CHEM 203

Summary of Topics to be Covered in the Course

INDEX

G. Alcohols p. 123

H. Carbohydrates p. 137

Lecture 1: Structural Theory of Organic Chemistry

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

Enormous impact of organic chemistry in the modern world, including biomedicine (nucleic acids, proteins, enzymes, lipids, carbohydrates, drugs ...), electronics, materials, etc.

of course it's difficult!!

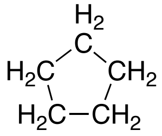
The problem with organic chemistry: early chemist relied on brute (= composition) formulas to identify compounds. This generally worked with simple inorganic substances [salt (NaCl), chalk ($CaSO_4$), etc.], but not with carbon-based ones. Whereas a material that analyzed as NaCl was always "salt," or one that that analyzed as $CaSO_4$ was always "chalk," no matter its origin or how it was produced, many distinct organic (=carbon-based) compounds were found to correspond to a given composition.

Milestones of organic chemistry: structural theory and electronic theory of organic chemistry

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

This principle explained why there is no correlation between the atomic composition (= the formula) of an organic compound and its individuality (contrary to what happens with many "inorganic" compounds). Thus, a given organic formula, e.g., C_5H_{10}, can represent many different compounds, each possessing a specific set of chemical properties, and each differing from the others for the way atoms are interconnected.

Examples:



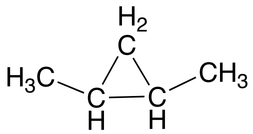
cyclopentane

$CH_2{=}CH{-}CH_2{-}CH_2{-}CH_3$

1-pentene

$CH_2{-}CH{=}CH{-}CH_2{-}CH_3$

2-pentene



1,2-dimethylcyclopropane

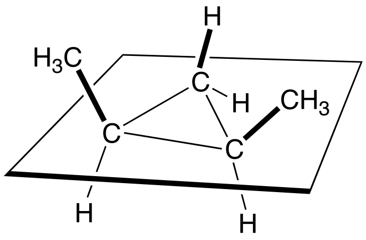
all C_5H_{10}, yet each is chemically different from the others...

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

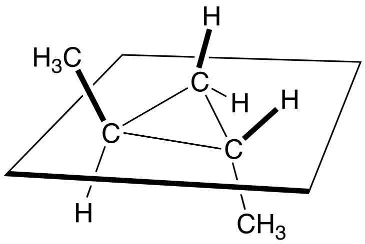
i. the atomic connectivity (= the *constitution*), and,

ii. the spatial orientation of atoms within a molecule (= the *configuration*).

To illustrate, *two* distinct chemical individuals exist for the *constitution* that we describe as 1,2-dimethycyclopropane. These differ for the orientation of the methyl groups relative to the geometric plane containing the ring; i.e., they differ in *configuration*:



CH_3 groups point in the same direction relative to the geometric plane containing the ring



CH_3 groups point in opposite directions relative to the geometric plane containing the ring

Inability of the structural theory of organic chemistry to rationalize the chemical reactivity of carbon compounds

Lecture 2: Electronic Theory of Organic Chemistry

Electronic theory of organic chemistry: an intellectual framework that allows one to rationalize and predict the chemical reactivity of organic compounds on the basis of the electronic properties of their molecules (= how electrons behave within a molecule)

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

Fundamental principles of the electronic theory of organic chemistry:

(i) A "reaction" is a movement of electrons.

(ii) During a reaction, electrons move under the influence of electrostatic fields; i.e., from regions of negative charge to regions of positive charge.

(iii) More accurately, electrons always move from an orbital of high electronic density (the "donor orbital": a fully or partially occupied orbital) to one of low electronic density (the "acceptor orbital": an unoccupied or partially occupied orbital).

(iv) Electron movement from one orbital to another is allowed only for certain relative orientations of donor and acceptor orbitals.

Electrostatic properties of molecules as important factors that influence their reactivity

Evaluating the electrostatic properties of molecules: formal charges, bond polarization, and oxidation states

Principle: atoms can produce bonded states in which significant electrostatic imbalance exists

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

The formal charge on an atom is calculated by:

(i) assuming that all the bonds in which the atom participates are covalent;

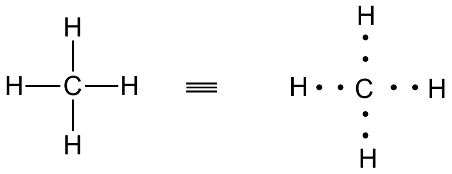
(ii) counting the total number of valence electrons that the atom contributes to the various bonds in which it participates; and

(iii) deciding whether these valence electrons balance out the nuclear charge, or are in deficit, or in surplus.

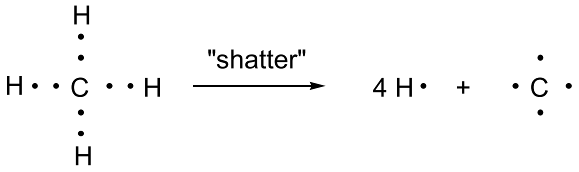
The case of CH_4, NH_4, and BH_4

The formal charge on the C atom in methane, CH_4

Step 1: *draw a complete Lewis structure of the molecule (electron dots, …):*



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 were present around each atom prior to bond formation:



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 out the nuclear charge.

- 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

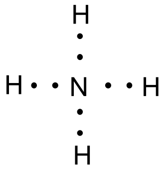
Notice that the formal charge on each H atom is also zero. Indeed, H atoms in *any* covalent molecule have always zero formal charge, as readily determined though the above logic.

* * *

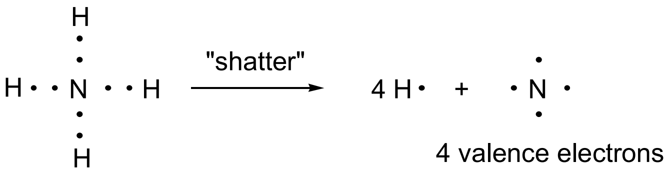
The formal charge on the N atom in NH_4

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

NH_4 =



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



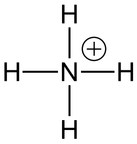
4 valence electrons

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

- N is in group 5: it needs 5 valence electrons to balance out the nuclear charge.
- The N atom in NH_4 has 4 valence electrons: 1 fewer than it should.
- The N atom in NH_4 is electrostatically imbalanced

Conclusion: the formal charge on N in 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 NH_4 is:



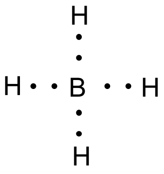
Why "formal" charge? Rigorously speaking, the + 1 charge present in NH_4^+ is delocalized all over the molecule, i.e., each atom (N and 4 H's in this case) bears a share of it. But for simplicity, it is convenient to think of it *as if it were* localized on the N atom. That's why one calls it a *formal* charge: because for chemical reasoning it is best to think of it as *formally* residing on the N atom.

* * *

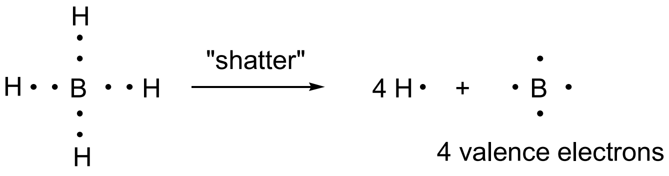
The formal charge on the B atom in BH_4

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

BH_4 =



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

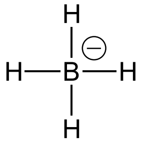


4 valence electrons

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

- B is in group 3: it needs 3 valence electrons to balance out the nuclear charge.
- The B atom in BH_4 has 4 valence electrons: 1 more than it should.
- The B atom in BH_4 is electrostatically imbalanced

Conclusion: the formal charge on B in BH_4 is **– 1**



Electronegativity and bond polarization

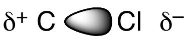
Permanent dipole moments (=electrostatic fields) within molecules displaying bonded atoms of unequal electronegativity

Reminder: the electronegativity of first-row elements starts at 1.0 with Li 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 permanent dipole moments on the chemical reactivity of a molecule; in particular, on the ability of that molecule to accept or donate electrons during chemical reactions.

Example: consider a C–Cl bond. The e.n. of C is ≈ 2.5; that of Cl ≈ 3.2 Therefore, the C–Cl bond will be polarized toward Cl; i.e., the Cl atom is the negative end of the dipole, while the C atom is the positive end thereof:



electron cloud in the bond is distorted toward the Cl atom

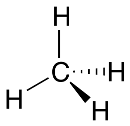
imagine an electron-rich, electrostatically negative agent approaching the above C–Cl bond in the course of a chemical reaction: will it interact preferentially with the C or the Cl atom? Obviously, the incoming agent will be electrostatically attracted to the C atom, but repelled by the Cl atom. We may anticipate that the C atom is likely to behave as an electron acceptor. By the same logic, the Cl atom is likely to behave as an electron donor.

Principle: as a result of bond polarization, an atom in a molecule may acquire more electronic density than necessary to balance out its nuclear charge (see the Cl atom above), i.e., it may acquire a partial negative charge. Likewise, always as a result of bond polarization, an atom in a molecule may be left with insufficient electron density to balance out its nuclear charge (see the C atom above), i.e., it may acquire a partial positive charge.

Oxidation state: a parameter that describes to what extent an atom in a bonded state has acquired/lost electronic density.

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 CH_4, CF_4, and CH_3F

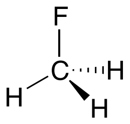


- the formal charge on C is zero
- C is more electronegative than H (2.5 vs. 2.1)
- Formally, C has "stolen" 1 electron from each of the 4 H's
- Formally, C has acquired 4 extra electrons in this bonded state

- Sum of bond polarization and formal charges for C:

  4 x (–1) [bond polarization] + 0 [formal charge on C]

  The oxidation state of C in CH_4 is – 4

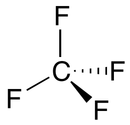


- the formal charge on C is zero
- C is more electronegative than H (2.5 vs. 2.1) and less electronegative than F (2.5 vs. 4)
- Formally, C has "stolen" 1 electron from each of the 3 H's and "lost" 1 electron to the F atom
- Overall, C has formally gained 2 extra electrons in this bonded state

- Sum of bond polarization and formal charges for C:

  3 x (–1) + (+1) [bond polarization] + 0 [formal charge on C]

  The oxidation state of C in CH_3F is – 2



- the formal charge on C is zero
- C is less electronegative than F (2.5 vs. 4)
- Formally, C has "lost" 1 electron to each of the F atoms
- Overall, C has formally lost 4 electrons in this bonded state

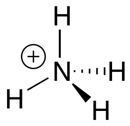
- Sum of bond polarization and formal charges for C:

  4 x (+1) [bond polarization] + 0 [formal charge on C]

  The oxidation state of C in CF_4 is + 4

Note: in the above molecules, the oxidation state of H is +1, and that of F is –1

The oxidation state of atoms possessing a formal charge: the case of NH_4^+:



- the formal charge on N is + 1
- 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 extra electrons in this bonded state

- Sum of bond polarization and formal charges for N:

  4 x (–1) [bond polarization] + (+1) [formal charge on C]

  The oxidation state of N in NH_4^+ is – 3

Principle: determining the oxidation state of an atom in a molecule allows one to make important predictions about chemical reactivity:

Example: the C atom in 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 tend to react as an electron donor; that is, it will give up electrons to electron acceptors. Likewise, one may predict that hypothetical reactions that would add electrons to that C atom will be extremely difficult; probably impossible.
>
> By contrast, the C atom in 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 CF_4 will behave as an electron acceptor; that is, it will tend to react with electron donors. Likewise, one may predict that hypothetical reactions that would subtract electrons from the C atom in question will be extremely difficult or impossible.

Principle: many elements favor a particular oxidation state, and therefore they tend to react so as to acquire that preferred state. For instance, O favors an o.s. of –2, N of –3, halogens of –1, H of +1, etc.

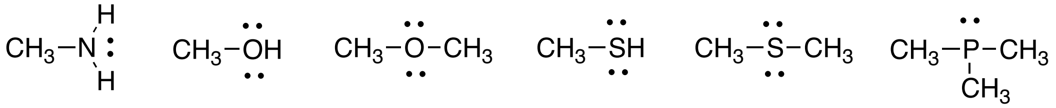
Lecture 3: Lewis Acid-Base Interactions

Principle: organic compounds may contain atoms other than C and H; for instance:

N, O, S, P, Si, halogens (F, Cl, Br, I), and even metals (Li, Mg, etc.) bound to C

Heteroatom: any atom other than C or H; e.g. N, O, S, P, Cl, Br, I, Li, Mg, ….

Issues of electrostatic imbalance (formal charges, oxidation states, bond polarization, molecular polarity, etc.) as significant aspects of the chemistry of organic molecules containing heteroatoms that possess unshared (lone, nonbonding) pairs of electrons, such as N, O, S, P, halogens, etc.:



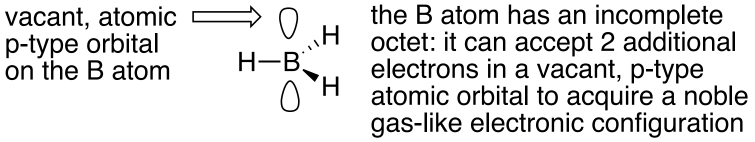
CH_3-NH_2 CH_3-OH CH_3-O-CH_3 CH_3-SH CH_3-S-CH_3 $CH_3-P(CH_3)-CH_3$

Ability of heteroatoms possessing unshared pairs to establish bonds by donating an electron pair to an appropriate species capable of accepting that electron pair

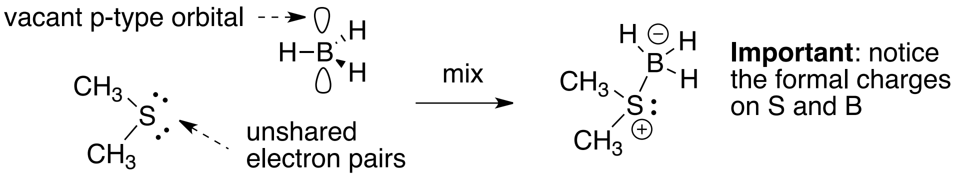
Principle: an atom / molecule can function as an acceptor of electron pairs only if it possesses a vacant orbital that can accommodate an incoming electron pair.

Dative bonds: those formed through the donation of an unshared pair of electrons from a Lewis base into a vacant orbital of a Lewis acid

Example of a molecule that can function as an acceptor of electron pairs: BH_3 (borane)



Predictable (and experimentally verifiable) reaction between, e.g., $CH_3–S–CH_3$ ("dimethyl sulfide") and BH_3:



Lewis base: a species possessing one (or more) unshared electron pair that could possibly be employed to establish a new bond by donation to a suitable acceptor

CH_3-S-CH_3 is a Lewis base because the S atom has 2 unshared pairs of electrons

Lewis acid: a species possessing a vacant orbital that could possibly be employed to establish a new bond by acceptance of an electron pair from a suitable donor

BH_3 is a Lewis acid because the B atom has a vacant orbital

Principle: one may find that a Lewis acid accepts electron pairs only from particular Lewis bases. Likewise, a Lewis base may be inclined to donate electron pairs only to particular Lewis acids

Necessity to distinguish between Lewis acidity / basicity (intrinsic molecular properties determined by the electronic configuration of atoms within molecules) and the actual expression of such potential reactivities in the course of a reaction

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

Lewis basic CH_3-S-CH_3 functions as a nucleophile in the above reaction

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

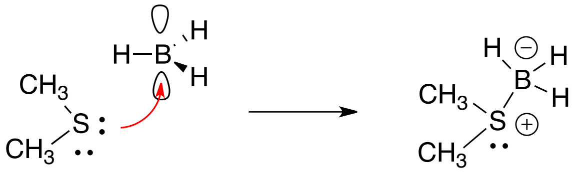
Lewis acidic BH_3 functions as an electrophile in the above reaction

Equivalently, one can distinguish between:

Lewis acidic / Lewis basic character:	a property determined solely 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 the movement of electrons (**not of atoms**) during a chemical reaction; i.e. the *mechanism* of the reaction

example: the red arrow below depicts the mechanism of the reaction of CH_3SCH_3 with BH_3:



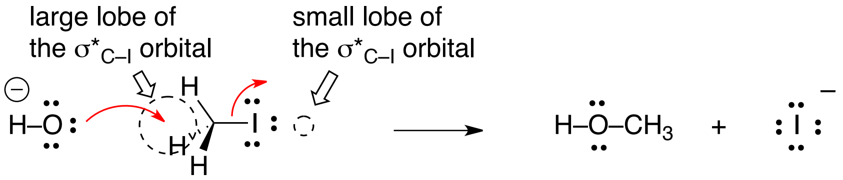
borane-dimethyl sulfide complex: a commercial form of borane

Interactions between a Lewis acid and Lewis base as a fundamental phenomenon that governs many organic chemical reactions

Obvious case of organic reactions involving Lewis acid-base interactions: the above reaction of borane, BH_3, with dimethyl sulfide, CH_3–S–CH_3

Less obvious case of organic reactions involving Lewis acid-base interactions: the S_N2 reaction

Example:



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

Reminder: bonding and antibonding orbitals always arise in pairs upon linear combination of atomic orbitals (LCAO) leading to molecular orbitals

Bond order (BO): BO = (# electrons in bonding orbitals – # electrons in antibonding orbitals) / 2
Weakening / breaking of a generic bond A–B upon introduction of electronic density into the corresponding antibonding orbital

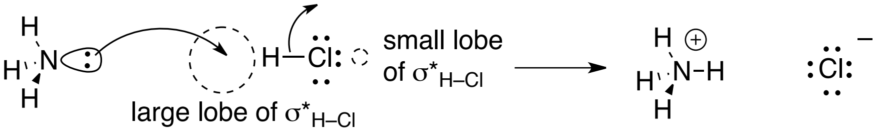
Example: In the above S_N2 reaction, the nucleophile (HO^-) introduces a pair of electrons into the vacant $s^*_{C\text{-}I}$ orbital. As a result, the BO of the C–I bond becomes:

BO = (2 e^- in bonding orbital – 2 e^- in antiboding orbital) / 2 = 0

The bond between C and I vanishes and the I^- becomes free to "float away."

Lecture 4: Bronsted Acid-Base Equilibria, Alkenes

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



Bronsted acids, Bronsted bases: proton donors (HCl above) / acceptors (NH_3), respectively

Bronsted acid-base equilibria as fundamental aspects of a great many organic chemical transformations

Electronic analogy between proton transfer reactions and S_N2 reactions

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. Therefore, pKa's and ΔpKa's are crucially important to understand proton exchange equilibria

Reminder: the pKa of a generic Bronsted acid H–A is defined as:

$$\mathrm{pKa} = -\log \mathrm{Ka}, \text{ where:}$$

$$\mathrm{Ka} = \frac{[A^-][H^+]}{[AH]} \qquad \text{for the equilibrium:} \quad H{-}A \rightleftharpoons H^+ + A^-$$

consequently: acid strength and pKa's are inversely proportional, that is:
strong acids have small pKa's
weak acids have large pKa's

moreover: the dissociation of a **strong** Bronsted acid releases a **weak** Bronsted base
the dissociation of a **weak** Bronsted acid releases a **strong** Bronsted base

The following expression holds true for the acid-base equilibrium between generic Bronsted acid AH and Bronsted base B^-:

$$A{-}H + B^{\ominus} \rightleftharpoons A^{\ominus} + B{-}H \qquad K_{eq} = \frac{[A^-][BH]}{[AH][B^-]}$$

If one expresses Keq as a function of the Ka's of HA and HB, one finds that:

$$Ka_{AH} = \frac{[A^-][H^+]}{[AH]} \quad \text{so: } \frac{[A^-]}{[AH]} = \frac{Ka_{AH}}{[H^+]} \quad \textbf{and} \quad Ka_{BH} = \frac{[B^-][H^+]}{[BH]} \quad \text{so: } \frac{[BH]}{[B^-]} = \frac{[H^+]}{Ka_{BH}}$$

$$K_{eq} = \frac{[A^-]\,[BH]}{[AH]\,[B^-]} = \frac{[A^-]}{[AH]}\;\frac{[BH]}{[B^-]} = \frac{Ka_{AH}}{[H^+]}\;\frac{[H^+]}{Ka_{BH}} = \frac{Ka_{AH}}{Ka_{BH}}$$

Therefore:

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

$$-\log K_{eq} = -\log Ka_{AH} - (-\log Ka_{BH})$$

$$pK_{eq} = pKa_{AH} - pKa_{BH}$$

and

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

Reminder: pKa's can be measured experimentally, but they cannot be deduced purely from molecular properties

Reminder: stronger Bronsted acids / stronger bases contain more energy than weaker acids / weaker bases; therefore:

> (i) a Bronsted acid-base equilibrium that consumes stronger acids/bases to produce weaker acids/bases releases energy (= it is exergonic; $\Delta G < 0$) and thermodynamically favorable;
>
> (ii) a Bronsted acid-base equilibrium that consumes weaker acids/bases to produce stronger acids/bases absorbs energy (= it is endergonic; $\Delta G > 0$) and thermodynamically unfavorable

Using pKa's to estimate equilibrium constants and ΔG's for Bronsted acid-base interactions:

1. Consider the reaction between a Bronsted acid A–H, of pKa = 5, with a base B^-, leading to A^- and a new Bronsted acid B–H, of pKa = 11. We want to know whether the reaction is thermodynamically favorable or unfavorable, to estimate the ΔG° for the process and the equilibrium concentrations of the various species in solution.

$$A{-}H \;+\; B^{\ominus} \rightleftharpoons A^{\ominus} + \; B{-}H$$

pKa = 5			pKa = 11
stronger acid	stronger base	weaker base	weaker acid

The pKa's immediately tell us that the process is consuming stronger acids/bases to create weaker acids/bases; therefore it should be favorable. The equilibrium constant is:

$$\log K_{eq} = pKa_{BH} - pKa_{BH} = 11 - 5 = 6;\ \text{so}\ K_{eq} = 10^6$$

We know that for a system at chemical equilibrium ΔG° is given by the Gibbs equation:

$$\Delta G^\circ = -\,nRT \ln K_{eq}$$

In the present case, for T = 298 °K (25 °C) and n = 1 mole,

$$\Delta G^\circ\ (\text{kcal/mol}) \approx -\,1.98 \times 10^{-3} \times 298 \times 2.303 \log 10^{6} \approx -\,8.1\ \text{kcal/mol} < 0 \rightarrow \textit{\textbf{favorable}}$$

A crude, but useful, estimate of the equilibrium concentrations of all species may be generated as follows: imagine starting with a solution that initially contains a 1M concentration of A–H and B^-. The K_{eq} is large; so the equilibrium will be shifted very much to the right; i.e., virtually all of the reactants will be converted into the products. But then, the equilibrium concentrations of A^- and B–H will be very nearly = 1M.

Moreover, formation of each molecule of A^- requires the disappearance of one molecule of A–H, and the formation of each molecule of B–H requires the disappearance of one molecule of B^-.

So, an equal number of molecules of A–H and B^- have vanished from the system.

If the initial concentrations of A–H and B^- were identical and equal to 1M, their equilibrium concentration (unknown) will also be identical; therefore:

$$\begin{array}{ccccccc} \text{A–H} & + & \text{B}^{\ominus} & \rightleftharpoons & \text{A}^{\ominus} & + & \text{B–H} \\ \multicolumn{3}{c}{\text{numerically equal}} & & \approx 1\ \text{M} & & \approx 1\ \text{M} \end{array} \qquad K_{eq} = \frac{[\text{A}^{\ominus}]\ [\text{B–H}]}{[\text{A–H}]\ [\text{B}^{\ominus}]} = 10^{6}$$

$$\frac{1 \cdot 1}{[\text{A–H}]^2} \approx 10^{6} \qquad [\text{A–H}] \approx \sqrt{\frac{1}{10^{6}}} = 10^{-3}\ \text{M} = [\text{B}^{\ominus}]$$

approximately 0.1% of the original A–H and B^- are present at equilibrium

2. Consider the reaction between a Bronsted acid A–H, of pKa = 18, with a base B^-, leading to A^- and B–H, of pKa = 10. We want to know whether the reaction is thermodynamically favorable or unfavorable, to estimate the ΔG° for the process and the equilibrium concentrations of the various species in solution.

$$\begin{array}{ccccccc} \text{A–H} & + & \text{B}^{\ominus} & \rightleftharpoons & \text{A}^{\ominus} & + & \text{B–H} \\ \text{pKa} = 18 & & & & & & \text{pKa} = 10 \\ \text{weaker acid} & & \text{weaker base} & & \text{stronger base} & & \text{stronger acid} \end{array}$$

The pKa's immediately tell us that the process is consuming weaker acids/bases to create stronger acids/bases; therefore it should be unfavorable. In fact:

$\log K_{eq} = pKa_{BH} - pKa_{BH} = 10 - 18 = -8$; so $K_{eq} = 10^{-8}$ and for n = 1 mol and T = 298 °K

$$\Delta G^\circ = -\,1.98 \times 10^{-3} \times 298 \times 2.303 \log 10^{-8} \approx +\,10.9\ \text{kcal/mol} > 0 \rightarrow \textbf{unfavorable}$$

Crude estimate of the equilibrium concentrations of all species: imagine a solution that initially contains a 1M concentration of A–H and B^-. The K_{eq} is small; so the equilibrium will be shifted very much to the left; i.e., virtually all of the reactants remain unaltered. But then, the equilibrium concentrations of A–H and B^- will be very nearly = 1M.

Moreover, for each molecule of A^- that forms, a molecule of B–H must also be created.

So, an equal number of molecules of A^- and B–H must form; i.e. $[A^-] = [B\text{–}H]$

Therefore:

$$\begin{array}{ccccccc} \text{A–H} & + & B^{\ominus} & \rightleftharpoons & A^{\ominus} & + & \text{B–H} \\ \approx 1\text{ M} & & \approx 1\text{ M} & & \multicolumn{3}{c}{\text{numerically equal}} \end{array} \qquad K_{eq} = \frac{[A^{\ominus}]\ [\text{B–H}]}{[\text{A–H}]\ [B^{\ominus}]} = 10^{-8}$$

$$\frac{[\text{B–H}]^2}{1 \cdot 1} \approx 10^{-8} \qquad [\text{B–H}] \approx \sqrt{10^{-8}} = 10^{-4}\ \text{M} = [A^{\ominus}]$$

approximately 0.01% of the original A–H and B^- react to form A^- and B–H

real example 1: we wish to predict whether the reaction of ammonia, NH_3, with hydrogen chloride, HCl is favorable or unfavorable, and how favorable / unfavorable it is, knowing that:

pKa of $NH_4^+ \approx +9$ (NH_4^+ is the weaker Bronsted acid, NH_3 is the stronger Bronsted base)

pKa of HCl ≈ -7 (HCl is the stronger Bronsted acid, Cl^- is the weaker Bronsted base)

One can tell immediately that the reaction in question will be favorable, because it consumes a stronger acid (HCl) and a stronger base (NH_3) to produce a weaker acid (NH_4^+) and a weaker base (Cl^-). Regardless, the equilibrium constant for the above reaction is:

$$\text{Keq} = \frac{[NH_4^+]\ [Cl^-]}{[NH_3]\ [HCl]} = \frac{[NH_4^+]}{[NH_3]} \cdot \frac{[Cl^-]}{[HCl]}$$

If one expresses the above Keq as a function of the Ka's of NH_4^+ and of HCl:

$$NH_4^+ \rightleftharpoons H^+ + NH_3 \therefore \text{Ka}_{NH_4^+} = \frac{[H^+]\ [NH_3]}{[NH_4^+]} = 10^{-9} \text{ (because pKa = 9), so}$$

$$\frac{[NH_4^+]}{[NH_3]} = \frac{[H^+]}{10^{-9}}$$

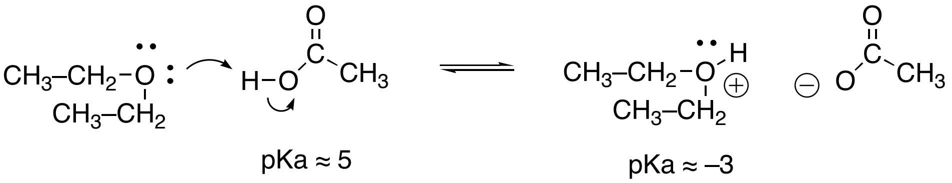
$$HCl \rightleftharpoons H^+ + Cl^- \therefore \text{Ka}_{HCl} = \frac{[H^+]\ [Cl^-]}{[HCl]} = 10^{7} \text{ (because pKa = –7), so}$$

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

$$\mathrm{Keq} = \frac{[\mathrm{H^+}]}{10^{-9}} \cdot \frac{10^{7}}{[\mathrm{H^+}]} = 10^{16}$$

Such a large, positive K_{eq} indicates that the reaction is highly favorable and that the equilibrium will be strongly shifted to the *right*.

real example 2: the protonation of diethyl ether with acetic acid:



One can tell immediately that the reaction in question will be unfavorable, because it consumes a weaker acid (acetic acid) and a weaker base (ether) to produce a stronger acid (protonated ether) and a stronger base (acetate ion).

Regardless, the equilibrium constant for the above reaction may be estimated as:

$$\Delta \mathrm{pKa} \approx \mathrm{pKeq} = 5 - (-3) = +\ 8 \qquad \mathrm{Keq} \approx 10^{-8} = \frac{[\,(CH_3\text{-}CH_2)_2\overset{\oplus}{OH}\,]\ [\,\overset{\ominus}{}OOC\text{-}CH_3]}{[\,(CH_3\text{-}CH_2)_2O\,]\ [HOOC\text{-}CH_3]}$$

The reaction is clearly unfavorable, because Keq < 1

One may even estimate the equilibrium concentration of the protonated form of ether by reasoning that:

- each molecule of $(CH_3\text{-}CH_2)_2OH^+$ that forms during this reaction must be accompanied by a molecule of $^-OOC\text{-}CH_3$; i.e., the equilibrium concentrations of $(CH_3\text{-}CH_2)_2OH^+$ and $^-OOC\text{-}CH_3$ must be numerically identical.
- because Keq is so small, only an insignificant portion of the reactants will have advanced to products at equilibrium. Therefore, the equilibrium concentrations of $(CH_3\text{-}CH_2)_2O$ and $HOOC\text{-}CH_3$ are nearly identical to the initial concentrations.
- Suppose then that the above equilibrium takes place in a solution that is initially 1M in both ether and acetic acid. We conclude that:

$$\mathrm{Keq} = \frac{\overset{\text{numerically equal}}{[\,(CH_3\text{-}CH_2)_2\overset{\oplus}{OH}\,]\ [\,\overset{\ominus}{}OOC\text{-}CH_3]}}{\underset{\text{both nearly 1 M at equilibrium}}{[\,(CH_3\text{-}CH_2)_2O\,]\ [HOOC\text{-}CH_3]}} = [\,(CH_3\text{-}CH_2)_2\overset{\oplus}{OH}\,]^{2} \approx 10^{-8}$$

$$\text{so:} \qquad [\,(CH_3\text{-}CH_2)_2\overset{\oplus}{OH}\,] \approx \sqrt{\mathrm{Keq}} = \sqrt{10^{-8}} = 10^{-4}$$

about one part in 10,000 of diethyl ether will exist in protonated form at equilibrium

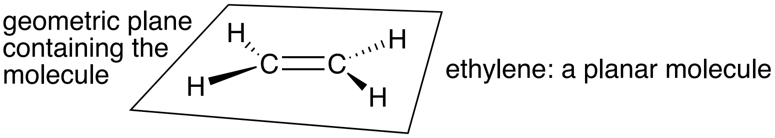
note: the above is not a precise treatment of the equilibrium (we are ignoring solvent effects and other important factors), but it provides a useful semiquantitative estimate of the position of the equilibrium.

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

Alkenes (=olefins) as ideal starting points to investigate the details of the electronic theory of organic chemistry, including the interaction of organic compounds with Bronsted acids

Alkenes: compounds in which two adjacent C atoms share a double bond

The simplest alkene: ethylene, $H_2C{=}CH_2$ (IUPAC name: ethene):

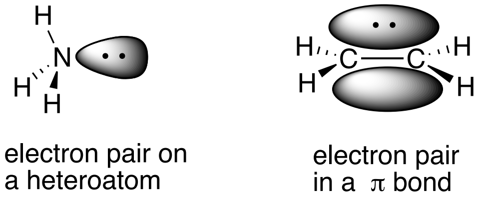


Bonding in olefins: σ framework, π bond, trigonal planar geometry and sp^2 hybridization of C atoms sharing the double bond, …

Restricted rotation about the C–C π bond: energy barrier (= energy of the π bond) in ethylene ≈ 63 kcal / mol = 264 kJ / mol

compare the rotational energy barrier in ethane ≈ 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 °C)

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

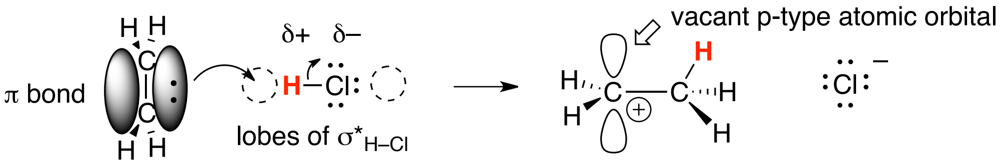


Predictable Lewis basic character of olefins (e.g, ethylene)

alkenes are thus anticipated to react with Lewis acids (Lewis acid-base reactions) and possibly with Bronsted acids (proton donors: Bronsted acid-base reactions)

Hypothetical interaction of an alkene – e.g. ethylene – with a Bronsted acid such as HCl

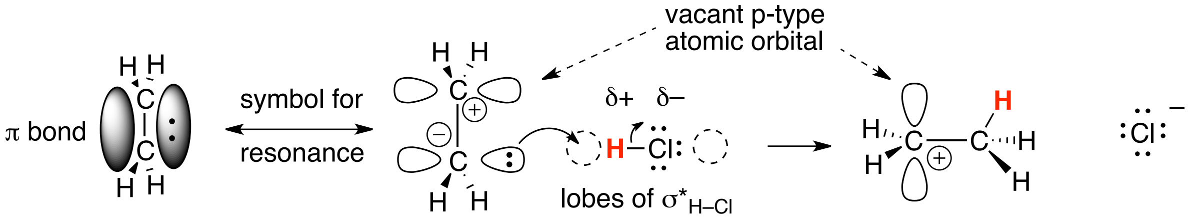
Anticipated course of events: protonation of (=transfer of a proton to) to the olefin:



electrons from the π bond are attracted to the positive end of the H–Cl dipole

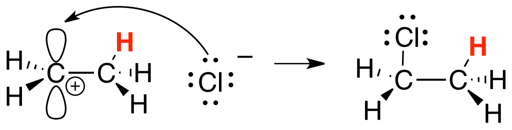
notice how we need *two* arrows to describe this electron movement

Alternative (if less accurate) way to imagine the above reaction:



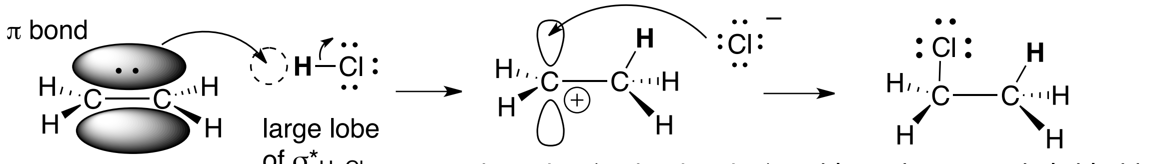
Highly Lewis acidic character of the positively charged carbon fragment created in the above reaction

Rapid combination of the above Lewis acidic, (+)-charged carbon fragments with Cl^- (nucleophilic Lewis base) leading to a new C–Cl bond and a new chemical individual:



Lecture 5: Electrophilic Addition of H–X to Alkenes

Carbocations, carbonium (carbenium) ions: the (+)-charged, highly Lewis acidic carbon fragments obtained upon protonation of alkenes



a carbocation (carbonium ion) (ethyl cation in this case)

chloroethane or ethyl chloride: an alkyl halide

Alkyl groups: fragments obtained upon removal of a hydrogen atom from an alkane; e.g:

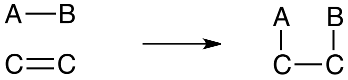
CH_4 (meth**ane**) → CH_3 (meth**yl**) CH_3–CH_3 (eth**ane**) → CH_3–CH_2 (eth**yl**)

prop**ane** → prop**yl** but**ane** → but**yl** alk**ane** → alk**yl**

Alkyl halides: compounds in which a halogen (F, Cl, Br, I) is attached to an alkyl group

The above transformation as an **addition reaction**: a process that involves the union of two molecules to produce a new chemical individual

Addition reactions: typical reactions of alkenes and of π systems in general. These processes may be represented with the following general equation (which says nothing about mechanism):



$$\begin{matrix} A{-}B \\ C{=}C \end{matrix} \longrightarrow \begin{matrix} A & B \\ | & | \\ C & \!\!{-}\!\! & C \end{matrix}$$

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

Reagent: the species that acts upon the organic compound undergoing the reaction (A–B in the above reaction)

Product: A–C–C–B in the above reaction

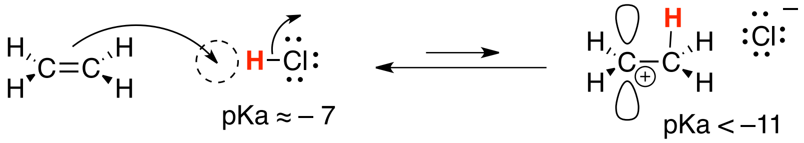
Description of the addition of HCl to ethylene as an *electrophilic addition*, because it is initiated by the interaction of the substrate with an electrophile (the "proton" carried by HCl)

Principle organic reactions, such as the electrophilic addition of HCl to alkenes, are normally carried out in solution phase, using appropriate non-reactive (inert) solvents

The first step of the mechanism of electrophilic addition of HCl (pKa ≈ –7) to ethylene as a Bronsted acid-base reaction

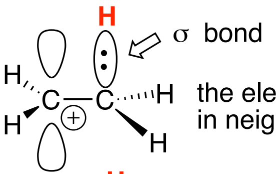
Simple carbonium ions as exceedingly strong Bronsted acids (pKa apparently < – 11), i.e., olefins as poor Bronsted bases

The protonation of simple olefins as an endergonic ($\Delta G >> 0$), thermodynamically highly unfavorable, and consequently easily reversible, reaction:

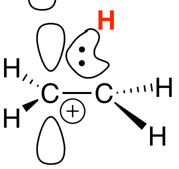


$K_{eq} < 10^{-4} \rightarrow \Delta G° = -n\,RT \ln K_{eq} > 0$!!!

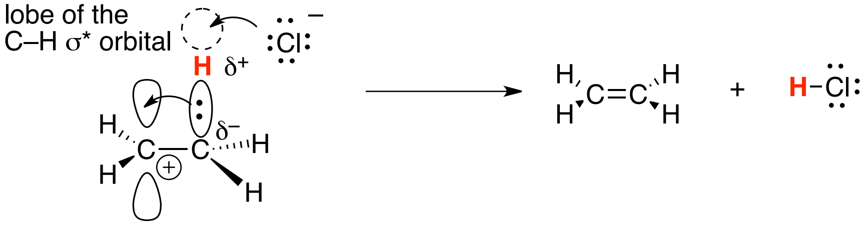
Mechanism of the reversal of the above protonation reaction:



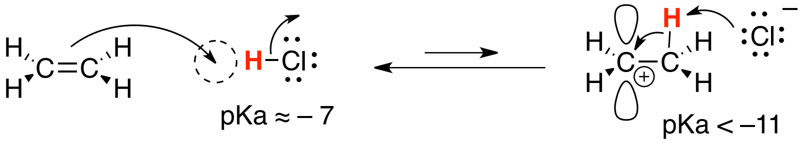
the electrostatic field of the carbocation strongly attacts electrons in neighboring C–H sigma bonds into the vacant p-type orbital ...



... polarizing, distorting, and weakening the C–H bonds to such a degree that even a weak base like Cl⁻ can now accept a proton from the cation and restore a π bond between the two carbon atoms:...



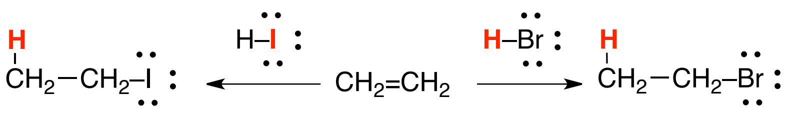
overall:



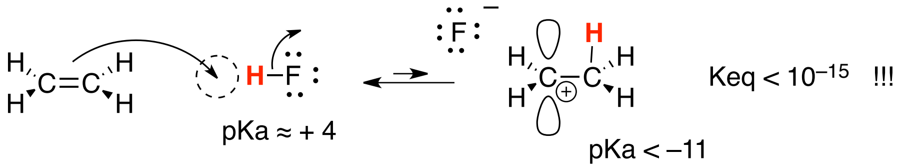
Principle: most olefins will undergo protonation (albeit to a modest extent) only upon reaction with acids with a pKa << 0

Thermodynamically highly favorable reaction of a carbocation with chloride ion (more generally, with a halide ion)

Faster reaction of ethylene with HBr (pKa ≈ –8) or HI (pKa ≈ –9) than with HCl (pKa ≈ 7), through the same mechanism seen for HCl, given their greater acidity and consequent formation of a greater instant concentration of carbocations



Failure of HF (pKa ≈ +4: too weak a Bronsted acid to protonate olefins) to undergo addition to most olefins due to exceedingly unfavorable protonation:



the protonation step is extremely unfavorable (Keq < 10^{-15}; ΔG >>0). The extent of formation of carbocations will be so insignificant that the rate of the reaction becomes enormously slow; i.e. it does not take place on the human time scale.

Principle: one may predict, purely on electronic grounds, that *any* alkene will undergo electrophilic addition of halogen acids, and this through the same mechanism seen above for ethylene.

More complex alkenes:

Nomenclature of alkenes: the names of alkenes are derived from those of the corresponding alkanes (studied in introductory chemistry) by replacing the ending –ane with the ending –ene:

$CH_3–CH_3$	eth**ane**		$CH_2=CH_2$	eth**ene** (=ethylene)	
$CH_3–CH_2–CH_3$	prop**ane**		$CH_2=CH–CH_3$	prop**ene**	
$CH_3–CH_2–CH_2–CH_3$	but**ane**	---->	but**ene**;		etc.

Positional isomerism in alkenes: the case of "butene"

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

$CH_2=CH–CH_3–CH_3$ and $CH_3–CH=CH–CH_3$

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: $\overset{1}{C}–\overset{2}{C}–\overset{3}{C}–\overset{4}{C}$

then we may describe $\overset{1}{CH_2}=\overset{2}{CH}–\overset{3}{CH_2}–\overset{4}{CH_3}$ as "1-butene," underscoring the fact that the double bond "starts" on the first C atom of the molecule

Likewise, we may call $\overset{1}{CH_3}–\overset{2}{CH}=\overset{3}{CH}–\overset{4}{CH_3}$ "2-butene," to convey the fact that the double bonds "starts" on the second atom of the molecule

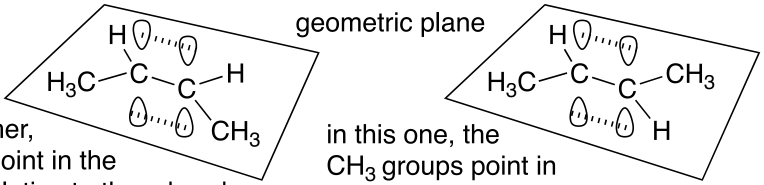
Reminder: indices are chosen so that an unequivocal name for a molecular object results from the smallest possible numerical value of such indices.

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:

$$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\overset{3}{C}H_2{-}\overset{4}{C}H_3 \quad \text{or} \quad \overset{4}{C}H_2{=}\overset{3}{C}H{-}\overset{2}{C}H_2{-}\overset{1}{C}H_3$$

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.

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



in this stereoisomer, the CH_3 groups point in the same direction relative to the π bond

in this one, the CH_3 groups point in opposite directions relative to the π bond

the two stereoisomers cannot interconvert because of restricted rotation about the π bond

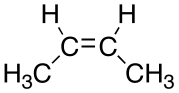
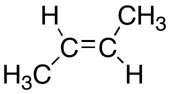
Geometric isomers: stereoisomers that arise as a consequence of restricted rotation about an olefinic π bond.

Reminder: various types of stereoisomers are known, e.g.

enantiomers	geometric --> cis / trans isomers of olefins
diastereomers	others yet

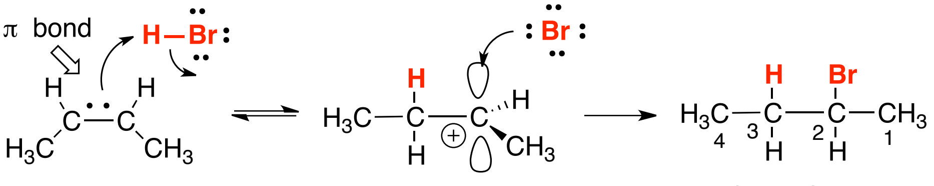
Cis and trans isomers of alkenes

cis isomer: alkyl groups point in the same direction relative to the π bond
trans isomer: alkyl groups point in opposite directions relative to the π bond


is therefore cis-2-butene;

is therefore trans-2-butene

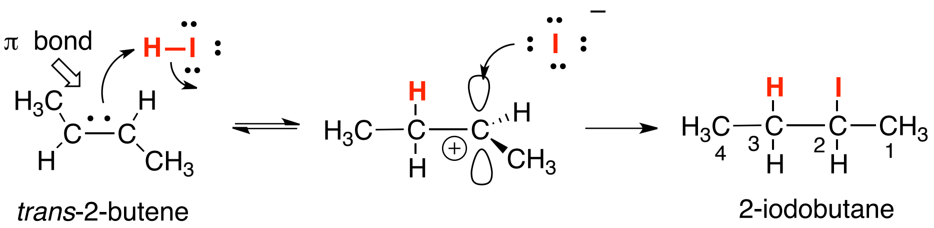
Principle: in generating a name for an alkene, one needs to specify both the position of the double bond in the molecule and the geometric isomer of the alkene in question.

Electrophilic addition of H–X (X = Cl, Br, I, *but not F*) to, e.g., *cis*- or *trans*-2-butene: the reaction occurs by the same mechanism developed above for ethylene:



cis-2-butene

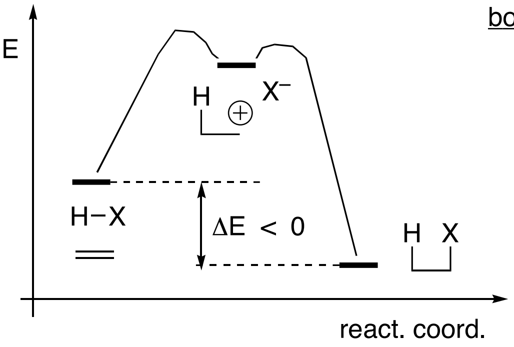
2-bromobutane



Principle: *any* reaction of alkenes is likely to commence with an interaction of the π electrons with a Lewis acid

Lecture 6: Regioselective Addition of H–X to Alkenes

Reaction profile and thermochemistry of the addition of H–X to alkenes:



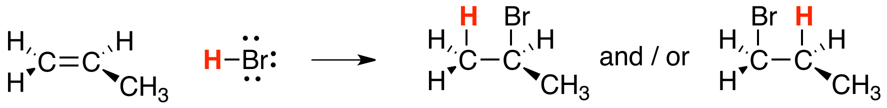
bond dissociation enthalpies (kcal/mol)				**ΔH (kcal/mol)**
C=C π ≈	60	C–H ≈	95	
H–Cl	103	C–Cl	85	**– 17**
H–Br	88	C–Br	78	**– 25**
H–I	71	C–I	57	**– 21**
H–F	136	C–F	108	**– 7**

The rate of the above reaction as a function of the instant concentration of carbocation:

$$\text{rate} = \frac{d[\,P\,]}{d\,[\,t\,]} \propto [\text{ carbocation }]$$

The problem of H–X addition to an unsymmetrical alkene: formation of isomeric products

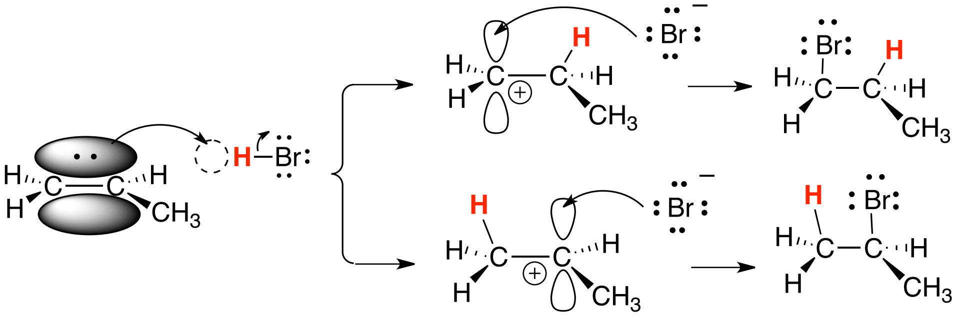
example: the electrophilic addition of H–Br to propene could afford 2 distinct products:



the two products are *constitutional isomers*; i.e., they are two distinct chemical individuals. This means that their chemical, physical and *thermodynamic* properties are different.

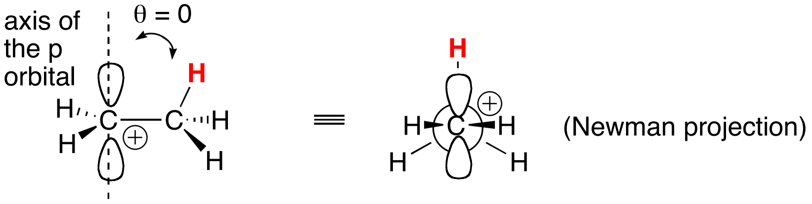
Could these differences promote the preferential formation of one product?

Principle: the alkyl bromide forms through the reaction of the halide ion with a carbocation, so if a preference is to be found, then one of the two possible carbocations must form preferentially



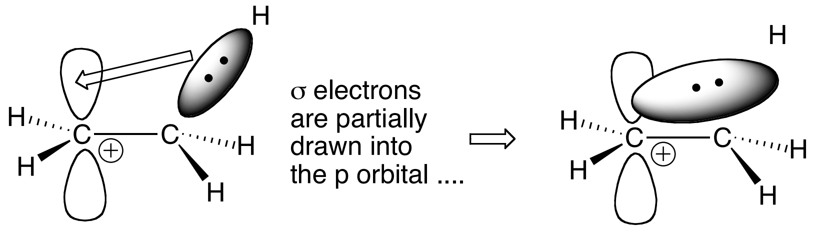
Conformational and electronic properties of carbocations; e.g., of the ethyl cation

Most favorable conformation of a carbocation, e.g. of the ethyl cation: one of the C–H σ bonds on the CH_3 group (cf. red H below) eclipses one of the lobes of the p-type orbital associated with the adjacent positive carbon:



The Bronsted acidity of a carbocation as a consequence of the great extent of polarization of adjacent σ bonds and consequent weakening thereof

Hyperconjugation: electron delocalization from an adjacent σ bond (e.g., a C–H bond) into a vacant p-type orbital:



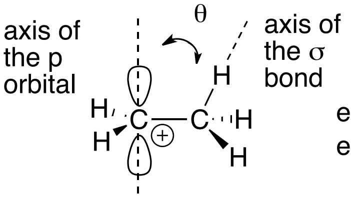
σ electrons are partially drawn into the p orbital ....

the σ cloud is "distorted": some σ electron density is delocalized away from H and toward the positive C

the positive C ends up with a charge smaller than +1, while the H atoms acquires a fractional + charge

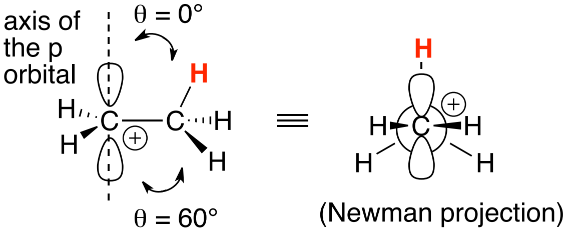
Stabilization of carbocations by hyperconjugation due to (i) dispersion of charge; (ii) increase in the volume of space occupied by the σ electrons

Principle: the extent of hyperconjugative electron delocalization depends on the $\cos^2$ of the dihedral angle between the axis of the σ bond donating electrons and that of the p-type atomic orbital associated with the positive carbon atom:



extent of hyperconjugative electron delocalization $\sigma \rightarrow p = f(\cos^2\theta)$

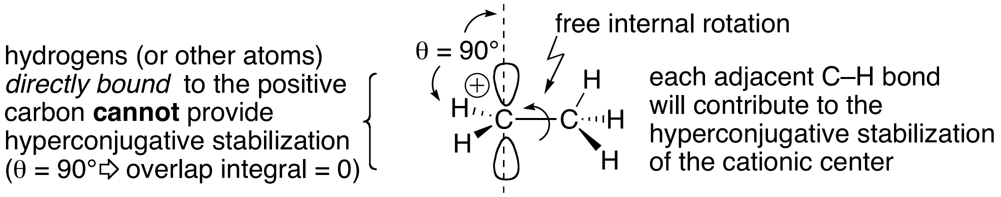
consequently, the C–H bond that eclipses the p-type orbital (the "vertical" C–H bond) provides maximum hyperconjugation, while each of the remaining two C–H bonds provides about ¼ of the hyperconjugative stabilization of the "vertical" C–H bond



The red C–H bond provides maximum hyperconjugation (θ = 0°, $\cos^2\theta = 1$)

The black C–H bonds provide diminished hyperconjugation (θ = 60°, $\cos^2\theta = 0.25$)

The ethyl cation as a carbocation stabilized by 3 hyperconjugative interactions with C–H bonds:

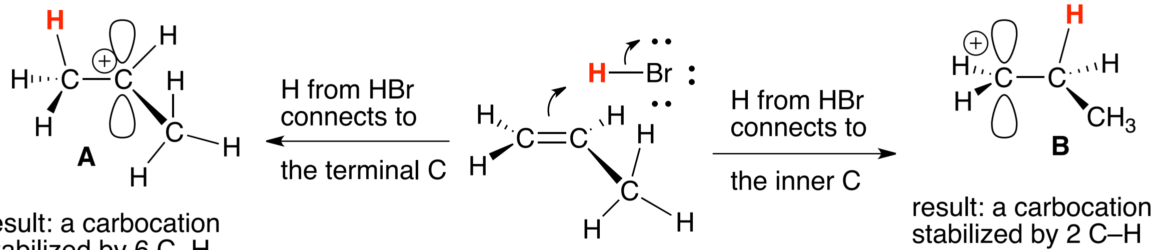


hydrogens (or other atoms) *directly bound* to the positive carbon **cannot** provide hyperconjugative stabilization (θ = 90° ⇨ overlap integral = 0)

each adjacent C–H bond will contribute to the hyperconjugative stabilization of the cationic center

the ethyl cation is stabilized by 3 hyperconjugative interactions with neighboring C–H bonds

Relative stability of the isomeric carbocations arising through protonation of an unsymmetrical olefin such as propene:



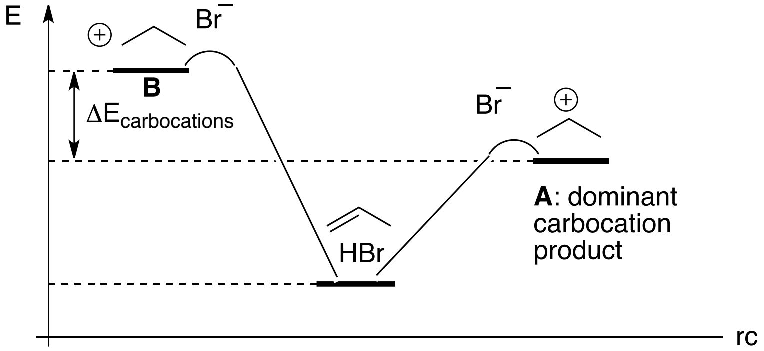
H from HBr connects to the terminal C

H from HBr connects to the inner C

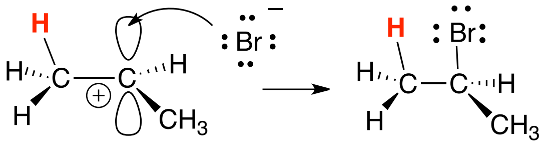
result: a carbocation stabilized by 6 C–H hyperconj. interactions
more favorable

result: a carbocation stabilized by 2 C–H and 1 C–C hyperconj. interactions (3 total)
less favorable

Principle: protonation of olefins is an unfavorable process that occurs reversibly; therefore, if the protonation of an olefin can yield two different carbocations, the more thermodynamically favorable (=more highly stabilized) ion (**A** in the example above) will form preferentially:

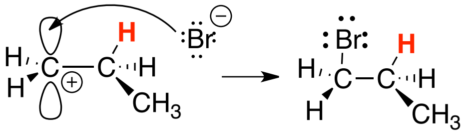


Ultimate products of the above reaction: the alkyl halide arising through addition of Br^- to the carbonium ions. Because carbocation **A** forms preferentially, alkyl bromide **A** below is predicted to be the major product of the reaction (confirmed by experiment!!).


cation **A**

product **A**

predicted **major** product


cation **B**

product **B**

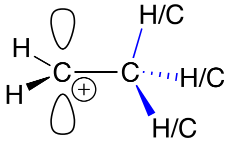
predicted **minor** product

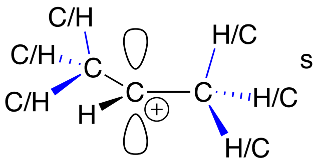
Primary (=bound to one other carbon), secondary (=bound to two other carbons), tertiary (=bound to three other carbons), carbon atoms

Primary, secondary, tertiary carbocation: one in which the charge resides on a primary, secondary, or tertiary C atom

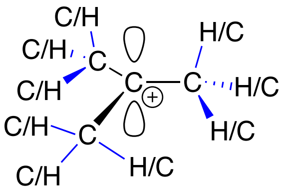
Note: generally speaking, a primary carbocation will be stabilized by 3 hyperconjugative interactions with neighboring σ bonds (C–H or C–C); a secondary one, by 6; a tertiary one, by 9 (structures below: the "blue" bonds are the ones providing hyperconjugative stabilization):

primary carbocation: 3 hyperconjugative interactions





secondary carbocation: 6 hyperconjugative interactions



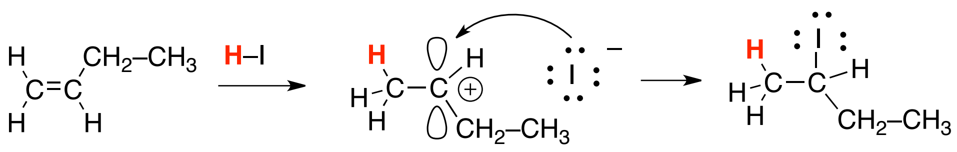
tertiary carbocation: 9 hyperconjugative interactions

Therefore, tertiary carbocations are generally more highly stabilized than secondary and primary ones, and secondary carbocations are generally more highly stabilized than primary ones

Principle: because carbocations obtained by protonation of an alkene form reversibly through an unfavorable (ΔG>0) process, the protonation of an alkene will yield preferentially the more highly stabilized (=less energetic) carbocation.

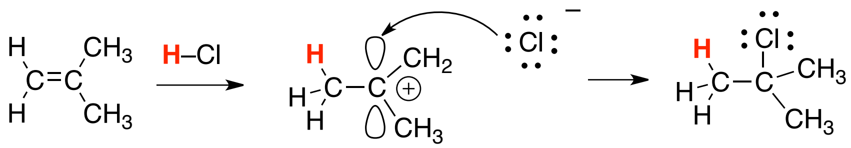
Therefore, a tertiary carbocation will for preferentially over a secondary or a primary one; and a secondary carbocation will form preferentially over a primary one.

Examples of electrophilic addition of H–X across the π bond of various alkenes



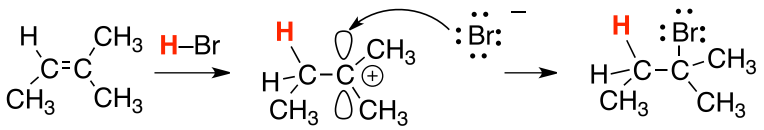
secondary carbocation:
forms selectively over
the primary cation

major product



tertiary carbocation:
forms selectively over
the primary cation

major product

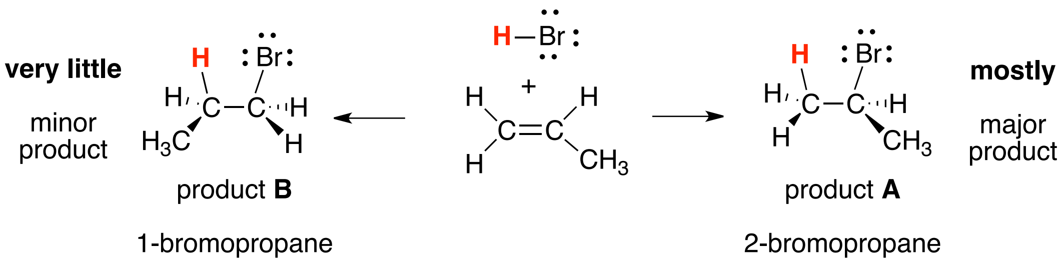


tertiary carbocation:
forms selectively over
the secondary cation

major product

Lecture 7: Regioselective Addition of H–X to Alkenes and Rearrangements

Selective reaction: one that yields preferentially one product out of a number of possible ones. In the case of propene reacting with HBr, one would say that the reaction is selective because **A** (2-bromopropane) is the major / exclusive product



the reaction selectively forms product **A**

The addition of halogen acids H–X (X = Cl, Br, I, **but not HF**) to alkenes as a selective reaction (=one one that yields largely / exclusively one product out of several possible ones):

Substituent: a generic atom or group of atoms, e.g. an H, an alkyl, a halogen, an OH, etc., attached to a given C atom within a molecule

example: the Br atom in the above molecules is a substituent, and so is the CH_3 group

Regioisomers (=positional isomers): two molecules that differ for the position of a particular substituent around an otherwise identical carbon chain

example: the above molecules of 1-bromopropane and 2-bromopane are regioisomers, because they differ for the location of the Br atom around an identical three-carbon chain

Regioisomers as special cases of constitutional isomers

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 HBr to propene

The addition of halogen acids H–X (X = Cl, Br, I, **but not HF**) to any unsymmetrical alkene as a regioselective reaction

Markownikov rule – old version: electrophilic addition of H–X (X = Cl, Br, I, **but not** F), to alkenes occurs so that the H connects to the C atom bearing the most H's, and the halogen, X, connects to the C atom bearing the most carbon atoms.

"Modern" Markownikov rule: electrophilic addition of H-X to alkenes occurs so that the major product results from the most highly stabilized cationic intermediate (which forms to a greater extent under conditions of reversible protonation of the alkene).
Primary, secondary, tertiary alkyl halides: compounds in which the halogen is connected to a primary, secondary or tertiary carbon atom, respectively

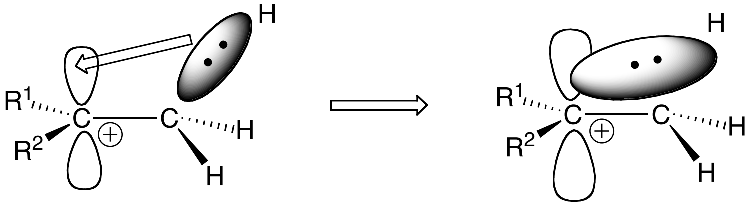
Quaternary carbon; one bound to four other carbons

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). Consequently, we may focus on C–H hyperconjugation when evaluating the degree of stabilization of carbocations

R-notation: in organic chemistry, "R" is used to denote a generic substituent in a molecule: H, alkyl, Cl, Br, OH, …

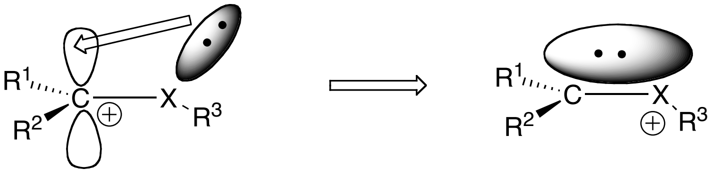
Enormous degree of stabilization provided to carbocations by adjacent heteroatoms possessing lone pairs of electrons, such as N, O, S:

hyperconjugative interaction: the "back-pull" of the nucleus of the H atom allows only a fraction of the C–H σ electron density to occupy the vacant p-orbital on the carbocation



the σ cloud is "distorted": some σ electron density is delocalized away from H and toward the positive C

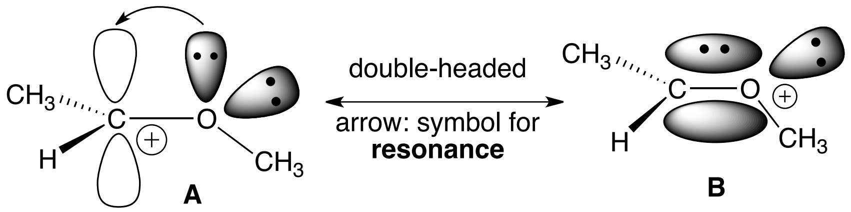
interaction of a carbocation with a neighboring heteroatom, X, possessing a lone pair: there is nothing to "pull back" the lone pair!



the lone pair is now free to establish a full π bond between X and C: every atom has a complete octet

"R" notation above (cf. R^1, R^2, R^3) indicates generic groups; e.g., alkyl groups

The stabilization of a carbocation by a neighboring heteroatom containing lone pairs, e.g., oxygen, as an example of resonance interaction:



reminder: resonance structures, e.g., **A** and **B** above, are used to depict extreme cases of electronic distribution within a molecule. They have no physical reality, but allow us to visualize the electronic configuration of the molecule as being "in between" such extremes

Origin of carbocation stabilization provided by a heteroatom: completion of a Lewis octet around the cationic carbon atom

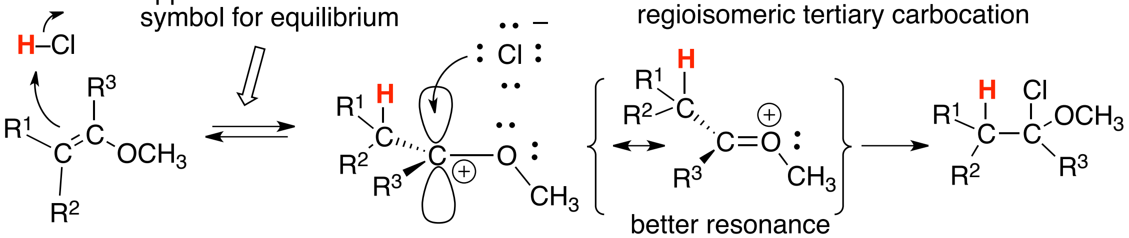
Principle: resonance structure **B** above describes the electron configuration of the cationic intermediate better than structure **A**:

> In **B**, each atom has a complete Lewis octet: this is an extremely favorable situation.
> in **A**, the carbon atom has only 6 valence electrons: this is highly unfavorable

General order of stability of carbocations: N/O/S-stabilized > tertiary > secondary > primary

> **Therefore**, an N/O/S-stabilized carbocation will form preferentially over a tertiary, secondary or primary one; a tertiary carbocation will for preferentially over a secondary or a primary one; a secondary carbocation will form preferentially over a primary one.

Electrophilic addition of H–X to alkenes bearing N, O, S substituents: the orientation of the addition process is controlled by the heteroatom, e.g.:

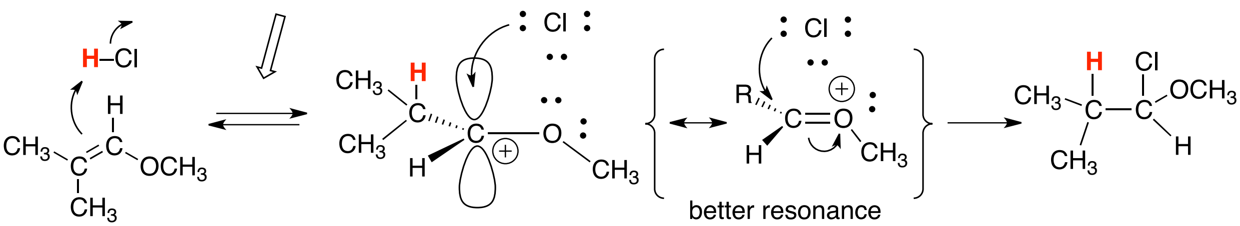


2 arrows pointing in opposite directions: symbol for equilibrium

heteroatom-stabilized "carbocation": even more favorable than the regioisomeric tertiary carbocation

better resonance form of the cation

Illustration of the fact that a heteroatom-stabilized carbocation is better stabilized than even a tertiary one:



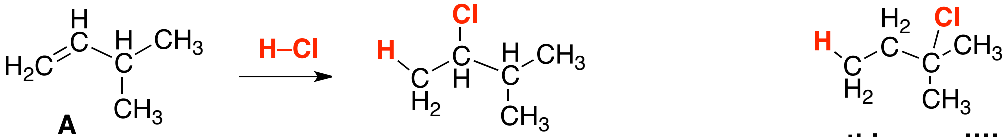
2 arrows pointing in opposite directions: symbol for equilibrium

heteroatom-stabilized "carbocation": even more favorable than the alternative tertiary carbocation

better resonance form of the cation

> notice how the "old" Markownikov rule ['in an electrophilic addition of H–X to alkenes, the H connects to the C atom bearing the most H atoms, and the halogen, X, connects to the C atom bearing the most carbon atoms"] fails in the above case.

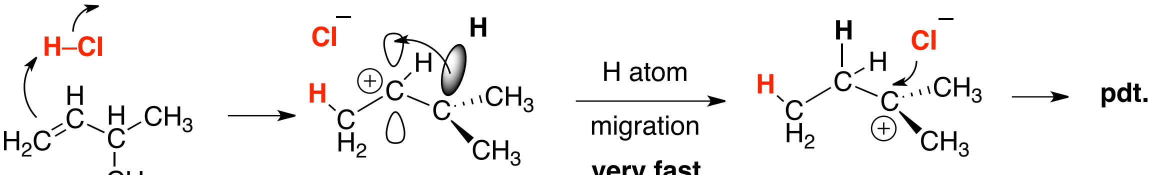
Addition of H-X (X = Cl, Br, I, **but not F**) to particular alkenes; e.g., **A**:



expected product
However, this is found to be the minor product of the reaction, the major product being instead . . . .

this one !!!!

Rationale for the formation of the unexpected product:



carbocation stabilized by 4 hyperconj. interact. with C–H bonds

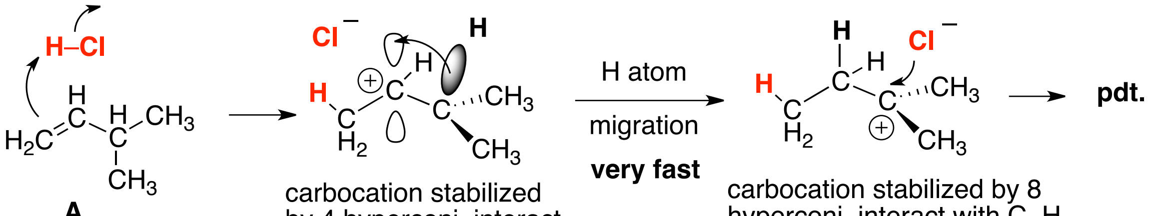
very fast

carbocation stabilized by 8 hyperconj. interact.with C–H bonds: more favorable

Description of the above process as a hydrogen migration

Lecture 8: Stereochemical Aspects of H–X Additions to Alkenes

Description of the process leading to the formation of the unexpected product of the reaction of alkene **A** with, e.g., HCl, as a **rearrangement** of the carbocation through a migration (or shift) of hydrogen



A

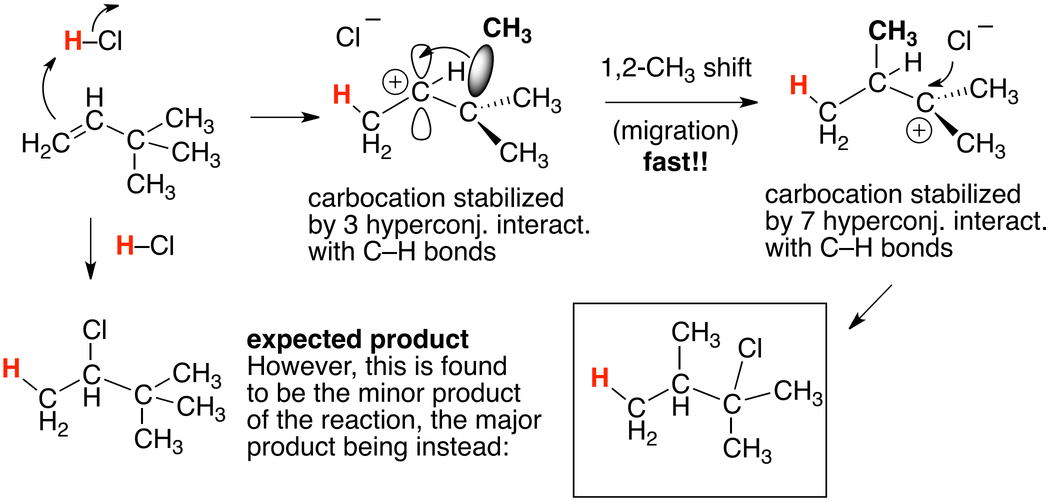
carbocation stabilized by 4 hyperconj. interact. with C–H bonds

carbocation stabilized by 8 hyperconj. interact.with C–H bonds: more favorable

Principle: rearrangements of carbocations by the above migratory mechanism (1,2-migration or 1,2-shift) occur extremely rapidly

Principle: because rearrangements of carbocations occur extremely rapidly, the occurrence of a rearrangement during an electrophilic addition to an olefin is strong evidence that the reaction involves carbocation intermediates. Likewise, the *absence* of rearrangements during an electrophilic addition to an olefin is evidence that the reaction *does not* involve carbocations.

Carbocation rearrangement through migration (or shift) of alkyl groups, e.g.:



carbocation stabilized by 3 hyperconj. interact. with C–H bonds

carbocation stabilized by 7 hyperconj. interact. with C–H bonds

expected product
However, this is found to be the minor product of the reaction, the major product being instead:

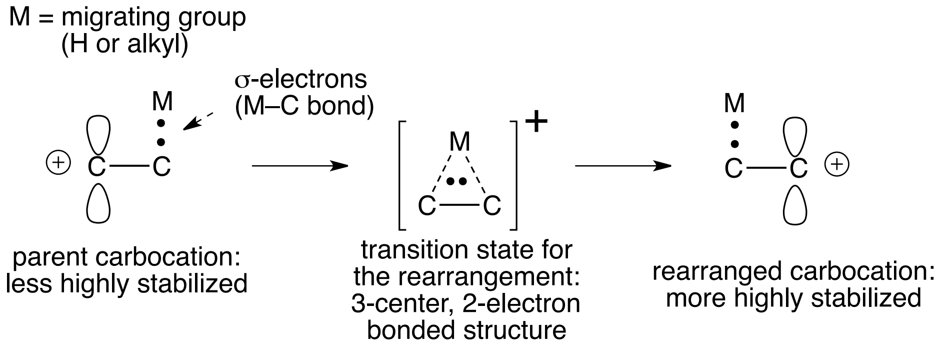
Significance of carbocation chemistry, including rearrangements, in biological chemistry

Example: cholesterol, an important component of lipid membranes and the progenitor of steroid hormones, is synthesized in certain liver cells. These generate a particular carbocation, which is transformed into cholesterol by various rearrangements and other chemical modifications

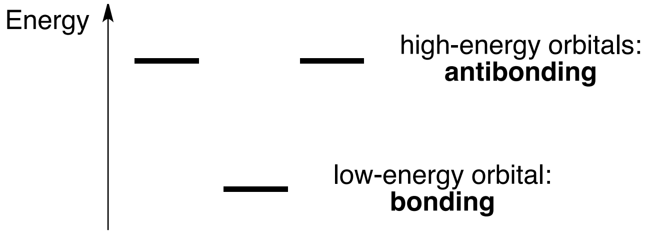
Principle: in CHEM 203 we may assume that carbocation rearrangements will occur only if the immediate product of a migration is more highly stabilized than the original ion.

Interpretation of carbocation rearrangements from the standpoint of molecular orbital theory

in the course of a rearrangement, a carbocation must attain a transition state (see below), which exhibits 3-center (= 3 atoms), 2-electron bonding:

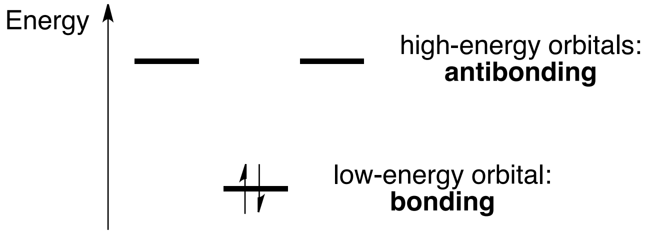


the molecular orbitals of this transition state result through a Linear Combination of Atomic Orbitals (LCAO) associated with the two C atoms and migrating atom M, each contributing 1 orbital. The 3 atomic orbitals combine (complex math…) to produce 3 molecular orbitals that may be represented with the following MO diagram:



***note**: the antibonding orbitals, shown above as being degenerate, may differ in energy depending on the precise molecular structure*

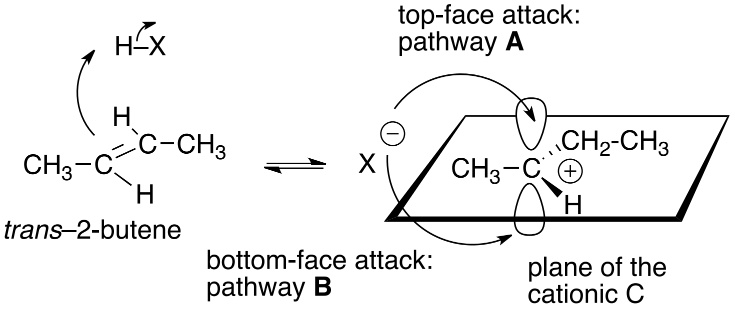
the above molecular orbitals will be populated by the 2 electrons "holding the transition state together." These electrons will populate the lowest-energy orbital first:



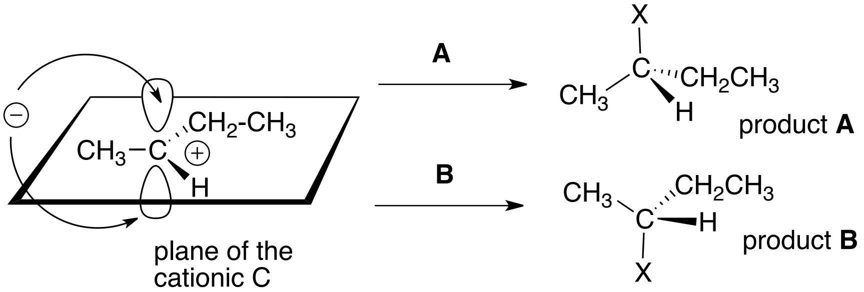
therefore, a considerable degree of bonding is retained during the rearrangement.

Stereochemical aspects of the electrophilic addition of H–X to simple alkenes: chiral products will be obtained in both enantiomeric forms:

Example: the reaction of *trans*-2-butene with a generic H–X (X = Cl, Br, I, **but not F**) leading to a 2-halobutane. The planar carbocation formed upon protonation of the alkene may react with X^- from either the top or the bottom face…



… the two modes of attack leading to enantiomeric products (**use molecular models!!**):



2-halobutane:
chiral molecule

A and **B** are
enantiomers

Stereogenic (occasionally **improperly** described as "chiral") carbon atom: one bound to four different ligands

Chiral nature of the product 2-halobutane

Equal probability of pathways **A** and **B**: formation of a 50:50 mixture of products **A** and **B**

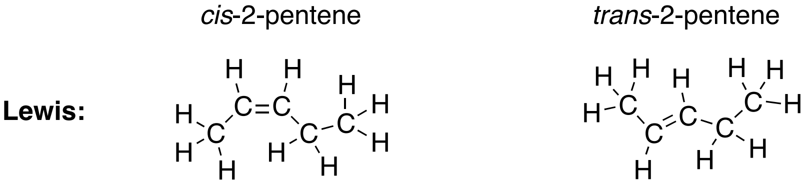
Racemic mixture, racemate: a 50:50 mixture of the two enantiomeric forms of a compound

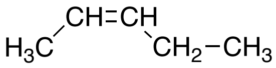
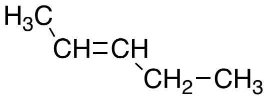
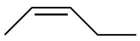
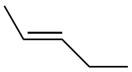
Principle: a reaction between an achiral substrate (such as *trans*-2-butene) and an achiral reagent (such as H–X) that leads to a chiral product will always produce a racemic mixture of products.

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

Drawing organic structures by the use of Lewis (painstaking to draw), condensed (easier to draw), and skeletal formulas (of most practical usage)

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



	cis-2-pentene	*trans*-2-pentene
condensed:	 $H_3C-CH=CH-CH_2-CH_3$	 $H_3C-CH=CH-CH_2-CH_3$
skeletal:		

Lecture 9: Hydration of Alkenes

Technological importance of alkyl halides in the chemical industry

Even greater technological significance of alcohols in the contemporary world

Reminder: an alcohol is an organic compound in which a carbon atom bears an OH group:

Hydration reaction of alkenes: the addition of water across the π bond leading to alcohols:

$$\mathrm{H{-}OH} \quad \mathrm{C{=}C} \xrightarrow{[\,?\,]} \overset{\mathrm{H}}{\mathrm{C}}{-}\overset{\mathrm{OH}}{\mathrm{C}}$$

Principle: no reaction is possible between an intact alkene and H_2O because both are Lewis bases

Possible reaction of Lewis basic H_2O with a carbocation generated by protonation of an alkene

Inability of H_2O (pKa ≈ 16) to protonate an alkene and consequent requirement for a strong Bronsted acid in the hydration reaction

Reminder: the pKa of H_2O as defined on the basis of the law of mass action is:

this is an abstraction: there is no free "H⁺" in solution

$$\mathrm{H{-}OH} \rightleftharpoons \mathrm{H^+} + {}^{\ominus}\mathrm{OH}$$

both = 10^{-7} M at equil. (25 °C)

$$\mathrm{Keq} = \mathrm{Ka} = \frac{[\mathrm{H^+}]\,[{}^{\ominus}\mathrm{OH}]}{[\mathrm{H_2O}]} = \frac{10^{-7} \times 10^{-7}}{55.55} = 1.8 \times 10^{-16}$$

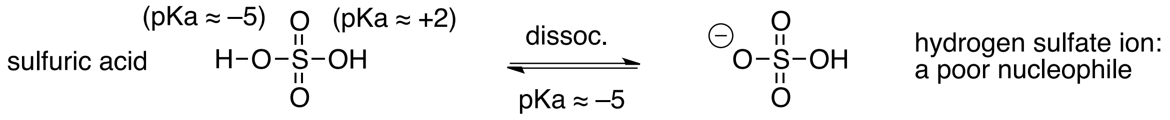
no. of moles of H_2O in one liter (≈ 1 kg) of H_2O ≈ 1000 g / 18 g/mol = 55.55 mol

$$\boxed{\text{therefore, } \mathrm{pKa_{H2O}} = -\log\,(1.8 \times 10^{-16}) \approx 15.7 \approx 16}$$

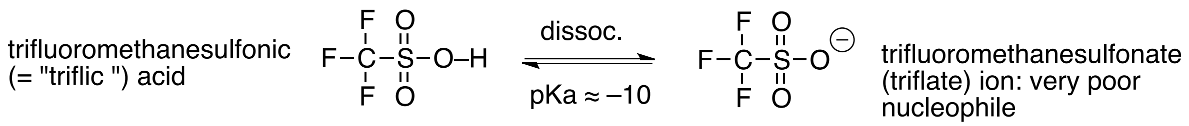
Inadequacy of HCl, HBr, HI for the hydration of olefins (nucleophilic Cl^-, Br^-, I^- are likely to capture the carbocation intermediate)

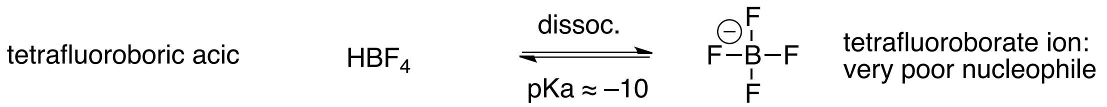
Requirement for Bronsted acids that are strong enough to protonate the olefin (pKa << 0), but that release a poorly nucleophilic conjugate base that is unlikely to compete effectively with H_2O for the intermediate carbocation

Sulfuric acid (pKa ≈ – 5), trifluoromethanesulfonic acid (pKa ≈ –10), tetrafluoroboric acid (pKa ≈ –10), as Bronsted acids that release poorly nucleophilic conjugate bases



$$\underset{\text{sulfuric acid}}{\mathrm{H{-}O{-}\overset{\overset{\mathrm{O}}{\|}}{\underset{\underset{\mathrm{O}}{\|}}{S}}{-}OH}} \underset{\mathrm{pKa}\,\approx\,-5}{\overset{\text{dissoc.}}{\rightleftharpoons}} {}^{\ominus}\mathrm{O{-}\overset{\overset{\mathrm{O}}{\|}}{\underset{\underset{\mathrm{O}}{\|}}{S}}{-}OH}$$

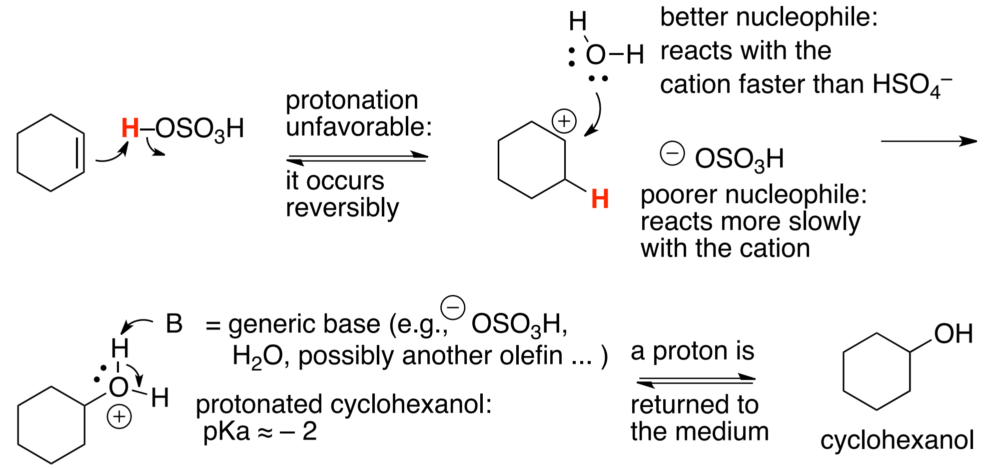




the conjugate bases of these acids are poor nucleophiles and are not overly inclined to react with carbocation intermediates, permitting faster capture of the cations by other nucleophiles

Principle: in the absence of prior knowledge, it is generally not easy / possible to predict whether the conjugate base of a Bronsted acid will be a good nucleophile, or a poor one: only experiment can ascertain the nucleophilic character of such conjugate bases.

General mechanism of the hydration reaction of an olefin, e.g., of cyclohexene:



Thermodynamically highly favorable capture of a carbocation by a molecule of H_2O (completion of a Lewis octet)

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

Catalysts: species that promote chemical reactions but that are not consumed in the process

The addition of water to alkenes as a process that is catalytic in protons (acid)

The hydronium ion, H_3O^+, as a strong Bronsted acid with pKa ≈ –2

Reminder: the pKa of H_3O^+ as defined on the basis of the law of mass action is:

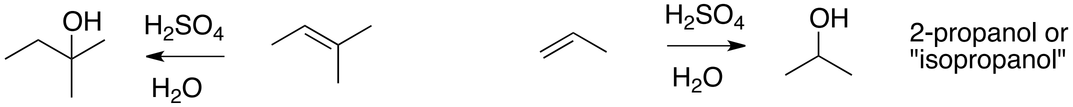
$$H_3O^+ \rightleftharpoons \underset{\Uparrow}{H^+} + H_2O \qquad K_{eq} = K_a = \frac{[\,H^+\,]\;[\,H_2O\,]}{[\,H_3O^+\,]} = [\,H_2O\,] = 55.55$$

this is an abstraction: there is no free "H+" in solution

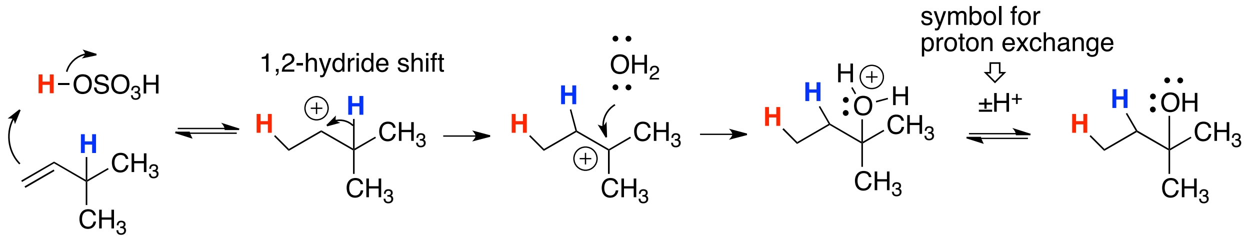
same thing!!

$$\boxed{\text{therefore, } pKa_{H3O^+} = -\log(55.55) \approx -1.7 \approx -2}$$

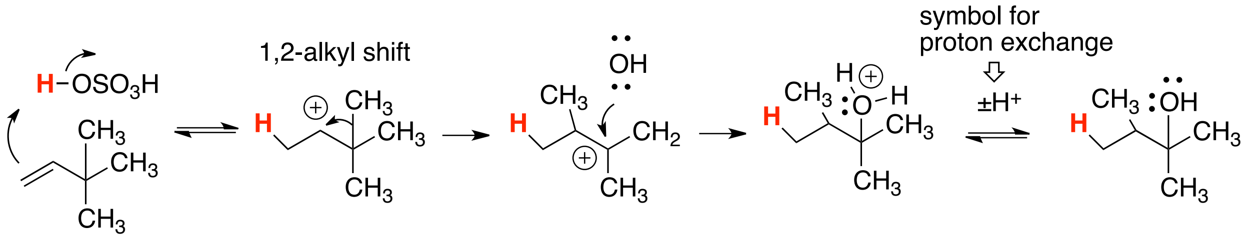
"Markownikov" selectivity in the addition of water to unsymmetrical alkenes: formation of alcohols derived from the more highly stabilized carbocation, e.g.:



Possibility of rearrangement during addition of water to alkenes as a consequence of the fact that the reaction involves carbocation intermediates. Examples:

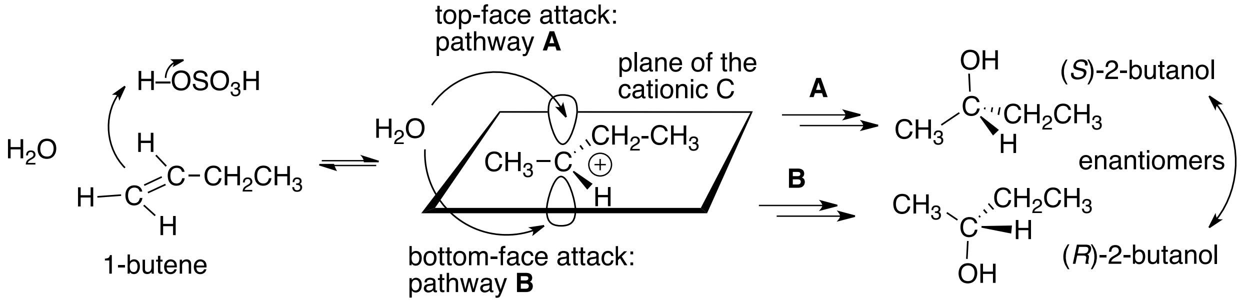


and



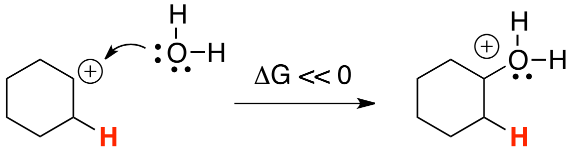
Stereochemical aspects of proton-initiated hydration of alkenes: formation of racemic alcohols (notes of Sept 25):

Example: the hydration of 1-butene leading to 2-butanol:



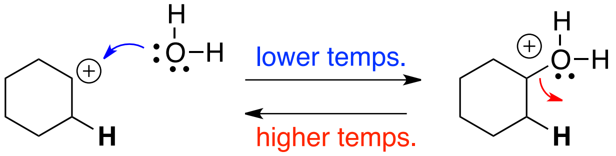
Lecture 10: Addition of "Water-Like" Molecules to Alkenes

Thermodynamically highly favorable capture of a carbocation by a molecule of water; e.g.:

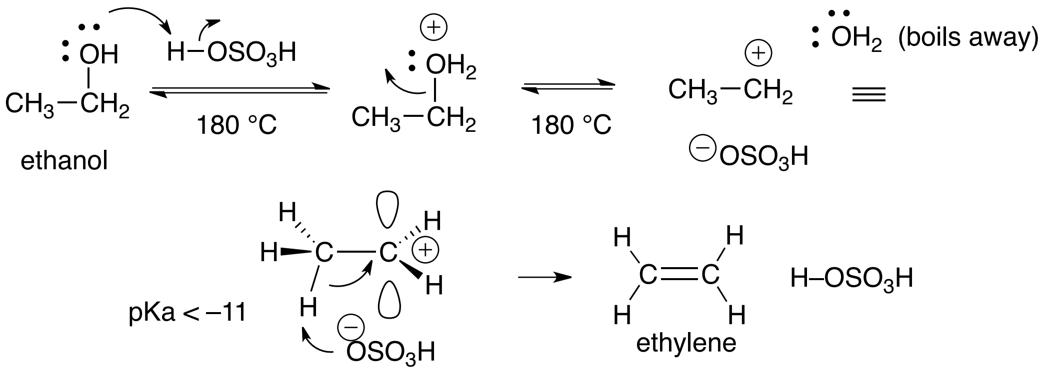


the cationic carbon, originally surrounded by only 6 valence electrons, completes its octet

Reversibility of the above step at higher temperatures (150-200 °C):

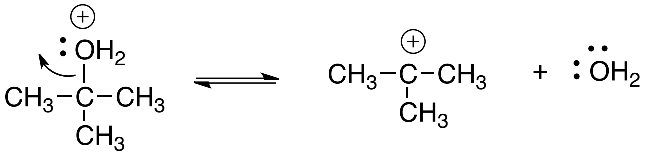


Dehydration of alcohols: conversion of alcohols into olefins; e.g.:

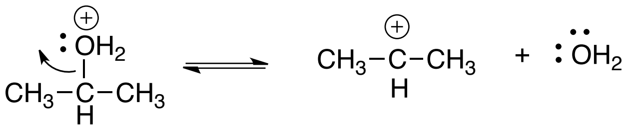


note: any alcohol (except CH_3OH) can be dehydrated in this fashion

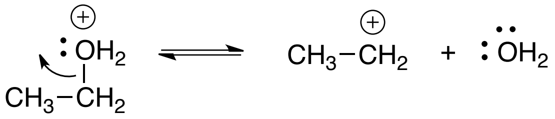
Relative ease of dehydration of alcohols: tertiary > than secondary >> than primary – **WHY?** Because the ease of dehydration correlates with the energy necessary to cause dissociation of H_2O away from the protonated alcohol:



tertiary carbocation formed:
most stabilized
least energetic --> most facile
fastest reaction

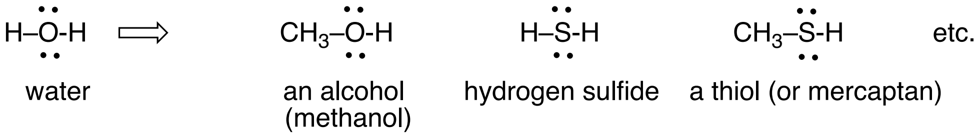


secondary carbocation formed: less stabilized
more energetic --> less facile
slower reaction



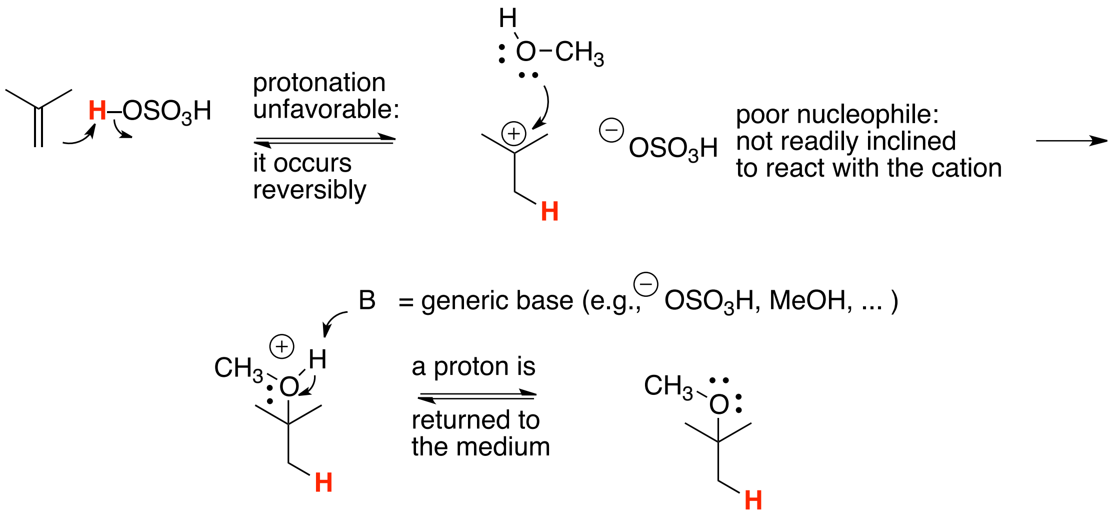
primary carbocation formed: least stabilized
most energetic --> least facile
slowest reaction

Addition of "water-like" molecules to the π system on an alkene under protonic catalysis

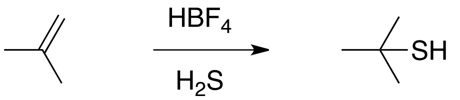


Principle: the mechanism of proton-catalyzed addition of alcohols, H_2S, thiols, or any other electronically similar molecules, to olefins is analogous to that of the hydration reaction.

examples: (i) addition of alcohols, e.g., methanol, CH_3OH, to olefins: formation of ethers, as exemplified by the preparation of methyl tert-butyl ether (MTBE, antiknock additive for gasoline):

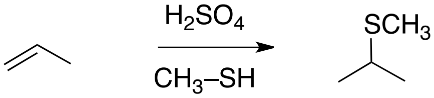


(ii) addition of H_2S to olefins catalyzed by strong acids such as H_2SO_4, HBF_4, ... : preparation of the sulfur analogs of alcohols ["mercaptans" or "thiols:" R–SH



the sulfur analog of an alcohol:
a mercaptan, a.k.a. a thiol

(iii) addition of mercaptans (thiols) to olefins catalyzed by H_2SO_4, HBF_4, ...: preparation of the sulfur analogs of ethers ("thioethers:" compounds of the type R^1–S–R^2 (R^1, R^2 = generic alkyl groups); e.g.:



the sulfur analog of
an ether: a thioether

Principle: all the reactions seen so far involve carbocations, therefore, in all such reactions rearrangements of the carbocation intermediates are possible.

Possible additions to the π system of alkenes that do not involve carbocation intermediates

Additions to alkenes initiated by an interaction of the π system with electrophiles other than H^+, such as:

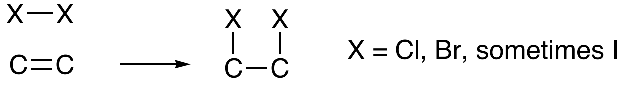
a. species that contain an electronegative element in a high oxidation state (molecular halogens, particular forms of oxygen, etc.)

b. certain metals in a high oxidation states

c. highly Lewis acidic molecules

Lecture 11: Halogenation of Alkenes & Stereochemical Aspects

Reaction of alkenes with molecular halogens (Cl_2, Br_2, sometimes I_2, but not F_2 – see below):



notice how the above reaction reflects the general pattern of reactivity of olefins (notes of Sept 18)

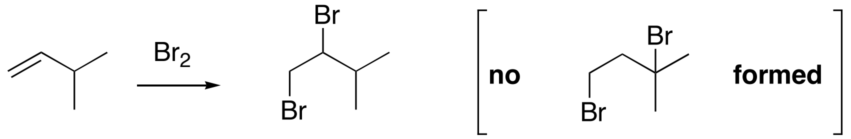
Violent, exothermic reaction of F_2 with alkenes (and organic matter in general) due to the extreme reactivity of F_2 toward carbon-based compounds, as a consequence of which the fluorination of alkenes is not a reaction of interest

Description of the above reaction as the halogenation (chlorination, bromination, iodination, …) of an alkene

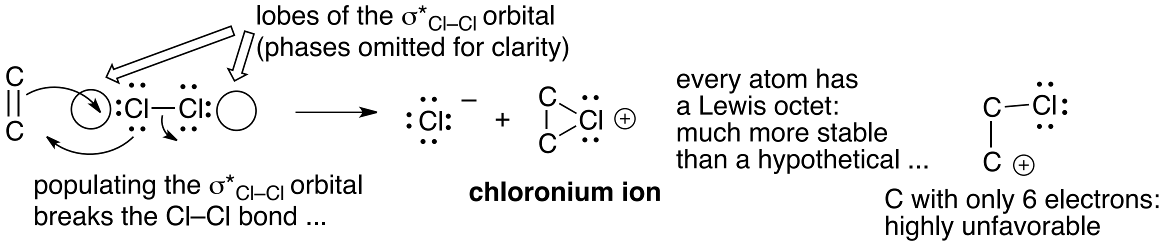
Description of the product as the above reaction as a 1,2-dihalide or vicinal dihalide (dichloride, dibromide, diiodide…)

Absence of rearrangements during the halogenation of olefins, ruling out the intervention of carbocation intermediates (notes of Sept. 25)

Example:



Mechanistic aspects of the halogenation reaction: predicted initial interaction of the π system with a halogen molecule, e.g., Cl_2, leading to a **chloronium ion**:



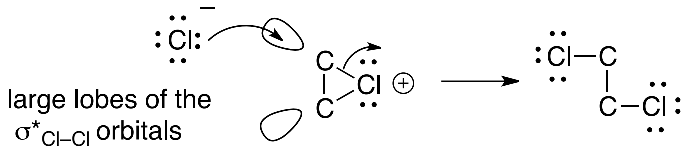
notice how electrons flow from the less electronegative C to the more electronegative Cl

Chloronium, bromonium, iodonium, … halonium ions

Concerted (= simultaneous creation / breakup of two or more bonds) formation of halonium ions

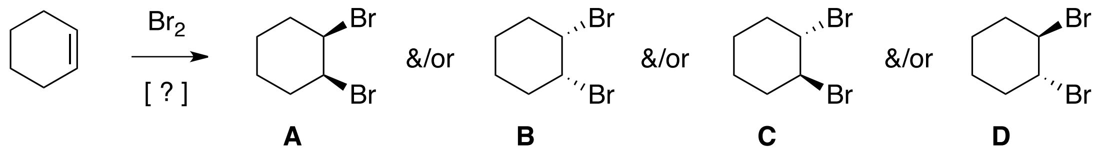
Halonium ions as exceedingly reactive, strained electrophiles, which nonetheless are isolable in some favorable cases

Rapid S_N2-like reaction of the halonium (chloronium, bromonium, …) ion with halide (chloride, bromide, …) ion through donation of an electron pair into the C–X σ* orbital:



Stereochemical aspects of the halogenation reaction: possible formation of stereoisomeric products.

Example. The addition of Br_2 to cyclohexene could produce the following stereoisomeric products:



In products **A** and **B** the Br atoms point in the same direction relative to the plane containing the ring.

The Br atoms are in a *cis* relationship

A and **B** are thus *cis* isomers

In products **C** and **D** the Br atoms point in opposite directions relative to the plane containing the ring.

The Br atoms are in a *trans* relationship

A and **B** are thus *trans* isomers

Now . . .

Structures **A** and **B** are different projections of the same molecule; i.e., they represent the same thing (the *cis* isomer)! This *cis* isomer is **achiral**, even though it possesses stereogenic carbons; therefore, it is a **meso** compound.

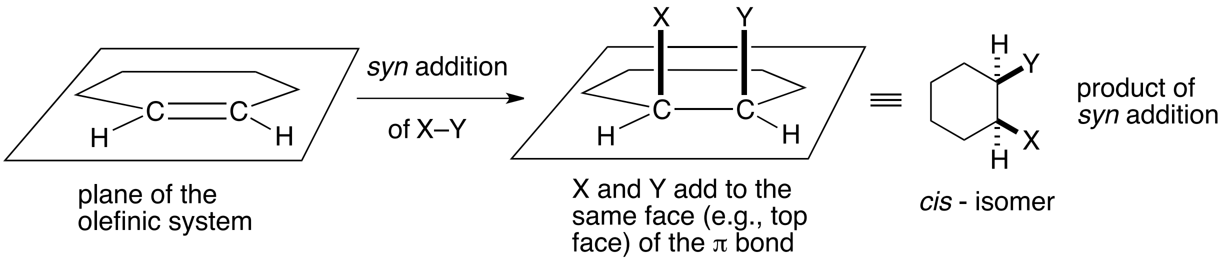
Structures **C** and **D** are enantiomeric forms of the *trans* isomer: their thermodynamic properties are identical: if they should form, they will be obtained as a 50:50 mixture.

The *cis* and the *trans* isomers are one a **diastereomer** of the other. **But…**: diastereomers possess distinct thermodynamic properties:

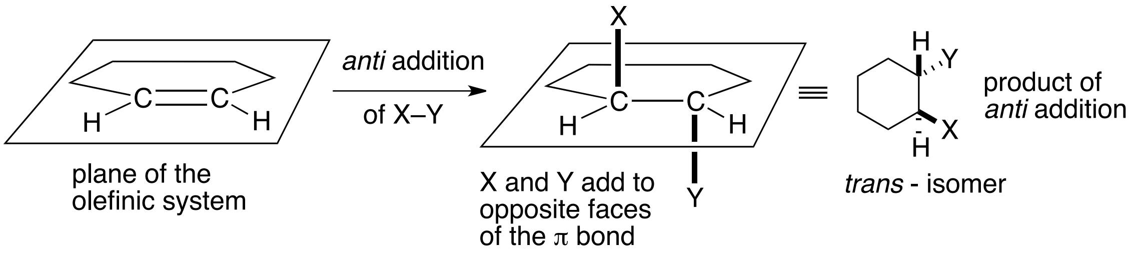
could the halogenation reaction form preferentially one type of diastereomeric product ?

Terminology used to describe the stereochemical outcome of the addition of a generic agent X–Y to a π system: *syn* and *anti* additions

Syn addition of a generic molecule X–Y to the π system of an alkene (e.g., cyclohexene): a process during which the X and Y atoms add from the same face of the π system:

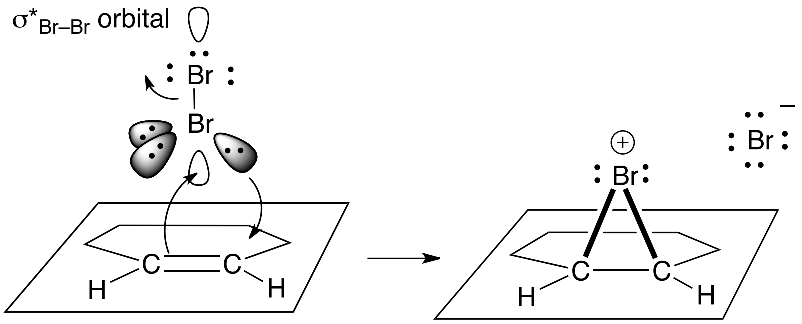


Anti addition of a generic molecule X–Y to the π system of an alkene (e.g., cyclohexene): a process during which the X and Y atoms add from opposite faces of the π system:

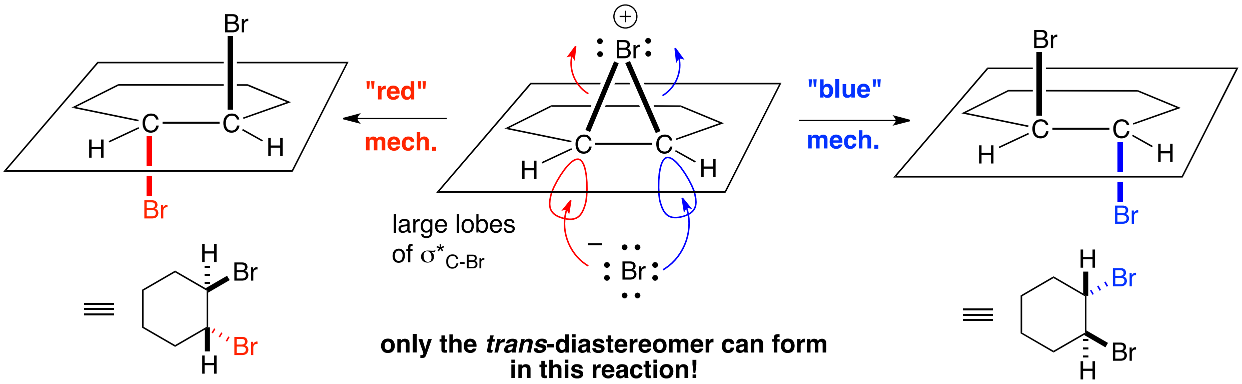


The formation of bromonium (halonium) ions as a *syn* addition process:

The reaction must start with the formation of a bromonium ion **without** the intervention of carbocationic intermediates. The halogen molecule "deposits" a Br atom onto the double bond through a mechanism that involves the simultaneous motion of three electron pairs (concerted mechanism):



then, the bromonium ion undergoes S_N2-like reaction with the halide (bromide, chloride..) ion:

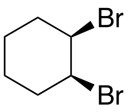


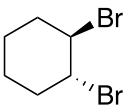
only the *trans*-diastereomer can form in this reaction!

The halogenation (e.g., bromination) of alkenes as an overall *anti* addition

consequence: the *cis*-isomer of the product is **unavailable** by any reaction yet known to us

cis-1,2-dibromocyclohexane (**unavailable** by any reaction yet known to us in CHEM 203)

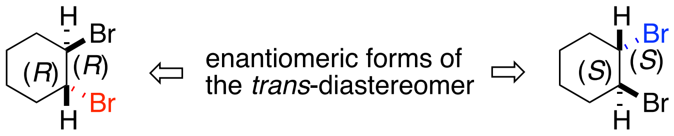




trans-1,2-dibromocyclohexane: available by bromination of cyclohexene

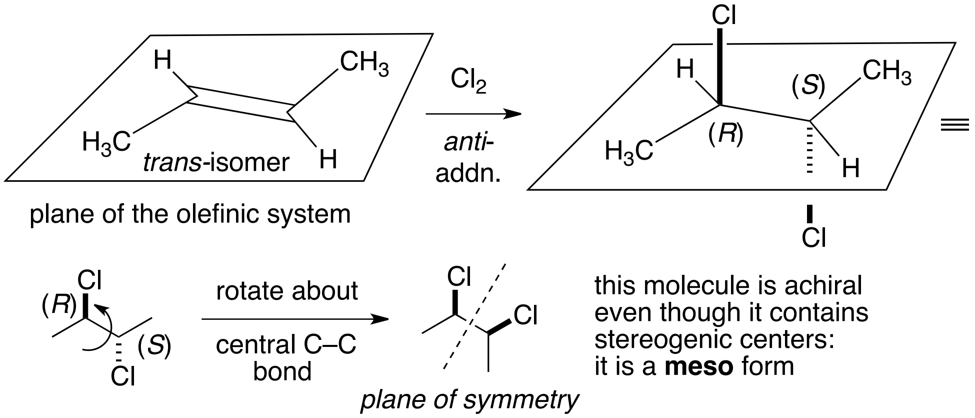
The halogenation of olefins as a diastereoselective reaction (it selectively forms one diastereomer)
Achiral nature of Br_2 (molecular halogens in general) and cyclohexene

Chiral nature of the product of bromination (halogenation) of cyclohexene (*trans*-1,2-dibromocyclohexane) and consequent formation of a racemic mixture through the statistically equally probable occurrence of the "red" and "blue" mechanisms above:

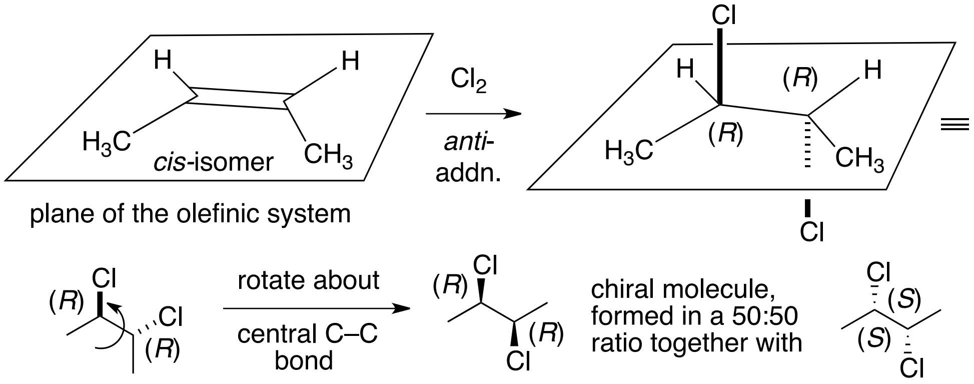


Principle: mechanistic constraints force the halogenation reaction of **any alkene** to proceed in the *anti* mode.

Stereochemical outcome of the halogenation of an acyclic olefin, e.g. the chlorination of *trans*- and *cis*-2-butene:



this molecule is achiral even though it contains stereogenic centers: it is a **meso** form



chiral molecule, formed in a 50:50 ratio together with

Enantiomeric relationship between the *R*,*R*- and the *S*,*S*-isomer (non-superimposable mirror images)

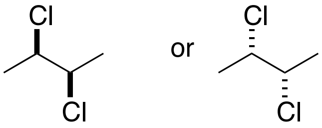
Diastereomeric relationship between *R*,*R*- and the *R*,*S*-isomer or the *S*,*S*- and the *R*,*S*-isomer (stereoisomers that are not mirror images)

Lecture 12: Halogenation, Halohydrins, Stereochemical Aspects

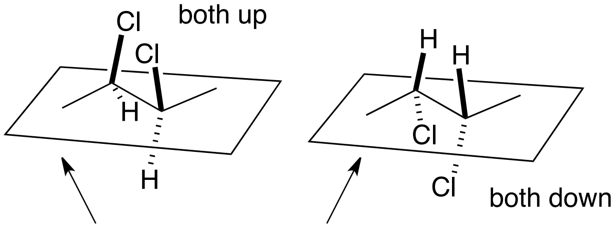
Syn and *anti* diastereomers of the product of chlorination of, e.g., 2-butene:

(a) draw the carbon backbone in an extended (*anti*-butane) conformation and consider the orientation of the halogen atoms relative to the geometric plane containing the main carbon chain

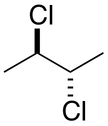
(b) if the halogen atoms are protruding out of the same face of the plane, then the stereoisomer in question is the *syn* diastereomer; if they are pointing in opposite directions, then the stereoisomer in question is the *anti* diastereomer:



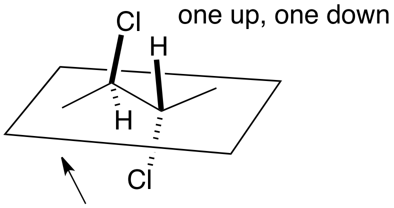
enantiomeric forms of the *syn* diastereomer, because in either molecule the Cl atoms reside on the same face of the plane defined by the main chain of the molecule in an extended conformation



molecular plane defined by the main chain in an extended conformation



anti diastereomer,because the Cl atoms reside on opposite faces of the plane defined by the main chain of the molecule in an extended conformation



molecular plane defined by the main chain in an extended conformation

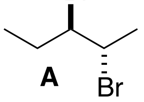
Attention: the stereochemical descriptors *syn* and *anti* as referred to the mode of addition to an alkene, or to a molecular property of diastereomers, mean two different things:

• as applied to the *mode* of addition, they indicate whether a generic X–Y adds to the π bond of an alkene in such a way that X and Y connect to the C atoms of the olefin from the same side (*syn* addition) or from opposite sides (*anti* addition) of the plane of the π bond.

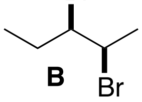
• as applied to a *diastereomer*, they indicate whether groups X and Y end up pointing toward the same face (*syn* diastereomer) or opposite faces (*anti* distereomer) of a geometric plane containing the main carbon chain of the molecule in an *extended (=anti-butane) conformation*.

Consequence of the stereochemical properties of the halogenation reaction:

suppose that we need to prepare the *anti*-diastereomer of 2,3-dibromopentane (compound **A** below) and the *syn*-diastereomer of the same molecule (compound **B**): how could we proceed?



A



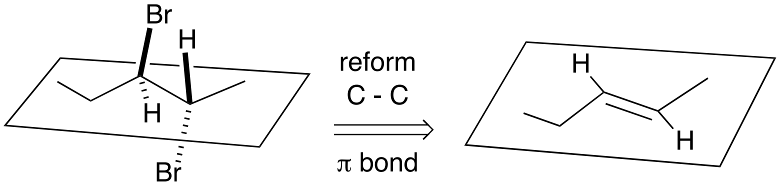
B

(i) both compounds are 1,2-dibromides, which are available by direct bromination of "2-pentene;"

(ii) the C atoms connected to the halogens must have been part of an olefinic system, which has has subsequently reacted with Br_2; **but** …

(ii) the addition of Br_2 to an alkene is a strictly *anti*-process; meaning that the halogens must have added from opposite faces of the π system. **So**:

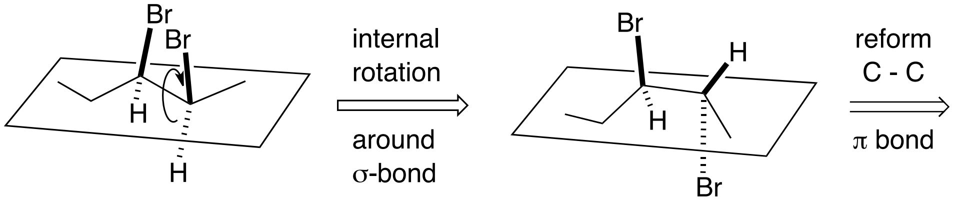
Compound **A** is an *anti*-diastereomer, which must have resulted from the *anti*-addition of Br_2 to *trans*-2-pentene:



Br's on opposite faces of the molecular plane

compound **A** can be made by *anti*-addition of Br_2 to *trans*-2-pentene

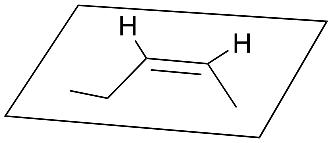
Compound **B** is an *syn*-diastereomer. One cannot produce **B** by the addition of Br_2 to *trans*-2-pentene, because the *anti*-nature of the addition process will furnish the *anti*-diastereomer (**A**). To deduce how we could create **B**, we must imagine a conformer of the molecule in which the halogen atoms are oriented in opposite directions relative to the molecular plane:



Br's on the same face of the molecular plane

Br's now on opposite faces of the molecular plane

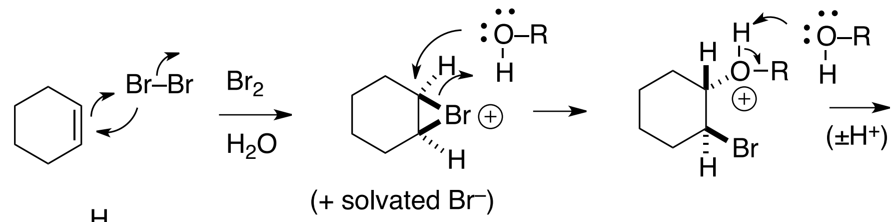
consequently . . .

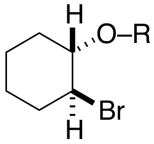


compound **C** can be made by *anti*-addition of Br_2 to *cis*-2-pentene

Driving force in the above reactions: the electronegative halogen atoms, initially in an unfavorable oxidation state of 0, are reduced to the favorable oxidation state of −1

Capture of halonium ions with nucleophiles other than halide ion: reaction of an olefin with Cl_2 (Br_2) and water or simple alcohols: formation of halohydrins (chlorohydrins, bromohydrins, etc.) or haloethers via an overall *anti* addition process:





anti-addition:
trans-product only

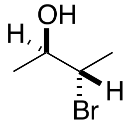
If R = H: the product is a bromohydrin
If R = CH_3, $CH_3–CH_2$, ... alkyl: the product is a bromoether

The halohydrin reaction as a strictly *anti*-addition to the π bond

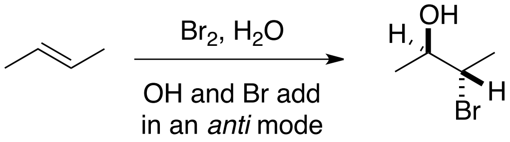
The halohydrin reaction as a diastereoselective process (*anti*-addition only)

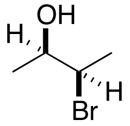
Technological importance of halohydrins

Additional examples: preparation of acyclic (= non-cyclic) halohydrins, e.g. bromohydrins, e.g.:

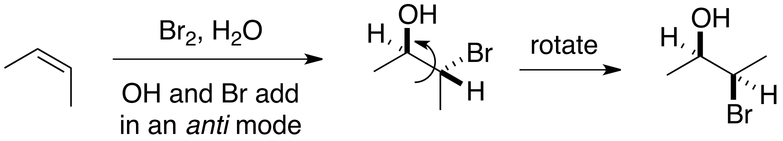


anti-bromohydrin accessible only from *trans*-2-butene:





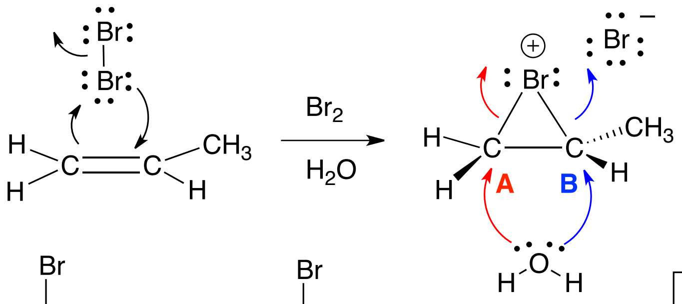
syn-bromohydrin accessible only from *cis*-2-butene:



Reminder: the halohydrins shown above are chiral molecules that are produced from achiral reactants; consequently, they will be obtained in racemic form. For convenience, we depict them as individual enantiomers, with the understanding that both enantiomers are actually present in equal proportions

Regioselectivity in halohydrin formation from unsymmetrical halonium ions; e.g.:

propene: a simple unsymmetrical alkene



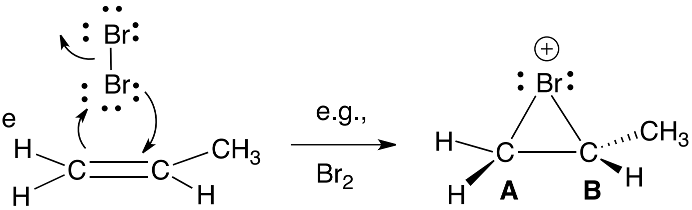
an unsymmetrical bromonium ion: H_2O could react at atom **A** or atom **B**

ultimate product of reaction at atom **A:**

ultimate product of reaction at atom **B:**

will the H_2O molecule prefer to attack atom **A** or **B** ?

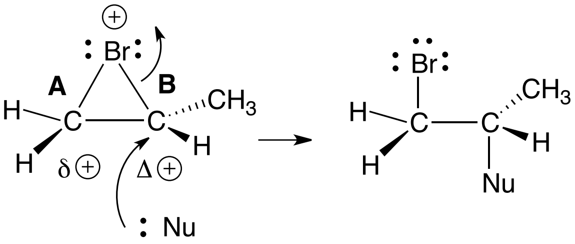
propene: a simple unsymmetrical alkene



an unsymmetrical bromonium ion: a nucleophile could react at atom **A** or at atom **B**

will a nucleophile prefer to attack atom **A** or **B** ?

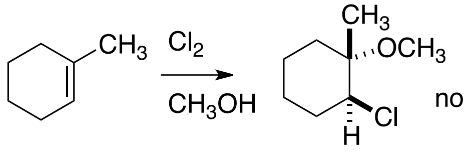
- The Br–C bonds are highly polarized (there is a + charge on Br), so the C atoms of the bromonium ion support a significant fraction of + charge.
- Carbon atom **B** accumulates a greater fraction of + charge than **A**, because it is better suited to sustain cationic character due to a greater number of C–H hyperconjugative interactions



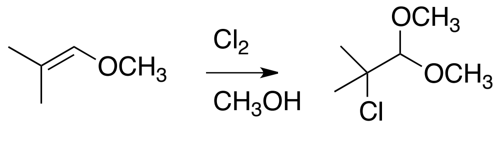
A nucleophile, Nu (=electron-rich species, therefore electrostaticallly negative), will be attracted to the site of greater + character, so one may predict that it will preferentially attack carbon atom **B**

Principle: an external nucleophile will attack an unsymmetrical chloronium (bromonium, … halonium) ion preferentially at the carbon that can sustains the greatest fraction of positive charge (= the more highly polarized C atom)

Additional examples of halohydrin-like reactions:

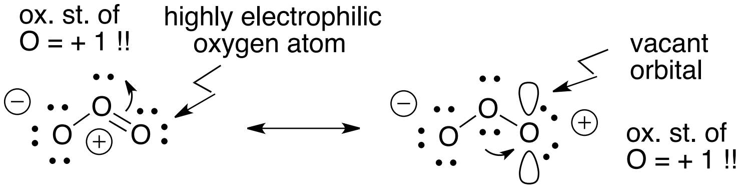


(racemic)
notice *anti* addition



Lecture 13: Ozonolysis of Alkenes

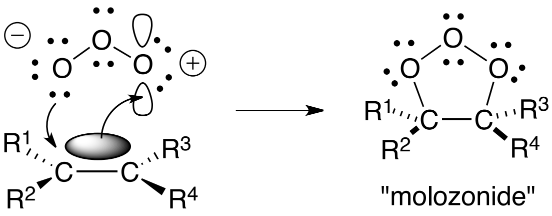
Reactions of alkenes with agents that incorporate an electronegative atom in a high oxidation state: the case of ozone, O_3



preferred resonance struct.

less accurate res. struct.

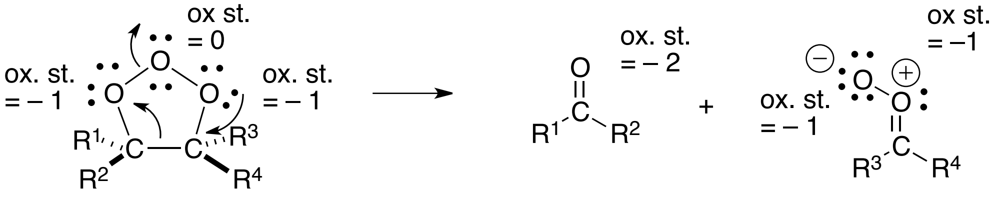
Concerted addition of ozone to olefins (easier to visualize from the poorer resonance structure):



note: elemental oxygen, O_2, can (and does) react with alkenes, but in a manner that will be discussed in more advanced courses

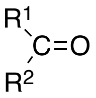
Concerted reaction: one in which two or more bonds are formed / broken simultaneously, through an orderly movement of multiple electron pairs, leading to a product through a single chemical event (= without the intervention of reaction intermediates)

Instability of molozonides: fast breakdown of the molozonide structure driven by the tendency of the O atoms to become reduced to a more favorable oxidation state



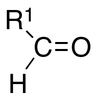
Carbonyl group: an atomic arrangement consisting of C atom doubly bonded to an O atom (i.e., a C=O system)

Carbonyl compound: a substance that incorporates a carbonyl group:

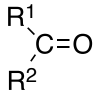


a carbonyl compound: R^1 and R^2 can be anything (H, alkyl, halogen, OH ...)

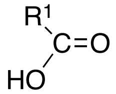
Major types of carbonyl compounds: aldehydes, ketones, carboxylic acids:



aldehyde: R^1 is an H or an alkyl group

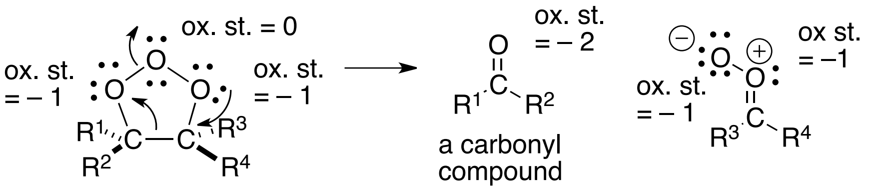


a ketone: R^1 and R^2 are both alkyl groups



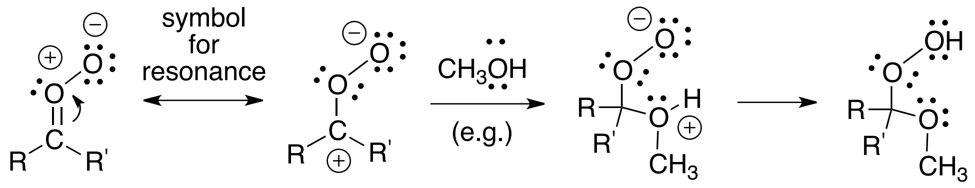
a carboxylic acid: R^1 is H or alkyl

Facile breakup of the molozonide, driven by the tendency of the O atom at the o.s of 0 to become reduced to the o.s. of – 1: formation of a carbonyl compound (aldehyde, ketone, …) and a carbonyl oxide

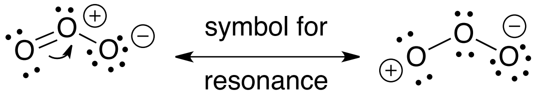


a "carbonyl oxide" -- highly reactive and electronically similar to ozone: can undergo cycloaddition to π systems

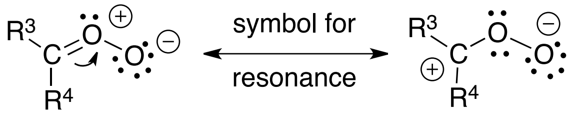
Carbonyl oxides as reactive electrophiles that exhibit "carbocation-like" reactivity; e.g.:



Similarity between the electronic configuration of a carbonyl oxide and that of ozone, and probable tendency of a carbonyl oxide to react with π systems, just like O_3 does

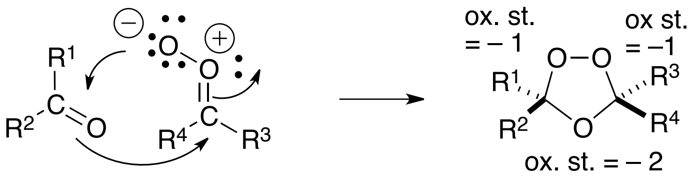


ozone



carbonyl oxide

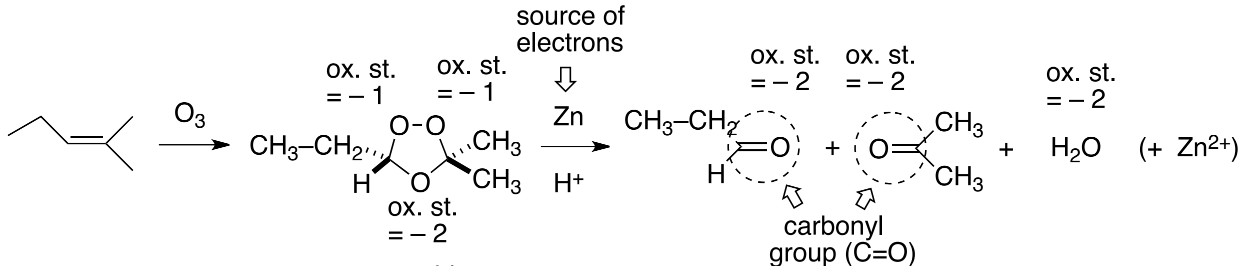
Facile recombination of the fragments resulting from the break-up of the molozonide: reaction of the carbonyl oxide with the carbonyl piece leading to an ozonide



ozonide: end product of the reaction of an alkene with ozone

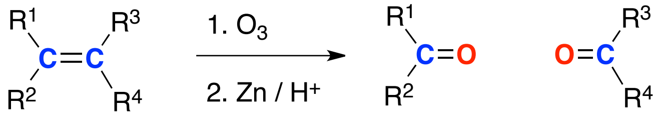
Tendency of the O atoms at the o.s. of – 1 to become reduced to the o.s. of –2

Reaction of ozonides with metallic zinc (source of electrons) and acid: formation of aldehydes and / or ketones (no mechanism for this reaction – yet…). E.g.:



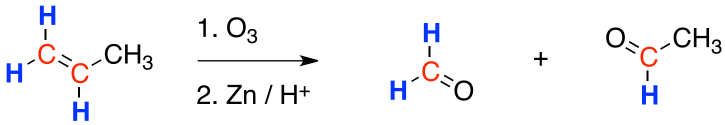
ozonide

Description of the overall process detailed above as the ozonolysis (= breakdown using ozone) of alkenes: the doubly bonded carbon atoms of the initial olefin separate, giving rise to two new molecules:

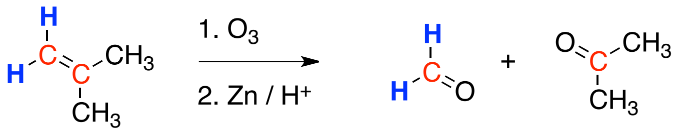


Examples of ozonolysis reactions

- ozonolysis of acyclic (=non-cyclic) alkenes:

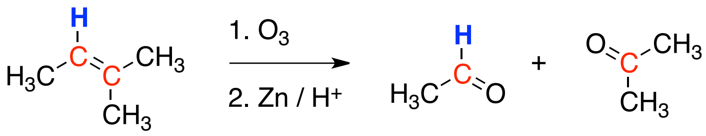


formaldehyde acetaldehyde

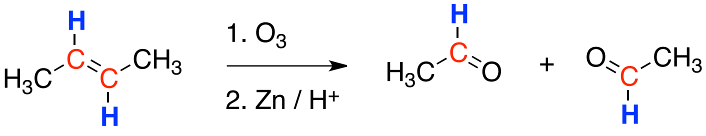


acetone: a ketone

formaldehyde

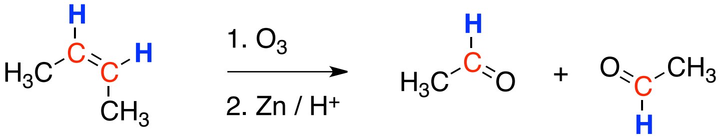


a ketone



trans-2-butene

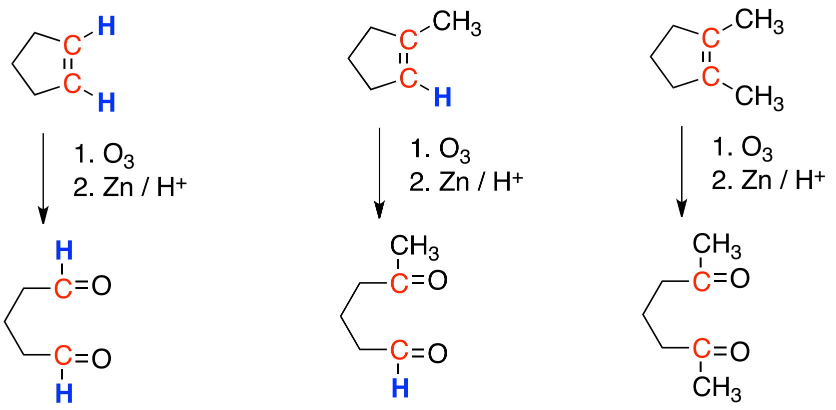
two molecules of acetaldehyde



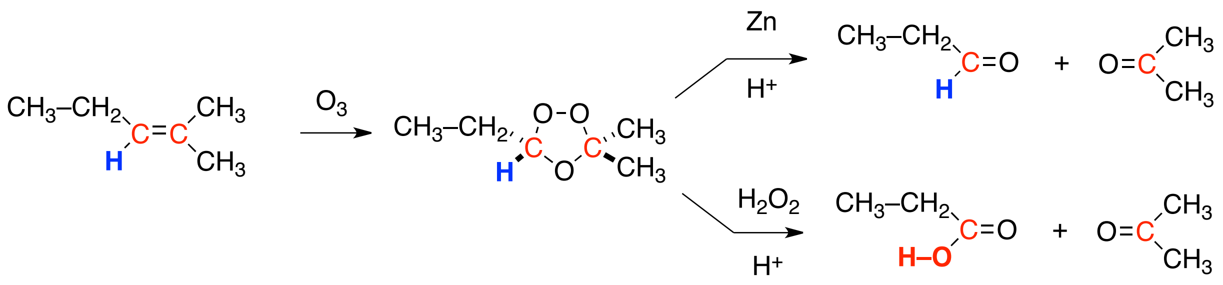
same products: ozonolysis does not distinguish between cis & trans alkene isomers

cis-2-butene

- ozonolysis of cyclic alkenes:

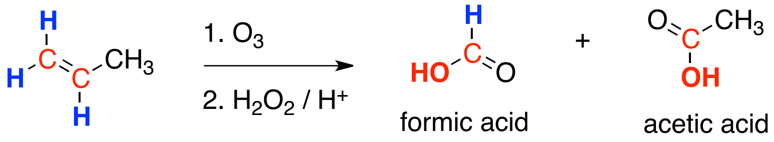


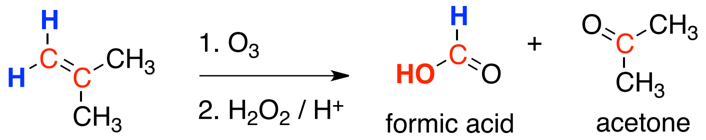
A twist on the ozonolysis reaction: fragments of the initial alkene that would be obtained as aldehydes if the ozonide were treated with Zn/H^+, emerge as carboxylic acids if the ozonide is treated with H_2O_2 and acid. Fragments that would emerge as ketones are still obtained as ketones (no mechanism yet for this reaction). Example:

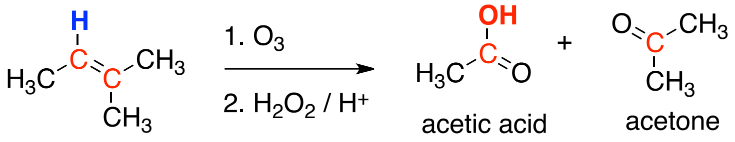


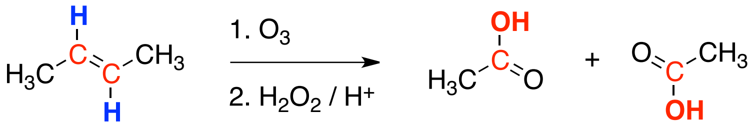
Further examples of ozonolysis reactions that involve treatment of the ozonide with H_2O_2 / H^+:

- ozonolysis of acyclic (=non-cyclic) alkenes:



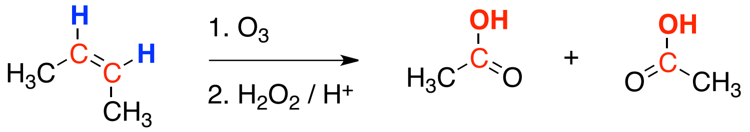






trans-2-butene

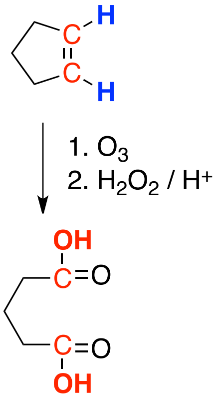
two molecules of acetic acid

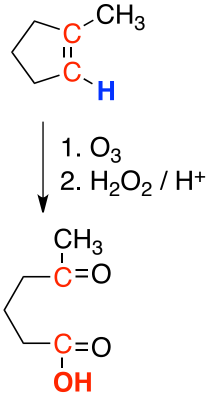


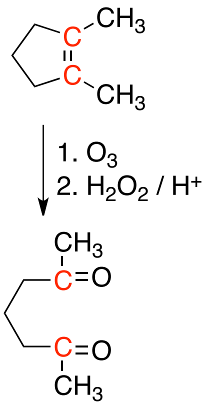
cis-2-butene

still two molecules of acetic acid:
ozonolysis does not distinguish between
cis & trans alkene isomers

- ozonolysis of cyclic alkenes:



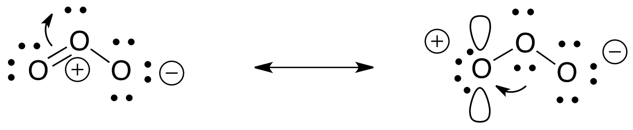




Lecture 14: Osmylation of Alkenes

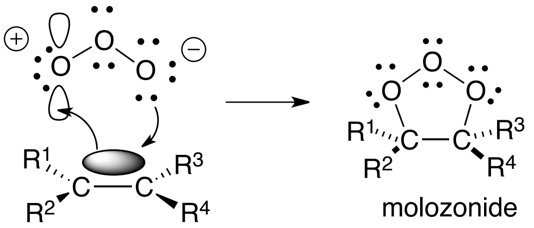
"Cycloaddition:" an addition reaction that forms a new ring, such as the formation of a molozonide from ozone + an alkene (or the formation of a halonium ion from a halogen molecule + an alkene)

Ozone as a "1,3-dipole:"



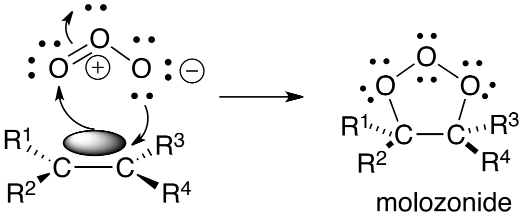
1,3-dipole!

The addition of O_3 to an alkene as a concerted "1,3-dipolar cycloaddition:"



1,3-dipolar cycloaddtion

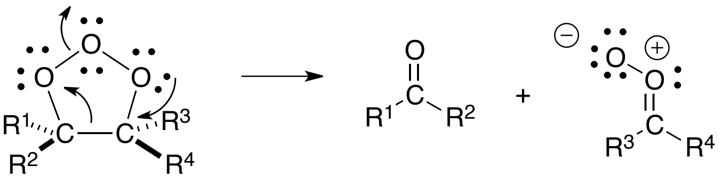
Drawing the above mechanism using the more accurate resonance form of O_3:



Pericyclic reaction: one that can be described as a "circular" movement of electrons

The above 1,3-dipolar cycloaddition as a *syn* addition reactions: new bonds form from the same face of the π system"

The breakup of the molozonide as an inverse 1,3-dipolar cycloaddition; i.e., a cycloreversion:



Concerted nature (multiple bonds broken/formed simultaneously) of the above cycloaddition and cycloreversion reactions

note: examples of concerted / non concerted reactions seen in CHEM 203 *concerted reactions*

- the formation of a halonium ion from an olefin + a molecular halogen
- the formation of a molozonide upon reaction of ozone with an alkene
- the reverse cycloaddition (=cycloreversion) of a molozonide to a carbonyl oxide + a carbonyl compound
- the formation of an ozonide upon reaction of a carbonyl oxide with a carbonyl compound

non-concerted reactions

- the addition of HBr to alkenes (first a carbocation forms, then Br^- adds to the carbocation)
- the hydration of alkenes (first a carbocation forms, then H_2O adds to the carbocation)
- the halogenation of alkenes (first a halonium ion forms, then a halide ion reacts with it)

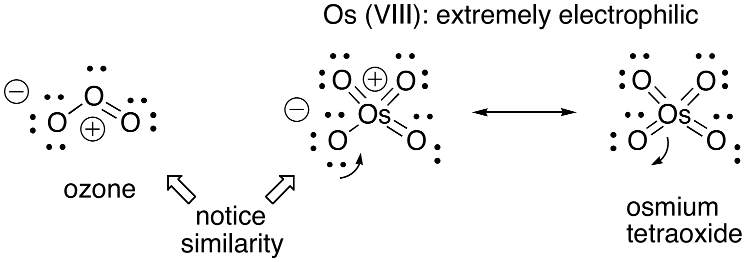
Absence of rearrangements during the ozonolysis of alkenes (= no cationic intermediates)

Peroxide: a molecule incorporating an O–O linkage

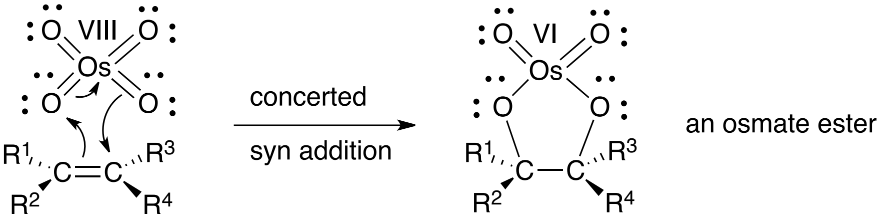
Instability and explosive properties of peroxidic compounds, including ozonides, due to the presence of O atoms at the oxidation state of –1

Agents containing metals in a high oxidation state: MnO_4^- (+7), RuO_4, OsO_4 (both +8), …

Analogy between the electronic distribution in the molecule of O_3 and in that of OsO_4:



Ability of OsO_4 to add to olefinic π bonds through a concerted mechanism similar to a 1,3-dipolar cycloaddition:



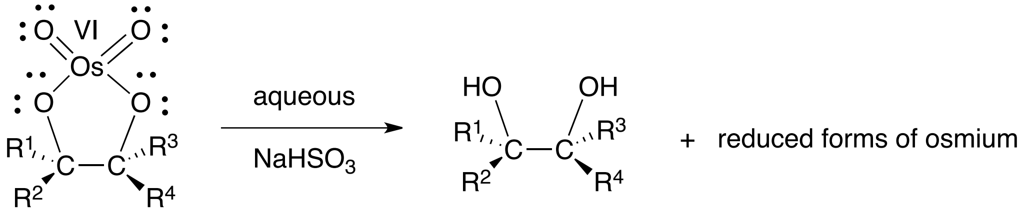
Driving force for the above reaction: reduction of Os(VIII) to Os(VI):

Strictly *syn* course of the addition of OsO_4 (but also of MnO_4^- and RuO_4) to alkenes

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

Stable character of osmate esters (unlike molozonides …)

Treatment of osmate esters with aqueous $NaHSO_3$ leading to the release of Os and formation of vicinal diols (also described as 1,2-diols. Diol = double alcohol):



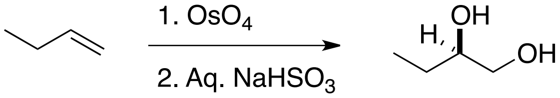
osmate ester
(stable)

a 1,2 diol
(vicinal diol)

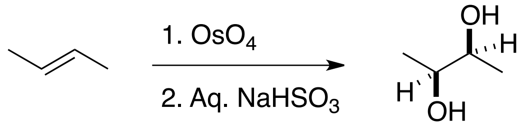
Dihydroxylation (osmylation) reaction: the conversion of an alkene to a 1,2-diol by reaction with OsO_4 followed by reduction of the intermediate osmate ester, e.g., with $NaHSO_3$

Strictly *syn* course of the dihydroxylation (osmylation) reaction

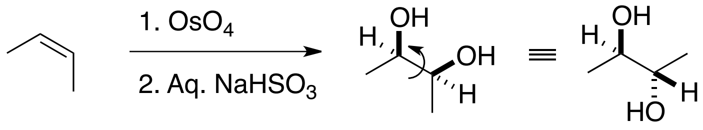
Representative examples of osmylation reactions:



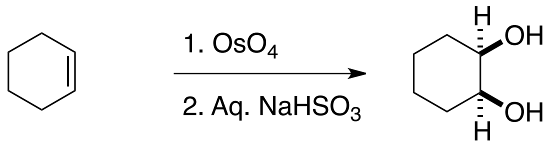
(chiral: formed as the racemate)



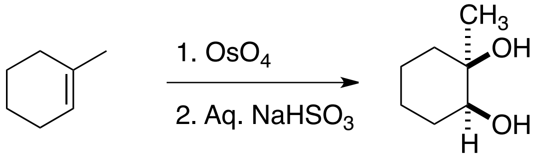
(chiral: formed as the racemate)



(meso compound: achiral)



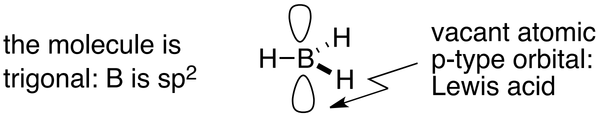
(meso compound: achiral)



(chiral: formed as the racemate)

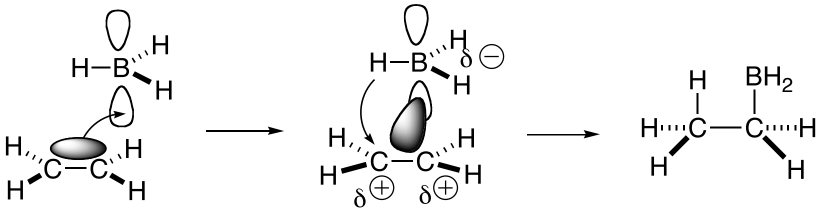
Lecture 15: Hydroboration of Alkenes

Chemically and technologically important reactions of alkenes initiated by the interaction of the π system with molecules containing a strongly Lewis acidic site: the case of borane, BH_3
Strongly Lewis acidic character of borane, BH_3



Probable initial interaction of the π electrons of the alkene with the vacant p orbital of BH_3

Development of positive character on the C atoms of the alkene as the BH_3 molecule draws electronic density away from the π system, resulting in the ultimate transfer of one of the H atoms (as a formal hydride) from boron to carbon:



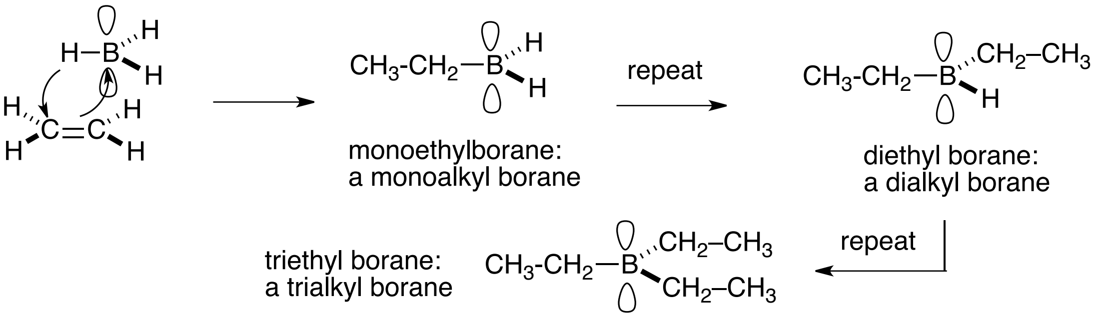
Hydroboration reaction: the addition of a B–H bond across the π system of an alkene

Alkylboranes or organoboranes: compounds containing a C–B bond

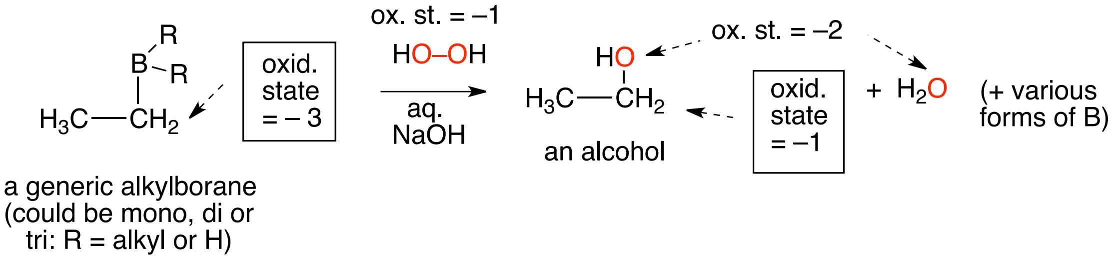
Rich chemistry and technological importance of alkylboranes

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

E.g., with ethylene:



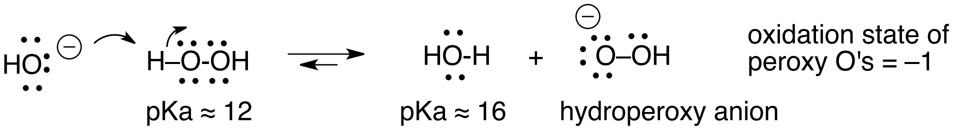
Important reaction of alkylboranes: oxidation of the C–B bond with H_2O_2 / aq. NaOH leading to the formation of alcohols



Description of the overall process shown above as the hydroboration / oxidation of alkenes

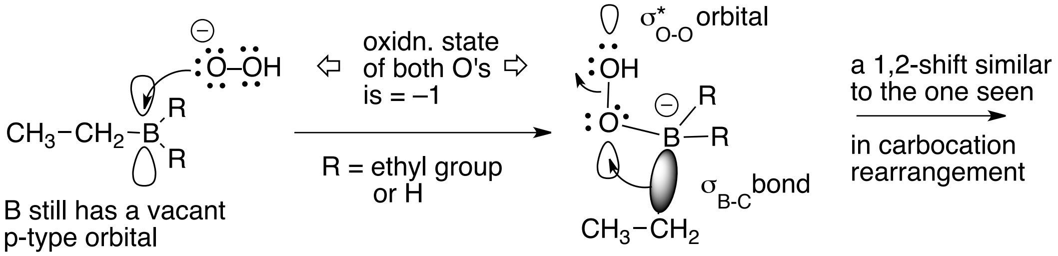
General mechanism of the oxidation of boranes with H_2O_2 / NaOH (aq.)

- deprotonation of H_2O_2 and formation of the hydroperoxy anion:



Then . . .

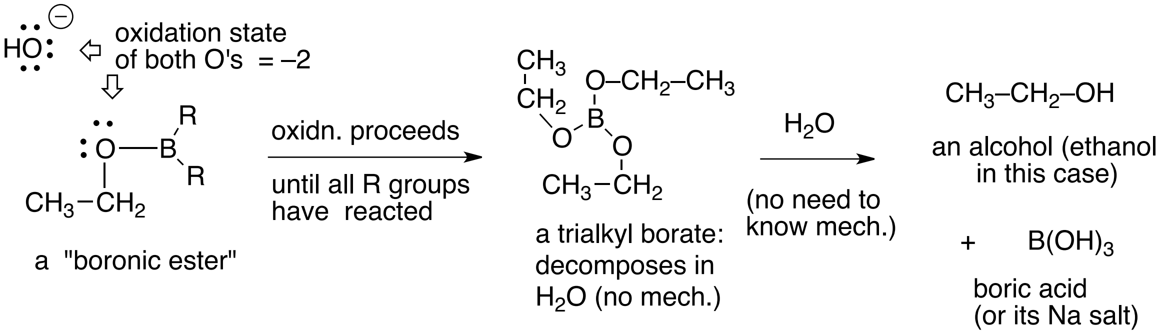
- significant nucleophilicity of the hydroperoxy anion and facile addition thereof to the B atom of an organoborane



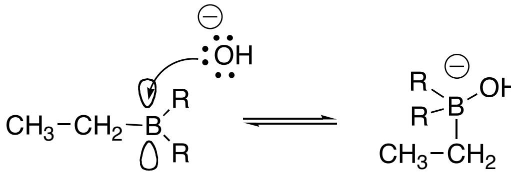
The oxygen atoms in the peroxy linkage "want" electrons, because they strive to attain the oxidation state of – 2. Additional electrons can be accommodated into the O–O σ* orbital.

Hyperconjugative interactions between the C–B σ bond and the O–O σ* orbital begin to weaken the O–O σ bond and the terminal OH group begins to depart by taking the pair of electrons connecting it to the internal O atom (i.e., the O–O σ electrons) with it.

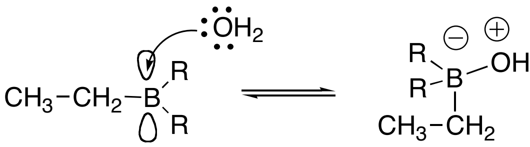
The departure of the OH group as HO^- would leave a highly unfavorable (+) charge on the O atom attached to B. An alkyl group migration occurring in concert with OH departure avoids formation of a highly energetic "O^+". Both O atoms thus reach the more favorable oxidation state of –2.



note: the alkylborane can certainly combine with OH^{-} or with water, both of which are Lewis basic and nucleophilic:



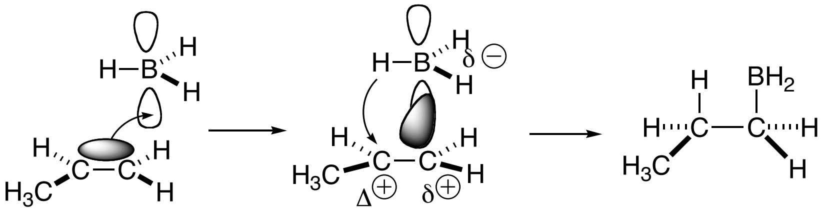
A



B

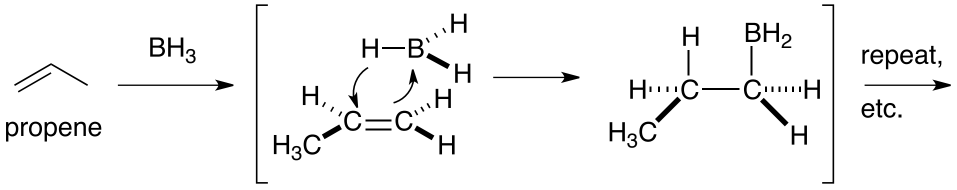
however, such events are non-productive, in the sense that they promote no further reaction. Then, the resulting complexes **A** and **B** will simply equilibrate back with the staring alkylborane. Only when HOO^{-} connects to the B atom will the complex undergo further chemical change (oxidation to an alcohol, as seen above)

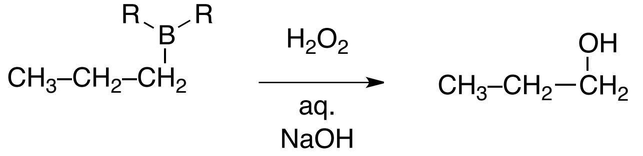
Regiochemical course of the hydroboration reaction of unsymmetrical olefins: the H atom of the H–B bond connects to the more highly substituted C atom of the alkene; the B atom, to the less highly substituted C:



as the interaction between the B atom and the π 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 BH_3.

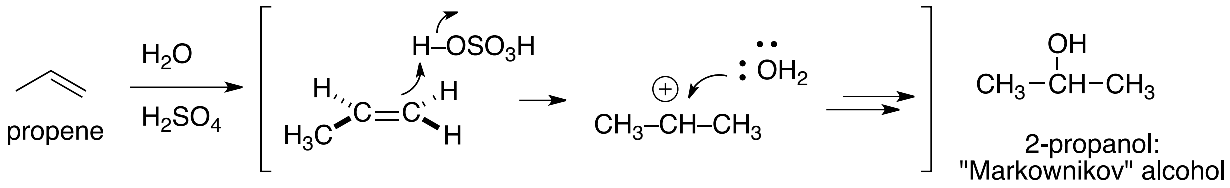
Interesting consequence of the hydroboration / oxidation of unsymmetrical olefins: formation of "anti-Markownikov" alcohols. E.g.:





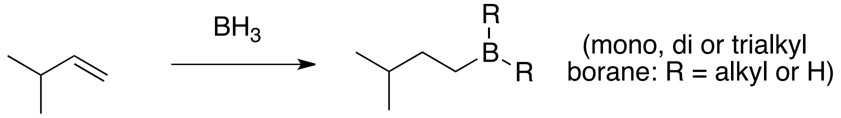
1-propanol: an
"anti-Markownikov"
alcohol

WHEREAS



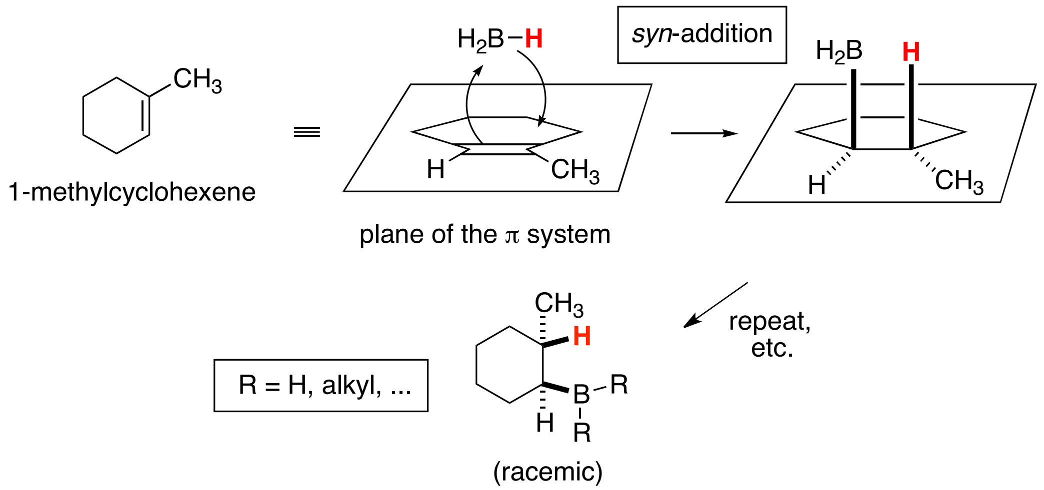
The hydroboration – oxidation process as a net "anti-Markownikov" addition of water to an alkene (i.e. the regioselectivity is opposite that of an acid-catalyzed hydration reaction)

Absence of rearrangements in the hydroboration reaction (no carbocation intermediates are formed); e.g.:



Stereochemical aspects of the hydroboration/oxidation reaction: the question of *syn* vs. *anti* addition of BH_3 to an alkene

e.g., with a more complex olefins such as 1-methylcyclohexene:



The hydroboration reaction as a strictly *syn* addition: B and H atoms must necessarily add from the same face of the π system.

Stereochemical aspects of the oxidation of alkylboranes to alcohols with H_2O_2 / aq. NaOH

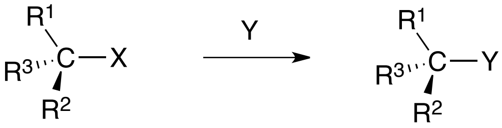
The oxidation of boranes is a substitution reaction

General pattern of a substitution reaction (no mechanism implied):

C—X + Y —> C—Y + X

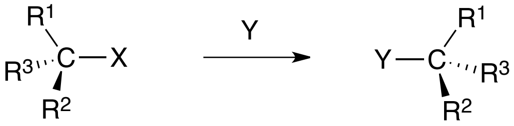
Possible stereochemical outcomes of a generic substitution reaction:

retention of configuration: the substituting group, Y, enters with the *same* orientation as the departing group, X:



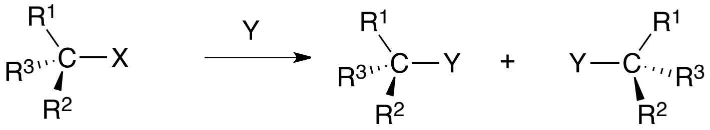
product resulting through **retention of configuration**

inversion of configuration: the substituting group, Y, enters with the *opposite* orientation relative to the departing group, X:



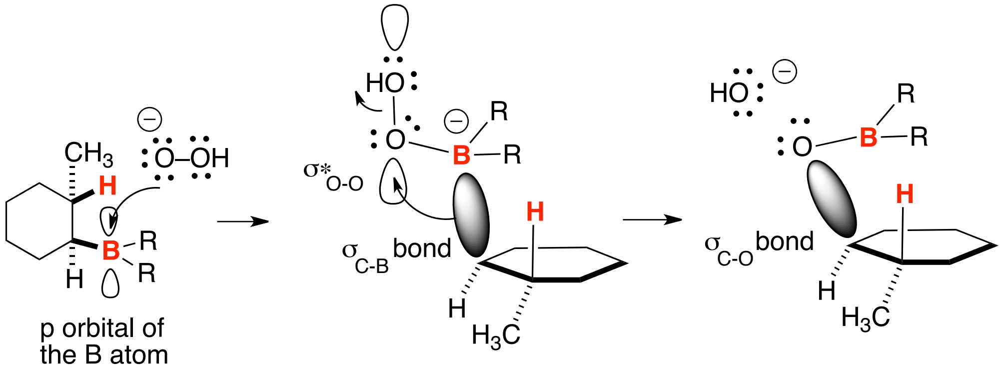
product resulting through **inversion of configuration**

loss of configuration: the substituting group, Y, enters partly with the same orientation and partly with the opposite orientation relative to the departing group, X

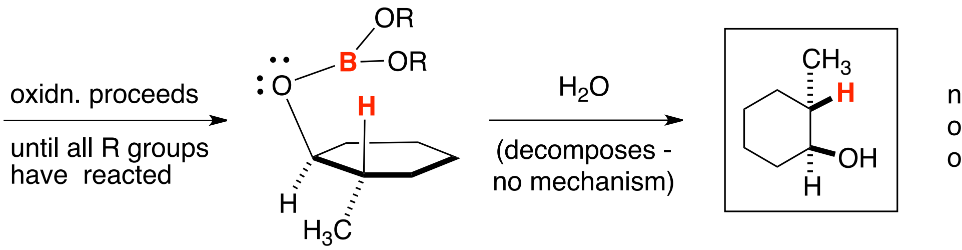


products resulting through **loss of configuration**

Strict **retention of configuration** observed during the oxidation of boranes, as a result of mechanistic constraints:



then

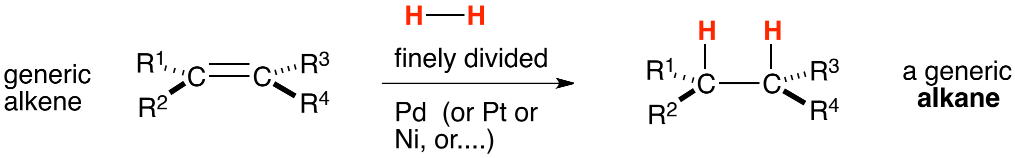


net *syn* addition of H_2O to the olefinic π bond

The hydroboration – oxidation process as a net "anti-Markownikov" *syn* addition of water to an alkene (i.e. the regioselectivity is opposite that of an acid-catalyzed hydration reaction)

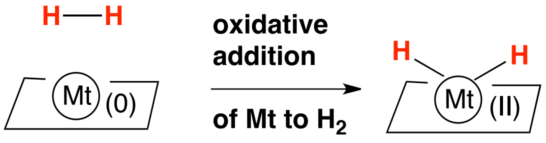
Lecture 16: Hydrogenation of Alkenes

Hydrogenation (= saturation) of olefins in the presence of finely divided transition metal catalysts (Ni, Pd, Pt, Rh, Ru ...):



The hydrogenation of alkenes as a method to form alkanes

Ability of elemental metals such as Ni, Pd, Pt, etc., to react with H_2 through **oxidative addition**:



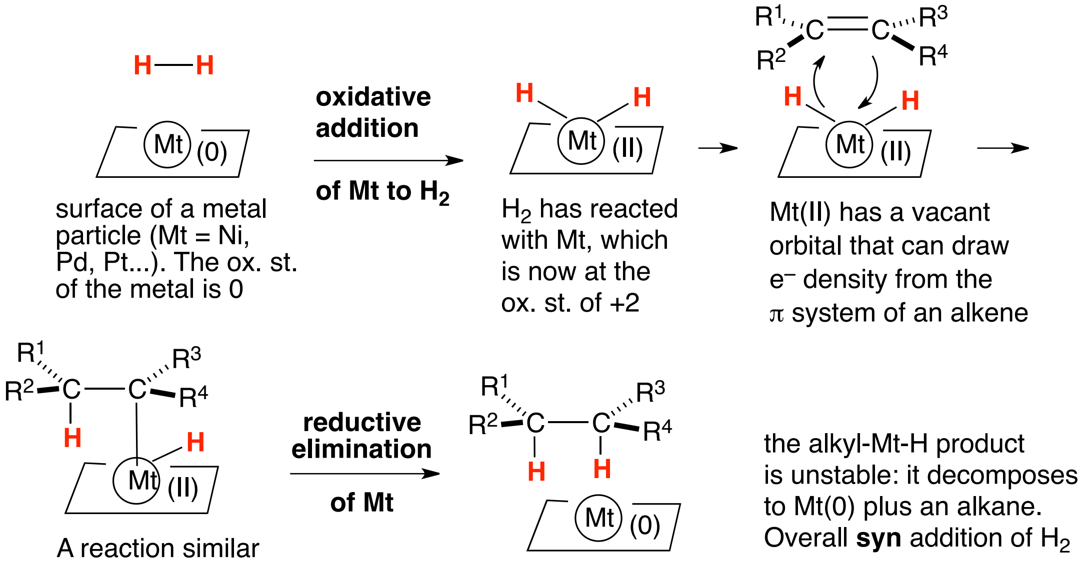
a metal atom on the surface of a microscopic metal particle or of an appropriate support (Mt = Ni, Pd, Pt...). The oxidn. state of the metal is 0

a metal hydride

H_2 has reacted with Mt, which is now at the ox. st. of +2

Greater electronegativity of H relative to most metals

Mechanistic outline of the hydrogenation reaction:



surface of a metal particle (Mt = Ni, Pd, Pt...). The ox. st. of the metal is 0

H_2 has reacted with Mt, which is now at the ox. st. of +2

Mt(II) has a vacant orbital that can draw e⁻ density from the π system of an alkene

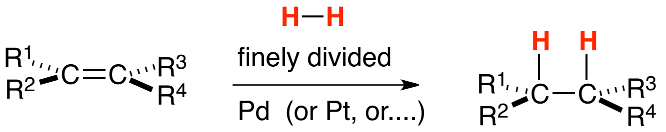
A reaction similar to a hydroboration takes place

the alkyl-Mt-H product is unstable: it decomposes to Mt(0) plus an alkane. Overall **syn** addition of H_2

Strictly **syn** course of the hydrogenation reaction

Technological importance of the hydrogenation of alkenes

Principle: the hydrogenation reaction is an exothermic process (ΔH <0):



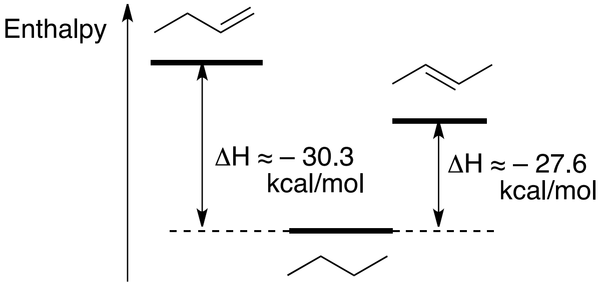
bonds broken (ΔH, kcal/mol)		bonds formed (ΔH, kcal/mol)
C=C π bond	ca. 60	2 C–H bonds @ ca. 95 ea.
H–H	ca. 100	
overall	**+ 160**	**– 190**

$$\Delta H_{react} \approx -30 \text{ kcal/mol}$$

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

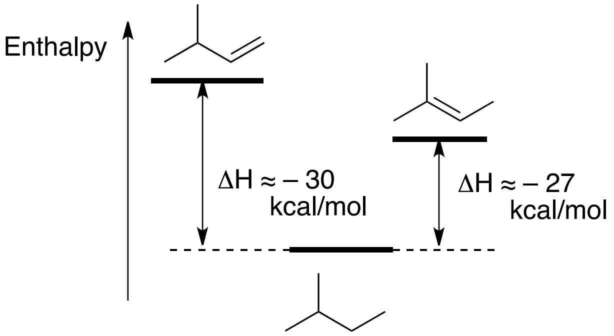
a. the stability of an alkene increases with increasing substitution around the C=C system; i.e., a more highly substituted alkene is more stable (=less energetic) than a less highly substituted isomer

Example 1: the hydrogenation of positional isomers of butene to butane:



trans-2-butene contains almost 3 kcal / mol less energy than 1-butene: it is the more stable isomer

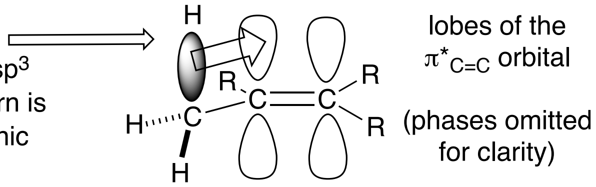
Example 2: the hydrogenation of positional isomers of methylbutenes to 2-methylbutane:



the olefinic linkage in 2-methyl-2-butene is more highly substituted: a stabilization of ca. 3 kcal / mol results

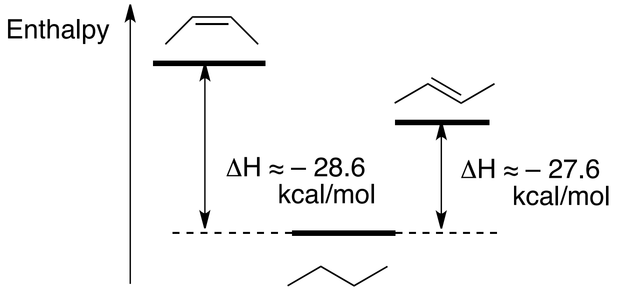
Putative origin of the greater stability of more highly substituted alkenes relative to less highly substituted isomers: hyperconjugative interactions between σ_{C-H} and $\pi^*_{C=C}$ orbitals:

"allylic hydrogens"
those bound to an sp^3
C atom, which in turn is
attached to an olefinic
sp^2-carbon atom



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

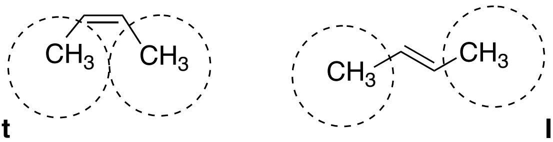
Example: the hydrogenation of *cis*- and *trans*-2-butenes to butane:



trans-2-butene contains
1 kcal / mol less energy
than cis-2-butene: it is
the more stable isomer

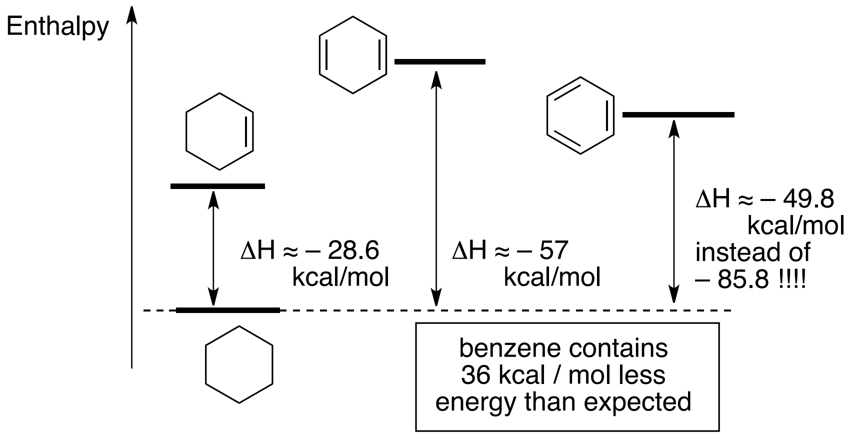
Putative origin of the greater stability of trans-alkenes relative to their cis isomers : absence of steric interactions between alkyl groups:

cis-isomer: electronic clouds around the CH_3 groups are compressed against each other:
more energetic arrangement



trans-isomer: electronic clouds around the CH_3 groups are well away from each other:
less energetic arrangement

c. benzene is unusually stable.

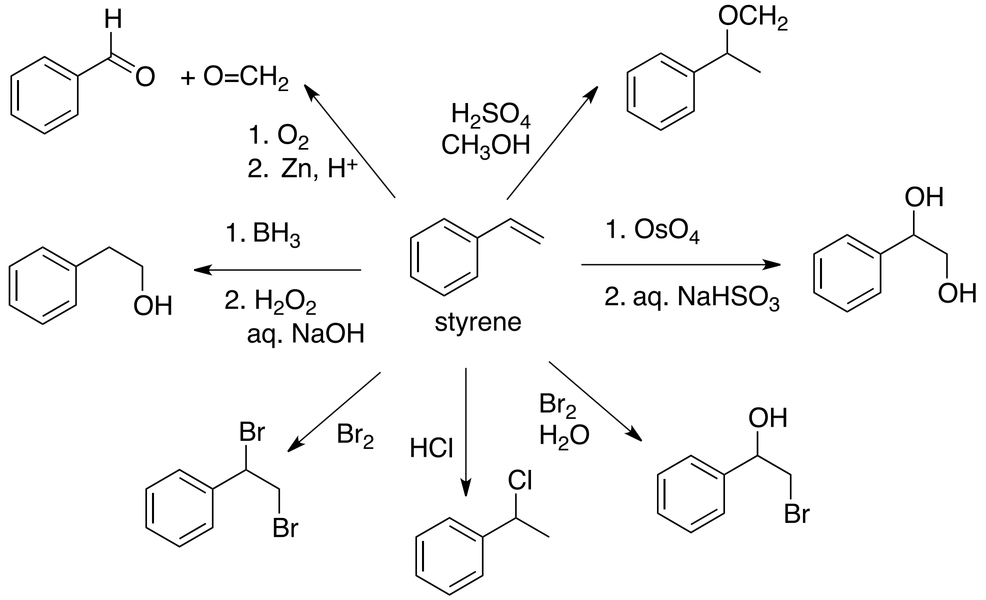


benzene contains
36 kcal / mol less
energy than expected

"Aromaticity" of benzene and of related compounds possessing 6 π electrons delocalized within a ring

Inertness of the "olefinic" bonds of benzene (and related compounds) to the various reagents encountered in CHEM 203

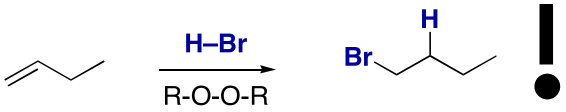
Examples:



the double bonds of benzene do not react with any of the above reagents !!

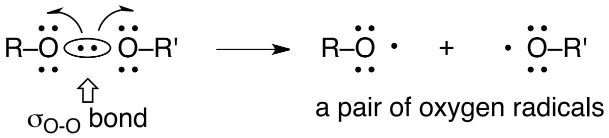
Lecture 17: Radical Addition to Alkenes - I

Addition of HBr to olefins in the presence of alkyl peroxides (**but not hydrogen peroxide**): anti-Markownikov addition

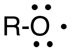


Weakness of the peroxidic linkage in alkyl peroxides (ΔH_{diss} RO–OR' ≈ 40 kcal/mol) and facile homolytic dissociation thereof at or near room temperature

Use of one-barbed arrows to indicate the movement of individual electrons when writing mechanisms, e.g.:



Radicals: species in which an atom possesses a complement of only 7 valence electrons and a formal charge of zero:



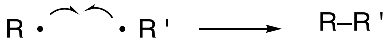
is an oxygen radical, in the sense that the O atom has only 7 valence electrons

Oxygen, carbon, halogen – centered radicals

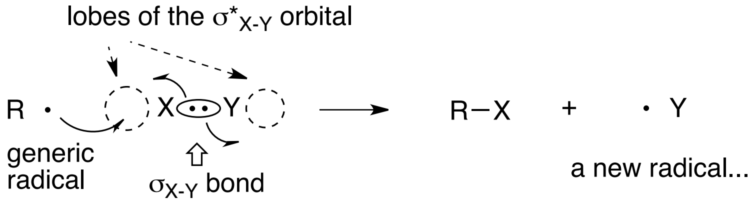
Radicals as extremely reactive, electron-deficient species that tend to react in such a way as to re-establish an octet of electrons around the electron-deficient atom

Possible ways in which a generic radical, $R^{\bullet}$, can reacquire an electronic octet:

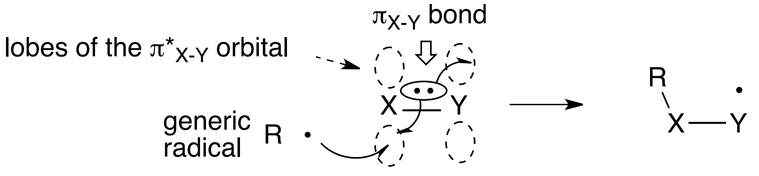
(i) Recombination with another radical (uninteresting case); e.g.:



(ii) Atom transfer reaction; e.g.:



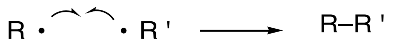
(iii) Addition to a π system, especially the π system of an olefin; e.g.:



Principle: radicals tend to undergo exothermic ($\Delta H < 0$) reactions.

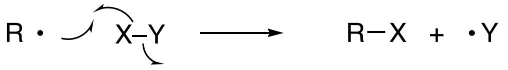
Consequence: processes through which radicals can reacquire a complete Lewis octet, such as atom transfer reactions and addition to π systems, occur especially readily if $\Delta H_{react} < 0$

- **recombination:**



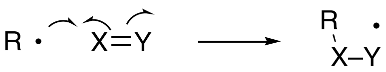
this reaction is necessarily exothermic ($\Delta H < 0$)

- **atom-transfer:**



the reaction will proceed substantially only if $\Delta H < 0$

- **addition to π-bond:**

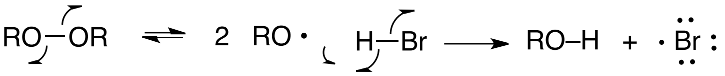


the reaction will proceed substantially only if $\Delta H < 0$

Principle: the ΔH of a reaction involving radicals can be estimated by determining the enthalpic balance between bonds broken and bonds formed (see homework 1)

Note: an extensive tabulation of bond dissociation enthalpies is available on the Internet as well as in your book

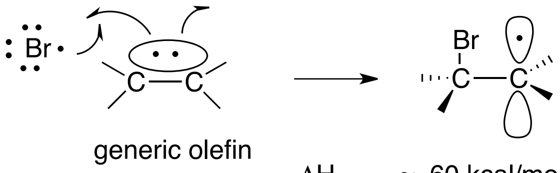
Thermodynamically favorable transfer of H from H–Br to an oxygen radical created by the homolytic dissociation of an **alkyl peroxide** (**NOT** H_2O_2: the O–O bond in H_2O_2 is much stronger than the the O–O bond in an alkyl peroxide):



$\Delta H_{H\text{–}Br} = 87$ kcal/mol
$\Delta H_{H\text{–}O} \approx 110$ kcal/mol

$\mathbf{\Delta H_{tot} \approx -23}$ **kcal/mol**

Thermodynamically favorable addition of Br• to the π system of an olefin — a special case of atom-transfer reaction — leading to the formation of a carbon radical:



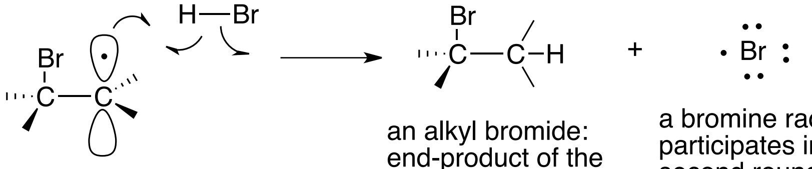
a carbon radical: the lone electron resides in a p-type atomic orbital. The electron-deficient C atom is essentially a trigonal planar sp^2 hybrid

$\Delta H_{C=C\ \pi} \approx 60$ kcal/mol
$\Delta H_{C\text{–}Br} \approx 70$ kcal/mol

$\Delta H_{tot} \approx -10$ kcal/mol

Nearly planar geometry of carbon radicals (sp^2 hybridization)

Thermodynamically favorable transfer of an H atom from H–Br to the carbon radical above:



an alkyl bromide: end-product of the reaction

a bromine radical: participates in a second round of the reaction ...

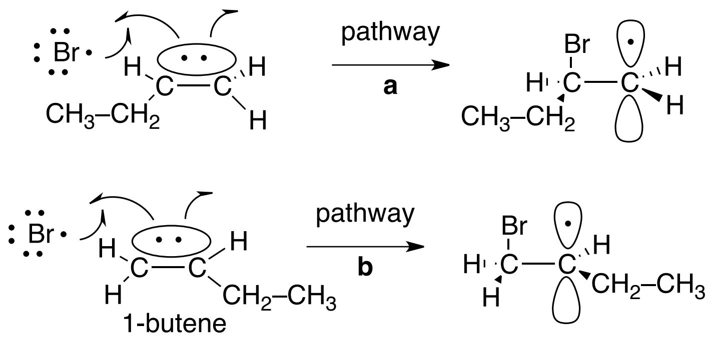
ΔH_{H-Br} = 87 kcal/mol
ΔH_{C-H} ≈ 95 kcal/mol

ΔH_{tot} ≈ –8 kcal/mol

Principle: the Br • regenerated in the course of the above step may add to an intact molecule of olefin, producing a carbon radical that can react with an intact molecule of HBr, thus creating more Br •, which sustains the reaction cycle. The process will continue until all reactants (olefin + HBr) are consumed.

Principle: like carbocations, carbon radicals are electron-deficient, so they are stabilized by hyperconjugative forces

Possible modes of addition of Br• to the π system of an unsymmetrical olefin, e.g., 1-butene:

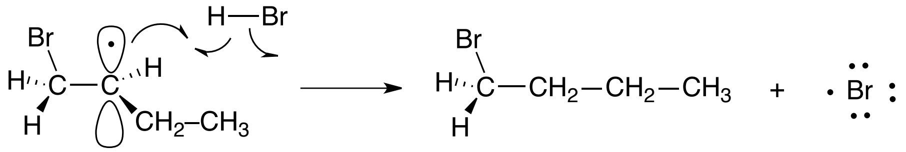


primary radical stabilized by 1 hyperconjugative interaction with C–H bonds: less highly stabilized
forms at a slower rate

secondary radical stabilized by 4 hyperconjugative interactions with C–H bonds: more highly stabilized
forms at a faster rate

just as in the case of carbocations, reaction pathway **b** will be dominant

Thermodynamically favorable H-atom transfer reaction from an intact molecule of HBr to the carbon radical generated via reaction pathway **a** above: regeneration of Br• :



"anti-Markownikov" alkyl bromide

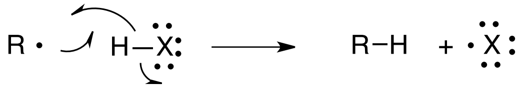
ΔH_{H-Br} = 87 kcal/mol
ΔH_{C-H} ≈ 95 kcal/mol

ΔH_{tot} ≈ –8 kcal/mol

Extremely fast rate of addition of HBr to olefins under radical conditions (all exothermic step) compared to ionic addition processes (endothermic formation of carbocations)

Failure of H–F, H–Cl, H–I to undergo anti-Markownikov addition to olefins under radical conditions, due to:

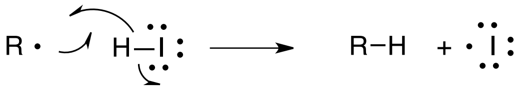
for H–F and H–Cl: thermodynamically unfavorable transfer of the H atom from the H–X bond and consequent inaccessibility of X$^{\bullet}$ under the above conditions (plus other reasons not covered in CHEM 203):



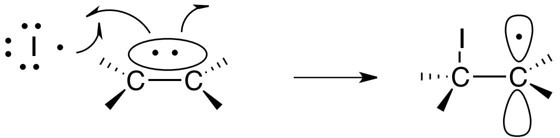
$\Delta H_{H-F} \approx$ 125 kcal/mol
$\Delta H_{H-Cl} \approx$ 110 kcal/mol
$\Delta H_{C-H} \approx$ 95 kcal/mol

unfavorable ! $\boxed{\Delta H_{tot} \approx +15 \text{ to } +30 \text{ kcal/mol}}$

for H–I: thermodynamically unfavorable addition of I$^{\bullet}$ to the π bond of an olefin:

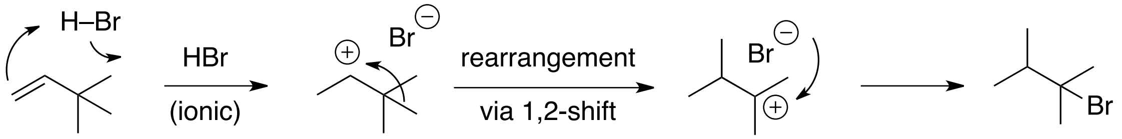


$\Delta H_{H-I} \approx$ 70 kcal/mol
$\Delta H_{C-H} \approx$ 95 kcal/mol
$\boxed{\Delta H_{tot} \approx -25 \text{ kcal/mol}}$ **OK, BUT...**

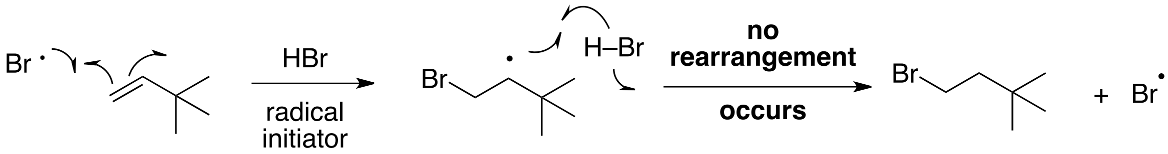


$\Delta H_{C=C\ \pi} \approx$ 60 kcal/mol
$\Delta H_{C-I} \approx$ 50 kcal/mol
$\boxed{\Delta H_{tot} \approx +10 \text{ kcal/mol}}$ **unfavorable !**

Principle: unlike carbocations, radicals **do not** undergo rearrangement by the 1,2-shift mechanism seen earlier; e.g.:



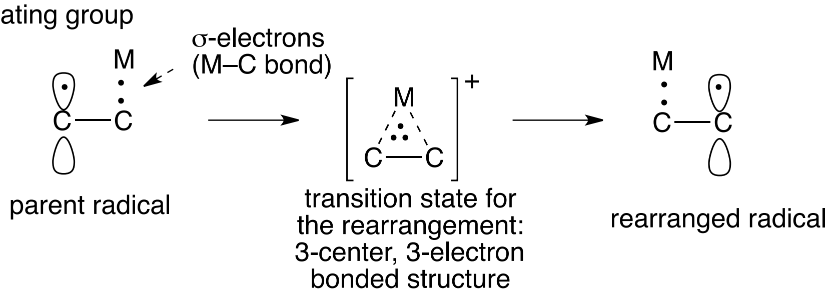
BUT

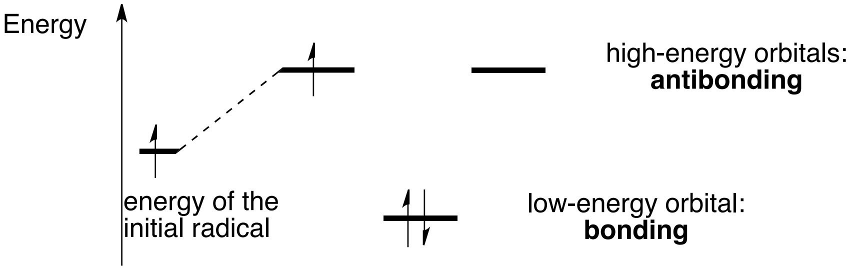


Note: the reason why radicals do not rearrange by the 1,2-shift mechanism seen earlier for carbocations becomes apparent only through a detailed analysis of the migration process based on MO theory.

This aspect of radical chemistry is beyond the scope of CHEM 203, but on the basis of what was said in class in response to one of your questions (see notes of Sept 25), one must conclude that a hypothetical 1,2-shift of a radical would require the promotion of the lone electron into a much more energetic antibonding orbital. The energy required is unavailable to the system under ordinary conditions:

M = migrating group

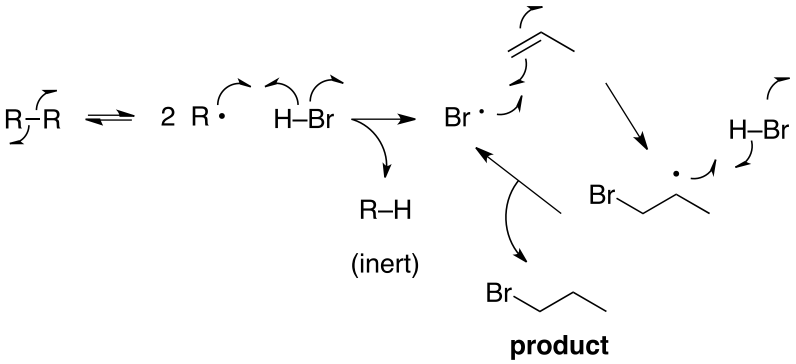




Lecture 18: Radical Additions to Alkenes - II

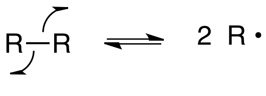
Terminology of radical chemistry

Radical chain reaction: a radical process like the "anti-Markownikov" addition of HBr to alkenes, which becomes self-sustaining through the constant regeneration of reactive radical species:

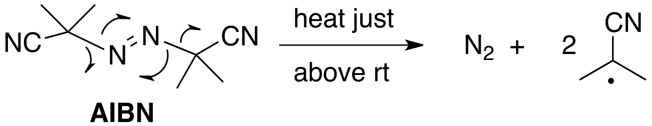


Radical initiators: molecules like peroxides (and many other compounds), that possess a weak bond (ΔH_{diss} < 50 kcal/mol), and that consequently can easily dissociate into a pair of radicals, thereby setting radical chain processes in motion:

a generic radical initiator
(many types known): the R–R bond
is weak (ΔH_{diss} < 50 kcal/mol)



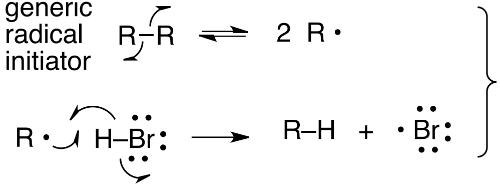
Hazardous properties of peroxides and example of a commonly used radical initiator that is safer to use: **A**zobis**I**so**B**utyro**N**itrile (AIBN)



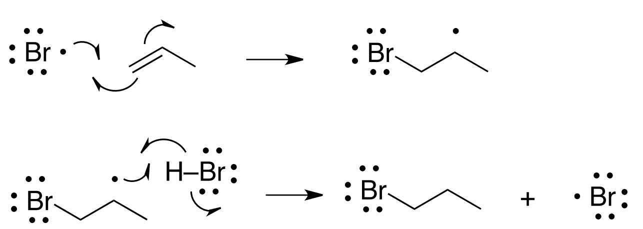
AIBN

Initiation, propagation, and termination steps of a radical chain process:

e.g. in the anti-Markownikov addition of HBr to propene:

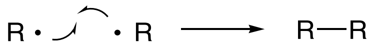


initiation steps: those that lead to the initial formation of the radical species responsible for the conversion of the substrate into the product (Br• in the present case)

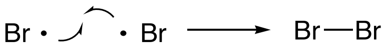


propagation steps: those that lead to the regeneration of the radical species responsible for the conversion of the substrate into the product (Br• in this case)

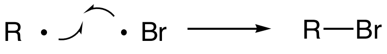
Radical termination steps: recombination events that interrupt the radical chain reaction. For example, the following termination steps could theoretically occur during the above reaction:



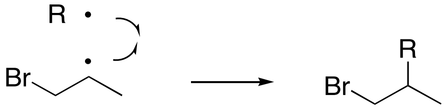
hypothetical recombination of radical fragments coming from the initiator



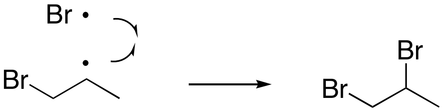
hypothetical recombination of Br radicals leading to the formation of Br_2



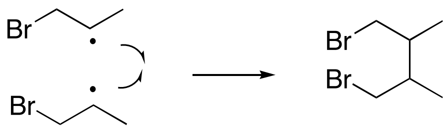
hypothetical recombination of a radical fragment from the initiator with Br •



hypothetical recombination of a radical fragment from the initiator with the carbon radical involved in product formation



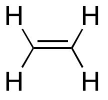
hypothetical recombination of a Br radical with the carbon radical involved in product formation



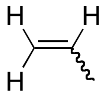
hypothetical recombination of a pair of carbon radicals involved in product formation

Principle: in a radical chain process, the number of radicals instantly present in the reaction medium is very small, so recombination events are statistically unlikely; i.e., insignificant amounts of radical recombination products are typically obtained from such reactions.

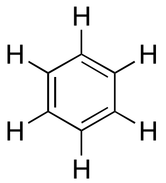
Vinyl group, phenyl group: the alkyl groups originating from ethylene and benzene, respectively:



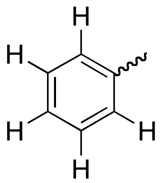
ethylene



vinyl group

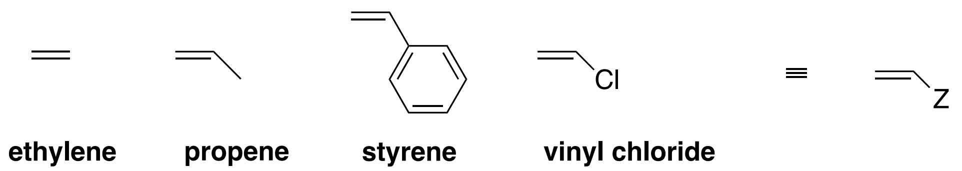


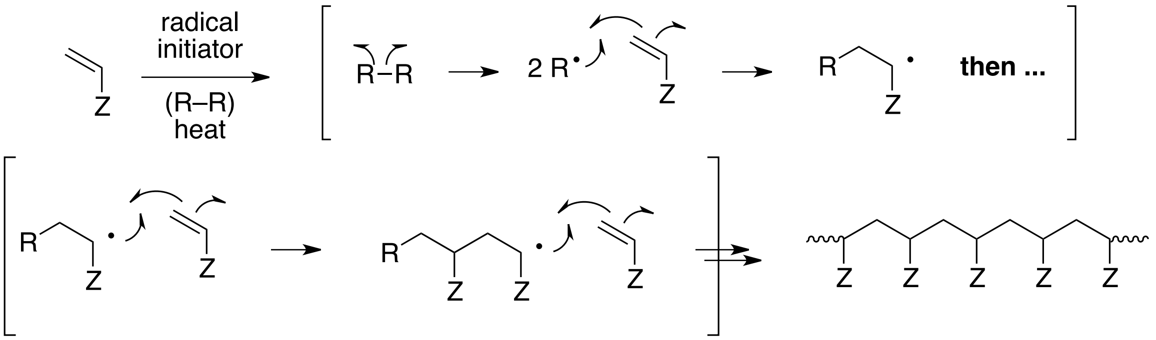
benzene



phenyl group

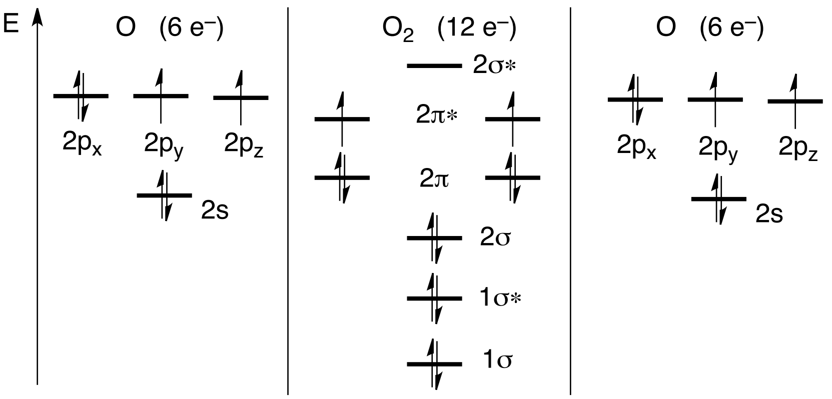
Radical polymerization of particular olefins (ethylene, propene, styrene, vinyl chloride, and many others, also described as *vinyl monomers*) induced by radical initiators, e.g., by AIBN (or related agents):





Elemental (atmospheric) oxygen as a diradical

Reminder: VB theory cannot account for the diradical nature of O_2, but MO theory does:



bond order =
0.5 x (8 – 4) = 2
The oxygen atoms in O_2 share a double bond, but the molecule has 2 unpaired electrons: it is a diradical (strongly paramagnetic)!

Ability of oxygen to initiate various radical reactions, including the polymerization of particular olefins

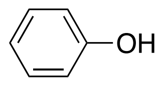
Toxicity of O_2 due to its ability to initiate radical processes in biological systems

Radical inhibitors (also described as antioxidants): molecules that react with / destroy radicals, thereby halting radical chain reactions.

These substances are of interest, e.g., as preservatives of chemical intermediates that can polymerize easily (e.g., styrene); processed foods containing unsaturated (olefinic) fats, rubber products (including chewing gum!), etc.

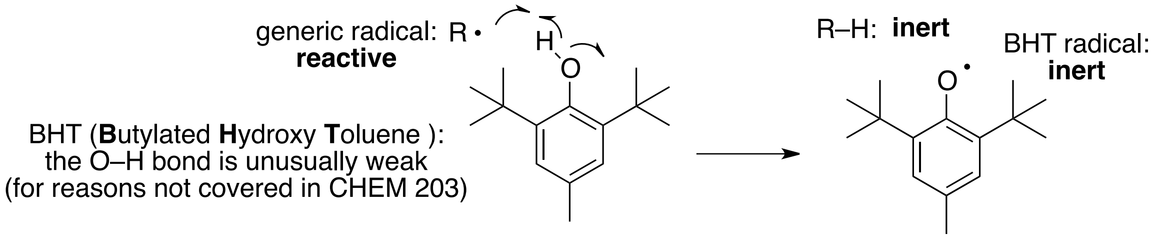
Unusual strength of the O–H bond in ordinary alcohols ($\Delta H_{diss} \approx 110$ kcal/mol), but unusual weakness of the O–H bond in a **phenol** (for reasons that are not covered in CHEM 203)

reminder: a *phenol* is a compound in which an OH group is directly attached to a benzene ring; e.g.:



Ability of the O–H bond of a phenol to transfer a hydrogen atom to a reactive radical, R•, creating an inert R–H and an equally inert "phenol radical"

Butylated **H**ydroxy **T**oluene (BHT) as a useful radical inhibitor



Widespread presence of antioxidants (phenolic or otherwise) in biological media to control the damage that oxygen inflicts to biomolecules.

Lecture 19: Chemistry of Alkynes

Alkynes or acetylenes: compounds in which two carbon atoms share a triple bond

$R^1{-}C{\equiv}C{-}R^2$ the R groups can be H or alkyl

Terminal and internal alkynes:

$R^1{-}C{\equiv}C{-}H$ a teminal alkyne

$R^1{-}C{\equiv}C{-}R^2$ an internal alkyne

Acetylene as the simplest possible alkyne

$H{-}C{\equiv}C{-}H$ acetylene

Principle: alkynes incorporate two independent π systems that engender reactivity analogous to that of alkenes. Consequently, they will undergo all of the reactions seen earlier for olefins

Principle: most of the addition processes seen for alkenes are of limited interest in the alkyne series. An exception is the hydrogenation reaction

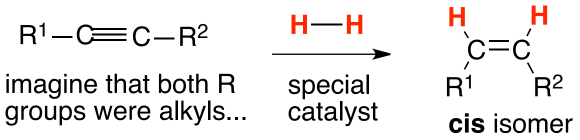
Complete hydrogenation of alkynes by reaction with two molecules of H_2: formation of alkanes:

$$R^1{-}C{\equiv}C{-}R^2 \xrightarrow[\text{Pd (or Pt or Ni, or....)}]{H_2\text{; finely divided}} R^1{-}CH_2{-}CH_2{-}R^2$$

one or both of the R groups may be H

High reactivity of the finely divided metals (Ni, Pd, Pt, Rh, Ru, …) typically employed as catalysts in hydrogenation reactions and consequent difficulty of stopping the reaction at the stage of the addition of only one molecule of H_2

Possible formation of a *cis* alkene upon addition of only 1 molecule of H_2 to the C-C triple bond, in the presence of an appropriate catalyst, due to the *syn* nature of the hydrogenation reaction

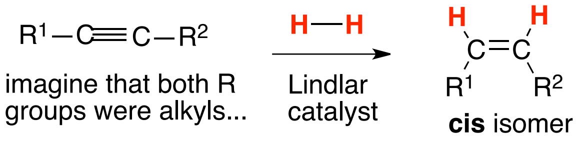


note: the cis geometry is a consequence of the syn course of the rx.

Technological importance of the "semihydrogenation" of alkynes, i.e., in the addition of only 1 molecule of H_2 to their π systems, as a route to *cis*-alkenes

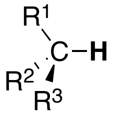
Lindlar catalyst: finely divided Pd deposited on $BaSO_4$ particles and modified with sulfur and other substances that moderate the reactivity of Pd

Semihydrogenation of alkynes with the Lindlar catalyst: conversion of alkynes to *cis*-alkenes through a *syn* addition of H_2:

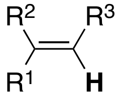


note: the cis geometry is a consequence of the syn course of the rx.

Unusually high electronegativity of sp-hybridized carbon atoms relative to sp^3 and sp^2 hybrids, as a result of considerable s-character (50%) in their orbitals:



e.n. sp^3-C ≈ 2.5



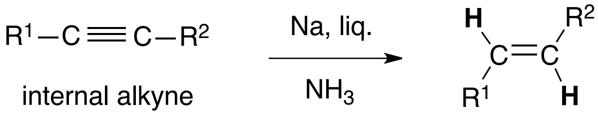
e.n. sp^2-C ≈ 2.6

R^1-C≡C-**H**

e.n. sp-C ≈ 2.8

Strong electron electron-accepting ability of sp-hybridized carbon atoms

Reactions that reflect the electron-accepting ability of carbon sp-hybrids: the semihydrogenation of alkynes with Na/$NH_{3(liq)}$ leading to the formation of *trans*-alkenes



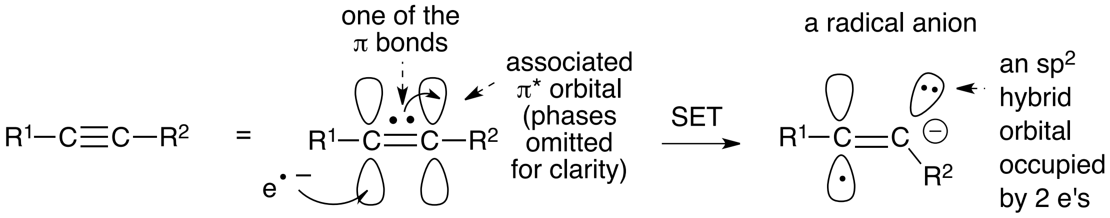
trans isomer

"Dissolving" metals: alkali metals such as Li, Na, K, that form stable solutions in liquid NH_3

Deep blue color of a solution of Li or Na or K in $NH_{3\,(liq)}$ due to the dissociation of metal atoms into a metal cation and a free solvated electron:

$$\dot{Mt}_{(solid)} \xrightarrow{NH_{3\,(liq.)}} \dot{Mt}_{(solution)} \rightleftharpoons Mt^{\oplus}_{(solvated)} + e^{-}_{(solvated)} \qquad \boxed{Mt = Li, Na, K}$$

Reducing properties of a solution of Li (or Na, or K) in liquid NH_3 (≈ a solution of electrons)
Presumed mechanism of the dissolving metal reduction of alkynes – part 1:

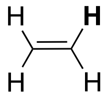


Radical anions

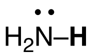
Single electron transfer reactions (SET processes)

Carbon anions ("carbanions") as the conjugate bases of hydrocarbons

Approximate pKa values for hydrocarbons and for NH_3:



C–H of alkene: pKa ≈ 40

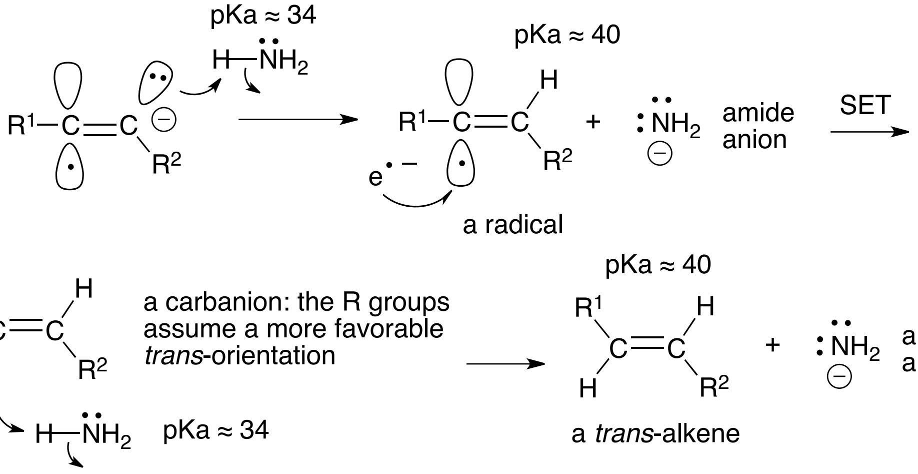


$H_2\ddot{N}{-}\mathbf{H}$

N–H of ammonia: pKa ≈ 34

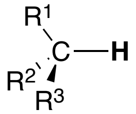
Basicity of carbanions and facile protonation thereof

Presumed mechanism of the dissolving metal reduction of alkynes – part 2:

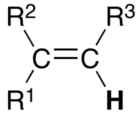


notice the use of one-barbed arrows to illustrate the movement of individual electrons

Increasing polarization of the C–H bond as the C atom goes from an sp^3 to an sp^2 to an sp hybridization state:



e.n. sp^3-C ≈ 2.5
e.n. of H ≈ 2.1
least polarized bond

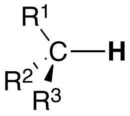


e.n. sp^2-C ≈ 2.6
e.n. of H ≈ 2.1
intermediate polarization

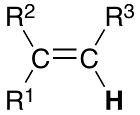
R^1-C≡C—**H**

e.n. sp-C ≈ 2.8
e.n. of H ≈ 2.1
highest polarization

Increasing C–H bond Bronsted acidity with increasing s-character of the carbon orbitals:



e.n. sp^3-C ≈ 2.5
e.n. of H ≈ 2.1
least degree of
C–H bond polarization
pKa sp^3-C–H ≈ 50



e.n. sp^2-C ≈ 2.6
e.n. of H ≈ 2.1
intermediate degree of
C–H bond polarization
pKa sp^3-C–H ≈ 40

R^1-C≡C—**H**

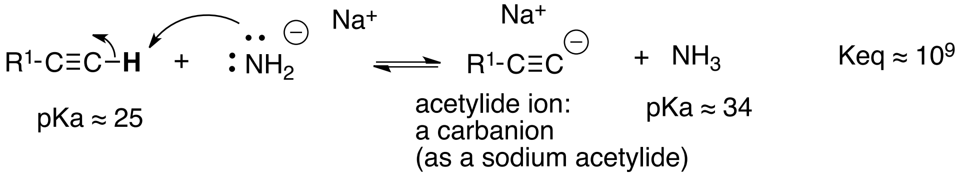
e.n. sp-C ≈ 2.8
e.n. of H ≈ 2.1
greatest degree of
C–H bond polarization
pKa sp^3-C–H ≈ 25

Deprotonation of terminal alkynes with strong bases such as $NaNH_2$

note: for the equilibrium:

$$\underset{\text{ammonia}}{H_2\ddot{N}{-}H} \rightleftharpoons \underset{\text{amide ion}}{H_2\ddot{N}:^{\ominus}} + H^{+} \qquad pKa \approx 34$$

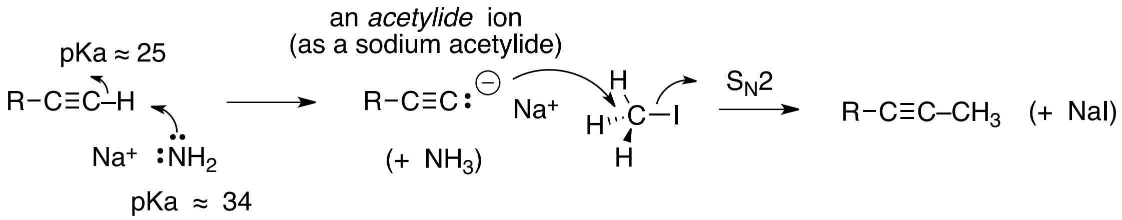
therefore, NH_2^{-} is a very strong base, and for the equilibrium:



Acetylide ion: the carbanion obtained by deprotonantion of a terminal alkyne

Nucleophilic properties of acetylide ions and their use as nucleophiles in S_N2 reactions

S_N2 Alkylation of the carbanion obtained upon deprotonation of terminal alkynes ("acetylide ion") with alkyl halides, e.g.:

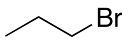


Notice how this reaction forms a new C–C bond

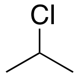
Lecture 20: Alkyl halides – Halogenation of C–H Bonds

The chemistry of alkyl halides

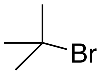
Primary, secondary, tertiary alkyl halides: those in which the halogen is attached to a primary, secondary, or tertiary C atom, respectively; e.g.:



1-bropropane:
a primary halide



2-chloropropane:
a secondary halide



2-bromo-2-methylpropane (*tert*-butyl bromide): a tertiary halide

Preparation of certain alkyl halides by radical halogenation of alkanes

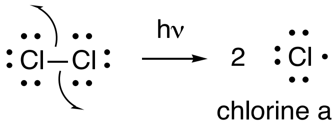
Radical fluorination reactions of alkanes as extremely exothermic processes, which are very difficult to control (explosions, etc.)

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

$$CH_4 \quad + \quad Cl_2 \quad \xrightarrow[\text{(= light)}]{h\nu} \quad CH_3\text{–}Cl \quad + \quad HCl$$

Mechanism of the radical chlorination of, e.g., methane, leading to monochloromethane:

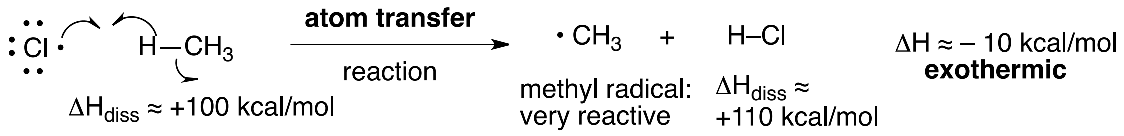
Initiation step: the dissociation of Cl_2 into a pair of Cl atoms. This process is endothermic (ΔH_{diss} Cl–Cl ≈ 59 kcal / mol). The energy required for this reaction is provided by a photon (indicated below as hν):

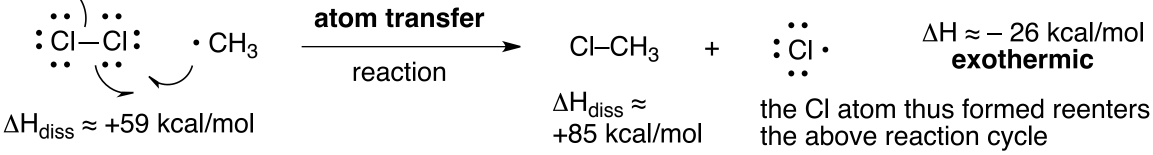


chlorine atoms:
very reactive

notice that the Cl is surrounded by only 7 valence electrons: it may be described as a chlorine **radical**.

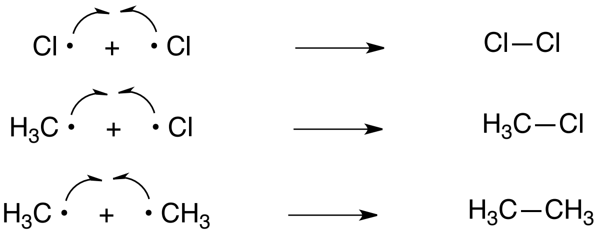
Propagation steps:





the Cl atom thus formed reenters the above reaction cycle

Possible termination steps (statistically unlikely because of the very low instant concentration of radical species during a radical chain reaction):



recombination of 2 Cl • to form a Cl_2 molecule

recombination of a CH_3• with a Cl • to form CH_3Cl

recombination of a pair of CH_3• 's to form CH_3–CH_3

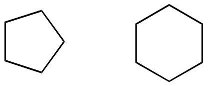
Possibility of multiple chlorination of methane under radical conditions, resulting in formation of CH_2Cl_2 (dichloromethane or methylene chloride); $CHCl_3$ (chloroform, sometimes called trichloromethane); CCl_4 (carbon tetrachloride, sometimes called tetrachloromethane). These compounds are common solvents in organic chemistry.

Limiting the occurrence of multiple chlorinations by controlling the stoichiometry of alkane + Cl_2 mixtures (a large excess of alkane ensures the formation of monochloro derivatives with only small amounts of di- tri- and tetra-chloro products)

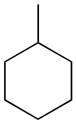
Principle: only alkanes in which all the H atoms are symmetry-equivalent, e.g., methane, ethane, simple cycloalkanes..., are useful substrates for radical chlorination. This avoids formation of a multitude of isomers. Example:

Good substrates for radical chlorination: the same monochloro derivative forms regardless of which C–H bond reacts with Cl•

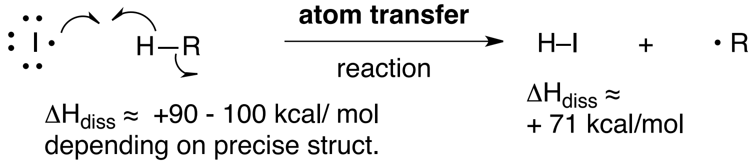
CH_4 CH_3–CH_3



Poor substrate for radical chlorination: mixtures of isomeric monochloro derivatives will form depending on which C–H bond reacts with Cl•

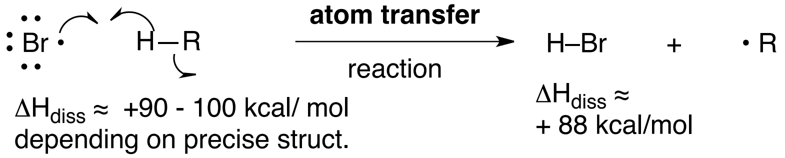


Radical iodination reactions of alkanes as unfeasible processes due to the strongly endothermic nature of the H-atom transfer from a C–H bond to an I radical (mentioned on Oct 26):



ΔH ≈ + 20 to + 30 kcal/mol **strongly endothermic**

Radical bromination of simple alkanes as a feasible, but generally impractical, process (with a few exceptions) due to the slightly / moderately endothermic nature of the transfer of an H atom from the substrate alkane to a Br radical:

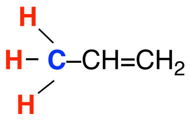


ΔH ≈ + 2 to + 12 kcal/mol **slightly to moderately endothermic**

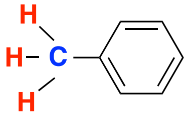
Successful radical bromination of unusually weak C–H bonds (those with a bond dissociation energy ≈ 85-90 kcal/mol)

Successful radical bromination of unusually weak C–H bonds, such as allylic, benzylic, propargylic, or tertiary ones (bond dissociation energy ≈ 85-90 kcal/mol)

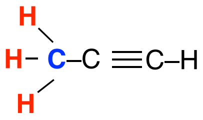
Allylic, benzylic, propargylic hydrogens: those connected to a carbon atom, which in turn is attached to an alkene, a benzene, or an alkyne framework:



red: allylic hydrogens
blue: allylic carbon

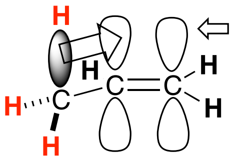


red: benzylic hydrogens
blue: benzylic carbon



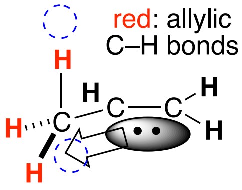
red: propargylic hydrogens
blue: propargylic carbon

Weakening of allylic, propargylic, and benzylic C–H bonds through hyperconjugative delocalization of electron density from the σ_{C-H} bond into the π^* orbital (notes of Oct. 16), and also of electron density from the neighboring π bond into the σ^*_{C-H} orbital:



lobes of the $\pi^*_{C=C}$ orbital (phases omitted for clarity)

allylic C–H bonds dissociation energy ≈ 85-90 kcal / mol



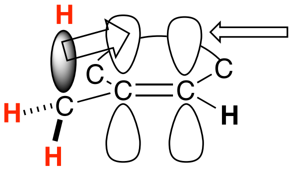
red: allylic C–H bonds

electron donation from the σ_{C-H} bond into the $\pi^*_{C=C}$ orbital (notes of Oct. 8) weakens the allylic bond . . .

as does electron donation from the $\pi_{C=C}$ bond into the allylic σ^*_{C-H} orbital orbital

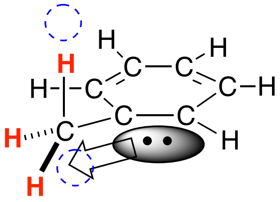
Identical considerations hold for propargylic and for benzylic C–H bonds; e.g.:

red: benzylic C–H bonds



lobes of a benzene $\pi^*_{C=C}$ orbital (phases omitted for clarity)

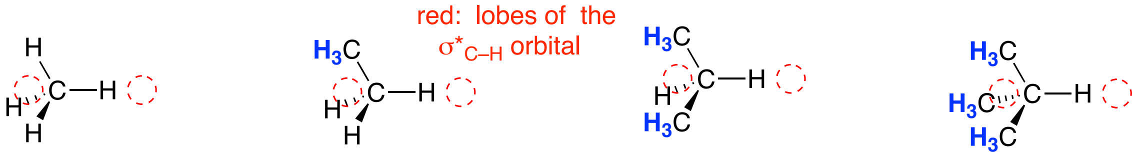
benzylic C–H bonds dissociation energy ≈ 85-90 kcal / mol



electron donation from σ_{C-H} bonds into a $\pi^*_{C=C}$ orbital of benzene weakens the benzylic C–H bonds . . .

as does electron donation from a $\pi_{C=C}$ bond of benzene into the the benzylic σ^*_{C-H} orbital

Weakening of tertiary C–H bonds through hyperconjugative delocalization of electron density from neighboring C–H bonds into the σ^*_{C-H} orbital:



methane:
no hyperconjugation
ΔH_{diss} C–H ≈ 105 kcal/mol

ethane:
3 hyperconj. (blue H's)
ΔH_{diss} C–H ≈ 101 kcal/mol

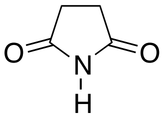
propane:
6 hyperconj. (blue H's)
ΔH_{diss} C–H ≈ 98 kcal/mol

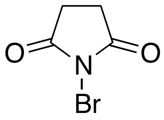
2-Me-propane:
9 hyperconj. (blue H's)
ΔH_{diss} C–H ≈ 95 kcal/mol

Radical bromination of allylic positions as a favorable process that is widely employed in contemporary organic chemistry

Principle: the success of an allylic radical bromination reaction depends on the presence of a ***very small instant quantity*** of Br_2 in the reaction medium (for reasons not covered in CHEM 203). This avoids addition of Br• or of Br_2 to the π bond, and other side reactions.

N-Bromosuccinimide ("NBS", structure below): a reagent that is especially valuable for the radical bromination of allylic positions, because it releases *very small amounts* of Br_2 over time during the reaction

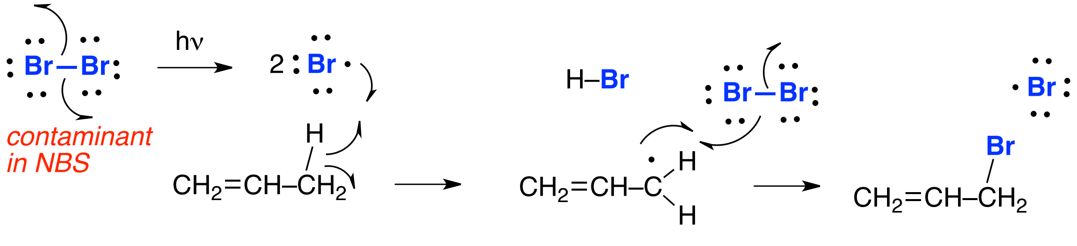

succinimide


N-bromo succinimide (NBS)

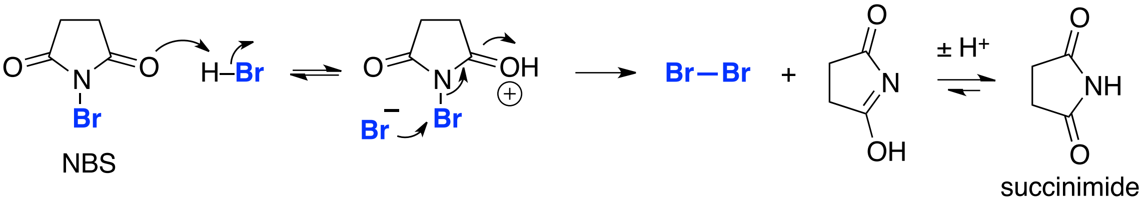
Radical bromination of allylic positions with NBS / light; e.g.:

$$CH_2{=}CH{-}CH_3 \xrightarrow[h\nu]{NBS} CH_2{=}CH{-}CH_2{-}Br$$

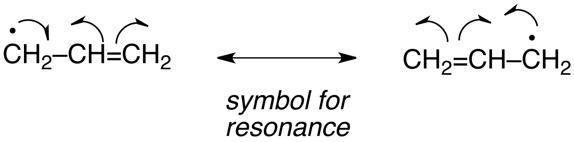
via :



Ability of NBS to react with the HBr formed in the above steps, leading to the release of Br_2:

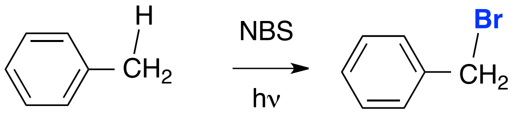


High degree of stabilization of allylic radicals through resonance interactions:

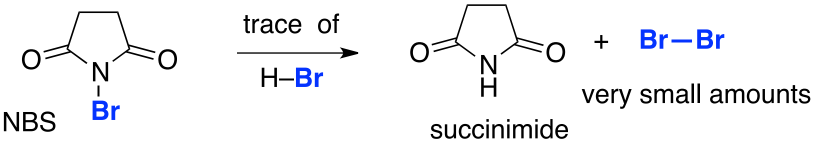


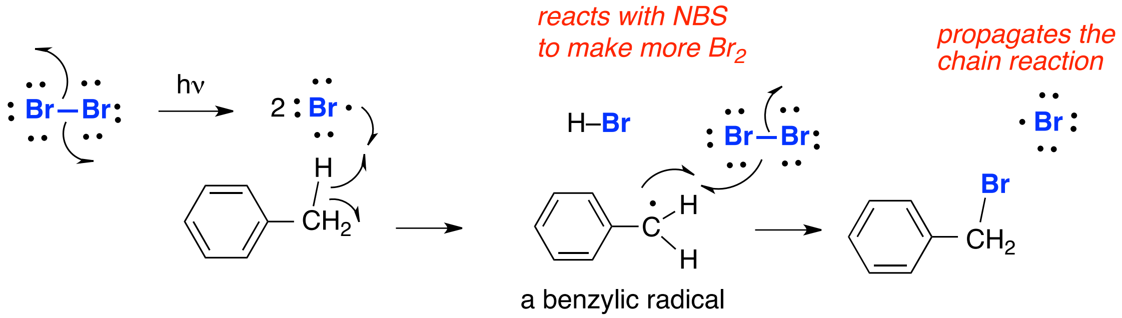
Lecture 21: S_N2 Reactions - I

Radical bromination of benzylic positions as a favorable process that is also widely employed in contemporary organic chemistry, and that works particularly well with NBS:



via :





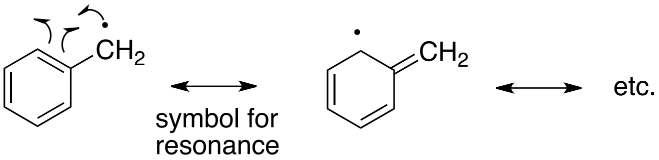
reacts with NBS to make more Br_2

propagates the chain reaction

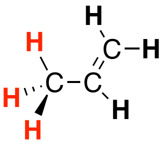
a benzylic radical

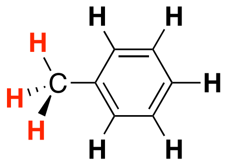
reminder: the "olefinic" bonds in a benzene ring are unusually unreactive toward Br_2, HBr, BH_3, OsO_4, radicals, etc, due to "aromaticity" (a set of properties, to be discussed in detail in CHEM 213, that cause the π bonds of benzene to behave differently from those of ordinary alkenes).

High degree of stabilization of benzylic radicals through resonance interactions:



Elevated strength of sp^2-C–H bonds: $\Delta H_{diss} \approx$ 110-120 kcal/mol:

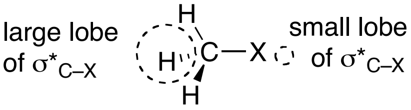




bold: C–H bonds connecting to an sp^2 carbon: unusually strong ($\Delta H_{diss} \approx$ 110 kcal/mol)

Radical bromination of tertiary C–H bonds as a feasible, but not particularly useful, reaction

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



Principle: alkyl halides tend to interact with electron-rich species, **A**, which introduce electrons into the above $\sigma^*_{C\text{–}X}$ orbital and promote **substitution reactions** according to the following general scheme:

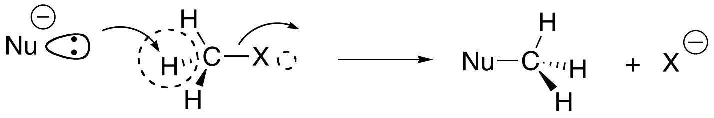
$$\text{C–X} \quad + \quad \text{A} \longrightarrow \text{C–A} \quad + \quad \text{X}^{\ominus}$$

Principle: substitution reactions of alkyl halides require the introduction of two electrons into the $\sigma^*_{C\text{–}X}$ orbital. These electrons may be introduced either simultaneously ("nucleophilic" or "ionic" mechanisms) or one at a time ("SET" mechanisms – notes of Oct. 23)

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

$$\text{C–X} \quad + \quad \text{A} \longrightarrow \text{C–A} \quad + \quad \text{X}^{\ominus}$$

Interaction of an electron pair from the nucleophile, Nu**:** , with the $\sigma^*_{C\text{–}X}$ orbital during a nucleophilic substitution reaction:



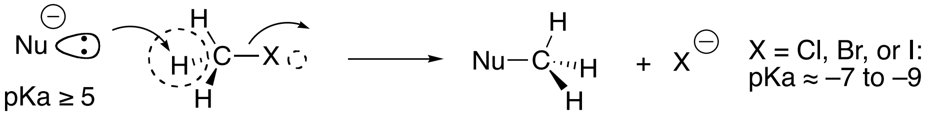
Rupture of the C–X bond as the Nu**:** introduces electron density into the $\sigma^*_{C\text{–}X}$ orbital

Leaving group or nucleofuge: that fragment of the substrate that is expelled by the incoming nucleophile in the course of a nucleophilic substitution reaction

> The halide ion X^- (chloride, bromide, iodide) in the above diagram functions as a leaving group (= nucleofuge) in the depicted substitution reaction

Thermodynamic driving force for the above substitution reaction: the decrease in the basicity of the system — as gauged from changes in pKa's — as a more Bronsted basic agent (Nu**:**) is consumed and a less Bronsted basic one (X^-) is released:

> changes in the basicity of the system (ΔpKa's) incurred during a nucleophilic substitution process can be correlated with approximate equilibrium constants, Keq, for the reaction, which in turn can be used to estimate the driving force (ΔG) for the reaction:



$\Delta pKa < -12 \Longrightarrow Keq > 10^{12} \Longrightarrow \Delta G° = -\,nRT \ln Keq << 0 \Longrightarrow$ **very** favorable

Principle: most nucleophiles that successfully engage alkyl halides in nucleophilic substitution processes are conjugate bases of weak acids (pKa ≥ 5)

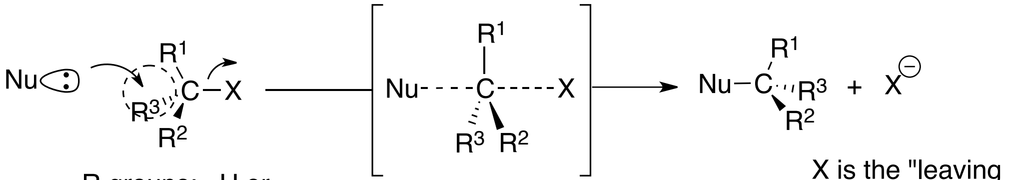
Correlation between the pKa of the conjugate acid of X^- and the ability of X^- to function as a leaving group in a substitution reaction of the above type:

H–X	H–F	H–Cl	H–Br	H–I
approx. pKa	+ 4	– 7	– 8	– 9
comments	F^- does not behave as a leaving group in the above rxs.	Cl^- is substituted fairly easily by nucleophiles in the above rxs.	Br^- is an even more rapidly substituted in the above rxs.	I^- is substituted the fastest in the above reactions

the ability of "X" to function as a leaving group in nucleophilic substitution reactions increases with decreasing Bronsted basicity (=weaker bases are better leaving groups)

Principle: the leaving group in a nucleophilic substitution reaction of the above type must be the conjugate base of a strong Bronsted acid with pKa < 0. Conjugated bases of weak Bronsted acids, e.g. F^-, cannot function as leaving groups in such reactions, regardless of how favorable (negative) ΔG_{react} may be, i.e., regardless of how strong the driving force for the reaction is.

Stereochemical aspects of nucleophilic substitution reactions of alkyl halides proceeding through the interaction of an electron pair from the nucleophile with the σ^*_{C-X} orbital:



R groups: H or alkyl substituents

transition state: the Nu–C bond not fully formed; the C–X bond is not fully broken. For an instant, the C atom is trigonal bipyramidal

X is the "leaving group" in this rx.

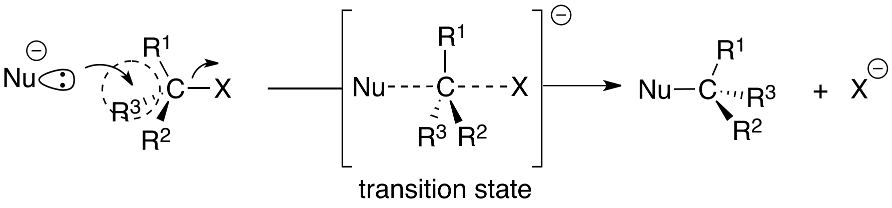
Note: the nucleophile, Nu, has become connected to the C atom with a spatial orientation that is *opposite* that of the original X: the reaction has occurred with **inversion of configuration**

"Backside" attack of the nucleophile onto the alkyl halide and consequent inversion of configuration during the substitution process

Lecture 22: S_N2 Reactions - II

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

Second-order kinetic rate law for a nucleophilic substitution reactions proceeding by the following mechanism:



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

This equation reflects the fact that 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). In turn, this is a function of the number of molecules of Nu and of the number of molecules of alkyl halide present in the reaction medium; i.e., of the *concentration* of Nu and of alkyl halide

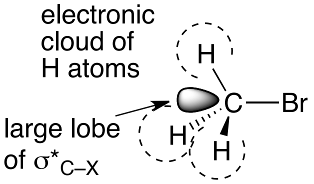
S_N2 reactions: those nucleophilic substitutions that are characterized by second-order kinetics and that proceed stereoselectively with inversion of configuration ("backside attack").

Walden inversion: the inversion of configuration observed in the S_N2 reaction

Principle: increasing substitution at the halogen-bearing C atom diminishes the accessibility of σ^*_{C-X} orbital, thereby retarding the rate of S_N2 reactions:

methyl halides

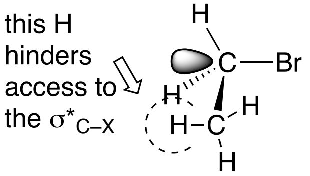
e.g., $CH_3–Br$



σ^*_{C-X} is well exposed: reacts the fastest in S_N2

primary alkyl halides

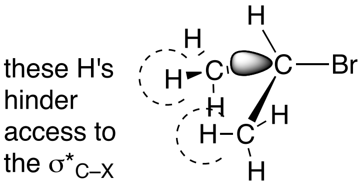
e.g., $CH_3–CH_2–Br$



σ^*_{C-X} less accessible: ca. 10 times slower-reacting than $CH_3–X$ in S_N2

secondary alkyl halides

e.g., $(CH_3)_2CH–Br$



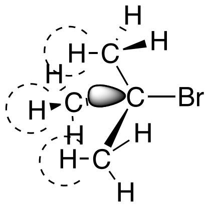
σ^*_{C-X} even less accessible: ca. 100 times slower-reacting than $CH_3–X$ in S_N2

Steric hindrance: the effect of alkyl groups that hamper access to a particular molecular feature; e.g., to the σ^*_{C-X} orbital of an alkyl halide

> The CH_3 groups in the above molecules are said to engender steric hindrance in the backside of the C–Br bond, thereby retarding the rate of S_N2 reaction

Inaccessibility of the σ^*_{C-X} orbital in tertiary alkyl halides, e.g in $(CH_3)_3C{-}Br$:

extreme steric hindrance in the backside of the C–Br bond: 3 H's block access to the σ^*_{C-X} orbital

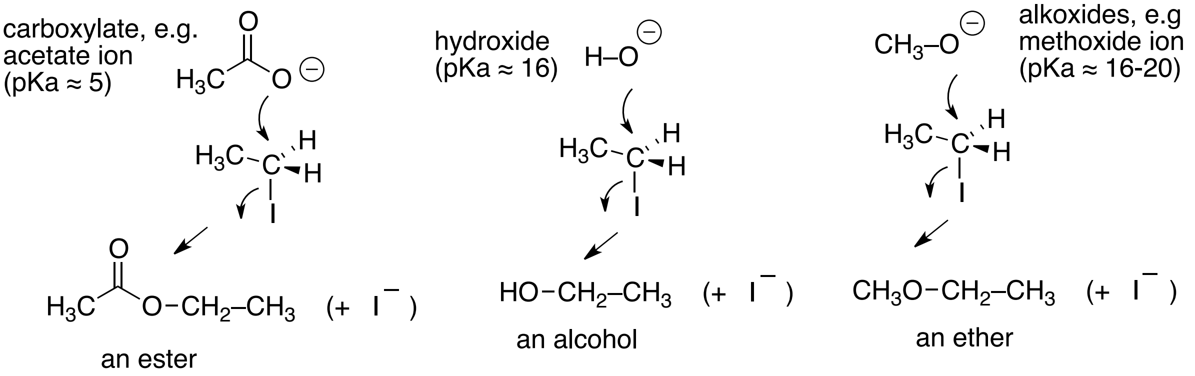


σ^*_{C-X} is now inaccessible: the tertiary alkyl halide cannot undergo S_N2 reaction

Principle: tertiary alkyl halides **do not undergo S_N2 reaction** (= they *can* undergo substitution, but not by the S_N2 mechanism). Consequently, S_N2 chemistry is characteristic of methyl, primary, and many secondary alkyl halides

Nucleophiles of special interest in S_N2 reactions: those based on C, N, O, and S (pKa values refer to the conjugate acid):

oxygen - based



Alkoxides ($R{-}O^-$) as the conjugate bases of alcohol, R–OH (pKa ≈ 17-19)

Williamson reaction (=Williamson ether synthesis): the preparation of ethers by SN2 reaction of an alkyl halide with an alkoxide

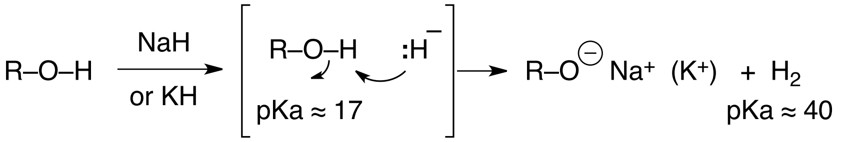
Conversion of alcohols into alkoxides ($R{-}O^-$) by reaction with reactive metals such as Li, Na, K:

$$R{-}O{-}H \xrightarrow[\text{or K}]{\text{Li, or Na}} R{-}\overset{\ominus}{O}\ \overset{\oplus}{Mt} \quad (\text{Mt} = \text{Li, Na, K}) \quad + \quad H_2$$

Hydride ion as the conjugate base of H_2 (pKa ≈ 40)

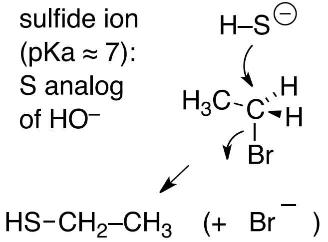
Hydride ion as a powerful base

Preparation of alkoxides by reaction of alcohols with metal hydrides such as NaH or KH:



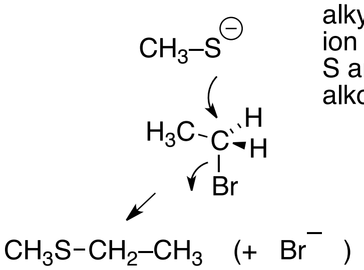
sulfur - based

hydrogen sulfide ion (pKa ≈ 7): S analog of HO⁻



a thiol

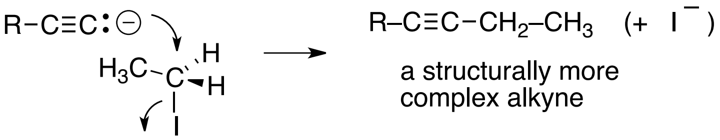
alkyl sulfide ion (pKa ≈ 10): S analog of alkoxide ion



a thioether

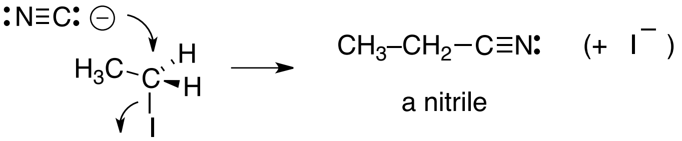
carbon - based

acetylide ions (pKa ≈ 25)



a structurally more complex alkyne

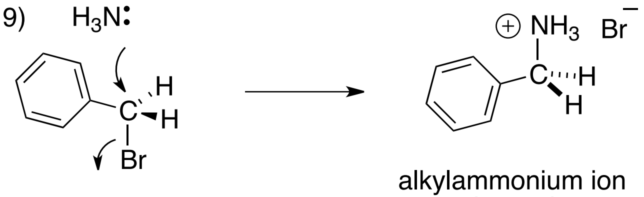
cyanide ion (pKa ≈ 10)



a nitrile

nitrogen - based

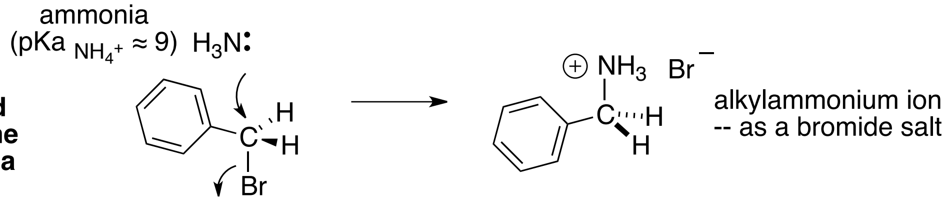
ammonia (pKa ≈ 9)



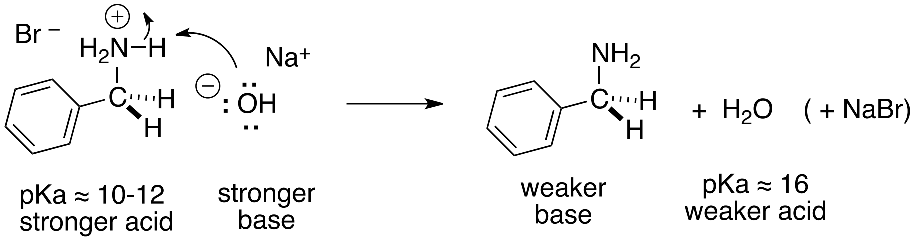
alkylammonium ion --as a bromide salt

Lecture 23: S_N2 vs. Elimination Reactions

nitrogen - based nucleophiles: the case of ammonia



Conversion of alkylammonium ions into amines ("free bases") by reaction with, e.g., aq. NaOH:

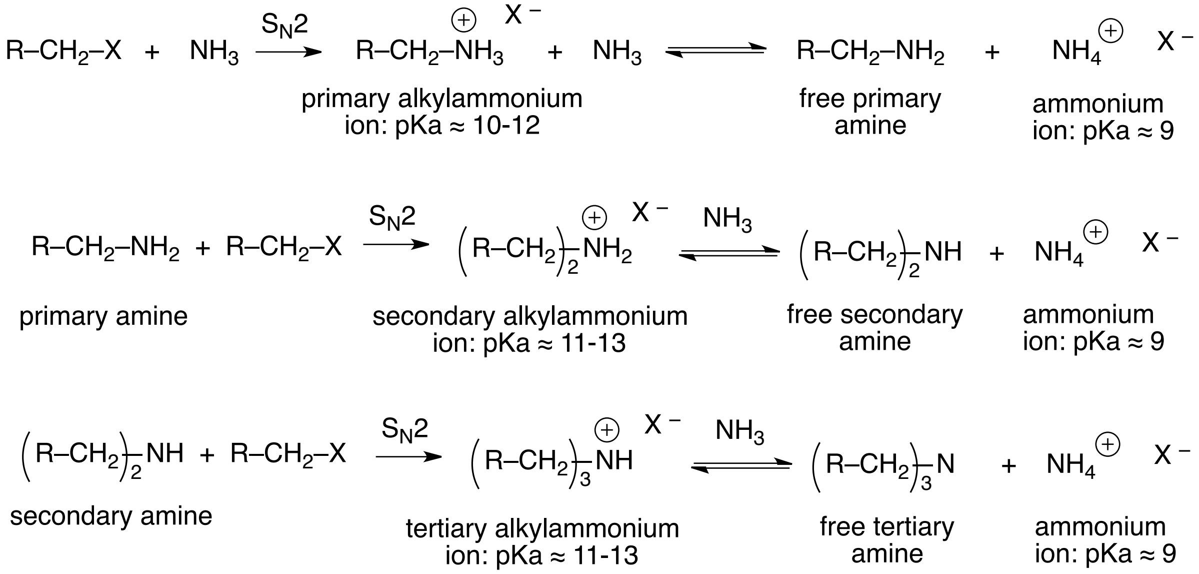


Primary amines: compounds of general formula R–NH_2, where R = alkyl

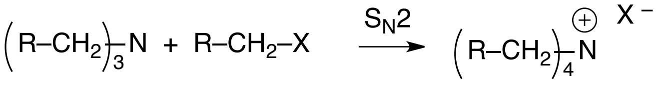
Technological importance of primary amines

Nucleophilic reactivity of primary amines

Problems with the S_N2 preparation of primary amines by reaction of ammonia with alkyl halides: possibility of multiple substitutions leading to mixtures of products in which 1,2,3 or even 4 alkyl groups have become attached to the N atom:



and even:

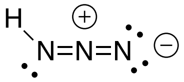


tertiary amine quaternary alkylammonium salt

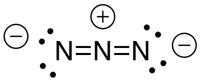
Secondary and tertiary amines: compounds in which the N atom carries 2 or 3 alkyl substituents

Nucleophilic reactivity of secondary and tertiary amines, as apparent from the foregoing, and potential problems with the preparation of such compounds by S_N2 chemistry

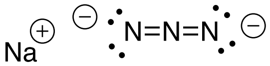
Azide ion (available as sodium azide, NaN_3) as the conjugate base of hydrazoic acid, pKa ≈ 5



hydrazoic acid



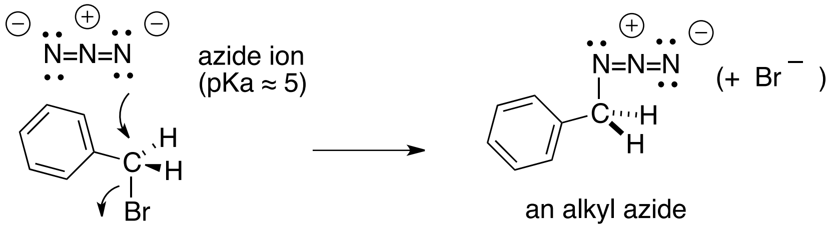
azide ion



sodium azide: the Na^+ salt of hydrazoic acid

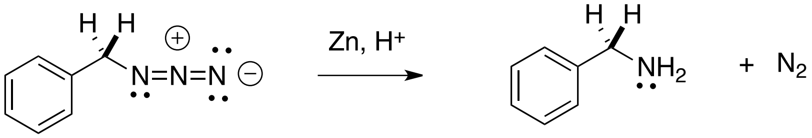
Azide ion as a powerful nucleophile

Interest of azide ion as a nucleophile in the above reactions: only 1 substitution event can occur



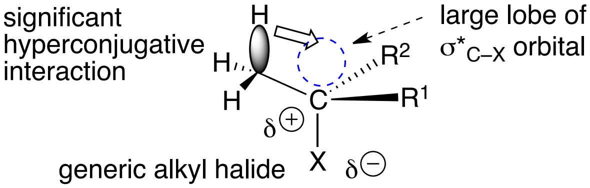
an alkyl azide

Reduction of alkyl azides to primary amines with Zn / H^+ (same reagent seen earlier for the reduction of ozonides) as a valuable method for the selective formation of primary amines:



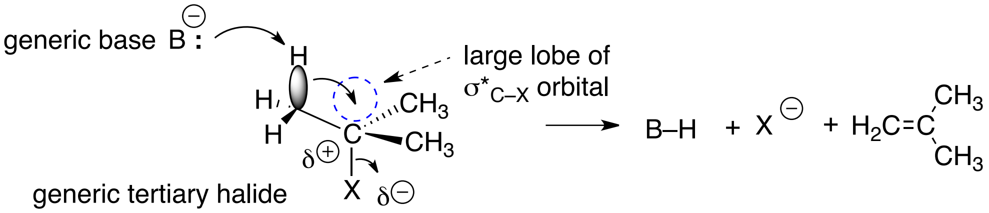
an alkyl azide a primary amine

Strong hyperconjugative interaction between the σ_{C-H} electrons of the C–H bond *anti* to the C–Br bond and the $\sigma^*_{C\text{-}Br}$ orbital, as a consequence of the partial (+) charge present on the C atom. This significantly enhances the Bronsted acidity of the C–H bond aligned with the $\sigma^*_{C\text{-}Br}$ orbital.



generic alkyl halide

Formation of alkenes (= olefins) upon reaction of tertiary halides with basic agents:



The enhanced acidity of the C–H bond aligned with the large lobe of the $\sigma^*_{C\text{-}Br}$ orbital may allow proton transfer to a suitable base, $B:^{(-)}$, thereby releasing the $\sigma_{C\text{-}H}$ electrons into the neighboring $\sigma^*_{C\text{-}Br}$ orbital. This would cause the break-up of the C–X bond, release of X as a halide ion, and formation of a C=C double bond

Description of the above process as an elimination reaction: one leading to formation of a double bond through expulsion of appropriate fragments from a substrate molecule

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

The elimination reaction as formally the reverse of an addition reaction:

the addition of HBr to 2-methyl-2-propene would lead to 2-bromo-2-methylpropane. But in the above transformation, a molecule of 2-bromo-2-methylpropane *eliminates* (="loses", or "expels") HBr to form 2-methyl-2-propene. So, the reaction is formally the inverse of an addition process

Nature of the basic agent required to induce the above elimination reaction: conjugate base of a weak acid with pKa ≥ 4-5

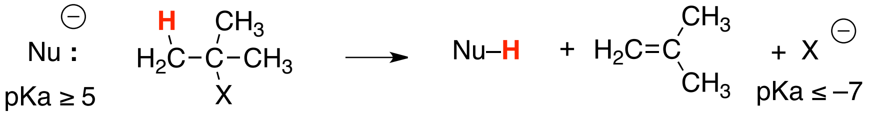
Bronsted basic properties (pKa of conjugate acid ≥ 5) of the nucleophiles commonly employed in S_N2 reactions (notes of Oct. 28)

Ability of the basic nucleophiles discussed on Oct 28, which are otherwise useful in S_N2 reactions, to induce elimination from tertiary alkyl halides

Nucleophilicity as carbon affinity; basicity as proton affinity

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

Driving force for the above elimination reaction: decrease in the basicity of the species present in the reacting medium:

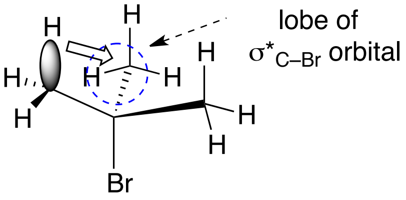


$$\Delta pKa \leq -13 \Rightarrow K_{eq} > 10^{13} \Rightarrow \Delta G << 0$$

Mechanistic picture for the above elimination reaction:

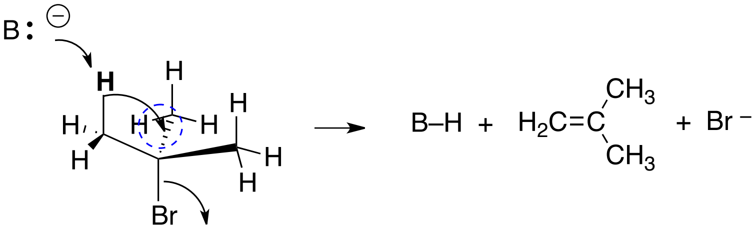
Hyperconjugative delocalization of σ electrons from adjacent C–H bonds into the $\sigma^*_{C\text{–}Br}$ orbital weakens the C–H bond, polarizes it so that the H atom acquires significant (+) character, and enhances its the Bronsted acidity. This effect is most significant for the C–H bond that is perfectly aligned with the $\sigma^*_{C\text{–}X}$ orbital (dihedral angle $\theta = 0°$), because experiences the extent of electron delocalization is a function of $\cos^2\theta$, so it is maximal for $\theta = 0°$ (notes of Sept. 21):

hyperconjugative weakening of adjacent C–H bonds is especially pronounced for those H's that are aligned with the $\sigma^*_{C\text{–}X}$ orbital. These H's become more positive and more Bronsted acidic



The basic agent attacks the weakened, highly polarized C–H bond in the substrate and takes up the proton, at the same time that the $\sigma_{C\text{–}H}$ electrons are funneled into the $\sigma^*_{C\text{-}Br}$ orbital, thereby breaking the C–Br bond and triggering the departure of the Br atom as a bromide ion:

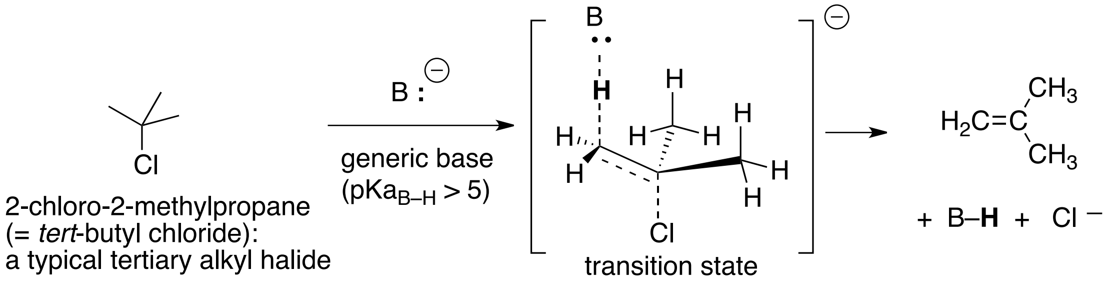
conjugate base of an acid with pKa > 5 (cannot access the $\sigma^*_{C\text{–}X}$ orbital due to steric hindrance)



Removal of the H and departure of Br^- may thus be thought as occurring simultaneously; i.e., in a concerted manner

Lecture 24: E2 Reactions

Predicted — and experimentally observed — second-order kinetics for elimination reactions of tertiary alkyl halides promoted by basic agents:



2-chloro-2-methylpropane
(= *tert*-butyl chloride):
a typical tertiary alkyl halide

the probability of that a molecule of alkyl halide and one base will interact as shown above (see also notes of Nov 2nd) is a function of the number of molecules of each present in solution at any point in time; i.e., it depends on the instant concentration of halide and base (see also notes of Oct 30)

$$\text{rate} = \frac{d\,[\text{alkene}]}{dt} = k\,[\,\text{B:}^-\,]\,[\text{alkyl halide}]$$

Description of the above process as an **E2 reaction**: an elimination reaction characterized by second-order kinetics and believed to proceed through the above mechanism

Principle: elimination reactions are always observed to occur in competition with nucleophilic substitution reactions (except in the case of methyl halides):

methyl halides react with basic nucleophiles in an S_N2 mode: E2 reaction is not possible

primary halides react with basic nucleophiles substantially in an S_N2 mode: elimination competes only to a minor / marginal extent;

secondary halides do undergo S_N2 reaction with many basic nucleophiles, but a greater extent of elimination is observed with these substrates;

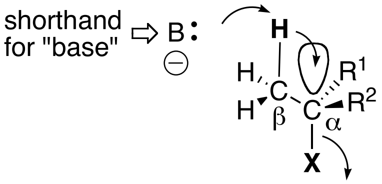
tertiary halides do not undergo S_N2 reaction when exposed to basic nucleophiles: only β-elimination occurs.

Principle: increasing basicity (pKa) of the nucleophile favors the occurrence of elimination reactions at the expenses of S_N2 processes

Ethanolic KOH as a traditional base for elimination reactions (now fallen into disuse)

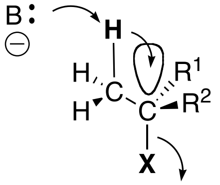
Properties of the E2 reaction:

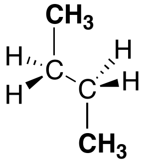
i. The E2 as a **β-elimination reaction**:



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

ii. The E2 as an ***anti*-elimination reaction**, due to the requirement that the departing H atom be oriented *anti* to the halogen atom:





anti-butane

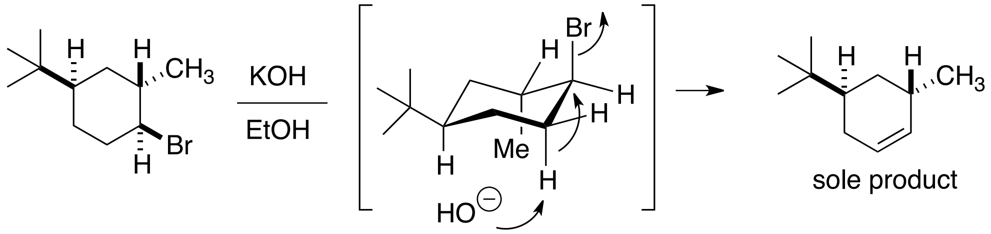
the conformational relationship between the H atom involved in an E2 reaction and the departing halogen, X, is reminiscent of that between the methyl groups in *anti*-butane; hence the term "*anti*-elimination."

Stereoelectronic control during a reaction: the fact that the reaction requires a particular orbital orientation in order to occur

Stereoelectronic control in the E2 reaction (*anti*-elimination)

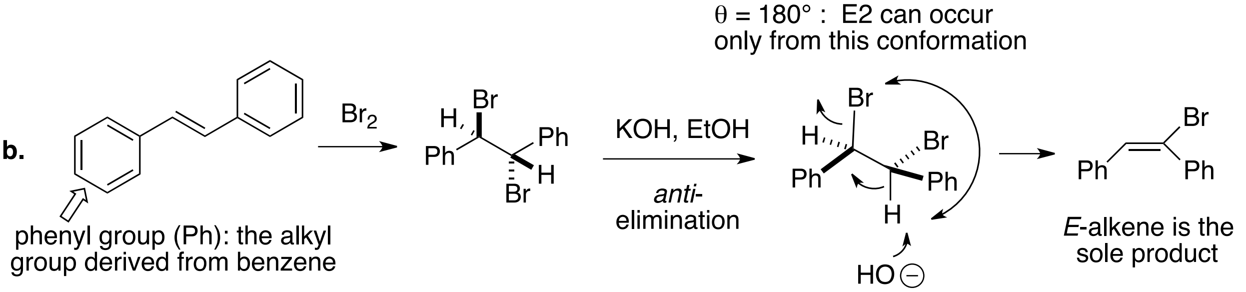
Some consequences of the stereoelectronic properties of the E2 reaction:

a.



E2 can occur only in this way

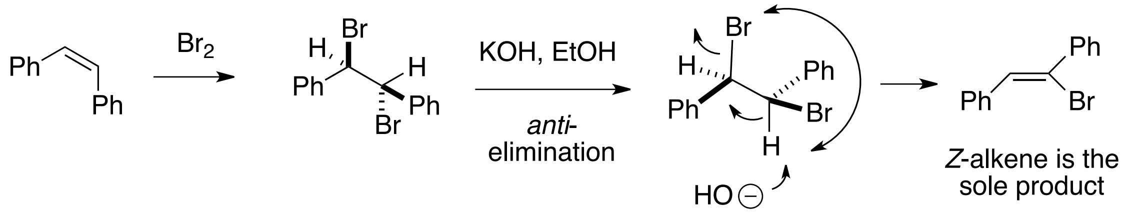
b.



likewise:

θ = 180° : E2 can occur only from this conformation

c.



anti-elimination

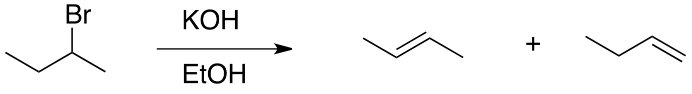
Z-alkene is the sole product

The Saitzeff rule: "if an alkyl halide can undergo E2 reaction to give isomeric olefins, the more highly substituted olefin tends to form preferentially." Examples:

a. In principle, 2-bromo-2-methylbutane can undergo E2 reaction to give either 2-methyl-1-butene or 2-methyl-2-butene. In fact, 2-methyl-2-butene will form preferentially:

2-bromo-2-methylbutane major product some

b. 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:

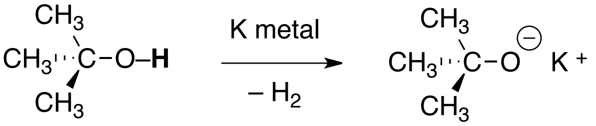


2-bromobutane major product some

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

Sterically hindered alkoxides: potassium tert-butoxide:

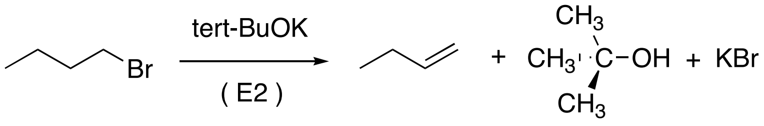
2-methyl-2-propanol
"*tert*-butanol"
pKa ≈ 19



potassium
tert-butoxide

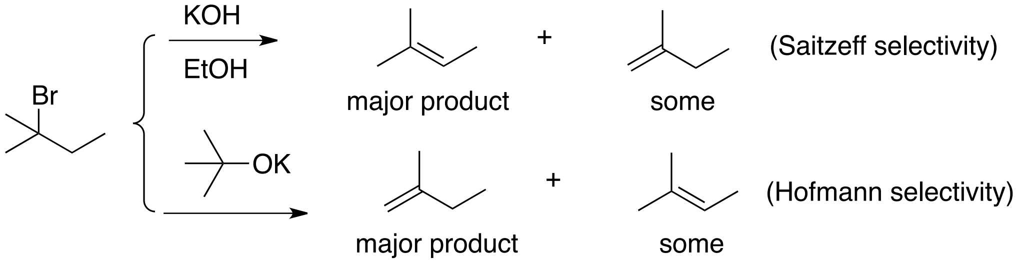
Poor nucleophilicity and good basicity of potassium tert-butoxide

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

Steric effects in the E2 reaction: Saitzeff vs. Hofmann Selectivity:



Lecture 25: S_N1 and E1 Reactions

Principle: hindered alkyl halides, such as tertiary ones, cannot undergo substitution by the S_N2 mechanism, but they can do so by alternative mechanisms

Principle: hindered alkyl halides, such as tertiary ones, may undergo substitution reactions, but typically with **non-basic nucleophiles** (i.e., nucleophiles that are the conjugate bases of acids with pKa's < 0; such as H_2O, CH_3OH, etc.) and **in media of high dielectric constant** ($\varepsilon > 20$)

Obviously, basic nucleophiles (pKa > 5) would promote E2 reaction of tertiary halides

Dielectric constant: a measurable property of bulk matter (solid, liquid or gas) that indicates the extent of weakening of the electrostatic force between two charges embedded in that matter, relative to the force between the same charges in a vacuum

reminder: the electrostatic force between two charges, q_1 and q_2, separated by a distance *d* and embedded in a medium (gas, liquid, or solid), is given by the **Coulomb equation**:

$$F = \frac{1}{4 \pi \varepsilon_0 \varepsilon_r} \frac{q_1 \cdot q_2}{d^2}$$

where:

ε_0 = dielectric permittivity of vacuum

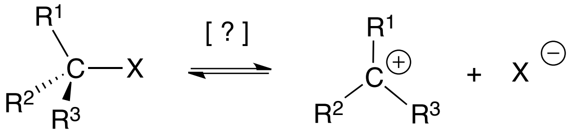
ε_r = dielectric constant of the medium

High dielectric constants of solvents such as CH_3OH ($\varepsilon_r \approx 30$), water ($\varepsilon_r \approx 80$), etc.

Polar solvent (medium): one of high dielectric constant, e.g. H_2O ($\varepsilon_r \approx 80$), CH_3OH ($\varepsilon_r \approx 30$), etc.

Nonpolar solvent (medium): one of low dielectric constant

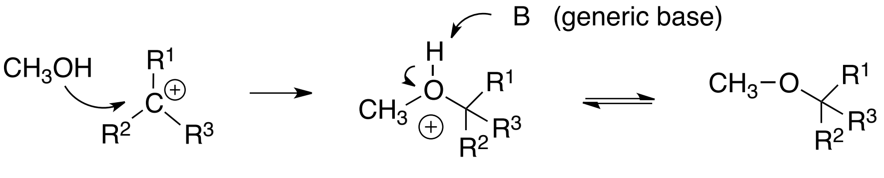
Possible dissociation of alkyl halides to give a carbocation plus a halide ion (analogous to the dissociation of H–X):



X = Cl, Br, I

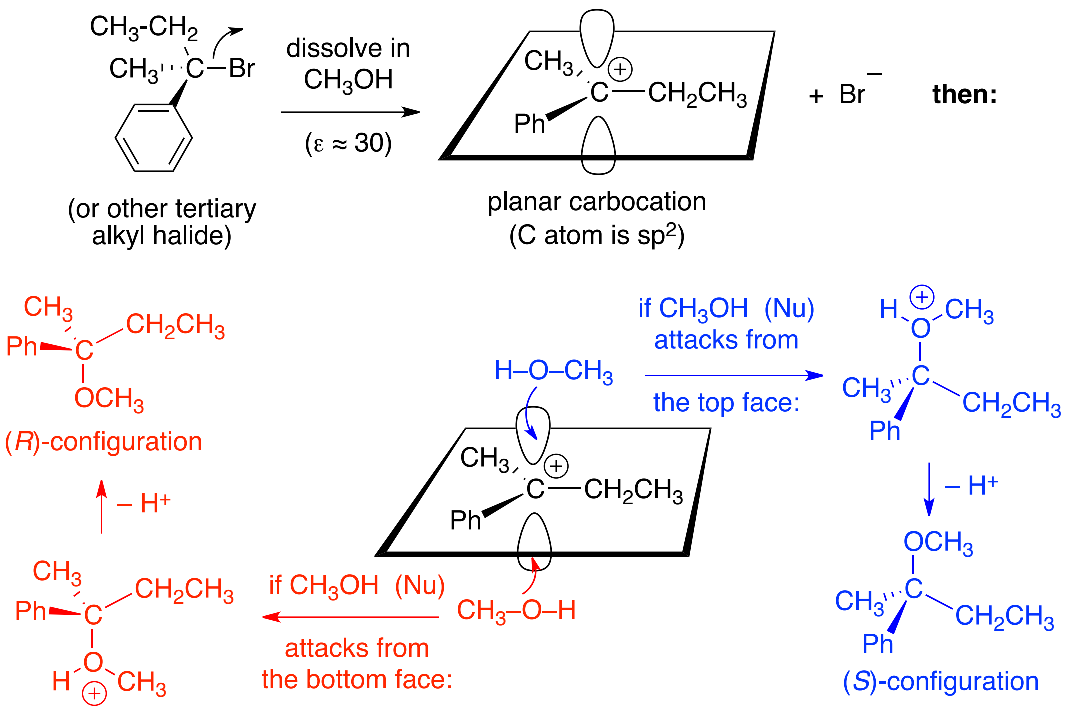
The above dissociative process as an energetically unfavorable one (one must separate a + charge from a – charge), which will be facilitated in a medium of high dielectric constant, such as an aqueous, methanolic, etc., solution

Principle: if the above dissociation reaction were to take place at all in a medium containing H_2O, CH_3OH, etc., the resultant carbocation would be intercepted by H_2O, CH_3OH, etc., to give an alcohol, an ether, etc.; e.g.:



Principle: the above dissociation reaction is likely to be easiest with tertiary alkyl halides, much less so with secondary halides, very difficult with primary halides, and virtually impossible with methyl halides, due to the relative degree of hyperconjugative stabilization of tertiary (most highly stabilized), secondary, primary and methyl (not at all stabilized) carbocations

Stereochemical aspects of the above reaction: loss of configuration:



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.

Kinetic aspects of the above reaction: unlike the S_N2 reaction, which proceeds in a single kinetic event (the Walden inversion), the substitution 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 the substitution reaction depends only on the rate of formation of the carbocation, i.e., the rate of dissociation of the alkyl halide)

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

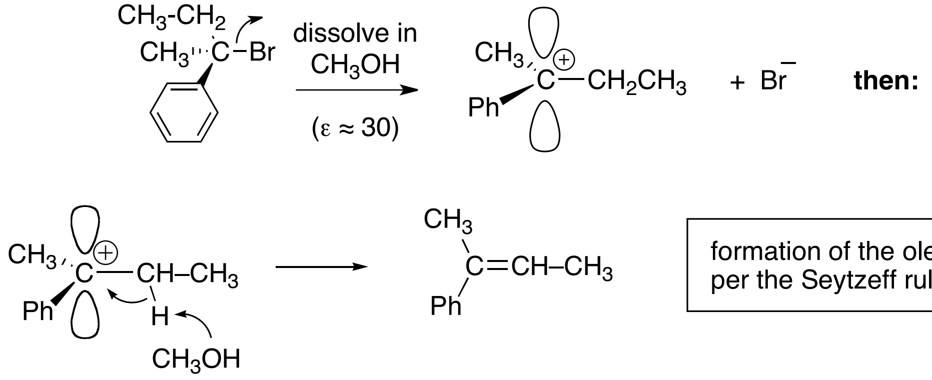
$$\text{rate} = \frac{d\,[\text{substitution product}]}{dt} = k\,[\text{alkyl halide}]$$

S_N1 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 Bronsted acidity of carbocations ($pKa < 10^{-11}$) 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

Exothermic nature of the deprotonation of the carbocation by CH_3OH, H_2O, etc. (fast, facile)

Preferential formation of the more highly substituted olefin isomer (Seytzeff rule) during deprotonation of carbocations; e.g.:



formation of the olefin as per the Seytzeff rule

The above process as a special type of β-elimination reaction

The dissociation of the starting alkyl halide (slow, difficult) as the rate-limiting step of the above elimination reaction (= the rate of the elimination reaction depends only on the rate of formation of the carbocation, i.e., the rate of dissociation of the alkyl halide)

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

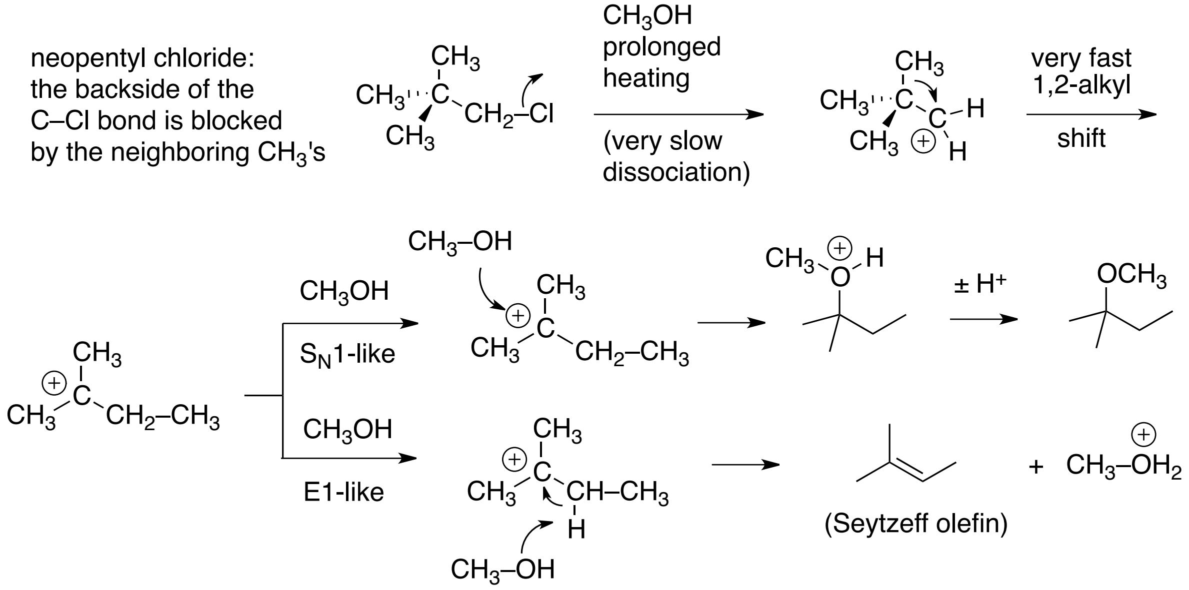
$$\text{rate} = \frac{d\,[\text{elimination product}]}{dt} = k\,[\text{alkyl halide}]$$

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

Principle: just as in the case of S_N2 and E2 reactions, S_N1 and E1 reactions always occur in competition with each other

Possible rearrangement of carbocations formed by ionization of alkyl halides

Example: the case of neopentyl chloride:



Lecture 26: SET Reactions of Alkyl Halides - Organometallics

Substitution reactions of alkyl halides believed to proceed by SET mechanisms

Carbon-based nucleophiles: carbon-centered anions ("carbanions") such as cyanide and acetylide ions, as agents that permit the formation of C–C bonds in an S_N2 mode, enabling the assembly of more complex carbon architectures from smaller building blocks

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

Principle: a carbon atom bound to an element of very low electronegativity will be likely to exhibit carbanionic character because of strong bond polarization

Bonding of carbon to electropositive metals such as Li, Mg, etc. (e.n. $\approx 1.0 - 1.3$) as a logical approach to the creation of carbanionic species

Substitutions reactions of alkyl halides that are believed to proceed through SET mechanisms: reaction of alkyl halides with electropositive metals such as Li, Mg, etc.

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

Organolithium compounds: organometallics of general structure R–Li obtained upon reaction of R–X (X = Cl, Br, I) with metallic Li; e.g.:

$$CH_3Br + 2\,Li \longrightarrow CH_3\text{–}Li + LiBr$$

Organomagnesium compounds: organometallics of general structure R–Mg-X obtained upon reaction of R–X (X = Cl, Br, I) with metallic Mg:

Grignard reagents (after Victor Grignard, 1912 Nobel Prize in chemistry): organomagnesium compounds of the type R–Mg–X (R = any alkyl, X = Cl, Br, I) obtained upon reaction of R–X (X = Cl, Br, I) with metallic Mg; e.g.:

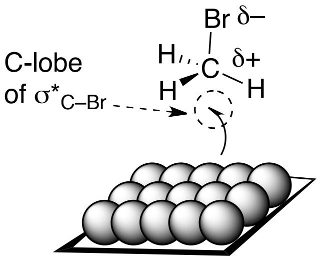
$$CH_3Br + Mg \longrightarrow CH_3\text{–}Mg\text{–}Br$$

Principle: Li and Mg form reactive, but well-behaved organometallic species; whereas other alkali (Na, K, …) or alkali earth (Be, Ca, …) metals, yield organometallics, the reactivity of which is difficult to control

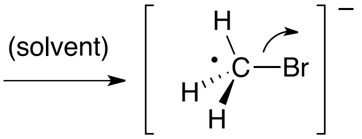
Preparation of organometallic species by the **direct method**: reaction of an alkyl halide with elemental Li or Mg

SET mechanisms in the reactions leading to the formation of organo-Li and –Mg compounds: the metal transfers electrons, one at a time, into the $\sigma^*_{C\text{–}X}$ orbital of an alkyl halide.

Organolithium compounds: organometallics of general structure R–Li obtained upon reaction of R–X (X = Br, Cl) with metallic Li; e.g., reaction of CH_3Br with Li:



if the molecule of organic halide gets sufficiently close to the metal surface, an electron may "jump" into the σ*$_{C-Br}$ orbital, attracted by the δ+ character of the carbon atom

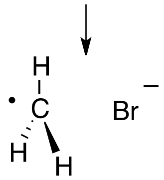


a radical anion: extremely short-lived. It breaks down into a radical and an anion

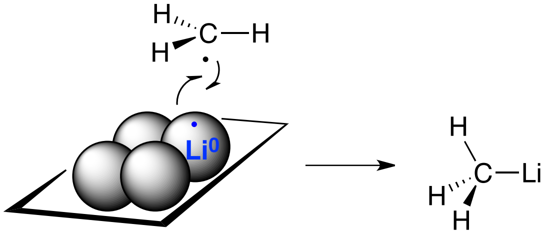
Li atoms (Li^0) on the surface of a metallic chip, surrounded by a "sea of electrons"

Li has 1 electron in a 2s orbital.
It tends to release the electron
to acquire a He-like electron config.

a methyl (alkyl) radical: wants to re-establish an electronic octet . . .

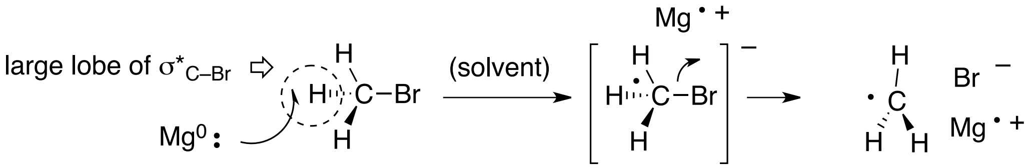


then, perhaps



"methyllithium"

Formation of Grignard reagents (RMgX) by reaction of an alkyl halide with metallic Mg; e.g., reaction of CH_3Br with Mg:

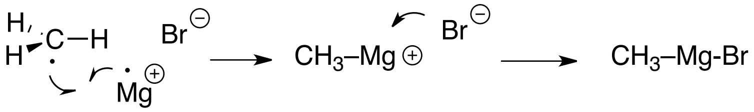


a Mg atom on the surface of a metallic chip: there are 2 electrons in a 3d orbital. It tends to release both to acquire a Ne-like electronic configuration

a radical anion: extremely short-lived. It breaks down into a radical and an anion

a methyl (alkyl) radical: wants to re-establish an electronic octet

so, perhaps:



Note: while the occurrence of an SET process in the first step of the reaction of alkyl halides with reactive metals is fairly well established, the precise sequence of events that lead to the formation of the ultimate organometallic reagent is unknown.

Organo-Mg (Grignard reagents) and– Li compounds as carriers of carbanions:

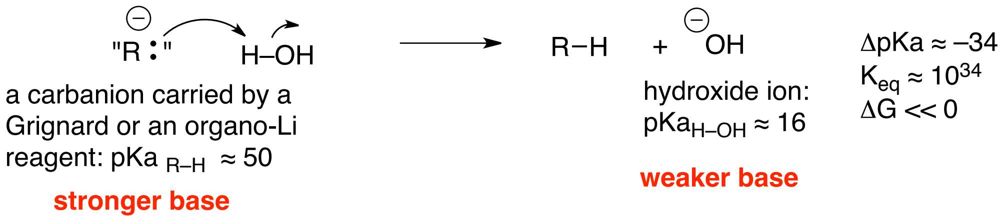
$$R{-}Li \quad \text{or} \quad R{-}MgBr \quad \approx \quad \text{"}\overset{\ominus}{R}\text{:"} \quad \overset{\oplus}{Li} \;/\; \overset{\oplus}{MgBr}$$

Carbanions as the conjugate bases of alkanes

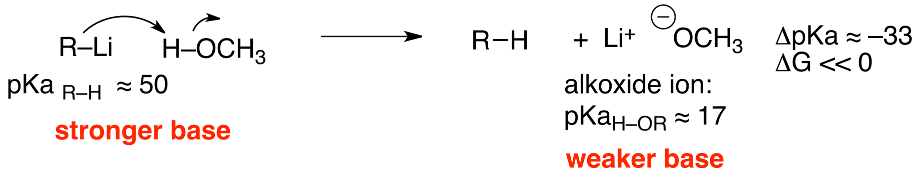
Basicity of carbanions carried by organo-Li or by Grignard reagents (pKa ≈ 50)

Protonation of Grignard and R-Li reagents will occur upon exposure to most Bronsted acids with a pKa < 35-38, such as strong protonic acids (pKa < 0), weak ones such as carboxylic acids (pKa ≈ 5), as well as:

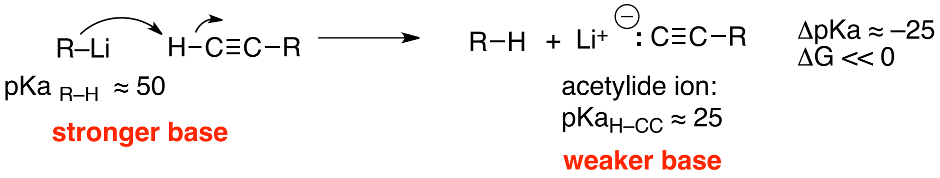
Water:



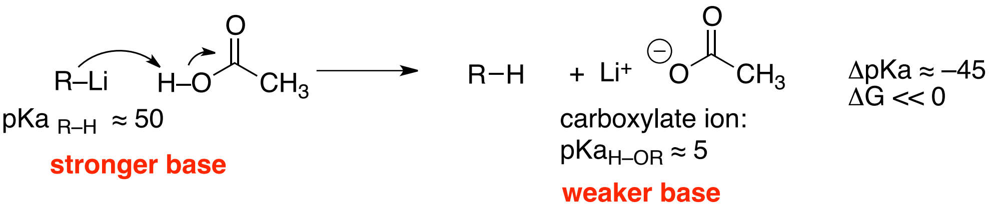
Alcohols:



Terminal alkynes:

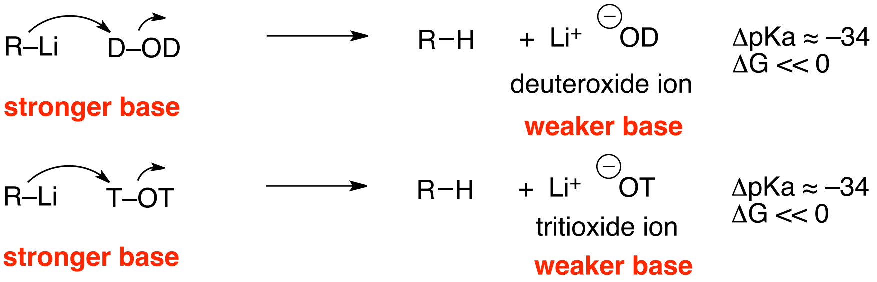


Carboxylic acids:



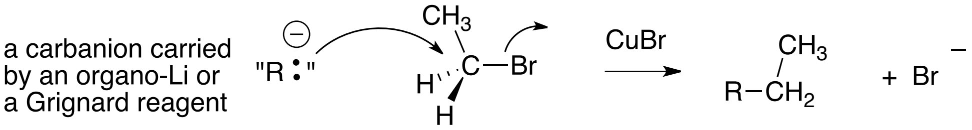
and others still . . .

Deuteration and tritiation of organometallic species as a method for the creation of deuterated / tritiated compounds of interest in biological / medicinal chemistry, physiology, pharmacology, etc. [**note**: tritiated compounds are radioactive (β-emitters)]:



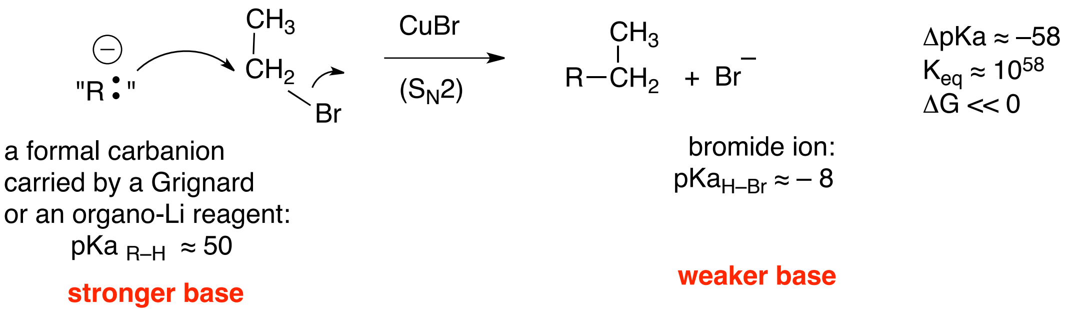
Note: the pKa's of D_2O and T_2O are similar to that of H_2O (≈ 16). Also, it is difficult to create pure T_2O, so the above formulation is a bit misleading: tritiated water is T_2O diluted in a considerable amount of H_2O, which leads to the formation of H–O–T.

Efficient S_N2 reactions of alkyl halides with Grignard and organolithium reagents in the presence of Cu(I) salts; e.g.:

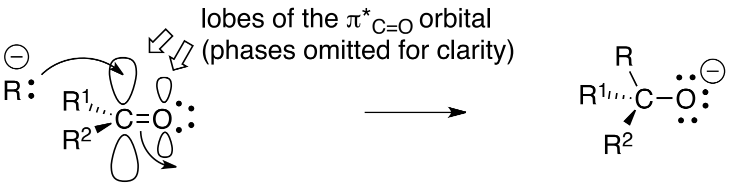


Note: the Cu salt is required to induce the formation of organo-Cu species that are much more effective nucleophiles than organo-Li or organo-Mg reagents. Details will be discussed in more advanced courses.

Change in the basicity of the medium (ΔpKa) as a powerful driving force for the reactions of carbanions

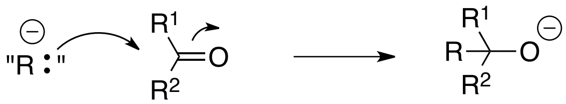


Hypothetical reaction of a carbanion with a carbonyl compound such as an aldehyde or a ketone: donation of electrons from the carbanion into the $\pi^*_{C=O}$ orbital:



Favorable change in the basicity of the medium (ΔpKa) during the above reaction

a formal carbanion carried
by a Grignard / organo-Li
reagent: pKa $_{R\text{–}H}$ ≈ 50



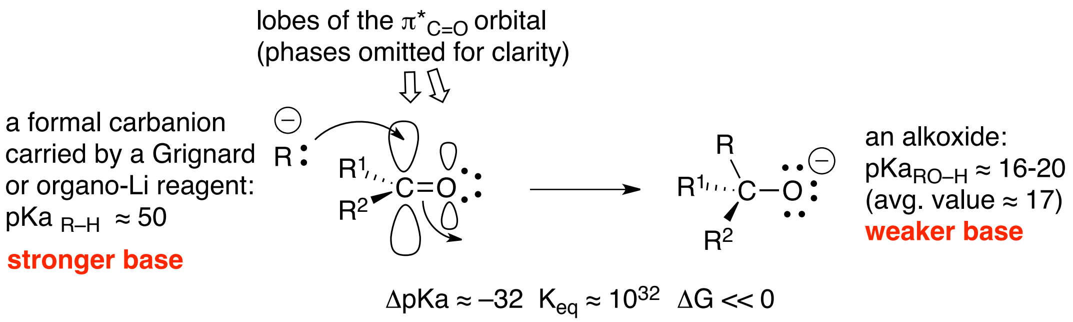
stronger base

$\Delta pKa \approx -33$
$K_{eq} \approx 10^{33}$
$\Delta G << 0$

an alkoxide: pKa$_{RO\text{–}H}$ ≈ 16-20
(avg. value ≈ 17) **weaker base**

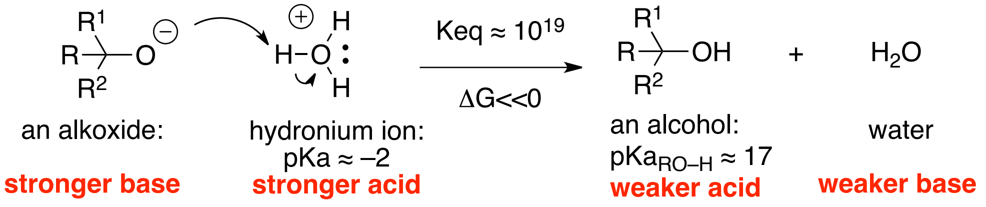
Lecture 27: Addition of Organometallics to Carbonyl Groups

Favorable change in the basicity of the medium (ΔpKa) during the hypothetical reaction of a carbanion with a carbonyl compound such as an aldehyde or a ketone:



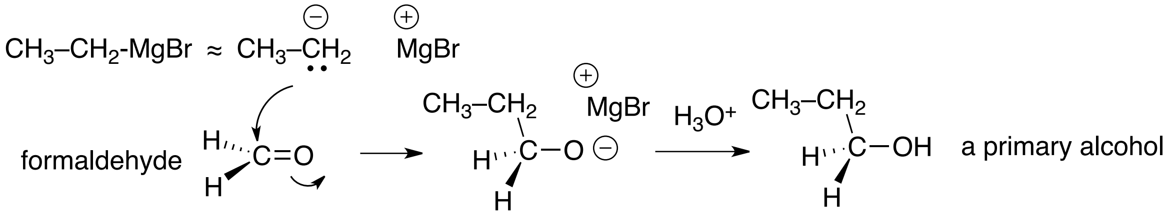
Description of the above process as a **nucleophilic addition** to the C=O group

Treatment of the above alkoxides with mild H_3O^+ to produce electrostatically neutral alcohols:

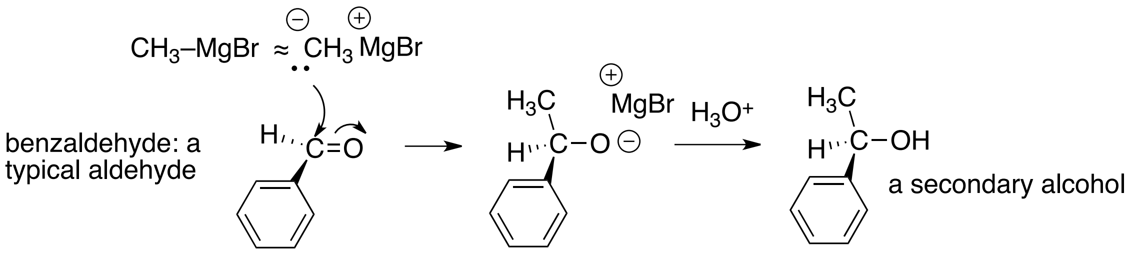


Nucleophilic addition of Grignard or lithium reagents to aldehydes and ketones:

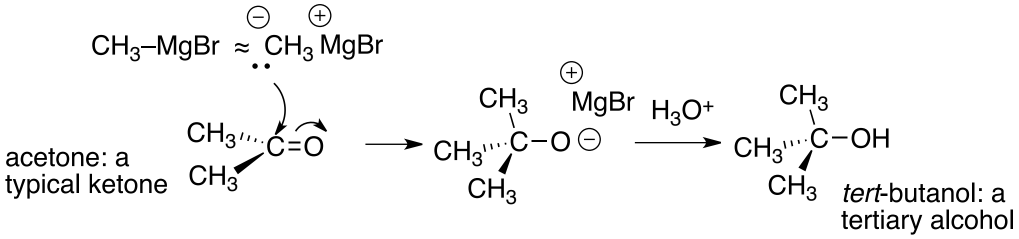
reaction of a Grignard (or organo-Li) reagent with formaldehyde: formation of primary alcohols; e.g.:



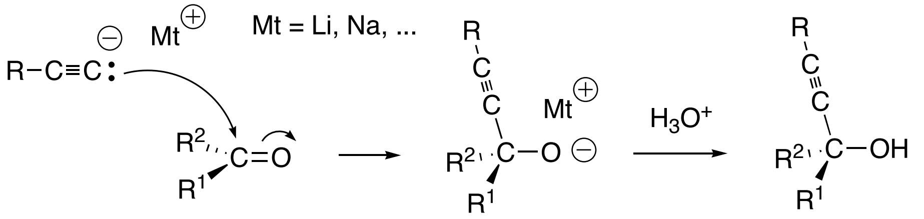
reaction of a Grignard (or organo-Li) reagent with generic aldehydes: formation of secondary alcohols; e.g.:



reaction of a Grignard (or organo-Li) reagent with generic ketones: formation of tertiary alcohols; e.g.:



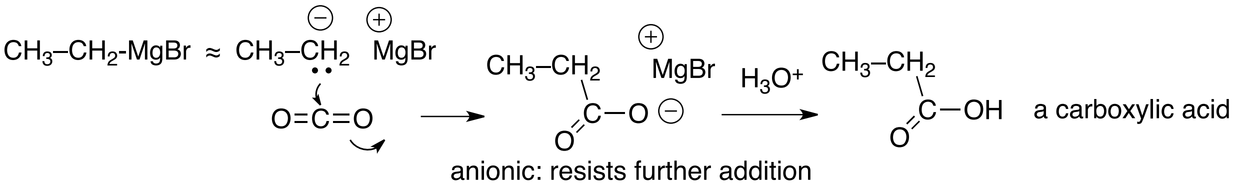
Nucleophilic addition of acetylide-type carbanions to aldehydes and ketones:



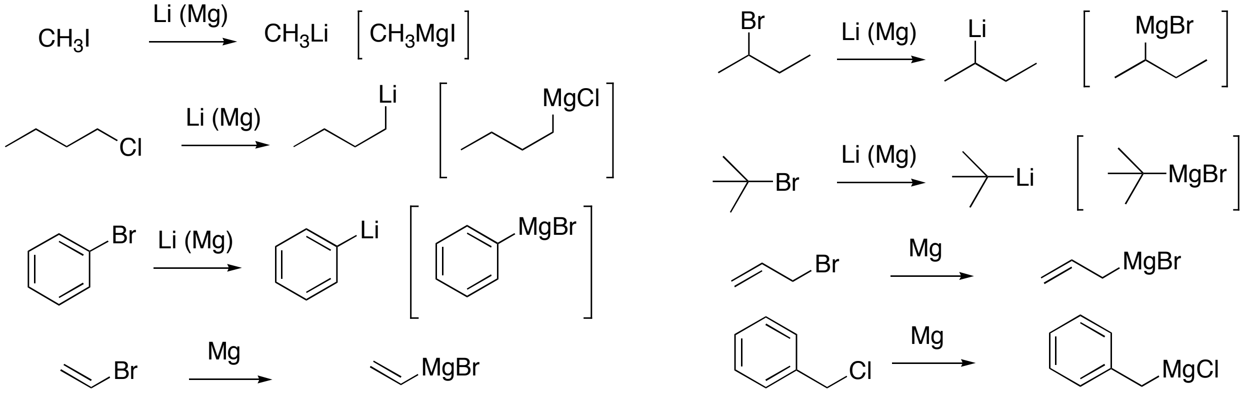
R^1 = H; R^2 = alkyl: aldehyde
R^1, R^2 = alkyl: ketone

R^1 = H; R^2 = alkyl: secondary alcohol
R^1, R^2 = alkyl: tertiary alcohol

Reaction of Grignard (or organo-Li) reagents with CO_2: formation of carboxylates and — upon protonation — of carboxylic acids; e.g.:

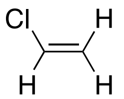


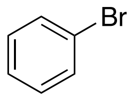
Principle: Grignard and organolithium reagents may be prepared from virtually any alkyl chloride, bromide or iodide (but not fluoride), including allylic, benzylic, vinyl, and aryl halides



reminder: vinyl halides are those in which the halogen atom is attached to the sp^2 carbon of an alkene; halides in which the halogen atom is attached to the sp^2 carbon of a benzene (more generally, of a benzene-like) ring are described as phenyl (more generally, aryl) halides:

vinyl chloride:
a vinyl halide

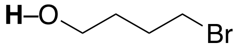




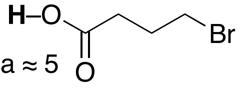
bromobenzene:
an aryl halide

Incompatibility of Grignard / organo-Li reagents with:

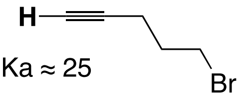
a. **Bronsted acidic groups** (pKa less than ca. 40) present on the same molecule, e.g.:



pKa ≈ 18



pKa ≈ 5

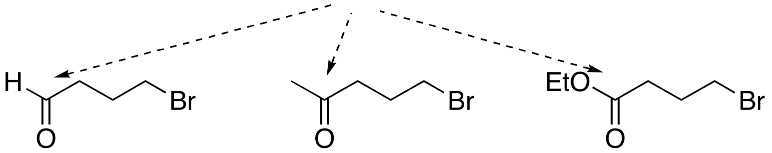


pKa ≈ 25

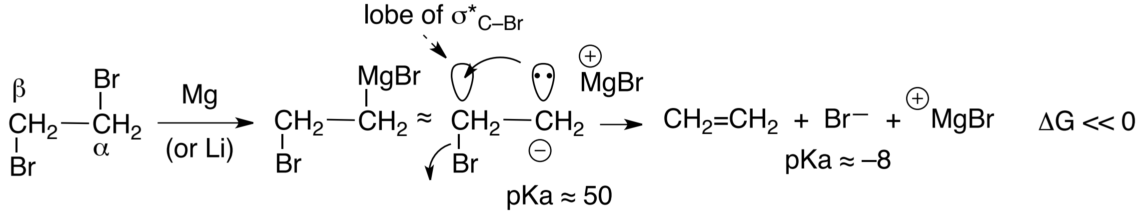
boldface **H**'s will protonate Grignard / organo-Li species

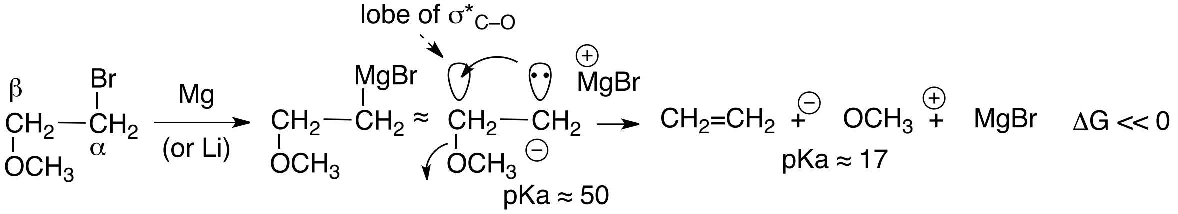
b. **Electrophilic groups** present on the same molecule, e.g.:

electrophilic: the Grignard rgt. would add to the C=O



c. **Potential leaving groups** present at the β-position, e.g.:





therefore, the above alkyl halides fail to yield stable Grignard or organolithium reagents

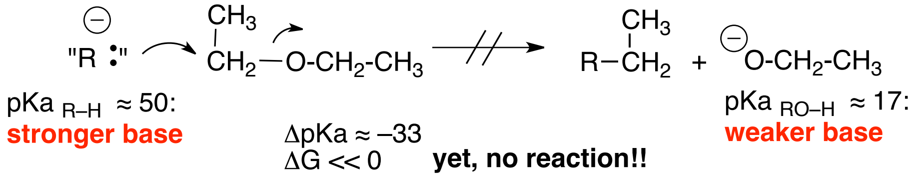
Compatibility of Grignard reagents with functional groups that are neither Bronsted acidic, nor electrophilic, nor potential leaving groups situated at the β-position; e.g.:

$$\mathrm{CH_3O{-}\overset{\gamma}{CH_2}{-}\overset{\beta}{CH_2}{-}\overset{\alpha}{CH_2}{-}Br \xrightarrow{Mg} CH_3O{-}CH_2{-}CH_2{-}CH_2{-}MgBr} \qquad \textbf{OK}$$

The CH_3O group in the above organometallic reagent is located at the γ, not the β, position; so it does not interact with the anionic site. **The Grignard reagent is stable.**

Preparation of organo-Li and Grignard reagents in ether solvents, e.g., in diethyl ether

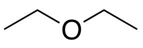
Reminder: the leaving group in an S_N2 reaction must be the conjugate base of a very strong acid (pKa < 0). Consequently, organo-Li or –Mg reagents could not possibly displace, e.g., $CH_3CH_2O^-$ from diethyl ether, even though ***theoretically*** the reaction is thermodynamically favorable:

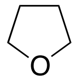


Lecture 28: Preparation of Ethers and Epoxides

Ethers: acyclic and cyclic

diethyl ether: a typical acyclic ether

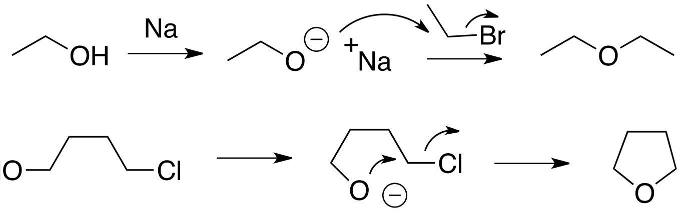




tetrahydrofuran (THF): a typical cyclic ether

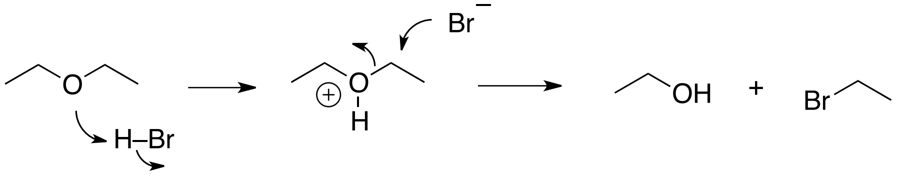
Poor reactivity of ethers and consequent use thereof as solvents for many organic reactions

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



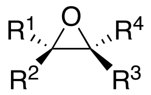
Cleavage of ethers with H–X resulting in formation of a molecule of alcohol and one of alkyl halide; e.g.:

via:



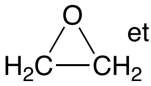
Epoxides or oxiranes: cyclic ethers in which the oxygen atom is part of a three membered ring:

a generic epoxide (oxirane):

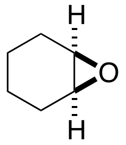


Enhanced reactivity of epoxides due to angle strain

Nomenclature of epoxides: attaching the term "oxide" to the name of the corresponding alkene:

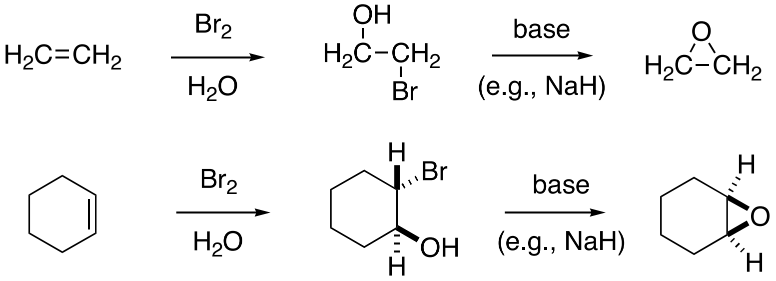


ethylene oxide

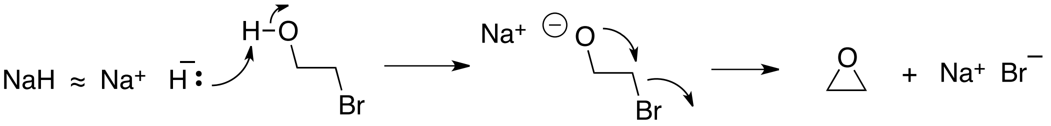


cyclohexene oxide

Preparation of epoxides by cyclization of halohydrins. Examples:

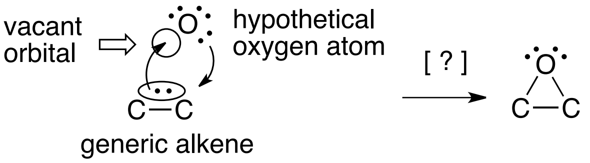


The base-promoted cyclization of halohydrins as an intramolecular variant of the Williamson reaction, which is itself a special case of S_N2 reaction; e.g.:



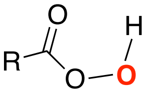
Direct conversion of olefins into epoxides by formal reaction with an "oxygen atom"

note: the electronic configuration of O shown in this diagram is not necessarily in the most favorable one



Peroxycarboxylic acids (formula below) as reagents that behave as formal carriers of "oxygen atoms" in epoxide-forming reactions

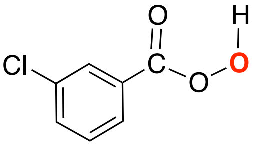
R = any alkyl group



the O atom that is transferable to an alkene is shown in **red**

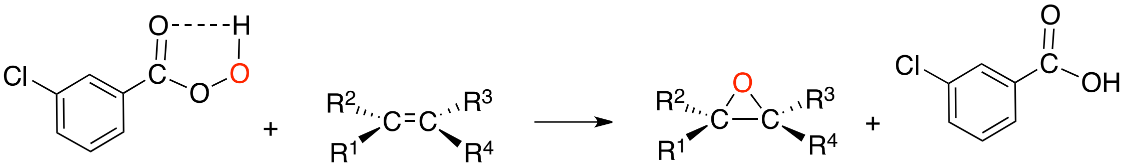
a peroxycarboxylic acid

Meta-chloroperoxybenzoic acid (MCPBA) as an especially convenient peroxyacid reagent for olefin epoxidation:



meta-chloroperoxybenzoic acid

The epoxidation reaction of alkenes: their conversion into epoxides, e.g., by reaction with MCPBA



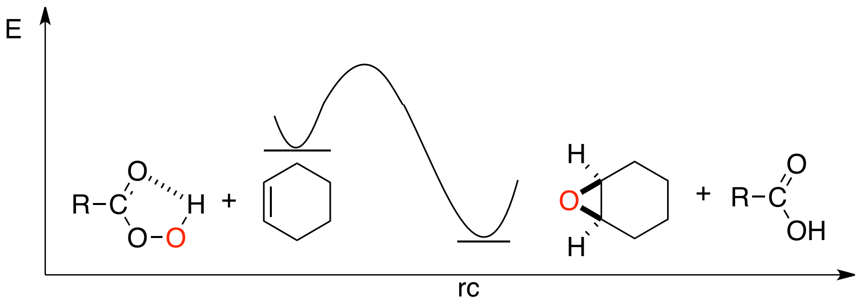
MCPBA
red: transferable O atom

a generic alkene

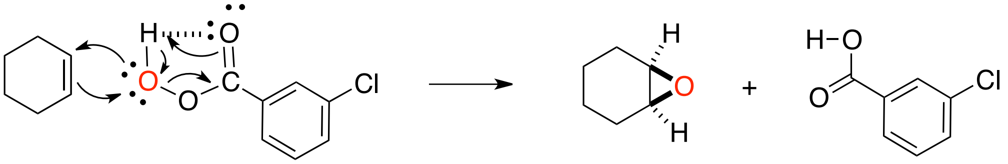
an epoxide

meta-chlorobenzoic
acid: largely inert

Concerted mechanism of peroxyacid epoxidation of alkenes: the epoxide forms in a single kinetic step though a mechanism that involves no radical or ionic intermediates:



Presumed mechanism of peroxyacid epoxidation of olefins; e.g., with MCPBA:

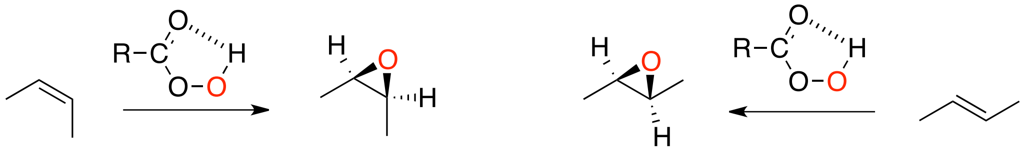


meta-chloroperoxybenzoic
acid (MCPBA)

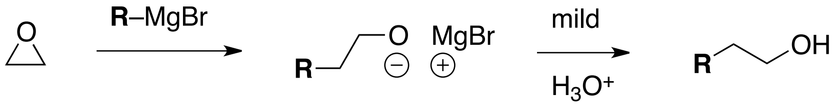
meta-chlorobenzoic acid

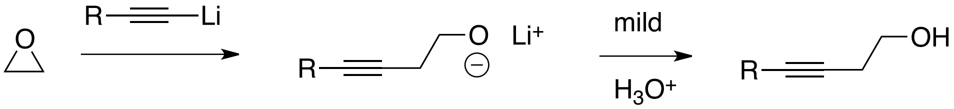
Strictly syn course of the epoxidation of alkenes with peroxyacid reagents: both C–O bonds form from the same face of the olefinic π system

Retention of olefin geometry during epoxidation reactions; e.g.:



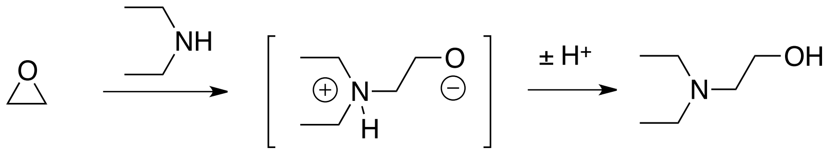
Principle: **more reactive, basic** nucleophiles (= conjugate bases of acids with pKa >10; such as Grignard reagents, acetylide ions, etc.), induce nucleophilic opening of epoxides through S_N2-type reactions *despite the poor leaving group abilities of the epoxide oxygen* (now departing as an alkoxide). These reactions are driven by release of strain. Examples:

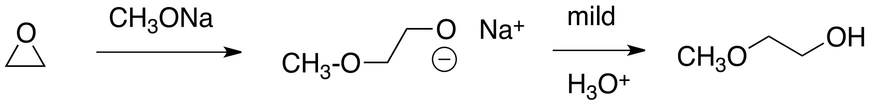

O
R–MgBr
R
O
MgBr
mild
H3O+
R
OH

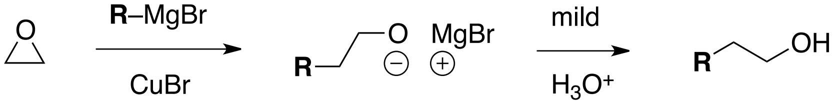

O
R
Li
R
O
Li+
mild
H3O+
R
OH

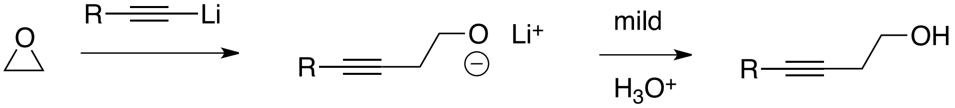
Lecture 29: Chemistry of Epoxides

Principle: **more reactive, basic** nucleophiles (= conjugate bases of acids with pKa >10; such as Grignard reagents, acetylide ions, alkoxides, hydroxide, amines, cyanide ion, etc.) induce nucleophilic opening of epoxides through S_N2-type reactions *despite the poor leaving group abilities of the epoxide oxygen* (now departing as an alkoxide). These reactions are driven by release of strain

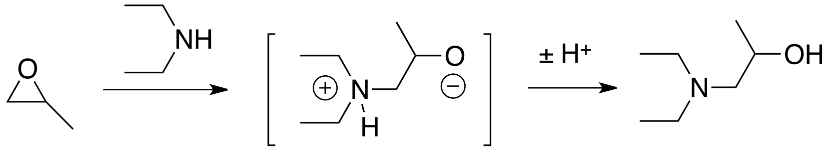


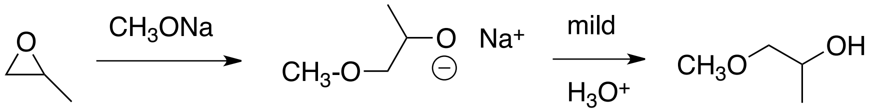


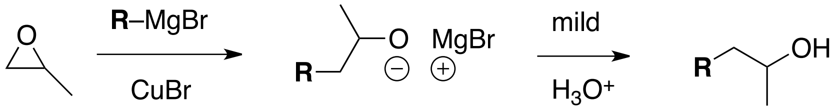


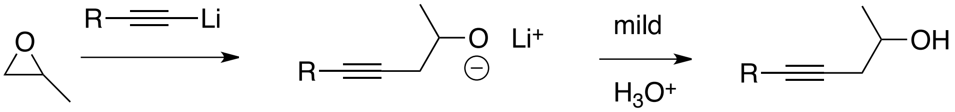


Regiochemical course of S_N2 cleavage of unsymmetrical epoxides with basic nucleophiles: attack at the less sterically hindered position (more accessible σ^*_{C-O} orbital). Examples:

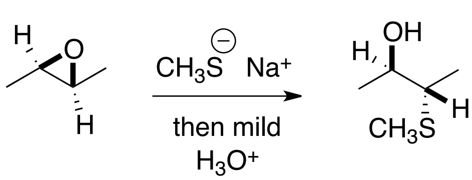


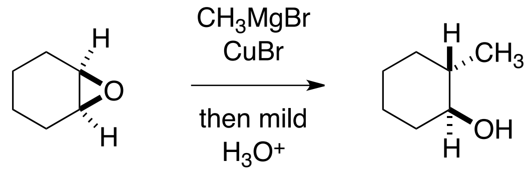


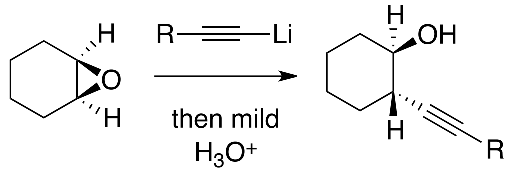


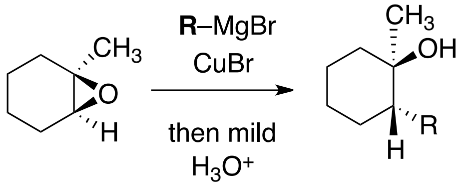


Inversion of configuration in the above reactions (the Nu: interacts with the σ^*_{C-O} orbital); e.g.:







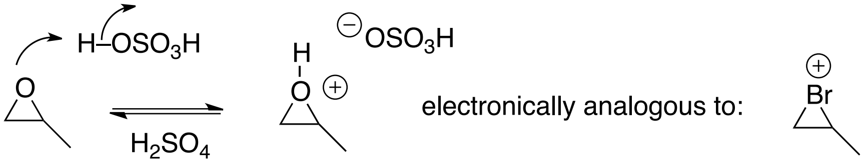


Principle: **weak, nonbasic** nucleophiles (= conjugate bases of acids with pKa < 0) such as H_2O, alcohols, etc. react with epoxides upon activation of the epoxide oxygen; e.g., by protonation

Approximate pKa of a protonated epoxide: ≈ -3

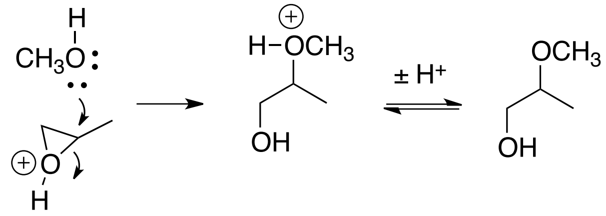
Requirement for a strong Bronsted acid (pKa < 0, such as H_2SO_4, H_3O^+, HCl, HBr ...) to generate concentrations of protonated epoxide sufficient to induce the above transformations

Electronic similarity between protonated epoxides and halonium ions and predictable halonium ion – like reactivity of protonated epoxides



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

- extreme degree of C–O bond polarization
- the more highly substituted carbon sustains more (+) charge than the less substituted one
- H_2O, alcohols, etc., tend to react at the more highly substituted carbon; e.g.:

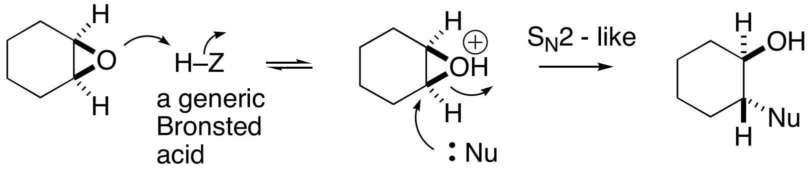


Inversion of configuration in acid-catalyzed epoxide opening (the nucleophile interacts with the large lobe of the σ^*_{C-O} orbital, which is associated with the C atom)

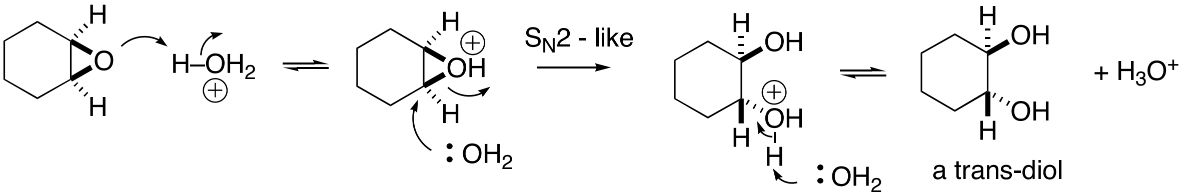
Type of nucleophiles that may be used in an acid-catalyzed opening of an epoxide: those nucleophiles such as H_2O, CH_3OH, Br^-, Cl^-, etc., that are conjugate bases of strong acids (pKa<0), and that therefore are relatively insensitive to the action of protonic acids.

> **Note:** basic nucleophiles (=conjugate bases of weak acids with pKa ≥ 5), such as amines, cyanide ion, alkoxide ions, acetylide ions, Grignard reagents, etc., **cannot be used in an acid-catalyzed opening of an epoxide**, because they would be protonated instantly and irreversibly by strong acids.

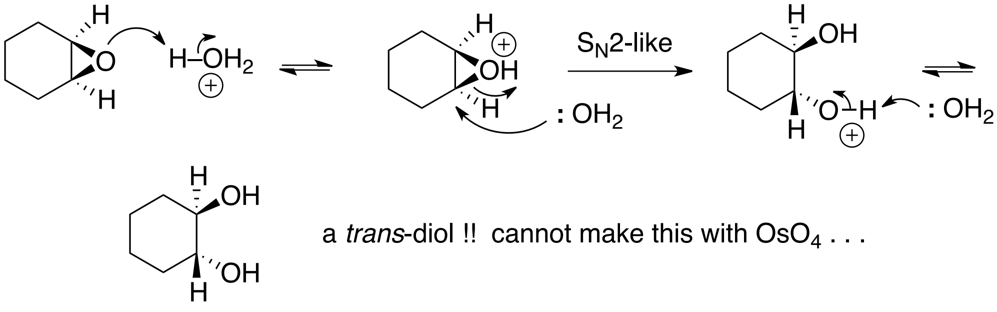
General mechanism of acid-promoted cleavage of epoxides by **weak**, **nonbasic** nucleophiles:



Reaction of epoxides with H_3O^+ (e.g., aqueous sulfuric acid): preparation of trans-diols by addition of water to (=hydration of) epoxides:

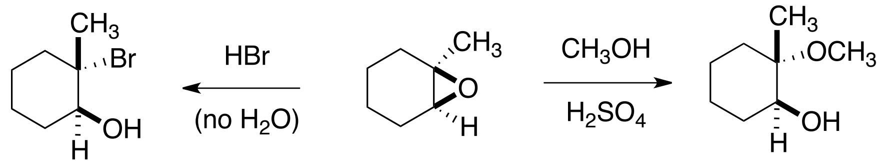


Stereochemical complementarity of the above process vs. the OsO_4 reaction:



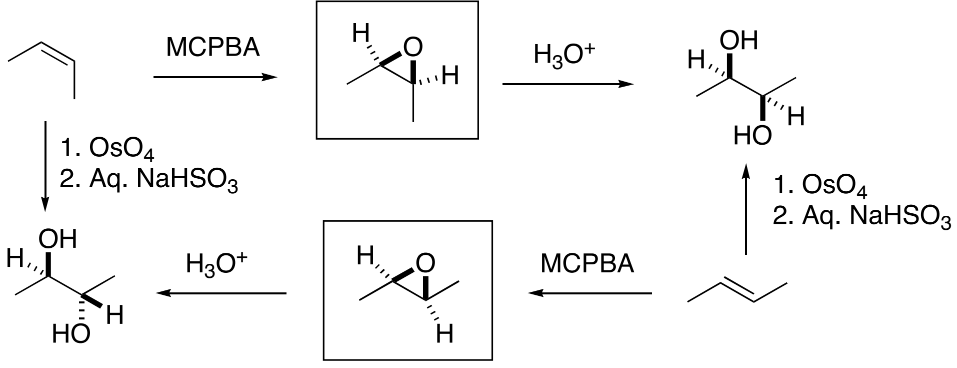
Stereochemical aspects of the nucleophilic opening of epoxides: inversion of configuration at the epoxide carbon being attacked by the nucleophile (S_N2 . . .) during the above reactions

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



moreover . . .

syn-1,2-diol

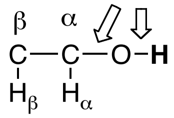


anti-1,2-diol

Lecture 30: Chemistry of Alcohols – Conversion into Halides

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

C–O and O–H: very reactive bonds



Principle: the reactivity of alcohols is controlled by the Bronsted acidity, the Bronsted basicity and the nucleophilicity of the OH group

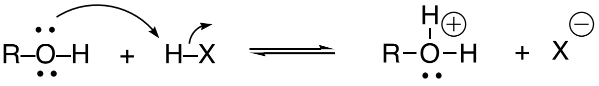
Weak Bronsted acidity of the O–H bond of alcohols (pKa = 17-20; average value ≈ 18)

Reminder: formation of alkoxides by reaction of alcohols with reactive metals (Li, Na, K, ...) or metal hydrides such as NaH or KH:

$$2\ \text{R–O-H} + 2\ \text{Mt} \xrightarrow{(\text{Mt} = \text{Li, Na, K})} 2\ \text{R–O-Mt} + H_2$$

$$\text{R–O-H} + \text{NaH} \longrightarrow \text{R–ONa} + H_2$$

Weak Bronsted basicity of alcohols: protonation of the OH group:

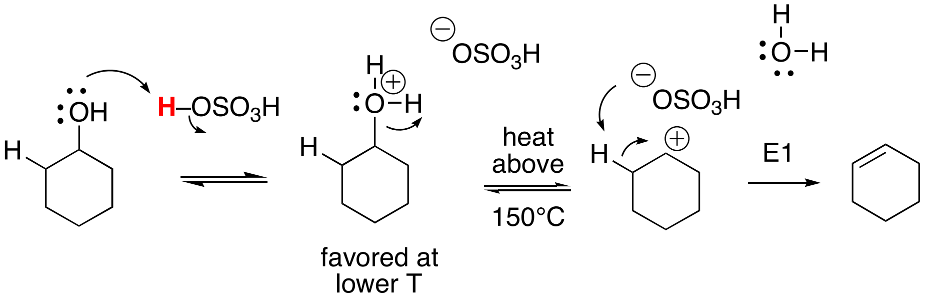


$$\text{R–}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{–H} + \text{H–X} \rightleftharpoons \text{R–}\overset{\text{H}\oplus}{\underset{\cdot\cdot}{\text{O}}}\text{–H} + \text{X}^{\ominus}$$

pKa ≈ –2 - –3

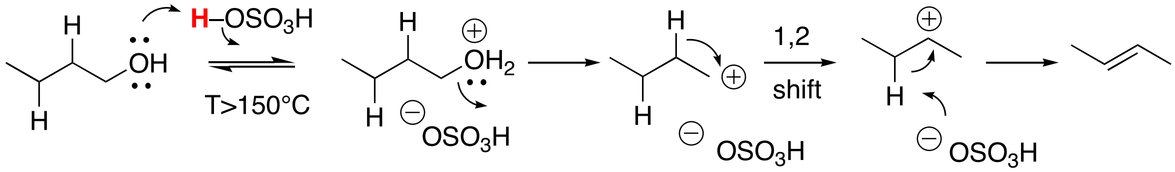
reminders:

(a) thermal activation of a protonated alcohol results in "dehydration" of alcohols vis dissociation and E1-like olefin formation:. Example:



(b) Ease of acid-catalyzed dehydration of alcohols: tertiary > secondary > primary due to the relative degree of stabilization of tertiary (best stabilized – faster-forming) vs. secondary (less stabilized – formed slower) vs. primary (least well stabilized: slow to form) carbocations

(c) Possibility of rearrangements during the dehydration of alcohols due to the intervention of carbocation intermediates; e.g.:



Principle: protonation of alcohols transforms the OH group into an incipient molecule of H_2O, which is the conjugate base of a strong Bronsted acid, H_3O^+ (pKa ≈ –2). So, H_2O can function as a leaving group in S_N2/S_N1 or E2/E1 reactions (cf. the case of ethers; notes of Nov. 16)

> **Note**: the OH group *per se* cannot function as a leaving group in S_N2/S_N1 or E2/E1 reactions, because then it would have to leave as HO^-, which is the conjugate base of the weak acid, H_2O (pKa≈16). Recall that only conjugate bases of strong acids (pKa<0) can function as leaving groups in such reactions (notes of Oct. 28).

Reactions in which a protonated alcohol undergoes nucleophilic substitution of H_2O:

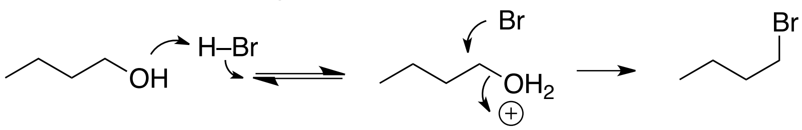
Reactions of alcohols with H–X: formation of alkyl halides:

$$R{-}OH \xrightarrow{H{-}X} R{-}X \qquad \boxed{X = Cl, Br, I}$$

primary, secondary or tertiary alcohol

primary, secondary or tertiary alkyl halide

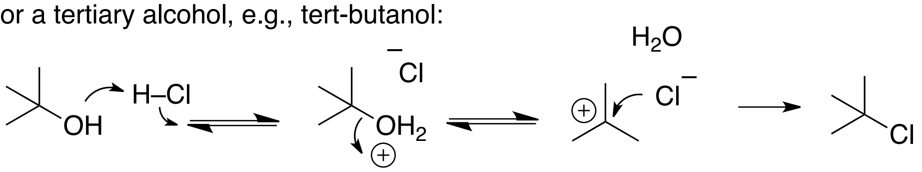
for a primary alcohol, e.g., 1-butanol:



primary: backside readily accessible

⇨ reacts by S_N2 mechanism

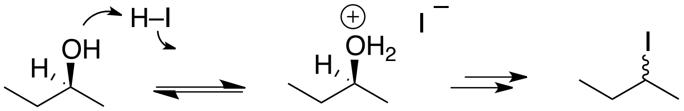
for a tertiary alcohol, e.g., tert-butanol:



tertiary: backside inaccessible

⇨ reacts by S_N1 mechanism

for a secondary alcohol, e.g., (*S*)-2-butanol:



alkyl halide may forms with partial erosion of stereochemical purity

secondary: backside fairly accessible

⇨ tends to react partly by S_N2 and partly by S_N1 mechanism: precise extent of S_N2 / S_N1 reactivity depends on structure and conditions

Principle: alkyl halides are best prepared from alcohols

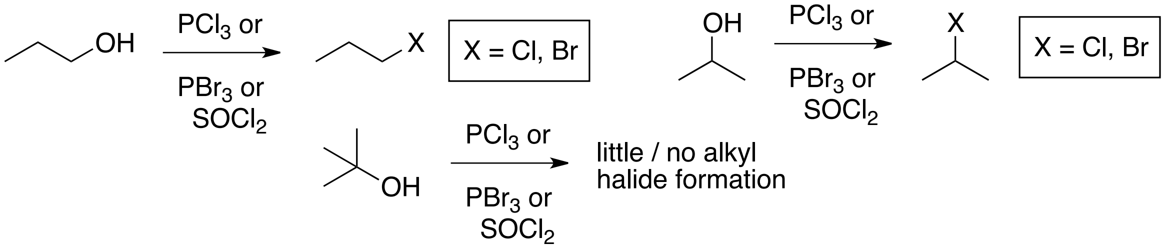
Potential usefulness of halogenation reagents that might permit the conversion of secondary alcohols into secondary halides in a stereochemically unequivocal manner (= 100% inversion or 100% retention of configuration)

Phosphorus and sulfur halides that convert alcohols to alkyl halides in a stereochemically clean manner: phosphorus trichloride / tribromide (PCl_3, PBr_3), thionyl chloride ($SOCl_2$)

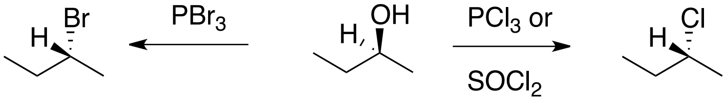
Electrophilic character of the above reagents and facile reaction thereof with nucleophiles

Principle: the above reagents rely on the **nucleophilic** properties of the OH group to achieve conversion of alcohols into alkyl halides

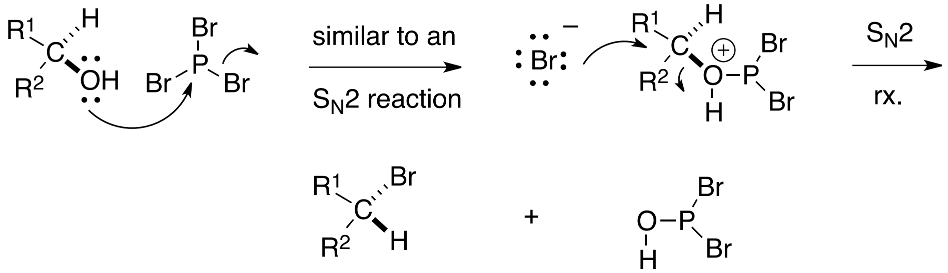
Principle: only primary and secondary alcohols are sufficiently nucleophilic to react with the above reagents. The OH group of tertiary alcohols is poorly nucleophilic due to steric hindrance:



Inversion of configuration during the reaction of secondary alcohols with the above reagents:



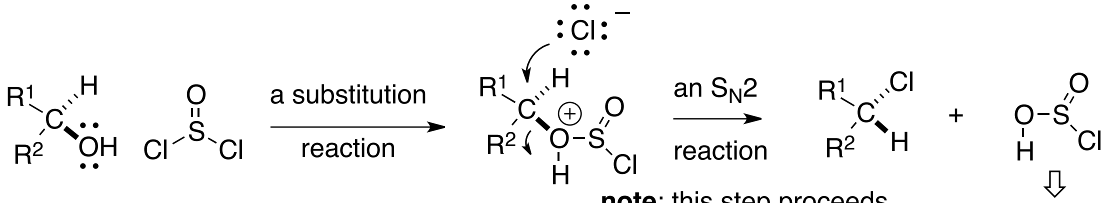
Probable mechanism of the conversion of primary / secondary alcohols to alkyl bromides with, e.g., PBr_3 (PCl_3 reacts in the same fashion):



notice inversion of config.
at the carbon atom

note: HO–PBr_2 still posseses P–Br bonds, so it may undergo a 2nd and a 3rd round of the same reaction, ultimately producing phosphorous acid, $P(OH)_3$

Probable mechanism of the conversion of primary and secondary alcohols into alkyl chlorides with $SOCl_2$:

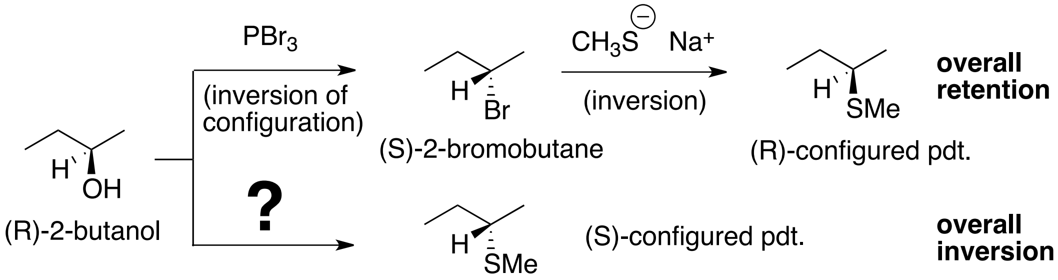


note: this step proceeds with inversion of config. at the carbon atom

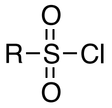
decomposes rapidly to HCl + SO_2

Lecture 31: Activation of Alcohols as Sulfonate Esters

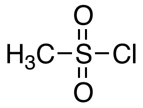
Desirability of a method for "alcohol activation" that would be stereochemically complementary to that involving reaction of an alcohol with P / S halides (notes of Nov 20):



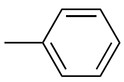
Sulfonyl chlorides: para-toluenesulfonyl ("tosyl") chloride, methanesulfonyl ("mesyl") chloride



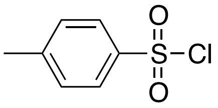
A generic sulfonyl chloride: R = any alkyl group



methanesulfonyl chloride ("mesyl chloride")

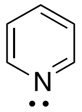


Toluene (= methyl benzene)



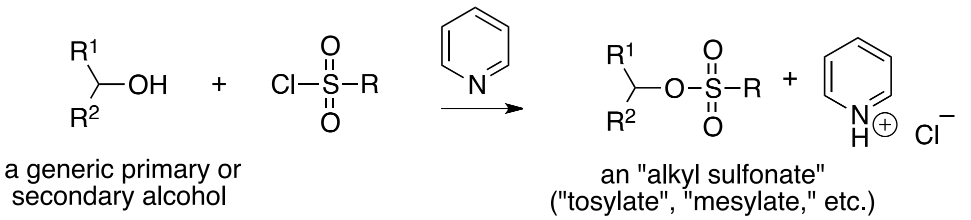
para-toluenesulfonyl chloride ("tosyl chloride")

Pyridine: a weakly basic, nucleophilic analog of benzene in which an N atom replaces a CH unit:



pyridine

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

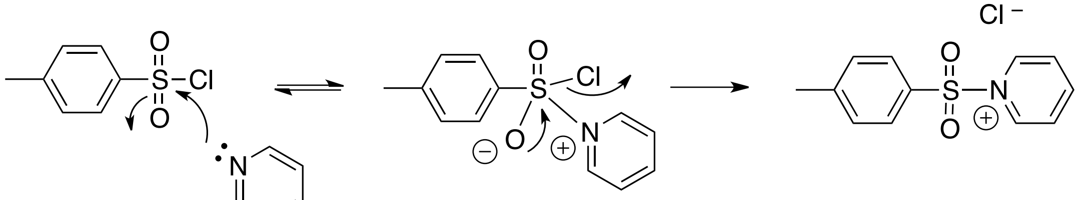


note: tertiary alcohols are insufficiently nucleophilic to react with sulfonyl chlorides

Presumed mechanism for the formation of sulfonate esters from primary and secondary (but not tertiary) alcohols and sulfonyl chlorides:

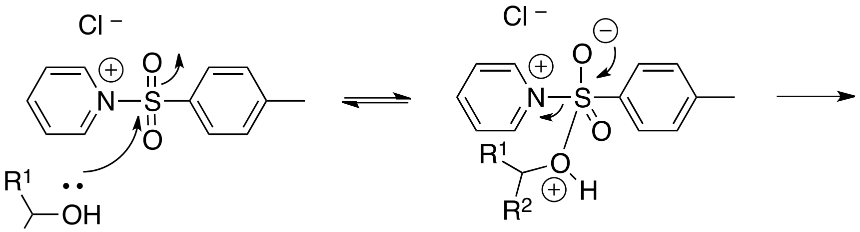
- slow rate of reaction of an alcohol with sulfonyl chlorides in the presence of generic bases
- pyridine as a **nucleophilic catalyst** that greatly accelerates the reaction of an alcohol with a sulfonyl chloride by:

(i) reacting with sulfonyl chloride first, leading to a complex …

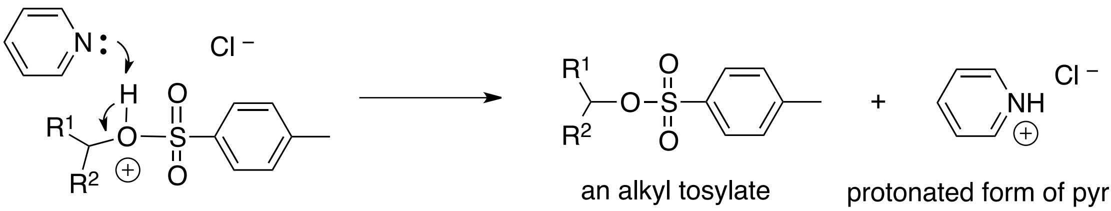


notice the mechanistic similarity with the chemistry of $SOCl_2$

(ii) which reacts at a very fast rate with primary and secondary alcohols:



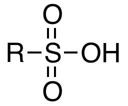
notice the mechanistic similarity with the chemistry of $SOCl_2$



an alkyl tosylate protonated form of pyridine

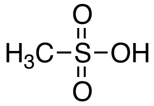
note: the reasons why the pyridine-sulfonyl group complex reacts with alcohols at a much faster rate than the parent sulfonyl chloride will be discussed in more advanced courses.

Sulfonic acids such as para-toluenesulfonic acid or methanesulfonic acids as strongly Bronsted acidic agents (sulfuric acid-like!!)



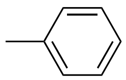
$$R-\overset{\overset{\Large O}{\|}}{\underset{\underset{\Large O}{\|}}{S}}-OH$$

A generic sulfonic acid: R = alkyl group

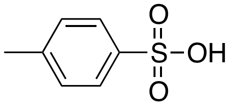


$$H_3C-\overset{\overset{\Large O}{\|}}{\underset{\underset{\Large O}{\|}}{S}}-OH$$

methanesulfonic acid



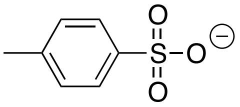
Toluene
(= methyl benzene)

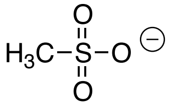


para-toluenesulfonic acid

Anions of sulfonic acids, i.e., sulfonate ions, as excellent leaving groups in S_N2 and E2 reactions, due to the fact that they are the conjugate bases of strong Bronsted acids (the parent sulfonic acids have pKa ≤ 0):

para-toluenesulfonate ion



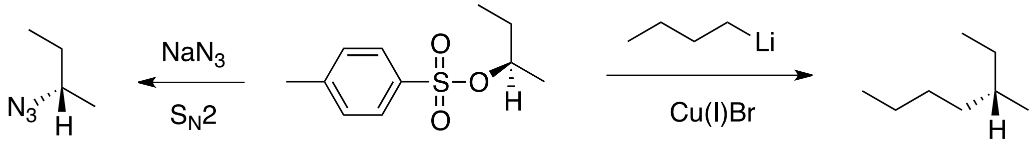


$$H_3C-\overset{\overset{\Large O}{\|}}{\underset{\underset{\Large O}{\|}}{S}}-O^{\ominus}$$

methanesulfonate ion

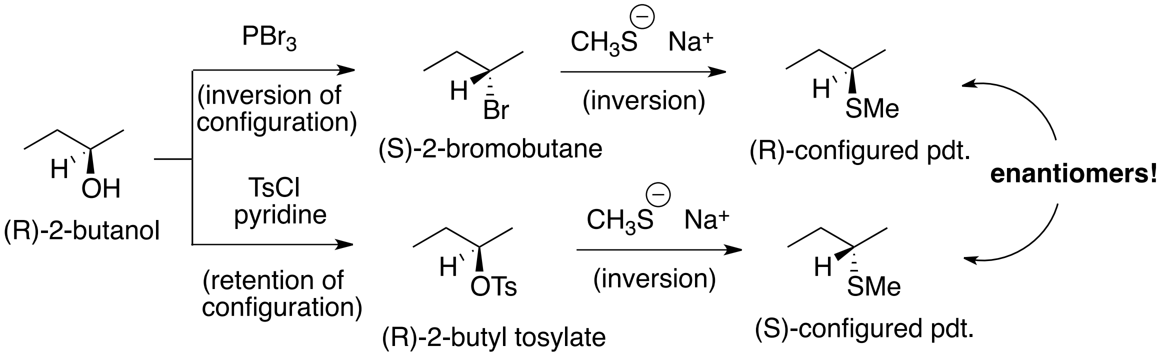
Principle: alkyl sulfonates undergo S_N2 and E2 reaction in a manner essentially identical to that of alkyl halides

Substitution reactions of sulfonate esters; e.g.:



(S)-2-azidobutane (R)-2-butyl tosylate

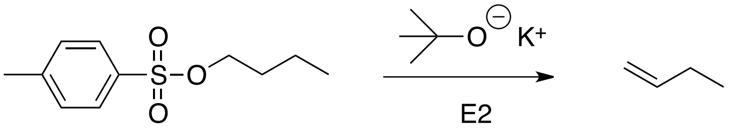
Stereochemical complementarity of sulfonate ester vs. PBr_3 technology:



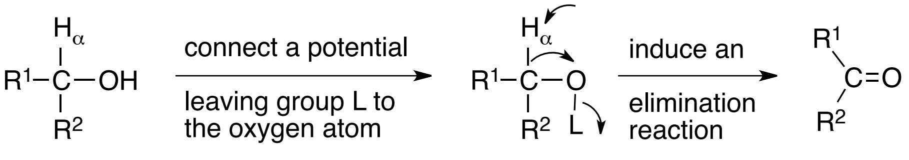
(R)-2-butanol (S)-2-bromobutane (R)-configured pdt. (R)-2-butyl tosylate (S)-configured pdt.

one may thus access either enantiomer of a product of S_N2 reaction of a suitably activated alcohol by the judicious choice of the activation method: sulfonate technology produces overall inversion of configuration; PBr_3 technology, overall retention (via a double inversion)

E2 reactions of sulfonate esters; e.g.:



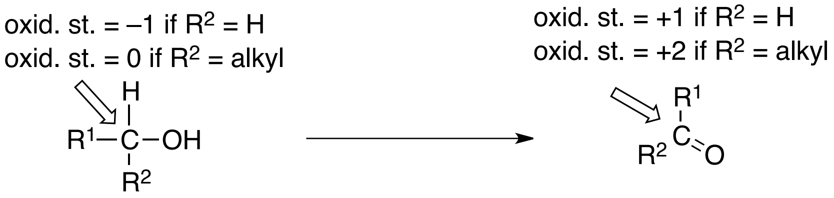
Possible mode of activation of the α-H of a primary or secondary alcohol:



a generic primary or secondary alcohol a carbonyl compound

Principle: activation of the α-H of a primary or secondary alcohol as seen above results in the conversion of the starting alcohol into a carbonyl compound

The conversion of an alcohol into a carbonyl compound as an oxidation reaction



the OH-bearing C atom goes from the oxidation state of –1 or 0 to that of +1 or +2: **it undergoes a two-electron oxidation; so "something else" must undergo a two-electron reduction...**

Principle: the leaving group L in the above reaction must undergo a two-electron reduction

Principle: the leaving group L in the above reaction is often a metal in a high oxidation state

Chromium (VI) as an especially valuable metal for the above reactions

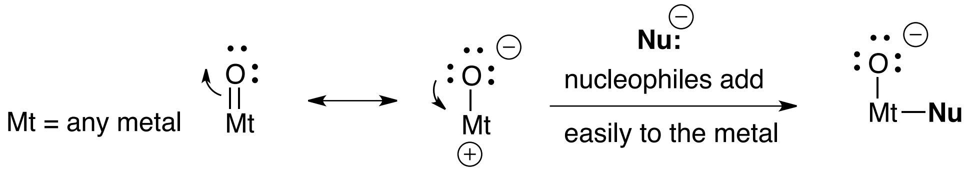
Lecture 32: Oxidation of Alcohols

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

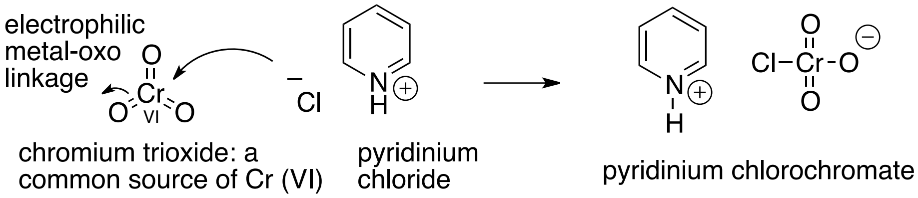
Chromiun trioxide, CrO_3 (inexpensive industrial chemical), as a convenient source of Cr(VI)

Toxic and carcinogenic properties of Cr(VI) compounds – including CrO_3

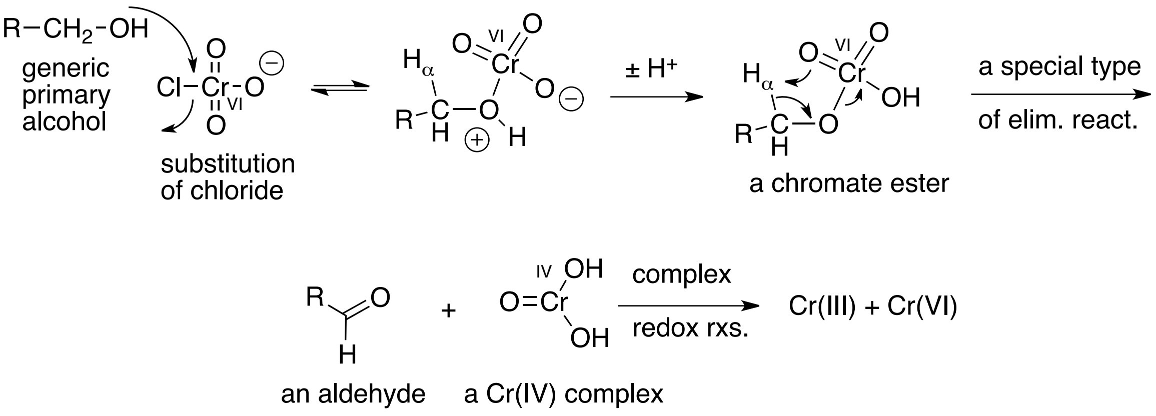
Electrophilic reactivity of metal-oxo linkages, Mt=O:



Pyridinium chlorochromate (PCC):

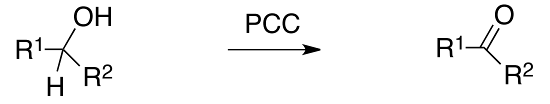


PCC oxidation of primary alcohols to aldehydes & secondary alcohols to ketones



fine details of the mechanism of PCC oxidation remain unclear. The mechanism shown above is one of a number of plausible mechanism that differ for the precise sequence of events leading to the Cr(VI) complex that ultimately decomposes to give the carbonyl product.

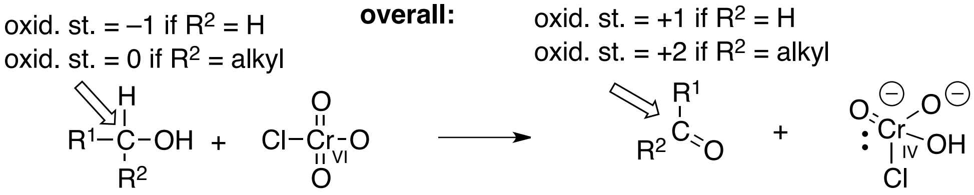
Likewise:



generic secondary alcohol

a ketone

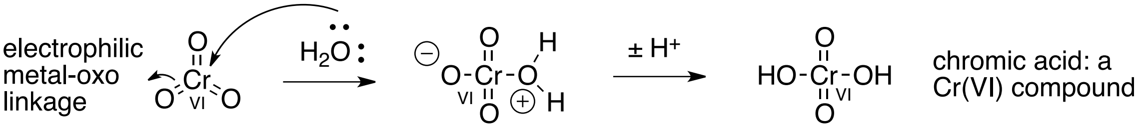
The conversion of an alcohol into a carbonyl compound as an oxidation reaction:



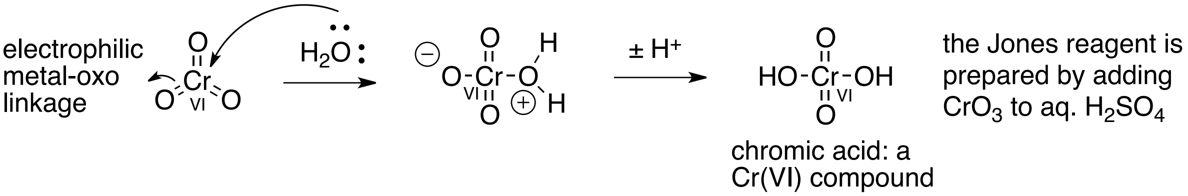
the OH-bearing C atom advances from the oxidation state of –1 or 0 to that of +1 or +2:
it undergoes a two-electron oxidation.
the Cr atom recedes from the oxidation state of +6 to that of +4:
it undergoes a two-electron reduction.

Inability of tertiary alcohols to undergo oxidation, due to the absence of α-H's

Conversion of chromium trioxide into chromic acid, H_2CrO_4 (the Cr analog of H_2SO_4)



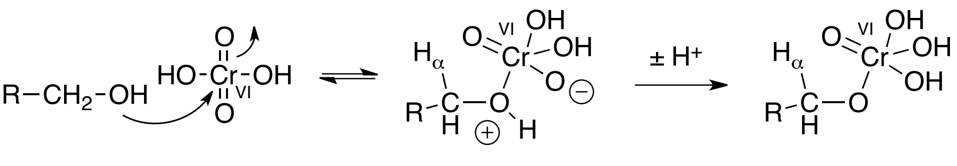
The Jones reagent: a solution of chromic acid, H_2CrO_4, in aqueous H_2SO_4:



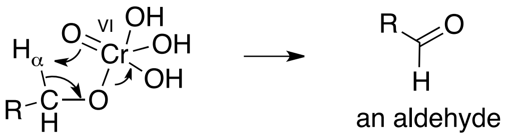
IMPORTANT: PCC is used ONLY in anhydrous (=water-free) media, while Jones rgt. is an aqueous solution. This seemingly minor difference has a major influence on the course of the reaction of primary alcohols with the two reagents.

The Jones reagent: oxidation of primary alcohols to carboxylic acids and secondary alcohols to ketones in aqueous medium

Reaction of the Jones reagent with primary alcohols: initial formation of a chromate ester:

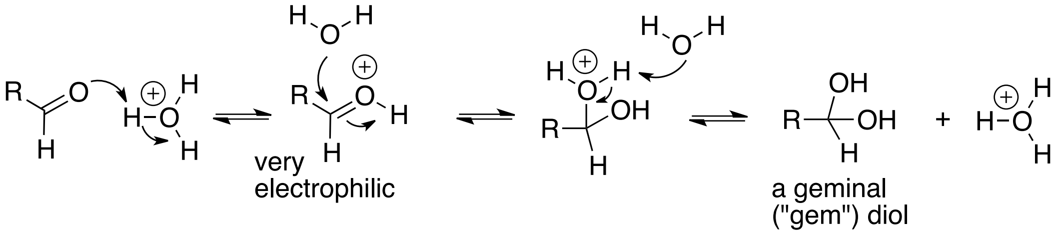


Reaction of the Jones reagent with primary alcohols: decomposition of the chromate ester to give an aldehyde:

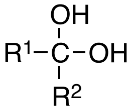


but the aldehyde is not the final product of the reaction (the carboxylic acid is): evidently, something must happen to the aldehyde that causes it to become a carboxylic acid…

Acid-promoted equilibration of the aldehyde with a geminal diol in aqueous acid:

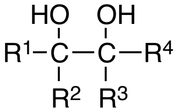


note: geminal diols (obtained by the reversible hydration of carbonyl functions) display a pair of OH groups connected to the same carbon atom. Vicinal diols (obtained by OsO_4 oxidation of alkenes) have their OH groups connected to adjacent carbon atoms:



$$R^1-\overset{\displaystyle OH}{\underset{\displaystyle R^2}{C}}-OH$$

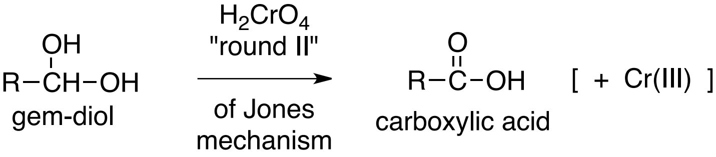
a geminal diol: both OH groups are attached to the same C atom



$$R^1-\overset{\displaystyle HO}{\underset{\displaystyle R^2}{C}}-\overset{\displaystyle OH}{\underset{\displaystyle R^3}{C}}-R^4$$

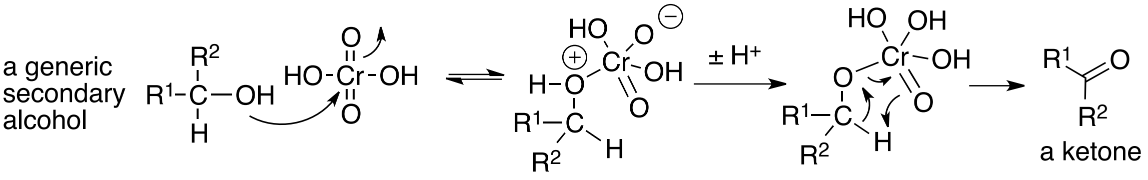
a vicinal diol: the OH groups are attached to adjacent C atoms

(iii) further oxidation of the *gem*-diol to an acid by Cr(VI) through a second round of the mechanism shown earlier:



$$\underset{\text{gem-diol}}{R-\overset{\displaystyle OH}{CH}-OH} \xrightarrow[\text{of Jones mechanism}]{H_2CrO_4 \text{ "round II"}} \underset{\text{carboxylic acid}}{R-\overset{\displaystyle O}{\overset{\|}{C}}-OH} \quad [\ +\ Cr(III)\ ]$$

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

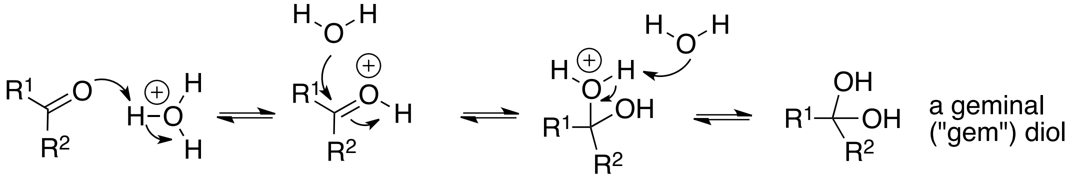


note: ketones can — and do — form geminal diols by reaction with H_3O^+, but the geminal diol of a ketone cannot undergo further oxidation because it has no α-H's

Summary of the above oxidation reactions:

R–CH_2–OH to R–CHO	possible only in a water-free medium: requires PCC
R–CH_2–OH to R–COOH	possible only in an aqueous medium: requires Jones reagent
R^1R^2CH–OH to R^1R^2C=O	may be achieved with either PCC or Jones reagent

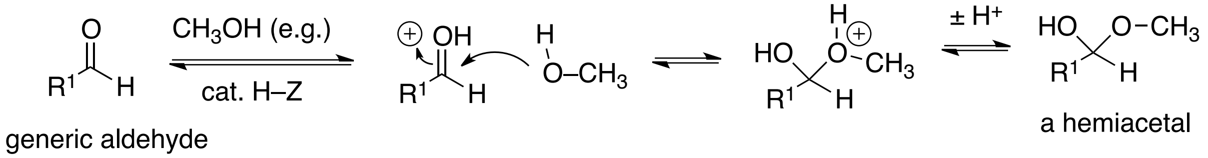
Principle: *any* carbonyl compound will equilibrate with the corresponding geminal (gem-) diol in an aqueous acidic medium. However, gem-diols are thermodynamically disfavored relative to carbonyls, and this primarily on entropic grounds. Therefore, any attempt to isolate gem-diols will actually return the corresponding carbonyl compounds (at least as far as the carbonyl compounds seen in CHEM 203 are concerned)



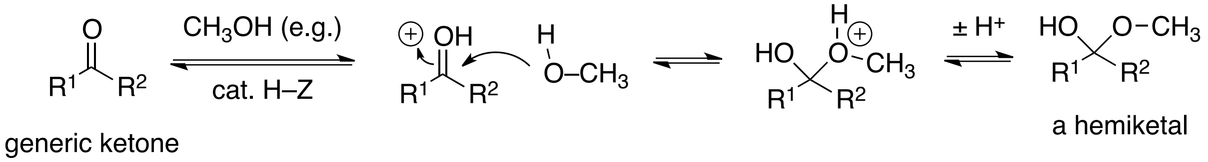
Overall ΔG slightly positive

Lecture 33: Addition of Alcohols to Aldehydes and Ketones

Principle: much like H_2O can add reversibly to protonated carbonyl groups of aldehydes and ketones to form germinal diols, so alcohols (e.g., methanol) can do the same thing, leading to the formation of special types of ethers called hemiacetals and hemiketals, respectively:



H–Z = generic Bronsted acid (HCl, H_2SO_4, para-toluenesulfonic acid....)

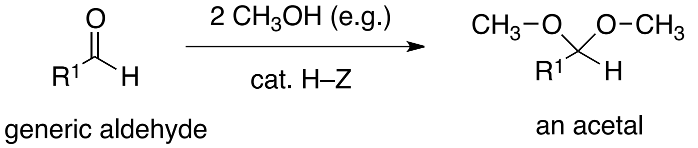


Note 1: other nucleophilic alcohols such as ethanol, 1-propanol, etc., react in a like manner

Note 2: hemiacetal = "half of an acetal"; hemiketal = "half of a ketal" …

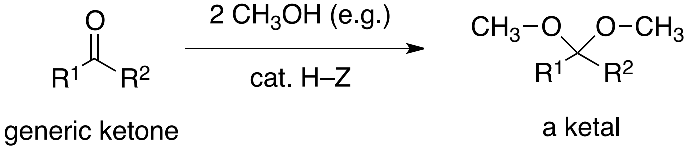
so, what are acetals and ketals?

Acetals: products of acid-catalyzed addition of **two** molecules of alcohol to an aldehyde:



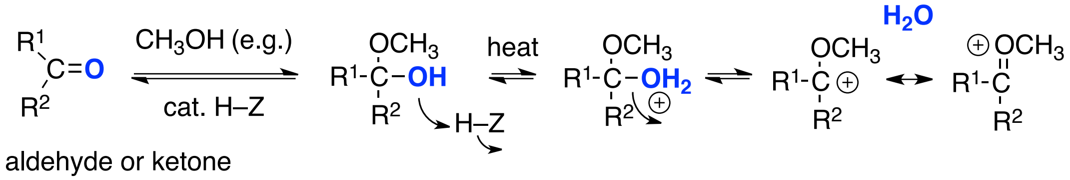
H–Z = generic Bronsted acid (HCl, H_2SO_4, para-toluenesulfonic acid....)

Ketals: products of acid-catalyzed addition of **two** molecules of alcohol to a ketone:

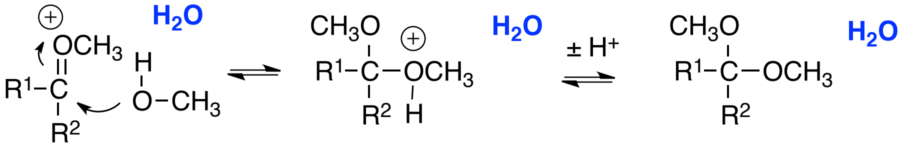


H–Z = generic Bronsted acid (HCl, H_2SO_4, para-toluenesulfonic acid....)

Presumed mechanism of formation of acetals and ketals:



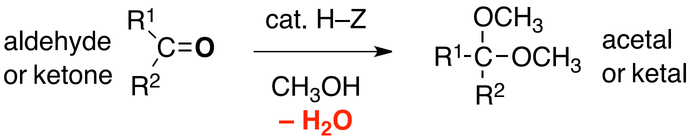
then:



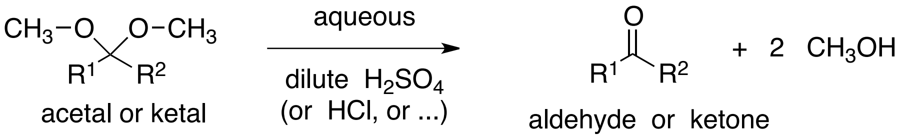
Principle: the above reactions occurs under conditions of reversibility; therefore, they establish an equilibrium between reactants and products

Slightly unfavorable nature ($\Delta G \geq 0$) of the above reaction

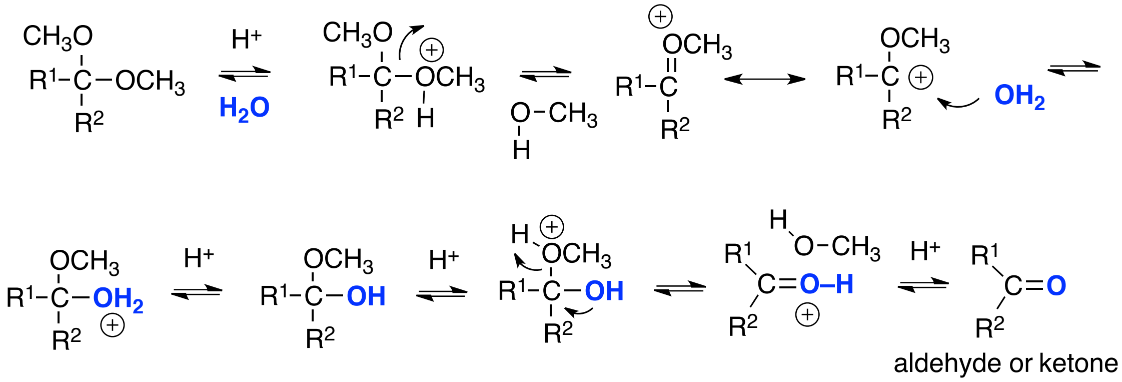
Removal of water (by any of a number of methods) from the above reaction mixture as a means to displace the equilibrium toward the formation of the acetal (Le Chatelier principle):



"Hydrolysis" of acetals and ketals: the treatment of these substrates with dilute aqueous acid, resulting in their breakdown into and aldehyde / ketone plus two molecules of alcohol, by a reversal of the above mechanism



via



Lecture 34: Carbohydrates - Monosaccharides

Carbohydrates: a group of naturally occurring aldehydes and ketones, *formally* composed of C atoms and H_2O molecules in a ratio equal or close to 1 : 1 [general formula: $(CH_2O)_n$ ... or close]

Immense biological importance of carbohydrates

- blood group determinants
- antigens, immune responses
- cancer cell markers
- energy storage & generation
- nucleic acids, glycoproteins
- extracellular support matrices
- genetic disease
- materials & fibers
- etc.

Simple sugars or monosaccharides: a family of carbohydrates of general formula $(CH_2O)_n$ ($3 \leq n \leq 9$) that possess a structure based on a linear polyhydroxy aldehyde or polyhydroxy ketone motif:

$$HOCH_2–(CHOH)_n–CHO \quad \text{or} \quad HOCH_2–(CHOH)_n–CO–CHOH \quad (1 \leq n \leq 6\text{-}7)$$

Complex sugars or polysaccharides: a family of carbohydrates of general formula $(CH_2O)_n - (H_2O)_m$ ($m << n$; i.e., carbohydrates slightly deficient in water) that upon treatment with dilute aqueous acid afford one or more types of monosaccharides (more about this later)

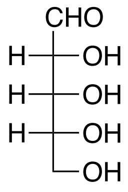
Aldoses (monosaccharides that possesses an aldehyde function) and ketoses (monosaccharides that possesses a ketone function)

Triose, tetrose, pentose hexose, heptose, octose ...: a monosaccharide incorporationg 3, 4, 5, 6, 7. 8 ... C atoms, respectively

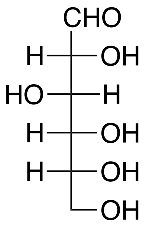
note: monosaccharides incorporating more than 6 C atoms are known, but they are quite rare, and rarity increases with increasing number of C atoms. Most monosaccharides of biological importance contain 5 or 6 C atoms

Frequent use of Fischer projections to represent monosaccharides. Examples:

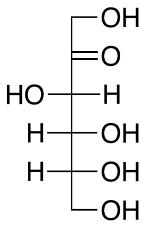
ribose



glucose



fructose



Ribose as a pentose, glucose and fructose as hexoses

Ribose and glucose as aldoses, fructose as a ketose

Ribose as an aldopentose, glucose as an aldohexose, fructose as a ketohexose

Monosaccharides as generally chiral molecules, due to the presence of multiple stereogenic C's

Principle: virtually all of the naturally occurring monosaccharides are enantiomerically pure

The simplest aldotriose: glyceraldehyde

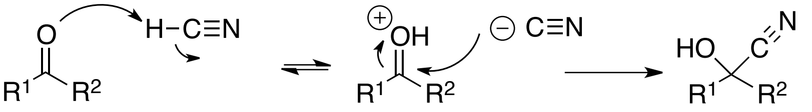
$$HO\text{-}CH_2\text{–}(CHOH)\text{–}CHO$$

D- and L-forms of glyceraldehyde:

L-(*S*)-(–)-glyceraldehyde (OH on the left)

D-(*R*)-(+)-glyceraldehyde (OH on the right)

Reaction of an aldehyde (or ketone) with hydrocyanic acid (HCN): formation of **cyanohydrins**

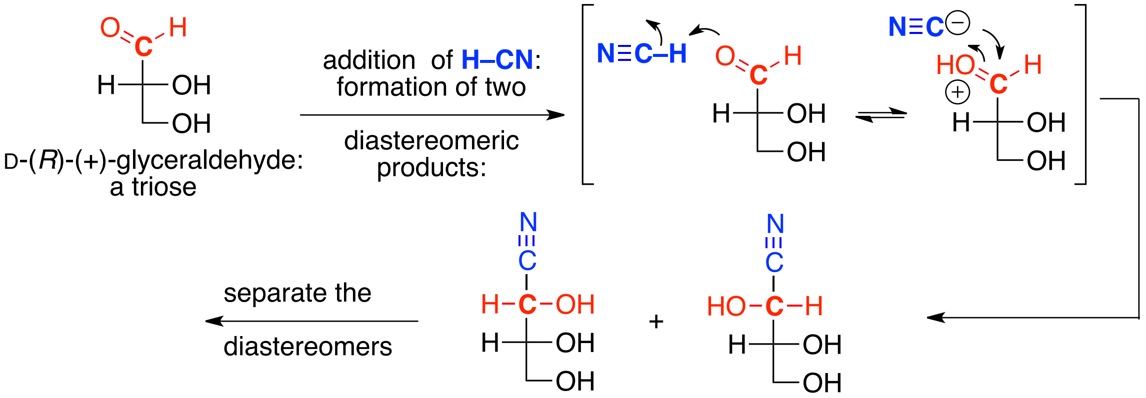


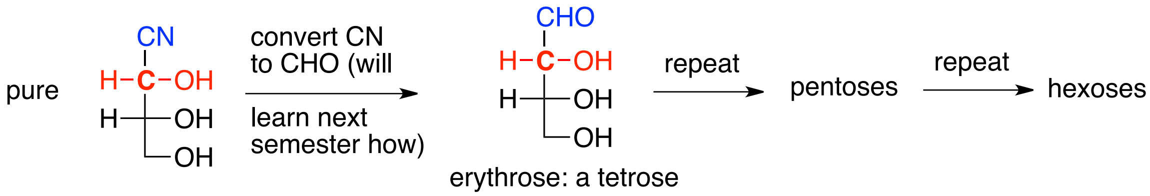
aldehyde or ketone

a cyanohydrin

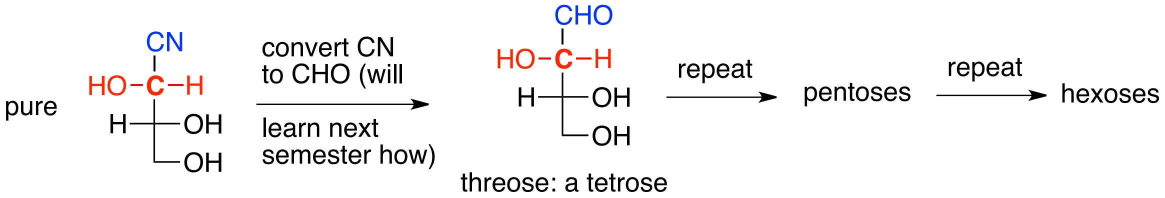
D-Glyceraldehyde as the formal progenitor of all common monosaccharides

The Fischer-Kiliani (F-K) method for the synthesis of monosaccharides from – e.g. – D-glyceraldehyde



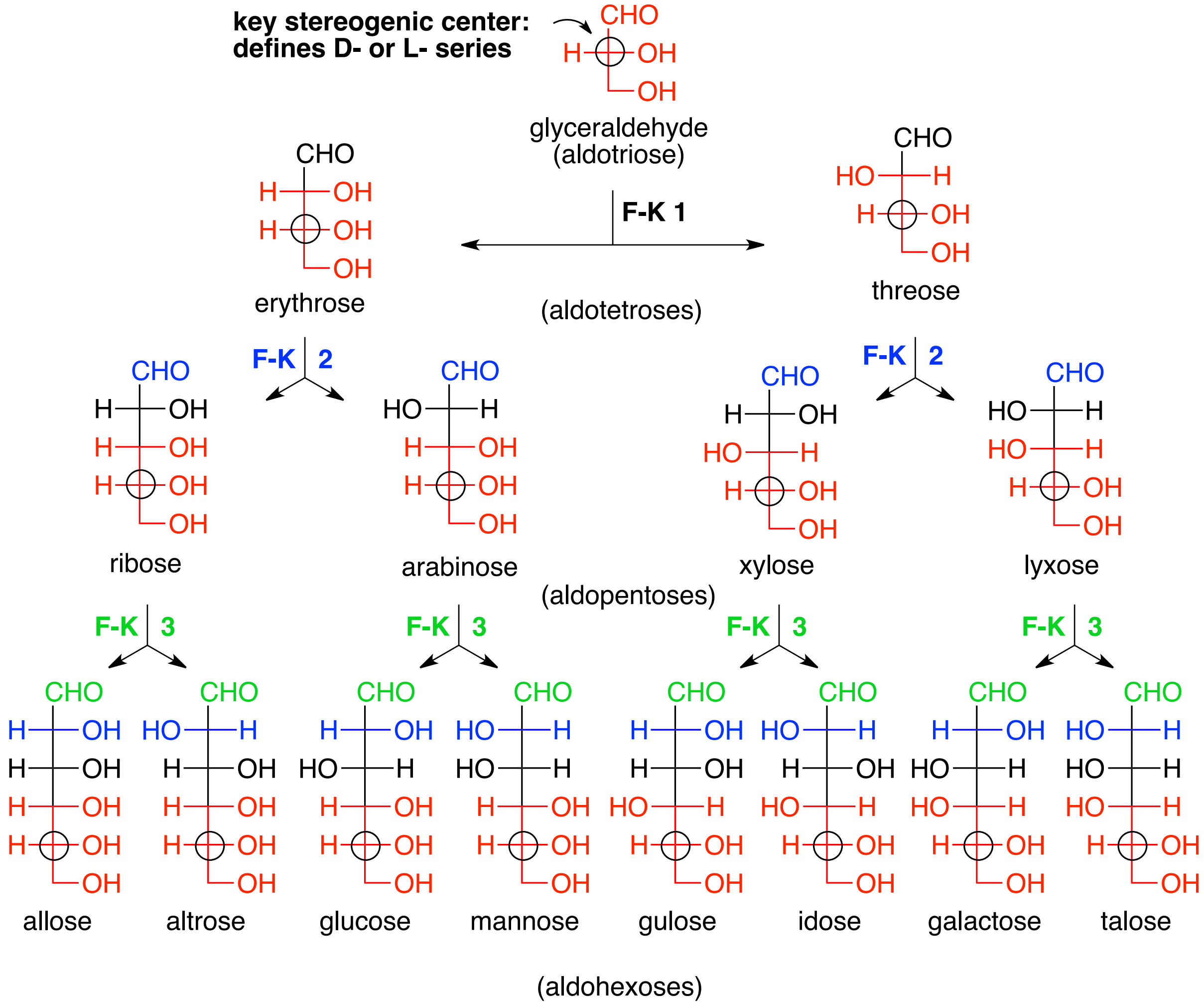


erythrose: a tetrose

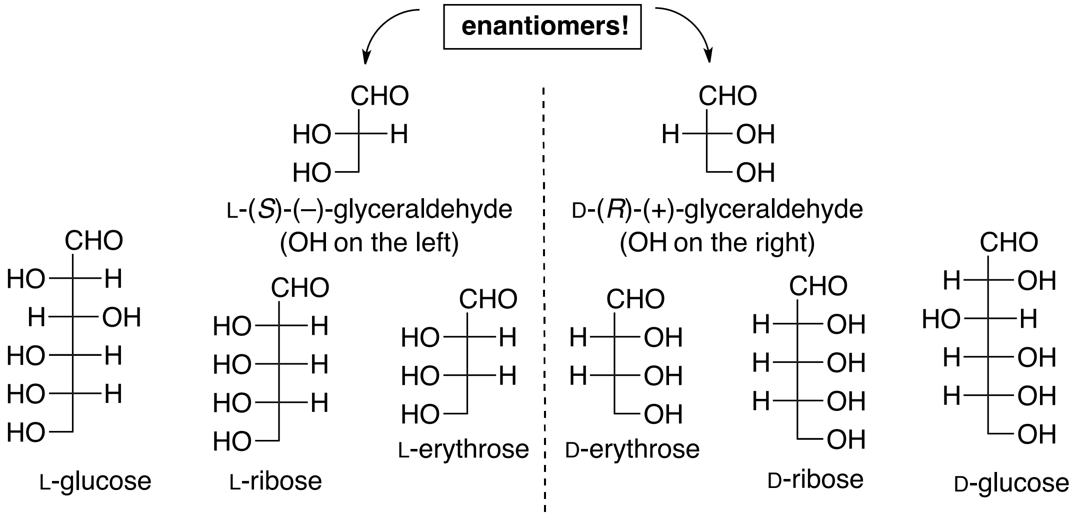


threose: a tetrose

Fischer structures of naturally occurring aldoses and stereochemical relationship thereof to glyceraldehyde of – e.g. – (*R*)-configuration (= D-(*R*)-glyceraldehyde):

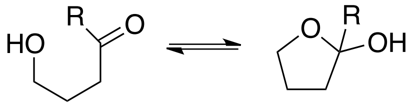


Stereochemical convention for monosaccharides: D and L sugars

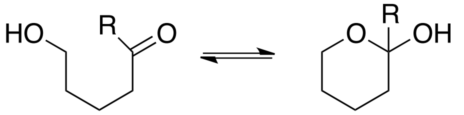


Principle: most natural monosaccharides belong to the D-stereochemical series. The much rarer L-sugars are produced primarily by certain fungal and microbial organisms for specialized uses.

Facile formation of cyclic hemiacetal / hemiketal structures (5- or 6-membered rings) in molecules incorporating both an alcohol and an aldehyde / ketone functionality:



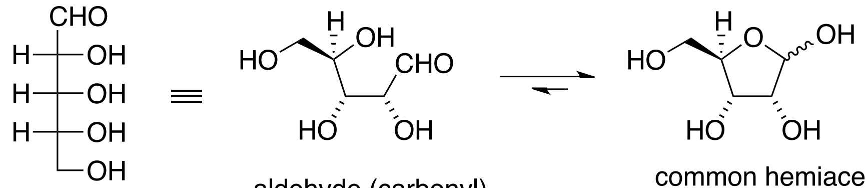
aldehyde (R = H) or ketone (R = alkyl) cyclic hemiacetal or hemiketal



aldehyde (R = H) or ketone (R = alkyl) cyclic hemiacetal or hemiketal

Chemical structure of carbohydrates: hemiacetal formation

hemiacetal forms of ribose (building block of RNA) and glucose:

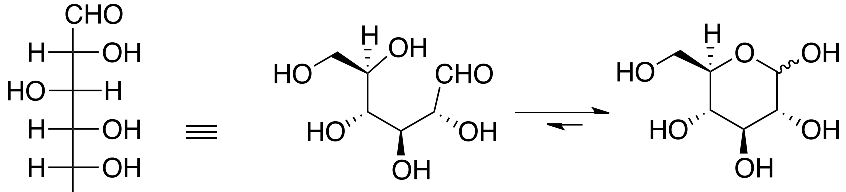


wavy line means that either configuration is possible

Fischer projection of D-ribose

aldehyde (carbonyl) form of D-ribose

common hemiacetal form of D-ribose (preferred)



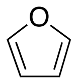
wavy line means that either configuration is possible

Fischer projection of D-glucose

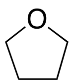
aldehyde (carbonyl) form of D-glucose

common hemiacetal form of D-glucose (preferred)

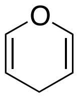
Furanose and pyranose forms of monosaccharides



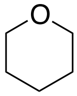
furan



tetrahydrofuran

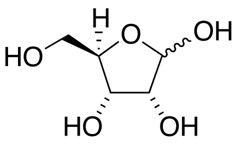


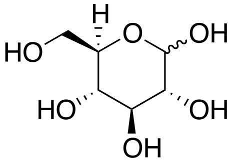
pyran



tetrahydropyran

furanose form of D-ribose ("D-ribofuranose")





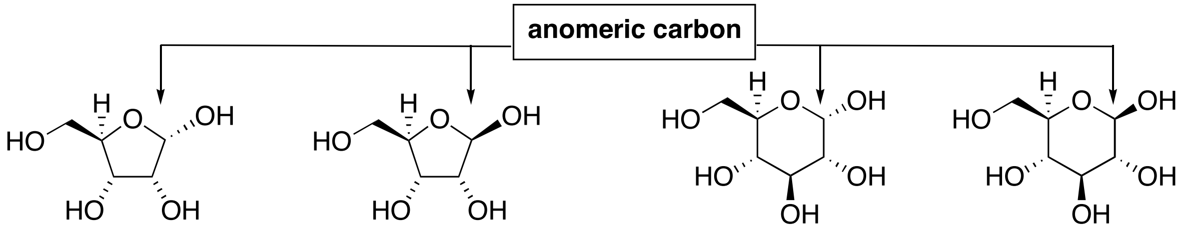
pyranose form of D-glucose ("D-glucopyranose")

Anomeric position (= anomeric carbon; anomeric center) of the cyclic form of a simple sugar (i.e., of a monosaccharide): the former carbonyl carbon that now sustains the hemiacetal system

Existence of **two** diastereomers of the hemiacetal form of a monosaccharide: α and β "anomers":

α-anomer: the OH group of the hemiacetal moiety is *trans* relative to the CH_2OH fragment connected to the carbon atom that defines the D/L stereochemical series

β-anomer: the OH group of the hemiacetal moiety is *cis* relative to the CH_2OH fragment connected to the carbon atom that defines the D/L stereochemical series



α-anomer of D-ribofuranose (α-D-ribofuranose)

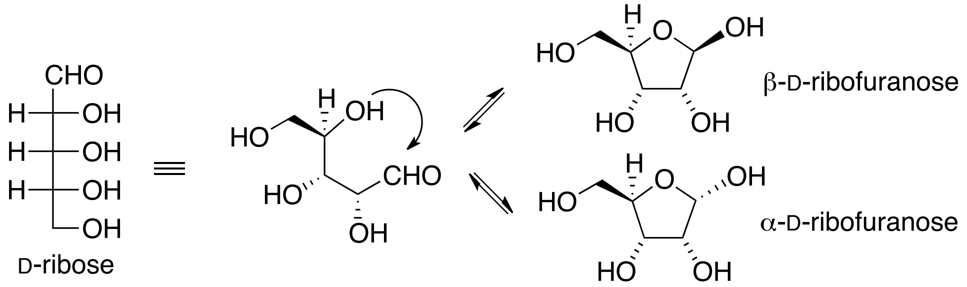
β-anomer of D-ribofuranose (β-D-ribofuranose)

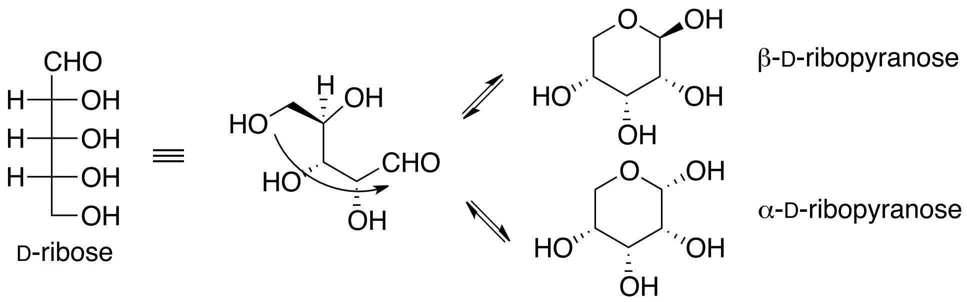
α-anomer of D-glucopyranose (α-D-glucopyranose)

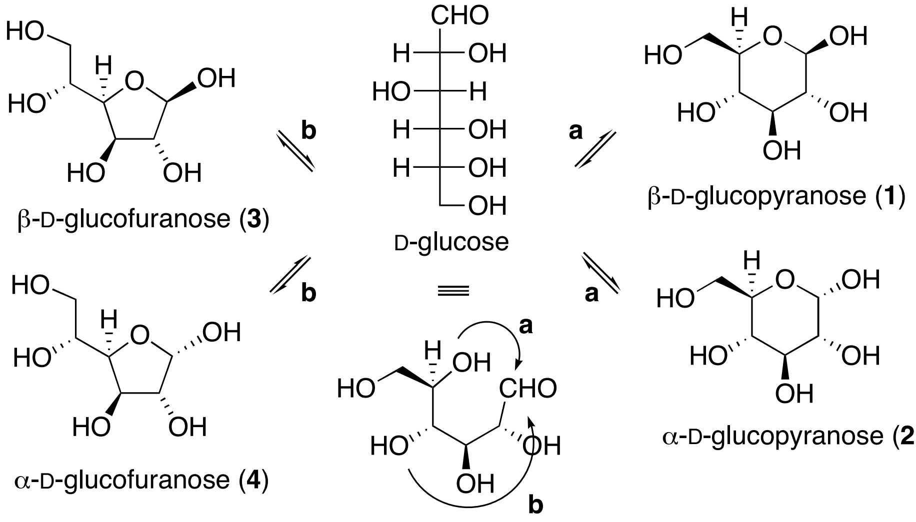
β-anomer of D-glucopyranose (β-D-glucopyranose)

Lecture 35: Mutarotation, Glycosides, Polysaccharides

Interconversion of furanose and pyranose forms and of α and β anomers of a monosaccharide in solution: the case of ribose and glucose



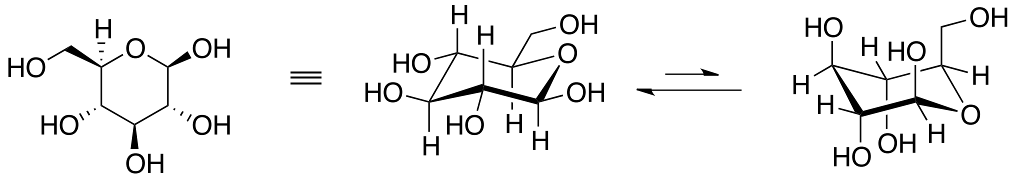




at equilibrium in H_2O: **1** ≈ 64%; **2** ≈ 36%; **3** + **4** < 1%

Conformations of pyranoses: the case of glucose

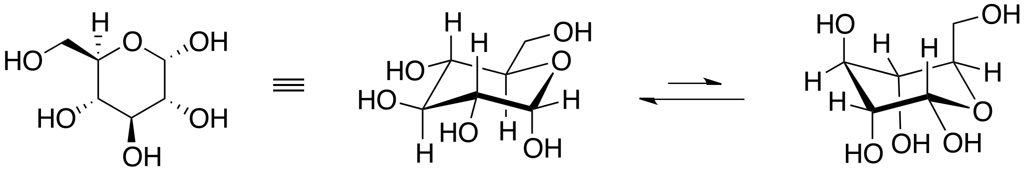
just like an ordinary cyclohexane, the six-membered ring of a pyranose favors a **chair** conformation in which as many groups as possible occupy an equatorial position



β-D-glucopyranose

all equatorial: **favored**

all axial: **disfavored**



α-D-glucopyranose

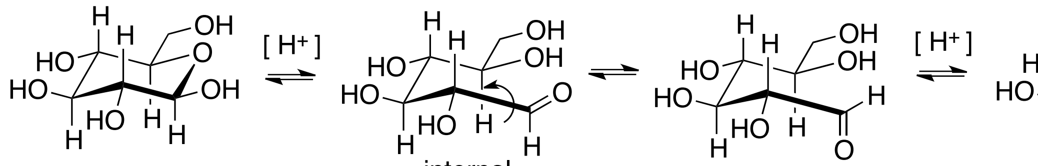
all but 1 OH equatorial: **favored**

all but 1 OH axial: **disfavored**

Mutarotation of monosaccharides: the case of glucose

It is possible to obtain pure α-D-glucopyranose or pure β-D-glucopyranose. These two anomeric forms of glucose, being diastereomeric, differ in solubility, melting point (146 °C for the α-anomer, 150 °C for the β-anomer), and specific optical rotation ($[\alpha]_D^{25}$ = +112° for the α-anomer, + 19° for the β-anomer).

However: if one prepares an aqueous solution of either pure anomer, and one measures the specific optical rotation of the solution over time, one observes that the rotation of a solution of pure α-anomer, initially equal to +112°, *drops* to a final value of ca. +53°, while that of a solution of pure β-anomer, initially equal to +19°, *increases* to a final value of ca. +53°. **WHY**?



β-D-glucopyranose
$[\alpha]_D$ = + 19°

α-D-glucopyranose
$[\alpha]_D$ = + 112°

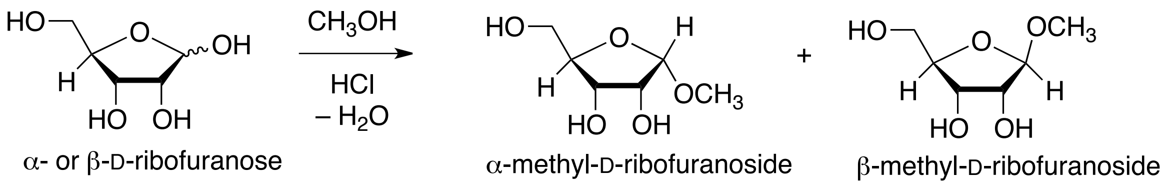
This phenomenon is termed **mutarotation** (="rotation change"). At equilibrium, the solution contains a mixture of ca. 64% of β-anomer (all equatorial, more stable) and ca. 36% of α-anomer:

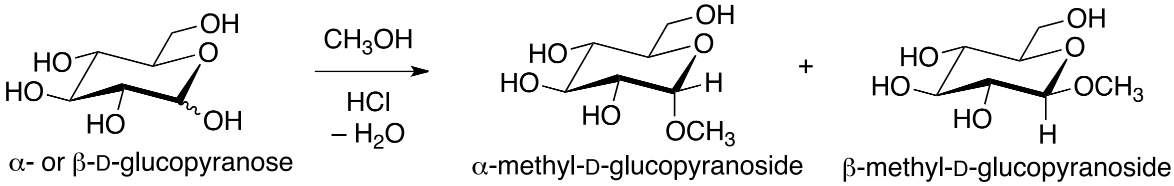
$$(0.64 \times 19°) + (0.36 \times 112°) = 12.2° + 40.3° = +52.5°$$

Chemical reactions of monosaccharides: because these compounds contain hemiacetal, OH and C=O groups, their chemistry reflects that of hemiacetals, alcohols and aldehydes / ketones

Important reactions of monosaccharides: **formation of glycosides** (= glycosidation). Much like a hemiacetal reacts with an alcohol in the presence of acid to form an acetal, so a monosaccharide will react under the same conditions to form a *glycoside* (riboside, glucoside, fructoside ...).

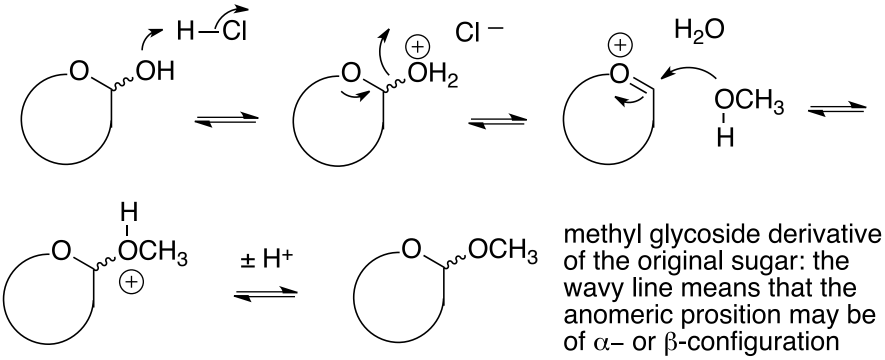
Examples:





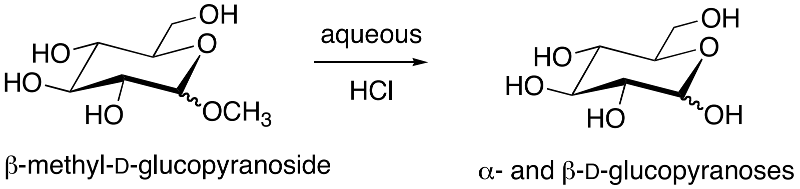
Note: the mechanism of glycoside formation is analogous to that seen earlier (notes of Nov 27) for the formation of acetals:

generic hemiacetal form (furanose or pyranose) of a monosaccharide



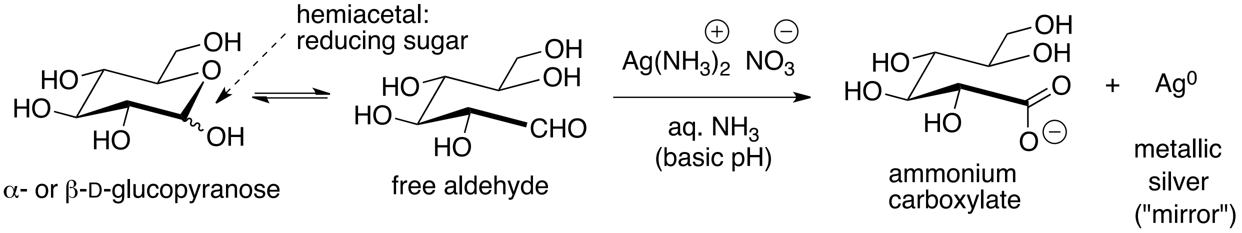
methyl glycoside derivative of the original sugar: the wavy line means that the anomeric prosition may be of α– or β-configuration

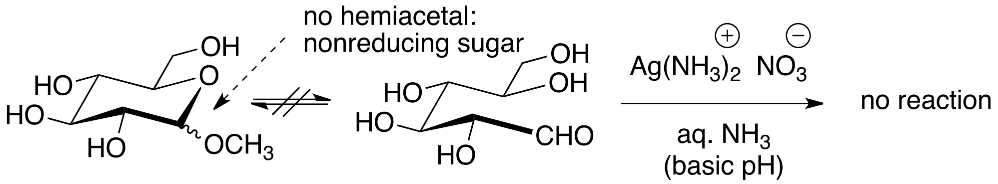
Reversibility of glycoside formation in aqueous acidic media (glycoside hydrolysis)



Note: the mechanism of glycoside hydrolysis is analogous to that seen earlier (notes of Nov 27) for the hydrolysis of acetals

Important difference between "free" sugars (hemiacetal present) and their glycoside derivatives (no hemiacetal present): **reducing and non-reducing sugars** and the Tollens test





α- or β-methyl-D-glucopyranoside free aldehyde

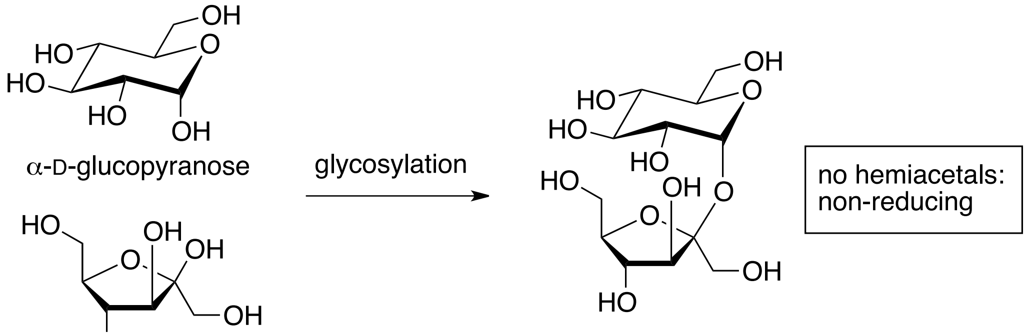
Historical importance of the Tollens test in the structural elucidation of natural carbohydrates

Glycosylation of a monosaccharide with another monosaccharide: formation of complex sugars or polysaccharides

Disaccharides, trisaccharides … polysaccharides: complex sugars composed of 2, 3, … many monosaccharide units

Important disaccharides: sucrose (table sugar), lactose, maltose:

the molecule of sucrose results upon glycosylation of α-D-glucopyranose with β-D-fructofuranose:



α-D-glucopyranose

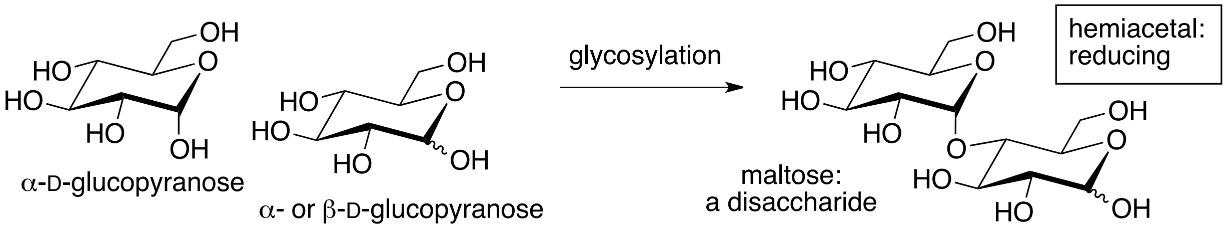
β-D-fructofuranose

sucrose (table sugar):
a disaccharide

α-D-galactopyranose

α- or β-D-glucopyranose

lactose (found in milk):
a disaccharide

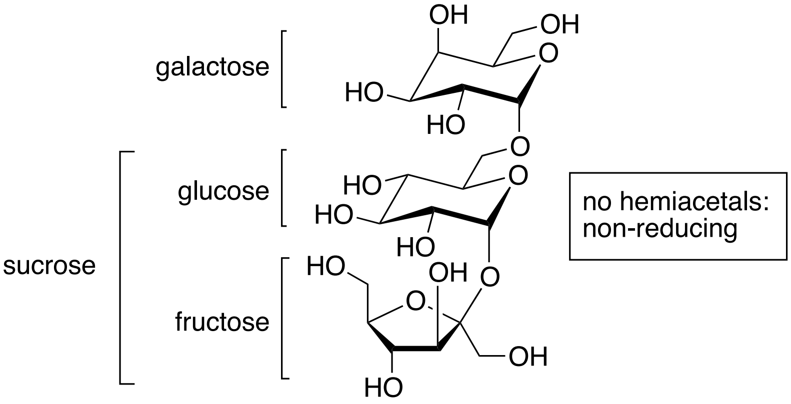


α-D-glucopyranose

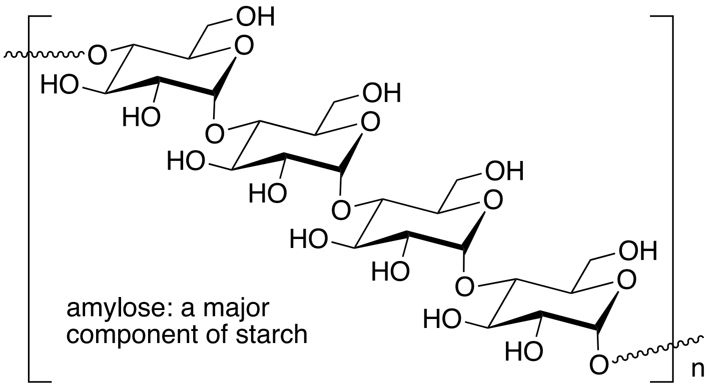
α- or β-D-glucopyranose

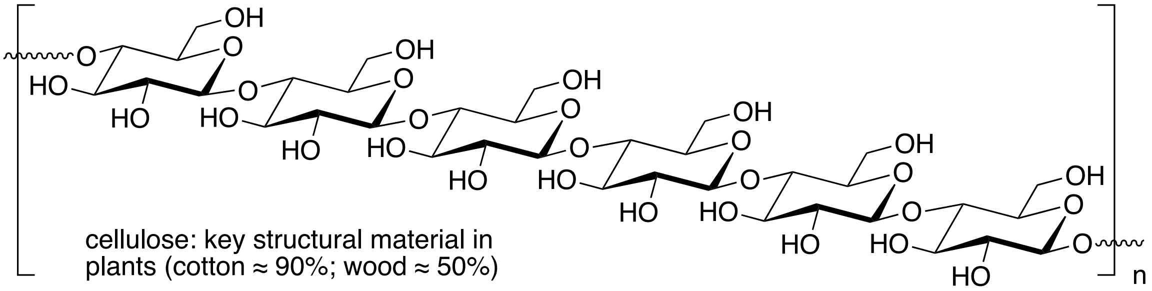
maltose:
a disaccharide

A trisaccharide: raffinose (found in beans, broccoli, cabbage, etc.):



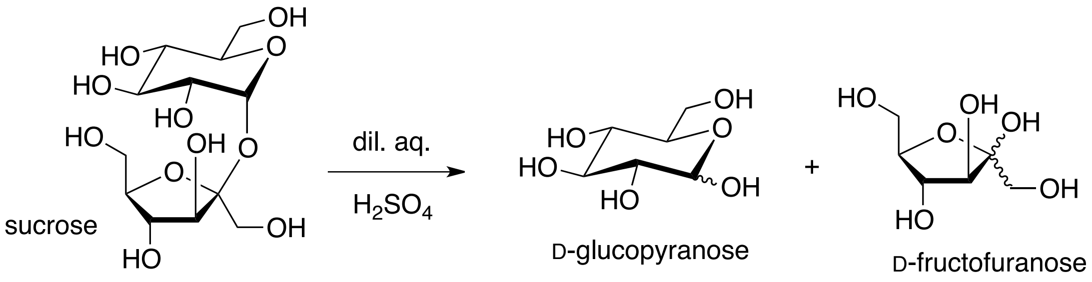
Important polysaccharides: amylose (starch) and cellulose

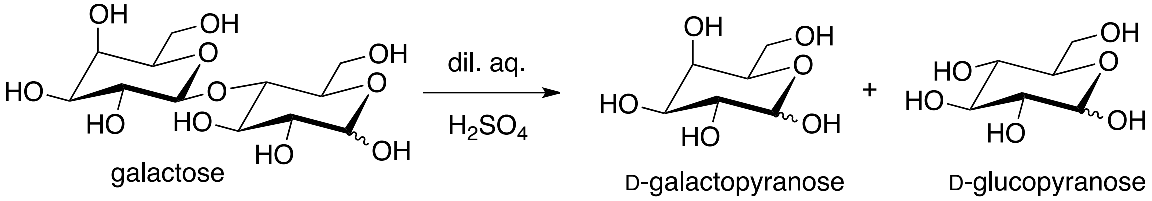


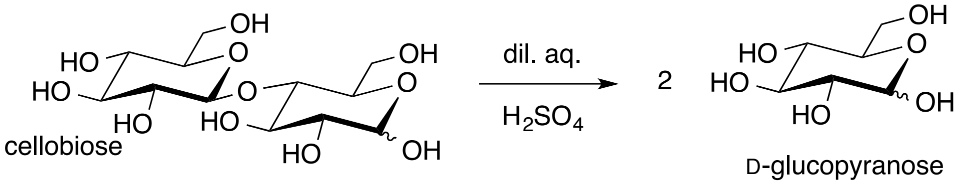


Lecture 36: Chemistry of Mono- and Polysaccharides, Nuclear Bases

Hydrolysis of a complex sugar (disaccharide, trisaccharide, ..., polysaccharide) to simpler carbohydrates with dilute aqueous acid; e.g.:

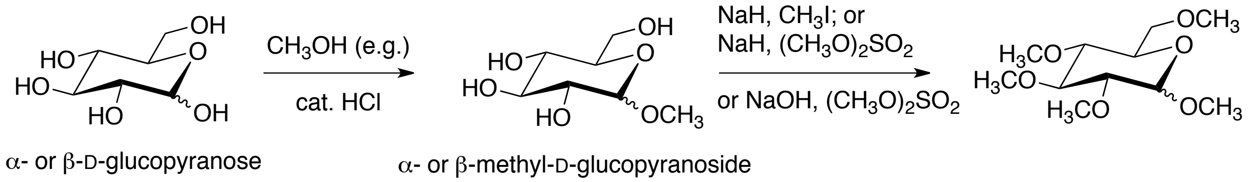






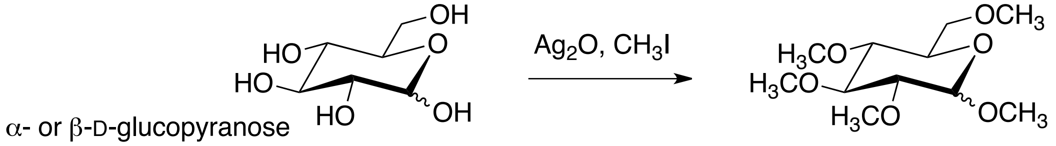
Important reactions of monosaccharides: **formation of ethers** by Williamson reactions

Principle: a reducing sugar is a generally poor substrate for a *traditional* Williamson reaction, and it must be first converted into a glycoside; e.g.:

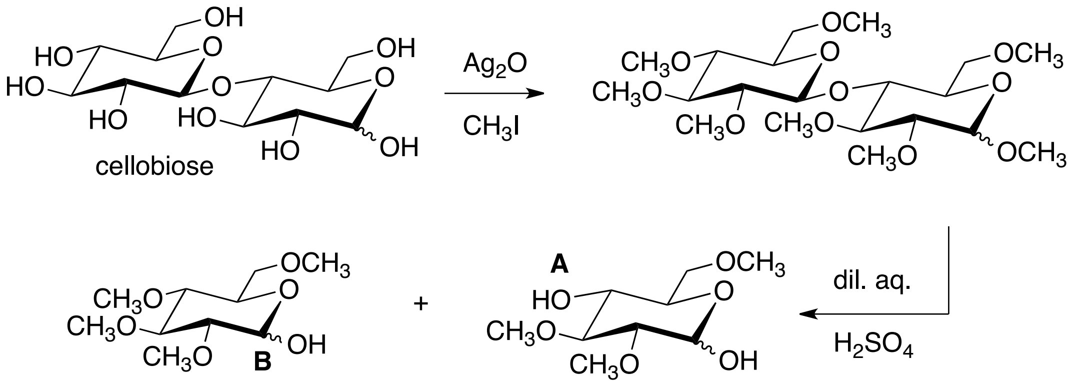


Reasons for the above: basic conditions induce undesirable reactions of aldehydes (CHEM 213)

Mild modification of the Williamson reaction: alkylation of an alcohol with MeI / Ag_2O:



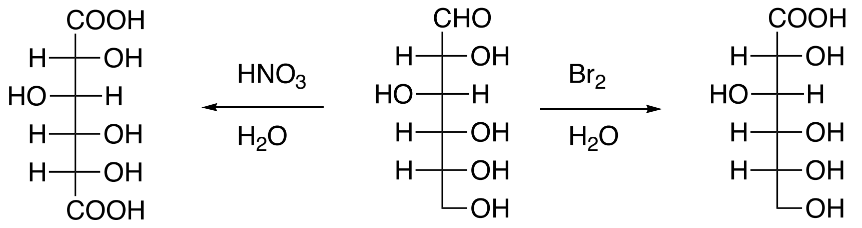
Complete methylation ("permethylation") of polysaccharides, followed by hydrolysis, as a means of structural elucidation; e.g., with cellobiose, a typical disaccharide:



the structures of the simple carbohydrates thus obtained indicates that, in the original disaccharide, OH group **A** must have been connected to the anomeric carbon **B**

Important redox reactions of monosaccharides: **oxidation of aldoses to aldonic acids and aldaric acids** (no mechanisms):

Monosaccharides react with aqueous Br_2 to produce aldonic acids and with nitric acid to form aldaric acids (complex reactions – no mechanism). Example with glucose:



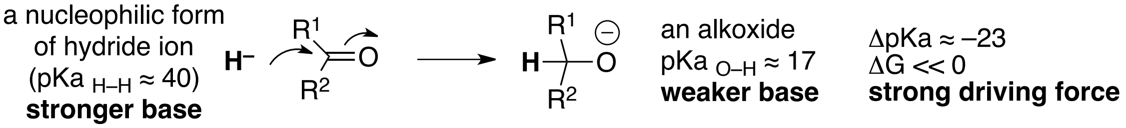
D-glucaric acid: an **aldaric** acid

D-glucose

D-gluconic acid: an **aldonic** acid

Important redox reactions of monosaccharides: **reduction to alditols**

Possible nucleophilic additions of hydride ion (H:⁻) to the C=O group of aldehydes or ketones:

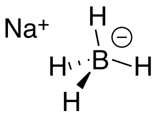


Metal hydrides: compounds possessing a metal – H bond: Mt–H (Mt = any metal)

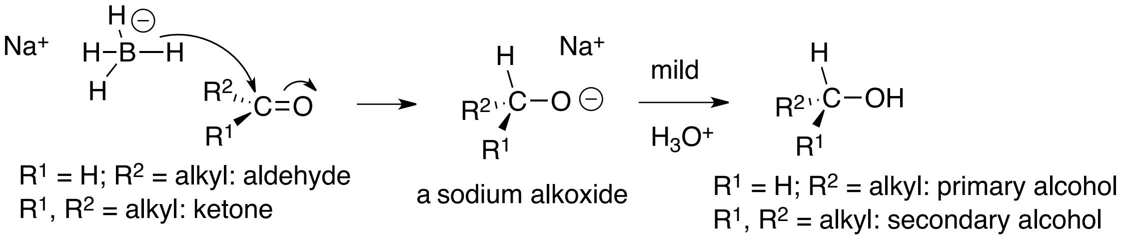
Principle: the nature of the metal influences the reactivity of the hydride ion carried by a Mt–H. Thus, certain metal hydrides carry a basic form of H^- (= an H^- that exhibits affinity for protons; e.g. NaH), while others carry a nucleophilic form of H^- (an H^- that exhibits affinity for carbon)

Sodium borohydride ($NaBH_4$): a reagent that carries a nucleophilic form of hydride ion:

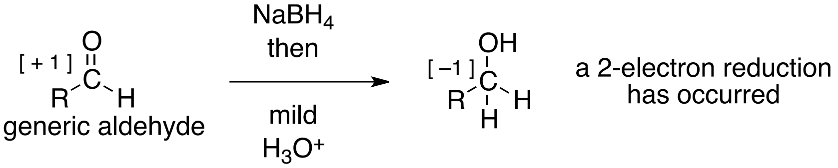
sodium borohydride

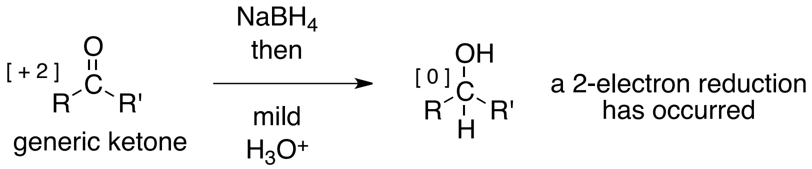


Sodium borohydride ($NaBH_4$) as a carrier of a nucleophilic form of hydride that adds easily to the C=O group of aldehydes and ketones

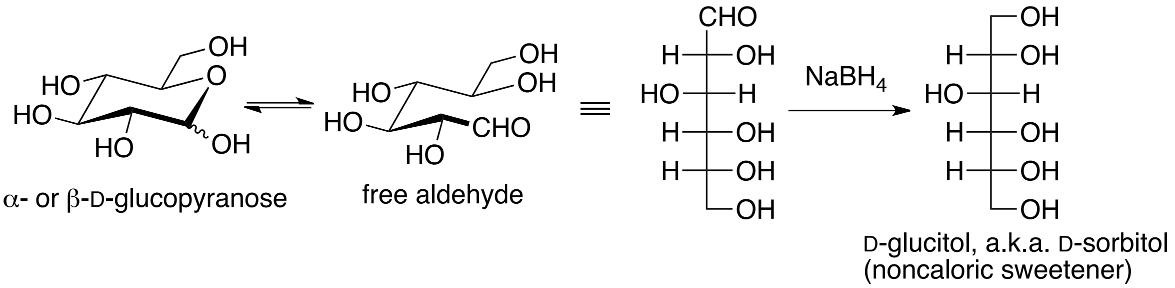


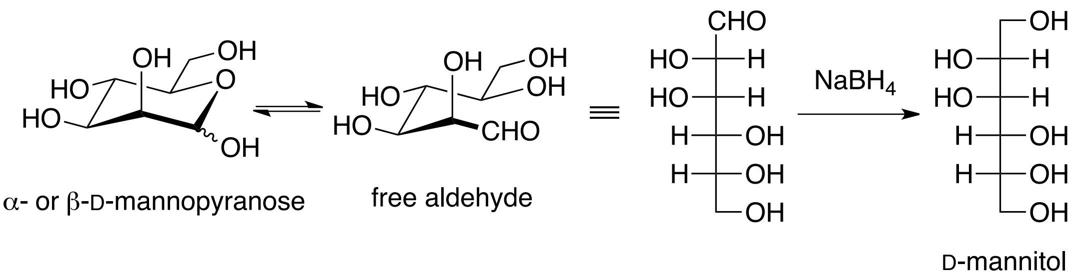
The addition of hydride ion to a carbonyl group as a reduction (the oxidation state of the carbonyl carbon becomes more negative):



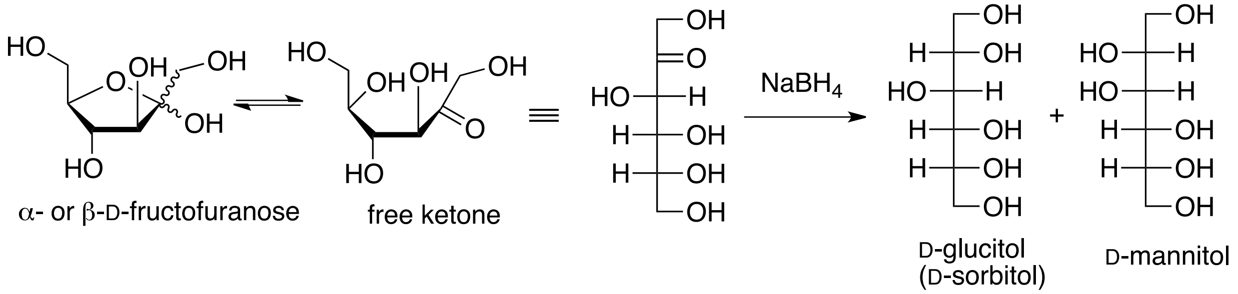


Conversion of aldoses to alditols by treatment with $NaBH_4$; e.g.:

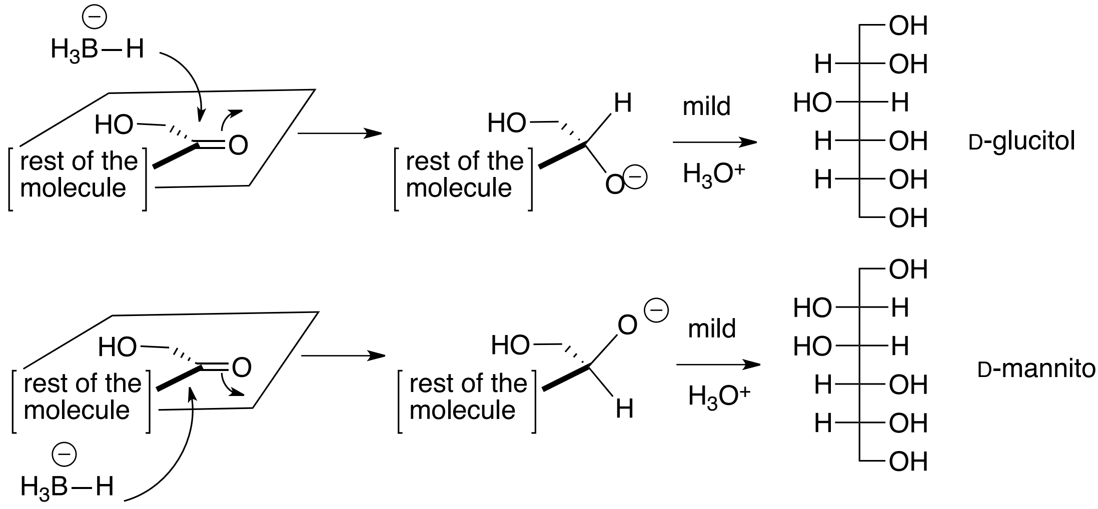




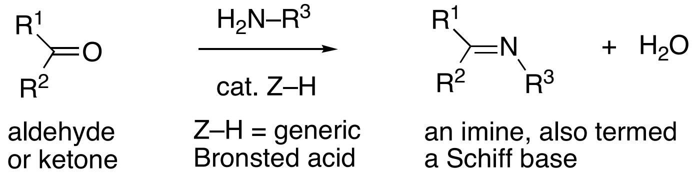
Conversion of ketoses to a mixture of **two** diastereomeric alditots by treatment with $NaBH_4$; e.g.:



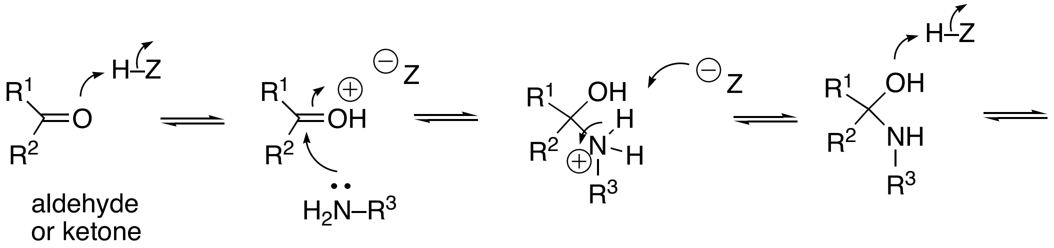
the formation of two diastereomeric products is easily rationalized by considering that $NaBH_4$ may deliver hydride ion to either face of the carbonyl group:

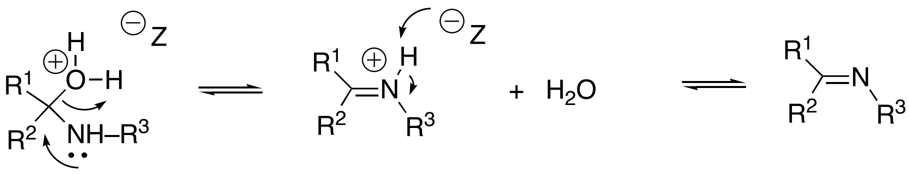


Acid-catalyzed reaction of aldehydes and ketones with primary amines: formation of imines (= Schiff bases: the nitrogen analogs of carbonyl systems):



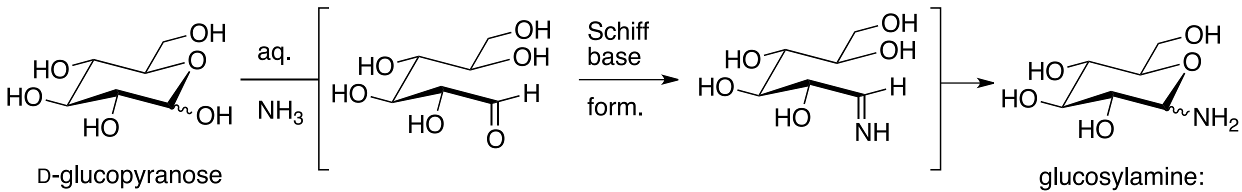
Presumed mechanism of the above reaction:





Enormous importance of Schiff bases (= imines) in biological chemistry (enzymatic reactions, aminoacid metabolism, biosynthetic pathways, etc.)

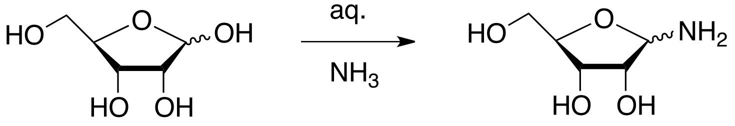
Important reactions of monosaccharides: **formation of glycosylamines**



D-glucopyranose

glucosylamine:
a glycosylamine

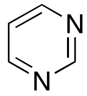
likewise:



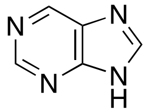
D-ribofuranose

ribosylamine: a glycosylamine

Pyrimidine and purine

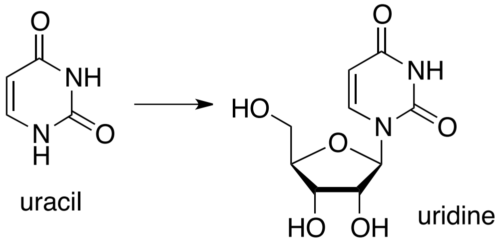


pyrimidine



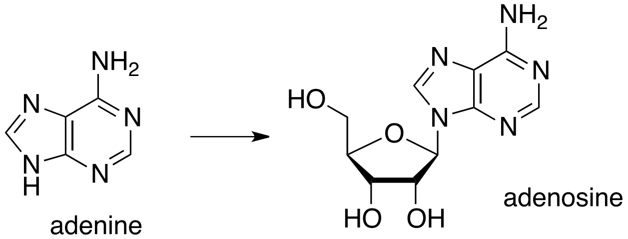
purine

Important pyrimidine and purine N-glycosides ("nucleosides"): building blocks of nucleic acids



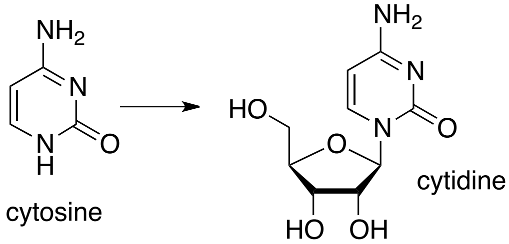
uracil

uridine



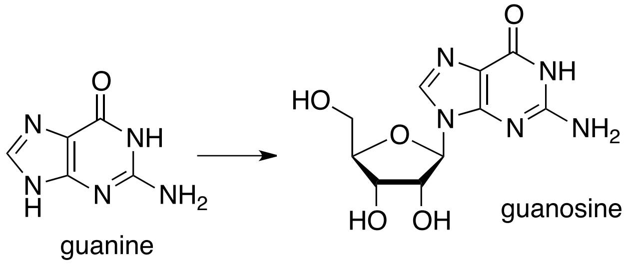
adenine

adenosine



cytosine

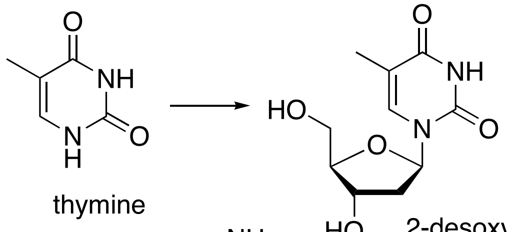
cytidine



guanine

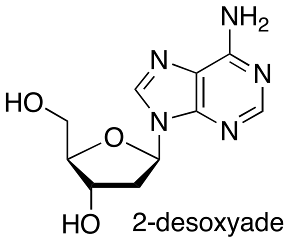
guanosine

(components of RNA)

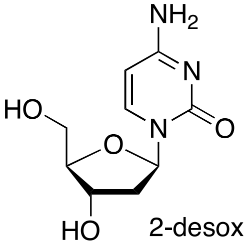


thymine

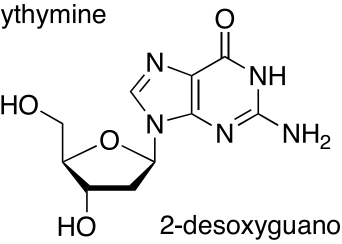
2-desoxythymine



2-desoxyadenosine



2-desoxycytidine



2-desoxyguanosine

(components of DNA)