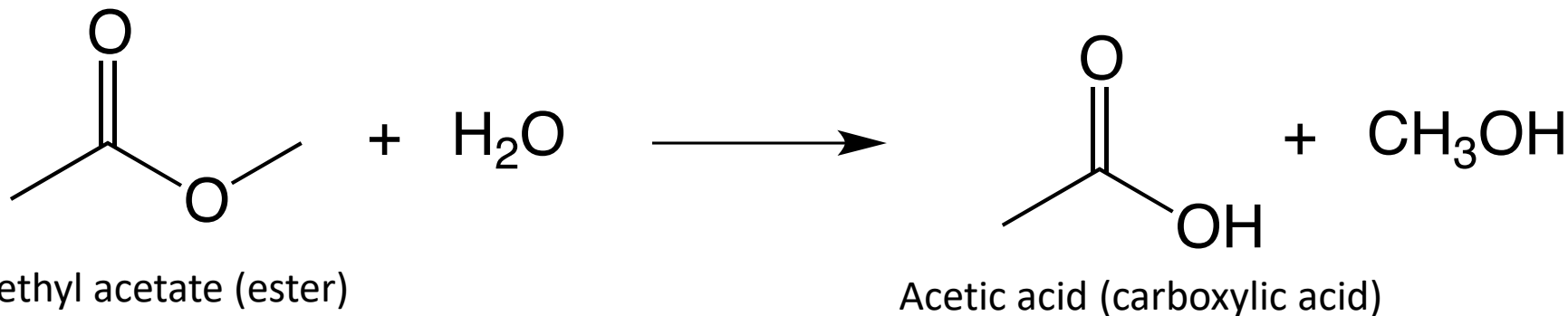
- Reactant splits into two products, one is usually small (i.e. HBr or H₂O)
- Occur by three different mechanisms (E1, E2, E1cB)
- Often equilibrium reactions
- Considered the opposite of addition reactions

E1 Elimination



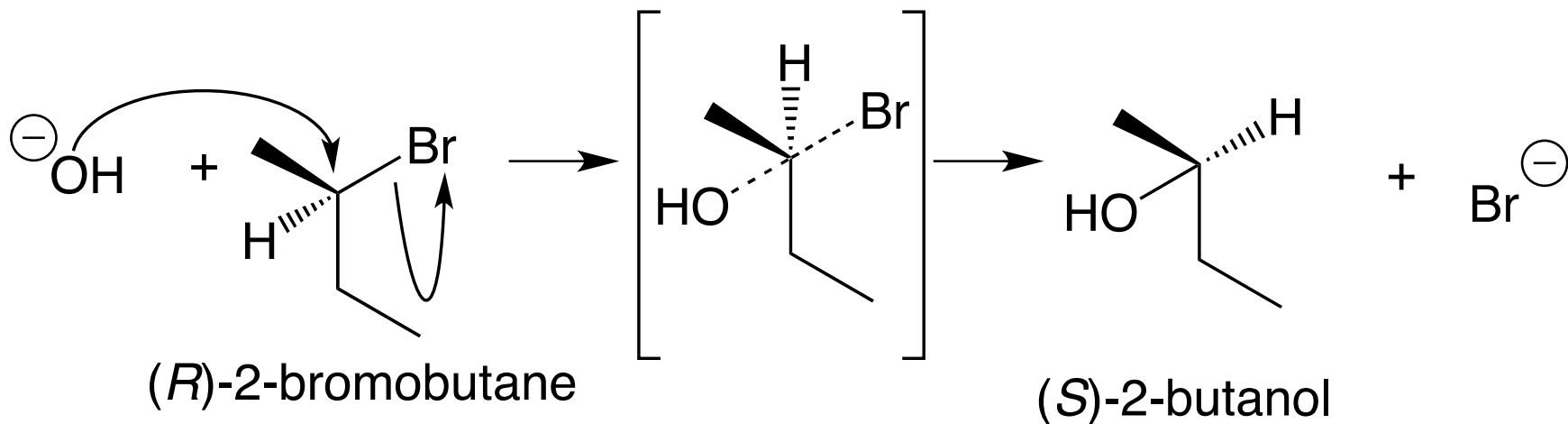
- C-OH bond breaks
- Carbocation intermediate formed
- Base removes proton
- Alkene product

Substitution Reactions



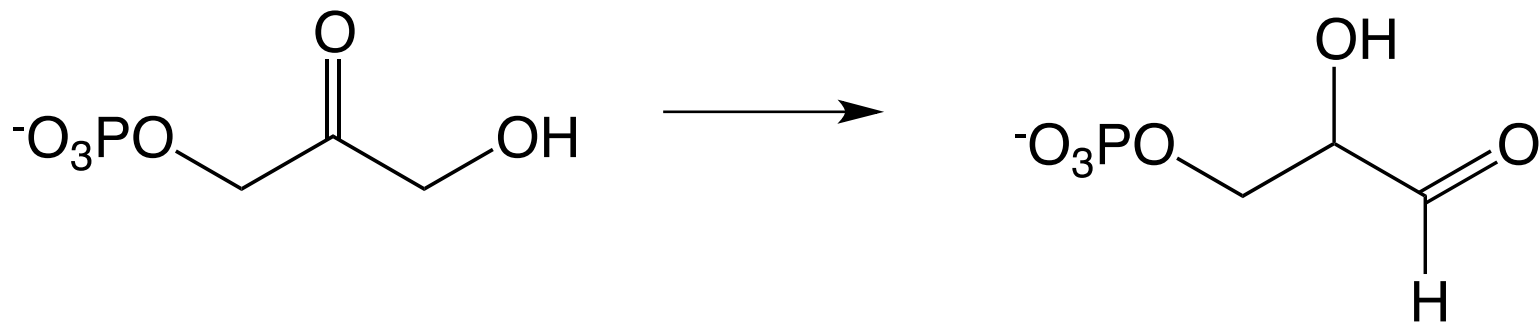
- One functional group of a compound is replaced by another function group
- Classified as either bimolecular or unimolecular depending on specific mechanism involved
- Carbocation, carbanion or radical intermediates
- Aliphatic or aromatic substrates
- Many occur in biological systems (e.g. fat metabolism)

S_N2 substitution reaction



- Nucleophilic OH[⊖] attacks the electrophilic carbon atom
- Planar transition state where C-OH bond is forming while C-Br bond is breaking
- Product has *inverted* stereochemistry

Rearrangement Reactions

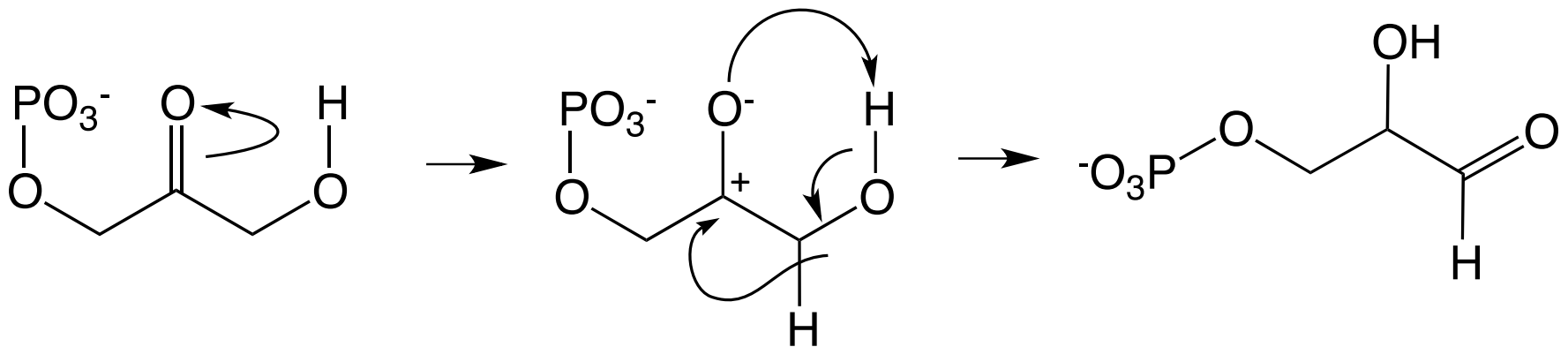


dihydroxyacetone phosphate

glyceraldehyde-3-phosphate

- Broad class of organic reactions where carbon skeleton is rearranged to give a constitutional (structural) isomer
- Not well described by “arrow pushing”
- Often involving orbital interactions (i.e. pericyclic reactions)
- Examples include 1,2-rearrangements, pericyclic reactions and olefin metathesis

Rearrangement reaction: 1,2-hydride shift



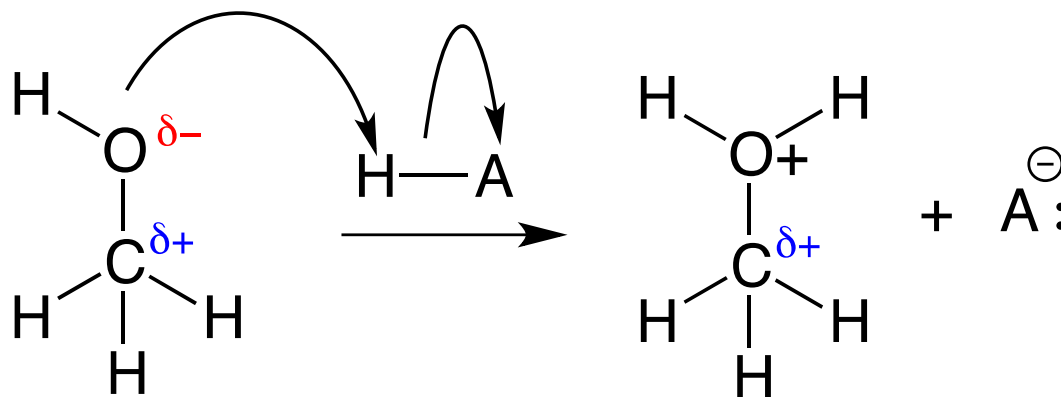
- Electrons of ketone double bond migrate to form alkoxide/carbocation intermediate

- Alkoxide oxygen abstracts proton from alcohol
- Electrons collapse to form aldehyde
- Hydride ion shifts to carbonyl carbon atom

- Rearrangement product

Polar bonds resulting from interaction of functional groups with Brønsted acids

Methanol C is *somewhat* electron poor due to bonding with electronegative oxygen atom

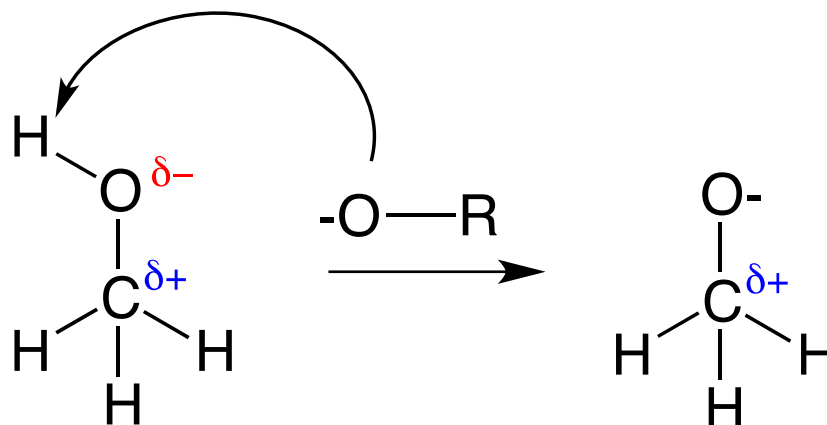


Upon protonation with acid, methanol C is *very* electron poor because electrons of C-O bond are also needed by two O-H bonds

As a result, C is much more electrophilic

Polar bonds resulting from interaction of functional groups with Brønsted bases

Methanol O is *somewhat nucleophilic* due to 2 lone pairs



Methoxide ion O is *very nucleophilic* due to 3 lone pairs