Organic Chemistry

Carbon-Based 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

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Number	English	German	Spanish	Danish
1	One	Ein	Uno	Én
2	Two	Zwei	Dos	To
3	Three	Drei	Tres	Tre
4	Four	Vier	Quatro	Fire
5	Five	Fünf	Cinco	Fem
Examples of Counting to 5 in Four Languages.				

Number of Carbons	Organic Prefix	Number of Carbons	Organic Prefix
1	Meth	11	Undeca
2	Eth	12	Dodeca
3	Prop	13	Trideca
4	But	14	Tetradeca
5	Pent	15	Pentadeca
6	Hex	16	Hexadeca
7	Hept	17	Heptadeca
8	Oct	18	Octadeca
9	Non or nona	19	Nonadeca
10	Dec or deca	20	Eicosa
Organic Prefixes in "Organic-ese"			
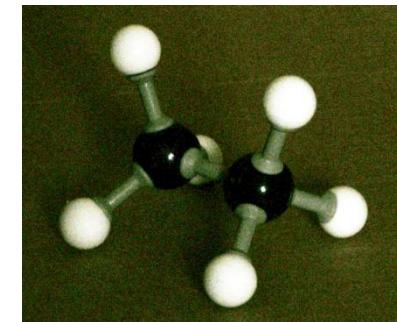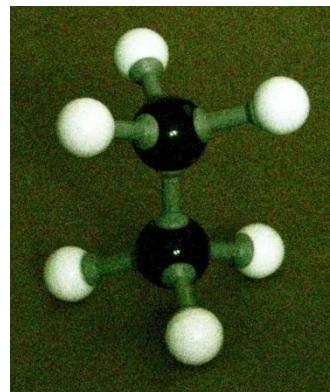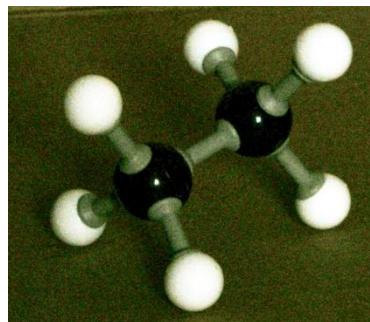
Alkanes

- The general formula of an alkane is C_nH_{2n+2}.

- All of the carbons in an alkane are in sp^3 hybridization and possess tetrahedral geometry.

- 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".
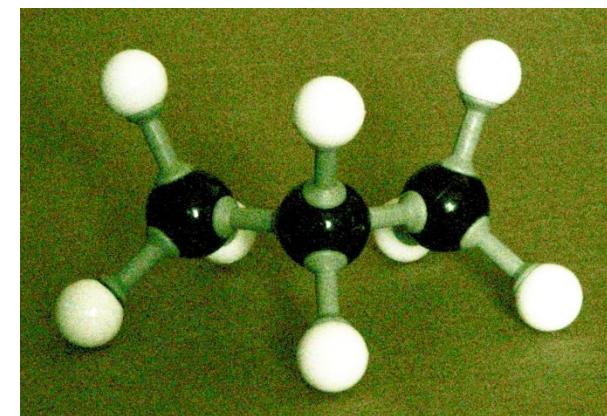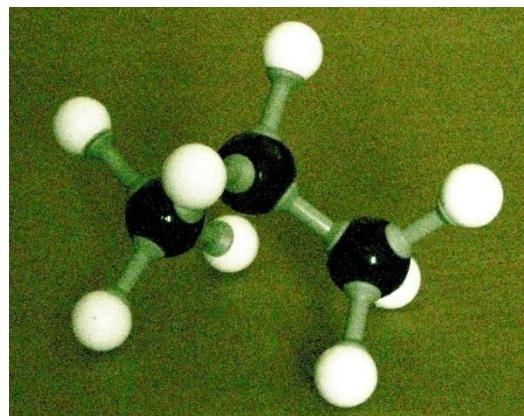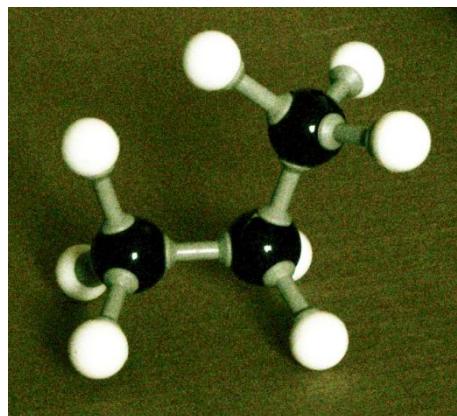
- The simplest of the alkanes is CH_4 or methane -- "meth" for one carbon and "ane" for the alkane.
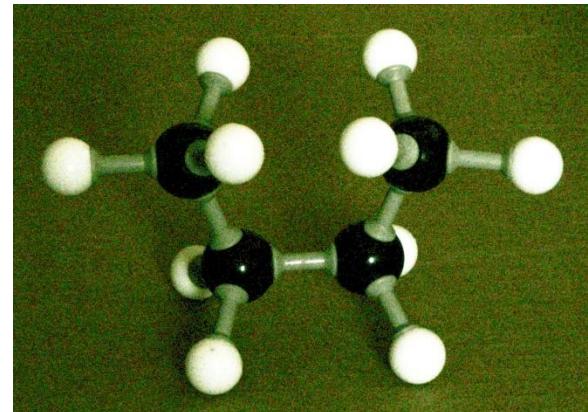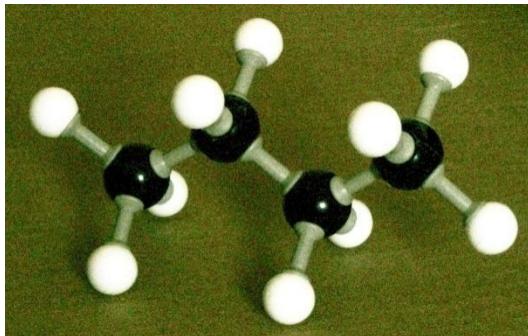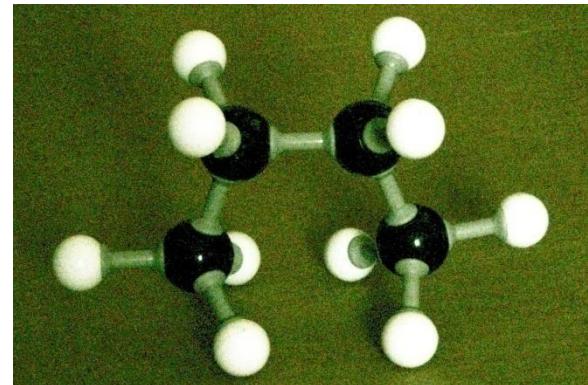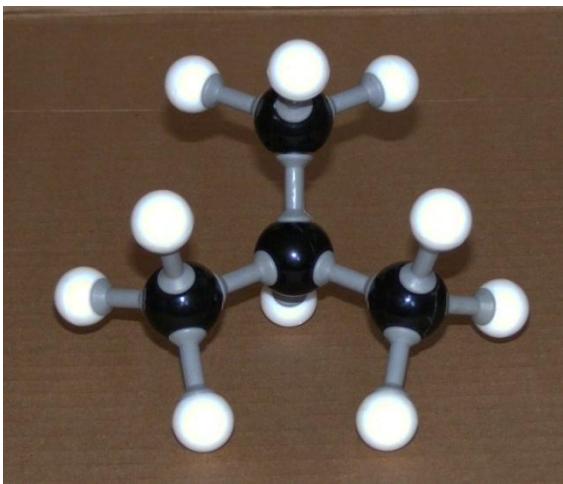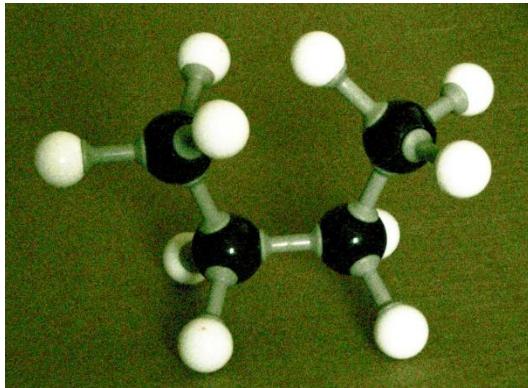
# Ethane has the formula C_2H_6 -- "eth" for two carbons and "ane" for the alkane.
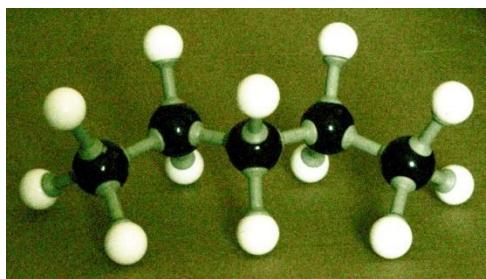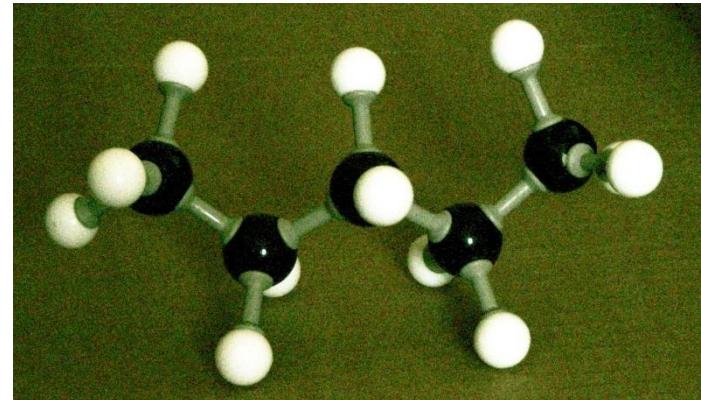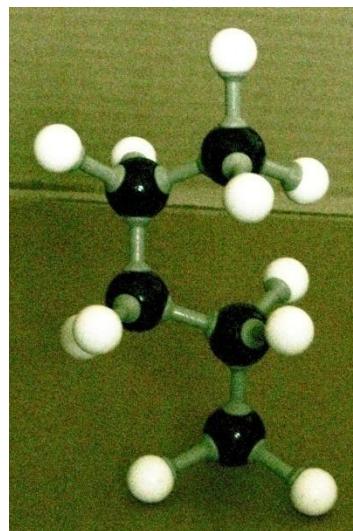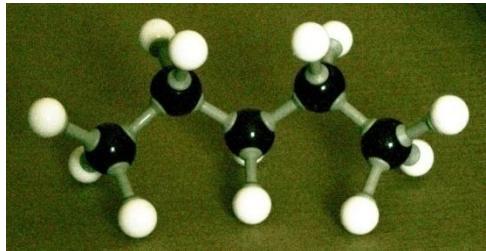

- Propane is C_3H_8:
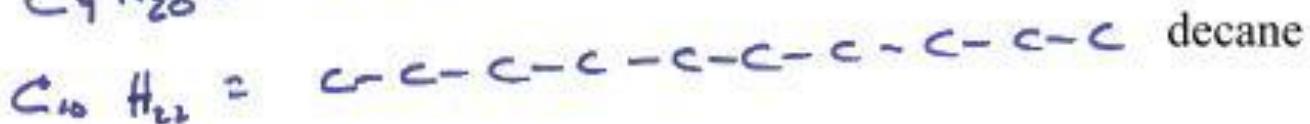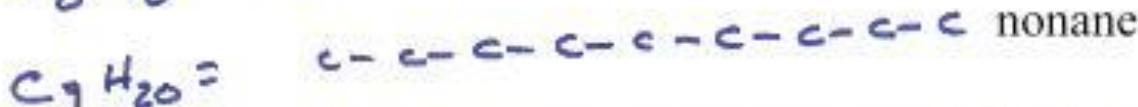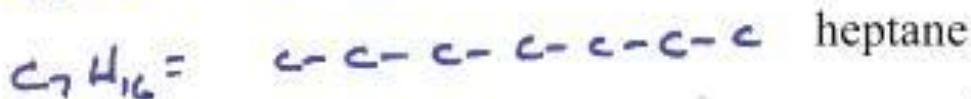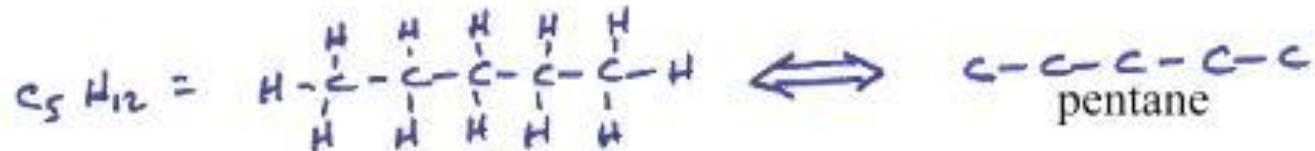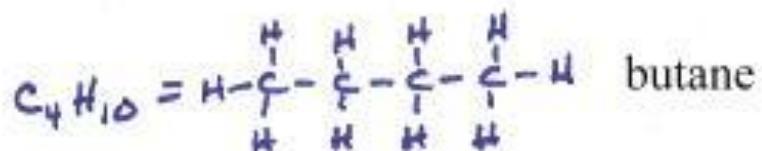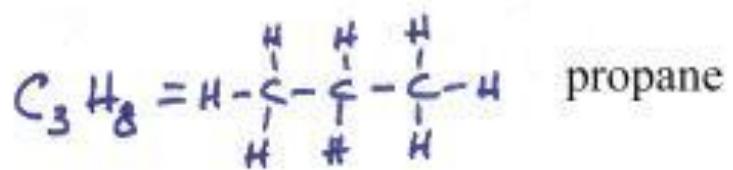
- Butane and Isobutane are C_4H_{10}:

Pentane is C_5H_{12}

$C_3 H_8 =$ propane

$C_4 H_{10} =$ butane

$C_5 H_{12} =$ $\Longleftrightarrow$ C−C−C−C−C pentane

$C_6 H_{14} =$ C−C−C−C−C−C hexane

$C_7 H_{16} =$ C−C−C−C−C−C−C heptane

$C_8 H_{18} =$ C−C−C−C−C−C−C−C octane

$C_9 H_{20} =$ C−C−C−C−C−C−C−C−C nonane

$C_{10} H_{22} =$ C−C−C−C−C−C−C−C−C−C decane
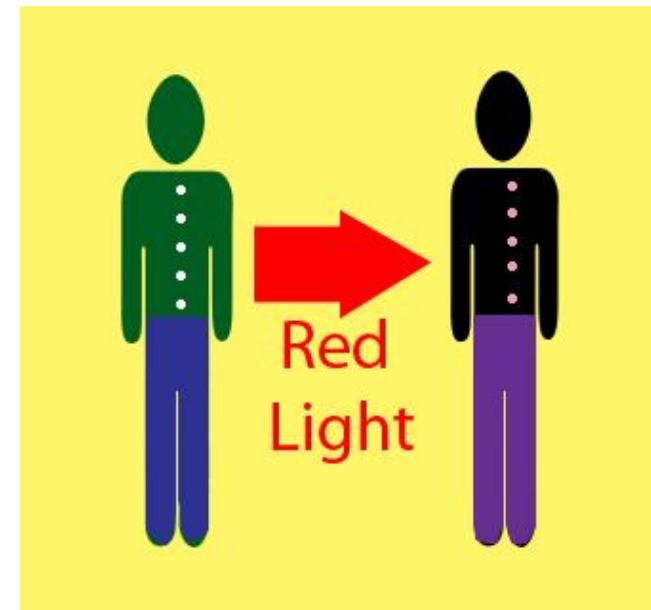
English and O. Chem.

- Note also, that one does NOT have to draw on each hydrogen atom in the structures.
- Each carbon can take 4 bonds.
- If there appears to be only one bond between the first and second carbon, then there must be 3 hydrogen's UNDERSTOOD to be present on the end carbons.
- If there appears to be one bond between carbons in the middle of the chain, i.e., one to the left and one to the right for 2 single bonds, then it follows that there must be 2 hydrogen atoms UNDERSTOOD to be present.
- If you think back to when you diagrammed sentences in high school, recall how you had to diagram the following sentence: Do it! What is the subject? An UNDERSTOOD "You"!

Applications of Light, Atoms and Energy in Organic Chemistry

- Colors are complimentary: 1 color plus its complement equals BLACK. For example, if one wore a green shirt into a photographic dark room that uses red light, the shirt would appear black

Red Light

- Yellow solutions absorb violet light (short wavelength);
- green solutions absorb red light (long wavelength);
- red/orange solutions absorb blue/green light (intermediate wavelengths).
- All of this is useful in the clinical lab, where colored species are studied electronically to determine how much of a particular substance is present in a person's plasma, serum, or urine, for example.
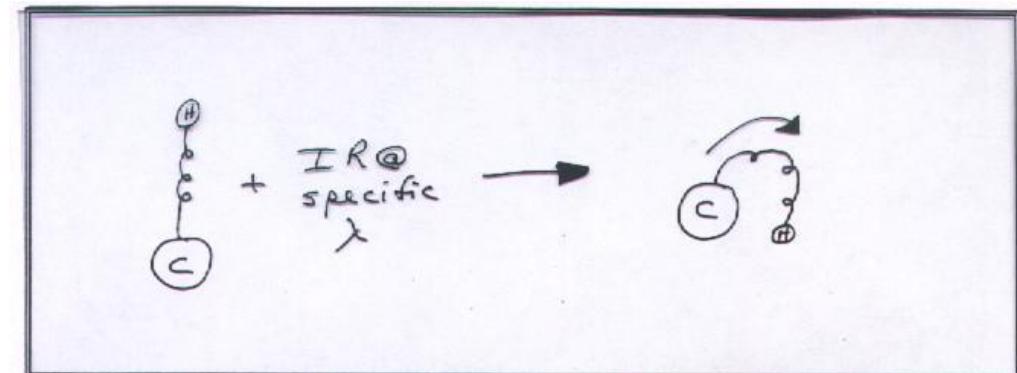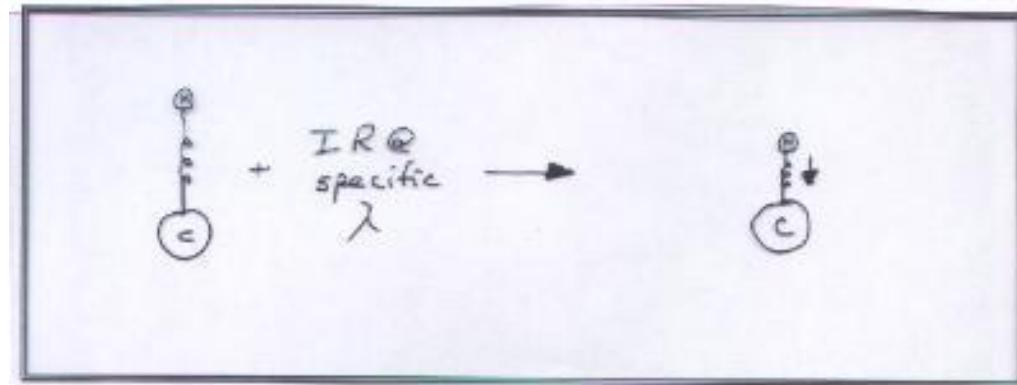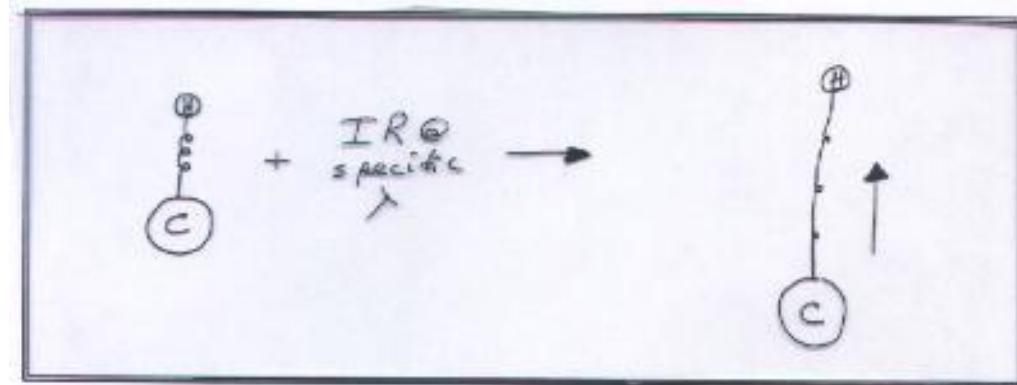
Ultraviolet-Visible (UV-Vis) Spectroscopy

- In general, UV-Vis spectroscopy works by "boosting" a "target" light acceptor up to another energy level.

- The UV portion, like the visible region mentioned in the earlier lecture, is also used to study substances in biological fluids.

- There will be more on UV-Vis spectroscopy in CHEM 122 and 220, later.

Infra-Red (IR) Spectroscopy

- IR energy is long wavelength (hence low energy) light below visible red in the spectrum.
- It is the same as what you feel in your toaster and what you [don't] see in your toaster.
- IR spectroscopy is interested in studying the twist, stretch, bend, rotation, rock, scissoring and vibrations of atoms in an organic molecule (carbon-based molecules).
- Specifically, IR spectroscopy is interested in studying functional groups, i.e., organic radicals that substitute for hydrogen on a hydrocarbon chain or ring (more on all of this at a later date/lecture).
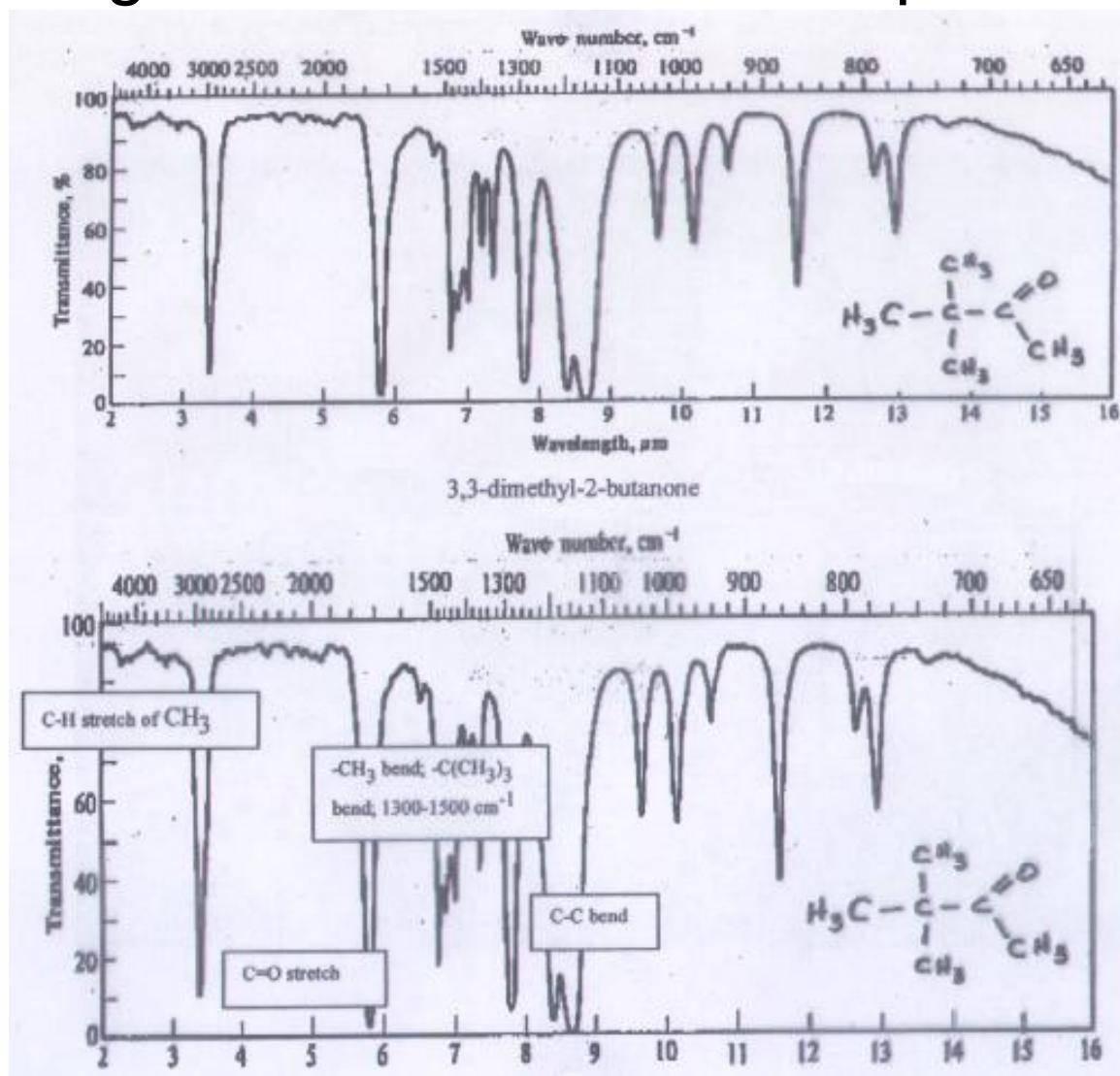
- "stretching" between bonds after IR electromagnetic energy (EME) stimulates the bonds
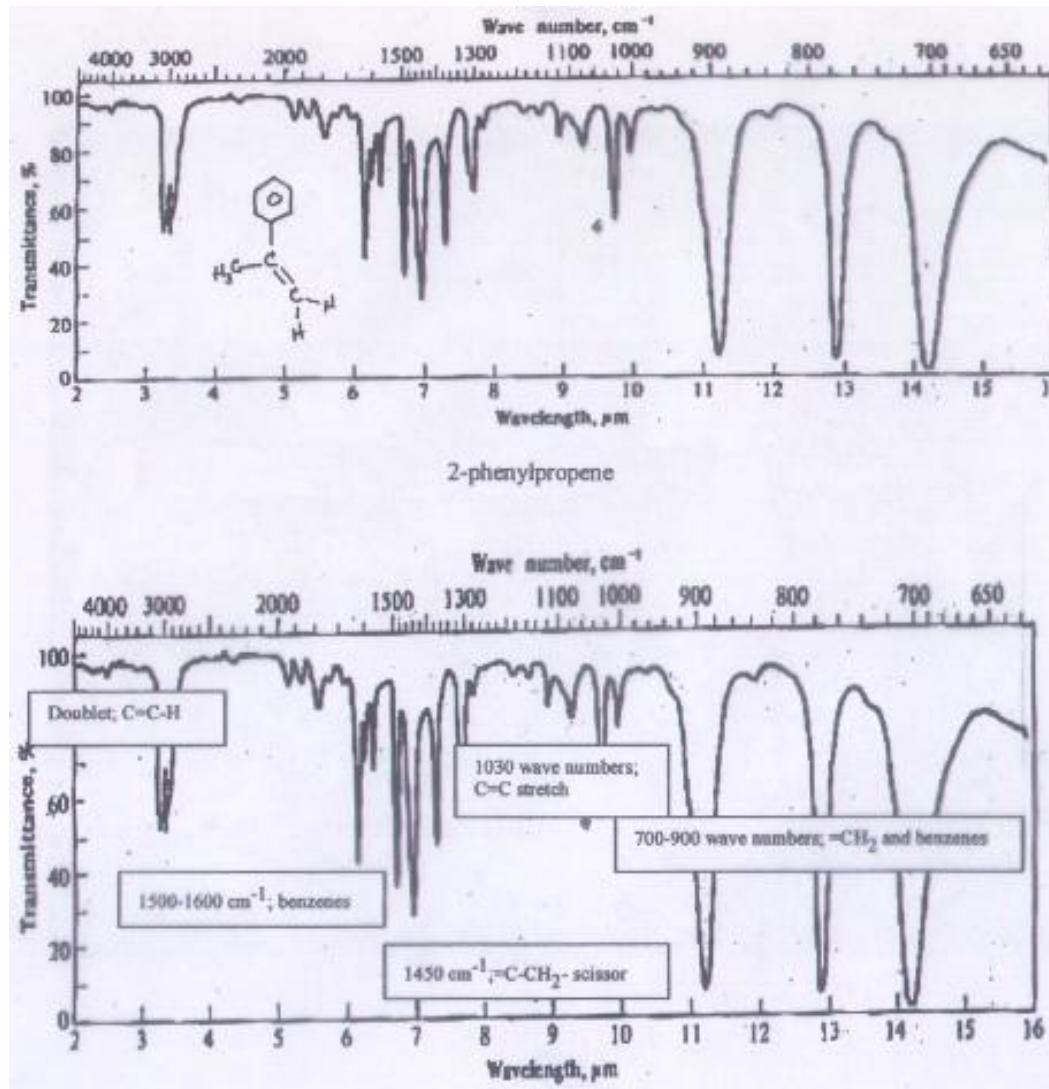
An Example of Bond Bending

- The next two slides illustrate the IR spectra (fingerprints, if you will) of two different compounds -- with and without peak labeling.
- Note that "peaks" on these IR spectra go down, not up -- they are pointed, blunt, rounded or dips.
- Each functional group interacts with IR EME differently than other groups and allows IR EME to help us determine what functional groups are present.
- Note also that sometimes peaks cover a range of wave numbers.
- Each spectrum has the structure of the whole organic molecule drawn in its boundaries.
- The spectrum labeling has been purposely distorted to accommodate the labeling and to emphasize peaks.

- Specific functional groups absorb specific IR EME to give a characteristic IR spectrum.

3,3-dimethyl-2-butanone

- Specific functional groups absorb specific IR EME to give a characteristic IR spectrum.

2-phenylpropene

Doublet; C=C-H

1030 wave numbers; C=C stretch

700-900 wave numbers; =CH₂ and benzenes

1500-1600 cm⁻¹; benzenes

1450 cm⁻¹;=C-CH₂- scissor
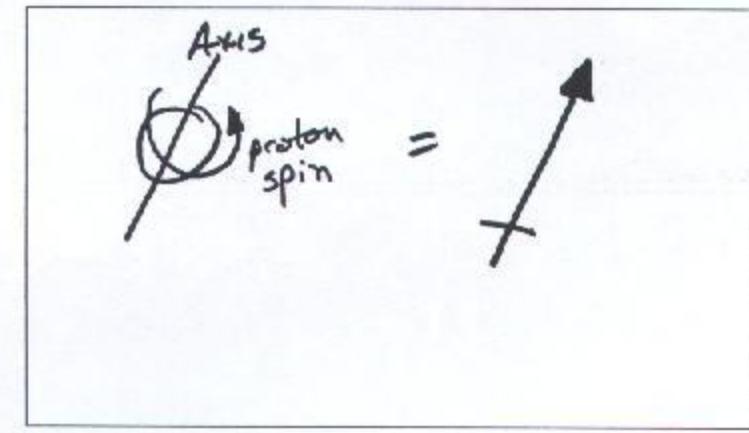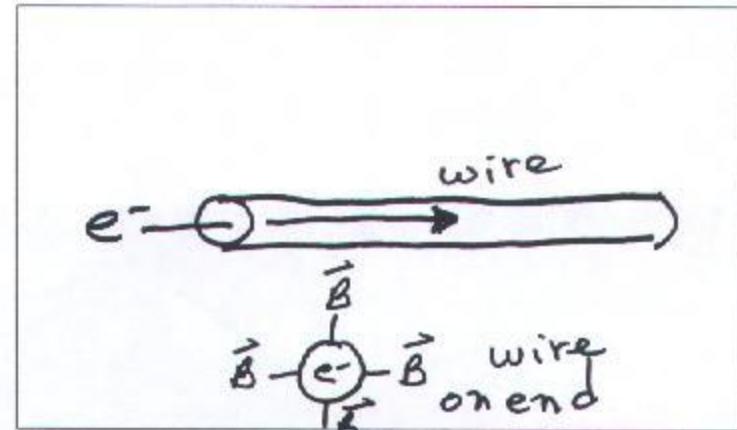
Nuclear Magnetic Resonance Spectroscopy

- Remember from our earlier discussion that electricity is defined as the flow of electrons through a wire.

- As the current flows through the wire, a magnetic field is induced perpendicular to the flow of electrons.

- To find this induced electromagnetic field (EMF), use the right hand rule: put your right thumb in the direction of the electron flow and curl your hand around the wire.

- The direction your hand curls is in the region of the generated magnetic field about the whole wire.

- Some nuclei spin, ^{1}H, ^{13}C, ^{19}F, ^{31}P -- these are the biggees.
- Remember that the nucleus contains neutrons and protons.
- Protons, specifically those in Protium (^{1}H), spin about the axis of the atom's rotation, Figure, top right, (the "B" with the vector sign is the induced magnetic field).
- This spin induces a very tiny magnetic field along the spin axis (like the electrons and wire).
- For our discussion, Figure, bottom right, represents equivalent ways in which to illustrate the spin axis.

- The effect of external magnetic fields on nuclear "magnetic fields" is this: quantum mechanics says that S = ± ½.
- In the presence, then, of an external magnetic field (represented by an arrow pointing from left to right with a "cross" through the left end), the proton-generated magnetic field will either
  - line up with the external field (called parallel alignment) or
  - line up against the magnetic field (called anti-parallel alignment).
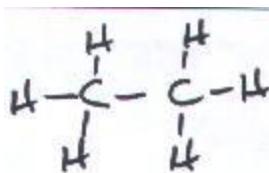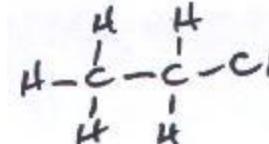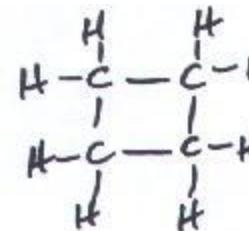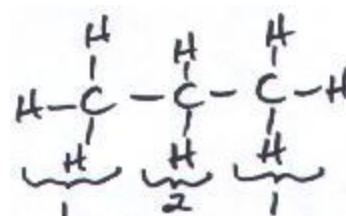
The table, below, summarizes this:

Parallel Alignment	Anti-parallel Alignment
More stable	Less stable
Preferred by nucleus	Requires energy for this "tweak"
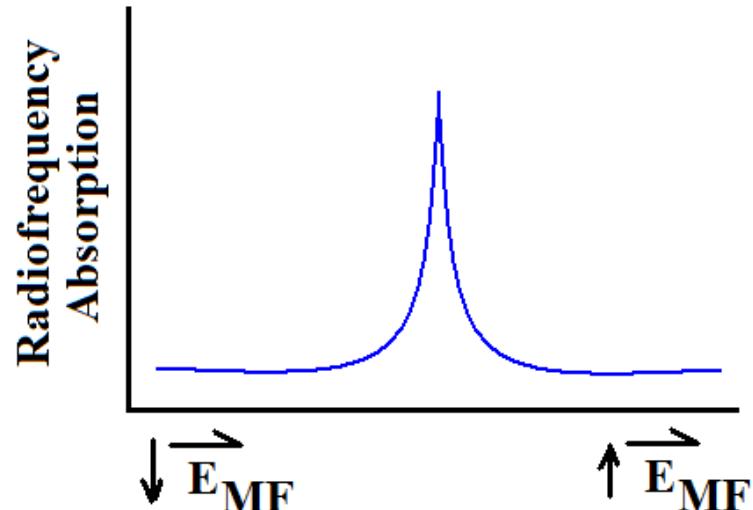
The way in which these alignments are caused is to spin the sample inside a magnet.

- Radiofrequency radiation effects alignment, as well.
- Remember that $\upsilon = c/\lambda$ and that $E = h\upsilon$.
- To detect the proton in Protium, it needs to be "tweaked" into the ANTI-PARALLEL alignment.
- It is the radiofrequency radiation (radiofrequency energy is less than IR energy) that makes the "tweak".
- At a fixed radiofrequency, all protons absorb at a constant radiofrequency energy.
- BUT when an external magnetic field strength is altered, protons absorb at different, specific, magnetic field energies

The table, below, illustrates, as well,
the idea that all protons (in this case H) are
not identical and will give different "signals"
under the right stimulation:
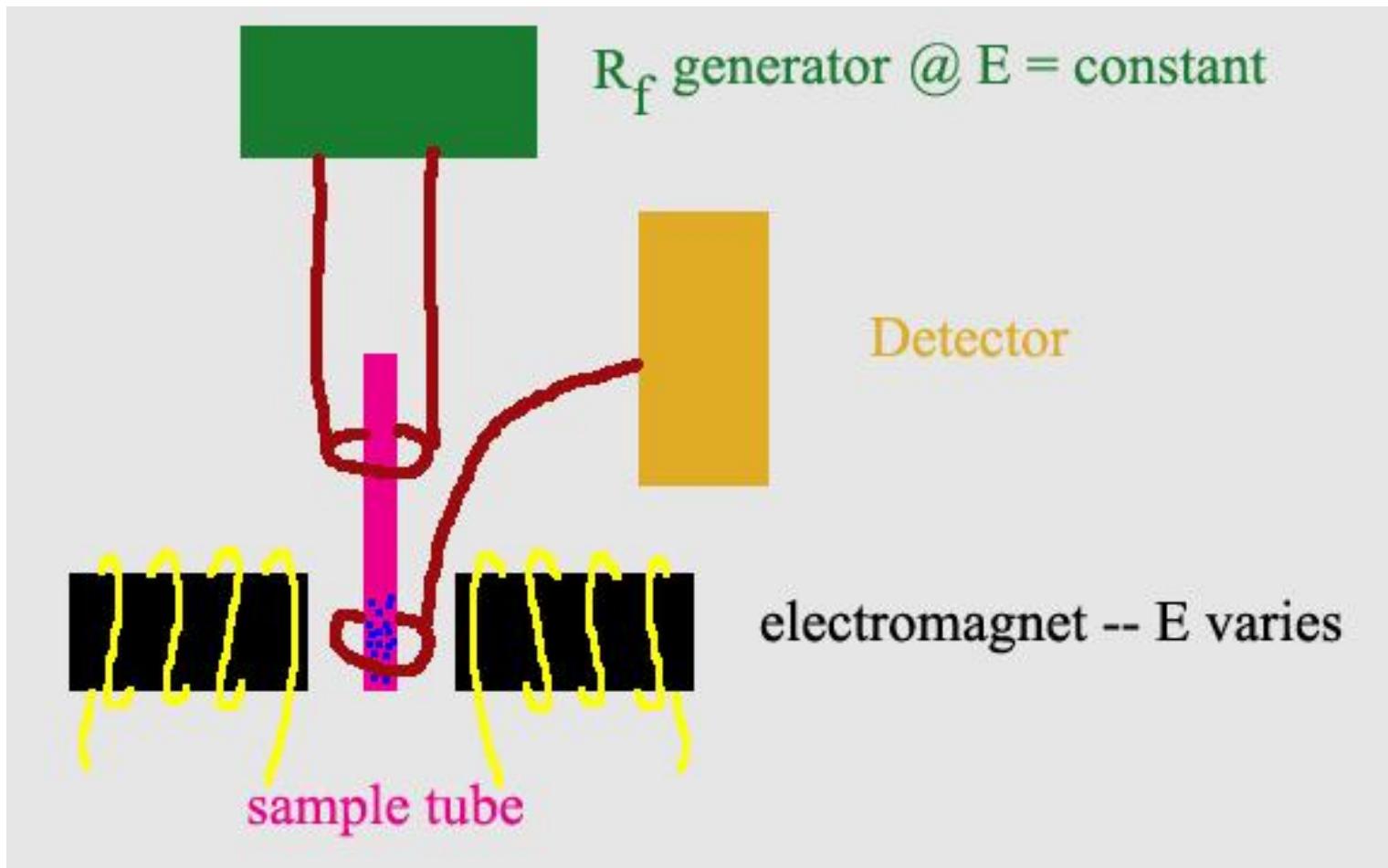
"Identical Protons" -- Each carbon atom has hydrogens bonded to them in an identical manner and will, then, give 1 signal.	"Non-Identical Protons" -- each carbon has different numbers of protons (H) bonded to it and will, then, give two different signals.

- Specific functional groups have specific magnetic field energy attractions (like what we saw with IR) and give a characteristic NMR spectrum as a function of altered radiofrequency absorption (R_f).

- Figure illustrates a generic representation of an NMR spectrum with the axes labeled.
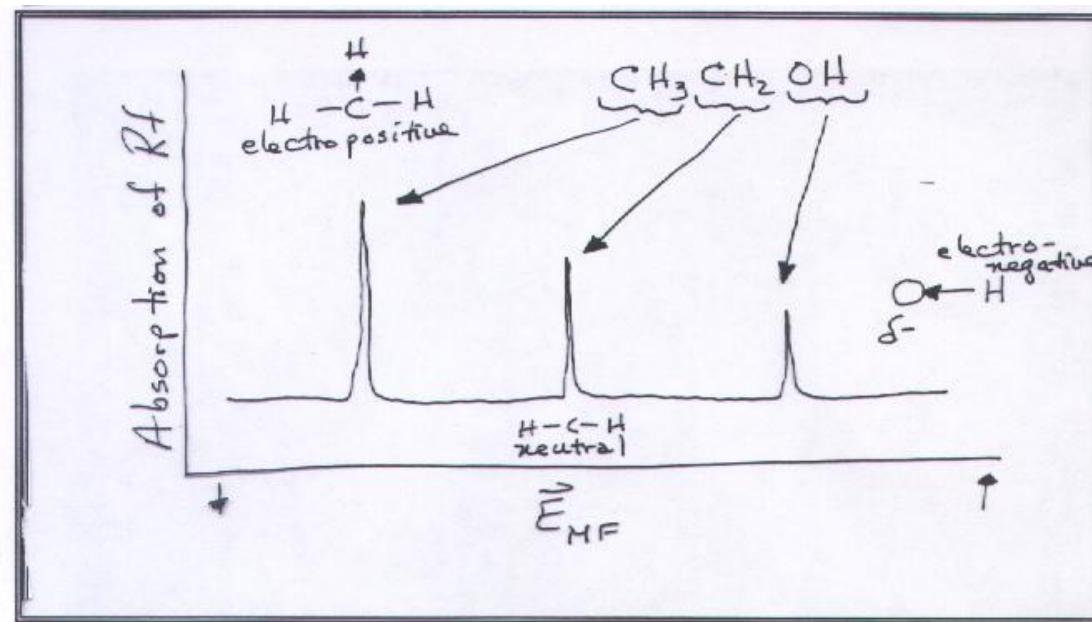
- The basic organization of the NMR spectrometer follows on the next slide.
- In general a sample is placed in the appropriate solvent and "dropped" inside the spinner in the magnet with variable energy.
- The sample is also surrounded by an R_f generator and a detector. The latter leads to some sort of display visualizer (screen, printer).

Magnetic Resonance Imaging
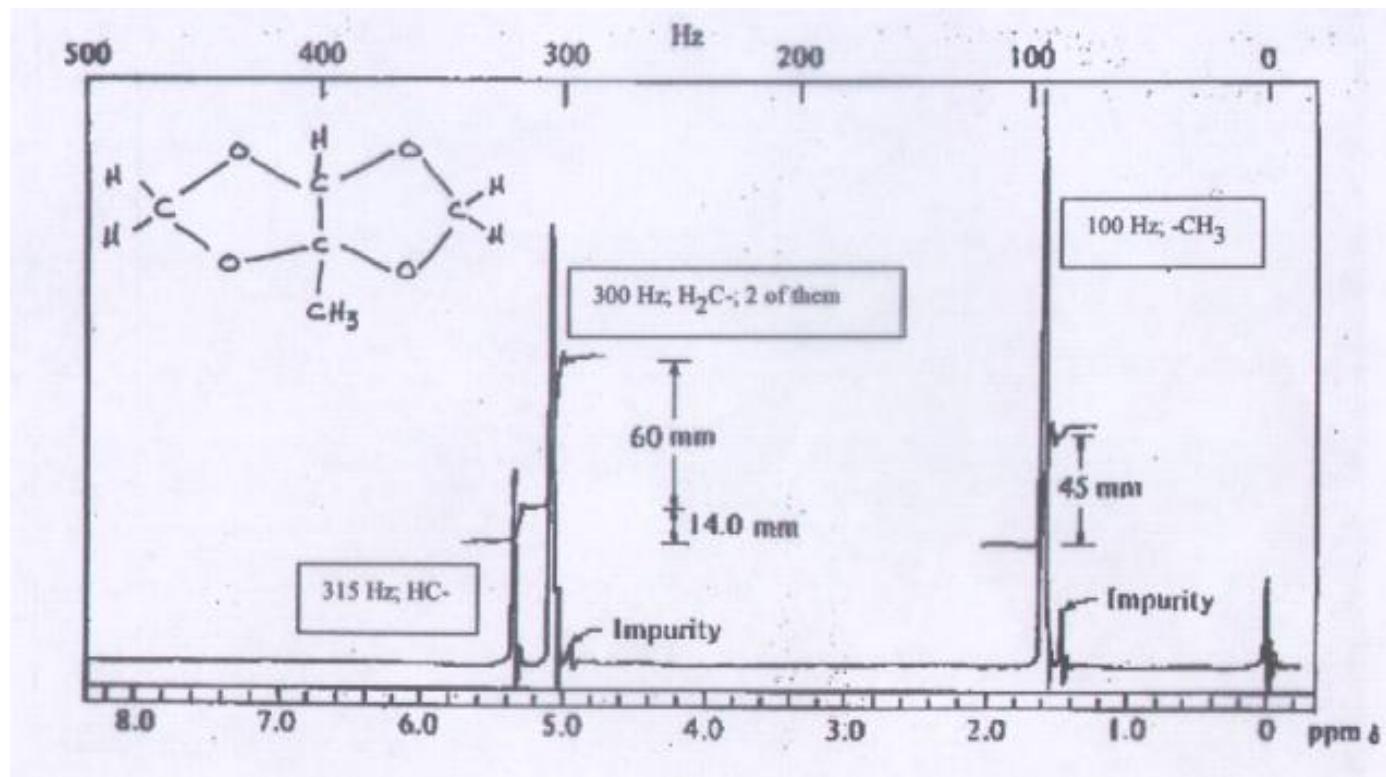
- Figure, below, illustrates a crude NMR spectrum for ethyl alcohol (EtOH; H_3CCH_2OH).
- Note that the CH_3 peak is the more electropositive and appears on the low end of the magnetic energy/field axis;
- the CH_2 is neutral and is roughly mid-way;
- the OH is more electronegative and is at the high electromagnetic field strength end.
- Note, too, the ratios of the peak areas to each other.
- The first is roughly 3 times as large as the last and the second is roughly twice that of the last.
- The ratio, then, is 3:2:1 -- note that that is the arrangement of the three parts of the EtOH as it was broken down.

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For Next Two Slides
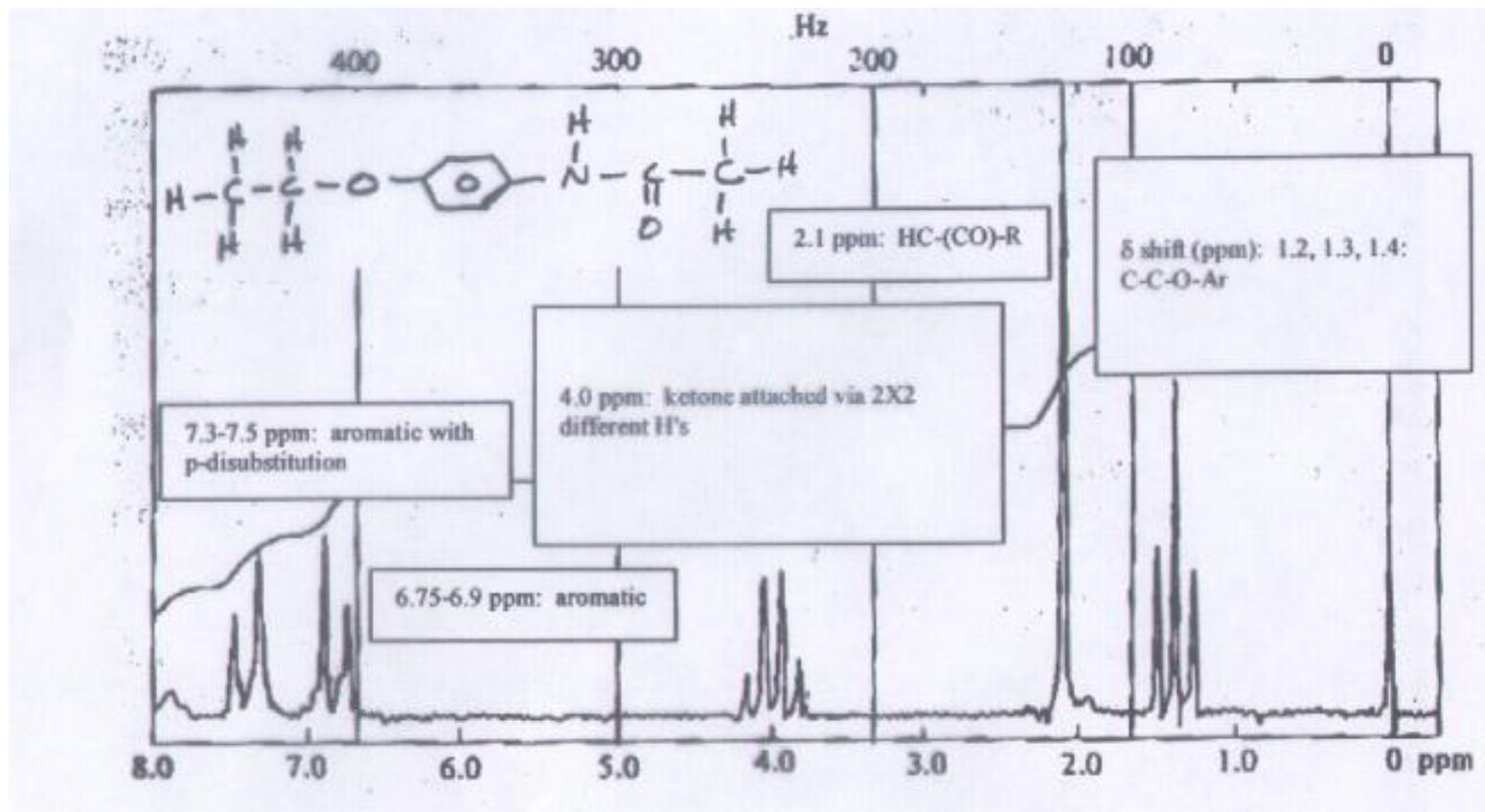
- Peaks are labeled.
- While I don't expect you to become expert spectroscopists over night, I do expect you to recognize the ratios of the peak areas compared to each other

Illustrative NMR Spectra for Two Different Organic Compounds

- Note the "s" shaped lines that go through the peaks on the spectrum.
- This is an integration line that is measured to obtain the height for each peak.
- These heights are then compared with each other.
- Note that the ratio of 60:45:14 is approximately 4:3:1.
- Note that there are three different kinds of protons on this molecule: 3 methyl protons (the "3"), 4 methelenyl protons (the "4") and 1 methynl protons (the "1").
- The integrator signals tell you information about the numbers of H's in proton NMR (pNMR).

The same idea using the bottom ppm scale instead of the top Hz scale.

The next logical step, then, is to examine how this might be used on a daily basis in health care.
That is by MRI.
MRI came about because when it first was used, the public felt frightened about the word "nuclear".
So a PR firm was hired to put a positive spin on it.
They decided to leave off the "N" and add the "I" for Imaging.
Still the same thing -- it's all in the presentation.

MRI: Human Applications

- Had to decide what to look for in the body. There are lots of organic compounds in the body that contain protons. Water, of which we are made up the most is HOH -- has a proton.
- The next problem was how to spin the patient in the magnet.
- The conditions necessary to make MRI work are to hold the R_f at a constant and the magnetic field energy at the energy for water (i.e., also a constant).

MRI: Drawbacks

- The patient can NOT have any magnetic items on or in their body. VERY dangerous!

- The patient must hold still and in less recent models the patient slot was small. That's getting better. It is also expensive.

- The plus is that the images are better and MRI gives better diagnostic capabilities than CT.

Mass Spectrometry

A Q&D Overview

Why Discuss Mass Spectromtery?

- Mass Spectrometry makes determining chemical formulas and structures fairly simple.

- Mass Spectrometry takes advantage of chemistry topics that you've already studied.

- The biggee is "Empirical Formulas" – these have applications to mass spectrometry

Empirical Formulas

- The empirical formula of a compound is defined as the "simplest whole number ratio of the atoms" in a compound.

- The best way to learn how to determine the empirical formula of a compound is to see the mechanics involved with the arithmetic manipulation of data:

- **E.g. 1: A compound contains 92.3% carbon and 7.7% hydrogen. Calculate the empirical formula of the compound.**

To solve this problem, there are four steps:

- 1) "Convert" % to grams.

$$92.3 \text{ g} + 7.7 \text{ g} = 100 \text{ g sample}$$

- 2) Determine the number of moles of each atom in the sample.

$$92.3 \, g \, C * \frac{1 \, mol}{12 \, g \, C} = 7.69 \, mol \approx 7.7 \, mol$$

$$7.7 \, g \, H * \frac{1 \, mol}{1 \, g \, H} = 7.7 \, mol$$

- 3) Divide both numbers of moles by the smallest number of moles (this step reduces the numbers to usable amounts).

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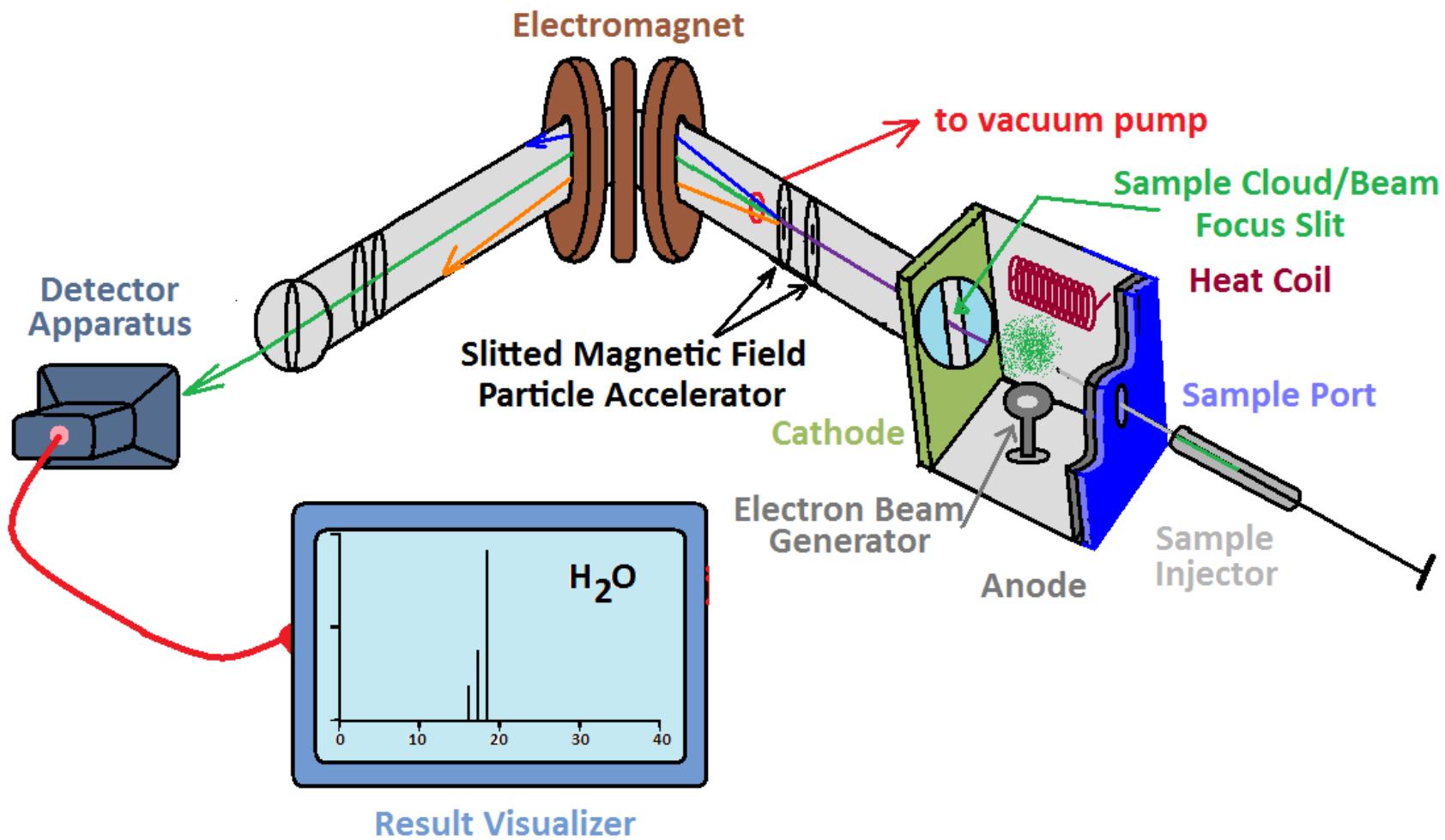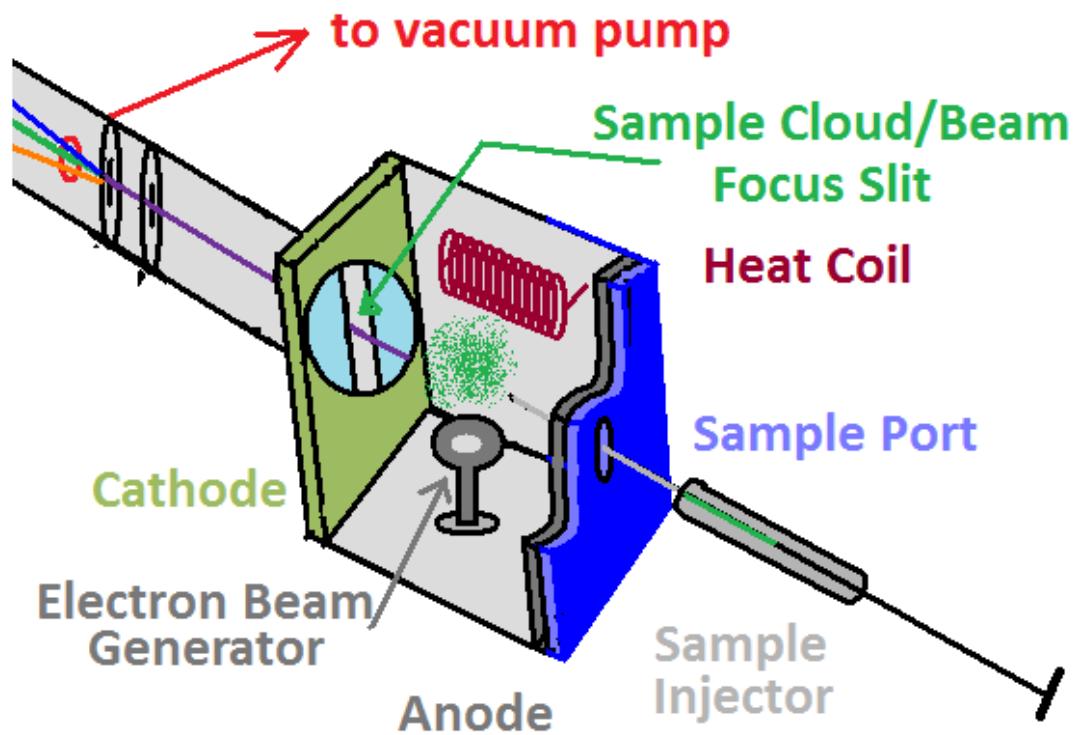
$$For\, C: \frac{7.7}{7.7} = 1$$

$$For\, H: \frac{7.7}{7.7} = 1$$
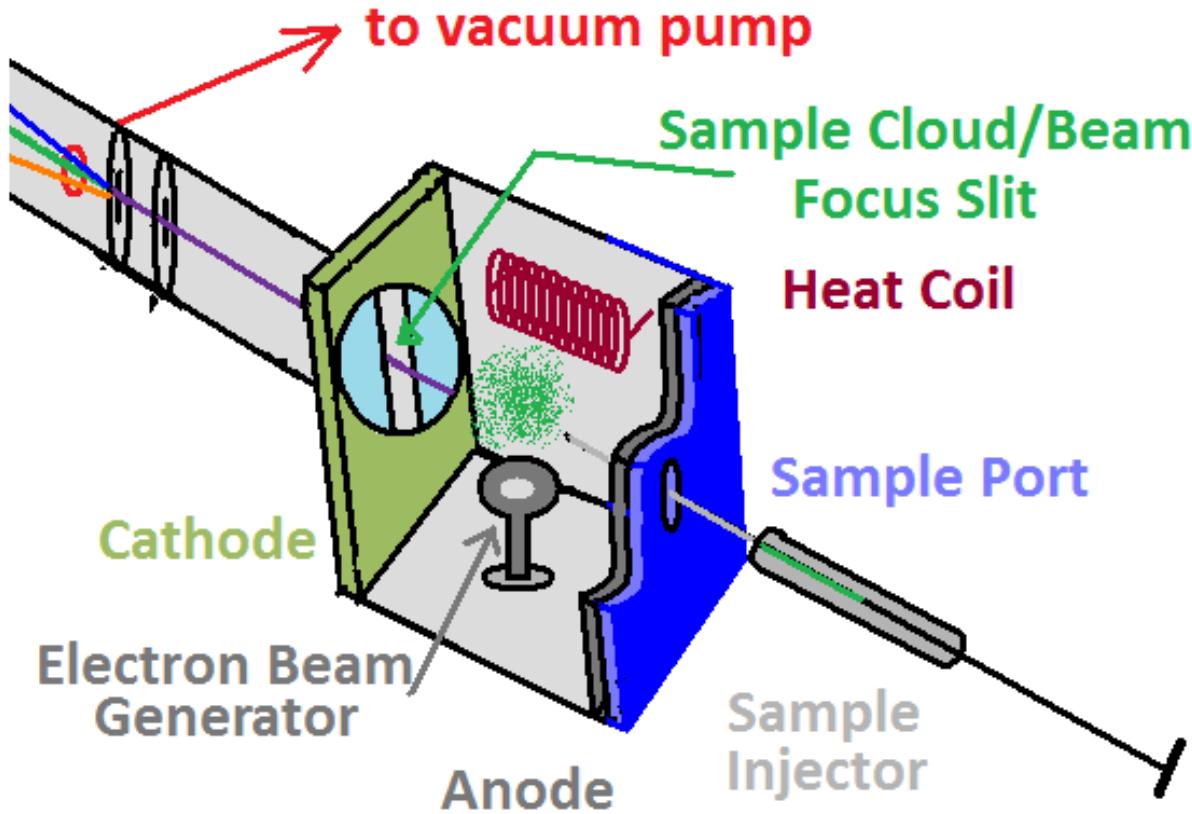
- 4) Write the empirical formula.

- C_1H_1 or CH

- What, though, would you do if you were told that the compound had a molecular weight of 26 and you needed to calculate the molecular formula?

- The simplest is to divide the molecular weight (26) by the empirical weight (13) and see that it is 2 (or twice as heavy as the empirical formula).

- Double the formula and you get: C_2H_2 or acetylene (ethyne).

- We take advantage of this knowledge when we perform mass spectroscopy.

Mass Spectrometer Layout
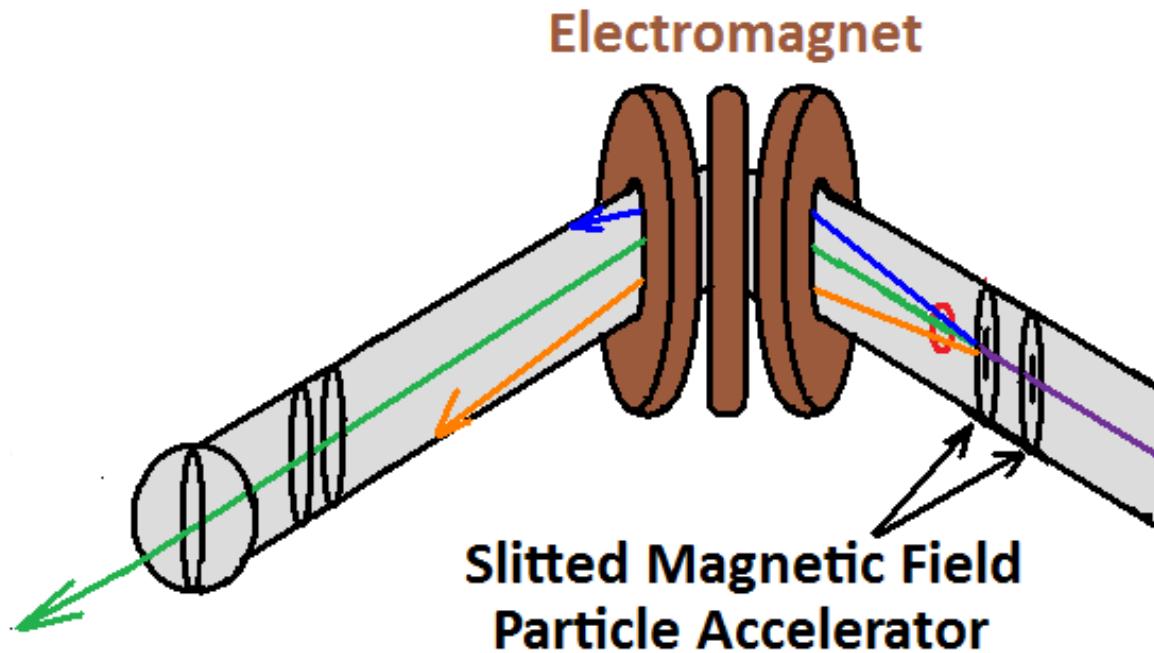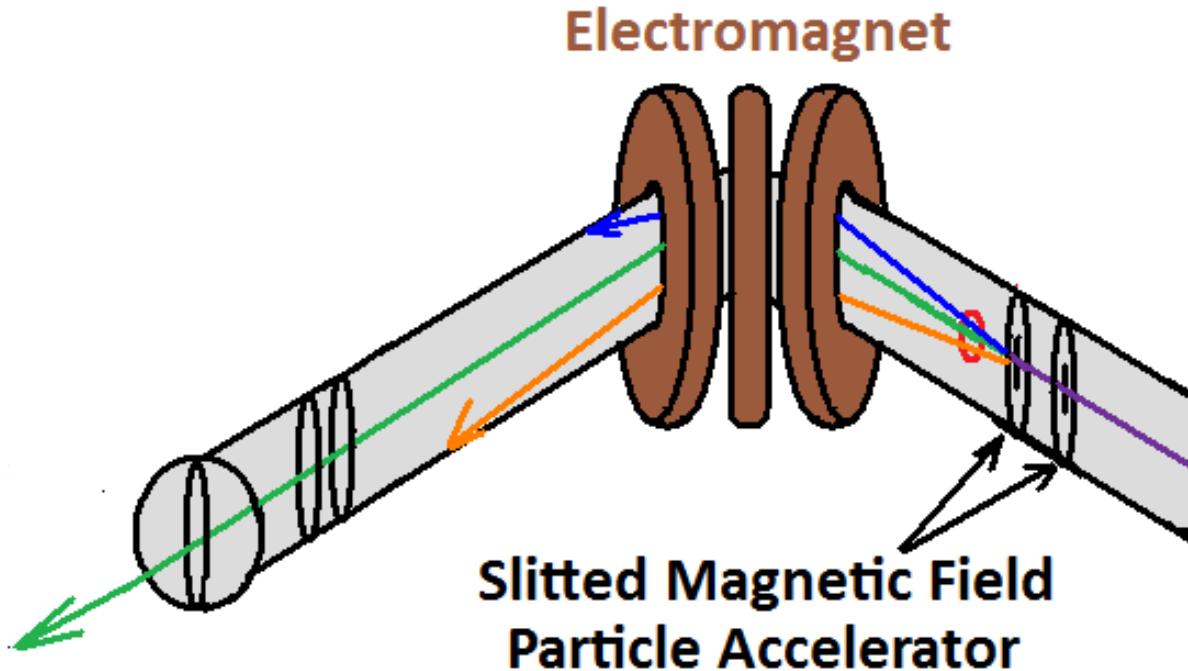
- Sample injected into sample holder/chamber
- Sample vaporized by heat coil
- Sample bombarded by electrons from electron beam generator (some folks call this an electron "gun")
- Excess electrons boil off generator and are attracted to the Anode (positively charged)

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to vacuum pump

Sample Cloud/Beam Focus Slit

Heat Coil

Sample Port

Cathode

Electron Beam Generator

Anode

Sample Injector

- Remainder of electrons interact with (bombard) the sample cloud to generate sample cations
- Cations attracted to cathode (negatively charged) and are partially focused into a beam to enter the MS Tube

Electromagnet

Slitted Magnetic Field
Particle Accelerator
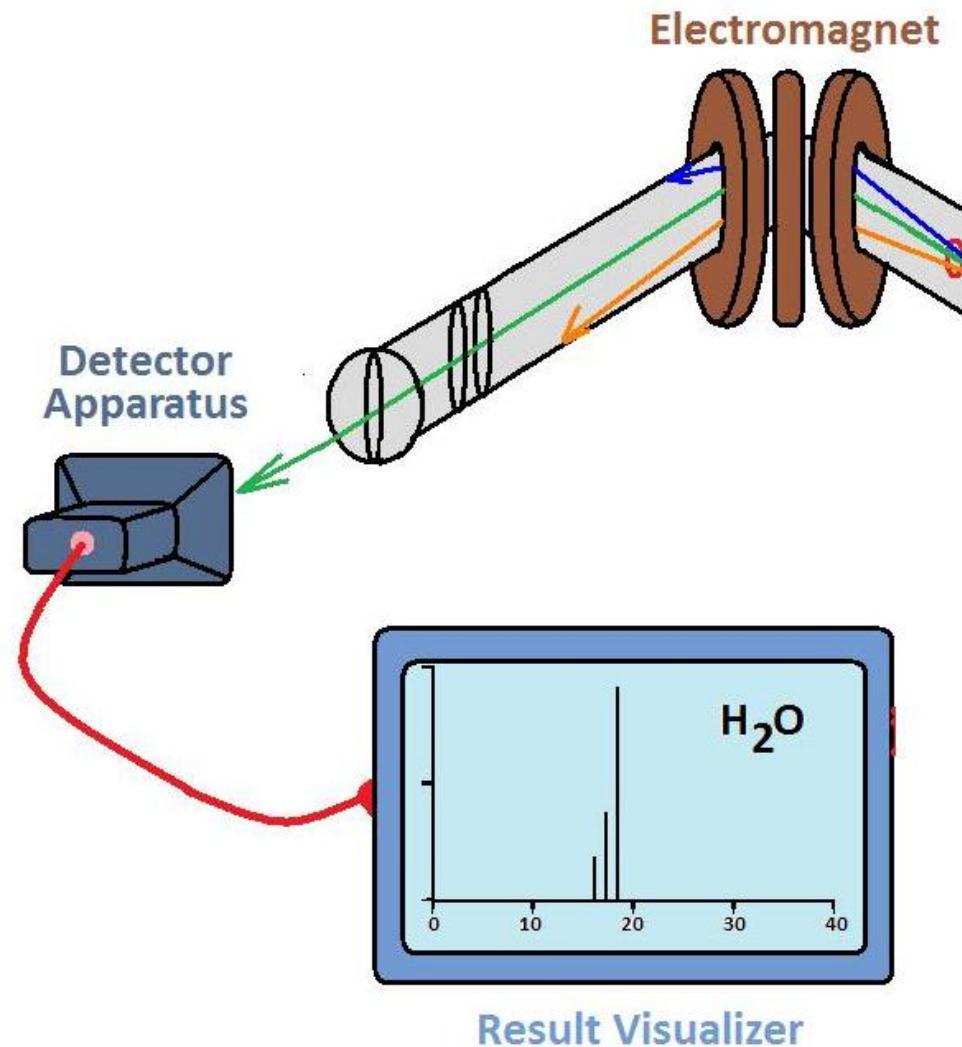
- Sample beam travels under vacuum to the slitted magnetic field particle accelerators – further focuses the beam of the sample cations and prepares the beam to "slingshot" around the tube bend.

Electromagnet

Slitted Magnetic Field
Particle Accelerator
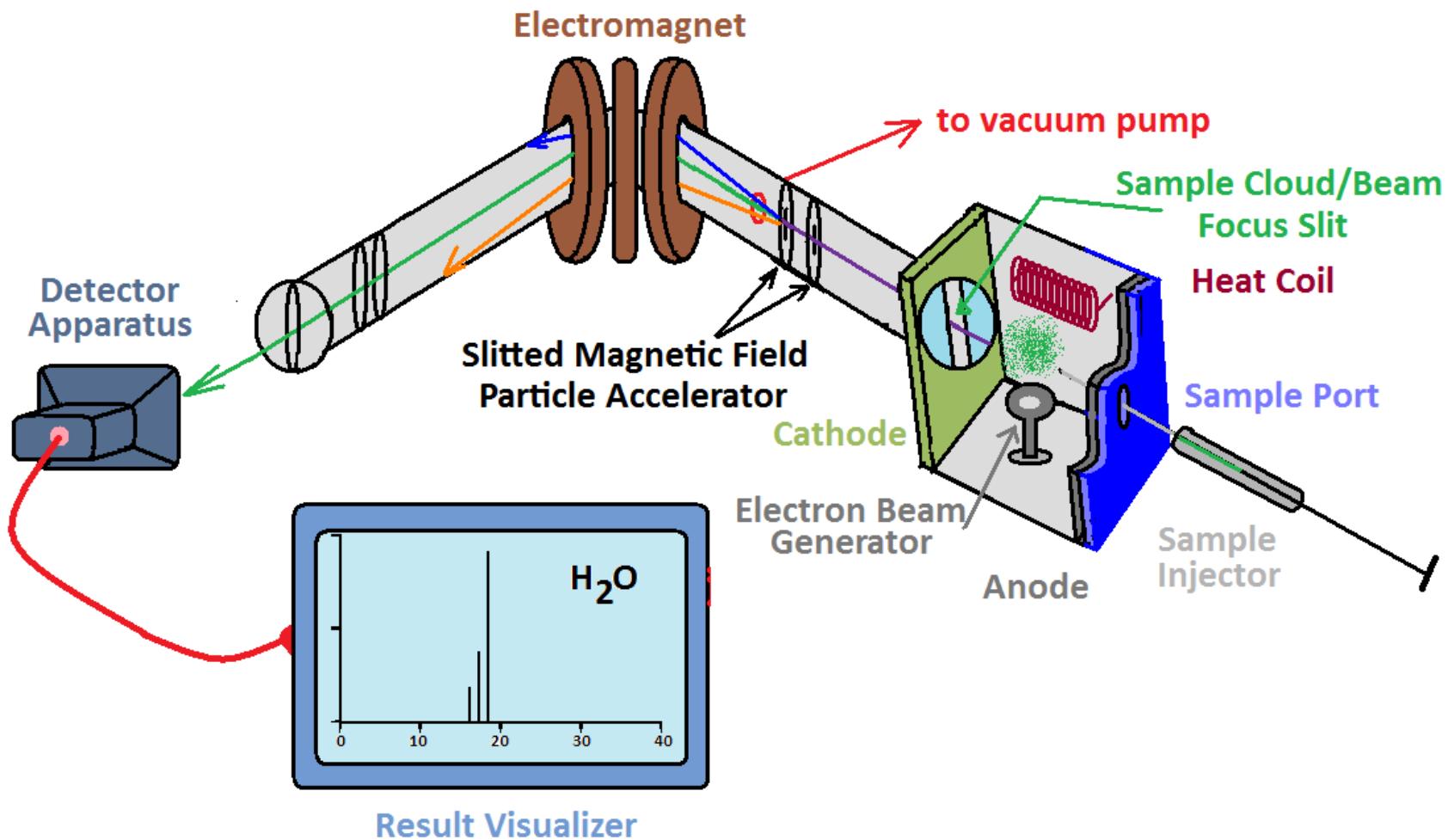
- As the beam approaches the electromagnet, the magnetic field causes the beam to split into "three" beams:
  - Heavy beam (**blue beam**)
  - "Correct beam" (**green beam**)
  - Light beam (**orange beam**)
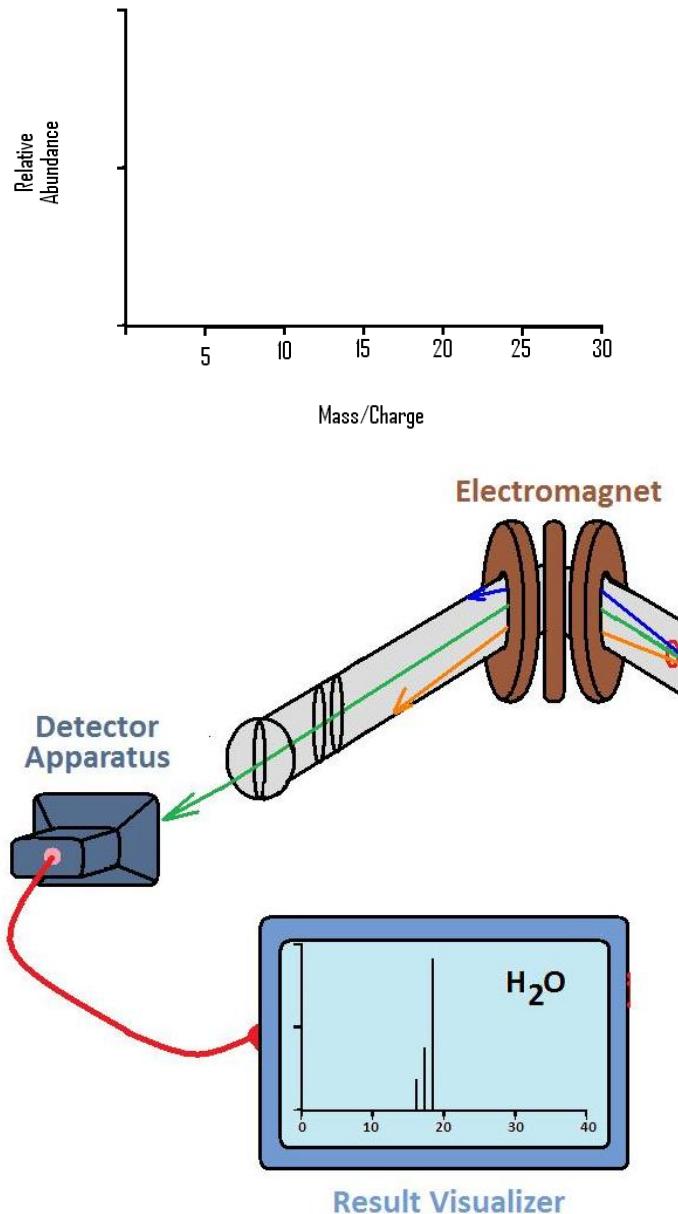
- "Correct beam" of fragments and/or molecules and/or ions hits the detector apparatus where it's digitized for read-out on the result visualizer.

- The mass spectrum on the visualizer is that of water: tallest peak is 18/1 (m/z; for water, itself); second highest is 17/1 (for OH fragment); third highest is 16/1 (for atomic oxygen).

Electromagnet

Detector Apparatus

H_2O

0   10   20   30   40

Result Visualizer
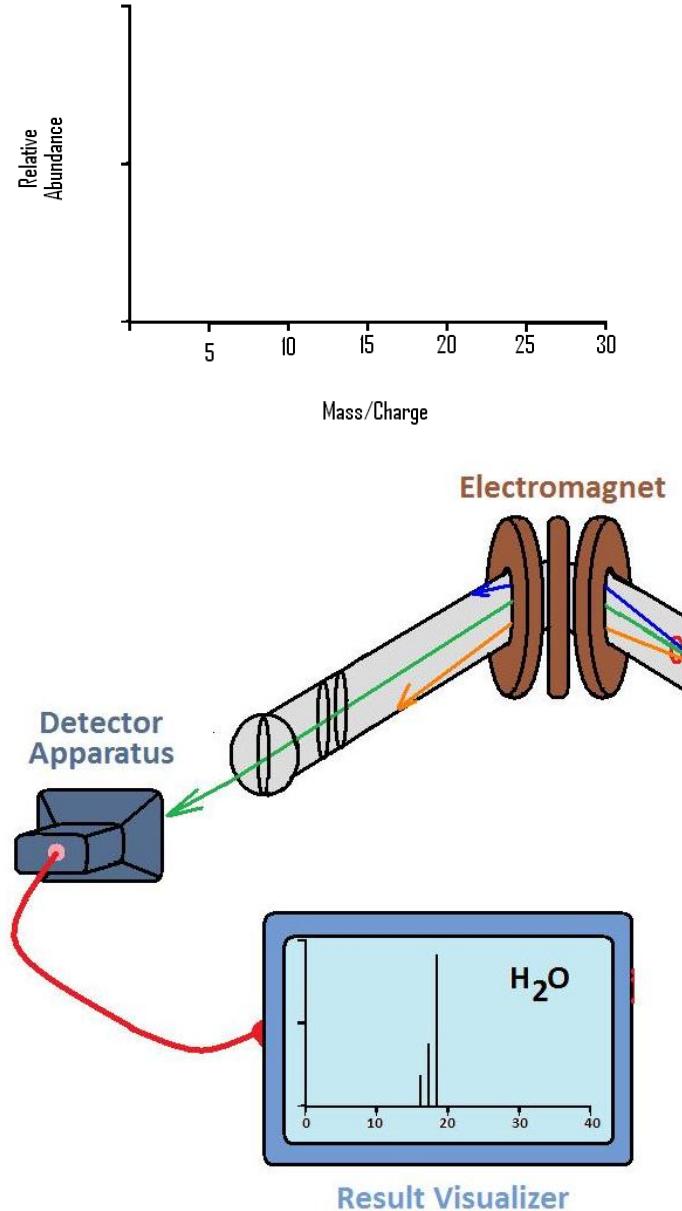
Mass Spectrometry: Some Examples
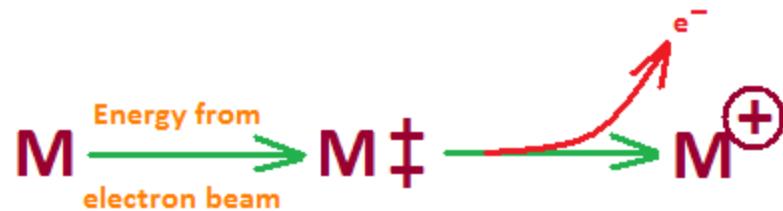
- The mass spectrum identifies molecular mass and molecular particle/fragment masses of a parent compound.
- When a mass spectrum is visualized, it is a "bar/line" graph set on a set of axes as at upper right.
- The mass spectrum for water, BTW, is lower right for an illustration of the "bar/line" graph.
- Newer MS' seem to be using "peaks" in some instances, rather than "lines".

Relative Abundance

Mass/Charge

Electromagnet

Detector Apparatus

H_2O

Result Visualizer

50

- The vertical axis is Relative Abundance – usually the highest peak is given the value of "100".

- The horizontal axis is the mass/charge ratio, often expressed as m/z or m/e.

Relative Abundance

Mass/Charge

Electromagnet

Detector Apparatus

H_2O

Result Visualizer

51
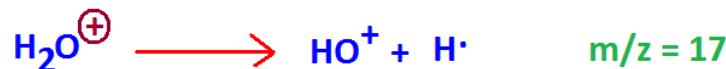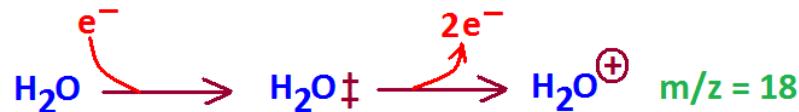
- How does one obtain the mass spectrum of a compound, barring the techno-mechanical portion of this activity?

$$M \xrightarrow[\text{electron beam}]{\text{Energy from}} M\ddagger \longrightarrow M^{\oplus} + e^-$$
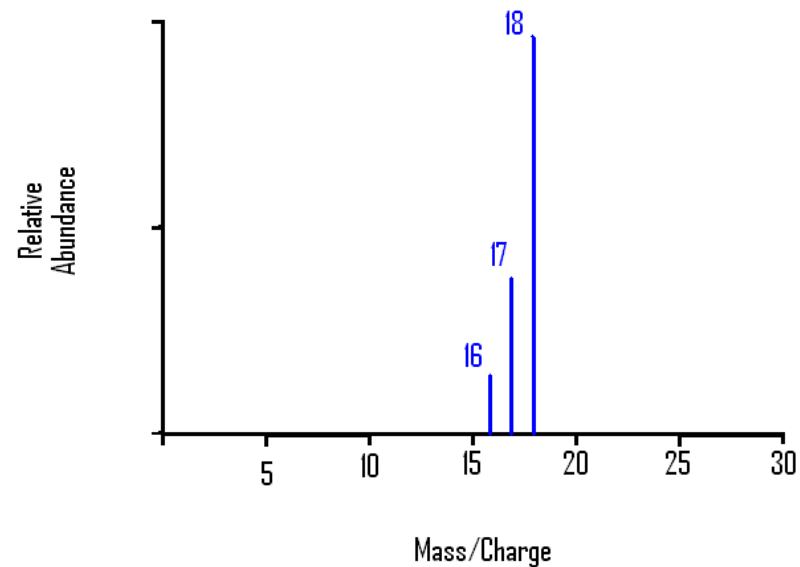
- "Circle +" = radical ion

Water Mass Spectrum

$H_2O \xrightarrow{e^-} H_2O\ddagger \xrightarrow{2e^-} H_2O^{\oplus}$ m/z = 18

$H_2O^{\oplus} \longrightarrow HO^+ + H\cdot$ m/z = 17

$HO^+ \longrightarrow O^+ + H\cdot$ m/z = 16
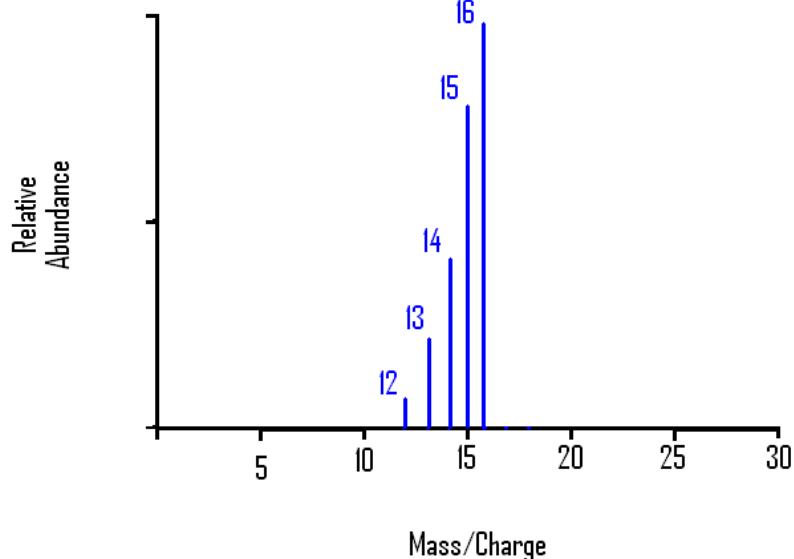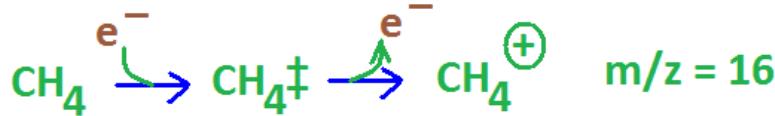
- What do we know combines to give a mass of 18?
- H = 1 and O = 16,
- 16 + 2 = 18
- Water (H_2O) is the correct response

Relative Abundance

Mass/Charge

Methane Mass Spectrum

$CH_4 \xrightarrow{e^-} CH_4{\ddagger} \xrightarrow{e^-} CH_4^{\oplus}$ m/z = 16

$CH_4^{\oplus} \longrightarrow CH_3^+ + H$ m/z = 15

$CH_3^{\oplus} \longrightarrow CH_2^+ + H$ m/z = 14

$CH_2^{\oplus} \longrightarrow CH^+ + H$ m/z = 13

$CH^{\oplus} \longrightarrow C^+ + H$ m/z = 12
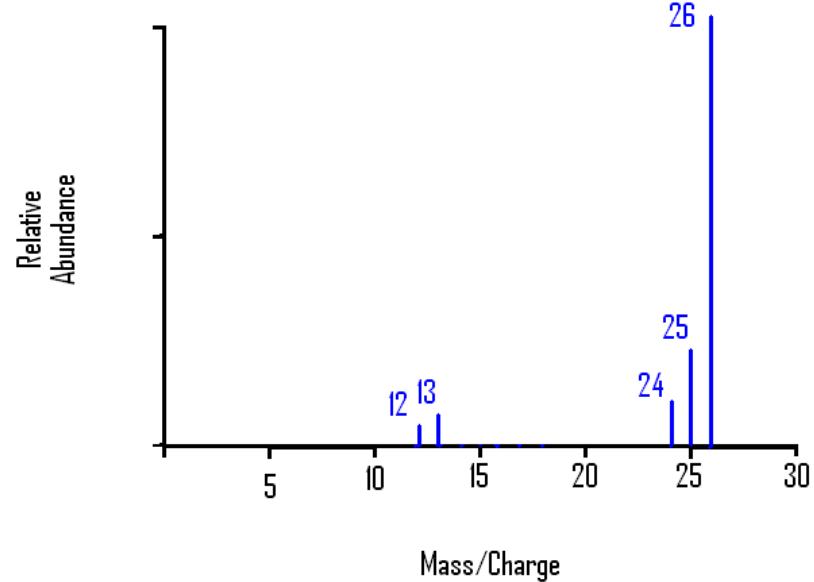
- What do we know combines to give a mass of 16?
- H = 1 and C = 12,
- 12 + 4 = 16
- Methane (CH_4) is the correct response

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Acetylene (Ethyne) Mass Spectrum
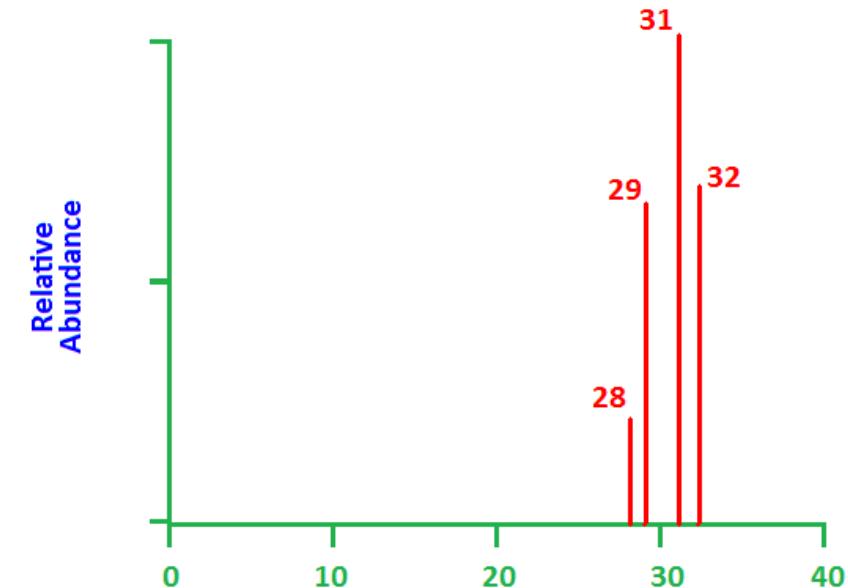
- Sample contains C and H.
- There is another way to determine the compound. That's to look at the smaller fragments and work forward.

- The smallest peak is 12 m/z
- The next smallest peak is 13 m/z
- 12 is pretty clear to be C
- 13 is equally as clear because there is only one element with a mass of 1: H, therefore, 13 must be for CH
- The peak with the highest MW is 26.
- 26/13 = 2, hence, the compound must be C_2H_2, or ethyne.

- The 25 peak is C_2H and the 24 peak is C_2

Methanol Mass Spectrum
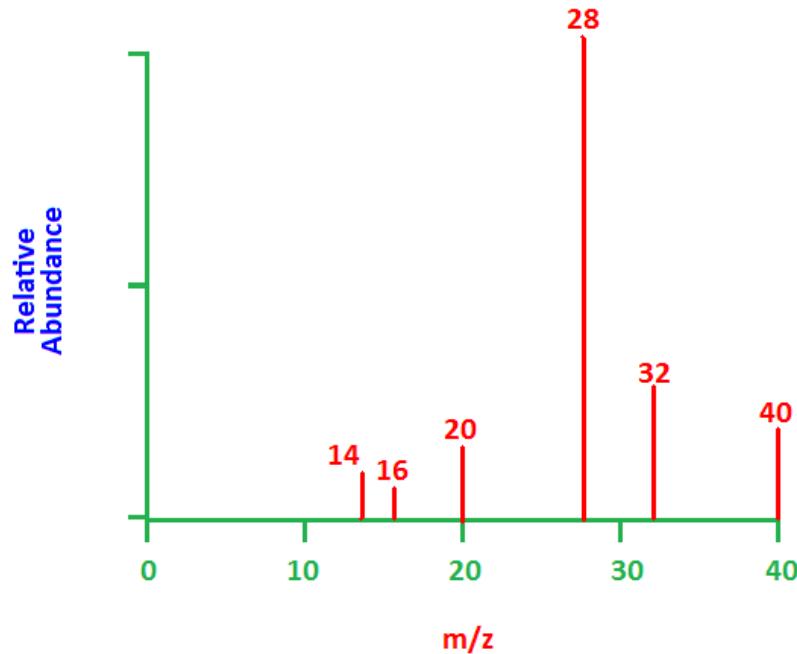
- Sample contains C, H, O
- Two oxygens is ruled out (r/o): smallest fragment peak would be 16 and there is no 16 peak.
- Smallest peak is 28: 12 for C and 16 for O makes 28
- Highest m/e peak is at 32, must be 4 H, as well.
- Formula is CH_4O – since there is NO CH_4O, it must be CH_3OH, or methanol

- 32 peak is CH_3OH
- 31 peak is CH_3O
- 29 peak is CHO
- 28 peak is CO
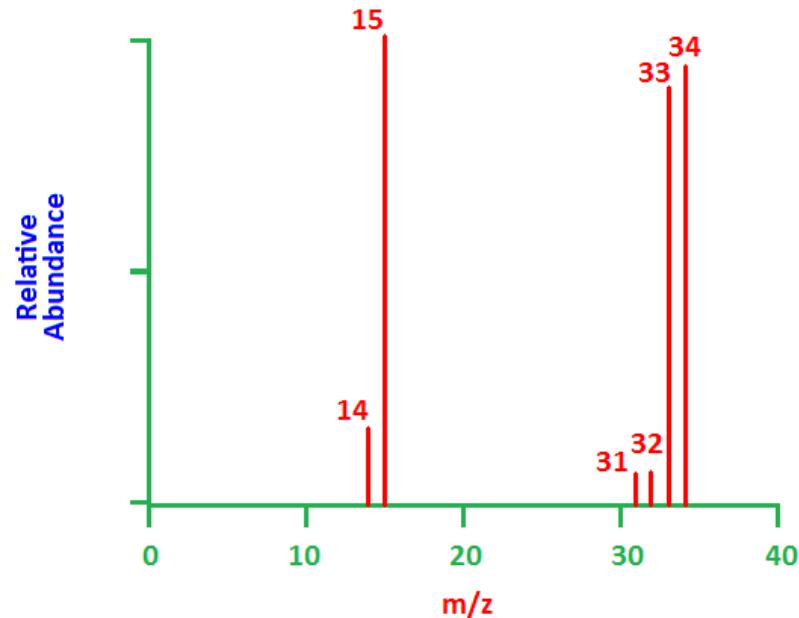
Air Mass Spectrum

- 40 = Ar
- Smallest peak is 14 = N
- Next smallest peak is 16 = O
- 20 peak is half of Ar (from a 2+ chg for Ar: 40/2 m/z)
- 28 peak is N_2
- 32 = O_2
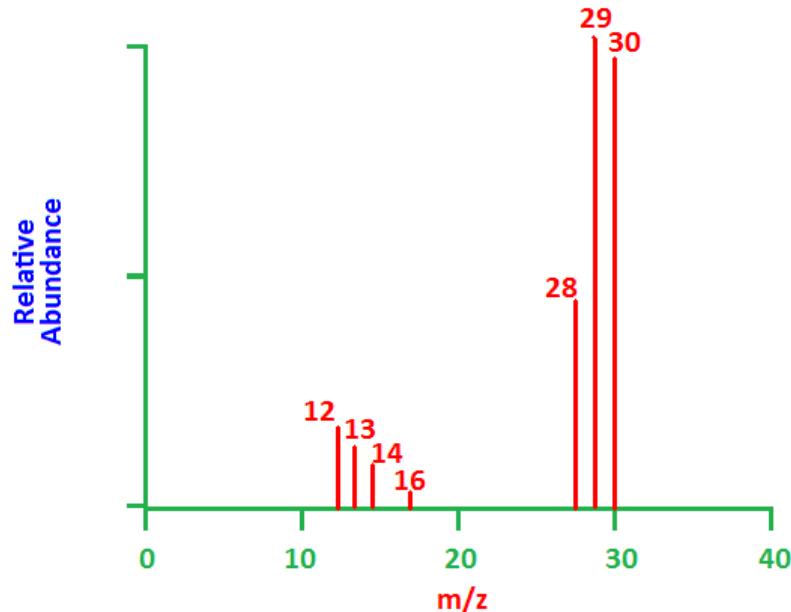
Fluoromethane Mass Spectrum

- 14 peak = 12 (C) and 2 (H)

- 15 peak = CH_3

- 34 peak = CH_3 + 19
  - Element with MW of 19 = F

- 33 peak = CH_2F

- 32 peak = CHF

- 31 Peak = CF

- Formula, then, is CH_3F
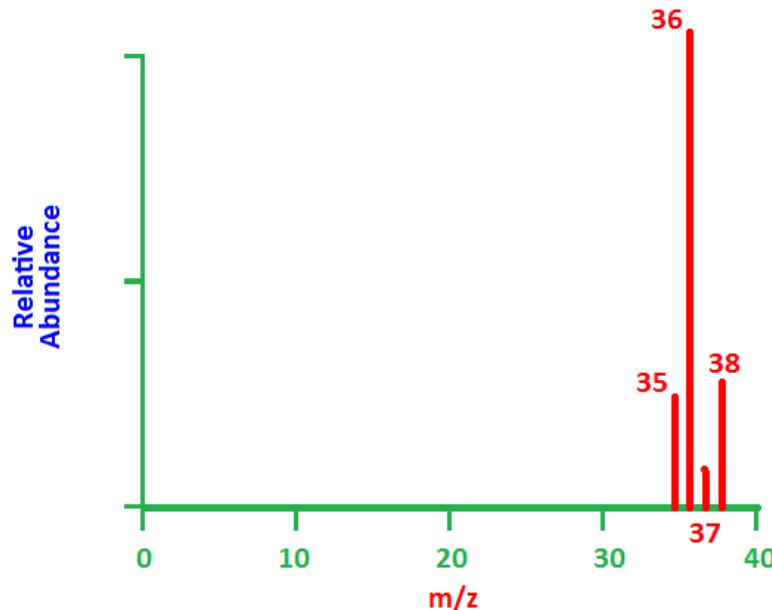
Formaldehyde Mass Spectrum

- 12 peak = C
- 13 peak = CH
- 14 peak = CH_2
- 16 peak = O
- 28 peak is 12 + 16 = CO
- 29 peak = COH
- 30 peak = COH_2
- The only thing that fits is formaldehyde – no element has a mass of 30

59
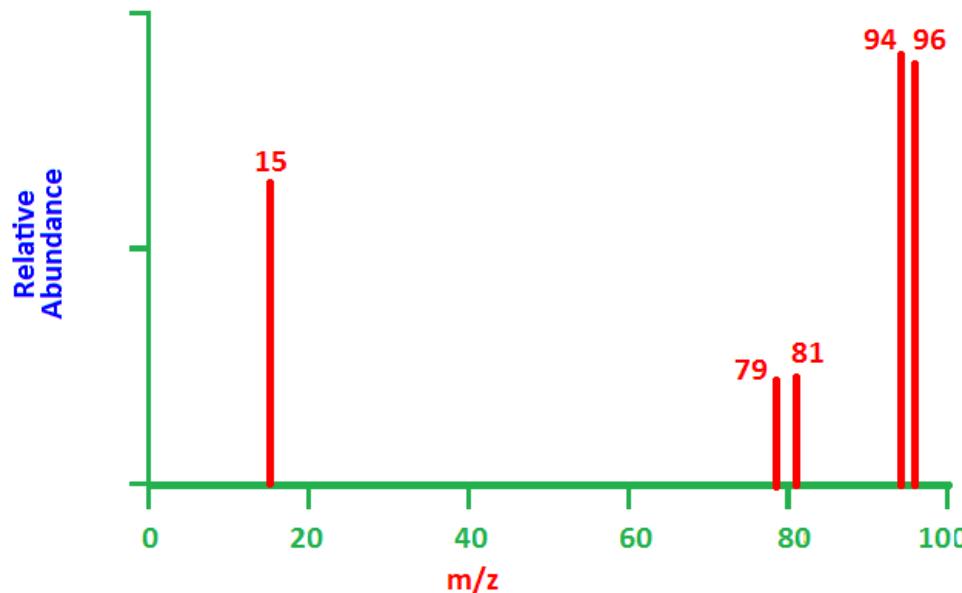
Mass Spectrometry Used to Determine Abundance of Isotopes in Nature

- Sample contains HCl – what's the proportion of ^{35}Cl to ^{37}Cl in nature?

- 35 peak is ^{35}Cl

- 37 peak is ^{37}Cl

- Ratio of peak heights = 3:1, hence 3X as much ^{35}Cl as there is ^{37}Cl

- 36 peak is from H ^{35}Cl

- 38 peak is from H ^{37}Cl

- 35 peak called "A" peak

- 37 peak called "A+2" peak since is 2 mass units heavier/beyond the 35 peak
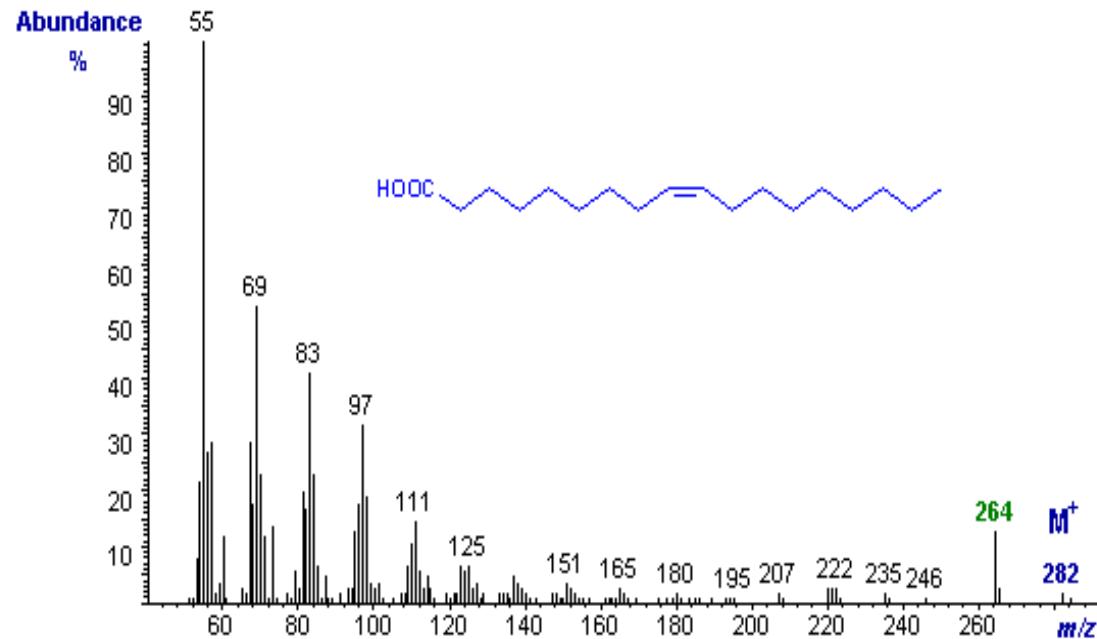
Mass Spectrometry Used to Determine Abundance of Isotopes in Nature
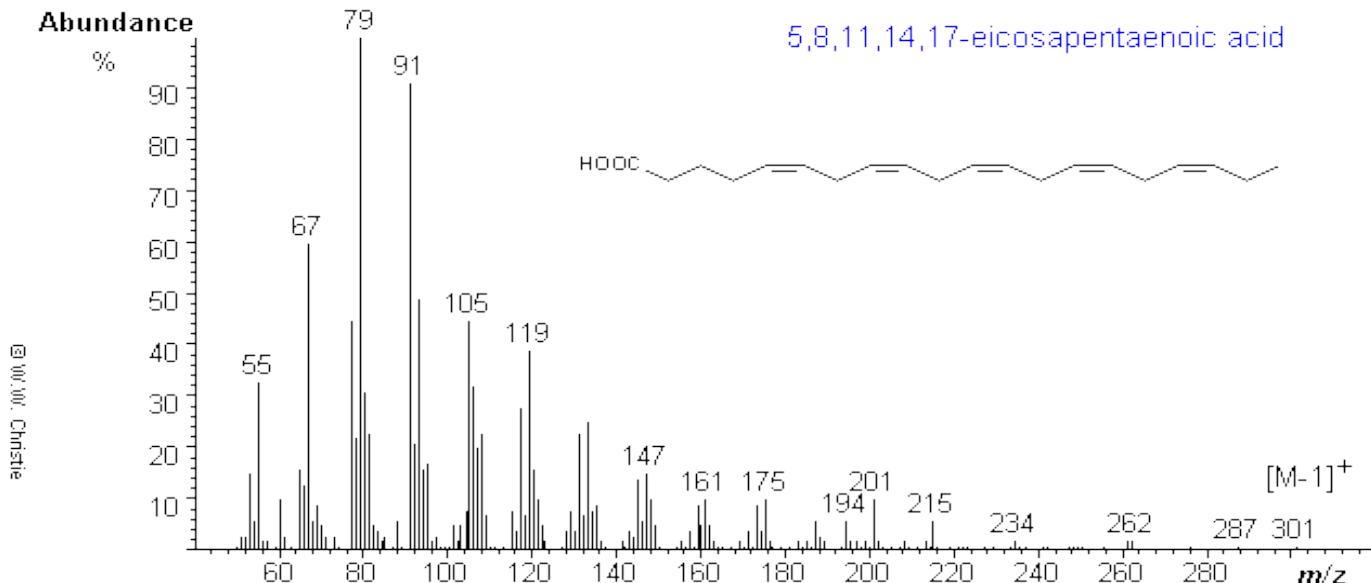
- Sample contains methyl bromide (bromomethane) – what's the proportion of ^{79}Br and ^{81}Br in nature?
- 15 peak is CH_3 peak
- 79 and 81 peaks in almost equal amounts – big clue
- Hence almost equal – one can actually calculate the numbers based on the actual peak heights
- 94-79 = 15 for the methyl
- 96-81 = 15 for the methyl
- Since the 94 and 96 peaks differ only by methyl, the peak heights are also another clue as to the abundance of the two isotopes

Mass Spectrum of Oleic Acid
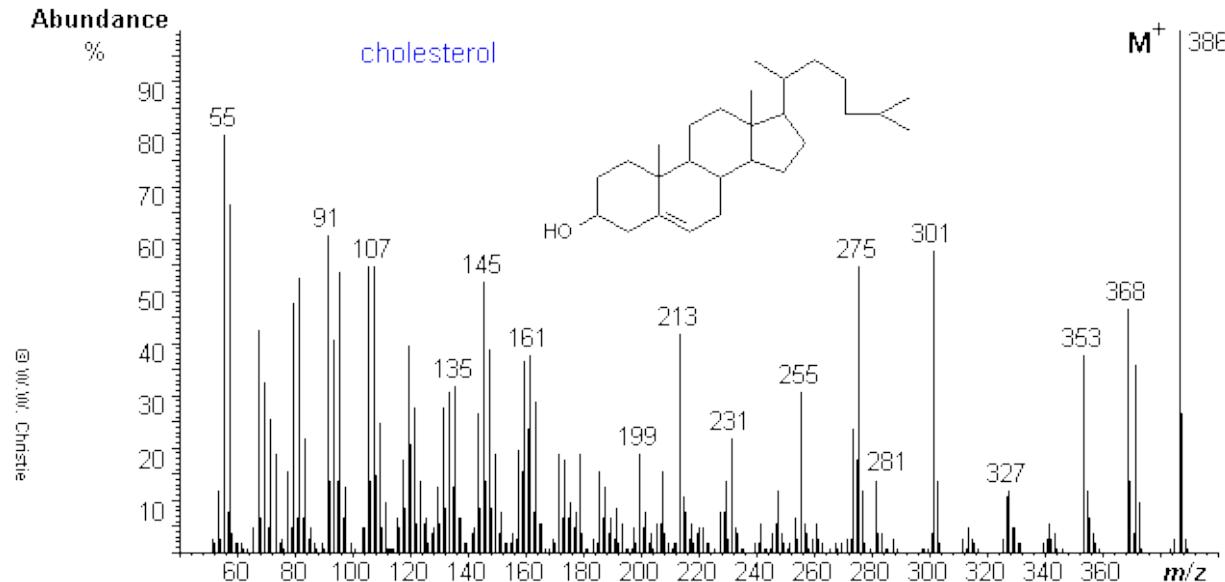
• Point of this spectrum is two-fold:

– 1) M+ is the m/z for the highest MW fragment of oleic acid – actual = 282.46

– 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

Mass Spectrum of EPA

- Point of this spectrum is two-fold:
  - 1) M-1 is the m/z for the highest MW fragment of EPA (20:5, n-3; actual MW = 302.46; spectrum didn't go out far enough)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

Mass Spectrum of Cholesterol
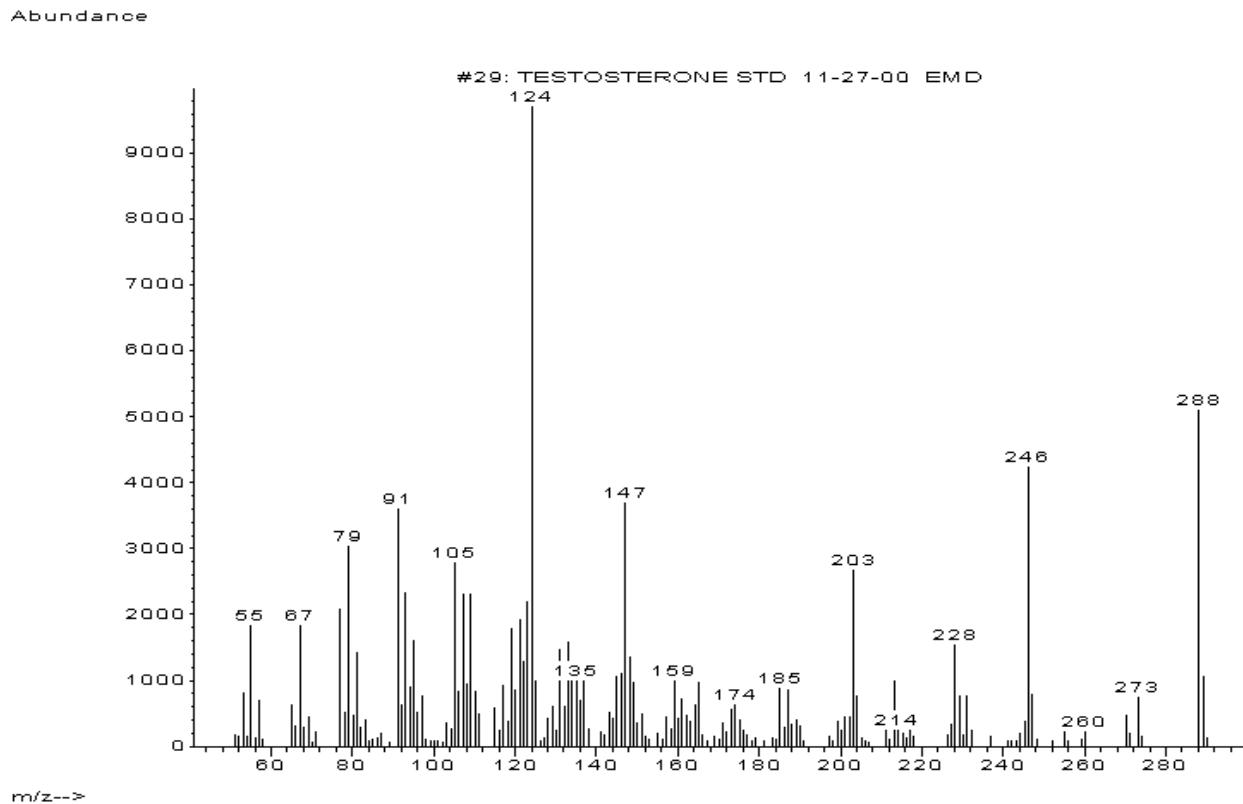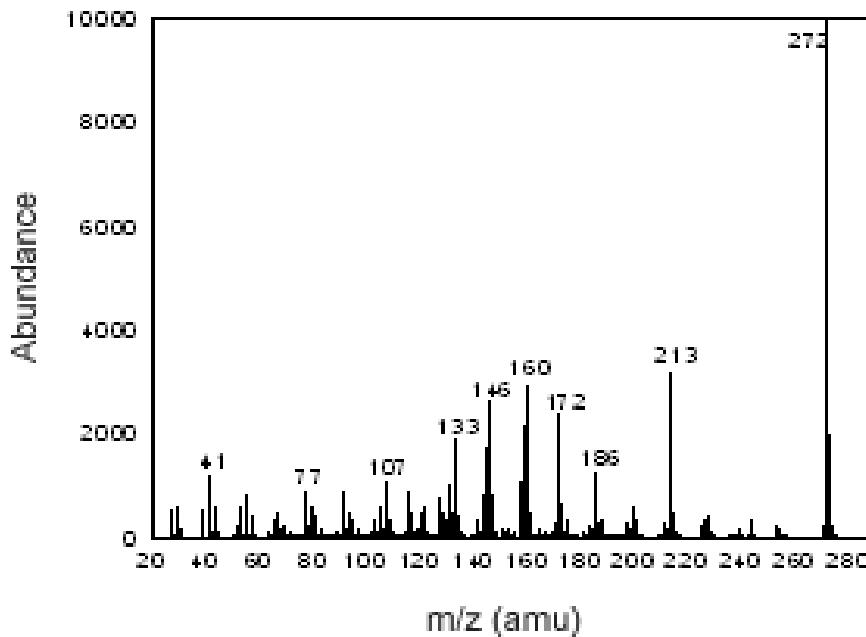
- Source: http://lipidlibrary.aocs.org/ms/arch_xyz/xyz_fa5/lip002.htm

- Point of this spectrum is two-fold:
  - 1) M+ is the m/z for the highest MW fragment of cholesterol (actual = 386.65)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

Mass Spectrum of Testosterone

Abundance

#29: TESTOSTERONE STD 11-27-00 EMD

m/z-->
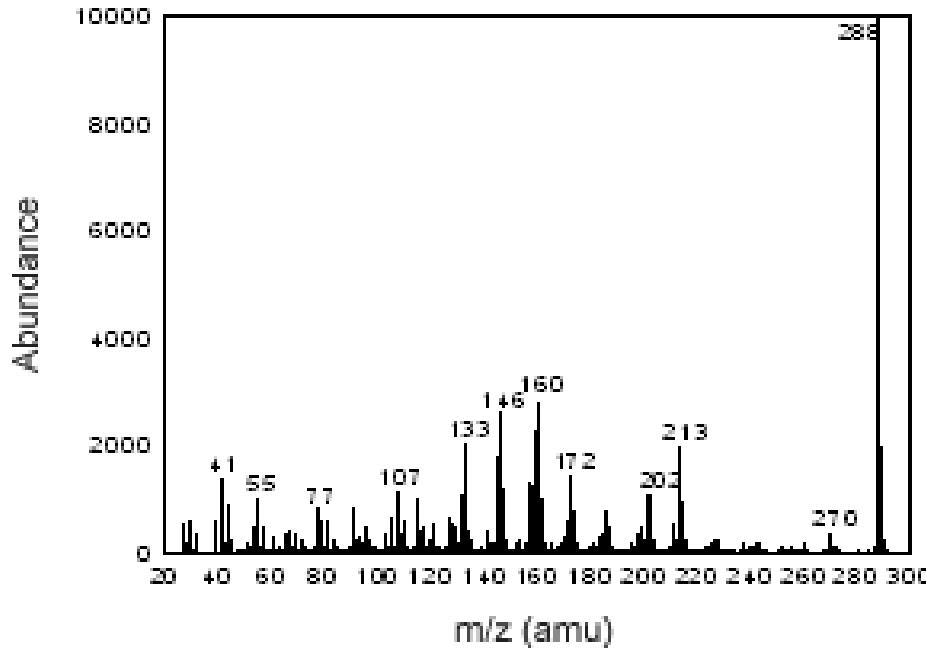
- Point of this spectrum is two-fold:
    - 1) M+ is the m/z for the highest MW fragment of testosterone (actual = 288.39)
    - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

65

Mass Spectrum of Estradiol

- Source: http://www.osha.gov/dts/sltc/methods/partial/pv2001/2001.html
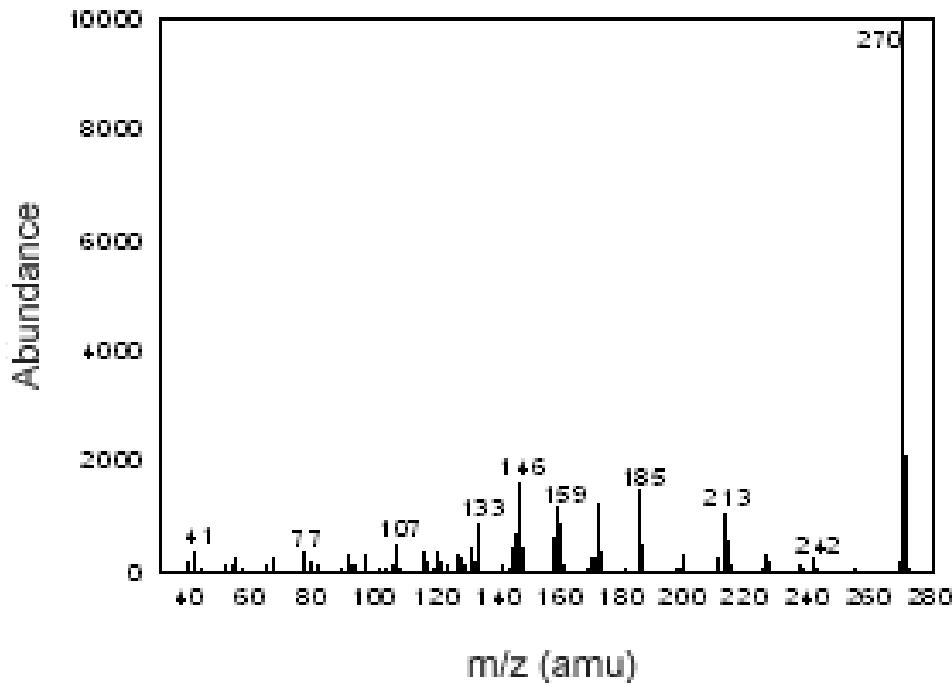
- Point of this spectrum is two-fold:
  - 1) M+ is the m/z for the highest MW fragment of estradiol (actual = 272.39)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

66

Mass Spectrum of Estriol

- Source: http://www.osha.gov/dts/sltc/methods/partial/pv2001/2001.html
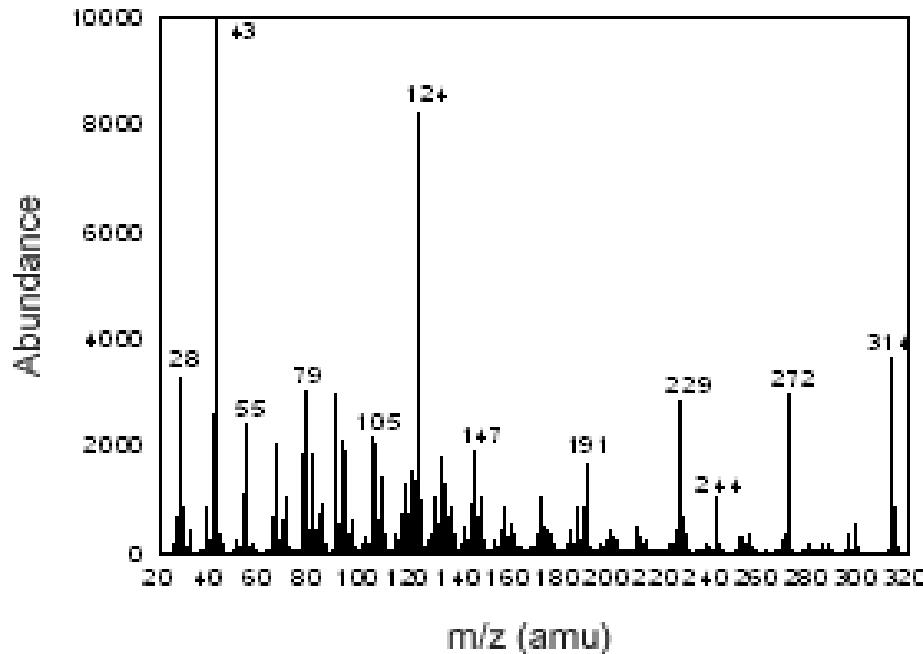
- Point of this spectrum is two-fold:
  - 1) M+ is the m/z for the highest MW fragment of estriol (actual = 288.39)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

Mass Spectrum of Estrone

- Point of this spectrum is two-fold:
  - 1) M+ is the m/z for the highest MW fragment of estrone (actual = 270.37)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

Mass Spectrum of Progesterone
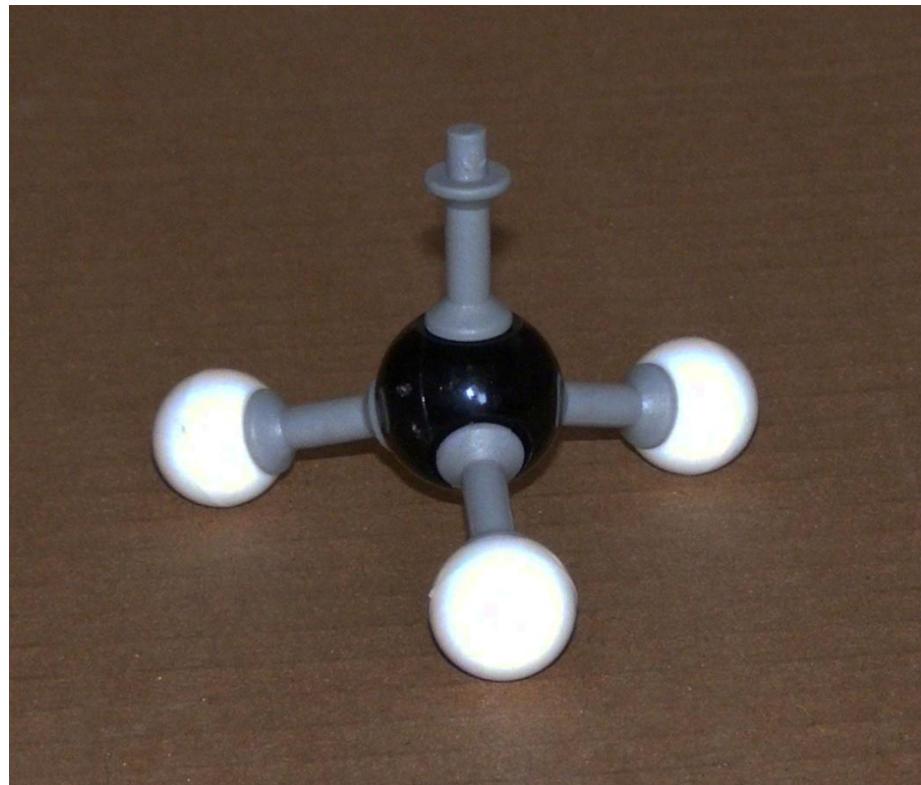
- Point of this spectrum is two-fold:
  - 1) M+ is the m/z for the highest MW fragment of progesterone (actual = 314.47)
  - 2) Mass Spectra are not as "clean" as the mass spec's that I built in Paint.

69
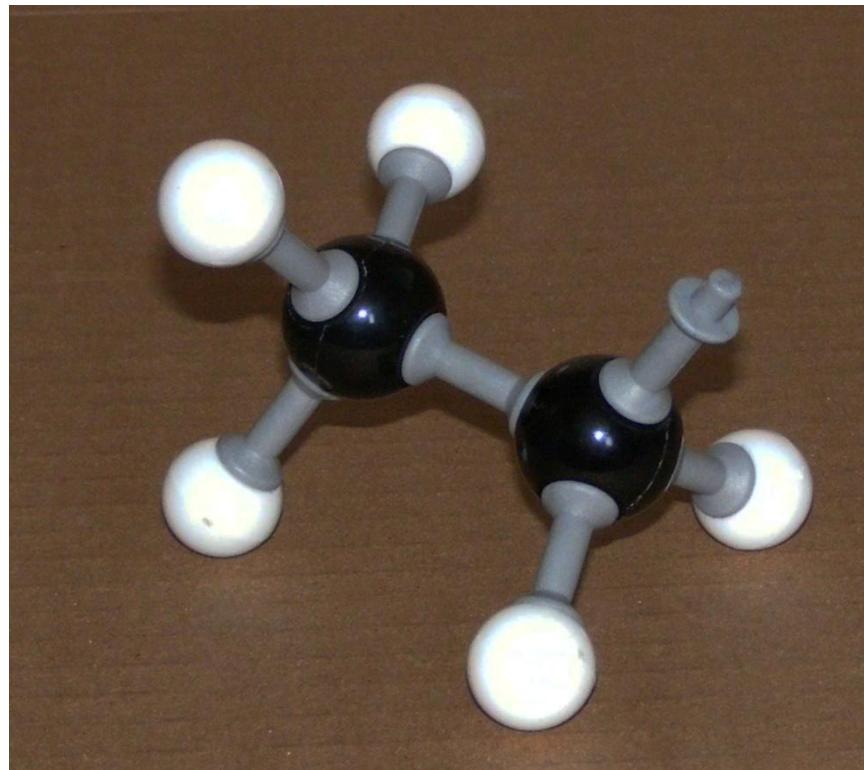
Alkyl groups

- 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

- If methane (CH_4) were to lose a hydrogen atom, it becomes the methyl radical ($CH_3 \cdot$), where the dot represents the left-behind electron after the hydrogen atom was removed from methane.
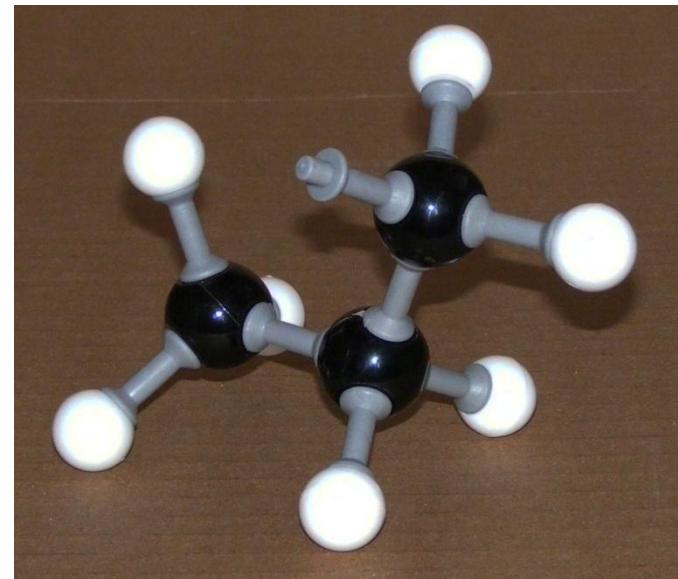
- The same applies to ethane (C_2H_6) when it loses an electron to become the ethyl radical: ($CH_3CH_2\bullet$).

- These are the two simplest alkyl radicals.

- The following radicals have isomers and require memorization.

- In most cases, their common names make NO sense -- that's why we have a systematic manner in which to name them coming up.
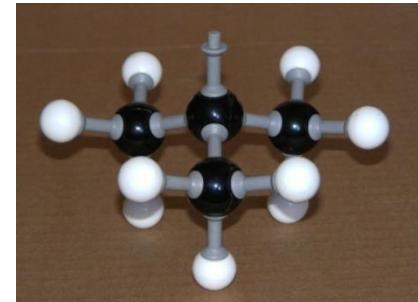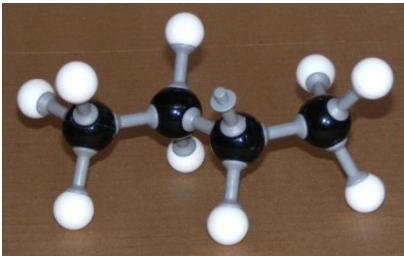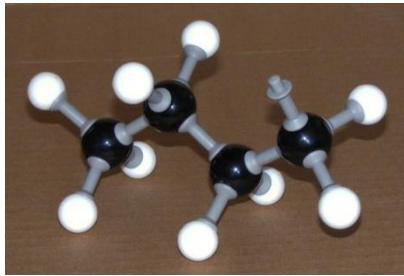
Propyl Radicals -- Detail
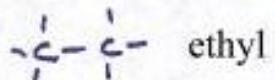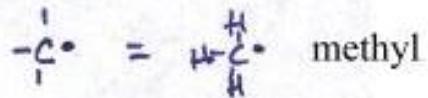
- When propane loses an electron, it may lose it from either one of the end carbons or from the middle carbon. The end carbons, notice, are directly bonded to only one other carbon atom. These carbons are called primary or first degree carbons. Hydrogen atoms or other substituting groups carry the same nomenclature when they are bound to first degree or primary carbons. The middle carbon, though, is bonded directly to two carbons. This carbon is a secondary or second-degree carbon. Hydrogen atoms or substituting groups onto a secondary carbon carry the same name, i.e., the hydrogen would be called a secondary hydrogen because it was bound to a secondary carbon.

- When the hydrogen atom is lost from one of the end carbons in propane, the radical is called the n-propyl radical and is a primary or first degree radical. When the hydrogen atom is lost from the middle carbon, this is called the isopropyl radical by common name. This radical is a secondary or second-degree radical. For propane, then, there are 2 isomers.
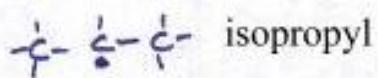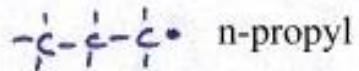
Butyl Radicals -- Detail

With butane, it gets a bit hairier. There are 4 isomers of the butyl radical. If the hydrogen atom is removed from the end carbon, the n-butyl radical is obtained. If the hydrogen atom is removed from the second carbon while all 4 carbons are in a 4-carbon chain, the secondary-butyl radical is obtained. These are the easy isomers. The more complicated isomers involve taking one carbon atom from the 4-carbon chain and attaching it to the middle carbon of the leftover 3-carbon chain. The center carbon, now, is directly bonded to 3 carbon atoms. This carbon is, then, a tertiary or third degree carbon and the hydrogen atom on it is a tertiary or third degree hydrogen atom. When the tertiary hydrogen is removed, the t-, tert-, or tertiary butyl radical is obtained. But, wait! What if you leave that one and remove a hydrogen atom from one of the primary carbons? Then, you obtain the isobutyl radical -- see what I mean about the common names not making sense? Do NOT try to make the common names or nicknames make sense -- won't work, e.g., the pentyl radical isomers.
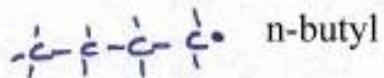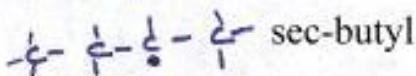
methyl

ethyl
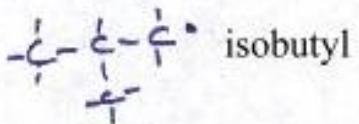
n-propyl

isopropyl
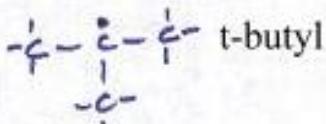
n-butyl
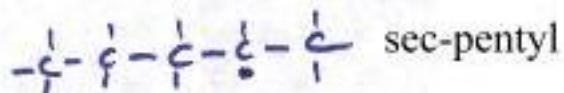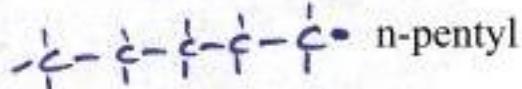
sec-butyl
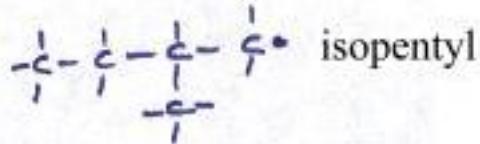
isobutyl
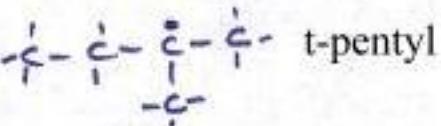
t-butyl
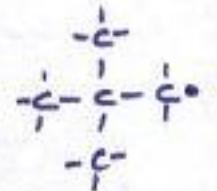
n-pentyl

sec-pentyl

isopentyl

t-pentyl

neopentyl
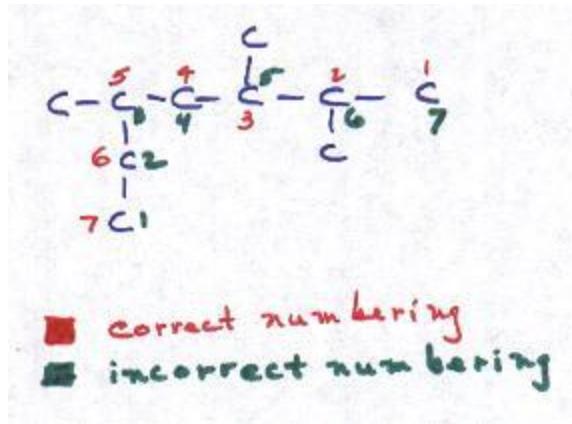
IUPAC -- the International Union for Pure and Applied Chemistry

- So now that we know that we can't make sense out of common names, what do we do?
- We fall back onto the IUPAC -- the International Union for Pure and Applied Chemistry.
- The IUPAC met to determine a systematic manner in which to name compounds so that EVERYONE would know exactly which compound EVERYONE was talking about.
- The rules are pretty straight-forward and we'll walk through a few of them as we delve deeper into this fascinating field of chemistry!

When naming alkanes

1. name the longest continuous "straight" chain (remember, the carbon atoms are in sp^3 hybridization so the chain is not "straight", rather it is "bent" continuously),

2. enumerate the substituting groups with the lowest numbers possible and

3. if there is more than one group, alphabetize the substituting groups regardless of enumeration.
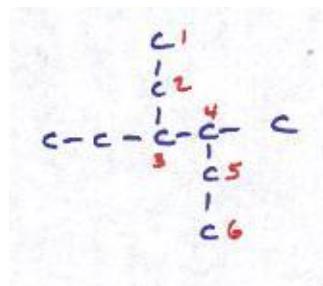
Example

Note that there are two ways in which count the numbers of carbon atoms: from the left or from the right. It is only after you assign numbers to the carbons in the longest chain that you can see that you number this one from the right going left. To do otherwise puts substituting groups at carbons 3, 5 and 6; when done, in this case, from the right, the substituting groups are now on carbons 2, 3 and 5.
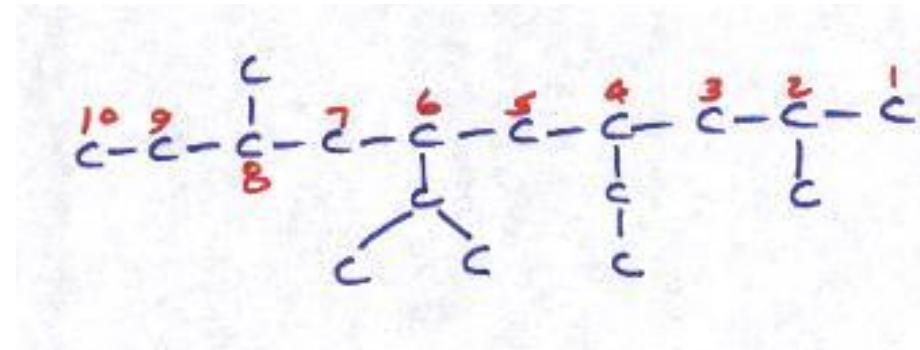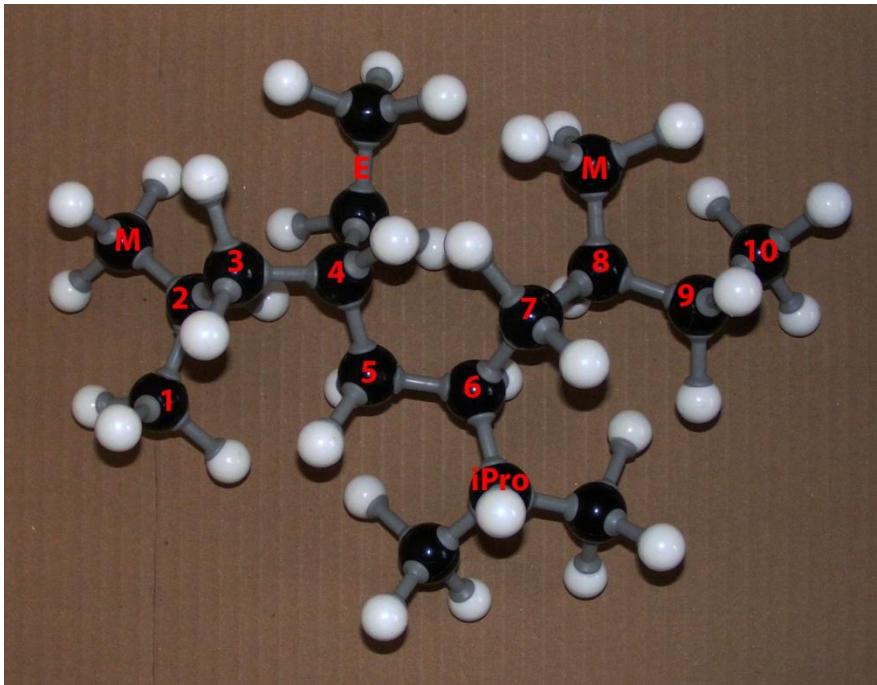
The longest continuous chain is 7 carbons: it's a heptane. The substituting groups are all methyl groups (CH_3·), and they are on carbons 2, 3 and 5. Since they are identical groups, we'll group them as "trimethyl" for "three methyl groups"; the "di" or "tri" type of prefixes are not used to alphabetize, BTW. To name the compound, it is 2,3,5-trimethylheptane. Note that this is ALL one word. Numerals are kept separated from each other by commas. Numbers and letters are separated by dashes. The name tells everyone that the longest chain is 7 carbons long, it's an alkane and there are methyl groups on carbons 2, 3 and 5.

Example
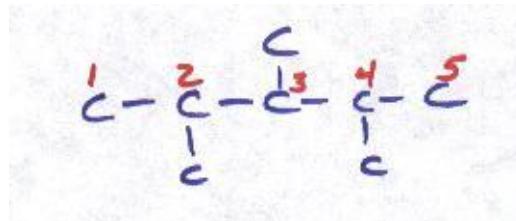
In this case, the longest chain is 6 carbons long. While it really doesn't matter how we enumerate the carbons in this example, for "neatness" we'll number from the top to the bottom (this makes the alphabetization easier). The longest chain is 6 carbons long and there are only single bonds between the carbons. The longest chain, then, is hexane. There are 2 substituting groups on the hexane: an ethyl group on #3 and a methyl group on #4. By alphabetizing the substituting groups, the name is 3-ethyl-4-methylhexane.

Example

The longest chain is 10 carbons long: decane. We enumerate the carbons from right to left (in right image and vice versa in left image; can you figure out why?).There are 2 methyl groups on carbons 2 and 8; an ethyl group on carbon 4 and an isopropyl group on carbon 6. The name, then, is **4-ethyl-6-isopropyl-2,8-dimethyldecane**. Do you see how the name makes it easy to draw the structures?

Example
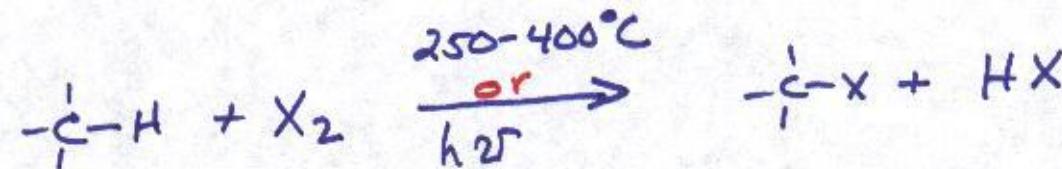
This is a symmetrical molecule, with the longest chain being 5 carbons long. The substituting groups are on carbons 2, 3 and 4 -- regardless how you count them. This molecule is 2,3,4-trimethylpentane.

A Couple of Reactions Characteristic of Alkanes: Halogenation and Combustion Reactions.
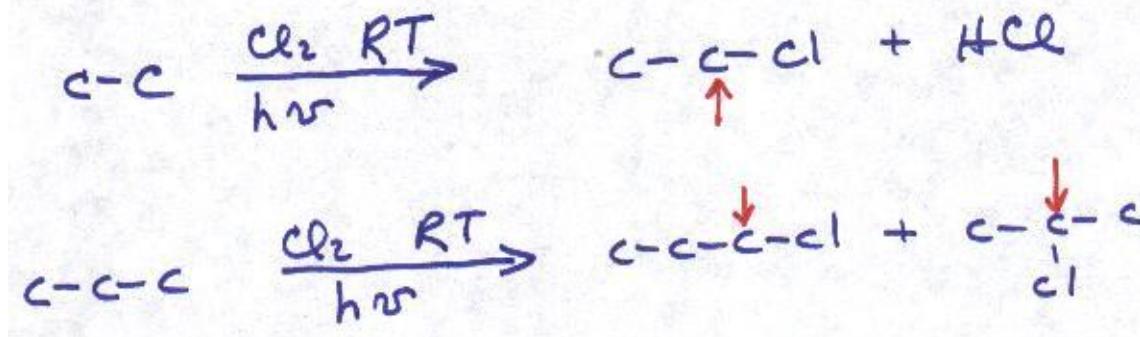
- Halogenation reactions do just what the name says: they put halogens on compounds.

- Chlorine is more reactive than bromine and tertiary hydrogens are more easily extracted than secondary hydrogens, which are more easily extracted than primary hydrogens.

- As a general rule, an "X" represents a halogen.

The Simplest Halogenation Reaction: The Halogenation of Methane

$$-\overset{|}{\underset{|}{C}}-H \;+\; X_2 \;\xrightarrow[\text{h}\nu]{\overset{250-400°C}{\text{or}}}\; -\overset{|}{\underset{|}{C}}-X \;+\; HX$$

The reaction is driven by either light (hν) and room temperature (RT) or by temps between 250 and 400° C. Note that the products are halomethane (chloromethane if we had used chlorine; bromomethane had we used bromine) and the hydrohalic acid (HCl or HBr, respectively, with our earlier example).
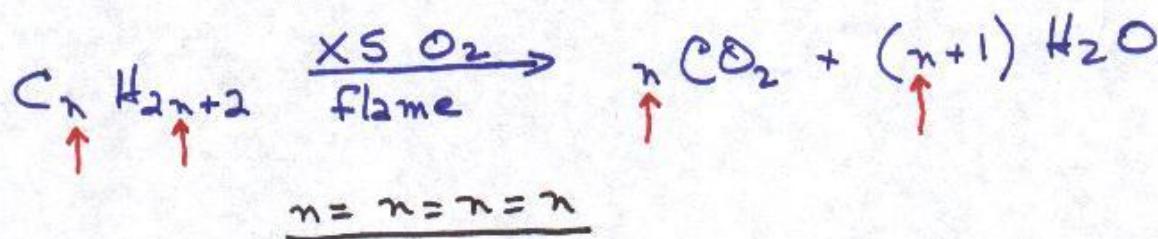
Halogenation Reaction Example

•The reaction with ethane is very straight-forward: chloroethane and hydrochloric acid are obtained.
•The reaction with propane, though, is not as clear. Remember those primary and secondary hydrogens? That's what makes it so murky. There will be two halohydrocarbon products: chloropropane and 2-chloropropane -- did I need to put a "1" in front of the chloropropane? No. If there is no number, it is understood to be the "1" substitution. In the latter reaction note that the HCl is not included. For my classes, it's not necessary to be as anal retentive with organic chemistry as it is in inorganic chemistry, i.e., I'm interested in the organic products, not the trivia.
• Note in the figure that there are arrows pointing to the two products of the halogenation of propane. Given the higher reactivity of secondary hydrogens, in the olden days, the 2-halopropane was considered the MAJOR product and the halopropane was considered the MINOR product. We now know that that is not necessarily the case.
•We'll discuss why this phenomenon occurs later in the course.
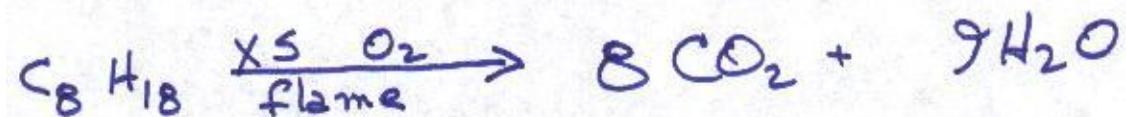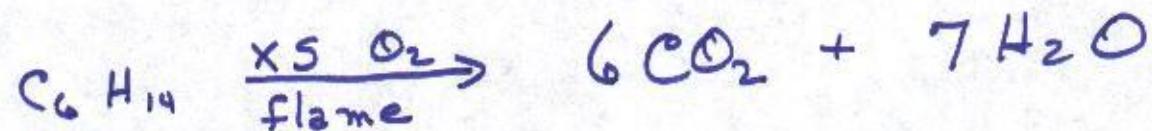
Combustion Reactions

- Go on around us every day: driving a car powered by gasoline or diesel, using natural gas water heaters or dryers or by burning coal for electricity.

- As a general rule, when an alkane is burned in the presence of excessive oxygen, carbon dioxide and water are formed:

$$C_n H_{2n+2} \xrightarrow[\text{flame}]{\text{x5 } O_2} n\, CO_2 + (n+1)\, H_2O$$

$$n = n = n = n$$

Note that you always get 1 more mole of water vapor than the number of carbons in the original alkane, e.g., if you were to combust eicosane, you would obtain 20 moles of carbon dioxide and 21 moles of water vapor.

Combustion Examples

$$C_6H_{14} \xrightarrow[\text{flame}]{\times 5\ O_2} 6\,CO_2 + 7\,H_2O$$

$$C_8H_{18} \xrightarrow[\text{flame}]{\times 5\ O_2} 8\,CO_2 + 9\,H_2O$$
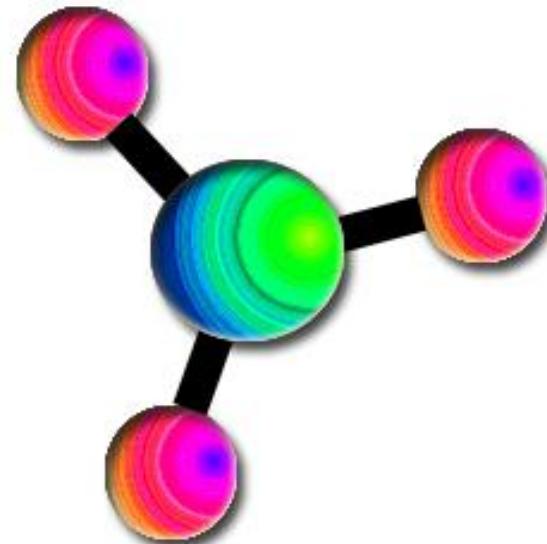
The first is the combustion of hexane to 6 moles of carbon dioxide and 7 moles of water vapor and the second is the combustion of octane to 8 moles of carbon dioxide and 9 moles of water vapor.

Incomplete, Abnormal, Combustion of Hydrocarbons
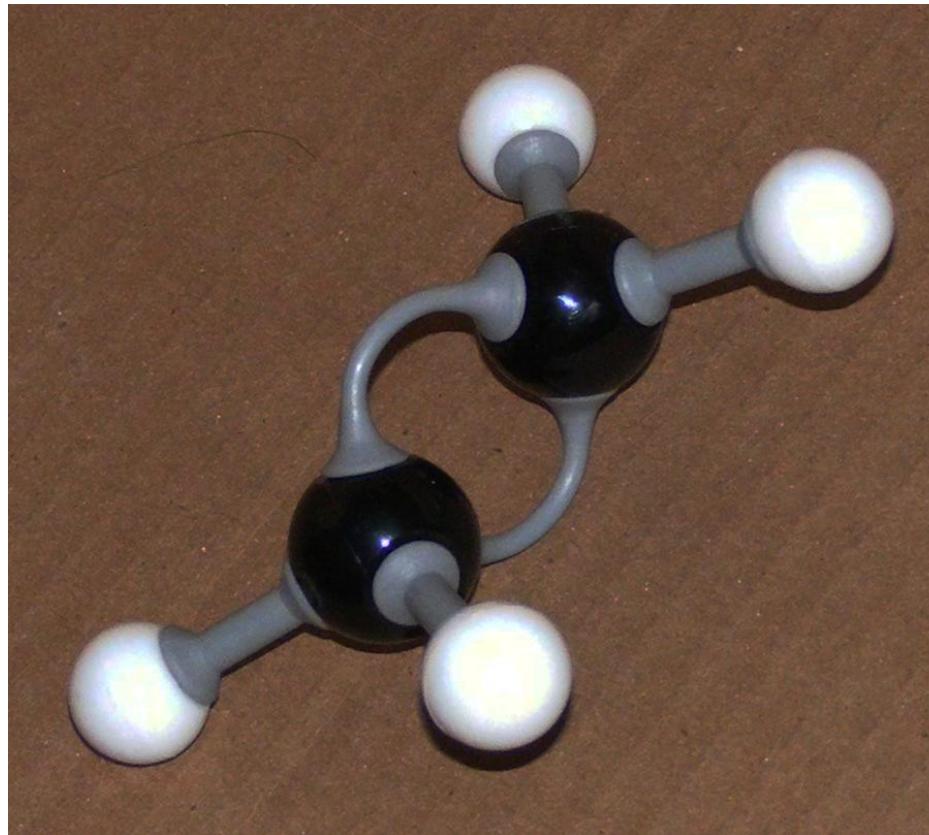
- Major Health Concern

- "Old", Inefficient Propane Burners

- $2\ C_3H_8 + 7\ O_2 \rightarrow 6\ $**CO**$ + 8\ H_2O + \text{heat}$

- Deadly

- From Gasoline, as well.
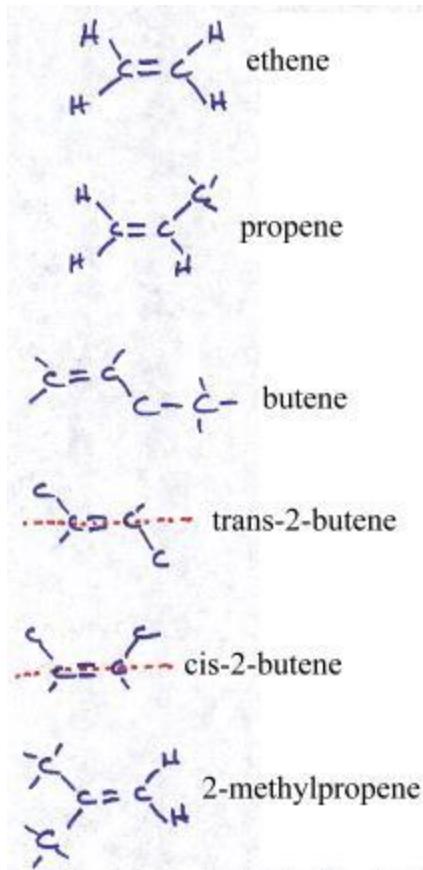
Alkenes

- 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 are in sp^2 hybridization and 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.

- The simplest alkene is ethene -- "eth" for 2 carbons and "ene" for the double bond -- C_2H_4
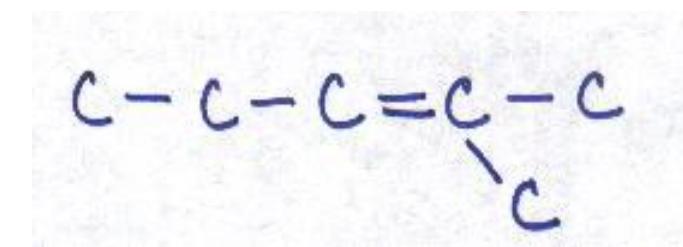
•Propene, C_3H_6, has only one conformation.
•The Butene family has 4 isomers.
•Butene has the double bond between the first two carbons in the 4-carbon chain. 2-butene has 2 isomers, both of which have the double bond between the 2d and 3d carbons. If you look at the first 2-butene, you'll note that the 2 hydrogen atoms on the carbons involved in the double bonds are across from each other and on opposite sides of the double bond plane. This is the trans isomer. Thus, this molecule is called trans-2-butene. The bottom 2-butene isomer you'll note has the hydrogen atoms on the same side of the plane of the double bond. This is the cis isomer. Thus, this molecule is called cis-2-butene. The last isomer in the butene family is a 3-carbon chain with a methyl group off the 2d carbon. It is called 2-methylpropene.

Naming alkenes is about as simple as naming alkanes.
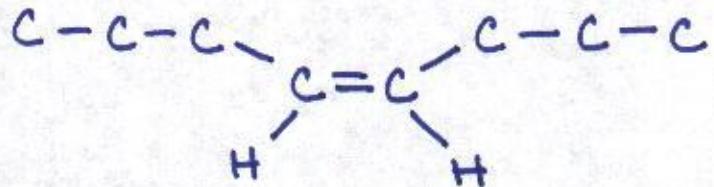
- Another rule, though, is to give the location of the double bond numerically and give it the lowest number possible.

Example
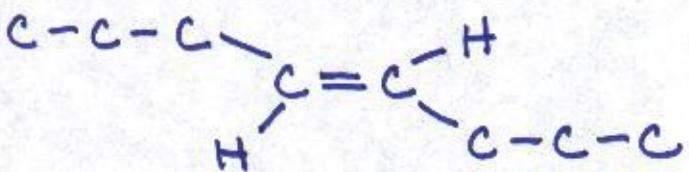
✓ The longest chain is 5 carbons long.
✓ The double bond is between carbons 2 and 3 -- thus it is a 2-ene.
✓ You only give the lowest number of the carbon in the double bond, not both numbers.
✓ There is a methyl group on carbon #2.
✓ The name of this compound is 2-methyl-2-pentene.

$$C - C - C = C - C$$
$$|$$
$$C$$

Example
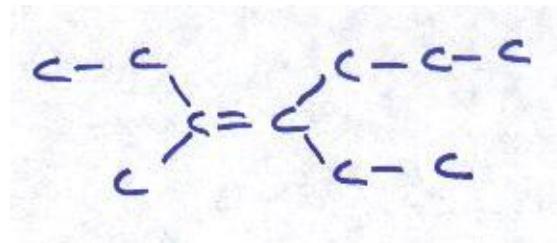
cis-4-octene

Trans-4-octene
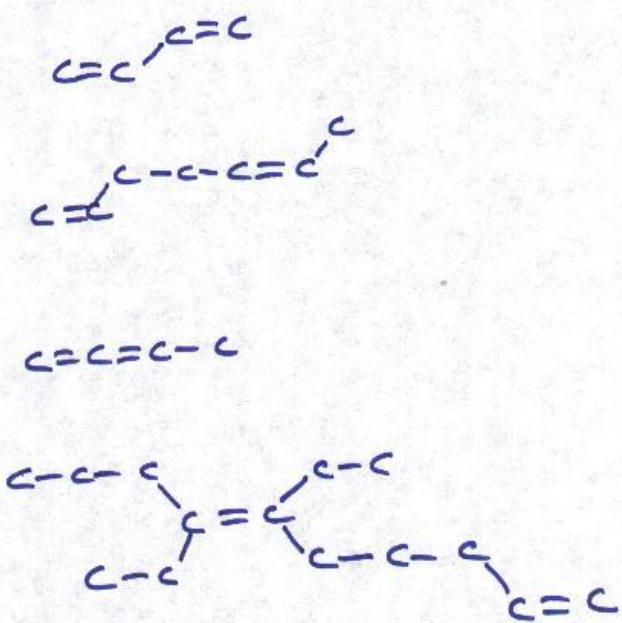
- cis-4-octene and trans-4-octene.
- Both have 8 carbon chains with a double bond between carbons 4 and 5.
- The former has both hydrogen atoms on the same side of the plane of the double bond and the latter has the hydrogens on opposite side of the plane of the double bond.

Example

There are 7 carbons in its longest continuous chain. There is a methyl group on carbon #3 and an ethyl group on carbon #4. There is a double bond between carbons 3 and 4. The name of this compound is 4-ethyl-3-methyl-3-heptene.
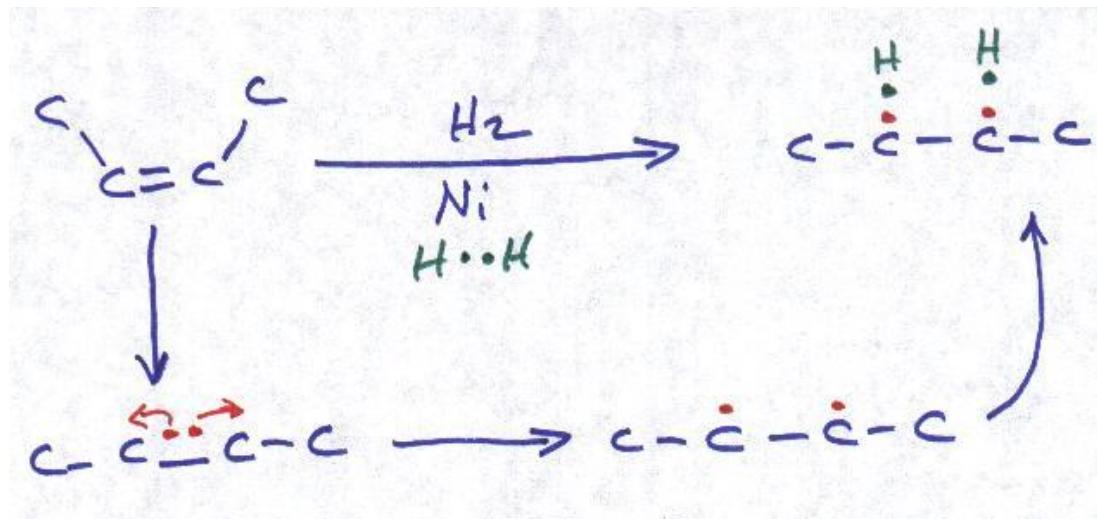
Di-enes

•A four carbon chain with double bonds between carbons 1 and 2 and carbons 3 and 4 is called 1,3-butadiene.

•A seven carbon chain with double bonds between carbons 1 and 2 and carbons 5 and 6 is called 1,5-heptadiene.

•A four carbon chain with double bonds between carbons 1 and 2 and carbons 2 and 3 is called 1,2-butadiene.

•The last example in this graphic has 10 carbons in its longest chain, double bonds between carbons #1 and 2 and carbons #6 and 7. Off carbon #6 is an ethyl group as there is off carbon #7. The name of this compound is 6,7-diethyl-1,6-decadiene.
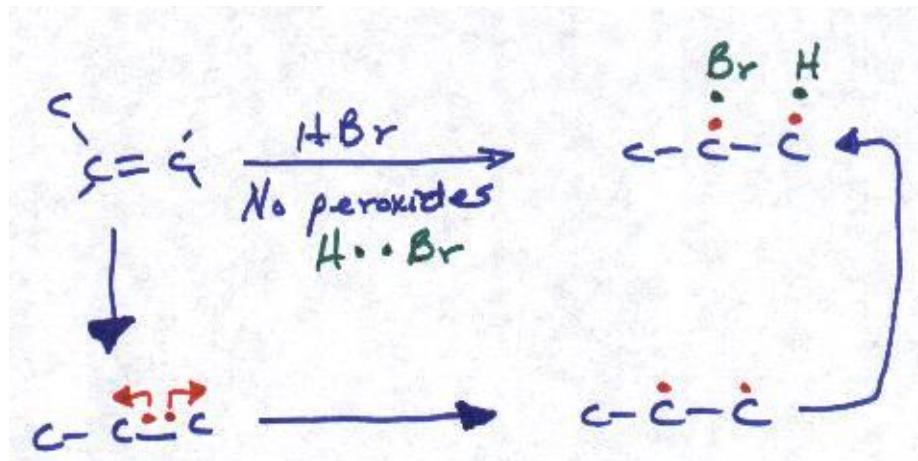
There are 3 reactions about which you need to be aware regarding alkenes; hydrogenation, hydrohalogenation and hydration.

Hydrogenation
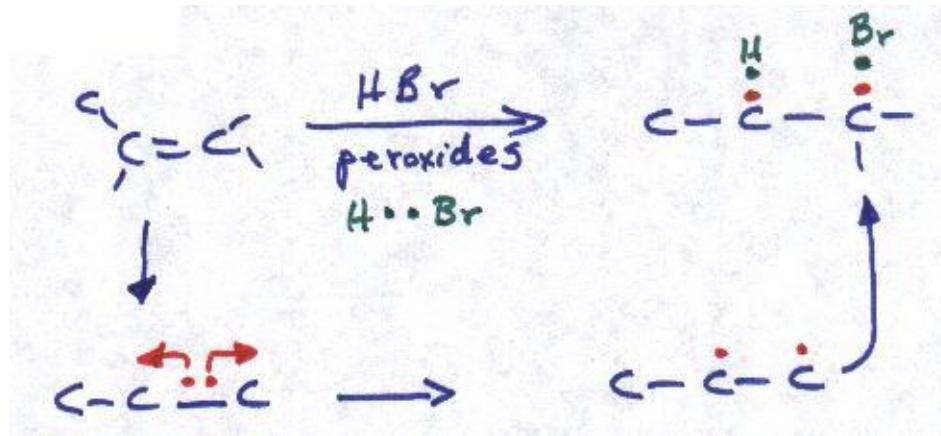
Molecular hydrogen requires a catalyst such as Rainey nickel, Pt or Pd to add across a double bond. The reason for this is that the molecular hydrogen spreads out across the powdered catalyst and "separates" into atomic hydrogen, making it more reactive. In the course of the reaction regarding 2-butene, the bond polarizes and the two electrons in one of the bonds are repelled forming a reactive radical on carbons 2 and 3. The atomic hydrogen reacts with these reactive moieties forming (reducing the alkene to) the alkane, butane.

Hydrohalogenation -- #1
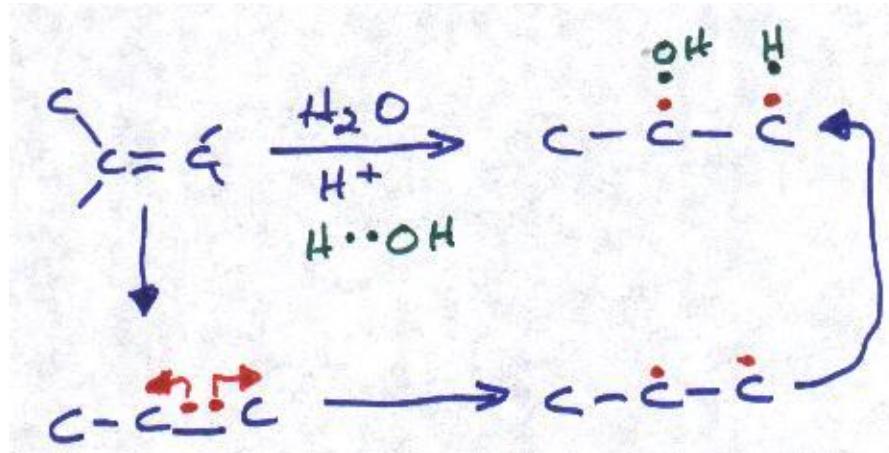
The use of a hydrohalic acid to add across the double bond, reducing the alkene to a haloalkane, may be performed under two conditions where HBr is concerned. The first is without the presence of peroxides. In this case, the H in the HBr adds to the carbon in the double bond with the most hydrogen atoms on it and the Br adds to the carbon in the double bond with the least number of hydrogen atoms. This is called Markovnikov addition. In short: them that has, gets! Or, the rich get richer. This means that the carbon in the double bond that is richer in hydrogen atoms gains the hydrogen atom from the HBr. The short version is that the bond polarizes and the Br separates (dissociates) from the H so that they may react with the reactive portions of the radical. The product of this reaction with propene is 2-bromopropane.

Hydrohalogenation -- #2

The second is an interesting phenomenon that seems to occurs **only with HBr**: in the presence of peroxides, the H and the Br react in an anti-Markovnikov fashion, i.e., the rich don't get richer. Or, them what don't have, gets. Using propene, again, when peroxides are present, the product is 1-bromopropane.
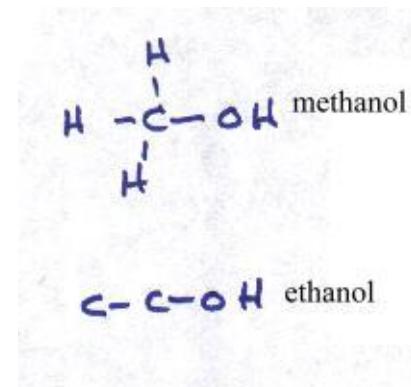
Hydration

•Is the addition of water (HOH) across the double bond.
•This reaction occurs in a Markovnikov manner and requires a mineral acid as the catalyst. The OH reacts with the 2d carbon in the double bond and the H reacts with the first carbon in the double bond.
•The product is, by common name, isopropyl alcohol or, by IUPAC, 2-propanol.
•Organic compounds that contain the OH group are called alcohols.
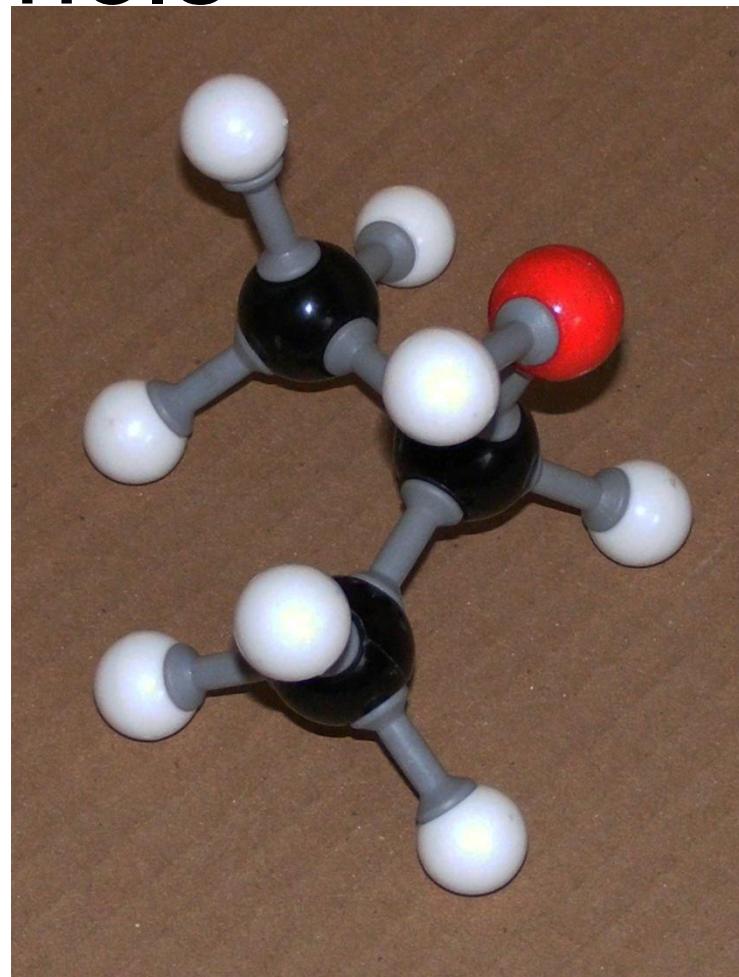
Alcohols
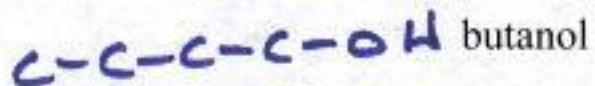
- Although they are a bit out of sequence, since they have been mentioned, above, we'll discuss alcohols at this time.

- Alcohols consist of carbon, hydrogen and oxygen.

- They are named by the same rules we've already discussed with one addition: by IUPAC, the name of an alcohol ends in "ol".

- The simplest alcohol is methanol (CH_3OH). Methanol (methyl alcohol by common name) is named as follows: "meth" for one carbon, "an" for the alkane and "ol" for the OH group.

- Ethanol (ethyl alcohol by common name), C_2H_5OH, has two carbons, all single carbon-carbon bonds and the OH group.
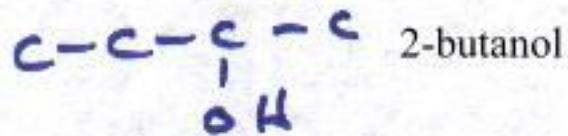
"Prop" alcohols

- Like the alkyl radicals, the alcohols have isomers that follow the radicals. In the propyl alcohol family, there are two isomers: 1-propanol (n-propyl alcohol by common name) and 2-propanol (isopropyl alcohol by common name). The numbers tell you where the OH group is on each isomer.

- Image, right, is of isopropyl alcohol or 2-propanol
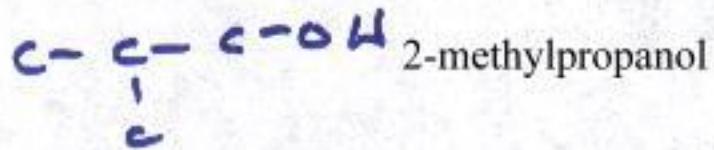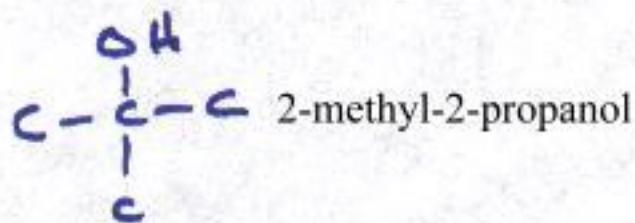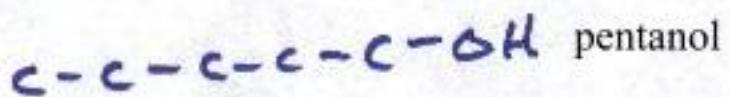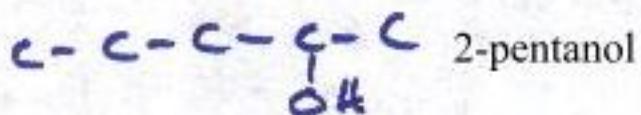
C-C-C-C-OH butanol

C-C-C-C 2-butanol
      |
      OH

C-C-C-OH 2-methylpropanol
    |
    C

    OH
    |
C-C-C 2-methyl-2-propanol
    |
    C

• Like the alkyl radicals, the alcohols have isomers that follow the radicals. In the propyl alcohol family, there are two isomers: 1-propanol (n-propyl alcohol by common name) and 2-propanol (isopropyl alcohol by common name). The numbers tell you where the OH group is on each isomer.
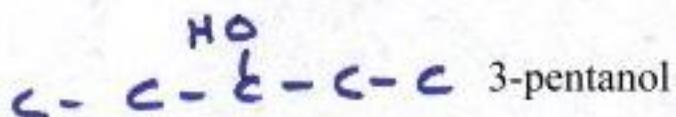
• In the butyl alcohol family, there are 4 isomers: 1-butanol (n-butyl alcohol by common name), 2-butanol (sec-butyl alcohol by common name), 2-methyl-1-propanol (iso-butyl alcohol by common name) and 2-methyl-2-propanol (t-, tert- or tertiary butyl alcohol).

$C-C-C-C-C-OH$ pentanol

$C-C-C-\underset{OH}{C}-C$ 2-pentanol

$C-C-\overset{HO}{C}-C-C$ 3-pentanol
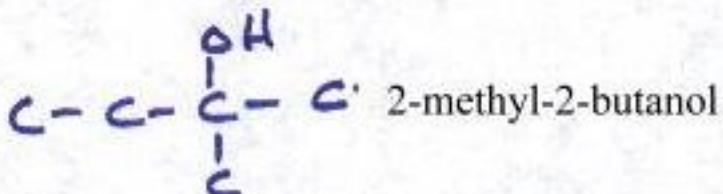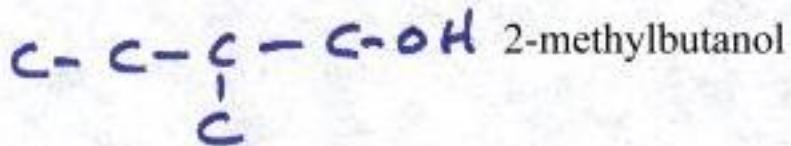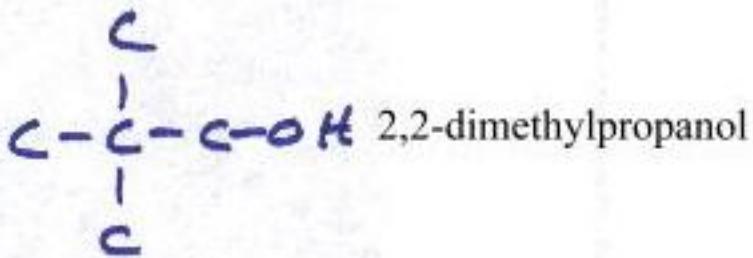
$C-C-\overset{OH}{\underset{C}{C}}-C$ 2-methyl-2-butanol

$C-C-\underset{C}{C}-C-OH$ 2-methylbutanol
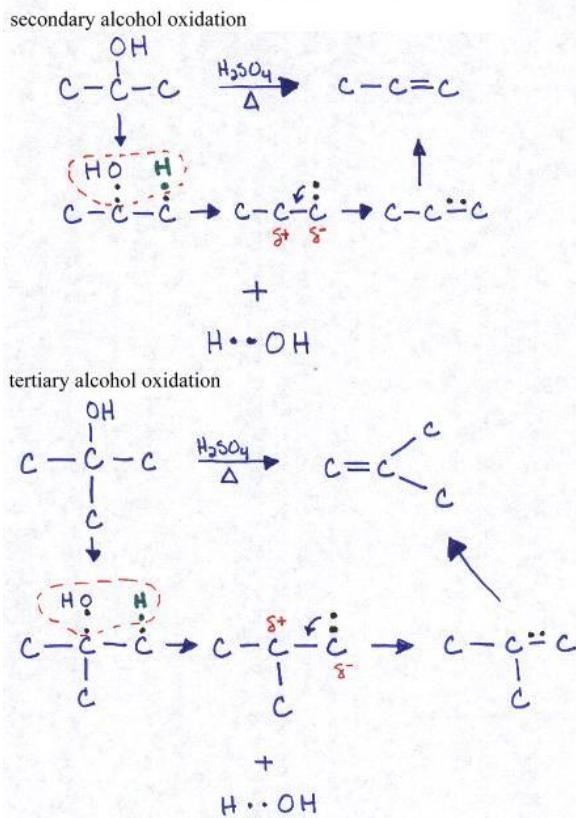
$C-\overset{C}{\underset{C}{C}}-C-OH$ 2,2-dimethylpropanol

•In the pentyl family, there are 6 isomers:
•1-pentanol (n-pentyl alcohol by common name),
•2-pentanol (sec-pentyl alcohol by common name),
•3-pentanol,
•2-methyl-1-butanol (isobutyl alcohol by common name),
•2,2-dimethyl-1-propanol (neopentyl alcohol by common name) and
•2-methyl-2-butanol (t-, tert- or tertiary-pentyl alcohol by common name).

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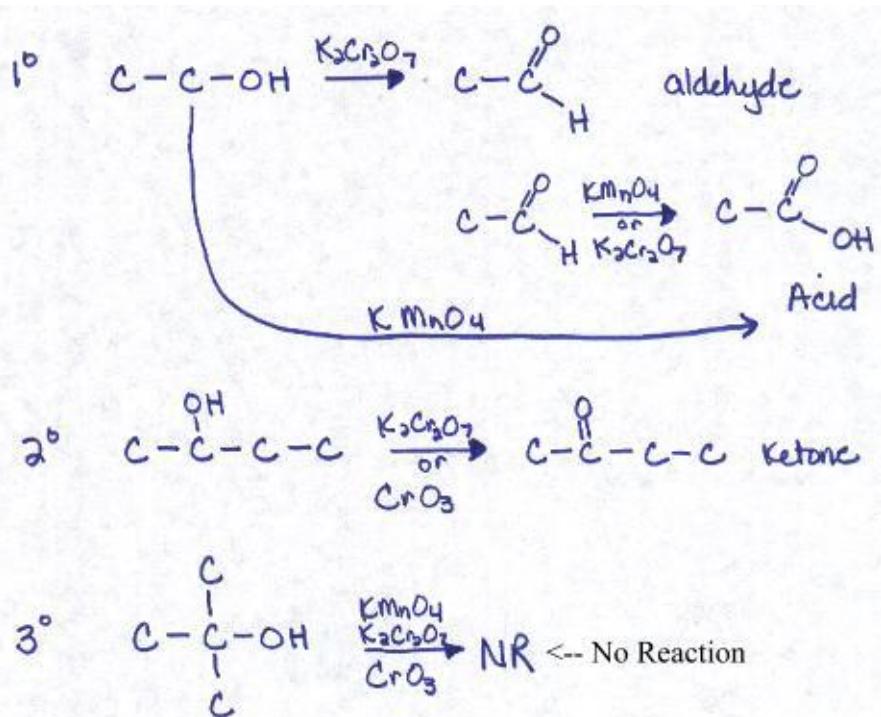
- The reactions of alcohols with which you need to be well versed are two: Dehydration and Oxidation.

Dehydration Reactions

•When dehydrating alcohols, the bottom line is two-fold: 1) tertiary alcohols are more reactive than secondary and secondary alcohols are more reactive then primary alcohols and 2) water is always removed in dehydration reactions.

• The dehydration of primary, secondary and tertiary alcohols follows the same general principles. The reaction requires heat and sulfuric acid. The OH is always lost as the hydroxide ion and the H is always removed as the proton -- note that $H^+ + OH^- \rightarrow HOH$. In general, the hydroxide ion and proton "lasso" each other leaving a negatively charged carbon ion behind (carbanion) where the proton was removed and a positively charged carbon ion behind (carbocation) where the hydroxide ion was removed.

•Since opposite charges attract, the two electrons on the carbanion "flip" down onto the carbocation, "sealing" the bond and leaving us with the alkene product, e.g., propene, propene and 2-methylpropene per the graphic in order.

Oxidation of Alcohols

•There are 3 general rules about which you need to know:
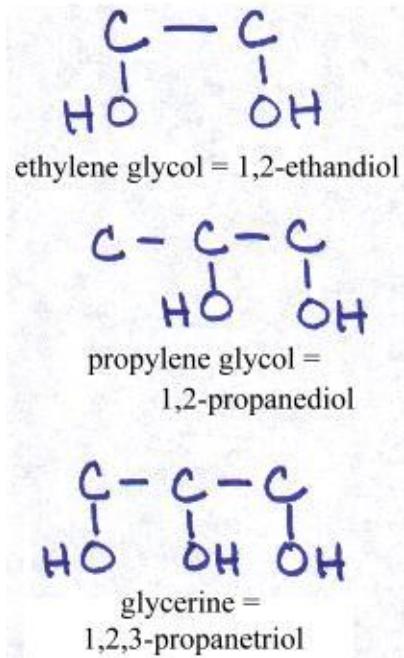
•1) primary alcohols are oxidized to aldehydes which may be oxidized to acids,

•2) secondary alcohols are oxidized to ketones and

•3) tertiary alcohols either do not react or explode violently.

•Oxidizing agents include potassium dichromate, potassium permanganate or chromium (VI) oxide.

•As you can see in the graphic, ethanol may be oxidized in a step-wise manner to ethanal (acetaldehyde by common name) which may then be oxidized to ethanoic acid ("eth" for 2 carbons, "an" for the alkane and "oic" as it's an organic acid; common name is acetic acid).

•2-butanol is directly oxidized to 2-butanone ("but" for 4 carbons, "an" for the alkane and "one" for the ketone; the "2" tells us that the double bonded oxygen atom is bonded on carbon number 2; the common name for this compound is methyl ethyl ketone or MEK). T-butyl alcohol, of course, doesn't react.

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Diols and Triols

ethylene glycol = 1,2-ethandiol

propylene glycol = 1,2-propanediol

glycerine = 1,2,3-propanetriol
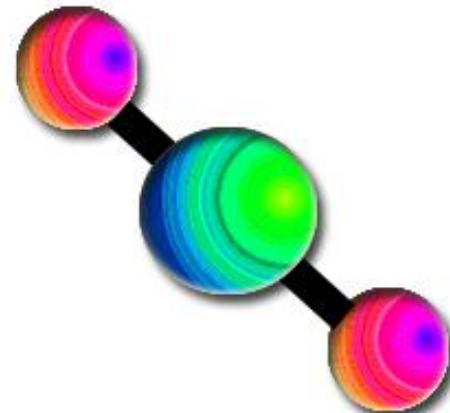
• Alcohols don't just come as a single OH group on a hydrocarbon. Sometimes there are 2 OH's (diols) or 3 OH's (triols).

• 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

- 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. Note that both pyran and furan each have an oxygen atom in the closed ring. At each corner is a carbon atom.

- Carbohydrates are generally seen as sources of quick energy. They consist of carbon, hydrogen and oxygen. 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.

- Carbohydrates will be discussed later in this course.
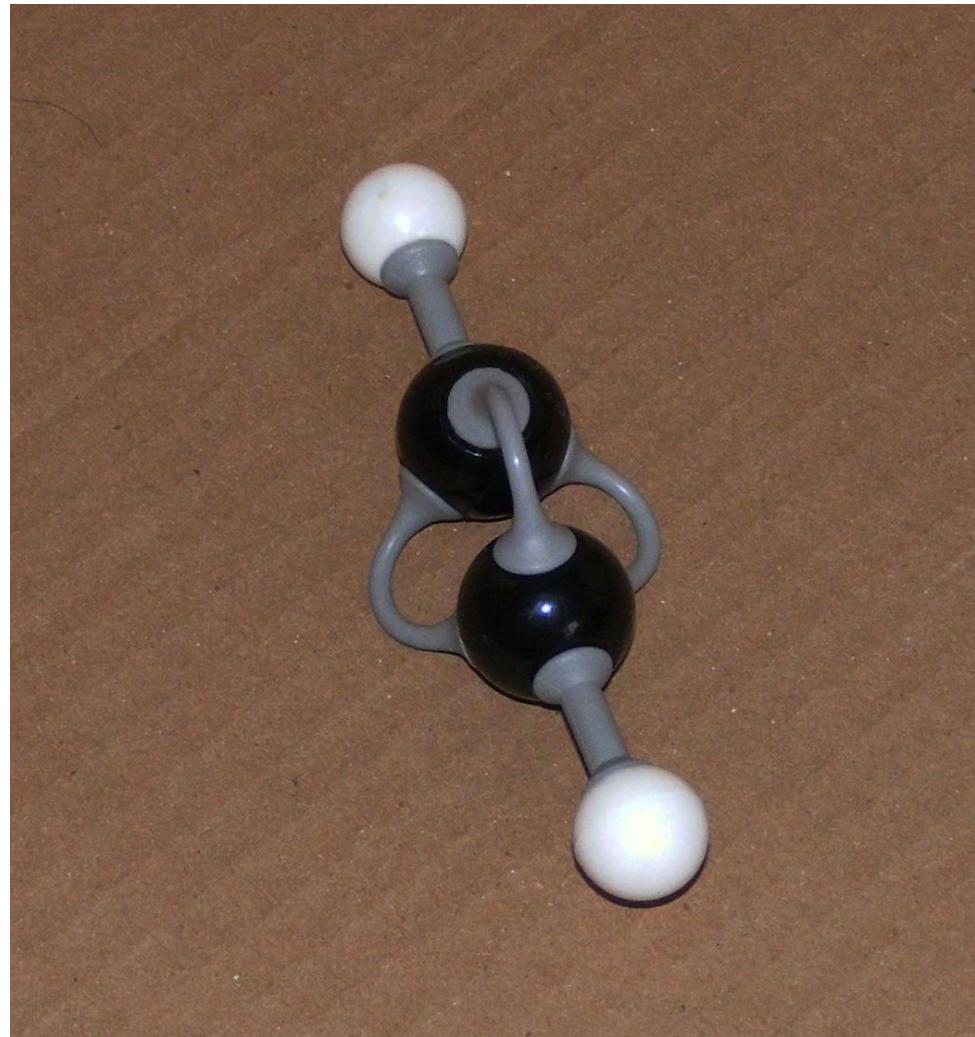
Alkynes
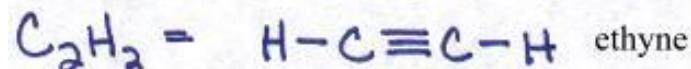
- Getting back into sequence with the hydrocarbons, our next functional group for discussion is the alKYNES.

- The general formula for the alkynes is C_2H_{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.
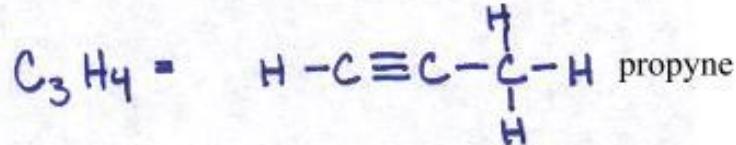
Ethyne

- The simplest alkyne is ethyne -- "eth" for 2 carbons and "yne" for the triple bond.

- The common name for ethyne is acetylene.

$C_2H_2 =$ $H-C\equiv C-H$ ethyne

$C_3H_4 =$ $H-C\equiv C-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}-H$ propyne

$C_4H_6 =$ $C-C\equiv C-C$ 2-butyne

   $C\equiv C-C-C$ butyne

$C_5H_8 =$ $C\equiv C-C-C-C$ pentyne

   $C-C\equiv C-C-C$ 2-pentyne

$C_6H_{10} =$ $C\equiv C-C-C-C-C$ hexyne

   $C-C\equiv C-C-C-C$ 2-hexyne
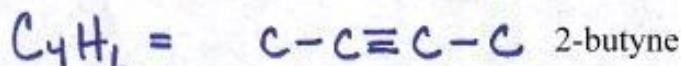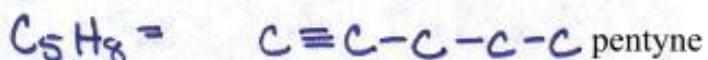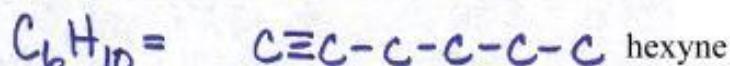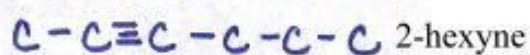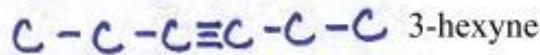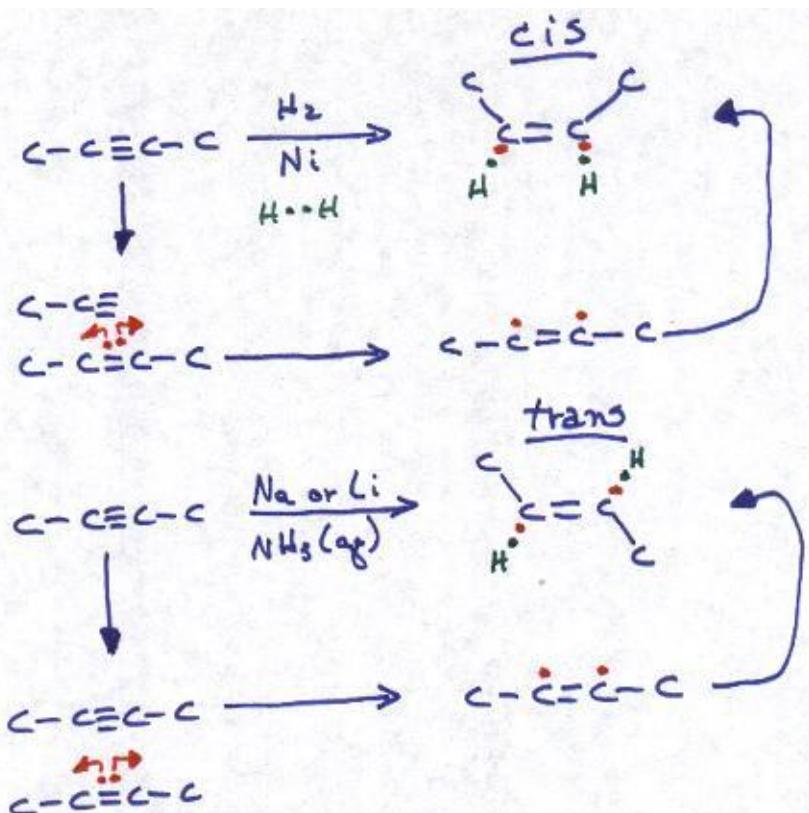
   $C-C-C\equiv C-C-C$ 3-hexyne

   + various isomers

•The next simplest alkyne is propyne.
•Once we get past propyne, we move into the alkynes that have isomers.
•In the butyl alkyne family, there are 2 isomers: 1- and 2-butyne where the triple bond is between carbons 1 and 2 and carbons 2 and 3, respectively.
•Likewise, the pentyl family has two continuous chain isomers: 1- and 2-pentyne.
•The hexyl family of alkynes is more complex and only a few isomers are shown for examples.

- There are two general kinds of reactions that you need to be aware of with alkynes: hydrogenation (reduction of the triple bond) and hydration.
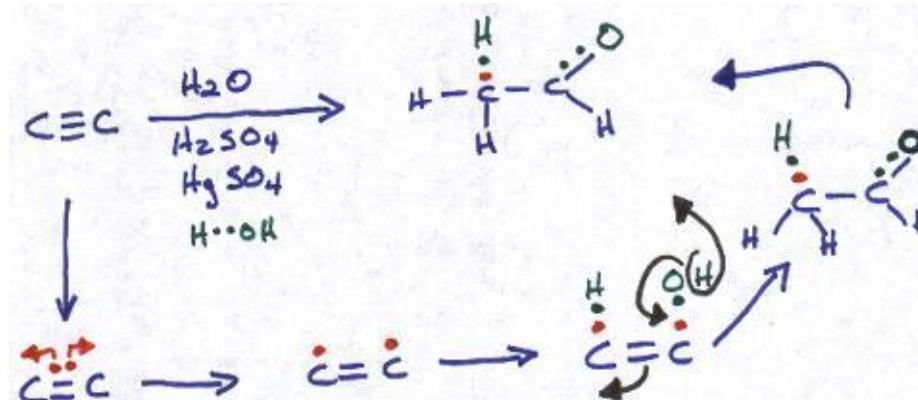
Hydrogenation

•The first is the hydrogenation of an alkyne with molecular hydrogen and Rainey Ni to reduce the alkyne to the cis alkene isomer, top. Again, simple mechanistics are used so that you can see the, more or less, elementary movement of electrons and bonds.
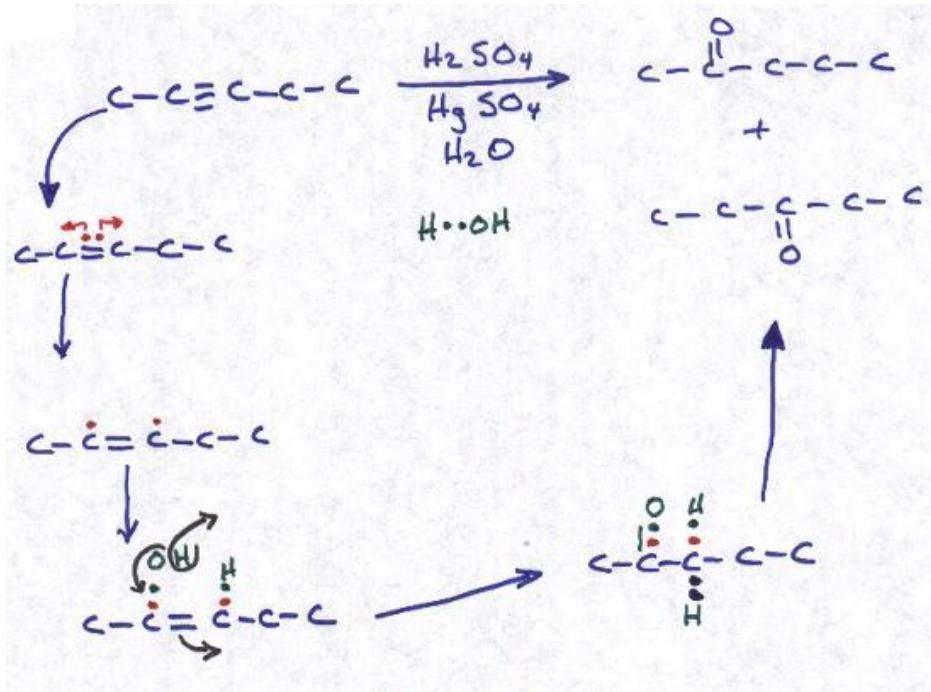
•The bottom of the figure shows the other hydrogenation reaction: the utilization of either sodium or lithium with aqueous ammonia to form the trans alkene isomer. This mechanism is not understood.

Hydration Reactions -- #1

•The production of an aldehyde from an alkyne is illustrated above.
•Ethyne reacts with water, sulfuric acid and mercuric sulfate to form ethanal (common name acetaldehyde; "eth" from 2 carbons, "an" for the alkane and "al" for the aldehyde functional group).
•In a nut-shell, two electrons in one of the pi bonds polarize and repel each other forming a reactive alkenyl group. Water reacts at each radical to form an alcohol-like intermediate. Simultaneously, the proton on the OH leaves. The 2 electrons left behind by the proton loss "flip" down to bond with the carbon atom. Since carbon can only take 4 bonds, one bond has to give somehow.
•The remaining pi bond then "flips" down much like how dominoes push each other over. The two electrons that just flipped down bind the proton, completing the reaction.

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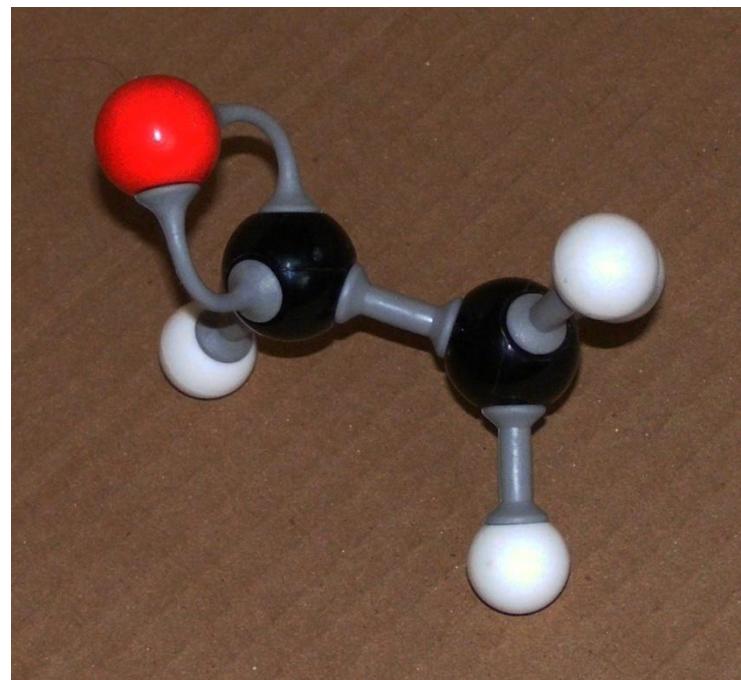
Hydration Reactions -- #2
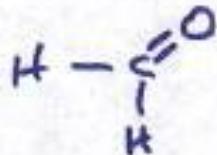
 In the case of an intra chain (i.e., mid-chain) triple bond, the mechanism is pretty much the same, albeit inside the carbon chain rather than on the end of the carbon chain. The products, though, are 1) different and 2) more than one. The products are ketones and there will be a mixture of two products. The first product from the reaction of 2-pentyne is 2-pentanone and the second product is 3-pentanone. "Pent" from 5 carbons, "an" for the alkane and "one" for the ketone; the numbers tell you that the double-bonded oxygen is on carbon #2 and carbon #3, respectively.

Aldehydes
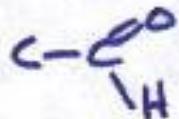
•The functional group of an aldehyde is an end carbon that is double bonded to an oxygen and single bonded to a hydrogen atom.

•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
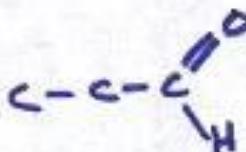
Aldehydes
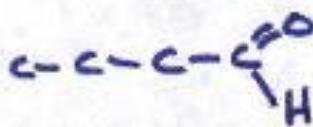
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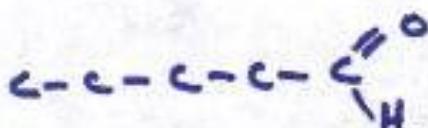
ethanal
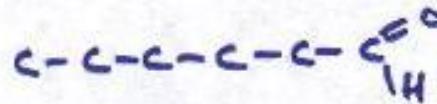
propanal
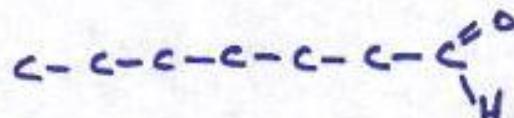
butanal
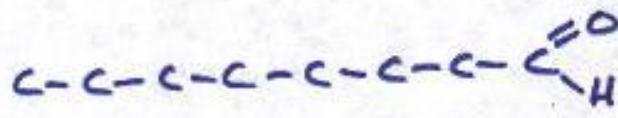
pentanal
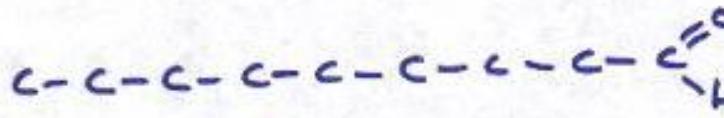
hexanal
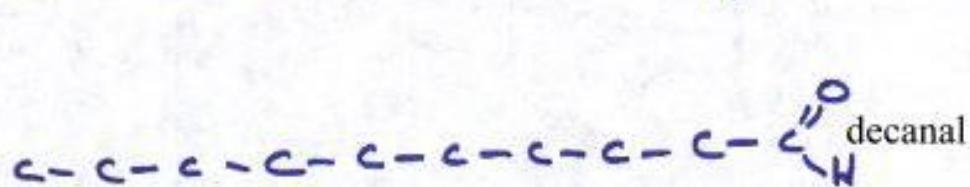
heptanal

octanal

nonanal

decanal

117
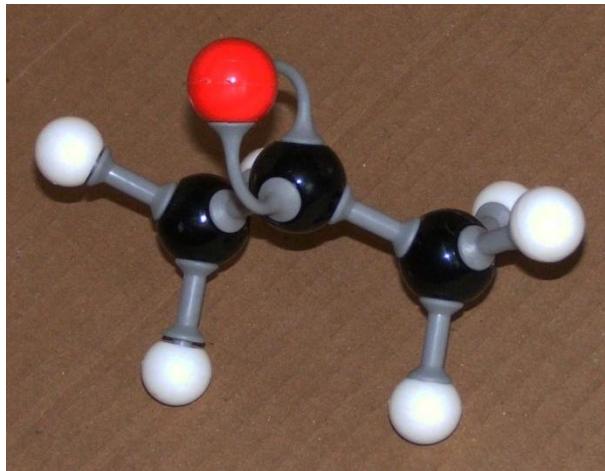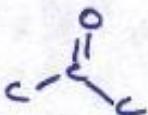
Ketones

- 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.
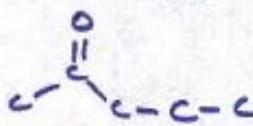
Ketones
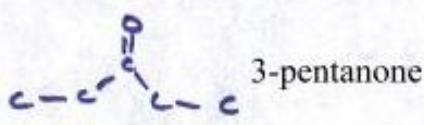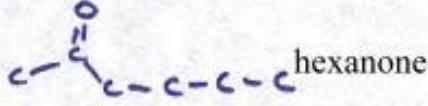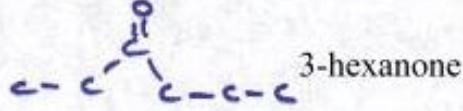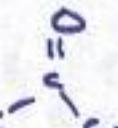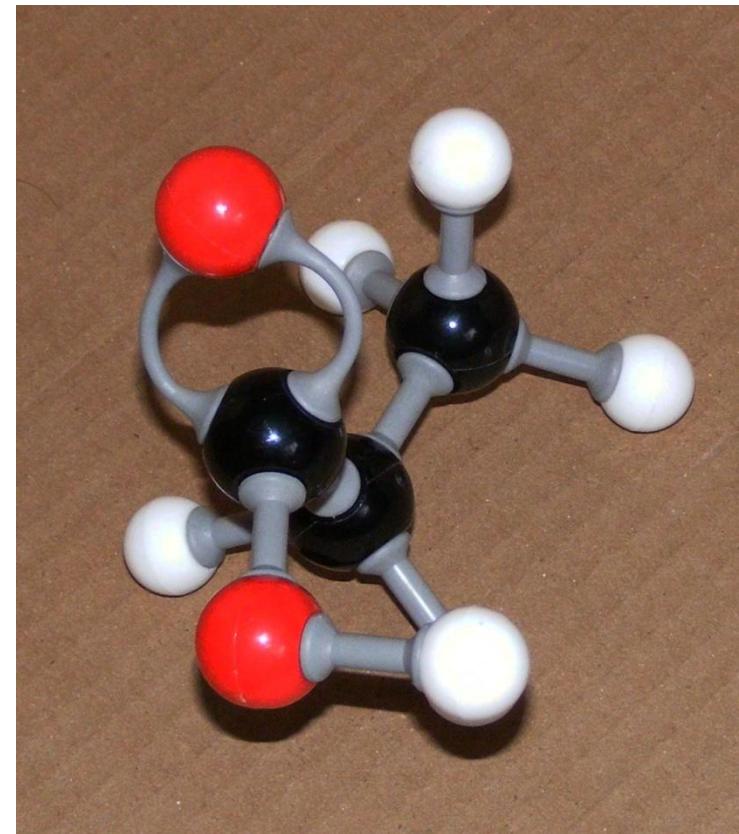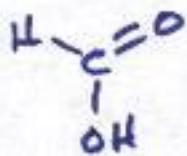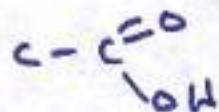
Carboxylic Acids

- The functional group of the organic acids is the end carbon double bonded to an oxygen and single bonded to an OH group.

- 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.
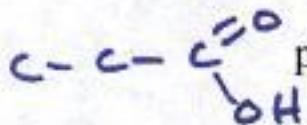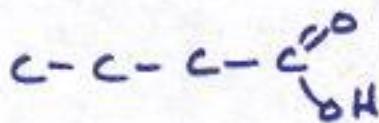
methanoic acid (formic acid)
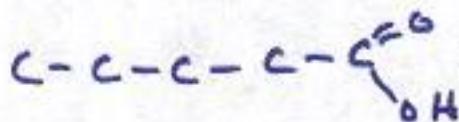
ethanoic acid (acetic acid)
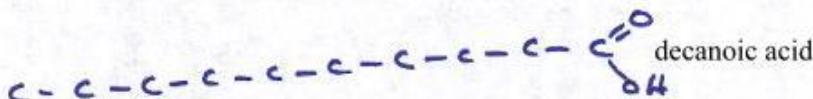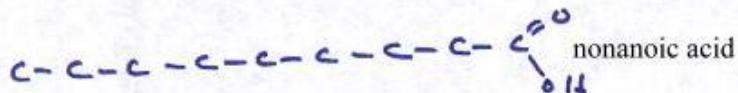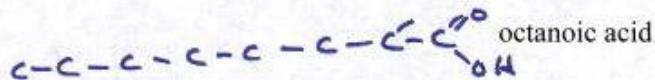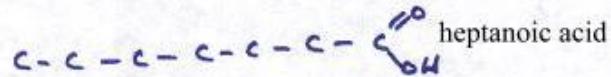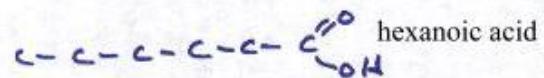
propanoic acid

butanoic acid

pentanoic acid

IUPAC Name of Acid	Common Name
Methanoic Acid	Formic acid
Ethanoic Acid	Acetic acid
Propanoic Acid	Propionic acid
Butanoic Acid	Butyric acid#
Pentanoic Acid	Valeric acid

from butyrium for butter

hexanoic acid

heptanoic acid

octanoic acid

nonanoic acid

decanoic acid

Hexanoic Acid	Caproic acid*
Heptanoic Acid	
Octanoic Acid	Caprylic acid*
Decanoic Acid	Capric acid*

*from Capricorn, the goat -- first isolated in goat urine or blood, depending on the author

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	Tetradecanoic acid	Hexadecanoic acid	Octadecanoic acid
found in coconut oil	found in coconut oil	found in lard	found in lard

More on these compounds later in the course.
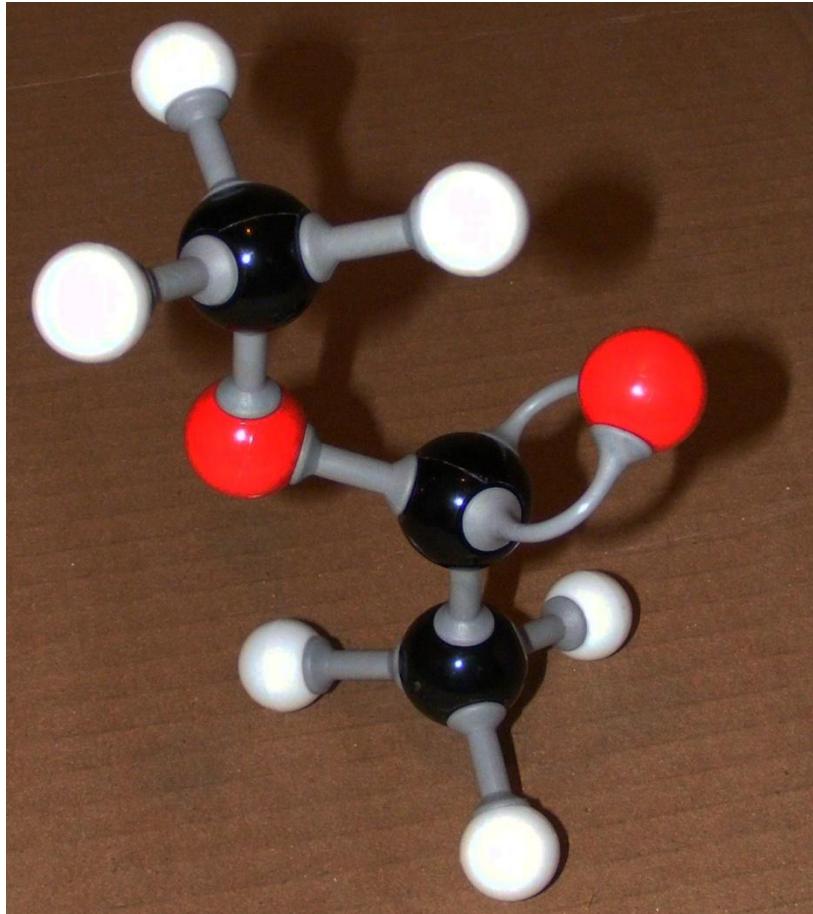
Fatty Acids – Special Carboxylic Acids – Un-Saturated

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	n-3 or ω 3	n-6 or ω 6	n-6 or ω 6
found in corn oil, soybean oil, cottonseed oil	found in leafy vegetables and vegetable oils	found in leafy vegetables and vegetable oils	found in peanut oil, brain/nervous tissue

More on these compounds later in the course.
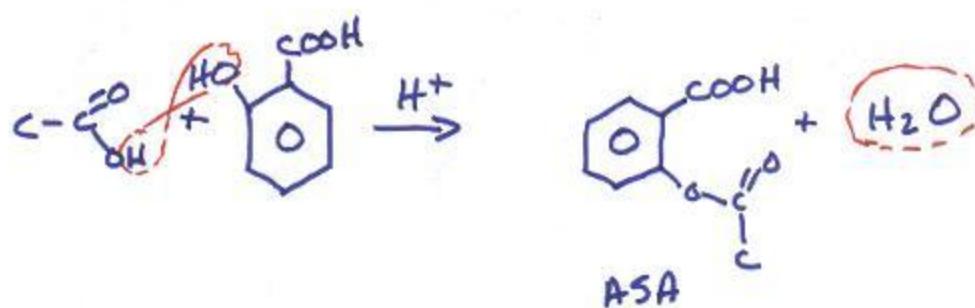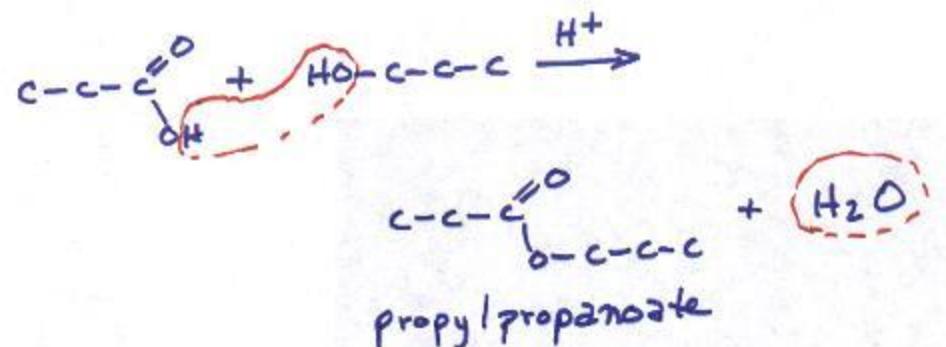
Esters

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

Esters

- To name the ester formed between propanoic acid and propanol, name the alcohol root first ("propyl"), then name the acid root ("propano") and add "ate" to the name, hence, propyl propanoate.
- Aspirin is another example of an ester (an ester has a hydrogen or a hydrocarbon on the acid side and a hydrocarbon on the alcohol side of the carboxyl group): acetylsalicylic acid, bottom.
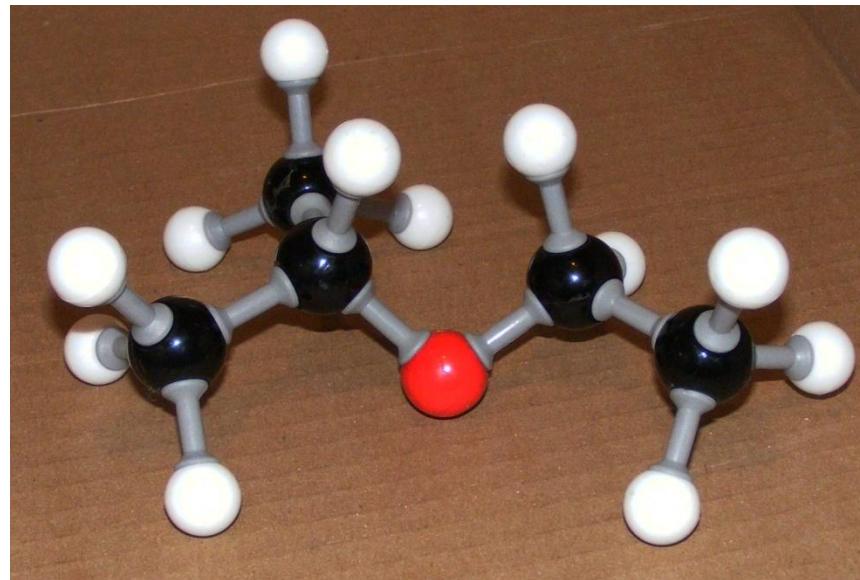
A Few Notable Esters

Esters	
Amyl acetate	Banana oil
Ethyl butyrate	Pineapple
Amyl butyrate	Apricots
Octyl acetate	Oranges
Isoamyl valerate	Apples

Esters are also used in perfumes, drugs and finger nail polish remover.
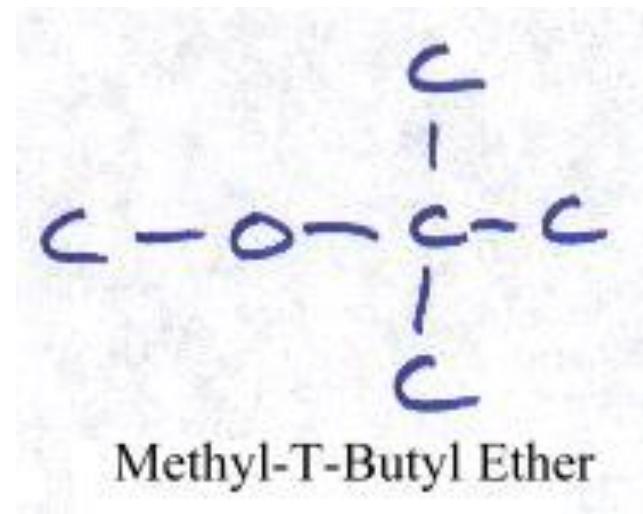
Ethers

- 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

MTBE

- An ether that has been in the news in the past is MTBE (methyl-t-butyl ether). MTBE was originally used for a gasoline additive to reduce emissions and smog in winter time in areas like Reno, NV. While it worked, it seems that since it was discovered to be leaking from underground gas tanks at filling stations at Lake Tahoe that a huge flurry about the potential for it to be disease causing or carcinogenic has erupted.

- MTBE was also used experimentally -- and may still be -- to dissolve gallstones that were made up primarily of cholesterol. The gall bladder would be visualized by ultrasound, then a needle would be introduced across the abdominal wall into the gall bladder and the MTBE would be injected into the gall bladder. The stone would dissolve within a couple of hours and be excreted in the bile through the small bowel. At the time, there were no known side effects of this treatment.

- It remains to reputable scientists to demonstrate whether or not MTBE causes disease or cancer without any external biasing pressures.

Methyl-T-Butyl Ether

Waxes

- Remember from earlier lectures that esters are formed from the reaction of an organic acid with an alcohol.
- We briefly discussed some of the lower molecular weight (MW) esters at that time.
- The higher MW esters are solid waxes.
- Examples include
    - ceryl cerotate ($H_3C(CH_2)_{24}COO(CH_2)_{25}CH_3$; in carnauba wax) and
    - myricyl palmitate ($H_3C(CH_2)_{14}COO(CH_2)_{29}CH_3$; in beeswax; aka triacontonyl palmitate).
- Ceryl cerotate consists of 2 hydrocarbon chains equal in length and that are long -- this imparts hardness to the wax.
- Myricyl palmitate consists of 2 hydrocarbon chains, one of which is about half the length of the other -- this imparts a softer property to the wax.

Spermaceti is rich in palmitoyl palmitate. This is an oil in the "wax family" that burns well in an oil lamp. It is a liquid wax by virtue of the shortness of the hydrocarbon chains on either side of the ester linkage.
Waxes are found on plant leaves and fruits, animals, algae, fungi and bacteria. All waxes are, not surprisingly, hydrophobic and consist, in general, of the following in the table, below:

n-alkanes	Ketones	Diketones
1° alcohols	2° alcohols	Aldehydes
Alkanoic acids	Terpenes	Mono-esters
All contain 12 to around 38 carbons in their chains.		

- "Wax" comes from the Old English "weax" which described the honeycomb of bee hives.
- Beeswax may, semantically, be viewed as the original, reference, wax.
- A generic definition of waxes is that they are esters of an alcohol (not to include glycerol), e.g., long chain (LC) alcohols, sterols, carotenoids, and a long hydrocarbon chain acid.
- As you might expect, waxes are saponifiable and are somewhat soluble in aromatic solvents, $CHCl_3$, R-O-R', esters and ketones.

- Waxes may be sub-categorized into three groups:
  - Animal,
  - Vegetal and
  - Mineral waxes.

Animal Waxes				
Beeswax	Chinese wax	Shellac wax	Whale spermaceti	Lanolin
-- secreted from 4 pairs of glands on the ventral surface of the worker bee abdomen -- color is dependent on the flowers visited by the bees -- primarily lemon yellow -- easily saponifiable and emulsifiable -- ~7000 tons/year produced -- 60% used for cosmetic and pharmacy industries	-- secreted by Coccus ceriferus and laid on tree branches -- 1500 insects produce 1 g of this wax -- purified wax used for candles and polish	-- produced by Tachardia lacca of India -- used in varnish and can replace carnauba wax	-- collected from a cavity in the head of sperm whales -- no longer harvested by virtue of international regulations -- 3 tons spermaceti per 15 meter whale -- about 1 ton found in adipose tissue in a 15 meter whale -- can be fused with beeswax -- was used in cosmetic/pharmacy industries -- "synthetic" cetyl palmitate has replaced it	-- aka wool fat -- secreted by sheep sebaceous glands -- collected from crude wool by detergent washing -- used since ancient times for cosmetics and dermatologicals -- also used in the fabric, ink and lubricant industries

Vegetal Waxes	
Carnauba wax	Jojoba (ho HO ba) oil
-- aka "queen of waxes" -- secreted by leaves of Copernica prunifera cerifera: -- ~ 100 g/year/tree produced -- contains esterified fatty dialcohols ("strange") -- high melting point (82-88° C) -- used for shoe polish, floor/furniture polishes -- used for candy and gum glazes, cosmetics	-- fluid -- melting point ~6° C -- from seeds of Simmondsia chinensis: Euphorbiacae -- resistant to oxidation -- used in cosmetics (shampoo, anti-solar oils) -- sulfonated/hydrogenated oils are used for lubricants

Mineral Waxes
Ozocerite
-- found in Galicia (at the risk of being politically incorrect, this is a province in the NW of Spain), Russia, Iran and US -- melting point about 90° C -- used for lubricants, lipsticks and polishes and adhesives -- generally obtained from the fractional distillation of petroleum, shale oil, lignite, or coal

Beeswax

- The preponderance of available information regarding waxes other than candle waxes involves beeswax.
- To that end, more space is included, below, to explore this fascinating topic/substance.
- Beeswax, when collected, appears yellow to brown-yellow.
- When cold, it is brittle, hard and glossy.
- When warm, it is plastic and soft. For all practical purposes, it is water insoluble; partially soluble in cold alcohol and benzene; soluble in hot alcohol.
- Beeswax is listed a generally regarded as safe (GRAS) by the FDA.
- Beeswax is helpful to skin in various types of cosmetics.
- When mixed homogeneously with mineral oil or olive oil, the product soothes and protects skin.
- The coating left behind is soft and flexible.
- It resists water but may be removed with soap.

Lanolin and paraffin have largely replaced beeswax in cosmetics since World War II. A simple mixture for a cold cream is as follows:

Component	Parts
Bleached Beeswax	1
Water	2
Clear Mineral Oil	3
Borax	5

Heat the wax and oil to 71° C. Heat Borax and water to the same temperature. Mix the two mixtures together and let cool to 60° C. Add fragrance and let cool to 48.9° C and pour into jars.

- Beeswax is prepared by either draining or centrifuging the honeycombs.
- The combs are melted with steam, hot water or by the sun and strained.
- Beeswax is easily cleaned.
- Refining is accomplished by melting the wax in hot water that contains either H_2SO_4 or lye.
- (While beeswax is a slow burner and has a melting point (MP) of 61.7-66.1° C, it is extremely flammable. Over a burner, extreme caution, low heat and close attention are mandatory.)
- Beeswax floats on top of the hot water while impurities settle out.
- The melted beeswax may then be ladled off the top and stored in either stainless steel or plastic pans (paper milk cartons, plastic milk and juice jugs are good, too).
- These latter 2 components (H_2SO_4 and lye) extract impurities.
- (Aqueous NaOH also seems to be the only common solvent that will loosen beeswax from candle molds.)
- Common inorganic beeswax contaminant effects include darkening when in contact with containers composed of Fe, Al, Cu, Zn, Brass.
- The wax produced in this manner is called yellow beeswax.
- The yellow beeswax is bleached white with peroxides or (preferred) by sunlight.
- Only 0.454 to 0.907 kg of beeswax are produced per 45.4 kg of honey produced.
- The honeybee is the only source of beeswax.
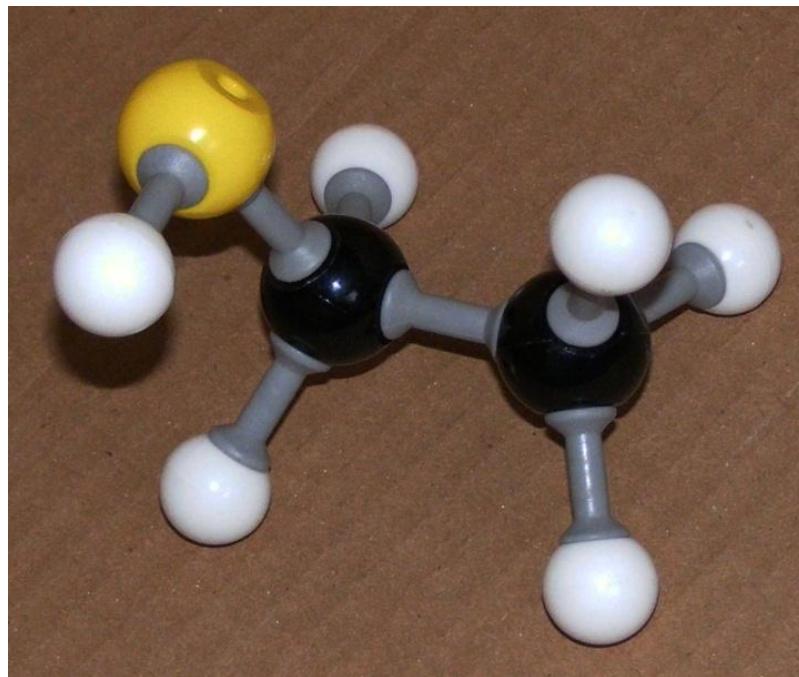
Specific Applications of Beeswax

The table, below, summarizes some specific uses of beeswax:

Automotive, textile, shoe manufacturing	Soft/glossy furniture and floor waxes	To wax nails to reduce wood splitting and bending of nails
Dental molds	Prevents rust formation on tools	Wax polishes for wood and leather
Waxing thread to make sewing easier and faster.		

NOTE: nails waxed with beeswax do not initially have the strength or bond with the wood to hold it together as well as a non-waxed nail. This changes with time as the beeswax wears off.

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.
- Image, above, is of thioethane.
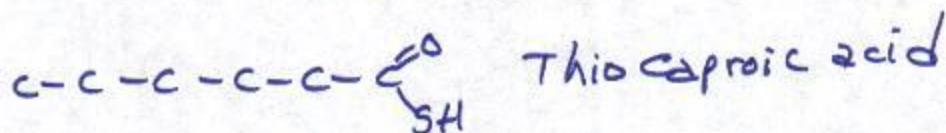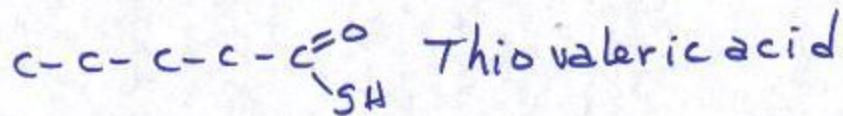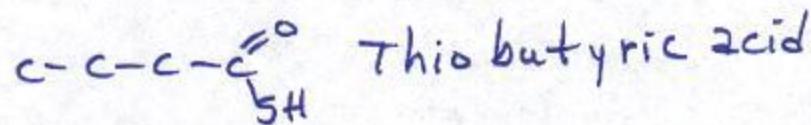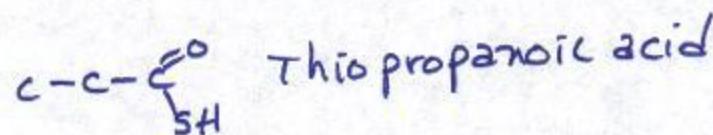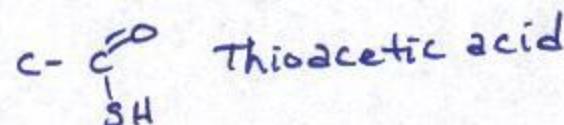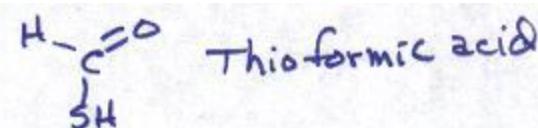
Thiols

- 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.

	common	IUPAC
H_3C-SH	"methyl mercaptan"	methanethiol
$C-C-SH$	ethyl mercaptan	ethanethiol
$C-C-C-SH$	n-propyl mercaptan	propanethiol
$C-C-C$ with SH on middle carbon	isopropyl mercaptan	propane-2-thiol

Thioacids

- Thioacids, instead of having a COOH group, have a COSH group. 6 examples of thioacids are to the right:

Nitrogen Containing Compounds:

Nitro Compounds, Amines, Amides
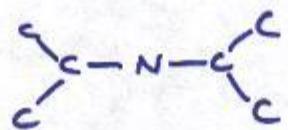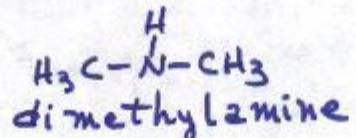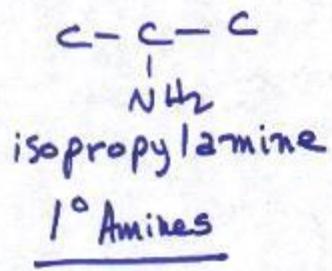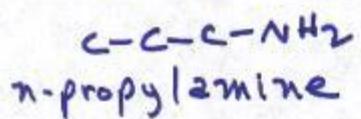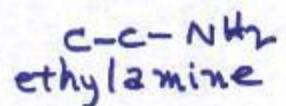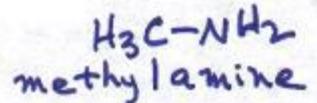
Nitro Compounds

- The functional group of this group of compounds for this course is R-O-NO$_2$ where R is a hydrocarbon. The illustrative nitro compound is nitrogylcerin. It's synthesis, is driven by reacting glycerine, nitric acid and a catalyst to form the nitroglycerin and water. Besides being used as an explosive, it is also used as a vasodilator for people with heart problems.

$$C-OH$$
$$C-OH + 3\ HO\ NO_2 \longrightarrow$$
$$C-OH$$

$$C-O\ NO_2$$
$$C-O\ NO_2 + 3H_2O$$
$$C-O\ NO_2$$
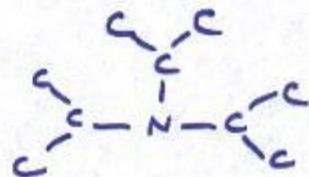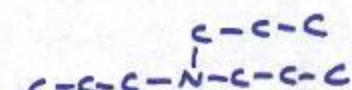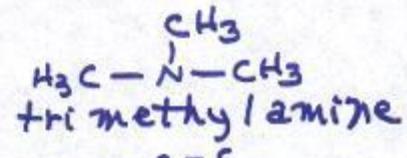
Amines

- 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.

H_3C-NH_2
methylamine

$C-C-NH_2$
ethylamine

$C-C-C-NH_2$
n-propylamine

$C-C-C$
  |
 NH_2
isopropylamine

1° Amines

$H_3C-\overset{H}{\overset{|}{N}}-CH_3$
dimethylamine

$C-C-N-C-C$

$C-C-C-N-C-C-C$

2° Amines

CH_3
 |
$H_3C-N-CH_3$
trimethylamine

$C-C$
  |
$C-C-N-C-C$

$C-C-C$
    |
$C-C-C-N-C-C-C$

3° Amines

147
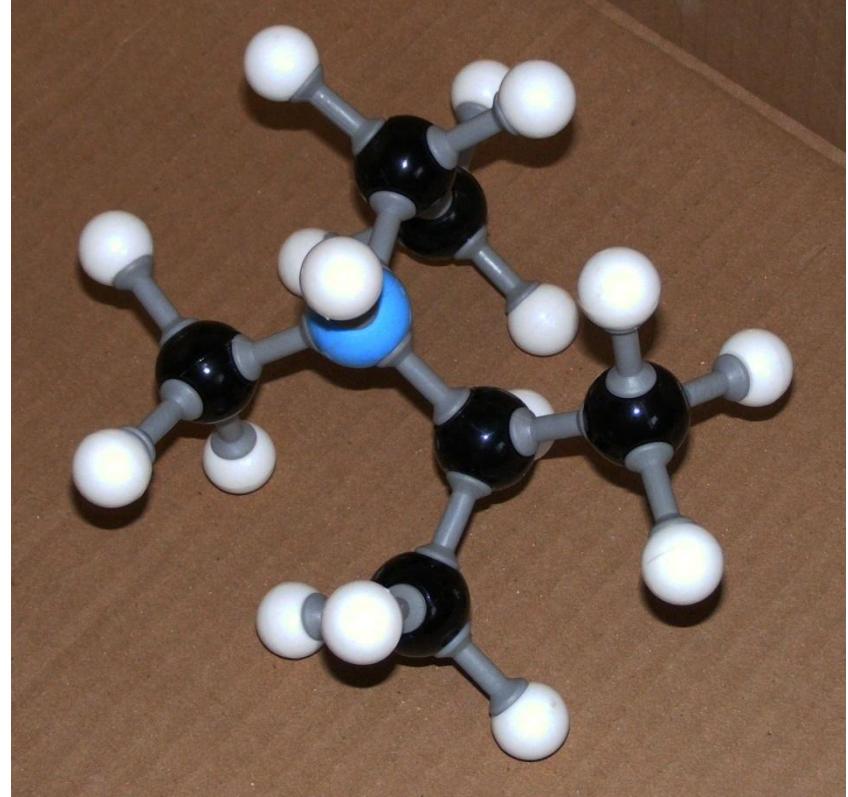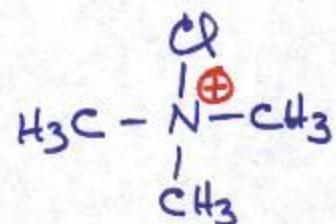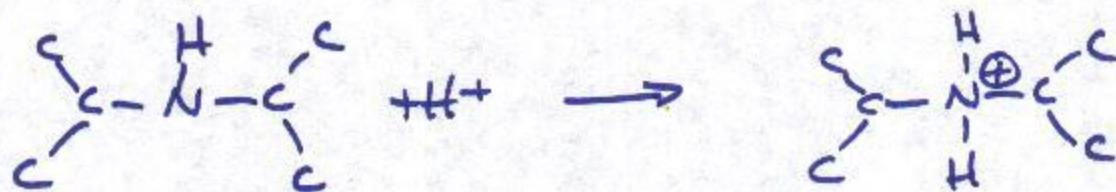
- Note needs to be made that these amines are insoluble in water. The simplest way in which to render these amines water-soluble is to add a bit of acid, protonating the nitrogen, making the ion polar -- remember, like dissolves like.

Image, above, is of the ethylisopropylmethylammonium ion

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$$C-NH_2 + H^+ \longrightarrow H_3C-\overset{\oplus}{N}H_3$$

$$C-C-NH_2 + H^+ \longrightarrow C-C-\overset{\oplus}{N}H_3$$
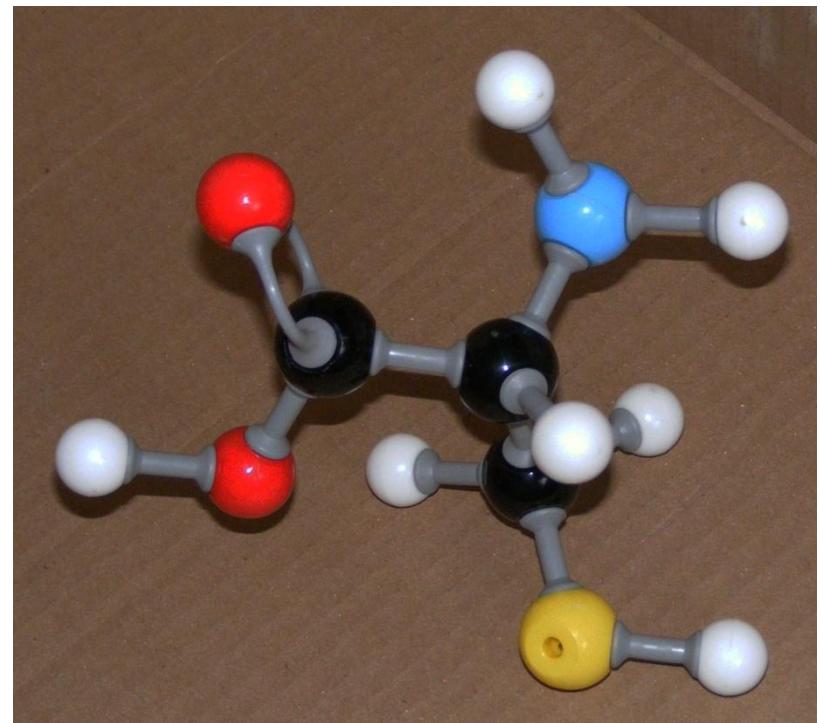
trimethyl ammonium chloride

Quaternary amine

149
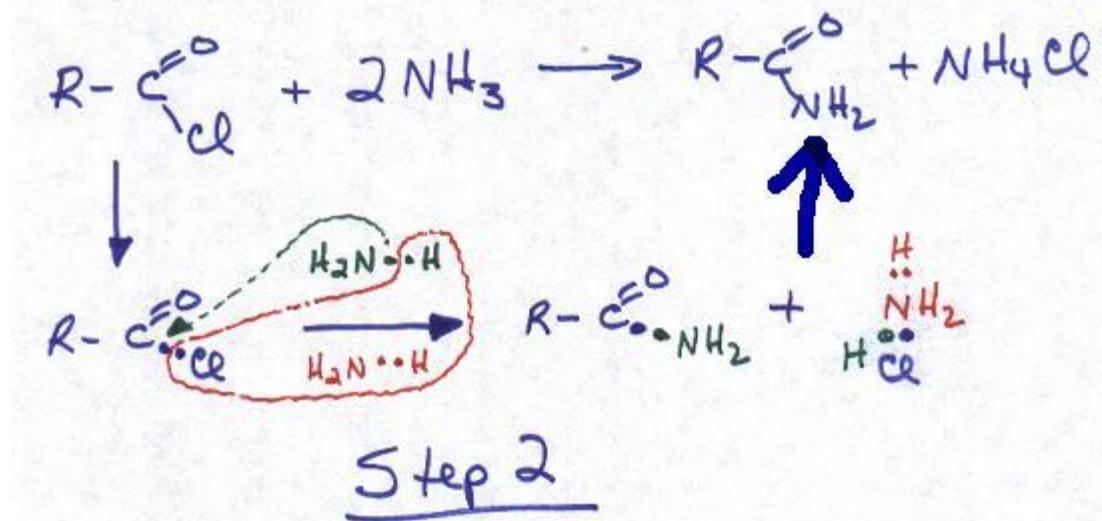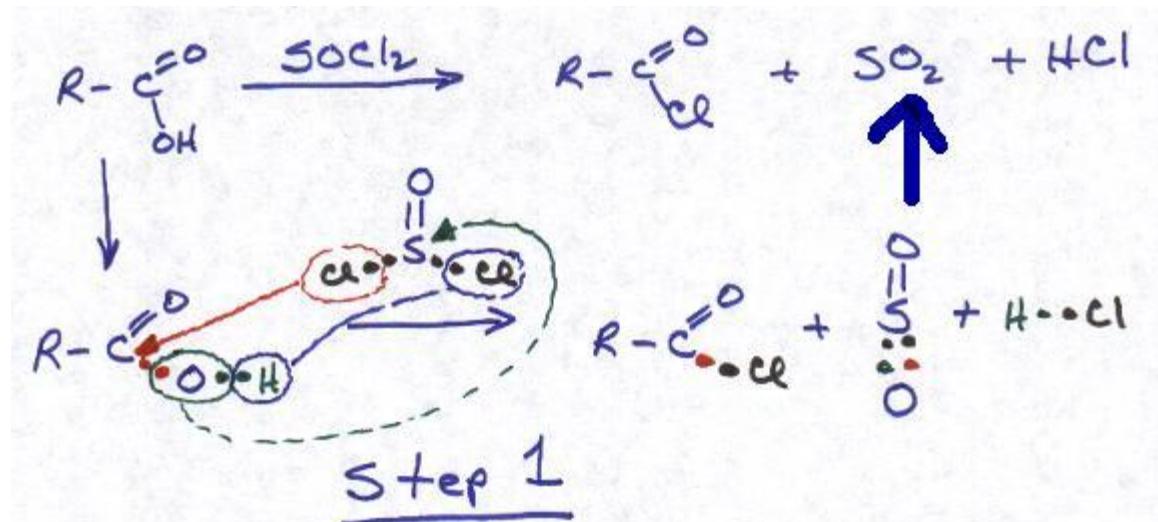
Amino Acids

- More in Biological Chemistry.

- 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
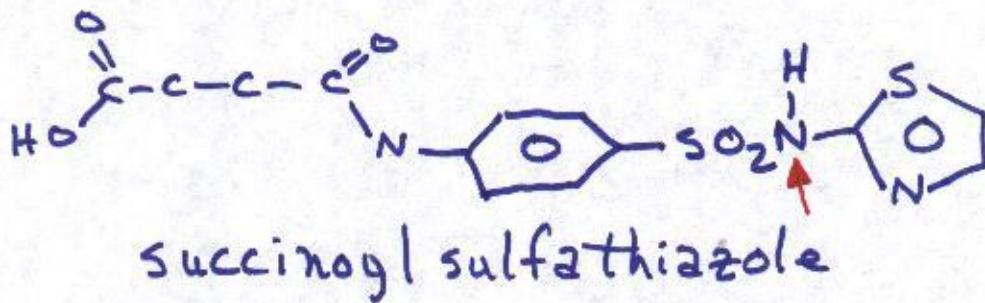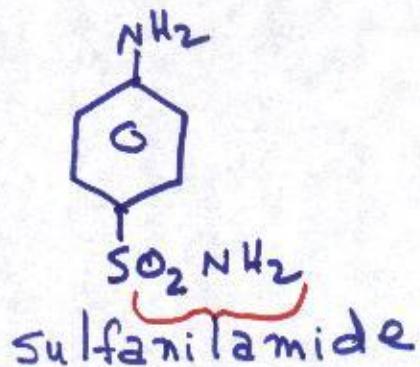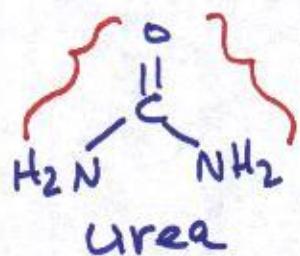
Amides

- 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.
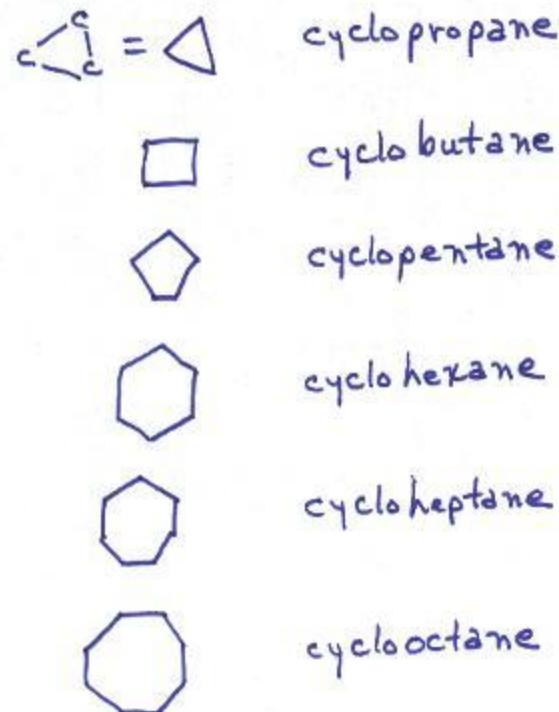
- The preparation of amides is a two step process. The first step is to react a carboxylic acid with thionyl chloride ($SOCl_2$). This forms an acid chloride (R-COCl in the graphic) SO_2 and HCl. The general mechanism is that one chlorine atom reacts with the hydrogen in the COOH group as the oxygen atom in the OH part of the COOH reacts with the sulfur and the other chlorine atom reacts with the CO . The second step is to react the acid chloride (R-COCl) with ammonia to form the amide and ammonium chloride. The elementary mechanism is that as the chlorine atom in the acid chloride reacts with one mol of ammonia and a hydrogen atom, the remaining NH_2 reacts with the R-CO to form the amide.

- Mechanism is on following slide.

Step 1

Step 2

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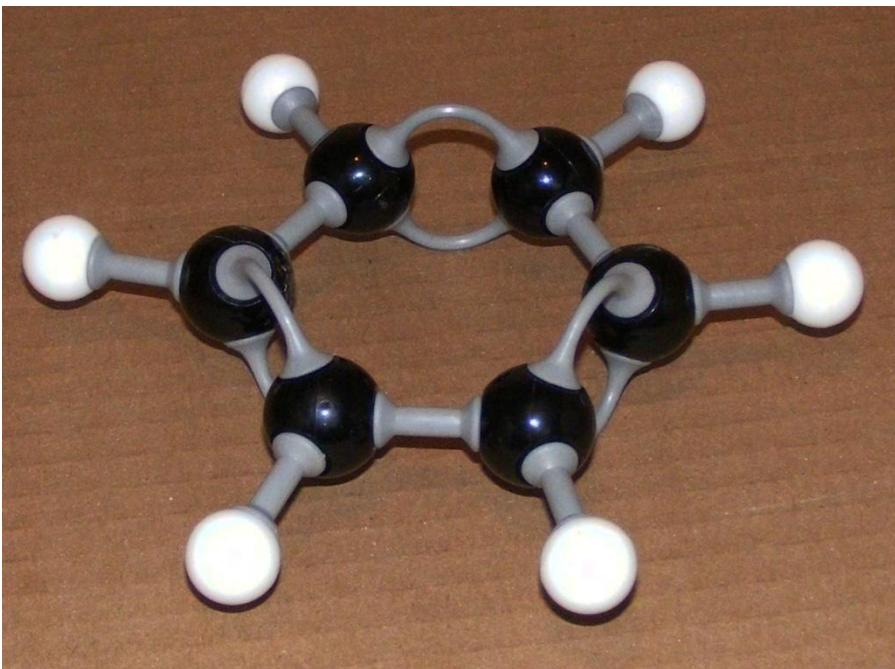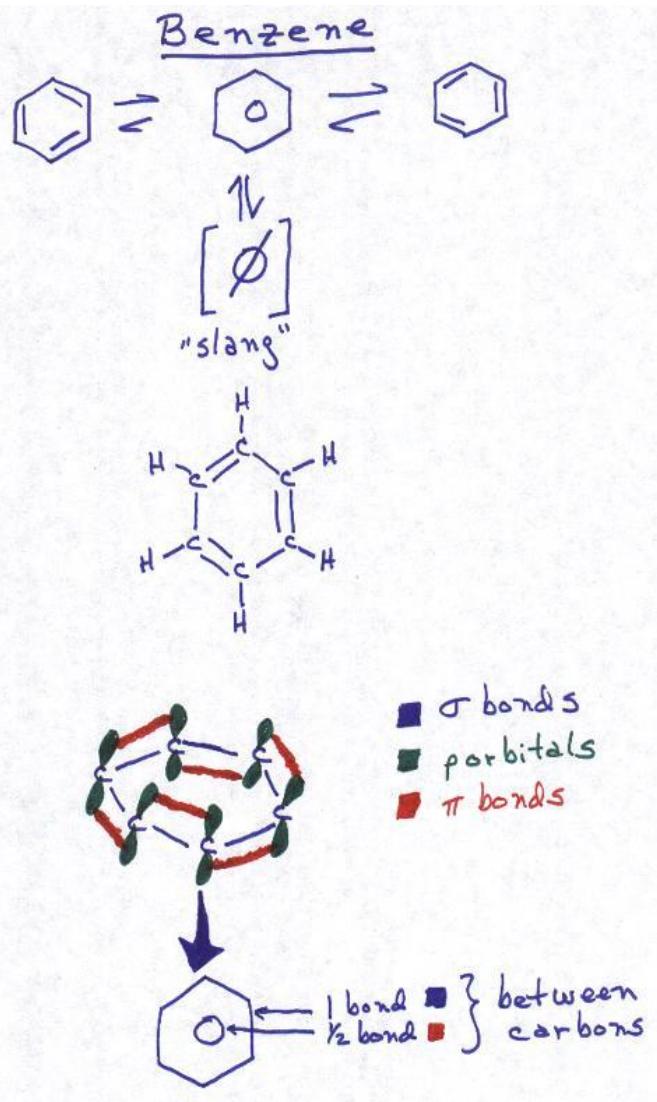
- The last group of aliphatic hydrocarbons, but the introductory group dealing with "ringed" structures of hydrocarbon compounds, to be discussed is shown in the graphic.
- These are compounds that form "ringed" compounds, i.e., a carbon chain that closes up onto itself resembling a "ring".
- These compounds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

cyclopropane

cyclobutane

cyclopentane

cyclohexane

cycloheptane

cyclooctane
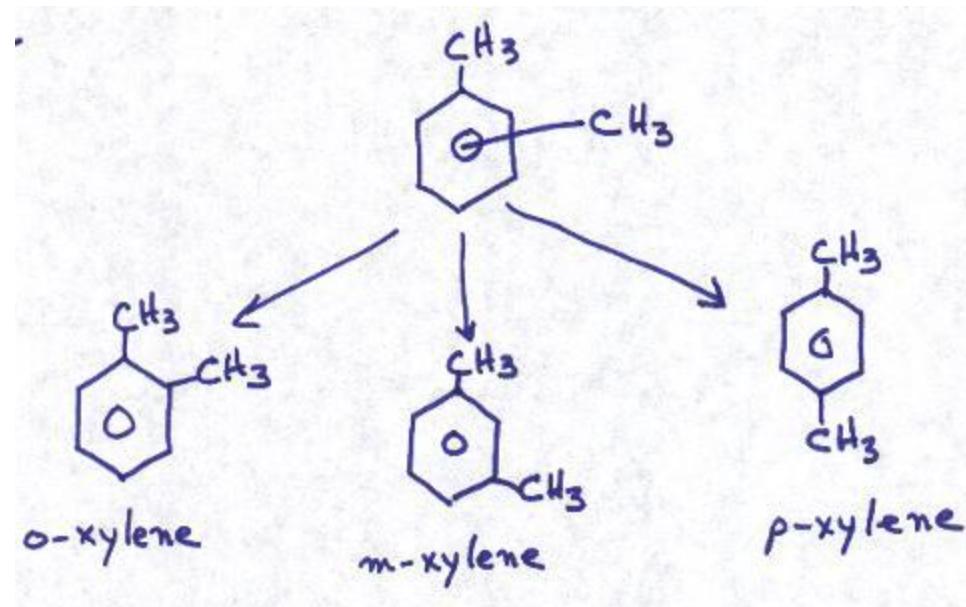
Aromatic Hydrocarbons: Benzene-Based Compounds … 'ish

- For the purposes of this course, 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.

Benzene

$\rightleftharpoons$

$\left[\varnothing \right]$

"slang"

$\Uparrow\Downarrow$

H, C, H structure (benzene)

■ σ bonds
■ p orbitals
■ π bonds

1 bond ■ } between
½ bond ■ } carbons

157
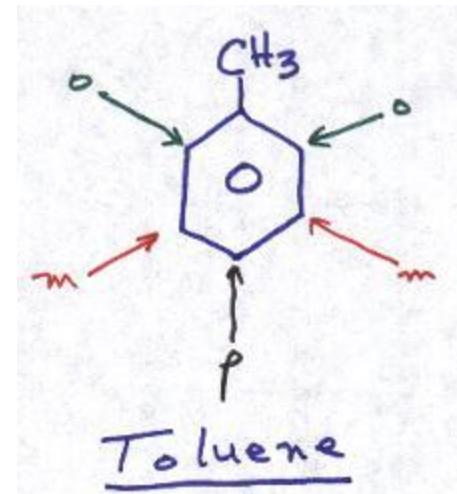
Substituted Benzene Compounds
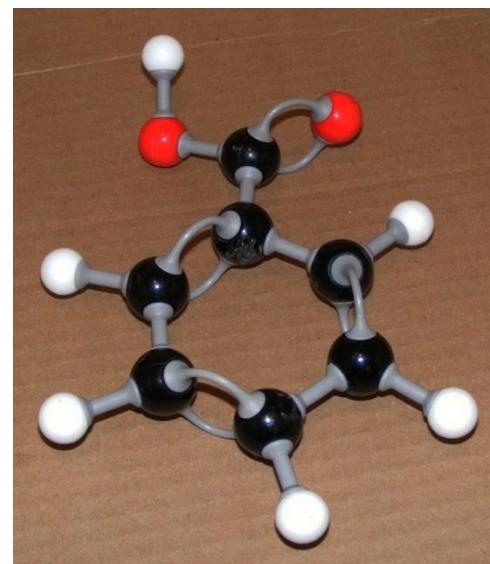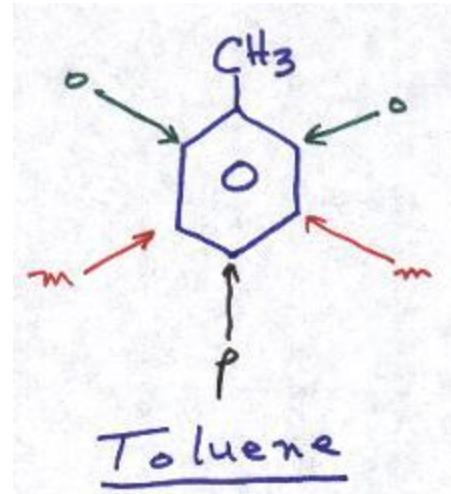
- There are a number of substituted benzene compounds that are important to have in your handbag of chemical knowledge.

- The top figure illustrates a generic way of drawing a xylene if the actual name is not given. What, though, happens if one of the three xylenes is drawn as in the bottom of the figure? How is it named?
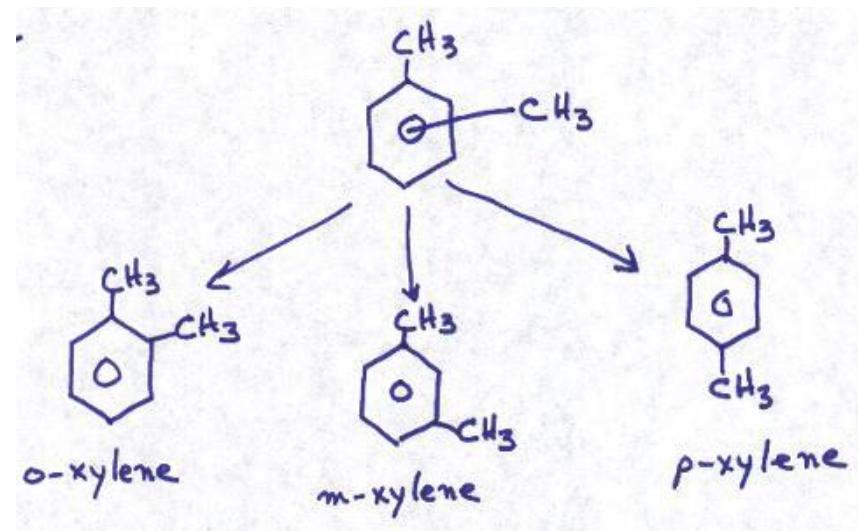
- Before we answer that question, let's look at the anatomy of a mono-substituted benzene compound like toluene.

- We'll put the methyl group that substitutes for the hydrogen on the top of the graphic.

- There are three positions on the ring that are un-substituted relative to the methyl group: 2 carbons next to the carbon with the substituting methyl group, 2 carbons that are located 2 carbons away from the carbon with the substituting methyl group and 1 carbon directly across the ring from the carbon with the substituting methyl group.

- In order, these other carbons in the benzene ring are called, ortho, meta and para -- "next to", "in between" and "across from".

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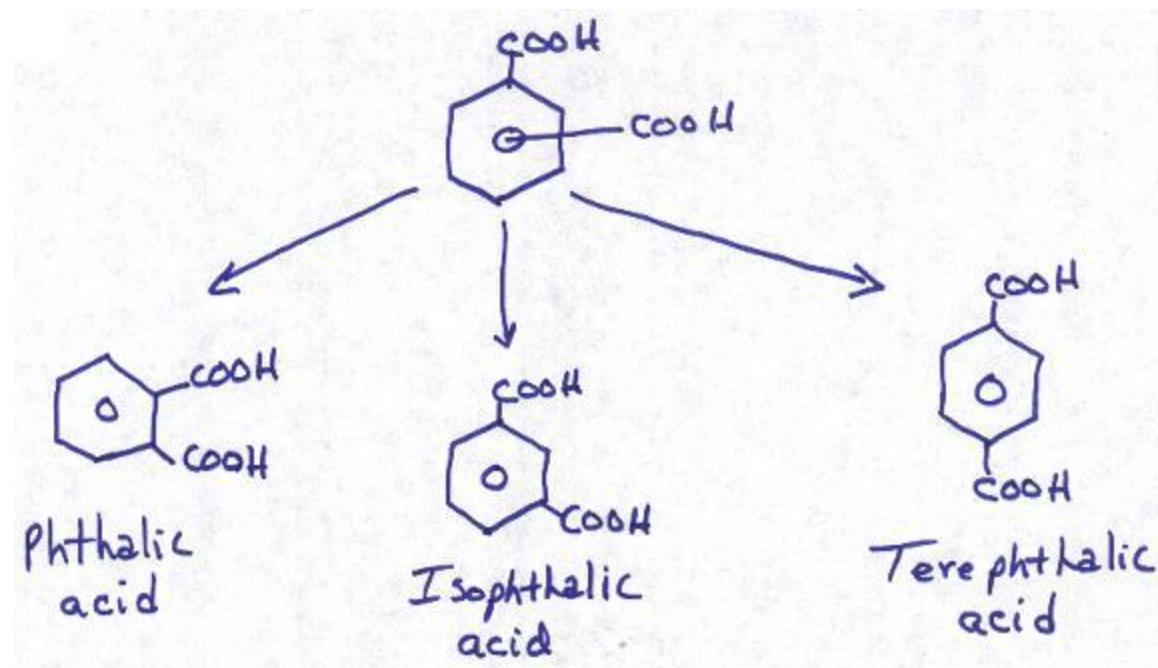
- When hydrogen atoms are substituted for on the ring by other groups, the substitutions occur following a very specific set of rules.

- These rules hinge on what substituting group makes it onto the benzene ring first.

- If groups like the -OH, -X add first, these will direct the next substituting groups into either the ortho OR the para positions. These groups are very small and take up a very small amount of space, i.e., have small steric hindrance.

- If groups like the nitro, carboxyl or trimethylammonium groups add first, these will direct the next substituting groups onto the meta position.

- The former group is called "ortho/para directors" and the latter group is called the "meta directors".

Toluene

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- So, now let's go back to the xylenes -- the dimethyl-substituted benzene compounds. The names, now, are fairly simple: ortho-xylene (o-xylene), meta-xylene (m-xylene) and para-xylene (p-xylene). Notice that the m-xylene doesn't make much sense as it's drawn. During the synthesis, though, it becomes easily seen how it's made -- that's for another course, though.
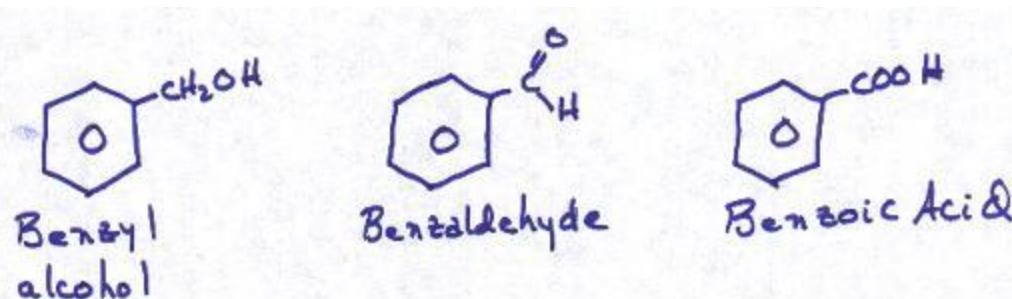
- Like wise, the phthalic (THAL ick) acids don't make sense as they are named, either, without knowing how they were synthesized (not discussed at this juncture). Note that phthalic, isophthalic and terephthalic acids are as drawn in this graphic.
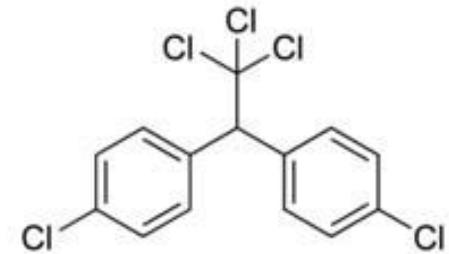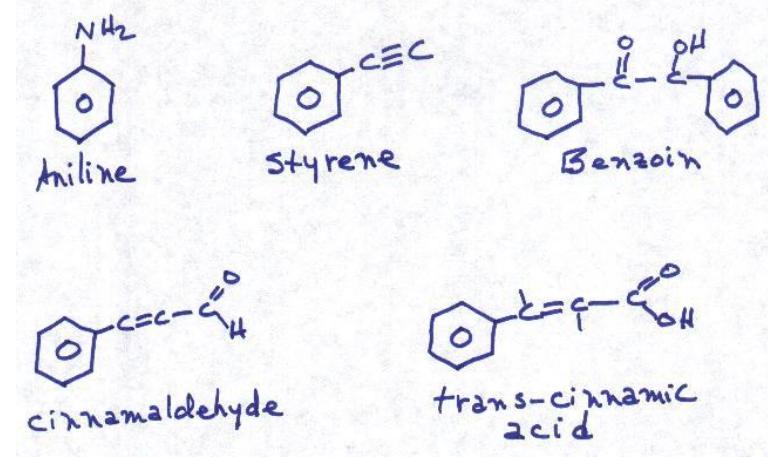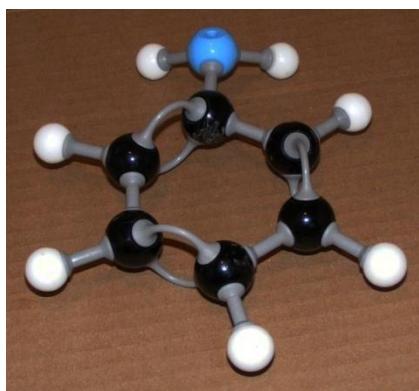
Generic Benzene Derivatives -- #1

- Benzyl alcohol, benzaldehyde and benzoic acid, are shown below. Note that the $C_6H_5CH_2\bullet$ is the benzyl radical, NOT the $C_6H_5\bullet$ radical, which is the phenyl radical. Benzaldehyde is artificial almond extract. Benzoic acid is used as a food preservative.
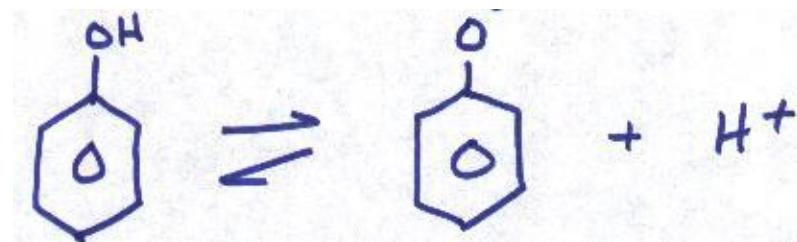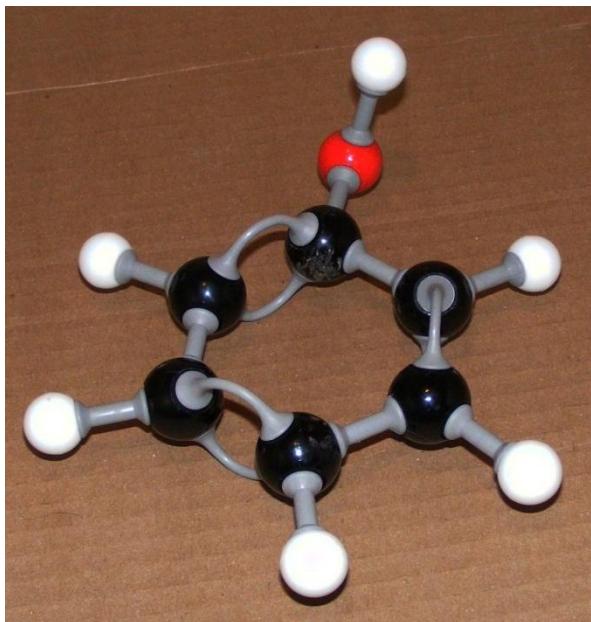
Generic Benzene Derivatives -- #2

- Cinnamaldehyde, trans-cinnamic acid, aniline, styrene and benzoin are benzene derivatives.

- Cinnamaldehyde is oil of cinnamon.

- DDT, or dichloro-diphenyl-trichloro-ethane, is also illustrated below. Controversies still surround DDT to this day, e.g., did it really cause eagles' egg shells to get weak and decimate the eagle populations?, could it have been the co-dumped mercury instead?, does DDT cause cancer in locations where there are still high levels of DDT in the soil?, what role did politics play in taking DDT off the market for use only with a special permit, now?
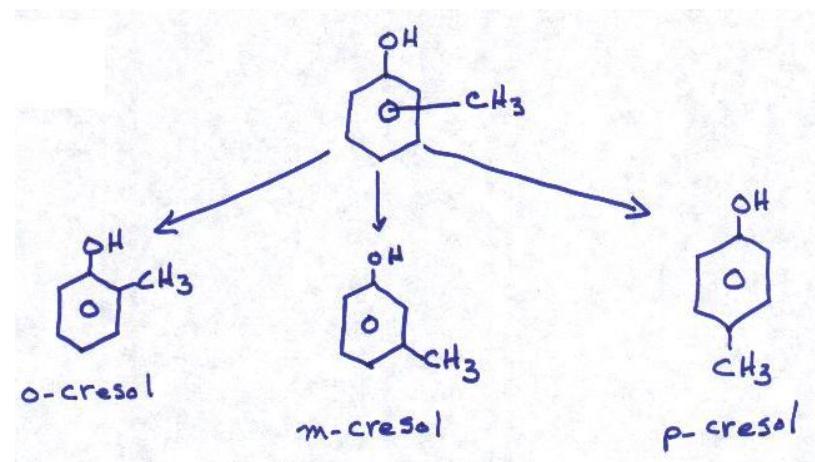
Phenols
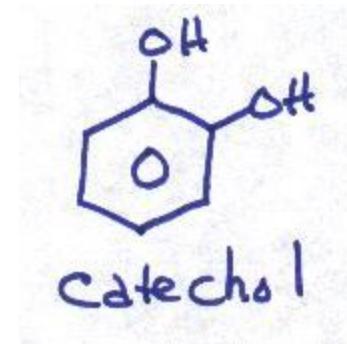
- Hydroxylated benzene compounds are based off of phenol (fuh NOLE), C_6H_5OH.

- 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.
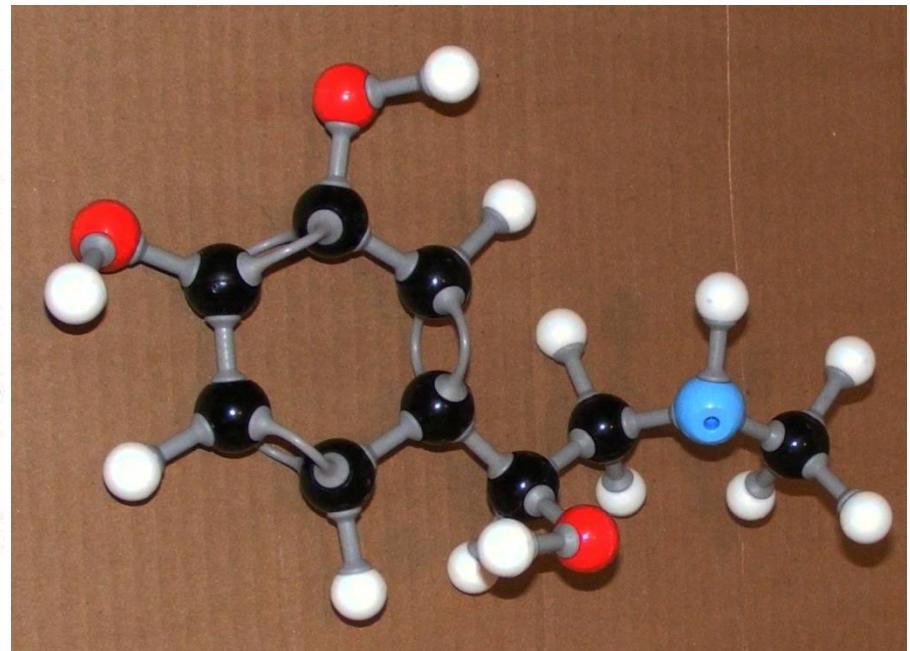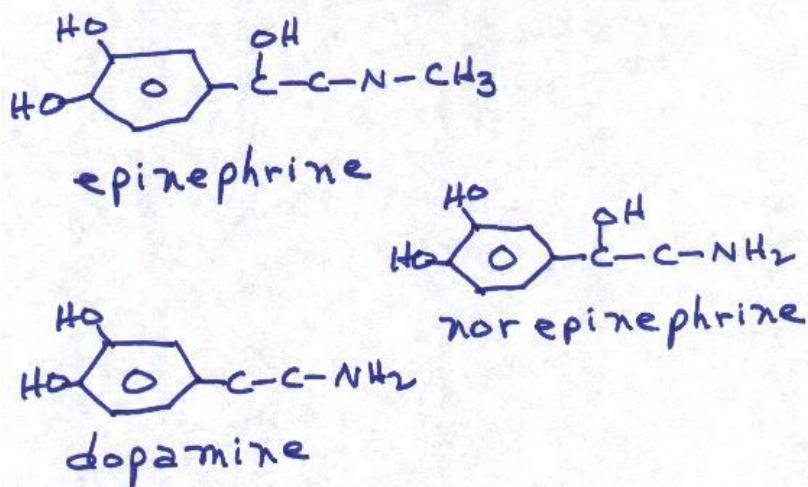
- There are a number of important hydroxylated benzene compounds. The first are the methyl-substituted phenols, or cresols (o-, m- and p-cresol). These are produced from the purification of coal tar.
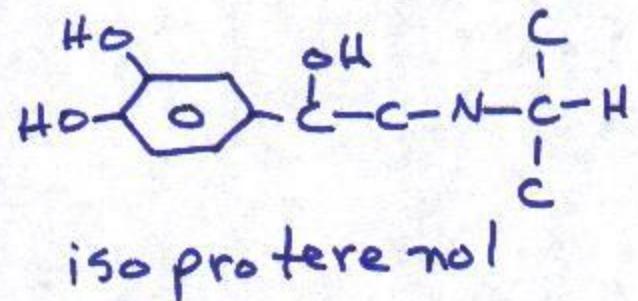
- The second group of important phenolic compounds is the catechols (KAY tuh koals). Catechol has the structure in the figure. Note that catechol is an ortho-substituted benzene "di-alcohol", or ortho-hydroxyphenol.
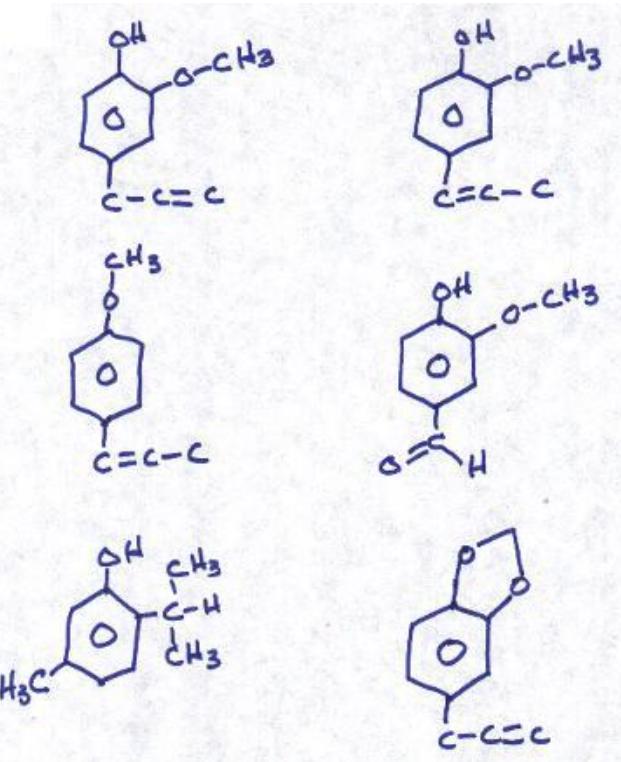
catechol

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

isoproterenol

- Isoproterenol is a synthetic catecholamine (drug) that mimics the effects of epinephrine.
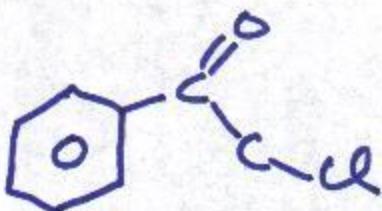
The third group of important phenolic compounds, or derivatives of phenol, are the essential oils
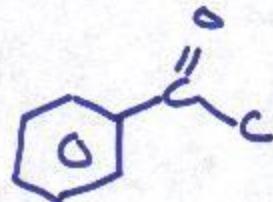
Eugenol (oil of cloves)	Isoeugenol (oil of nutmeg)
Anethole (oil of aniseed)	Vanillin (oil of vanilla bean)
Thymol (oil of thyme and mint)	Safrole (oil of sassafras)

Aromatic Ketones

- Two aromatic ketones jump out: chloroacetophenone and acetophenone. The former is a lacrimator (what is that?) and the latter is a hypnotic -- simply by removing the chlorine atom from the lacrimator!
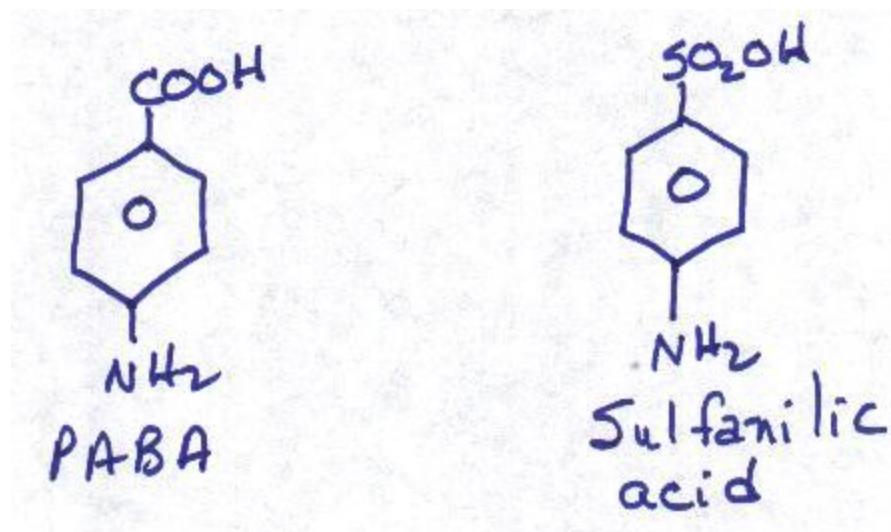
chloroacetophenone   acetophenone

Antimetabolites
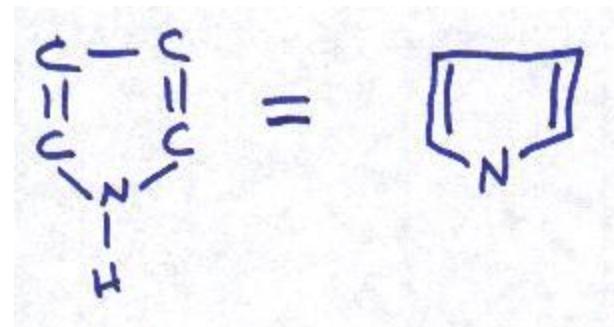
- For folic acid to be fully activated for use by bacteria for growth and reproduction, it requires PABA (para-aminobenzoic acid). Scientists figured out that if they modified a compound to LOOK like PABA, it might confuse the micro-organism and it would die. The parent/generic compound they came up with is sulfanilamide -- both shown below -- that came from sulfanilic acid.
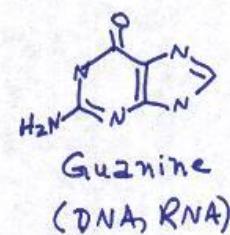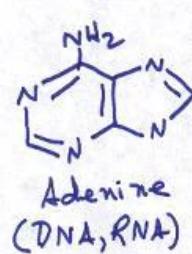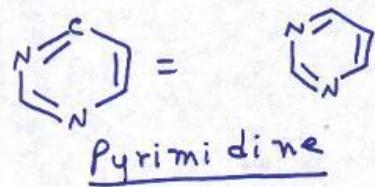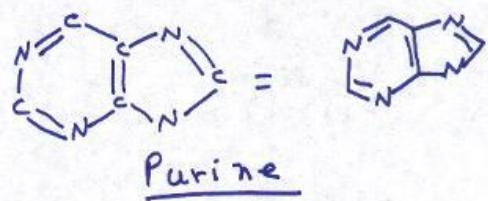
Heterocyclic Compounds of Nitrogen

- 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.
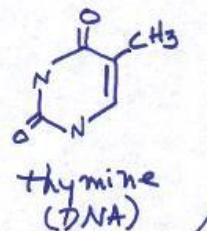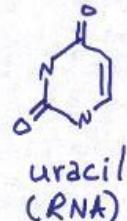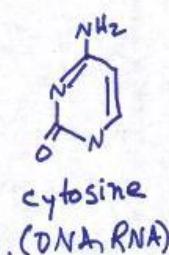
- Heterocyclic compounds also may follow the Hückel rule to be classified as aromatic.
- Pyrrole **does not** conform to Hückel's rule, but is, nevertheless, a cyclic compound that contains a nitrogen atom in the ring, below.
- It only has 4 p electrons, and does not conform to Hückel's rule for aromaticity.
- 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.

- The next two heterocyclic compounds are purine and pyrimidine.
- 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.
- Each compound gives rise to special groups of heterocyclic nitrogenous compounds found in DNA and/or RNA, images follow.
- G, C, A, and T are found in DNA; G, C, A, and U are found in RNA.
- More in the Biological Chemistry Lecture.

Purine

Pyrimidine

Adenine
(DNA, RNA)

Guanine
(DNA, RNA)

} "Purines"

cytosine
(DNA, RNA)

uracil
(RNA)

thymine
(DNA)

"Pyrimidines"

176
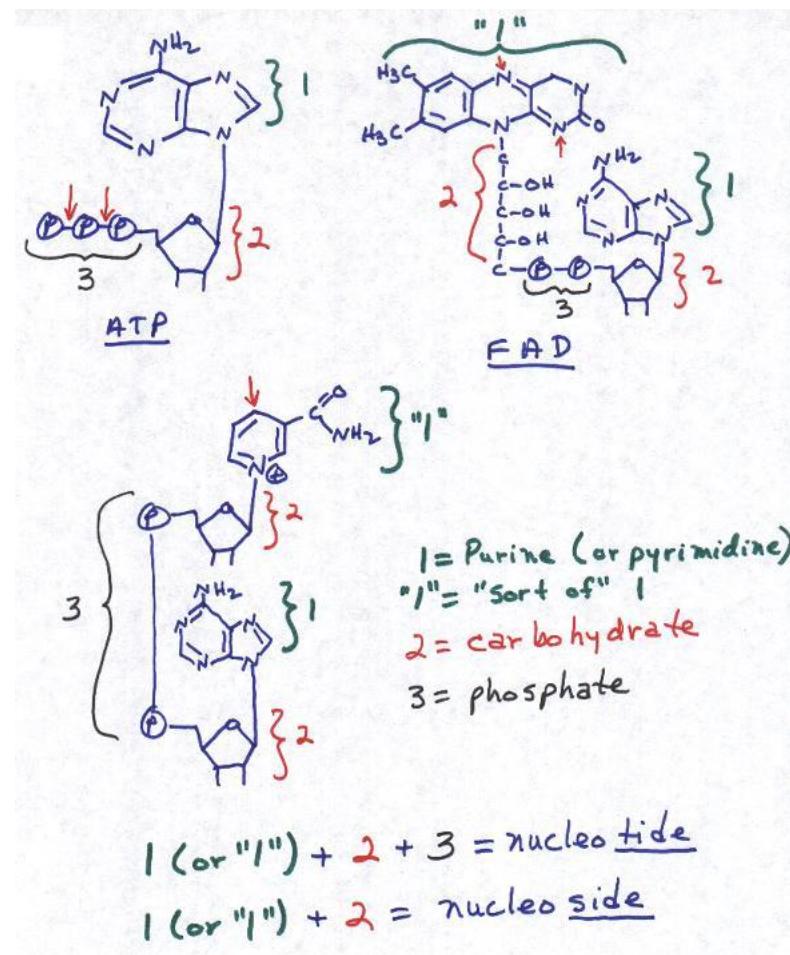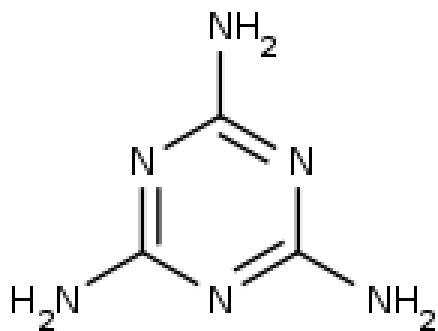
The last group of aromatic heterocyclic compounds is the nucleotides. These consist of three parts: a purine or pyrimidine, ribose and phosphate (a "P" with a circle around it is biochemist's short hand for phosphate). Three representative molecules are shown below. All three are involved in energy production in the body.

1 = Purine (or pyrimidine)
"1" = "Sort of" 1
2 = carbohydrate
3 = phosphate

1 (or "1") + 2 + 3 = nucleo _tide_

1 (or "1") + 2 = nucleo _side_

177
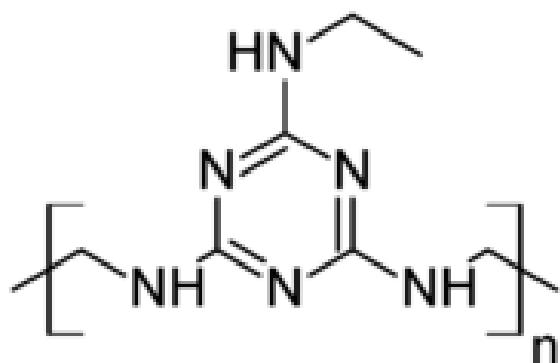
Triazine Compounds

- Melamine is a small, nitrogen-containing molecule that has a number of industrial uses, including as a binding agent, flame retardant, and as part of a polymer in the manufacture of cooking utensils and plates, plastic resins, and components of paper, paperboard, and industrial coatings. Melamine is not approved for direct addition to human or animal foods marketed in the United States.

- Melamine also has been used as a fertilizer in some parts of the world. It is not registered for use as a fertilizer in the United States.
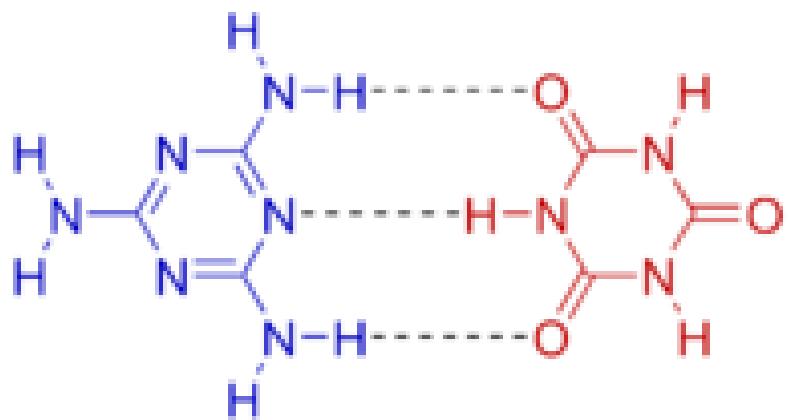
•Melamine use as non-protein nitrogen (NPN) for cattle was described in a 1958 patent.
•In 1978, however, a study concluded that melamine "may not be an acceptable non-protein N source for ruminants" because its hydrolysis in cattle is slower and less complete than other nitrogen sources such as cottonseed meal and urea.
•Melamine is sometimes illegally added to food products in order to increase the apparent protein content.
•Standard tests such as the Kjeldahl and Dumas tests estimate protein levels by measuring the nitrogen content, so they can be misled by adding nitrogen-rich compounds such as melamine.

Triazine Compounds
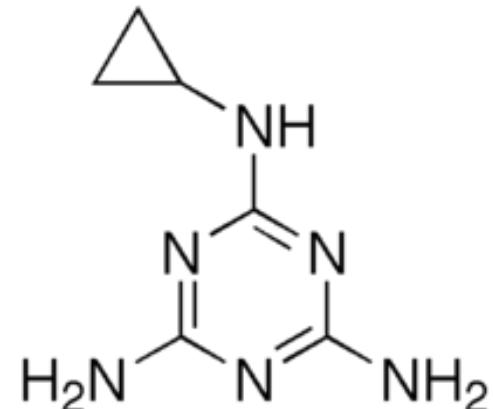
- Melamine is combined with formaldehyde to produce melamine resin, a very durable thermosetting plastic used in Formica, and melamine foam, a polymeric cleaning product. The end products include countertops, dry erase boards, fabrics, glues, housewares and flame retardants.

- Melamine is one of the major components in Pigment Yellow 150, a colorant in inks and plastics.

- The use of melamine as fertilizer for crops had been envisaged during the 1950s and 1960s because of its high nitrogen content (2/3). However, the hydrolysis reactions of melamine leading to the nitrogen mineralization in soils are very slow, precluding a broad use of melamine as fertilizing agent.

- Melamine-related compounds are in the same family of chemicals as melamine, and include **cyanuric acid**, ammeline, and ammelide.

- (Melamine-related compounds are also known as melamine analogues.)

- Melamine and its related compounds have no approved use as direct ingredients in human or animal food in the United States.

- The melamine-cyanuric acid complex is remarkably toxic.

Cyromazine

- Melamine is also a metabolite of cyromazine, a pesticide.

- **Cyromazine** is a triazine insect growth regulator used as an insecticide and an acaricide. It is a cyclopropyl derivative of melamine. Cyromazine works by affecting the nervous system of the immature larval stages of certa

- It is formed in the body of mammals who have ingested cyromazine. It has been reported that cyromazine can also be converted to melamine in plants and in insects.

1. http://www.fda.gov/oc/opacom/hottopics/melamine_qa.html
2. http://en.wikipedia.org/wiki/Melamine_resin
3. Pesticide Fact Sheet from Pesticide Management Education Program, Cornell University
4. Report on cyromazine of the European Medicines Agency
5. Lori 0. Lim, Susan J. Scherer, Kenneth D. Shuler, and John P. Toth. Disposition of Cyromazine in Plants under Environmental Conditions *J. Agric. Food Chem.* 1990, 38, 860–864
6. FAO report on cyromazine
7. http://en.wikipedia.org/wiki/Melamine
8. Hauck, R.D.; H.F. Stephenson (1964). "Nitrification of triazine nitrogen". *Fertilizer Nitrogen Sources* **12** (2): 147.
9. Barrett MP, Gilbert IH (2006). "Targeting of toxic compounds to the trypanosome's interior". *Adv. Parasitol.* **63**: 125–83. doi:10.1016/S0065-308X(06)63002-9. PMID 17134653.
10. "Ruminant feed compositions, Robert W. Colby and Robert J. Mesler Jr., U.S. Patent No. 2819968, 1958
11. "Melamine as a dietary nitrogen source for ruminants", G.L.Newton and P.R.Utley, Journal of Animal Science, vol.47, p1338–44, 1978, Abstract
12. "Protein Pretense", Alison Snyder, Scientific American Magazine, August 2008

Polymerization Reactions.

- Let's add a few more definitions to your vocabulary, then move on to specific synthetic reactions, e.g.,
  - Neoprene,
  - Natural Rubber,
  - Vulcanization,
  - Nylon 66,
  - SBS Rubber and
  - Polycarbonate.
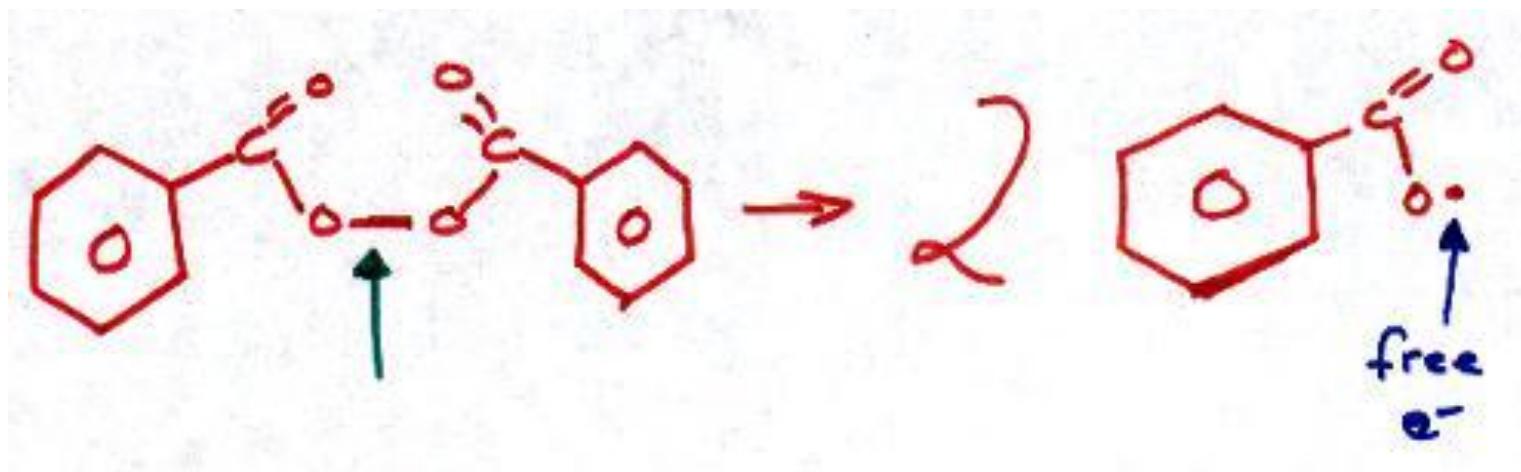
•Polymers (many [poly]; units [mer]) consist of monomers (single; one [mono]) that bond together to form long chains.
•While polymers are sometimes called macromolecules, the latter term is generally reserved for polymers of a biological nature, e.g., proteins, nucleic acids, complex carbohydrates.
• We've used polymers for millenia in various forms, Table, below:

Table of Polymers			
Oils	Tars	Resins	Teflon (TM)
Cotton	Wool	Rubber	Nylon
Plastics	Neoprene	Gums	

• It is possible, today, to prepare on a bulk scale, polymeric compounds over a broad spectrum of heat resistance, strength, cost, density and brittleness.

•Like micro-organisms, polymers are ubiquitous, Table, below:

Table of Polymers			
Product	**Polymer**	**Product**	**Polymer**
Diapers	**Polyethylene**	**Elastic**	**Natural rubber**
Diaper packing	**Polyacrylic acid**	**Toothbrush bristles**	**Nylon**
Shampoo thickener	**Hydroxyethylcellulose**	**Conditioners**	**Silicones**
Hair spray	**Polyvinylpyrrolidone**	**Bedpan**	**Polyethylene**
Insoles	**Polyurethane**	**Elastic bandages**	**Polyisoprene**
Animal "fur"	**Polyacrylonitrile**		

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- Free radicals are molecules with an unpaired electron, e.g., benzoyl peroxide.

- Note in the graphic that the free radical is located at the carboxyl end of the molecule.

- Benzoyl peroxide makes a particularly useful initiator of polymerization reactions as it has two very electronegative atoms bonded to each other -- they don't "like" that, so they separate easily.
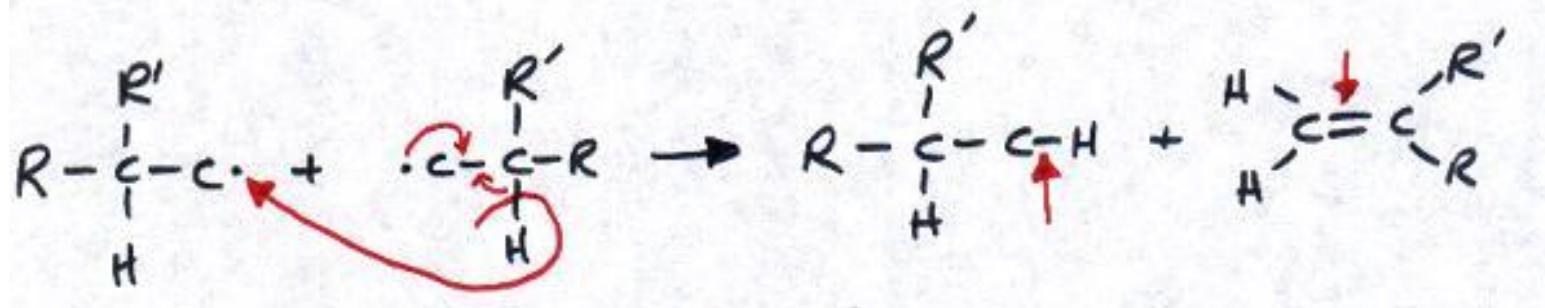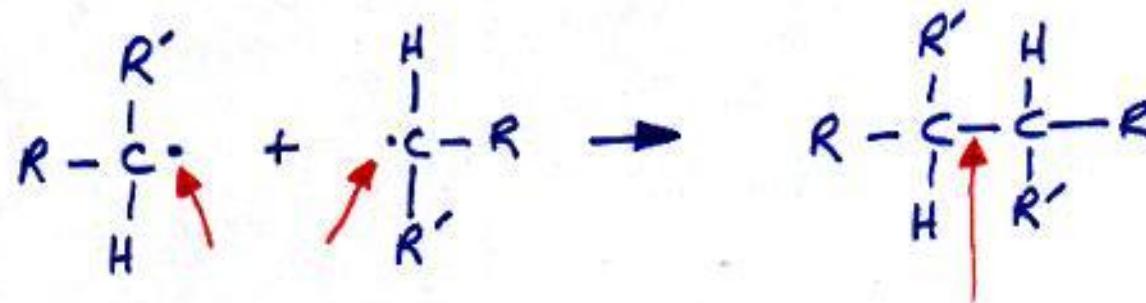
- Stability is a measure of the reactivity of free radicals with other chemicals;

- Unstable radicals are very reactive;

- Stable radicals are not very reactive.

- Active centers are where the reaction occurs; it is at the site of the unpaired electron; the active center moves progressively down the growing chain to perpetuate the polymerization reaction.

- Addition polymerization occurs when monomers are added one by one to the active center on the elongating chain.

- Initiation, propagation and termination reactions have been superficially covered in Elementary Reaction Rates.
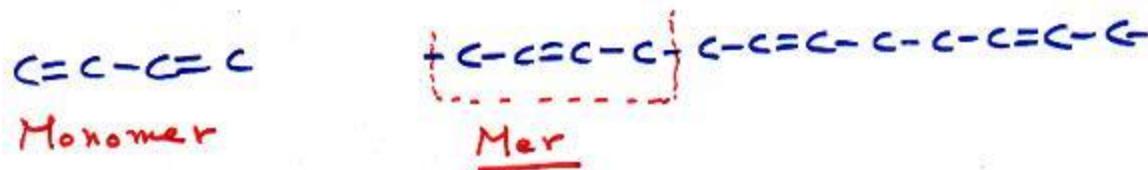
Two types of termination reactions generally occur: combination and disproportionation.

- **Combination Reactions**
- occur when the propagation reaction ceases due to 2 chains combining to form one chain.

- Disproportionation Reactions
- stop propagation when a hydrogen atom is removed from one chain by the free radical of the other chain.
- Note the double bond formed as a reaction product in the graphic.
- Disproportionation reactions may also occur when impurities are present to react with the free radical.
- Polymerization reactions MUST be performed under clean conditions.

Combination – Top
Disproportionation -- Bottom
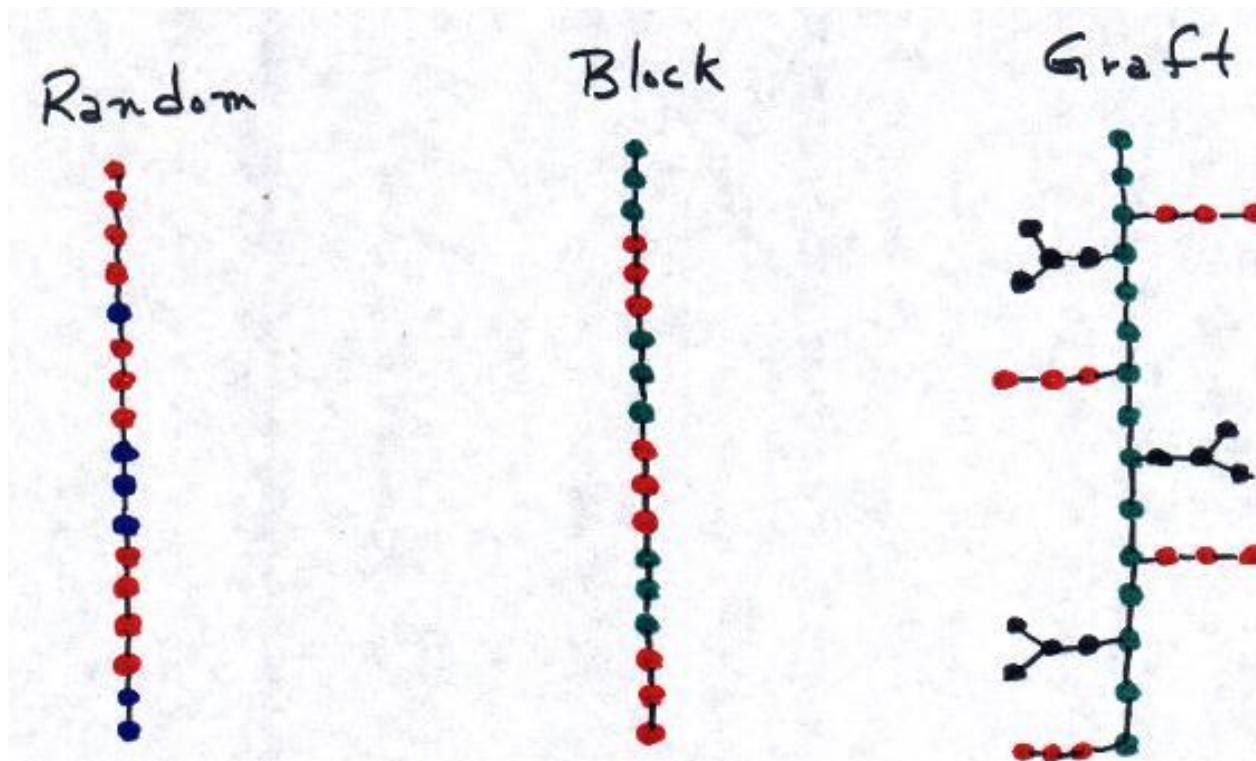
- Living polymerization does not undergo termination.
- The reaction progresses until no more monomers are present.
- The reaction will continue if more monomers are added to the reaction vessel.
- Mer is the smallest repetitive unit in a polymer.
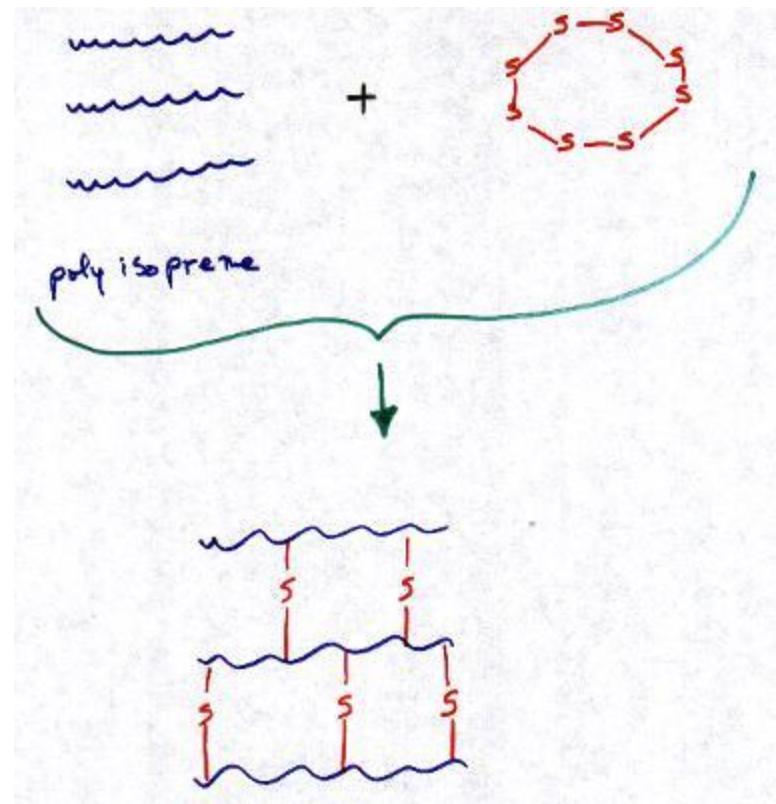
- Degree of polymerization (DP) is equal to the quotient between the molecular weight and the mer weight (DP values can be as high as 10,000.):

$$DP = \frac{Polymer\ Molecular\ Weight}{mer\ weight} = \frac{mers}{mol} \approx generally\ between\ 75\ and\ 750$$

- Copolymers are polymers that consist of more than one type of monomer in the chain.
- There are three kinds of copolymers: random, block, graft.
- Random copolymers contain a random organization of the monomers.
- Block copolymers contain specific areas in the chain with the same monomers.
- Graft copolymers have a main chain that consists of one type of monomer and has side chains of other monomers.

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- Cross-linking occurs when bonds form between polymer chains.
- A low enough degree of cross-linking causes "memory" and allows the material to stretch, then return to its original shape, e.g., vulcanization.
- Vulcanization caused natural rubber to remain soft and pliable when cold and when warm, rather than hard/brittle and runny (sticky), respectively.
- Charles Goodyear did this in 1839.
- [Sulfur] cross-links prevent the chains from sliding over each other when warm (melting) and aren't easily separated when cold (brittle).

- Polymers may be classified in two general classes: Elastomers and Plastics.

- Elastomers with low numbers of cross-links (about 1 per 100 mers) have memory and bounce.

- Elastomers with high numbers of cross-links (about 1 per every 30 mers) are rigid and brittle polymers.

- Plastics can be shaped or molded under the correct pressure and temperature conditions.

- Plastics have great stiffness and once shaped, remain in that shape.

- NOTE: all plastics are polymers; not all polymers are plastics.
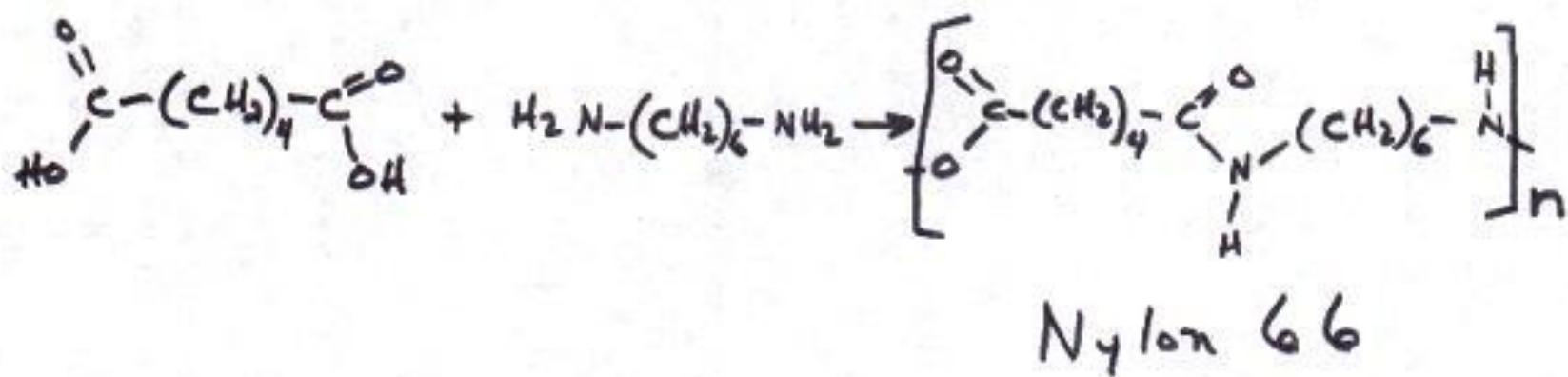
The table, below,
lists common applications of several polymers:

Elastomers	Plastics		Fibers	
	Low Density Polyethylene	**High Density Polyethylene**	**Natural**	**Synthetic**
Rubber (isoprene monomer)	**Low density; lots of branching**	**High density; little to no branching**	**Cotton, wool, silk**	**Polyester, rayon, acrylic, nylon**
SBR Rubber, aka Buna-S (butadiene and styrene copolymer)	**Soft, pliable**	**Rigid**		**Nylon developed in 1930's; used for parachutes in WW II**
Tires	**Plastic bags, containers, textiles, wire insulation**	**Plastic tubing, bottles, bottle caps**	**Clothing**	**Nylon used for clothing, carpeting, builds up static charge, too**

Specific Polymerization Reactions
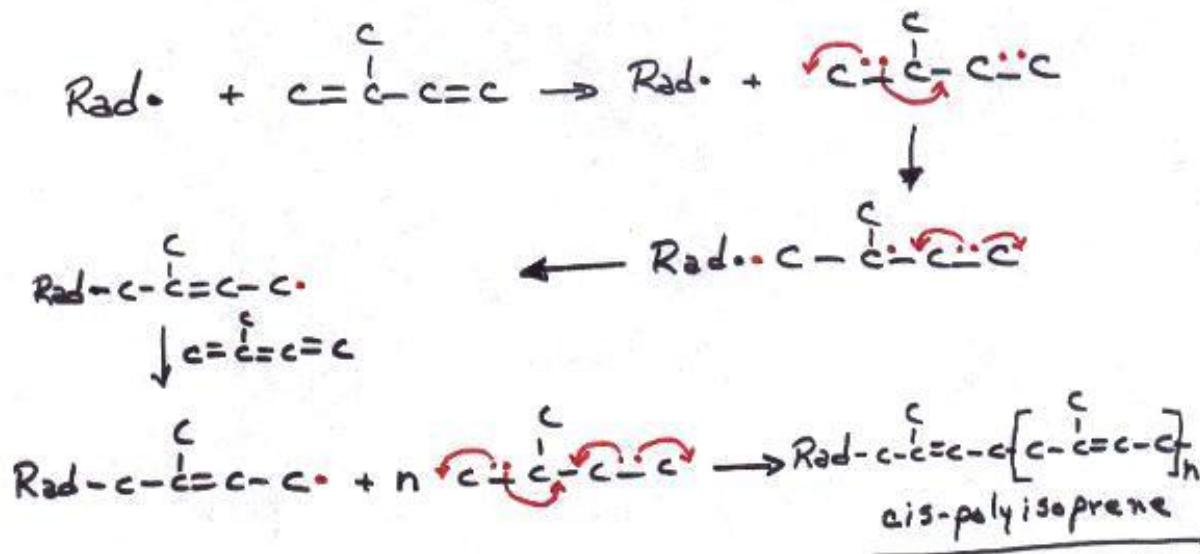
Nylon 66 Synthesis

- This copolymer gets its name from the 6 carbons in adipic acid and the 6 carbons in hexamethylene diamine.
- Without going into the complete mechanism (which gets very confusing very quickly -- you'll learn it in the year Organic Chemistry course, anyways), the synthesis may be explained as follows.
- A diamine is being reacted with a dicarboxylic acid.
- The final product of these compounds will be held together by amide bonds and each bond will be formed with the loss of water.

Nylon 66

Natural Rubber Synthesis

- In brief, this reaction begins with isoprene and the addition of a free radical ("Rad·" in the graphic).
- In this reaction, the free electron in the radical attacks an end carbon.
- This causes the two electrons in the first double bond (closest to the methyl group in the chain) to un-pair.
- One electron "flips" out to mate with the electron on the free radical, to form a single bond.
- The second "flips" between the next two carbon atoms.
- At the same time, the two electrons in the other double bond "flip": one to mate with the single electron in the middle of the center 2 carbon atoms and the other to the "tail" of the former isoprene monomer.
- The reaction continues with the addition of more isoprene monomers with the "flipping" of electrons until the completed polyisoprene polymer is completed.
- **Natural rubber is in the all-cis configuration.**
- Synthetic (artificial) "natural rubber" was a cis/trans mixture until 1955.
- New methods and catalysts were used, then, to prepare all-cis-polyisoprene.
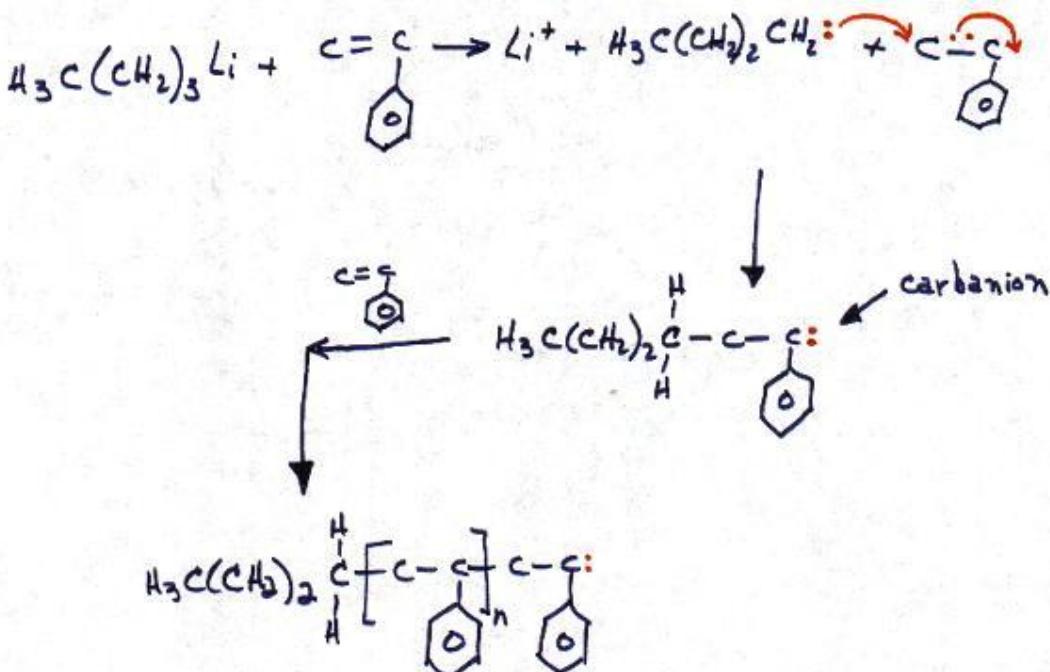
SBS (Buna-S) Rubber Synthesis

- SBS is a block copolymer.
- It was called Buna-S from Butadiene (Bu), sodium (Na) and Styrene (S) until after WW II when the rubber industry renamed it SBS for polyStyrene-polyButadiene-polyStyrene.
- SBS is rubbery without being cross-linked as natural rubber requires.
- It is synthesized via living polymerization.
- This specific kind of living polymerization is anionic, as carbanions are generated to perpetuate the reaction.
- This mechanism requires 4 steps.

- Butyl lithium is used as the anionic initiator and reacts with styrene.
- In the course of the reaction, the lithium ion is removed, leaving behind an extra electron on a carbon atom (carbanion!).
- The carbanion attacks the carbon that does not have a substituted benzene on it, causing the two electrons in the second bond (remember a double bond has 2 double bonds) to "flip" out, making the carbon that has the substituting benzene another carbanion.
- This reacts with another styrene monomer, perpetuating the reaction, i.e., to form a chain of polystyrene.
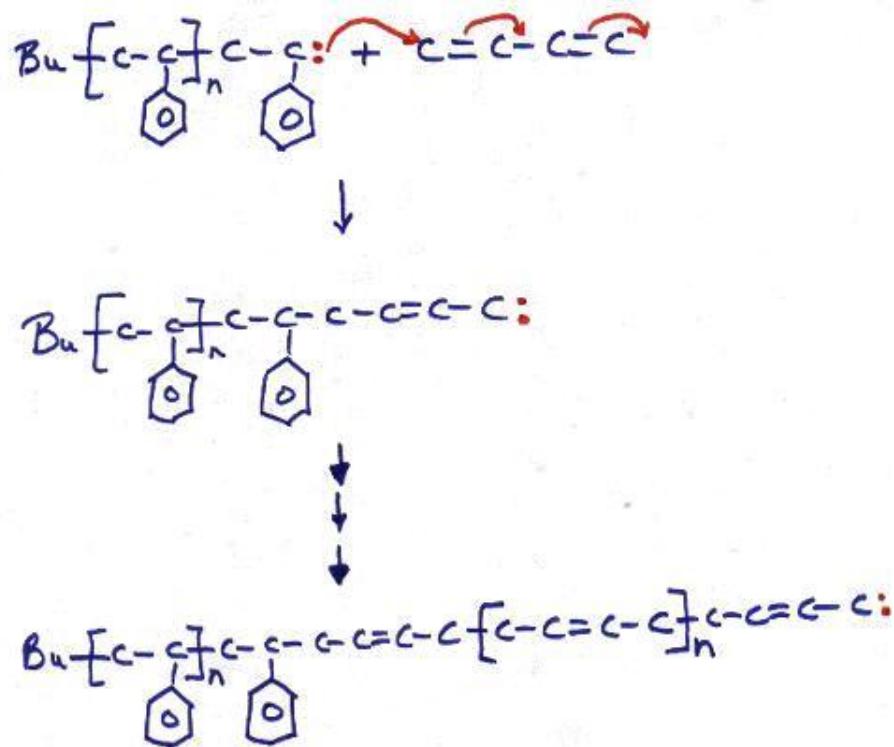
poly Styrene chain
= carbanion

Note: $H_3C(CH_2)_2\overset{H}{\underset{H}{C}}- = \underline{Bu}$ in

upcoming graphics

Step 2
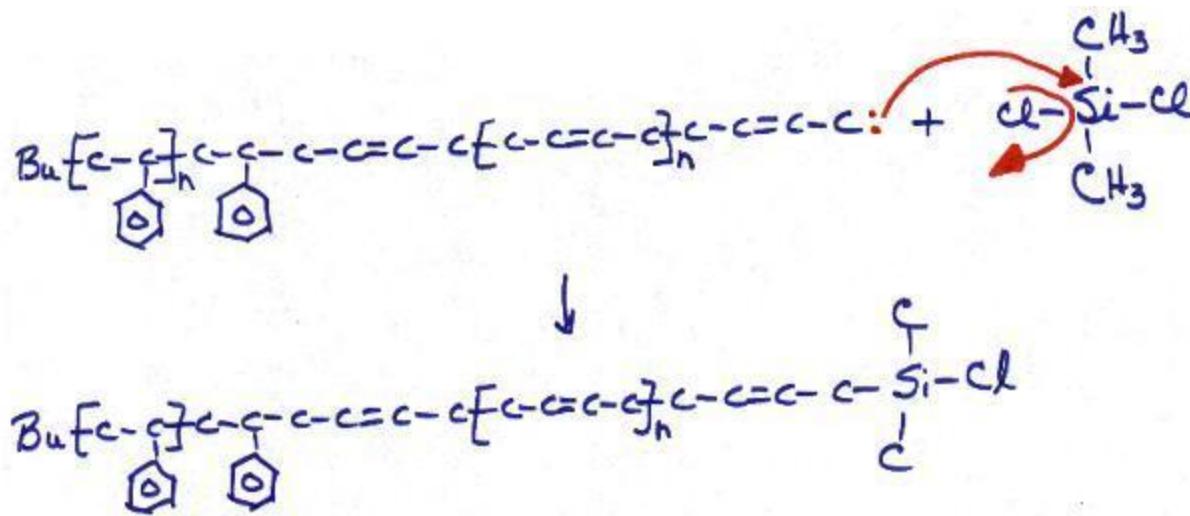
- To the polystyrene chain, 1,3-butadiene is added.
- When the carbanion attacks the end carbon, the electrons all begin to play "dominoes", flipping in such a manner that the first double bond is "moved" from between the 1st and 2d carbon atoms to the 2d and 3d carbon atoms.
- The electrons in the second double bond (between carbon atoms 3 and 4) then "flip" out to make another carbanion.
- More 1,3-butadiene is added until a polystyrene-polybutadiene polymer is obtained.
- There is now a problem: the butadiene adds easily to the polystyrene.
- The last polystyrene, though, won't add to the end of the polystyrene-polybutadiene copolymer.
- How to get around it?
- Add a compound called dichlorodimethylsilane (DCDMS) to the end of the polystyrene-polybutadiene copolymer.

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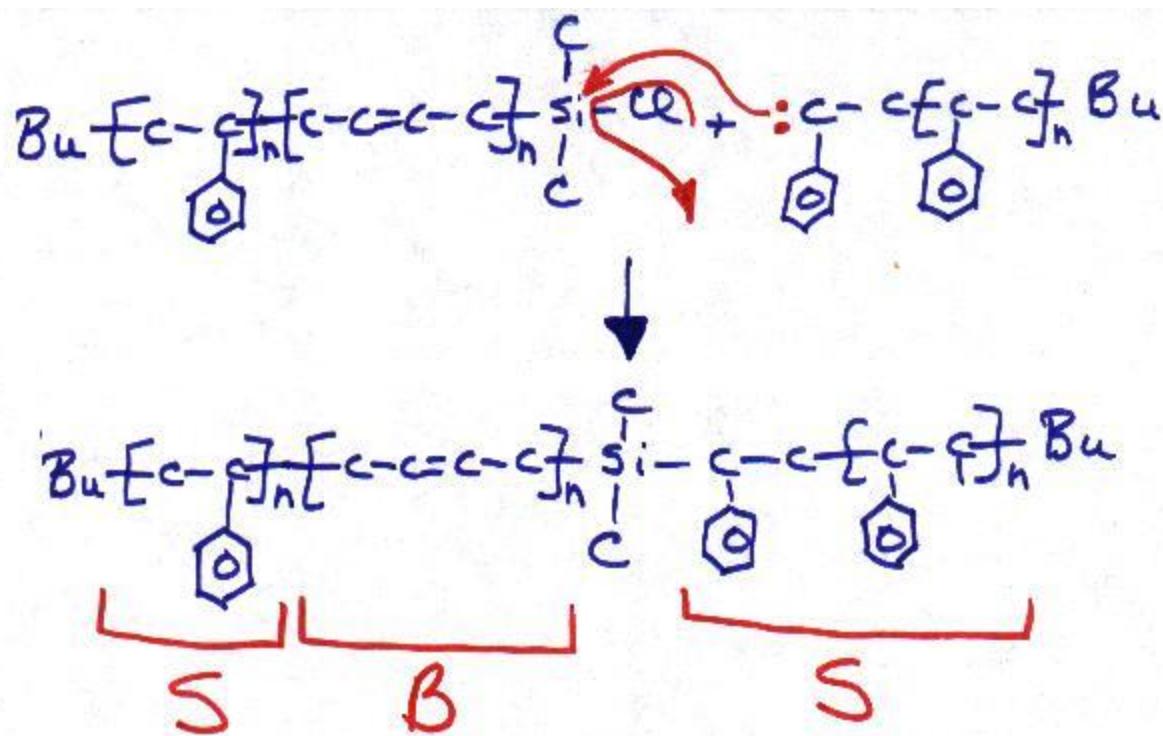
Step 3

- The DCDMS (dichlorodimethylsilane) is added.
- In the course of the reaction, one chloride ion is lost as the carbanion attacks at the Si, forming the new intermediate.
- This polymer is now no longer "<u>alive</u>".
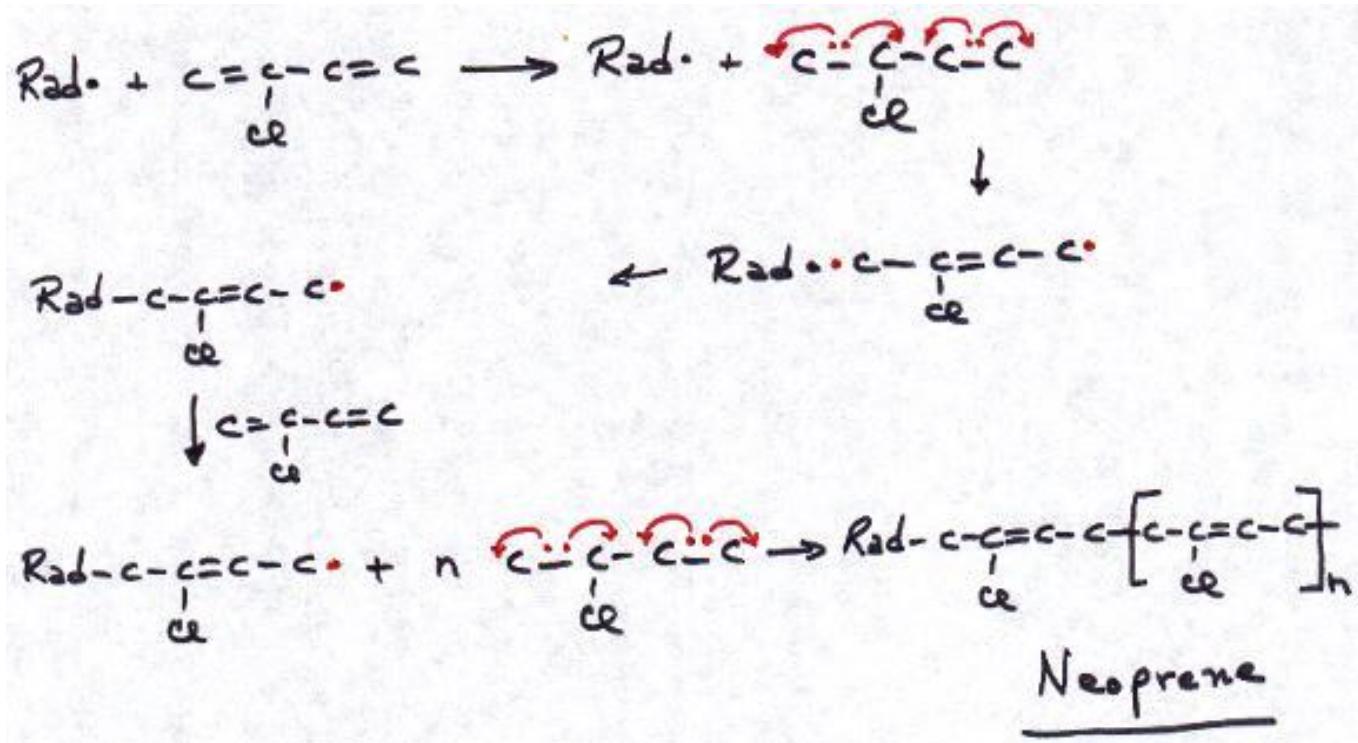
Step 4

- To finish the synthesis, polystyrene is added to the "dead" copolymer from the previous step.
- In this case, the carbanion on the end of the polystyrene chain attacks the Si, removing another chloride ion.
- At the end, SBS rubber is synthesized.

Neoprene™ Synthesis

- The synthesis of Neoprene follows the synthesis of all-cis-polyisoprene in terms of electron movement. As such, this mechanism is left to the student to walk through and observe the similarities between the two reactions.

- While Neoprene isn't 100% as great as natural rubber in some of its properties, it IS superior in its resistance to oils, gas, greases and other organic solvents, making it excellent for use by mechanic-types of occupations.
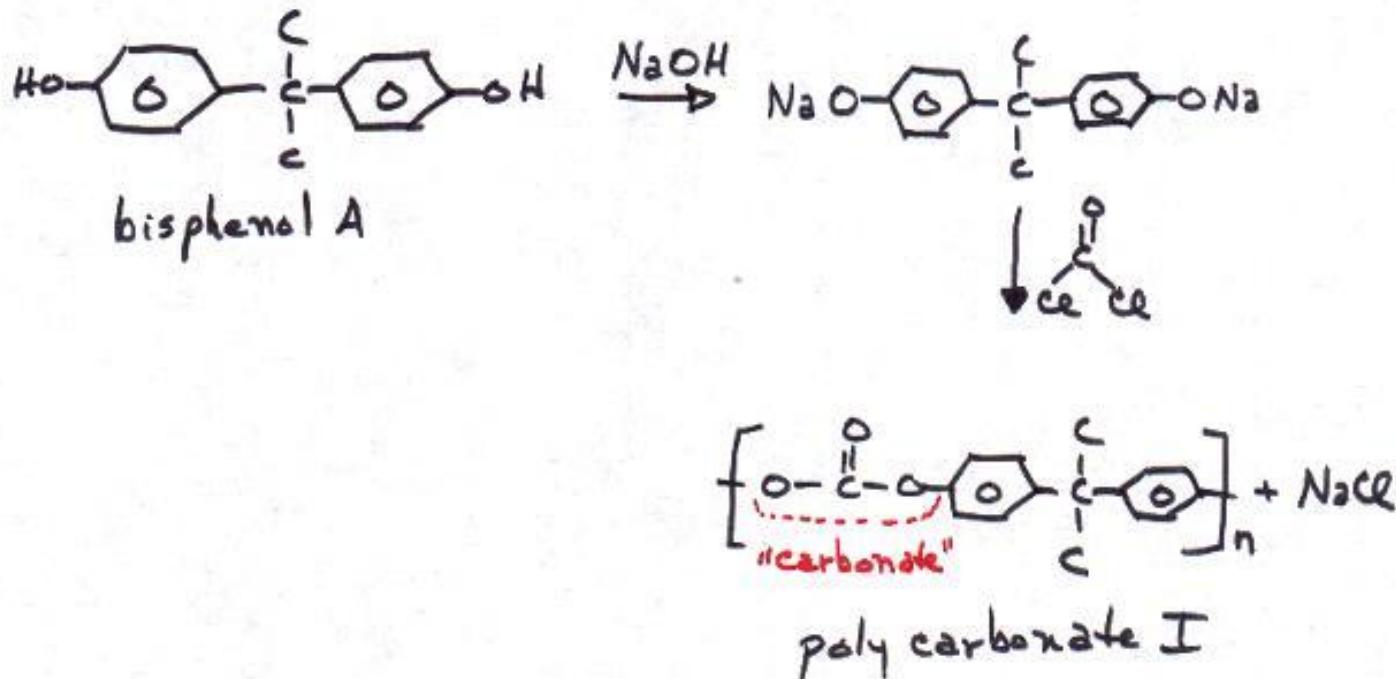
Polycarbonate

- We'll discuss the superficial synthesis of TWO kinds of polycarbonate -- each with its own title. Polycarbonate is a clear plastic. It is used to make shatterproof windows and lightweight glasses lenses.

Polycarbonate I Synthesis

- For the synthesis of the first type of polycarbonate, bisphenol A, NaOH and phosgene are required.
- In brief, the NaOH reacts with the bisphenol A, removing the two phenolic protons and replacing them with sodium ions.
- This sodium salt then reacts with phosgene to form sodium chloride and the "carbonate" portion on the bisphenol A ion.
- This form of polycarbonate is great unless your vision is really terrible.
- Then, a different polycarbonate is required.

bisphenol A

poly carbonate I
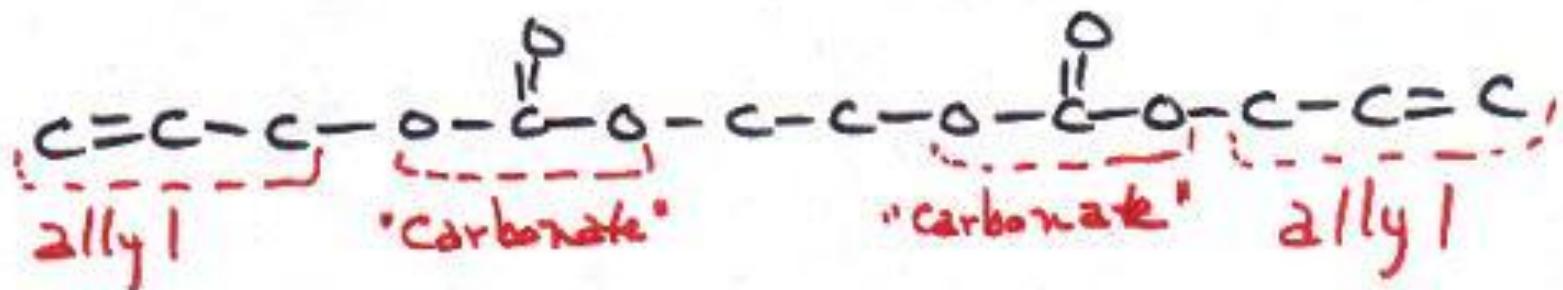
ASIDE: Phosgene

- I've seen reports of this used as a "nerve gas" in WW I online.

- I'm concerned about this as I was taught that due to its reactivity with water, it was used in the trenches during WW I as an inhalant gas.

- When it was inhaled, it reacted with the water in the soldiers' lungs to form HCl, which caused pulmonary edema.

- It was to the point that it, literally, caused the soldiers to drown.

Polycarbonate II Synthesis

- The different polycarbonate is based off of a compound that has an allyl group at each end of the monomer and is held together between the two "carbonates" by an ethyl group.
- The chains cross-link together tightly and densely.
- This causes the material to bend light more than glass.
- This kind of polycarbonate is used in ultra-lightweight lenses when glass lenses would be WAY too heavy for the wearer.

Structure/Function Relationships
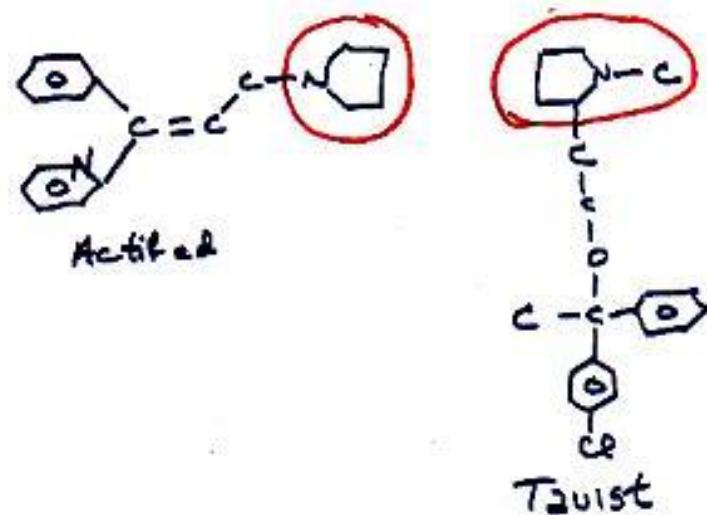
- As many of you have already learned in A&P, structure begets function. This section of CHEM 220 applies these concepts to the chemical structure of a selected number of drugs to give you a bit of a taste, so to speak, of why it is that many medications "work" as they do.

Antihistamines

Histidine $\xrightarrow{\;CO_2\;}$ Histamine
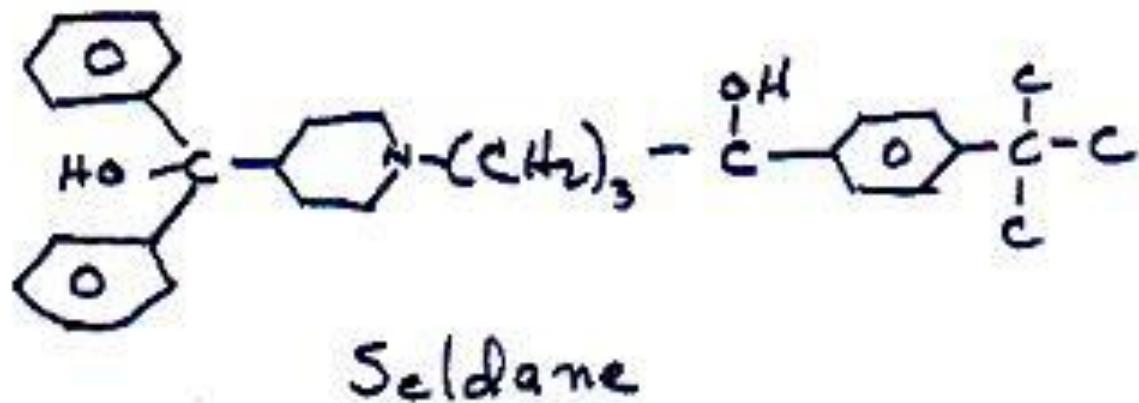
- The simplest group with which to start is the antihistamines. Remember that the amino acid histidine is the precursor molecule for histamine. Histamine initiates a cascade of events that culminates in allergic reactions.
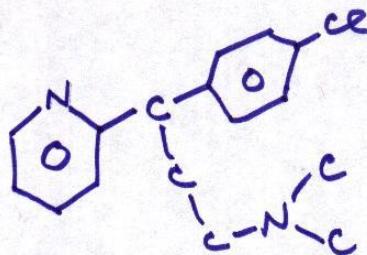
- Antihistamines provide antagonism against histamine because many of them "look" like histamine to the H receptors and inhibit the binding of histamine to them. Two examples are actifed and tavist. Both sort of look like histamine (see red circled area in graphic) to the receptor. Due to the high degree of steric hindrance they provide, the satisfactorily block histamine from binding to its receptor.

Actifed

Tavist
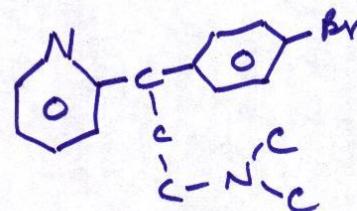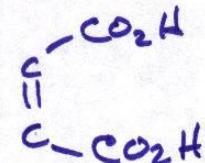
- Seldane, now, while an antihistamine has a different sort of structure. Its effects begin within one to two hours and is specifically H_1 antagonistic.

Seldane

- The last two antihistamines, chlorpheniramine maleate and brompheniramine maleate, have slightly different structures, as well, yet inhibit histamine binding.
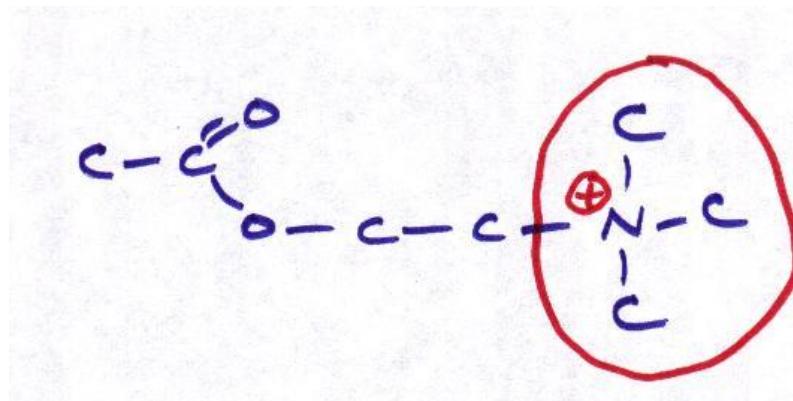
chlorpheniramine · maleate
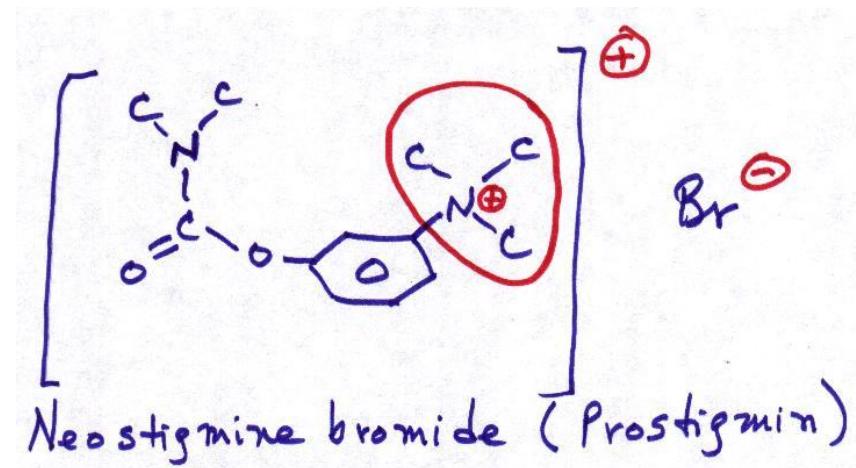
Brompheniramine · maleate

Anti-cholinergics
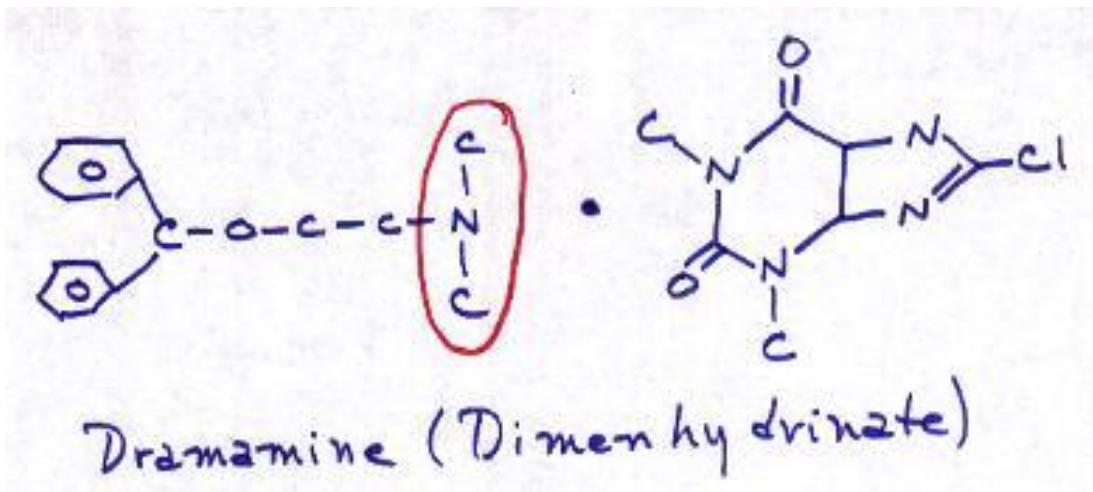
- The next class of drugs are the anticholinergics.

- These drugs are designed to look like acetylcholine (Ach).

- Ach is a neurotransmitter that is used to "drive" an electrical signal through nerves for muscular activity.

- Anticholinergics, at least for this course, inhibit acetylcholinesterase (AchE) activity.
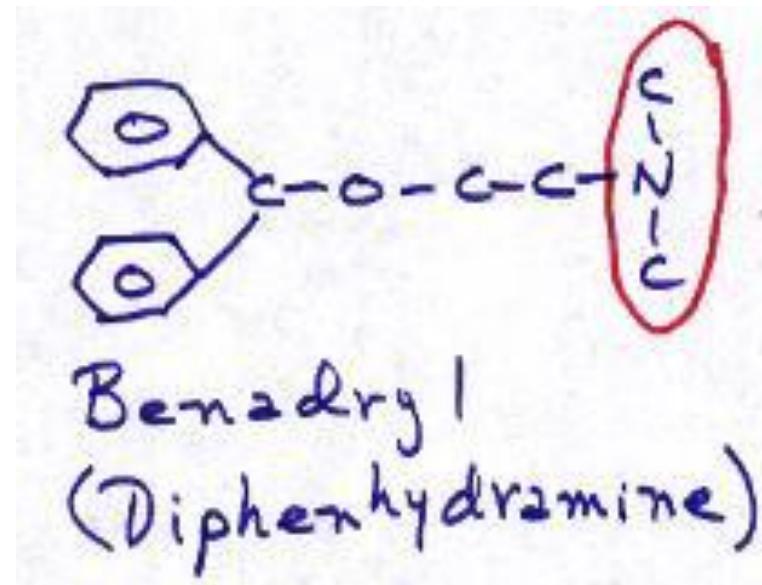
- Prostigmin (neostigmine bromide) is one example. This drug reverses the effects of some general anesthetics after surgery, e.g., curare-like drugs. It may induce pre-term labor near term following intravenous administration. Note the tertiary amine structure similarities between Ach and the anticholinergics.

Neostigmine bromide (Prostigmin)
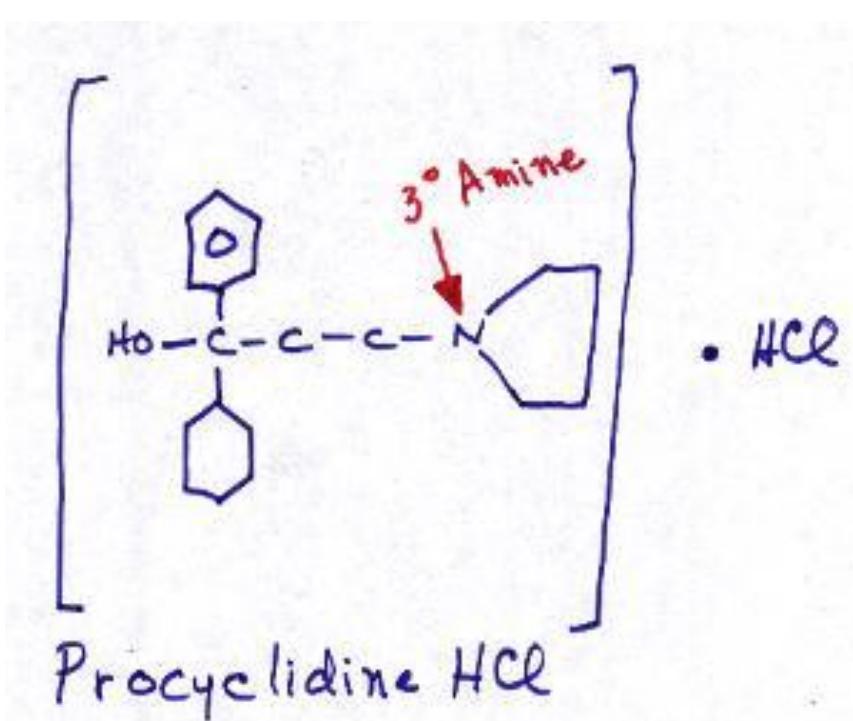
- Dramamine (dimenhydrinate) is used to prevent motion sickness. While its mechanism is unclear, it does appear that its actions may be exerted in both anticholinergic and antihistamine activitites.

Dramamine (Dimenhydrinate)

- Benadryl (diphenhydramine) is an antihistamine that has the added benefit of being an almost innocuous medication that may be used to help some patients fall asleep.

Benadryl (Diphenhydramine)
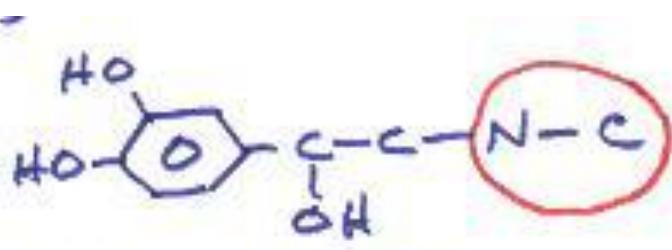
- Another anticholinergic, Procyclidine hydrochloride, is an anti-Parkinsonian medication.

Procyclidine HCl
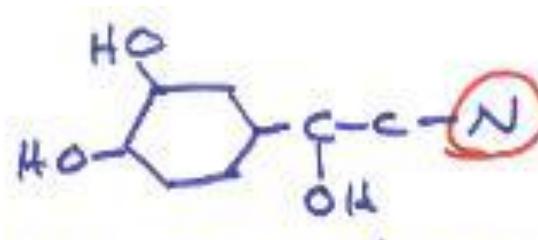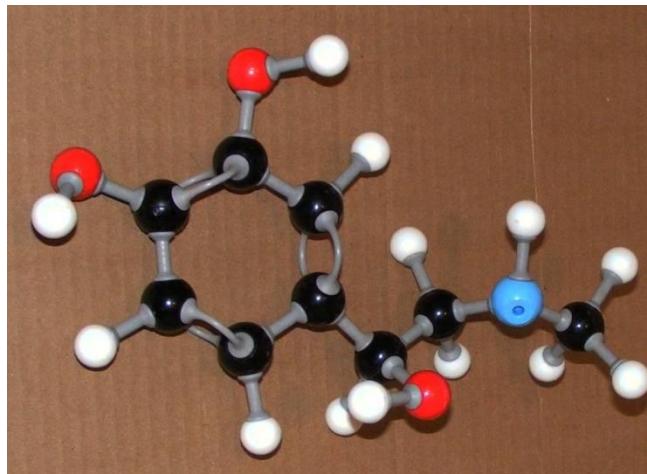
Sympathomimetics

- This class of drugs mimics ("mimetic") sympathetic ("sympatho") catecholamines. Epinephrine elevates the blood pressure, constricts vessels, elevates the respiratory rate, causes bronchodilation and reduces the rate of digestion. Norepinephrine increases the efficiency of muscle contractions and is the neurotransmitter of rage.

Epinephrine
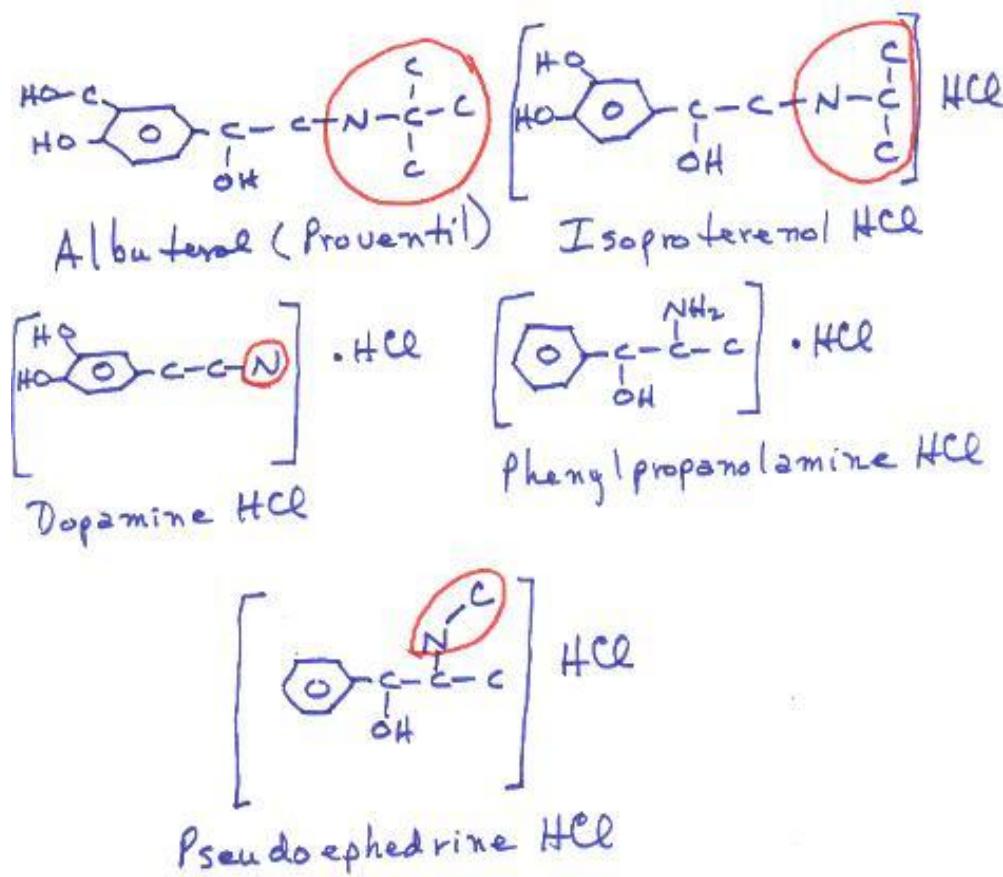
Norepinephrine
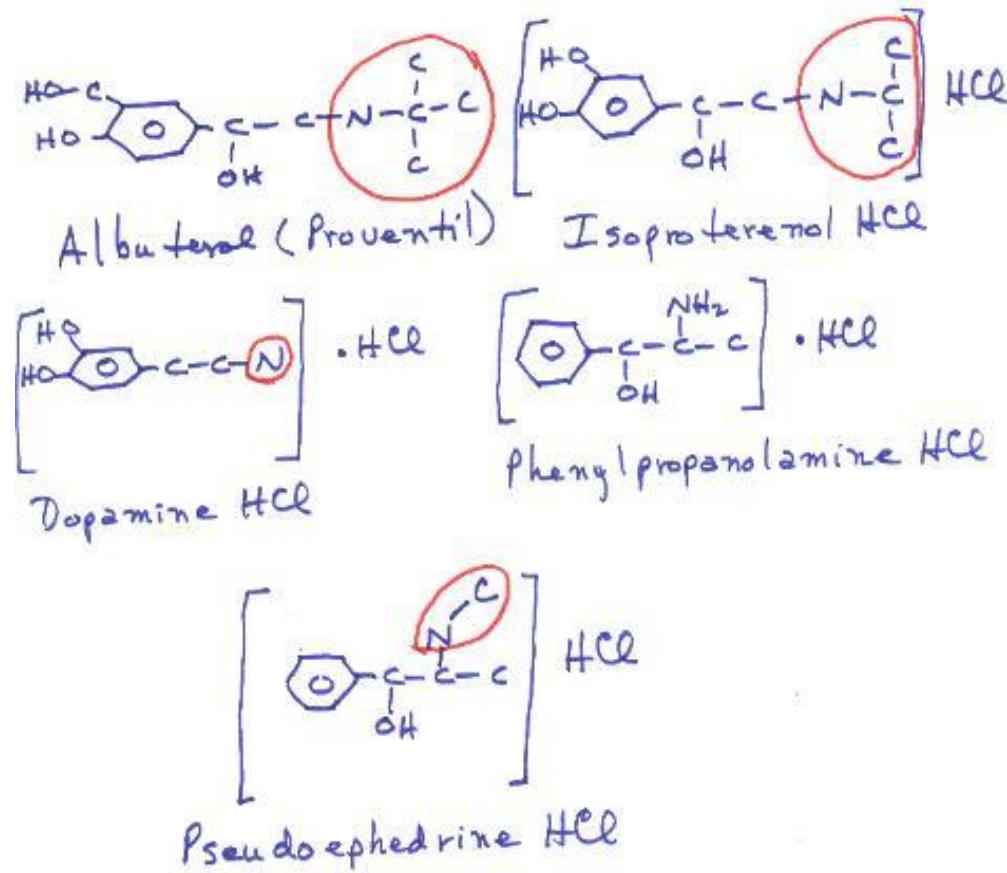
- 5 sympathomimetics and their use follow.

- Note the red-circled parts of their structures and how similar they are to either epinephrine or norepinephrine.

- REMEMBER: we don't use "adrenalin" or "noradrenalin" any more.

- Albuterol: prevention and relief of bronchospasm; may cause tachycardia.

- Dopamine hydrochloride: used to treat mild shock (without major deterioration of kidneys and/or blood pressure).

- Isoproterenol HCl: Aka Duo-Medihaler (Isuprel) -- treats bronchospasm after surgery; management of shock; cardiac arrest.

Albuterol (Proventil)

Isoproterenol HCl

Dopamine HCl

Phenyl propanolamine HCl

Pseudoephedrine HCl
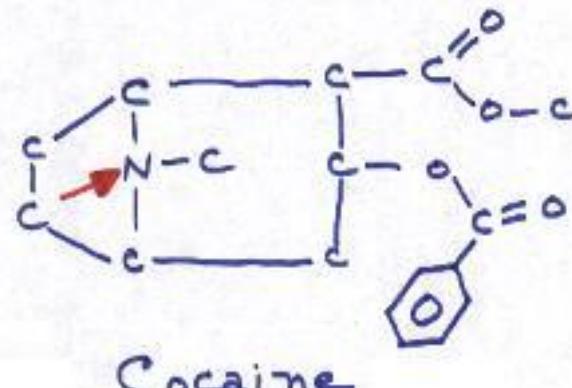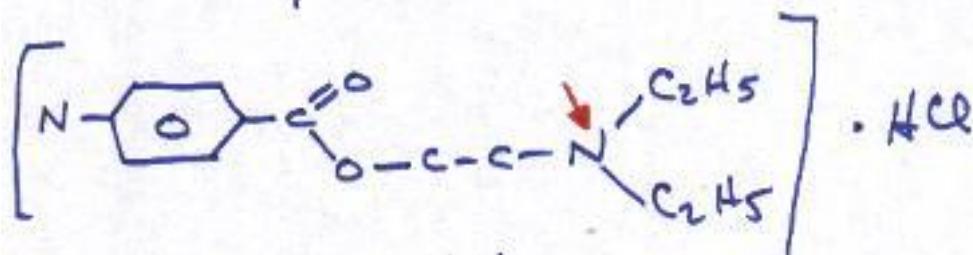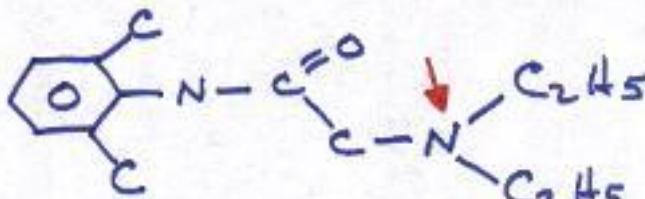
- Phenylpropanolamine HCL: PPA; Used to be the active ingredient in Dexatrim (an appetite suppressor), Naldecon (a nasal decongestant) and Dimetapp (decongestant/ antihistamine); was pulled ca 2000-2001 as it was causing serious cerebrovascular problems for part of the population.

- Pseudoephedrine HCl: PPA "replacement"; in Actifed, Sudafed, Phenergan-D; nasal decongestant (causes "dilated" vessels to "constrict").

Albuterol (Proventil)

Isoproterenol HCl

Dopamine HCl

Phenylpropanolamine HCl

Pseudoephedrine HCl
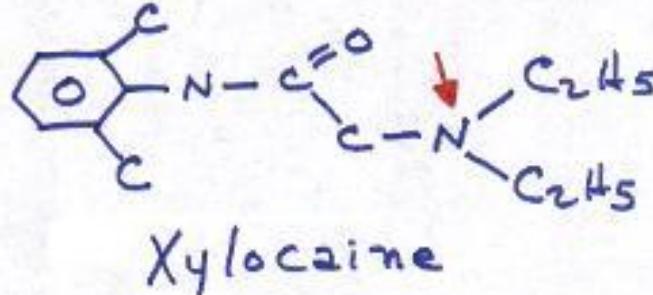
Local Anesthetics
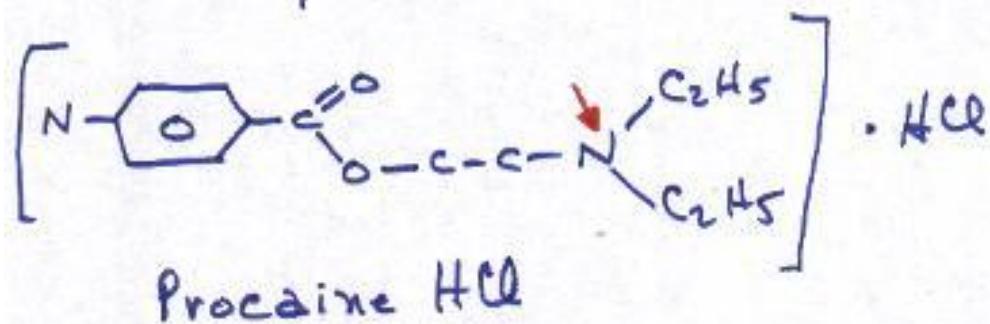
- Act in several ways.
- They act on ion channels that are integral with the cell membrane.
- One mechanism is that they "flow into" the membrane around the Ach receptor, swell and shut down the sodium ion channel.

Xylocaine

Procaine HCl
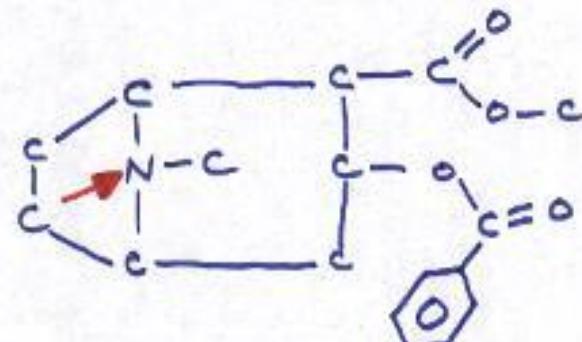
Cocaine

- The second mechanism is that it inhibits directly at the Ach receptor.

Xylocaine
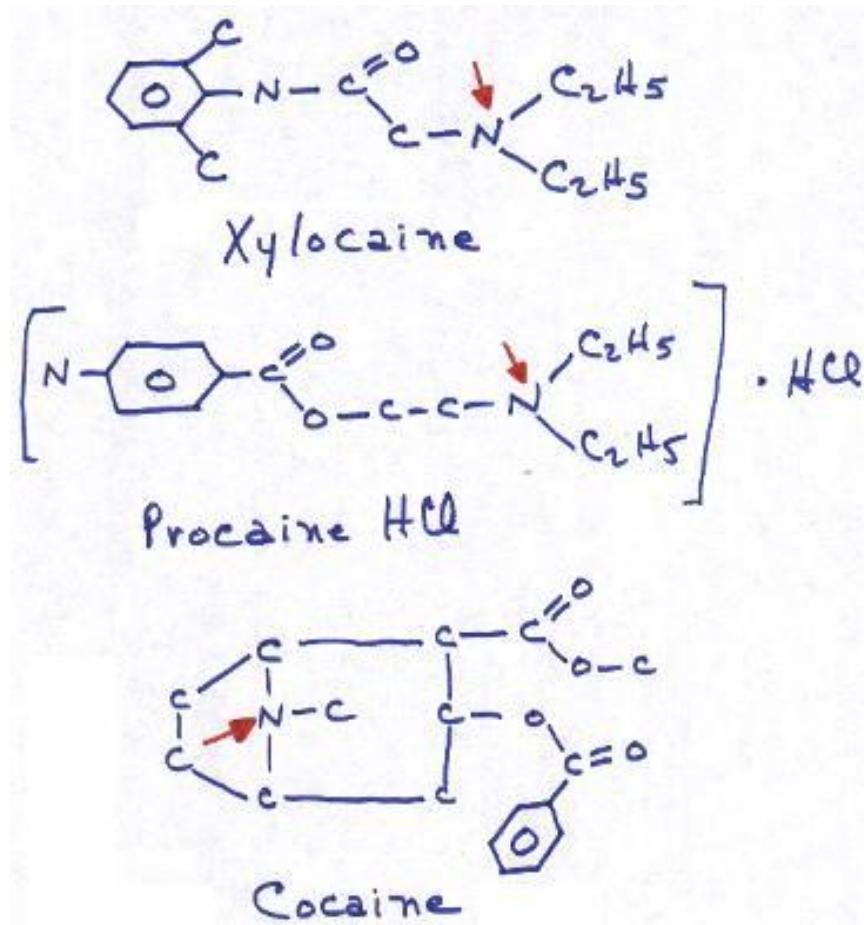
Procaine HCl
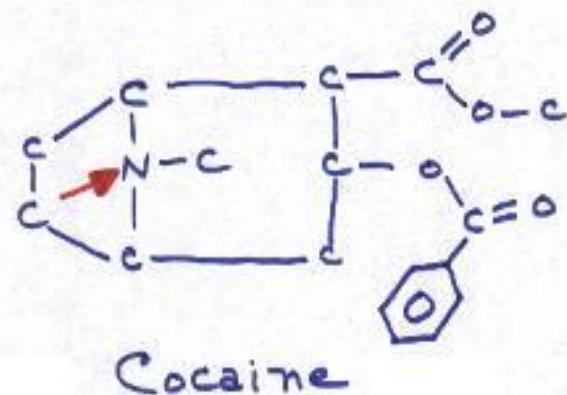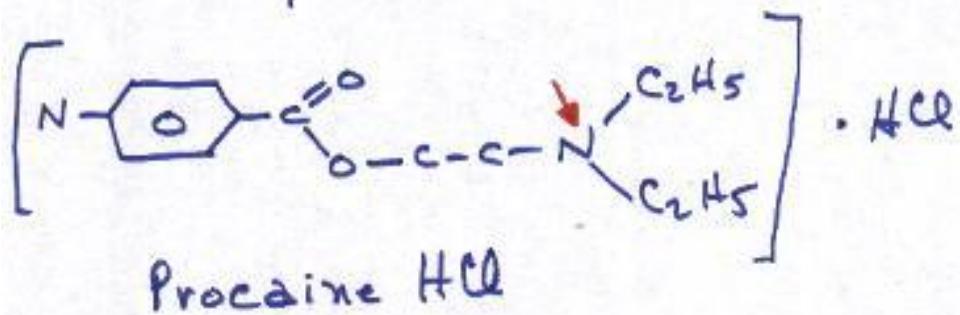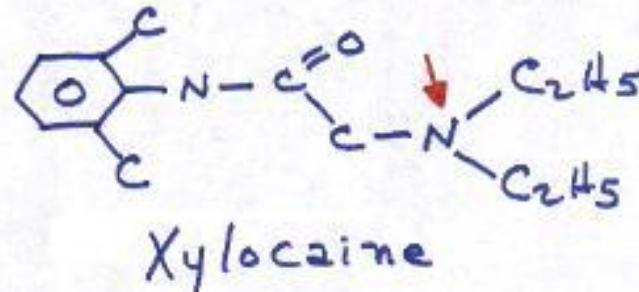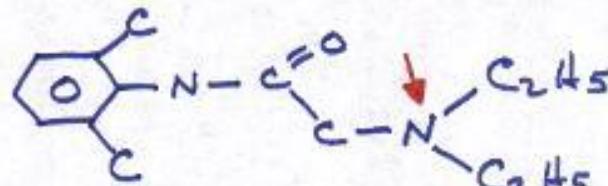
Cocaine

- Lidocaine (Xylocaine) is not only a local anesthetic, it is also a "cardiac relaxer" and ion channel blocker.

- It is often used to treat premature ventricular contractions (PVC's) so that they won't shut the heart off.

Xylocaine

Procaine HCl
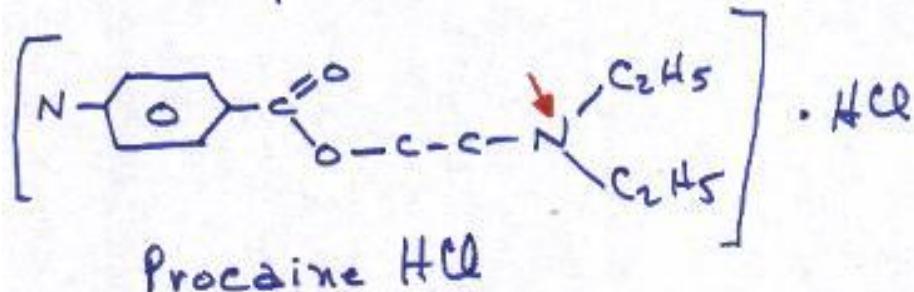
Cocaine

- Procaine-HCl is commonly known as Novocaine.
- This is used in the dental field.

Xylocaine

Procaine HCl
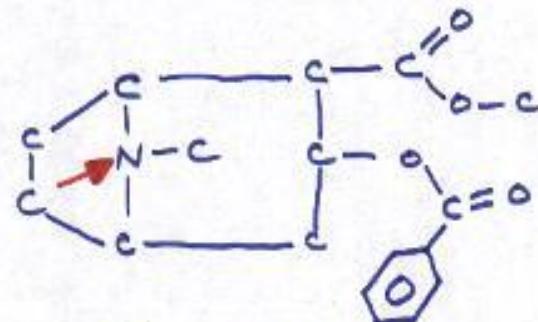
Cocaine

- Cocaine is better known for its street effects.
- It is pyrogenic.
- The onset of cocaine fever is marked by a chill.
- It acts -- when inhaled -- above the brain stem to first reduce the heart rate and elevate the blood pressure, then elevate the heart rate and reduce the blood pressure, cardiovascularly.
- A 5-10% aqueous solution is commonly used to spritz the nasal membranes with when setting a broken nose.

Xylocaine
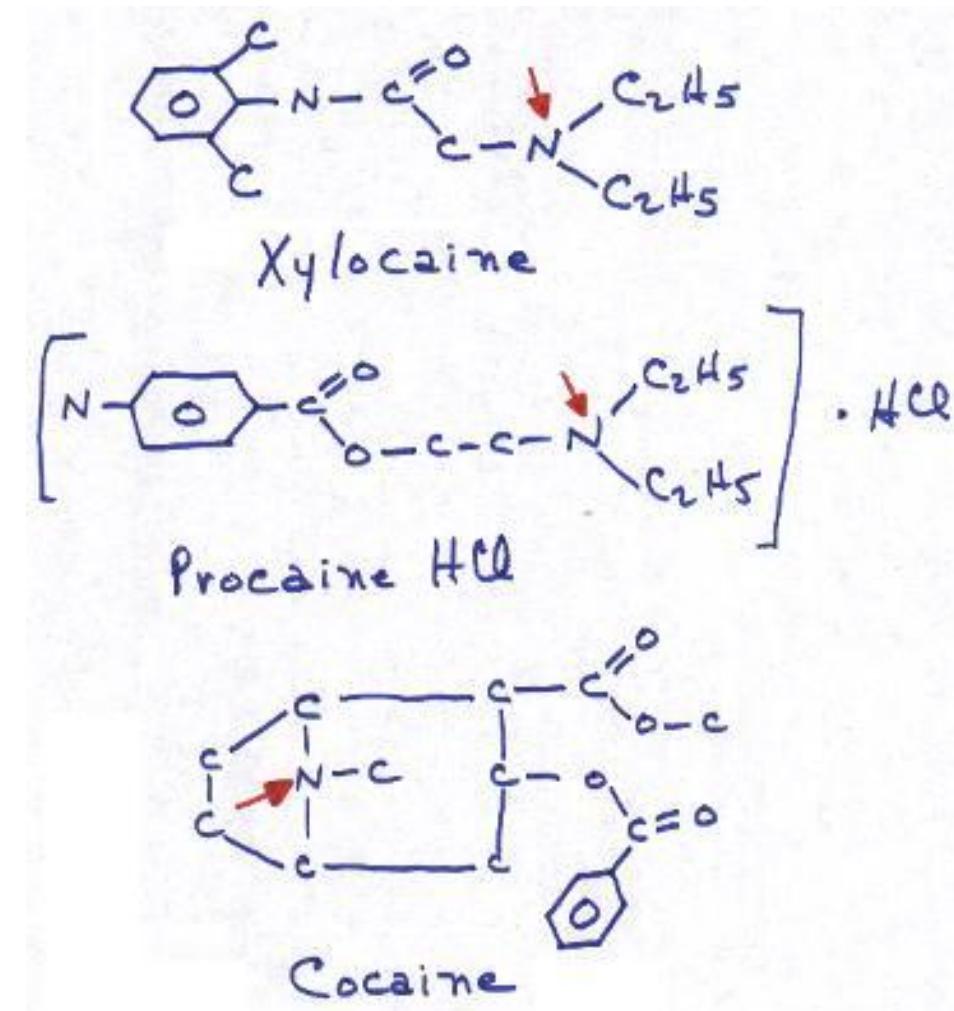
Procaine HCl
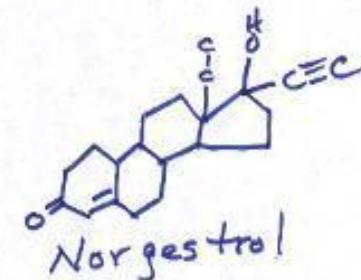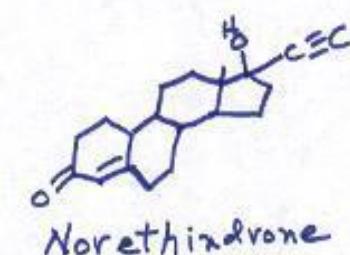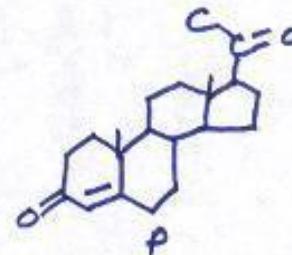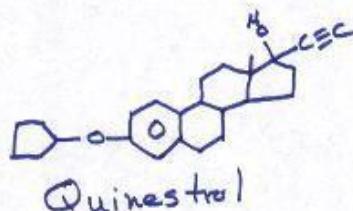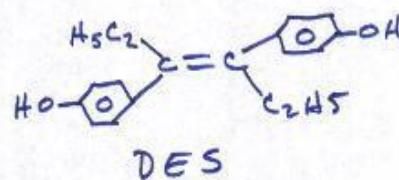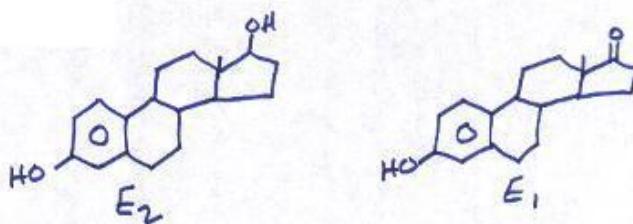
Cocaine

- A note of caution: when any member of the "caine" family is used injudiciously, i.e., without the supervision of a qualified health care provider, they may become hyper-allergenic.
- Benzocaine preps are the worst offenders as it is present in topical, sprayed on, sunburn pain relievers.

Xylocaine

Procaine HCl

Cocaine

Contraceptives

- Contraceptives are based off of the estrogens, E_1 or E_2, and progesterone.
- For the most part, they fool the body into thinking it's pregnant -- since no secondary oocyte is released, sexual activities do not culminate in an unwanted pregnancy, i.e., this inhibits ovulation and pregnancy.
- Nothing, remember, is 100% safe.
- There are a rare number of women who do become pregnant using oral contraceptives.
- **There are more who become pregnant while taking oral contraceptives and some antibiotics, e.g.. penicillin, cephalosporins and tetracyclines, and anti-fungals, e.g., griseofulvin.**

- Oral contraceptives also play a role in aiding women with PMS and dysmennorhea.

- They seem to reduce both PMS symptoms and reduce the cramping associated with painful menstruation.

- There are numerous oral contraceptives available.

- Some come in gradient (multi-level) dosages, e.g., week 1 is highest, week 2 is medium dose, week 3 is lowest dose and week 4 is placebo to initiate breakthrough bleeding.

- In some instances, these sorts of pills don't seem to have enough hormones in the 3d week dose for some women who experience severe PMS.

- For these women, dosages of high, medium, medium, placebo (week 1, 2, 3, 4 dosages, respectively) are available.

- In this day and age of better living through chemistry, e.g., oral contraceptives, selective serotonin reuptake inhibitors (SSRI's), NSAID's, to name a few, there is virtually no pharmacological reason why a woman needs to succumb to the effects, e.g., misery, emotional pain or physiological symptomatology, of PMS (or the newly recognized PMDD) or dysmenorrhea.

- A woman's family physician or ob/gyn working with the woman can find a combination of meds that are best for her to relieve her symptoms.

- Appropriately treated, women who have succumbed to these conditions find a whole new perspective on life that allows them to see the world in a whole new, positive and constructive light.
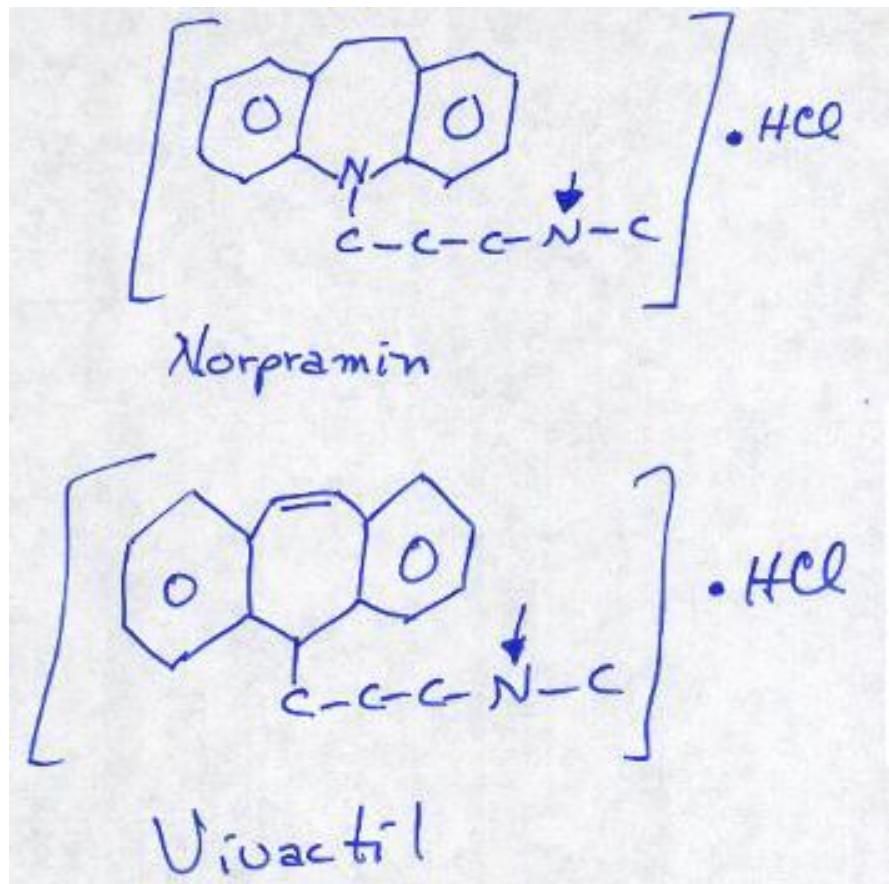
ACADEMIC ASIDE

- Although this is somewhat a non sequitur, and may or may not fit in with PMS and/or PMDD, it seems reasonable to comment on levels of 5-HIAA (5-hydroxyindoleacetic acid -- primary serotonin metabolite).

- 5-HIAA levels found in the CSF of patients who died from violent suicide were incredibly low.

- 5-HIAA levels were also low in murderers and other violent offenders.

- 5-HIAA levels were elevated in obsessive compulsive disorders, sociopaths and those with guilt complexes.

- In each case, these levels (too low or too high) cause clinical depression.

- Excessively high levels of norepinephrine lead to a manic state, while exceedingly low levels of norepinephrine lead to depression.
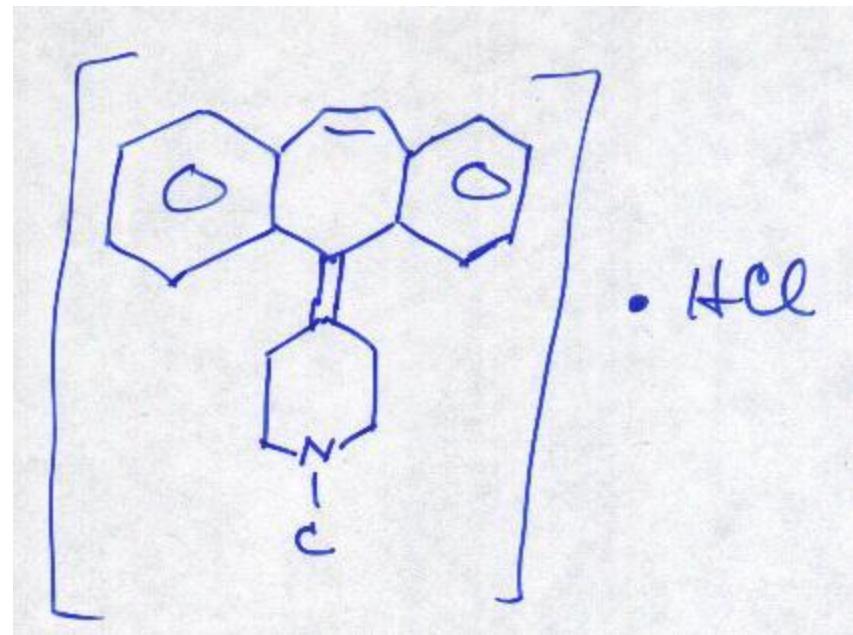
END OF ASIDE

Tricyclic Anti-Depressants

- Norpramin and Vivactil are representative of this group of medications. Tricyclics, so called because of the 3 (tri) fused rings (cyclic) in their structures, putatively block the reuptake of norepinephrine and serotonin, thereby elevating intra-synaptic concentrations of norepinephrine and serotonin. This elevation of neurotransmitter concentrations in the synapse provides relief of symptoms.
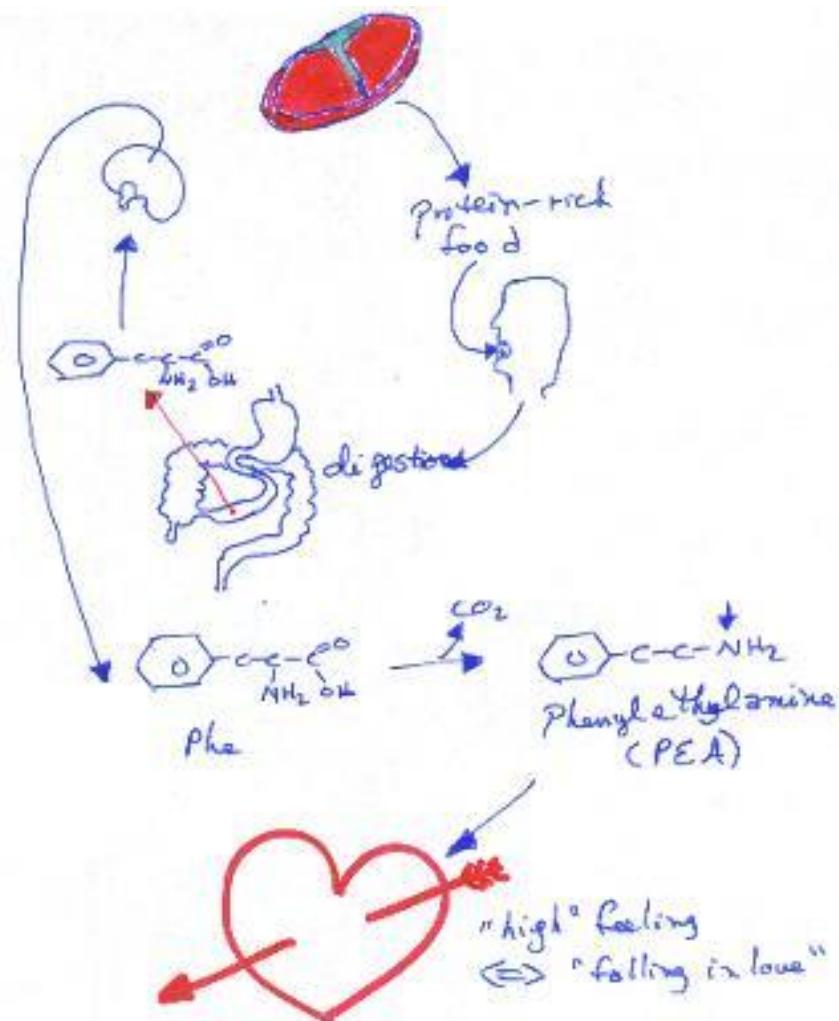
- Although Periactin is included in this portion of the discussion on tricyclics, it seems to be more anti-histaminergic and anti-serotonergic.
- While it is used primarily for allergies, it is the one drug that temporarily and rapidly overcomes the inhibitory effects of SSRI's on libido, e.g., if one wishes to participate in sexual intercourse, at the "right" moment, one takes the periactin and participates in that activity, successfully.
- The drawback is that periactin is such a powerful anti-histamine that it rapidly induces deep sleep, i.e., no cuddling afterwards.

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- Some tricyclics have weak H_1 activities; other "classical" antipsychotic drugs have both H_1 and H_2 antagonistic activity, e.g., hydroxyzine hydrochloride.
- Pretty interesting the relationship between norepinephrine, serotonin and histamine, huh?! Hard to separate them from each other, many times.

Phenylethylamines
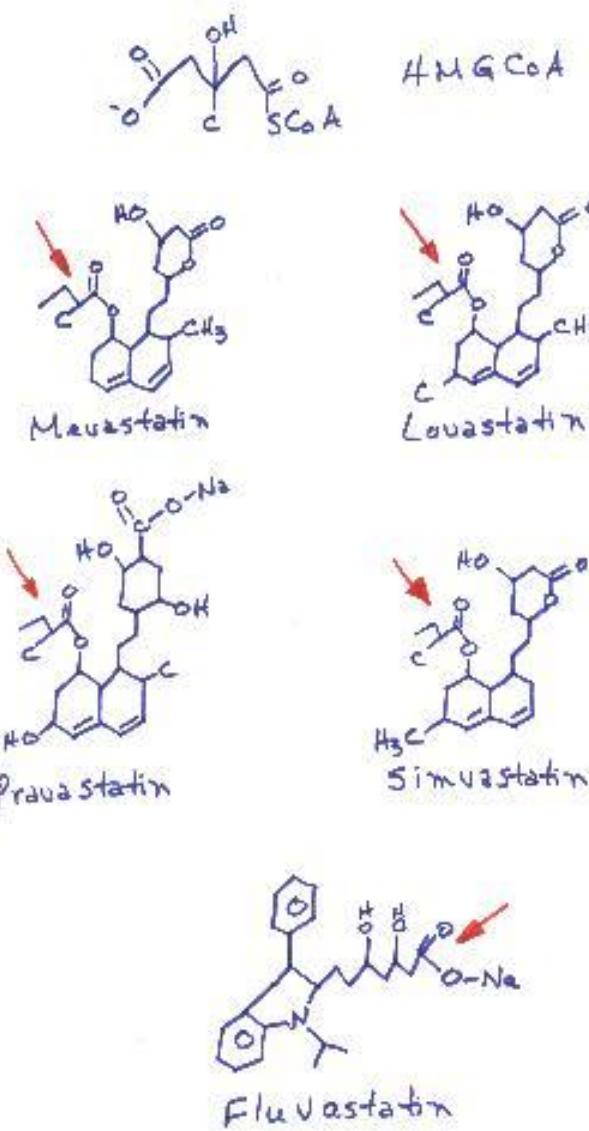
- While we're on the subject of mind altering compounds, the phenylethylamines deserve some mention.

- These are a class of compound that is obtained by eating protein-rich food that contains high levels of phenylalanine.

- When digested and absorbed, the brain decarboxylates phe to phenylethylamine (PEA).

- PEA is released, driving the neurosis of "falling in love" and the concurrent "high" feeling that goes along with it.

- Truly, the way to a partner's heart, so to speak, is through his or her stomach.
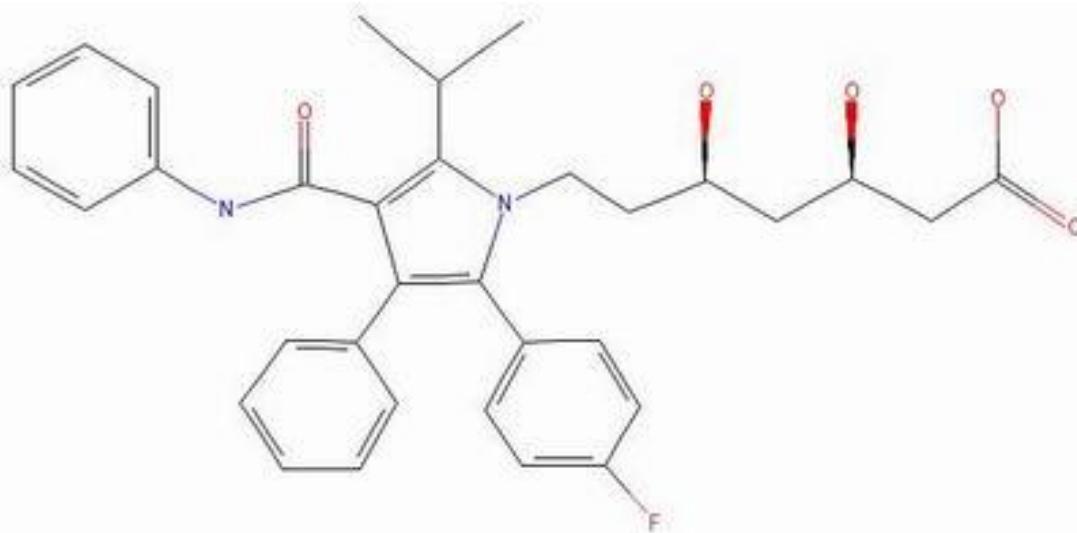
HMGCoA Reductase Inhibitors

- Are used to treat hypercholesterolemia.
- They, as their name implies, inhibit HMGCoA reductase.
- Remember that this is the enzyme of major control in cholesterol biosynthesis.
- If you look closely at the portion of each inhibitor, you'll notice in the graphic a red arrow.
- The red arrow points to the region of the molecule that fits into the active site of the enzyme.
- It fits because it "looks" like HMGCoA.

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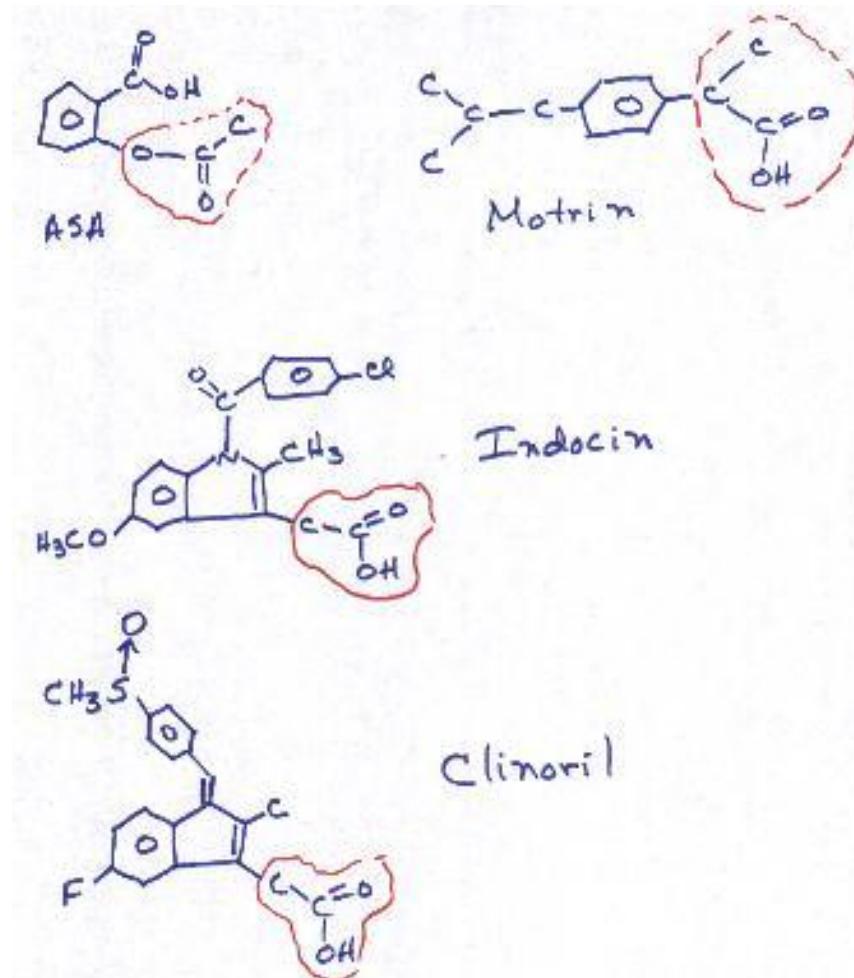
Lipitor -- atorvastatin

This medication does not work on its own. The patient must be willing to alter their daily routines, including their daily diet and their level of daily exercise. Eating high cholesterol and foods high in saturated fats while taking this medication may result in unpleasant side effects including anal leakage, distressed gaseous releases, and sour auditory releases. These effects can be embarrassing and can cause the patient to become deterred from a healthier lifestyle.

http://www.medicalook.com/reviews/Atorvastatin.html
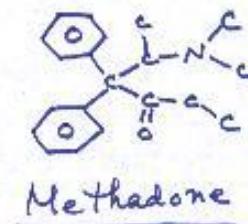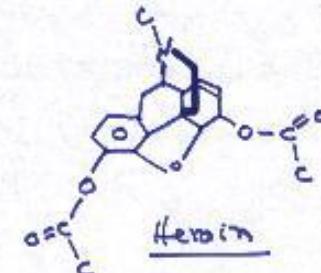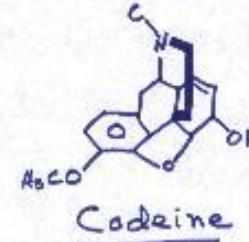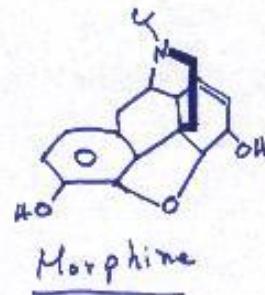
Cyclo-oxygenase inhibitors

- This group is rapidly changing with the isolation, identification and purification of two types of the enzyme: cyclo-oxygenase I (COX-I) and COX-II.

- For the purposes of this course, we'll limit our discussion, brief as it is, to COX inhibitors of the broadest nature.

- The regions circled in red are the regions of these non-steroidal anti-inflammatory drugs (NSAID's) that bind to COX, thereby inhibiting prostaglandin synthesis.

- Recently (12'ish/2004), COX-II inhibitors (e.g., Celebrex and Vioxx) have come under scrutiny because of their increased risk of MI
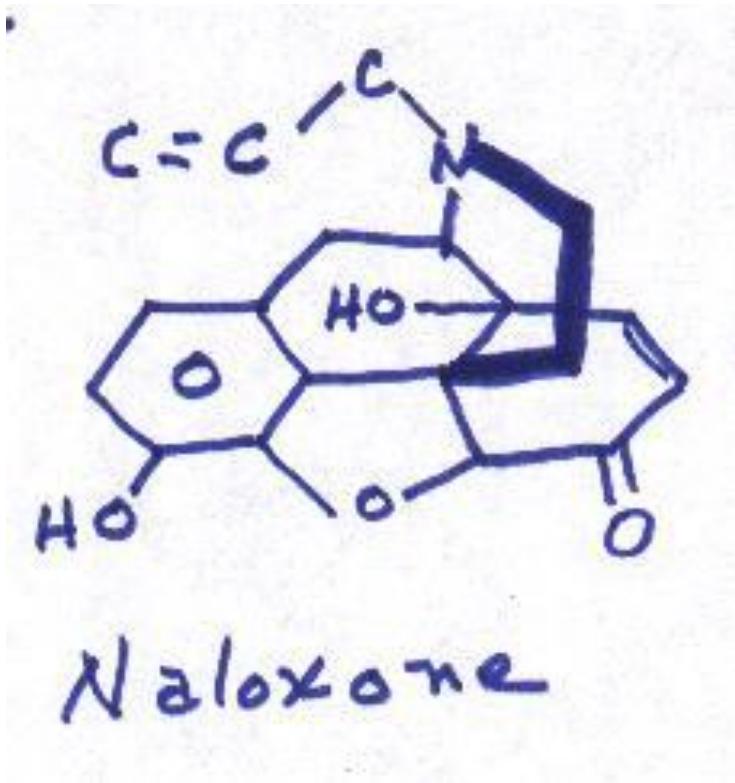
Opiates

- Morphine, codeine and heroin are all structurally related.
- Note that the difference between the 3 are slight and that each has a ring that lies perpendicular to the flat 4-fused ring structure of each compound.
- It is this shape that gives the function to these drugs.

Morphine

Codeine

Heroin

Methadone
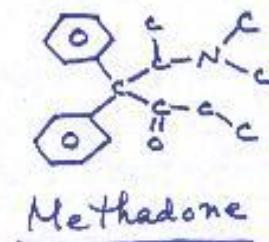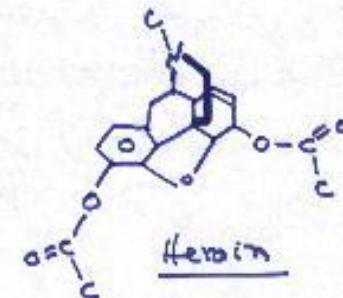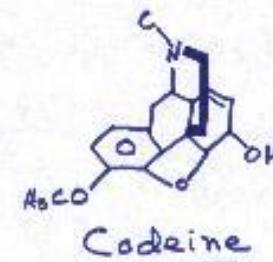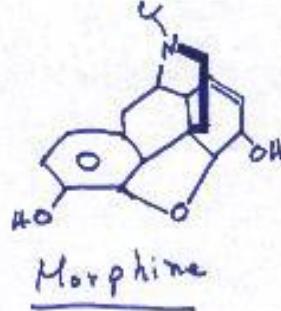
= portion of ring coming out of plane towards you

- Also structurally related to opiates, is useful in treating opiate overdoses as it possesses anti-opiate activity.

- It is better known as Narcan.

Naloxone
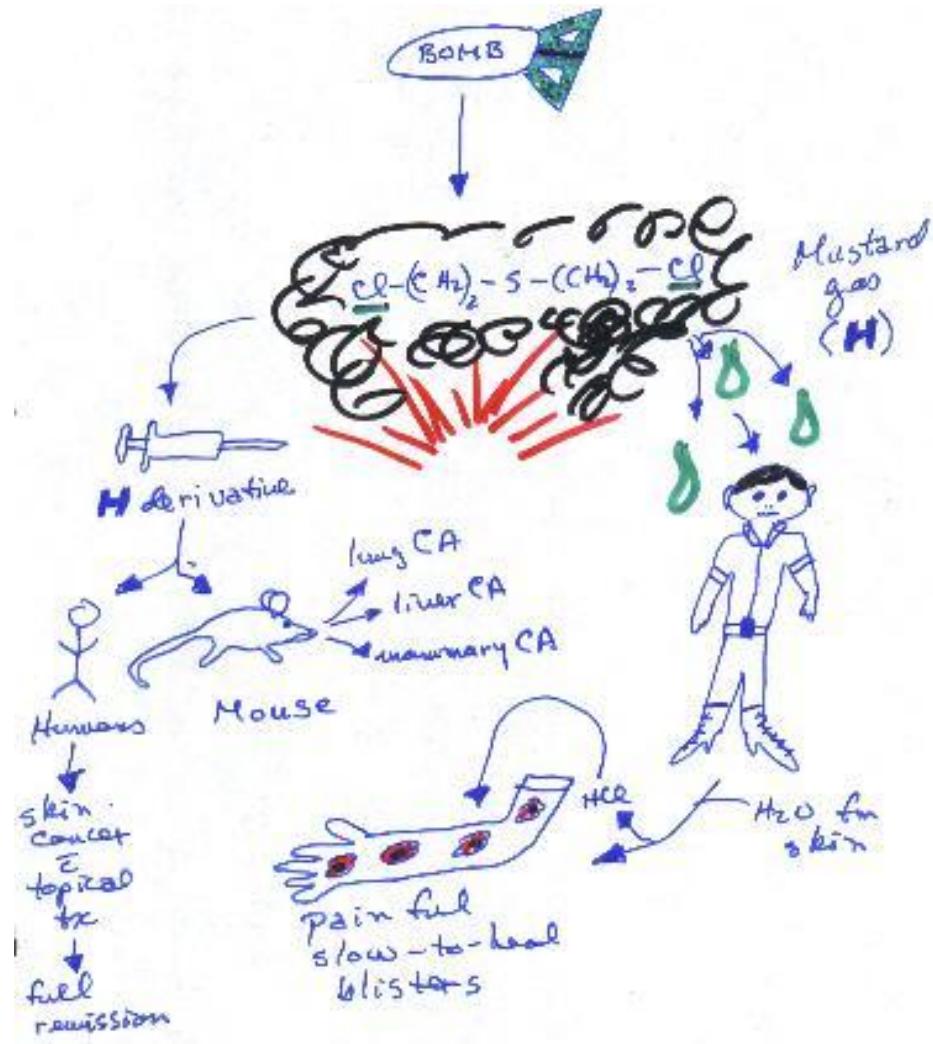
- While not exactly structurally equivalent to heroin, has been used for a number of years to treat heroin addicts.

- It seems, though that these addicts are now addicted to the methadone which they receive from government-operated clinics.

Morphine

Codeine

Heroin

Methadone

= portion of ring coming out of plane towards you
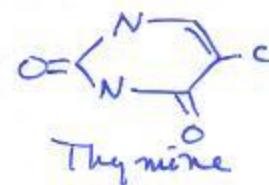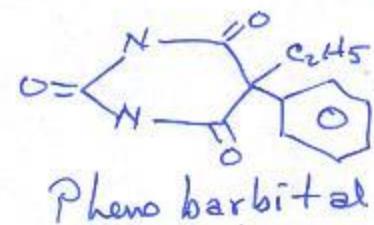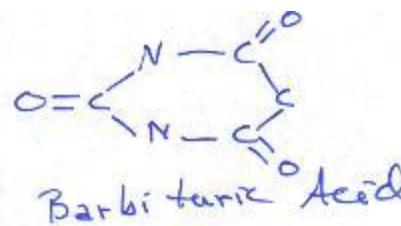
Alkylating Agents

- Less clear, but interesting to study are alkylating agents.
- These are agents that transfer alkyl groups to biologically active compounds.
- The best example is mustard gas.
- This was developed as a warfare agent that could be dropped in bomb form.
- When it exploded, the "mustard" got on the soldiers and reacted with the skin water causing painful, slow to heal blisters.
- By a fluke, it was discovered that derivatives of mustard gases, when injected into mice, would treat lung, liver and mammary cancer.
- When put topically onto some human skin cancers, it caused full remission.

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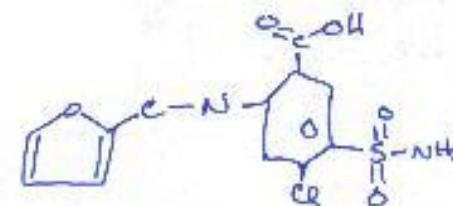
Barbiturates

- Barbiturates are derivatives of barbituric acid.
- The story goes that the scientist who developed barbituric acid was dating a young lady named Barbara.
- Whether true or not, we have barbituric acid -- don't know how the relationship thing turned out, either.
- Phenobarbital, a derivative of barbituric acid, is an anti-convulsant.
- There are two potential problems with this medication: 1) when taken with alcohol, the actions are beyond synergistic and cause death at doses independently non-lethal and 2) it effects protein synthesis.
- Phenobarbital resembles thymine.
- Enzymes confuse thymine with phenobarbital and cause the synthesis of abnormal proteins.
- Care is mandated when taking this medication -- as with all medications.

Barbituric Acid

Phenobarbital

Thymine
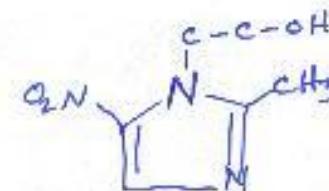
Miscellaneous and Unclassified
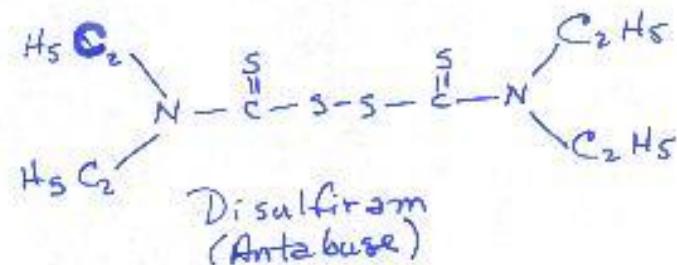
- This category is a just for fun part of this section.
- These drugs cover the gamut of diuresis (Lasix), T. vaginalis, G. lamblia and Clostridial infections (Flagyl) and aldehyde dehydrogenase inhibition (Antabuse).
- The latter effect was discovered by the 2 Danish physicians who were originally studying this drug as an anti-helminthic (to treat worm infestations in humans).
- They had taken the drug and experienced the effects at a cocktail party.
- Antabuse is rarely used, any more, as its effects can be fatal.
- It was originally used to treat recovering alcoholics to discourage them from drinking: when taken with alcohol, they became violently ill -- some died.

Furosemide (Lasix)

Metronidazole (Flagyl)

Disulfiram (Antabuse)

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Vitamins with Bio-Organic Chemical Applications

Introduction to Intra-Cellular Metabolism

Enzyme Review: Enzymes are Biological Reaction Catalysts

Enzymes have specific functions and are categorized into 6 activities according to the Enzyme Commission.

- Oxidoreductases (EC 1.x.x.x): catalyze redox reactions -- involve NAD and FAD

- Transferases (EC 2.x.x.x): catalyze group transfers

- Hydrolases (EC 3.x.x.x): use water to lyse bonds

- Lyase (EC 4.x.x.x): nonhydrolytic and non-oxidative group removal

- Isomerases (EC 5.x.x.x): catalyse isomerization reactions

- Ligase (EC 6.x.x.x): catalyzes reactions requiring ATP hydrolysis

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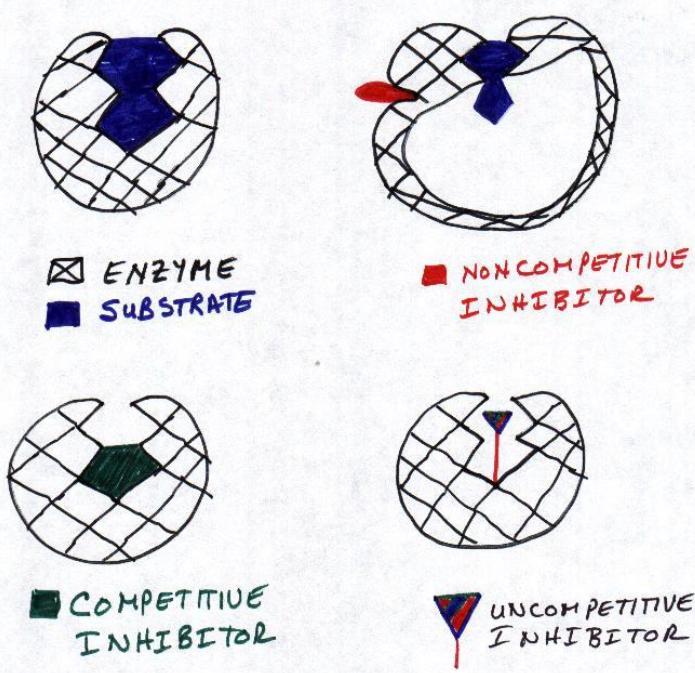
Enzymes

- 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.

Enzymes

- There are two generally accepted models for the functioning of enzymes:
  - the lock and key model and
  - the induced fit model

Enzyme Inhibition

☒ ENZYME
■ SUBSTRATE

■ NONCOMPETITIVE INHIBITOR

■ COMPETITIVE INHIBITOR

▼ UNCOMPETITIVE INHIBITOR

1. <u>ES</u> – Normal – Lock-n-Key – post-Induced Fit, as well

2. <u>Competitive inhibition</u> 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.

3. <u>Uncompetitive inhibition</u>: 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.

4. <u>Noncompetitive inhibition</u>. 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.

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Enzymes

- May also be activated, i.e., turned on, to provide necessary substrates for biochemical pathways

- Also done non-competitively (like the inhibition only in reverse), called allosteric regulation

- aka positive feedback

- As a general rule, whenever you hear "kinase", think ATP and magnesium ions.

- Hexokinase is a generic enzyme, capable of "working" on most hexoses.

- PFK is one of the major regulatory enzymes in the EMP pathway.

Solubility
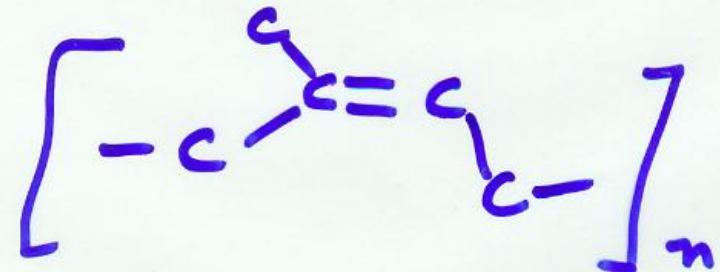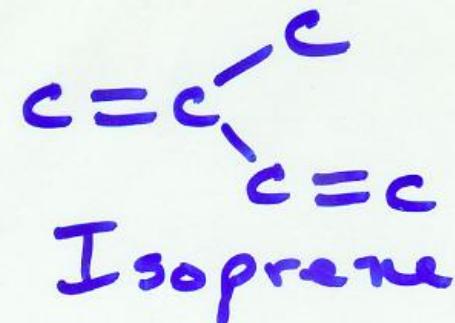
- **Fat Soluble**
- K
- A
- D
- E

- **Water Soluble**
- Ascorbic acid (C)
- Biotin
- Folic acid
- Pantothenic acid
- Thiamin (B_1)
- Riboflavin (B_2)
- Nicotinic acid
- Pyridoxine (B_6)
- Cynocobalamin (B_{12})

The Fat Soluble Vitamins:

Vitamins A, D, E, and K
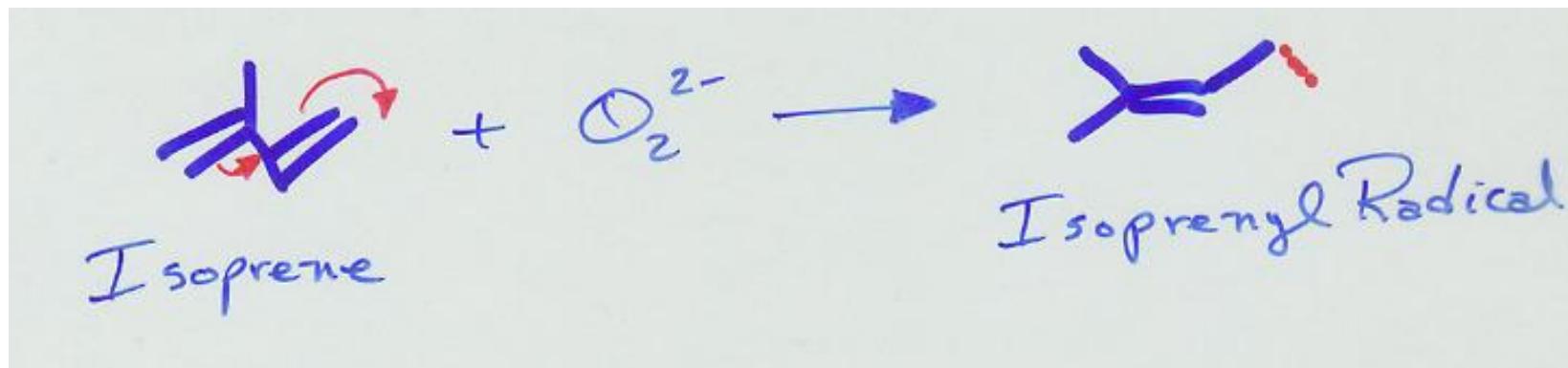
Fat Soluble Vitamins and Isoprenes

- What is the relationship between fat soluble vitamins and isoprenes?
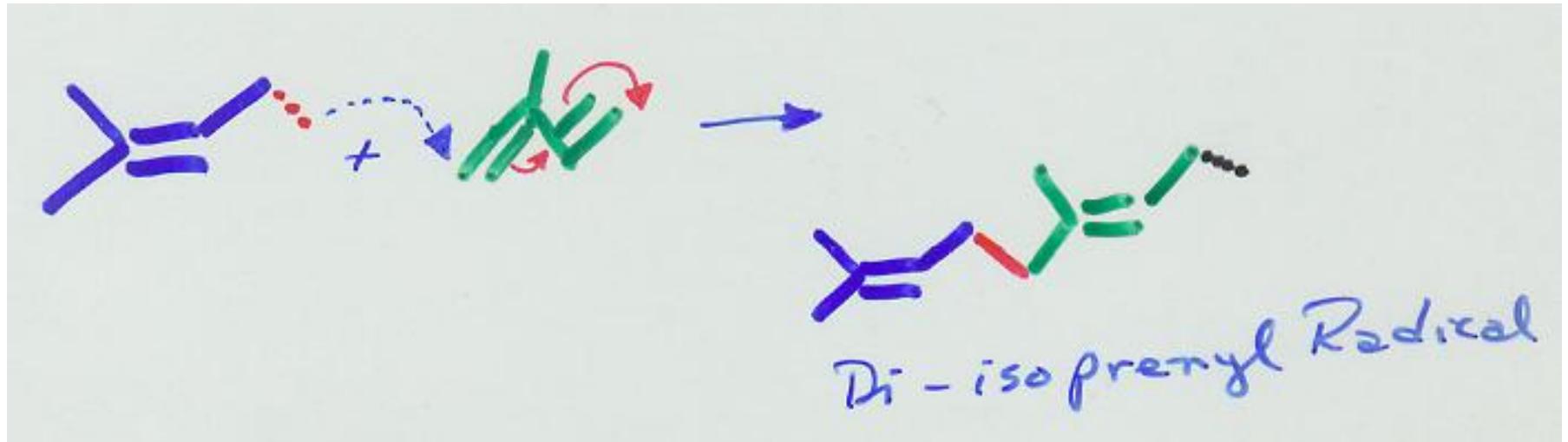
Natural Rubber Synthesis
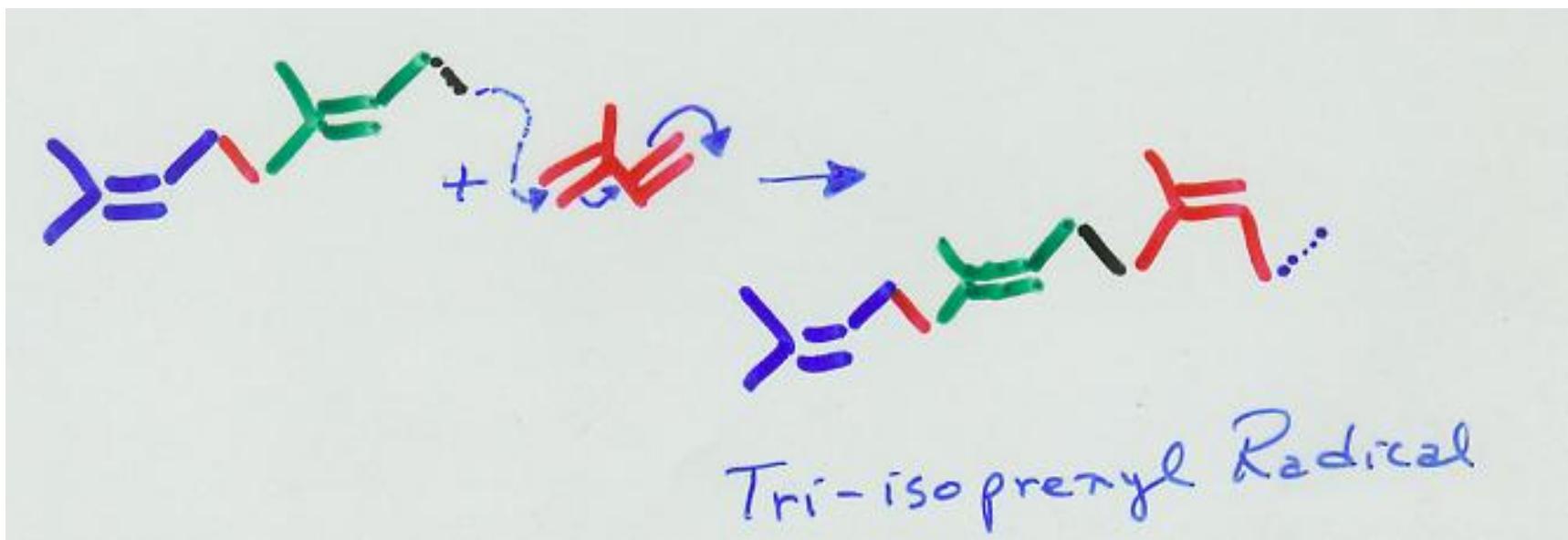
- Free Radical Addition
- Free Radical = an atom or group of atoms possessing an odd (unpaired) electron

Isoprene + O_2^{2-} $\longrightarrow$ Isoprenyl Radical

- Di-isoprenyl Radical formation

Di - iso prenyl Radical

- Tri-isoprenyl Radical Formation

Tri-isoprenyl Radical

- All cis-polyisoprene

255
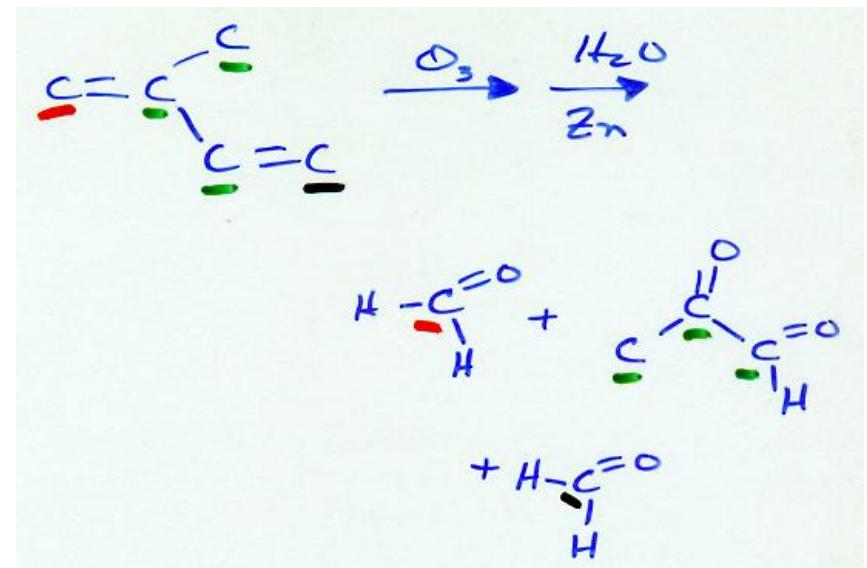
- Vitamins A, D, E and K are isoprenoids
- Cholesterol is an isoprenoid

Ozonolysis

- Same thing happens to rubber in tires even though they have vulcanized rubber in them

- Just goes slower is all
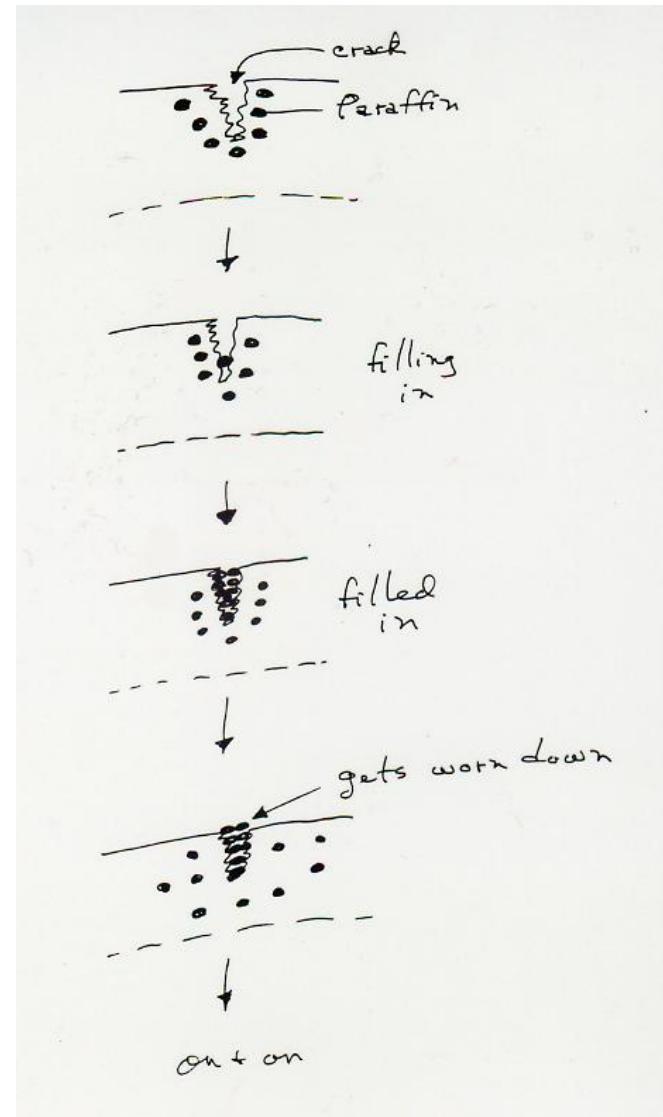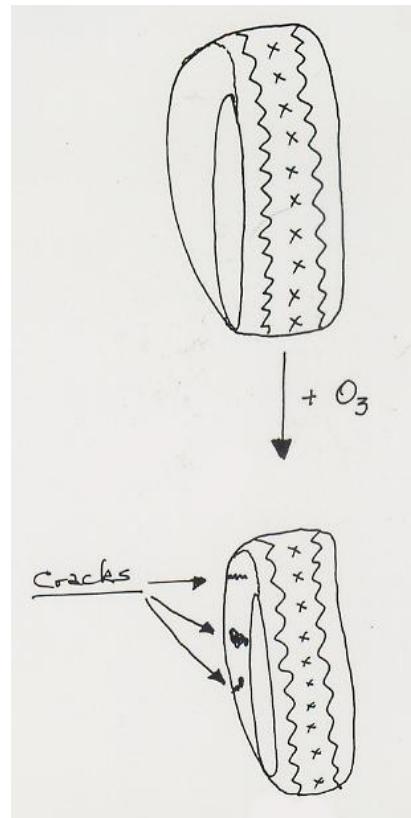
- How to stop this ozonolysis?
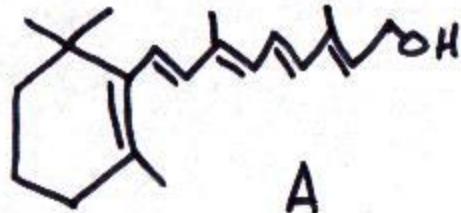
- Paraffins

- Migrates to the surface of the tire to fill gap created by loss of surface paraffins

- Wax seals cracks -- automatically

Vitamin A

- The chemical structure of Vitamin A (specifically, all-trans-retinol).
- Dry forms are stable.
- Vitamin A is commonly used as a supplement.
- When dilute and exposed to light, oxygen and high temperatures, it is polymerized, oxidized and isomerized.

- The major site of lipid hydrolysis is the upper small bowel.

- This is important, for retinol in the bile salt-micelle is well absorbed (70-90%) from the small bowel. β-carotene (precursor for vitamin A) is cleaved into two molecules of retinol by mucosal cells in the small bowel.

- As general rule, 1 IU = 0.3 mg ALL trans-retinol and 1 IU = 0.6 mg PURE β-carotene. β-carotene is the most active pre-vitamin A compound.

- On average, other precursors have about 50% the growth promoting action of β-carotene.

Functions of Vitamin A

- Vitamin A has specific effects on vision (as an electron carrier) and cell differentiation.

- Decreased Vitamin A levels effect amino acid metabolism, the immune system, the reproductive system, the structure/function of most cells in the body and reduces food intake.

- In terms of cell differentiation, hypovitaminosis A causes mucous secreting cells to be replaced by keratin producing cells in many tissues.

- The converse has been demonstrated in tissue culture.

- This suggests that vitamin A triggers differentiation by creating specific metabolic imbalances (putatively in ions, amino acids or other essential metabolites).

- There is data that also suggests that vitamin A mediates the effects of hormones.

- Reproduction is particularly dependent on normal vitamin A levels.

- Vitamin A also influences embryogenesis.

Vitamin A Deficiency

- Signs in pre-school children include night blindness (due to reduced levels of rhodopsin), reduced vitamin A blood levels, eye disorders involving conjunctiva and cornea.

- All appear to be secondary to reductions in mucous secreting cells of the cornea and conjunctiva.

- In general, skin changes occur (phrynoderma; toad skin), hair follicles become enlarged and/or obstructed due to low levels of vitamin A and increased susceptibility to infection.

Hypervitaminosis A

- There are two syndromes:
  - Acute -- a high dose taken one time which corresponds to 200 mg vitamin A or greater in an adult or 100 mg or greater in a child -- and
  - Chronic -- many smaller doses over a prolonged period of time.

Acute Hypervitaminosis A

- The acute syndrome is characterized by N/V, headache, diplopia, and increased cerebrospinal pressure.

- For patients who have taken more than 200 mg, the S/S include drowsiness, inappetence, decreased physical activity, optic itching and vomiting.

- For doses much, much, much greater than 200 mg, this can be LETHAL, leading to deep coma, convulsions, respiratory irregularities and death.

Chronic Hypervitaminosis A

- The chronic syndrome leads to
  - spontaneous abortions,
  - birth defects (e.g., cleft palate),
  - permanent learning disabilities,
  - embryonic imperfections,
  - microcephaly,
  - microtia, cleft palate,
  - congenital heart disease and
  - CNS disorders.

- S/S include
  - alopecia,
  - bone pain,
  - diarrhea,
  - edema,
  - epistaxis,
  - fatigue,
  - fever,
  - headache,
  - insomnia,
  - menstrual irregularities,
  - polydipsia and
  - weight loss.
- Yellow skin also goes along with increased carotenoids.
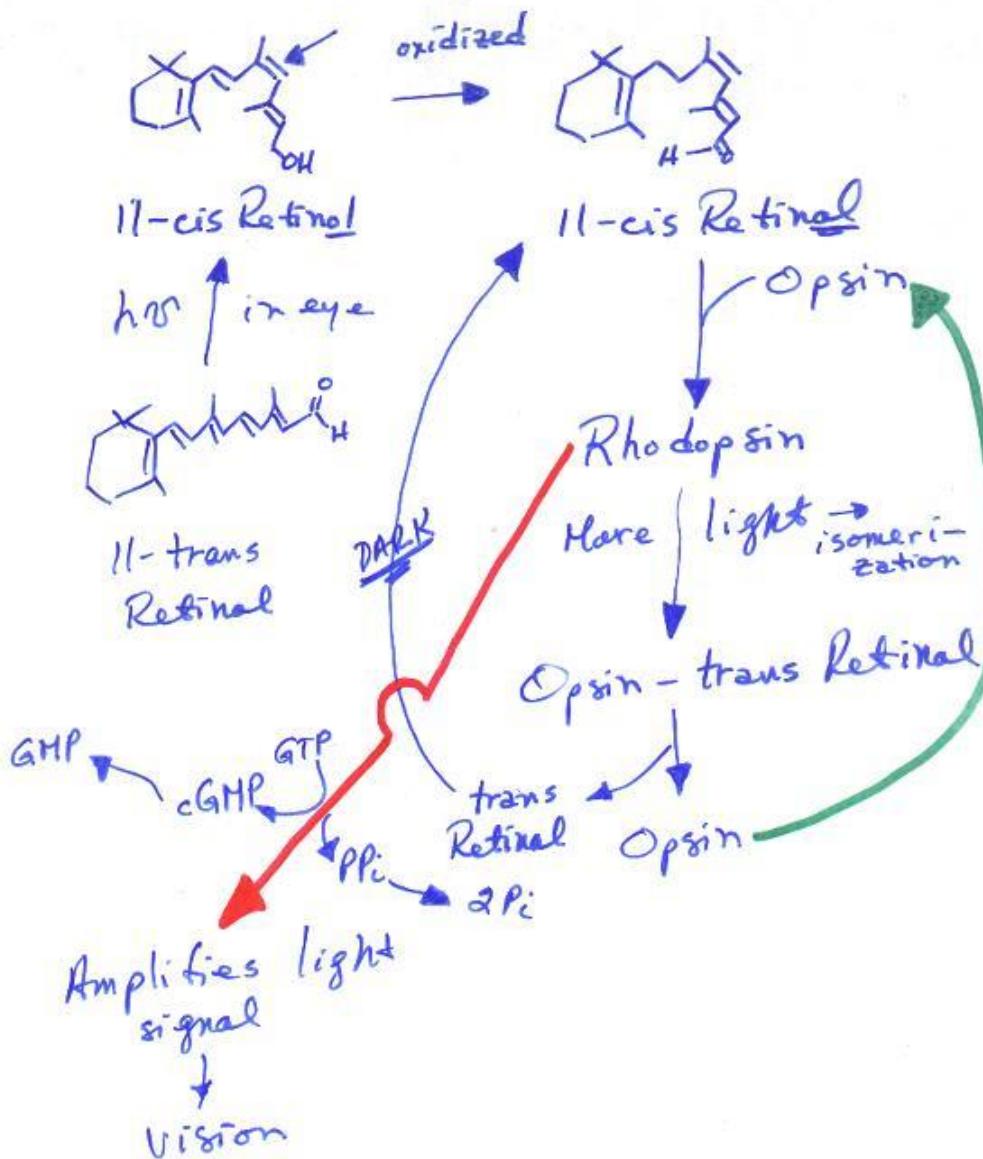
High Risk Clinical Situations

- These situations include
  - prematurely born infants during the 1st two months of life,
  - fat malabsorption syndrome (gall bladder disease, diarrhea, cirrhosis),
  - reduced digestion/absorption of vitamin A,
  - total parenteral nutrition (TPN; creates another problem as vitamin A may be adsorbed by the tubing).
- Ethanol (grain alcohol), halogenated hydrocarbons and phenobarbital all reduce liver reserves of vitamin A.
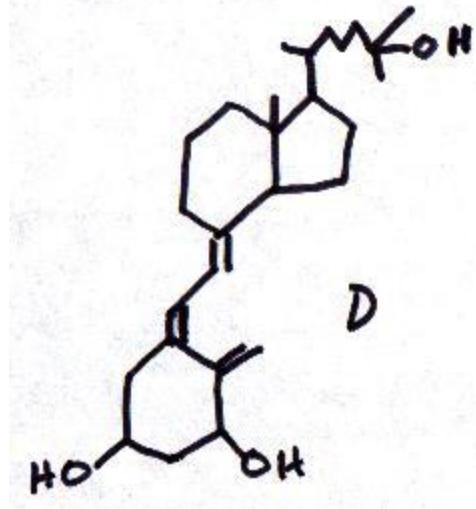
Vitamin A Food Sources

- Pre-formed vitamin A:
  - liver,
  - whole milk,
  - whole eggs,
  - chicken meat, and
  - fat-containing products.

- Pro-A carotenoids:
  - carrots,
  - spinach,
  - yams,
  - dark green leaf lettuce, tomatoes,
  - yellow maize, papayas,
  - ripe mangoes, oranges,
  - deep green fruits and
  - vegetables.

- The significance of Vitamin A for vision.
- Once Vitamin A or β-carotene are ingested, they are either taken up (Vitamin A) or hydrolyzed in the gut (β-carotene) to Vitamin A derivatives.
- Following appropriate metabolic schema, the product that we are most interested in is 11-all-trans-retinal, Figure, following slide.
- When light enters the eye, it causes the 11-all-trans-retinal to undergo isomerization and reduction to 11-cis-retinol.
- The 11-cis-retinol is then oxidized to 11-cis-retinal.
- This latter molecule reacts with opsin to form rhodopsin.
- Rhodopsin amplifies the light signal in the retina which permits vision to occur.
- Once more light enters the eye, it causes further isomerization to 11-cis-retinal, permitting MORE rhodopsin to be formed for vision.
- Note, too, that in order for the light signal to be amplified that it requires a great deal of energy, i.e., GTP being hydrolyzed to cGMP and the equivalent of 2 phosphates.
- When light no longer enters the eye, rhodopsin is hydrolyzed to form opsin and 11-cis-retinal, both of which will be available for the next cycle of light entering the eye.
- We know, of course, that low intake of Vitamin A leads to night blindness, among other things.
- Fat uptake also effects the uptake of Vitamin A across the bowel.

oxidized

11-cis Retinol

11-cis Retinal

hν in eye

Opsin

11-trans Retinal

DARK

Rhodopsin

More | light → isomeri-zation

Opsin - trans Retinal

GMP

cGMP

GTP

trans Retinal

Opsin

PPi → 2 Pi

Amplifies light signal

↓

Vision

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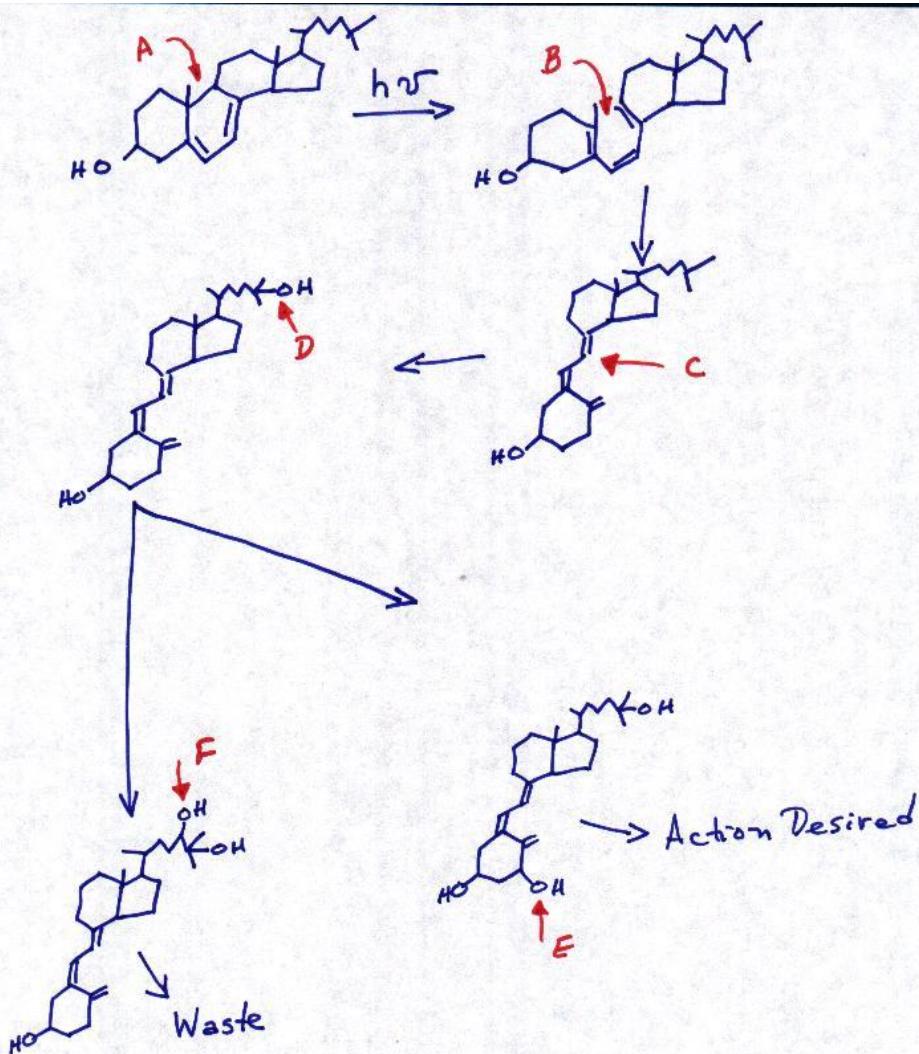
Vitamin D

- The chemical structure of active vitamin D_3 (1α, 25-dihydroxy vitamin D_3).

- Absorption of vitamin D occurs with food fats, therefore, inhibition of normal fat absorption (e.g., steatorrhea) causes reduced absorption of INGESTED vitamin D (sources include full fat dairy products, egg yolk, tuna/cod fish oils).

- Chronic pancreatitis and biliary obstruction causes reduced absorption of vitamin D.

- Absorption occurs in the jejunum/ileum.

- BILE IS REQUIRED! for absorption.

- Vitamin D concentrates rapidly in the liver where is it oxidized to 25-hydroxy vitamin D_3.

- The biosynthesis of vitamin D begins in the skin with 7-dehydrocholesterol. Sunlight causes one of the carbon-carbon bonds in ring B to open up to form pre-vitamin D_3. Pre-vitamin D_3 swivels around to form cholecalciferol. The latter makes up 96% of product at 36 hours and the former makes up 4% of the product at 36 hours. Cholecalciferol is then transported to the liver via a vitamin D binding protein (DBP), where it is hydroxylated by 25-hydroxylase to form 25-hydroxy vitamin D_3. If no Vitamin D is needed, the 25-hydroxy vitamin D_3 is stored in the liver. If Vitamin D is needed, another binding protein transports 25-hydroxy vitamin D_3 to the kidney, where another enzyme, 1a-hydroxylase will place an hydroxyl group on the number 1 carbon in ring A to make $1\alpha,25$-dihydroxy vitamin D_3 -- the active form of vitamin D. This requires PTH (review BIOL 223 notes) and low blood phosphate levels.

- Once enough $1\alpha,25$-dihydroxy vitamin D_3 has been made, it is inactivated and excreted. When in excess, the substrate for the reaction, 25-hydroxy vitamin D_3, will be inactivated by being hydroxylated on the number 24 carbon to form 24R, 25-dihydroxy vitamin D_3. This reaction is mediated by high calcium blood levels, high phosphate blood levels, low PTH levels and excessive amounts of vitamin D.

The biosynthetic pathway for the synthesis of vitamin D.
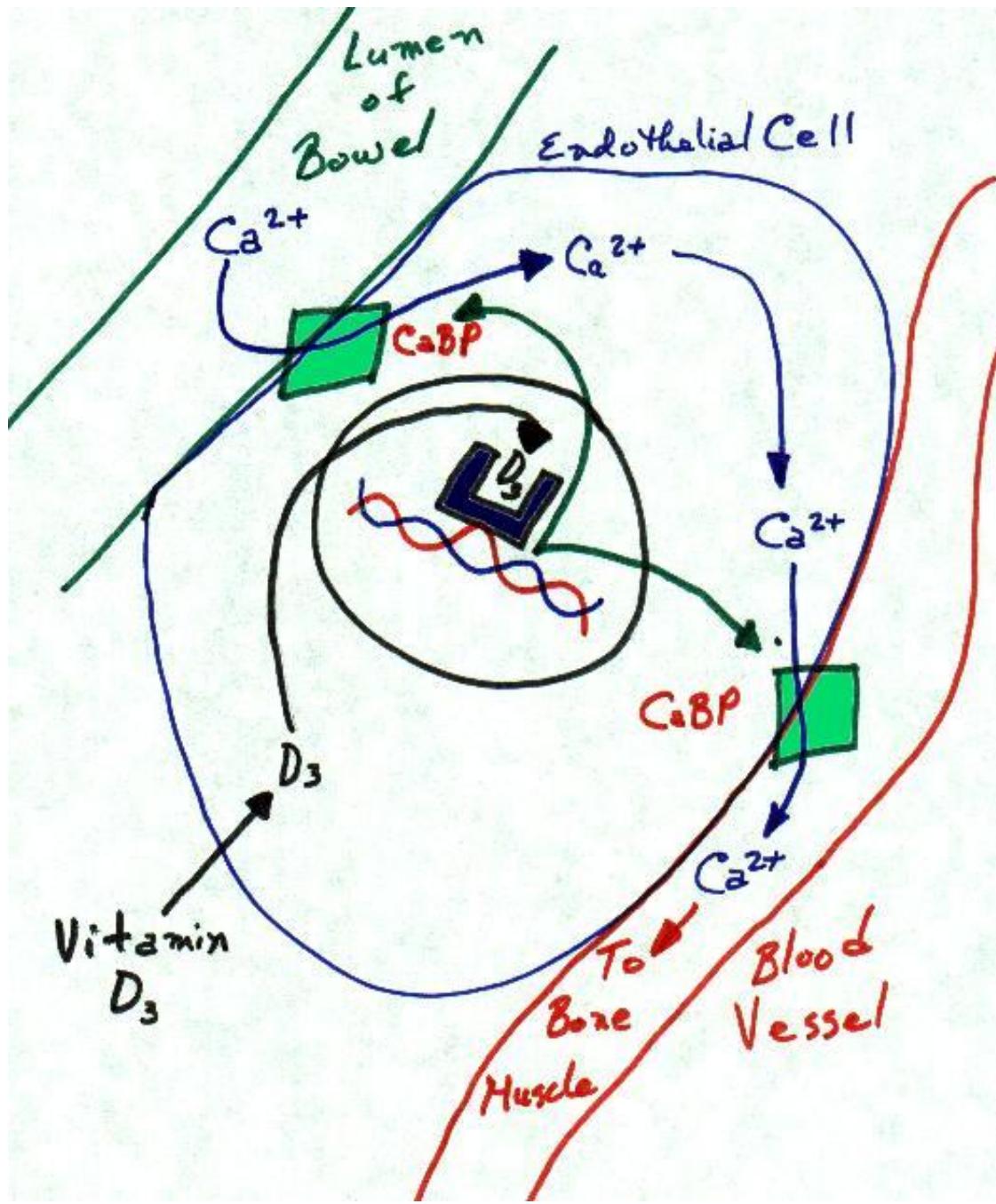
6 points of interest are indicated by red letters:

A) shows the carbon-carbon bond that will be photolyzed in the skin,

B) shows the intermediate after photolysis,

C) shows the rearrangement of the molecule,

D) shows the -OH group added by 25-hydroxylase,

E) shows the 1α-OH group added by the 1α-hydroxylase and

F) shows the -OH group added onto the #24 carbon by the 24R-hydroxylase to inactivate 25-hydroxy vitamin D_3. **Product F is excreted as waste and Product E is the active form of the vitamin.**

Vitamin D Functions

- Vitamin D plays a major role in normal bone calcification, preventing rickets in the young and osteomalacia in the adult.

- It prevents hypocalcemic tetany and is essential for calcium absorption.

- To increase plasma calcium and phosphate ions in the blood,
  - vitamin D activates active transport of calcium and phosphorus in the small bowel,
  - it improves renal absorption of calcium and
  - stimulates the mobilization of calcium ions from the bone fluid compartment.

- These three steps result in increased plasma levels of calcium and phosphate ions to the normal levels required for bone mineralization.

- The active transport of calcium across the gut into endothelial cells, thence into the blood is mediated by a calcium binding protein (CaBP).

- Vitamin D_3, being a steroid, diffuses across cell membranes to bind with a nuclear receptor bound to DNA.

- When bound, that causes transcription and translation (review BIOL 223 notes or BIOL 208 notes), resulting in the placement of the CaBP in either side of the endothelial cell.

- On the bowel side, calcium ions are transported inside the cell.

- On the blood side, calcium ions are transported out of the endothelial cell into the blood for uptake by bone and/or muscle.

- The Figure, following, illustrates this concept.

Vitamin D Deficiencies

Osteomalacia, in adults, is characterized by low blood calcium levels, phosphate levels and increased alkaline phosphatase activity.

In adults, the ossified matrix LOSES calcium, softening the bones.

Rickets, in children, is characterized by low blood levels of calcium ions, phosphate ions and elevated levels of alkaline phosphatase activity.

In children, newly synthesized matrix FAILS to mineralize.

ASIDE

Alkaline phosphatase is produced by osteoblasts to assist with osseous mineralization.

It is increased in osteogenic sarcoma and in developing bone.

Do NOT confuse this enzyme with the enzyme of the same name from the liver.

END OF ASIDE
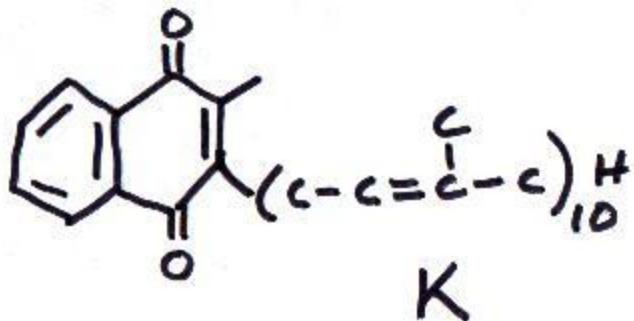
- Osteoporosis is the loss of skeletal calcium that leads to, for all intents and purposes, holey bones.
- This effects both sexes, but is particularly devastating to and focused on post-menopausal women.
- Post-menopausal women require estrogens to increase vitamin D-dependent uptake of calcium with boron.
- Also estrogens release calcium which inhibits PTH from stimulating D_3 synthesis.
- There are concerns about the chances of developing cancer when a woman is on hormone replacement therapy (HRT).
- The literature is showing that, in spite of conflicting data and alternative therapies, that estrogen replacement with progesterone replacement is choice number one for women to at least stop and, in many cases, rebuild a little bone mass, post-menopausally.
- The second choice is Fosamax (alendronate sodium). Fosamax inhibits osteoclast mediated bone resorption.
- While inhibiting osteoclastic activity by binding to bone beneath the osteoclasts, bone formation occurs on top of the Fosamax and beneath the osteoclasts (review BIOL 223 notes).
- It seems that the risk for developing cancer from the current low doses of estrogens is minimal.
- The big side effect of Fosamax is the risk of erosion of the esophagus (drink lots of water when taking it and do not lie down for 2 hours).

- Alternative therapies for stopping and, in some cases reversing, osteoporosis include Wild Yam (doesn't work) preparations and progesterone creams.

- The latter is being touted as a "save all" with no risk.

- The scientific, reviewed, refereed literature is inconclusive on the application of progesterone creams for problems of a post-menopausal nature.

- Popular presses are pounding out testimonials and anecdotal reports lacking scientific confirmation/basis for the use of these creams.

- In addition, these creams may be obtained without prescription -- that's a red flag that the dosage is either so low as to be useless or that there is so little (like in OTC preparations of cortisone) that, while it won't hurt you, it won't help you much, either.

- The proponents of progesterone creams have an uphill battle to definitively demonstrate that their product does as advertised and is not acting as a "damned good placebo" (John Lee, M.D., proponent for progesterone creams).

- It is also of interest and concern that the FDA does not seem to be involved in the regulation of this product.

Hypervitaminosis D

- This causes elevated blood calcium levels with increased urinary calcium levels due to huge doses of vitamin D (BTW: we make enough vitamin D in our skin following 15 minutes of exposure to the sun to last for 3 days).

- Hypervitaminosis D can lead to irreversible renal damage, cardiac damage and aortic damage due to the prolonged hypercalcemia.

- This syndrome also includes nephrocalcinosis, molding of the bridge of the nose and early epiphyseal space closure.

- In addition, this can also cause pre-natal early closure of the fontanels.

- Calcium deposits in tissues may lead to cerebral, cardiovascular and renal damage.

- Late toxic S/S include headache, increased thirst, bone pain, anorexia and general malaise.

- The treatment is to withdraw vitamin D until the patient is eucalcemic.

- Calcitonin (CT) may be needed for therapy, as well, to drive calcium out of the blood into bone and urine.

Vitamin K
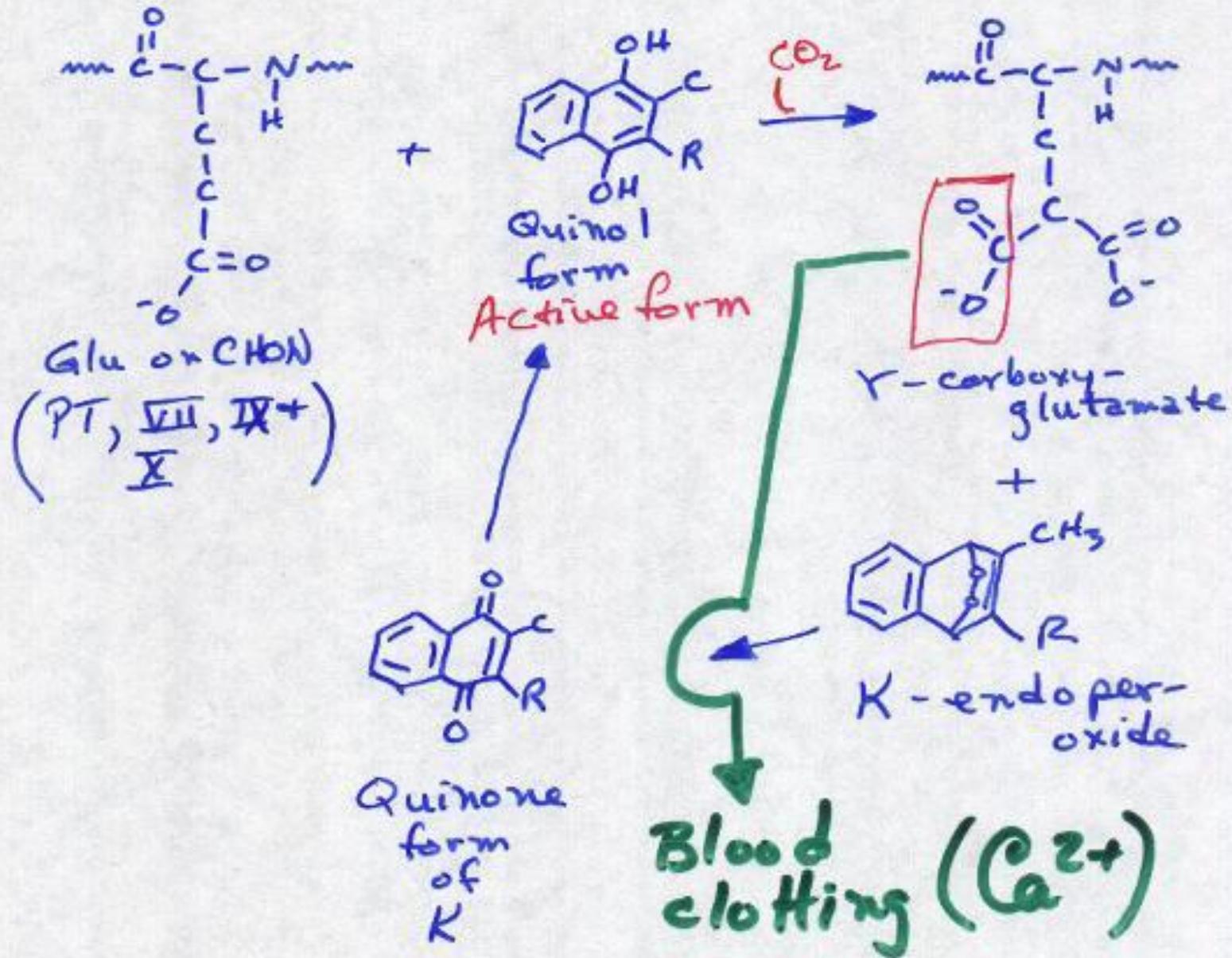
- The chemical structure of Vitamin K.

- Vitamin K requires bile/pancreatic juices for optimal effectiveness/uptake.

- Vitamin K from the diet is absorbed in the small bowel. 8-30% is recoverable in urine over a 3-day period, 40-60% in feces over a 5-day period.

- The point, here, is that vitamin K is NOT stored as well as vitamins A and D.

- Mineral oil (a non-absorbable lipid) decreases the absorption of vitamin K in animals.

Vitamin K Content in Food Sources		
Poor (< 10 μg/100 g)	Moderate (40-99 μg/100 g)	Good (> 100 μg/100 g)
Cow's milk, human milk, chicken liver, ground beef, corn oil, bread, rice, banana, peach, black tea	Bacon, beef liver	Broccoli, kale, spinach, turnip greens, green tea (the latter 4 are REALLY good sources)

Physiological Function of Vitamin K

- The physiological function of vitamin K is to regulate clotting.

- The immediately next Figure illustrates hemostasis from an anatomical point of view.

- The following Figure illustrates the physiology behind the clotting cascades.

- A note to remember is that the Roman numerals in the second Figure represent a specific clotting protein -- they are known by those numerals, as well as specific names (you don't have to learn the names, only the numerals).

Glu or CHON

$\left(PT, \underline{VII}, \frac{IX}{X}+\right)$

Quinol form
Active form

CO_2

γ - carboxy-glutamate

+

Quinone form of K

K - endoperoxide

Blood clotting (Ca^{2+})

- The significance of Vitamin K is illustrated in Figure, previous.

- The active form of Vitamin K is the quinol (kwin OLE) form.

- The quinol form permits glutamic acid residues on clotting proteins (prothrombin, factors VII, IX and X) to bind carbon dioxide to form the γ-carboxyglutamic acid residue.

- This new compound is now divalently negatively charged, i.e., capable of binding the divalent cation calcium to propagate clotting -- coagulation.

- In the process, the quinol form of Vitamin K is oxidized to the endoperoxide form of Vitamin K which is further oxidized to the quinone form.

- This quinone form is then reduced to the quinol form in a redox cycle to propagate coagulation as necessary.

- Vitamin K is antagonized by Vitamin E.

Liver

It's important to recognize that the liver, while of great digestive importance as a detoxification center, is also important in blood clotting.

Figure, right, illustrates the effects of blood clotting after receiving a wound.
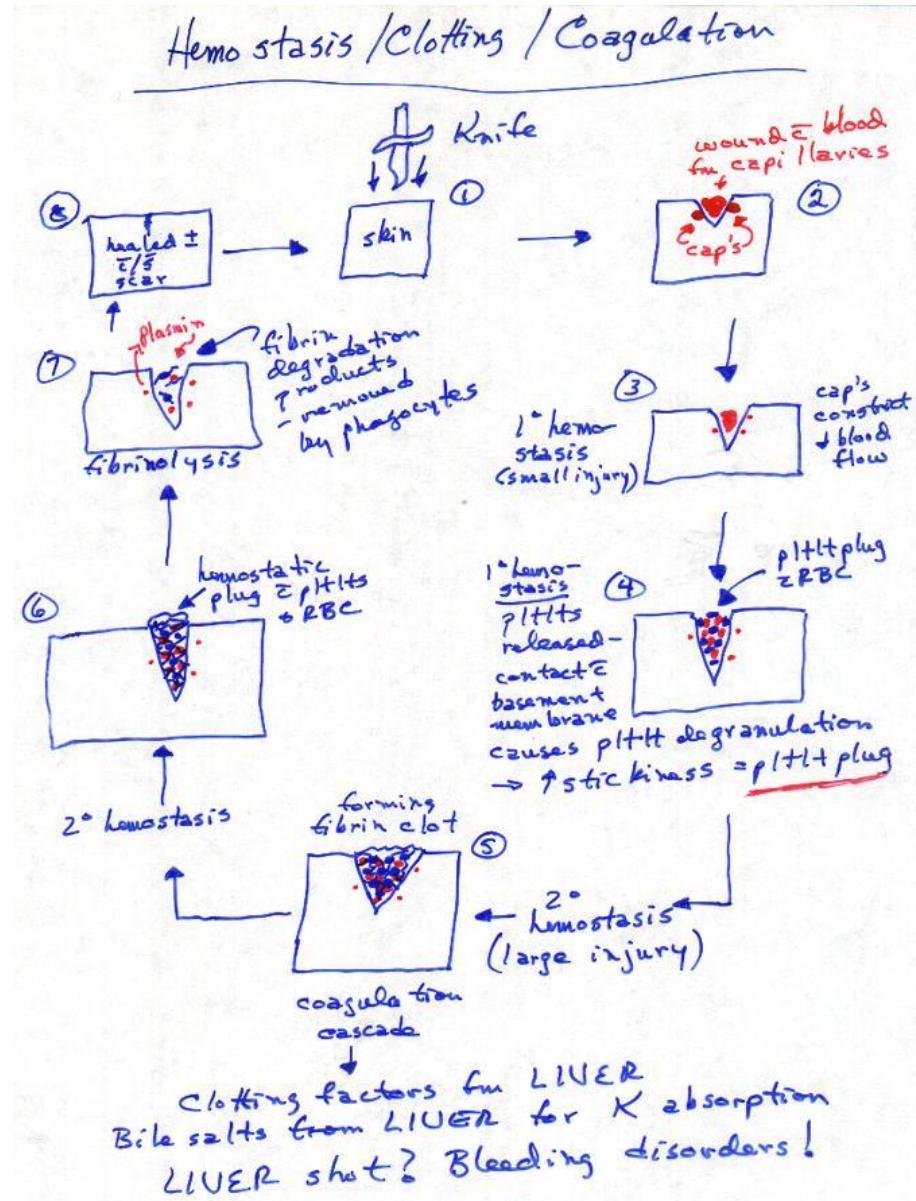
Starting at cartoon #1, running clockwise, the skin is sliced by a knife. The wound fills with blood from the damaged capillaries. The capillaries then constrict to reduce the flow of blood out of the body.

In the case of a small injury, this is primary hemostasis. Platelets are then released. Contact between the platelets and the basement membrane causes platelet degranulation which increases the "stickiness" of the platelets that then form a platelet plug with the red blood cells (RBC) in the wound.

During secondary hemostasis (or following a larger wound), the next step is to form a fibrin clot.

Clotting factors come from the LIVER! Bile salts are manufactured by the liver for vitamin K absorption.

If the liver is shot, expect bleeding disorders.

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Liver
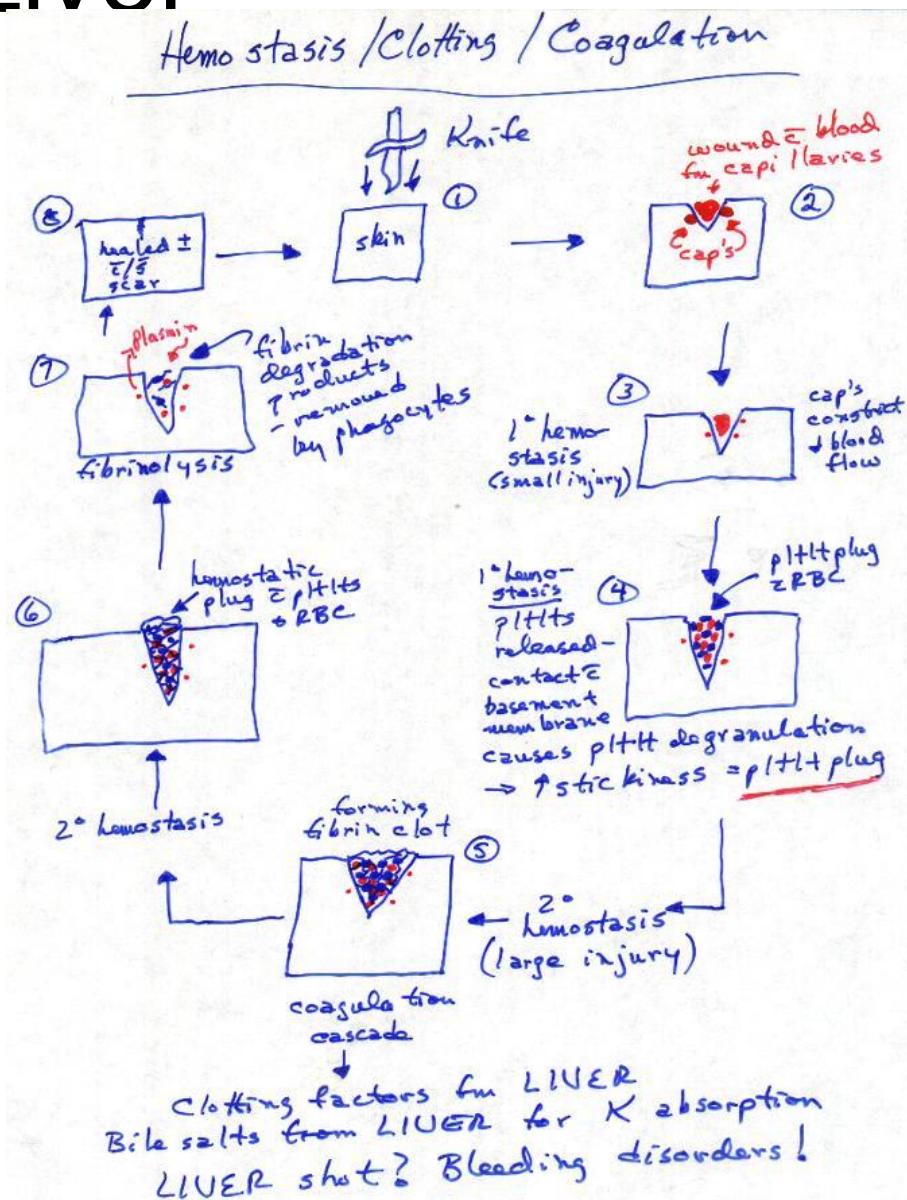
To continue with cartoon #6, a hemostatic plug is formed between the RBC, fibrin and platelets.

Once healing begins (review A&P I) or a pathological process is in place, plasmin is released to dissolve the fibrin strands. The degradation products are removed by phagocytosis.

Clinically, "fibrin split products" are measured to determine the extent of blood clotting ability.
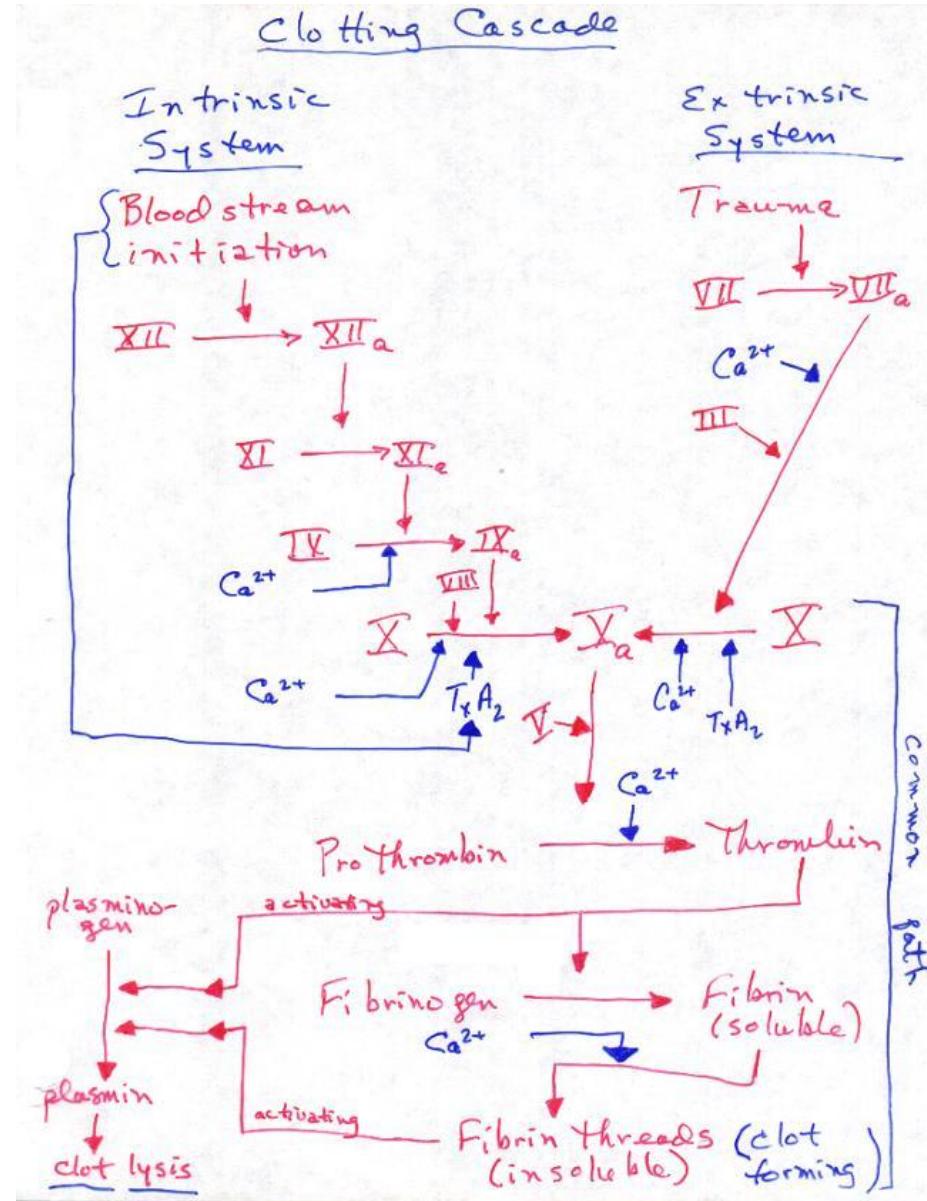
The higher the FSP are, the less the person may be able to clot effectively, i.e., the higher the fibrin split products, the more thrombin, fibrin polymerization and platelet aggregation are INHIBITED from forming a clot.

In cartoon #8, the wound has healed, more or less with or without scar formation – again, review primary, secondary and tertiary wound healing in A&P I.

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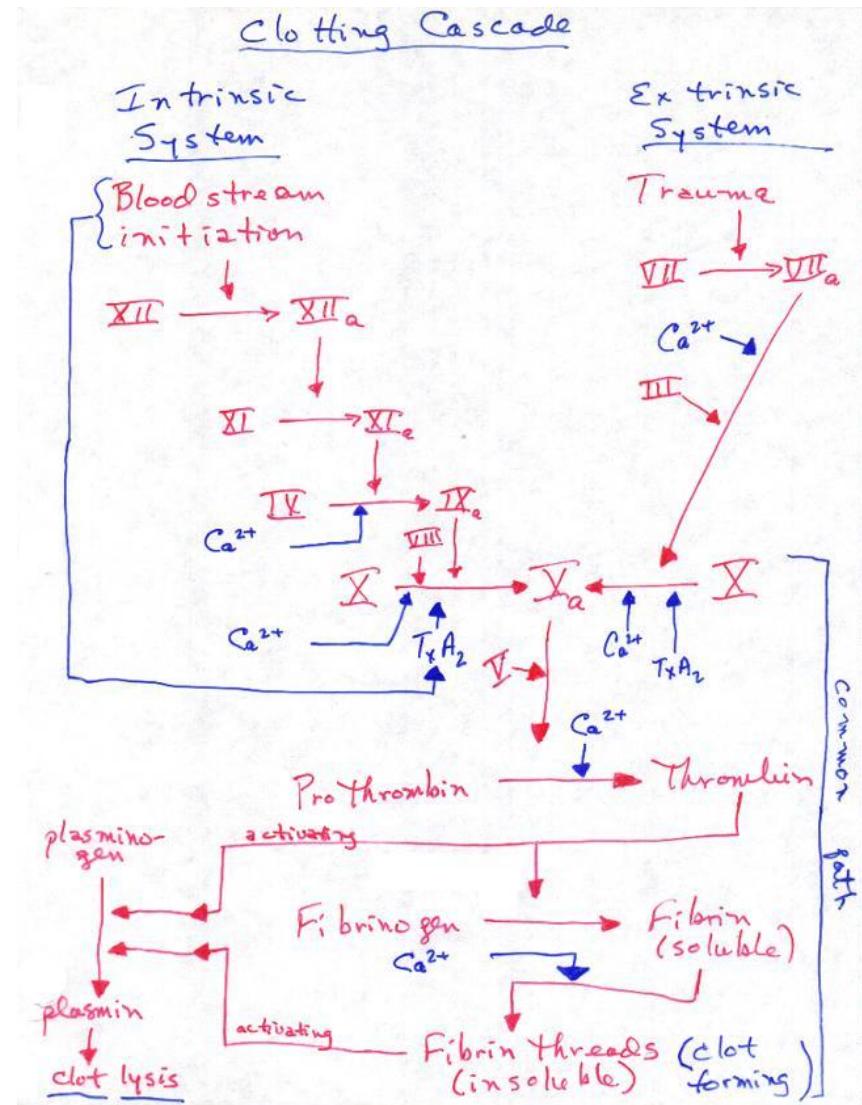
# Coagulation and the Liver

•Two pathways are used by the body to produce clots:

    – the extrinsic and

    – intrinsic systems.

Clotting Cascade
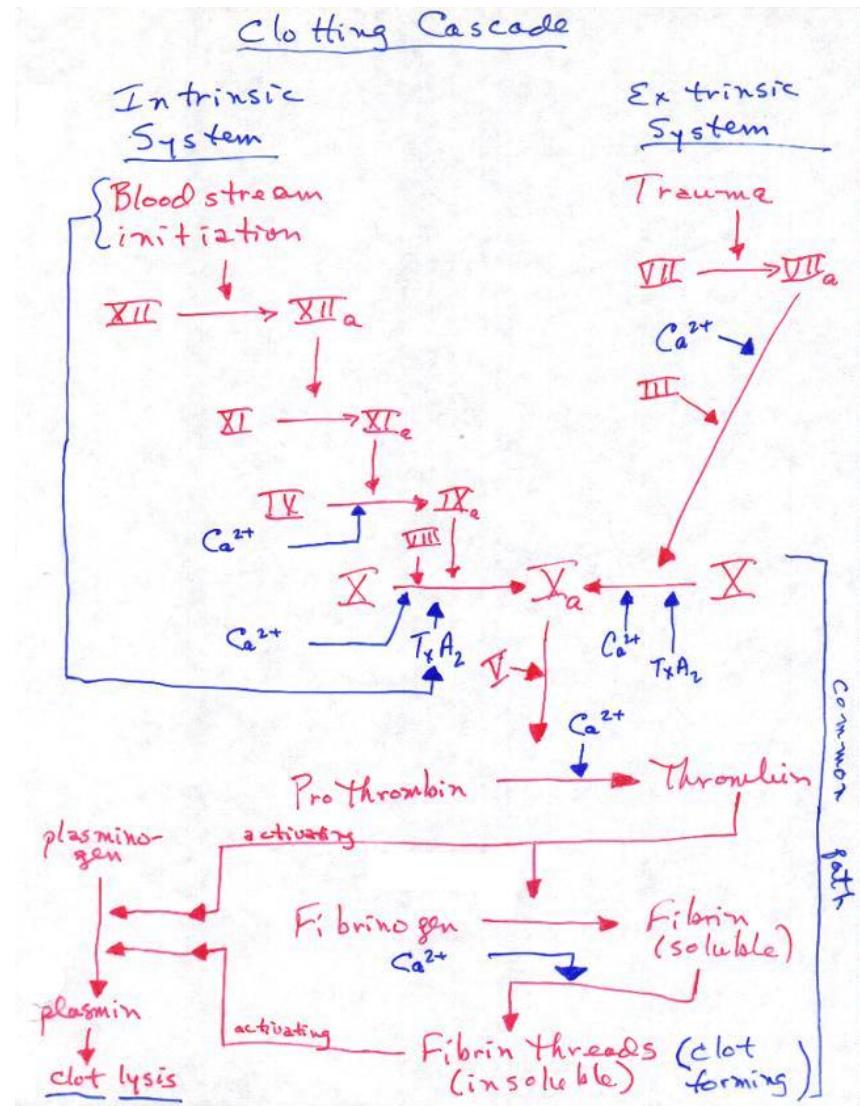
Extrinsic System

•The extrinsic system is generally initiated by some sort of trauma, including venipuncture. Trauma activates factor VII to factor VII_a (the "a" is for "active" factor, in this case, VII). VII_a with calcium ions and III (the factors are usually represented only by their Roman numerals), then activate X to X_a. This latter process also requires the presence of special prostaglandins called thromboxane A_2 (TXA_2; makes the platelets sticky, too). We'll stop here for a moment.
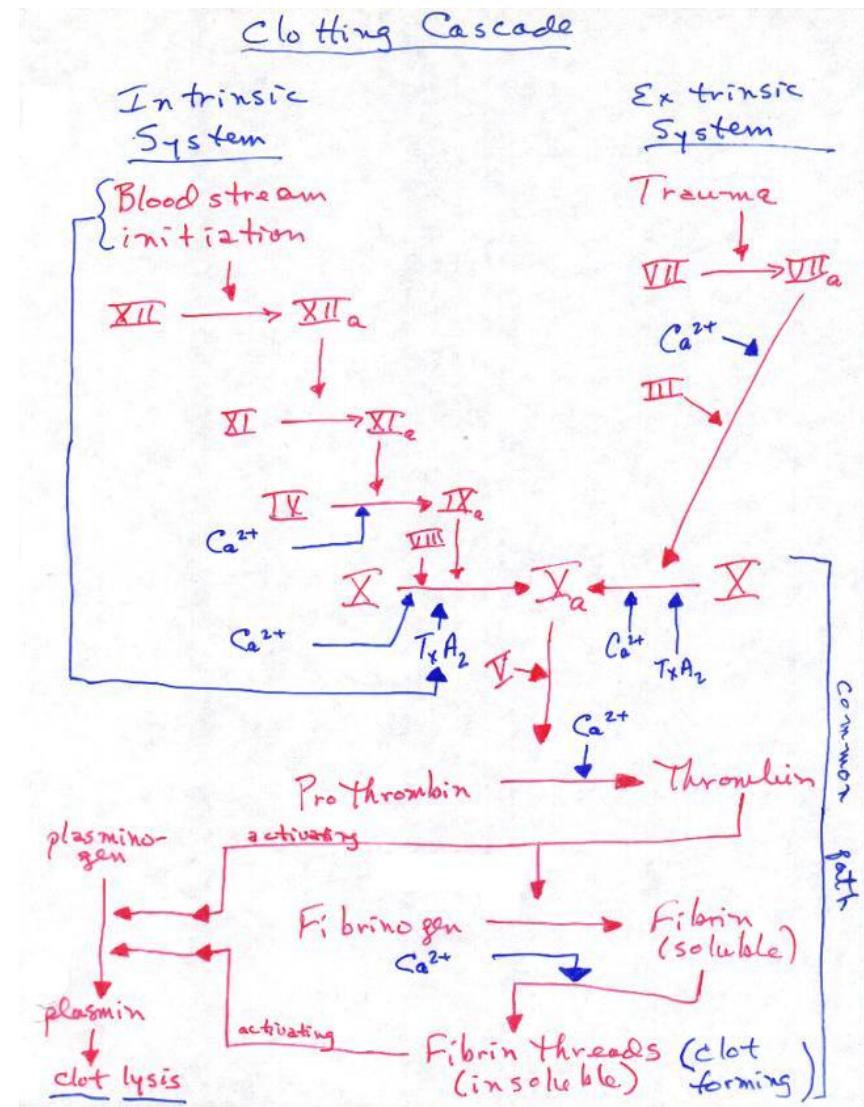
Intrinsic System

•The intrinsic pathway is initiated by the blood stream. That process activates XII to XII_a. XII_a, in turn, activates XI to XI_a, which activates IX to IX_a, which activates X to X_a along with calcium ions and TXA_2.
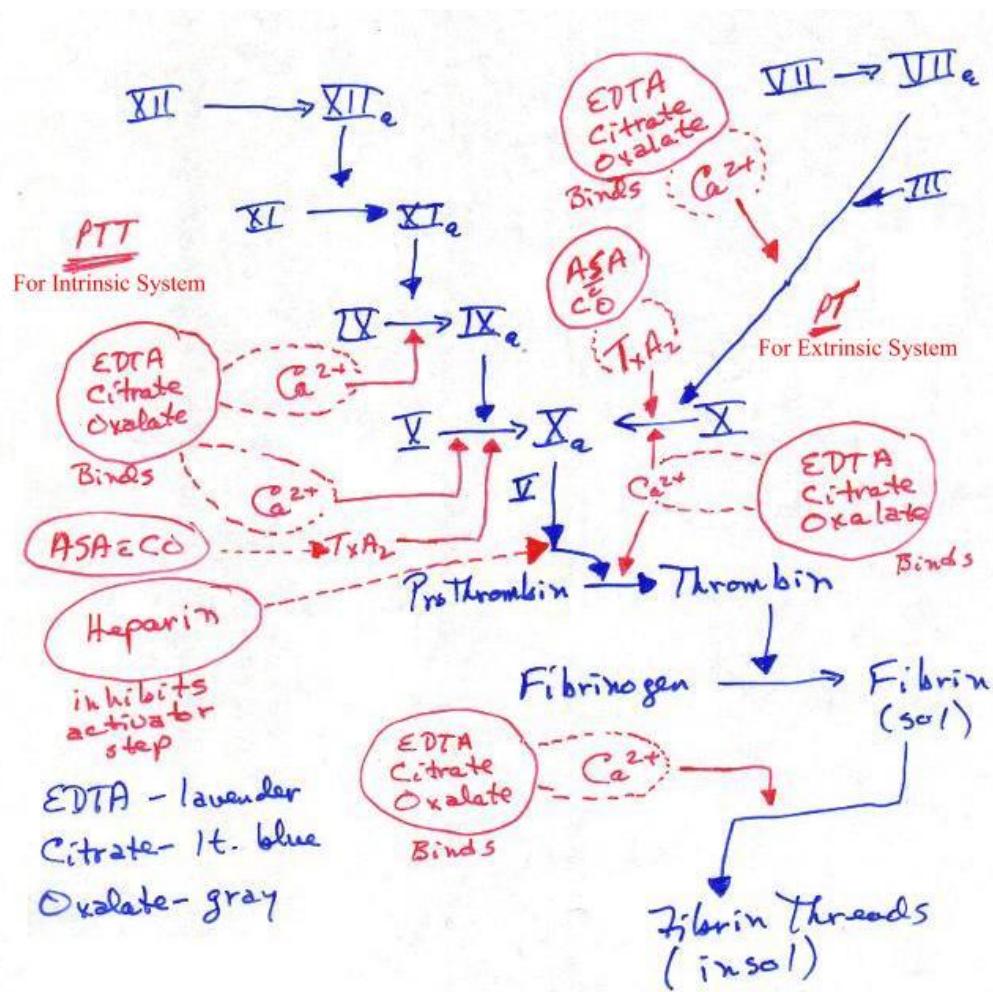
Common Pathway
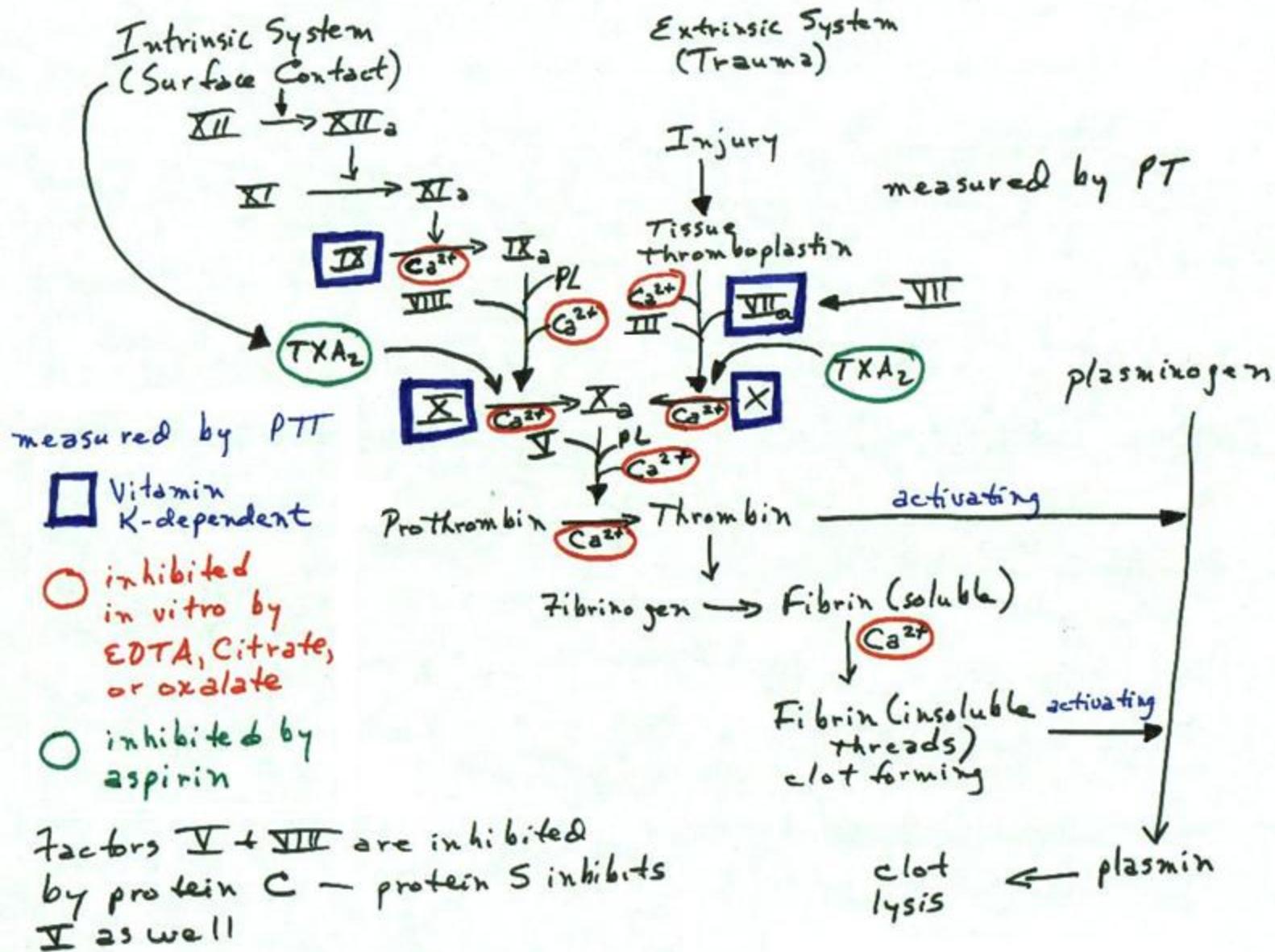
•Once factor X_a is formed, the clotting cascade begins the "common pathway".

•It's called the common pathway because both systems utilize the same pathway from X_a on to accomplish coagulation.

•Factor V, with X_a, and calcium ions "convert" prothrombin to thrombin.

•Thrombin causes fibrinogen to "change to" soluble fibrin. Calcium ions causes the soluble fibrin to become insoluble fibrin threads, i.e., clot-forming.

•With either wound healing or a pathological process, the thrombin and insoluble fibrin threads activate plasminogen.

•The active form of this protein is plasmin.

•Plasmin causes clot lysis.

•Plasmin not only causes clot lysis, hematologically, but also causes semen to un-clot, as well, after ejaculation (see A&P II Reproduction lecture for this process).

The Clotting Cascade with Anticoagulants

•Note that wherever calcium ions are required to propagate a step in the cascade that it is inhibitable with EDTA, citrate or oxalate -- lavender top tubes, light blue top tubes or gray top tubes, respectively.

•TXA_2 is inhibited by aspirin through the primary enzyme of prostaglandin synthesis, cyclo-oxygenase.

• Heparin inhibits the conversion of prothrombin to thrombin.

•Clinically, the partial thromboplastin time (PTT) is used to measure the efficiency of the intrinsic system, while the protime (PT) is used to measure the efficiency of the extrinsic system.

•The PT is used, traditionally, to follow coumadin anticoagulation therapy and the PTT is used, traditionally, to follow heparin therapy for anticoagulation.

•Coumadin inhibits II, VII, IX, X, C, S, Z (latter three are clotting proteins) via Vitamin K epoxide reductase

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Intrinsic System
(Surface Contact)

$XII \rightarrow XII_a$

$XI \rightarrow XI_a$

IX Ca^{2+} IX_a

VIII PL Ca^{2+}

TXA_2

measured by PTT

□ Vitamin K-dependent

○ inhibited in vitro by EDTA, Citrate, or oxalate

○ inhibited by aspirin

Factors V + $VIII$ are inhibited by protein C — protein S inhibits V as well

Extrinsic System
(Trauma)

Injury

measured by PT

Tissue thromboplastin

Ca^{2+} VII_a ← VII

III

TXA_2

X Ca^{2+} X_a Ca^{2+} X

V PL Ca^{2+}

Prothrombin Ca^{2+} Thrombin

Fibrinogen → Fibrin (soluble)

Ca^{2+}

Fibrin (insoluble threads)
clot forming

activating

plasminogen

activating

clot lysis ← plasmin

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Vitamin K Deficiency

- Reduced ability for coagulation leads to severe bleeding after injury.

Coumarin Anticoagulants

- Dicumarol (top Figure) and warfarin (rat poison; Coumadin; bottom Figure) both antagonize vitamin K.

- Notice some of the superficial chemical similarities between Vitamin K and these two anticoagulants.

Hemorrhagic Disease of The Newborn

- Real problem!
- The placenta is a poor transmitting organ for lipids.
- The infant's gut is sterile for the first few days after birth (breast milk is one-eighth that of cow's milk concentration of vitamin K and one half of the neonatal requirement).
- With reduced vitamin K levels, the risk of hemorrhage increases.
- The recommendation, then, is 1-mg vitamin K intramuscular at birth.
- In addition, women on Dilantin (an anticonvulsant) need prophylactic vitamin K since Dilantin antagonizes vitamin K.

Complications with The Newborn

- Diarrhea, malabsorption, cystic fibrosis, idiopathic cholestasis, atresia of the bile duct, prolonged TPN ALL require IM or IV vitamin K administration.

- ALSO, cephalosporins wipe out bacteria in the gut, which causes a reduction in vitamin K availability.

Additional Causes of Vitamin K Deficiency
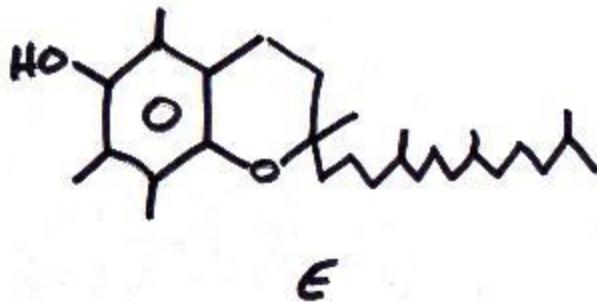
- Biliary obstruction (gall stones), malabsorption, syndromes (cystic fibrosis), drug therapy (Coumarins, salicylates) and antibiotics.

Menadione

- A form of vitamin K_2.
- It is water-soluble which causes high toxicity.
- It used to be used in infant formulas, which caused an increase in hemorrhagic disease of the newborn.
- It is NOT used any more.
- Very Dangerous!
- It also causes liver damage and anemia from high doses of vitamin K_2.

- Vitamin E antagonizes vitamin K and causes hypersensitivity to coumarin anticoagulant drugs.
- With megadoses of vitamin E, the PT increases.
- After the vitamin E is d/c'd, the PT returns to normal.
- With megadoses of vitamin E, it worsens clotting defects in vitamin K deficiencies.
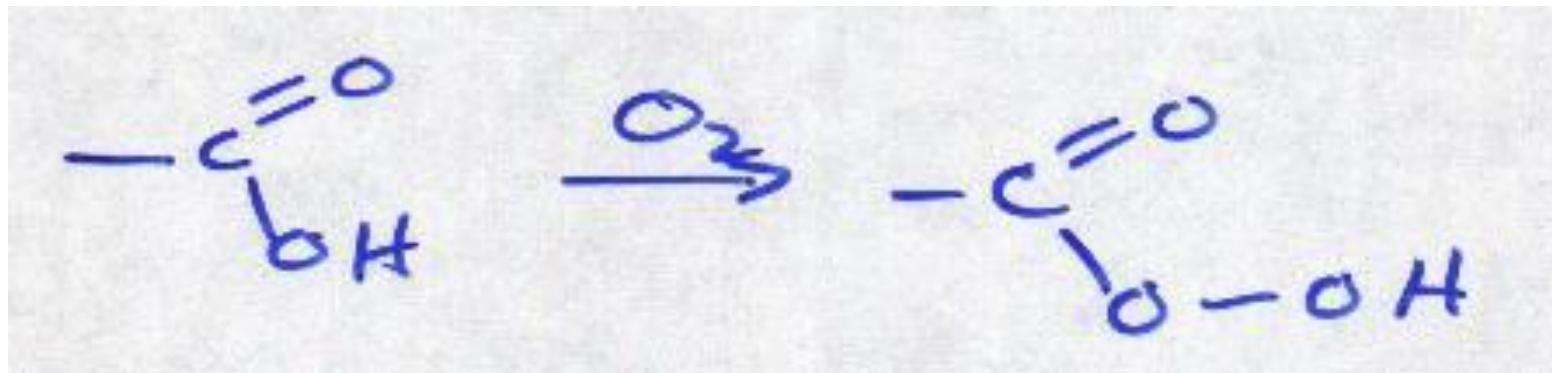
Vitamin E

- The correct chemical structure of Vitamin E (α-tocopherol).
- The chemistry of vitamin E is more complex since there are 8 naturally occurring vitamers (isomers of a vitamin) with vitamin E activity.
- α-tocopherol is the one in which we have an interest.
- Other vitamers have about one-half to one-hundredth the activity of a-tocopherol.

Biological Activity

- Vitamin E seems to have anti-oxidant activity, i.e., it protects lipids in membranes from forming highly reactive peroxides.

- These would destroy the membrane and, hence, the function of the cell or cells.

Dietary Sources

- Sources include
  - vegetable/seed oils (corn, soybean, safflower, sunflower, wheat germ oil (very good source))
  - milk is low,
  - whole wheat bread is low, but has 4 times more than that of white bread.

Absorption, Transport and Storage

- Absorption is dependent on same as the other three fat-soluble vitamins.

- However, the efficiency of the absorption of α-tocopherol decreases with increased quantities ingested.

- Plasma and RBC α-tocopherol exchanges very rapidly at the RBC membrane, presumably to protect the RBC membrane from oxidation and RBC lysis.

- α-tocopherol is taken up by the lungs, liver, heart, skeletal muscle and adipose tissue.

- Tissues with lots of adipose tissue store α-tocopherol in high concentrations.

- CONTRARY to other tissues, fat accumulates and sequesters Vitamin E (in contrast to vitamin K).

- While this is a "store" of vitamin E, it is IMPORTANT to remember that this α-tocopherol is NOT readily available to other tissues.

- This latter observation remains to be explained, mechanistically, to a reasonable degree of satisfaction -- nevertheless, it's a documented fact.

Vitamin E Deficiencies

- Hemolysis and anemia effects the RBC in humans and monkeys.

- Neuronal degeneration affects axons in rats, monkeys and probably humans.

- Nutritional "muscular dystrophy" effects skeletal muscle in rabbit, guinea pig, fowl, sheep and maybe humans.

- Myocardial necrosis effects cardiac muscle in calves and rats and hamsters.

- Reproductive failure resulting in fetal death or testicular degeneration effects the placenta (???) or testicle, respectively in rat, mouse, guinea pig, dog, monkey and probably humans.

Nutritional Requirements
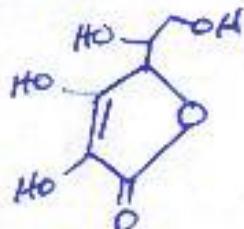
- Due to the ubiquitous nature of tocopherols in a healthy diet, the RDA has been largely determined by dietary analysis.
- The level of "tocopherol equivalents" ingested by adults may range from 6-15 mg/day for adults.
- The minimum daily requirement remains to be determined.
- Studies have shown, however, that for adult men, the level is above 2 mg/day of dietary α-tocopherol.
- Requirements of vitamin E increase when the ingestion of PUFA's is substantially increased.
- Satisfactory RDA's, then, are 10 mg of α-tocopherol for young adults and for infants to 3 months of age is 2 mg/day.

- Megavitamin therapy with vitamin E has not been shown to have been adequately investigated, with two exceptions:
  - 1) between 400 and 800 IU of vitamin E per day has been shown to be cardioprotective and
  - 2) doses in excess of 1200 IU/day have been shown to reduce the time of appearance of Alzheimer's S/S.
- Keep in mind to quit taking aspirin if you take these sorts of doses of vitamin E.
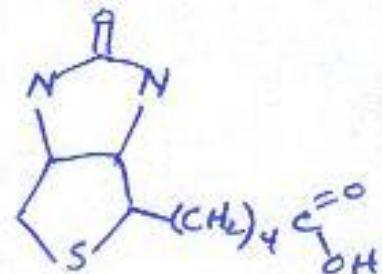
The Water Soluble Vitamins

- The structures of Vitamin C (ascorbic acid), biotin, folic acid, pantothenic acid
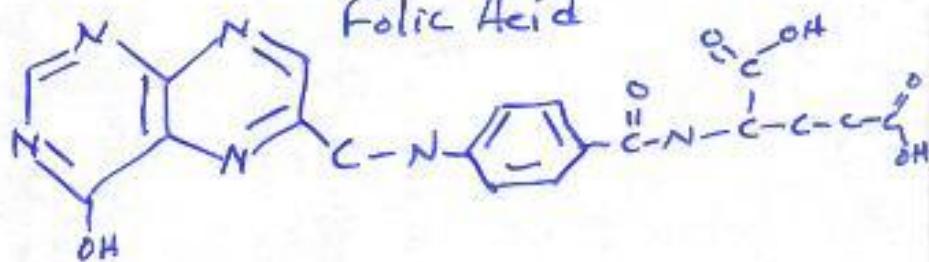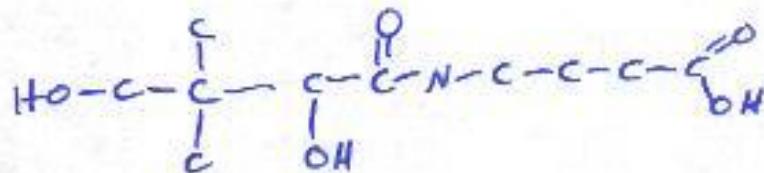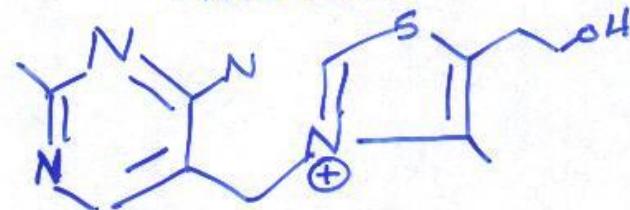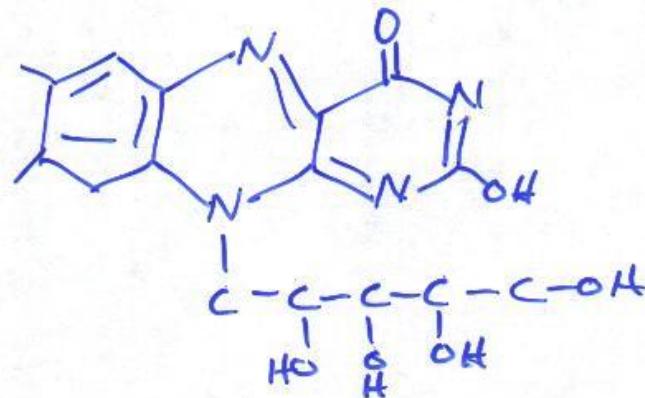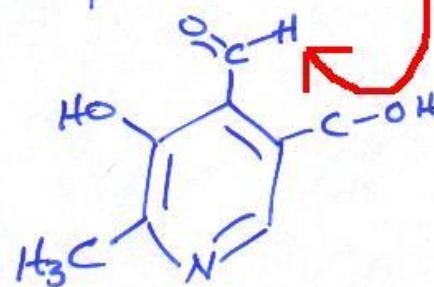
thiamin, riboflavin, pyridoxal

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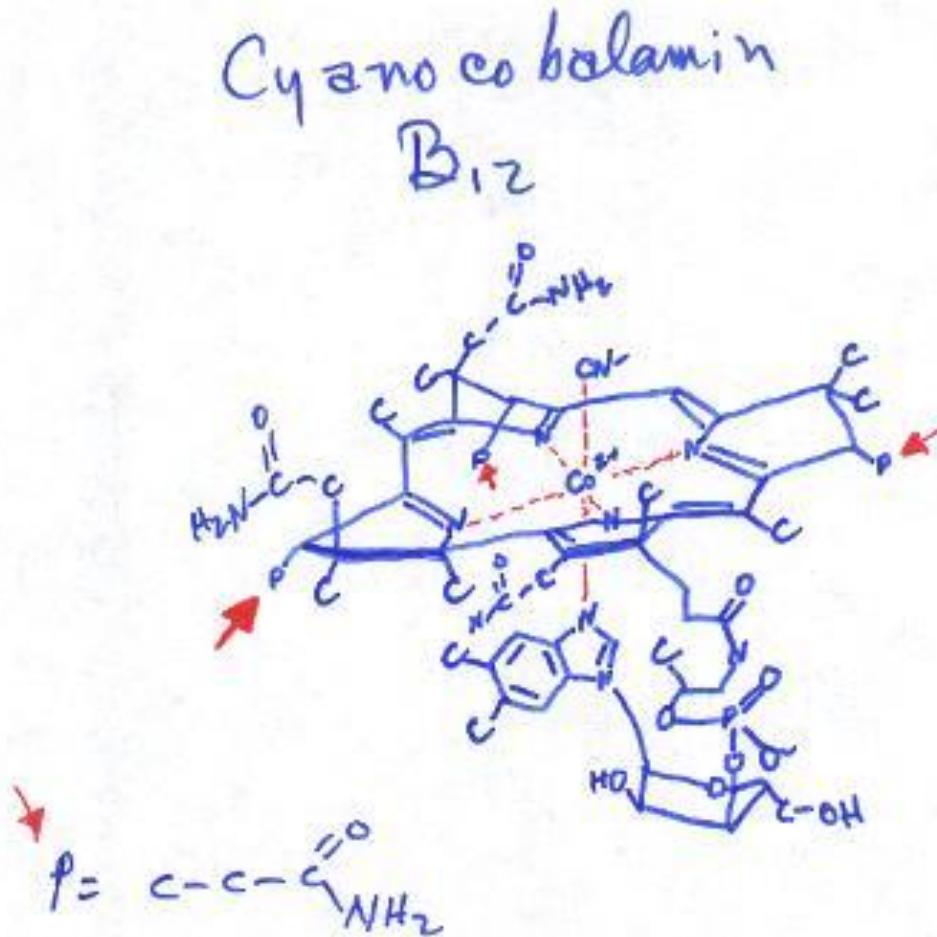
- nicotinic acid, nicotinamide
- PLEASE note that there is a BIG difference between the water soluble vitamins nicotinic acid and nicotinamide and nicotine from tobacco. Do NOT confuse them. In addition, if one were to inject the same amount of nicotine into their veins that they inhaled, they would die.

- cyanocobalamin (B$_{12}$)

314
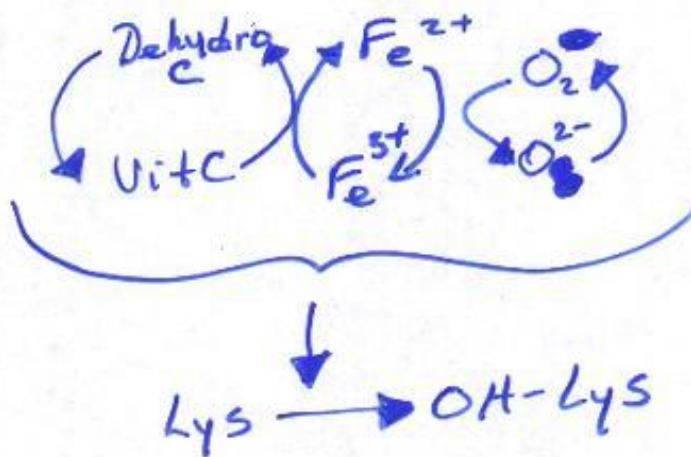
Ascorbic acid (Vitamin C)

- Ascorbic acid is unique in that we are lacking 2 enzymes to synthesize this carbohydrate-looking molecule.

- Goats, on the other hand (OTOH), have the enzymes and do not require exogenous ascorbate as do humans.

- The significant reaction involving ascorbic acid is that as it is oxidized, something else must be reduced, Figure, following. In the process, dehydroascorbic acid is formed.

- Ascorbic acid is used to synthesize connective tissue like collagen (review BIOL 223).

- Vitamin C is used in a redox cycle with iron to oxidize the amino acid lysine to hydroxy-lysine which is used to make collagen.

- A similar redox cycle is what keeps salads fresh when you spritz them with lemon juice to prevent the salad from turning brown.

- In addition, ascorbate does the same sort of redox through copper for epinephrine and norepinephrine synthesis (review BIOL 223).

HO−C−C 〇 =O
HO
HO   OH

Ascorbic
Acid

→ O_2 →

HO−C−C 〇 =O
HO
O   O

Dehydro ascor-
bic Acid
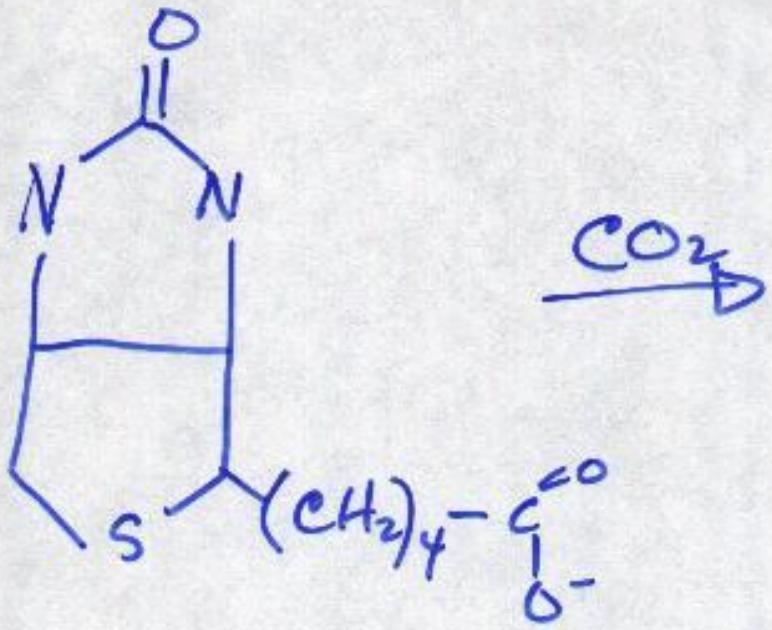
Used to synthesize connective
tissue : collagen
↑ [Lys] → ↑ [OH-Lys]

Dehydro Fe^{2+} O_2
C
Vit C Fe^{3+} O^{2-}

Lys → OH-Lys

316
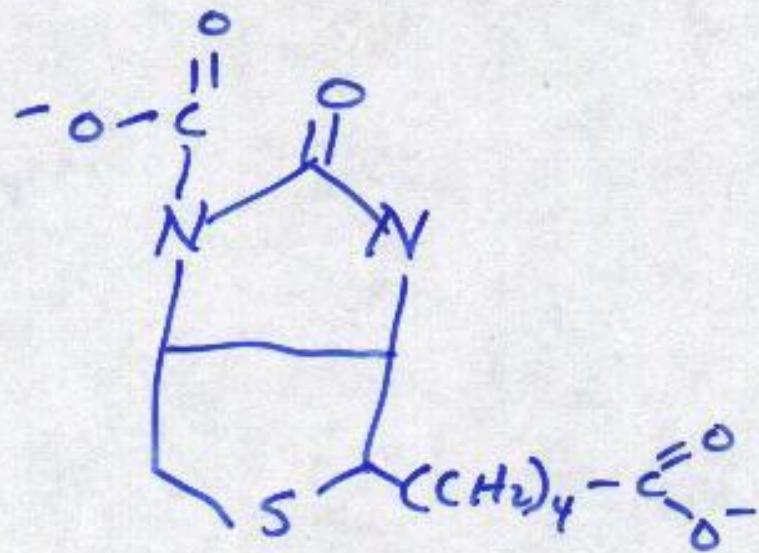
Biotin

- Biotin is the carbon dioxide fixating vitamin, Figure, following.

- In short, biotin reacts with carbon dioxide to form carboxybiotin.

- This compound is useful in lipid and carbohydrate metabolism.

- Biotin is inhibited by avidin, a protein found in raw eggs.

- Avidin binds with the biotin preventing its uptake across the bowel.

- Cooked eggs do not have this effect on biotin.

$$\text{Biotin} \xrightarrow{\;CO_2\;} \text{Carboxy biotin}$$

318
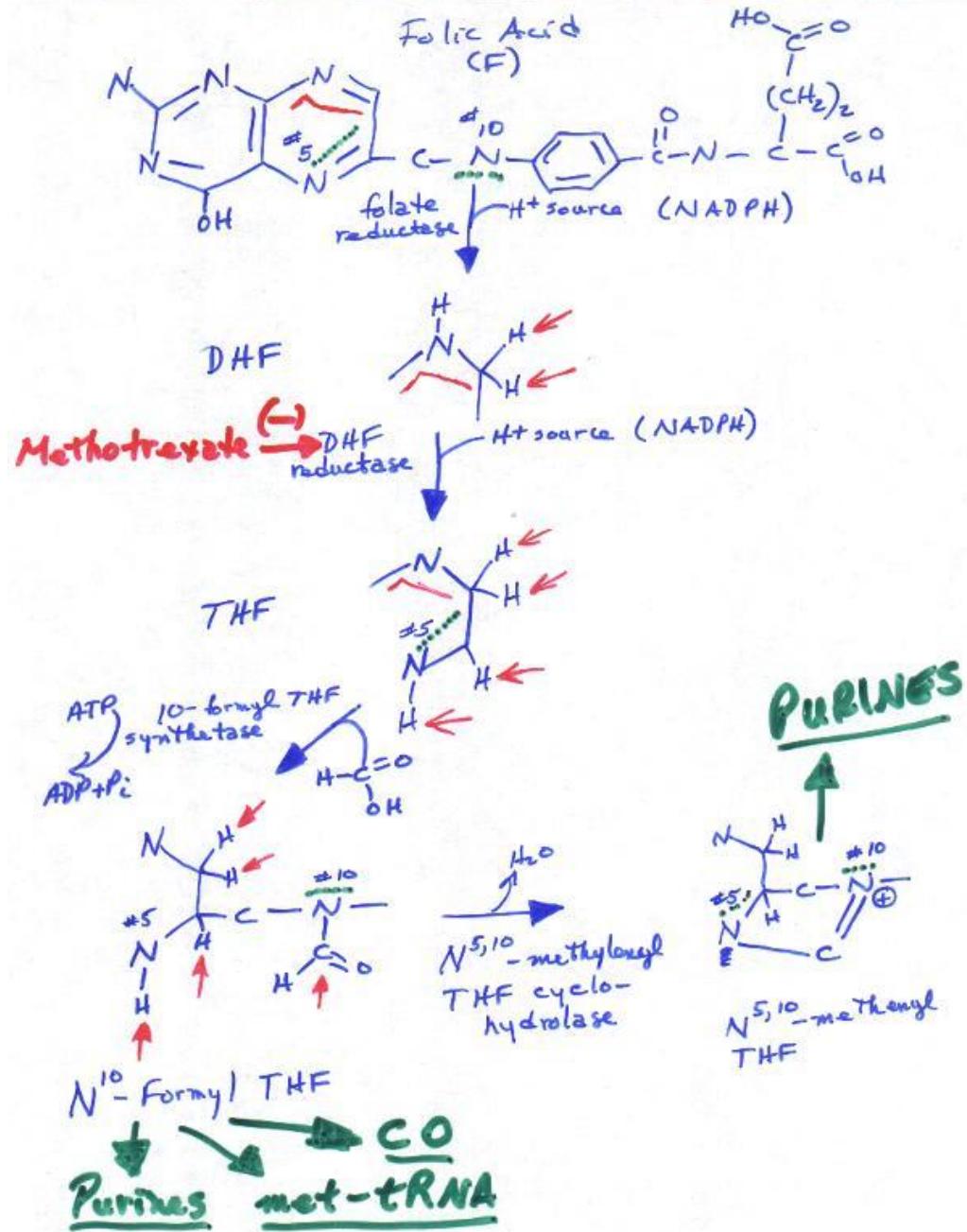
Folic Acid

- Probably one of the most complex vitamins, folic acid plays multiple roles throughout nature from the synthesis of methane in the gas gland of the Portuguese Man of War to preventing birth defects such as spina bifida in humans.

- The following 2 figures walk you through a very simplified schematic of the biochemistry of folic acid.

Note that in the first figure there are some parts of folate that are marked with **green or with red**. That is not by accident. Those regions are what we will examine as we go through these pathways, i.e., we will not be looking at the WHOLE molecule, rather some if its "parts".

In order for folic acid to be activated, it requires two reductions: one by folate reductase to form dihydrofolate and one by dihydrofolate reductase (DHFR) to form tetrahydrofolate (THF).
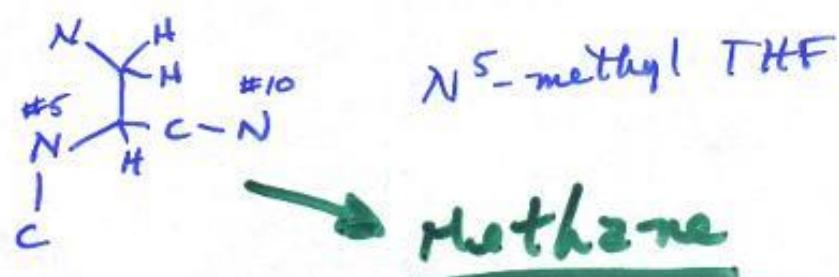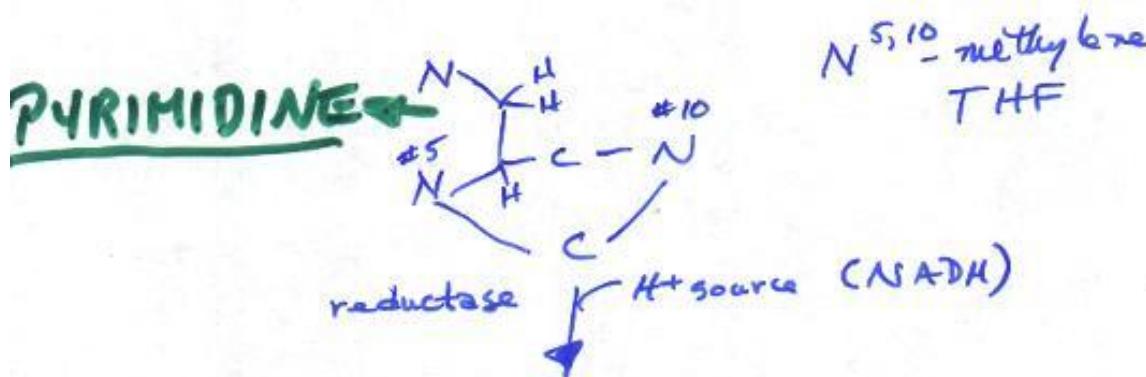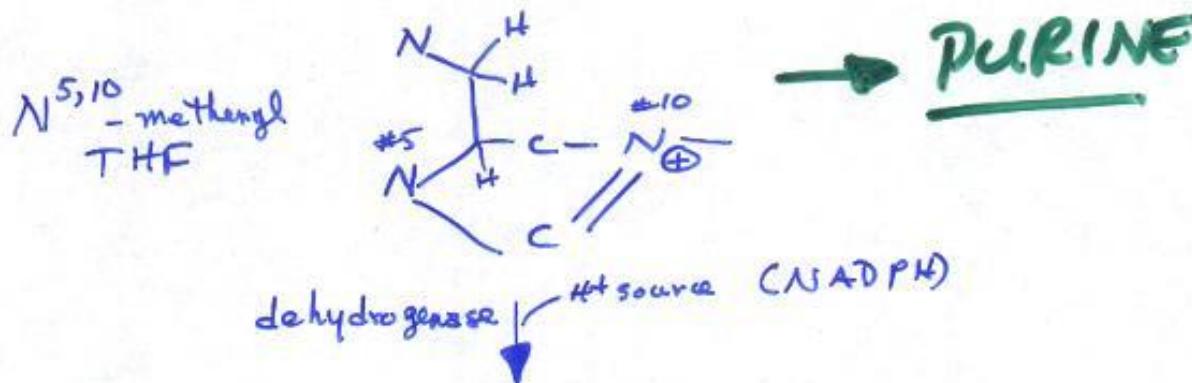
Note that the former reduces the carbon adjacent to the N marked in red and the latter reduces the carbon adjacent to N #5 AND N #5 (all marked with red arrows in the graphic).

THF is then acted on by 10-formyl-THF synthetase with formic acid and the hydrolysis of ATP to ADP and phosphate to form N^{10}-formyl-THF.

This compound is used directly in the synthesis of purines, met-tRNA and carbon monoxide.

It is also used, under conditions directing it, to synthesize $N^{5,10}$-methenyl-THF.

This requires $N^{5,10}$-methylenyl-THF-cyclohydrolase and releases water.

$N^{5,10}$ - methenyl
THF

N — H, H

$#5$ N — H

C — $N^{\oplus}$ $#10$

C

→ **PURINE**

dehydrogenase ← H+ source (NADPH)

$N^{5,10}$ - methylene
THF

PYRIMIDINE ← N — H, H

$#5$ N — H

C — N $#10$

C

reductase ← H+ source (NADH)

N — H, H

$#5$ N — H

C — N $#10$

C

N^{5} - methyl THF

→ **Methane**

In gas gland
of Portugese
man-of-war

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$N^{5,10}$-methenyl-THF is used in purine synthesis or in pyrimidine synthesis.

If it is used in the latter, previous figure, it requires $N^{5,10}$-methenyl-THF dehydrogenase and a proton source (NADPH).
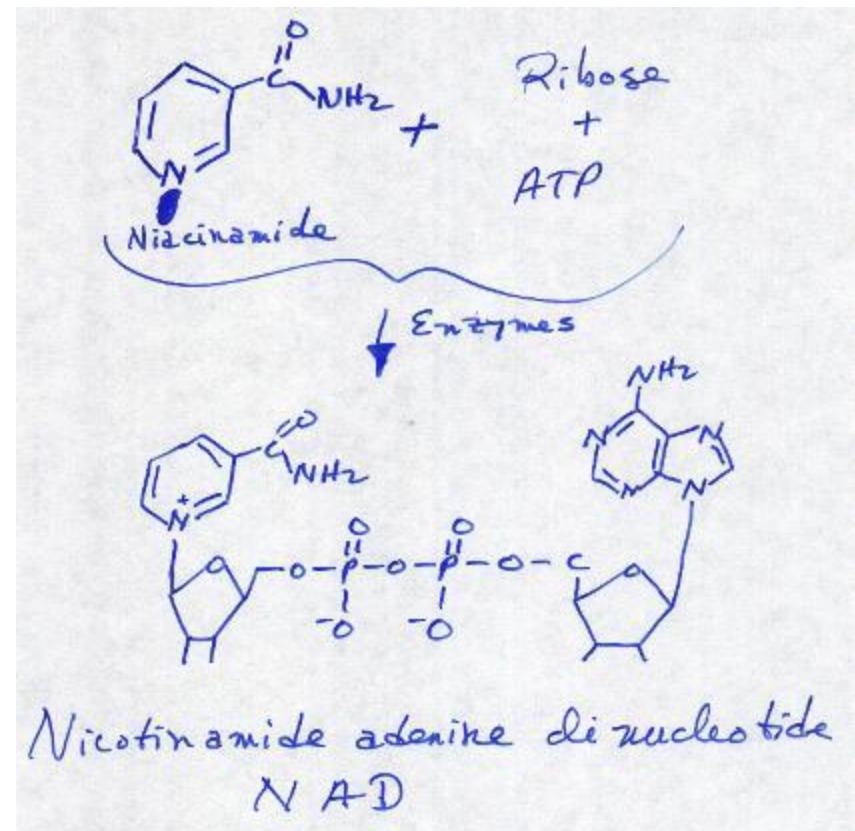
The product of this reaction is $N^{5,10}$-methylene THF. In the gas gland of the Portuguese man of War, $N^{5,10}$-methylene-THF reductase reduces the substrate to N^5-methyl-THF for methane synthesis. The bottom line with folate is that it is primarily involved in one carbon metabolism.
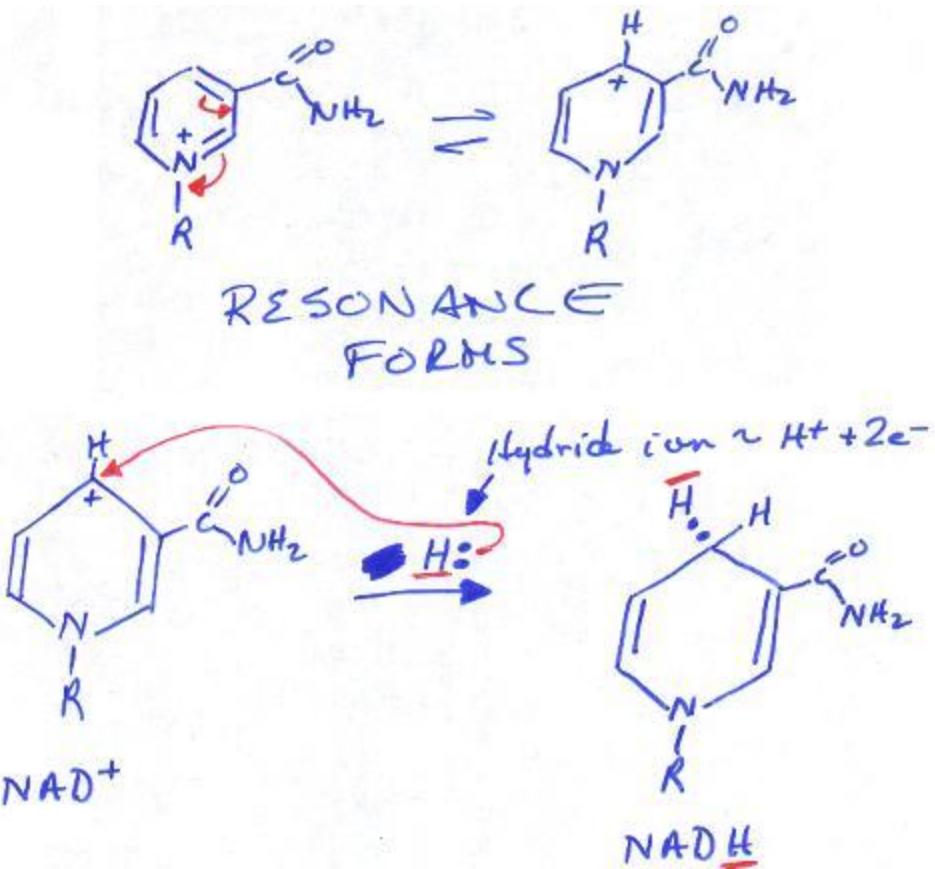
Nicotinamide
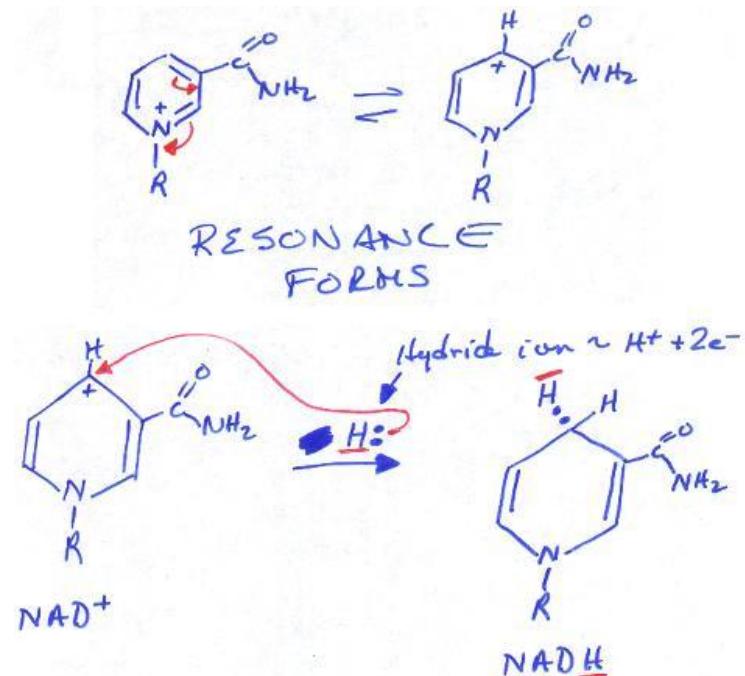
- Nicotinamide is also known as niacinamide.
- This, plus ribose and ATP, with the appropriate enzymes reacts together to form nicotinamide adenine dinucleotide (NAD), Figure.
- NAD is an electron and proton acceptor in metabolism.
- Its reduced form (NADH) is equivalent in energy to 3 ATP molecules.

- Figure illustrates the resonant forms of the nicotinamide moiety in NAD.

- Resonance means a molecule that may be represented by 2 or more structures with the only difference being the electron arrangement, i.e., there is no rearrangement of atomic nuclei.


RESONANCE FORMS

Hydride ion ~ $H^+ + 2e^-$

NAD^+

$H:$

$NADH$
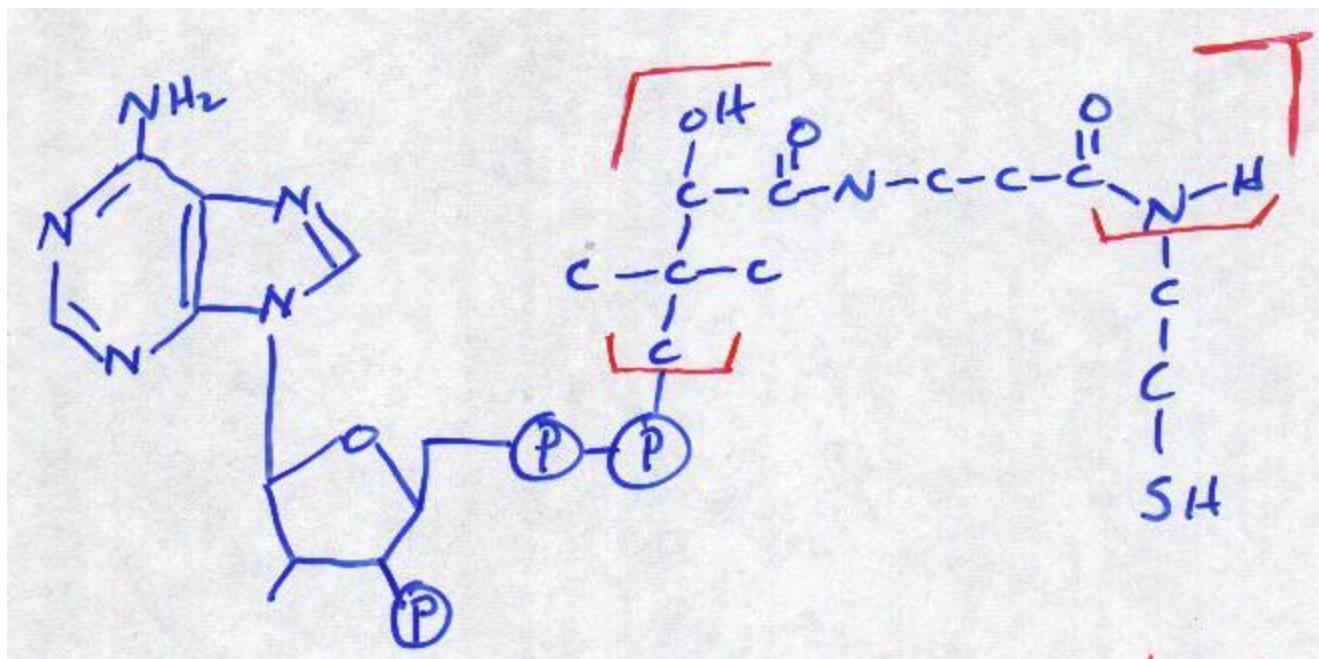
- The active site of NAD is the carbon para to the nitrogen in the nicotinamide ring.
- Once the aromaticity has re-arranged to form a pseudo-cyclic diene, the carbon para to the nitrogen becomes positively charged (a carbocation).
- The hydride ion (roughly equivalent to a proton and 2 electrons) is very reactive with the carbocation.
- When it reacts, it forms the reduced form of NAD, called NADH.
- In most reactions requiring NAD$^+$ (the "+" sign is due to the resonant structure's carbocation; it is typically left off but is understood to be present), hydride ion and hydrogen ion (proton) are involved.
- The reduced product is most appropriately written as NADH + H$^+$ -- we tend to leave off the "+ H$^+$" and just remember that it is present.

RESONANCE FORMS

Hydride ion $\approx$ H$^+$ + 2e$^-$

NAD$^+$

NADH
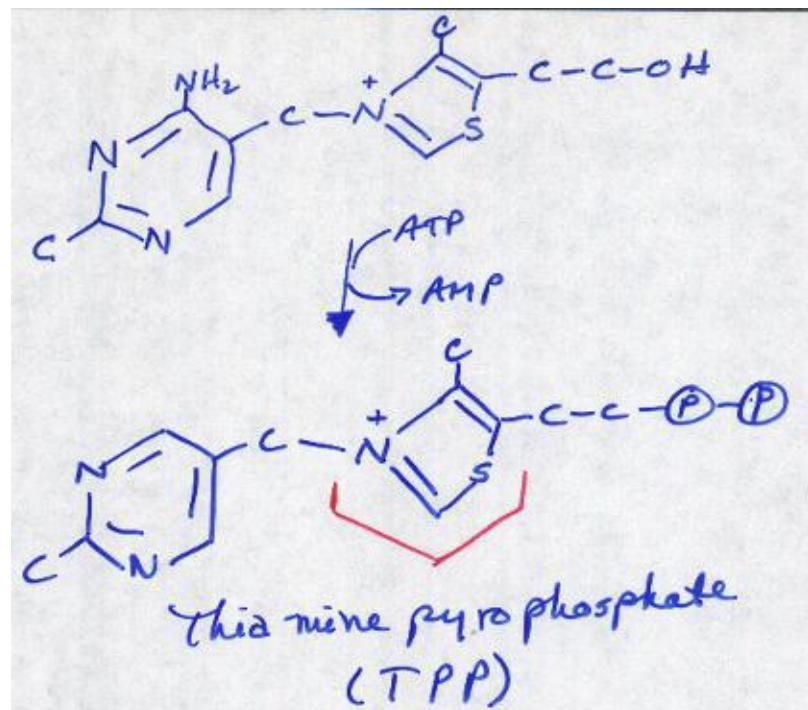
Pantothenic acid

- the structure of Coenzyme A (CoA).
- The area marked in red is pantothenic acid.
- The working end of this molecule is the -SH group.
- CoA is used to "charge" or activate, molecules for metabolism.
- Its role is more thoroughly covered in lipid metabolism.
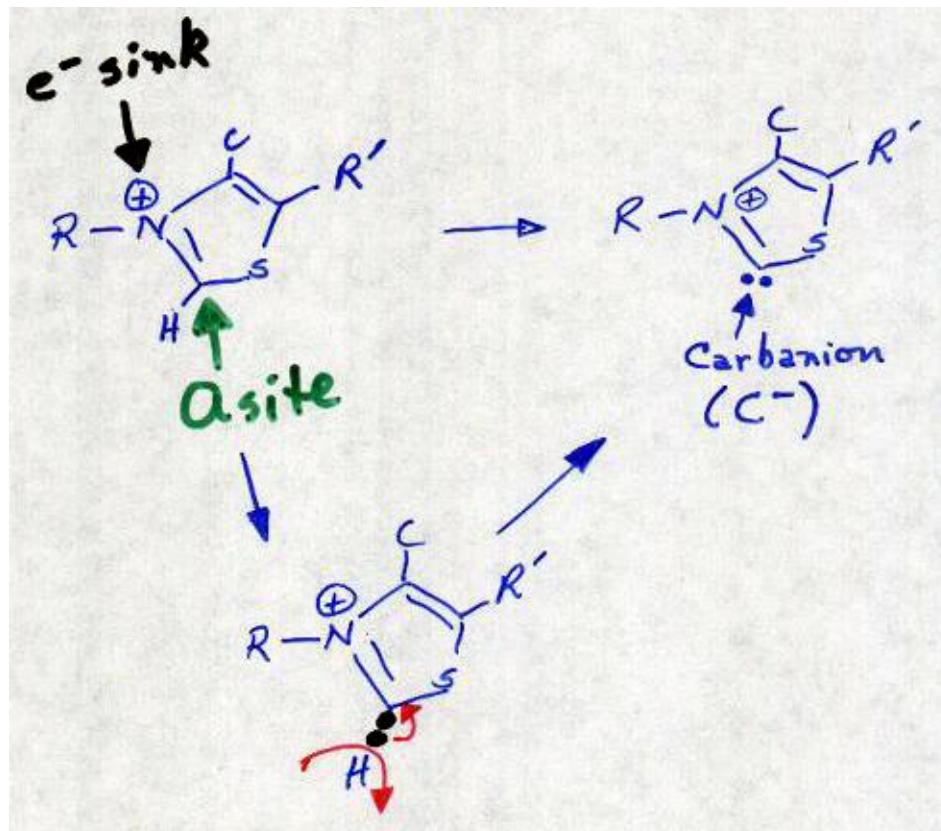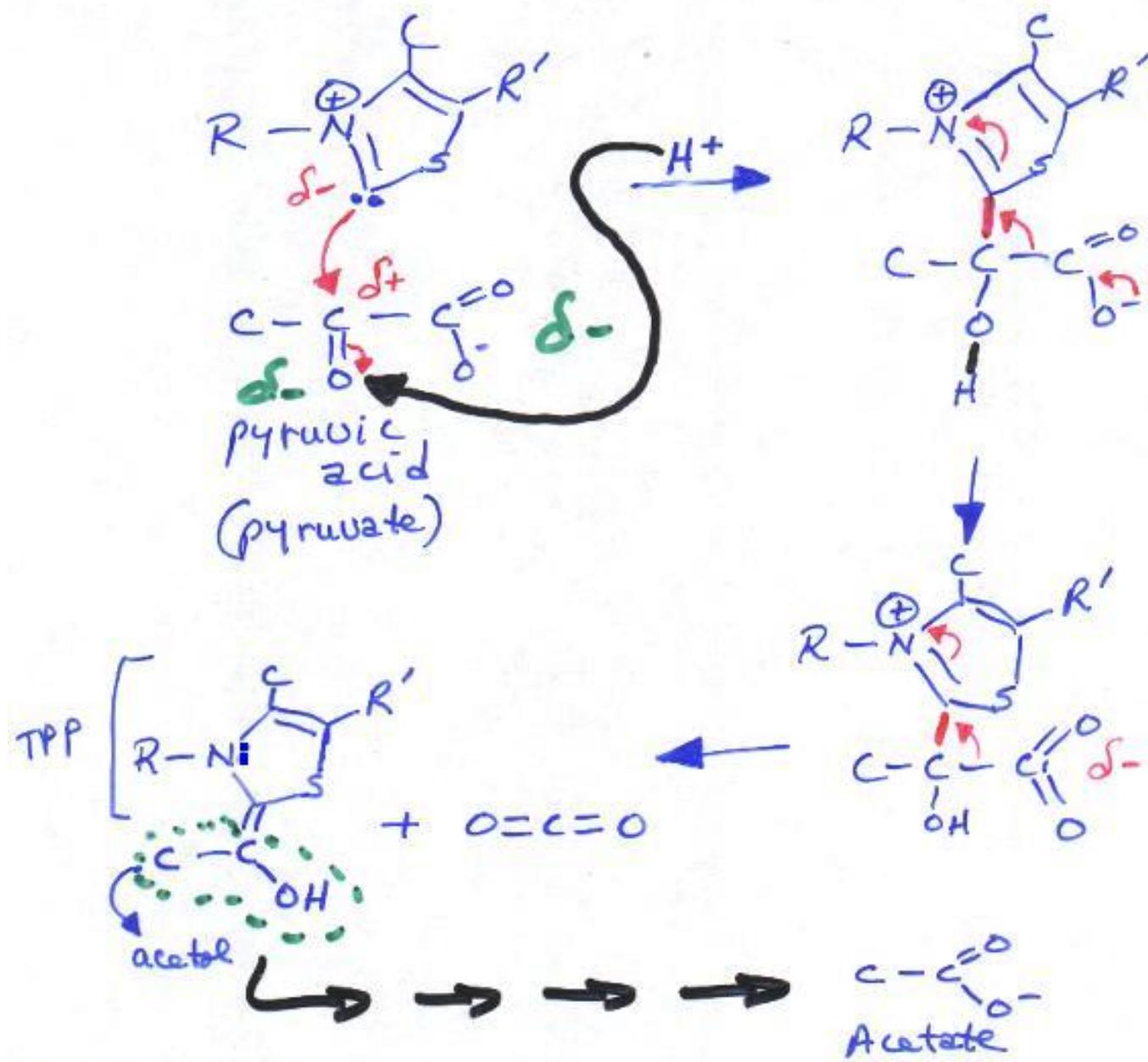
Thiamin

- **The active form of thiamin is thiamin pyrophosphate (TPP), Figure.**

- **In order to form the phosphorylated form, thiamin is enzymatically reacted with ATP.**

- **The active portion of this vitamin is marked with the red "bracket" in the graphic.**

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- **The positively charged nitrogen in the heterocyclic ring acts as an electron sink, i.e., it attracts electrons to it.**
- **In order for this to work, the proton on the carbon between the nitrogen and sulfur must leave, leaving behind a carbanion (negatively charged carbon ion).**

pyruvic acid
(pyruvate)

H+

TPP

acetol

+ O=C=O

C—C
    ‖   ＝O
    O   O⁻
Acetate
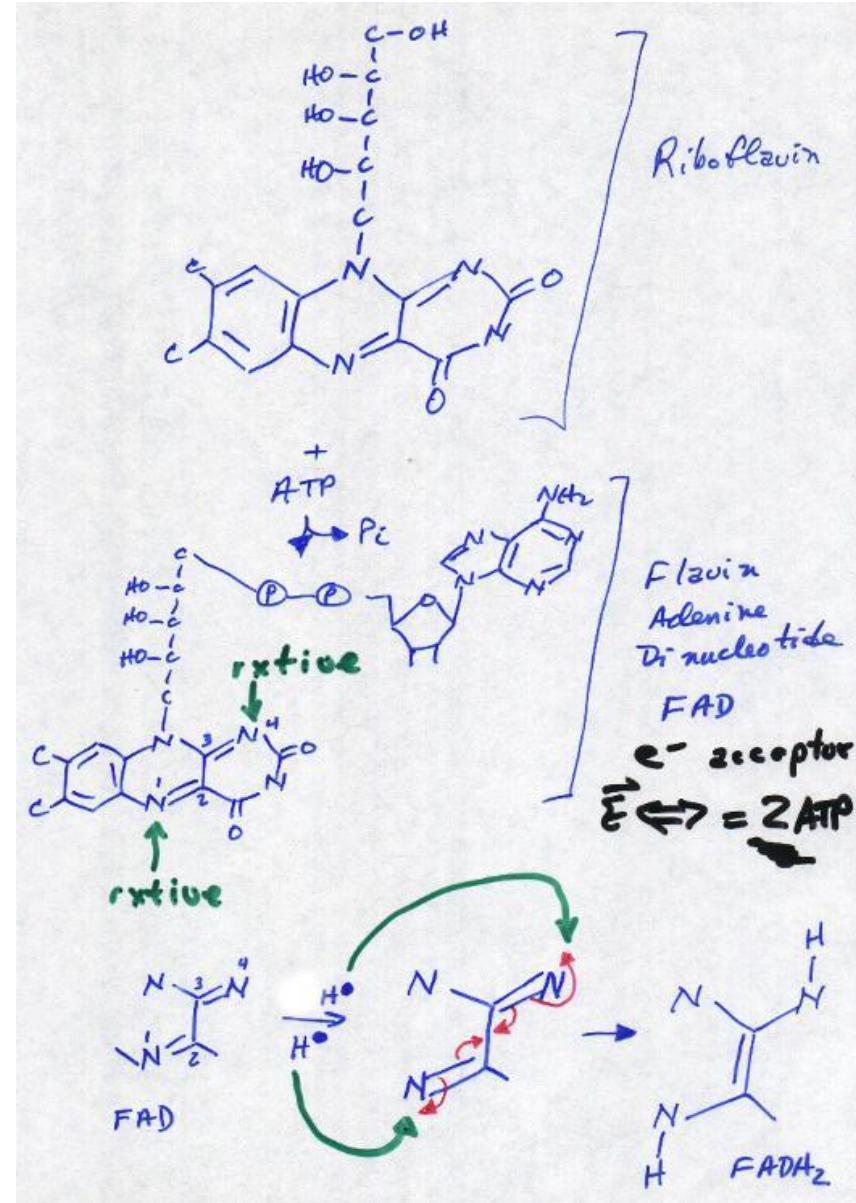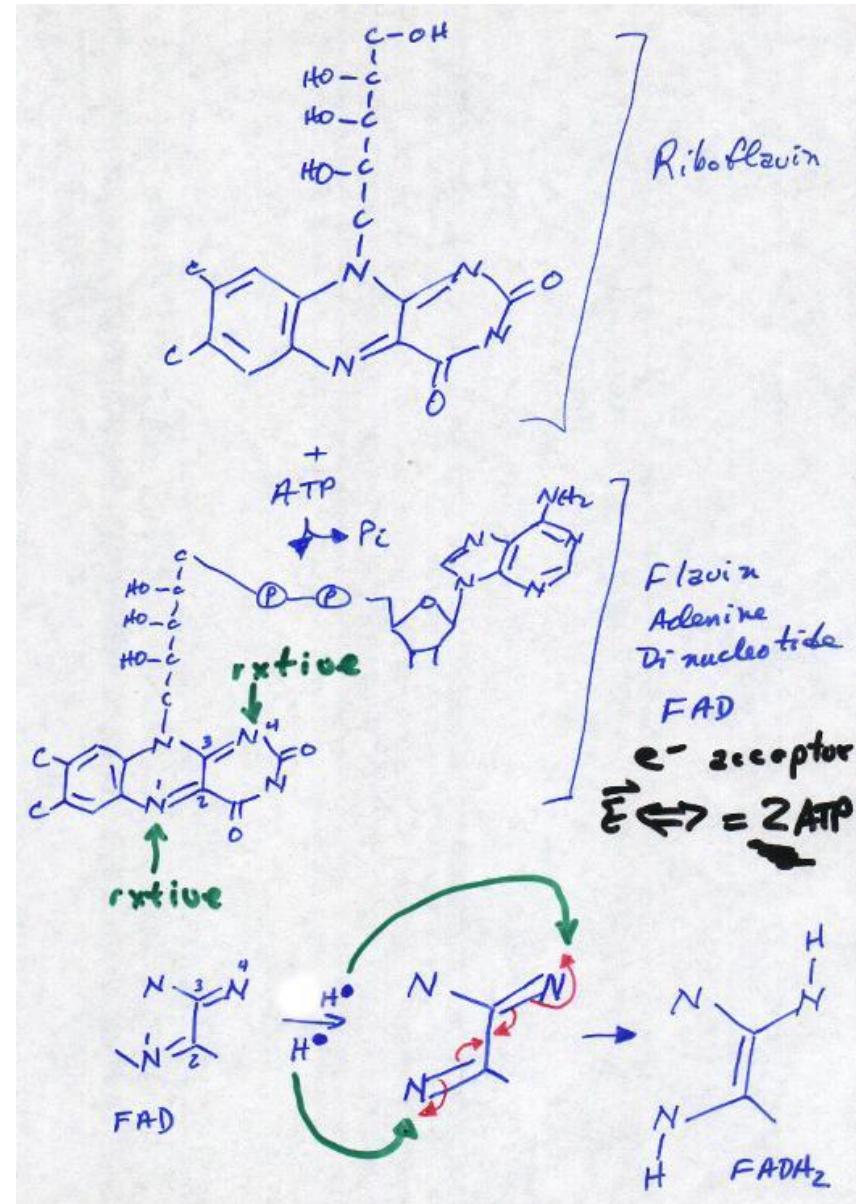
- TPP is required for decarboxylation reactions (loss of the CO_2H group) and transketolation reactions (transferring ketones as in the HMP).
- Previous Slide illustrates the decarboxylation of pyruvate with TPP.
- Enzymes have been left out in order to focus on the chemistry. The carbanion (mentioned above) attacks the carbonyl carbon in pyruvate.
- When this happens, two electrons in one of the bonds on the oxygen are "pushed away" from the carbon, permitting 2 things to happen: 1) the TPP and pyruvate intermediate bond and 2) the proton previously lost reacts with the unbonded pair of electrons on the oxygen forming an alcohol.
- Once this happens, the 2 electrons on the carboxylate group "flip" up forming an intermediate with 1½ bonds between the carboxyl carbon and the two oxygens.
- This "overload" of electrons causes the electrons between the carboxyl carbon and the alpha carbon to "flip up" forming an acetol-TPP intermediate with the release of CO_2.
- Note that the acetol-TPP intermediate is now uncharged as the electrons from the "flipping" have negated the positive charge on the nitrogen.
- Eventually, the acetol is released and oxidized to form acetate.

Riboflavin

- The structure of riboflavin.
- When it reacts with ATP, flavin adenine dinucleotide (FAD) is formed.
- FAD is an electron acceptor in metabolism.
- Its reduced form, FADH$_2$ is the equivalent of the energy of 2 molecules of ATP.
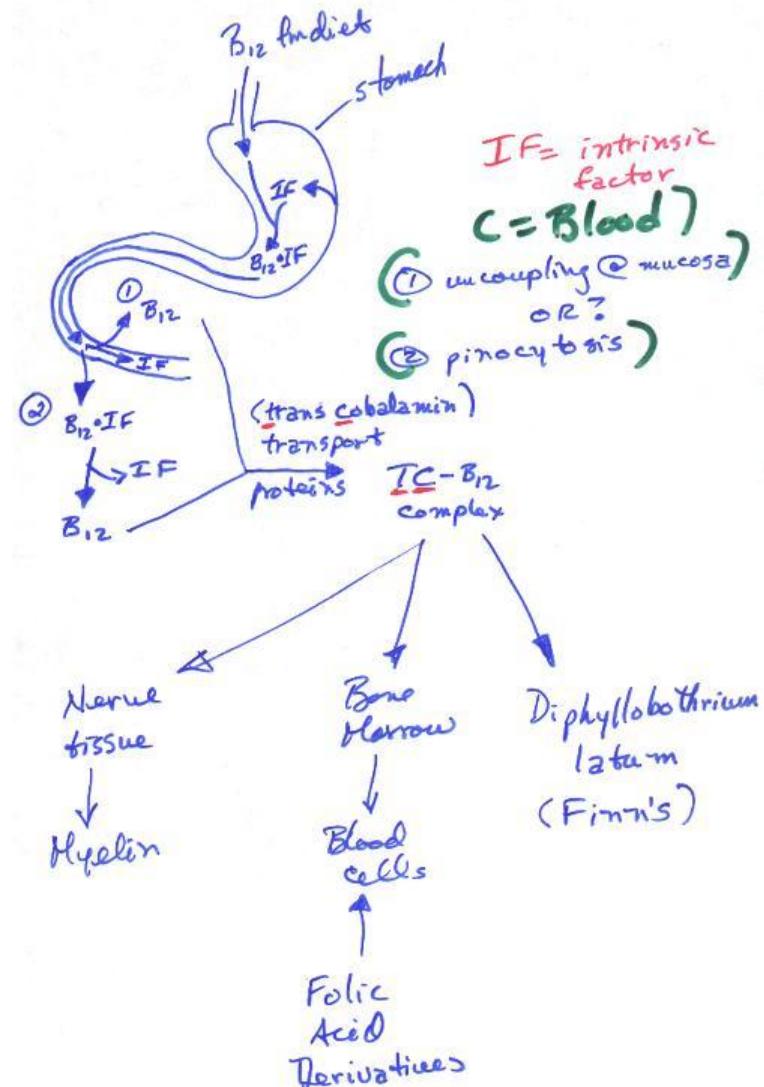
- The active sites of FAD are Nitrogen's 1 and 4.
- When hydrogen ATOMS react with FAD, they reduce these two nitrogens.
- As one electron from the double bond between C_3 and N_4 flips up to react with, form the bond with, the atomic hydrogen, the other flips down between C_2 and C_3.
- The same thing happens from N_1.
- The final product, $FADH_2$, has N_1 and N_4 fully reduced and a new double bond between C_2 and C_3.
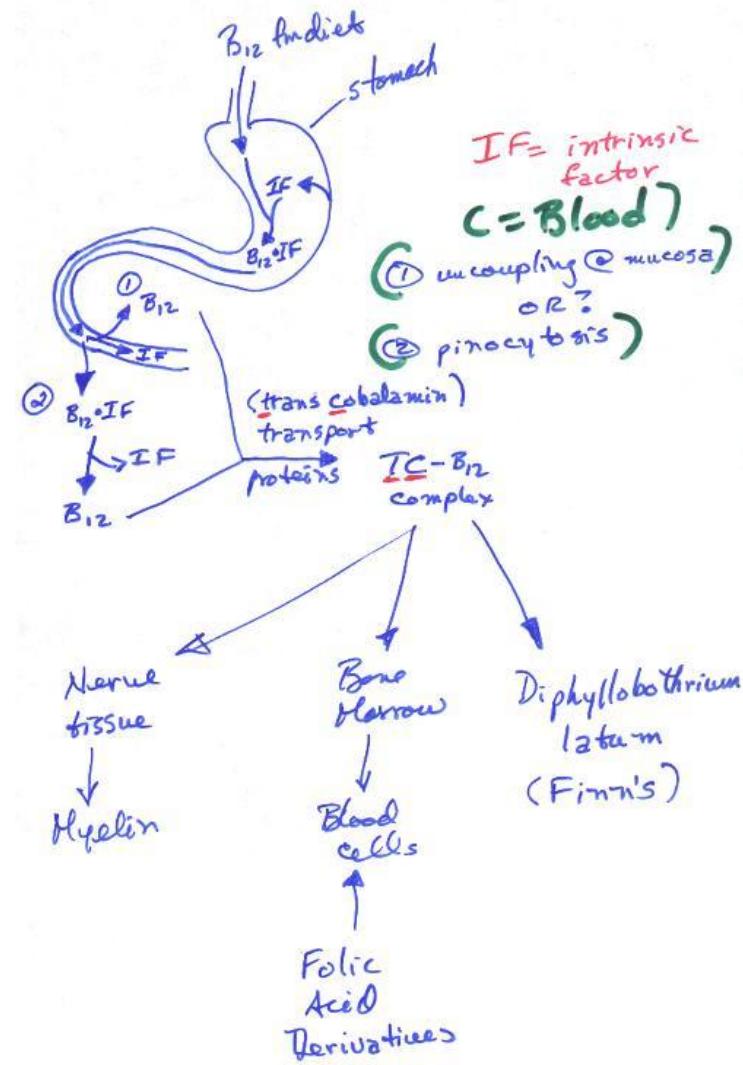
Cyanocobalamin (Vitamin B$_{12}$)

- In the case of this vitamin, I <u>will</u> refer to it as its letter and number -- easier to spell.

- B$_{12}$ has to come from either organ meats or supplements.

- Pure vegetarians HAVE TO take supplements to ward off developing pernicious anemia.
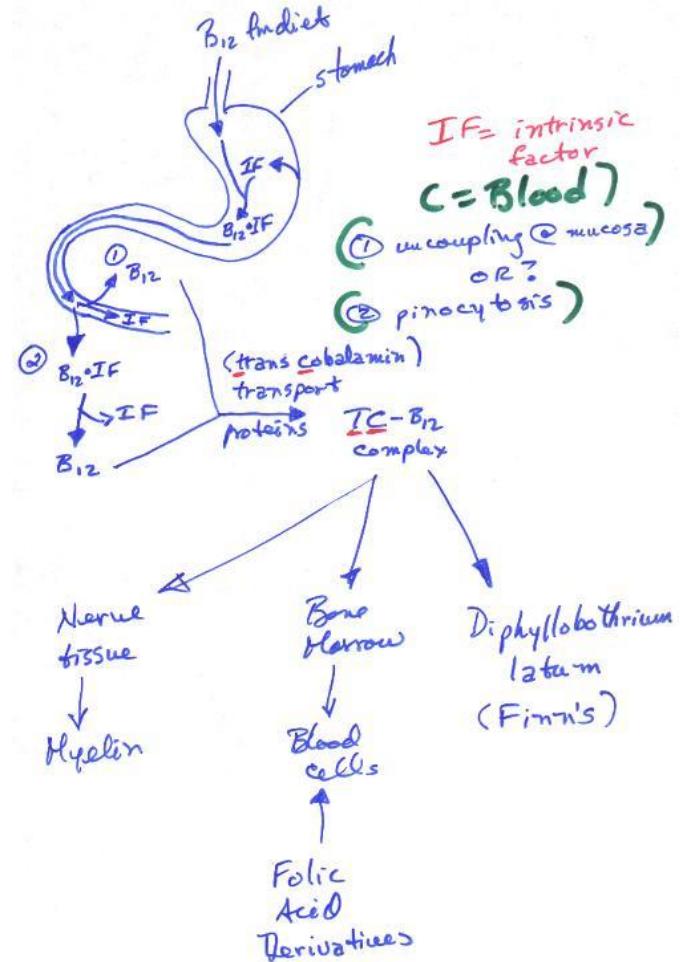
Cyanocobalamin (Vitamin B$_{12}$)

- B$_{12}$ is taken up from the diet.
- Once it gets into the stomach, the lining of the stomach releases Intrinsic Factor (IF).
- IF binds the B$_{12}$ for further uptake. BTW: no IF secretion means NO B$_{12}$ uptake -- no matter HOW much B$_{12}$ you give a person by mouth.
- The B$_{12}$-IF complex travels to the small bowel.
- It is at this point that the mechanism of uptake is a bit murky.
- Either the B$_{12}$ is released from the IF and is taken up across the bowel mucosa OR the whole B$_{12}$-IF complex is taken up by pinocytosis after which the B$_{12}$ is released.


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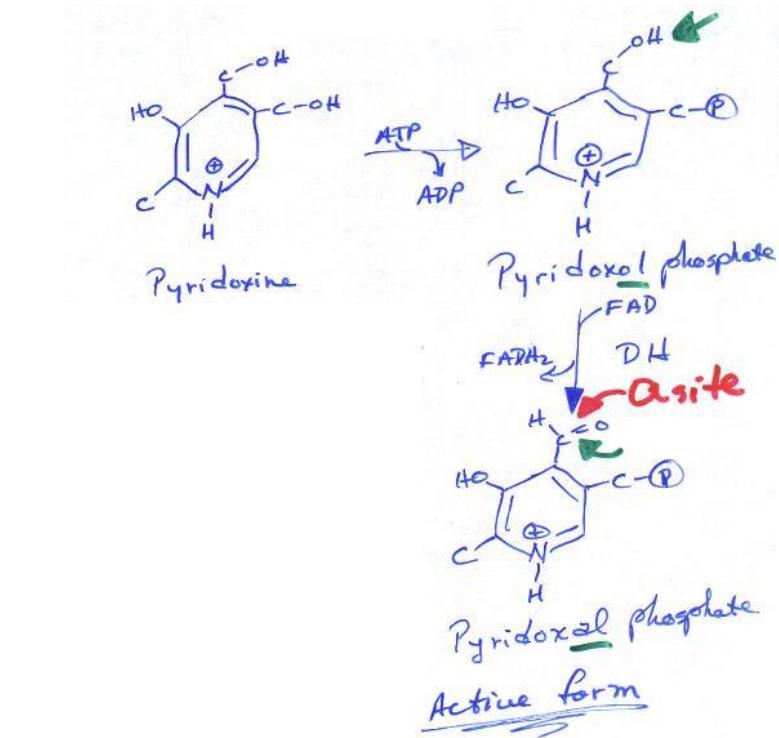
Cyanocobalamin (Vitamin B$_{12}$)

- Regardless of this mechanism, the free B$_{12}$ is then bound by transcobalamin (TC; a transport protein) and transported to nervous tissue (for myelin synthesis) and to bone marrow (to work with folate on hematopoiesis).

- Pathologically, B$_{12}$ is stripped from the blood by the fish tapeworm, Diphyllobothrium latum, when raw, smoked or pickled infected fish are eaten as is the case in Finland.

- The pernicious anemia that follows is readily reversible by treating/eradicating the worm.
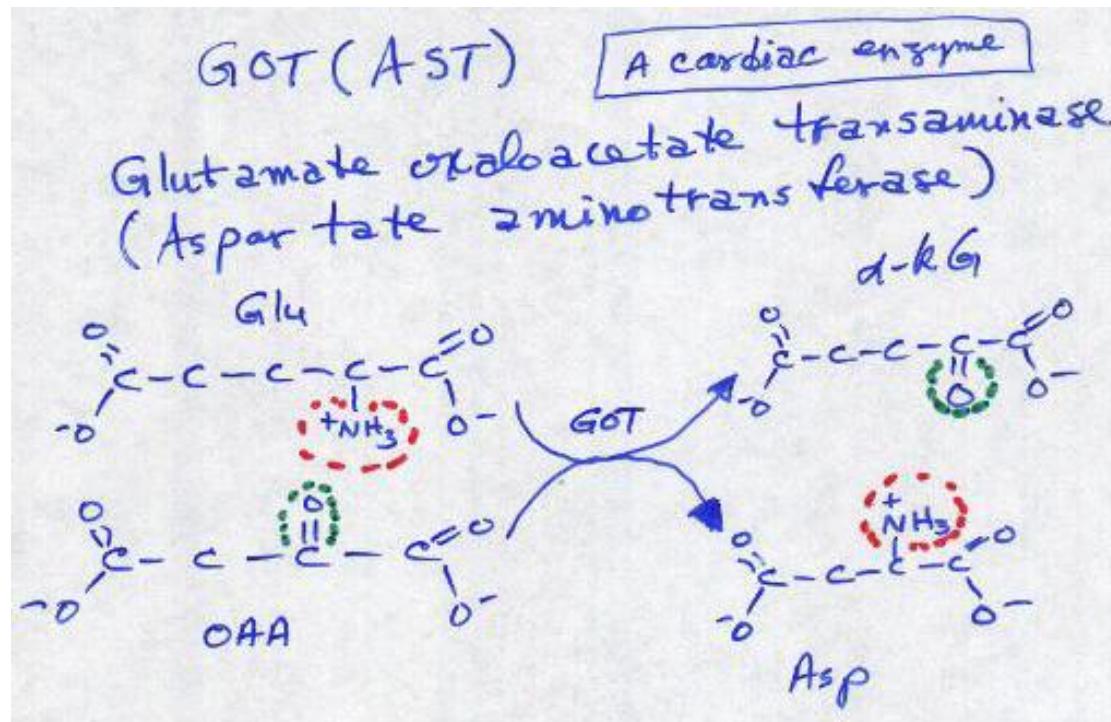
Pyridoxine

- The active form of pyridoxine is pyridoxal phosphate.
- It's required for 6 different kinds of reactions: transamination, decarboxylation, racemization, desulfhydration, amine oxidation and deamination.
- The activation of pyridoxine is pretty straight-forward, Figure.
- Pyridoxine is first phosphorylated to form pyridoxol phosphate.
- This product is then reduced by pyridoxol phosphate dehydrogenase with FAD to form pyridoxal phosphate (PalP).
- The active site is the aldehyde group, marked with the green and red arrows in the graphic.
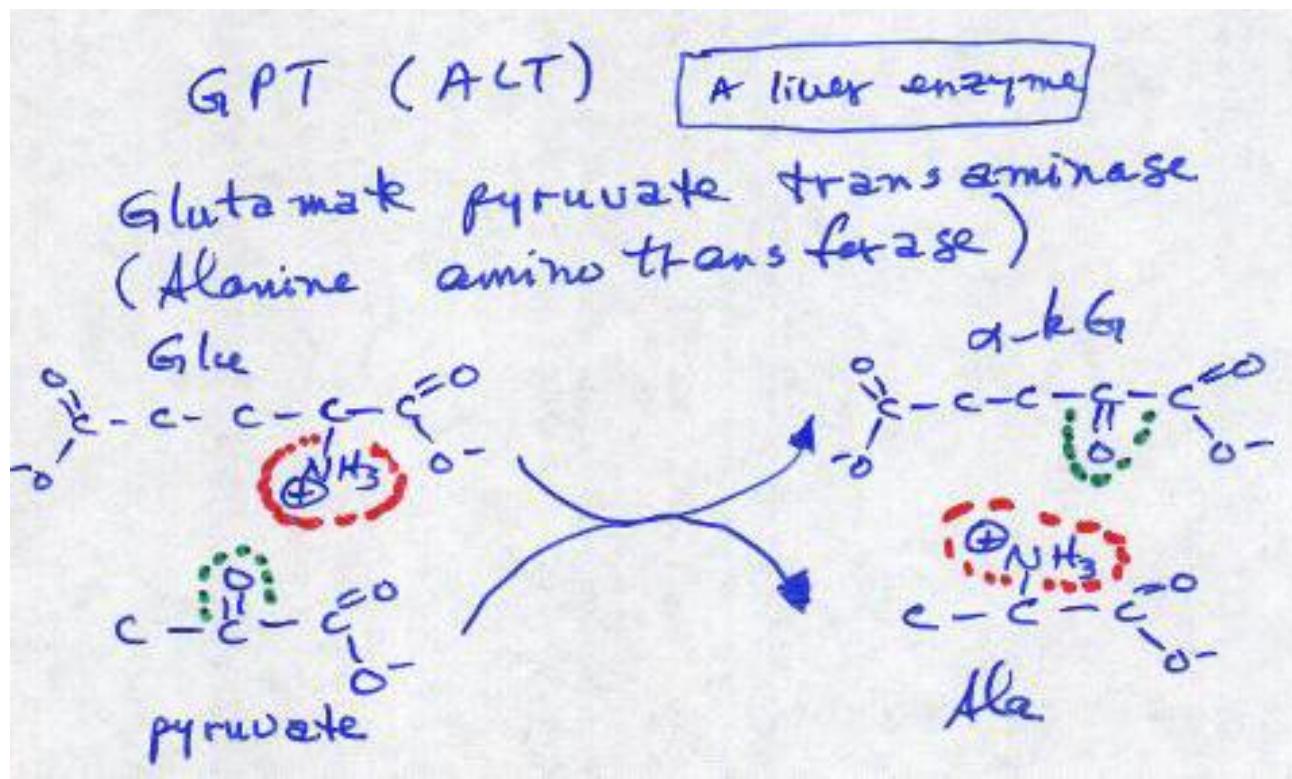
Transamination

- Two examples of transamination reactions.
- I chose these two reactions for their clinical relevancy.
- GOT (glutamate oxaloacetate transaminase) is aka AST (aspartate amino transferase).
- It is also known as SGOT, where the "S" stands for "serum".
- SGOT is a cardiac enzyme.
- In the myocardial cell it causes the amine from glu to flip with the ketone of OAA to form a-ketoglutarate (a TCA intermediate) and asp.
- Its extracellular significance is that it shows up in the blood after infarction as the heart muscle dies and explodes, releasing the enzyme into the circulation.


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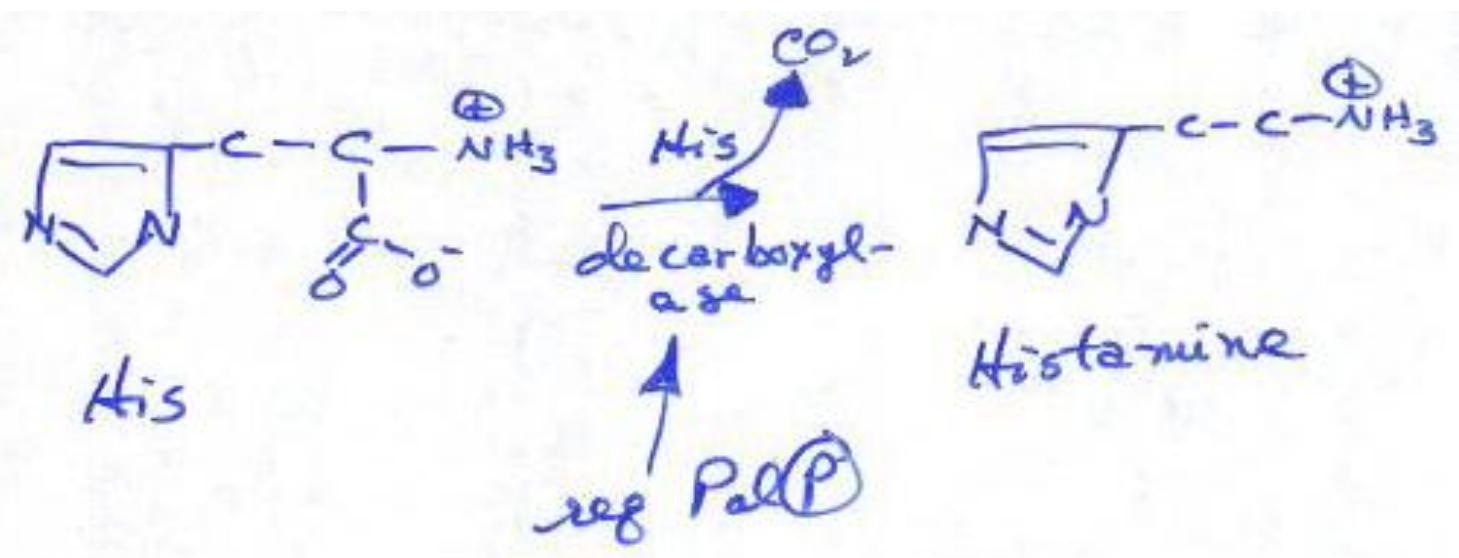
- GPT (glutamate pyruvate transaminase) is a liver enzyme aka ALT (alanine aminotransferase).

- The intracellular activity is to flip the ketone of pyruvate with the amine of glu to form ala and α-ketoglutarate.

- Again, elevated levels are due to release into the blood.

Decarboxylation
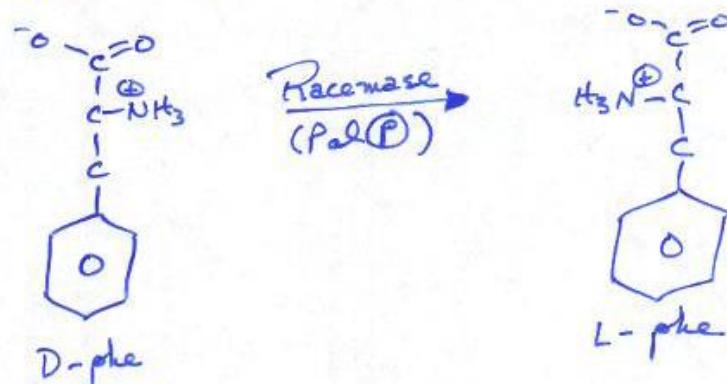
- Decarboxylation of histidine.
- Requires PalP to remove the CO_2 from his to form histamine.
- Anyone who has allergies can attest as to the efficiency of this reaction.

Racemization
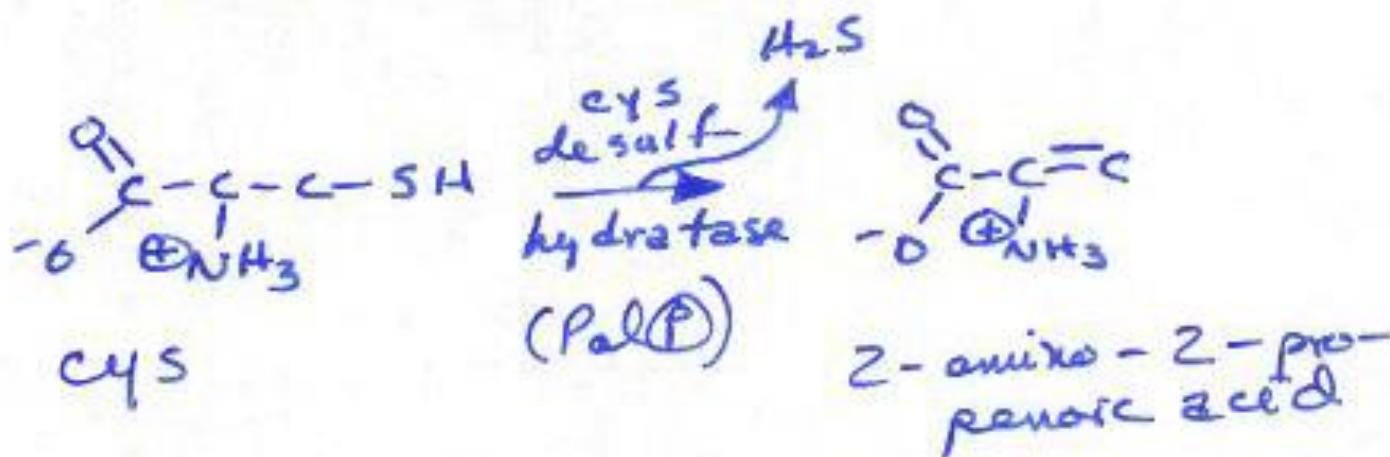
- The racemization of D-phe to L-phe.

- Compounds that are racemic consist of 2 isomers that are rendered optically inactive when present in equal amounts, e.g., 50% D and 50% L forms of the same compounds.

- In the case of the racemization of phe, the enzyme racemase is required.

- Remember that humans metabolize L-amino acids.

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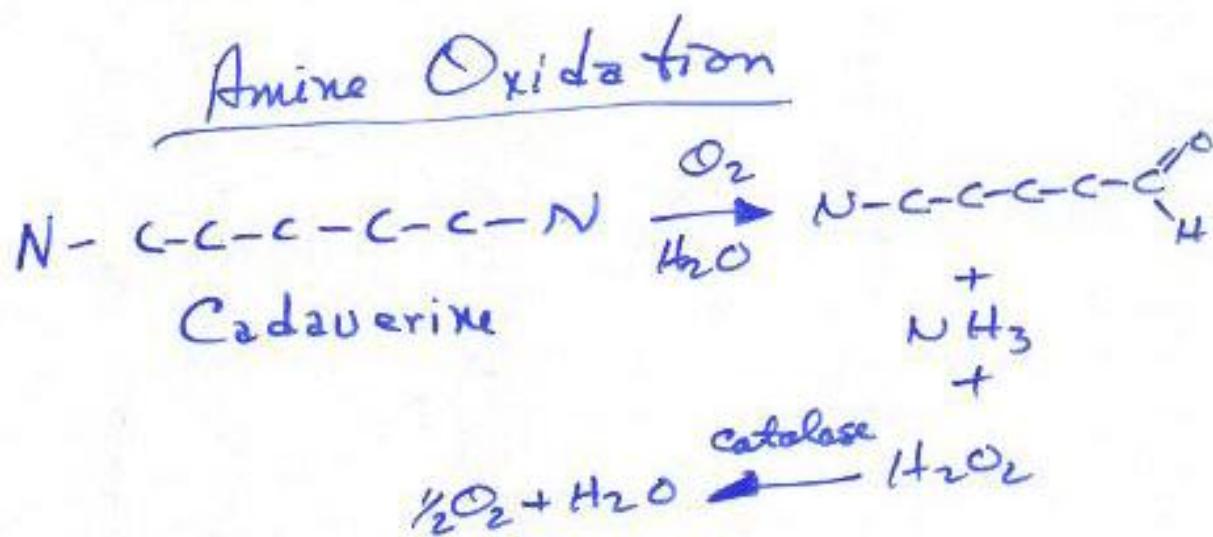
Desulfhydration

- PalP with cysteine desulfhydratase removes the S from cys as H$_2$S, leaving 2-amino-2-propenoic acid as the product.

Amine Oxidation

- Using PalP with water and oxygen.

- Cadaverine's terminal amine is oxidized to an aldehyde plus ammonia plus hydrogen peroxide (easily dealt with be catalase; review BIOL 251 for this reaction).

- Cadaverine got its name, BTW, as it's a very prominent, odoriferous diamine found in rotting corpses.

Amine Oxidation

$$N - C - C - C - C - C - N \xrightarrow[H_2O]{O_2} N - C - C - C - C - C{\overset{O}{\underset{H}{\diagdown}}}$$

$$+$$
$$\overset{+}{N}H_3$$
$$+$$

$$\tfrac{1}{2}O_2 + H_2O \xrightarrow{catalase} H_2O_2$$

Oxidative Deamination

- Glu is oxidatively deaminated to α-ketoglutarate by the enzyme glutamate dehydrogenase (GDH).

- GDH requires water and either NAD OR NADP.

- The other products besides the TCA intermediate are ammonia and NADH OR NADPH.