

## CHEM 203

### Topics Discussed on Sept. 6

Organic chemistry as the study of carbon-based compounds ("organic" compounds)

Unique propensity of carbon atoms to form bonds to other C atoms, giving rise to complex molecular architectures

Organic compounds:

- Almost always contain H bound to C. Example: methane, CH<sub>4</sub>
- Often contain O, N, S, P, halogens (F, Cl, Br, I), etc., bound to C
- May contain metals (Li, Mg, etc.) bound to C

Heteroatom: any atom other than C or H

Enormous impact of organic chemistry in the modern world

Agriculture & food

Energy (hydrocarbon fuels)

Environment (pollution control & decontamination)

Materials (fibers, plastics, ...)

Preservation and transmission of information & cultural heritage (computers & electronics; conservation & restoration of human artifacts, including art)

Human health (medicines)

Life (nucleic acids, proteins, enzymes, lipids, carbohydrates ....)

Of course it's difficult!

Milestones of organic chemistry: structural theory (1920's) & electronic theory (1940's - 50's)

Structural theory of organic chemistry: chemical individuality is determined by the precise atomic arrangement within (= the structure of) a molecule

Principle: the structure of an organic compound is defined by both

- (i) atomic connectivity, and
- (ii) spatial orientation of atoms within a molecule

Electronic theory of organic chemistry: chemical reactivity may be understood and predicted on the basis of the way electrons behave within a molecule

Principle: the electronic theory permits an approach to mastering organic chemistry that relies on logical reasoning, not on memorization.

## Topics Discussed on Sept. 8

### chapter 1 of Brown-Foote-Iverson

Covalent bonding in organic molecules

Covalent bonding as "electron-sharing" between atomic pairs

Particularly stable electronic configuration of inert (= noble) gases

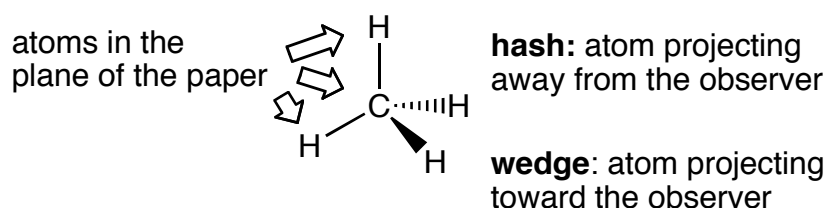
Principle: atoms in a bonded state tend to acquire an electronic configuration similar to that of a noble gas

Bonding in methane:  $\sigma$ -bonds

Valence Shell Electron Pair Repulsion (VSEPR)

Tetrahedral shape of methane predicted by VSEPR and confirmed by experiment

Use of wedges-and-dashed lines to represent the spatial orientation of atoms in a molecule

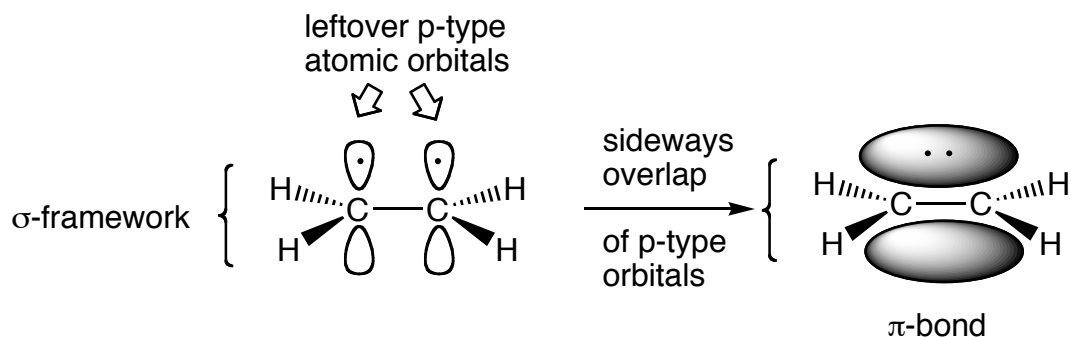


Association of tetrahedral geometry about a carbon atom with  $\text{sp}^3$  hybridization

Possible occurrence of multiple bonds (double, triple) between atoms in an molecule

Bonding in ethene (ethylene),  $\text{CH}_2=\text{CH}_2$ : a molecule containing a C-C double bond

$\sigma$ -Framework and  $\pi$ -bonds

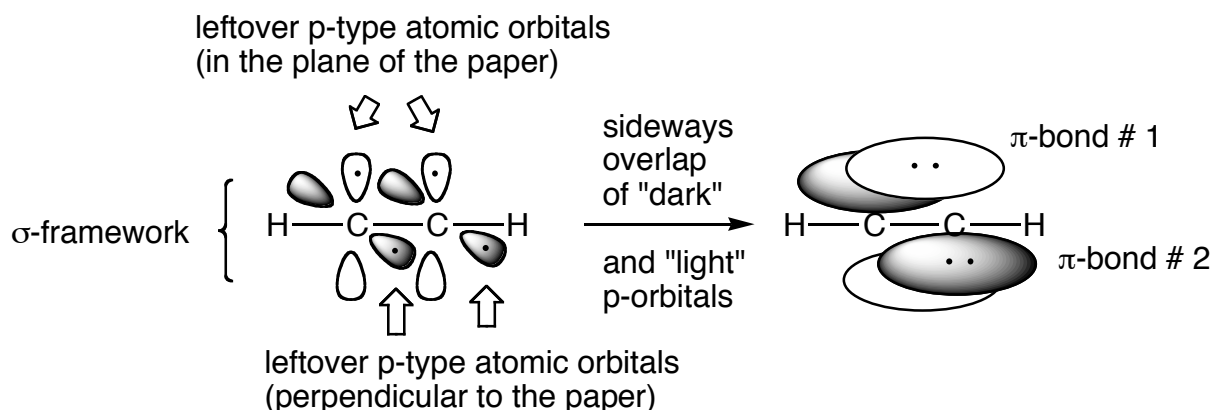


Trigonal geometry of the carbon atoms in ethene (ethylene) and related structures as predicted by VSEPR and as confirmed by experiment

Association of trigonal geometry about a carbon atom with  $sp^2$  hybridization

Bonding in ethyne (acetylene),  $H-C\equiv C-H$ : a molecule containing a C-C triple bond

Presence of two independent  $\pi$ -bonds in acetylene



Linear geometry of the carbon atoms in acetylene and related structures as predicted by VSEPR and as confirmed by experiment

Association of linear geometry about a carbon atom with  $sp$  hybridization

Principle: atoms can produce bonded states in which significant electrostatic unbalances exist

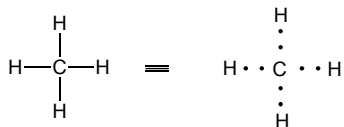
Formal charge of an atom in a molecule: a parameter that indicates whether the atom in question is electrostatically balanced or unbalanced

The formal charge on an atom is calculated by counting the total number of valence electrons that the atom contributes to the various covalent bonds in which it participates, and by deciding whether these valence electrons balance out the nuclear charge or are in deficit or in surplus.

The case of  $CH_4$  vs.  $NH_4$  vs.  $BH_4$

#### The formal charge on the C atom in methane, $CH_4$

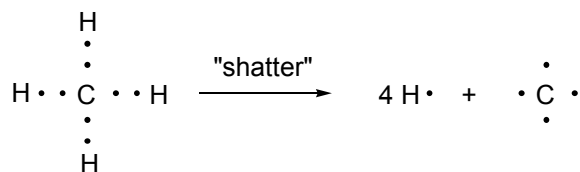
**Step 1:** draw a complete Lewis structure of the molecule:



**Step 2:** count the number of valence electrons around the atom of interest.

Each atom in a bonded pair of atoms has contributed one of its valence electrons to the electron pair that we call "bond." If we "shatter" the molecule so that each atom in a bonded pair retrieves

one of the two electrons that form the bond (i.e., if we "undo" covalent bonds) we will see how many valence electrons are present around each atom:



Conclusion: the C atom in methane is surrounded by 4 valence electrons

**Step 3:** *determine whether valence electrons cancel the nuclear charge out.*

- Carbon is in group 4 of the periodic table, so it requires 4 valence electrons to balance the nuclear charge out.
- The C atom in methane has 4 valence electrons
- The C atom in methane is electrostatically balanced

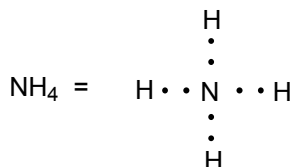
Conclusion: the formal charge on C in methane is zero

**Notice** that the formal charge on each H atom is also zero. Indeed, H atoms in *any* covalent molecule have always zero formal charge, as readily determined through the above logic.

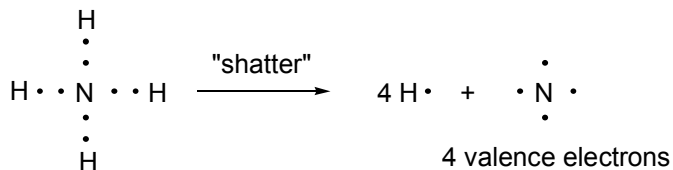
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**The formal charge on the N atom in NH<sub>4</sub>**

**Step 1:** *draw a complete Lewis structure of the molecule:*



**Step 2:** *count the number of valence electrons around the atom of interest.*

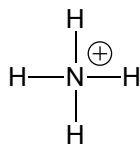


**Step 3:** *determine whether valence electrons balance the nuclear charge out.*

- N is in group 5: it needs 5 valence electrons to balance out the nuclear charge.
- The N atom in NH<sub>4</sub> has 4 valence electrons: 1 fewer than it should.
- The N atom in NH<sub>4</sub> is electrostatically unbalanced

Conclusion: the formal charge on N in  $\text{NH}_4$  is  $+1$

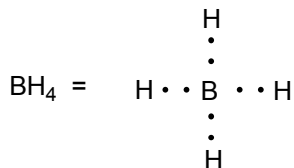
**Important:** formal charges are integral parts of a chemical structure and must be clearly indicated. This is done with encircled  $+$  or  $-$  signs. So, the correct way to draw  $\text{NH}_4$  is:



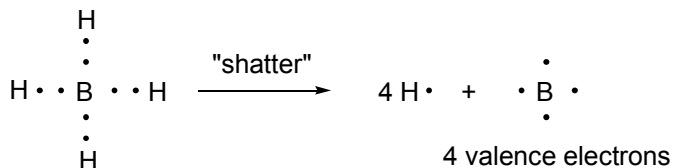
**Why "formal" charge?** Rigorously speaking, the  $+1$  charge present in  $\text{NH}_4^+$  is delocalized all over the molecule, i.e., each atom (N and 4 H's in this case) bears a share thereof. For simplicity, however, it is convenient to think of it as *if it were* localized on the N atom. That's why one calls it a *formal* charge: because for chemical reasoning it is best to think of it as *formally* residing on the N atom.

**The formal charge on the B atom in  $\text{BH}_4$**

**Step 1:** draw a complete Lewis structure of the molecule:



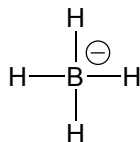
**Step 2:** count the number of valence electrons around the atom of interest.



**Step 3:** determine whether valence electrons balance the nuclear charge out.

- B is in group 3: it needs 3 valence electrons to balance out the nuclear charge.
- The B atom in  $\text{BH}_4$  has 4 valence electrons: 1 more than it should.
- The B atom in  $\text{BH}_4$  is electrostatically unbalanced

Conclusion: the formal charge on B in  $\text{BH}_4$  is  $-1$



Isoelectronic molecules: molecules that possess identical electronic configuration by this criterium,  $\text{CH}_4$ ,  $\text{NH}_4^+$  and  $\text{BH}_4^-$  are isoelectronic

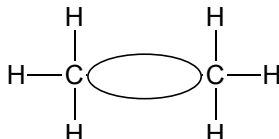
Electronegativity as the ability of an atom to exert an attractive force upon valence electrons

The electronegativity of first-row elements starts at 1.0 and it increases by 0.5 units per column:

Li = 1.0; Be = 1.5; B = 2.0; C = 2.5; N = 3.0; O = 3.5; F = 4

Influence of atomic electronegativity on the electron distribution within bonds

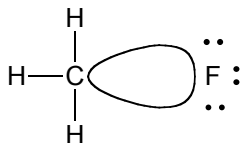
Case of the C–C bond in ethane,  $\text{H}_3\text{C}-\text{CH}_3$



**bond between two atoms of identical electronegativity (C and C):**

each atom "pulls" equally strongly on the  $\sigma$ -electron pair that makes up the C–C bond. The electron distribution within the bond will be symmetrical relative to the midpoint of the bond, thereby approximating a "football" shape

Case of the C–F bond in fluoromethane,  $\text{H}_3\text{C}-\text{F}$



**bond between two atoms of differing electronegativities (F more electronegative than C):**

the F atom "pulls" more strongly than the C atom on the  $\sigma$ -electron pair that makes up the C–F bond. The electron distribution within the bond will be distorted toward the F atom (i.e., the electrons will reside closer to the F atom), thereby approximating a "pear" shape

### Topics Discussed on Sept. 11 chapter 1 of Brown-Foote-Iverson

Polar bonds

Dipole moment

Vector nature of the dipole moment

Principle: molecules incorporating multiple polar bonds may or may not possess a net dipole moment, depending on the magnitude of the vector sum of individual bond dipoles

Polar molecules: those in which bond dipoles do not cancel out, , e.g,  $\text{CH}_3\text{-F}$

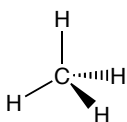
Nonpolar molecules: those in which bond dipoles cancel out, e.g,  $\text{CF}_4$

Influence of bond polarization on the chemical reactivity of a species, in particular on the ability of the species to accept or donate electrons during chemical reactions.

Principle: as a result of bond polarization, an atom in a molecule may acquire an electronic configuration that more closely resembles that of the successive noble gas or that of the preceding noble gas.

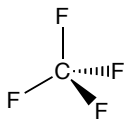
Oxidation state: a parameter that describes to what extent an atom in a bonded state possesses an electronic configuration that more closely resembles that of the successive or the preceding noble gas.

Example: the oxidation state of C in  $\text{CH}_4$  and in  $\text{CF}_4$



- C is more electronegative than H (2.5 vs. 2.1)
- Formally, C has "stolen" 1 electron from each of the 4 H's
- Formally, C has acquired 4 electrons in this bonded state

The oxidation state of C in  $\text{CH}_4$  is  $-4$ : the C atom in  $\text{CH}_4$  has an electronic configuration that is closer to that of **neon** than to that of helium



- C is less electronegative than F (2.5 vs. 4.0)
- Formally, C has "lost" 1 electron to each of the 4 F's
- Formally, C has lost 4 electrons in this bonded state

The oxidation state of C in  $\text{CF}_4$  is  $+4$ : the C atom in  $\text{CF}_4$  has an electronic configuration that is closer to that of **helium** than to that of neon

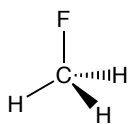
Principle: determining whether the bonded state of a given atom resembles more closely the preceding or the successive noble gas allows one to make important predictions about chemical reactivity:

**Example:** the C atom in  $\text{CH}_4$  has formally acquired 4 electrons, thereby assuming the oxidation state of  $-4$ . This produces a significant concentration of electronic density around the C atom. One may predict that the C atom in methane will behave as an electron donor in its reactions; that is, it will tend to react with electron acceptors. Likewise, one may predict that hypothetical reactions that would add more electrons to the C atom in question will be extremely difficult or impossible to perform.

By contrast, the C atom in  $\text{CF}_4$  has formally lost 4 electrons, thereby assuming the oxidation state of  $+4$ . This produces significant electron-deficiency around the C atom. One may predict that the C atom in  $\text{CF}_4$  will behave as an electron acceptor in its reactions; that is, it will tend to react with electron donors. Likewise, one may predict that hypothetical reactions that would subtract more electrons from the C atom in question will be extremely difficult or impossible to perform.

The oxidation state of an atom in a generic molecule as the algebraic sum of bond polarization and formal charge

Example: the oxidation state of C in  $\text{CH}_3\text{-F}$



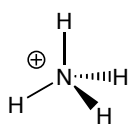
- C is more electronegative than H (2.5 vs. 2.1)
- Formally, C has "stolen" 1 electron from each of the 3 H's
- Bonding with H produces a partial oxidation state of  $-3$  for C

- C is less electronegative than F (2.5 vs. 4.0)
- Formally, C has "lost" 1 electron to the 4 F atom
- Bonding with F produces a partial oxidation state of  $+1$  for C

- There is no formal charge on C in  $\text{CH}_4$

The oxidation state of C in  $\text{CH}_3\text{-F}$  is:  $-3 + 1 = -2$   
 The electronic configuration of the C atom in  $\text{CH}_4$  resembles more closely that of **neon** than to that of helium

Example: the oxidation state of N in  $\text{NH}_4^+$ :



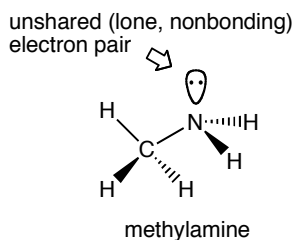
- N is more electronegative than H (3.0 vs. 2.1)
- Formally, N has "stolen" 1 electron from each of the 4 H's
- Formally, N has acquired 4 electrons in this bonded state

- There is a  $+1$  formal charge on N in  $\text{NH}_4^+$

The oxidation state of N in  $\text{NH}_4^+$  is:  $-4 + 1 = -3$   
 The electronic configuration of the N atom in  $\text{NH}_4^+$  resembles very much that of **neon**

Issues of electrostatic unbalance (formal charges, bond polarization, molecular polarity, oxidation states, etc.) as significant aspects of the chemistry of organic molecules containing heteroatoms, especially N, O, S, P, halogens

Presence of unshared pairs of electrons in molecules containing the above heteroatoms, e.g.:

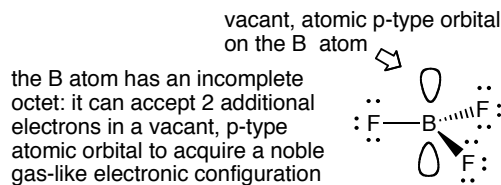


Ability of heteroatoms possessing unshared pairs to establish new bonds through interactions with appropriate species capable of accepting electron pairs

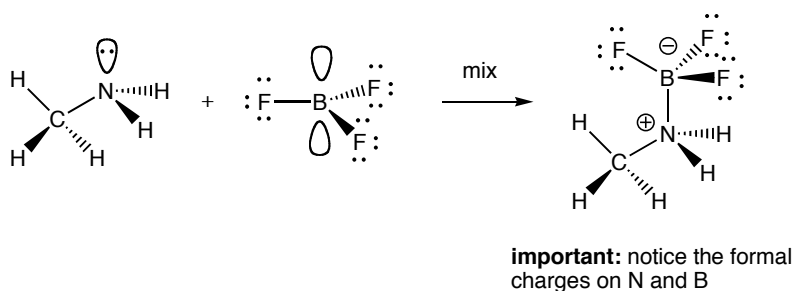


Principle: an atom / molecule can function as an acceptor of electron pairs only if it possesses a vacant orbital that can accommodate the incoming electron pair.

Example of a molecule that can function as an acceptor of electron pairs:  $\text{BF}_3$



Predictable (and experimentally verifiable) reaction between methylamine and  $\text{BF}_3$ :



Lewis acid: a species capable of accepting an electron pair from a suitable donor  
The  $\text{BF}_3$  in the above reaction behaves as a Lewis acid

Lewis base: a species capable of donating an electron pair to a suitable acceptor  
The  $\text{CH}_3\text{-NH}_2$  in the above reaction behaves as a Lewis base

### Topics Discussed on Sept. 13 see chapter 4 of Brown-Foote-Iverson

Electrophile: a Lewis acidic agent (= one that possesses a vacant orbital) that actually expresses such Lewis acidity during a chemical reaction

Nucleophile: a Lewis basic agent (= one that possesses an unshared pair of electrons) that actually expresses such Lewis basicity during a chemical reaction

Principle: one may find that a Lewis acid expresses electrophilicity only when it interacts with particular Lewis bases. Likewise, a Lewis base may happen to express nucleophilicity only when it interacts with particular Lewis acids. Hence, the distinction between:

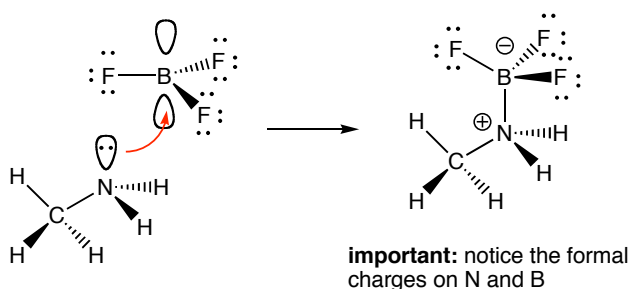
Lewis acidic / Lewis basic character:	a property determined by the electronic configuration of a molecule
and	

electrophilic / nucleophilic character:

ability of a Lewis acid / base to express their inherent reactivity

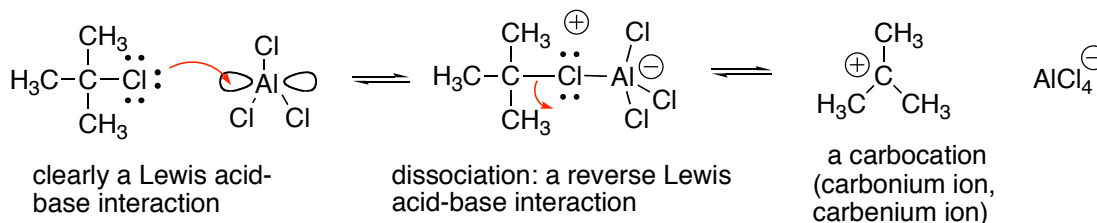
Curved arrows formalism to represent movement of electrons (**not of atoms**) during chemical reactions

Curved arrows formalism (red arrow below) to describe the reaction of, e.g.,  $\text{CH}_3\text{NH}_2$  with  $\text{BF}_3$ :



Interactions between Lewis acids and Lewis bases as a fundamental phenomenon that governs organic chemical reactions

Obvious case of organic reactions involving Lewis acid-base interactions: activation of certain organohalogen compounds ("*alkyl halides*") leading to the formation of carbocations (= carbonium ions, carbenium ions):

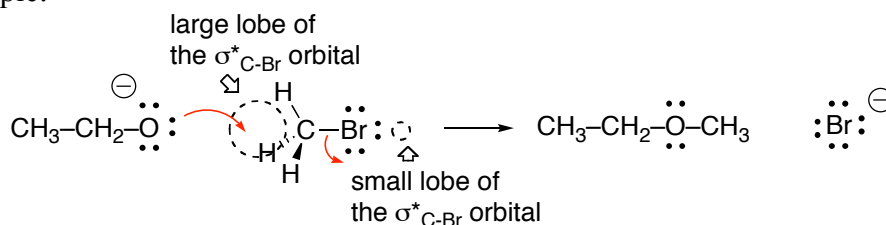


Reactive nature of carbocations and special importance of their chemistry in the petrochemical industry

Alkyl group: a molecular segment composed of C and H atoms, e.g. the  $(\text{CH}_3)_3\text{C}$  unit in the above organohalogen compound

Less obvious case of organic reactions involving Lewis acid-base interactions: the  $\text{S}_{\text{N}}2$  reaction

Example:



The  $\text{CH}_3\text{Br}$  in the above reaction accepts a pair of electrons into the vacant  $\sigma^*_{\text{C-Br}}$  orbital, thereby behaving as a Lewis acid

Bonding and antibonding orbitals arising through LCAO (Linear Combination of Atomic Orbitals)

Bond order (BO):  $\text{BO} = (\# \text{ electrons in bonding orbitals} - \# \text{ electrons in antibonding orbitals}) / 2$

Weakening / breaking of a generic bond A–B upon introduction of electronic density into the corresponding antibonding orbital

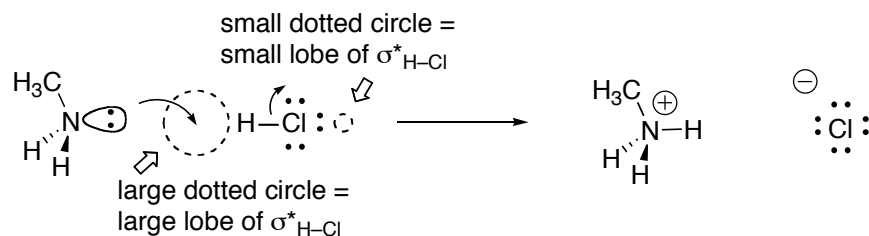
Example: In the above  $\text{S}_{\text{N}}2$  reaction, the nucleophile introduces a pair of electrons into the vacant  $\sigma^*_{\text{C-Br}}$  orbital. As a result, the BO of the C–Br bond becomes

$$\text{BO} = (2 \text{ e}^- \text{ in bonding orbital} - 2 \text{ e}^- \text{ in antibonding orbital}) / 2 = 0$$

That is, the bond between C and Br vanishes and the  $\text{Br}^-$  becomes free to "float away."

### Topics Discussed on Sept. 15 see chapter 4 of Brown-Foote-Iverson

Special case of Lewis acid-base reactions: proton transfer (=protonation) reactions, e.g.:



Analogy between proton transfer reactions and  $\text{S}_{\text{N}}2$  reactions

Bronsted acids, Bronsted bases: proton donors / acceptors, respectively

$\text{pK}_{\text{a}}$  of a generic Bronsted acid H–A:  $\text{pK}_{\text{a}} = -\log K_{\text{a}}$ , where:

$$K_{\text{a}} = \frac{[\text{H}^+][\text{A}^-]}{[\text{H-A}]}$$

for the equilibrium:  $\text{H-A} \rightleftharpoons \text{H}^+ + \text{A}^-$

**reminder:** acid strength and  $\text{pK}_{\text{a}}$ 's are inversely proportional, that is:  
**strong** acids have small  $\text{pK}_{\text{a}}$ 's

**moreover:** **weak** acids have large pKa's  
the dissociation of a **strong** Bronsted acid releases a **weak** Bronsted base  
the dissociation of a **weak** Bronsted acid releases a **strong** Bronsted base

Principle: the chemical behavior of a system in which proton transfers are likely to occur may be predicted on the basis of changes in the acidity / basicity of the medium, which in turn can be gauged from the pKa's of the reacting species.

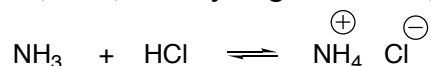
Relationship between pKa, acid-base equilibrium constants and standard free energy changes ( $\Delta G^\circ$ )

**reminder:** the equilibrium constant for a Bronsted acid-base equilibrium is calculated from the difference in pKa's of the reacting species (see handout on pKa's).  
Furthermore, a generic chemical equilibrium that may be expressed with an equilibrium constant,  $K_{eq}$ , comports a standard free energy change,  $\Delta G^\circ$ , which is given by the Gibbs equation:

$$\Delta G^\circ = -n RT \ln K_{eq}$$

Therefore, free energy changes (= thermodynamic driving forces) associated with proton-transfer reactions may be estimated from the pKa's of the reacting species through the Gibbs equation

Example: the reaction of ammonia,  $\text{NH}_3$ , with hydrogen chloride,  $\text{HCl}$ :



we wish to predict the chemical behavior of the system, that is, whether the reaction is favorable or unfavorable, and how favorable / unfavorable it is, knowing that:

pKa of  $\text{NH}_4^+ \approx +9$  ( $\text{NH}_4^+$  is the weaker Bronsted acid,  $\text{NH}_3$  is the stronger Bronsted base)  
pKa of  $\text{HCl} \approx -7$  ( $\text{HCl}$  is the stronger Bronsted acid,  $\text{Cl}^-$  is the weaker Bronsted base)

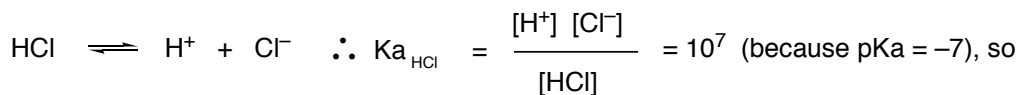
One can tell immediately that the reaction in question will be favorable, because it consumes a stronger acid ( $\text{HCl}$ ) and a stronger base ( $\text{NH}_3$ ) to produce a weaker acid ( $\text{NH}_4^+$ ) and a weaker base ( $\text{Cl}^-$ ). Regardless, the equilibrium constant for the above reaction is:

$$K_{eq} = \frac{[\text{NH}_4^+][\text{Cl}^-]}{[\text{NH}_3][\text{HCl}]} = \frac{[\text{NH}_4^+]}{[\text{NH}_3]} \cdot \frac{[\text{Cl}^-]}{[\text{HCl}]}$$

One can easily express the above  $K_{eq}$  as a function of the pKa's of  $\text{NH}_4^+$  and of  $\text{HCl}$ :

$$\text{NH}_4^+ \rightleftharpoons \text{H}^+ + \text{NH}_3 \therefore K_{a_{\text{NH}_4^+}} = \frac{[\text{H}^+][\text{NH}_3]}{[\text{NH}_4^+]} = 10^{-9} \text{ (because pKa} = 9\text{), so}$$

$$\frac{[\text{NH}_4^+]}{[\text{NH}_3]} = \frac{[\text{H}^+]}{10^{-9}}$$



$$\frac{[\text{Cl}^-]}{[\text{HCl}]} = \frac{10^7}{[\text{H}^+]}$$

$$K_{\text{eq}} = \frac{[\text{H}^+]}{10^{-9}} \cdot \frac{10^7}{[\text{H}^+]} = 10^{16}$$

$$\text{notice: } pK_{\text{eq}} = -16 = pK_{\text{a}}(\text{HCl}) - pK_{\text{a}}(\text{NH}_4^+) = -7 - (+9)$$

Indeed,  $K_{\text{eq}}$  is large and positive, reflecting a favorable reaction. To determine "how favorable" the reaction is, we need to estimate its  $\Delta G^\circ$ :

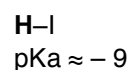
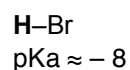
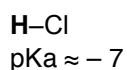
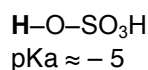
$$\Delta G^\circ = -n RT \ln K_{\text{eq}} \quad \text{so, for } n = 1 \text{ mol @ } 25^\circ\text{C:}$$

$$\Delta G^\circ = -1.98 \cdot 10^{-3} \text{ kcal/mol}^\circ\text{K} \cdot (25 + 273)^\circ\text{K} \cdot \ln 10^{16} = -1.98 \cdot 10^{-3} \cdot 298 \cdot 36.8$$

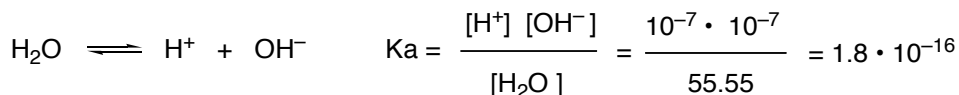
$$\Delta G^\circ = -21.7 \text{ kcal/mol}$$

Wide range of  $pK_{\text{a}}$ 's for the Bronsted acid dissociation of molecules of interest in organic chemistry

Strong Bronsted acids: those with a  $pK_{\text{a}} < 0$ , e.g.:



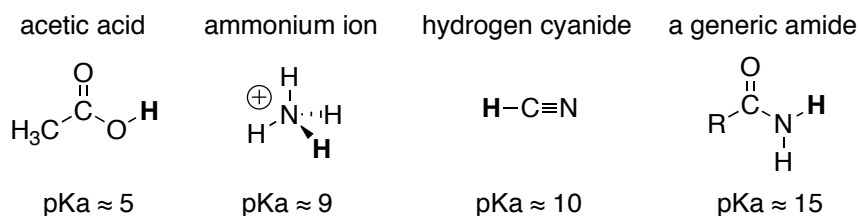
The  $pK_{\text{a}}$  of  $\text{H}_2\text{O} = \text{ca. } 16$ :



$$\text{so, } pK_{\text{a}}(\text{H}_2\text{O}) = -\log(1.8 \cdot 10^{-16}) = 15.7 \approx 16$$

↖ number of moles of  $\text{H}_2\text{O}$  (mw = 18) in 1 L (=1 kg) of  $\text{H}_2\text{O}$

Weak Bronsted acids: those with  $0 < pK_{\text{a}} < 16$ , e.g.:



Carbonyl group: the atomic arrangement  $\text{C}=\text{O}$ , wherein a C atom establishes a double bond to an O atom

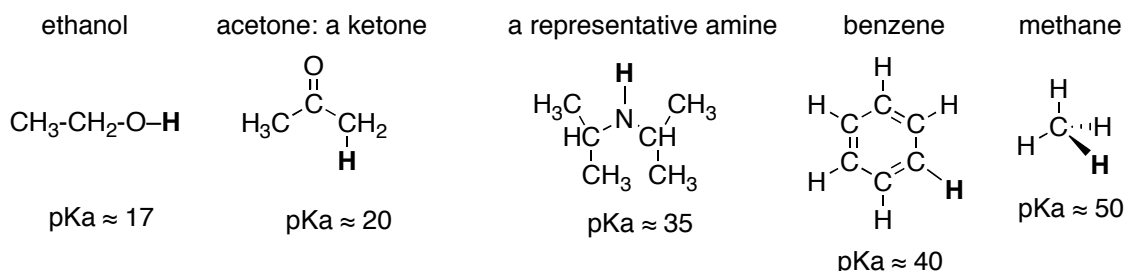
Acid, carboxylic acid: a molecule such as acetic acid, wherein an OH group is connected to a carbonyl group

"R" notation to represent a generic group connected to given atom of an organic molecule

Amide, carboxamide: a molecule wherein an N atom is connected to a carbonyl group.

Widespread occurrence of amide units in biologically relevant molecules such as proteins, etc.

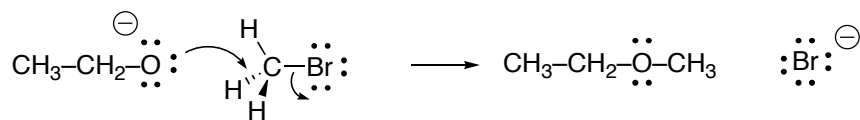
Very weak Bronsted acids: those with a  $pK_a > 16$ , e.g.:



Ketone: a carbonyl compound wherein the  $\text{C=O}$  unit is bound to two alkyl groups

Changes in the acidity / basicity of the medium during a chemical reaction — as gauged from the  $pK_a$ 's of the species involved ( $\Delta pK_a$ 's) — as *significant components* (**but not sole components**) of the overall driving force of *any* reaction involving Bronsted acidic / basic agents.

**example:** the  $S_N2$  reaction



- $\text{CH}_3\text{-CH}_2\text{-O}^-$  is the conjugate Bronsted base of ethanol,  $\text{CH}_3\text{-CH}_2\text{-OH}$
- the  $pK_a$  of ethanol for dissociation of the O-H bond is  $\approx 17$
- $\text{Br}^-$  is the conjugate Bronsted base of HBr,  $pK_a \approx -8$

The above reaction consumes a stronger Bronsted base (ethoxide ion) to produce a weaker Bronsted base. Therefore, it may be anticipated to be favorable on the basis of overall change in the basicity of the medium. If one interprets the above reaction as a Bronsted equilibrium, one may estimate a  $K_{eq}$  as follows:

$$pK_{eq} = pK_a(\text{Br}^-) - pK_a(\text{CH}_3\text{-CH}_2\text{-O}^-) = -8 - (17) = -25 \quad \text{so, } K_{eq} = 10^{25}$$

corresponding to a thermodynamic driving force ( $n=1$ ,  $T = 25^\circ\text{C} = 298^\circ\text{K}$ ) of:

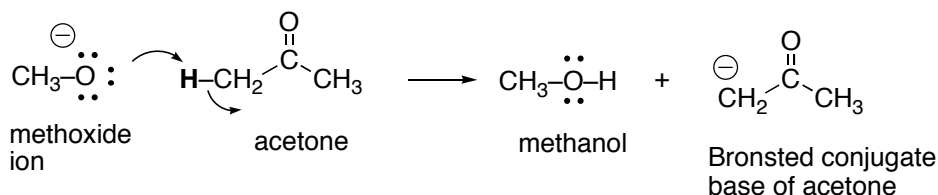
$$\Delta G^\circ = -nRT \ln K_{eq} = -1.98 \cdot 10^{-3} \cdot 298 \cdot \ln 10^{25} \approx -34.0 \text{ kcal/mol}$$

as far as Bronsted acid/base properties of the system are concerned

Use of pKa's to generate quantitative estimates of other aspects of the reactivity of systems involving chemical interactions between Lewis basic agents, such as equilibrium concentrations of reactive species, reaction rates, etc.

**example:** the weak Bronsted acidity of acetone ( $pK_a \approx 20$ , see above) allows one to generate the corresponding conjugate base and cause it to participate in a range of chemical reactions. The rate of such reactions will necessarily be a function of the instant concentration of the base in question.

Suppose that an organic chemical experiment requires us to estimate the concentration of the conjugate base of acetone generated through reaction of acetone with methoxide ion,  $CH_3O^-$ , which is the conjugate base of methanol,  $CH_3O-H$ ,  $pK_a \approx 16$ . Suppose also that the initial concentrations of acetone and methoxide ion are both equal to 1 M:



- The reaction generates a stronger Bronsted base at the expenses of a weaker Bronsted base, so it will be unfavorable.
- The Keq for the reaction is:

$$pK_{eq} = pK_a(\text{acetone}) - pK_a(\text{methanol}) = 20 - 16 = 4 \quad \text{therefore } K_{eq} \approx 10^{-4}$$

$$K_{eq} = \frac{[CH_3OH] [CH_3-CO-CH_2^-]}{[CH_3O^-] [CH_3-CO-CH_3]} \approx 10^{-4}$$

(**note:** since  $K_{eq} < 1$ ,  $\Delta G^\circ > 0$ , i.e., the reaction is indeed thermodynamically unfavorable)

- Because formation of one molecule of conjugate base of acetone comports a simultaneous formation of one molecule of methanol, the concentration terms in the numerator of the Keq expression will be numerically identical, i.e.,  $[CH_3OH] = [CH_3-CO-CH_2^-]$
- Because Keq is very small, the reaction will hardly progress to the products; that is, the concentration of reactants will remain very close to 1 M at equilibrium. Therefore, both concentration terms in the denominator of the Keq expression will be essentially = 1.

But then:

$$K_{eq} = \frac{[CH_3OH] [CH_3-CO-CH_2^-]}{[CH_3O^-] [CH_3-CO-CH_3]} \approx 10^{-4} \approx [CH_3-CO-CH_2^-]^2 \Rightarrow$$

$$[CH_3-CO-CH_2^-] \approx 10^{-2} \text{ M}$$

roughly 1% of the initial quantity of acetone will have been converted to the corresponding conjugate base under these conditions

**Topics Discussed on Sept. 18**  
**see chapters 5-6 of Brown-Foote-Iverson**

Alkenes or olefins: organic molecules that incorporate a carbon-carbon double bond

Functional groups: particular atomic arrangements that possess characteristic chemical behavior

The carbon-carbon double bond as the functional group of alkenes

Nomenclature of alkenes: the names of alkenes are derived from the names of simple hydrocarbons studied in introductory chemistry by replacing the ending -ane with -ene:

$\text{CH}_3\text{--CH}_3$	<b>ethane</b>	$\text{CH}_2\text{=CH}_2$	<b>ethene</b> (=ethylene)
$\text{CH}_3\text{--CH}_2\text{--CH}_3$	<b>propane</b>	$\text{CH}_2\text{=CH--CH}_3$	<b>propene</b>
butane ----> <b>butene</b> ;			
pentane ----> <b>pentene</b>			
etc.			

Positional isomerism in alkenes: the case of "butene"

The term "butene" may be applied to two distinct molecules:



the two molecules differ for the *position* of the double bond within an otherwise identical molecular framework. They may thus be described as **positional isomers**

Distinguishing positional isomers by "tagging" carbon atoms in a molecule with appropriate numerical indices, and by expressing the position of the double bond with an index that defines the "starting point" of the double bond:

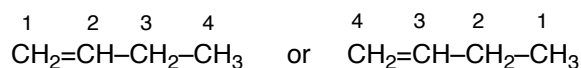
if we "tag" the four C atoms in "butene" as follows:  $\begin{array}{cccc} 1 & 2 & 3 & 4 \\ \text{C} & \text{--} & \text{C} & \text{--} & \text{C} \end{array}$

then we may describe  $\text{CH}_2\text{=CH--CH}_2\text{--CH}_3$  as "1-butene," underscoring the fact that the double bond "starts" on the first C atom of the molecule

Likewise, we may call  $\text{CH}_3\text{--CH=CH--CH}_3$  "2-butene," to convey the fact that the double bonds "starts" on the second atom of the molecule

Reminder: indices are chosen so that an unequivocal name for a molecular object results from the smallest possible numerical value of such indices.

**Example:** one could number the atoms in that molecule of butene in which the C=C system is located at a terminal position in two different ways:



The first numbering system would allow us to describe the molecule as "1-butene;" the second, as "3-butene." The first numbering system allows us to generate an unequivocal name by using a numerically smaller value of the index (1 vs. 3). Therefore, the first system

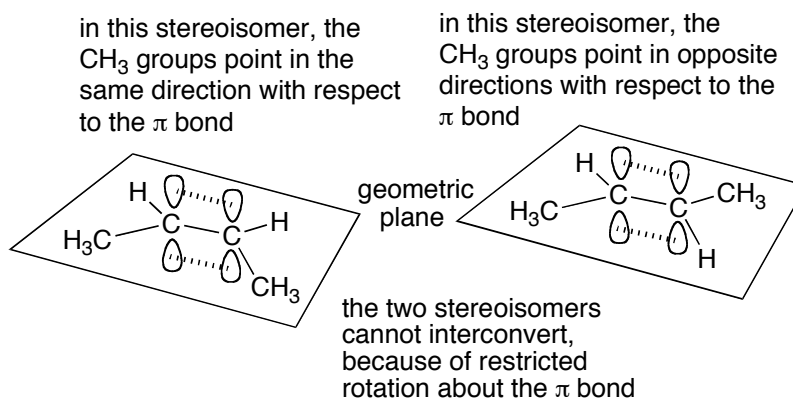


represents the correct numbering method.

Restricted rotation about the C–C  $\pi$  bond: energy barrier (= energy of the  $\pi$  bond) in ethylene  $\approx$  63 kcal / mol = 264 kJ / mol

compare the rotational energy barrier in ethane  $\approx$  3 kcal / mol or 12 kJ / mol. At room temperature, ethane undergoes ca.  $10^{11}$  internal revolutions per second, while ethylene is conformationally fixed. Internal rotation in ethylene may occur only at very high temperatures (  $T > 500\text{ }^{\circ}\text{C}$  )

Stereoisomerism (differences between molecular objects due to the spatial orientation of molecular segments) in alkenes as a consequence of restricted rotation: the case of 2-butene



Methyl, ethyl, propyl, butyl, .... alkyl groups

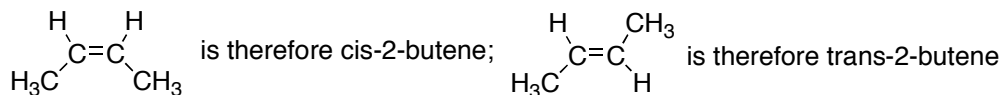
Geometric isomers: stereoisomers that arise as a consequence of restricted rotation about an olefinic  $\pi$  bond.

**Reminder:** various types of stereoisomers are known, e.g.  
enantiomers  
diastereomers  
geometric --> cis / trans isomers of olefins  
others yet

Cis and trans isomers of alkenes

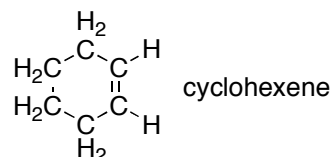
cis isomer: alkyl groups point in the same direction relative to the  $\pi$  bond

trans isomer: alkyl groups point in opposite directions relative to the  $\pi$  bond



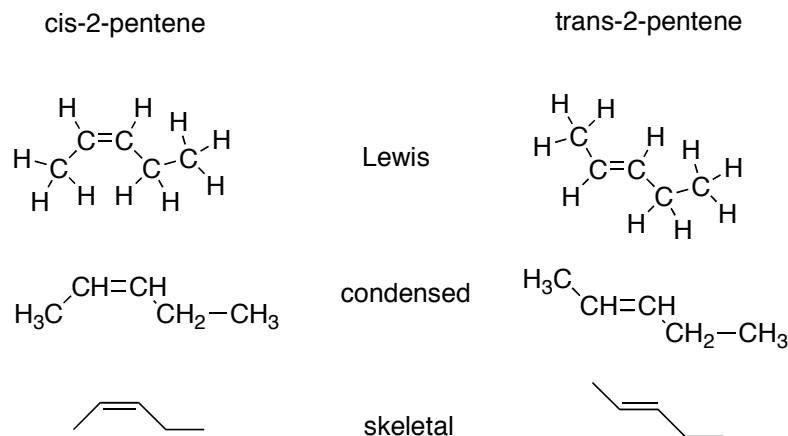
Principle: in generating a name for an alkene, one needs to specify both the position of the double bond in the molecule and the geometric isomer of the alkene in question.

Cyclic alkenes (=cycloalkenes): alkenes in which the double bond is part of a ring structure, e.g.:

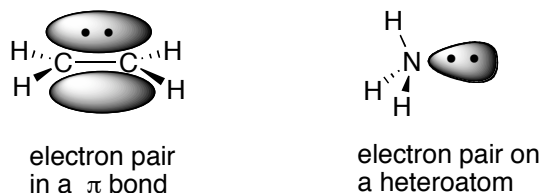


Representation of organic molecules with Lewis formulas (painstaking to draw), condensed formulas (easier to draw), skeletal formulas (of most practical usage).

**Example:** Lewis, condensed, and skeletal structures of cis-2-pentene and of trans-2-pentene:



Electronic analogy between the electron pair that forms the  $\pi$  bond in alkenes and the electron pairs found on heteroatoms such as N, O, S.



Predictable Lewis basic character of olefins, i.e., anticipated tendency thereof to react with Lewis acids.

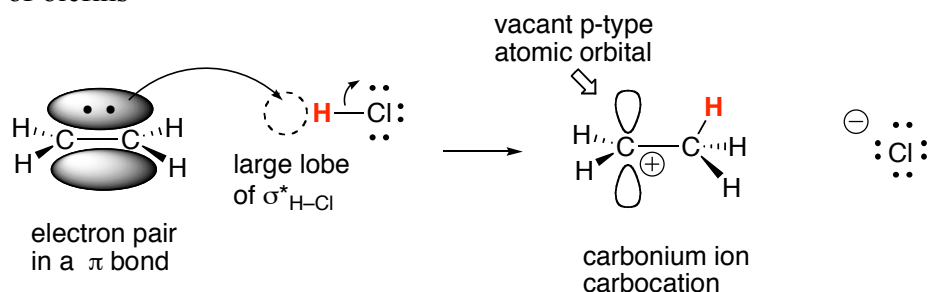
### Topics Discussed on Sept. 20 see chapter 6 of Brown-Foote-Iverson

Predictable Lewis basic character of alkenes and anticipated tendency thereof to react with Lewis acids.

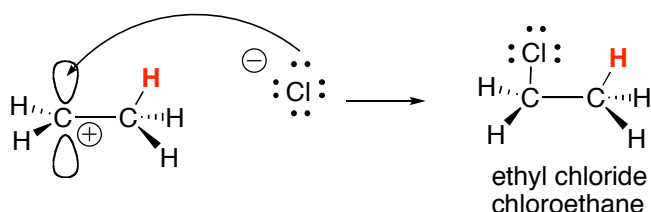
Principle: *any* reaction of alkenes will necessarily be set in motion by an interaction of the  $\pi$  electrons with a Lewis acid (=an electrophile)

Interaction of alkenes with the simplest possible Lewis acid: a proton carried by a Bronsted acid

## Protonation of olefins



Carbonium ions (= carbocations) as extremely reactive Lewis acids & their reaction with Lewis bases, e.g.  $\text{Cl}^-$



Alkyl halides (chloride, bromide, iodide, etc.)

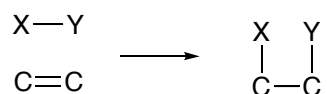
Substrate (the organic compound that undergoes the reaction: ethylene in the above reaction)

Reagent (the species that acts upon the organic compound undergoing the reaction: HCl in the above reaction)

Mechanism of a reaction: a detailed depiction of the electron movement that occurs during a chemical transformation

Reaction of ethylene (or of any other alkene) with HBr or HI: formation of ethyl bromide (bromoethane) / ethyl iodide (iodoethane) .... alkyl bromides, iodides, etc.

Addition reactions: typical reactions of alkenes and of  $\pi$  systems in general. These processes may be represented with the following general equation:



Electrophilic addition: an addition reaction initiated by the interaction of the substrate with an electrophilic agent (a proton in the above reactions)

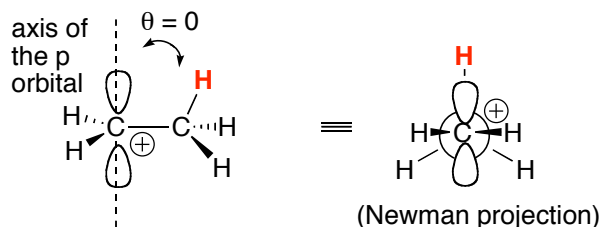
Failure of HF to undergo addition to most olefins

Carbonium ions as strong Bronsted acids ( $\text{pK}_a < 0$ ), i.e., olefins as poor Bronsted bases

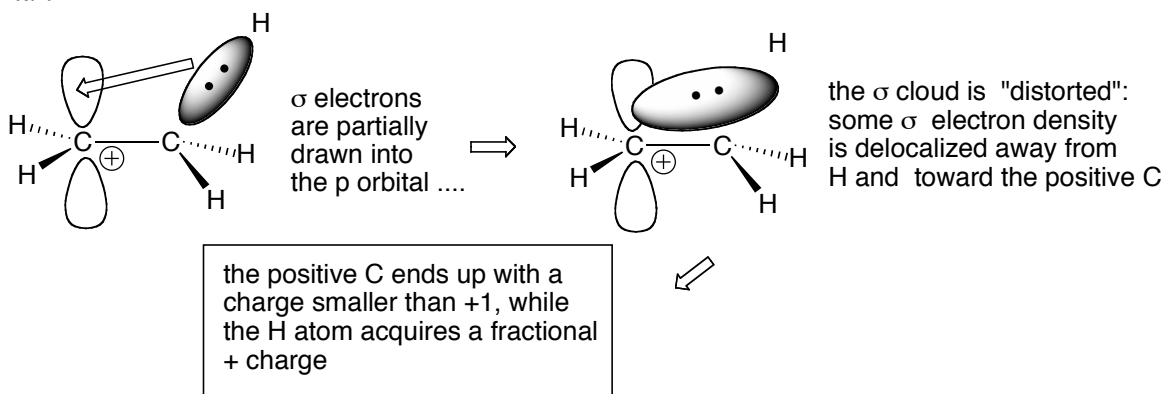
Principle: most olefin will be protonated only by acids with  $\text{pK}_a < 0$

$\text{pK}_a$  of  $\text{H-F} \approx +4$ :  $\text{HF}$  is too weak a Bronsted acid to protonate olefins

Most favorable conformation of a carbonium ion, e.g. of the ethyl cation: one of the  $\text{C-H}$   $\sigma$  bonds on the  $\text{CH}_3$  group (cf. red H below) eclipses one of the lobes of the p-type orbital associated with the adjacent positive carbon:



Hyperconjugation: electron delocalization from adjacent  $\text{C-H}$   $\sigma$  bond into a vacant p-type orbital:



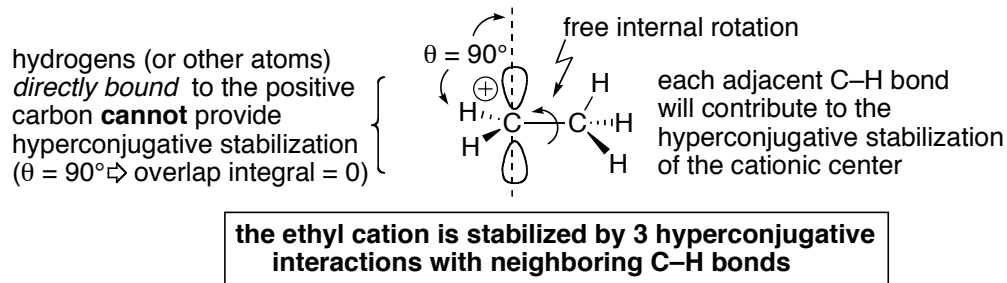
Stabilization of carbonium ions by hyperconjugation due to:

- dispersion of charge
- increase in the volume of space occupied by the  $\sigma$  electrons

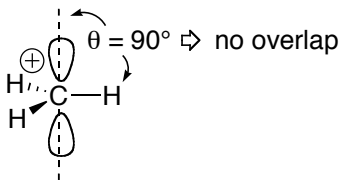
### Topics Discussed on Sept. 22 see chapter 6 of Brown-Foote-Iverson

Principle: most organic reactions are carried out in liquid phase in appropriate inert solvents

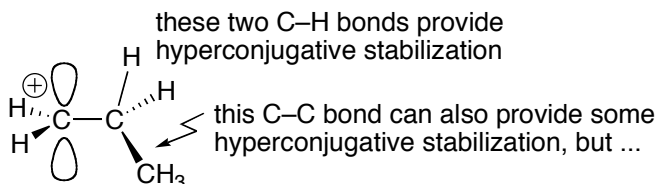
The ethyl cation as a carbonium ion stabilized by 3 hyperconjugative interactions with  $\text{C-H}$  bonds:



The methyl cation (unavailable by protonation of an alkene, but accessible by other means) as a cation that benefits from **no** hyperconjugative interactions:

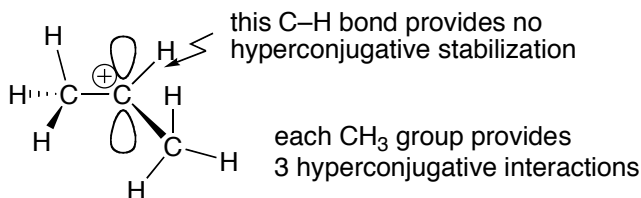


Example of a cation stabilized by **two** hyperconjugative interactions with neighboring C-H bonds:

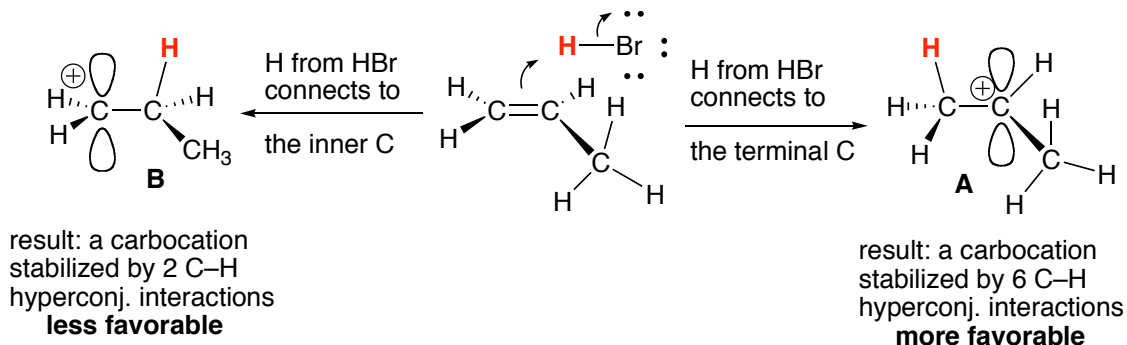


Relative hyperconjugative ability of C-H vs. C-C bonds: C-H is more effective due to lower electronegativity of H (2.1) vs. C (2.5). As a consequence, we may consider only C-H hyperconjugation when examining carbocations

Example of a cation stabilized by **six** hyperconjugative interactions with neighboring C-H bonds:



Protonation of an unsymmetrical olefin such as propene: possible formation of two cationic intermediates:

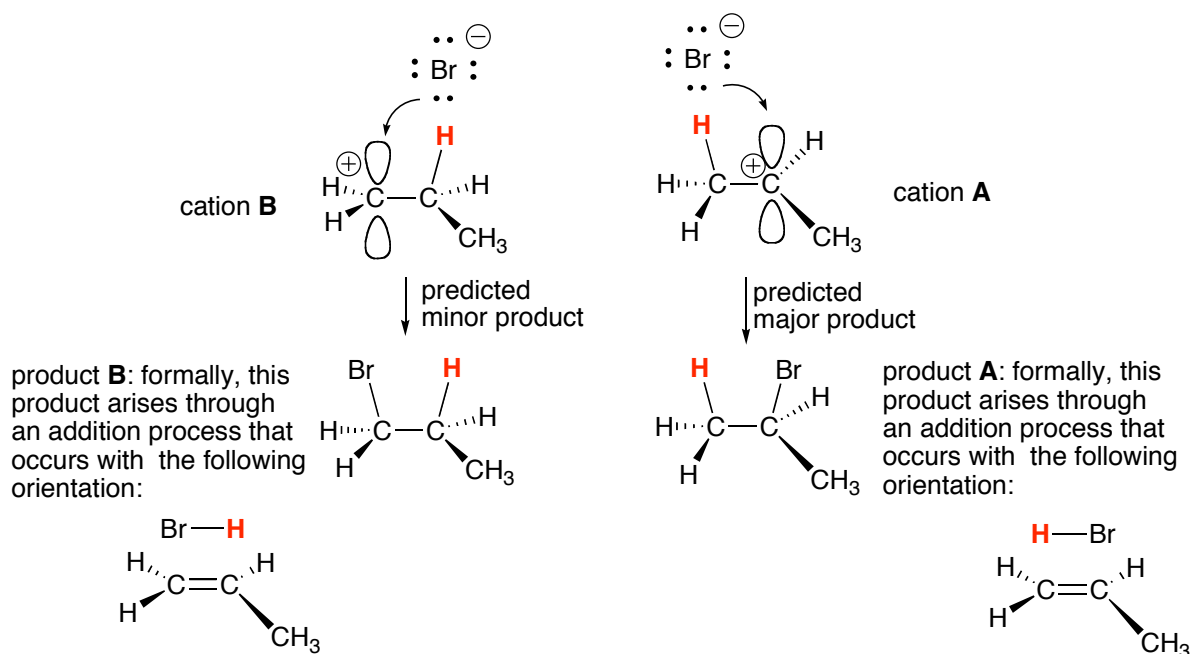


Primary (=bound to one other carbon), secondary (=bound to two other carbons), tertiary (=bound to three other carbons) carbon atoms

Primary, secondary, tertiary carbonium ions: intermediate **B** above is a primary carbocation, intermediate **A** above is a secondary carbocation,

Principle: protonation of olefins is an unfavorable process that occurs reversibly. Therefore, the dominant product of these reactions will be the thermodynamically more favorable (= the more highly stabilized) carbocation: **A** in the example above

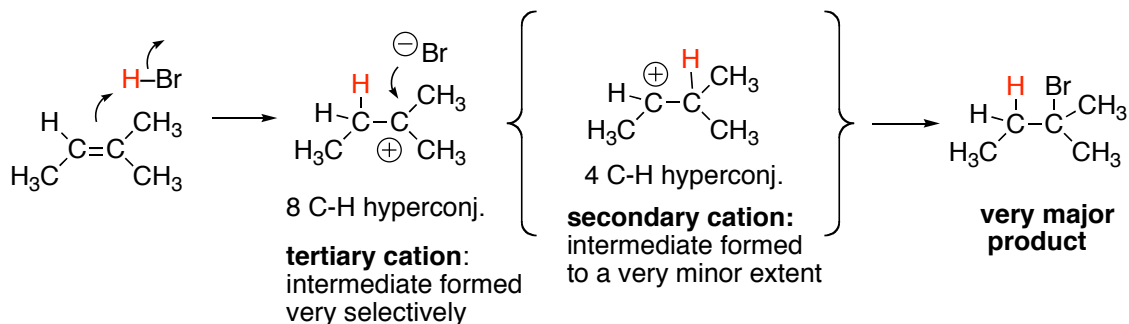
Ultimate products of the above reaction: the alkyl halide arising through addition of  $\text{Br}^-$  to the carbonium ions. Because carbocation **A** forms preferentially, alkyl bromide **A** below is predicted to be the major product of the reaction (confirmed by experiment!!).



Selective reaction: one that yields largely / exclusively one product out of several possible ones

Regioselective reaction: one in which selectivity is due to one orientation of the reactants being favored relative to another, as seen in the above addition of  $\text{HBr}$  to propene

Additional example of regioselective  $\text{H-X}$  additions to olefins:



Principle: an unsymmetrical olefin will undergo electrophilic addition of  $\text{H-X}$  to give preferentially the product arising from the most highly stabilized carbonium ion

Primary, secondary, tertiary alkyl halides

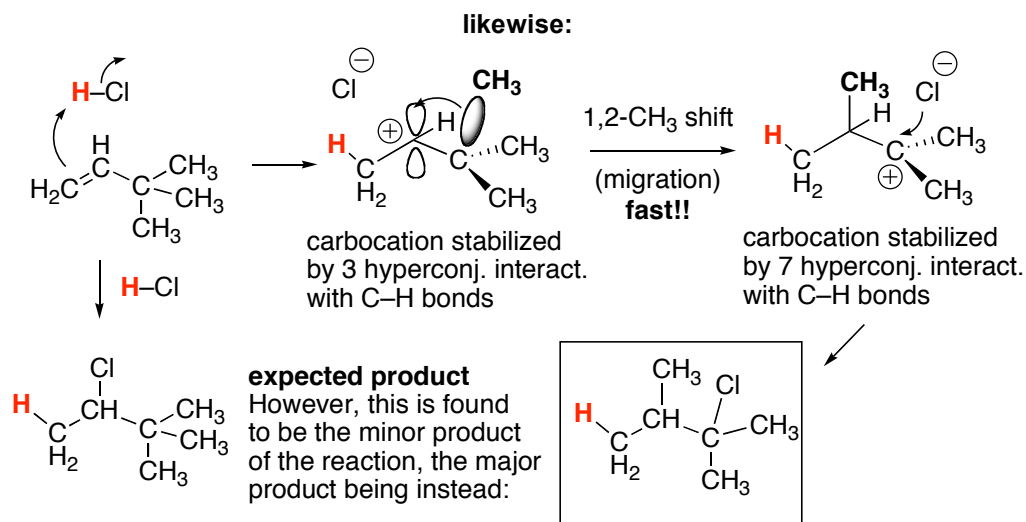
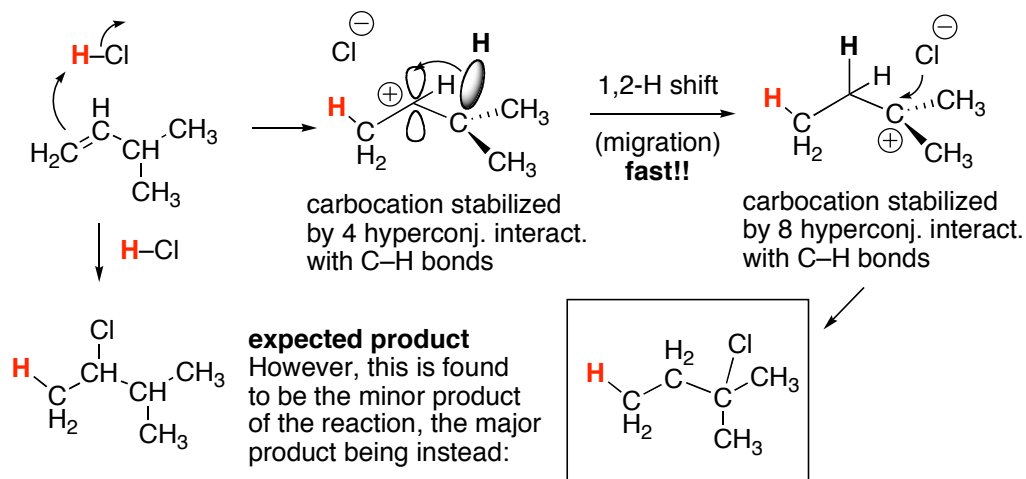
Substitution, substituents: alkyl groups attached to a C atom

Markownikov rule: electrophilic addition of halogen halides,  $\text{H-X}$  ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ , **but not F**: see notes of Sept. 20), to alkenes occurs so that the halogen,  $\text{X}$ , connects to the more highly substituted olefinic carbon (.... OF COURSE!!).

Order of stability of carbonium ions: tertiary > secondary > primary ( $\gg \text{CH}_3^+$ )

**Topics Discussed on Sept. 25**  
**see chapter 6 of Brown-Foote-Iverson**

Rearrangements of carbonium ions promoted by hyperconjugative interactions, e.g.:



1,2-Migrations or shifts: the movement of an H or an alkyl group from one carbon atom to an adjacent carbocationic center:

Principle: rearrangements of carbonium ions occur extremely rapidly

Principle: The occurrence of a rearrangement during an electrophilic addition to an olefin is strong evidence that the reaction involves carbonium ions

Possible reaction of a carbocation (a Lewis acid) with an alkene (a Lewis base)

Biosynthesis of steroids as a process that involves carbocation chemistry (see web handout)

Other reactions of alkenes initiated by a protonation step: the hydration (= the process of formal addition of water across the double bond) reaction



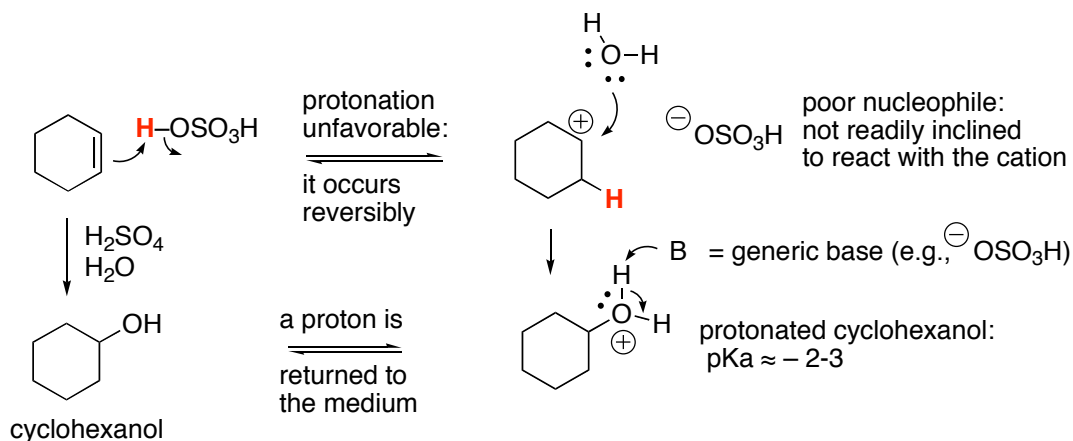
Alcohols: compounds of the general type R-OH (R = alkyl group)

Inability of H<sub>2</sub>O (pK<sub>a</sub> ≈ 16) to protonate an alkene and consequent requirement for a strong Bronsted acid in the hydration reaction

Principle: the hydration reaction works best when employing Bronsted acids such as H<sub>2</sub>SO<sub>4</sub> that release a poorly nucleophilic conjugate base (the hydrogen sulfate ion, HO-SO<sub>2</sub>-O<sup>-</sup> in this case).

This is because the conjugate base will not be overly inclined to react with the intermediate carbocation, permitting nucleophilic capture of the cation by H<sub>2</sub>O

Mechanism of the hydration reaction of, e.g., cyclohexene:



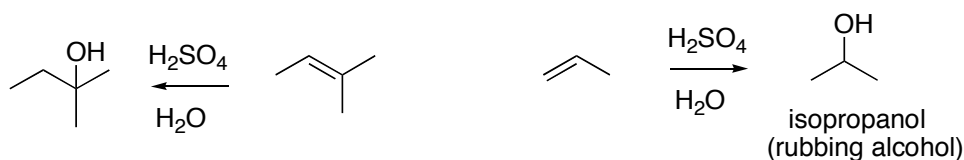
Principle: acid (=protons) are not consumed during the hydration of alkenes

Catalysts: species that promote chemical reactions but that are not consumed in the course of such reactions

The hydration reaction as a process that is catalytic in acid (protons)

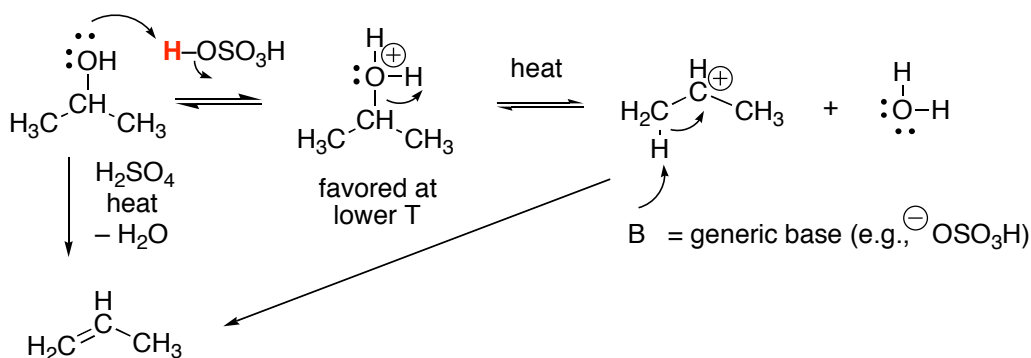


"Markownikov" selectivity in the hydration of unsymmetrical alkenes: formation of alcohols derived from the more highly stabilized carbocation, e.g.:



Possibility of rearrangements during hydration of alkenes: a consequence of the fact that the reaction involves carbocation intermediates

Reversibility of the hydration reaction at high temperatures: "dehydration" of alcohols to form olefins. Example:



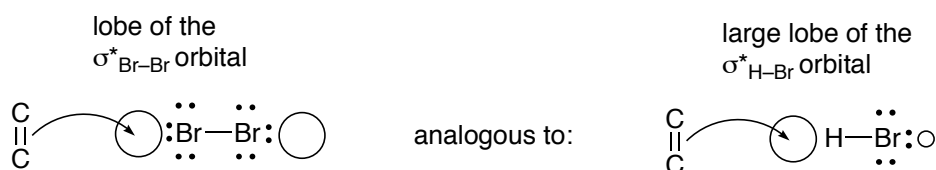
Reactions of alkenes initiated by an interaction of the  $\pi$  system with electrophiles other than  $\text{H}^+$ : the halogenation (bromination, chlorination) reaction



Addition of  $\text{F}_2$  to alkenes as a difficult reaction due to the extreme reactivity of  $\text{F}_2$  toward organic matter (powerful exothermic formation of  $\text{HF}$  and  $\text{CF}_4$  – analogous to combustion)

Absence of rearrangements during addition of halogens to olefins: the mechanism of the reaction **does not** involve carbonium ion intermediates

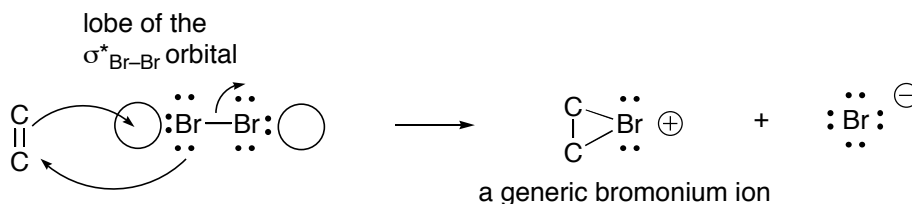
Initial interaction of the  $\pi$  electrons of the alkene with the  $\sigma^*_{\text{X-X}}$  orbital of the  $\text{X}_2$  molecule, e.g.:



**Topics Discussed on Sept. 27**  
**see chapter 6 of Brown-Foote-Iverson**

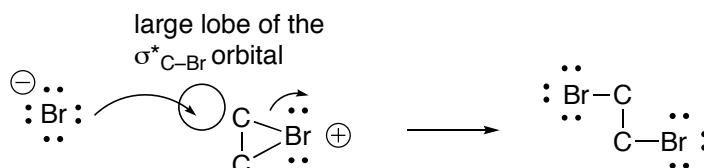
Halonium (bromonium, chloronium, iodonium) ions:

Concerted (= in one step and with no intervention of carbocationic species) formation of a halonium ion and a halide ion through the reaction of an alkene with a halogen molecule, e.g.:

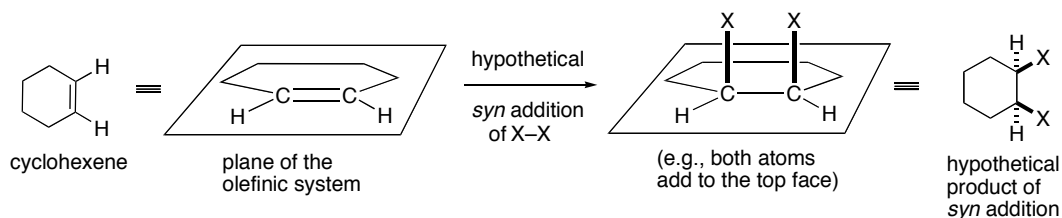


Halonium ions as exceedingly reactive electrophiles that nonetheless may be isolated in certain special cases

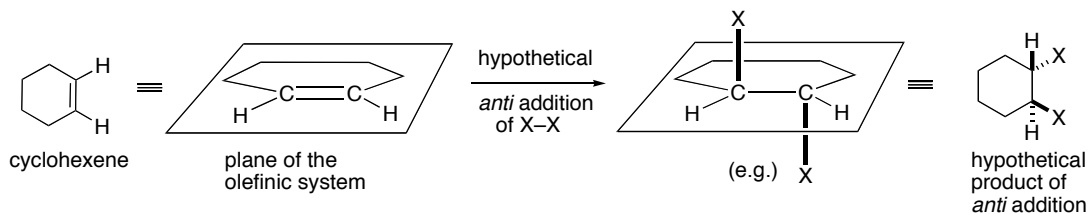
Rapid  $\text{S}_{\text{N}}2$ -like reaction of the halonium ion with the halide (bromide, chloride...) ion: involvement of the  $\text{C}-\text{X}$   $\sigma^*$  orbital in such reactions:



Hypothetical *syn* addition of a molecule  $\text{X}-\text{X}$  to the  $\pi$  system of an alkene (e.g., cyclohexene): a process during which the  $\text{X}$  atoms add from the same face of the  $\pi$  system:

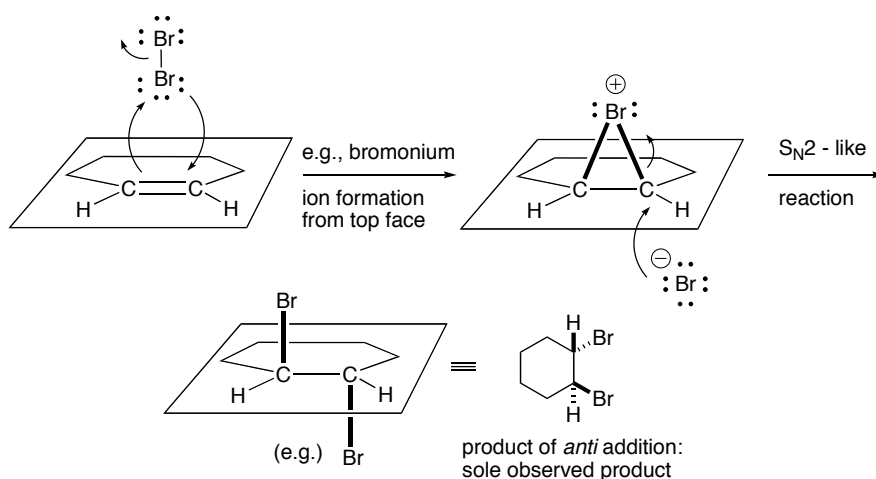


Hypothetical *anti* addition of a molecule  $\text{X}-\text{X}$  to the  $\pi$  system of an alkene (e.g., cyclohexene): a process during which the  $\text{X}$  atoms add from opposite faces of the  $\pi$  system:



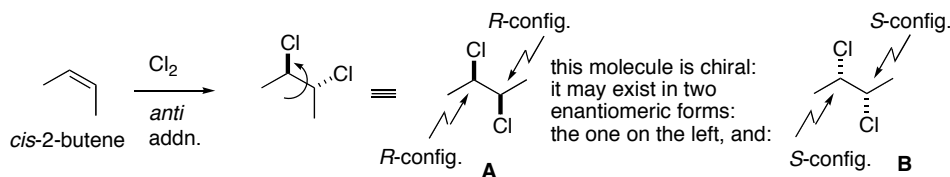
Diastereomeric relationship between the product of *syn* addition and the product of *anti* addition

Principle: mechanistic constraints force the halogenation reaction to proceed in an *anti* mode:



Diastereoselective reaction: one that preferentially produces one out of several possible diastereomeric products

Stereoselectivity in the addition of  $\text{Cl}_2$  ( $\text{Br}_2$ ) to *cis*-2-butene:

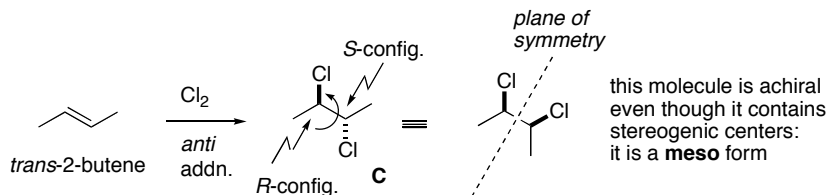


Chiral nature of the product of chlorination (bromination) of *cis*-2-butene

Racemates or racemic mixtures: equimolecular (= 50:50) mixtures of the two enantiomers of a chiral molecule

Principle: a reaction between an achiral substrate, such as *cis*-2-butene, and an achiral reagent, such as  $\text{Cl}_2$ , that leads to a chiral product (such as compounds **A** and **B** above) will always produce the racemate of the product

Stereoselectivity in the addition of  $\text{Cl}_2$  ( $\text{Br}_2$ ) to *trans*-2-butene



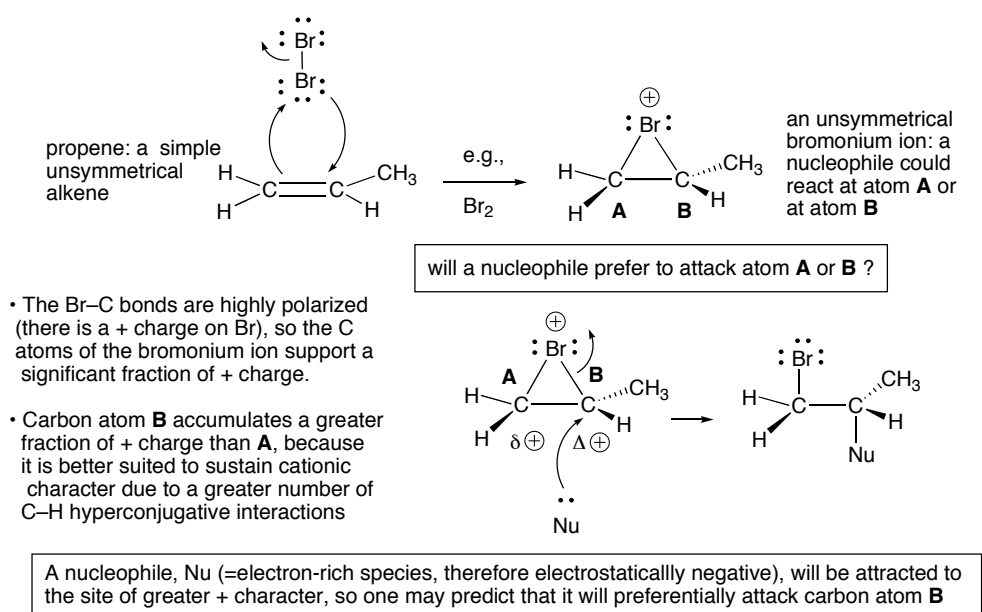
Achiral nature of the product **C** of chlorination (bromination) of *trans*-2-butene (meso-diastereomer)

Principle: for the sake of convenience, the structure of a chiral product obtained through a reaction that furnishes the racemate thereof may be depicted as a single enantiomer. It is understood that the reaction will actually give both enantiomers of the product in equal amounts.

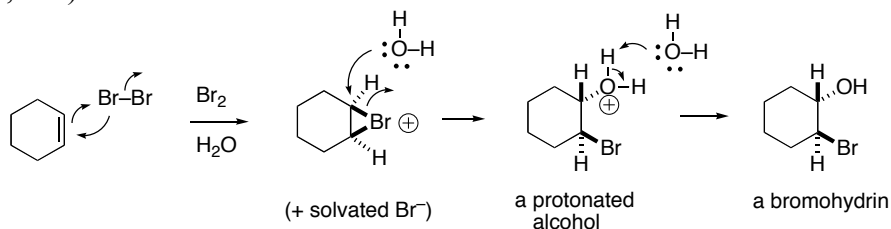
Principle: the halogenation of a generic olefin such as 2-butene will produce a specific diastereomer of the product depending on the geometry, *cis* or *trans*, of the double bond

Stereospecific reaction: a stereoselective reaction (like the halogenation reaction) in which mechanistic constraints cause a stereochemical property of the substrate (*cis* / *trans* isomerism in the present case) to become responsible for the exclusive formation of a particular diastereomer of the product (chiral vs. meso in the present case)

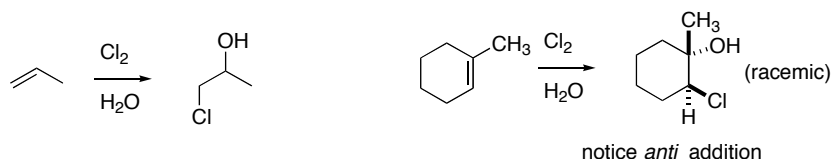
The question of regioselectivity in the S<sub>N</sub>2-like reaction of bromonium (halonium) ions:



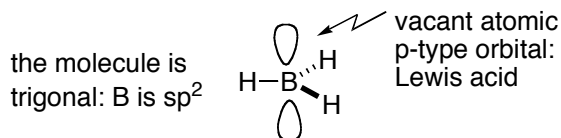
Reaction of an olefin with Br<sub>2</sub> (Cl<sub>2</sub>) and water: formation of halohydrins (chlorohydrins, bromohydrins, etc.):



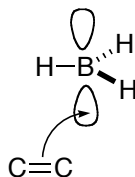
Regioselectivity of halohydrin formation:



Reactions of alkenes initiated by an interaction of the  $\pi$  system with strongly Lewis acidic molecules: the case of borane,  $\text{BH}_3$



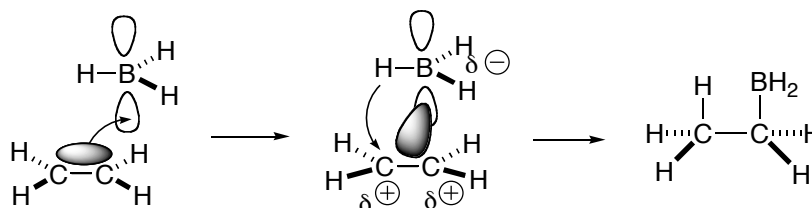
Probable initial interaction of the  $\pi$  electrons of the alkene with the vacant p orbital of  $\text{BH}_3$ :



**Topics Discussed on Sept. 29**  
**see chapter 6 of Brown-Foote-Iverson**

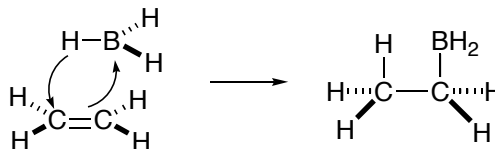
Ability of the B–H bond to function as a donor of hydride ion,  $\text{H}^-$

Development of positive character on the C atoms of the alkene as the  $\text{BH}_3$  molecule draws electronic density away from the  $\pi$  system, resulting in the ultimate transfer of one of the H atoms (as a formal hydride) from boron to carbon:



Hydroboration reaction: the addition of a B–H bond across the  $\pi$  system of an alkene

Absence of 1,2-shifts during hydroboration: no intervention of "full fledged" carbocation intermediates, therefore concerted addition of the B–H bond to the  $\pi$  system:



Strictly *syn* course of the hydroboration reaction: B and H atoms must necessarily add from the same face of the  $\pi$  system

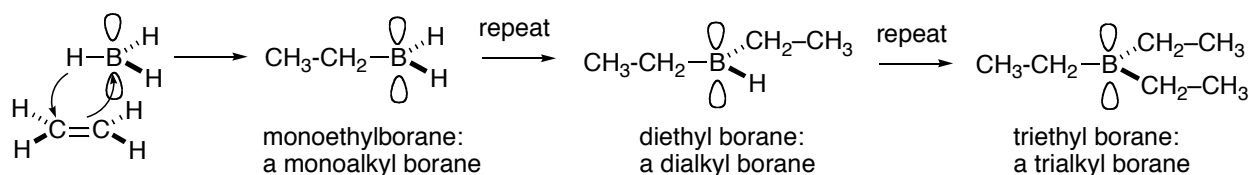
Organometallic compounds: those containing a C–metal bond

Metal-like chemical behavior of boron in organic chemistry: classification of B as a metal

Organoboranes or alkylboranes: compounds containing a C–B bond

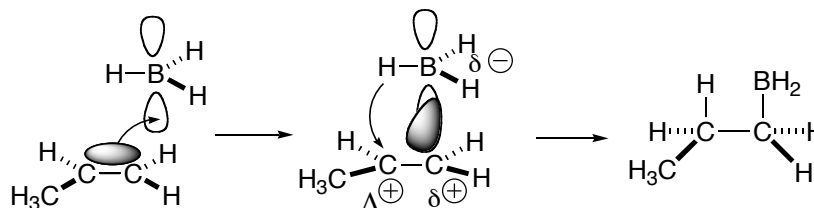
Lewis acidic character of the B atom in an alkylborane and possible formation of mono, di-, trialkylboranes through multiple cycles of hydroboration until all B–H bonds have reacted:

E.g., with ethylene:



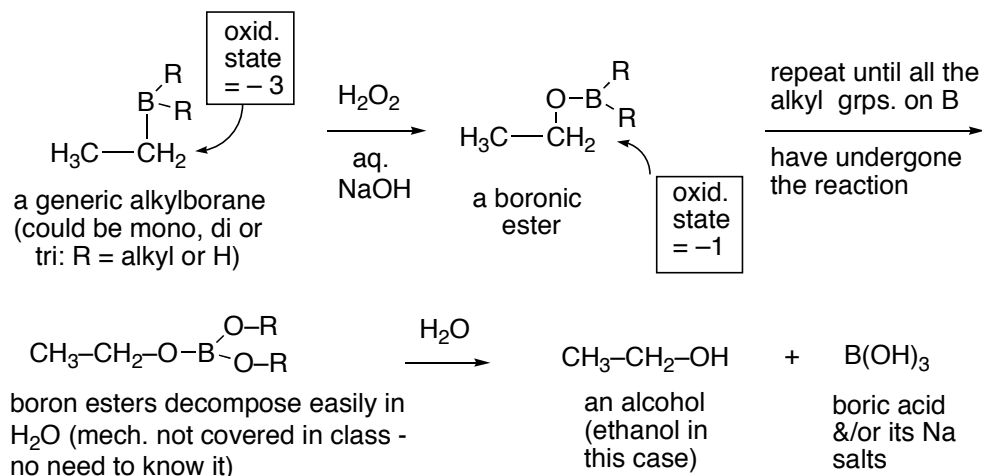
**note:** the B atom in the trialkylborane still has a vacant p-type orbital, but no further hydroboration rx. is possible because all B–H bonds have been used up

Regiochemical course of the hydroboration reaction of unsymmetrical olefins: the H atom of the H–B bond connects to the more highly substituted C atom of the alkene; the B atom, to the less highly substituted C:

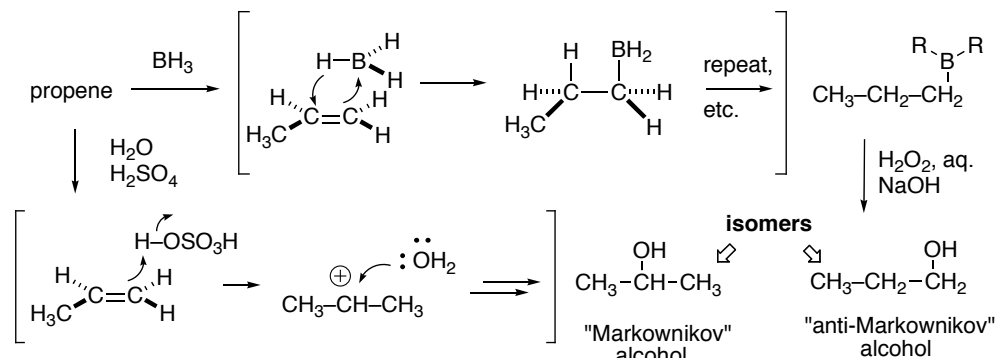


as the interaction between the B atom and the  $\pi$  system becomes stronger, the more highly substituted C atom acquires a greater fraction of positive charge (better hyperconjugative stabilization). Consequently, it is the more highly substituted, more positive C atom that captures the (formal) hydride from  $\text{BH}_3$ . In addition, steric factors also favor the connection of the bulkier  $\text{BH}_2$  segment to the less hindered carbon atom

Rich chemistry of alkylboranes and oxidation thereof with  $\text{H}_2\text{O}_2$  / aq. NaOH as their most important reaction:



Interesting consequence of the oxidation of alkylboranes obtained through hydroboration of unsymmetrical olefins: formation of "anti-Markownikov" alcohols. E.g.:

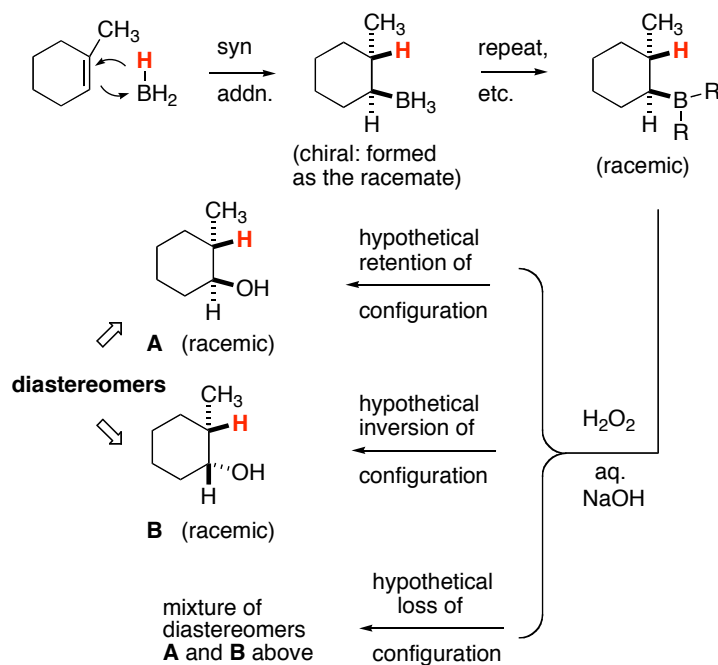


The oxidation of boranes as a substitution reaction, i.e., the replacement of one atom / group of atoms with another

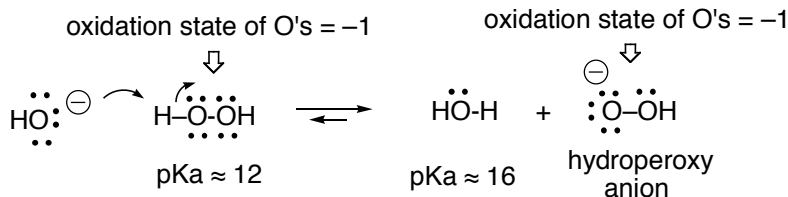
Possible stereochemical outcome of a substitution reaction:

- retention** of configuration: the substituting atom enters with the *same* orientation as the departing atom
- inversion** of configuration: the substituting atom enters with the *opposite* orientation relative to the departing atom
- loss** of configuration: the substituting atom enters partly with the same orientation and partly with the opposite orientation relative to the departing atom

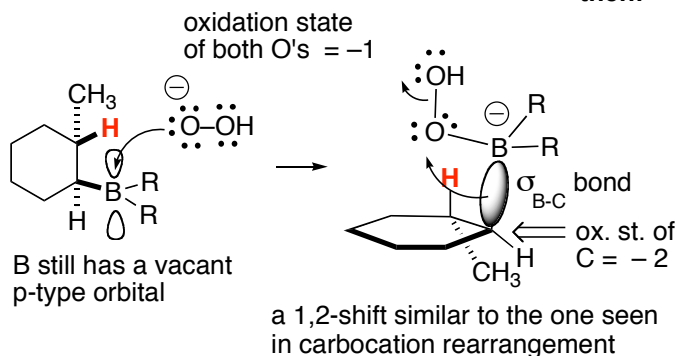
Example: the alkylborane obtained upon hydroboration of 1-methylcyclohexene could undergo oxidation (a substitution reaction) to give:



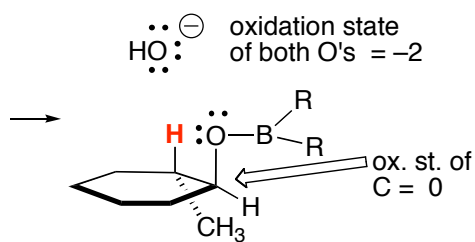
Mechanism of the oxidation of boranes and strict **retention of configuration** observed during the process:



**then:**



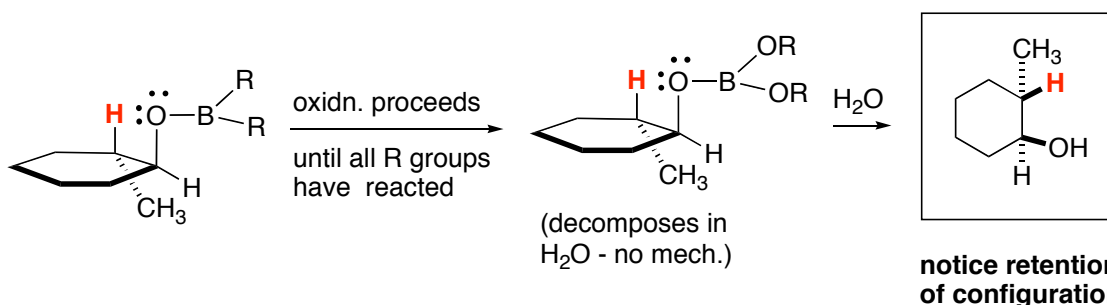
In an effort to become reduced to the ox. st. of  $-2$ , the terminal O atom tends to depart as  $\text{OH}^-$ , but this would leave a highly unfavorable  $+$  charge on the O atom attached to B. An alkyl group migration occurring in concert with OH departure avoids formation of a highly energetic " $\text{O}^+$ "



the oxidation state of the  
O atoms has gone from  $-1$  to  
 $-2$ : they have become reduced

the oxidation state of the  
C atom has gone from  $-2$  to  $0$ :  
the C has become oxidized

the mechanism of the migration reaction causes the O-for-B substitution to proceed with **retention** of configuration

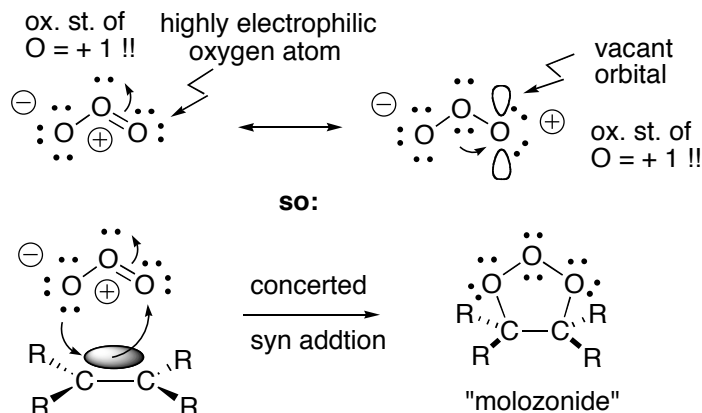


The hydroboration – oxidation process as a net syn addition of water to an alkene in an "anti-Markownikov" sense (= with the opposite selectivity compared to an acid-catalyzed hydration reaction)



**Topics Discussed on Oct. 2**  
**see chapter 6 of Brown-Foote-Iverson**

Ozone and its reaction with olefins

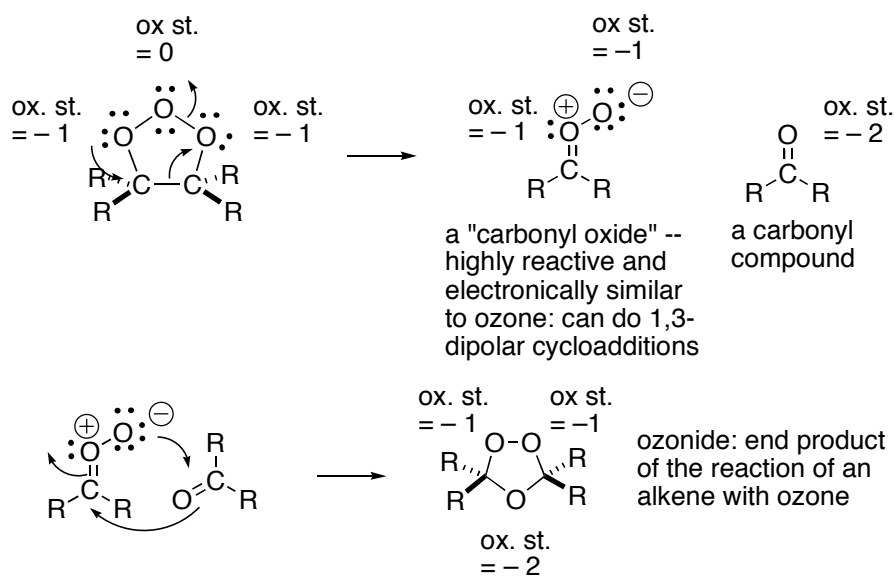


"Cycloaddition:" an addition reaction that forms a new ring (cf. the formation of a molozonide from ozone + an alkene)

Ozone as a "1,3-dipole:" 1,3-dipolar cycloaddition

Absence of rearrangements in reactions involving O<sub>3</sub> (= no cationic intermediates)

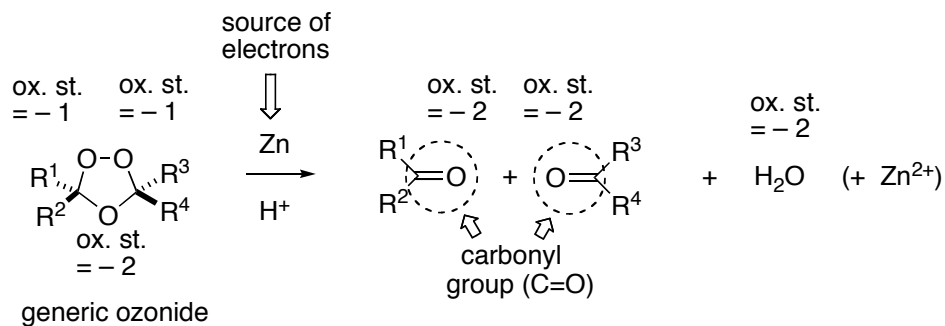
Instability of molozonides: fast isomerization to ozonides driven by the tendency of the O atoms to become reduced to a more favorable oxidation state



Carbonyl oxides as reactive dipolar intermediates

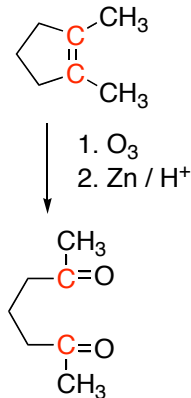
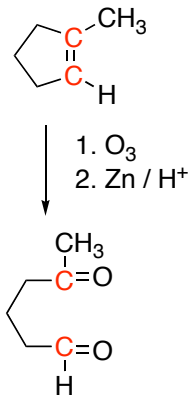
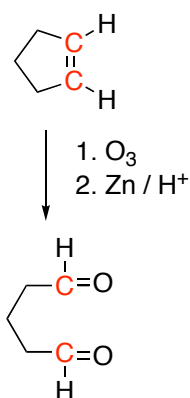
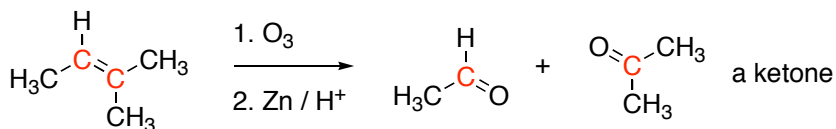
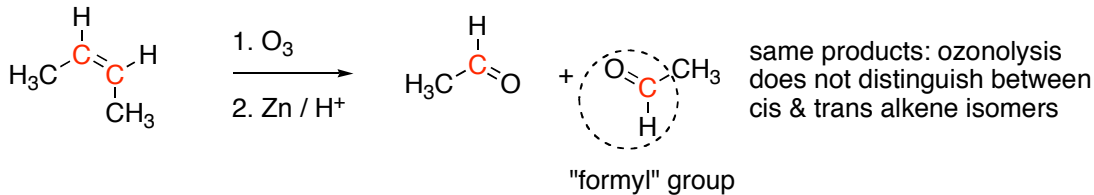
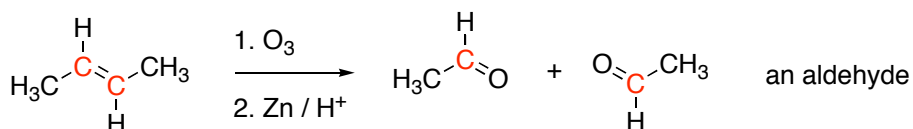
Instability and explosive properties of ozonides due to the presence of O atoms at the oxidation state of -1

Reaction of ozonides with metallic zinc (source of electrons) and acid: formation of a pair of carbonyl compounds plus water (no mechanism):



Ozonolysis: the break-up of an alkene into a pair of carbonyl compounds by reaction with ozone

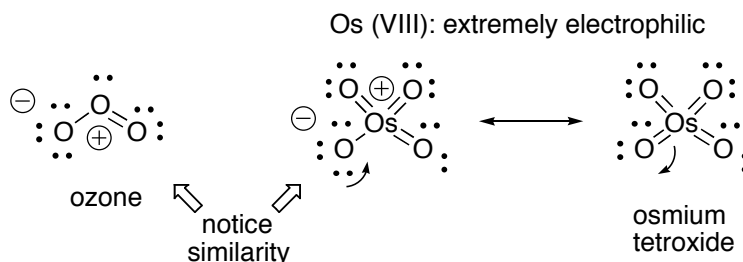
Examples:



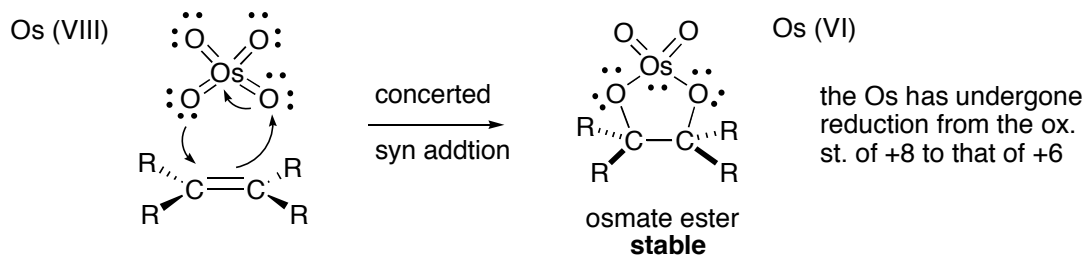
Formyl group (CHO)

Aldehydes & Ketones

Analogy between the electronic distribution in the molecule of  $O_3$  and in that of osmium tetroxide,  $OsO_4$



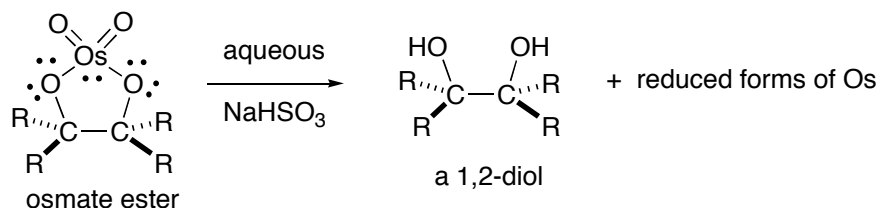
Addition of  $OsO_4$  to the  $\pi$  system of alkenes through a mechanism reminiscent of a 1,3-dipolar cycloaddition



Strictly syn course of the addition of  $OsO_4$  to alkenes

Absence of rearrangements in reactions involving  $OsO_4$  (= no cationic intermediates)

Osmate esters and their reduction with aqueous  $NaHSO_3$

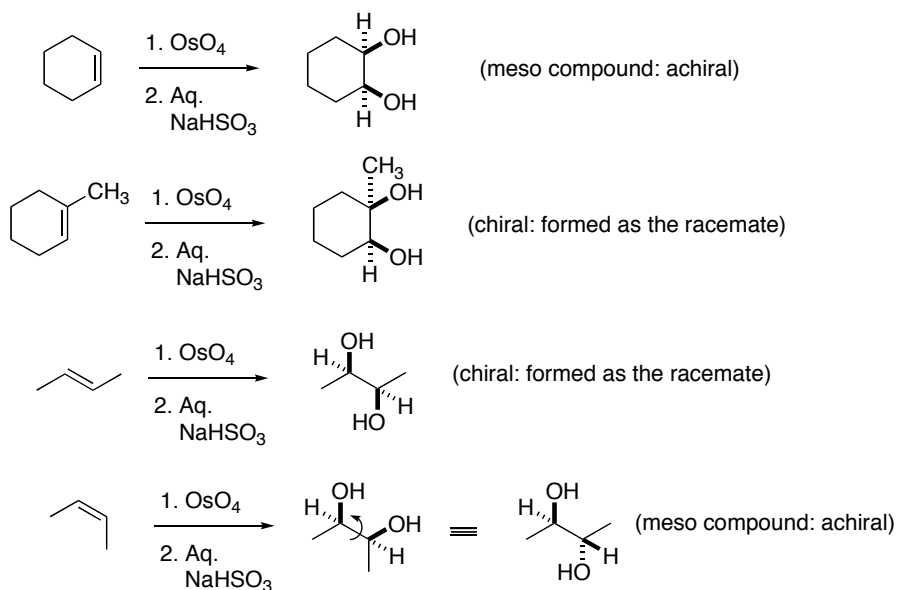


1,2-diols (= double alcohol)

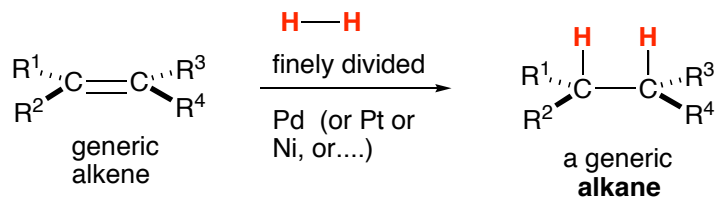
**Topics Discussed on Oct. 2**  
**see chapters 6-7 of Brown-Foote-Iverson**

Osmylation reaction: the conversion of an alkene to a 1,2-diol by reaction with  $OsO_4$  followed by reduction of the intermediate osmate ester

Examples of osmylation reactions:

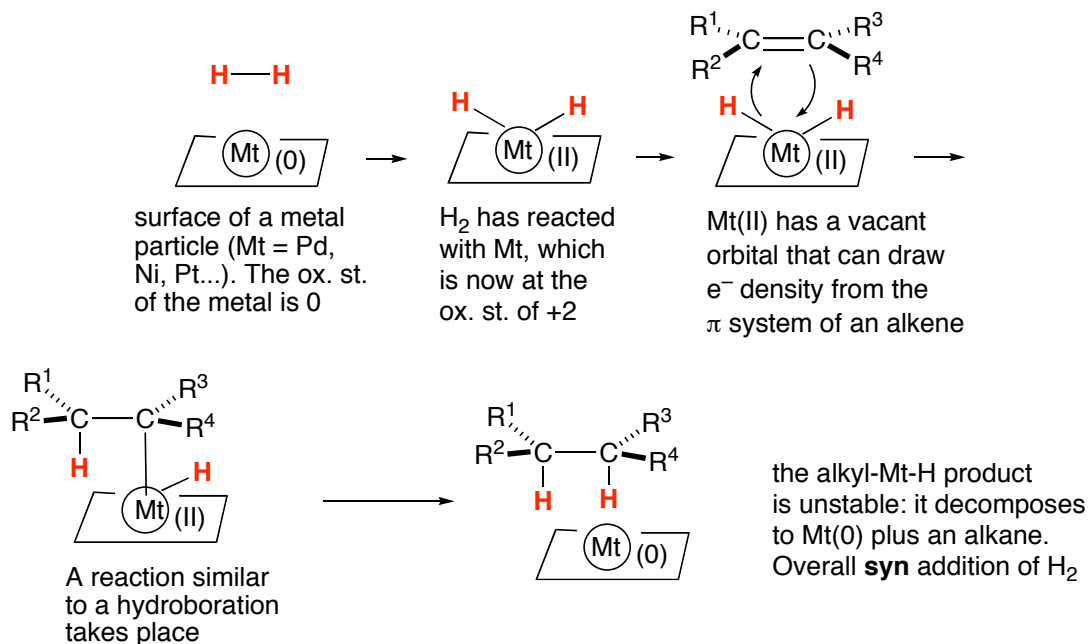


Hydrogenation of olefins in the presence of Pd, Ni, Pt catalysts: formation of alkanes:



Syn course of the hydrogenation reaction

General mechanistic outline of the hydrogenation reaction:

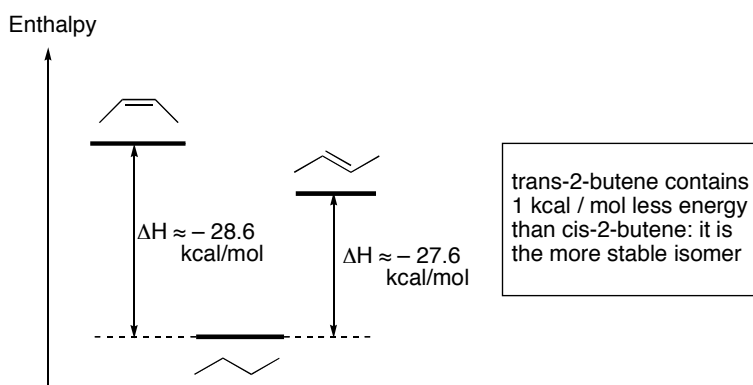


Principle: the hydrogenation reaction is an exothermic process ( $\Delta H < 0$ )

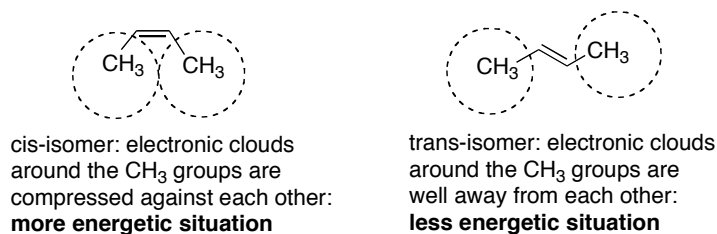
Important physical properties of alkenes that transpire from a thermochemical study of the hydrogenation reaction:

a. **trans alkenes are more stable (=less energetic) than their cis isomers.**

Example: the hydrogenation of cis and trans 2-butenes to butane:

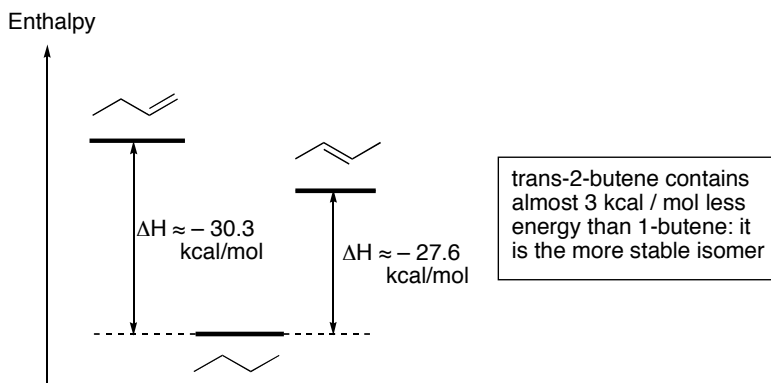


Putative origin of the greater stability of trans-alkenes relative to their cis isomers :  
absence of steric interactions between alkyl groups:

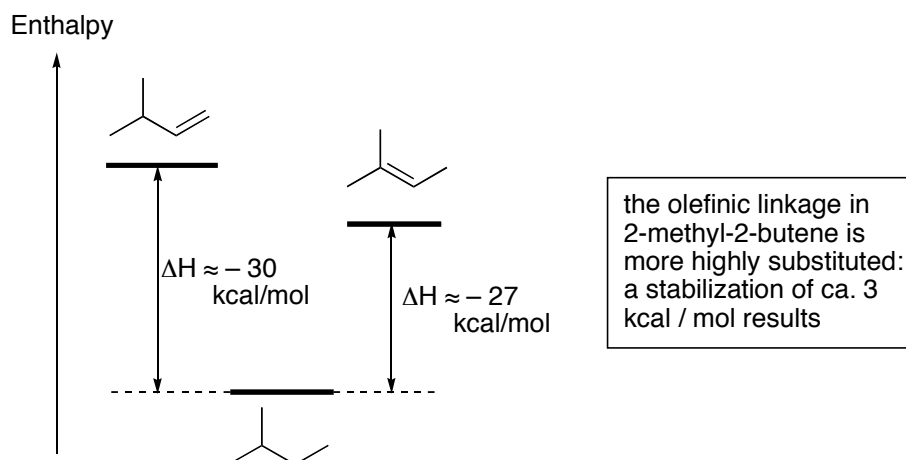


b. **the stability of an alkene increases with increasing substitution around the C=C system; i.e., a more highly substituted alkene is more stable (=less energetic) than a less highly substituted isomer**

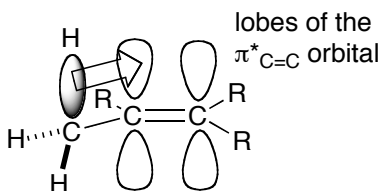
Example: the hydrogenation of positional isomers of butene to butane:



Example: the hydrogenation of positional isomers of methylbutenes to 2-methylbutane:



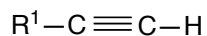
Putative origin of the greater stability of more highly substituted alkenes relative to their less highly substituted isomers: hyperconjugative interactions between  $\sigma_{C-H}$  and  $\pi^*_{C=C}$  orbitals:



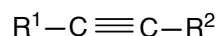
### Alkynes (Ch. 7 of BFI)

Similarities between the chemistry of alkenes and that of alkynes

Terminal and internal alkynes:



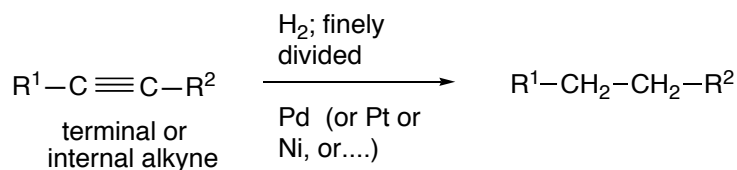
a terminal alkyne



an internal alkyne

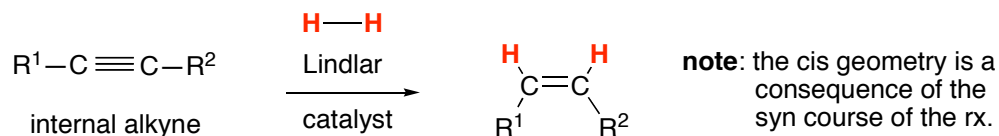
Unusual properties of the C-H bond in terminal alkynes (to be discussed on Fri. Oct. 6)

Complete hydrogenation of alkynes under the conditions seen for alkenes: formation of alkanes:



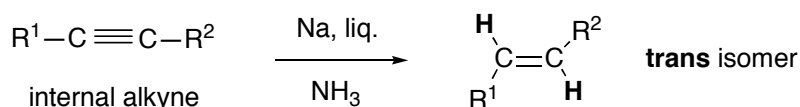
Lindlar catalyst: finely divided Pd deposited onto BaSO<sub>4</sub> particles and modified with sulfur and / or other substances

Semihydrogenation of alkynes with the Lindlar catalyst: conversion of internal alkynes to cis-alkenes:

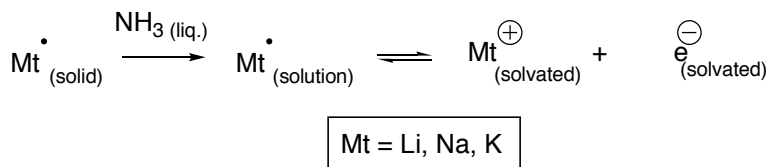


### Outline of topics to be discussed on Oct. 6 see chapter 7 of Brown-Foote-Iverson

Semihydrogenation of alkynes with Na/NH<sub>3</sub>(liq): formation of trans-alkenes



Dissolving metals (Li, Na, K) in liquid ammonia as sources of electrons:



Deep blue color of a solution of Li or Na or K in NH<sub>3</sub>(liq) due to the presence of free (solvated) electrons

Powerful reducing properties of a solution of Li (or Na, or K) in liquid NH<sub>3</sub> (≈ a solution of electrons)

Unusually high electronegativity of sp-hybridized C atoms due to the high degree of s-orbital character in the bonds

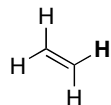
Single electron transfer (SET) reactions

Use of one-barbed arrows to indicate movement of individual electrons

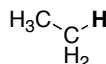
Radical anions

Carbanions as the conjugate bases of hydrocarbons

Approximate pKa values for hydrocarbons and for NH<sub>3</sub>:



C-H of  
alkene:  
pKa ≈ 45



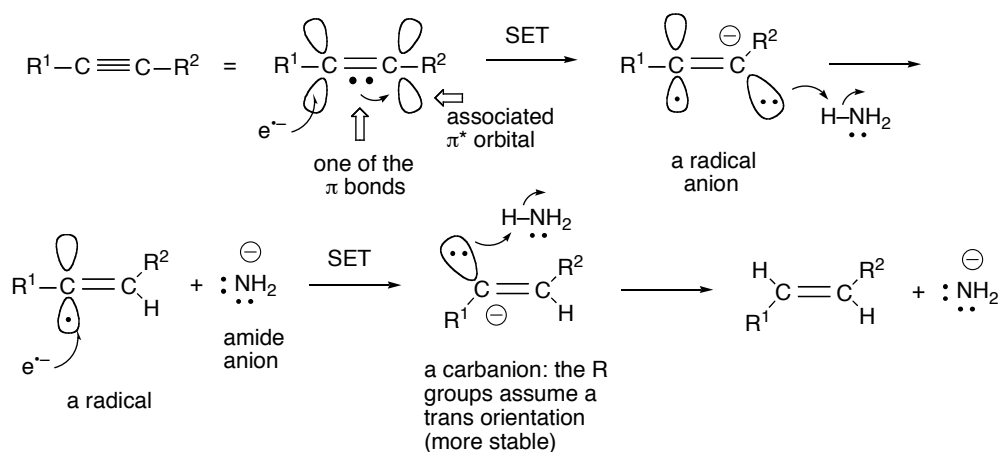
C-H of  
alkane:  
pKa ≥ 50



N-H of  
ammonia:  
pKa ≈ 35

Facile protonation of carbanions

Mechanism of the dissolving metal reduction of alkynes:



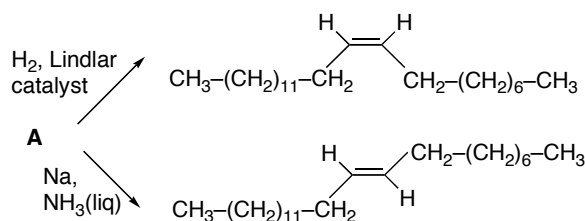
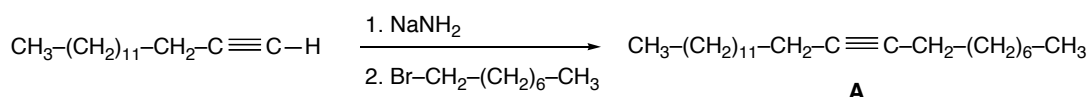
Acidity of terminal alkynes: pKa ≈ 25

Deprotonation of terminal alkynes with strong bases such as NaNH<sub>2</sub> or BuLi

S<sub>N</sub>2 Alkylation of the anion of terminal alkynes with alkyl halides

Insect pheromones and their importance in environmentally benign methods of insect control (public health, agriculture, etc.)

Practical applications of the semihydrogenation reaction of alkynes: synthesis and structural determination of muscalure (sex pheromone of the female house fly)



cis-isomer: active, identical to the pheromone isolated from female houseflies. **muscalure**

trans-isomer: inactive. Not the same as the actual pheromone

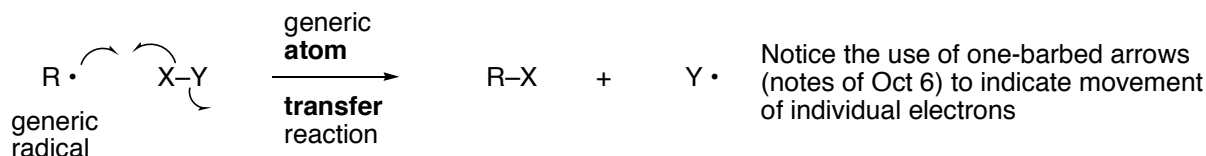


**Topics Discussed on Oct. 11**  
**see chapter 8 of Brown-Foote-Iverson**

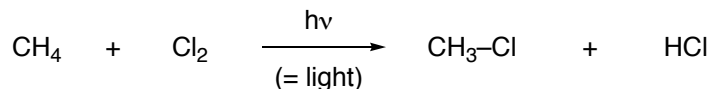
Radicals: reactive intermediates in which an atom has a complement of only 7 valence electrons

Ionic vs. radical reactions: those that proceed with formation of ionic intermediates (such as the addition of HX, X<sub>2</sub>, etc. to olefins) vs. those that proceed with formation of radical intermediates.

Principle: radicals tend to participate in exothermic processes ( $\Delta H < 0$ ); in particular, in exothermic **atom transfer** reactions:

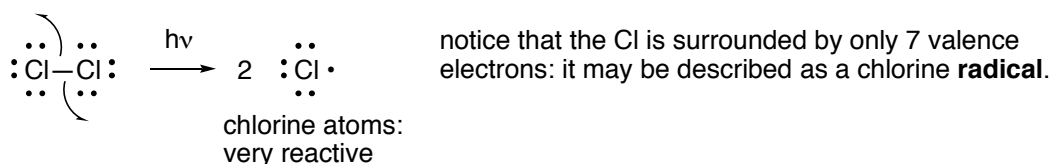


Radical chlorination of particular alkanes as a means to prepare chlorides, e.g.:

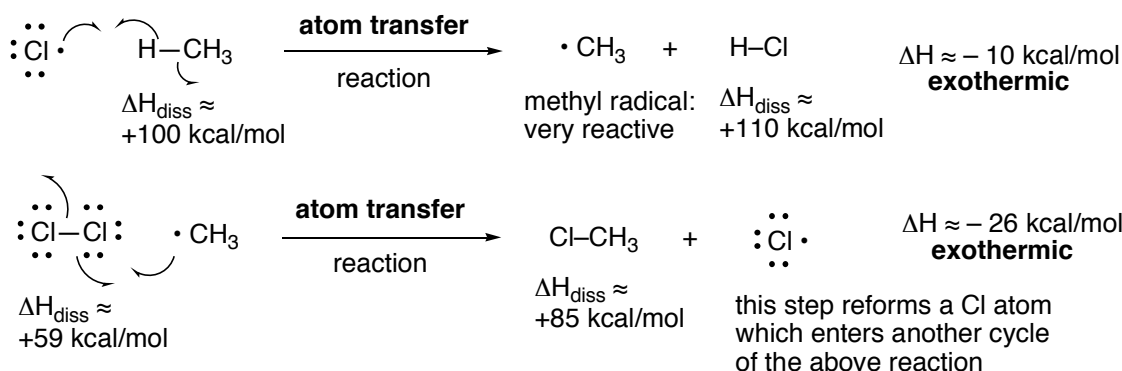


Principle: radical chlorinations are useful only when applied to those alkanes in which all the hydrogen atoms are symmetry-equivalent, e.g., methane, ethane, simple cycloalkanes. This avoids formation of a multitude of isomers.

Mechanism of the radical chlorination of, e.g., methane:



the dissociation of Cl<sub>2</sub> to a pair of Cl atoms is endothermic ( $\Delta H \approx +59$  kcal/mol). The energy required for this reaction is provided by a photon



Radical chain reactions: processes that become self-sustaining due to continuous regeneration of reactive radical intermediates

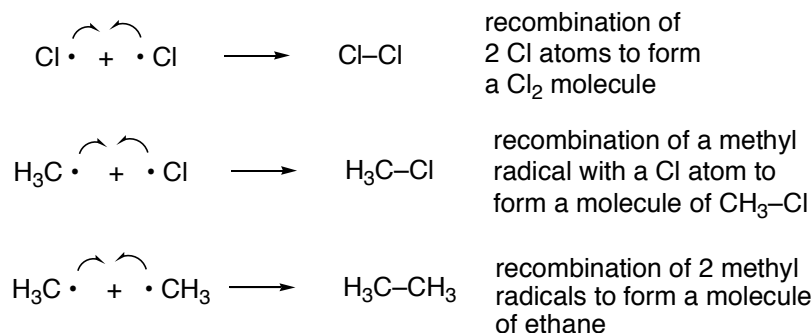
Key steps in a radical chain process:

**Initiation step:** the process responsible for the initial generation of radicals (the light-promoted dissociation of  $\text{Cl}_2$  in the above case)

**Propagation step(s):** the atom transfer reaction(s) that regenerate reactive radical intermediates

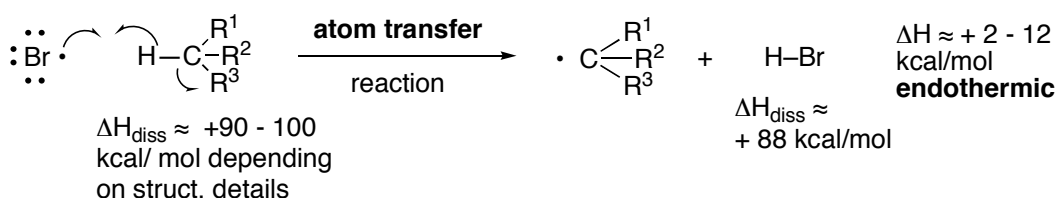
Termination steps: events such as the recombination of radicals that halt a radical chain reaction.

Possible termination steps in the radical chlorination of methane:

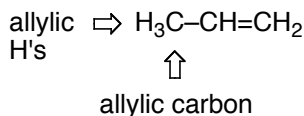


Principle: radical recombination during a radical chain reaction is statistically unlikely because of the very low instant concentration of radical species.

Radical bromination of simple alkanes as a feasible, but generally impractical, process due to the endothermic nature of the transfer of an H atom from the substrate alkane to a Br radical:

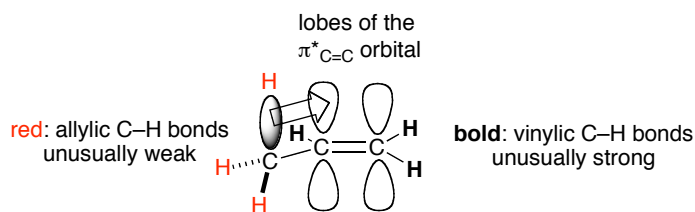


Allylic positions: those adjacent to a  $\text{C}=\text{C}$  bond, e.g. in propene:

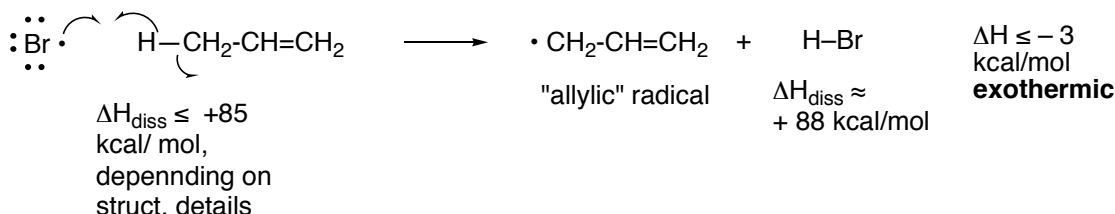


Unusual weakness of allylic  $\text{C}-\text{H}$  bonds ( $\Delta H_{\text{diss}} \approx 85 \text{ kcal/mol}$ ) due to hyperconjugative interactions between the  $\sigma_{\text{C-H}}$  electrons and the  $\pi^*_{\text{C}=\text{C}}$  orbital (notes of Oct. 4)

Unusual strength of alkenic  $\text{C}-\text{H}$  bonds ("vinylic"  $\text{C}-\text{H}$  bonds;  $\Delta H_{\text{diss}} \approx 110 \text{ kcal/mol}$ ) due to the high content of s-character in the carbon  $\text{sp}^2$  orbitals utilized to establish such bonds. E.g. in propene:



Exothermic nature of the transfer of an allylic H atom to a Br radical; e.g.:

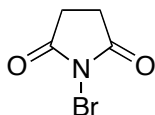


Radical bromination of allylic position as a favorable process

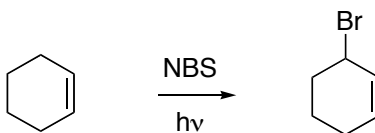
Principle: radical chain reactions proceed at an extremely rapid rate, much faster than ionic processes.

Principle: the success of an allylic radical bromination reaction depends on the presence of a **very small instant quantity** of  $\text{Br}_2$  in the reaction medium. This avoids addition of  $\text{Br}_2$  to the olefin.

N-Bromosuccinimide ("NBS", structure below): a reagent that releases very small amounts of  $\text{Br}_2$  over time through reaction with traces of  $\text{HBr}$



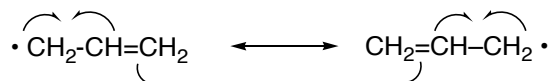
Allylic bromination with NBS / light; e.g., with cyclohexene:



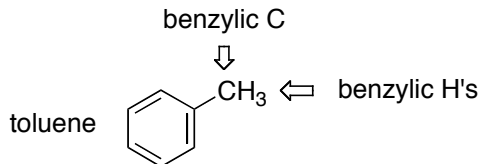
**note:** the mechanism of this reaction is identical to that seen for the radical chlorination of alkanes — except that  $\text{Br}_2$  is now the halogen.

**Topics Discussed on Oct. 13**  
**see chapters 8 - 9 and 10 of Brown-Foote-Iverson**

Unusual degree of stabilization of allylic radicals through resonance interactions:



Benzylic position: an "allylic-like" position external to a benzene ring. E.g., in toluene (methylbenzene):

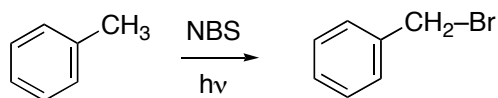


Unusual weakness of benzylic C–H bonds ( $\Delta H_{\text{diss}} \approx 85$  kcal/mol) due to hyperconjugative interactions between the  $\sigma_{\text{C-H}}$  electrons and an adjacent  $\pi^*_{\text{C=C}}$  orbital (see notes of Oct. 11)

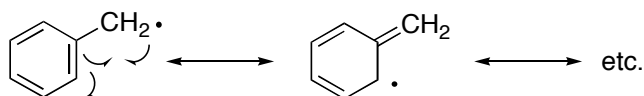
Unusual strength of the C–H bonds in a benzene ring ( $\Delta H_{\text{diss}} \approx 110$  kcal/mol; see notes of Oct. 11)

Exothermic nature of the transfer of a benzylic H atom to a Br radical: radical bromination of benzylic position as a favorable process (cf. case of allylic radical bromination, notes of Oct 11)

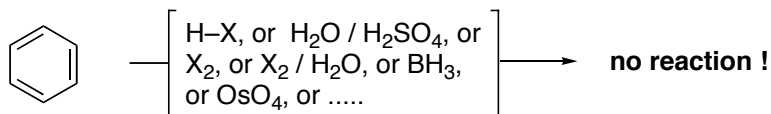
Benzylic bromination with NBS / light; e.g., with toluene:



Unusual degree of stabilization of benzylic radicals through resonance interactions:



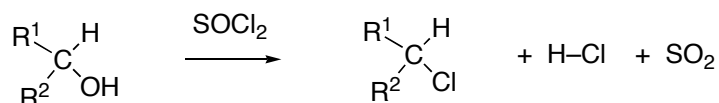
Unusual lack of reactivity of the "olefinic" bonds in a benzene ring:



"Aromaticity" of benzene and of related molecules: a set of properties (to be discussed in detail next semester) that cause the  $\pi$  bonds in these systems to behave differently from the  $\pi$  bonds of ordinary alkenes.

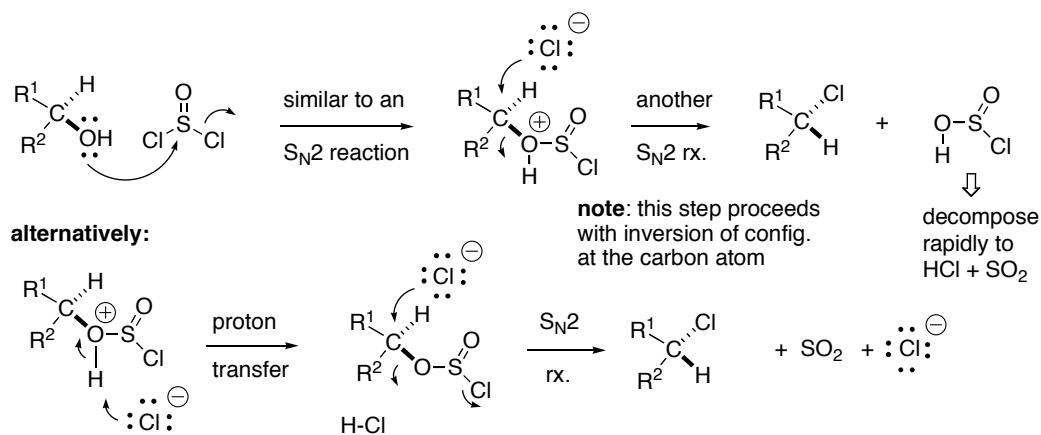
Principle: often, alkyl halides are best prepared from alcohols

Conversion of alcohols such as  $\text{R}^1\text{--CHOH--R}^2$  ( $\text{R}^1, \text{R}^2 = \text{H}$  or alkyl) to alkyl chlorides with thionyl chloride,  $\text{SOCl}_2$  (see ch. 10 of BFI):



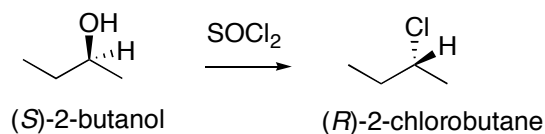
Reactive, electrophilic nature of  $\text{SOCl}_2$ : facile reaction with nucleophilic agents resulting in substitution of Cl atoms

Possible mechanisms for the above reaction:

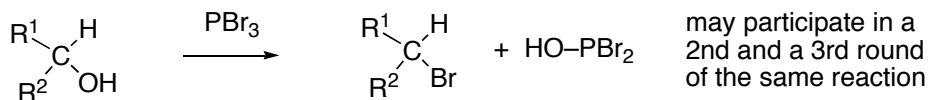


either mechanism is reasonable: the details of what actually happens are unknown

Inversion of configuration observed in the course of the  $\text{SOCl}_2$  chlorination of alcohols, due to the intervention of an  $\text{S}_{\text{N}}2$  reaction at the C atom, e.g.:

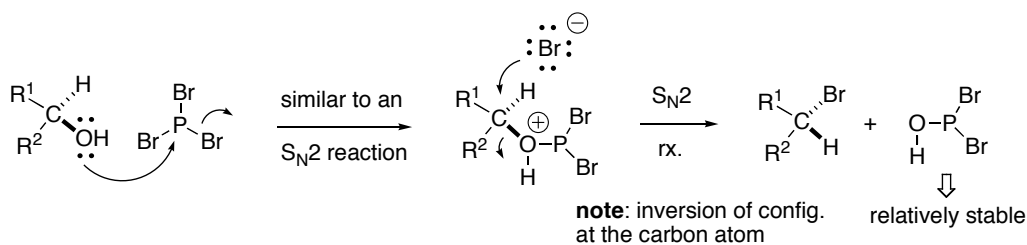


Conversion of alcohols such as  $\text{R}^1\text{-CHOH-R}^2$  ( $\text{R}^1, \text{R}^2 = \text{H}$  or alkyl) to alkyl bromides with phosphorous tribromide,  $\text{PBr}_3$  (see ch. 10 of BFI):



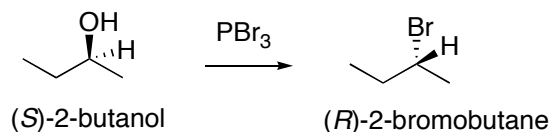
Reactive, electrophilic nature of  $\text{PBr}_3$ : facile reaction with nucleophilic agents resulting in substitution of Br atoms

Possible mechanism for the above reaction:



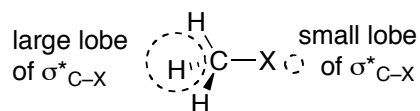
**note:**  $\text{HO-PBr}_2$  still possesses P-Br bonds, so it may undergo a 2nd and a 3rd round of the same reaction, ultimately producing phosphorous acid,  $\text{P}(\text{OH})_3$

Inversion of configuration observed in the course of the  $\text{PBr}_3$  bromination of alcohols, due to the intervention of an  $\text{S}_{\text{N}}2$  reaction at the C atom, e.g.:

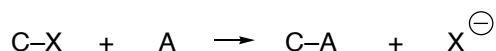


## Reactions of alkyl halides (ch. 9 of BFI)

Principle: the chemistry of alkyl halides is largely controlled by the low-lying carbon-halogen sigma antibonding orbital:

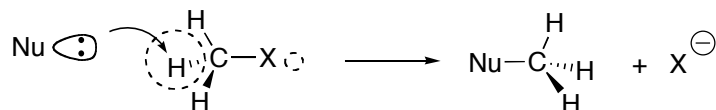


Principle: alkyl halides tend to participate in substitution reactions:



Nucleophilic substitution: a process in which a nucleophilic Lewis base functions as the A reagent in the equation above

Interaction of an electron pair from the nucleophile,  $\text{Nu:}$ , with the  $\sigma^*_{\text{C-X}}$  orbital (see also notes of Sept 15), during a nucleophilic substitution reaction:



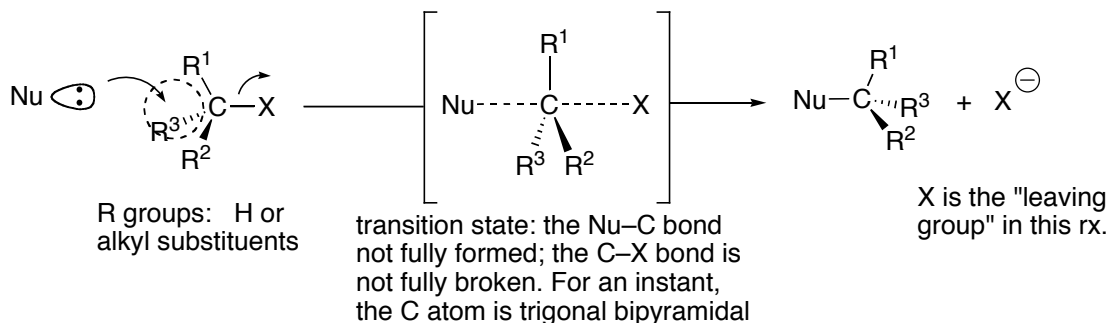
Rupture of the C-X bond as the  $\text{Nu:}$  introduces electron density into the  $\sigma^*_{\text{C-X}}$  orbital

Primary, secondary, tertiary alkyl halides (notes of Sept. 22)

### Topics Discussed on Oct. 16 see chapter 9 of Brown-Foote-Iverson

Nucleophilic substitution reactions of alkyl halides proceeding through the interaction of an electron pair from the nucleophile with the  $\sigma^*_{\text{C-X}}$  orbital

Backside attack and consequent inversion of configuration in such nucleophilic substitutions



**Note:** the nucleophile Nu has become connected to the C atom with a spatial orientation that is *opposite* that of the original X: the reaction has occurred with **inversion of configuration**

Walden inversion: the inversion of configuration observed in the above reactions

Principle: nucleophiles capable of participating in nucleophilic substitution with halides are often the conjugate bases of weak Bronsted acids ( $pK_a > 5$ )

Leaving group: the "X<sup>-</sup>" in the above reaction (in the present case, a halide ion)

Principle: the leaving group in a nucleophilic substitution reaction must be the conjugate base of a Bronsted acid with  $pK_a < 0$

Changes in the basicity of the system, as measured by  $\Delta pK_a$ , incurred during a nucleophilic substitution process as a powerful driving force for the reaction

Correlation between the  $pK_a$  of the conjugate acid of X<sup>-</sup> and the ability of X<sup>-</sup> to function as a leaving group in a substitution reaction of the type above:

H-X	H-F	H-Cl	H-Br	H-I
approx. $pK_a$	+ 4	- 7	- 8	- 9
comments	F <sup>-</sup> does not behave as a leaving group in the above rxns.	Cl <sup>-</sup> is a good leaving group in the above reactions	Br <sup>-</sup> is an even better leaving group in the above rxns.	I <sup>-</sup> is the best leaving group in the above reactions

**the ability of "X" to function as a leaving group in S<sub>N</sub>2 reactions increases with decreasing Bronsted basicity (=weaker bases are better leaving groups)**

Kinetic rate laws: differential equations that relate the velocity of a reaction (= the infinitesimal change in concentration of product or of starting material over time) to the instant concentrations of the various reactants

Second-order kinetic law for the above reaction:

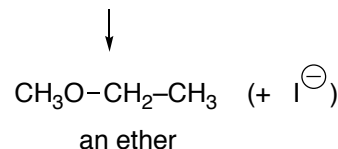
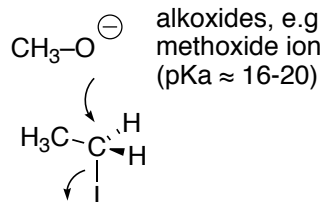
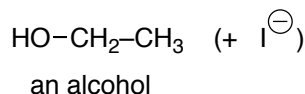
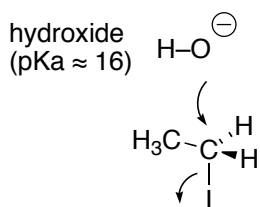
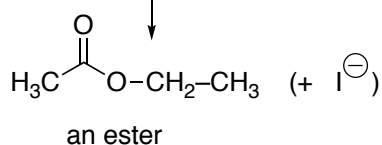
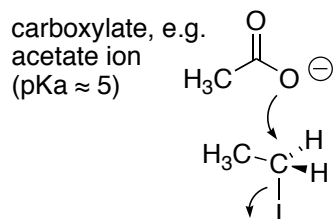
$$\text{rate} = \frac{d[\text{product}]}{dt} = k [\text{Nu}] [\text{alkyl halide}]$$

because the occurrence of the substitution process is a function of the probability that a molecule of Nu will collide with one of alkyl halide (with the correct orientation), which in turn is a function of the number of molecules of Nu and of the number of molecules of alkyl halide present in the reaction medium

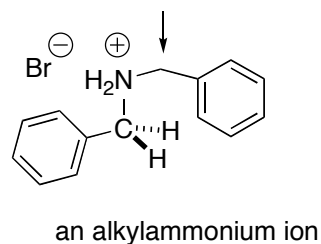
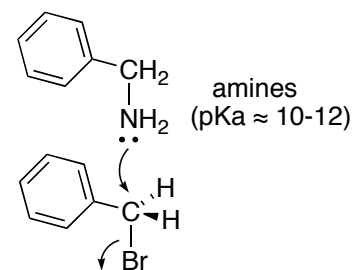
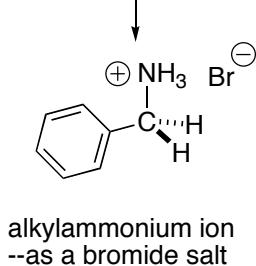
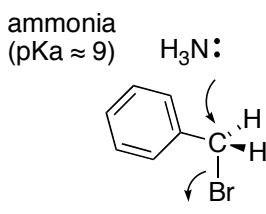
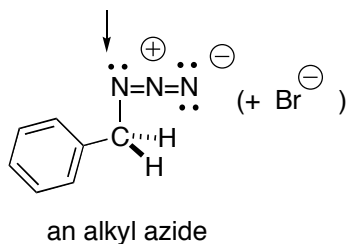
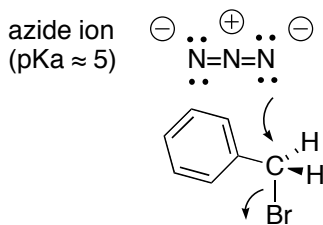
$S_N2$  reactions: those nucleophilic substitutions that are characterized by second-order kinetics and that proceed stereoselectively with inversion of configuration.

Nucleophiles of special interest in  $S_N2$  reactions:

#### oxygen - based



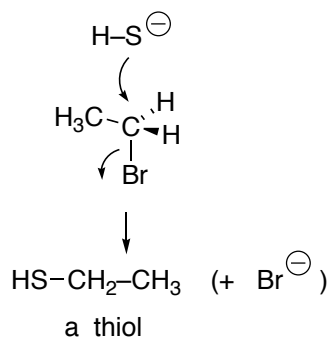
#### nitrogen - based



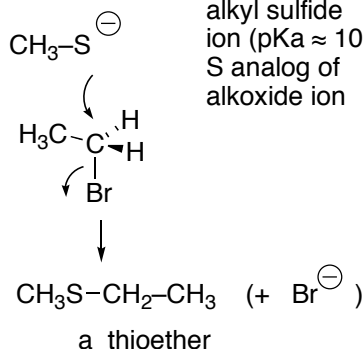


### sulfur - based

hydrogen  
sulfide ion  
(pKa  $\approx$  7):  
S analog  
of HO<sup>-</sup>

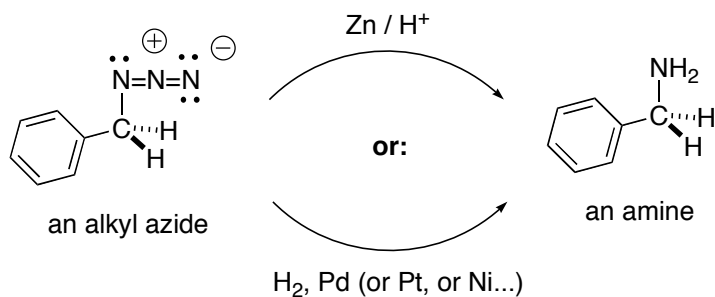


alkyl sulfide  
ion (pKa  $\approx$  10):  
S analog of  
alkoxide ion



Toxic and explosive properties of azide salts

Facile conversion of alkyl azides to amines with Zn/H<sup>+</sup> or by hydrogenation (no mechanism):



Potential problem with the reaction of alkyl halides with ammonia or with amines: formation of products of multiple reactions at nitrogen

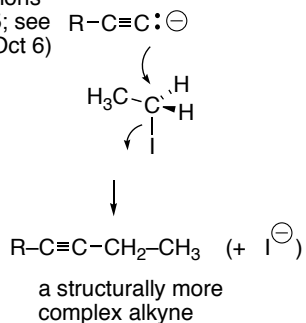
Usefulness of azide technology for the selective conversion of an alkyl halide to an amine of the type R-NH<sub>2</sub> (a "primary amine")

### Topics Discussed on Oct. 18 see chapter 9 of Brown-Foote-Iverson

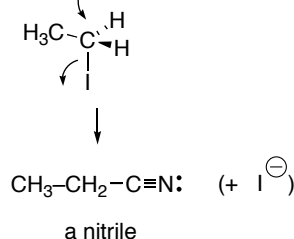
Nucleophiles of special interest in S<sub>N</sub>2 reactions – part II:

### carbon - based

acetylide ions  
(pKa  $\approx$  25; see  
notes of Oct 6)



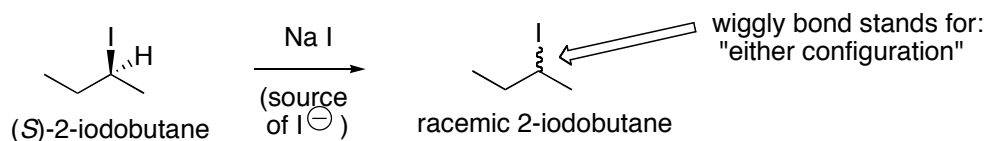
cyanide ion  
(pKa  $\approx$  10)



Other nucleophiles of interest in S<sub>N</sub>2 reactions: halide ions such as I<sup>-</sup> and to a lesser extent Br<sup>-</sup> and Cl<sup>-</sup>

Unusual properties of iodide ion in S<sub>N</sub>2 reactions: excellent leaving group as well good nucleophile

Racemization of enantiomerically pure alkyl halides by halide ion, especially iodide ion. E.g.:



Entropy of mixing as the driving force for the above racemization reaction

Effect of substitution at the halogen-bearing C atom on the rate of S<sub>N</sub>2 reactions: increasing substitution diminishes the accessibility of σ\*<sub>C-X</sub> orbital, thereby retarding the rate of S<sub>N</sub>2 reactions:

methyl halides

highly reactive

primary alkyl halides

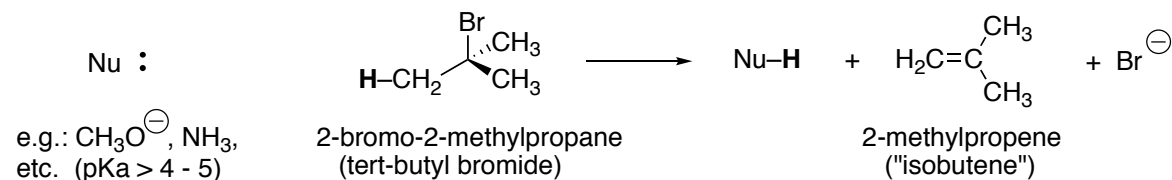
about 5 - 10 times less reactive than CH<sub>3</sub>-X

secondary alkyl halides

about 100 times less reactive than CH<sub>3</sub>-X

Inaccessibility of the σ\*<sub>C-X</sub> orbital in tertiary alkyl halides

Principle: tertiary halides react with basic nucleophiles (pK<sub>a</sub> > 4-5) that are otherwise successful in S<sub>N</sub>2 reactions to give alkene products (= olefins) instead. E.g.:



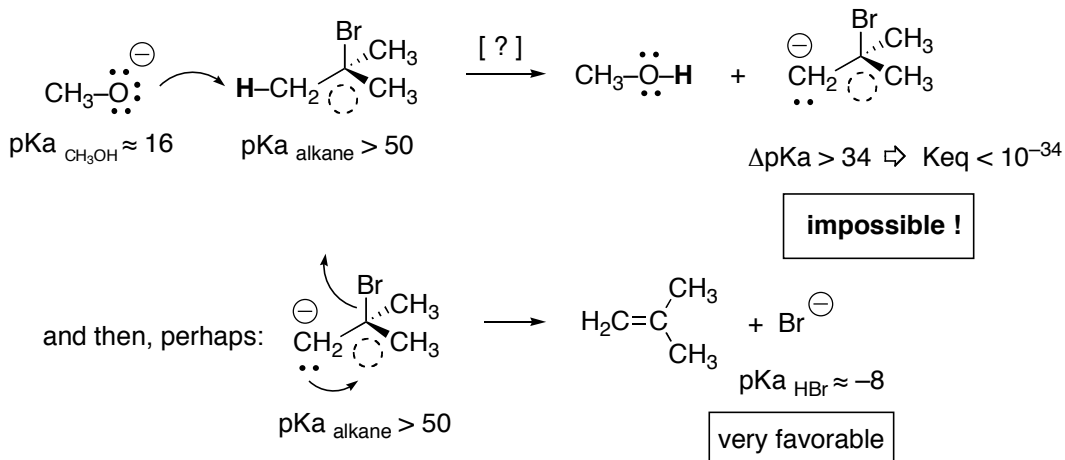
Elimination reactions: those leading to formation of double bonds through expulsion of appropriate fragments from a substrate molecule.

in the example above, the molecule of tert-butyl bromide expels HBr to form the alkene, 2-methyl-2-propene ("isobutene")

Behavior of the "nucleophile" as a Bronsted base in the above reaction

Possible mechanisms for the above reaction, e.g. with Nu = CH<sub>3</sub>O<sup>-</sup> :

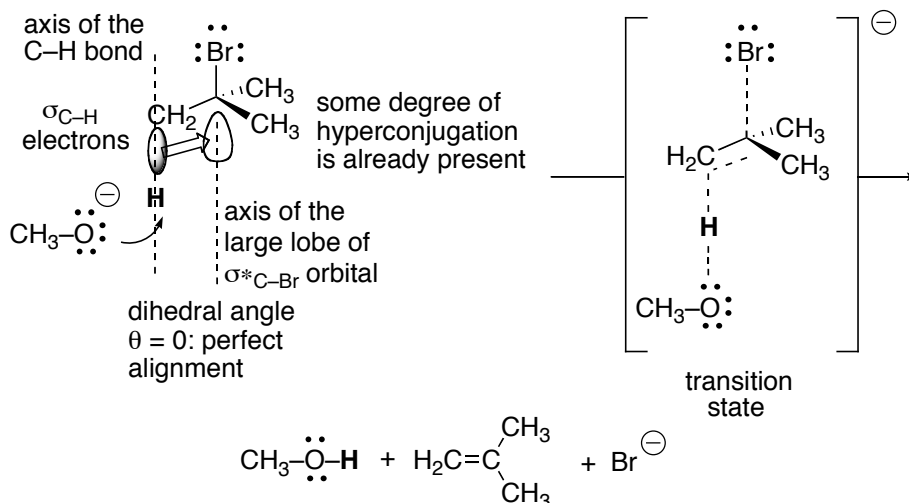
possibility 1: the Nu, now acting as a Bronsted base, deprotonates the substrate, then the ensuing anionic species expels Br<sup>-</sup> through some kind of "internal" nucleophilic substitution:



**this mechanistic picture is untenable**, because there is no way that the nucleophile can possibly deprotonate the alkane-type C–H bond of the substrate. On the other hand, if deprotonation did occur, the expulsion of  $\text{Br}^-$  from the anion would be very favorable

**how can the substrate molecule undergo deprotonation without ever forming a carbanion?**

possibility 2: the deprotonation of the substrate occurs in concert with the departure of  $\text{Br}^-$ . The  $\sigma_{\text{C-H}}$  electrons in the C–H bond about to be attacked by the Nu (now acting a Bronsted base) already experience hyperconjugation with the  $\sigma^*_{\text{C-Br}}$  orbital. As Nu takes up the proton, the  $\sigma$  electrons are funneled into the  $\sigma^*_{\text{C-Br}}$  orbital, thereby avoiding accumulation of negative charge on the carbon atom. **This is possible only if the  $\sigma$  C–H bond and the  $\sigma^*_{\text{C-Br}}$  orbital are perfectly aligned during the reaction:**



**this mechanism is plausible.** Evidence in support of it may be obtained through a kinetic study of the reaction. In particular, the above mechanism requires that the reaction rate be a function of the instant concentration of both Nu and substrate (**Why?** see notes of Oct. 16 for the  $\text{S}_{\text{N}}2$  reaction), i.e., overall second order

Experimentally observed second-order kinetics for the above elimination reaction:

$$\text{rate} = \frac{d[\text{alkene}]}{dt} = k [\text{Nu}] [\text{alkyl halide}]$$

E2 reactions: those elimination reactions that are characterized by second-order kinetics and that are believed to proceed through the above concerted mechanism.

Principle:

halides with a readily accessible C-X backside (location of the large lobe of the  $\sigma^*_{\text{C-X}}$  orbital), such as most primary and many secondary alkyl halides, tend to react with basic nucleophiles ( $\text{pK}_a > 4-5$ ) in an  $\text{S}_{\text{N}}2$  sense

halides with an inaccessible C-X backside, such as tertiary alkyl halides as well as certain primary and some secondary ones, tend to react with basic nucleophiles in an E2 sense

### Topics Discussed on Oct. 20 see chapter 9 of Brown-Foote-Iverson

Steric hindrance: the effect of alkyl groups that block access to a particular location within a molecule.

example: in the molecule of 2-bromo-2-methylpropane (notes of Oct 18), a triad of methyl groups produces steric hindrance at the backside of the C-Br bond, suppressing  $\text{S}_{\text{N}}2$  reactions and favoring E2 reactions.

Bronsted basic properties of nucleophiles utilized in  $\text{S}_{\text{N}}2$  reactions

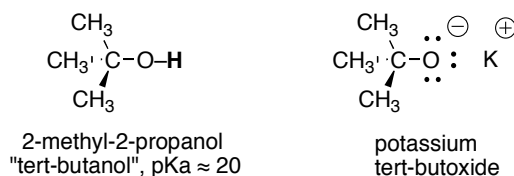
Nucleophilicity as carbon affinity

Basicity as proton affinity

Principle: elimination reactions are always observed to occur in competition with nucleophilic substitution reactions

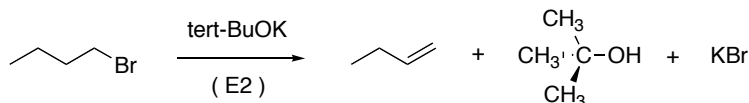
Principle: steric hindrance around the nucleophile, as well as the substrate, disfavors substitution and favors elimination

Sterically hindered alkoxides: potassium tert-butoxide:



Poor nucleophilicity and good basicity of potassium tert-butoxide

Sterically hindered alkoxides such as potassium tert-butoxide as effective bases for E2 reactions of alkyl halides, even primary ones:

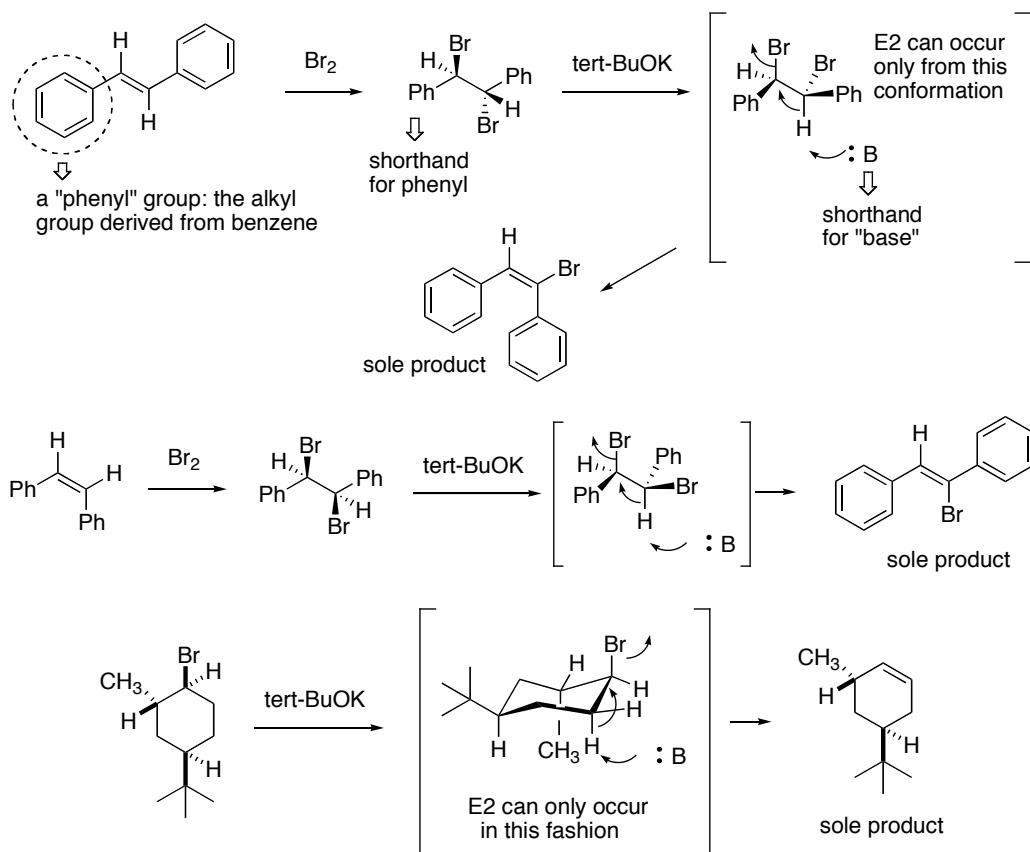


the tert-butoxide ion is too hindered to function as a nucleophile: it only expresses basic reactivity (=proton affinity) toward the halide

Stereoelectronic control: the fact that the occurrence of a reaction is subordinate to the substrate attaining a conformation that results in a particular alignment of the orbitals involved in the reaction in question

Stereoelectronic control in the E2 reaction: the fact that the  $\sigma_{\text{C-H}}$  orbital and the  $\sigma^*_{\text{C-X}}$  orbital must be eclipsed ( $\theta = 0$ ) for the E2 reaction to occur (notes of Oct. 18)

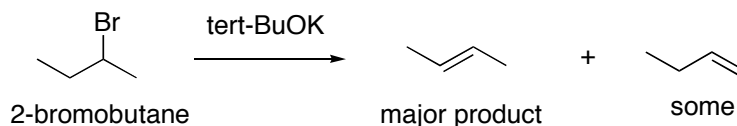
Consequences of the stereoelectronic properties of the E2 reaction:



Regioselectivity of the elimination reaction: the Saytzeff rule

"if an alkyl halide can undergo E2 reaction to give isomeric olefins, the more highly substituted olefin will form preferentially"

**example:** in principle, 2-bromobutane can undergo E2 reaction to give either 1-butene or 2-butene. In fact, 2-butene (mostly trans) will form preferentially:



Polar solvents: those with a high dielectric constant ( $\epsilon > 20$ )

Protonic ("protic") polar solvents: solvents such as alcohols, water, etc., that have a high dielectric constants and that possess O–H groups

Non-protonic ("aprotic") polar solvents: solvents such as acetonitrile, dimethyl sulfoxide ("DMSO"), etc., that have a high dielectric constants but that do not possess O–H groups

Solvation of anions, and of electron-rich species in general, in protic solvents through hydrogen bonding

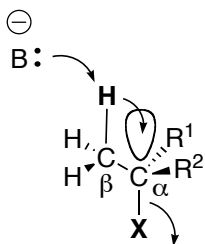
Decrease in nucleophilic / basic reactivity of an electron-rich species dissolved in a protic solvent due to involvement of its  $e^-$  pairs in H-bonding

"Free" nature of anions in aprotic solvents and consequent increase in their nucleophilic / basic reactivity

Usefulness of aprotic solvents such as  $\text{CH}_3\text{CN}$  and DMSO for the conduct of  $\text{S}_\text{N}2$  and E2 reactions

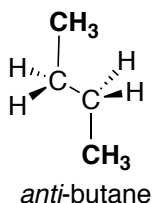
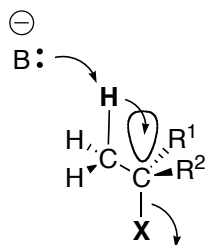
### Topics Discussed on Oct. 23 see chapter 9 of Brown-Foote-Iverson

The E2 reaction as a  $\beta$ -elimination:



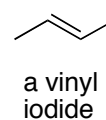
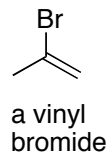
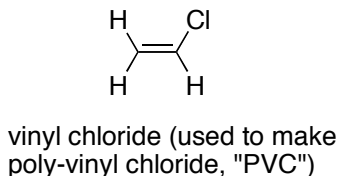
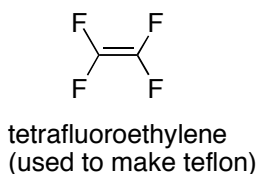
the E2 reaction occurs with removal of a proton situated on a carbon atom adjacent to the halogen-bearing carbon. If one takes the halogen-bearing carbon as a point of reference (the " $\alpha$ " carbon), then the proton is lost from the " $\beta$ " carbon; hence the term " $\beta$ -elimination,"

The E2 reaction as an "anti-elimination" due to the stereoelectronic requirement that the departing H atom be oriented anti to the halogen atom

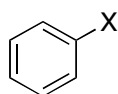


the conformational relationship between the H atom involved in an E2 reaction and the departing halogen, **X**, is reminiscent of that between the methyl groups in *anti*-butane; hence the term "*anti*-elimination."

Vinyl halides: those in which the halogen atom is bound to an  $sp^2$  carbon of an alkene



Aryl halides: those in which the halogen atom is bound to an  $sp^2$  carbon of a benzene ring



X = halogen

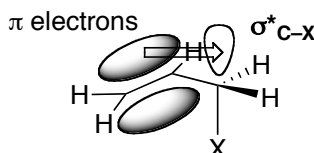
Lack of reactivity of vinyl and aryl halides in  $S_N2$  reactions on accounts of:

- hindered backside, especially in the case of aryl halides
- greater strength of  $sp^2$ -C – X bond relative to the  $sp^3$ -C – X bond
- resonance interactions that generate some double bond character between C and X
- greater electronegativity of  $sp^2$ -carbons relative to  $sp^3$ -carbons and consequent *decrease* in C – X bond polarization

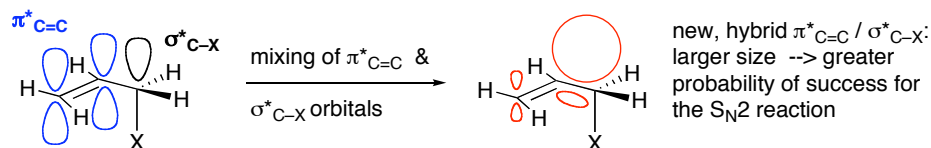
**note:** vinyl and aryl halides *do* undergo elimination reactions. This chemistry, however, is beyond the scope of CHEM 203.

High reactivity of allyl and benzyl halides in  $S_N2$  reactions because of:

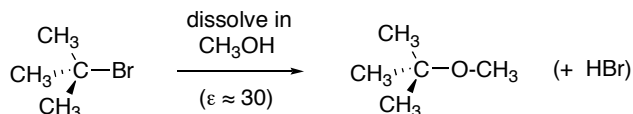
- **weakening of the C–X bond** through hyperconjugative donation of electronic density from the neighboring  $\pi$  bond into the  $\sigma^*_{C-X}$  orbital



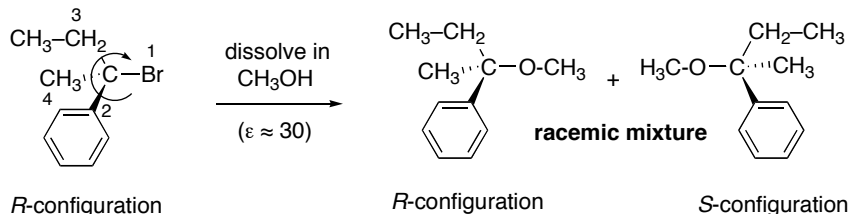
- **greater probability of successful  $S_N2$  reaction** due to an interaction between  $\pi^*_{C=C}$  and  $\sigma^*_{C-X}$  orbitals that leads to a larger (less energetic, more readily accessible) antibonding orbital at the backside of the C–X bond:



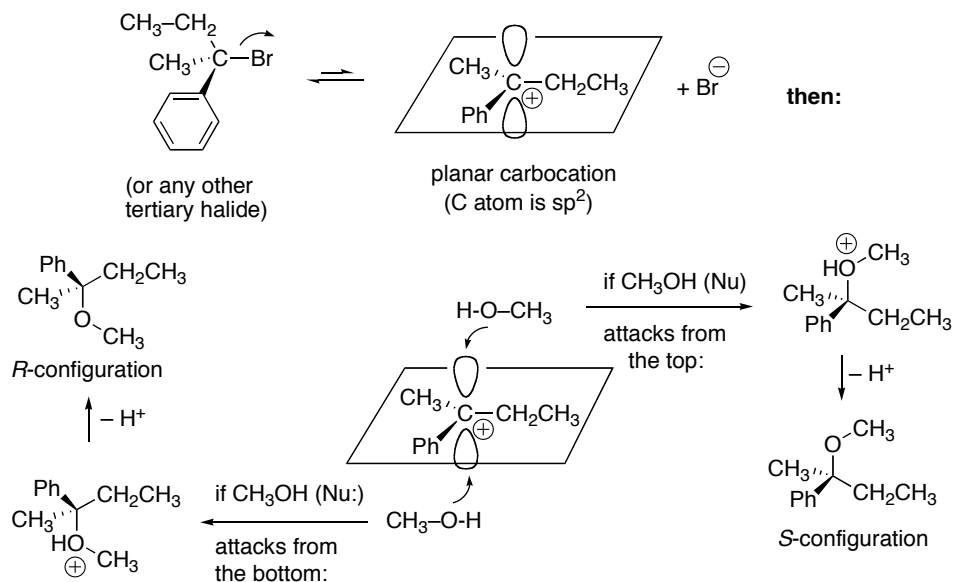
Principle: hindered alkyl halides, such as tertiary ones, may undergo substitution reactions, but only with **non-basic nucleophiles** ( $H_2O$ ,  $CH_3OH$ , etc.: basic nucleophiles promote E2 reaction) in media of high dielectric constant ( $\epsilon > 20$ ), e.g.:



Loss of configuration during substitution reactions of tertiary halides under the above conditions: formation of racemic products from enantiopure alkyl halides, e.g.:



Mechanistic interpretation of the above observations: ionization of the substrate, formation of a planar carbocation, reaction of the latter with the nucleophile:



there is no reason why  $CH_3OH$  (in general, the nucleophile) should favor attack from one side or the other (top or bottom) of the carbocation. Therefore, top- and bottom-face attack will occur with equal probability, leading to a 1:1 mixture of (*S*)- and (*R*)-products, i.e., to a racemic mixture.



Principle: unlike the S<sub>N</sub>2 reaction, which proceeds in a single kinetic step, the process outlined above involves two distinct and independent steps: ionization of the starting halide and nucleophilic capture of the resulting carbocation

Endothermic nature of the dissociative process leading to formation of the carbocation (slow, difficult)

Exothermic nature of the capture of the carbocation by the nucleophile (fast, facile)

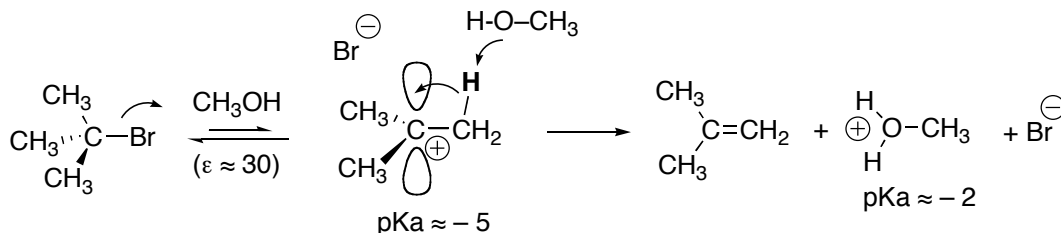
The dissociation of the starting alkyl halide (slow, difficult) as the rate-limiting step of the above substitution reaction

The rate of formation of the carbocation (= the overall rate of the above substitution process) as a function of the instant concentration of alkyl halide *only*; i.e., the reaction proceeds with first order kinetics

$$\text{rate} = \frac{d[\text{product}]}{dt} = k [\text{alkyl halide}]$$

S<sub>N</sub>1 reactions: those nucleophilic substitutions (i) typical of tertiary (in general, hindered) alkyl halides reacting with non-basic nucleophiles in media of high dielectric constants, (ii) characterized by first-order kinetics, and (iii) proceeding with loss of configuration.

Strong Brønsted acidity of carbocations (notes of Sept 22) and consequent possibility that the carbocation generated through dissociation of, e.g., a tertiary halide in a medium of high dielectric constant may release a proton and form an olefin:



The above process as an elimination reaction

Principle: unlike the E2 reaction, which proceeds in a single kinetic step, the process outlined above involves two distinct and independent steps: ionization of the starting halide and deprotonation of the resulting carbocation

Endothermic nature of the dissociative process leading to formation of the carbocation (slow, difficult)

Exothermic nature of the deprotonation of the carbocation (fast, facile)

The dissociation of the starting alkyl halide (slow, difficult) as the rate-limiting step of the above elimination reaction

The rate of formation of the carbocation (= the overall rate of the above elimination process) as a function of the instant concentration of alkyl halide *only*; i.e., the reaction proceeds with first order kinetics

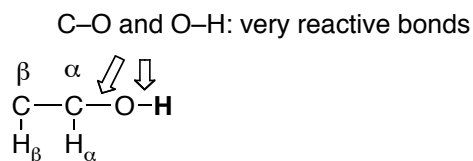
$$\text{rate} = \frac{d[\text{alkene}]}{dt} = k [\text{alkyl halide}]$$

E1 reactions of alkyl halides: those elimination reactions that occur as a consequence of dissociation of, e.g., tertiary alkyl halides in media of high dielectric constants, and that proceed with first-order kinetics.

### Topics Discussed on Nov. 6 see chapter 10 of Brown-Foote-Iverson

Primary, secondary, tertiary alcohols

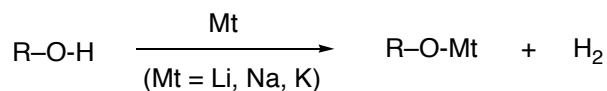
The OH group as a highly reactive functionality that "activates" neighboring atoms, in particular, the  $\alpha$  and  $\beta$  C atoms and the H atoms attached to them, toward a variety of transformations.



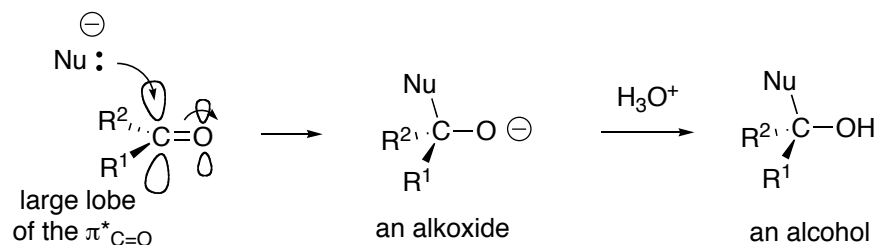
Reactions already studied in class that involve the C–O bond and the  $\beta$ -H: olefin hydration, alcohol dehydration, hydroboration-oxidation

Weak acidity of the O–H bond of alcohols ( $\text{pK}_a = 16\text{--}20$ )

Formation of alkoxides by reaction of alcohols with reactive metals such as Li, Na, K, ...:



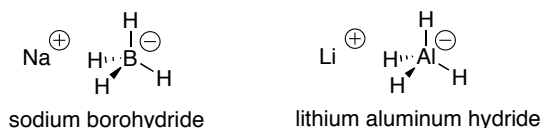
Preparation of alcohols by reaction of carbonyl compounds with appropriate nucleophiles: the "master plan."



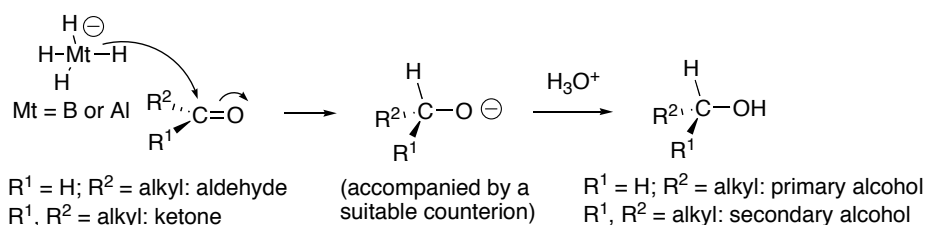
**note:** the starting carbonyl compound could be an aldehyde, a ketone, an ester ... etc. We already know that aldehydes and ketones are available through the ozonolysis of olefins.

Reactions in which "Nu:<sup>-</sup>" above is hydride ion (H:<sup>-</sup>): reduction of carbonyls to alcohols

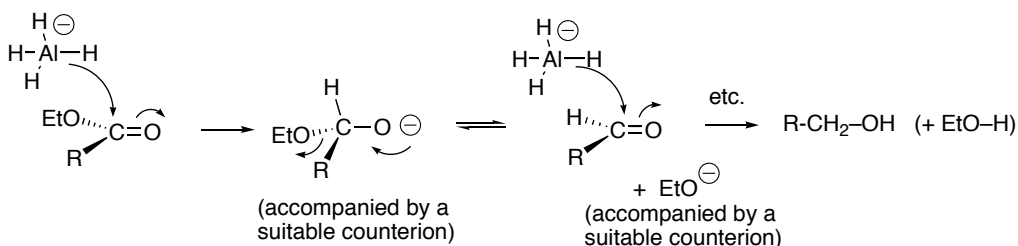
Reagents that act as carriers of nucleophilic forms of hydride ion: sodium borohydride (mild: reacts only with aldehydes and ketones) and lithium aluminum hydride ("LAH;" vigorous: reacts with any type of carbonyl compound)



Reaction of NaBH<sub>4</sub> or of LiAlH<sub>4</sub> with aldehydes and ketones: formation of primary and secondary alcohols, respectively



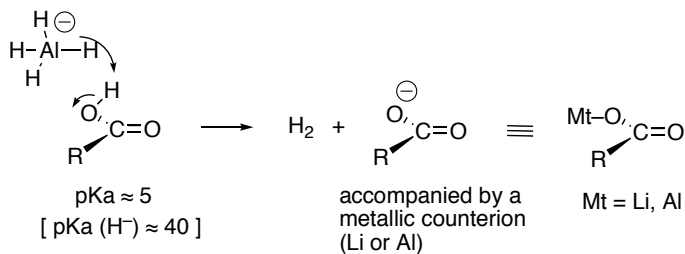
Reaction of LiAlH<sub>4</sub> with esters: formation of primary alcohols



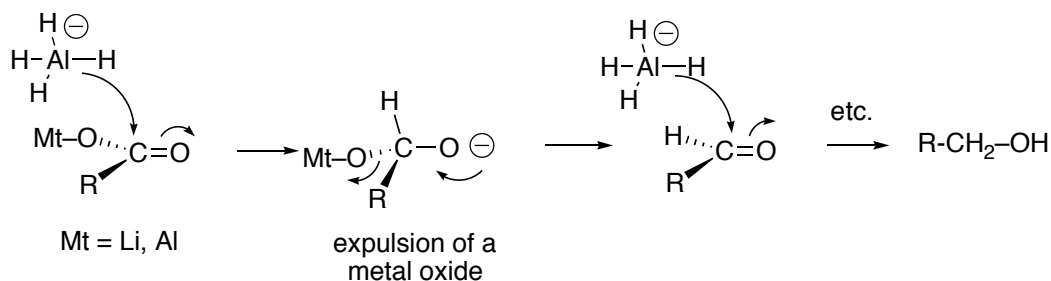
### Topics Discussed on Nov. 8 see chapter 10 of Brown-Foote-Iverson

Reaction of LiAlH<sub>4</sub> with carboxylic acids: formation of primary alcohols

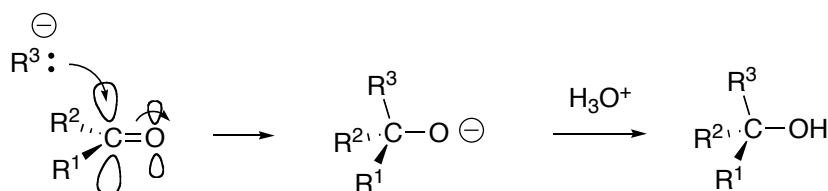
First interaction between a carboxylic acid and LAH: protonation of hydride ion to give molecular hydrogen plus a metal carboxylate:



Great reactivity of LAH and ability thereof to transfer a hydride even to a metal carboxylate:



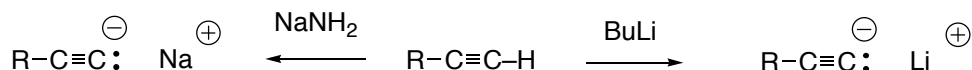
Preparation of alcohols by reaction of carbonyl compounds with carbon-centered nucleophiles:



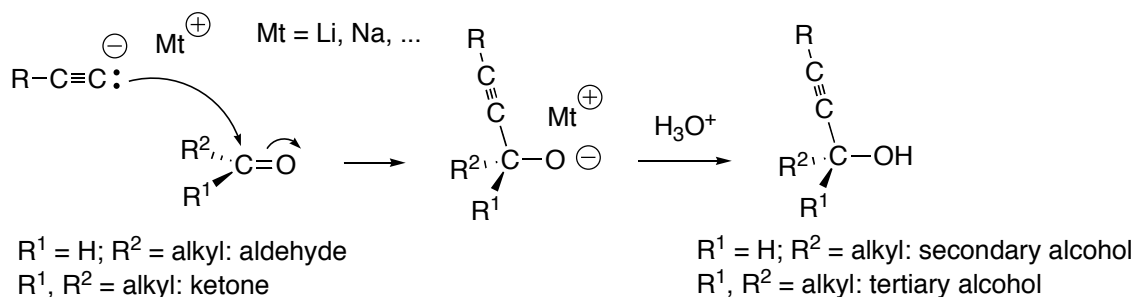
**note:** the starting carbonyl compound could be an aldehyde, a ketone, or an ester

Requirement for a "carbon anion" (= a "carbanion") for the conduct of the above transformation

Carbonions already encountered in class: acetylide ions (notes of Oct 6)



Addition of acetylide ions to aldehydes and ketones:



Desirability of a general method for the creation of a "carbanion" from any alkyl segment

Principle: connection of a carbon atom to an electropositive metal (Mg, Li, etc.) engenders carbanionic character on that carbon atom

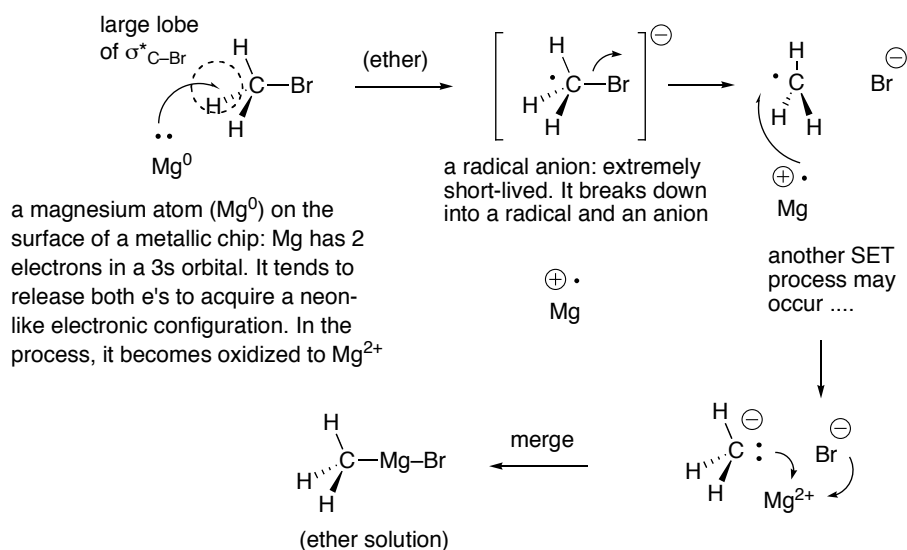
Organometallic agents: organic compounds in which a carbon atom is bound to a metal

Preparation of organometallic agents by the reaction of alkyl halides with reactive metals such as Mg, Li, etc.

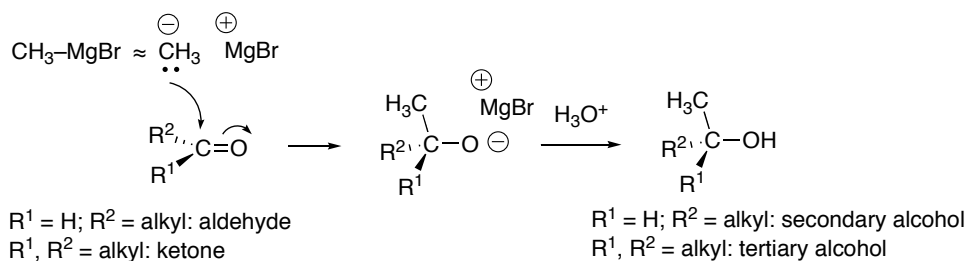
Grignard reagents (after Victor Grignard, 1912 Nobel Prize in chemistry): alkylmagnesium halides of the type  $R-Mg-X$  ( $R$  = any alkyl,  $X = Cl, Br, I$ )

Formation of Grignard reagents through the interaction of an alkyl halide with metallic magnesium in a solvent such as diethyl ether ( $CH_3-CH_2-O-CH_2-CH_3$ )

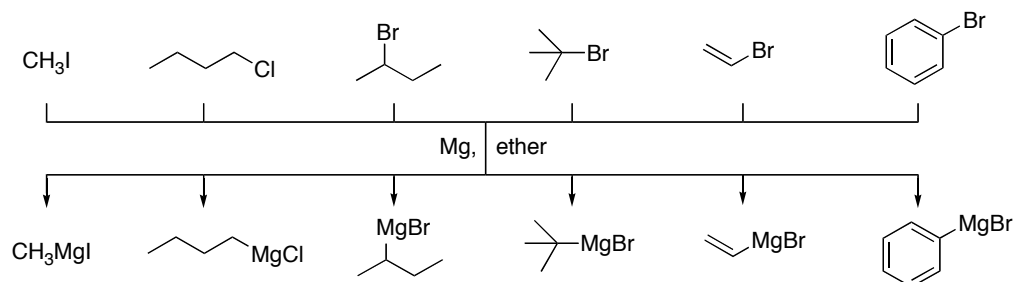
SET mechanisms in the formation of Grignard reagents; e.g., reaction of  $CH_3Br$  with Mg:



Addition of Grignard reagents, e.g., of  $CH_3MgBr$ , to aldehydes and ketones:

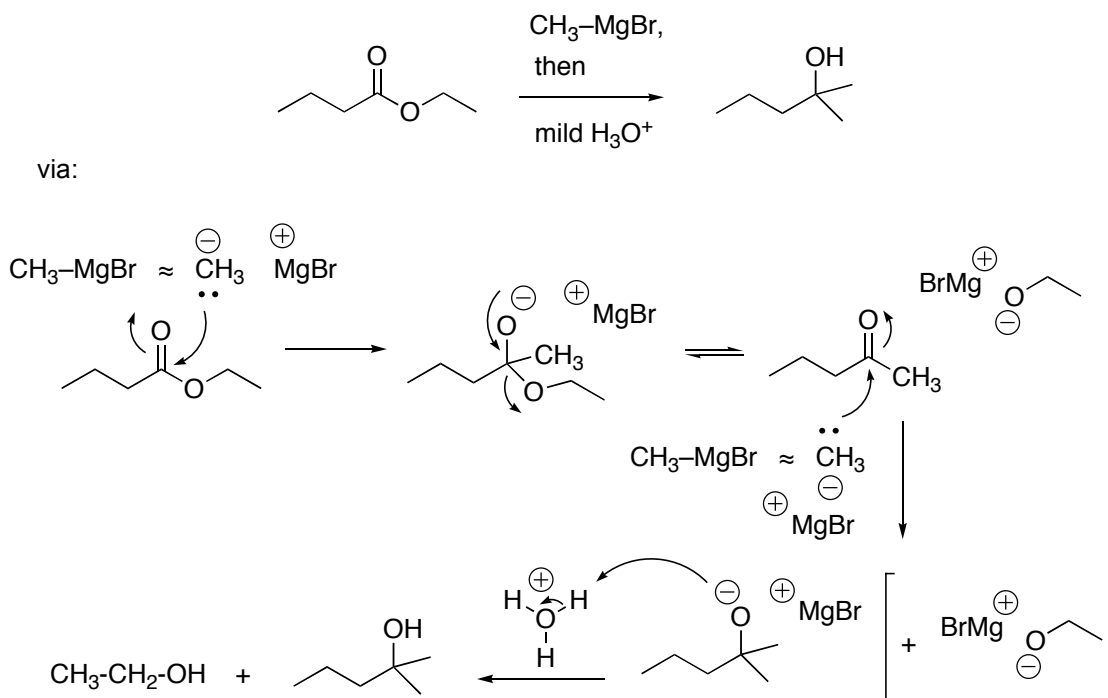


Principle: Grignard reagents may be prepared from virtually any alkyl chloride, bromide or iodide, e.g.:

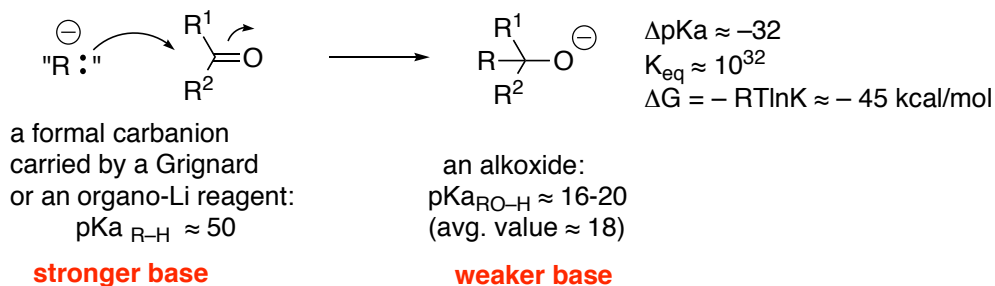
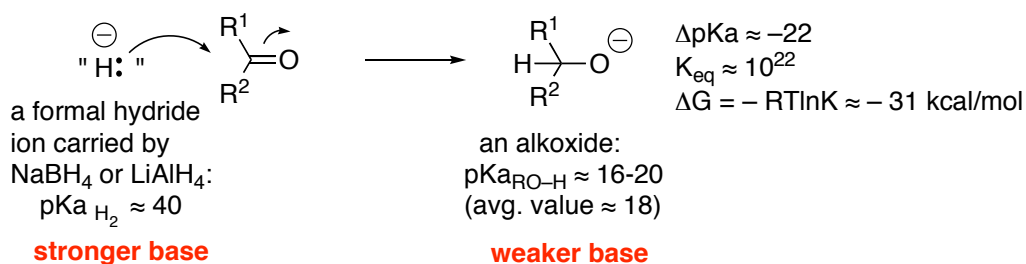


**CHEM 203**  
**Topics Discussed on Nov. 10**  
**see chapter 10 of Brown-Foote-Iverson**

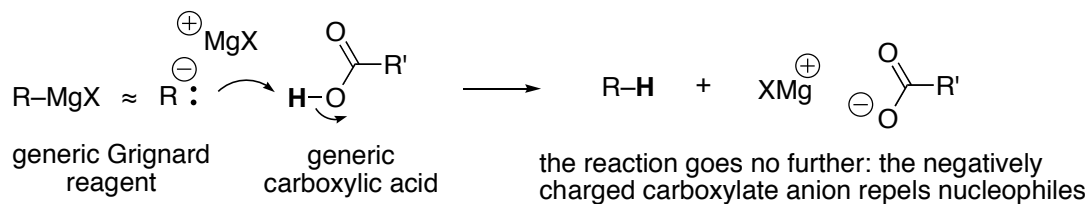
Reaction of Grignard reagents with esters: formation of tertiary alcohols through addition of two molecules of RMgX to the carbonyl group. Example:



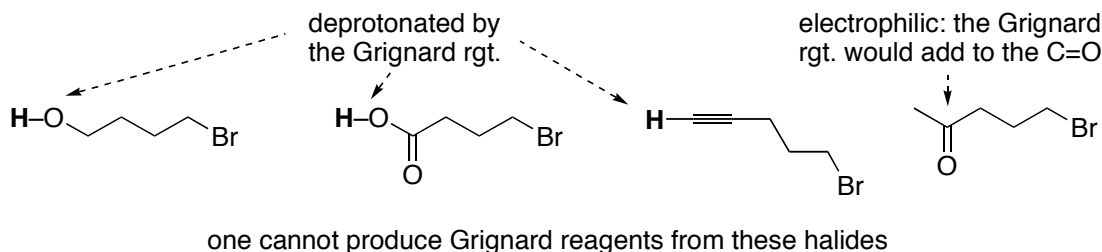
Change in the basicity of the medium, as gauged by changes in pKa's during the reaction, as a powerful driving force for the addition of hydride ions and of carbanions to carbonyl groups:



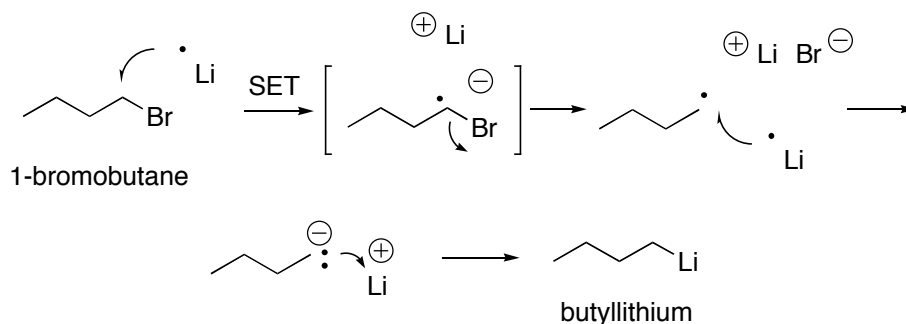
Reaction of Grignard reagents with carboxylic acids: protonation



Incompatibility of Grignard reagents with acidic ( $\text{pK}_a \leq 30\text{-}35$ ) or electrophilic functional groups possibly present on the same molecule, e.g.:



Organolithium compounds: organometallics of general structure  $\text{R-Li}$  obtained upon reaction of  $\text{R-X}$  ( $\text{X} = \text{Br}, \text{Cl}$ ) with metallic  $\text{Li}$ . Example:



Similar reactivity of organo-Li compounds and of Grignard reagents

### Topics Discussed on Nov. 15 see chapter 10 of Brown-Foote-Iverson

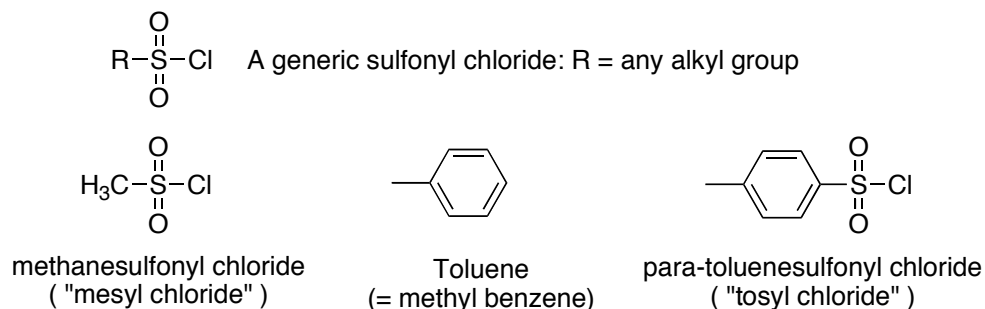
Principle: the chemistry of alcohols is controlled by the basicity and by the nucleophilicity of the OH group

example of a reaction of alcohols that is promoted by the basicity of the OH group:  
dehydration with  $\text{H}_2\text{SO}_4$  / heat

example of a reaction of alcohols that is promoted by the nucleophilicity of the OH group:  
conversion to alkyl halides with  $\text{SOCl}_2$  or with  $\text{PBr}_3$

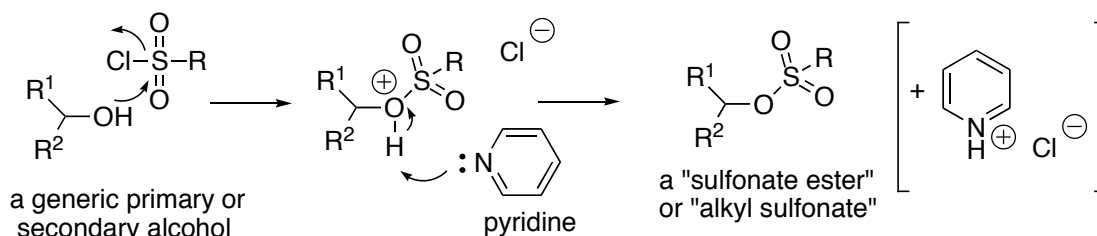
Inability of the OH function *per se* to participate in substitution or elimination reactions of the type seen in class due to an excessively high pKa of the conjugate acid of HO<sup>-</sup> (i.e., water)

Sulfonyl chlorides: para-toluenesulfonyl ("tosyl") chloride, methanesulfonyl ("mesyl") chloride



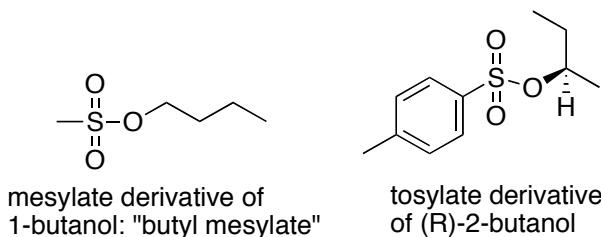
Electrophilic reactivity of sulfonyl chlorides

Reaction of primary and secondary alcohols with sulfonyl chlorides in the presence of pyridine: formation of sulfonate esters (= alkyl sulfonates)



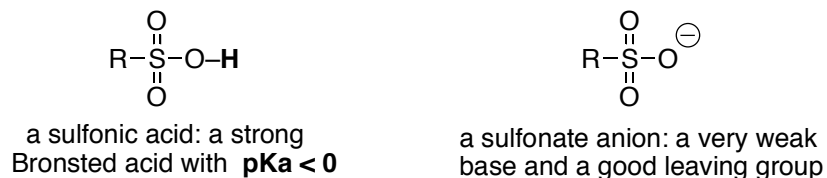
**note:** the actual mechanism of formation of sulfonate esters differs slightly from the one presented in class

Alkyl tosylates, mesylates:



Inability of tertiary alcohols to form sulfonate esters due to poor nucleophilicity (steric problems)

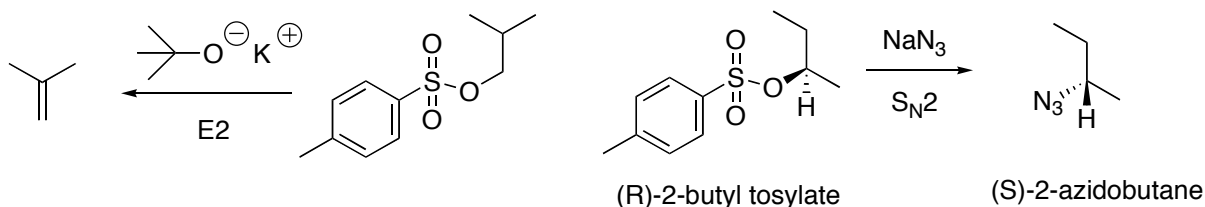
Strong acidity of sulfonic acids and consequent weak basicity / good leaving group properties of sulfonate anions:



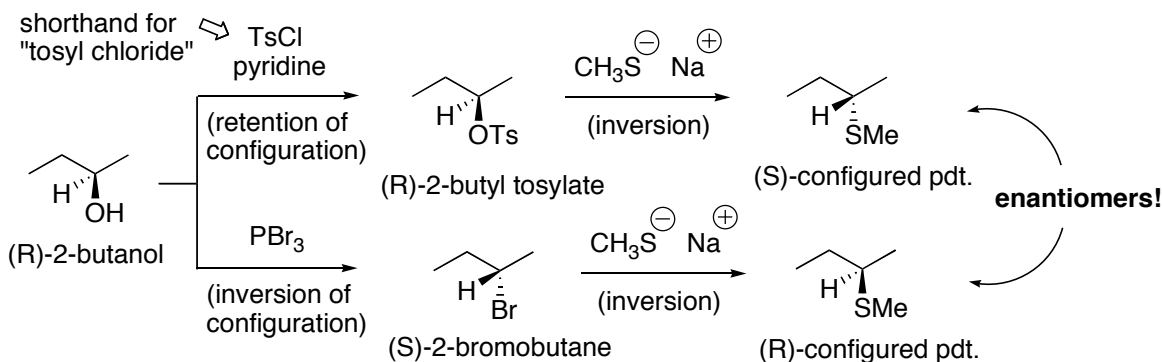


Principle: alkyl sulfonates exhibit chemistry essentially identical to that of alkyl halides

Substitution & elimination reactions of sulfonate esters; e.g.:



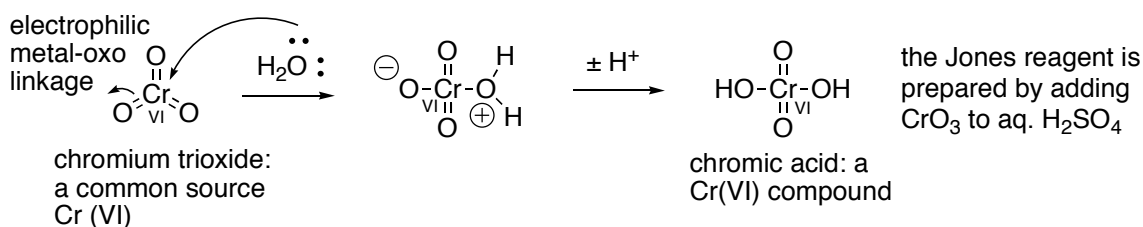
Stereochemical complementarity of sulfonate ester vs.  $\text{PBr}_3$  technology:



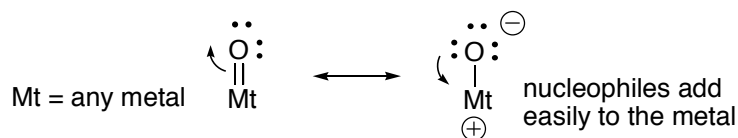
one may thus access either enantiomer of a product of  $\text{S}_{\text{N}}2$  reaction of a suitably activated alcohol by the judicious choice of the activation method: sulfonate technology produces overall inversion of configuration;  $\text{PBr}_3$  technology, overall retention (via a double inversion)

Oxidation of alcohols to carbonyl compounds with Cr(VI) – based reagents

Jones reagent: a solution of chromic acid,  $\text{H}_2\text{CrO}_4$ , in aqueous  $\text{H}_2\text{SO}_4$ :

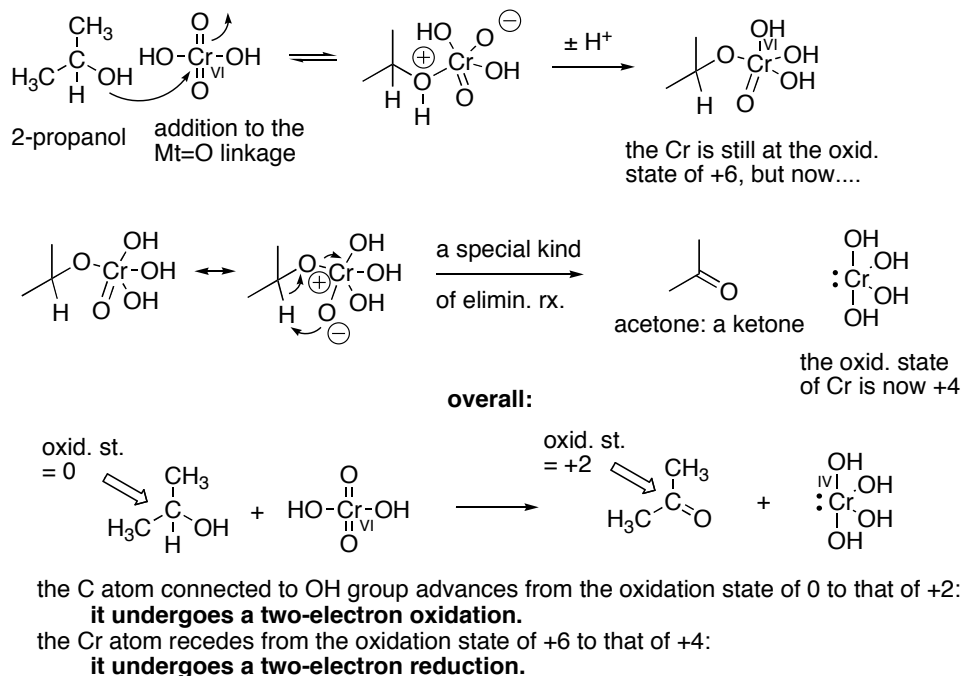


Electrophilic reactivity of metal-oxo linkages,  $\text{Mt}=\text{O}$ :



Tendency of Cr(VI) to become reduced to Cr(III): the stable oxidation state of Cr

Oxidation of secondary alcohols to ketones with the Jones reagent; e.g.:

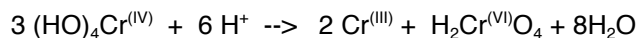


**note:** we will discuss the fate of the Cr(IV) intermediate thus produced on Nov 17

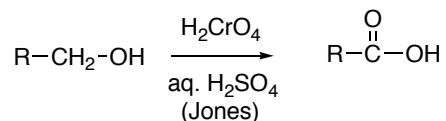
### Topics Discussed on Nov. 17

see chapter 10 of Brown-Foote-Iverson

Fate of the Cr(IV) intermediate produced during the Jones oxidation: disproportionation to the more stable Cr(III) form plus chromic acid:

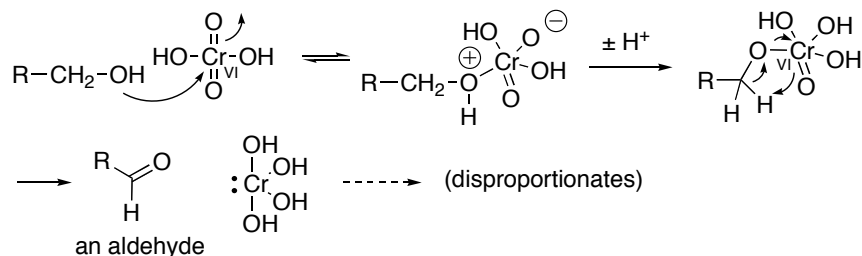


Oxidation primary alcohols to carboxylic acids with the Jones reagent:

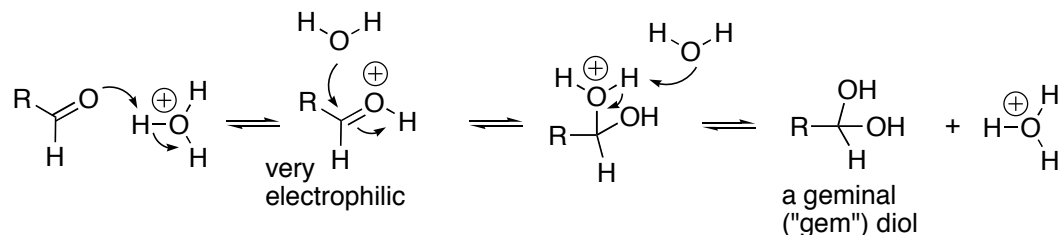


Mechanism of the Jones oxidation of a primary alcohol to a carboxylic acid:

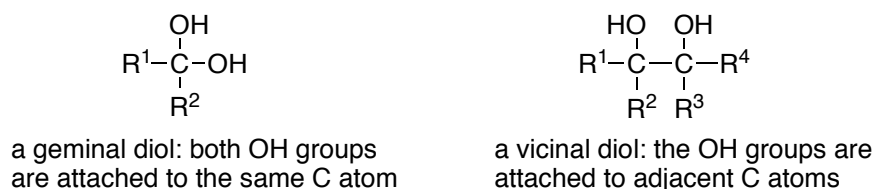
(i) initial oxidation to an aldehyde:



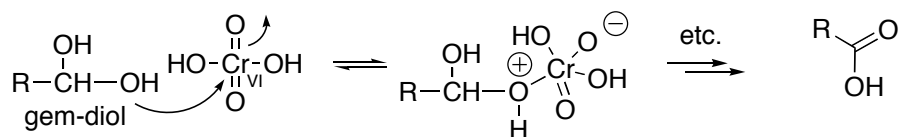
(ii) Rapid equilibration of the aldehyde with a geminal diol promoted by the aq.  $\text{H}_2\text{SO}_4$  (i.e., the  $\text{H}_3\text{O}^+$ ) present in the Jones reagent:



**note:** geminal diols (obtained by the reversible hydration of carbonyl functions and ) display a pair of OH groups connected to the same carbon atom. Vicinal diols (obtained by  $\text{OsO}_4$  oxidation of alkenes) are such that the OH groups are connected to adjacent carbon atoms:

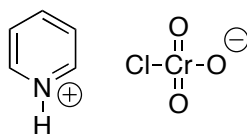


(iii) Further oxidation of the *gem*-diol to an acid by the usual Jones mechanism:

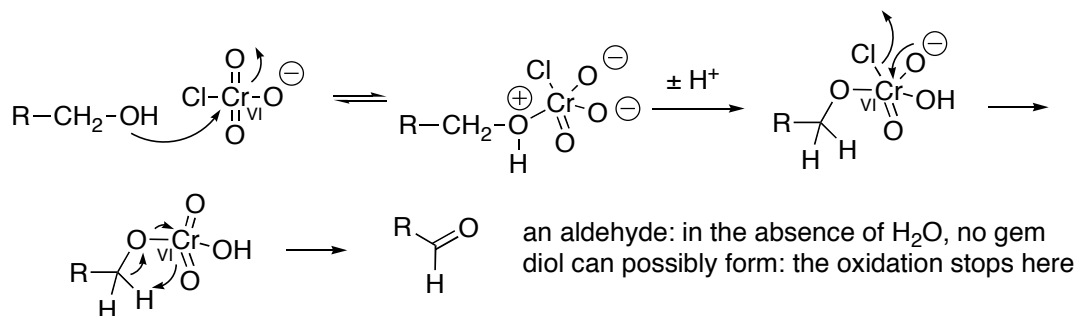


The problem of oxidizing a primary alcohol to an aldehyde: requirement for a Cr(VI) reagent that works in an anhydrous (=water-free) medium

Pyridinium chlorochromate (PCC):



PCC oxidation of primary alcohols to aldehydes and of secondary alcohols to ketones in anhydrous media:



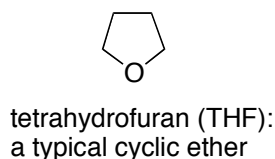
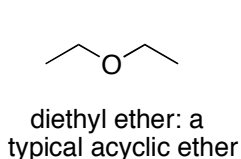
**note 1:** fine details of the mechanism of PCC oxidation remain unknown. The mechanism shown above is one of a number of plausible mechanism that differ for the precise sequence of events leading to the C(VI) complex that ultimately decomposes to give the aldehyde.

**note 2:** the mechanism of PCC oxidation of secondary alcohols to ketones is substantially identical to the one outlined above.

Inability of tertiary alcohols to undergo oxidation to carbonyls

**Topics Discussed on Nov. 20**  
**see chapter 11 of Brown-Foote-Iverson**

Ethers: acyclic and cyclic

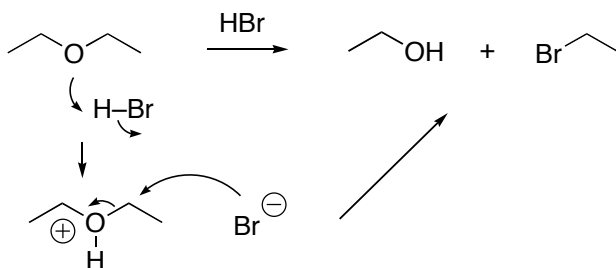


Heterocyclic compounds: those like THF, in which a ring structure incorporates a heteroatom (oxygen, in the case of THF).

The Williamson reaction: synthesis of ethers via the  $S_N2$  alkylation of a metal alkoxide with an appropriate alkyl halide

Unreactivity of ethers and consequent use thereof as solvents

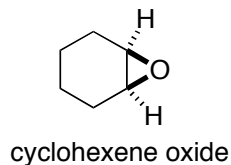
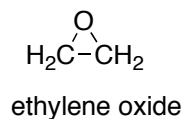
Cleavage of ethers with H-X resulting in formation of a molecule of alcohol and one of alkyl halide. Example:



Ability of an alcohol,  $R-OH$ , to function as a leaving group in an  $S_N2$  reaction due to its nature as the conjugate base of a strong protonic acid,  $R-OH_2^+$  ( $pK_a \approx -2$ )

Epoxides or oxiranes: cyclic ethers in which the oxygen atom is part of a three membered ring:

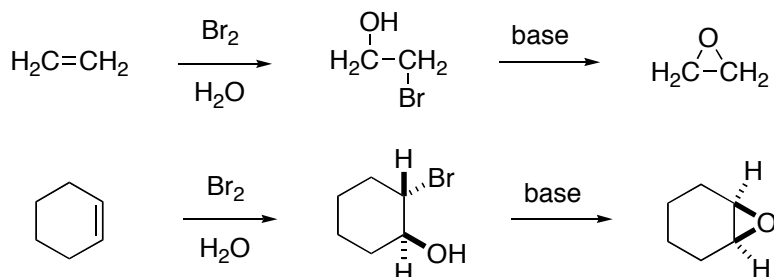
Common nomenclature of epoxides: attaching the term "oxide" to the name of the corresponding alkene, e.g.:



Angle strain in epoxides

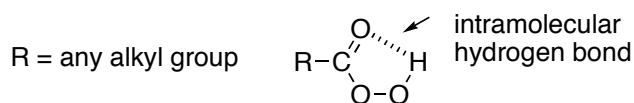
Enhanced reactivity of epoxides because of strain

Preparation of epoxides by cyclization of halohydrins. Examples:

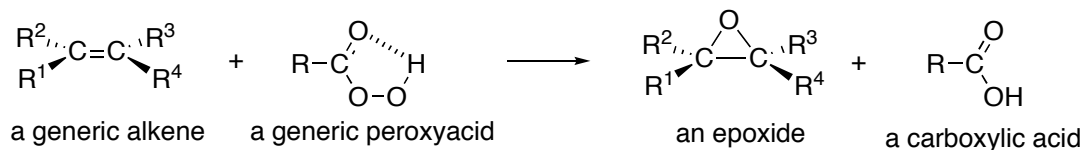


The cyclization of halohydrins as an intramolecular variant of the Williamson reaction

Peroxydicarboxylic acids: compounds of general formula

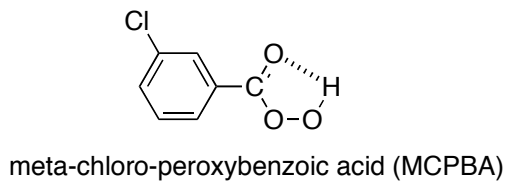


Preparation of epoxides by oxidation of alkenes with peroxydicarboxylic acids:

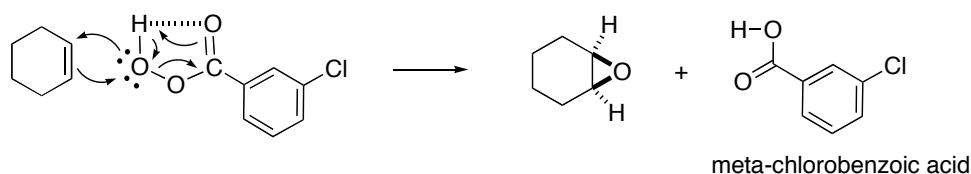


Peroxydicarboxylic acids as formal carriers of an electrophilic oxygen *atom*

Meta-chloroperoxybenzoic acid (MCPBA) as a particularly convenient peroxyacid reagent for olefin epoxidation:



Mechanism of peracid epoxidation of olefins (cf. mech. of formation of halonium ions):

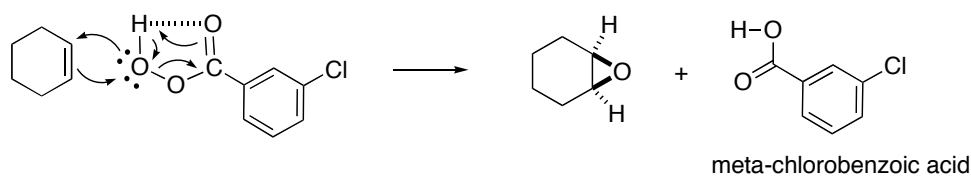


Retention of olefin geometry during epoxidation reactions

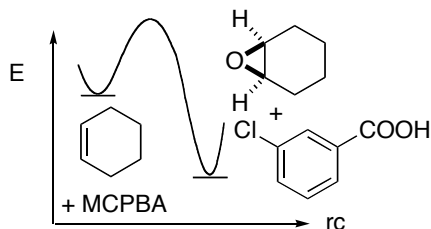
Syn course of the epoxidation reaction

**Topics Discussed on Nov. 22**  
**see chapter 11 of Brown-Foote-Iverson**

Syn course of the epoxidation reaction with peroxyacid reagents, e.g., with MCPBA

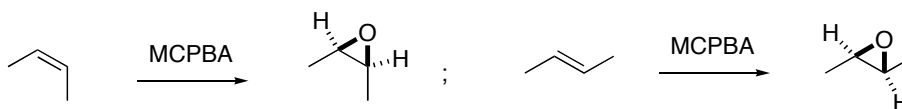


Concerted mechanism of peroxyacid (e.g., MCPBA) epoxidation of alkenes: the epoxide forms in a single kinetic step though a mechanism that involves no radical or ionic intermediates:



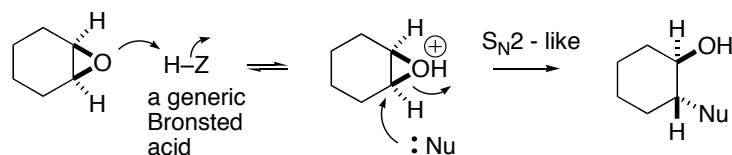
Retention of olefin geometry during epoxidation reactions (mentioned also on Nov 20).

Examples:



Nucleophilic cleavage of epoxides with or without initial protonic activation

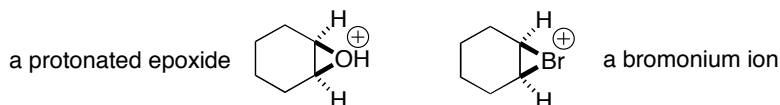
General mechanism for the acid-promoted cleavage of epoxides:



Approximate pKa of a protonated epoxide:  $\approx -2$

Requirement for a strong Bronsted acid ( $\text{pK}_a < 0$ , such as HCl, HBr,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{O}^+$ ...) to generate concentrations of protonated epoxide sufficient to induce the above transformations

Electronic similarity between protonated epoxides and halonium ions, and predictability of the chemistry of protonated epoxides by analogy with the reactivity of halonium ions

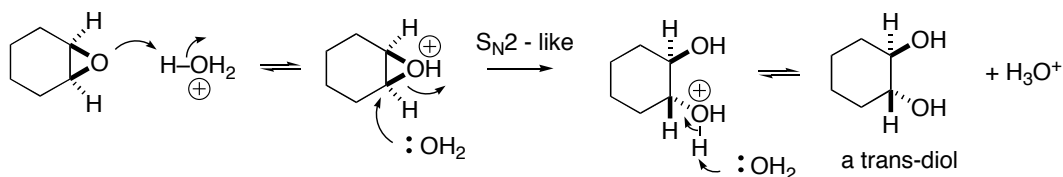


Type of nucleophiles that may be used in an acid-catalyzed opening of an epoxide: those nucleophiles such as  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{OH}$ ,  $\text{Br}^-$ ,  $\text{Cl}^-$ , etc., that are conjugate bases of strong acids ( $\text{pK}_a < 0$ ), and that therefore are relatively insensitive to the action of protonic acids.

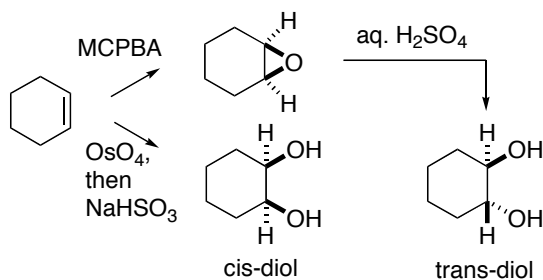
Nucleophiles that **cannot** be used in an acid-catalyzed opening of an epoxide: those such as amines, cyanide ion, acetylide ions, Grignard reagents, etc., that are conjugate bases of weak acids ( $\text{pK}_a > 10$ ), and that consequently would be irreversibly protonated by strong acids.

Inversion of configuration in acid-catalyzed epoxide opening (the nucleophile interacts with the  $\sigma^*_{\text{C-O}}$  orbital)

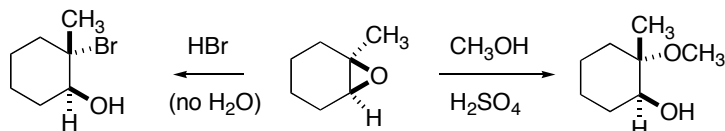
Reaction of epoxides with  $\text{H}_3\text{O}^+$  (e.g., aqueous sulfuric acid): preparation of trans-diols



Stereochemical complementarity of the above process vs. the  $\text{OsO}_4$  reaction:

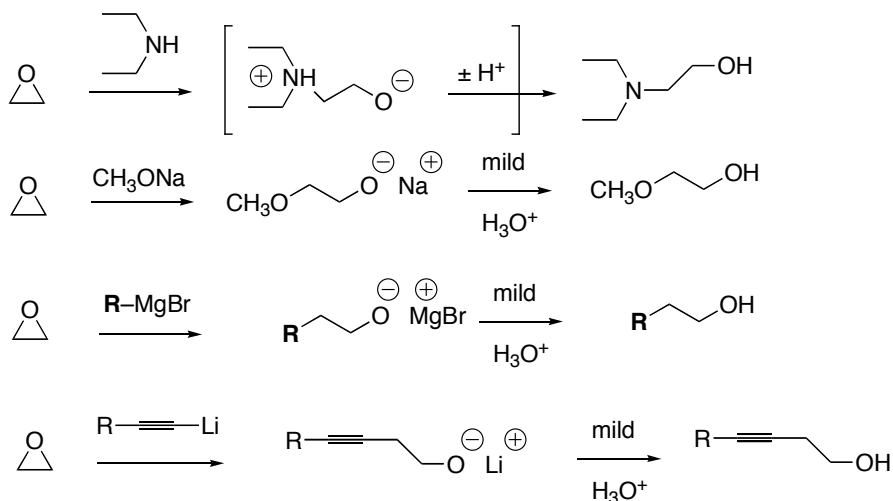


Regiochemical course of acid-catalyzed epoxide opening: attack at the more substituted position (site of greatest + charge density — direct consequence of the "halonium ion-like" nature of a protonated epoxide):



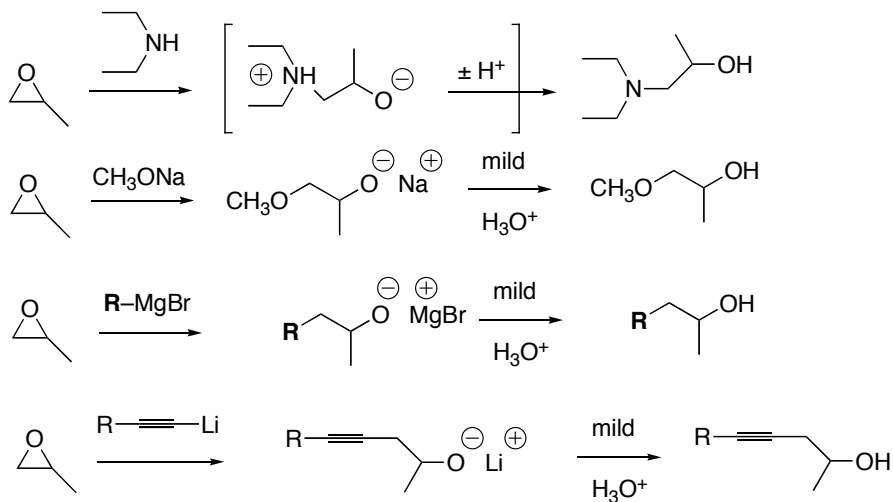
## S<sub>N</sub>2 opening of epoxides by basic nucleophiles

Nucleophiles that successfully open epoxides without the assistance of protonic acid catalysis: basic nucleophiles such as amines, cyanide ion, hydroxide ion, acetylide ions, Grignard reagents, etc., that are conjugate bases of weak acids ( $\text{pK}_a \geq 10$ ):



Regiochemical course of S<sub>N</sub>2 epoxide opening with basic nucleophiles: attack at the less sterically hindered position.

Examples:

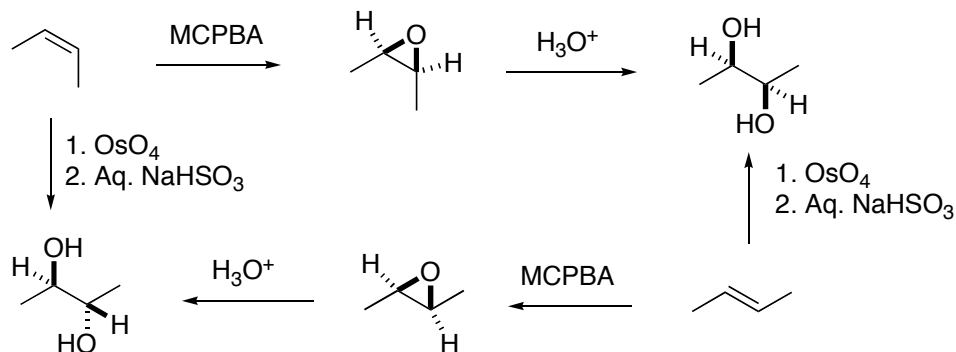


**Topics Discussed on Nov. 24**  
**see chapter 11 of Brown-Foote-Iverson**

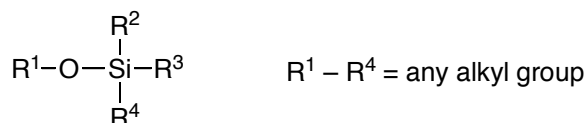
Retention of olefin geometry during epoxidation reactions (mentioned also on Nov 20, Nov 22).



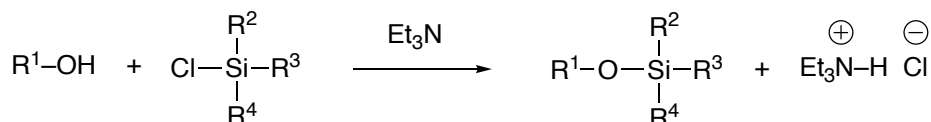
Stereochemical complementarity of the acid-catalyzed opening of epoxides with water (=hydration of epoxides) and of the osmylation reaction (See notes of Oct. 2 – 4). E.g.:



Alkyl silyl ethers: compounds of the following general structure



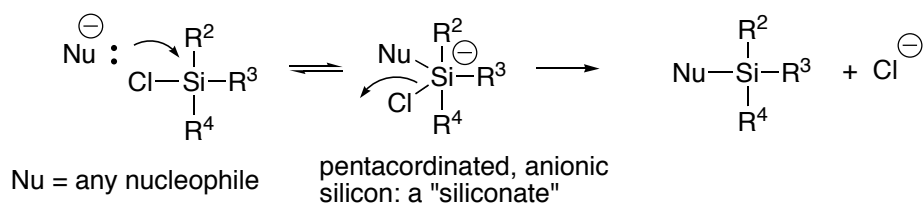
Preparation of silyl ethers by reaction of an alcohol with a trialkylsilyl chloride in the presence of an amine base (e.g., pyridine, triethylamine, etc.)



Apparent mechanism of the above reaction: S<sub>N</sub>2-like displacement of Cl<sup>−</sup> by the nucleophilic alcohol

Noteworthy differences in reactivity between trialkylsilyl halides and tert-alkyl halides: silyl halides undergo facile nucleophilic substitution with basic and nonbasic nucleophiles alike, while tertiary alkyl halides undergo substitution by the S<sub>N</sub>1 mechanism only with nonbasic nucleophiles: basic nucleophiles promote E2 reaction instead.

Probable associative mechanism for nucleophilic substitutions at silicon:

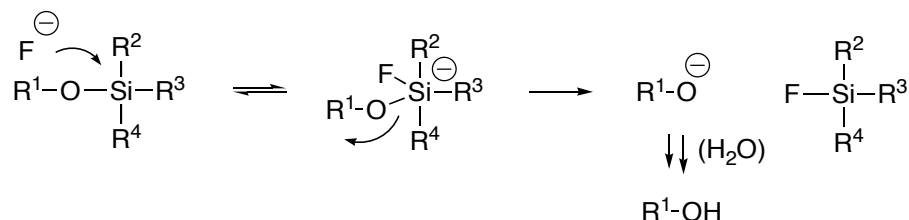


Probable intervention of d-orbitals in the above associative mechanism

Cleavage of silyl ethers under acidic conditions

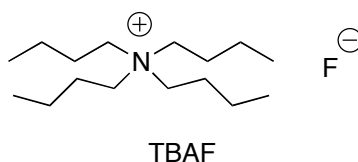
Great strength of the Si–F bond

Cleavage of silyl ethers by reaction with fluoride ion ( $F^-$ )



Poor solubility of most metal fluorides in organic solvents

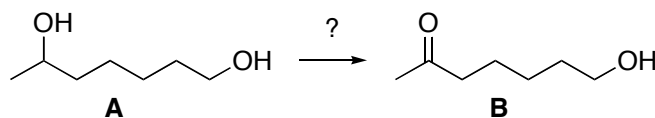
Tetrabutylammonium fluoride ("TBAF") a convenient carrier of  $F^-$  that is soluble in common organic solvents



Protecting groups: units that are temporarily attached to a reactive functionality in order to suppress its interfering reactivity during a chemical operation.

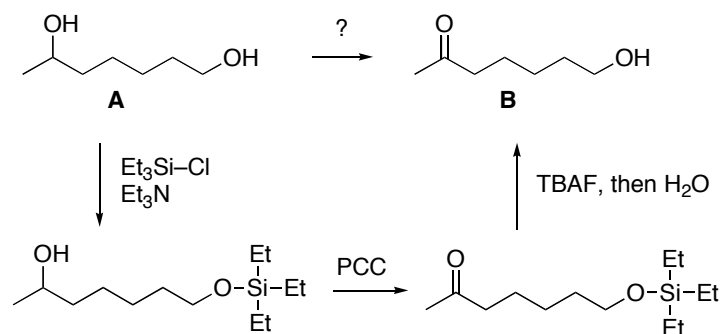
Use of silyl ethers as protecting groups for alcohols

**Example:** suppose that in connection with the synthesis of an important drug intermediate we were faced with the problem of oxidizing compound **A** to substance **B**.



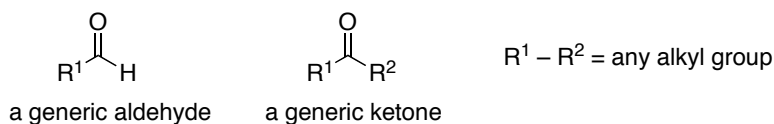
- For oxidation to occur, an OH group must express nucleophilic reactivity toward, e.g., a  $Cr=O$  group.
- Primary alcohols are less hindered, and consequently more nucleophilic, than secondary alcohols
- Therefore, any attempt to oxidize **A** with the Cr reagents known to us may result in selective oxidation of the primary OH, but not the secondary one.

We can take advantage of the greater nucleophilic reactivity of the primary OH group to convert it to a silyl ether, which is largely insensitive to the action of  $Cr(VI)$  reagents. The primary OH is thus "protected" from the action of the oxidant. The silyl group functions as a "protecting group." We can now carry out the oxidation of the secondary alcohol, and finally cleave the silyl ether with TBAF. For instance:



**Topics Discussed on Nov. 29**  
**see chapter 16 of Brown-Foote-Iverson**

Aldehydes and ketones



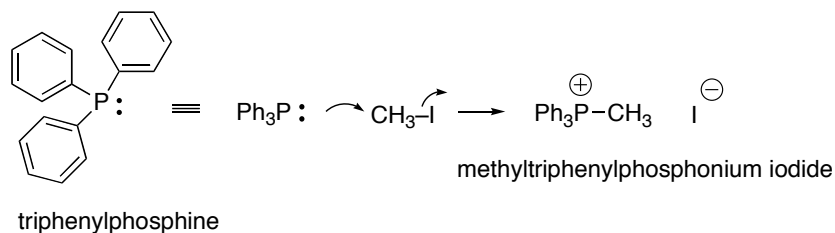
Importance of the carbonyl function in organic and biological chemistry

General pattern of reactivity of aldehydes and ketones: Nucleophilic addition (=addition of nucleophiles) to the C=O group

Principle: basic nucleophiles (carbanions and the like) readily add to intact C=O groups; non basic nucleophiles (H<sub>2</sub>O, alcohols, etc.) generally add only to C=O groups that have been activated through protonation

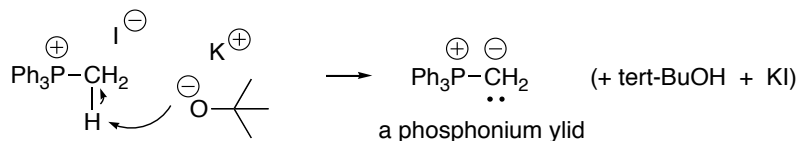
The Wittig reaction: conversion of an aldehyde or a ketone to an olefin through reaction with a phosphorus-stabilized carbon nucleophile:

nucleophilic character of phosphines, e.g., of triphenylphosphine:



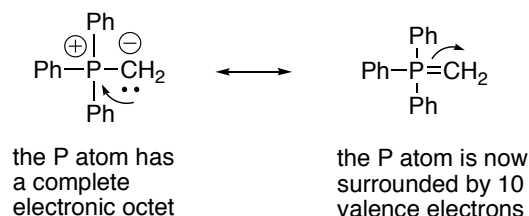
phosphonium salts (Wittig salts)

acidity of the C–H bonds adjacent to the P atom in a phosphonium salt due to the presence of a (+) charge on the P atom and to other factors not covered in CHEM 203  
 deprotonation of phosphonium salts with strong bases, e.g., with tBuOK:



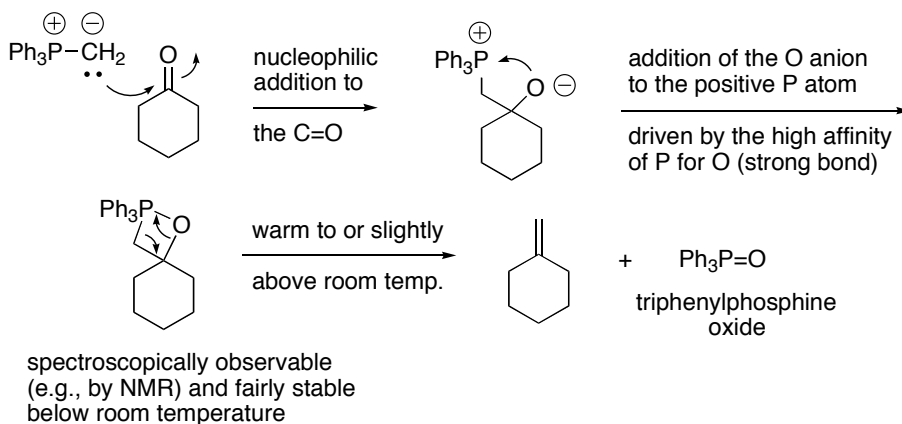
Phosphonium ylids (Wittig reagents): "carbanions" stabilized by a neighboring positively charged P atom. Notice that the ylid is electrostatically neutral, because the formal charges on P and C atoms cancel out

Possible resonance in phosphonium ylids and consequent valence shell expansion at the level of the P atom:

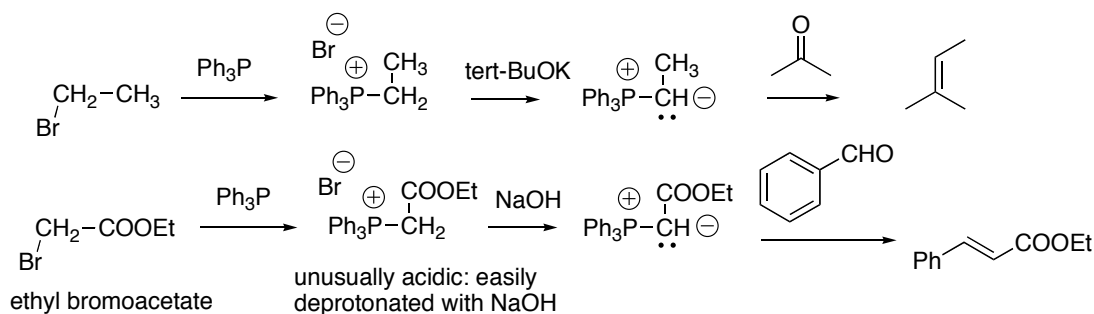


Nucleophilic character of the C atom of a phosphonium ylid: addition to the C=O group of aldehydes and ketones

Olefination of carbonyl groups with Wittig reagents:



Additional examples of Wittig reactions:



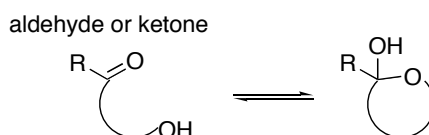
**note:** the second reaction selectively produces the *trans* isomer of the alkene. In fact, appropriate experimental techniques allow the operator to generate either geometric isomer of an alkene through Wittig chemistry. These aspects of the Wittig reaction are beyond the scope of CHEM 203.

Acid-catalyzed addition of water to (=hydration of) carbonyl groups (already discussed in connection with the Jones oxidation; see notes of Nov. 17)

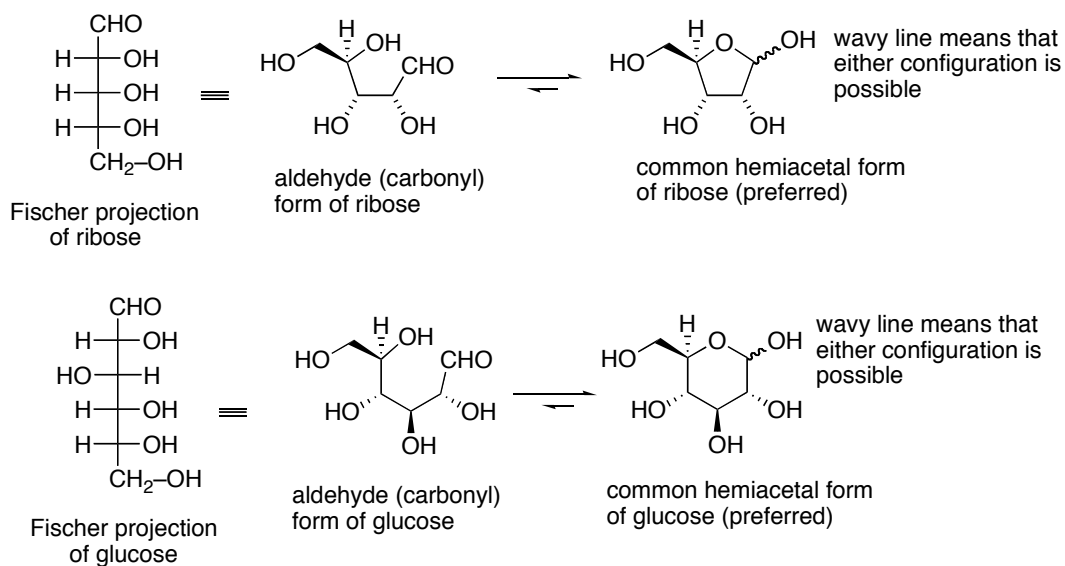
Acid-catalyzed addition of alcohols to aldehydes and ketones: formation of hemiacetals, acetals / ketals, and use of acetals / ketals as carbonyl protecting groups: See pp. 600-609 of the book.

The disruptive behavior of some students forced me to assign this portion of ch. 16 as self-study. Make sure you thoroughly understand all aspects of this chemistry, including mechanisms.

Spontaneous formation of hemiacetal structures in molecules incorporating both an alcohol and an aldehyde / ketone functionality:

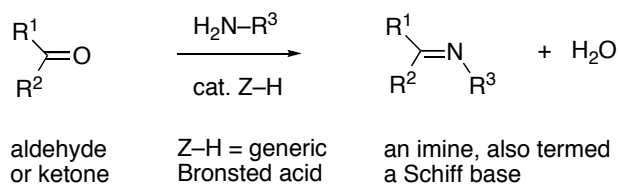


Examples drawn from carbohydrate chemistry: ribose (building block of RNA) and glucose:

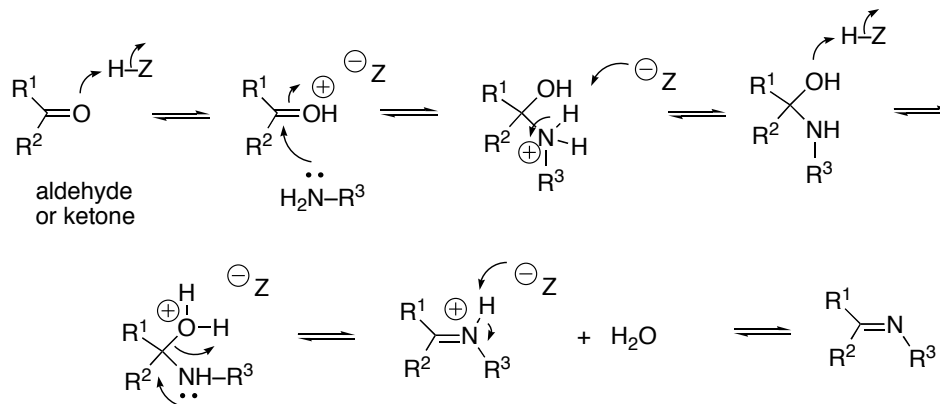


**Topics Discussed on Dec. 1st**  
**see chapter 16 of Brown-Foote-Iverson**

Acid-catalyzed reaction of aldehydes and ketones with primary amines: formation of imines (= Schiff bases):



Probable mechanism of the above reaction:

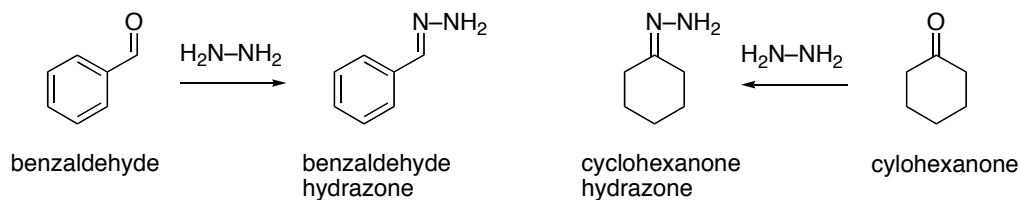


Use of a dehydrating agent, such as  $\text{MgSO}_4$ , to drive the above reaction to completion by removing the water produced together with the imine

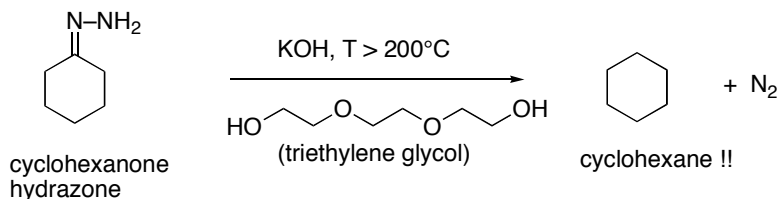
Enormous importance of Schiff bases (= imines) in biological chemistry

Hydrazine: a substance of formula  $\text{H}_2\text{N-NH}_2$

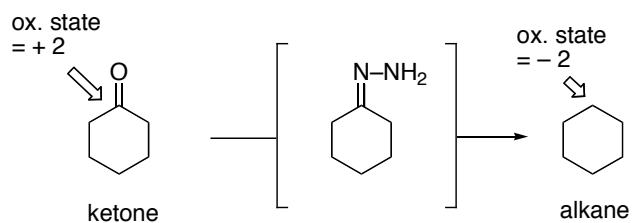
Hydrazone: imine-like compounds obtained through the reaction of aldehydes or ketones with hydrazine according to the above mechanism:



Reactivity of hydrazones (especially ketone hydrazones) toward bases: conversion to alkanes.  
Example:



Noteworthy aspect of the above reaction: deoxygenation of a carbonyl function



The above process as a reduction

Description of the above process as the Wolff-Kishner reduction

Likely mechanism of the Wolff-Kishner reduction:

