

A Brief Review Of Organic Chemistry

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Abstract

Summer is long. It's been even longer for those who last saw organic chemistry in the Fall semester last year. I don't expect that most students will have much recall of the topics presented in the organic chemistry course. But you did pass that course and that means something; it means that you were able to understand organic chemistry at one point in your career. So you will be able to rebuild your understanding quickly. In the real world you will be expected to make use of the skills that you developed at U.P.E.I. Nobody expects you to remember everything that you learned in university but you will be expected to relearn these skills on your own when they are called for.

Now your organic chemistry skills are called for once again. You will need to review the necessary topics when they are required to better your understanding of the chemistry of biochemistry. To make this a little easier, I wrote this tutorial to provide a very brief and incomplete overview of organic chemistry. Along with your organic chemistry textbook and class notes, this tutorial will help you to use your dormant organic chemistry skills once more.

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1 Introduction

To understand biochemistry you must have a good background in organic chemistry. I realize that most of my students are not chemistry majors but a basic knowledge of organic chemistry is absolutely essential for biochemistry. The more you understand organic chemistry, the easier biochemistry will be.

Organic chemistry is the alphabet of biochemistry. You should work to understand the reactions and processes presented in class and in the textbook from an organic chemistry point of view. Keep your notes from Chem 241/242/243 handy as you study. I advise you to keep your textbook from Chem 241/242/243 close by as well.

All of the topics covered in this document can be found in the relevant section of your organic chemistry textbook.

If you have difficulty with the organic chemistry presented in class please consult this review and the relevant sections your organic chemistry textbook. Understanding the organic chemistry of biochemistry will make the course much more enjoyable.

Please let me know about any errors or sections where the grammar is poor. Most of this tutorial was hastily written in a caffeine-induced haze and typos may be common. Please help me to improve this tutorial.

2 Atomic Connections

2.1 Quantum Nature of Atoms

In the atmosphere of the Sun, there exists so much energy that atoms do not associate with each other. The nuclei of atoms do not even associate with electrons. This mixture of nuclei and electrons is called plasma. At the temperatures and pressures that exist on Earth (as opposed to the center of the Sun), atoms will associate with electrons to satisfy the mutual attraction between opposite charges. Electrons are very light particles and move at such a speed that they behave more like electromagnetic energy (wavelength) rather than particles (velocity and position). Nuclei, being much more massive than electrons, mostly behave like particles.

When electrons are included around a nucleus they must enter into a system where their wavelength fits an even number of times around the nucleus. This is the source of the principal quantum number, n . Depending on n , there may be room for more than one shape to the wave system, e.g. there are 4 ways to arrange an electron orbital at $n = 2$. These shapes give rise to the atomic orbitals described by the angular momentum quantum number, l , which describes s, p and d orbitals, etc. . . and the magnetic quantum number, m , which describes which p or d orbital we are observing. See the next section for more details.

This was an grand oversimplification but it's all that we need to know about quantum numbers for this course.




2.2 Atomic Orbitals

To satisfy the wavelengths of these electrons the electronic structure of atoms comes to involve the quantum energy levels and each electron can be described by the 4 quantum numbers (See Table 1). The first three quantum numbers describe each atomic orbital for the atoms (see Table 2) and the last quantum number describes each of the two electrons that may occupy that orbital. These atoms (a nucleus with its associated electrons) can associate with other atoms in a variety of manners to satisfy mutual repulsions and attractions. Some of these associations are weak (e.g. Van der Waals forces, dipole interactions) and some are strong (e.g. covalent bonds).

Tab. 1: Quantum numbers for describing electrons associated with an atom.

Symbol	Description	Values
n	principle quantum number	$n = 1, 2, 3 \dots$
l	angular momentum quantum no.	$l = 0, 1, \dots, n - 1$
m_l	magnetic quantum number	$m_l = -l, \dots, 0, \dots, l$
m_s	spin quantum number	$m_s = -\frac{1}{2} \text{ or } \frac{1}{2}$

Tab. 2: Some example atomic orbitals.

Quantum Level	Graphical Representation	Quantum Numbers	Example
1s		$n, l, m_l = 1, 0, 0$	hydrogen atom
2s		$n, l, m_l = 2, 0, 0$	the outer s orbital of carbon
2p		$n, l, m_l = 2, 1, (-1, 0, 1)$	the outer p orbitals of carbon

2.3 Covalent Bonds

Neutral carbon, hydrogen, oxygen and other similar atoms are in their most stable arrangement if they can share unpaired electrons with other atoms so that each atom can fill its valence shell. Hydrogen requires 2 electrons in its valence shell. Most other elements we will see prefer 8 electrons in their outer valence shell. Some larger elements, such as phosphorous and sulfur, are perfectly happy with either 8 or 10 electrons in the outer valence shell.

Covalent bonds are the strong interactions between atoms that are sharing electrons to fill their mutual valence shells. An example is methane: A neutral carbon atom with 4 electrons in its outer valence shell can share electrons with 4 neutral hydrogen atoms with one electron each in their outer valence shells. The four electrons from the hydrogen atoms fill up the carbon valence shell to the most stable arrangement of 8 electrons. One electron from carbon is shared with each hydrogen atom and fills the hydrogen atom's valence shell to the preferred 2 electrons (Figure 1).

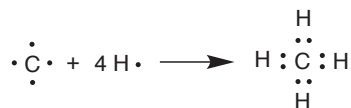


Fig. 1: Lewis structure of methane.

2.4 Ionic Associations

Some elements easily give up or accept an electron to become positively or negatively charged, respectively. Charged elements can form associations due to opposite charge attractions. An example is table salt, NaCl. Sodium easily gives up an electron and chlorine readily accepts an electron and so they are of opposite charge. Salt crystals form from the ionic associations of Na^+ and Cl^- atoms. Electrons are NOT shared in ionic associations; the force between the atoms is due to opposite charge attraction.

2.5 Van der Waals Forces

Ionic atoms can repel or attract each other depending on their mutual charges. Neutral atoms do not repel or attract each other; they are neutral in charge so there is no electromagnetic interaction over medium to large distances. However, when the distance between atoms is small there will be induced dipole interactions. The nucleus of one atom can be electrostatically attracted to the electrons of the other and vice-versa. This attraction is very weak and only becomes important when a neutral molecule of significant size is in Van der

Waals contact with another similar molecule. The weak attractions between all the atoms may be enough to hold the two molecules near each other. This is why hexane can be a liquid. Hexane molecules have no attraction for each other than Van der Waals interactions, however these interactions are enough to hold a collection of these molecules together as a liquid below temperatures of 69 °C.

3 Molecular Structure

3.1 Molecular Orbitals

It is important to realize that molecules are more than balls connected by sticks, they are nuclei of atoms positioned in such a way that a stable electronic structure can form to allow for electron sharing in covalent bonds and the existence of stable non-bonded electron pairs. In a given molecule the atoms and non-bonded electron pairs will arrange themselves to be as far apart as possible while maintaining a distance such that electron pairing can occur. This idea that atoms will position themselves thus is called the valence shell electron repulsion theory (VSEPR). The atomic orbitals of the individual atoms that are sharing electrons will combine into molecular orbitals that define the electron configuration the bond between the two atoms involved.

3.1.1 σ Bonds

When two orbitals overlap to form a single bond, they will overlap in the most stable form possible. This is almost always to orient them along an axis of infinite rotation (you can rotate the orbital any amount, large or small, and you wouldn't know that you had done so). The combined atomic orbital will form a new molecular orbital. Two orbitals CANNOT occupy the same space at the same time. But they can combine into a new pair of molecular orbitals and will do so if the new molecular orbital system is lower in energy than the original two atomic orbitals. This new molecular orbital will also have infinite rotational symmetry and is designated a σ bond because of that symmetry.

3.1.2 π Bonds

Often two atoms joined by a σ bond will have p-orbitals available for overlap to form a second or a third bond between the atoms. p-Orbitals have two-fold symmetry (they can be rotated 180° and you wouldn't know it) and the molecular orbital formed by their overlap will also have two-fold symmetry and is designated a π bond because of that symmetry.

3.2 Hybrid Orbitals

3.2.1 sp_3

In order to explain the σ bond system of atoms it is convenient to invoke fictional hybrid orbitals. Methane has 4 hydrogen atoms bonded to a central carbon atom; they are spaced in a tetrahedral arrangement 104° apart in agreement with the VSEPR theory. We need 4 carbon atomic orbitals to overlap individually with 4 hydrogen atomic orbitals to construct the 4 single bonds of methane. Carbon has a 2s and three 2p orbitals in its valence shell. These four orbitals could each be overlapped with a 1s orbital from each hydrogen atom but that would not explain the geometry of methane. Each p-orbital is 90° from the other, not 104° as is observed in methane. In reality, the hydrogen atoms spread out around the carbon to maximize the distance between them and each will overlap with a part of each of the 2s and the three 2p atomic orbitals of the carbon atom depending on how close each hydrogen atom is to each carbon atomic orbital. It is as if the 2s and three 2p atomic orbitals are combined to form 4 new sp_3 atomic orbitals spaced 104° from each other. Basically, when we say a carbon is tetrahedral we also can say is a sp_3 carbon.

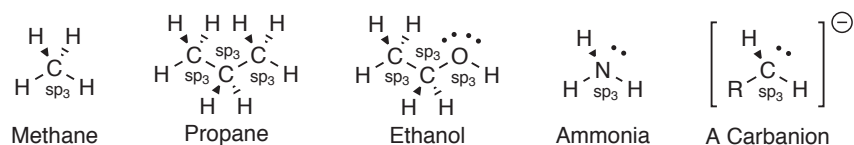


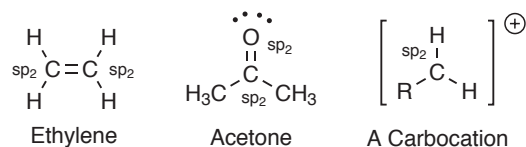
Fig. 2: Tetrahedral sp_3 hybridized carbon atoms.

3.2.2 sp_2

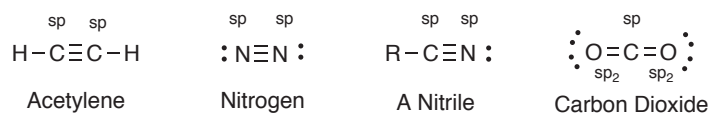
Similarly, a carbon with three substituents will adopt a trigonal planar arrangement and three atomic orbitals are needed to establish the 3 hybrid atomic orbitals that define the σ bond system. The 2s and 2 2p atomic orbitals of the carbon atom will be mathematically combined to create the three fictional sp_2 orbitals. There will be a spare 2p atomic orbital left over orthogonal to the plane of the 3 sp_2 orbitals. It can overlap with another p orbital of an adjacent atom to create a π bond. sp_2 hybridized carbons often are observed with two single (σ bonds) and a double bond (σ bond + π bond). When a carbon is trigonal planar we can say it is a sp_2 carbon.

3.2.3 sp

Also, sp hybridized carbons are invoked to describe the σ bond system of a carbon with two substituents. According to VSEPR theory, the two substituents

Fig. 3: Trigonal planar sp^2 hybridized carbon atoms.

will be on opposite sides of the carbon atom to form a linear system. Two sp hybrid atomic orbitals are formed from the mathematical combination of a $2s$ and a $2p$ atomic orbital of a carbon atom. This leaves two non-hybridized $2p$ atomic orbitals on the carbon atom that can overlap with p orbitals in the adjacent atoms and form two π bonds. This may result in a triple bond (σ bond + 2 π bonds) to one substituent and a single bond to the other or double bonds (σ bond + π bond) to both substituents. When a carbon is part of a linear system we can say that it is a sp carbon.

Fig. 4: Linear sp hybridized carbon atoms.

3.3 Summary

In a nutshell, hybrid orbitals are used to describe the geometry of a system. They are fictional mathematical combinations of actual atomic orbitals that result in combine atomic orbitals that fit the σ -bond network of the molecule.

- SP_3 hybrid orbitals are tetrahedral systems that have 4 σ -bonds and/or lone pairs that are arranged about 104° from each other.
- SP_2 hybrid orbitals are planar systems with 3 σ -bonds and/or lone pairs that are arranged about 120° from each other. An unused p -orbital is perpendicular to the plane and can be involved in a π -bond to an adjacent atom.
- SP hybrid orbitals are linear systems with 2 σ -bonds and/or lone pairs that are arranged about 180° from each other. Two unused p -orbitals are perpendicular to the line and each other and can be involved in π -bonds to an adjacent atom or atoms.

3.4 Questions

Discuss the following questions with your classmates. Try to agree on your answer.

1. Identify the hybridization of each non-hydrogen atom in the following molecules:
 - (a) The acetyl group of acetyl-CoA
 - (b) Palmitic acid
 - (c) Glucose
 - (d) Adenine (remember, the NH_2 group is coplanar with the ring)
 - (e) Oxidation and Reduction

In organic molecules, when we add or remove substituents, we may often add or remove electrons with these groups. Changing the number of electrons in a molecule or part of a molecule will alter the oxidation level of that molecule or group. Oxidation/reduction as it relates to carbon groups is often described in terms of adding or removing hydrogen atoms. It is more correct to think of adding or removing electrons. Remember, the hydrogen atoms have electrons. Removing a pair of hydrogen atoms will also remove a pair of electrons.

4 Oxidation and Reduction

In organic molecules, when we add or remove substituents, we may often add or remove electrons with these groups. Changing the number of electrons in a molecule or part of a molecule will alter the oxidation level of that molecule or group. Oxidation/reduction as it relates to carbon groups is often described in terms of adding or removing hydrogen atoms. It is more correct to think of adding or removing electrons. Remember, the hydrogen atoms have electrons. Removing a pair of hydrogen atoms will also remove a pair of electrons.

4.1 Oxidation States

The oxidation state of a carbon center can be described by adding up the electrons it controls. Substituents with the same electronegativity as carbon (like another carbon) do not result in a carbon owning any more electrons and so count as “0” in calculating the oxidation state. Substituents that are less electronegative than carbon, such as hydrogen, result in the carbon owning an extra electron and so count as “-1” (electrons are negative). Substituents that are more electronegative than carbon, like oxygen, nitrogen or halogens, will result in the carbon owning one less electron per bond to the substituent and so count as “+1”.

For example:

- Methane: 4 hydrogen substituents ($4 \times (-1) = -4$), oxidation state = -4
- 1-Carbon of propane (at end): 3 hydrogen substituents ($3 \times (-1) = -3$), 1 carbon substituent (0), oxidation state = -3
- 2-Carbon of propane (centre carbon): 2 hydrogen substituents ($2 \times (-1) = -2$), 2 carbon substituents (2×0), oxidation state = -2
- Acetylene carbon: 2 hydrogen substituents ($2 \times (-1) = -2$), 2 bonds to a carbon substituent (2×0), oxidation state = -2
- Acetone carbonyl carbon (a ketone): 2 carbon substituents (2×0), 2 bonds to oxygen substituent ($2 \times (+1) = +2$), oxidation state = $+2$
- Carbon dioxide: 2 bonds each to 2 oxygen groups ($2 \times 2 \times (+1) = +4$), oxidation state = $+4$

Adding electrons to a carbon (moving toward a more negative oxidation state) is reduction (adding electrons is often analogous to adding hydrogen atoms). Remember that the electrons came from somewhere so another molecule or group of a molecule must donate those electrons and end up with fewer electrons. When a molecule gives up electrons it is being oxidized. We will see more of oxidation and reduction in functional group transformations.

4.2 Questions

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 - (d) Adenine

5 Functional Groups

Your basic organic molecule might be a saturated carbon chain like propane. Such fully reduced carbon chains are difficult to alter chemically. In biological molecules we will have substituents on the carbon chains that impart functional chemistry and can be altered by chemical processes to produce energy or operate biochemical machinery. These functional groups are generally easier to

alter than non-functionalized carbon chains and act as “handles” where most biological chemical transformations can take place. Having said that there are numerous cases where non-functionalized aliphatic carbon chains are altered by biological systems, a feat that is difficult even in our own chemical laboratories.

For more information on the nomenclature and structure of functional groups see your organic chemistry textbook.

5.1 Unsaturated bonds

A saturated carbon chain has only single bonds between carbons and hydrogen atoms on each carbon so that there is a total of 4 bonds (all sp^3 carbons). If we dehydrogenate the carbon chain we remove 2 hydrogen atoms, usually as a proton and a hydride (a proton and 2 electrons). We now have a double bond and each carbon has a higher oxidation state (from -2 to -1 for each carbon for carbons internal to the chain). Compounds that contain a carbon-carbon double bond are called alkenes.

See your organic chemistry textbook for more information on alkenes

Further dehydrogenation would result in a triple bond and the carbons now have an oxidation state of 0 (assuming the triple bond is internal to the chain). Such compounds are called alkynes.

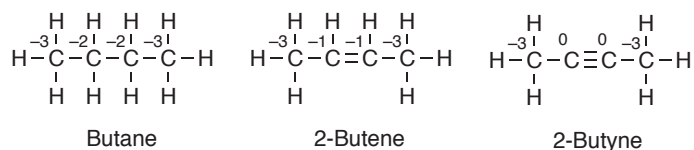


Fig. 5: Saturated and unsaturated hydrocarbons with carbon oxidation states indicated.

5.2 Oxygen groups

5.2.1 Alcohols

Perhaps the most familiar functional group is the alcohol group, a hydroxyl connected to a carbon by a single bond (carbon oxidation state is noted below for each type of alcohol)

See your organic textbook for more information on alcohols

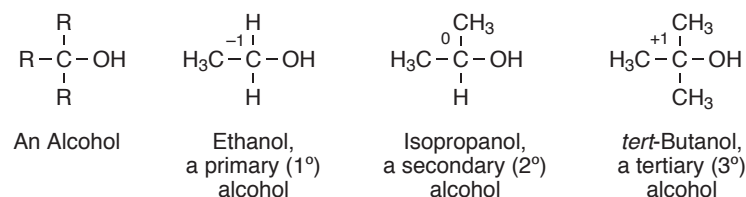


Fig. 6: Some alcohols with carbon oxidation states indicated.

5.2.2 Aldehydes

Dehydrogenating a primary alcohol will give an aldehyde, a carbon group with two bonds to an oxygen atom and a single bond to a hydrogen atom (carbon oxidation state is generally -1)

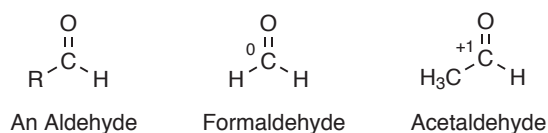


Fig. 7: Some aldehydes with carbon oxidation states indicated.

See your organic chemistry textbook for more information on aldehydes.

5.2.3 Carboxylic Acids

A carbon with a double bond to an oxygen atom and a single bond to a hydroxyl group is a carboxylic acid (carbon oxidation state is generally +3).

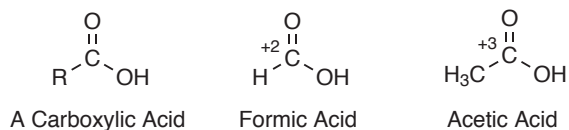


Fig. 8: Some carboxylic acids with carbon oxidation states indicated.

5.2.4 Ketones

Dehydrogenating a secondary alcohol will give a ketone, a carbon with 2 bonds to an oxygen atom and no hydrogen groups (carbon oxidation state is +2).

See your organic chemistry textbook for more information on aldehydes and ketones

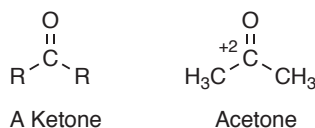


Fig. 9: Some ketones with carbon oxidation states indicated.

Other important oxygen groups found in biological molecules are listed below with the oxidation state of the carbon indicated.

5.2.5 Esters

Esters can be considered to be the product of a condensation of an alcohol with a carboxylic acid.

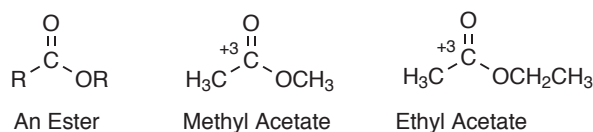


Fig. 10: Some esters with carbon oxidation states indicated.

See your organic chemistry textbook for more information on esters.

5.2.6 Ethers

can be considered to be the product of a condensation of an alcohol with another alcohol.

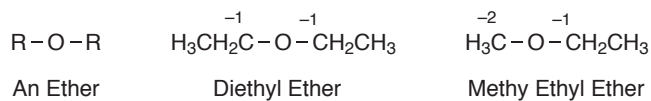


Fig. 11: Some ethers with carbon oxidation states indicated.

5.2.7 Hemiacetals

The result of an alcohol oxygen atom adding to the carbon atom of an aldehyde group. The reaction is easily reversed to give the original alcohol and aldehyde.

See your organic chemistry textbook for more information on hemiacetals and hemiketals

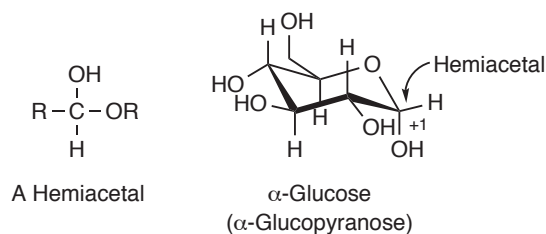


Fig. 12: A hemiacetal with the hemiacetal carbon oxidation state indicated.

5.2.8 Acetals

Can be thought of as a hemiacetal where the free hydroxyl group has been alkylated with a carbon group. Acetals have a carbon group on the hydroxyl (this is an ether linkage) and hemiacetals have a hydrogen atom on the hydroxyl (think of H is for “hemi”).

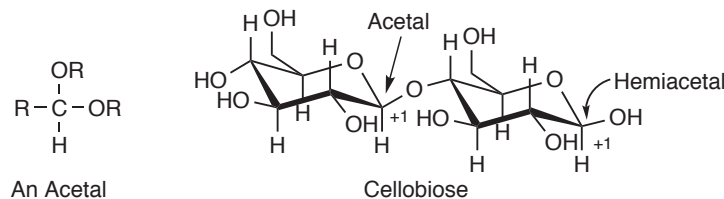


Fig. 13: An acetal with the acetal carbon oxidation state indicated.

See your organic chemistry textbook for more information on acetals and ketals

5.3 Nitrogen Groups

5.3.1 Amines

A nitrogen atom with single bonds to carbons or hydrogen atoms is an amine. As in the case of alcohols, the number of carbon substituents determines if the amine is primary, secondary or tertiary.

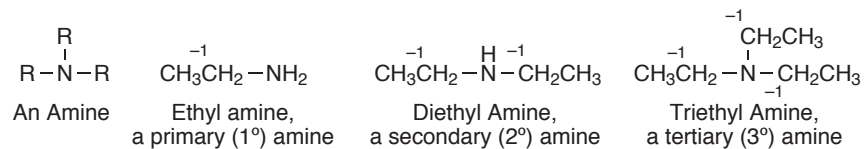


Fig. 14: Amines with the carbon oxidation states indicated.

See your organic chemistry textbook for more information on amines.

5.3.2 Imines

If we dehydrogenate a primary or secondary amine we can get an imine or Schiff base, which is a nitrogen with a double bond to a carbon.

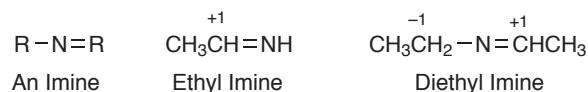


Fig. 15: Imines with carbon oxidation states indicated.

See your organic chemistry textbook for more information on imines.

Imines can be easily hydrated to give a hemiaminal. Hemiaminals can be easily dehydrated to give imines.

A hemiaminal is also easily formed from the addition of an amine to a carbonyl group of a ketone or aldehyde. So we can see that addition of an amine to an aldehyde followed by dehydration (both easy, reversible reactions in water) can lead to the formation of an imine. THIS IS ONE OF THE MOST IMPORTANT REACTIONS IN BIOCHEMISTRY! You will see this reaction many, many times in Chemistry 353.

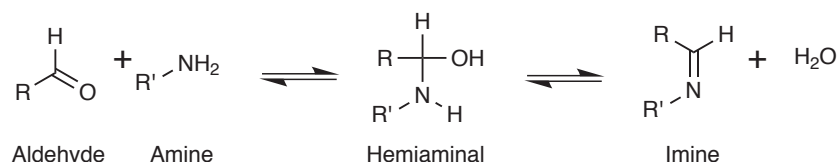


Fig. 16: Formation of hemiaminals and imines from an aldehyde or group and an amine group.

See your organic chemistry textbook for more information on imine formation from aldehydes and ketones.

5.3.3 Amides

A carbon atom with a double bond to an oxygen atom and a single bond to an amine is an amide. The carbon atom and oxygen atoms are sp_2 hybridized, as expected. The nitrogen might be expected to be sp_3 hybridized as it has three groups attached plus a non-bonded electron pair for a total of 4 groups (which would prefer to be tetrahedral according to VSEPR theory). However, it is more stable to have the lone pair in a p-orbital parallel to the p-orbitals of the carbon and oxygen so that they can be stabilized by overlapping with the p-orbitals in the π -bond between the C and the O. Because the p-orbital is overlapping with the π -bond it is not available to contribute to the hybrid atomic orbitals and

the result is a sp^2 hybridized nitrogen atom and the C-atom, the O-atom and the N-atom and its substituents will all be in the same plane.

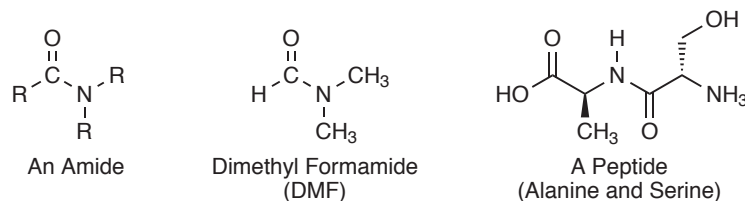


Fig. 17: Amides.

We will see that amide groups are often called peptide bonds or peptide linkages when they occur between two amino acids.

See your organic chemistry textbook for more information on amides.

5.3.4 Guanidine

A SP^2 carbon with three nitrogen substituents is a guanidine group (not to be confused with the guanine nitrogenous base of DNA and RNA). If the group is protonated it will be able to share the positive charge among all three nitrogen groups to create the stable guanidinium cation.

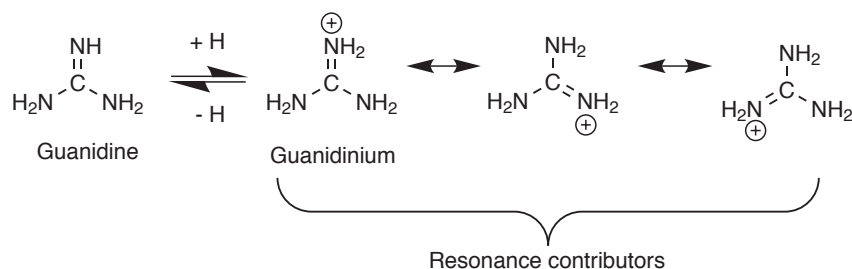


Fig. 18: Guanidine and guanidinium

The pK_a of the cationic, acidic form of guanidine is 13.7 (12.5 in arginine) indicating that guanidine group will always be in its positively charged, acidic, protonated form in any living cell.

5.4 Aromatic Compounds

Cyclic conjugated compounds may be aromatic if the π -bond system in the ring contains 2,6 or 10 electrons ($2n + 2$ rule, $n = 0, 1, 2, \dots$). Benzene is the most famous aromatic system. Benzene rings are often called phenyl rings

when they are part of another molecule. All atoms in an aromatic system are sp_2 hybridized and the system is planar.

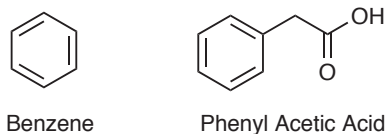


Fig. 19: Examples of compounds with phenyl rings.

See your organic chemistry textbook for more information on aromatic compounds.

5.5 Heterocycles

Some important heterocyclic compounds are present in one form or another in biochemistry. Cyclic forms of sugars can be described as having a hydrated furan or pyran skeleton. Nucleotide bases like uridine and cytidine are derivatives of pyrimidine and guanine and adenine are derivatives of purine.

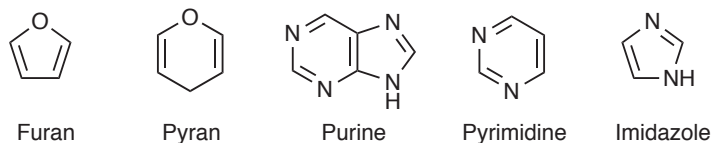


Fig. 20: Examples of heterocyclic compounds.

See your organic chemistry textbook for more information on heterocyclic compounds.

5.6 Questions

Discuss the following questions with your classmates. Try to agree on your answer.

1. Identify the functional groups in the following molecules:
 - (a) The acetyl group of acetyl-CoA
 - (b) Palmitic acid
 - (c) Glucose
 - (d) Adenine
 - (e) Cytosine

- (f) Histidine
- (g) Arginine
- (h) Cysteine
- (i) Serine
- (j) Phenylalanine
- (k) Tyrosine

6 Molecular Structures II

6.1 Structural Representations

Usually, I will present molecules using stick notation for the carbon skeleton and any non-carbon atoms other than hydrogen. Hydrogen atoms will only be shown if they are connected to non-carbon atoms or are necessary to make a point. Carbon atoms should be assumed to have the correct number of hydrogen atoms.

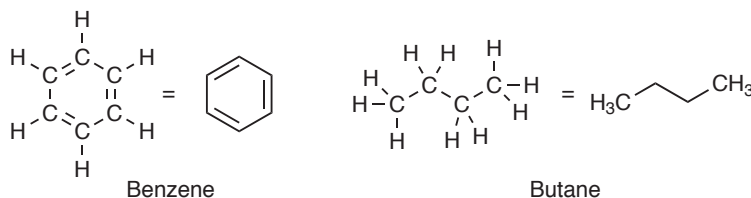


Fig. 21: Graphical structural representations of organic molecules.

6.2 Stereochemistry

Organic molecules that contain one or more sp^3 (tetrahedral) carbons will have a three dimensional structure. Three-dimensional structure around a carbon can be indicated by “wedges” that indicate if a substituent is in front of the carbon (solid wedge) or behind (dotted wedge) relative to the observer.

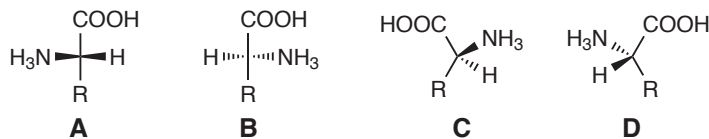


Fig. 22: 3-Dimensional graphical structural representations of an organic molecule.

Structure A, above, obviously has the amine group and the hydrogen atom in front of the carbon atom. Since carbon is tetrahedral with 4 groups (sp^3 hybridized), the carboxylic acid group and the substituent (R group can be any group) are behind. Structure B is the same compound rotated 180° and we are choosing to indicate the amine group and the hydrogen atom behind the carbon atom and the carboxylic acid group and the substituent (R group can be any group) are therefore in front. Structures C and D are also the same molecule as A.

6.3 Chiral Molecules

The above structure A is obviously an amino acid and like most amino acids it has 4 different substituents around a carbon atom. This carbon atom is thus asymmetrical – there is no symmetry operation that one can perform (e.g.: rotation; mirror reflection; improper rotation) that would result in a redundant structure. A carbon atom that is asymmetrically substituted is called a chiral carbon or a chiral centre. A molecule with one or more chiral carbon atoms is a chiral molecule (that statement is not always true, but I won't get into the exceptions now).

As a result of containing an asymmetric carbon, a chiral molecule is also asymmetric. Chiral molecules have no symmetry operations that would result in a redundant structure. Another way to say this is to state that there is no way to superimpose the mirror image of a chiral molecule on top of the original molecule.

There are two possible configurations for a chiral center; each is a mirror image of the other. These two possibilities are termed enantiomers. Structure A and B below may look identical but look closely. Structure B is the mirror image of structure A. It cannot be rotated to be superimposed upon A.

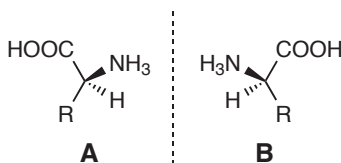


Fig. 23: Two enantiomers of an amino acid.

See your organic chemistry textbook for more on chiral compounds

6.4 Questions

Discuss the following questions with your classmates. Try to agree on your answer.

1. Draw the 3-dimensional representations (wedges and dashed lines) for the following molecules:
 - (a) Alanine
 - (b) Isoleucine
 - (c) D-Ribose
 - (d) α -D-Ribofuranose

7 Acids and Bases

See your organic chemistry textbook for more information on acids and bases. Most freshman and high school chemistry textbooks contain discussions on acid/base equilibria as well. This is a very, very important topic in biochemistry.

7.1 Definitions

The Brönsted definition of acids and bases is that acids are compounds that can donate a proton to a base and a base is a compound that can accept a proton from an acid. This definition of acids and bases is adequate for the understanding of biochemistry.

An acid cannot be an acid unless there is a base onto which to donate the proton. Let us consider a carboxylic acid group in a molecule and an amine group in another molecule. If they encounter each other the proton will likely be donated to the amine as amine groups have a high affinity for protons and carboxylic acids only have a moderate affinity for protons.



Fig. 24: Exchange of an acid proton between a carboxylic acid and a basic amine.

7.2 Water

Water is both an acid and a base (Figure 25 on the next page). H_2O can donate a proton to another H_2O to give a hydroxide ion (HO^-) and a hydronium ion (H_3O^+). In pure water at 25°C the concentration of hydroxide and hydronium is 10^{-7} moles/L.

For the conventions of biochemistry, we will almost always write the dissociation of water as H_2O “splitting” into hydroxide and free proton (Figure 26 on the following page). Free proton will NEVER exist in water. Protons will only ever



Fig. 25: Acid equilibrium of water.

be transferred from an acid to a base in water (and water may be the acid, the base, or in this case both). This convention is used because of historical reasons (before the hydronium ion was thought to exist).



Fig. 26: Acid dissociation of water.

The equilibrium constant for this equilibrium is $10^{-15.7}$.

$$K_{eq} = \frac{[\text{OH}^-][\text{H}^+]}{[\text{H}_2\text{O}]} \quad (1)$$

$$K_{eq} = \frac{10^{-7} M \cdot 10^{-7} M}{55.6 M} = 10^{-15.7} M \quad (2)$$

Note: The concentration of water in pure water is $(1000 \text{ g/L}) / (18 \text{ g/mole}) = 55.6 \text{ mole/L}$.

Other acids dissolved in water can donate their proton onto water, which would be the base. Water, acting as an acid, can donate a proton to a base.

7.3 Conjugate Acids and Bases

Anything that has a proton that can be donated can be an acid, anything that can accept a proton can be a base. When an acid donates its proton it is now a molecule that can accept a proton back, so it is now a base. The base that results when a proton is removed from an acid is the conjugate base of that acid. The acid that results when a base accepts a proton is the conjugate acid of that base.

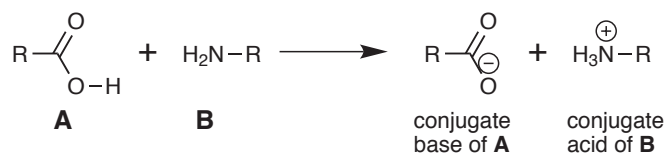


Fig. 27: Conjugate acid and base.

7.4 Strong Acids and Bases

Some acids will dissociate completely in water. Hydrochloric acid (HCl) is an example. HCl will donate its proton to water and the concentration of hydronium ion will be the same as the concentration of HCl added. This is a strong acid. Any acid that dissociates completely in water is a strong acid. The concentration of hydronium can be assumed to be the concentration of acid added (unless there is another base present as well).

Some basic compounds will accept as much proton from water as there is base added resulting in a hydroxide ion concentration equal to the concentration of base added. These are strong bases. A good example is sodium hydroxide (NaOH), which dissociates completely to sodium ion and hydroxide ion in water.

7.5 pH

If a solution of 10 millimolar (mM) of hydrochloric acid is created, the concentration of acid proton (hydronium ion in water) will be also 10 mM as HCl completely dissociates in water. So the concentration of acid is 0.01 M or 10^{-2} M. To simplify description of acid proton concentration in water, we invoke the p function.

$$p(x) = -\log(x)$$

So $p(10^{-2})$ is $-\log(10^{-2})$ which is equal to 2.

$p[H]$ is written as pH. The $-\log$ of acid proton concentration in water is pH. From pH we can quickly know the concentration of acid proton (hydronium ion) and the concentration of hydroxide ion. Obviously, if the pH is 4 then the concentration of acid proton is 10^{-4} M. We also know the concentration of hydroxide ion because we know the acid dissociation constant for the dissociation of water to be $10^{-15.7}$.

For the dissociation of water we have the reaction described in Figure 26 on the previous page. The equilibrium constant for that reaction is stated in equation 1. For acid dissociation we will refer to the equilibrium constant for acid dissociation as K_a instead of K_{eq} .

So the acid dissociation constant, K_a , is given by the equilibrium equation:

$$K_a = \frac{[^-OH][H^+]}{[H_2O]} \quad (3)$$

The concentration of water in dilute solutions does not change significantly with changes in pH. So $[H_2O]$ can be treated as a constant and combined with the acid dissociation constant, K_a , to create a new term called K_w .

$$K_w = K_a \cdot [H_2O] = [^-OH][H^+] \quad (4)$$

K_w is the equilibrium constant for the dissociation of water multiplied by the concentration of water, which is considered to be constant. We will use the concentration of water in pure water, 55.6 M.

$$K_w = 10^{-15.7} M^{-1} \cdot 55.6 M = 10^{-14} \quad (5)$$

So

$$K_w = 10^{-14} = [OH^-] [H^+] \quad (6)$$

Applying the p function we get

$$pK_w = 14 = pOH + pH \quad (7)$$

So if the pH is 2 then the pOH must be 12 so $[OH^-] = 10^{-2}$. Obviously, the lower the pH value, the more acidic the water and the higher the pH value, the more basic the water. In biochemistry we will use the pH scale only.

7.6 Weak Acids and Bases

Strong acids dissociate completely (this is a simplified view) and there is no equilibrium between the acid and the water onto which it is transferring the proton. A weak acid is an acid that is not strong enough to push all of its acid protons onto water molecules but establishes an equilibrium with water in which it is only partially dissociated.

Let us use acetic acid (AcOH) as an example. In water, AcOH will be in acid equilibrium with water...



Fig. 28: Acid-base equilibrium between acetic acid and water

The equilibrium constant is given by

$$K_{eq} = \frac{[\text{AcO}^-] \cdot [\text{H}_3\text{O}^+]}{[\text{AcOH}] \cdot [\text{H}_2\text{O}]} \quad (8)$$

As before, in dilute solution the concentration of water is considered to be constant and can be ignored in the equilibrium equation, which can be rewritten as...



Fig. 29: Acid dissociation of acetic acid

This equilibrium is the acid equilibrium (ignoring water). We use a new equilibrium constant to describe the above equilibrium; this is the acid dissociation constant, K_a . As in the case of K_w , K_a is the equilibrium constant multiplied by the concentration of water, which is constant.

$$K_a = K_{eq} \cdot [H_2O] \quad (9)$$

So substituting eq. 8 on the preceding page into eq. 9 (remember, $[H^+]$ and $[H_3O^+]$ are the same thing) gives eq. 10

$$K_a = \frac{[AcO^-] \cdot [H^+]}{[AcOH]} \quad (10)$$

which is the equilibrium constant equation for Figure 29 on the previous page.

For a general equation we can say that an acid (AH) dissociates to its conjugate base (A) and an acid proton (H) as outlined in Figure 30 (charges ignored for simplicity).



Fig. 30: A generic scheme for acid dissociation

The acid equilibrium (in water) for the generic acid dissociation scheme is described in eq. 11

$$K_a = \frac{[A] \cdot [H]}{[AH]} \quad (11)$$

The larger the K_a value, the stronger the acid. We can simplify comparisons of K_a values by applying the p function. The acid dissociation constants for acids are usually presented as a pK_a value. We can apply the p function to eq. 11 to get the famous Hendersson-Hasselbach equation.

$$pK_a = pH - \log \frac{[A]}{[AH]} \quad (12)$$

Inspection of the HH equation reveals that if one arranges the pH of a solution of acid to be the same value as the pK_a , then half of the acid will be dissociated. A lower pK_a value indicates a stronger acid (more acid proton concentration needed to ensure 50% is protonated).

We can use pK_a values to discuss bases as well. The pK_a is the p function of the acid dissociation constant for the conjugate acid of the base. So we start with the protonated base and write the reaction equation for dissociation of the protonated base (conjugate acid of the base)

The larger the pK_a value, the stronger the base. We would expect that the acid dissociation constant, K_a , for the conjugate acid of a base would be small



Fig. 31: A base is an acid when it has accepted a proton

(basic compounds hold onto protons more strongly than acidic compounds) and so pK_a values for bases would be larger than for acids.

Remember, pK_a values represent how easily a protonated compound donates the proton to water (the acid is in equilibrium with water, which is the base in this equilibrium). Low values indicate a compound that readily donates protons to water. High values indicate a compound that will not easily donate protons to water.

7.7 Review.

pK_a values, as used in biochemistry (and most chemical fields) refer to acid equilibrium in water. A protonated acid donates a proton to water to create the deprotonated conjugate base of the acid and a hydronium ion (recall Fig. 28 on page 22 for an example). The acid equilibrium contains a term for the concentration of water (recall eq. 8 on page 22). In the case of dilute solutions we can say that the concentration of water is a constant and ignore it in the acid dissociation equation (recall Fig. 29 on page 22). The acid dissociation equation represents the acid molecule giving up its proton in a water molecule but we do not have water in the equation because its concentration does not change. The acid dissociation constant equation, eq. 10 on the preceding page, is eq. 8 rearranged so that K_{eq} and $[\text{H}_2\text{O}]$ are combined to create the new acid dissociation constant, K_a . (recall eq. 9).

7.8 pK_a of Water and Hydronium Ion

Hydronium ion is the strongest acid that can exist in significant concentrations in water. Acids stronger than hydronium will donate most of their protons to water to make hydronium ion in the same concentration as acid originally added. Hydronium ion is an acid (it has a proton it can donate to a base) and can donate a proton to a water molecule (the water is the base in this case).

The acid dissociation for hydronium ion is shown in Figure 32.



Fig. 32: Acid dissociation of the hydronium ion

And the acid dissociation constant equation is

$$K_a = \frac{[H_2O] \cdot [H^+]}{[H_3O^+]} \quad (13)$$

The K_a for hydronium ion is measured to be 101.7 (at 25 °C) The large value indicates that it is a strong acid. The pK_a is -1.7. The low value of the pK_a indicates that it is a strong acid.

Water can act as an acid and donate a proton to another water giving hydronium ion and hydroxide ion. This is the acid dissociation of water as discussed above (see Figure 27 and 3 on page 21). The expression for K_a of water (eq. 3) is reproduced below.

The K_a for water is measured to be 10^{-15.7} (at 25 °C) The large value indicates that it is a very, very weak acid (The pK_a is 15.7). The high value of the pK_a indicates that it is a very, very weak acid. Conversely, the conjugate base of water, hydroxide ion, is a strong base. Hydroxide ion is the strongest base that can exist in water at a significant concentration. Stronger bases (bases whose conjugate acid has a larger pK_a value) will accept the protons from water to make as much hydroxide ion as base originally added.

7.9 pK_a Values of Weak Acids and Bases

Acids with a pK_a value of less than -1.7 are considered to be strong acids. If the conjugate acid of a base has a pK_a value greater than 15.7 it is considered to be a strong base. Weak acids and bases have pK_a values between these two extremes.

We can use the famous Hendersson-Hasselbach equation (eq. 12 on page 23) to calculate the percent of an acid (or base) that is in its acidic form (protonated) and its basic form (deprotonated).

Example 1. If we have a cell whose internal pH is measured to be 6.5, what is the percent of methylamine in its basic form in these conditions?

The pK_a of methylamine is known to be 10.7 (see Table 3 on the following page). We know the pH and we need to know the $[A]/[AH]$ ratio to calculate the percentage of methylamine in its basic form (this would be the conjugate base, A, of the acid, AH, in the Hendersson-Hasselbach equation)

Tab. 3: pK_a values for selected acids and bases.

Acid	pK_a
HI	-10.
HCl	-7.
H_3O^+	-1.7
H_3PO_4	2.1
CH_3COOH	4.8
$H_2PO_4^-$	-7.2
NH_4^+	9.4
$CH_3NH_3^+$	10.7
HPO_4^{2-}	12.3
CH_3OH	15.5
H_2O	15.7
NH_3	36.
CH_3NH_2	40.
CH_4	50.

So lets put in the values we know...

$$\begin{aligned}pK_a &= pH - \log \frac{[A]}{[AH]} \\10.7 &= 6.5 - \log \frac{[A]}{[AH]} \\-4.2 &= \log \frac{[A]}{[AH]} \\\frac{[A]}{[AH]} &= 10^{-4.2} = 6.3 \times 10^{-5}\end{aligned}$$

We can convert the $[A]/[HA]$ ration to %A using the formula for converting a fraction to a percent. If the ratio is a value, x, the percent of the numerator is given by...

$$\%numerator = 100\% \times \left(\frac{x}{x+1} \right)$$

and the percent of the denominator is given by

$$\%denominator = 100\% \times \left(\frac{1}{x+1} \right)$$

So the % of the A form (the basic form) is 0.0063%. Obviously almost all of the methylamine is in its positively charged acidic form (99.994%) at that pH value.

Example 2. What if the pH of a solution of methylamine is arranged to be 10.7? What is the percent in its basic form under that condition?

Note that in this case the pH value is identical to the pK_a of the protonated methylamine. Lets do the math...

$$\begin{aligned}pK_a &= pH - \log \frac{[A]}{[AH]} \\10.7 &= 10.7 - \log \frac{[A]}{[AH]} \\0 &= \log \frac{[A]}{[AH]} \\\frac{[A]}{[AH]} &= 10^0 = 1\end{aligned}$$

If the $[A]/[HA]$ ratio is 1 then we obviously have 50% in the basic form. Observe that when the pH of a solution is the same as the pK_a of an acid, the acid will be 50% deprotonated. As you can see in table 4.

Tab. 4: Percent deprotonation for protonated methylamine ($pK_a = 10.7$) in water at various pH values.

pH	% Deprotonated
7.7	0.10
8.7	1.0
9.7	9.1
10.7	50.0
11.7	90.9
12.7	99.0
13.7	99.9

Note the trends. When we are at a more basic pH value than the pK_a of the acid we have mostly the basic, deprotonated form (conjugate base of the acid). When we are at a more acidic pH value than the pK_a of the acid we have mostly the acidic, protonated form.

7.10 Questions

Discuss the following questions with your classmates. Try to agree on your answer.

1. What is the basic form of the following compounds? Draw out the molecule and include any charges.
 - (a) Acetic acid
 - (b) Methylamine
 - (c) Ethanol
 - (d) Histidine (The imidazole group on the sides chain)
2. The side chain group of glutamic acid has a pK_a value of 4.3. At what pH value will this group be 90% in its basic form?
3. We are titrating the side chain group of histidine and find that it is 50% in its acidic form at pH 6.0. What is the pK_a of the side chain group?
4. A given enzyme is known to require that an aspartic acid residue in the active site be in its basic form for activity. The activity of the enzyme is directly proportional to the percent of active sites containing basic aspartate. If this is the only factor that affects activity, what will the change in rate be between pH 7 and pH 8? Between pH 4 and pH 5?

8 Other Topics of Interest

8.1 Dipole Moments.

See your organic chemistry textbook for more information on dipole moments

8.2 Sugar Structure

See your organic chemistry textbook for more information on cycloalkane conformation as it relates to sugar structure.

9 Errors

This document was written in haste and I take sole responsibility for all errors within. It is likely that there are many small mistakes and maybe some major ones. If you find an error, please inform me so that the next version can be corrected.

Document Notes

This document was typeset using the L^AT_EX typesetting system. The L^YX document processor was used to generate the L^AT_EX code. See “Tutorial 26: Introducing L^AT_EX” for more information on obtaining and using L^YX and L^AT_EX. Chemical structures were created using ChemDraw 11.0 and exported to EPS files for inclusion in the document.

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