Bio-Organic Chemistry

Carbon-Based Life Chemistry

Compare and Contrast Inorganic and Organic Compounds

Inorganic Compounds
Composed of various combinations of more than 100 elements
Very few inorganic compounds will burn. They have high melting points, above 350° C; some vaporize at high temperatures.
Inorganic compounds (excluding compounds of the transition metals) are usually odorless and colorless and are soluble in water to varying degrees.
Inorganic compounds are "held together" by ionic bonding and ionize in aqueous solutions.
Compared to organic compounds, there are only a few isomers of inorganic compounds. Remember that "isomers" means equal units, e.g., same chemical formula, but a different geometrical arrangement.

Organic Compounds
Organic compounds are composed of only a few elements. Carbon always -- organic chemistry is the chemistry of carbon compounds. Hydrogen, oxygen and nitrogen are usually involved and sulfur, phosphorus, chlorine, bromine and iodine, occasionally, are present, as well.
Nearly all-organic compounds burn. They tend to have low melting points, much less then 350° C. Some char and decompose rather than melt.
Organic compounds tend to possess color and odor; e.g., benzaldehyde is artificial oil of almond.
Organic compounds are soluble in organic compounds and are typically insoluble in water. Notable exceptions include acetone and ethanol.
Organic compounds are generally held together by covalent bonds. A few, e.g., carboxylic acids and phenols, ionize and effect the pH of solutions. There are many isomers of organic compounds -- you'll be introduced to a few of them as we go along.

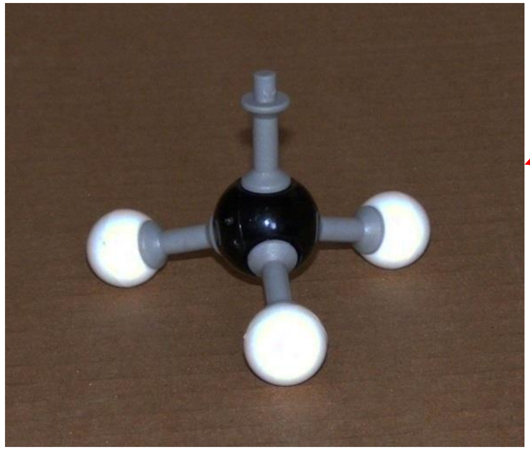
We Use Carbon-Based Compounds Every Day	
Health	food, digestion, metabolism, drugs, vitamins, hormones
Daily Use and Survival	heat, electricity, flavorings, colorants, sweeteners, containers
Transportation	gas, diesel, oil, grease, plastics, tires
Clothing	nylon, rayon, dacron, Kevlar
Personal Use	soap, detergents, perfumes, paints, ink, explosives, photography, PVC pipe

Organic Chemistry

Alkanes

- The general formula of an alkane is C_nH_{2n+2}.
- All of the carbons in an alkane possess tetrahedral geometry (methane at right).
- There is one sigma bond between the carbon atoms that permits freedom of rotation about the carbon-carbon single bond.
- They also consist only of carbon and hydrogen, hence the name "hydrocarbon".

- If methane (above; CH_4) were to lose a hydrogen atom, it becomes the methyl radical (below; $CH_3•$), where the dot represents the left-behind electron after the hydrogen atom was removed from methane.



Alkyl groups

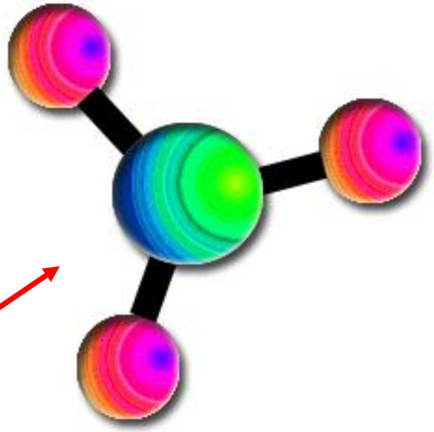
- While alkanes can be and are exciting in and of themselves, there is more to organic chemistry than just looking at alkanes.
- We must have a way in which to name them when they become reactive or when an organic functional group substitutes onto a hydrocarbon chain for a hydrogen atom.
- When an alkane loses a hydrogen atom, the left over hydrocarbon becomes an "alkyl" group -- "alk" for the parent hydrocarbon and "yl" to indicate that it is a reactive radical

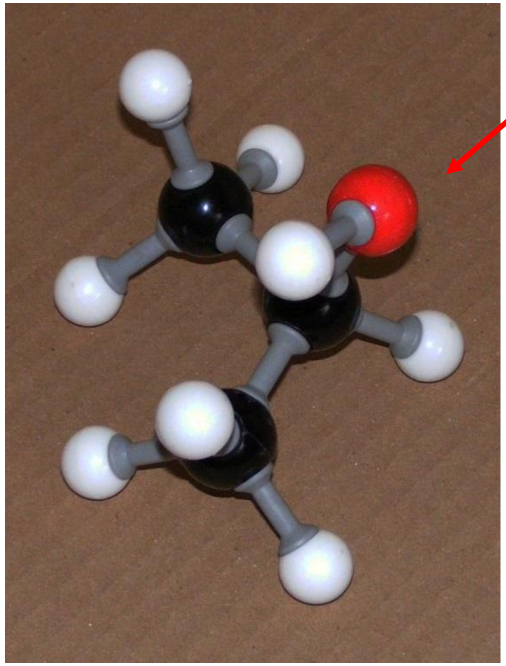
Incomplete, Abnormal, Combustion of Hydrocarbons

- Major Health Concern
- “Old”, Inefficient Propane Burners
- $2\ C_3H_8 + 7\ O_2 \rightarrow 6\ \mathbf{CO} + 8\ H_2O$ + heat
- Deadly – common in camper trailers and horse trailers with sleeping quarters.
- From Gasoline (using octane as the gasoline form), as well.
- $2C_8H_{18} + 17O_2 \rightarrow 16CO + 18H_2O$ + heat

Alkenes

- AlkENES are hydrocarbons that contain one double bond between two carbon atoms.
- The general formula for an alkene is C_nH_{2n}.
- The two carbons have a planar triangular (trigonal planar) geometry.
- There is 1 sigma bond and 1 pi bond between the two carbon atoms.
- There is NO freedom of rotation about the double bond as there is in the single bonds in alkANES.

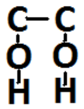




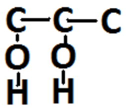
Alcohols

- Although they are a bit out of sequence, we'll discuss alcohols at this time.
- Alkenes are easily hydrated to form alcohols
- Alcohols consist of carbon, hydrogen and oxygen.
- 2-propanol (isopropyl alcohol; rubbing alcohol) shown at left

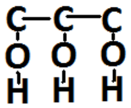
Diols and Triols



ethylene glycol = 1,2-ethanediol



propylene glycol = 1,2-propanediol

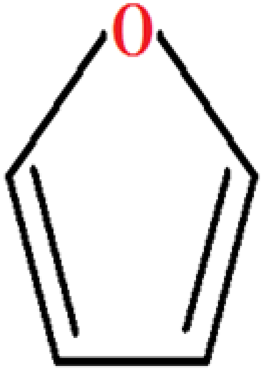


glycerine = 1,2,3-propanetriol

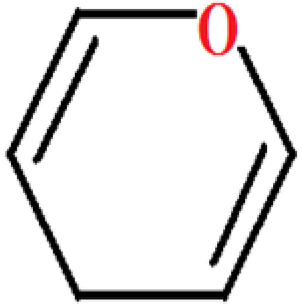
- Alcohols don't just come as a single OH group on a hydrocarbon. Sometimes there are 2 OH's (diols) or 3 OH's (triols).
- Ethylene glycol is known as 1,2-ethanediol and is used as an antifreeze. Efforts are being made to reduce its use as it's not environmentally friendly.
- Propylene glycol is known as 1,2-propanediol and is used as a preservative.
- Glycerin is also known as 1,2,3-propanetriol. It is used as a lubricant and a precursor in the synthesis of nitroglycerine. One way that cardiac patients can tell if their nitro is going bad is if the headache they get while using it doesn't hurt as bad. Explosives people who work in the nitro shack often go home with headaches from working around nitro all day.

Poly-ols: Carbohydrates

- “Sugars”



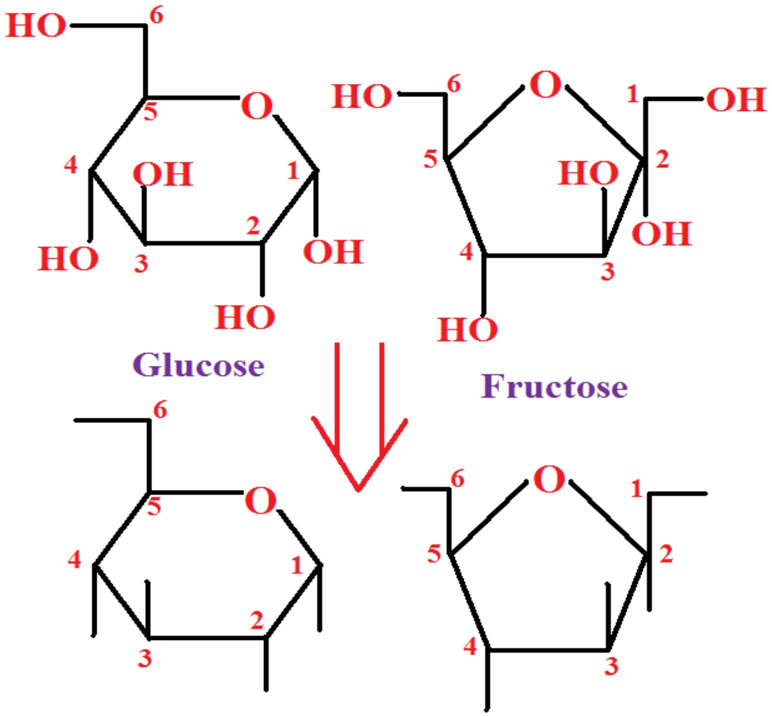
Furan



Pyran

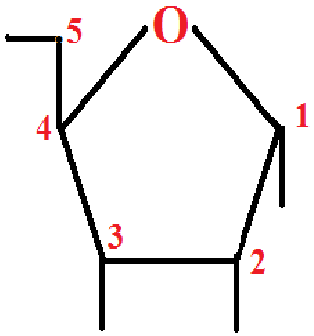
- Carbohydrates are generally seen as sources of quick energy.
- They consist of carbon, hydrogen and oxygen.
- The last group of alcohols for discussion are the "polyols" or the carbohydrates. There are, for all intents and purposes, 2 classes of carbohydrates: pyranoses and furanoses. These two classes are so called because their carbon skeletons are based off of pyran and furan. Both pyran and furan each have an oxygen atom in the closed ring. At each corner is a carbon atom.
  - Glucose and fructose are both hexoses (6-carbon sugars); glucose is a pyranose and fructose is a furanose.
- In the old days, they were named carboHYDRATES as the ratio of hydrogen to oxygen was thought to be 2:1.
- We now know differently, although the name has stuck throughout time.
- There are three categories of carbohydrates in which we have interest: monosaccharides, disaccharides and polysaccharides.

- Two of the simplest carbohydrates are glucose and fructose, the sugar in our blood and fruit sugar.
- As you can see, both have unique geometric shapes in their base structures and each has a unique orientation of the -OH groups upon the base structure.
- Remember that at each corner, there is a carbon atom and that carbon takes 4 bonds.
- The hydrogen atoms that are by themselves are not shown but are understood to be present.
- Biochemists developed a short-hand for quickly sketching carbohydrates called the Hayworth projections.
- The graphics on the right of each of the above sugars show the Hayworth projections, where the -OH's are replaced with lines going in the correspondingly correct directions.

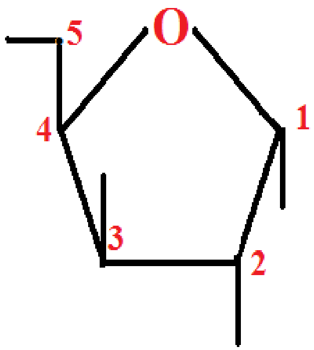


Monosaccharides -- Furanoses

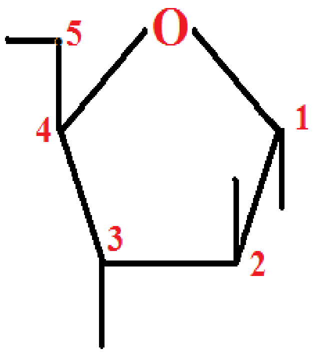
- These two compounds (furan and pyran) provide the framework for numerous monosaccharides (single sugars).
- Ribose is found in ribonucleic acid (RNA); xylose is wood sugar and is non-fermentable; arabinose is gum sugar -- it may sometimes be found in urine.
- A form of ribose is found in deoxyribonucleic acid (DNA): deoxy-ribose. Ribose must lose the -OH on the 2' carbon to become deoxy-ribose.
- Note that ribose, xylose and arabinose are pentoses (5 carbon sugars).
- In addition, the proper names of the above furanoses are: D-ribofuranose, D-xylofuranose and D-arabinofuranose.



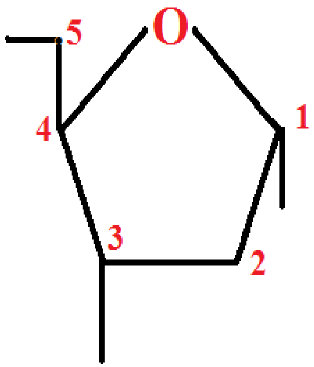
Ribose



Xylose

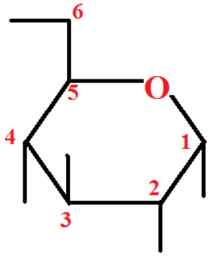


Arabinose

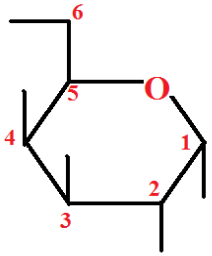


deoxy-ribose

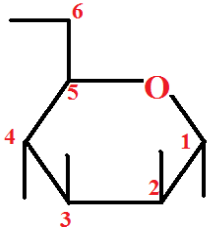
Pyranoses



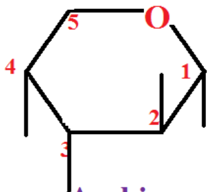
Glucose



Galactose



Mannose

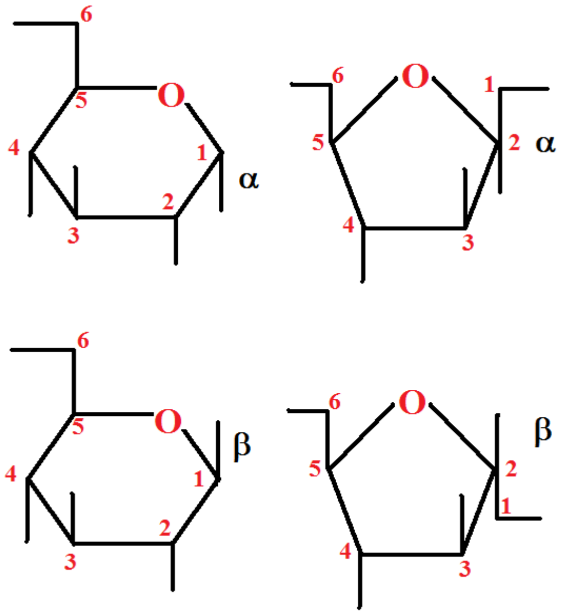


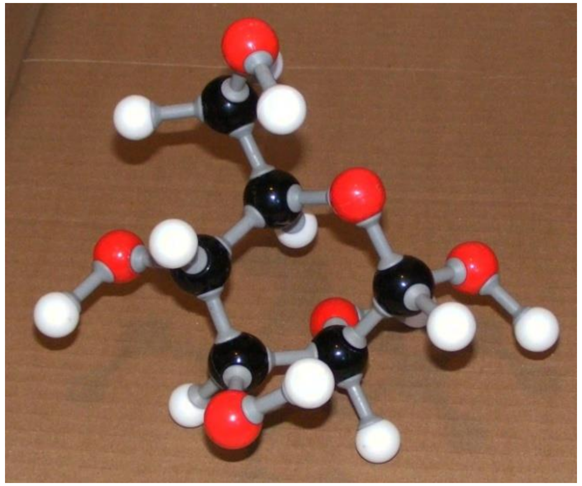
Arabinose (2d Structure)

- Glucose, we've briefly discussed.
- Galactose is of significance in that it forms half of the disaccharide (double sugar) lactose (milk sugar).
- Mannose is a plant sugar.
- Note that these sugars differ in their geometric structure simply by the orientation of the -OH groups.
- Indeed, the orientation of the -OH groups -- only differing by the position of 1 -OH group -- changes the sweetness of the sugar.
- To remember these sugars, I've got three mnemonics for you.
- They are based off the first 4 carbons (1,2,3,4) and #5 carbon has no -OH group on it and #6 carbon is always up and to the left for our purposes.
- To remember glucose, the mnemonic is DDUD: down, down, up, down.
- This describes the orientation of the -OH groups on the first four carbons.
- Galactose is DDUU, while mannose is DUUD.
- The proper names for the above pyranoses are: D-glucopyranose, D-galactopyranose and D-mannopyranose.

Anomeric Carbon

- We can go another step in naming monosaccharides based upon the position of the -OH on carbon #1.
- This carbon is called the anomeric carbon in glucose; in fructose, it's carbon #2.
- When the -OH group is down on carbon #1 (or #2 in fructose), that is said to be in the α-configuration.
- When the -OH group is up on carbon #1 (or #2 in fructose), it is said to be in the β-configuration.
- Humans metabolize monosaccharides in the α-configuration.
- The graphic illustrates glucose in both configurations.

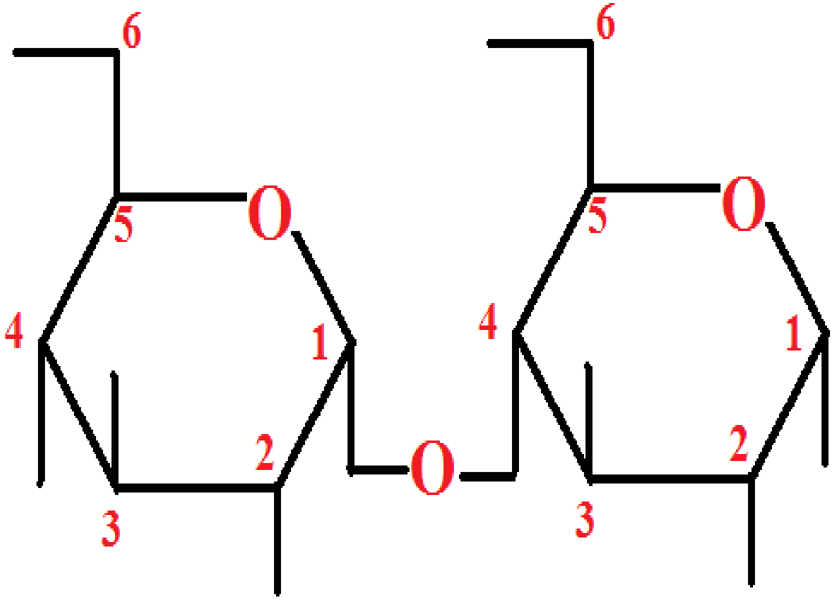




The Disaccharides

Maltose

- Maltose is also known as malt sugar;
- Maltose consists of two glucose molecules bonded together;



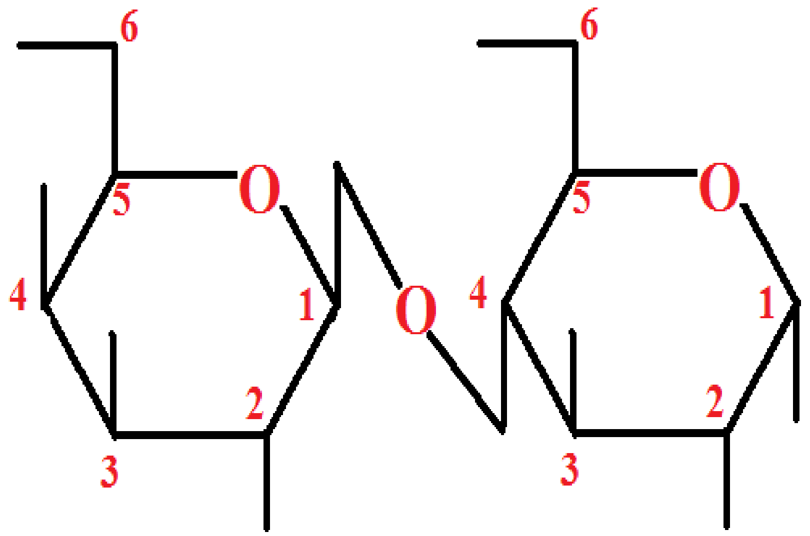
The bonds that hold these sugars together are called glycoside bonds.

An oxygen atom between the first and 4th carbons of each respective glucose molecule (see above) connects the two glucose molecules linked together in maltose.

Since the linkage is from an -OH group on the left glucose molecule that is in the α-configuration, this is called an α1 to 4 link, or $\alpha 1 \rightarrow 4$ link.

Lactose

- Lactose is milk sugar;
- Lactose consists of one molecule of galactose and one molecule of glucose -- pretty clever considering that young animals living on mother's milk use the glucose for quick energy and send the galactose to their livers where it will stored for future energy needs as glycogen -- bonded together;

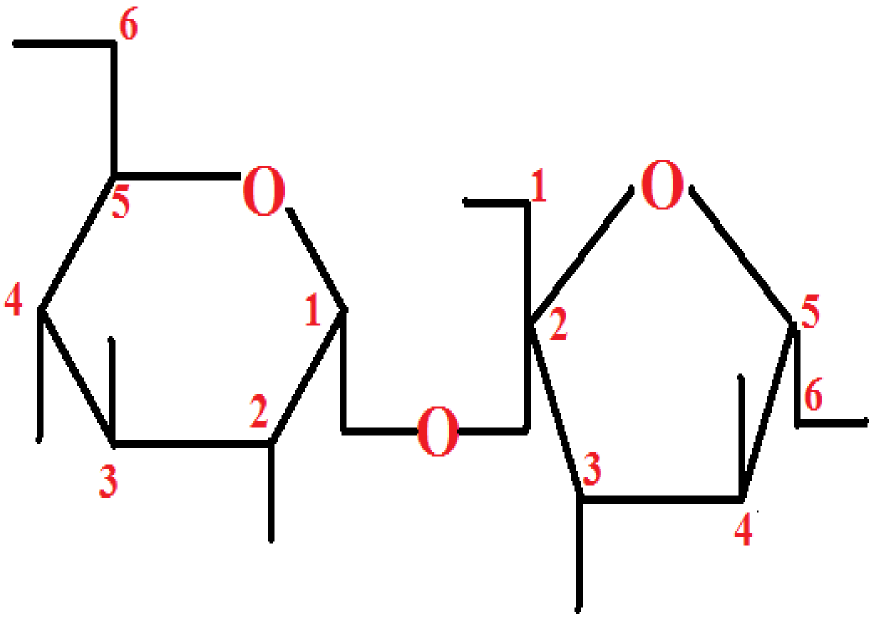


The bonds that hold these sugars together are called glycoside bonds.

Since the linkage between the galactose molecule and the glucose molecule starts in the β-configuration and is also between the 1st and 4th carbons via an oxygen atom, this is called a β 1 to 4 link, or β 1 → 4 link.

Sucrose

- Sucrose is table sugar.
- Sucrose consists of one molecule of glucose and one molecule of fructose bonded together.



The bonds that hold these sugars together are called glycoside bonds.

The linkage between the glucose and fructose molecules in sucrose occurs through the 1st and 2nd carbons of glucose and fructose, respectively.

This is an α 1 to 2 link, or α 1 $\rightarrow$2 link.

Remember, also, that there are NO carbons in any of the actual glycoside bond[s]: ONLY an oxygen atom links the monosaccharides together.

The Polysaccharides

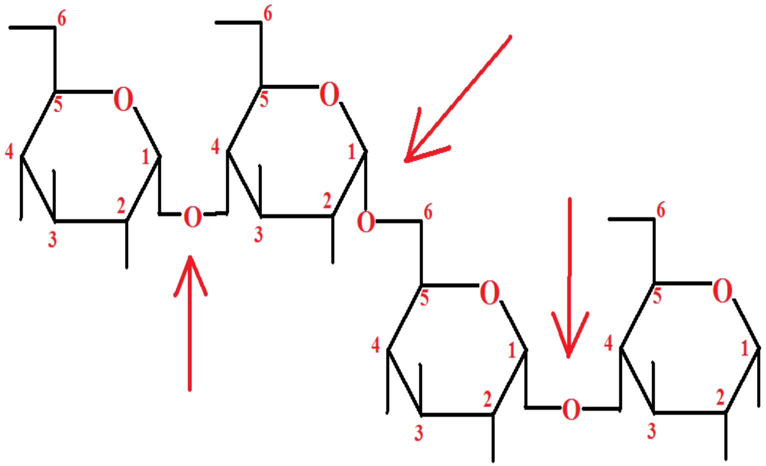
We are interested in three polysaccharides: starch, glycogen and cellulose.

Starch consists of two forms of complex carbohydrates: amylose and amylopectin

Amylose	Amylopectin
Is the less abundant form and forms α helix	The more abundant form in starch
Iodine "crawls" into the helix and forms <u>inclusion compounds</u> which turns a dark blue	Forms BOTH α 1→ 4 and α 1→ 6 links (shown in glycogen below)
Starch is found in PLANTS	Similar to glycogen due to the branching caused by the α 1→ 6 links
Amylose is hydrolyzed by amylase in our mouths	Has lesser helix amount, hence less iodine binding; the color obtained is a red-violet color
	Found in PLANTS

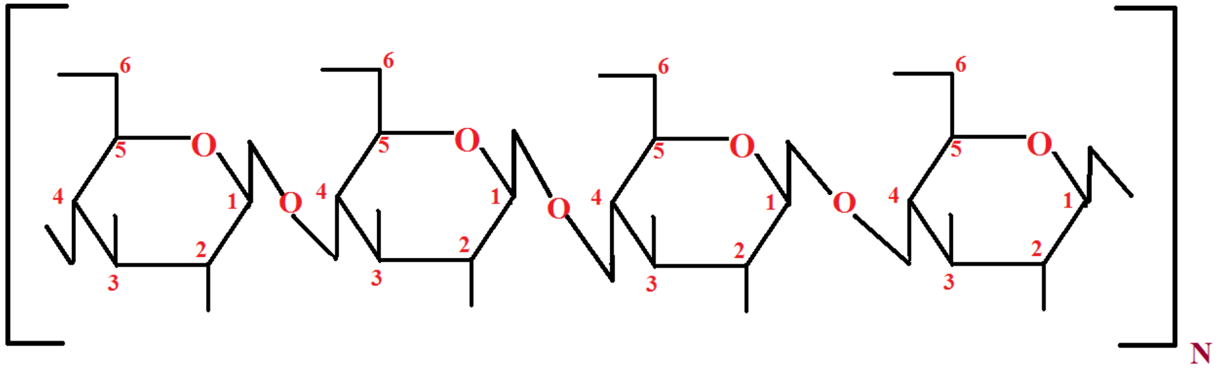
Glycogen

- Glycogen is found in ANIMALS, specifically in the skeletal muscle and liver of animals.
- It is also found in fetal hearts and fetal lungs.
- Fetal hearts run off glycogen while adult hearts run off lipids.
- The glycogen in fetal lungs is necessary to form surfactant to make oxygen passage into the body from the lungs easier when the fetus is in room air rather than the womb.
- Glycogen branches due to the same sort of linkages found in amylopectin (α 1→6 links).



- Having both α1 to 4 and α1 to 6 links lets the glycogen molecule become very dense and be very efficient for storage.
- Approximately 1/3 of the weight of the human liver is glycogen.
- The branches that are formed are then "de-formed" by an enzyme called the "debranching enzyme" when glycogen is needed for energy.
- Although glycogen has some helix, it is more like amylopectin: it forms less inclusion compounds with iodine.
- The color obtained is amber red and may be stabilized with the addition of the dihydrate of calcium chloride.
- Each glycogen molecule contains approximately 100,000 molecules of glucose per molecule of glycogen.

Cellulose



- Cellulose, our last carbohydrate, is a bit different.
- In order to hold the glucose molecules together, they are linked by β1→4 linkages.
- Humans can not metabolize these β links, while ruminants can.
- Ruminants digest cellulose because they have bacteria in their stomachs that contain the enzyme cellulase that hydrolyzes these links.
- Cellulose is the most abundant carbohydrate on earth; humans utilize it as dietary fiber.

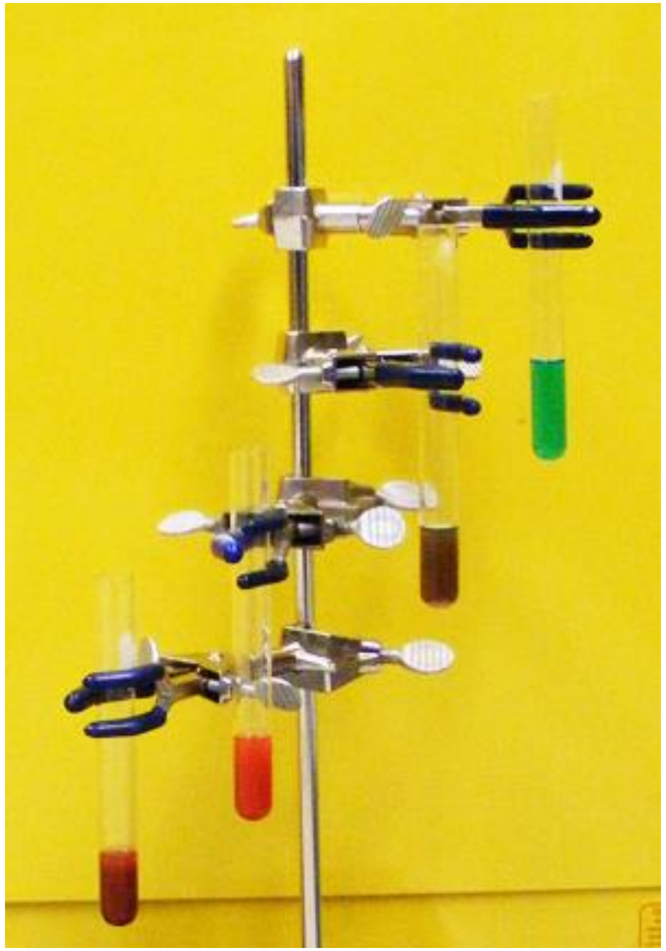
Reducing Sugars

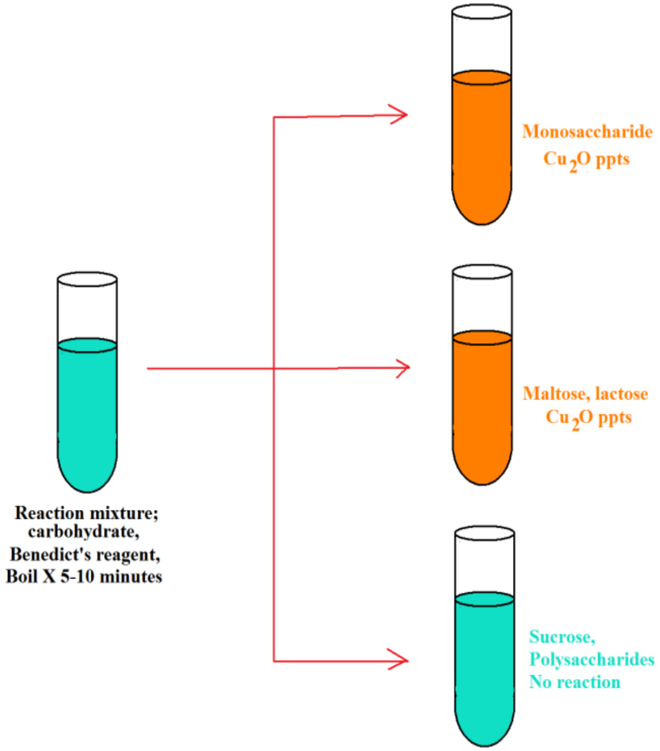
- ANY CHO which can reduce an alkaline solution of Cu(II)
  - Remember redox in the CHEM Intro?
  - What is Reduction?
  - What is Oxidation?
- ALL monosaccharides
- Lactose and Maltose
- NOT sucrose!!!!!!

IN GENERAL: if a free –OH is on the **ANOMERIC CARBON**, the CHO is a reducing sugar.

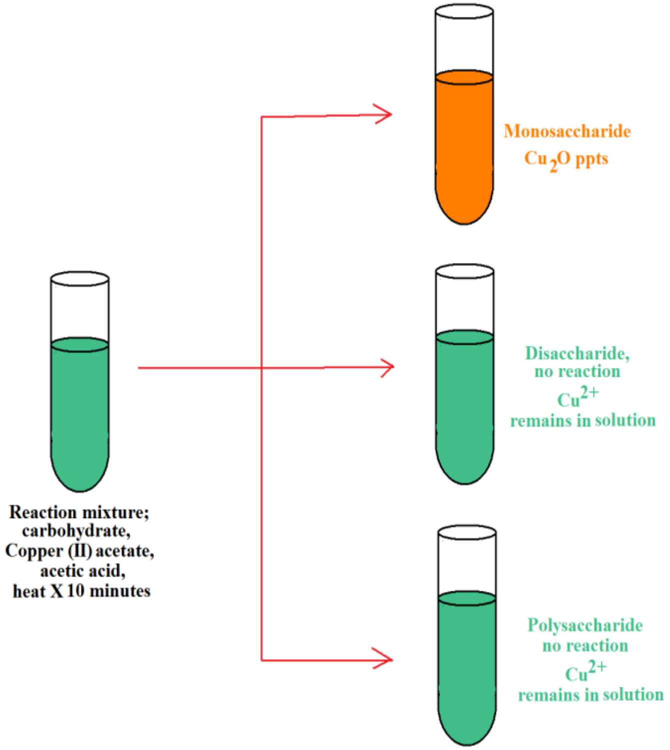
Benedict’s Test

- **Benedict’s test** is basis for Clinitest: urine test for urinary sugar excretion in diabetes
- Green: NO glucose in urine
- Brick Red: > 2 g glucose/100 mL urine





- In acid solution, Cu(II) is a WEAKER oxidizing agent
- **Barfoed's Test** is used to differentiate BETWEEN mono- and di-saccharides
- If the solutions are heated for > 10 minutes, false positive results will be obtained.



Tollen's Test

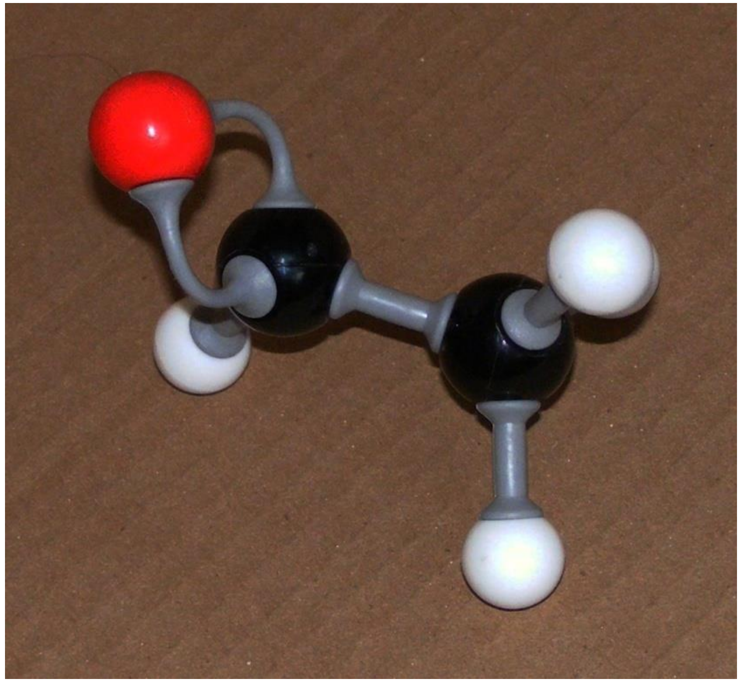
Alkynes

- Getting back into sequence with the hydrocarbons, our next functional group for discussion is the alKYNES.
- The general formula for the alkynes is C_nH_{2n-2}.
- An alkyne is a hydrocarbon that has a triple bond between two carbons: one a sigma bond and the other 2 are pi bonds.
- The geometry is linear and the hybridization is sp.
- There is no freedom of rotation about the triple bond.
- Aldehydes, Ketones and Carboxylic Acids can all be derived from Alkynes.

Aldehydes, Ketones and Acids

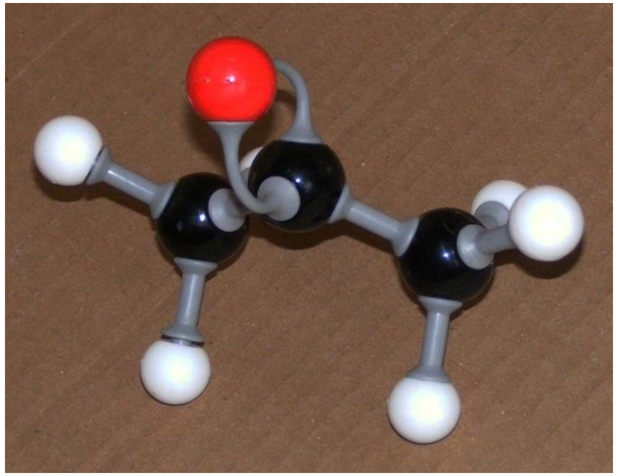
Aldehydes

- The functional group of an aldehyde is an end carbon that is double bonded to an oxygen and single bonded to a hydrogen atom.
- The remaining fourth bond may be bound to either another hydrogen atom (to make formaldehyde -- methanal by IUPAC) or to a hydrocarbon "tail".
- The names that end in "al" are the IUPAC names.
- Image, right, is of ethanal or acetaldehyde



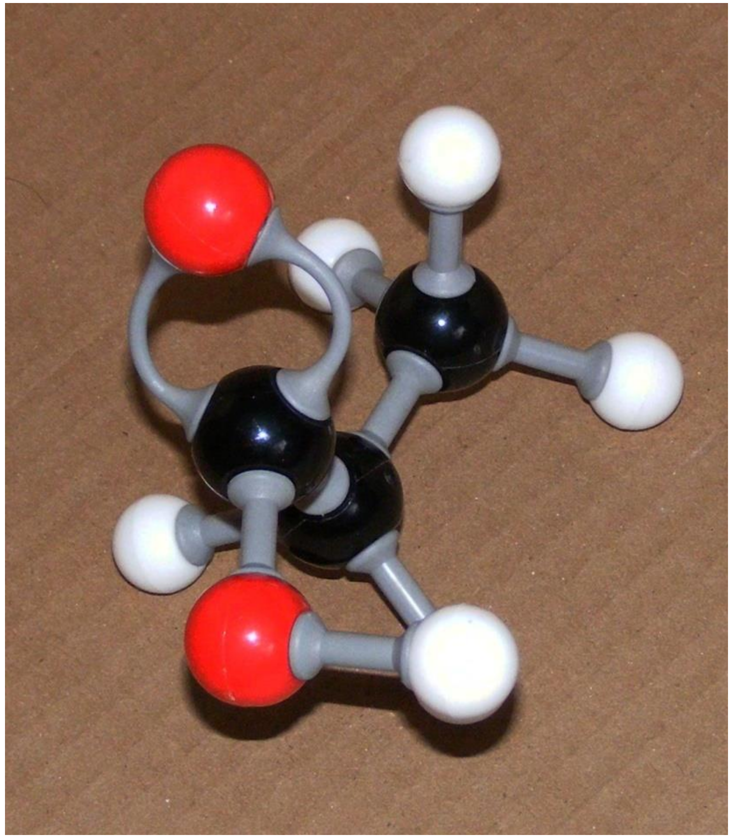
Ketones

- The functional group of a ketone is a double bonded oxygen atom to a carbon atom. That carbon atom MUST be bonded to two other hydrocarbons to make the ketone.
- The simplest ketone is acetone for this very reason. The IUPAC name for acetone is propanone -- "prop" for 3 carbons, "an" for the alkane and "one" for the ketone.
- It's not necessary to enumerate the ketone in either propanone or butanone. Once one moves into the pentanone family and beyond, it is necessary to enumerate where the ketone is on the chain.
- Ketones are generally used as solvents. Acetone (above) is used as finger nail polish remover; MEK is finding some use in that area, as well.



Carboxylic Acids

- The functional group of the organic acids is the end carbon double bonded to an oxygen and single bonded to an OH group (propanoic acid at right).
- The COOH group, or carboxyl, or CO_2H group ionizes and causes changes in the pH of solutions.
- The fourth remaining bond may be bound to a hydrogen atom (making formic acid or methanoic acid by IUPAC) or to a hydrocarbon tail.
- NOTE: the carboxyl hydrogen fairly easily dissociates to a proton (H^+) and leaves the carboxyl group negatively charged as the carboxylate group (COO^- or CO_2^-)



Lipids: An introduction

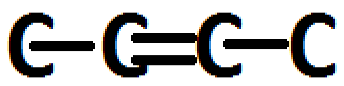
Fatty Acids

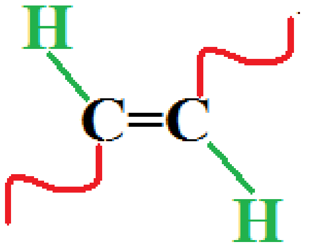
- The simplest lipids are the fatty acids.
- These are long chain hydrocarbons with carboxyl groups (COOH groups).
- We are interested in two groups of fatty acids: saturated and unsaturated fatty acids.
- Saturated fatty acids are so called because each carbon atom in the chain holds all the possible hydrogen atoms it can.
- These lipids tend to be solids at room temperature.
- These are also the sorts of lipids found around organs in the human body, acting as cushions.
- The only bonds present between the carbon atoms are single bonds.

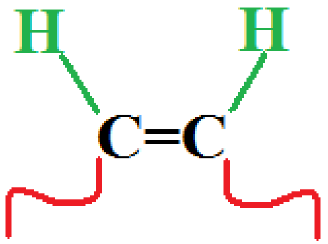
C—C

Fatty Acids

- Unsaturated fatty acids do not have all the hydrogens they can hold, for there are occasional carbon-carbon double bonds in addition to the single bonds between carbon atoms.
- These fatty acids tend to be liquids at room temperature and are the primary type of lipid found in skin deposits.
- Naturally occurring unsaturated fatty acids contain double bonds that are in the "cis" form and artificial unsaturated fatty acids contain double bonds that are in the "trans" form.
- The trans-fatty acids are found in oleo and margarine and have a high link with heart disease.
- Below is a graphic of the two types of double bonds.
- The squiggly lines represent the rest of the molecule.
- The top graphic shows the hydrogens across from each other in the double bond. This is the "trans" form.
- The bottom graphic shows the hydrogens on the same side of the double bond. This is the "cis" form.

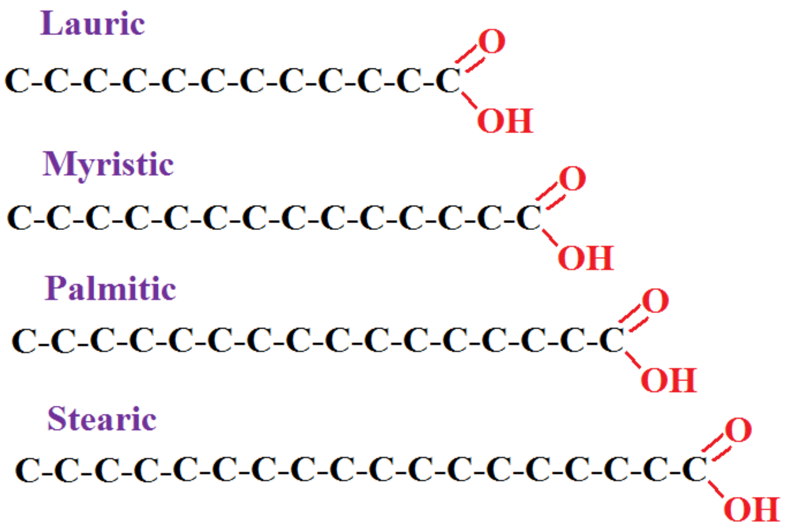






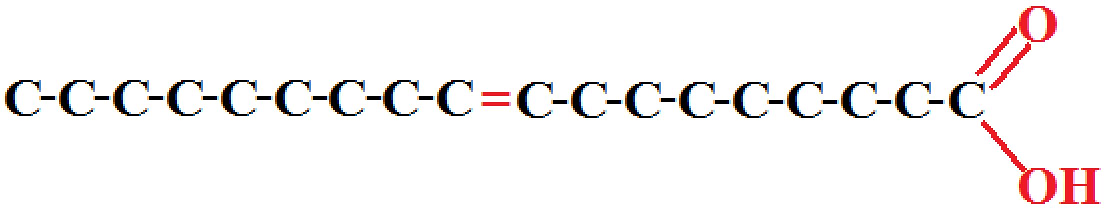
Fatty Acids – Special Carboxylic Acids -- Saturated

Lauric Acid	Myristic Acid	Palmitic Acid	Stearic Acid
$C_{12}H_{24}O_2$	$C_{14}H_{28}O_2$	$C_{16}H_{32}O_2$	$C_{18}H_{36}O_2$
Dodecanoic acid 12:0	Tetradecanoic acid 14:0	Hexadecanoic acid 16:0	Octadecanoic acid 18:0
found in coconut oil	found in coconut oil	found in lard	found in lard



- There are 4 unsaturated fatty acids that are important to remember, as well.
- NOTE: EFA = essential fatty acid.
- There are three items that need discussion, here, before examining the fatty acids:
  - 1) the "n-" nomenclature,
  - 2) the "*w*" (omega) system of nomenclature and
  - 3) the "delta" system of nomenclature.
- The "n-" system of nomenclature comes from going to the CH_3 end of the molecule and counting in from the end (end - [e + d] = n) to the carbon with the first double bond.
- The omega system is the same system, just another name.
- The delta (Δ) system of nomenclature of fatty acids, specifically unsaturated fatty acids, is equally as simple: the first number is the number of carbon atoms in the hydrocarbon chain.
- The number after the colon is the number of double bonds in the whole molecule between carbon atoms.
- The numbers superscripted above the delta (Δ) sign tell you the location of the double bonds, e.g., $^{\Delta\,9,\,12,\,15}$: the double bonds are between carbons 9 and 10, 12 and 13 and 15 and 16, where we only identify the carbons by the lowest number in the double bonds.

Mono-Un-Saturated Fatty Acids (MUFA)



$$\mathrm{C{-}C{-}C{-}C{-}C{-}C{-}C{-}C{-}C{=}C{-}C{-}C{-}C{-}C{-}C{-}C{-}C{-}C(=O)OH}$$

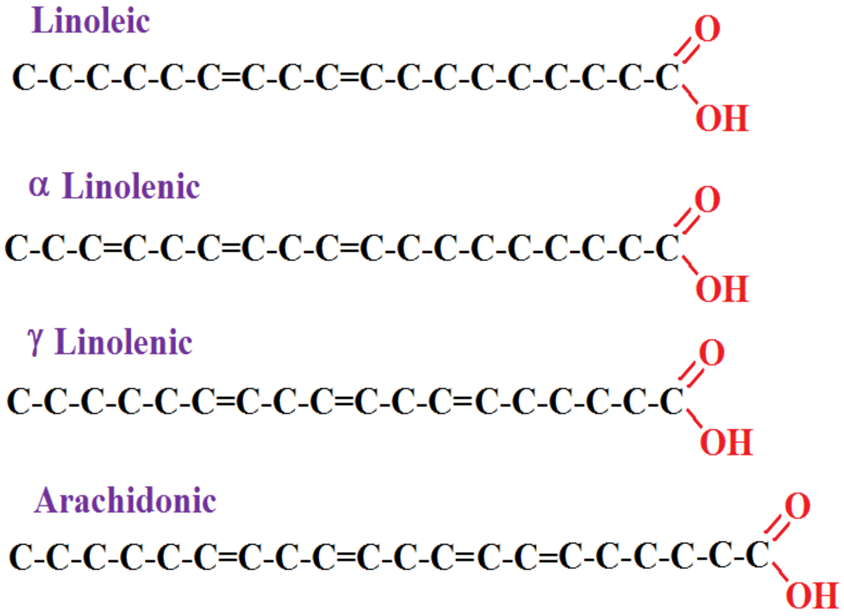
- 18:1, n-9 or 18:1 ω9 or $18{:}1\Delta^9$
- Oleic Acid
- Cis-9-octadecenoic acid (trans isomer is elaidic acid and causes a great deal of cardiovascular troubles)
- Olive oil (best)
- Canola oil, grapeseed oil, avocado oil, avocado, almond oil, pecan oil, peanut oil, HOSO’s (high oleic sun/safflower oil) pretty good, too
- Slows development of heart disease; seems to lower blood pressure in hypertensives
- Lowers total cholesterol levels
- Raises HDLs
- Lowers LDLs
- See also: http://www.spectracell.com/media/supplement-oleic-acid.pdf

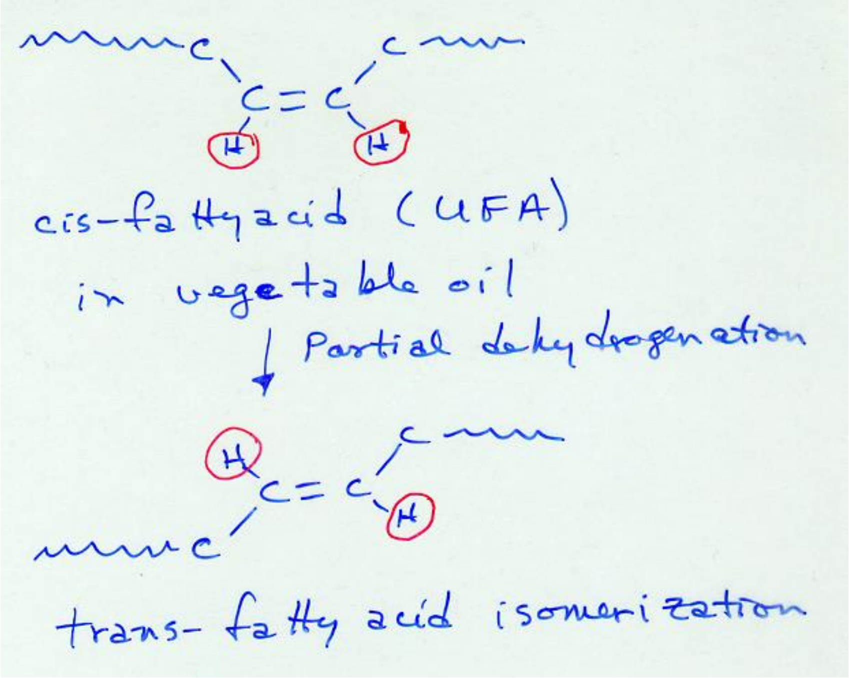
Poly-Un-Saturated Fatty Acid (PUFA) Nomenclature

Linoleic Acid	**α-Linolenic Acid**	γ-Linolenic Acid	Arachidonic Acid
9,12-octadecadienoic acid	**9,12,15-octadecatrienoic acid**	6,9,12-octadecatrienoic acid	5,8,11,14-eicosatetraenoic acid
ESSENTIAL for life			
$18{:}2\ \Delta^{9,\ 12}$	**$18{:}3\ \Delta^{9,\ 12,\ 15}$**	$18{:}3\ \Delta^{6,\ 9,\ 12}$	$20{:}4\ \Delta^{5,\ 8,\ 11,\ 14}$
n-6 or ω 6 18:2, n-6	**n-3 or ω 3** **18:3, ω 3**	n-6 or ω 6 18:3, n-6	n-6 or ω 6 20:4, ω 6
found in corn oil, soybean oil, cottonseed oil	**found in leafy vegetables and vegetable oils, flaxseed/meal (ALA), walnuts**	found in leafy vegetables and vegetable oils	found in peanut oil, brain/nervous tissue

Fatty Acid Anomalies

- PUFA Structures, below

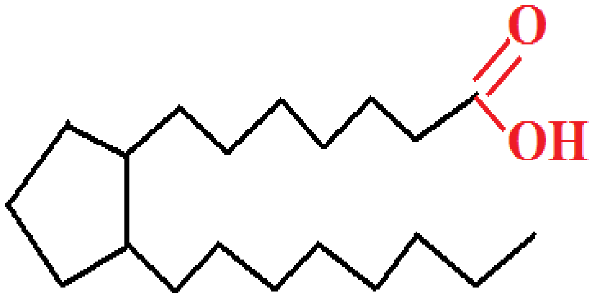




- "hydrogenated" margarines contain 15-40% trans fatty acids
- ↑ trans-fatty acids → hypercholesterolemia → ↑ CAD, ASHD, CHD

Arachidonic Acid

- Why is Arachidonic acid important?
- It is important because it is the precursor fatty acid for prostaglandin and leukotriene biosynthesis.
- These compounds are known as eicosanoids, i.e., compounds based off 20 carbons.



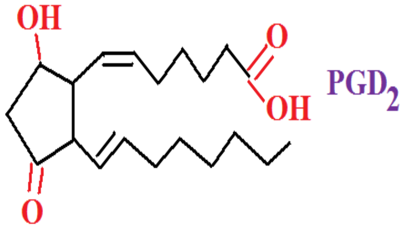
Prostanoic Acid

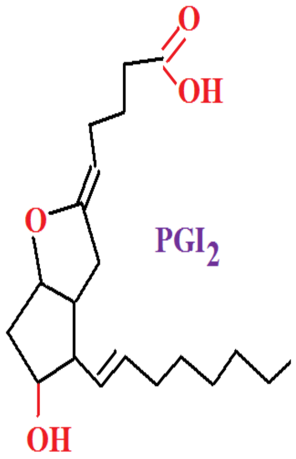
PG's and LT's

- Prostaglandins are based off prostanoic acid; representative PG's and leukotrienes (LT's) are shown, as well.
- There are nomenclature rules that follow prostaglandins, too. PG is short for prostaglandin.
- The **letter** tells us about the ring constituents and the **subscripted number** tells us how many double bonds there are on the side chains.
- PG's may be inhibited at the level of synthesis with aspirin; anti-leukotriene agents are now available for treating airway diseases, e.g., Accolate, Singulair, Zyflo.

PGD$_2$

Mediates niacin skin flush



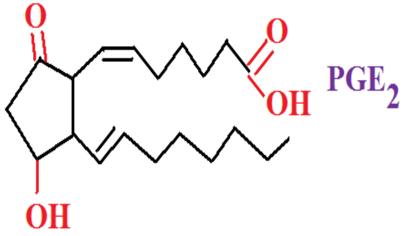


PGI$_2$

aka prostacyclin; vasodilator; anti-aggregator

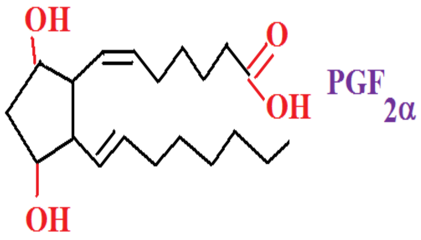
PGE$_2$

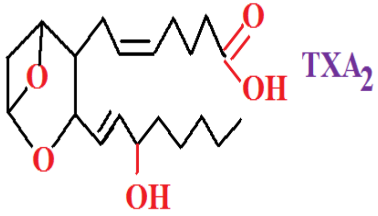
vasodilator



PGF$_2$

uterine muscle contractant





TXA$_2$

vasoconstrictor; platelet aggregator

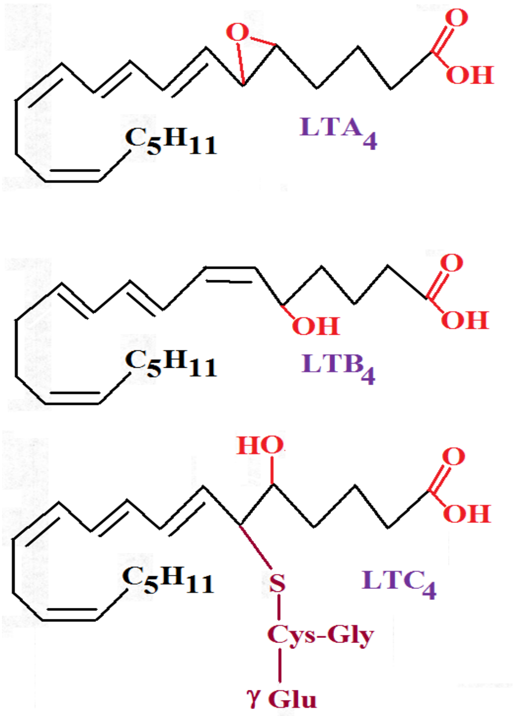
LTA$_4$

Its biological actions are determined primarily by its metabolites.

LTB$_4$

chemotactic agent for PMN's (segmented neutrophils); has been proposed to play a role in a variety of acute and chronic inflammatory diseases such as arthritis, dermatoses, inflammatory bowel disease (IBD), and chronic obstructive pulmonary disease (COPD). In particular, LTB$_4$ seems to play a role in the recruitment of inflammatory cells to the site of tissue injury.

(http://ajrccm.atsjournals.org/cgi/content/full/161/2/S1/S25)



LTC$_4$

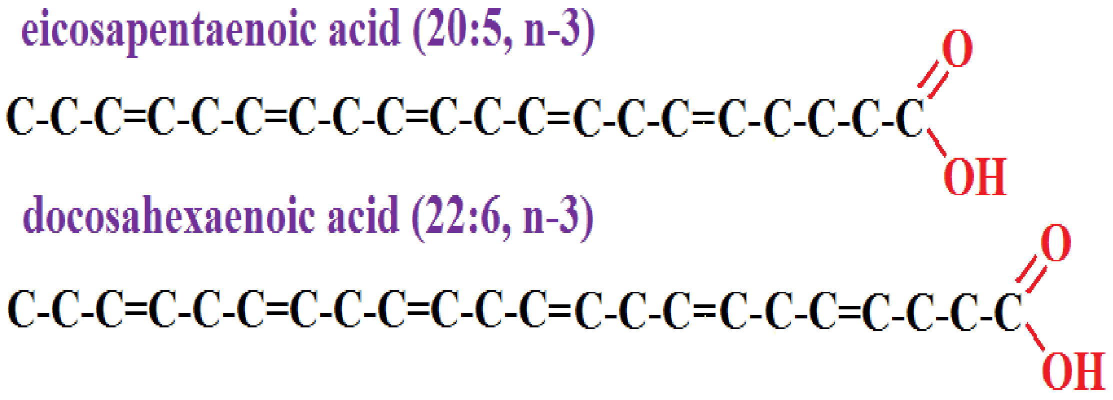
involved in allergy and anaphylaxis; more potent than HISTAMINE in shutting down airways and increasing swelling; component of SRS-A; bronchoconstrictor and vasodilator

JAOA
The Journal of the American Osteopathic Association

Role of Antileukotriene Agents in Asthma Therapy

- **SM Gawchik; CL Saccar : ABSTRACT:** *Leukotrienes are proinflammatory mediators with special significance in asthma. Released by numerous cell types, particularly after exposure to allergens, leukotrienes cause a potent contraction of bronchial smooth muscle, resulting in reduced airway caliber. Further, they cause plasma to leak from the vessels, resulting in edema, and enhance the secretion of mucus--both events that increase airway obstruction. Thus, leukotrienes have been a target of basic research in asthma.*
- *To date, a number of antileukotriene agents have been developed, and three are currently being used in clinical practice in the United States:* ***zafirlukast [ACCOLATE]*** *and* ***montelukast [SINGULAIR]*** *act by antagonizing the leukotriene receptor, and* ***zileuton [ZYFLO]*** *inhibits leukotriene synthesis. Studies have shown that these agents improve asthma symptoms, pulmonary function, and patient quality of life.*
- *Antileukotriene agents have generally been associated with a low incidence of side effects and good tolerability.*
- *Currently recommended for mild-to-moderate, persistent asthma, these agents have enabled patients to reduce their use of corticosteroids.*
- **JAOA • Vol 100 • No 1 • January 2000 • 32 – Cited in whole; All Drug Trade Names are Proprietarily Trademarked and External to the Abstract**

ω3 PUFA's


eicosapentaenoic acid (20:5, n-3)

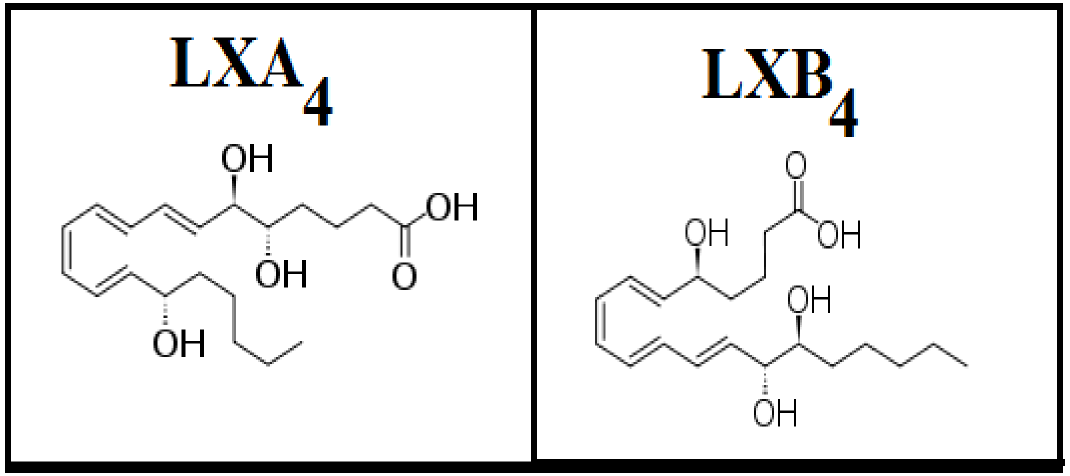
$$\text{C-C-C=C-C-C=C-C-C=C-C-C=C-C-C=C-C-C-C-}\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}$$

docosahexaenoic acid (22:6, n-3)

$$\text{C-C-C=C-C-C=C-C-C=C-C-C=C-C-C=C-C-C=C-C-C-}\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}$$

- Note that arachidonic acid gives rise to the PG„$_{2}$” series of prostaglandins – most of these are pro-inflammatory and can lead to serious consequences, e.g. myocardial infarction.
- Recently, two significant PUFA's (EPA and DHA) in fish oils have found more and more use for the treatment of various hyperlipidemias because they are n-3 fatty acids which produce the PG„$_{3}$” family which are primarily anti-inflammatory and, hence, heart healthy (EPA and DHA are illustrated above).
- There is some preliminary research (2010) that suggests that mammalian cells can elongate ALA (18:1, n-3) to 20:5, n-3 (EPA) – the conversion is not very efficient: 11 g of ALA (10 Tbsp of flaxseed meal a day!) are needed to biosynthesize 1 g EPA.
- It also seems that 20:5, n-3 is elongated to 22:6, n-3

Lipoxin’s



Lipoxins
anti-inflammatory

“LX’s”: derived from ω3 fatty acids (EPA) as well as ω6 fatty acids such as $20{:}4^{\Delta 5,8,11,14}$

ASA CHANGES COX-2 activity to produce anti-inflammatory lipoxins

PUFA Update: PI-PUFA

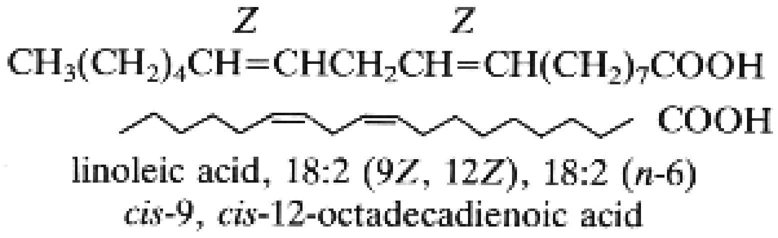
To describe the unsaturated fatty acids, two methods are available:

- ***The chemist's terminology:***

  The carbon atoms are counted from the carboxyl group which put the emphasis on the double bond closest to this group (Δ-notations).

- As an example:

  - 18:2 Δ9,12 or 18:2 $^{\Delta 9,12}$
  - cis-9, cis-12-octadecadienoic acid,
  - the trivial name: linoleic acid.



$CH_3(CH_2)_4CH\overset{Z}{=}CHCH_2CH\overset{Z}{=}CH(CH_2)_7COOH$

linoleic acid, 18:2 (9*Z*, 12*Z*), 18:2 (*n*-6)
cis-9, *cis*-12-octadecadienoic acid

- The double bonds have usually a Z (cis) configuration (but can have also an E (trans) configuration): Z9,Z12-octadecadienoic acid

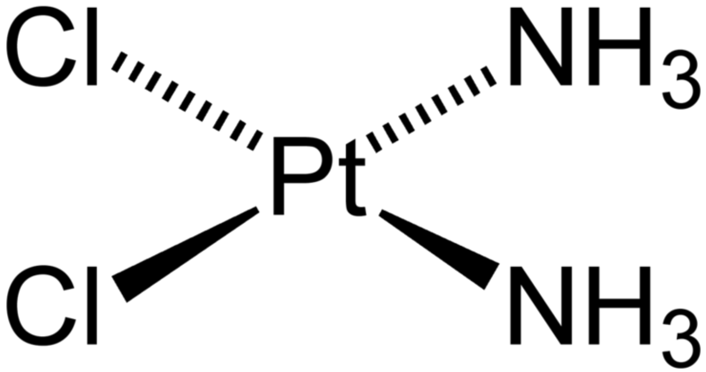
  The biochemist's and physiologist's terminology:

  Holman RT proposed in 1964 a new numbering system for the unsaturation of fatty acids, the "omega nomenclature". The double bonds are counted from the methyl group determining the metabolic family, noted by ωx (ω for the terminal carbon) or the equivalent n-x (n for the total number of carbon, x being the position of the distal double bond) method. The other double bonds are deduced from the first one by adding 3 (this is the most frequent structure, non-conjugated fatty acids, but sometimes by adding 2, these double bonds are called conjugated).

  Thus, linoleic acid or cis-9, cis-12-octadecadienoic acid is also named using the shorthand nomenclature 18:2 (n-6). This compound has 18 carbon atoms, 2 double bonds and 6 carbon atoms from the last double bond to the terminal methyl group. In the old literature it was designated 18:2ω6: 18-6=12, 12-3=9, hence Δ9,12.

Sources (09/14/2011): http://www.cyberlipid.org/fa/acid0001.htm
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=79929

cisplatin



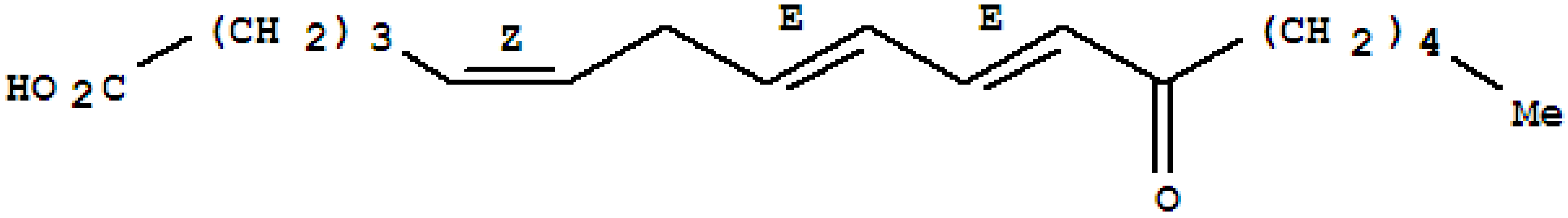
- Cisplatin is a cancer chemotherapeutic agent which is used in treating cancers including: sarcoma, small cell lung cancer, germ cell tumors, lymphoma, and ovarian cancer.

- It is often considered an alkylating agent, however, it contains no alkyl groups and does not instigate alkylating reactions, so is most appropriately designated as an alkylating-like drug.

- It causes DNA cross-linking and drives apoptosis to kill the malignant cells.

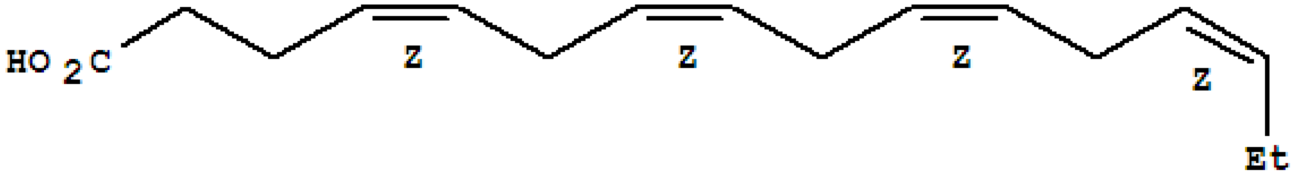
- NCI link: http://www.cancer.gov/cancertopics/druginfo/cisplatin

12-oxo-Z5,E8,E10-heptadecatrienoic acid



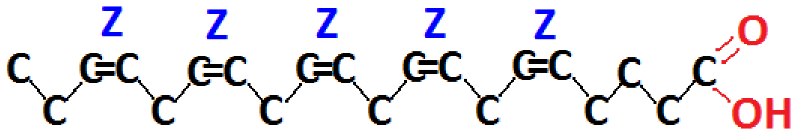
- KHT (acronym)
  - Z = cis
  - E = trans
- Platinum Induced PolyUnsaturated Fatty Acid: PI-PUFA
- Inhibits action of some cancer chemotherapeutic agents, e.g., cis-platin
- Also found in Fish Oils – NOT to be taken with many chemotherapy agents!

16:4 (n-3)
hexadeca-Z4,Z7,Z10,Z13-tetraenoic acid (HDTA)



- Also CA Tx inhibitory – PI-PUFA
- Also found in fish oils
- Also need to stop if receiving CA Tx

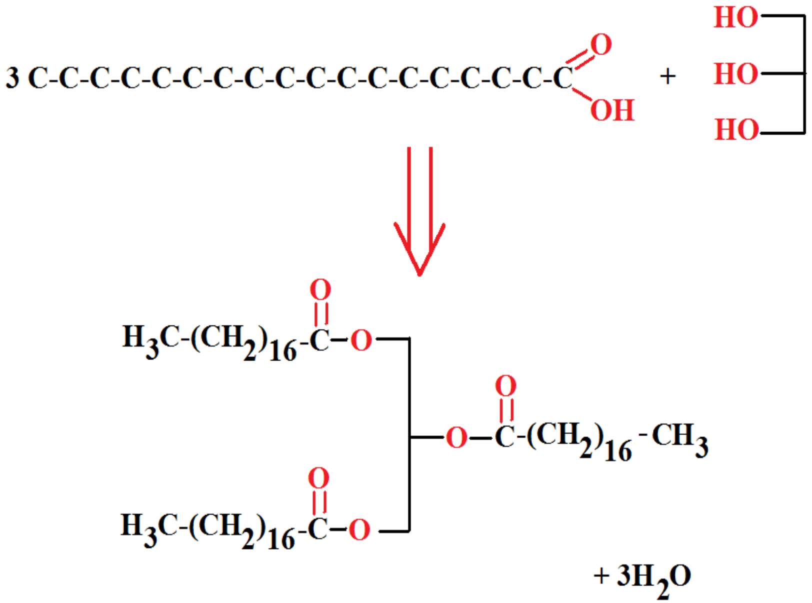
20:5 (n-3)
all-Z-5,8,11,14,17-Eicosapentaenoic acid (EPA)

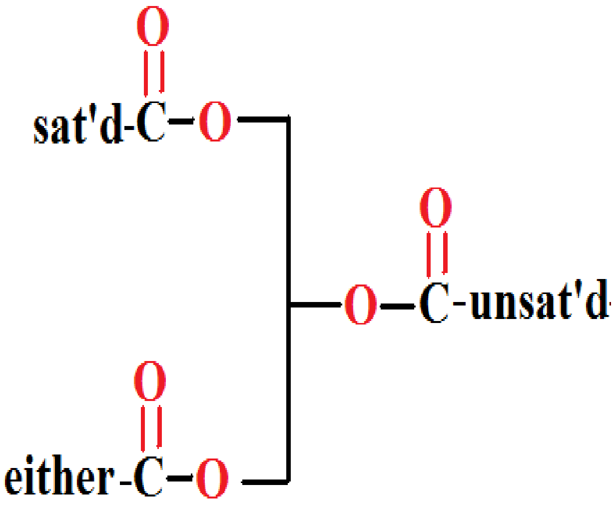


- One of three important n-3 fatty acids
- Other two are:
    - 22:6, n-3 (DHA)
    - 18:3, n-3 (ALA)
- EPA used as control in PI-PUFA determination: no impact on the PI-PUFA biosynthesis

Triglycerides (TG's or TAG's)

- TG is fairly self explanatory; TAG's are triacyl glycerols - the same thing, just a slightly different name. TAG's are made by condensing one molecule of glycerol with three molecules of fatty acids.
- The products are the triglyceride (in this case, tristearin) and 3 moles of water.

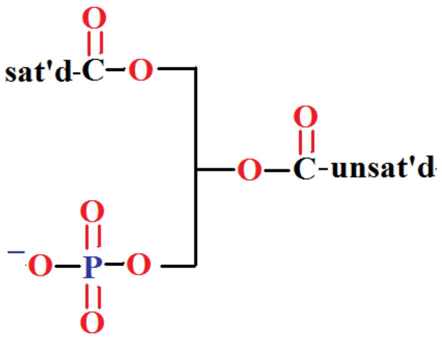


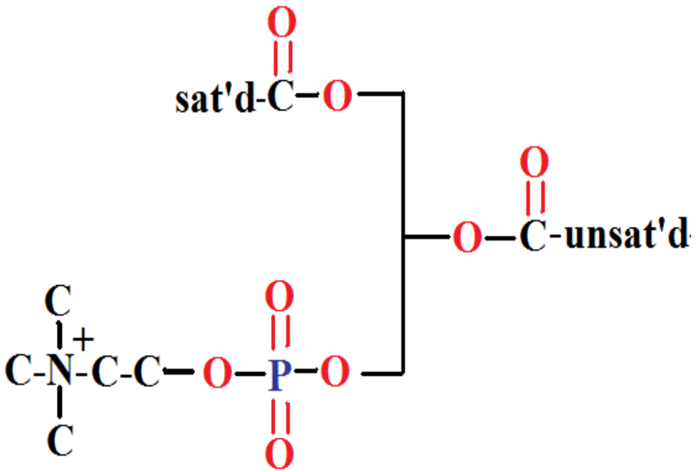


- As a general rule, fatty acids align themselves on a glycerol molecule in such a manner that the #1 carbon has a saturated fatty acid bound to it, #2 carbon has an unsaturated fatty acid bound to it and #3 is fair game.

PL’s

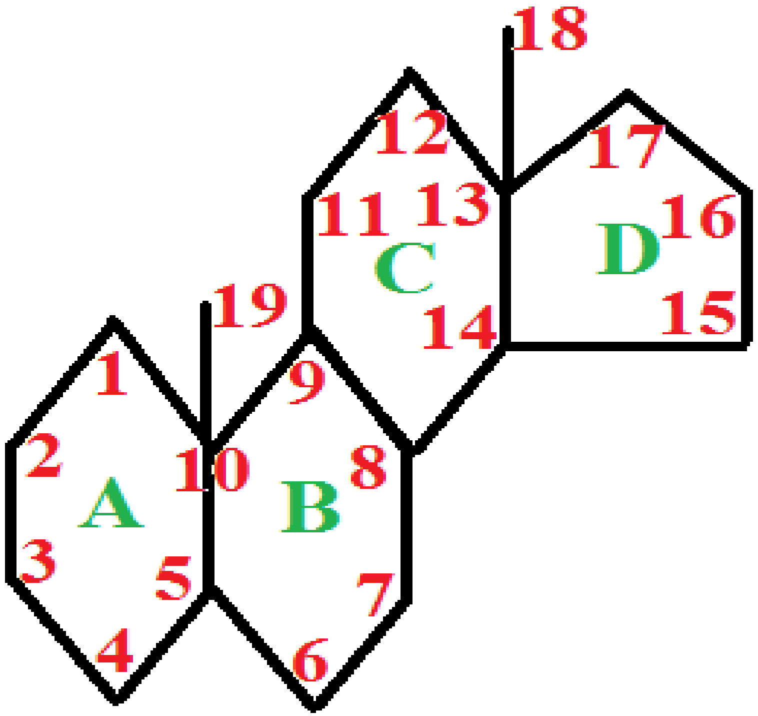
- A lipid related to the TAG is the phospholipid (PL).
- Instead of a third fatty acid bound, proper, to the #3 carbon on glycerol, a phosphate is bound there.
- Other groups will bind with the phosphate.
- Figure is representative of phosphatidic acid.
- A representation/illustration of phosphatidyl choline (PC) or lecithin is below.
  - You may know the latter name as it is in non-dairy creamers as an emulsifying agent.
  - PC is also important in cell membranes by assisting in membrane rigidity.
- A related PL, cardiolipin, is a sort of "dimer" of PC.
  - Cardiolipin is found in the inner mitochondrial membrane.
  - This PL causes the inner mitochondrial membrane to be more fluid so that the protein complexes on electron transport will be brought closer together during active cellular respiration.





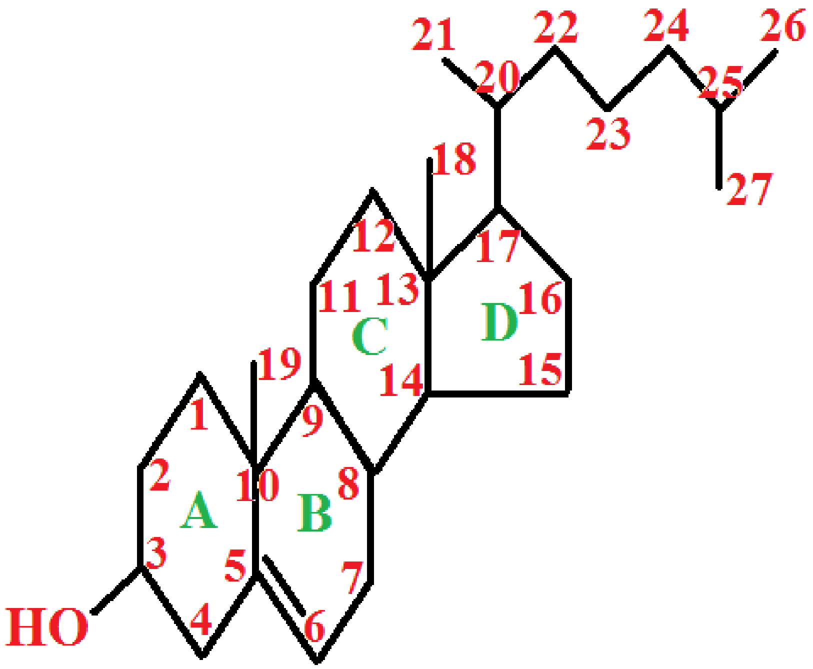
The Steroids

- The steroids are ALL based off of a 4-fused ring system.
- The rings are labeled A thru D. Each carbon is numbered as shown in the graphic.



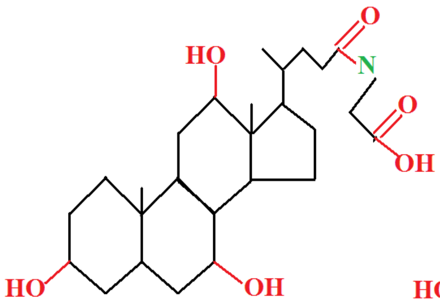
Cholesterol

- The primary steroid, i.e., that one compound from which all steroids are derived is cholesterol.
- As you can see, the enumeration of cholesterol (once you are beyond the basic 4 ring system) is different than what one might expect.
- Carbons 18 and 19 are called bridging carbons.
- On carbon #3 is an -OH group and between carbons 5 and 6 is a double bond.
- The hydrocarbon tail off carbon 17 is enumerated for you, above. In addition, the hydrocarbon chain will be modified by the body as necessary for the synthesis of specific steroids.

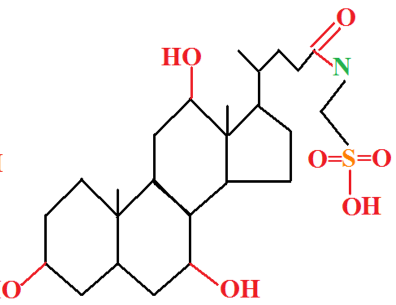


Digestive Detergents

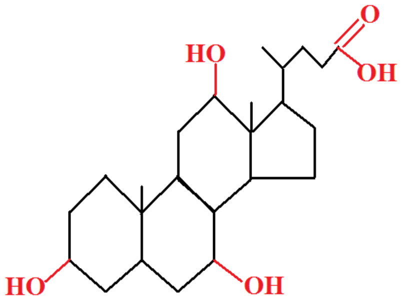
- Cholesterol also plays an important role in digestion.
- The manner in which this occurs is that a derivative of cholesterol (cholic acid) reacts with one of two amino acids or derivatives to form detergents.
- Detergents emulsify fat in the small bowel as small particles so that the enzymes in our small bowels may begin digesting the lipid.
- The two big bile salts, as these detergents are called, are glycocholic acid and taurocholic acid.
- Glycocholic acid is formed by the reaction of gly with cholic acid.
- Taurocholic acid is formed by reacting the oxidized product of cys, taurine, with cholic acid.
- Note that there is a polar, charged end and a nonpolar, uncharged, lipid-like end.
- It is due to these features that detergents work, i.e., the lipid-like end binds the lipid-like molecules and the polar end interacts with the water, in effect lifting the grease into the water.



Glycocholic Acid



Taurocholic Acid



Cholic Acid

The Most Complex Lipids: The Lipoproteins of The Blood

- Lipid Complexed with Water-Soluble Proteins

We are interested in 4 categories of lipoproteins: Chylomicrons, VLDL's, LDL's and HDL's (very low density lipoproteins, low density lipoproteins and high density lipoproteins). The table below describes the characteristics of the lipoproteins:

Classes of Lipoproteins				
	% Protein	% TAG	% PL	% Cholesterol esters
Chylomicrons	1-2	85-95	3-6	2-4
VLDL	6-10	50-65	15-20	16-22
LDL	18-22	4-8	18-24	45-50
HDL	45-55	2-7	26-32	15-20

Comments

- Chylomicrons, by and large, are artifactual in the sense that they appear after we've eaten or if we have some sort of lipid metabolizing disease, e.g. diabetes mellitus, and are usually rapidly cleared from the blood stream under normal circumstances.
- The LDL's are the cholesterol forms we hear about as the "bad" cholesterol.
  - This portion is true as when we get too many LDL's, the cholesterol plates out in our arteries and forms atherosclerotic plaques.
- While the HDL's are touted as the "good" cholesterol, it is important to remember that it is ONE form of the HDL that is the good cholesterol.
- ASIDE: Not all cholesterol is "bad" cholesterol.
  - Remember, we need some cholesterol in our diets to synthesize steroid hormones.
  - While our bodies WILL synthesize steroids from smaller molecules, they prefer cholesterol as the starting molecule.
- Note that LDL-cholesterol runs about half cholesterol.

LDL-Cholesterol

- In many instances, it is difficult to obtain an actual lab analysis of the LDL-cholesterol. In that case, it may be calculated in one of two ways:

Method 1:

- $\text{LDL} = \text{Cholesterol}_{(\text{total})} - (\text{VLDL} + \text{HDL})$

Method 2:

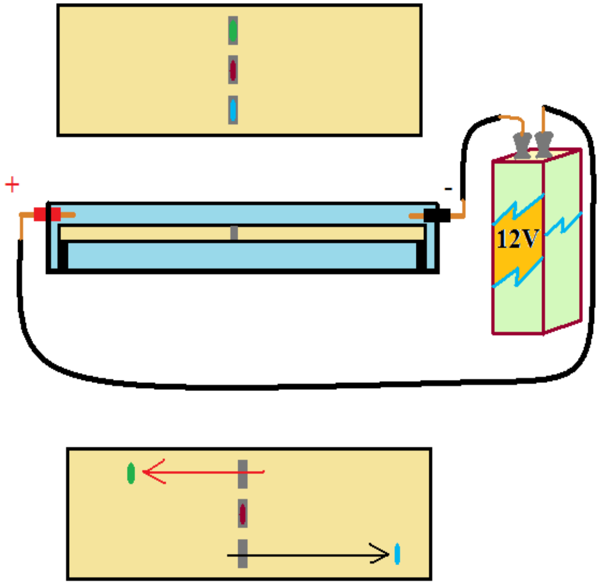
- $\text{LDL} = \text{Cholesterol}_{(\text{total})} - [(0.2 * \text{TAG}) + \text{HDL}]$

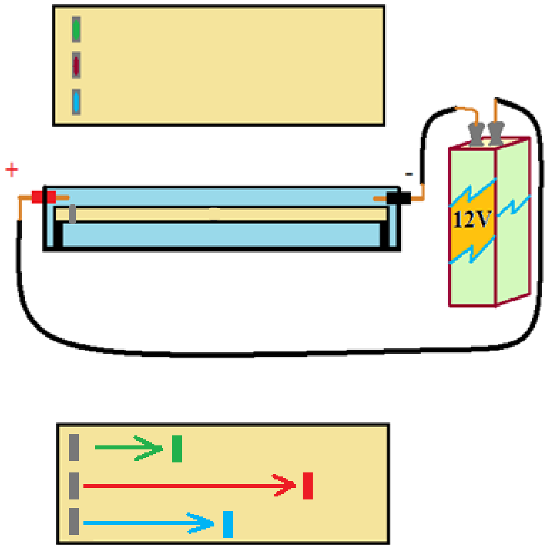
where TAG are the triglycerides in your blood

Electrophoresis

- Defined: separation of particles in a gel by an electrical charge
- Each entity migrates to its point of electrical neutrality: its pI (isoelectric point)

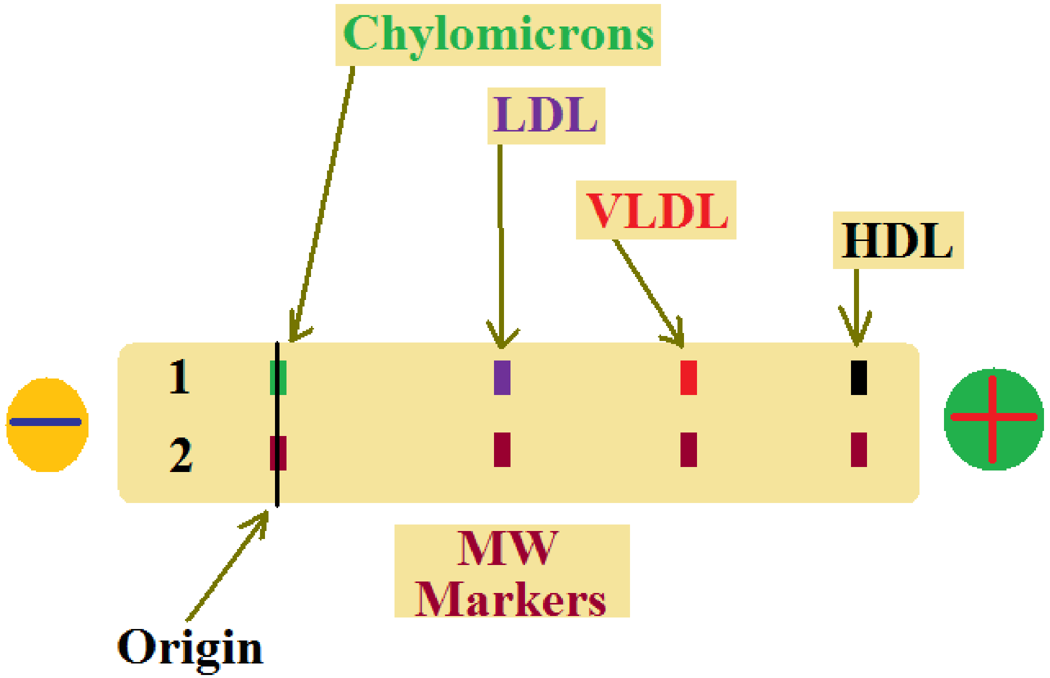
$$pI = \frac{\sum 2\,\text{closestpK Values}}{2}$$



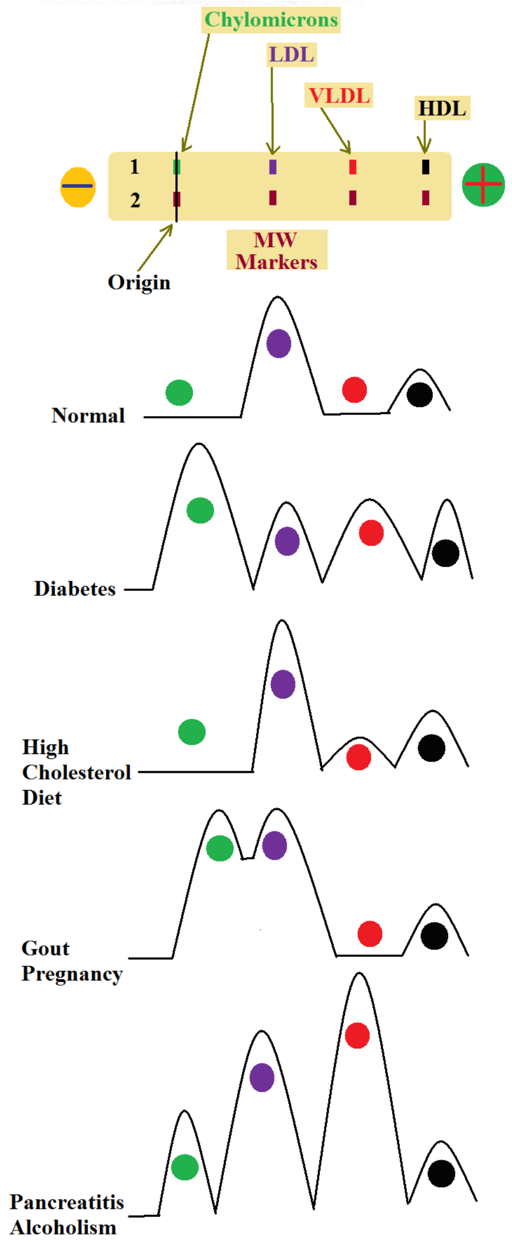


- These lipoproteins may be separated in a polyacrylamide gel or in an agarose gel that is in an appropriate buffer by applying an electrical current.
- This is called electrophoresis (separation by electricity).
- As the molecules migrate into the gel under the influence of the current, they "are looking" for the region of the gel at that particular pH and charge where the medium is most "like themselves".
  - pH is determined by knowing the pK values of the overall protein, based on their amino acid content.
- Once these molecules reach that region, they stop migrating and may be analyzed.
- At right is a representative graphic that demonstrates the separation of these lipoproteins at pH 8.6

- Note that with the exception of the Chylomicrons, the other lipoproteins are attracted to the positive side of the gel (or paper), indicating that their charges are more negative.
- The origin is the place where the samples are place in tiny wells in the gel.
- The Chylomicrons did not move from the origin.
- Information like this is very useful, clinically.

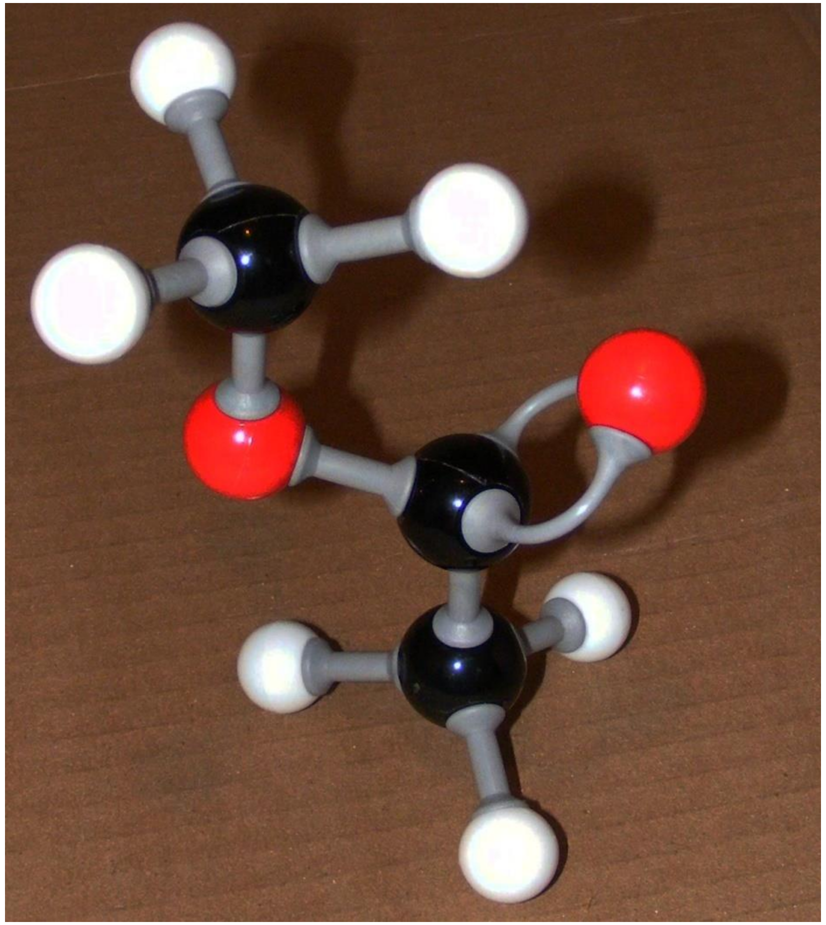


- Information like this is very useful, clinically. Patterns of lipoproteins may be detected by utilizing a gel scanner that uses light to detect how much of a particular lipoprotein is present. Some sample scans and their associated disease states are presented to the right.
- Note that
    - **diabetics have elevated Chylomicrons and VLDL's with lowered LDL-cholesterol;**
    - **those eating a high cholesterol diet have elevated LDL's and VLDL's;**
    - **those with gout have elevated LDL's and VLDL's, as do pregnant women;**
    - **those with pancreatitis or alcoholism have elevated Chylomicrons, LDL's and VLDL's.**



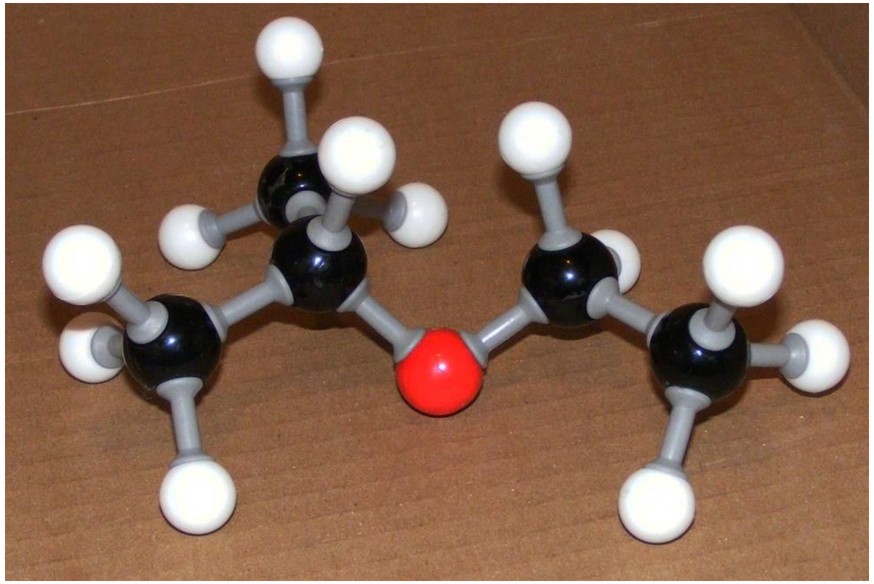
Esters

- When an organic acid and an alcohol react in the presence of a mineral acid catalyst, an ester is obtained.
- Image, below, is methylethanoate.



Ethers

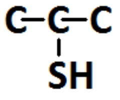
- NOT to be confused with esters, ethers are hydrocarbons linked to each other through an oxygen atom. The most commonly known ether is diethyl ether ($CH_3CH_2OCH_2CH_3$). R-O-R’
- It was used as an anesthetic until it became very obvious that it caused more problems than it solved. It is currently used as a starter fluid with diesel tractors.
- Image, below, is of ethylisopropyl ether

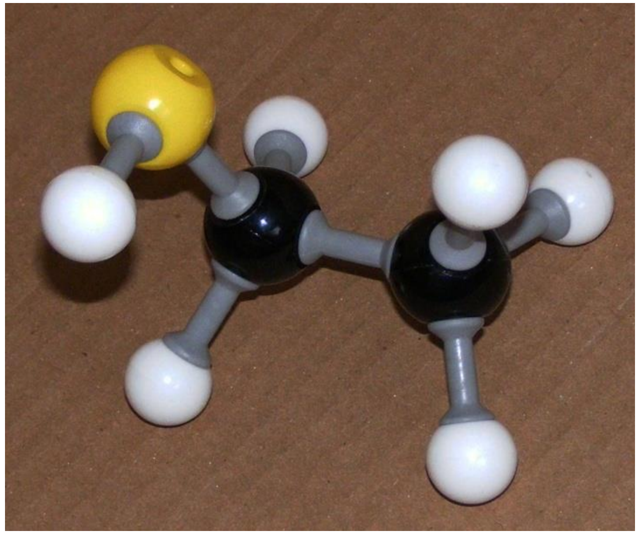


Sulfur Derivatives

Thiols

- A thiol sounds just like what you might think -- it's a sulfur alcohol, i.e., the functional group of a thiol is the SH group.
- 4 examples of thiol compounds are below. The old way of naming these compounds was to add "mercaptan" at the end of the phrase; IUPAC says you name it by thio followed by its alkane name, e.g., methyl mercaptan is thiomethane, ethyl mercaptan is thioethane, ad nauseum. The significant reaction between thiols is the formation of disulfide bonds -- more on this in the amino acid section.
- Image, right, is of thioethane.

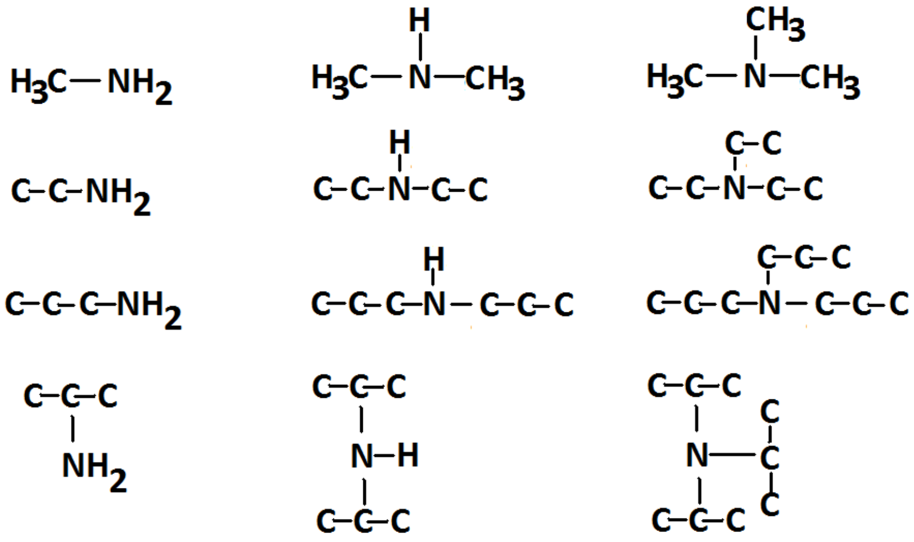
H_3CSH	**methylmercaptan**	**thiomethane**
$C-C-SH$	**ethylmercaptan**	**thioethane**
 $C-\underset{SH}{\underset{\vert}{C}}-C$	**isopropylmercaptan**	**2-thiopropane**



Nitrogen Containing Compounds:

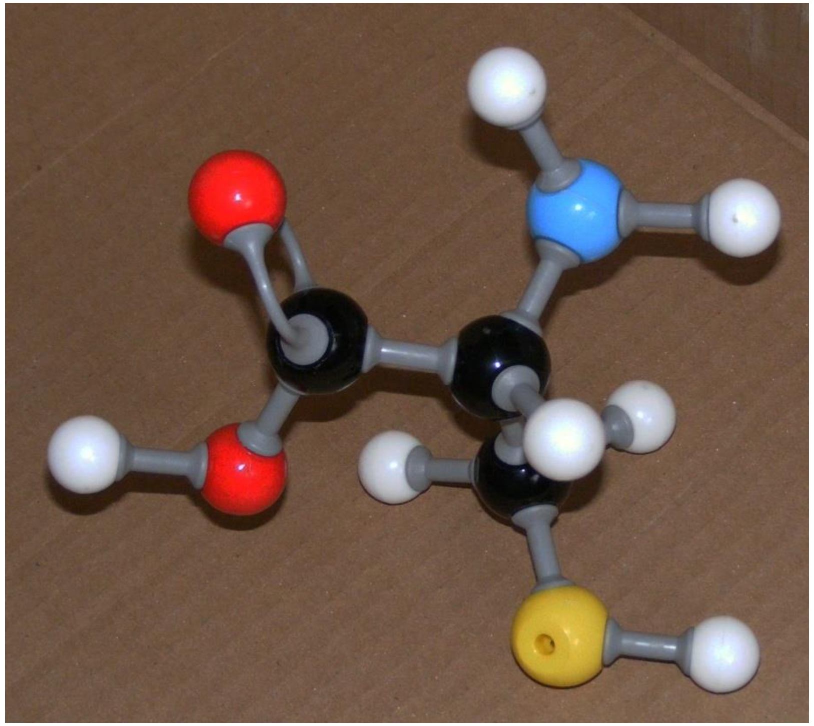
- The functional group of an amine is the NH_2 group.
- Primary, secondary and tertiary amine illustrations follow this page. Note that the degree of an amine depends upon the number of hydrogen atoms that are replaced by a hydrocarbon group, e.g., primary amines have had one hydrogen replaced with one hydrocarbon; secondary amines have had 2 hydrogens replaced with hydrocarbons; tertiary amines have had 3 hydrogens replaced by hydrocarbons. The simplest primary amine is methylamine. Other examples, ethyl, n-propyl and isopropyl amine are shown in the figure.
- The simplest secondary amine is dimethylamine, i.e., there are two methyl groups on the nitrogen. Diethyl, di-n-propylamine and di-isopropylamine are illustrated, as well.
- The simplest tertiary amine is trimethylamine, i.e., there are 3 methyl groups on the nitrogen. Triethyl, tri-n-propyl and tri-isopropylamine are illustrated, as well.
- Note needs to be made that these amines are insoluble in water. The simplest way in which to render these amines water-soluble is to add a bit of acid, protonating the nitrogen, making the ion polar -- remember, like dissolves like.

Amines



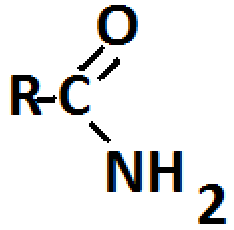
Amino Acids

- Suffice it to say that these compounds contain a carboxyl group (acid) and an amine (NH_2)
- Image is of Cysteine, a sulfur containing (thio) amino acid found in hair and nails and hooves and horns

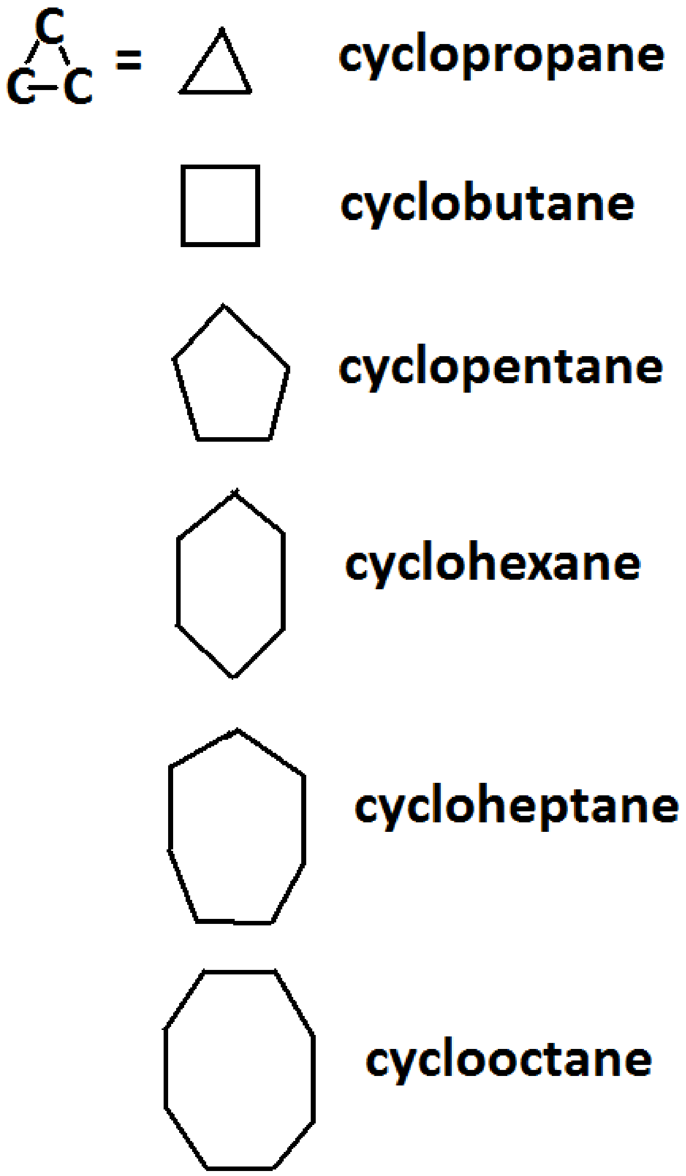


Amides

- The functional group of the amide is a carbon atom double bonded to an oxygen atom, single bonded to the NH_2 group and either a single bonded hydrogen (to make formamide or methanamide by IUPAC) or a hydrocarbon tail.



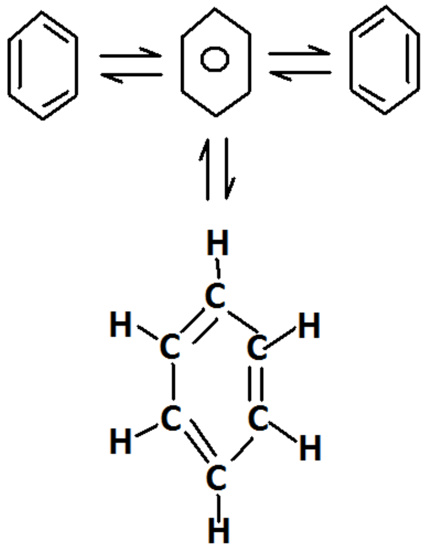
- The last group of aliphatic hydrocarbons, but the introductory group dealing with "ringed" structures of hydrocarbon compounds, to be discussed is shown in the graphic.
- These are compounds that form "ringed" compounds, i.e., a carbon chain that closes up onto itself resembling a "ring".
- These compounds are named, first, with "cyclo" in front and the alkane name after the prefix.

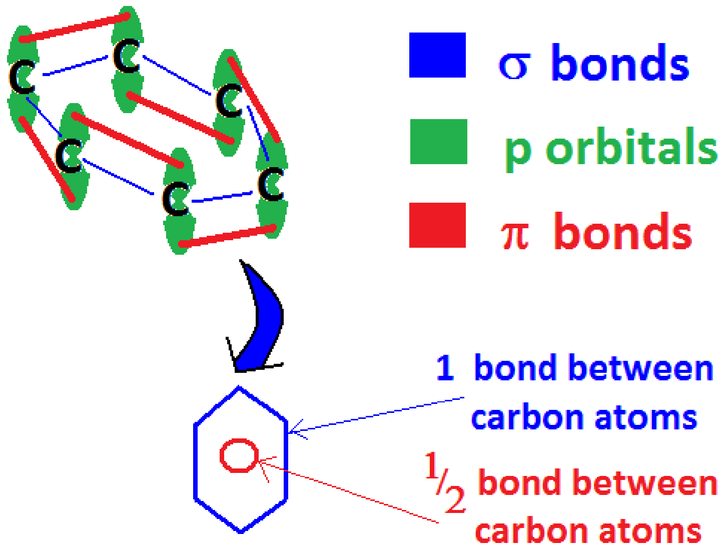


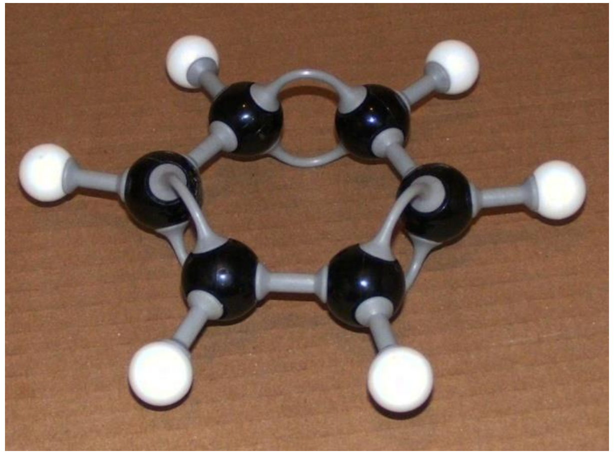
Aromatic Hydrocarbons

Benzene

- For the purposes of this introduction, the aromatic hydrocarbons are based off of benzene, C_6H_6. Note that there are several ways in which to draw the structure of benzene. These different forms are called resonant structures, i.e., the atoms are arranged in a constant manner, but the electrons in the second of the bonds are distributed slightly differently. The middle structure is the more correct form.
- This structure was determined in the 1800's by Kekule'. The story has it that he was working on the structure of benzene without the benefit of the technology we have, now, and he dreamed one night of a snake biting its tail. That gave him the idea for the circle in the middle of the benzene ring.
- The circle represents a floating half bond between carbons. Remember, that for the second bond in a double bond (the pi bond), one needs overlap of both the upper and lower lobes of the p orbitals. In benzene, though, there is only half an overlap, i.e., either top halves overlap or the bottom halves overlap, alternately, creating a bond and a half between the carbon atoms in the ring. Turns out that Kekule' was correct.

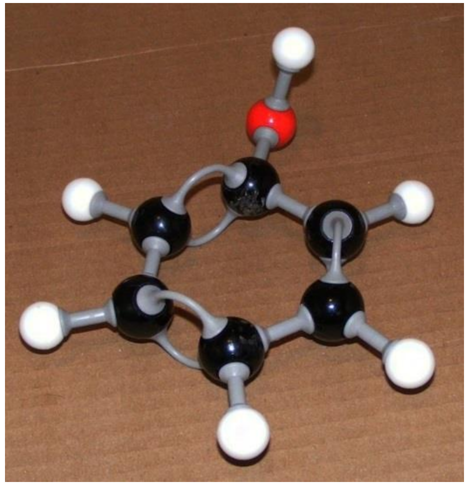


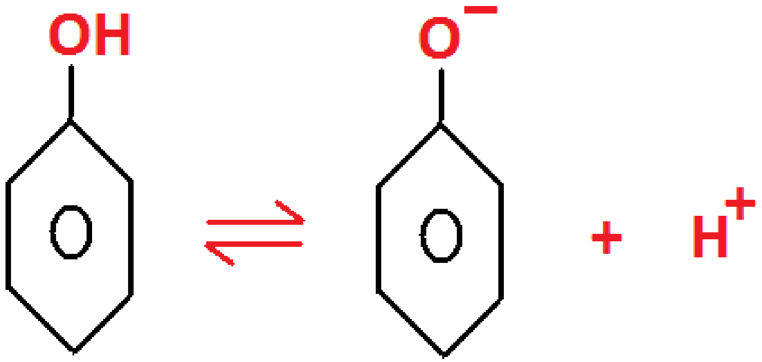




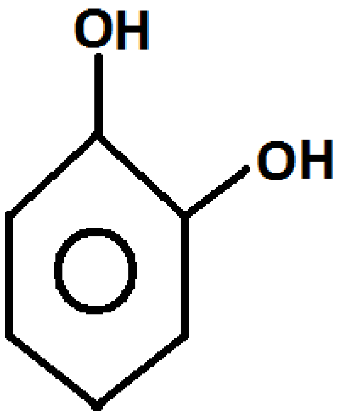
Phenols

- Hydroxylated benzene compounds are based off of phenol (fuh NOLE), C_6H_5OH.
- Phenol is a bit different than the aliphatic alcohols in that its proton DOES dissociate, effecting the pH of solutions unlike the proton on aliphatic alcohols.



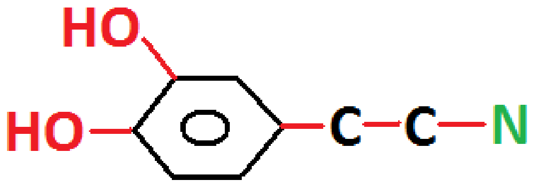


- The second group of important phenolic compounds is the catechols (KAY tuh koals). Catechol has the structure in the figure. Note that catechol is an ortho-substituted benzene "di-alcohol", or ortho-hydroxyphenol.



Catechol

- The hormone epinephrine, neurotransmitter norepinephrine and the vasoactive dopamine are all biologically important catecholamines



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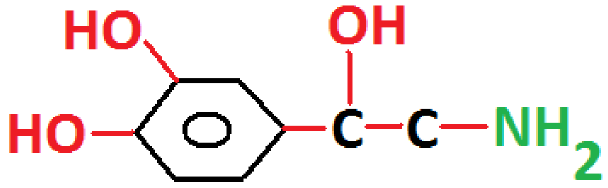
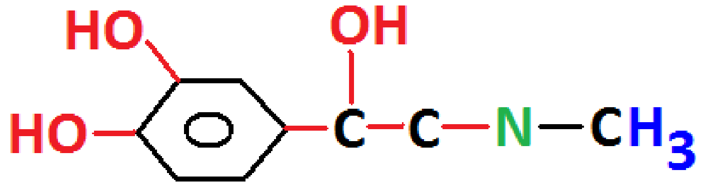


NE



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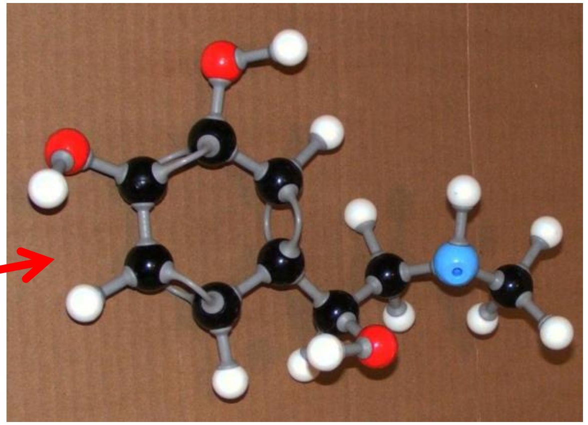
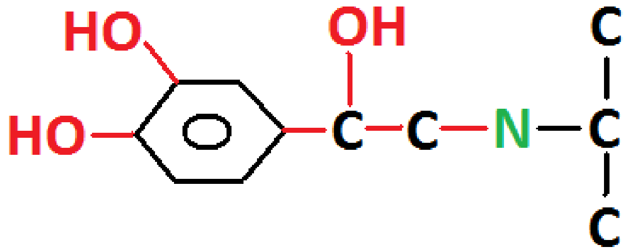




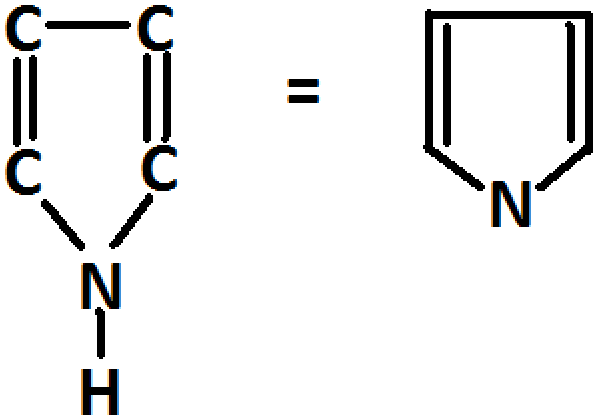
iPro

Isoproterenol is a synthetic catecholamine (drug) that mimics the effects of epinephrine.

Heterocyclic Compounds of Nitrogen

- Heterocyclic means that there is more than one kind of atom in the closed ring of an organic ringed compound. These compounds have been saved for this point of the lecture as many of them are aromatic, as well.
- By definition, an aromatic compound (nowadays; in the "olden days" all a compound had to be was a derivative of benzene to be considered aromatic) is a compound that "contains cyclic clouds of delocalized p electrons above and below the plane of the molecule ... furthermore, the p clouds must contain a total of (4n+2) p electrons" to be aromatic.
- This is the Hückel rule. This means that if n=1, there must be 6 p electrons for the compound to be aromatic; if n=2, there must be 10 p electrons for the compound to be aromatic; if n=3, then there must be 14 p electrons for the compound to be aromatic, ad nauseum. The numbers 6, 10 and 14 are called Hückel numbers.
- Hence, benzene is aromatic as it has 6 p electrons, i.e., the Hückel hextet.

- Heterocyclic compounds also may follow the Hückel rule to be classified as aromatic.
- Pyrrole **does not** conform to Hückel's rule, but is, nevertheless, a cyclic compound that contains a nitrogen atom in the ring, below.
- It only has 4 p electrons, and does not conform to Hückel's rule for aromaticity.
- 4 pyrrole rings are found in each hemoglobin molecule in our red blood cells and 4 are also found in each chlorophyll molecule in plants.
- Hemoglobin binds iron(II) and chlorophyll binds magnesium through these pyrrole rings.



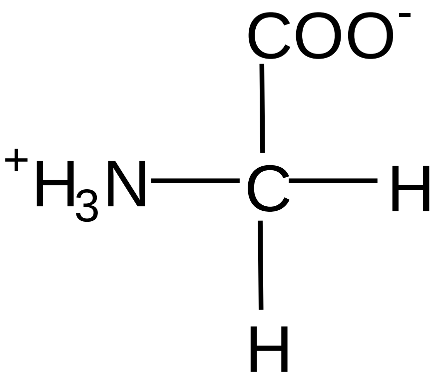
Introduction

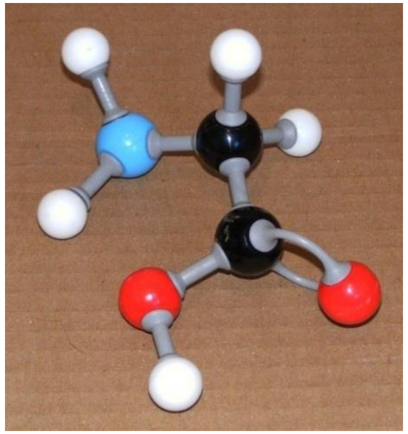
- **Any time one deals with anything in Biology, one must also contend with proteins: the products of gene activation.**
- **To understand proteins, it is necessary to understand amino acids, to learn their structures and to learn a few of the functions and essentiality of the amino acids.**
- **There are 20 amino acids and 1 imino acid we will study:**

glycine (gly)
alanine (ala)
valine (val)
leucine (leu)
isoleucine (ile or ileu)
proline (pro) ← imino acid
phenylalanine (phe)
tyrosine (tyr)
tryptophan (trp)
serine (ser)

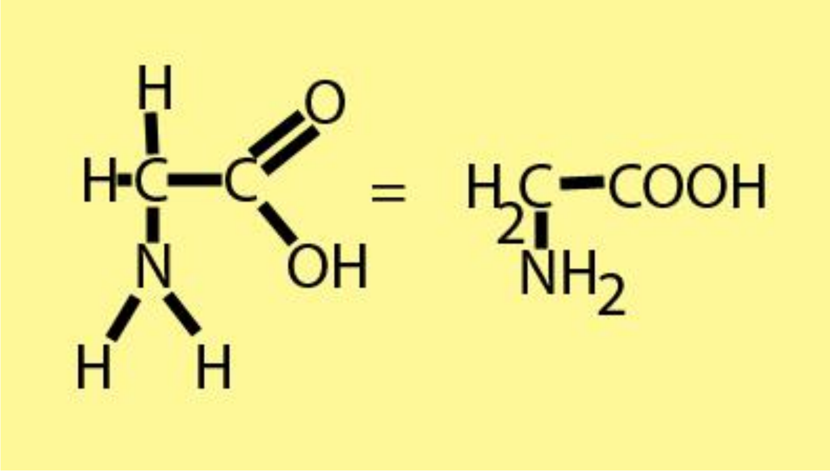
cysteine (cys)
cystine (cys-cys)
threonine (thr)
methionine (met)
aspartic acid (aspartate; asp)
asparagine (asn)
glutamic acid (glutamate; glu)
glutamine (gln)
histidine (his)
lysine (lys)
arginine (arg)

- The simplest amino acid is glycine (gly).
- It consists of two carbon atoms covalently bonded to each other.
- To one carbon atom, two oxygen atoms are bonded; to the other carbon atom, an amino group (NH_2) or if protonated an ammonium group (NH_3+ -- note that nitrogen has 4 bonds on it: 3 covalent and 1 coordinate covalent) and 2 hydrogen atoms are bonded to the α carbon.
- The carbon that is directly attached to the COOH (carboxyl group that has no charge) or the carboxylate group (CO_2^- when deprotonated) is called the α-carbon.
- It is this carbon that makes all amino acids used by man the α -amino acids.
- Gly is typically found in proteins where there are turns in the amino acid sequence, as it is very small and has a small "R" group (a hydrogen).
- R groups are radical groups, representative groups or reactive groups.
- In this case, and for the case of all the amino acids, we will use the second definition of R group to mean the rest of the amino acid molecule beyond the 2d carbon in the back bone of the amino acid.
- Gly is an amino acid with an uncharged polar R group.





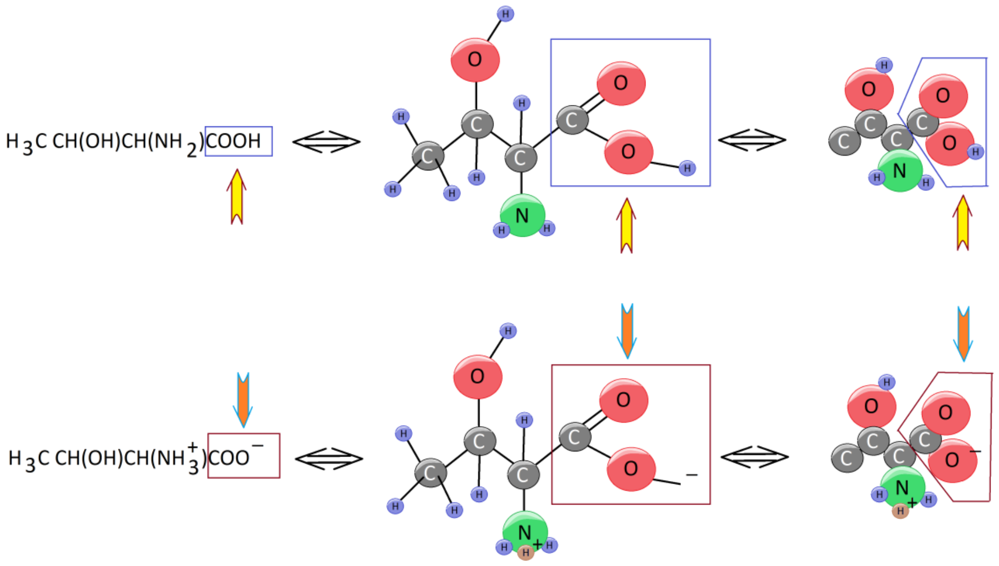
Glycine (gly)



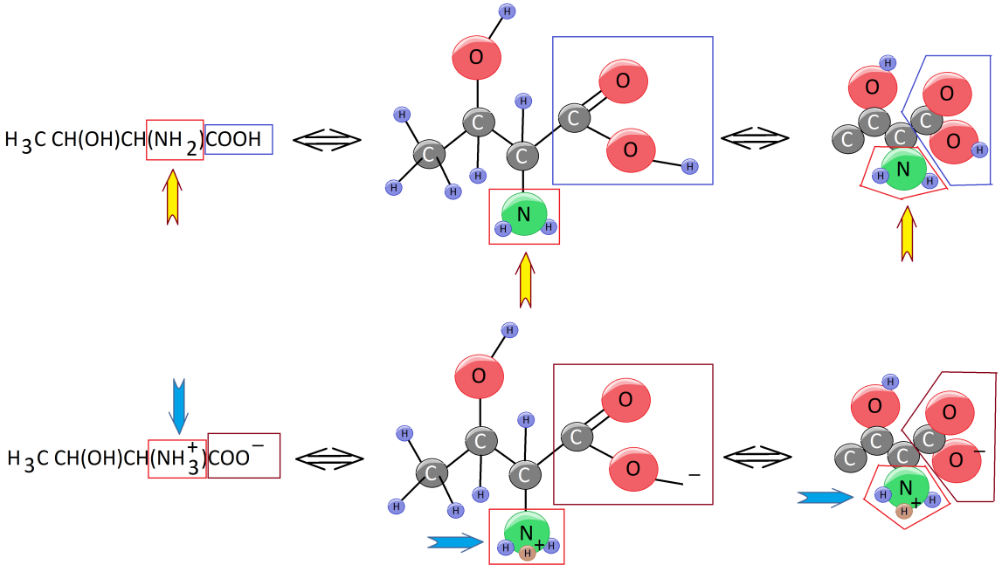
Another way to look at Glycine.

The same manner may be used with the other 19 amino acids.

Examples of carboxyl vs carboxylate groups *et* amine vs ammonium groups

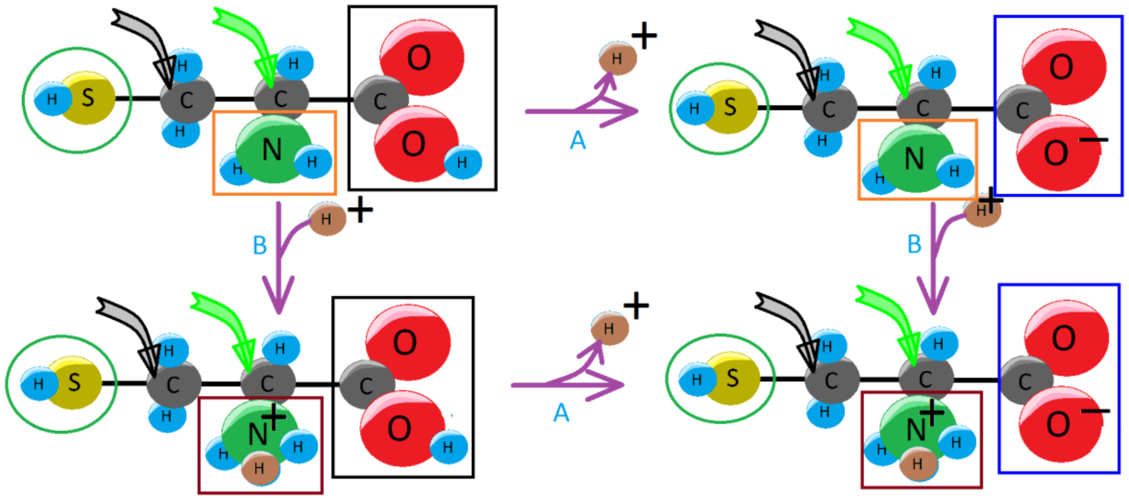


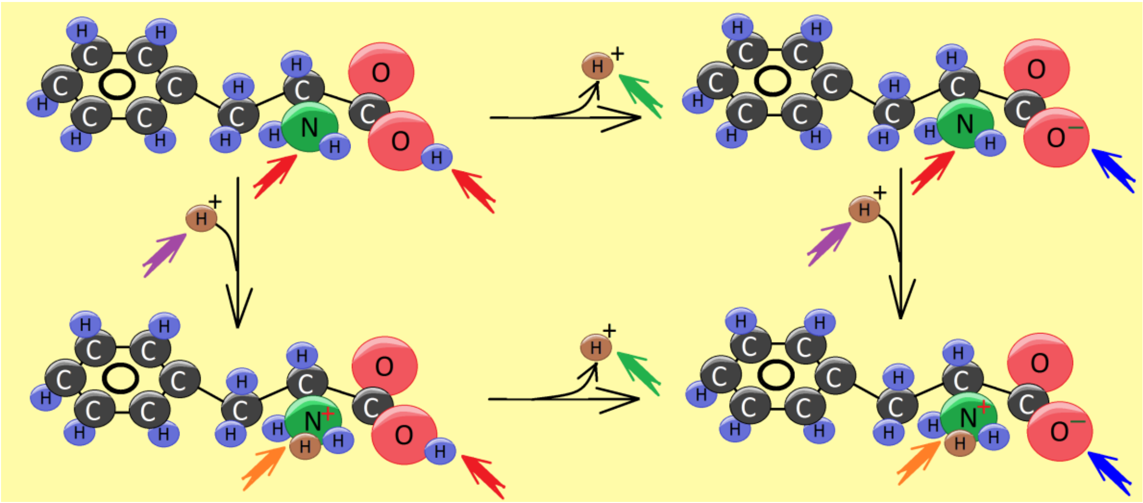
- Above – amino acid = threonine
- Above top – brown/yellow arrows pointing out carboxyl groups
- Above bottom – blue/orange arrows pointing out the carboxylate groups



- Above – amino acid = threonine
- Above top – brown/yellow arrows pointing out amine/amino groups
- Above bottom – blue/orange arrows pointing out the ammonium groups

More Examples: COOH vs CO_2^- *et* NH_2 vs NH_3^+



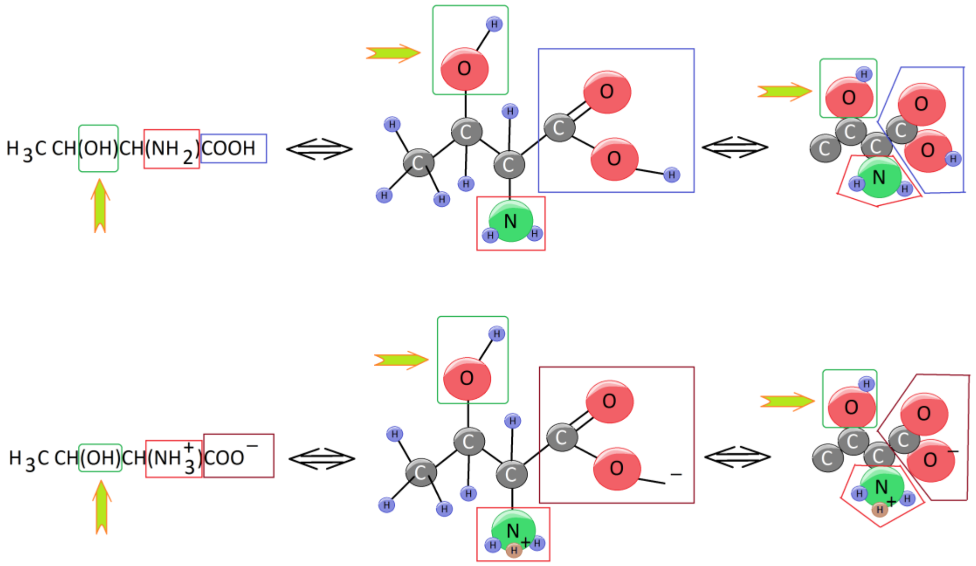


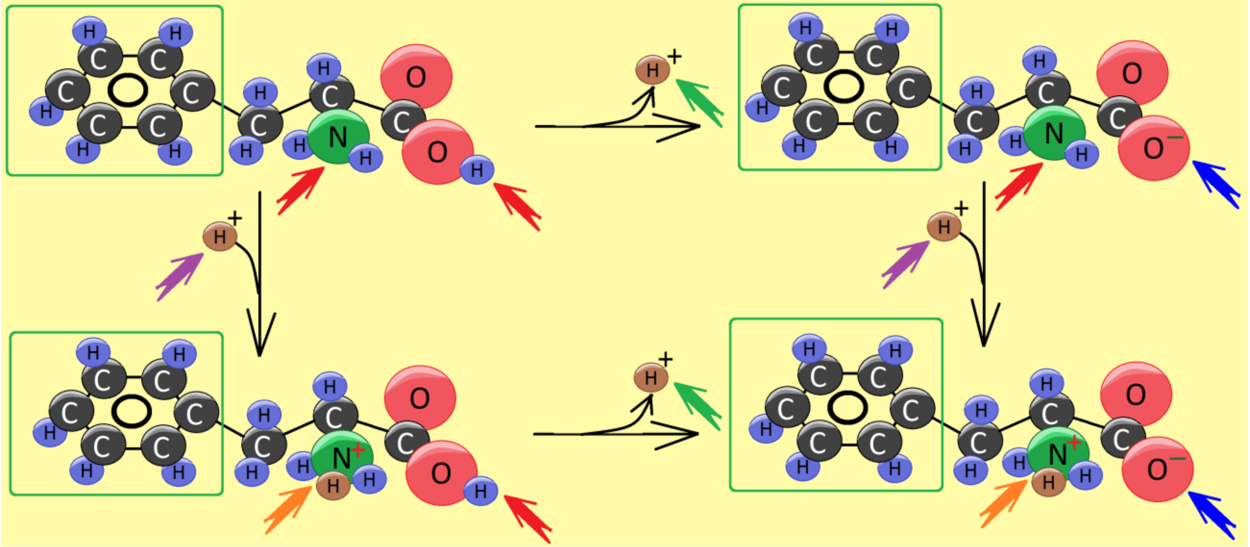
- Above – cysteine

- Carboxyl groups in rectangular black
- Carboxylate groups in blue reactangle
- Amino/amine groups in orange
- Ammonium group in brown squares
- ASIDE: R group (SH – thiol) in green circle

- Above – phenylalanine
- Carboxyl groups (COOH) indicated by red arrows pointing from right to left
- Carboxylate groups (COO^- or CO_2^-) indicated by blue arrows pointing from right to left.
- Amine/amino (NH_2)groups indicated by red arrows pointing from left to right.
- Ammonium groups (NH_3^+)indicated by orange arrows pointing from left to right

R Group Examples





- Threonine above

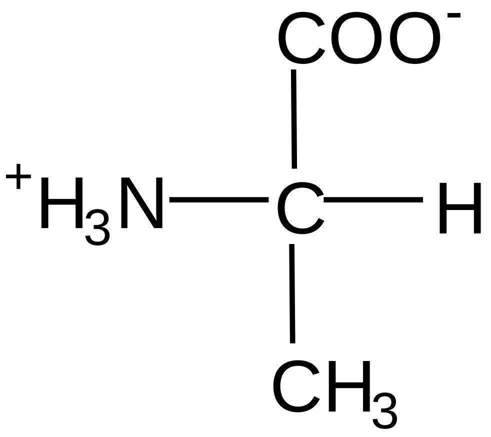
- Alcohol (R group) in green rounded rectangle

- Phenylalanine above

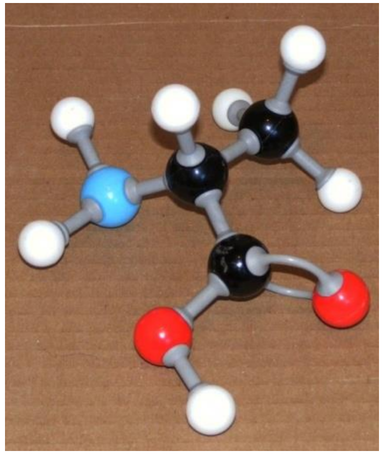
- Benzene ring (phenyl group – R group) in green rounded rectangle

Amino Acids with Hydrophobic R Groups

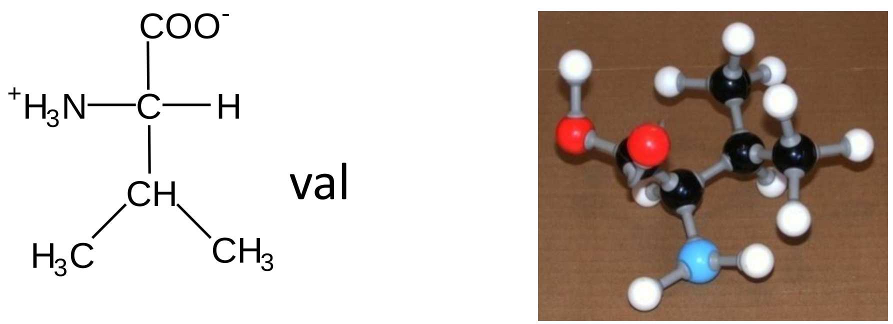
- The next simplest amino acid is alanine. The difference between ala and gly is that the H in gly has been replaced by a CH_3 in ala. Ala is a small amino acid, especially suited for diffusing from muscle cells into the blood to be transported by the blood to the liver for utilization in gluconeogenesis.



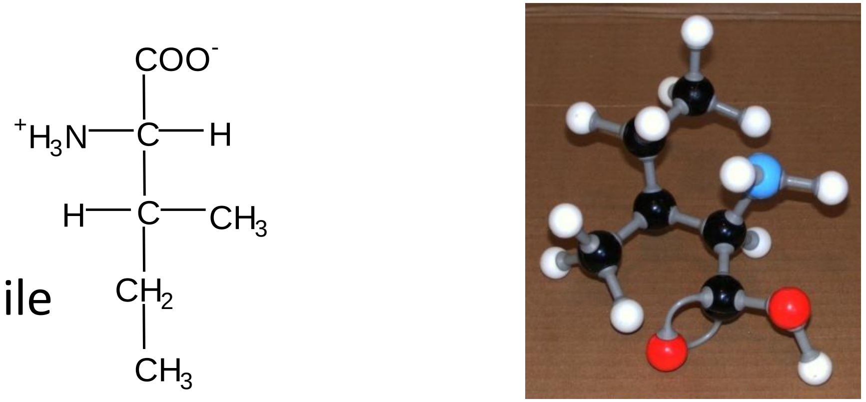
Alanine (ala)



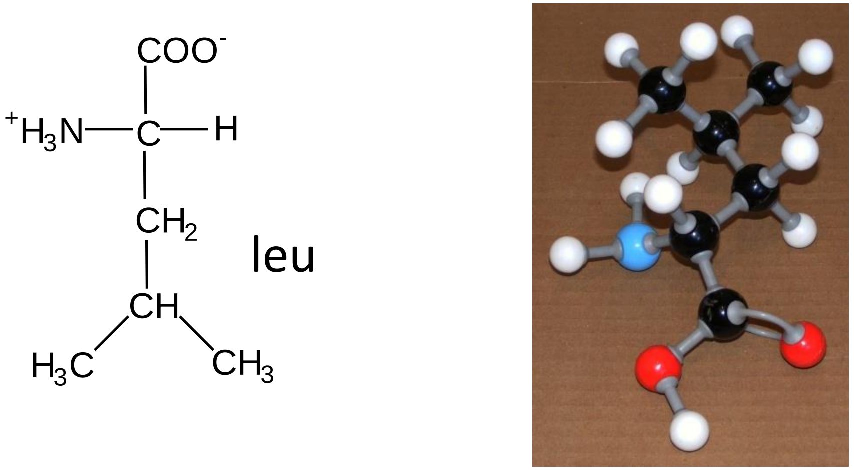
- Valine (val), leucine (leu) and isoleucine (ile or ileu) are the next three simplest amino acids.
- These three amino acids are called branched chain amino acids (BCAA's) and are utilized for the synthesis of substrates for gluconeogenesis and for ketogenesis.
- Leu is the only purely ketogenic amino acid.
- Ketones are <u>usually</u> associated with someone who has diabetes mellitus and who is in diabetic coma.
- It is the ketones, or ketone bodies, that give the patient the sweet, fruity smelling breath of diabetic coma.



val

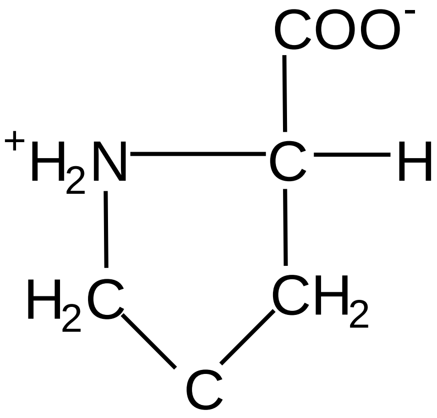


ile

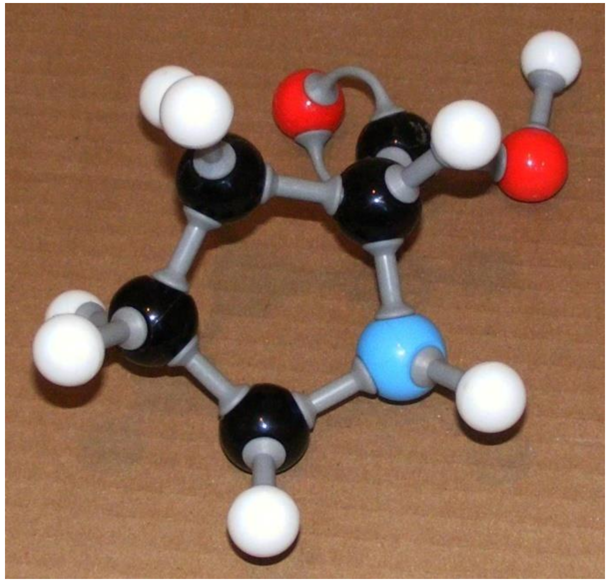


leu

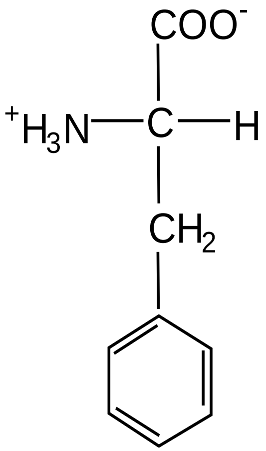
- Proline is actually an *imino* acid.
- Note that it is a closed ring amino acid.
- Pro, like gly, is usually found in proteins where turns are required.
- A derivative of proline, hydroxyproline is found in connective tissue and helps make the tissue stronger.



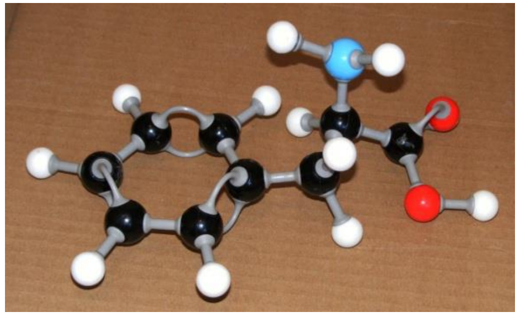
Pro

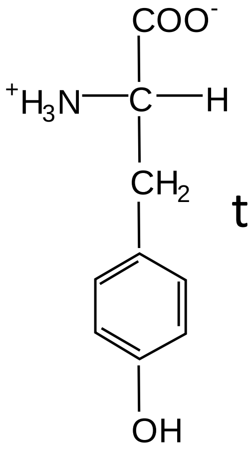


- Phenylalanine is alanine with a benzene ring attached to it (C_6H_6).
- Phenylalanine is necessary for the synthesis of the catecholamines dopa, dopamine, norepinephrine and epinephrine.
- Some people are born lacking an enzyme that regulates the catabolism of phe.
- When this happens, a metabolite of phe, phenylpyruvic acid, builds up in nervous tissue and causes severe mental retardation.
- This condition is known as phenylketonuria, or PKU.
- The people who have PKU are generally blonde, blue-eyed and fair complected.
- The reason for this is that phe is also necessary for the synthesis of a pigment called melanin that contributes to eye, hair and skin color.
- People who have PKU must eat a diet low in phe the rest of their life.
- Since phe is required by the body to initiate the synthesis of the catecholamines for neurotransmitter and hormonal functions, people who have PKU must add tyrosine to their diet -- the product of the hydroxylation of phe that doesn't occur in PKU.

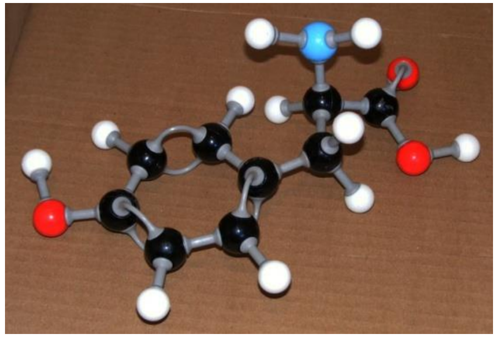


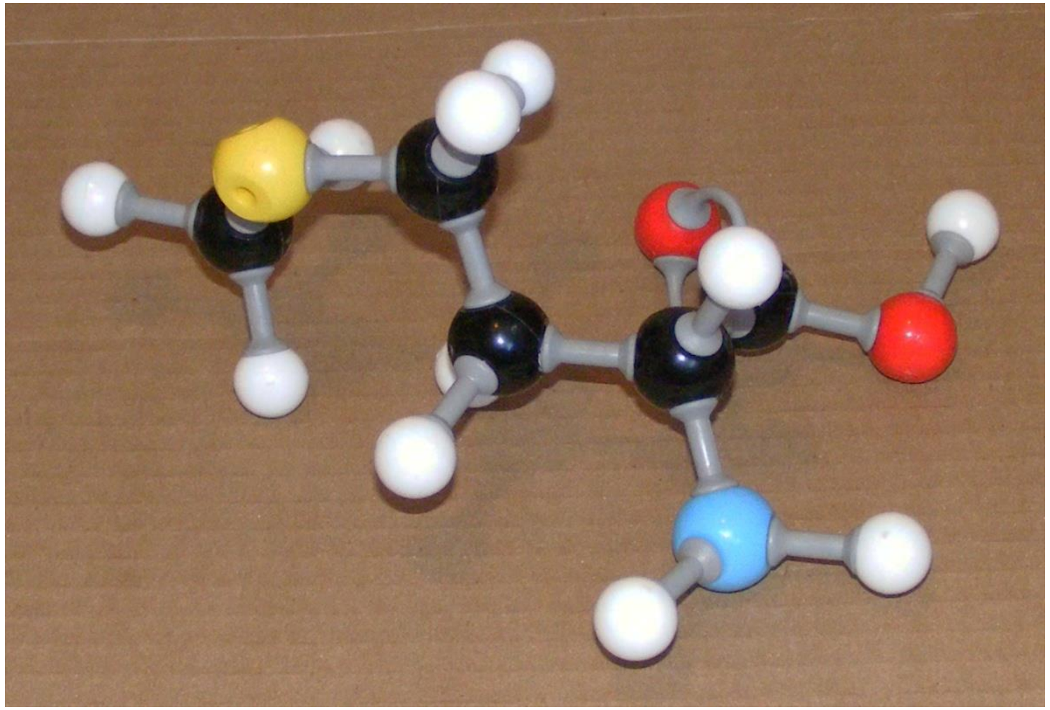
phe

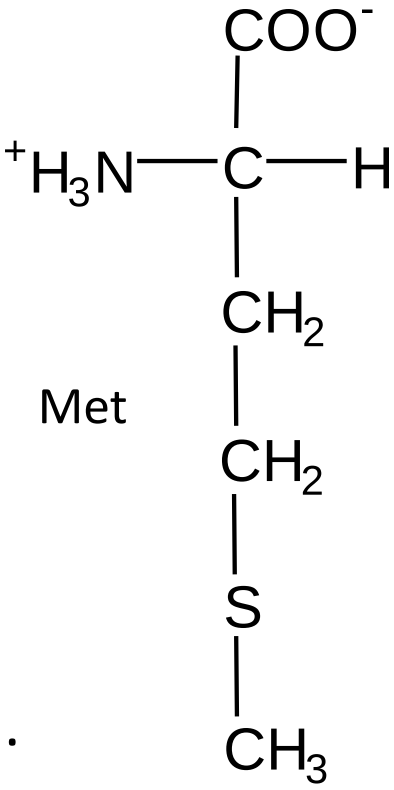




tyr



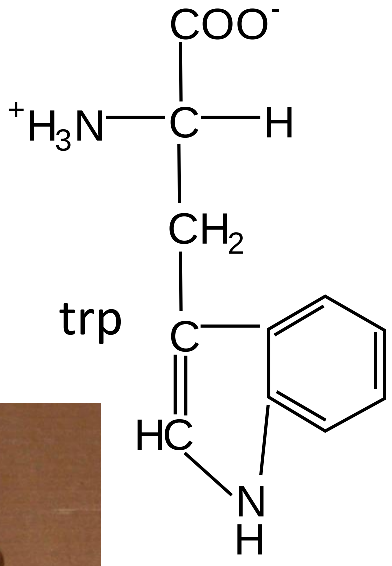


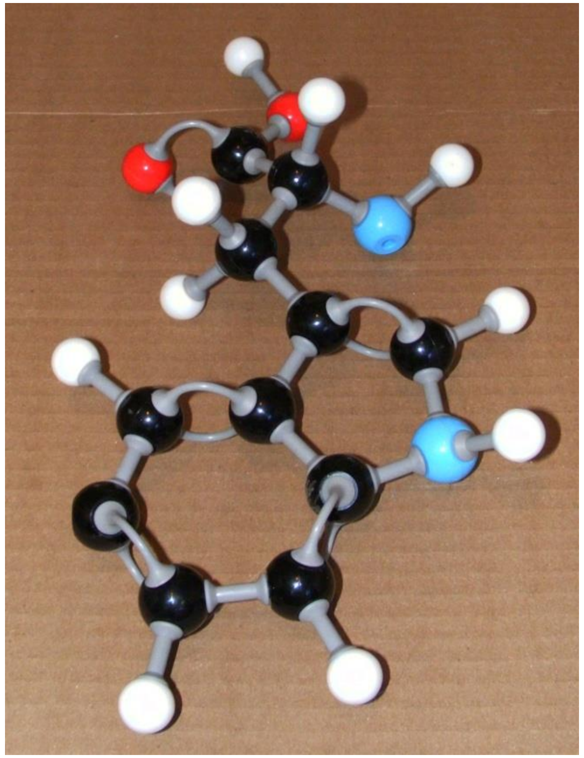


Met

- Methionine is a sulfur containing amino acid.
- Its necessity is to provide the methyl group (CH_3) to acceptor molecules in one-carbon metabolism.
- One-carbon metabolism is important in the production of red blood cells, white blood cells and platelets.

- Tryptophan (trp) is the last of the amino acids with hydrophobic R groups.
- Trp is the precursor for the synthesis of serotonin (aka nature's downer).
- Serotonin from the health food store will NOT cross the blood brain barrier; trp is required for this to occur.
- Turkey and milk have high levels of trp.
- There seems to be some controversy as to whether or not there is enough trp in milk (especially warm milk) to render a person drowsy so that they will fall asleep when it is difficult for them to do so without assistance.
- In recent times, *selective serotonin reuptake inhibitors* have seen use in depression, eating disorders, obsessive compulsive disorder, to name a few, e.g. prozac, celexa





Amino Acids with Uncharged Polar R Groups

At physiologic pH, the R groups are not ionized as are the amino and carboxyl groups of the amino acids.

Glycine has already been mentioned.

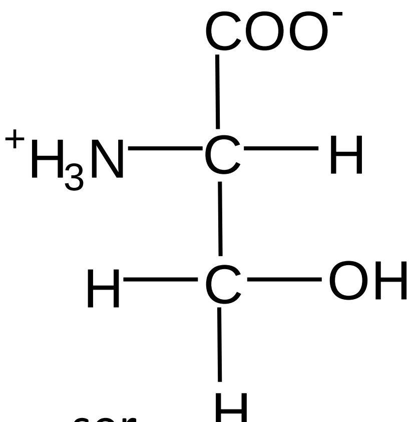
Serine (ser) is alanine with an -OH group replacing a -H.

As a rule, ser has a function similar to that of threonine (thr), another hydroxylated amino acid: it serves as an activation site in enzymes, i.e., when it is phosphorylated or dephosphorylated, the enzyme is turned on or off.

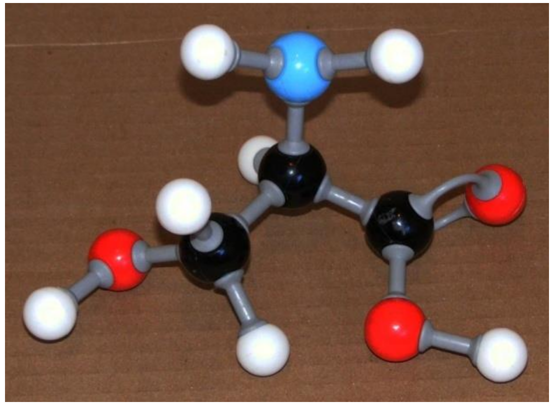
The last hydroxylated amino acid is tyrosine (tyr – with phe discussion).

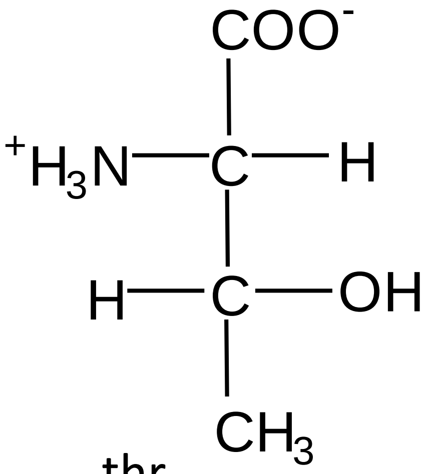
It is, simply, hydroxy phenylalanine, with the -OH group straight across the benzene ring from the alanine moiety.

Tyr has been discussed, previously, as well.

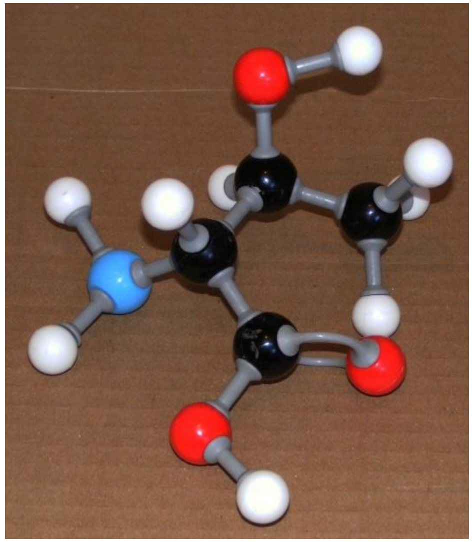


ser

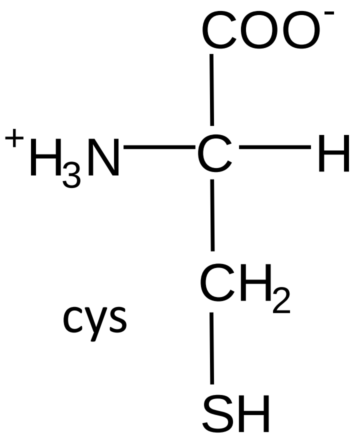




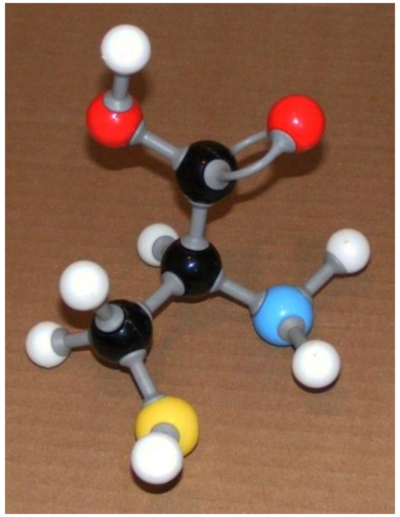
thr

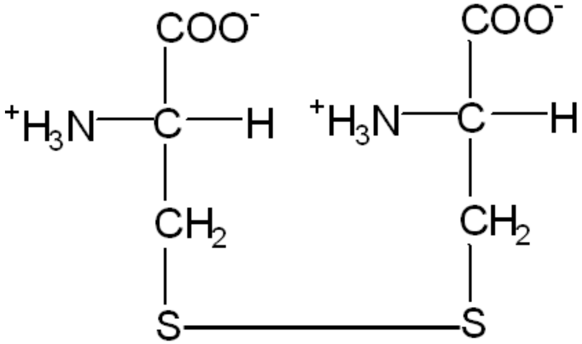


- Cysteine (cys) is a sulfur containing amino acid.
- It is found in most connective tissues.
- The most often thought about site of cys, though, is the hair.
- Hair maintains its shape by the presence of disulfide bonds (-S-S-).
- The disulfide bonds come from the loss of -H from the -SH group of two cys molecules in the hair which then bond to hold the hair in its appropriate shape to form cystIne (cys-cys).
- Cosmetologists, beauticians utilize this property every day when they give perms.
- They first reduce the natural disulfide bonds in hair, then place the hair in the shape the customer asks, then finish the job with an oxidizing agent that forces the formation of the disulfide bonds and, voila!, a new style comes out from under the curlers, drier, *etc*.

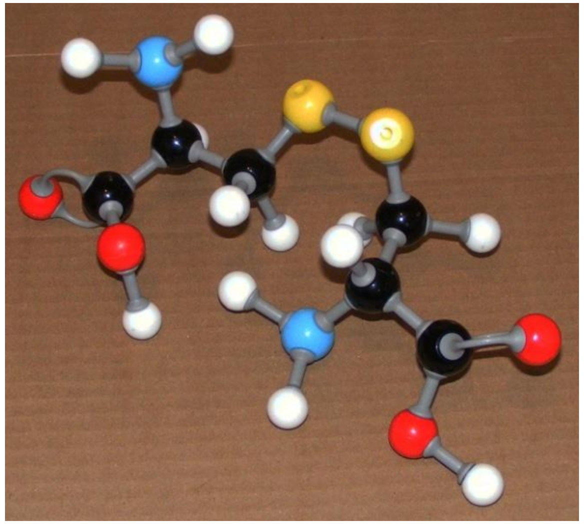


cys

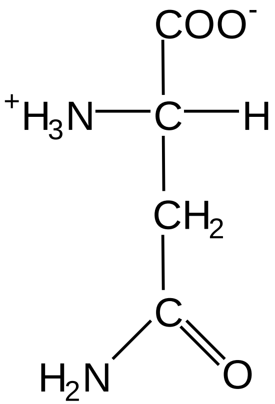




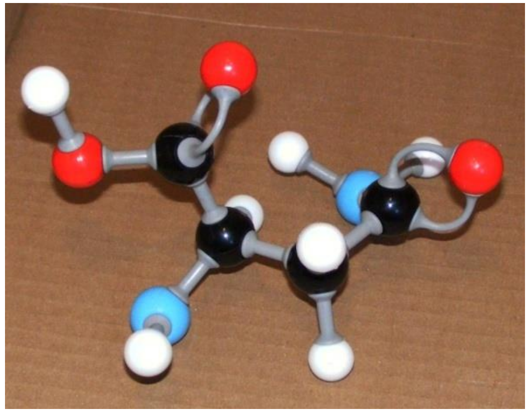
cys-cys

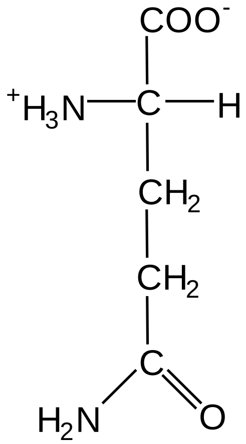


- Asparagine (asn) and glutamine (gln) are 4 and 5 carbons in length, respectively.
- They are derivatives of the dicarboxylic amino acids aspartate and glutamate (coming up on next slide).
- Note that each has an extra NH_2 group on the carbon double bonded to an oxygen <u>farthest</u> from the α-carbon.
- These two molecules serve as ammonia transporters to the liver and kidney for urea synthesis.
- Urea is a small, non-toxic compound (compared to ammonia's effects on the cell) that is excreted via the urine.

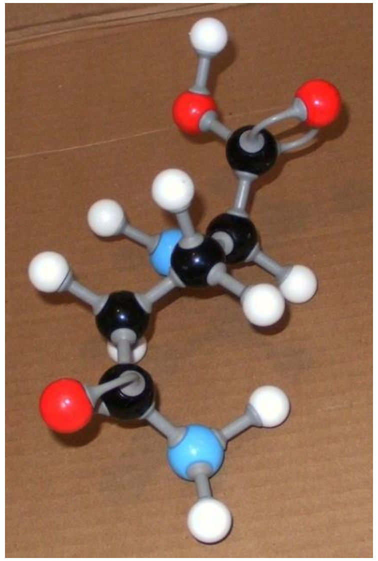


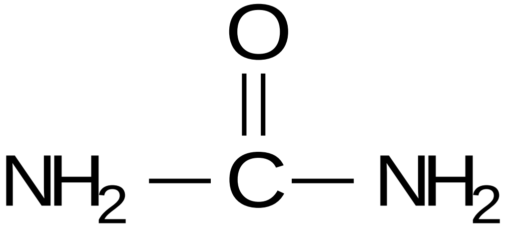
asn





gln





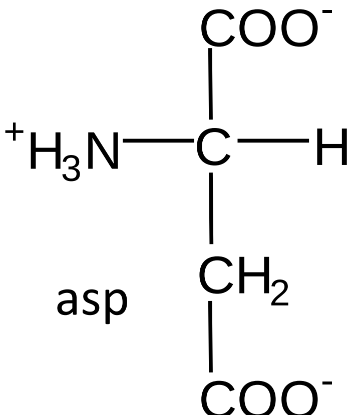
$$NH_2 - \overset{\overset{\displaystyle O}{\|}}{C} - NH_2$$

Urea

Amino Acids with Negatively Charged R Groups at Physiological pH

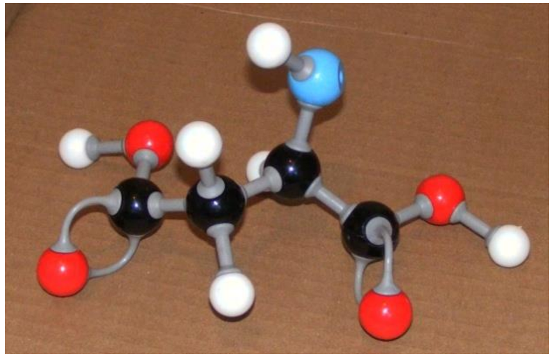
The next two amino acids under study are the acids aspartate (asp) and glutamate (glu)--the precursor amino acids of asn and gln, respectively.

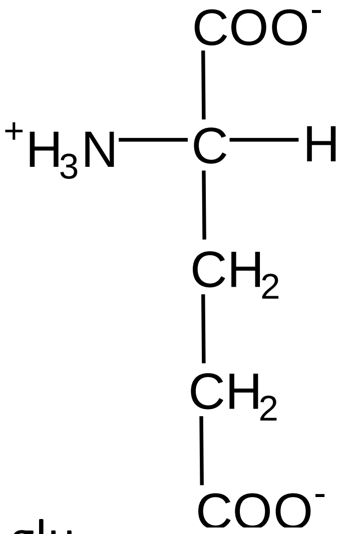
Both are dicarboxylic amino acids, i.e., there is a COOH group on each end of the molecules.



$$\begin{array}{c} COO^- \\ | \\ {}^+H_3N - C - H \\ | \\ CH_2 \\ | \\ COO^- \end{array}$$

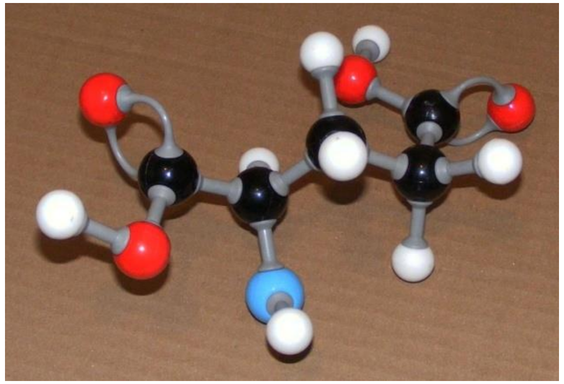
asp





$$\begin{array}{c} COO^- \\ | \\ {}^+H_3N - C - H \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COO^- \end{array}$$

glu



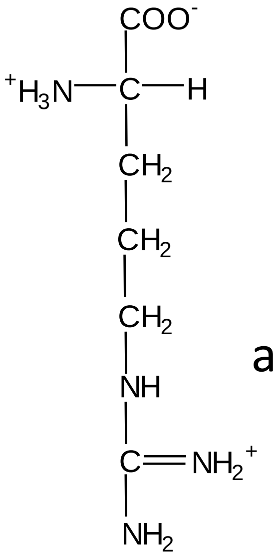
Amino Acids with Positively Charged R Groups at Physiological pH

Arginine (arg) and lysine (lys) have positively charged R groups at physiological pH.

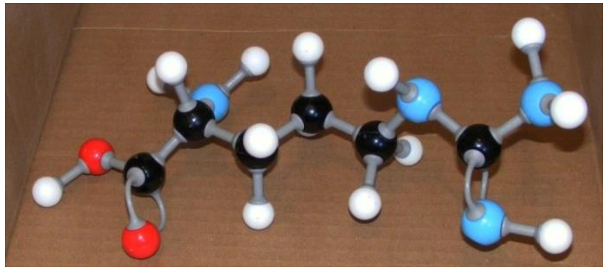
Lysine is heavily involved in connective tissue biosynthesis.

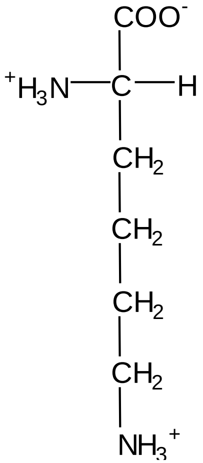
Children with low levels of arginine tend to be mentally retarded (hypoargininemia).

Arginine is the last product of the urea cycle from which urea is clipped for excretion.

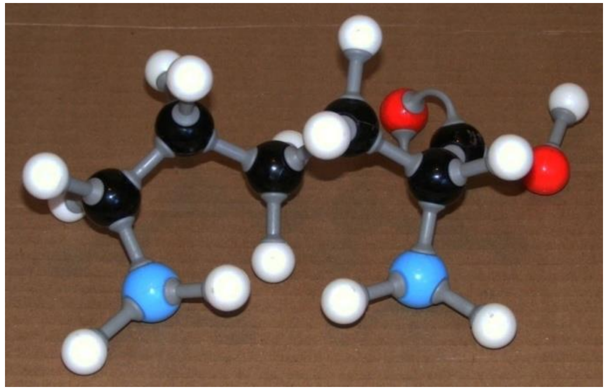


arg

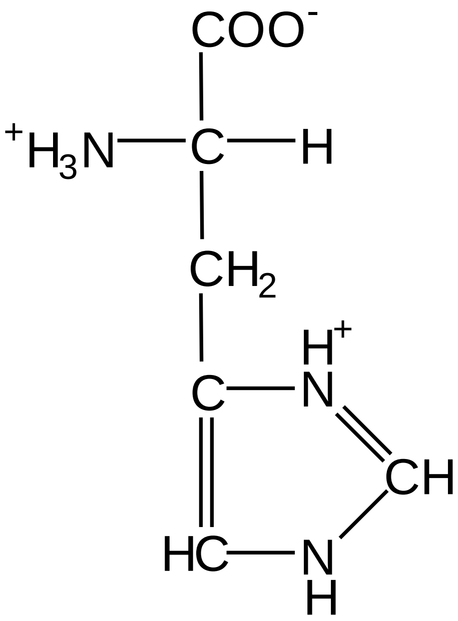




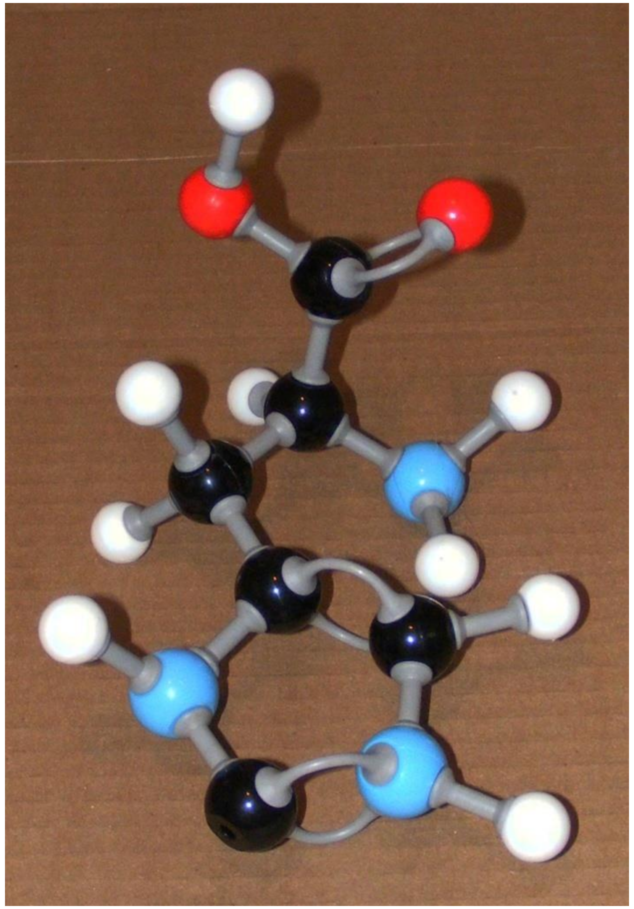
lys



- Histidine (his) is positively charged at a pH of approximately 6 or below.
- His is the precursor molecule to histamine, the compound that causes many allergic reactions and which may be blocked by the use of anti-histamines.
- Histamine synthesis may be stimulated by the influence of norepinephrine or psychological stress.
- Because of this, many people who have itching-related health problems may be prescribed a drug like doxepin which has both histamine antagonistic properties and anxiolytic properties: both of which combat the health problem by reducing the anxiety felt by the patient which reduces the itching, which reduces the anxiety which reduces the itching, *ad nauseum*.

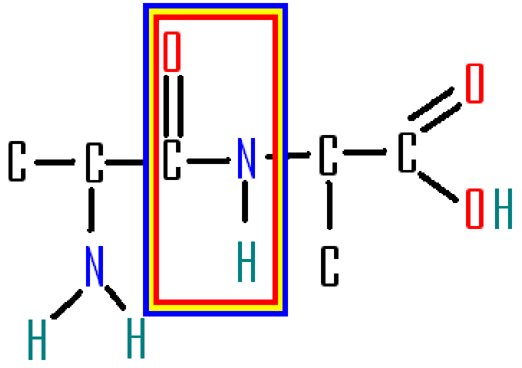


his

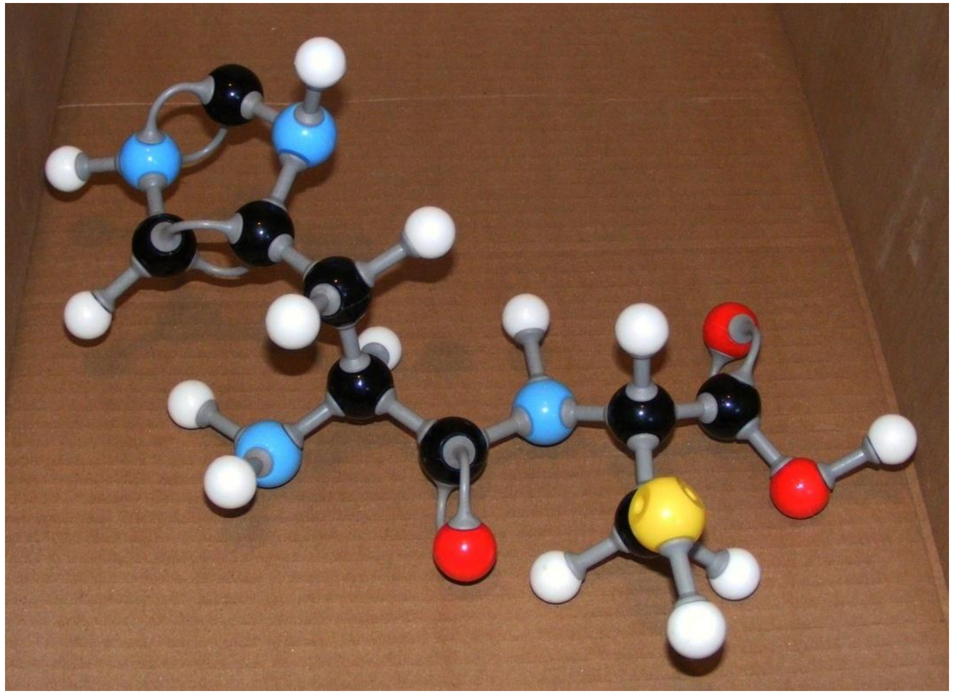


- Of these 20 amino acids,
    - 8 are essential (humans require them in their diets as humans lack the enzymes to synthesize them from scratch) and
    - 2 are semi-essential (required for growth by the young human).
- The essential amino acids are phe, val, trp, thr, ile, met, lys, leu.
- The semi-essential amino acids are his and arg.
- A helpful mnemonic to remember these is: PVT TIM HALL, where the first letter of each amino acid makes up this mnemonic.

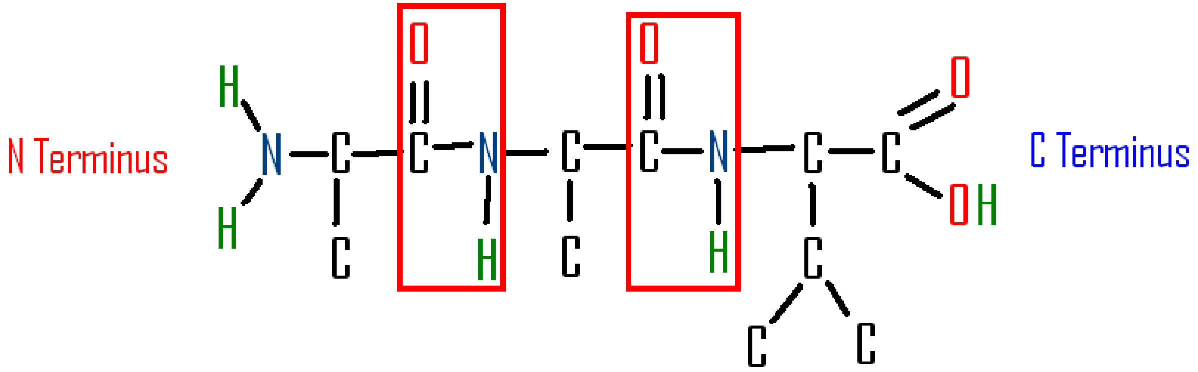
Peptides and Peptide Bond

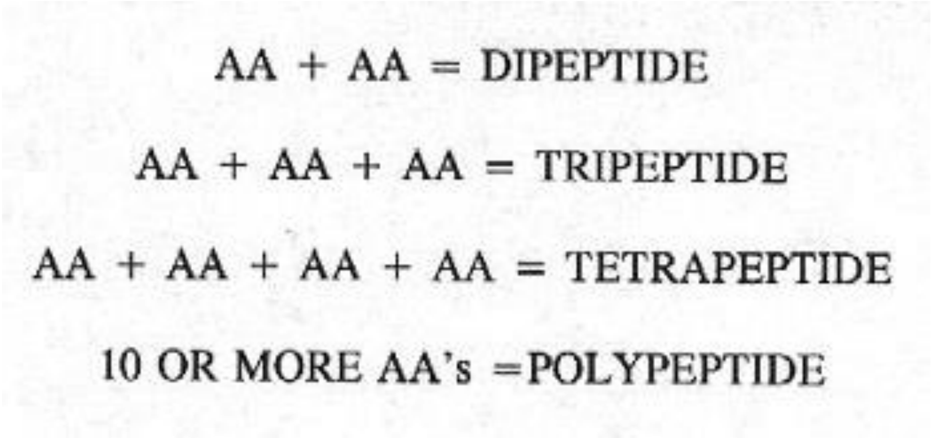


- Amino acids are the building blocks of proteins.
- In order for the amino acids to link together to form the numerous proteins necessary to keep a human functioning, they form a special bond between each other: the peptide bond.
- The peptide bond is formed between the carboxyl group of the first amino acid and the amino group of the second amino acid to form a dipeptide.
- The peptide bond is unique in that it appears to be a single bond, but has the characteristic of a double bond, i.e., it is a rigid bond.
- This kind of bond only occurs between amino acids.
- As the amino acid chain increases, the next amino acid adds onto the previous carboxyl group by its amino group.



Peptide Bond and Peptides





AA + AA = DIPEPTIDE

AA + AA + AA = TRIPEPTIDE

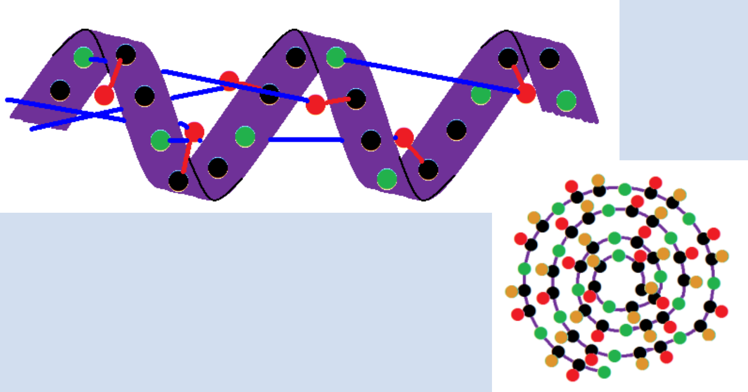
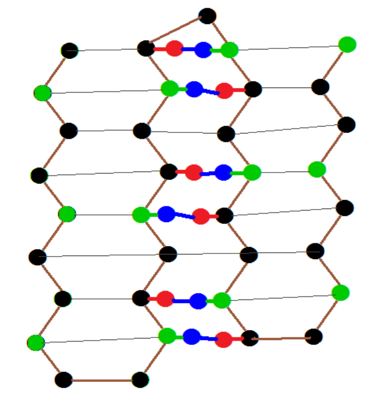
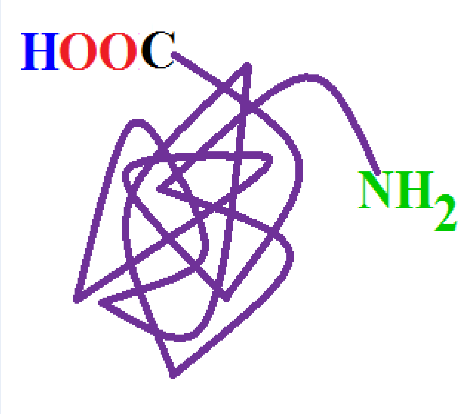
AA + AA + AA + AA = TETRAPEPTIDE

10 OR MORE AA's =POLYPEPTIDE

- By convention, the left amino acid is always #1; is the free amino end or the N-terminus.
- The farthest amino acid residue to the right is the amino acid in the protein that has the highest number and, as a general rule, is the free carboxyl end or the C-terminus.
- In some cases, the -OH may be replaced with an NH_2, making it an amide.
- When dealing with peptides, there is always one LESS peptide bond than there are amino acid residues in the protein, i.e., a tripeptide has 2 peptide bonds and three amino acids; a hexapeptide has five peptide bonds and six amino acids, *ad nauseum*.
- The sequence[s] of the amino acids held together by peptide bonds ONLY is called the primary structure of a protein.

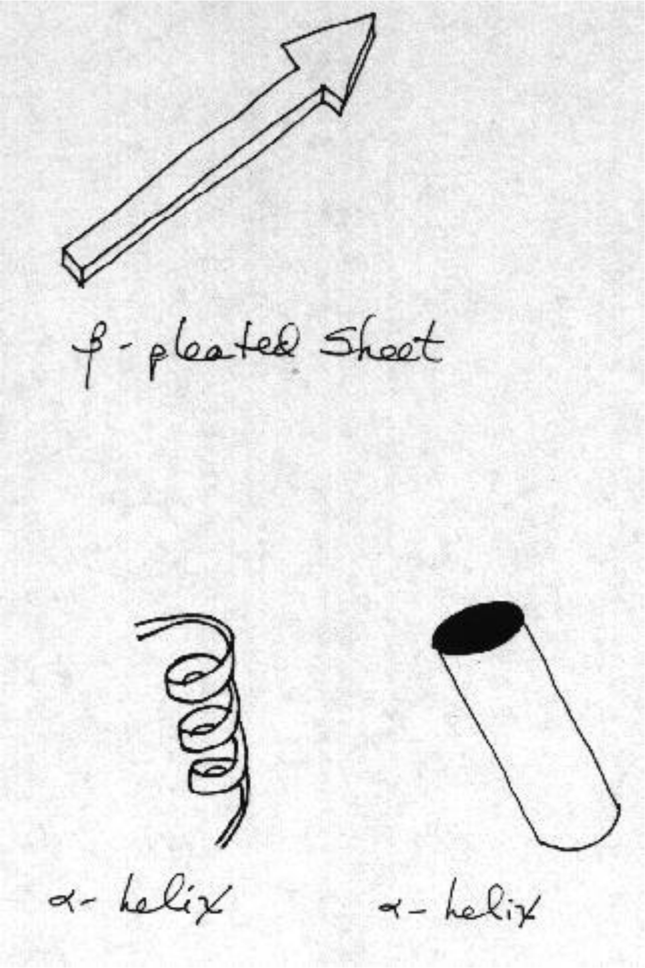
Secondary Structure of Proteins

- The secondary structure of proteins is determined by how the amino acid sequence (the primary structure) folds upon itself and bonds with hydrogen bonds, i.e., non-covalent attractive forces.
- There are, for this course, 3 secondary structures:
  - α-helix, β-pleated sheet, Thermodynamic random coil

α-helix	**β-pleated sheet**	**Thermodynamic Random Coil**
		
Top Image: A protein that coils on itself in a right handed turn is called an α-helix -- Green = N; black = C; red = O, blue = H Bottom Image: The α-helix permits tissues to stretch a bit, like hair. Note that the H bonds are between the carbonyl oxygen and the amino hydrogen. Only a PORTION of a protein is in alpha-helix, NOT the whole protein. Black = C; red = O; green = N; orange'ish = R groups	The second of the secondary structures of proteins is called the pleated sheet or, some times, the β-pleated sheet. The pleated sheet is in the anti-parallel organization, i.e., the peptide chains making up the sheet are running in opposite directions to each other. Pleated sheets tend to make proteins that do not "give", e.g., silk, it doesn't seem to be of great importance to other proteins.	The last secondary structure about which we have interest is the thermodynamic random coil. Although we call this a random coil, nature tells us that there is a reason for every structure. We call it random as we have not worked out the "code" of this structure. In addition, if we denature this structure, the protein loses its function.

Secondary Structure "Short-Hands"

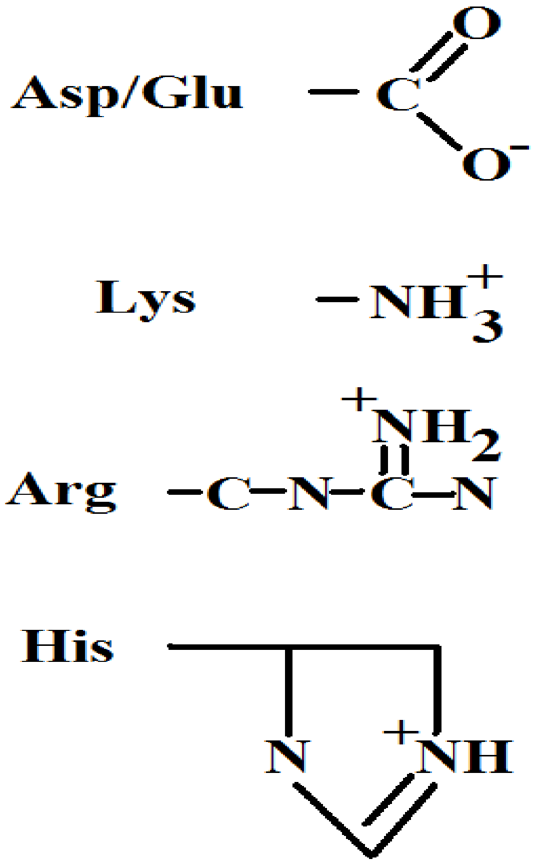
When discussing the regulation of genetic activities, eventually, it is important to remember that proteins regulate many of these activities. In addition, Figure, right, illustrates a shorthand way in which α-helices may be drawn and how β-pleated sheets may be drawn. These shapes are of significance as they are how we will viewed the three types of DNA regulatory proteins.



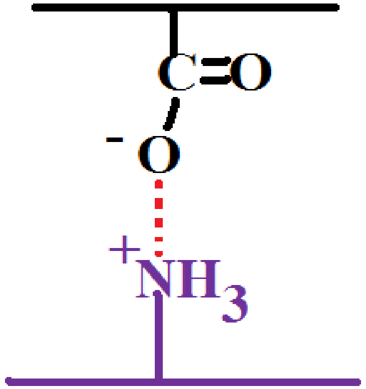
Tertiary Structure

- The tertiary structure of a protein is, for all intents and purposes the three dimensional shape of the protein brought about by interaction forces of ionic, hydrophobic and covalent disulfide links of the one protein chain.
- Two examples include the β-chain of hemoglobin and the myoglobin molecule.
- Tertiary structure, put another way, is the manner in which the R groups assist the protein in secondary structure formation to fold, twist, bend, kink, AGAIN, upon itself.
- Water soluble proteins fold so that hydrophobic R groups are tucked inside the protein and hydrophilic R groups are on the outside of the protein. WHY?
- This way, the protein may interact with the solvent (water) and not precipitate or otherwise be inactivated.
- Water insoluble proteins fold so that hydrophilic R groups are tucked inside the protein and hydrophobic R groups are on the outside of the protein. WHY?
- This is so that a protein, e.g., an ion channel in a cell membrane, may insert itself in a non-polar environment so that polar particles may be transported into or out of regions compartmentalized from each other.

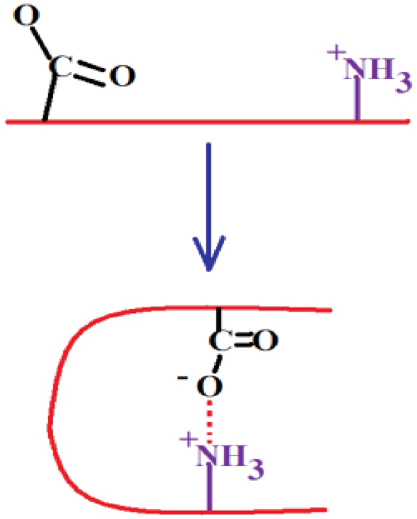
- Ionic interactions also stabilize tertiary structures.
- Where, though, are the ionic groups?
- They’re the R groups!
  - The carboxyl groups on asp and glu;
  - the ε-amino group on lys;
  - the guanidino group on arg;
  - the imidazole ring on his.



R groups “cross-link” to form a “salt link”

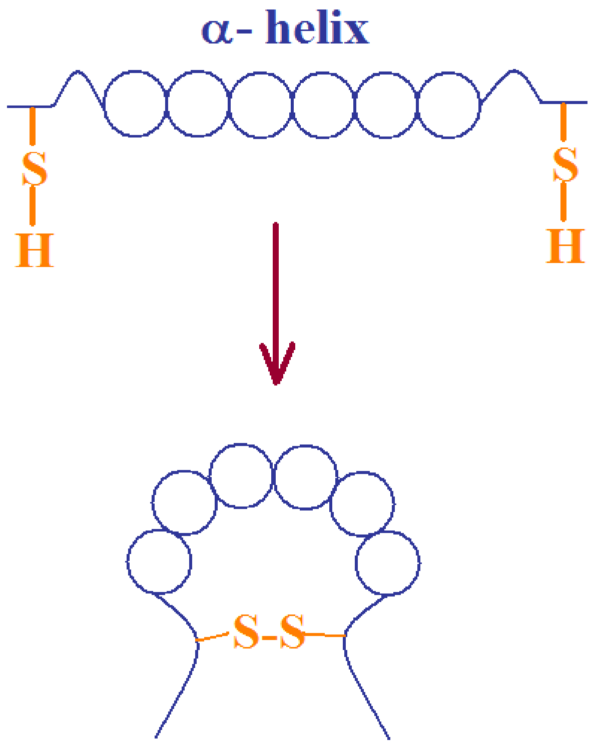


- Top: 2 individual protein chains linked



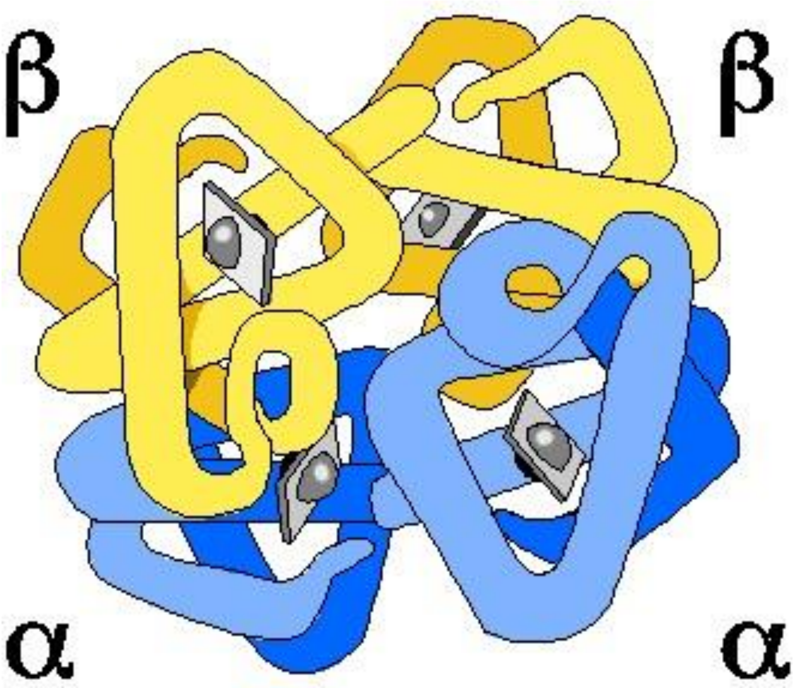
- Bottom: an intra-chain link

- Disulfide bonds assist in tertiary structure by allowing the protein chain to interconnect itself and introduce a hair-pin into its structure -- just like how straight hair is curled and curly hair is straightened out



Quaternary Structure -- Hgb

- The last structure of proteins in which we have interest is called the quaternary structure: the organization of two or more protein chains to bind together in such a manner as to give the group of proteins a single function, e.g., the tetramer of hemoglobin.
- The 4 proteins are held together by salt links, hydrophobic and hydrophilic interactions.
- In Hemoglobin, disruption of these forces (to form deoxy hemoglobin) cause the hemoglobin molecule to become smaller than oxy-hemoglobin.
- Tetramer – salt-linked
- Each protein contains a heme group
- Each heme group binds Fe $^{2+}$
- NOT Fe $^{3+}$



Protein Denaturation

- The denaturation of proteins includes anything that disrupts secondary, tertiary and/or quaternary structure of proteins:
  - heat,
  - alcohol,
  - salts,
  - heavy metals,
  - freeze/thaw,
  - acids/bases.
- All cause inactivation of proteins.

Groups of Proteins

- Fibrous proteins include:
- Collagens: connective tissue; after it's boiled, the soluble part is called gelatin (found in JELLO)
- Elastins: in stretching tissues
- Keratins: water-proofing proteins
- Myosins: in muscle
- Fibrin: blood clotting protein

- Globular proteins include:
- Albumins: water soluble; transporters and increase blood osmotic pressure
- Globulins: saline soluble; transporters and antibodies
- Enzymes: biological reaction catalysts

Enzymes Have Specific Functions

- Enzymes are categorized into one of 6 biological activities according to the Enzyme Commission:
- E.C. #.#.#.#
  - Oxidoreductases: catalyze redox reactions -- involve NAD and FAD – E.C. 1
  - Transferases: catalyze group transfers -- E.C. 2
  - Hydrolases: use water to lyse bonds – E.C. 3
  - Lyase: nonhydrolytic and non-oxidative group removal – E.C. 4
  - Isomerases: catalyse isomerization reactions – E.C. 5
  - Ligase: catalyzes reactions requiring ATP hydrolysis – E.C. 6

Practical Conditions

- To Study Enzymes:
- Substrate (S) must be converted to product (P) by the enzyme (E) under the following conditions:
    - The reaction is thermodynamically feasible
    - S goes through and above the appropriate E_a for P to form

Example

Reaction	Catalyst	E_a (@ RT)
$2H_2O_2 \rightarrow 2H_2O + O_2$	None	319.2 kcal/mol
$2H_2O_2 \rightarrow 2H_2O + O_2$	I^-	239.4 kcal/mol
$2H_2O_2 \rightarrow 2H_2O + O_2$	Catalase	33.6 kcal/mol

Efficiency of Enzymes

- Increases rate of reaction without being consumed themselves
- Lower the E_a; no effect on K_{eq}
- Permit reactions to reach equilibrium quicker
- Have pH and temperature requirements
- Cause reactions to go within seconds as opposed to lab reactions that may take years
- Necessity to/for life

E.g., $CO_2 + H_2O \leftrightarrow H_2CO_3$

- Catalyzed by carbonic anhydrase at a rate of $6*10^5$ molecules of CO_2 condensed per second

Specificity of Enzymes

- In reaction types catalyzed
- In substance involved in the reaction (S)
  - Absolute specificity ≡ catalyzes reaction with only one S
  - Relative specificity ≡ catalyzes reaction of substrates with similar structures
  - Stereochemical specificity ≡ D vs L – more later in class

Enzyme Regulation

- Cell regulates which enzymes function and when, i.e., not ALL enzymes are working at the same time
- Some catalyze uni-directional; some catalyze bi-directional

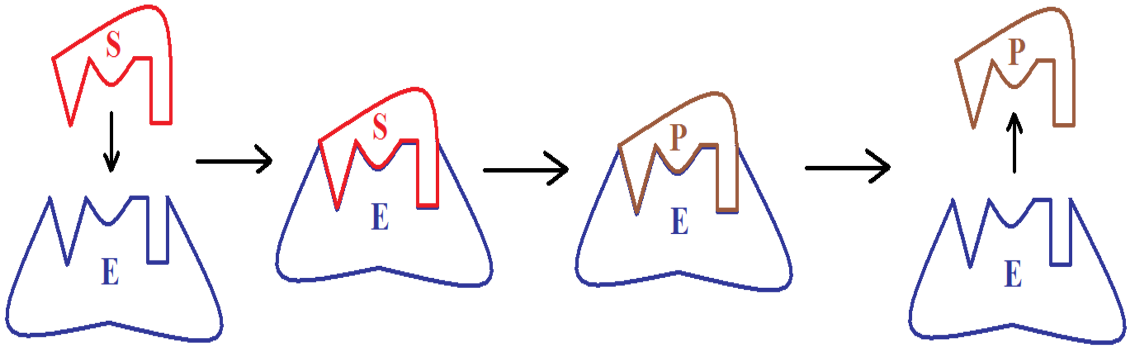
Enzyme Activity

- $\equiv$ catalytic capacity of enzyme to increase reaction rate
- Turnover number $\equiv$ # of S molecules acted upon by ONE enzyme molecule per minute
- Enzyme assays $\equiv$ measure enzyme activity

Enzyme Models

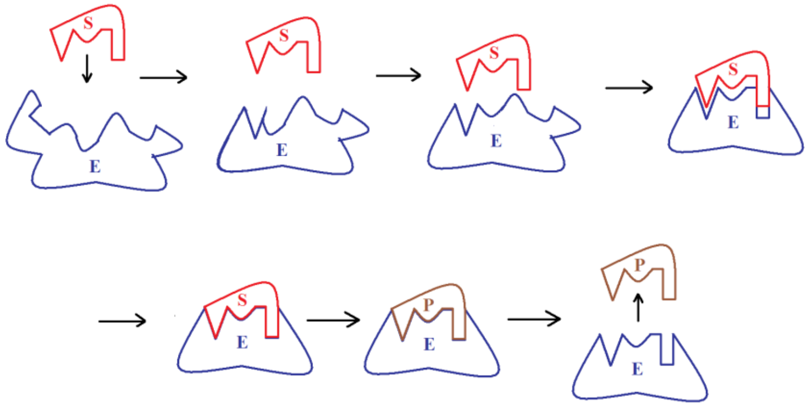
- Of significance, of course, is the fact that the shape of the enzyme gives it its function (the shape of a protein gives it its function).
- Enzymes speed up the reaction rate in biological systems 100,000 - 1,000,000 fold!
- Enzymes have specific substrates (chemical group upon which the enzyme works), but can work on limited kinds of substrates.
- There are two generally accepted models for the functioning of enzymes: the lock and key model and the induced fit model.
    - A third model, the Three Point Attachment Theory is making a controversial “come-back” of sorts in enzymology
    - This model […] developed in the 1940's by A.G. Ogston, before […] X-ray crystallography altered the way […] proteins were viewed. […] The three-point attachment model needs to be revised to incorporate new findings. [http://cbc.arizona.edu/classes/bioc462/462bh2008/462bhonorsprojects/462bhonors2000/ramin/models.html]
    - The Four Point Attachment Theory is newer and seems to make up for the short-comings in the Three Point Attachment Theory: The need for recognition of four locations versus three arises because the binding sites of some enzymes can be approached from the front or the back. [http://cbc.arizona.edu/classes/bioc462/462bh2008/462bhonorsprojects/462bhonors2000/ramin/models.html]
- We will address the lock and key model first, followed by the induced fit model – the 3 and 4 point attachment theories are succinctly introduced above.

Model #1: Lock-n-Key



- In this model, see graphic, above, the substrate (S) is complimentary to the binding/active site in the enzyme (E). This is likened to the lock and key, where the lock is complimentary to the key. As the E and S bind, they form the Enzyme-Substrate complex (ES). This is an intermediate in the reaction that will cause S to be changed into a product (P).
- The enzyme acts as a sort of scaffold, holding the substrate so that one specific reaction may occur.
- In this case, a bond (or bonds) is (are) broken as the enzyme changes its shape ever so slightly, causing the substrate to break exactly where it's supposed to, releasing the new products and the enzyme for use, again.
- Remember that the active sites (a, b, c) of the enzyme are complimentary to the SHAPE of the substrate.

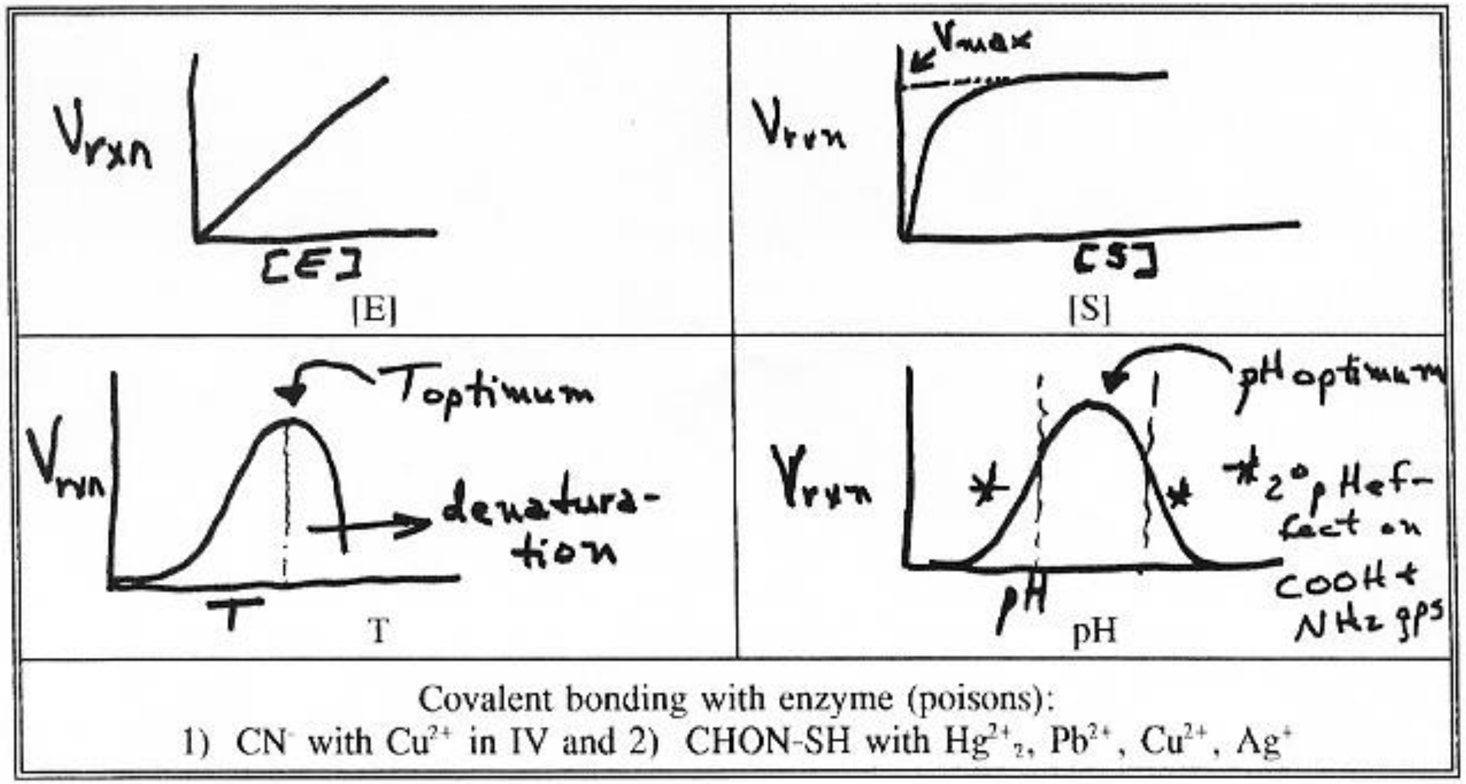
Model #2: Induced Fit



- The second model is called the induced fit model.
- This means that as the S gets closer to the E, the E actually undergoes a conformational change (shape change) to fit the S, i.e., its shape is INDUCED to change by the presence of the substrate.
- Note that as S gets closer to E, the active site "a" changes shape to match the complimentary site on S.
- As S continues to get even closer, site "b" shifts its shape, as does site "c" when S is all but bound to the enzyme.
- Once ES is formed, this model conforms to the remainder of the lock and key theory of enzyme-substrate binding.

What Effects Enzyme Activity?

Easy Answer: [E], [S], T, pH and covalent bonding



Covalent bonding with enzyme (poisons):
1) CN^- with Cu^{2+} in IV and 2) CHON-SH with Hg^{2+}_2, Pb^{2+}, Cu^{2+}, Ag^+

Anything Else?

- YES!!!!
- Effectors
  - Non-substrate that turns on E, e.g., calmodulin (in most cells) and troponin (in muscle cells {skeletal and cardiac}). To activate E's, both must bind Ca^{2+}

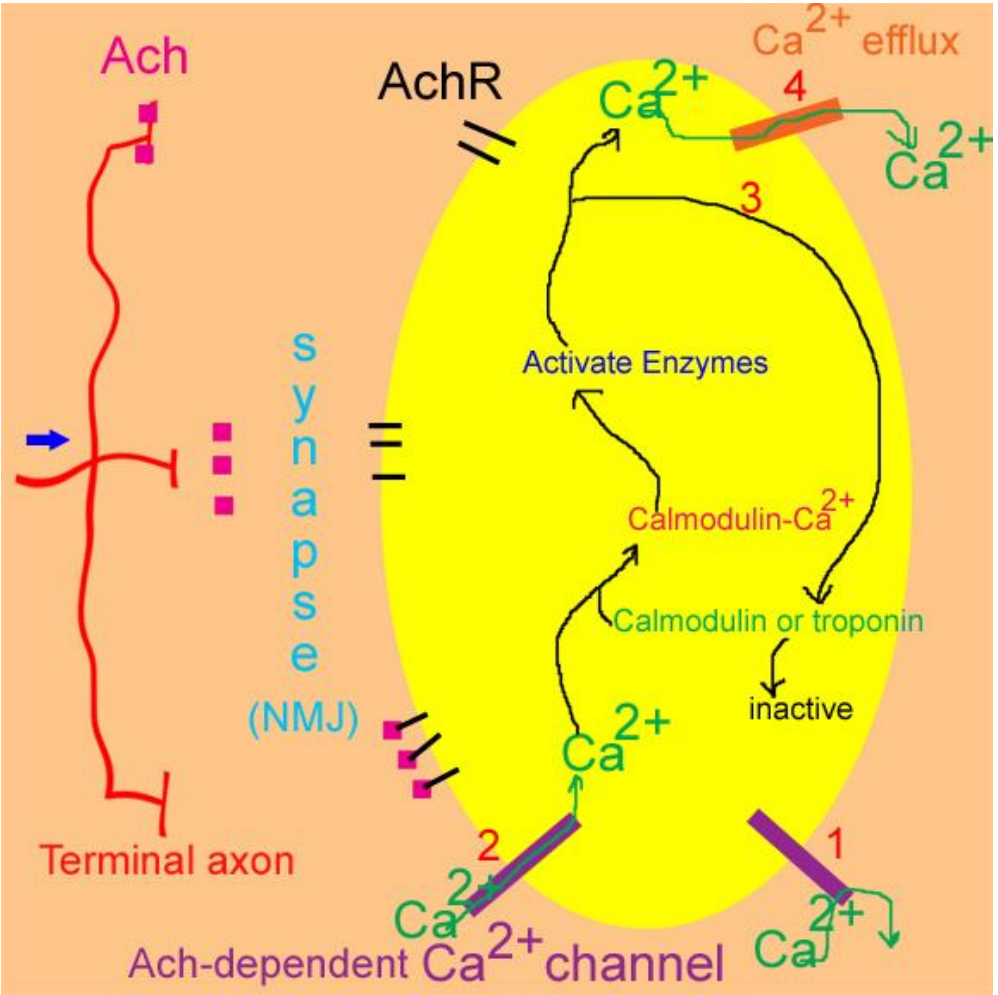
Academic Aside: Cellular [Calcium Ion]

BIG PROBLEM!!!

- Ca^{2+} HAS to stay outside the cell or separate from the cytosol until and when it is exactly needed. WHY???
  1. Inside the cell $[Ca^{2+}] = 0.0$ M; $[P_i] = 0.001$ M
  2. If you add high $[Ca^{2+}]$ with this $[P_i]$ it will form an intracellular $Ca_3(PO)_4$ ppt.
- So, HOW do you get the Ca ion inside the cell or into the cytosol WITHOUT causing a precipitate?
- NERVE SIGNALS – a.k.a. neurotransmitters

NMJ

1. no neurotransmitter bound to receptor to turn it on
2. 2. When neurotransmitter binds to receptor, it turns on the calcium ion channel and increases calcium ion influx
3. Calcium ion won’t ppt as calcium phosphate because this reaction is FAST!
4. When Ach is released from receptor calcium ion efflux is activated – is active transport



✓The graphic at right illustrates some of the intracellular processes clinicians must be able to treat pharmacologically when a person is experiencing a myocardial infarction with concurrent intracellular metabolic acidosis.

✓grey thick bars are the intercalated disks;

✓**thin blue bars** are the striations found in myocardiocytes;

✓**red thick bars** represent the cell membrane;

✓**purple oval** a Na^+ -- Ca^{2+} exchange transport protein;

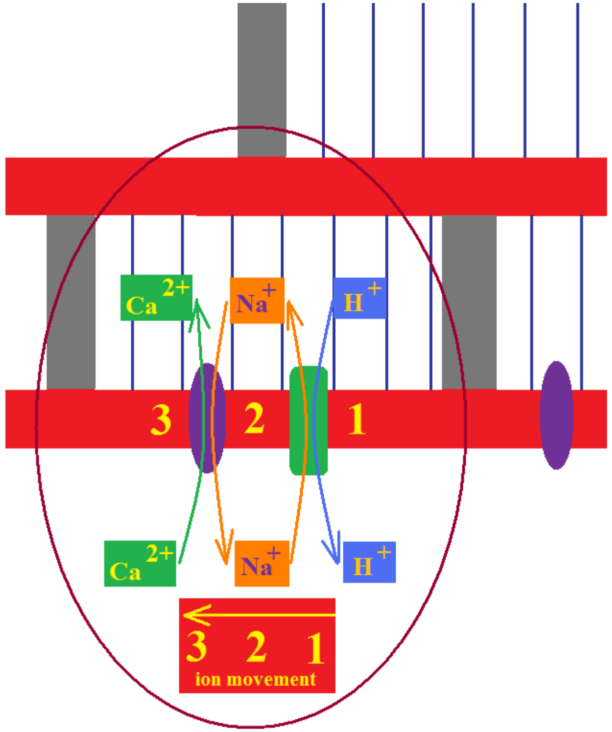
✓**green rectangle** a H^+ -- Na^+ transport protein;

✓**numbers in yellow** indicate the direction of ionic transport**)**

✓

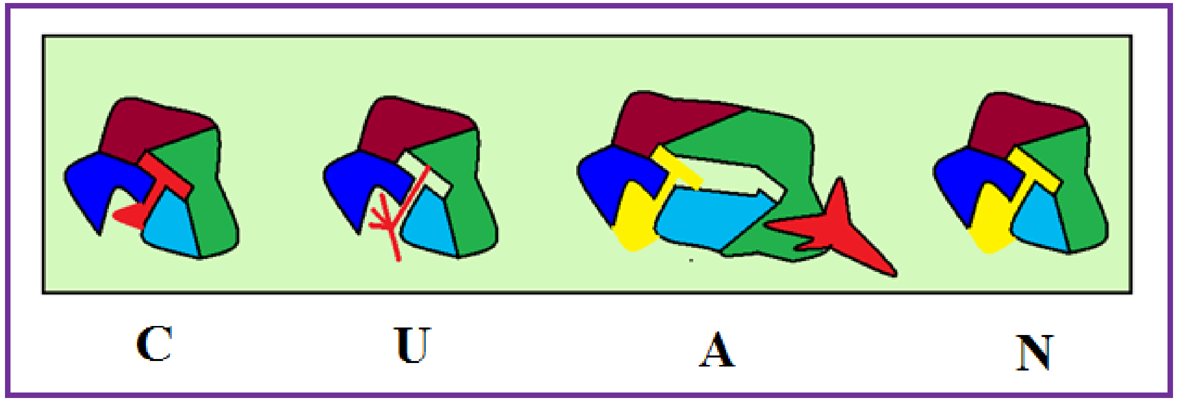
✓One of the biggest concerns clinicians have regarding heart health during a myocardial infarction (MI; heart attack) is that the $[H^+]$ may increase due to a build-up (and dissociation) of lactate and/or fatty acids, which may contribute to a metabolic acidosis in the heart muscle, which will thus kill more and more heart muscle.

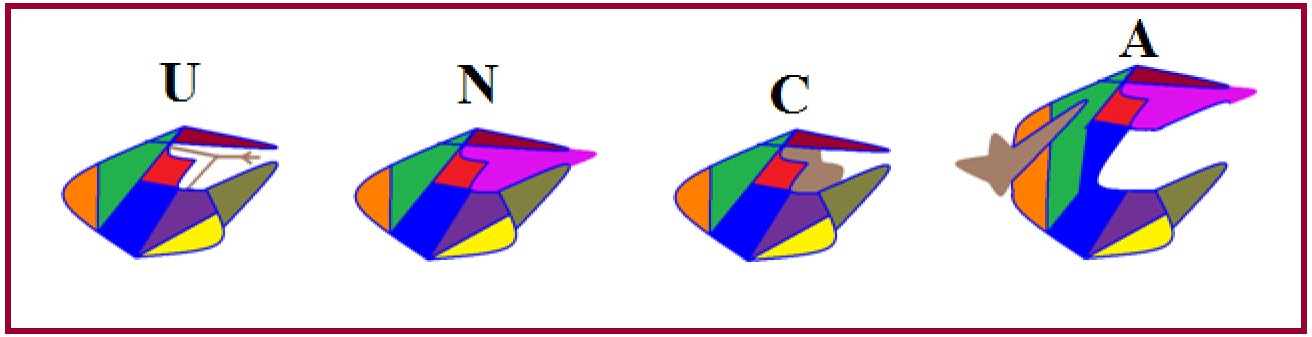
✓This process is rendered even more critical in that as the H^+ are exchanged OUT of the cardiac cells to compensate for the intracellular metabolic acidosis, Na^+ and Ca^{2+} exchange occurs leading to excessively high levels of Ca^{2+} in the cells which may progress to further cell, and, hence, organ, death.

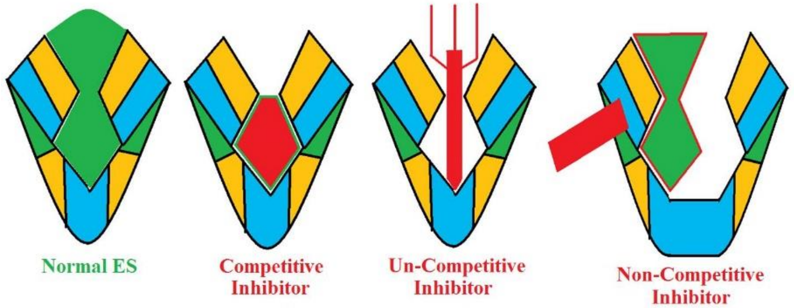


Enzyme Inhibition

Descriptive Introduction

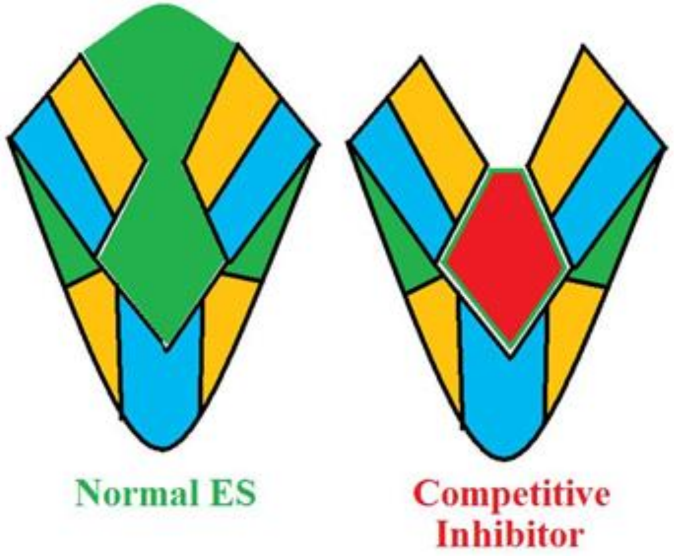






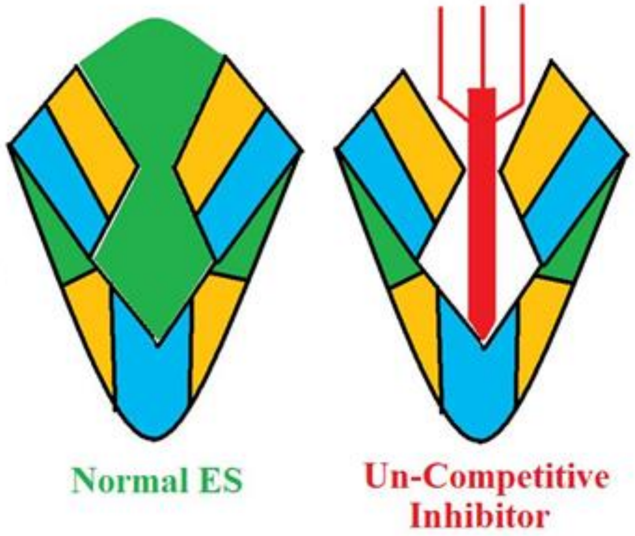
Competitive Inhibition

- The right graphic represents competitive inhibition of an enzyme, i.e., an inhibitor specific to this enzyme COMPETES with the substrate for the active site of this enzyme.
- It is reversible; will block S from binding.
- One example of this sort of inhibition is carbamoyl choline that competitively inhibits acetylcholinesterase.



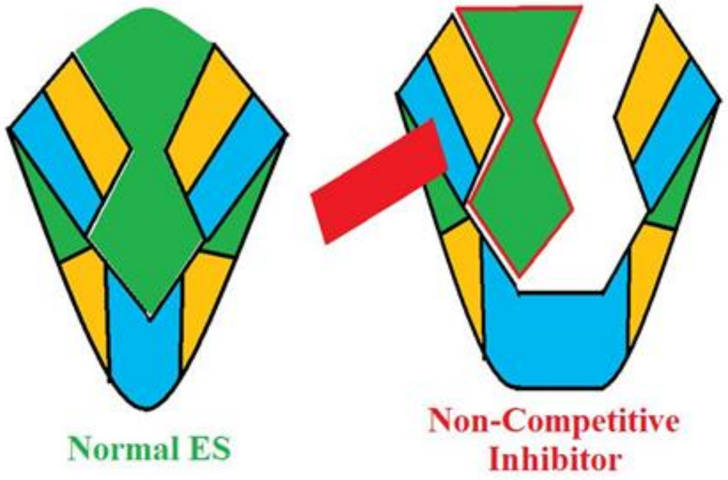
Uncompetitive Inhibition

- The right graphic represents uncompetitive inhibition.
- This sort of inhibition involves covalently bound inhibitor and inactivates the enzyme irreversibly.
- Two examples of this sort of inhibitor are nerve gas and organophosphates that inhibit acetylcholinesterase.
- Organophosphate poisoning may be reversed by injecting a drug called 2-PAM.
- Valium and atropine are useful to treat muscle spasms and breathing difficulties, as well.



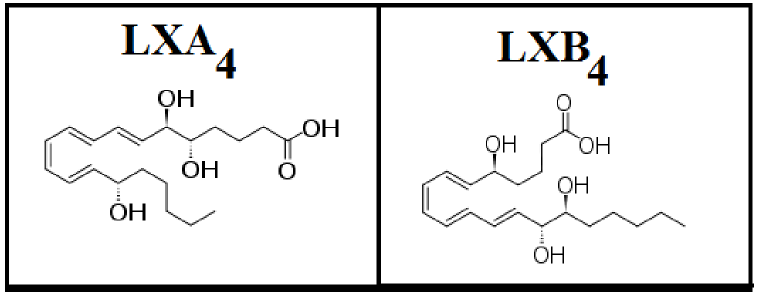
Non-Competitive Inhibition

- The right graphic represents noncompetitive inhibition.
- Note that the inhibitor does NOT bind to the active site of the enzyme, rather it has its own unique binding site.
- When a noncompetitive inhibitor binds to an enzyme, it causes the enzyme to change shape and shuts off its activity reversibly by not allowing S to bind completely.
- This sort of inhibition is also referred to as allosteric inhibition and plays major roles in metabolic regulation.
- An example of a noncompetitive inhibitor is aspirin.
- Aspirin inhibits cyclo-oxygenase which is the main enzyme in prostaglandin biosynthesis.
- Prostaglandins mediate pain, inflammation, blood pressure, gastric mucous secretion, blood clotting, labor and delivery, to name a few.



Mixed Inhibitor Types

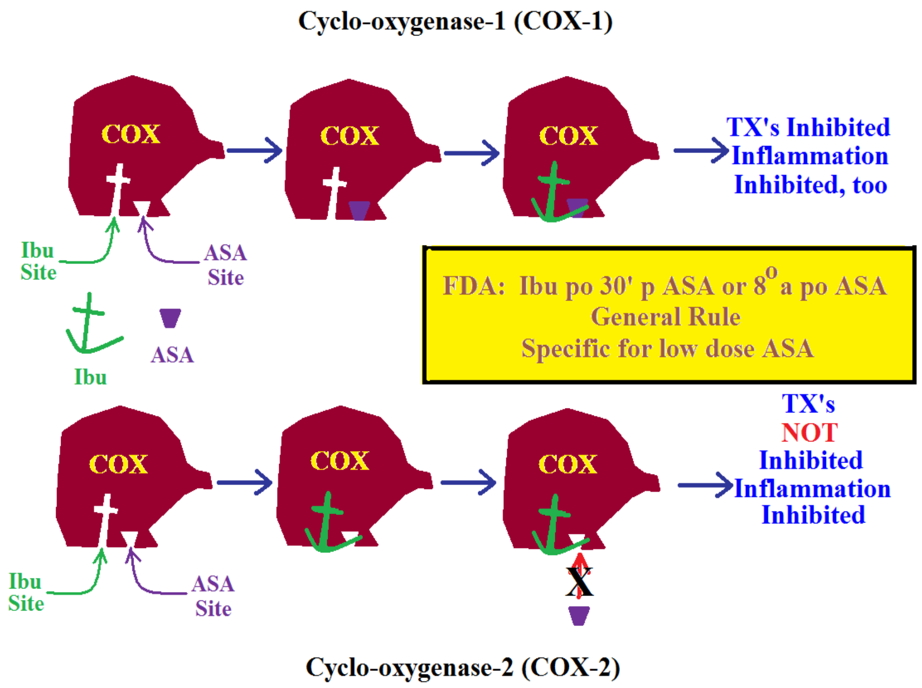
- An example of mixed inhibitor types is aspirin (ASA) and Ibuprofen (IBU).
- ASA is an **UN**competitive inhibitor of COX-1 (CycloOXygenase type 1).
- ASA and IBU inhibit cyclo-oxygenase variants which is the main enzyme in prostaglandin biosynthesis.
- Prostaglandins mediate pain, inflammation, blood pressure, gastric mucous secretion, blood clotting, labor and delivery, dysmenorrhea, to name a few.
- This inhibition is IR-reversible – unlike other NSAID's (Non-Steroidal Anti-Inflammatory Drug's).
- ASA acetylates COX-1 to inhibit it.
- The half life ($t_{½}$) of ASA varies by dosage: 250 mg dose $t_{½}$ = 2-4.5 hrs; 1 g dose $t_{½}$ = 5 hrs; 2 g dose $t_{½}$ = 9 hours; > 4 g $t_{½}$ = 15-30 hrs.
- ASA CHANGES COX-2 activity to produce anti-inflammatory lipoxins ("LX's"; derived from ω3 fatty acids (EPA) as well as ω6 fatty acids such as $20{:}4^{\Delta 5,8,11,14}$), see image at right.



Lipoxins
anti-inflammatory

Mixed Inhibitor Types

- IBU is a **NON**competitive inhibitor of COX-2.
- It is reversible in its inhibition.
- IBU works primarily through COX-2 (Like Vioxx and Celebrex by reducing PGI$_2$.
- This permits “normal” TX(A$_2$ or B$_2$) production which increases the incidence of blood clots [IBU has lowest incidence of GI/Hematological Sx of the NSAID’s, by the way]).
- The half life for IBU is unique in that it’s about 1.8-2 hrs while its duration of action is about 2-4X the t$_{½}$.
- The problem with these two medications is that IBU binds to COX-2 inhibiting the production of PGI$_2$ – the natural titrant of TX’s.
- What does this mean? Blood clots, potentially. If one is a cardiac patient and is taking low dose po ASA to prevent blood clot formation, yet needs IBU for pain control, what is one to do?
- Per http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm, the patient needs to take their ASA first and wait 30 minutes to take their IBU (top of graphic at bottom of previous page) or take their IBU 8 hours before their ASA dose.
- If IBU is taken first or is not taken long enough before the ASA dose, IBU not only binds, it also blocks the binding of ASA, to COX-1 and COX-2 (graphic). Should this occur, the potential for a fatal MI due to thrombosis of [a] coronary arter[y]ies is elevated.



Medical Uses of Enzymes and Enzyme Assays

- When cells die or are injured, they dump some or all of their E’s into the blood. Assays are used to make diagnoses, e.g.,
  - C[P]K, LDH 2° MI (myoglobins and troponins are being used, as well)
  - GPT (ALT) 2° liver problems
  - GOT (AST) 2° MI or liver
  - Ratios
    - GPT:GOT – normal = 0.75; viral hepatitis = 1.6
    - LD_1:LD_2 – normally < 1; 48° after MI, > 1 and is called the LD_1-LD_2 “flip”
- Calcium ion channel blockers – block calcium ion influx via channel which leads to reduced calcium ion inside the cell which leads to reduced muscle contraction which makes it easier for the heart to beat to reduce the risk of MI or death after MI.

Introduction to Nucleic Acids

Definitions

By definition, nucleic acids are biomolecules that store genetic information in cells or that transfer this information from old cells to new cells.

There are two groups of nucleic acids:

DeoxyRiboNucleic Acid (DNA)

DNA codes for the functioning of the cell

DNA is located mainly in the nucleus of the cell (with a small amount in the mitochondrion of eukaryotic cells -- to be discussed at a later date);

DNA is double stranded

RiboNucleic Acid (RNA)

RNA is the "worker" that helps get the DNA message out to the rest of the cell.

RNA is primarily in the cytosol of the cell.

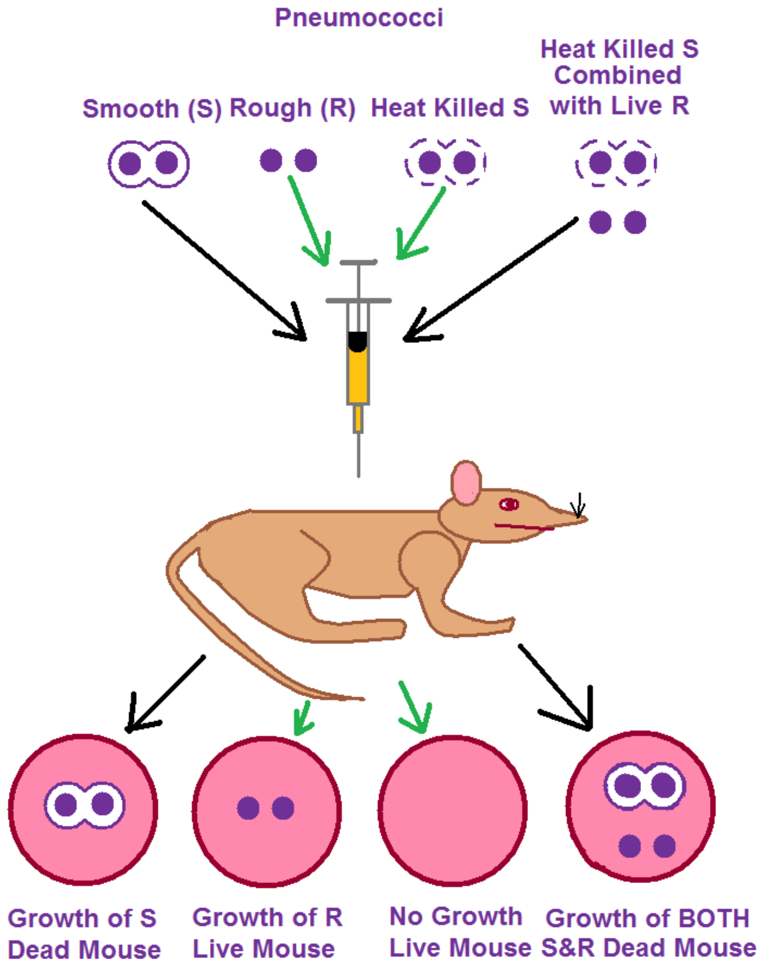
RNA is single stranded – with one “exception”.

BOTH are "codes" for the cell and, hence, the body's activities at the cellular level.

Griffith’s Transformation

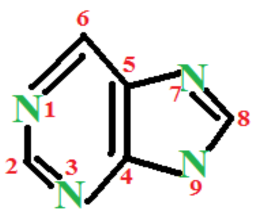
- The first evidence that DNA was responsible for transmitting genetic information was shown by Griffith in 1928, LONG before Watson and Crick showed the secondary structure of DNA to be a double strand of DNA in an α-helix.
- Griffith's transformation, as his experiment has become known, demonstrated conclusively that DNA was "the stuff of heredity".

- Griffith began his experiment by astutely observing that when some strains of *Streptococcus pneumoniae* were injected into mice, they didn't die, while other strains of the same bacterium caused the mice to die.
- As Griffith delved further into this mystery, he noticed that there was a big difference between the two bacterial strains: one had a capsule around itself (he called this the smooth or "S" strain) and the other did not (he called this the rough or "R" strain).
- He then took some of the smooth bacterium (this was the one that had previously killed the mouse) and heat-killed it.
- This dead bacterium was injected into a mouse and the mouse lived.
- Up to this point, whenever Griffith had injected bacteria into the mouse, he had always been able to culture it.
- After injecting the heat-killed bacteria, he was unable to re-isolate any bacteria.
- This was a positive thing, for it conclusively demonstrated that the bacteria was, indeed, dead.
- It was the next step in Griffith's experiments that turned the heredity world on its head: Griffith took BOTH heat-killed smooth bacteria and live rough bacteria and injected them simultaneously into another mouse.
- The mouse died and when Griffith isolated bacteria from this animal, he observed the growth of both S and R strains of the bacteria in culture.
- Since the S strains were previously heat-killed, the only other answer to explain this phenomenon was that the R strains of the bacterium had taken up [some of] the genetic material and begun synthesizing and releasing a capsule based upon that genetic information.

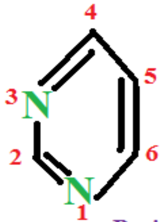


Nucleic Acids

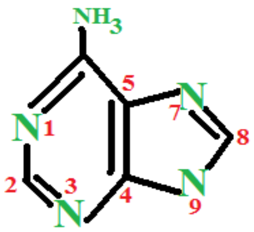
- Nucleic acids consist of nitrogenous compounds called purines or pyrimidines, a carbohydrate and phosphate.
- The figure shows what the structures of purine and pyrimidine look like in the lower right-hand corner.
- Both are aromatic as each has 6 p electrons. Note the short hand notation in the graphic as to the drawn structures of each compound.
- Purine is a 2-fused ring system that consists of one 6-membered ring fused to a 5-membered ring.
- In each ring, there are 2 nitrogens.
- Pyrimidine has only the 6-membered ring with the 2 nitrogens.
- G, C, A, and T are found in DNA; G, C, A, and U are found in RNA.



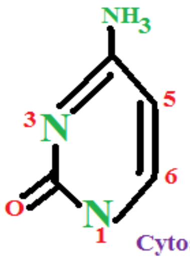
Purine



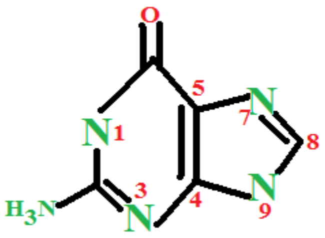
Pyrimidine



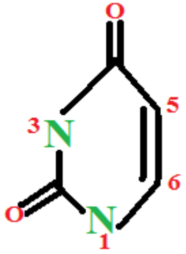
Adenine



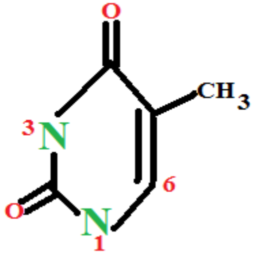
Cytosine



Guanine



Uracil



Thymine

Purines

- The two purines of significance are adenine and guanine.
- Note that they differ very simply:
  - adenine has an amino group on the top of the 6-membered ring,
  - while guanine has an amino group between the 2 nitrogens on the 6-membered ring, a double bonded oxygen in place of adenine's amino group (called a ketone) and has lost a double bond to accommodate the ketone.

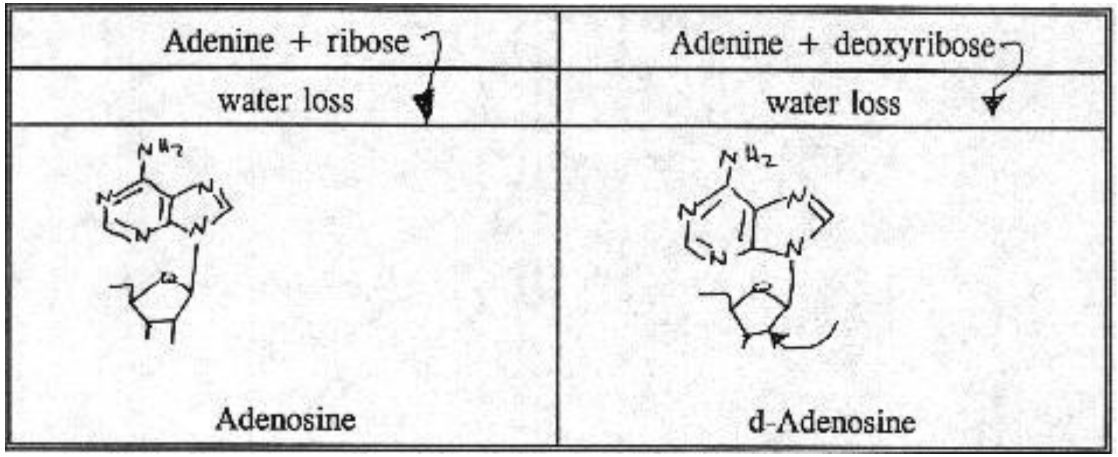
Pyrimidines

- There are three pyrimidines of interest in Biological Chemistry:
- Cytosine
  - Cytosine has a ketone between its two nitrogens, an amino group atop its ring and has lost a double bond to accommodate the ketone.
- Uracil
  - Uracil is a modified form of cytosine, where the amino group is replaced by a ketone and a double bond in the ring is lost to accomodate the new ketone.
- Thymine
  - Thymine is uracil with a CH_3 (methyl) group attached adjacent to the ketone at the top of the ring.

- Generally, the 5 nitrogenous compounds with their carbohydrate moiety are abbreviated as one letter abbreviations: A, G, C, U, T.
- It is important to keep in mind that when referring to RNA, these shortcuts are o.k.
- When referring to them in DNA, it is important to remember that we're discussing dA, dG, dC, dU, dT.
- The reason for this is shown in the d-R.
- The carbohydrate that binds with the nitrogenous compounds in RNA is ribose.
- The carbohydrate that binds with the nitrogenous compounds in DNA is deoxy-ribose.
- Deoxyribose is ribose that has had the 2' -OH group removed.
- The last portion of nucleic acids is the phosphate group.
- This group is of immense importance, as it is through this group that DNA and RNA are "held together".

NucleoSides

- In the hierarchy of nucleic acid structure, there are two more levels of nomenclature: nucleoSides and nucleoTides.
- We'll address the nucleoSides first.
- Nucleosides consist of a purine or pyrimidine and a carbohydrate.
- When a purine or a pyrimidine reacts with ribose or deoxy-ribose, water is always one of the products.
- When the purine is adenine and it reacts with ribose, the other product is adenosine (A).
- When adenine reacts with deoxy-ribose, the other nucleoside is deoxy-adenosine (d-adenosine or dA).
- Likewise with the remainder purines and pyrimidines.
- One point to keep in mind is that d-uridine and thymidine are produced only in the lab, not in DNA or RNA, respectively.



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- When the purine is guanine and it reacts with ribose, the other product is guanosine (G).
- When guanine reacts with deoxy-ribose, the other nucleoside is deoxy-guanosine (d-guanosine or dG).
- Likewise with the remainder purines and pyrimidines.
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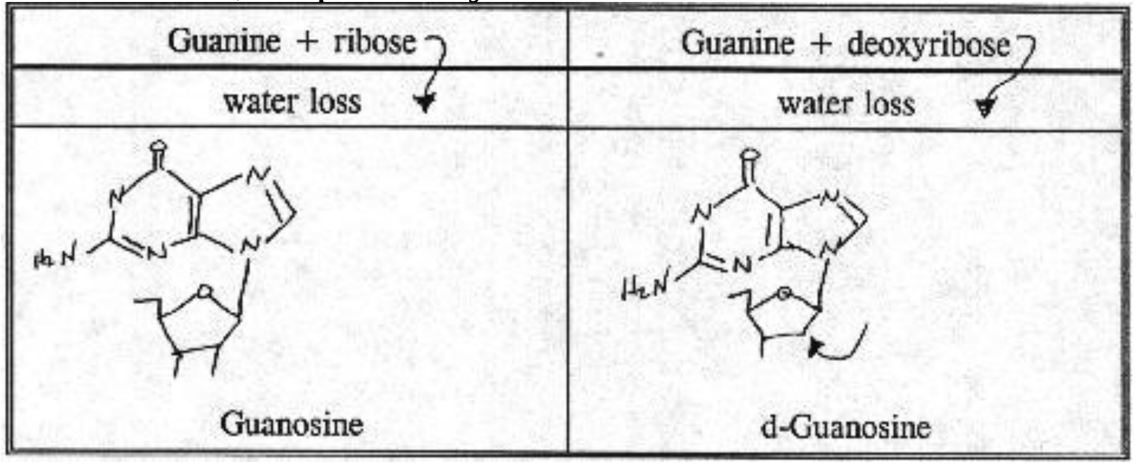

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- When the purine is cytosine and it reacts with ribose, the other product is cytidine (C).
- When cytosine reacts with deoxy-ribose, the other nucleoside is deoxy-cytidine (d-cytidine or dC).
- Likewise with the remainder purines and pyrimidines.
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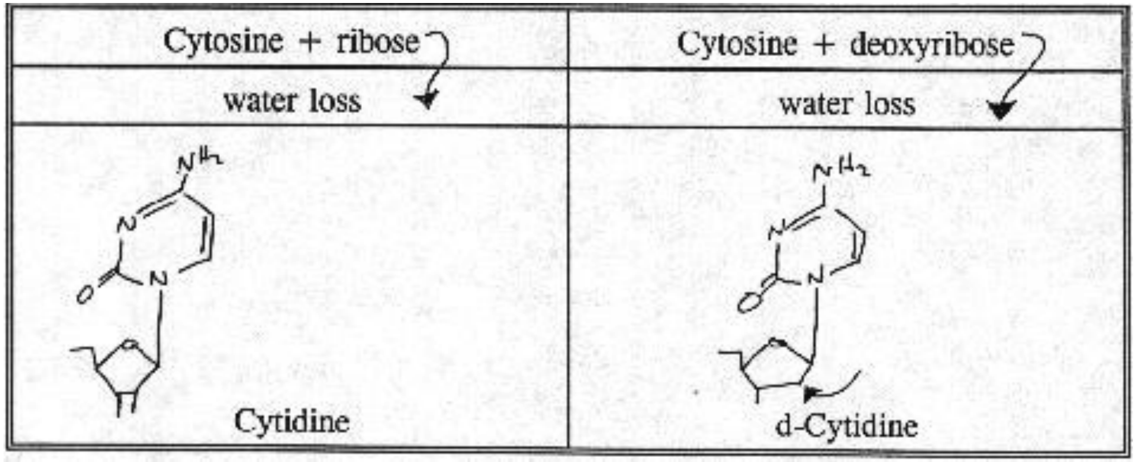

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- When a purine or a pyrimidine reacts with ribose or deoxy-ribose, water is always one of the products.
- When the purine is uracil and it reacts with ribose, the other product is uridine (U).
- When uracil reacts with deoxy-ribose, the other nucleoside is deoxy-uridine (d-uridine or dU).
- Likewise with the remainder purines and pyrimidines.
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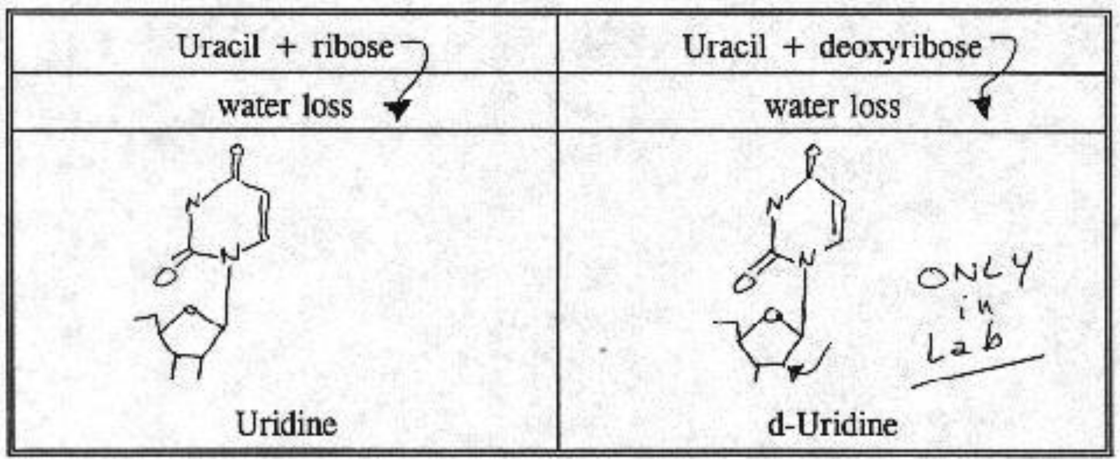

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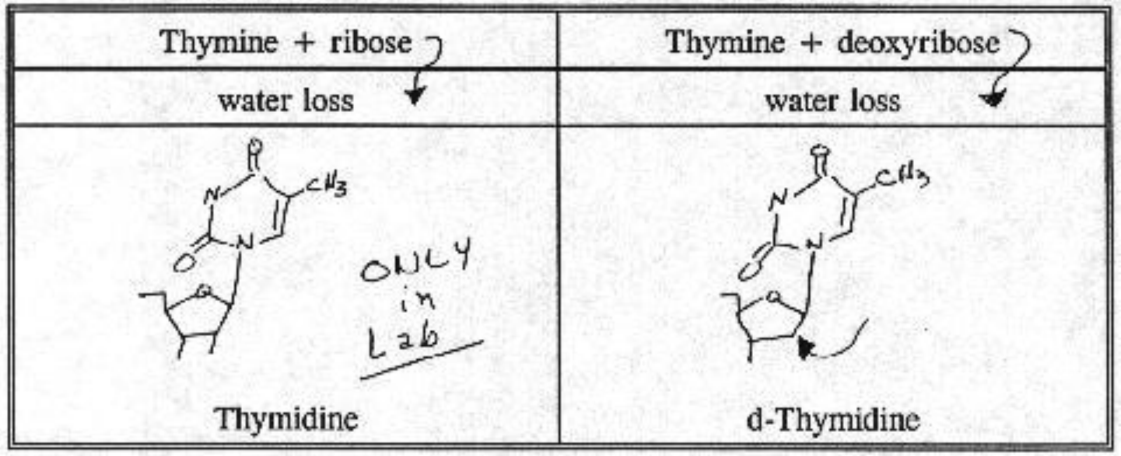
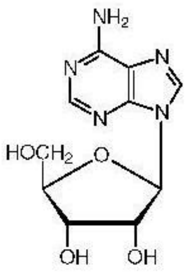
- When a purine or a pyrimidine reacts with ribose or deoxy-ribose, water is always one of the products.
- When the purine is thymine and it reacts with ribose, the other product is thymidine (T).
- When thymine reacts with deoxy-ribose, the other nucleoside is deoxy-thymidine (d-thymidine or dT).
- Likewise with the remainder purines and pyrimidines.
- One point to keep in mind is that d-uridine and thymidine are produced only in the lab, not in DNA or RNA, respectively.



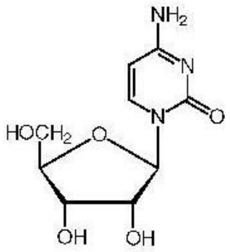
Thymine + ribose	Thymine + deoxyribose
water loss	water loss
ONLY in Lab Thymidine	d-Thymidine

Nucleosides

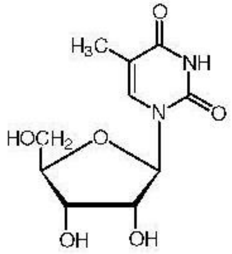


Adenosine
A

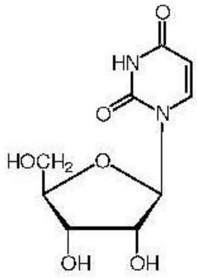
Guanosine
G



Cytidine
C



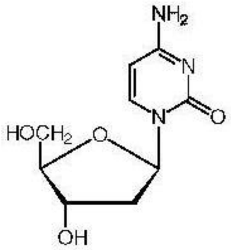
Thymidine
T



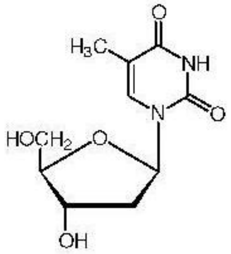
Uridine
U

deoxy-
Adenosine
dA

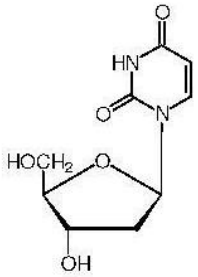
deoxy-
Guanosine
dG



deoxy-
Cytidine
dC



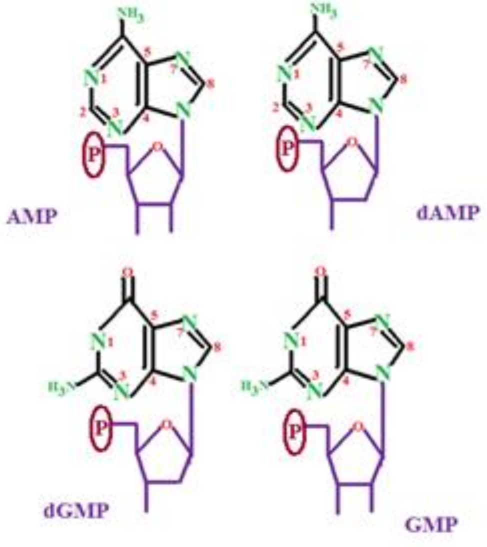
deoxy-
Thymidine
dT

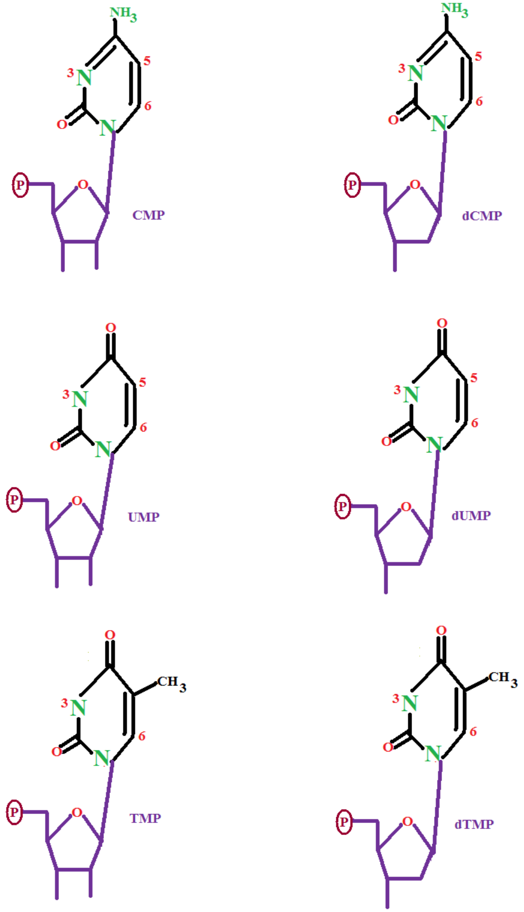


deoxy-
Uridine
dU

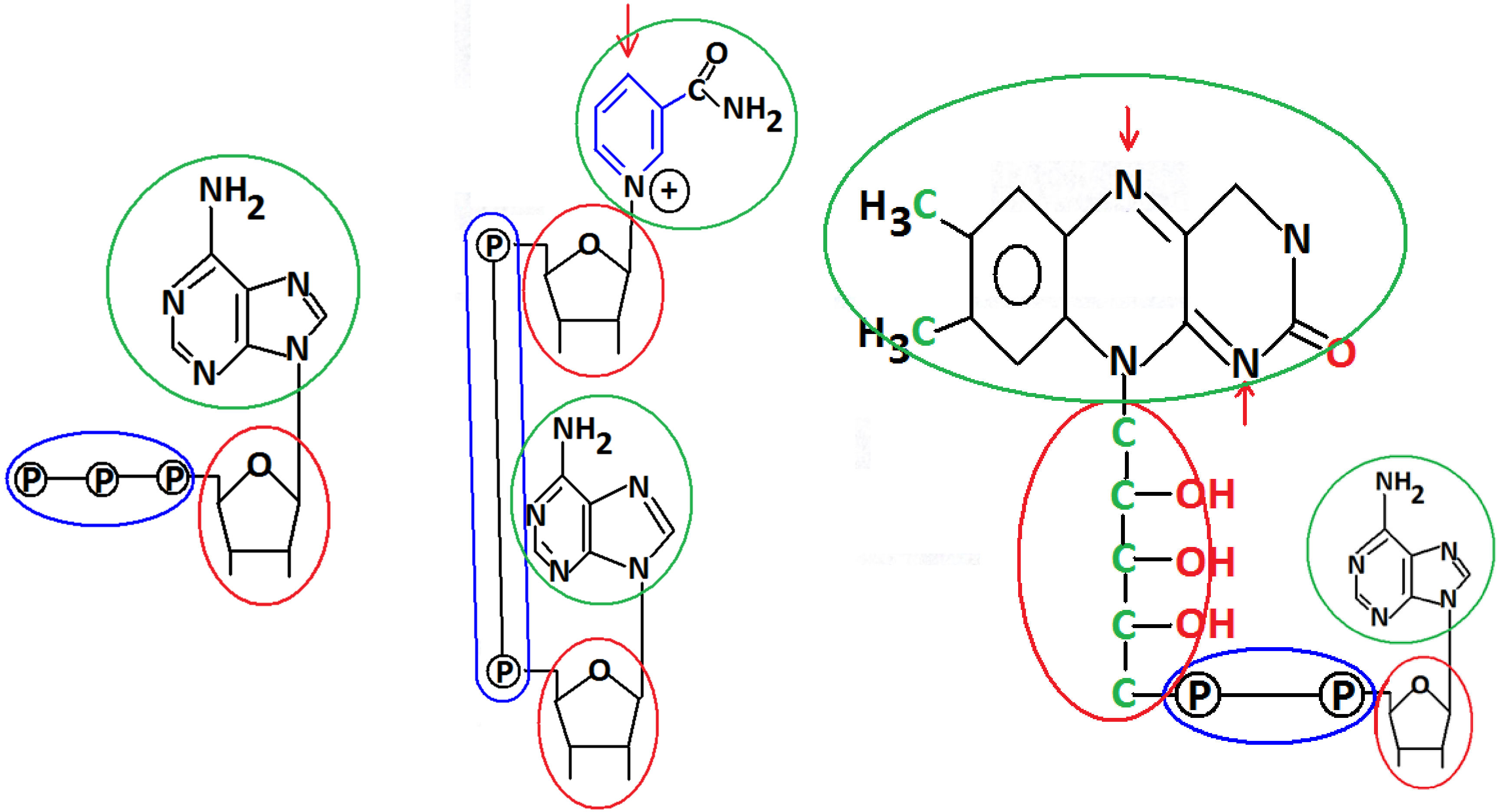
NucleoTides

- The last simple level of nucleic acid nomenclature hierarchy is the nucleoTide.
- Nucleotides are nucleosides that have added a phosphate group to the 5' carbon of ribose or deoxy-ribose.
- Biochemist's short-hand the PO_4^{-3} as a "P" with a circle around it (Ⓟ).
- Note that if there were three (3) phosphates instead of one, the names would end as "triphosphate", hence, ATP is adenosine triphosphate and dATP is deoxy-adenosine triphosphate.

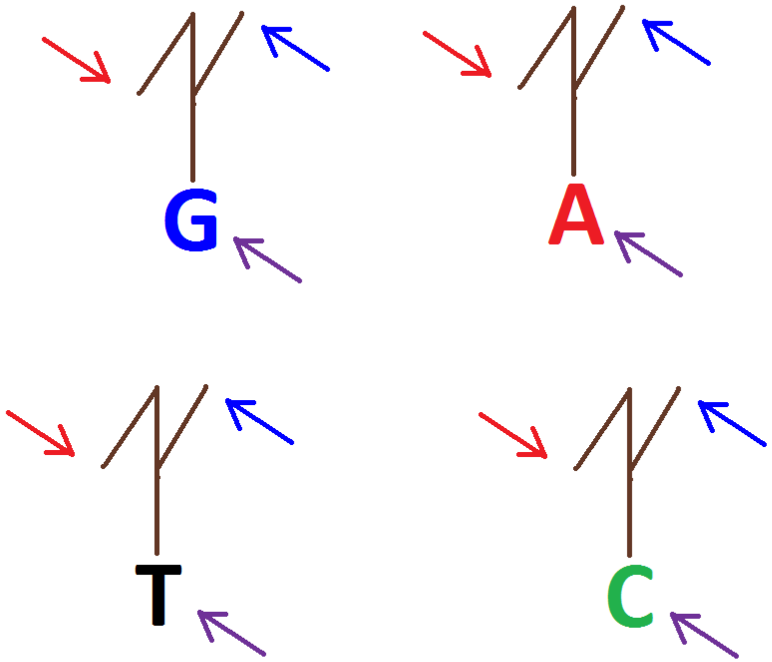




The last group of aromatic heterocyclic compounds is the nucleotides. These consist of three parts: a purine or pyrimidine, ribose and phosphate (a "P" with a circle around it is biochemist's short hand for phosphate). Three representative molecules are shown below. All three are involved in energy production in the body. ATP, NAD^+ and FAD.



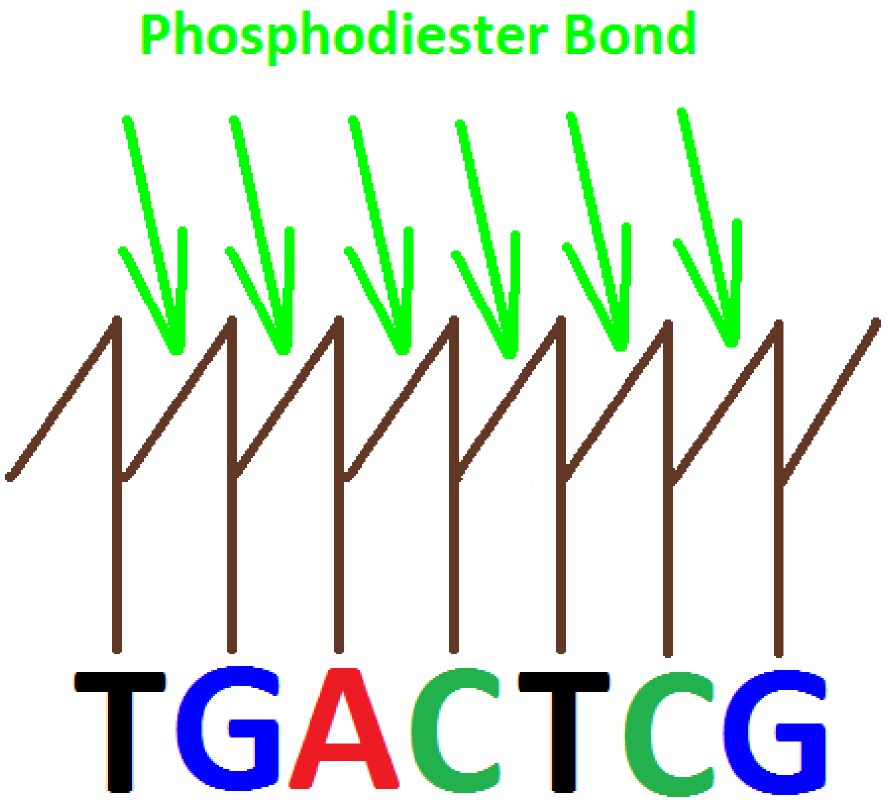
Nucleotide Shorthand



5’ end

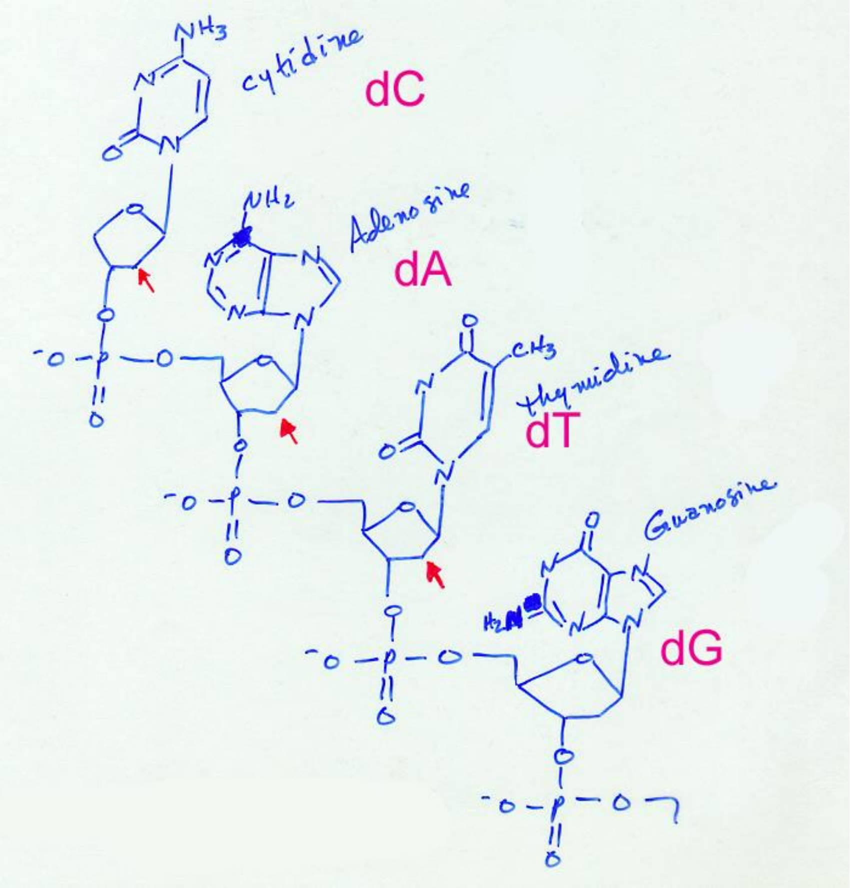
3’ end

Nitrogenous base



5' to 3': TGACTCG

Primary Structure of Nucleic Acids



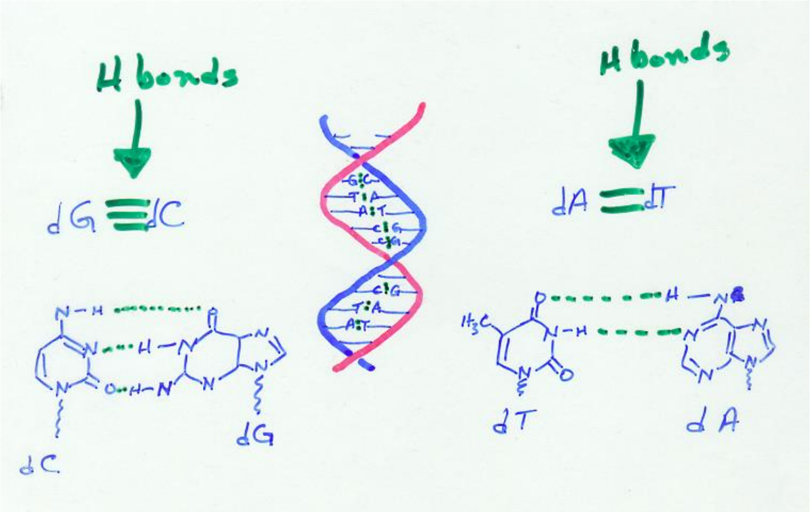
- DNA, at right, linked by phosphodiester bonds between [d] ribose.

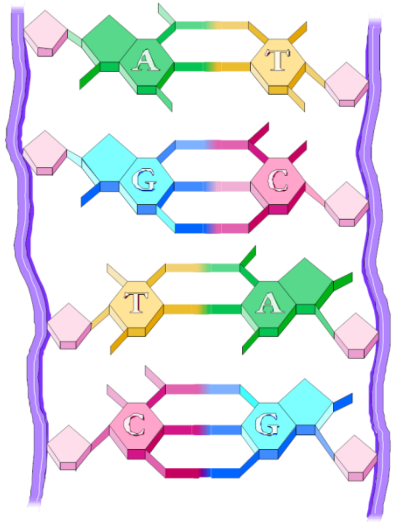
- GC AT DNA

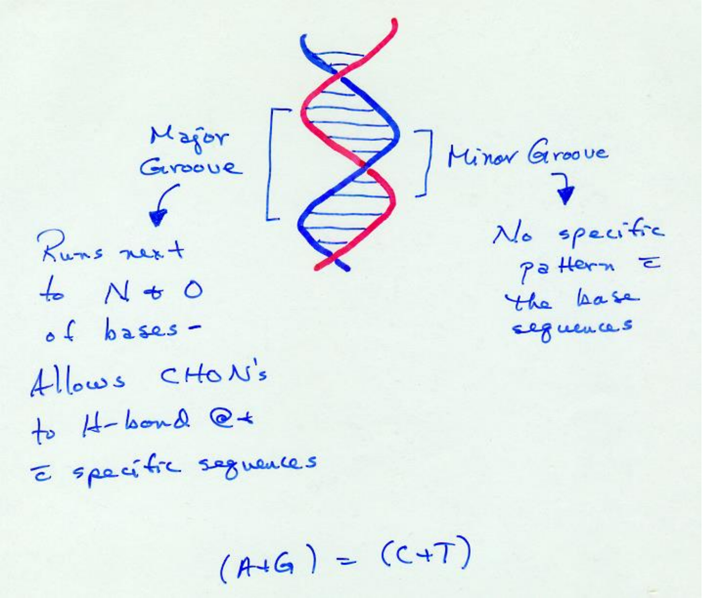
- (dGdC dAdT DNA)

- RNA primary structure is also linked by phosphodiester bonds in the same manner as DNA
- Difference is that U is substituted for T in RNA
- GC AU RNA

Secondary Structure of DNA



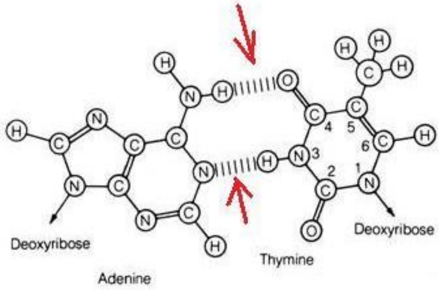




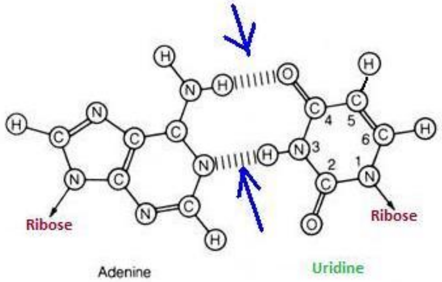
Runs next to N + O of bases - Allows CHON's to H-bond @+ c̄ specific sequences

No specific pattern c̄ the base sequences

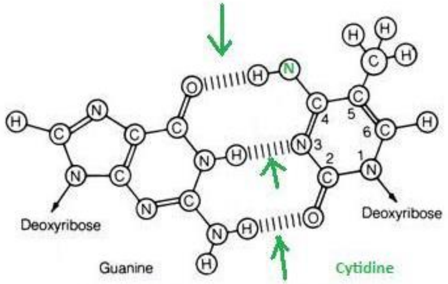
(A+G) = (C+T)



In DNA, dA and dT pair up with 2 H bonds linking them; editors reduce the dA and dT to simply A and T to save $$$.



In RNA, A and U pair up with 2 H bonds linking them -- no editorial reduction needed (A,G,C,U are in RNA). G and C continue to pair up, as well, in RNA.



In DNA, dG and dC pair up with 3 H bonds linking them; editors reduce the dG and dC to simply G and C to save $$$.

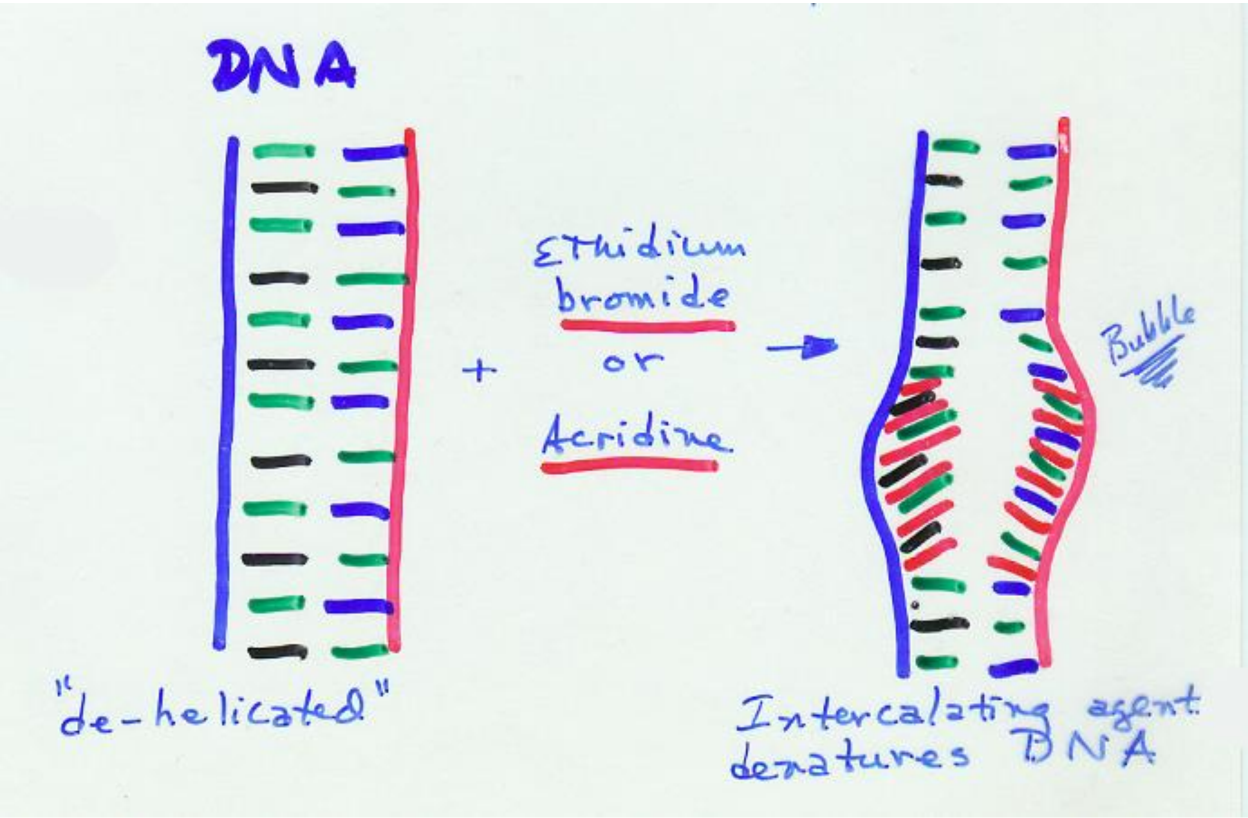
- 2 Linear strands of DNA in right handed double helix
- These strands run in ANTI-parallel directions:
- 3’---5’
- 5’---3’

DNA – Secondary Structure Comments

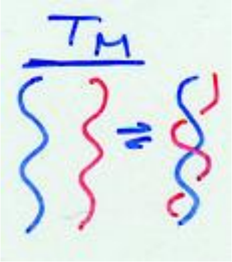
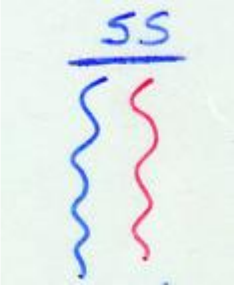
1. CHO-P backbone is on OUTSIDE of helix
2. Nitrogenous bases are on INSIDE of helix
3. OUTSIDE of helix is HYDROPHILIC
4. Inside of helix is HYDROPHOBIC

Cont’d

Bases are almost perpendicular to helical direction:



Other Physical Property Changes with Denaturation

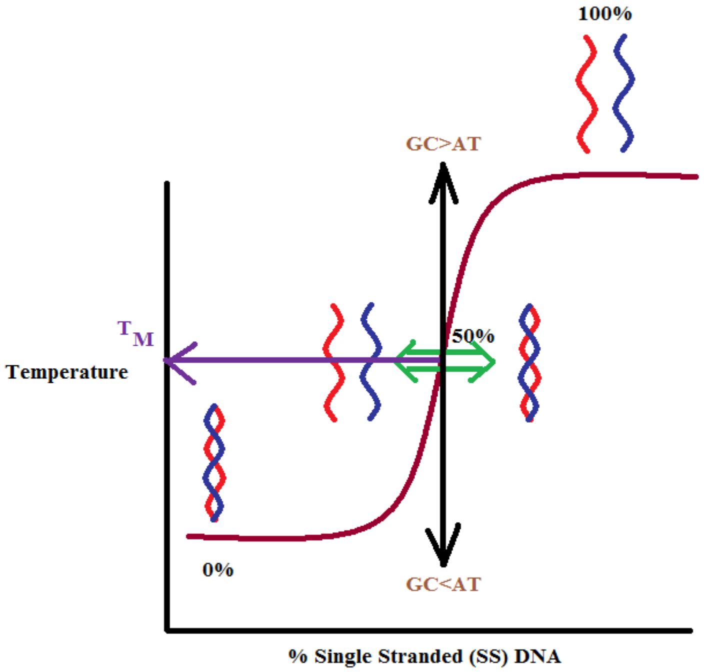
<table>
<tr><td></td><td> </td><td> </td><td> </td></tr>
<tr><td>A_{260}</td><td>↓</td><td>↑</td><td>↑↑↑</td></tr>
<tr><td colspan="4">Purines unstacking and opening up for greater absorption.</td></tr>
<tr><td>Viscosity</td><td>↑</td><td>↓</td><td>↓↓↓</td></tr>
<tr><td colspan="4">The less organized the DNA, the faster it flows.</td></tr>
<tr><td>Buoyant Density</td><td>↑</td><td>↓</td><td>↓↓↓</td></tr>
<tr><td colspan="4">The less organized the DNA, the less dense it is.</td></tr>
</table>

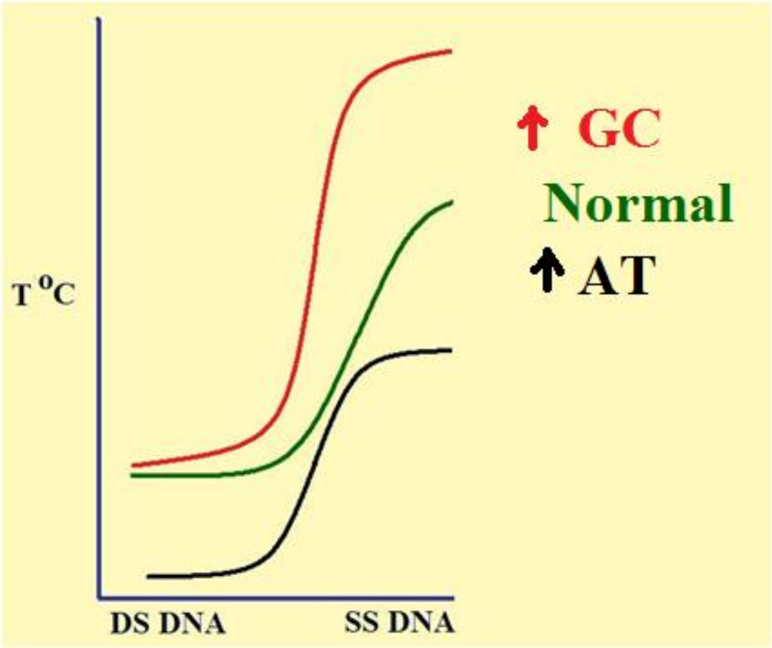
- As DS DNA is denatured, three physical properties of DNA are altered (following slides).
- These are
  - the absorbance of light at 260 nm,
  - the viscosity and
  - the buoyant density.
- DNA easily absorbs light at 260 nm. When the DNA is DS, not as much of this ultra-violet light is absorbed.
- This is because the nitrogenous bases are stacked up tightly and do not permit much of this light to be absorbed.
- As the DS DNA denatures, the ability to absorb light at 260 nm increases as the DS DNA denatures.
- This is because the purines unstack and open up to absorb much more light and is called the **hyperchromic shift**.
- The reverse process is called the **hypochromic shift**.

- The viscosity of DS DNA is very high, i.e., it doesn't flow well: it's rather sticky.
- You can liken this to when you have a cold and blow copious amounts of mucous from your nose.
- The mucous contains some cellular debris and lots of DNA.
- Consider how sticky (flow resistant; sort of viscous) the mucous is and you have a good idea about how viscous DNA in the DS state is.
- As the temperature heats up, the viscosity of the DNA is greatly reduced.
- This is because the less organized the DNA, the faster it will flow (i.e., the less sticky it is).

- When DNA is in the DS state, it has a very high buoyant density, the density at which it will float.
- As the DNA becomes more disorganized, the buoyant density drops.
- This is because as the DNA becomes less organized, it becomes less dense.

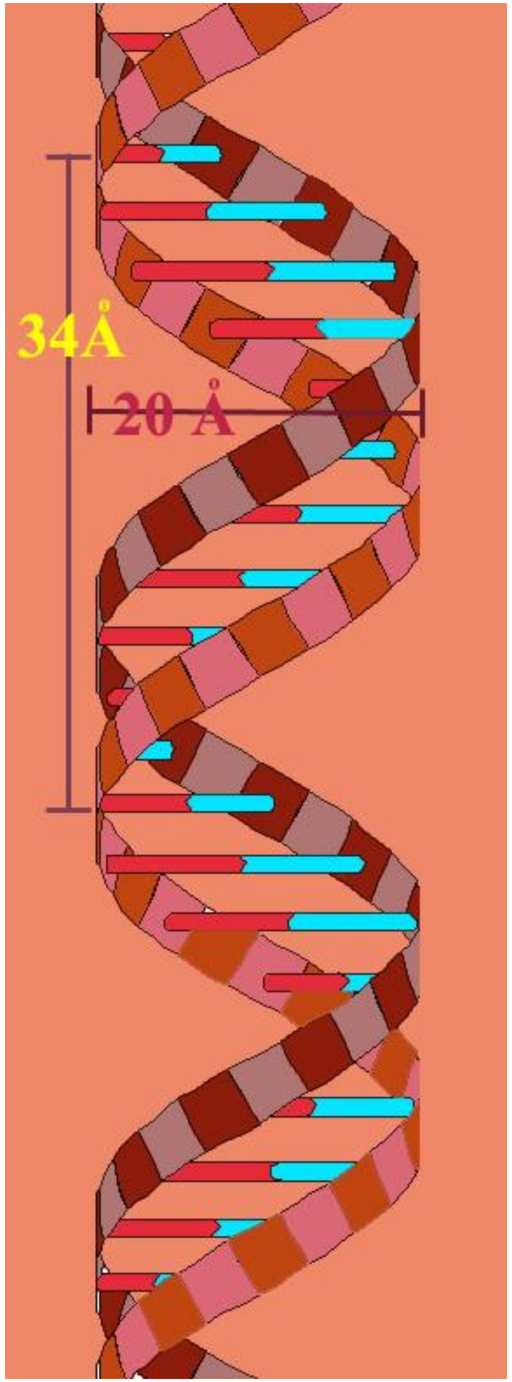
Physical Properties of DNA – Still on Secondary Structure





All dependent upon H bonds!

- A segment of DNA that illustrates the width of the helix (2 nm) and the distance per turn of the helix (3.4 nm).
- Ångstroms, as seen, were the old way of measuring distances: 10 Å = 1 nm.
- As a general rule, one turn of the helix consists of 10 base pairs (bp).
- Remember this is DS DNA, so we refer to distance in terms of bp's.
- Each bp is roughly 0.34 nm in height.
- The form of DNA in the graphic is called the "B-form" of DNA.

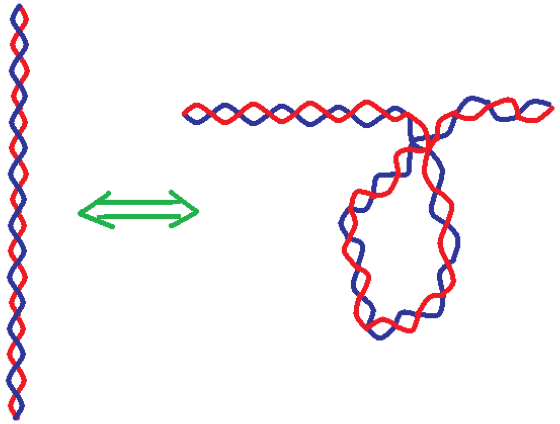


There are 3 forms of DNA known to man, Table below:

DNA Types			
	A-form	**B-form**	Z-form
Turn of helix	Right	**Right**	Left
Nucleotides/rotation	11 bp	**10 bp**	6 bp
Length of 1 rotation	18 Å	**34 Å**	45 Å
Thickness of one residue	2.55 Å	**3.4 Å**	3.7 Å
Turn (°)/nucleotide	33 (per bp)	**36 (per bp)**	-60 (per bp)
Major/minor grooves	No	**Yes**	Sort of
Phosphate backbone	Smooth	**Smooth**	"Z"-shaped; jagged
Physiological	No	**Yes**	No

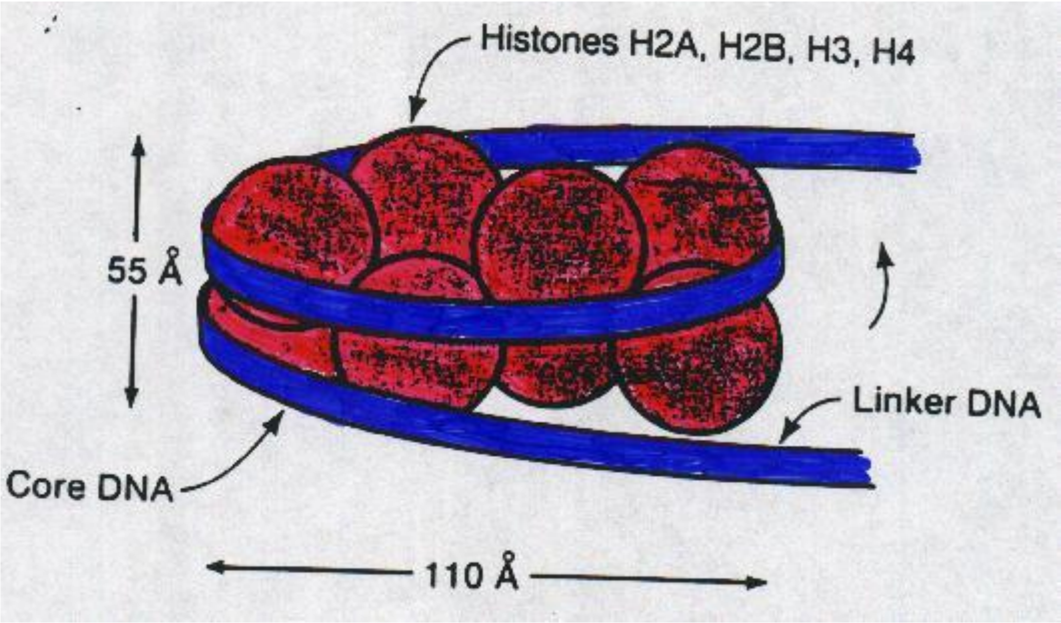
1° & 2° Structures do NOT Account for All the Physical Properties in DNA

- What else is there????
- 3° and 4° structures!



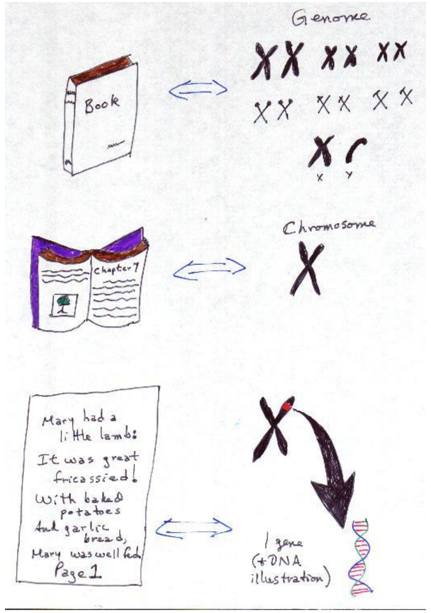
4° Structure

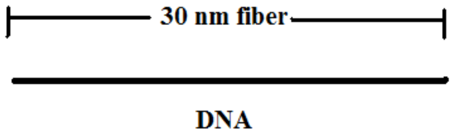
Depends on 5 classes of positively charged proteins called histones.		
Name	Quantity	Type
H1	1	Linker
H2A	2	Core
H2B	2	Core
H3	2	Core
H4	2	Core



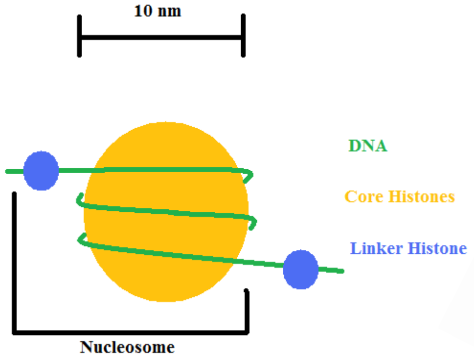
- "H" and the number refer to histones, e.g., H2B is histone 2B. H1 is a linker histone that holds DNA together from a region outside the "core".
- The core consists of the other 4 types of histones around which DNA has wrapped itself, above. There are a total of 8 histones inside this core. The reason these histones are so tightly bound to the DNA is because these histones are positively charged and the phosphate backbone of the DNA is so negatively charged.
- Depending on the literature source, the DNA is wrapped around the core histones anywhere from 1.6 to 1.9 turns.

DNA “Compression” – Rapid Summary

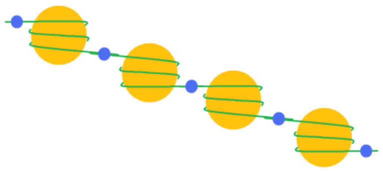




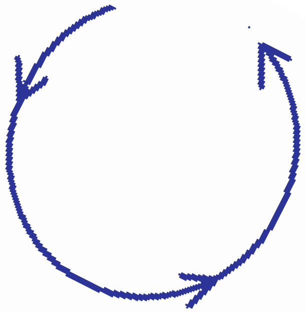
Step 1: 30 nm fiber of DNA

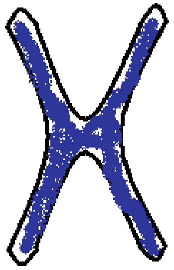


Step 2: “Bead on a String”

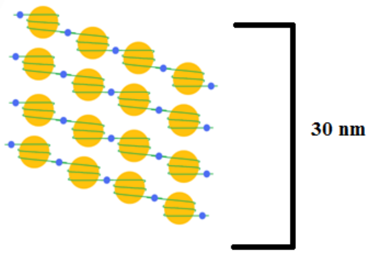


Step 2a: “Bead on a String”





Last step, many steps later: quaternary and super-secondary structure gives a chromosome, ca 1400 nm wide.



Step 3: “30 nm fiber” of DNA more densely packed