

CHEM 3013

Survey of Organic Compounds

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Semester Overview

Bonding and Shape (review from General Chemistry)

- Electron configuration
- Lewis structures
- Bonding
- Shapes of molecules
- Polarity
- Resonance (new)

Acids and Bases (review from General Chemistry)

Functional Groups

- Naming
- Structure
- Physical properties

Reactions and Mechanisms

- Reactants
- Products
- Reagents
- Mechanisms
- Reaction intermediates

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What is Organic Chemistry?

Modern organic chemistry is the study of the structure and reactivity of compounds consisting mainly of carbon

The main components of organic chemistry are the following:

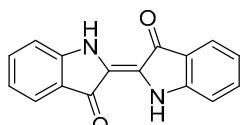
- **Structure determination:** How to determine the structure of newly synthesized or isolated organic molecules which may be available only in invisibly small quantities
- **Theoretical organic chemistry:** How to understand those structures in terms of atoms and the electrons that bind them together
- **Reaction mechanisms:** How to find out how organic molecules react with each other and how to predict their reactivity
- **Synthesis:** How to design new molecules and then how to make them
- **Biological Chemistry:** How to find out what nature does and how the structures of biologically active molecules are related to their function

>95% of all known compounds contain carbon

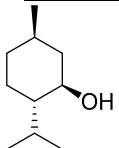
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Organic Chemistry is Crucial to Our Way of Life

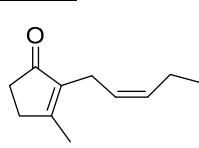
Dyes, Perfumes, Glues, Paints, Materials (Polymers), Petroleum, Pesticides, Medications, a Molecular Understanding of the Human Body. For example:

Colors & Dyes:

Indigo - the color of Blue Jeans

**Flavors & Scents:**

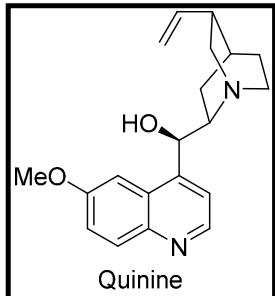
Menthol



cis-Jasmone

Quinine:

Cinchona Tree Bark

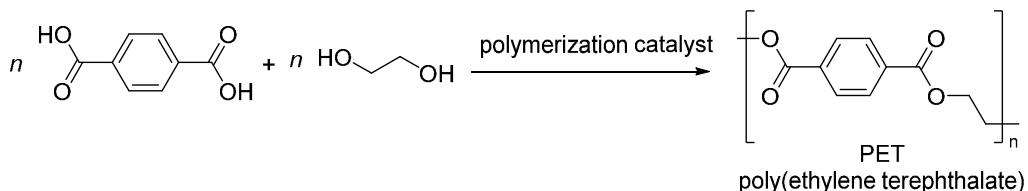


Treatment of Fever, Malaria

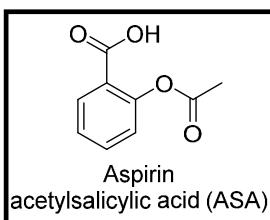
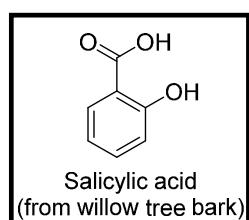
Tonic Water

Organic Synthesis: Use as Chiral Organocatalyst

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PET & Polyester:**Aspirin & Salicylic Acid:**

Can be used to remove the outer layer of skin



Oral use possible

Nonsteroidal anti-inflammatory drug

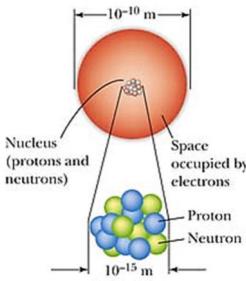
Lowers risk of heart attacks and strokes

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Chapter 1: Covalent Bonding and Shapes of Molecules

1.1 Atomic Structure

Atoms



Nucleus

- small, dense core of protons and neutrons
- Atomic number (Z)
- positively charged

Orbitals

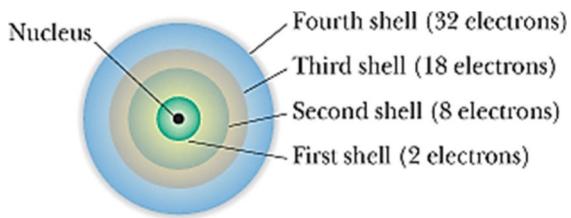
Regions around the nucleus where an electron is most likely to be found

- Each orbital may hold only 2 electrons
- Orbital types – s, p, d, f

- In organic chemistry we can focus on *s* and *p* orbitals as organic molecules often only contain carbon, hydrogen, nitrogen, and oxygen

1.1

Shells



- Organization of orbitals by size and energy
- Different numbers and kinds of orbitals in each shell
- Correspond to rows in the periodic table
- Electrons nearest to the positively charged nucleus are held more tightly and have the lowest energy

Valence shell

- outermost shell of an atom's electronic configuration
- Valence electrons are important for chemical bonding and are responsible for atomic properties

Example: How many electrons does oxygen have in total and how many of these are valence electrons?

1.2

Elements

- differ by the number of _____ (atomic number Z)

Isotopes

- atoms of the same _____ (Z stays the same)
- differ by the number of _____

Example: How many protons, electrons, and neutrons does each of the following carbon isotopes have?

	<i>protons</i>	<i>electrons</i>	<i>neutrons</i>
¹² C			
¹³ C			
¹⁴ C			

Ground-state electron configuration of atoms

Lowest-energy arrangement of electrons in the available orbitals

- Fill the orbitals in order of energy
(1s → 2s → 2p → 3s → 3p → 4s → 3d)
- An orbital may contain a maximum of two electrons which must have opposite spins
- If two or more of the same orbital type is present, place one electron in each orbital then go back and pair up the electrons.

Example: **Sulfur**

1.3

1.2 Chemical Bonds and the Octet Rule

How many electrons are required in the valence shell for a given atom to reach a stable electron configuration?

Octet Rule

- In organic molecules, most atoms (e.g. C, N, O, F) except H desire an octet
- Atoms tend to react in such a way that allows them to achieve 8 valence electrons.

Example: **Mg**

Ion formation by a) gaining 6 electrons or b) losing 2 electrons

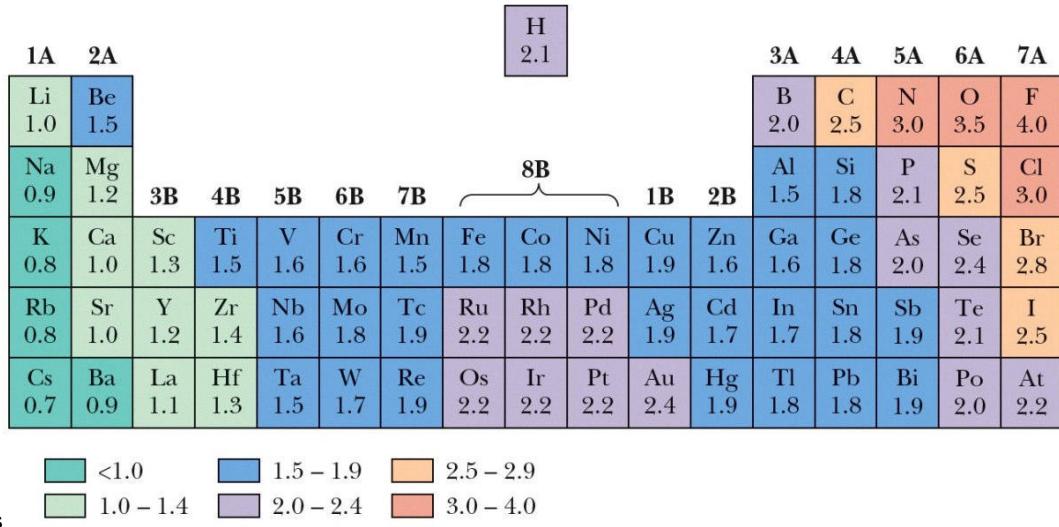
- Losing 2 electrons is more favorable

Valence (not valence electrons) is the number of electrons needed to achieve a full octet (or the number of bonds the atom in question can form to other atoms)

C tetravalent	N trivalent	O divalent	F monovalent
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Types of bonds

- Covalent or ionic bonds
- Depends on electronegativity (EN) difference between atoms
- Electronegativity is a measure of how much an atom wants electrons
- An atom's attraction for electrons shared in a chemical bond

Pauling Electronegativity

Ionic Bonds: one electron (or more) is completely transferred from one atom to another atom

- Ionic bonds are the result of reactions between atoms with an electronegativity difference of more than 1.9
- Usually the type of bond between a (low-valent) metal and a halide
- When dissolved in a polar solvent, the ions separate

Example of salt formation:



Anion – atom that becomes a negatively (-)-charged ion

Cation – atom that becomes a positively (+)-charged ion

Nonpolar Covalent Bonds: a pair of electrons is shared mutually between the bonded atoms

- Stable bond type that requires a lot of energy to be broken
- Electronegativity difference less than 0.5

Example: C-H

Polar Covalent Bonds: an unequal sharing of a bonding electron pair

- The more electronegative atom draws the bonding electrons more strongly to itself, resulting in an unequal electron distribution between the atoms
- δ^- indicates the more electronegative atom
- δ^+ indicates the more electropositive atom
- Electronegativity difference of 0.5-1.9

Example: C-F

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Review: Count the valence electrons and determine the number of bonds and lone pairs these atoms have after achieving their octet.

Atom	# of valence electrons	# of bonds	# of lone pairs
H			
C			
O			
N			
Cl			

1.3 Covalent Bonds and Lewis Structures

Covalent bonds: When two or more atoms of the same or similar electronegativities react, these atoms achieve noble gas configurations by sharing electrons.

Molecules: neutral collection of atoms held together by covalent bonds

Ions: (+) or (-) charged species

Lewis structures – representations of atoms used to determine bonding and shape

- **Electron-dot structures** show valence electrons as dots around a central elemental symbol
- Useful but chemists simplify them by representing bonds as lines and nonbonding electron as dots in so-called dash structural formulae
- Paired non-bonding electrons (two dots) can also be represented as lines
- **Nonbonding electrons (lone-pair electrons)** play an important part in reactions: *Don't forget to draw these in if they are crucial to your reaction!*

Organic chemists generally represent molecules as dash formulae when asked to draw a Lewis structure.

1.9

Guidelines to Drawing Lewis Structures of Molecules and Ions:

1. Determine the number of valence electrons in the molecule or ion (for anions, add one electron; for cations subtract one electron)
2. Determine arrangement of atoms
(H and halogens are monovalent and only form one single bond)
3. Connect the atoms with single bonds (a dash represents 2 electrons)
4. Arrange the remaining electrons in pairs to give each atom a full valence shell (Tip: start with most electronegative atom; assign 8 electrons to all elements except hydrogen which gets 2 electrons)
5. Lone pair electrons (non-bonding electrons) are shown as (:)
6. Multiple covalent bonds: More than one pair of bonding electrons may be shared to give all atoms an octet.
Single bond:
Double bond:
Triple bond:
7. Exception to the octet rule: Elements of the third row and below can accommodate more than 8 electrons in their valence shell and may form more than 4 bonds. Most commonly this is encountered with sulfur (e.g. SF₆, H₂SO₄) and phosphorus (e.g. PCl₅, POCl₃)

Draw the Lewis structures of the following molecules:
Chloroform (CHCl_3) **H_2CO_3**

HCN **CO_2** **Ethanol ($\text{C}_2\text{H}_6\text{O}$)** **NH_2^-** **Ethane (C_2H_6)****Ethene (Ethylene, C_2H_4)****Ethyne (Acetylene, C_2H_2)**

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1.4 Formal Charges and How to Calculate Them

Formal Charge: charge on each atom in a molecule or ion

- Used to determine which atom(s) in a polyatomic ion or molecule possess the charge
- Must have a valid Lewis structure first

Formal Charge = valence electrons - $\frac{1}{2}$ of the shared electrons- lone pair electrons

$$F = Z - (1/2)S - U$$

With
 F = formal charge
 Z = group number of the element
 S = the number of shared electrons
 U = the number of unshared electrons

- The arithmetic sum of all the formal charges in a molecule or ion will equal the overall charge on the molecule or ion.**

Assign formal charges to all atoms of the following molecules. What is the overall charge?

Nitric Acid (HNO_3)**Acetate (CH_3CO_2^-)**

1.5. Structural Formulae (Summary)

There are many different ways to draw organic molecules. Chemists chose often the one requiring the least time to draw but which has all the essential information for that particular application.

For example, 2-propanol can be represented many different ways:

a) Ball-and stick model (molecular model kit)



b) Electron-dot formula

c) Dash formula

d) Condensed formula

Organic chemists use the following:

e) Bond-line formula

f) Three-dimensional formula (for showing three-dimensional geometry)

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1.6 VSEPR (valence shell electron-pair repulsion) Theory

- Angles are predicted by all electron pairs (bonds and lone pairs)
- Shapes of molecules are predicted by bonds only

Atomic and molecular shape based on Lewis structure and hybridization

linear

trigonal planar

tetrahedral

180°

120°

109.5°

TABLE 1.3 SHAPES OF MOLECULES AND IONS FROM VSEPR THEORY

Number of Electron Pairs at Central Atom			Hybridization State of Central Atom	Shape of Molecule or Ion ^a	Examples
Bonding	Nonbonding	Total			
2	0	2	<i>sp</i>	Linear	BeH_2
3	0	3	<i>sp</i> ²	Trigonal planar	BF_3 , CH_3^+
4	0	4	<i>sp</i> ³	Tetrahedral	CH_4 , NH_4^+
3	1	4	$\sim\text{sp}^3$	Trigonal pyramidal	NH_3 , CH_3^-
2	2	4	$\sim\text{sp}^3$	Angular	H_2O

Exercise: Complete the following table

Molecule	# of VE at central atom	Lewis structure and angles between bonds	Shape of molecule
CH ₄			
NH ₃			
BH ₃			
H ₂ O			

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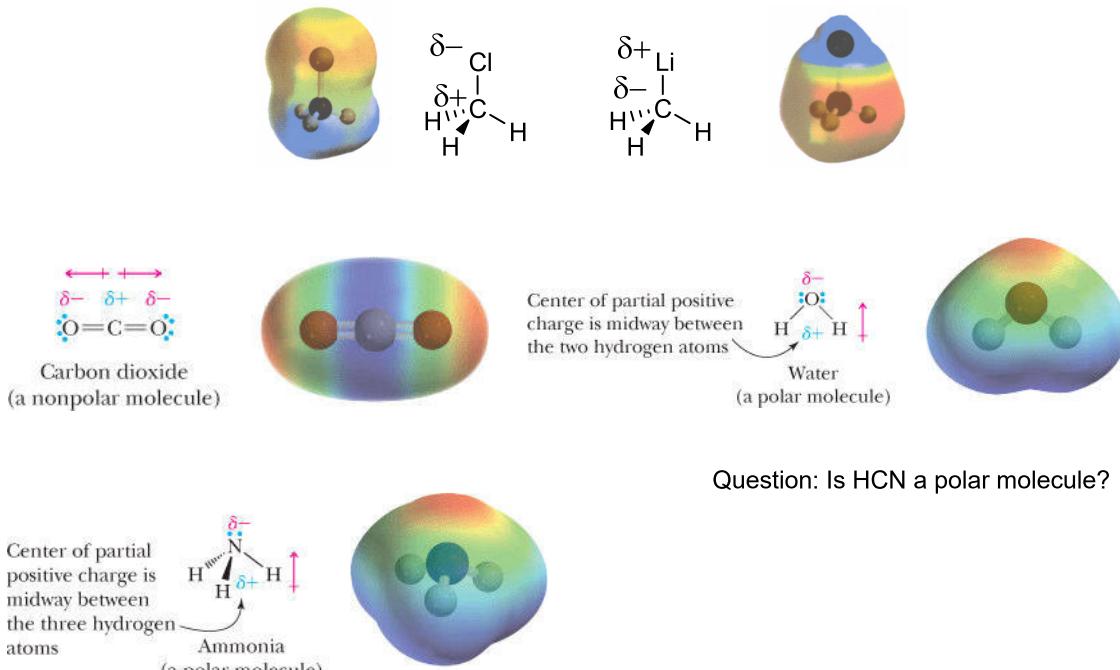
Exercise: Complete the following table (continued)

Molecule	# of VE at central atom	Lewis structure and angles between bonds	Shape of molecule
H ₂ CO			
HCCH			
CO ₂			

1.16

1.7 Polar and Nonpolar Molecules

How can we predict whether a molecule is overall polar or nonpolar?
By knowing its shape and the electronegativity of the atoms



1.17

1.8 Resonance Structures

Resonance Structures exist only on paper. They are representations of a molecule or ion that differs only in the distribution of its valence electrons which all contribute to the real (hybrid) structure of a compound

Rules for Drawing Resonance Structure

1. All structures have same number of valence electrons
2. The connectivity of the atoms does not change; however, bond orders can differ in the individual resonance structures. Do not move atoms!
3. All structures must be proper Lewis structures, e.g. no atom may have more than a full valence shell. (H: max 2 electrons, row 2 elements: max 8 electrons, and row 3 elements: max 12 electrons)

Example 1: CH_3CO_2^-

Valence electrons:

Lewis structure:

Resonance structures:

Example 2: HNO_3

Valence electrons:

Lewis structure:

Resonance structures:

Arrows move from (-) to (+)

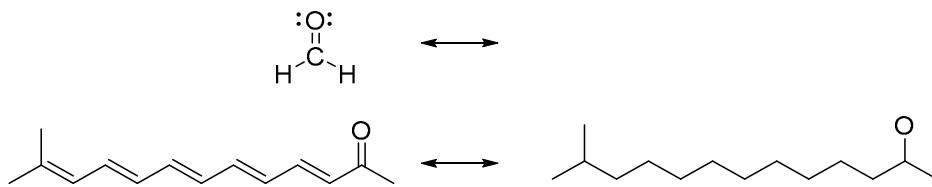
Not all structures carry the same weight

Fewer charged atoms is better

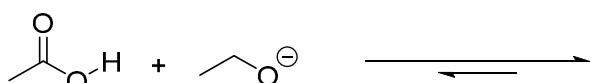
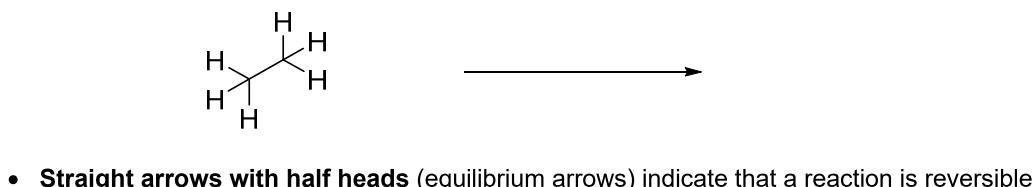
If (+) and (-) formal charges appear in same structure, closer together is better

1.9 Summary of Different Types of Arrows

- **Curved arrows ("Curly arrows")** always show that *a pair of electrons* is moving from the atom at the tail of the arrow to the atom at the head of the arrow
- **Double-headed straight arrows** indicate resonance



- **Fishhook arrows** show movement of *one electron*
- **Straight arrows** (reaction arrows) point from reactants to products



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1.10 From Atomic Orbitals to Molecular Orbitals

Bonding: Atoms approach each other which allows their atomic orbitals to overlap either in-phase (resulting in a bonding molecular orbital) or out-of-phase (giving rise to antibonding orbitals).

σ bonds: have spherical symmetry about the bond and may be formed by overlap of any of the following orbitals

	atomic orbitals	bonding molecular orbital	antibonding molecular orbital
s-s overlap			
s-p overlap			
p-p overlap (end-on)			

π bonds: result from side-on overlap of p orbitals and are rigid

	atomic orbitals	bonding molecular orbital	antibonding molecular orbital
p-p overlap (π bond)			

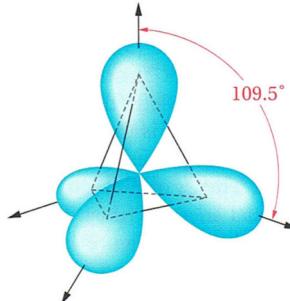
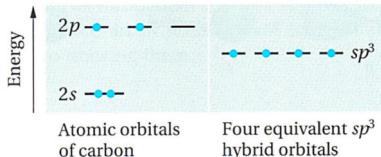
1.11 Hybridization

Hybridization: mixing of orbitals to give identical hybrid orbitals

- Four orbitals are available on C for bonding – s, p_x, p_y, p_z
- Carbon atoms occur in three different hybridizations: sp³, sp², and sp

sp³ – Single bonds, tetrahedral shape

Formation of four sp³ hybrid orbitals:



Overlap of sp³ orbitals with s orbitals leads to single bonds:

Example: Methane

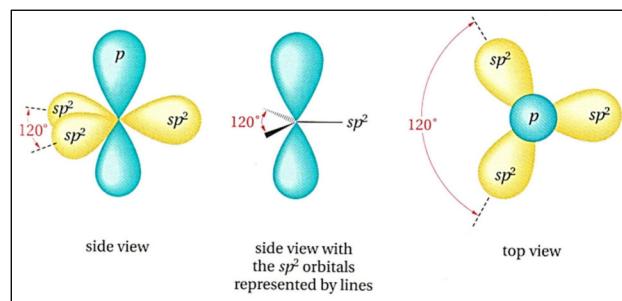
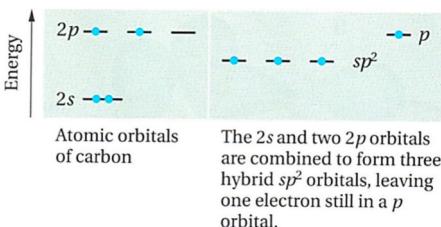
Overlap of two sp³ orbitals leads to single bonds:

Example: Ethane

1.21

sp² – Double bonds, trigonal planar shape

Formation of three sp² hybrid orbitals:



Formation of a C=C double bond:

Example: Ethylene (Ethene)

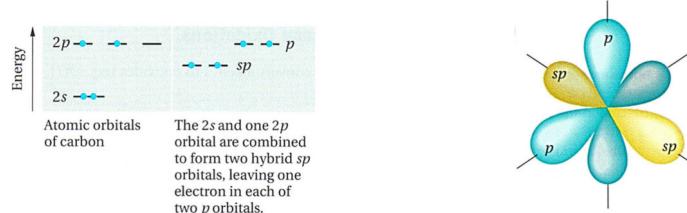
Cis-Trans Isomerism (a type of stereoisomerism)

Due to the restricted rotation about double bonds, cis-trans isomerism can be observed:

cis-1,2-Dichloroethene

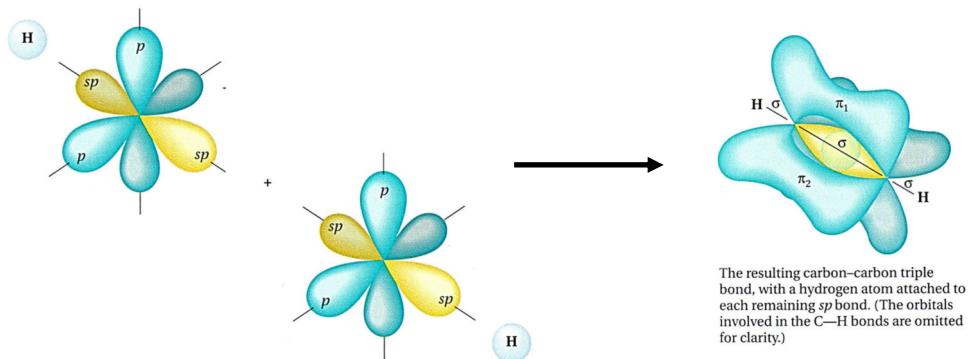
trans-1,2-Dichloroethene

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sp – Triple bonds, linear shape

Formation of C≡C triple bond:

Example: Acetylene (Ethyne)

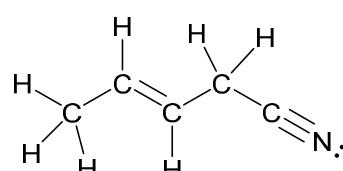
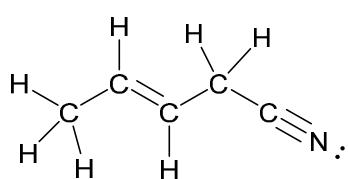


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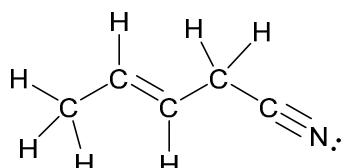
Exercise: Provide type of bonds, hybridization, and bond angles for the following compound.

Types of bonds?

Hybridization?



Bond angles?



1.24

1.12 Functional Groups

Functional groups are common and specific arrangements of atoms that govern reactivity and properties of (organic) molecules.

At this point you are expected to know the following functional groups:

a) Alcohols

-OH (hydroxyl) group bonded to a tetrahedral carbon

Primary alcohol

Secondary alcohol

Tertiary alcohol

b) Amines

-NR₂ (amino) group: Nitrogen atom bonded to 1, 2, or 3 carbon atoms

Primary amine

Secondary amine

Tertiary amine

1.25

c) Aldehydes and Ketones

C=O (carbonyl) group

Aldehydes

Ketones

d) Carboxylic Acids, Esters, and Amides

Carboxyl group

Carboxylate

Carbamide

Carboxylic acid

Ester

Amide

Chapter 2: Acids and Bases

2.1 Brønsted-Lowry Definition of Acids and Bases

Acid – donates a hydrogen ion (H^+ or proton)

Base – accepts the hydrogen ion

Conjugate Base – what the acid becomes after losing a proton

Conjugate Acid – what the base becomes after gaining a proton

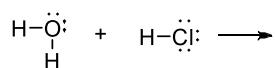
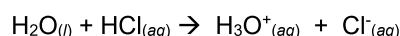


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2.2 Properties of Acids and Bases

Strong acids or bases completely ionize in H_2O

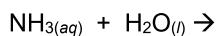
Dissolving HCl (g) in water leads to complete ionization:



Examples of strong acids: HCl, HBr, HI, HNO₃, H₂SO₄

Examples of strong bases: LiOH, NaOH, KOH, NaOEt, KO'Bu

Weak acids or bases partially ionize in H_2O



2.2

TABLE 2.1 Some Acids and Their Conjugate Bases

	Acid	Name	Conjugate Base	Name	
Strong Acids	HI	hydroiodic acid	I ⁻	iodide ion	Weak Bases
	HCl	hydrochloric acid	Cl ⁻	chloride ion	
	H ₂ SO ₄	sulfuric acid	HSO ₄ ⁻	hydrogen sulfate ion	
	HNO ₃	nitric acid	NO ₃ ⁻	nitrate ion	
	H ₃ O ⁺	hydronium ion	H ₂ O	water	
	HSO ₄ ⁻	hydrogen sulfate ion	SO ₄ ²⁻	sulfate ion	
	H ₃ PO ₄	phosphoric acid	H ₂ PO ₄ ⁻	dihydrogen phosphate ion	
	CH ₃ COOH	acetic acid	CH ₃ COO ⁻	acetate ion	
	H ₂ CO ₃	carbonic acid	HCO ₃ ⁻	bicarbonate ion	
	H ₂ S	hydrogen sulfide	HS ⁻	hydrogen sulfide ion	
	H ₂ PO ₄ ⁻	dihydrogen phosphate ion	HPO ₄ ²⁻	hydrogen phosphate ion	
	NH ₄ ⁺	ammonium ion	NH ₃	ammonia	
	HCN	hydrocyanic acid	CN ⁻	cyanide ion	
	C ₆ H ₅ OH	phenol	C ₆ H ₅ O ⁻	phenoxide ion	
	HCO ₃ ⁻	bicarbonate ion	CO ₃ ²⁻	carbonate ion	
	HPO ₄ ²⁻	hydrogen phosphate ion	PO ₄ ³⁻	phosphate ion	
	H ₂ O	water	OH ⁻	hydroxide ion	Strong Bases
	C ₂ H ₅ OH	ethanol	C ₂ H ₅ O ⁻	ethoxide ion	

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2.3

Acids can be (+), neutral or (-)Examples: H₃O⁺, H₂CO₃, H₂PO₄⁻

Depending on the number of acidic protons, acids can be classified as *monoprotic*, *diprotic*, or *triprotic* (HNO₃, H₂SO₄, H₃PO₄)

Bases can be (-) or neutralExamples: HO⁻, RO⁻, H₂O, NH₃Amphoteric compounds can act as either acid or base

Water acts as either an acid or a base

2.4

2.3 The Strength of Brønsted-Lowry Acids and Bases: K_a and pK_a

Acidity equilibrium constant – K_a or proton-donating ability



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

$$pK_a = -\log K_a$$

- The lower the pK_a value, the stronger the acid (and the weaker its conjugate base)
- The higher the pK_a value, the weaker the acid (and the stronger its conjugate base)
- A strong acid will have a weak conjugate base (acid and base strength are inversely proportional)
- Equilibrium favors the formation of weak acids & bases (neutralization)

pK_a values are tabulated and can be used to determine the position of the equilibrium in acid base reactions.

2.5

pKa Values for Some Organic and Inorganic Acids

	Acid	Formula	pK_a	Conjugate Base	
Stronger acid	ethane	CH_3CH_3	51	CH_3CH_2^-	Stronger base
	ammonia	NH_3	38	NH_2^-	
	ethanol	$\text{CH}_3\text{CH}_2\text{OH}$	15.9	$\text{CH}_3\text{CH}_2\text{O}^-$	
	water	H_2O	15.7	HO^-	
	methylammonium ion	CH_3NH_3^+	10.64	CH_3NH_2	
	bicarbonate ion	HCO_3^-	10.33	CO_3^{2-}	
	phenol	$\text{C}_6\text{H}_5\text{OH}$	9.95	$\text{C}_6\text{H}_5\text{O}^-$	
	ammonium ion	NH_4^+	9.24	NH_3	
	carbonic acid	H_2CO_3	6.36	HCO_3^-	
	acetic acid	CH_3COOH	4.76	CH_3COO^-	
	benzoic acid	$\text{C}_6\text{H}_5\text{COOH}$	4.19	$\text{C}_6\text{H}_5\text{COO}^-$	
	phosphoric acid	H_3PO_4	2.1	H_2PO_4^-	
	hydronium ion	H_3O^+	-1.74	H_2O	
	sulfuric acid	H_2SO_4	-5.2	HSO_4^-	
	hydrogen chloride	HCl	-7	Cl^-	
	hydrogen bromide	HBr	-8	Br^-	
	hydrogen iodide	HI	-9	I^-	
Stronger acid					Weaker base

2.6

2.4 Determination of the Position of Equilibrium in an Acid-Base Reaction

How to Determine the Position of Equilibrium for Acid-Base Reaction



1. Identify the two acids.
2. Determine the stronger and weaker acid using pK_a values.
3. Identify the stronger and weaker base. Remember the stronger acid yields the weak conjugate base and vice versa
4. The position of the equilibrium lies towards the weaker acid and weaker base.

Examples: Complete the following acid-base reactions with the appropriate arrows.

	Acid	Formula	pK_a		
Weak acid	ethane	CH_3CH_3	51	$\text{CH}_3\text{CO}_2\text{H} + \text{NaHCO}_3$	$\text{CH}_3\text{CO}_2^- + \text{H}_2\text{CO}_3$
	ammonia	NH_3	38		
	ethanol	$\text{CH}_3\text{CH}_2\text{OH}$	15.9		
	water	H_2O	15.7		
	methylammonium ion	CH_3NH_3^+	10.64		
	bicarbonate ion	HCO_3^-	10.33	$\text{CH}_3\text{CO}_2\text{H} + \text{NH}_3$	$\text{CH}_3\text{CO}_2^- + \text{NH}_4^+$
	phenol	$\text{C}_6\text{H}_5\text{OH}$	9.95		
	ammonium ion	NH_4^+	9.24		
	hydrogen cyanide	HCN	9.21		
	carbonic acid	H_2CO_3	6.36		
	acetic acid	CH_3COOH	4.76	$\text{CH}_3\text{CO}_2\text{H} + \text{H}_2\text{O}$	$\text{CH}_3\text{CO}_2^- + \text{H}_3\text{O}^+$
	benzoic acid	$\text{C}_6\text{H}_5\text{COOH}$	4.19		
	phosphoric acid	H_3PO_4	2.1		
	hydronium ion	H_3O^+	-1.74		
	sulfuric acid	H_2SO_4	-5.2		
	hydrogen chloride	HCl	-7	$\text{CH}_3\text{CO}_2\text{H} + \text{NaOH}$	$\text{CH}_3\text{CO}_2^-\text{Na}^+ + \text{H}_2\text{O}$
	hydrogen bromide	HBr	-8		
	hydrogen iodide	HI	-9		

2.7

If you only have half of the equation, you will have to decide which molecule is the stronger acid.

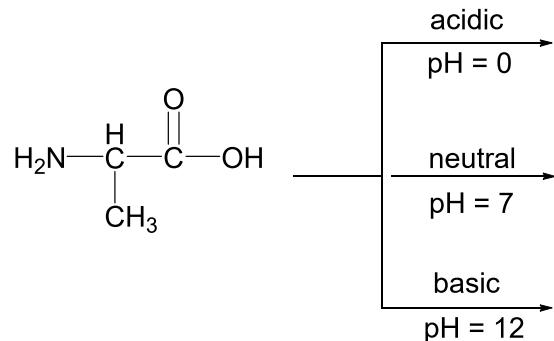
	Acid	Formula	pK_a	
Weak acid	ethane	CH_3CH_3	51	$\text{CH}_3\text{NH}_2 + \text{H}_2\text{O}$
	ammonia	NH_3	38	
	ethanol	$\text{CH}_3\text{CH}_2\text{OH}$	15.9	
	water	H_2O	15.7	
	methylammonium ion	CH_3NH_3^+	10.64	
	bicarbonate ion	HCO_3^-	10.33	$\text{HCO}_3^- + \text{OH}^-$
	phenol	$\text{C}_6\text{H}_5\text{OH}$	9.95	
	ammonium ion	NH_4^+	9.24	
	hydrogen cyanide	HCN	9.21	
	carbonic acid	H_2CO_3	6.36	
	acetic acid	CH_3COOH	4.76	
	benzoic acid	$\text{C}_6\text{H}_5\text{COOH}$	4.19	
	phosphoric acid	H_3PO_4	2.1	
	hydronium ion	H_3O^+	-1.74	
	sulfuric acid	H_2SO_4	-5.2	
	hydrogen chloride	HCl	-7	$\text{NaHCO}_3 + \text{HCl}$
	hydrogen bromide	HBr	-8	
	hydrogen iodide	HI	-9	

2.8

2.5 Acids with Multiple Acidic Hydrogen Atoms: Amino Acids

Alanine, an amino acid

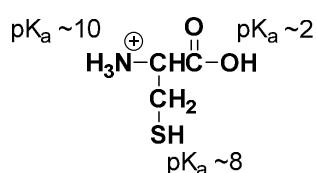
Changing the pH of a system, changes also the extent of protonation. When pH of the solution > pK_a of the dissolved acid, a proton is lost.



2.9

b) Cysteine

What is the predominant structure of cysteine at pH = 1, 4, 7, 9, and 12?



2.6 Structural Factors that Influence Acidity

a) Periodic trends

1A	2A											H 2.1	3A	4A	5A	6A	7A
Li 1.0	Be 1.5												B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
Na 0.9	Mg 1.2	3B	4B	5B	6B	7B	8B			1B	2B	Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.8	Ni 1.8	Cu 1.9	Zn 1.6	Ga 1.8	Ge 2.0	As 2.4	Se 2.8	Br 2.5	
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sh 1.9	Te 2.1	I 2.5	
Cs 0.7	Ba 0.9	La 1.1	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.8	Bi 1.9	Po 2.0	At 2.2	

- Electronegativity of A-H:

Acidity of H-A in a row is determined by the stability of A⁻
(Greater electronegativity of A = greater stability of A⁻ = stronger HA)

H ₃ C-H	H ₂ N-H	HO-H	F-H
pK _a =	pK _a =	pK _a =	pK _a =

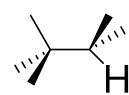
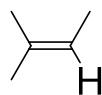
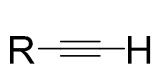
- Bond strength of X-H: Within a column, acidity increases due to weaker bonds

F-H	pK _a =
Cl-H	pK _a =
Br-H	pK _a =
I-H	pK _a =

2.11

b) Hybridization

- The more s-character the C-H orbital has, the more acidic is the C-H bond.



c) Inductive Effects

- Works through σ-bonds (polarity of bonds)
- Removal of electron density from H-A bond by withdrawing groups

Example 1: Why is CCl₃CO₂H less acidic than CF₃CO₂H?

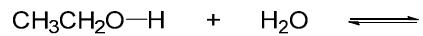
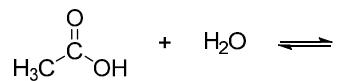
Example 2: Why is CH₃CHClCO₂H more acidic than CH₂ClCH₂CO₂H?

2.12

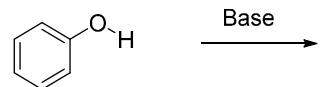
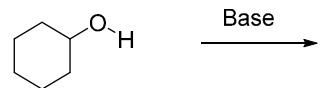
d) Resonance Effect / Delocalization of Charge**d) Resonance Effect / Delocalization of Charge**

- Distributing the resulting charge over several atoms (by resonance) stabilizes the conjugate base and makes the acid stronger
- Works through π -bonds (and lone-pairs)

Example 1: Why is acetic acid more acidic than ethanol?

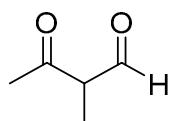
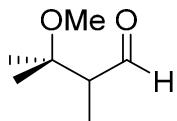


Example 2: Why is phenol more acidic than cyclohexanol?

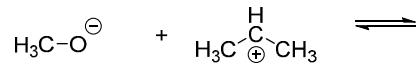
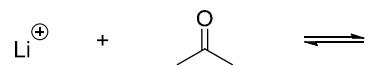
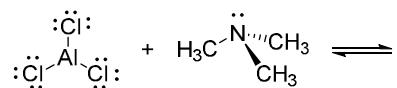
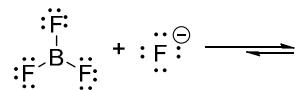
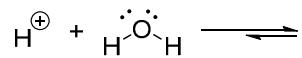
Phenol*Cyclohexanol*

2.13

Example 3: Which is the most acidic hydrogen and why?



2.14

2.7. Lewis Acids and Lewis Bases (Definition)*Lewis Acid* – accepts a lone pair of electrons into a vacant valence orbital*Lewis Base* – has an atom with a lone pair of electrons that is donated to the acid

2.15

Chapter 3: Alkanes and Cycloalkanes

3.1 Hydrocarbons and Drawing Organic Molecules

Hydrocarbons are non-polar compounds that contain only carbon and hydrogen atoms. Hydrocarbons can be divided into the following classes of saturated and unsaturated compounds:

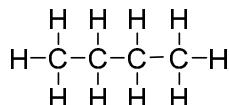
	Alkanes	Alkenes	Alkynes	Arenes (aromatic compounds)
Types of C,C bonds	only	one (or more)	one (or more)	one (or more)
Structure				
Saturated/ Unsaturated				
Formula		(for one C=C bond)	(for one C≡C bond)	(one aromatic ring)

3.2 Alkanes and Constitutional Isomers

Alkanes are saturated hydrocarbons (*aliphatic hydrocarbons*) which consist of only carbon and hydrogen atoms connected by single bonds

Alkanes can either be *unbranched (n-alkanes)* or *branched*.

- 4 bonds to each carbon atom
- All angles are 109.5°
- General formula C_nH_{2n+2}



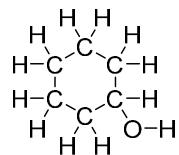
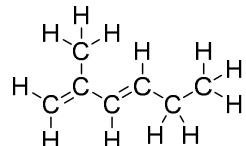
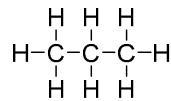
a) Condensed Structures

- Simplified versions of expanded structures
- Saves time but still unnecessarily complicated
- Often used by chemical companies in catalogs

b) Drawing Line-Angle (Skeletal) Structures

1. Each line represents a bond.
2. Each kink in the line represents a carbon atom unless another functional group is shown explicitly.
3. H atoms bound to C are only shown if needed to give a three-dimensional perspective to the molecule (see below), otherwise they are inferred by assuming that each carbon atom has a full octet.
4. If a carbon atom symbol is written explicitly, then all its substituents including hydrogen must be shown.
5. H is always shown if bonded to an atom different from carbon.

Draw the line-angle structure of the following molecules:



c) Constitutional Isomerism

Isomers are compounds that have the same molecular formula but different structures.

Constitutional Isomers: compounds that have the same molecular formula but differ in the connectivity of the atoms. They usually have different physical and chemical properties.

Branched and unbranched alkanes of the same molecular formula are constitutional isomers.

Example C_5H_{12} :

3.3 Nomenclature of Alkanes and Cycloalkanes (The IUPAC System)

a) Unbranched Hydrocarbons

Name	Number of Carbon Atoms	Structure	Name	Number of Carbon Atoms	Structure
Methane	1	CH_4	Undecane	11	$\text{CH}_3(\text{CH}_2)_9\text{CH}_3$
Ethane	2	CH_3CH_3	Dodecane	12	$\text{CH}_3(\text{CH}_2)_{10}\text{CH}_3$
Propane	3	$\text{CH}_3\text{CH}_2\text{CH}_3$	Tridecane	13	$\text{CH}_3(\text{CH}_2)_{11}\text{CH}_3$
Butane	4	$\text{CH}_3(\text{CH}_2)_2\text{CH}_3$	Tetradecane	14	$\text{CH}_3(\text{CH}_2)_{12}\text{CH}_3$
Pentane	5	$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	Pentadecane	15	$\text{CH}_3(\text{CH}_2)_{13}\text{CH}_3$
Hexane	6	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	Hexadecane	16	$\text{CH}_3(\text{CH}_2)_{14}\text{CH}_3$
Heptane	7	$\text{CH}_3(\text{CH}_2)_5\text{CH}_3$	Heptadecane	17	$\text{CH}_3(\text{CH}_2)_{15}\text{CH}_3$
Octane	8	$\text{CH}_3(\text{CH}_2)_6\text{CH}_3$	Octadecane	18	$\text{CH}_3(\text{CH}_2)_{16}\text{CH}_3$
Nonane	9	$\text{CH}_3(\text{CH}_2)_7\text{CH}_3$	Nonadecane	19	$\text{CH}_3(\text{CH}_2)_{17}\text{CH}_3$
Decane	10	$\text{CH}_3(\text{CH}_2)_8\text{CH}_3$	Eicosane	20	$\text{CH}_3(\text{CH}_2)_{18}\text{CH}_3$

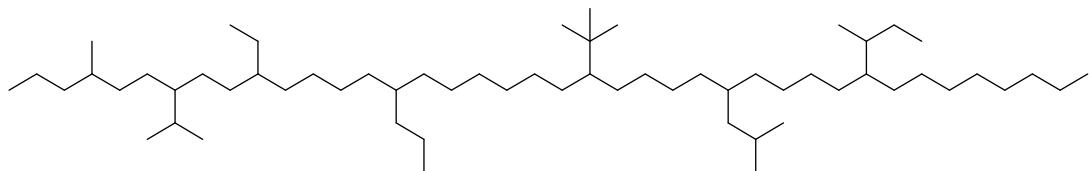
b) Branched and Substituted Hydrocarbons

Alkyl Groups (as substituents – a group of atoms that are substituted in place of one hydrogen on the parent carbon chain)

R is used as a general symbol to represent any alkyl group.

Alkane	Alkyl group	Abbreviation	Bond-line
Methane		Me	
Ethane		Et	
Propane		Pr (or n-Pr)	
		i-Pr	
Butane		Bu (or n-Bu)	
		sec-Bu	
		tert-Bu	
		i-Bu	

Identify the alkyl substituents:



c) Primary, Secondary, Tertiary and Quaternary Carbons

Carbons are classified as 1°, 2°, 3°, or 4° based on what is attached:

Primary (1°) carbon	Secondary (2°) carbon	Tertiary (3°) carbon	Quaternary (4°) carbon
bonded to 1 other carbon	bonded to 2 other carbons	bonded to 3 other carbons	bonded to 4 other carbons

R is used as a general symbol to represent any alkyl group.

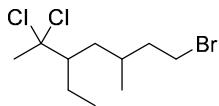
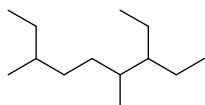
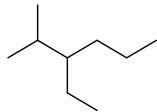
General 1° alcohol

Specific 1° alcohols

d) Guidelines for naming branched-chain alkanes (IUPAC system)

1. Find the parent chain
 - longest continuous carbon chain
 - if two chains of equal length are present, use the one with more substituents
2. Number the atoms in the main chain beginning at the end nearest to the first branch point
 - If substituents are equal distant from each end, begin numbering to give 3rd branch the lowest number
 - If no 3rd branch is present, go by alphabetical order
3. Identify and number the substituents
4. Write the name as a single word
 - (-) between a letter and a number
 - (,) between numbers
 - place substituents in alphabetical order
 - use **di-, tri-, tetra-** prefixes to indicate multiple substituents of the same name
 - don't include **di-, tri-, tetra-, sec-, or tert-** when alphabetizing
 - do include **iso-** when alphabetizing
 - **halogens** are treated the same as alkyl substituents (use fluoro-, chloro-, bromo-, iodo-)

Name the following branched hydrocarbons:



Draw the following structures:

3-isopropyl-2-methylhexane

2,2-dimethyl-4-propyloctane

4-ethyl-3,4-dimethyloctane

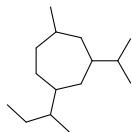
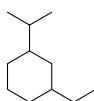
Cycloalkanes

General formula: C_nH_{2n}

Nomenclature of substituted cycloalkanes:

- Count the number of carbons in the ring and add **cyclo-** to the corresponding alkane to make the parent name
- With substituents, name the substituents and then number from the one with alphabetical priority around the ring to give the second substituent the lowest number

Write the IUPAC names for the following structures:



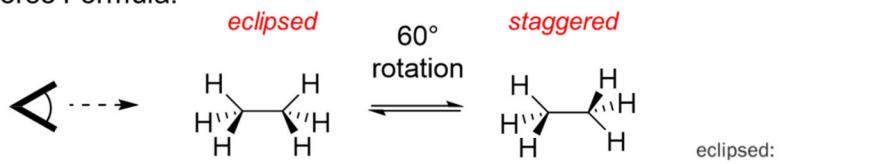
3.11

3.4 Conformational Analysis of Acyclic Compounds - sp^3-sp^3 Conformations – different arrangements of atoms that result from rotation

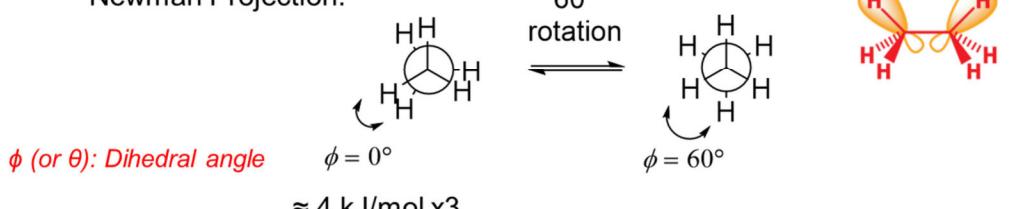
Conformers (Conformational Isomers) – Isomers that differ from each other by rotation about a single bond

a) Ethane

Sawhorse Formula:



Newman Projection:



ϕ (or θ): Dihedral angle

$\phi = 0^\circ$

$\phi = 60^\circ$

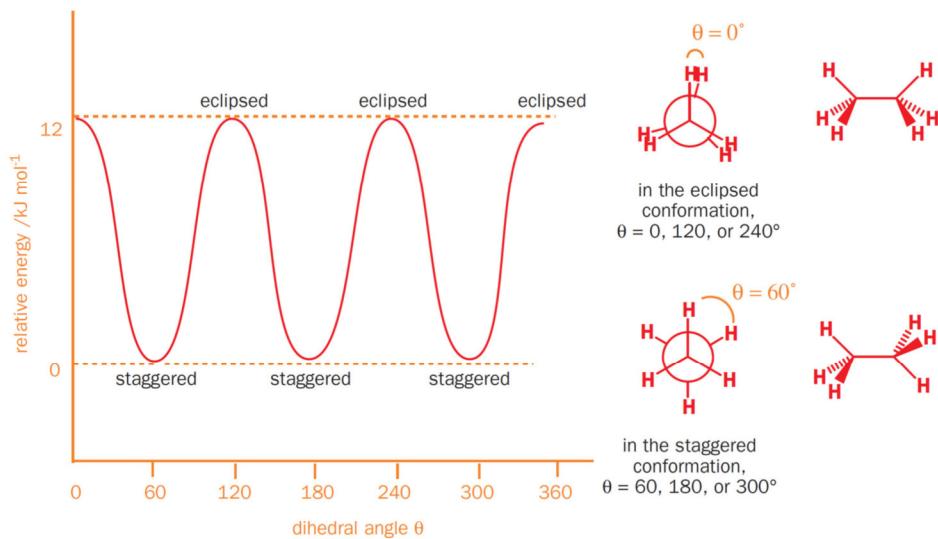
$\approx 4 \text{ kJ/mol} \times 3$

Barrier to rotation in ethane is 12 kJ/mol - Torsional energy

3.12

Ethane (continued)

- Barrier to rotation in ethane is 12 kJ/mol - *Torsional energy*
- *Torsional strain* - Repulsion between neighboring bonds (electron clouds) in the eclipsed conformation
- Different conformations arise from rotation about a single (sp^3 - sp^3) bond



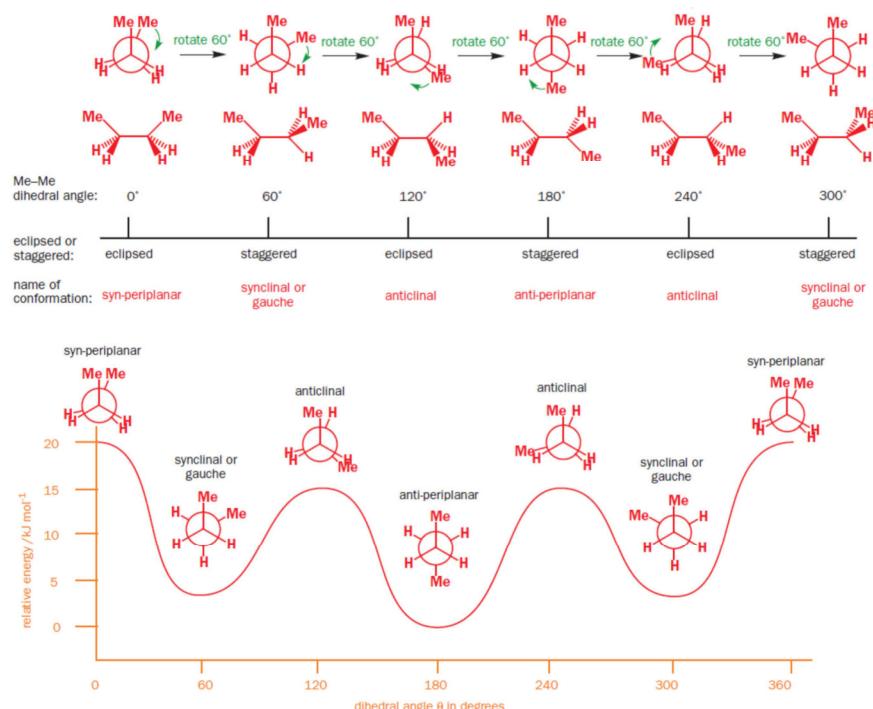
3.13

b) 1,2-Dichloroethane (as example)

Draw the Newman projections for 1,2-dichloroethane both in its staggered and eclipsed conformation.

Which is the lower energy conformation?

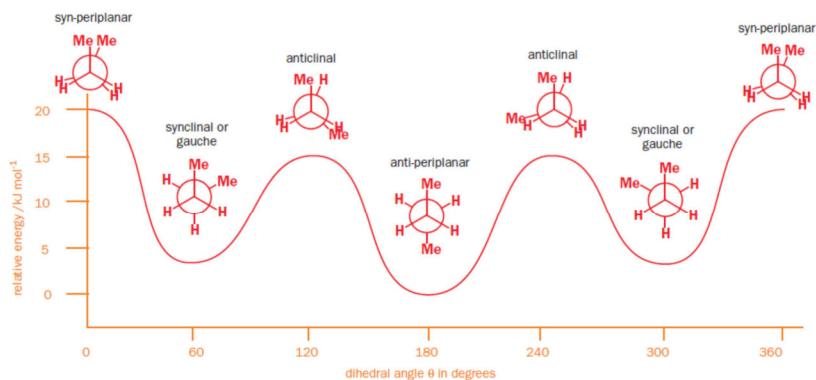
3.14

c) Butane

3.15

Conformations ≠ Conformers

Butane exists in an infinite number of *conformations* (of which only the "extremes" are shown in the energy diagram) but only has three *conformers* (= potential energy minima).



3.16

3.5 Conformational Analysis of Cycloalkanes

a) Cyclopropane is symmetrical with 60° bond angles

- Deviation from 109.5° is caused by angle strain results in cyclopropane being more reactive



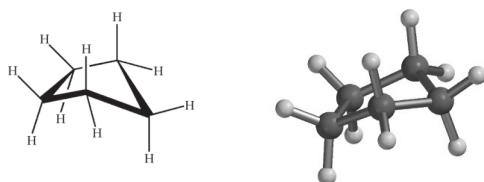
b) Cyclobutane & Cyclopentane are slightly puckered causing smaller angles and some angle strain

- Puckering relieves eclipsing of adjacent C-H bonds

Cyclobutane:



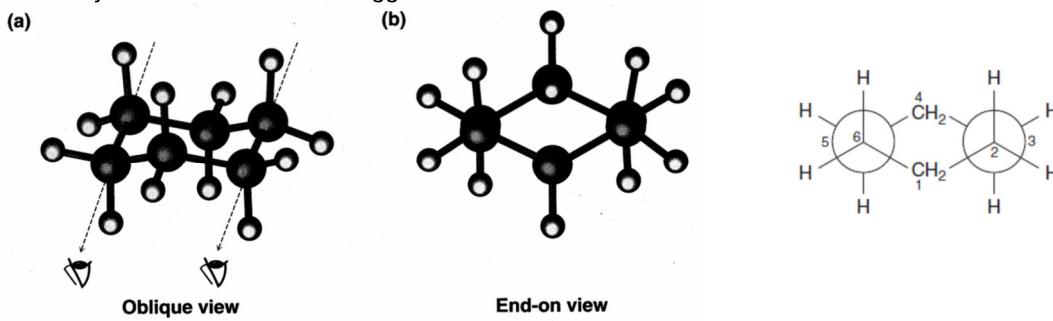
Cyclopentane:



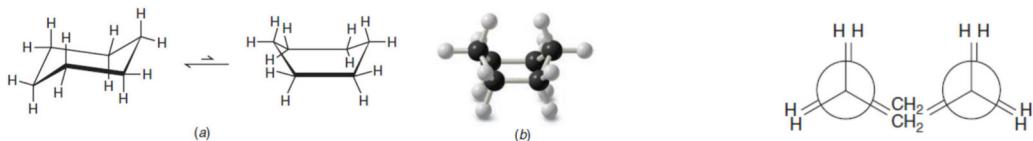
3.17

c) Cyclohexane has a **chair conformation** that is strain-free

- Bond angles are approx. 109.5°
- All adjacent C-H bonds are staggered



Cyclohexane can adopt the following conformations: Chair, Half-chair, Twist boat, and Boat. The chair conformation is generally the most stable one.



3.18

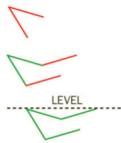
3.6. How to Draw Cyclohexane Chairs Correctly

Copied from *Organic Chemistry*, Clayden et al., Oxford University Press.

The carbon skeleton

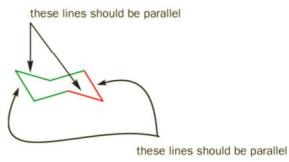
Trying to draw the chair conformation of cyclohexane in one continuous line can lead to some dreadful diagrams. The easiest way to draw a chair conformation is by starting off with one end.

Next draw in two parallel lines of equal length.

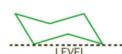


At this stage, the top of the new line should be level with the top of the original pair.

Finally, the last two lines should be added. These lines should be parallel to the first pair of lines as shown



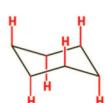
and the lowest points should also be level.



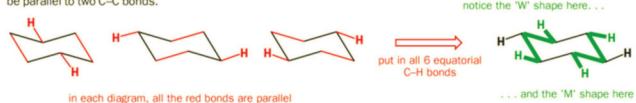
Adding the hydrogen atoms

This is often the trickiest part. Just remember that you are trying to make each of the carbon atoms look tetrahedral. (Note that we don't normally use wedged and hashed bonds; otherwise things get really messy.)

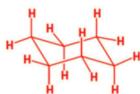
The axial bonds are relatively easy to draw in. They should all be vertically aligned and alternate up and down all round the ring.



The equatorial bonds require a little more care to draw. The thing to remember is that each equatorial bond must be parallel to two C-C bonds.

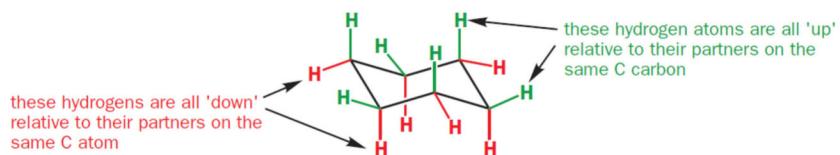


The complete diagram with all the hydrogen atoms should look like this.



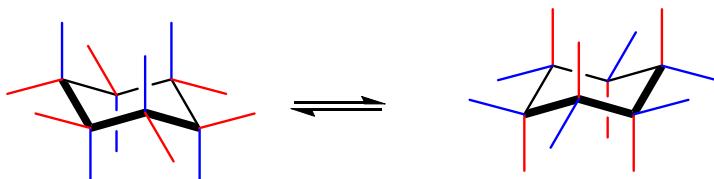
3.19

3.7 Conformational Changes During the Inversion of Cyclohexane



“Ring flip”

Axial and equatorial hydrogen atoms interchange during a “ring-flip”:



In unsubstituted cyclohexane, the interconversion of one chair to the other occurs at room temperature, thus preventing isolation of the conformers.

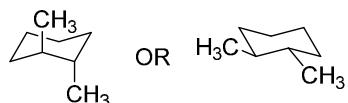
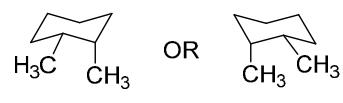
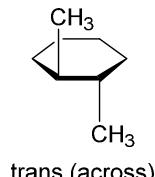
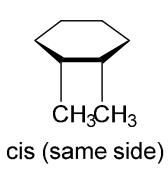
3.20

3.8 Monosubstituted Cyclohexanes

Cyclohexanol

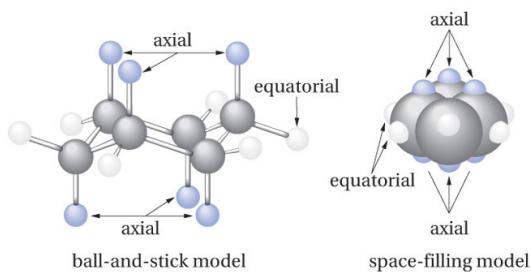
1,3-diaxial interactions

3.21

3.9 Cis-Trans Isomers in Cycloalkanes*cis*-1,2-Dichlorocyclopropane*trans*-1,2-Dichlorocyclopropane**Stereoisomers** - same connections, but differ in spatial orientation*Cis-trans* isomers are separate, unique compounds that do not interconvert by rotation around C-C bonds

3.22

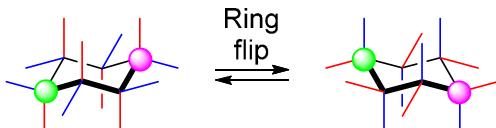
3.10 Conformational Mobility in Substituted Cyclohexanes



Notice that the 3 axial hydrogens on the same face almost touch

- If H is replaced by larger substituents, axial crowding becomes worse
- Steric strain caused by large groups experiencing 1,3-diaxial interactions decreases stability
- Steric strain can be reduced by a ring-flip which moves large groups out of an axial position into an equatorial position

Ring flip:



3.23

cis-1-*tert*-butyl-4-fluorocyclohexane

trans-1-*tert*-butyl-4-fluorocyclohexane

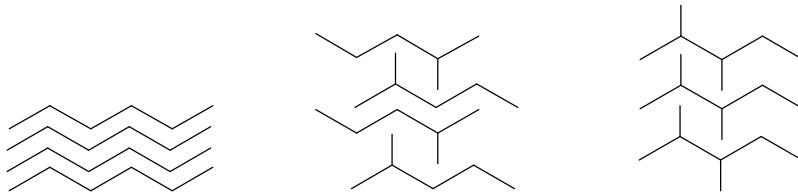
Cis and *trans* isomers are different compounds and therefore have different physical properties.

cis-1,4-cyclohexanediol (m.p. 113-114 °C)

trans-1,4-cyclohexanediol (m.p. 143-144 °C)

3.11 Properties of Alkanes

- 1–4 Carbons in the molecule = gas
- >4 Carbons in the molecule = liquid (density ~0.7–0.8 g/mL)
- Boiling point, melting point, and density increase as molecular weight increases
- Alkanes have lower b.p. than other compounds of similar MW due to weak van der Waals attractions
- Alkanes with more branching will have lower b.p. due to decreased van der Waals interactions



Known as paraffins for their “slight affinity” for other substances

- Will react with oxygen (combustion) and the halogens (radical)
- Do not normally react with acids, bases, or oxidizing or reducing agents

Chapter 4: Alkenes and Alkynes

4.1. Review: Alkenes and Alkynes

Alkene: molecule containing C and H only with at least one C=C

Alkyne: molecule containing C and H only with at least one C≡C

Unsaturated molecule: any molecule having fewer Hs than the corresponding alkane due to the existence of *double bonds or triple bonds*.

Arenes (Aromatic Molecules)

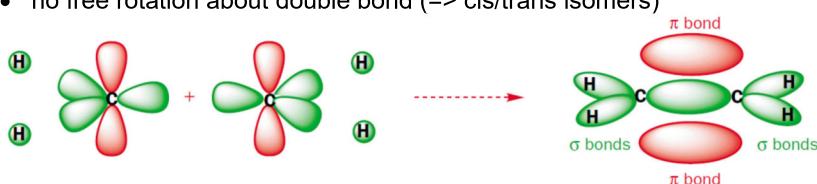
- Simplest arene (=aromatic molecule) is benzene
- Chemistry is quite different from alkenes (see chapter 9)
- Generally inert (=non-reactive) under conditions where alkenes react



4.1

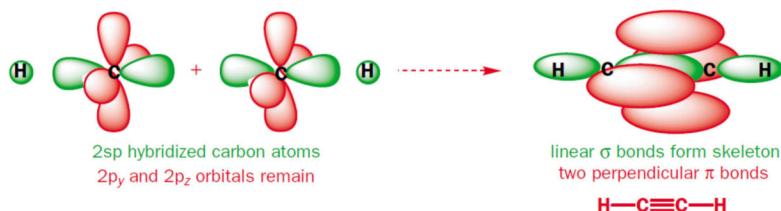
Electronic Structure of Alkenes

- sp²-hybridized orbitals – trigonal planar
- unhybridized p orbital
- π bond made by overlapping of unhybridized orbitals
- no free rotation about double bond (=> cis/trans isomers)



Electronic Structure of Alkynes

- sp-hybridized orbitals – linear
- 2 unhybridized p orbitals
- π bond made by overlapping of unhybridized orbitals
- no free rotation



4.2

4.2 Substituted Alkenes and Their Relative Stabilities

a) Terminal alkenes

Terminal alkenes can be mono or disubstituted.

Common substituents with a terminal double bond are the vinyl, allyl and methylene groups.

Vinyl

Allyl

Methylene

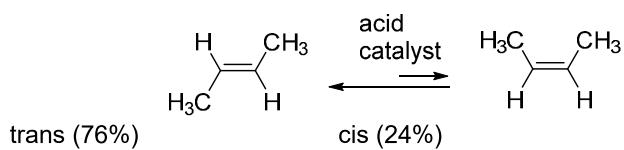
4.3

b) Cis and trans alkenes

Disubstituted ***internal alkenes*** show ***cis-trans*** isomerism.

- *Cis* and *trans* isomers a type of stereoisomers (same connectivity of atoms but different spatial arrangement)

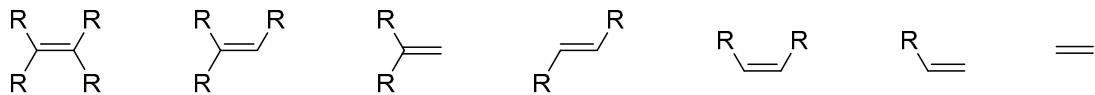
- *Cis* and *trans* isomers are different compounds and can be isolated because the double bond is rigid and rotation does not occur spontaneously.
 - In the presence of an acid catalyst, *cis-trans* interconversion can occur and an equilibrium is established.



4.4

c) Overall Relative Stabilities of Alkenes

- The more substituted the double bond is, the lower in energy the molecule



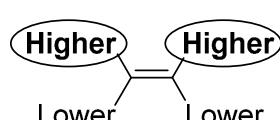
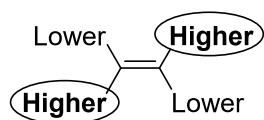
4.5

4.3 Nomenclature of Alkenes, Cycloalkenes, and Alkynes (IUPAC)

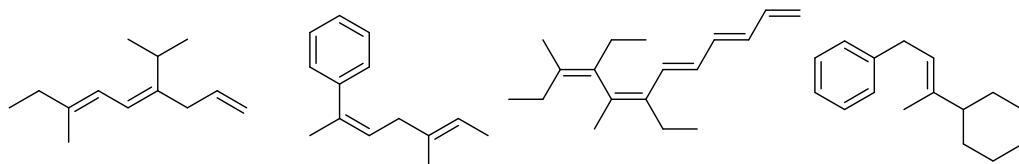
While cis/trans can be used *only* for disubstituted alkenes, the E/Z designation is applicable to all substituted alkenes

a) E,Z Designation for Di-, Tri-, and Tetrasubstituted Alkenes

- E and Z can be assigned to all unequally substituted alkenes
- The same sequence rules as for assigning R/S to stereogenic centers are used to rank the substituents of the double bond

**E (entgegen, opposite)****Z (zusammen, together)**

Assign E or Z to the double bonds if applicable:

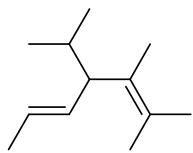
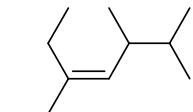


4.6

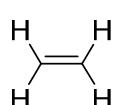
b) Nomenclature of Alkenes

1. Name the parent hydrocarbon
 - find the longest chain containing both ends of the C=C
 - name the chain length with the –ene ending
2. Number the C atoms in the chain
 - start at the end closest to the C=C
 - if the C=C is equidistant from both ends, give the first branch the lowest number
3. Write the full name
 - number the substituents as with alkanes
 - indicate the C=C position by giving the first C number in the bond
 - if more than one C=C, give a number to each double bond and use diene, triene,...
4. Assign E or Z to the double bonds if appropriate
 - cis and trans may be used instead for disubstituted alkenes

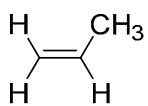
Provide the IUPAC name for the following unsaturated molecules:



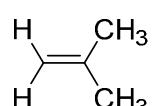
4.7

Common trivial names

ethene
ethylene



propene
propylene



2-methylpropene
isobutylene

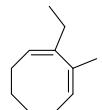
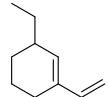
4.8

c) Nomenclature of Cycloalkenes

Cycloalkenes are named the same way as open-chain alkenes with the additional rules that

- C=C is given position numbers (1 and 2) so that the remaining substituents have the lowest possible locants
- There is no need to assign E and Z for smaller rings than cyclooctane: due to structural constraints only the Z (cis) form is isolable in 3-7 membered rings.

Examples:



Attention: the designations cis and trans in cyclic systems is ambiguous and can be used both for relative stereochemistry of two substituents or/and for

Cis -Trans Isomerism in Cycloalkenes

Cyclooctene is the smallest ring that can contain a *trans* double bond\



5



6



7



8

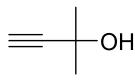
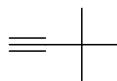
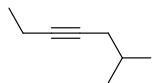


8

4.9

d) Nomenclature of Alkynes

- Follow the general rules for alkanes and alkenes
- -yne ending for the parent chain
- C≡C position is indicated by the first number in the chain
- Numbering of the chain begins at the end closest to the C≡C
- Triple bonds take priority over double bonds when assigning numbers.



4.4 Acidity of Terminal Alkynes

Acidity of Alkanes, Alkenes, and Alkynes:

Water	$pK_a = 15.7$
Alkyne	$pK_a = 25$ sp (50% s-character)
Alkene	$pK_a = 44$ sp^2 (33% s-character)
Alkane	$pK_a = 51$ sp^3 (25% s-character)

Example: Deprotonation of terminal alkyne by amide base:



4.11

Chapter 5: Reactions of Alkenes and Alkynes

5.1. Characteristic Reactions of Alkenes

Hydrochlorination (Hydrohalogenation):

Hydration:

Bromination (Halogenation):

Hydroboration:

Hydrogenation (Reduction):

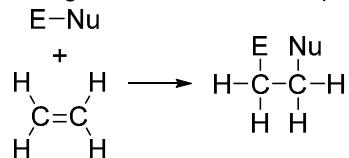
5.1

5.2 Reaction Mechanisms

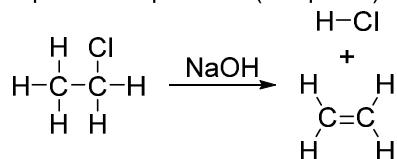
Reaction mechanisms describe in detail exactly what happens at each stage of a chemical transformation including which bonds are broken, which bonds are formed, which sequence of reactions leads to the observed product(s), what the reaction order is, and why we observe a given reaction rate

a) Types of Reactions

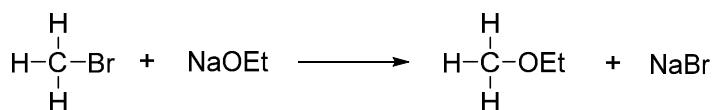
Addition Reactions: 2 reactants come together to form one compound



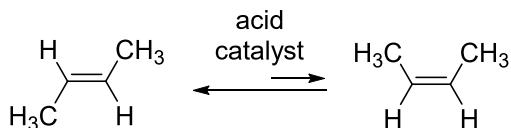
Elimination Reactions: 1 reactant splits into 2 products (Chapter 7)



Substitution Reactions: 2 reactants exchange parts to make 2 new products (Chapter 7)



Rearrangement Reactions: 1 reactant undergoes a reorganization of bonds and atoms to give a single isomeric product



5.3

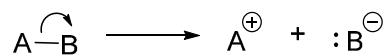
b) Bond Cleavage and Formation

Ionic Reactions: Heterolytic Cleavage and Heterogenic Formation

Only species with paired electrons in valence shell are involved in ionic reactions (e.g. nucleophiles and electrophiles, Lewis acids and bases).

Ionic reactions generally involve the formation or cleavage of strong, polar bonds.

Heterolytic Cleavage



Polar: Unequal breaking of a bond

Heterogenic Formation



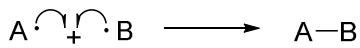
5.4

Radical Reactions: Homolytic Cleavage and Homogenous Formation

Radical species contain unpaired electrons in the valence shell (most often they have an uneven number of electrons) and can be formed by homolytic cleavage of weak (often apolar) bonds.

Homolytic Cleavage***Homogenous Formation***

Two radicals can recombine to form a bond:



5.5

c) Electrophiles and Nucleophiles

Electrophile = A species with an empty orbital it would like to fill.

- All Lewis acids are electrophiles.
- The carbon atoms of carbonyl groups are electrophilic

Nucleophile = A species with a pair of electrons it would like to donate/share.

- All Lewis bases can act as nucleophiles
- Electron-rich π -bonds (e.g. double bonds) can act as nucleophile.

Example 1: Nucleophilic attack on a carbonyl group

Example 2: Nucleophilic Substitution on a saturated carbon atom (sp^3 hybridized)

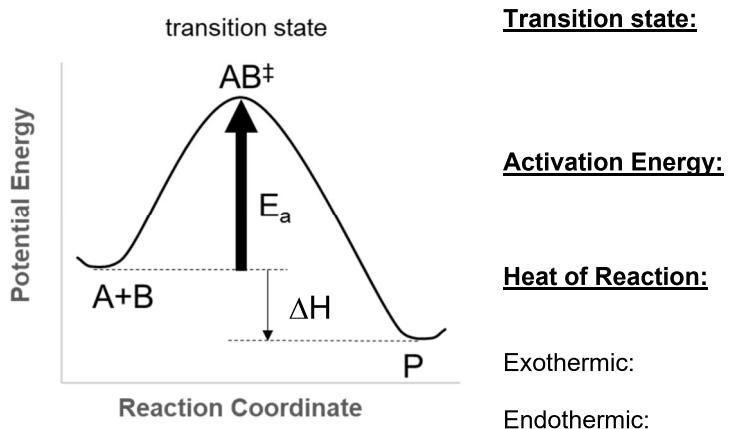
Example 3: Reaction of a nucleophile with a carbocation

5.6

d) Energy Diagrams and Reaction Mechanisms

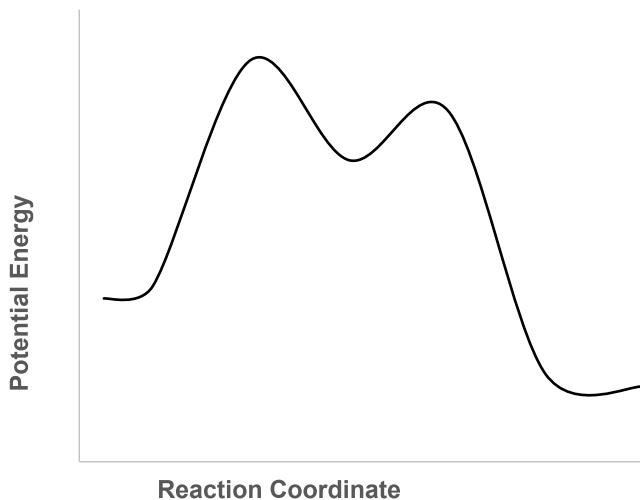
Energy diagrams show the energy changes that occur during a reaction.

Example of an energy diagram for a one-step reaction:



5.7

Example of an energy diagram for a reaction involving intermediates:



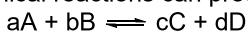
Reaction Intermediate:

Rate-determining step:

5.8

e) Review of Thermodynamics and Kinetics**Reaction Equilibrium: Thermodynamics**

Chemical reactions can proceed in both directions (are reversible)



$$K_{eq} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

The equilibrium constant, K_{eq} , tells us which direction is favored $K_{eq} > 1$ – products (C & D) are favored $K_{eq} < 1$ – reactants (A & B) are favored

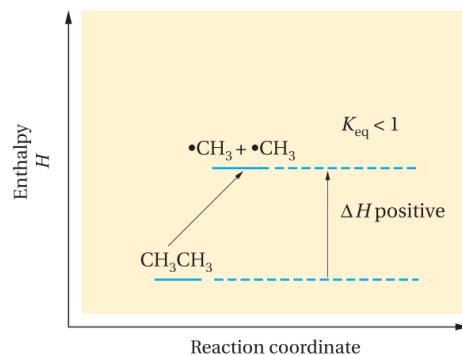
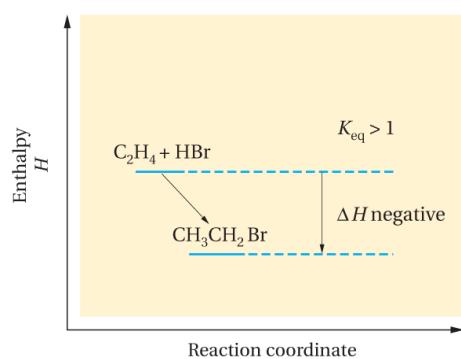
5.9

Reactions occur when the products are more stable than reactants

Reactions want to go from high energy to low energy

Heat is released in these **exothermic** reactions ΔH (change in enthalpy) = energy difference between reactants and products

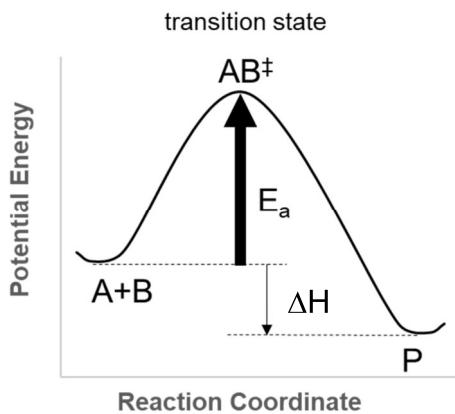
- negative ΔH indicates a favored, **exothermic** reaction
- If heat or energy is required for the reaction to proceed, the reaction is **endothermic** and unfavored



Reaction Rates: How fast are reactions? (Kinetics)

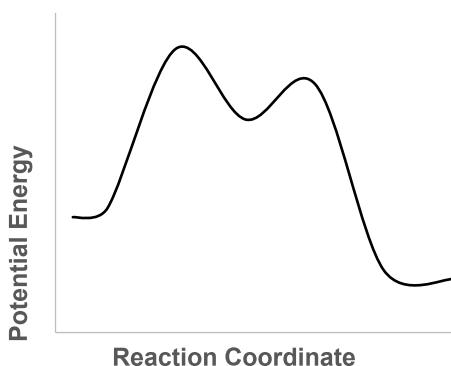
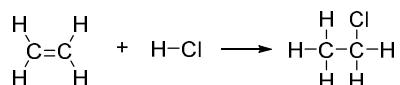
Molecules must collide with enough energy and in the right orientation so bonds can be made and broken

The higher the energy barrier the slower the reaction
Rates also affected by temperature and catalysts



5.11

Review: Answer the questions below regarding the reaction profile which belongs to the following reaction:



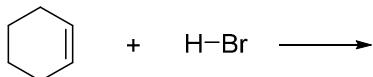
1. Is the first step exothermic or endothermic? Why?
2. Is the second step exothermic or endothermic? Why?
3. Which is the rate-determining step? Why?

5.12

5.3 Electrophilic Addition of H-X to Alkenes and Alkynes

a) Electrophilic addition of H-Br across the double bond

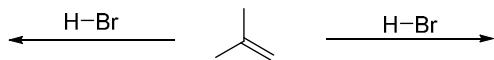
Electrophilic addition of H-Br across the double bond of a symmetrical alkene:



Points to note regarding the mechanism:

1. Draw the arrow beginning from the *middle* of the double bond with the electrons moving out *through the carbon* that is picking up the proton in the first step.
2. Because the substrate is symmetrical, either carbon could pick up the proton. Important is, that the carbocation is on the other carbon.

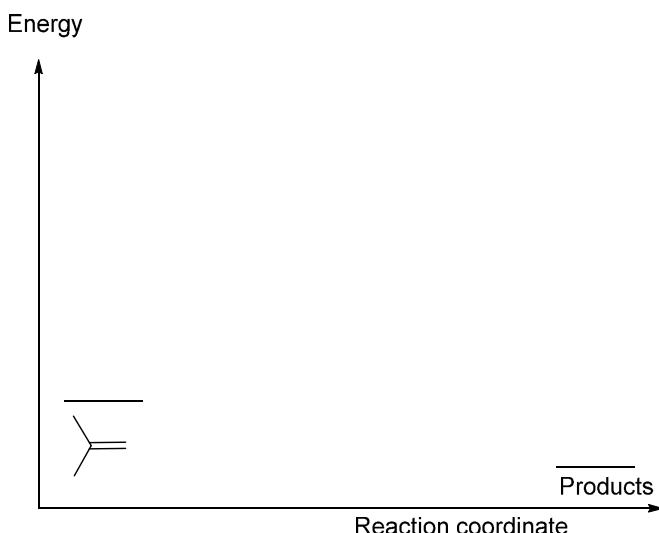
Electrophilic addition of H-Br across the double bond of an unsymmetrical alkene:



5.13

The addition of HBr is *regioselective* for the more substituted alkyl bromide being formed when unsymmetrical alkenes are used. Why?

Reaction Profiles of the Two Possible Pathways:



- The *higher energy reactive carbocation intermediate* has a *higher energy transition state*.
- Formation of *more stabilized carbocation intermediate* during RDS is **faster** due to its lower energy pathway via the *lower energy transition state*.

The more substituted product is often called **Markovnikov product**, and the addition reaction leading to it can be called a **Markovnikov addition**.



5.15

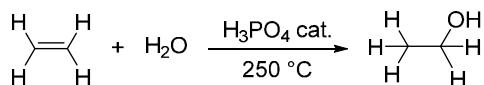
b) Addition of Hydrogen Halides to Alkynes

The electrophilic addition of hydrogen halides to triple bonds can be stopped after addition of one equivalent of HX (HCl, HBr, HI) if added stoichiometrically.

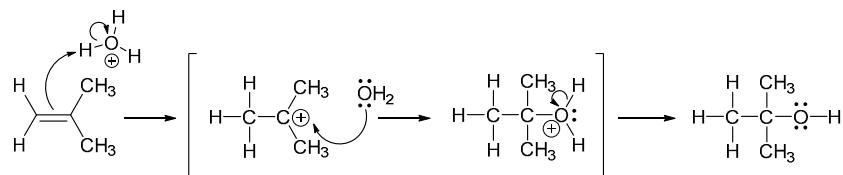
As with double bonds, this reaction results in the more substituted halide (follows Markovnikov's rule):



5.16

5.4 Acid catalyzed hydration: Addition of water across an unsaturated C,C bond

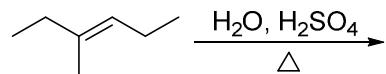
Mechanism:



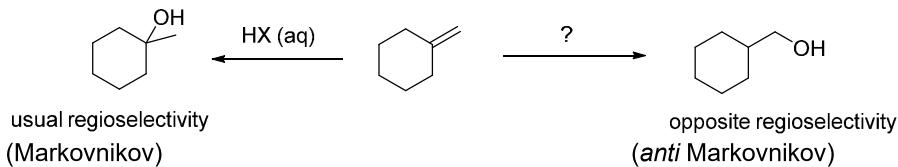
Important points:

- The acid is only needed in catalytic quantities
- The catalytic acid must have a conjugate base which is a worse nucleophile than water. Good choices are: phosphoric acid (H_3PO_4) and sulfuric acid (H_2SO_4)

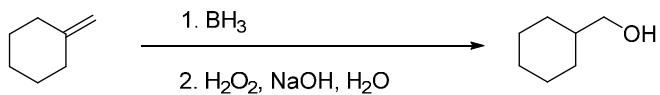
With unsymmetrically substituted alkenes, the more substituted alcohol is obtained (Markovnikov product).



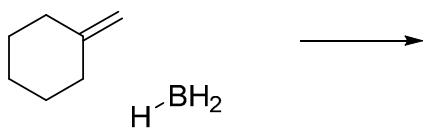
5.17

5.5 Hydroboration-Oxidation: anti-Markovnikov Syn Addition of water across an unsaturated C,C bond

Hydroboration-Oxidation: Addition of water with opposite regioselectivity:



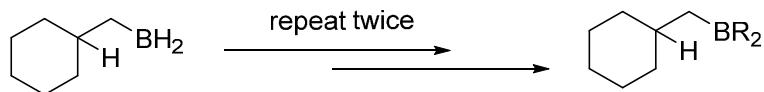
5.18

Step 1: Borane Addition

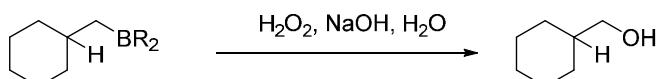
Reasons for the observed *regioselectivity*:

- *Electronics:* the π -bond electrons are being donated into the empty p-orbital of the boron atom (which is sp^2 hybridized). The partial positive charge this generates needs to go onto the carbon atom best able to stabilize this positive charge.
- *Sterics:* BH_3 is larger than H so it ends up where there is less steric hindrance.

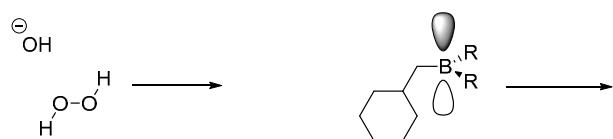
With BH_3 , this process can occur three times, giving the trialkylated borane:



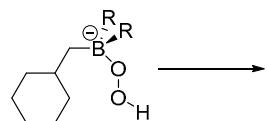
5.19

Step 2. Oxidation using an aqueous mixture of NaOH and H_2O_2 Mechanism:

In a first step, hydrogen peroxide is deprotonated by hydroxide and then forms the Lewis Acid-Base adduct with borane:



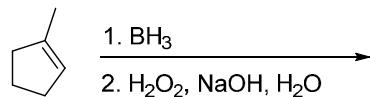
The O-O bond is weak and can break, losing OH^- at the same time as forming a strong C-O bond:



5.20

Stereochemical Outcome of the Hydroboration-Oxidation Reaction:

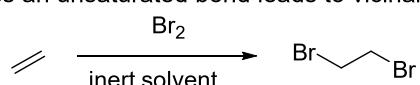
Syn addition of H and OH to the double bond



5.21

5.6 Electrophilic Addition of X_2 to Alkenes and Alkynes**a) Electrophilic Addition of X_2 to Alkenes**

Electrophilic addition of Br_2 across an unsaturated bond leads to vicinal dibromides:

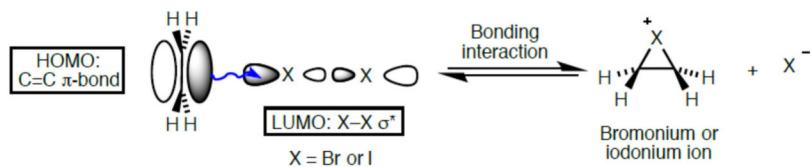


Mechanism: The addition of halogens to the double bond occurs in two steps.

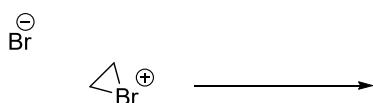
1. Formation of bromonium (iodonium) ion (reactive intermediate):



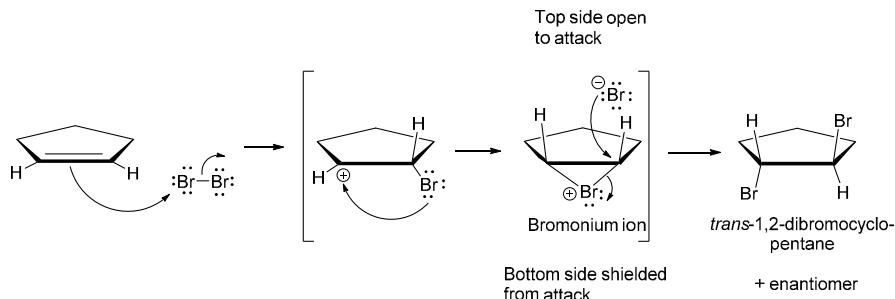
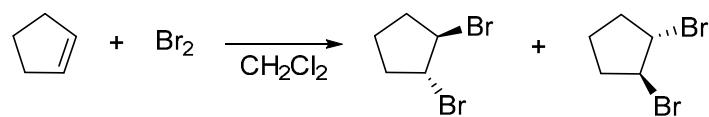
Orbital picture:



2. The bromonium (iodonium) is attacked by the bromide/iodide ion formed in the first step via a $\text{S}_{\text{N}}2$ reaction:

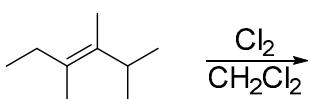
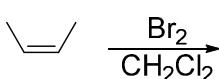
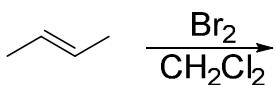


5.22

Stereochemical Outcome of Bromination of Cyclopentene:

- Anti addition
- Stereospecific reaction
- Multiple products: bromonium ion can form on both sides of the double bond & the bromide can attack either of the carbons in the second step

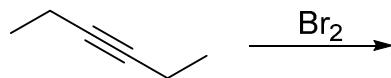
5.23

What are the products of these reactions?

5.24

b) Electrophilic Addition of Bromine to Alkynes

Anti stereochemistry



5.25

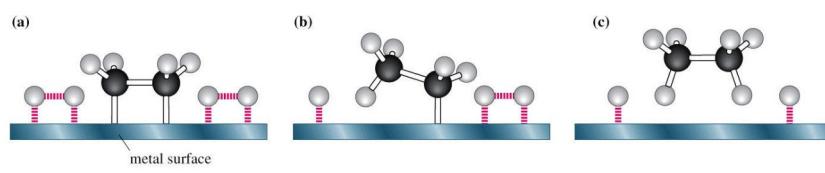
5.7 Hydrogenation of Alkenes and Alkynes

Reduction: Addition of H_2 (or removal of O).

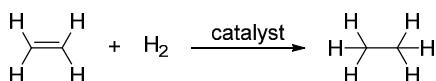
Hydrogenation of alkenes:

Hydrogenation of alkynes:

The role of the catalyst: Activation of hydrogen and lowering the transition state energy

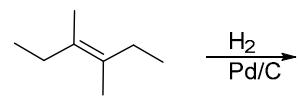
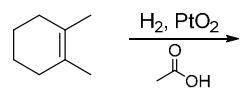


Energy diagram

a) Hydrogenation of Alkenes

Catalysts = Pd, PtO₂, or Ni

Hydrogenation of alkenes occurs with *syn* stereochemistry and is another example of a *stereospecific* reaction.

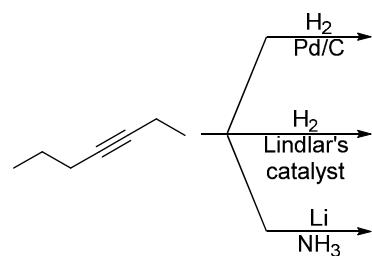


5.27

b) Hydrogenation of Alkynes

Three possibilities:

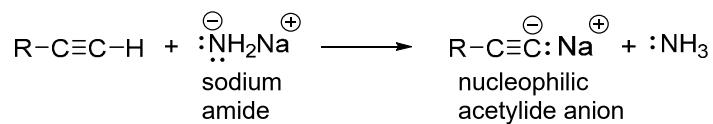
1. Full reduction to alkane
2. Reduction to *cis*-alkene (**Syn addition of hydrogen with Lindlar's catalyst**)
3. Reduction to *trans*-alkene (**Anti addition of hydrogen by dissolving metal reduction**)



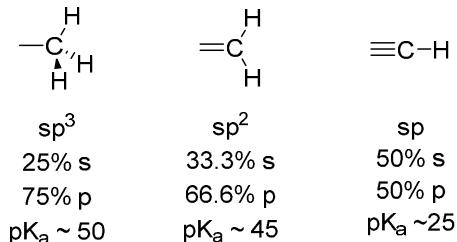
5.28

5.8 Formation and Use of Acetylide Anions

Terminal C≡C-H are weakly acidic ($pK_a \approx 25$) and can be deprotonated by strong bases such as amides.



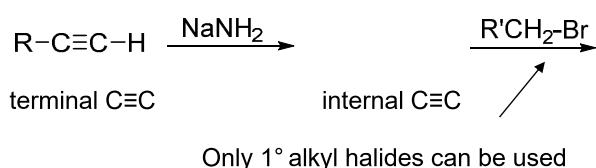
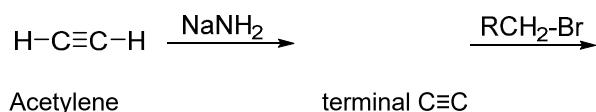
Acidity of terminal H is due to hybridization



- As hybridization of C becomes more s-like the acidity of the attached H increases
- Though acidic, terminal alkynes are far less acidic than H_2O
- In the presence of H_2O , acetylides react to give alkynes
- Internal alkynes have no exceptionally acidic Hs

5.29

Alkylation of acetylides:



5.30

Chapter 6: Chirality: The Handedness of Molecules

6.1. Chirality and Stereochemistry

What does chirality mean?

Chiral objects are not superimposable on their mirror images



Achiral objects contain a plane of symmetry (mirror plane) and are superimposable on their mirror image



6.1

Are the following objects chiral or achiral?

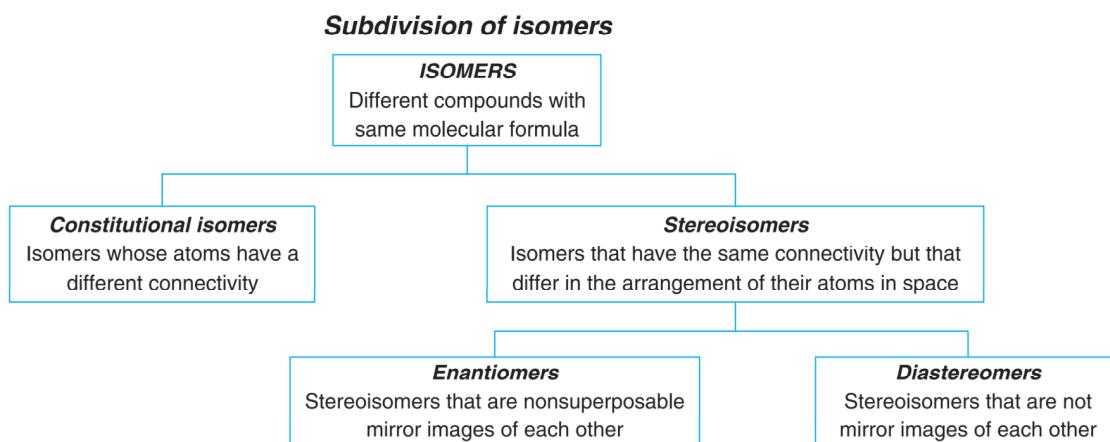


A G H J L E

W Q Y B P T

6.2

6.2 The Relationship Between Different Isomers



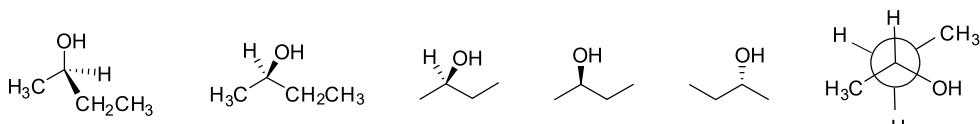
Achiral molecules are optically inactive and have a plane of symmetry (mirror plane) which makes their mirror image superimposable with the original

Chiral molecules are **optically active** molecules and contain either a stereogenic center or another chiral element which makes their mirror image non-superimposable with the original

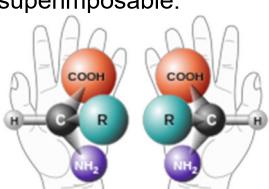
6.3

Stereocenter (Stereogenic center): carbon with 4 different groups attached = chiral center

Graphical representation of stereogenic centers



Enantiomers – A pair of **chiral** molecules which behave like image and mirror image and are not superimposable.



- Identical physical properties (except when in chiral environment)
- Opposite rotation of plane-polarized light ("optically active")

Diastereomers – Stereoisomers which are not enantiomers.

Molecules with the same connectivity which **do not** behave like image and mirror image and are not superimposable. They have different physical properties.

6.4

Exercise

1. Draw all stereoisomers of 1,2-dimethylcyclohexane. How many are there?

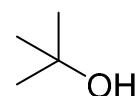
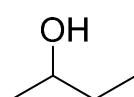
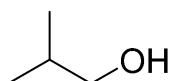
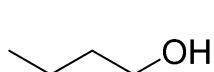
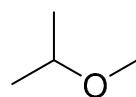
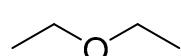
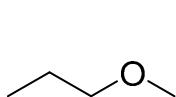
2. Label all the stereocenters with "*".

3. Which molecules are chiral, which are achiral?

4. Which molecules are enantiomers?

5. Which molecules are diastereomers?

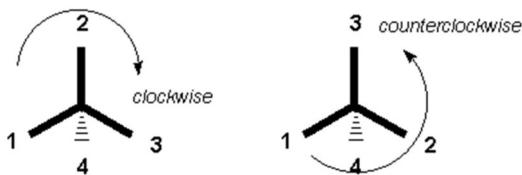
6.5

6.3 Molecules with one Stereogenic Center: EnantiomersC₄H₁₀

6.6

The R,S-System for Naming Stereocenters (Cahn-Ingold-Prelog Sequence Rules)

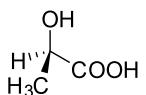
- Determine the priority of the substituents (see below)
- Turn the lowest priority group away
- Trace the three remaining groups from Rank 1 to Rank 2 to Rank 3



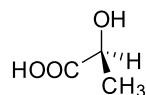
Priority: 1>2>3>4 (4: lowest priority, in the back)

How to determine priority

- Atomic numbers
- Isotopes
- Multiple Bonds
- If 1st sphere no difference, then 2nd sphere, etc.



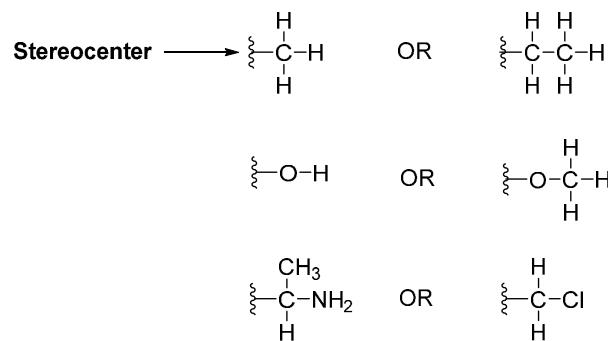
(-)lactic acid



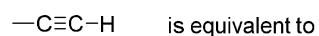
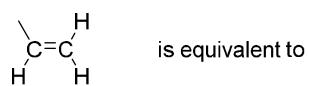
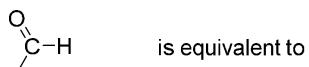
(+)-lactic acid

Note: There is **no** connection between R/S and +/-
Which substituent has the higher priority?

6.7

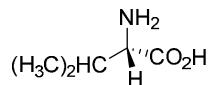
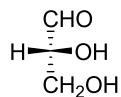
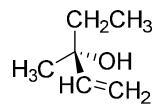


Multiple bonds are equivalent to the same number of single bonded atoms.



6.8

Examples: Assign (R) and (S) configurations to all stereogenic centers



(2S,3R)-2-bromo-3-fluorobutane

6.9

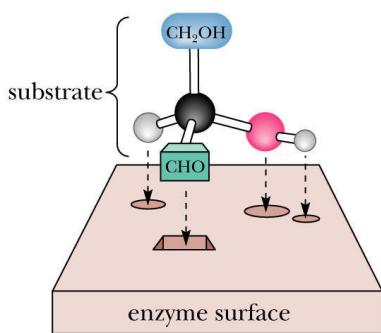
6.4 Biological Significance of Chirality and Asymmetric Synthesis

Interactions between molecules in living systems take place in a chiral environment, a molecule and its enantiomer or one of its diastereomers elicit different physiological responses.

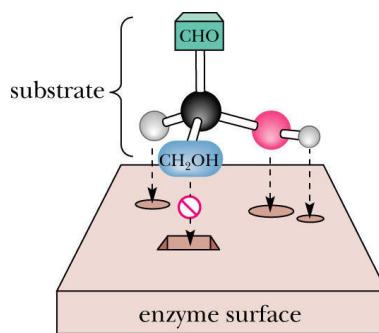
Enzymes (catalytic proteins) are made up of individual amino acids which all have a chiral center (except glycine).

- Chymotrypsin has 251 stereocenters and exists as one single stereoisomer
- the maximum number of stereoisomers possible is

Because enzymes are chiral substances; most either produce or react with only substances that match their stereochemical requirements.



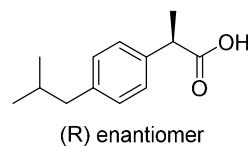
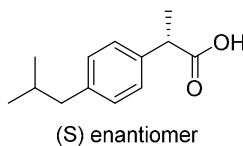
This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface



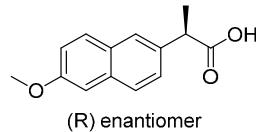
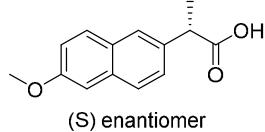
This enantiomer of glyceraldehyde does not fit the same binding sites

Chiral drugs

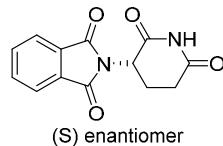
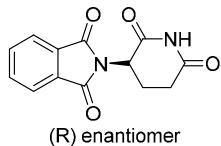
- (S)-ibuprofen is a pain and fever reliever, its R enantiomer is inactive.



- (S)-naproxen is an anti-inflammatory pain reliever; its R enantiomer is a liver toxin.



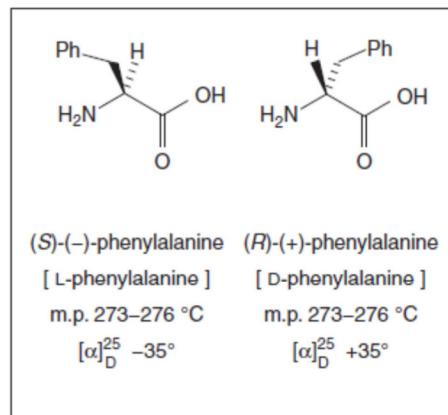
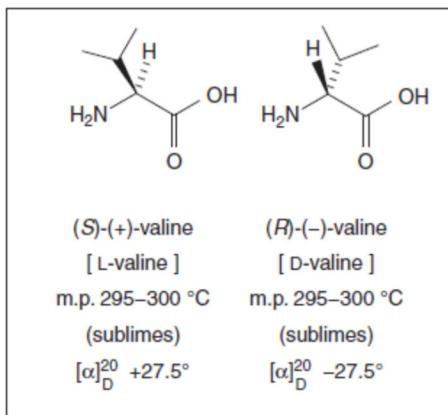
- (R)-thalidomide is a sedative; its S enantiomer is teratogenic



6.11

6.5 Properties of Chiral Molecules: Optical Activity

Pure enantiomers have identical physical and chemical properties unless they are in an asymmetric environment where they interact with chiral substances. Two sets of enantiomerically pure amino acids demonstrate this:



One way to distinguish pure enantiomers is to measure their optical rotation. Enantiomers rotate plane-polarized light by equal amounts but in opposite directions.

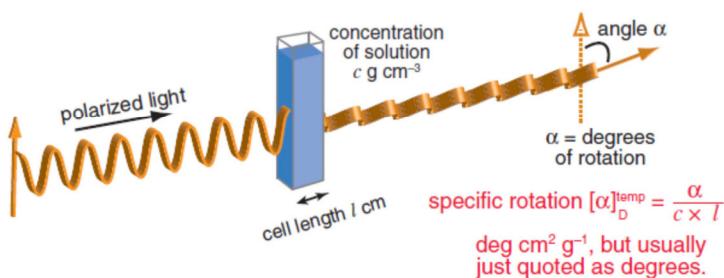
Levorotatory (L or −) – rotation to the left

Dextrorotatory (D or +) – rotation to the right

6.12

Optical activity of enantiomers

The rotation of plane-polarized light is measured using an instrument known as a *polarimeter*, which is illustrated schematically below.



Specific Rotation: observed rotation when the wavelength (λ) of light used is 589.6 nm
How far the plane rotates depends on the structure of the molecules and the concentration of the sample:

$$[\alpha]_D = \frac{\text{observed rotation } (\text{°})}{\text{path length } (\text{dm}) \times \text{conc } (\text{g/mL})} = \frac{\alpha}{l \times C}$$

A 1.20 g sample of cocaine, $[\alpha]_D = -16^\circ$, was dissolved in 7.50 mL of chloroform and placed in a sample tube having a path length of 5.00 cm. What was the observed rotation?

6.13

Enantiomeric Excess (also called optical purity)

For known compounds (with known specific rotations) we can calculate how much of each enantiomer is present in a mixture.

Enantiomeric excess (e.e.) is defined as:

$$\% \text{ Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

$$\% \text{ Enantiomeric excess} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}} \times 100$$

A racemic mixture (a racemate) is a 50:50 mixture of enantiomers.

Because enantiomers rotate plane polarized light by equal amount but in opposite directions, a racemic mixture exhibits no optical activity

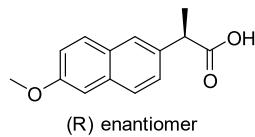
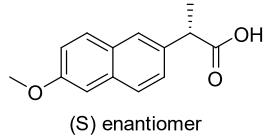
Examples:

- A sample of D-phenylalanine ((R)-(+)-phenylalanine) has an optical purity of 98%. How much of the D- and L-enantiomers are present?
- For a sample of D-phenylalanine ((R)-(+)-phenylalanine, $[\alpha]_D = +35^\circ$) a rotation of 30° is observed. What is the enantiomeric excess?

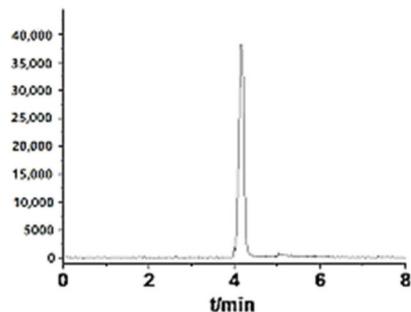
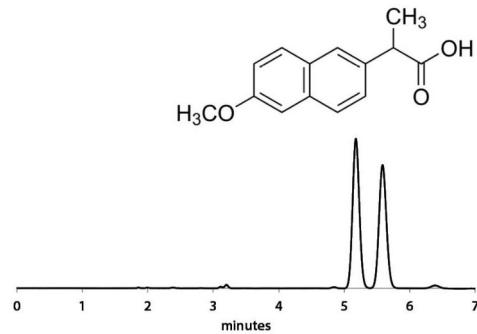
6.14

How to determine enantiomeric excess of (new) compounds.

Example from earlier: (S)-naproxen is an anti-inflammatory pain reliever; its R enantiomer is a liver toxin.



How do pharma companies ensure that only the S-enantiomer is present?

Chiral HPLC (most common)**HPLC with a normal (achiral) column:****HPLC with a chiral column:**

6.15

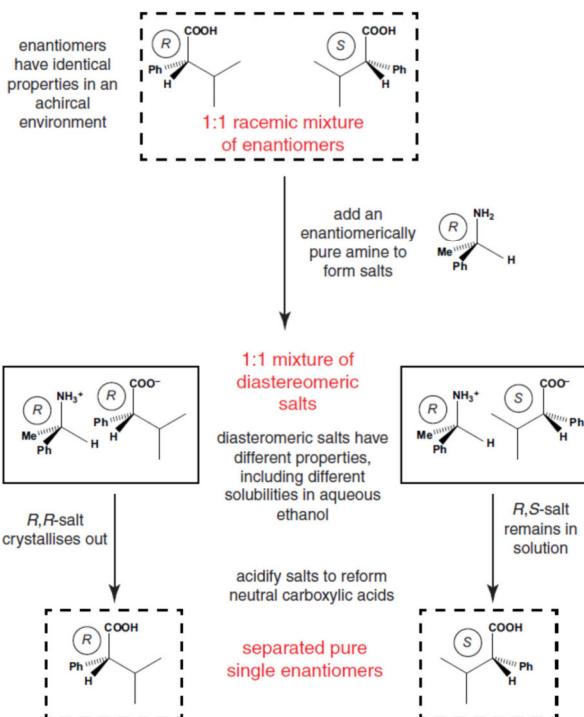
6.6 Racemic Forms and Resolution of Enantiomers

A racemic mixture (a racemate) is a 50:50 mixture of enantiomers.

Resolution of enantiomers:

Separation of a racemic mixture

Reaction of a racemic mixture with a (enantiopure) chiral molecule converts the enantiomers into diastereomers



6.16

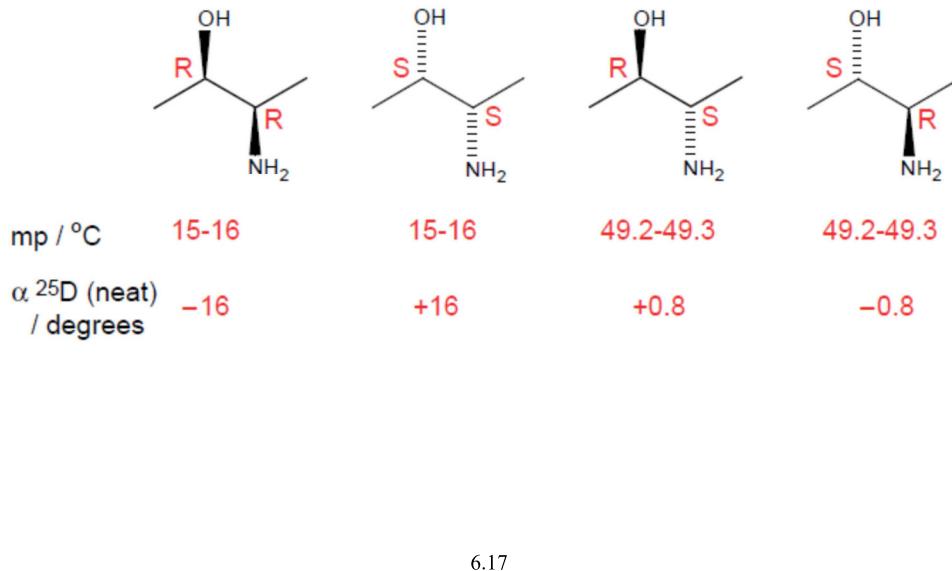
6.7 Molecules with Two or More Stereogenic Centers

Diastereomers, Enantiomers, Meso Compounds

The number of stereocenters dictates how many stereoisomers *may* occur.

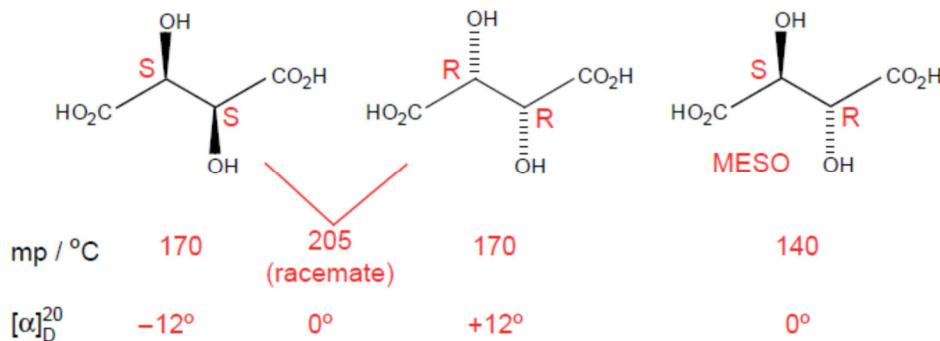
- 2^n stereoisomers are possible for n stereocenters.
- some may be too strained to actually exist
- some may lead to meso compounds

Example: Stereoisomers of 3-amino-butan-2-ol



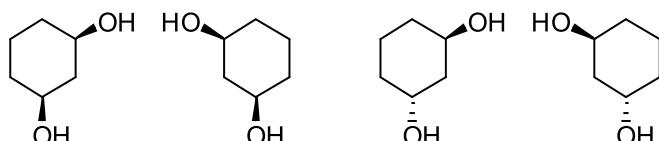
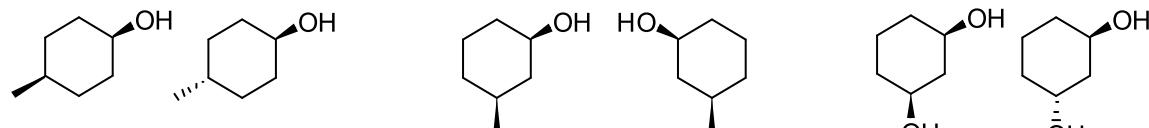
It is not necessary for all diastereomers to be optically active.

Example: Tartaric acid only has three diastereomers.



Why is R,S-tartaric acid not optically active?

Exercise: Which molecules are chiral? Which are meso-structures?
What is the relationship between each pair of molecules?

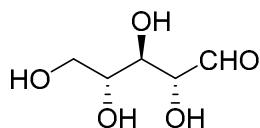


6.19

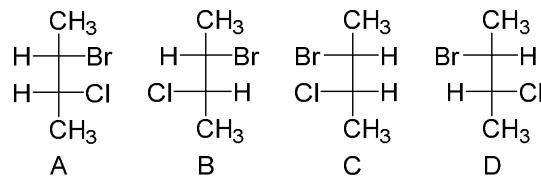
6.8 Fischer Projections

Often used in Biochemistry, e.g. representation of sugars.

Example: (D)-ribose



- 2-bromo-3-chlorobutane has 2 stereogenic centers and exists as 4 different stereoisomers:
-

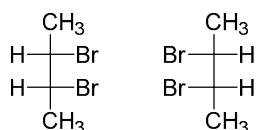


What is the relationship between these stereoisomers?

- A+B
A+C
A+D
B+C
B+D
C+D

6.20

2,3-dibromobutane only has 3 stereoisomers:



Meso compounds:

- Contain 2 or more stereocenters and a plane of symmetry
- Because of the plane of symmetry, they are identical and achiral.
- Are optically inactive.

6.21

6.9 Revision of Definitions

Isomers: different compounds with the same molecular formula.

Constitutional Isomers: isomers with different order of attachment (connectivity).

Conformers: same connectivity and are interconvertible by rotation about single bonds.

Stereoisomers: isomers with same order of attachment but different 3-D orientations of atoms in space.

Chiral: mirror image not superimposable on itself.

Achiral: molecule and mirror image are identical.

Enantiomers: mirror images; have opposite configuration at all stereocenters.

Diastereomers: stereoisomers but not mirror images; have same configuration at 1 or more stereocenters, but differ at remaining stereocenters.

Meso compound: mirror images (with at least 2 stereocenters) that are identical due to a plane of symmetry (mirror plane).

Racemic mixture: 1:1 mixture of enantiomers.

6.22

Chapter 7: Haloalkanes

7.1. Alkyl Halides

- C(sp³)-X
- Polar covalent bonds

C-X	ΔEN
C-F	
C-Cl	
C-Br	
C-I	

- Methyl halides, primary, secondary and tertiary alkyl halides

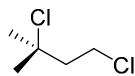
- Me-X bond strengths and bond lengths

Me-X	C-X bond strength [kJmol ⁻¹]	C-X bond length
Me-F		
Me-Cl		
Me-Br		
Me-I		

7.1

7.2 Nomenclature of Haloalkanes

1. Find the longest chain
2. Number the carbons beginning at the end nearest the first substituent -R and -X have the same naming priority
3. Assign R/S, E/Z, cis/trans where applicable
4. Write the name



Common names

CH ₂ Cl ₂ Dichloromethane (Methylene chloride)	CHCl ₃ Trichloromethane (Chloroform)	CCl ₄ Tetrachloromethane (Carbon tetrachloride)	CH ₂ =CHCl Chloroethene (Vinyl chloride)
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7.2

7.3. Nucleophilic Substitution Reactions and β -Elimination Reactions

General nucleophilic substitution reaction:

General nucleophilic substitution reaction:

Nucleophile: The nucleophile is always a Lewis base (electron pair donor).

Leaving Group: The leaving group is replaced by the incoming nucleophile. When it leaves the substrate, it always takes the electron pair of the broken bond with it.

Substrate (here R-X): The electrophile (for example, an alkyl halide) which carries the leaving group and is attacked by the nucleophile.

There are two possible mechanisms for nucleophilic substitution reactions:

The S_N2 Reaction

The S_N1 Reaction

7.3

General β -elimination reactions:

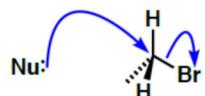
Since all nucleophiles are bases, β -elimination reactions are competing with nucleophilic substitution reactions.

Again, there are two possible mechanisms for β -elimination reactions, the *E1 reaction* and the *E2 reaction* which will be described in more detail later (Chapter 7.10 and 7.11, respectively).

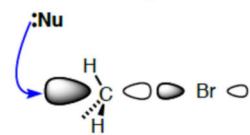
7.4. The S_N2 Reaction

The reaction starts with a nucleophilic attack on a saturated alkyl halide

Curly arrow description:

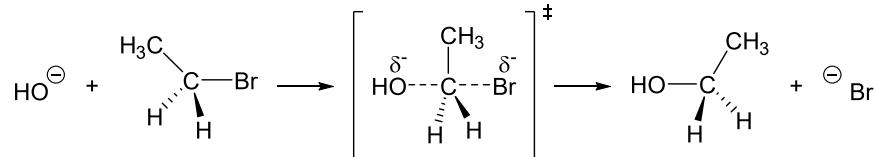


Orbital description:



HOMO: lone pair orbital
LUMO: C-Br σ* orbital

Mechanism: The S_N2 reaction is *concerted* (occurs in one step).



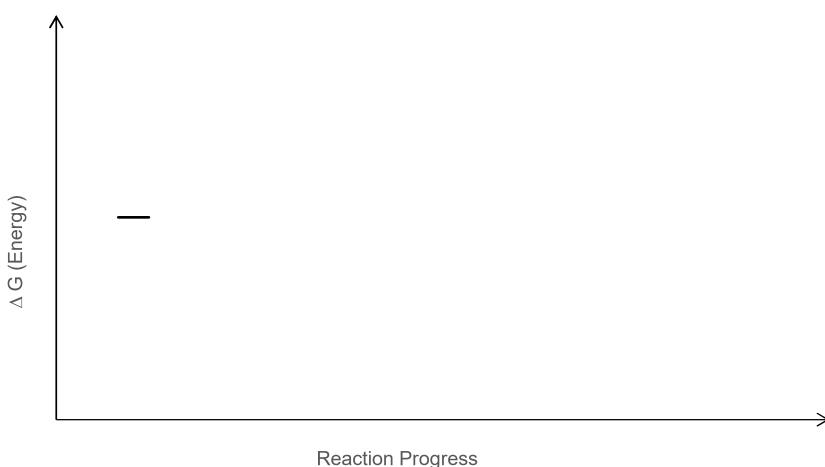
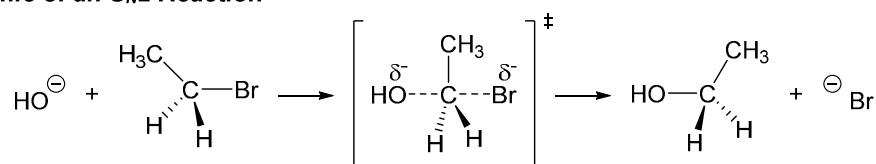
S_N2 Reaction: Nucleophilic substitution *bimolecular/second order*

The rate determining step is *product formation* and *rate of reaction* depends on both the concentration of the substrate and the concentration of the nucleophile as can be seen from the rate equation:

Rate equation:

7.5

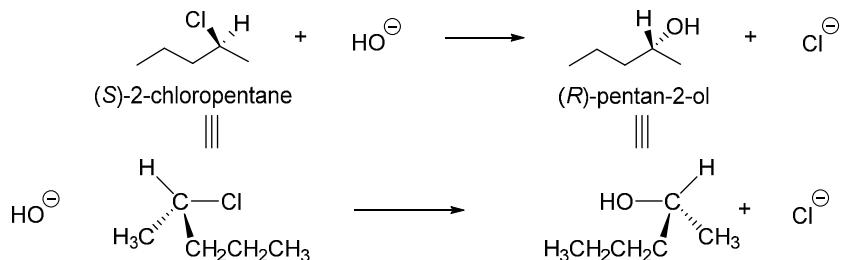
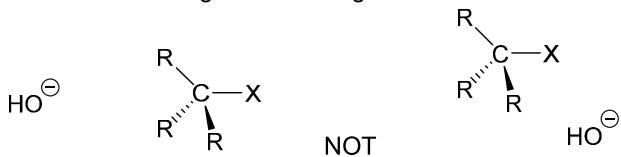
Energy Profile of an S_N2 Reaction



7.6

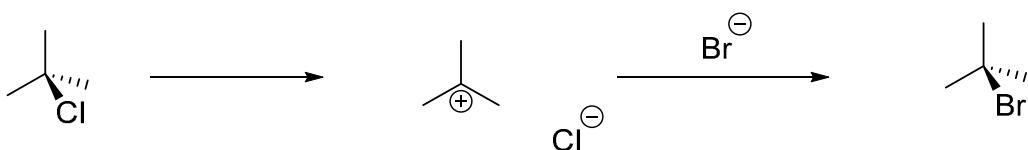
Stereochemistry of S_N2 Reaction:

Backside attack leads to inversion of configuration during an S_N2 reaction.

**7.5. The S_N1 Reaction**

The S_N1 reaction occurs in two steps: First the leaving group is lost thereby creating a carbocation intermediate which reacts rapidly in a second step with the nucleophile.

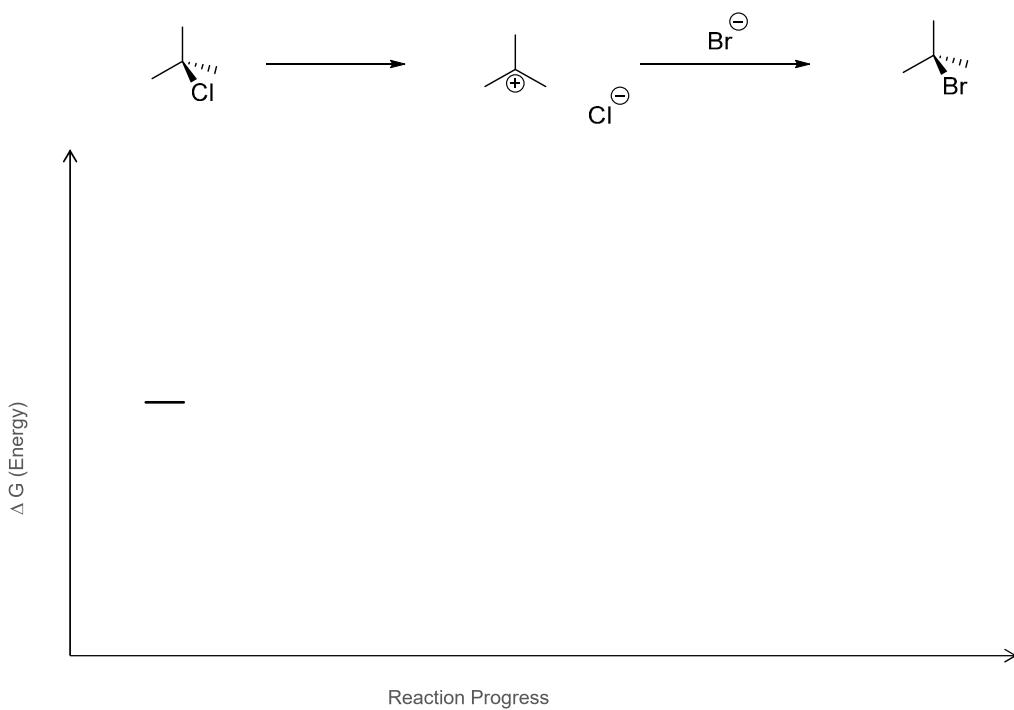
Mechanism: reaction occurs in 2 steps



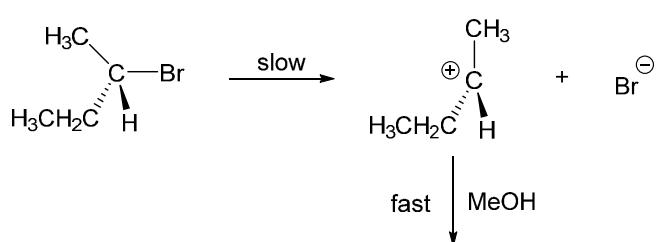
S_N1 Reaction: Nucleophilic substitution *unimolecular/first order*

The rate determining step is *the formation of the carbocation (reactive intermediate)* and the *rate of reaction depends **only** on the concentration of the substrate*:

Rate Equation:

Energy Profile of an S_N1 Reaction**Stereochemistry:**

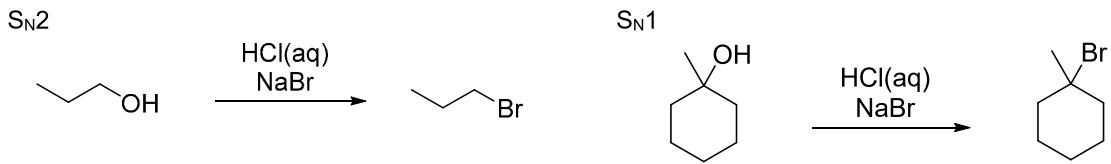
Due to the formation of the carbocation intermediate, the product of an S_N1 reaction on a chiral alkyl halide is generally obtained as racemic mixture.



7.6 Factors Affecting the Rates of S_N1 and S_N2 Reactions

S_N1 or S_N2 Mechanism?

In each case, an OH group is converted to a Br, but the mechanism by which the reaction takes place is not the same.



The main factors that influence this fundamental difference in mechanism are:

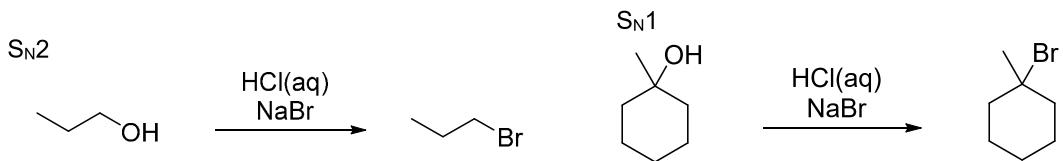
1. Substrate structure
2. Nucleophile
3. Leaving Group
4. Solvent

7.11

a) Substrate Structure

Differences in substrate structure which determine the outcome of reaction and might favor one mechanism over the other:

- a) **Steric hindrance:** ease of nucleophile approach and transition state formation
(Reaction on previous page)



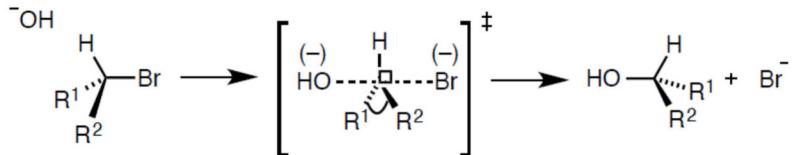
- b) **Factors that influence carbocation stability (in S_N1 reactions):** hyperconjugation, π-bond and lone pair donation

7.12

Steric Hindrance (S_N2)

S_N2 reactions become less likely the more substituents the attacked carbon has: increased steric hindrance makes the approach of the nucleophile more difficult.

Transition state: 5-coordinate, trigonal bipyramidal structure



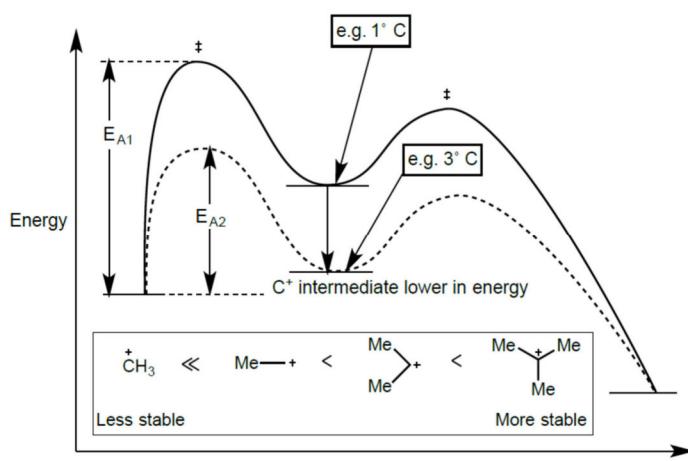
7.13

Carbocation Stability (S_N1)

Carbocation Stability (CH₃)
Carbocation: planar (sp^2 hybridized), **not** tetrahedral (sp^3 hybridized)!



The more substituted carbocations are, the more stable they are and the more likely it is that they will form.



7.14

Summary of S_N1 versus S_N2 based on Substrate Structure

Substrate:	Me—X			
Substrate Type:	Me	1°	2°	3°
S_N1 Mechanism:	Bad	Bad	Poor	Excellent
S_N2 Mechanism:	Excellent	Good	Poor	Bad

7.15

b) Nature of Nucleophile

S_N1 reaction: the nucleophile is **not** important because the rate determining step (RDS) is the loss of the leaving group:

S_N2 reaction: the nucleophile is **very** important because the RDS is bimolecular and involves the nucleophilic attack on the saturated carbon. *The better the nucleophile or/and the higher its concentration, the faster the reaction.*

7.16

Role of Nucleophile in S_N2 Reactions

For a range of nucleophiles involved in S_N2 reactions where the atom forming the new bond *is the same*, **nucleophilicity correlates well with basicity**.

In this case, anions of weak acids are the best nucleophiles.

Oxyanion Nucleophile:	OH ⁻	PhO ⁻	AcO ⁻	TsO ⁻
Conjugate Acid:	H ₂ O	PhOH	AcOH	TsOH
Approximate pK _a :	16	10	5	0

If the atoms of a range of nucleophiles involved in S_N2 reactions are *not the same*, **nucleophilicity often does not correlate with basicity**.

- The nucleophilicity will increase down a group in the periodic table:

Example: MeBr + X⁻

Nucleophile X	Conjugate acid HX	Approximate pK _a of HX	Relative Rate
PhS ⁻	PhSH	6.4	5.0 x 10 ⁷
PhO ⁻	PhOH	10.0	2.0 x 10 ³

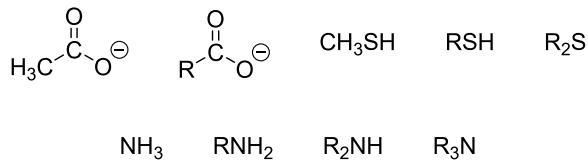
7.17

Examples of nucleophiles:

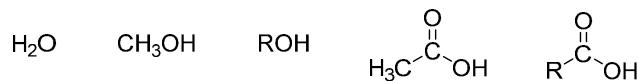
Good nucleophiles:



Moderate nucleophiles:



Poor nucleophiles:



S_N2 – Good nucleophiles displace leaving group faster

S_N1 – good, moderate, and poor nucleophiles all will work

7.18

c) Nature of Leaving Group

The leaving group is important for both S_N1 and S_N2 reactions; departure of the leaving group is involved in the RDS of both mechanisms.

a) Halides (F, Cl, Br, I) as leaving group

- Overall, due to the decrease in C-X bond strength and greater anion stability, I⁻ is the best leaving group and F⁻ is a poor leaving with Br⁻ and Cl⁻ in between.
- Note: I⁻ is both the best nucleophile but also the best leaving group!

b) OH derivatives

This reaction rarely happens:

Normally the nucleophile is basic enough and instead will simply deprotonate the alcohol instead:

OH⁻ is normally **not** a leaving group in S_N1 or S_N2 reactions but it can easily be converted to an excellent leaving group.

Two possible way to convert OH to a good leaving group:

- Protonation*
- Sulfonate ester formation*

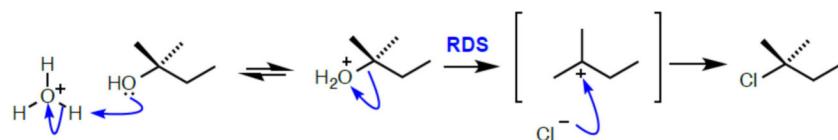
7.19

Protonation

Protonation activates OH for both S_N1 and S_N2 reactions



Important: Protonation occurs fast and *before the RDS* (which for the S_N1 reaction is the loss of water):

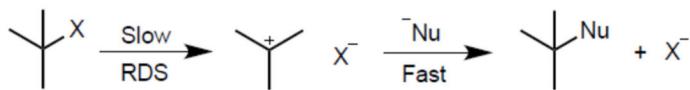


- Bad leaving group OH⁻ with pK_{aH} = 15.7 (H₂O) is converted to a good leaving group pK_{aH} = -1.7 (H₃O⁺)
- The reaction would **not** work without acid; Cl⁻ is a fairly bad nucleophile.

7.20

d) Solvent

S_N1 reaction: best in *polar, protic solvents* (e.g. water, methanol, acidic acid)

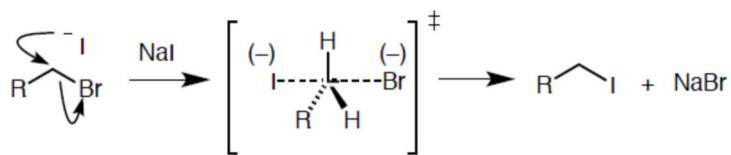


Polar protic solvents stabilize both the carbocation **and** the leaving group:

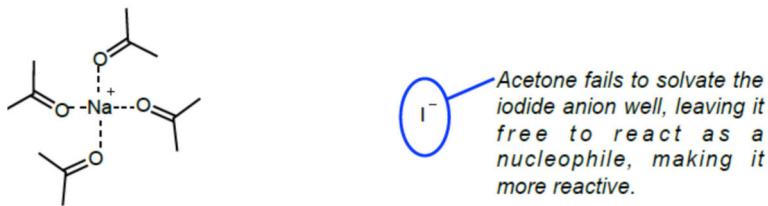


7.21

S_N2 reaction: best in *polar, aprotic solvents* (e.g. acetone, DMSO, DMF)



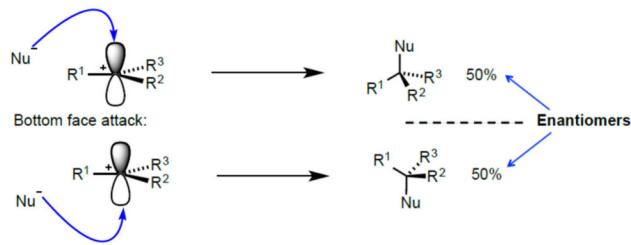
- No ions are formed in the S_N2 reaction
- While cations are well solvated in polar, aprotic solvents, anions cannot interact with most polar, aprotic solvents
- Aprotic solvents increase the reactivity of the nucleophile



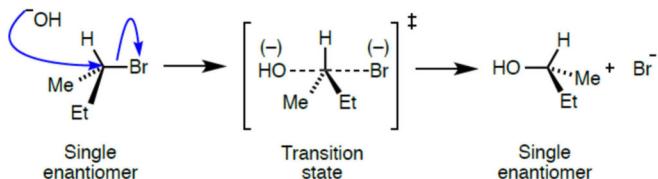
7.22

7.7. Stereochemical consequences of the S_N1 and S_N2 reaction processes

S_N1 Reaction: Normally results in a racemic mixture



S_N2 Reaction: Inversion of configuration, single enantiomer

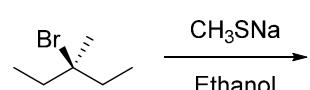
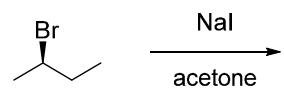
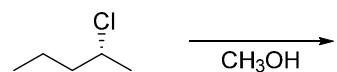


The S_N2 reaction is an example of a *stereospecific reaction* (i.e. a reaction where the mechanism determines the stereochemical outcome). The reaction **must** give a single enantiomer if the reaction proceeds purely by a S_N2 pathway.

7.23

Exercise:

Are these reactions S_N1 or S_N2 and what are the products?

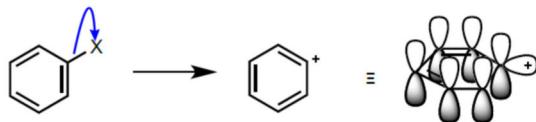


7.24

7.8 Vinyl and Phenyl Halides

The importance of hybridization state: no S_N1 or S_N2 at sp² centers

No S_N1 because no charge stabilization of carbocation possible:



No S_N2 for many reasons, e.g. with aromatic rings:

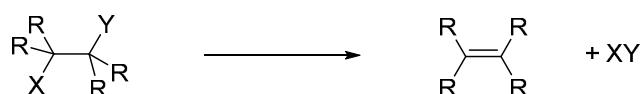
1. Approach of nucleophile repelled by electron density in double bonds.	2. Approach of nucleophile into σ^* blocked by rest of aromatic ring.	3. Inversion of centre attacked is impossible.

7.25

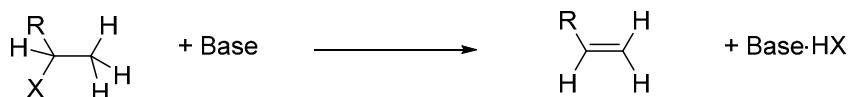
7.9. Elimination Reactions as Competing Reactions to S_N1 and S_N2

Elimination reactions are the most important way for synthesizing alkenes.

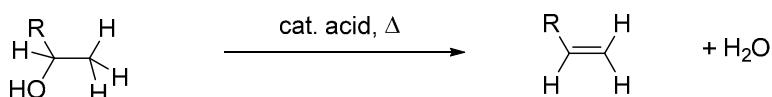
General Scheme:



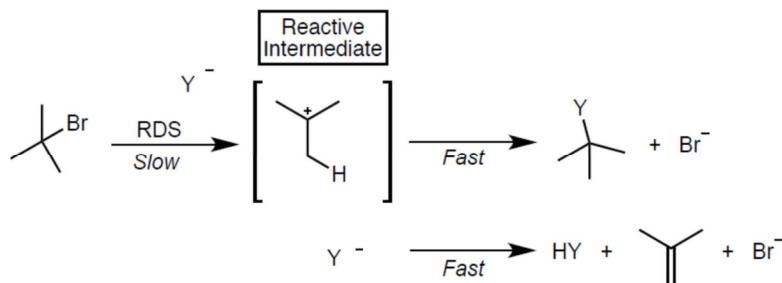
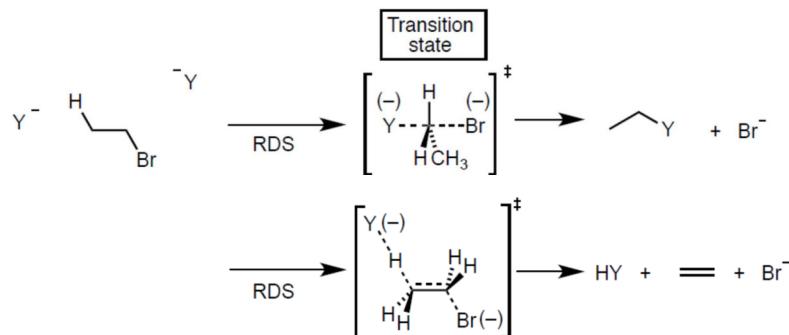
Dehydrohalogenation of alkyl halides:



Dehydration of alcohols:



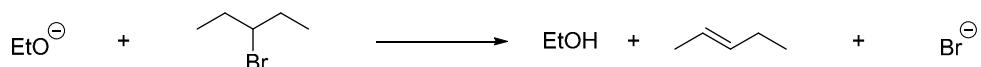
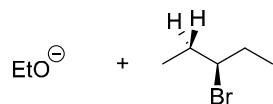
7.26

E1 Mechanism (versus S_N1 Reaction):**E2 Mechanism (versus S_N2 Reaction):**

7.27

7.10. The E2 Reaction

The E2 reaction occurs in one step with the base removing the proton from the β-carbon as the double bond forms and the leaving group leaves from the α-carbon.

**Mechanism:****Rate Law and Rate Equation:**

- bimolecular reaction
- 2nd order kinetics

Since the E2 reaction occurs in a concerted fashion, the *rate of reaction* depends on both the concentration of the substrate (alkyl halide) and the base:

$$\text{Rate} =$$

Energy Profile of an E2 Reaction

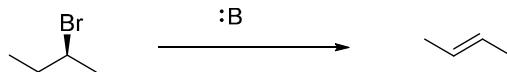
Regioselectivity in E2 Reactions:

The regioselectivity of the E2 reaction depends on the size of the base.

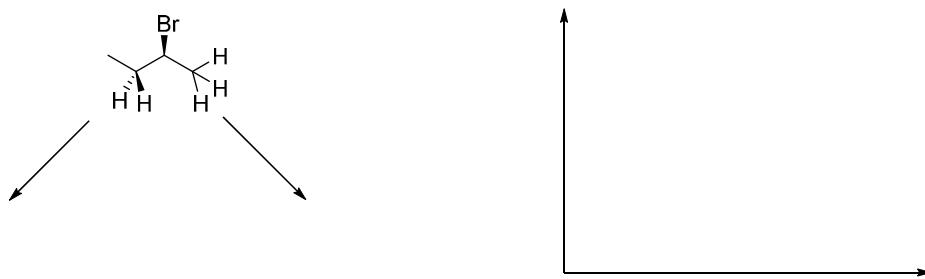
a) small base

- Examples of small, strong bases:

- Formation of the more substituted alkene



- More stable product but also lower transition state:



7.29

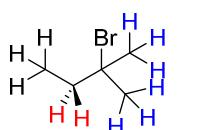
Regioselectivity in E2 Reactions:

The regioselectivity of the E2 reaction depends on the size of the base.

b) bulky base

- Examples of strong bulky bases:

- Less substituted alkene is formed faster

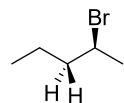


7.30

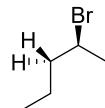
Stereochemistry of E2 Reactions:

The E2 reaction is a stereospecific reaction and the stereochemical outcome depends on the structure of the starting material.

a) Anti-Elimination preferred

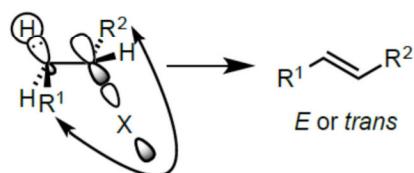


Syn-Elimination unfavorable

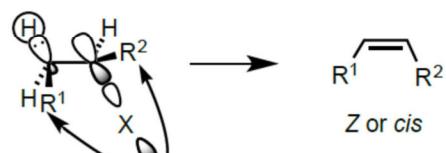


b) Starting material determines outcome:

R^1 and R^2 fixed on opposite sides in correct elimination arrangement and in the product:



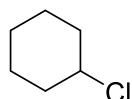
R^1 and R^2 fixed on the same side in correct elimination arrangement and in the product:



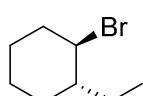
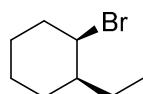
7.31

E2 Reactions on substituted cyclohexanes

The leaving group must adopt an axial position for anti-elimination to occur.



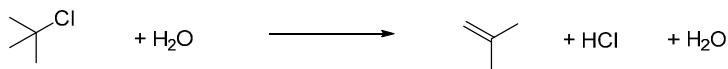
Exercise: Which is the major (and minor) elimination product of the following two diastereomers if a small base is used?



7.32

7.11. The E1 Reaction

The E1 reaction occurs in two steps: First the leaving group is lost thereby creating a carbocation intermediate. The loss of the proton in the second step is fast.



Mechanism:



E1 reactions almost always accompany S_N1 reactions.

Rate Law and Rate Equation:

- unimolecular reaction
- first order kinetics

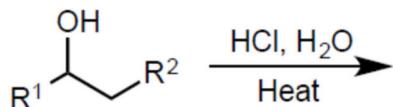
Rate =
Energy Profile of an E1 Reaction

The rate determining step is *the formation of the carbocation (reactive intermediate)* and the *rate of reaction depends only* on the concentration of the substrate:

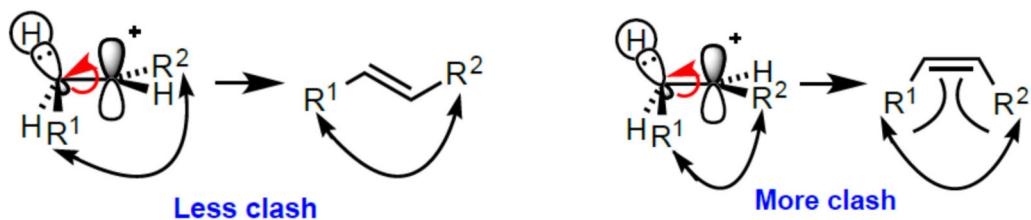
7.33



Stereochemistry of E1:



With secondary substrates E1 Elimination normally gives the *trans*-isomer as major product and the *cis*-isomer as minor product.



7.35

7.12 Comparison of E1 and E2 Reactions**a) Substrate Structure**

Electrophile:						
Substrate Type	1°	2°	3°	α-alkoxy	Allylic	Benzyllic
E1 Mechanism:	No	OK	Good	Good	Good	Good
E2 Mechanism:	Good	OK	Also possible	Also possible	Also possible	Also possible

Tertiary substrates: Elimination mechanism for tertiary substrates can be either E1 (with weak bases) or E2 (with strong bases). The outcome is the same with tertiary structures!

Substrates that cannot undergo elimination:

7.36

b) Leaving Group

The leaving group ability for E1 and E2 is the same as in nucleophilic substitutions.

Leaving Group:	Halide (Usually Br ⁻ /I ⁻)	OH ⁻	OH ₂ ⁺	TsO ⁻	NR ₃ ⁺
E1 Mechanism:	Good	Never	Good (OH under acidic conditions)	Good	Good
E2 Mechanism:	Good	Never	Never (E2 always carried out under basic conditions)	Good (convert OH to OTs for successful E2)	Good

7.37

7.13 Substitution or Elimination?**a) Substrate Structure**

Typical S_N1 reaction substrates can also work well in E1 (and often E2) elimination; those which work well in S_N2 reactions are good for E2 (and sometimes E1) elimination.

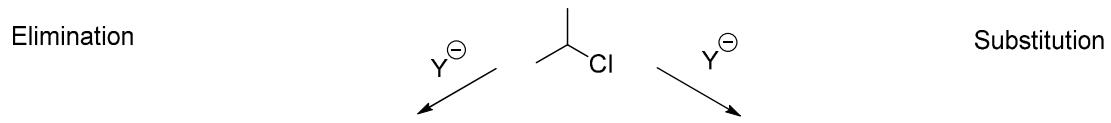
Substrates that cannot undergo elimination:

- molecules that do not have a β-hydrogen
- compounds that cannot become planar
- compounds that have a β-hydrogen but are unable to adopt an anti-periplanar conformation

7.38

b) Basicity of the Nucleophile

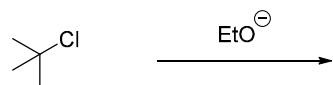
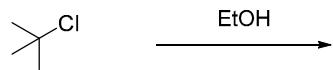
Strong bases give mainly elimination, weak bases result in substitution:



In terms of relating basicity to *overall* reaction pathway taken, pK_{aH} values are once again important.

Change of reaction outcome depending on base strength:

Treating *tert*-butyl chloride with EtOH or EtO⁻: The outcome of the reaction (substitution versus elimination) can be predicted using base strength alone.



7.39

c) Size of the Nucleophile

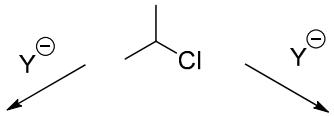
Basic and bulky nucleophiles prefer elimination over substitution.

- If Y^- is small: Substitution dominates for **1° substrates**:
 - If Y^- is large (e.g. KOtBu as base): Elimination generally preferred, even for 1° substrates:

d) Temperature

Higher temperatures favor elimination over substitution.

Elimination



Substitution

The fundamental reason for this lies in **entropy**: because two molecules become three in elimination and two molecules form two in substitution, ΔS is greater for elimination than for substitution.

Remember:

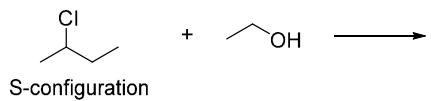
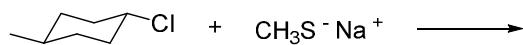
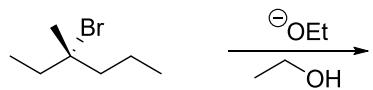
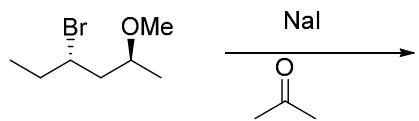
The reaction is favorable if the free energy ΔG is negative.



7.41

7.14 Summary: Elimination versus Substitution

Nucleophile/Base Type →		Poor e.g. H ₂ O, ROH	Weakly basic e.g. I ⁻ , RS ⁻	Strongly basic unhindered e.g. EtO ⁻	Strongly basic hindered e.g. 'BuO ⁻
Substrate Structure ↓					
Methyl	Me—X	No reaction	S _N 2	S _N 2	S _N 2
Primary (unhindered)		No reaction	S _N 2	S _N 2	E2
Primary (hindered)		No reaction	S _N 2	E2	E2
Secondary		S _N 1, E1 (slow)	S _N 2	E2	E2
Tertiary		S _N 1 or E1	S _N 1 or E1	E2	E2

7.15 Practice Examples: What are the products of these reactions?

7.43

Chapter 8: Alcohols, Ethers, and Thiols

8.1 Structure, Nomenclature and Properties of Alcohols

Naming Priority

Carbonyl ($C=O$) groups

OH

NH

SH

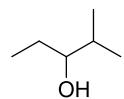
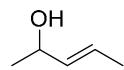
$C\equiv C$

$C=C$

Ethers, sulfides, alkyl, halogens

a) Nomenclature of Alcohols

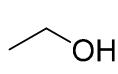
1. Find the longest chain containing the $-OH$ substituent and if $C=C$ or $C\equiv C$ are present, include them in the longest chain
2. Replace $-e$ on the parent name with $-ol$
3. Number the chain beginning at the end closest to the $-OH$
4. Number all substituents according to their position (don't forget to give the $-OH$ a number!)
5. Write the complete name.



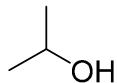
8.1



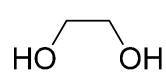
b) Common Alcohols



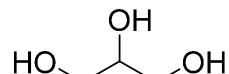
Ethanol
ethyl alcohol



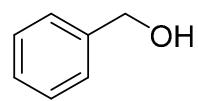
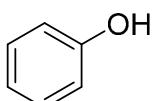
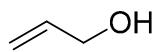
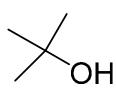
Isopropanol
isopropyl alcohol



ethylene glycol
ethane-1,2-diol



glycerol or glycerin
propane-1,2,3-triol



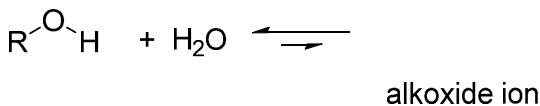
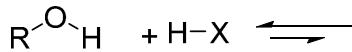
8.2

c) Properties of Alcohols**Hydrogen bonding**

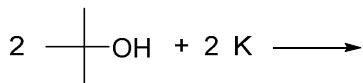
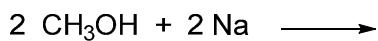
- Alcohols and phenols have significantly higher boiling points than alkanes or haloalkanes due to hydrogen bonding
- Accounts for complete miscibility of lower alcohols with water

Reactivity of alcohols

- Alcohols and phenols are weakly basic and weakly acidic:



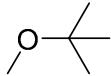
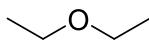
- Alcohols react with alkali metals such as sodium and potassium to form the sodium or potassium alkoxide and hydrogen gas:



8.3

8.2 Structure, Nomenclature and Properties of Ethers**a) Nomenclature of Ethers**

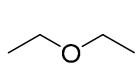
- Simple ethers with no other functional groups:
Name the two oxygen substituents and add the word ether



- More complex ethers which contain more than one ether or other functional groups: Longest carbon chain as parent name and -OR part becomes an alkoxy substituent



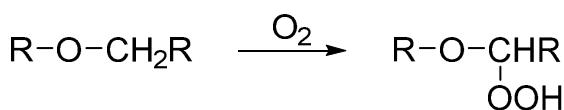
1,2-Dimethoxyethane (DME)

b) Common Ethersdiethyl ether
'ether'Tetrahydrofuran
'THF'1,4-dioxane
'dioxane'

ethyleneoxide

c) Properties of Ethers

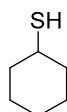
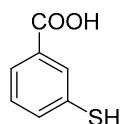
- Ethers have lower boiling points than alcohols (closer to hydrocarbons)
- Relatively inert –good solvents for reactive compounds
- Important in Grignard reactions: Ether solvents are required as they stabilize Grignard reagents (Chapter 12)
- Ethers oxidize upon exposure to air-to peroxides which can be explosive



8.5

8.3 Structure, Nomenclature and Properties of Thiols**a) Nomenclature of Thiols**

- Same as alcohols, with -thiol suffix
- SH as a substituent = mercapto



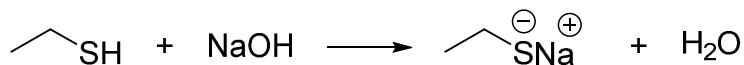
8.6

b) Properties of Thiols

- Low molecular weight thiols stink
- Responsible for unpleasant odor from skunk, rotten eggs, and sewage

Acidity

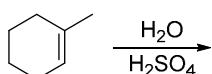
- H₂S is a stronger acid than H₂O and RSH is a stronger acid than ROH



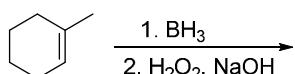
8.7

8.4 Synthesis of Alcohols from Alkenes (see Chapter 5)

- a) Acid catalyzed hydration:

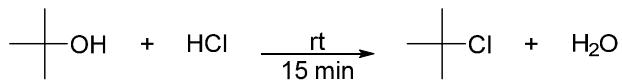


- b) Hydroboration-Oxidation:



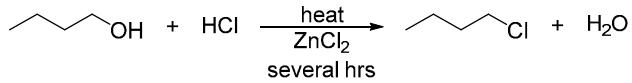
8.5 Conversion of Alcohols into Alkyl Halides

a) using HX



Reactivity of alcohols:

Reactivity of HX:

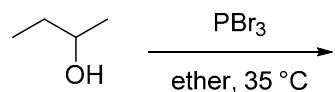
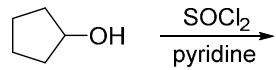


Because chloride is such a weak nucleophile, ZnCl_2 (or another Lewis acid) is required for converting primary or secondary alcohols to alkyl chlorides.

8.9

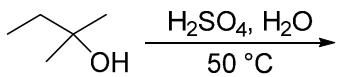
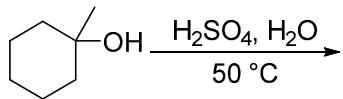
b) using PBr_3 or $SOCl_2$

Only works with primary and secondary alcohols.



8.6 Acid Catalyzed Dehydration of Alcohols to Alkenes

E1 mechanism

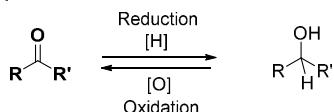


Reactivity of alcohols:

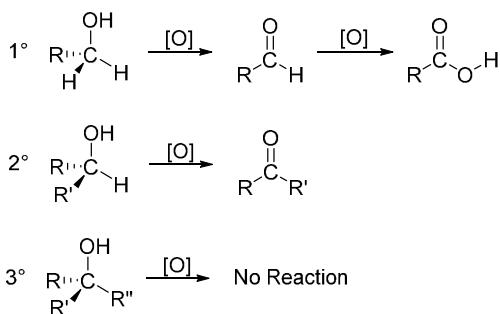
8.11

8.7 Oxidation of Alcohols to Carbonyl Compounds

Redox reactions in organic chemistry:



Oxidation of alcohols:

**Oxidation methods for alcohols (there are more)**

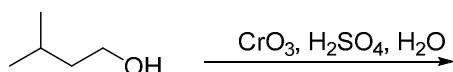
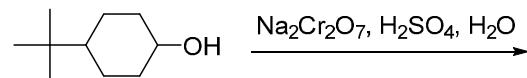
Substrates	Method of Oxidation/Product	
primary alcohol	aq H ₂ CrO ₄ (Jones Reagent)	PCC
secondary alcohol	carboxylic acid	aldehyde
tertiary alcohol	ketone	ketone
	-	-

8.12

a) Chromic Acid (H_2CrO_4) Oxidation ("Jones Oxidation")

The **Jones Reagent** is a mixture of chromic trioxide or sodium dichromate in diluted sulfuric acid, which forms chromic acid in situ:

The Jones Oxidation allows a relatively inexpensive conversion of secondary alcohols to ketones and of most primary alcohols to carboxylic acids.

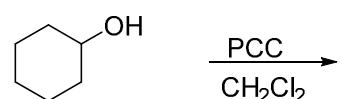
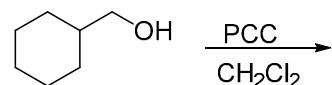


8.13

b) Pyridinium Chlorochromate (PCC) Oxidation of Alcohols

Chlorochromic acid can be prepared by the dissolution of chromium trioxide in 6 M aq. hydrochloric acid. Addition of pyridine gives pyridinium chlorochromate (**PCC**) as orange crystals.

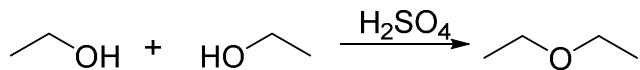
Oxidation of primary alcohols with PCC yields aldehydes while secondary alcohols give ketones.



8.14

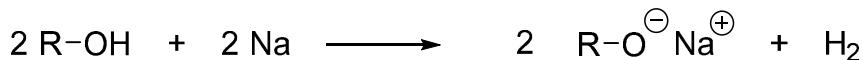
8.8 Synthesis of Ethers**a) Synthesis of Symmetrical Ethers**

Under acid catalysis primary alcohols can form symmetrical ethers by intermolecular dehydration:

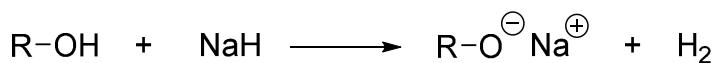
**b) Synthesis of Unsymmetrical Ethers: Williamson Ether Synthesis**

S_N2 process works best with primary alkyl halides which are attacked by an alkoxide.

Formation of alkoxide:

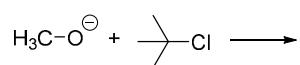
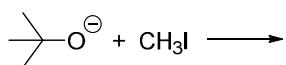
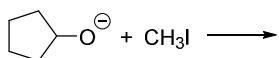


or

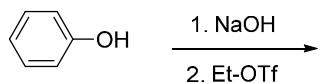


8.15

Williamson ether synthesis:



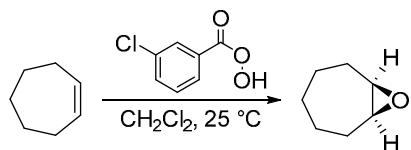
Phenols in the Williamson ether synthesis:



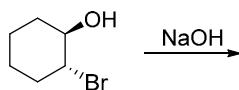
8.16

8.9 Synthesis of Epoxides (Oxiranes)**a) Synthesis of Epoxides by Epoxidation of Alkenes**

Alkene + peroxyacid (RCO_3H) \rightarrow epoxide



Stereochemical Outcome:

b) Synthesis of Epoxides in 2 Steps from Alkenes via Halohydrins

8.17

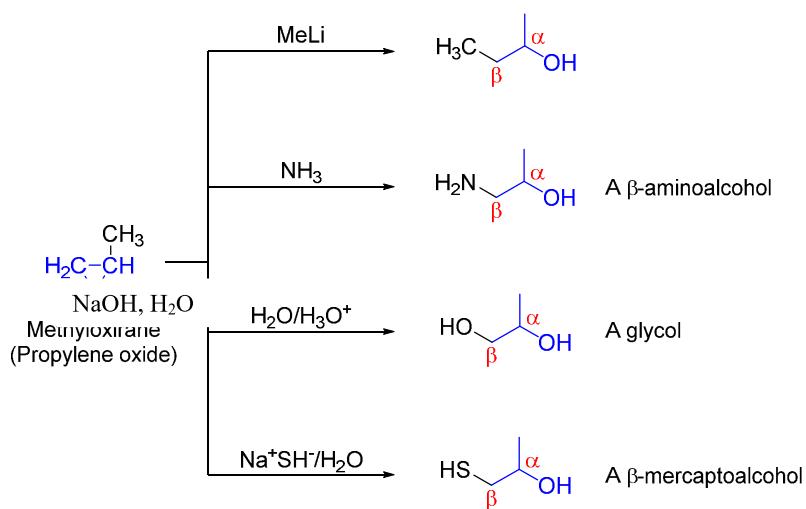
8.10 Reactions of Epoxides

Epoxides are very reactive ethers due to ring strain.

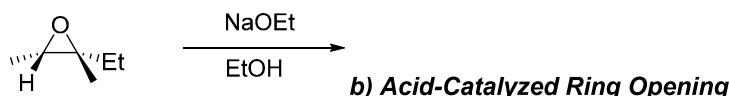
a) Base-Catalyzed Ring Opening

Base-catalyzed ring opening of an unsymmetrical epoxide occurs by attack of the nucleophile at the less substituted carbon atom.

Examples:



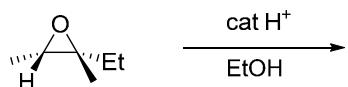
Stereochemistry: Epoxide opening is a stereospecific reaction:



- Acid-catalyzed ring opening of an unsymmetrical epoxide occurs by attack of the nucleophile at the more substituted carbon atom.

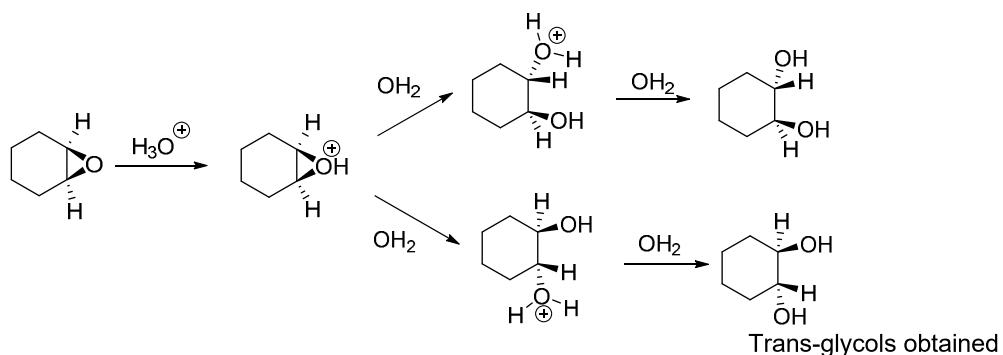


Stereochemistry: Epoxide opening is a stereospecific reaction:

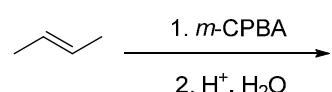
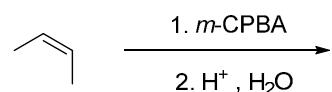


8.19

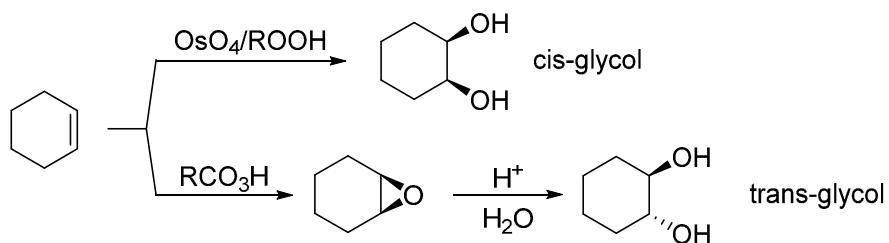
c) Anti 1,2-dihydroxylation of Alkenes via Epoxides



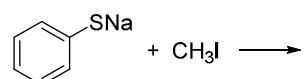
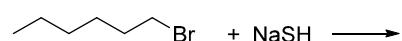
Stereochemical outcome:



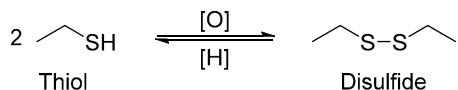
8.20

Cis vs Trans Glycols

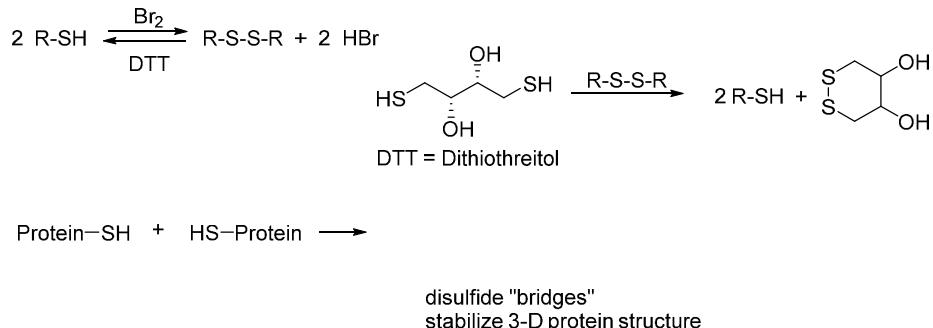
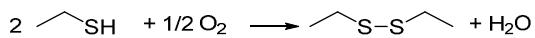
8.21

8.11 Thiol Synthesis and Reactions

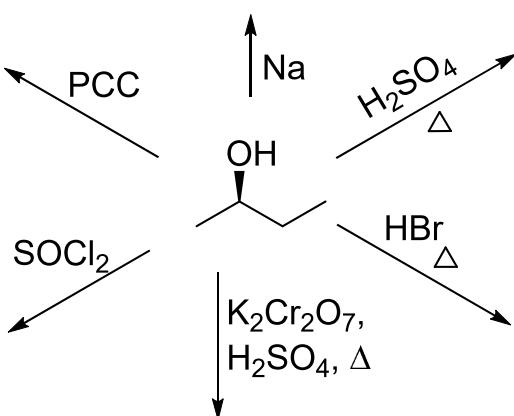
8.22

Oxidation:

Thiols are susceptible to oxidation in the presence of air:



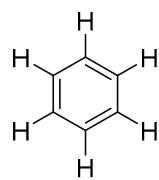
8.23

8.12 Exercise

8.24

Chapter 9: Aromatic Compounds: Benzene and Its Derivatives

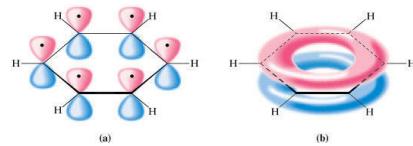
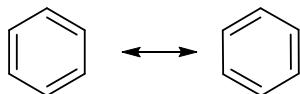
9.1 Structure of Benzene



All 6 carbons and all 6 hydrogens are equivalent
All carbon atoms are sp^2 -hybridized: benzene is planar

C-C (benzene) = 139 pm

Compare to: C-C = 154 pm long
C=C = 134 pm long



Electrons are delocalized around the ring

A short-hand representation that shows the delocalization of the electrons:
(not useful for drawing mechanisms)

14.1

9.2 Aromaticity

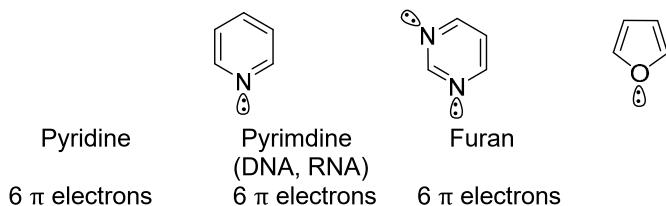
Aromatic molecules are unsaturated cyclic compounds which due to their aromaticity show different reactivity than alkenes.

According to Hückel's criteria, a cyclic system is aromatic if

- each atom of the ring has one 2p orbital (all atoms in the ring must be sp^2 -hybridized)
- it is **planar**
- contains **$4n+2 \pi$ electrons** ($n=0, 1, 2, \text{etc.} \rightarrow 2, 6, 10, \text{etc } \pi \text{ electrons}$)

Examples:

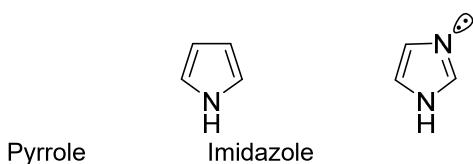
Heterocyclic compounds may be aromatic. Do determine the number of π electrons, you must know whether lone pairs are able to overlap with the π system or not.



=N- Don't count lone pair electrons on the N (perpendicular to π cloud)

-N- Count the electrons on the N (NH in plane while lone pair can overlap)

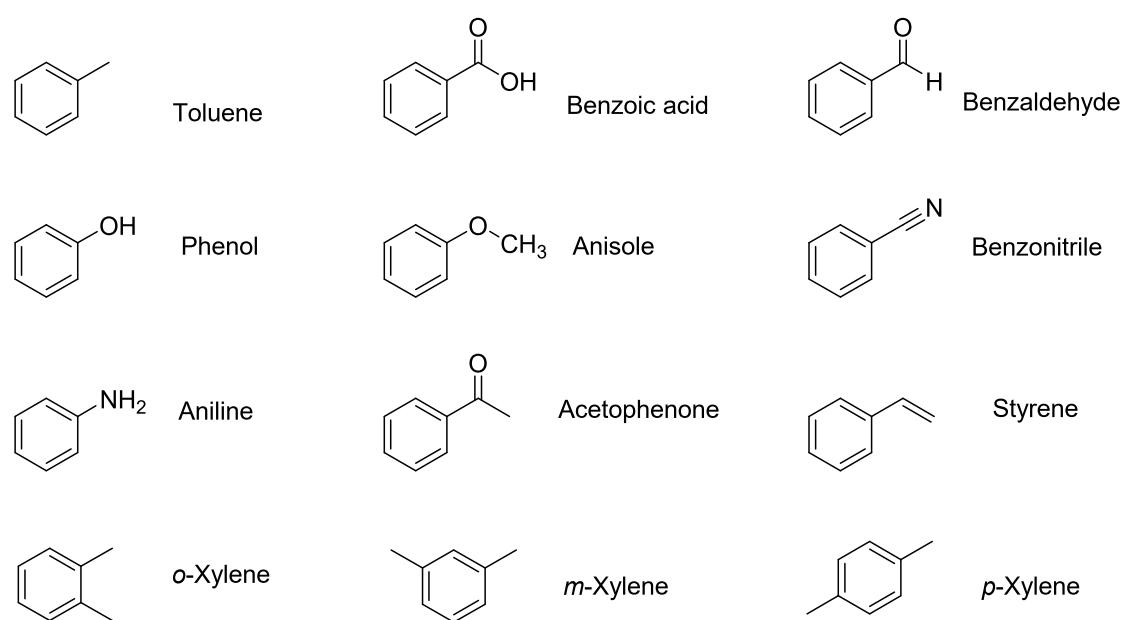
-O- Count one pair of electrons on the O (the other one is in the plane of molecule and cannot overlap)



14.3

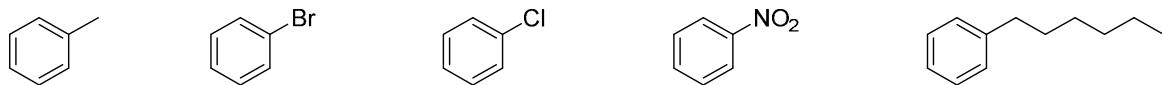
9.3 Nomenclature of Aromatic Compounds

a) Common Names allowed by IUPAC

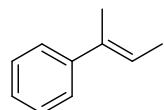


14.4

b) Monosubstituted benzene derivatives are named like hydrocarbons with benzene as the parent name (or by their IUPAC approved common name)

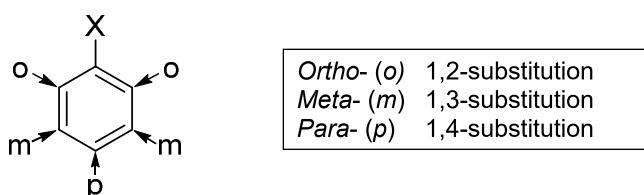


Aromatic rings can also be substituents

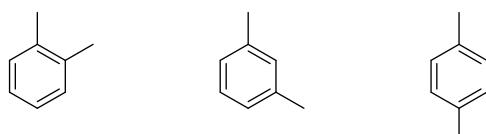


14.5

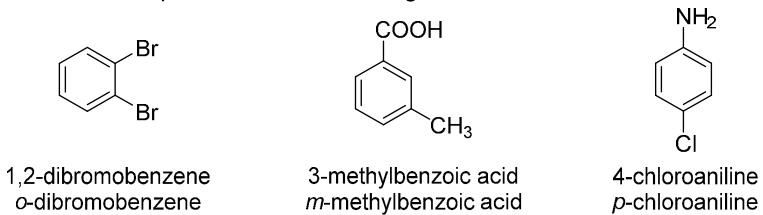
c) Disubstituted benzene derivatives



Xylenes are benzene derivatives with two methyl substituents. 3 different isomers exist:



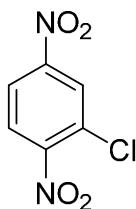
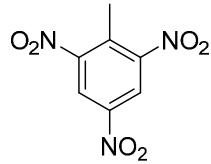
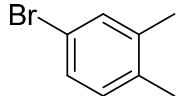
When one of the substituents is part of an IUPAC recognized name, that substituent is in position 1.



14.6

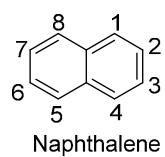
d) More than 2 substituents on a benzene ring

- Number the substituents so that lowest possible numbers are used
- List substituents alphabetically
- Only specific common names can be used as parent name instead of benzene. The special substituent is then on carbon 1

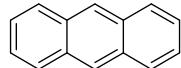


2,6-dimethylbenzaldehyde

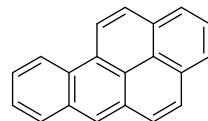
14.7

e) Polycyclic Aromatic Hydrocarbons (PAHs)

Naphthalene



Anthracene

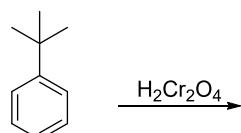
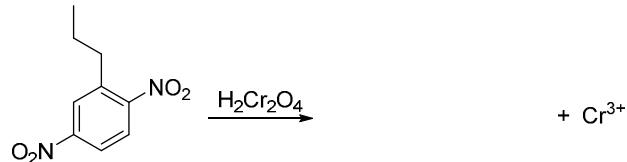
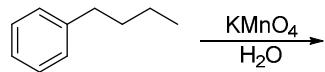


Benzo[a]pyrene

Graphite – infinite sheet of hexagonally arranged carbonsNaphthalene – used as moth repellent and insecticide for wools and fursBenzo[a]pyrene – very potent carcinogen and mutagen in gasoline engine exhaust and cigarette smoke

9.4 Oxidation at the Benzylic Position

While aromatic systems are unreactive towards strong oxidizing agents such as KMnO_4 and H_2CrO_4 , benzylic carbons of alkyl substituents containing at least one H atom are oxidized to benzoic acid

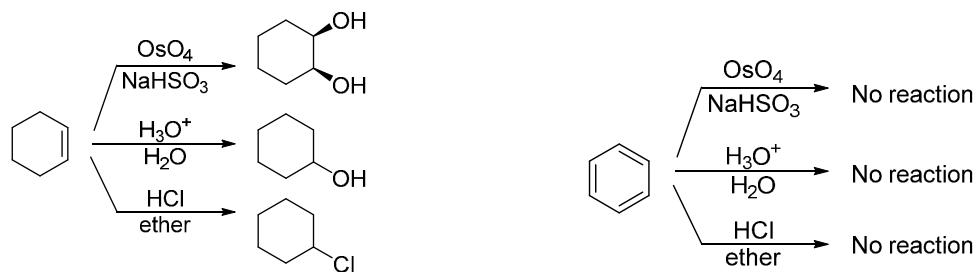


9.9

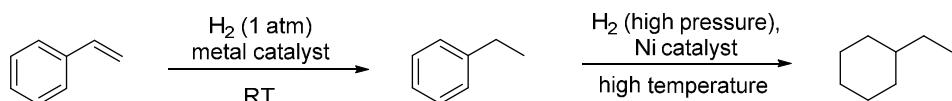
9.5 Reactions of Benzene

Reactions of aromatic compounds will be discussed in detail in Chapter 15. For the moment, it is important to note that although benzene has a high degree of unsaturation, it does not react under the conditions “normal” alkenes react.

For example, benzene does not react to give addition products.



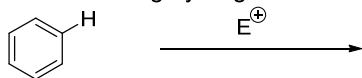
Hydrogenation of a benzene molecule only takes place at very high temperatures and under pressure.



9.10

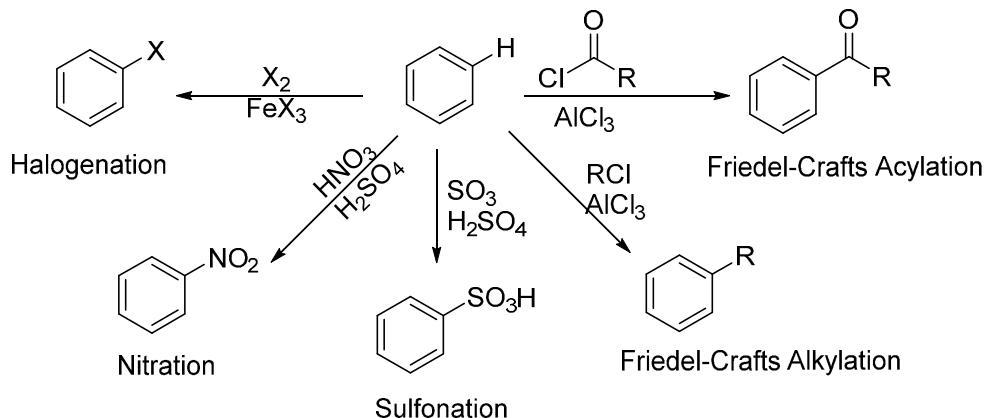
9.6 Electrophilic Aromatic Substitution

The electron-poor electrophile (E^+) reacts with electron-rich aromatic ring (Nu). This leads to the loss of one of the ring hydrogens in a second step, resulting in net substitution.



Electrophilic Aromatic Substitution

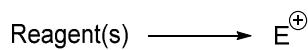
Aromatic rings are less reactive toward electrophiles than alkenes which is why only very strong electrophiles will react with benzene. Lewis acids can make the electrophiles more electrophilic.



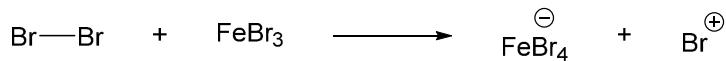
9.11

Mechanism of Electrophilic Aromatic Substitution

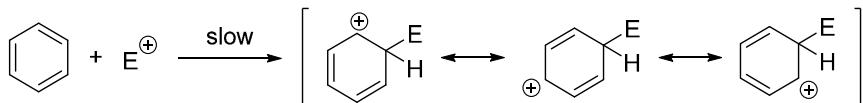
Step 1: Formation of the electrophile (E^+)



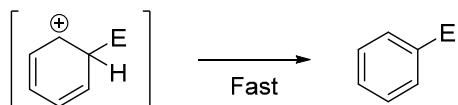
Example:



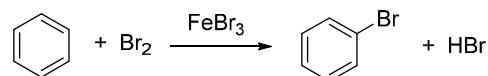
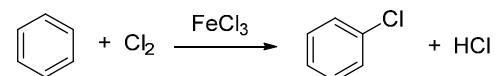
Step 2: The aromatic ring (nucleophile) attacks the electrophile (E^+)



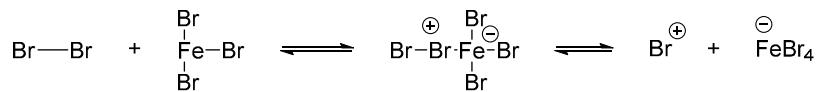
Step 3: Regeneration of the aromatic ring



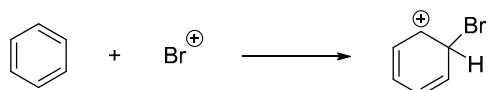
9.12

a) Halogenation of Benzene**Bromination****Chlorination**

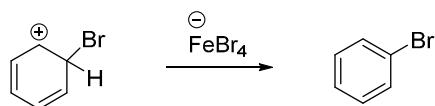
Step 1: FeX_3 (cat.) makes X_2 more electrophilic



Step 2: slowest step, RDS



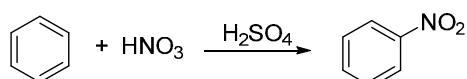
Step 3: fast, aromaticity recovered



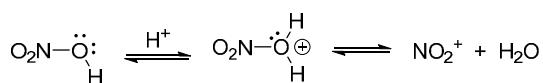
9.13

b) Nitration

The electrophile NO_2^+ (nitronium ion) is formed in situ from sulfuric acid and nitric acid.

**Mechanism:**

1. Formation of nitronium ion:

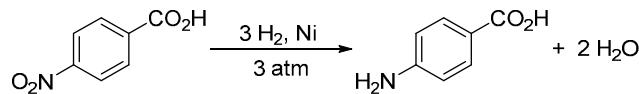


2. Reaction with benzene:

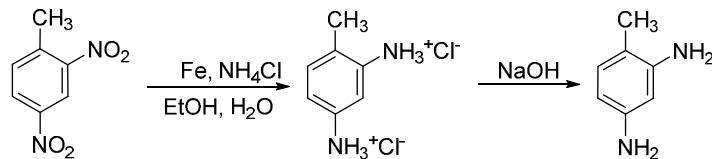
3. Loss of proton:

The nitration reaction is useful for introducing $-\text{NH}_2$ groups via subsequent reduction.

Hydrogenation:



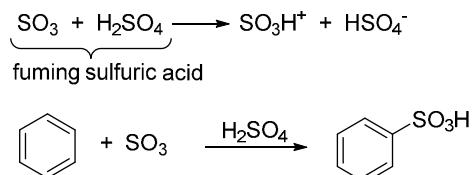
Reduction by a metal (Fe, Zn, Sn) in presence of a proton source:



9.15

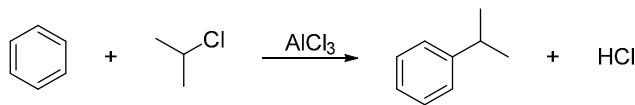
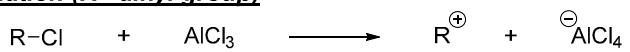
c) Sulfonation (formation of benzenesulfonic acid)

Formation of the sulfonium ion:



Note that the text book lists only H_2SO_4 in the reaction but mentions in the text SO_3 or HSO_3^+ as the electrophile.

9.16

d) Friedel-Crafts Alkylation (R= alkyl group)

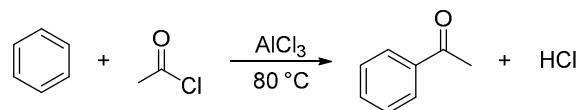
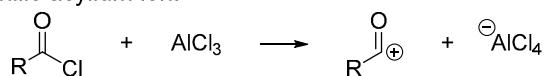
- Mechanism of Friedel-Crafts Alkylation is similar to $\text{Cl}_2/\text{FeCl}_3$ mechanism
- Only alkyl halides work, aryl halides do not work!
- Does not work with 1° alkyl halides (why not?)
- Does not work with $-\text{NO}_2$, $-\text{C}\equiv\text{N}$, $-\text{SO}_3\text{H}$, or –acyl group already attached to the ring since these groups deactivate the catalyst

9.17

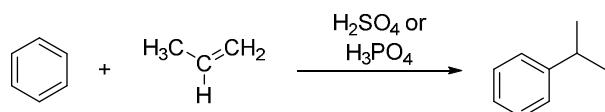
e) Friedel-Crafts Acylation (R= alkyl group)

Carboxylic acid chloride, $\text{R}-\overset{\text{O}}{\parallel}\text{C}-\text{Cl}$, with AlCl_3 as catalyst adds an acyl group to the aromatic ring.

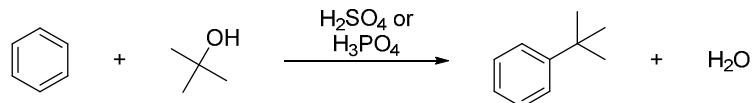
Formation of the electrophilic acylium ion:



9.18

f) Other Electrophilic Aromatic Alkylation**Benzene + alkene**

Follow's Markovnikov's Rule: the more stable carbocation is formed

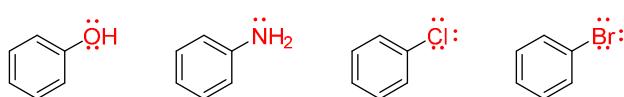
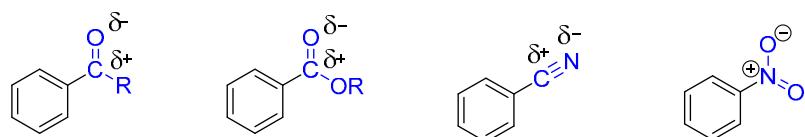
Benzene + alcohol

9.19

9.7 Substituent Effects**Substituents already present increase or decrease the reactivity of the aromatic ring**

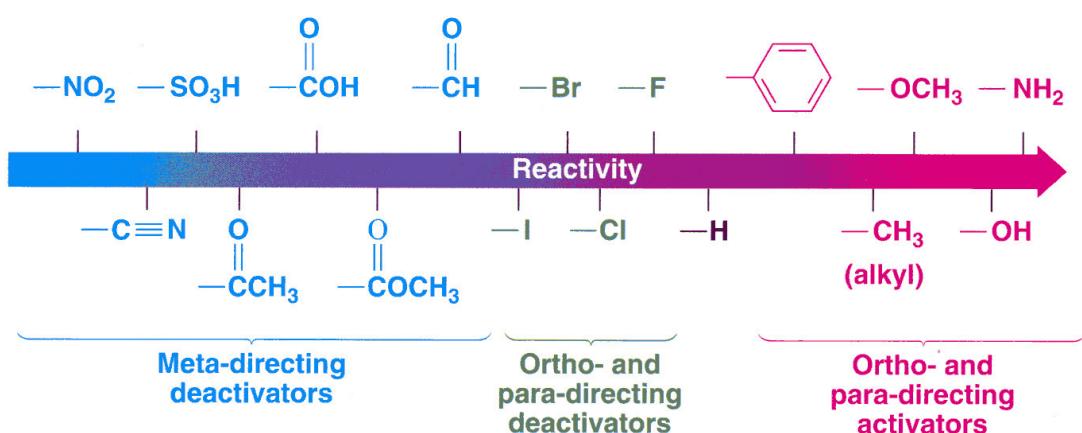
Activating groups: donate electrons to the ring by inductive effect or resonance effect

Deactivating groups: withdraw electron density from the ring

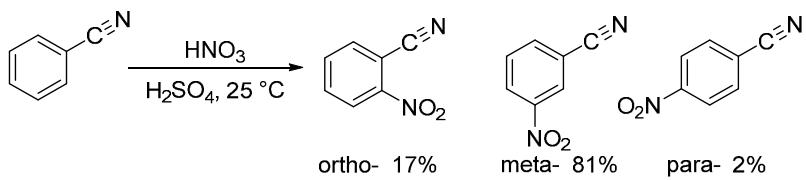
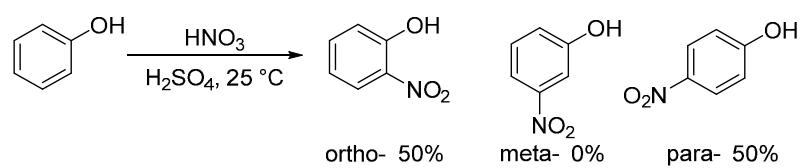
Substituents already present determine the position of the new substituent*o-/p-* **directing***m*-directing

9.20

Substituents already present determine the position of the new substituent



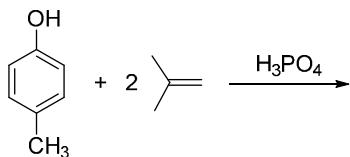
9.21



9.22

Electrophilic aromatic substitution on rings with several substituents

If two or more substituents are already present on the aromatic ring, the strongest activator determines the position of the new group.



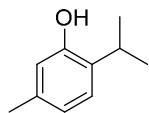
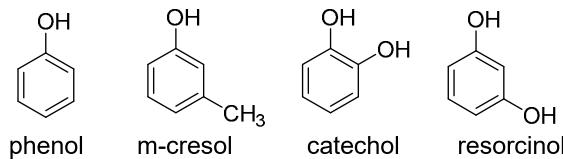
When designing a multistep synthesis involving electrophilic aromatic substitution, we must keep in mind the directing and activating effects of the groups involved

Starting from benzene, how would you synthesize m-chloronitrobenzene?

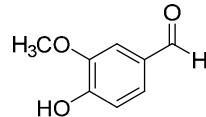
9.23

Starting from benzene, how would you synthesize p-bromobenzoic acid?

9.24

9.8 Phenols

2-isopropyl-5-methylphenol
(thymol)
Thyme

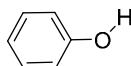


4-hydroxy-3-methoxybenzaldehyde
(vanillin)
Vanilla beans

9.25

Acidity of Phenols:

Phenols are significantly more acidic than alcohols:



pK_a = 9.95



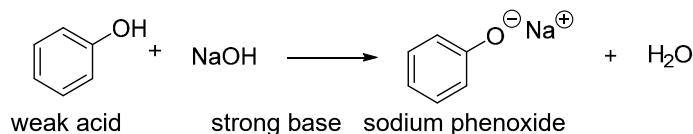
pK_a = 15.9

resonance is possible to
remove electrons from -OH

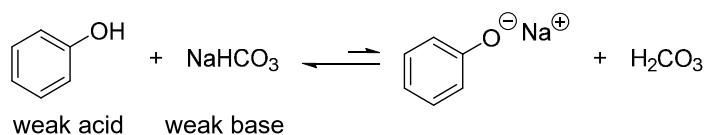
electrons stuck on -OH

Resonances Structures of Phenoxide:

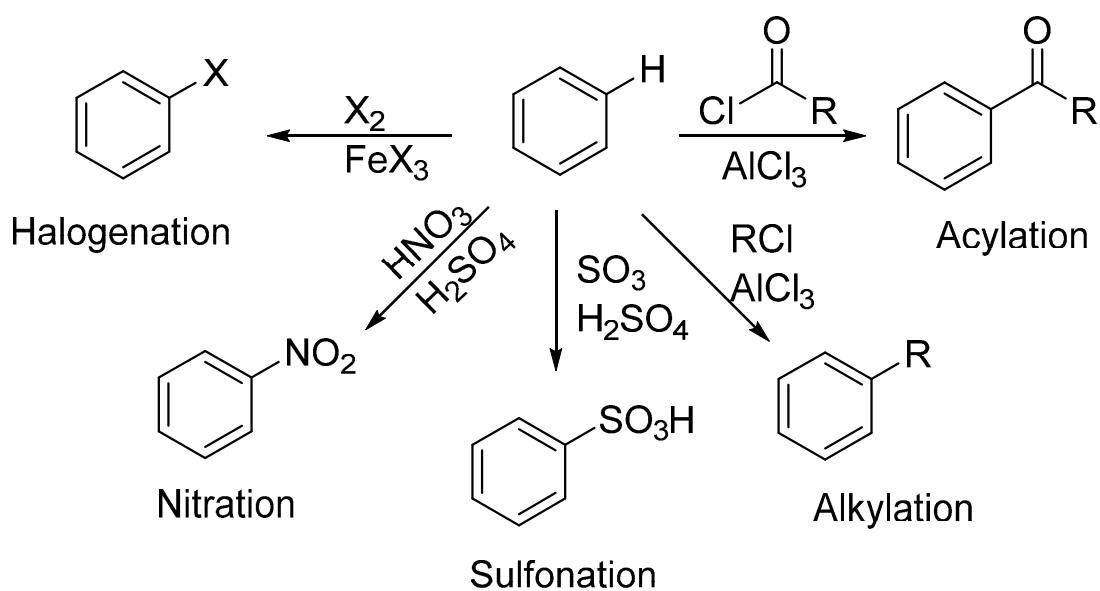
Phenols are completely deprotonated by strong bases:



Most phenols do not react with weak base because the equilibrium is shifted strongly towards the phenol



9.26

9.9 Review: Electrophilic Aromatic Substitution Reaction Diagram

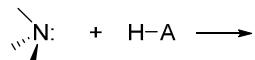
Chapter 10: Amines

10.1 Amines Classification

1° 2° 3° 4°

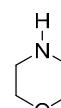
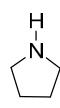
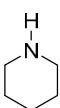
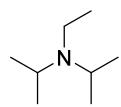
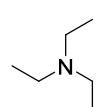
Structure and Properties of Amines
 sp^3 -hybridized (aliphatic amines)
 highly polar

Amines are basic compounds and react with acids:

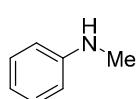
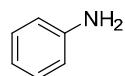


10.1

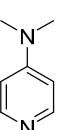
Aliphatic Amines



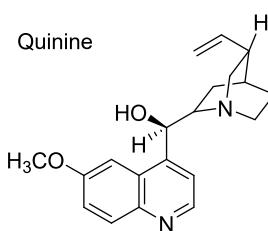
Aryl Amines



Heterocyclic Aromatic Amines



Natural Products



10.2

10.2 Nomenclature of Amines

Rules:

If there are no higher-priority functional groups:

- Name the three substituents in alphabetical order and add “amine”.
- Use the prefixes “di” and “tri” if the groups are the same.
- If two or three -NH₂ groups are present use di and tri before the parent name

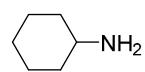
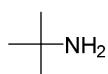
With unsymmetrically N-substituted secondary and tertiary amines:

- The largest organic group is the parent chain
- The location of the smaller groups are indicated by the prefix “N”

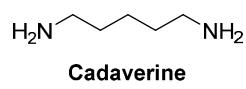
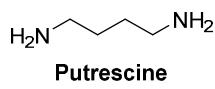
With higher-priority functional groups:

- Name -NH₂ as a substituent- “amino”

Examples:

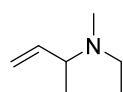
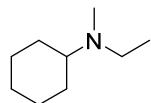
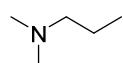
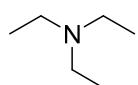
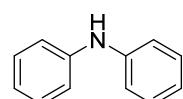


Common names

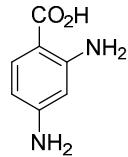
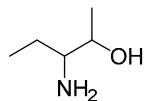


IUPAC

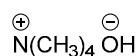
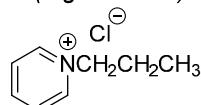
10.3



10.4

 **4° ammonium salts**

- Replace amine with ammonium (or pyridinium)
- Add the name of the anion (e.g. chloride)

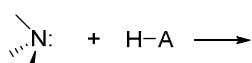


10.5

10.3 Structure and Properties of Amines

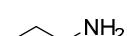
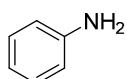
sp^3 -hybridized (aliphatic amines)
highly polar

Amines are basic compounds and react with acids:



Much stronger bases than alcohols, ethers, or water

Aryl amines are weaker bases than alkyl amines due to resonance moving electrons away from the N

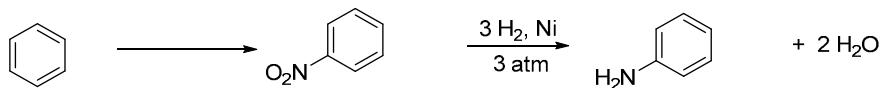


Amides (RCONH_2) are non-basic due to resonance

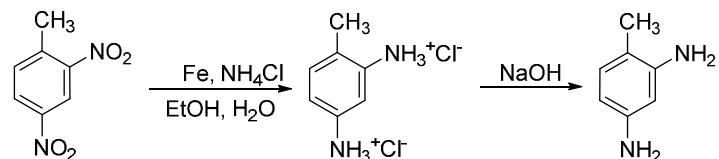
10.4 Synthesis of Arylamines

Nitration followed by reduction.

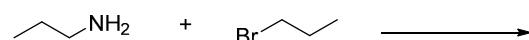
Hydrogenation:



Reduction by a metal (Fe, Zn, Sn) in presence of a proton source:



10.7

10.5 Amines as Nucleophiles

10.8

Chapter 11: Spectroscopy (Infrared Spectroscopy)

IR is used to identify functional groups. It is particularly useful to distinguish between different functional groups containing C=O, O-H, N-H or NH₂, triple bonds and double bonds.

11.1 Review Functional Groups

Functional groups are common and specific arrangements of atoms that govern reactivity and properties of (organic) molecules.

A table below provides a summary of the most important functional groups:

TABLE 2.3 IMPORTANT FAMILIES OF ORGANIC COMPOUNDS								
	Family							
	Alkane	Alkene	Alkyne	Aromatic	Haloalkane	Alcohol	Phenol	Ether
Functional group	C—H and C—C bonds			Aromatic ring				
Functional group	Amine	Aldehyde	Ketone	Carboxylic Acid	Ester	Amide	Nitrile	

11.1

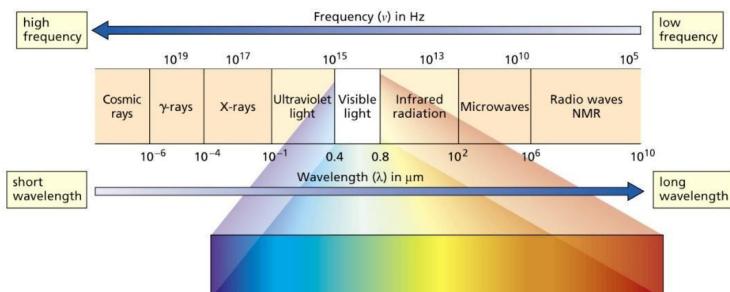
11.2 Infrared Spectroscopy: Physical Background

Infrared Spectroscopy (IR) is one of the most useful physical methods to **identify functional groups** in unknown compounds and use their presence or absence to confirm a hypothetical structure.



a) The Electromagnetic Spectrum

IR depends on the interaction of molecules with infrared radiation



11.2

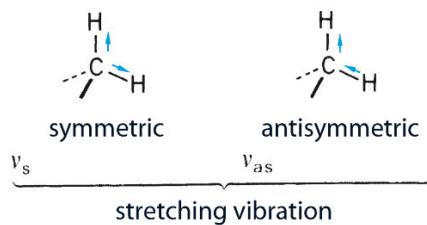
b) IR Spectroscopy and Energy

An infrared spectrum is obtained by passing infrared radiation through the sample. The energy of this radiation is

The Wavenumber ($\bar{\nu}$) is another way to describe the frequency of electromagnetic radiation.

Note: High frequencies, large wavenumbers, and short wavelengths are associated with *high energy*.

Because organic molecules are flexible structures, IR radiation can cause their bonds to stretch and contract, atoms to wag, and other motions to occur.

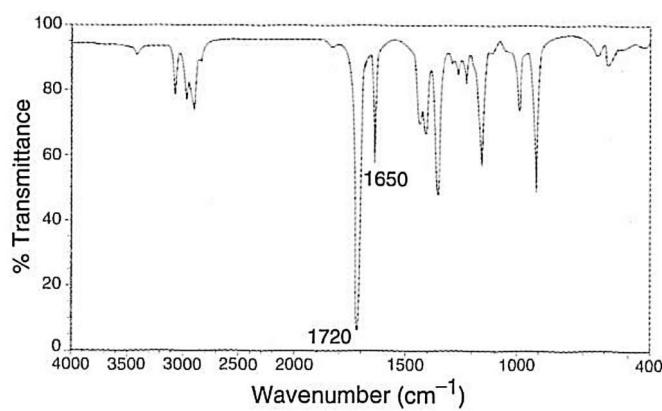


These stretching and bending motions occur with frequency of the IR radiation matches the frequency of the bond vibration. This results in an absorption band (peak) in an IR spectrum.

11.3

11.3 A typical IR Spectrum

A typical IR spectrum is shown here

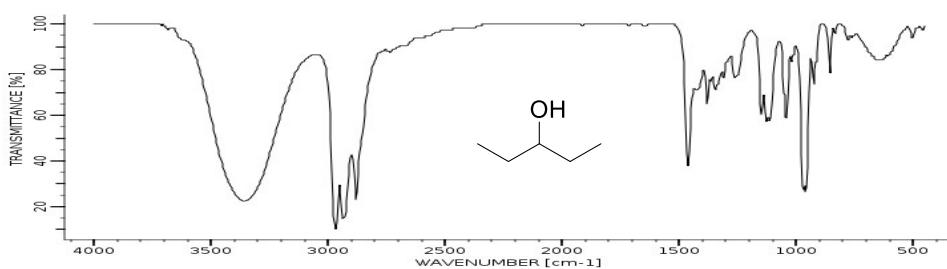
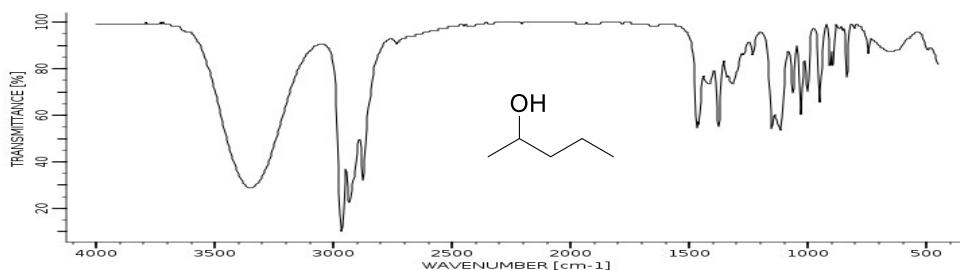


Some points to note:

- IR spectra are plotted as percentage *transmission* versus frequency (in cm^{-1}).
- The frequency is plotted in *wavenumbers* (cm^{-1}).
- Wave numbers are directly proportional to frequency.

IR spectra confirm the presence or absence of functional groups within a molecule

Spectra of compounds containing the same functional groups will differ in the *fingerprint region* ($1500 - 400 \text{ cm}^{-1}$) or by slight changes in frequency of the major functional groups.



11.5

11.4. Frequencies (wavenumbers) of IR absorptions

Where a bond absorbs in the IR spectrum depends both on the bond strength (triple>double>single) and the reduced mass.

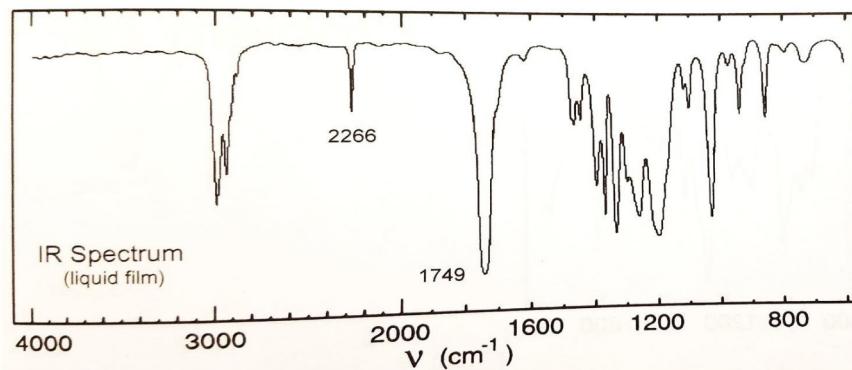
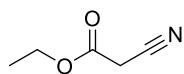
$$k_{\text{C}\equiv\text{C}} > k_{\text{C}=\text{C}} > k_{\text{C}-\text{C}}$$

$$\mu = \frac{m_1 \cdot m_2}{m_1 + m_2} = \text{reduced mass}$$

These are combined in Hooke's law (vibration frequency of a harmonic oscillator):

$$\nu_{\text{osc}} = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}}$$

Example:



We can broadly assign four regions to certain types of bonds.

O-H
N-H
C-H

C≡C
C≡N
C≡O
X=Y=Z

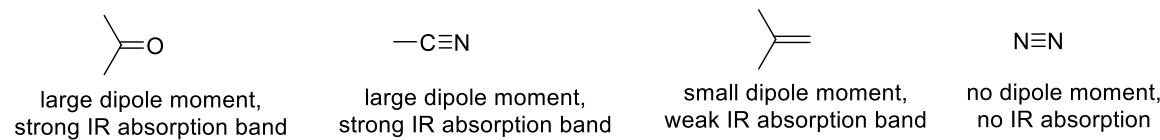
C=O
C=C
C=N
N=O

C-O
single bonds
"Fingerprint" region

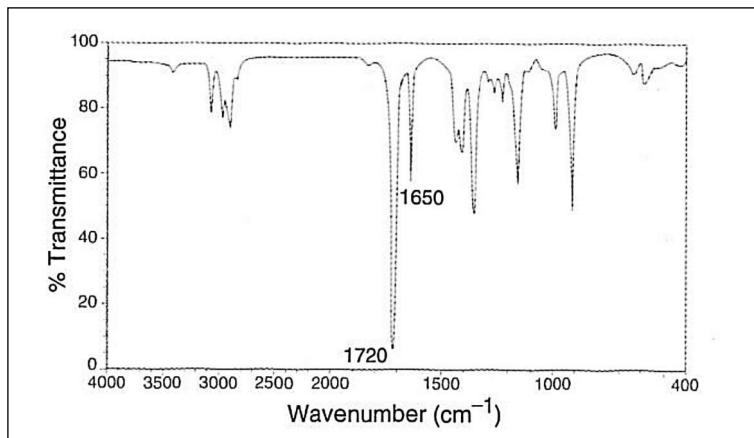
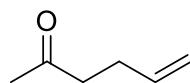
11.6

11.5 Strength of IR Absorptions

- The larger the change in dipole moment of the corresponding molecule, the stronger the IR absorption.
- If there is no change in dipole moment for a certain stretching or bending vibration, *no* IR peak will be observed (IR inactive).



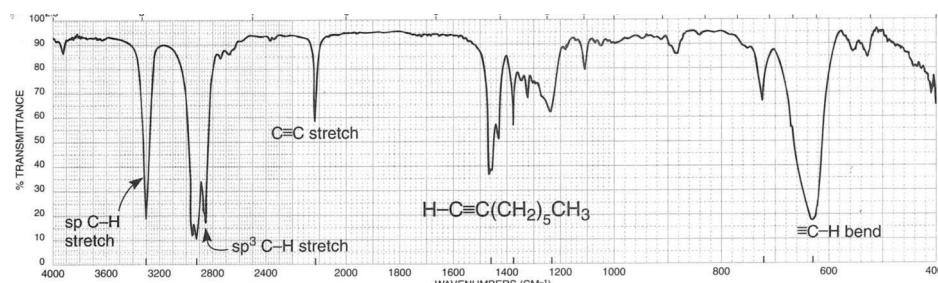
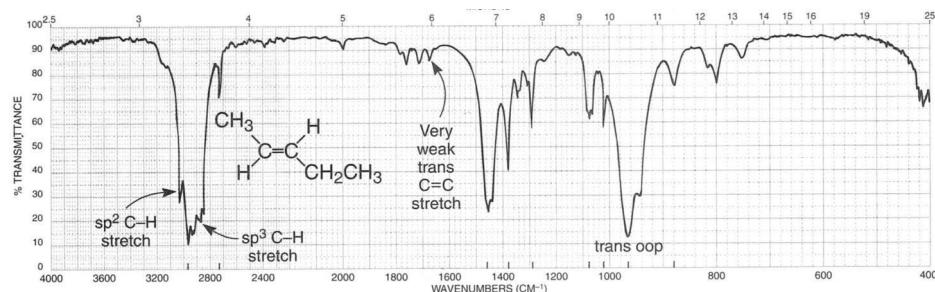
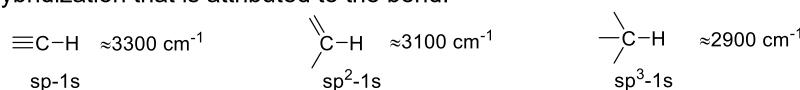
Example:



11.7

11.6 The X-H Region (4000-2500 cm⁻¹): N-H, O-H, and C-H bonds

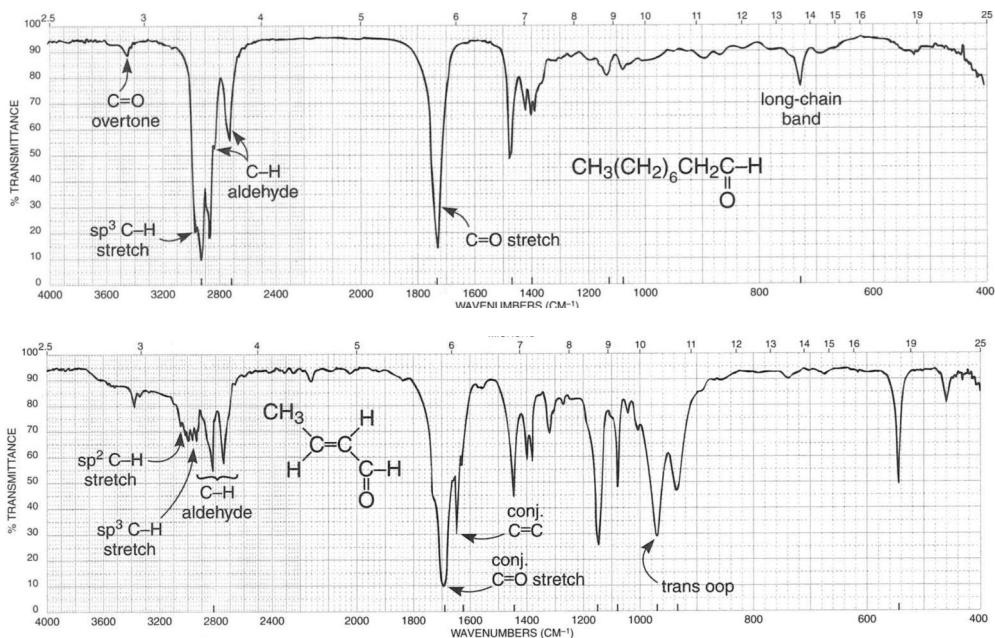
C-H bonds: C-H stretching frequencies can range from 3300 to 2750 cm⁻¹ and depend on hydrocarbons mostly on the hybridization that is attributed to the bond.



11.8

(C–H bonds)

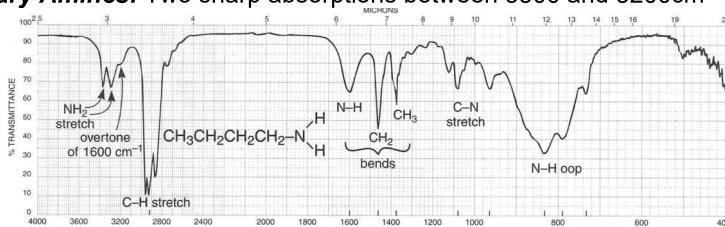
Aldehydes (see Chapter 16.14A) show two characteristic weak bands in the 2700–2775 cm⁻¹ and 2820–2900 cm⁻¹ regions which differentiates them from other carbonyl containing functional groups.



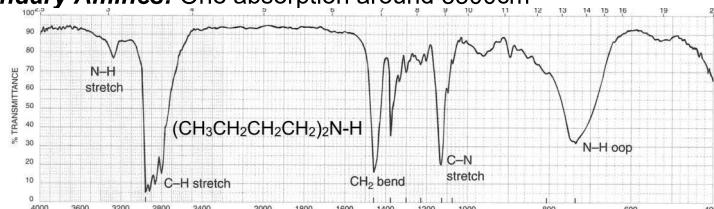
11.9

N–H bonds: Primary, secondary, and tertiary amines are easily distinguished from each other by IR spectroscopy (see Chapter 2 and Chapter 20.11B)

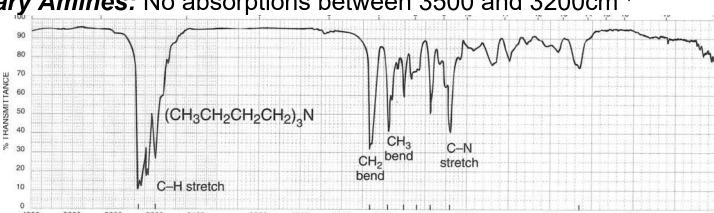
Primary Amines: Two sharp absorptions between 3500 and 3200 cm⁻¹



Secondary Amines: One absorption around 3300 cm⁻¹



Tertiary Amines: No absorptions between 3500 and 3200 cm⁻¹

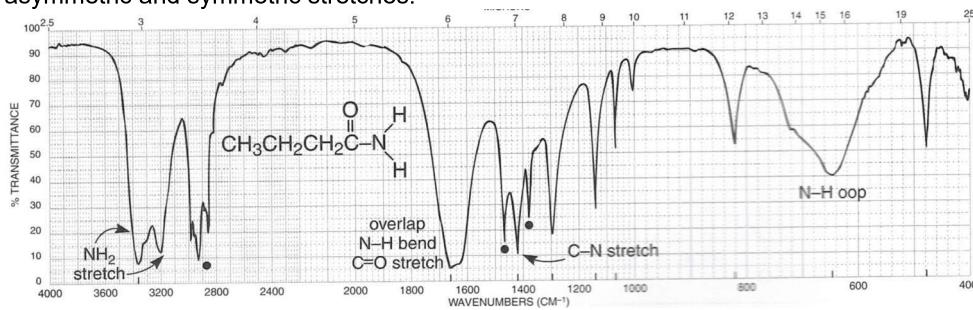


11.10

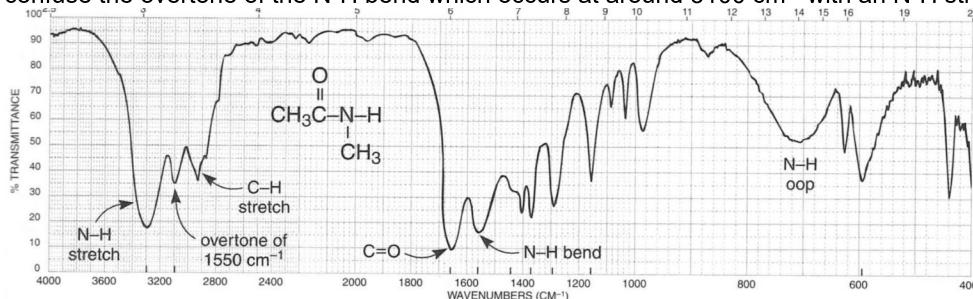
(N-H bonds)

N-H bonds are also present in other functional groups.

Unsubstituted amides ($\text{R}-\text{CO}-\text{NH}_2$) show two bands in the range of $3500\text{-}3200 \text{ cm}^{-1}$ arising from the asymmetric and symmetric stretches.



Monosubstituted amides ($\text{R}-\text{CO}-\text{NH}-\text{R}$) show as expected only one band in that region. Be careful not to confuse the overtone of the N-H bend which occurs at around 3100 cm^{-1} with an N-H stretch.



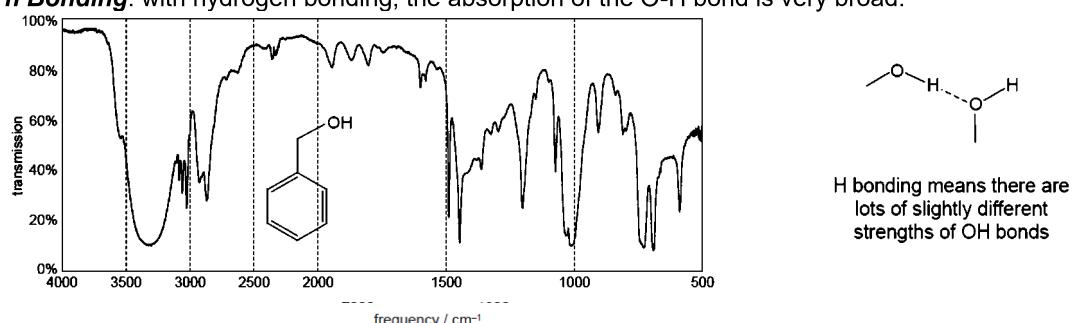
11.11

O-H bonds

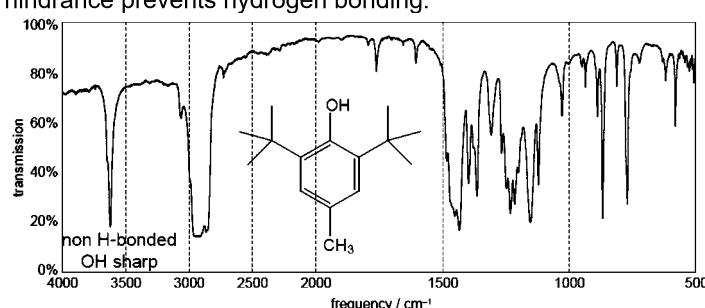
Alcohols: The shape of an O-H bond stretch in alcohols depends on whether hydrogen bonding is possible or not.

O-H with Hydroge

n Bonding: with hydrogen bonding, the absorption of the O-H bond is very broad.

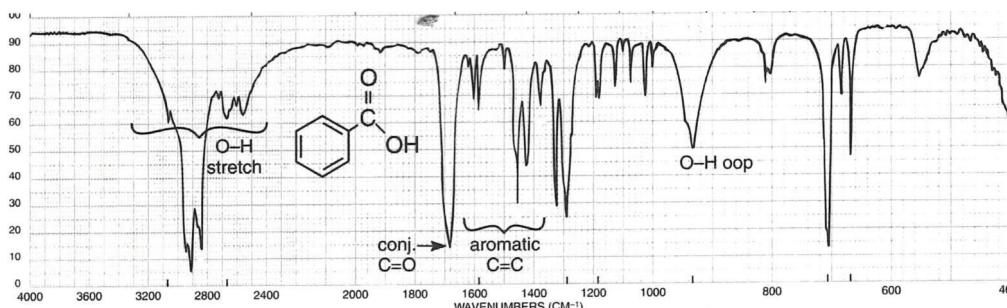
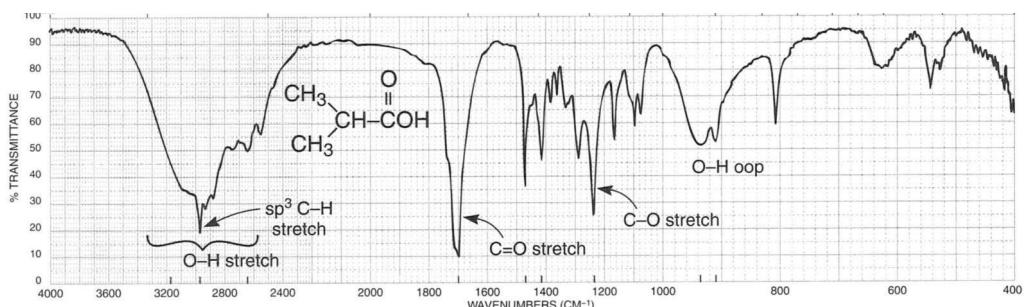


O-H without Hydrogen Bonding: Sharp O-H stretches are observed at 3600 cm^{-1} when steric hindrance prevents hydrogen bonding.



11.12

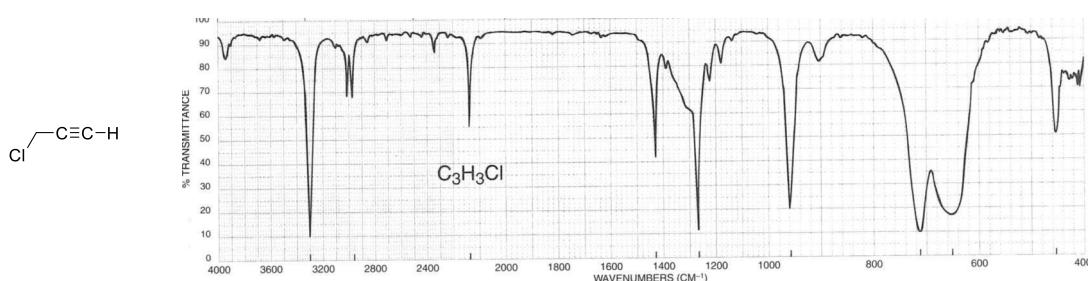
O-H of Carboxylic Acids: The V-shape of the O-H stretch in carboxylic acids allows us to distinguish alcohols from carboxylic acids. Carboxylic acid O-H stretches are very broad and can range from 3500-2500 cm⁻¹. They can be easily missed if the C-H stretches are strong in comparison!



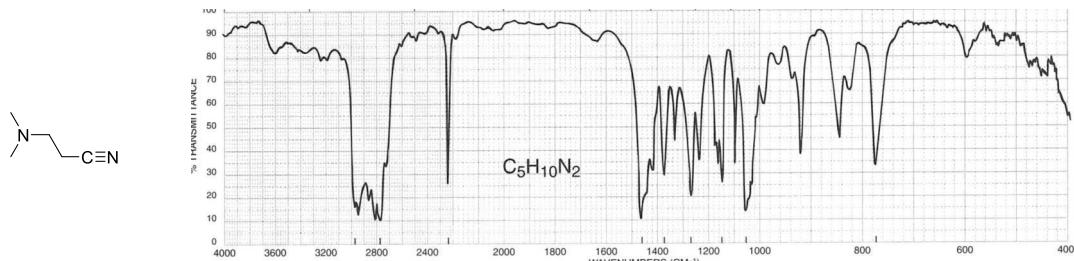
11.13

11.7 The Triple Bond Region (2000-2500 cm⁻¹)

Alkynes: Terminal alkynes will show a clearly visible CC triple bond absorption around 2150 cm⁻¹. Internal alkynes generally have a very weak triple absorption which may disappear into the baseline.



Nitriles: have a sharp absorption around 2250 cm⁻¹. Conjugation with a double bond or an aromatic ring can lower the frequency of absorption.



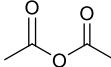
11.14

11.8 The Double Bond Region ($2000\text{-}1500\text{ cm}^{-1}$): C=O, C=C, N=O, C=N

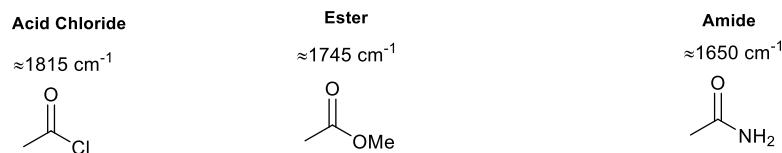
C=O always has a strong absorption

It is possible in most cases to identify the specific functional group based on the wavenumber observed.

Typical values for **unconjugated, unstrained carbonyl groups** are:

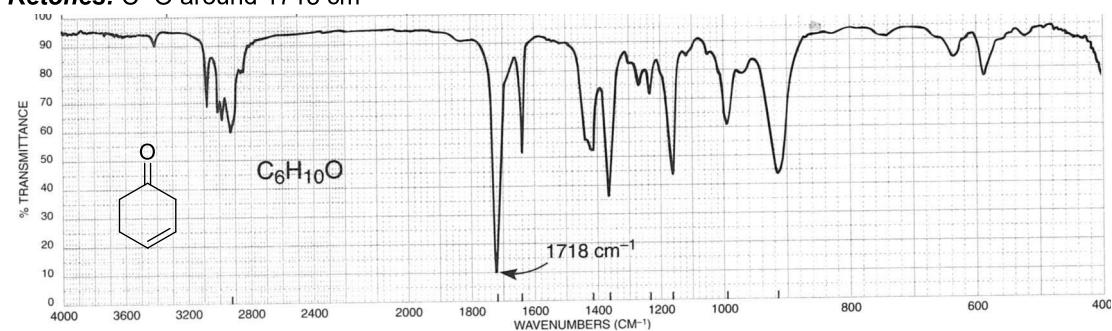
Acid Chloride	Acid Anhydride	Ester	Carboxylic Acid	Aldehyde	Ketone	Amide
						
$\approx 1815\text{ cm}^{-1}$	$\approx 1810\text{ cm}^{-1}$ (band 1) $\approx 1790\text{ cm}^{-1}$ (band 2)	$\approx 1745\text{ cm}^{-1}$	$\approx 1730\text{ cm}^{-1}$	$\approx 1730\text{ cm}^{-1}$	$\approx 1715\text{ cm}^{-1}$	$\approx 1650\text{ cm}^{-1}$

The C=O IR frequency is a direct measure of the strength of the carbonyl bond. Electron-withdrawing substituents strengthen the carbonyl bond, electron-donating substituents weaken the carbonyl bond due to resonance.

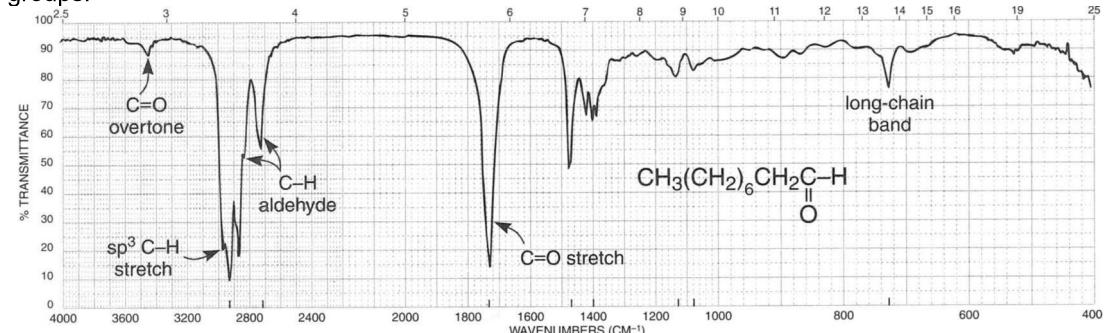


11.15

Ketones: C=O around 1715 cm^{-1}

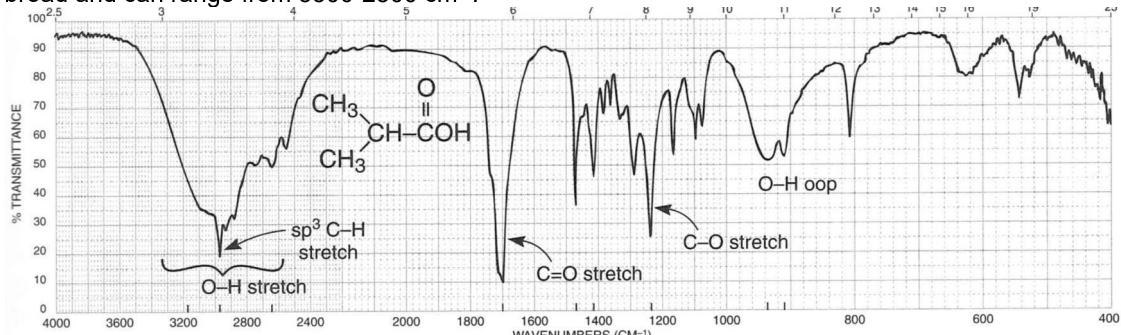


Aldehydes: C=O around 1730 cm^{-1} . Aldehydes have two characteristic weak bands in the $2700\text{-}2775\text{ cm}^{-1}$ and $2820\text{-}2900\text{ cm}^{-1}$ regions which differentiates them from other carbonyl containing functional groups.

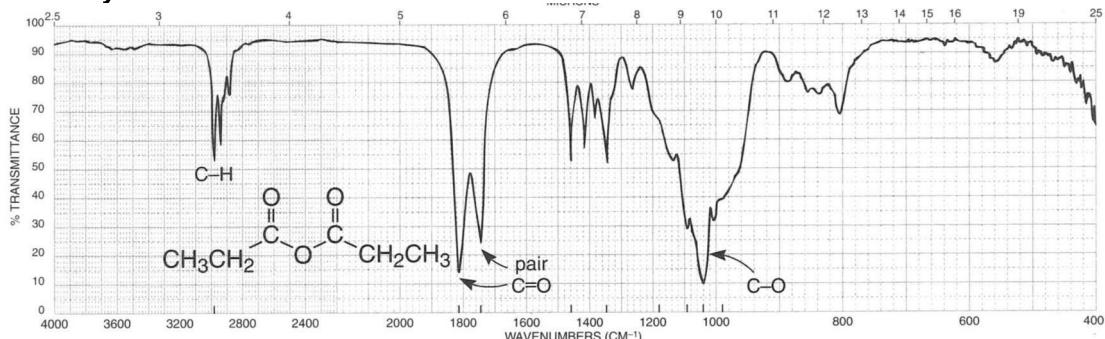


11.16

Carboxylic Acids: C=O around 1730 cm^{-1} but can vary significantly depending on the method of recording the IR spectrum. Carboxylic acids have characteristic V-shaped O-H stretches that are very broad and can range from $3500\text{-}2500\text{ cm}^{-1}$.

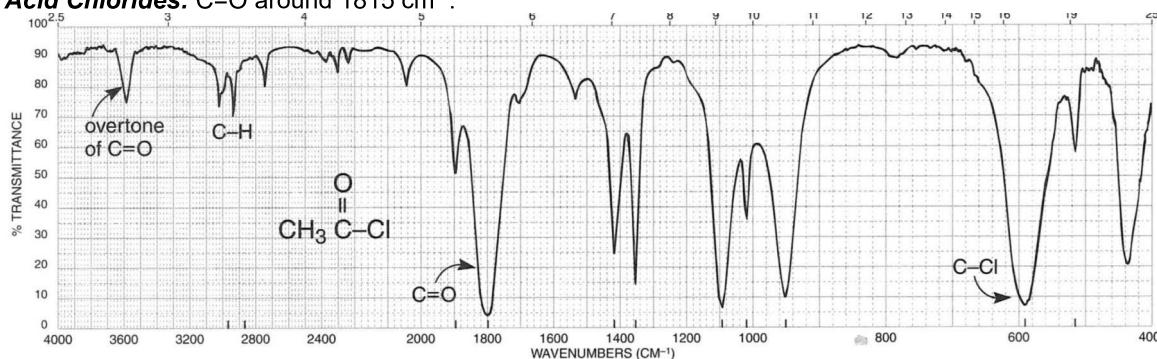


Acid Anhydrides: Two C=O bands around 1810 and 1760 cm^{-1} .

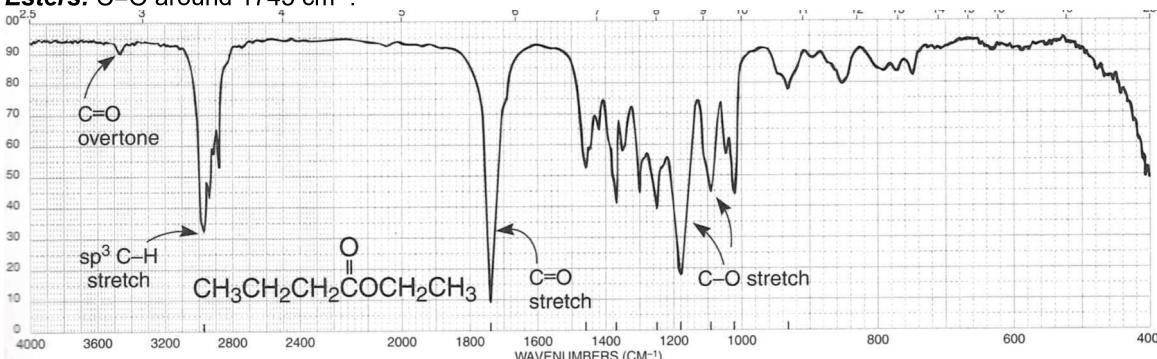


11.17

Acid Chlorides: C=O around 1815 cm^{-1} .

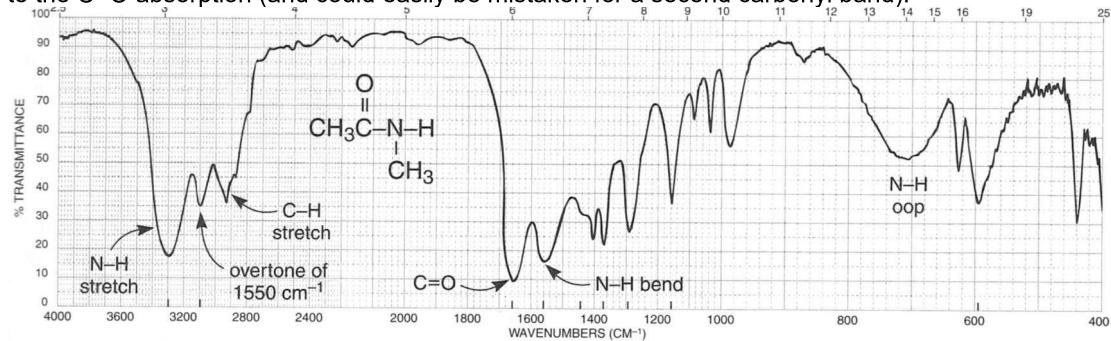


Esters: C=O around 1745 cm^{-1} .



11.18

Amides: C=O around 1650 cm^{-1} . The N–H bending frequency in primary and secondary amides is close to the C=O absorption (and could easily be mistaken for a second carbonyl band).



Effects of conjugation and ring strain

- Conjugation (with π electrons or lone pairs) weakens the C=O bond and lowers its absorption frequency
- Ring strain strengthens the C=O bond and increases its absorption frequency

11.19

Conjugative effects can significantly lower the IR frequency of the carbonyl group.

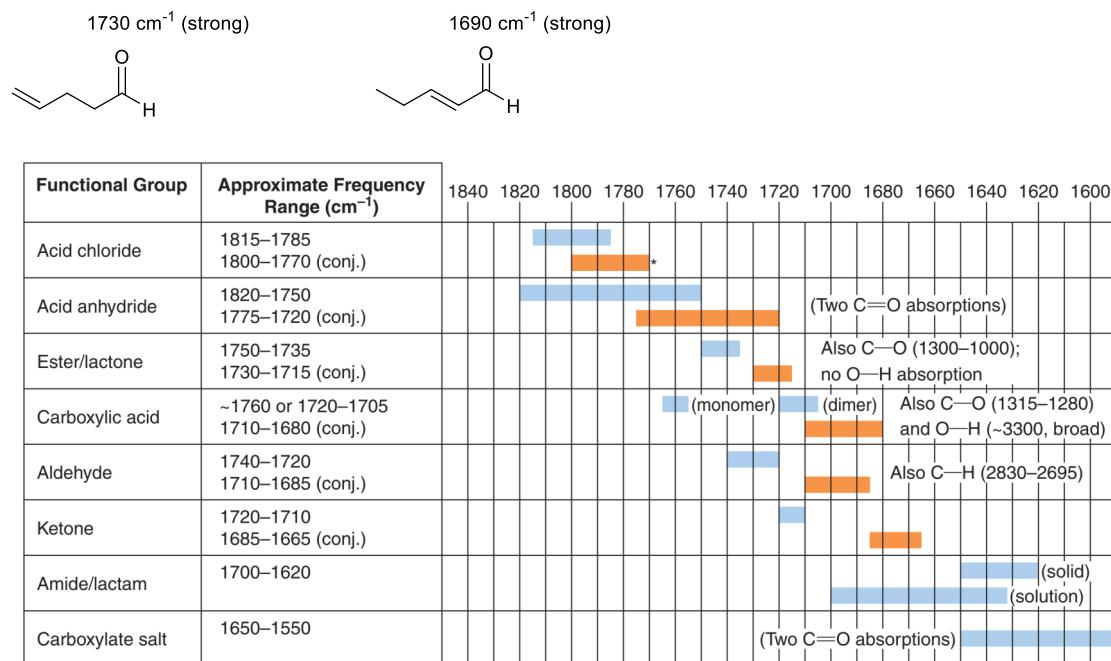
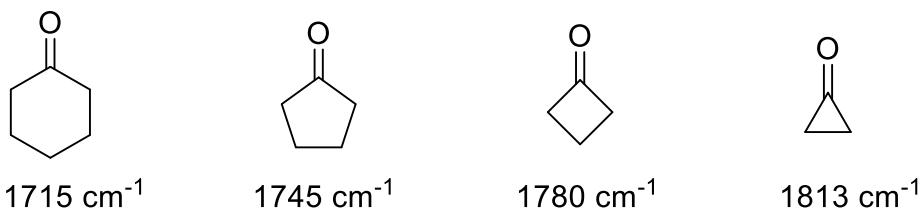


FIGURE 17.2 Approximate carbonyl IR absorption frequencies. (Frequency ranges based on Silverstein and Webster, reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds*, Sixth Edition. Copyright 1998.)

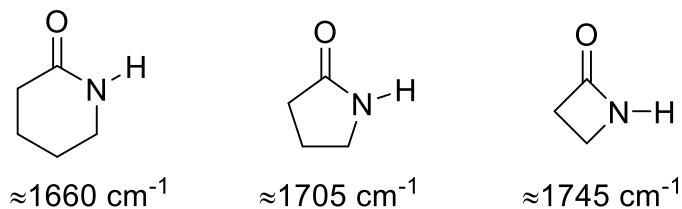
11.20

Ring strain strengthens the C=O bond and increases its absorption frequency

Cyclic ketones



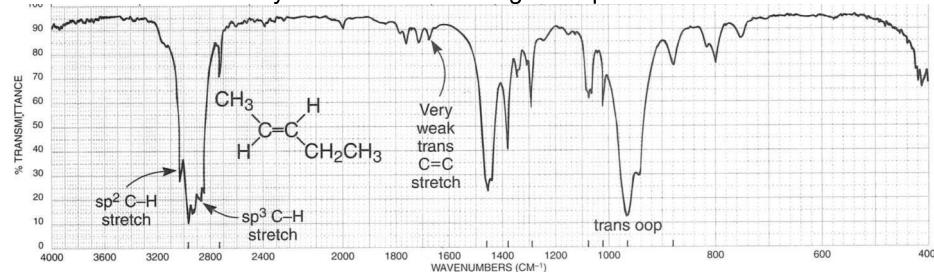
Cyclic amides (lactams)



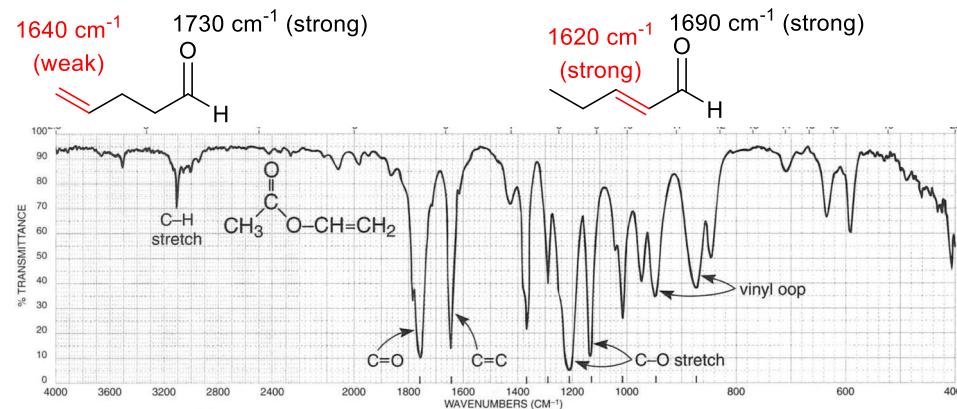
11.21

C=C bonds: are generally weak unless in conjugation with a polar group

trans-alkenes have very weak C=C stretching absorptions in the absence of other functional groups

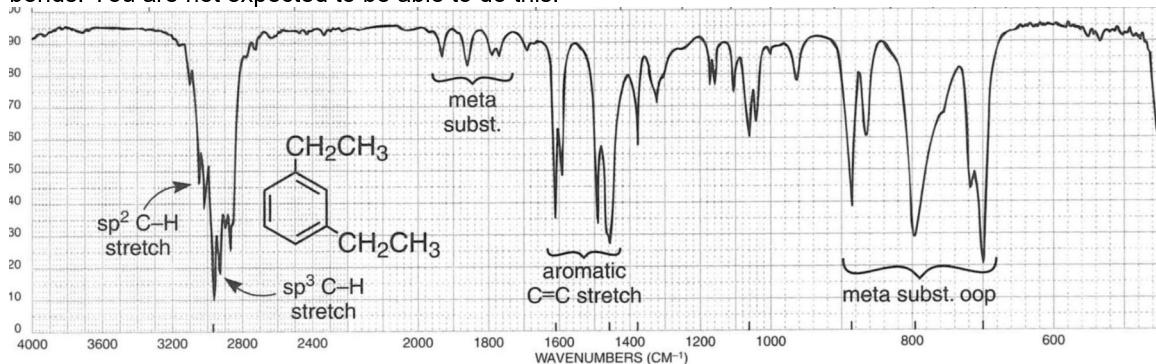


C=C bonds conjugated with π bonds or lone pairs show strong absorptions (at lower IR frequencies)



11.22

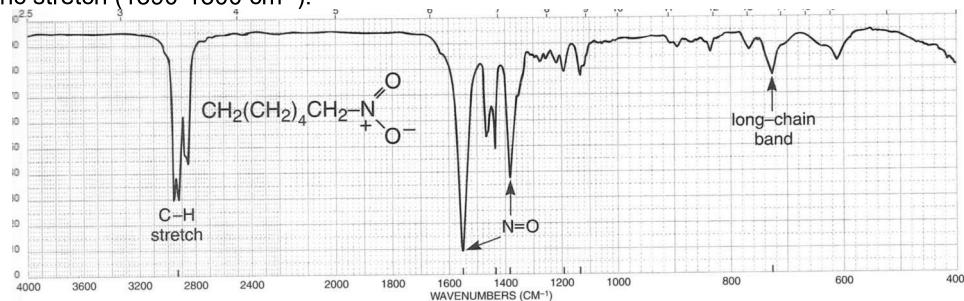
Aromatic CC bonds typically show stretching frequencies between 1600 and 1400 cm⁻¹. Experts are able to distinguish ortho, meta, and para substitution patterns based on the IR frequencies of the CC bonds. You are not expected to be able to do this.



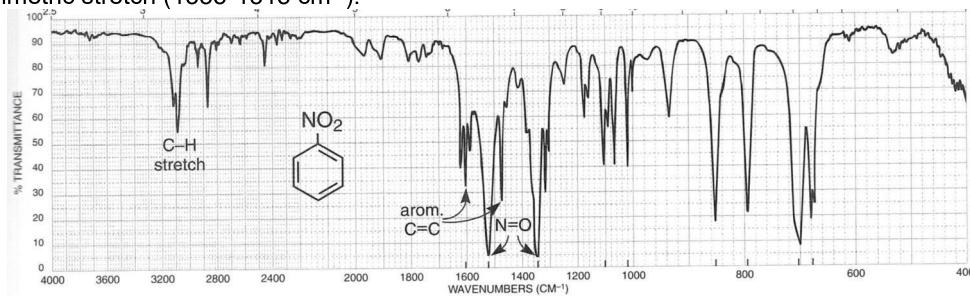
11.23

N=O bonds

Aliphatic nitro compounds show a strong asymmetric stretch (1600-1530 cm⁻¹) and a medium symmetric stretch (1390-1300 cm⁻¹).



Aromatic nitro compounds show two strong IR absorptions: asymmetric stretch (1550-1490 cm⁻¹) and symmetric stretch (1355-1315 cm⁻¹).



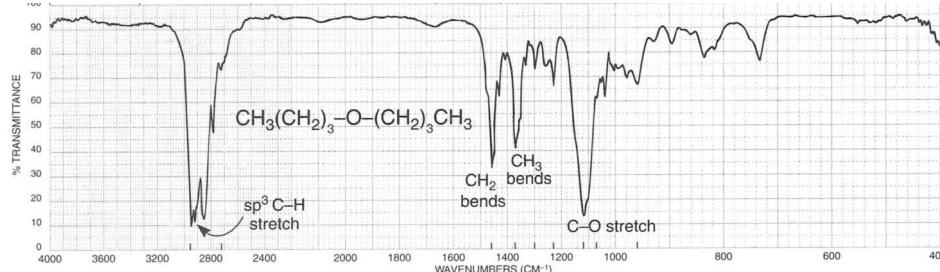
11.24

11.9 The Fingerprint Region (< 1500 cm⁻¹)

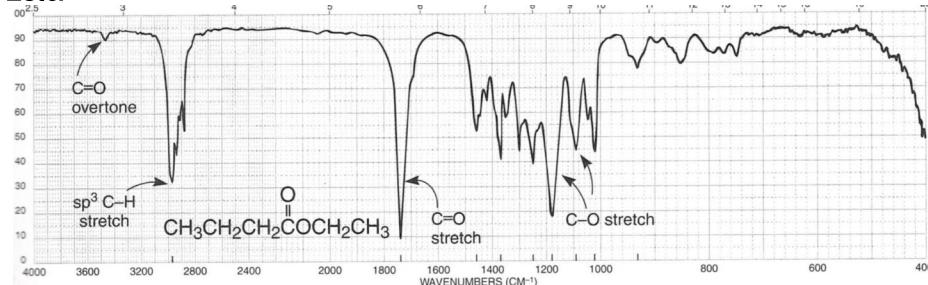
With exception of the C-O single bond, absorptions in the fingerprint region are not used for primary identification of functional groups.

The C-O single bond shows strong absorptions in the region between 1260-1000 cm⁻¹ and indicates the presence of one of the following groups: **Ether, alcohol, ester, or carboxylic acid.**

Example Ether



Example Ester



11.25

11.10 Tables and Useful Tools for solving IR problems

Characteristic IR Absorptions

CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES

Bond	Compound Type	Frequency range, cm ⁻¹
C(sp ₃)-H	Alkanes	2960-2850 (strong)
C(sp ₂)-H	Alkenes, Aromatic Rings,	3100-3000 (medium)
C(sp)-H	Alkynes	3333-3267 (strong)
C(sp ₂)-H	Aldehydes	2850 and 2750 (weak)
C=C	Alkenes	1680-1640 (medium, weak)
C≡C	Alkynes	2260-2100 (weak, sharp)
C=C	Aromatic Rings	1600 and 1500 (weak)
C-O	Alcohols, Ethers, Carboxylic acids, Esters	1260-1000 (strong)
C=O	Aldehydes, Ketones, Carboxylic acids, Esters	1760-1670 (strong)
O-H	Alcohols, Phenols	3600-3200 (broad, U-shaped)
	Carboxylic acids	3300-2500 (very broad, V-shaped)
N-H	Amines	3500-3300 (medium)
C≡N	Nitriles	2260-2220 (varies)

Suggested strategy for IR spectrum interpretation

1. Look first at the high-frequency end of the spectrum ($> 1500 \text{ cm}^{-1}$) and concentrate initially on the major bands.
2. For each band, short list the possibilities by using a correlation chart.
3. Use the lower-frequency end of the spectrum for the confirmation or elaboration of possible structural elements.
4. Do not expect to be able to assign every band in the spectrum.
5. Keep cross-checking wherever possible. For example, an aldehyde should absorb near 1730 cm^{-1} and also in the region $2900\text{-}2700 \text{ cm}^{-1}$.
6. Exploit negative evidence as well as positive evidence. For example, if there is no band in the $1850\text{-}1600 \text{ cm}^{-1}$ region, it is most unlikely that a carbonyl group is present.
7. Band intensities should be treated with some caution. Under some circumstances they may vary considerably for the same group.

Chapter 12: Aldehydes and Ketones

12.1 The Carbonyl Group: Structure and Reactivity

The Carbonyl Group:

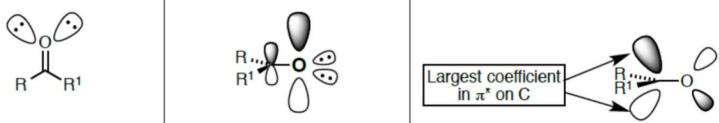


Functional groups containing the carbonyl group:

Polarity of Carbonyl Compounds



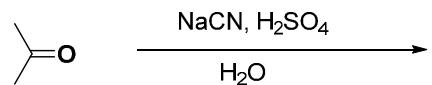
View from above and side:



b) Typical Reaction Scheme of a Nucleophilic Addition to C=O

Two mechanistic steps:

1. Nucleophilic addition to the carbonyl group
2. Protonation of the resulting anion



12.2 Nomenclature of Aldehydes and Ketones

Functional group priorities with examples:

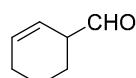
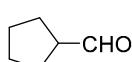
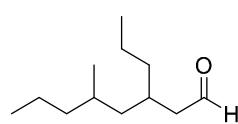
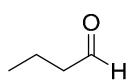
TABLE 12.1 Increasing Order of Precedence of Six Functional Groups

Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Carboxyl	-oic acid	—		
Aldehyde	-al	oxo-	3-Oxopropanoic acid	
Ketone	-one	oxo-	3-Oxobutanal	
Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	
Amino	-amine	amino-	2-Amino-1-propanol	
Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	

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a) Aldehydes

- Find parent chain containing CHO (and C=C or C≡C if present)
- Replace the -e with -al
hexane →
hexene →
- Number the chain beginning with the carbon of the CHO as #1
- Include all substituents in the name
- For -CHO as substituent, e.g. on a ring, use *carbaldehyde*

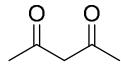
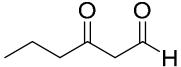
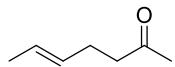
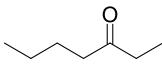


Common names:



b) Ketones

1. Find the parent chain containing the C=O
2. Replace -e with -one
3. Number the chain from the end closest to the C=O
4. Include all substituents in the name
5. For =O as substituent use *oxo*-



Common names:

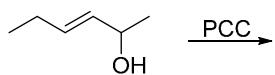
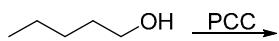
Acetone

Dicyclohexylketone

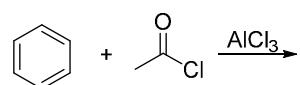
12.3 Synthesis of Aldehydes and Ketones

a) Oxidation of Alcohols

- Aldehydes are obtained by reacting 1° alcohols with PCC
- Ketones obtained by reacting 2° alcohols with PCC, CrO₃, or NaCr₂O₇

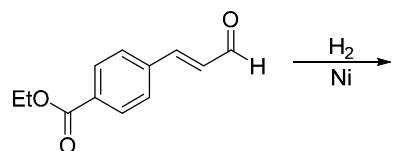
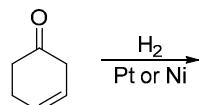
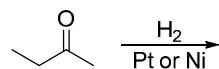


b) Friedel-Crafts Acylation



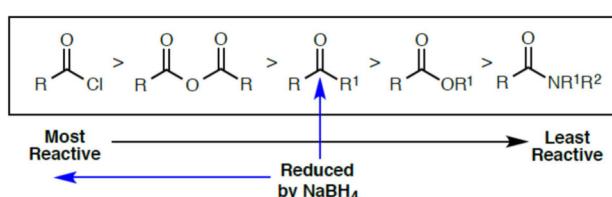
12.4 Catalytic Reduction of Carbonyl Compounds with H₂ (Hydrogenation)

Hydrogenation reduces aldehydes and ketones but not esters. Alkene or alkyne groups present are normally also reduced.



12.5 Reduction of Carbonyl Compounds with Hydride Reagents

Relative Reactivity of Carbonyl Compounds towards Nucleophilic Attack:



Reduction of **acid chlorides/anhydrides** to **alcohols** with **sodium borohydride**

Reduction of **esters** to **alcohols** using **lithium aluminium hydride**

Reduction of **amides** to **amines** using **lithium aluminium hydride**

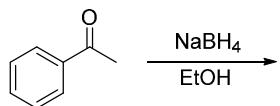
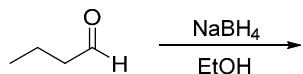
a) Reduction of Aldehydes and Ketones



Two common reductants that are employed in reducing carbonyl compounds are sodium borohydride (NaBH_4) and lithium aluminum hydride (LiAlH_4).

Sodium Borohydride as Reducing Agent for Ketones and Aldehydes

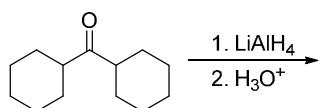
NaBH_4 is weak enough to be used in ethanol, a protic solvent, which can act directly as proton source for the resulting alkoxide.



Mechanism of a Sodium Borohydride Reduction in Ethanol:

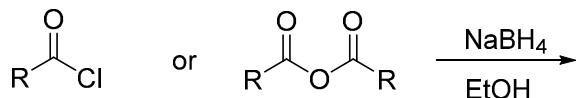
Lithium Aluminum Hydride as Reducing Agent

LiAlH_4 reacts violently with protic solvents by forming H_2 and must therefore be used in an inert solvent such as THF or diethyl ether. This requires an individual step to protonate the alkoxide (aqueous work up) which must be carried out very slowly.



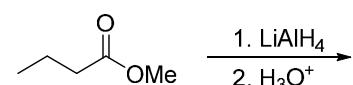
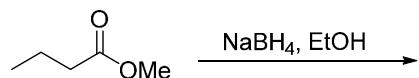
Mechanism:

b) Reduction of Acid Chlorides and Anhydrides to Alcohols: NaBH_4

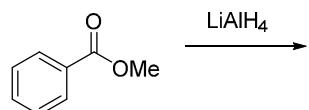


c) Reduction of Esters to Alcohols: LiBH_4 or LiAlH_4

Esters are not reduced by NaBH_4 , however, the slightly stronger reducing agent LiBH_4 is capable of reducing esters. LiAlH_4 will work as well but requires inert conditions and a second work-up step.



Mechanism of the Reduction of Esters to Alcohols with LiAlH₄:



12.6 Grignard Reagents and Organolithium Compounds

Organometallic compounds have carbon-metal bonds which range from primarily ionic (e.g. Na⁺ or K⁺ salts), covalent with significant ionic character (organolithium and Grignard reagents) to primarily covalent (e.g. Cu, Hg, Ti).

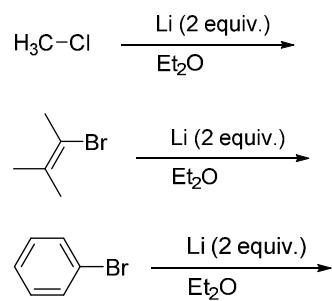
Sodium acetylides:

Organolithiums:

Grignard reagents:

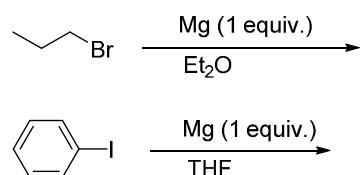
12.5.1 Synthesis of Organolithium Reagents

"Lithium-Halogen Exchange": 2 equivalents of Lithium are needed to generate one equivalent of the desired organolithium compound.



2.5.2 Synthesis of Grignard Reagents

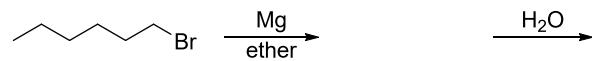
"Mg Insertion": Use of Mg turnings in an ether solvent results in a Mg insertion into the carbon-halide bond. Examples of ether solvents: Et₂O, THF, dioxane



b) Reactions of Grignard Reagents with Acidic Protons

Grignard reagents and organolithium compounds react with acids and electrophiles (HCl, H₂O, R-OH) by accepting H⁺ and forming hydrocarbons.

Reaction of Grignard reagent with water:



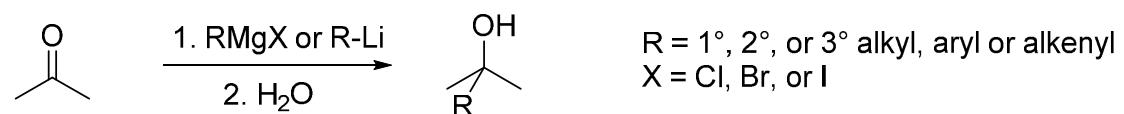
Reaction of organolithium reagent with ethanol:

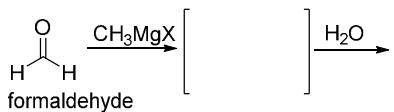
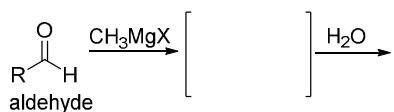
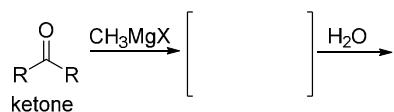
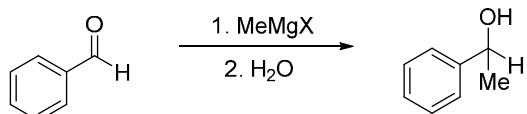
Use of Grignard and organolithium reagents to prepare alkynyl organometallic reagents:

12.15

c) Reactions with Carbonyl Compounds

Grignard reagents (RMgX) and organolithium compounds are nucleophilic and attack the electrophilic carbon of carbonyl compounds:

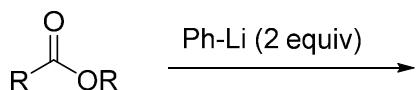


Aldehydes and ketones react once with Grignard reagents or organolithium reagents**Mechanism:**

12.17

Esters react twice with organometallic reagents

The ketone intermediate *cannot* be isolated when esters are used as starting materials because it is more reactive towards the nucleophile than the starting ester.

**Important:**

- The ketone will react with the organometallic species *more quickly* than the starting ester
- If only one equivalent of the organometallic reagent is present, the major product will be the alcohol (resulting from double addition) with about 50% of the starting material remaining.

12.18

d) Restrictions on the Synthesis and Use of Grignard Reagents

Grignard reagents cannot be prepared if the following functional groups are present:

- -OH, -NH, -SH, -COOH, terminal alkynes

- X and C=O are in the same molecule

12.19

12.7 Protecting Groups**a) for Alcohols: Silyl Protecting Groups**

TBS-Cl

TMS-Cl

TIPS-Cl

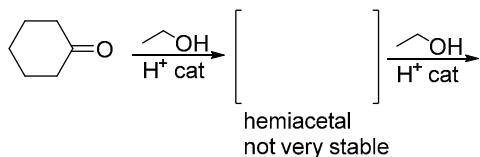
Preparation of a silyl ether:

Removal of silyl protecting groups:

12.20

b) for Aldehydes and Ketones**Acetals are Common Protecting Groups for Aldehydes and Ketones**

- Alcohols add to aldehydes and ketones to form hemiacetals, then acetals

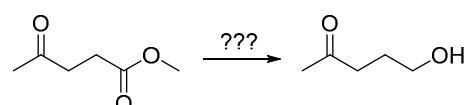


Acetal formation is reversible

- If H_2O is removed then acetal is favored
- If H_2O is added then $\text{C}=\text{O}$ is favored

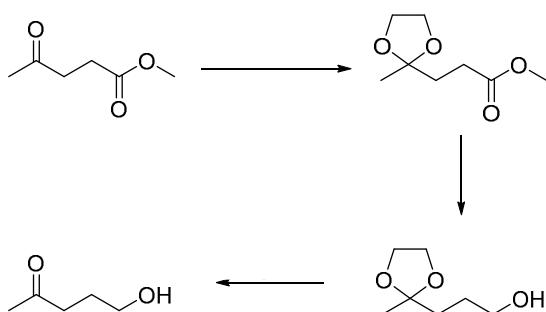
12.21

Exercise: How would you synthesize the following compound?



LiAlH_4 would reduce the ester but also the ketone.

If the ketone is to be part of the product it needs to be protected.



12.22

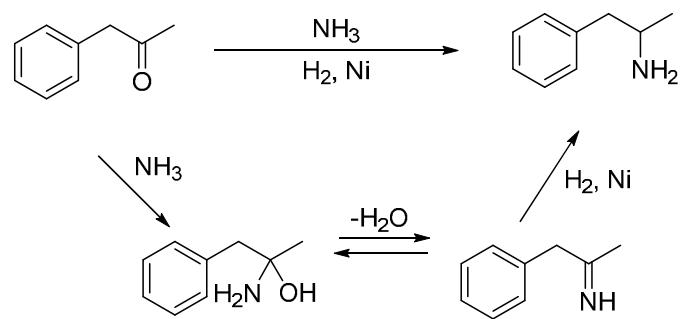
12.8 Reactions of Carbonyl Groups with Amines**a) Imine Formation**

A 1° amine adds to aldehyde or ketone to give an imine ($\text{R}_2\text{C}=\text{NR}$)



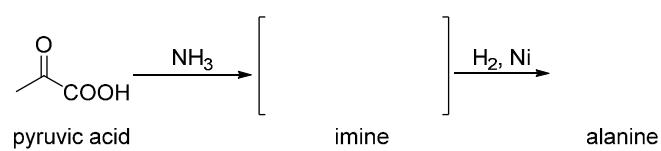
Common in biological pathways
Only works with ammonia and 1° amines

12.23

b) Reductive Amination of Aldehydes and Ketones

Ammonia and RNH₂ may be used to obtain 1° and 2° amines, respectively

12.24

c) Synthesis of an Amino Acid by Reductive Amination

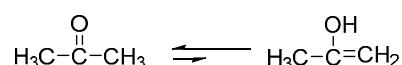
12.25

12.9 Keto-Enol Tautomerism

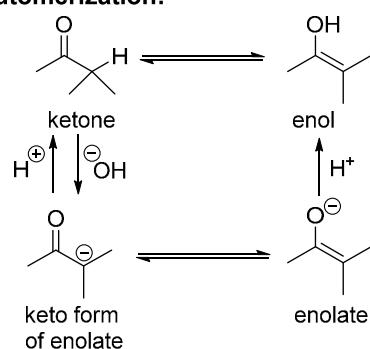
Tautomers are constitutional isomers readily interconvert. Tautomerism can occur with double bonds to O, S, or N if a protic α -hydrogen is present.

a) Keto and Enol Forms of Carbonyl Compounds

The keto form is more stable than the enol form:



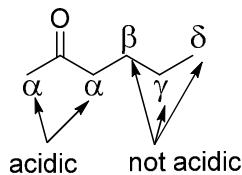
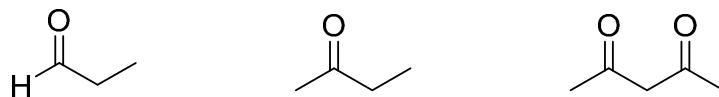
Equilibration of the keto-enol equilibrium can be catalyzed by acid or base. Tautomerism requires the presence of an acidic α -hydrogen.

Mechanism of base catalyzed tautomerization:

12.26

b) Acidity of α -Hydrogens in Carbonyl Compounds

Which hydrogen atoms are acidic?

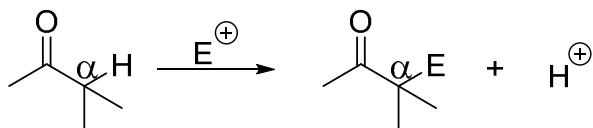


Racemization at α -carbons:

12.27

c) α -Halogenation

α -Halogenation is catalyzed both by acid and base since it involves an enol or enolate intermediate. Enols react with electrophiles Br_2 , Cl_2 , I_2 .

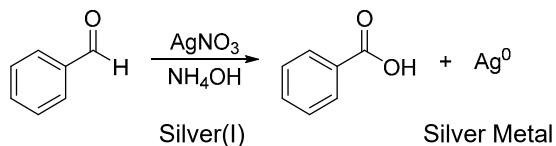


12.28

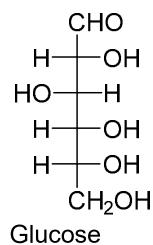
12.10 Oxidation of Aldehydes

CrO₃ or NaCr₂O₇ oxidizes aldehydes to carboxylic acids (see Chapter 8):

The Tollens' Reagent oxidizes only aldehydes.



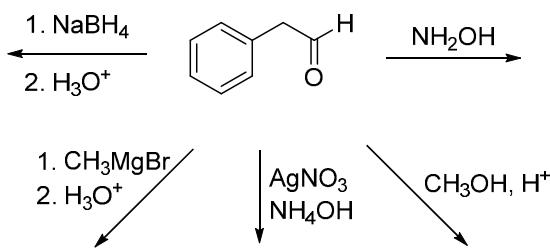
It is used in biological research as test for the presence of aldose sugars (e.g. glucose) which contain an aldehyde group in their open form.



12.29

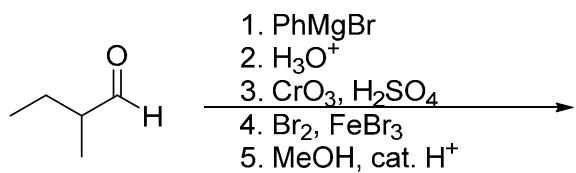
12.11 Exercises

a) What is the product?



12.30

b) What is the product after each of these steps?

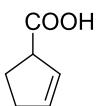
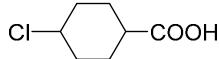
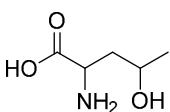
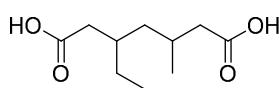
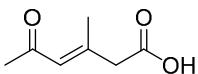
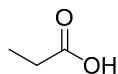


12.31

Chapter 13: Carboxylic Acids

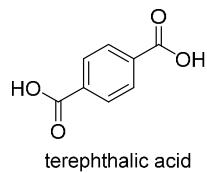
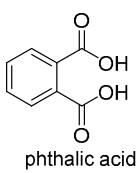
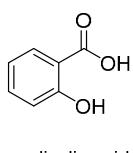
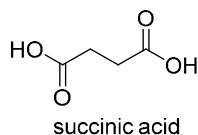
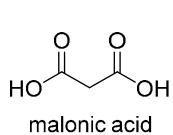
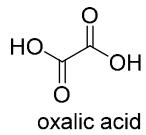
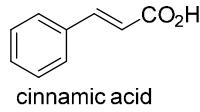
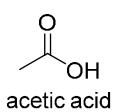
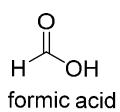
13.1 Nomenclature of Carboxylic Acids (IUPAC)

1. Find longest chain containing the carboxylic acid
2. Replace –e with –oic acid
3. Number the chain starting from the carboxylic acid carbon
4. Dicarboxylic acids are named by adding *di* to the suffix (dioic acid)
5. A carboxylic acid containing an aliphatic ring with the carboxylic acid directly bound to it is named by giving the name of the ring and adding carboxylic acid to it. Being the highest priority group, the ring carbon attached to the $-\text{CO}_2\text{H}$ will be given the locant 1.
6. The simplest aromatic carboxylic acid is benzoic acid. Substituents can be added to the name with the appropriate locants. (Rules Chapter 9)
7. Aromatic dicarboxylic acids are named by adding *dicarboxylic acid* to *benzene*. Many have common names.



13.1

IUPAC and common names:



13.2

13.2 Properties of Carboxylic Acids

a) Hydrogen Bonding

Strong H-bonding results in dimer formation in solids and non-polar solvents.

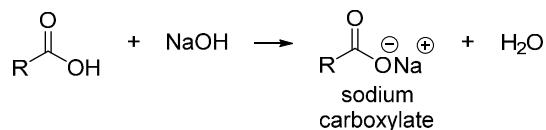
Significantly higher boiling points compared to alkanes or alkyl halides

Good solubility in polar solvents.

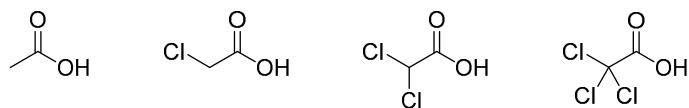
13.3

b) Acidity

Carboxylic acids are more acidic than alcohols due to resonance stabilization in the resulting carboxylate.

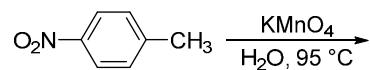
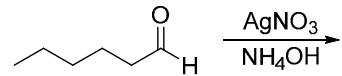
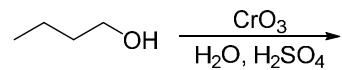


Electron-withdrawing groups increase the acidity through inductive effects:

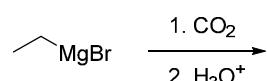


Benzoic acids are more acidic than aliphatic carboxylic acids.

13.4

13.3 Synthesis of Carboxylic Acids**a) Oxidation of Benzylic Carbons gives Benzoic Acid Derivatives****b) Oxidation of Aldehydes with Silver(I)****c) Oxidation of Primary Alcohols to Carboxylic Acids**

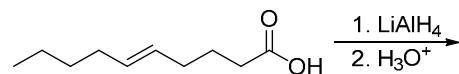
13.5

d) Addition of Grignard Reagents to Carbon Dioxide

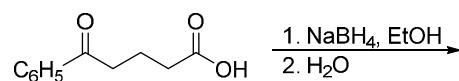
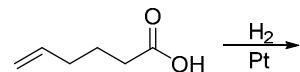
13.6

13.4 Reactions of Carboxylic Acids

a) Reduction of Carboxylic Acids to Primary Alcohols

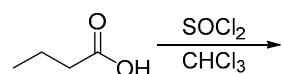


- Much slower than aldehyde or ketone reductions
- LiAlH_4 must be used instead of NaBH_4
- Attention: Any aldehydes, ketones, esters, acid chlorides or acid anhydrides will also be reduced
Selective reductions of other functional groups in the presence of carboxylic acids.
- The carboxylic acid group is inert to hydrogenation.
- Carboxylic acids are not reduced by NaBH_4 and LiBH_4

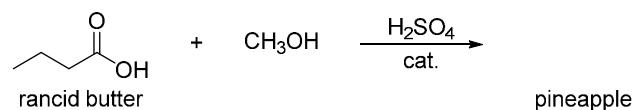


13.7

b) Conversion of Carboxylic Acids to Acid Chlorides



13.8

c) Conversion of Carboxylic Acids to Esters (Fischer Esterification)

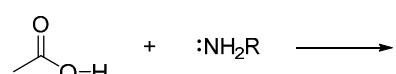
The Fischer esterification is reversible.

Removal of the resulting water byproduct draws the equilibrium to the side of the ester.

13.9

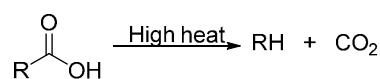
d) Conversion of Carboxylic Acids to Amides

Direct conversion of carboxylic acids to amides is difficult because any amine will react with the carboxylic acid in an acid-base reaction.

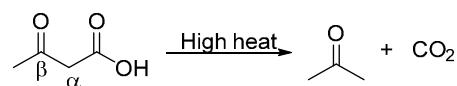


The most successful route is to first convert the carboxylic acid to an ester and then convert the ester to an amide. This is also how coupling agents (peptide synthesis) operate.

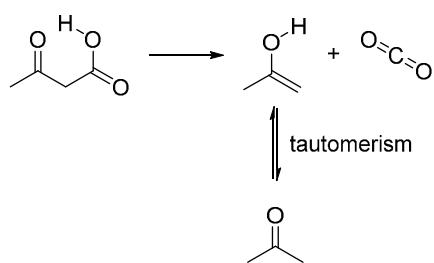
13.10

e) Decarboxylation Reactions

β -ketoacids are particularly prone to decarboxylate upon heating.

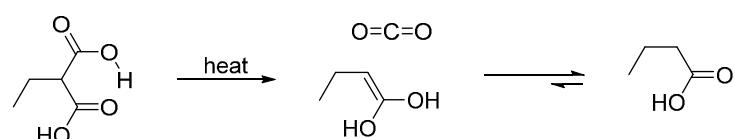


Mechanism:



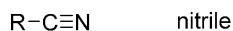
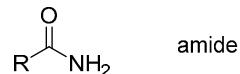
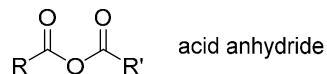
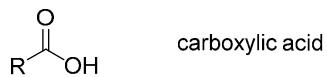
13.11

β -dicarboxylic acid also decarboxylate easily:



13.12

Chapter 14: Functional Derivatives of Carboxylic Acids



14.1

14.1 Nomenclature of Carboxylic Acid Derivatives

a) Acid Halides

- Acid halides are named by changing the suffix *-ic acid* in the name of the parent carboxylic acid to *-yl halide*.

Acetyl chloride:

Benzoyl chloride:

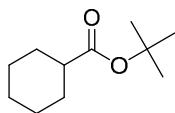
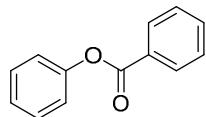
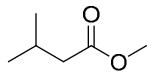
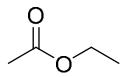
b) Acid Anhydrides

- Symmetrical anhydrides are named by changing the suffix *acid* in the name of the parent carboxylic acid to *anhydride*.
- Mixed anhydrides are named by identifying the two parent carboxylic acids from both acyl groups and placing those names in alphabetical order before without the *acid* part of the name before the word *anhydride*.
- Acetic anhydride: Acetic benzoic anhydride:

14.2

c) Esters

- The alkyl or aryl group attached to the -O- is named first followed by the name the carboxylic acid in which *-ic acid* has been replaced with *-ate*.



14.3

d) Amides

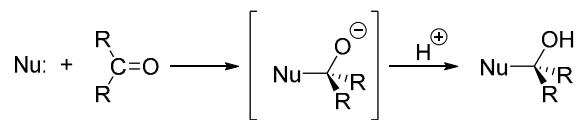
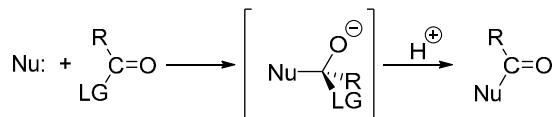
- Amides are named by dropping the suffix *-oic acid* from the IUPAC name for the parent acid (or *-ic acid* from common names) and adding amide.
- If the nitrogen atom of an amide is bonded to an alkyl or aryl group, the group is named and its location on the nitrogen is indicated by *N*-.

Acetamide

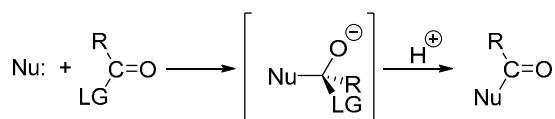
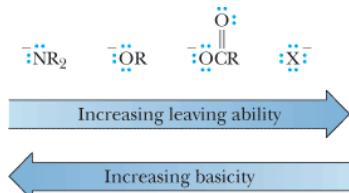
N-Methylacetamide

N,N-Dimethylformamide

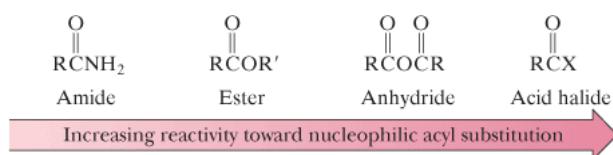
14.4

14.2 Characteristic Reactions of Carboxylic Acid Derivatives**Aldehydes and Ketones: Nucleophilic Acyl Addition Reactions (Ch 12)****Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions**

14.5

Reactivity of Carboxylic Acid Derivatives in the Nucleophilic Acyl Substitution Reaction**Leaving Groups**

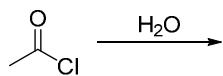
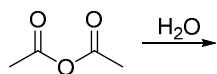
Best Leaving Group = highest reactivity toward substitution



14.6

14.3 Hydrolysis of Carboxylic Acid Derivatives to Carboxylic Acids

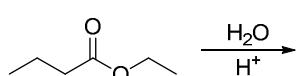
Reaction of carboxylic acid derivatives with water: Hydrolysis.

a) Hydrolysis of Acyl Halides**b) Hydrolysis of Acid Anhydrides**

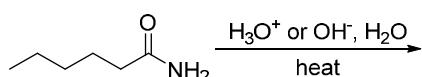
14.7

c) Hydrolysis of Esters to Acids

Under acidic conditions:



Under basic conditions (Saponification):

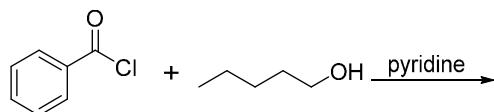
**d) Hydrolysis of Amides**

Very slow, requires prolonged heating under strongly acidic or basic conditions.

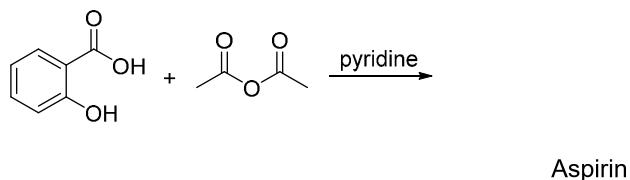
14.8

14.4 Reactions of Carboxylic Acid Derivatives with Alcohols

Ester formation.

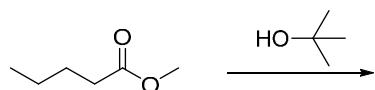
a) Acyl Halides to Esters

Role of pyridine:

b) Acid Anhydrides to Esters

Anhydrides are less efficient because only half of the anhydride is used, the other half is wasted

14.9

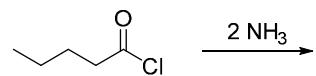
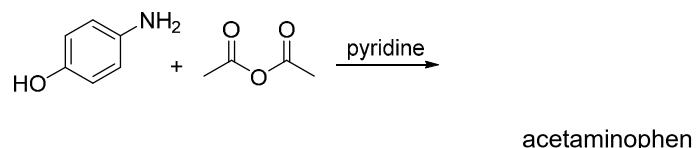
c) Esters to Esters (Transesterification)**d) Amides to Esters?**

Amides cannot be converted directly to esters since they are less reactive.

14.10

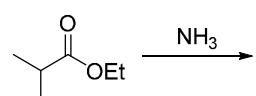
14.5 Reactions of Carboxylic Acid Derivatives with Amines

Amide formation with ammonia, 1°, or 2° amine.

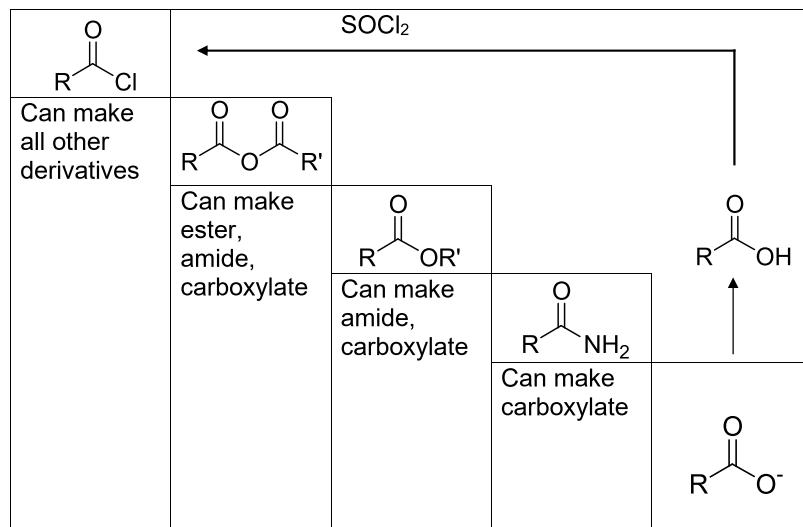
a) Acyl Halide to Amide**b) Acid Anhydrides to Amides**

Anhydrides are less efficient than acid chlorides because half of the anhydride is “wasted”.

14.11

c) Esters to Amides

14.12

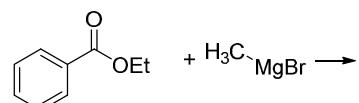
14.6 Interconversion of Carboxylic Acid Derivatives (Summary)

14.13

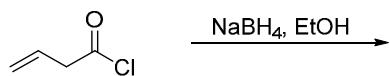
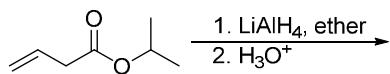
14.7 Reaction of Esters with Grignard Reagents

Esters are first reduced to ketones which will react then to 3° alcohols.

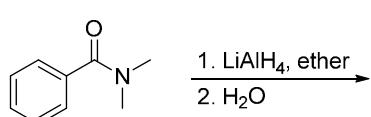
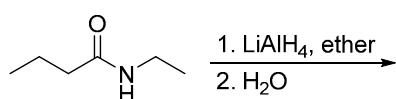
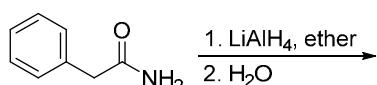
Grignard adds twice to the carbonyl carbon: because ketones are more reactive (more electrophilic), it is **impossible to isolate** the ketone intermediate.



14.14

14.8 Reduction of Carboxylic Acid Derivatives**a) Acid Chlorides to 1° Alcohols****b) Esters to 1° Alcohols**

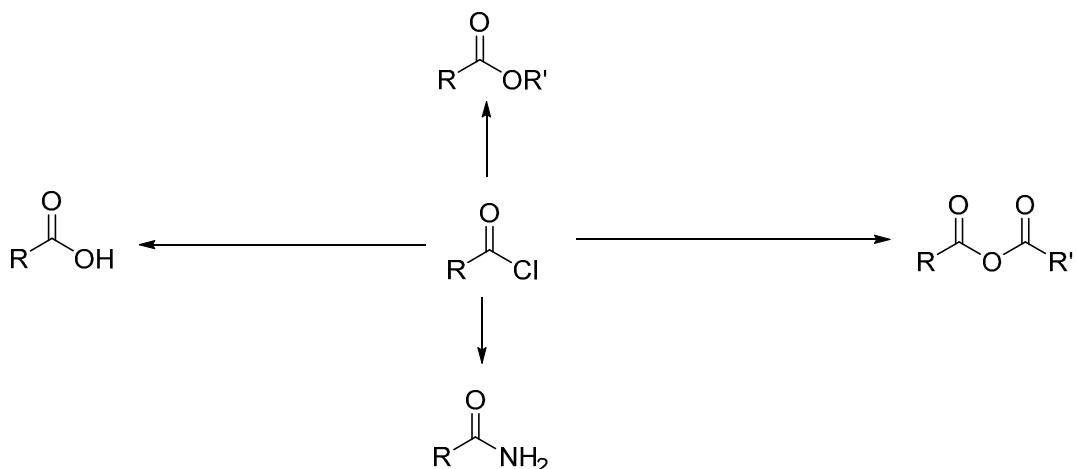
14.15

b) Amides to Amines

14.16

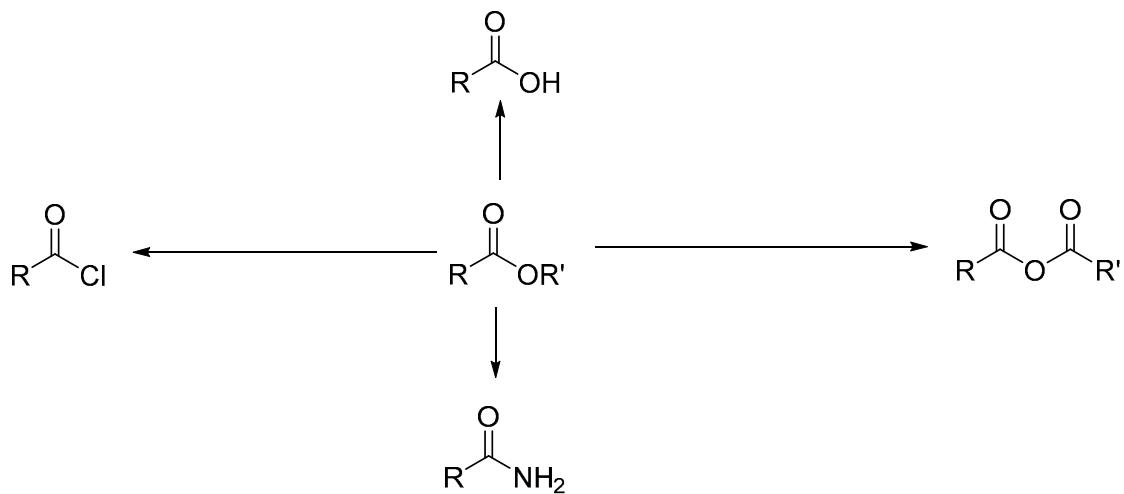
Review

Provide conditions for these transformations. More than one step may be required



14.17

Provide conditions for these transformations. More than one step may be required.

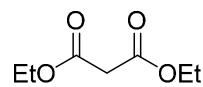
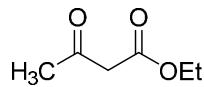
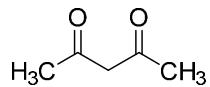
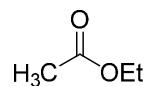
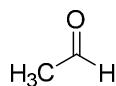
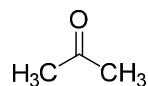


14.18

Chapter 15: Enolate Anions

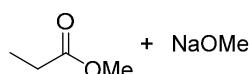
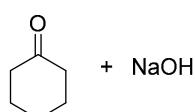
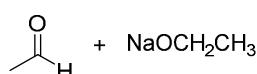
15.1 Acidity of α -Hydrogens and Enolate Formation

a) Acidity of α -Hydrogens



15.1

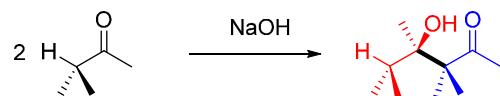
b) Formation of enolate anions



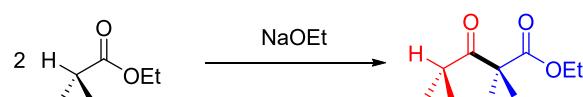
15.2

c) Use of Enolates to Form New C-C Bonds

Enolate anions can act as nucleophiles in carbonyl addition reactions (Aldol reaction).



Enolate anions can act as nucleophiles in nucleophilic acyl substitution reactions (Claisen condensation).

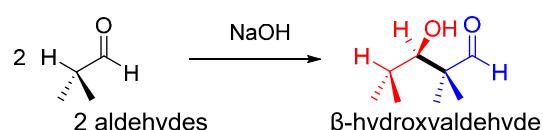
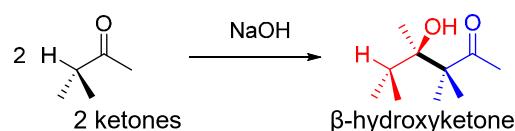


15.3

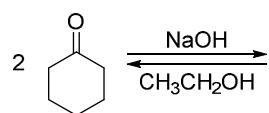
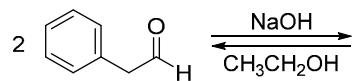
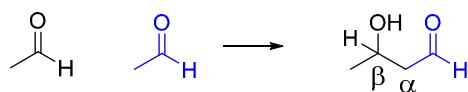
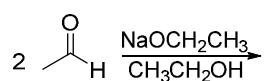
15.2 Aldol Reaction and Aldol Condensation

a) Aldol Reaction

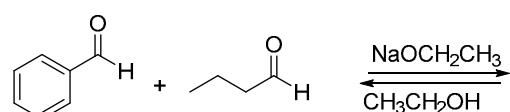
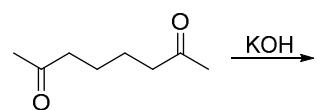
Enolate anions of aldehydes and ketones act as nucleophiles in carbonyl addition reactions.



15.4

Examples:

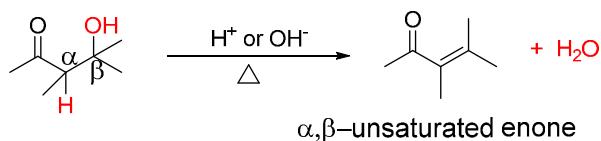
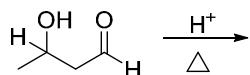
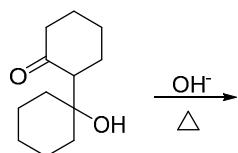
15.5

b) Crossed Aldol Reaction**c) Intramolecular Aldol Reaction**

15.6

d) Dehydration of Aldol Product (Aldol Condensation)

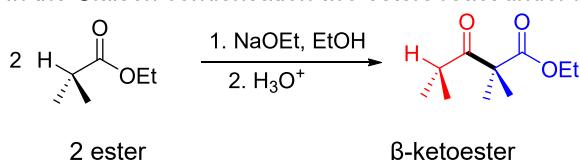
Dehydration of the aldol product is either acid or base catalyzed and generally requires heating. The result is an α,β -unsaturated carbonyl compound.

**Acid catalyzed mechanism:****Base catalyzed mechanism:**

15.7

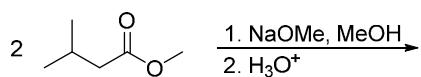
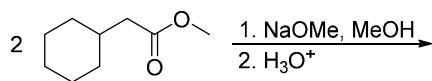
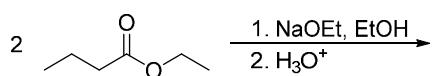
15.3 Claisen Condensation and Dieckmann Condensation**a) Claisen Self-Condensation**

In the Claisen condensation two esters react under basic conditions to form a new C-C-bond.



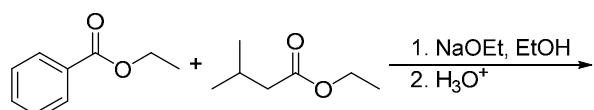
Note: Aqueous base such as NaOH cannot be used. Why not?

15.8



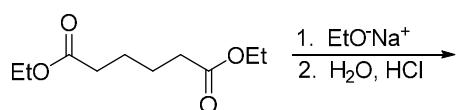
15.9

b) Crossed Claisen Condensation



c) Dieckmann Condensation

The Dieckmann Condensation is an intramolecular Claisen condensation. 5- or 6-membered rings are formed preferentially.



15.10

d) Hydrolysis and Decarboxylation of β -Ketoesters

Claisen condensation gives a β -ketoester:

Hydrolysis (Saponification) of the β -ketoester followed by acidification results in a β -ketoacid:

β -Ketoacids undergo decarboxylation upon heating:

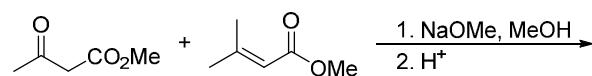
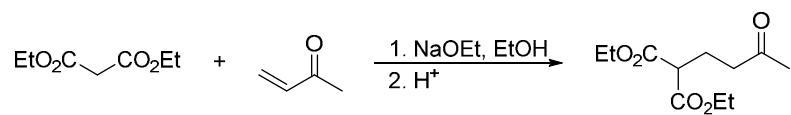
15.11

15.4 Michael Addition Reaction

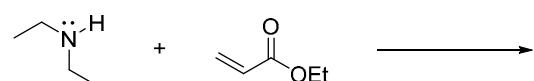
Michael addition reactions are conjugate additions to α,β -unsaturated carbonyl compounds. They are also called 1,4-additions to α,β -unsaturated carbonyl compounds.

a) 1,4-Additions versus 1,2-Additions to α,β -Unsaturated Carbonyl Compounds

15.12

b) Michael Addition (1,4-Addition) of Enolate Anions to α,β -Unsaturated Carbonyl Compounds

15.13

c) Michael Addition (1,4-Addition) of Amines to α,β -Unsaturated Carbonyl Compounds

15.14