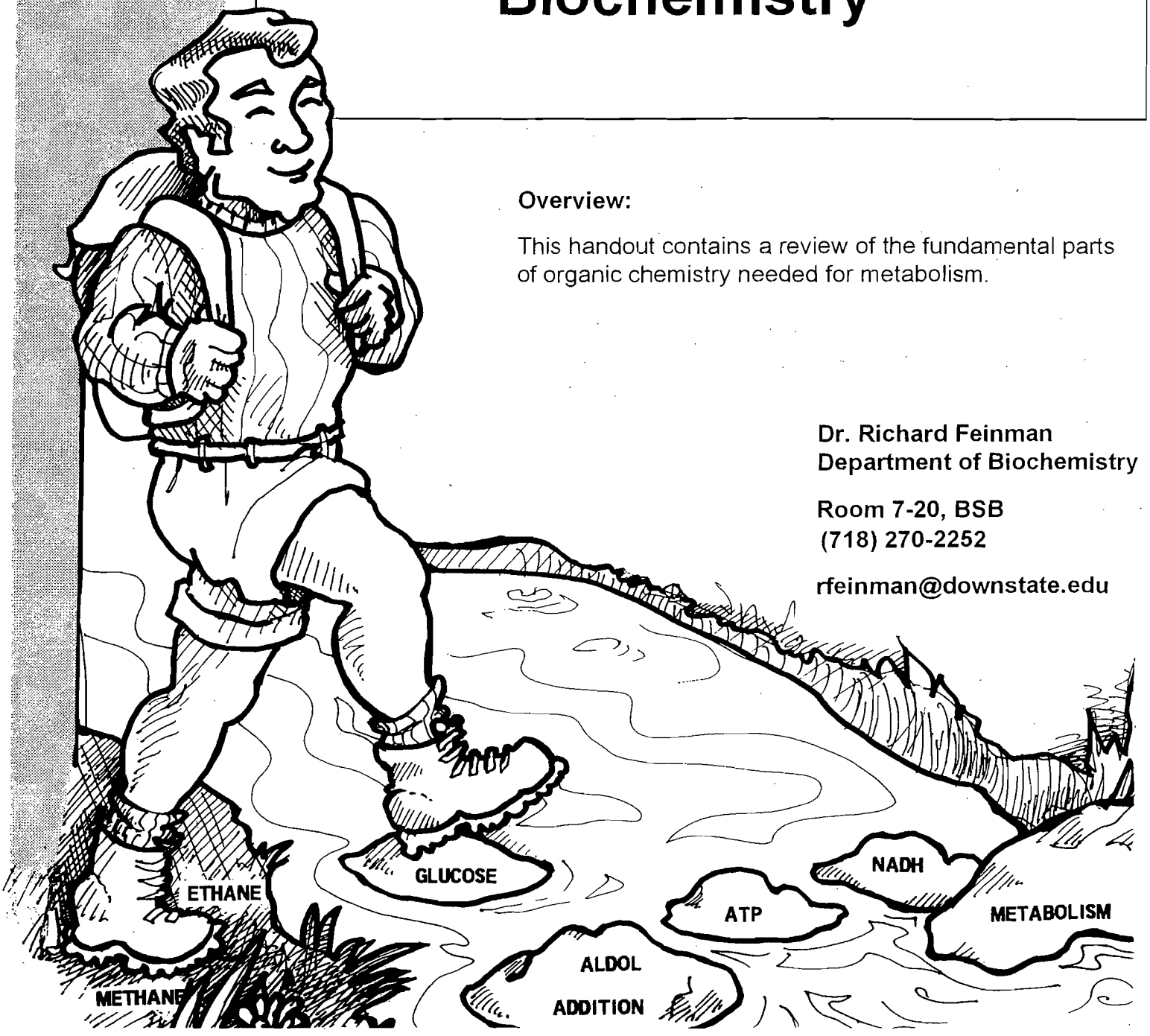
Review: Step by Step from Organic Chemistry to Biochemistry



Overview:

This handout contains a review of the fundamental parts of organic chemistry needed for metabolism.

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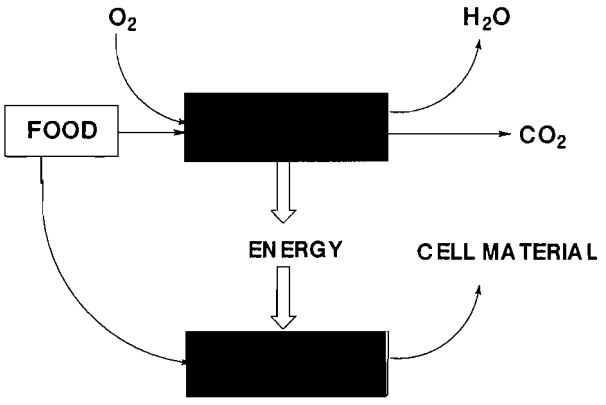
CHAPTER 0. INTRODUCTION



Where we're going. The big picture in nutrition and metabolism is shown in a block diagram or "black box" diagram. A black box approach shows inputs and outputs to a process that may not be understood. It is favored by engineers who are the group that are most uncomfortable with the idea that they don't know anything at all. The black box approach can frequently give you some insight because it organizes whatever you do know. For example:

1. Even though the block diagram is very simple, just looking at the inputs and outputs gives us some useful information. The diagram says animals obtain energy by the oxidation of food to CO_2 and water. Although you knew this before, the diagram highlights the fact that understanding biochemistry probably involves understanding oxidation-reduction reactions.

2. The diagram also indicates what might not be obvious: a major part of the energy obtained from oxidation of food is used to make new cell material. Although we think of organisms using energy for locomotion or to do physical work, in fact, most of the energy used is **chemical energy**.

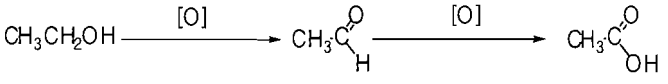
3. Inside the black boxes in the diagram contain are the (organic) chemical reactions that convert food into energy and cell material. Biochemistry is the study of these organic reactions, the structure of the proteins and enzymes (catalysts) that control these processes and the genetic material that specifies which proteins are to be made for each cell and organism.

4. **The Strategy**:

   1. We are going to break into the black boxes: Our first intuition from the black box, consistent with our everyday experience, is that food is oxidized, like fuel in a car, to obtain energy. Unlike a car however, which uses one step explosive reactions, biological systems must carry out the reaction in small steps in order to capture the energy in chemical compounds. Metabolism is the step-by-step conversion of food into break-down products for energy (**catabolism**) and the step-by-step conversion of some food to cell material (**anabolism**).

   2. Organic chemistry. To a large extent, nutrition and metabolism is applied organic chemistry. There's more to it than that, but most of it is organic reactions. The good news is that only a small part of what you learned in organic chemistry is critical for understanding biochemistry.

   3. The model reaction and a preview. When ethanol is ingested, the liver converts it to acetaldehyde and then to acetic acid. This sequence, **alcohol ⟶ aldehyde ⟶ carboxylic acid**, are the first steps in a larger process which ultimately converts the carbons of ethanol to CO_2. This is an oxidation (indicated by [O] and, in this sense, ingested alcohol can be burned as a fuel to produce energy for life. This series of reactions is of clear medical importance itself. In addition, it defines the three most important types of compounds you have to know from organic chemistry.



5. **How To Use This Book**: If you are comfortable with these structures -- if you recognize ethanol, acetaldehyde and acetic acid, you can go to directly to **Chapter 4. The Big Four: Alcohols, Amines, Carbonyls And Carboxylic Acids.** If you want a more complete review, go to **Chapter 1** which starts from scratch.

6. Study Methods.

1. Some of the sections in this book are of the "workbook" type and require that you fill in answers. We recommend that you do these and not go on until you are sure that you understand the answers asked for. You may need to look things up in the text. Answers are provided at the end but you will get the most out of this if you try it yourself first.

2. It is a good idea to time yourself, especially when studying metabolic pathways or learning the names of compounds like the amino acids. These projects can seem large and daunting. By seeing exactly how long each Chapter takes, you will discover that they are less demanding than you thought. Chapters are designed for about a half hour, but even if they take longer, you will know what you are up against.

7. The Importance of Nomenclature.

1. Chemistry is a language and cannot be used in a loose way. One of the reasons that you study organic chemistry is to develop precision in language. Looking ahead, if you prescribe klonopin (anti-convulsant) when you mean clonidine (anti-hypertensive) you may not get the best result. (That may be why they changed the name of clonopin to klonopin). The systematic (IUPAC) language is more precise than English because it is more logical.

2. Biochemical compounds were discovered before the IUPAC and so many have common names or sometimes only semi-systematic names. We recommend that, whenever possible, you **give an IUPAC name** to a compound even if it has a common name. This allows you to get a feel for the nature of the compound. In general, you want to feel that, as much as possible, you are not memorizing things but associating names with properties. So, for example, to identify the name **alanine**, first calling it **2-amino propanoic acid** will help you see it as an **amino acid**. When you study the way alanine is converted to pyruvic acid and pyruvic acid is converted to lactic acid, recognizing them as **2-amino propanoic**, **2-oxo propanoic** and **2-hydroxy propanoic** will help you see how they are related to each other. Also, it is easier than learning two non-systematic names, like, you know, demerol® and meperidine.

8. The Three Big Ideas for Going from Organic Chemistry to Biochemistry.

1. **Generalization is the name of the game.** Every compound has two parts: the hydrocarbon backbone or ring, relatively inert, and the functional group, which contains electronegative atoms such as oxygen and nitrogen. This is where the chemical reactions occur. We assume that all **functional groups behave in a similar way** and that two different alcohols, for example, will have the same chemical properties even though the overall structure that includes the hydrocarbon part may be different.

2. Almost all compounds in biochemistry are made of **only six functional groups and phosphoric acid.** The functional groups are: "big four:" alcohols, amines, carbonyls and carboxylic acids, that were studied in undergraduate organic chemistry, thiols (sulfur analog of alcohols) and double bond compounds.

3. The great majority of reactions studied in biochemistry fall into only three big classes:

    1. Oxidation-reduction reactions.
    2. Acyl and phosphoryl transfer (acyl refers to derivatives of carboxylic acids).
    3. Nucleophilic addition reactions to carbonyl groups (aldehydes and ketones) and the reverse reaction.

9. Objectives of Chapters 1-6:

1. To review some of the basics ideas of organic chemistry.
2. To re-emphasize the **generalizing power of organic nomenclature and organic functional groups.** The goal is to see individual biochemical reactions as 'variations on a theme' and thereby to reduce memorization.
3. To understand that the great majority of biochemical compounds contain or are made from only six organic functional groups and phosphoric acid.
4. To understand that the great majority of biochemical reactions are of only the three major types.

CHAPTER 1. FIRST STEPS

Methane and ethane. Methanol and ethanol.
Getting back into bonding. The idea of functional groups. The alcohols.

Note: this chapter contains a very fundamental review. It emphasizes nomenclature. You should be sure that you do, in fact, understand this section. Biochemistry is a pyramid and if you can develop a strong base, it makes it much easier when we pile stuff on top later.

Where are we going ? The goal in organic chemistry is to develop logical principles so that not everything has to be memorized. The main tool is to divide substances into big classes, learn the properties of the class and recognize individual compounds as examples of the class. Looking ahead, biochemistry can be thought of as applied organic chemistry.

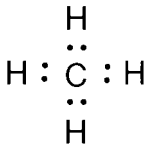
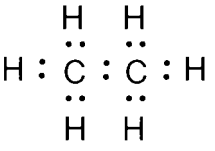
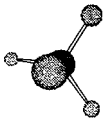
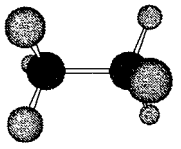
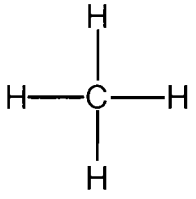
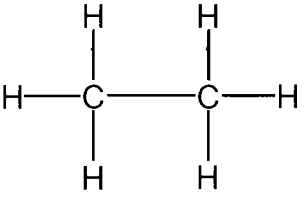
How do we get there ? We'll compare two big classes of compounds: **the saturated hydrocarbons** -- compounds with just CH bonds, and the **alcohols**, compounds that contain an OH group. We'll look at the two simplest compounds in each group: 1) methane and ethane and 2) methanol and ethanol. These two pairs are representative of the two major substances in organic -- and ultimately in biochemistry -- 1) the hydrocarbons are non-polar, unreactive, water-insoluble and 2) the alcohols are polar, chemically reactive and soluble in water. The emphasis here is on the electrical polarity of the chemical bond and the compound containing it.

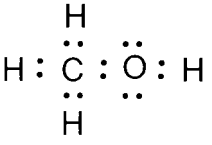
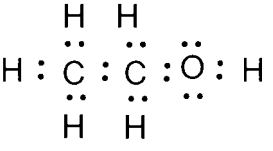
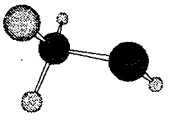
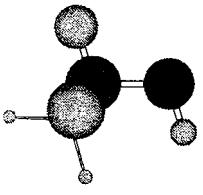
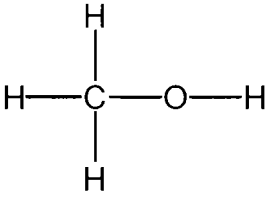
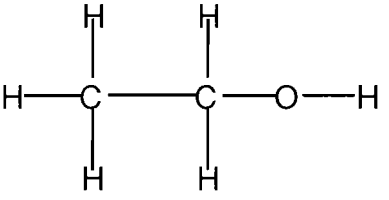
STEP 1. Where do we start ? First, the Lewis structure: this is our formal way of writing the electrons in the bonds holding molecules together. If you never were really comfortable with this, now's the time. Look at methane and ethane first in the figure on the next page.

1. Each carbon atoms has four chemical bonds. Each oxygen, two. Each hydrogen, one.
2. Each chemical bond includes two electrons that are shared -- the covalent bond: one bond, two electrons. The shared electrons are localized to bonds or molecular orbitals.
3. Since chemical reactivity is in the movement of the electrons, sometimes we show the electron pairs in each orbital, or sometimes just the bond ad indicated by a straight line. So all the structures shown in the figure are equivalent ways of representing the same thing.
4. The only difference in the bonding, comparing methane and ethane, is that there is one more carbon-carbon bond which replaces a carbon-hydrogen bond. You undoubtedly remember that continuing to do this builds up chains of carbon atoms which is the basis of the hydrocarbons. But first, the comparison group.

STEP 2. What about methanol and ethanol ? We can write the same kind of pictures for methanol and ethanol. The figure on the next page gives you a number of different ways of writing methanol and ethanol (note: some of the hydrogens on ethanol are not clearly visible in the figure). It is the same system for the hydrocarbons but different atoms are involved. The key to organic chemistry is that the fundamental nature of the covalent bonds in these compounds are different. We divide the molecule into two parts. The part with the **hydrocarbon**, C and H, and the part with the **functional group**, the **OH part**. Recall that when we want to write a "generic" alcohol we write R-OH, where R stands for the hydrocarbon part (CH_3- in methanol, CH_3-CH_2- in ethanol).

STEP 3. What's the big difference ? The big difference is that the carbon-oxygen bond and the hydrogen-oxygen bond are not symmetrical -- the electrons are not equally distributed: they bunch up on the oxygen. In other words, both the C-O and the O-H bond are polar bonds, that is, they have a + end (carbon or hydrogen) and a - end (oxygen). The OH part of alcohol molecule looks like water and from this we predict (and experience confirms) that methanol or ethanol are soluble in water. Since methane and ethane are gases we don't have direct experience but we expect that these are not soluble in water. In other words, methanol and ethanol have a water-like part and a hydrocarbon-like part, while methane and ethane are entirely hydrocarbon like.

	METHANE	ETHANE
Lewis Structure		
3-D Configuration		
Structural Formula		
Short-hand	CH_4	$CH_3–CH_3$

	METHANOL	ETHANOL
Lewis Structure		
3-D Configuration		
Structural Formula		
Short-hand	CH_3OH	$CH_3–CH_2–OH$

STEP 4. The organic chemistry system. The principal that we just defined can be extended to whole series of compounds. We build up the series of hydrocarbons by making chains of carbon atoms. Hydrogens are added to the carbon atoms to insure that every carbon has four bonds. Knowing this system of compounds is the fundamental commandment of organic and biological chemistry. Figure 2 asks you to list the first ten compounds in this group. You only have to memorize how to "count from one to ten" in organic language. The system that follows from this will allow you to give unambiguous logical names to other compounds as well. This systematic method is called the IUPAC system (International Union of Pure and Applied Chemists).

By themselves, these compounds are known as the **alkanes** or **saturated hydrocarbons** (they're "saturated" with hydrogen, in the sense that they have the maximum number of carbon-hydrogen bonds). You may recognize by the names that they are used as gasolines and other fuels. As such we don't deal with them much in biochemistry. The names, however, are the **basis of the nomenclature system for other compounds**. Also, many biological compounds such as fats contain a high percentage of hydrocarbons and these molecules will have non-polar gasoline-like properties. Before you go further, make sure you know the names of the first ten hydrocarbons. To check, it's worth filling out the following chart, writing the missing name, Lewis structure, structural formulas and shorthand structure. **Answers are at the end of the chapter.**

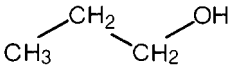
# C	NAME	LEWIS STRUCTURE	STRUCTURAL FORMULA	SHORTHAND
1	Methane			
2	Ethane			
3	Propane			
4	Butane			
5				
6		Leave out the shaded area; you should have the idea by now.		
7				
8				
9				
10				

STEP 5. Back to the simple alcohols. You can now build up a system of alcohols by simply adding an OH group in place of one of the hydrogens as you did for methanol and ethanol. The rule of **nomenclature**:

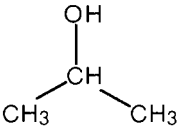
1. Count the number of carbons.
2. Drop the final "-e" in the hydrocarbon name and add the suffix "-ol."

With this principle, you should be satisfied that the name of the five-carbon alcohol is "pentanol."

STEP 6. Isomers. Of course, once you have more than two carbons there's a choice as to where to put the OH group. As soon as you come to the three carbon alcohol, propanol, there is an additional problem, the OH group could go on any one of the three carbons, that is, you have **isomer**s, compounds with the same formula but different structure. You undoubtedly recall, that the first and third carbons are really the same -- there's no way to call one carbon 1 and the other carbon 3, so there are actually two isomeric propanols. The rule is that you use the lowest possible numbers. That is, the two propanols are 1-propanol and 2-propanol -- the expression "3-propanol" is not a meaningful name -- no such thing.



1-propanol



2-propanol

Obviously, as you go to higher and higher alcohols there will be more isomers.

Q1: write the structure of 3-octanol.

Method 1:
1) Write a chain of 8 carbon atoms.
2) Add an OH group to the third carbon from one end; either end. Add an H to this carbon.
3) Add -H atoms to all the other carbons so that the total number of bonds to each C is four.

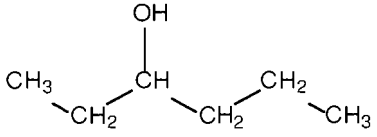
Method 2:
1) Write a CH_3- group.
2) Connect it to a CH_2 group (you know the chain isn't finished and all carbons have to have 4 bonds).
3) The next carbon will be carbon 3 so attach an OH group to it and write it as a CH- group.
4) Keep attaching CH_2- groups until you have seven carbons.
5) Attach a CH_3 group to the end.

Do it. Make sure you understand how both methods work:

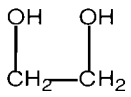
Q2. Write all the isomers of octanol, and give names to each compound..

Ans. You should have come up with 1-, 2-, 3- and 4-octanols. (Putting the OH on carbon "5" would be the same as carbon 4 (just turn the molecule around).

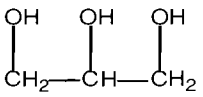
Q3. Give an accurate IUPAC name for the following compound.



STEP 7. Polyols: variations on a theme. If a carbon compound has two -OH functional groups, it is called a diol. If it has three, it is called a triol. **Ethane diol** and **propane triol** are shown below. If the number of OH groups is smaller than the number of carbons, then to precisely define the compound, you have to use numbers, e.g. 3, 4-pentane diol.

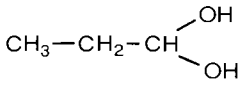


ethane diol (ethylene glycol)



propane triol (**glycerol**)

Important point: the rule of functional groups applies to polyols, that is, you assume a diol really behaves just like two alcohols. Any chemical properties you may remember for alcohols and any properties we study will apply to each hydroxyl group in the diol. This is an approximation, but for the moment it is a good one. Also, once you put two functional groups on the **same** carbon, all bets are off. **This is a new functional group**. So although the following compound is occasionally called a *gem*-diol (*gem*- meaning twin) it does **not** behave like two alcohols and you may recall it is accurately called an aldehyde hydrate -- we'll see it later -- and will avoid loose talk like "*gem*-diol."



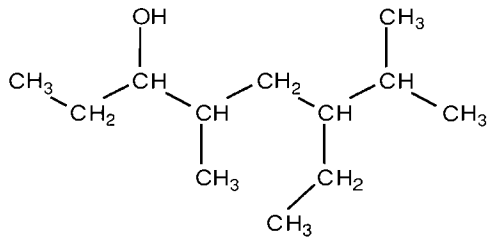
propanal hydrate
("*gem*-diol" -- not a real diol)

STEP 8. Propane triol is always called by its common name, **glycerol**. It shows up in biochemistry as the basis of the class of molecules that includes fats and oils, the triacylglycerols. **Our suggestion**:

When confronted with a new biological molecule with a common name, like glycerol, whenever possible, try to give it a systematic IUPAC name, here, propane triol. The process of using the IUPAC system forces you to "psyche out" the functional group and therefore you get a clue to the chemistry of the compound.

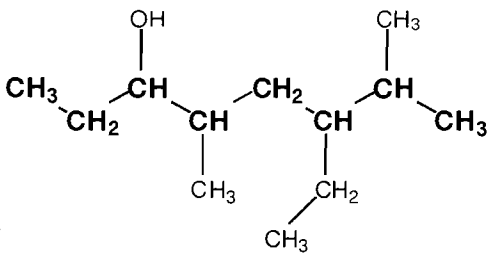
STEP 9. What about branched chains ? We have, so far, only considered compounds where the carbon "backbone" lies in a straight line. For compounds with branched chains, the rules are as described below in the context of a problem. **Again, although this problem may seem elementary, make sure you have control over it.**

Q4. Give a correct IUPAC name for the following compound:



Here are the rules:

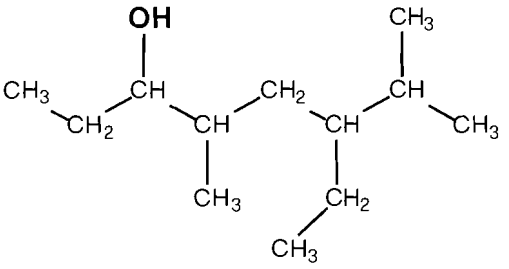
1. **Find the longest continuous chain of carbon atoms** and count them and name the compound as derived from this chain. (These may not lie in a straight line on paper. The graphic representation may be designed to emphasize the functional group and the longest carbon chain may "snake around."



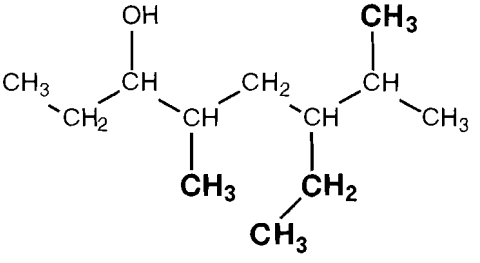
The longest chain (in bold) is eight carbons. The tentative name then is "octane." Here the longest chain is in a straight line.

2. **Identify the functional groups** (so far we are only considering alcohols) and number the carbons of the chain so that the functional group has the lowest possible number.

The compound is now tentatively a "**3**-octan**ol**" (Note that if you had started counting at the right, you would have come up with **6**-octanol which is not the lowest number.



3. **Now, identify the hydrocarbon groups ("side chains" or "substituents") that come off the main chain.** The general "adjective name" for a hydrocarbon group as a side chain is alkyl. The specific names are methyl- (CH_3-), ethyl- ($CH_3\,CH_2$-), propyl, butyl, pentyl-, etc. Assign the appropriate number and put the names of the substituents in **alphabetical order**.



There are obviously 2 methyl groups, and one ethyl group. Remember that the alcohol is on carbon 3 so that would make the methyl groups on carbon 4 and 7 and the ethyl group on carbon 6. The substituent groups are listed alphabetically.

The answer: 6-ethyl 4,7-dimethyl 3-octanol.

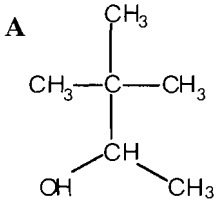
PRACTICE QUESTIONS. Nomenclature is at the heart of the systematic approach to organic chemistry. If you can see it as a logical game, like a crossword puzzle, the need for memorization will disappear.

Q5. Draw the structure of 3, 3-dimethyl-2-hexanol. This problem reminds you that if there are two alkyl groups attached to a single carbon you must not only indicate how many (di-) but also indicate the number twice (3,3).

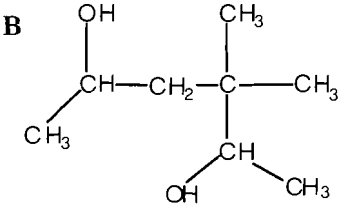
Q6. The hydrocarbon chain can fold back on itself giving rise to cyclic structures. In this case, the prefix "cyclo-" is used and if the ring that is formed is small, only the geometry of the carbon atoms is shown. For example, the cyclic hydrocarbon of six carbons is called cyclohexane. **Write the structure of 1, 3-dimethyl cyclohexane.**

Q7. Give good IUPAC names to the following compounds.

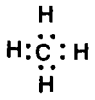
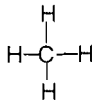
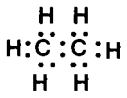
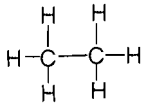
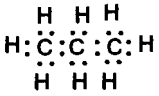
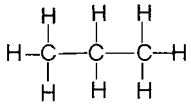
A



B



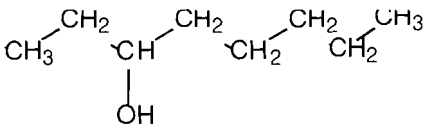
ANSWERS TO CHAPTER 1.

NAME	LEWIS STRUCTURE	STRUCTURAL FORMULA	SHORTHAND
METHANE			CH_4
ETHANE			CH_3CH_3
PROPANE			$CH_3CH_2CH_3$

BUTANE, PENTANE, HEXANE, HEPTANE, OCTANE, NONANE, DECANE

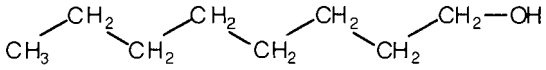
Q1: write the structure of 3-octanol.

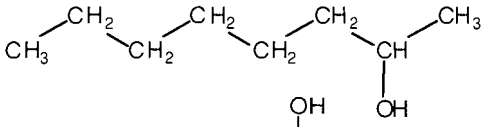
Method 1:
1) Write a chain of 8 carbon atoms.
2) Add an OH group to the third carbon from one end; either end.
3) Add -H atoms to each carbon so that the total number of bonds to each C is four.

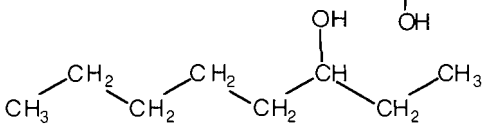


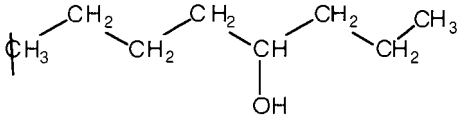
3-octanol

Q2. Write all the isomers of octanol, and give names to each compound.

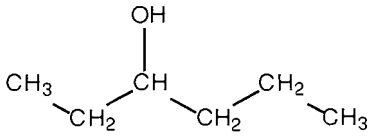
1-octanol 

2-octanol 

3-octanol 

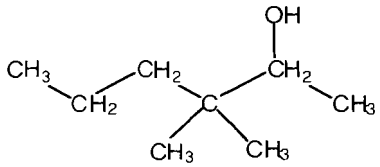
4-octanol 

Give an accurate IUPAC name for the following compound. **Q3.**

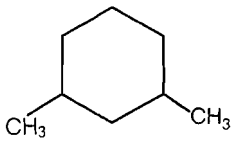


ANS: 3-hexanol

Q5. Draw the structure of 3, 3-dimethyl-2-hexanol. This problem reminds you that if there are two alkyl groups attached to a single carbon you must not only indicate how many (di-) but also indicate the number twice (3,3).

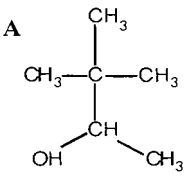


Q6. The hydrocarbon chain can fold back on itself giving rise to cyclic structures. In this case, the prefix "cyclo-" is used and if the ring that is formed is small, only the geometry of the carbon atoms is shown. For example, the cyclic hydrocarbon of six carbons is called cyclohexane. **Write the structure of 1, 3-dimethyl cyclohexane.**



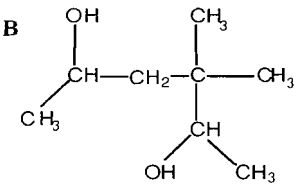
Q7. Give good IUPAC names to the following compounds.

A



3, 3 dimethyl 2-butanol

B



3, 3 dimethyl 2, 5 hexane diol

Notice that, in **B**, the longest chain is not in a simple path.

ω end of chapter

CHAPTER 2. POLARITY OF BONDS

Electronegativity. Polarity of bonds. Structure of water. The amines.

Where are we now ? We have established the idea that organic chemistry is a workable enterprise because there's only one kind of force (electrostatic: plus attracts minus; like charges repel). There are, then, roughly two types of compounds: polar and non-polar, exemplified by the hydrocarbons and the alcohols. The difference between the two types of compounds is in the distribution of electrons, that is, electric charge. In other words, the C-O bond and the O-H bonds are polar, the negative charge bunching up on the oxygen, whereas the C-C and C-H bonds are non-polar.

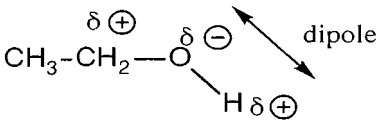
What's the next step ? We are going to ask: How do you know when a bond will be polar or non-polar? We will put a number, the **electronegativity**, on the tendency of atoms to become charged. We will recognize oxygen and nitrogen as **electronegative atoms**. We predict that these atoms will show both chemical reactivity and charged interactions, e.g. with solvents. Ideally, we will have a sense of predictive power about new compounds and have less to memorize. We will use this concept of polarity to develop the idea of the hydrogen bond and look at the nature of water.

STEP 1. **Electronegativity is the tendency of an atom in a covalent bond to attract electrons from the bond.** In other words, in a covalent bond, the shared electrons are not shared equally. The consequence of this is that electric charge is not equally distributed and alcohols are polar compared to hydrocarbons because **oxygen has a high electronegativity**. Another way of looking at this is to say that all compounds are covalent with a certain per cent of ionic character, that is, they all have some of the properties of the two extremes (pure ionic vs. pure covalent) that you studied in general chemistry. The per cent ionic character can be calculated (in theory) from the electronegativity. Part of the periodic table of the elements with some of the electronegativities.

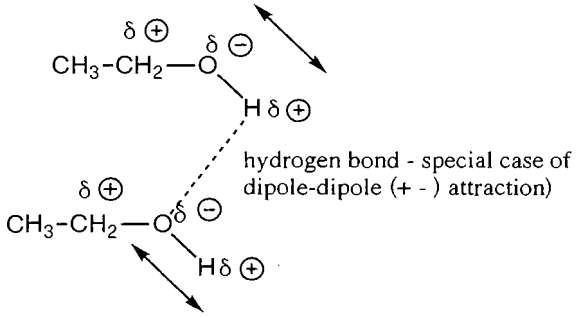
H 2.1									He
Li 1.0	Be 1.5				B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	Ne
Na 0.9	Mg 1.2					Si 1.8	P 2.1	S 2.5	Cl 3.0	Ar
K 0.8	Ca 1.0								Br 2.8	

STEP 2. **How do you use the electronegativity** ? We are really only interested in a semi-quantitative use. Looking at the table above and consider NaCl, a compound that you expect to be almost completely ionic. We can calculate the difference in electronegativity (ΔEN) between sodium and chlorine = 3.5 - 0.9 = 2.6. This gives you a place to stand: 2.6 means almost completely ionic. At the other extreme is a binary molecule like Cl_2 where, obviously, the difference is 0 and this is completely covalent. The ΔEN for C-H bond is then 0.4 and for an O-H bond it is 1.4. *The general rule is that any bond with a ΔEN of more than one is somewhat polar.* This is consistent with the idea that hydrocarbons are non-polar and alcohols are polar. The precise number for the O-H bond is about 35 % ionic character.

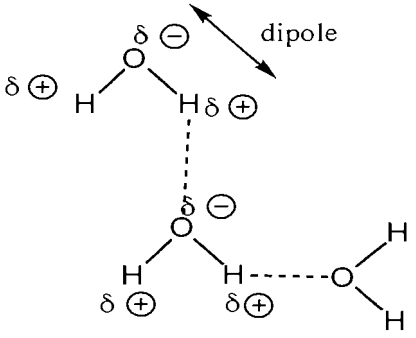
STEP 3. **Summary**: polar bonds are those that contain electronegative atoms: O-H, N-H, C-O and C-N. Non-polar bonds occur between atoms of similar electronegativity as in C-H. Polar bonds are indicated by using the small Greek delta, δ, to indicate a partial charge as in the following structure for ethanol:



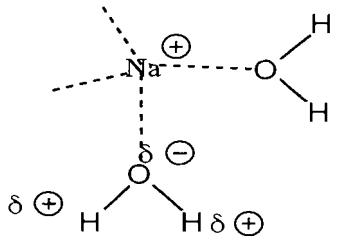
STEP 4. Molecules containing polar bonds (dipoles) can form associations due to dipole-dipole attractions. These are electrostatic (plus-minus attractions) as shown below:



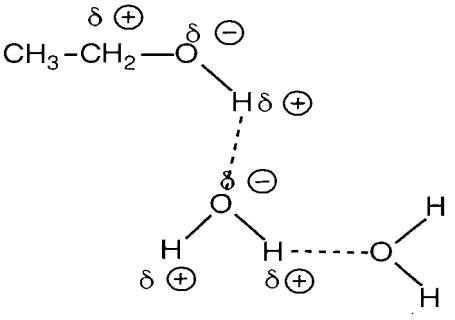
STEP 5. The **special dipole-dipole** interaction known as **hydrogen bond** is the attraction between a hydrogen bound to an electronegative atom and an electronegative atom on a different compound. This is the type of dipole-dipole interaction shown above. The unusual properties of water (high boiling point, for example) are due to hydrogen bonds between the **hydrogens on one water molecule** and **oxygens on another water molecule** causing extensive intermolecular associations.



hydrogen bonding in water.



solvation of ions

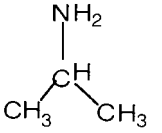


solvation of polar compound

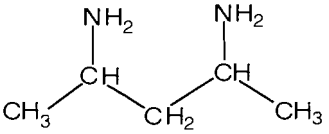
STEP 6. **Charged or polar substances are soluble in water**. Sodium ions, for example, are solubilized by formation of ion-dipole interactions with water. Polar substances, such as ethanol, form hydrogen bonds with the solvent. Non-polar substances such as the saturated hydrocarbons cannot form dipole-dipole interactions and so are insoluble in water. The low molecular alcohols are soluble due to hydrogen bonding with participation by the alcohol OH group. Generally, the fraction of the molecule that is hydrocarbon will determine whether or not a compound is soluble. Of the simple alcohols, propanol is completely soluble. Butanol is poorly soluble and pentanol is not soluble at all. Of the biologically important compounds, **glycerol is very soluble in water because of all the OH groups**.

STEP 7. **Compounds with other electronegative atoms: amines**. **The amines,** which could be thought of as the **nitrogen analog of alcohols,** are also polar. Of course amines are bases so, at pH 7, they will be protonated and water soluble as ionic species. Even as free bases, however, they are capable of hydrogen bonding because of their polarity.

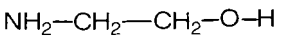
STEP 8. The nomenclature for amines can be seen in the following examples (For simple compounds there are two acceptable IUPAC methods of nomenclature:



2-amino propane
-or- 2-propanamine.



2, 4-diaminopentane

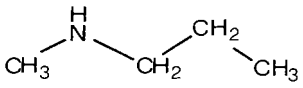


Aminoethanol
(common name:
ethanolamine)

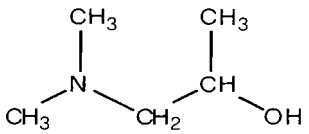
Q1. Using these examples as models, **write structures for**

a. 2-butanamine **b.** 3, 4-dihydroxy 1-hexanamine **c.** 1, 3-diaminopropane.

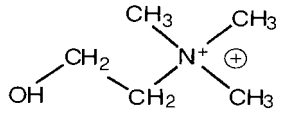
STEP 9. Secondary and tertiary amines and quaternary ammonium ions. Recall that amines can also be substituted on the nitrogen atom. Secondary and tertiary amines are named as if derived from the primary amine. The substituent is indicated as N-methyl-, N, N-dimethyl-, or N, N, N-trimethyl- (ammonium), for example. Most important for biochemistry is the compound **choline**: N, N, N-trimethyl ethanol ammonium ion. (In general, you would have to indicate the alcohol as "hydroxy"). You should learn the structures and IUPAC name of choline and the primary amine from which it is derived **ethanolamine**.



N-methylpropanamine



N, N-dimethyl 2-hydroxypropanamine

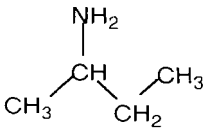


N, N, N-trimethyl ethanolammonium (choline)

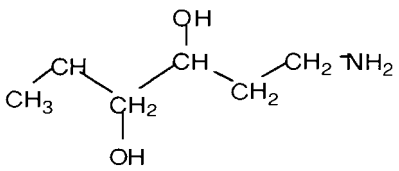
SUMMARY:

1. Electronegativity is the tendency of an atom in a covalent bond to attract electrons from the bond. The electronegative atoms that are important in biochemistry are oxygen and nitrogen.
2. Polar bonds include atoms of different electronegtivies: O-H, N-H, C-O and C-N.
3. Non-polar bonds occur between atoms of similar electronegativity as in C-H.
4. Molecules containing polar bonds (dipoles) can form associations due to dipole-dipole attractions.
5. The special dipole-dipole interaction known as hydrogen bonds is the attraction between a hydrogen on one electronegative atom for an electronegative atom on a different compound.
6. The unusual properties of water are due to hydrogen bonds between the hydrogens on one water molecule and oxygens on another water molecule.
7. Charged or polar substances ares soluble in water. Non-polar substances such as the saturated hydrocarbons are not. The low molecular alcohols are soluble. For higher alcohols, the fraction of the molecule that is hydrocarbon will determine whether or not it is soluble. In practice, methanol, ethanol and propanol are water soluble, whereas butanol is only very slightly water soluble.

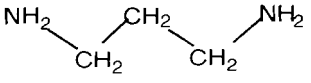
Answers to **Q1**.



2-butanamine.



3, 4-dihydroxy 1-hexanamine



1, 3-diaminopropane

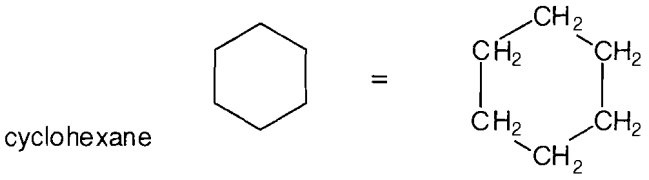
CHAPTER 3. MORE HYDROCARBON BACKBONES.

Cyclic hydrocarbons. Double bond compounds. Aromatic rings.

Where we are now. Organic molecules consist of two parts:

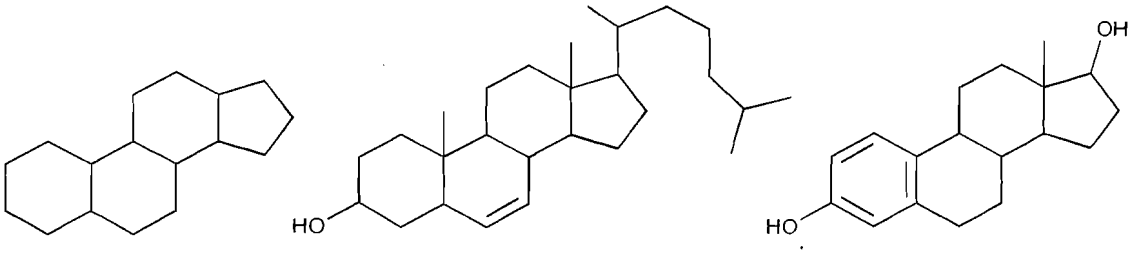
1) the functional group which is the chemically reactive part -- so far we've only looked at alcohols and amines.
2) the hydrocarbon backbone which gives the particular identity or geometrical shape to the molecule but which is chemically inert. The functional group usually contains electronegative atoms, oxygen, nitrogen which contribute not only chemical reactivity but also water solubility. Because of the low polarity of the C-H bond, the hydrocarbon backbone generally contributes chemical inertness and water insolubility.

STEP 1. The next step: Cyclic hydrocarbons. The ability of carbon to form chains is what accounts for the multitude of organic compounds. An obvious extension of the group of hydrocarbon backbones is to allow the chain of carbon atoms to fold back on itself to form the cyclic hydrocarbons (see Q6. in Chapter 1). With cyclic hydrocarbons, the prefix "cyclo-" is used and, if the ring that is formed is small, only the geometry of the carbon atoms is shown. For example, the cyclic hydrocarbon of six carbons is called cyclohexane:



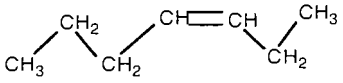
STEP 2. Fused rings. The cholestane structure. Two cyclic hydrocarbons can come together. You may remember structures as complicated as norbornane which had multiple fused rings. There are a few fused ring structures that appear in biochemistry and some of the stranger ones appear in certain drugs. Conceptually, these are not really different from the simple single cyclic hydrocarbons and will be typically hydrocarbon-like in properties: insoluble and chemically unreactive. The most important in biochemistry is probably the cholestane nucleus which is four fused rings. As the name indicates it is the building block of cholesterol as well as a large group of compounds known as steroids which include many hormones, one of which, estradiol, is shown below.

You would not, of course, memorize these structures but you should be able to identify features of their structure -- largely hydrocarbon but cholesterol and estradiol are alcohols. They have one other feature, double bonds, which is the next topic you have to bring back from organic chemistry.

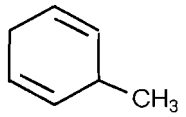


Cholestane Cholesterol Estradiol (estrogen)

STEP 3. The double bond is both a new kind of backbone structure and a new functional group. Simple compounds with a double bond are called alkenes or olefins and the nomenclature is a simple variation of the saturated compounds: the compound is named according to the usual procedure for alkanes, but the suffix is changed to "ene." The double bond is numbered so that it has the lowest possible number. Thus, 1-butene, not 2-butene, if the double bond is between carbons 1 and 2. From the examples below, you should be able to get a good feeling for the rules. Notice that if there is more than one double bond, the term "diene, triene, etc. is used.



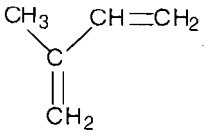
3-heptene



3-methyl 1, 4-cyclohexadiene

Q1. The structure shown below is one of the major building blocks of biochemistry. (It is, for example, the structure from which cholesterol and the steroid hormones is built. The common name is **isoprene**. The correct IUPAC name would be:

(A) 1-methyl - 2, 4-butadiene
(B) 2-methyl - 2, 4-butadiene
(C) 2-methyl - 1, 3-butadiene
(D) 3-methyl - 1, 3-butadiene



STEP 4. Unsaturated compounds with a functional group. The usual rules apply. The longest chain in the backbone is found, the functional group, alcohol for example, gets precedence (the lowest number), and the double bond is indicated with the lowest possible number that is left. Sometimes its not easy to make a reasonably sounding name with all these rules but precision is more important than euphony. Most compounds in biochemistry with awkward nomenclature also have common names.

Q2. A derivative of the structure shown above is one of the actual building blocks in cholesterol synthesis. Its common name is isopentenol. The correct IUPAC name would be 3-methyl-3-butene-1-ol. Draw the structure:

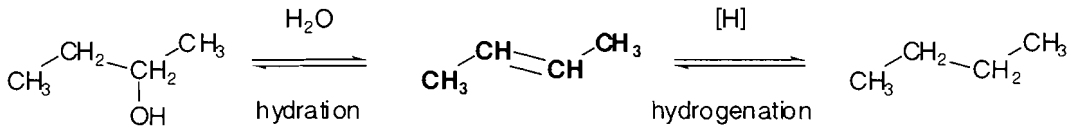
You would, of course, always call this isopentenol (pronounced iso-pen-teen-ol) but by asking you to draw the structure from the IUPAC name, the question forces you to recognized the double bond and the alcohol group.

STEP 5. Other double bond compounds in biochemistry. If you say "unsaturated" most people will think of "fats." The double bonds in unsaturated fatty acids are of great biological importance. Also, the double bond -- unlike the carbon-carbon single bond --- is chemically reactive. Thus if a double bond can be created in a compound, this will allow further chemical reactions. Frequently the detoxification of foreign material or drugs involves introducing unsaturation followed by further chemical reaction, addition of water, e.g., leading to solubility in water and ultimately excretion.

STEP 6. **Reactions of the double bonds.** The electrons in the second bond of a double bond are more reactive than those in the first bond. The presence of a carbon-carbon double bond in an organic compound means we have a new kind of alkyl (more precisely alkenyl) group but there is also a new reactive group. There are several major reactions,and we will study these as we come to them in metabolism but at this point you should know the following two types of reactions. The **general reaction is addition across the double bond**. The important cases are:

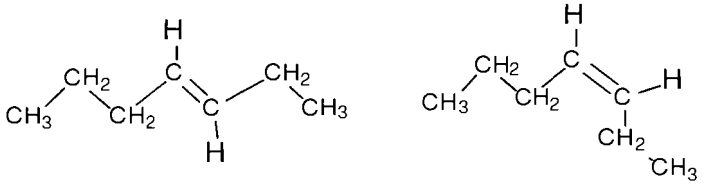
1. **Hydrogenation and dehydrogenation.** This was probably the simplest reaction you ever studied but, of course, the catalytic hydrogenation with molecular hydrogen and metal catalyst that you learned in organic chemistry will not be possible for living systems. We will find specific hydrogen donors. The product, of course, is the corresponding saturated compound.

2. **Hydration of the double bond.** Hydrogenation was the simplest but hydration is also extremely common in biochemistry. The product is an alcohol.



2-butanol *2*-butene butane

STEP 7. Isomers. There is no free rotation about the double bond as there is about the single bond. This means there is the potential for isomerization around the bond. For a hydrocarbon chain, the compound in which the chain follows on the same side of the double bond is referred to as *cis*- and if the path is across the double bond, the compound is *trans*.

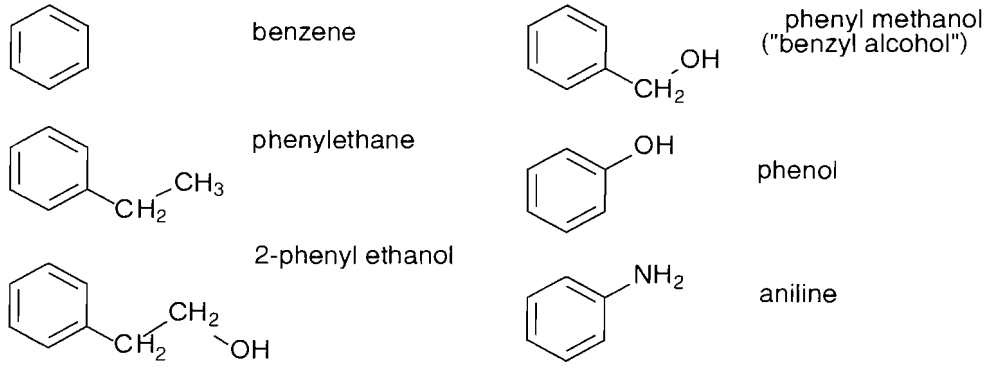


trans-3-heptene *cis*-3-heptene

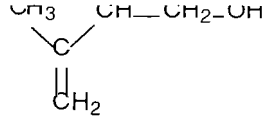
An important feature of these isomers is that the *trans* isomer follows roughly the zig-zag nature of the saturated compound whereas the *cis* configuration causes a bend in the molecule. Looking ahead, we will see that naturally occurring fatty acids are all *cis* and the significance of this is that when incorporated (as lipid) in a cell membrane, it imparts structure and will affect the fluidity of the membrane and thereby the responsiveness of the proteins imbedded in that membrane.

STEP 8. Aromatic compounds. It turns out that most of the special reactions of benzene and other aromatic compounds are not of great importance for most of what we do in biochemistry, but compounds containing these groups are extremely common. At this point, it is only important that you recognize them and keep the confusing and illogical nomenclature straight.

1. Benzene is the hydrocarbon molecule by itself.
2. When the benzene ring is a substituent on another molecule, the name is phenyl.
3. If the benzene ring is attached to a methyl group which is a substituent, this is, as expected, phenyl-methyl. However, the old name for this substituent is benzyl. Don't be confused if you see it -- there is a **big** difference between benzyl and phenyl. You should always use phenylmethyl but you should recognize the term benzyl.



ANSWERS: Q1. (c) 2-methyl - 1, 3-butadiene. The lowest possible numbers are given to the double bonds.

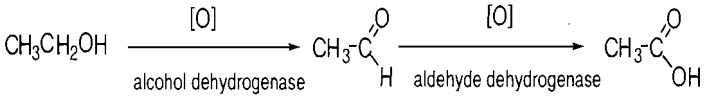


Q2. isopentenol (3-methyl-3-butene-1-ol).

CHAPTER 4.
THE BIG FOUR: ALCOHOLS, AMINES, CARBONYLS AND CARBOXYLIC ACIDS.

The good news: only a few functional groups, only a few reactions.

Where we're going: the name of the game is generalization:. When you ingest alcohol, the liver converts it to acetaldehyde and then to acetic acid. These are the first steps in a larger process which ultimately converts the carbons of ethanol to CO_2. The reactions are of obvious biological importance but, in addition, they serve as a main theme in metabolism. We will encounter a number of sequences where alcohols are oxidized to carbonyl compounds, or carbonyl compounds are oxidized to acids, or some other variation. In other words, the trick is to have model reactions and generalize from them. Our approach is to consider that the first steps of alcohol metabolism shown below will serve as an important model.

(1) 

The three functional groups in these reactions -- alcohols, carbonyl compounds, and carboxylic acids -- are the most common groups in biochemistry. In combination with the amines, they constitute the four most important structures in biochemistry. Many compounds are either a combination of these groups (amino acids are compounds with an amine group and an acid group), or are derived from them (acids react with amines to form amides).

Is this all there is ? Almost. Reactions of the big four cover most of biochemistry. The double bonds in unsaturated compounds are also important -- particularly in their hydration to make alcohols. and there are two groups that are peculiar to biochemistry -- that you don't study in laboratory organic: thiols (which are the sulfur analog of alcohols) and phosphoric acids (which are analogous to carboxylic acids. If you look at the **Summary Sheet of the Functional Groups**, you can see that almost all of biochemistry is made from only six organic functional groups plus phosphoric acids (shown in yellow). If you get control of these seven groups, then, you can pretty much figure out everything else. Again, the name of the game is generalization. As we go through the course and learn new reactions, you can come back and look at this chart and see where the new reaction fits in. In this way, you won't feel that new material is totally new but, rather, variations on what you already know.

More good news. The great majority of biochemical reactions fall into only three big classes:

1. Oxidation-reduction reactions.
2. Acyl (carboxylic acid derivative) and phosphoryl transfers.
3. Nucleophilic addition to carbonyls or the reverse.

Reactions (1) are obviously oxidations and, in this sense, ingested alcohol can be burned as a fuel and is in some way, a simple model for a food. (Of course, at some point, ingested alcohol becomes a drug).

The plan: we will go through the big four functional groups to get control of these structures. Then, we'll go back to alcohol metabolism and 1) develop the idea of oxidation-reduction reactions and 2) see where it fits in to metabolism, and what some of the biomedical implications of this reaction are.

Recommended technique: again, emphasize the IUPAC system of nomenclature. Even though many biochemical compounds have common names which have to be learned, this approach stresses the logical approach to organic chemistry -- figuring out names of compounds as a puzzle rather than memorizing isolated terms. I f you can name the compound accurately, you know what the functional groups are and that's where the action is.

STEP 1. THE BIG FOUR: TWO WE ALREADY KNOW. The four **most** important functional groups are the alcohols, the amines, the carbonyl groups (aldehydes and ketones) and the carboxylic acids. The four groups are distinguished by how many bonds to the electronegative atom (oxygen or nitrogen) there are in the functional group.

Alcohols and amines. Chapters 1 and 2 discussed the properties of alcohols and amines. The general formulas: R-OH and R-NH_2 (and R_2-NH and R_3-N). We discussed their physical properties: they formed hydrogen bonds and, depending on the relative amounts of hydrocarbon and oxygen or nitrogen, we could guess their water solubility. To review this,

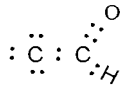
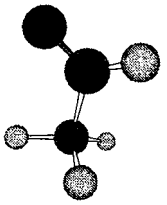
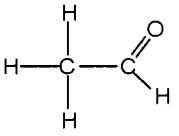
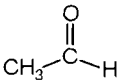
***Q1. Write the structures for 1-propanol and the structure for 1-aminopropane.**

STEP 2. THE CARBONYL FUNCTIONAL GROUP.

The combination of a carbon with two bonds to oxygen is referred to as a carbonyl group. The fact that there are more bonds to oxygen means that a carbonyl carbon is **oxidized** compared to the alcohols. The carbon with the oxygen is called the carbonyl carbon. An **aldehyde** has one R- group, that is, one bond to carbon and one bond to hydrogen. This is shown, in several representations for the 2-carbon aldehyde, **acetaldehyde**.

***Q2. Write representations for the ketone, acetone.**

ACETALDEHYDE

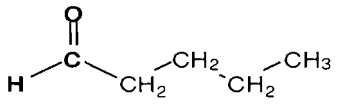
Lewis Structure	3-D Configuration	Structural Formula	Short-hand
			 -or- CH_3CHO

ACETONE

Lewis Structure	3-D Configuration	Structural Formula	Short-hand

STEP 3. Nomenclature of the aldehydes and ketones. We'll do this by examples. First you should know that the one- and two-carbon aldehydes would, theoretically, be called methanal and ethanal but these names are almost never used. The trivial names, formaldehyde and acetaldehyde are the ones that are used. As we go along, we'll also do a few problems that are of the type that might bear on biochemistry. First review the different representations and make sure that you can recognize the carbonyl group: you obviously can't name the compound unless you're sure of what type it is.

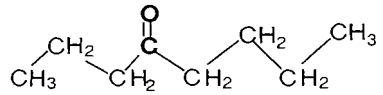
Q3. Give a good IUPAC name for the following compound:



How to do it:

1. First, recognize that the compound is an aldehyde (has the general formula RCHO) so when you are finished it will have the suffix "-al."
2. Count the number of carbons (including the carbonyl group): there are five.
3. Take the hydrocarbon name "pentane" and drop the "-e" and add "-al." The compound is called **pentanal**. Notice that no numbers are needed since an aldehyde always has the functional group on carbon 1.

Q4. Give a good IUPAC name for the following compound:



How to do it:

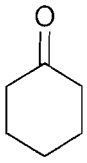
1. First, recognize that the compound is a ketone, has the general formula R(C=O)R, so when you are finished it will have to have the suffix "-one."
2. Count the number of carbons (including the carbonyl group): there are eight.
3. Take the hydrocarbon name "octane" and drop the "-e" and add "-one" The compound is an **octanone**. You now have to number the carbons to tell where the carbonyl groups is. If you number from the left you get 4, if you number from the right you get 5. Always pick the lowest number, so the compound is **4-octanone**.

Of course, for the cyclic ketones, you don't need a number if there is only one functional group. For example,

Q5. Write the structure of cyclohexanone:

***Q6**. Write the structure of 3-methyl cyclohexanone.

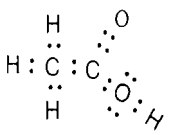
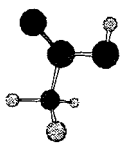
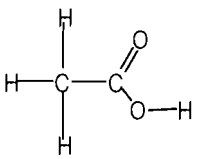
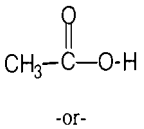
ANS:



STEP 4. CARBOXYLIC ACIDS.

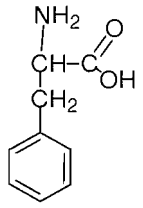
The obvious property of carboxylic acids is that they dissociate to form hydrogen ions and the salt form of the acid (carboxyl**ate**). You may have to review acid dissociation, but for the moment, we only need to know the bottom line. At pH 7.0, which is normal for most biological systems (blood pH is about 7.4), carboxylic acids are far from their pKa (the point at which they are half dissociated). For this reason, in biochemistry we frequently **refer to acids by the salt name**. So, the terms **"acetate" and "acetic acid" mean the same thing**: acetic acid in a solution where it is completely ionized.

ACETIC ACID

Lewis Structure	3-D Configuration	Structural Formula	Short-hand
			 -or- CH_3COOH

STEP 5. Nomenclature of the acids. The one and two carbon acids are called formic and acetic. The three and four carbon acids are sometimes called propionic and butyric, respectively, but the IUPAC systematic name is generally preferred. In the IUPAC system, the **carboxylic acid** carbon is **carbon 1** and everything is numbered accordingly. To determine the name of the parent compound, the "-e" is dropped from the hydrocarbon name and "oic acid" is added. For example:

Q7. Give a good IUPAC name for the following compound:



How to do it:

1. There are three carbons in the longest chain, the first of which is an acid. The compound is some kind of **propan**oic acid.
2. Since the acid is carbon 1, the amino group is on carbon 2 and the phenyl group is on carbon 3, so:
3. The compound is **2-amino 3-phenyl propanoic acid**. (The common name is phenylalanine).

NOTE: The priority of functional groups is carboxylic acids > ketones > hydroxyls > amines > hydrocarbons.

STEP 6. Biomolecules: combinations of the functional groups studied so far.

In Q7. We worked over the nomenclature of a carboxylic acid. The particular compound, however, contained two functional groups, an amino group and a carboxyl group. Not surprisingly, such compounds are referred to as **amino acids** and you probably already now that it is the monomer of which proteins are composed. Many compounds that are important in biochemistry have more than one functional group.

More: again, to psyche out the functional groups, it is recommended that you give the compound an IUPAC name even if it is usually called by a common name. The following is a catalog of some of the small molecules that are important themselves or are the building blocks of biopolymers.

1. **Amino acids**. The simplest is glycine (amino acetic acid); the next simplest is alanine (IUPAC name: **2-amino propanoic acid**). Many others can be looked at as if they were derivatives of alanine (Phenylalanine is an obvious example.

   ***Q8**. Write the structure of the amino acid **alanine.** Write on the left and leave room for the next two structures.

2. **Hydroxy-carboxylic acid**. An important example: lactic acid (**2-hydroxy propanoic acid**). This is the end product of energy metabolism for bacteria and human cells under anaerobic conditions (no oxygen).

   ***Q9. Write the structure of lactic acid next to the structure above.**

3. **Keto-carboxylic acid**. Pyruvic acid (2-oxo-propanoic acid) will turn out to be a key player. From the structure (and the IUPAC name), you might guess that the compound might be related to lactic acid and alanine. Understanding this relation will be an important part of understanding metabolism.

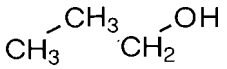
   ***Q10. Write the structure of pyruvic acid next to the structures above.**

4. **Hydroxy aldehydes and ketones = sugars.** The simplest sugar is **glyceraldehyde**. The systematic name is: **dihydroxy propanal.**

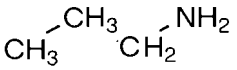
***Q11. Write the structure of glyceraldehyde:**

ANSWERS:

*Q1



1-propanol

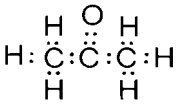


1-aminopropane

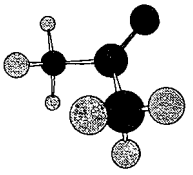
*Q2

ACETONE

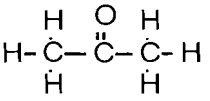
Lewis Structure



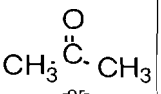
3-D Configuration



Structural Formula



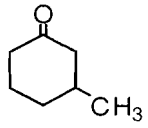
Short-hand



-or-

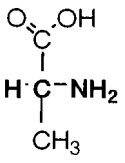
$(CH_3)_2C=O$

*Q6

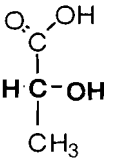


3-methyl cyclohexanone

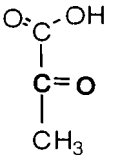
*Q8 - *Q10



alanine
(2-amino propanoic acid)

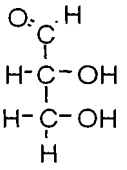


lactic acid
(2-hydroxy propanoic acid)



pyruvic acid
(2-oxo propanoic acid)

*Q11



glyceraldehyde
(dihydroxy propanal)

ω

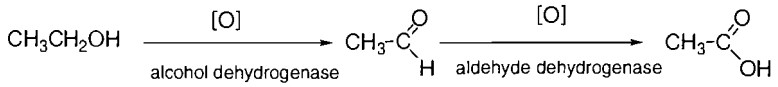
end of chapter

CHAPTER 5.
ALCOHOL METABOLISM, OXIDATION-REDUCTION AND A QUICK STEP INTO BIOCHEMISTRY.

Objectives. In this section, we go back to alcohol metabolism. The goal is:

1. To develop the alcohol dehydrogenase and aldehyde dehydrogenase reactions as a model. Specifically, we use this reaction
   1. To develop the idea of oxidation-reduction reactions in biochemistry.
   2. To demonstrate the generalizing power of functional groups with the case of methanol poisoning
2. To expand the model to include reactions of compounds with more than one functional group, lactate and pyruvate.
3. To preview some aspects of metabolism using these reactions

STEP 1. Alcohol metabolism: relations to the big four. When ethanol is ingested, the liver converts it to acetaldehyde and then to acetic acid. This sequence, alcohol ⟶ carbonyl ⟶ carboxylic acid, are the first steps in a larger process which ultimately converts the carbons of ethanol to CO_2. This is an oxidation and, in this sense, ingested alcohol can be burned as a fuel and energy for life processes obtained in this way.



STEP 2. Oxidation-reduction reactions in biochemistry. The following is a quick review of the definitions of oxidation-reduction for organic systems. We define the oxidation state of a carbon atom as the **number of bonds to oxygen minus** the **number of bonds to hydrogen**. In other words:

a. Any bond to oxygen contributes +1 to the oxidation state of the atom.
b. Any bond to hydrogen contributes **-1** to the oxidation state of the atom.
c. Carbon-carbon bonds contributes **0** to the oxidation state of the atom.
d. Oxidation is an increase in the number of bonds to O or a loss of bonds to H.
e. Reduction is associated with formation of new bonds to H or a loss of bonds to O.
f. Oxidizing agents (oxidants) add O or remove H.
g. Reducing agents (reductants) add H or remove O.

Bottom line: The overall reactions shown above are a step-wise oxidation of ethanol ⟶ acetaldehyde ⟶ acetic acid.

STEP 3. Enzymes and coenzymes.

1. In laboratory organic we had specific oxidizing agents like dichromate and you could make the reaction go forward by using a lot of the reagent and high heat. Obviously, such reactive reagents or high heat can't be used in living cells. In biochemistry, acceleration of the reaction is achieved by enzymes. The oxidizing power is supplied by compounds known as coenzymes which take part in many redox reactions and have the feature that they are less drastic than the ones you might use in an organic lab. The most common enzymes that catalyze oxidation-reduction reactions have the general name dehydrogenase. It is important to understand that an enzyme **catalyzes a reaction in both directions** since it cannot affect the final outcome of the reaction, only the speed with which it is attained. The name usually describes the reaction in one direction and dehydrogenase are named for the *oxidation* (removal of hydrogen) of the substrate.

2. The most common oxidation-reduction coenzyme and the one that is used in the metabolism of ethanol is **NAD^+**. (Later, we'll look at the structure but for the moment we'll just use the abbreviation). NAD^+ is the oxidized form (easy to remember since + is associated with oxidation); when it is reduced, the coenzyme is written **NADH** (easy to remember since adding a hydrogen is a reduction). So, in the metabolism of ethanol, the oxidizing agent is NAD^+, and it gets reduced to NADH (the extra hydrogen from ethanol shows up as H^+ which might be added to the equation if we were writing a balanced reaction. We just want the main idea so, for the moment, you can ignore the H^+.

Write the whole reaction for a) **oxidation of ethanol by NAD+**, and b) **oxidation of acetaldehyde by NAD**

a. _____ + NAD+ ⟶ _____ + NADH

b. _____ + NAD+ ⟶ _____ + NADH

STEP 4. Biochemical effects of alcohol.

1. As we study metabolism you will see that the fact that alcohol can be converted to acetic acid -- you may already know about acetyl CoA and the Krebs cycle. This means that alcoholt can be used to produce energy and, in that sense, it is a food -- at least at low levels. At higher levels, however, some of the consequences of alcohol metabolism present problems (aside from intoxication). The first product, acetaldehyde is quite toxic because, like all aldehydes, it reacts with amines --- in the biological case, amino groups of proteins.

2. If intake is high, as in the case of alcoholics, the normal metabolic processes can't oxidize the acetaldehyde fast enough and the demand for oxidizing agents becomes a problem. The liver is the major site of oxidations and this tissue most obviously reflects the effect of excessive alcohol and its oxidation products. In order of severity, the effects are termed fatty liver, hepatitis and cirrhosis. Looking ahead to the big picture, in order for oxidative metabolism to continue it must be possible to re-generate NAD+. Continued input of an NADH-generating system puts a load on this process. Consider the following exam-type question:

Q 1. The negative effects of excessive alcohol ingestion are usually exacerbated in alcoholics because they tend to eat very little else and so alcohol is the primary source of food. This leads to several kinds of imbalance. One of the metabolic consequences of alcohol abuse is that the **level of NADH** in the liver:

(A) is drastically increased.
(B) is drastically decreased.
(C) is maintained within the normal range.

ANS. (A) You can figure out the answer by remembering that metabolism of alcohol takes place by **oxidation**. The oxidizing agent is NAD+and the product is NADH (has the hydrogen). Although, the NADH is normally re-cycled, at high alcohol levels, the NAD+ cannot be replenished because metabolism cannot keep up. There is therefore an excess of NADH. Looking ahead -- or if you are re-reading this section after studying carbohydrates -- the consequence is that gluconeogenesis (synthesis of glucose) is impaired and, since alcoholics frequently consume nothing else, the patient may become hypoglycemic. Also, we will see that one way in which NADH can be used to re-generate NAD+ is in the formation of lactic acid. In combination with high production of acetic acid this can lead to acidosis.

Summary: Ingested alcohol is converted to acetaldehyde by oxidation with NAD+, the enzyme is alcohol dehydrogenase. The acetaldehyde is then converted to acetic acid by another oxidation with NAD+ catalyzed by aldehyde dehydrogenase. The acetic acid can be processed by cells to produce energy but if alcohol consumption is too high there will be a decrease in NAD+ for further oxidative metabolism. From the chemical standpoint, **NAD-dependent dehydrogenases** have oxidized an alcohol to an aldehyde and the aldehyde to a carboxylic acid.

STEP 6. ENZYME IMPAIRMENT GENETIC OR PHARMACOLOGIC.

People afflicted with a genetic deficiency in aldehyde dehydrogenase cannot consume alcohol because of the severe reaction to the build up of acetaldehyde. This phenomenon is used in the design of the drug **disulfiram** (®antabuse) as negative reinforcement for behavioral control of alcoholism. Disulfiram is a covalent inhibitor of the aldehyde dehydrogenase.

Q 2. A genetic deficiency in aldehyde dehydrogenase would be expected to lead to unusually high levels of :

(A) ethanol.
(B) acetaldehyde.
(C) acetone.
(D) acetic acid.
(E) both ethanol and acetaldehyde.

ANS. (E) Agents that block a chemical pathway will lead to build-up of the compounds in the pathway preceding the block. On an actual exam, we would accept (B) since it is the immediate precursor, but answer (E) is probably better.

STEP 7. VARIATIONS ON A THEME: METHANOL POISONING.

1. The idea that we have stressed in the transition from organic to biochemistry is that if you know the reaction of a functional group then you know the reactions of any compound containing that functional group. So, in theory, *any* alcohol will be capable of being oxidized to the corresponding aldehyde and the aldehyde will be capable of being oxidized to the carboxylic acid. This is theoretical since enzymes, in general, have evolved to have high specificity but it turns out that alcohol dehydrogenase is an enzyme of relatively low specificity and methanol, the one carbon alcohol is, in fact, recognized by the (ethanol) alcohol dehydrogenase because of its structural similarity to the normal substrate, ethanol. The reaction follows the same pattern as the normal substrate and formaldehyde is formed. Similarly, formaldehyde can be converted to formic acid by aldehyde dehydrogenase, also an enzyme of low specificity. The toxic effect of methanol is due to these products, the formaldehyde reacts with proteins leading to, among other symptoms, blindness, and the formic acid is the usual cause of death in severe methanol poisoning. The effect is apparently local -- the eye has an alcohol dehydrogenase: formaldehyde poisoning does not usually lead to blindness. Generalizing from this mechanism you should be able to write the reactions.

Write the reaction for a) **oxidation of methanol by NAD+**, and b) **oxidation of formaldehyde by NAD+**.

a. _____ + _____ ⟶ _____ + _____

b. _____ + _____ ⟶ _____ + _____

2. **Competitive inhibition and clinical treatment of methanol poisoning.** From the discussion above, ethanol and ethanol are competing substrates for alcohol dehydrogenase. When they are both present, each compound is a **competitive inhibitor** of the other. You can take advantage of this competition effect clinically. If methanol poisoning is suspected you can administer ethanol while tests are being done. The methanol itself will then be excreted. Since it is not methanol but rather the products of the enzymatic reaction that are harmful this can be an effective treatment, although the preferred long term treatment is dialysis.

Q3. With respect to liver alcohol dehydrogenase, ingested methanol acts as:

(A) An irreversible covalent blocker.
(B) A competitive inhibitor.
(C) A non-competitive inhibitor.
(D) A negative allosteric effector.

STEP 8. PROBLEMS USING WHAT YOU JUST LEARNED FOR OTHER ASPECTS OF METABOLISM.

In these problems, you are asked to generalize the chemical reactions you learned with alcohol dehydrogenase to other metabolic systems you will study in the future. For the moment, only the chemistry is stressed with only a minimal indication of the metabolic setting. When you study these aspects of metabolism, you should come back to these questions and try to convince yourself that the new material is a variation on something you already learned. You will have to look up some structures in the text to do the problems. (This is part of the exercise).

PROB 1. The following oxidation-reduction reactions of three carbon compounds are a central part of metabolism. We will look at it first from a simplified view and in problem 2 extend it slightly to give you the actual biological form. The alcohol **glycerol** is a trihydroxy alcohol (propane triol). In metabolism, it can be oxidized to the corresponding aldehyde glyceraldehyde (call the carbon at the top carbon-1). The enzyme is an NAD-dependent dehydrogenase, exactly analogous to alcohol dehydrogenase, which recognizes carbon 1 of the substrate. The product is, an aldehyde, glyceraldehyde (see Chapter 4), which, in turn, can be oxidized to the carboxylic acid, glyceric acid. Write the structures of glyceraldehyde and glyceric acid. What would be the likely names of enzymes that would catalyze these reactions ?

$\longrightarrow$ $\longrightarrow$

glycerol glyceraldehyde glyceric acid

PROB 2. The problem above is slightly simplified. In metabolism, the actual compounds that are used are the phosphate esters of the hydroxyl group at position 3. The phosphate is not part of the chemical reaction which is fundamentally the same as the one above but the true reaction is: glycerol-3-phosphate -> glyceraldehyde-3-phosphate -> glyceric acid 3-phosphate. Write these reactions and give a revised (more accurate) name for the enzymes. (If you already know some metabolism or are re-reading this you will know that the second reaction is actually done in two steps in glycolysis. Why?).

$\longrightarrow$ $\longrightarrow$

glycerol-3-phosphate glyceraldehyde 3-phosphate 3-phosphoglyceric acid

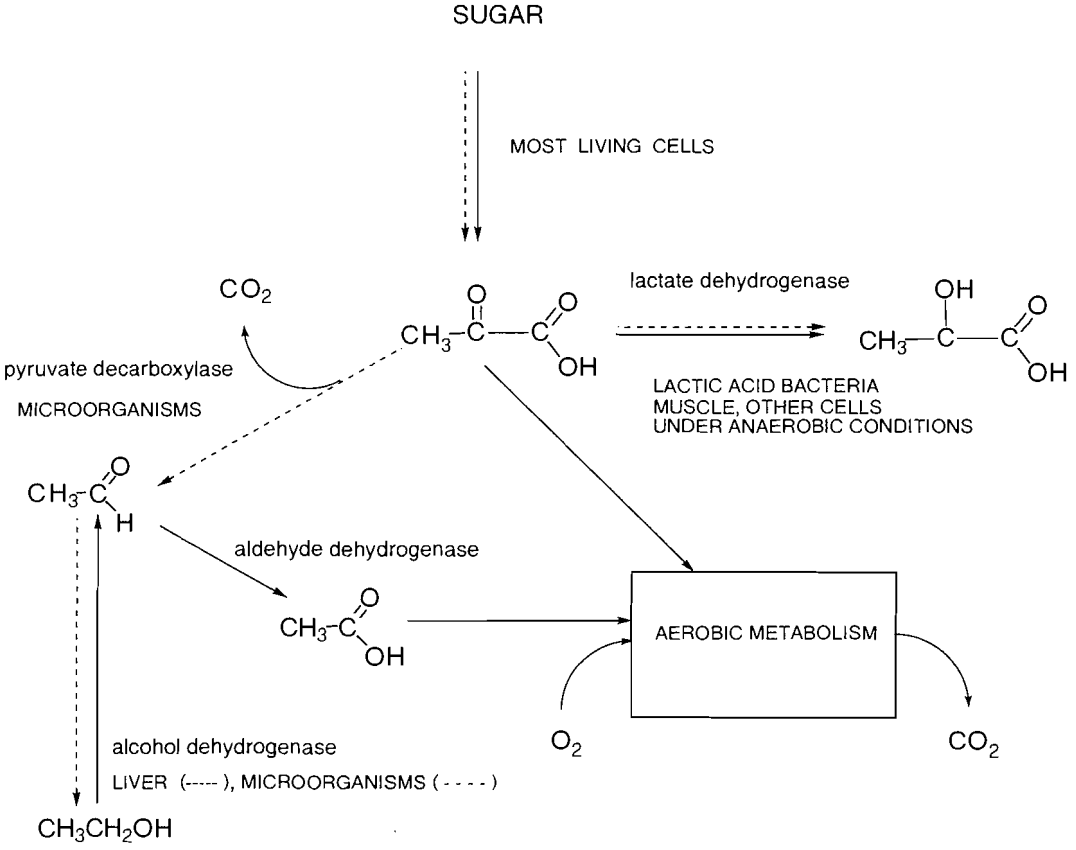
STEP 9. Variations on a theme -- lactic dehydrogenase reaction.

1. **Lactate.** In Chapter 4, we considered combinations of functional groups. Lactic acid, e.g. contains an alcohol and a carboxylic acid: IUPAC name 2-hydroxy propanoic acid. This compound is important because it is the end product of energy metabolism for bacteria and human cells under anaerobic conditions (no oxygen). Under extreme exercise, muscle cells carry out substantial anaerobic metabolism and the production of lactic acid is a controlling factor in muscle fatigue.

2. **Pyruvate.** Pyruvic acid (2-oxo-propanoic acid) is a key player in metabolism. It can be converted to lactic acid (in one step). It comes from sugar (in several steps). You can tell from the name where its importance lies: ("pyr" means fire as in pyromaniac) -and- "uvo" in italian or spanish means grape. (The word occurs in English in uvula, the (grape-like appendage at the back of the palate) So, pyruvate comes from "firing grapes" that is making wine, or fermentation.

3. **Lactic dehydrogenase reaction.** Now, looking back at our model reaction, the alcohol dehydrogenase reaction: we oxidized an alcohol (one bond to oxygen) to aldehyde (two bonds to oxygen). A fermenting organism uses a similar reaction to convert acetaldehyde to ethanol (this is where the alcohol comes from in the first place). In the liver, the acetaldehyde is carried away by further oxidation and other reactions so the alcohol keeps being used. In fermentation, glucose is continually supplied and the reaction keeps going forward until the organism has "polluted" its environment with alcohol. From an organic standpoint your expectation should be that the properties of lactic acid are just the properties of an alcohol and a carboxylic acid. In terms of the reactions we have studied so far, one that is important is that the hydroxy group can be oxidized to a ketone (and the ketone could be reduced back to the alcohol). The same kind of reaction for interconversion of ethanol and acetaldehyde is catalyzed by the enzyme lactic dehydrogenase except here the alcohol is on position two of the compound to be oxidized and the product is a ketone although it is still part of an acid.

STEP 10. **Grooving on pyruvate.** We are now in a position to tie a lot of individual molecules together. We will add one new piece of information. The carboxyl group of pyruvic acid can be converted to CO_2 (leaving acetaldehyde). So: living tissues convert **sugar,** or other substrates, to **pyruvate.** The fate of pyruvate then varies quite a bit in different tissues. Fermenting microorganisms, turn pyruvate into **acetaldehyde.** The enzyme is called, not surprisingly, **pyruvate decarboxylase.** Brewer's yeast and other alcoholic organisms now reduce the acetaldehyde to **ethanol.** This is the same kind of enzyme that exists in liver for the processing of ethanol. Some microorganisms (yoghurt-making organisms) and some tissues of the body, convert **pyruvate to lactate.** This is summarized in the following figure. **As an exercise, you should write in the names of the compounds in the figure.**



SUMMARY: **Alcohol dehydrogenase** catalyzes the oxidation of ethanol by NAD^+. Similar enzymes function in some organisms (yeast or other fermenting microorganisms) to **produce** alcohol from acetaldehyde. Regardless of the way the reaction goes in reality, the enzyme is named for the oxidation. In a second step, acetaldehyde is converted to acetic acid by **aldehyde dehydrogenase**-catalyzed oxidation. An analogous reaction catalyzed by lactate dehydrogenase reduces pyruvate to lactate.

SO FAR. The compounds that we've studied:

1. **Alcohols.** Key compounds: ethanol, methanol, glycerol, (lactic acid -OH group)..
2. **Aldehydes and ketones.** Key compounds: acetaldehyde, formaldehyde, (glyceraldehyde and pyruvic acid =O group).
3. **Carboxylic acids.** Key compound: acetic acid, formic acid, glyceric acid.

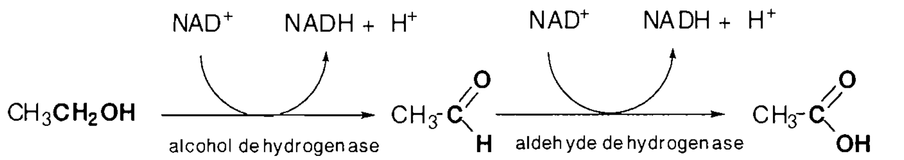
The combinations of functional groups

4. **Hydroxy carboxylic acids.** Key compound: lactic acid
5. **Keto carboxylic acids.** Key compound: pyruvic acid.
6. **Hydroxy aldehydes (sugars)**: glyceraldehyde.

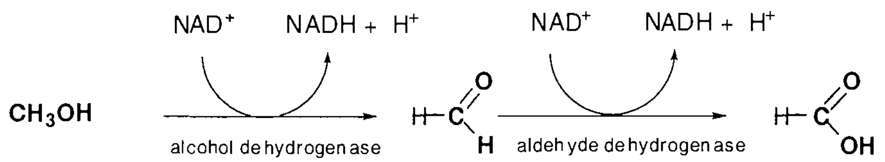
ANSWERS -

Q3. **(B)** The paragraph above the question points out that methanol and ethanol are, in effect, competitive inhibitors of each other. More precisely they are competitive substrates which would be another way to phrase the question.

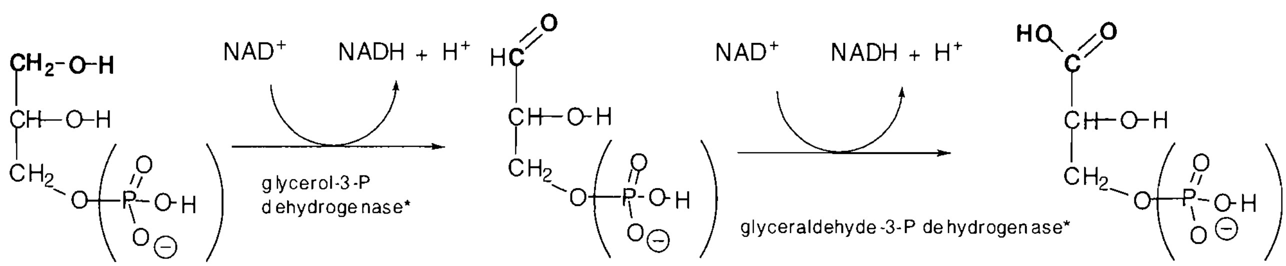
Fill in reactions and PROBS. 1. and 2:



ethanol acet**aldehyde** acetic **acid**



methan**ol** form**aldehyde** formic **acid**



glycer**ol** (-3-phosphate) glycer**aldehyde** (-3-phosphate) (3-phospho)-glyceric **acid**

*For heuristic purposes these reactions are shown as taking place in one step. In fact, in the first reaction glycerol-phosphate is oxidized to the ketone and then isomerized to glyceraldehyde-3-P dehydrogenase. The second reaction also takes place in two steps.

CHAPTER 6
BIOMOLECULES - INTRO AND THE EXAMPLE OF ESTERS

1. **Where are we now ?** We have reviewed the big four functional groups. We've looked at a number of compounds that contain more than one of these functional groups such as amino acids, lactic acid and pyruvic acid. Two major ideas that were to make biochemistry easier were proposed: 1) most biologically important compounds are one of the big four, thiols or phosphoric acid or some combination of these, and 2) there are only three major types of reactions: redox, acyl and phosphoryl transfer and nucleophilic addition reactions.

2. **Biomolecules**. The major classes of biomolecules are carbohydrates, fats, proteins and nucleic acids. The next few sections we will look at these compounds in the context of the major functional groups and the three main types of reaction.

3. **Acyl and Phosphoryl Derivatives**. Of the basic reactions, acyl and phosphoryl transfer are the easiest to understand because the product acyl derivative is obviously related to the reactants. In the general case, a carboxylic or phosphoric acid reacts with a compound RX and an OH group of the acid is replaced by X and water is produced. In the reverse reaction, hydrolysis, the OH of water is added to the acyl group and XH is regenerated. If RX is a ROH, that is, an alcohol then the product is an ester. If RX is RNH_2 (amine), then the product is an amide. A run-down of the common acyl derivatives is given at the end of this chapter, but it is instructive to take a step-by-step look at esters and see how using the generalizing power of functional groups leads us into several important bio-molecules.

4. **Step-by-step from esters to lipids and other esters.** As usual, the **name of the game is generalization**: an ester is an ester is an ester.

STEP 1. Recall the general reaction. An ester is made from a carboxylic acid and an alcohol. It is a separate functional group but it you should always remember where it came from. In ester formation (**esterification**), the OH group of the acid is replaced by the OR group of the alcohol. In the reverse reaction, **hydrolysis of an ester**, water replaces the OR group. The general reaction (leaving out catalysts and reaction conditions):

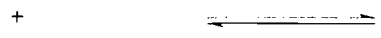
carboxylic acid alcohol ester

STEP 2. A simple example. The ester formed from ethanol and acetic acid is the simplest example. The name of the product shows one way to name an ester. In the systematic IUPAC system, an ester is called by the substituent name of the alcohol (ethyl) and the salt name of the acid (acetate): ethyl acetate.

acetic acid (carboxylic acid) ethanol (alcohol) ethyl acetate (ester)

STEP 3. Q1. Do one. Use the reaction above as a model to write the formation of methyl butanoate.

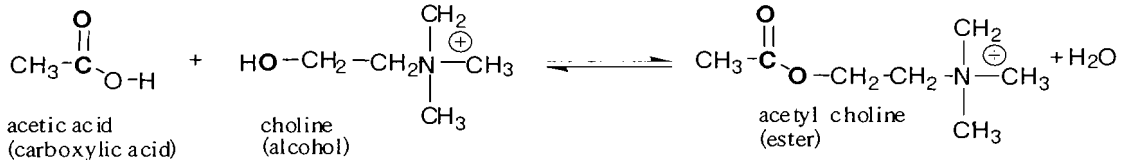
Q1.



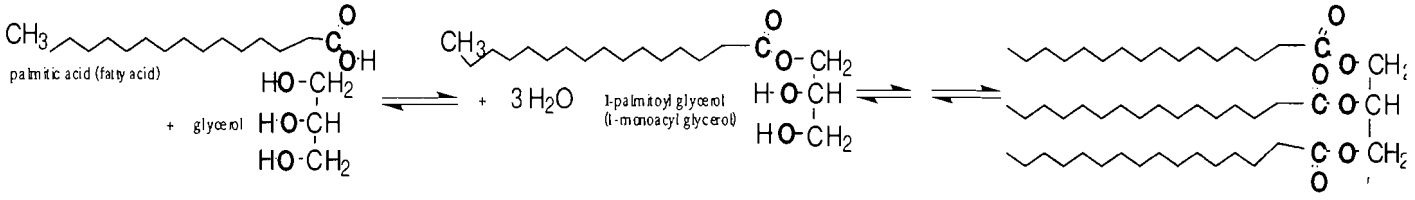
STEP 4. Variation: example from neurotransmission. A simple variation on Step 2 is an ester where the alcohol is **choline** (N, N, N-trimethylammonium *ethanol*). The acid is still acetic acid. Be sure you see that the examples in steps 2-4 are just variations of the basic scheme in step 1. The nomenclature here is different: the compound is named as an acyl derivative of the alcohol: **acetyl choline**. The general term acyl derivative means any compound in which the OH of a carboxylic acid is replaced by another group, analogous to the term alkyl for a derivative of a hydrocarbon. Acetyl is the specific acyl group. (Of course, acetyl choline could be given an IUPAC name):

Q2. what is the IUPAC name for acetyl choline ? _____

Acetyl choline is a neurotransmitter and termination of neuronal stimulation is brought about by hydrolysis. When you study this in detail you should see that the structure and reaction are a familiar ones.

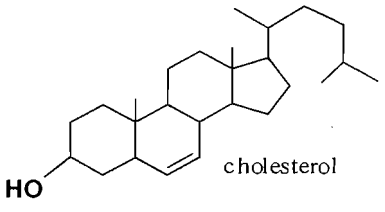


STEP 5. Variation: structure of fat. A long chain carboxylic acid (more than about 6 carbons) is called a fatty acid. There are many of importance in biochemistry but the "generic" fatty acid is palmitic acid (16 C). The chemical properties of the carboxylic acid group are, of course, the same as a simple acidS like acetic acid, and esters such as ethyl palmitoate (or, another name: palmitoyl ethanol) could be formed. Dietary and storage fats are esters of the alcohol glycerol. Glycerol (propane triol) can form three ester bonds with a fatty acid. The final product is triacyl glycerol (TAG; old name: triglyceride):



STEP 6. Variation: it doesn't matter how weird the alcohol is. The generalizing power of functional groups is substantial. At first sight, the alcohol cholesterol, shown below, seems extremely complicated but you now know how to deduce one of its properties. It's an alcohol and like all alcohols is, at least in theory, capable of forming an ester. In fact, when we study lipid metabolism, we will see that Cholesterol forms esters with fatty acids: (fatty) acyl cholesterols, or cholesteryl esters.

Q3. Draw the structure of the ester of cholesterol and a fatty acid, e.g. palmitic acid.



Q3.

Note on properties of esters: In general, esters are much less polar than the alcohols or the acids from which they are formed. Ethyl acetate, for example is not soluble in water. The obvious exception, on this page, is acetyl choline which is polar because of the tertiary ammonium ion. This is presumably why this particular ester evolved as a neurotransmitter. Now cholesterol is itself very non-polar -- we usually consider the relative amounts of polar groups (-OH) and hydrocarbon (the fused ring backbone) to decide how polar a compound is. For storage in vesicles or transport in the blood, however, where you want no leaking into an aqueous medium, cholesterol is packaged as cholesterol esters which are even more non-polar.

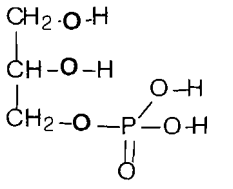
STEP 7. Kick it up a notch: phosphate esters. The formation of esters from carboxylic acids by substitution of -OR for -OH, can be generalized to other acids, in particular, phosphoric acid. An example that will be of great biological importance is the phosphate ester of glycerol, the triol in STEP 5. Now, whereas glycerol is symmetrical, the ester is called glycerol-**3**-phosphate. (I know. It should be glycerol-1-phosphate but once the phosphate is attached this is an optically active compound and has a "stereospecific numbering" (you sometimes see the term *sn*). The details are really not interesting : just call it glycerol-3-phosphate).

STEP 8. The big payoff: test yourself with a phospholipid. You can now test whether you're on to the generalizing ability of organic structure. We will write a seemingly difficult compound but one that is made of familiar components with all the bonds, ester bonds. We'll start the structure with glycerol-3-phosphate. Now at the 1 and 2 positions, we will make ester bonds with fatty acids, analogous to the way we put together diacylglycerol. (As it turns out, *in vivo*, when fat is made, you start with glycerol-3-phosphate). The structure so far is 1, 2-diacyl glycerol-3-phosphate. This compound has the common name **phosphatidic acid**.

Q4. Draw the structure of phosphatidic acid.

Now because phosphoric acid is a polyprotic acid, phosphatidic acid can still form another phosphoester bond with another alcohol. In living systems there are many phosphatidyl esters. The most common is phosphatidyl choline (common name: lecithin) in which, as you would guess choline forms an ester with the phosphoric acid part of phosphatidic acid.

Q5. Draw the structure of phosphatidyl choline (refer to structures above0.



glycerol-3-phosphate

Q4.

Q5.

5. **Where do we go from here.** Once you've successfully answered 5., you know the game. Phosphatidyl choline is an extremely complicated molecule but by assembling it from the separate parts, you can see where it came from and what it's characteristics are (has a hydrophobic part, two fatty acids; has a charged part, the choline and the phosphate). This is the approach we will take with other biomolecules, the carbohydrates, proteins and nucleic acids. These molecules are polymers and to understand their structure, you need to be familiar with the structure of the components, the monomers. The next few chapters, provide this background.

CHAPTER 7. Summary of the Structure of Simple Sugars. In chapter 4, we saw the structure of the simplest sugar, glyceraldehyde. The simple sugars, are, in fact all polyhydroxy aldehydes and ketones. Because there are several hydroxyl groups, the nomenclature and the stereochemistry is quite complicated but, it turns out, most of the problems are in the names. This summary is meant to give you a quick guide to the terminology. This one page chapter summarizes the structures of the simple sugars.

CHAPTER 8. Nucleophilic Addition Reactions: Cyclic form of Glucose. You constantly encounter sugars in the cyclic form. This section leads you step by step through formation of the cyclic form. It is one of the more complicated bits of chemistry but once you go through it step by step you should own it.

CHAPTERS 9-12. Amino Acids. This is at the heart of modern biology. The four chapters provide a step-by-step method for learning them. Part of the method depends on their metabolism which provides a preview of this subject.

CHAPTER 13. Nucleotide Structure. This is both a preview and a reference for structures that you will encounter in Genes to Cells and in metabolism.

CHAPTER 14. Nucleophilic Addition Reactions: Summary. This is a fairly complex chart and you should use it as a reference. Notice that the examples given cover a very wide range from biochemical topics, one of which is the cyclic structure of glucose (reaction of aldehyde with oxygen nucleophile). The idea is that many reactions will fall into this broad classification and it will be much easier to learn them as examples of a general process than as isolated reactions.

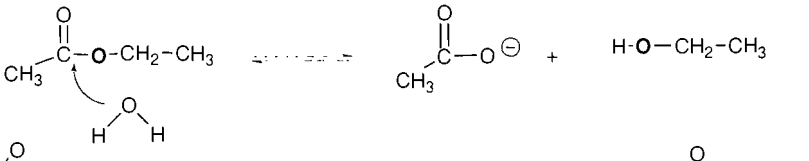
HYDROLYSIS AND SYNTHESIS OF ACYL AND PHOSPHORYL DERIVATIVES

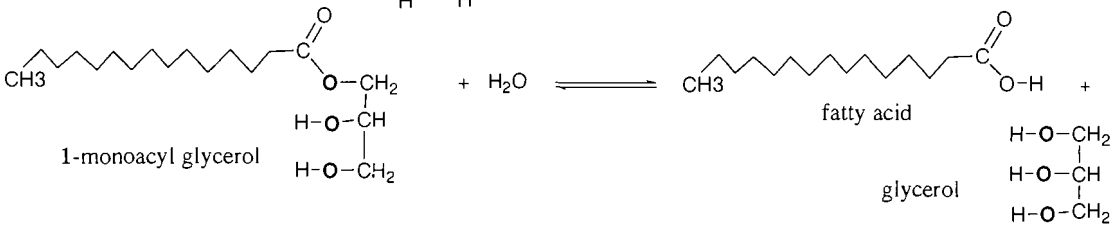
GENERAL

AMIDE

Ala-Ala + H_2O ⇌ 2 Ala

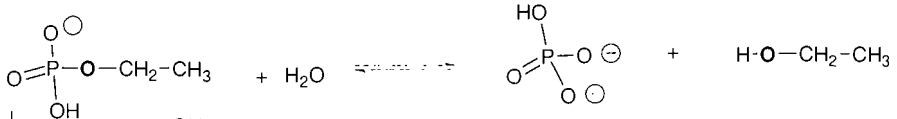
ESTER

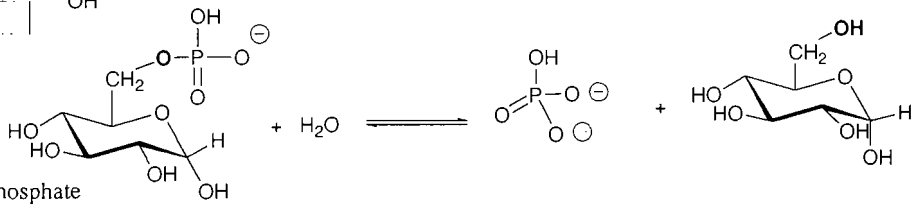




1-monoacyl glycerol

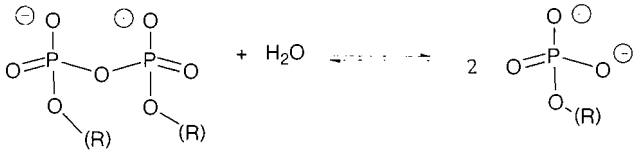
PHOSPHATE ESTER



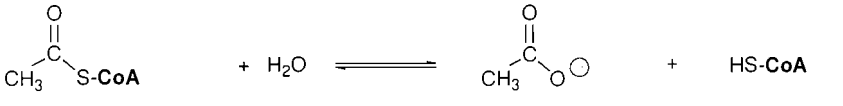


glucose-6-phosphate

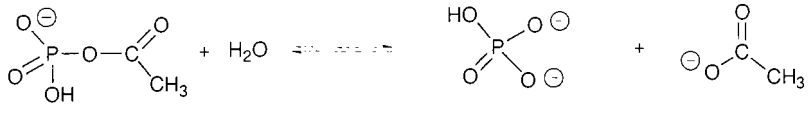
PHOSPHATE ANHYDRIDE



THIOESTER

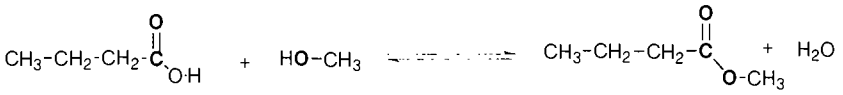


PHOSPHATE-CARBOXYLIC ANHYDRIDE



ANSWERS TO QUESTIONS.

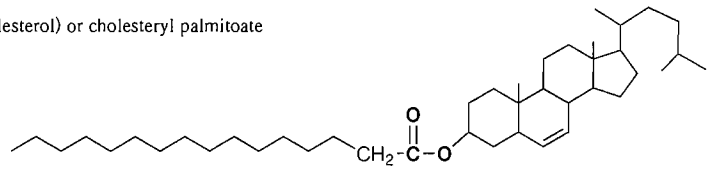
Q1. Formation and hydrolysis of methyl butanoate (You may remember from organic chemistry that esters are contribute to the odor of many plants; methyl butanoate is a component of the odor of apples).



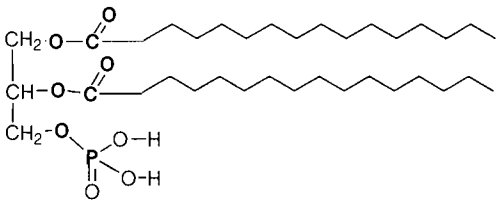
butanoic acid (carboxylic acid) | methanol (alcohol) | methyl butanoate (ester)

Q2. Acceptable IUPAC name for acetyl choline: (N, N, N -trimethyl-2-ammonium)-ethyl acetate.

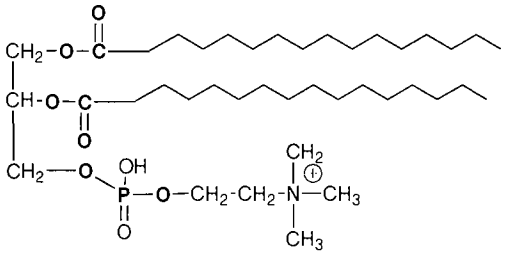
Q3. Fatty acyl cholesterol (palmitoyl cholesterol) or cholesteryl palmitoate



Q4. phosphatidic acid
(1, 2-diacyl glycerol-3-phosphate)

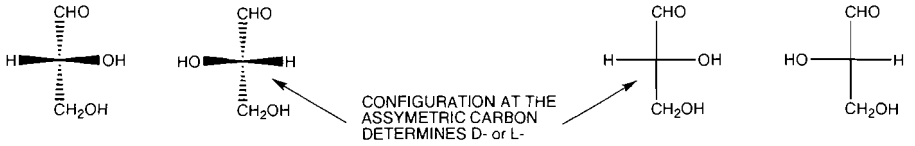


Q5. phosphatidyl choline (lecithin)



CHAPTER 7 - SUMMARY OF STRUCTURE OF SIMPLE SUGARS

1. Glyceraldehyde. the simplest sugar has one assymetric center. There are, therefore, two **enantiomers**.

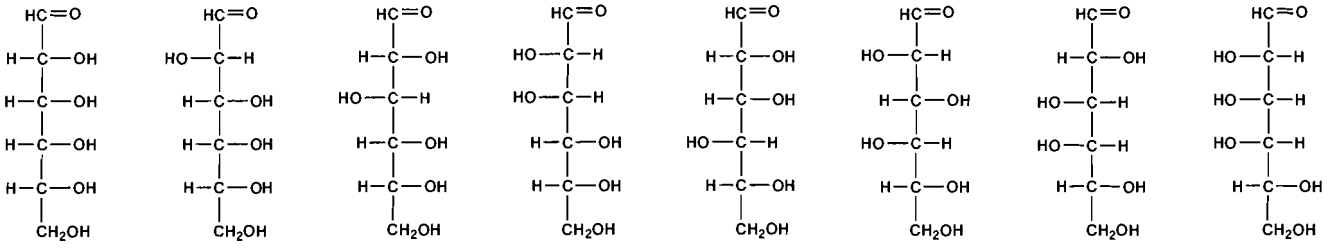


The Fischer projection is a short-hand for wedge and dash pictures. The rule is that the wedges (bonds coming out of the paper) are horizontal and dashes (bonds going back) are vertical. In representing the configuration around the assymetric carbon of glyceraldehyde, the number 1 carbon is placed at the top.

Special nomenclature is used for sugars and related biological compounds. The system is based on glyceraldehyde: the R- isomer of glyceraldehyde is called D- and the S- isomer, is called L. Most naturally occurring sugars are D-.

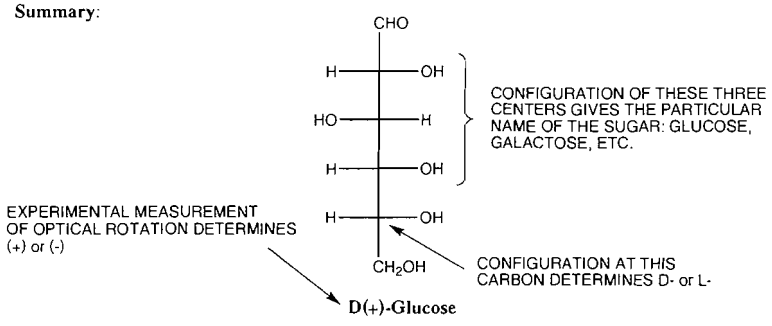
2. **General Terms**. Carbohydrates are polyhydroxy aldehydes and ketones: the general terms are **aldose** and **ketose**. Thus, glyceraldehyde is in the class of aldoses. There is also a **three-carbon ketose, dihydroxy acetone** (dihydroxy propanone); there is only one since there is no asymmetric center. General terms for the number of carbons in a sugar follow the usual conventions: tri-, tetra-, penta-, hexa-, hepta-, etc. Thus glyceraldehyde and dihydroxy acetone are **trioses**. The general terms can be combined. Thus, there are **two aldotrioses** and **one ketotriose**.

3. **Larger sugars**. An aldose with N carbons will have N-2 asymmetric centers (the last carbon is symmetric and carbon-1 will have the carbonyl group). We'll consider the hexoses since they are the most common, but the priniciples apply to tetroses, pentoses, etc. So, the aldohexoses will have four optical centers and hence $2^4 = 16$ isomers. Now, we could name them along the lines of 2R-, 3S-, 4R-, 5R- etc. but the conventions in carbohydrate chemistry are simpler, if less systematic. First, the configuration around the next-to-last carbon is determined as D- or L-. Then, each arrangement of the other carbons is given a specific name. For example, for the aldohexoses, the compound with all hydroxyls pointing to the right in a Fischer projection is called D-allose. The hexose in which, all were pointed to the left would be L-allose, the mirror image. So, for the hexoses, there are 8 pairs of **enantiomers**. The D- forms are shown below, all of which are diastereomers. Two diastereomers that differ at only a single carbon are called **epimers**. Thus, looking at the chart of aldohexoses, D-galactose is the 4-epimer of D-glucose.



4. **Indication of optical activity**. The ability of asymmetric compounds to rotate plane polarized light is an experimental observation indicated with a (+) or (-) depending on whether light is rotated to the right or left. Although this phenomenon is due to the asymmetry, it is not possible to predict the direction of rotation from the structure, in other words, any particular sugar might be D(+), D(-), L(+) or L(-). This is information you would have to be given. Of course, if you were told that D-glucose is (+), you could tell that L-glucose is (-). In summary, D and L are indicators of structure; (+) and (-) indicate the experimental observation about optical rotation.

Summary:



5. **What about ketoses** ? The same general principles apply to ketoses although only 2-ketoses are commonly studied in most courses. A ketose with N carbons will have N-3 asymmetric centers (the first and last carbon is symmetric and one carbon, usually carbon-2 will have the carbonyl group). The same procedure holds. For ketohexoses, There will be 3 optical centers and hence $2^3 = 8$ isomers. So, again, the configuration around the next-to-last carbon is determined as D- or L-. Then each arrangement of the other carbons is given a specific name. For example, the most common ketohexose is **D-fructose** which has the same configuration at carbons 3, 4 and 5 as D-glucose.

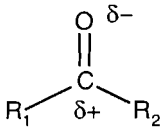
CHAPTER 8
NUCLEOPHILIC ADDITION REACTIONS: OXYGEN NUCLEOPHILES

CYCLIC FORMS OF SUGARS STEP-BY-STEP

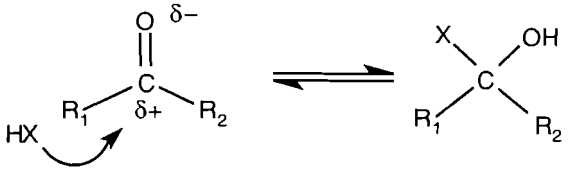
Where we are going. You can't go very far in biochemistry without running into the cyclic structure of sugars. Alone, or in polysaccharides, it is the most common form. Although it is common, students are not always comfortable with it. It looks complex and is, after all, a hemiacetal, which seems to be everybody's least favorite functional group. It's worth getting control over this structure because it's encountered so often. We will carry out the transformation (on paper) starting with the open chain form and winding up with the cyclic form. The principle is that the cyclic structure will be easier to understand if you see where it comes from. We'll work with glucose because it's the most common sugar and, if you know glucose, then you can always change it to another hexose by looking on a chart and changing the configuration of the relevant OH group. Going through the sequence of folding up the glucose molecule should make you comfortable with this structure.

What to look for: The hard part is that, unlike reactions such as acyl transfer, the products in cyclic sugar formation don't obviously resemble the reactants and it is sometimes hard to see which atom came from which. Always try to relate the atoms in you cyclic structure back to the straight chain form.

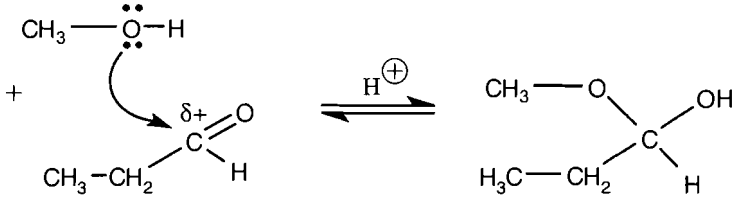
STEP 1. WHAT'S A HEMIACETAL AND WHY DO I NEED IT ? Let's start with the fundamental property of carbonyl compounds. Recall that the carbonyl bond is a polarized bond. Because oxygen is so much more electronegative than carbon, the carbonyl carbon bears a slight positive charge and the carbonyl oxygen is, likewise, slightly negative. The carbonyl carbon is then subject to nucleophilic attack by compounds with a negative charge or a free pair of electrons. (In the diagram, remember that if one of the R groups = H, the compound is an aldehyde, otherwise a ketone.



The general reaction:



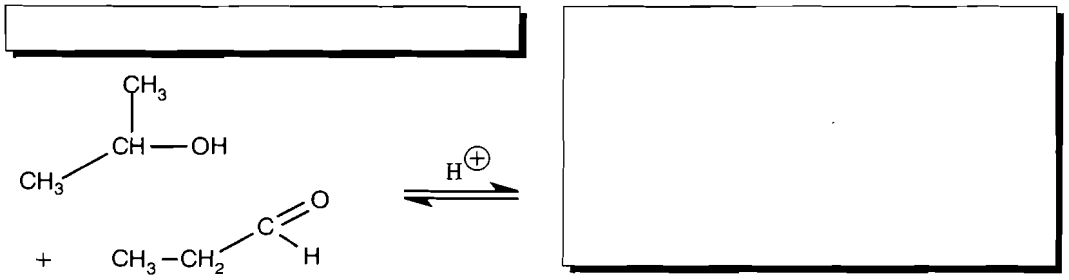
Hemiacetals are the products of reaction of aldehydes or ketones with alcohols. An example, the reaction of ethanol with propanal, is shown below (recall that curved arrows mean the movement of the electrons, so this is a nucleophilic attack of the oxygen on the carbonyl carbon). The reaction is usually catalyzed (shown here as acid catalysis) but this is a detail: for now, focus on the reactants and products.



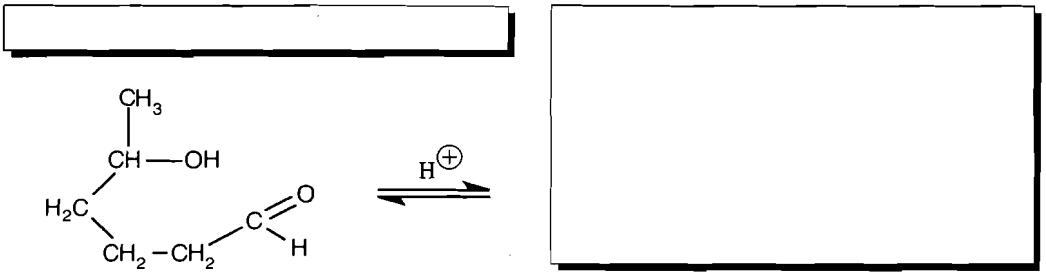
methyl hemiacetal of propanal.

A difficult reaction to understand. The reaction involves oxygen atoms from both reactants and the product (a tetrahedral compound) does not obviously resemble the starting carbonyl compound. (Unlike derivatives of carboxylic acids). To be sure you have a grip on things, **on the diagram, circle the oxygen in the product that used to be the carbonyl oxygen of propanal.**

STEP 2. YOU DO ONE. First, name the alcohol and then using the previous question as a model, draw the structure of the product.

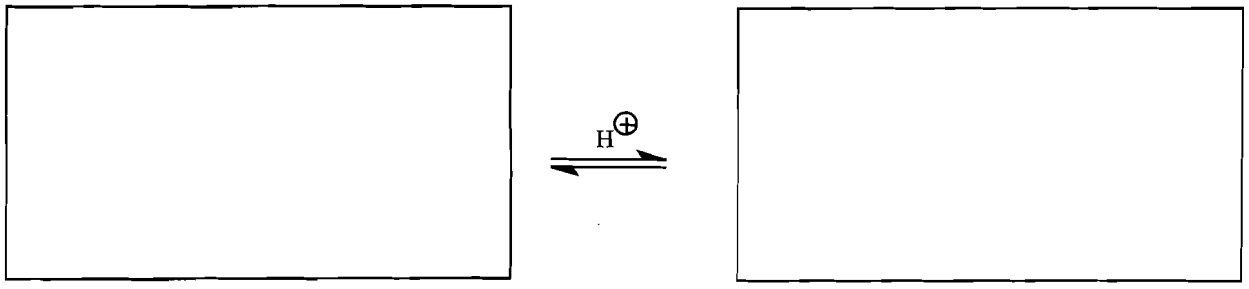


STEP 3. THE BIG STEP. A compound that has both an alcohol group and a carbonyl group (here, a hydroxy aldehyde) is capable of forming an **internal (cyclic) hemiacetal**. Nothing has really changed here, except the hydroxyl is on the same molecule as the carbonyl group. So now we follow the model above to form a **cyclic** hemiacetal. Although the chemistry is the same, one thing is different: because the product is now a cyclic compound and in a stable six-membered ring, the product is favored over the reactant and the cyclic hemiacetal form is more stable than the open chain form (this is what will happen with the sugars). **First, name the compound and then draw the structure of the product.** On your final drawing **circle the oxygen that used to be the alcohol oxygen.**

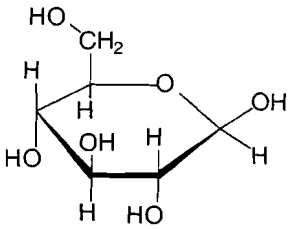


STEP 4. WHAT ABOUT SUGARS ? We can do the same thing: we'll fold up glucose into a ring by forming an internal hemiacetal. The only problem is that for a hexose, for example, you know where the carbonyl group is, but there are **5** hydroxyls. Which one reacts with the carbonyl ? Look back at the reaction that you just did. From the stability of that compound, you can guess that the driving force is the stable geometry that you get from 5- and 6-membered rings. For glucose, the 6-membered ring is usually formed. Here's how to do it:

1. Rewrite the reaction you just worked with. Write **both** the reactant and the cyclic structure.
2. The ring oxygen comes from carbon 5 of glucose: **label the 5 carbon** (with number 5).
3. The carbon that the ring oxygen is attached to used to be the carbonyl oxygen so l**abel it carbon 1**.
4. Now **replace a hydrogen with a hydroxyl group on carbons 2, 3, 4 and 6.** For the moment don't worry about the orientation of the carbon atoms. Do you see that you have written the structure and cyclization of an aldohexose ?



Your structure should look like the structures below although you may have pointed the OH groups in different directions. Next we will explain how to put the hydroxyls in the right place.



STEP 5. THE HAWORTH PROJECTION. The Haworth projection is a stylized picture of the cyclic structure that arises from hemiacetal formation. The orientation of the OH groups is also a stylized representation of their orientation in space. Finally, you notice there are two ways to attach the OH to carbon 1.

How do you represent the stereochemistry ? There **is** a rule: OH groups that point to the right in Fischer projections, point down in Haworth projections. You can remember the rule but many students find it easier to just draw a few glucose structures and learn the glucose as a graphic object. Of course, once you draw glucose, any other hexose can be deduced from a table of Fischer projections and reversing the direction of the appropriate OH groups. After you've drawn a few structures you will notice that the 2, 3 and 4 OH groups point **Down, Up** and **Down** respectively, if you want to remember it that way. The easiest way to draw the cyclic form of glucose turns out to be, paradoxically, the most sophisticated way, the chair form. Before we look at this, though, we have to work out the problem at carbon 1.

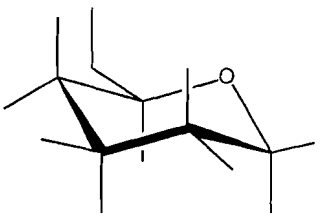
When the reaction takes place at carbon 1 a new asymmetric center is formed: the carbonyl is converted to a tetrahedral carbon. So there are two possible orientations of the hydroxyl group (the oxygen that used to be the carbonyl). The terms that are used are **α if the hydroxyl points down** and **β if it points up**. Which is formed in aqueous solution ? Both. The reason is:

1. The hydroxyl is attacking a roughly symmetrical center and could come in from either side.
2. Whichever forms is still capable of opening up -- remember the reaction is reversible so it could go back to the straight-chain structure re-fold the other way.

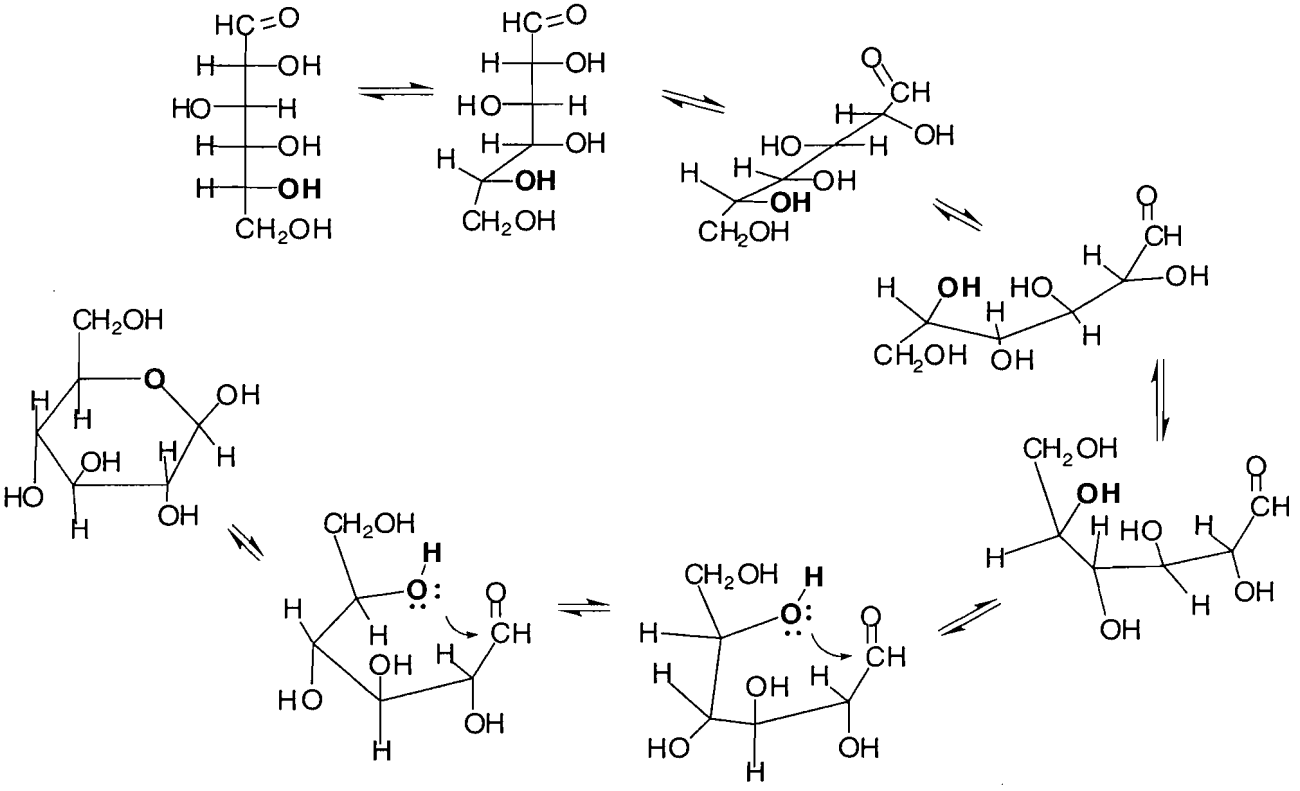
In fact, the β form is slightly more stable (64:36 and 0.02 % open form). The new asymmetric center is called the **anomeric carbon**. The two cyclic forms, α-D-glucose and β-D-glucose, are said to be **anomers** of each other. The configuration around this carbon has great biological significance so, even though the two forms of the aldohexose are in equilibrium, it is important that you recognize the difference between the α- and β- configurations at the anomeric carbon. Now, what about the **easy way to write the stereochemistry of glucose** ?

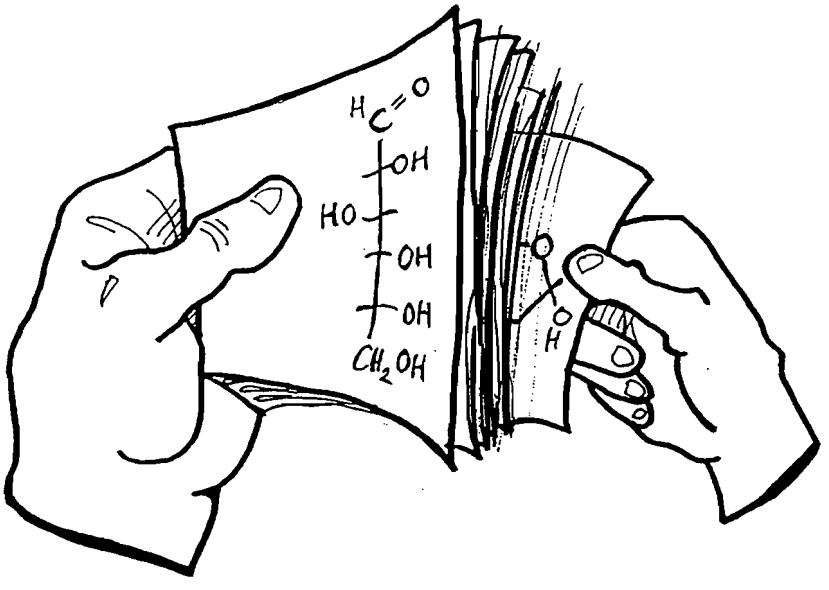
STEP 6. THE CHAIR FORM. The Haworth projection is an abstraction of the true form of a cyclic sugar. The most accurate representation of what the molecule, just as with cyclohexane, is a chair (this gives the most stable angles). To draw the chair form, **draw the oxygen first.** Make the chair around it as shown. To finish the structure, all you have to do is draw all the OH's in the equatorial position (pointing horizontally as much as possible). This will lead to the most stable form because the oxygen atoms will be as far away from each other as possible. If you draw carbon 1, the anomeric carbon as equatorial you will be drawing the β-form. **Fill in the OH groups on this diagram. Don't forget carbon 6 which is already pointing equatorial but needs an OH group.**

The significance of the chair form: Glucose and, especially the β-form, is the most stable of the aldohexoses because all of the OH groups are equatorial. It is presumably for this reason that glucose is the most common hexose in biology. In fact, the β-form is the monomer (subunit) of the polysaccharide cellulose which is the most common organic molecule in the living world.



STEP 7. CONSOLIDATING WHAT YOU KNOW. Getting control over the cyclic form of sugars means being able to convert the Fischer projection into a Haworth or chair projection. Good practice is to make a "movie" of the transition. Below, I have indicated some "frames" of the movie. You should try to make one like this yourself. You can be a little free with how you twist the bonds around (this is onlyt the movies) but make sure you understand that in the real case there is rotation but no change in the configuration at each carbon. Keep your eye on the fact that the ring oxygen is from carbon 5, and the aldehyde becomes the OH at the anomeric carbon. Before you start you might make the oxygen on carbon 5 **bold as below so** you can see that it becomes the ring oxygen. If you made the frames on individual pieces of paper, you can staple them together and have a flip-movie of the cyclization of glucose. (This is optional).





CHAPTER 9
STEP BY STEP THROUGH THE AMINO ACIDS: I. THE EASIEST TEN.

Protein structure is so central to the understanding of biology that a knowledge of the details is pretty much a necessity. One might say that for an educated person in the twenty-first century, knowing the names of the amino acids would be like knowing the names of the kings of England for a Shakespearian audience. The idea, however, is not simply to memorize the names of the amino acids but rather to associate the name with the property, for example: proline has a funny shape like Richard III. We focus on the individual personalities of the amino acids in two major contexts:

1. **The role of the side chains of the amino acids in protein structure.** Depending on your background at this point, you may want to review (preview ?) the big ideas of protein structure, in particular the forces that maintain the 3-dimensional structure of proteins. **The big generalizations to look for**: Two major classes of proteins that need to be considered are **globular proteins** such as hemoglobin and most enzymes that are soluble in water or aqueous solutions (blood, cell fluid), and **membrane-bound proteins**, proteins that are imbedded in cell membranes that have more-or-less form barrel-like structures. The major structural difference is that it is now currently believed that the **globular proteins are held together substantially by hydrophobic interactions,** that is, non-polar side-chains are found buried in the interior of the molecules. Those side chains that develop electric charge -- because they are part of ionizable groups -- point to the outside of the molecule and provide interaction with water. Membrane-bound proteins, on the other hand, have hydrophobic amino acid side-chains on the outside of the barrel allowing them to interact with the fat-like properties of the membrane. The inside of the barrel-like membrane-bound proteins will have more polar or charged groups.

2. **The role of amino acids in metabolism and nutrition.** The main function of amino acids is to make proteins. However, there is no storage of amino acids the way there is for carbohydrates and fats. Amino acids that are not used for protein synthesis are oxidized and used for energy or for synthesizing other cell material. The nitrogen is frequently excreted. Amino acids themselves are involved in the excretion of nitrogen. Also, the amino acids that are turned into proteins, come themselves, primarily from dietary protein, directly or indirectly. So, another feature of amino acids that can help you remember the structure and name is their role in metabolism.

WHERE WE ARE GOING: OBJECTIVES

1. To learn the structures of ten of the naturally occurring amino acids and the three-letter and one-letter codes.
2. To understand some basic ideas about the roles of the different types of amino acids in proteins structure.
3. To understand the roles of some of the amino acids in nitrogen metabolism.

STEP 0. How to use this handout. There are about twenty common amino acids that occur in most proteins. We will do the ten simplest in this section. This is a do-it-yourself learning exercise. You can follow it step by step from scratch, looking up each amino acid or checking each structure. Alternatively, you can study the amino acids in your text book first and then do the step by step looking up the structures or codes you can't remember. It is recommended that you time yourself on this kind of project. Learning twenty amino acids seems daunting but you may find that you can learn half in a short time: along the lines of 20 minutes. Some of the metabolic reactions will seem fuzzy at this time but you want to try to keep your eye on the overall goal -- using metabolism as a way to learn the amino acids. Your understanding of metabolism itself will be deepened later. There are different methods for classifying amino acids -- polar, non-polar, aromatic, heterocyclic, etc. We will try to think about these classifications as we go through the list.

STEP 1. Write the general structure of an amino acid indicating the side chain by R. This is the form of all amino acids. There are approximately twenty R groups (about the same number as the kings of England before Elizabeth I) and we will study how each R group makes them different. From the general structure make sure you see what they have in common.

STEP 2. A step to the side ? Write a fragment of a polypeptide chain showing three amino acids with side-chains R_1, R_2 and R_3. The point is to visualize amino acids in a peptide or protein, a progression of C(=O)-N-C bonds like a rope with the R groups sticking out from this **polypeptide backbone**. The side chains sticking out from the backbone will then contribute to the character of the over-all molecule, and the chemical interaction between side chains will contribute to the structure.

STEP 3. Start with glycine. This is the one to learn first because it is the simplest. Since R = H, glycine is the only amino acid that is not optically active. Because of its small size (no side chain) the components of the peptide backbone, the carbonyl oxygen and nitrogen of glycine may be important in protein structure and function. In terms of its function outside of protein synthesis, glycine is one of the amino acids that is by itself (not in a protein or polypeptide) a neurotransmitter. Looking ahead, glycine is the source of the nitrogens in the heme ring. **Write the structure for glycine, its three-letter code and its one-letter code.** Also, **write the systematic IUPAC name** (again, this is to help you remember the structure).

THREE LETTER CODE ONE LETTER

IUPAC NAME

STEP 4. Alanine.. The next most complicated amino acid simply has a methyl group. It's good to learn this second because when you know Ala you also get **Phenylalanine** for nothing. The one-letter code for phenylalanine prepares you (in a gentle sort of way) for the fact that the one letter codes are not all initials. **Write the structures for alanine and phenylalanine, their three-letter code and their one-letter code. Write the systematic IUPAC names.**

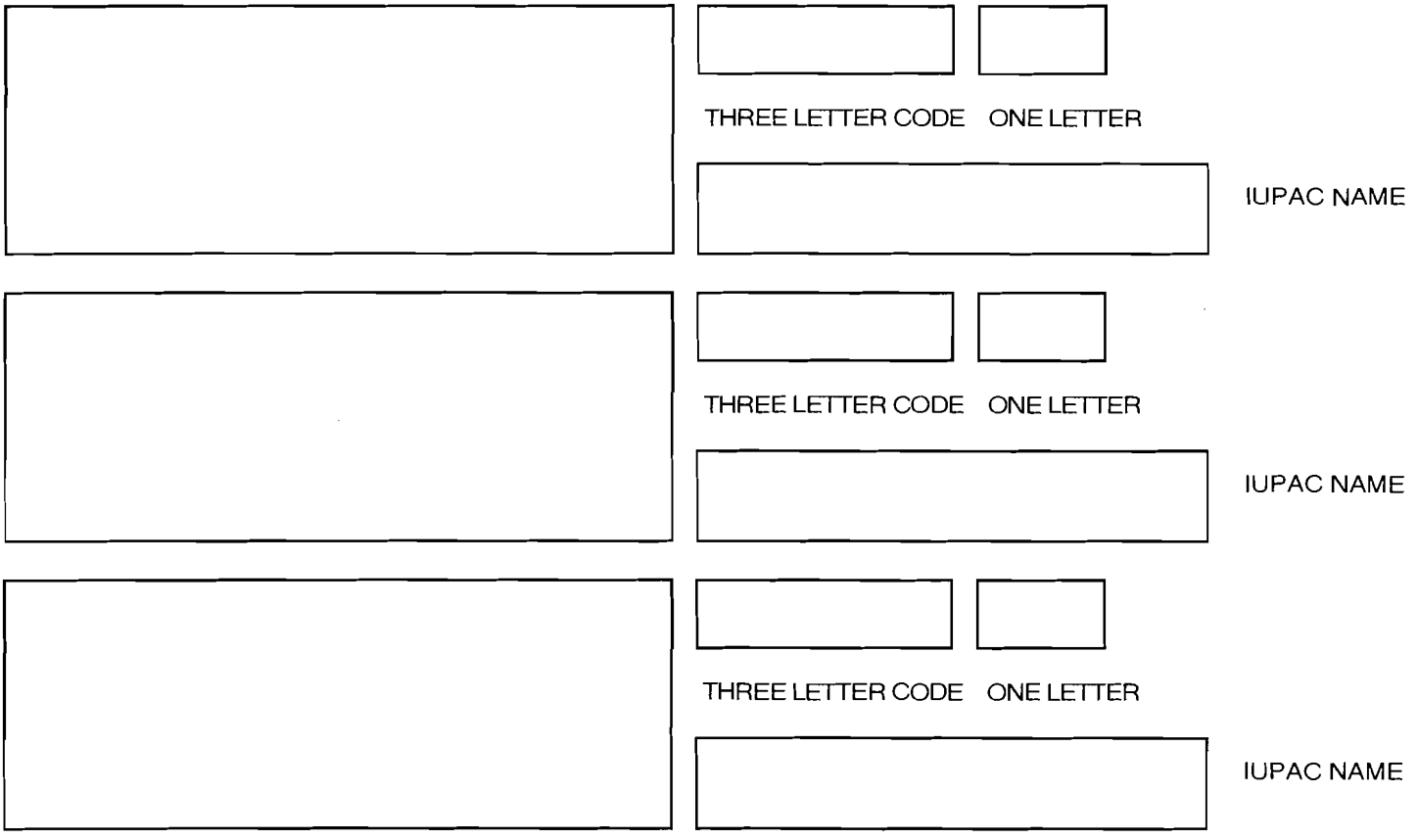
THREE LETTER CODE ONE LETTER

IUPAC NAME

THREE LETTER CODE ONE LETTER

IUPAC NAME

STEP 5. As long as we are talking hydrophobic amino acids, it's generally believed that the structure of proteins is strongly affected by hydrophobic interactions. The interior of globular proteins are assembled with different hydrophobic side-chains coming together so you need different shape pieces. Remember the van der Waals interaction is essentially a geometrical fit (because of the sharp dependence of the energy on distance between atoms) so you need different pieces to fit things together as in the computer game Tetris (Does anybody remember Tetris ?). Anyway, **Valine** has a side chain (isopropyl) in the shape of a **V** (the one letter code). In the same vein , you might say that **Leucine** is in the shape of an **L**, but then maybe a better case could be made for **Isoleucine (I)**. No professor who is a good person would ask you to remember the difference between leucine and isoleucine. You should just understand that they are both branched-chain hydrophobic amino acids (with four carbons in the side chain) likely, again, to be found on the interior of a globular protein like hemoglobin. These three, V, I and L are referred to as **branched-chain amino acids** although they fall in the larger classification of hydrophobic (with alanine and phenylalanine). **Write the structures for valine, leucine and isoleucine, their three-letter code and their one-letter codes.**



STEP 6. The big picture and some odd facts. What happens to amino acids that are not used for protein synthesis or other products ? As noted at the beginning, there is no storage of proteins the way there is of fat or, to some extent, carbohydrate. If the right collection of amino acids is not available for protein synthesis at the right moment or, if there is simply an excess of amino acids, they are **oxidized and the nitrogen is excreted**. The oxidation of amino acids can then be used to obtain energy. Most amino acids oxidation occurs in the liver. However, in the case of the branched chain amino acids, oxidation occurs in muscles.

The enzyme that does the oxidation is sometimes deficient. An unusual disease state that results from the loss of oxidizing enzymes for branched chain amino acids is called **Maple Syrup Urine Disease**, so named because the urine smells like maple syrup or caramel. This is an inherited metabolic disease. It can be fatal and occurs with a frequency greater than 1 in a million. The disease is apparent in the first few days after birth. The diagnosis must be made for the missing or reduced concentration of the enzyme (which is a decarboxylase -- removes the carboxyl group from the breakdown product of V, L or I). It points up the important point that amino acids are not stored and problems will occur unless excess amino acids are disposed of. The treatment, therefore, requires providing a diet where proteins are replaced with amino acid mixtures that do not contain these branched-chain amino acids. Since these are essential amino acids (see next section), once normal levels have been achieved, an appropriate diet must now supply them at levels that are just sufficient for metabolism.

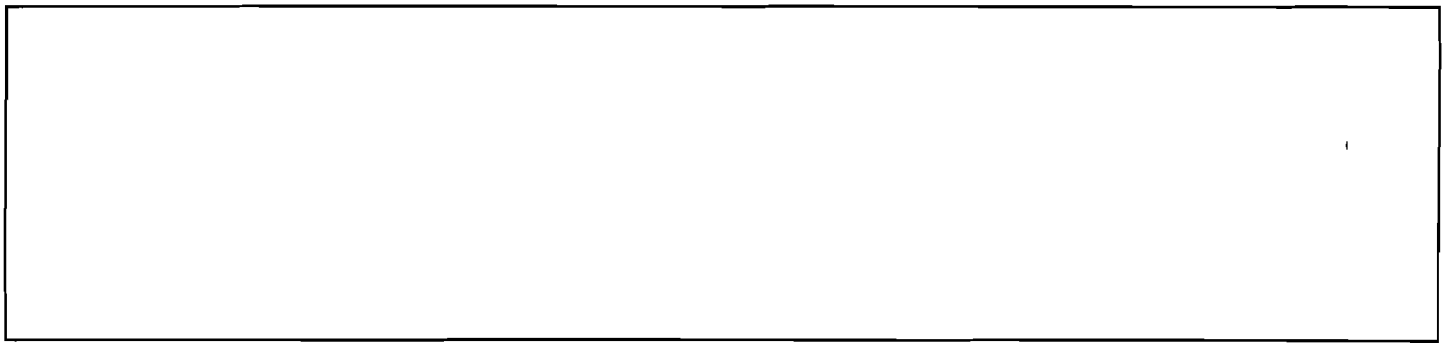
STEP 7. The story on essential amino acids. Animals that have a varied diet and live in a relatively predictable environment (unlike bacteria) can gain tremendous selective advantage in losing the genes for making a particular amino acid. (Synthesis of cell material is almost always an energy consuming process) . Of course, an animal thereby becomes dependent on the environment for a complete collection of amino acids, that is, all the amino acids needed to make their own protein. An animal may still be able to make some amino acids from others, or from another source of food, but some amino acids will be **essential** (essential in the diet). From the human dietary standpoint we speak of **complete sources of protein**, meaning those that contain a sufficient amount of the essential amino acids. You should understand that for humans, **a diet may have a high protein content but be nutritionally deficient because essential amino acids are missing**.

Of the twenty common amino acids, humans can inter-convert or synthesize ten. The other ten are the essential amino acids. There is rarely a reason to know the essential amino acids together as a list, but, for the record, the mnemonic is the "GI," **PVT. TIM HALL.** This mnemonic does not use one letter codes but rather the first names of the amino acids:

Phenylalanine-**VALINE-T**hreonine. **T**ryptophan-**ISOLEUCINE-Me**thionine **H**istidine-**A**rginine-**LEUCINE-L**ysine.

Notice that the three of the essential amino acids (in capital letters) are the branched chain amino acids. This is probably because, as we will study later, these amino acids have a carbon skeleton that is not inter-converted with other substances in metabolism but are used primarily to make protein. For this reason, an organism that doesn't have to make them has an advantage. Whereas arginine is one of the amino acids that can be produced in the body, depending on the condition, the body may not be able to keep up with the demand - it is generally considered essential for children but not for adults.

STEP 8. How are we doing ? We have 6 out of 20 or **30 %**. How long did that take ? They get harder but you're almost one third of the way there. We now know the hydrophobic amino acids (although glycine would **not** be considered in this category). We can predict that these will be buried in a globular protein. For practice -- make sure you still know how to write a peptide bond. **Draw the structure of glycinyl phenylalaninyl valine.**



STEP 9. What about the acidic and basic amino acids ? There are two carboxylic acid side-chains **Aspartic Acid** and **Glutamic Acid**, there is one obviously basic amino acid, **Lysine.** (The most basic amino acid, arginine, is discussed separately in the next section). Here we emphasize the **bottom line**: what is the effect of acid-base properties on proteins. **Answer**: Since the pK's of the side chains of acid groups (Glu and Asp) are far from pH 7 they are negatively **charged**; since the pK's of the side chains of the basic groups (Lys and Arg) are far from pH 7 (in the other direction) they are protonated, i.e., positively **charged**. For globular proteins, or the exposed part of membrane proteins, this will allow solvation by the aqueous environment. (Histidine has a pK in the neutral range and we will see it function as an acid base catalyst -- an entity that goes back and forth between acid and base forms.)

> **NOTE**: To write the IUPAC names of the acidic amino acids, you need to know the accepted names for dicarboxylic acids. Whereas one used to have to write butane dioic acid for the **four-carbon dicarboxylic acid**, the IUPAC has really loosened up -- now, they're generally considered wild and crazy guys -- and **succinic acid** is the accepted form. It's worth learning them because they keep coming up in biochemistry. A table is shown on the next page. If you've already studied metabolism, you recognize *derivatives* of these dicarboxylic acids: α-oxo glutarate (α-keto glutarate), succinate itself and succinyl CoA, malonyl CoA, hydroxy methyl glutaryl CoA.

carbons	name
2	oxalic
3	malonic
4	succinic
5	glutaric
6	adipic

Write the structure of Aspartic Acid, Glutamic Acid and Lysine, their three letter names and their one letter codes. To maintain contact with the home base (organic chemistry) also **write the IUPAC names for these amino acids** using the chart above.

THREE LETTER CODE ONE LETTER

IUPAC NAME

THREE LETTER CODE ONE LETTER

IUPAC NAME

THREE LETTER CODE ONE LETTER

IUPAC NAME

STEP 10. The mutation in **sickle cell anemia**. We are now in a position to appreciate the **molecular change** that gives rise to sickle cell anemia. The mutation in this disease is the substitution of **Valine for Glutamic Acid**, in other words, the substitution of a hydrophobic amino acid for an acidic amino acid. As we expect, Glu is on the surface of the normal hemoglobin molecule and provides charge and solvation. The substitution of Val creates a hydrophobic center, the so-called "sticky-patch." This is the center for polymerization of hemoglobin-S (hemoglobin-A is normal hemoglobin): hydrophobic forces cause the hemoglobin molecules to stick to together. This leads to formations of rods that cause the red blood cell to collapse (and assume a "sickle" shape) and to get stuck in the capillaries causing the symptoms of the disease.

STEP 11. Where are we now. We have learned the hydrophobic amino acids and those amino acids whose side chains are acids or bases. This is about half of what we have to learn. We have emphasized the role in protein structure. When a globular protein folds up into its tertiary structure, the hydrophobic amino acids tend to be in the center, and the charged amino acids are on the exterior in contact with solvent (water). Be sure you understand how to answer the following type of question.

(A) Alanine
(B) Glutamic acid.
(C) Leucine.
(D) Lysine.
(E) Phenylalanine.

_____ 1. The amino acid that contains an aromatic side chain.

_____ 2. The amino acid whose side chain has the highest pK_a.

_____ _____ _____ 3. The **three** amino acids in the list that would be likely to be found on the interior of a globular protein.

STEP12. Proline, the odd man out. This is an unusual amino acid because it contains a cyclic five-membered amine. The chemical nomenclature of this compound is unfortunate and nobody will ever ask you to remember. For the record, the name of the ring is pyrrolidine (the name of the amino acid actually comes from PyRrOLidINE). It is, however, useful to know that when a carboxylic acid group is considered as a complicated ring as substituent it is simply called "carboxylic acid." so the correct organic name for proline would be pyrrolidine carboxylic acid. You don't have to remember that but you should know that it is **not** an "imino acid" as is frequently stated in biochemistry texts. Imines have the functional group -C=N- and come from the reaction of an amine with an aldehyde or ketone (looking at the structure you could think of them as the nitrogen analog of an aldehyde or ketone. See the chapter on nucleophilic addition to carbonyls).

In terms of remembering the structure of proline, it may help to imagine it as coming from glutamic acid folding up on itself to form a five-membered ring. This is actually the way proline is synthesized although the actual substrate is the "semi-aldehyde, " that is, the side chain carboxyl group of glutamate is reduced to the aldehyde. Now an aldehyde can react with an amino group to form an imine. In this case it is an internal imine. This intermediate is a true "imino acid") and probably explains why people use the term for proline itself. The five-member imine is then reduced to give you proline. Fill in the scheme below. You may study this sequence in amino acid metabolism but here it is shown as an aid in remembering the structure of the amino acid.

glutamic acid ----> glutamic semi-aldehyde ---------> internal five-membered imine ---> proline.

What is the function of proline ? The presence of proline in a protein usually has the effect of is disrupting a helix due to its geometry which will not accommodate a helical turn. Looking back at the structure of the hemoglobin subunit, you can see that the polypeptide chain follows a path of several helices some of which are connected by the turn including a proline.

ω

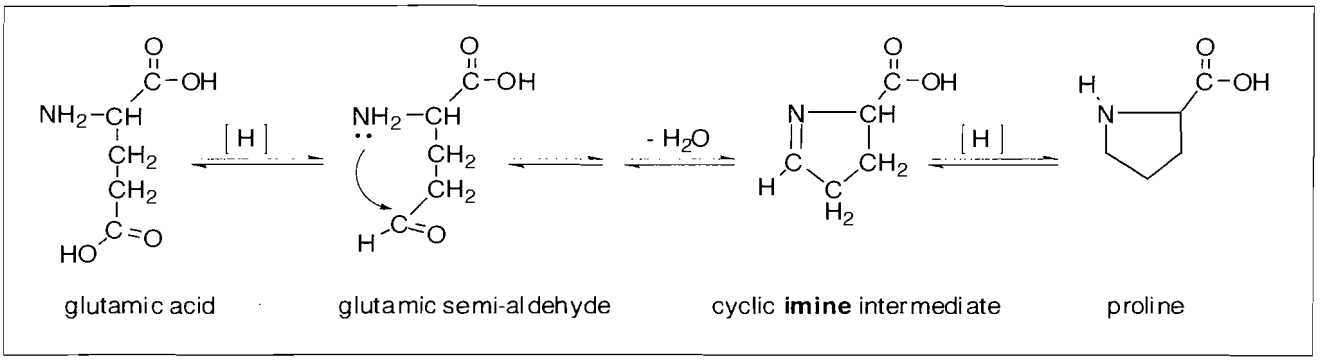
Answers. IUPAC names of the amino acids.

STEP	common name	IUPAC name
3.	Glycine	aminoacetic acid
4.	Alanine	2-amino propanoic acid
	Phenylalanine	2-amino 3-phenyl propanoic acid
5.	Valine	2-amino 3-methyl butanoic acid
	Leucine	2-amino 4-methyl pentanoic acid
	Isoleucine	2-amino 3-methyl pentanoic acid
9.	Aspartic Acid	2-amino succinic acid
	Glutamic Acid	2-amino glutaric acid
	Lysine	2, 6-diamino hexanoic acid

STEP 11.

1. (E)
2. (D), note: this is the highest pK_a in the list. But arginine, overall, has the highest pK_a.
3. (A), (C) (E). To some extent, "likely to be found on the interior of a globular protein" is the definition of hydrophobic for the side chains of amino acids. Later we will see amino acids like tryptophan which are largely hydrophobic but contain electronegative atoms and we describe them as both hydrophobic and polar since, for tryptophan, about half the time they are buried in the interior of globular proteins.

STEP 12. Cyclization of glutamic acid to make proline:



CHAPTER 10.
STEP BY STEP THROUGH THE AMINO ACIDS. II. THE TOUGHEST: ARGININE.

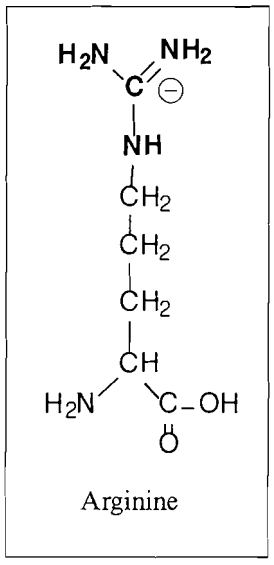
WHERE WE ARE GOING: GOALS OF THIS CHAPTER.

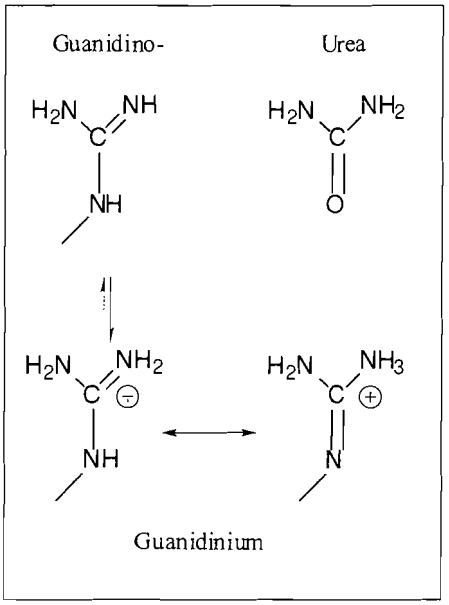
1. To recognize the guanidino group and to know the structure of urea.
2. To understand that nitrogen is excreted in the form of urea.
3. To learn the structure of arginine by understanding that it is the carrier of urea.

STEP 1. A few names and the structure of arginine. The structure of arginine is the most complicated of the amino acids.

The unusual looking complex of three nitrogens bonded to a single carbon is referred to as guanidine. As a substituent, in amino acids, for example, the group of atoms is called **guanidino-**. In this way, a good systematic name for arginine would be 2-amino 5-guanidino pentanoic acid -- can you see this ? Because it is very basic (arginine is the most basic amino acid, pK_a ~ 12), it is usually protonated and is written as the **guanidinium ion**. (Do not confuse the name with guanosine and guanine, components of nucleic acids; the names do indicate the historical importance of guano (bird droppings) as a source of organic compounds).

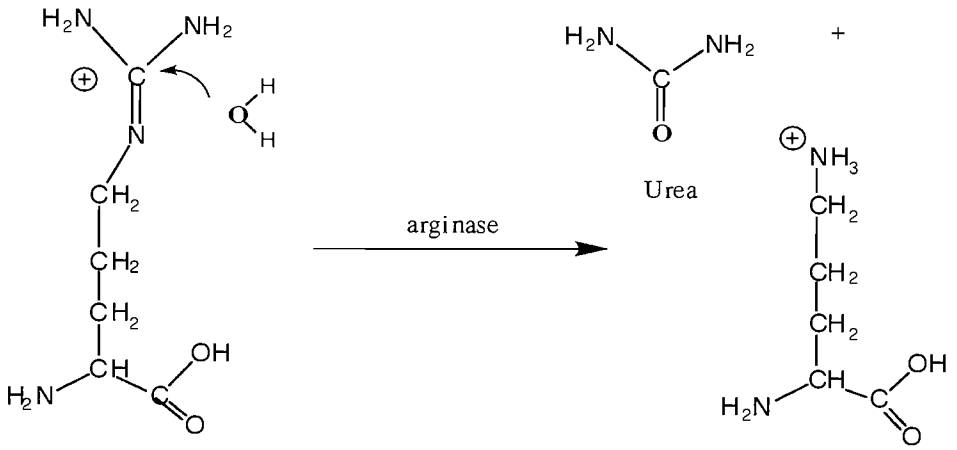
STEP 2. Urea. The compound **urea** is the **carrier of nitrogen that is to be excreted**. We made the point above that, unlike fat and carbohydrates, there is little storage of amino acids. Amino acids that are not used are excreted. In the liver, two nitrogens from amino acids are combined, in multiple steps, with a molecule of carbon dioxide to make urea. The urea is then excreted in the urine. The east way to remember the structure of arginine is to understand that **arginine is the carrier of urea**. Of course, you do have to learn the structure of urea but that's simple (it's small). It may also help to see that guanidine, itself, could be thought of as the nitrogen analog of urea.





STEP 3. The arginase reaction. Looking at one of the resonance forms of arginine (next page) emphasizes how much the guanidino group looks like a derivative of urea. You might, in fact, think of it as the imine of urea and an amine. Imines can be hydrolyzed (check the handout on nucleophilic reactions). The enzyme that catalyzes the hydrolysis of arginine to produce urea is called, simply enough, **arginase**.

The arginase reaction is the final step in the production of urea. The piece that is left over is called **ornithine**. The side chain of this amino acid is, in fact, the amino group that forms the "imine" with urea. At this point, you need not remember ornithine since it is an amino acid that is not incorporated into proteins. (When you do have to remember it -- in studying amino acid metabolism, or liver function -- you can associate the root "ornith-" meaning bird, with guano). Ornithine resembles another basic amino acid, lysine, except it has one less amino acid. To reinforce your understanding of the structure of lysine and arginine, you should draw the structure of lysine and compare it to ornithine.



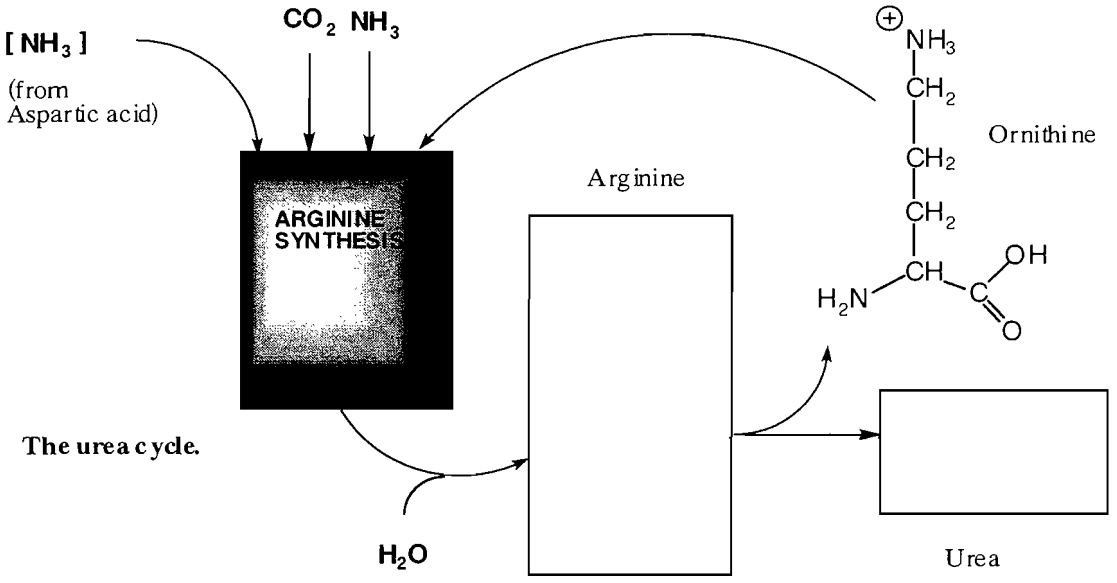
Arginine (resonance form emphasizing relation to urea).

Ornithine

Draw the structure of lysine for comparison with ornithine.

STEP 4. Arginine synthesis and the urea cycle. The process of forming arginine is fairly complicated. The "black-box" of urea synthesis has as inputs: ornithine (the scaffold on which we assemble Arg), **carbon dioxide** (the carbon for guanidino group), and the **two nitrogens**. One nitrogen comes in as **ammonia** and the other, is supplied as part of the amino acid **aspartic acid**. For simplicity, you can just consider that both nitrogens come from ammonia. The details of the process are studied in amino acid metabolism. Here, we just want to use the metabolic process as a way of learning the structure, so the details are not important. Of course, once we have arginine, we will hydrolyze it and excrete the urea. This will leave behind ornithine which is re-cycled through another round of the process. The urea cycle, is a one way cycle -- it is an excretion process. Ornithine is the assembly mold and arginine is the final carrier and then nitrogens are lost.

STEP 5. Problems. To reinforce what you have learned, fill in the structures of urea and arginine on the next page. You should try to do this after you have studied the material. That is, don't look back (except to check your answer). Start with the structure of Ornithine that is given and ask yourself how you could build up the guanidino group.



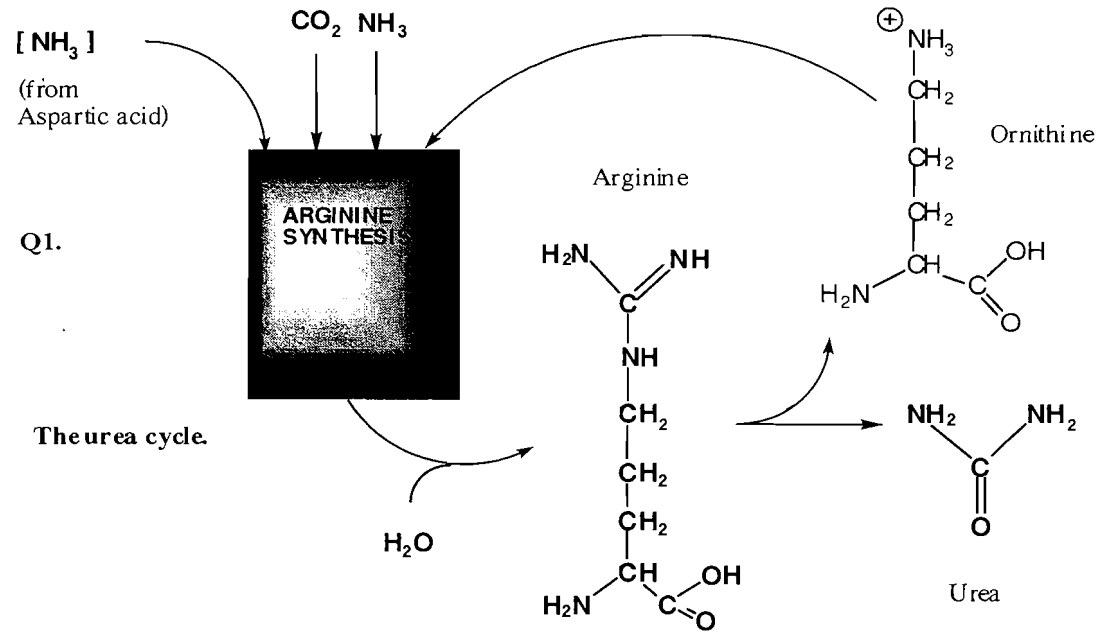
Q1. Fill in the structures of urea and arginine.

Q2. The compound creatine is used as part of a process of storing energy for muscle contraction. Creatine is made in two steps: first **arginine** and **glycine** react to form the compound **guanidino-acetic acid**. (In a second step, guanidino acetic acid is converted to N-methyl guanidinoacetic acid, the systematic name for creatine). Write the structure of guanidino-acetic acid.

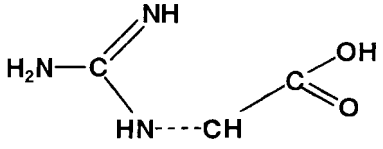
Q3. In the biosynthesis of creatine, the first step is the reaction of arginine and glycine to form guanidinoacetic acid. The other product formed in this reaction is:

(A) aspartic acid
(B) urea
(C) ornithine
(D) proline

Answers to Problems:

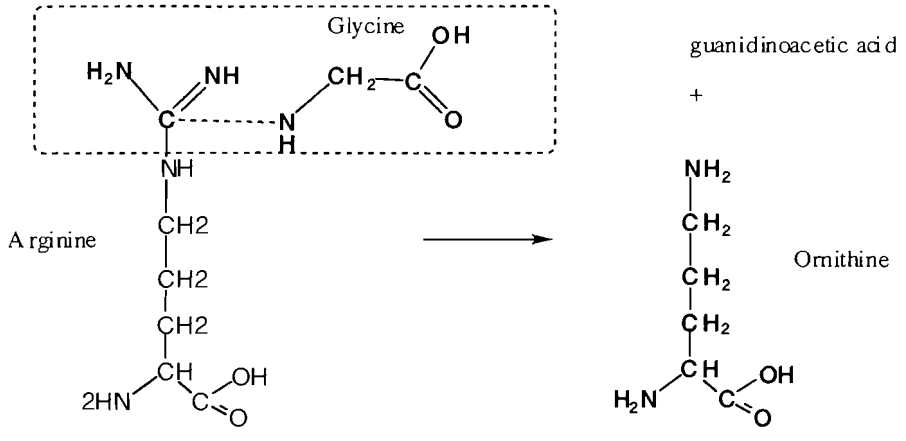


Q2. To write the structure of guanidinoacetic acid, you simply attach the guanidino group to acetic acid:



Guanidino- acetic acid.

Q3. To figure out the other product, use the "building block" approach: assemble what you know and see what's left. Since you started with glycine, one of the nitrogens probably came from that compound. This means the arginine must have supplied one carbon and two nitrogens. This is same group that got transferred to the oxygen of water to make urea. So, the generalization is that the two processes are similar: the N-C=N combination gets transferred to oxygen to make urea, or to nitrogen to make guanidinoacetic acid. (For the record (you don't have to remember this), the N-C=N combination is called amidino-)



STEP-BY-STEP THROUGH THE AMINO ACIDS
CHAPTER 11: III - LEARNING AMINO ACIDS THROUGH METABOLISM

Where are we ? We have been through the simple amino acids A, G and F. We followed A and F with the other hydrophobic amino acids -- the branched chain amino acids, I, V and L. We learned the basic amino acid K, and the two acidic amino acid D, and E. Finally, we saw that P was a "folded up" form of E. These were the easiest ten to learn. R was the hardest but we learned it by visualizing it as the carrier of urea. The atoms of urea were assembled on another basic amino acid ornithine, one that is not incorporated into proteins (and one that you only learn when you are studying metabolism).

Where are going. We're going to look a little deeper into the biology of the amino acids as a method of learning two new amino acids: glutamine and asparagine. The bottom line is that ammonia is toxic and any ammonia that is generated in the tissues during oxidation must be transported in a "safe" form. The reactions that are used are amide synthesis and hydrolysis. The source of the carboxyl group is the side chain of glutamic acid which is converted to an amide in the tissues, transported through the blood to the liver where the amide is hydrolyzed, the glutamic acid is recycled and the ammonia is incorporated into urea. Then, we see that asparagine is to aspartic acid as glutamine is to glutamic acid -- just the amide form.

Goals of this part.

1. To learn the structures, three-letter and one-letter codes for glutamine and asparagine. To review the structures of glutamic acid and aspartic acid and arginine.
2. To obtain a broad overview of the flow of nitrogen in metabolism and the roles of these amino acids in nitrogen metabolism. Specifically to know how ammonia is transported in the circulation and the final step in its excretion as urea.

Transport of ammonia. Ammonia is toxic and any produced in metabolism must be transported to the liver for conversion to urea and excretion. The chemistry of ammonia transport boils down to one cyclic process: amide formation and hydrolysis. The general reaction:

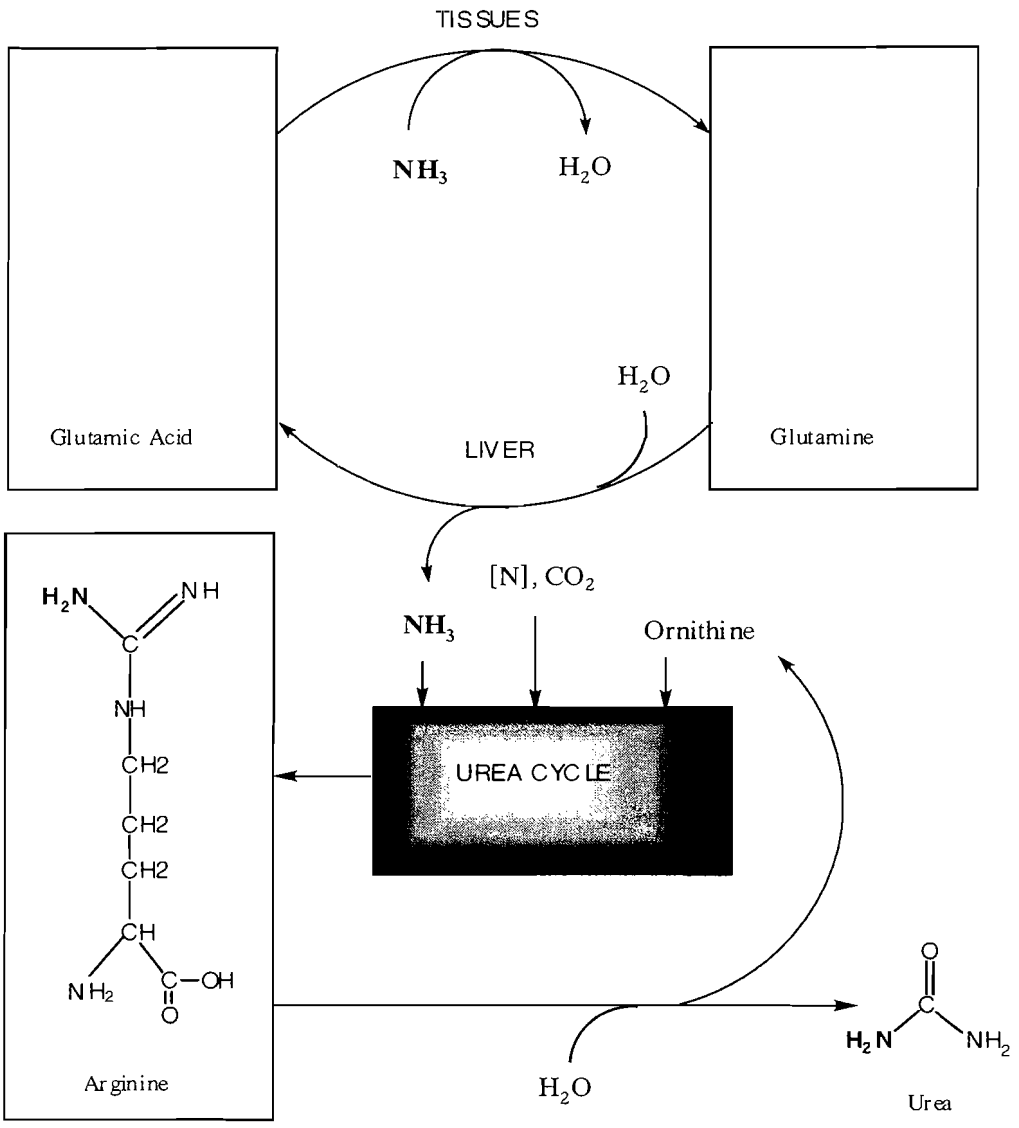
In metabolism, the carboxyl group is the side chain of glutamic acid. This will carry ammonia by making an amide bond. The product (unfortunately called **glutamine** instead of being named as an "amide" is carried to the liver where it is hydrolyzed and the ammonia that is released is incorporated into urea and excreted. So, the two amino acids, glutamate and glutamine, are just different forms of the carrier molecule.

The overall process is shown on the next page. **Fill in the structures for glutamic acid and glutamine**. Indicate the three letter and one letter codes.

Bottom line: in the last chapter we saw that urea was the molecule that is used for the excretion of nitrogen. The carbon comes from a molecule of CO_2 the two nitrogen atoms are excreted with every urea. One of these is the nitrogen that was transported as glutamine. The other comes from the nitrogen in the amino acid **aspartate**.

The two reactions form a cycle whose net effect is transport. Amino acids were oxidized in one place. The ammonia was transported to another place and excreted. The ammonia levels of the blood were kept low.

Ammonia + Glu $\rightarrow$ Gln + H_2O , followed by Gln + H_2O $\rightarrow$ ammonia + Glu .



Asparagine. Once you understand the structure of glutamine, the structure of asparagine is easy (only the name is a problem). The side-chain carboxyl group forms an amide with ammonia, although asparagine does not play the same role as glutamine in detoxifying ammonia. In fact, the nitrogen in asparagine comes from glutamine which is converted to glutamic acid.

Q1. The enzyme that synthesizes asparagine is called **asparagine synthetase**. Normal cells can make and process asparagine but some tumor cells are deficient in asparagine synthetase and rely on asparagine in the blood. On this basis, a therapeutic approach to treating such tumors might be administering the enzyme:

(**A**) arginase
(**B**) glutaminase.
(**C**) asparaginase.
(**D**) asparagine synthetase.

ANS. (**C**) The clue in the choices is that you should recognize the first two enzymes which simply hydrolyze their substrates: arginase catalyzes the reaction Arg + $H_2O \rightarrow$ Urea + ornithine, and glutaminase, the reaction: Gln + $H_20 \rightarrow$ ammonia + Glu. You could guess from this that asparaginase catalyzes Asn + $H_2O \rightarrow$ ammonia + Asp, thereby destroying the asparagine which the tumor is dependent on. Choice (D) would have the opposite effect, making more asparagine for the tumor.

CHAPTER 12
STEP-BY-STEP THROUGH THE AMINO ACIDS IV - POLAR AMINO ACIDS AND RINGS.

STEP 1. Polar and non-polar amino acids. The first amino acids in this step-by-step method were at the extremes of polarity: amino acids whose side chains were hydrophobic like Phe, Val, Ile and Leu, and amino acids whose side chains were completely in the ionized form: aspartate and glutamate (carboxylate) and lysine (ammonium). Arginine, the most basic amino acid has a side chain that is also completely ionized.

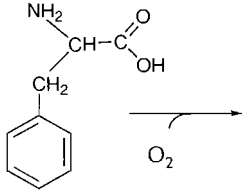
STEP 2. Gln and Asn, however, are in-between. Not ionized but highly polar, Asn and Gln might be expected to participate in hydrogen bonding in protein structure.

STEP 3. Several other amino acids also have polar side chains which, although they are not generally ionized, can take part in hydrogen bonded structures. Also, because of their polar nature, they also play a role in enzymatic activity.

The two simplest polar amino acids are **serine** (hydroxyl side chain) and **cysteine** (thiol side chain). A more complicated polar amino acid is tyrosine. The side chain is phenol, although biologically it is a derivative of phenylalanine. **Draw the structures and write the three letter codes and the one letter codes.**

Serine

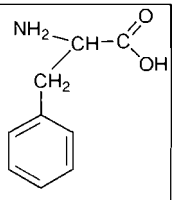
Cysteine



Phenylalanine Tyrosine

Phe F

STEP 4. As long as we're talking Phe -> Tyrosine, you can reinforce learning these structures by understanding that this is the reaction that is defective in the inborn error of metabolism known as **phenylketonuria**. Infants born with phenylketonuria have an absence or a defective form of the enzyme (phenylalanine hydroxylase) that converts phenylalanine to tyrosine. The danger is not only that tyrosine becomes required in the diet but that Phe builds up and the oxidation products, phenyl pyruvic acid and phenyl lactic acid are toxic and cause nerve damage. Treatment involves providing a diet that has low phenylalanine and sufficient tyrosine. This is the reason for warnings on food artificially sweetened with aspartame, (Nutrasweet®) which contains phenylalanine. To gain control over these structures draw phenylpyruvic acid (2-oxo 3-phenylpropanoic acid), phenyl lactic acid (2-hydrocy 3-phenylpropanoic acid), and, at least because it's an irresistable exam question, aspartame (aspartyl phenylalaninyl methyl ester).



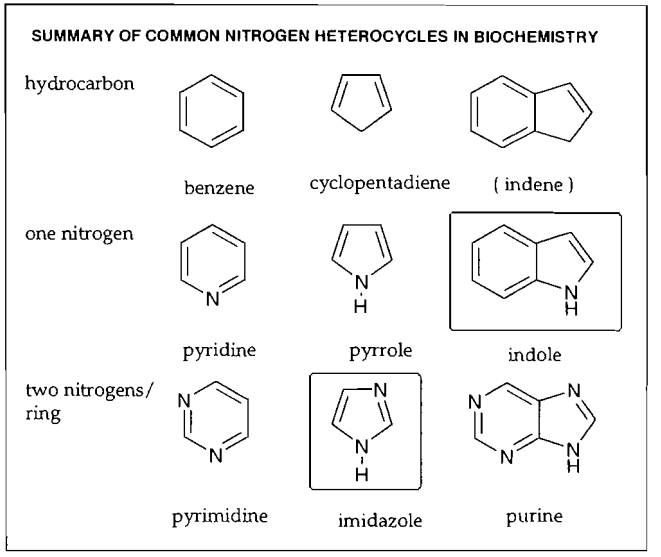
Phenylalanine

Phenyl pyruvic acid

Phenyl lactic acid

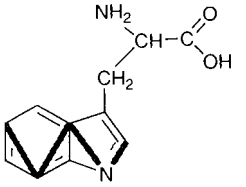
Aspartyl phenylananinyl methyl ester
(Aspartame, Nutrasweet®)

STEP 5. Phenylalanine and tyrosine, of course, amino acids that contain ring structures, benzene and phenol, respectively. There are also two amino acids that contain heterocyclic rings (rings with non-carbon atoms, nitrogen in this case. Heterocycles are always hard to deal with because of the similarity of the names so it might be good to review the common nitrogen heterocycles.



Draw structures, three letter codes and one letter codes for histidine (imidazole side chain). The tryptophan structure is shown (indole side chain) with a graphic that maybe shows why W was picked for tryptophan

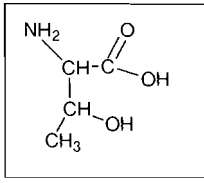
Histidine



Tryptophan

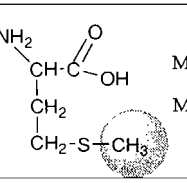
Trp W

STEP 6. The last two amino acids are best learned, for the moment, by brute force. Threonine is like serine except one more carbon. Methionine is an amino acid that is important, as the name implies, in transferring methyl groups and will be studied later in detail. For now, notice that it has a methyl group attached to a sulfur atom but is one carbon longer than cysteine



Threonine

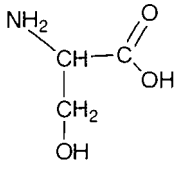
Thr T



Methionine

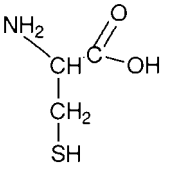
Met M

CHAPTER 12 STEP-BY-STEP THROUGH THE AMINO ACIDS ANSWERS TO PART IV - POLAR AMINO ACIDS AND RINGS.



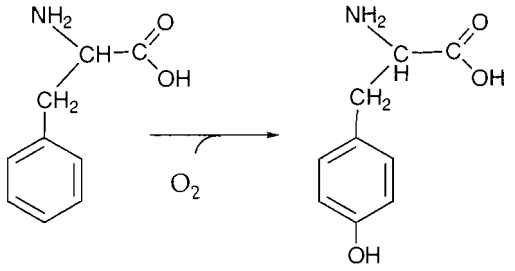
Serine

Ser S



Cysteine

Cys C

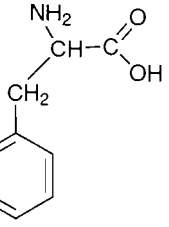


Phenylalanine

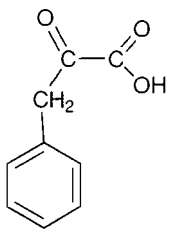
Phe F

Tyrosine

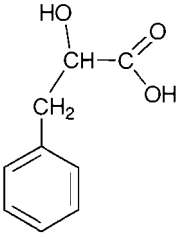
Tyr Y



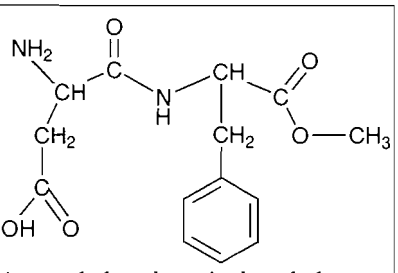
Phenylalanine



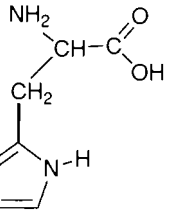
Phenyl pyruvic acid



Phenyl lactic acid

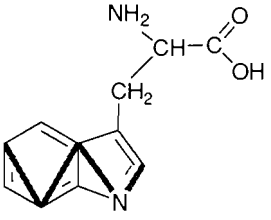


Aspartyl phenylananinyl methyl ester (Aspartame, Nutrasweet®)



Histidine

His H



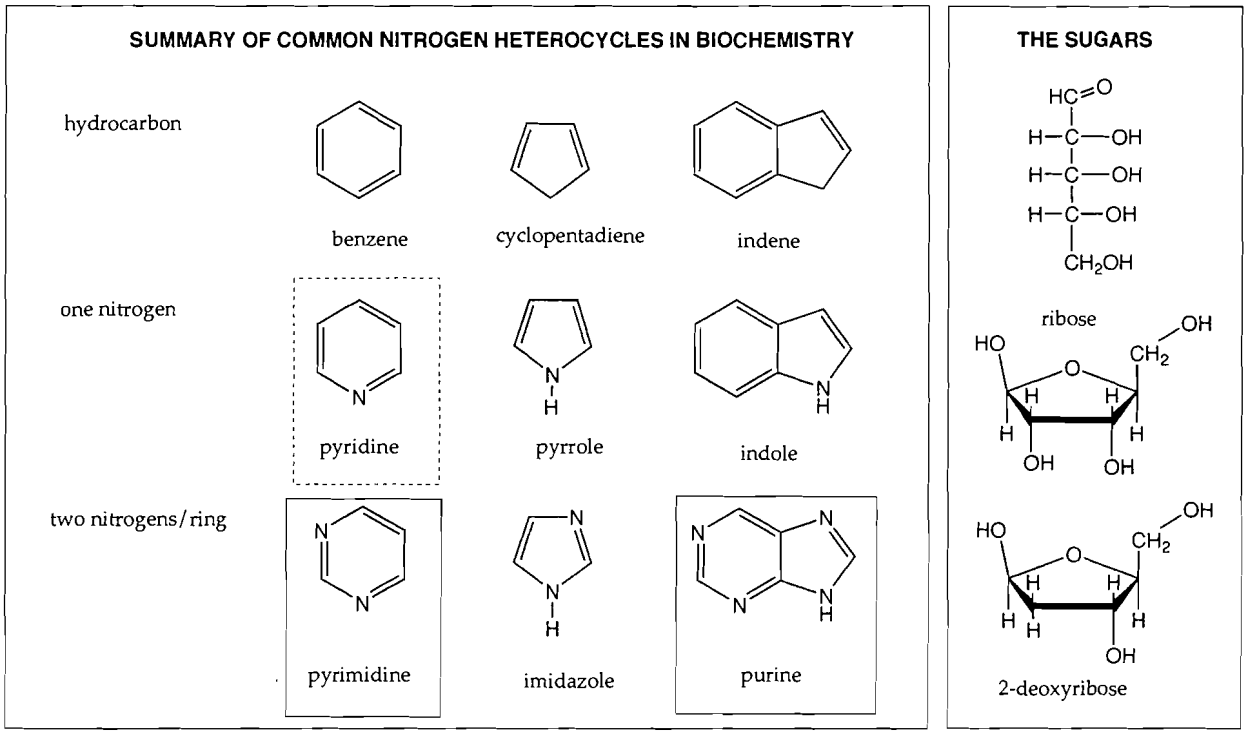
Tryptophan

Trp W

CHAPTER 13 - STEP-BY-STEP THROUGH NUCLEOTIDES

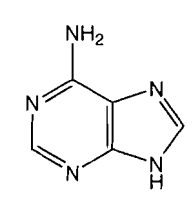
Nucleotides are the building blocks of several coenzymes of metabolism: ATP, NADH, Coenzyme A and others. They are, of course, also the building blocks of nucleic acids, DNA andRNA. The three components to nucleotide structure are: heterocyclic compounds known as **bases**, **sugars** and **phosphate**.

Step 1. The bases, the sugars. The easiest way to get a feel for the heterocycles is to look at them as if they were derived (on paper) from the hydrocarbons: benzene, cyclopentadiene and the fused 5- and 6-membered ring. In the chart the two heterocycles that are widely used in nucleotides are circled. Pyridine (dotted line) is used in the nucleotide NAD. The two **sugars** that are important in nucleotide structure are ribose and 2-deoxyribose.

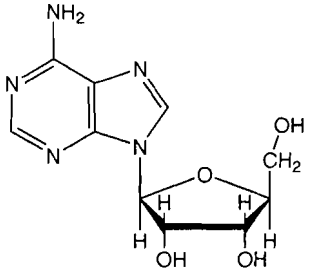


Step 2. Strategy: Adenine Nucleotides first. Nucleotide structure is best acquired by learning one compound in detail and then going back and learning the other bases. The easiest purine to learn is adenine (A). It's the most common constituent of nucleotides. There is only one substituent on the ring, an amino group. So, aminopurine is called adenine. (For the record, it's 6-aminopurine but no need to know the numbering system).

Step 3. Nucleosides. A nucleoside is composed of a base and a sugar. The sugar to which adenine is attached is ribose. The attachment is a variation of the way sugars are attached to each other, namely the glycoside bond. Recall that in a glycoside you substitute an alcohol for the OH in the cyclic sugar structure. In an **N-riboside** you substitute an amine for the OH group. A nucleoside is, thus, an N-riboside formed with one of the bases and ribose. The bad news is that they have common names that are, in fact, widely used. Adenine riboside is called **adenosine**.



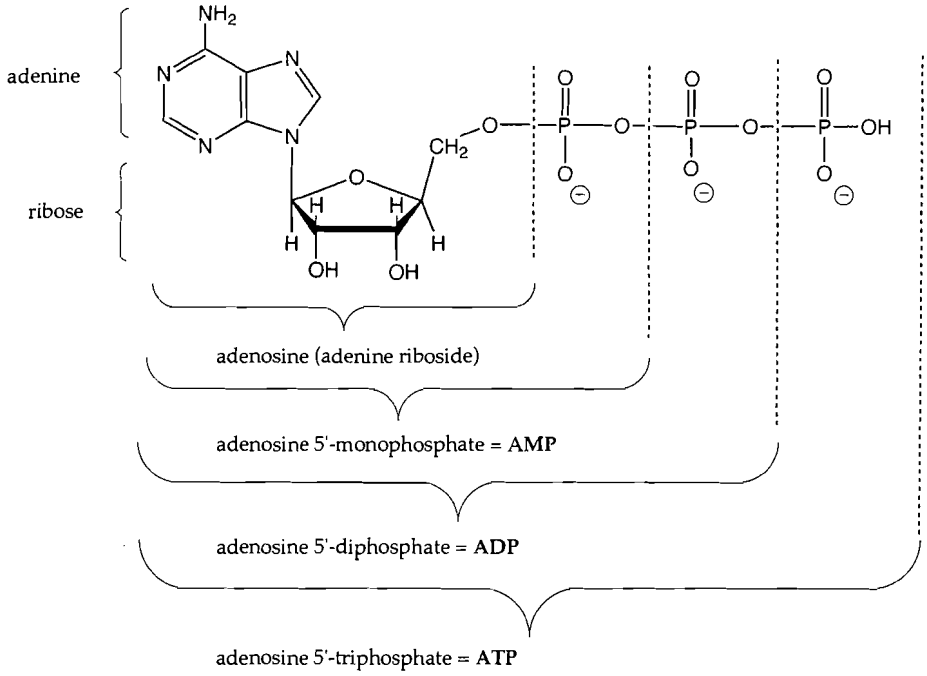
6-Amino purine = Adenine



Adenine-N-riboside = Adenosine

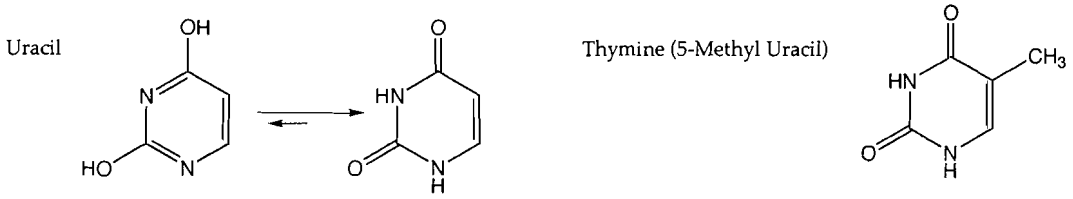
Step 4. Nucleotides. The final pieces to nucleotide structures are the phosphate groups. Ribose has three hydroxyl groups that might form further bonds. One obvious reaction of the hydroxyl group is ester formation, either with a carboxylic acid, or, in this case, with phosphoric acid. Note on nomenclature: In the assignment of numbers, the bases are numbered first (you never have to know the actual numbering system) and the carbons of the ribose are given primes (′). Thus, the point of attachment to the ring is the 1′ carbon of ribose. Nucleotides are nucleoside 5′-phosphate esters, that is the hydroxyl of the 5′-carbon forms an ester with phosphoric acid.

Step 5. The adenine nucleotides. The 5'-phosphate ester of adenine is called adenosine-5'-mononucleotide or AMP. AMP is an acid and is sometimes referred to as adenylic acid. Because phosphate is a triprotic acid, it can form additional phosphoryl derivatives. If an additional phosporic acid group is added (making a phosphate anhydride bond), the structure is called adenosine-5'-**di**nucleotide or ADP. Similarly, for ATP:



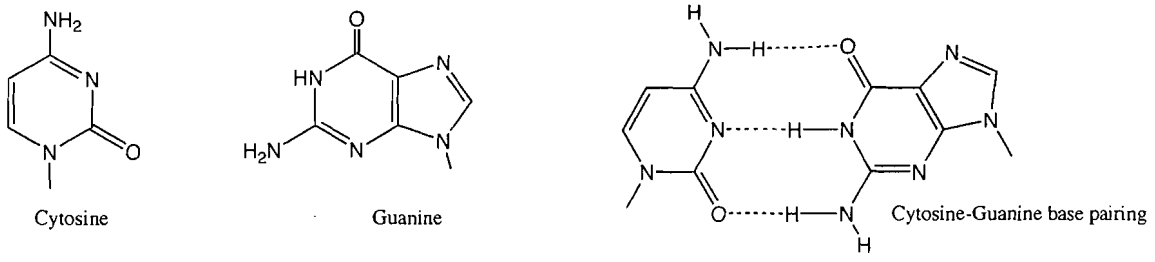
Step 6. What is the significance of the adenine nucleotide structure ? Metabolic energy is stored in the structure of ATP. The two distal phosphates (called β and γ) are phosphate anhydrides, that is, highly reactive compounds, like carboxylic acid anhydrides; the phosphate bond at the α center is, of course, a simple phosphate ester. If you are reading this after having been through bioenergetics, you know that the free energy of hydrolysis of these bonds can drive reactions that are otherwise energetically unfavorable. Adenine nucleotides are also components of the coenzyme NAD^+, so it's a structure that is worth knowing well.

Step 7. What about the other bases ? The easiest pyrimidine is uracil because although it has two substituents, both are oxygens. You could think of these oxygens as hydroxyls, O analogs to the amino group in adenine. The structures would then be enols, but, like most enols, they are more stable in the keto form. **Uracil**, therefore, is dioxopyrimidine. Uracil is almost only used in RNA. Its methyl derivative thymidine, is the corresponding base in DNA. In this way the base defines a difference between RNA and DNA. Enzymes that can control DNA synthesis, for example, can look for thymine rather than uracil.

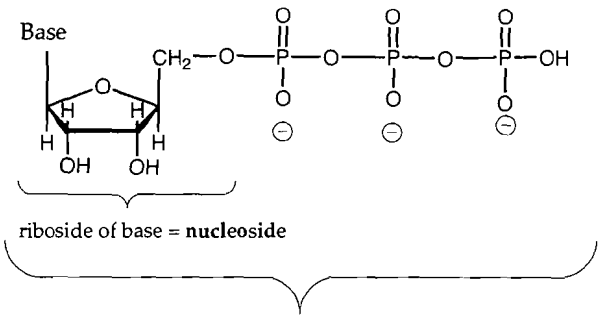


Step 8. Although you rarely have to know the detailed structure of individual bases, they are easy to learn if you follow the following mnemonics. First, you have to be confident of the two simplest: adenine we use all the time: aminopurine. Uracil (and thymidine, its methyl derivative) have two substituents, both of which are keto groups.

Step 9. Now, the two remaining bases can be identified because, most simply, they're not A (for purines) or not U (if they're pyrimidines). If you want to remember the structures, a mnemonic is to think of guanine, the other purine, as the "opposite" of adenine, that is it has O where adenine has N and the other position (between the ring nitrogens) has N. There is no quick way to learn the structure of cytosine since it has one N and one O and the only thing to compare it to is U. When you really need to know it, and can't live with a 50:50 shot, you can write guanine and then try to write the Watson-Crick base pairing from DNA, although this is a structure that may require brute force memorization.

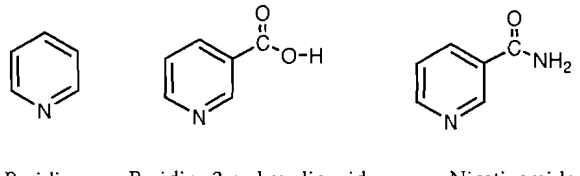


Step 12. Nucleotides. Summary of the structure and common names of nucleotides.



Base		Nucleoside	Nucleotide: monophosphate	di- and triphosphate		role in metabolism
			purines			
A	Adenine	Adenosine	Adenylic Acid = Adenosine 5'-monophosphate (AMP)	ADP	ATP	energy, general.
G	Guanine	Guanosine	Guanylic Acid GMP	GDP	GTP	protein synthesis, miscellaneous.
			pyrimidines			
C	Cytosine	Cytidine	Cytodylic Acid CMP	CDP	CTP	lipid metabolism.
U	Uracil	Uridine	Uridylic Acid UMP	UDP	UTP	carbohydrate metaobolism.

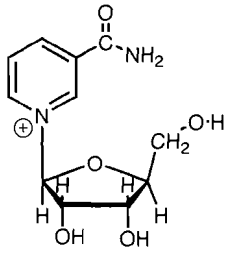
Step 13.. Nucleotide coenzymes: structure of NAD. Several coenzymes are nucleotides or are clearly derived from nucleotides. Others, which appear to have complicated structures, can be seen to be composed of different parts, one of which may be a nucleotide. Enzymes that use these coenzymes have a site which recognizes the nucleotide, and a site which recognizes other parts of the molecule. In this sense, the nucleotide acts as a "flag" for the enzyme and the chemical reaction may be at a different part of the molecule. The redox coenzyme, NAD, is one of the most important structures that can be analyzed in this way. Taking it step-by-step:



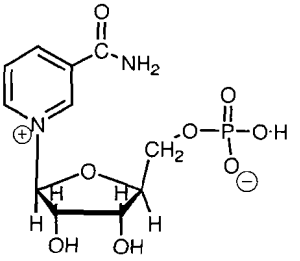
Pyridine

Pyridine 3-carboxylic acid (nicotinic acid

Nicotinamide

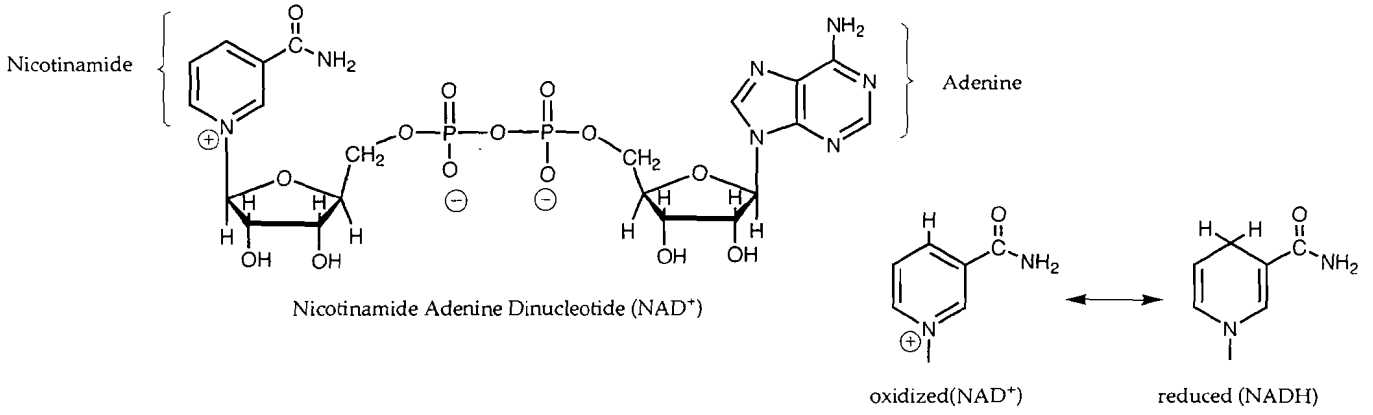


Nicotinamide-N-riboside (nucleoside)



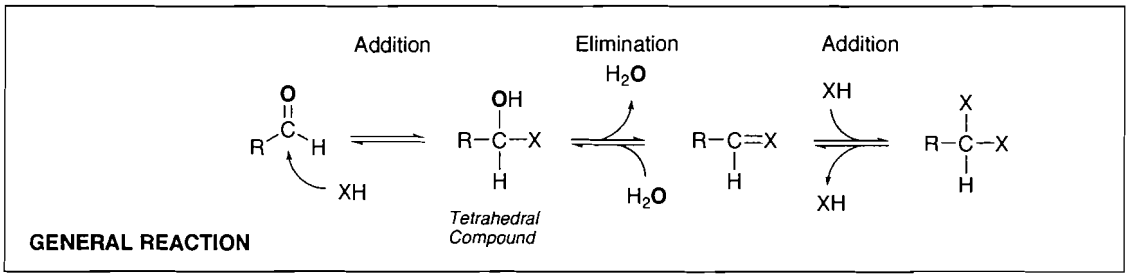
Nicotinamide-N-riboside-5'-monophosphate (Nicotinamide mononucleotide)

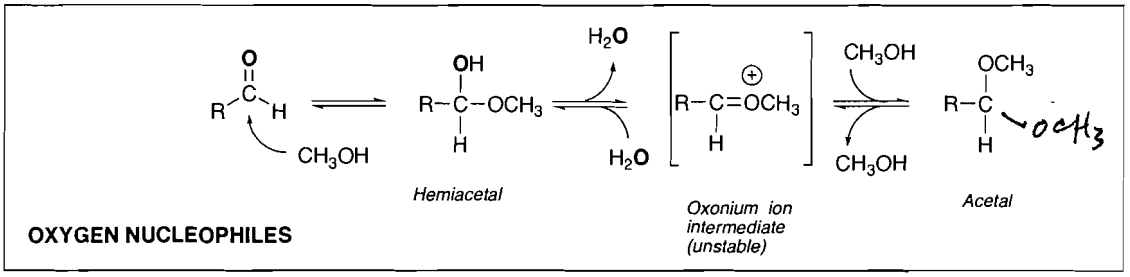
Putting this together with AMP, we have the redox coenzyme NAD. (In cells, NAD is formed from the reaction of nicotinamide mononucleotide with ATP.) In its role as a redox coenzyme, the adenine part of coenzyme contributes to the recognition by enzymes. The action end of the molecule is in the pyridine ring which exists in an oxidized form (NAD^+) and a reduced form (NADH).



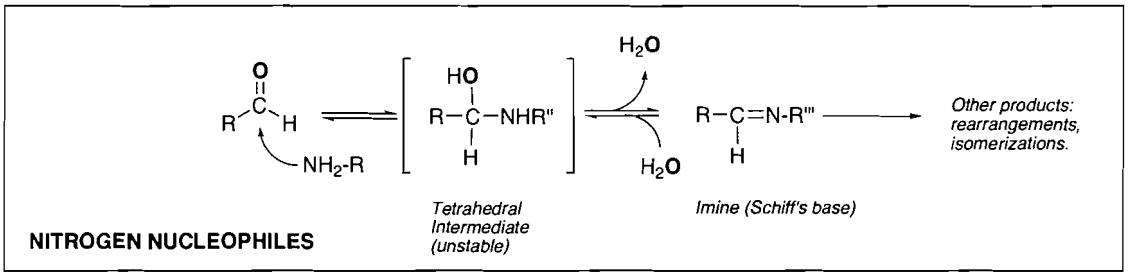
CHAPTER 14 - SUMMARY OF NUCLEOPHILIC ADDITION REACTIONS

Many seemingly different reactions fit into the general category of nucleophilic addition reactions and have overall similarities. You may want to scan down the page to see the similarities. The general case: 1) Addition of the nucleophile to form a tetrahedral intermediate, stable for some nucleophiles, but unstable for others. 2) The intermediate can go back to the original compound or can eliminate water to form an unsaturated compound which, again, may or may not be stable. 3) The double bond compound may undergo addition of a second mole of nucleophile. The product may rearrange in special cases.



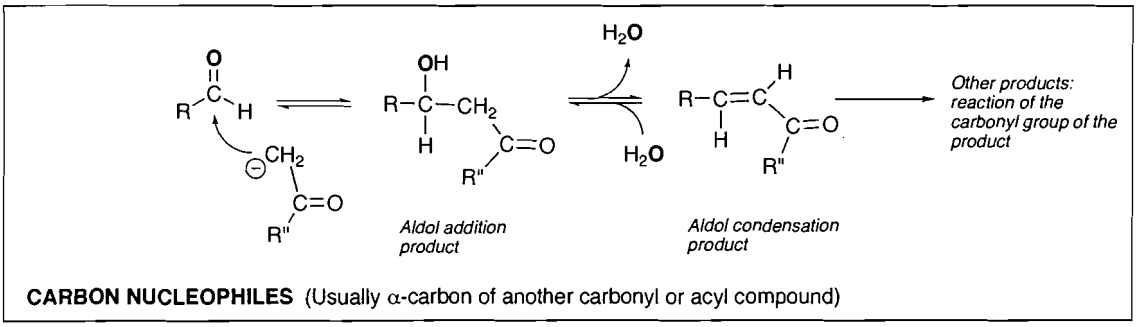


EXAMPLE: Cyclization of glucose (hemiacetal: see CYCLIC FORMS OF SUGARS, page 31) and formation of glycoside (acetal). For glucose, the reaction is intramolecualr: the attacking group is the oxygen on carbon 5 of the same molecule. The second alcohol can be another glucose molecule (glycoside formation) or an external alcohol such as the serine hydroxyl (formation of glycoproteins).



EXAMPLE 1: When there is high blood glucose (aldehyde), as in diabetes, the glucose reacts with amino groups on blood proteins, notably hemoglobin. The resulting imine (which can rearrange to a stable derivative) is called hemoblobin A_{1C}. This derivative is used diagnostically as an indicator of diabetes and to monitor the course of treatment.

EXAMPLE 2: Pyridoxal phosphate reacts with the amino group of amino acids to form imines. These can undergo rearrangement to create a different imine. Hydrolysis (reverse reaction) has the effect of converting the amino acid to a keto acid and leaving the pyridoxamine form of the coenzyme. This, in turn, can react with a keto acid and, by the same sequence, create a new amino acid.



EXAMPLE 1: The aldolase reaction in glycolysis, as you can tell from the name, is an aldol addition reaction. (This is the most common example and maybe the most confusing because of all the extra OH groups that do not take part in the reaction) Aldol additions, like most additions to carbonyls, are reversible and you usually study the reverse reaction first in glycolysis. The forward addition reaction would be in the opposite direction: gluconeogenesis. The carbonyl that is attacked is the aldehyde of glyceraldehyde-3-phosphate. The attacking nucleophile is the alpha carbon adjacent to the keto group of dihydroxyacetone phosphate. The product is fructose-1,6-bisphosphate.

EXAMPLE 2: In the structural protein, collagen, the triple helix of individual strands is stabilized by cross links. The side chain lysyl amino groups are oxidized to aldehyde groups (the resulting amino acid is called allysine). These aldehydes undergo aldol condensation reactions forming a cross-link between two peptide chains. Aldol reaction products still contain a reactive carbonyl group and can undergo another addition reaction with another allysine or with a nitrogen nucleophile such as the side chain of normal lysine or the imidazole group of histidine.

END OF STEP-BY-STEP FROM ORGANIC TO BIOCHEMISTRY