ADVANCED PHARMACEUTECAL ANALYSIS

Quantitative Analysis

Tetracycline

Colorimetric Method

Fifth stage

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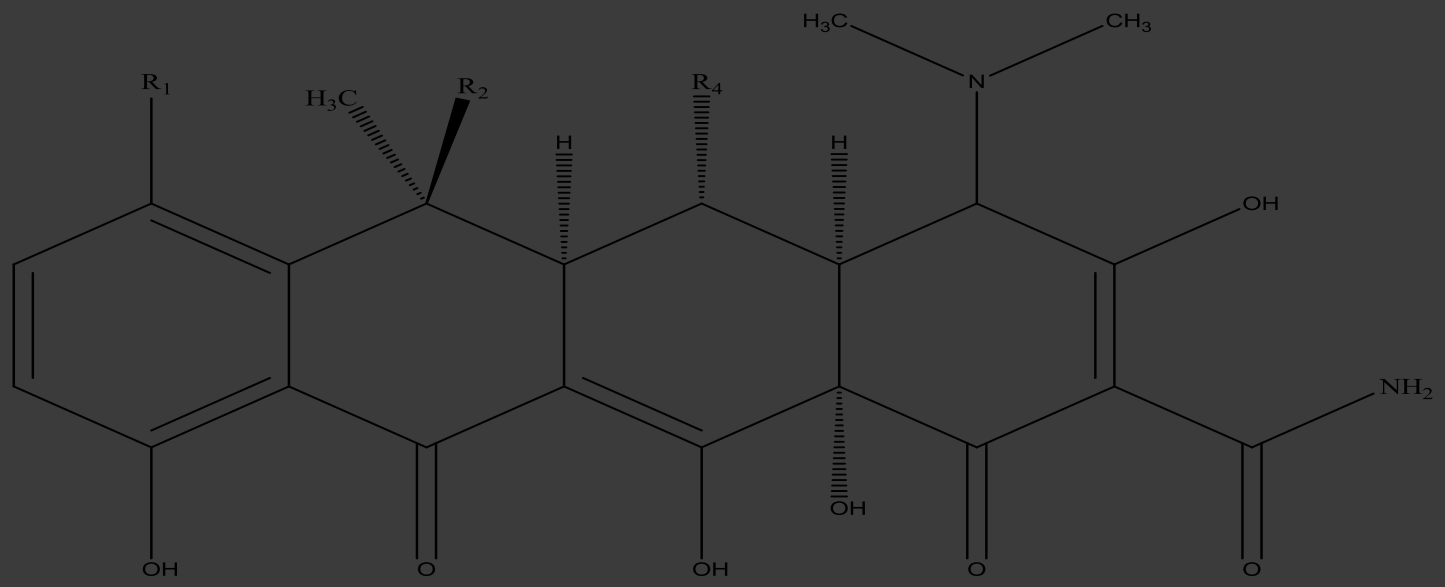
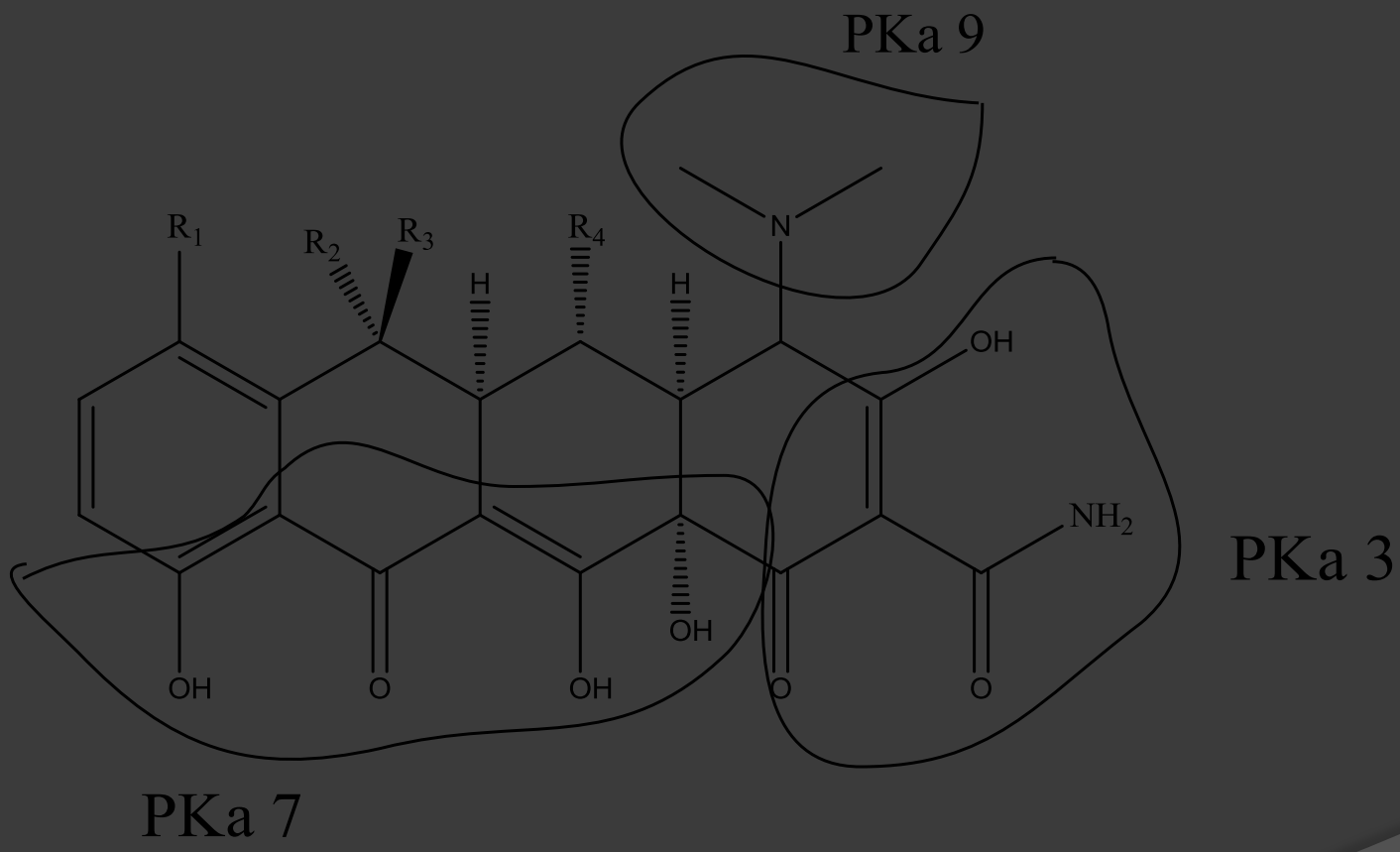
Structure of Tetracycline



Tetracyclines	R1	R2
Tetracycline	H	H
Chlortetracycline	Cl	H
Oxy*Tetracycline*	H	OH


PKa 9
R1
R2
R3
R4
H
H
N
OH
NH2
OH
O
OH
OH
O
O
PKa 3
PKa 7

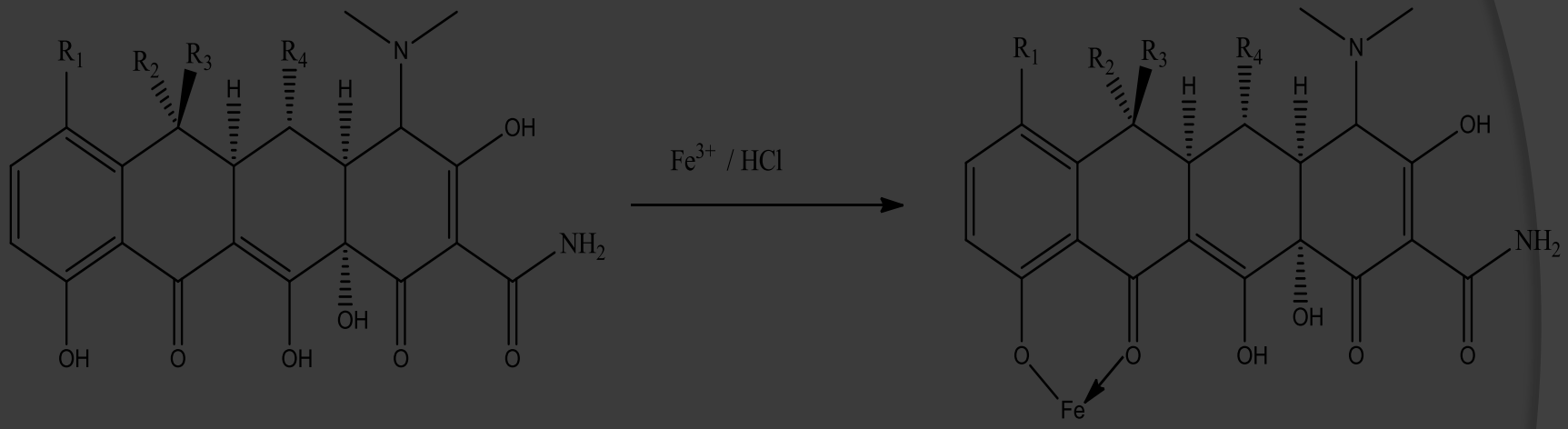
Tetracycline:

Tetracyclines form salts with acids and bases

- The hydrochloride salts are used commonly for oral administration and usually are encapsulated because they are bitter.
- Water soluble salts also are obtained from bases such as sodium and potassium salts but they are not stable in aqueous solutions.
- Divalent and polyvalent metals form insoluble salts.
- TC should not be given with antacid, milk, iron salts (at the same time),(stable chelate complexes with many metals calcium, magnesium, and iron are formed which are insoluble in water and not absorbed.
- Tetracycline shouldn't be given for children under 8 years of age due to its affinity for calcium which results in its incorporation into newly forming bones and teeth as tetracycline calcium orthophosphate complexes, these deposits in teeth cause a yellow discoloration that darkens over time (photochemical reaction)

Chemical principle of the general method;

- It depends on the reaction of tetracycline with the Ferric ion in acidic medium to form a soluble orange —brown chelate with metal ligand ratio 1:3



Tetracycline

Acidic medium is necessary to form the soluble chelate

colored chelate
(Orange_ Brown) Stable for 2 hours

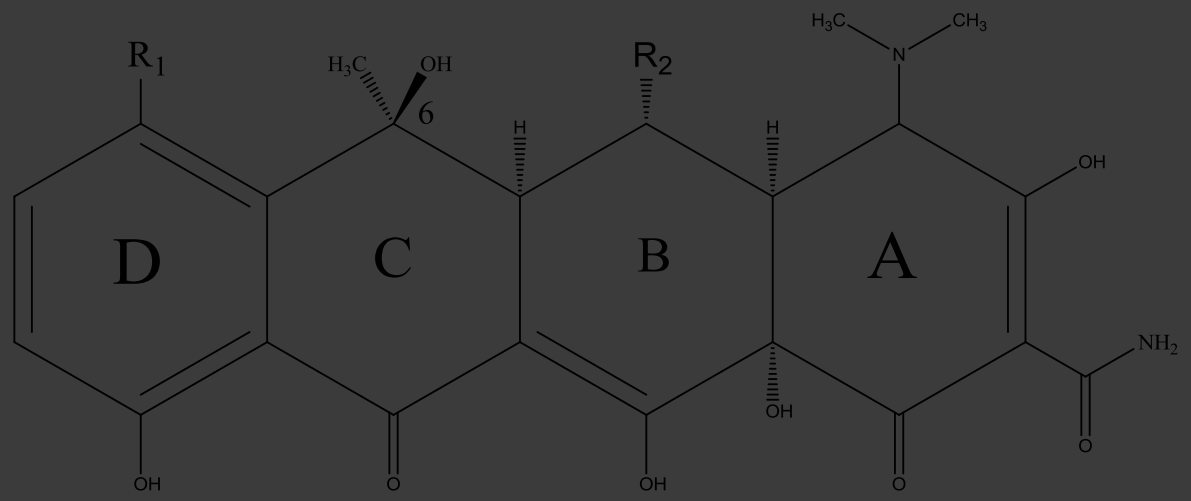
Today's Experiment:

From the stock solution 0.25 mg/ml (freshly prepared) we prepare five standard solutions as follows:

Std.	I	II	III	IV	V
Stock	2	3	4	5	6ml
0.01 N HCl	8	7	6	5	4ml
0.05% FeCl3	10	10	10	10	10 ml

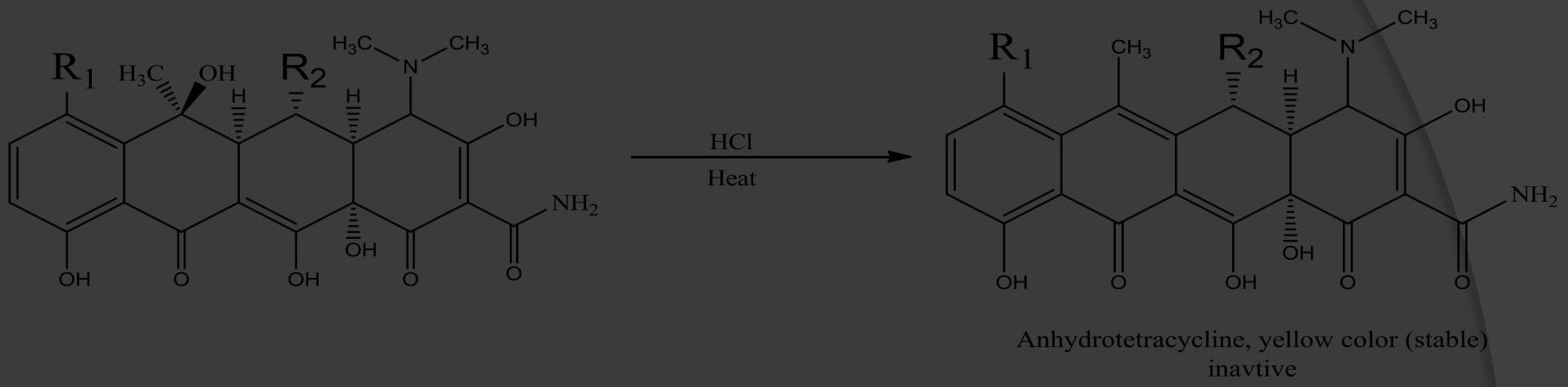
Mix and stand at room temp. for 10 minutes.
Orange- brown color appear then read at ƫ max 490 nm.
And follow the procedure and read the unknown

Acid Base Colorimetric method:



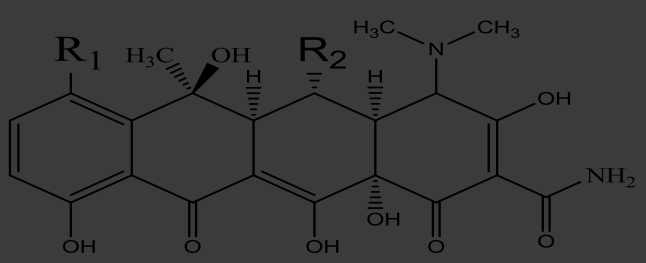
- Strong acids and strong bases attack TC with a hydroxyl group on C6 causing a loss in activity through modification of the C ring
- At pH less than 2, TC eliminate molecule of water that is lead to aromatization of ring C forming the more energetically favored resonant system of the naphthalene group found in the inactive anhydrotetracyclines.
- Bases promote a reaction between the 6-OH group and Ketone group at the 11 and 11a atoms to cleave forming the lactone ring in the inactive isotetracycline.

Acid Colorimetric Method:

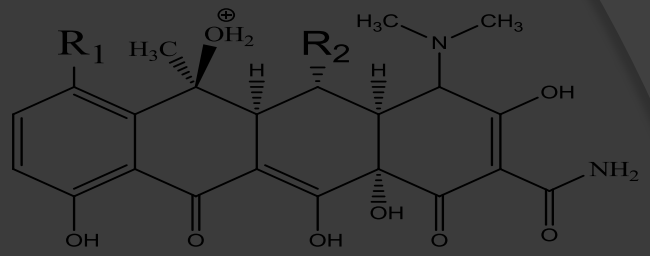


* This method is used for both tetracycline and chlotetracycline since when heated with HCI acid develop a stable yellow color while oxytetracycline doesn't give this reaction and it's solution remains colorless.
*In this method a blank is needed for each standard solution and for each a Known.
* TC in presence of HCI (without heating) give pale yellow color and in order to cancel the effect of this from the std. that contain the anhydrotetracycline we use a blank for each.
* Anhydrotetracycline differs from TC in both molecular and structural formula and inactive as antibacterial.

Mechanism of Acid Colorimetric :



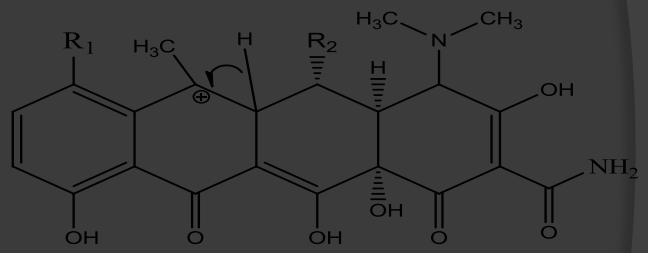
HCl
Heat



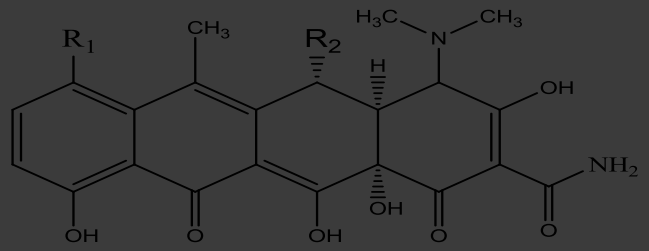
The hydroxyl group is bad leaving group but in presence of proton leads to

Formation of oxonium ion

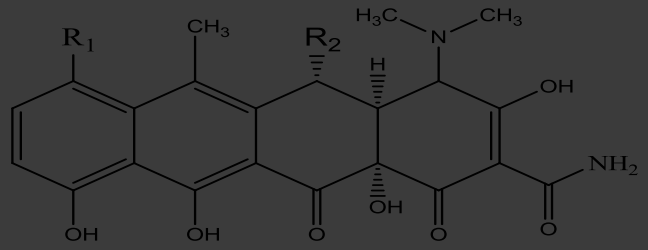
$- H_2O$



Carbocation



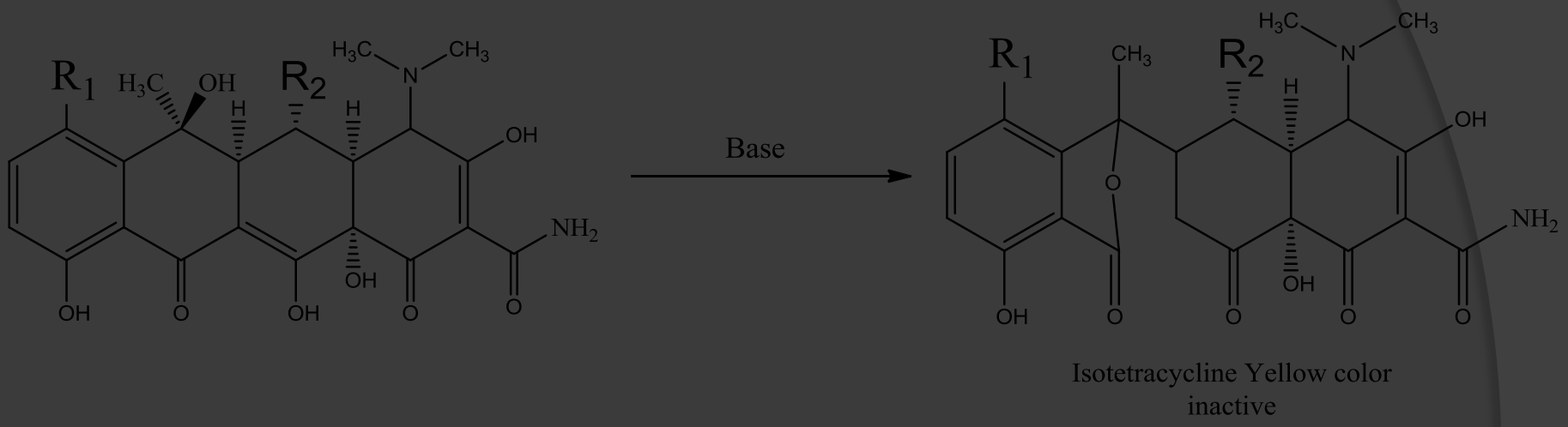
Tautomerism



An hydrotetracycline, Deep yellow color (stable)

Assist L: Abdulkareem Hamad

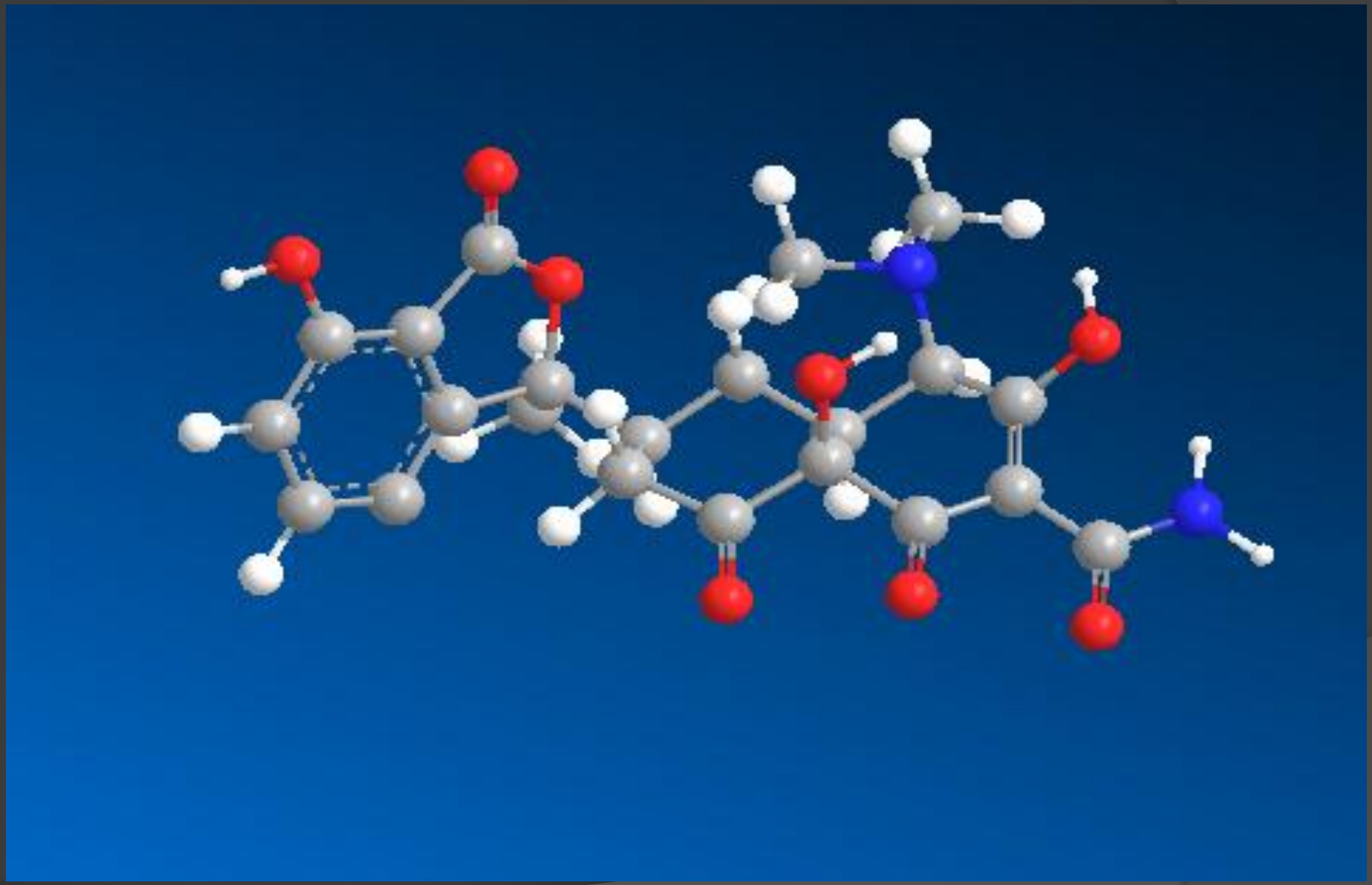
Base Colorimetric Method:
Chemical Principle:



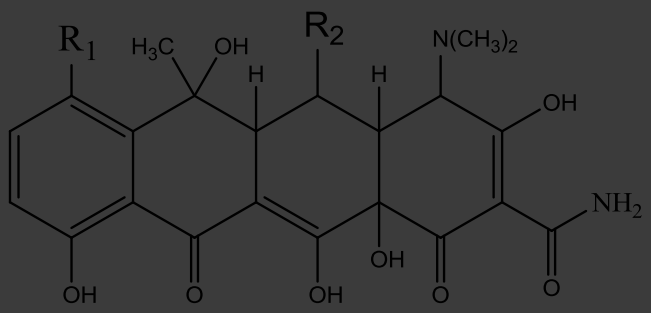
Isotetracycline Yellow color inactive

- This method used for tetracycline and oxytetracycline since the addition of alkali to their solutions produces a yellow color having an absorption maximum at 380 nm. While chlorotetracycline gives a yellow color that rapidly disappears and gives practically no absorption at 380 nm.
- The disadvantage of the method: reading of absorbance should be within exactly 6 minutes after the addition of alkali because there is a slow but definite decrease in absorbance with time(intensity of color decreases with time)
- Isotetracycline has the same molecular formula as TC but different structural formula and it is inactive.

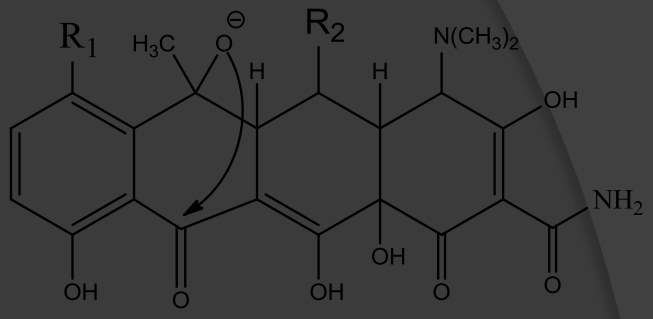
3D of TC in Base Colorimetric Method:



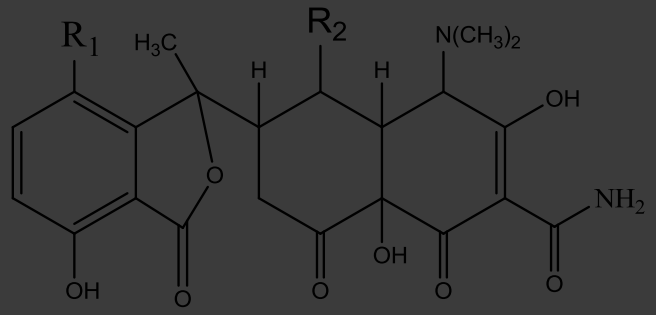
Mechanism of Base method:



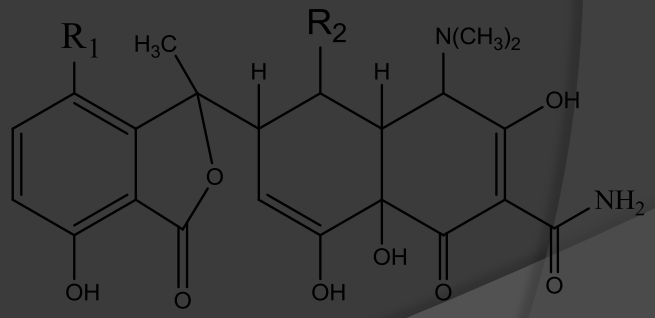
Strong Base



1- Formation of alkoxide anion (strong) (unstable)
2- Attack of the carbonyl groub and cleavage of 11-11a bond



Toutomerism



Isotetracycline
yellow color with absorption maximum at 380 nm
inactive as antibacterial

Formation of Lactone ring
(cyclic ester)

Procedure of acid method:

From the stock solution 1mg/ml (freshly prepared) we prepare five standard solutions as follows:

Standard

	I	II	III	IV	V
Stock	0.5	0.7	1	1.3	1.5 ml
D.W.	1.5	1.3	1	0.7	0.5 ml
HCl	5	5	5	5	5 ml
D.W.	-	-	-	-	-

Blank

	I	II	III	IV	V
Stock	0.5	0.7	1	1.3	1.5 ml
D.W.	1.5	1.3	1	0.7	0.5 ml
HCl	-	-	-	-	-
D.W.	5	5	5	5	5 ml

Heat in water bath for 5 min. then cool,

HCl : - - - - -
: 5 5 5 5 5 ml

Complete the volume to 50 ml with D.W. and read A at ɧ max 440 nm

Procedure for Unknown:

Unknown	***Unknown Blank***
2 ml	***2 ml***
5 ml HCl	***5 ml D.W.***
Heat in water bath for 5 minutes then cool	
-	***5 ml HCl***

Complete the volume to 50 ml with D.W. amd read at ɧ max 440 nm

Report :

- Name: Assay of tetracycline or chlortetracycline by acid colorimetric method
- Aim: Determination of unknown concentration
- No. of unk.
- No. of instrument
- Results:
- Table of std. A, C
- Mathematical details CiV1=C2V2 •
  Unk. A, C
- Plot (in details)

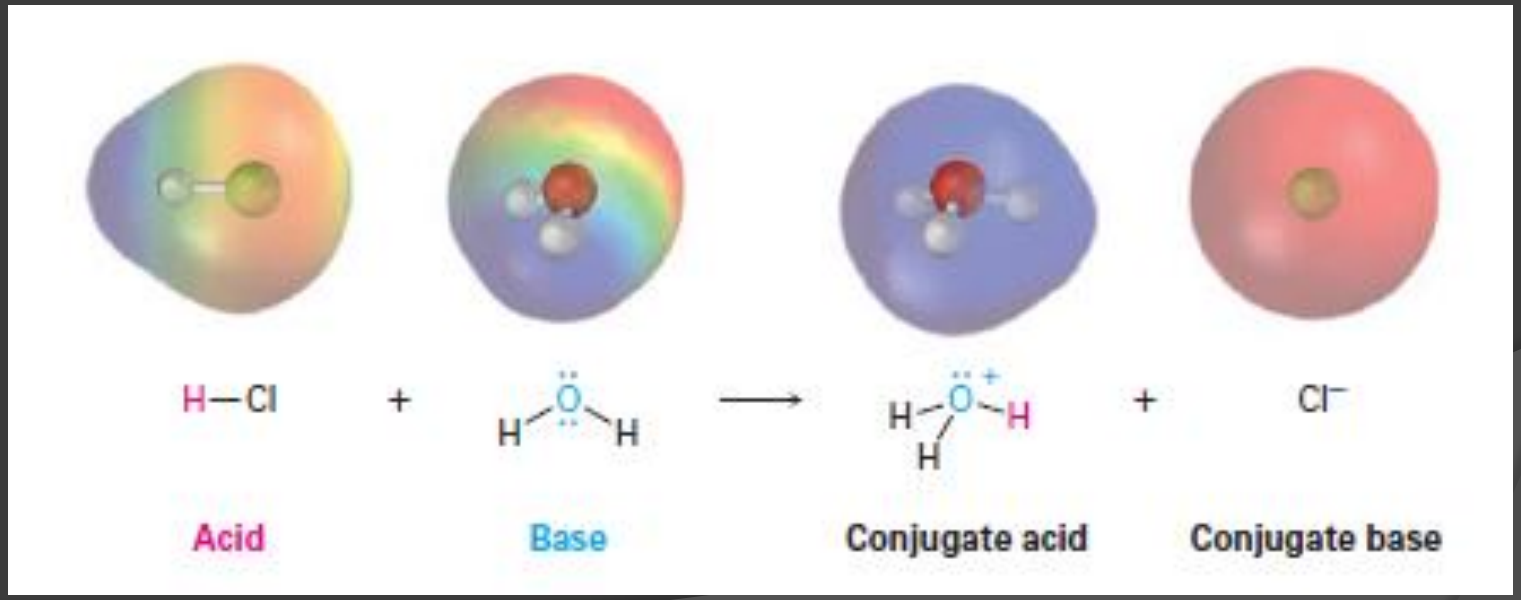
Determination of % Purity:

$$\text{Practical} / \text{Theoretical} \times 100\%$$

Acid-Base Theory

Broensted-Lowry definition

A *Broensted-Lowry acid* is a substance that donates a H^+, and a *base* accepts a H^+. When HCl gas dissolves in water, HCl donates a proton and a water molecule accepts it, yielding hydroxonium ion (H_3O^+) and Cl^-. Cl^-, the product that results when the acid loses a H^+, is called the *conjugate base of the acid*, and H_3O^+ is called the *conjugate acid of the base*.



Stronger acids react almost completely with water, whereas weaker acids react only slightly. The exact strength of a given acid in water can be expressed by its *acidity constant*, K_a.

$$HA + H_2O \rightleftharpoons A^- + H_3O^+$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Acid strengths are normally given using pK_a values. A stronger acid (larger K_a) has a smaller pK_a, and a weaker acid (smaller K_a) has a larger pK_a.

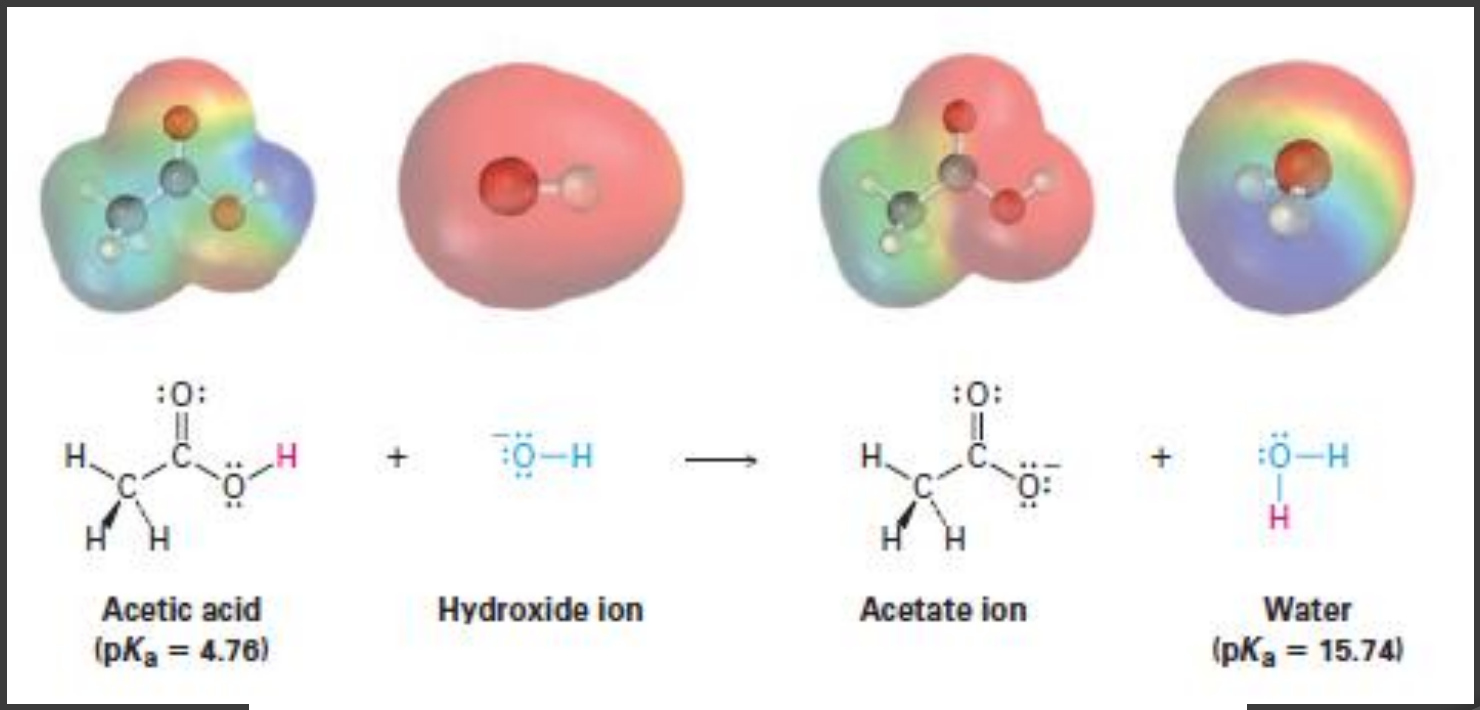
$$pK_a = -\log K_a$$

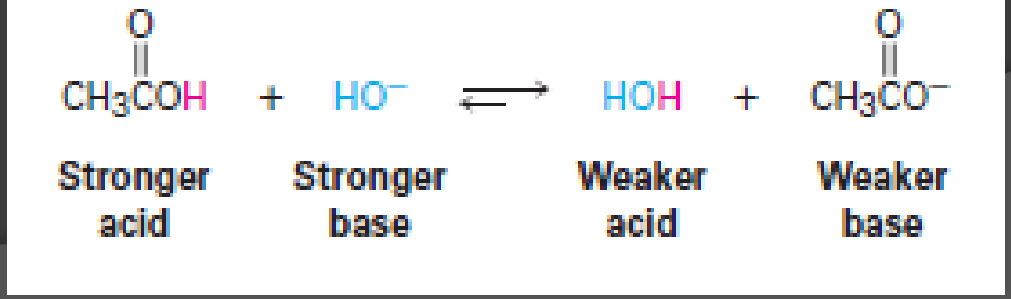
A strong acid yields a weak conjugate base, and a weak acid yields a strong conjugate base. In general, a proton always goes from the stronger acid to the stronger base, meaning that an acid donates a proton to the conjugate base of any acid that is weaker.

Table 1.2 Relative Strengths of Some Common Acids and Their Conjugate Bases

	Acid	Name	pK_a	Conjugate base	Name	
Weaker acid	CH_3CH_2OH	Ethanol	16.00	$CH_3CH_2O^-$	Ethoxide ion	Stronger base
	H_2O	Water	15.74	HO^-	Hydroxide ion	
	HCN	Hydrocyanic acid	9.31	CN^-	Cyanide ion	
	$H_2PO_4^-$	Dihydrogen phosphate ion	7.21	HPO_4^{2-}	Hydrogen phosphate ion	
	CH_3CO_2H	Acetic acid	4.76	$CH_3CO_2^-$	Acetate ion	
	H_3PO_4	Phosphoric acid	2.16	$H_2PO_4^-$	Dihydrogen phosphate ion	
	HNO_3	Nitric acid	−1.3	NO_3^-	Nitrate ion	
Stronger acid	HCl	Hydrochloric acid	−7.0	Cl^-	Chloride ion	Weaker base

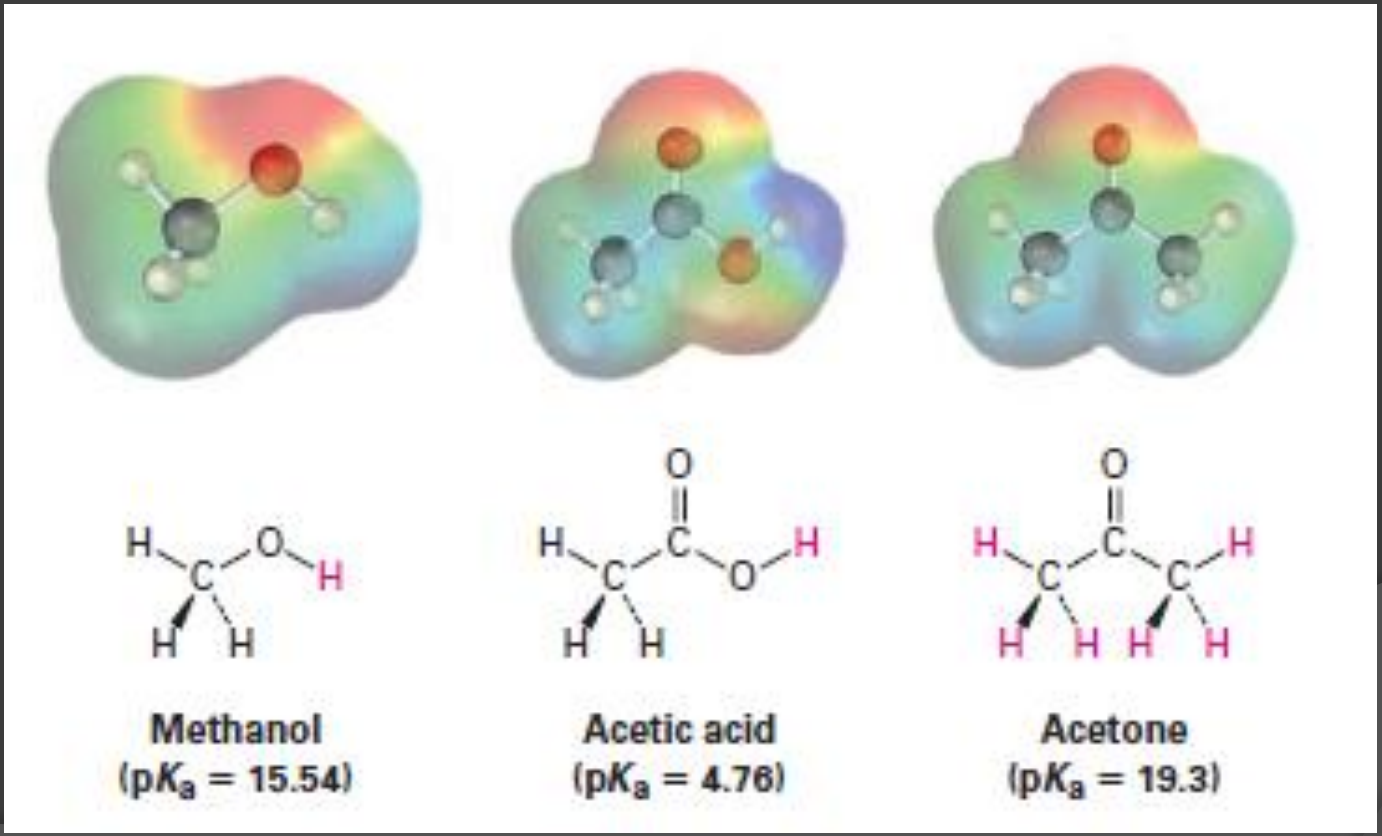
For example, the data in table above indicate that HO^- reacts with CH_3COOH to yield the acetate ion and H_2O. Because water (pK_a=15.74) is a weaker acid than acetic acid (pK_a=4.76), the HO^- holds a proton more tightly than acetate ion does. The product acid and base must be weaker and less reactive than the starting acid and base.



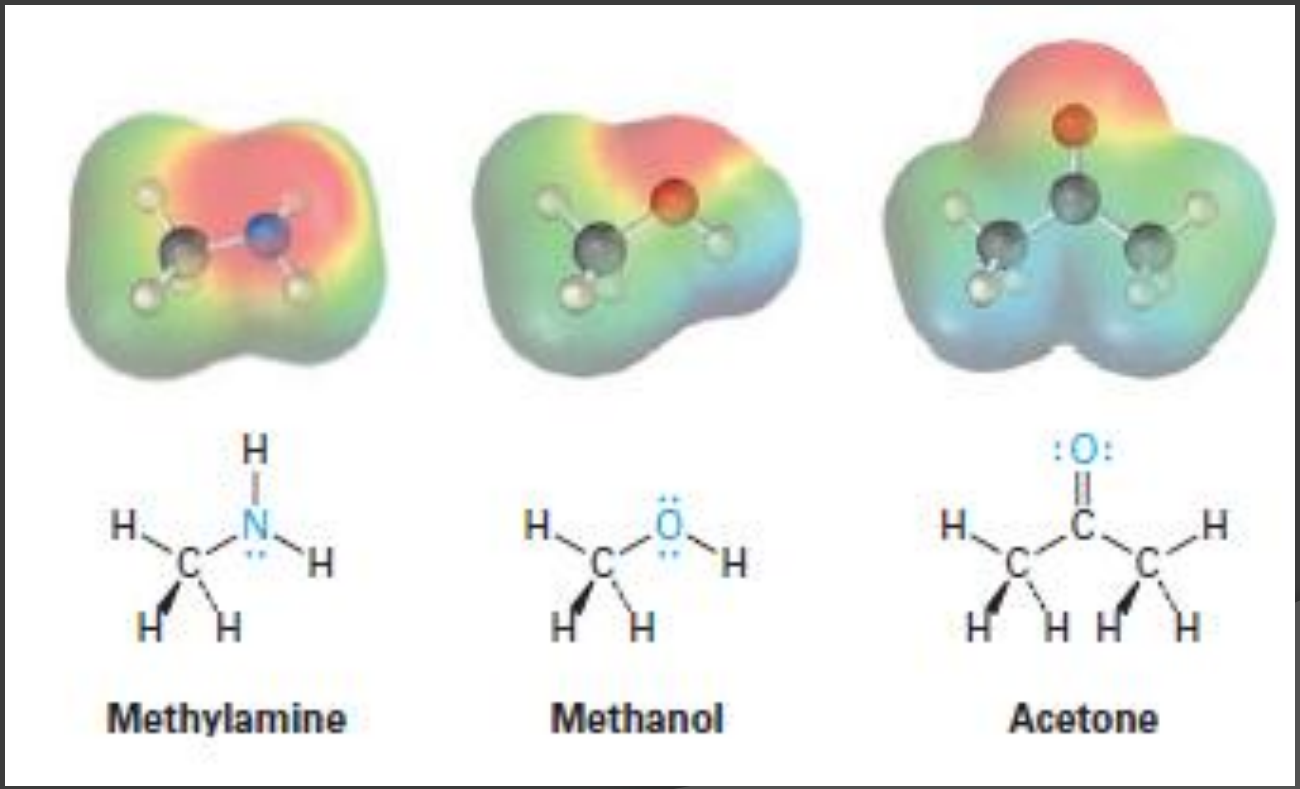


Many of the reactions, including essentially biological reactions, involve *organic acids* and *organic bases*.

Organic acids are of two main kinds: those acids (methanol, acetic acid) that contain a hydrogen atom *bonded to an electronegative oxygen atom* (O-H) and those (acetone) that contain a hydrogen atom *bonded to a carbon atom next to a C=O double bond*.



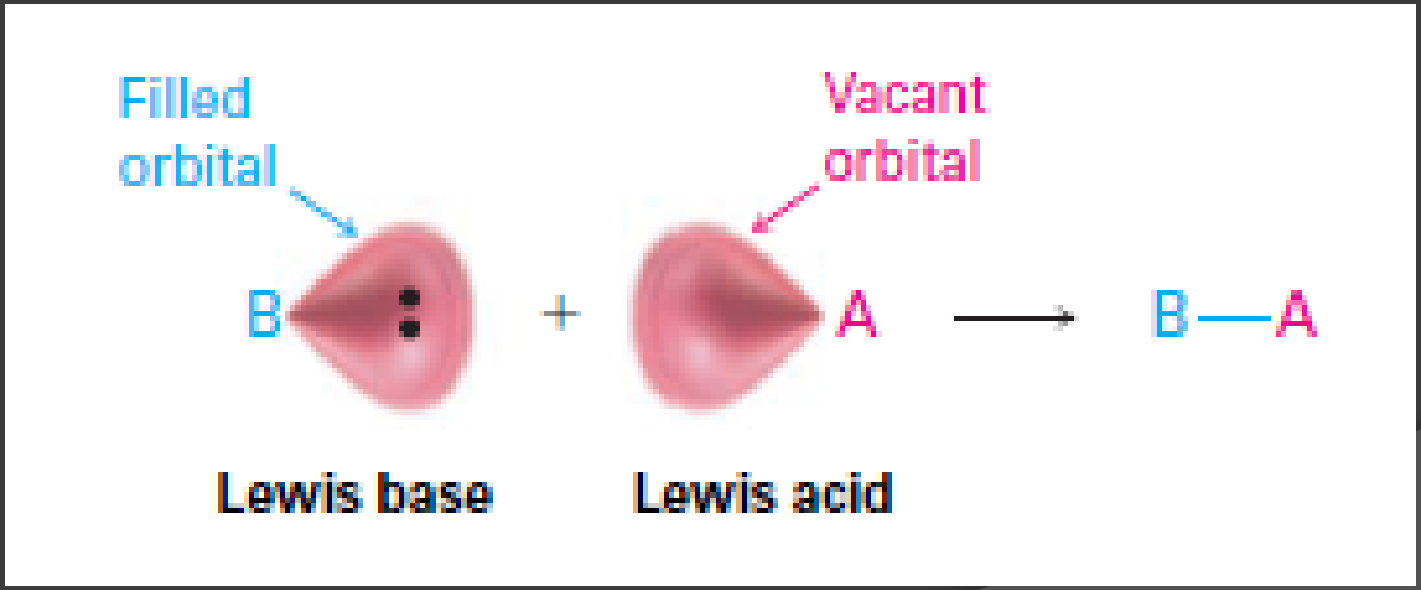
Organic bases are characterized by the presence of an atom with a lone pair of electrons that can bond to H^+. Nitrogen containing compounds are the most common organic bases, but oxygen containing compounds can also act as bases when reacting with sufficiently strong acid. Some oxygen containing compounds can act as both acids and bases depending on the circumstances.



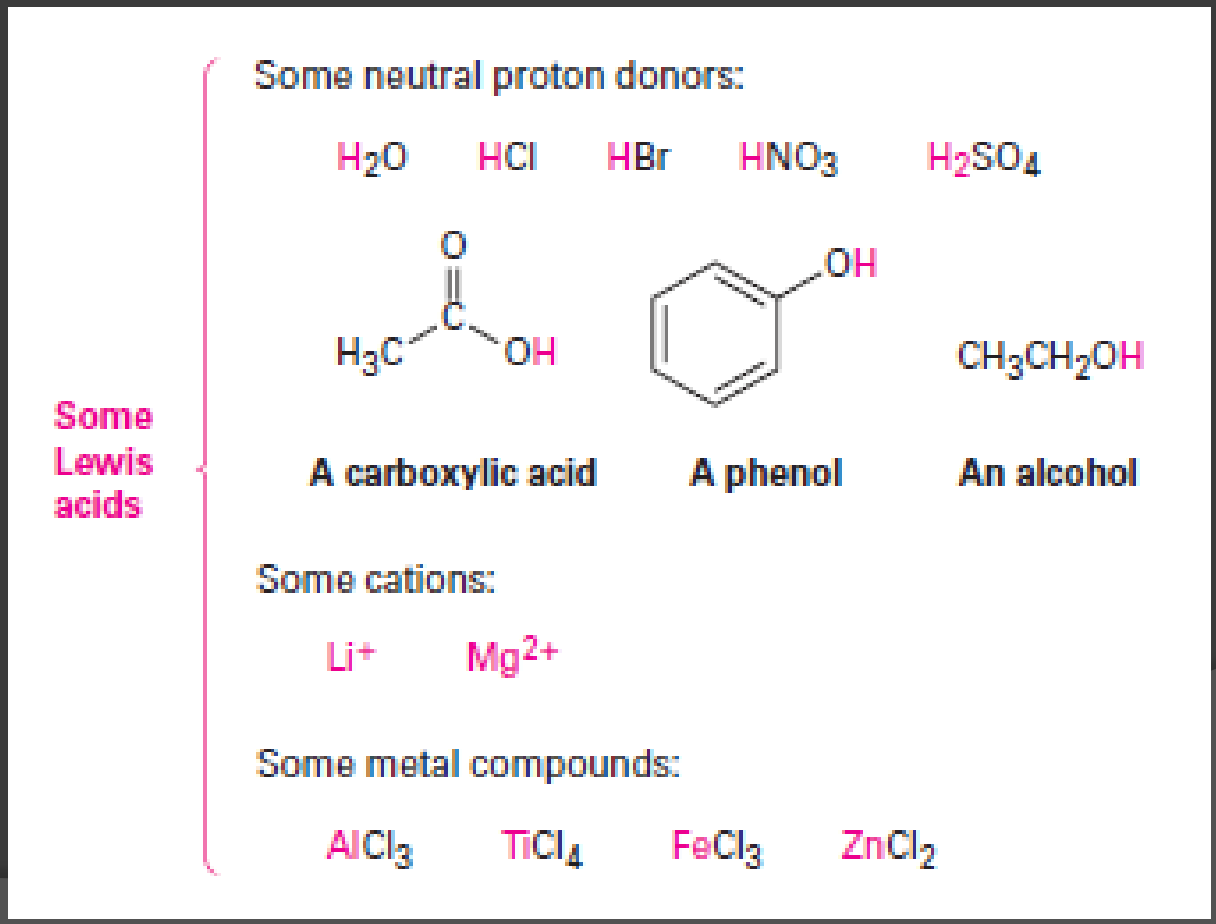
Lewis definition

The Lewis definition of acids and bases is broader and more encompassing than the Broensted-Lowry definition, because it is not limited to substances that donate or accept protons.

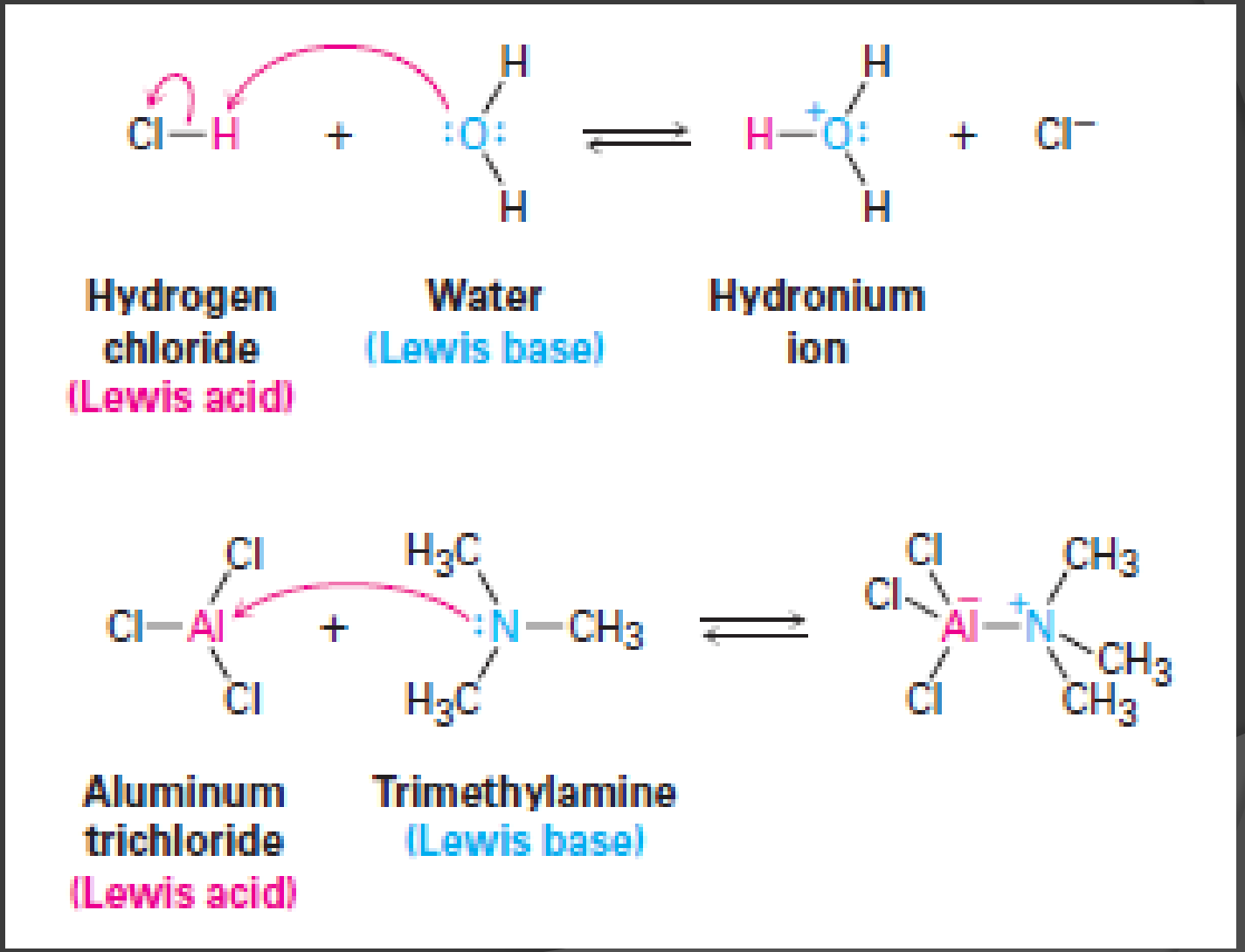
A **Lewis acid** *accepts an electron pair* and a **Lewis base** *donates an electron pair*. The donated electron pair is shared between the acid and the base in a covalent bond.



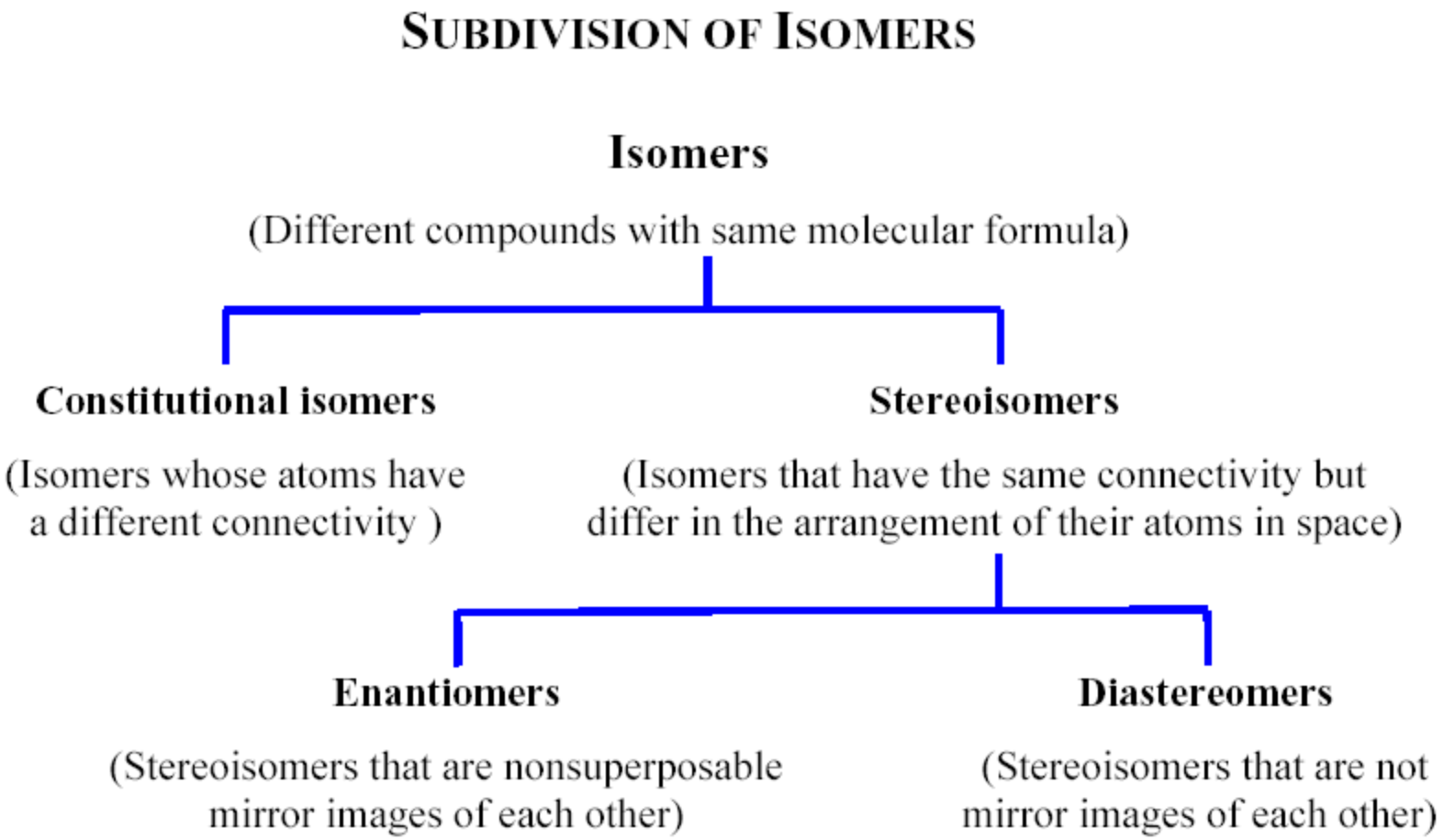
A Lewis acid must have either a vacant, low-energy orbital or a polar bond to hydrogen so that it can donate H^+. Thus, the Lewis acid definition of acidity includes many species in addition to H^+. For example, various metal cations (Mg^{2+}), metal compounds ($AlCl_3$) are Lewis acids because they have unfilled valence orbitals and can accept electron pairs from Lewis bases.



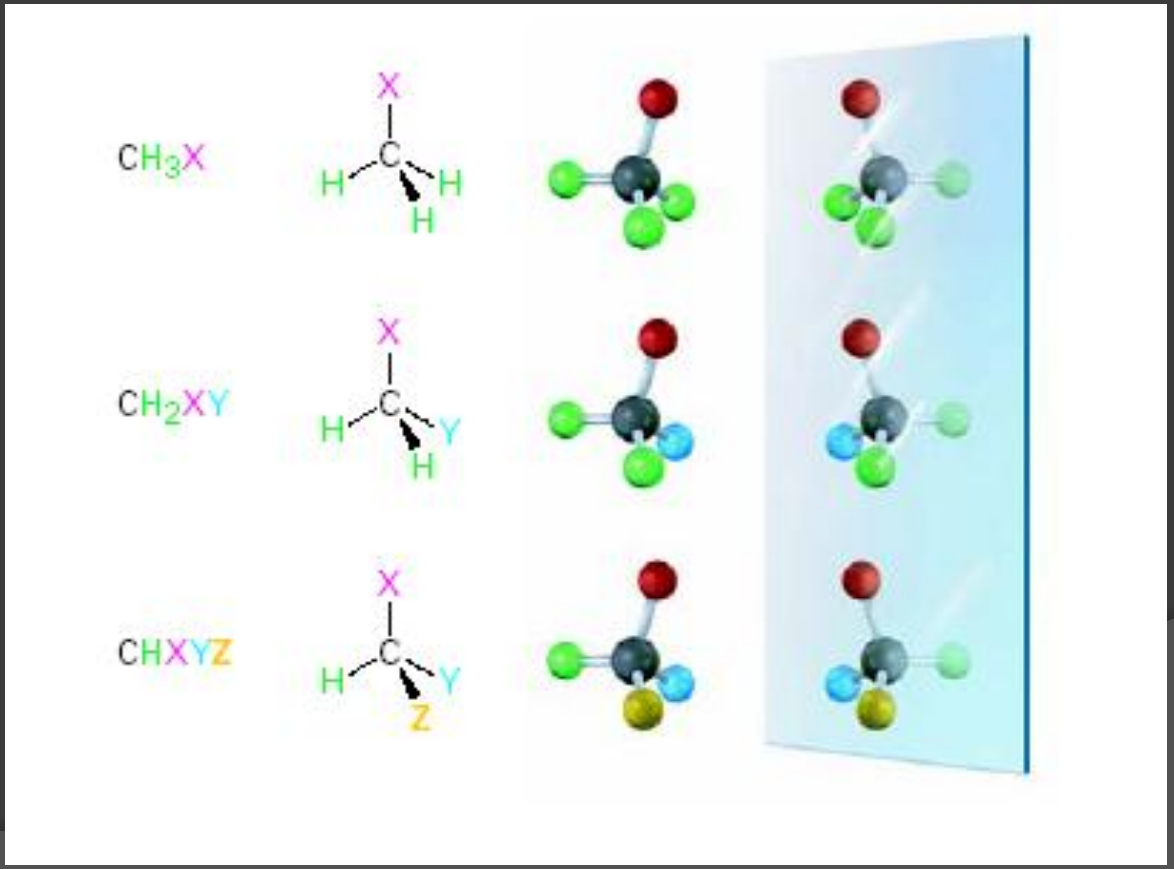
Lewis acid and Lewis base reactions



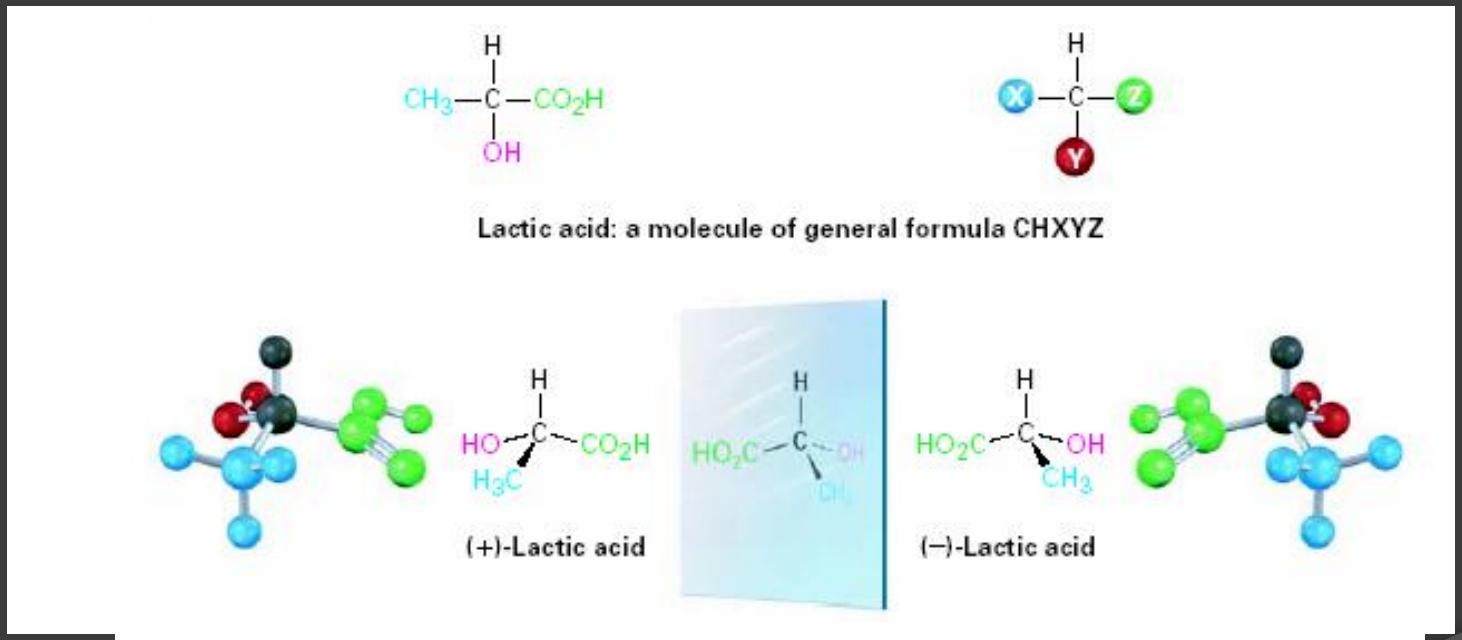
Isomerism

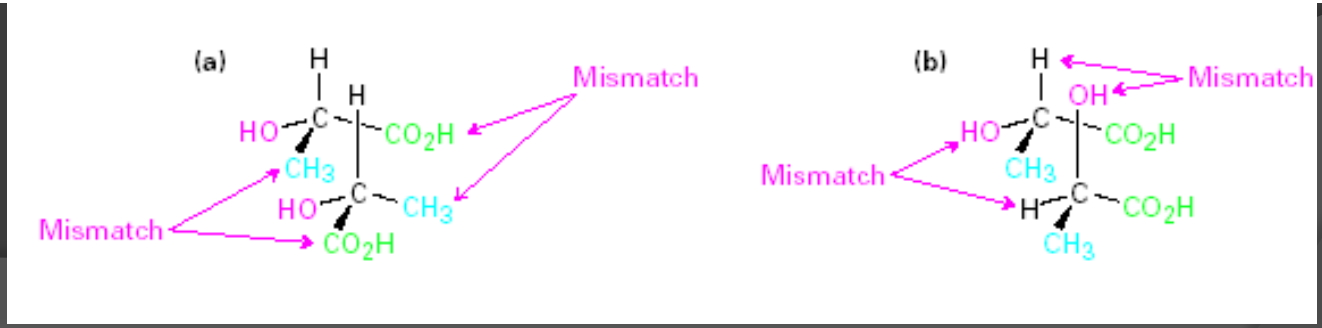

SUBDIVISION OF ISOMERS
Isomers
(Different compounds with same molecular formula)
Constitutional isomers
(Isomers whose atoms have a different connectivity)
Stereoisomers
(Isomers that have the same connectivity but differ in the arrangement of their atoms in space)
Enantiomers
(Stereoisomers that are nonsuperposable mirror images of each other)
Diastereomers
(Stereoisomers that are not mirror images of each other)

What causes *molecular handedness*? To see how *molecular handedness arises*, look at generalized molecules of the type CH_3X, CH_2XY, and CHXYZ. On the left are three molecules, and on the right are their images reflected in a mirror. The CH_3X and CH_2XY molecules are *identical to their mirror images and thus are not handed*. A molecular model of each molecule and its mirror image can be superimposed one on the other. The CHXYZ molecule, by contrast, *is not identical to its mirror image*. You can't superimpose a model of the molecule on a model of its mirror image for the same reason that you can't superimpose a left hand on a right hand: they simply aren't the same.



Molecules that are not identical to their mirror images are kinds of stereoisomers called **enantiomers** (Greek *enantio*, meaning "opposite"). Enantiomers are related to each other as a right hand is related to a left hand and result whenever a *tetrahedral carbon is bonded to four different substituents* (one need not be H). For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups (H, OH, CH_3, and CO_2H) bonded to the central carbon atom. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.

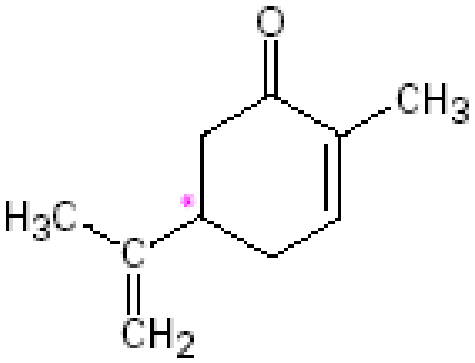




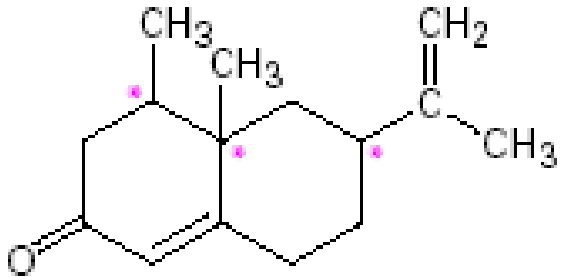
A molecule that is not identical to its mirror image is said to be **chiral** (**ky**-ral, from the Greek *cheir*, meaning "hand"). You can't take a chiral molecule and its enantiomer and place one on the other so that all atoms coincide.

How can you predict whether a given molecule is or is not chiral? By far the most common (although not the only) cause of chirality in an organic molecule is the presence of a carbon atom bonded to four different groups – for example, the central carbon atom in lactic acid. Such carbons are referred to as *stereocenters (and indicated with asterisk)*, or **chirality centers**. Note that *chirality* is a *property* of the entire molecule, whereas a chirality *center* is the *cause* of chirality.

You might note that carbons in CH_2 , CH_3, C=O, C=C, and C≡C groups *can't* be chirality centers.



Carvone (spearmint oil)



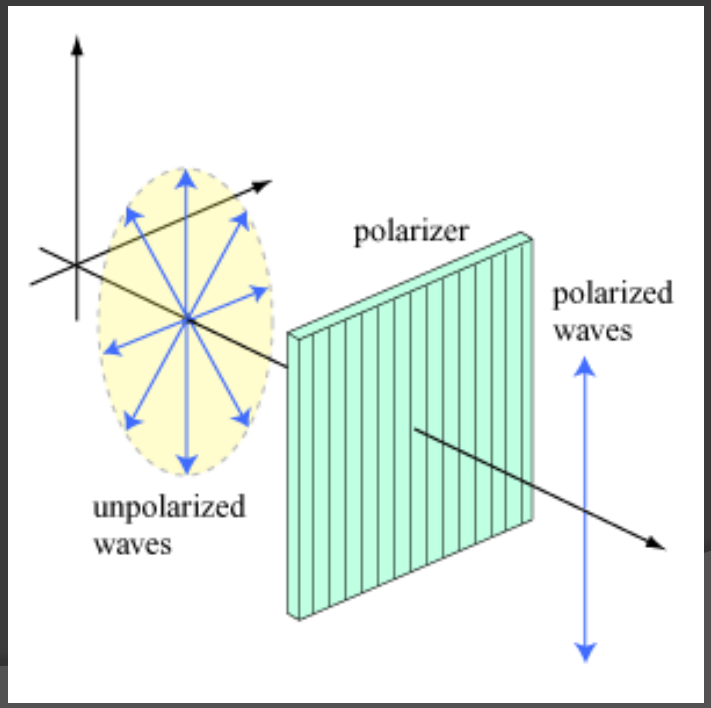
Nootkatone (grapefruit oil)

Optical activity

A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a beam of ordinary light is passed through a device called a *polarizer*, however, only the light waves oscillating in a single plane pass through and the light is said to be *plane-polarized*. Light waves in all other planes are blocked out.

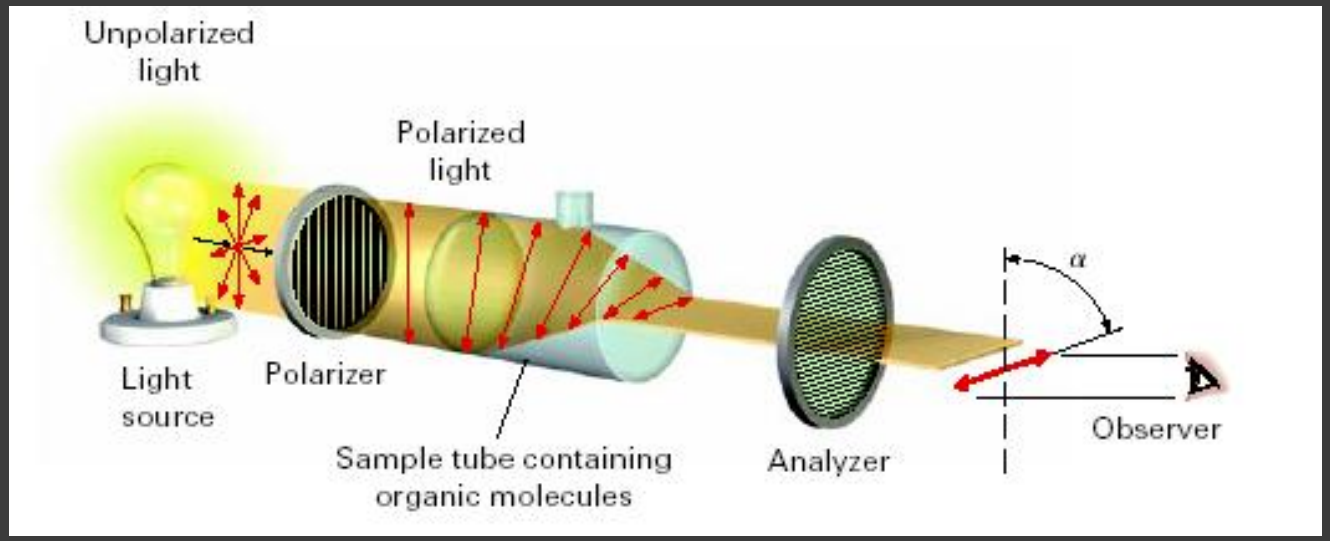
Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is *rotated* through an angle. Not all organic substances exhibit this property, but those that do are said to be **optically active**.

Oscillation of the electrical field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.



The plane of oscillation of the electrical field of plane-polarized light. In this example the plane of polarization is vertical.

The angle of rotation can be measured with an instrument called a *polarimeter.* A solution of optically active organic molecules is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the polarization plane occurs. The light then goes through a second polarizer called the *analyzer.* By rotating the analyzer until the light passes through it, we can find the new plane of polarization and can tell to what extent rotation has occurred.



To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The **specific rotation, $[\alpha]^D$,** of a compound is defined as the observed rotation when light of 589.6 nm (1 nm= 10^{-9} m) wavelength is used with a sample path length *l* of 1 decimeter (dm; 1 dm= 10 cm) and a sample concentration *c* of 1 g/cm^3.

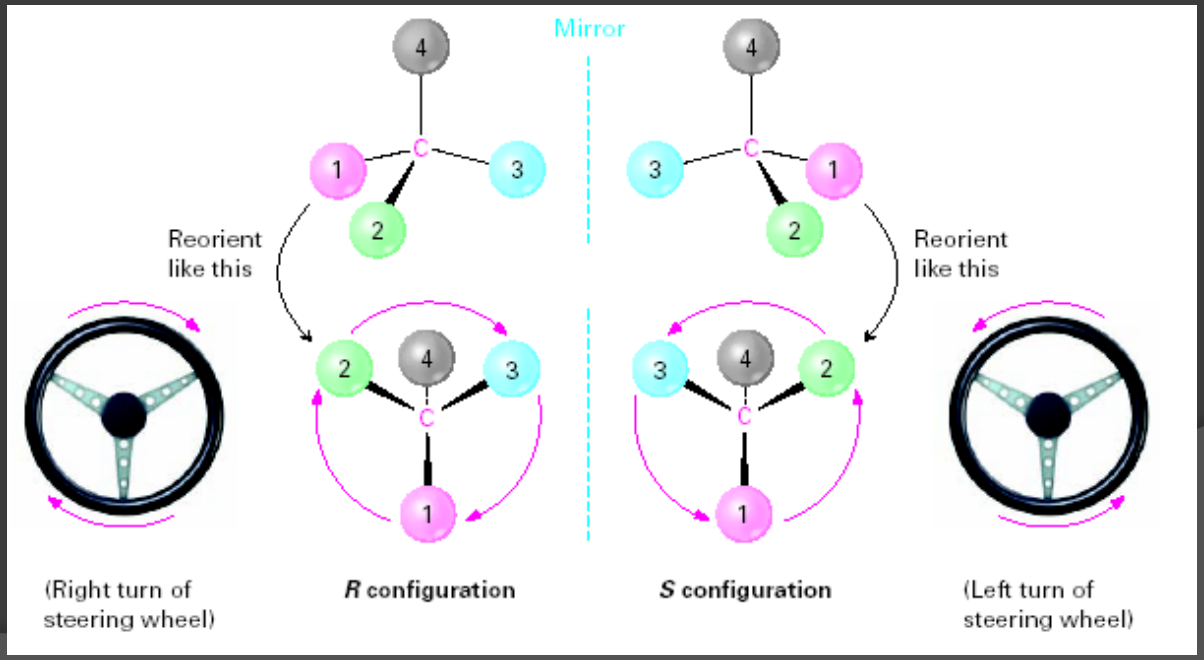
$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{ Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

Absolute and relative configuration

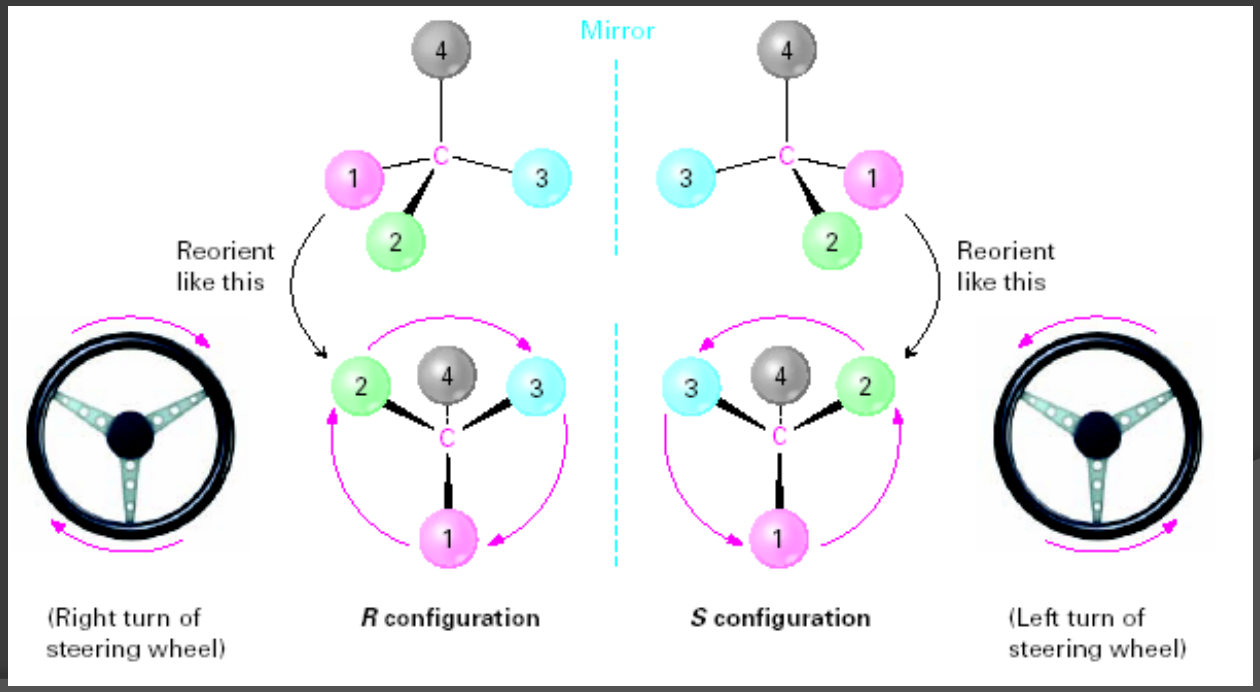
RULE 1: Look at the four atoms directly attached to the chirality center, and rank them according to atomic number. The atom with the highest atomic number has the highest ranking (first), and the atom with the lowest atomic number (usually hydrogen) has the lowest ranking (fourth).

RULE 2: If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found.

RULE 3: Multiple-bonded atoms are equivalent to the same number of single bonded atoms.

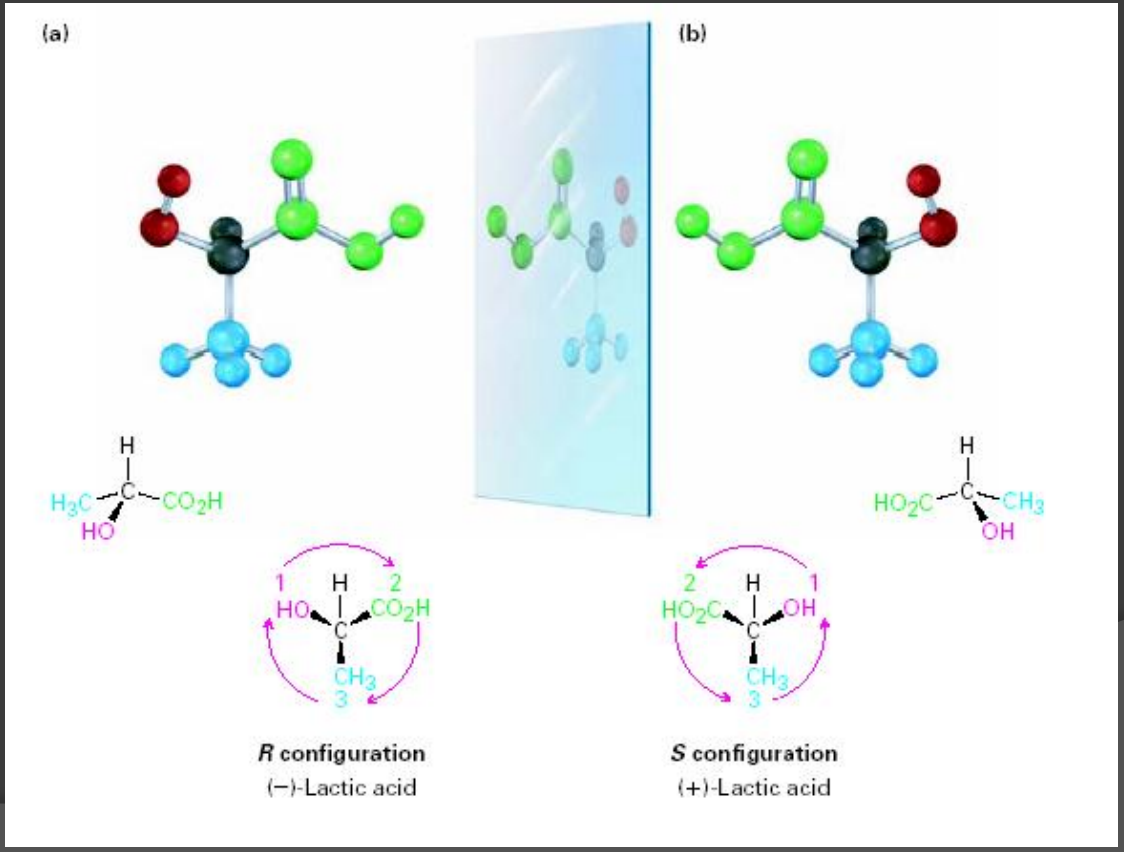


Having ranked the four groups attached to a chirality center, we describe the ***stereochemical configuration*** around the carbon by orienting the molecule so that the group with the lowest ranking (**4**) points directly back, away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel. If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent (**1** → **2**→ **3**) is clockwise, we say that the chirality center has the ***R* configuration** (Latin *rectus,* meaning "right"). If an arrow from **1** → **2** → **3** is counterclockwise, the chirality center has the ***S* configuration** (Latin *sinister,* meaning "left"). To remember these assignments, think of a car's steering wheel when making a ***R***ight (clockwise) turn.



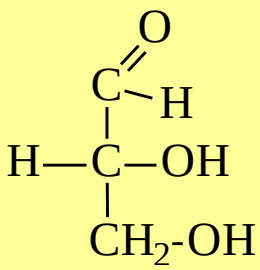
(-)-Lactic acid for example:

Sequence rule 1 says that OH is ranked **1** and H is ranked **4**, but it doesn't allow us to distinguish between CH_3 and CO_2H because both groups have carbon as their first atom. *Sequence rule 2*, however, says that CO_2H ranks higher than CH_3 because O (the highest second atom in CO_2H) outranks H (the highest second atom in CH_3). Now, turn the molecule so that the fourth-ranked group (H) is oriented toward the rear, away from the observer. Since a curved arrow from **1** (OH) to **2** (CO_2H) to **3** (CH_3) is clockwise (right turn of the steering wheel), (-)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.

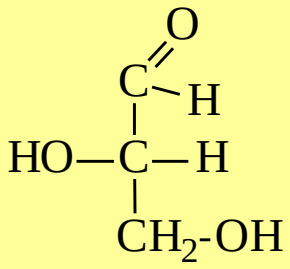


Relative configurations

Before 1951 only *relative configurations* of chiral molecules were known.
All configurations were related to a single compound that
had been chosen to be a standard – *glyceraldehyde*.
Chemists (Emil Fischer) decided arbitrarily to assign the D-configuration to the (+)-enantiomer.

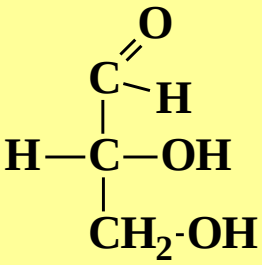


D-(+)-glyceraldehyde

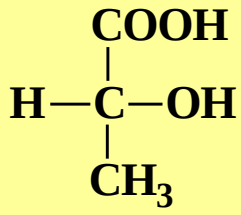


L-(-)-glyceraldehyde

Configurations of chiral molecules were related to one glyceraldehyde enantiomer or the other through reactions of known stereochemistry.



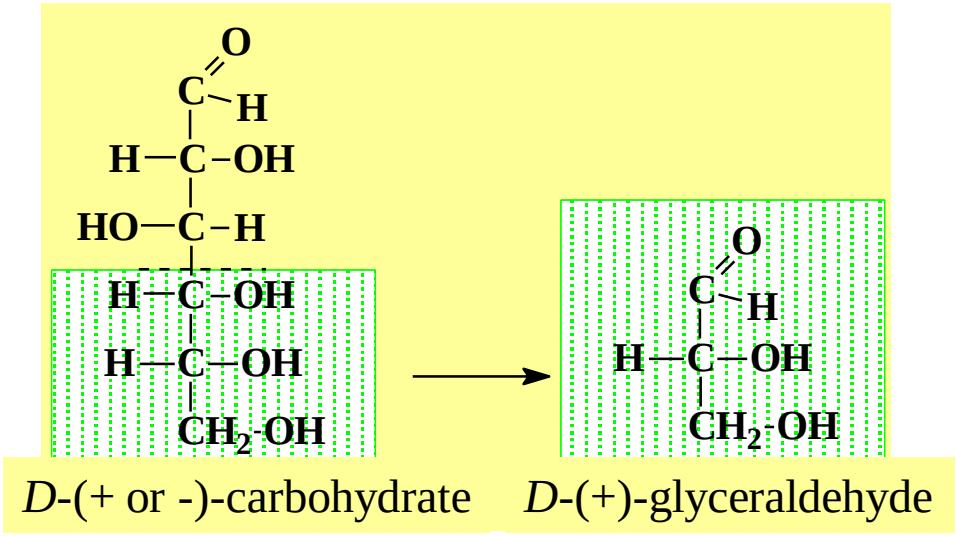
D-(+)-glyceraldehyde



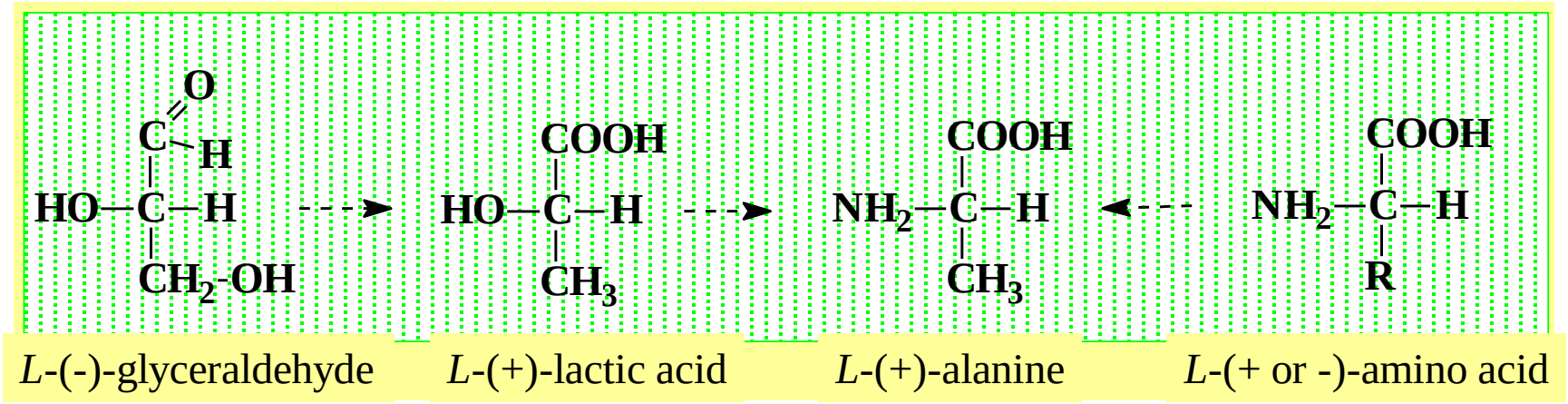
D-(-)-lactic acid

D- and L-system of nomenclature is still widely used in biochemistry.
The configuration of natural carbohydrates can be related to D(+)-glyceraldehyde, therefore they have also D-configuration with (+) or (-) rotation of plane-polarized light.

Important: No obvious correlation exists between the configuration of enantiomers and the direction in which they rotate plane-polarized light.



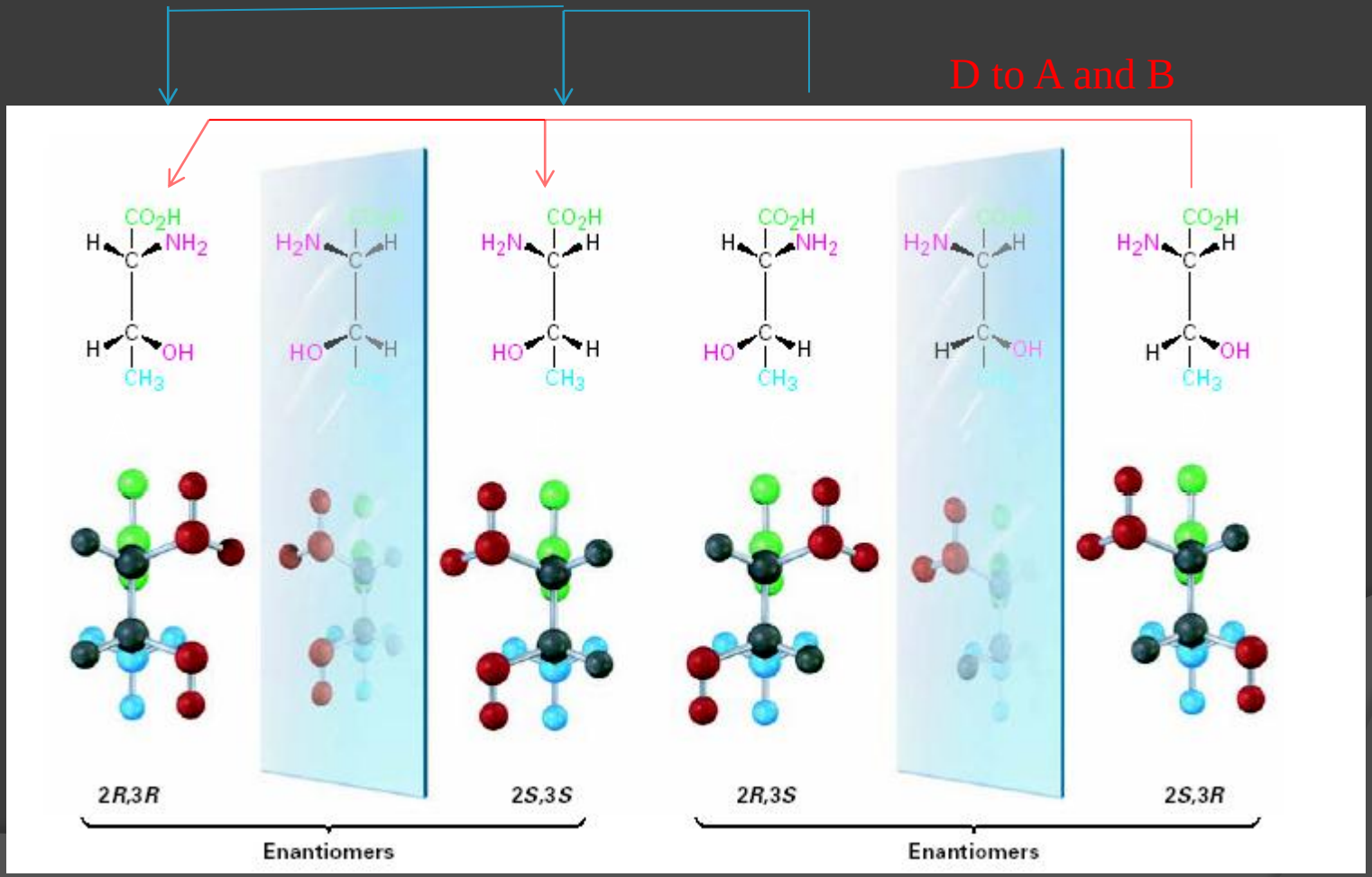
The natural amino acids have L-configuration, they correlate with L(+)-alanine:



Diastereomers

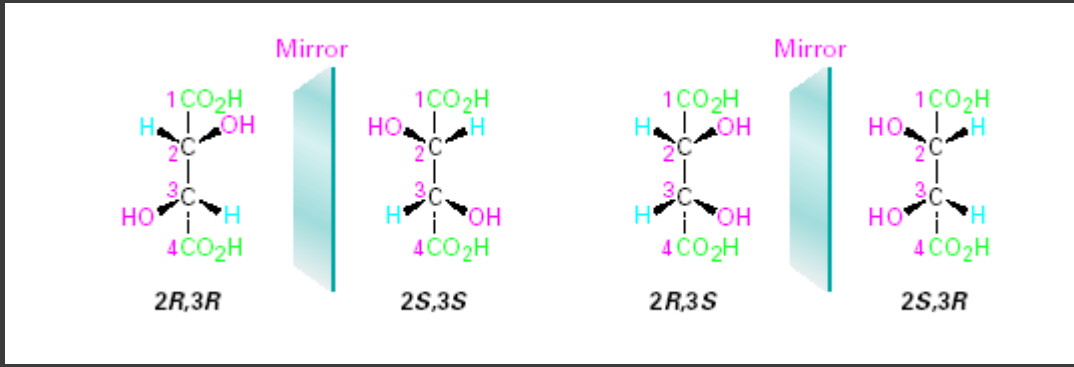
Diastereomers are stereoisomers that are *not mirror images of each other*. The difference between enantiomers and diastereomers: enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others.

Diastereomer relationship: C to A and B

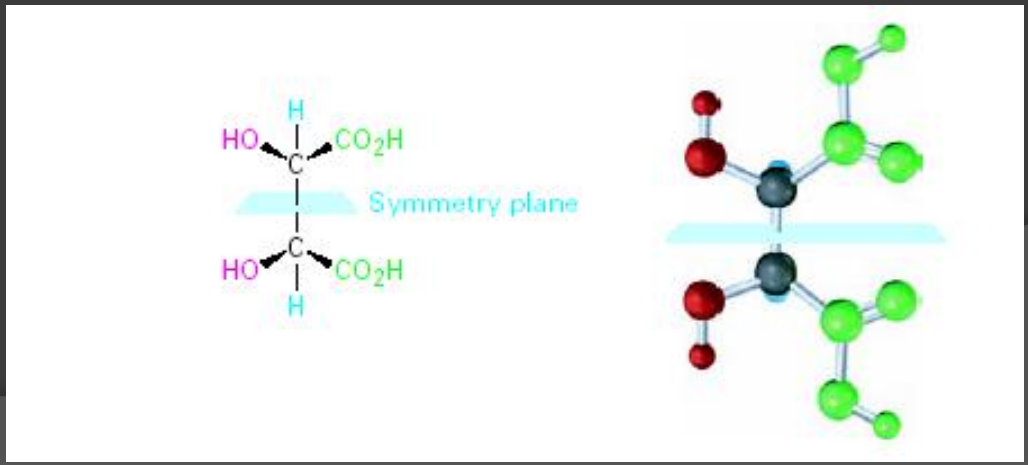


Meso compounds

The mirror-image 2*R*,3*R* and 2*S*,3*S* structures are not identical and therefore represent an *enantiomeric pair*. A careful look, however, shows that the 2*R*,3*S* and 2*S*,3*R* structures *are identical*, as can be seen by rotating one structure 180°.



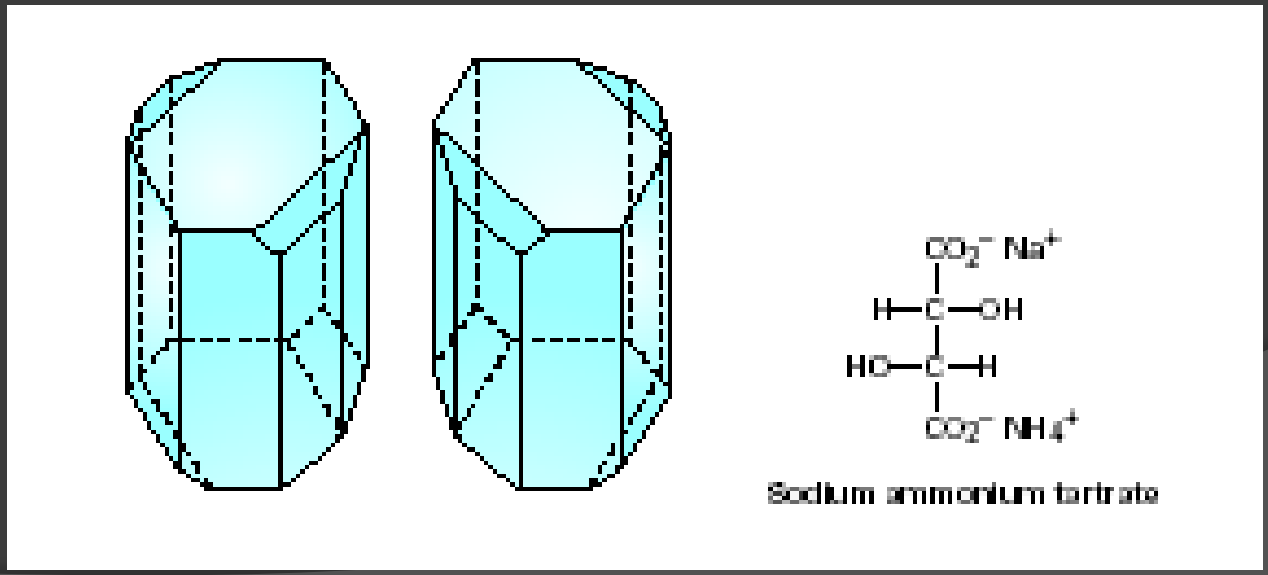
The 2*R*,3*S* and 2*S*,3*R* structures are identical because the molecule has a ***plane of symmetry*** and is therefore achiral. The symmetry plane cuts through the C2-C3 bond, making one half of the molecule a mirror image of the other half. Because of the plane of symmetry, the tartaric acid stereoisomer shown in figure below is achiral, despite the fact that it has two chirality centers. Such compounds that are achiral, yet contain chirality centers, are called **meso** compounds.



Racemates and resolution

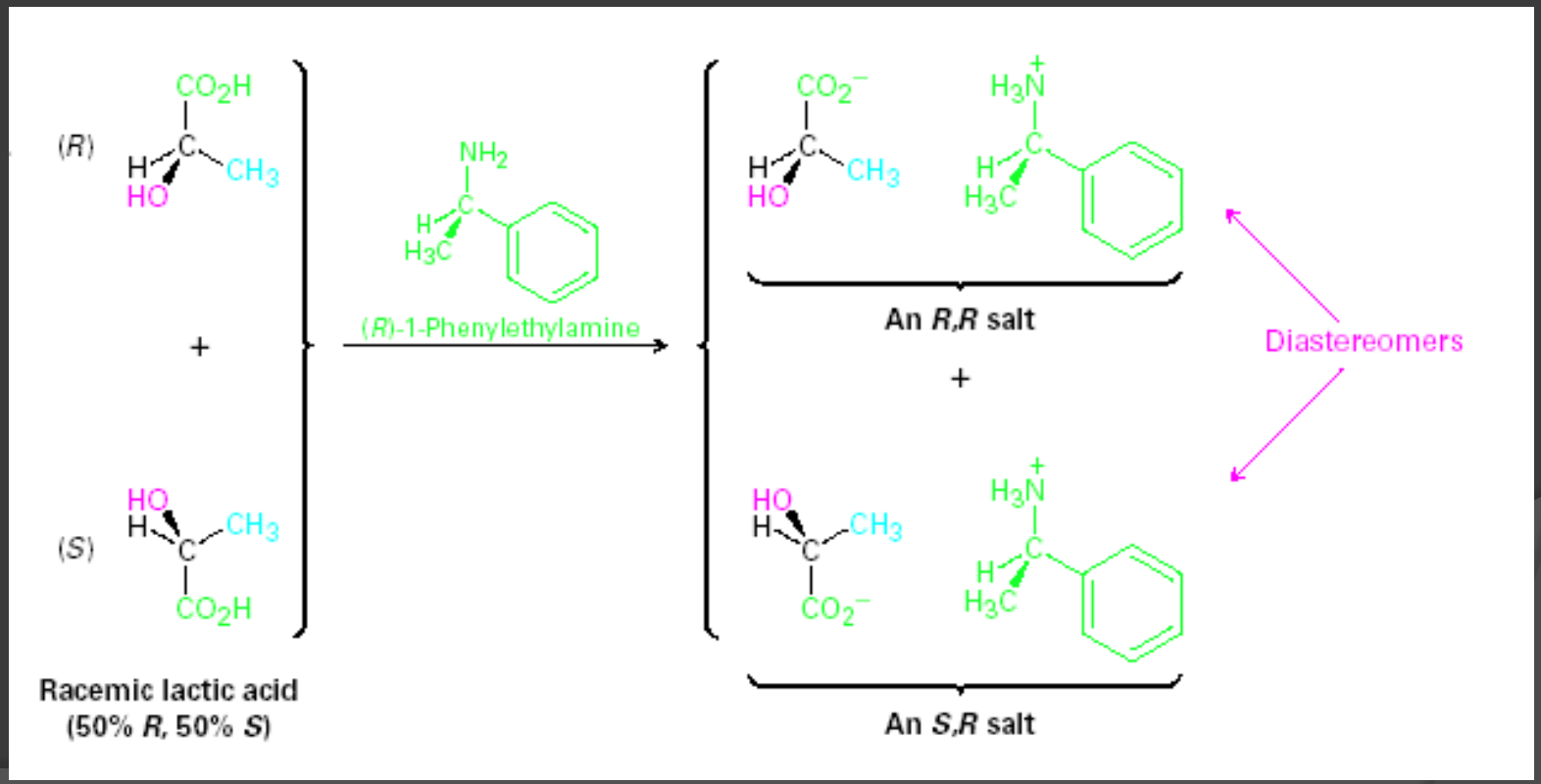
Pasteur started with a 50: 50 *mixture* of the two chiral tartaric acid enantiomers. Such a mixture is called a *racemic mixture*, or **racemate** (**ra**-suh-mate). Racemic mixtures are often denoted by the symbol (±) or by the prefix *d,l* to indicate that they contain *equal amounts of dextrorotatory and levorotatory enantiomers*. Such mixtures show no optical activity because the (+) rotation from one enantiomer exactly cancels the (-) rotation from the other. Through good luck, Pasteur was able to separate, or **resolve**, the racemate into its (+) and (-) enantiomers. Unfortunately, the crystallization technique he used doesn't work for most racemic mixtures, so other methods are required.

The most common method of resolution uses an acid-base reaction between a racemic mixture of chiral carboxylic acid (RCO_2H) and an amine base (RNH_2) to yield an ammonium salt.



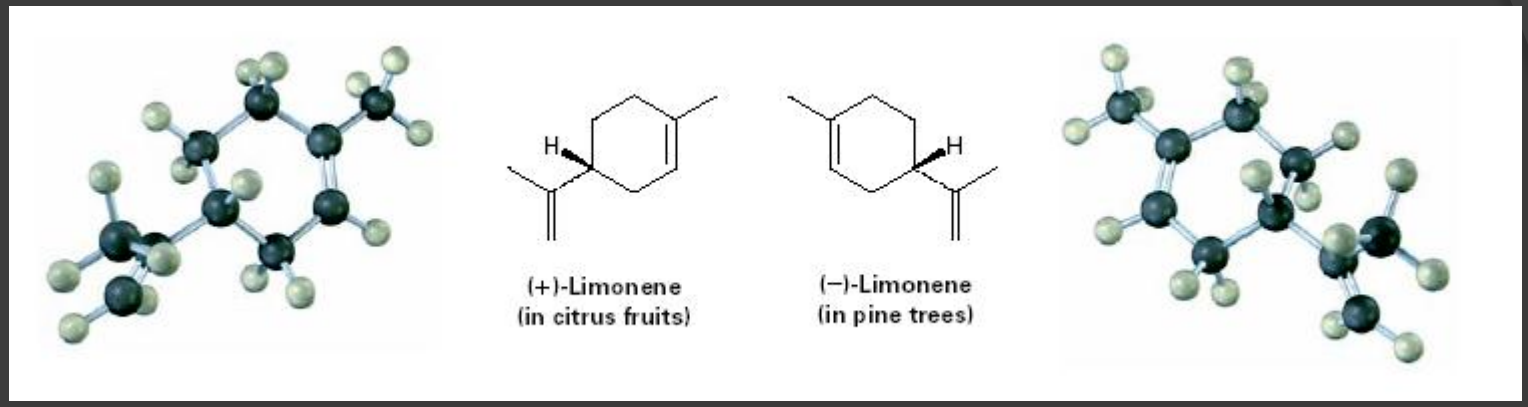
In the same way, (*R*)- and (*S*)-lactic acids react with (*R*)-1-phenylethylamine to give two different products. (*R*)-Lactic acid reacts with (*R*)-1-phenylethylamine to give the *R,R* salt, whereas (*S*)-lactic acid reacts with the same *R* amine to give the *S,R* salt. *The two salts are diastereomers of each other.*

They have different chemical and physical properties, and it may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with HCl then allows us to isolate the two pure enantiomers of lactic acid and recover the chiral amine for further use.

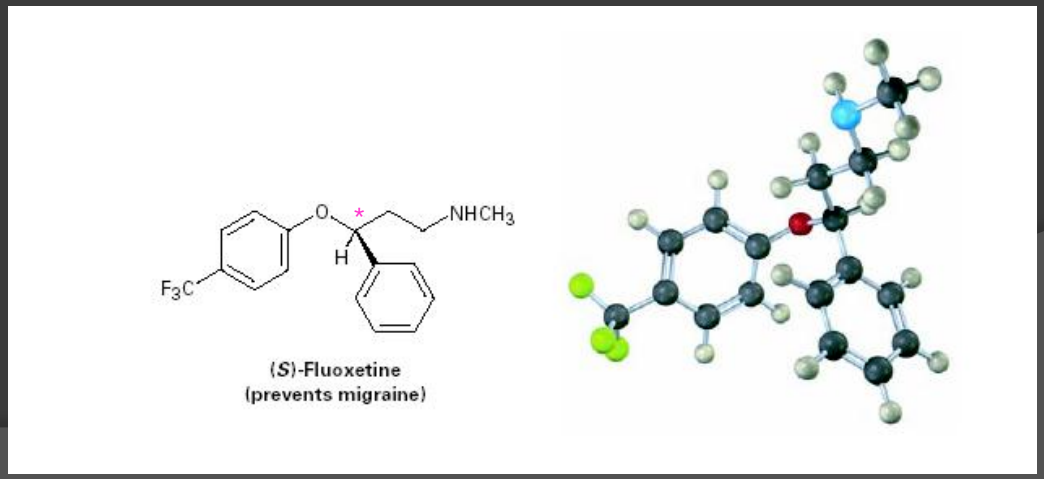


Chirality in nature and environment

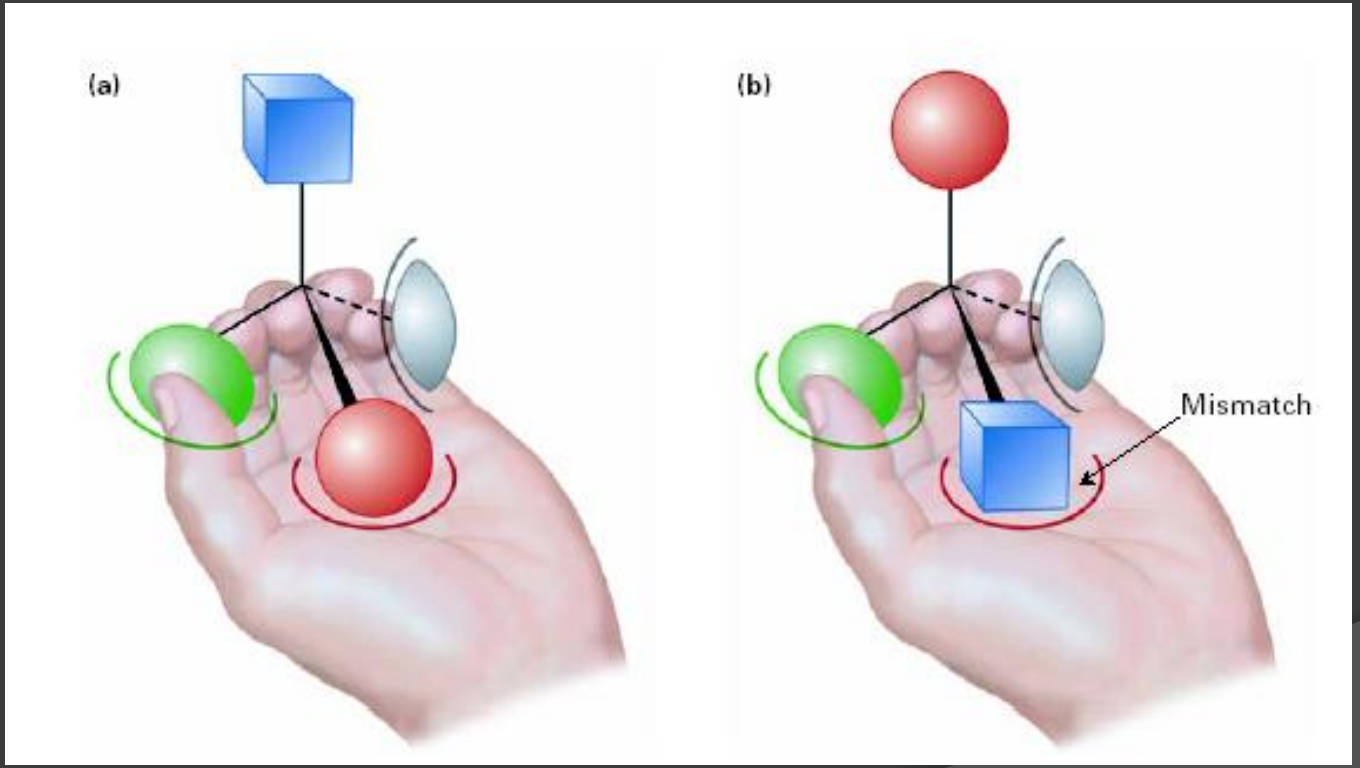
Although the different enantiomers of a chiral molecule have the same physical properties, they almost always have different biological properties. For example, the (+) enantiomer of limonene has the odor of oranges and lemons, but the (-) enantiomer has the odor of pine trees.



More dramatic examples of how a change in chirality can affect the biological properties of a molecule are found in many drugs, such as fluoxetine, a heavily prescribed medication (Prozac). Racemic fluoxetine is an extraordinarily effective antidepressant, but it has no activity against migraine. The pure *S* enantiomer, however, works remarkably well in preventing migraine.



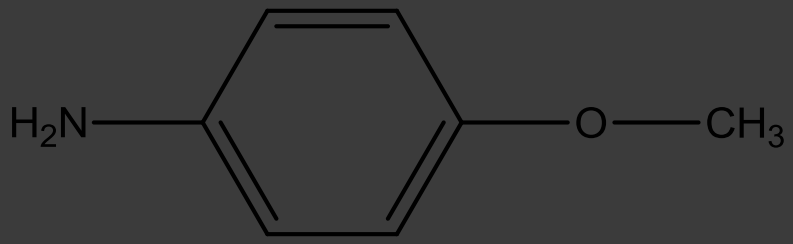
To have a biological effect, a substance typically must fit into an appropriate receptor in the body that has an exactly complementary shape. But because biological receptors are chiral, only one enantiomer of a chiral substrate can fit in, just as only a right hand will fit into a right-handed glove. The mirror-image enantiomer will be a misfit, like a left hand in a right-handed glove. In figure below, one enantiomer fits the receptor perfectly, but the other does not.



Nomenclature of Organic Compounds

Trivial name: simple, short, pronounciation is easy, but structure can not be elucidated.

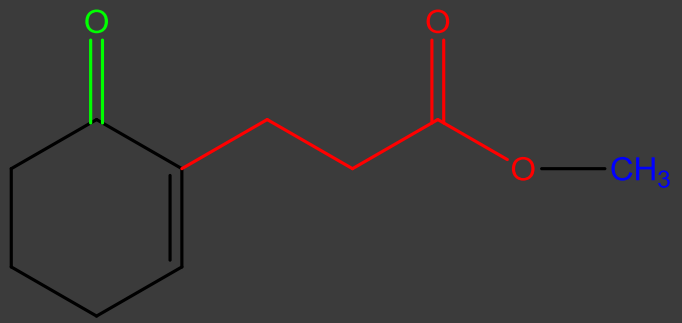
IUPAC name: long, pronounciation is difficult, based on this name you can get information on structure.



4-methoxyaniline

p-anisidine

Naming a monofunctional compound is reasonably straightforward, but even experienced chemists often encounter problems when faced with naming a complex polyfunctional compound. The following compound has three functional groups: ester, ketone, and C=C, but how should it be named? As an ester with an *-oate* ending, a ketone with an *-one* ending, or an alkene with an *-ene* ending? It's actually named *methyl 3-(2-oxocyclohex-6-enyl)propanoate*.

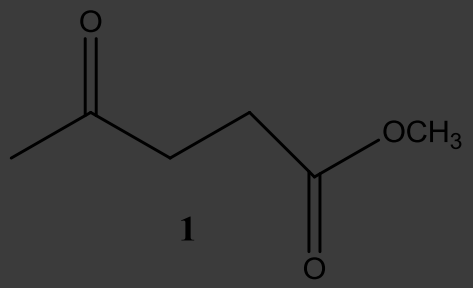


methyl 3-(2-oxocyclohex-6-enyl)propanoate

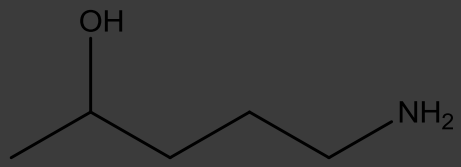
The name of a polyfunctional organic molecule has four parts – **suffix, parent, prefixes, and locants –** which must be identified and expressed in the proper order and format.

Name Part 1. The Suffix: Functional-Group Precedence

Although a polyfunctional organic molecule might contain several different functional groups, we must choose just *one suffix* for nomenclature purposes. Thus, keto ester **1** must be named either as a ketone with an -*one* suffix or as an ester with an -*oate* suffix, but it can't be named as an -*onoate*. Similarly, amino alcohol **2** must be named either as an alcohol (-*ol*) or as an amine (-a*mine*), but it can't be named as an -*olamine* or -*aminol*. The only ***exception*** to the rule requiring a single suffix is when naming *compounds that have double or triple bonds*. Thus, the unsaturated acid $H_2C{=}CHCH_2CO_2H$ is *but-3-enoic acid*, and the acetylenic alcohol $HC{\equiv}CCH_2CH_2CH_2OH$ is *pent-5-yn-1-ol*.



1



2

How do we choose which suffix to use? Functional groups are divided into two classes, **principal groups** and **subordinate groups.** *Principal groups* can be cited either *as prefixes or as suffixes*, while *subordinate groups* are cited only *as prefixes*. Within the principal groups, an order of priority has been established, with the proper suffix for a given compound determined *by choosing the principal group of highest priority*. For example keto ester **1** should be named as an ester rather than as a ketone because an ester functional group is higher in priority than a ketone. Similarly, amino alcohol **2** should be named as an alcohol rather than as an amine. Thus, the name of **1** is *methyl 4-oxopentanoate*, and the name of **2** is *5-aminopentan-2-ol*.

priority

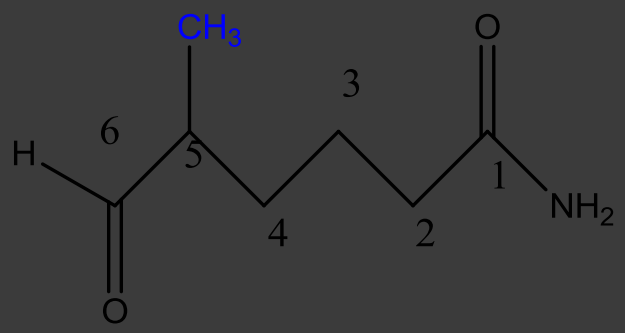
Table A.2 Classification of Functional Groups[a]

Functional group	Name as suffix	Name as prefix
Principal groups	-oic acid	carboxy
Carboxylic acids	-carboxylic acid	
Acid anhydrides	-oic anhydride -carboxylic anhydride	—
Esters	-oate -carboxylate	alkoxycarbonyl
Thioesters	-thioate -carbothioate	alkylthiocarbonyl
Acid halides	-oyl halide -carbonyl halide	halocarbonyl
Amides	-amide -carboxamide	carbamoyl
Nitriles	-nitrile -carbonitrile	cyano
Aldehydes	-al -carbaldehyde	oxo
Ketones	-one	oxo
Alcohols	-ol	hydroxy
Phenols	-ol	hydroxy
Thiols	-thiol	mercapto
Amines	-amine	amino
Imines	-imine	imino
Ethers	ether	alkoxy
Sulfides	sulfide	alkylthio
Disulfides	disulfide	—
Alkenes	-ene	—
Alkynes	-yne	—
Alkanes	-ane	—
Subordinate groups		
Azides	—	azido
Halides	—	halo
Nitro compounds	—	nitro

[a]Principal groups are listed in order of decreasing priority; subordinate groups have no priority order.

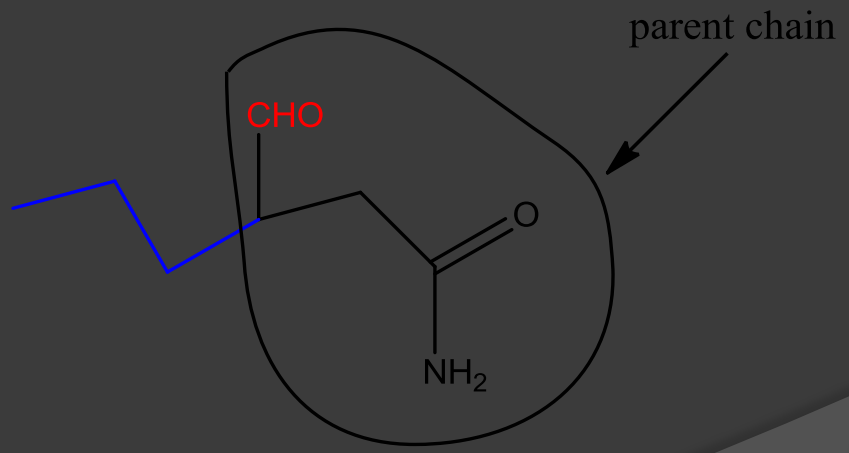
Name Part 2. The Parent: Selecting the Main Chain or Ring

The parent, or base name of a polyfunctional organic compound is usually easy to identify. If the principal group of highest priority is part of an open chain, the parent name is that of the *longest chain containing the largest number of principal groups*. For example, compounds **3** and **4** are isomeric *aldehydo amides*, which must be named as amides rather than as aldehydes according to Table A.2. The longest chain in compound **3** has six carbons, and the substance is therefore named *5-methyl-6-oxohexanamide*. Compound **4** also has a chain of six carbons, but the longest chain that contains *both* principal functional groups has only four carbons. The correct name of **4** is *4-oxo-3-propylbutanamide*.



5-methyl-6-oxohexanamide

3

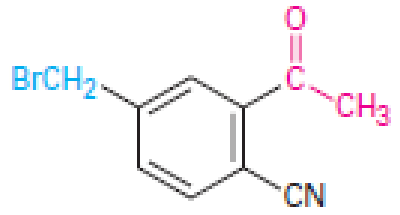


4-Oxo-3-propylbutanamide

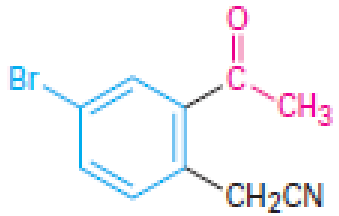
4

If the highest-priority principal group is attached to a ring, *the parent name is that of the ring system*. Compounds **8** and **9** are isomeric keto nitriles and must both be *named as nitriles* according to Table A.2. Substance **8** is named as a benzonitrile because the -CN functional group is a substituent on the aromatic ring, but substance **9** is named as an acetonitrile because the -CN functional group is on an open chain. The correct names are *2-acetyl-(4-bromomethyl)benzonitrile* (**8**) and *(2-acetyl-4-bromophenyl)acetonitrile* (**9**).

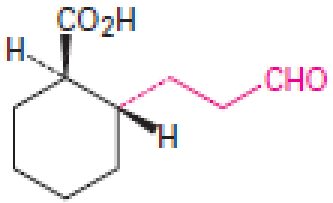
As further examples, compounds **10** and **11** are both keto acids and must be *named as acids*, but the parent name in (**10**) is that of a ring system (cyclohexanecarboxylic acid) and the parent name in (**11**) is that of an open chain (propanoic acid). The full names are *trans-2-(3-oxopropyl)cyclohexanecarboxylic acid* (**10**) and *3-(2-oxocyclohexyl)propanoic acid* (**11**).



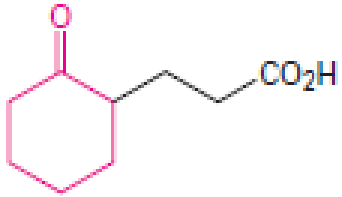
8. 2-Acetyl-(4-bromomethyl)benzonitrile



9. (2-Acetyl-4-bromophenyl)acetonitrile



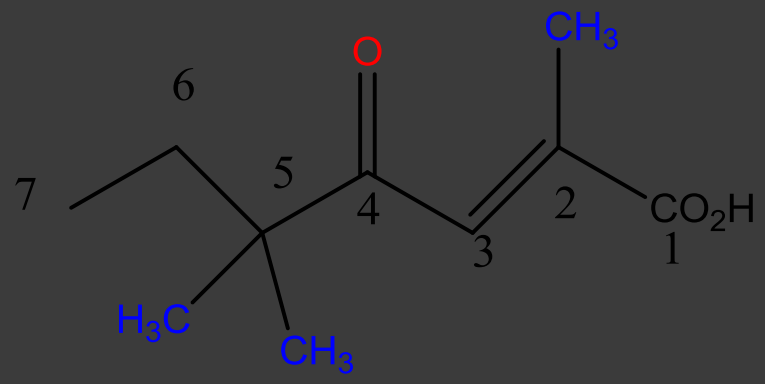
10. *trans*-2-(3-oxopropyl)cyclo-hexanecarboxylic acid



11. 3-(2-Oxocyclohexyl)propanoic acid

Name Parts 3 and 4. The Prefixes and Locants

With the parent name and the suffix established, the next step is to identify and give numbers, or *locants*, to all substituents on the parent chain or ring. These substituents include all alkyl groups and all functional groups other than the one cited in the suffix. For example, compound **12** contains three different functional groups (carboxyl, keto, and double bond). Because the carboxyl group is highest in priority and because the longest chain containing the functional groups has seven carbons, **12** is a heptenoic acid. In addition, the main chain has a keto (oxo) substituent and three methyl groups. Numbering from the end nearer the highest-priority functional group, **12** is named *(E)-2,5,5-trimethyl-4-oxohept-2-enoic acid*. Look back at some of the other compounds we've named to see other examples of how prefixes and locants are assigned.



(*E*)-2,5,5-trimethyl-4-oxohept-2-enoic acid

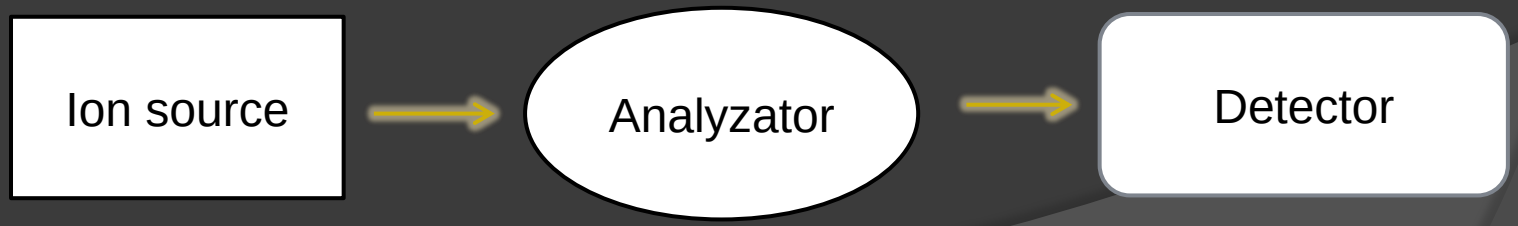
12

Spectroscopic identification of organic compounds

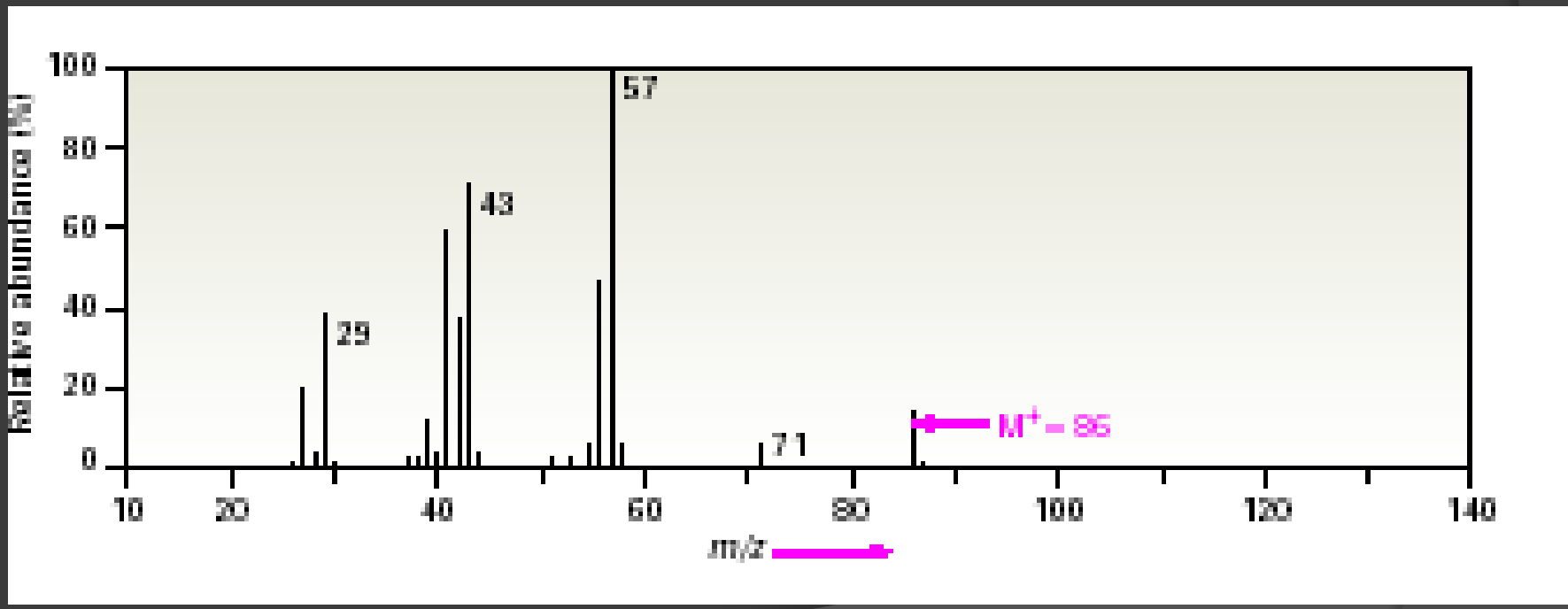
- **Mass spectrometry**
- **Infrared spectroscopy**
- **UV spectroscopy**
- **NMR spectroscopy**

Mass spectrometry

Many different kinds of commercial mass spectrometers are available depending on the intended application, but all have three basic parts:
an *ionization source* in which sample molecules are given an electrical charge;
a *mass analyzer* in which ions are separated by their mass-to-charge ratio, *m*/*z;*
and a *detector* in which the separated ions are observed and counted.
Since the number of charges *z* on each ion is usually 1, the value of *m*/*z* for an ion is simply its mass, *m.* Masses up to approximately 2500 atomic mass units (amu) can be analyzed with an accuracy up to four decimal places.

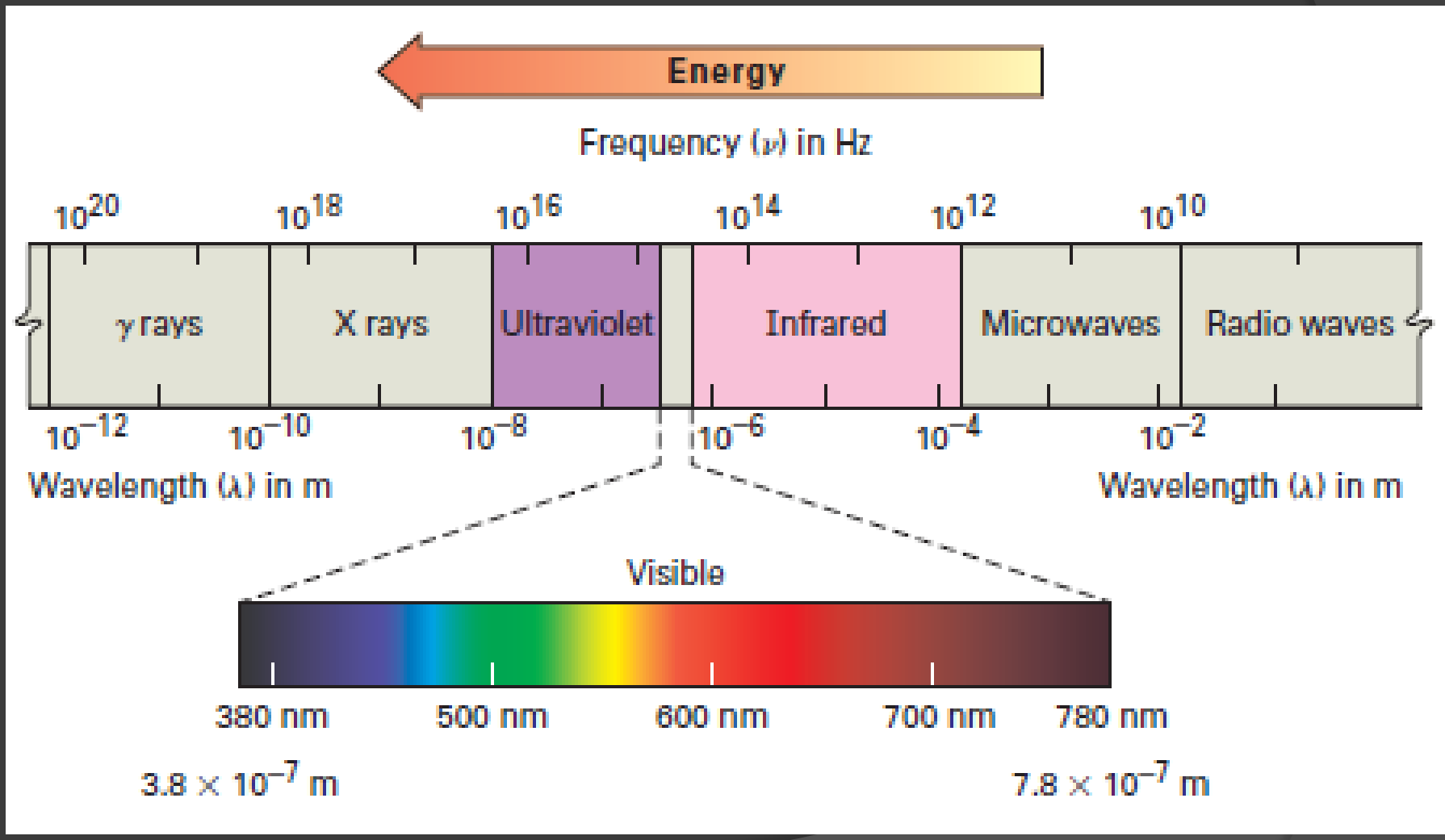


A typical mass spectrum, like that of hexane in figure below, is normally presented as a bar graph with *m*/*z* on the horizontal axis and relative abundance of ions on the vertical axis. The tallest peak, assigned an intensity of 100%, is called the *base peak*, and the peak that corresponds to the unfragmented ion is called the *parent peak*, or the *molecular ion (M)*. Hexane, for instance, shows M 86, corresponding to a formula of C_6H_{14}. Peak at 87 is isotope peak from ^{13}C. In addition to giving a molecular ion, most molecules fragment in the mass spectrometer, giving rise to numerous other ions that can provide structural information when interpreted. Hexane, for instance, shows peaks at *m*/*z* 71 corresponding to loss of a CH_3 group, *m*/*z* 57 corresponding to loss of an CH_3CH_2 group, *m*/*z* 43 corresponding to loss of a $CH_3CH_2CH_2$ group, and so on …



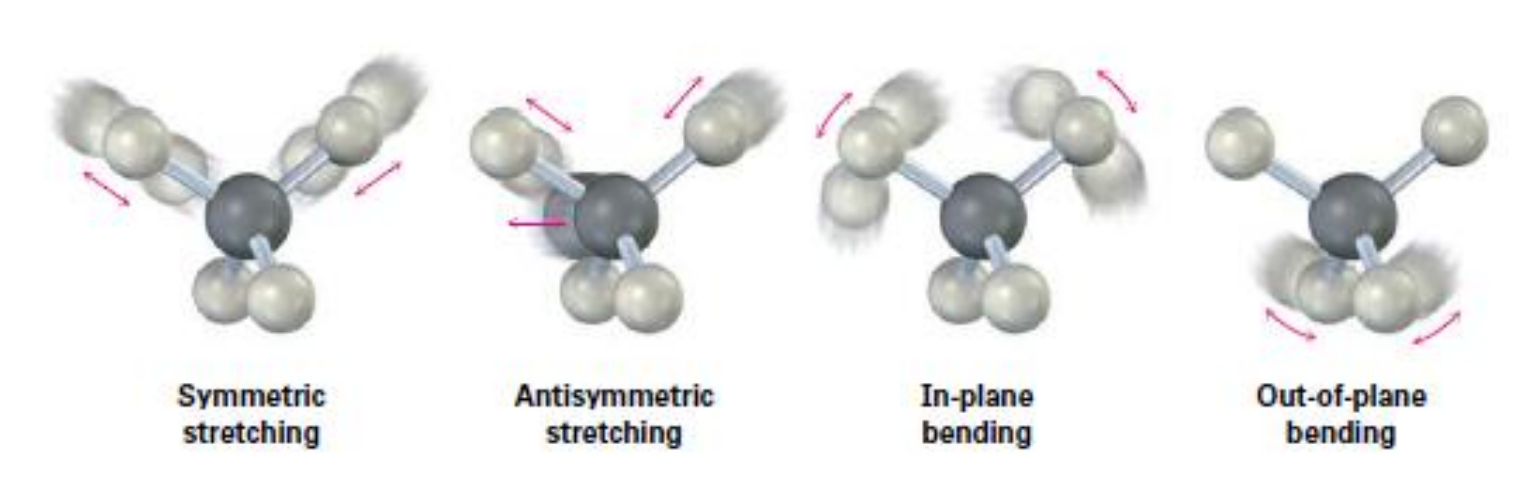
Mass spectrum of hexane

Electromagnetic spectrum



IR spectroscopy

All molecules have a certain amount of energy and are in constant motion. Their bonds stretch and contract, atoms wag back and forth, and other molecular vibrations occur. Some of the kinds of allowed vibrations are shown below:



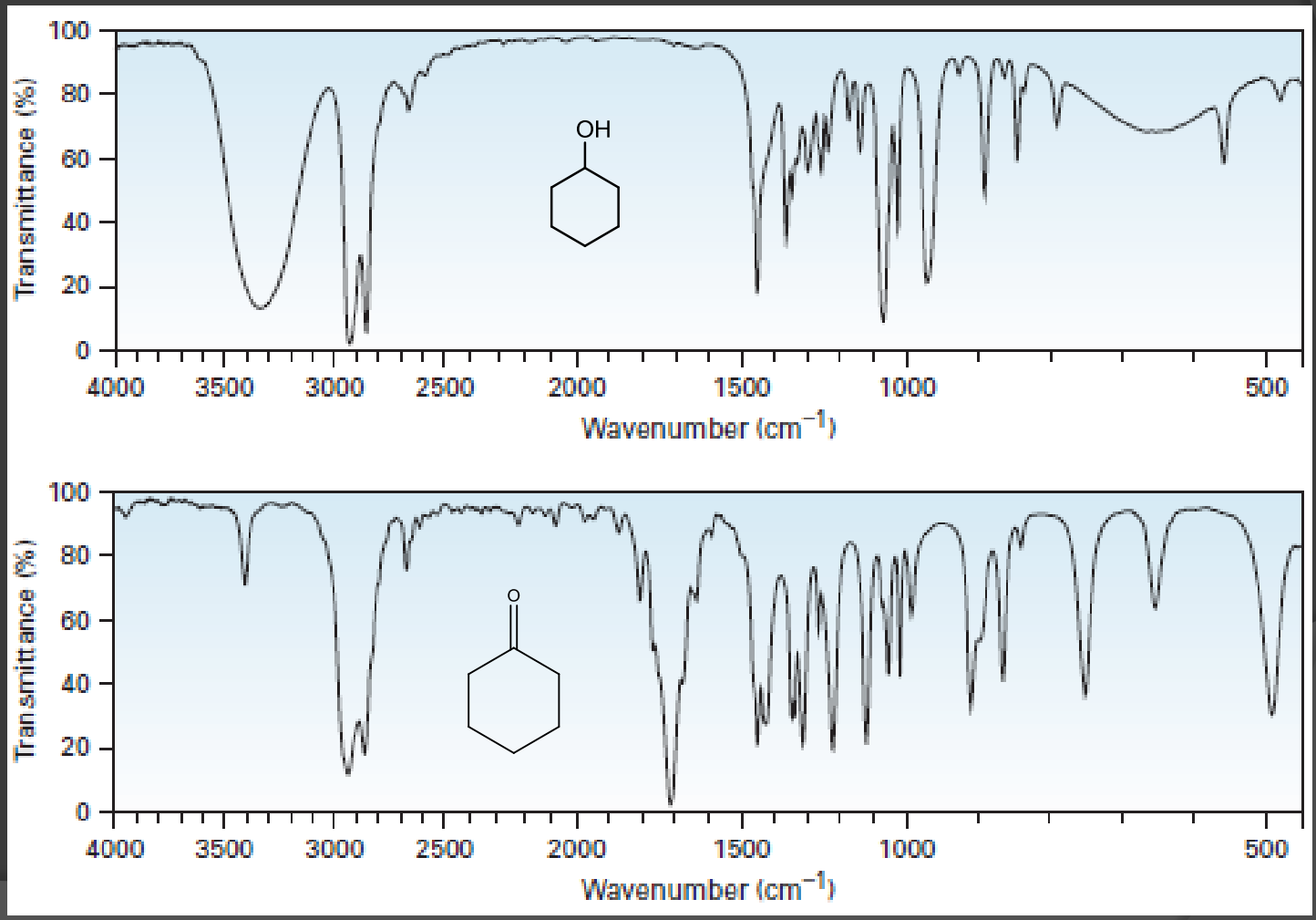
The amount of energy a molecule contains is not continuously variable but is *quantized*. That is, a molecule can stretch or bend only at specific frequencies corresponding to specific energy levels. Take bond stretching, for instance.

Although we usually speak of bond lengths as if they were fixed, the numbers given are really averages. In fact, a typical C-H bond with an average bond length of 110 pm is actually vibrating at a specific frequency, alternately stretching and contracting as if there were a spring connecting the two atoms.

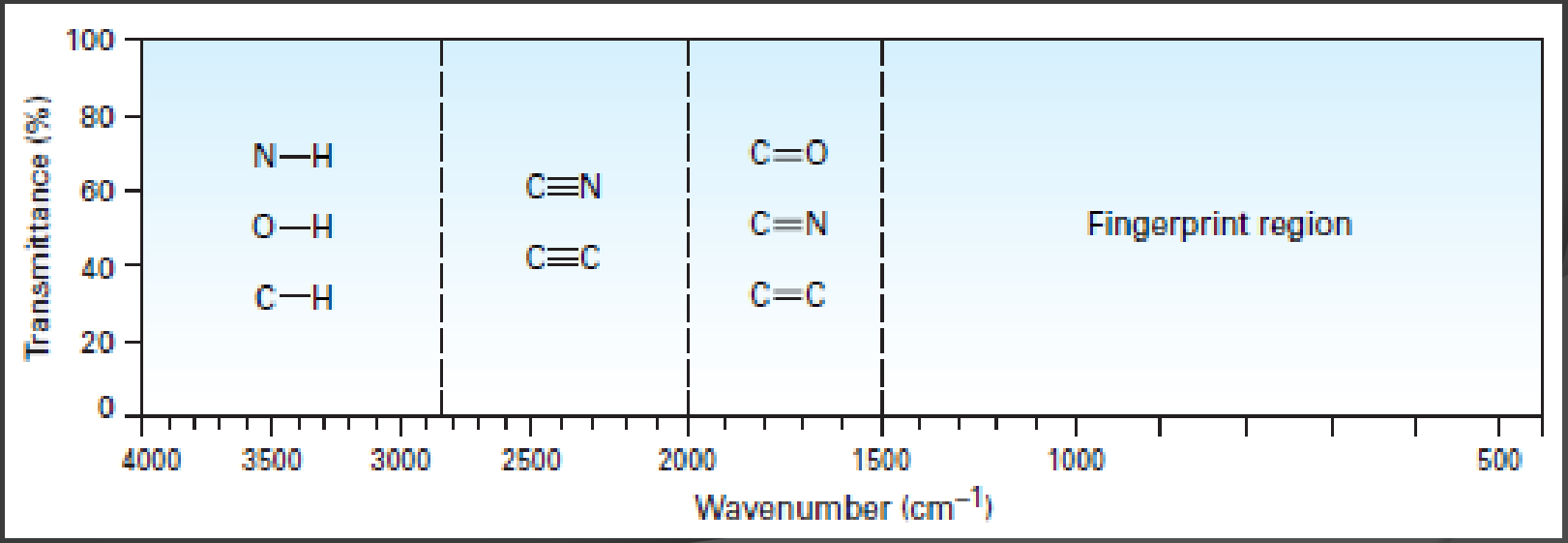
Table 13.1 Characteristic Infrared Absorptions of Some Functional Groups

Functional Group	Absorption (cm^{-1})	Intensity
Alkane		
C–H	2850–2960	Medium
Alkene		
=C–H	3020–3100	Medium
C=C	1640–1680	Medium
Alkyne		
≡C–H	3300	Strong
C≡C	2100–2260	Medium
Alkyl halide		
C–Cl	600–800	Strong
C–Br	500–600	Strong
Alcohol		
O–H	3400–3650	Strong, broad
C–O	1050–1150	Strong
Arene		
C–H	3030	Weak
Aromatic ring	1660–2000	Weak
	1450–1600	Medium
Amine		
N–H	3300–3500	Medium
C–N	1030–1230	Medium
Carbonyl compound		
C=O	1670–1780	Strong
Aldehyde	1725	Strong
Ketone	1715	Strong
Ester	1735	Strong
Amide	1690	Strong
Carboxylic acid	1710	Strong, broad
Carboxylic acid		
O–H	2500-3100	Strong, broad
Nitrile		
C≡N	2210–2260	Medium
Nitro		
NO_2	1540	Strong

The spectra of cyclohexanol and cyclohexanone show how IR spectroscopy can be used. Although both spectra contain many peaks, the characteristic absorptions of the different functional groups allow the compounds to be distinguished. Cyclohexanol shows a characteristic alcohol O-H absorption at 3300 cm^{-1} and a C-O absorption at 1060 cm^{-1}; cyclohexanone shows a characteristic ketone C=O peak at 1715 cm^{-1}.

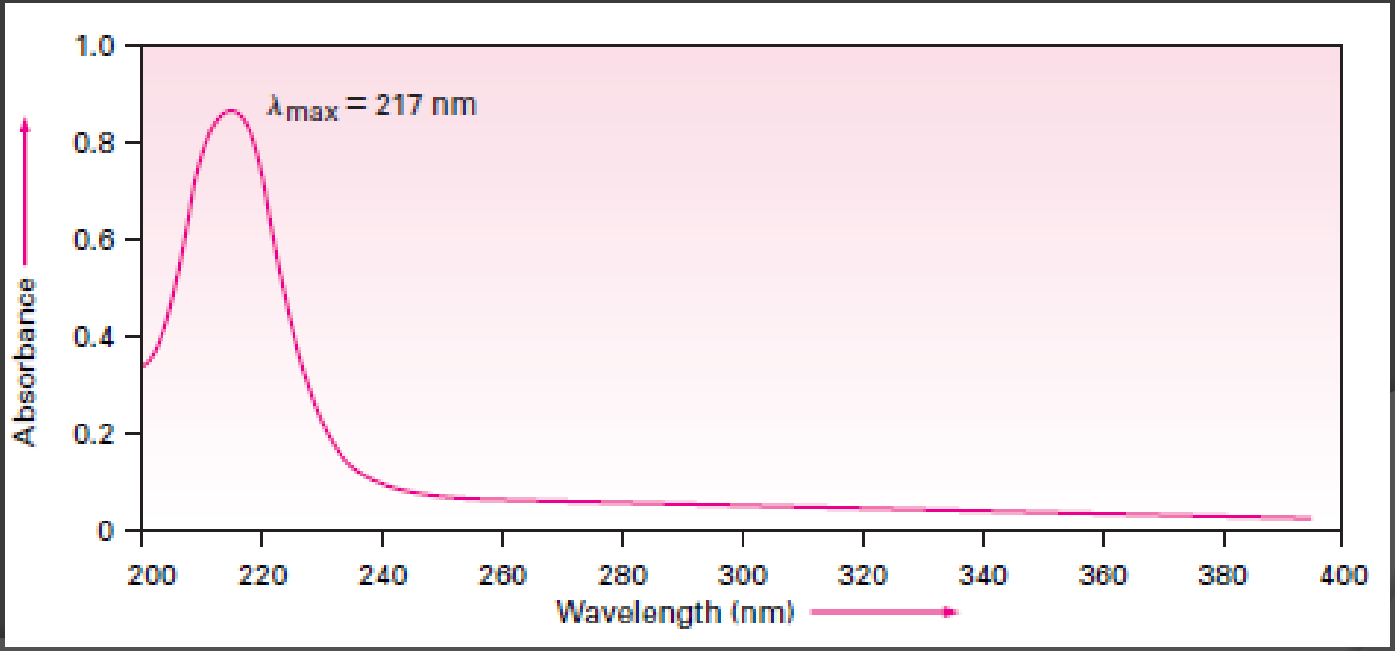


- The region from 4000 to 2500 cm^{-1} corresponds to absorptions caused by N-H, C-H, and O-H single-bond stretching motions. N-H and O-H bonds absorb in the 3300 to 3600 cm^{-1} range; C-H bond stretching occurs near 3000 cm^{-1}.
- The region from 2500 to 2000 cm^{-1} is where triple-bond stretching occurs. Both C≡N and C≡C bonds absorb here.
- The region from 2000 to 1500 cm^{-1} is where double bonds (C=O, C=N, and C=C) absorb. Carbonyl groups generally absorb in the range 1670 to 1780 cm^{-1}, and alkene stretching normally occurs in the narrow range 1640 to 1680 cm^{-1}.
- The region below 1500 cm^{-1} is the fingerprint portion of the IR spectrum. A large number of absorptions due to a variety of C-C, C-O, C-N, and C-X single-bond vibrations occur here, forming a unique pattern that acts as an identifying fingerprint of each organic compound.



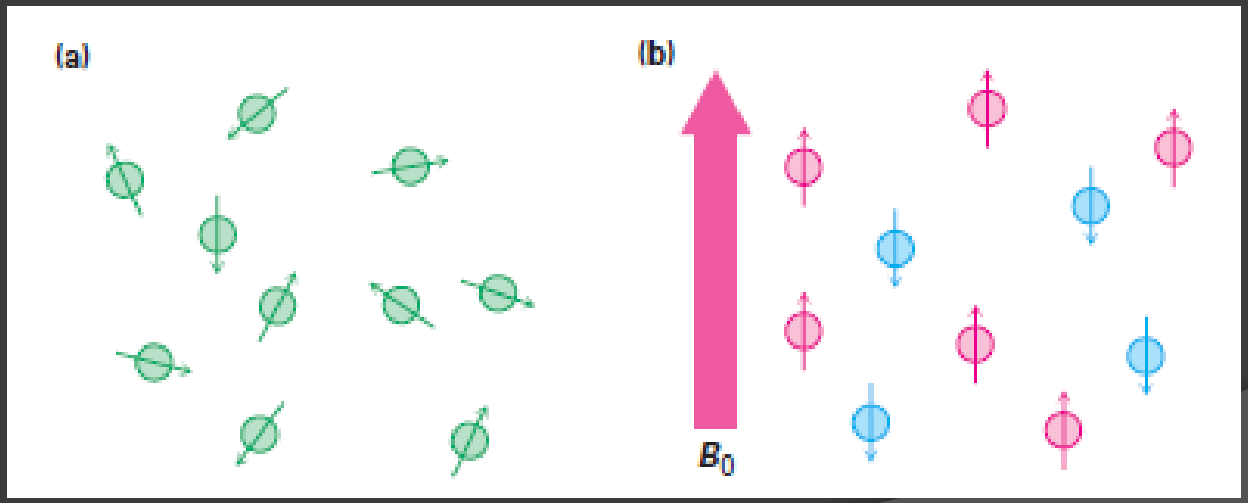
UV-spectroscopy

A typical UV spectrum – that of buta-1,3-diene – is shown below. Unlike IR spectra, which generally have many peaks, UV spectra are usually quite simple. Often, there is only a single broad peak, which is identified by noting the wavelength at the very top, indicated as max. For buta-1,3-diene, λ_{max} = 217 nm. Note that UV spectra differ from IR spectra in the way they are presented. For historical reasons, IR spectra are usually displayed so that the baseline corresponding to zero absorption runs across the top of the chart and a valley indicates an absorption, whereas UV spectra are displayed with the baseline at the bottom of the chart so that a peak indicates an absorption.



NMR spectroscopy

Many kinds of nuclei, including ^{1}H and ^{13}C, behave as if they were spinning about an axis. Because they're positively charged, these spinning nuclei act like tiny magnets and interact with an external magnetic field (denoted $\boldsymbol{B}_0$). In the absence of an external magnetic field, the nuclear spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^{1}H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy and therefore aren't equally likely. The parallel orientation is slightly lower in energy, making this spin state slightly favored over the antiparallel orientation.



No magnetic field External magnetic field

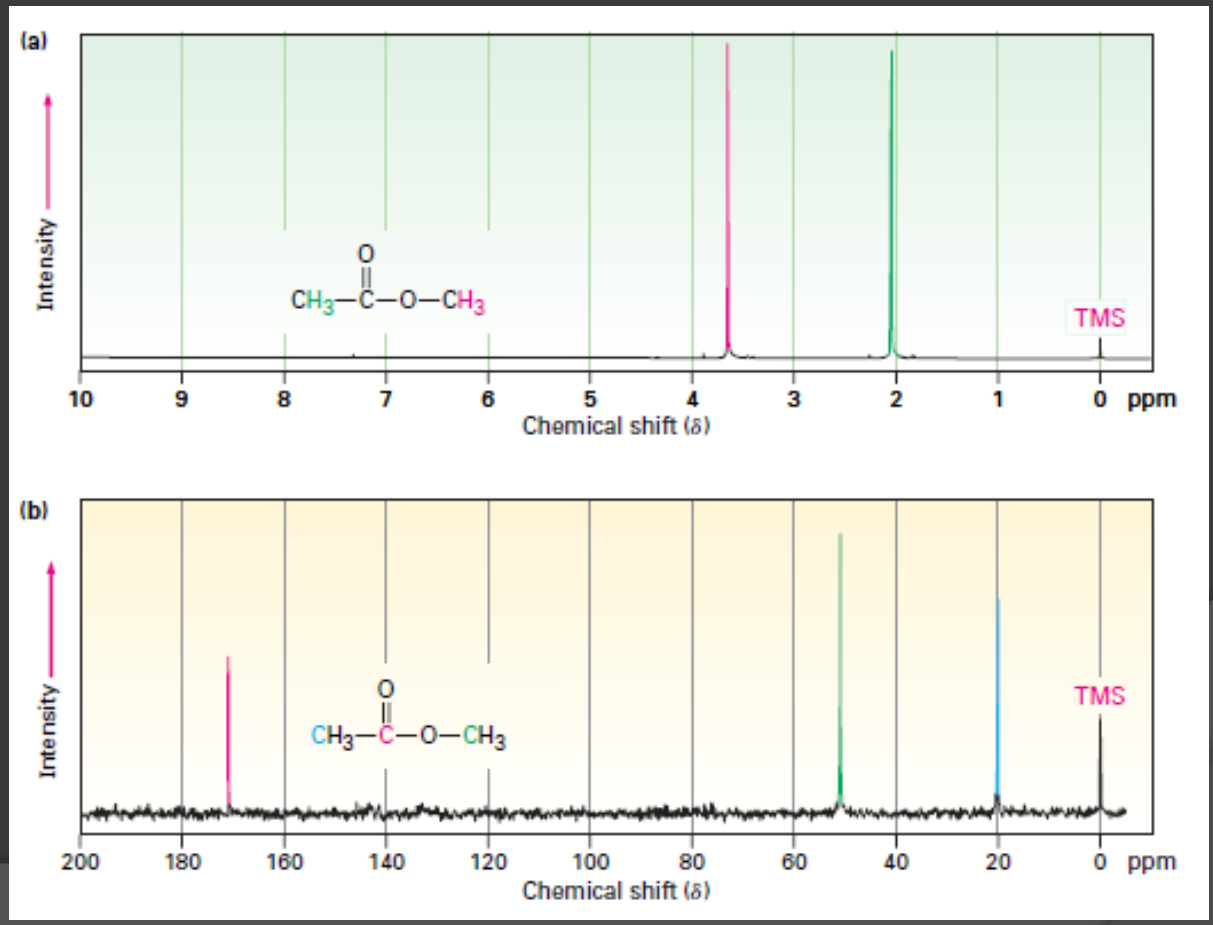
If the oriented nuclei are now irradiated with electromagnetic radiation of the right frequency, energy absorption occurs and the lower-energy state "spin-flips" to the higher-energy state. When this spin-flip occurs, the nuclei are said to be in resonance with the applied radiation – hence the name *nuclear magnetic resonance.*

All nuclei are surrounded by electrons. When an external magnetic field is applied to a molecule, the moving electrons around nuclei set up tiny local magnetic fields of their own. These local fields act in opposition to the applied field, so that the *effective* field actually felt by the nucleus is a bit weaker than the applied field.

$$\boldsymbol{B}_{\text{effective}} = \boldsymbol{B}_{\text{applied}} - \boldsymbol{B}_{\text{local}}$$

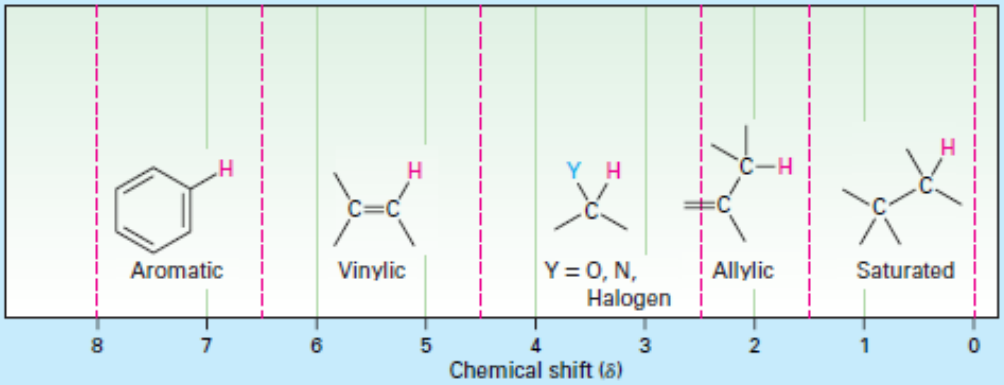
In describing this effect of local fields, we say that the nuclei are **shielded**. All nuclei are surrounded by electrons. When an external magnetic field is applied to a molecule, the moving electrons around nuclei set up tiny local magnetic fields of their own. These local fields act in opposition to the applied field, so that the *effective* field actually felt by the nucleus is a bit weaker than the applied field.

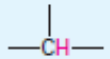
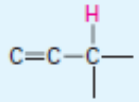
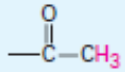
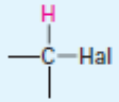
The ^{13}C spectrum of methyl acetate in figure has three peaks, one for each of the three chemically distinct carbons in the molecule. The ^{1}H spectrum shows only *two* peaks, however, even though methyl acetate has *six* hydrogens. One peak is due to the $CH_3C{=}O$ hydrogens and the other to the OCH_3 hydrogens. Because the three hydrogens in each methyl group have the same chemical (and magnetic) environment, they are shielded to the same extent and are said to be *equivalent*. Chemically equivalent nuclei always show a single absorption. The two methyl groups themselves, however, are nonequivalent, so the two sets of hydrogens absorb at different positions.

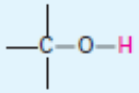
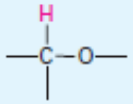
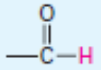
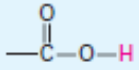


Chemical shifts in ^{1}H NMR

Table 13.3 Correlation of ^{1}H Chemical Shift with Environment



Type of hydrogen		Chemical shift (δ)
Reference	$Si(CH_3)_4$	0
Alkyl (primary)	$-CH_3$	0.7–1.3
Alkyl (secondary)	$-CH_2-$	1.2–1.6
Alkyl (tertiary)		1.4–1.8
Allylic		1.6–2.2
Methyl ketone		2.0–2.4
Aromatic methyl	$Ar-CH_3$	2.4–2.7
Alkynyl	$-C\equiv C-H$	2.5–3.0
Alkyl halide		2.5–4.0

Type of hydrogen		Chemical shift (δ)
Alcohol		2.5–5.0
Alcohol, ether		3.3–4.5
Vinylic		4.5–6.5
Aryl	Ar—H	6.5–8.0
Aldehyde		9.7–10.0
Carboxylic acid		11.0–12.0