OIT (LUND): ORGANIC CHEMISTRY WITH A BIOLOGICAL EMPHASIS (SODERBERG)



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OIT (Lund): Organic Chemistry with a Biological Emphasis (Soderberg)

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CHAPTER OVERVIEW

1: Introduction to Organic Structure and Bonding I

In this chapter, you will be introduced to some of the most fundamental principles of organic chemistry. With the concepts we learn about, we can begin to understand how carbon and a very small number of other elements in the periodic table can combine in predictable ways to produce a virtually limitless chemical repertoire. As you read through, you will recognize that the chapter contains a lot of review of topics you have probably learned already in an introductory chemistry course, but there will likely also be a few concepts that are new to you, as well as some topics which are already familiar to you but covered at a greater depth and with more of an emphasis on biologically relevant organic compounds.

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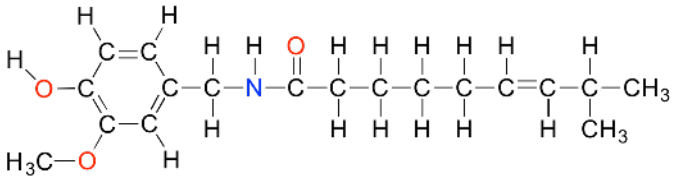
1.0: Prelude to Atoms, Electron Configurations, and Lewis Structures

It's a hot August evening at a park in the middle of North Hudson, Wisconsin, a village of just under 4000 people on the St. Croix river in the western edge of the state. A line of people are seated at tables set up inside a canvas tent. In front of a cheering crowd of friends, family, and neighbors, these brave souls are about to do battle . . .with a fruit plate.



Unfortunately for the contestants, the fruit in question is the habanero, one of the hotter varieties of chili pepper commonly found in markets in North America. In this particular event, teams of five people will race to be the first to eat a full pound of peppers. As the eating begins, all seems well at first. Within thirty seconds, though, what begins to happen is completely predictable and understandable to anyone who has ever mistakenly poured a little to much hot sauce on the dinner plate. Faces turn red, sweat and tears begin to flow, and a copious amount of cold water is gulped down.

Although technically the contestants are competing against each other, the real opponent in this contest - the cause of all the pain and suffering - is the chemical compound 'capsaicin', the source of the heat in hot chili peppers.

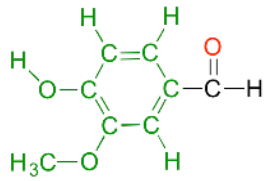


capsaicin

Composed of the four elements carbon, hydrogen, oxygen and nitrogen, capsaicin is produced by the pepper plant for the purpose of warding off hungry mammals. The molecule binds to and activates a mammalian receptor protein called TrpV1, which in normal circumstances has the job of detecting high temperatures and sending a signal to the brain - 'it's hot, stay away!' This strategy works quite well on all mammalian species except one: we humans (some of us, at least) appear to be alone in our tendency to actually seek out the burn of the hot pepper in our food.

Interestingly, birds also have a heat receptor protein which is very similar to the TrpV1 receptor in mammals, but birds are not at all sensitive to capsaicin. There is an evolutionary logic to this: it is to the pepper's advantage to be eaten by a bird rather than a mammal, because a bird can spread the pepper seeds over a much wider area. The region of the receptor which is responsible for capsaicin sensitivity appears to be quite specific - in 2002, scientists were able to insert a small segment of the (capsaicin-sensitive) rat TrpV1 receptor gene into the non-sensitive chicken version of the gene, and the resulting chimeric (mixed species) receptor was sensitive to capsaicin (*Cell* **2002**, *108*, 421).

Back at the North Hudson Pepperfest, those with a little more common sense are foregoing the painful effects of capsaicin overload and are instead indulging in more pleasant chemical phenomena. A little girl enjoying an ice cream cone is responding in part to the chemical action of another organic compound called vanillin.



vanillin

What is it about capsaicin and vanillin that causes these two compounds to have such dramatically different effects on our sensory perceptions? Both are produced by plants, and both are composed of the elements carbon, hydrogen, oxygen, and (in the case of capsaicin) nitrogen. Since the birth of chemistry as a science, chemists have been fascinated - and for much of that history, mystified - by the myriad properties of compounds that come from living things. The term 'organic', from the Greek *organikos*, was applied to these compounds, and it was thought that they contained some kind of 'vital force' which set them apart from 'inorganic' compounds such as minerals, salts, and metals, and which allowed them to operate by a completely different set of chemical principles. How else but through the action of a 'vital force' could such a small subgroup of the elements combine to form compounds with so many different properties?

Today, as you are probably already aware, the term 'organic,' - when applied to chemistry - refers not just to molecules from living things, but to all compounds containing the element carbon, regardless of origin. Beginning early in the 19th century, as chemists learned through careful experimentation about the composition and properties of 'organic' compounds such as fatty acids, acetic acid and urea, and even figured out how to synthesize some of them starting with exclusively 'inorganic' components, they began to realize that the 'vital force' concept was not valid, and that the properties of both organic and inorganic molecules could in fact be understood using the same fundamental chemical principles.

They also began to more fully appreciate the unique features of the element carbon which makes it so central to the chemistry of living things, to the extent that it warrants its own subfield of chemistry. Carbon forms four stable bonds, either to other carbon atoms or to hydrogen, oxygen, nitrogen, sulfur, phosphorus, or a halogen. The characteristic bonding modes of carbon allow it to serve as a skeleton, or framework, for building large, complex molecules that incorporate chains, branches and ring structures.

Although 'organic chemistry' no longer means exclusively the study of compounds from living things, it is nonetheless the desire to understand and influence the chemistry of life that drives much of the work of organic chemists, whether the goal is to learn something fundamentally new about the reactivity of a carbon-oxygen bond, to discover a new laboratory method that could be used to synthesize a life-saving drug, or to better understand the intricate chemical dance that goes on in the active site of an enzyme or receptor protein. Although humans have been eating hot peppers and vanilla-flavored foods for centuries, we are just now, in the past few decades, beginning to understand how and why one causes searing pain, and the other pure gustatory pleasure. We understand that the precise geometric arrangement of the four elements in capsaicin allows it to fit inside the binding pocket of the TrpV1 heat receptor - but, as of today, we do not yet have a detailed three dimensional picture of the TrpVI protein bound to capsaicin. We also know that the different arrangement of carbon, hydrogen and oxygen atoms in vanillin allows it to bind to specific olfactory receptors, but again, there is much yet to be discovered about exactly how this happens.

In this chapter, you will be introduced to some of the most fundamental principles of organic chemistry. With the concepts we learn about, we can begin to understand how carbon and a very small number of other elements in the periodic table can combine in predictable ways to produce a virtually limitless chemical repertoire.

As you read through, you will recognize that the chapter contains a lot of review of topics you have probably learned already in an introductory chemistry course, but there will likely also be a few concepts that are new to you, as well as some topics which are already familiar to you but covered at a greater depth and with more of an emphasis on biologically relevant organic compounds.

We will begin with a reminder of how chemists depict bonding in organic molecules with the 'Lewis structure' drawing convention, focusing on the concept of 'formal charge'. We will review the common bonding patterns of the six elements necessary for all forms of life on earth - carbon, hydrogen, nitrogen, oxygen, sulfur, and phosphorus - plus the halogens (fluorine, chlorine, bromine, and iodine). We'll then continue on with some of the basic skills involved in drawing and talking about organic molecules: understanding the 'line structure' drawing convention and other useful ways to abbreviate and simplify structural drawings, learning about functional groups and isomers, and looking at how to systematically name simple organic molecules. Finally, we'll bring it all

together with a review of the structures of the most important classes of biological molecules - lipids, carbohydrates, proteins, and nucleic acids - which we will be referring to constantly throughout the rest of the book.

Before you begin your study of organic chemistry, you may need to do some review of General Chemistry because it will be assumed that you already understand some basic chemistry concepts. A great way to review is to watch the following series of tutorials from Khan Academy:

Review tutorials

- Atoms, compounds and ions
- Electronic structure of atoms
- Chemical bonds and drawing Lewis structures

Here are some practice exercises to try before moving on:

? Exercise 1.1

How many protons and neutrons do the following isotopes have?

a. ^{31}P, the most common isotope of phosphorus
b. ^{32}P, a radioactive isotope of phosphorus used often in the study of DNA and RNA.
c. ^{37}Cl, one of the two common isotopes of chlorine.
d. tritium (^{3}H), a radioactive isotope of hydrogen, used often by biochemists as a 'tracer' atom.
e. ^{14}C, a radioactive isotope of carbon, also used as a tracer in biochemistry.

Exercise 1.2

The electron configuration of a carbon atom is $1s^2 2s^2 2p^2$, and that of a sodium cation (Na^+) is $1s^2 2s^2 2p^6$. Show the electron configuration for:

a. a nitrogen atom
b. an oxygen atom
c. a fluorine atom
d. a magnesium atom
e. a magnesium cation (Mg^{2+})
f. a potassium atom
g. a potassium ion (K^+)
h. a chloride anion (Cl^-)
i. a sulfur atom
j. a lithium cation (Li^+)
k. a calcium cation (Ca^{2+})

Exercise 1.3

Draw Lewis structures for the following species (use lines to denote bonds, dots for lone-pair electrons). All atoms should have a complete valence shell of electrons.

a. ammonia, NH_3
b. ammonium ion, NH_4^+
c. amide ion, NH_2^-
d. formaldehyde, HCOH
e. acetate ion, CH_3COO^-
f. methyl amine, CH_3NH_2
g. ethanol, CH_3CH_2OH
h. diethylether, $CH_3CH_2OCH_2CH_3$
i. cyclohexanol (molecular formula $C_6H_{12}O$, with six carbons bonded in a ring and an OH group)
j. propene, CH_2CHCH_3

k. pyruvate, CH_3COCO_2H

Exercise solutions

Contributors and Attributions

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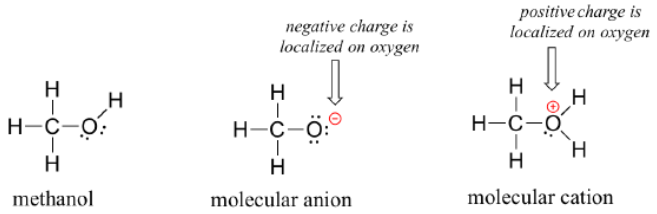
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1.1: Drawing Organic Structures

Formal Charges

Now that you have had a chance to go back to your introductory chemistry textbook to review some basic information about atoms, orbitals, bonds, and molecules, let's direct our attention a little more closely to the idea of charged species. You know that an **ion** is a molecule or atom that has an associated positive or negative charge. Copper, for example, can be found in both its neutral state (Cu^0, which is the metal), or in its Cu^{+2} state, as a component of an ionic compound like copper carbonate ($CuCO_3$), the green substance called 'patina' that forms on the surface of copper objects.

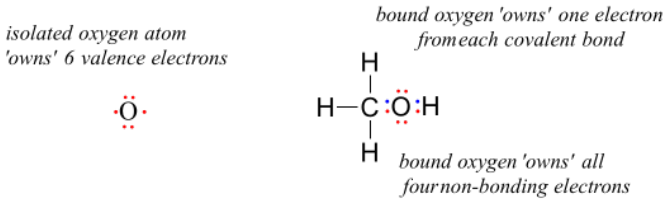
Organic molecules can also have positive or negative charges associated with them. Consider the Lewis structure of methanol, CH_3OH (methanol is the so-called 'wood alcohol' that unscrupulous bootleggers sometimes sold during the prohibition days in the 1920's, often causing the people who drank it to go blind). Methanol itself is a neutral molecule, but can lose a proton to become a molecular anion (CH_3O^-), or gain a proton to become a molecular cation ($CH_3OH_2^{+)}$.



The molecular anion and cation have overall charges of -1 and +1, respectively. But we can be more specific than that - we can also state for each molecular ion that a **formal charge** is located specifically on the oxygen atom, rather than on the carbon or any of the hydrogen atoms.

Figuring out the formal charge on different atoms of a molecule is a straightforward process - it's simply a matter of adding up valence electrons.

A unbound oxygen atom has 6 valence electrons. When it is bound as part of a methanol molecule, however, an oxygen atom is surrounded by 8 valence electrons: 4 nonbonding electrons (two 'lone pairs') and 2 electrons in each of its two covalent bonds (one to carbon, one to hydrogen). In the formal charge convention, we say that the oxygen 'owns' all 4 nonbonding electrons. However, it only 'owns' one electron from each of the two covalent bonds, because covalent bonds involve the sharing of electrons between atoms. Therefore, the oxygen atom in methanol owns 2 + 2 + (½ x 4) = 6 valence electrons.



The formal charge on an atom is calculated as the number of valence electrons owned by the isolated atom minus the number of valence electrons owned by the bound atom in the molecule:

Determining formal charge on an atom

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of valence electrons owned by the bound atom)

or . . .

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of non-bonding electrons on the bound atom)

- (½ the number of bonding electrons on the bound atom)

Using this formula for the oxygen atom of methanol, we have:

formal charge on oxygen =

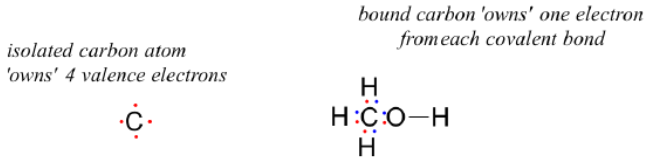
(6 valence electrons on isolated atom)

- (4 non-bonding electrons)

- (½ x 4 bonding electrons)

= 6 - 4 - 2 = **0**. Thus, oxygen in methanol has a formal charge of zero (in other words, it has *no formal charge*).

How about the carbon atom in methanol? An isolated carbon owns 4 valence electrons. The bound carbon in methanol owns (½ x 8) = 4 valence electrons:



formal charge on carbon =

(4 valence electron on isolated atom)

- (0 nonbonding electrons)

- (½ x 8 bonding electrons)

= 4 - 0 - 4 = **0**. So the formal charge on carbon is zero.

For each of the hydrogens in methanol, we also get a formal charge of zero:

formal charge on hydrogen =

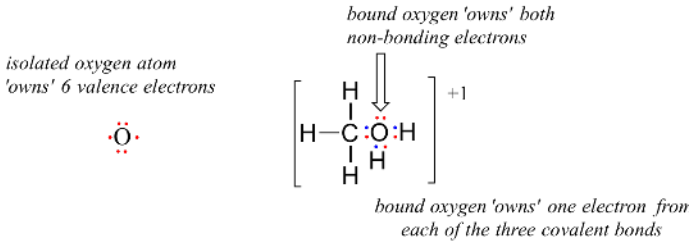
(1 valence electron on isolated atom)

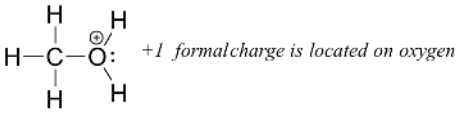
- (0 nonbonding electrons)

- (½ x 2 bonding electrons)

= 1 - 0 - 1 = **0**

Now, let's look at the cationic form of methanol, $CH_3OH_2^+$. The bonding picture has not changed for carbon or for any of the hydrogen atoms, so we will focus on the oxygen atom.





The oxygen owns 2 non-bonding electrons and 3 bonding elections, so the formal charge calculations becomes:

formal charge on oxygen =

(6 valence electrons in isolated atom)

- (2 non-bonding electrons)

- (½ x 6 bonding electrons)

= 6 - 2 - 3 = **1**. A formal charge of +1 is located on the oxygen atom.

For methoxide, the anionic form of methanol, the calculation for the oxygen atom is:

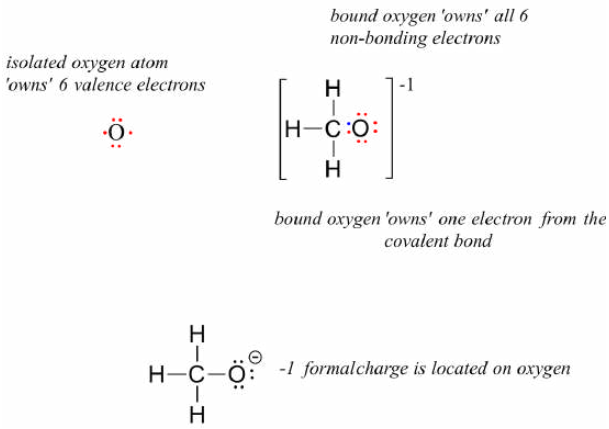
formal charge on oxygen =

(6 valence electrons in isolated atom)

- (6 non-bonding electrons)

- (½ x 2 bonding electrons)

= 6 - 6 - 1 = **-1**. A formal charge of -1 is located on the oxygen atom.

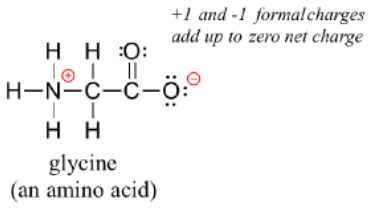


A very important rule to keep in mind is that *the sum of the formal charges on all atoms of a molecule must equal the net charge on the whole molecule.*

When drawing the structures of organic molecules, it is very important to show all non-zero formal charges, being clear about where the charges are located. *A structure that is missing non-zero formal charges is not correctly drawn, and will probably be marked as such on an exam!*

At this point, thinking back to what you learned in general chemistry, you are probably asking "What about dipoles? Doesn't an oxygen atom in an O-H bond 'own' more of the electron density than the hydrogen, because of its greater electronegativity?" This is absolutely correct, and we will be reviewing the concept of bond dipoles later on. For the purpose of calculating formal charges, however, bond dipoles don't matter - we always consider the two electrons in a bond to be shared equally, even if that is not an accurate reflection of chemical reality. Formal charges are just that - a formality, a method of electron book-keeping that is tied into the Lewis system for drawing the structures of organic compounds and ions. Later, we will see how the concept of formal charge can help us to visualize how organic molecules react.

Finally, don't be lured into thinking that just because the net charge on a structure is zero there are no atoms with formal charges: one atom could have a positive formal charge and another a negative formal charge, and the net charge would still be zero. **Zwitterions,** such as amino acids, have both positive and negative formal charges on different atoms:

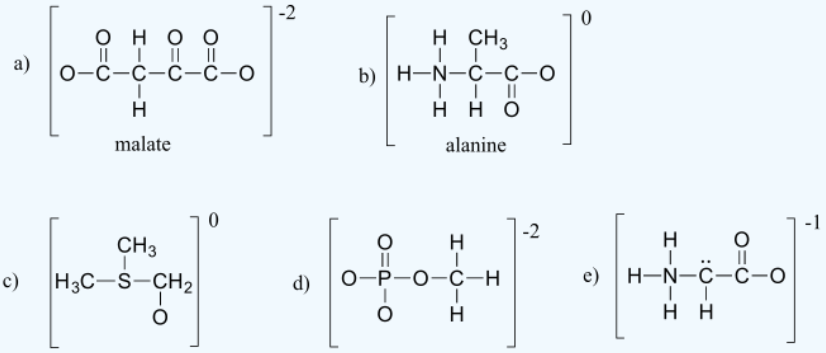


glycine
(an amino acid)

Even though the *net* charge on glycine is zero, it is still neccessary to show the location of the positive and negative formal charges.

? Exercise 1.4

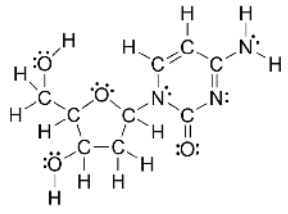
Fill in all missing lone pair electrons and formal charges in the structures below. Assume that all atoms have a complete valence shell of electrons. Net charges are shown outside the brackets.



Solutions to exercises

Common bonding patterns in organic structures

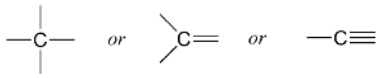
The methods reviewed above for drawing Lewis structures and determining formal charges on atoms are an essential starting point for a novice organic chemist, and work quite will when dealing with small, simple structures. But as you can imagine, these methods become unreasonably tedious and time-consuming when you start dealing with larger structures. It would be unrealistic, for example, to ask you to draw the Lewis structure below (of one of the four nucleoside building blocks that make up DNA) and determine all formal charges by adding up, on an atom-by-atom basis, the valence electrons.



2'-deoxycytidine

And yet, as organic chemists, and especially as organic chemists dealing with biological molecules, you will be expected soon to draw the structure of large molecules such as this on a regular basis. Clearly, you need to develop the ability to quickly and efficiently draw large structures and determine formal charges. Fortunately, this ability is not terribly hard to come by - all it takes is a few shortcuts and some practice at recognizing common bonding patterns.

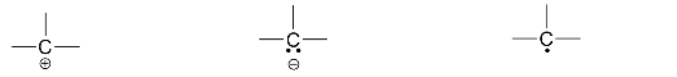
Let's start with carbon, the most important element for organic chemists. Carbon is said to be tetravalent, meaning that it tends to form four bonds. If you look at the simple structures of methane, methanol, ethane, ethene, and ethyne in the figures from the previous section, you should quickly recognize that in each molecule, the carbon atom has four bonds, and a formal charge of zero.



carbon usually has 4 bonds

This is a pattern that holds throughout most of the organic molecules we will see, but there are also exceptions.

In carbon dioxide, the carbon atom has double bonds to oxygen on both sides (O=C=O). Later on in this chapter and throughout this book we will see examples of organic ions called 'carbocations' and carbanions', in which a carbon atom bears a positive or negative formal charge, respectively. If a carbon has only three bonds and an unfilled valence shell (in other words, if it does not fulfill the octet rule), it will have a positive formal charge.



3 bonds, no lone pair: carbocation

3 bonds + lone pair: carbanion

3 bonds + unpaired electron: carbon radical

If, on the other hand, it has three bonds plus a lone pair of electrons, it will have a formal charge of -1. Another possibility is a carbon with three bonds and a single, unpaired (free radical) electron: in this case, the carbon has a formal charge of zero. (One last possibility is a highly reactive species called a 'carbene', in which a carbon has two bonds and one lone pair of electrons, giving it a formal charge of zero. You may encounter carbenes in more advanced chemistry courses, but they will not be discussed any further in this book).

You should certainly use the methods you have learned to check that these formal charges are correct for the examples given above. More importantly, you will need, before you progress much further in your study of organic chemistry, to simply recognize these patterns (and the patterns described below for other atoms) and be able to identify by quick inspection carbons that bear positive and negative formal charges.

The pattern for hydrogens is easy: hydrogen atoms have only one bond, and no formal charge. The exceptions to this rule are the proton, H^+, and the hydride ion, H^-, which is a proton plus two electrons. Because we are concentrating in this book on organic chemistry as applied to living things, however, we will not be seeing 'naked' protons and hydrides as such, because they are too reactive to be present in that form in aqueous solution. Nonetheless, the *idea* of a proton will be very important when we discuss acid-base chemistry, and the *idea* of a hydride ion will become very important much later in the book when we discuss organic oxidation and reduction reactions. As a rule, though, all hydrogen atoms in organic molecules have one bond, and no formal charge.

Let us next turn to oxygen atoms. Typically, you will see an oxygen bonding in three ways, all of which fulfill the octet rule.



neutral oxygen: 2 bonds + 2 lone pairs

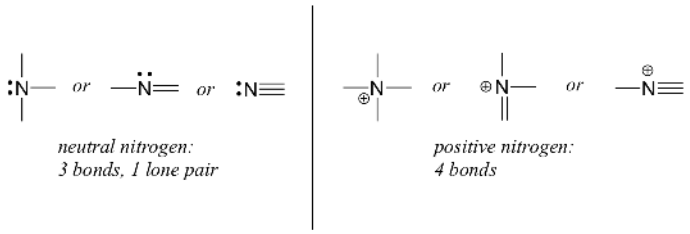
negative formal charge: 1 bond + 3 lone pairs

positive formal charge: 3 bonds + 1 lone pair

If an oxygen atom t has two bonds and two lone pairs, as in water, it will have a formal charge of zero. If it has one bond and three lone pairs, as in hydroxide ion, it will have a formal charge of-1. If it has three bonds and one lone pair, as in hydronium ion, it will have a formal charge of +1.

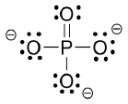
When we get to our discussion of free radical chemistry in chapter 17, we will see other possibilities, such as where an oxygen atom has one bond, one lone pair, and one unpaired (free radical) electron, giving it a formal charge of zero. For now, however, concentrate on the three main non-radical examples, as these will account for virtually everything we see until chapter 17.

Nitrogen has two major bonding patterns, both of which fulfill the octet rule:



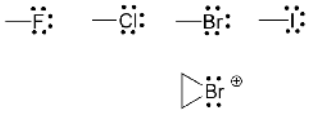
If a nitrogen has three bonds and a lone pair, it has a formal charge of zero. If it has four bonds (and no lone pair), it has a formal charge of +1. In a fairly uncommon bonding pattern, negatively charged nitrogen has two bonds and two lone pairs.

Two third row elements are commonly found in biological organic molecules: sulfur and phosphorus. Although both of these elements have other bonding patterns that are relevant in laboratory chemistry, in a biological context sulfur almost always follows the same bonding/formal charge pattern as oxygen, while phosphorus is present in the form of phosphate ion (PO_4^{3-}), where it has five bonds (almost always to oxygen), no lone pairs, and a formal charge of zero. Remember that atoms of elements in the third row and below in the periodic table have 'expanded valence shells' with *d* orbitals available for bonding, and the the octet rule does not apply.



phosphate

Finally, the halogens (fluorine, chlorine, bromine, and iodine) are very important in laboratory and medicinal organic chemistry, but less common in naturally occurring organic molecules. Halogens in organic compounds usually are seen with one bond, three lone pairs, and a formal charge of zero. Sometimes, especially in the case of bromine, we will encounter reactive species in which the halogen has two bonds (usually in a three-membered ring), two lone pairs, and a formal charge of +1.



These rules, if learned and internalized so that you don't even need to think about them, will allow you to draw large organic structures, complete with formal charges, quite quickly.

Once you have gotten the hang of drawing Lewis structures, it is not always necessary to draw lone pairs on heteroatoms, as you can assume that the proper number of electrons are present around each atom to match the indicated formal charge (or lack thereof). Occasionally, though, lone pairs are drawn if doing so helps to make an explanation more clear.

? Exercise 1.5

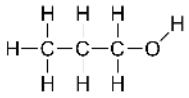
Draw one structure that corresponds to each of the following molecular formulas, using the common bonding patters covered above. Be sure to include all lone pairs and formal charges where applicable, and assume that all atoms have a full valence shell of electrons. More than one correct answer is possible for each, so you will want to check your answers with your instructor or tutor.

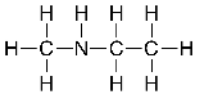
a) $C_5H_{10}O$ b) C_5H_8O c) $C_6H_8NO^+$ d) $C_4H_3O_2^-$

Solutions to exercises

Using the 'line structure' convention

If you look ahead in this and other books at the way organic compounds are drawn, you will see that the figures are somewhat different from the Lewis structures you are used to seeing in your general chemistry book. In some sources, you will see **condensed structures** for smaller molecules instead of full Lewis structures:

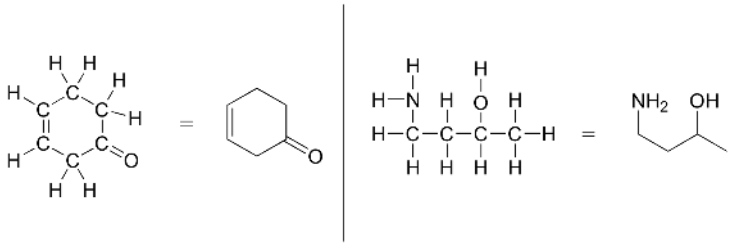




Lewis structures

$CH_3CH_2CH_2OH$ $CH_3NHCH_2CH_3$ Condensed structures

More commonly, organic and biological chemists use an abbreviated drawing convention called **line structures**. The convention is quite simple and makes it easier to draw molecules, but line structures do take a little bit of getting used to. Carbon atoms are depicted not by a capital C, but by a 'corner' between two bonds, or a free end of a bond. Open-chain molecules are usually drawn out in a 'zig-zig' shape. Hydrogens attached to carbons are generally not shown: rather, like lone pairs, they are simply implied (unless a positive formal charge is shown, all carbons are assumed to have a full octet of valence electrons). Hydrogens bonded to nitrogen, oxygen, sulfur, or anything other than carbon *are* shown, but are usually drawn without showing the bond. The following examples illustrate the convention.

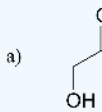


As you can see, the 'pared down' line structure makes it much easier to see the basic structure of the molecule and the locations where there is something other than C-C and C-H single bonds. For larger, more complex biological molecules, it becomes impractical to use full Lewis structures. Conversely, very small molecules such as ethane should be drawn with their full Lewis or condensed structures.

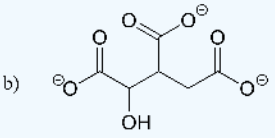
Sometimes, one or more carbon atoms in a line structure will be depicted with a capital C, if doing so makes an explanation easier to follow. *If you label a carbon with a C, you also must draw in the hydrogens for that carbon.*

? Exercise 1.6

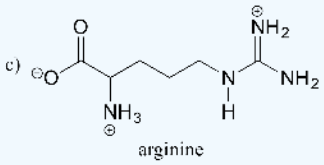
A good way to test your understanding of the line structure convention is to determine the number of hydrogen atoms in a molecule from its line structure. Do this for the structures below.



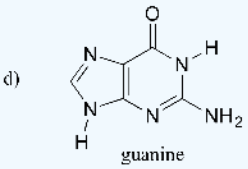
a) dihydroxyacetone



b) isocitrate



c) arginine

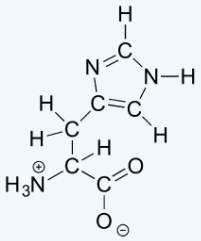


d) guanine

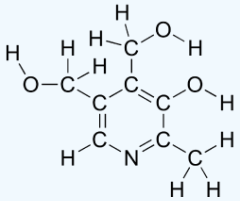
Exercise 1.7

a) Draw a line structure for the DNA base 2-deoxycytidine (the full structure was shown earlier)

b) Draw line structures for histidine (an amino acid) and pyridoxine (Vitamin B_6).



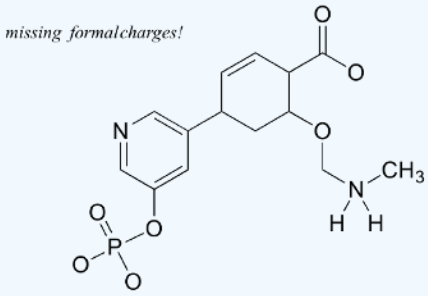
histidine



pyridoxine
(Vitamin B_6)

Exercise 1.8

Add non-zero formal charges to the structural drawing below. The net charge is -2.



Exercise 1.9

Find, anywhere in chapters 2-17 of this textbook, one example of each of the common bonding patterns specified below. Check your answers with your instructor or tutor.

a) carbon with one double bond, two single bonds, no lone pairs, and zero formal charge

b) oxygen with two single bonds, two lone pairs, and zero formal charge

c) oxygen with one double bond, two lone pairs, and zero formal charge

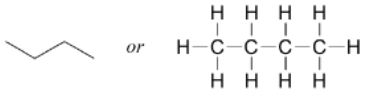
d) nitrogen with one double bond, two single bonds, and a +1 formal charge

e) oxygen with one single bond, three lone pairs, and a negative formal charge

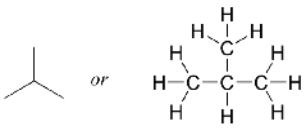
Solutions to exercises

Constitutional isomers

Now that we have reviewed how to draw Lewis structures and learned the line structure shortcut, it is a good time to learn about the concept of constitutional isomers. Imagine if you were asked to draw a structure (Lewis or line) for a compound with the molecular formula C_4H_{10}. This would not be difficult - you could simply draw:



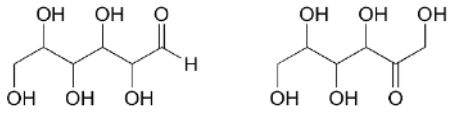
But when you compared your answer with that of a classmate, she may have drawn this structure:



Who is correct? The answer, of course, is that both of you are. A molecular formula only tells you *how many* atoms of each element are present in the compound, not what the actual atom-to-atom connectivity is. There are often many different possible structures

for one molecular formula. Compounds that have the same molecular formula but different connectivity are called **constitutional isomers** (sometimes the term '**structural isomer**' is also used). The Greek term '*iso*' means 'same'.

Fructose and glucose, two kinds of sugar molecules, are constitutional isomers with the molecular formula $C_6H_{12}O_6$.



glucose fructose

Later, we will see other types of isomers that have the same molecular formula and the same connectivity, but are different in other respects.

? Exercise 1.10

Draw a constitutional isomer of ethanol, CH_3CH_2OH.

Exercise 1.11

Draw all of the possible constitutional isomers with the given molecular formula.

a. C_5H_{12}
b. $C_4H_{10}O$
c. C_3H_9N

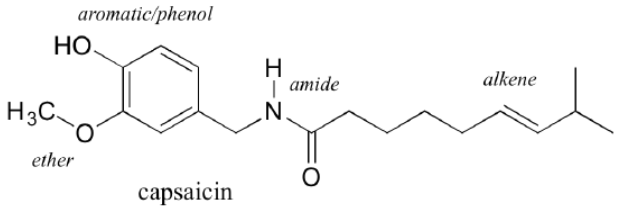
Solutions to exercises

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1.2: Functional groups and organic nomenclature

Functional groups are structural units within organic compounds that are defined by specific bonding arrangements between specific atoms. The structure of capsaicin, the compound discussed in the beginning of this chapter, incorporates several functional groups, labeled in the figure below and explained throughout this section.

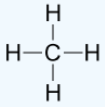


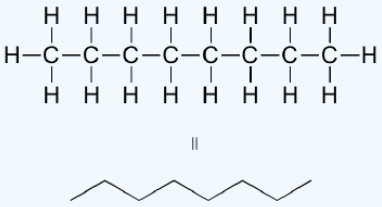
capsaicin

As we progress in our study of organic chemistry, it will become extremely important to be able to quickly recognize the most common functional groups, because *they are the key structural elements that define how organic molecules react*. For now, we will only worry about drawing and recognizing each functional group, as depicted by Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups behave in organic reactions.

The 'default' in organic chemistry (essentially, the *lack* of any functional groups) is given the term **alkane**, characterized by single bonds between carbon and carbon, or between carbon and hydrogen. Methane, CH_4, is the natural gas you may burn in your furnace. Octane, C_8H_{18}, is a component of gasoline.

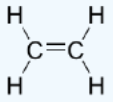
Alkanes

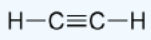

methane


octane

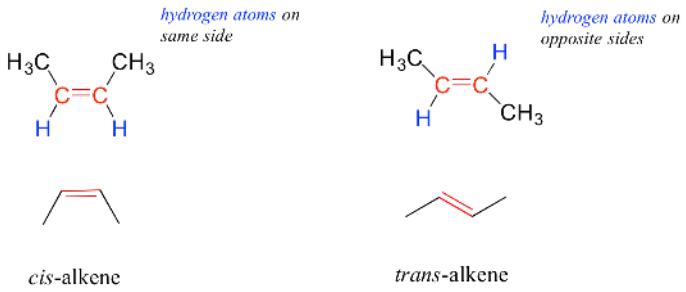
Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along with an apple - the apple emits ethene gas, setting off the ripening process in the bananas). Ethyne, commonly called acetylene, is used as a fuel in welding blow torches.

Alkenes and alkynes


ethene
(an alkene)


ethyne
(an alkyne)

In chapter 2, we will study the nature of the bonding on alkenes and alkynes, and learn that that the bonding in alkenes is trigonal planar in in alkynes is linear. Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans***. The *cis* and *trans* forms of a given alkene are different molecules with different physical properties because, as we will learn in chapter 2, there is a very high energy barrier to rotation about a double bond. In the example below, the difference between *cis* and *trans* alkenes is readily apparent.

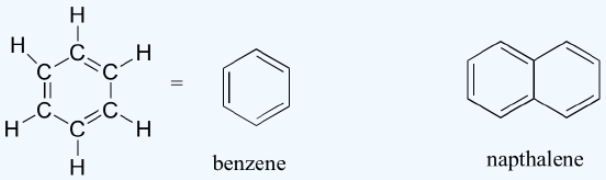


We will have more to say about the subject of *cis* and *trans* alkenes in chapter 3, and we will learn much more about the reactivity of alkenes in chapter 14.

Alkanes, alkenes, and alkynes are all classified as **hydrocarbons**, because they are composed solely of carbon and hydrogen atoms. Alkanes are said to be **saturated hydrocarbons**, because the carbons are bonded to the maximum possible number of hydrogens - in other words, they are *saturated* with hydrogen atoms. The double and triple-bonded carbons in alkenes and alkynes have fewer hydrogen atoms bonded to them - they are thus referred to as **unsaturated hydrocarbons**. As we will see in chapter 15, hydrogen can be added to double and triple bonds, in a type of reaction called 'hydrogenation'.

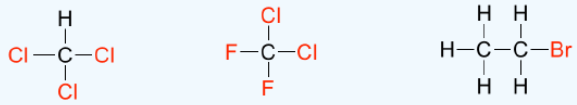
The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We will learn more about the structure and reactions of aromatic groups in chapters 2 and 14.

Aromatics



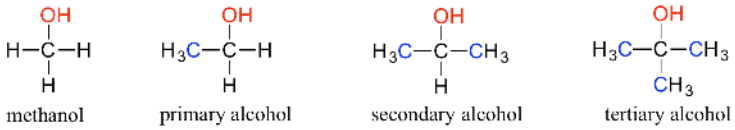
When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol sprays until the late twentieth century, but its use was discontinued after it was found to have harmful effects on the ozone layer. Bromoethane is a simple alkyl halide often used in organic synthesis. Alkyl halides groups are quite rare in biomolecules.

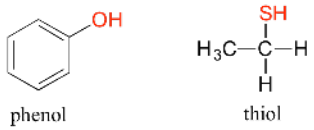
Haloalkanes



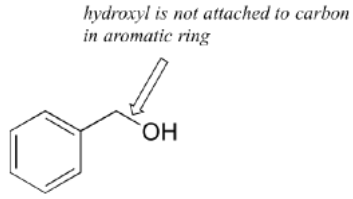
In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded to only one other carbon. In a **secondary alcohol** and **tertiary alcohol,** the carbon is bonded to two or three other carbons, respectively. When the hydroxyl group is *directly* attached to an aromatic ring, the resulting group is called a **phenol**. The sulfur analog of an alcohol is called a **thiol** (from the Greek *thio*, for sulfur).

Alcohols, phenols, and thiols





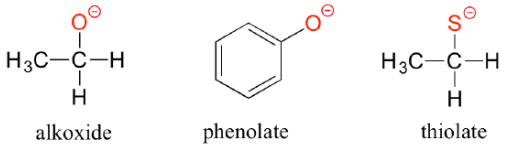
Note that the definition of a phenol states that the hydroxyl oxygen must be *directly* attached to one of the carbons of the aromatic ring. The compound below, therefore, is *not* a phenol - it is a primary alcohol.

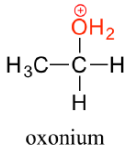


primary alcohol
(*not* a phenol)

The distinction is important, because as we will see later, there is a significant difference in the reactivity of alcohols and phenols.

The deprotonated forms of alcohols, phenols, and thiols are called **alkoxides**, **phenolates**, and **thiolates**, respectively. A protonated alcohol is an **oxonium** ion.

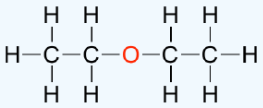




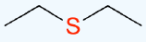
oxonium

In an **ether** functional group, a central oxygen is bonded to two carbons. Below is the structure of diethyl ether, a common laboratory solvent and also one of the first compounds to be used as an anesthetic during operations. The sulfur analog of an ether is called a **thioether** or **sulfide**.

Ethers and sulfides



an ether

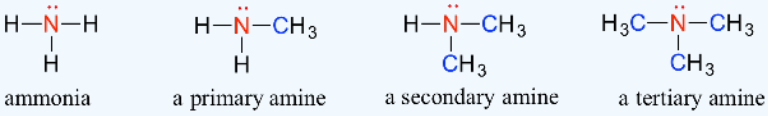


a sulfide

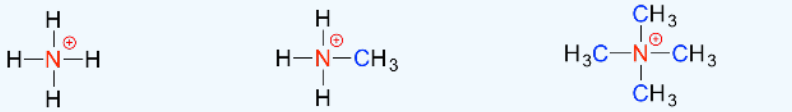
Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

One of the most important properties of amines is that they are basic, and are readily protonated to form **ammonium** cations. In the case where a nitrogen has four bonds to carbon (which is somewhat unusual in biomolecules), it is called a quaternary ammonium ion.

Amines



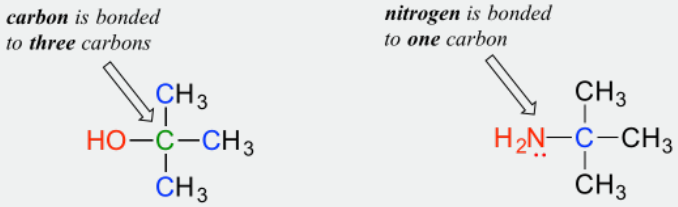
ammonia | a primary amine | a secondary amine | a tertiary amine



ammonium ion | a primary ammonium ion | a quaternary ammonium ion

Note

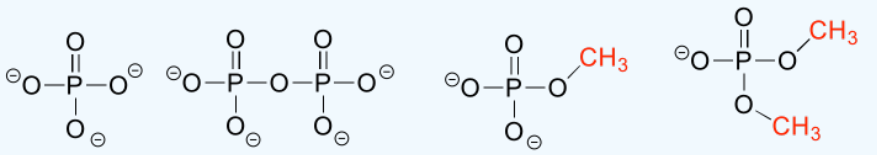
Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols versus amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.



a *tertiary* alcohol | a *primary* amine

Phosphate and its derivative functional groups are ubiquitous in biomolecules. Phosphate linked to a single organic group is called a **phosphate ester**; when it has two links to organic groups it is called a **phosphate diester**. A linkage between two phosphates creates a **phosphate anhydride**.

Organic phosphates

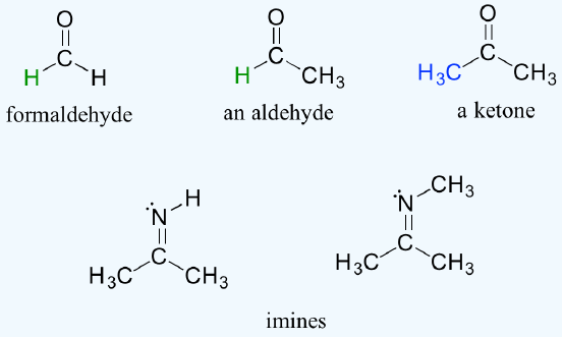


Chapter 9 of this book is devoted to the structure and reactivity of the phosphate group.

There are a number of functional groups that contain a carbon-oxygen double bond, which is commonly referred to as a **carbonyl**. **Ketones** and **aldehydes** are two closely related carbonyl-based functional groups that react in very similar ways. In a ketone, the carbon atom of a carbonyl is bonded to two other carbons. In an aldehyde, the carbonyl carbon is bonded on one side to a hydrogen, and on the other side to a carbon. The exception to this definition is formaldehyde, in which the carbonyl carbon has bonds to two hydrogens.

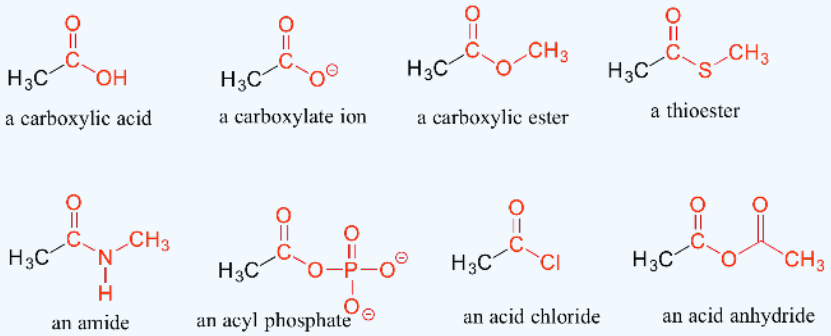
A group with a carbon-nitrogen double bond is called an **imine**, or sometimes a **Schiff base** (in this book we will use the term 'imine'). The chemistry of aldehydes, ketones, and imines will be covered in chapter 10.

Aldehydes, ketones, and imines



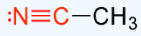
When a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to an oxygen, nitrogen, or sulfur, the functional group is considered to be one of the '**carboxylic acid derivatives**', a designation that describes a set of related functional groups. The eponymous member of this family is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl group. The conjugate base of a carboxylic acid is a **carboxylate**. Other derivatives are carboxylic esters (usually just called '**esters**'), **thioesters**, **amides**, **acyl phosphates**, **acid chlorides**, and **acid anhydrides**. With the exception of acid chlorides and acid anhydrides, the carboxylic acid derivatives are very common in biological molecules and/or metabolic pathways, and their structure and reactivity will be discussed in detail in chapter 11.

Carboxylic acid derivatives



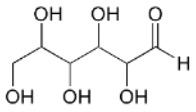
Finally, a **nitrile** group is characterized by a carbon triple-bonded to a nitrogen.

Nitriles

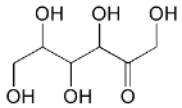


acetonitrile

A single compound often contains several functional groups, particularly in biological organic chemistry. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').

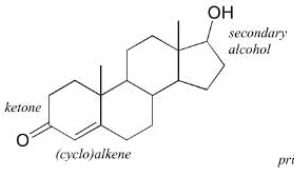


glucose

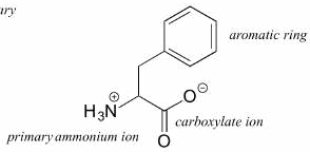


fructose

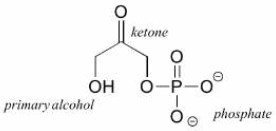
The hormone testosterone, the amino acid phenylalanine, and the glycolysis metabolite dihydroxyacetone phosphate all contain multiple functional groups, as labeled below.



testosterone



phenylalanine



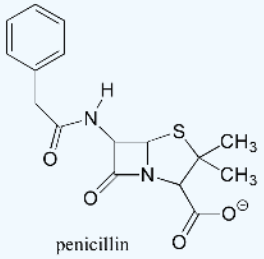
dihydroxyacetone phosphate (DHAP)

While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological organic chemistry. Table 9 in the tables section at the back of this book provides a summary of all of the groups listed in this section, plus a few more that will be introduced later in the text.

Exercise 1.12

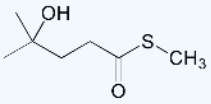
Identify the functional groups (other than alkanes) in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.

a)

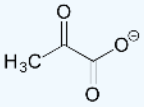


penicillin

b)

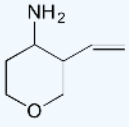


c)



pyruvate

d)



Solutions to exercises

Exercise 1.13

Draw one example each of compounds fitting the descriptions below, using line structures. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule). There are many possible correct answers for these, so be sure to check your structures with your instructor or tutor.

a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

Naming organic compounds

A system has been devised by the International Union of Pure and Applied Chemistry (IUPAC, usually pronounced ***eye**-you-pack*) for naming organic compounds. While the IUPAC system is convenient for naming relatively small, simple organic compounds, it is not generally used in the naming of biomolecules, which tend to be quite large and complex. It is, however, a good idea (even for biologists) to become familiar with the basic structure of the IUPAC system, and be able to draw simple structures based on IUPAC names.

Naming an organic compound usually begins with identify what is referred to as the **'parent chain'**, which is the longest straight chain of carbon atoms. We'll start with the simplest straight chain alkane structures. CH_4 is called **methane**, and C_2H_6 **ethane**. The table below continues with the names of longer straight-chain alkanes: be sure to commit these to memory, as they are the basis for the rest of the IUPAC nomenclature system (and are widely used in naming biomolecules as well).

✔ Names for straight-chain alkanes:

1 carbon: methane

2 carbons: ethane

3 carbons: propane

4 carbons: butane

5 carbons: pentane

6 carbons: hexane

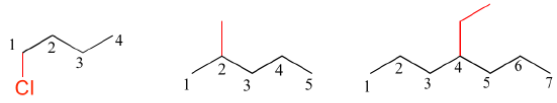
7 carbons: heptane

8 carbons: octane

9 carbons: nonane

10 carbons: decane

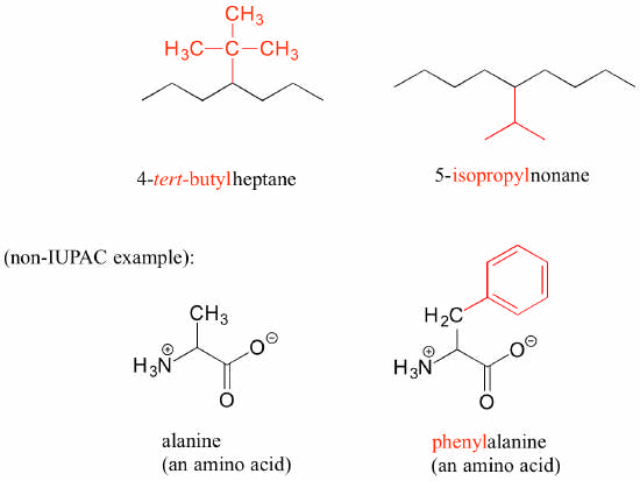
Substituents branching from the main parent chain are located by a carbon number, with *the lowest possible numbers* being used (for example, notice in the example below that the compound on the left is named 1-chlorobutane, *not* 4-chlorobutane). When the substituents are small alkyl groups, the terms **methyl**, **ethyl**, and **propyl** are used.



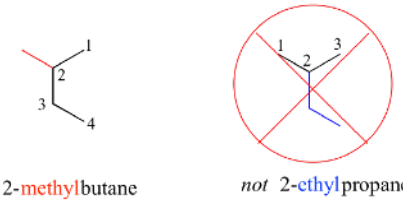
1-chlorobutane 2-methylpentane 4-ethylheptane

Other common names for hydrocarbon substituent groups are **isopropyl**, ***tert*-butyl** and **phenyl**.

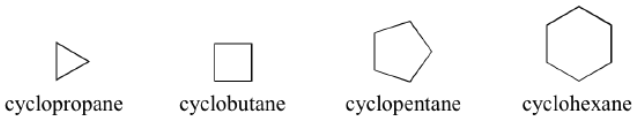
https://chem.libretexts.org/@go/page/393386



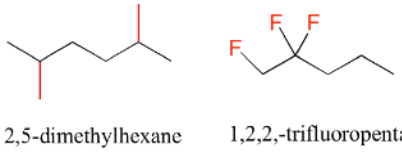
Notice in the example below, an 'ethyl group' (in blue) is not treated as a substituent, rather it is included as part of the parent chain, and the methyl group is treated as a substituent. The IUPAC name for straight-chain hydrocarbons is always based on the *longest possible parent chain*, which in this case is four carbons, not three.



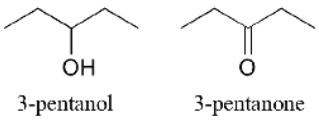
Cyclic alkanes are called cyclopropane, cyclobutane, cyclopentane, cyclohexane, and so on:



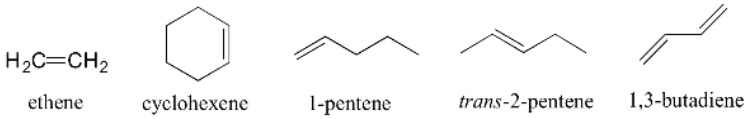
In the case of multiple substituents, the prefixes *di*, *tri*, and *tetra* are used.



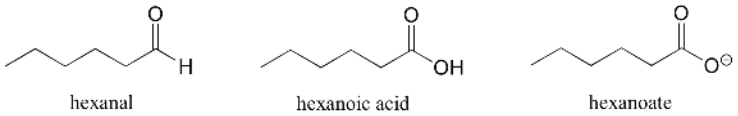
Functional groups have characteristic suffixes. Alcohols, for example, have '**ol**' appended to the parent chain name, along with a number designating the location of the hydroxyl group. Ketones are designated by '**one**'.



Alkenes are designated with an 'ene' ending, and when necessary the location and geometry of the double bond are indicated. Compounds with multiple double bonds are called dienes, trienes, etc.

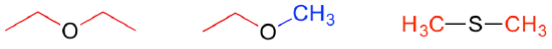


Some groups can only be present on a terminal carbon, and thus a locating number is not necessary: aldehydes end in ‘al’, carboxylic acids in ‘oic acid’, and carboxylates in ‘oate’.



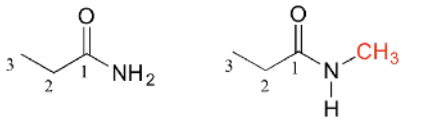
hexanal hexanoic acid hexanoate

Ethers and sulfides are designated by naming the two groups on either side of the oxygen or sulfur.



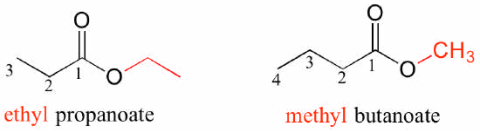
diethyl ether ethyl methyl ether dimethyl sulfide

If an amide has an unsubstituted –NH_2 group, the suffix is simply ‘amide’. In the case of a substituted amide, the group attached to the amide nitrogen is named first, along with the letter ‘*N*’ to clarify where this group is located. Note that the structures below are both based on a three-carbon (propan) parent chain.



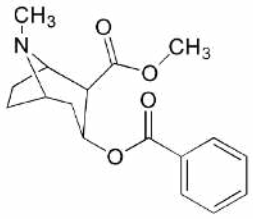
propanamide *N*-methylpropanamide

For esters, the suffix is 'oate'. The group attached to the oxygen is named first.



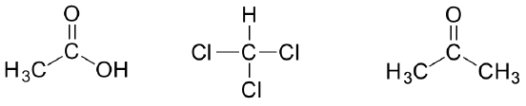
ethyl propanoate methyl butanoate

All of the examples we have seen so far have been simple in the sense that only one functional group was present on each molecule. There are of course many more rules in the IUPAC system, and as you can imagine, the IUPAC naming of larger molecules with multiple functional groups, ring structures, and substituents can get very unwieldy very quickly. The illicit drug cocaine, for example, has the IUPAC name 'methyl (1*R*,2*R*,3*S*,5*S*)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1] octane-2-carboxylate' (this name includes designations for stereochemistry, which is a structural issue that we will not tackle until chapter 3).



cocaine
(methyl (1*R*,2*R*,3*S*,5*S*)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1] octane-2-carboxylate)

You can see why the IUPAC system is not used very much in biological organic chemistry - the molecules are just too big and complex. A further complication is that, even outside of a biological context, many simple organic molecules are known almost universally by their ‘common’, rather than IUPAC names. The compounds acetic acid, chloroform, and acetone are only a few examples.



acetic acid chloroform acetone

In biochemistry, nonsystematic names (like 'cocaine', 'capsaicin', 'pyruvate' or 'ascorbic acid') are usually used, and when systematic nomenclature is employed it is often specific to the class of molecule in question: different systems have evolved, for example, for fats and for carbohydrates. We will not focus very intensively in this text on IUPAC nomenclature or any other nomenclature system, but if you undertake a more advanced study in organic or biological chemistry you may be expected to learn one or more naming systems in some detail.

Exercise 1.14

Give IUPAC names for acetic acid, chloroform, and acetone.

Exercise 1.15

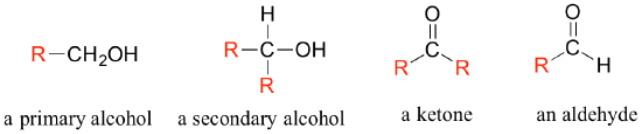
Draw line structures of the following compounds, based on what you have learned about the IUPAC nomenclature system:

a. methylcyclohexane
b. 5-methyl-1-hexanol
c. 2-methyl-2-butene
d. 5-chloropentanal
e. 2,2-dimethylcyclohexanone
f. 4-penteneoic acid
g. *N*-ethyl-*N*-cyclopentylbutanamide

Solutions to exercises

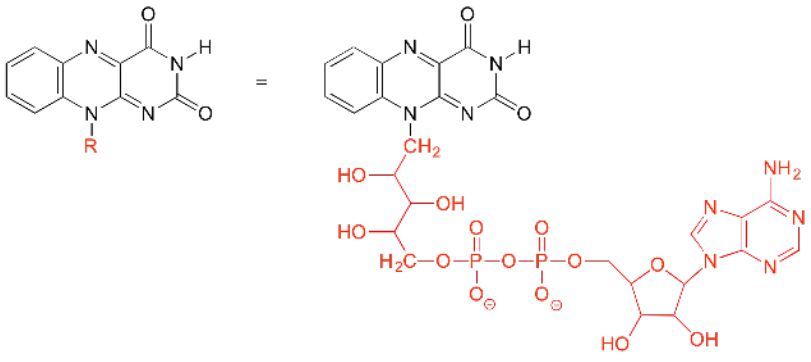
Drawing abbreviated organic structures

Often when drawing organic structures, chemists find it convenient to use the letter 'R' to designate part of a molecule outside of the region of interest. If we just want to refer in general to a functional group without drawing a specific molecule, for example, we can use 'R groups' to focus attention on the group of interest:



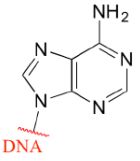
a primary alcohol | a secondary alcohol | a ketone | an aldehyde

The 'R' group is a convenient way to abbreviate the structures of large biological molecules, especially when we are interested in something that is occurring specifically at one location on the molecule. For example, in chapter 15 when we look at biochemical oxidation-reduction reactions involving the flavin molecule, we will abbreviate a large part of the flavin structure which does not change at all in the reactions of interest:

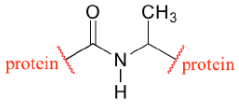


flavin adenine dinucleotide (FAD)

As an alternative, we can use a 'break' symbol to indicate that we are looking at a small piece or section of a larger molecule. This is used commonly in the context of drawing groups on large polymers such as proteins or DNA.

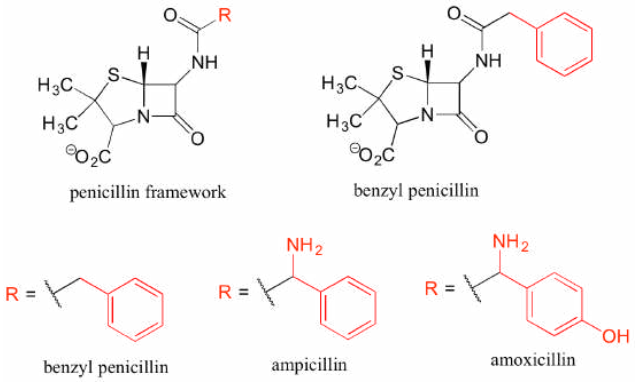


an adenine base in DNA



a small section of a protein

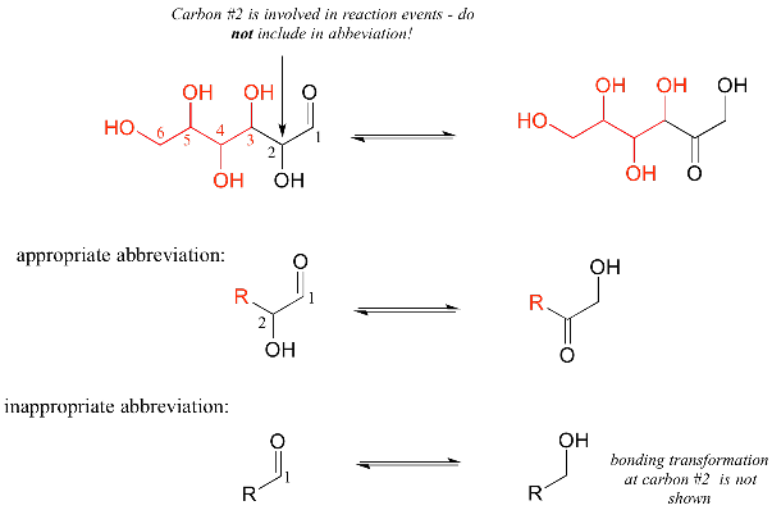
Finally, 'R' groups can be used to concisely illustrate a series of related compounds, such as the family of penicillin-based antibiotics.



Using abbreviations appropriately is a very important skill to develop when studying organic chemistry in a biological context, because although many biomolecules are very large and complex (and take forever to draw!), usually we are focusing on just one small part of the molecule where a change is taking place.

> As a rule, *you should never abbreviate any atom involved in a bond-breaking or bond-forming event that is being illustrated:* only abbreviate that part of the molecule which is not involved in the reaction of interest.

For example, carbon #2 in the reactant/product below most definitely is involved in bonding changes, and therefore should not be included in the 'R' group.

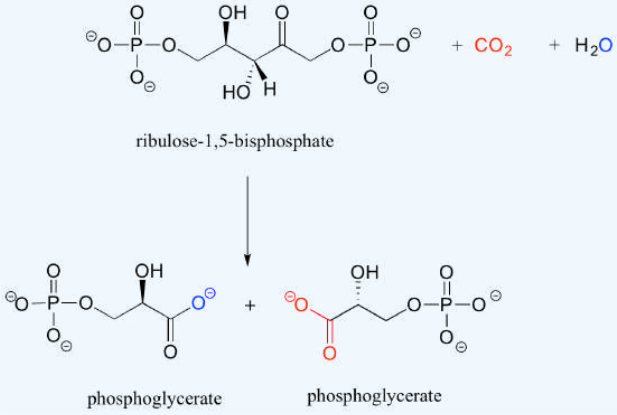


If you are unsure whether to draw out part of a structure or abbreviate it, the safest thing to do is to draw it out.

? :

a) If you intend to draw out the chemical details of a reaction in which the methyl ester functional group of cocaine (see earlier figure) was converted to a carboxylate plus methanol, what would be an appropriate abbreviation to use for the cocaine structure (assuming that you *only* wanted to discuss the chemistry specifically occurring at the ester group)?

b) Below is the (somewhat complicated) reaction catalyzed by an enzyme known as 'Rubisco', by which plants 'fix' carbon dioxide. Carbon dioxide and the oxygen of water are colored red and blue respectively to help you see where those atoms are incorporated into the products. Propose an appropriate abbreviation for the starting compound (ribulose 1,5-bisphosphate), using two different 'R' groups, R_1 and R_2.



Solutions to exercises

Khan Academy video tutorial on functional groups

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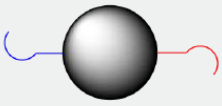
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1.3: Structures of some important biomolecules

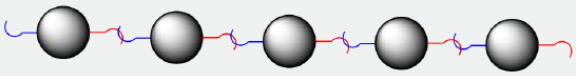
Because we are focusing in this textbook on biologically relevant organic chemistry, we will frequently be alluding to important classes of biological molecules such as lipids, carbohydrates, proteins, and nucleic acids (DNA and RNA). Now is a good time to go through a quick overview of what these molecules look like. These are large, complex molecules and there is a *lot* of information here: you are not expected to memorize these structures or even, at this point, to fully understand everything presented in this section. For now, just read through the section and get what you can out of it, and work on recognizing the fundamental things you have just learned: common bonding patterns, formal charges, functional groups, and so forth. Later, you can come back to this section for review when these biomolecules are referred to in different contexts throughout the remainder of the book.

Polymers

Many of the biomolecules that we will be talking in this section are **polymers**. To understand what a polymer is, simply picture a long chain made by connecting lots of individual beads, each of which is equipped with two hooks. In chemical terminology, each bead is a **monomer** compound, the hooks are **linking groups**, and the whole chain is a polymer.



monomer



polymer

Although lipids can be described as biopolymers, we will use the monomer-linking group terminology in particular when we talk about carbohydrates, protein, and nucleic acids.

Click on the links below to learn about each of these important types of biological molecules:

- Lipids
- Carbohydrates
- Amino acids and proteins
- Nucleic acids

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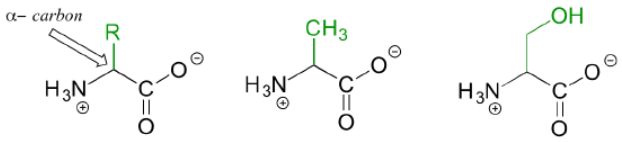
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1.3.0: Introduction to Amino Acids and Proteins

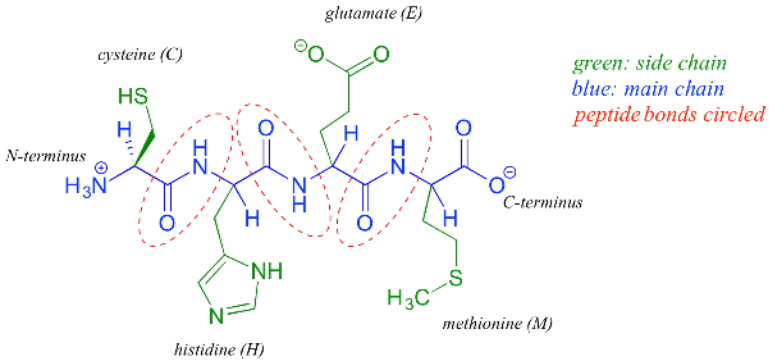
Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded to the alpha-carbon.



amino acid alanine serine

There are twenty different side chains in naturally occurring amino acids, and it is the identity of the side chain that determines the identity of the amino acid: for example, if the side chain is a -CH_3 group, the amino acid is alanine, and if the side chain is a -CH_2OH group, the amino acid is serine. Many amino acid side chains contain a functional group (the side chain of serine, for example, contains a primary alcohol), while others, like alanine, lack a functional group, and contain only a simple alkane.

The two 'hooks' on an amino acid monomer are the amine and carboxylate groups. Proteins (polymers of ~50 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. Which amino acids are linked, and in what order - the protein **sequence** - is what distinguishes one protein from another, and is coded for by an organism's DNA. Protein sequences are written in the amino terminal (N-terminal) to carboxylate terminal (C-terminal) direction, with either three-letter or single-letter abbreviations for the amino acids (see amino acid table). Below is a four amino acid peptide with the sequence "cysteine - histidine - glutamate - methionine". Using the single-letter code, the sequence is abbreviated CHEM.



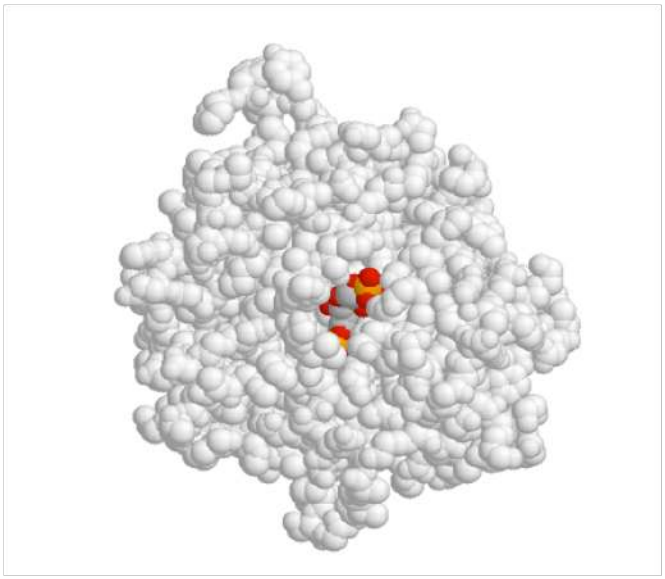
CHEM peptide

When an amino acid is incorporated into a protein it loses a molecule of water and what remains is called a **residue** of the original amino acid. Thus we might refer to the 'glutamate residue' at position 3 of the CHEM peptide above.

Once a protein polymer is constructed, it in many cases folds up very specifically into a three-dimensional structure, which often includes one or more 'binding pockets' in which other molecules can be bound. It is this shape of this folded structure, and the precise arrangement of the functional groups within the structure (especially in the area of the binding pocket) that determines the function of the protein.

Enzymes are proteins which catalyze biochemical reactions. One or more reacting molecules - often called **substrates** - become bound in the **active site** pocket of an enzyme, where the actual reaction takes place. **Receptors** are proteins that bind specifically to one or more molecules - referred to as **ligands** - to initiate a biochemical process. For example, we saw in the introduction to this chapter that the TrpVI receptor in mammalian tissues binds capsaicin (from hot chili peppers) in its binding pocket and initiates a heat/pain signal which is sent to the brain.

Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase (in grey), with the substrate molecule bound inside the active site pocket.



(x-ray crystallographic data are from *Protein Science* **1999**, 8, *291*; pdb code 4ALD. Image produced with JMol First Glance)

Intro to nucleic acids ⇒

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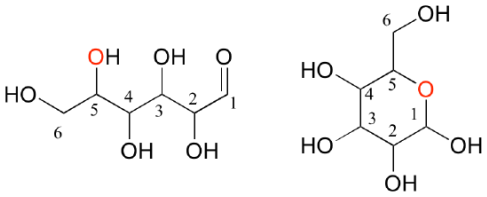
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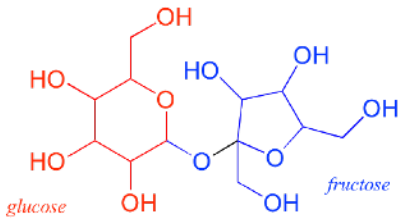
1.3.1: Introduction to carbohydrate structure

The term 'carbohydrate', which literally means 'hydrated carbons', broadly refers to monosaccharides, disaccharides, oligosaccharides (shorter polymers) and polysaccharides (longer polymers). We will cover the chemistry of carbohydrates more completely in chapter 10, but the following is a quick overview.

Monosaccharides (commonly called 'sugars') are four- to six-carbon molecules with multiple alcohol groups and a single aldehyde or ketone group. Many monosaccharides exist in aqueous solution as a rapid equilibrium between an open chain and one or more cyclic forms. Two forms of a six-carbon monosaccharide are shown below.

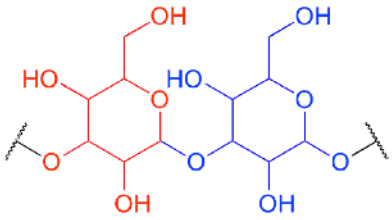


Disaccharides are two monosaccharides linked together: for example, sucrose, or table sugar, is a disaccharide of glucose and fructose.



sucrose

Oligosaccharides and **polysaccharides** are longer polymers of monosaccharides. **Cellulose** is a polysaccharide of repeating glucose monomers. As a major component of the cell walls of plants, cellulose is the most abundant organic molecule on the planet! A two-glucose stretch of a cellulose polymer is shown below.



cellulose

The linking group in carbohydrates is not one that we have covered in this chapter - in organic chemistry this group is called an acetal, while biochemists usually use the term **glycosidic bond** when talking about carbohydrates (again, the chemistry of these groups in the context of carbohydrate structures will be covered in detail in chapter 10).

The possibilities for carbohydrate structures are vast, depending on which monomers are used (there are many monosaccharides in addition to glucose and fructose), which carbons are linked, and other geometric factors which we will learn about later. Multiple linking (branching) is also common, so many carbohydrates are not simply linear chains. In addition, carbohydrate chains are often attached to proteins and/or lipids, especially on the surface of cells. All in all, carbohydrates are an immensely rich and diverse subfield of biological chemistry.

Intro to amino acids and proteins

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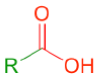
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1.3.2: Introduction to Lipid Structure

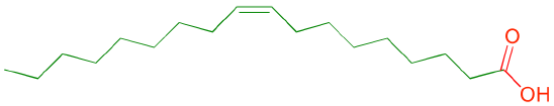
Lipids are a class of biomolecules which includes fats, oils, waxes, and compounds such as cholesterol that are referred to as 'isoprenoids'.. Fats, oils, and waxes all incorporate **fatty acids**, which are composed of hydrocarbon chains terminating in a carboxylic acid/carboxylate group (we will learn in Chapter 7 that carboxylic acids are predominantly in their anionic, carboxylate form in biological environments). Saturated fatty acids contain only alkane carbons (single bonds only), mononsaturated fatty acids contain a single double bond, and polyunsaturated fatty acids contain two or more double bonds. The double bonds in naturally occurring fatty acids are predominantly in the *cis* configuration.



fatty acid

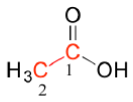


palmitic acid
(a 16-carbon saturated fatty acid)

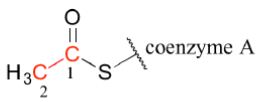


oleic acid
(an 18-carbon monounsaturated fatty acid)

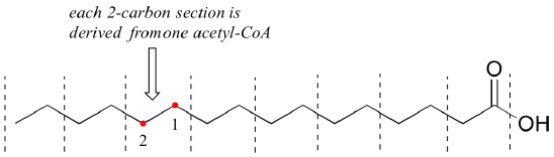
Fatty acids are synthesized in the body by a process in which the hydrocarbon chain is elongated two carbons at a time. Each two-carbon unit is derived from a metabolic intermediate called **acetyl-coA**, which is essentially an acetic acid (vinegar) molecule linked to a large 'carrier' molecule, called coenzyme A, by a thioester functional group. We will see much more of coenzyme A when we study the chemistry of thioesters in chapter 11.



acetic acid

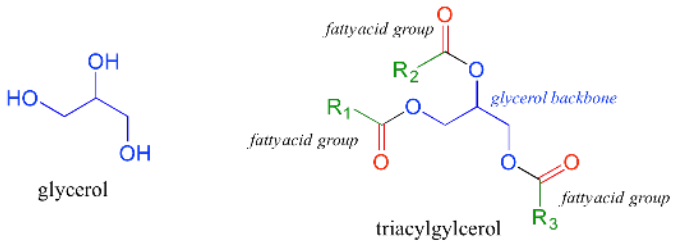


acetyl-coA



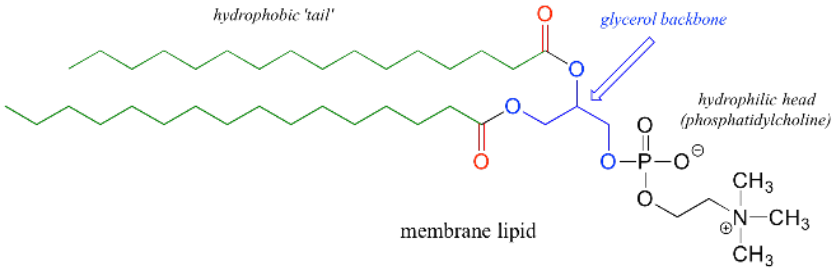
The breakdown of fatty acids in the body also occurs two carbons at a time, and the endpoint is again acetyl-coenzyme A. We will learn about the details of all of the reactions in these metabolic pathways at various places in this book. If you go on to take a biochemistry course, you will learn more about the big picture of fatty acid metabolism - how it is regulated, and how is fits together with other pathways of central metabolism.

Fats and oils are forms of **triacylglycerol**, a molecule composed of a glycerol backbone with three fatty acids linked by ester functional groups.



Solid fats (predominant in animals) are triacylglycerols with long (16-18 carbon) saturated fatty acids. Liquid oils (predominant in plants) have unsaturated fatty acids, sometimes with shorter hydrocarbon chains. In chapter 2 we will learn about how chain length and degree of unsaturation influences the physical properties of fats and oils.

Cell membranes are composed of **membrane lipids**, which are **diacylglycerols** linked to a hydrophilic '**head group**' on the third carbon of the glycerol backbone. The fatty acid chains can be of various lengths and degrees of saturation, and the two chains combined make up the hydrophobic 'tail' of each membrane lipid molecule.



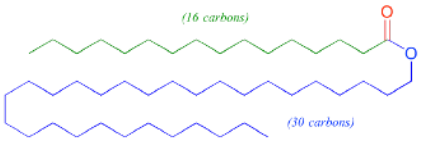
In chapter 2 we will see how these molecules come together to form a cell membrane.

Exercise 1.17

What functional group links the phosphatidylcholine 'head' group to glycerol in the membrane lipid structure shown above?

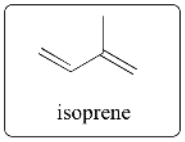
Solutions to exercises

Waxes are composed of fatty acids linked to long chain alcohols through an ester group. Tricontanyl palmitate is a major component of beeswax, and is constituted of a 16-carbon fatty acid linked to a 30-carbon alcohol.

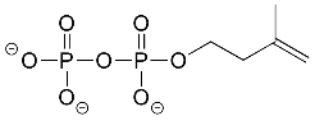


tricontanyl palmitate

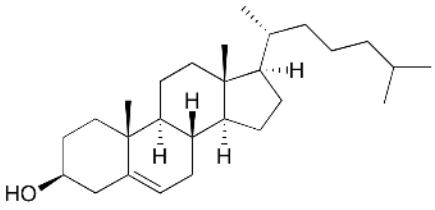
Isoprenoids, a broad class of lipids present in all forms of life, are based on a five-carbon, branched-chain building block called isoprene. In humans, cholesterol and hormones such as testosterone are examples of isoprenoid biomolecules. In plants, isoprenoids include the deeply colored compounds such as lycopene (the red in tomatoes) and carotenoids (the yellows and oranges in autumn leaves).



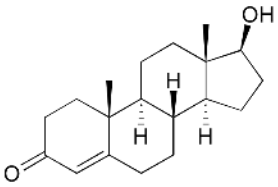
isoprene



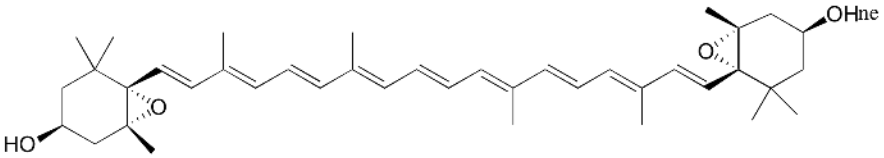
isopentenyl diphosphate



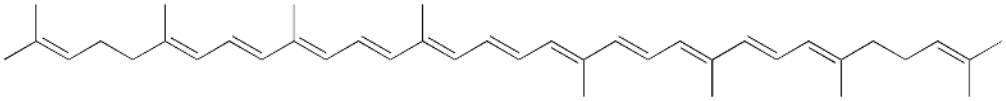
cholesterol



test
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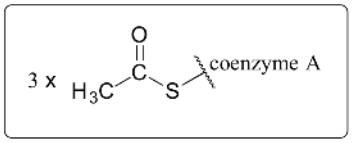


violaxanthin
(a carotenoid)



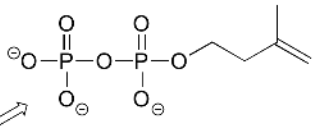
lycopene

In almost all eukaryotes, isopentenyl diphosphate (the building block molecule for all isoprenoid compounds) is synthesized from three acetyl-Coenzyme A molecules. Bacteria and the plastid organelles in plants have a different biosynthetic pathway to isopentenyl diphosphate, starting with pyruvate and glyceraldehyde phosphate.



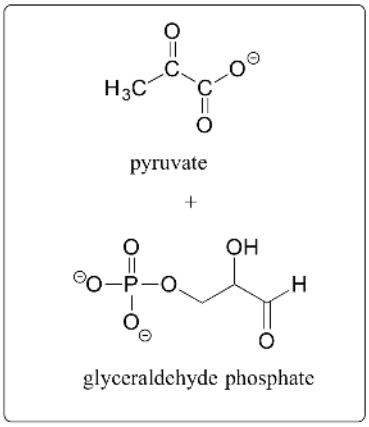
3 x coenzyme A

eukaryotes, archaea



isopentenyl diphosphate

bacteria



pyruvate

+

glyceraldehyde phosphate

isoprenoid compounds

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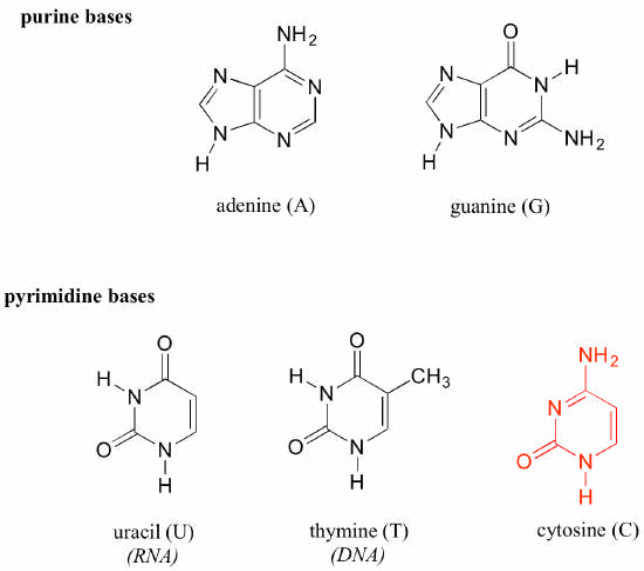
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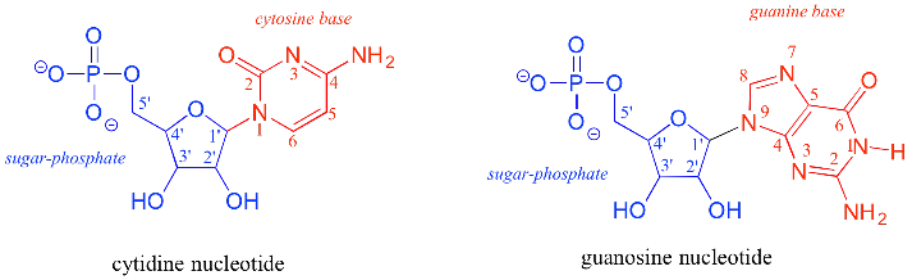
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1.3.3: Introduction to nucleic acid (DNA and RNA) structure

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are polymers composed of monomers called **nucleotides**. An RNA nucleotide consists of a five-carbon sugar phosphate linked to one of four nucleic acid **bases**: guanine (G), cytosine (C), adenine (A) and uracil (U).



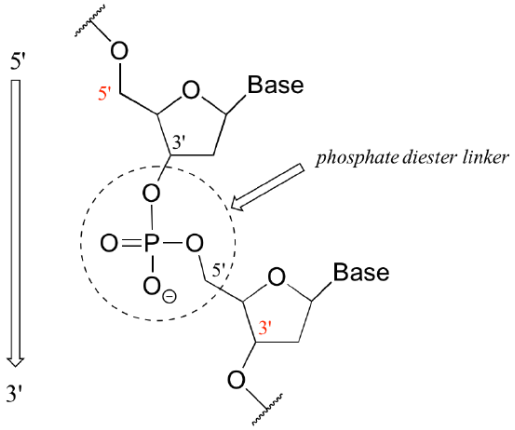


cytidine nucleotide

guanosine nucleotide

In a DNA nucleototide, the sugar is missing the hydroxyl group at the 2' position, and the thymine base (T) is used instead of uracil. The conventional numbering system used for DNA and RNA is shown here for reference - the prime (') symbol is used to distinguish the sugar carbon numbers from the base carbon numbers.

The two 'hooks' on the RNA or DNA monomer are the 5' phosphate and the 3' hydroxyl on the sugar, which in DNA polymer synthesis are linked by a 'phosphate diester' group. By convention, DNA and RNA sequences are written in 5' to 3' direction.



Contributors and Attributions

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1.4: Solutions to Chapter 1 Exercises

E1.1:

a) The atomic number of P (phosphorus) is 15, meaning there are 15 protons. The mass number for the ^{31}P isotope is 31, so:

15 protons + **16 neutrons** = mass number 31

(recall that mass number is number of protons and neutrons).

(for parts b-d, use the same reasoning as above)

b) 15 protons + **17 neutrons** = mass number 32

c) 17 protons + **20 neutrons** = mass number 37

d) 1 proton + **2 neutrons** = mass number 3

e) 6 protons + **8 neutrons** = mass number 14

E1.2:

a) $1s^2 2s^2 2p^3$

b) $1s^2 2s^2 2p^4$

c) $1s^2 2s^2 2p^5$

d) $1s^2 2s^2 2p^6 3s^2$

e) $1s^2 2s^2 2p^6$ (same as Neon atom)

f) $1s^2 2s^2 2p^6 3s^2 3p^6 4s^1$

g) $1s^2 2s^2 2p^6 3s^2 3p^6$ (same as Argon atom)

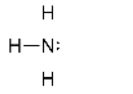
h) $1s^2 2s^2 2p^6 3s^2 3p^6$ (same as Argon atom)

i) $1s^2 2s^2 2p^6 3s^2 3p^4$

j) $1s^2$ (same as Helium atom)

k) $1s^2 2s^2 2p^6 3s^2 3p^6$ (same as Argon atom)

E1.3:



a) ammonia



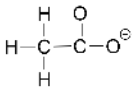
b) ammonium ion



c) amide ion



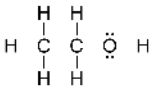
d) formaldehyde



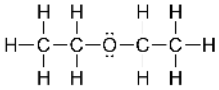
e) acetate ion



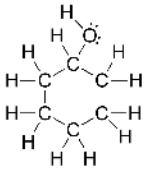
f) methylamine



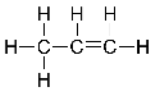
g) ethanol



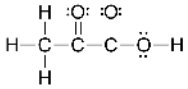
g) diethylether



i) cyclohexanol

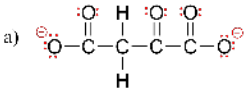


j) propene

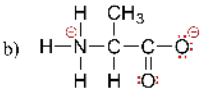


k) pyruvic acid

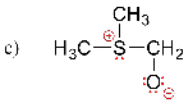
E1.4:



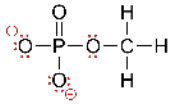
a) malate



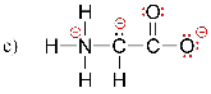
b) alanine



c)



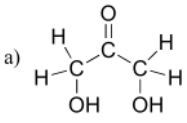
d)



e)

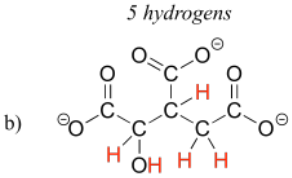
E1.6: Below are full structural drawings, showing all carbons and hydrogens:

6 hydrogens



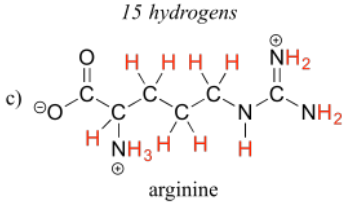
a) dihydroxyacetone

5 hydrogens



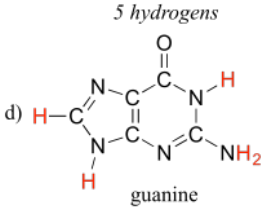
b) isocitrate

15 hydrogens



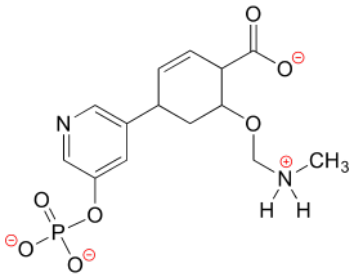
c) arginine

5 hydrogens



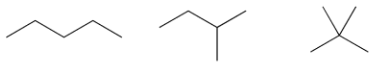
d) guanine

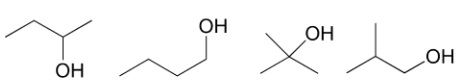
E1.8:

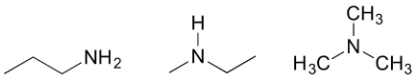


E1.10: There is only one constitutional isomer of ethanol: dimethyl ether CH_3OCH_3

E1.11:

a) 

b) 

c) 

E1.12:

a) carboxylate, sulfide, aromatic, two amide groups (one of which is cyclic)

b) tertiary alcohol, thioester

c) carboxylate, ketone

d) ether, primary amine, alkene

E1.14:

acetic acid: ethanoic acid

chloroform: trichloromethane

acetone: propanone (not 2-propanone, because the '2' in this case would be redundant: if the carbonyl carbon were not in the #2 position, the compound would be an aldehyde not a ketone)

E1.17: The linking group is a phosphate diester

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1.E: Problems for Chapter 1

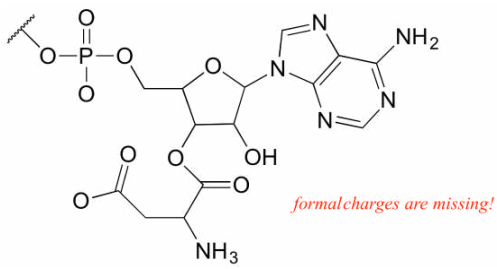
Solutions to selected Chapter 1 problems

P1.1: The figure below illustrates a section of an intermediate compound that forms during the protein synthesis process in the cell. Lone pairs are not shown, as is typical in drawings of organic compounds.

a) The structure as drawn is incomplete, because it is missing formal charges - fill them in.

b) How many hydrogen atoms are on this structure?

c) Identify the two important biomolecule classes (covered in section 1.3) in the structure.



P1.2: Find, in Table 6 ('Structures of common coenzymes', in the tables section at the back of this book), examples of the following:

a) a thiol b) an amide c) a secondary alcohol d) an aldehyde

e) a methyl substituent on a ring f) a primary ammonium ion

g) a phosphate anhydride h) a phosphate ester

P1.3: Draw line structures corresponding to the following compounds. Show all lone pair electrons (and don't forget that non-zero formal charges are part of a correctly drawn structure!)

a) 2,2,4-trimethylpentane b) 3-phenyl-2-propenal

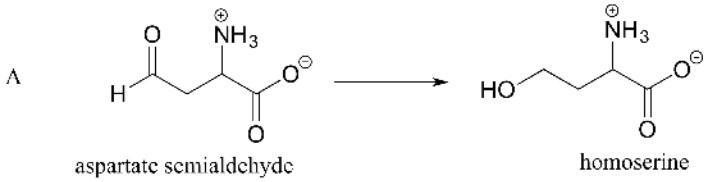
c) 6-methyl-2,5-cyclohexadienone d) 3-methylbutanenitrile

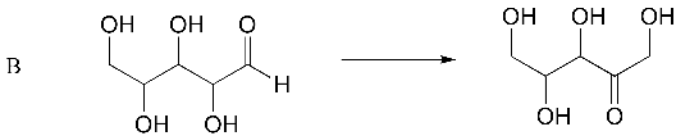
e) 2,6-dimethyldecane f) 2,2,5,5-tetramethyl-3-hexanol

g) methyl butanoate h) *N*-ethylhexanamide

i) 7-fluoroheptanoate j) 1-ethyl-3,3-dimethylcyclohexene

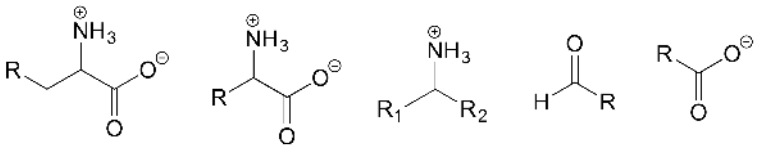
P1.4: Reaction A below is part of the biosynthetic pathway for the amino acid methionine, and reaction B is part of the pentose phosphate pathway of sugar metabolism.





a) What is the functional group transformation that is taking place in each reaction?

b) Keeping in mind that the 'R' abbreviation is often used to denote parts of a larger molecule which are *not* the focus of a particular process, which of the following abbreviated structures could be appropriate to use for aspartate semialdehyde when drawing out details of reaction A?



c) Again using the 'R' convention, suggest an appropriate abbreviation for the reactant in reaction B.

P1.5: Find, in the table of amino acid structures (Table 5), examples of the following:

a) a secondary alcohol b) an amide c) a thiol

d) a sulfide e) a phenol f) a side chain primary ammonium

g) a side chain carboxylate h) a secondary amine

P1.6: Draw correct Lewis structures for ozone (O_3), azide ion, (N_3^-), and bicarbonate ion, HCO_3^-. Include lone pair electrons and formal charges, and use your General Chemistry textbook to review VSEPR theory, which will enable you to draw correct bond geometries.

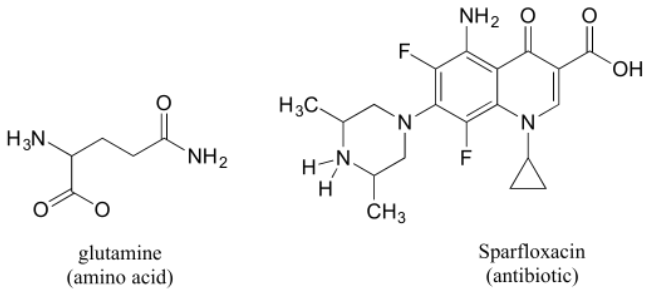
P1.7: Draw one example each of compounds fitting the descriptions below, using line structures. Be sure to include all non-zero formal charges. All atoms should fit one of the common bonding patters discussed in this chapter. There are many possible correct answers - be sure to check your drawings with your instructor or tutor.

a) an 8-carbon molecule with secondary alcohol, primary amine, amide, and *cis*-alkene groups

b) a 12-carbon molecule with carboxylate, diphosphate, and lactone (cyclic ester) groups.

c) a 9-carbon molecule with cyclopentane, alkene, ether, and aldehyde groups

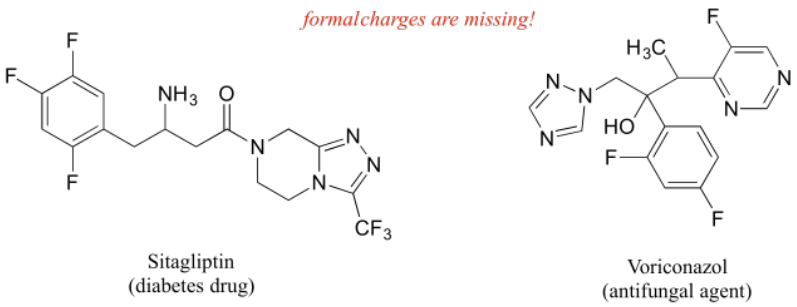
P1.8: Three of the four structures below are missing formal charges.



glutamine
(amino acid)

Sparfloxacin
(antibiotic)

formal charges are missing!



Sitagliptin
(diabetes drug)

Voriconazol
(antifungal agent)

a) Fill in all missing formal charges (assume all atoms have a complete octet of valence electrons).

b) Identify the following functional groups or structural elements (there may be more than one of each): carboxylate, carboxylic acid, cyclopropyl, amide, ketone, secondary ammonium ion, tertiary alcohol.

c) Determine the number of hydrogen atoms in each compound.

https://chem.libretexts.org/@go/page/393396

P1.9:

a) Draw four constitutional isomers with the molecular formula C_4H_8.

b) Draw two open-chain (non-cyclic) constitutional isomers of cyclohexanol (there are more than two possible answers).

P1.10: Draw structures of four different amides with molecular formula C_3H_7NO.

Solutions to selected Chapter 1 problems

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

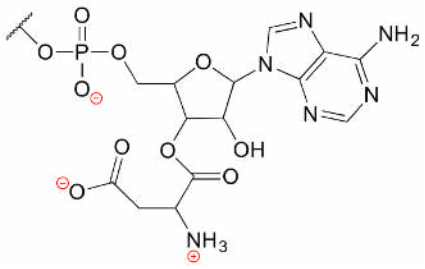
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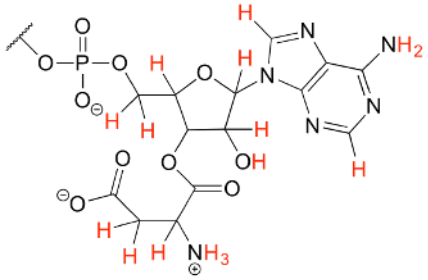
1.0: Solutions to selected Chapter 1 problems

P1.1:

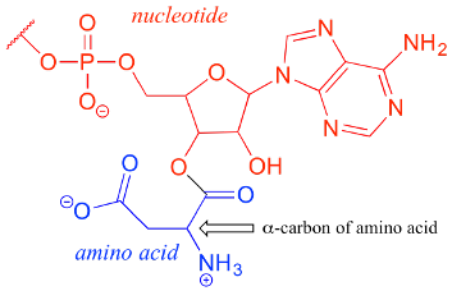
a) Formal charges are located as shown.



b) There are 16 hydrogen atoms:



c) The structure contains a nucleotide segment and an amino acid segment:



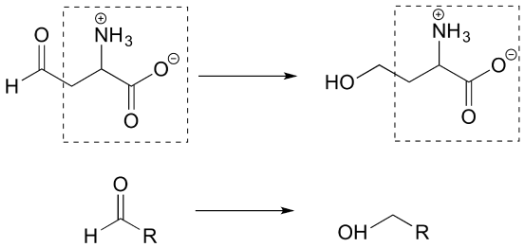
P1.4:

a)

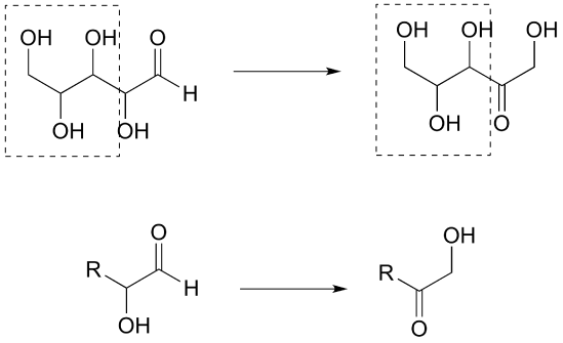
Reaction A: aldehyde to primary alcohol

Reaction B: Secondary alcohol to ketone; aldehyde to primary alcohol

b) The second structure from the right is an appropriate abbreviation. The part of the molecule in the box does not change in the reaction, and this can be abbreviated with 'R'.



c) The part of the molecule in the box does not change in the reaction, and this can be abbreviated with 'R'.



P1.5:

a) Threonine contains a secondary alcohol.

b) Glutamine and asparagine contain amides.

c) Cysteine contains a thiol.

d) Methionine contains a sulfide.

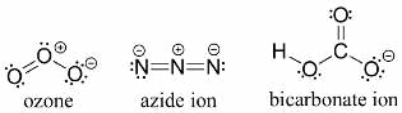
e) Tyrosine contains a phenol.

f) The lysine side chain contains a primary ammonium.

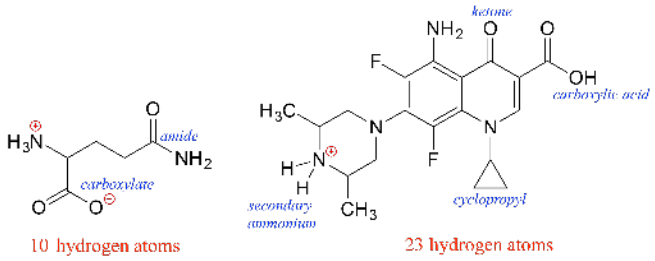
g) The glutamate and aspartate side chains contain carboxylates.

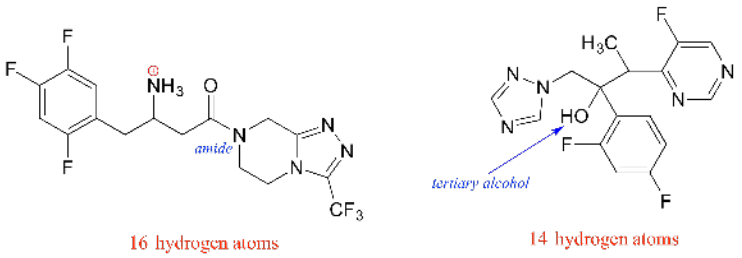
h) Proline contains a secondary amine.

P1.6: Note that according to VSEPR theory, ozone has bent geometry, azide ion is linear, and the geometry around the oxygen and carbon atoms of bicarbonate is bent.

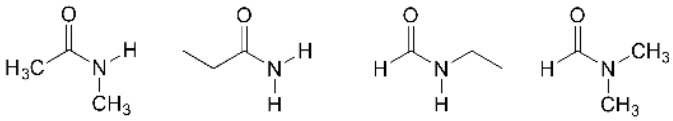


P1.8:





P1.10:



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CHAPTER OVERVIEW

2: Introduction to Organic Structure and Bonding II

While organic and biological chemistry is a very diverse field of study, one fundamental question that interests all organic chemists is how the structure of an organic molecule determines its physical properties. We will look more closely at the nature of single and double covalent bonds, using the concepts of 'hybrid orbitals' and 'resonance' to attempt to explain how orbital overlap results in characteristic geometries and rotational behavior for single and double bonds, as well as bonds that have characteristics of somewhere in between single and double. Then we will move on to a review of the noncovalent interactions between molecules - Van der Waals, ion-ion, dipole-dipole and ion-dipole interactions, and hydrogen bonds - and how they are manifested in the observable physical properties of all organic substances.

2.0: Prelude to Organic Structure and Bonding II

2.1: Valence Bond Theory

2.2: Molecular orbital theory- conjugation and aromaticity

2.3: Resonance

2.4: Non-covalent interactions

2.5: Physical properties of organic compounds

2.6: Solutions to Chapter 2 exercises

2.P: Problems for Chapter 2

1.0: Solutions to selected chapter 2 problems

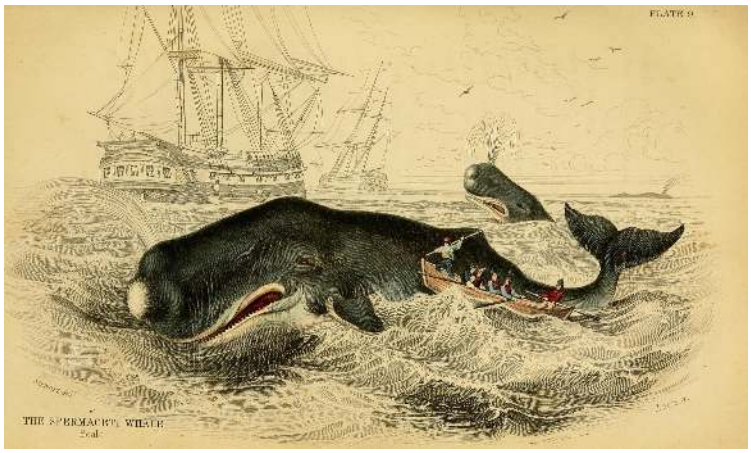
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2.0: Prelude to Organic Structure and Bonding II

What does Moby Dick have in common with train engines and skin cream?

> *"Towards thee I roll, thou all-destroying but unconquering whale; to the last I grapple with thee; from hell's heart I stab at thee; for hate's sake I spit my last breath at thee. Sink all coffins and all hearses to one common pool! and since neither can be mine, let me then tow to pieces, while still chasing thee, though tied to thee, thou damned whale! THUS, I give up the spear!" The harpoon was darted; the stricken whale flew forward; with igniting velocity the line ran through the grooves;--ran foul. Ahab stooped to clear it; he did clear it; but the flying turn caught him round the neck, and voicelessly as Turkish mutes bowstring their victim, he was shot out of the boat, ere the crew knew he was gone. Next instant, the heavy eye-splice in the rope's final end flew out of the stark-empty tub, knocked down an oarsman, and smiting the sea, disappeared in its depths.*
>
> *Herman Melville, Moby Dick*

In the classic 19th century novel 'Moby Dick', Herman Melville's Captain Ahab obsessively hunts down the enormous albino sperm whale which years before had taken one of his legs, the monomaniacal quest ending with Ahab being dragged by the neck to the bottom of the sea by his enormous white nemesis. It is fitting, somehow, that one of the most memorable fictional characters in modern literature should be a real-life 50 ton monster – sperm whales are such fantastic creatures that if they didn't in fact exist, it would stretch the imagination to make them up. They are the largest predator on the planet, diving to depths of up to three kilometers and staying down as long as 90 minutes to hunt the giant squid and other deep-dwelling species that make up the bulk of their diet.



(Credit: https://www.flickr.com/photos/biodivlibrary/)

It would be hard for anyone to mistake a sperm whale for any other creature in the ocean, due to their enormous, squared-off foreheads. It is what is inside this distinctive physical feature, though, that brought them to the edge of extinction in the middle of the 20th century. For over 200 years, sperm whales had been prized by whalers for the oil that fills the 'spermaceti' and 'melon' compartments which make up the bulk of the front part of their bodies. Whalers in the 17th and 18th centuries would lower one of their crew into a hole cut into a captured whale, and he would literally ladle out the 'sperm oil ' by the bucketful, often filling eight barrels from the head of one animal. The different processed components obtained from raw sperm oil had properties that were ideal for a multitude of applications: as a lubricant for everything from sewing machines to train engines, as a fuel for lamps, and as a prized ingredient in cosmetics and skin products.

'Sperm oil' is not really an oil – it is mostly liquid wax. The composition of waxes in sperm oil is complex and variable throughout the life of the animal, but in general contains waxes with saturated and unsaturated hydrocarbon chains ranging from 16 to 24

carbons.

Remarkably, scientists are still not sure about the function of the enormous wax-filled reservoirs in the sperm whale's forehead. The most prevalent hypothesis holds that they play a role in echolocation. In the pitch-black void of the deep ocean a whale's eyes are useless, but it is able to navigate and locate prey in the same way that a bat does, using the reflection of sound waves. In fact, the sonic clicks generated by the sperm whale are the loudest sounds generated by any animal on earth. The wax reservoirs may be used somehow for the directional focusing of these sound waves.

Another intriguing but unproven hypothesis is that the reservoir serves as a buoyancy control device. The wax is normally liquid and buoyant at the whale's normal body temperature, but solidifies and becomes denser than water at lower temperatures. If the diving whale could cool the wax by directing cold seawater around the reservoir and restricting blood flow to the region, it could achieve negative buoyancy and thus conserve energy that otherwise would be expended in swimming down. When it needs to return to the surface, blood could be redirected to the wax, which would melt and become positively buoyant again, thus conserving energy on the upward trip.

Whatever its natural function, it is inarguable that the physical and chemical properties of sperm oil make it valuable, both to the whale and to humans. Fortunately for the world's population of whales, both economic forces and conservation efforts have made virtually all trade in sperm oil a thing of the past. Beginning in the late 19th century, the discovery of new oil fields and advances in petroleum processing led to the use of cheaper mineral oil alternatives for many of the major applications of sperm oil, one of the most notable substitutions being the use of kerosene for lamps. More recently, the 'oil' from the Jojoba plant, a native of the American southwest, has been found to be an excellent substitute for sperm oil in cosmetics and skin products, exhibiting many of the same desirable characteristics. Jojoba oil, like sperm oil, is composed primarily of liquid waxes rather than actual oils, and a major selling point of both is that the oily substance produced by human skin, called sebum, is also composed of about 25% wax.

While organic and biological chemistry is a very diverse field of study, one fundamental question that interests all organic chemists is how the structure of an organic molecule determines its physical properties. To understand why sperm oil has properties that made it both a useful industrial lubricant for humans and an effective buoyancy control and/or sonic lens for a hunting sperm whale, we first have to understand the nature of both the forces holding each wax molecule together – the covalent single and double bonds between atoms – and also the forces governing the noncovalent interactions between one wax molecule and all the others around it – the so-called 'intermolecular forces' which determine physical properties such as viscosity, melting point, and density.

That is what we will learn about in this chapter. First, we will look more closely at the nature of single and double covalent bonds, using the concepts of 'hybrid orbitals' and 'resonance' to attempt to explain how orbital overlap results in characteristic geometries and rotational behavior for single and double bonds, as well as bonds that have characteristics of somewhere in between single and double. Then we will move on to a review of the noncovalent interactions between molecules - Van der Waals, ion-ion, dipole-dipole and ion-dipole interactions, and hydrogen bonds - and how they are manifested in the observable physical properties of all organic substances.

Before reading any further on this chapter, you will probably need to go back and review some topics from your Introductory Chemistry course. Be sure that you understand the concepts of atomic orbitals, atomic electron configuration, and that you are able to describe *s* and *p* orbitals and orbital lobes and nodes. Now would also be a very good time to review *VSEPR* theory. You might want to watch review tutorials from Kahn academy on atomic orbitals and electron configuration and dot structures and VSEPR theory.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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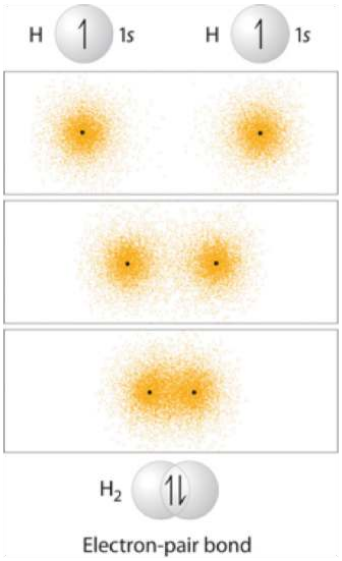
2.1: Valence Bond Theory

As we have been discussing how to use Lewis structures to depict the bonding in organic compounds, we have been very vague so far in our language about the actual nature of the chemical bonds themselves. We know that a covalent bond involves the 'sharing' of a pair of electrons between two atoms - but how does this happen, and how does it lead to the formation of a bond holding the two atoms together?

Valence bond theory is most often used to describe bonding in organic molecules. In this model, bonds are considered to form from the overlap of two atomic orbitals on different atoms, each orbital containing a single electron. In looking at simple inorganic molecules such as molecular hydrogen (H_2) or hydrogen fluoride (HF), our present understanding of *s* and *p* atomic orbitals will suffice. In order to explain the bonding in organic molecules, however, we will need to introduce the concept of **hybrid orbitals**.

The sigma bond in the H_2 molecule

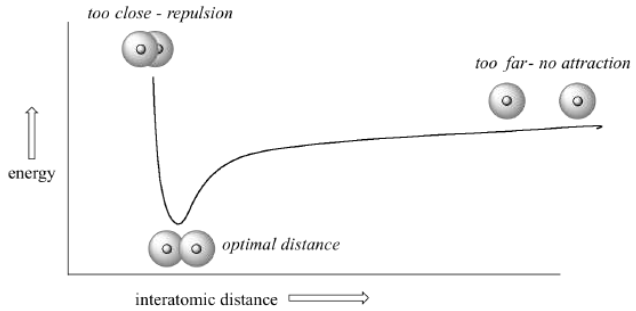
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two hydrogen nuclei share their electrons to form a covalent bond, what we mean in valence bond theory terms is that the two spherical 1*s* orbitals (the grey spheres in the figure below) overlap, and contain two electrons with opposite spin.



These two electrons are now attracted to the positive charge of *both* of the hydrogen nuclei, with the result that they serve as a sort of 'chemical glue' holding the two nuclei together.

How far apart are the two nuclei? If they are too far apart, their respective 1*s* orbitals cannot overlap, and thus no covalent bond can form - they are still just two separate hydrogen atoms. As they move closer and closer together, orbital overlap begins to occur, and a bond begins to form. This lowers the potential energy of the system, as new, *attractive* positive-negative electrostatic interactions become possible between the nucleus of one atom and the electron of the second.

But something else is happening at the same time: as the atoms get closer, the *repulsive* positive-positive interaction between the two nuclei also begins to increase.



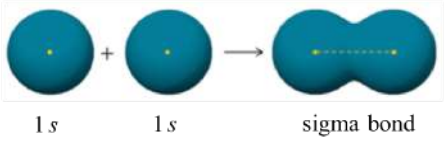
At first this repulsion is more than offset by the attraction between nuclei and electrons, but at a certain point, as the nuclei get even closer, the repulsive forces begin to overcome the attractive forces, and the potential energy of the system rises quickly. When the two nuclei are 'too close', we have an unstable, high-energy situation. There is a defined optimal distance between the nuclei in which the potential energy is at a minimum, meaning that the combined attractive and repulsive forces add up to the greatest overall attractive force. This optimal internuclear distance is the **bond length**. For the H_2 molecule, the distance is 74 pm (picometers, 10^{-12} meters). Likewise, the difference in potential energy between the lowest energy state (at the optimal internuclear distance) and the state where the two atoms are completely separated is called the **bond dissociation energy,** or, more simply**, bond strength**. For the hydrogen molecule, the H-H bond strength is equal to about 435 kJ/mol.

Every covalent bond in a given molecule has a characteristic length and strength. In general, the length of a typical carbon-carbon single bond in an organic molecule is about 150 pm, while carbon-carbon double bonds are about 130 pm, carbon-oxygen double bonds are about 120 pm, and carbon-hydrogen bonds are in the range of 100 to 110 pm. The strength of covalent bonds in organic molecules ranges from about 234 kJ/mol for a carbon-iodine bond (in thyroid hormone, for example), about 410 kJ/mole for a typical carbon-hydrogen bond, and up to over 800 kJ/mole for a carbon-carbon triple bond.

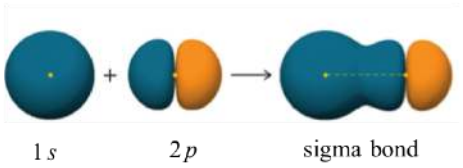
Table of bond lengths and bond energies

It is not accurate, however, to picture covalent bonds as rigid sticks of unchanging length - rather, it is better to picture them as *springs* which have a defined length when relaxed, but which can be compressed, extended, and bent. This 'springy' picture of covalent bonds will become very important in chapter 4, when we study the analytical technique known as infrared (IR) spectroscopy.

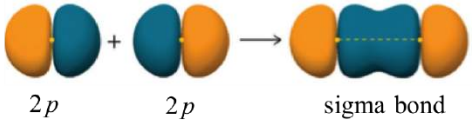
One more characteristic of the covalent bond in H_2 is important to consider at this point. The two overlapping 1*s* orbitals can be visualized as two spherical balloons being pressed together. This means that the bond has **cylindrical symmetry**: if we were to take a cross-sectional plane of the bond at any point, it would form a circle. This type of bond is referred to as a **sigma (σ) bond**.



A sigma bond can be formed by overlap of an *s* atomic orbital with a *p* atomic orbital. Hydrogen fluoride (HF) is an example:

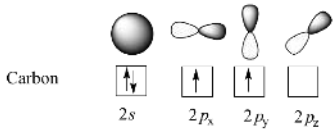


A sigma bond can also be formed by the overlap of two *p* orbitals. The covalent bond in molecular fluorine, F_2, is a sigma bond formed by the overlap of two half-filled 2*p* orbitals, one from each fluorine atom.

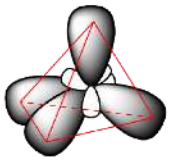


sp^3 hybrid orbitals and tetrahedral bonding

Now let's look more carefully at bonding in organic molecules, starting with methane, CH_4. Recall the valence electron configuration of a carbon atom:



This picture is problematic when it comes to describing the *bonding* in methane. How does the carbon form four bonds if it has only two half-filled *p* orbitals available for bonding? A hint comes from the experimental observation that the four C-H bonds in methane are arranged with **tetrahedral** geometry about the central carbon, and that each bond has the same length and strength. In order to explain this observation, valence bond theory relies on a concept called **orbital hybridization**. In this picture, the four valence orbitals of the carbon (one 2*s* and three 2*p* orbitals) combine mathematically (remember: orbitals are described by wave equations) to form four equivalent **hybrid orbitals**, which are called ***sp*^{3} orbitals** because they are formed from mixing one *s* and three *p* orbitals. In the new electron configuration, each of the four valence electrons on the carbon occupies a single sp^3 orbital.



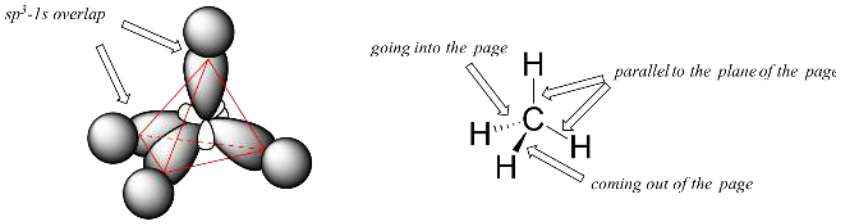
four sp^3 orbitals in tetrahedral orientation

interactive 3D model

(*select 'load sp^3' and 'load H 1s' to see orbitals*)

This geometric arrangement makes perfect sense if you consider that it is precisely this angle that allows the four orbitals (and the electrons in them) to be as far apart from each other as possible. This is simply a restatement of the Valence Shell Electron Pair Repulsion (VSEPR) theory that you learned in General Chemistry: electron pairs (in orbitals) will arrange themselves in such a way as to remain as far apart as possible, due to negative-negative electrostatic repulsion.

Each C-H bond in methane, then, can be described as a sigma bond formed by overlap between a half-filled 1*s* orbital in a hydrogen atom and the larger lobe of one of the four half-filled sp^3 hybrid orbitals in the central carbon. The length of the carbon-hydrogen bonds in methane is 109 pm.



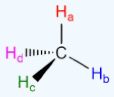
tetrahedral sp^3 bonding in methane

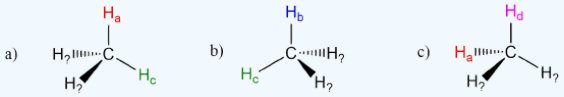
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: the solid / dashed wedge system. In this convention, a solid wedge simply represents a bond that is meant to be pictured emerging from the plane of the page. A dashed wedge represents a bond that

is meant to be pictured pointing into, or behind, the plane of the page. Normal lines imply bonds that lie in the plane of the page. This system takes a little bit of getting used to, but with practice your eye will learn to immediately 'see' the third dimension being depicted.

Exercise 2.1

Imagine that you could distinguish between the four hydrogen atoms in a methane molecule, and labeled them H_a through H_d. In the images below, the *exact same* methane molecule is rotated and flipped in various positions. Draw the missing hydrogen atom labels. (It will be much easier to do this if you make a model.)



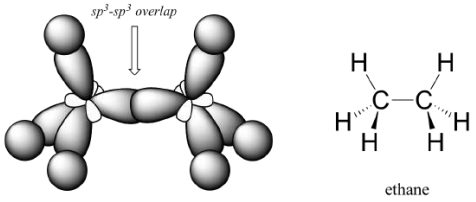


Exercise 2.2

What kind of orbitals overlap to form the C-Cl bonds in chloroform, $CHCl_3$?

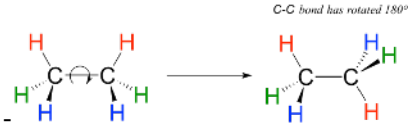
Solutions to exercises

How does this bonding picture extend to compounds containing carbon-carbon bonds? In ethane (CH_3CH_3), both carbons are sp^3-hybridized, meaning that both have four bonds with tetrahedral geometry. The carbon-carbon bond, with a bond length of 154 pm, is formed by overlap of one sp^3 orbital from each of the carbons, while the six carbon-hydrogen bonds are formed from overlaps between the remaining sp^3 orbitals on the two carbons and the 1*s* orbitals of hydrogen atoms. All of these are sigma bonds.



Interactive model of ethane

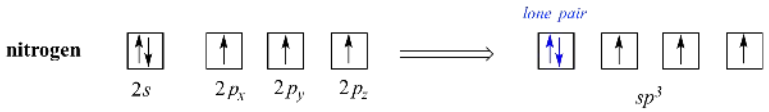
Because they are formed from the end-on-end overlap of two orbitals, *sigma bonds are free to rotate*. This means, in the case of ethane molecule, that the two methyl (CH_3) groups can be pictured as two wheels on an axle, each one able to rotate with respect to the other.

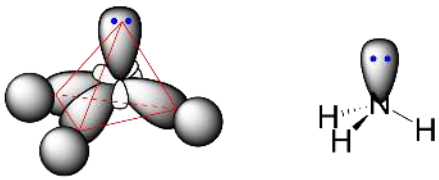


Video

In chapter 3 we will learn more about the implications of rotational freedom in sigma bonds, when we discuss the 'conformation' of organic molecules.

The sp^3 bonding picture is also used to described the bonding in amines, including ammonia, the simplest amine. Just like the carbon atom in methane, the central nitrogen in ammonia is sp^3-hybridized. With nitrogen, however, there are five rather than four valence electrons to account for, meaning that three of the four hybrid orbitals are half-filled and available for bonding, while the fourth is fully occupied by a nonbonding pair (lone pair) of electrons.



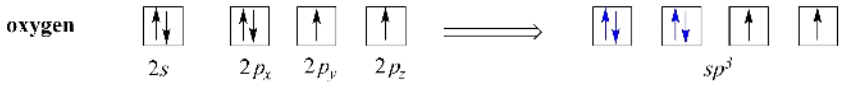


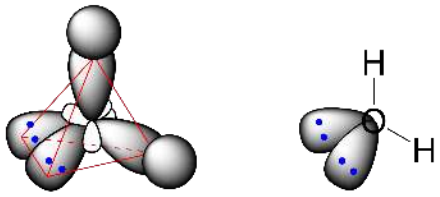
ammonia

space-filling image

The bonding arrangement here is also tetrahedral: the three N-H bonds of ammonia can be pictured as forming the base of a trigonal pyramid, with the fourth orbital, containing the lone pair, forming the top of the pyramid. Recall from your study of VSEPR theory in General Chemistry that the lone pair, with its slightly greater repulsive effect, 'pushes' the three N-H s bonds away from the top of the pyramid, meaning that the H-N-H bond angles are slightly less than tetrahedral, at 107.3˚ rather than 109.5˚.

VSEPR theory also predicts, accurately, that a water molecule is 'bent' at an angle of approximately 104.5˚. The bonding in water results from overlap of two of the four sp^3 hybrid orbitals on oxygen with 1*s* orbitals on the two hydrogen atoms. The two nonbonding electron pairs on oxygen are located in the two remaining sp^3 orbitals.





water

Exercise 2.3

Draw, in the same style as the figures above, orbital pictures for the bonding in a) methylamine, and b) ethanol.

Solutions to exercises

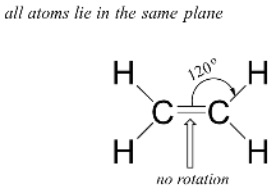
video tutorial on sp^3 orbitals and sigma bonds

sp^2 and **sp** hybrid orbitals and pi bonds

The valence bond theory, along with the hybrid orbital concept, does a very good job of describing double-bonded compounds such as ethene. Three experimentally observable characteristics of the ethene molecule need to be accounted for by a bonding model:

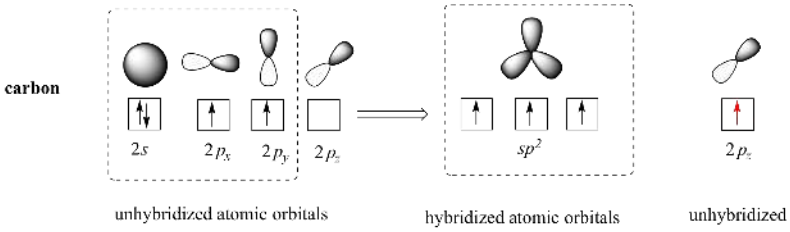
1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 134 pm, significantly shorter than the 154 pm single carbon-carbon bond in ethane.

3. There is a significant barrier to rotation about the carbon-carbon double bond.

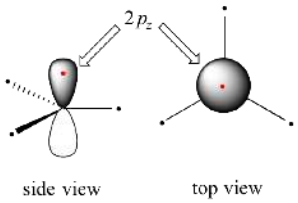


ethene

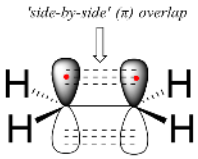
Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$ orbitals – combine to form three ***sp*^{2} hybrids**, leaving the $2p_z$ orbital unhybridized.



The three sp^2 hybrids are arranged with trigonal planar geometry, pointing to the three corners of an equilateral triangle, with angles of 120° between them. The unhybridized $2p_z$ orbital is *perpendicular* to this plane (in the next several figures, sp^2 orbitals and the sigma bonds to which they contribute are represented by lines and wedges; only the $2p_z$ orbitals are shown in the 'space-filling' mode).



The carbon-carbon double bond in ethene consists of one sigma bond, formed by the overlap of two sp^2 orbitals, and a second bond, called a **pi (π) bond**, which is formed by the *side-by-side* overlap of the two unhybridized $2p_z$ orbitals from each carbon.

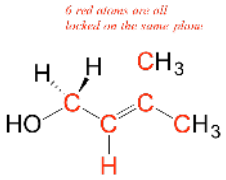


animation

video tutorial

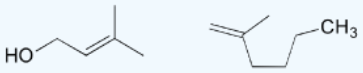
Interactive 3D model *(select 'show resulting pi orbital')*

Unlike a sigma bond, a pi bond does *not* have cylindrical symmetry. If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane. This argument extends to larger alkene groups: in each case, six atoms lie in the same plane.



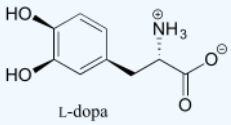
Exercise 2.4

Redraw the structures below, indicating the six atoms that lie in the same plane due to the carbon-carbon double bond.



Exercise 2.5

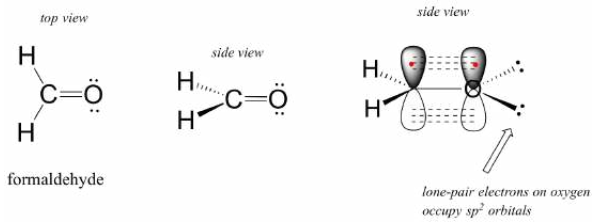
What is wrong with the way the following structure is drawn?



L-dopa

Solutions to exercises

A similar picture can be drawn for the bonding in carbonyl groups, such as formaldehyde. In this molecule, the carbon is sp^2-hybridized, and we will assume that the oxygen atom is also sp^2 hybridized. The carbon has three sigma bonds: two are formed by overlap between sp^2 orbitals with 1*s* orbitals from hydrogen atoms, and the third sigma bond is formed by overlap between the remaining carbon sp^2 orbital and an sp^2 orbital on the oxygen. The two lone pairs on oxygen occupy its other two sp^2 orbitals.



spacefilling image

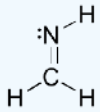
interactive 3D model

The pi bond is formed by side-by-side overlap of the unhybridized $2p_z$ orbitals on the carbon and the oxygen. Just like in alkenes, the $2p_z$ orbitals that form the pi bond are perpendicular to the plane formed by the sigma bonds.

Exercise 2.6

a: Draw a diagram of hybrid orbitals in an sp^2-hybridized nitrogen.

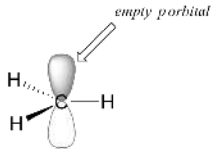
b: Draw a figure showing the bonding picture for the imine below.



c: In your drawing for part b, what kind of orbital holds the nitrogen lone pair?

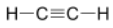
Solutions to exercises

Recall that carbocations are transient, high-energy species in which a carbon only has three bonds (rather than the usual four) and a positive formal charge. We will have much more to say about carbocations in this and later chapters. For now, though, the important thing to understand is that a carbocation can be described as an sp^2-hybridized carbon with an ***empty*** *2p* orbital perpendicular to the plane of the sigma bonds.



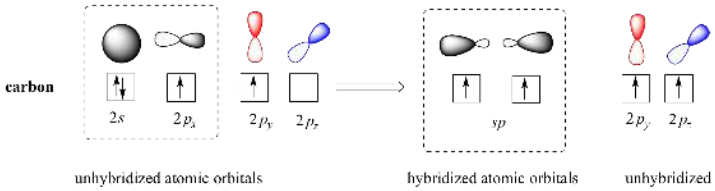
methyl carbocation, CH_3^+

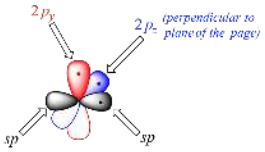
Finally, the hybrid orbital concept applies as well to triple-bonded groups, such as alkynes and nitriles. Consider, for example, the structure of ethyne (common name acetylene), the simplest alkyne.



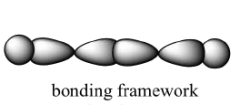
ethyne
(common name acetylene)

Both the VSEPR theory and experimental evidence tells us that the molecule is linear: all four atoms lie in a straight line. The carbon-carbon triple bond is only 120 pm long, shorter than the double bond in ethene, and is very strong, about 837 kJ/mol. In the hybrid orbital picture of acetylene, both carbons are ***sp*-hybridized**. In an *sp*-hybridized carbon, the 2*s* orbital combines with the $2p_x$ orbital to form two *sp* hybrid orbitals that are oriented at an angle of 180° with respect to each other (eg. along the x axis). The $2p_y$ and $2p_z$ orbitals remain unhybridized, and are oriented perpendicularly along the y and z axes, respectively.

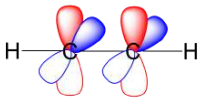




The carbon-carbon sigma bond, then, is formed by the overlap of one *sp* orbital from each of the carbons, while the two carbon-hydrogen sigma bonds are formed by the overlap of the second *sp* orbital on each carbon with a 1*s* orbital on a hydrogen. Each carbon atom still has two half-filled $2p_y$ and $2p_z$ orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two perpendicular pairs of 2*p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds).



bonding framework
in ethyne



π overlap in ethyne

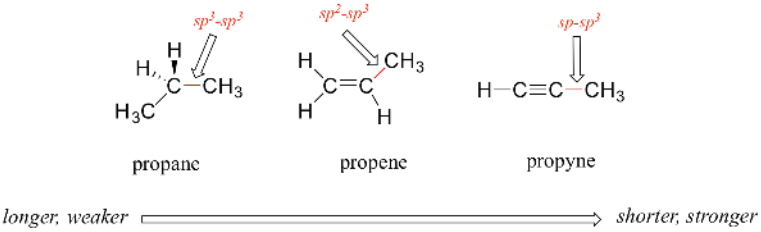
interactive 3D model

Exercise 2.7

Look at the structure of thiamine diphosphate in the 'structures of common coenzymes' table. Identify the hybridization of all carbon atoms in the molecule.

Solutions to exercises

The hybrid orbital concept nicely explains another experimental observation: single bonds adjacent to double and triple bonds are progressively shorter and stronger than single bonds adjacent to other single bonds. Consider for example, the carbon-carbon single bonds in propane, propene, and propyne.

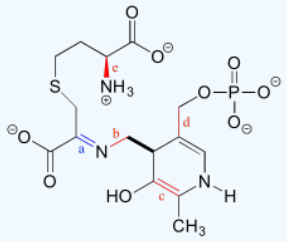


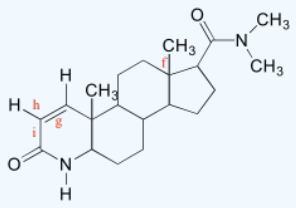
All three are single (sigma) bonds; the bond in propyne is shortest and strongest, while the bond in propane is longest and weakest. The explanation is relatively straightforward. An *sp* orbital is composed of one *s* orbital and one *p* orbital, and thus it has 50% *s* character and 50% *p* character. sp^2 orbitals, by comparison, have 33% *s* character and 67% *p* character, while sp^3 orbitals have 25% *s* character and 75% *p* character. Because of their spherical shape, 2*s* orbitals are smaller, and hold electrons closer and 'tighter' to the nucleus, compared to 2*p* orbitals. It follows that electrons in an *sp* orbital, with its greater *s* character, are closer to the nucleus than electrons in an sp^2 or sp^3 orbital. Consequently, bonds involving sp-sp^3 overlap (as in propyne) are shorter and stronger than bonds involving sp^2-sp^3 overlap (as in propene). Bonds involving sp^3-sp^3 overlap (as in propane) are the longest and weakest of the three.

? Exercise 2.8

a) What kinds of orbitals are overlapping in bonds b-i indicated below? Be sure to distinguish between sigma and pi bonds. An example is provided for bond 'a'.

b) In what kind of orbital is the lone pair of electrons located on the nitrogen atom of bond a? Of bond e?


intermediate compound in amino acid metabolism


Finasteride
(trade name Propecia, a hair-loss drug for men from Merck Pharmacueticals)

Bond a:
sigma bond: overlap of sp^2 orbital on N and sp^2 orbital on C
pi bond: overlap of 2*p* orbital on N and 2*p* orbital on C

Solutions to exercises

Khan Academy video tutorial on valence bond theory / hybrid orbitals

Contributors and Attributions

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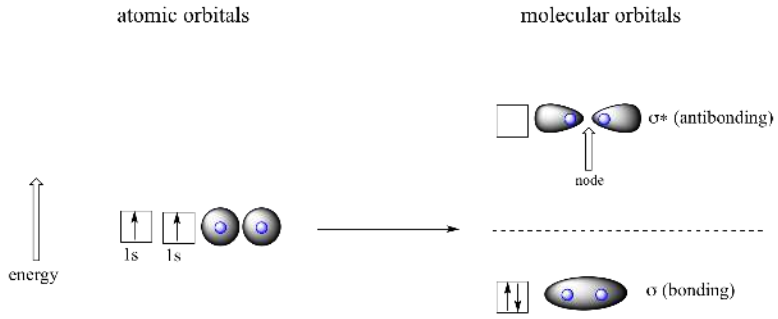
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2.2: Molecular orbital theory- conjugation and aromaticity

Valence bond theory does a remarkably good job at explaining the bonding geometry of many of the functional groups in organic compounds. There are some areas, however, where the valence bond theory falls short. It fails to adequately account, for example, for some interesting properties of compounds that contain alternating double and single bonds. In order to understand these properties, we need to think about chemical bonding in a new way, using the ideas of molecular orbital (MO) theory.

Let's go back and consider again the simplest possible covalent bond: the one in molecular hydrogen (H_2). When we described the hydrogen molecule using valence bond theory, we said that the two 1*s* orbitals from each atom overlap, allowing the two electrons to be shared and thus forming a covalent bond. In molecular orbital theory, we make a further statement: we say that the two atomic 1*s* orbitals mathematically combine to form two new orbitals. Recall that an atomic orbital (such as the 1s orbital of a hydrogen atom) describes a region of space around a single atom inside which electrons are likely to be found. *A molecular orbital describes a region of space around two or more atoms inside which electrons are likely to be found.*

Mathematical principles tell us that when orbitals combine, the number of orbitals before the combination takes place must equal the number of new orbitals that result from the combination – orbitals don't just disappear! We saw this previously when we discussed hybrid orbitals: one *s* and three *p* orbitals make four sp^3 hybrids. When two atomic 1*s* orbitals combine in the formation of H_2, the result is *two* **sigma (σ) orbitals**.



Molecular orbitals for H_2

According to MO theory, one sigma orbital is lower in energy than either of the two isolated atomic 1*s* orbitals –this lower sigma orbital is referred to as a **bonding molecular orbital**. The second, **'sigma star' (sigma*, σ*) orbital** is higher in energy than the two atomic 1*s* orbitals, and is referred to as an **antibonding molecular orbital**.

The bonding sigma orbital, which holds both electrons in the ground state of the molecule, is egg-shaped, encompassing the two nuclei, and with the highest likelihood of electrons being in the area between the two nuclei. The high-energy, antibonding sigma* orbital can be visualized as a pair of droplets, with areas of higher electron density near each nucleus and a 'node', (area of zero electron density) midway between the two nuclei.

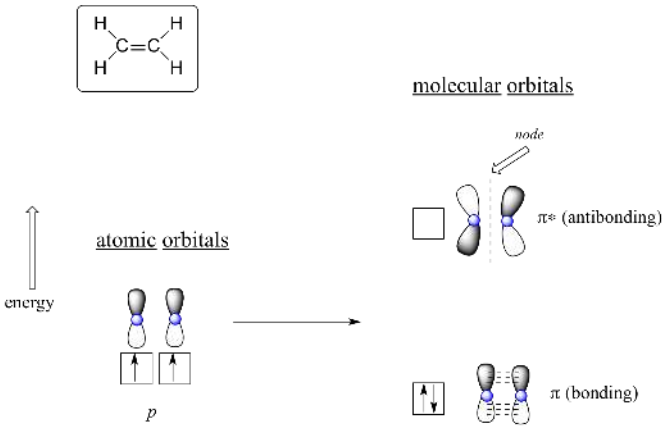
Remember that we are thinking here about electron behavior as *wave behavior*. When two separate waves combine, they can do so with **constructive interference**, where the two amplitudes build up and reinforce one another, or **destructive interference**, where the two amplitudes cancel one another out. Bonding MOs are the consequence of constructive interference between two atomic orbitals, which results in an attractive interaction and an increase in electron density between the nuclei. Antibonding MO's are the consequence of destructive interference which results in a repulsive interaction and a region of zero electron density between the nuclei (in other words, a node).

Following the same *aufbau* ('building up') principle you learned in General Chemistry for writing out electron configurations, we place the two electrons in the H_2 molecule in the lowest energy molecular orbital, which is the (bonding) sigma orbital. The bonding (attracting) MO is full, and the antibonding (repulsing) MO is empty.

MO theory and conjugated pi bonds

The advantage of using MO theory to understand bonding in organic molecules becomes more apparent when we think about pi bonds. Let's first consider the pi bond in ethene from an MO theory standpoint (in this example we will be disregarding the sigma

bonds in the molecule, and thinking *only* about the pi bond). We start with two atomic orbitals: one unhybridized 2p orbital from each carbon. Each contains a single electron. In MO theory, the two atomic combine mathematically to form two **pi (π) molecular orbitals**, one a low-energy pi bonding orbital and one a high-energy pi* (π*) antibonding orbital.



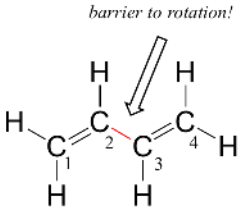
Molecular orbitals for ethene (ethylene)

In the bonding pi orbital, the two shaded lobes of the *p* orbitals interact *constructively* with each other, as do the two unshaded lobes (remember, the arbitrary shading choice represents mathematical (+) and (-) signs for the mathematical wavefunction describing the orbital). There is increased electron density between the two carbon nuclei in the molecular orbital - it is a bonding interaction.

In the higher-energy antibonding pi* orbital, the shaded lobe of one *p* orbital interacts *destructively* with the unshaded lobe of the second *p* orbital, leading to a node between the two nuclei and overall repulsion between the carbon nuclei.

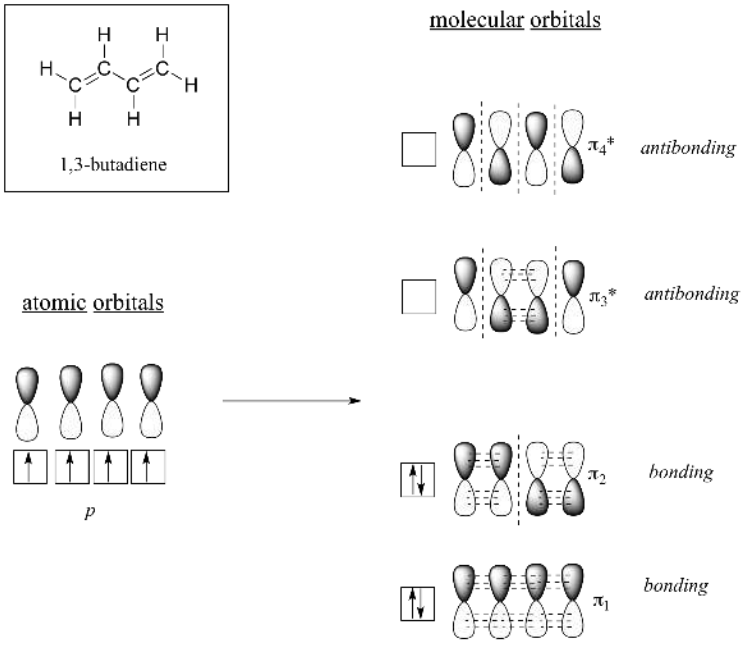
Again using the 'building up' principle, we place the two electrons in the lower-energy, bonding pi molecular orbital. The antibonding pi* orbital remains empty.

Next, we'll consider the 1,3-butadiene molecule. From valence orbital theory alone we might expect that the C_2-C_3 bond in this molecule, because it is a sigma bond, would be able to rotate freely.



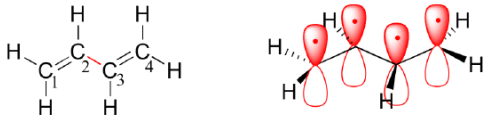
Experimentally, however, it is observed that there is a significant barrier to rotation about the C_2-C_3 bond, and that the entire molecule is planar. In addition, the C_2-C_3 bond is 148 pm long, shorter than a typical carbon-carbon single bond (about 154 pm), though longer than a typical double bond (about 134 pm).

Molecular orbital theory accounts for these observations with the concept of **delocalized pi bonds**. In this picture, the four *2p* atomic orbitals combine mathematically to form four pi molecular orbitals of increasing energy. Two of these - the bonding pi orbitals - are lower in energy than the *p* atomic orbitals from which they are formed, while two - the antibonding pi* orbitals - are higher in energy.



The lowest energy molecular orbital, pi_1, has only constructive interaction and zero nodes. Higher in energy, but still lower than the isolated *p* orbitals, the pi_2 orbital has one node but two constructive interactions - thus it is still a bonding orbital overall. Looking at the two antibonding orbitals, pi_3* has two nodes and one constructive interaction, while pi_4* has three nodes and zero constructive interactions.

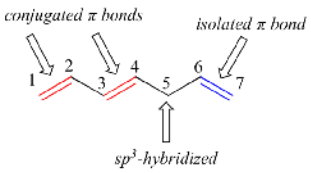
By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding pi_1 and pi_2 MO's. Because pi_1 includes constructive interaction between C_2 and C_3, there is a degree, in the 1,3-butadiene molecule, of pi-bonding interaction between these two carbons, which accounts for its shorter length and the barrier to rotation. The valence bond picture of 1,3-butadiene shows the two pi bonds as being isolated from one another, with each pair of pi electrons 'stuck' in its own pi bond. However, molecular orbital theory predicts (accurately) that the four pi electrons are to some extent delocalized, or 'spread out', over the whole pi system.



1,3-butadiene

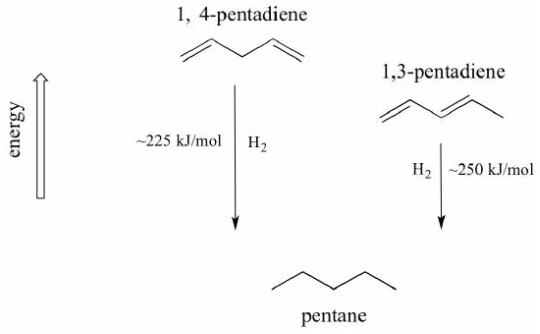
space-filling view

1,3-butadiene is the simplest example of a system of **conjugated pi bonds**. To be considered conjugated, two or more pi bonds must be separated by only one single bond – in other words, there cannot be an intervening sp^3-hybridized carbon, because this would break up the overlapping system of parallel *p* orbitals. In the compound below, for example, the C_1-C_2 and C_3-C_4 double bonds are conjugated, while the C_6-C_7 double bond is **isolated** from the other two pi bonds by sp^3-hybridized C_5.



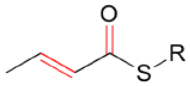
A very important concept to keep in mind is that *there is an inherent thermodynamic stability associated with conjugation.* This stability can be measured experimentally by comparing the **heat of hydrogenation** of two different dienes. (Hydrogenation is a reaction type that we will learn much more about in chapter 15: essentially, it is the process of adding a hydrogen molecule - two

protons and two electrons - to a pi bond). When the two *conjugated* double bonds of 1,3-pentadiene are 'hydrogenated' to produce pentane, about 225 kJ is released per mole of pentane formed. Compare that to the approximately 250 kJ/mol released when the two *isolated* double bonds in 1,4-pentadiene are hydrogenated, also forming pentane.

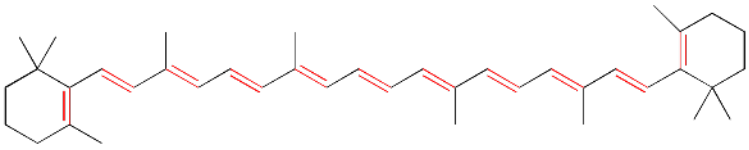


The conjugated diene is lower in energy: in other words, it is more stable. In general, conjugated pi bonds are more stable than isolated pi bonds.

Conjugated pi systems can involve oxygen and nitrogen atoms as well as carbon. In the metabolism of fat molecules, some of the key reactions involve alkenes that are conjugated to carbonyl groups.



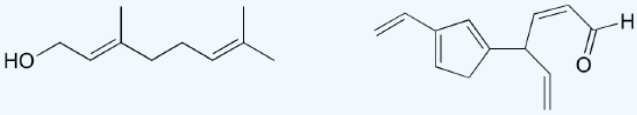
In chapter 4, we will see that MO theory is very useful in explaining why organic molecules that contain extended systems of conjugated pi bonds often have distinctive colors. beta-carotene, the compound responsible for the orange color of carrots, has an extended system of 11 conjugated pi bonds.



beta-carotene

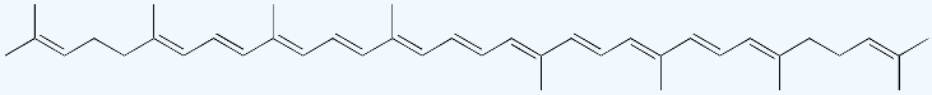
Exercise 2.9

Identify all conjugated and isolated double bonds in the structures below. For each conjugated pi system, specify the number of overlapping *p* orbitals, and how many pi electrons are shared among them.



Exercise 2.10

Identify all isolated and conjugated double bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?

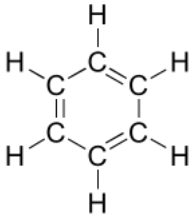


lycopene

Solutions to exercises

Aromaticity

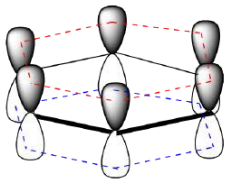
Molecular orbital theory is especially helpful in explaining the unique properties of **aromatic** compounds such as benzene:



3D interactive model of benzene

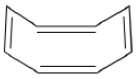
Although benzene is most often drawn with three double bonds and three single bonds, in fact all of the carbon-carbon bonds are exactly the same length (138 pm). In addition, the pi bonds in benzene are significantly less reactive than 'normal' pi bonds, either isolated or conjugated. Something about the structure of benzene makes its pi bonding arrangement especially stable. This 'something' has a name: it is called 'aromaticity'.

What exactly is this 'aromatic' property that makes the pi bonds in benzene so stable? In large part, the answer to this question lies in the fact that benzene is a *cyclic* molecule in which all of the ring atoms are sp^2-hybridized. This allows the pi electrons to be delocalized in molecular orbitals that extend all the way around the ring, above and below the plane. For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly. Benzene is indeed known to be a flat molecule.



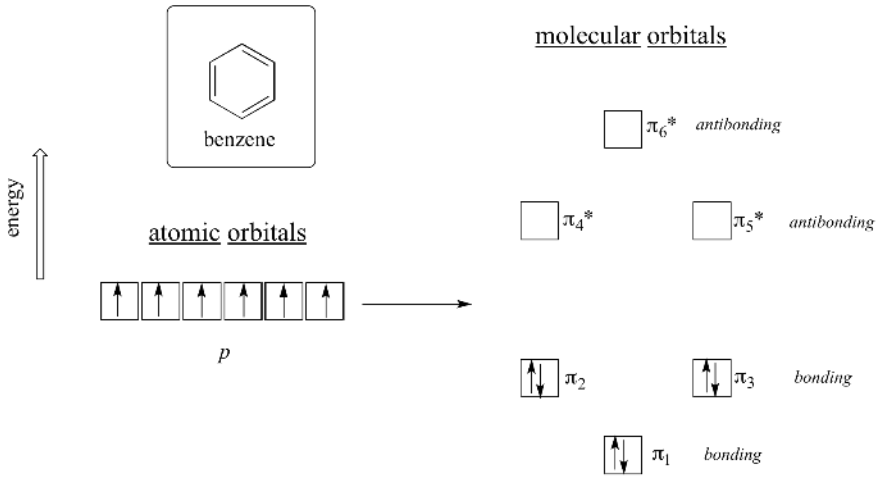
π electrons delocalized around the ring, above and below the plane

Do all cyclic molecules with alternating single and double bonds have this same aromatic stability? The answer, in fact, is 'no'. The eight-membered cyclooctatetraene ring shown below is *not* flat, and its pi bonds react like 'normal' alkenes. π



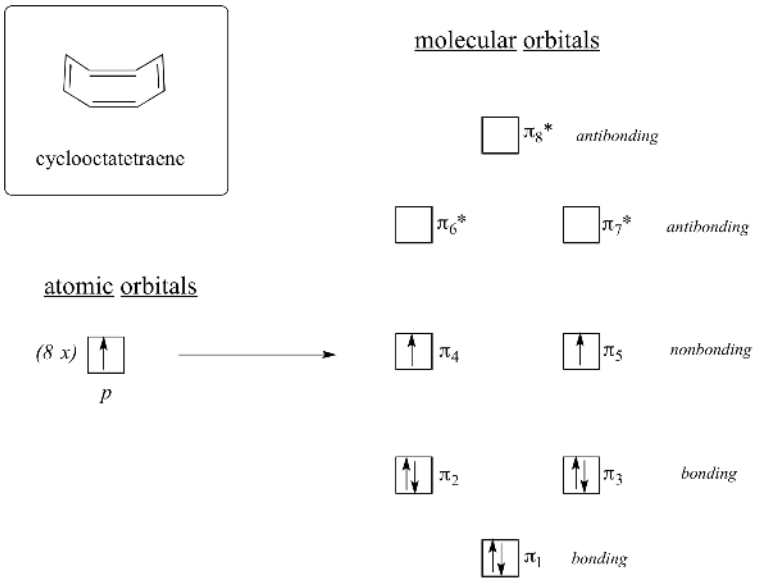
cyclooctatetraene
(not aromatic)

Clearly it takes something more to be aromatic, and this can best be explained with molecular orbital theory. Let's look at an energy diagram of the pi molecular orbitals in benzene.



Quantum mechanical calculations tell us that the six pi molecular orbitals in benzene, formed from six atomic *p* orbitals, occupy four separate energy levels. pi_1 and pi_6* have unique energy levels, while the pi_2 - pi_3 and pi_4*- pi_5* pairs are **degenerate**, meaning they are at the same energy level. When we use the *aufbau* principle to fill up these orbitals with the six pi electrons in benzene, we see that the bonding orbitals are completely filled, and the antibonding orbitals are empty. This gives us a good clue to the source of the special stability of benzene: a full set of bonding MO's is similar in many ways to the 'full shell' of electrons in the atomic orbitals of the stable noble gases helium, neon, and argon.

Now, let's do the same thing for cyclooctatetraene, which we have already learned is *not* aromatic.



The result of molecular orbital calculations tells us that the lowest and highest energy MOs (pi_1 and pi_8*) have unique energy levels, while the other six form degenerate pairs. Notice that pi_4 and pi_5 are at the same energy level as the isolated $2p_z$ atomic orbitals: these are therefore neither bonding nor antibonding, rather they are referred to as **nonbonding MOs**. Filling up the MOs with the eight pi electrons in the molecule, we find that the last two electrons are unpaired and fall into the two degenerate nonbonding orbitals. Because we don't have a perfect filled shell of bonding MOs, our molecule is not aromatic. As a consequence, each of the double bonds in cyclooctatetraene acts more like an *isolated* double bond.

Here, then, are the conditions that must be satisfied for a molecule or group to be considered aromatic:

✔ Criteria for aromaticity:

The molecule or group must be cyclic.

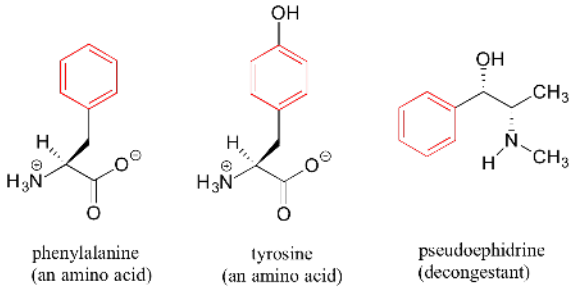
The ring must be planar.

Each atom in the ring must be sp^2-hybridized.

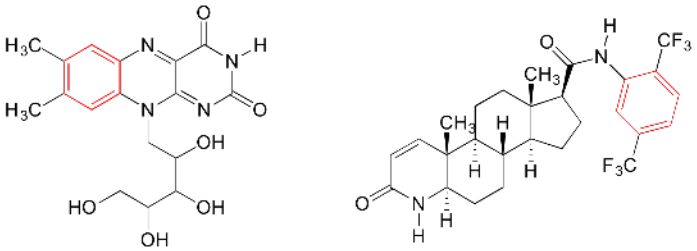
The number of pi electrons in the ring must equal $4n+2$, where n is any positive integer including zero.

Rule #4 is known as the **Hückel rule**, named after Erich Hückel, a German scientist who studied aromatic compounds in the 1930's. If $n = 0$, the Hückel number is **2**. If $n = 1$, the Hückel number is **6** (the Hückel number for benzene). The series continues with **10, 14, 18, 22,** and so on. Cyclooctatetraene has eight pi electrons, which is *not* a Hückel number. Because six is such a common Hückel number, chemists often use the term **'aromatic sextet'**.

Benzene rings are ubiquitous in biomolecules and drugs - below are just a few examples.



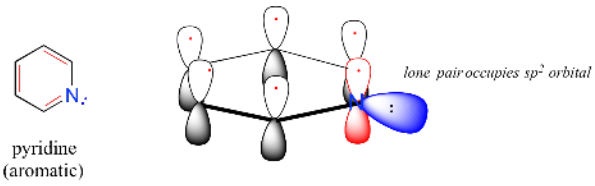
phenylalanine (an amino acid) | tyrosine (an amino acid) | pseudoephidrine (decongestant)



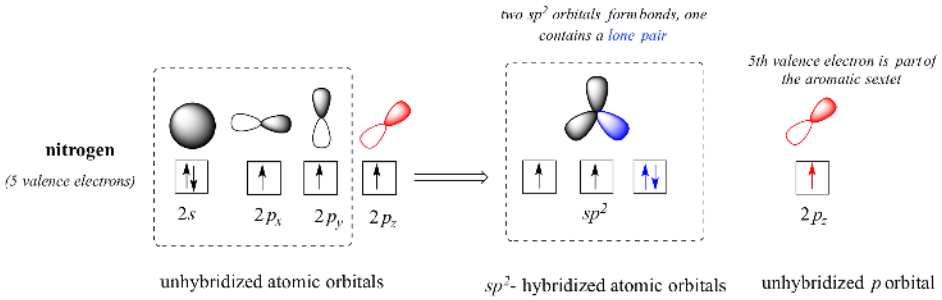
riboflavin (a vitamin) | dutasteride (GlaxoSmithKline drug for urinary condition in men)

Recall that a benzene ring with a hydoxyl substituent -such as seen in the tyrosine structure above - is called a **phenol**.

Heterocycles - cyclic structures in which the ring atoms may include oxygen or nitrogen - can also be aromatic. Pyridine, for example, is an aromatic heterocycle. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring.



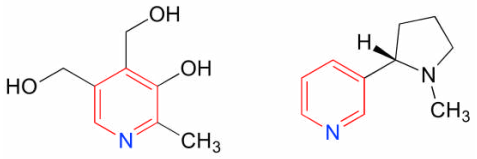
pyridine (aromatic)



unhybridized atomic orbitals | sp^2- hybridized atomic orbitals | unhybridized p orbital

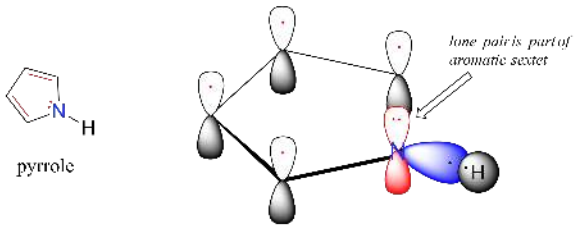
another image of orbitals in pyridine

Pyridoxine, commonly known as vitamin B_6, and nicotine are both substituted pyridines.

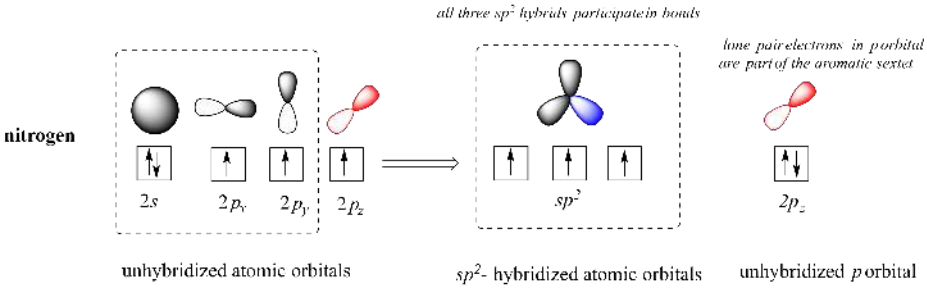


pyridoxine (vitamin B_6) nicotine

Pyrrole is a five-membered aromatic heterocycle. In pyrrole, the lone pair electrons on the sp^2-hybridized nitrogen are part of the aromatic sextet (contrast this to pyridine, where the lone pair occupies one of the sp^2 hybrid orbitals).



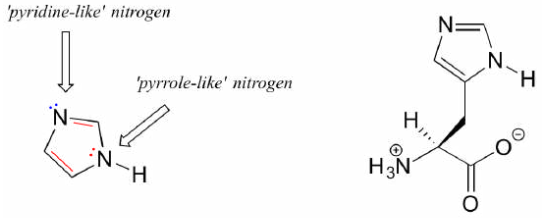
pyrrole



unhybridized atomic orbitals sp^2- hybridized atomic orbitals unhybridized p orbital

Why don't we assume that the nitrogen in pyrrole is sp^3-hybridized, like a normal secondary amine? The answer is simple: if it were, then pyrrole could not be aromatic, and thus it would not have the stability associated with aromaticity. In general, *if a molecule or group can be aromatic, it will be*, just as water will always flow downhill if there is a downhill pathway available.

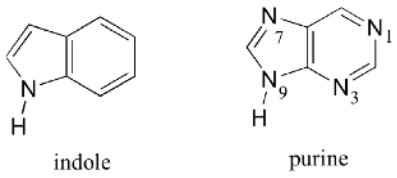
Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring.



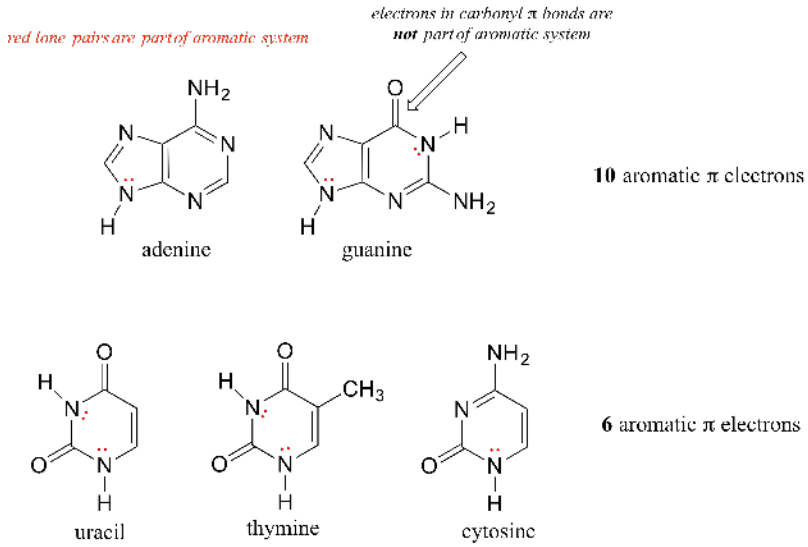
imidazole histidine

In imidazole, one nitrogen is 'pyrrole-like' (the lone pair contributes to the aromatic sextet) and one is 'pyridine-like' (the lone pair is located in an sp^2 orbital, and is *not* part of the aromatic sextet).

Fused-ring structures can also fulfill the Hückel criteria, and often have many of the same properties as monocyclic aromatic compounds, including a planar structure. Indole (a functional group on the side chain of the amino acid tryptophan) and purine (found in guanine and adenine nucleotide bases) both have a total of ten pi electrons delocalized around two rings.



The nucleic acid bases of DNA and RNA - guanine, adenine, cytosine, thymine, and uracil - are all aromatic systems, with the characteristic aromatic properties of planarity and delocalized pi electron density. When you study the structure and function of DNA and RNA in a biochemistry or molecular biology course, you will see that the planar shape of the bases plays a critically important role.

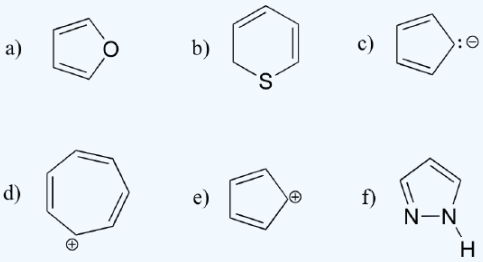


Exercise 2.11

Classify the nitrogen atoms of indole and purine as either 'pyrrole-like' or 'pyridine-like', in terms of where the lone pair electrons are located.

Exercise 2.12

Are the following molecules/ions aromatic? Explain, using criteria you learned in this section.



Solutions to exercises

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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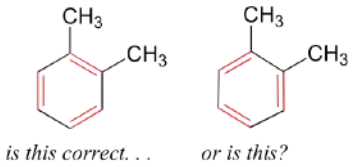
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2.3: Resonance

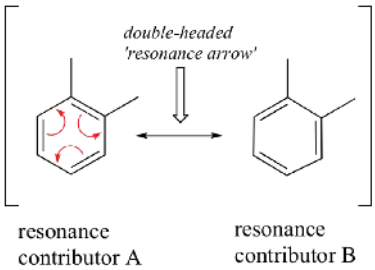
What is resonance?

If we were to draw the structure of an aromatic molecule such as 1,2-dimethylbenzene, there are two ways that we could draw the double bonds:



Which way is correct? There are two simple answers to this question: 'both' and 'neither one'. Both ways of drawing the molecule are equally acceptable approximations of the bonding picture for the molecule, but neither one, by itself, is an accurate picture of the delocalized pi bonds. The two alternative drawings, however, *when considered together*, give a much more accurate picture than either one on its own. This is because they imply, together, that the carbon-carbon bonds are not double bonds, not single bonds, but about halfway in between.

These two drawings are an example of what is referred to in organic chemistry as **resonance contributors**: two or more different Lewis structures depicting the same molecule or ion that, when considered together, do a better job of approximating delocalized pi-bonding than any single structure. By convention, resonance contributors are linked by a double-headed arrow, and are sometimes enclosed by brackets:

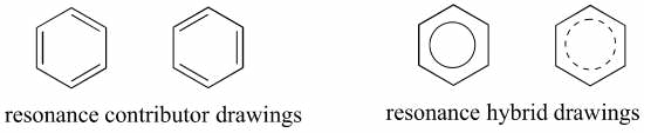


In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the ‘movement’ of two pi electrons. A few chapters from now when we begin to study organic reactions - a process in which electron density shifts and covalent bonds between atoms break and form - this ‘curved arrow notation’ will become extremely important in depicting electron movement. In the drawing of resonance contributors, however, this electron ‘movement’ occurs only in our minds, as we try to visualize delocalized pi bonds. Nevertheless, use of the curved arrow notation is an essential skill that you will need to develop in drawing resonance contributors.

The depiction of benzene using the two resonance contributors A and B in the figure above does *not* imply that the molecule at one moment looks like structure A, then at the next moment shifts to look like structure B. Rather, at all moments, the molecule is a combination, or **resonance hybrid** of both A and B.

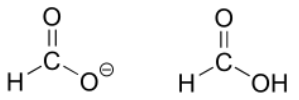
> **Caution**! It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken place.

Usually, derivatives of benzene (and phenyl groups, when the benzene ring is incorporated into a larger organic structure) are depicted with only one resonance contributor, and it is assumed that the reader understands that resonance hybridization is implied. This is the convention that will be used for the most part in this book. In other books or articles, you may sometimes see benzene or a phenyl group drawn with a circle inside the hexagon, either solid or dashed, as a way of drawing a resonance hybrid.

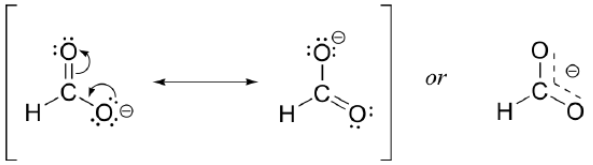


Resonance contributors for the carboxylate group

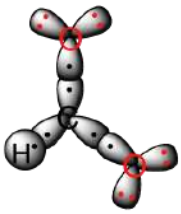
The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let's next consider the carboxylate ion (the conjugate base of a carboxylic acid). As our example, we will use formate, the simplest possible carboxylate-containing molecule. The conjugate acid of formate is formic acid, which causes the painful sting you felt if you have ever been bitten by an ant.



Usually, you will see carboxylate groups drawn with one carbon-oxygen double bond and one carbon-oxygen single bond, with a negative formal charge located on the single-bonded oxygen. In actuality, however, the two carbon-oxygen bonds are the same length, and although there is indeed an overall negative formal charge on the group, it is shared equally between the two oxygens. Therefore, the carboxylate can be more accurately depicted by a *pair* of resonance contributors. Alternatively, a single structure can be used, with a dashed line depicting the resonance-delocalized pi bond and the negative charge located in between the two oxygens.

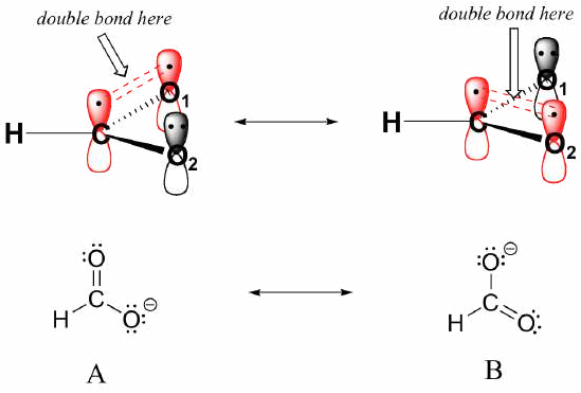


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sigma bonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.

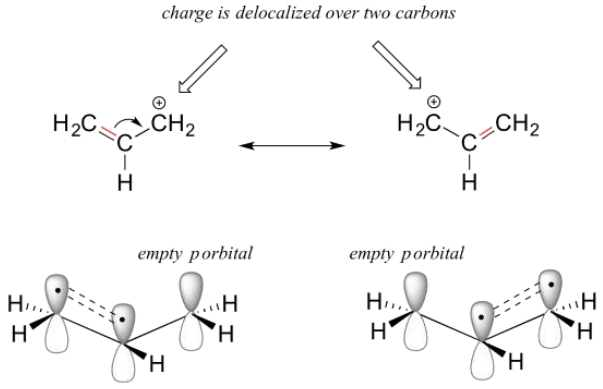


Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals sharing four delocalized pi electrons*. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of –1. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

? Exercise 2.13

There is a third resonance contributor for formate (which we will soon learn is considered a 'minor' contributor). Draw this resonance contributor.

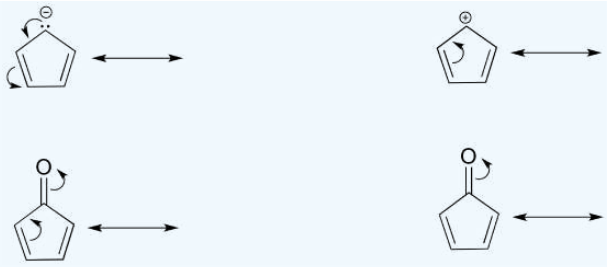
Here's another example, this time with a carbocation. Recall from section 2.1 that carbocations are sp^2-hybridized, with an empty *2p* orbital oriented perpendicular to the plane formed by three sigma bonds. If a carbocation is adjacent to a double bond, then three *2p* orbitals can overlap and share the two pi electrons - another kind of conjugated pi system in which the positive charge is shared over two carbons.



three *p* orbitals sharing two ≠ electrons

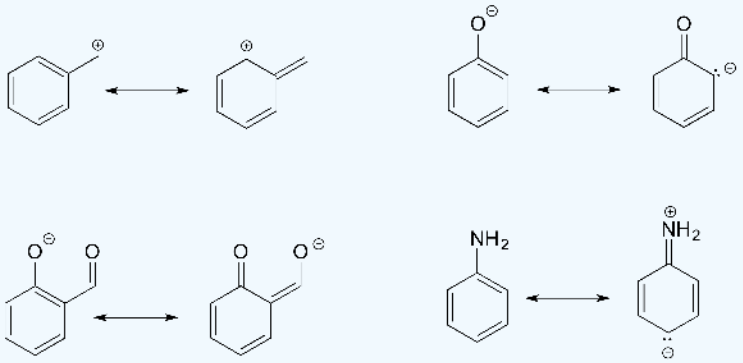
? Exercise 2.14

Draw the resonance contributors that correspond to the curved, two-electron movement arrows in the resonance expressions below.



Exercise 2.15

In each resonance expression, draw curved two-electron movement arrows on the left-side contributor that shows how we get to the right-side contributor. Be sure to include formal charges.



Solutions to exercises

Rules for drawing resonance structures

As you work on learning how to draw and interpret resonance structures, there are a few basic rules that you should keep in mind in order to avoid drawing nonsensical structures. All of these rules make perfect sense as long as you keep in mind that resonance contributors are merely a human-invented convention for depicting the delocalization of pi electrons in conjugated systems.

Rules for drawing resonance structures:

1) When you see two different resonance contributors, you are *not* seeing a chemical reaction! Rather, you are seeing the exact same molecule or ion depicted in two different ways.

2) Resonance contributors involve the 'imaginary movement' of pi-bonded electrons or of lone-pair electrons that are adjacent to (*i.e.* conjugated to) pi bonds. You can *never* shift the location of electrons in sigma bonds – if you show a sigma bond forming or breaking, you are showing a chemical reaction taking place (see rule #1). Likewise, the positions of *atoms* in the molecule cannot change between two resonance contributors.

3) All resonance contributors for a molecule or ion must have the same *net* charge.

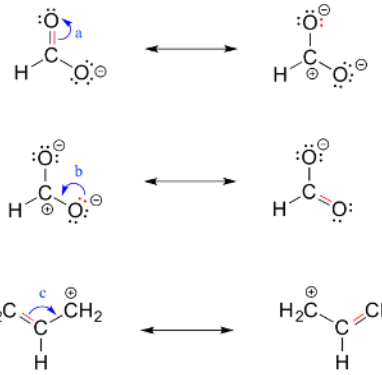
4) All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron movement' arrows that would lead to a situation where a second-row element (ie. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. Sometimes, however, we will draw resonance contributors in which a carbon atom has only six electrons (ie. a carbocation). In general, all oxygen and nitrogen atoms should have a complete octet of valence electrons.

To expand a bit on rule #4, there are really only three things we can do with curved arrows when drawing resonance structures:

First, we can take the two electrons in a pi bond and shift them to become a lone pair on an adjacent atom (arrow 'a' below).

Second, we can take a lone pair on an atom and put those two electrons into a pi bond on the same atom (arrow 'b').

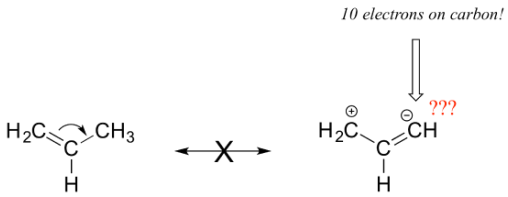
Third, we can shift a pi bond one position over (arrow c).



Resonance arrows can also be combined - below, we show arrows a and b together:

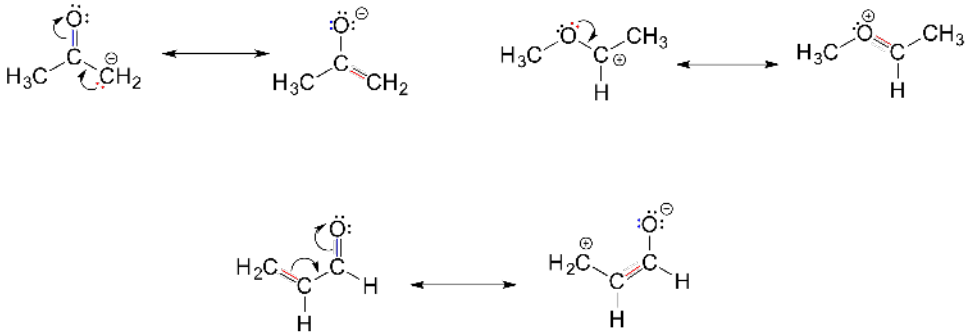


Notice that we do not exceed the octet rule on any atoms when we move electrons with arrows a, b and c. The resonance picture below shows an 'illegal' movement of electrons, because it would result in a carbon with five bonds, or 10 valence electrons (this would break the octet rule):



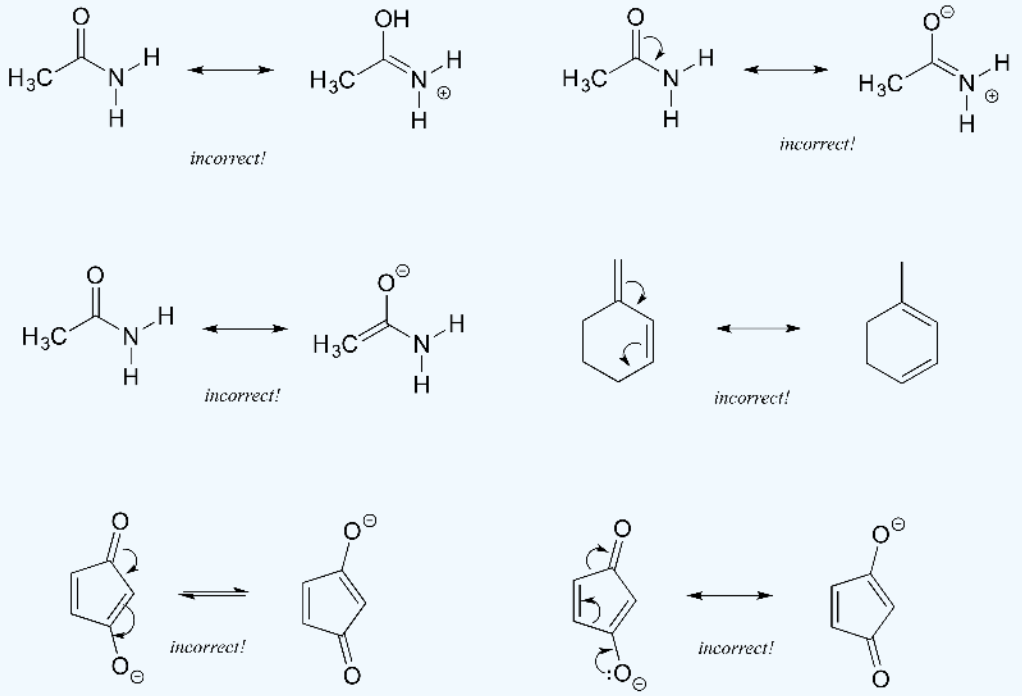
Always be very careful when drawing resonance structures that your arrows do ***only*** the three types of electron movement described above, and that you ***never*** exceed the octet rule on a second-row element. It is often helpful (but optional), to include all lone-pair electrons on oxygen and nitrogen in the drawing in order to keep track of valence electrons, avoid breaking the octet rule, and recognize when atoms have a negative or positive formal charge. Getting the 'electron accounting' correct is a big part of working with resonance contributors.

Below are a few more examples of 'legal' resonance expressions. Confirm for yourself that the octet rule is not exceeded for any atoms, and that formal charges are correct.



? Exercise 2.16

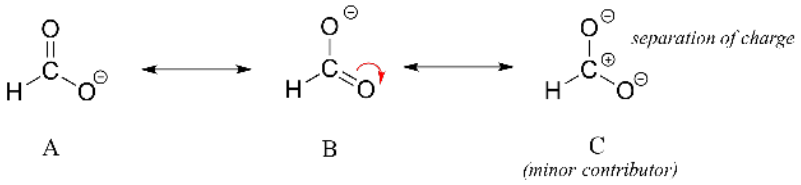
Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in each.



Solutions to exercises

Major vs minor resonance contributors

Different resonance contributors do not always make the same contribution to the overall structure of the hybrid - rather, in many cases one contributor comes closer to depicting the actual bonding picture than another. In the case of carboxylates, contributors A and B below are equivalent in terms of their relative contribution to the hybrid structure. However, there is also a third resonance contributor 'C, in which the carbon bears a positive formal charge and both oxygens are single-bonded and bear negative charges.



Structure C makes a less important contribution to the overall bonding picture of the group relative to A and B. How do we know that structure C is the 'minor' contributor? There are four basic rules which you need to learn in order to evaluate the relative importance of different resonance contributors. We will number them 5-8 so that they may be added to in the 'rules for resonance' list earlier on this page.

Rules for determining major and minor resonance contributors:

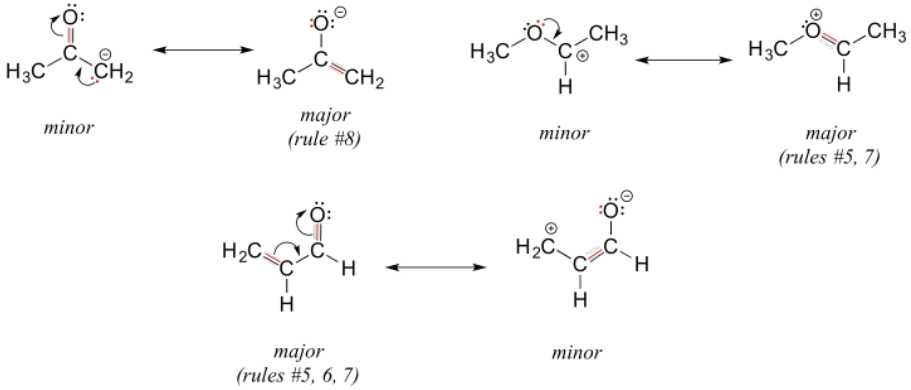
5) The carbon in contributor C does not have an octet – in general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important.

6) In structure C, a separation of charge has been introduced that is not present in A or B. In general, resonance contributors in which there is a greater separation of charge are relatively less important.

7) In structure C, there are only three bonds, compared to four in A and B. In general, a resonance structure with a lower number of total bonds is relatively less important.

8) The resonance contributor in which a negative formal charge is located on a more electronegative atom, usually oxygen or nitrogen, is more stable than one in which the negative charge is located on a less electronegative atom such as carbon. *An example is in the upper left expression in the next figure.*

Below are some additional examples of major and minor resonance contributors:



Why do we worry about a resonance contributor if it is the minor one? We will see later that very often a minor contributor can still be extremely important to our understanding of how a molecule reacts.

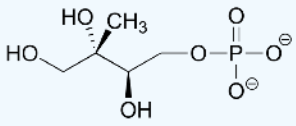
? Exercise 2.17

a) Draw a minor resonance structure for acetone (IUPAC name 2-propanone). Explain why it is a minor contributor.

b) Are acetone and 2-propanol resonance contributors of each other? Explain.

Exercise 2.18

Draw four additional resonance contributors for the molecule below. Label each one as major or minor (the structure below is of a major contributor).



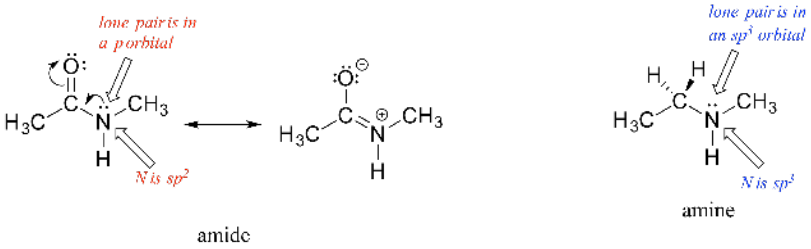
Exercise 2.19

Draw three resonance contributors of methyl acetate (IUPAC name methyl methanoate), and order them according to their relative importance to the bonding picture of the molecule. Explain your reasoning.

Solutions to exercises

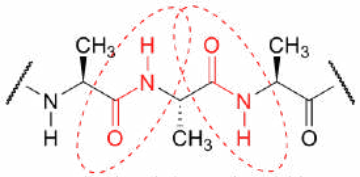
Resonance and peptide bonds

What is the hybridization state of the nitrogen atom in an amide? At first glance, it would seem logical to say that it is sp^3-hybridized, because, like the nitrogen in an amine, the Lewis structure shows three single bonds and a lone pair. The picture looks quite different, though, if we consider another resonance contributor in which the nitrogen has a double bond to the carbonyl carbon: in this case, we would have to say that applicable hybridization is sp^2, and the bonding geometry trigonal planar rather than tetrahedral.



In fact, the latter picture is more accurate: the lone pair of electrons on an amide nitrogen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system, and the bonding geometry around the nitrogen is trigonal planar as expected for sp^2 hybridization. This is a good illustration of an important point: conjugation and the corresponding delocalization of electron density is stabilizing, thus if conjugation can occur, it probably will.

One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



peptide bonds in a polypeptide

Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, *the C-N bond in a peptide linkage has a significant barrier to rotation*, indicating that to some degree, C-N pi overlap is present - in other words, there is some double bond character, and the nitrogen is sp^2 hybridized with trigonal planar geometry.



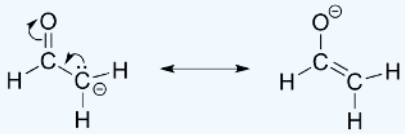
The barrier to rotation in peptide bonds is an integral part of protein structure, introducing more rigidity to the protein's backbone. If there were no barrier to rotation in a peptide bond, proteins would be much more 'floppy' and three dimensional folding would be very different.

? Exercise 2.20

Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in methyl amide. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping *2p* orbitals are sharing how many pi-bonded electrons?

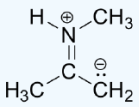
Exercise 2.21

Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in the 'enolate' anion shown below. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping 2*p* orbitals are sharing how many pi-bonded electrons?



Exercise 2.22

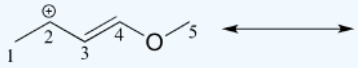
Below is a minor resonance contributor of a species known as an 'enamine', which we will study more in chapter 12. Draw the major resonance contributor for the enamine, and explain why your contributor is the major one (refer to resonance rules #5-8 from this section).



Solutions to exercises

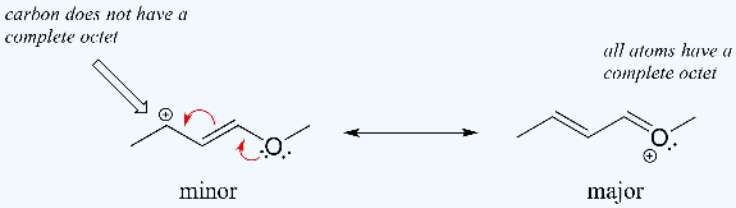
Solved example

Draw the major resonance contributor of the structure below. Include in your figure the appropriate curved arrows showing how you got from the given structure to your structure. Explain why your contributor is the major one. In what kind of orbitals are the two lone pairs on the oxygen?



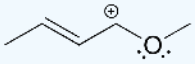
Solution

In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see the rules for drawing resonance contributors to convince yourself that these are 'legal' moves).



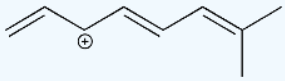
The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #5 and #7 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, and C_4, plus one on oxygen) sharing four pi electrons. One lone pair on the oxygen is in an unhybridized *2p* orbital and is part of the conjugated pi system, and the other is located in an sp^2 orbital.

Also note that one additional contributor can be drawn, but it is also minor because it has a carbon with an incomplete octet:



Exercise 2.23

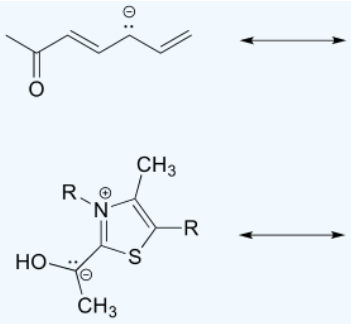
a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.



b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Exercise 2.24

Draw the major resonance contributor for each of the anions below.



c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

Exercise 2.25

The figure below shows how the negative formal charge on the oxygen can be delocalized to the carbon indicated by an arrow. More resonance contributors can be drawn in which negative charge is delocalized to three other atoms on the molecule.

a) Circle these atoms.

b) Draw the two most important resonance contributors for the molecule.



Solutions to exercises

A word of advice

Becoming adept at drawing resonance contributors, using the curved arrow notation to show how one contributor can be converted to another, and understanding the concepts of conjugation and resonance delocalization are some of the most challenging but also most important jobs that you will have as a beginning student of organic chemistry. If you work hard now to gain a firm grasp of these ideas, you will have come a long way toward understanding much of what follows in your organic chemistry course. Conversely, if you fail to come to grips with these concepts now, a lot of what you see later in the course will seem like a bunch of mysterious and incomprehensible lines, dots, and arrows, and you will be in for a rough ride, to say the least. More so than many other topics in organic chemistry, *understanding bonding, conjugation, and resonance is something that most students really need to work on 'in person' with an instructor or tutor, preferably using a molecular modeling kit*. Keep working problems, keep asking questions, and keep at it until it all makes sense!

Khan Academy video tutorials

- Drawing resonance structures
- More on resonance

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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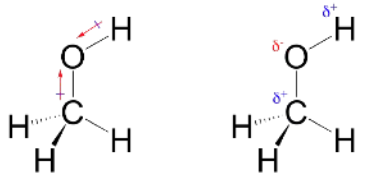
2.4: Non-covalent interactions

Until now we have been focusing on understanding the covalent bonds that hold individual molecules together. We turn next to a review on the subject of non-covalent interactions *between* molecules, or between different functional groups within a single molecule. You have probably learned all of these concepts already in your general chemistry course, but this review will focus on applications to organic and biological chemistry, and specifically will allow us to explain differences in physical properties -such boiling points, melting points, and solubility - between different organic compounds. An understanding of noncovalent interactions is also critical for looking at the environment inside the active site of an enzyme, where much of the chemistry that we will study in this book takes place.

Dipoles

To understand the nature of noncovalent interactions, we first must return to covalent bonds and delve into the subject of dipoles. Many of the covalent bonds that we have seen – between two carbons, for example, or between a carbon and a hydrogen –involve the approximately equal sharing of electrons between the two atoms in the bond. In these examples, the two atoms have approximately the same **electronegativity**. Recall from your general chemistry course that electronegativity refers to " the power of an atom in a molecule to attract electrons to itself" (this is the definition offered by Linus Pauling, the eminent 20th-century American chemist who was primarily responsible for developing many of the bonding concepts that we have been learning).

However, quite often in organic chemistry we deal with covalent bonds between two atoms with different electronegativities, and in these cases the sharing of electrons is not equal: the more electronegative nucleus pulls the two electrons closer. In the carbon-oxygen bond of an alcohol, for example, the two electrons in the sigma bond are held more closely to the oxygen than they are to the carbon, because oxygen is significantly more electronegative than carbon. The same is true for the oxygen-hydrogen bond, as hydrogen is slightly less electronegative than carbon, and much less electronegative than oxygen.

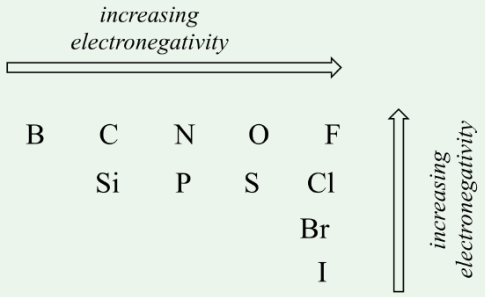


bond dipole arrows partial charge notation

The result of this unequal sharing is what we call a **bond dipole**, which exists in a **polar covalent bond**. A bond dipole has both negative and positive ends, or poles, where electron density is lower (the positive pole) and higher (the negative pole). The difference in electron density can be expressed using the Greek letter *delta* to denote 'partial positive' and 'partial negative' charge on the atoms. 'Dipole arrows', with a positive sign on the tail, are also used to indicated the negative (higher electron density) direction of the dipole.

The degree of polarity in a covalent bond depends on the difference in electronegativity between the two atoms. Electronegativity is a periodic trend: it increases going from left to right across a row of the periodic table of the elements, and also increases as we move up a column. Therefore, oxygen is more electronegative than nitrogen, which is in turn more electronegative than carbon. Oxygen is also more electronegative than sulfur. Fluorine, in the top right corner of the periodic table, is the most electronegative of the elements. Hydrogen is slightly less electronegative than carbon.

Periodic trends in electronegativity

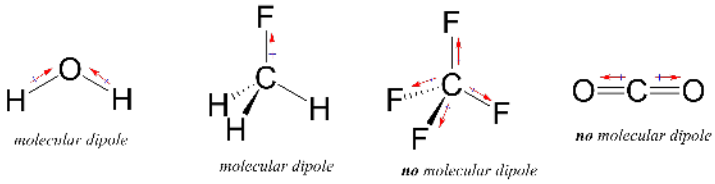


Exercise 2.26

Using what you about atomic orbitals, rationalize the periodic trends in electronegativity. Why does it increase from left to right, and decrease from top to bottom? This is a good question to talk through with classmates and an instructor or tutor.

Solutions to exercises

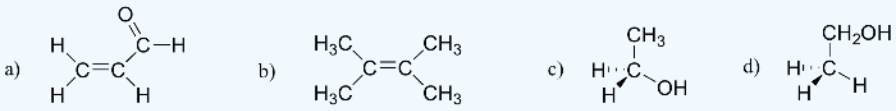
Most molecules contain both polar and nonpolar covalent bonds. Depending on the location of polar bonds and bonding geometry, molecules may posses a net polarity, called a **molecular dipole moment**. Water, as you probably recall, has a dipole moment that results from the combined dipoles of its two oxygen-hydrogen bonds. Fluoromethane also has a dipole moment.



Tetrafluoromethane, however, has four polar bonds that pull equally in to the four corners of a tetahedron, meaning that although there are four bond dipoles there is no overall *molecular* dipole moment. Carbon dioxide also lacks a molecular dipole moment.

Exercise 2.27

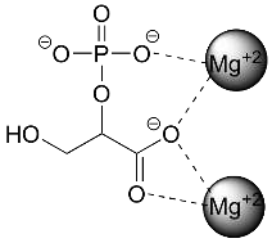
Which of the molecules below have molecular dipole moments?



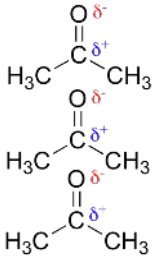
Solutions to exercises

Ion-ion, dipole-dipole and ion-dipole interactions

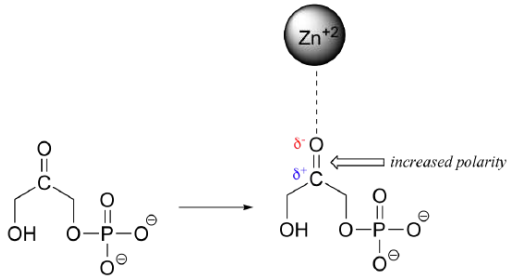
The strongest type of non-covalent interaction is between two ionic groups of opposite charge (an **ion-ion** or **charge-charge interaction**). You probably saw lots of examples of ionic bonds in inorganic compounds in your general chemistry course: for example, table salt is composed of sodium cations and chloride anions, held in a crystal lattice by ion-ion interactions. One of the most common examples in biological organic chemistry is the interaction between a magnesium cation (Mg^{+2}) and an anionic carboxylate or phosphate group. The figure below shows 2-phosphoglycerate, an intermediate in the glycolysis pathway, interacting with two Mg^{+2} ions in the active site of a glycolytic enzyme called enolase.



Polar molecules – those with an overall dipole moment, such as acetone – can align themselves in such a way as to allow their respective positive and negative poles to interact with each other. This is called a **dipole-dipole interaction**.



When a charged species (an ion) interacts favorably with a polar molecule or functional group, the result is called an **ion-dipole interaction**. A common example of ion-dipole interaction in biological organic chemistry is that between a metal cation, most often Mg^{+2} or Zn^{+2}, and the partially negative oxygen of a carbonyl.



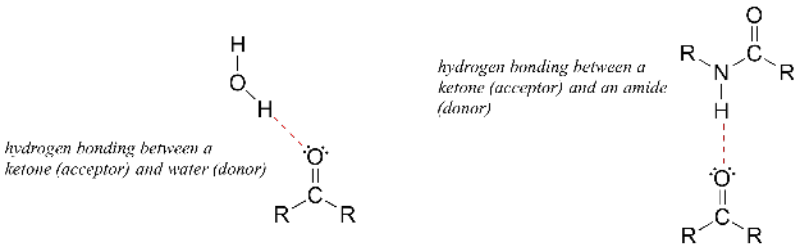
Because the metal cation is very electronegative, this interaction has the effect of pulling electron density in the carbonyl double bond even further toward the oxygen side, increasing the partial positive charge on carbon. As we shall later, this has important implications in terms of the reactivity of carbonyl groups in biochemical reactions.

Van der Waals forces

Nonpolar molecules such as hydrocarbons also are subject to relatively weak but still significant attractive noncovalent forces. **Van der Waals forces** (also called **London dispersion forces** or **nonpolar interactions**) result from the constantly shifting electron density in any molecule. Even a nonpolar molecule will, at any given moment, have a weak, short-lived dipole. This transient dipole will induce a neighboring nonpolar molecule to develop a corresponding transient dipole of its own, with the end result that a transient dipole-dipole interaction is formed. These van der Waals forces are relatively weak, but are constantly forming and dissipating among closely-packed nonpolar molecules, and when added up the cumulative effect can become significant.

Hydrogen bonds

Hydrogen bonds result from the interaction between a hydrogen bonded to an electronegative heteroatom – specifically a nitrogen, oxygen, or fluorine – and lone-pair electrons on a nitrogen, oxygen, or fluorine a neighboring molecule or functional group. Because a hydrogen atom is just a single proton and a single electron, when it loses electron density in a polar bond it essentially becomes an approximation of a ‘naked’ proton, capable of forming a strong interaction with a lone pair on a neighboring electronegative atom.

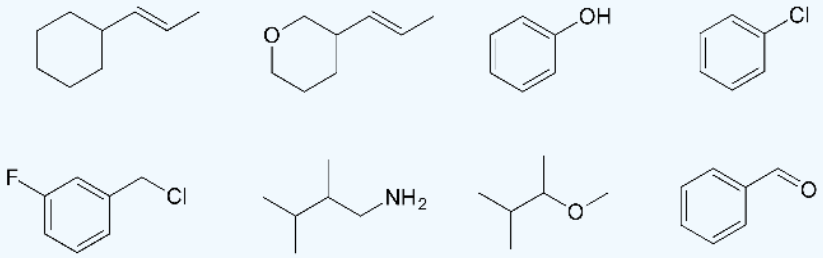


Hydrogen bonds are usually depicted with dotted lines in chemical structures. A group that provides a proton to a hydrogen bond is said to be acting as a **hydrogen bond donor**. A group that provides an oxygen or nitrogen lone pair is said to be acting as a **hydrogen bond acceptor**. Many common organic functional groups can participate in the formation of hydrogen bonds, either as donors, acceptors, or both. Water and alcohols, for example, can be both hydrogen bond donors and acceptors. A carbonyl, as it lacks a hydrogen bound to an oxygen or nitrogen, can only act as a hydrogen bond acceptor.

? Exercise 2.28

Classify the structures below as:

a. capable of being both a hydrogen bond donor and acceptor
b. capable of being a hydrogen bond acceptor, but not a donor
c. not capable of participating in hydrogen bonding.



Exercise 2.29

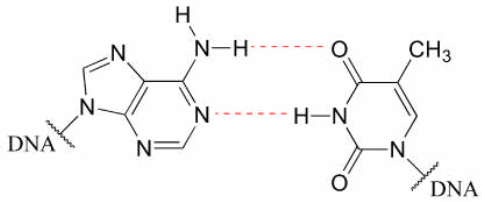
Draw figures that show the hydrogen bonds described below.

a. A hydrogen bond between methanol (donor) and water (acceptor).
b. A hydrogen bond between methanol (acceptor) and water (donor).
c. Two possible hydrogen bonds between methyl acetate and methylamine.

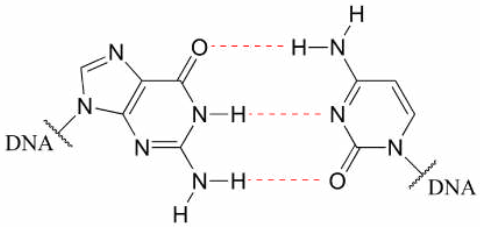
Solutions to exercises

In general, hydrogen bonds are stronger than dipole-dipole interactions, but also much weaker than covalent bonds. The strength of hydrogen bonds has enormous implications in biology. Copying of DNA in the cell, for example, is based on very specific hydrogen bonding arrangements between DNA bases on complimentary strands: adenine pairs with thymine, while guanine pairs with cytosine:

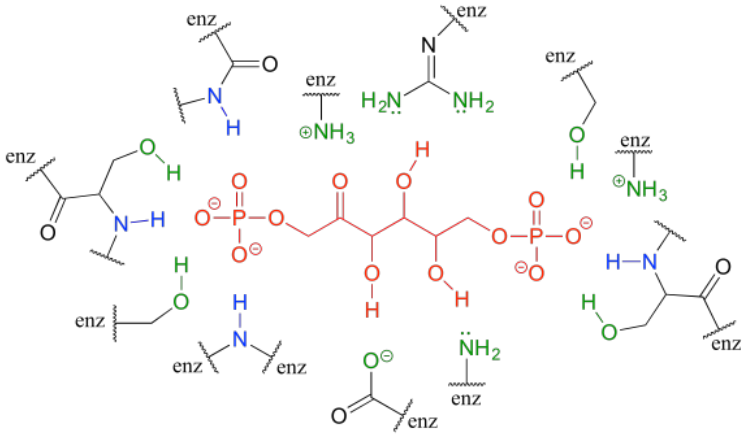
A-T base pair:



G-C base pair:



Hydrogen bonds, as well as the other types of noncovalent interactions, are very important in terms of the binding of a ligand to a protein. In section 1.3, we saw a 'space-filling' picture of an enzyme with its substrate bound in its active site. Here, in a two-dimensional approximation, is an image of the same substrate-enzyme pair showing how amino acid side chain (green) and parent chain (blue) groups surround and interact with functional groups on the substrate (red).



Khan Academy video tutorial on noncovalent intermolecular interactions

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2.5: Physical properties of organic compounds

An understanding of the various types of noncovalent forces allows us to explain, on a molecular level, many observable physical properties of organic compounds. In this section, we will concentrate on solubility (especially solubility in water), melting point, and boiling point.

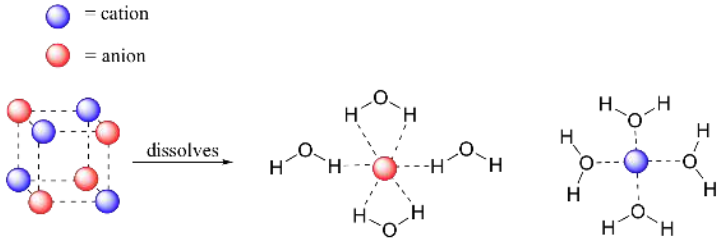
Solubility

Virtually all of the organic chemistry that you will see in this course takes place in the solution phase. In the organic laboratory, reactions are often run in nonpolar or slightly polar solvents such as toluene (methylbenzene), dichloromethane, or diethylether. In recent years, much effort has been made to adapt reaction conditions to allow for the use of ‘greener’ (in other words, more environmentally friendly) solvents such as water or ethanol, which are polar and capable of hydrogen bonding. In biochemical reactions the solvent is of course water, but the 'microenvironment' inside an enzyme's active site - where the actual chemistry is going on - can range from very polar to very non-polar, depending on which amino acid residues are present.

You probably remember the 'like dissolves like’ rule you learned in general chemistry, and even before you took any chemistry at all, you probably observed at some point in your life that oil does not mix with water. Let’s revisit this rule, and put our knowledge of covalent and noncovalent bonding to work.

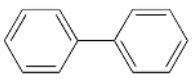
When considering the solubility of an organic compound in a given solvent, the most important question to ask ourselves is: how strong are the noncovalent interactions between the compound and the solvent molecules? If the solvent is polar, like water, then a smaller hydrocarbon component and/or more charged, hydrogen bonding, and other polar groups will tend to increase the solubility. If the solvent is non-polar, like hexane, then the exact opposite is true.

Imagine that you have a flask filled with water, and a selection of substances that you will test to see how well they dissolve in the water. The first substance is table salt, or sodium chloride. As you would almost certainly predict, especially if you’ve ever inadvertently taken a mouthful of water while swimming in the ocean, this ionic compound dissolves readily in water. Why? Because water, as a very polar molecule, is able to form many ion-dipole interactions with both the sodium cation and the chloride anion, the energy from which is more than enough to make up for energy required to break up the ion-ion interactions in the salt crystal.



The end result, then, is that in place of sodium chloride crystals, we have individual sodium cations and chloride anions surrounded by water molecules – the salt is now *in solution*. Charged species as a rule dissolve readily in water: in other words, they are very **hydrophilic** (water-loving).

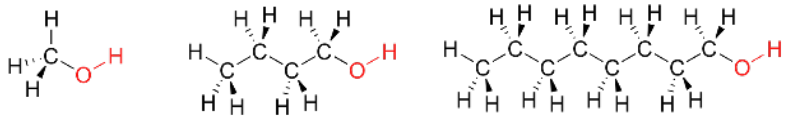
Now, we’ll try a compound called biphenyl, which, like sodium chloride, is a colorless crystalline substance.



biphenyl

Biphenyl does not dissolve at all in water. Why is this? Because it is a very non-polar molecule, with only carbon-carbon and carbon-hydrogen bonds. It is able to bond to itself very well through nonpolar van der Waals interactions, but it is not able to form significant attractive interactions with very polar solvent molecules like water. Thus, the energetic cost of breaking up the biphenyl-to-biphenyl interactions in the solid is high, and very little is gained in terms of new biphenyl-water interactions. Water is a terrible solvent for nonpolar hydrocarbon molecules: they are very **hydrophobic** (water-fearing).

Next, you try a series of increasingly large alcohol compounds, starting with methanol (1 carbon) and ending with octanol (8 carbons).



methanol
very soluble in water

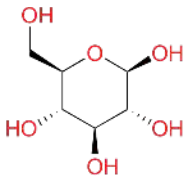
butanol
slightly soluble in water

octanol
very insoluble in water

You find that the smaller alcohols - methanol, ethanol, and propanol - dissolve easily in water, at any water/alcohol ratio that you try. This is because the water is able to form hydrogen bonds with the hydroxyl group in these molecules, and the combined energy of formation of these water-alcohol hydrogen bonds is more than enough to make up for the energy that is lost when the alcohol-alcohol (and water-water) hydrogen bonds are broken up. When you try butanol, however, you begin to notice that, as you add more and more to the water, it starts to form a layer on top of the water. Butanol is only sparingly soluble in water.

The longer-chain alcohols - pentanol, hexanol, heptanol, and octanol - are increasingly non-soluble in water. What is happening here? Clearly, the same favorable water-alcohol hydrogen bonds are still possible with these larger alcohols. The difference, of course, is that the larger alcohols have larger nonpolar, hydrophobic regions in addition to their hydrophilic hydroxyl group. At about four or five carbons, the influence of the hydrophobic part of the molecule begins to overcome that of the hydrophilic part, and water solubility is lost.

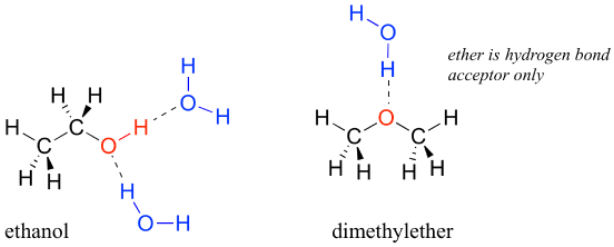
Now, try dissolving glucose in the water – even though it has six carbons just like hexanol, it also has five hydrogen-bonding, hydrophilic hydroxyl groups in addition to a sixth oxygen that is capable of being a hydrogen bond acceptor.



glucose

We have tipped the scales to the hydrophilic side, and we find that glucose is quite soluble in water.

We saw that ethanol was very water-soluble (if it were not, drinking beer or vodka would be rather inconvenient!) How about dimethyl ether, which is a constitutional isomer of ethanol but with an ether rather than an alcohol functional group? We find that diethyl ether is much less soluble in water. Is it capable of forming hydrogen bonds with water? Yes, in fact, it is –the ether oxygen can act as a hydrogen-bond acceptor. The difference between the ether group and the alcohol group, however, is that the alcohol group is both a hydrogen bond donor *and* acceptor.

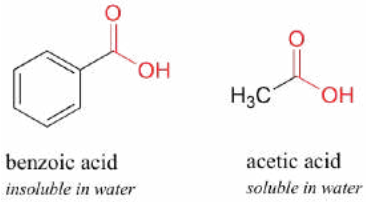


ethanol

dimethylether

The result is that the alcohol is able to form more energetically favorable interactions with the solvent compared to the ether, and the alcohol is therefore much more soluble.

Here is another easy experiment that can be done (with proper supervision) in an organic laboratory. Try dissolving benzoic acid crystals in room temperature water – you'll find that it is not soluble. As we will learn when we study acid-base chemistry in a later chapter, carboxylic acids such as benzoic acid are relatively weak acids, and thus exist mostly in the acidic (protonated) form when added to pure water.

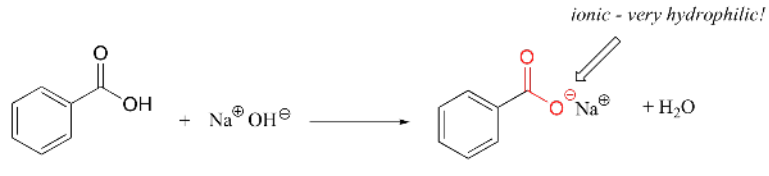


benzoic acid
insoluble in water

acetic acid
soluble in water

Acetic acid (vinegar) is quite soluble. This is easy to explain using the small alcohol vs large alcohol argument: the hydrogen-bonding, hydrophilic effect of the carboxylic acid group is powerful enough to overcome the hydrophobic effect of a single hydrophobic methyl group on acetic acid, but not the larger hydrophobic effect of the 6-carbon benzene group on benzoic acid.

Now, try slowly adding some aqueous sodium hydroxide to the flask containing undissolved benzoic acid. As the solvent becomes more and more basic, the benzoic acid begins to dissolve, until it is completely in solution.



benzoic acid
insoluble in water

sodium benzoate
soluble in water

What is happening here is that the benzoic acid is being converted to its conjugate base, benzoate. The *neutral* carboxylic acid group was not hydrophilic enough to make up for the hydrophobic benzene ring, but the carboxylate group, with its *full negative charge*, is much more hydrophilic. Now, the balance is tipped in favor of water solubility, as the powerfully hydrophilic anion part of the molecule drags the hydrophobic part into solution. Remember, charged species usually dissolve readily in water. If you want to precipitate the benzoic acid back out of solution, you can simply add enough hydrochloric acid to neutralize the solution and reprotonate the carboxylate.

If you are taking a lab component of your organic chemistry course, you will probably do at least one experiment in which you will use this phenomenon to physically separate an organic acid like benzoic acid from a hydrocarbon compound like biphenyl.

Similar arguments can be made to rationalize the solubility of different organic compounds in nonpolar or slightly polar solvents. In general, the greater the content of charged and polar groups in a molecule, the less soluble it tends to be in solvents such as hexane. The ionic and very hydrophilic sodium chloride, for example, is not at all soluble in hexane solvent, while the hydrophobic biphenyl is very soluble in hexane.

Because we are concentrating on the biologically relevant chemistry, let's take a minute to review how to evaluate a compound's solubility in water, the biological solvent:

Summary of factors contributing to water solubility

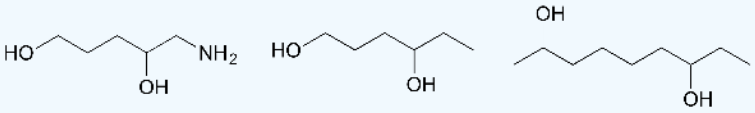
A: How many carbons? All else being equal, more carbons means more of a non-polar/hydrophobic character, and thus lower solubility in water.

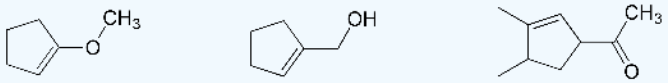
B: How many, and what kind of hydrophilic groups? The more, the greater the water solubility. In order of importance:

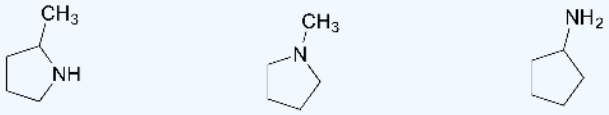
1. Anything with a **charged** group (eg. ammonium, carboxylate, phosphate) is almost certainly water soluble, unless has a vary large nonpolar group, in which case it will most likely be soluble in the form of micelles, like a soap or detergent (see next section).
2. Any functional group that can **donate a hydrogen bond** to water (eg. alcohols, amines) will significantly contribute to water solubility.
3. Any functional group that can only **accept a hydrogen bond** from water (eg. ketones, aldehydes, ethers) will have a somewhat smaller but still significant effect on water solubility.
4. Other groups that contribute to polarity (eg. alkyl halides, thiols sulfides) will make a small contribution to water solubility.

? Exercise 2.30

Rank each set of three compounds below according to their solubility in water (most soluble to least):

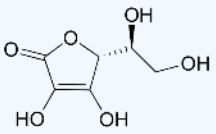
a) 

b) 

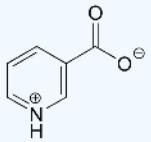
c) 

Exercise 2.31

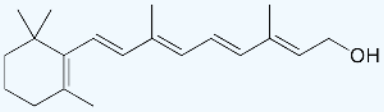
Vitamins can be classified as water-soluble or fat-soluble (consider fat to be a very non-polar 'solvent'. Decide on a classification for each of the vitamins shown below.



Vitamin C
(ascorbic acid)



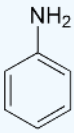
Vitamin B_3
(niacin)



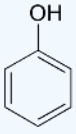
Vitamin A
(retinol)

Exercise 2.32

Both aniline and phenol are mostly insoluble in pure water. Predict the solubility of these two compounds in 10% aqueous hydrochloric acid, and explain your reasoning.



aniline



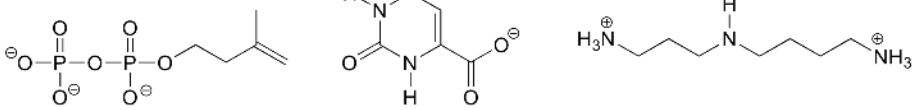
phenol

Exercise 2.33

Would you predict methanol or 2-propanol (rubbing alcohol) to be a better solvent for cyclohexanone? Why?

Solutions to exercises

Because water is the biological solvent, most biological organic molecules, in order to maintain water-solubility, contain one or more charged functional groups: most often phosphate, ammonium or carboxylate.



ispentenyl diphosphate
an early precuror to cholesterol

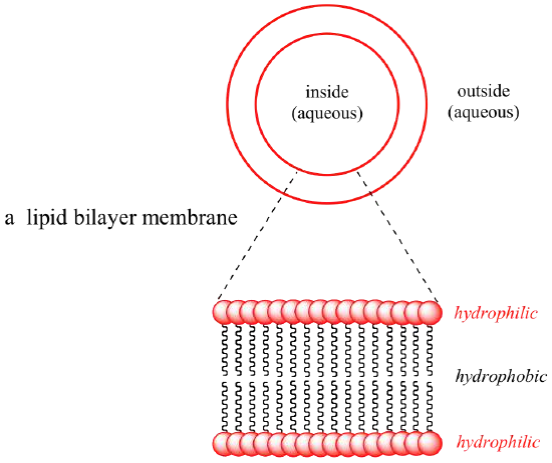
orotate
a precursor to the RNA base uridine

spermidine
binds tightly to DNA in rapidly dividing cells

Note that the charge on these functional groups depends on their protonation state: spermidine, for example, could be drawn with three (uncharged) amine groups rather than the charged ammonium groups as shown, and orotate could be drawn in the uncharged carboxylic acid form. It turns out, however, that these three functional groups are all charged when in a buffer at the physiological pH of approximately 7.3. We will have much more to say about the acid-base aspects of these groups in chapter 7.

Carbohydrates often lack charged groups, but as we discussed in our 'thought experiment' with glucose, they are quite water-soluble due to the presence of multiple hydroxyl groups, which can hydrogen bond with water.

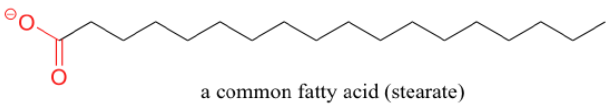
Some biomolecules, in contrast, contain distinctly hydrophobic components. Membrane lipids are **amphipathic**, meaning that they contain both hydrophobic and hydrophilic components. Cell membranes are composed of membrane lipids arranged in a 'bilayer', with the hydrophobic 'tails' pointing inward and the hydrophilic 'heads' forming the inner and outer surfaces, both of which are in contact with water.



Interactive 3D images of a fatty acid soap molecule and a soap micelle (Edutopics)

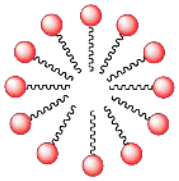
The nonpolar interior of the lipid bilayer is able to 'dissolve' hydrophobic biomolecules such as cholesterol. Polar and charged biomolecules, on the other hand, are not able to cross the membrane, because they are repelled by the hydrophobic environment of the bilayer's interior. The transport of water-soluble molecules across a membrane can be accomplished in a controlled and specific manner by special transmembrane transport proteins, a fascinating topic that you will learn more about if you take a class in biochemistry.

A similar principle is the basis for the action of soaps and detergents. Soaps are composed of fatty acids such as stearate obtained through basic hydrolysis of triacylglycerols in fats and oils.



a common fatty acid (stearate)

Like membrane lipids, fatty acids are amphipathic. In aqueous solution, the fatty acid molecules in soaps will spontaneously form **micelles**, a spherical structure that allows the hydrophobic tails to avoid contact with water and simultaneously form favorable van der Waals contacts with each other.

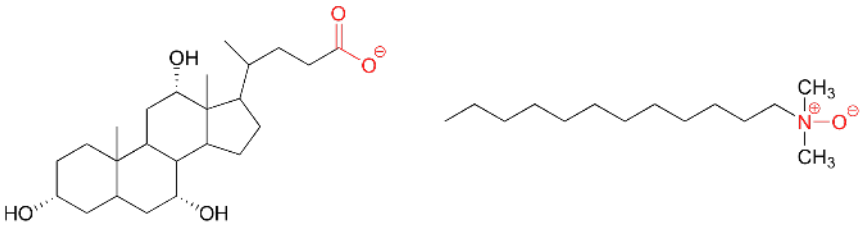


micelle

Interactive 3D images of a fatty acid soap molecule and a soap micelle (Edutopics)

Because the outside of the micelle is charged, the structure as a whole is soluble in water. Micelles will form spontaneously around small particles of oil that normally would not dissolve in water, and will carry the particle away with it into solution. We will learn more about the chemistry of soap-making in chapter 11.

Synthetic detergents are non-natural amphipathic molecules that work by the same principle as that described for soaps.

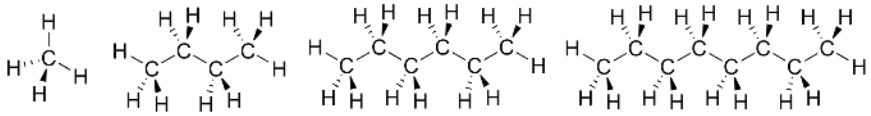


synthetic detergents

Boiling point and melting point

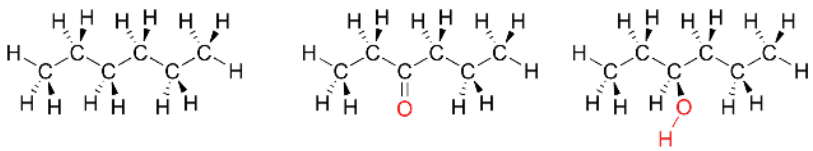
The observable melting and boiling points of different organic molecules provides an additional illustration of the effects of noncovalent interactions. The overarching principle involved is simple: *how well can a compound bind to itself*? Melting and boiling are processes in which noncovalent interactions between identical molecules in a pure sample are disrupted. The stronger the noncovalent interactions, the more energy that is required, in the form of heat, to break them apart.

As a rule, larger molecules have higher boiling (and melting) points. Consider the boiling points of increasingly larger hydrocarbons. More carbons and hydrogens means a greater surface area possible for van der Waals interaction, and thus higher boiling points. Below zero degrees centigrade (and at atmospheric pressure) butane is a liquid, because the butane molecules are held together by Van der Waals forces. Above zero degrees, however, the molecules gain enough thermal energy to break apart and enter the gas phase. Octane, in contrast, remains in the liquid phase all the way up to 128^{o}C, due to the increased van der Waals interactions made possible by the larger surface area of the individual molecules.



methane bp = -164°C; butane bp = 0°C; hexane bp = 68°C; octane bp = 128°C

The strength of intermolecular hydrogen bonding and dipole-dipole interactions is reflected in higher boiling points. Look at the trend for hexane (van der Waals interactions only), 3-hexanone (dipole-dipole interactions), and 3-hexanol (hydrogen bonding). In all three molecules, van der Waals interactions are significant. The polar ketone group allows 3-hexanone to form intermolecular dipole-dipole interactions, in addition to the weaker van der Waals interactions. 3-hexanol, because of its hydroxyl group, is able to form intermolecular hydrogen bonds, which are stronger yet.

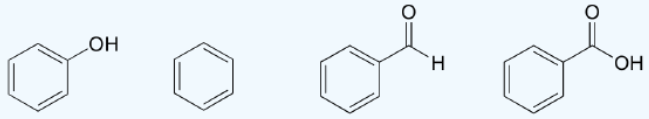


hexane bp = 69°C; 3-hexanone bp = 123 °C; 3-hexanol bp =135°C

Of particular interest to biologists (and pretty much anything else that is alive on the planet) is the effect of hydrogen bonding in water. Because it is able to form tight networks of intermolecular hydrogen bonds, water remains in the liquid phase at temperatures up to 100 ^{O}C despite its small size. The world would obviously be a very different place if water boiled at 30 ^{O}C.

? Exercise 2.34

Based on their structures, rank phenol, benzene, benzaldehyde, and benzoic acid in terms of lowest to highest boiling point. Explain your reasoning.

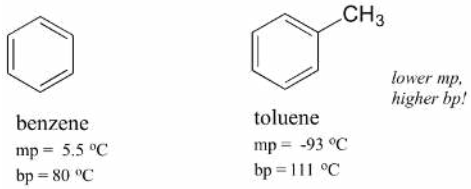


Solutions to exercises

By thinking about noncovalent intermolecular interactions, we can also predict relative melting points. All of the same principles apply: stronger intermolecular interactions result in a higher melting point. Ionic compounds, as expected, usually have very high melting points due to the strength of ion-ion interactions. Just like with boiling points, the presence of polar and hydrogen-bonding groups on organic compounds generally leads to higher melting points. The size of a molecule influences its melting point as well as its boiling point, again due to increased van der Waals interactions between molecules.

What is different about melting point trends, that we don't see with boiling point or solubility trends, is the importance of a molecule's shape and its ability of pack tightly together. Picture yourself trying to make a stable pile of baseballs in the floor. It just doesn't work, because spheres don't pack together well - there is very little area of contact between each ball. It is very easy, though, to make a stack of flat objects like books.

The same concept applies to how well molecules pack together in a solid. The flat shape of aromatic compounds allows them to pack efficiently, and thus aromatics tend to have higher melting points compared to non-planar hydrocarbons with similar molecular weights. Comparing the melting points of benzene and toluene, you can see that the extra methyl group on toluene disrupts the molecule's ability to pack tightly, thus decreasing the cumulative strength of intermolecular van der Waals forces and lowering the melting point.



Note also that the boiling point for toluene is significantly above the boiling point of benzene! The key factor for the boiling point trend in this case is *size* (toluene has one more carbon), whereas for the melting point trend, *shape* plays a much more important role. This makes sense when you consider that melting involves 'unpacking' the molecules from their ordered array, whereas boiling involves simply separating them from their already loose (liquid) association with each other.

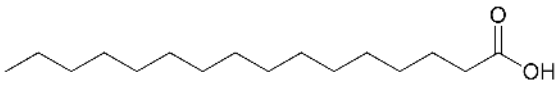
Exercise 2.35

Which would you expect to have the higher melting point, 2,3-dimethylbutane or hexane? Explain.

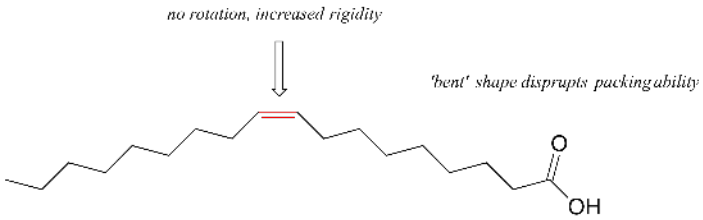
Physical properties of lipids and proteins

Lipids

An interesting biological example of the relationship between molecular structure and melting point is provided by the observable physical difference between animal fats like butter or lard, which are solid at room temperature, and vegetable oils, which are liquid. Recall that fats and oils are triacylglycerols: fatty acids linked to a glycerol backbone. In vegetable oils, the fatty acid components are unsaturated, meaning that they contain one or more double bonds. Solid animal fat, in contrast, contains mainly saturated hydrocarbon chains, with no double bonds.



palmatic acid
(a saturated fatty acid)



oleic acid
(an unsaturated fatty acid)

Interactive 3D image of a saturated triacylglycerol (BioTopics)

Saturated vs mono-unsaturated fatty acid (BioTopics)

The double bond(s) in vegetable oils cause those hydrocarbon chains to be more rigid, and 'bent' at an angle (remember that rotation is restricted around double bonds), with the result that they don't pack together as closely, and thus can be broken apart (melted) more readily.

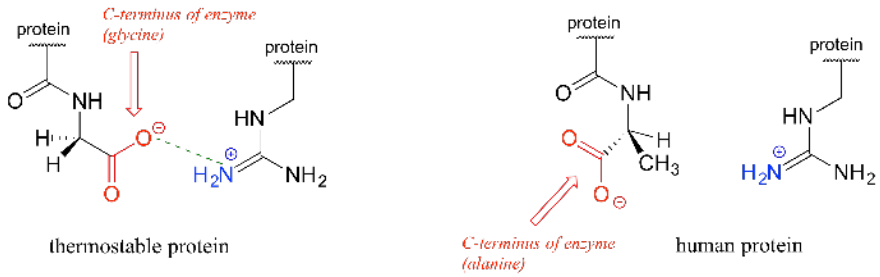
In a related context, the fluidity of a cell membrane (essentially, the melting point) is determined to a large extent by the length and degree of unsaturation of the fatty acid 'tails' on the membrane lipids. Longer and more saturated fatty acids make the membrane less fluid (they are able maximize van der Waals interactions), while shorter and more unsaturated fatty acids cause the membrane to be more fluid.

Proteins

The very same noncovalent forces we have just learned about are also integral to protein structure: when a protein folds up, it does so in such a way that very specific non-covalent interactions form between amino acid residues on different regions of the chain, each one becoming part of the 'molecular glue' that holds the chain together in its correctly folded shape. Hydrogen bonds and charge-charge interactions are particularly important in this respect. In general, the interior of a folded protein is relatively hydrophobic, while the outside surface, which of course is in constant contact with water, is very hydrophilic - many charged side chains such as aspartate, glutamate, lysine, and arginine point out of the surface of a protein structure.

Most of the proteins of 'mesophilic' organisms (those who thrive in intermediate temperatures, including humans) will denature - come unfolded - at high temperatures, as the heat disrupts the specific noncovalent interactions holding the protein chain together. Unfolded proteins usually are not water soluble because the more hydrophobic interior regions are no longer hidden from the solvent, so denaturing is accompanied by precipitation. Obviously, an unfolded protein also loses its functionality.

In the last few decades, we have become aware that a wide variety of microbes naturally inhabit extremely hot environments such as the boiling water of hot springs in Yellowstone National Park, or the base of a deep-sea thermal vent. How do the proteins of these 'thermophiles' hold up to the heat? There is nothing extraordinary about these proteins that makes them so resistant to heat, other than the fact that they have evolved so that they simply have *more* molecular 'glue' holding them together - in particular, more ionic interactions between oppositely charged residues. In just one of many examples, the three-dimensional structure of an enzyme from *Pyrococcus horikoshii*, a microbe isolated from a thermal vent deep in the Pacific Ocean, was compared to a very similar enzyme in humans. The thermophilic protein has a stabilizing charge-charge interaction between the terminal carboxylate group on the last amino acid in the chain and an arginine residue near the beginning of the chain.



This interaction is not present in the human version of the protein because the terminal carboxylate group is angled away from the positively-charged group on the arginine. The single charge-charge interaction is not by itself responsible for the thermostability of *the P. horikoshii* protein - other similar interactions throughout the protein structure also contribute (see the original report at *PLOS Biology* 2011, *9*, e1001027).

Conversely, proteins from 'psychrophilic' organisms - those which live in extremely cold temperatures, such as in arctic soils or in small water pockets in polar ice - have fewer stabilizing charge-charge interactions. This gives them the flexibility to function at temperatures in which mesophilic human or *E. coli* proteins would be frozen and inactive. On the other hand, a typical psychrophilic protein will rapidly unfold, precipitate, and lose its functionality at room temperature.

Scientists are extremely interested in thermostable proteins, because the ability to function at high temperatures can be a very desirable trait for a protein used in industrial processes. In fact, thermostable DNA polymerase from *Thermus aquaticus* (the enzyme is known to molecular biologists as *'Taq* polymerase') is the enzyme that makes the PCR (polymerase chain reaction) process possible, and has earned billions of dollars in royalties for drug company Hoffman La Roche, the patent owner. Many research groups are searching for useful enzymes in thermophilic species, and others are working on ways to engineer heat stability into existing mesophilic enzymes by tinkering with their amino acid sequences to introduce new stabilizing charge-charge interactions.

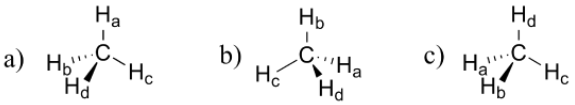
Khan Academy video tutorials on solubility, boiling point

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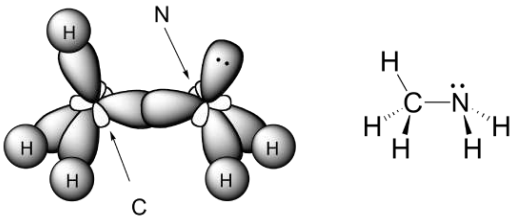
2.6: Solutions to Chapter 2 exercises

E2.1:

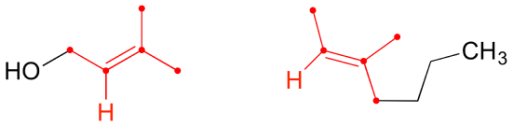


E2.2: sp^3 orbital on carbon overlapping with *3p* orbital on chlorine.

E2.3: Both the carbon and the nitrogen atom in CH_3NH_2 are sp^3-hybridized. The C-N sigma bond is an overlap between two sp^3 orbitals.



E2.4: Atoms in red all lie in the same plane.

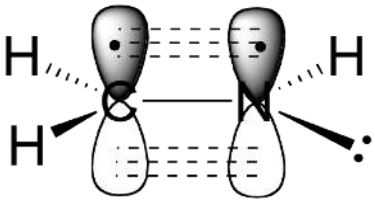


E2.5: The carbon atoms in an aromatic ring are sp^2 hybridized, thus bonding geometry is trigonal planar: in other words, the bonds coming out of the ring are in the same plane as the ring, *not* pointing above the plane of the ring as the wedges in the incorrect drawing indicate. A correct drawing should use lines to indicate that the bonds are in the same plane as the ring:



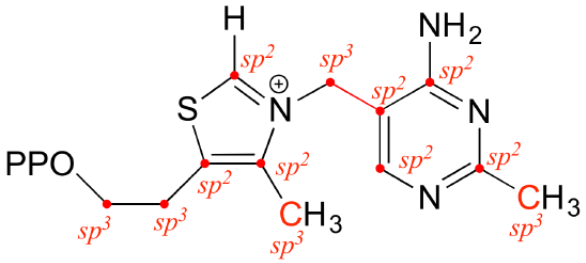
E2.6:

a) The carbon and nitrogen atoms are both sp^2 hybridized. The carbon-nitrogen double bond is composed of a sigma bond formed from two sp^2 orbitals, and a pi bond formed from the side-by-side overlap of two unhybridized *2p* orbitals.



b) As shown in the figure above, the nitrogen lone pair electrons occupy one of the three sp^2 hybrid orbitals.

E2.7:



E2.8:

a)

bond b: Nsp^2-Csp^3 (this means an overlap of an sp^2 orbital on N and an sp^3 orbital on C)

bond c: Csp^2-Csp^2 plus C2p-C2p (pi)

bond d: Csp^2-Csp^3

bond e: Csp^3-Csp^3

bond f: Csp^3-Csp^3

bond g: Csp^2-Csp^2 (s) plus C2p-C2p (pi)

bond h: Csp^2-H1s

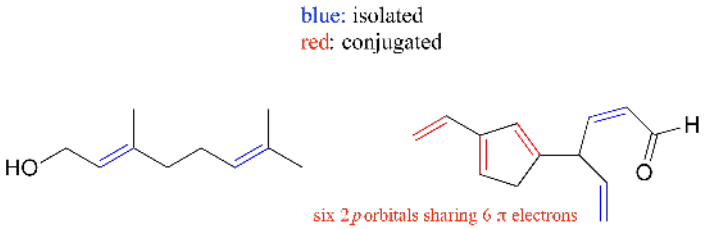
bond i: Csp^2-Csp^2

b)

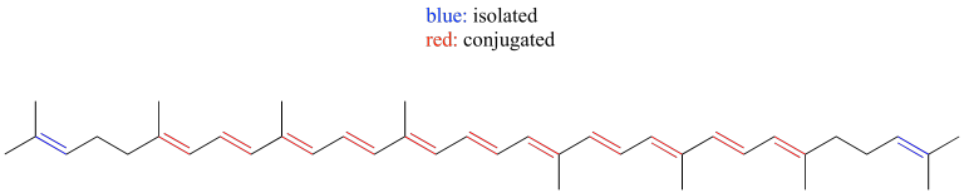
bond a: lone pair on N occupies an sp^2 orbital

bond e: lone pair on N occupies an sp^3 orbital

E2.9:



E2.10: The conjugated system contains 22 2p orbitals sharing 22 pi electrons

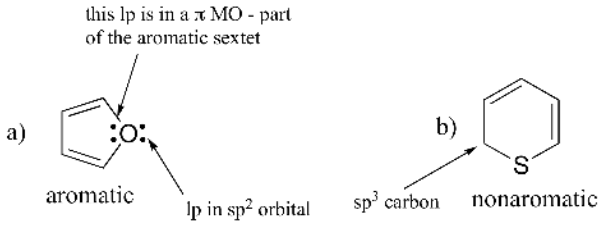


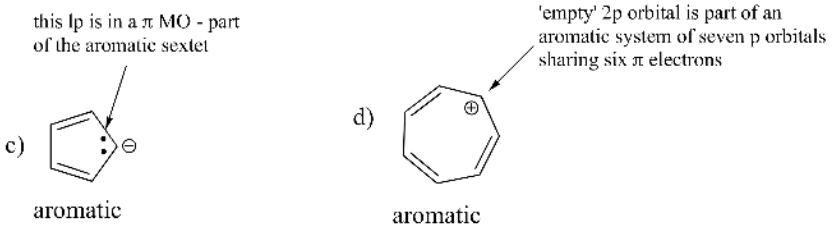
E2.11:

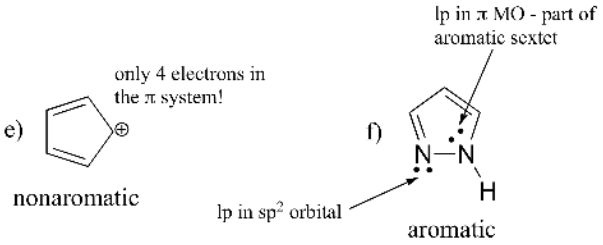
Indole: nitrogen is 'pyrrole-like' (lone pair is part of aromatic ring)

Purine: N_1, N_3, and N_7 are pyridine-like (lone pair in sp^2 orbital); N_9 is 'pyrrole-like'.

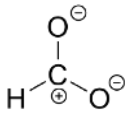
E2.12:



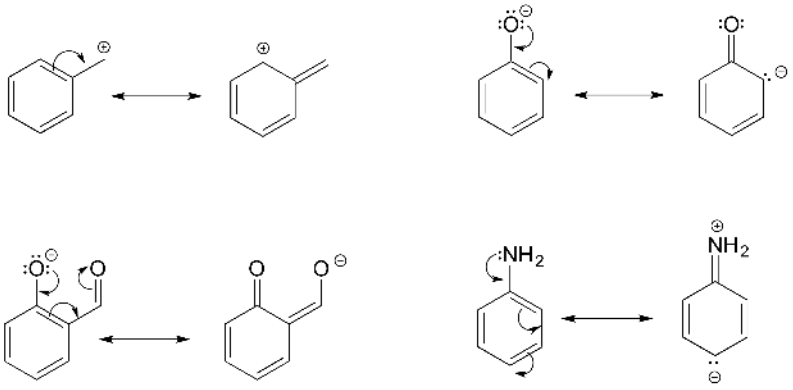




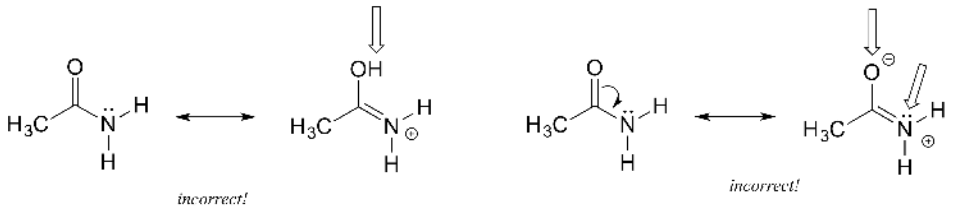
E2.13:



E2.15:

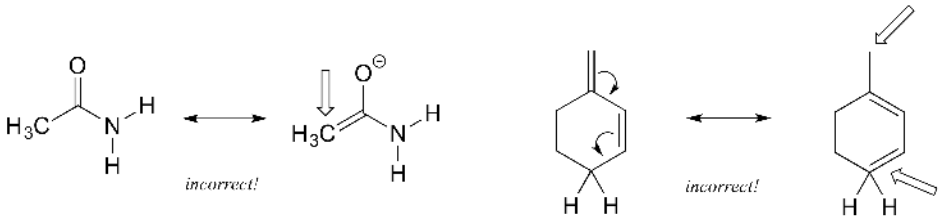


E2.16:



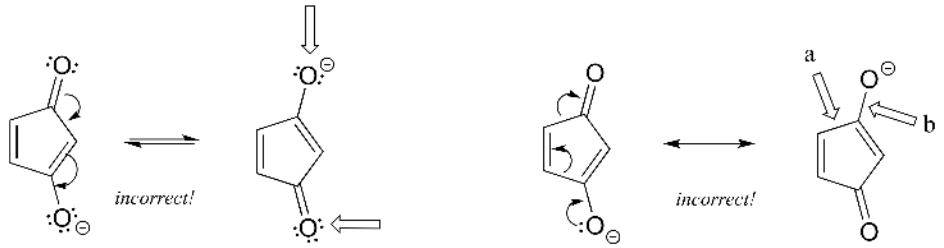
Left: an H atom has been added - in resonance contributors, only pi electrons and lone pairs are rearranged.

Right: Following the curved arrow, the oxygen atom should have only 6 electrons and thus a positive formal charge. Also the nitrogen is breaking the octet rule (remember that drawing lone pairs is optional, so even if they are not drawn you need to assume they are there).



Left: The CH_3 carbon is breaking the octet rule with 5 bonds.

Right: One carbon would have a positive formal charge if the arrows are followed, and the other breaks the octet rule with 5 bonds (keep careful track of hydrogen atoms when they are not drawn in line structures!)

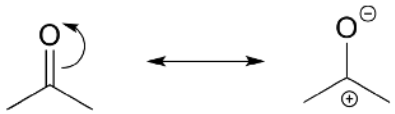


Left: One oxygen should have a positive formal charge, and one breaks the octet rule.

Right: a) the arrow shows this single bond breaking - you can't break single bonds in a resonance contributor. b) the arrow shows a triple bond forming here, which would also mean the oxygen is breaking the octet rule.

E2.17:

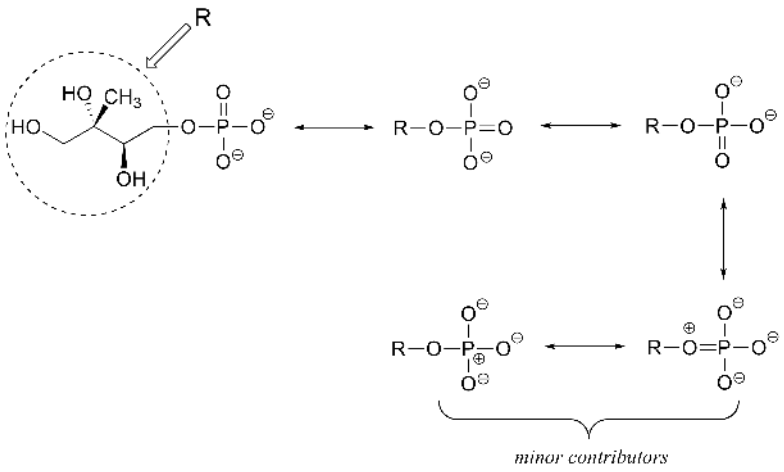
a)



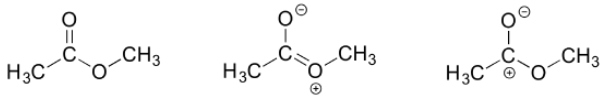
The contributor on the left is minor because it a) has a separation of charges, and b) the carbon has an incomplete octet.

b) Acetone and 2-propanol have the same molecular formula but different atom-to-atom bonding arrangements. Therefore, they are constitutional isomers, *not* resonance contributors.

E2.18: Minor contributors have additional separation of charge.



E2.19:



The contributor on the left is the most stable: there are no formal charges.

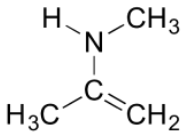
The contributor on the right is least stable: there are formal charges, and a carbon has an incomplete octet.

The contributor in the middle is intermediate stability: there are formal charges, but all atoms have a complete octet.

E2.20: Consult your instructor or tutor for an evaluation of your orbital drawings. Both contributors should show three overlapping *p* orbitals (on the oxygen, carbonyl carbon, and nitrogen) sharing four pi electrons.

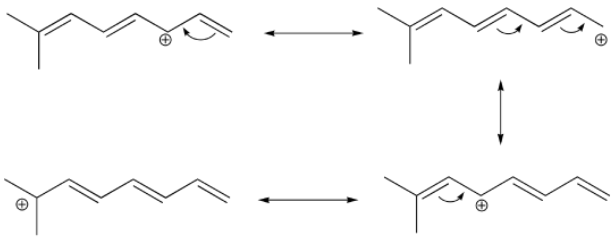
E2.21: Consult your instructor or tutor for an evaluation of your orbital drawings. Both contributors should show three overlapping *p* orbitals sharing four pi electrons.

E2.22: This contributor is major because there are no formal charges.



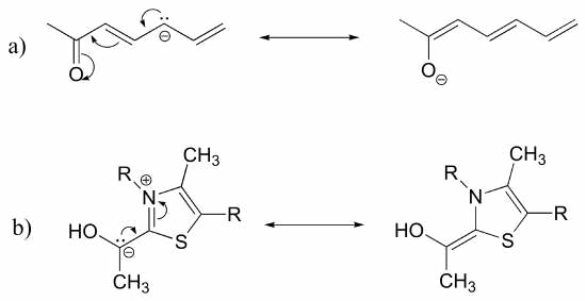
E2.23:

a)



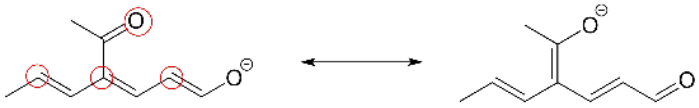
b) The conjugated pi system in this carbocation is composed of **seven** *2p* orbitals containing **six** delocalized pi electrons.

E2.24:



c) The conjugated pi system in structure a) is composed of **seven** 2*p* orbitals containing **eight** delocalized pi electrons.

E2.25: The two major contributors or those in which the negative formal charge is located on an oxygen rather than on a carbon.

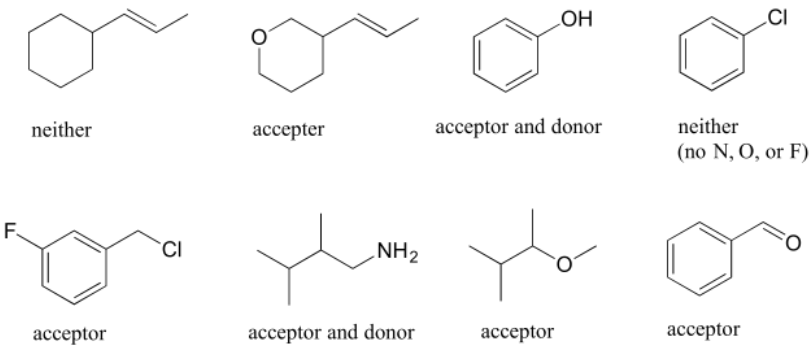


E2.26: The horizontal trend is based on atomic number (the number of protons in the nucleus). For example, fluorine is more electronegative than carbon, because the fluorine nucleus contains three more protons, the positive charges on which pull negatively-charged electrons closer to the nucleus.

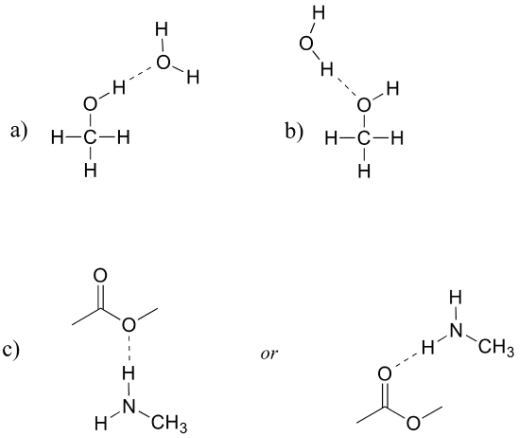
The vertical trend is based on atom size, specifically the size of the 'electron cloud' surrounding the nucleus. For example, fluorine is more electronegative than chlorine (even though chlorine contains more protons) because the outermost valence electrons on fluorine, which are in the n = 2 "shell", are closer to the nucleus than the valence electrons in chlorine, which occupy the *n* = 3 "shell". The fluorine electron cloud, therefore, is subject to greater electrostatic attractive forces from protons (electrostatic forces decrease rapidly as the distance between the positive and negative charges increases.)

E2.27: Only molecule (b) does *not* have a molecular dipole, due to its symmetry (bond dipoles are equal and in opposite directions).

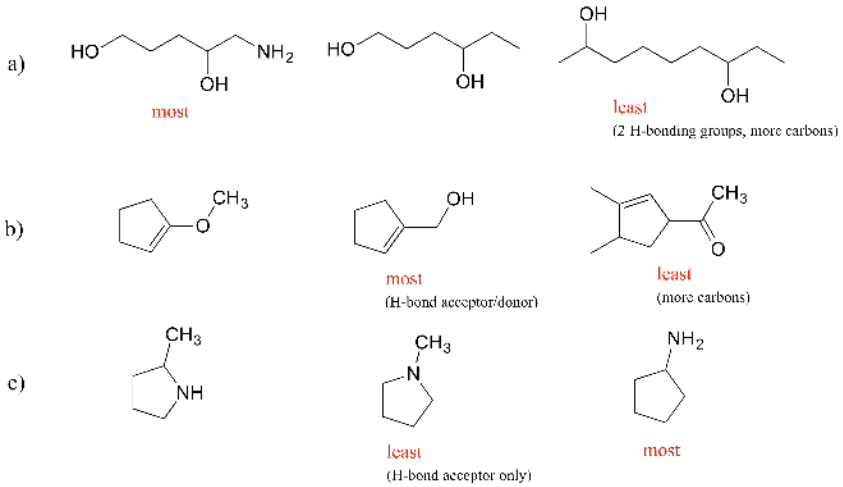
E2.28: To be a hydrogen bond donor, the molecule needs to have a hydrogen bound to N, O, or F. To be an acceptor, it merely needs an N, O, or F.



E2.29: Note in part (c) that methyl acetate can only be a hydrogen bond acceptor, *not* a donor.



E2.30: The main factors in these examples are the number of H-bonding groups, whether groups are H-bond acceptors *and* donors or just acceptors, and the number of carbons.

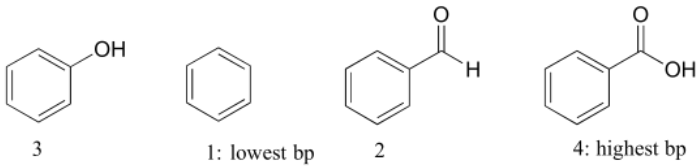


E2.31: Ascorbic acid and niacin are water soluble (lots of hydrophilic groups relative to the number of carbons). Retinol is fat-soluble (only one hydrophilic alcohol group, a large hydrophobic hydrocarbon group.

E2.32: Aniline is basic and would be protonated (and thus cationic) in aqueous HCl. Charged species are generally water soluble. On the other hand, phenol is not basic and thus would remain as a neutral, water-insoluble molecule.

E2.33: Both alcohol solvents could form H-bonds with cyclohexanone, but isopropanol is less polar (it has three carbons), and thus would be the better solvent for the relatively nonpolar cyclohexanone.

E2.34: Benzene has no polar groups and thus has the lowest boiling point (nonpolar interactions only holding molecules together). Benzaldehyde can form intermolecular dipole-dipole interactions; phenol and benzaldehyde can both form intermolecular H-bonds, but benzaldehyde has more dipole-dipole interactions due to the additional oxygen atom.



Contributors and Attributions

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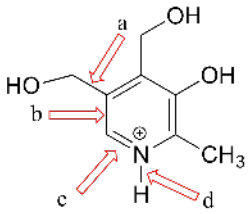
2.P: Problems for Chapter 2

Solutions to selected problems

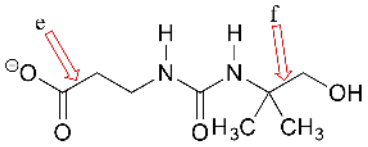
In questions involving drawing resonance contributors, assume that all second-row atoms should have a complete octet in all structures with the exception of positively-charged carbons.

P2.1: For each of the bonds indicated by arrows b-f in the figures below, describe the bonding picture. An example is given for bond 'a'. Note that for a double bond (bond 'c'), you will need to describe *two* bonds. Note: you are being asked to describe the bonding picture for one specific resonance contributor.

Example answer for bond a: "this is a sigma bond formed by the overlap of an sp^3 orbital on one carbon and an sp^2 orbital on another carbon."



pyridoxine
(vitamin B_6)

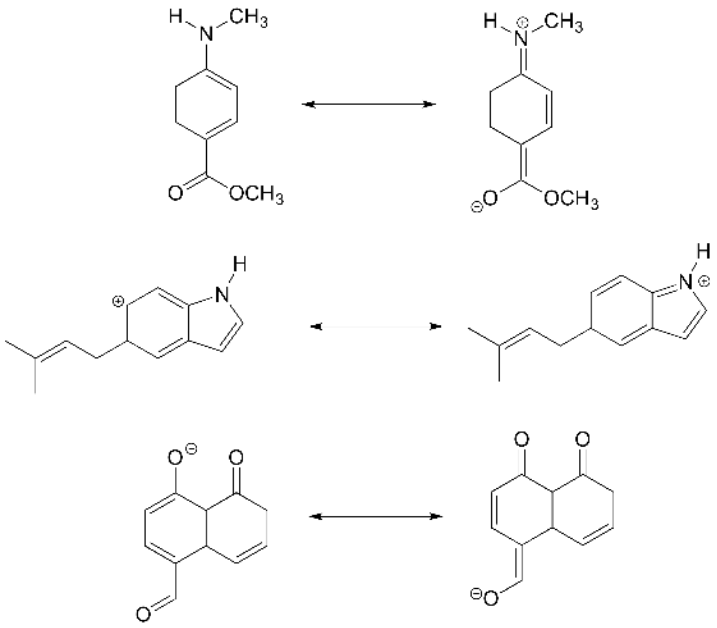


pantothenate
(vitamin B_5)

P2.2:

a) Draw curved arrows showing how each of the resonance contributors on the left could be converted to the one on the right.

b) Label contributors as major, minor, or approximately equivalent to each other.



P2.3: Draw a 3D-accurate picture showing the orbitals involved in bonding in the molecules below. Draw *all* bonds, both sigma and pi, as overlapping orbitals. Indicate whether each orbital is *s*, *p*, *sp*, sp^2, or sp^3, and indicate (with words or a color scheme) orbitals that are pointed into or out of the plane of the page. Locate all lone pairs in their appropriate orbitals. It is highly recommended to check your drawing with your instructor or tutor.

a) dimethyl ether (CH_3OCH_3)

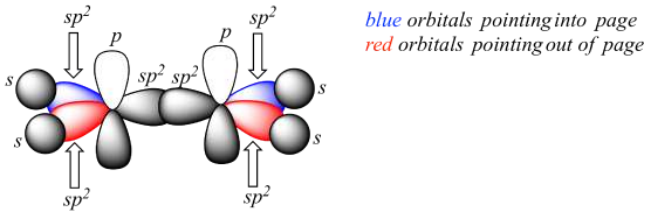
b) ethanol (CH_3CH_2OH)

https://chem.libretexts.org/@go/page/393415

c) acetaldehyde (CH_3COH)

d) hydrogen cyanide (HCN)

An example is provided for ethene, CH_2CH_2:

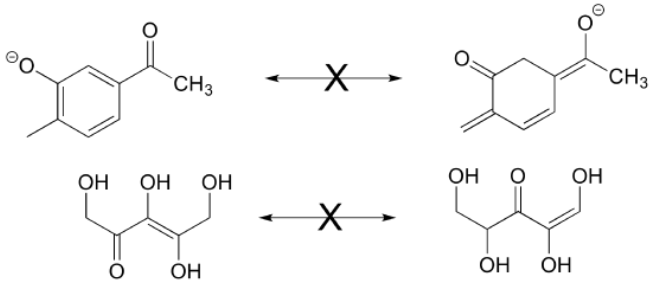


orbital overlap in ethene

P2.4: Neither of the pairs of structures below are pairs of resonance contributors.

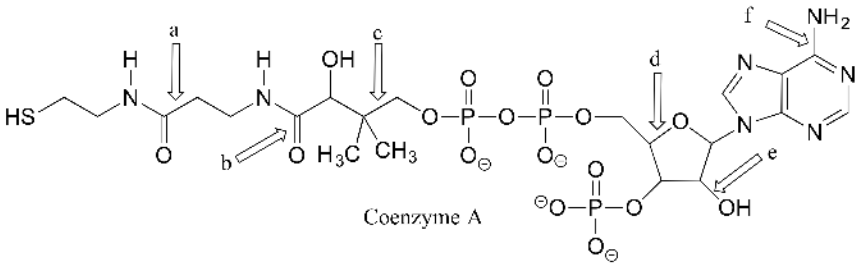
a) Explain why not.

b) What in fact is the relationship between them?

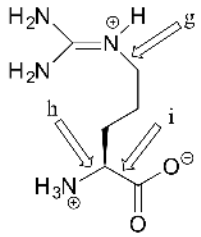


P2.5:

a-i) Describe the orbitals involved in the bonds indicated by the arrows, as in problem 2.1.



Coenzyme A



arginine

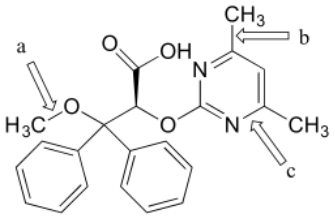
P2.6: The four compounds below appeared in the October 9 and October 25, 2006 issues of Chemical and Engineering News.

https://chem.libretexts.org/@go/page/393415

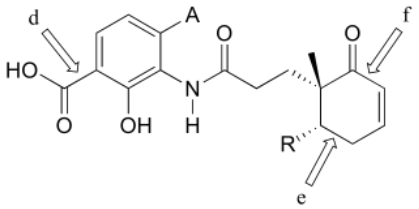
a-k) For each bond indicated by an arrow, specify the types of orbitals that are overlapping (for example, overlap between two *sp3*-hybridized carbons would be denoted C_{sp3}-C_{sp3})

l) (functional group review) Which compound contains two aldehydes? Which contains an ether? Which contains an amide? Which contains a terminal alkene? Which contains an amine (and is this amine primary, secondary, tertiary, or quaternary?)

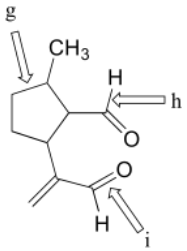
m) Give the molecular formula for the walking-stick compound



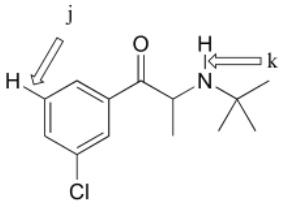
a hypertension drug



a newly-discovered antibiotic compound

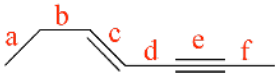


a defensive chemical extracted from a walking stick insect

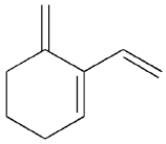


a drug for smoking cessation

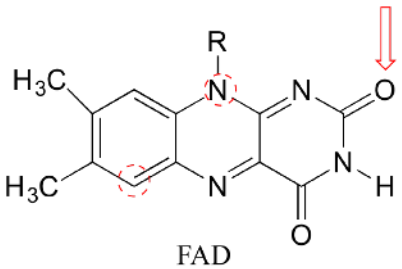
P2.7: Rank the bonds a-f below according to increasing bond length.



P2.8: Redraw the structure below, showing the $2p_z$ orbitals that make up the conjugated pi bond system.

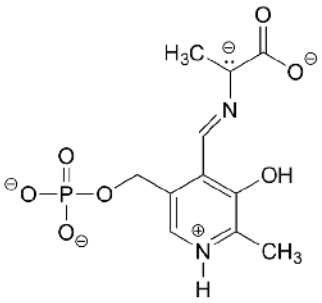


P2.9: Draw two different (minor) resonance contributors of the structure below (the flavin group of flavin adenine dinucleotide (FAD), a biochemical oxidation/reduction molecule) in which the oxygen indicated by an arrow bears a negative formal charge and one of the circled atoms bears a positive formal charge. Include curved arrows to account for the changing positions of electrons and pi bonds.



FAD

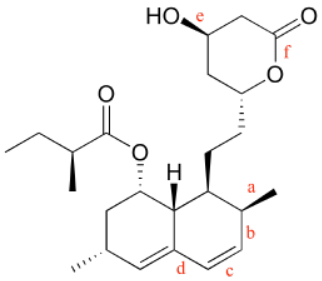
P2.10: The structure below shows an intermediate species in a reaction involving the amino acid alanine, attached to pyridoxal phosphate (vitamin B6). Draw a resonance contributor in which the only formal charges are on the oxygens.



P2.11: Below is the structure of the cholesterol-lowering drug Lovastatin. Predict the trend in bond length for

a) bonds a, b, c, and d

b) bonds e and f



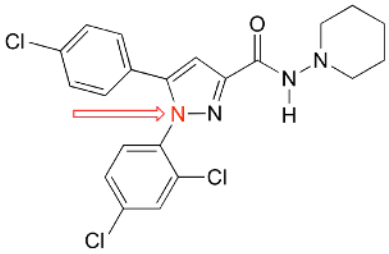
Lovastatin

P2.12: In problem P1.10, you were asked to draw four different amides with molecular formula C_3H_7NO. One of these constitutional isomers is significantly less soluble in water than the other three. Which one, and why?

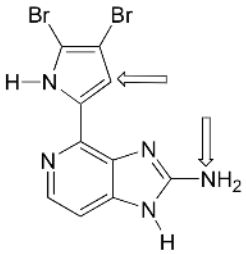
P2.13: Below is the structure of Rimonabant, a drug candidate which is being tested as a possible treatment for alcohol/tobacco dependence and obesity (see *Chemical and Engineering News*, October 15, 2006, p. 24). Draw minor resonance contributors in which

a) there is a separation of charge between the nitrogen indicated by the arrow and the oxygen.

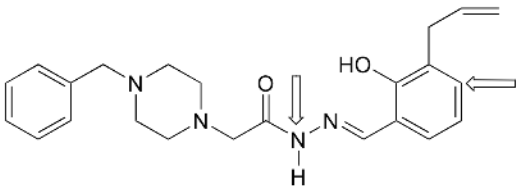
b) there is a separation of charge between a chlorine (positive) and one of the three nitrogens.



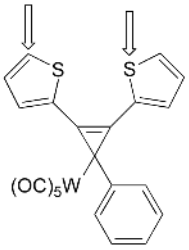
P2.14: For the molecules below, draw minor resonance contributors in which formal charges are placed on the atoms indicated by arrows. Use curved arrows to show how you are rearranging electrons between resonance contributors.



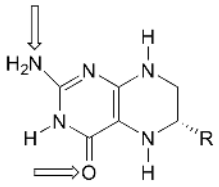
ageladine A, a potential cancer drug
Org. Lett. 2006, 8, 1443



PAC-1, a molecule that trigers cell death
Nature Chemical Biology 2006, 2, 543

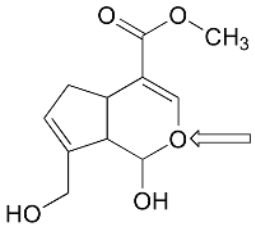


a new building block molecule for optoelectronic materials
Organometallics 2006, 25, 5176



tetrahydrofolate, a coenzyme

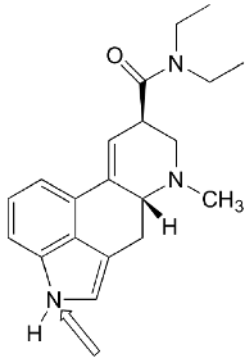
P2.15: Genipin was recently identified as the active compound in gardenia fruit extract, a traditional Chinese medicine for the treatment of diabetes (*Chemical and Engineering News* June 12, 2006, p. 34; *Cell Metab*. 2006, *3*, 417). Resonance contributors can be drawn in which the oxygen atom indicated by an arrow bears a positive formal charge. Indicate where the corresponding negative formal charge would be located in the most important of these contributors.



genipin

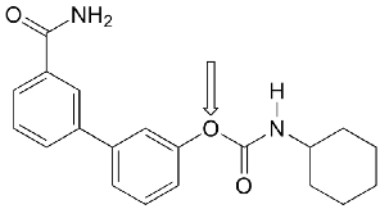
P2.16: Identify any *isolated* alkene groups in the PAC-1 structure in problem P2.14, and in the genipin structure in problem P2.15.

P2.17: The February 27, 2006 issue of *Chemical and Engineering News* contains an interesting article on the 100th birthday of Albert Hofmann, the inventor of the hallucinogen LSD. The structure of LSD is shown below. Several minor resonance contributors can be drawn in which the nitrogen atom indicated by an arrow bears a positive formal charge. Indicate atoms where a corresponding negative formal charge could be located in these contributors.



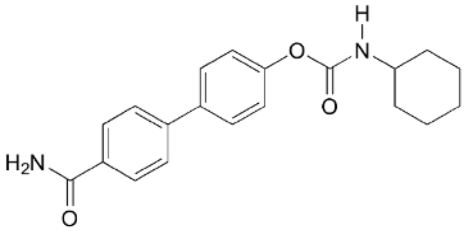
D-lysergic acid diethylamine (LSD)

P2.18: The human brain contains naturally occurring cannabinoid compounds which are related in structure to D^9-tetrahydrocannabinol, the active compound in cannabis. Cannabinoids are thought to exert an antidepressant effect. Researchers at the University of California, Irvine are studying synthetic compounds, such as the one shown below, which inhibit the degradation of natural cannabinoids in the brain. This compound has been shown to have antidepressant-like effects in rats and mice. (*Chemical and Engineering News*, December 19, 2005, p. 47; *Proc. Natl. Acad. Sci. USA* 2005, *102*, 18620.)



a) Several resonance contributors can be drawn in which the oxygen atom indicated by an arrow bears a positive formal charge. Indicate atoms where a corresponding negative formal charge could be located in these contributors.

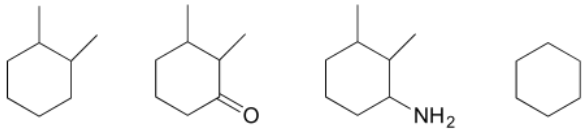
b) Answer the same question again, this time with the structural isomer shown below.

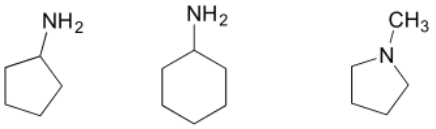


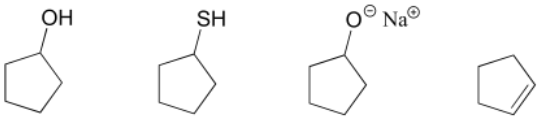
P2.19: Give the expected trend (lowest to highest) in boiling points for the following series of compounds.

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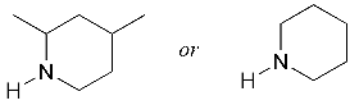
a) CH_3CHF_2 CH_2F_2 HF CH_3F

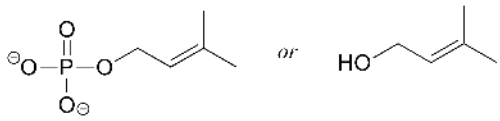
b) 

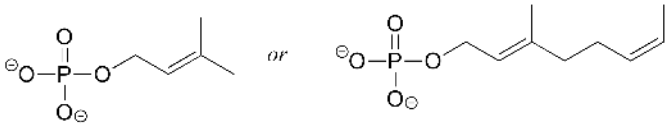
c) 

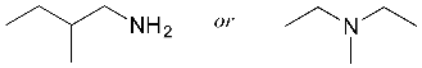
d) 

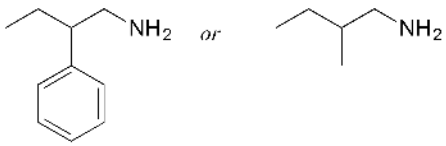
P2.20: For each pair of molecules below, choose the one that is more water-soluble, and explain your choice.

a) 

b) 

c) 

d) 

e) 

P2.21: Intermolecular forces: For *a-c* below, you may want to review amino acid/protein structure basics and the amino acid table. Use abbreviations as appropriate to focus the viewer's attention on the interaction in question.

a) Which of the 20 natural amino acids have *side chains* capable of forming hydrogen bonds with water?

b) Draw a picture of a hydrogen bond in a protein between an alanine main chain nitrogen and a glutamate side chain.

c) Draw a picture of a hydrogen bond in a protein between a tyrosine main chain (acting as donor) and a threonine side chain (acting as acceptor).

d) Draw a picture of an charge-charge (ionic) interaction in a protein between an aspartate and a lysine.

P2.22: In properly folded protein structures, main chain nitrogens often participate in hydrogen bonding interactions in the role of donor, but rarely as acceptor. Speculate as to why this might be so, using what you have learned in this chapter.

https://chem.libretexts.org/@go/page/393415

P2.23: Ozone, O_3, is an uncharged, non-cyclic molecule. Draw a Lewis structure for ozone. Are the two oxygen-oxygen bonds the likely to be the same length? What is the bond order? Explain.

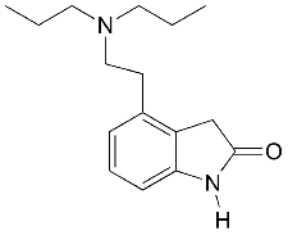
P2.24: Imagine that you hear a description of the bonding in water as being derived directly from the atomic orbital theory, without use of the hybrid orbital concept. In other words, the two bonds would be formed by the overlap of the half-filled $2p_y$ and $2p_z$ orbitals of oxygen with the 1s orbitals of hydrogen, while the two lone pairs on oxygen would occupy the 2s and $2p_x$ orbitals. What is wrong with this picture? How would the bonding geometry differ from what is actually observed for water?

P2.25:

a) Draw a picture showing the geometry of the overlapping orbitals that form the bonding network in allene, H_2CCCH_2. Then, draw a Lewis structure for the molecule, using the solid/dash wedge bond convention as necessary to indicate the correct geometry of the s bonds.

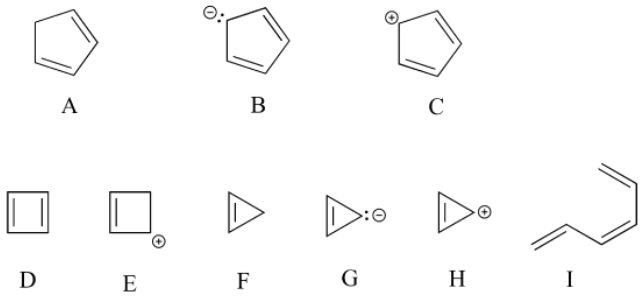
b) Draw a picture showing the geometry of the overlapping orbitals that form the bonding network in carbon dioxide.

P2.26 Below is the structure of ropinerol, a drug made by GlaxoSmithKline for the treatment of Parkinson's disease. Is the five-membered ring part of the aromatic system? Explain your answer.

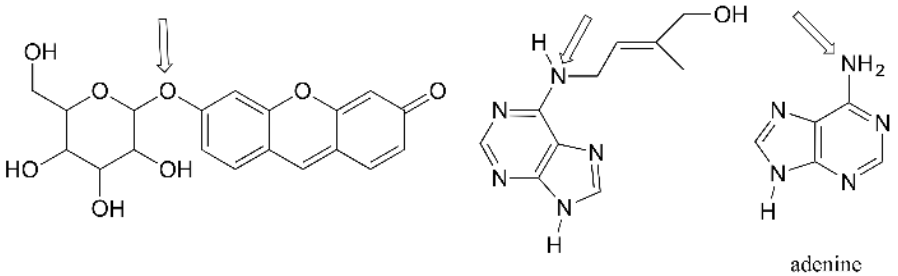


roprinol

P2.27: Classify each of the molecules/ions below as aromatic or not aromatic. Explain your reasoning.



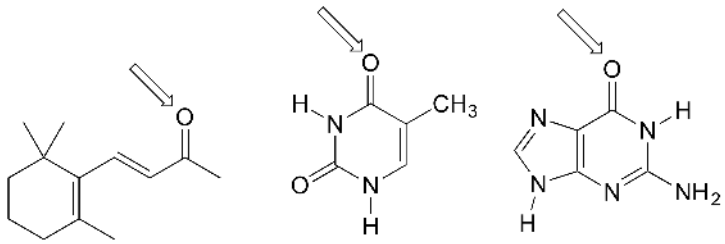
P2.28: For each of the compounds below, several minor resonance contributors can be drawn in which the atom indicated by an arrow bears a positive formal charge. Circle all atoms which could bear the corresponding negative formal charge.



zeatin, a plant ripening hormone

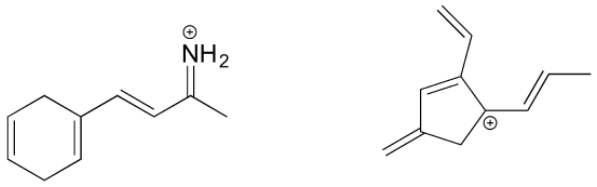
adenine

P2.29: For each of the compounds below, several minor resonance contributors can be drawn in which the atom indicated by an arrow bears a negative formal charge. Circle all atoms which could bear the corresponding positive formal charge.



beta-ionone - tomato aroma thymine guanine

P2.30: In each of the cation structures below, circle all carbon atoms to which the positive formal charge can be delocalized by resonance.



Solutions to selected problems

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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1.0: Solutions to selected chapter 2 problems

P2.1:

bond a is a sigma bond formed by the overlap of an sp^3 orbital on one carbon and an sp^2 orbital on another carbon.

bond b is a sigma bond formed by the overlap of an sp^2 orbital on one carbon and an sp^2 orbital on another carbon.

bond c is a sigma bond formed by the overlap of an sp^2 orbital on a carbon and an sp^2 orbital on a nitrogen, combined with a pi bond formed by the overlap of a 2*p* orbital on a carbon and a 2*p* orbital on a nitrogen.

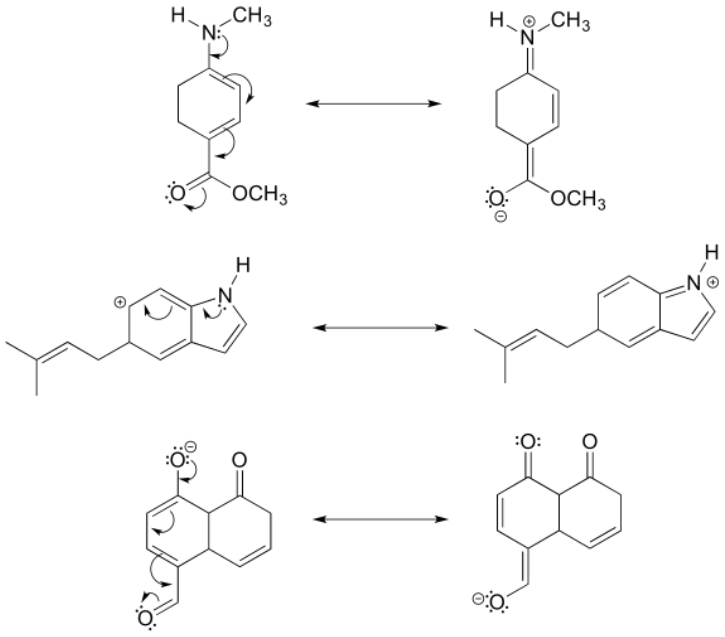
bond d is a sigma bond formed by the overlap of an sp^2 orbital on a nitrogen and a 1s orbital on a hydrogen.

bond e is a sigma bond formed by the overlap of an sp^2 orbital on one carbon and an sp^3 orbital on another carbon.

bond f is a sigma bond formed by the overlap of an sp^3 orbital on one carbon and an sp^3 orbital on another carbon.

P2.2:

a)



b)

Top: the contributor on the right is minor due to separation of charge.

Middle: the contributor on the left is minor due to one carbon not having a complete octet.

Bottom: The contributors shown are roughly equivalent.

P2.5:

bond a is a sigma bond formed by the overlap of an sp^2 orbital on one carbon and an sp^3 orbital on another carbon.

bond b is a sigma bond formed by the overlap of an sp^2 orbital on a carbon and an sp^2 orbital on an oxygen, combined with a pi bond formed by the overlap of a 2*p* orbital on a carbon and a 2*p* orbital on an oxygen.

bond c is a sigma bond formed by the overlap of an sp^3 orbital on a carbon and an sp^3 orbital on another carbon.

bond d is a sigma bond formed by the overlap of an sp^3 orbital on a carbon and an sp^3 orbital on an oxygen.

bond e is a sigma bond formed by the overlap of an sp^3 orbital on a carbon and an sp^3 orbital on an oxygen.

bond f is a sigma bond formed by the overlap of an sp^2 orbital on a carbon and an sp^3 orbital on a nitrogen.

bond g is a sigma bond formed by the overlap of an sp^3 orbital on a carbon and an sp^2 orbital on a nitrogen.

bond h is a sigma bond formed by the overlap of an sp^3 orbital on a carbon and an sp^3 orbital on a nitrogen.

bond i is a sigma bond formed by the overlap of an sp^2 orbital on one carbon and an sp^3 orbital on another carbon.

P2.6:

a) $C_{sp3} - O_{sp3}$ b) $C_{sp2} - C_{sp3}$ c) $C_{sp2} - N_{sp2}$ d) $C_{sp2} - C_{sp2}$ e) $C_{sp3} - C_{sp3}$ f) $C_{sp2} - C_{sp2}$

g) C_{sp3}- C_{sp3} h)$C_{sp2} - H_{1s}$ i) $C_{sp2} - O_{sp2}$ j) $C_{sp2} - Cl_{3p}$ k) N$sp^3 - H_{1s}$

l) The walking stick compound contains two aldehydes, compound one contains an ether, compound 2 contains an amide, compound 3 contains a terminal alkene, and compound 4 contains a secondary amine.

m) The molecular formula of the walking stick compound is $C_{10}H_{14}O_2$.

P2.7:

shortest

bond e (triple bond)

bond c (double bond)

bond d (single bond between sp^2 and sp hybridized carbons)

bond f (single bond between sp and sp^3 hybridized carbons)

bond b (single bond between sp^2 and sp^3 hybridized carbons)

bond a (single bond between two sp^3 hybridized carbons)

longest

P2.11:

shortest

bond c (double bond)

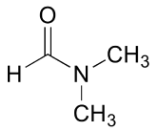
bond d (single bond between two sp^2 hybridized carbons)

bond b (single bond between sp^2 and sp^3 hybridized carbons)

bond a (single bond between two sp^3 hybridized carbons)

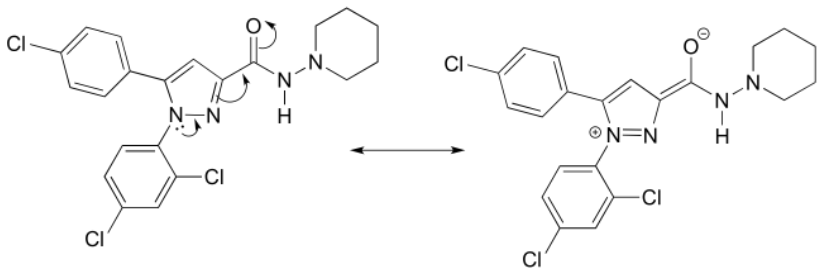
longest

P2.12: The amide shown below is not capable of acting as a hydrogen bond donor (it does not have any N-H bonds), and thus is expected to be less soluble in water. The other three amides of the same formula have one or more N-H bonds, and can thus participate in hydrogen bonding with water as both donor and acceptor.

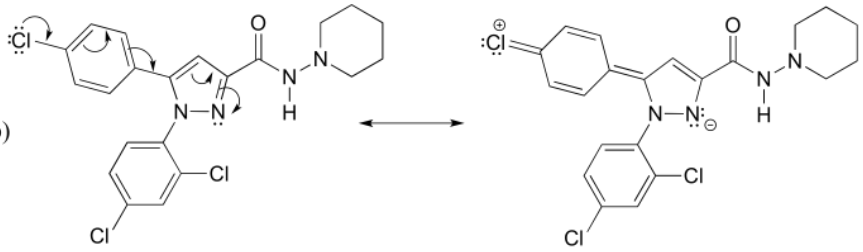


P2.13:

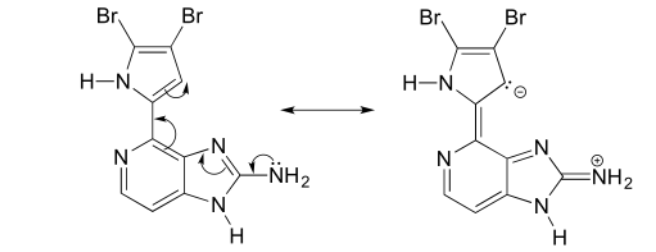
a)

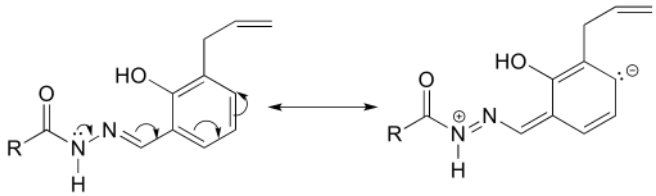


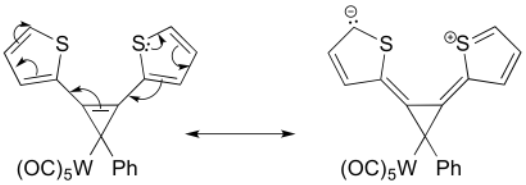
b)

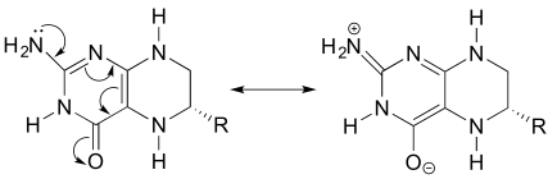


P2.14:

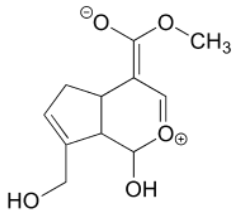




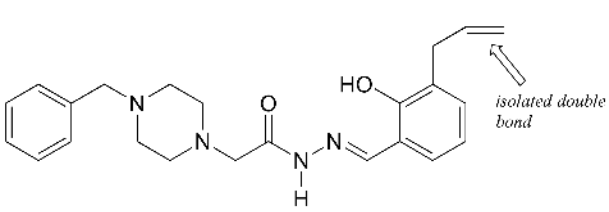




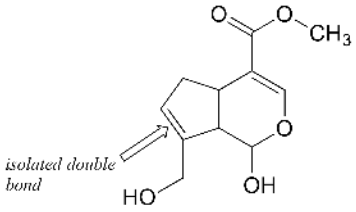
P2.15:



P2.16:

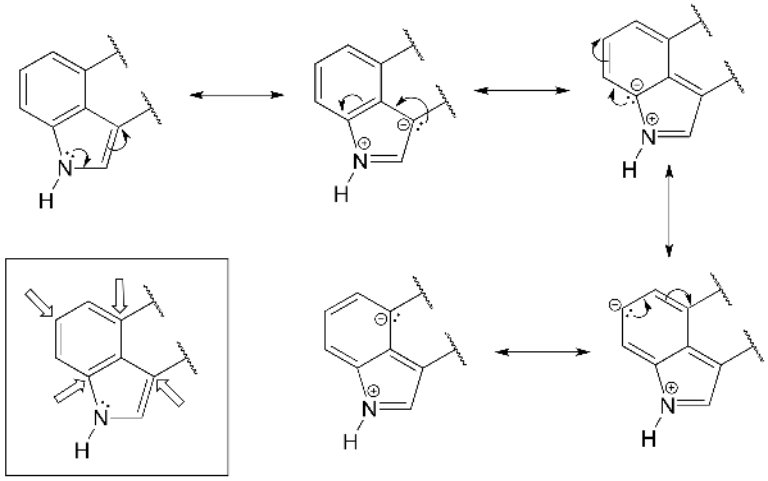


PAC-1

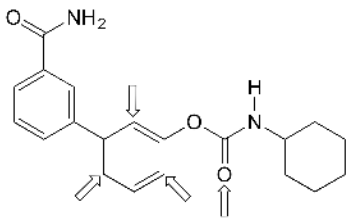


genipin

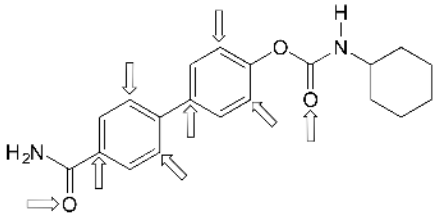
P2.17:



P2.18:



a)



b)

P2.19:

a)

1:CH_3F

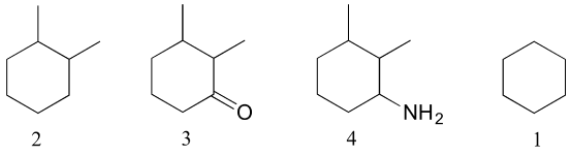
2: CH_2F_2

3: CH_3CHF_2

4: HF

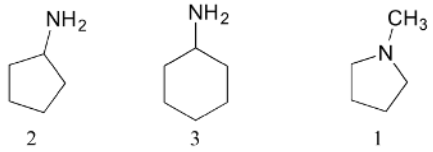
2 and 3 have two fluorines and are more polar than 1, so they have stronger intermolecular dipole-dipole interactions. 3 has one more carbon than 2, and therefore stronger van der Waals interactions. 4 is capable of hydrogen bonding, so it has the strongest intermolecular interactions and the highest boiling point.

b)



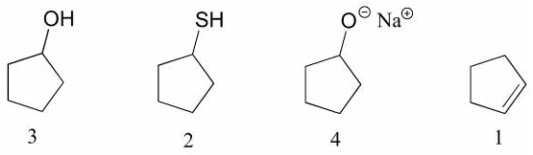
1 and 2 have only van der Waals interactions, but 2 has more carbons so these interactions are slightly stronger. 3 has a polar carbonyl group, and 4 is capable of hydrogen bonding.

c)



1 is not capable of hydrogen bonding. 2 and 3 both have hydrogen bonding groups, but 3 has one more carbon and therefore stronger overall van der Waals interactions.

d)



1 has only van der Waals interactions. 2 has a polar thiol group, but 3 has a hydroxyl group which is capable of hydrogen bonding. 4 is a salt: the charge-charge interactions are very strong and lead to a very high boiling point.

P2.20:

a) The compound on the right is more soluble (fewer hydrophobic carbons)

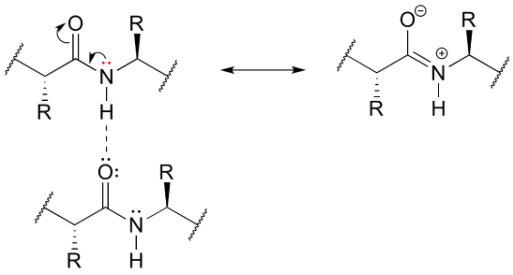
b) The compound on the left is more soluble (ionic phosphate group)

c) The compound on the left is more soluble (fewer hydrophobic carbons)

d) The compound on the left is more soluble (capable of hydrogen bonding)

e) The compound on the right is more soluble (fewer hydrophobic carbons)

P2.22: The lone pair electrons on the peptide nitrogen are conjugated to the carbonyl pi bond, and thus are not available to act as hydrogen bond acceptors.



P2.23: Both bonds are the same length, and have a bond order of 1.5 (one part single bond, one part double bond). The central oxygen is sp^2 hybridized (note the 'bent' geometry).



P2.26: The five-membered ring is *not* part of the aromatic system, due to the presence of an sp^2 hybridized carbon in the ring.

P2.27:

A is *not* aromatic (sp^3 hybridized carbon in the ring)

B is aromatic (count the lone pair and you get 10 pi electrons, which is a Huckel number)

C is *not* aromatic (the 2*p* orbital on the carbocation is empty, thus there are only four pi electrons in the system, which is not a Huckel number)

D is *not* aromatic (four pi electrons, not a Huckel number)

E is *not* aromatic (sp^3 hybridized carbon in the ring)

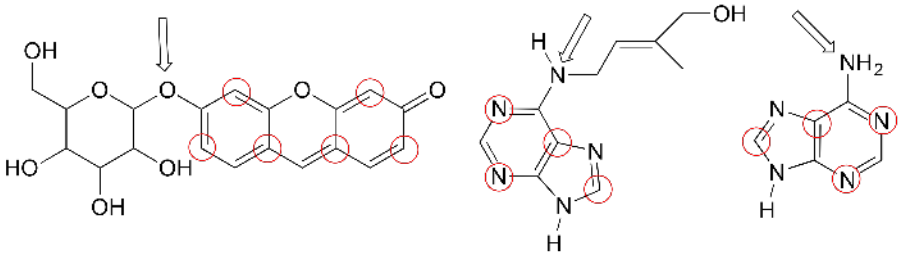
F is *not* aromatic (sp^3 hybridized carbon in the ring)

G is *not* aromatic (lone pair electrons count as part of pi system, thus there are four pi electrons which is not a Huckel number.

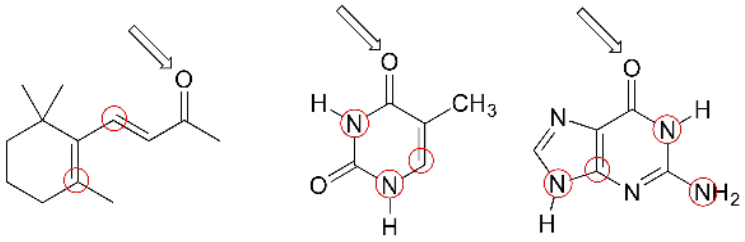
H is aromatic (carbocation is sp^2 hybridized, the 2*p* orbital is empty, so there are two pi electrons in the system, and 2 is a Huckel number)

I is *not* aromatic (there are three conjugated pi bonds with six pi electrons in the system, but the compound is not cyclic).

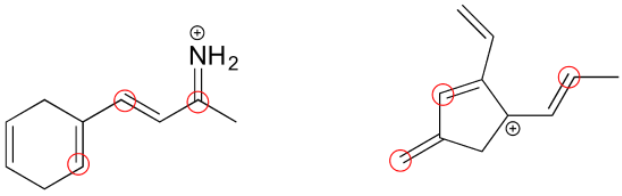
P2.28:



P2.29:



P2.30:



Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

3: Conformations and Stereochemistry

Stereochemistry is the study of how bonds are oriented in three-dimensional space. It is difficult to overstate the importance of stereochemistry in nature, and in the fields of biology and medicine in particular. As Pasteur so convincingly demonstrated, life itself is chiral: living things recognize different stereoisomers of organic compounds and process them accordingly.

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3.1: Conformations of open-chain organic molecules
3.2: Conformations of cyclic organic molecules
3.3: Chirality and stereoisomers
3.4: Naming chiral centers- the R and S system
3.5: Optical Activity
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3.0: Prelude to Conformations and Stereochemistry

Molecular models are your friend!

*Because this chapter deals extensively with concepts that are inherently three-dimensional in nature, it will be very important for you to use a molecular modeling kit that is specifically intended for organic chemistry. Many of the ideas we will be exploring can be extremely confusing if you are limited to the two dimensions of this page. Be prepared to follow along with these discussions in **three** dimensions, with a molecular model in your hands!*

Introduction: Louis Pasteur and the discovery of molecular chirality

In 1848, a 25 year old chemist named Louis Pasteur made a startling - and some thought brash - claim to the scientific community. Pasteur was inexperienced, to say the least: he had only earned his doctorate the previous year, and had just started his first job as an assistant to a professor at the *Ecole normale superieure*, a university in Paris. Jean-Baptiste Biot, a highly respected physicist who had already made major contributions to scientific fields as diverse as meteorites, magnetism, and optics, was intrigued but unconvinced by Pasteur's claim. He invited the young man to come to his laboratory and reproduce his experiments.



(Photo credit: https://www.flickr.com/photos/nate/)

Decades earlier, Biot had discovered that aqueous solutions of some biologically-derived substances, such as tartaric acid, quinine, morphine, and various sugars, were optically active: that is, the plane of polarized light would rotate in either a positive (clockwise, or right-handed) or negative (counter-clockwise, or left-handed) direction when passed through the solutions. Nobody understood the source of this optical property. One of the biological substances known to be optically active was a salt of tartaric acid, a compound found in abundance in grapes and a major by-product of the wine-making industry.

The compound was dextrorotatory in solution – in other words, it rotated plane-polarized light in the positive (right-handed, or clockwise) direction. Curiously, though, chemists had also found that another form of processed tartaric acid was optically *in*active, despite that fact that it appeared to be identical to the optically active acid in every other respect. The optically inactive compound was called '*acide racemique*', from the Latin *racemus*, meaning 'bunch of grapes'.

Louis Pasteur's claims had to do with experiments he said he had done with the 'racemic' acid. Jean-Babtise Biot summoned Pasteur to his laboratory, and presented him with a sample of racemic acid which he himself had already confirmed was optically inactive. With Biot watching over his shoulder, and using Biot's reagents, Pasteur prepared the salt form of the acid, dissolved it in water, and left the aqueous solution in an uncovered flask to allow crystals to slowly form as the water evaporated.

Biot again summoned Pasteur to the lab a few days later when the crystallization was complete. Pasteur placed the crystals under a microscope, and began to painstakingly examine their shape, just as he had done in his original experiments. He had recognized that the crystals, which had a regular shape, were asymmetric: in other words, they could not be superimposed on their mirror

image. Scientists referred to asymmetric crystals and other asymmetric objects as being 'chiral', from the Greek word for 'hand'. Your hands are chiral objects, because although your right hand and your left hand are mirror images of one another, they cannot be superimposed. That is why you cannot fit your right hand in a left-handed glove.

More importantly, Pasteur had claimed that the chiral crystals he was seeing under the lens of his microscope were of two different types, and the two types were mirror images of each other: about half were what he termed 'right handed' and half were 'left-handed'. He carefully separated the right and left-handed crystals from each other, and presented the two samples to Biot. The eminent scientist then took what Pasteur told him were the left-handed crystals, dissolved them in water, and put the aqueous solution in a polarimeter, an instrument that measures optical rotation. Biot knew that the processed tartaric acid he had provided Pasteur had been optically inactive. He also knew that unprocessed tartaric acid from grapes had right-handed optical activity, whereas left-handed tartaric acid was unheard of. Before his eyes, however, he now saw that the solution was rotating light to the left. He turned to his young colleague and exclaimed, " *Mon cher enfant, j'ai tant aime´ les sciences dans ma vie que cela me fait battre le coeur*!' (My dear child, I have loved science so much during my life that this makes my heart pound!)

Biot had good reason to be so profoundly excited. Pasteur had just conclusively demonstrated, for the first time, the concept of **molecular chirality**: molecules themselves - not just macroscopic objects like crystals - could exhibit chirality, and could be separated into distinct right-handed and left-handed 'stereoisomers'. Tying together ideas from physics, chemistry, and biology, he had shown that nature could be chiral *at the molecular level*, and in doing do he had introduced to the world a new subfield which came to be known as 'stereochemistry'.

About ten years after his demonstration of molecular chirality, Pasteur went on to make another observation with profound implications for biological chemistry. It was already well known that 'natural' tartaric acid (the right-handed kind from grapes) could be fermented by bacteria. Pasteur discovered that the bacteria were selective with regard to the chirality of tartaric acid: no fermentation occurred when the bacteria were provided with pure left-handed acid, and when provided with racemic acid they specifically fermented the right-handed component, leaving the left-handed acid behind.

Pasteur was not aware, at the time of the discoveries described here, the details of the structural features of tartaric acid at the molecular level that made the acid chiral, although he made some predictions concerning the bonding patterns of carbon which turned out to be remarkably accurate. In the more than 150 years since Pasteur's initial tartaric acid work, we have greatly expanded our understanding of molecular chirality, and it is this knowledge that makes up the core of this chapter. Put simply, stereochemistry is the study of how bonds are oriented in three-dimensional space. It is difficult to overstate the importance of stereochemistry in nature, and in the fields of biology and medicine in particular. As Pasteur so convincingly demonstrated, life itself is chiral: living things recognize different stereoisomers of organic compounds and process them accordingly.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

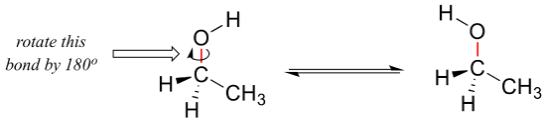
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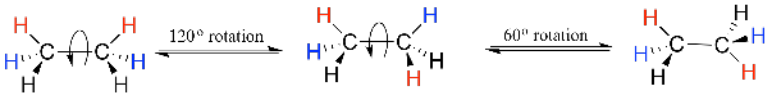
3.1: Conformations of open-chain organic molecules

Before we begin our exploration of stereochemistry and chirality, we first need to consider the subject of **conformational isomerism**, which has to do with rotation about single bonds.

We learned in section 2.1 that single bonds in organic molecules are free to rotate, due to the 'end-to-end' (sigma) nature of their orbital overlap. Consider the carbon-oxygen bond in ethanol, for example: with a 180^o rotation about this bond, the shape of the molecule would look quite different:

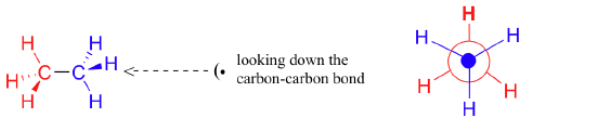


Or ethane: rotation about the carbon-carbon sigma bond results in many different possible three-dimensional arrangements of the atoms.



These different arrangements, resulting from sigma bond rotation, are referred to in organic chemistry as **conformations**. Any one specific conformation is called a **conformational isomer**, or **conformer**.

In order to better visualize different conformations of a molecule, it is convenient to use a drawing convention called the **Newman projection**. In a Newman projection, we look lengthwise down a specific bond of interest – in this case, the carbon-carbon bond in ethane. We depict the 'front' atom as a dot, and the 'back' atom as a larger circle.



'staggered' conformation
(Newman projection)

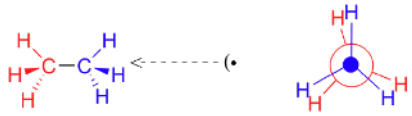
Interactive mode of ethane conformationsl

The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons. Note that we do *not* draw bonds as solid or dashed wedges in a Newman projection.

Looking down the C-C bond in this way, the angle formed between a C-H bond on the front carbon and a C-H bond on the back carbon is referred to as a **dihedral angle**. (The dihedral angle between the hour hand and the minute hand on a clock is 0^o at noon, 90^o at 3:00, and so forth).

The lowest energy conformation of ethane, shown in the figure above, is called the '**staggered'** conformation: all of the dihedral angles are 60^o, and the distance between the front and back C-H bonds is maximized.

If we now rotate the front CH_3 group 60° clockwise, the molecule is in the highest energy '**eclipsed**' conformation, where the dihedral angles are all 0^o (we stagger the bonds slightly in our Newman projection drawing so that we can see them all).

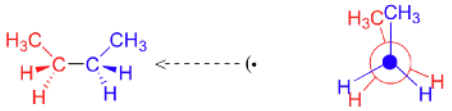


'eclipsed' conformation

The energy of the eclipsed conformation, where the electrons in the front and back C-H bonds are closer together, is approximately 12 kJ/mol higher than that of the staggered conformation.

Another 60° rotation returns the molecule to a second staggered conformation. This process can be continued all around the 360° circle, with three possible eclipsed conformations and three staggered conformations, in addition to an infinite number of conformations in between these two extremes.

Now let's consider butane, with its four-carbon chain. There are now three rotating carbon-carbon bonds to consider, but we will focus on the middle bond between C_2 and C_3. Below are two representations of butane in a conformation which puts the two CH_3 groups (C_1 and C_4) in the eclipsed position, with the two C-C bonds at a 0^o dihedral angle.



eclipsed (A)

Interactive model of butane conformations

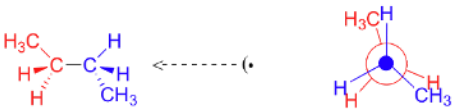
If we rotate the front, (blue) carbon by 60° clockwise, the butane molecule is now in a staggered conformation.



gauche

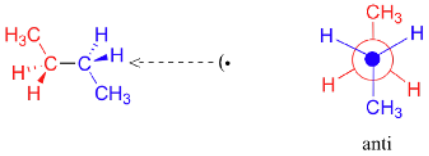
This is more specifically referred to as the **gauche** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be.

A further rotation of 60° gives us a second eclipsed conformation (B) in which both methyl groups are lined up with hydrogen atoms.



eclipsed (B)

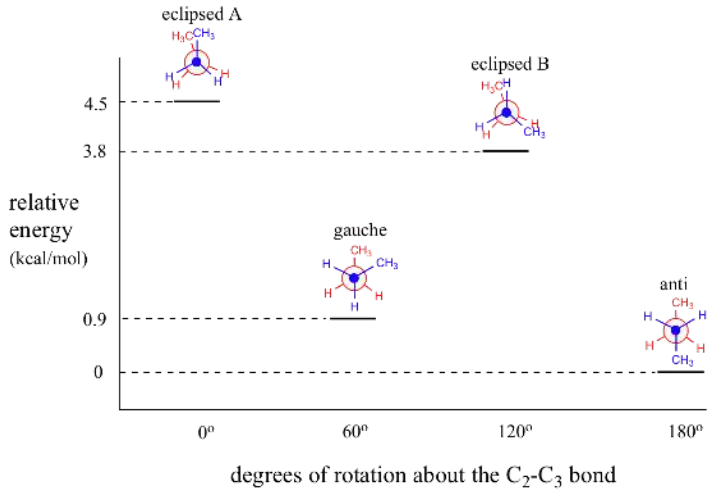
One more 60 rotation produces another staggered conformation called the **anti** conformation, where the two methyl groups are positioned opposite each other (a dihedral angle of 180^o).



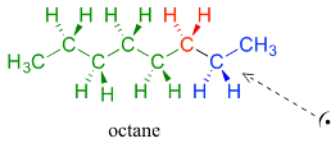
anti

As with ethane, the staggered conformations of butane are energy 'valleys', and the eclipsed conformations are energy 'peaks'. However, in the case of butane there are two different valleys, and two different peaks. The gauche conformation is a higher energy valley than the anti conformation due to **steric strain**, which is the repulsive interaction caused by the two bulky methyl groups being forced too close together. Clearly, steric strain is lower in the anti conformation. In the same way, steric strain causes the eclipsed A conformation - where the two methyl groups are as close together as they can possibly be - to be higher in energy than the two eclipsed B conformations.

The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.



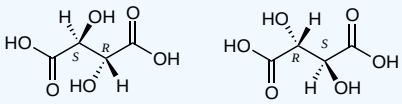
Because the anti conformation is lowest in energy (and also simply for ease of drawing), it is conventional to draw open-chain alkanes in a 'zigzag' form, which implies anti conformation at all carbon-carbon bonds. The figure below shows, as an example, a Newman projection looking down the C_2-C_3 bond of octane.





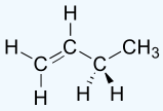
? Exercise 3.1

Using free rotation around C-C single bonds, show that (R,S) and (S,R)-tartaric acid are identical molecules.



Exercise 3.2

Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below (C_2 should be your *front* carbon).



Solutions to exercises

Online lectures from Khan Academy

Newman projections part I

Newman projections part II

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Layne Morsch (University of Illinois Springfield)

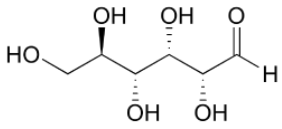
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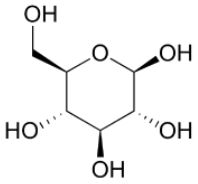
3.2: Conformations of cyclic organic molecules

Browse through a biochemistry textbook and you will see any number of molecules with cyclic structures. Many of these cyclic structures are aromatic, and therefore planar. Many others, though, are composed of sp^3-hybridized atoms, and it is these cyclic structures that are the topic of discussion in this section.

When discussing cyclic organic molecules, we will often use sugars as examples, because they are such important molecules in biological chemistry. It is important to recall that many sugars exist in aqueous solution as both open-chain and cyclic forms. You need not worry at this point about understanding how the cyclic form is named, or the reaction by which the cyclization occurs - this will be covered in chapter 10.

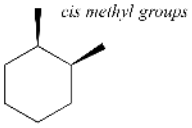


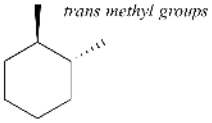
open-chain glucose

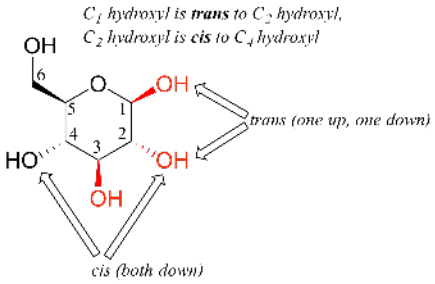


cyclic glucose (β-glucopyranose)

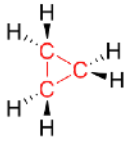
One thing that you should notice in the cyclic structure shown above is that atoms or groups bonded to tetrahedral ring carbons are either pointing up (out of the plane of the page) or down (into the plane of the page), as indicated by the use of dashed or solid wedge bonds. When two substituents on the same ring are both pointing toward the same side of the ring, they are said to be ***cis*** to each other. When they are pointed to opposite sides, they are said to be ***trans*** to each other.



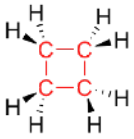




Ring structures in organic molecules are usually five-membered or six-membered. Three-and four-membered rings are occasionally found in nature, but are significantly higher in energy. The relative instability of these smaller ring structures can be explained by a concept called **angle strain**, in which the four bonds around the sp^3-hybridized carbons are forced out of their preferred tetrahedral angles.

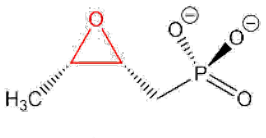


cyclopropane

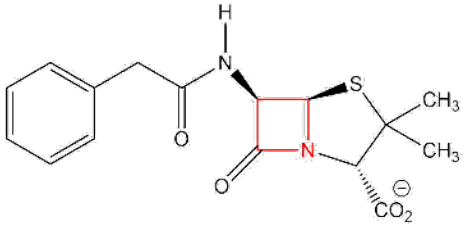


cyclobutane

If one of the carbon-carbon bonds is broken, the ring will ‘spring’ open, releasing energy as the bonds reassume their preferred tetrahedral geometry. The effectiveness of two antibiotic drugs, fosfomycin and penicillin, is due in large part to the high reactivity of the three- and four-membered rings in their structures.

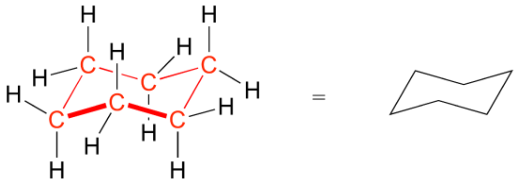


fosfomycin



penicillin G

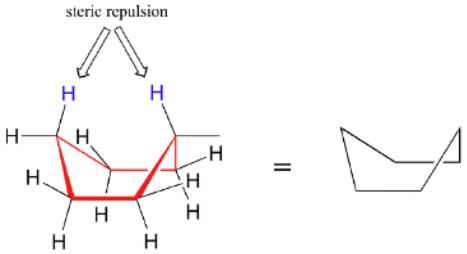
In six-membered cycloalkane structures, bonding angles are close to tetrahedral, and thus ring strain is not a factor – these rings are in fact very stable. However, the 'flat' drawings we have been using up to now do not accurately show the actual three-dimensional shape of a five- or six-membered ring. If cyclohexane were indeed flat, the bond angles would have to be distorted from 109.5° to 120°. If you build a model, though, you will find that when you rotate the carbon-carbon bonds so as to put the ring into a shape that resembles a reclining beach chair, all of the carbon-carbon bonds are able to assume tetrahedral bonding angles.



'chair' conformation of cyclohexane

This **chair conformation** is the lowest energy conformation for cyclohexane and other six-membered rings.

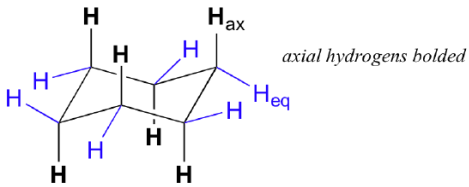
An alternate conformation for a six-membered ring is called the **'boat'**:



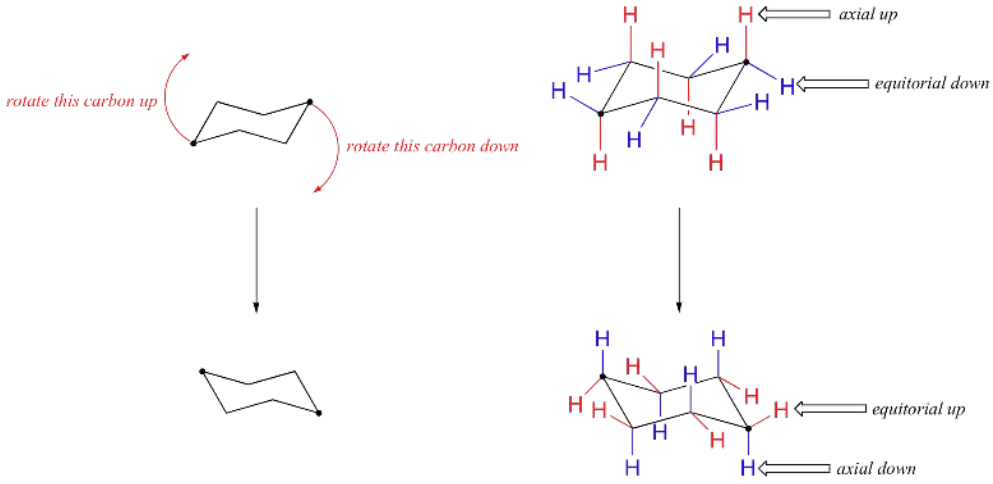
Interactive model of cyclohexane conformations

In the boat conformation, two of the substituents – those on the 'bow' and the 'stern' if you will – are brought close enough to each other to cause steric strain. An additional cause of the higher energy of the boat conformation is that adjacent hydrogen atoms on the 'bottom of the boat' are forced into eclipsed positions. For these reasons, the boat conformation is a high energy conformation of cyclohexane, about 30 kJ/mol less stable than the chair conformation.

If you look carefully at your model of cyclohexane in the chair conformation, you will see that all twelve hydrogens are not equivalent in terms of their three-dimensional arrangement in space. Six hydrogens are **axial** – that is, they are pointing either straight up or straight down relative to the ring. The other six hydrogens are **equatorial**, meaning that they are pointing away from the perimeter of the ring, either slightly up or slightly down. *(The equatorial vs axial distinction is often hard to see at first - it would be a very good idea at this point to sit down with your instructor or tutor and work with a modeling kit).*



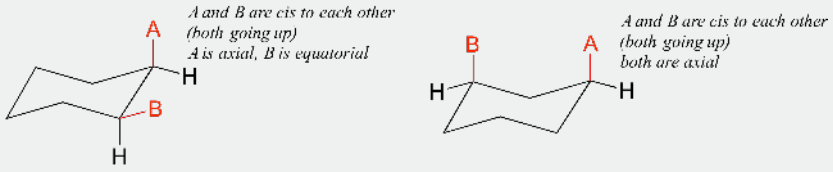
This is not the only possible chair conformation for cyclohexane. On your model, rotate one of the 'up' carbons down, and one of the 'down' carbons up. You now have a new, alternate chair conformation – this process is called **ring inversion**.



What you should recognize here is that, as a result of the ring inversion process, all of the axial and equatorial hydrogens have traded positions – axial hydrogens have become equatorial, and vice-versa. Notice, however, that the 'down' hydrogens are still pointing down, and the 'up' hydrogens are still pointing up regardless of whether they are axial or equatorial. At room temperature, cyclohexane is constantly inverting between two chair forms of equal energy – it is a rapid equilibrium situation. Thus, except at very low temperatures, we are not able to distinguish between axial and equatorial hydrogens, as they are constantly switching back and forth.

axial/equatorial *vs cis/trans*

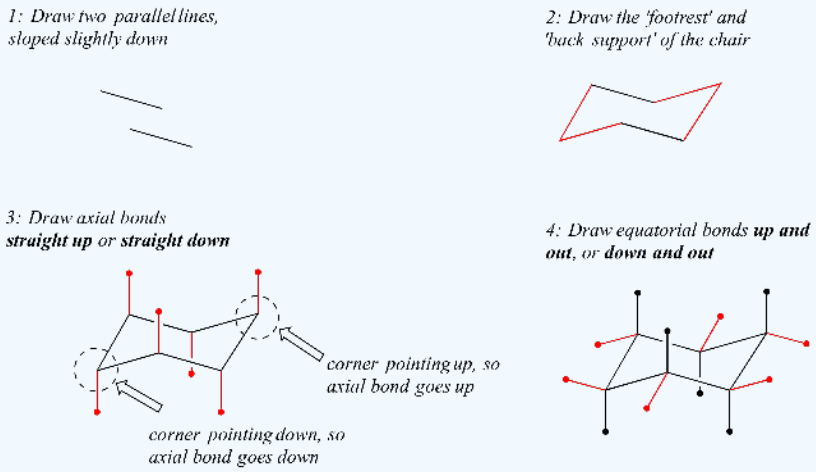
A very common error made by organic chemistry students as they begin to learn about chair conformations is to confuse the terms axial and equatorial with the terms *cis* and *trans*. **These are completely different things!** For example, when two substituents on a ring are *cis* in relation to one another, it means that they are pointed to the same side of the ring (both up or both down). Depending on their positions on the ring, they might both be axial, both be equatorial, or one of each.



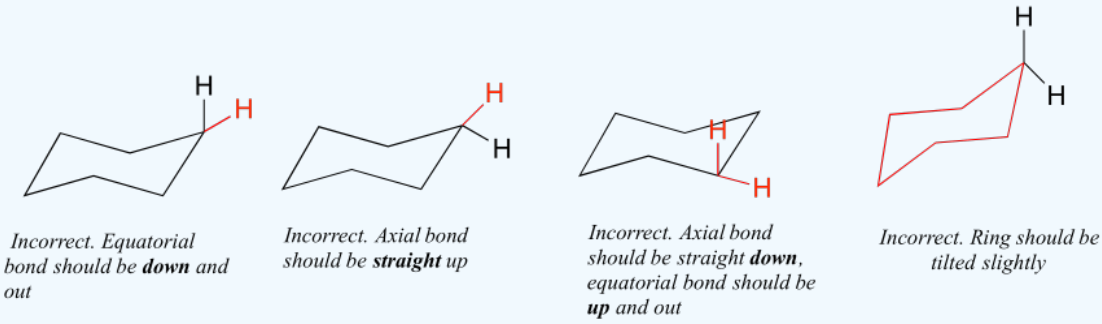
Do not make the mistake of calling two substituents *trans* to each other merely because one is equatorial and one is axial, or *cis* because the are both axial or both equatorial.

How to draw the cyclohexane chair conformation

As an organic chemistry student, you will be expected to be able to draw an accurate representation of the chair conformations of six-membered cycloalkanes, which includes being able to draw axial and equatorial substituents with their correct orientations. Here, then, are some guidelines to follow:



How **not** to draw the chair:



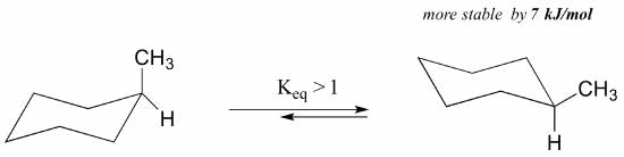
*Incorrect. Equatorial bond should be **down** and out*

*Incorrect. Axial bond should be **straight** up*

*Incorrect. Axial bond should be straight **down**, equatorial bond should be **up** and out*

Incorrect. Ring should be tilted slightly

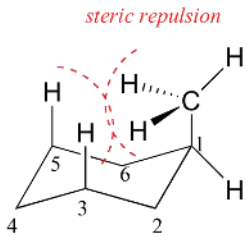
What happens to the relative energies of chair conformations when the ring has a large substituent, such as a methyl group? Now, the two chair conformations are quite different: in one, the methyl group is equatorial and in the other it is axial.



methyl group axial

methyl group equatorial

When the methyl group is in the axial position, it is brought close enough to the axial hydrogens on carbons two bonds away to cause destabilizing steric repulsion: this is referred to as **1,3-diaxial repulsion**.



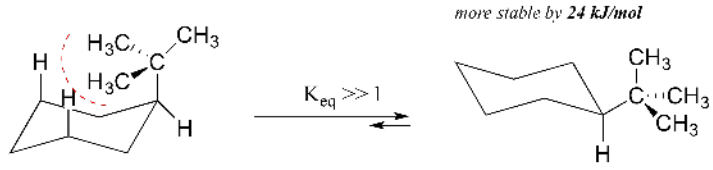
When in the equatorial position, the methyl group is pointing up and *away* from the rest of the ring, eliminating the unfavorable 1,3-diaxial interaction. As a consequence, the conformation in which the methyl group is in the equatorial position is more stable, by approximately 7 kJ/mol. At room temperature, methylcyclohexane exists as a rapid equilibrium between the two chair forms (and many other intermediate conformations), but the equilibrium constant (K_{eq}) favors the conformation where the methyl group is equatorial.

Exercise 3.3

Here's some General Chemistry review: what is the value of K_{eq} at 25 °C for the axial to equatorial interconversion of methylcyclohexane as shown in the previous figure?

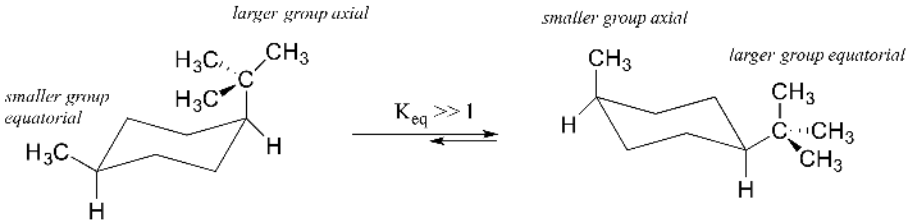
Solutions to exercises

The importance of the steric strain factor increases with the increasing size of a substituent. For example, the difference in energy between the two chair conformations of *tert*-butyl cyclohexane (24 kJ/mol) is much larger than for methylcyclohexane (7 kJ/mol), because a *tert*-butyl group is larger than a methyl group and results in more energetically unfavorable 1,3-diaxial interactions.



tert-butyl group axial — *tert*-butyl group equatorial

In the case of a disubstituted cyclohexane ring in which both substituents cannot be equatorial, the lower energy conformation generally places the bulkier substituent in the equatorial position.



more stable conformation

As a general rule, the most stable chair conformation of a six-membered ring will be that in which the bulkiest groups are in the equatorial position.

? Exercise 3.4

Draw the lower energy chair conformations of a) *trans*-1,2-dimethylcyclohexane, and b) *trans*-1-isopropyl-3-methylcyclohexane. Draw all substituents on all carbons (including hydrogens), being sure that the axial or equatorial orientation is clear. Be sure to check your drawing with your instructor or tutor.

Exercise 3.5

Predict which of the following disubstituted hexanes has a greater energy difference between its two chair conformations, and state your reasons for your choices.

a) *cis*-1,3-dimethylcyclohexane or *cis*-1,4-dimethylcyclohexane

b) *cis*-1,2-dimethylcyclohexane or *trans*-1,2-dimethylcyclohexane

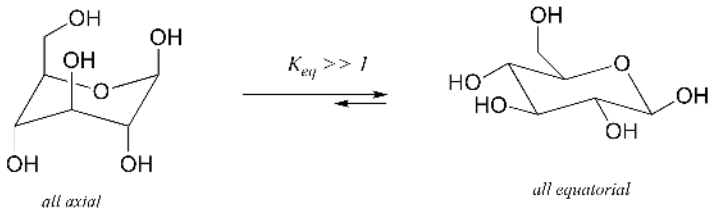
c) *trans*-1,2-dimethylcyclohexane or *trans*-1-isopropyl-2-methylcyclohexane

Exercise 3.6

Can a 'ring inversion' change a *cis*-disubstituted cyclohexane to *trans*? Explain.

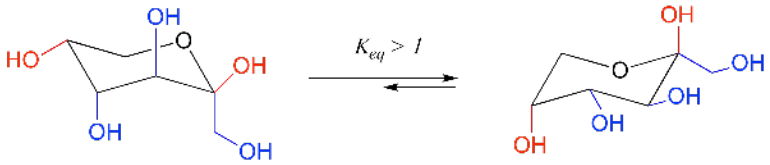
Solutions to exercises

Recall that five- and six-carbon sugars such as glucose and fructose exist in solution in open chain and cyclic forms. Glucose, in its most abundant form in solution, is a six-membered ring adopting a chair conformation with all substituents equatorial.



glucose
(β-glucopyranose form)

The most abundant form of fructose in aqueous solution is also a six-membered ring.

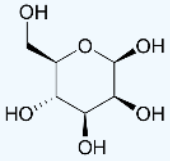


fructose
(β-fructopyranose form)

The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position.

? Exercise 3.7

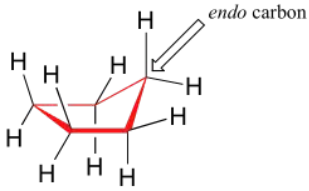
Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.



mannose

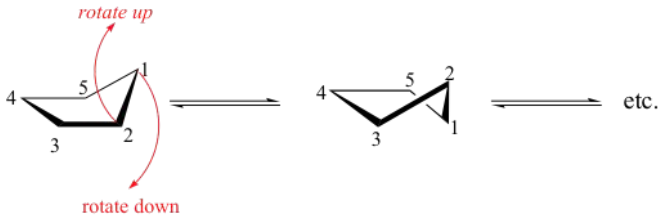
Solutions to exercises

The lowest energy conformation of cyclopentane and other five-membered rings is known as the 'envelope', with four of the ring atoms in the same plane and one out of plane (notice that this shape resembles an envelope with the flap open). The out-of-plane carbon is said to be in the ***endo*** position ('*endo*' means 'inside').

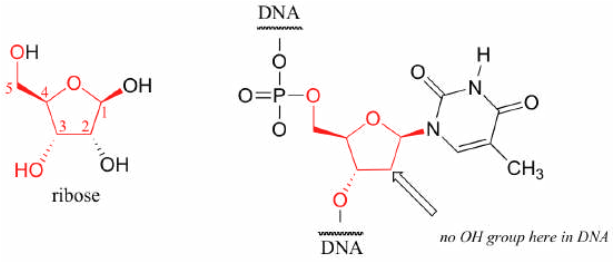


The 'equatorial' vs 'axial' distinction discussed in the context of 6-membered rings does not apply to five-membered rings.

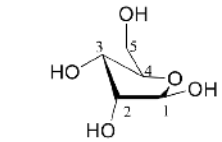
At room temperature, cyclopentane undergoes a rapid **pseudorotation** process in which each of the five carbons takes turns being in the *endo* position.



One of the most important five-membered rings in nature is a sugar called ribose – recall from section 1.3E that DNA and RNA are both constructed upon 'backbones' derived from ribose. Pictured below is one thymidine (T) deoxy-nucleotide from a stretch of DNA:



The lowest-energy conformations for ribose are envelope forms in which either C_3 or C_2 are *endo*, on the same side as the C_5 substituent.



This has very important implications for oligonucleotide structure – in DNA, it is C_2 that is in the *endo* position, while in RNA it is C_3.

Khan Academy video tutorial on conformation of cycloalkanes

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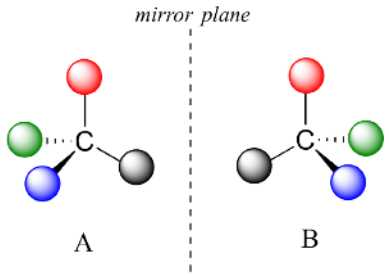
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3.3: Chirality and stereoisomers

We turn now to concept of chirality that formed the basis of the story about Louis Pasteur in the beginning of this chapter. Recall that the term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Your hands, of course, are chiral - you cannot superimpose your left hand on your right, and you cannot fit your left hand into a right-handed glove (which is also a chiral object). Another way of saying this is that your hands do not have a **mirror plane of symmetry**: you cannot find any plane which bisects your hand in such a way that one side of the plane is a mirror image of the other side. *Chiral objects do not have a plane of symmetry*.

Your face, on the other hand is **achiral** - lacking chirality - because, some small deviations notwithstanding, you could superimpose your face onto its mirror image. If someone were to show you a mirror image photograph of your face, you could line the image up, point-for-point, with your actual face. Your face has a plane of symmetry, because the left side is the mirror image of the right side.

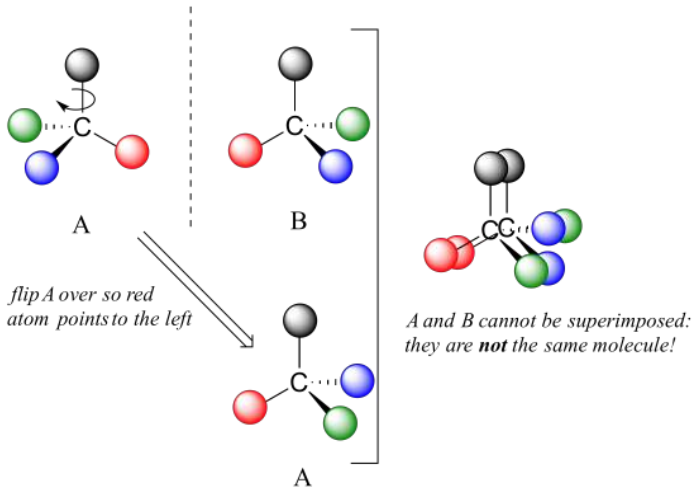
What Pasteur, Biot, and their contemporaries did not yet fully understand when Pasteur made his discovery of molecular chirality was the *source* of chirality at the molecular level. It stood to reason that a chiral molecule is one that does not contain a plane of symmetry, and thus cannot be superimposed on its mirror image. We now know that chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral (sp^3-hybridized) carbons with four different substituents. Consider the cartoon molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors (for the time being, don't worry about exactly what these substituents could be - we will see real examples very soon).



Another image

The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.

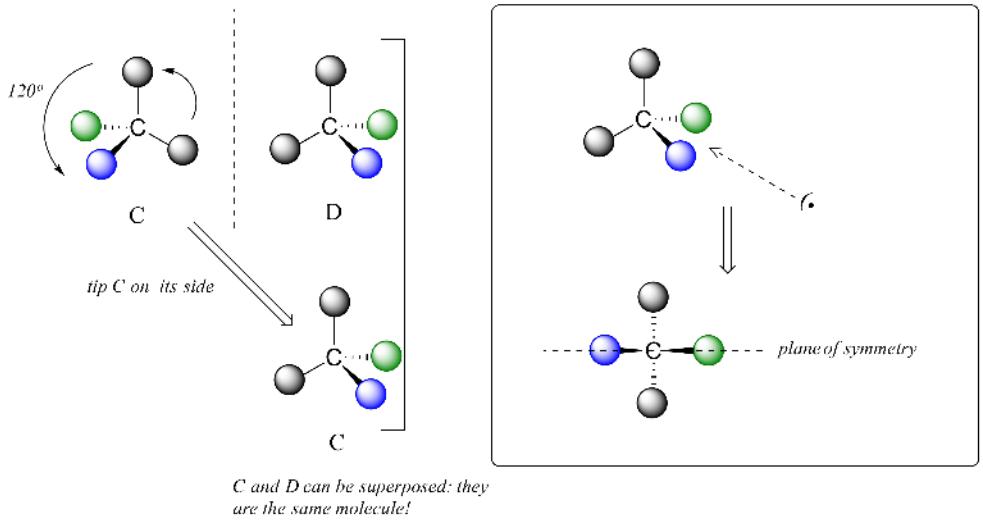


A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule. Also notice in the figure below (and convince yourself with models) that neither A nor B has an internal plane of symmetry.

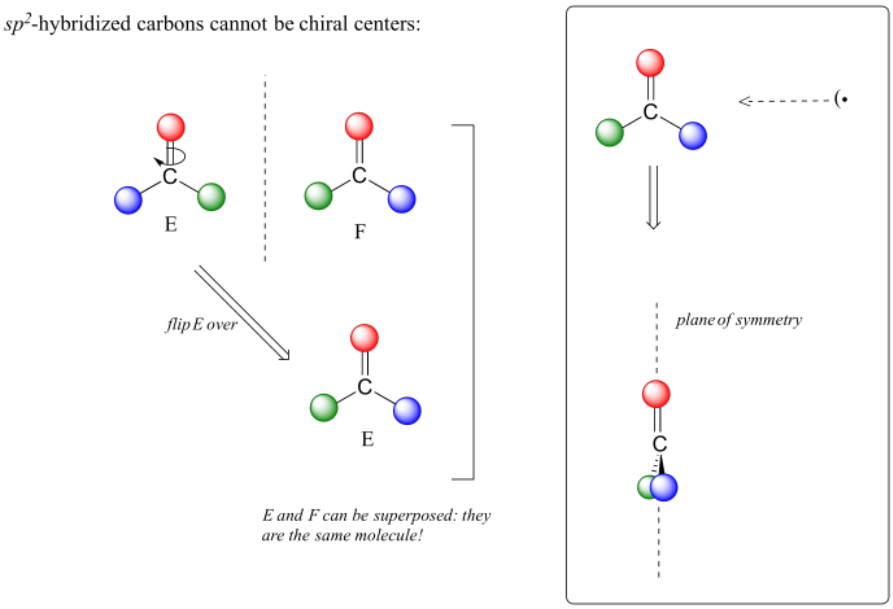
A and B are **stereoisomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. There are two types of stereoisomers: enantiomers and diastereomers. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

Diastereomers are stereoisomers which are *not* mirror images of each other. For now, we will concentrate on understanding enantiomers, and come back to diastereomers later.

We defined a chiral center as a tetrahedral carbon with four different substituents. If, instead, a tetrahedral carbon has two identical substituents (two black atoms in the cartoon figure below), then of course it still has a mirror image (*everything* has a mirror image, unless we are talking about a vampire!) However, it is superimposable on its mirror image, and has a plane of symmetry.



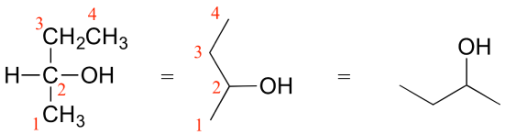
This molecule is **achiral** (lacking chirality). Using the same reasoning, we can see that a trigonal planar (sp^2-hybridized) carbon is also not a chiral center.



Notice that structure E can be superimposed on F, its mirror image - all you have to do is pick E up, flip it over, and it is the same as F. This molecule has a plane of symmetry, and is achiral.

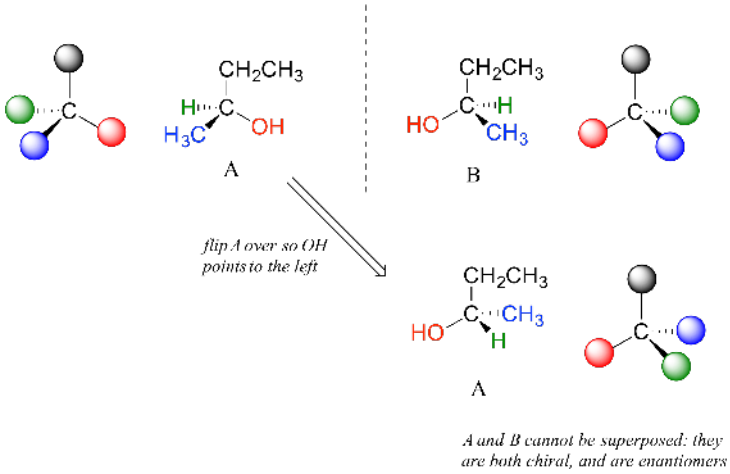
Let's apply our general discussion to real molecules. For now, we will limit our discussion to molecules with a single chiral center. It turns out that tartaric acid, the subject of our chapter introduction, has *two* chiral centers, so we will come back to it later.

Consider 2-butanol, drawn in two dimensions below.



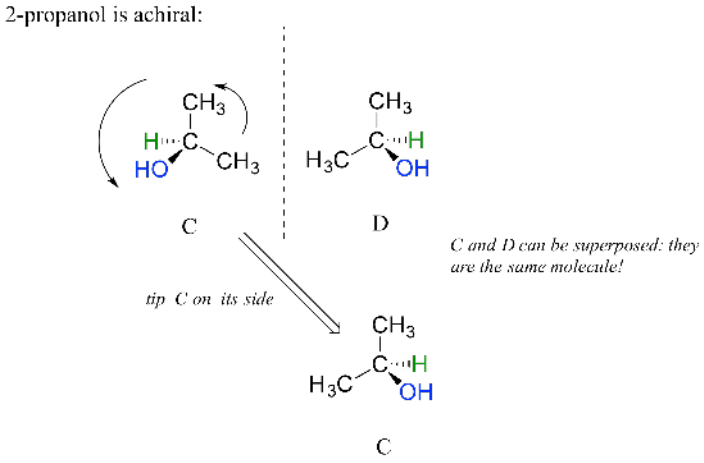
2-butanol
(drawn in 2D)

Carbon #2 is a chiral center: it is sp^3-hybridized and tetrahedral (even though it is not drawn that way above), and the four things attached to is are different: a hydrogen, a methyl ($-CH_3$) group, an ethyl ($-CH_2CH_3$) group, and a hydroxyl (OH) group. Let's draw the bonding at C_2 in three dimensions, and call this structure A. We will also draw the mirror image of A, and call this structure B.



When we try to superimpose A onto B, we find that we cannot do it. A and B are both chiral molecules, and they are enantiomers of each other.

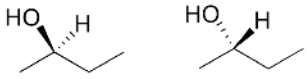
2-propanol, unlike 2-butanol, is *not* a chiral molecule. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral center.



Notice that 2-propanol is superimposable on its own mirror image.

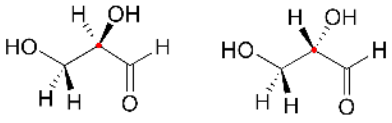
When we look at very simple molecules like 2-butanol, it is not difficult to draw out the mirror image and recognize that it is not superimposable. However, with larger, more complex molecules, this can be a daunting challenge in terms of drawing and three-dimensional visualization. The easy way to determine if a molecule is chiral is simply to look for the presence of one or more chiral centers: molecules with chiral centers will (almost always) be chiral. We insert the 'almost always' caveat here because it is possible to come up with the exception to this rule - we will have more to say on this later, but don't worry about it for now.

Here's another trick to make your stereochemical life easier: if you want to draw the enantiomer of a chiral molecule, it is not necessary to go to the trouble of drawing the point-for-point mirror image, as we have done up to now for purposes of illustration. Instead, keep the carbon skeleton the same, and simply reverse the solid and dashed wedge bonds on the chiral carbon: that accomplishes the same thing. You should use models to convince yourself that this is true, and also to convince yourself that swapping *any two substituents* about the chiral carbon will result in the formation of the enantiomer.

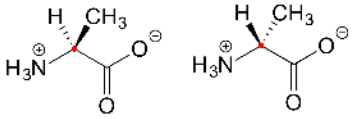


two enantiomers of 2-butanol

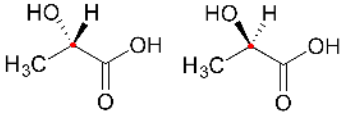
Here are four more examples of chiral biomolecules, each one shown as a pair of enantiomers, with chiral centers marked by red dots.



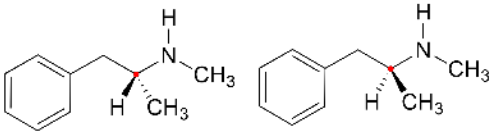
glyceraldehyde



alanine

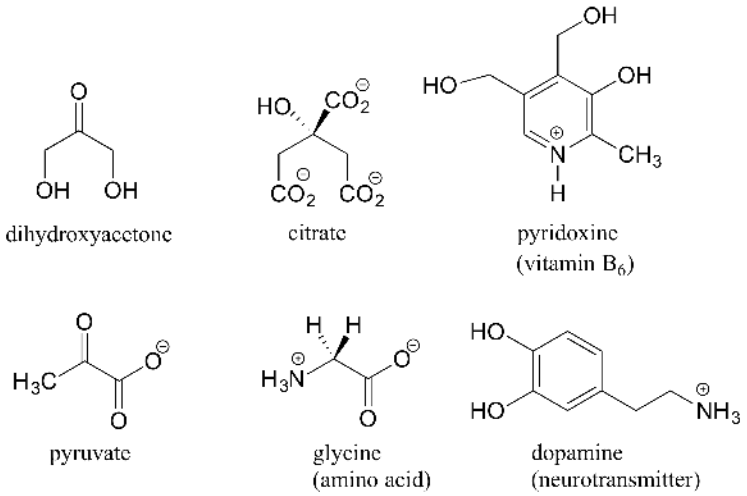


lactic acid



methamphetamine

Here are some examples of ***achiral*** biomolecules - convince yourself that none of them contain a chiral center:

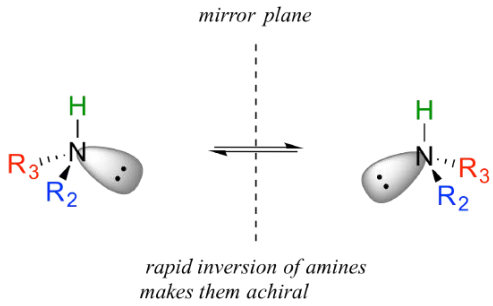


When looking for chiral centers, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are *not* chiral centers – look, for example, at the drawings of glycine and citrate in the figure above.

Can a chiral center be something other than a tetrahedral carbon with four different substituents? The answer to this question is 'yes' - however, these alternative chiral centers are very rare in the context of biological organic chemistry, and outside the scope of our discussion here.

You may also have wondered about amines: shouldn't we consider a secondary or tertiary amine to be a chiral center, as they are tetrahedral and attached to four different substituents, if the lone-pair electrons are counted as a 'substituent'? Put another way, isn't an amine non-superimposable on its mirror image?

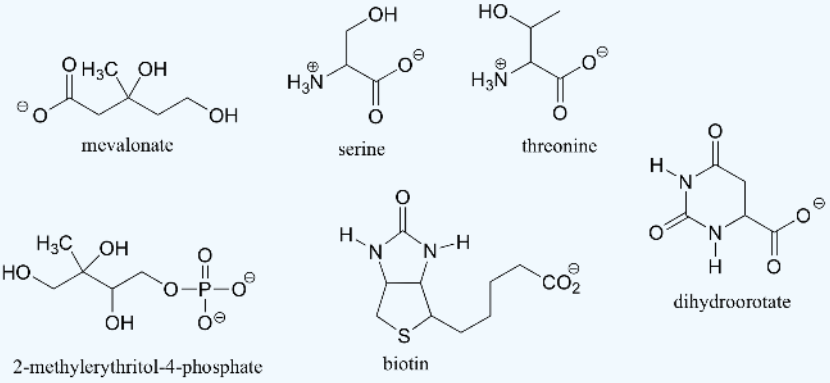
The answer: yes it is, in the static picture, but in reality, the nitrogen of an amine is rapidly and reversibly inverting, or turning inside out, at room temperature.



If you have trouble picturing this, take an old tennis ball and cut it in half. Then, take one of the concave halves and flip it inside out, then back again: this is what the amine is doing. The end result is that the two 'enantiomers' if the amine are actually two rapidly interconverting forms of the same molecule, and thus the amine itself is not a chiral center. This inversion process does *not* take place on a tetrahedral carbon, which of course has no lone-pair electrons.

? Exercise 3.8

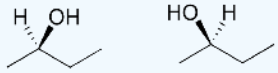
Locate all of the chiral centers (there may be more than one in a molecule). Remember, hydrogen atoms bonded to carbon usually are not drawn in the line structure convention - but they are still there!



Exercise 3.9

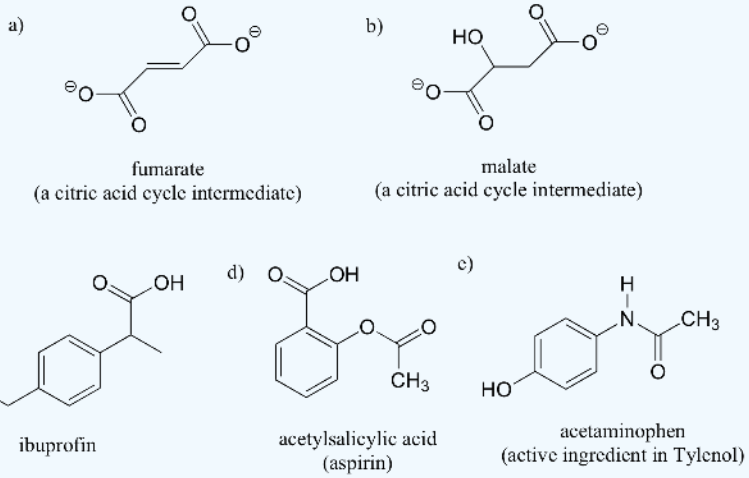
a) Draw two enantiomers of i) mevalonate and ii) serine.

b) Are the two 2-butanol structures below enantiomers?



Exercise 3.10

Label the molecules below as chiral or achiral, and locate all chiral centers.



Solutions to exercises

Khan Academy video tutorials

Chirality

Enantiomers

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3.4: Naming chiral centers- the R and S system

Chemists need a convenient way to distinguish one stereoisomer from another. The **Cahn-Ingold-Prelog system** is a set of rules that allows us to unambiguously define the stereochemical configuration of any stereocenter, using the designations '***R*** ' (from the Latin *rectus*, meaning right-handed) or ' ***S*** ' (from the Latin *sinister*, meaning left-handed).

The rules for this system of stereochemical nomenclature are, on the surface, fairly simple.

Rules for assigning an R/S designation to a chiral center

1: Assign priorities to the four substituents, with #1 being the highest priority and #4 the lowest. Priorities are based on the atomic number.

2: Trace a circle from #1 to #2 to #3.

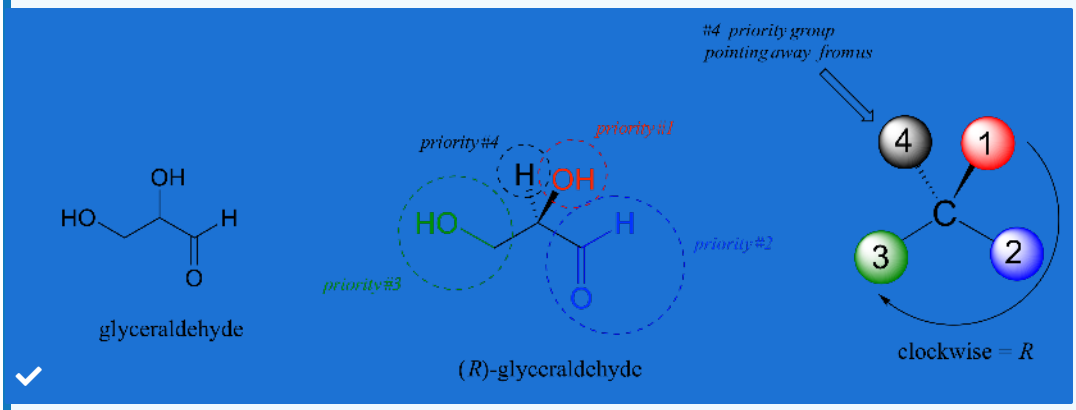
3: Determine the orientation of the #4 priority group. If it is oriented into the plane of the page (away from you), go to step 4a. If it is oriented out of the plane of the page (toward you) go to step 4b.

4a: *(#4 group pointing away from you*): a clockwise circle in part 2 corresponds to the *R* configuration, while a counterclockwise circle corresponds to the *S* configuration.

4b: *(#4 group pointing toward you*): a clockwise circle in part 2 corresponds to the *S* configuration, while a counterclockwise circle corresponds to the *R* configuration.

We'll use the 3-carbon sugar glyceraldehyde as our first example. The first thing that we must do is to assign a **priority** to each of the four substituents bound to the chiral center. We first look at the atoms that are directly bonded to the chiral center: these are H, O (in the hydroxyl), C (in the aldehyde), and C (in the CH_2OH group).

Assigning R/S configuration to glyceraldehyde

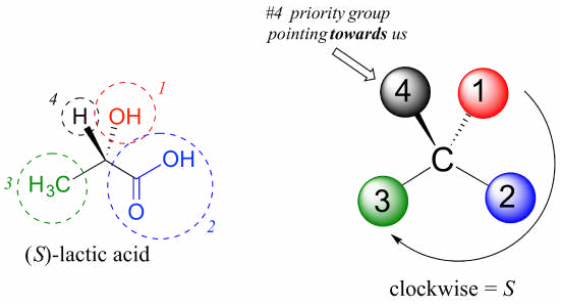


Two priorities are easy: hydrogen, with an atomic number of 1, is the lowest (#4) priority, and the hydroxyl oxygen, with atomic number 8, is priority #1. Carbon has an atomic number of 6. Which of the two 'C' groups is priority #2, the aldehyde or the CH_2OH? To determine this, we move one more bond away from the chiral center: for the aldehyde we have a *double* bond to an oxygen, while on the CH_2OH group we have a *single* bond to an oxygen. If the atom is the same, double bonds have a higher priority than single bonds. Therefore, the aldehyde group is assigned #2 priority and the CH_2OH group the #3 priority.

With our priorities assigned, we look next at the #4 priority group (the hydrogen) and see that it is pointed back away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The circle is clockwise, which by step 4a tells us that this carbon has the '*R*' configuration, and that this molecule is (*R*)-glyceraldehyde. Its enantiomer, by definition, must be (*S*)-glyceraldehyde.

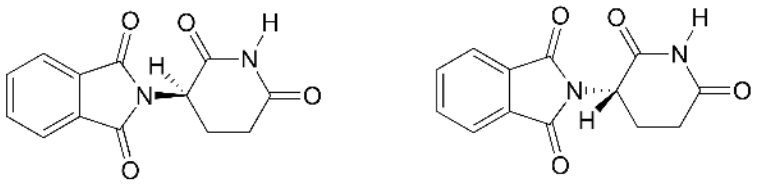
Next, let's look at one of the enantiomers of lactic acid and determine the configuration of the chiral center. Clearly, H is the #4 substituent and OH is #1. Owing to its three bonds to oxygen, the carbon on the acid group takes priority #2, and the methyl group

takes #3. The #4 group, hydrogen, happens to be drawn pointing *toward* us (out of the plane of the page) in this figure, so we use step 4b: The circle traced from #1 to #2 to #3 is clockwise, which means that the chiral center has the *S* configuration.



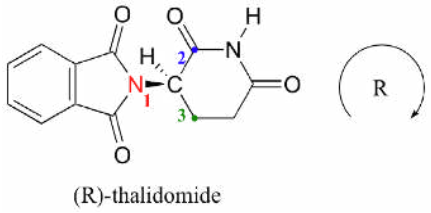
Interactive model of (S)-alanine

The drug thalidomide is an interesting - but tragic - case study in the importance of stereochemistry in drug design. First manufactured by a German drug company and prescribed widely in Europe and Australia in the late 1950's as a sedative and remedy for morning sickness in pregnant women, thalidomide was soon implicated as the cause of devastating birth defects in babies born to women who had taken it. Thalidomide contains a chiral center, and thus exists in two enantiomeric forms. It was marketed as a **racemic mixture**: in other words, a 50:50 mixture of both enantiomers.



two enantiomers of thalidomide

Let's try to determine the stereochemical configuration of the enantiomer on the left. Of the four bonds to the chiral center, the #4 priority is hydrogen. The nitrogen group is #1, the carbonyl side of the ring is #2, and the $-CH_2$ side of the ring is #3.



The hydrogen is shown pointing away from us, and the prioritized substituents trace a clockwise circle: this is the *R* enantiomer of thalidomide. The other enantiomer, of course, must have the S configuration.

Although scientists are still unsure today how thalidomide works, experimental evidence suggests that it was actually the *R* enantiomer that had the desired medical effects, while the *S* enantiomer caused the birth defects. Even with this knowledge, however, pure (*R*)-thalidomide is not safe, because enzymes in the body rapidly convert between the two enantiomers - we will see how that happens in chapter 12.

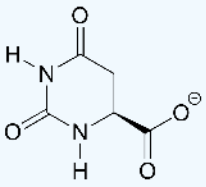
As a historical note, thalidomide was never approved for use in the United States. This was thanks in large part to the efforts of Dr. Frances Kelsey, a Food and Drug officer who, at peril to her career, blocked its approval due to her concerns about the lack of adequate safety studies, particularly with regard to the drug's ability to enter the bloodstream of a developing fetus. Unfortunately, though, at that time clinical trials for new drugs involved widespread and unregulated distribution to doctors and their patients across the country, so families in the U.S. were not spared from the damage caused.

Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of

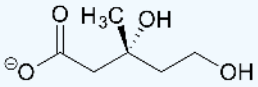
leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

Exercise 3.11

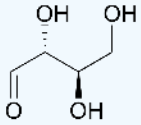
Determine the stereochemical configurations of the chiral centers in the biomolecules shown below.



dihydroorotate



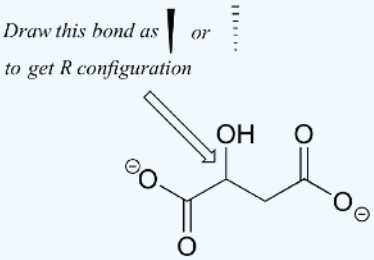
mevalonate



(D)-erythrose

Exercise 3.12

Should the (*R*) enantiomer of malate have a solid or dashed wedge for the C-O bond in the figure below?



(*R*)-malate

Exercise 3.13

Using solid or dashed wedges to show stereochemistry, draw the (*R*) enantiomer of ibuprofen and the (*S*) enantiomer of 2-methylerythritol-4-phosphate (structures are shown earlier in this chapter without stereochemistry).

Solutions to exercises

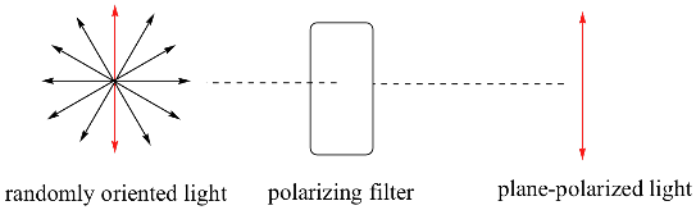
Khan Academy video tutorial on the R-S naming system

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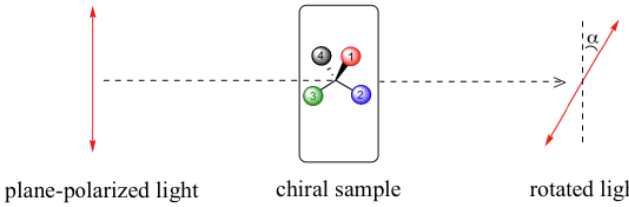
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3.5: Optical Activity

Chiral molecules, as we learned in the introduction to this chapter, have an interesting optical property. You may know from studying physics that light waves are oscillating electric and magnetic fields. In ordinary light, the oscillation is randomly oriented in an infinite number of planes. When ordinary light is passed through a polarizer, all planes of oscillation are filtered out except one, resulting in **plane-polarized light**.



A beam of plane-polarized light, when passed through a sample of a chiral compound, interacts with the compound in such a way that the angle of oscillation will rotate. This property is called **optical activity**.



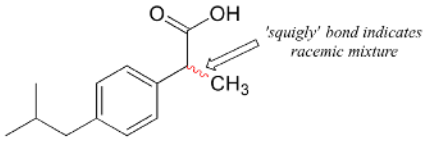
If a compound rotates plane polarized light in the clockwise (+) direction, it is said to be **dextrorotatory**, while if it rotates light in the counterclockwise (-) direction it is **levorotatory**. The magnitude of the observed optical activity is dependent on temperature, the wavelength of light used, solvent, concentration of the chiral sample, and the path length of the sample tube (path length is the length that the plane-polarized light travels through the chiral sample). Typically, optical activity measurements are made in a 1 decimeter (10 cm) path-length sample tube at 25 °C, using as a light source the so-called “D-line” from a sodium lamp, which has a wavelength of 589 nm. The **specific rotation** of a pure chiral compound at 25° is expressed by the expression:

$$[\alpha]_{D}^{25} = \frac{\alpha_{obs}}{lc}$$

where α_{obs} is the observed rotation, l is path length in decimeters, and c is the concentration of the sample in grams per 100 mL. In other words, the specific rotation of a chiral compound is the optical rotation that is observed when 1 g of the compound is dissolved in enough of a given solvent to make 100 mL solution, and the rotation is measured in a 1 dm cuvette at 25 ^{o}C using light from a sodium lamp.

Every chiral molecule has a characteristic specific rotation, which is recorded in the chemical literature as a physical property just like melting point or density. Different enantiomers of a compound will always rotate plane-polarized light with an equal but opposite magnitude. (*S*)-ibuprofen, for example, has a specific rotation of +54.5^{o} (dextrorotatory) in methanol, while (*R*)-ibuprofen has a specific rotation of -54.5^{o}. *There is no relationship between chiral compound's R/S designation and the direction of its specific rotation.* For example, the *S* enantiomer of ibuprofen is dextrorotatory, but the *S* enantiomer of glyceraldehyde is levorotatory.

A 50:50 mixture of two enantiomers (a racemic mixture) will have no observable optical activity, because the two optical activities cancel each other out. In a structural drawing, a 'squigly' bond from a chiral center indicates a mixture of both *R* and *S* configurations.



(+/-) ibuprofen
(racemic)

Chiral molecules are often labeled according to whether they are dextrorotatory or levorotatory as well as by their *R/S* designation. For example, the pure enantiomers of ibuprofen are labeled (*S*)-(+)-ibuprofen and (*R*)-(-)-ibuprofen, while (±)-ibuprofen refers to the racemic mixture, which is the form in which the drug is sold to consumers.

? Exercise 3.14

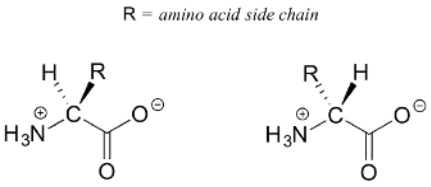
The specific rotation of (*R*)-limonene is +11.5º in ethanol. What is the expected observed rotation of a sample of 6.00 g (*S*)-limonene dissolved in ethanol to a total volume of 80.0 mL in a 1.00 dm (10.0 cm) pathlength cuvette?

Exercise 3.15

The specific rotation of (*S*)-carvone is +61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a mixture of *R* and *S* carvone is measured at -23°. Which enantiomer is in excess in the mixture?

Solutions to exercises

All of the twenty natural amino acids except glycine have a chiral center at their alpha-carbon (recall that basic amino acid structure and terminology was introduced in section 1.3). Virtually all of the amino acids found in nature, both in the form of free amino acids or incorporated into peptides and proteins, have what is referred to in the biochemical literature as the 'L' configuration:



L-amino acids
(common in nature)

D-amino acids
(rare in nature)

All but one of the 19 L-amino acids have *S* stereochemistry at the a-carbon, using the rules of the *R/S* naming system.

D-amino acids are very rare in nature, but we will learn about an interesting example of a peptide containing one D-amino acid residue later in chapter 12.

? Exercise 3.16

Which of the 20 common L-amino acids found in nature has the *R* configuration? Refer to the amino acid table for structures.

Solutions to exercises

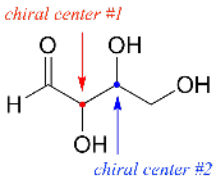
Khan Academy video tutorial on optical acitivity

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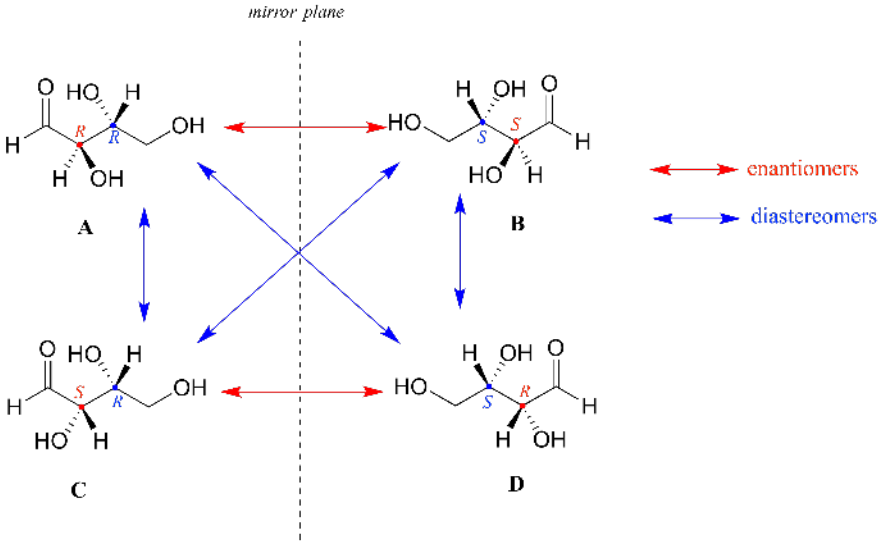
3.6: Compounds with multiple chiral centers

So far, we have been analyzing compounds with a single chiral center. Next, we turn our attention to those which have multiple chiral centers. We'll start with some stereoisomeric four-carbon sugars with two chiral centers.



To avoid confusion, we will simply refer to the different stereoisomers by capital letters.

Look first at compound A below. Both chiral centers in have the *R* configuration (you should confirm this for yourself!). The mirror image of Compound A is compound B, which has the *S* configuration at both chiral centers. If we were to pick up compound A, flip it over and put it next to compound B, we would see that they are *not* superimposable (again, confirm this for yourself with your models!). A and B are nonsuperimposable mirror images: in other words, enantiomers.



Now, look at compound C, in which the configuration is *S* at chiral center 1 and *R* at chiral center 2. Compounds A and C are stereoisomers: they have the same molecular formula and the same bond connectivity, but a different arrangement of atoms in space (recall that this is the definition of the term 'stereoisomer). However, they are *not* mirror images of each other (confirm this with your models!), and so they are *not* enantiomers. By definition, they are **diastereomers** of each other.

Notice that compounds C and B also have a diastereomeric relationship, by the same definition.

So, compounds A and B are a pair of enantiomers, and compound C is a diastereomer of both of them. Does compound C have its own enantiomer? Compound D is the mirror image of compound C, and the two are not superimposable. Therefore, C and D are a pair of enantiomers. Compound D is also a diastereomer of compounds A and B.

This can also seem very confusing at first, but there some simple shortcuts to analyzing stereoisomers:

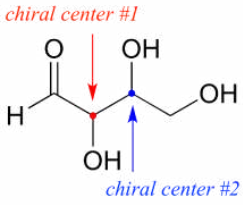
Stereoisomer shortcuts

If ***all*** of the chiral centers are of opposite R/S configuration between two stereoisomers, they are enantiomers.

If ***at least one, but not all*** of the chiral centers are opposite between two stereoisomers, they are diastereomers.

(*Note: these shortcuts to not take into account the possibility of additional stereoisomers due to alkene groups: we will come to that later)*

Here's another way of looking at the four stereoisomers, where one chiral center is associated with red and the other blue. Pairs of enantiomers are stacked together.

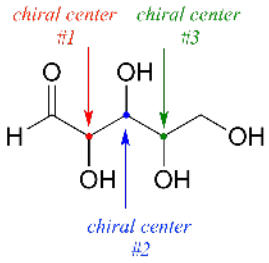


possible configurations:

RR *RS*
SS *SR*

We know, using the shortcut above, that the enantiomer of RR must be SS - both chiral centers are different. We also know that RS and SR are diastereomers of RR, because in each case one - but not both - chiral centers are different.

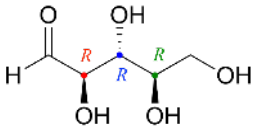
Now, let's extend our analysis to a sugar molecule with three chiral centers. Going through all the possible combinations, we come up with eight total stereoisomers - four pairs of enantiomers.



possible configurations:

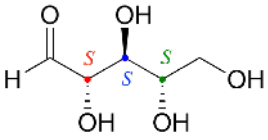
RRR RRS RSR RSS
SSS SSR SRS SRR

Let's draw the *RRR* stereoisomer. Being careful to draw the wedge bonds correctly so that they match the *RRR* configurations, we get:



RRR stereoisomer

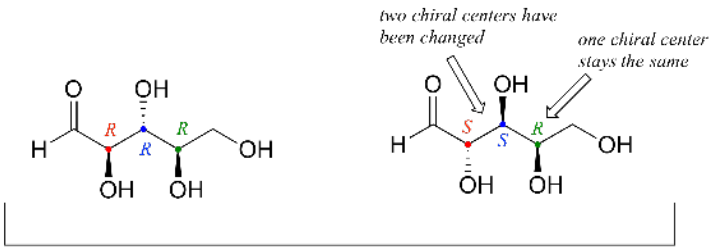
Now, using the above drawing as our model, drawing any other stereoisomer is easy. If we want to draw the enantiomer of *RRR*, we don't need to try to visualize the mirror image, we just start with the *RRR* structure and invert the configuration at *every* chiral center to get *SSS*.



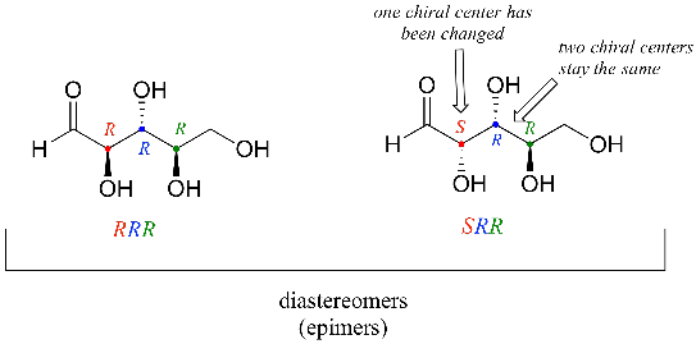
SSS stereoisomer

Try making models of *RRR* and *SSS* and confirm that they are in fact nonsuperimposable mirror images of each other.

There are six diastereomers of *RRR*. To draw one of them, we just invert the configuration of at least one, but not all three, of the chiral centers. Let's invert the configuration at chiral center 1 and 2, but leave chiral center 3 unchanged. This gives us the *SSR* configuration.



One more definition at this point: diastereomers which differ at only a single chiral center are called **epimers**. For example, *RRR* and *SRR* are epimers:



The *RRR* and *SSR* stereoisomers shown earlier are diastereomers but *not* epimers because they differ at *two* of the three chiral centers.

? Exercise 3.17

a) Draw the structure of the *enantiomer* of the *SRS* stereoisomer of the sugar used in the previous example.

b) List (using the *XXX* format, not drawing the structures) all of the epimers of *SRS*.

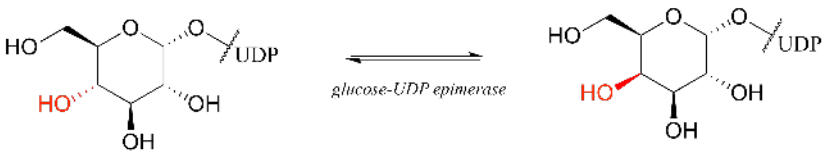
c) List all of the stereoisomers that are diastereomers, but not epimers, of *SRS*.

Solutions to exercises

The epimer term is useful because in biochemical pathways, compounds with multiple chiral centers are isomerized at one specific center by enzymes known as **epimerases**. Two examples of epimerase-catalyzed reactions are below.



ribulose-5-phosphate xylulose-5-phosphate

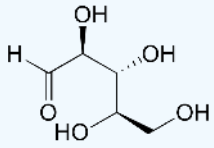


glucose-UDP galactose-UDP

We know that enantiomers have identical physical properties and equal but opposite magnitude specific rotation. Diastereomers, in theory at least, have *different* physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that it is very difficult to distinguish between them. In addition, the specific rotation values of diastereomers are unrelated – they could be the same sign or opposite signs, similar in magnitude or very dissimilar.

? Exercise 3.18

The sugar below is one of the stereoisomers that we have been discussing.



?

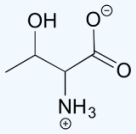
The only problem is, it is drawn with the carbon backbone in a different orientation from what we have seen. Determine the configuration at each chiral center to determine which stereoisomer it is.

Exercise 3.19

Draw the enantiomer of the xylulose-5-phosphate structure in the previous figure.

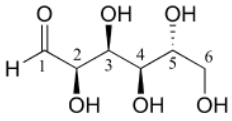
Exercise 3.20

The structure of the amino acid D-threonine, drawn without stereochemistry, is shown below. D-threonine has the (S) configuration at both of its chiral centers. Draw D-threonine, it's enantiomer, and its two diastereomers.



Solutions to exercises

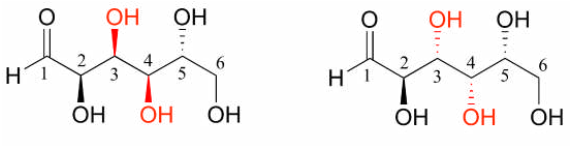
Here is some more practice in identifying isomeric relationships. D-glucose is the monosaccharide that serves as the entrance point for the glycolysis pathway and as a building block for the carbohydrate biopolymers starch and cellulose. The 'D' in D-glucose stands for *dextrarotatory* and is part of the specialized nomenclature system for sugars, which we will not concern ourselves with here. The open-chain structure of the sugar is shown below.



D-glucose

Because D-glucose has four chiral centers, it can exist in a total of 2^4 = 16 different stereoisomeric forms: it has one enantiomer and 14 diastereomers.

Now, let's compare the structures of the two sugars D-glucose and D-gulose, and try to determine their relationship.

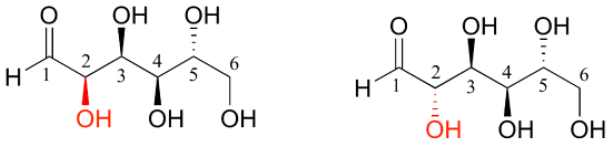


D-glucose D-gulose

(diastereomers)

The two structures have the same molecular formula and the same connectivity, therefore they must be stereoisomers. They each have four chiral centers, and the configuration is different at two of these centers (at carbons #3 and #4). They are diastereomers.

Now, look at the structures of D-glucose and D-mannose.

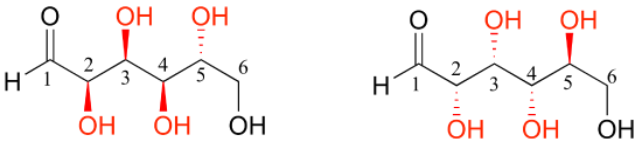


D-glucose D-mannose

(epimers)

Here, everything is the same except for the configuration of the chiral center at carbon #2. The two sugars differ at only one of the four chiral centers, so again they are diastereomers, and more specifically they are epimers.

D-glucose and L-glucose are enantiomers, because they differ at all four chiral centers.

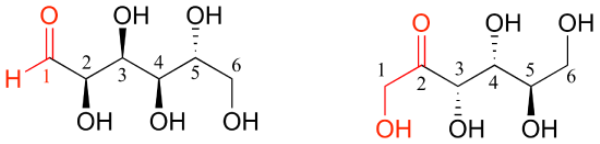


D-glucose L-glucose

(enantiomers)

D-glucose is the enantiomer commonly found in nature.

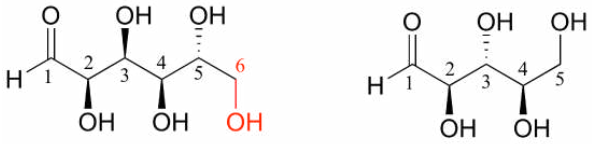
D-glucose and D-fructose are not stereoisomers, because they have different bonding connectivity: glucose has an aldehyde group, while fructose has a ketone. The two sugars do, however, have the same molecular formula, so by definition they are constitutional isomers.



D-glucose D-fructose

(constitutional isomers)

D-glucose and D-ribose are not isomers of any kind, because they have different molecular formulas.

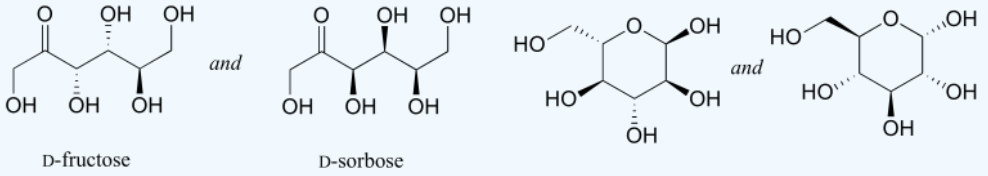


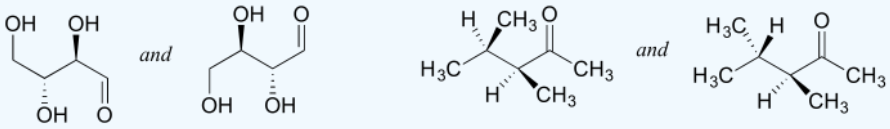
D-glucose D-ribose

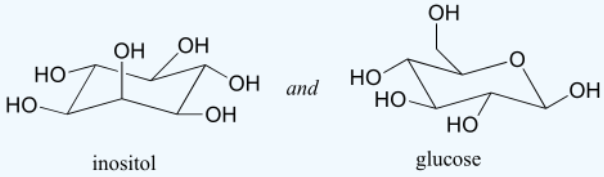
(not isomers)

? Exercise 3.21

Identify the relationship between each pair of structures. Your choices are: not isomers, constitutional isomers, diastereomers but not epimers, epimers, enantiomers, or same molecule

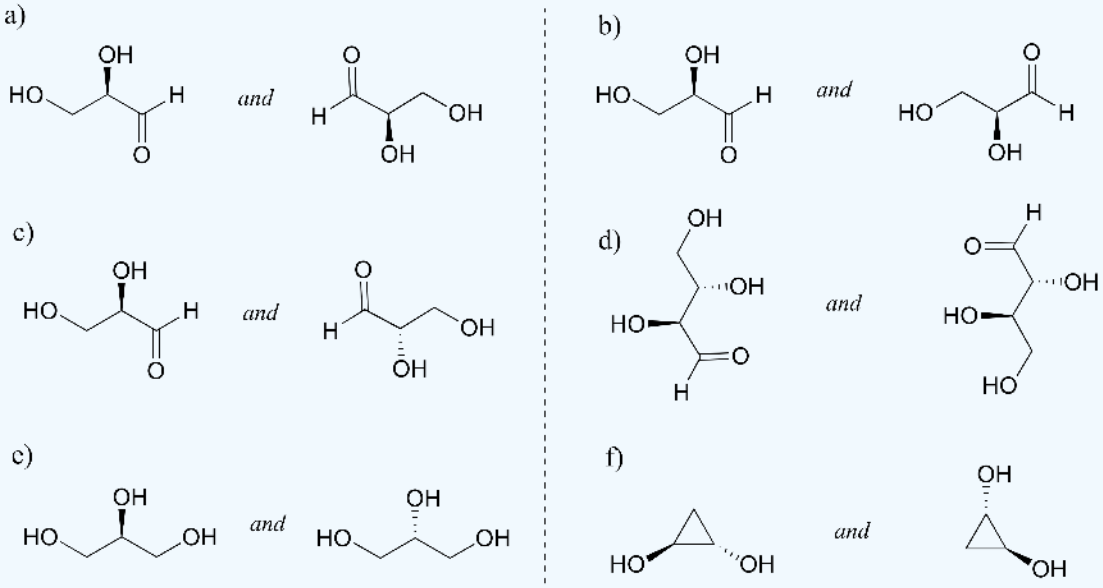






Exercise 3.22

Identify the relationship between each pair of structures. *Hint* - figure out the configuration of each chiral center.



Solutions to exercises

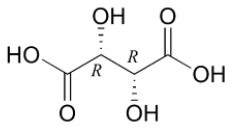
Khan Academy video tutorial on stereoisomeric relationships

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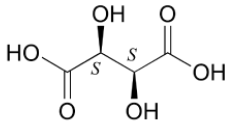
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3.7: Meso Compounds

The levorotatory and dextrorotatory forms of tartaric acid studied by Louis Pasteur were, as we now know, the (*S*,*S*) and (*R*,*R*) enantiomers, respectively:



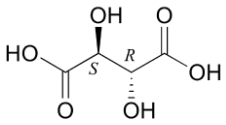
(*R*,*R*)-(+)-tartaric acid
('natural' isomer from grapes)



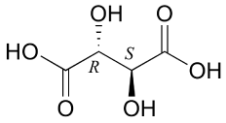
(*S*,*S*)-(-)-tartaric acid

What the 19th century chemists referred to as *'acide racemique'* was just that: a racemic mixture of the *R*,*R* and *S*,*S* enantiomers, the racemization a result of how the natural *R*,*R* isomer had been processed.

But tartaric acid has two chiral centers: shouldn't there be another pair of enantiomers?



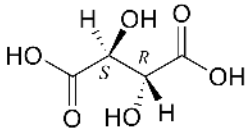
(*S*,*R*)-tartaric acid



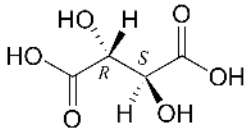
(*R*,*S*)-tartaric acid

There in fact is another stereoisomer of tartaric acid: *but only one*. The two structures above are actually superimposable on one another: ***they are the exact same molecule***. The figure below illustrates this, and also that the structure has a plane of symmetry. However, you should be sure to build models and confirm these assertions for yourself.

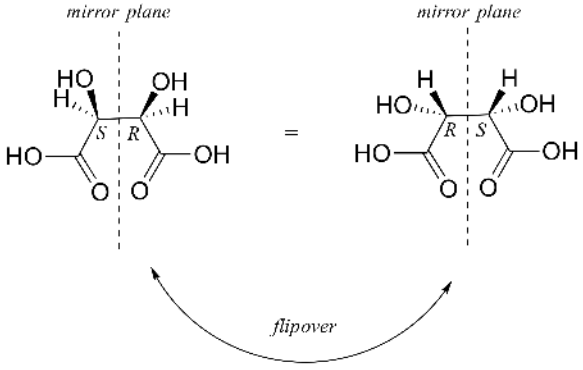
(*S*,*R*)-tartaric acid



(*R*,*S*)-tartaric acid



rotate right side down

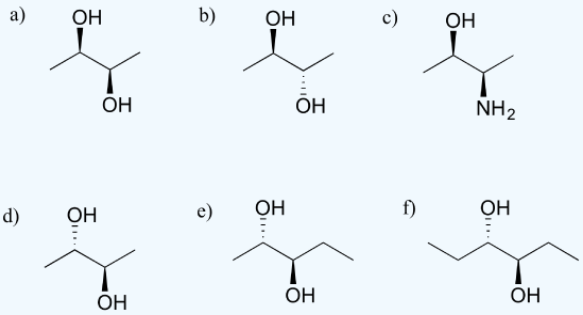


This tartaric acid isomer is an *achiral* diastereomer of the both the levorotatory and dextrorotatory isomers. It is a special case, called a ***meso*** compound: it has two apparent chiral centers but due to its internal symmetry it is not in fact chiral, and does not exhibit optical activity. Note that the *meso* form of tartaric acid did not play a part in Pasteur's experiments.

There are many more possible examples of *meso* compounds, but they really can be considered 'exceptions to the rule' and quite rare in biologically relevant chemistry.

? Exercise 3.23

Which of the following compounds are *meso*? Hint: build models, and then try to find a conformation in which you can see a plane of symmetry.



Solutions to exercises

Khan Academy video tutorial on meso compounds

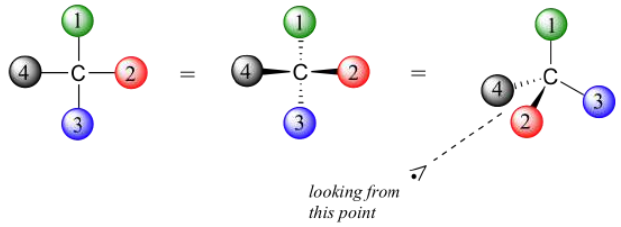
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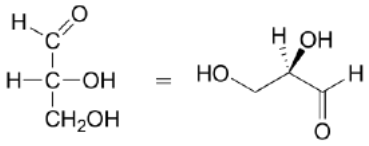
3.8: Fischer and Haworth projections

When reading the chemical and biochemical literature, you are likely to encounter several different conventions for drawing molecules in three dimensions, depending on the context of the discussion. While organic chemists prefer to use the dashed/solid wedge convention to show stereochemistry, biochemists often use drawings called **Fischer projections** and **Haworth projections** to discuss and compare the structure of sugar molecules.

Fisher projections show sugars in their open chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.

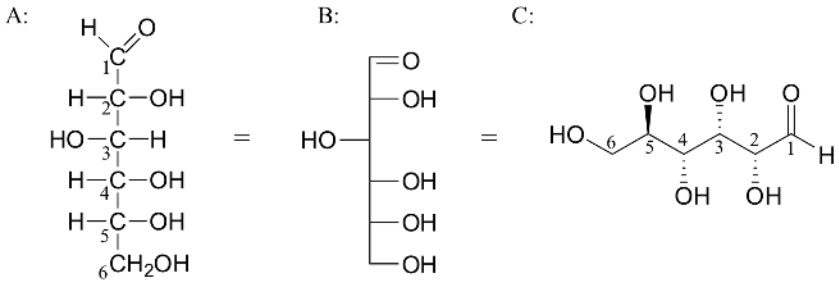


Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):

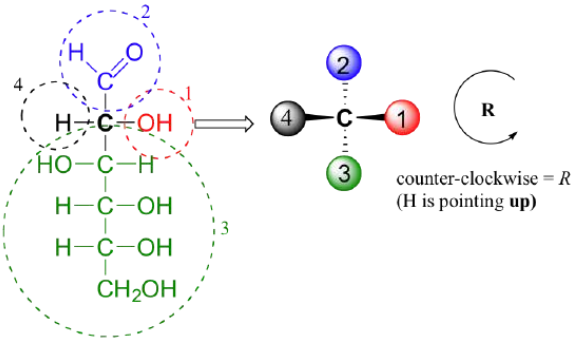


(R)-glyceraldehyde
(D-glyceraldehyde)

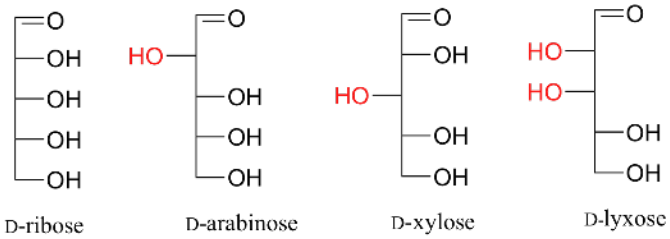
Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection (A), in the “line structure” variation of the Fischer projection in which carbons and hydrogens are not shown (B), and finally in the 'zigzag' style (C) that is preferred by organic chemists.



Care must be taken when ‘translating’ Fischer projection structures into' zigzag' format – it is easy to get the stereochemistry wrong. Probably the best way to make a translation is to simply assign *R*/*S* configurations to each stereocenter, and proceed from there. When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond, is pointing *towards* you – therefore, a counterclockwise circle means *R*, and a clockwise circle means *S* (the opposite of when the hydrogen is pointing away from you).

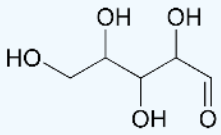


Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



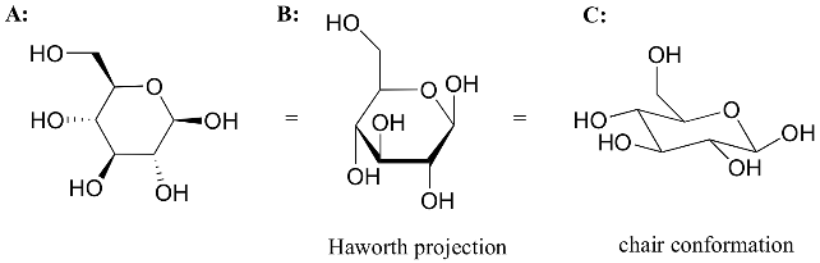
Exercise 3.24

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure above. Label all stereocenters *R* or *S*. To make it easy to check your answers, draw your structures using the framework below.



Solutions to exercises

While Fischer projections are used for sugars in their open-chain form, Haworth projections are often used to depict sugars in their cyclic forms. The beta diastereomer of the cyclic form of glucose is shown below in three different depictions, with the Haworth projection in the middle.



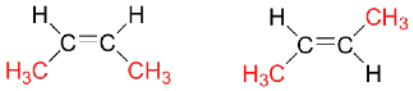
Notice that although a Haworth projection is a convenient way to show stereochemistry, it does not provide a realistic depiction of conformation. To show *both* conformation and stereochemistry, you must draw the ring in the chair form, as in structure C above.

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3.9: Stereochemistry of alkenes

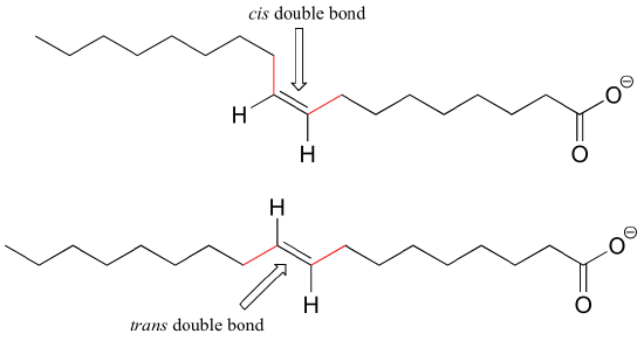
When we talk about stereochemistry, we are not always talking about chiral compounds and chiral centers. Consider *cis*- and *trans*-2-butene:



cis-2-butene *trans*-2-butene

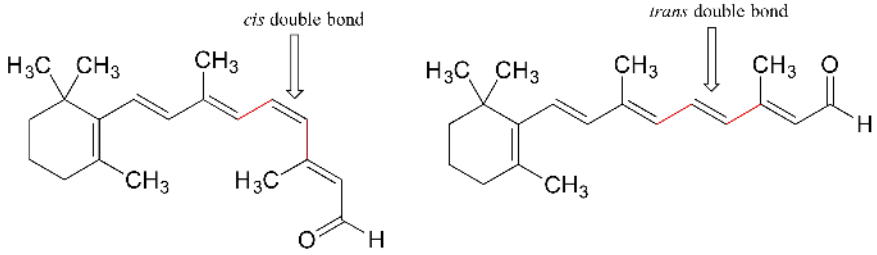
Each can be superimposed on its own mirror image, and neither is chiral (also, note the lack of a chiral center!) However, they both have the same molecular formula and the same bonding connectivity, so by definition they are stereoisomers of each other. Because they are not mirror images, they must be diastereomers. An alkene group which can exist in two stereoisomeric forms is referred to as **stereogenic**.

Alkene groups in natural unsaturated fatty acids are normally *cis*, but *trans*-fatty acids (which are thought to be associated with heart disease and other health problems) are found in some food products.



cis and *trans* fatty acids

Retinal is a light-sensitive molecule, derived from vitamin A, that is found in the rod cells of the eye. When light enters the eye through the retina, one form of retinal is converted to a diastereomer when a *cis* double bond is converted to *trans* (we"ll learn how this happens in chapter 13). This changes the shape of the molecule and the way that it binds to the vision protein rhodopsin, which in turn initiates a chain of events that leads to a signal being sent to the vision center of the brain.

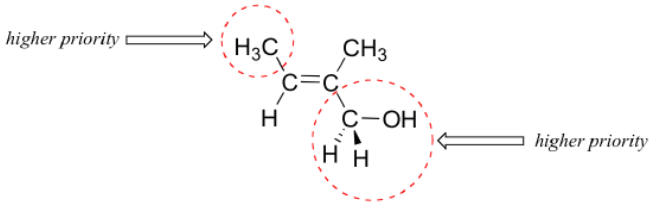


11-*cis*-retinal all-*trans*-retinal

While the terms *cis* and *trans* are quite clear in the examples above, in some cases they can be ambiguous, and a more rigorous stereochemical designation is required. To unambiguously designate alkene stereochemistry, it is best to use the designators '*E*' and 'Z' rather than *trans* and *cis*. To use this naming system, we first decide which is the higher priority group on each carbon of the double bond, using the same priority rules that we learned for the *R/S* system. If the higher-priority groups are one the same side of the double bond, it is a *Z*-alkene, and if they are on the opposite side it is an *E*-alkene. A memory device that many students find helpful is the phrase *'Z = zame zide'*.

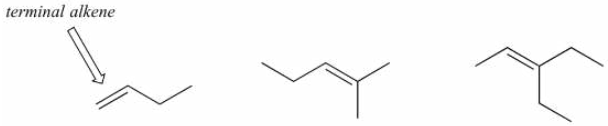
Shown below is an example of an *E*-alkene: notice that, although the two methyl groups are on the same side relative to one another, the alkene has *E* stereochemistry according to the rules of the *E/Z* system because one of the methyl groups takes a higher

priority (relative to a hydrogen) and the other takes lower priority (relative to a primary alcohol). The *cis/trans* terms would be ambiguous for this compound.



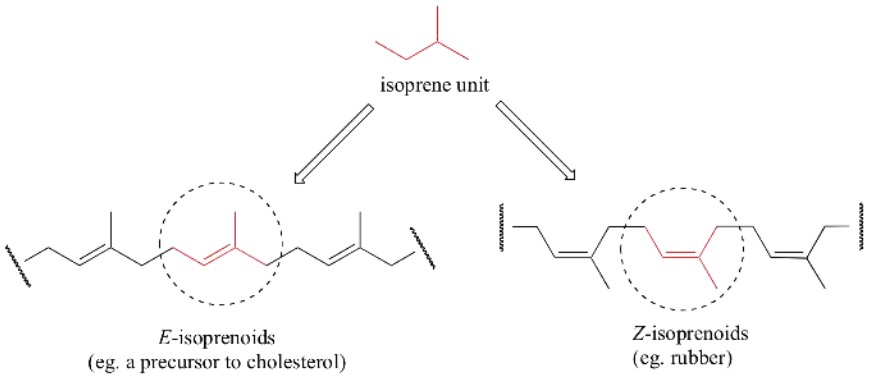
an *E*-alkene

Not all alkenes can be labeled *E* or *Z:* if one (or both) of the double-bonded carbons has identical substituents, the alkene is not stereogenic, and thus cannot be assigned an E or Z configuration. Terminal alkenes, in which one of the alkene carbons is bonded to two hydrogen atoms, are the most commonly seen type of nonstereogenic alkene.



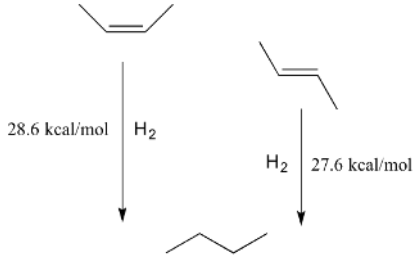
nonstereogenic alkenes (cannot be labelled *E* or *Z)*

Natural rubber is a polymer composed of five-carbon isoprenoid building blocks linked with *Z* stereochemistry. The same isoprenpoid building blocks can also be connected with *E* stereochemistry, leading to a polymer that is a precursor to cholesterol and many other natural isoprenoid compounds found in all forms of life.



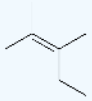
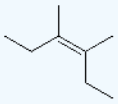
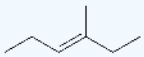
Alkenes located inside a five- or six-membered ring, such as in cyclohexene, are not generally labeled *E* or *Z*, simply because the closed geometry of the ring allows for only one stereochemical possibility. (*E*)-cyclohexene is not physically possible, so it is not necessary to include the (*Z*) designator for cyclohexene. Larger rings, however, can hypothetically have *E* or *Z* alkene groups: two actual examples are included in exercise 3.26 below.

As a general rule, alkenes with the bulkiest groups on opposite sides of the double bond are more stable, due to reduced steric strain. The *trans* (*E)* diastereomer of 2-butene, for example, is slightly lower in energy than the *cis (Z)* diastereomer, as seen by their relative heats of hydrogenation to butane (see section 2.2C for a reminder of the meaning of 'heat of hydrogenation'.)



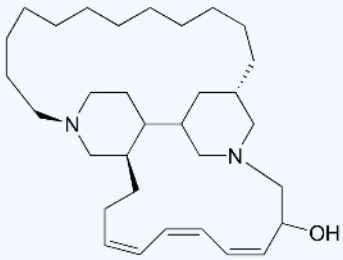
Exercise 3.25

Label the alkene groups below as *E*, *Z*, or *N* (for a nonstereogenic alkene).

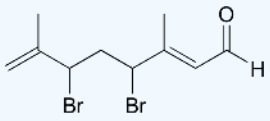
a)  b)  c)  d) 

Exercise 3.26

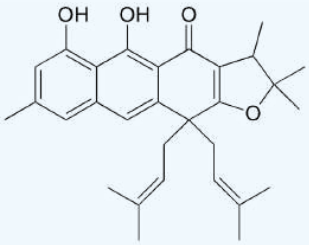
The compounds shown below were all isolated from natural sources and their structures reported in a 2007 issue of the *Journal of Natural Products*, an American Chemical Society publication. Label all alkene groups that are not inside 5- or 6-membered rings as *E*, *Z*, or *N* (for a nonstereogenic alkene).



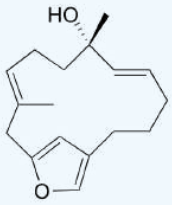
from marine sponge
J. Nat. Prod. **2007**, *70*, 538



from algea
J. Nat. Prod. **2007**, *70*, 596



from Nketto plant in Cameroon
J. Nat. Prod. **2007**, *70*, 600



from tree bark in Thailand
J. Nat. Prod. **2007**, *70*, 659

How many possible stereoisomers?

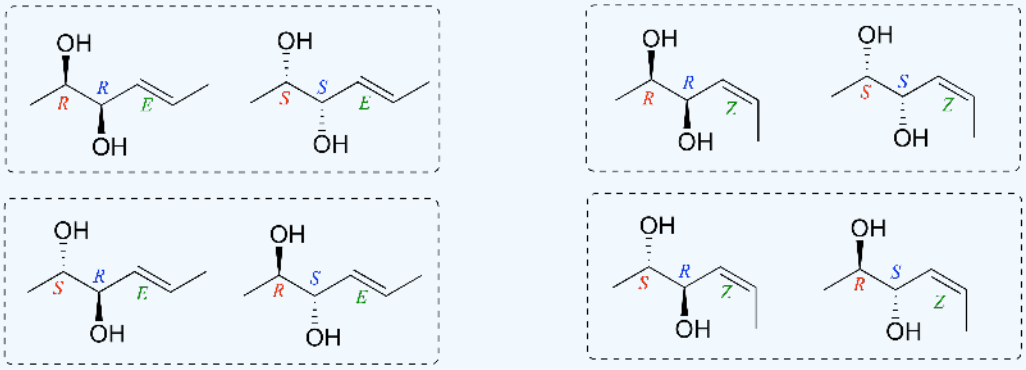
How do we know how many stereoisomers are possible for a given structure? There is actually a straightforward way to figure this out. All we need to do is count the number of chiral centers and stereogenic alkene groups, the use this following rule:

number of stereoisomeric forms = 2^n

. . . where *n* = the number of chiral centers ***plus*** the number of stereogenic alkene groups

(the rare exception to this rule is when a meso *form is possible - in this case, the rule becomes 2^n-1)*

Consider for example a molecule with two chiral centers and one stereogenic alkene. By the rule stated above, we know right away that there must be eight possible stereoisomers. Drawing out all the possibilities, we see:



8 stereoisomers of a compound with two chiral centers plus one stereogenic alkene

We see that, for example, *RRE* has one enantiomer, the *SSE* compound. The six other stereoisomers are all diastereomers of *RRE*.

It needs to be stressed that the enantiomer of the *RRE* compound is the *SSE* compound, ***not*** the *SSZ* compound. Remember, the *E/Z* relationship is diastereomeric, not enantiomeric. Use models to convince yourself that the *RRE* and the *SSE* isomers are mirror images of each other, while *RRE* and *SSZ* compounds are not. In general, to get the enantiomer of a compound, we invert all chiral centers *but leave all stereogenic alkenes the same.*

? Exercise 3.27

Draw the enantiomer of each the compounds below, and assign configurations to all chiral centers and stereogenic alkenes. How many diastereomers are possible for each of the structures you drew?



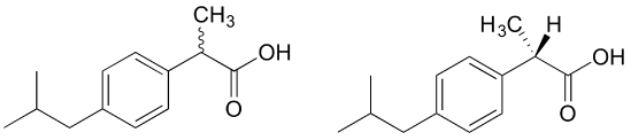
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3.10: Stereochemistry in biology and medicine

While challenging to understand and visualize, the stereochemistry concepts we have explored in this chapter are integral to the study of living things. The vast majority of biological molecules contain chiral centers and/or stereogenic alkene groups. Most importantly, proteins are chiral, which of course includes all of the the enzymes which catalyze the chemical reactions of a cell, the receptors which transmit information within or between cells, and the antibodies which bind specifically to potentially harmful invaders. You know from your biology classes that proteins, because they fold up into a specific three dimensional shape, are able to very specifically recognize and bind to other organic molecules. The ligand or substrate bound by a particular protein could be a small organic molecule such as pyruvate all the way up to a large biopolymer such as a specific region of DNA, RNA, or another protein. Because they are chiral molecules, *proteins are very sensitive to the stereochemistry of their ligands*: a protein may bind specifically to (*R*)-glyceraldehyde, for example, but not bind to (*S*)-glyceraldehyde, just as your right hand will not fit into a left-handed baseball glove (see end of chapter for a link to an animation illustrating this concept).

The over-the-counter painkiller ibuprofen is currently sold as a racemic mixture, but only the *S* enantiomer is effective, due to the specific way it is able to bind to and inhibit the action of prostaglandin H_2 synthase, an enzyme in the body's inflammation response process.



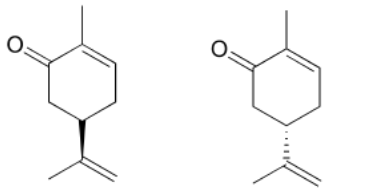
racemic ibuprofen

(*S*)-ibuprofen
(active enantiomer)

The *R* enantiomer of ibuprofen does not bind to prostaglandin H_2 synthase in the same way as the *S* enantiomer, and as a consequence does not exert the same inhibitory effect on the enzyme's action (see *Nature Chemical Biology* **2011**, *7*, 803 for more details). Fortunately, (*R*)-ibuprofen apparently does not cause any harmful side effects, and is in fact isomerized gradually by an enzyme in the body to (*S*)-ibuprofen.

Earlier in this chapter we discussed the tragic case of thalidomide, and mentioned that it appears that it is specifically the *S* enantiomer which caused birth defects. Many different proposals have been made over the past decades to try to explain the teratogenic (birth defect-causing) effect of the drug, but a clear understanding still evades the scientific community. In 2010, however, a team in Japan reported evidence that thalidomide binds specifically to a protein called 'thereblon'. Furthermore, when production of thereblon is blocked in female zebra fish, developmental defects occur in her offspring which are very similar to the defects caused by the administration of thalidomide, pointing to the likelihood that thalidomide binding somehow inactivates the protein, thus initiating the teratogenic effect. (http://news.sciencemag.org/2010/03/t...-partner-crime)

You can, with a quick trip to the grocery store, directly experience the biological importance of stereoisomerism. Carvone is a chiral, plant-derived molecule that contributes to the smell of spearmint in the *R* form and caraway (a spice) in the *S* form.



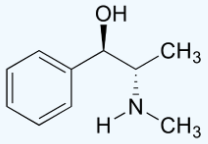
(*R*)-carvone
(spearmint odor)

(*S*)-carvone
(caraway odor)

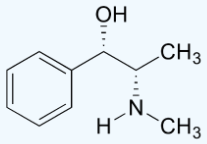
Although details are not known, the two enantiomers presumably interact differently with one or more smell receptor proteins in your nose, generating the transmission of different chemical signals to the olfactory center of your brain.

Exercise 3.28

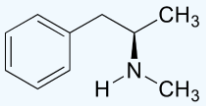
Ephedrine, found in the Chinese traditional medicine *ma huang*, is a stimulant and appetite suppressant. Both pseudoephedrine and levomethamphetamine are active ingredients in over-the-counter nasal decongestants. Methamphetamine is a highly addictive and illegal stimulant, and is usually prepared in illicit 'meth labs' using pseudoephedrine as a starting point.



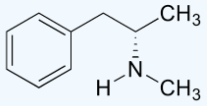
ephedrine



pseudoephedrine



methamphetamine



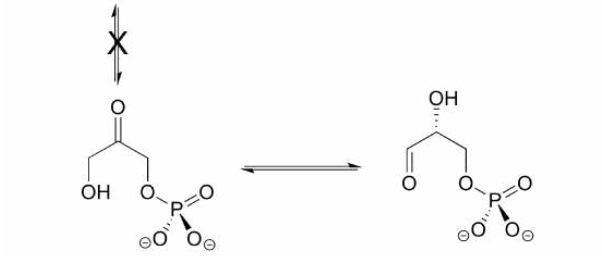
levomethamphetamine

What is the relationship between ephedrine and pseudoephedrine? Between methamphetamine and levomethamphetamine? Between pseudoephedrine and methamphetamine? Your choices are: not isomers, constitutional isomers, diastereomers, enantiomers, or same molecule.

Solutions to exercises

Enzymes are very specific with regard to the stereochemistry of the reactions they catalyze. *When the product of a biochemical reaction contains a chiral center or a stereogenic alkene, with very few exceptions only one stereoisomer of the product is formed.* In the glycolysis pathway, for example, the enzyme triose-phosphate isomerase catalyzes the reversible interconversion between dihydroxyacetone (which is achiral) and (*R*)-glyceraldehyde phosphate. The (*S*)-glyceraldehyde enantiomer is not formed by this enzyme in the left-to-right reaction, and is not used as a starting compound in the right-to-left reaction - it does not 'fit' in the active site of the enzyme.

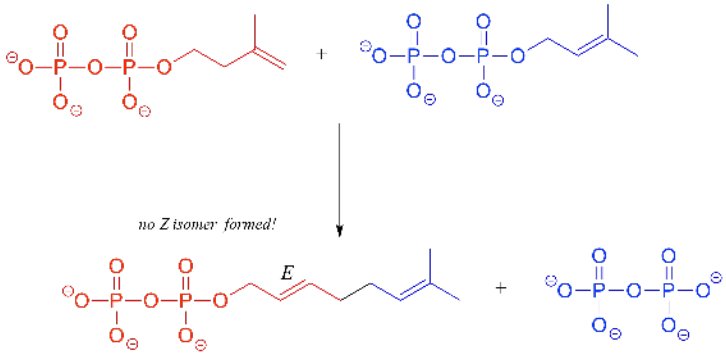
(*S*)-glyceraldehyde phosphate



dihydroxyacetone phosphate
(achiral)

(*R*)-glyceraldehyde phosphate

In the isoprenoid biosynthesis pathway, two five-carbon building-block molecules combine to form a ten-carbon chain containing an *E*-alkene group. The enzyme does *not* catalyze formation of the *Z* diastereomer.



In chapters 9-17 of this book, and continuing on into your study of biological and organic chemistry, you will be learning about how enzymes are able to achieve these feats of stereochemical specificity. If you take a more advanced class in organic synthesis, you will also learn how laboratory chemists are figuring out ingenious ways to exert control over the stereochemical outcomes of nonenzymatic reactions, an area of chemistry that is particularly important in the pharmaceutical industry.

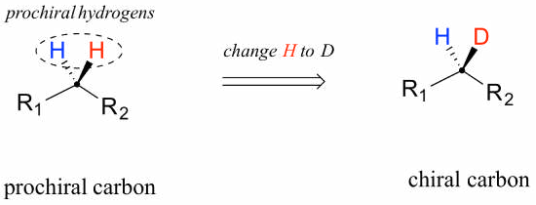
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3.11: Prochirality

Prochiral carbons

When a tetrahedral carbon can be converted to a chiral center by changing only one of the attached groups, it is referred to as a '**prochiral**' carbon. The two hydrogens on the prochiral carbon can be described as 'prochiral hydrogens'.

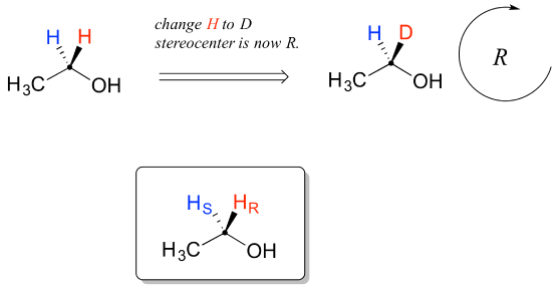


Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the ^{2}H isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

Prochirality is an important concept in biological chemistry, because enzymes can distinguish between the two 'identical' groups bound to a prochiral carbon center due to the fact that *they occupy different regions in three-dimensional space*. Consider the isomerization reaction below, which is part of the biosynthesis of isoprenoid compounds. We do not need to understand the reaction itself (it will be covered in chapter 14); all we need to recognize at this point is that the isomerase enzyme is able to distinguish between the prochiral 'red' and the 'blue' hydrogens on the isopentenyl diphosphate (IPP) substrate. In the course of the left to right reaction, IPP specifically loses the 'red' hydrogen and keeps the 'blue' one.



Prochiral hydrogens can be unambiguously designated using a variation on the *R/S* system for labeling chiral centers. For the sake of clarity, we'll look at a very simple molecule, ethanol, to explain this system. To name the 'red' and 'blue' prochiral hydrogens on ethanol, we need to engage in a thought experiment. If we, in our imagination, were to arbitrarily change red H to a deuterium, the molecule would now be chiral and the chiral carbon would have the *R* configuration (D has a higher priority than H).



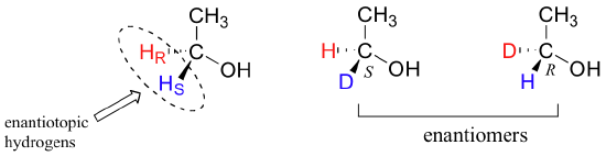
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it H_R. Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be *S*, so we can refer to blue H as the *pro-S* hydrogen of ethanol, and label it H_S.

Looking back at our isoprenoid biosynthesis example, we see that it is specifically the *pro-R* hydrogen that the isopentenyl diphosphate substrate loses in the reaction.



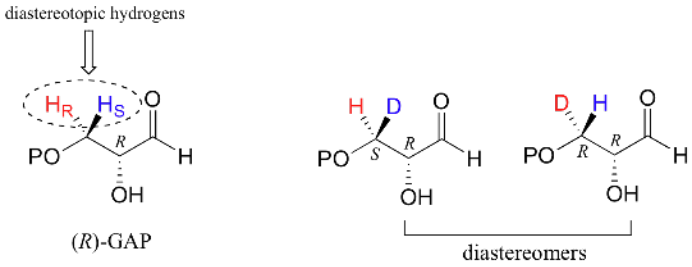
isopentenyl diphosphate dimethylallyl diphosphate

Prochiral hydrogens can be designated either enantiotopic or diastereotopic. If either H_R or H_S on ethanol were replaced by a deuterium, the two resulting isomers would be enantiomers (because there are no other stereocenters anywhere on the molecule).



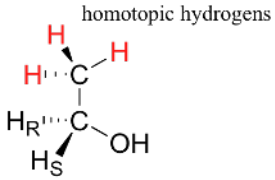
Thus, these two hydrogens are referred to as **enantiotopic**.

In (*R*)-glyceraldehyde-3-phosphate ((*R*)-GAP), however, we see something different:



R)-GAP already has one chiral center. If either of the prochiral hydrogens H_R or H_S is replaced by a deuterium, a second chiral center is created, and the two resulting molecules will be diastereomers (one is *S*,*R*, one is *R*,*R*). Thus, in this molecule, H_R and H_S are referred to as **diastereotopic** hydrogens.

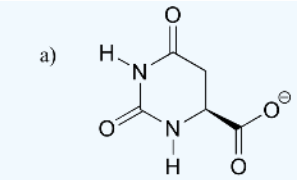
Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl (CH_3) group of ethanol (and on *any* methyl group) are homotopic.



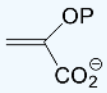
An enzyme cannot distinguish among homotopic hydrogens.

? Exercise 3.29

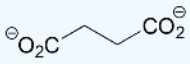
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as H_R or H_S.



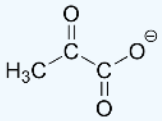
dihydroorotate
(a nucleotide biosynthesis intermediate)



phosphoenolpyruvate
(a glycolysis intermediate)



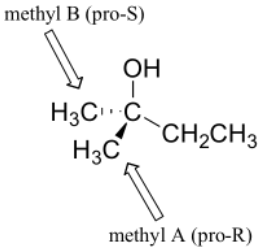
succinate
(a citric acid cycle intermediate)



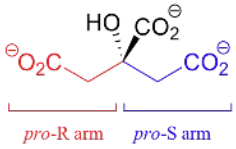
pyruvate
(endpoint of glycolysis)

Solutions to exercises

Groups other than hydrogens can be considered prochiral. The alcohol below has two prochiral methyl groups - the red one is *pro-R*, the blue is *pro-S*. How do we make these designations? Simple - just arbitrarily assign the red methyl a higher priority than the blue, and the compound now has the *R* configuration - therefore red methyl is *pro-R*.

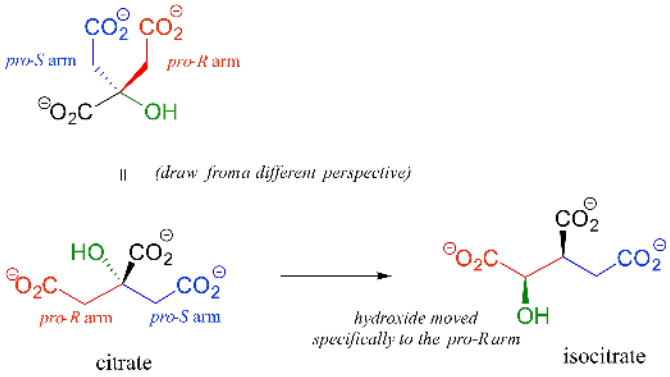


Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro-S*.



citrate

In an isomerization reaction of the citric acid (Krebs) cycle, a hydroxide is shifted specifically to the *pro-R* arm of citrate to form isocitrate: again, the enzyme catalyzing the reaction distinguishes between the two prochiral arms of the substrate (we will study this reaction in chapter 13).



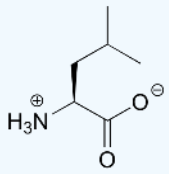
citrate

isocitrate

https://chem.libretexts.org/@go/page/393441

? Exercise 3.30

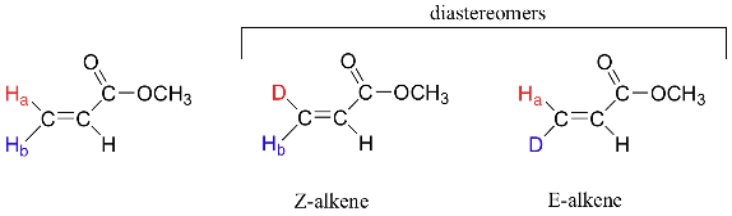
Assign *pro-R* and *pro-S* designations to all prochiral groups in the amino acid leucine. (*Hint*: there are two pairs of prochiral groups!). Are these prochiral groups diastereotopic or enantiotopic?



leucine

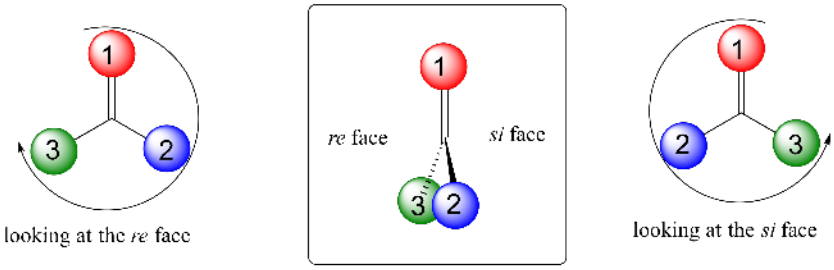
Solutions to exercises

Although an alkene carbon bonded to two identical groups is *not* considered a prochiral center, these two groups *can* be diastereotopic. H_a and H_b on the alkene below, for example, are diastereotopic: if we change one, and then the other, of these hydrogens to deuterium, the resulting compounds are *E* and *Z* diastereomers.

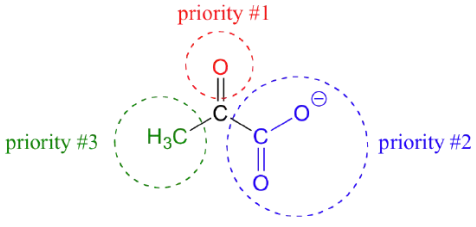


Prochiral carbonyl and imine groups

Trigonal planar, sp^2-hybridized carbons are not, as we well know, chiral centers– but they can be prochiral centers if they are bonded to three different substitutuents. We (and the enzymes that catalyze reactions for which they are substrates) can distinguish between the two planar 'faces' of a prochiral sp^2 - hybridized group. These faces are designated by the terms ***re*** and ***si***. To determine which is the *re* and which is the *si* face of a planar organic group, we simply use the same priority rankings that we are familiar with from the R/S system, and trace a circle: *re* is clockwise and *si* is counterclockwise.

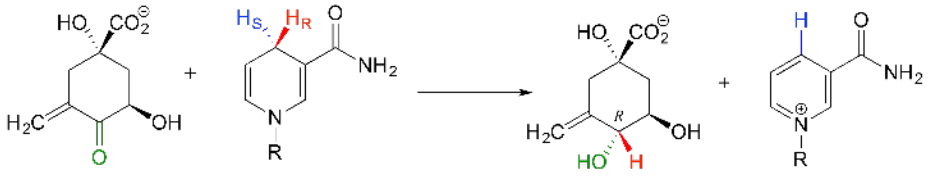


Below, for example, we are looking down on the *re* face of the ketone group in pyruvate:



If we flipped the molecule over, we would be looking at the *si* face of the ketone group. Note that the carboxylate group does not have *re* and *si* faces, because two of the three substituents on that carbon are identical (when the two resonance forms of carboxylate are taken into account).

As we will see in chapter 10, enzymes which catalyze reactions at carbonyl carbons act specifically from one side or the other.

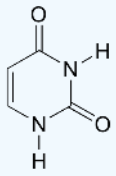


*we are looking at the **si** face of the ketone*

We need not worry about understanding the details of the reaction pictured above at this point, other than to notice the stereochemistry involved. The *pro-R* hydrogen (along with the two electrons in the C-H bond) is transferred to the *si* face of the ketone (in green), forming, in this particular example, an alcohol with the *R* configuration. If the transfer had taken place at the *re* face of the ketone, the result would have been an alcohol with the *S* configuration.

? Exercise 3.31

For each of the carbonyl groups in uracil, state whether we are looking at the *re* or the *si* face in the structural drawing below.



uracil

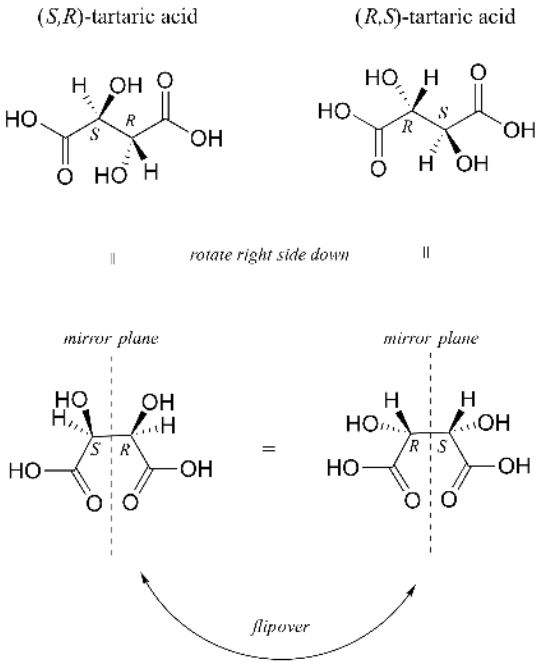
Solutions to exercises

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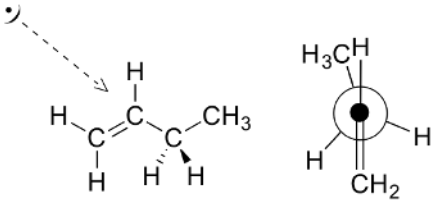
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3.12: Solutions to Chapter 3 exercises

E3.1:



E3.2:



E3.3: Recall from your General Chemistry course that ΔG^0, the standard Gibbs Free Energy change of a reaction (or in this case, a conformational change) is related to the equilibrium constant K_{eq} by:

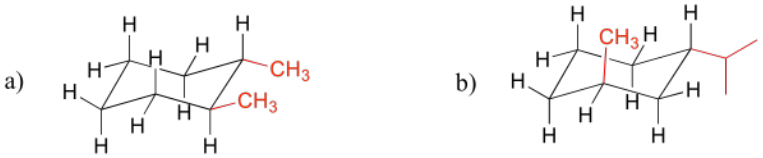
$\Delta G^0 = RT\ln K_{eq}$ *or* $K_{eq} = e^{\wedge}(-\Delta G^0/RT)$

. . . where R is the gas constant 8.314 J mol^{-1} K^{-1}

Using T = 298K (25°C) and ΔG^0 = -7.0 kJ/mol, we calculate $\mathbf{K_{eq} = 17}$.

Note that ΔG^0 has a negative value because the methyl-axial to methyl-equatorial ring flip is an energetically downhill process. Because the equatorial conformation is more stable, it makes sense that the equilibrium constant for the ring flip is greater than 1.

E3.4: Note in (b) that one of the substituents *must* be in the axial position. In the lower energy chair conformation, it is the *smaller* methyl group that assumes the axial position.



E3.5: To answer these questions, you will want to draw out the chair conformations of the compounds specified.

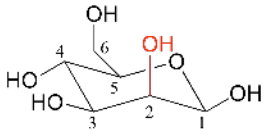
a) ***cis*-1,3-dimethylcyclohexane**: the two methyl groups are either both equatorial or both axial. In *cis*-1,4-dimethylcyclohexane, one methyl group is always axial and one equatorial, so the two conformations have the same energy.

b) ***trans*-1,2-dimethylcyclohexane**: the two methyl groups are either both equatorial or both axial. In *cis*-1,2-dimethylcyclohexane, one methyl group is always axial and one equatorial, so the two conformations have the same energy.

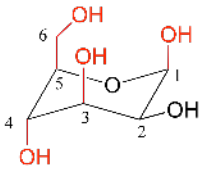
c) ***trans*-1-isopropyl-2-methylcyclohexane**: both compounds are either diaxial or diequatorial, but the larger isopropyl substituent means that the difference between the diaxial and diequatorial conformations is larger.

E3.6: No. In order to change the relationship of two substituents on a ring from *cis* to *trans*, you would need to break and reform two covalent bonds. Ring flips involve only *rotation* of single bonds

E3.7:

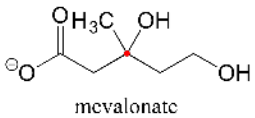


major chair form of mannose
(only one substituent axial)

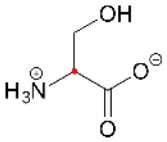


minor chair form of mannose
(four substituents axial)

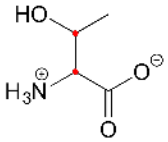
E3.8: Chiral centers are designated with a dot.



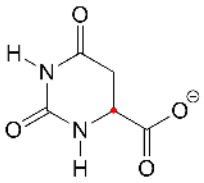
mevalonate



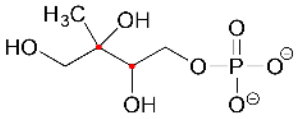
serine



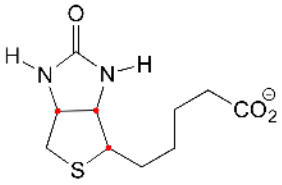
threonine



dihydroorotate



2-methylerythritol-4-phosphate



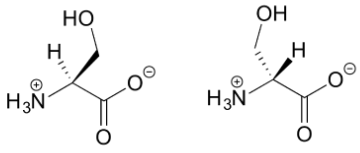
biotin

E3.9: (there are other ways that the two enantiomers can be drawn correctly - check your drawing with your instructor or tutor)

a)



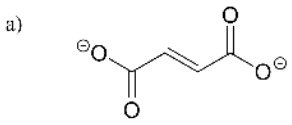
mevalonate



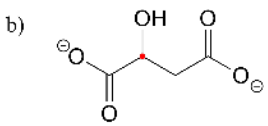
serine

b) No, the two structures are identical. In both drawings, the bond to the OH is pointing *out of the plane of the page* - it doesn't matter whether the solid wedge is pointing to the left or the right. Make models of the two drawings and you will see they are exactly the same.

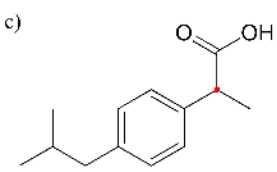
E3.10:



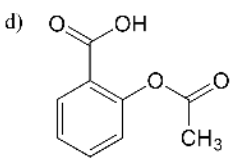
fumarate
(achiral)



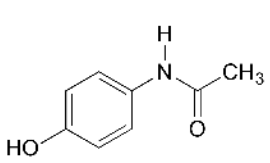
malate
(chiral)



ibuprofen
(chiral)

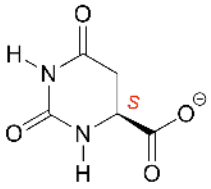


acetylsalicylic acid
(achiral)

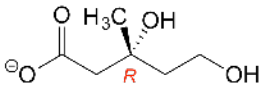


acetaminophen
(achiral)

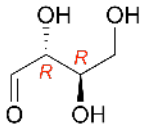
E3.11:



dihydroorotate



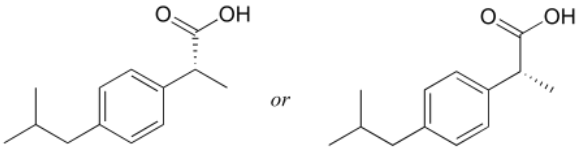
mevalonate



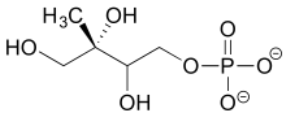
(D)-erythrose

E3.12: The C-O bond should be drawn as a dash to get the *R* configuration.

E3.13:



(*R*)-ibuprofen



(*S*)-2-methylerythritol-4-phosphate

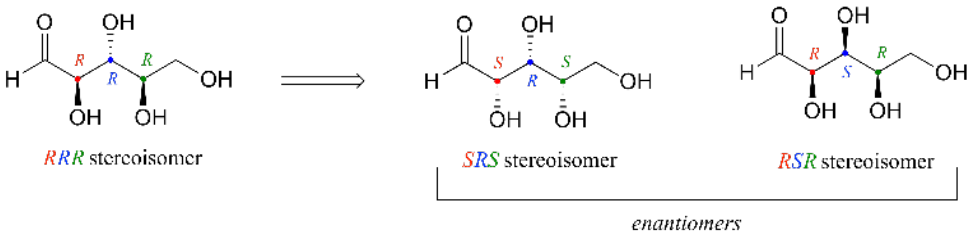
E3.14: The value of *c* is 7.50 g/100 mL, so using the definition of specific rotation, the observed rotation is expected to be (11.5)(7.5) = 86.3º.

E3.15: The observed rotation of the mixture is levorotary (negative, counter-clockwise), and the specific rotation of the pure *R* enantiomer is given as dextrorotary (positive, clockwise), meaning that the pure *S* enantiomer must be levorotary, and the mixture must contain more of the *S* enantiomer than of the *R* enantiomer.

E3.16: Cysteine is the only common L-amino acid with *S* configuration. This is solely due to the rules of the naming system: the carbon of the side chain - which is directly bonded to a sulfur - has higher priority than the carboxylate carbon. In the other 19 amino acids, the carboxylate carbon has priority #2, and the side chain carbon has priority #3.

E3.17:

a) Starting with the RRR stereoisomer (which is given in the example), we flip the first and third chiral center to get SRS. The enantiomer of the SRS stereoisomer is that in which all three chiral centers are flipped: the RSR stereoismer.

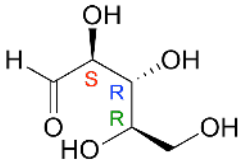


b) Epimers of the SRS stereoismer are RRS, SSS, and SRR (in each case, one of the three chiral centers has been flipped)

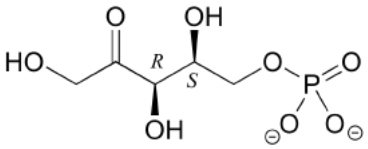
c) How to find the compounds that are diastereomers of the SRS stereoisomer, but not epimers? Start with the list of the eight possible stereoisomers given in the example. Cross out SRS itself, and its enantiomer RSR (determined in part (a) above). Then cross out the three epimers we found in part (b). We are left with three isomers: RRR, SSR, and RSS. Each of these have one chiral center in common with SRS, and two that are flipped.

RRR RRS RSR RSS
SSS SSR SRS SRR

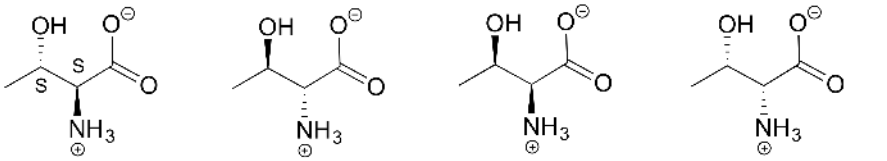
E3.18: This is the SRR stereoisomer:



E3.19:



E3.20:



E3.21: Going left to right, top to bottom:

Diastereomers (two chiral centers are flipped).

Enantiomers (all five chiral centers are flipped).

Identical (drawing is flipped vertically but they are the same structure).

Identical (the carbon which appears to be flipped in the drawing is *not* a chiral center).

Constitutional isomers (same molecular formula, but notice that inositol does not have a ring oxygen. Is not a monosaccharide, it is a cyclohexane with six hydroxyl substituents.)

E3.22:

a) Identical. They have the same molecular formula and connectivity; there is only one chiral center, which is *R* in both structures.

b) Enantiomers. The compound on the left is *R*, compound on the right is *S*.

c) Enantiomers. The compound on the left is *R*, compound on the right is *S*.

d) Enantiomers. The compound on the left is *SS*, compound on the right is *RR*.

e) Identical. The structures are both glycerol, which is *not* chiral (the left and right 'arms' are the same, so the middle carbon is not a chiral center)

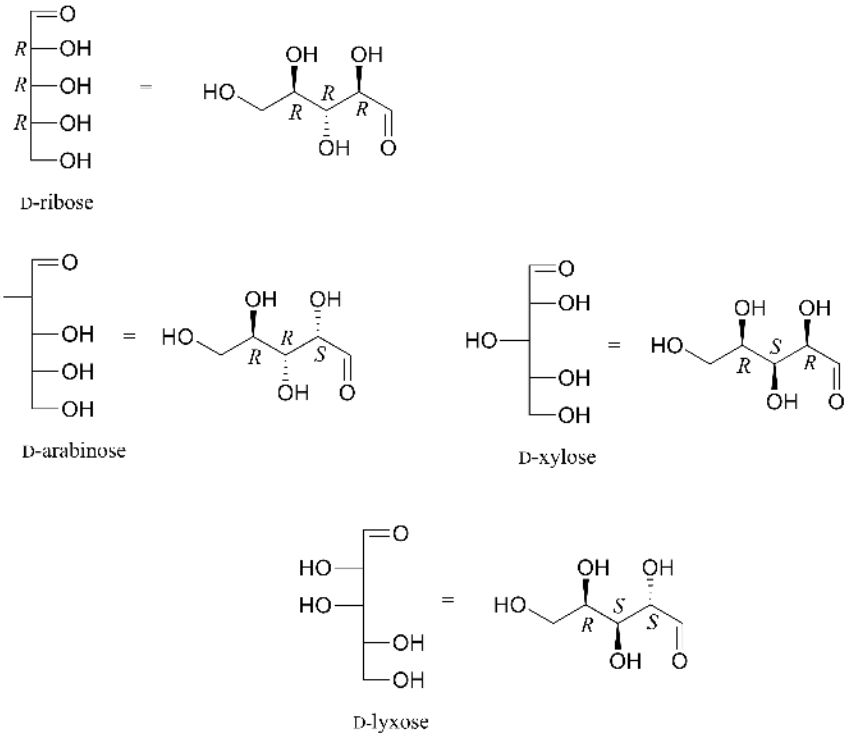
f) Identical. Both structures are *SS*. Also, notice that if you rotate the right-side structure 120 degrees clockwise, it becomes exactly the same as the left-side structure.

E3.23:

a) Not *meso* b) *Meso*. c) Not meso

d) *Meso* e) Not *meso* f) *Meso*

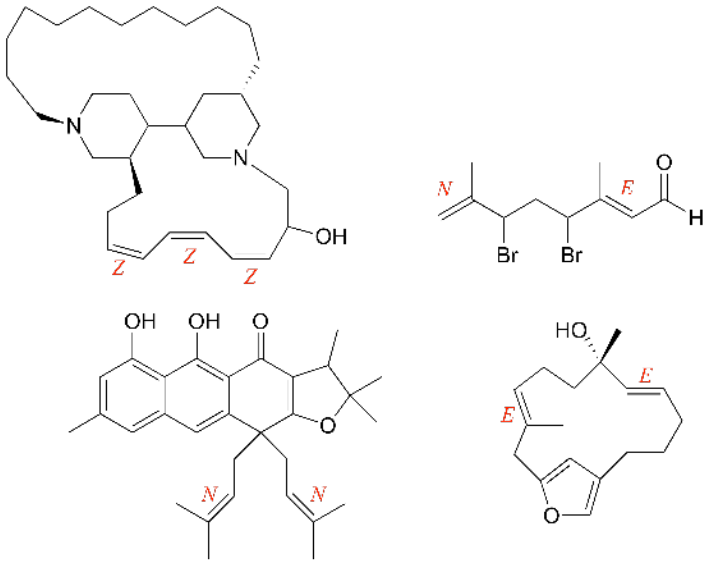
E3.24:



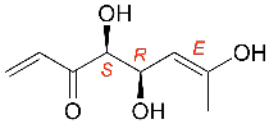
E3.25:

a) *E* b) *N* c) *Z* d) *E*

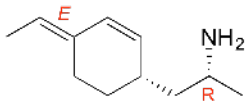
E3.26:



E3.27: The enantiomers of the compounds shown are below. Note that the chiral centers are flipped, but the stereogenic alkenes are not.



8 total stereoisomers possible (including this one).



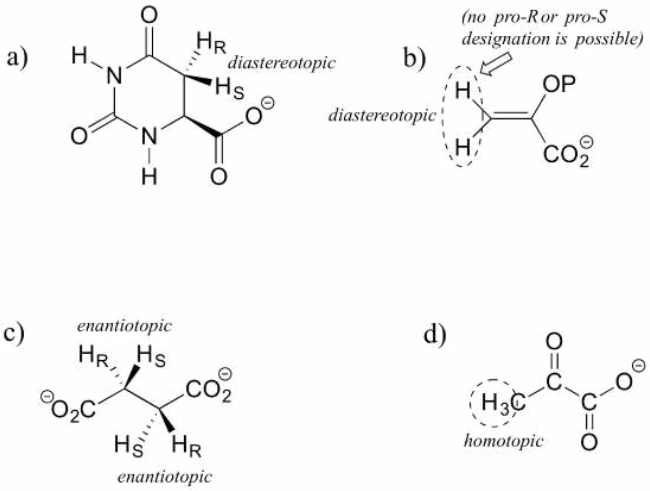
4 total stereoisomers possible (including this one).

E3.28:

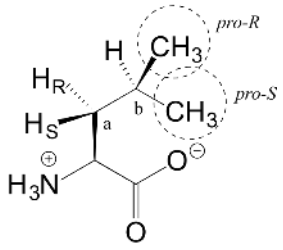
Ephedrine and pseudoephedrin are diastereomers (epimers). There are two chiral centers, and one of them (the OH) is flipped.

Methamphetamine and *levo*-methamphetamine are enantiomers (only one chiral center, and it is flipped). Methamphetamine technically should be called *dextro*-methamphetamine.

E3.29:

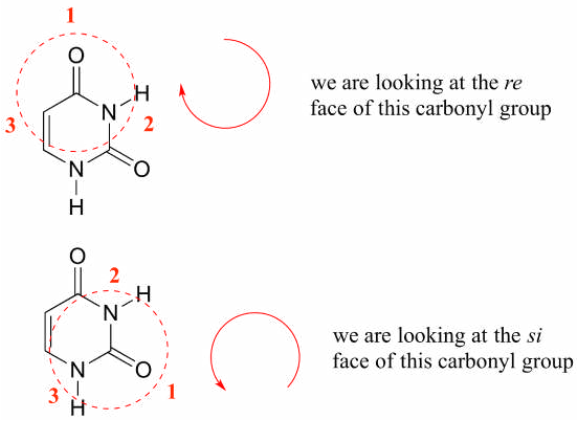


E3.30:



leucine

E3.31:



Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Layne Morsch (University of Illinois Springfield)

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3.P: Problems for Chapter 3

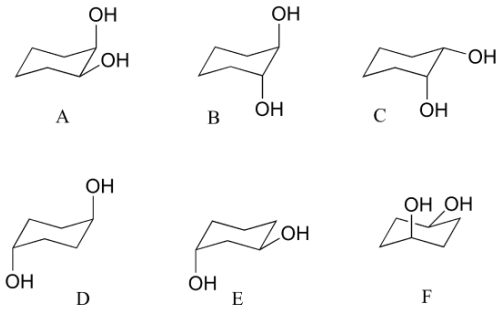
Solutions to selected problems

P3.1: Draw an energy vs dihedral angle graph for rotations about the C_2-C_3 bond of 2-methylbutane. Start with the highest-energy conformation as the 0º point. For each energy peak and valley, draw a corresponding Newman projection.

P3.2:

a) Which has the highest energy diaxial chair conformation: *trans*-1,2-dimethylcyclohexane, *cis*-1,3-dimethylcyclohexane, or *trans*-1,4-dimethylcyclohexane? Explain.

b) Which of the following are *trans* disubstituted cyclohexanes?



c) Draw A-F above in two dimensions (rings in the plane of the page, substituents drawn as solid or dashed wedges).

d) Structure D does not have any chiral centers. Explain.

e) Draw a diastereomer of structure D (in two dimensions, as in part c).

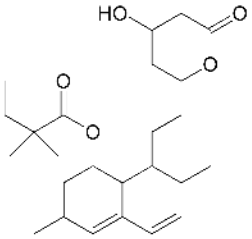
f) Are structure D and its diastereomer chiral?

g) Assign R/S designations to the two chiral centers in structure B (hint: making a model will be *very* helpful!)

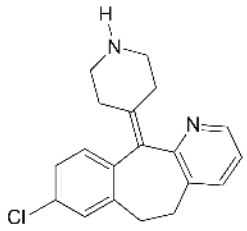
P 3.3: The following are structures, drawn in two dimensions, of drugs listed on the products web page of Merck Pharmaceutical. One of the compounds is achiral.

a) Circle all chiral centers. (Hint: *Don't panic*! Remember - you are looking for sp^3-hybridized carbons with four different substituents.)

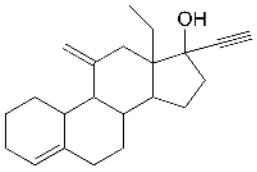
https://chem.libretexts.org/@go/page/393437



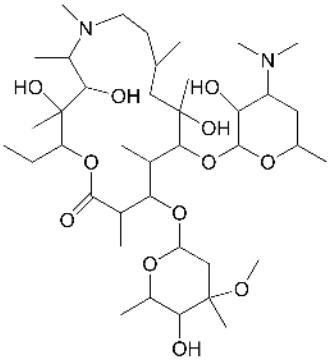
simvastatin
(active ingredient in Zocor, for high cholesterol



desloratadine
(Clarinex, for seasonal allergies)



desogestrel
(an active ingredient in Cyclessa, an oral contraceptive)

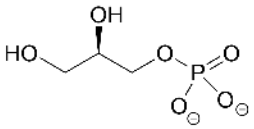


azithromycin
(an antibiotic in AzaSite, for conjunctivitis)

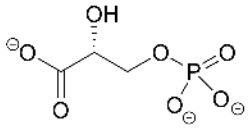
b) How many diastereomers are possible for desogestrel?

c) Draw two epimeric forms of simvastatin

P3.4: Three of the four structures below are chiral. Assign R/S designations to all chiral centers, and identify the achiral molecule.

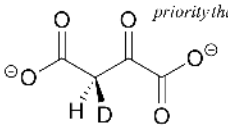


glycerol phosphate

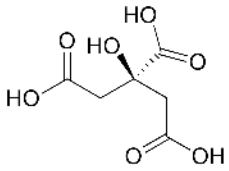


phosphoglycerate

D = deuterium, the ^2H isotope of hydrogen. D has a higher priority than H, lower priority than C.

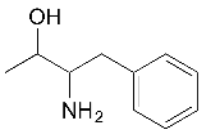


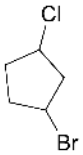
(^{2}H)-oxaloacetate

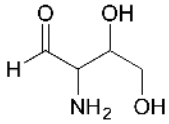


citric acid

P3.5: Draw the *R,R* stereoisomers of the structures below.

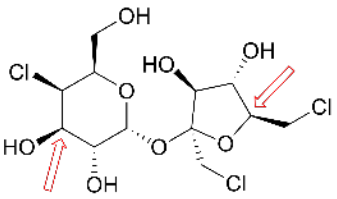




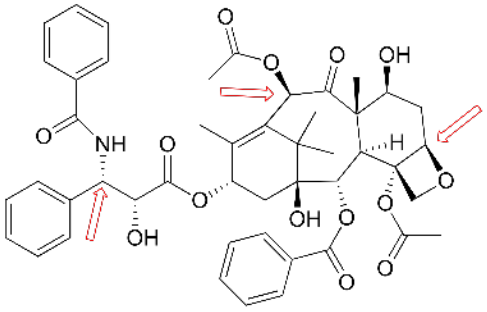


https://chem.libretexts.org/@go/page/393437

P3.6: Below are the structures of sucralose, the artificial sweetener with the brand name Splenda (TM), and the cancer drug Paclitaxel. Give an *R* or *S* designation to chiral centers indicated with an arrow.



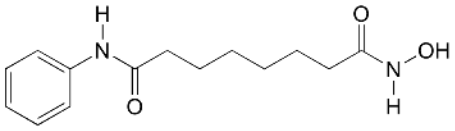
sucralose



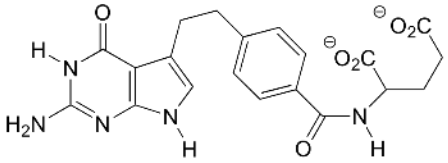
Paclitaxel

P3.7: The four drugs below were featured in a *Chemical & Engineering News* article (April 16, 2007, p. 42) on new drugs that had been developed in university labs.

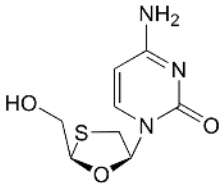
a) Identify each as chiral or achiral, and identify all stereocenters. Also, state how many possible stereoisomers exist for each structure.



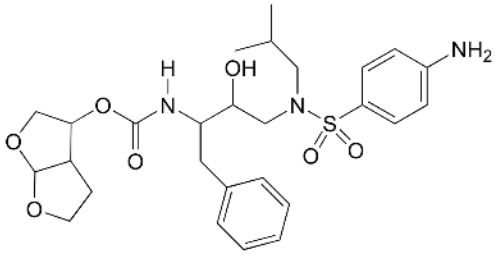
SAHA (suberoylanilide hydroxamic acid)



Alimta

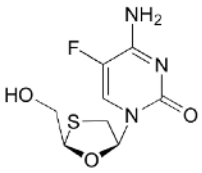


Epivir

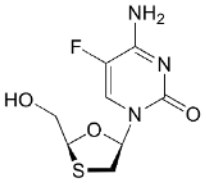


Darunavir

b) Two fluorinated Epivar derivatives (structures A and B below) were also mentioned in this article. What is the relationship between structures A and B? (Your choices: not isomers, constitutional isomers, diastereomers but not epimers, epimers, enantiomers, identical)



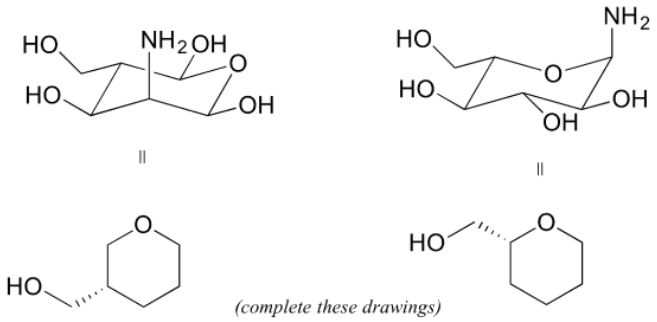
A



B

P3.8: Redraw the following structures in the flat ring, solid/dash wedge convention (the drawings have been started for you).

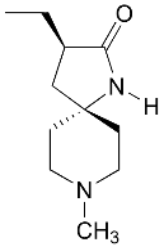
https://chem.libretexts.org/@go/page/393437



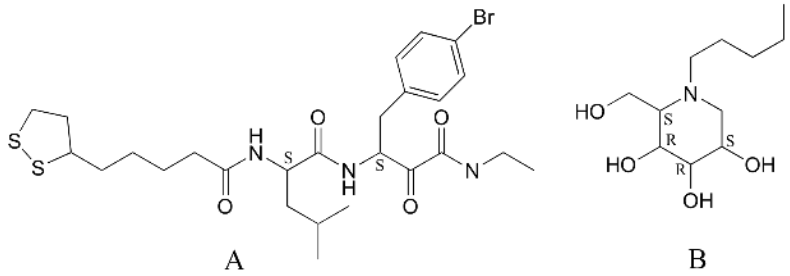
P3.9: Below is an experimental drug for Alzheimer's disease that was mentioned in the March 13, 2007 issue of *Chemical and Engineering News*.

a) Label all stereocenters as *R* or *S*.

b) Draw the enantiomer of the molecule shown.



P3.10: The molecules below are potential new drugs for the treatment of Duchenne muscular dystrophy (molecule A) and skin cancer (molecule B) (*Chemical and Engineering News* Sept 26, 2005, p. 39). Given the *R/S* designations, redraw the structure showing the correct stereochemistry.



P3.11: Draw the structure of the following molecules:

a) (*R*)-3-methyl-3-hexanol

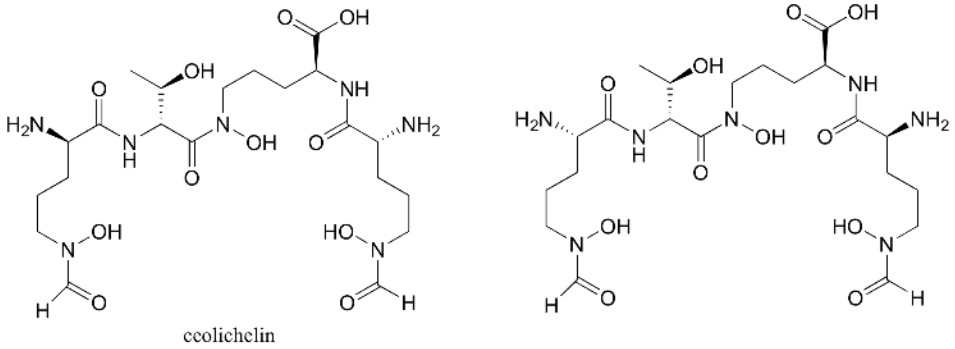
b) (*R*)-1-chloro-1-phenylethane

c) (2*R*, 3*R*)-2,3-dihydroxybutanedioic acid (tartaric acid)

d) (*S*)-(*E*)-4-chloro-3-ethyl-2-pentenoic acid

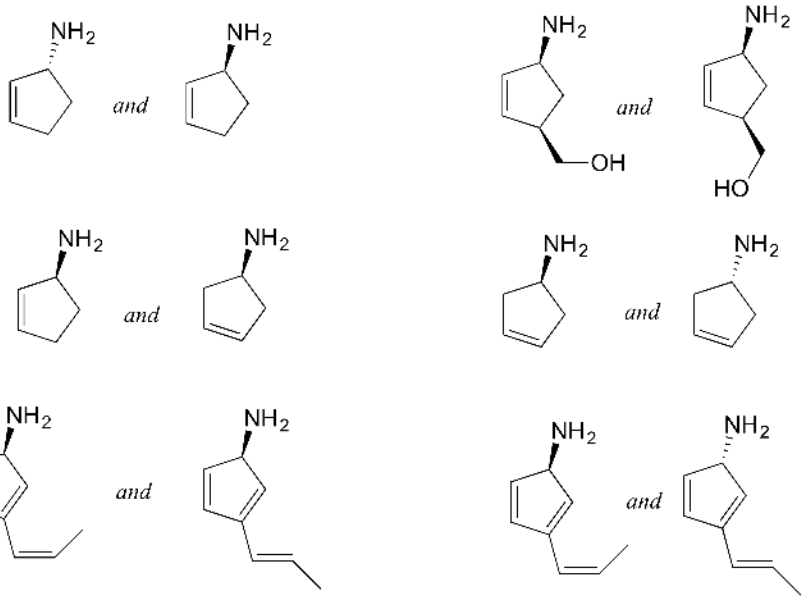
e) (1*S*, 3*R*)-1-chloro-3-ethylcyclohexane

P3.12: Coelichelin (the structure below to the left) is a natural product from soil bacteria that was identified using a technique known as 'genome mining' (*Chemical and Engineering News* Sept. 19, 2005, p. 11). What is the relationship between coelichelin and the compound shown below and to the right?

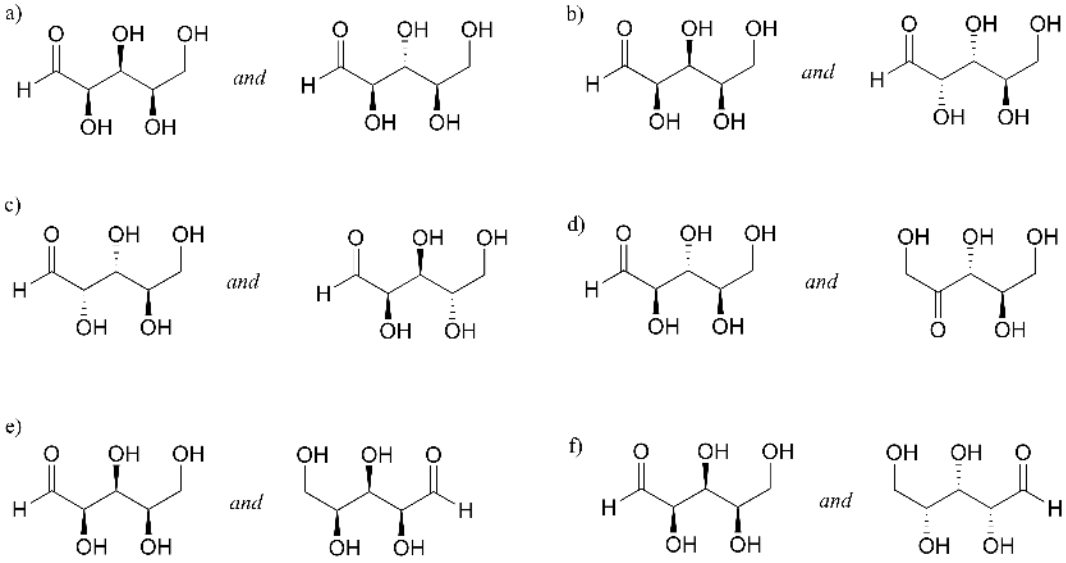


ecolichelin

P3.13: Identify the relationships between the following pairs of structures (Not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical)



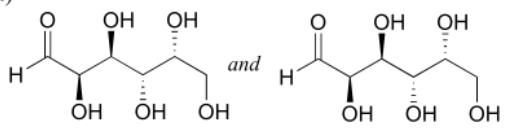
P3.14: Identify the relationships between each of the following pairs of pentose sugars (not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical).



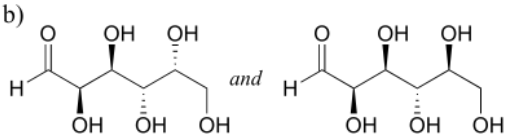
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P3.15: Identify the relationships between each of the following pairs of hexose sugars (not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical).

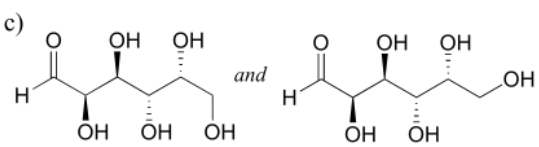
a)



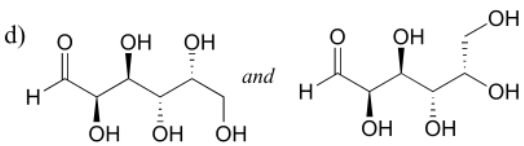
b)



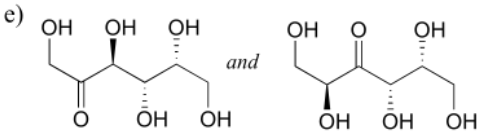
c)



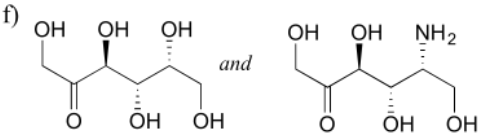
d)



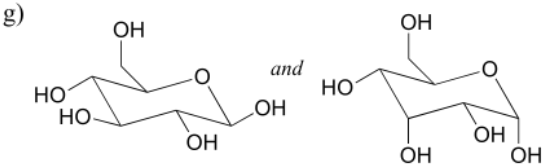
e)



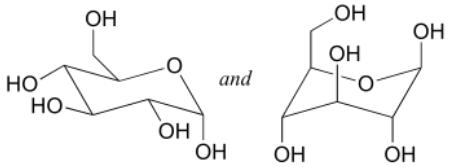
f)



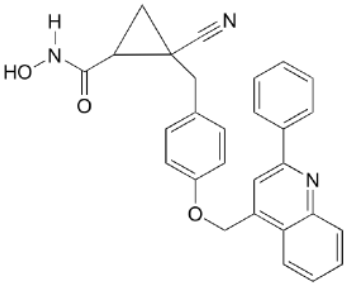
g)



h)



P3.16: The compound drawn below (not showing stereochemistry) has been identified as a potential anti-inflammatory agent by scientists at Schering-Plough a pharmaceutical company (see *Chemical and Engineering News* Nov. 28, 2005 p. 29). How many stereoisomers are possible for the compound?

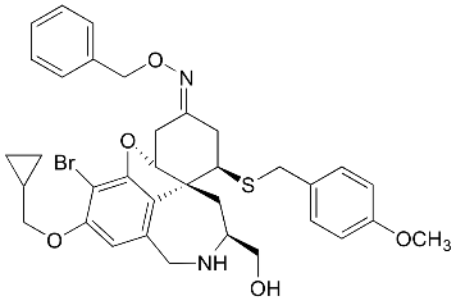


P3.17: Secramine is a synthetic compound that has been shown to interfere with the transport of newly synthesized proteins in the cell (see *Chemical and Engineering News* Nov. 28, 2005, p. 27). Also drawn below is a (hypothetical) isomer of secramine.

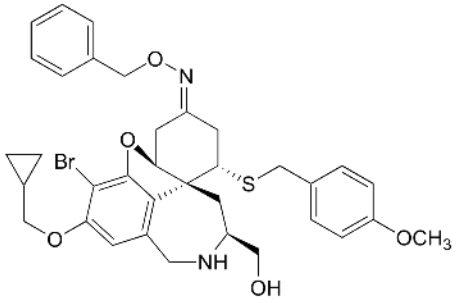
a) Identify the relationship between the two isomers: are they consitutional isomers, confomational isomers, enantiomers, or diastereomers?

b) Locate a five-membered ring in the secramine structure.

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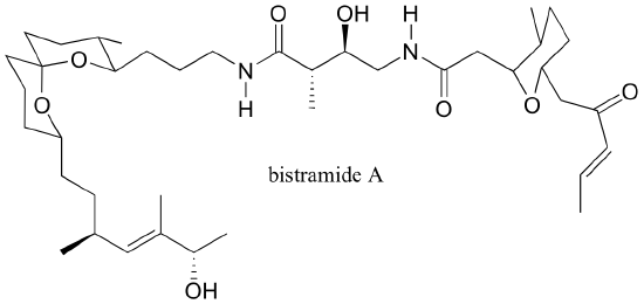


secramine



isomer of secramine

P3.18: The natural product bistramide A has been shown to bind to actin, an important structural protein in the cell, and supress cell proliferation (see *Chemical and Engineering News* Nov. 21, 2005, p. 10).



bistramide A

a) Label the alkene functional groups as *E*, *Z*, or *N* (no *E/Z* designation possible)

b) Theoretically, how many stereoisomers are possible for bistramide A?

P3.19:

a) Draw Newman projections of the *gauche* and the *anti* conformations of 1,2-ethanediol.

b) Why might the *gauche* conformation be expected to be the more stable of the two?

c) Do you think that *gauche* is also the most stable conformation of 1,2-dimethoxyethane? Explain.

P3.20: Draw the chair conformation of *cis*-1,2-dimethylcyclohexane.

a) Label the stereochemical configuration at C_1 and C_2 for the structure you drew.

b) Build a model of your molecule, and try out different possible boat conformations. Can you find one in which there is a plane of symmetry?

c) Is *cis*-1,2-dimethylcyclohexane a chiral molecule?

d) is *cis* -1,4-dimethylcyclohexane chiral? How about *trans*-1,4-dimethylcyclohexane? How about *trans*-1-chloro-4-fluorocyclohexane?

P3.21: In some special cases, a 'chiral center' can be composed of several atoms instead of just one, and molecules which contain such multi-atom chiral centers are indeed chiral. What is the relationship between the two two difluorallene compounds below? It will be very helpful to make models, and review the fundamental definitions in this chapter.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

4: Structure Determination I- UV-Vis and Infrared Spectroscopy, Mass Spectrometry

In the first three chapters of this text, we have focused our efforts on learning about the structure of organic compounds. Now that we know what organic molecules look like, we can start to address the question of *how* chemists are able to elucidate organic structures. The individual atoms and functional groups in organic compounds are far too small to be directly observed or photographed, even with the best electron microscope. How, then, are chemists able to draw with confidence the bonding arrangements in organic molecules, even simple ones such as acetone or ethanol?

The answer lies, for the most part, in a field of chemistry called **molecular spectroscopy**. Spectroscopy is the study of how electromagnetic radiation, across a spectrum of different wavelengths, interacts with molecules - and how these interactions can be quantified, analyzed, and ultimately interpreted to gain information about molecular structure.

After first reviewing some basic information about the properties of light and introducing the basic ideas behind spectroscopy, we will move to a discussion of infrared (IR) spectroscopy, a technique which is used in organic chemistry to detect the presence or absence of common functional groups. Next, we will look at ultraviolet-visible (UV-vis) spectroscopy, in which light of a shorter wavelength is employed to provide information about organic molecules containing conjugated p-bonding systems.

In the final section of this chapter, we will change tack slightly and consider another analytical technique called mass spectrometry (MS). Here, we learn about the structure of a molecule by, in a sense, taking a hammer to it and smashing it into small pieces, then measuring the mass of each piece. Although this metaphorical description makes mass spectrometry sound somewhat crude, it is in fact an extremely powerful and sensitive technique, one which has in recent years become central to the study of life at the molecular level.

Looking ahead, Chapter 5 will be devoted to the study of nuclear magnetic resonance (NMR) spectroscopy, where we use ultra-strong magnets and radio frequency radiation to learn about the electronic environment of individual atoms in a molecule. For most organic chemists, NMR is the single most powerful analytical tool available in terms of the wealth of detailed information it can provide about the structure of a molecule. It is the closest thing we have to a ‘molecular camera’.

In summary, the analytical techniques we will be studying in this chapter and the next primarily attempt to address the following questions about an organic molecule:

- Infrared (IR) spectroscopy: *What functional groups does the molecule contain?*
- Ultraviolet-visible (UV-vis) spectroscopy:*To what extent does the molecule contain a system of conjugated pi bonds?*
- Mass spectrometry (MS): *What is the atomic weight of the molecule and its common fragments?*
- Nuclear magnetic resonance spectroscopy (NMR): *What is the overall bonding framework of the molecule?*

4.0: Prelude to Structure Determination I

4.1: Introduction to molecular spectroscopy

4.2: Mass Spectrometry

4.3: Infrared spectroscopy

4.4: Ultraviolet and visible spectroscopy

4.P: Problems for Chapter 4

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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4.0: Prelude to Structure Determination I



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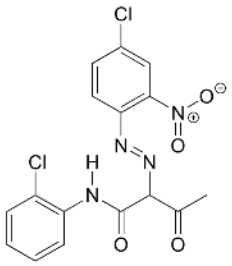
Introduction: a foiled forgery

In the end, it was a 'funky yellow color' that led to the demise of Charles Heller's not-so-illustrious career in the world of collectable art.

William Aiken Walker was a 19th-century 'genre' painter, known for his small scenes of sharecroppers working the fields in the post-Civil War south. For much of his career, he traveled extensively, throughout the southern states but also to New York City and even as far as Cuba. He earned a decent living wherever he went by setting up shop on the sidewalk and selling his paintings to tourists, usually for a few dollars each. While he never became a household name in the art world, he was prolific and popular, and his paintings are today considered collectible, often selling for upwards of ten thousand dollars.

In August, 1994, Robert Hicklin, an art gallery owner in Charleston, South Carolina, was appraising a Walker painting brought to him by another South Carolina art dealer named Rick Simons. Hicklin's years of experience with Walker paintings told him that something just wasn't right with this one - he was particularly bothered by one of the pigments used, which he later described in a story in the *Maine Antique Digest* as a 'funky yellow color'. Reluctantly, he told Simons that it almost certainly was a fake.

Hoping that Hicklin was wrong, Simons decided to submit his painting to other experts for analysis, and eventually it ended up in the laboratory of James Martin, whose company *Orion Analytical* specializes in forensic materials analysis. Using a technique called infrared spectroscopy, Martin was able to positively identify the suspicious yellow pigment as an organic compound called 'pigment yellow 3'.



pigment yellow 3

As it turns out, Pigment Yellow 3 had not become available in the United States until many years after William Aiken Walker died.

Simons had purchased his painting from a man named Robert Heller for $9,500. When Heller approached him again to offer several more Walker paintings for sale, Simons contacted the FBI. A few days later, with FBI agents listening in, Simons agreed to buy two more Walker paintings. When he received them, they were promptly analyzed and found to be fake. Heller, who turned out to be a convicted felon, was arrested and eventually imprisoned.

(For more details on this story, see Chemical and Engineering News, Sept 10, 2007, p. 28).

*****

In the first three chapters of this text, we have focused our efforts on learning about the structure of organic compounds. Now that we know what organic molecules look like, we can begin to address, in the next two chapters, the question of how we get this knowledge in the first place. How are chemists able to draw with confidence the bonding arrangements in organic molecules, even simple ones such as acetone or ethanol? How was James Martin at Orion Analytical able to identify the chemical structure of the pigment compound responsible for the 'funky yellow color' in the forged William Aiken Walker painting?

This chapter is devoted to three very important techniques used by chemists to learn about the structures of organic molecules. First, we will learn how mass spectrometry can provide us with information about the mass of a molecule as well as the mass of fragments into which the molecule has been broken. Then, we will begin our investigation of molecular spectroscopy, which is the study of how electromagnetic radiation at different wavelengths interacts in different ways with molecules - and how these interactions can be quantified, analyzed, and interpreted to gain information about molecular structure. After a brief overview of the properties of light and the elements of a molecular spectroscopy experiment, we will move to a discussion of infrared (IR) spectroscopy, the key technique used in the detection of the Walker forgery, and a way to learn about functional groups present in an organic compound. Then, we will consider ultraviolet-visible (UV-vis) spectroscopy, with which chemists gain information about conjugated pi-bonding systems in organic molecules. Among other applications, we will see how information from UV-vis spectroscopy can be used to measure the concentration of biomolecules compounds in solution.

Looking ahead, Chapter 5 will be devoted to nuclear magnetic resonance (NMR) spectroscopy, where we use ultra-strong magnets and radio frequency radiation to learn about the electronic environment of individual atoms in a molecule and use this information to determine the atom-to-atom bonding arrangement. For most organic chemists, NMR is one of the most powerful analytical tools available in terms of the wealth of detailed information it can provide about the structure of a molecule.

The structure determination techniques we will be studying in this chapter and the next primarily attempt to address the following questions about an organic molecule:

Chapter 4:

Mass spectrometry (MS): What is the atomic weight of the molecule and its common fragments?

Infrared (IR) spectroscopy: what functional groups does the molecule contain?

Ultraviolet-visible (UV-Vis) spectroscopy: What is the nature of conjugated pi-bonding systems in the molecule?

Chapter 5:

Nuclear magnetic resonance spectroscopy (NMR): What is the overall bonding framework of the molecule?

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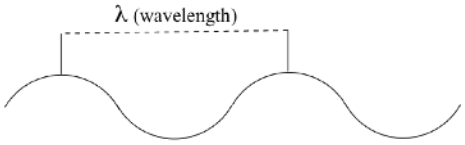
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4.1: Introduction to molecular spectroscopy

The electromagnetic spectrum

Electromagnetic radiation, as you may recall from a previous chemistry or physics class, is composed of electrical and magnetic waves which oscillate on perpendicular planes. Visible light is electromagnetic radiation. So are the gamma rays that are emitted by spent nuclear fuel, the x-rays that a doctor uses to visualize your bones, the ultraviolet light that causes a painful sunburn when you forget to apply sun block, the infrared light that the army uses in night-vision goggles, the microwaves that you use to heat up your frozen burritos, and the radio-frequency waves that bring music to anybody who is old-fashioned enough to still listen to FM or AM radio.

Just like ocean waves, electromagnetic waves travel in a defined direction. While the speed of ocean waves can vary, however, the speed of electromagnetic waves – commonly referred to as the speed of light – is essentially a constant, approximately 300 million meters per second. This is true whether we are talking about gamma radiation or visible light. Obviously, there is a big difference between these two types of waves – we are surrounded by the latter for more than half of our time on earth, whereas we hopefully never become exposed to the former to any significant degree. The different properties of the various types of electromagnetic radiation are due to differences in their wavelengths, and the corresponding differences in their energies: *shorter wavelengths correspond to higher energy.*



High-energy radiation (such as gamma- and x-rays) is composed of very short waves – as short as 10^{-16} meter from crest to crest. Longer waves are far less energetic, and thus are less dangerous to living things. Visible light waves are in the range of 400 – 700 nm (nanometers, or 10^{-9} m), while radio waves can be several hundred meters in length.

The notion that electromagnetic radiation contains a quantifiable amount of energy can perhaps be better understood if we talk about light as a stream of *particles*, called **photons**, rather than as a wave. (Recall the concept known as 'wave-particle duality': at the quantum level, wave behavior and particle behavior become indistinguishable, and very small particles have an observable 'wavelength'). If we describe light as a stream of photons, the energy of a particular wavelength can be expressed as:

$$E = \frac{hc}{\lambda} \tag{4.1.1}$$

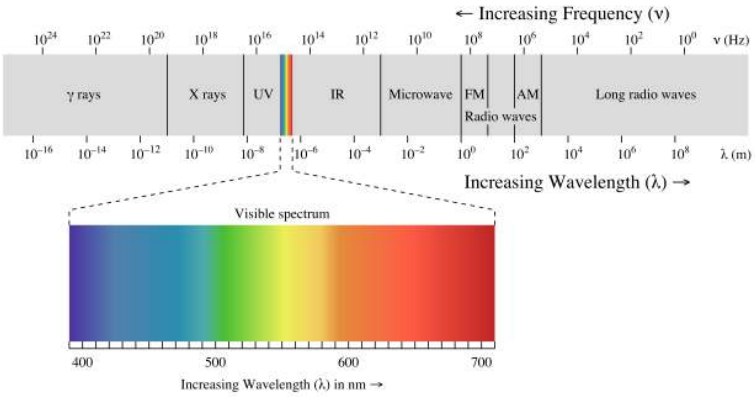
where E is energy in kJ/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^{8} m/s (the speed of light), and *h* is 3.99 x 10^{-13} kJ·s·mol^{-1}, a number known as **Planck's constant**.

Because electromagnetic radiation travels at a constant speed, each wavelength corresponds to a given frequency, which is the number of times per second that a crest passes a given point. Longer waves have lower frequencies, and shorter waves have higher frequencies. Frequency is commonly reported in hertz (Hz), meaning 'cycles per second', or 'waves per second'. The standard unit for frequency is s^{-1}.

When talking about electromagnetic waves, we can refer either to wavelength or to frequency - the two values are interconverted using the simple expression:

$$\lambda\nu = c \tag{4.1.2}$$

where **ν** (the Greek letter '*nu*') is frequency in s^{-1}. Visible red light with a wavelength of 700 nm, for example, has a frequency of 4.29 x 10^{14} Hz, and an energy of 40.9 kcal per mole of photons. The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



(Image from Wikipedia commons)

Notice that visible light takes up just a narrow band of the full spectrum. White light from the sun or a light bulb is a mixture of all of the visible wavelengths. You see the visible region of the electromagnetic spectrum divided into its different wavelengths every time you see a rainbow: violet light has the shortest wavelength, and red light has the longest.

? Exercise 4.4

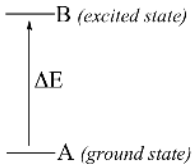
Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kJ/mol of photons?

Solutions

Overview of a molecular spectroscopy experiment

In a spectroscopy experiment, electromagnetic radiation of a specified range of wavelengths is allowed to pass through a sample containing a compound of interest. The sample molecules absorb energy from some of the wavelengths, and as a result jump from a low energy 'ground state' to some higher energy 'excited state'. Other wavelengths are *not* absorbed by the sample molecule, so they pass on through. A detector on the other side of the sample records which wavelengths were absorbed, and to what extent they were absorbed.

Here is the key to molecular spectroscopy: *a given molecule will specifically absorb only those wavelengths which have energies that correspond to the energy difference of the transition that is occurring.* Thus, if the transition involves the molecule jumping from ground state A to excited state B, with an energy difference of **ΔE**, the molecule will specifically absorb radiation with wavelength that corresponds to **ΔE**, while allowing other wavelengths to pass through unabsorbed.



By observing which wavelengths a molecule absorbs, and to what extent it absorbs them, we can gain information about the nature of the energetic transitions that a molecule is able to undergo, and thus information about its structure.

These generalized ideas may all sound quite confusing at this point, but things will become much clearer as we begin to discuss specific examples.

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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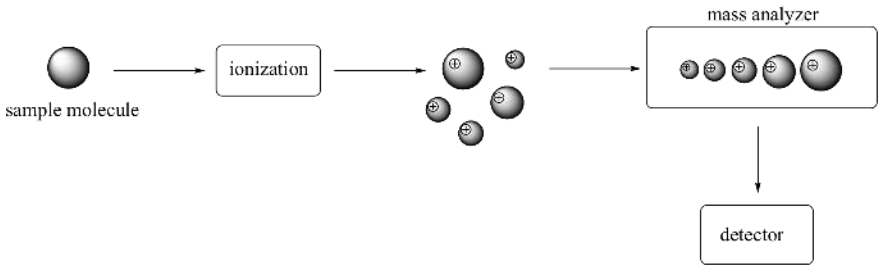
4.2: Mass Spectrometry

Mass spectrometry (MS) is a powerful analytical technique widely used by chemists, biologists, medical researchers, and environmental and forensic scientists, among others. With MS, we are looking at the mass of a molecule, or of different fragments of that molecule.

The basics of a mass spectrometry experiment

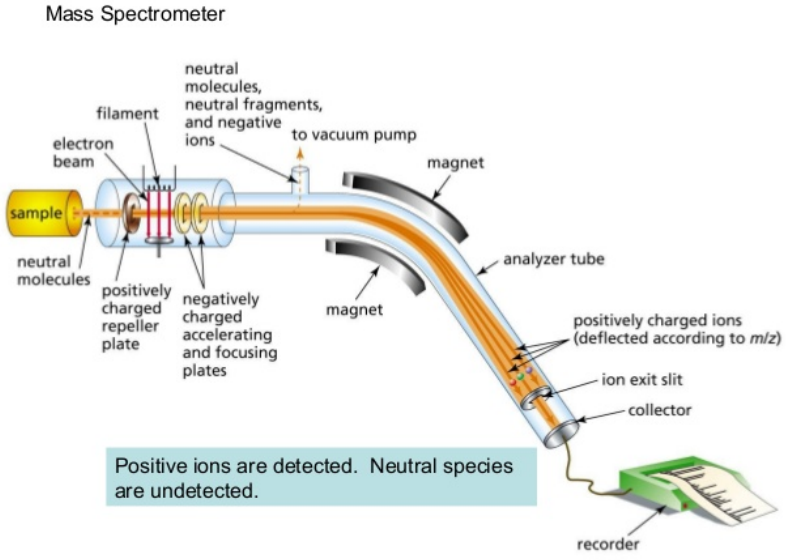
There are many different types of MS instruments, but they all have the same three essential components. First, there is an ionization source, where the molecule is given a positive electrical charge, either by removing an electron or by adding a proton. Depending on the ionization method used, the ionized molecule may or may not break apart into a population of smaller fragments. In the figure below, some of the sample molecules remain whole, while others fragment into smaller pieces.

Next in line there is a mass analyzer, where the cationic fragments are separated according to their mass.



Finally, there is a detector, which detects and quantifies the separated ions.

One of the more common types of MS techniques used in the organic laboratory is **electron ionization**. In the ionization source, the sample molecule is bombarded by a high-energy electron beam, which has the effect of knocking a valence electron off of the molecule to form a **radical cation**. Because a great deal of energy is transferred by this bombardment process, the radical cation quickly begins to break up into smaller fragments, some of which are positively charged and some of which are neutral. The neutral fragments are either adsorbed onto the walls of the chamber or are removed by a vacuum source. In the mass analyzer component, the positively charged fragments and any remaining unfragmented **molecular ions** are accelerated down a tube by an electric field.

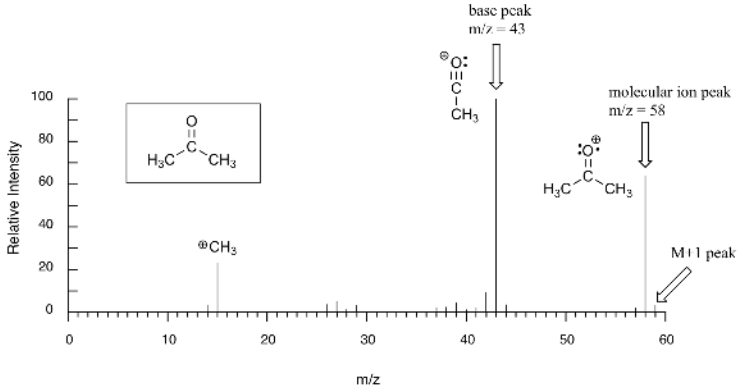


(Image from Wikipedia Commons)

This tube is curved, and the ions are deflected by a strong magnetic field. Ions of different mass to charge (m/z) ratios are deflected to a different extent, resulting in a 'sorting' of ions by mass (virtually all ions have charges of z = +1, so sorting by the mass to charge ratio is the same thing as sorting by mass). A detector at the end of the curved flight tube records and quantifies the sorted ions.

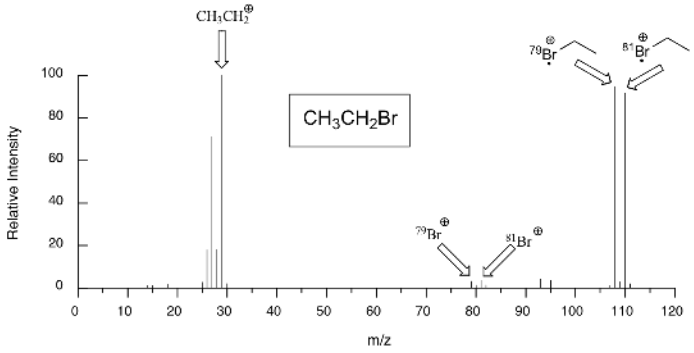
Looking at mass spectra

Below is typical output for an electron-ionization MS experiment (MS data in the section is derived from the Spectral Database for Organic Compounds, a free, web-based service provided by AIST in Japan.



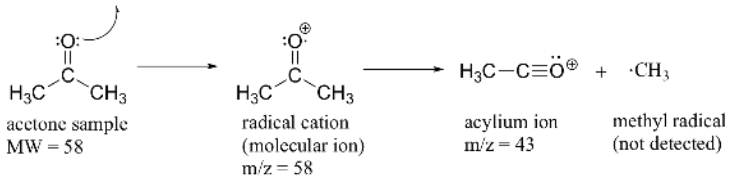
The sample is acetone. On the horizontal axis is the value for m/z (as we stated above, the charge z is almost always +1, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set to 100%, and all other peaks are recorded relative to this value. For acetone, the base peak is at m/z = 43 - we will discuss the formation of this fragment a bit later. The molecular weight of acetone is 58, so we can identify the peak at m/z = 58 as that corresponding to the **molecular ion peak**, or **parent peak**. Notice that there is a small peak at m/z = 59: this is referred to as the **M+1 peak**. How can there be an ion that has a greater mass than the molecular ion? Simple: a small fraction - about 1.1% - of all carbon atoms in nature are actually the ^{13}C rather than the ^{12}C isotope. The ^{13}C isotope is, of course, heavier than ^{12}C by 1 mass unit. In addition, about 0.015% of all hydrogen atoms are actually deuterium, the ^{2}H isotope. So the M+1 peak represents those few acetone molecules in the sample which contained either a ^{13}C or ^{2}H.

Molecules with lots of oxygen atoms sometimes show a small **M+2 peak** (2 m/z units greater than the parent peak) in their mass spectra, due to the presence of a small amount of ^{18}O (the most abundant isotope of oxygen is ^{16}O). Because there are two abundant isotopes of both chlorine (about 75% ^{35}Cl and 25% ^{37}Cl) and bromine (about 50% ^{79}Br and 50% ^{81}Br), chlorinated and brominated compounds have very large and recognizable M+2 peaks. Fragments containing both isotopes of Br can be seen in the mass spectrum of ethyl bromide:

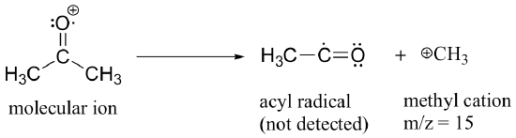


Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it is worthwhile to see a few representative examples, even if we don't attempt to understand the exact process by which the fragmentation occurs. We saw, for example, that the base peak in the mass spectrum of acetone is

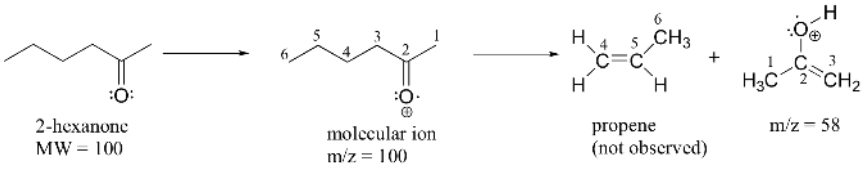
m/z = 43. This is the result of cleavage at the ‘alpha’ position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



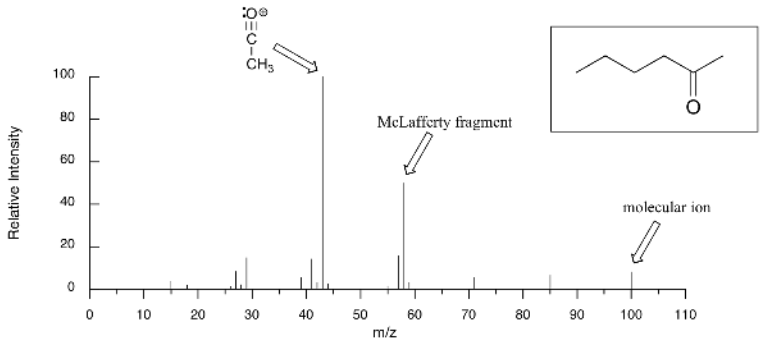
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



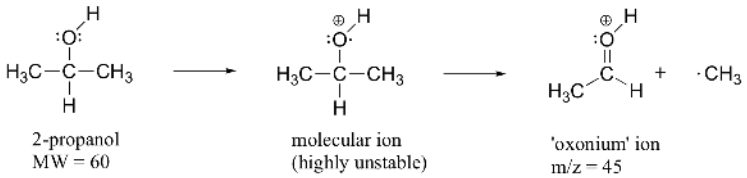
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

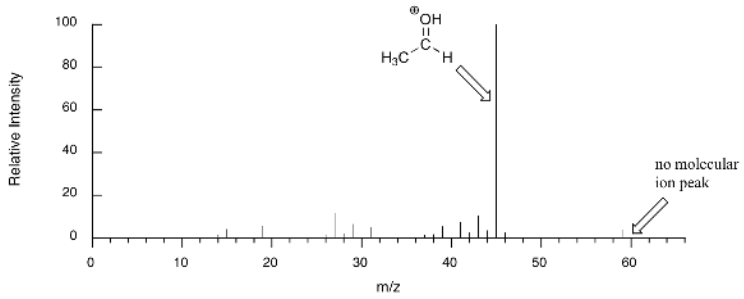


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



When alcohols are subjected to electron ionization MS, the molecular ion is highly unstable and thus a parent peak is often not detected. Often the base peak is from an ‘oxonium’ ion.





Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often 'put the puzzle together' and make some very confident predictions about the structure of the starting sample. You can see many more actual examples of mass spectra in the Spectral Database for Organic Compounds

? Exercise 4.2.1

Using the fragmentation patterns for acetone as a guide, predict the signals that you would find in the mass spectra of:

a) 2-butanone; b) 3-hexanone; c) cyclopentanone

? Exercise 4.2.1

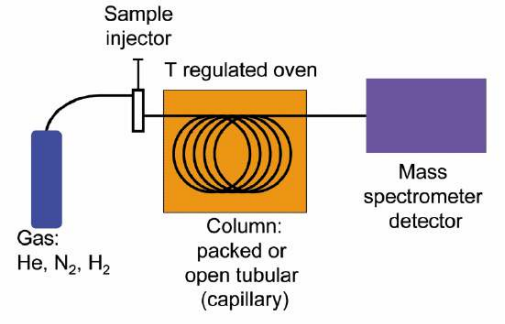
Predict some signals that you would expect to see in a mass spectrum of 2-chloropropane.

? Exercise 4.2.3

The mass spectrum of an aldehyde shows a parent peak at *m/z* = 58 and a base peak at *m/z* = 29. Propose a structure, and identify the two species whose *m/z* values were listed.

Gas Chromatography - Mass Spectrometry

Quite often, mass spectrometry is used in conjunction with a separation technique called gas chromatography (GC). The combined GC-MS procedure is very useful when dealing with a sample that is a mixture of two or more different compounds, because the various compounds are separated from one another before being subjected individually to MS analysis. We will not go into the details of gas chromatography here, although if you are taking an organic laboratory course you might well get a chance to try your hand at GC, and you will almost certainly be exposed to the conceptually analogous techniques of thin layer and column chromatography. Suffice it to say that in GC, a very small amount of a liquid sample is vaporized, injected into a long, coiled metal column, and pushed though the column by helium gas. Along the way, different compounds in the sample stick to the walls of the column to different extents, and thus travel at different speeds and emerge separately from the end of the column. In GC-MS, each purified compound is sent directly from the end of GC column into the MS instrument, so in the end we get a separate mass spectrum for each of the compounds in the original mixed sample. Because a compound's MS spectrum is a very reliable and reproducible 'fingerprint', we can instruct the instrument to search an MS database and identify each compound in the sample.



Gas chromatography-mass spectrometry (GC-MS) schematic

(Image from Wikipedia by K. Murray)

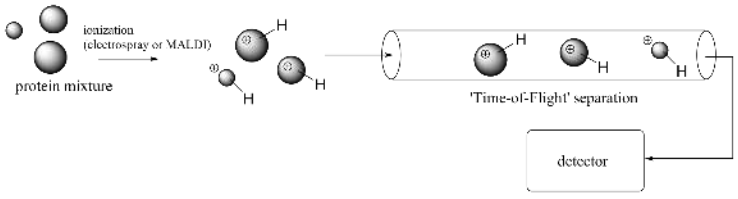
The extremely high sensitivity of modern GC-MS instrumentation makes it possible to detect and identify very small trace amounts of organic compounds. GC-MS is being used increasingly by environmental chemists to detect the presence of harmful organic contaminants in food and water samples. Airport security screeners also use high-speed GC-MS instruments to look for residue from bomb-making chemicals on checked luggage.

Mass spectrometry of proteins - applications in proteomics

Electron ionization mass spectrometry is generally not very useful for analyzing biomolecules: their high polarity makes it difficult to get them into the vapor phase, the first step in EIMS. Mass spectrometry of biomolecules has undergone a revolution over the past few decades, with many new ionization and separation techniques being developed. Generally, the strategy for biomolecule analysis involves **soft ionization**, in which much less energy (compared to techniques such as EIMS) is imparted to the molecule being analyzed during the ionization process. Usually, soft ionization involves adding protons rather than removing electrons: the cations formed in this way are significantly less energetic than the radical cations formed by removal of an electron. The result of soft ionization is that little or no fragmentation occurs, so the mass being measured is that of an intact molecule. Typically, large biomolecules are digested into smaller pieces using chemical or enzymatic methods, then their masses determined by 'soft' MS.

New developments in soft ionization MS technology have made it easier to detect and identify proteins that are present in very small quantities in biological samples. In **electrospray ionization** (ESI), the protein sample, in solution, is sprayed into a tube and the molecules are induced by an electric field to pick up extra protons from the solvent. Another common 'soft ionization' method is 'matrix-assisted laser desorption ionization' (**MALDI**). Here, the protein sample is adsorbed onto a solid matrix, and protonation is achieved with a laser.

Typically, both electrospray ionization and MALDI are used in conjunction with a time-of-flight (TOF) mass analyzer component.



The proteins are accelerated by an electrode through a column, and separation is achieved because lighter ions travel at greater velocity than heavier ions with the same overall charge. In this way, the many proteins in a complex biological sample (such as blood plasma, urine, etc.) can be separated and their individual masses determined very accurately. Modern protein MS is extremely sensitive – recently, scientists were even able to detect the presence of *Tyrannosaurus rex* protein in a fossilized skeleton! (Science **2007**, 316, 277).

Soft ionization mass spectrometry has become in recent years an increasingly important tool in the field of **proteomics**. Traditionally, protein biochemists tend to study the structure and function of individual proteins. Proteomics researchers, in contrast, want to learn more about how large numbers of proteins in a living system interact with each other, and how they respond to changes in the state of the organism. One important subfield of proteomics is the search for protein 'biomarkers' for human disease: in other words, proteins which are present in greater quantities in the tissues of a sick person than in a healthy person.

Detection in a healthy person of a known biomarker for a disease such as diabetes or cancer could provide doctors with an early warning that the patient may be especially susceptible to the disease, so that preventive measures could be taken to prevent or delay onset.

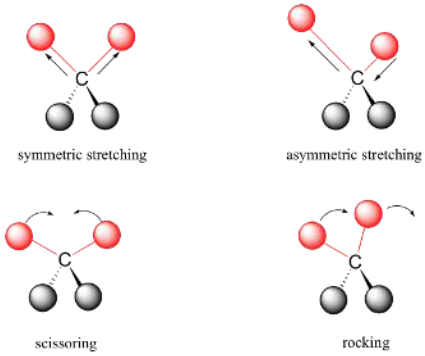
In a 2005 study, MALDI-TOF mass spectrometry was used to compare fluid samples from lung transplant recipients who had suffered from tissue rejection to samples from recipients who had not suffered rejection. Three peptides (short proteins) were found to be present at elevated levels specifically in the tissue rejection samples. It is hoped that these peptides might serve as biomarkers to identify patients who are at increased risk of rejecting their transplanted lungs. (Proteomics **2005**, 5, 1705).

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4.3: Infrared spectroscopy

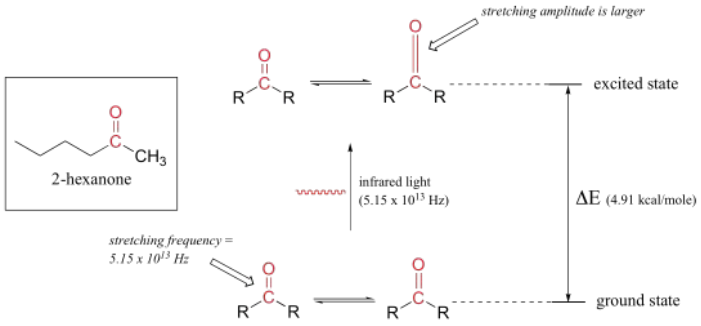
Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few of which are illustrated below.



The energy of molecular vibration is *quantized* rather than continuous, meaning that a molecule can only stretch and bend at certain 'allowed' frequencies. If a molecule is exposed to electromagnetic radiation that matches the frequency of one of its vibrational modes, it will in most cases absorb energy from the radiation and jump to a higher vibrational energy state - what this means is that the *amplitude* of the vibration will increase, but the vibrational *frequency* will remain the same. The difference in energy between the two vibrational states is equal to the energy associated with the wavelength of radiation that was absorbed. It turns out that it is the *infrared* region of the electromagnetic spectrum which contains frequencies corresponding to the vibrational frequencies of organic bonds.

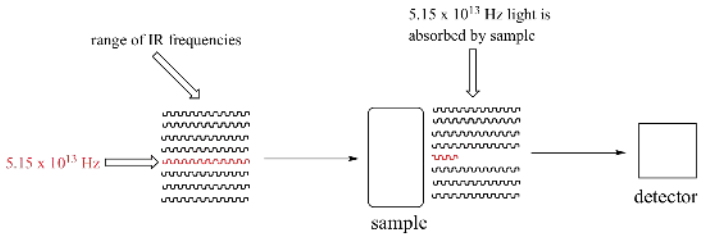
Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring that is constantly bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond. In the space of one second, the spring 'bounces' back and forth 5.15 x 10^{13} times - in other words, the ground-state frequency of carbonyl stretching for a the ketone group is about 5.15 x 10^{13} Hz.

If our ketone sample is irradiated with infrared light, the carbonyl bond will specifically absorb light with this same frequency, which by equations 4.1 and 4.2 corresponds to a wavelength of 5.83 x 10^{-6} m and an energy of 4.91 kcal/mol. When the carbonyl bond absorbs this energy, it jumps up to an excited vibrational state.



The value of **ΔE** - the energy difference between the low energy (ground) and high energy (excited) vibrational states - is equal to 4.91 kcal/mol, the same as the energy associated with the absorbed light frequency. The molecule does not remain in its excited vibrational state for very long, but quickly releases energy to the surrounding environment in form of heat, and returns to the ground state.

With an instrument called an infrared spectrophotometer, we can 'see' this vibrational transition. In the spectrophotometer, infrared light with frequencies ranging from about 10^{13} to 10^{14} Hz is passed though our sample of cyclohexane. Most frequencies pass right through the sample and are recorded by a detector on the other side.



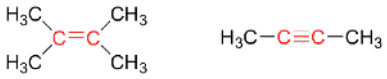
Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

The vibrations of a 2-hexanone molecule are not, of course, limited to the simple stretching of the carbonyl bond. The various carbon-carbon bonds also stretch and bend, as do the carbon-hydrogen bonds, and all of these vibrational modes also absorb different frequencies of infrared light.

The power of infrared spectroscopy arises from the observation that *different functional groups have different characteristic absorption frequencies*. The carbonyl bond in a ketone, as we saw with our 2-hexanone example, typically absorbs in the range of 5.11 - 5.18 x 10^{13} Hz, depending on the molecule. The carbon-carbon triple bond of an alkyne, on the other hand, absorbs in the range 6.30 - 6.80 x 10^{13} Hz. The technique is therefore very useful as a means of identifying which functional groups are present in a molecule of interest. If we pass infrared light through an unknown sample and find that it absorbs in the carbonyl frequency range but not in the alkyne range, we can infer that the molecule contains a carbonyl group but not an alkyne.

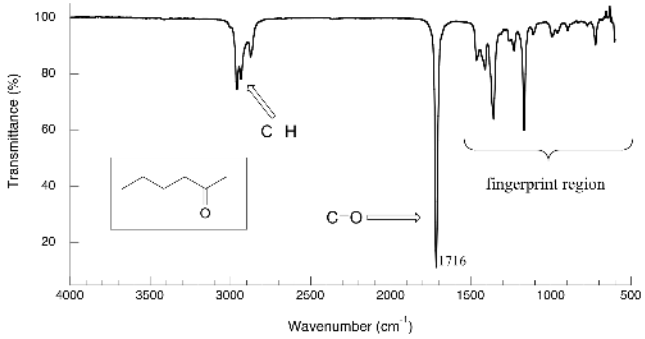
Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule*. Such vibrations are said to be **infrared active**. In general, the greater the polarity of the bond, the stronger its IR absorption. The carbonyl bond is very polar, and absorbs very strongly. The carbon-carbon triple bond in most alkynes, in contrast, is much less polar, and thus a stretching vibration does not result in a large change in the overall dipole moment of the molecule. Alkyne groups absorb rather weakly compared to carbonyls.

Some kinds of vibrations are **infrared inactive**. The stretching vibrations of completely symmetrical double and triple bonds, for example, do not result in a change in dipole moment, and therefore do not result in any absorption of light (but other bonds and vibrational modes in these molecules *do* absorb IR light).



infrared-inactive double and triple bonds

Now, let's look at some actual output from IR spectroscopy experiments. Below is the IR spectrum for 2-hexanone.



There are a number of things that need to be explained in order for you to understand what it is that we are looking at. On the horizontal axis we see IR wavelengths expressed in terms of a unit called **wavenumber** (cm^{-1}), which tells us how many waves fit into one centimeter. On the vertical axis we see '**% transmittance**', which tells us how strongly light was absorbed at each

frequency (100% transmittance means no absorption occurred at that frequency). The solid line traces the values of % transmittance for every wavelength – the 'peaks' (which are actually pointing down) show regions of strong absorption. For some reason, it is typical in IR spectroscopy to report wavenumber values rather than wavelength (in meters) or frequency (in Hz). The 'upside down' vertical axis, with absorbance peaks pointing down rather than up, is also a curious convention in IR spectroscopy. We wouldn't want to make things too easy for you!

Exercise 4.5

Express the wavenumber value of 3000 cm^{-1} in terms of wavelength (in meter units) frequency (in Hz), and associated energy (in kJ/mol).

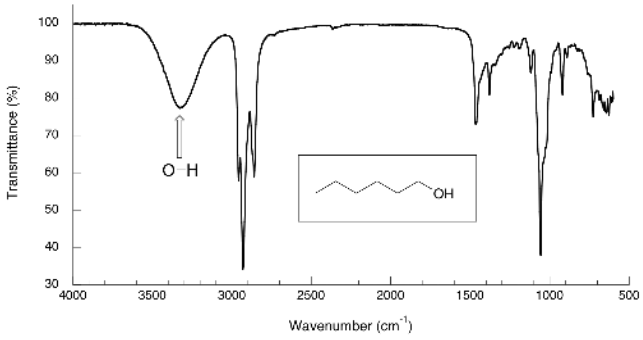
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The key absorption peak in this spectrum is that from the carbonyl double bond, at 1716 cm^{-1} (corresponding to a wavelength of 5.86 mm, a frequency of 5.15 x 10^{13} Hz, and a **Δ**E value of 4.91 kcal/mol). Notice how strong this peak is, relative to the others on the spectrum: *a strong peak in the 1650-1750 cm^{-1} region is a dead giveaway for the presence of a carbonyl group*. Within that range, carboxylic acids, esters, ketones, and aldehydes tend to absorb in the shorter wavelength end (1700-1750 cm-1), while conjugated unsaturated ketones and amides tend to absorb on the longer wavelength end (1650-1700 cm^{-1}).

The jagged peak at approximately 2900-3000 cm^{-1} is characteristic of tetrahedral carbon-hydrogen bonds. This peak is not terribly useful, as just about every organic molecule that you will have occasion to analyze has these bonds. Nevertheless, it can serve as a familiar reference point to orient yourself in a spectrum.

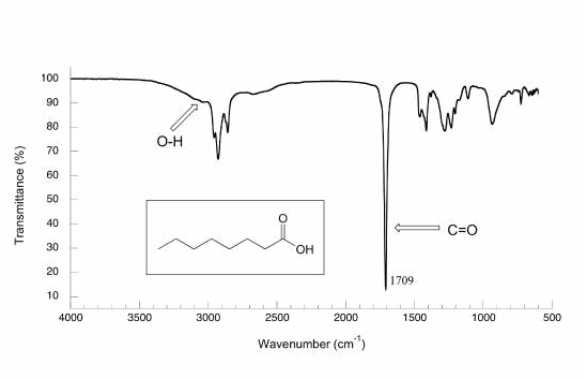
You will notice that there are many additional peaks in this spectrum in the longer-wavelength 400 -1400 cm^{-1} region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, nevertheless, contain valuable information. The reason for this is suggested by the name: just like a human fingerprint, the pattern of absorbance peaks in the fingerprint region is unique to every molecule, meaning that the data from an unknown sample can be compared to the IR spectra of known standards in order to make a positive identification. It was the IR fingerprint region of the suspicious yellow paint that allowed for its identification as a pigment that could not possibly have been used by the purported artist, William Aiken Walker.

Now, let's take a look at the IR spectrum for 1-hexanol.



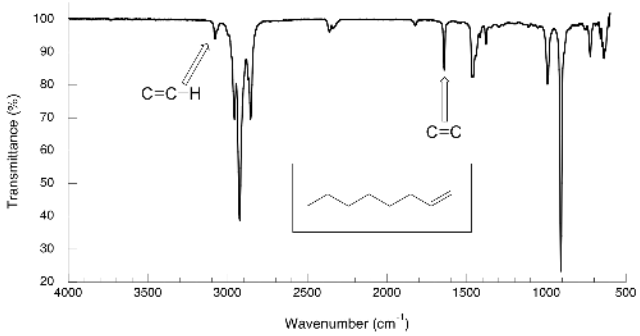
As you can see, the carbonyl peak is gone, and in its place is a very broad 'mountain' centered at about 3400 cm^{-1}. This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen bonding between molecules.

In the spectrum of octanoic acid we see, as expected, the characteristic carbonyl peak, this time at 1709 cm^{-1}.



We also see a low, broad absorbance band that looks like an alcohol, except that it is displaced slightly to the right (long-wavelength) side of the spectrum, causing it to overlap to some degree with the C-H region. This is the characteristic carboxylic acid O-H single bond stretching absorbance.

The spectrum for 1-octene shows two peaks that are characteristic of alkenes: the one at 1642 cm^{-1} is due to stretching of the carbon-carbon double bond, and the one at 3079 cm-1 is due to stretching of the s bond between the alkene carbons and their attached hydrogens.



Alkynes have characteristic IR absorbance peaks in the range of 2100-2250 cm^{-1} due to stretching of the carbon-carbon triple bond, and terminal alkenes can be identified by their absorbance at about 3300 cm-1, due to stretching of the bond between the sp-hybridized carbon and the terminal hydrogen.

You can see many more examples of IR spectra in the Spectral Database for Organic Compounds

? Exercise 4.6

Explain how you could use the C-C and C-H stretching frequencies in IR spectra to distinguish between four constitutional isomers: 1,2-dimethylcyclohexene, 1,3-octadiene, 3-octyne, and 1-octyne.

Exercise 4.7

Using the online Spectral Database for Organic Compounds, look up IR spectra for the following compounds, and identify absorbance bands corresponding to those listed in the table above. List actual frequencies for each signal to the nearest cm^{-1} unit, using the information in tables provided on the site.

a) 1-methylcyclohexanol

b) 4-methylcyclohexene

c) 1-hexyne

d) 2-hexyne

e) 3-hexyne-2,5-diol

Exercise 4.8

A carbon-carbon single bond absorbs in the fingerprint region, and we have already seen the characteristic absorption wavelengths of carbon-carbon double and triple bonds. Rationalize the trend in wavelengths. (*Hint* - remember, we are thinking of bonds as springs, and looking at the frequency at which they 'bounce').

Solutions

It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily recognized functional groups, which are summarized in table 1 in the tables section at the end of the text.

As you can imagine, obtaining an IR spectrum for a compound will not allow us to figure out the complete structure of even a simple molecule, unless we happen to have a reference spectrum for comparison. In conjunction with other analytical methods, however, IR spectroscopy can prove to be a very valuable tool, given the information it provides about the presence or absence of key functional groups. IR can also be a quick and convenient way for a chemist to check to see if a reaction has proceeded as planned. If we were to run a reaction in which we wished to convert cyclohexanone to cyclohexanol, for example, a quick comparison of the IR spectra of starting compound and product would tell us if we had successfully converted the ketone group to an alcohol (this type of reaction is discussed in detail in chapter 15.

Khan Academy video tutorials on infrared spectroscopy

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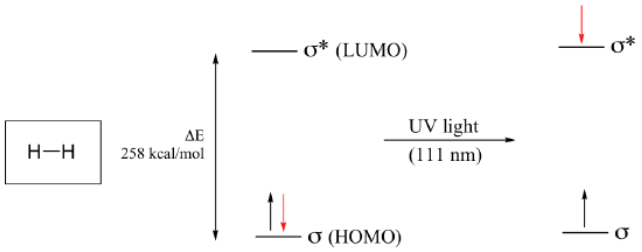
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4.4: Ultraviolet and visible spectroscopy

While interaction with infrared light causes molecules to undergo vibrational transitions, the shorter wavelength, higher energy radiation in the UV (200-400 nm) and visible (400-700 nm) range of the electromagnetic spectrum causes many organic molecules to undergo **electronic transitions**. What this means is that when the energy from UV or visible light is absorbed by a molecule, one of its electrons jumps from a lower energy to a higher energy molecular orbital.

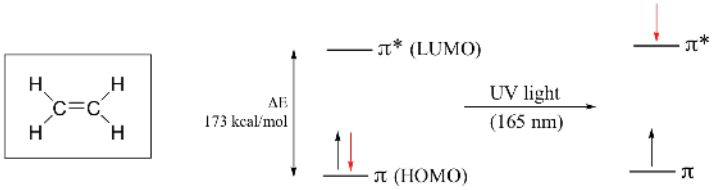
Electronic transitions

Let's take as our first example the simple case of molecular hydrogen, H_2. As you may recall from section 2.1A, the molecular orbital picture for the hydrogen molecule consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).



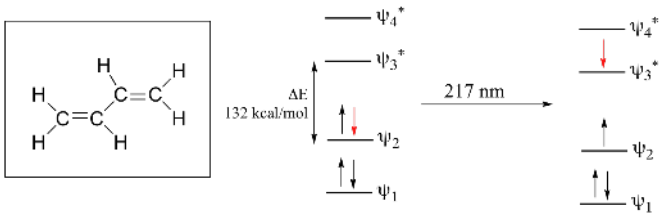
If the molecule is exposed to light of a wavelength with energy equal to **Δ**E, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. **Δ**E for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition.** Because π- π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.



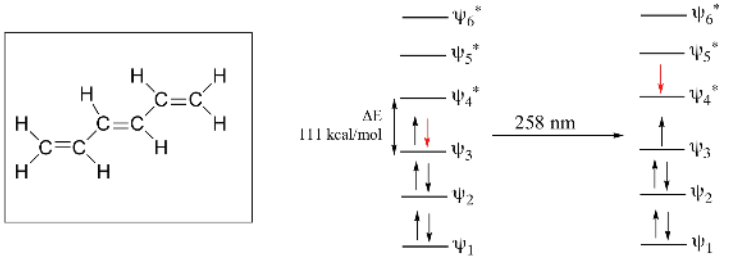
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with conjugated π systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

Let's revisit the MO picture for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are bonding, while the upper two are antibonding.

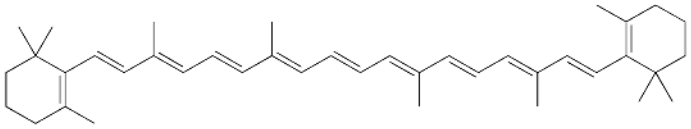


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **Δ**E of 111 kcal/mol.

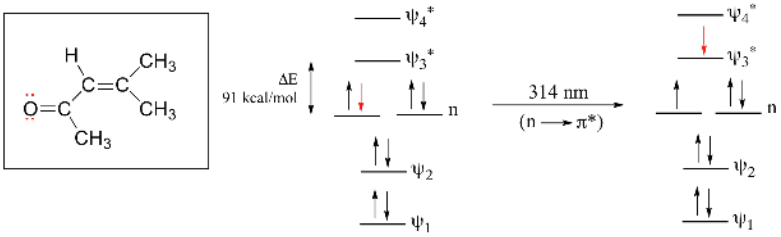


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



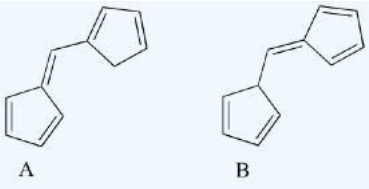
This is referred to as an **n - π* transition**. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n \rightarrow \pi^*$ transition is smaller that that of a π - π* transition – and thus the n - π* peak is at a longer wavelength. In general, n - π* transitions are weaker (less light absorbed) than those due to π - π* transitions.

? Exercise 4.9

What is the energy of the photons (in kJ/mol) of light with wavelength of 470 nm, the l_{max} of b-carotene?

Exercise 4.10

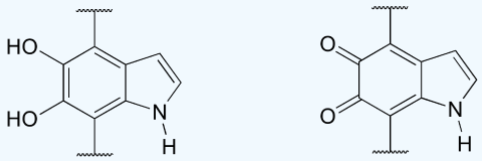
Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



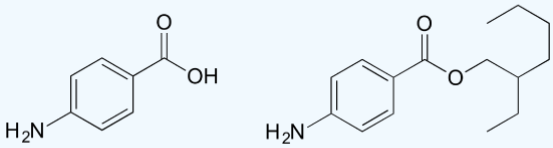
Solutions

Protecting yourself from sunburn

Human skin can be damaged by exposure to ultraviolet light from the sun. We naturally produce a pigment, called melanin, which protects the skin by absorbing much of the ultraviolet radiation. Melanin is a complex polymer, two of the most common monomers units of which are shown below.



common monomer units in melanin

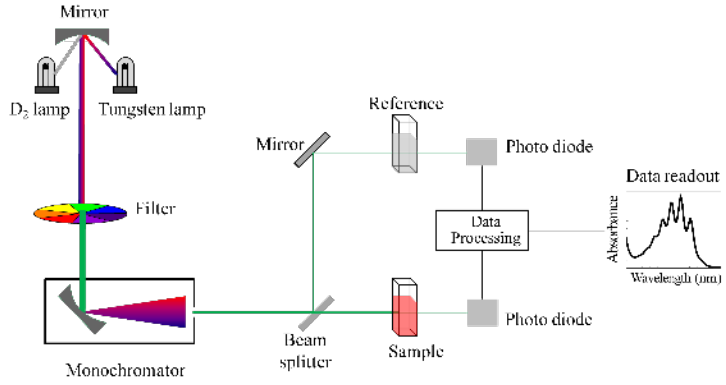


PABA Padimate-O

Overexposure to the sun is still dangerous, because there is a limit to how much radiation our melanin can absorb. Most commercial sunscreens claim to offer additional protection from both UV-A and UV-B radiation: UV-A refers to wavelengths between 315-400 nm, UV-B to shorter, more harmful wavelengths between 280-315 nm. PABA (*para*-aminobenzoic acid) was used in sunscreens in the past, but its relatively high polarity meant that it was not very soluble in oily lotions, and it tended to rinse away when swimming. Many sunscreens today contain, among other active ingredients, a more hydrophobic derivative of PABA called Padimate O.

Looking at UV-vis spectra

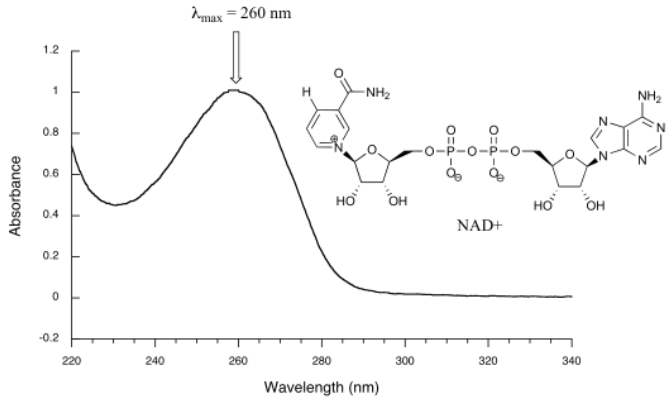
We have been talking in general terms about how molecules absorb UV and visible light – now let's look at some actual examples of data from a UV-vis absorbance spectrophotometer. The basic setup is the same as for IR spectroscopy: radiation with a range of wavelengths is directed through a sample of interest, and a detector records which wavelengths were absorbed and to what extent the absorption occurred.



Schematic for a UV-Vis spectrophotometer

(Image from Wikipedia Commons)

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



You'll notice that this UV spectrum is much simpler than the IR spectra we saw earlier: this one has only one peak, although many molecules have more than one. Notice also that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Peaks in UV spectra tend to be quite broad, often spanning well over 20 nm at half-maximal height. Typically, there are two things that we look for and record from a UV-Vis spectrum. The first is λ_{max}, which is the wavelength at maximal light absorbance. As you can see, NAD^+ has $\lambda_{max} = 260\ nm$. We also want to record how much light is absorbed at λ_{max}. Here we use a unitless number called **absorbance**, abbreviated 'A'. This contains the same information as the 'percent transmittance' number used in IR spectroscopy, just expressed in slightly different terms. To calculate absorbance at a given wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log \frac{I_0}{I} \tag{4.3.1}$$

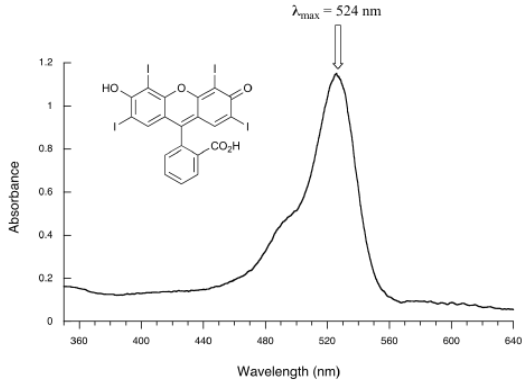
You can see that the absorbance value at 260 nm (A_{260}) is about 1.0 in this spectrum.

Exercise 4.11

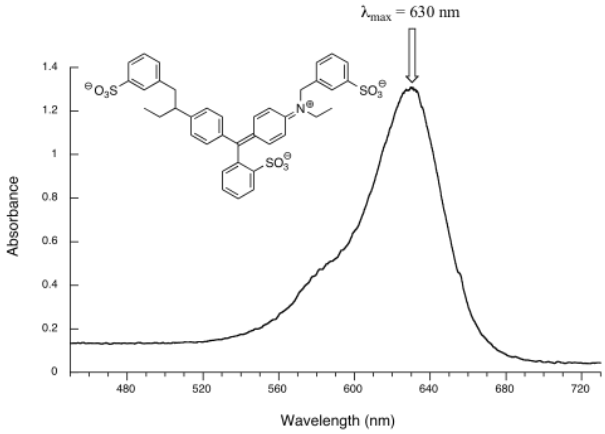
Express A = 1.0 in terms of percent transmittance (%T, the unit usually used in IR spectroscopy (and sometimes in UV-vis as well).

Solutions

Here is the absorbance spectrum of the common food coloring Red #3:



Here, we see that the extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes. Now, take a look at the spectrum of another food coloring, Blue #1:



Here, maximum absorbance is at 630 nm, in the orange range of the visible spectrum, and the compound appears blue.

Applications of UV spectroscopy in organic and biological chemistry

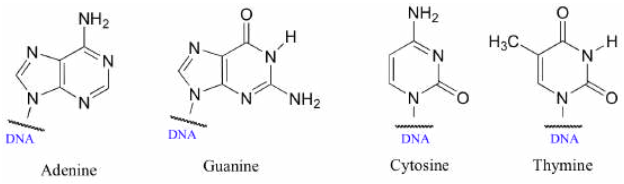
UV-vis spectroscopy has many different applications in organic and biological chemistry. One of the most basic of these applications is the use of the **Beer - Lambert Law** to determine the concentration of a chromophore. You most likely have performed a Beer – Lambert experiment in a previous chemistry lab. The law is simply an application of the observation that, within certain ranges, the absorbance of a chromophore at a given wavelength varies in a linear fashion with its concentration: the higher the concentration of the molecule, the greater its absorbance.

If we divide the observed value of A at λ_{max} by the concentration of the sample (*c*, in mol/L), we obtain the **molar absorptivity**, or **extinction coefficient** (**ε**), which is a characteristic value for a given compound.

$$\epsilon = \frac{A}{c} \tag{4.3.2}$$

The absorbance will also depend, of course, on the **path length** - in other words, the distance that the beam of light travels though the sample. In most cases, sample holders are designed so that the path length is equal to 1 cm, so the units for molar absorptivity are $L_* mol^{-1}{}_* cm^{-1}$. If we look up the value of e for our compound at λ_{max}, and we measure absorbance at this wavelength, we can easily calculate the concentration of our sample. As an example, for NAD^+ the literature value of ε at 260 nm is 18,000 $L_* mol^{-1}{}_* cm^{-1}$. In our NAD^+ spectrum we observed A_{260} = 1.0, so using equation 4.4 and solving for concentration we find that our sample is 5.6 x 10^{-5} M.

The bases of DNA and RNA are good chromophores:



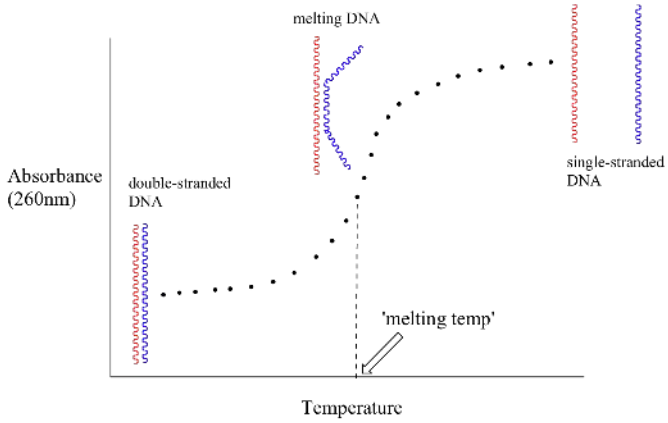
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 $ng^{-1} \times mL$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Exercise 4.12

50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?

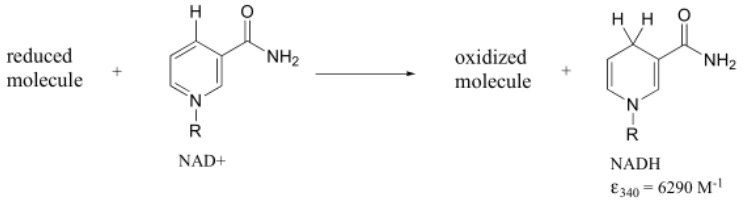
Solutions

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

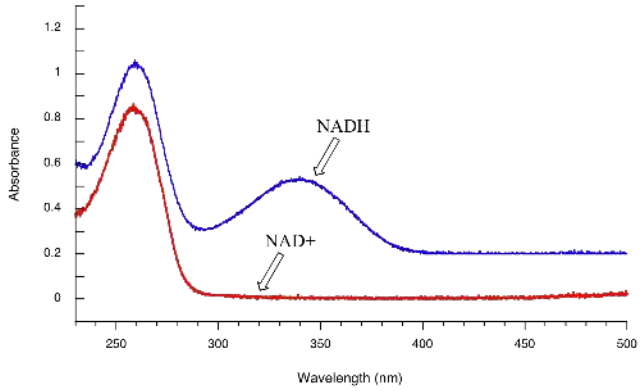


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

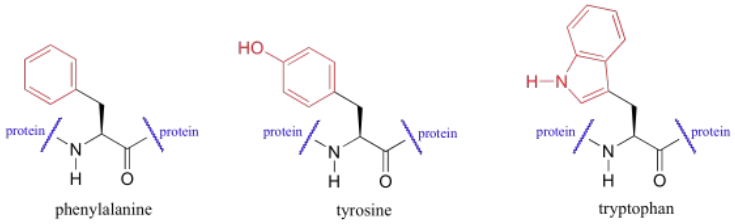


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L*mol^{-1}*cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:



By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

Khan Academy video tutorials on UV-Vis spectroscopy

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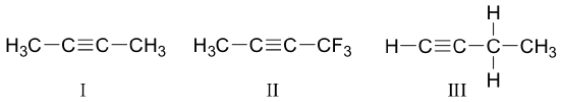
4.P: Problems for Chapter 4

link to Solution Manual

P4.1: Which represents a higher energy frequency of electromagnetic radiation, 1690 cm^{-1} or 3400 cm^{-1}? Express each of these in terms of wavelength (meters) and frequency (Hz).

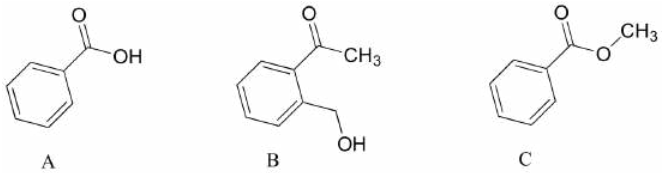
P4.2: Calculate the value, in kcal/mol, of the energy gap associated with a typical ketone carbonyl stretching transition at 1720 cm^{-1}.

P4.3: Explain how you could use IR spectroscopy to distinguish between compounds I, II, and III.



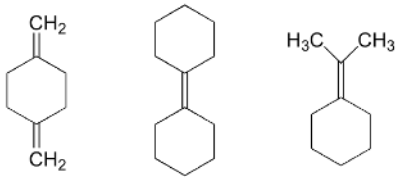
I II III

P4.4: Explain how you could use IR spectroscopy to distinguish between compounds A, B, and C.



A B C

P4.5: Explain how you could use IR spectroscopy to distinguish between compounds X, Y, and Z.

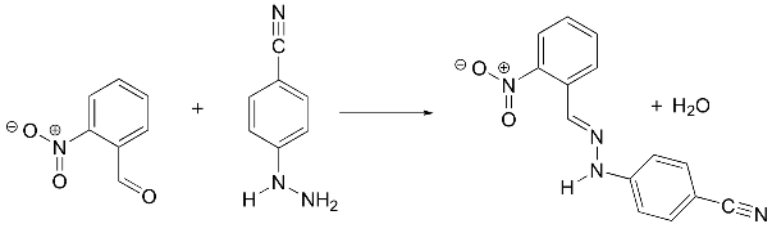


X Y Z

P4.6: A 0.725 mL aqueous solution of NADH shows an absorbance at 340 nm of 0.257. Express (in nanamole (nm) units) how much NADH is contained in the sample.

P4.7: A 1 mL enzymatic reaction mixture contains NADH as one of the reactants, and has a starting A_{340} = 0.345. After the reaction is allowed to run for five minutes, the researcher records a value of A_{340} = 0.125. How many nm of NADH are used up per minute, on average, in this reaction?

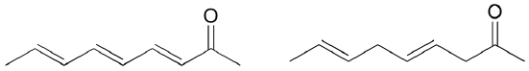
P4.8: The reaction below is of a type that we will study in Chapter 11. While the two starting materials are only slightly colored, the product is an intense orange-red. Account for this observation.



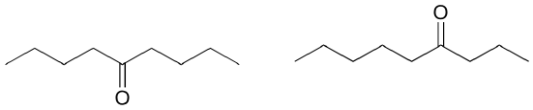
P4.9: Predict five fragments that you would expect to be evident in the mass spectrum of 3-methyl-2-pentanone.

P4.10: One would expect the mass spectrum of cyclohexanone to show a molecular ion peak at m/z = 98. However, the m/z = 98 peak in the cyclohexanone spectrum is unusually tall, compared to the molecular ion peaks in the mass spectra of other ketones such as 2-hexanone or 3-hexanone. Explain.

P4.11: Which would be more useful in distinguishing the two compounds shown below: IR or UV spectroscopy? Explain.



P4.12: Which analytical technique – IR, UV, or MS - could best be used to distinguish between the two compounds below? Explain.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

5: Structure Determination II - Nuclear Magnetic Resonance Spectroscopy

In the previous chapter, we learned about three important analytical techniques which allow us to deduce information about the structure of an organic molecule. In IR spectroscopy, transitions in the vibrational states of covalent bonds lead to the absorbance of specific infrared frequencies, telling us about the presence or absence of functional groups in the molecule of interest. In UV-Vis spectroscopy, transitions in the energy levels of electrons in pi bonds lead to the absorbance of ultraviolet and visible light, providing us with information about the arrangement of double bonds in a molecule. And in mass spectrometry, we are usually able to learn the molecular weight of a sample molecule, in addition to other kinds of information from analysis of the masses of molecular fragments.

Although all three of these techniques provide us with valuable information about a molecule of interest, in most cases they do not – even in combination – tell us what we, as organic chemists, most want to know about our molecule. Specifically, these techniques do not allow us to determine its overall molecular structure – the framework, in other words, of its carbon-carbon and carbon-hydrogen bonds. It is this information that we need to have in order to be able to draw a Lewis structure of our molecule, and it is this information that is provided by an immensely powerful analytical technique called nuclear magnetic resonance (NMR) spectroscopy.

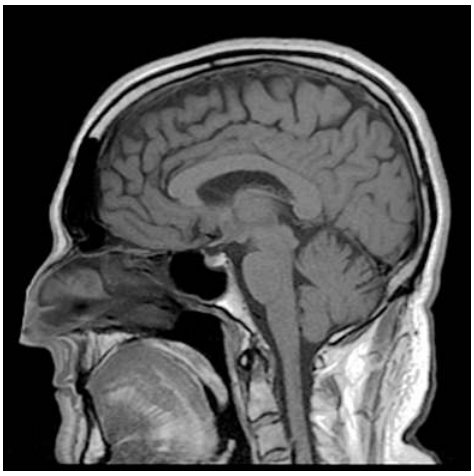
In NMR, the nuclei of hydrogen, carbon, and other important elements undergo transitions in their magnetic states, leading to the absorbance of radiation in the radio frequency range of the electromagnetic spectrum. By analyzing the signals from these transitions, we learn about the chemical environment that each atom inhabits, including information about the presence of neighboring atoms. In this chapter, we will see how information from NMR, especially when combined with data from IR, UV-Vis, and MS experiments, can make it possible for us to form a complete picture of the atom-to-atom framework of an organic molecule.

5.0: Prelude to Structure Determination
5.1: The Origin of the NMR Signal
5.2: Chemical Equivalence
5.3: The 1H-NMR experiment
5.4: The Basis for Differences in Chemical Shift
5.5: Spin-Spin Coupling
5.6: 13C-NMR Spectroscopy
5.7: Solving Unknown Structures
5.8: Complex Coupling in Proton Spectra
5.9: Other Applications of NMR
5.E: Structure Determination (Exercises)
5.S: Structure Determination (Summary)

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5.0: Prelude to Structure Determination

One morning in a suburb of Edinburgh, Scotland, an active, athletic teenager named Charli found that she did not have her usual appetite for breakfast. She figured she was just feeling a little under the weather, and was not to worried. But as the days passed, her appetite did not return. Before long, she stopped eating lunch as well, and eventually she was hardly eating anything at all. She had to withdraw from her soccer team because she didn't have enough energy to make it through the practices. When her weight began to drop alarmingly and she began to suffer from crippling headaches, her parents took her to her doctor, who diagnosed a glandular disorder.



To make things worse, Charli started getting teased at her school, enduring constant comments from other kids about her weight loss and gossip about an eating disorder. Almost two years went by, filled with doctors visits and various diagnoses and treatments, none of which were effective.

Finally, on a September day when Charli was fifteen, things came to a head. She was rushed to the hospital after suffering a massive stroke. Once she was stabilized, her doctors ordered an MRI scan of her brain. The images showed that she had a large tumor in her brain – it was benign, but its sheer size and the pressure it exerted had been enough to cause the devastating symptoms that Charli had been suffering for the past year and a half. Her doctors told her that if the tumor had not been detected, it could eventually have been fatal. After enduring an 8-hour brain surgery, Charli finally was able to start down her road to recovery. Speaking later to a journalist, Charli said of her stroke, “it was the best thing that ever happened to me”.

In Austin, Texas, a 28 year-old man named Alex was fed up with the back pain he had been suffering, the result, he assumed, of the damage from some old sports injuries catching up to him. His friend John, who was a radiological technician, convinced him to come in for an MRI scan on the chance that doctors might be able to spot something that could lead to a treatment. Alex agreed, and took a day off work to come in to his friend's clinic. With John at the controls, Alex tried to relax as he was slowly rolled into the claustrophobic MRI chamber. After finishing the scan of his friend's back and saving the images, John decided to ask a little favor. He had just installed some new software for head scans and needed to test it out on an actual subject, so he asked Alex if he would mind lying still for just a few minutes more so that he could take a test scan of his head. Unlike x-rays and CAT scans, the MRI procedure does not subject patients to potentially harmful radiation - just strong but harmless magnetic fields combined with radio waves – so there was no risk to undergoing an unnecessary scan. Alex agreed, and John proceeded with the test scan.

When the first image appeared, John was alarmed by what he saw. The new software was working just fine, but there was an ominous-looking lump behind Alex's right eye that should not have been there. Not wanted to scare his friend unduly, he merely mentioned that he thought he might have seen something that should be checked out by a neurologist. Alex was feeling fine other than the back pain – no headaches, blurred vision, or dizziness, so it was probably nothing at all to worry about.

It turned out that Alex had a golf ball-sized brain tumor. His neurologist told him that because it happened to be located in an area of the brain that was not responsible for any critical functions, he was not yet experiencing any symptoms. But if the tumor had remained undetected for a few more years, it would have continued to grow and begun to press on other areas of Alex's brain - and at that point, it probably would have been very difficult to remove safely.

Alex underwent a successful surgery to remove the tumor and was able to go on with his life, thanks to having an observant friend in the right place at the right time, with access to a powerful diagnostic technology.

The common denominator in these two stories – and in countless others from around the world – is the power of MRI to detect hidden but deadly medical problems, without causing any harm or pain to the patient. In this chapter, we are going to learn about an analytical tool used by organic chemists called nuclear magnetic resonance (NMR) spectroscopy, which works by the same principles as an MRI scanner in a hospital. While doctors use MRI peer inside the human body, we will see how NMR allows chemists to piece together, atom by atom and bond by bond, the structure of an organic molecule.

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5.1: The Origin of the NMR Signal

The Magnetic Moment

Nuclear magnetic resonance spectroscopy is an incredibly powerful tool for organic chemists because it allows us to analyze the connectivity of carbon and hydrogen atoms in molecules. The basis for NMR is the observation that many atomic nuclei generate their own magnetic field, or magnetic moment, as they spin about their axes. Not all nuclei have a magnetic moment. Fortunately for organic chemists, though, hydrogen (^1H), the ^{13}C isotope of carbon, the ^{19}F isotope of fluorine, and the ^{31}P isotope of phosphorus all have magnetic moments and therefore can be observed by NMR – they are, in other words, NMR-active. Other nuclei - such as the common ^{12}C and ^{16}O isotopes of carbon and oxygen - do not have magnetic moments, and cannot be directly observed by NMR. Still other nuclei such as the hydrogen isotope deuterium (^2H) and nitrogen (^{14}N) have magnetic moments and are NMR-active, but the nature of their magnetic moments is such that analysis of these nuclei by NMR is more complex.

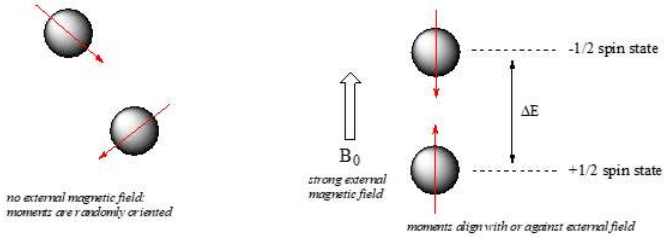
In practice it is ^1H and ^{13}C nuclei that are most commonly observed by NMR spectroscopy, and it is on those techniques that we will focus in this chapter, beginning with ^1H-NMR. The terms ‘proton’ and ‘hydrogen’ are used interchangeably when discussing because the ^1H nucleus is just a single proton.

Table 5.2.1 : Some examples of magnetic and nonmagnetic nuclei relevant to biological organic chemistry.

Magnetic Nuclei	Nonmagnetic Nuclei
^1H	^{12}C
^2H	^{16}O
^{13}C	^{32}S
^{14}N	
^{19}F	
$^{3}1P$	

Spin States and the Magnetic Transition

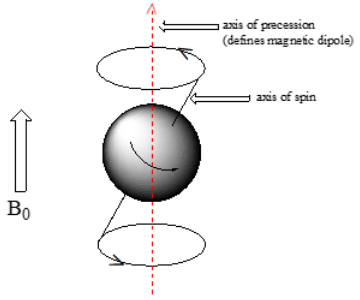
When a sample of an organic compound is sitting in a flask on a laboratory bench, the magnetic moments of all of its protons are randomly oriented. However, when the same sample is placed within the field of a very strong superconducting magnet (this field is referred to by NMR spectroscopists as the applied field, abbreviated B_0) each proton will assume one of two possible quantum spin states. In the +½ spin state, the proton's magnetic moment is aligned with the direction of B_0, while in the -½ spin state it is aligned opposed to the direction of B_0.



+½ spin state is slightly lower in energy than the -½ state, and the energy gap between them, which we will call ΔE, depends upon the strength of B_0: a stronger applied field results in a larger ΔE. For a large population of organic molecules in an applied field, slightly more than half of the protons will occupy the lower energy +½ spin state, while slightly less than half will occupy the higher energy -½ spin state. It is this population difference (between the two spin states) that is exploited by NMR, and the difference increases with the strength of the applied magnetic field.

At this point, we need to look a little more closely at how a proton spins in an applied magnetic field. You may recall playing with spinning tops as a child. When a top slows down a little and the spin axis is no longer completely vertical, it begins to exhibit precessional motion, as the spin axis rotates slowly around the vertical. In the same way, hydrogen atoms spinning in an applied

magnetic field also exhibit precessional motion about a vertical axis. It is this axis (which is either parallel or antiparallel to B_0) that defines the proton's magnetic moment.

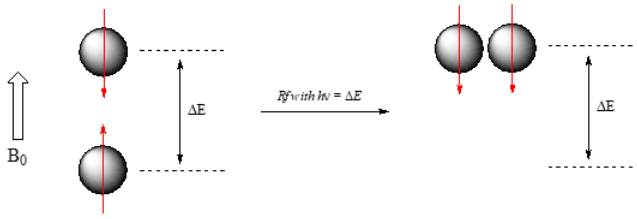


Watch the first minute or so of this video of spinning tops: look for the precessional motion

The frequency of precession (also called the Larmour frequency, abbreviated ν_L) is simply the number of times per second that the proton precesses in a complete circle. A proton`s precessional frequency increases with the strength of B_0.

If a proton that is precessing in an applied magnetic field is exposed to electromagnetic radiation of a frequency νthat matches its precessional frequency ν_L, we have a condition called resonance. In the resonance condition, a proton in the lower-energy +½ spin state (aligned with B_0) will transition (flip) to the higher energy –½ spin state (opposed to B_0). In doing so, it will absorb radiation at this resonance frequency n - and this frequency corresponds to ΔE,

the energy difference between the proton's two spin states. With the strong magnetic fields generated by the superconducting magnets used in modern NMR instruments, the resonance frequency for protons falls within the radio-wave range, anywhere from 100 MHz to 800 MHz depending on the strength of the magnet.



Think back for a moment to the other two spectroscopic techniques we have learned about: IR and UV-Vis spectroscopy. Recall from section 4.2 that photons of electromagnetic radiation of a given frequency correspond to energy (E) given by $E = h\nu$, where h is Plank's constant and n is the frequency in waves per second, or Hz. Recall also from section 4.3 that the energy gap between vibrational states corresponds to the energy associated with infrared radiation, and from section 4.4 that the energy gap between electronic states in conjugated p-bonding systems corresponds to the energy associated with light in the ultraviolet and visible regions of the electromagnetic spectrum. Now, we know that in NMR, the energy gap ΔE between the +½ and -½ spin states of an atomic nucleus in a strong magnetic field corresponds to the energy associated with radiation in the radio frequency (Rf) region of the spectrum.

By detecting the frequency of Rf radiation that is absorbed, we can gain information about the chemical environment of protons in an organic molecule.

? Exercise 5.2.1

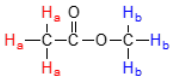
In a general sense, how big is the energy gap for the nuclear spin transition observed in NMR compared to the energy gap for the vibrational transition observed in IR spectroscopy? Much bigger? Much smaller? Slightly bigger or smaller? About the same? How can you tell from the information presented in this section?

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5.2: Chemical Equivalence

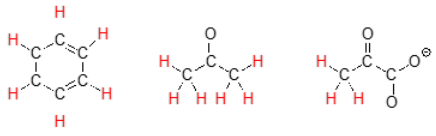
The frequency of radiation absorbed by a proton (or any other nucleus) during a spin transition in an NMR experiment is called its 'resonance frequency'. If all protons in all organic molecules had the same resonance frequency, NMR spectroscopy but would not be terribly useful for chemists. Fortunately for us, however, resonance frequencies are not uniform for different protons in a molecule - rather, the resonance frequency varies according to the electronic environment that a given proton inhabits. In methyl acetate, for example, there are two distinct ‘sets’ of protons.



methyl acetate

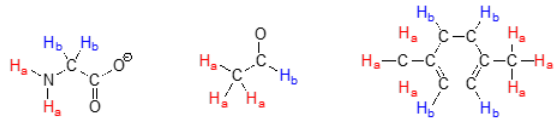
The three methyl acetate protons labeled Ha above have a different resonance frequency compared to the three Hb protons, because the two sets of protons are in non-identical electronic environments: the H_a protons are on a carbon next to a carbonyl carbon, while the H_b protons or on a carbon next to the an oxygen. In the terminology of NMR, all three H_a protons are chemically equivalent to each other, as are all three H_b protons. The H_a protons are, however, chemically nonequivalent to the H_b protons. As a consequence, the resonance frequency of the H_a protons is different from that of the H_b protons. For now, do not worry about why the different electronic environment gives rise to different resonance frequencies - we will get to that soon.

The ability to recognize chemical equivalancy and nonequivalency among atoms in a molecule will be central to understanding NMR. Each of the molecules below contains only one set of chemically equivalent protons: all six protons on benzene, for example, are equivalent to each other and have the same resonance frequency in an NMR experiment. Notice that any description of the bonding and position of one proton in benzene applies to all five other protons as well.



benzene acetone pyruvate

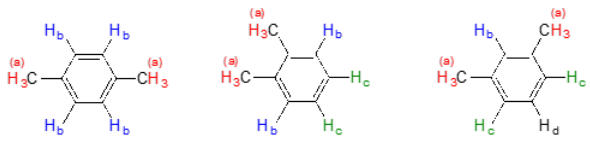
Each of the molecules in the next figure contains two sets of chemically equivalent protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



glycine acetaldehyde 1,4-dimethylbenzene

Take acetaldehyde as an example: a description of the bonding and position of the H_b proton does not apply to the three H_a protons: H_b is bonded to an sp^2-hybridized carbonyl carbon while the H_a protons are bonded to an sp^3-hybridized methyl carbon.

Note that while all four aromatic protons in 1,4-dimethylbenzene are chemically equivalent, its constitutional isomer 1,2 dimethylbenzene has two sets of aromatic protons in addition to the six methyl (H_a) protons. The 1,3-substituted isomer, on the other hand, has three sets of aromatic protons.

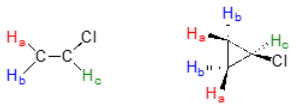


1,4-dimethylbenzene 1,2-dimethylbenzene 1,3-dimethylbenzene

In 1,2-dimethylbenzene, both H_b protons are adjacent to a methyl substituent, while both H_c protons are two carbons away. In 1,3-dimethylbenzene, H_b is situated between two methyl groups, the two H_c protons are one carbon away from a methyl group, and H_d is two carbons away from a methyl group.

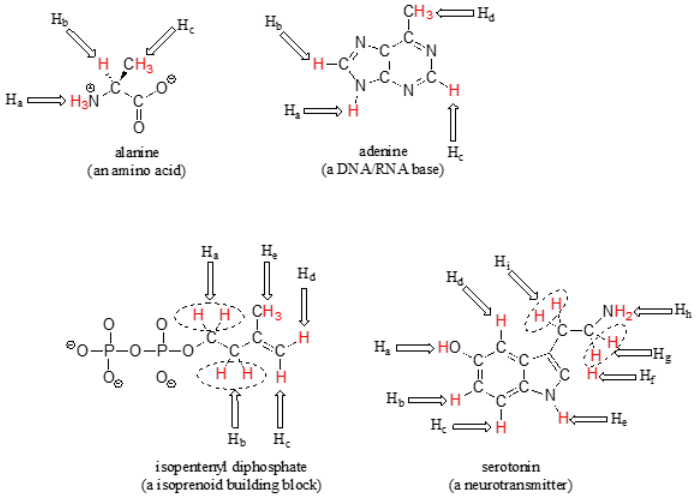
As you have probably already realized, chemical equivalence or non-equivalence in NMR is closely related to symmetry. Different planes of symmetry in the three isomers of dimethylbenzene lead to different patterns of equivalence.

Stereochemistry can play a part in determining equivalence or nonequivalence of nuclei in NMR. In the chloroethene (commonly known as vinyl chloride, the compound used to make polyvinyl chloride or PVC), H_a and H_b are in nonequivalent electronic environments, because H_a is *cis* to the chlorine atom while Hb is trans. Likewise, Ha and Hb in chlorocyclopropane are nonequivalent due to their positions either on the same or opposite side of the ring relative to chlorine.



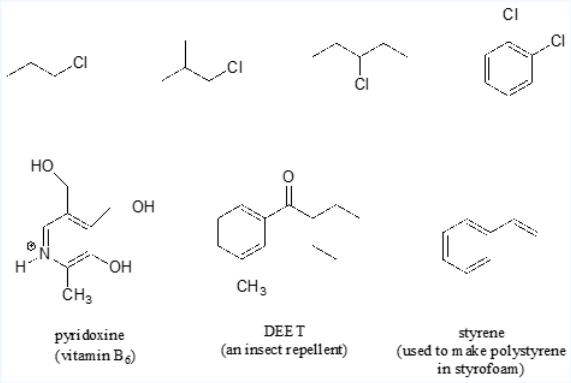
If you think back to our discussion of prochirality in section 3.11, you should recognize that the H_a and H_b protons in the examples above are diastereotopic pairs.

Most organic molecules have several sets of protons in different chemical environments, and each set will have a different resonance frequency in ^1H-NMR spectroscopy. Below we see some examples of multiple sets of protons in biological molecules.



? Exercise 5.3.1

How many sets of equivalent protons do the following molecules contain?

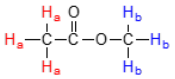


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5.3: The 1H-NMR experiment

In an NMR experiment, a sample compound (we'll again use methyl acetate as our example) is placed inside a very strong applied magnetic field (B_0) generated by a superconducting magnet in the instrument. (The magnetic fields generated by modern NMR instruments are strong enough that users must take care to avoid carrying any magnetics objects anywhere near them. They are also notorious for erasing the magnetic strips on credit cards!)



methyl acetate

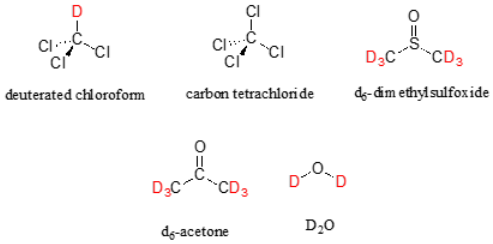
At first, the magnetic moments of (slightly more than) half of the protons in the sample are aligned with B_0, and half are aligned against B_0. Then, the sample is exposed to a range of radio frequencies. Out of all of the frequencies which hit the sample, only two - the resonance frequencies for H_a and H_b - are absorbed, causing those protons which are aligned with B_0 to 'spin flip' so that they align themselves against B0. When the 'flipped' protons flip back down to their ground state, they emit energy, again in the form of radio-frequency radiation. The NMR instrument detects and records the frequency and intensity of this radiation, making using of a mathematical technique known as a 'Fourier Transform'.

Note

The above description of an NMR experiment is an oversimplification of what is happening in a modern NMR instrument, but is adequate for our purpose here. If you take a more advanced course in molecular spectroscopy you will learn about the process is much greater detail.

In most cases, a sample being analyzed by NMR is in solution. If we use a common laboratory solvent (diethyl ether, acetone, dichloromethane, ethanol, water, etc.) to dissolve our NMR sample, however, we run into a problem – there many more solvent protons in solution than there are sample protons, so the signals from the sample protons will be overwhelmed. To get around this problem, we use special NMR solvents in which all protons have been replaced by deuterium. Deuterium is NMR-active, but its resonance frequency is far outside of the range in which protons absorb, so it is `invisible` in 1H-NMR. Some common NMR solvents are shown below.

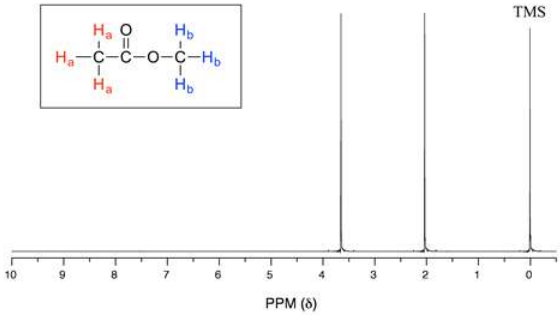
Common NMR solvents



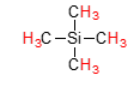
deuterated chloroform | carbon tetrachloride | d_6-dimethylsulfoxide

d_6-acetone | D_2O

Let's look at an actual ^1H-NMR spectrum for methyl acetate. Just as in IR and UV-vis spectroscopy, the vertical axis corresponds to intensity of absorbance, the horizontal axis to frequency. However, you will notice right away that a) there is no y-axis line or units drawn in the figure, and b) the x-axis units are not Hz, which you would expect for a frequency scale. Both of these mysteries will become clear very soon.



We see three absorbance signals: two of these correspond to H_a and H_b (don't worry yet which is which), while the peak at the far right of the spectrum corresponds to the 12 chemically equivalent protons in tetramethylsilane (TMS), a standard reference compound that was added to our sample.



tetramethylsilane (TMS)

First, let's talk about the x-axis. The 'ppm' label stands for 'parts per million', and simply tells us that the two sets of equivalent protons in our methyl acetate sample have resonance frequencies about 2.0 and 3.6 parts per million higher than the resonance frequency of the TMS protons, which we are using as our reference standard. This is referred to as their chemical shift.

The reason for using a relative value (chemical shift expressed in ppm) rather than the actual resonance frequency (expressed in Hz) is that every NMR instrument will have a different magnetic field strength, so the actual value of resonance frequencies expressed in Hz will be different on different instruments - remember that DE for the magnetic transition of a nucleus depends upon the strength of the externally applied magnetic field. However, the resonance frequency values relative to the TMS standard will always be the same, regardless of the strength of the applied field. For example, if the resonance frequency for the TMS protons in a given NMR instrument is exactly 300 MHz (300 million Hz), then a chemical shift of 2.0 ppm corresponds to an actual resonance frequency of 300,000,600 Hz (2 parts per million of 300 million is 600). In another instrument (with a stronger magnet) where the resonance frequency for TMS protons is 400 MHz, a chemical shift of 2.0 ppm corresponds to a resonance frequency of 400,000,800 Hz.

A frequently used symbolic designation for chemical shift in ppm is the lower-case Greek letter δ (delta). Most protons in organic compounds have chemical shift values between 0 and 10 ppm relative to TMS, although values below 0 ppm and up to 12 ppm and above are occasionally observed. By convention, the left-hand side of an NMR spectrum (higher chemical shift) is called downfield, and the right-hand direction is called upfield.

In modern research-grade NMR instruments, it is no longer necessary to actually add TMS to the sample: the computer simply calculates where the TMS signal should be, based on resonance frequencies of the solvent. So, from now on you will not see a TMS peak on NMR spectra - but the 0 ppm point on the x-axis will always be defined as the resonance frequency of TMS protons.

A Chemical Shift Analogy

If you are having trouble understanding the concept of chemical shift and why it is used in NMR, try this analogy: imagine that you have a job where you travel frequently to various planets, each of which has a different gravitational field strength. Although your body mass remains constant, your measured weight is variable - the same scale may show that you weigh 60 kg on one planet, and 75 kg on another. You want to be able to keep track your body mass in a meaningful, reproducible way, so you choose an object to use as a standard: a heavy iron bar, for example. You record the weight of the iron bar and yourself

on your home planet, and find that the iron bar weighs 50 kg and you weigh 60 kg. You are 20 percent (or pph, parts per hundred) heavier than the bar. The next day you travel (with the iron bar in your suitcase) to another planet and find that the bar weighs 62.5 kg, and you weigh 75 kg. Although your measured weight is different, you are still 20% heavier than the bar: you have a 'weight shift' of 20 pph relative to the iron bar, no matter what planet you are on.

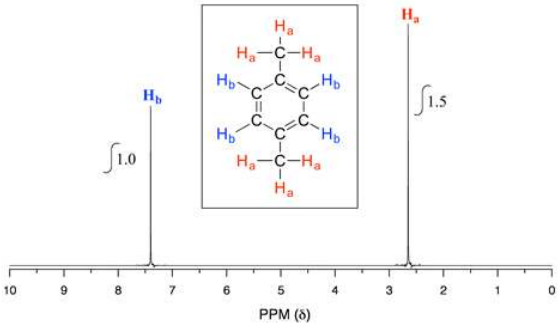
? Exercise 5.4.1

a. What is the chemical shift, expressed in Hz, of proton signals at 2.0 ppm and 3.6 ppm for an NMR instrument in which the TMS protons have a resonance frequency of exactly 500 MHz?
b. What is the actual resonance frequency (in Hz) of these two protons in that same instrument?

We have already pointed out that, on our spectrum of methyl acetate, there is there is no y-axis scale indicated. With y-axis data it is relative values, rather than absolute values, that are important in NMR. The computer in an NMR instrument can be instructed to mathematically integrate the area under a signal or group of signals. The signal integration process is very useful, because in ^1H-NMR spectroscopy the area under a signal is proportional to the number of protons to which the signal corresponds. When we instruct the computer to integrate the areas under the H_a and H_b signals in our methyl acetate spectrum, we find that they have approximately the same area. This makes sense, because each signal corresponds to a set of three equivalent protons.

Be careful not to assume that you can correlate apparent peak height to number of protons - depending on the spectrum, relative peak heights will not always be the same as relative peak areas, and it is the relative areas that are meaningful. Because it is difficult to compare relative peak area by eye, we rely on the instrument's computer to do the calculations.

Take a look next at the spectrum of 1,4-dimethylbenzene:



As we discussed earlier, this molecule has two sets of equivalent protons: the six methyl (H_a) protons and the four aromatic (H_b) protons. When we instruct the instrument to integrate the areas under the two signals, we find that the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at 7.4 ppm. The ratio 1.5 to 1 is of course the same as the ratio 6 to 4. This integration information (along with the actual chemical shift values, which we'll discuss soon) tells us that the peak at 7.4 ppm must correspond to H_b, and the peak at 2.6 ppm to H_a.

The integration function can also be used to determine the relative amounts of two or more compounds in a mixed sample. If we take a ^1H-NMR spectrum of a sample that is a equimolar mixture of benzene and acetone, for example, we will see two signals, one for the six equivalent acetone protons and one for the six equivalent benzene protons. The integrated area under the acetone signal will be the same as the area under the benzene sample, because both signals represent six protons. If we have an equimolar mixture of acetone and cyclopentane, on the other hand, the ratio of the acetone peak area to the cylopentane peak area will be 3:5 (or 6:10), because the cyclopentane signal represents ten protons.

Exercise 5.4.2

You take a 1H-NMR spectrum of a mixed sample of acetone and dichloromethane. The integral ratio of the two signals (acetone to dichloromethane) is 2.3 to 1. What is the molar ratio of the two compounds in the sample?

Exercise 5.4.3

You take the 1H-NMR spectrum of a mixed sample of 36% 1,4-dimethylbenzene and 64% acetone (these are mole percentages). What is the expected integration ratio of the signals that you would observe? Order the ratio from highest to lowest numbers.

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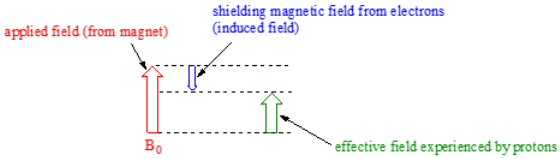
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5.4: The Basis for Differences in Chemical Shift

Diamagnetic shielding and deshielding

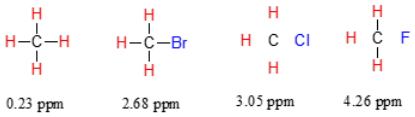
We come now to the question of why nonequivalent protons have different resonance frequencies and thus different chemical shifts. The chemical shift of a given proton is determined primarily by interactions with the nearby electrons. The most important thing to understand is that when electrons are subjected to an external magnetic field, they form their own small induced magnetic fields in opposition to the external field.

Consider the methane molecule (CH_4) in which the four equivalent protons have a chemical shift of 0.23 ppm (this is a value we can look up in any chemistry reference source). The valence electrons around the methyl carbon, when subjected to B0, generate their own very small induced magnetic field that opposes B_0. This induced field, to a small but significant degree, shields the nearby protons from experiencing the full force of B_0, an effect known as local diamagnetic shielding. In other words, the methane protons do not quite experience the full force of B_0 - what they experience is called B_{eff}, or the effective field, which is slightly weaker than B_0 due to the influence of the nearby electrons.



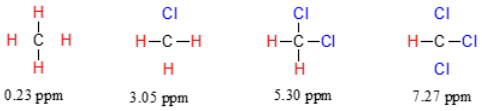
Because B_{eff} is slightly weaker than B0, the resonance frequency (and thus the chemical shift) of the methane proton is slightly lower than what it would be if it did not have electrons nearby and was feeling the full force of B_0. (You should note that the figure above is not to scale: the applied field is generated by a superconducting magnet and is extremely strong, while the opposing induced field from the electrons is comparatively very small.)

Now consider methyl fluoride, CH3F, in which the protons have a chemical shift of 4.26 ppm, significantly higher than that of methane. This is caused by something called the deshielding effect. Recall that fluorine is very electronegative: it pulls electrons towards itself, effectively decreasing the electron density around each of the protons. For the protons, being in a lower electron density environment means less diamagnetic shielding, which in turn means a greater overall exposure to B_0, a stronger B_{eff}, and a higher resonance frequency. Put another way, the fluorine, by pulling electron density away from the protons, is deshielding them, leaving them more exposed to B_0. As the electronegativity of the substituent increases, so does the extent of deshielding, and so does the chemical shift. This is evident when we look at the chemical shifts of methane and three halomethane compounds (remember that electronegativity increases as we move up a column in the periodic table, so flourine is the most electronegative and bromine the least).

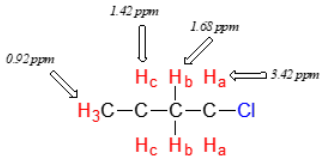


To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton.

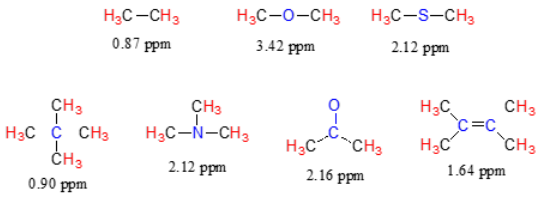
The chemical shift of trichloromethane (common name chloroform) is, as expected, higher than that of dichloromethane, which is in turn higher than that of chloromethane.



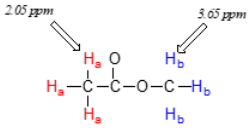
The deshielding effect of an electronegative substituent diminishes sharply with increasing distance:



The presence of an electronegative oxygen, nitrogen, sulfur, or sp^2-hybridized carbon also tends to shift the NMR signals of nearby protons slightly downfield:

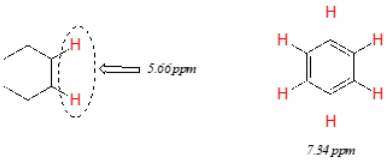


Now we can finally assign the two peaks in the the ^1H-NMR spectrum of methyl acetate. We can predict that the methyl ester protons (H_b), which are deshielded by the adjacent oxygen atom, will have a higher chemical shift than the acetate protons (H_a), which are deshielded to a lesser extent by the carbonyl group. Therefore, the signal at 3.7 must correspond to H_b, and the signal at 2.0 to H_a.



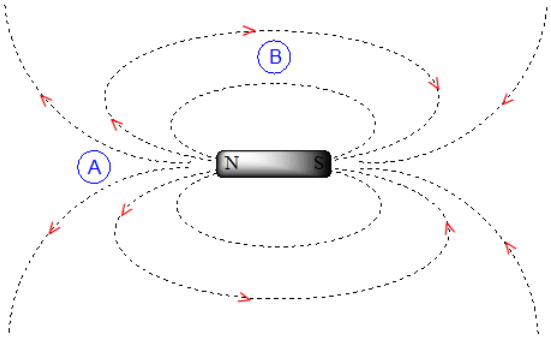
Diamagnetic anisotropy

Vinylic protons (those directly bonded to an alkene carbon) and aromatic protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Note the chemical shifts of the vinylic and aromatic protons in cyclohexene and benzene:



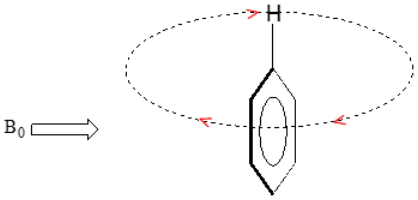
We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a ring current, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the p electrons does not shield the aromatic protons from B_0 as you might expect– rather, it causes the protons to experience a stronger magnetic field in the direction of B_0 – in other words, it adds to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of diamagnetic anisotropy (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.



If we are at point A in the figure above, we feel a magnetic field pointing in a northerly direction. If we are at point B, however, we feel a field pointing to the south.

In the induced field generated by the aromatic ring current, the aromatic protons are at the equivalent of 'point B' – this means that the induced current in this region of space is oriented in the same direction as B_0, so it adds to B_0 rather than subtracting from it.



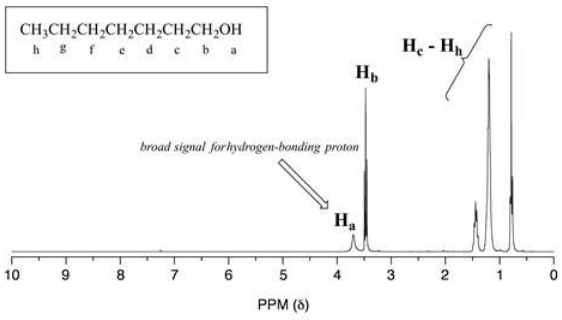
end result is that aromatic protons, due to the anisotropy of the induced field generated by the *pi* ring current, appear to be highly deshielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

Diamagnetic anisotropy is also responsible for the downfield chemical shifts of vinylic protons (4.5-6.5 ppm) and aldehyde protons (9-10 ppm). These groups are not aromatic and thus do not generate ring currents does benzene, but the p electrons circulate in such a way as to generate a magnetic field that adds to B_0 in the regions of space occupied by the protons. Carboxylic acid protons are very far downfield (10-12 ppm) due to the combined influence of the electronegative oxygen atom and the nearby *pi* bond.

Hydrogen bonded protons

Protons that are directly bonded to oxygen or nitrogen have chemical shifts that can vary widely depending on solvent and concentration. These protons can participate to varying degrees in hydrogen bonding interactions, and the degree hydrogen bonding greatly influences the electron density around the proton - and thus the chemical shift. Signals for hydrogen bonding protons also tend to be broader than those of hydrogens bonded to carbon, a phenomenon that is also due to hydrogen bonding.

Alcohol protons, for example, will usually show broad signals anywhere between 1-5 ppm. The signal for H_a in the spectrum of 1-heptanol is a typical example of a broadened NMR signal for an alcohol proton.



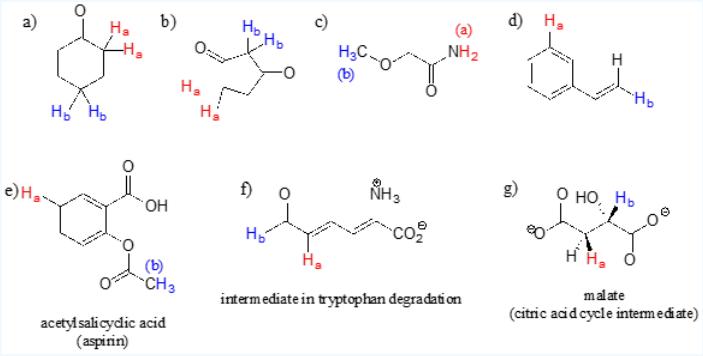
The table below provides a summary of approximate chemical shift ranges for protons in different bonding arrangements. A more detailed table can be found in the appendix.

Table 5.5.1 : Typical chemical shift ranges in ^1H-NMR.

Type of proton	Chemical shift range (ppm)
bonded to sp^3 carbon	0.5 - 4
bonded to N (amine)	1 - 3
bonded to O (alcohol)	1 - 5
alkene/ vinylic	3.5 - 6.5
terminal alkyne	2 - 3
bonded to N (amide)	5 - 9
aromatic	6 - 9
aldehyde	9.5 - 10
carboxylic acid	10 - 13

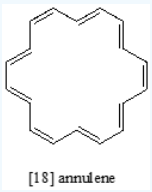
Exercise 5.5.1

For each pair of protons colored red (H_a) and blue (H_b) in the structures below, state which is expected to have the higher chemical shift in ^1H-NMR. For some of these it will be helpful to consult Table 2 at the back of the book.



Exercise 5.5.2

The ^1H-NMR spectrum of the aromatic compound [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (a negative chemical shift, upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.



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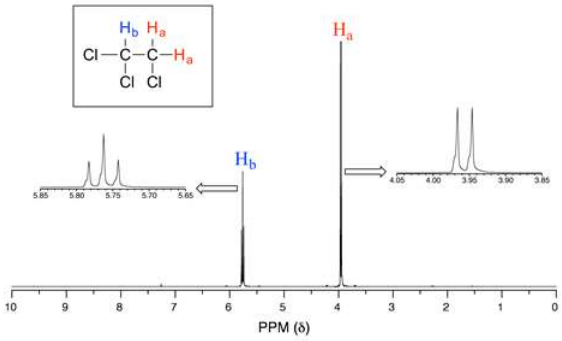
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5.5: Spin-Spin Coupling

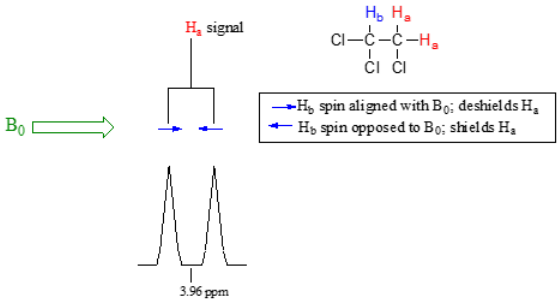
The ^1H-NMR spectra that we have seen so far (of methyl acetate and 1,4-dimethylbenzene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^1H-NMR spectra of most organic molecules contain proton signals that are 'split' into two or more sub-peaks. Rather than being a complication, however, this splitting behavior is actually very useful because it provides us with more information about our sample molecule.

Consider the spectrum for 1,1,2-trichloroethane. In this and in many spectra to follow, we show enlargements of individual signals so that the signal splitting patterns are recognizable.



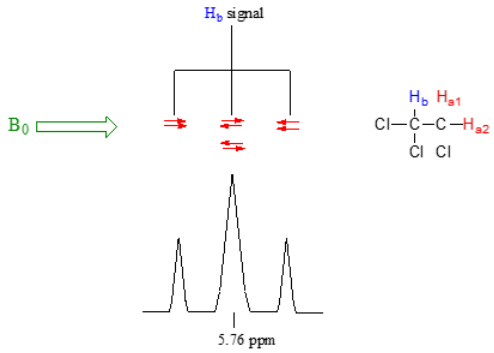
The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a doublet. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were to integrate each subpeak, we would see that the area under the middle peak is twice that of each of the outside peaks. This is called a triplet.

The source of signal splitting is a phenomenon called spin-spin coupling, a term that describes the magnetic interactions between neighboring, non-equivalent NMR-active nuclei. (The terms 'splitting' and 'coupling' are often used interchangeably when discussing NMR.) In our 1,1,2 trichloromethane example, the H_a and H_b protons are spin-coupled to each other. Here's how it works, looking first at the H_a signal: in addition to being shielded by nearby valence electrons, each of the H_a protons is also influenced by the small magnetic field generated by H_b next door (remember, each spinning proton is like a tiny magnet). The magnetic moment of H_b will be aligned with B_0 in slightly more than half of the molecules in the sample, while in the remaining molecules it will be opposed to B_0. The Beff 'felt' by H_a is a slightly weaker if H_b is aligned against B_0, or slightly stronger if H_b is aligned with B_0. In other words, in half of the molecules H_a is shielded by H_b (thus the NMR signal is shifted slightly upfield) and in the other half H_a is deshielded by H_b (and the NMR signal shifted slightly downfield). What would otherwise be a single H_a peak has been split into two sub-peaks (a doublet), one upfield and one downfield of the original signal. These ideas an be illustrated by a splitting diagram, as shown below.



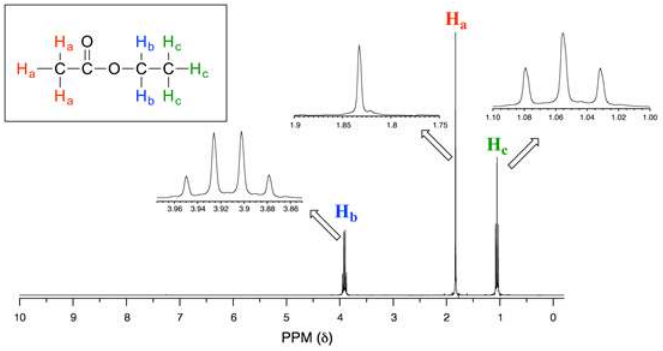
Now, let's think about the H_b signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_a1 and H_a2. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_a1 and H_a2 could be aligned with B_0, which would deshield H_b, shifting its NMR signal slightly downfield. Second, both the H_a1 and H_a2 magnetic fields could be aligned opposed to B_0, which would shield H_b, shifting its resonance signal slightly upfield. Third and fourth, H_a1 could be with B_0 and H_a2 opposed, or H_a1 opposed to B_0 and H_a2 with B_0. In each of the last two

cases, the shielding effect of one H_a proton would cancel the deshielding effect of the other, and the chemical shift of H_b would be unchanged.



So in the end, the signal for H_b is a triplet, with the middle peak twice as large as the two outer peaks because there are two ways that H_a1 and H_a2 can cancel each other out.

Consider the spectrum for ethyl acetate:



We see an unsplit 'singlet' peak at 1.83 ppm that corresponds to the acetyl (H_a) protons – this is similar to the signal for the acetate protons in methyl acetate that we considered earlier. This signal is unsplit because there are no adjacent protons on the molecule. The signal at 1.06 ppm for the H_c protons is split into a triplet by the two H_b protons next door. The explanation here is the same as the explanation for the triplet peak we saw previously for 1,1,2-trichloroethane.

The Hb protons give rise to a quartet signal at 3.92 ppm – notice that the two middle peaks are taller then the two outside peaks. This splitting pattern results from the spin-coupling effect of the three adjacent Hc protons, and can be explained by an analysis similar to that which we used to explain the doublet and triplet patterns.

? Exercise 5.6.1

a. Explain, using a splitting diagram, the possible combinations of nuclear spin states for the H_c protons in ethyl acetate, and why the H_b signal is split into a quartet.

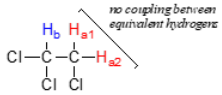
b. The integration ratio of the two 'sub-peaks' in a doublet is 1:1, and in triplets it is 1:2:1. What is the integration ratio of the H_b quartet in ethyl acetate? (Hint – use the illustration that you drew in part a to answer this question.)

By now, you probably have recognized the pattern which is usually referred to as the n + 1 rule: if a set of protons has n neighboring, non-equivalent protons, it will be split into n + 1 subpeaks. Thus the two H_b protons in ethyl acetate split the H_c signal into a triplet, and the three H_c protons split the H_b signal into a quartet. H_a, with zero neighboring protons, is a singlet. This is very useful information if we are trying to determine the structure of an unknown molecule: if we see a triplet signal, we know that the

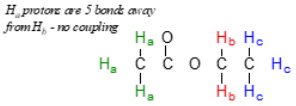
corresponding proton or set of protons has two `neighbors`. When we begin to determine structures of unknown compounds using ^1H-NMR spectral data, it will become more apparent how this kind of information can be used.

Four important points need to be emphasized at this point.

First, signal splitting only occurs between non-equivalent protons – in other words, H_a1 in 1,1,2-trichloroethane is not split by H_a2, and vice-versa.



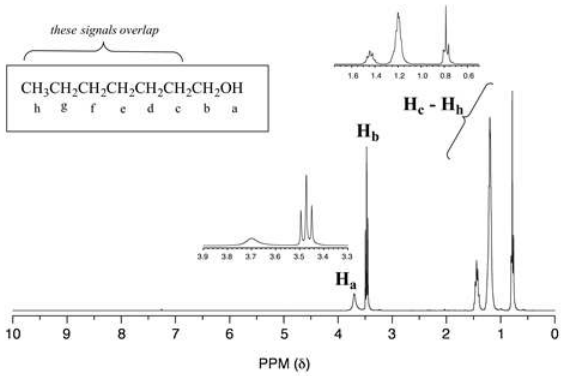
Second, splitting occurs primarily between protons that are separated by three or fewer bonds. This is why the H_a protons in ethyl acetate form a singlet– the nearest proton neighbors are five bonds away, too far for coupling to occur.



With more sensitive instruments we will sometimes see 4-bond and even 5-bond splitting, but in our treatment of NMR, for the sake of simplicity we will always assume that only three-bond splitting is seen.

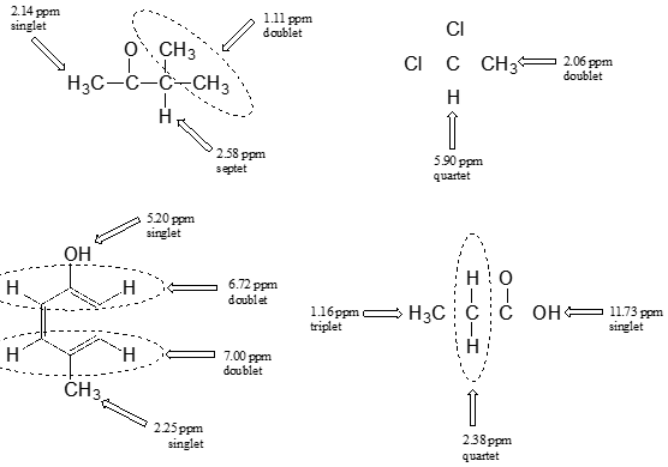
Third, protons that are bonded to oxygen or nitrogen generally do not split - and are not split by - adjacent protons. OH and NH protons are acidic enough to rapidly exchange between different molecules, so the neighboring protons never actually 'feels' their influence.

The spectrum of 1-heptanol has a characteristically broad alcohol proton signal at 3.7 ppm (labeled Ha below).



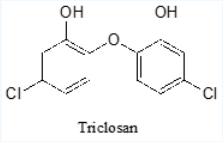
Notice in this spectrum that H_b is a triplet, coupled to the two H_c protons but not coupled to H_a. The signals corresponding to H_c through Hh are complex due to overlapping - when this happens (as it often does!), detailed analysis becomes more challenging.

Below are a few more examples of chemical shift and splitting pattern information for some relatively simple organic molecules.



Exercise 5.6.2

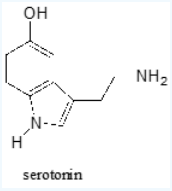
How many proton signals would you expect to see in the ^1H-NMR spectrum of triclosan (a common antimicrobial agent in soap)? For each of the proton signals, predict the splitting pattern, assuming that you can see only 3-bond splitting.



Triclosan

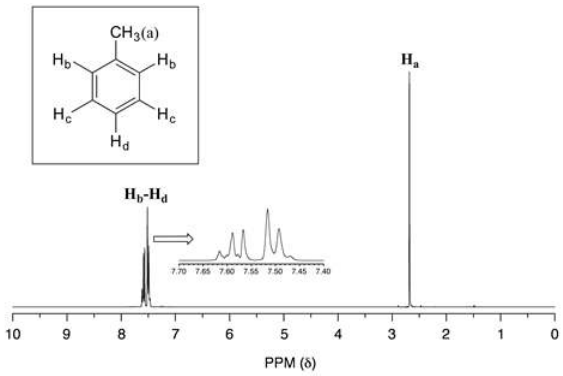
Exercise 5.6.3

How many proton signals would you expect to see in the ^1H-NMR spectrum of the neurotransmitter serotonin? For each of the proton signals, predict the splitting pattern, again assuming only 3-bond splitting.



serotonin

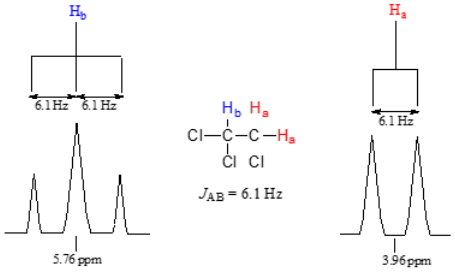
In an ideal world, all NMR spectra would be as easy to interpret as those we have seen so far: every peak would be separated from the others, the peak integration would be obvious, and the multiplicity (singlet, doublet, etc.) would be easy to recognize. The real world, unfortunately, is not always so pretty: peaks with similar chemical shifts overlap, making interpretation much more difficult. We have already seen this is the spectrum of 1-heptanol above. In the spectrum of methylbenzene, we would expect the signal for H_a to be a singlet, H_b to be a doublet, and H_c and H_d to be triplets. Looking at relative integration values for the four peaks, we would expect to see a 3:2:2:1 ratio.



In practice, however, the three aromatic proton sets H_b, H_c and H_d have very similar chemical shifts so their signals overlap substantially, and we cannot recognize doublet or triplet splitting patterns. In this case, we would refer to the aromatic part of the spectrum as a multiplet. We can report the integration ratio of the H_a peak compared to the combined aromatic peaks as 3 to 5, or the equivalent 1 to 1.67.

The magnitude of spin-spin coupling can be expressed using the coupling constant, abbreviated with the capital letter J. The coupling constant is simply the difference, expressed in Hz, between two adjacent sub-peaks in a split signal, and is a measure of the extent to which one nucleus 'feels' the magnetic dipole of its neighbor.

For our doublet in the 1,1,2-trichloroethane spectrum, for example, the two subpeaks are separated by 6.1 Hz, and thus we write $^3J_{a-b} = 6.1Hz$.

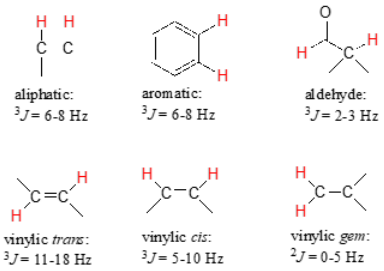


The superscript '3' tells us that this is a three-bond coupling interaction, and the 'a-b' subscript tells us that we are talking about coupling between H_a and H_b. Unlike the chemical shift value, the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR magnet. The strength of the magnetic moment of a neighboring proton, which is the source of the spin-spin coupling phenomenon, does not depend on the applied field strength. For this reason, coupling constants are normally given in Hz, not ppm.

When we look closely at the triplet signal in 1,1,2-trichloroethane, we see that the coupling constant - the 'gap' between subpeaks - is 6.1 Hz, the same as for the doublet. The coupling constant $^3J_{a-b}$ quantifies the magnetic interaction between the Ha and Hb hydrogen sets, and this interaction is of the same magnitude in either direction. In other words, spin-spin coupling is reciprocal: H_a influences H_b to the same extent that H_b influences H_a.

Coupling constants between proton sets on neighboring sp^3-hybridized carbons is typically in the region of 6-8 Hz. Coupling constants for neighboring vinylic protons can range from 0 Hz (no coupling at all) to 18 Hz, depending on the bonding arrangement.

Typical proton-proton coupling constants



For vinylic protons in a trans configuration, we see coupling constants in the range of $^3J = 11 - 18Hz$, while cis protons couple in the $^3J = 5 - 10Hz$ range. The 2-bond coupling between protons on the same alkene carbon (referred to as geminal protons) is very fine, generally 5 Hz or lower.

Fine coupling (2-3 Hz) is often seen between an aldehyde proton and a three-bond neighbor.

? Exercise 5.6.4

Give the expected splitting patterns and approximate coupling constants for the labeled protons in the compound below.

Presenting NMR data in table format

Information from NMR can be recorded conveniently in a condensed form without having to reproduce the actual spectrum. For example, the information from the ^1H-NMR specta of ethyl acetate and methylbenzene (see earlier figures) can be presented in tabular format, listing the chemical shift, the peak splitting pattern, and the relative area under peaks (usually, the smallest peak is set to 1). Coupling constant information is not shown in the example tables below.

Table 5.6.1 : ^1H-NMR spectrum of ethyl acetate

ppm	splitting	integration
3.92	q	1
1.83	s	1.5
1.06	t	1.5

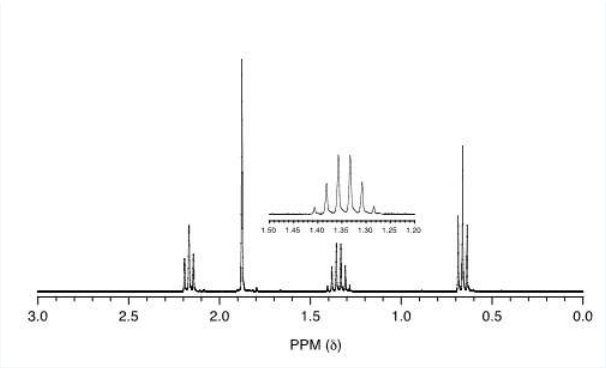
Table 5.6.2 : $^1H - NMR$ spectrum of methylbenzene.

ppm	splitting	integration
7.45 - 7.63	m	1.67
2.64	s	1

(abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet)

? Exercise 5.6.5

Match the ^1H-NMR spectrum below to its corresponding compound, and assign all of the signals.



a) cyclopentanone b) 3-pentanone c) butaldehyde

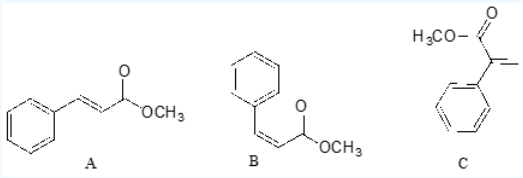
d) 2-pentanone e) 4-heptanone f) 1-butene

Exercise 5.6.6

a. Which of the compounds in the previous exercise is expected to have an ^1H-NMR spectrum consisting of two triplets and a sextet?
b. Which would have a spectrum consisting of two triplets?
c. Which would have a spectrum that includes a signal above 8 ppm?

Exercise 5.6.7

Explain how you could distinguish among the ^1H-NMR spectra of the three isomers below.



Video tutorials: proton NMR spectroscopy

Video of an actual NMR experiment

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5.6: 13C-NMR Spectroscopy

The ^{12}C isotope of carbon - which accounts for up about 99% of the carbons in organic molecules - does not have a nuclear magnetic moment, and thus is NMR-inactive. Fortunately for organic chemists, however, the ^{13}C isotope, which accounts for most of the remaining 1% of carbon atoms in nature, has a magnetic dipole moment just like protons. Most of what we have learned about ^{1}H-NMR spectroscopy also applies to ^{13}C-NMR, although there are several important differences.

The magnetic moment of a ^{13}C nucleus is much weaker than that of a proton, meaning that NMR signals from ^{13}C nuclei are inherently much weaker than proton signals. This, combined with the low natural abundance of ^{13}C, means that it is much more difficult to observe carbon signals: more sample is required, and often the data from hundreds of scans must be averaged in order to bring the signal-to-noise ratio down to acceptable levels. Unlike ^{1}H-NMR signals, the area under a ^{13}C-NMR signal cannot easily be used to determine the number of carbons to which it corresponds. The signals for some types of carbons are inherently weaker than for other types – peaks corresponding to carbonyl carbons, for example, are much smaller than those for methyl or methylene (CH_2) peaks. For this reason, peak integration is generally not useful in ^{13}C-NMR spectroscopy.

The resonance frequencies of ^{13}C nuclei are lower than those of protons in the same applied field - in an instrument with a 7.05 Tesla magnet, protons resonate at about 300 MHz, while carbons resonate at about 75 MHz. This is fortunate, as it allows us to look at ^{13}C signals using a completely separate 'window' of radio frequencies. Just like in ^{1}H-NMR, the standard used in ^{13}C-NMR experiments to define the 0 ppm point is tetramethylsilane (TMS),

although of course in ^{13}C-NMR it is the signal from the four equivalent *carbons* in TMS that serves as the standard. Chemical shifts for ^{13}C nuclei in organic molecules are spread out over a much wider range than for protons – up to 200 ppm for ^{13}C compared to 10-12 ppm for protons (see Table 3 for a list of typical ^{13}C-NMR chemical shifts).

The chemical shift of a ^{13}C nucleus is influenced by essentially the same factors that influence a proton's chemical shift: bonds to electronegative atoms and diamagnetic anisotropy effects tend to shift signals downfield (higher resonance frequency). In addition, sp^2 hybridization results in a large downfield shift. The ^{13}C-NMR signals for carbonyl carbons are generally the furthest downfield (170-220 ppm), due to both sp^2 hybridization and to the double bond to oxygen.

Exercise 5.15

How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 5.2?

Exercise 5.16

How many sets of non-equivalent carbons are there in:

a) methylbenzene

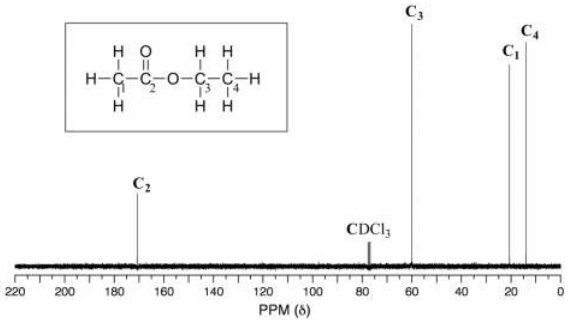
b) 2-pentanone

c) 1,4-dimethylbenzene

d) triclosan

(all structures are shown earlier in this chapter)

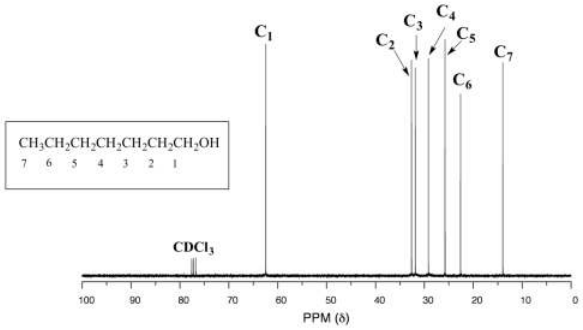
Because of the low natural abundance of ^{13}C nuclei, it is very unlikely to find two ^{13}C atoms near each other in the same molecule, and thus *we do not see spin-spin coupling between neighboring carbons in a ^{13}C-NMR spectrum*. ^{13}C nuclei are coupled to nearby protons, however, which results in complicated spectra. For clarity, chemists generally use a technique called **broadband decoupling**, which essentially 'turns off' C-H coupling, resulting in a spectrum in which all carbon signals are singlets. Below is the proton-decoupled ^{13}C-NMR sectrum of ethyl acetate, showing the expected four signals, one for each of the carbons. We can also see a signal for the carbon atom in the deuterated chloroform ($CDCl_3$) solvent (although a detailed discussion is beyond our scope here, it is interesting to note that this signal is split into a triplet by deuterium, which is NMR active and has *three* possible spin states rather than two). We can ignore the solvent signal when interpreting ^{13}C-NMR spectra.



While broadband decoupling results in a much simpler spectrum, useful information about the presence of neighboring protons is lost. However, another NMR technique called DEPT (Distortionless Enhancement by Polarization Transfer) allows us to determine how many hydrogens are bound to each carbon. This information is usually provided in problems in which you are asked to interpret the ^{13}C-NMR spectrum of an unknown compound. (Details of how the DEPT technique works is beyond the scope of this book, but will be covered if you take a more advanced course in spectroscopy.)

One of the greatest advantages of ^{13}C-NMR compared to ^{1}H-NMR is the breadth of the spectrum - recall that carbons resonate from 0-220 ppm relative to the TMS standard, as opposed to only 0-12 ppm for protons. Because of this, ^{13}C signals rarely overlap, and

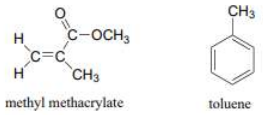
we can almost always distinguish separate peaks for each carbon, even in a relatively large compound containing carbons in very similar environments. In the proton spectrum of 1-heptanol we saw earlier only the broad singlet of the alcohol proton (H_a) and the triplet for (H_b) are easily analyzed. The other proton signals overlap, making analysis difficult. In the ^{13}C spectrum of the same molecule, however, we can easily distinguish each carbon signal, and we know from this data that our sample has seven nonequivalent carbons. (Notice also that, as we would expect, the chemical shifts of the carbons get progressively lower as they get farther away from the deshielding oxygen.)



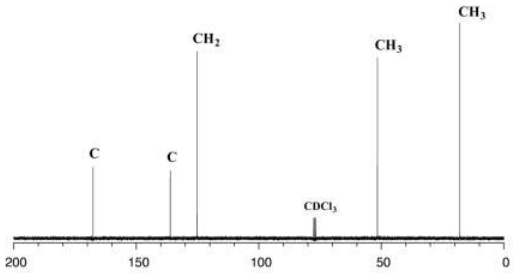
This property of ^{13}C-NMR makes it very helpful in the elucidation of larger, more complex structures.

Exercise 5.17

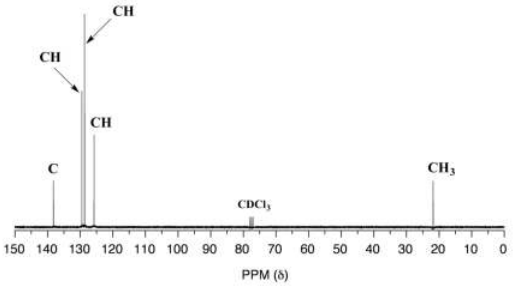
Below are ^{13}C-NMR spectra for methylbenzene (common name toluene) and methyl methacrylate. Match the spectra to the correct structure, and make peak assignments.



Spectrum A:



Spetrum B:



Exercise 5.18

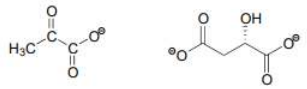
^{13}C-NMR data for some common biomolecules are shown below (data is from the Aldrich Library of ^{1}H and ^{13}C NMR). Match the NMR data to the correct structure, and make complete peak assignments.

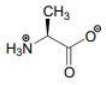
spectrum a: 168.10 ppm (C), 159.91 ppm (C), 144.05 ppm (CH), 95.79 ppm (CH)

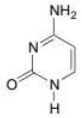
spectrum b: 207.85 ppm (C), 172.69 ppm (C), 29.29 ppm (CH_3)

spectrum c: 178.54 ppm (C), 53.25 ppm (CH), 18.95 ppm (CH_3)

spectrum d: 183.81 ppm (C), 182. 63 ppm (C), 73.06 ppm (CH), 45.35 ppm (CH_2)





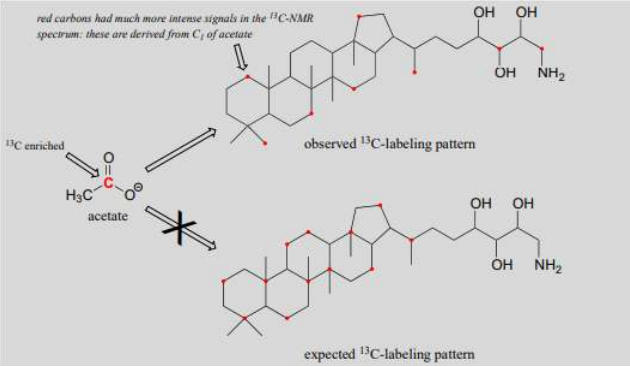


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^{13}C-NMR in Isotopic Labeling Studies

Although only about 1 out of 100 carbon atoms in a naturally occurring organic molecule is a 13C isotope, chemists are often able to synthesize molecules that are artificially enriched in 13C at specific carbon positions. This can be very useful in biochemical studies, because it allows us to 'label' one or more carbons in a small precursor molecule and then trace the presence of the 13C label through a biosynthetic pathway all the way to the final product, providing insight into how the biosynthesis occurs. For example, scientists were able to grow bacteria in a medium in which the only source of carbon was acetate enriched in 13C at the C1 (carbonyl) position. When they isolated an isoprenoid compound called amino-bacterio-hopanetriol synthesized by the bacteria and looked at its 13C-NMR spectrum, they observed that the 13C label from acetate had been incorporated at eight specific

positions. They knew this because the 13C-NMR signals for these carbons were much stronger compared to the same signals in a control (unlabeled) compound.



This result was very surprising - the scientists had expected a completely different pattern of 13C incorporation based on what they believed to be the isoprenoid biosynthesis pathway involved. This unexpected result led eventually to the discovery that bacteria synthesize isoprenoid compounds by a completely different pathway then yeasts, plants, and animals. The newly discovered bacterial metabolic pathway is currently a key target for the development of new antibiotic and antimalaria drugs. (Eur. J. Biochem. 1988, 175, 405).

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5.7: Solving Unknown Structures

Now it is finally time to put together all that we have studied about structure determination techniques and learn how to actually solve the structure of an organic molecule 'from scratch' - starting, in other words, with nothing but the raw experimental data. For this exercise, we will imagine that we have been given a vial containing a pure sample of an unknown organic compound, and that this compound to our knowledge has never before been synthesized, isolated, or characterized - we are the first to get our hands on it. Can we figure out its structure? While of course the exact method of determining an unknown structure will depend on the compound in question and, in the real world of research, will probably involve some techniques that are beyond the scope of this book, here is an overview of an approach that could be taken to analyze a pure sample of a relatively simple organic compound, using the techniques we have learned about.

Step 1: Use MS and combustion analysis to determine the molecular formula

Before we start analyzing spectroscopic data, we need one very important piece of information about our compound - its molecular formula. This can be determined through the combined use of mass spectrometry and combustion analysis. We will not go into the details of combustion analysis - for now, it is enough to know that this technique tells us the mass percent of each element in the compound. Because molecular oxygen is involved in the combustion reaction, oxygen in the sample is not measured directly - but we assume that if the mass percentages do not add up to 100%, the remainder is accounted for by oxygen.

When we obtain our unknown compound, one of the first things we will do is to send away a small quantity to an analytical company specializing in combustion analysis. They send us back a report stating that our compound is composed, by mass, of 52.0% carbon, 38.3% chlorine, and 9.7% hydrogen. This adds up to 100%, so our compound does not contain any oxygen atoms.

In order to determined the molecular formula of our compound from this data, we first need to know its molar mass. This piece of information, as you recall from chapter 4, we determine by looking at the 'molecular ion peak' in the mass spectrum of our compound. In this example, we find that our MS data shows a molecular ion peak at m/z = 92, giving us a molar mass of 92 g/mole (remember that in the MS experiment, charge (z) is almost always equal to 1, because we are looking at +1 cations).

So, one mole of our compound is 92g. How many moles of carbon atoms are in one mole of the compound? Simple: 52% of 92g is 47.8g. So in one mole of our compound, there is about 48 g of carbon, which means four moles of carbon. With similar calculations, we find that one mole of our compound contains nine hydrogens and one chlorine. Therefore our molecular formula is C_4H_9Cl.

Step 2: Calculate the Index of Hydrogen Deficiency

The next step is to calculate a number called the Index of Hydrogen Deficiency (IHD) from the molecular formula. The IHD will tell us how many multiple bonds and/or ring structures our molecule has - very useful information. The idea behind the IHD is very simple: the presence of a double bond or a ring structure means that two fewer hydrogen atoms can be part of the compound. The formula for calculating IHD from a molecular formula is:

Calculating Index of Hydrogen Deficiency:

$$IHD = \frac{(2n+2) - A}{2} \tag{5.7.1}$$

where:

n = number of carbon atoms

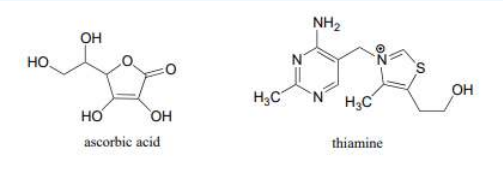
A = (number of hydrogen atoms) + (number of halogen atoms) - (number of nitrogen atoms) - (net charge)

For example, a molecule with the molecular formula C_6H_{14} would have n = 6 and A = 14, so we can calculate that IHD = 0 and thereby know that a compound with this formula has no double bonds or ring structures. Hexane and 2-methyl pentane are two examples of compounds that apply.

A molecular formula of C_6H_{12}, on the other hand, corresponds to IHD = 1, so a compound with this formula should have one double bond or one ring structure. Cyclohexane (one ring structure) and 2-hexene (one double bond) are two possibilities. Benzene (C_6H_6) , and methyl benzene (C_7H_8) both have IHD = 4, corresponding in both cases to three p bonds and one ring. An IHD value of 4 or greater is often an indicator that an aromatic ring is present.

Exercise 5.8.1

a. What is the IHD that corresponds to a molecular formula $C_6H_{12}O$? Draw the structures of three possible compounds that fit.
b. The amino acid alanine has molecular formula $C_2H_8NO_2^+$ in aqueous buffer of $pH = 2$. Calculate the IHD. Then, draw the relevant structure to confirm that this IHD makes sense.
c. What is the IHD of the compounds below? (Hint: you don't need to figure out molecular formulas!)



The formula for our structure determination sample, C_4H_9Cl, corresponds to IHD = 0, meaning that our compound contains no multiple bonds or rings.

Step 3: Use available spectroscopy data to identify discrete parts of the structure.

In this problem, we have proton and carbon NMR data to work with (other problems may include IR and/or UV/Vis data).

^1H-NMR

ppm	splitting	integration
3.38	d	2
1.95	m	1
1.01	d	6

$^{13}C-NMR$:

52.49 (CH_2)

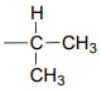
31.06 (CH)

20.08 (CH_3)

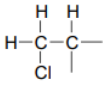
The process of piecing together an organic structure is very much like putting together a puzzle. In every case we start the same way, determining the molecular formula and the IHD value. After that,

there is no set formula for success- what we need to do is figure out as much as we can about individual pieces of the molecule from the NMR (and often IR, MS, or UV-Vis) data, and write these down. Eventually, hopefully, we will be able to put these pieces together in a way that agrees with all of our empirical data. Let's give it a go.

We see that there are only three signals in each NMR spectrum, but four carbons in the molecule, which tells us that two of the carbons are chemically equivalent. The fact that the signal at 1.01 ppm in the proton spectrum corresponds to six protons strongly suggests that the molecule has two equivalent methyl (CH_3) groups. Because this signal is a doublet, there must be a CH carbon bound to each of these two methyl groups. Taken together, this suggests:

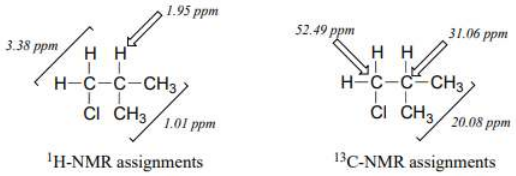


The ^1H-NMR signal at 3.38 ppm must be for protons bound to the carbon which is in turn bound to the chlorine (we infer this because this signal is the furthest downfield in the spectrum, due to the deshielding effect of the electronegative chlorine). This signal is for two protons and is a doublet, meaning that there is a single nonequivalent proton on an adjacent carbon.



Step 4: Try to put the pieces of the puzzle together, and see if everything fits the available data.

At this point, we have accounted for all of the atoms in the structure, and we have enough information to put together a structure that corresponds to 1-chloro-2-methylpropane.



^{1}H-NMR assignments ^{13}C-NMR assignments

To confirm, we make assignment all NMR signals to their corresponding atoms and make sure that our structure fits all of the NMR data. Notice that the proton peak at 1.95 ppm might be expected to be a '9-tet' because of its eight 3-bond neighbors: however, two of the neighbors are different from the other six, and may not couple to exactly the same extent. The signal at 1.95 will not, then, be a 'clean' 9-tet, and we would call it a multiplet.

? Exercise 5.8.1

Three constitutional isomers of 1-chloro-2-methylpropane produce the following NMR data. Assign structures to the three compounds, and make all peak assignments.

a. **Compound A: (2-chloro-2-methylpropane)**

$^{1}H-NMR$:

1.62 ppm, $9H$, s

$^{13}C-NMR$:

67.14 ppm (C)

34.47 ppm (CH_3)

b. **Compound B: (1-chlorobutane)**

$^{1}H-NMR$:

3.42 ppm, $2H$, t

1.68 ppm, $2H$, p

1.41 ppm, $2H$, sextet

0.92 ppm, $3H$, t

$^{13}C-NMR$:

44.74 ppm (CH_2)

34.84 ppm (CH_2)

20.18 ppm (CH_2)

13.34 ppm (CH_3)

c. **Compound C: (2-chlorobutane)**

^1H-NMR:

3.97 ppm, $1H$, sextet

1.71 ppm, $2H$, p

1.50 ppm, $3H$, d

1.02 ppm, $3H$, t

$^{13}C-NMR$:

60.34 ppm (CH)

33.45 ppm (CH_2)

24.94 ppm (CH_3)

11.08 ppm (CH_3)

Let's try another problem, this time incorporating IR information.

Example 5.8.2

The following data was obtained for a pure sample of an unknown organic compound:

Combustion analysis:

C: 85.7%

H: 6.67%

MS: Molecular ion at m/z = 210

^1H-NMR:

7.5-7.0, 10H, m

5.10, 1H, s

2.22, 3H, s

$^{13}C-NMR$:

206.2 (C) 128.7 (CH) 30.0 (CH_3)

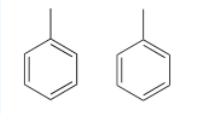
138.4 (C) 127.2 (CH)

129.0 (CH) 65.0 (CH)

IR: 1720 cm-1, strong (there are of course many other peaks in the IR spectrum, but this is the most characteristic one)

The molecular weight is 210, and we can determine from combustion analysis that the molecular formula is $C_{15}H_{14}O$ (the mass percent of oxygen in the compound is assumed to be 100 - 85.7 - 6.67 = 7.6 %). This gives us IHD = 9.

Because we have ten protons with signals in the aromatic region (7.5-7.0 ppm), we are probably dealing with two phenyl groups, each with one substituted carbon. The $^{13}C-NMR$ spectrum shows only four signals in the range for aromatic carbons, which tells us that the two phenyl groups must be in equivalent electronic environments (if they are in different environments, they would give rise to eight signals).

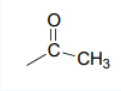


This accounts for 12 carbons, 10 hydrogens, and 8 IHD units. Notice that the carbon spectrum has only six peaks - and only four peaks in the aromatic region! This again indicates that the two phenyl groups are in chemically equivalent positions

The IR spectrum has a characteristic carbonyl absorption band, so that accounts for the oxygen atom in the molecular formula, the one remaining IHD unit, and the $^{13}C-NMR$ signal at 206.2 ppm.



Now we only have two carbons and four hydrogens left to account for. The proton spectrum tells us we have a methyl group (the 2.22 ppm singlet) that is not split by neighboring protons. Looking at the table of typical chemical shifts, we see that this chemical shift value is in the range of a carbon next to a carbonyl.



Finally, there is one last proton at 5.10 ppm, also a singlet. Putting the puzzle together, the only possibility that fits is 1,1-diphenyl-2-propanone:

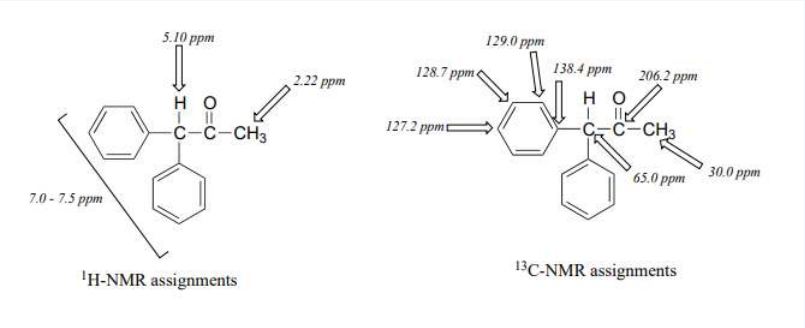


fig 43

Answer

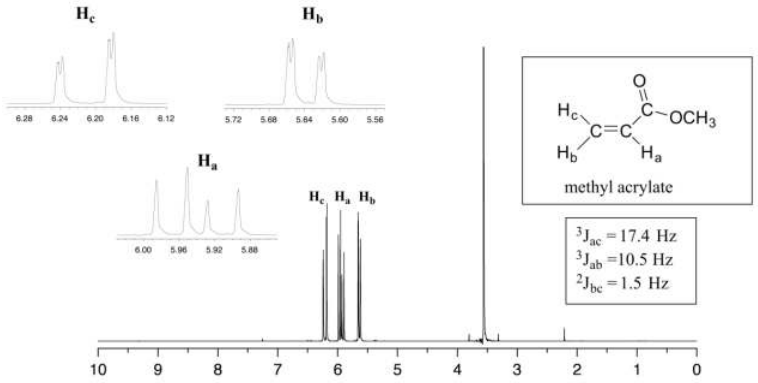
Add answer text here and it will automatically be hidden if you have a "AutoNum" template active on the page.

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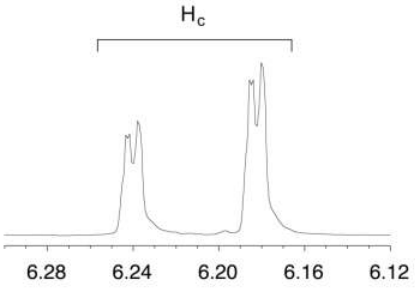
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5.8: Complex Coupling in Proton Spectra

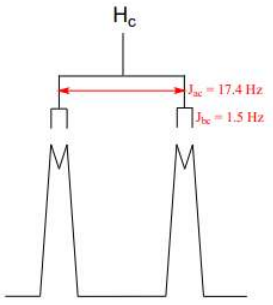
In all of the examples of spin-spin coupling we saw in our discussion of proton NMR, the observed splitting resulted from the coupling of one set of protons to just one neighboring set of protons. When a set of protons is coupled to two sets of nonequivalent neighbors, with significantly different coupling constants, the result is a phenomenon called complex coupling. A good illustration is provided by the ^1H-NMR spectrum of methyl acrylate:



Note that all three vinylic protons in methyl acrylate (designated above as H_a, H_b and H_c) are separated from each other by three bonds or less, and thus are all spin-coupled. For example, H_c is gem-coupled to H_b (J = 1.5 Hz), and H_c is also trans-coupled to H_a (J = 17.4 Hz). You might think that the $n+1$ rule would tell us that because H_c has two nonequivalent neighbors - H_a and H_b - its NMR signal should be a triplet. This would be correct if J_{ac} and J_{bc} were the same, or very close. However, because the two coupling constants are in fact very different from each other, the signal for H_c is clearly not a triplet. Here is a further expansion of the H_c signal:



You can see that the H_c signal is actually composed of four sub-peaks. Why is this? A splitting diagram can help us to understand what we are seeing. H_a is trans to H_c across the double bond, and splits the H_c signal into a doublet with a coupling constant of $^3J_{ac}$ = 17.4 Hz. In addition, each of these H_c doublet sub-peaks is split again by H_b (geminal coupling) into two more doublets, each with a much smaller coupling constant of $^2J_{bc}$ = 1.5 Hz.



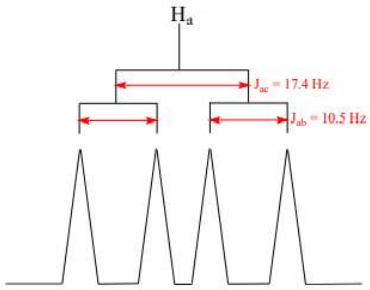
The result of this `double splitting` is a pattern referred to as a doublet of doublets, abbreviated `**dd**`.

The reported chemical shift of H_c is 6.210 ppm, the average of the four sub-peaks.

Exercise 5.9.1

Assume that on a 300 MHz spectrometer, the chemical shift of H_c, expressed in Hz, is 1863.0 Hz. What is the chemical shift, to the nearest 0.1 Hz, of the furthest upfield subpeak in the H_c signal?

The signal for H_a at 5.950 ppm is also a doublet of doublets, with coupling constants $^3J_{ac}$ = 17.4 Hz and $^3J_{ab}$ = 10.5 Hz.



The signal for H_b at 5.64 ppm is split into a doublet by H_a, a *cis* coupling with $^3J_{ab}$ = 10.4 Hz. Each of the resulting sub-peaks is split again by H_c, with the same geminal coupling constant $^2J_{bc}$ = 1.5 Hz that we saw previously when we looked at the H_c signal. The overall result is again a doublet of doublets, this time with the two `sub-doublets` spaced slightly closer due to the smaller coupling constant for the *cis* interaction.

Exercise 5.9.2

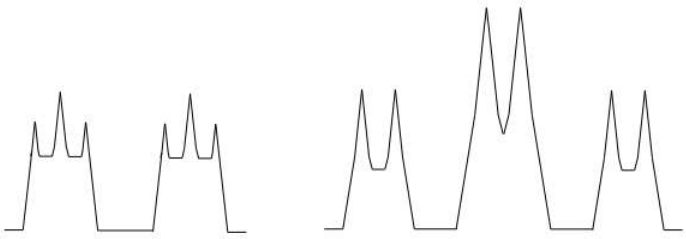
Construct a splitting diagram for the Hb signal in the ^1H-NMR spectrum of methyl acrylate. The chemical shift of H_b, in Hz, is 1691 Hz - label the chemical shifts (in Hz) of each of the four sub-peaks.

Exercise 5.9.3

Explain how the signals for H_b and H_c of methyl acrylate can be unambiguously assigned.

When constructing a splitting diagram to analyze complex coupling patterns, it is conventional (and simpler) to show the broader splitting first, followed by the finer splitting: thus we show the broad H_a-H_c splitting first, then the fine H_b-H_c splitting.

In the methyl acrylate spectrum, the signals for each of the three vinylic protons was a doublet of doublets (abbreviated '**dd**'). Other complex splitting patterns are possible: triplet of doublets (td), doublet of triplets (dt), doublet of quartets (dq), and so on. Remember that the broader splitting is listed first, thus a triplet of doublets is different from a doublet of triplets.

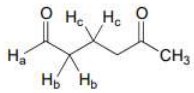


a doublet of triplets

a triplet of doublets

Exercise 5.9.4

Draw a predicted splitting diagram for the signal corresponding to H_b in the structure below, using approximate coupling constants. What would you call the splitting pattern for the H_b signal in this example?



Exercise 5.9.5

A signal in a proton ***NMR*** spectrum has multiple sub-peaks with the following chemical shifts values, expressed in Hz: 1586, 1583, 1580, 1572, 1569, 1566. Identify the splitting pattern, and give the coupling constant(s) and the overall chemical shift value (in Hz).

When we start trying to analyze complex splitting patterns in larger molecules, we gain an appreciation for why scientists are willing to pay large sums of money (hundreds of thousands of dollars) for higher-field ***NMR*** instruments. Quite simply, the stronger our magnet is, the more resolution we get in our spectrum. In a 100 MHz instrument (with a magnet of approximately 2.4 Tesla field strength), the 12 ppm frequency 'window' in which we can observe proton signals is 1200 Hz wide. In a 500 MHz (~12 Tesla) instrument, however, the window is 6000 Hz - five times wider. In this sense, ***NMR*** instruments are like digital cameras and HDTVs: better resolution means more information and clearer pictures (and higher price tags!)

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5.9: Other Applications of NMR

Magnetic resonance imaging

In the introduction to this chapter, we heard two stories about people whose lives were potentially saved when brain tumors were discovered during a magnetic resonance imaging (MRI) scan. MRI is a powerful diagnostic technique because it allows doctors to visualize internal body tissues while sparing the patient from surgery and potentially harmful, high energy x-rays. The basis for MRI is essentially the same as for NMR: an MRI scanner has a very strong superconducting magnet large enough to completely surround a whole person, much the same way in which a small glass sample tube in an NMR experiment is surrounded by the instrument's magnet. Once exposed to the strong magnetic field, water protons in the body resonate at different radio frequencies - the variation in resonance frequencies is due to water binding in different ways to different tissue types, creating slightly different electronic environments for the protons. The software in the MRI scanner then translates variations in resonance frequencies to a color scheme, which creates a visual image of the body tissues in the scanned area.



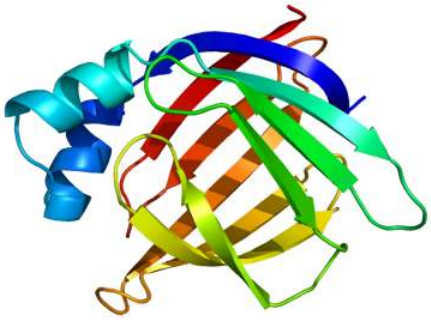
NMR of proteins and peptides

In this chapter you have learned enough about NMR to be able to understand how it is used to solve the structures of relatively small organic molecules. But what about really big organic molecules, like proteins?

X-ray crystallography, not NMR, is the most common way to determine the precise three-dimensional structure of a protein, and in a biochemistry class you will look at many images of protein structures derived from x-ray crystallography. While it is an immensely powerful tool for analyzing protein structure, crystallography has two major drawbacks. First, it relies on a researcher being able to get a protein to form regular, ordered crystals, which can be very challenging. Most proteins are globular, meaning they are (very roughly) spherical in shape. For a molecule to form crystals, it must pack together tightly in an ordered, repeating way: think of a neat stack of cube-shaped objects. Spheres, however, are inherently difficult to pack this way. Imagine trying to make a pile of tennis balls - they just roll apart, because so little of each ball's surface area comes into contact with its neighbor, thus there is very little friction (ie. noncovalent interactions!) holding them together. A large percentage of known proteins simply will not crystallize under any conditions that have been tried - therefore, we cannot determine their structure using x-ray crystallography.

Secondly, a lot of what is most interesting about proteins is how they move: flaps open and close when a substrate binds, or one part of the protein moves over to connect with another part. Protein action is dynamic. A crystal, on the other had, is static, or frozen. A protein structure determined by x-ray crystallography is like a still photograph of leaping dancer: we can infer from the picture what kind of movement might be taking place, but we can't get a full appreciation of the motion.

This leads to NMR, which of course is done in solution. It is easy to get most proteins into aqueous solution, so there are no worries about trying to make crystals. Also, a protein in solution is free to move, so NMR can potentially capture elements of protein dynamics. So why don't scientists always use NMR to look at proteins?



After working through a few NMR structure determination problems in this chapter, you have an appreciation for the brainwork required to figure out the structure of a small organic molecule based on its NMR structure: now imagine doing this with a protein, with its thousands of carbon and hydrogen atoms! Nevertheless, spectroscopists are gradually getting better and better at using NMR and computer-power to do just this. The advanced NMR techniques and methods of analysis are far beyond the scope of our discussion here, but you can see how useful it could be to protein scientists to be able to 'see' what a protein looks like using NMR, and if you are interested in this area of research you can learn about it in more advanced courses.

Note: The Spectral Database of Organic Compounds is a great resource for looking at NMR spectra (both proton and carbon) for a large number of compounds - the more examples you see, the better!

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5.E: Structure Determination (Exercises)

P5.1:

a. For each molecule below, draw in all hydrogen atoms, and label them H_a, H_b, etc., with chemically equivalent hydrogens having the same label.
b. Predict splitting patterns for all proton signals.



P5.2: For each of the 20 common amino acids, predict the number of signals in the proton-decoupled $^{13}C-NMR$ spectrum.

P5.3: Match spectra below to their corresponding structures A-F. Make complete peak assignments for all structures.

(in all $^{1}H-NMR$ data tables in the following problems, peak relative integration values are listed in which the smallest area peak is equal to 1)

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5.S: Structure Determination (Summary)

Before moving on to the next chapter, you should:

- Be able to identify groups of chemically equivalent protons and carbon atoms in a structure.
- Be able to explain the basis of an NMR experiment in terms of the spin state of a nucleus, the ground state to excited state transition involved, and the frequency of radiation absorbed.
- Understand the differences between proton and carbon NMR experiments, and explain why carbon spectra generally have more noise, do not show coupling, and do not suffer from the disadvantage of overlapping peaks. You should be able to explain why $^{13}C-NMR$ peaks are not usually integrated.
- Understand how to look at an NMR spectrum, including the meaning of the ppm label on the x-axis, the meaning of 'chemical shift', and the definition of zero ppm on the chemical shift scale.
- Be able to predict trends in chemical shifts for protons and carbon atoms in different bonding positions, and provide a rationale for the trend. You should also be able to roughly estimate the chemical shift of a given proton or carbon using Table X or a similar table from another source.
- Understand how to use proton peak integration values to determine how many protons a particular peak is 'worth'.
- Be able to explain the physical basis for spin-spin coupling in $^{1}H-NMR$ spectra, and be able to use the 'n+1 rule'.
- Be able to interpret, and draw splitting diagrams for, $^{1}H-NMR$ spectra with complex coupling.
- Be able to use a $^{13}C-NMR$ spectrum to identify the number of magnetically nonequivalent types of carbon in an unknown compound."
- Be confident at working problems in which you are asked to match structures to ^{1}H- and/or $^{13}C-NMR$ spectra.
- Given a molecular formula (or a combination of combustion and MS data), you should be confident in your ability to solve an unknown structure based on a ^{1}H- spectrum, possibly in combination with data from $^{13}C-NMR$, IR, or UV-Vis spectroscopy.

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CHAPTER OVERVIEW

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6.0: Prelude to Organic Reactivity

September 5, 1966, turned out to be a very good day for Hudson Freeze. An undergraduate microbiology major at Indiana University, he was a few weeks away from the first day of classes in his junior year, but on this September day he was far away from the oppressive heat and humidity of late summer in the midwest. Instead, he was working at the edge of Mushroom Spring in Yellowstone National Park, one of one of the many geothermal hot springs for which the park is so famous.



At the end of his sophomore year, Freeze had approached Dr. Thomas Brock, one of his microbiology professors, to ask about the possibility of working as a research assistant over the summer. Brock took him up on the offer, inviting him to come out to Yellowstone for a few weeks in late summer to help with some fieldwork.

For the past few years, Brock had been studying microbes that inhabited the hot springs: these 'extremophile' organisms were fascinating to him because they appeared to thrive in conditions that until quite recently had been thought to be too hot to support life. The currently accepted upper limit at which life was believed to be possible was 73 ºC, but during his work in Yellowstone the previous summer Brock was convinced that he had observed microbial life – a pink colored, filamentous bacteria - in water as hot as 88 ºC. Unfortunately, all of his attempts to culture these life forms in the lab had been unsuccessful. He had decided to focus his efforts this summer on Mushroom Spring, where the water was 73 ºC, right at the supposed limit for life, and assigned Freeze the task of collecting microbial samples from the waters of the spring. On September 5, Freeze collected a promising-looking sample, which he took back to a makeshift lab in Brock's cabin to prepare for transport back to Indiana.

A few weeks later, working in his professor's lab in between classes and homework, Freeze was engaged in the challenge of figuring out how to get his microbes to grow outside their natural environment, so that he could isolated and eventually characterize them. The work was frustrating at first – attempting to get the bacterial to grow in a liquid medium, he never observed the characteristic turbidity that usually signals success. In some samples, however, he did observe the appearance of salt crystals on the bottom of the test tubes. He allowed these samples to incubate for a few more days, and noticed that more crystals had formed. Just to be thorough, he decided to look at some of the crystals under a microscope – and hit the jackpot. Clinging to the crystals themselves were the recognizable shapes of microbial cells.

In subsequent work with Thomas Brock, Freeze was able to improve his culturing techniques and characterize the new species of bacterium, which was later named *Thermus aquaticus*, or 'Taq' for short. He also was able to demonstrate that enzymes isolated from the bacterium remained intact and active even in boiling water.

Even though Yellowstone is a beautiful place to spend a few weeks in the summer doing field work, it turned out that making the trip to Wyoming was not really necessary – Thomas Brock later was able to isolate cultures of Taq from samples taken from the hot water system right there on the Indiana University campus, as well as from many other hot-water environments around the world.

Brock and Freeze went on to publish a paper in the Journal of Bacteriology (1969, 98, 289) describing their newly discovered species, and donated live cultures of Taq to the American Type Culture Collection, a biological repository in Washington D.C.

Years later, a scientist named Kary Mullis working at Cetus, a biotechnology firm in the San Francisco Bay area, purchased a culture of Taq - a direct descendent of the very culture that Hudson Freeze had taken from Mushroom Spring on September 5, 1966 - from the ATCC repository. Cetus paid $35 for the sample. It turned out to be a pretty good investment.

Mullis and his colleagues at Cetus were intrigued by Freeze's report years earlier that enzymes isolated from Taq were stable at high temperatures, unlike enzymes isolated from E. coli and other common model organisms. They cultured their Taq sample, purified the DNA-copying enzyme DNA polymerase from the Taq cells, and using the heat-stable polymerase were able to come up with a remarkably efficient method for copying short stretches of DNA. Their 'polymerase chain reaction', or PCR, went on to revolutionize the fields of molecular/cellular biology and biochemistry – read through the experimental section of any recent research paper in one of these fields and chances are you will see that the researchers used PCR. If you take a lab course in molecular biology, you will probably perform at least one PCR procedure. When your professor purchases the purified Taq polymerase enzyme and other reagents for your lab, part of the price will go towards paying royalty fees to the pharmaceutical giant Hoffmann-LaRoche: Kary Mullis and Cetus obtained a patent for their PCR process, and in 1992 sold patent rights to Hoffmann-LaRoche for $300 million. Mullis was awarded the 1993 Nobel Prize in Chemistry for his work on PCR.

What makes the PCR technique so powerful is that it harnesses a biological catalyst - the DNA polymerase enzyme naturally produced by the Taq microbe - to vastly increase the rate of a very specific and very useful chemical reaction, under environmental conditions (high temperature) that until then had been fatal for other enzymes. Taq polymerase, the $300 million molecule, is the most visible example (for now!) of how scientists might harness the power of biological catalysis to great advantage, but many researchers are hard at work, in Yellowstone and many other locations around the world, writing more chapters in the story that was begun by Hudson Freeze and Thomas Brock on a September day in 1966.

Up to this point, we have been focusing on the structure of organic molecules: essentially, how these molecule are put together. Now our focus shifts to the study of reactivity: what happens, in other words, when covalent bonds within a molecule break and new covalent bonds form, as molecule A is transformed into molecule B. The story of Taq and PCR is centered around a biochemical reaction - the polymerization of DNA starting with an existing DNA 'template'. We are about to begin our exploration of chemical reactivity: how a reaction is depicted on paper, whether it absorbs or releases energy, how fast it goes, and how a catalyst might be able to make it go much faster.

In your previous college general chemistry and high school chemistry courses (and perhaps in biology courses as well), you have no doubt seen many different examples of chemical reactions. Most likely, these reactions were depicted by chemical equations, showing the starting materials (reactants) and the finished products connected by a 'reaction arrow'. In most cases, the structures of reactants and products were not considered - they were defined only by molecular formula and perhaps by physical state (solid, liquid, gas, or solution). The reaction below, showing the decomposition of dinitrogen pentoxide ($\mathbf{N_2O_5}$) to nitrogen dioxide and oxygen, is a typical example of the 'equation' treatment of chemical reactivity which you might have seen in your General Chemistry textbook.

$$\mathbf{N_2O_5\,(s) \longrightarrow 2\,NO_2\,(g) + \tfrac{1}{2}\,O_2\,(g)} \tag{6.0.1}$$

This way of talking about chemical reactions is perfectly adequate in introductory chemistry classes, when fundamental chemical concepts like stoichiometry, thermodynamics, and kinetics are being explained for the first time. In organic chemistry, beginning with this chapter, we will go much further. We will certainly review the important fundamental concepts of thermodynamics and kinetics that you learned previously. But in our discussion of organic reactivity, we will bring our understanding of organic structure into the picture, and think about how reactions take place: which bonds break, which bonds form, why a particular bond breaks or forms, the order in which bond-breaking and bond-forming takes place, and the nature of any intermediate species that might form during the course of the reaction. We also will think about how catalysts - enzymes in particular - are able to increase the rate of a particular reaction. Taken together, a description of a chemical reaction at this level is called a reaction mechanism. Beginning here, and continuing throughout the rest of the text, our main job will be to understand the mechanisms of the most important types of reactions undergone by organic molecules in living organisms.

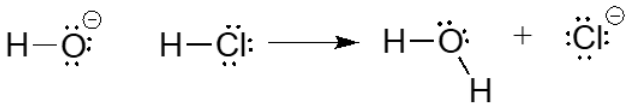
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6.1: A First Look at Some Organic Reaction Mechanism

An acid-base (proton transfer) reaction

We'll begin with a relatively simple type of reaction that you are no doubt familiar with from previous chemistry classes: an acid-base reaction. Note that in chapter 7, we will come back to consider acid-base reactivity in much greater detail. Here is the acid-base reaction between hydroxide ion and hydrochloric acid:



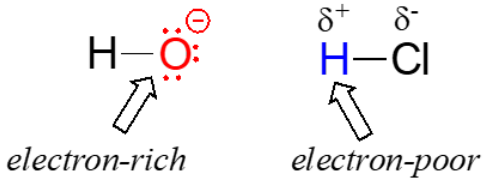
Note

A reaction such as the one above would of course include a spectator cation, such as sodium (Na^+) or potassium (K^+). In most of the reaction figures that we'll see throughout this book, the spectator ion is not shown in the interest of simplicity.

A proton is transferred from HCl, the acid, to hydroxide ion, the base. The product is water (the conjugate acid of hydroxide ion) and chloride ion (the conjugate base of HCl).

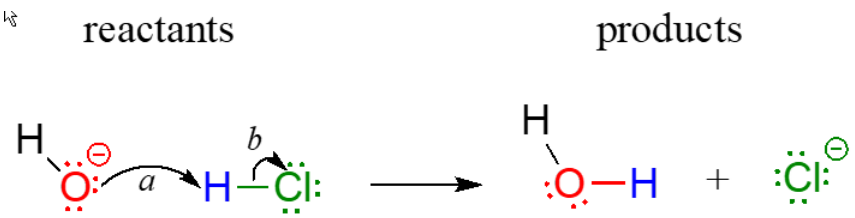
Despite its simplicity (and despite the fact that the reactants and products are inorganic rather than organic), this reaction allows us to consider for the first time many of the fundamental ideas of organic chemistry that we will be exploring in various contexts throughout this text.

One very important key to understanding just about any reaction mechanism is the concept of electron density, and how it is connected to the electron movement (bond-breaking and bond-forming) that occurs in a reaction. The hydroxide ion – specifically, the oxygen atom bearing the negative formal charge – has high electron density: it is electron-rich.



The hydrogen atom in HCl, on the other hand, has low electron density: it is electron-poor, because chlorine is more electronegative than hydrogen. As you might expect, an atom that is electron-rich is likely to be attracted to an atom that is electron-poor. As hydroxide and HCl move closer to each other, a new bond forms between oxygen and hydrogen, and the hydrogen-chlorine bond breaks. The end result is a water molecule and a chloride anion.

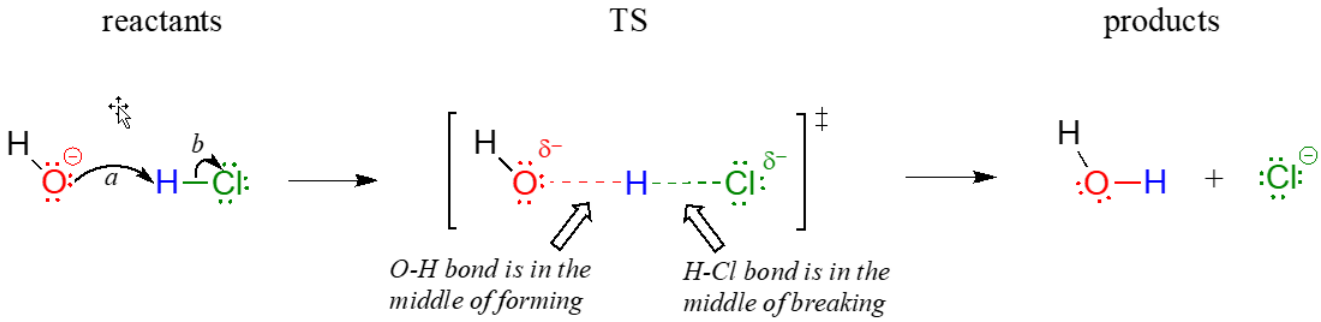
In organic chemistry terms, a reaction mechanism is a formalized description of how a reaction takes place - how we get, in other words, from reactants to products. Previously (section 2.3) , we saw how curved arrows were used to depict the 'imaginary' movement of two electrons when illustrating the conversion between two resonance contributors of the same molecule or ion (remember from that discussion that the conversion between two resonance contributors is not a reaction - it is merely an illustration of two different ways to draw the same molecule). The same curved arrow convention is used in mechanism drawings to show the electron movement that takes place in chemical reactions, where bonds are actually broken and formed. The mechanism for the $HCl + OH^-$ reaction, for example, can be depicted by drawing two curved arrows.



Arrow (a) in the mechanistic drawing originates at one of the lone pairs on the hydroxide oxygen and points to the 'H' symbol in hydrochloric acid, illustrating the 'attack' of the oxygen lone pair and subsequent formation of a new hydrogen-oxygen bond. Arrow (b) originates at the middle of hydrogen-chlorine bond and points to the '**Cl**' symbol, indicating that this bond is breaking: the two electrons that make the bond are 'leaving' and becoming a lone pair on chloride ion. Always keep in mind that these curved arrows by definition depict the movement of two electrons. (When we study radical reactions in chapter 17, we will see how to depict the movement of a single electron.)

When two (or more) curved arrows are drawn in the same figure of a mechanism, the intended meaning is that the electron movements being shown are occurring simultaneously. For example, in the figure above, the electron movement illustrated by arrow (a) (**O–H** bond formation) is occurring at the same time as the **H–Cl** bond breaking illustrated by arrow (b).

The transition state (TS) of a chemical step is a point at which bonds are in the process of breaking and/or forming. (More specifically, we will see below when discussing energy diagrams that the transition state is the point of highest energy in the chemical step). Transition states are illustrated by drawing the forming/breaking bonds as dotted lines, and are enclosed by brackets with the 'double-dagger' symbol. For example, the transition state in the acid-base reaction between hydroxide and **HCl** can be illustrated as:



Notice in the drawing above that both the oxygen and the chlorine bear partial negative charges at the transition state: the formal charge on oxygen changes from -1 to 0 during the course of the reaction step, while the formal charge on chlorine changes from 0 to -1.

While it can sometimes be instructive to include a transition state drawing in an organic mechanism diagram, they are not 'obligatory' elements of such a diagram. When asked to draw a reaction mechanism in the exercises and problems in this book, you need not include TS drawings in your answer unless specifically directed to do so.

? Exercise 6.2.1

Draw electron movement arrows to illustrate mechanism of the acid-base reaction between acetic acid, CH_3CO_2H, and ammonia, NH_3. Draw out the Lewis structures of reactants and products, including all lone pairs and formal charges. Include a transition state drawing in your mechanism.

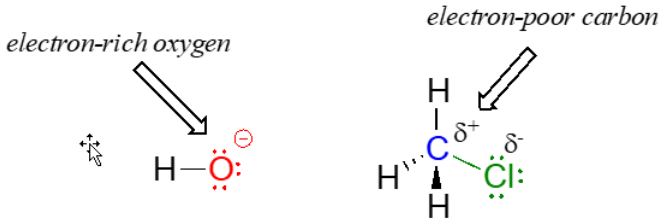
? Exercise 6.2.2

Draw electron movement arrows to illustrate the mechanism of the reverse of the reaction in Exercise 6.2.1 : the acid-base reaction between acetate ion ($CH_3CO_2^-$, acting as a base) and ammonium (NH_4^+), acting as an acid). Again, draw out the Lewis structures of reactants and products, including all lone pairs and formal charges.

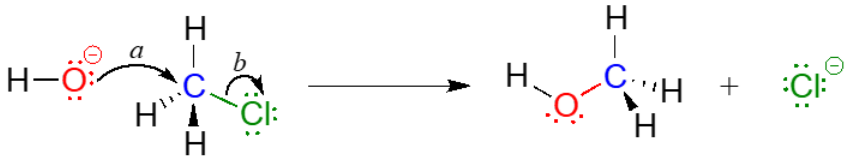
A one-step nucleophilic substitution reaction

The reaction between hydroxide and **HCl** is a simple example of a Brønsted acid-base (proton transfer) reaction. We now continue our introduction to the essential ideas of organic reactivity with a different type of reaction in which bonds to a carbon atom are rearranged. Consider what might happen if a hydroxide ion encountered a chloromethane molecule. The hydroxide is an electron-rich species, and thus might be expected to act as a base and 'attack' a hydrogen as it did in the previous example with hydrochloric

acid. In this case, though, the three hydrogens on chloromethane are not electron-poor, as they are bound not to chlorine but to carbon, which is not very electronegative. However, there is a relatively electron-poor atom in chloromethane: the carbon itself.



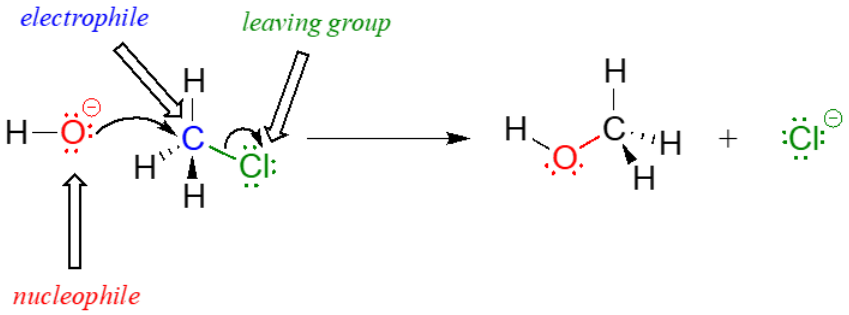
Due to the relative electronegativity of chlorine, the carbon-chlorine bond is polar. It stands to reason that a lone pair of electrons on the electron-rich hydroxide oxygen will be attracted to the electron-poor carbon nucleus.



In the mechanism drawing above, curved arrow (a) shows the lone pair electrons on the hydroxide oxygen moving to fill up an sp^3 orbital on chloromethane, forming a new carbon-oxygen s bond. However, in order for this new bond to form, one of the bonds already on the carbon must simultaneously break - otherwise, there will be five bonds to carbon and the octet rule will be violated (remember that the 'octet rule' tells us that elements in the second row of the periodic table can have a maximum of eight valence electrons). Curved arrow (b) illustrates how the two electrons in the carbon-chloride bond break out of their s bond and become a lone pair on the chloride ion product. In other words, arrow (b) illustrates the breaking of the carbon-chlorine bond. (We will see a transition state drawing for this reaction in chapter 8, when we study this type of reaction mechanism in much greater detail).

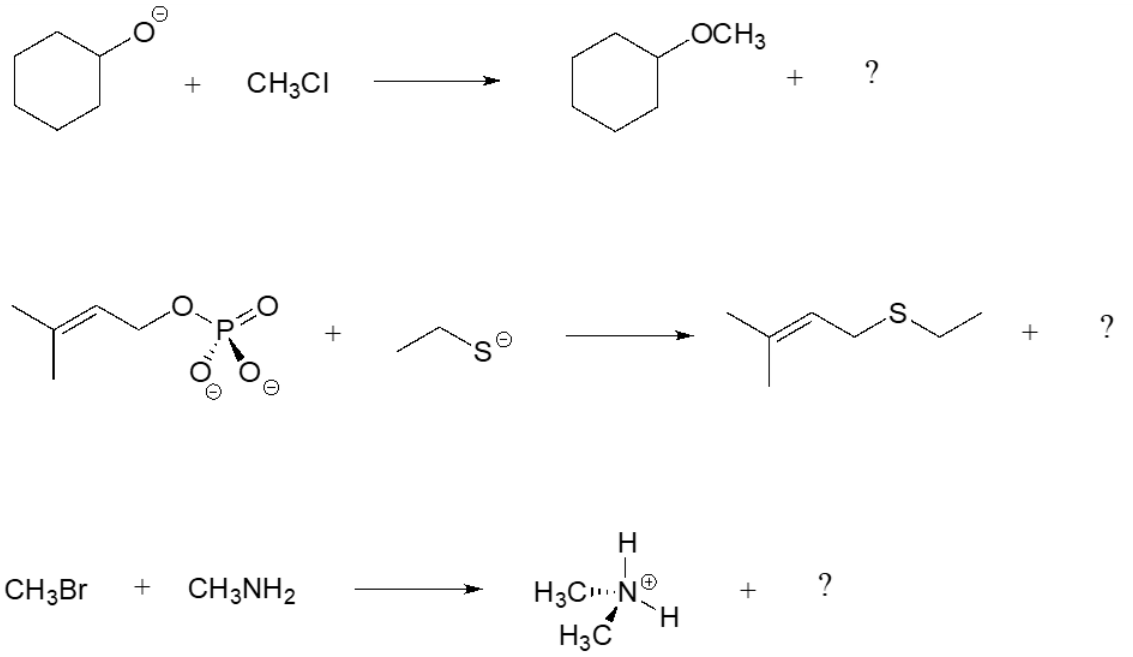
The reaction mechanism illustrated above called a nucleophilic substitution. The 'substitution' term is easy to understand: just recognize how hydroxide substitutes for chlorine as the fourth bond to the central carbon. The term 'nucleophilic' means 'nucleus-loving' and refers to the electron-rich species, the hydroxide oxygen. This oxygen is a nucleophile: it is electron-rich and attracted to the electron-poor nucleus of the carbon atom, and 'attacks' with a lone pair to form a new covalent bond.

There are two more terms that come into play here, both of which you will see again and again as you continue to study organic reactions. Because the carbon atom in methyl chloride is electron-poor, it is attracted to anything that is electron rich - anything nucleophilic, in other words. Thus, the carbon is referred to in this context as an electrophile. The chlorine, because it leaves with two electrons to become a chloride ion, is termed a leaving group.



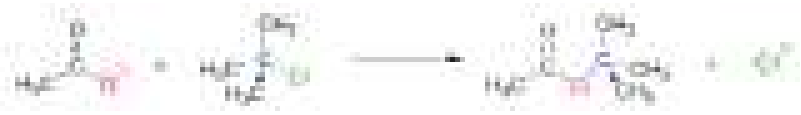
? Exercise 6.2.3

In each of the nucleophilic substitution reactions below, identify the nucleophile, electrophile, and leaving group, and fill in the missing product.



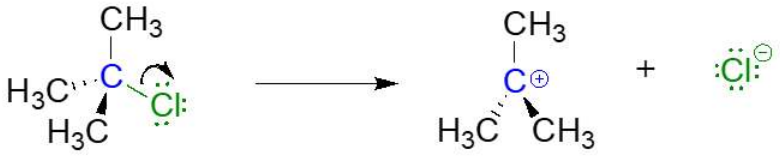
A Two-step Nucleophilic Substitution Mechanism

Reaction mechanisms describe not only the electron movement that occurs in a chemical reaction, but also the order in which bond-breaking and bond-forming events occur. Some nucleophilic substitution reactions, for example, can occur by a two-step mechanism that is different from the one-step mechanism we just saw between hydroxide ion and chloromethane. Look, for example, at the substitution reaction between acetate ion and 2-chloro-2-methyl propane (common name tert-butyl chloride).

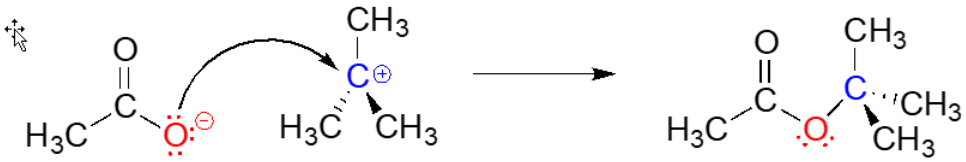


Unlike the chloromethane plus hydroxide reaction, in which the substitution process took place in a single, concerted step, it turns out that this mechanism involves two separate steps. The leaving group, chloride anion, leaves first, *before* the acetate nucleophile attacks.

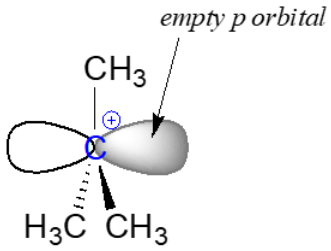
Step 1: Loss of leaving group (slow)



Step 2: Nucleophilic Attack (fast)



Because the central carbon (colored blue in the figure above) has lost its share of the two electrons in what was the carbon-chlorine bond, it is now positively charged. Recall from section 2.1 that we can picture a carbocation as a planar, sp^2-hybridized carbon center with three bonds, an empty p orbital, and a full positive charge.



The carbocation is highly reactive, and does not exist for very long before participating in a subsequent bond-forming event. In the language of organic mechanisms, it is referred to as a **reaction intermediate**.

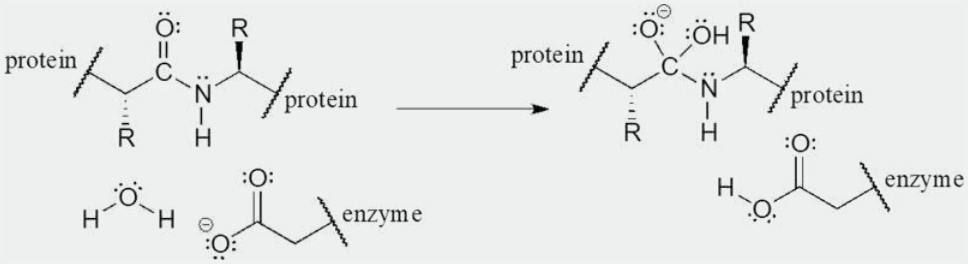
With its empty p orbital, the carbocation intermediate is clearly electron-poor, and thus is a powerful electrophile. The negatively charged acetate ion is electron dense and a nucleophile, and as such is strongly attracted to the carbocation electrophile. Attack by the nucleophile results in a new carbon-oxygen s bond and formation of the substitution product.

We will have much more to say about nucleophilic substitutions, nucleophiles, electrophiles, and leaving groups in chapter 8. The take home message at this point, however, is simply that two reactions that look quite similar in terms of the reactants and products can occur by different mechanisms.

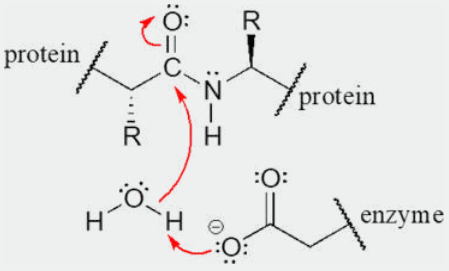
Curved Arrows

You can probably appreciate by now how essential it is to understand and be able to work with curved arrows - it is something that will use constantly during the remainder of your study of organic reactivity.

For example, although you are not yet familiar with the relevant reaction mechanism (it is the HIV protease reaction, covered in chapter 11), given reactant and intermediate structures:



with practice you should at this point be able to recognize the bond-forming and bond-breaking electron movement that is taking place, and draw the appropriate curved arrows:



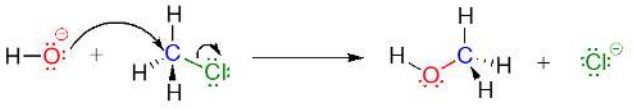
An additional word of caution: many beginning organic students make the mistake of using curved arrows to depict the motion of atoms. This is incorrect! The curved arrows in an organic mechanism always refer to the motion of electrons.

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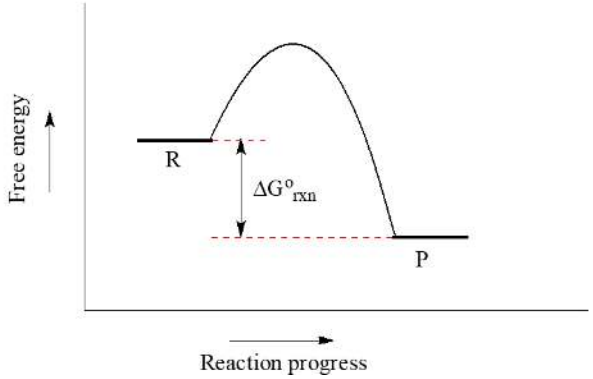
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6.2: A Quick Review of Thermodynamics and Kinetics

You may recall from general chemistry that it is often convenient to illustrate the energetics of a chemical reaction with a reaction coordinate diagram. In a reaction coordinate diagram, the vertical axis represents the overall potential energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting reactants R to final products P. (Many students find it helpful to envision the horizontal axis in an reaction coordinate diagram as being analogous to the progress bar at the bottom of a youtube video). The diagram for a typical one-step nucleophilic substitution reaction such as that between hydroxide and methyl chloride might look like this:



reactants (R) **products (P)**



Despite its apparent simplicity, this diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the thermodynamics of a reaction, we are concerned primarily with the difference in energy between reactants (R) and products (P): whether the reaction as a whole is uphill or downhill. When we talk about kinetics, on the other hand, we are concerned with the rate of the reaction: how fast it goes from reactants to products, regardless of whether that transformation is energetically uphill or downhill.

Thermodynamics

First, a quick review of some key thermodynamics terms. Recall that the standard Gibbs free-energy change of a reaction (ΔG^o) is the difference in energy between reactants and products at standard conditions. Gibbs free-energy change is a combination of enthalpy change (ΔH^o) and entropy change (ΔS^o):

$$\Delta G = \Delta H^o - T\Delta S^o \tag{6.2.1}$$

where

- T is the temperature in Kelvin (recall that the Kelvin temperature is simply the Celsius temperature plus 273.15).
- Enthalpy change (ΔH^o) is the heat released or absorbed by the reaction.
- Entropy change (ΔS^o) is the change in disorder from reactants to products. In a reaction in which one molecule cleaves into two smaller molecules, for example, disorder increases, so ΔS^o is positive.

The equilibrium constant (K_{eq}) for a reaction is an expression of the relative concentrations of reactants and products after the reaction has reached equilibrium. The equilibrium constant is defined as:

this means that w molecules of compound A react with x molecules of compound B)

$$wA + xB \rightleftharpoons yC + zD$$

$$Keq = \frac{[products]}{[reactants]} = \frac{[C]^y\,[D]^z}{[A]^w[B]^x}$$

Now, let's review what the above energy diagram tells us about the thermodynamics of the reaction. Note that the energy level of the products is lower than that of the reactants. This tells us that the Gibbs free-energy change for the reaction is negative, and the step is exergonic, or energy releasing. We can also say the reaction is 'thermodynamically favorable', or, more informally, 'downhill'.

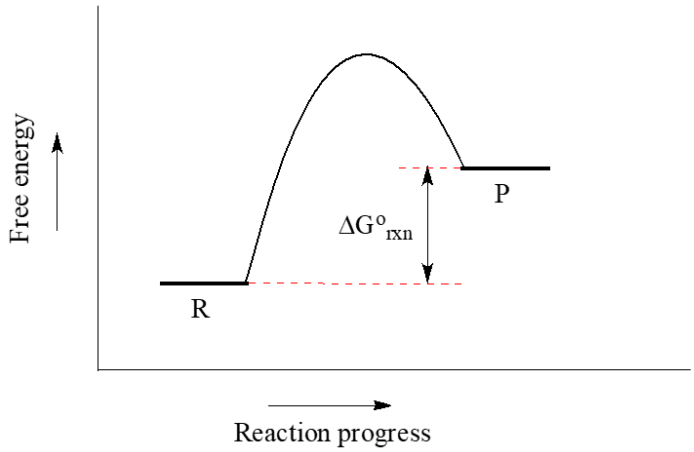
Recall from General Chemistry that the standard Gibbs free energy change for a reaction can be related to the reaction's equilibrium constant (Keq) by the equation:

$$\Delta G^o = -RT \ln K_{eq} \tag{6.2.2}$$

where R is the gas constant (8.314 J/mol×K) and T is the temperature in Kelvin (K).

If you do the math, you see that a negative value for ΔG_{rnx}° (an exergonic reaction) corresponds to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

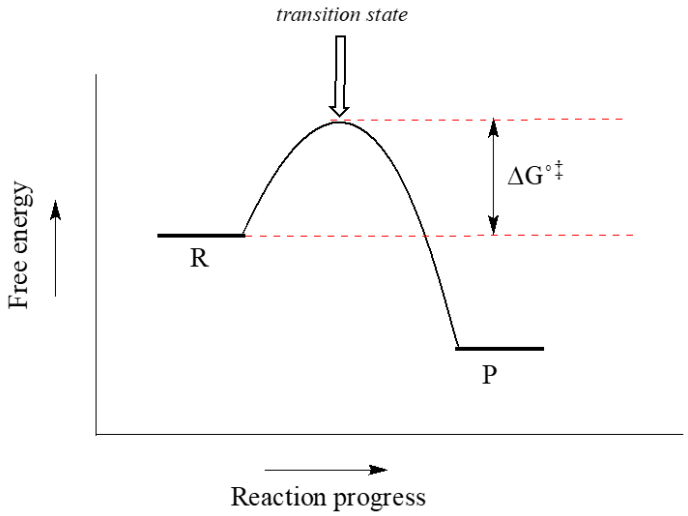
Conversely, an endergonic reaction is one in which the products are higher in energy than the reactants, and energy is absorbed. An endergonic reaction has a positive value of ΔG_{rnx}°, and a K_{eq} between 0 and 1.



Acid-base reactions provide convenient examples of thermodynamically favorable and unfavorable reactions. The reaction of a strong acid like HCl with a strong base like hydroxide ion, for example, is highly favorable, and has an equilibrium constant much greater than one. The reaction of a weak acid such as acetic acid with a weak base such as water, on the other hand, is unfavorable and has an equilibrium constant that is a very small (much less than 1) positive number: we can visualize this in a reaction coordinate diagram as an 'uphill' reaction, in which ΔG_{rnx}° is positive.

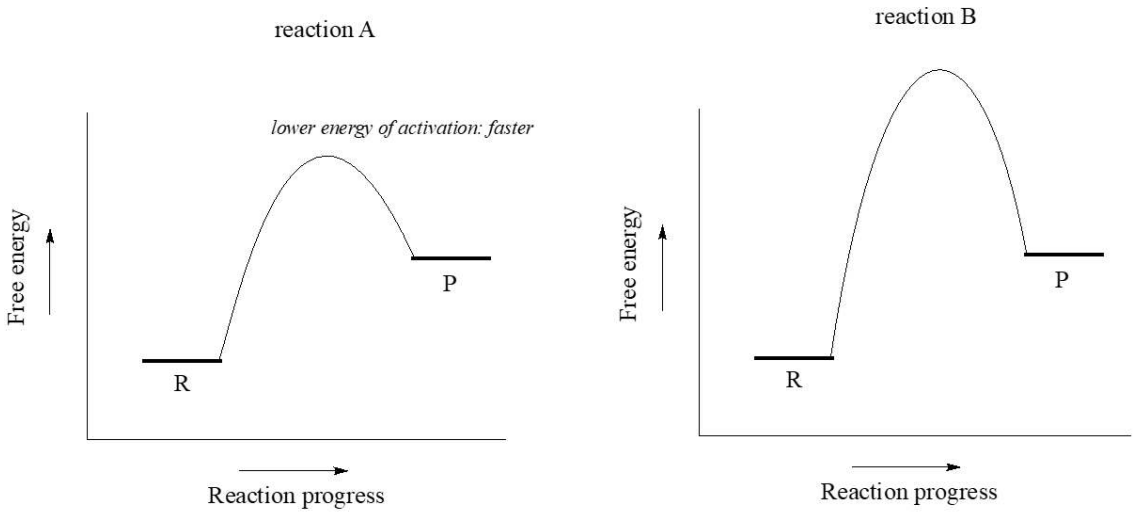
When talking about exergonic, or 'downhill' reactions, chemists sometimes use the term 'driving force' to describe the chemical factor or factors that drive the reaction from higher energy reactant to lower energy product. Using the 'downhill' analogy again, when water flows downhill, the driving force is gravity. In an exergonic chemical reaction, the driving force generally is based on a combination of two factors: a) the stability of positive and negative charges in the product relative to those in the reactant, and b) the total bond energy in the product relative to the reactant. That may not make a lot of sense right now, but keep it in the back of your mind and we will come back to the idea of driving force when we study different reaction types in greater detail.

Now, let's move to kinetics. Look again at the diagram for an exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier is called the standard free energy of activation ($\Delta G^{\circ}_{+}{}^{+}$). The activation energy, in combination with the temperature at which the reaction is being run, determines the rate of a reaction: the higher the activation energy, the slower the reaction. At the very top of the energy barrier, the reaction is at its transition state (TS), which you should recall is defined as the highest energy structure in the transition from reactant to product.

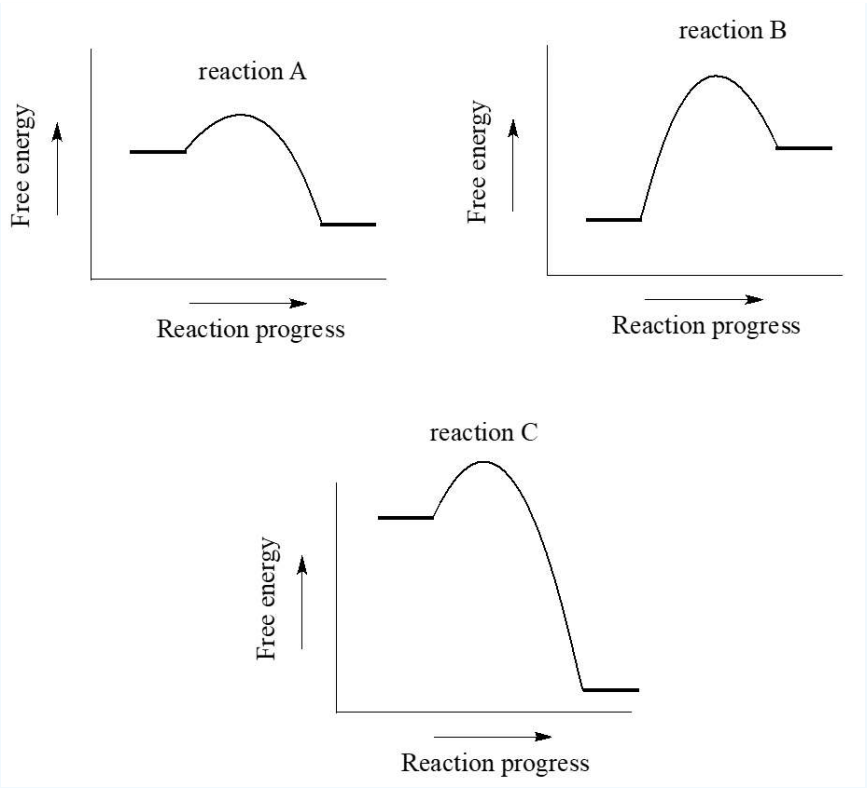
Consider the hypothetical reaction reaction coordinate diagrams below.



Both reaction A and reaction B are slightly endergonic, or uphill: ΔG°_{rxn} for both is positive, meaning that K_{eq} for both is between 0 and 1. However, the energy of activation is higher for reaction B. From this observation, we know that reaction A will proceed faster than reaction B in both forward and reverse directions (temperature and other conditions being equal), so reaction A will reach equilibrium in less time.

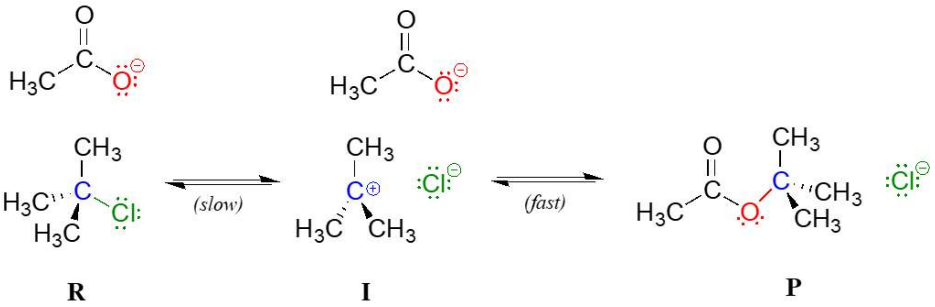
? Exercise 6.3.1

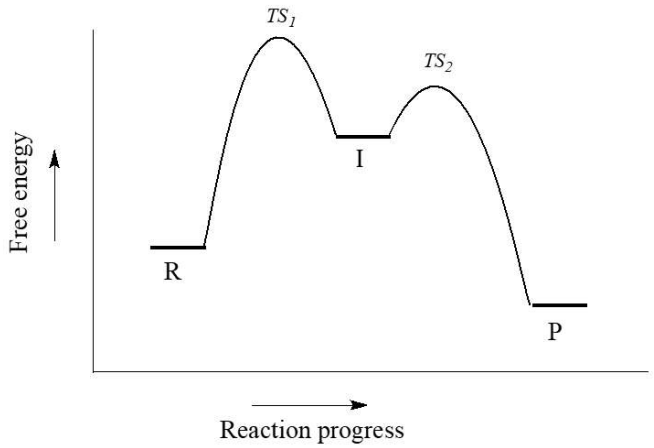
Consider the hypothetical reaction coordinate diagrams below, and assume that they are on the same scale.



a. Which of the diagrams describe(s) a reaction with $K_{eq} < 1$?
b. Which of the diagrams describes the fastest reaction?
c. Which of the diagrams describes the reaction with the highest value of K_{eq}?
d. Which of the diagrams describes the reaction with the largest $\Delta G^{\circ +}_{rxn}$ for the reverse reaction?
e. Copy the diagram for your answer to part (d), and add a label which graphically illustrates the value of $\Delta G^{\circ +}_{rxn}$ for the reaction in the reverse direction.

We turn our attention next to a two-step reaction mechanism, such as the nucleophilic substitution reaction between acetate and tert-butyl chloride. The reaction coordinate diagram for this reaction looks somewhat different from what we have seen until now:





Because there are two steps involved, there are also two transition states and two activation energies to consider, as well as a carbocation intermediate (denoted by the letter I). The first, bond-breaking step from R to I, passing over transition state TS_1, can be depicted as a highly endergonic (uphill) reaction, because the carbocation-chloride ion pair is significantly higher in energy than the reactants. The second step, attack on the carbocation electrophile by the acetate nucleophile and formation of the new carbon-oxygen bond, is a highly exergonic step that passes over a second, lower energy transition state TS_2. The intermediate (I) is thus depicted as an energy 'valley' (a local energy minimum) situated between the two energy peaks TS_1 and TS_2.

Notice that the activation energy for the first step is higher than the activation energy for the second, meaning that the first step is slower. This should make intuitive sense, because the first step involves bond-breaking, separation of charge, and formation of a carbocation, which is high in energy due to lacking a complete octet. Conversely, the second step involves bond-forming and neutralization of charge. In a multi-step reaction, the slowest step - the step with the highest energy of activation - is referred to as the rate-determining step (rds). The rds can be thought of as the 'bottleneck' of the reaction: a factor which affects the rds will affect the overall rate of the reaction. Conversely, a factor which affects a much faster step will not significantly affect the rate of the overall reaction.

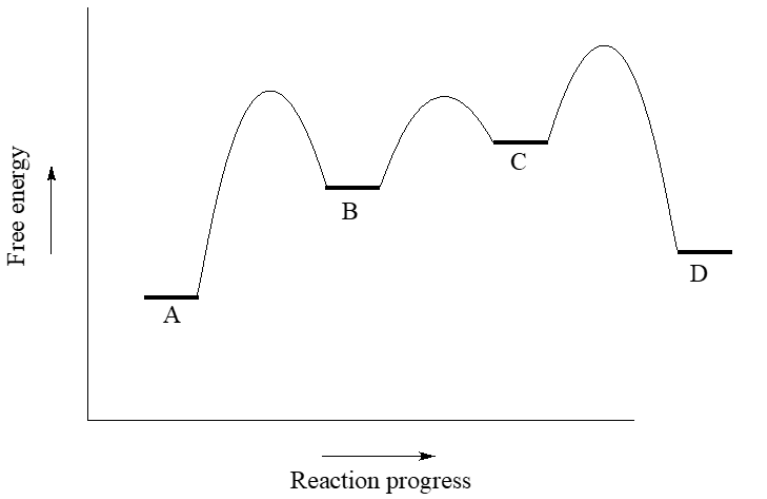
? Exercise 6.3.2

Imagine that you are trying to extinguish a burning campfire using buckets of water filled from a faucet some distance from the fire. It takes 20 seconds to fill a bucket at the faucet, and two seconds to carry the bucket to the fire and dump it on the flames. You have plenty of people to carry the buckets, but only one faucet so you can only fill one bucket at a time.

a. If you double the speed at which you carry the buckets by running instead of walking, what effect will this have on how fast you get water to the fire?
b. If, instead, you realize you can double the speed at which you fill up the buckets by using a second faucet, what effect will this have on how fast you get water to the fire?
c. What is the rate-determining step for the process?

? Exercise 6.3.3

Use the reaction coordinate diagram below to answer the questions.



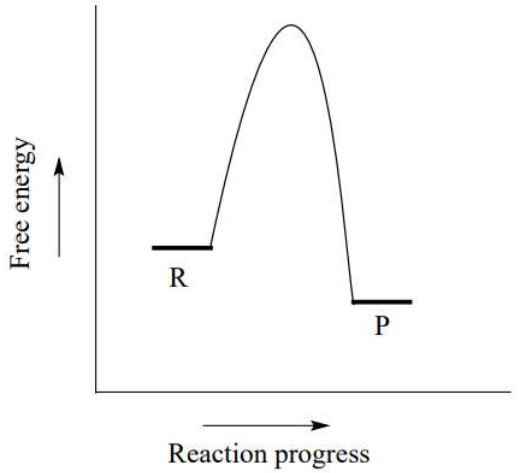
a. Is the overall reaction endergonic or exergonic in the forward (A to D) direction?
b. How many steps does the reaction mechanism have?
c. How many intermediates does the reaction mechanism have?
d. Redraw the diagram and add a label showing the activation energy for the rate-determining step of the forward reaction.
e. Add a label showing ΔG°_{rxn} for the reverse reaction (D to A).
f. What is the fastest reaction step, considering both the forward and reverse directions?

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6.3: Catalysis

Consider a hypothetical reaction $\mathbf{R} \rightarrow \mathbf{P}$ described by the diagram below.



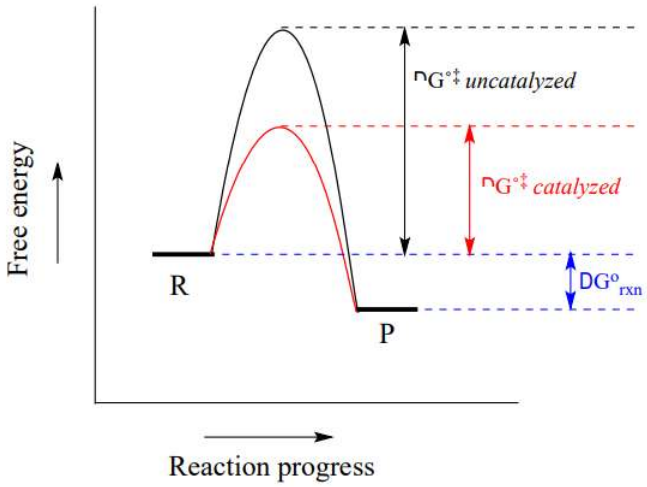
We notice two things about this reaction: it is exergonic, and it has a high activation energy. What this means is that although it is thermodynamically favorable, it is also slow: in other words, equilibrium favors product over reactants, but it will take a long time to reach equilibrium.

There are three ways that we could increase the rate of the reaction. First, we could add energy to the system by increasing the temperature, which gives the reacting molecules more energy to pass over the transition state. Increasing the temperature will increase the value of the rate constant k in the rate expression:

$$\text{rate} = k[R] \tag{6.3.1}$$

In the laboratory, many organic reactions are run at high temperatures for this very purpose. We could also increase the concentration of the reaction R, which would increase the rate of the reaction without increasing the value of k.

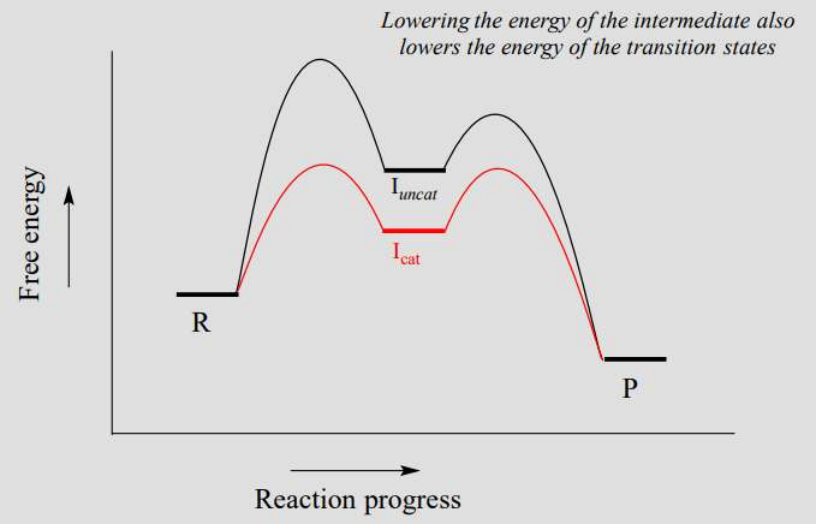
When talking about the biochemical reactions happening in a living cell, however, increasing the reaction temperature or reactant concentration is not a reasonable option. As an alternative, we could provide a new route from point R to point P in which the activation energy is lower. The role of a catalyst is to accelerate a reaction by stabilizing the transition state, and thus lowering the activation energy.



Catalysts, while they participate in the mechanism, are not consumed, so one catalyst molecule can catalyze multiple reaction cycles. Notice also that while the catalyst lowers the energy of the transition state (and thus the activation energy), it has no effect

on ΔG_{rxn}. A catalyst increases the rate of a reaction, but does not get consumed in the reaction and does not alter the equilibrium constant. In other words, a catalyst affects the kinetics of a reaction, but not the thermodynamics. Catalysts play a hugely important role in biochemical reactions.

Most organic reactions involve more than a single mechanistic step. Below is a reaction coordinate diagram illustrating rate acceleration of a two-step reaction by a catalyst:



Notice that the catalyst lowers the energy of the intermediate species. A concept known as the Hammond Postulate (the details of which are beyond our scope here) tells us that when a catalyst lowers the energy of an intermediate, it also lowers the energy of the adjacent transition states. Note in this diagram above that the energy barrier for the rate-determining first step is much lower in the catalyzed reaction - thus, the overall reaction is faster. When studying how an enzyme catalyzes a biochemical reaction, chemists often are actually looking at how the enzyme interacts with - and stabilizes - an intermediate species following a rate-determining step. The Hammond postulate tells us that an understanding of enzyme-intermediate interactions will also apply to enzyme-transition state interactions.

Acids and bases as are commonly used as catalysts in organic chemistry, and chemists have come up with a huge arsenal of catalysts, many of them metals, to speed up the rates of useful laboratory reactions. Almost all biochemical reactions are catalyzed by enzymes, which are protein catalysts. In the introduction to this chapter, we heard the story of the discovery of a heat-stable DNA polymerizing enzyme which turned out to be very useful to the scientific world.

How do enzymes accomplish their role as biochemical catalysts? Recall from section 1.3 that enzymes have an active site pocket in which substrates (reactant molecules) are bound. It is inside these active site pockets that most biochemical reactions take place. Enzymes achieve catalysis in the active site by some combination of the following:

1. By positioning two reacting molecules close to each other in the active site, in precisely the orientation necessary for them to react. Compare this to an uncatalyzed reaction in which completion depends on the two reactant molecules happening to collide, by chance, in the correct orientation.
2. By binding substrates in such a way that they assume the proper conformation necessary for a reaction to occur.
3. By increasing the reactivity of the substrates: making acidic protons more acidic, nucleophiles more nucleophilic, electrophiles more electrophilic, and leaving groups better at leaving. Very often, these feats are accomplished with acidic and/or basic amino acid side chains lining the active site pocket. As we go on to study many different types of biochemical reactions, we get a better of how this works.
4. By stabilizing the transition states of the slower, rate-determining steps of the reaction. If a transition state has a negative charge, for example, the enzyme might provide a positively charged amino acid side chain, or a bound metal cation such as Zn^{+2}, as a stabilizing factor. A lower-energy transition state, of course, means a lower activation energy and a faster reaction step.

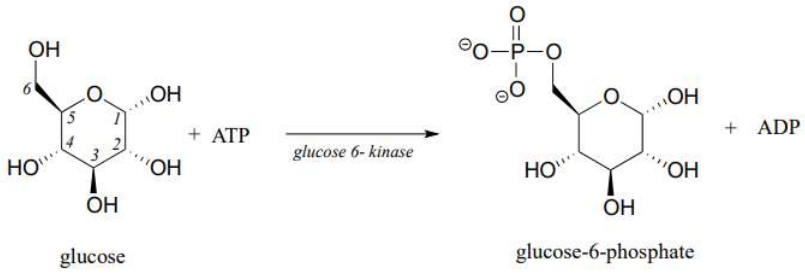
Enzymes are capable of truly amazing rate acceleration. Typical enzymes will speed up a reaction by anywhere from a million to a billion times, and the most efficient enzyme currently known to scientists is believed to accelerate its reaction by a factor of about 1017 over the uncatalyzed reaction (see Chemical and Engineering News, March 13, 2000, p. 42 for an interesting discussion about this nucleotide biosynthesis enzyme called 'orotidine monophosphate decarboxylase').

At this point, it is not necessary for you to fully understand the four ideas listed above: just keep them in mind as we go on to study a variety of common biological organic reactions and see in greater detail how enzymes have evolved to catalyze them.

? Exercise 6.4.1

Table sugar, or sucrose, is a high-energy dietary compound, as are the fats in vegetable oil. Conversion of these compounds, along with oxygen gas $\mathbf{O_2}$, to water and carbon dioxide releases a lot of energy. If they are both so high in energy (in other words, thermodyamically unstable), how can they sit for years on your kitchen shelf without reacting?

Another very important point to keep in mind about enzymes is the specificity with which they catalyze reactions. We have already discussed, in chapter 3, the idea that enzymes exert a very high level of control over the stereochemistry of a reaction: if two or more stereoisomeric products could potentially form in a reaction, an enzyme will likely only catalyze the formation of one stereoisomer, with negligible formation of other side products. Likewise, enzymes demonstrate remarkable control of regiochemistry in their reactions. The glycolysis pathway enzyme glucose-6-kinase, for example, transfers a phosphate group specifically to the hydroxyl group on carbon #6 of glucose, and not to any of the other four hydroxyl groups. We'll look more closely at this reaction and others like it in chapter 9.



glucose

glucose-6-phosphate

Finding ways to maintain control over stereochemistry and regiochemistry is a constant challenge for synthetic organic chemists working with non-enzymatic reactions, and the techniques that have been developed in this arena are a big part of what you will study if you go on to take a more advanced course focusing on organic synthesis.

Finally, we will encounter many biochemical reactions in this book in which the enzyme catalyzing the reaction does so with the assistance of a coenzyme. A coenzyme is a small (relative to a protein) molecule that binds in the active site of a partner enzyme and participates in some manner with the reaction being catalyzed. Table 6 at the back of the book shows the structures of several coenzymes commonly seen in biochemical reactions.

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6.4: Comparing Biological Reactions to Laboratory Reactions

The focus of this book is on organic chemistry in a biological context. At various points in our investigation of organic reactivity, however, we will also be considering some non-biological, laboratory counterparts of reactions that occur in living cells. The reason for this is two-fold: first of all, it is often instructive to compare and contrast similar reactions taking place in very different environments, and sometimes the similarities are quite striking. Secondly, even those who intend to pursue a career in the life or health sciences can benefit from some exposure to the kind of challenges that professional organic or medicinal chemists work on: if you are working as a biologist for a pharmaceutical company for example, you will be better able to appreciate the contributions of your chemist colleagues if you are able to make the intellectual connection between the reactions they are running in flasks and the those that are taking place in the cells you are studying.

Below we briefly outline the differences between laboratory and biological reactions:

- **Catalysts**: The vast majority of biological organic reactions are catalyzed by enzymes. While chemists synthesizing molecules in the laboratory sometimes make use of enzyme-catalyzed reactions, it is much more common to use non-biological catalysts (often containing transition metals), acids or bases as catalysts, or no catalyst at all.
- **Solvent**: Biological organic reactions occur in the aqueous environment of the cell. In the laboratory, organic reactions can be run in a wide variety of solvents, ranging from the very nonpolar (such as hexane) to the very polar, such as methanol,water, or even ionic liquids. Most commonly, though, laboratory reactions are run in relatively non-polar solvents such as diethyl ether or dichloromethane.
- **Reactant mixture**: The aqueous environment of a cell is an extremely complex mixture of thousands of different biomolecules in solution at low concentrations (usually nanomolar to millimolar), whereas the components of a laboratory reaction have usually been purified, and are present in much higher concentrations.
- **Temperature**: Biological reactions take place within a narrow temperature range specific to the organism: a little too cold and the enzymes catalyzing the reactions are 'frozen', a little too hot and the enzymes will come unfolded, or 'denature'. Laboratory reactions can be run at a variety of temperatures, sometimes at room temperature, sometimes at the boiling point of the solvent, and sometimes at very low temperatures (such as when a reaction flask is immersed in a dry ice-acetone bath).
- **pH**: Biological reactions take place in aqueous solution buffered to a specific pH: about pH 7 for most living things. Accordingly, highly acidic or basic species are unlikely to be reactants or intermediates in a biological reaction mechanism. Laboratory reactions are often carried out in the presence of strong acids or bases.

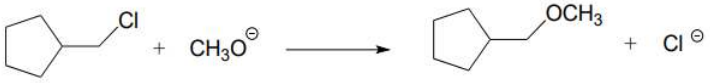
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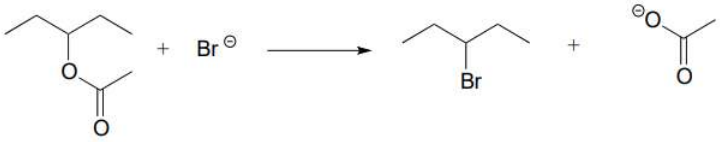
6.E: Overview of Organic Reactivity (Exercises)

P6.1: For each of the nucleophilic substitution reactions below, identify the atoms which are acting as nucleophile, electrophile, and leaving group, and draw a curved-arrow diagram showing a one-step mechanism.

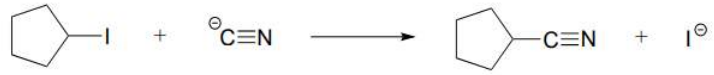
a.



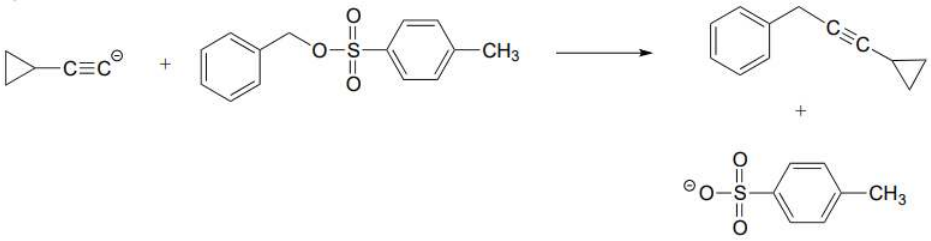
b.



c.

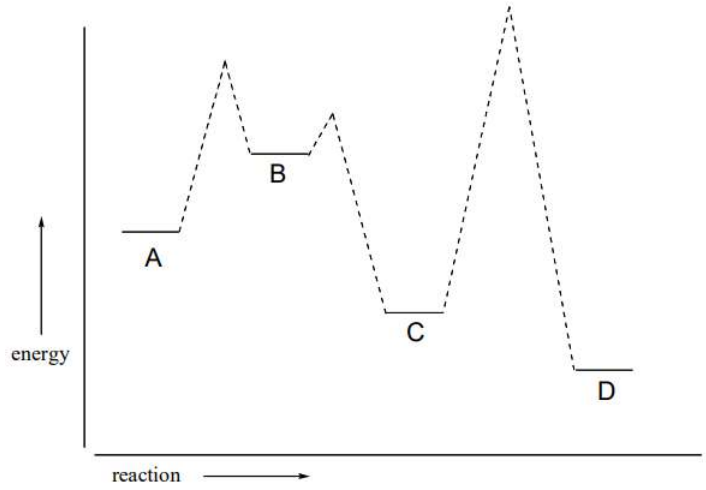


d.

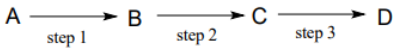


P6.2: Below is a reaction coordinate diagram for a hypothetical reaction.

a. What can you say about the value of K_{eq} for the overall A to D transformation?
b. What is the rate determining step for the overall A to D transformation?
c. Which step is faster, A to B or B to C?
d. Which transformation is more thermodynamically favorable, A to B or C to D?

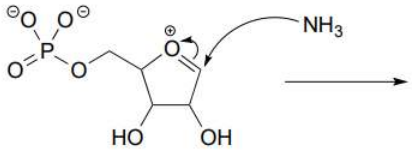


e. Below is a diagram of a hypothetical reaction. Step 2 is the rate-determining step, C is the least stable species, B is higher energy than D, and the overall reaction has an equilibrium constant $K_{eq} = 0.33$. Draw a diagram that corresponds to all of this information.

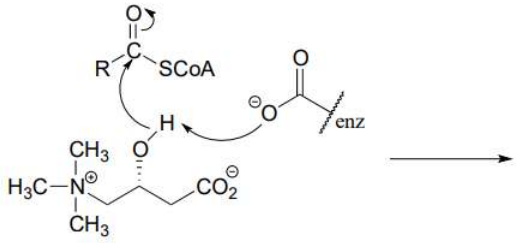


P6.3: Illustrated below are individual steps in some biochemical reaction mechanisms that we will be studying later. For each step, draw the products or intermediate species that would form according to the electron-movement arrows given. Be sure to include all formal charges. You do not need to show stereochemistry.

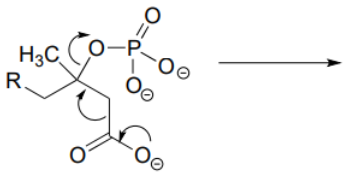
a.



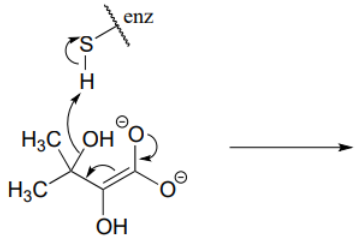
b.



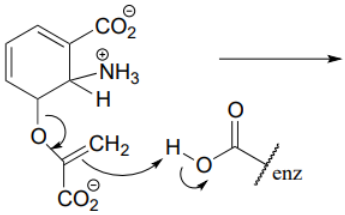
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d.

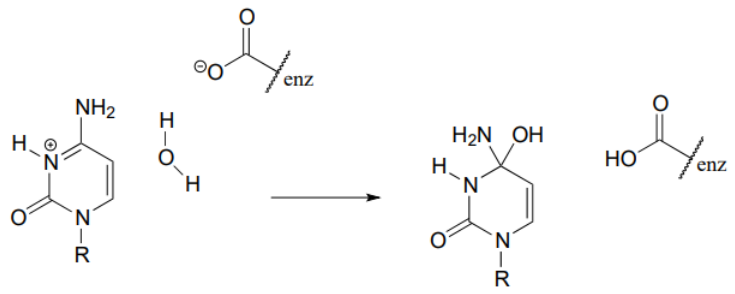


e.

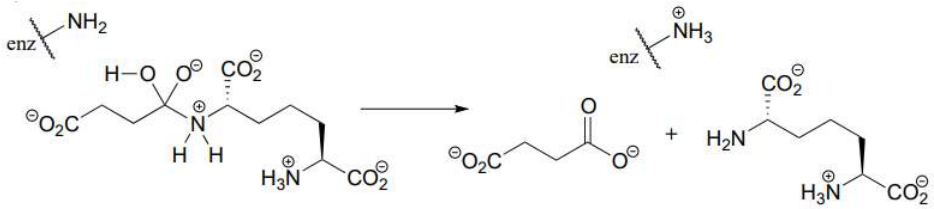


P6.4: Shown below are individual steps in some biochemical reaction mechanisms that we will be studying later. For each, draw curved arrows showing the electron movement taking place.

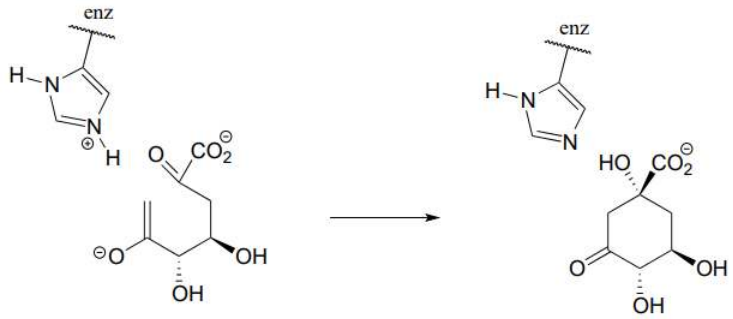
a.



b.



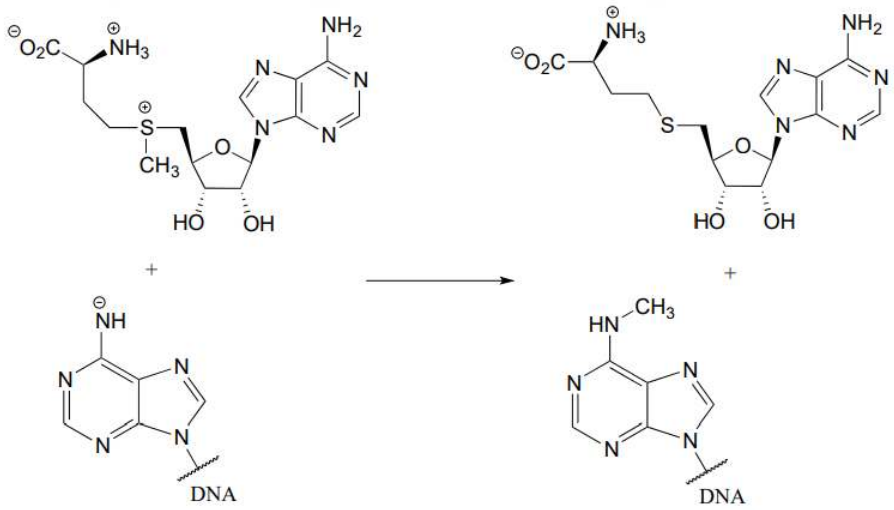
c.



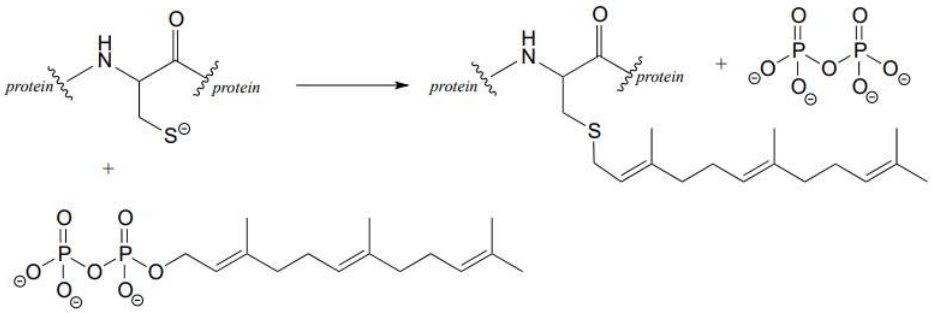
P6.5:

a. In the biochemical nucleophilic substitution reactions illustrated below, identify the atoms which are acting as nucleophile, electrophile, and leaving group.

Reaction 1:



Reaction 2:



b. Using appropriate 'R' abbreviations for regions of the molecules that are not directly involved in bond-breaking or bond-forming events above, draw curved arrows showing the electron movement that takes place in each step. Assume that both are one-step mechanisms.

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6.S: Overview of Organic Reactivity (Summary)

You should be confident in interpreting and using the curved arrow drawing convention for showing two-electron movement. Given a set of curved arrows describing a reaction step, you should be able to draw the product indicated by the arrows. Alternatively, given the starting structure and a product for a reaction step, you should be able to draw the curved arrows showing how bonds were broken and formed. You need not understand (yet) the chemistry behind these steps, you just need to be able to use the drawing formality.

- You should be able to recognize three reaction mechanism types: an acid-base reaction, a one-step nucleophilic substitution, and a two-step nucleophilic substitution.
- Given an example reaction, you should be able to identify a nucleophile, electrophile, and in many cases a leaving group.
- Given an example reaction mechanism, you should be able to recognize one or more reaction intermediates.
- Given a reaction coordinate diagram for a hypothetical reaction, you should be able to recognize whether the reaction is endergonic or exergonic, and whether the equilibrium constant is greater than or less than 1. You should be able to identify the point(s) on the diagram corresponding to transition state(s) and reaction intermediate(s). In a multi-step reaction diagram, you should be able to identify the rate determining step.
- Given a detailed reaction process showing starting reactant(s), intermediate(s), and product(s) with associated curved arrows, you should be able to sketch a reaction coordinate diagram that that is consistent with the details of the reaction mechanism.
- You should be able to explain the role of a catalyst in a reaction.
- You should be able to list the major differences between a typical biological reaction and a typical laboratory reaction.

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CHAPTER OVERVIEW

7: Acid-base Reactions

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7.2: The Acidity Constant
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7.4: Acid-base Properties of Phenols
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7.8: Effects of enzyme microenvironment on acidity and basicity
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7.S: Acid-base Reactions (Summary)

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7.0: Prelude to Acid-base Reactions



The glass flask sitting on a bench in Dr. Barry Marshall's lab in Perth, Western Australia, contained about thirty milliliters of a distinctly unappetizing murky, stinking yellowish liquid.

A few days earlier, Dr. Marshall, in consultation with his mentor and research partner Dr. J. Robin Warren, had poured a nutrient broth into the flask, then dropped in a small piece of tissue sample taken from the stomach of a patient suffering from chronic gastritis. Gastritis is an inflammation of the stomach lining characterized by lingering pain, nausea, and vomiting, and is often is the precursor to a peptic ulcer. Now, after several days of incubating in a warm water bath, the flask contained a living liquid culture, swarming with billions of bacterial cells. According to the medical textbooks lining Dr. Marshall's bookshelves, the bacteria should not have been there – nothing should have grown in the broth, because the highly acidic environment inside the stomach was supposed to be sterile. Also according to the textbooks, the cause of his patient's stomach ailment was stress, or perhaps a poor diet – but most definitely not a bacterial infection.

Dr. Marshall took a good, long, look at the contents of the flask. Then he gave it a final swirl, and drank it down.

Five days later, his stomach started to hurt.

This is the story of how two doctors dared to think what no one else had thought, and turned an established medical doctrine upside-down. Dr. J. Robin Warren was a pathologist at the Royal Perth Hospital in Perth, Western Australia. One day, when examining an image taken from a stomach biopsy from a patient with severe gastritis, he noticed what appeared to be spiral-shaped bacteria in the tissue, a surprising observation given the medical consensus that bacteria could not live in the stomach.

The microbe-like shapes were very hard to see, but when he tried treating the sample with a silver stain they became much more apparent. He decided to start looking at silver-stained sections of every stomach biopsy he examined, and before long he noticed a pattern: the presence of the spiral bacteria coincided with gastritis in the patient, and the tissues which were more severely inflamed seemed also to have more bacteria present. Could there be a causal link between the bacteria and the illness?

When he discussed his observations with colleagues, they dismissed the results as coincidental contamination – nothing important.

Warren wasn't willing to just let it go. He was able to interest Barry Marshall, a young internal medicine resident training at the same hospital, in taking on a research project to try and solve the mystery of the bacteria that were not supposed to exist. Marshall started by doing a thorough search of the literature, and found that his mentor was not the first to report seeing spiral-shaped bacteria in stomach tissue – there were in fact several such observations in the literature, the oldest going back to the middle of the 19th century. All of them had been dismissed as unimportant artifacts.

Warren and Marshall started sending stomach biopsies from gastritis patients to the microbiology lab in the hospital, to see if bacteria from the samples could be cultured in a petri dish. For many months, they got nothing. Then one Tuesday morning, right after the four-day Easter holiday, Marshall got a call from an excited microbiology technician: he had neglected to dispose of the latest round of test cultures before going home for the holiday, and instead had left them in the incubator the whole time. After growing for a full five days, the dishes had colonies of bacteria growing in them. All this time, the technicians had been throwing the cultures away after two days when no bacterial growth was evident – standard procedure when working with other bacteria – but apparently these bacteria were especially slow-growing.

Now that he could culture the bacteria in the lab, he was able to isolate and study them in more detail, and gave them the name Helicobacter pylori. Marshall confirmed Warren's earlier observation of a correlation between stomach bacteria and gastritis: only those patients suffering from gastritis or ulcers seemed to have the bacteria in their stomachs. There seemed to be strong evidence that H. pylori infection led to gastritis, which in turn lead eventually to stomach ulcers.

Despite the new data, Warren and Marshall's colleagues in the gastroenterology field were still unconvinced of the link between bacteria and gastritis or ulcers. Scientists are inherently skeptical people, and it was difficult to overcome the long-entrenched theory that the stomach was sterile, and that ulcers were caused by stress. Interviewed much later by Discovery Magazine, Marshall recalled: “To gastroenterologists, the concept of a germ causing ulcers was like saying that the Earth is flat”.

Poring once more over the available literature, Marshall learned that acid-reducing drugs – an enormously profitable product– were able to relieve ulcer symptoms, but only temporarily. One interesting piece of information stood out to him, though: an over-the-counter antacid containing the element bismuth (similar the brand-name medicine Pepto-Bismol) provided much longer-lasting relief compared to the other drugs – and in some cases seemed to effect a permanent cure. Marshall soaked a small circle of filter paper in the bismuth medicine, and placed it on a petri dish that he had inoculated with H. pylori. After five days in the incubator, there was a clear circle of non-growth around the filter paper. The medicine had killed the bacteria.

Everything seemed to fit together: almost all patients with gastritis or ulcers had H. pylori infections, and a drug which was able to kill the bacteria was also effective against the stomach ailment. But to convince the medical community that the root cause of ulcers was H. pylori infection, Warren and Marshall needed more direct evidence: they had to show that a healthy stomach – free from gastritis and uninfected by H. pylori – would develop gastritis as a result of intentional infection, and that clearing up the infection would also cure the gastritis. They tried experiments with pigs first, then rats, and then mice, but to no avail – they were not able to induce an H. pylori infection in the animal models. Marshall was getting desperate: all around him he saw patients suffering terribly, getting only temporary relief from acid blockers and eventually needing to have parts of their stomachs removed, and he was convinced that simple antibiotic therapy would cure them if only their doctors could be convinced to try it. Because animal models had failed, he decided to move to a model system that he knew would work: humans. Ethical and regulatory considerations prevented him from intentionally infecting human volunteers - so his only option was to use himself as a guinea pig.

We are now at the point in the story where Barry Marshall, in the name of science and medicine, took his disgusting but undeniably courageous gulp of bacteria-laden broth. He had already undergone an endoscopy to ascertain that his stomach was free from both inflammation and H. pylori. As we already know, he started to develop symptoms of gastritis about five days after drinking the bacteria – the same amount of time that it took for H. pylori colonies to appear in the petri dish cultures. After a few more days, he underwent another endoscopy, and was overjoyed to be told that his stomach was indeed inflamed, and was infested with spiral-shaped bacteria. He initially wanted to carry on the experiment for a few more days of further tests, but his wife had a different opinion on the matter and convinced him to begin antibiotic treatment, which quickly cleared up both his infection and his stomach inflammation.

Marshall and Warren now had clear, direct evidence that the stomach inflammation which leads to ulcers was caused by bacteria, and could be cured with antibiotics. They submitted a summary of their results for presentation at a meeting of the Gastroenterological Society of Australia, but were rejected. Apparently, 67 submissions had come in and there was only time for 56 presentations; unfortunately their results were not considered important enough to make the cut. They persevered, and eventually published their findings in the June, 1984 issue of the British medical journal The Lancet.

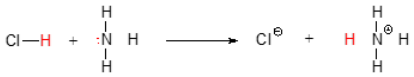
The paper gained some notice, especially from microbiologists, but did not have an immediate impact in clinical practice. Around the world, gastroenterologists continued to treat ulcers with acid blockers. Outside of the mainstream medical community, however, word was getting out that two Australian doctors had a cure for ulcers, and more people started coming to them for treatment. Stories about Warren and Marshall appeared in places like Reader's Digest and The National Enquirer, and eventually in the United States the National Institutes of Health and the Food and Drug Administration responded by fast-tracking the clinical testing and approval process, and publicizing the new treatment option.

Stomach ulcers, which have been tormenting human beings since the beginning of recorded history, are today considered an easily curable condition, and the idea that they are caused by H. pylori infection is fully accepted by the medical community. Drs. J. Robin Warren and Barry Marshall shared the 2005 Nobel Prize in Medicine.

The now-discredited idea that the stomach is a sterile place made perfectly good biochemical sense at the time: the stomach is like a bathtub full of hydrochloric acid, which you probably recall from previous chemistry classes and labs is a very strong, dangerously corrosive acid. It is very difficult to imagine how a microbe could survive in such an environment. We now know that H. pylori can thrive there in part because its spiral shape allows it to burrow deep into the protective layer of mucus that coats the stomach wall. In addition, H. pylori cells produce large amounts of an enzyme called urease, which catalyzes a reaction between urea and water to form carbon dioxide and ammonia.



Ammonia - the main component of window-washing liquid - is a fairly strong base, and reacts rapidly and completely with hydrochloric acid to neutralize it.



Although scientists are still unsure of all the details, it is likely that these two protective strategies used by H. pylori somehow play a role in causing the inflammation that can lead to peptic ulcers, where the stomach lining becomes exposed to the harsh action of hydrochloric acid.

The idea of acidity is at the heart of our story about the discovery of H. pylori, and is the subject of this chapter. From here on in our study of organic chemistry, we will be learning about how organic molecules react, and how their structure determines their reactivity. The reaction between an acid and a base - where a proton is donated from the former and accepted by the latter - is the first kind of organic reaction that we will explore. After reviewing some basic ideas about acid-base equilibria with which you are probably already familiar from General Chemistry, we will dive into some very challenging new waters, as we attempt to use our understanding of organic structure to predict how different organic functional groups will react in an acid-base context. Many of the ideas that are introduced in this chapter, though perhaps difficult to grasp at first, will be crucial to understanding not only acid base chemistry but all of the other organic reaction types that we will see throughout the remainder of the book.

Additional reading:

The Dr. Who Drank Infectious Broth, Gave Himself an Ulcer, and Solved a Medical Mystery

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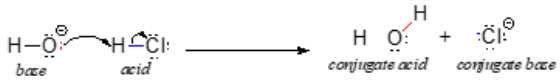
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7.1: Overview of Acid-Base Reactions

The Brønsted-Lowry definition of acidity and basicity

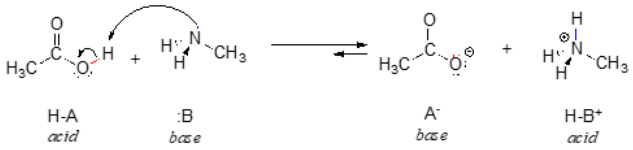
We'll begin our discussion of acid-base chemistry with a couple of essential definitions. The first of these was proposed in 1923 by the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry, and has come to be known as the Brønsted-Lowry definition of acidity and basicity. An acid, by the Brønsted-Lowry definition, is a species which acts as a proton donor, while a base is a proton acceptor. We have already discussed in the previous chapter one of the most familiar examples of a Brønsted-Lowry acid-base reaction, between hydrochloric acid and hydroxide ion:



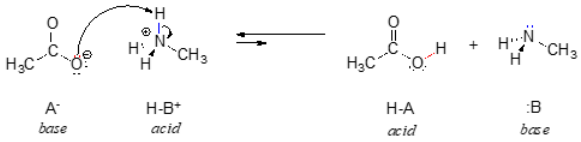
In this reaction, a proton is transferred from HCl (the acid, or proton donor) to hydroxide ion (the base, or proton acceptor). As we learned in the previous chapter, curved arrows depict the movement of electrons in this bond-breaking and bond-forming process.

After a Brønsted-Lowry acid donates a proton, what remains is called the conjugate base. Chloride ion is thus the conjugate base of hydrochloric acid. Conversely, when a Brønsted-Lowry base accepts a proton it is converted into its conjugate acid form: water is thus the conjugate acid of hydroxide ion.

Here is an organic acid-base reaction, between acetic acid and methylamine:



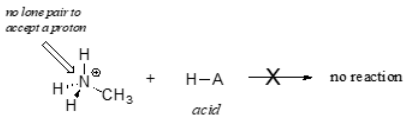
In the reverse of this reaction, acetate ion is the base and methylammonium ion (protonated methylamine) is the acid.



What makes a compound acidic (likely to donate a proton) or basic (likely to accept a proton)? Answering that question is one of our main jobs in this chapter, and will require us to put to use much of what we learned about organic structure in the first two chapters, as well as the ideas about thermodynamics that we reviewed in chapter 6.

For now, let's just consider one common property of bases: in order to act as a base, a molecule must have a reactive pair of electrons. In all of the acid-base reactions we'll see in this chapter, the basic species has an atom with a lone pair of electrons. When methylamine acts as a base, for example, the lone pair of electrons on the nitrogen atom is used to form a new bond to a proton.

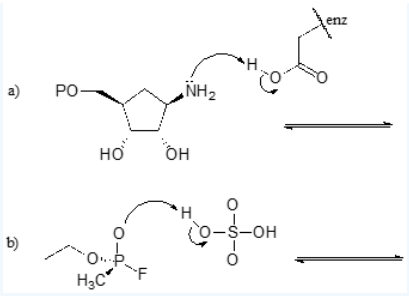
Clearly, methylammonium ion cannot act as a base – it does not have a reactive pair of electrons with which to accept a proton.



Later, in chapter 14, we will study reactions in which a pair of electrons in a bond of an alkene or aromatic ring act in a basic fashion - but for now, will concentrate on the basicity of non-bonding (lone pair) electrons.

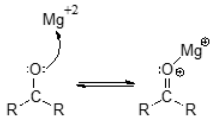
? Exercise 7.2.1

Complete the reactions below - in other words, draw structures for the missing conjugate acids and conjugate bases that result from the curved arrows provided.



The Lewis definition of acidity and basicity

The Brønsted-Lowry picture of acids and bases as proton donors and acceptors is not the only definition in common use. A broader definition is provided by the Lewis definition of acidity and basicity, in which a Lewis acid is an electron-pair acceptor and a Lewis base is an electron-pair donor. This definition covers Brønsted-Lowry proton transfer reactions, but also includes reactions in which no proton transfer is involved. The interaction between a magnesium cation (Mg+2) and a carbonyl oxygen is a common example of a Lewis acid-base reaction in enzyme-catalyzed biological reactions. The carbonyl oxygen (the Lewis base) donates a pair of electrons to the magnesium cation (the Lewis acid).



While it is important to be familiar with the Lewis definition of acidity, the focus throughout the remainder of this chapter will be on acid-base reactions of the (proton-transferring) Brønsted-Lowry type.

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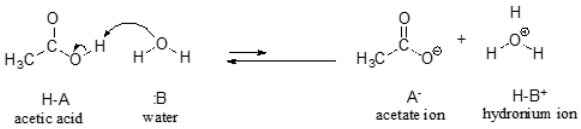
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7.2: The Acidity Constant

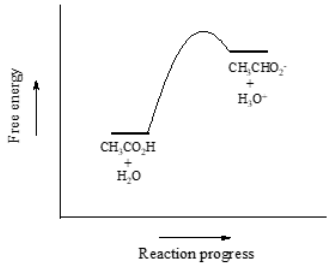
Defining the acidity constant

You are no doubt aware that some acids are stronger than others. The relative acidity of different compounds or functional groups – in other words, their relative capacity to donate a proton to a common base under identical conditions – is quantified by a number called the acidity constant, abbreviated K_a. The common base chosen for comparison is water.

We will consider acetic acid as our first example. If we make a dilute solution of acetic acid in water, an acid-base reaction occurs between the acid (proton donor) and water (proton acceptor).



Acetic acid is a weak acid, so the equilibrium favors reactants over products - it is thermodynamically 'uphill'. This is indicated in the figure above by the relative length of the forward and reverse reaction arrows.



The equilibrium constant K_{eq} is defined as:

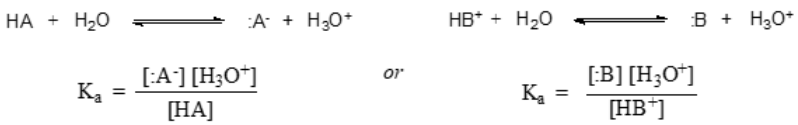
$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][H_2O]} \tag{7.2.1}$$

Remember that this is a dilute aqueous solution: we added a small amount of acetic acid to a large amount of water. Therefore, in the course of the reaction, the concentration of water (approximately 55.6 mol/L) changes very little, and can be treated as a constant.

If we move the constant term for the concentration of water to the left side of the equilibrium constant expression, we get the expression for K_a, the acid constant for acetic acid:

$$K_a = K_{eq}[H_2O] = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} \tag{7.2.2}$$

In more general terms, the dissociation constant for a given acid HA or HB+ is expressed as:



The value of K_a for acetic acid is 1.75×10^{-5} - much less than 1, indicating there is much more acetic acid in solution at equilibrium than acetate and hydronium ions.

Conversely, sulfuric acid, with a K_a of approximately 10^9, or hydrochloric acid, with a K_a of approximately 10^7, both undergo essentially complete dissociation in water: they are very strong acids.

A number like 1.75×10^{-5} is not very easy either to say, remember, or visualize, so chemists usually use a more convenient term to express relative acidity. The pK_a value of an acid is simply the log (base 10) of its K_a value.

$$pK_a = -logK_a \qquad K_a = 10^{-pK_a} \tag{7.2.3}$$

Doing the math, we find that the pK_a of acetic acid is 4.8. The pK_a of sulfuric acid is -10, and of hydrochloric acid is -7. The use of pK_a values allows us to express the relative acidity of common compounds and functional groups on a numerical scale of about –10 (for a very strong acid) to 50 (for a compound that is not acidic at all). The lower the pK_a value, the stronger the acid.

The ionizable (proton donating or accepting) functional groups relevant to biological organic chemistry generally have pK_a values ranging from about 5 to about 20. The most important of these are summarized below, with very rough pK_a values for the conjugate acid forms. More acidic groups with pK_a values near zero are also included for reference.

Typical pK_a values

group	approximate pK_a
hydronium ion	0
protonated alcohol	0
protonated carbonyl	0
carboxylic acids	5
protonated imines	7
protonated amines	10
phenols	10
thiols	10
alcohols, water	15
α-carbon acids *	20

*α-carbon acids will be explained in section 7.6A

It is highly recommended to commit these rough values to memory now - then if you need a more precise value, you can always look it up in a more complete pK_a table. The appendix to this book contains a more detailed table of typical pK_a values, and much more complete tables are available in resources such as the Handbook of Chemistry and Physics.

pK_a vs. pH

It is important to realize that pK_a is not the same thing as pH: the former is an inherent property of a compound or functional group, while the latter is a measure of hydronium ion concentration in a given aqueous solution:

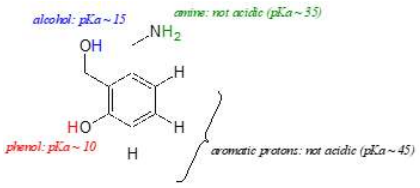
$$pH = -log[H_3O^+] \tag{7.2.4}$$

Knowing pK_a values not only allows us to compare acid strength, it also allows us to compare base strength. The key idea to remember is this: the stronger the conjugate acid, the weaker the conjugate base. We can determine that hydroxide ion is a stronger base than ammonia (NH_3), because ammonium ion ($NH4^+$, $pK_a = 9.2$) is a stronger acid than water ($pK_a = 15.7$).

Exercise 7.3.1

Which is the stronger base, \(CH_3O^-\) or \(CH_3S^-\)? Acetate ion or ammonia? Hydroxide ion or acetate ion?

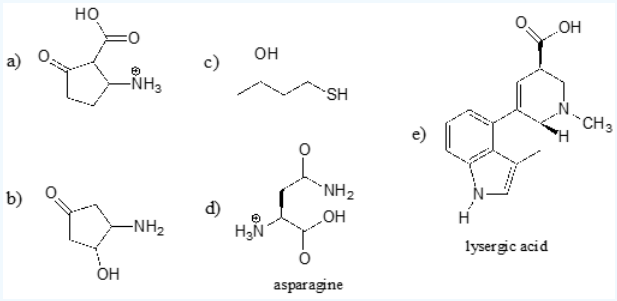
Let's put our understanding of the pK_a concept to use in the context of a more complex molecule. For example, what is the pK_a of the compound below?



We need to evaluate the potential acidity of four different types of protons on the molecule, and find the most acidic one. The aromatic protons are not all acidic - their pK_a is about 45. The amine group is also not acidic, its pK_a is about 35. (Remember, uncharged amines are basic: it is positively-charged protonated amines, with pK_a values around 10, that are weakly acidic.) The alcohol proton has a pK_a of about 15, and the phenol proton has a pK_a of about 10: thus, the most acidic group on the molecule above is the phenol. (Be sure that you can recognize the difference between a phenol and an alcohol - remember, in a phenol the OH group is bound directly to the aromatic ring). If this molecule were to react with one molar equivalent of a strong base such as sodium hydroxide, it is the phenol proton which would be donated to form a phenolate anion.

? Exercise 7.3.2

Identify the most acidic functional group on each of the molecules below, and give its approximate \(pK_a\).



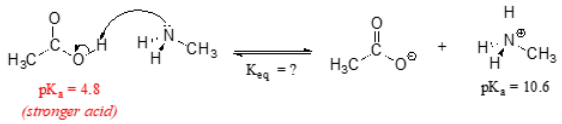
Using pK_a values to predict reaction equilibria

By definition, the pK_a value tells us the extent to which an acid will react with water as the base, but by extension we can also calculate the equilibrium constant for a reaction between any acid-base pair. Mathematically, it can be shown that:

$$K_{eq} = 10^{\Delta pK_a} \tag{7.2.5}$$

$$\Delta pK_a = \text{(pKa of product acid minus pKa of reactant acid)} \tag{7.2.6}$$

Consider a reaction between methylamine and acetic acid:

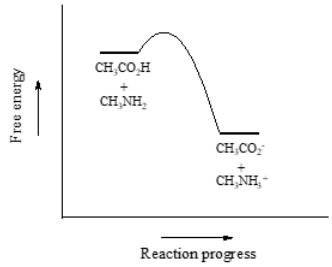


The first step is to identify the acid species on either side of the equation, and look up or estimate their pK_a values. On the left side, the acid is of course acetic acid while on the right side the acid is methyl ammonium ion (in other words, methyl ammonium ion is the acid in the reaction going from right to left). We can look up the precise pK_a values in table 7 (at the back of the book), but we already know (because we have this information memorized, right?!) that the pK_a of acetic acids is about 5, and methyl ammonium is about 10. More precise values are 4.8 and 10.6, respectively.

Without performing any calculations at all, you should be able to see that this equilibrium lies far to the right-hand side: acetic acid has a lower pK_a, meaning it is a stronger acid than methyl ammonium, and thus it wants to give up its proton more than methyl ammonium does. Doing the math, we see that

$$K_{eq} = 10^{\Delta pK_a} = 10^{(10.6-4.8)} = 10^{5.8} = 6.3 \times 10^5 \tag{7.2.7}$$

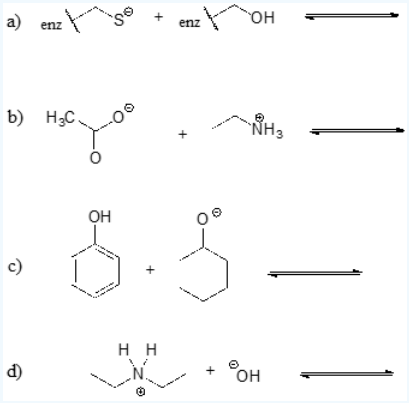
So K_{eq} is a very large number (much greater than 1) and the equilibrium for the reaction between acetic acid and methylamine lies far to the right-hand side of the equation, just as we had predicted. This also tells us that the reaction has a negative Gibbs free energy change, and is thermodynamically favorable.



If you had just wanted to quickly approximate the value of K_{eq} without benefit of precise pK_a information or a calculator, you could have approximated pK_a 5 (for the carboxylic acid) and pK_a 10 (for the ammonium ion) and calculated in your head that the equilibrium constant should be somewhere in the order of 10^5.

? Exercise 7.3.3

Show the products of the following acid-base reactions, and roughly estimate the value of K_{eq}.



Organic molecules in buffered solution: the Henderson-Hasselbalch equation

The environment inside a living cell, where most biochemical reactions take place, is an aqueous buffer with pH 7. Recall from your General Chemistry course that a buffer is a solution of a weak acid and its conjugate base. The key equation for working with buffers is the Henderson-Hasselbalch equation:

The Henderson-Hasselbalch equation

$$pH = pK_a + \log\left(\frac{\text{concentration of conjugate base}}{\text{concentration of weak acid}}\right) \tag{7.2.8}$$

The equation tells us that if our buffer is an equimolar solution of a weak acid and its conjugate base, the pH of the buffer will equal the pK_a of the acid (because the log of 1 is equal to zero). If there is more of the acid form than the base, then of course the pH of the buffer is lower than the pK_a of the acid.

Exercise 7.3.4

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pKa of acetic acid is 4.8.

The Henderson-Hasselbalch equation is particularly useful when we want to think about the protonation state of different biomolecule functional groups in a $pH7$ buffer. When we do this, we are always assuming that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids).

Imagine an aspartic acid residue located on the surface of a protein in a human cell. Being on the surface, the side chain is in full contact with the $pH7$ buffer surrounding the protein. In what state is the side chain functional group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)? Using the Henderson-Hasselbalch equation, we fill in our values for the pH of the buffer and a rough pK_a approximation of $pK_a = 5$ for the carboxylic acid functional group. Doing the math, we find that the ratio of carboxylate to carboxylic acid is about 100 to 1: the carboxylic acid is almost completely ionized (in the deprotonated state) inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules: in the physiological environment, carboxylic acids are almost completely deprotonated.

Now, let's use the equation again, this time for an amine functional group, such as the side chain of a lysine residue: inside a cell, are we likely to see a neutral amine ($R-NH_2$) or an ammonium cation ($R-NH_3^+$?) Using the equation with $pH = 7$ (for the biological buffer) and $pK_a = 10$ (for the ammonium group), we find that the ratio of neutral amine to ammonium cation is about 1 to 100: the group is close to completely protonated inside the cell, so we will see $R-NH_3^+$, not $R-NH_2$.

We can do the same rough calculation for other common functional groups found in biomolecules.

Note

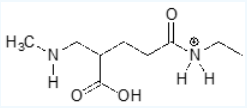
At physiological pH:

Carboxylic acids are deprotonated (in the carboxylate anion form)
Amines are protonated (in the ammonium cation form)
Thiols, phenols, alcohols, and amides are uncharged
Imines are a mixture of the protonated (cationic) and deprotonated (neutral) states.

We will talk about the physiological protonation state of phosphate groups in chapter 9.

Exercise 7.3.5

The molecule below is not drawn in the protonation state that we would expect to see it at physiological pH. Redraw it in the physiologically relevant protonation state.



While we are most interested in the state of molecules at $pH7$, the Henderson-Hasselbalch equation can of course be used to determine the protonation state of functional groups in solutions buffered to other pH levels. The exercises below provide some practice in this type of calculation.

Exercise 7.3.6

What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid $pK_a = 4.8$ is dissolved in a buffer of $pH 2.8$? $pH 3.8$? $pH 4.8$? $pH 5.8$? $pH 6.8$?

Exercise 7.3.7

Would you expect phenol to be soluble in an aqueous solution buffered to $pH 2$? $pH 7$? $pH 12$? Explain your answer.

Exercise 7.3.8

Methylamine is dissolved in a $pH 9.0$ buffer. What percent of the solute molecules are charged? What is the average charge on solute molecules?

Exercise 7.3.9

What is the approximate net charge on a tetrapeptide Cys-Asp-Lys-Glu in $pH 7$ buffer?

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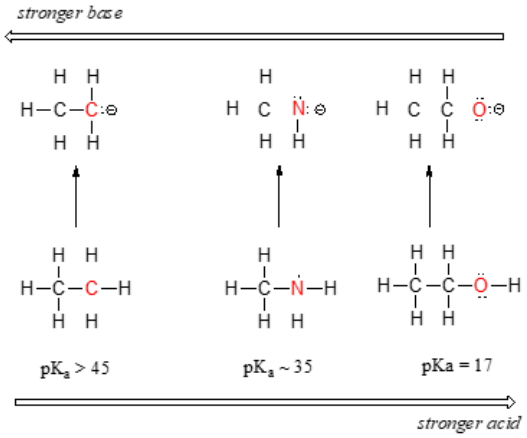
7.3: Structural Effects on Acidity and Basicity

Now that we know how to quantify the strength of an acid or base, our next job is to gain an understanding of the fundamental reasons behind why one compound is more acidic or more basic than another. This is a big step: we are, for the first time, taking our knowledge of organic structure and applying it to a question of organic reactivity. Many of the ideas that we'll see for the first here will continue to apply throughout the book as we tackle many other organic reaction types.

Periodic trends

First, we will focus on individual atoms, and think about trends associated with the position of an element on the periodic table. We'll use as our first models the simple organic compounds ethane, methylamine, and ethanol, but the concepts apply equally to more complex biomolecules with the same functionalities, for example the side chains of the amino acids alanine (alkane), lysine (amine), and serine (alcohol).

Horizontal periodic trend in acidity and basicity:



We can see a clear trend in acidity as we move from left to right along the second row of the periodic table from carbon to nitrogen to oxygen. The key to understanding this trend is to consider the hypothetical conjugate base in each case: the more stable (weaker) the conjugate base, the stronger the acid. Look at where the negative charge ends up in each conjugate base. In the conjugate base of ethane, the negative charge is borne by a carbon atom, while on the conjugate base of methylamine and ethanol the negative charge is located on a nitrogen and an oxygen, respectively. Remember from section 2.4A that electronegativity also increases as we move from left to right along a row of the periodic table, meaning that oxygen is the most electronegative of the three atoms, and carbon the least.

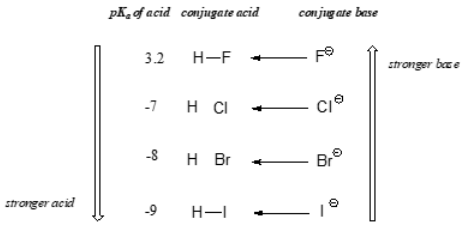
Note

The more electronegative an atom, the better able it is to bear a negative charge. Weaker bases have negative charges on more electronegative atoms; stronger bases have negative charges on less electronegative atoms.

Thus, the methoxide anion is the most stable (lowest energy, least basic) of the three conjugate bases, and the ethyl carbanion anion is the least stable (highest energy, most basic). Conversely, ethanol is the strongest acid, and ethane the weakest acid.

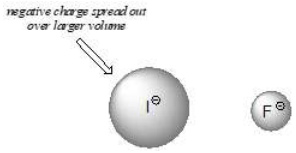
When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best illustrated with the haloacids and halides: basicity, like electronegativity, increases as we move up the column.

Vertical periodic trend in acidity and basicity:



Conversely, acidity in the haloacids increases as we move down the column.

In order to make sense of this trend, we will once again consider the stability of the conjugate bases. Because fluorine is the most electronegative halogen element, we might expect fluoride to also be the least basic halogen ion. But in fact, it is the least stable, and the most basic! It turns out that when moving vertically in the periodic table, the size of the atom trumps its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodide ion, the negative charge is spread out over a significantly larger volume:



This illustrates a fundamental concept in organic chemistry:

Electrostatic charges, whether positive or negative, are more stable when they are ‘spread out’ over a larger area.

We will see this idea expressed again and again throughout our study of organic reactivity, in many different contexts. For now, we are applying the concept only to the influence of atomic radius on base strength. Because fluoride is the least stable (most basic) of the halide conjugate bases, HF is the least acidic of the haloacids, only slightly stronger than a carboxylic acid. HI, with a pK_a of about -9, is almost as strong as sulfuric acid.

More importantly to the study of biological organic chemistry, this trend tells us that thiols are more acidic than alcohols. The pK_a of the thiol group on the cysteine side chain, for example, is approximately 8.3, while the pK_a for the alcohol group on the serine side chain is on the order of 17.

Remember the concept of 'driving force' that was introduced in section 6.2? Recall that the driving force for a reaction is usually based on two factors: relative charge stability, and relative total bond energy. Let's see how this applies to a simple acid-base reaction between hydrochloric acid and fluoride ion:

$$HCl + F^- \rightarrow HF + Cl^- \tag{7.3.1}$$

We know that HCl (pK_a -7) is a stronger acid than HF (pK_a 3.2), so the equilibrium for the reaction lies on the product side: the reaction is exergonic, and a 'driving force' pushes reactant to product.

What explains this driving force? Consider first the charge factor: as we just learned, chloride ion (on the product side) is more stable than fluoride ion (on the reactant side). This partially accounts for the driving force going from reactant to product in this reaction: we are going from less stable ion to a more stable ion.

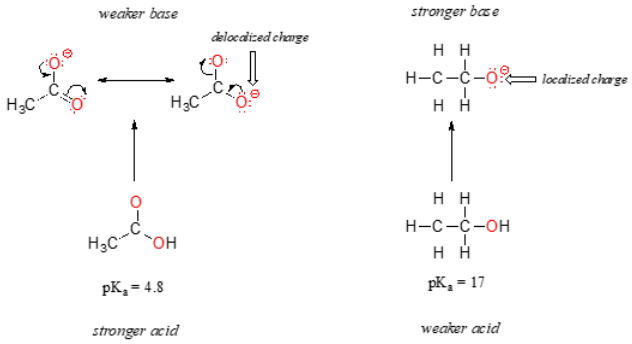
What about total bond energy, the other factor in driving force? If you consult a table of bond energies, you will see that the H-F bond on the product side is more energetic (stronger) than the H-Cl bond on the reactant side: 570 kJ/mol vs 432 kJ/mol, respectively). This also contributes to the driving force: we are moving from a weaker (less stable) bond to a stronger (more stable) bond.

Resonance effects

In the previous section we focused our attention on periodic trends - the differences in acidity and basicity between groups where the exchangeable proton was bound to different elements. Now, it is time to think about how the structure of different organic groups contributes to their relative acidity or basicity, even when we are talking about the same element acting as the proton

donor/acceptor. The first model pair we will consider is ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups.

Despite the fact that they are both oxygen acids, the pKa values of ethanol and acetic acid are strikingly different. What makes a carboxylic acid so much more acidic than an alcohol? As before, we begin by considering the stability of the conjugate bases, remembering that a more stable (weaker) conjugate base corresponds to a stronger acid.

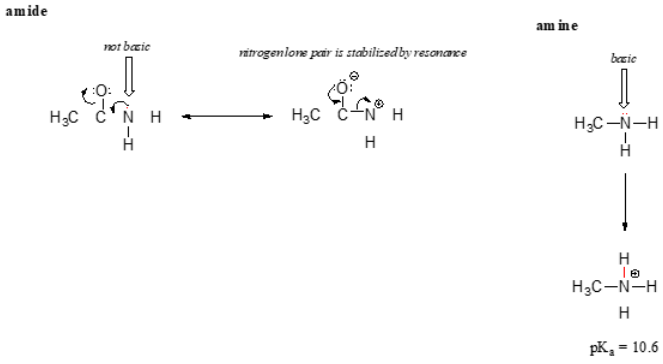


In both species, the negative charge on the conjugate base is located on oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: two resonance contributors can be drawn for the conjugate base, and the negative charge can be delocalized (shared) over two oxygen atoms. In the ethoxide ion, by contrast, the negative charge is localized, or 'locked' on the single oxygen – it has nowhere else to go. This makes the ethoxide ion much less stable.

Recall the important general statement that we made a little earlier: 'Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one location.' Now, we are seeing this concept in another context, where a charge is being 'spread out' (in other words, delocalized) by resonance, rather than simply by the size of the atom involved.

The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 12 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so we are talking about a factor of 10^{12} between the K_a values for the two molecules!)

The resonance effect also nicely explains why a nitrogen atom is basic when it is in an amine, but not basic when it is part of an amide group. Recall that in an amide, there is significant double-bond character to the carbon-nitrogen bond, due to a minor but still important resonance contributor in which the nitrogen lone pair is part of a π bond.



Whereas the lone pair of an amine nitrogen is 'stuck' in one place, the lone pair on an amide nitrogen is delocalized by resonance. Notice that in this case, we are extending our central statement to say that electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not available for bonding with a proton – these two electrons are too 'comfortable' being part of the delocalized π-bonding system. The lone pair on an amine nitrogen, by contrast, is not so comfortable - it is not part of a delocalized π system, and is available to form a bond with any acidic proton that might be nearby.

If an amide group is protonated, it will be at the oxygen rather than the nitrogen.

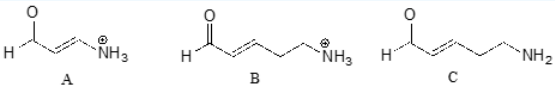
Exercise 7.4.1

a. Draw the Lewis structure of nitric acid, HNO_3.

b. Nitric acid is a strong acid - it has a pK_a of -1.4. Make a structural argument to account for its strength. Your answer should involve the structure of the conjugate base of nitric acid.

Exercise 7.4.2

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

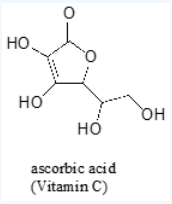


Exercise 7.4.3

Often it requires some careful thought to predict the most acidic proton on a molecule. Ascorbic acid, also known as Vitamin C, has a \(pK_a\) of 4.1 - the fact that this is in the range of carboxylic acids suggest to us that the negative charge on the conjugate base can be delocalized by resonance to two oxygen atoms. Which if the four OH protons on the molecule is most acidic? Draw the structure of ascorbate, the conjugate base of ascorbic acid, then draw a second resonance contributor showing how the negative charge is delocalized to a second oxygen atom.

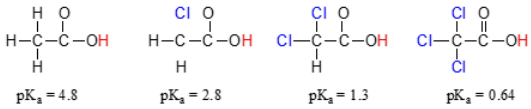
Hint

Try deprotonating each OH group in turn, then use your resonance drawing skills to figure out whether or not delocalization of charge can occur.



Inductive effects

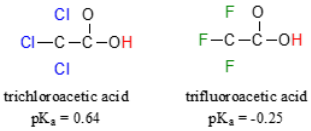
Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:



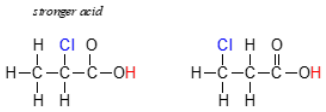
The presence of the chlorine atoms clearly increases the acidity of the carboxylic acid group, but the argument here does not have to do with resonance delocalization, because no additional resonance contributors can be drawn for the chlorinated molecules. Rather, the explanation for this phenomenon involves something called the inductive effect. A chlorine atom is more electronegative than a hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. In effect, the chlorine atoms are helping to further spread out the electron density of the conjugate base, which as we know has a stabilizing effect. In this context, the chlorine substituent can be referred to as an electron-withdrawing group. Notice that the pK_a-lowering effect of each chlorine atom, while significant, is not as dramatic as the delocalizing resonance effect illustrated by

the difference in pK_a values between an alcohol and a carboxylic acid. In general, resonance effects are more powerful than inductive effects.

Because the inductive effect depends on electronegativity, fluorine substituents have a more pronounced pK_a-lowered effect than chlorine substituents.

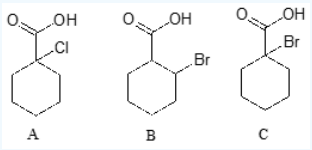


In addition, the inductive takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away.



Exercise 7.4.4

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

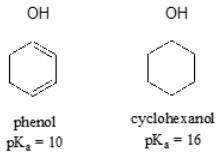


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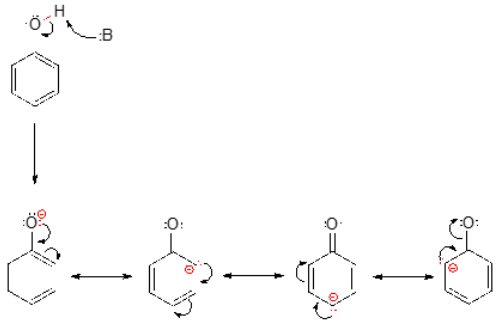
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7.4: Acid-base Properties of Phenols

Resonance effects involving aromatic structures can have a dramatic influence on acidity and basicity. Notice, for example, the difference in acidity between phenol and cyclohexanol.



Looking at the conjugate base of phenol, we see that the negative charge can be delocalized by resonance to three different carbons on the aromatic ring.

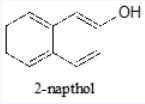


Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

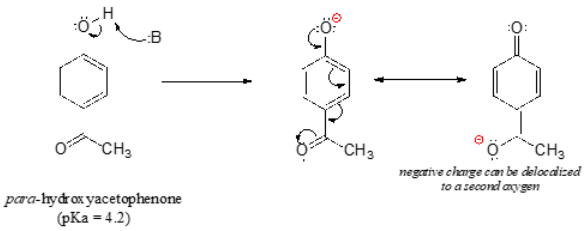
As we begin to study in detail the mechanisms of biological organic reactions, we'll see that the phenol side chain of the amino acid tyrosine (see table 5 at the back of the book), with its relatively acidic pK_a of 9-10, often acts as a catalytic proton donor/acceptor in enzyme active sites.

? Exercise 7.5.1

Draw the conjugate base of 2-napthol (the major resonance contributor), and on your drawing indicate with arrows all of the atoms to which the negative charge can be delocalized by resonance.



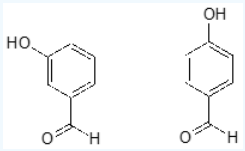
The base-stabilizing effect of an aromatic ring can be accentuated by the presence of an additional electron-withdrawing substituent, such as a carbonyl. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen atoms. The ketone group is acting as an electron withdrawing group - it is 'pulling' electron density towards itself, through both inductive and resonance effects.

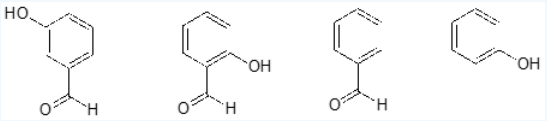
? Exercise 7.5.2

The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



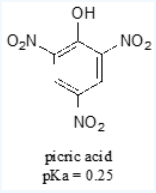
? Exercise 7.5.3

Rank the four compounds below from most acidic to least.



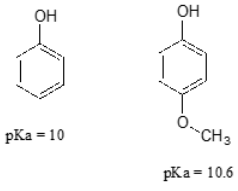
? Exercise 7.5.4

Nitro groups are very powerful electron-withdrawing groups. The phenol derivative picric acid has a pKa of 0.25, lower than that of trifluoroacetic acid.



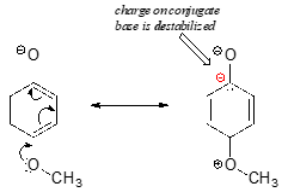
Use a resonance argument to explain why picric acid has such a low pKa.

Consider the acidity of 4-methoxyphenol, compared to phenol.



Notice that the methoxy group increases the pKa of the phenol group - it makes it less acidic. Why is this? At first inspection, you might assume that the methoxy substituent, with its electronegative oxygen, would be an electron-withdrawing group by induction. That is correct, but only to a point. The oxygen atom does indeed exert an electron-withdrawing inductive effect, but the lone pairs on the oxygen cause the exact opposite effect – the methoxy group is an electron-donating group by resonance. A resonance

contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



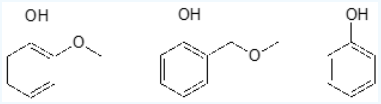
Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making it more basic. It may help to visualize the methoxy group 'pushing' electrons towards the lone pair electrons of the phenolate oxygen, causing them to be less 'comfortable' and more reactive.

When resonance and induction compete, resonance usually wins!

The example above is a somewhat confusing but quite common situation in organic chemistry - a functional group, in this case a methoxy group, is exerting both an inductive effect and a resonance effect, but in opposite directions (the inductive effect is electron-withdrawing, the resonance effect is electron-donating). As stated earlier, as a general rule a resonance effect is more powerful than an inductive effect - so overall, the methoxy group is acting as an electron donating group.

? Exercise 7.5.5

Rank the three compounds below from lowest pKa to highest, and explain your reasoning. Hint - think about both resonance and inductive effects!

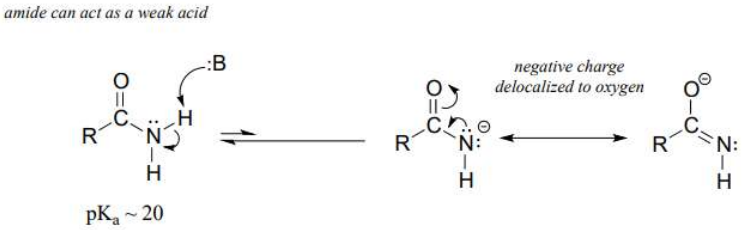


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7.5: Acid-base properties of nitrogen-containing functional groups

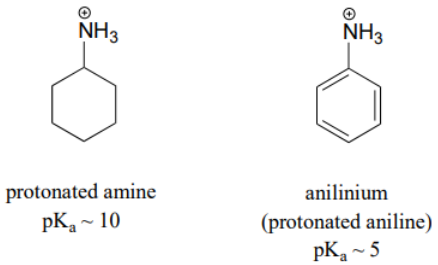
Many of the acid-base reactions we will see throughout our study of biological organic chemistry involve functional groups which contain nitrogen. In general, a nitrogen atom with three bonds and a lone pair of electrons can potentially act as a proton-acceptor (a base) - but basicity is reduced if the lone pair electrons are stabilized somehow. We already know that amines are basic, and that the pKa for a protonated amine is in the neighborhood of 10. We also know that, due to resonance with the carbonyl bond, amide nitrogens are not basic (in fact they are very slightly acidic, with a pKa around 20).



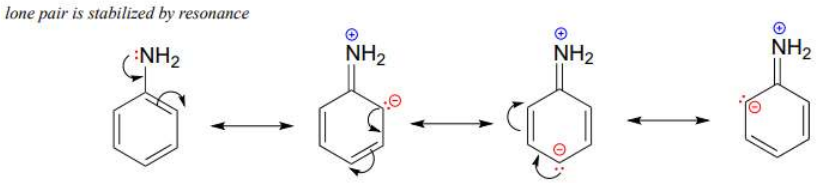
Next, let's consider the basicity of some other nitrogen-containing functional groups.

Anilines

Aniline, the amine analog of phenol, is substantially less basic than an amine.

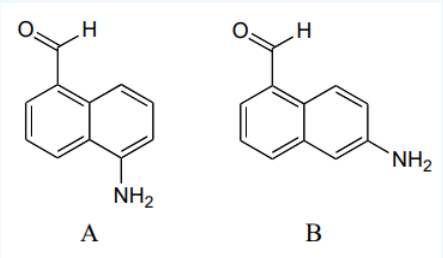


We can use the same reasoning that we used when comparing the acidity of a phenol to that of an alcohol. In aniline, the lone pair on the nitrogen atom is stabilized by resonance with the aromatic p system, making it less available for bonding and thus less basic.



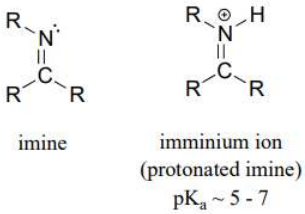
? Exercise 7.6.1

With anilines just as with phenols, the resonance effect of the aromatic ring can be accentuated by the addition of an electron-withdrawing group, and diminished by the addition of an electron-donating group. Which of the two compounds below is expected to be more basic? Use resonance drawings to explain your reasoning.



Imines

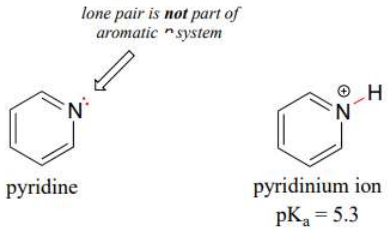
Imines are somewhat less basic than amines: pK_a for a protonated imine is in the neighborhood of 5-7, compared to ~10 for protonated amines. Recall that an imine functional group is characterized by an sp2-hybridized nitrogen double-bonded to a carbon.



The lower basicity of imines compared to amines can be explained in the following way:

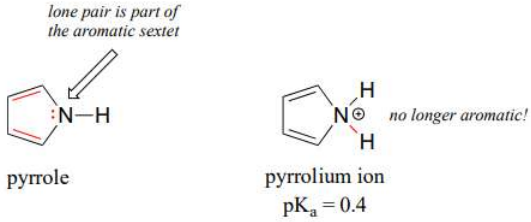
- The lone pair electrons on an imine nitrogen occupy an sp^2 hybrid orbital, while the lone pair electrons on an amine nitrogen occupy an sp^3 hybrid orbital.
- sp^2 orbitals are composed of one part s and two parts p atomic orbitals, meaning that they have about 33% s character. sp^3 orbitals, conversely, are only 25% s character (one part s, three parts p).
- An s atomic orbital holds electrons closer to the nucleus than a p orbital, thus s orbitals are more electronegative than p orbitals. Therefore, sp^2 hybrid orbitals, with their higher s-character, are more electronegative than sp^3 hybrid orbitals.
- Lone pair electrons in the more electronegative sp^2 hybrid orbitals of an imine are held more tightly to the nitrogen nucleus, and are therefore less 'free' to break away and form a bond to a proton - in other words, they are less basic.

The aromatic compound pyridine, with an imine nitrogen, has a pK_a of 5.3. Recall from section 2.2C that the lone pair electrons on the nitrogen atom of pyridine occupy an sp2-hybrid orbital, and are not part of the aromatic sextet - thus, they are available for bonding with a proton.

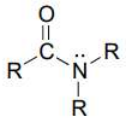
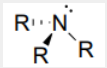
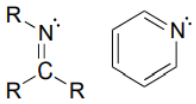
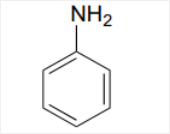
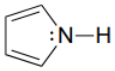


Pyrrole

In the aromatic ring of pyrrole, the nitrogen lone pair electrons are part of the aromatic sextet, and are therefore much less available for forming a new bonding to a proton. Pyrrole is a very weak base: the conjugate acid is a strong acid with a pK_a of 0.4.

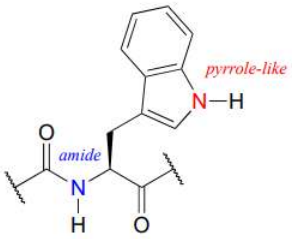


Below is a summary of the five common bonding arrangements for nitrogen and their relative basicity:

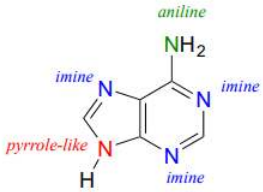
nitrogen group	structure	pK_a of conjugate acid
amide		NA (amide nitrogens are not basic)
amine		~ 10
imine		~ 5 - 7
aniline		~ 5
pyrrole		~ 0

Learning and being able to recognize these five different 'types' of nitrogen can be very helpful in making predictions about the reactivity of a great variety of nitrogen-containing biomolecules. The side chain of the amino acid tryptophan, for example, contains a non-basic 'pyrrole-like' nitrogen (the lone pair electrons are part of the 10-electron aromatic system), and the peptide chain nitrogen, of course, is an amide. The nucleotide base adenine contains three types of nitrogen.

.

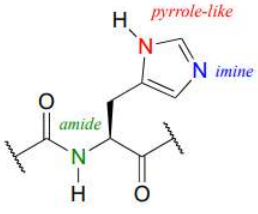


tryptophan

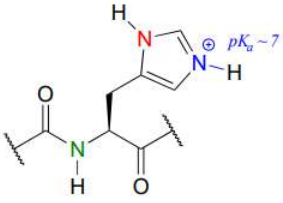


adenine

The side chain on a histidine amino acid has both a 'pyrrole-like' nitrogen and an imine nitrogen. The pKa of a protonated histidine residue is approximately 7, meaning that histidine will be present in both protonated and deprotonated forms in physiological buffer. Histidine residues in the active site of enzymes are common proton donor-acceptor groups in biochemical reactions.



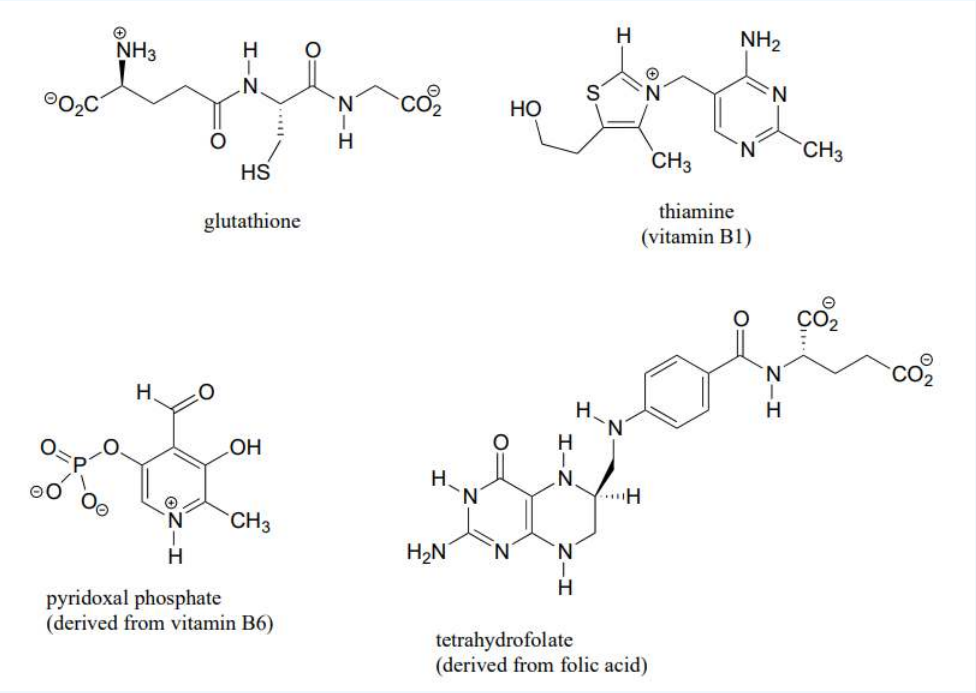
histidine
(deprotonated)



histidinium
(protonated)

Exercise 7.6.2

Below are the structures of four 'coenzyme' molecules necessary for human metabolism (we will study the function of all of these in chapter 17).



a. When appropriate, assign a label to each nitrogen atom using the basicity classifications defined in this section ('pyrrole-like', etc.).

b. There is one nitrogen that does not fall into any of these types - is it basic? Why or why not? What would be a good two-word term to describe the group containing this nitrogen?

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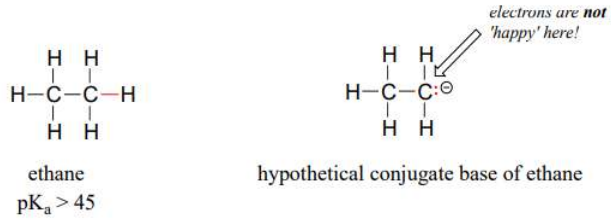
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7.6: Carbon Acids

So far, we have limited our discussion of acidity and basicity to heteroatom acids, where the acidic proton is bound to an oxygen, nitrogen, sulfur, or halogen. However, carbon acids - in which the proton to be donated is bonded to a carbon atom - play an integral role in biochemistry.

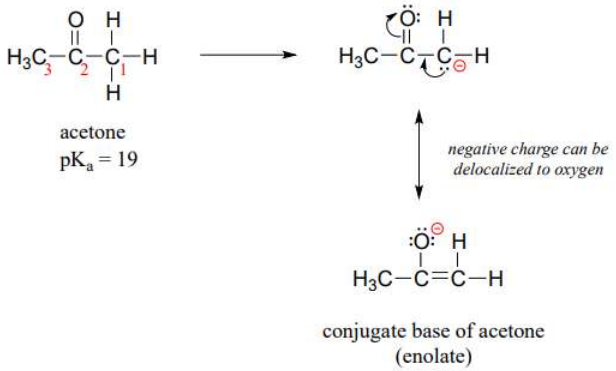
The acidity of α-protons

A hydrogen on an alkane is not at all acidic – its pK_a is somewhere on the order of 50, about as non-acidic as it gets in the organic chemistry world. The reason for this is that if the hydrogen were to be abstracted, the electrons from the broken bond would be localized on a single carbon atom.

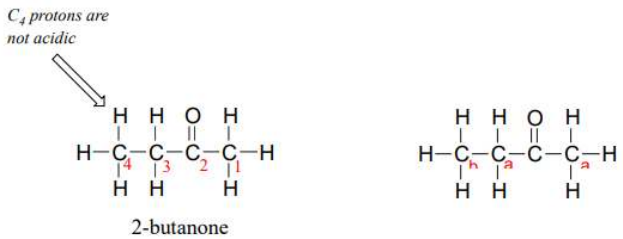


Because carbon is not electronegative and is terrible at holding a negative charge, such carbanion species are extremely unstable.

How, then, can a proton bonded to a carbon be acidic? Remember that an acid becomes stronger if the conjugate base is stabilized, an in particular if the negative charge on the conjugate base can be delocalized to an electronegative atom such as an oxygen. This is possible when a carbon is located adjacent to a carbonyl group. Consider, for example, the conjugate base of acetone.

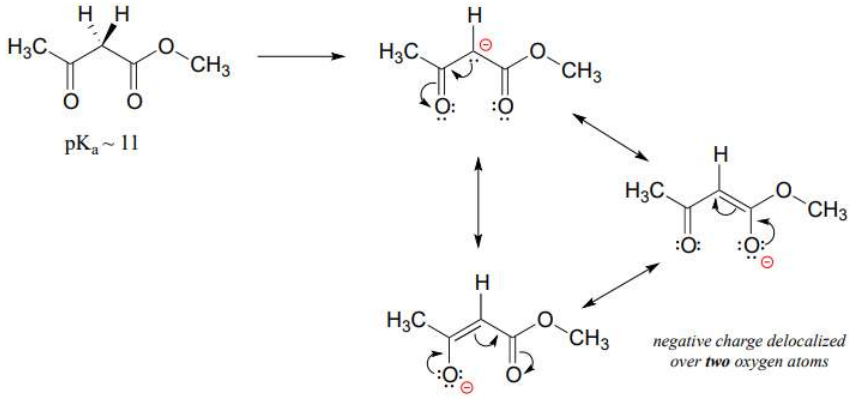


One resonance contributor puts the negative charge on the carbon #1. Due to the presence of the adjacent carbonyl group, however, a second resonance contributor can be drawn in which the negative charge is located on the carbonyl oxygen, where it is much more stable. This type of stabilized carbanion species is specifically referred to as an enolate. Acetone is in fact weakly acidic, with a pK_a of about 19. The importance of the position of the carbonyl group is evident when we consider 2-butanone: here, the protons on carbons #1 and #3 are somewhat acidic (in the neighborhood of $pK_a = 20$), but the protons on carbon #4 are not acidic at all, because carbon #4 is not adjacent to the carbonyl.

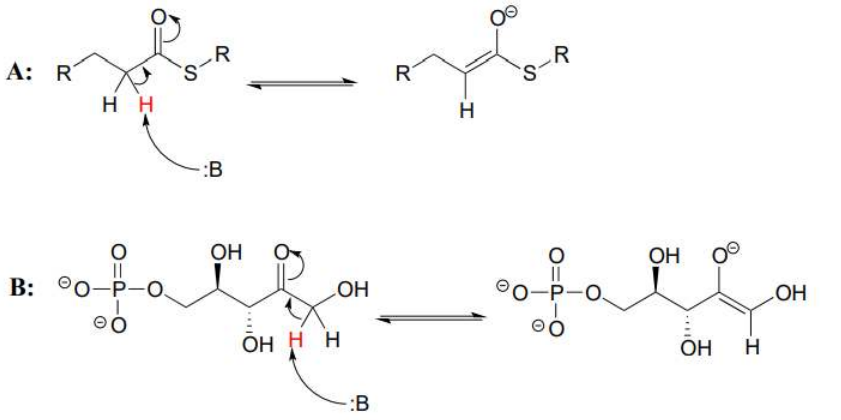


A carbon that is located next to a carbonyl group is referred to as an a-carbon, and any proton bound to it is an a-proton. In 2-butanone, carbons #1 and #3 are a-carbons, and their five protons are a-protons. Carbon #4 is a b-carbon, as it is two positions removed from the carbonyl carbon.

An active methylene is a carbon in the α position relative to two carbonyl groups rather than just one. Protons on active methylene carbons are more acidic than other a-protons, because the charge on the conjugate base can be localized to two different oxygen atoms, not just one. This keto-ester compound, for example, has a pK_a of approximately 11, close to that of phenol.



As we alluded to above, the acidity of a-protons is an extremely important concept in biological organic chemistry. Look through a biochemistry textbook, and you will see reaction after reaction in which the first mechanistic step is the abstraction of an a-proton to form an enolate intermediate. Two chapters in this book (chapters 12 and 13) are devoted to such reactions, and the initial proton-extraction step of three example reactions are previewed below. Reaction A is from fatty acid oxidation, while reactions B and C are both part of carbohydrate metabolism.

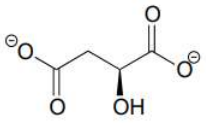


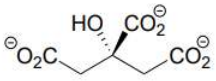
Exercise 7.7.1

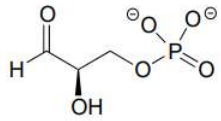
For each molecule shown below,

a. Show the location of all α-protons.

b. Draw the structure(s) of all possible enolate conjugate bases.

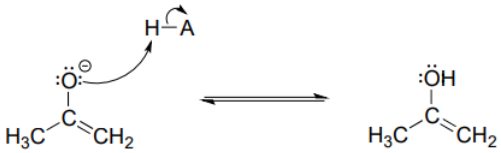

malate


citrate


glyceraldehyde-3-phosphate

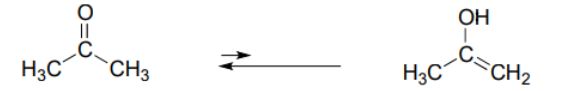
Keto-enol tautomers

An enolate ion can, of course, be reprotonated at the α-carbon to return the molecule to the ketone or aldehyde form. An alternate possibility is that the oxygen atom, rather than the α-carbon, could be protonated. The species that results from this step is referred to as an enol (this term reflects the fact that an enol contains structural elements of both an aklene and an alcohol).


enolate enol

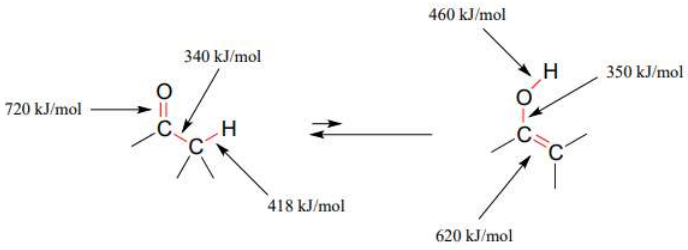
In fact, most ketones and aldehydes exist in rapid equilibrium with their enol form. A ketone/aldehyde and its corresponding enol are tautomers: a pair of constitutional isomers which can be rapidly and reversibly interconverted, and which vary in terms of the site of protonation and location of a double bond. As we will see going forward, tautomerization - the interconversion of two tautomers - is a ubiquitous step in biological organic chemistry. Often, when discussing tautomerization, the ketone (or aldehyde) isomer is referred as the keto form.

As a general rule, the keto form is lower in energy than the corresponding enol form, and thus the keto form predominates at equilibrium. Acetone, for example, is present at >99% keto form at equilibrium, and the enol form at less than 1%.


keto form of acetone (>99% at equilibrium)

enol form of acetone (<1% at equilibrium)

The 'driving force' for the enol to keto conversion can be understood in terms of the energies of the three bonds involved in the process: the sum of the three bond energies is about 48 kJ/mol greater in the keto form than in the enol form.



keto total 1478 kJ/mol

enol total 1430 kJ/mol

? Exercise 7.7.2

Draw all of the possible enol forms of the following aldehydes/ketones.

a. 3-pentanone

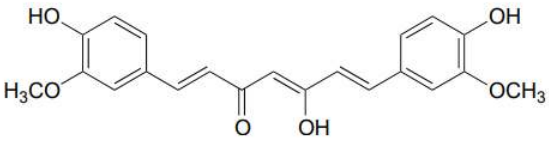
b. acetaldehyde (IUPAC name ethaldehyde)
c. cyclohexanone
d. 2-pentanone

? Exercise 7.7.3

Draw three examples of aldehyde or ketone compounds for which there is no possible enol form.

? Exercise 7.7.4

In some special cases, the enol form of a compound is more stable than the keto form and thus predominates at equilibrium. Curcumin is the compound mainly responsible for the characteristic yellowish color of tumeric, a ubiquitous spice in south/southeast asian cuisine. The extended system of p bonds present in the enol form causes it to be lower in energy than the tautomer in which there are two ketone groups (called the diketo form). Draw the diketo form of curcumin, and explain how the conjugated p system is disrupted.



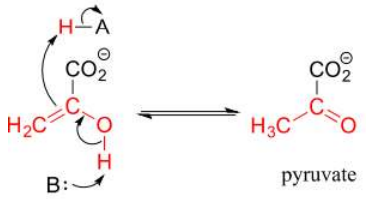
curcumin
(enol form)

? Exercise 7.7.5

The phenol functional group can also be thought of a kind of enol.

a. Draw the 'keto' form of phenol.
b. The 'keto' form of phenol is highly disfavored compared to the 'enol' form - why?

Keto-enol tautomerization steps can be found in many biochemical reactions. For example, there is an enol to keto tautomerization step in the glycolysis reaction catalyzed by pyruvate kinase (EC 2.7.1.40). Shown below is just the tautomerization part of this reaction; we will see the complete reaction in chapter 9.

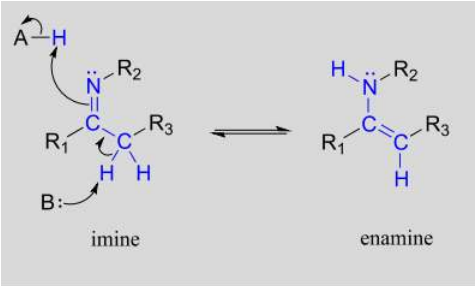


enolpyruvate pyruvate

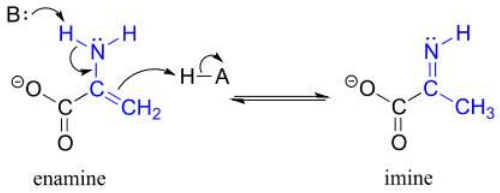
Imine-enamine tautomers

Another common tautomeric relationship in biological organic chemistry is the equilibrium between imines (also known as Schiff bases) and enamines, which are essentially the nitrogen equivalents of enols.

Mechanism for imine - enamine tautomerization

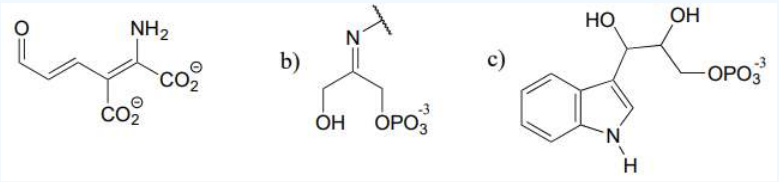


The degradation of serine, for example, involves an enamine to imine tautomerization step: (EC 4.2.1.13)



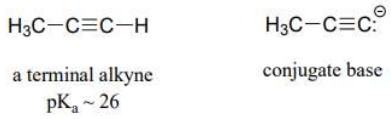
? Exercise 7.7.6

The structures below all contain either an imine or an enamine group. For each, draw the structure of an alternate tautomer.



Acidity of terminal alkynes

Terminal alkynes are another kind of carbon acid which are relevant more to laboratory organic chemistry than to biological chemistry.



Terminal alkynes are more acidic than alkenes or alkanes for the same reason that protonated imines are more acidic than protonated amines: the alkyne carbon is ***sp***-hybridized, meaning that it has 50% ***s***-orbital character and is therefore more electronegative. With a pK_a of approximately 26, alkynes are only weakly acidic, but nonetheless can be fully deprotonated through the use of a strong base such as sodium amide ($NaNH_2$).

? Exercise 7.7.7

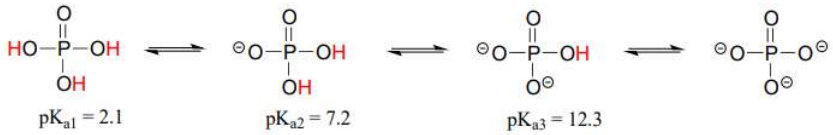
Hydrogen cyanide, HCN, is another example of a relatively strong carbon acid, with a pK_a of 9.2. Suggest a rationale for the acidity of this proton.

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7.7: Polyprotic Acids

Polyprotic acids are capable of donating more than one proton. The most important polyprotic acid group from a biological standpoint is triprotic phosphoric acid. Because phosphoric acid has three acidic protons, it also has three pK_a values.



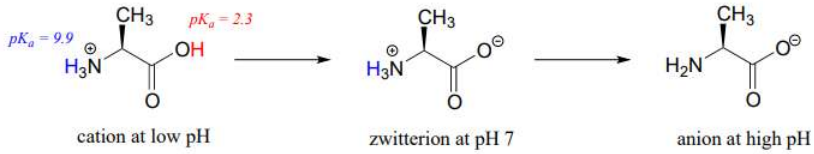
The pK_a values for any polyprotic acid always get progressively higher, because it becomes increasingly difficult to stabilize the additional electron density that results from each successive proton donation. H_3PO_4 is a strong acid because the (single) negative charge on its conjugate base $H_2PO_4^-$ can be delocalized over two oxygen atoms.

$H_2PO_4^-$ is substantially less acidic, because proton donation now results in the formation of an additional negative charge: a –2 charge is inherently higher in energy than a –1 charge because of negative-negative electrostatic repulsion. The third deprotonation, resulting in formation of a third negative charge, has an even higher pK_a. We will have more to say about the acidity of phosphate groups in chapter 9, when we study the reactions of phosphate groups on biomolecules.

? Exercise 7.8.1

In a buffer at physiological pH, what form(s) of phosphoric acid predominate? What is the average net charge?

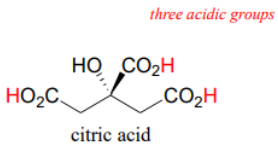
Free amino acids are polyprotic, with pK_a values of approximately 2 for the carboxylic acid group and 9-10 for the ammonium group. Alanine, for example, has the acid constants $pK_{a1} = 2.3$ and $pK_{a2} = 9.9$.



The Henderson-Hasselbalch equation tells us that alanine is almost fully protonated and positively charged when dissolved in a solution that is buffered to $pH0.5$. At $pH7$, alanine has lost one proton from the carboxylic acid group, and thus is a **zwitterion** (it has both a negative and a positive formal charge). At pH levels above 12, the ammonium group is fully deprotonated, and alanine has a negative overall charge.

Some amino acids (arginine, lysine, aspartate, glutamate, tyrosine, and histidine) are triprotic, with a third pK_a value associated with an ionizable functional group on the side chain.

Many biological organic molecules have several potentially ionizable functional groups and thus can be considered polyprotic acids. Citric acid, found in abundance in oranges, lemons, and other citrus fruits, has three carboxylic acid groups and pK_a values of 3.1, 4.8, and 6.4.

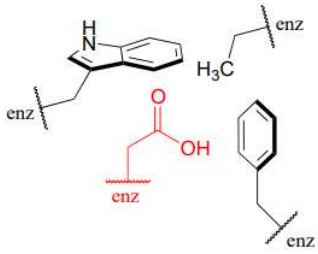


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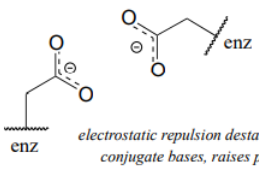
7.8: Effects of enzyme microenvironment on acidity and basicity

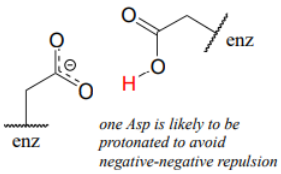
Virtually all biochemical reactions take place inside the active site pocket of an enzyme, rather than free in aqueous solution. The microenvironment inside an enzyme's active site can often be very different from the environment outside in the aqueous solvent. Consider, for example, the side chain carboxylate on an aspartate residue in an enzyme. The literature pK_a of this carboxylic acid group is listed as 3.9, but this estimate assumes that the group is positioned on the surface of the protein, exposed to water. In the physiological buffer of pH 7, a carboxylic acid group with $pK_a = 3.9$ will be fully deprotonated and negatively charged. If, however, an aspartate side chain happens to be buried deep inside the interior of the protein's active site, and is surrounded primarily by nonpolar side chains such as alanine, phenylalanine, tryptophan, etc., the situation is very different.



Cut off from the environment of the bulk solvent, the carboxylate group (red in the above figure) is now in a very nonpolar microenvironment, a situation in which the protonated, uncharged state is stabilized relative to the deprotonated, negatively charged state (this is simply another application of the 'like dissolves like' principle you learned in General Chemistry - a charged group is highly destabilized by a nonpolar environment). The overall effect is that the pK_a for this aspartate residue is actually higher than 3.9 – it is less acidic, and more likely to be in its protonated form inside the protein.

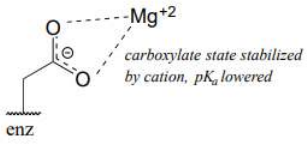
A similar effect would be observed in a situation where the side chain carboxylate groups of two aspartate residues are located in close proximity to one another in an enzyme active site. Two negatively charged groups close to each other represents a very high energy, repulsive situation, and this can be relieved if one of the two side chains is protonated.





In this microenvironment, the proximity of one amino acid group directly effects the pKa of its neighbor.

Now consider a situation where a metal ion such as magnesium (Mg^{+2}) or zinc (Zn^{+2}) is bound in the interior of the enzyme, in close contact with an aspartate side chain. With a cation to interact with, the anionic, deprotonated state of the amino acid is stabilized, so the pK_a of this Asp residue is likely to be substantially lower than 3.9.



The metal ion in this situation is considered to be acting as a Lewis acid, accepting electron density from the carboxylate group.

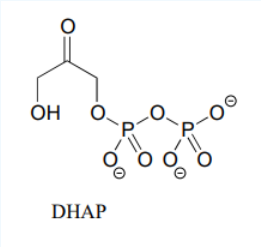
The pK_a-lowering effect of a metal cation can be dramatic – it has been estimated that a water molecule coordinated to a Cu^{+2} or Zn^{+2} ion can have a pK_a as low as 7 (compare this to the 'normal' water pK_a of 15.7!)

? Exercise 7.9.1

A lysine residue located deep in the interior of a protein is surrounded by nonpolar residues. In what direction will this alter the 'normal' pK_a of the lysine side chain, and why?

Exercise 7.9.2

In many biochemical reactions which involve the formation of an enolate intermediate, the carbonyl oxygen of the substrate is coordinated to a divalent metal ion (usually zinc or magnesium) in the active site. Explain, with structural drawings, how this ion-dipole interaction effects the acidity of the α-protons of dihydroxyacetone phosphate (DHAP), an intermediate compound in the glycolysis pathway.



DHAP

[Video tutorials: organic acid-base chemistry]

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7.E: Acid-base Reactions (Exercises)

P7.1: For each pair of molecules below, choose the stronger acid, and explain your choice.

a.



b.



c.



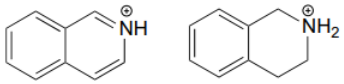
d.



e.



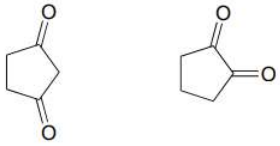
f.



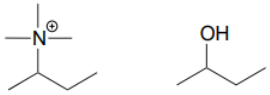
g.



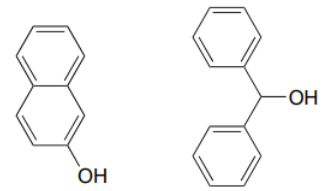
h.



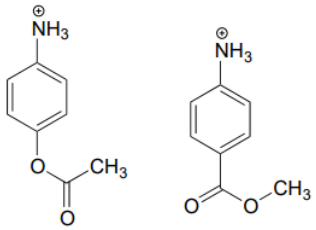
i.



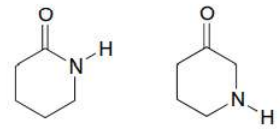
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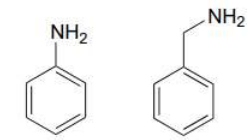


l.

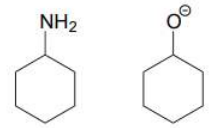


P7.2: For each pair of molecules below, choose the stronger base, and explain your choice.

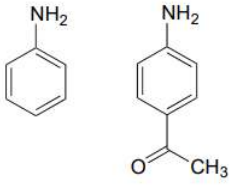
a.



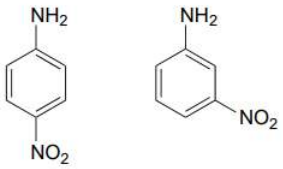
b.



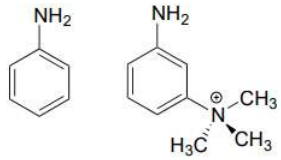
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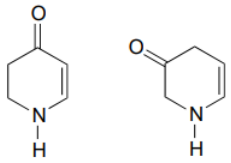
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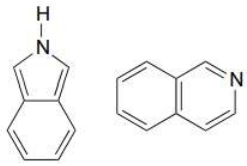
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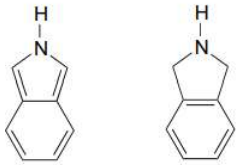
f.



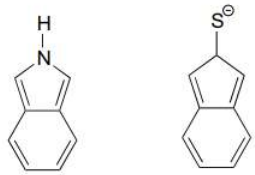
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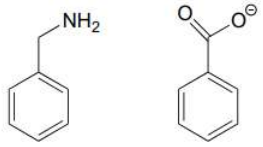
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i.

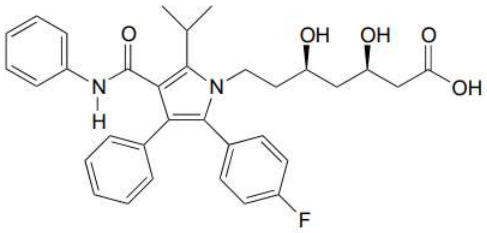


j.

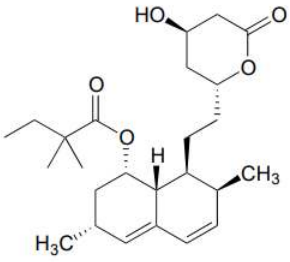


P7.3: Below are the structures of some well-known drugs.

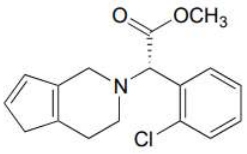
a. What is the most acidic proton on Lipitor? What is its approximate pK_a value? (Lipitor is a brand name for atorvastatin, a cholesterol-lowering drug.)
b. What is the most acidic proton on Zocor? What is its approximate pK_a value? (Zocor is a brand name for simvastatin, a cholesterol-lowering drug.)
c. Where is the most basic site on Plavix? What is the approximate pK_a value of the conjugate acid? (Plavix is a brand name for clopidogrel, a drug to prevent blood clots after a stroke.)
d. Identify the most acidic proton on methadone, and draw the conjugate base that would form if this proton were abstracted by a base. (Methadone is an opiate used in the treatment of heroin addiction.)



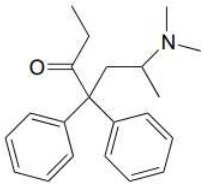
Lipitor



Zocor



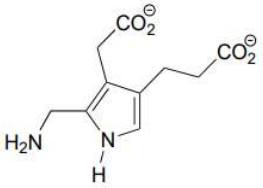
Plavix



methadone

P7.4:

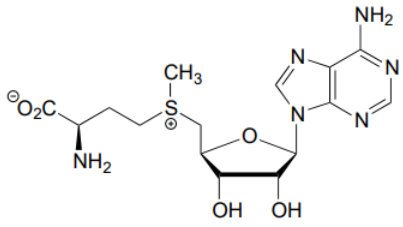
a. Porphobilinogen is a precuror to the biosynthesis of chlorophyll and many other biological molecules. Draw the form of the molecule with a +1 net charge. What would the net charge of the molecule be at physiological ***pH***?



porphobilinogen

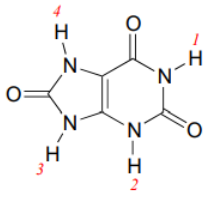
b. Look up the structures of the hormones adrenaline and estrogen (estrone). Estrogen can diffuse across a cell membrane, while adrenaline cannot. Use your knowledge of cell membranes, physical properties of organic molecules, and acid-base chemistry to explain this observation.

P7.5: Classify each of the nitrogen atoms in the coenzyme S-adenosylmethionine as an amine, amide, 'aniline-like', 'pyridine-like', or 'pyrrole-like'. Which nitrogen is most basic? Which is least basic?



S-adenosylmethionine

P7.6: Uric acid, an intermediate in the catabolism (breakdown) of the nucleotide adenosine, has four protons. Which would you expect to be the least acidic? Use resonance structures to explain your reasoning. Hint: consider protons 1-4 in turn, and what the conjugate base would look like if each proton were donated to a base: how well could the resulting negative charge be stabilized by resonance?



uric acid

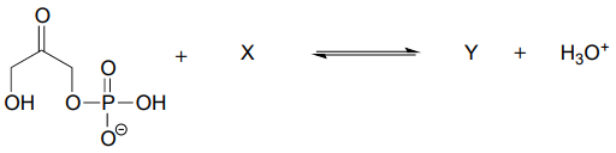
P7.7: Estimate the net charge on a peptide with the sequence P-E-P-T-I-D-E (single-letter amino acid code), when it is dissolved in a buffer with $pH = 7$ (don't forget to consider the terminal amino and carboxylate groups).

P7.8: Estimate the net charge on a dipeptide of sequence D-I.

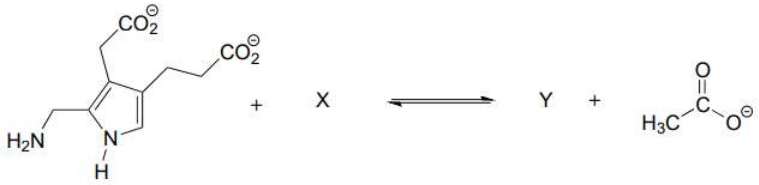
a. in a buffer with $pH = 4.0$
b. in a buffer with $pH = 7.3$
c. in a buffer with $pH = 9.6$

P7.9: Show the structures of species X and Y in the following acid-base reactions, and estimate the value of K_{eq} using the pK_a table. Assume that reactions involve equimolar amounts of acid and base.

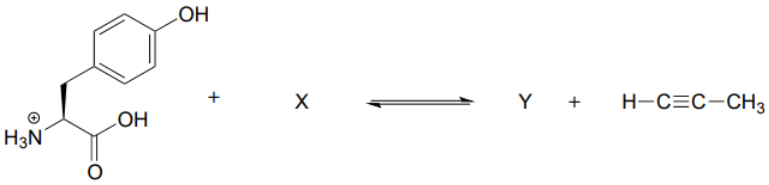
a.



b.



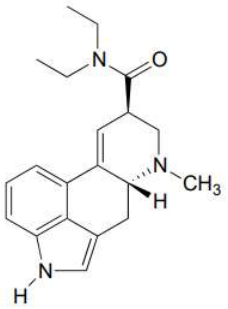
c.



d.



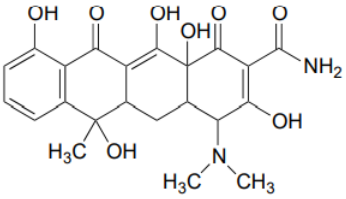
P7.10: Locate the most basic site on the structure of the hallucinogenic drug known as LSD.



lysergic acid diethylamide
(LSD)

P7.11:

a. Identify the most acidic proton on the antibiotic tetracycline, and explain your choice.
b. Identify two additional protons which would be expected to have pK_a values close to 5.



tetracycline

P7.12: In an enzyme active site, a lysine side chain is surrounded by phenylalanine, alanine, tryptophan, and leucine residues. Another lysine side chain is located on the surface of the protein, pointing out into the surrounding water. Which residue has the higher pK_a, and why?

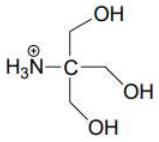
P7.13: (a-d) How would the immediate proximity of a magnesium ion affect the pK_a of the side chains of the following amino acids (relative to the 'typical' pK_a values given in the text)? Assume that all residues are located in the interior of the protein structure, not in direct contact with the outside buffer solution.

a. a glutamate residue
b. a lysine residue?
c. a histidine residue?
d. a tyrosine residue?
e. How would contact with a magnesium ion effect the pK_a of a bound water molecule in the interior of a protein?

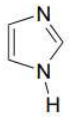
P7.14: The side chain of lysine has a pK_a of approximately 10.5, while the pK_a of the arginine side chain is approximately 12.5. Use resonance structures to rationalize this difference.

P7.15: The a-protons of ketones are, in general, significantly more acidic than those of esters. Account for this observation using structural arguments.

P7.16: 2-amino-2-hydroxymethylpropane-1,3-diol, (commonly known as 'Tris') and imidazole are very commonly used as buffers in biochemistry and molecular biology laboratories. You make two buffer solutions: One is 50 mM Tris at pH 7.0, the other 50 mM imidazole at pH 7.0 For each solution, calculate the concentration of buffer molecules in the cationic protonation state.



'Tris' buffer
$pK_a = 8.1$



imidazole
$pK_a = 7.0$

P7.17: The compound pictured below is an unusual carbon acid (pK_a 16) that does not contain any heteroatoms. Explain why it is so much more acidic than other hydrocarbons.



$pK_a \sim 16$

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7.S: Acid-base Reactions (Summary)

Before you move on to the next chapter, you should:

- Know the Bronsted-Lowry definition of acidity and basicity: a Bronsted acid is a proton donor, a Bronsted base is a proton acceptor.
- Know the Lewis definition of acidity and basicity: a Lewis acid is an electron acceptor, a Lewis base is an electron donor.
- Understand that the Lewis definition is broader: all Bronsted acids are also Lewis acids, but not all Lewis acids are also Bronsted acids.
- Be able to draw a curved arrow mechanism for both Bronsted and Lewis acid-base reactions.
- Know the expressions for K_a and pK_a.
- Commit to memory the approximate pKa values for the following functional groups:
  - H_3O^+, protonated alcohol, protonated carbonyl (~ 0)
  - carboxylic acids (~ 5)
  - imines (~ 7)
  - protonated amines, phenols, thiols (~ 10)
  - water, alcohols (~ 15)
  - α-carbon acids (~ 20)
- Be able to use pK_a values to compare acidity: a lower pK_a corresponds to a stronger acid.
- Know that:
  - For a given pair of acids, the stronger acid will have the weaker conjugate base.
  - For a given pair of basic compounds, the stronger base will have the weaker conjugate acid.
- Be able to identify the most acidic/basic groups on a polyfunctional molecule.
- Be able to calculate the equilibrium constant of an acid base equation from the pK_a values of the acids on either side of the equation.
- Be able to use the Henderson-Hasselbalch equation to determine the protonation state/charge of an organic compound in an aqueous buffer of a given pH.
- Understand the idea that the best way to compare the strength of two acids is to compare the stability of their conjugate bases: the more stable (weaker) the conjugate base, the stronger the acid.
- Be able to compare the acidity or basicity of compounds based on periodic trends:
  - acidity increases left to right on the table, so alcohols are more acidic than amines
  - acidity increases top to bottom on the table, so a thiol is more acidic than an alcohol.
- Be able to compare the acidity or basicity of compounds based on protonation state: H_3O^+ is more acidic than H_2O, NH_4^+ is more acidic than NH_3.
- Understand how the inductive effect exerted by electronegative groups influences acidity.
- Understand how resonance delocalization of electron density influences acidity.
- Be able to explain/predict how orbital hybridization affects the relative acidity of terminal alkynes, alkenes, and alkanes.
- Be able to explain why phenols are more acidic than alcohols, and how electron-withdrawing or donating groups influence the acidity of phenols.
- Be able to identify the relative basicity of a nitrogen-containg group in a compound, based on whether it is an amine, amide, imine, aniline, or 'pyrrole-like'.
- Be able to identify □-carbon(s) on a carbonyl compound, and explain why □□protons are weakly acidic. You should be able to draw the enolate conjugate base of a carbonyl compound.
- Be able to identify tautomeric relationships, specifically keto-enol and imine-enamine tautomers.
- Understand what a polyprotic acid is, what is meant by multiple pKa values, and why these values get progressively higher.

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CHAPTER OVERVIEW

8: Nucleophilic Substitution Reactions

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8.1: Two Mechanistic Models for Nucleophilic Substitution
8.2: Nucleophiles
8.3: Electrophiles
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8.5: Regiochemistry of SN1 Reactions with Allylic Electrophiles
8.6: SN1 or SN2? Predicting the Mechanism
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8.E: Nucleophilic Substitution Reactions (Exercises)
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8.0: Prelude to Nucleophilic Substitution Reactions

Dr. Tim Spector, Professor of Genetic Epidemiology at Kings College in London, knows a thing or two about twins. He should: as head of the Department of Twin Research at Kings College, Spector works with about 3500 pairs of identical twins, researching the influence of a person's genetic blueprint on everything from how likely they are to be obese, to whether or not they hold religious beliefs, to what kind of person they fall in love with. Anyone who is a twin, or has ever known a pair of identical twins, can attest to how remarkably similar they are to each other, even in the rare cases of adopted twins raised in separate homes. Dr. Spector, however, has over the course of his research become much more interested in how they are different.

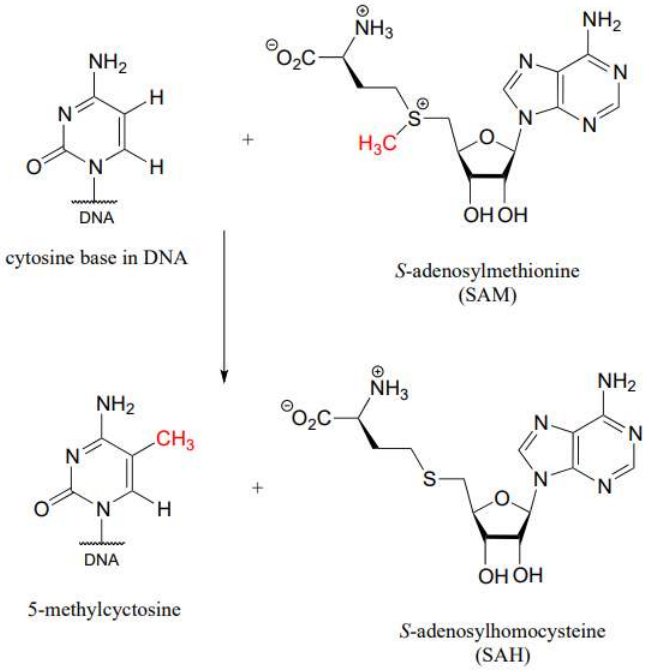


A recent article about Spector in the British newspaper The Guardian (June 1, 2013) begins with an introduction to two middle-aged twin sisters named Barbara and Christine, one of the pairs of twins in the Kings College study group. Although they were treated almost as a single person when growing up, with identical haircuts and clothes, the twins began to diverge in their teenage years as they gained the freedom to make their own choices. They began to dress quite differently, with Christine choosing much more conservative styles than Barbara. Christine describes herself as being self-conscious, while Barbara has always been more confident. Christine suffers from depression, but Barbara does not.

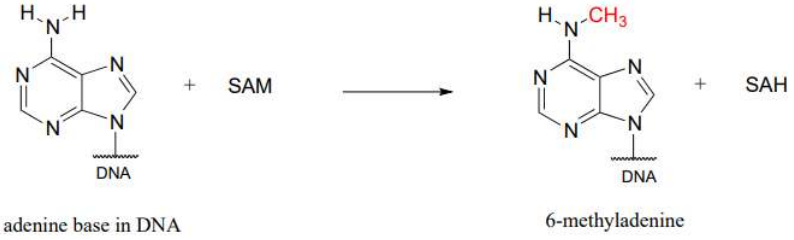
Given that they were born with the exact same DNA and were raised in the same home, where do these differences come from? In public debates about why people are the way they are, a catch phrase that often comes up is 'nature vs. nurture': people argue, in other words, about the relative influence of a person's genes vs. the influence of their environment. In Barbara and Christine's case, one would assume that the 'nature' is identical, and given that they grew up in the same house, the 'nurture' side of the equation should also be quite similar.

As it turns out, the 'nature' component may not be so identical after all. Based on his work with twins, Spector now thinks that subtle changes to Barbara's and Christine's DNA after conception - and indeed, throughout their lifetimes - may be a much more important determinant of their physical and psychological characteristics than was previously believed. As we age from infants to adulthood, some of our DNA bases are modified by methylation: in other words, a methyl (CH_3) group replaces a hydrogen. In humans and other mammals, this mainly happens to cytosine (C) bases, while in bacteria it is mainly adenosine (A) bases which are methylated. The biomolecule that serves as the methyl group donor in both cases is called S-adenosyl methionine, or 'SAM' for short.

Methylation of cytosine



Methylation of adenine



In mammals, gene methylation seems to occur in different patterns in different people - even in identical twins - in response to environmental factors. Methylation also seems to have the effect of amplifying or muting a gene's function, by altering how it interacts with regulatory proteins. The combined effect of many gene methylation events can be profound, as groups of interrelated genes are 'turned up' or 'turned down' in concert. Professor Spector thinks that the many differences between Barbara and Christine probably stem, at least in part, from differences in how their genes have been methylated over the course of their lives so far.

In this chapter, we delve for the first time into 'real' organic reactions, beyond the simple proton transfer events of Bronsted acid-base reactions that we looked at in chapter 7. The methylation of DNA is an excellent example of a type of organic reaction called nucleophilic substitution, to which we were introduced briefly in chapter 6 as a model for learning about some of the fundamental concepts of organic reactivity. Now we will delve more deeply into three crucial players in this bond-forming and bond-breaking process: the nucleophile, the electrophile, and the leaving group. In doing so, we will get a chance to practice and refine our skills in drawing organic reaction mechanisms using the curved arrow formality, and we will think about what a transition state and a reactive intermediate of a reaction might look like, and how the structure of these species determines the regiochemical and stereochemical outcome of a nucleophilic substitution reaction. Perhaps, in the time spent working on this chapter, some of the cytosines in your DNA will undergo nucleophilic substitution reactions to become methylated - and who knows how this will influence who you go on to become?

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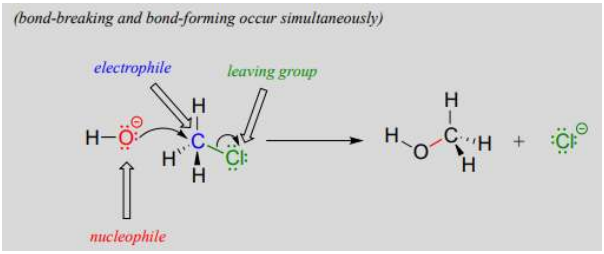
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8.1: Two Mechanistic Models for Nucleophilic Substitution

As we begin our study of nucleophilic substitution reactions, we will focus at first on simple alkyl halide compounds. While the specific reactions we'll initially consider do not occur in living things, it is nonetheless useful to start with alkyl halides as a model to illustrate some fundamental ideas that we must cover. Later, we will move on to apply what we have earned about alkyl halides to the larger and more complex biomolecules that are undergoing nucleophilic substitution right now in your own cells.

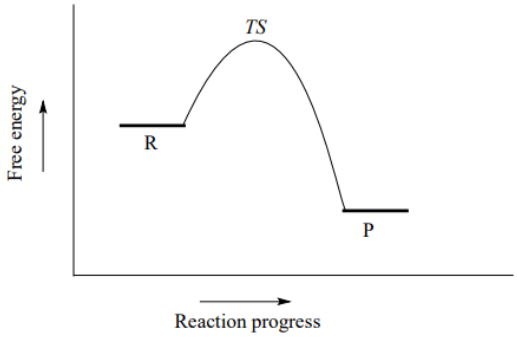
The S_N2 mechanism

You may recall from our brief introduction to the topic in chapter 6 that there are two mechanistic models for how a nucleophilic substitution reaction can proceed. In one mechanism, the reaction is concerted: it takes place in a single step, and bond-forming and bond-breaking occur simultaneously. This is illustrated by the reaction between chloromethane and hydroxide ion:

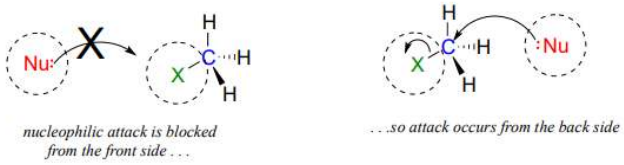


Recall that the hydroxide ion in this reaction is acting as a nucleophile (an electron-rich, nucleus-loving species), the carbon atom of chloromethane is acting as an electrophile (an electron-poor species which is attracted to electrons), and the chloride ion is the leaving group (where the name is self-evident).

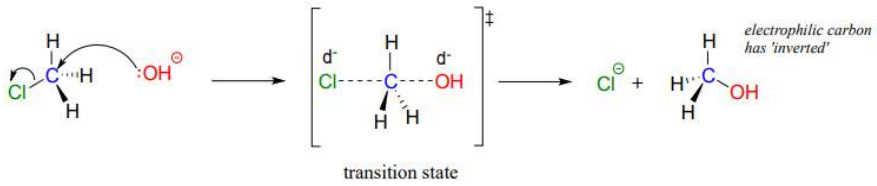
Organic chemists refer to this mechanism by the term 'S_N2', where S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a bimolecular reaction: the overall rate depends on a step in which two separate species collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



The geometry of an S_N2 reaction is specific: the reaction can only occur when the nucleophile collides with the electrophilic carbon from the opposite side relative to the leaving group. This is referred to as backside attack. Approach from the front side simply doesn't work: the leaving group - which, like the nucleophile is an electron-rich group - blocks the way.



The result of backside attack is that the bonding geometry at the electrophilic carbon *inverts* (turns inside-out) as the reaction proceeds.



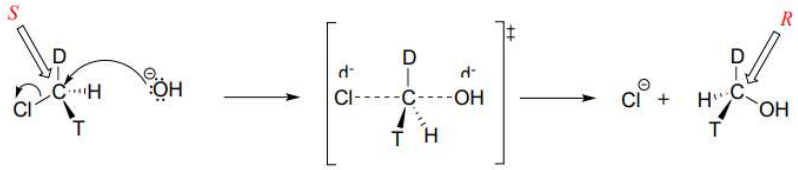
The transition state of the reaction is illustrated by drawing dotted lines to represent the covalent bonds that are in the process of breaking or forming. Because the formal charge on the oxygen nucleophile changes from negative one to zero as the reaction proceeds, and conversely the charge on the chlorine leaving group changes from zero to negative one, at the transition state both atoms are shown bearing a partial negative charge (the symbol δ-). One other drawing convention for transition states is to use brackets, with the double-dagger symbol in subscript.

Notice that the transition state for an S_N2 reaction has trigonal bipyramidal geometry: the nucleophile, electrophile, and leaving group form a straight line, and the three substituents on carbon (all hydrogen atoms in this case) are arranged in the same plane at **120°** angles.

? Exercise 8.2.1

What is the measure in degrees) of the $H-C-O$ angle in the S_N2 transition state illustrated above?

Consider what would happen if we were to replace one of the hydrogen atoms in chloromethane with deuterium (the ^2H isotope), and one with tritium (the radioactive ^3H isotope). Now, because it has four different substituents, our carbon electrophile is a chiral center. We'll arbitrarily assume that we start with the S enantiomer.



As the hydroxide nucleophile attacks from the backside and the bonding geometry at carbon inverts, we see that the stereochemistry of the product reflects this inversion: we end up with the R enantiomer of the chiral product.

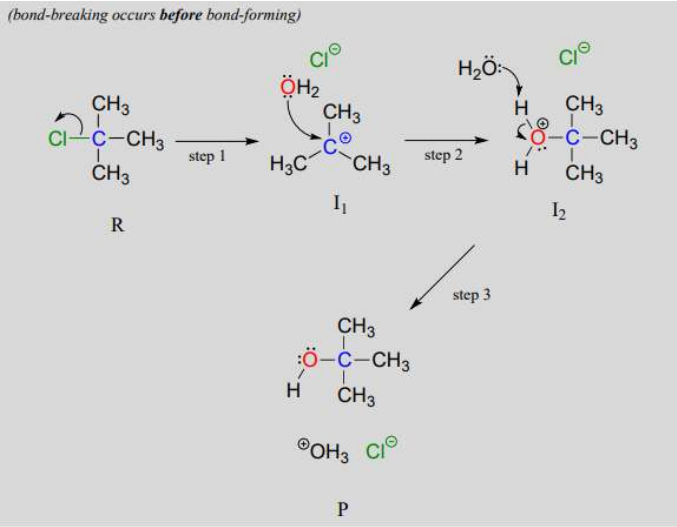
S_N2 reactions proceed with inversion of stereochemical configuration at the electrophilic carbon.

video tutorial/animation: inversion of configuration during SN2 reactions

The S_N1 mechanism

A second model for the nucleophilic substitution reaction is called the S_N1 mechanism. The '1' in S_N1 indicates that the rate-determining step of the reaction is unimolecular: in other words, the rate-determining step involves a single molecule breaking apart (rather than two molecules colliding as was the case in the S_N2 mechanism.)

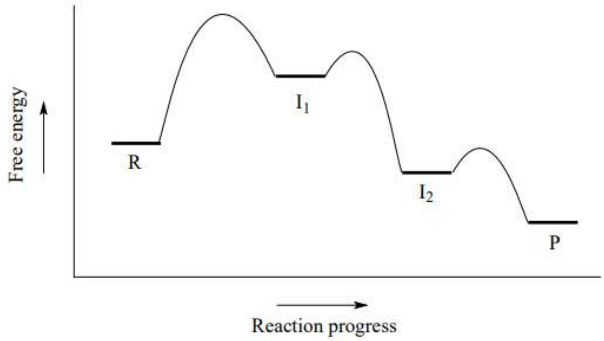
In an S_N1 mechanism the carbon-leaving group bond breaks first, before the nucleophile approaches, resulting in formation of a carbocation intermediate (step 1):



A carbocation is a powerful electrophile: because the carbon lacks a complete octet of valence electrons, it is 'electron-hungry'. In step 2, a lone pair of electrons on the water nucleophile fills the empty p orbital of the carbocation to form a new bond.

Notice that this is actually a three-step mechanism, with a final, rapid acid-base step leading to the alcohol product.

A potential energy diagram for this S_N1 reaction shows that each of the two positively-charged intermediate stages (I_1 and I_2 in the diagram) can be visualized as a valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the transition states.



The first, bond-breaking step is the slowest, rate-determining step - notice it has the highest activation energy and leads to the highest-energy species (I_1, the carbocation intermediate). Step 2 is rapid: a new covalent bond forms between a carbocation and and a water nucleophile, and no covalent bonds are broken. Recall from chapter 7 that Bronsted-Lowry proton transfer steps like step 3 are rapid, with low activation energies.

hydrolysis

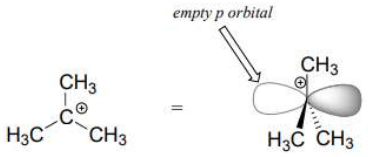
The nucleophilic substitution reactions we have seen so far are examples of hydrolysis. This term is one that you will encounter frequently in organic and biological chemistry. Hydrolysis means 'breaking with water': in a hydrolysis reaction, a water molecule (or hydroxide ion) participates in the breaking of a covalent bond. There are many reaction types other than nucleophilic substitution that can accurately be described as hydrolysis, and we will see several examples throughout the remaining chapters of this book.

Solvolysis is a more general term, used when a bond in a reagent is broken by a solvent molecule: usually, the solvent in question is water or an alcohol such as methanol or ethanol.

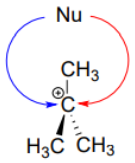
Exercise 8.2.2

Draw a mechanism for the \(S_N1\) solvolysis of tert-butyl chloride in methanol. What new functional group has been formed?

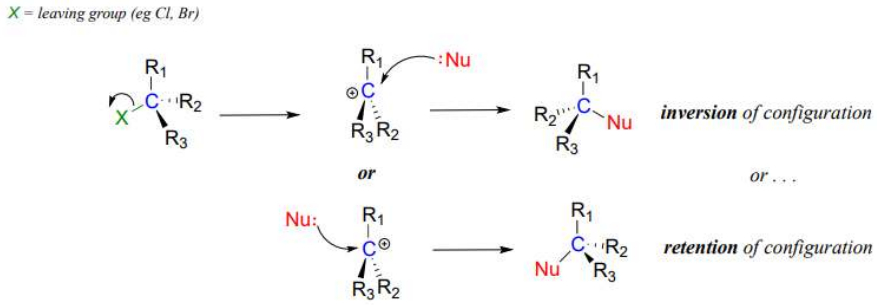
We saw that S_N2 reactions result in inversion of stereochemical configuration at the carbon center. What about the stereochemical outcome of S_N1 reactions? Recall that a carbocation is sp^2-hybridized, with an empty p orbital perpendicular to the plane formed by the three sigma bonds:



In the second step of an S_N1 reaction, the nucleophile can attack from either side of the carbocation (the leaving group is already gone, and thus cannot block attack from one side like in an S_N2 reaction).

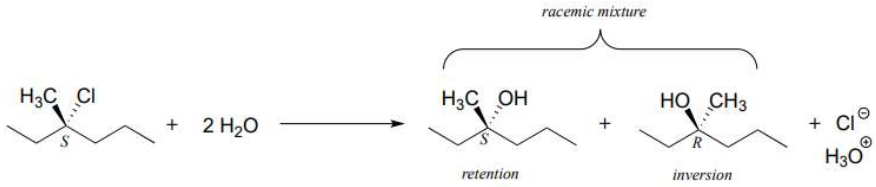


Consider an S_N1 reaction with a chiral tertiary alkyl chloride:



Because the nucleophile is free to attack from either side of the carbocation electrophile, the reaction leads to a 50:50 mixture of two stereoisomeric products. In other words: In general nonenzymatic SN1 reaction can occur with either retention or inversion of configuration at the electrophilic carbon, leading to racemization if the carbon is chiral.

For an example, consider the hydrolysis of (S)-3-chloro-3-methylhexane.



The result of this (nonenzymatic) reaction is a racemic mixture of chiral alcohols.

It is important to remember, however, that enzymatic reactions are in almost all cases very specific with regard to stereochemical outcome. A biochemical S_N1 reaction, as we shall see later, can result in either inversion or retention of configuration at the electrophilic carbon, but generally not a mixture of both: the two reactants are bound with specific geometry in the enzyme's active site, so that the nucleophile can approach from one side only.

(The following exercises refer to nonbiological reactions)

Exercise 8.2.3

a. Draw a complete mechanism for the hydrolysis reaction in the previous figure, showing all bond-breaking and bond-forming steps, and all intermediate species.
b. Draw structures representing TS1 and TS2 in the reaction. Use the solid/dash wedge convention to show three dimensions.
c. What is the expected optical rotation of the product mixture?
d. Could the two organic products be separated on a silica column chromatography?

Exercise 8.2.4

a. Draw the product(s) of the hydrolysis of (R)-3-chloro-3-methyl heptane.
b. What can you predict, if anything, about the optical rotation of the product(s)?
c. Draw the product(s) of the hydrolysis of (3R,5R)-3-chloro-3,5-dimethyl heptane.
d. What can you predict, if anything, about the optical rotation of the product(s)?

Before we go on to look at some actual biochemical nucleophilic substitution reactions, we first need to lay the intellectual groundwork by focusing more closely on the characteristics of the three principal partners in the nucleophilic substitution reaction: the nucleophile, the electrophile, and the leaving group. In addition, we need to consider the carbocation intermediate that plays such a key role in the S_N1 mechanism. For the sake of simplicity, we will continue to use simple, non-biological organic molecules and reaction examples as we work through the basic concepts.

Video tutorial/animation: SN1 reactions

Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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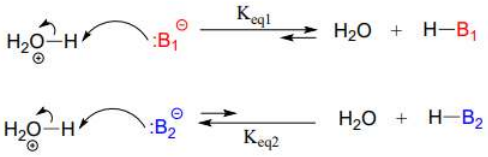
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8.2: Nucleophiles

What is a nucleophile?

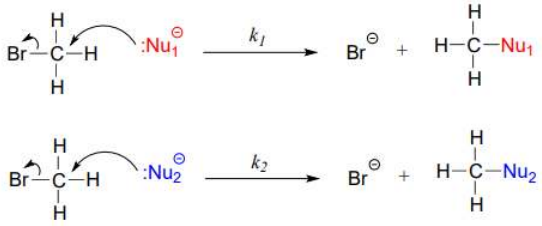
A nucleophile is an atom or functional group with a pair of electrons (usually a non-bonding, or lone pair) that can be shared. The same, however, can be said about a base: in fact, bases can act as nucleophiles, and nucleophiles can act as bases. What, then, is the difference between a base and a nucleophile?

A Brønsted-Lowry, as you will recall from chapter 7, uses a lone pair of electrons to form a new bond with an acidic proton. We spent much of chapter 7 discussing how to evaluate how basic a species is. Remember that when we evaluate basicity - the strength of a base - we speak in terms of thermodynamics: where does equilibrium lie in a reference acid-base reaction?



$Base_1$ is stronger than $Base_2$: equilibrium lies further to the right in reaction with a common acid.
$Keq_1 > Keq_2$

We will spend much of this section discussing how to evaluate how nucleophilic a species is - in other words, its nucleophilicity. A nucleophile shares its lone pair of electrons with an electrophile - an electron-poor atom other than a hydrogen, usually a carbon. When we evaluate nucleophilicity, we are thinking in terms of kinetics - how fast does the nucleophile react with a reference electrophile?

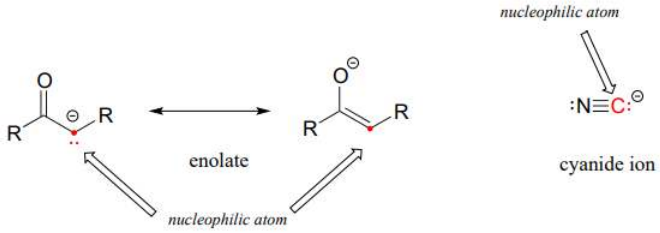


*$Nucleophile_1$ is more powerful than $Nucleophile_2$: reacts **faster** with a common electrophile.*
rate constant $k_1 > k_2$

In both laboratory and biological organic chemistry, the most common nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic compounds and functional groups are water/hydroxide ion, alcohols, phenols, amines, thiols, and sometimes carboxylates.

In laboratory (non-biological) reactions, halide (I^-, Br^-, Cl^-, F^-) and azide (N_3-) anions are also commonly seen acting as nucleophiles in addition to the groups mentioned above.

Carbon atoms can also be nucleophiles - enolate ions (section 7.6) are common carbon nucleophiles in biochemical reactions, while the cyanide ion (CN^-) is just one example of a carbon nucleophile commonly used in the laboratory.



Understanding carbon nucleophiles will be critical when we study, in chapters 12 and 13, the enzyme-catalyzed reactions in which new carbon-carbon bonds are formed in the synthesis of biomolecules such as DNA and fatty acids. In the present chapter, however, we will focus on heteroatom (non-carbon) nucleophiles.

Now, let's consider a number of factors that influence how nucleophilic an atom or functional group is. We'll start with protonation state.

Protonation state

The protonation state of a group has a very large effect on its nucleophilicity. A negatively-charged hydroxide ion is much more nucleophilic (and basic) than a water molecule. In practical terms, this means that a hydroxide nucleophile will react in an S_N2 reaction with chloromethane several orders of magnitude faster than will a water nucleophile.

Likewise, a thiolate anion is more nucleophilic than a neutral thiol, and a neutral amine is nucleophilic, whereas an ammonium cation is not.

In a non-biological context, S_N2 reactions tend to occur with more powerful, anionic nucleophiles, where the nucleophile can be thought of as actively displacing ('pushing') the leaving group off the carbon. S_N1 reactions, in contrast, tend to be solvolysis reactions, with a weak, neutral nucleophile such as water or an alcohol.

Periodic trends in nucleophilicity

Just as with basicity, there are predictable periodic trends associated with nucleophilicity. Moving horizontally across the second row of the periodic table, the trend in nucleophilicity parallels the trend in basicity:

The horizontal periodic trend in nucleophilicity

more nucleophilic NH_2- > OH- > F- *less nucleophilic*

more nucleophilic R-NH_2 > R-OH *less nucleophilic*

Recall from section 7.3 that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger volume, which tends to increase stability (and thus reduce basicity).

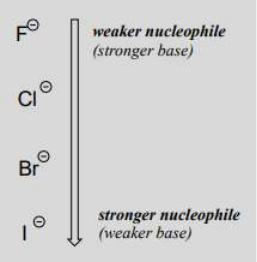
The vertical periodic trend for nucleophilicity is somewhat more complicated that that for basicity, and depends on the solvent in which the reaction is taking place. Take the general example of the S_N2 reaction below:



where Nu^- is one of the halide ions: fluoride, chloride, bromide, or iodide, and X is a common leaving group. If this reaction is occurring in a protic solvent (that is, a solvent that has a hydrogen atom bonded to an oxygen or nitrogen - water, methanol and ethanol are protic solvents), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.

The vertical periodic trend in nucleophilicity in water and other protic solvents

(opposite of the trend in basicity!)

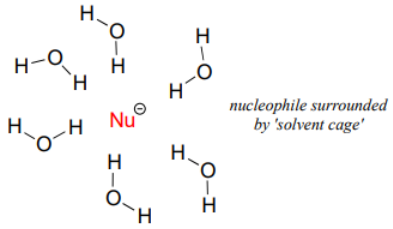


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This is the opposite of the vertical periodic trend in basicity (section 7.3), where iodide is the least basic. What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction running in a protic solvent like water. Protic solvent molecules form strong noncovalent interactions with the electron-rich nucleophile, essentially creating a 'solvent cage' of hydrogen bonds:

artwork needed



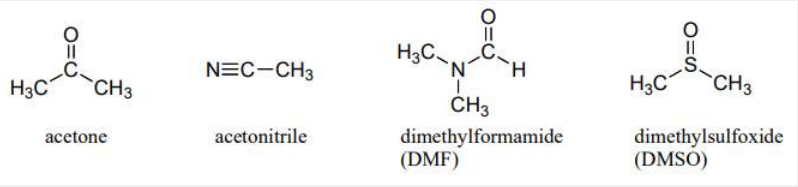
For the nucleophile to attack in an S_N2 reaction, the nucleophile-solvent hydrogen bonds must be disrupted - in other words, the nucleophilic electrons must 'escape through the bars' of the solvent cage. A weak base like iodide ion interacts weakly with the protons of the solvent, so these interactions are more readily disrupted. Furthermore, because the valence electrons on iodide ion are far from the nucleus, the electron cloud is polarizable - electron density can readily be pulled away from the nucleus, through the solvent cage and toward the electrophile.

A smaller, more basic anion such as fluoride is more highly shielded by stronger interactions with the solvent molecules. The electron cloud of the fluoride ion is smaller and much less polarizable than that of an iodide ion: in water solvent, the larger iodide ion is a more powerful nucleophile than the smaller fluoride ion.

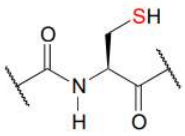
Note

The above discussion of the vertical periodic trend in nucleophilicity applies to biochemical reactions, because the biological solvent is water. The picture changes for laboratory reactions if we switch to a **polar aprotic solvent**, such as acetone, which is polar enough to solvate the polar and ionic compounds in the reaction but is not a hydrogen bond donor, and does not form a strong 'solvent cage' like water does. In acetone and other polar aprotic solvents, the trend in nucleophilicity is the same as the trend in basicity: fluoride is the strongest base and the strongest nucleophile.

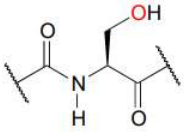
Structures of some of the most common polar aprotic solvents are shown below. These solvents are commonly used in laboratory nucleophilic substitution reactions.



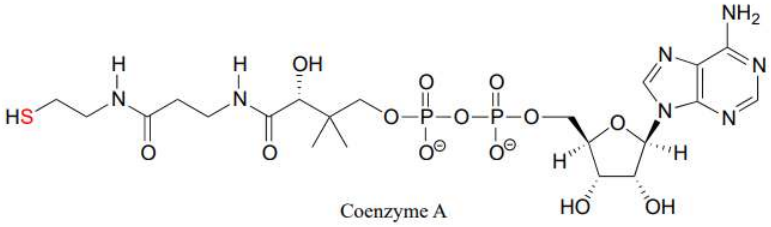
In biological chemistry, the most important implication of the vertical periodic trend in nucleophilicity is that thiols are more *nucleophilic* than alcohols. The thiol group in a cysteine amino acid residue, for example, is more nucleophilic than the alcohol group on a serine, and cysteine often acts as a nucleophile in enzymatic reactions. The thiol group on coenzyme A is another example of a nucleophile we will see often in enzymatic reactions later on. Of course, reactions with oxygen and nitrogen nucleophiles are widespread in biochemistry as well.



cysteine residue



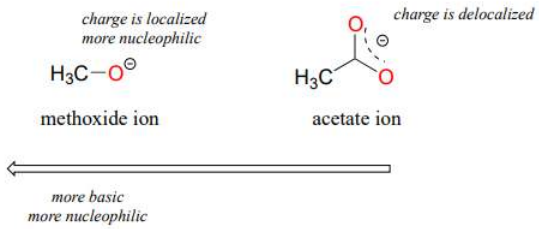
serine residue



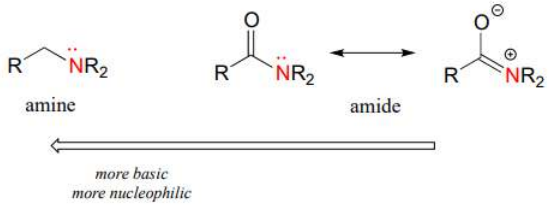
Coenzyme A

Resonance effects on nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity (see section 7.3). If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In an alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.



The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



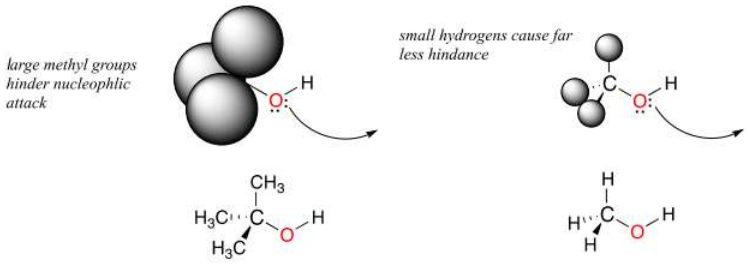
? Exercise 8.3.1

Which amino acid has the more nucleophilic side chain - serine or tyrosine? Explain.

Steric effects on nucleophilicity

Steric hindrance is an important consideration when evaluating nucleophility. For example, tert-butanol is less potent as a nucleophile than methanol. The comparatively bulky methyl groups on the tertiary alcohol effectively block the route of attack by

the nucleophilic oxygen, slowing the reaction down considerably (imagine trying to walk through a narrow doorway while carrying three large suitcases!).



A final note: when it comes to comparing the rate of nucleophilic substitution reactions, the strength of the nucleophile only matters for S_N2 reactions. It is irrelevant for S_N1 reactions, because the rate-determining step (when the leaving group departs and a carbocation intermediate forms) does not involve the nucleophile.

Video tutorial: nucleophiles

Exercise 8.3.2

Which is the better nucleophile - a cysteine side chain or a methionine side chain? A serine or a threonine? Explain.

Exercise 8.3.3

In each of the following pairs of molecules/ions, which is expected to react more rapidly with CH3Cl in acetone solvent? Explain your choice.

a. phenolate (deprotonated phenol) or benzoate (deprotonated benzoic acid)?
b. water or hydronium ion?
c. trimethylamine or triethylamine?
d. chloride anion or iodide anion?
e. CH3NH- or CH3CH2NH2?
f. acetate or trichloroacetate?
g. aniline or 4-methoxyaniline?
h. phenolate or 2,6-dimethylphenolate?

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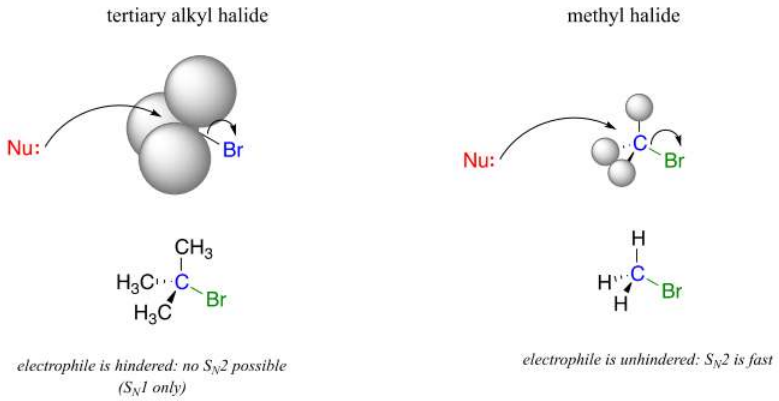
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8.3: Electrophiles

Next, we turn to electrophiles. In the vast majority of the nucleophilic substitution reactions you will see in this and other organic chemistry texts, the electrophilic atom is a carbon bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom is an attractive target for something that is electron-rich, i.e. a nucleophile. However, we must also consider the effect of steric hindrance on electrophilicity.

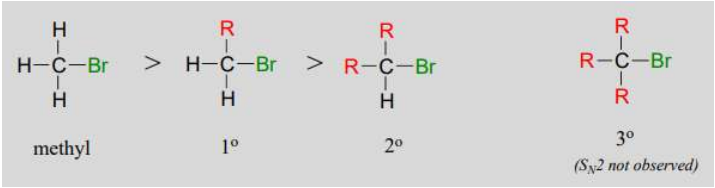
Steric hindrance at the electrophile

One of the most important factors to consider when looking at the electrophile in a nucleophilic substitution reaction is steric hindrance. Consider two hypothetical S_N2 reactions: one in which the electrophile is a methyl carbon and another in which it is tertiary carbon.



Because the three substituents on the methyl electrophile are hydrogen atoms, the nucleophile has a relatively clear path for backside attack, and the S_N2 reaction will take place readily. However, backside attack on the tertiary carbon electrophile is blocked by the bulky methyl groups, preventing access to the site of electrophilicity.

S_N2 reactions occur at methyl, primary, and secondary carbon electrophiles. The degree of steric hindrance determines relative rates of reaction: unhindered methyl electrophiles react fastest, and more hindered secondary carbon electrophiles react slowest, assuming all other reactions conditions are identical. S_N2 reactions do not occur to an appreciable extent at tertiary carbon electrophiles.

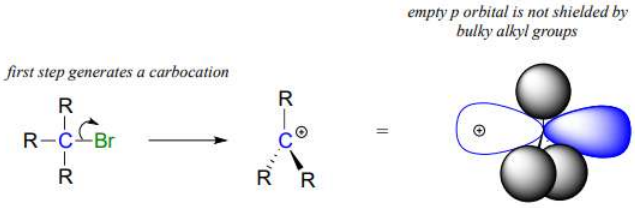


? Exercise 8.4.1

Which would be expected to react more rapidly in an S_N2 reaction with an azide ion (N_3^-) nucleophile in acetone solvent: 1-bromo-2,2-dimethylbutane or 1-bromo-3-methylbutane?

What about the S_N1 pathway? Steric hindrance around the electrophilic carbon is not a significant factor in slowing down an S_N1 reaction. This makes perfect sense from a geometric point of view: the limitations imposed by sterics are significant in an S_N2 displacement because the electrophile being attacked is an sp3-hybridized tetrahedral carbon with relatively 'tight' angles of $109.5°$. Remember that in an S_N1 mechanism, the leaving group leaves first, and then the nucleophile attacks an sp^2-hybridized carbocation intermediate, which has trigonal planar geometry with 'open' $120°$ angles.

artwork needed



With this open geometry, the empty p orbital of the carbocation is no longer significantly shielded from the approaching nucleophile by the bulky alkyl groups, and is an 'easy target' for a nucleophile: this step is fast, and is not the rate-determining step for an S_N1 reaction.

Carbocation stability

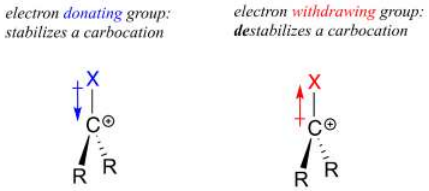
What, then, are the characteristics of an electrophile that favor an S_N1 reaction pathway as opposed to an S_N2 pathway? We know that the rate-limiting step of an S_N1 reaction is the first step: loss of the leaving group and formation of the carbocation intermediate. Accordingly, the rate of an S_N1 reaction depends to a large extent on the stability of the carbocation intermediate.

The critical question now becomes:

What stabilizes a carbocation?

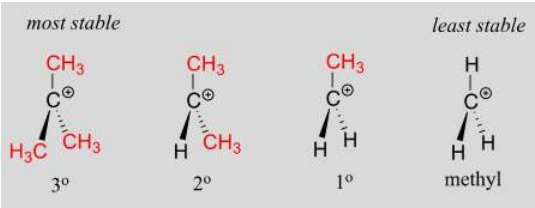
Think back to Chapter 7, when we were learning how to evaluate the strength of an acid. The critical question there was: “how stable is the conjugate base that results when this acid donates its proton”? In many cases, this conjugate base was an anion – a center of excess electron density. Anything that can draw some of this electron density away– in other words, any electron withdrawing group – will stabilize the anion.

Conversely, a carbocation is stabilized by an electron donating group, and **de**stabilized by an electron withdrawing group.

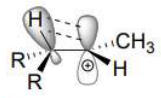


A positively charged species such as a carbocation is electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Alkyl groups, because of the electrons in their carbon-carbon and carbon-hydrogen bonds, are weak electron-donating groups, and will stabilize nearby carbocations. What this means is that, in general, more substituted carbocations are more stable: a tert-butyl carbocation, for example, is more stable than an isopropyl carbocation. Primary carbocations are highly unstable and not often observed as reaction intermediates; methyl cations are even less stable.

More substituted carbocations are more stable:



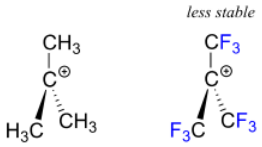
Another way to explain this trend in carbocation stability involves the phenomenon of hyperconjugation, in which the empty p orbital of a carbocation is stabilized by overlap with a σ bond on an adjacent carbon. This overlap effectively spreads the positive charge over a larger area. The figure below shows the empty p orbital of a secondary carbocation being stabilized by hyperconjugation with an adjacent $C-H$ σ bond.



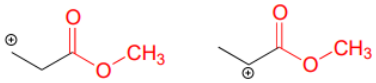
hyperconjugation

Hyperconjugation is not possible with a methyl cation as there is no adjacent σ bond available to overlap the empty p orbital. As the degree of substitution on a carbocation increases, so does the capacity for stabilizing hyperconjugation interactions.

The presence of an electron-withdrawing group - such as a fluorine atom - will significantly destabilize a carbocation through the inductive effect.



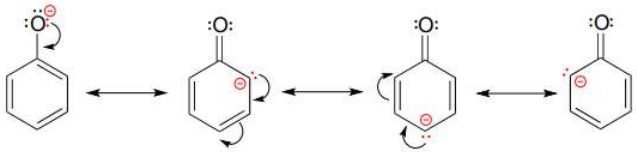
Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the $C=O$ double bond. It is possible to demonstrate in the laboratory (we'll see how in problem 14.x) that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.



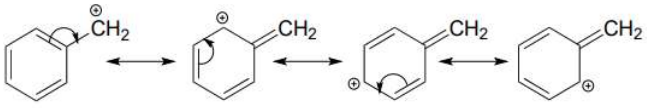
A: more stable **B**: less stable

The positive charge in cation B is closer to the electron withdrawing carbonyl substitution, and as we learned in section 7.3, the inductive effect of an electron withdrawing group decreases with distance.

Stabilization of a carbocation can also occur through resonance effects. Recall from section 7.4 that the negative charge on a phenolate ion is stabilized by resonance, because the charge can be delocalized to three of the carbons on the aromatic ring.



A positive charge is also stabilized when it can be delocalized over more than one atom. Consider a benzylic carbocation, where the positively-charged carbon is bonded directly to an aromatic ring. A benzylic carbocation is stabilized by the resonance electron-donating effect of the aromatic ring. Three additional resonance structures can be drawn for the carbocation in which the positive charge is located on one of three aromatic carbons:



? Exercise 8.4.2

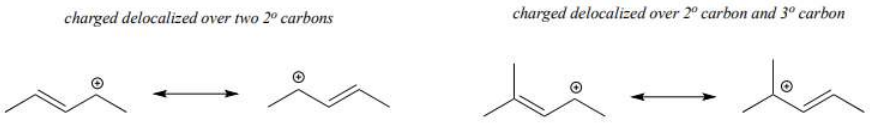
Fill in the missing numbers in this statement: The conjugated \(p\) system in the benzylic carbocation above is composed of _____ \(p\) orbitals overlapping to share _____ \(\pi \) electrons.

Allylic carbocations, where the positively charged carbon is adjacent to a double bond, are stabilized by resonance delocalization of the posive charge.



an allylic carbocation

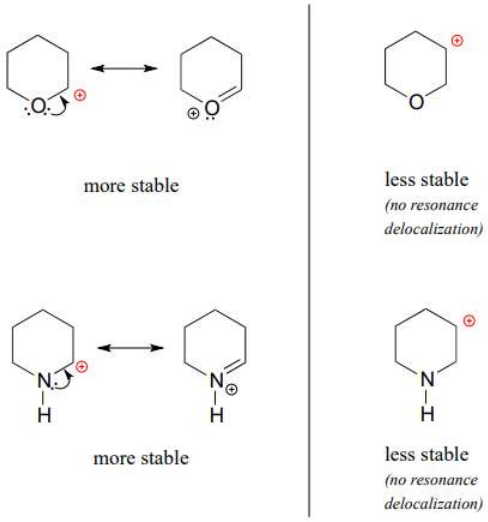
Often, we must consider more than one factor when predicting carbocation stability. For example, the carbocation on the right in the figure below is more stable than the carbocation on the left. Both are allylic with the charge delocalized over two carbons, but on the more stable carbocation, one of the carbons is tertiary.



less stable more stable

Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would be carbocation-destabilizing electron withdrawing groups. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the right position, the overall effect can be carbocation stabilization. Although these heteroatoms are indeed electron withdrawing groups by induction, they can be electron donating groups by resonance, and, as we learned earlier (section 7.3) in the context of acid-base chemistry, resonance effects are in general more powerful than inductive effects when the two operate in opposite directions.

Consider the two pairs of carbocation species below:



more stable

less stable
(no resonance delocalization)

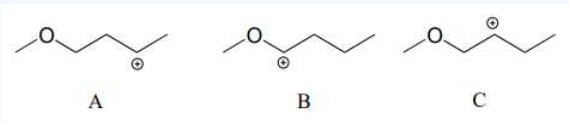
more stable

less stable
(no resonance delocalization)

In the more stable carbocations, the heteroatom acts as an electron donating group by resonance: in effect, the lone pair on the heteroatom is available to delocalize the positive charge. Note also that every atom in the major resonance contributor has a complete octet of valence electrons.

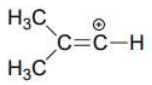
? Exercise 8.4.3

Rank the following carbocations from most to least stable:



A B C

Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are highly unstable.



a vinylic carbocation
(very unstable)

? Exercise 8.4.4

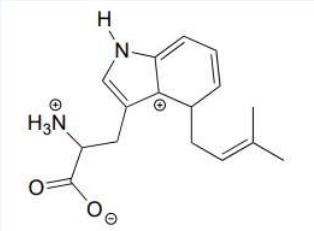
Explain why vinylic carbocations are unstable. (Hint:)

Hint

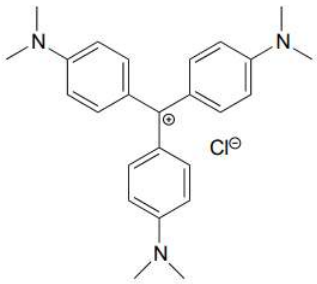
Think about hybridization and electronegativity.

? Exercise 8.4.5

The carbocation below is an intermediate species in a reaction that is part of the biosynthesis of a hallucinogenic compound in a fungus. Draw a resonance contributor that shows how it is stabilized by resonance with the nitrogen atom.



For the most part, carbocations - even 'relatively stable' carbocations such as those that are tertiary and/or benzylic - are still highly reactive, transient intermediate species in organic reactions, which briefly form and then react again right away. However, there are some unusual examples of carbocation species that are so stable that they can be put in a jar and stored on the shelf as a salt. Crystal violet is the common name for the chloride salt of the carbocation whose structure is shown below. Notice the structural possibilities for extensive resonance delocalization of the positive charge, and the presence of three electron-donating amine groups.



crystal violet

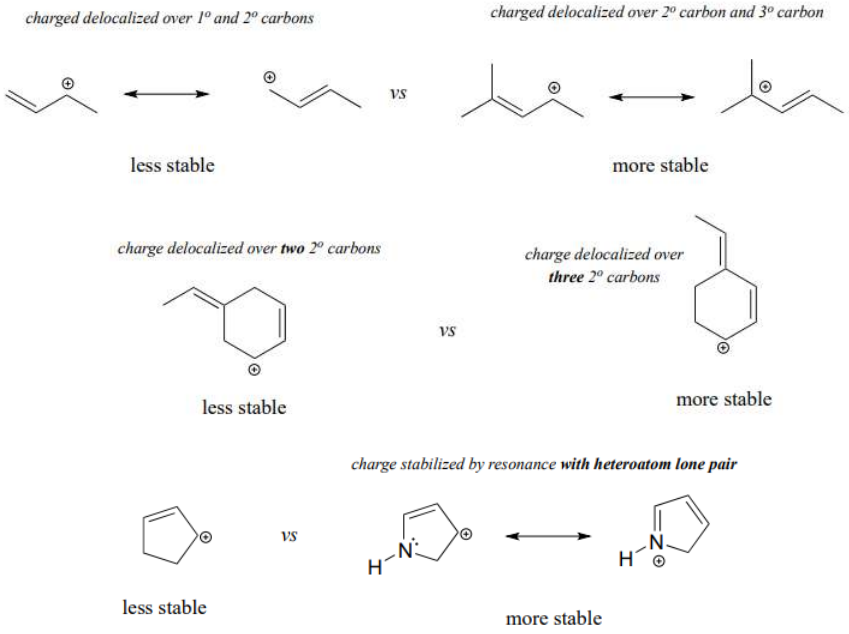
? Exercise 8.4.6

a. Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.
b. Notice that crystal violet is deeply colored. Explain why you could have predicted this from looking at its chemical structure.
c. The conjugated system of crystal violet consists of how many overlapping p orbitals sharing how many p electrons?

Summary of factors influencing carbocation stability

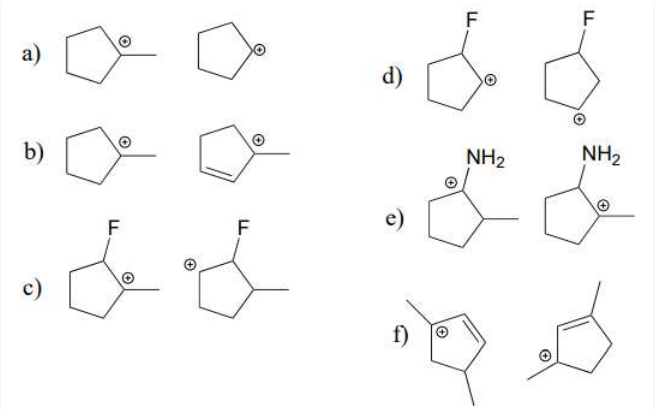
I. More substituted carbocations are more stable than less substituted carbocation (eg. tertiary carbocations are more stable than secondary carbocations).
II. Nearby electronegative atoms can decrease carbocation stability by the inductive effect.
III. Allylic and benzylic carbocations are stabilized by resonance delocalization of the positive charge .
IV. Delocalization of the positive charge by resonance with the lone pair electrons on a heteroatom contributes to carbocation stability.

Below are three examples illustrating how we can make predictions about relative carbocation stability:



Exercise 8.4.7

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.



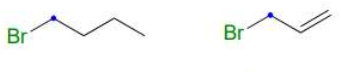
Now, back to our discussion of the electrophile in an S_N1 reaction:

An S_N1 reaction requires a stabilized carbocation intermediate. The more stable the relevant carbocation intermediate, the more favored the S_N1 reaction pathway.

S_N1 reactions in general do not occur at methyl or primary carbon electrophiles: the carbocation intermediates involved would be too unstable and the rate-determining (carbocation-generating) step would have a very high energy barrier. Substitution on these electrophiles will occur through the S_N2 pathway.

The S_N1 reaction pathway is possible, however, with secondary and tertiary carbon electrophiles, or with any other carbon electrophile in which departure of the leaving group generates a carbocation which is stabilized by resonance.

For example: a primary alkyl bromide would not be expected to undergo nucleophilic substitution by the $S_N1$pathway. An allylic primary alkyl bromide, on the other hand, would generate a relatively stable allylic carbocation and thus the S_N1 pathway is possible.



1°: no S_N1 | allylic 1°
S_N1 possible

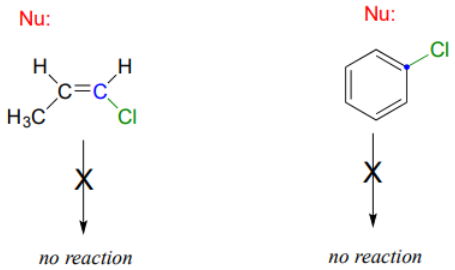
An allylic secondary alkyl bromide would undergo S_N1 substitution more rapidly than the allylic primary alkyl bromide, because the relevant carbocation is more substituted and thus more stable.



allylic 1°
slower S_N1 | allylic 2°
faster S_N1

sp^2-hybridized carbons

Nucleophilic substitution generally does not occur at sp^2-hybridized carbons, either by the S_N2 or S_N1 pathway.



Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the bond between an sp^2 carbon and a potential leaving group (such as the chlorine atom in the figure above). In addition, steric considerations play a part here: in order to attack from behind the leaving group in an S_N2-like fashion, the nucleophile would need to approach in the plane of the carbon-carbon double bond.

Substitution by an S_N1 pathway is equally unlikely because of the inherent instability of a vinylic (double-bonded) carbocation.

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8.4: Leaving Groups

Next, we investigate what makes a good leaving group. It's really quite straightforward: everything that we learned in chapter 7 about evaluating base strength will apply to leaving groups:

Weaker bases are better leaving groups

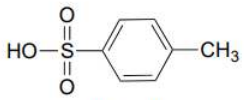
In our general discussion of nucleophilic substitution reactions, we have until now been using chloride ion as our common leaving group. Alkyl chlorides are indeed common reactants in laboratory nucleophilic substitution reactions, as are alkyl bromides and alkyl iodides. Iodide, which is the least basic of the four common halides (F, Cl, Br, and I), is the best leaving group among them. Fluoride is the least effective leaving group among the halides, because fluoride anion is the most basic. This rule applies to both S_N2 and S_N1 reactions, because in both cases the rate-determining step involves loss of the leaving group.

best leaving group I^- > Br^- > Cl^- > F^- *worst leaving group*

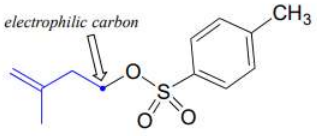
This trend is evident when you compare the relative rates of S_N2 reactions of four halomethanes with a common nucleophile and solvent: iodomethane reacts fastest, fluoromethane the slowest.

fastest S_N2 reaction CH_3I > CH_3Br > CH_3Cl > CH_3F slowest SN_2 reaction

The conjugate base of toluenesulfonic acid is a leaving group commonly used in the organic synthesis laboratory. Toluenesulfonic acid is a strong organic acid with a pK_a of -2.8, so its conjugate base is a weak base and excellent leaving group.



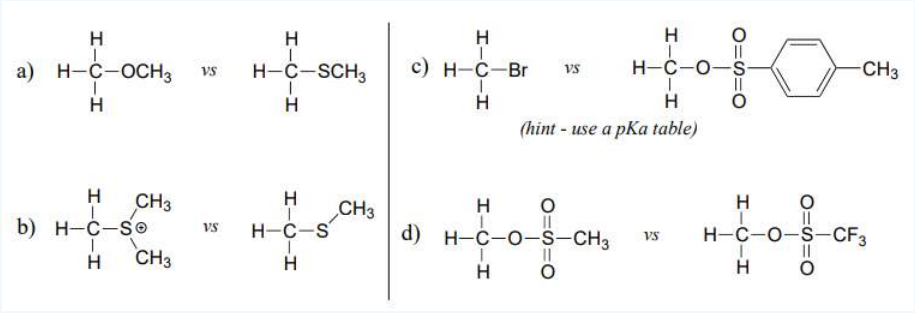
para-toluenesulfonic acid
(pKa -2.8)



organic electrophile with *para*-toluenesulfonate leaving group

? Exercise 8.5.1

In each pair (A and B) below, which electrophile would be expected to react more rapidly with cyanide ion nucleophile in acetone solvent? Explain your reasoning.



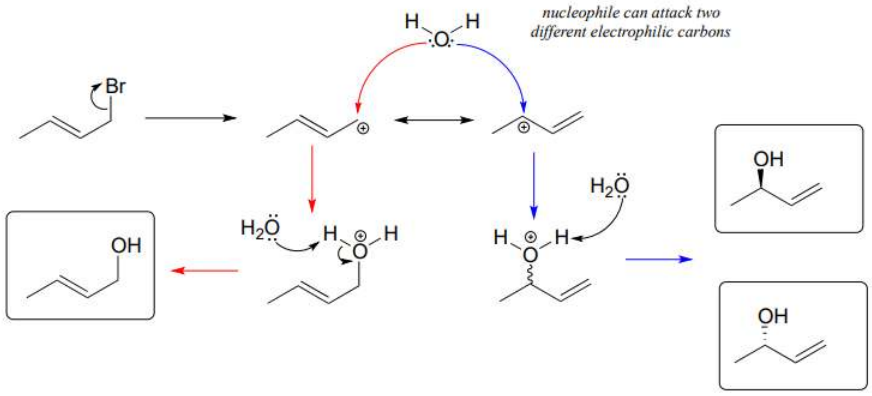
Beginning later in this chapter and throughout the rest of our study of organic reactivity, we will see examples of leaving group 'activation': in other words, conversion of a strong base/poor leaving group into a weak base/good leaving group. In some cases this is as simple as protonation: an acidic group may be positioned in the active site in order to protonate a poor leaving group (eg. hydroxide ion in the case of an alcohol) as it leaves, thus converting it into a weak base and good leaving group. In many other enzymatic reactions, alcohols are converted into phosphates, which can be excellent biochemical leaving groups. We will learn much more about the structure and reactions of organic phosphate compounds in chapter 9.

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8.5: Regiochemistry of SN1 Reactions with Allylic Electrophiles

S_N1 reactions with allylic electrophiles can often lead to more than one possible regiochemical outcome - resonance delocalization of the carbocation intermediate means that more than one carbon is electrophilic. For example, hydrolysis of this allylic alkyl bromide leads to a mixture of primary and secondary allylic alcohols.



In an enzyme-catalyzed reaction of this kind, however, generally only one product will form, because enzymes maintain strict control over the regiochemistry and stereochemistry of the reactions they catalyze. The nucleophilic and electrophilic substrates are bound specifically in the active site so that nucleophilic attack is directed at one - and only one - electrophilic carbon. Problem 15, 17, and 19 at the end of this chapter provide some examples of regio- and stereospecific biochemical substitution reactions at allylic carbon electrophiles.

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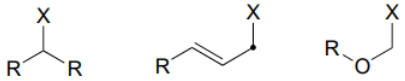
8.6: SN1 or SN2? Predicting the Mechanism

First of all, it is important to understand that the S_N1 and S_N2 mechanism models are just that: models. While many nucleophilic substitution reactions can be described as proceeding through 'pure' S_N1 or S_N2 pathways, other reactions - in particular some important biochemical reactions we'll see later - lie somewhere in the continuum between the S_N1 and the S_N2 model (more on this later). With that being said, here are some guidelines to help you predict whether a reaction is likely to have more of an S_N1 or S_N2 character.

First, look at the electrophile: as stated above, an S_N1 reaction requires that a relatively stable carbocation intermediate be able to form. An S_N2 reaction requires a relatively unhindered electrophilic center. Therefore, methyl and primary carbon electrophiles will react by the S_N2 pathway, and tertiary carbon electrophiles will react by the S_N1 pathway.

Secondary carbon electrophiles, or primary carbon electrophiles adjacent to a potential carbocation-stabilizing group (double bond or heteroatom) can react by either or both pathways. The reasoning here is that these electrophiles are unhindered (favoring S_N2), but can also form stabilized carbocation intermediates (favoring S_N1)

Can react by S_N1 *or* S_N2



Next, look at the nucleophile. More powerful nucleophiles, particularly anionic nucleophiles such as hydroxides, alkoxides or thiolates, favor an S_N2 pathway: picture the powerful nucleophile 'pushing' the leaving group off the electrophile. Weaker, uncharged nucleophiles like water, alcohols, and amines, favor the S_N1 pathway: they are not nucleophilic enough to displace the leaving group, but will readily attack a carbocation intermediate.

Finally look at the solvent in the reaction. As a general rule, water and other protic solvents (for example methanol or ethanol) favor S_N1 pathways, due to the ability of the solvents to stabilize carbocation intermediates, combined with their tendency to weaken the nucleophile by enclosing it in a 'solvent cage'. In laboratory reactions, the presence of a polar aprotic sovent such as acetone or dimethylformamide points to the probability of an S_N2 reaction.

factors favoring the two pathways

Factors favoring the S_N1 pathway:

- hindered electrophile
- potential for a tertiary, secondary, or resonance-stabilized carbocation intermediate
- uncharged nucleophile
- protic solvent such as water

Factors favoring the S_N2 pathway:

- Unhindered (methyl or primary) electrophile
- powerful, anionic nucleophile
- polar aprotic solvent

Video tutorial: nucleophilic substitution reactions

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8.7: Biological Nucleophilic Substitution Reactions

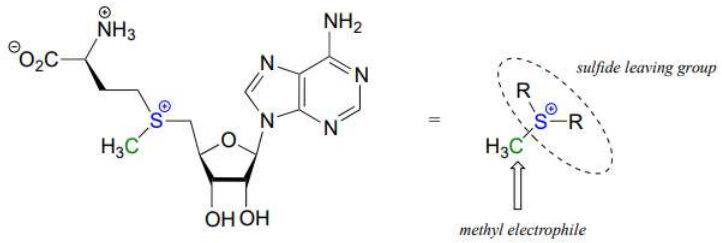
The nucleophilic substitution reactions we have seen so far have all been laboratory reactions, rather than biochemical ones. Now, finally, let's take a look at a few examples of nucleophilic substitutions in a biological context. All of the principles we have learned so far still apply to these biochemical reactions, but in addition we need to consider the roles of the enzyme catalysts.

A word of encouragement

This is the first time that we will be seeing 'real' biological organic reaction mechanisms. **Do not be intimidated by the size and complexity of the reacting biomolecules** - they are just organic molecules, with the same bonding patterns and functional groups that you are already familiar with. Focus on the reacting parts of the molecule: what is the nucleophile? The electrophile? The leaving group? In most biological organic reactions, the main bulk of the biomolecule is just 'going along for the ride', and can often be abbreviated with an 'R group' (section 1.2) to simplify the picture.

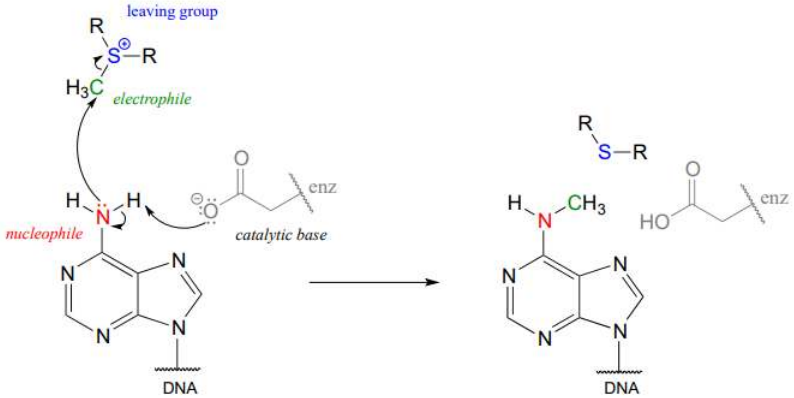
A biochemical S_N2 reaction

One very important class of nucleophilic substitution reactions in biochemistry are the S_N2 reactions catalyzed by ***S*-adenosyl methionine (SAM)** – dependent methyltransferase enzymes. SAM is a coenzyme (section 6.3) that plays the role of methyl group donor: you can think of SAM in this context as being simply a methyl carbon electrophile attached to a sulfide leaving group.

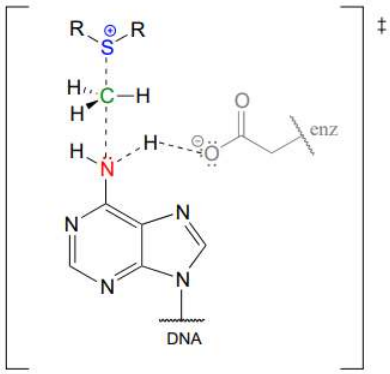


S-adenosylmethionine
(SAM)

There are many variations of SAM-dependent methylation reactions in nature. In the introduction to this chapter, we were introduced to a reaction occurring in bacterial DNA in which a methyl carbon is transferred from SAM to a nitrogen atom on adenine (this type of reaction is often referred to as ***N*-methylation).



In the figure above, we are showing how an aspartate residue in the active site of the enzyme acts as a catalytic base: transfer of a proton from substrate to the aspartate side chain begins to enhance the nucleophilicity of the amine nitrogen as it approaches the electrophilic methyl carbon of SAM, and formation of the new $N-C$ bond and cleavage of the $C-S$ bond begins. These four bond-rearranging events probably take place in concerted fashion. A likely transition state is approximated below:



Of course, there are many other noncovalent interactions between active site enzyme residues and the substrate (the adenine base) and cofactor (SAM), but in the interest of clarity these are not shown. These interactions, many of which are hydrogen-bonds, help to position the adenine base and SAM in just the right relative orientation inside the active site for the nucleophilic attack to take place. (If you have access to American Chemical Society journals, a paper about an enzyme catalyzing a similar N-methylation reaction contains some detailed figures showing hydrogen-bond and charge-dipole interactions between the enzyme active site and the two substrates: see Biochemistry 2003, 42, 8394, figure 4).

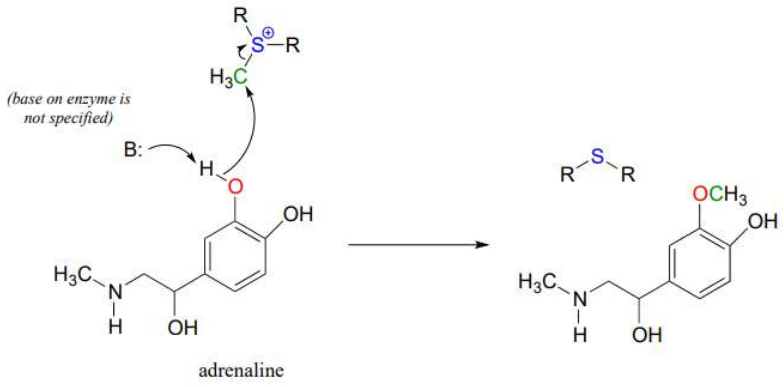
The electrophile is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The carbon is electrophilic (electron-poor) because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, because as it leaves, it becomes a neutral and very stable sulfide. All in all, we have a good nucleophile (enhanced by the catalytic base), an unhindered electrophile, and an excellent leaving group. We can confidently predict that this reaction is S_N2. An S_N1 mechanism is extremely unlikely: a methyl cation is very unstable and thus is not a reasonable intermediate to propose.

Notice something else about the SAM methylation mechanism illustrated in the previous figure. It is termolecular: there are three players acting in concert: the catalytic base, the nucleophile, and the electrophile. This is possible because the all three players are bound in a very specific geometry in the active site of the enzyme. In a reaction that takes place free in solution, rather than in an active site, the likelihood of three separate molecules colliding all at once, with just the right geometry for a reaction to take place, is very, very low. You should notice going forward that when we illustrate the mechanism of a reaction that takes place free in solution, we will only see bimolecular steps - two molecules colliding. Almost all of the biochemical reactions we see in this book will be enzyme-catalyzed - and termolecular steps will be common - while almost all of the laboratory reactions we see will take place free in solution, so we will only see unimolecular and bimolecular steps. (Synthetic chemists often employ non-biological catalysts that mimic enzyme active sites, but these examples are well beyond the scope of our discussion).

? Exercise 8.8.1

Think back to the acid-base chapter: the \(pK_a\) of a protonated ether is approximately zero, indicating that an ether is a very weak base. Considering periodic trends in acidity and basicity, what can you say about the relative basicity of a sulfide?

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-*O*-methyltransferase. The substrate here is epinephrine, also known as adrenaline, and the reaction is part of the pathway by which adrenaline is degraded in the body.



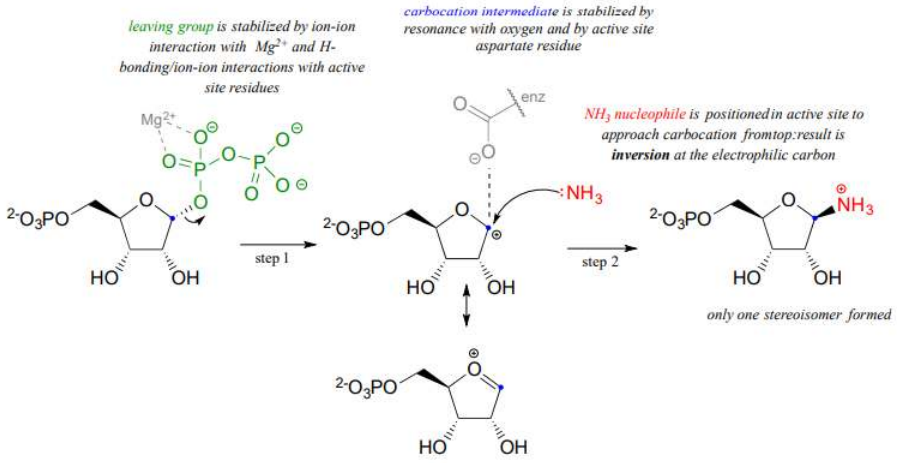
Notice that in this example, the attacking nucleophile is a phenol oxygen rather than a nitrogen (that's why the enzyme is called an *O*-methyltransferase). In many cases when drawing biochemical reaction mechanisms, we use the abbreviations B: for a catalytic base and $H-A$ for a catalytic acid, in order to keep the drawings from getting too 'busy' (it's also possible that the identity of the acidic or basic group may not be known).

? Exercise 8.8.2

SAM is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP). Draw a mechanism for this reaction, and explain why you chose either an S_N1 or and S_N2 pathway.

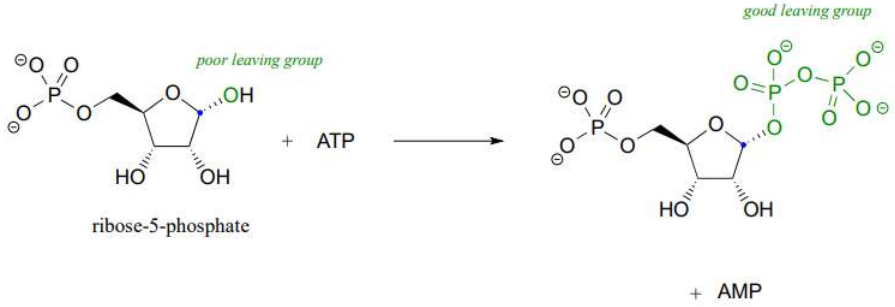
A biochemical S_N1 reaction

As we will see in chapter 10, enzyme-catalyzed S_N1 reactions play a critical role in carbohydrate and DNA/RNA nucleotide metabolism. The reaction below is part of nucleotide biosynthesis:



Notice a few things here: first, the diphosphate leaving group is stabilized by interactions with Mg^{+2} ion bound in the active site and also by hydrogen-bonding with active site amino acid residues (not shown). The carbocation intermediate is stabilized by resonance with the lone pairs on the oxygen (see section 8.5), and also by an active site aspartate side chain. The ammonia nucleophile is positioned in the active site so that it approaches from the 'top' side of the planar carbocation intermediate, and the substitution results in inversion of configuration. Remember: S_N1 reactions which occur free in solution tend to result in a mixture of stereoisomers, but enzyme-catalyzed reactions - including enzymatic S_N1 reactions such as this one - are generally stereo- and regio-specific, meaning that they almost always result in a single isomeric product, not a mixture of products.

Recall the statement from section 8.4 that poor leaving groups often need to be converted into good leaving groups. Backing up one metabolic step from the reaction depicted above, we see that a poor (hydroxide) leaving group on ribose-5-phosphate is first converted to a good (diphosphate) leaving group, which can stabilized through interactions with the active site of the enzyme catalyzing the S_N1 reaction.

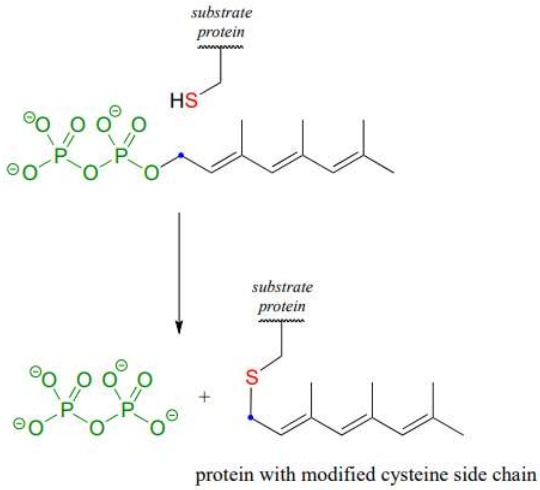


ribose-5-phosphate

This preliminary phosphorylation step, which requires ATP (adenosine triphosphate) as the donor of the diphosphate group, is a reaction that we will study in much more detail in chapter 9.

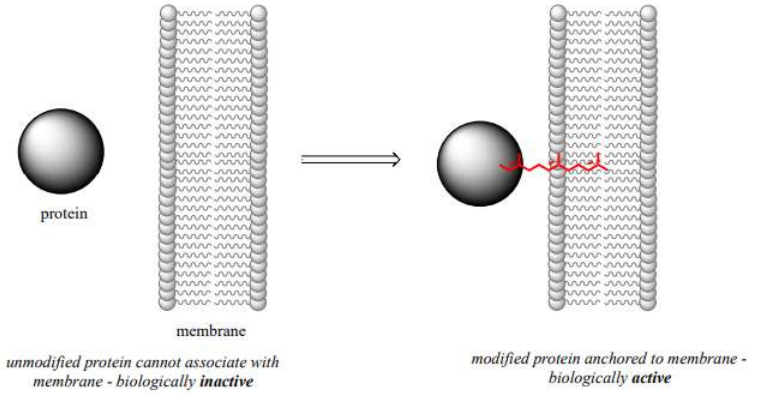
A biochemical S_N1/S_N2 hybrid reaction

The cysteine residues of certain proteins are modified by addition of a 15-carbon isoprene chain (section 1.3) to the side chain thiol group.



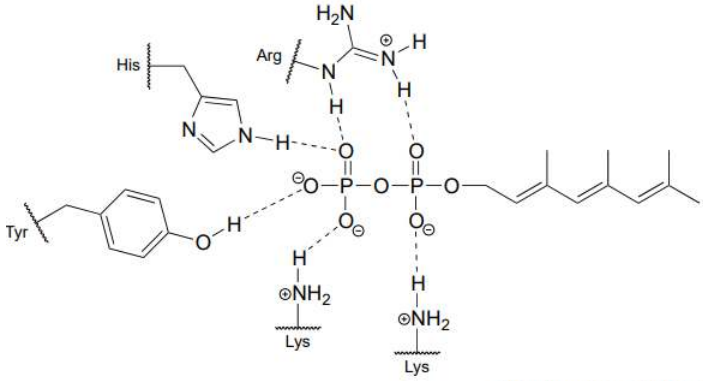
protein with modified cysteine side chain

The mechanistic details of this reaction are of particular interest to biomedical scientists. The proteins that are substrates for this type of modification are involved in cell signaling processes, and they are not able to carry out their biological functions unless they are anchored to a cell's lipid membrane. The hydrocarbon group that becomes attached to a cysteine residue in this reaction serves as the anchor.



Some of these proteins have been implicated in tumor formation. Scientists hope that if they can find a way to shut down the cysteine modification reaction, the tumor-causing proteins will not be able to anchor to cell membranes and thus will remain inactive. The search is on for an effective inhibitor of this enzyme to serve as a potential anti-tumor drug.

How does the enzyme lower the energy barrier for this reaction? Experimental evidence indicates that when a substrate protein is bound to the active site of the enzyme, the cysteine thiol associates with a zinc ion bound in the active site. As we learned in section 7.8, this association will lower the pKa of the thiol to the point where it loses a proton and exists as a thiolate anion in the active site - a thiolate is a very potent nucleophile! Studies also show that the diphosphate group forms stabilizing interactions with several amino acid residues (two lysines, an arginine, a histidine, and a tyrosine) in the enzyme's active site, making it a weaker base and thus a better leaving group.



Biochemistry **1998**, *37*, 16601

Is protein prenylation an S_N1 or S_N2 reaction? In other words, to what extent does the nucleophile displace, or 'push' the leaving group off, or to what extent does the leaving group leave on its own, without a 'push' from the nucleophile? Along the same lines, to what extent does a positive charge develop on the carbon center (development of a full positive charge implies an S_N1 mechanism). First, consider the electrophile: it is a primary allylic carbon, so either pathway is possible (it is relatively unhindered for S_N2 attack, but could also form a resonance-stabilized carbocation intermediate in an S_N1 pathway). The nucleophile is a very powerful thiolate ion, suggestive of an S_N2 mechanism where a strong nucleophile actively displaces the leaving group.

In fact, experiments designed to address this very question (see problem P8.19) have provided evidence that the reaction is a mechanistic hybrid: essentially S_N2, but with elements of S_N1. In other words, at the transition state the electrophilic carbon takes on some degree of positive charge, but a true carbocation intermediate does not form. The take-home message here is that the S_N1 and S_N2 mechanistic pictures we have studied in this chapter are models, and while they are useful for learning about chemical principles and accurate for describing many substitution reactions, other reactions are not necessarily 'pure' S_N1 or S_N2, but actually lie somewhere in between.

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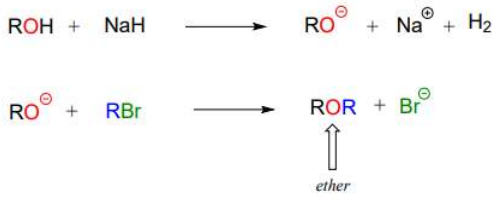
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8.8: Nucleophilic substitution in the Lab

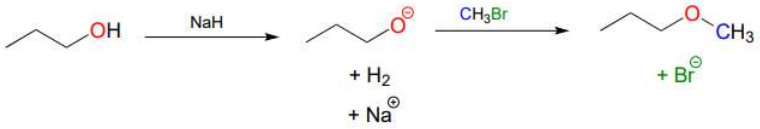
The Williamson ether synthesis

Synthetic organic chemists often make use of a reaction that is conceptually very similar to the SAM-dependent methylation reactions we saw earlier. The 'Williamson ether synthesis' is named for Alexander William Williamson, who developed the reaction in 1850.

In the Williamson ether synthesis, an alcohol is first deprotonated by a strong base, typically sodium hydride. An alkyl halide is then added to the reaction mixture, and the alkoxide ion, a powerful nucleophile, displaces the halide leaving group in an S_N2 reaction.

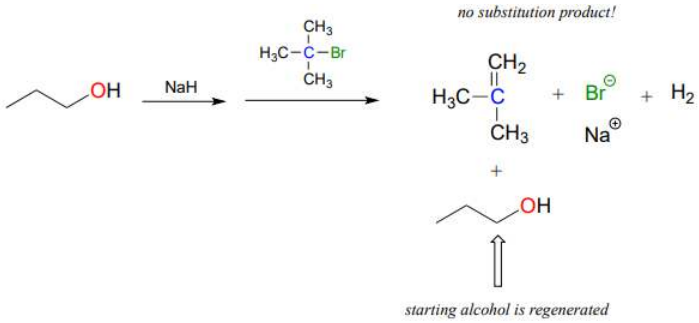


For example, below we see methyl bromide performing the role of methyl group donor, analogous to the role played by SAM in biochemical methylation reactions:



Notice the difference between this non-biological laboratory reaction and the biological, enzyme-catalyzed SAM methylation reaction we saw earlier. Deprotonation of the nucleophile occurs as a separate step, before the nucleophile attacks. Contrast this solution reaction (with two bimolecular steps) to the enzyme-catalyzed S_N2 reaction (SAM methylation) we saw earlier, which involves a single, concerted trimolecular step. Also notice that this non-biological reaction involves a highly basic reagent (sodium hydride) and intermediate (propanoate anion), which would be unreasonable to propose for a reaction taking place under physiological conditions.

The Williamson ether synthesis will only work with methyl or primary alkyl halides. If a secondary or tertiary alkyl halide is used, the result will be formation of an alkene in what is called an 'elimination' reaction:



We will study elimination reactions in chapter 14.

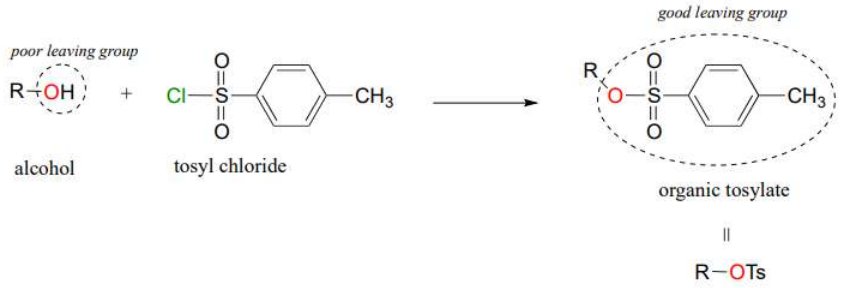
? Exercise 8.9.1

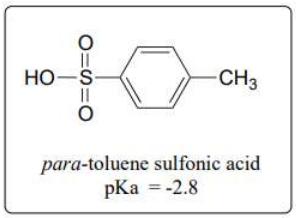
A rookie organic chemist ran the reaction shown above, hoping to synthesize an ether. Instead, he got the alkene shown. What alkyl halide/alcohol combination should he have used instead to get the ether product he was trying for?

Turning a poor leaving group into a good one - tosylates

In section 8.4 it was mentioned how, in metabolic pathways, the relatively poor OH leaving group of an alcohol can be converted into a phosphate or diphosphate, which when stabilized by noncovalent interactions inside an enzyme active site can be a very good leaving group.

In laboratory synthesis, a similar goal can be accomplished by converting an alcohol (a poor leaving group)to an organic tosylate (a good leaving group) using tosyl chloride (the terms 'tosylate' and 'OTs', are abbreviations for para-toluene sulfonate). The alcohol to tosylate reaction is not something we are equipped yet to understand, but if we consider that the pKa of para-toluene sulfonic acid is -2.8, we realize that the para-toluene sulfonate anion is a very weak base and thus an very good leaving group. Conversion of alcohols to organic tosylates is a very common step in organic synthesis schemes.



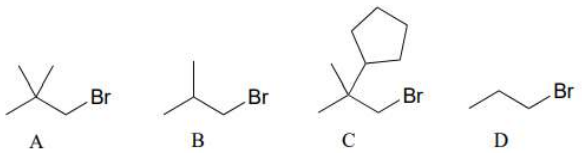


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8.E: Nucleophilic Substitution Reactions (Exercises)

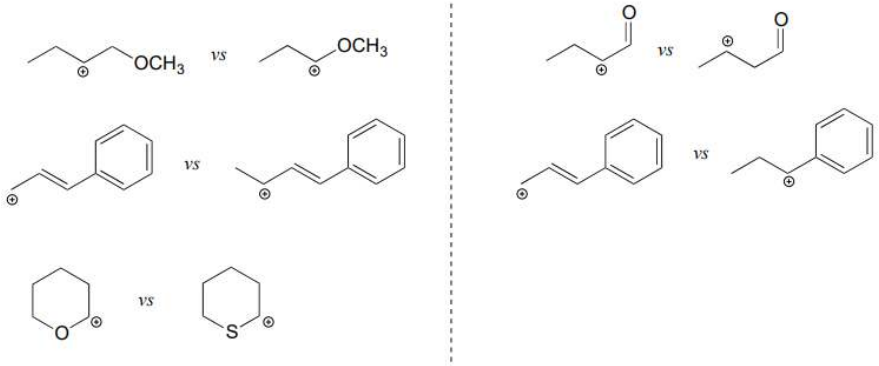
P8.1: Rank the following molecules in order of how fast they would be expected to react with CH_3SNa in acetone. (CH_3SNa is simply the sodium salt of CH_3S^-. Na^+ is a spectator ion.)



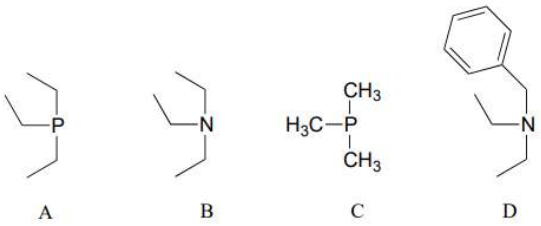
P8.2: Draw line structures representing the most stable cation with the given molecular formula:

a. $C_3H_7^+$
b. $C_4H_9^+$
c. $C_3H_8N^+$
d. $C_4H_7^+$

P8.3: For each pair of carbocations below, choose the one that is more stable, and explain your reasoning.

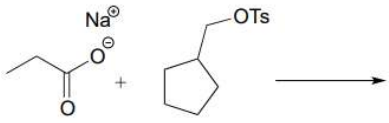


P8.4: Arrange the following species in order of increasing nucleophilicity in protic solvent:

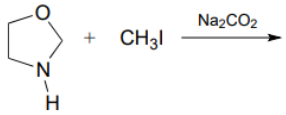


P8.5: Predict the organic products of the following nucleophilic substitution reactions, all of which are carried out in polar aprotic solvent. Show stereochemistry at chiral carbons. Hints: Na_2CO_3, sodium carbonate, is a weak base. For part (f): What is the conjugate acid of NH_2^-? What is the pK_a of this conjugate acid, and what is the pK_a of a terminal alkyne?

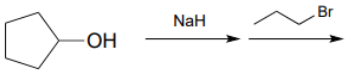
a.



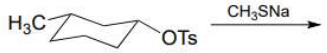
b.



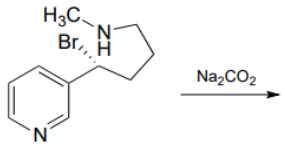
c.



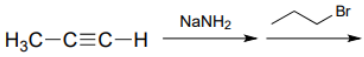
d.



e.



f.



P8.6: Which of the reactions in the previous problem has a unimolecular rate determining step? Explain.

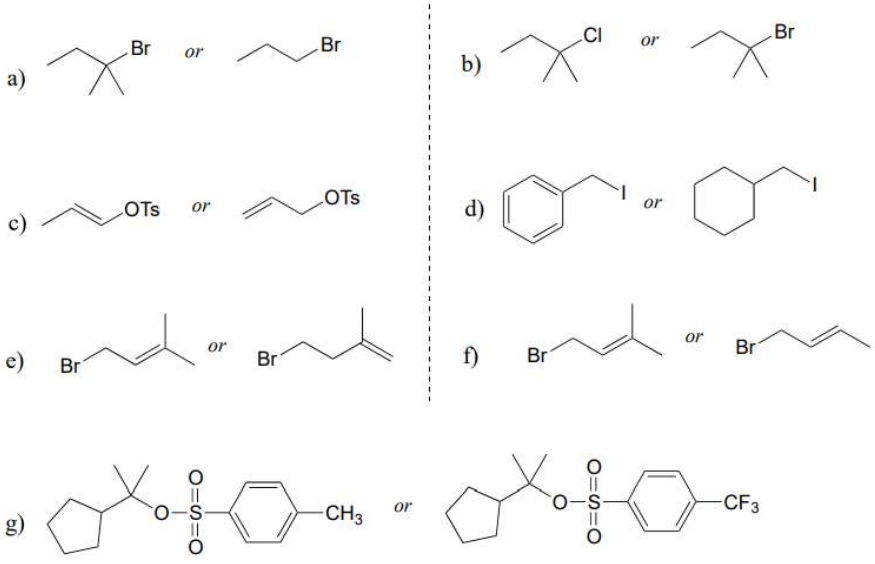
P8.7: From the following pairs, select the compound that would react more rapidly with bromomethane in acetone solvent.

a. water or hydroxide ion
b. CH_3S^- or CH_3OH
c. CH_2S^- or CH_3SH
d. acetate ion or hydroxide ion
e. diethyl sulfide or diethyl ether
f. dimethylamine or diethylether
g. trimethylamine or 2,2-dimethylpropane

P8.8: Methyl iodide (0.10 mole) is added to a solution that contains 0.10 mole $NaOCH_3$ and 0.10 mole $NaSCH_3$.

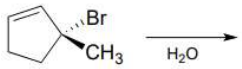
a. Predict the most abundant neutral organic product that would form, and explain your reasoning.
b. Assume that you isolate a mixture the major product (which you predicted in part) along with a smaller amount of a different nucleophilic substitution product. Explain briefly but specifically how you could use ^1H-NMR to determine the ratio of the two products in the mixture.

P8.9: For each pair of compounds, predict which will more rapidly undergo solvolysis in methanol solution.

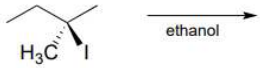


P8.10: Predict the solvolysis product(s) of each of the reactions below. Consider both regiochemistry and stereochemistry.

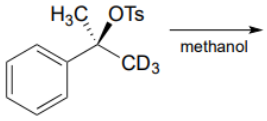
a.



b.



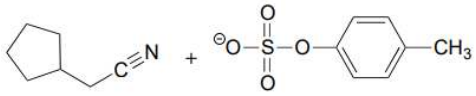
c.



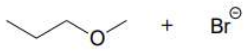
d. Draw a complete curved-arrow mechanism for the formation of the secondary allylilc alcohol product in part (a).

P8.11: Show starting compounds that would lead to the following products through nucleophilic substitution reactions.

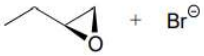
a.



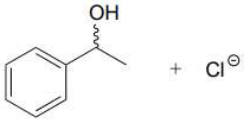
b.



c.



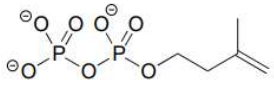
d.



P8.12: The fused ring compound shown below is very unreactive to nucleophilic substitution, even with a powerful nucleophile.. Explain. (Hint – consider bond geometry - a model will be very helpful!)



P8.13: Laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules (section 1.3A) - was accomplished by first converting isopentenyl alcohol into an alkyl tosylate then displacing the tosylate group with an inorganic pyrophosphate nucleophile. Based on this verbal description, draw a mechanism for the second (nucleophilic substitution) step, showing starting and ending compounds for the step and curved arrows for electron movement.



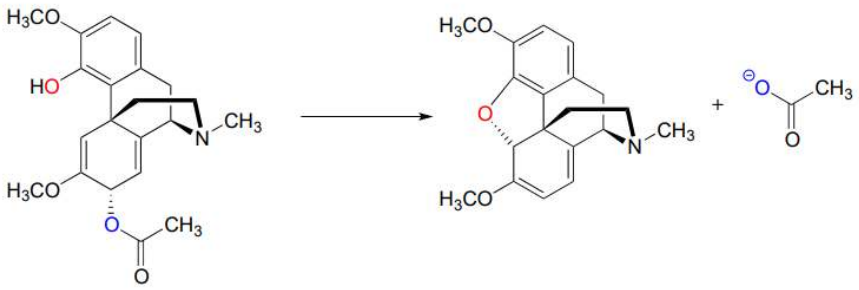
isopentenyl diphosphate

P8.14: Choline, an important neutotransmitter in the nervous system, is formed from 2-(N,N-dimethylamino)ethanol:



a. Besides the enzyme and the starting compound, what other important biomolecule do you expect plays a part in the reaction?
b. Draw a mechanism for the reaction.
c. Briefly explain how ^1H-NMR could be used to distinguish between the substrate and the product of this reaction.

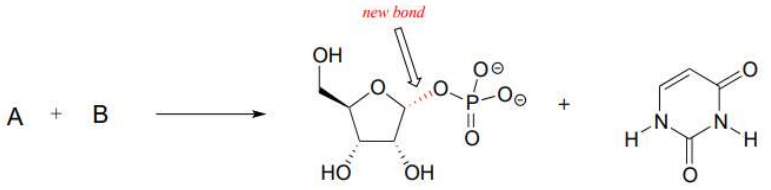
P8.15: The following is a reaction in the biosynthesis of morphine in opium poppies. (Science 1967, 155, 170; J. Biol. Chem 1995, 270, 31091).



a. Draw a complete mechanism, assuming an S_N1 pathway.
b. What would you expect to be the most noticeable difference between the IR spectrum of the product and that of the substrate?
c. This reaction is an example of the regiospecificity of enzymatic nucleophilic substitution reactions noted earlier in the chapter. Draw two alternate nucleophilic, ring-closing steps for this reaction (leading to different products from what is shown above), and explain why these alternate pathways are both less favorable than the actual reaction catalyzed by the enzyme.

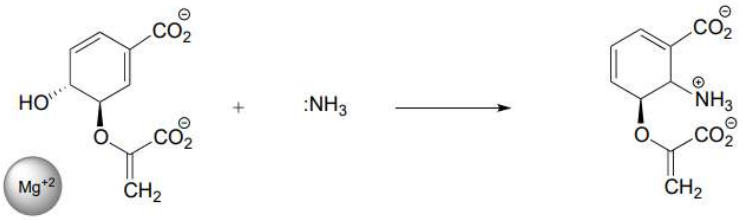
P8.16: The enzymatic reaction below, which is part of the metabolism of nucleic acids, proceeds by an S_N1 mechanism. The new bond formed in the substitution is indicated.

a. Predict the structures of the two substrates A and B.
b. Draw a complete mechanism, and use resonance drawings to illustrate how both the carbocation intermediate and the leaving group are stabilized.

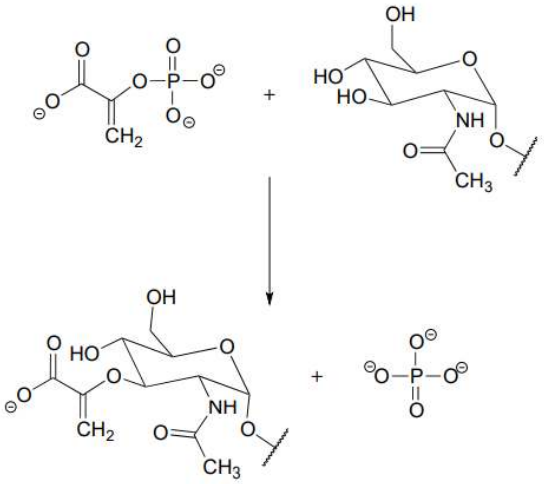


P8.17: Below is the first step of the reaction catalyzed by anthranilate synthase, an enzyme involved in biosynthesis of the amino acid tryptophan.

a. This reaction is somewhat unusual in that the leaving group is a hydroxide anion, which is of course is normally thought to be a very poor leaving group. However, studies show that an Mg^{+2} ion is bound in the active site close to the hydroxide. Explain how the presence of the magnesium ion contributes to the viability of hydroxide as a leaving group.
b. Draw a complete mechanism for the reaction, assuming an S_N1 pathway.

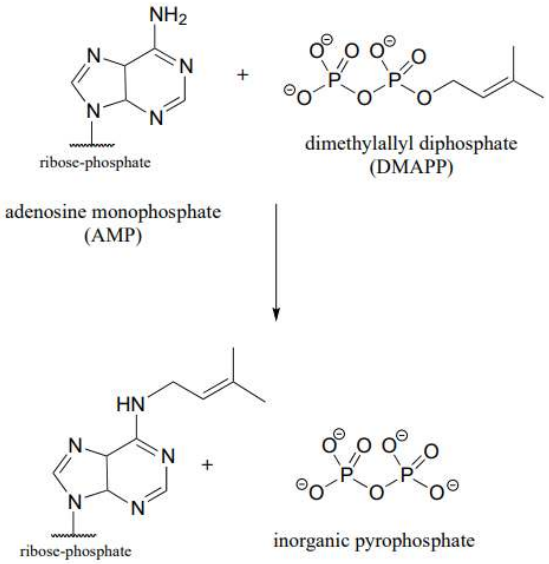


P8.18: The reaction below is part of the biosynthesis of peptidoglycan, a major component of bacterial cell walls. Is it likely to proceed by a nucleophilic substitution mechanism? Explain.

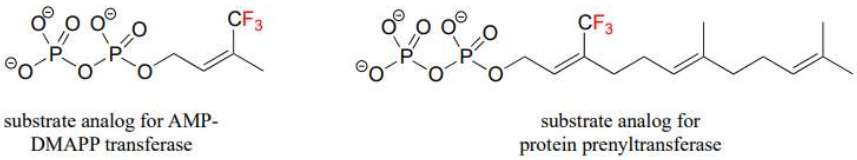


P8.19: Compare the reaction below, catalyzed by the enzyme AMP-DMAPP transferase, to the protein prenyltransferase reaction we learned about in section 8.8, the mechanism of which, as we discussed, is thought to be mostly S_N2-like with some S_N1-like character.

a. Is the AMP-DMAPP transferase reaction below likely to have more or less S_N1-like character compared to the protein prenyltransferase reaction? Explain.



b. Given your answer to part (a), which reaction is likely to be more dramatically slowed down when a fluorinated isoprenoid substrate analog is substituted for the natural substrate? Explain.



P8.20: In a classic experiment in physical organic chemistry, (*R*)-2-iodooctane was allowed to react (non-enzymatically) with a radioactive isotope of iodide ion, and the researchers monitored how fast the radioactive iodide was incorporated into the alkane (the rate constant of incorporation, k_i) and also how fast optical activity was lost (the rate constant of racemization, k_r). They found that

the rate of racemization was, within experimental error, equal to twice the rate of incorporation. Discuss the significance of this result - what does it say about the actual mechanism of the reaction?

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8.S: Nucleophilic Substitution Reactions (Summary)

Before you move on to the next chapter, you should be comfortable with the following concepts and skills:

Nucleophilic substitution basics

- Illustrate the transition state for an S_N2 reaction
- Draw a complete mechanism for an S_N1 reaction, in particular a hydrolysis or other solvolysis S_N1 reaction.
- Illustrate all transition states that are part of an S_N1 reaction.
- Understand that non-enzymatic S_N1 reactions result in both inversion and retention of configuration (racemization) at the electrophilic carbon. Enzymatic S_N1 reactions are stereospecific, usually resulting in inversion at the electrophilic carbon.

Nucleophiles

- Be able to recognize the nucleophile, electrophile, and leaving group in an SN1 or SN2 reaction.
- Understand that – with the exception of the vertical periodic trend in protic solvents – in most cases anything that makes something a stronger base also makes it a more powerful nucleophile:
  - The vertical periodic trend in nucleophilicity for reactions in polar aprotic solvents: chloride ion is a better nucleophile than bromide ion in acetone solvent.
- Inductive effect: electron-withdrawing groups decrease nucleophilicity
- Resonance effects:
  - Delocalization of negative charge/electron density decreases nucleophilicity. For example, methoxide ion (CH3O-) is a stronger nucleophile than acetate ion.
- In addition:
  - The vertical periodic trend in protic solvent (water or alcohol) is opposite the trend in basicity: for example, thiols are more nucleophilic than alcohols.
- Electrophiles
  - Less hindered electrophiles will react faster in SN2 reactions: for example chloromethane is a better electrophile than a primary alkyl chloride.

Leaving groups

- Common laboratory leaving groups are halides and para-toluenesulfonate (abbreviated tosyl, or OTs).
- Common biochemical leaving groups are phosphates and sulfide.

Carbocation stability

- More substituted carbocations are more stable: for example, a tertiary carbocation is more stable than a secondary carbocation.
- The presence of electron-withdrawing groups (by inductive or resonance effects) decreases carbocation stability.
- The presence of a heteroatom can stabilize a nearby carbocation by the resonance-based electron donating effect. Otherwise, heteroatoms act as weakly electron withdrawing carbocation-destabilizing groups by inductive effects.

General concepts and skills

- Be able to predict whether a given substitution reaction is likely to proceed by S_N2 or S_N1 mechanisms, based on the identity of the nucleophile, the electrophile, and the solvent.
  - S_N1 reactions involve weaker nucleophiles relatively stable carbocations, and are accelerated by protic solvents.
- Be able to 'think backwards' to show the starting compounds in a substitution reaction, given a product or products.
- Understand how S-adenosylmethionine (SAM) acts as a methyl group donor in biochemical S_N2 reactions.
- Be able to select appropriate alkyl halide and alcohol starting compounds to synthesize a given ether product, using the Williamson ether synthesis procedure.

Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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CHAPTER OVERVIEW

9: Phosphate Transfer Reactions

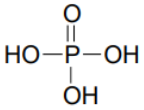
This chapter is about the chemistry of phosphates, a ubiquitous functional group in biomolecules that is based on phosphoric acid.

9.0: Prelude to Phosphate Transfer Reactions
9.1: Overview of Phosphate Groups
9.2: Phosphate Transfer Reactions - An Overview
9.3: ATP, The Principal Phosphate Group Donor
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9.9: NMR of phosphorylated compounds
9.E: Phosphate Transfer Reactions (Exercise)
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9.0: Prelude to Phosphate Transfer Reactions

This chapter is about the chemistry of phosphates, a ubiquitous functional group in biomolecules that is based on phosphoric acid:



phosphoric acid

In late 2010, people around the world found themselves getting a crash course in phosphate chemistry as they watched the evening news. Those who paid close attention to the developing story also got an interesting glimpse into the world of scientific research and debate.

It all started when the American National Aeronautics and Space Administration (NASA) released the following statement to the news media:

> ***"NASA will hold a news conference at 2 p.m. EST on Thursday, Dec. 2, to discuss an astrobiology finding that will impact the search for evidence of extraterrestrial life."***

The wording of the statement attracted widespread media attention, and had some people holding their breath in anticipation that NASA would be introducing a newly discovered alien life form to the world. When December 2nd came, however, those hoping to meet ET were disappointed – the life form being introduced was a bacterium, and it was from our own planet. To biologists and chemists, though, the announcement was nothing less than astounding.

The NASA scientists worked hard to emphasize the significance of their discovery during the news conference. Dr. Felicia Wolfe-Simon, a young postdoctoral researcher who had spearheaded the project, stated that they had "cracked open the door to what's possible for life elsewhere in the universe - and that's profound". A senior NASA scientist claimed that their results would "fundamentally change how we define life", and, in attempting to convey the importance of the discovery to a reporter from the newspaper USA Today, referred to an episode from the original Star Trek television series in which the crew of the Starship Enterprise encounters a race of beings whose biochemistry is based on silica rather than carbon.

The new strain of bacteria, dubbed 'GFAJ-1', had been isolated from the arsenic-rich mud surrounding salty, alkaline Mono Lake in central California. What made the strain so unique, according to the NASA team, was that it had evolved the ability to substitute arsenate for phosphate in its DNA. Students of biology and chemistry know that phosphorus is one of the six elements that are absolutely required for life as we know it, and that DNA is a polymer linked by phosphate groups. Arsenic, which is directly below phosphorus on the periodic table, is able to assume a bonding arrangement like that of phosphate, so it might seem reasonable to wonder whether arsenate could replace phosphate in DNA and other biological molecules. Actually finding a living thing with arsenate-linked DNA would indeed be a momentous achievement in biology, as this would represent a whole new chemistry for the most fundamental molecule of life, and would change our understanding of the chemical requirements for life to exist on earth - and potentially other planets.

In 1987, Professor F.H. Westheimer of Harvard University published what would become a widely read commentary in Science Magazine entitled "Why Nature Chose Phosphates". In it, he discussed the chemical properties that make the phosphate group so ideal for the many roles that it plays in biochemistry, chief among them the role of a linker group for DNA polymers. One of the critical characteristics of phosphate that Westheimer pointed out was that the bonds linking phosphate to organic molecules are stable in water. Clearly, if you are selecting a functional group to link your DNA, you don't want to choose one that will rapidly break apart in water. Among the functional groups that Westheimer compared to phosphate in terms of its suitability as a potential DNA linker was arsenate –but he very quickly dismissed the idea of arsenate-linked DNA because it would be far too unstable in water.



Mono Lake, California. (photo credit https://www.flickr.com/photos/slolane/)

Given this background, it is not hard to imagine that many scientists were puzzled, to say the least, by the NASA results. While the popular media took the announcement at face value and excitedly reported the results as a monumental discovery – NASA is, after all, a highly respected scientific body and the study was being published in Science Magazine, one of the most prestigious scientific journals in the world – many scientists quickly voiced their skepticism, mainly in the relatively new and unconstrained venue of the blogosphere. Microbiologist Rosie Redfield of the University of British Columbia, writing in her blog devoted to 'open science', wrote a detailed and highly critical analysis of the study. She pointed out, among other things, that the experimenters had failed to perform the critical purification and mass spectrometry analyses needed to demonstrate that arsenate was indeed being incorporated into the DNA backbone, and that the broth in which the bacteria were being grown actually contained enough phosphate for them to live and replicate using normal phosphate-linked DNA. Science journalist Carl Zimmer, in a column in the online magazine Slate, contacted twelve experts to get their opinions, and they were overwhelmingly negative. One of the experts said bluntly, “This paper should not have been published". Basically, the NASA researchers were making an astounding claim that, if true, would refute decades of established knowledge about the chemistry of DNA – but the evidence they presented was far from convincing. Carl Sagan's widely quoted dictum - “extraordinary claims require extraordinary evidence” - seemed to apply remarkably well to the situation.

What followed was a very public, very lively, and not always completely collegial debate among scientists about the proper way to discuss science: the NASA researchers appeared to dismiss the criticism amassed against their study because it came from blogs, websites, and Twitter feeds. The proper venue for such discussion, they claimed, was in the peer-reviewed literature. Critics countered that their refusal to respond to anything outside of the traditional peer-review system was disingenuous, because they had made full use of the publicity-generating power of the internet and mainstream media in the first place when they announced their results with such fanfare.

The traditional venue for debate, while quite a bit slower than the blogosphere, did eventually come through. When the full paper was published in Science a few months later, it was accompanied by eight 'technical comments' from other researchers pointing out deficiencies in the study, an 'editors note', and a broader news article about the controversy. In July of 2012, a paper was published in Science under the title “GFAJ-1 Is an Arsenate-Resistant, Phosphate-Dependent Organism”. The paper reported definitive evidence that DNA from GFAJ-1, under the conditions described in the NASA paper, did not have arsenate incorporated into its structure. Just like professor Westheimer discussed in the 1980s, it appears that nature really did choose phosphate – and only phosphate – after all . . . at least on this planet.

Background reading and viewing:

- Youtube video of the NASA press conference: http://www.youtube.com/watch?v=WVuhBt03z8g.
- Wolfe-Simon, F. et al. Science Express, Dec 2, 2010. The first preview article on the proposed 'arsenic bacteria'.
- Wolfe-Simon, F. et al., Science 2011, 332, 1163. The full research paper in Science Magazine.
- Westheimer, F.H. Science 1987, 235, 1173. The article by Westheimer titled 'Why Nature Chose Phosphates'.

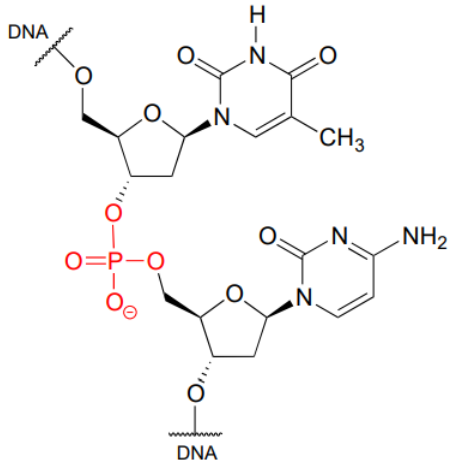
- Zimmer, Carl, Slate, Dec 7, 2010: Blog post by Carl Zimmer titled 'This Paper Should Not Have Been Published'. http://www.slate.com/articles/health...published.html
- Redfield, R. Blog post Dec 4, 2010: http://rrresearch.fieldofscience.com...ria-nasas.html
- Science 2012, 337, 467. The paper in Science Magazine refuting the validity of the arsenic bacteria claim.

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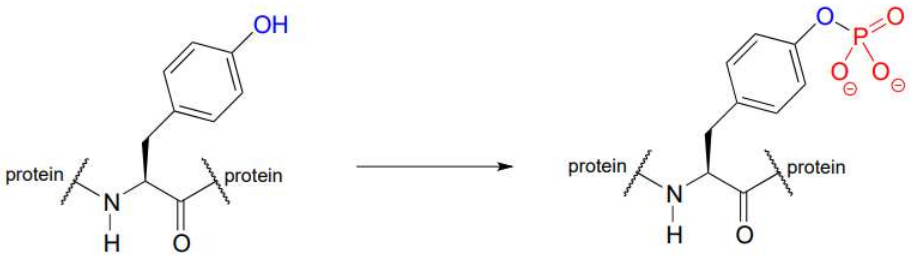
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9.1: Overview of Phosphate Groups

Phosphate is everywhere in biochemistry. As we were reminded in the introduction to this chapter, our DNA is linked by phosphate:



The function of many proteins is regulated - switched on and off - by enzymes which attach or remove a phosphate group from the side chains of serine, threonine, or tyrosine residues.



tyrosine residue

phosphotyrosine residue

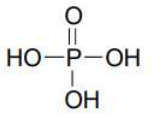
Countless diseases are caused by defects in phosphate transferring enzymes. As just one example, achondroplasia, a common cause of dwarfism, is caused by a defect in an enzyme whose function is to transfer a phosphate to a tyrosine residue in a growth-related signaling protein.

Finally, phosphates are excellent leaving groups in biological organic reactions, as we will see many times throughout the remainder of this book.

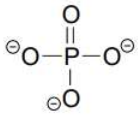
Clearly, an understanding of phosphate chemistry is central to the study of biological organic chemistry. We'll begin with an overview of terms used when talking about phosphates.

Terms and abbreviations

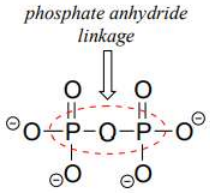
The fully deprotonated conjugate base of phosphoric acid is called a phosphate ion, or inorganic phosphate (often abbreviated 'P_i'). When two phosphate groups are linked to each other, the linkage itself is referred to as a 'phosphate anhydride', and the compound is called 'inorganic pyrophosphate' (often abbreviated PP_i).



phosphoric acid

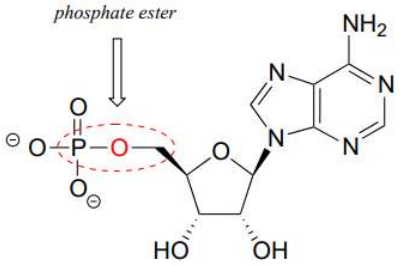


inorganic phosphate (P_i)



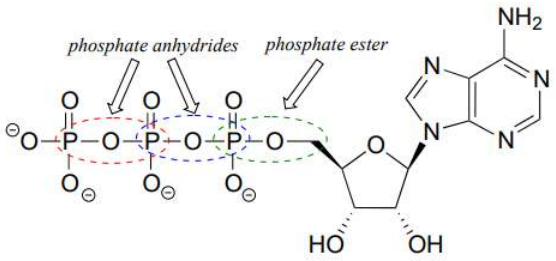
inorganic pyrophosphate (PP_i)

The chemical linkage between phosphate and a carbon atom is a phosphate ester. Adenosine monophosphate (AMP) has a single phosphate ester linkage.



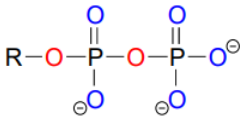
adenosine monophosphate (AMP)

Adenosine triphosphate has one phosphate ester linkage and two phosphate anhydride linkages.



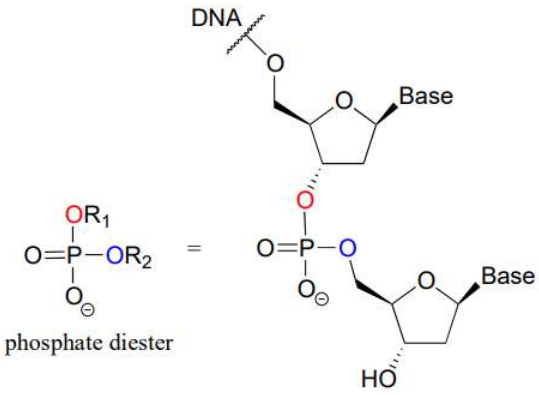
adenosine triphosphate (ATP)

Oxygen atoms in phosphate groups are referred to either as 'bridging' or 'non-bridging', depending on their position. An organic diphosphate has two bridging oxygens (one in the phosphate ester linkage and one in the phosphate anhydride linkage) and five non-bridging oxygens:

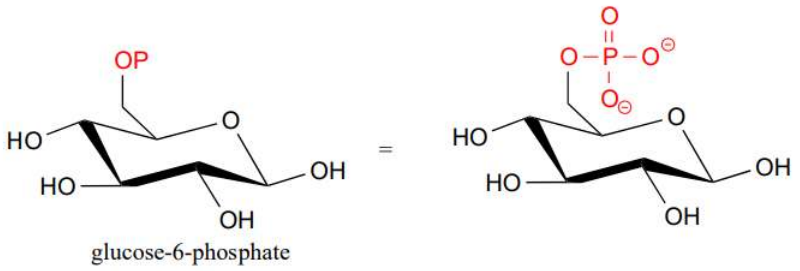


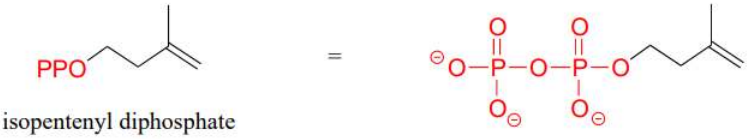
red = bridging oxygen
blue = non-bridging oxygen

A single phosphate is linked to two organic groups is called phosphate diester. The backbone of DNA is linked by phosphate diesters.



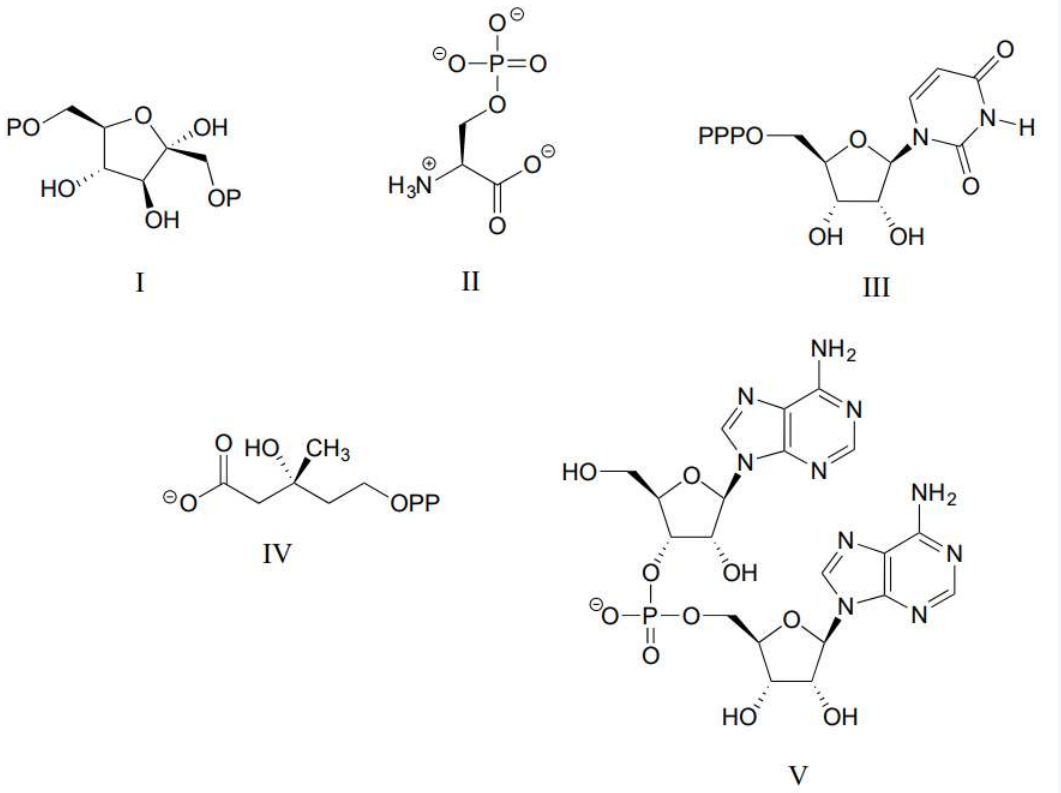
Organic phosphates are often abbreviated using '*OP*' and '*OPP*' for mono- and diphosphates, respectively. For example, glucose-6-phosphate and isopentenyl diphosphate are often depicted as shown below. Notice that the 'P' abbreviation includes the associated oxygen atoms and negative charges.





? Exercise 9.2.1

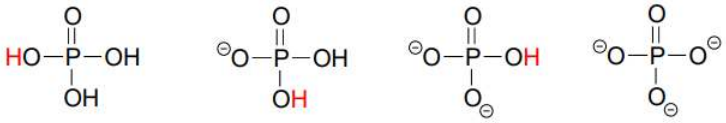
Consider the biological compounds below, some of which are shown with abbreviated structures:



a. For each compound, specify the number of bridging and non-bridging oxygens in the phosphate group.

Acid constants and protonation states

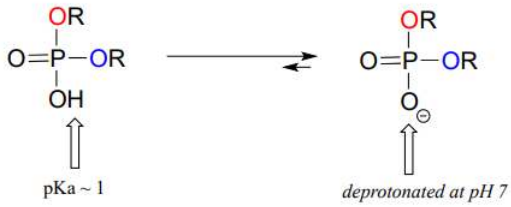
Phosphoric acid is triprotic, meaning that it has three acidic protons available to donate, with pK_a values of 1.0, 6.5, and 13.0, respectively. (da Silva and Williams)



H_3PO_4 pKa = 1.0 | $H_2PO_4^{-1}$ pKa = 6.5 | HPO_4^{-2} pKa = 13.0 | PO_4^{-3}

These acid constant values, along with the Henderson-Hasselbalch equation (section 7.2) tell us that, at the physiological pH of approximately 7, somewhat more than half of the phosphate species will be in the HPO_4^{-2} state, and slightly less than half will be in the $H_2PO_4^{-1}$ state, meaning that the average net charge is between -1.5 and -2.0.

Phosphate diesters have a pK_a of about 1, meaning that they carry a full negative charge at physiological pH.



Organic monophosphates, diphosphates, and triphosphates all have net negative charges and are partially protonated at physiological pH, but by convention are usually drawn in the fully deprotonated state.

? Exercise 9.2.2

Explain why the second pK_a of phosphoric acid is so much higher than the first pK_a.

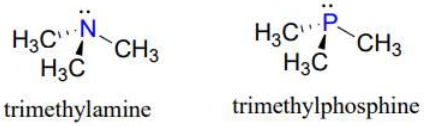
? Exercise 9.2.3

What is the approximate net charge of inorganic phosphate in a solution buffered to $pH1$?

Recall from section 8.4 that good leaving groups in organic reactions are, as a rule, weak bases. In laboratory organic reactions, leaving groups are often halides or toluenesulfonates (section 8.4), both of which are weak bases. In biological organic reactions, phosphates are very common leaving groups. These could be inorganic phosphate, inorganic pyrophosphate, or organic monophosphates, all of which are weakly basic, especially when coordinated to metal cations such as Mg^{+2} in the active site of an enzyme. We will see many examples of phosphate leave groups in this and subsequent chapters.

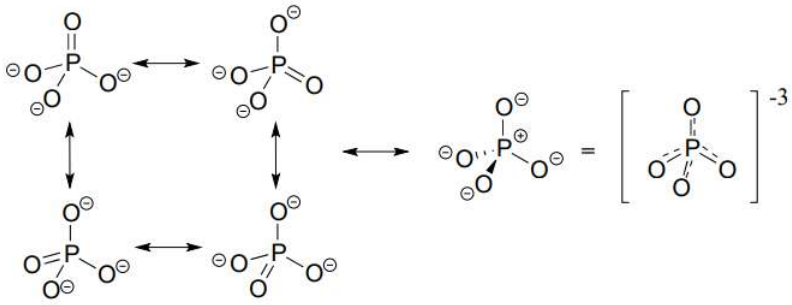
Bonding in phosphates

Looking at the location of phosphorus on the periodic table, you might expect it to bond and react in a fashion similar to nitrogen, which is located just above it in the same column. Indeed, phosphines - phosphorus analogs of amines - are commonly used in the organic laboratory.



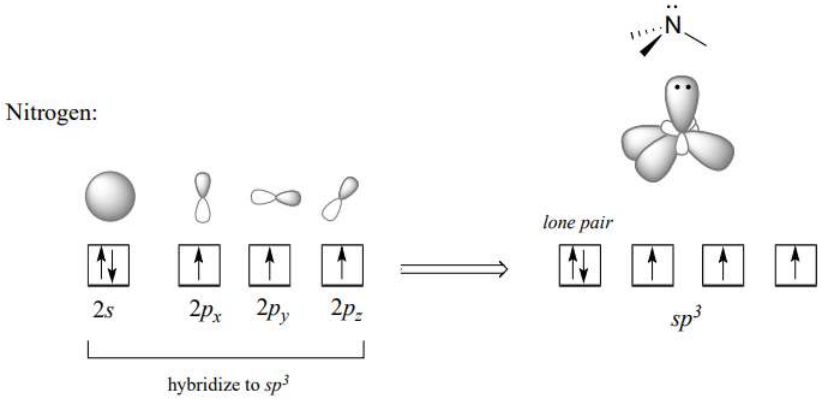
However it is in the form of phosphate, rather than phosphine, that phosphorus plays its main role in biology.

The four oxygen substituents in phosphate groups are arranged about the central phosphorus atom with tetrahedral geometry, however there are a total of five bonds to phosphorus - four s bonds and one delocalized π bond.

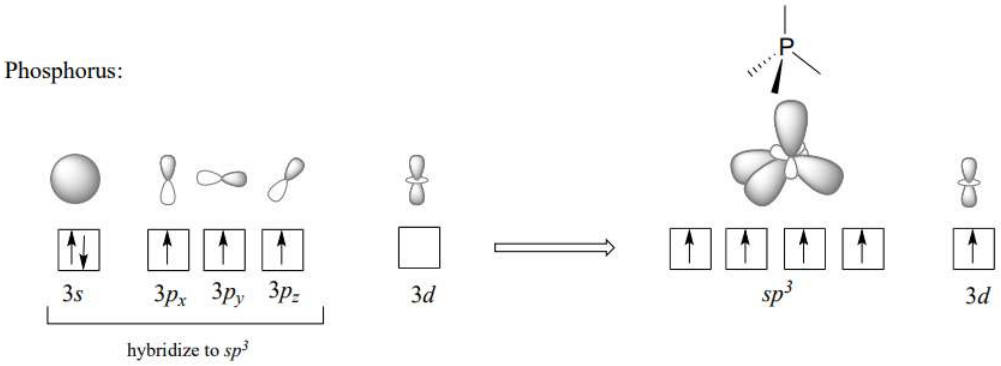


Phosphorus can break the 'octet rule' because it is on the third row of the periodic table, and thus has d orbitals available for bonding. The minus 3 charge on a fully deprotonated phosphate ion is spread evenly over the four oxygen atoms, and each phosphorus-oxygen bond can be considered to have 25% double bond character: in other words, the bond order is 1.25.

Recall from section 2.1 the hybrid bonding picture for the tetrahedral nitrogen in an amine group: a single **2*s*** and three **2*p*** orbitals combine to form four sp^3 hybrid orbitals, three of which form s bonds and one of which holds a lone pair of electrons.

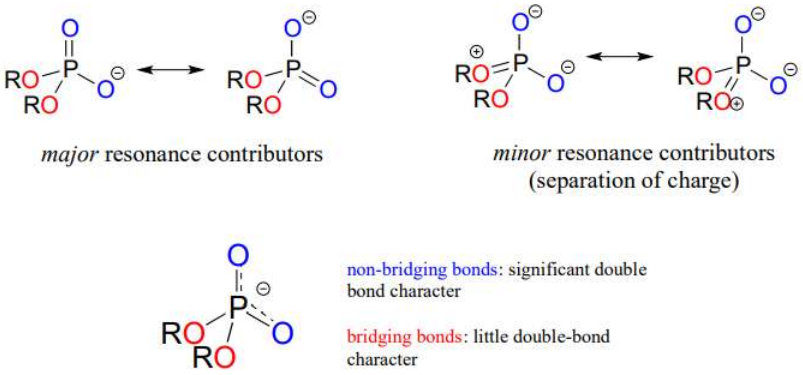


In the hybrid orbital picture for phosphate ion, a single **3*s*** and three **3*p*** orbitals also combine to form four sp^3 hybrid orbitals with tetrahedral geometry. In contrast to an amine, however, four of the five valance electrons on phosphorus occupy sp^3 orbitals, and the fifth occupies an unhybridized **3*d*** orbital.



This orbital arrangement allows for four s bonds with tetrahedral geometry in addition to a fifth, delocalized p bond formed by p overlap between the half-filled **3*d*** orbital on phosphorus and **2*p*** orbitals on the oxygen atoms.

In phosphate esters, diesters, and anhydrides the π bonding is delocalized primarily over the non-bridging bonds, while the bridging bonds have mainly single-bond character. In a phosphate diester, for example, the two non-bridging oxygens share a -1 charge, as illustrated by the two major resonance contributors below. The bonding order for the bridging $P-O$ bonds in a phosphate diester group is about 1, and for the non-bridging $P-O$ bonds about 1.5. In the resonance contributors in which the bridging oxygens are shown as double bonds (to the right in the figure below), there is an additional separation of charge - thus these contributors are minor and make a relatively unimportant contribution to the overall bonding picture.



? Exercise 9.2.4

Draw all of the resonance structures showing the delocalization of charge on a (fully deprotonated) organic monophosphate. If a 'bond order' of 1.0 is a single bond, and a bond order of 2.0 is a double bond, what is the approximate bond order of bridging and non-bridging $P-O$ bonds?

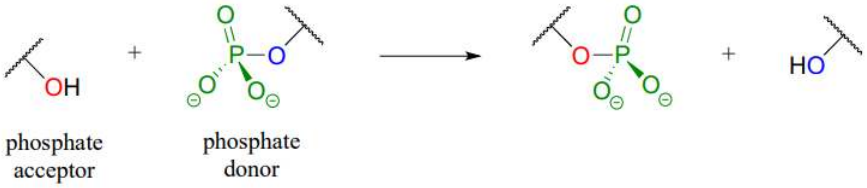
Throughout this book, phosphate groups will often be drawn without attempting to show tetrahedral geometry, and π bonds and negative charges will usually be shown localized to a single oxygen. This is done for the sake of simplification - however it is important always to remember that the phosphate group is really tetrahedral, the negative charges are delocalized over the non-bridging oxygens, and that there is some degree of protonation at physiological pH (with the exception of the phosphate diester group).

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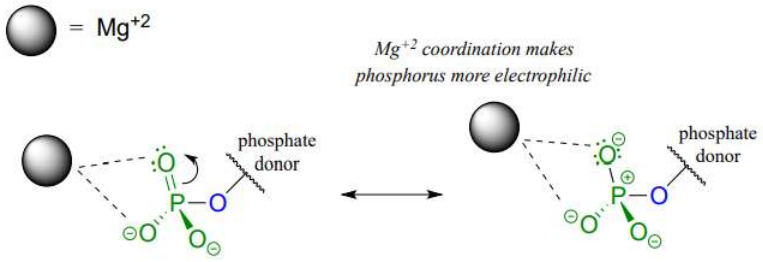
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9.2: Phosphate Transfer Reactions - An Overview

In a phosphate transfer reaction, a phosphate group is transferred from a **phosphate group** donor molecule to a phosphate group acceptor molecule:



A very important aspect of biological phosphate transfer reactions is that the electrophilicity of the phosphorus atom is usually enhanced by the Lewis acid (electron-accepting) effect of one or more magnesium ions. Phosphate transfer enzymes generally contain a Mg^{2+} ion bound in the active site in a position where it can interact with non-bridging phosphate oxygens on the substrate. The magnesium ion pulls electron density away from the phosphorus atom, making it more electrophilic.

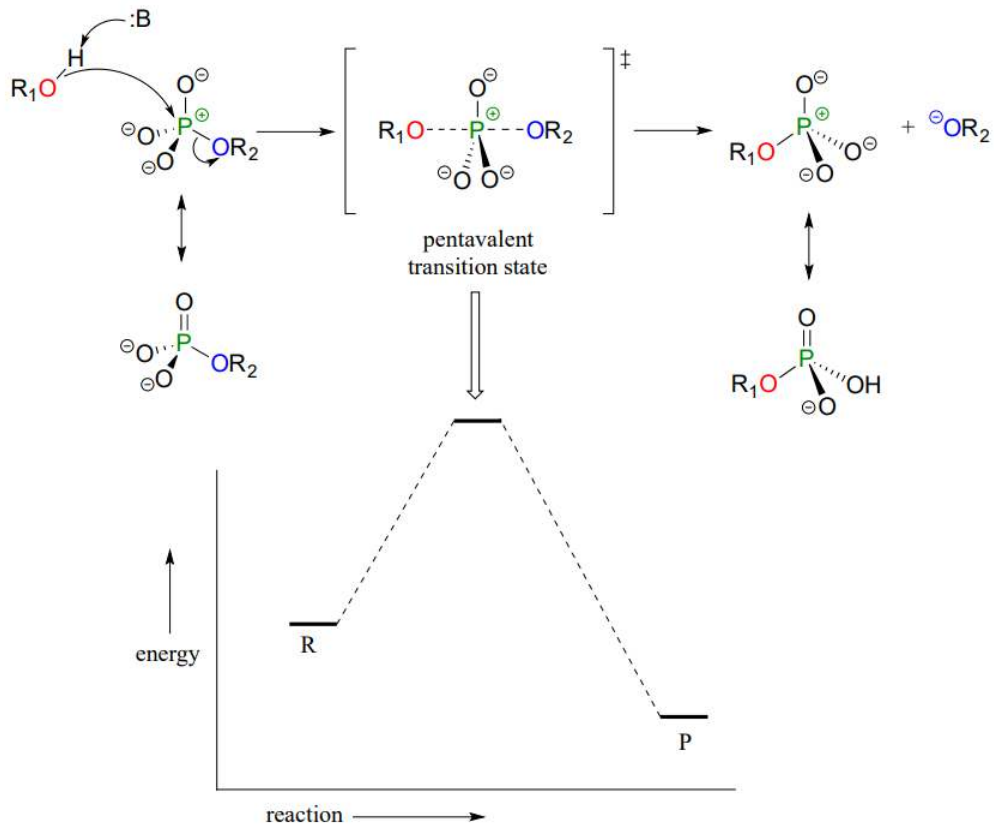


Without this metal ion interaction, a phosphate is actually a poor electrophile, as the negatively-charged oxygens shield the phosphorus center from attack by a nucleophile.

> **Note**
>
> For the sake of simplicity and clarity, we will not draw the magnesium ion or other active site groups interacting with phosphate oxygens in most figures in this chapter - but it is important to keep in mind that these interactions play an integral role in phosphate transfer reactions.

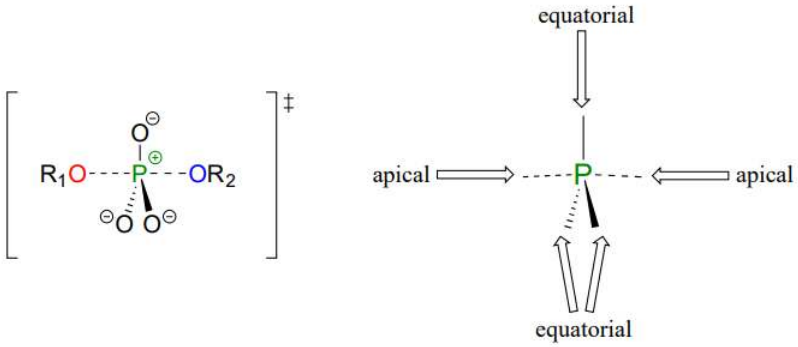
Mechanistically speaking, a phosphate transfer reaction at a phosphorus center can be though of as much like a S_N2 reaction at a carbon center. Just like in an S_N2 reaction, the nucleophile in a phosphoryl transfer approaches the electrophilic center from the backside, opposite the leaving group:

Concerted model:

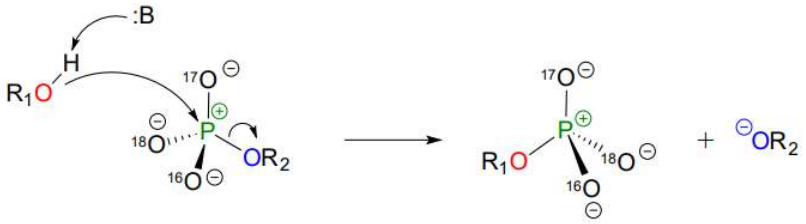


As the nucleophile gets closer and the leaving group begins its departure, the bonding geometry at the phosphorus atom changes from tetrahedral to trigonal bipyramidal at the pentavalent (5-bond) transition state. As the phosphorus-nucleophile bond gets shorter and the phosphorus-leaving group bond grows longer, the bonding picture around the phosphorus atom returns to its original tetrahedral state, but the stereochemical configuration has been 'flipped', or inverted.

In the trigonal bipyramidal transition state, the five substituents are not equivalent: the three non-bridging oxygens are said to be equatorial (forming the base of a trigonal bipyramid), while the nucleophile and the leaving group are said to be apical (occupying the tips of the two pyramids).



Although stereochemical inversion in phosphoryl transfer reactions is predicted by theory, the fact that phosphoryl groups are achiral made it impossible to observe the phenomenon directly until 1978, when a group of researchers was able to synthesize organic phosphate esters in which stable oxygen isotopes ^{17}O and ^{18}O were specifically incorporated. This created a chiral phosphate center.



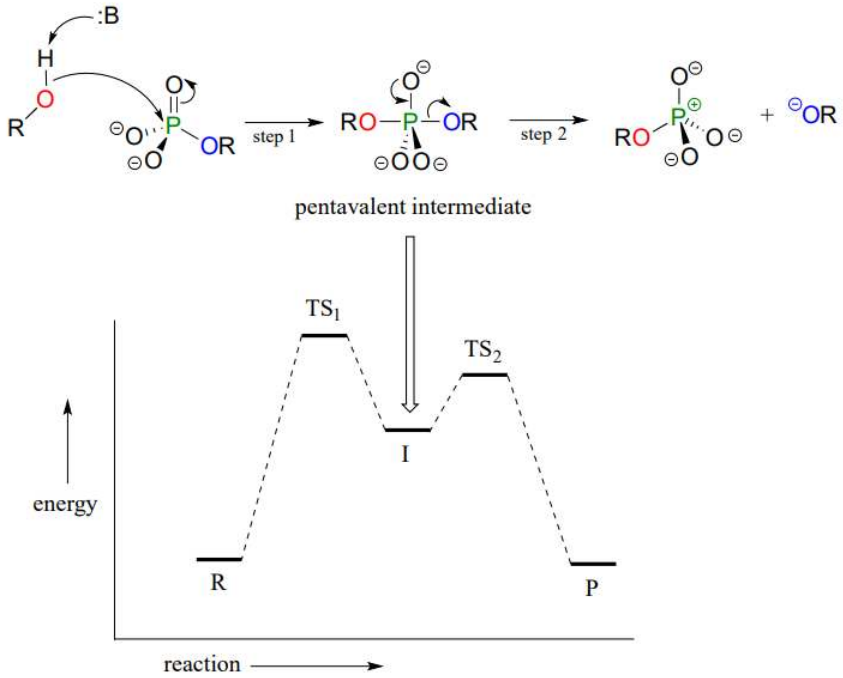
phosphate has *S* configuration phosphate has *R* configuration

Subsequent experiments with phosphoryl transfer-catalyzing enzymes confirmed that these reactions proceed with stereochemical inversion. (Nature 1978 275, 564; Ann Rev Biochem 1980 49, 877).

The concerted (S_N2-like) is not the only mechanism that has been proposed for these reactions - in fact, two other possible mechanisms have been suggested. In an alternative two-step mechanistic model, the nucleophile could attack first, forming

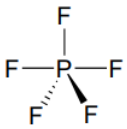
a pentavalent, trigonal bipyramidal intermediate (as apposed to a pentavalent transition state). The reaction is completed when the leaving group is expelled. The intermediate species would occupy an energy valley between the two transition states.

Addition-elimination model:

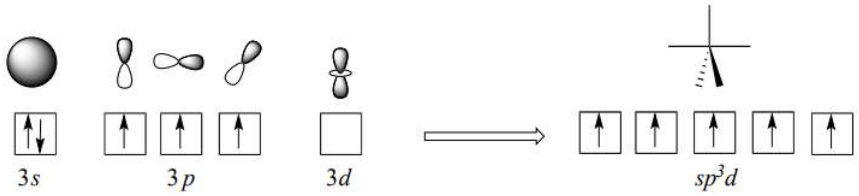


This is often referred to as an 'addition-elimination' mechanism - the nucleophile adds to the phosphate first, forming a pentavalent intermediate, and then the leaving group is eliminated.

An addition-elimination mechanism with a pentavalent intermediate is not possible for an S_N2 reaction at a carbon center, because carbon, as a second-row element, does not have any d orbitals and cannot form five bonds. Phosphorus, on the other hand, is a third-row element and is quite capable of forming more than four bonds. Phosphorus pentachloride, after all, is a stable compound that has five bonds to chlorine arranged in trigonal bipyramidal geometry around the central phosphorus.

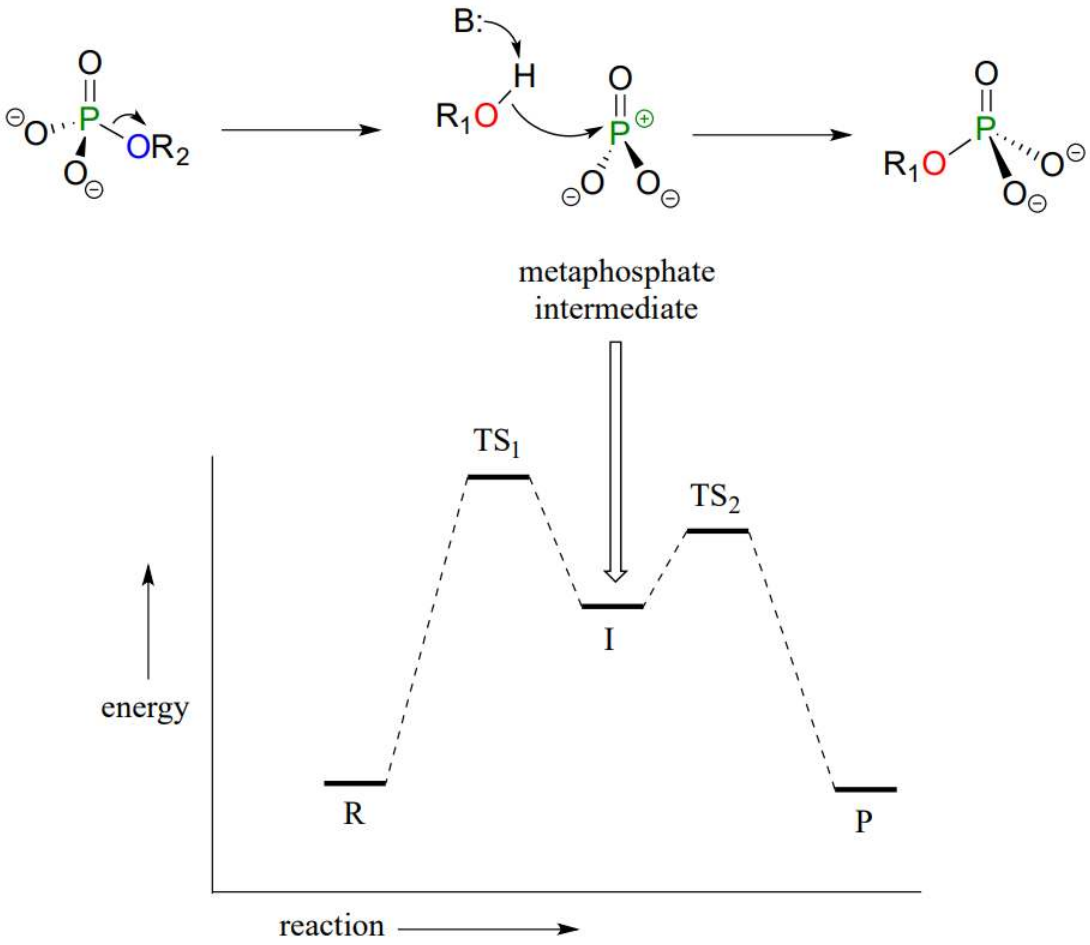


The phosphorus atom in PCl_5 (and in the hypothetical pentavalent intermediate pictured above) is considered to be sp^3d hybridized:



There is a third possibility: the reaction could proceed in an S_N1-like manner: in other words, elimination-addition. In this model, the phosphorus-leaving group bond breaks first, resulting in a metaphosphate intermediate. This intermediate, which corresponds to the carbocation intermediate in an S_N1 reaction and like a carbocation has trigonal planar geometry, is then attacked by the nucleophile to form the reaction product.

Elimination-addition model:



So which mechanistic model - concerted (SN_2-like), addition-elimination, or elimination-addition - best describes enzymatic phosphate transfer reactions? Chemists love to investigate and debate questions like this! Just like with the S_N1/S_N2 argument discussed in chapter 8, it really boils down to one question: which happens first, bond-forming or bond-breaking - or do these two events occur at the same time? From the evidence accumulated to date, it appears that many enzymatic phosphate transfer reactions can best be described by the concerted model, although there is still argument about this, and still many unanswered questions about other details of how these reactions are catalyzed in active sites. Considering the importance of phosphate transfer reactions in metabolic pathways, this area is clearly a very promising one for further investigation. If you are interesting in learning more

about this research, a great place to start is a review article written by Professor Daniel Herschlag at Stanford University (Annu. Rev. Biochem. 2011, 80, 669).

For the sake of simplicity and clarity, phosphoryl transfers in this text will be depicted using the concerted model.

Exercise 9.3.1

Predict the approximate angles between the two bonds indicated in a phosphate transfer transition state. O_a refers to an oxygen at the apical position, and O_e to an oxygen in the equatorial position.

a. $O_a - P - O_a$

b. $O_a - P - O_e$

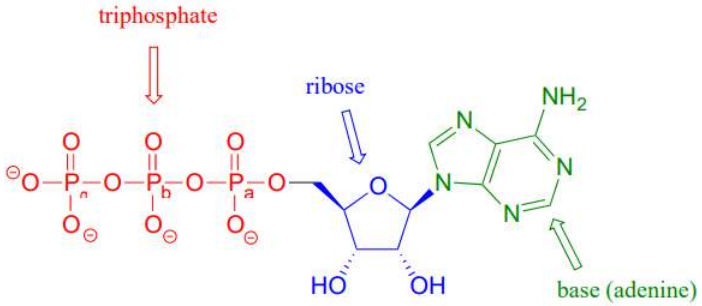
c. $O_e - P - O_e$

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9.3: ATP, The Principal Phosphate Group Donor

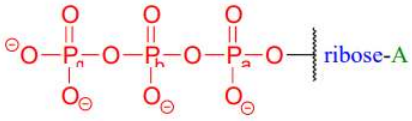
Thus far we have been very general in our discussion of phosphate transfer reactions, referring only to generic 'donor' and 'acceptor' species. It's time to get more specific. The most important donor of phosphate groups in the cell is a molecule called adenosine triphosphate, commonly known by its abbreviation ATP.

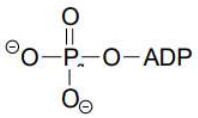


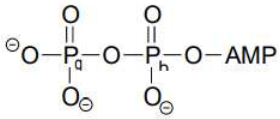
adenosine triphosphate (ATP)

that there are essentially three parts to the ATP molecule: an adenine nucleoside 'base', a five-carbon sugar (ribose), and triphosphate. The three phosphates are designated by Greek letters a, b, and g, with the a phosphate being the one closest to the ribose. Adenosine diphosphate (ADP) and adenosine monophosphate (AMP) are also important players in the reactions of this chapter.

ATP is a big molecule, but the bond-breaking and bond-forming events we will be studying in this chapter all happen in the phosphate part of the molecule. You will see structural drawings of ATP, ADP, and AMP abbreviated in many different ways in this text and throughout the biochemical literature, depending on what is being illustrated. For example, the three structures below are all abbreviated depictions of ATP:



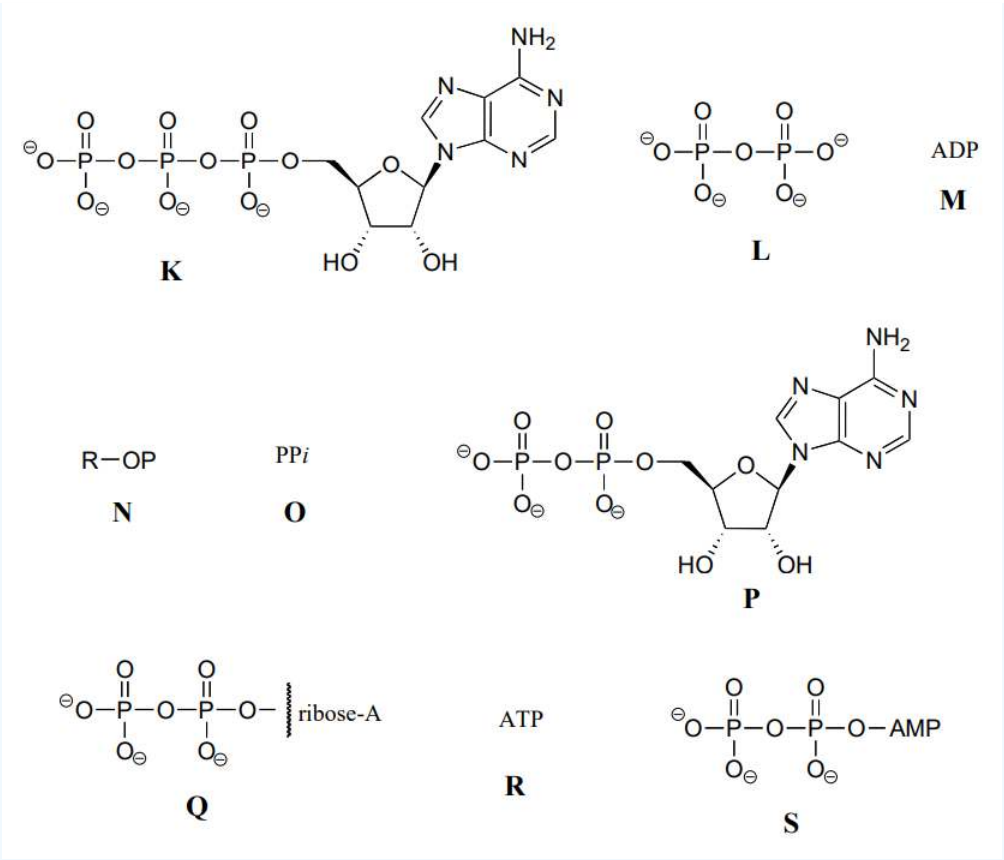




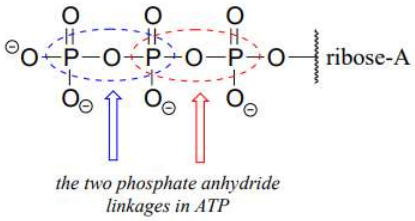
The following exercise will give you some practice in recognizing different abbreviations for ATP and other biological molecules that contain phosphate groups.

? Exercise 9.4.1

Below are a number of representations, labeled A-S, of molecules that contain phosphate groups. Different abbreviations are used. Arrange A-S into groups of drawings that depict the same species (for example, group together all of the abbreviations which depict ATP).

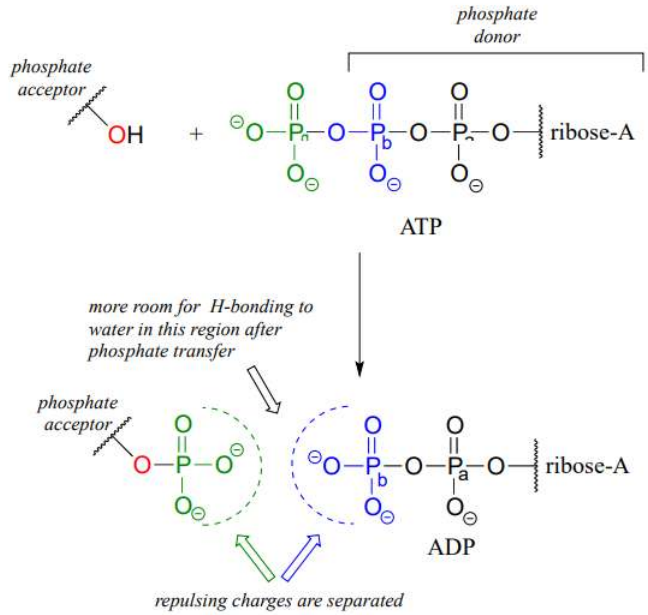


You are probably familiar with the physiological role of ATP from your biology classes - it is commonly called 'the energy currency of the cell'. What this means is that ATP stores energy we get from the oxidation of fuel molecules such as carbohydrates or fats. The energy in ATP is stored in the two high-energy phosphate anhydride linkages.



the two phosphate anhydride linkages in ATP

When one or both of these phosphate anhydride links are broken as a phosphate group is transferred to an acceptor, a substantial amount of energy is released. The negative charges on the phosphate groups are separated, eliminating some of electrostatic repulsion that existed in ATP. One way to picture this is as a coil springing open, releasing potential energy.

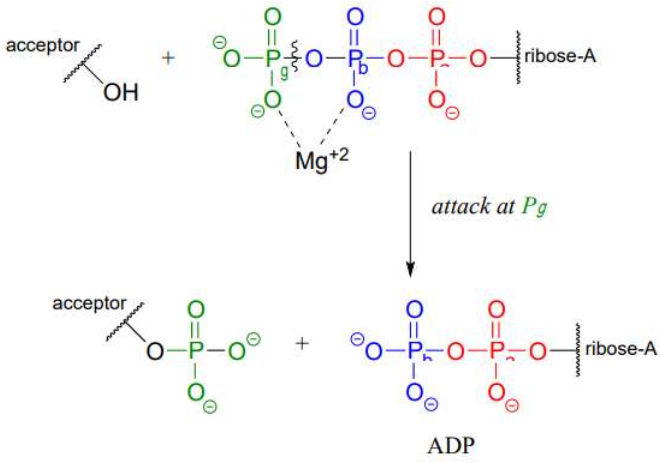


In addition, cleavage of a phosphate anhydride bond means that surrounding water molecules are able to form more stabilizing hydrogen-bonding interactions with the products than was possible with the starting materials, again making the reaction more 'downhill', or exergonic.

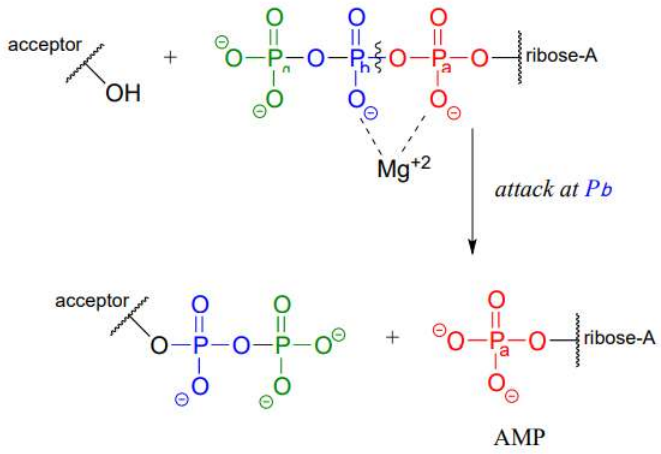
It is important to understand that while the phosphate anhydride bonds in ATP are thermodynamically unstable (they contain a great deal of chemical energy), they are at the same time kinetically stable: ATP-cleaving reactions are exothermic, but also have a high energy barrier, making them very slow unless catalyzed by an enzyme. In other words, the release of the energy contained in ATP is highly energetic but also subject to tight control by the interaction of highly evolved enzymes in our metabolic pathways.

ATP is a versatile phosphate group donor: depending on the site of nucleophilic attack (at the α, β, or γ phosphorus), different phosphate transfer outcomes are possible. Below are the three most common patterns seen in the central metabolic pathways. A 'squigly' line in each figure indicates the $P-O$ bond being broken. We will study specific examples of each of these in the coming sections.

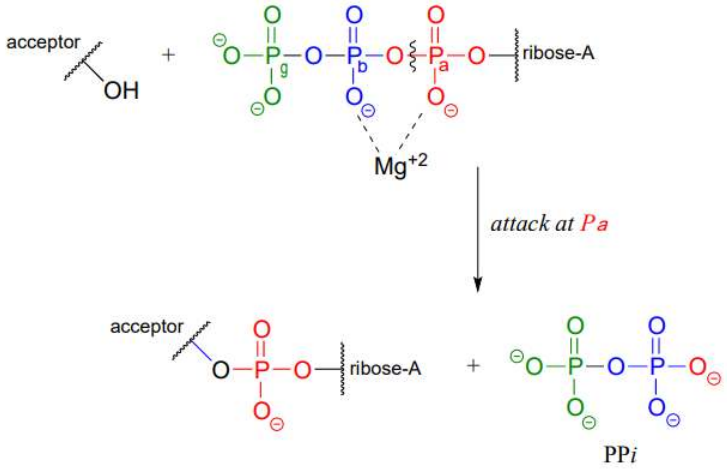
Attack at the γ-phosphate:



Attack at the β-phosphate:



Attack at the α-phosphate:



Note

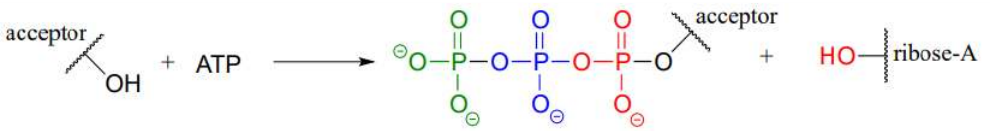
The common thread running through all of the ATP-dependent reactions we will see in this section is the idea that the phosphate acceptor molecule is undergoing a thermodynamically 'uphill' transformation to become a more reactive species. The energy for this uphill transformation comes from breaking a high-energy phosphate anhydride bond in ATP. That is why ATP is often referred to as 'energy currency': the energy in its anhydride bonds is used to 'pay for' a thermodynamically uphill chemical step.

Exercise 9.4.2

Propose a fourth hypothetical phosphate transfer reaction between ATP and the generic acceptor molecule in the figure above, in which inorganic phosphate (Pi) is a by-product.

Exercise 9.4.3

Why is this hypothetical phosphate transfer reaction less energetically favorable compared to all of the possible ATP-cleaving reactions shown in the figure above?



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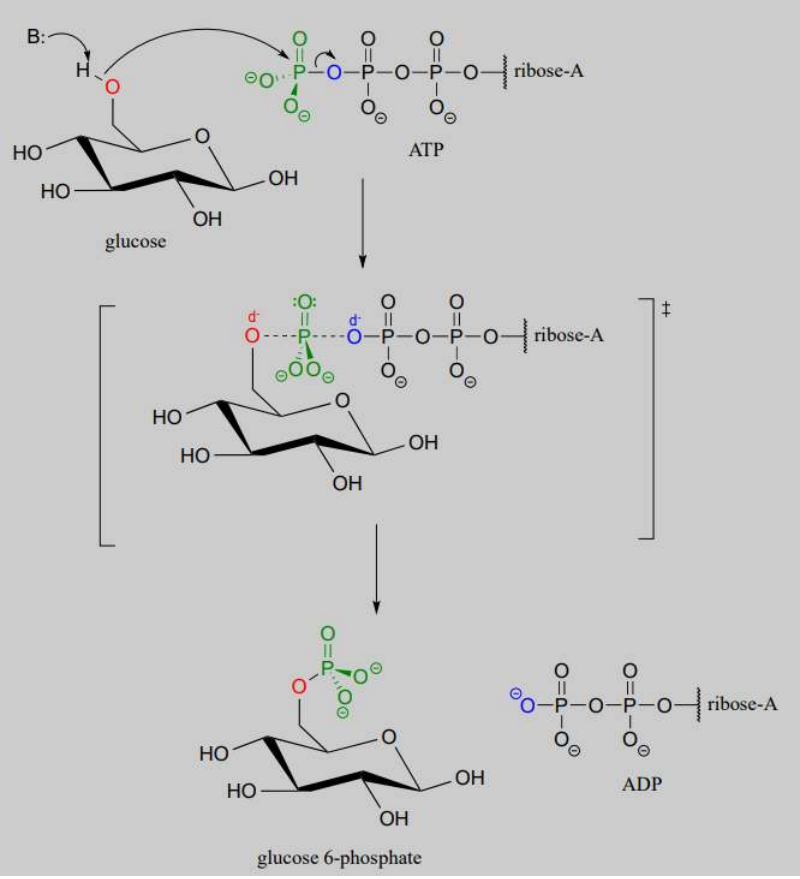
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9.4: Phosphorylation of Alcohols

A broad family of enzymes called kinases catalyze transfer of a phosphate group from TP to an alcohol acceptor. Mechanistically, the alcohol oxygen acts as a nucleophile, attacking the electrophilic g-phosphorus of TP and expelling ADP.

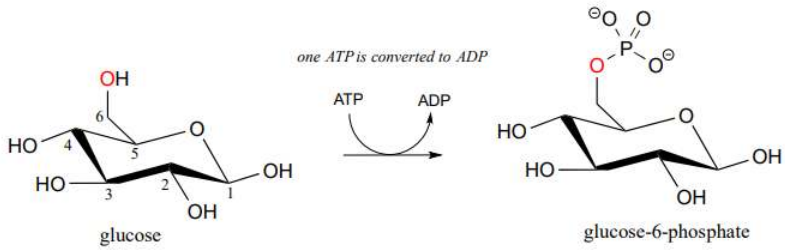
Glucose is phosphorylated in the first step of the glycolysis pathway by the enzyme hexose kinase (EC 2.7.1.1), forming glucose-6-phosphate.

Hexose kinase mechanism

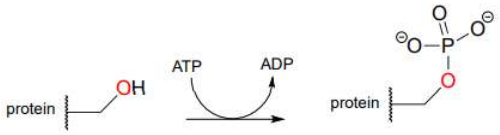


Video Tutorial

Here is a shorthand way to depict this reaction. Notice the "ATP in, ADP out" notation used below, indicating that ATP is one of the reactants and ADP is one of the products. From here on, we will frequently use this common convention to indicate reaction participants whose structures are not drawn out in a figure.



The biological activity of many proteins is regulated by protein kinases. In a protein kinase reaction, the side chain hydroxyl groups on serine, threonine, or tyrosine residues of certain proteins are phosphorylated by ATP:



serine residue phosphoserine residue

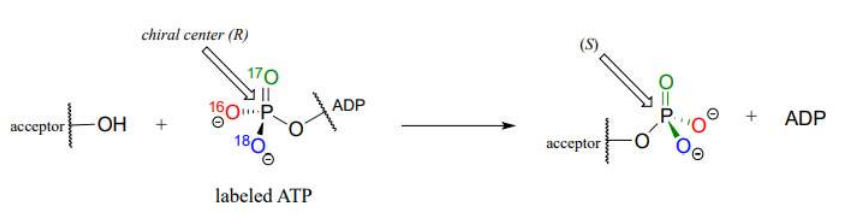
The conversion of a neutral hydroxyl group to a charged phosphate represents a very dramatic change in the local architecture of the protein, potentially altering its folding pattern and ability to bind to small molecules or other proteins. A protein's biological function can be 'switched on' by phosphorylation of a single residue, and switched off again by removal of the phosphate group. The latter reaction we will examine later in this chapter.

Exercise 9.5.1

a. Threonine kinase catalyzes the phosphorylation of the side chain hydroxyl group of threonine residues in proteins. Draw the structure, including the configuration of all stereocenters, of a phosphothreonine residue. Explain how you can predict the stereochemistry of the side chain.

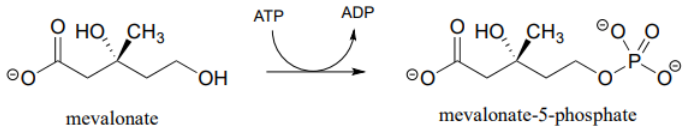
Note

Although stereochemical inversion in phosphate transfer is predicted by theory, the fact that phosphate groups are achiral made it impossible for a long time to verify the phenomenon directly. This was finally accomplished in the late 1970's, when a group of researchers demonstrated phosphate inversion in kinase enzymes using chemically synthesized ATP in which three different isotopes of oxygen were incorporated into the g-phosphate, thus creating a chiral phosphorus center. (Ann. Rev. Biochem. 1980 49, 877).

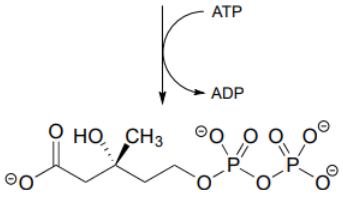


labeled ATP

Alcohols can be converted into organic diphosphates in two different ways. A two-step process simply involves successive transfers of the g-phosphate groups of two ATP donors, such as in these sequential steps in isoprenoid biosynthesis. (EC 2.7.1.36; EC 2.7.4.2). A compound called mevalonate is diphosphorylated in this way in the early phase of the biosynthetic pathway for cholesterol, steroid hormones, and other isoprenoid molecules.



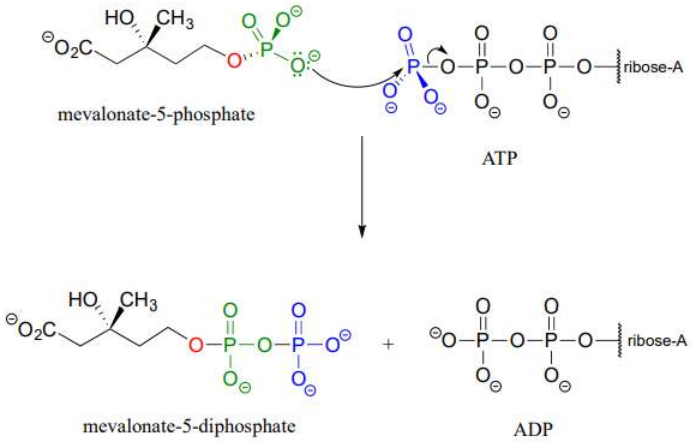
mevalonate mevalonate-5-phosphate



mevalonate-5-diphosphate

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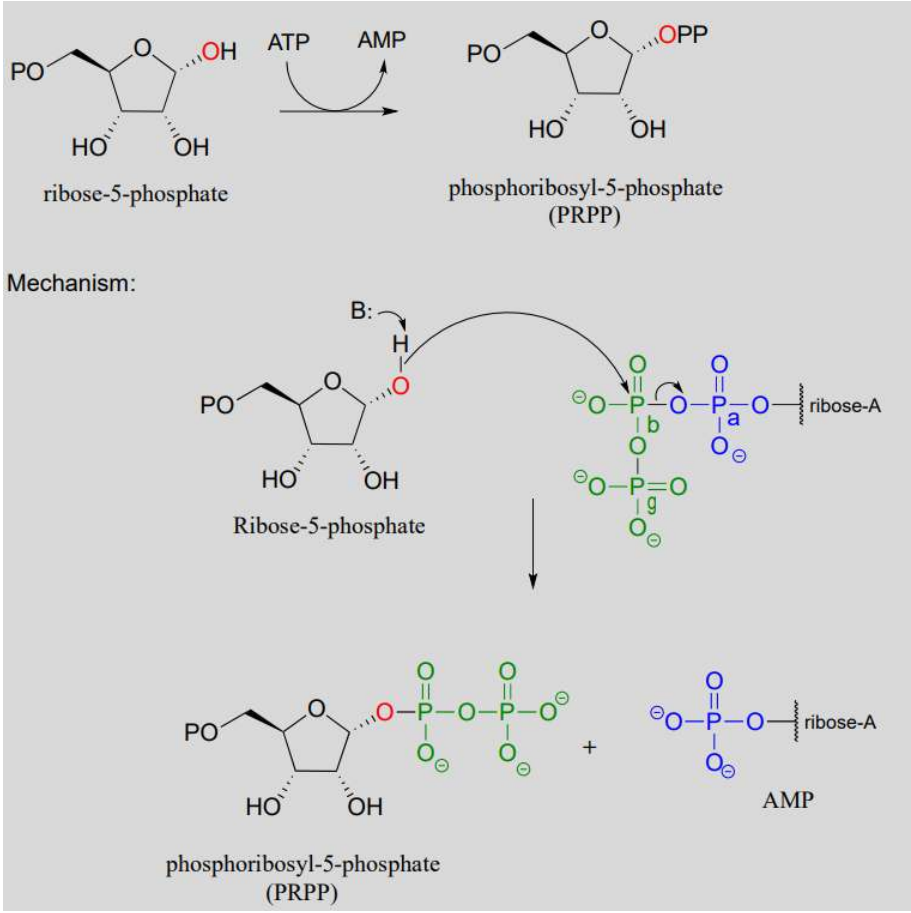
The mechanism for the first phosphorylation step is analogous to that for an alcohol kinase reaction, which we have just seen. In the second phosphate transfer step, catalyzed by a separate enzyme, one of the phosphate oxygens on the organic monophosphate acts as a nucleophilic phosphate acceptor, attacking the g-phosphate of a second ATP.



In some metabolic pathways, diphosphorylation occurs by a different mechanism from the one above. stead of sequentially transferring two phosphates from two ATP donors, the alternate mechanism occurs in a single step: the nucleophilic acceptor molecule attacks the b-phosphate of ATP, rather than the g-phosphate. After formation of the trigonal bipyramidal intermediate, it is AMP (not ADP) which is expelled, and what started out as the b and g phosphates of ATP both remain with the acceptor.

In the biosynthesis of DNA and RNA nucleotides, one of the hydroxyl groups on ribose-5-phosphate is diphosphorylated (EC 2.7.6.1) in a one-step mechanism:

A one-step alcohol diphosphorylation reaction (PRPP synthase):



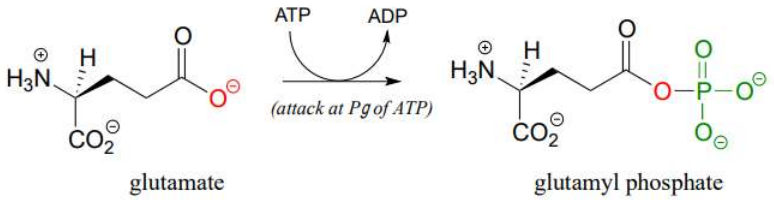
The metabolic role of both of the diphosphorylation processes we just saw is to convert a hydroxyl group into a good leaving group (recall that hydroxide ions are strong bases and poor leaving groups, while phosphates/diphosphates, especially when stabilized in an enzyme active site, are weak bases and very good leaving groups). In nucleoside biosynthesis pathways, the diphosphate group of PRPP acts as a leaving group in the very next metabolic step, which is an S_N1 reaction: we have already seen this reaction in section 8.7).

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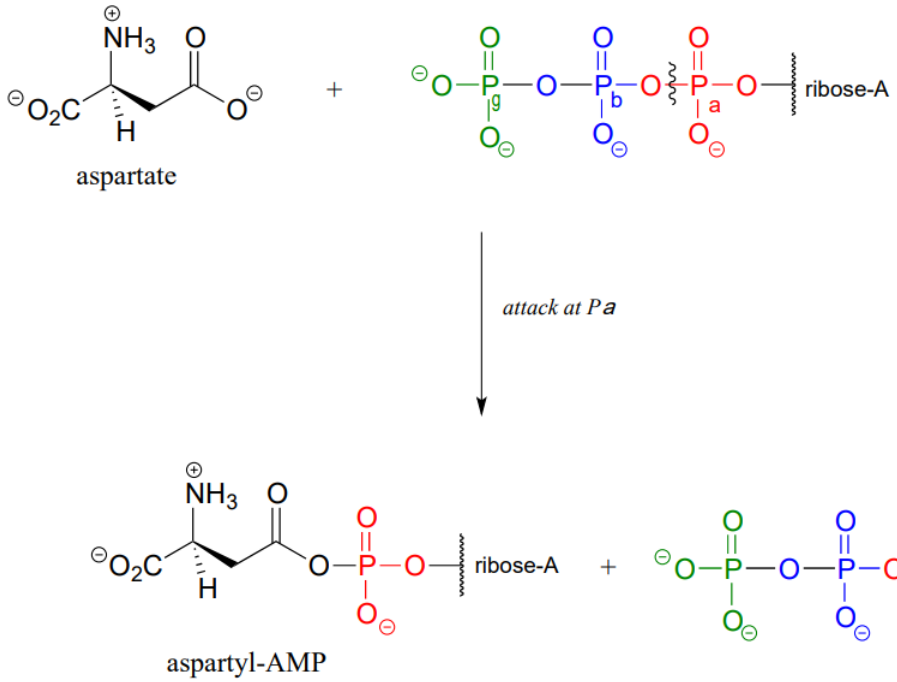
9.5: Phosphorylation of Carboxylates

Thus far we have seen hydroxyl oxygens and phosphate oxygens acting as nucleophilic accepting groups in ATP-dependent phosphate transfer reactions. Carboxylate oxygens can also accept phosphate groups from ATP. This typically happens in two different ways. First, the carboxylate can attack the g-phosphate of ATP to accept phosphate, generates a species known as an 'acyl phosphate'. An example is the first part of the reaction catalyzed by glutamine synthase (EC 6.3.1.2):



glutamate glutamyl phosphate

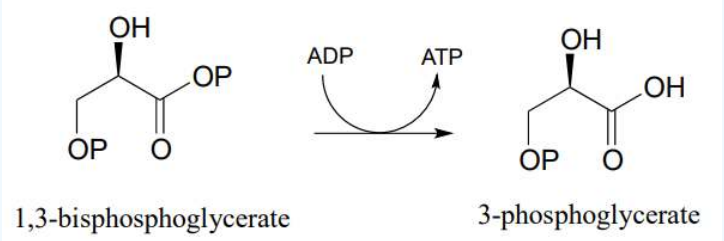
Alternatively, carboxylate groups are often converted into a species referred to as an 'acyl-AMP' . Here, the carboxylate oxygen attacks the α-phosphate of ATP leading to release of inorganic pyrophosphate. An example is the first part of the reaction catalyzed by the enzyme asparagine synthetase: (EC 6.3.5.4):



aspartate aspartyl-AMP

? Exercise 9.6.1

Draw a curved-arrow mechanism for the phosphate transfer reaction shown below (EC 2.7.2.3), which is from the glycolysis pathway. Note that ADP is on the reactant side and ATP is a product (the opposite of what we have seen so far). Hint: What functional group is the nucleophile? What functional group is the leaving group?



1,3-bisphosphoglycerate 3-phosphoglycerate

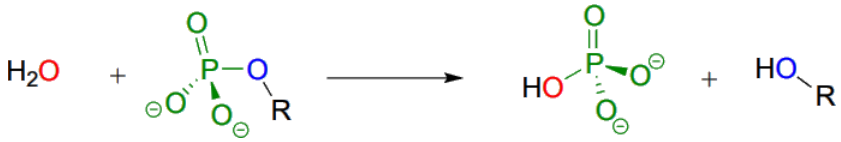
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9.6: Hydrolysis of Organic Phosphates

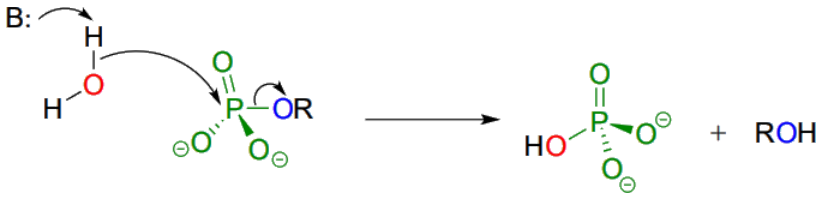
While kinase enzymes catalyze the phosphorylation of organic compounds, enzymes called phosphatases catalyze dephosphorylation reactions. The reactions catalyzed by kinases and phosphatases are not the reverse of one another: kinases irreversibly transfer phosphate groups from ATP (or sometimes other nucleoside triphosphates) to various organic acceptor compounds, while phosphatases transfer phosphate groups from organic compounds to water: these are hydrolysis reactions. Kinase reactions involve an inherently 'uphill' step (phosphorylation of an alcohol, for example) being paid for with an inherently 'downhill' step (cleavage of an anhydride bond in ATP). Phosphatase reactions, on the other hand, are thermodynamically 'downhill', and while they require an enzyme to speed them up, they do not involve 'spending' energy currency the way kinase reactions do.

Phosphatase reaction:

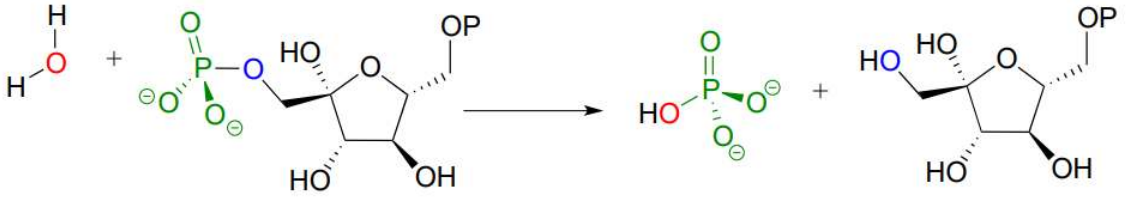


There are two possible general mechanisms for a phosphatase reaction. Some enzymes catalyze direct hydrolysis reactions, in which the phosphate group is removed by direct attack of a water molecule at the phosphate center:

Phosphatase mechanism (direct hydrolysis):



One of the two phosphate groups on fructose 1,6-bisphosphate is hydrolyzed in such a way late in the gluconeogenesis pathway. (Biochemistry 2000, 39, 8565; EC 3.1.3.11)



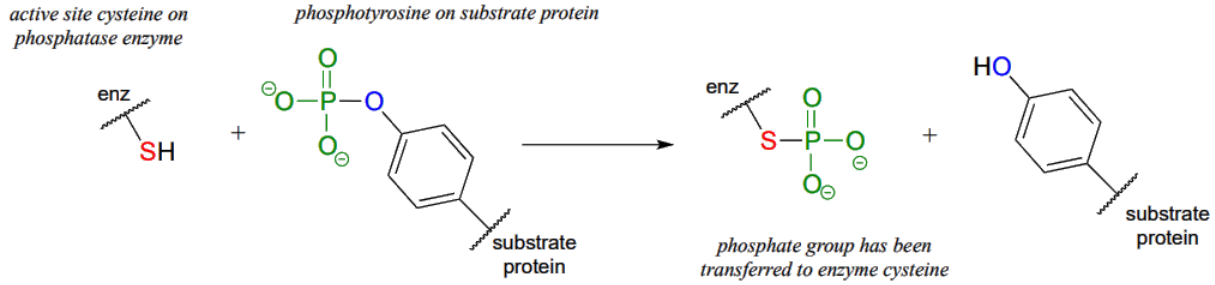
fructose 1,6-bisphosphate

fructose-6-phosphate

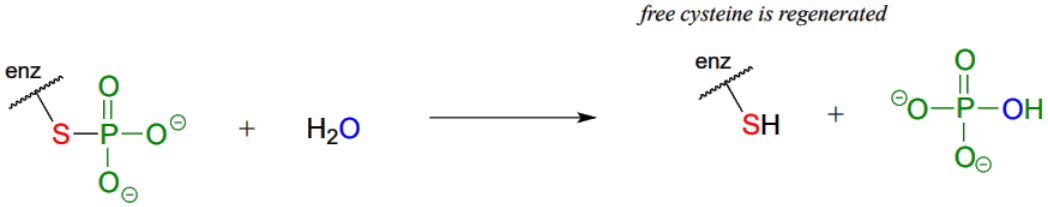
Many phosphatase reactions, however, operate by a slightly more complicated mechanism than what is shown above. In the first phase, a nucleophilic enzyme group (typically a cysteine, aspartate, glutamate, or histidine side chain, designated in the figure below as 'X') attacks the phosphate group. In the second phase, the phosphorylated residue is hydrolized. For example, protein tyrosine phosphatase catalyzes the dephosphorylation of phosphotyrosine residues in some proteins - this is the other half of the regulatory 'on-off switch' that we discussed earlier in the context of protein kinases. In the first step, the phosphate group is directly donated to a cysteine side chain in the phosphatase enzyme's active site. In the second step, the phosphocysteine intermediate is cleaved by water to form inorganic phosphate and regenerate the free cysteine in the active site.

Indirect phosphatase reaction:

Step 1:



Step 2:



Notice that in the end, the phosphate group has still been transferred to a water molecule, albeit indirectly. How would you know, just by looking at the substrate and product of the protein tyrosine phosphatase reaction, that the phosphate is not transferred directly to a water molecule? Simply put, you wouldn't know this information without the benefit of knowledge gained from biochemical experimentation.

? Exercise 9.7.1

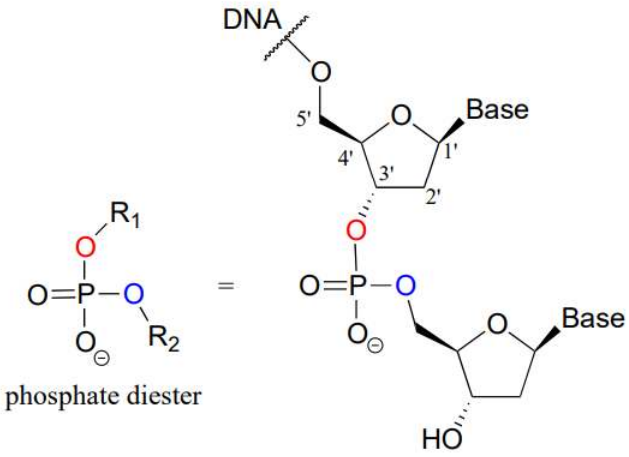
If you were to look just at the substrates and products of a phosphatase reaction without knowing anything about the mechanism, it is apparent that a *nucleophilic substitution* mechanism could theoretically account for the products formed. Draw out a hypothetical nucleophilic substitution mechanism for the hydrolysis of a phosphoserine residue and show how researchers, by running the reaction in H218O, (isotopically labeled water), could potentially distinguish between a nucleophilic substitution and phosphate group transfer mechanism by looking at where the 18O atom ends up in the products.

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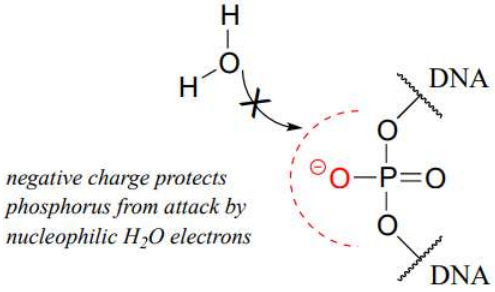
9.7: Phosphate Diesters in DNA and RNA

Phosphate diesters play an absolutely critical role in nature - they are the molecular 'tape' that connect the individual nucleotides in DNA and RNA via a sugar-phosphate backbone. Take note of the 1' - 5' carbon numbering shown below for the ribose sugar - these numbers will be used frequently in the coming discussion. The 'prime' symbol (') is used to distinguish the ribose carbon numbers from the nucleotide base carbon numbers (which are not shown here).



The introduction to this chapter referenced a widely-read 1987 commentary in Science Magazine, in which F.H. Westheimer of Harvard University addressed the question of why phosphates were 'chosen' by nature for critical biochemical job of linking DNA (Science 1987, 235, 1173). He emphasizes how critical it is for the phosphate diester linkage in DNA to be stable in water – in other words, it must be resistant to spontaneous (nonenzymatic) hydrolysis. Even very infrequent occurrence of such an undesired hydrolysis event could be disastrous for an organism, given that an intact DNA strand is a long-term storage mechanism for genetic information.

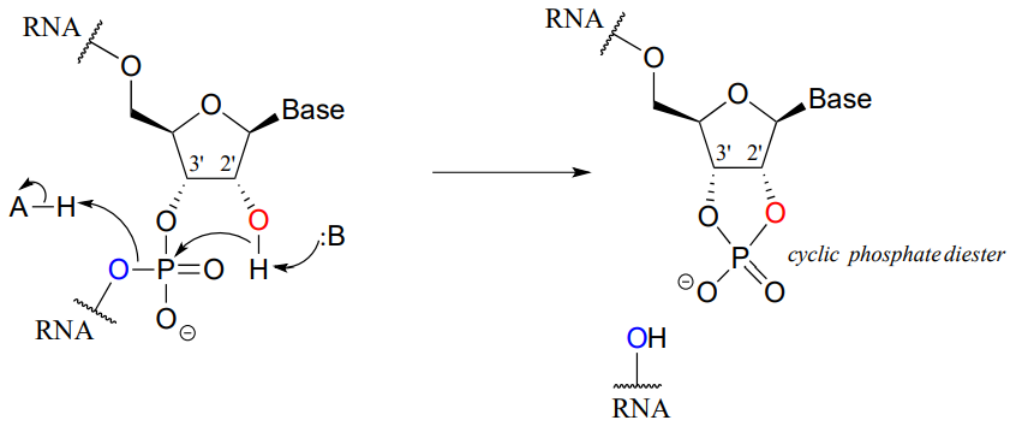
Westheimer pointed out that the inherent stability of DNA is a due in large part to the negative charge on the non-bridging oxygen of the phosphate diester linker, which effectively repels nucleophilic water molecules and shields the electrophilic phosphorus atom from attack.



While DNA is quite stable with regard to spontaneous hydrolysis, it of course can be degraded by specific enzymatic hydrolysis, where the phosphate electrophile is activated for attack through noncovalent interactions (eg. with Mg^{2+}) in the active site. Enzymes that hydrolyze the phosphate diester bonds in DNA are called nucleases, and we will learn more about them in section 9.8.

Unlike DNA, RNA is quite vulnerable to spontaneous hydrolysis in aqueous solution. This does not present a physiological dilemma, because the function of RNA is to encode genetic information on a temporary rather than long-term basis. Why does hydrolysis occur so much more rapidly in RNA than in DNA? The answer has everything to do with the lowered entropic barrier to the reaction (you might want to quickly review the concept of entropy at this point). RNA nucleotides, unlike the deoxynucleotides of DNA, have a hydroxyl group at the neighboring 2' carbon. The 2' hydroxyl group is right next to the electrophilic phosphorus

atom, poised in a good position to make a nucleophilic attack, breaking the RNA chain and forming a cyclic phosphate diester intermediate (see figure below).



Researchers working with RNA have to be careful to store their samples at very cold temperatures, preferably freeze-dried or precipitated in ethanol, to avoid hydrolysis. The problem of RNA decomposition is compounded by the fact that RNAase enzymes, which catalyze RNA hydrolysis, are present on the surface of human skin and are very stable, long-lived, and difficult to destroy.

In contrast, DNA samples can be safely stored in aqueous buffer in a refrigerator, or in a freezer for longer-term storage.

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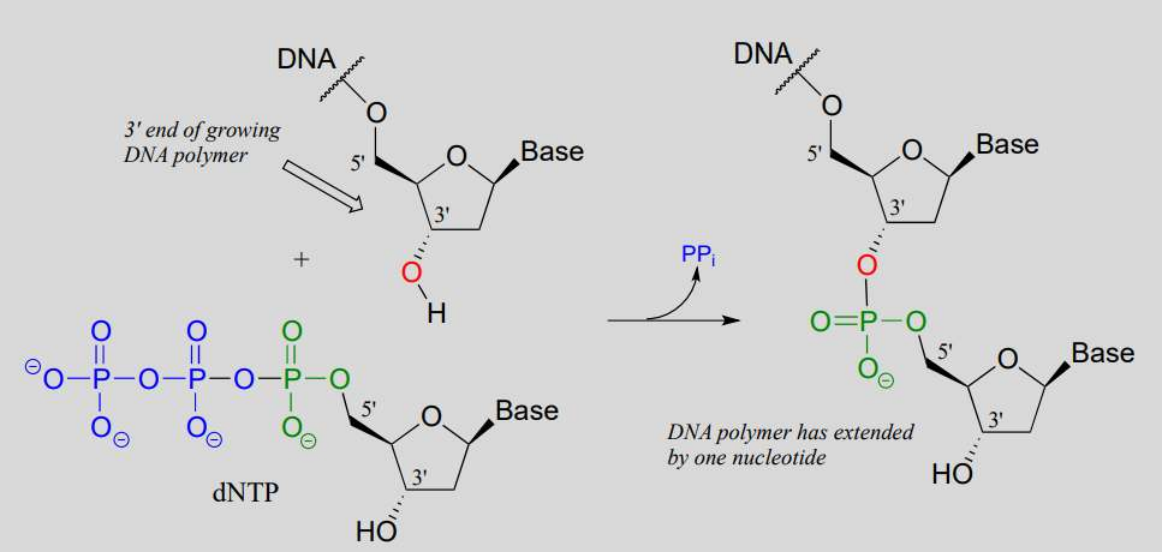
9.8: The Organic Chemistry of Genetic Engineering

Many enzymes that catalyze reactions involving the phosphate diester bonds of DNA have been harnessed for use in genetic engineering - techniques in which we copy, snip, and splice DNA in order to create custom versions of genes. The tools of genetic engineering have become indispensable and commonplace in the past decade, and most researchers working on the biological side of chemistry use them extensively. The days of painstakingly purifying an enzyme from bacterial cultures or ground-up cow livers are pretty much gone. Now scientists clone the gene that encodes the enzyme, make any desired changes (by site-directed mutagenesis, for example), and use a host such as E. coli or yeast to produce 'recombinant' enzyme from the cloned gene. You will learn the details of many of these procedures in a biochemistry or molecular biology course. What we will focus on now is applying what we have learned about phosphate group transfer reactions so that we can recognize some of the organic chemistry that is happening in a cloning experiment.

The first thing you have to do in a gene cloning procedure is to copy a DNA strand. This is accomplished by an enzyme called DNA polymerase (EC 2.7.7.7), which uses a single strand of DNA as a template to synthesize a second, complementary strand (the full picture of this complex process is well beyond the scope of this book, but recall that we talked about the discovery of thermostable DNA polymerase in the introduction to chapter 6).

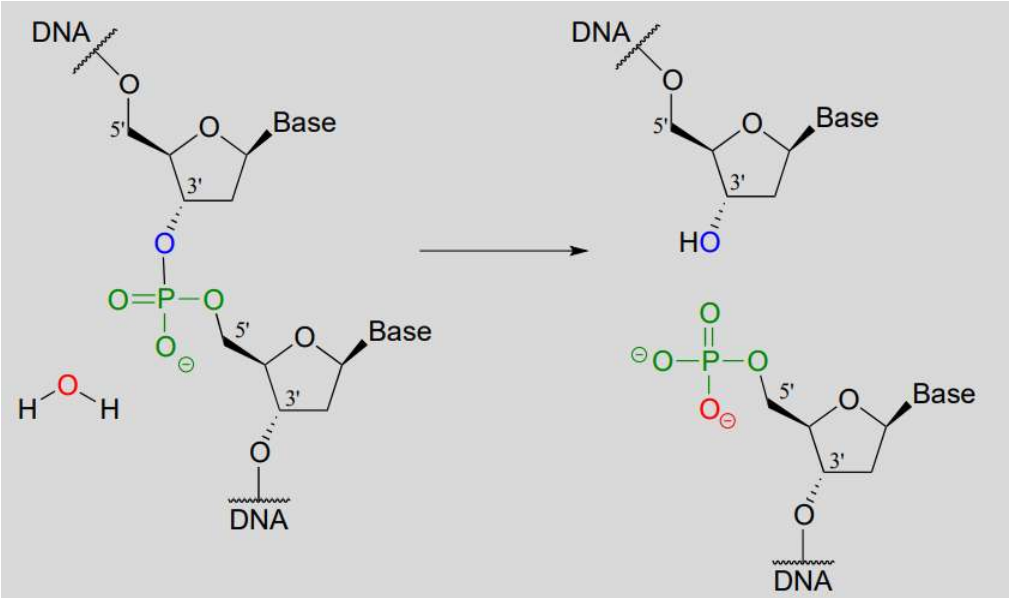
may have learned in a biology class that DNA is synthesized in the 3' to 5' direction. Notice below that the 3' hydroxyl group on the end of the growing DNA strand attacks the a-phosphate of a 2'-deoxynucleoside triphosphate (dNTP), expelling inorganic pyrophosphate.

DNA polymerase reaction:



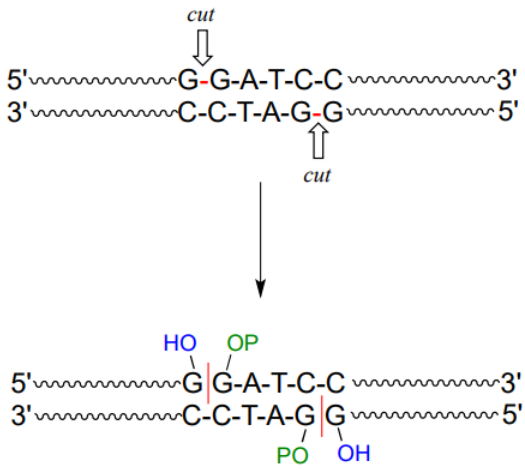
Scientists are able to cut DNA using 'molecular scissor' enzymes called restriction endonucleases that cleave double-stranded DNA by hydrolysis at specific base sequences.

DNA hydrolysis by restriction endonucleases:



Notice that the result of this hydrolytic cleavage reaction is one segment of DNA with a hydroxy group at the 3' position, and a second segment with a phosphate group at the 5' position.

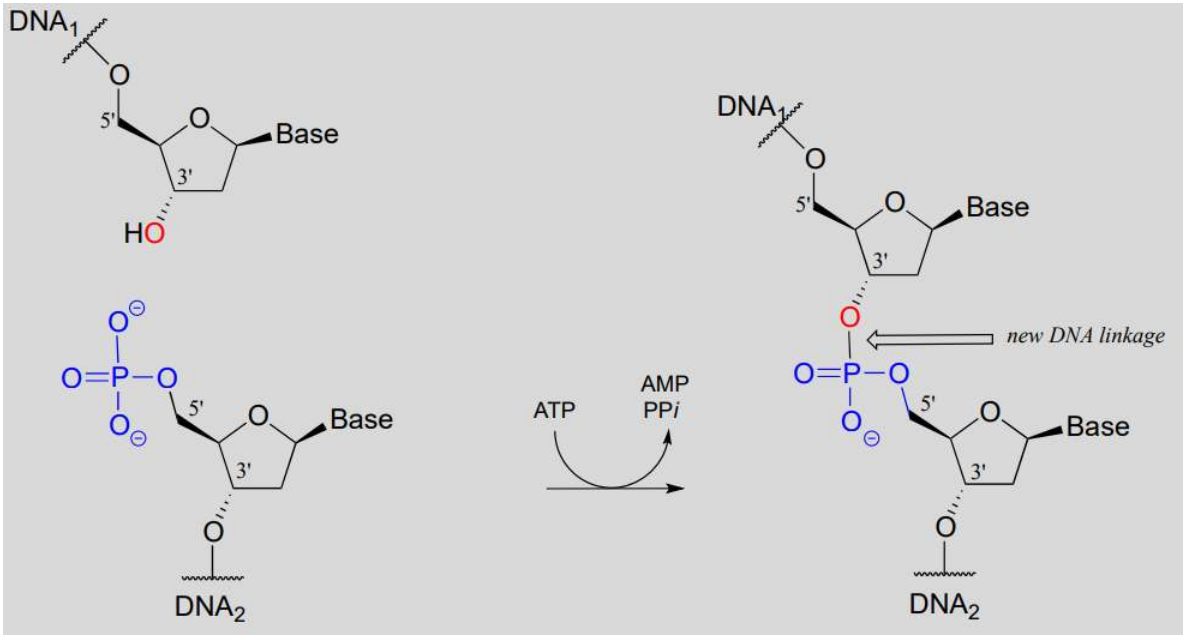
A commonly used restriction endonuclease called 'BamHI' cleaves double-stranded DNA specifically at the following 6-base sequence:



Notice that a 'staggered' cut is made: this is a common (and useful) property of many endonucleases, although some make 'blunt-ended' cuts.

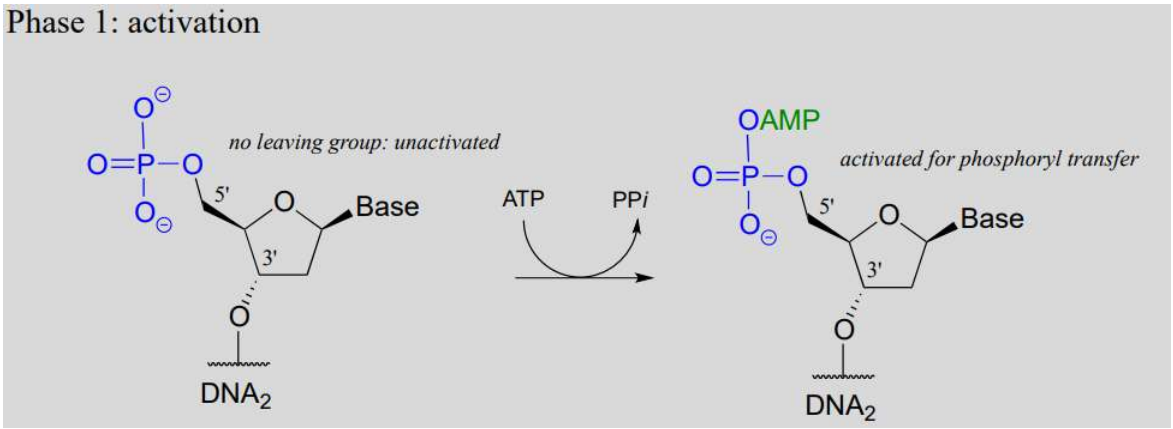
While an endonuclease cleaves a phosphodiester linkage in a DNA strand, DNA ligase (EC 6.5.1.1) accomplishes the reverse process: it catalyzes the formation of a new 3'-5' link between two strands:

DNA ligase reaction:

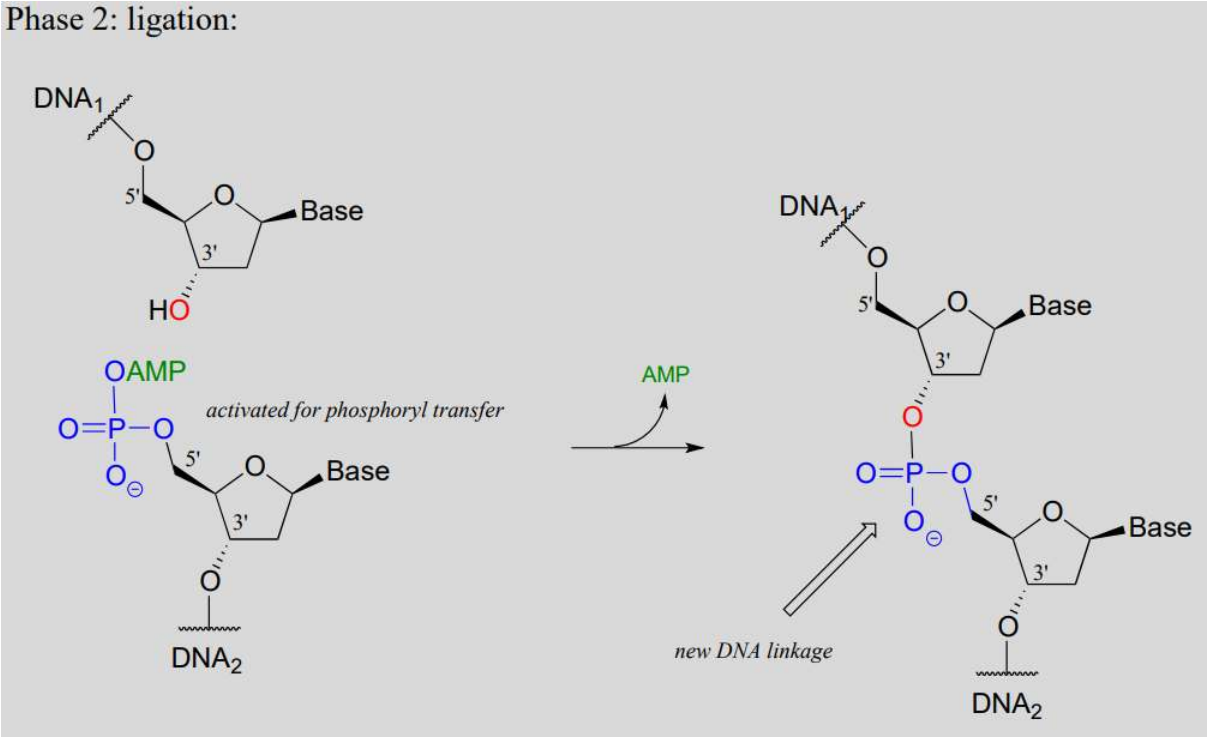


Note that there is initially no leaving group on the 5' phosphate of DNA2, which makes a direct phosphate transfer reaction impossible. The strategy employed by the DNA ligase enzyme is to first activate the 5' phosphate of DNA2 using ATP (phase 1 below), then the ligation reaction can proceed (phase 2)

DNA ligation

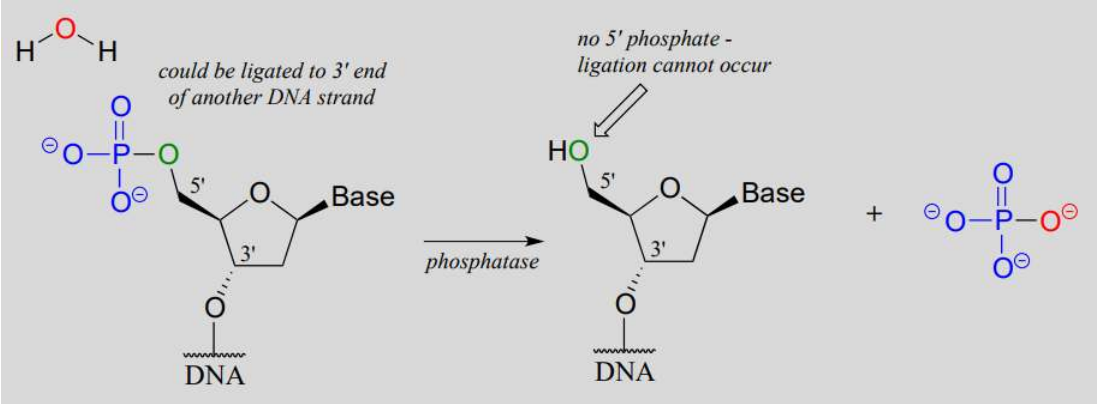


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One more enzymatic tool in the genetic engineering arsenal bears mention. In some cloning procedures, a researcher may want to prevent unwanted ligation of DNA. This can be accomplished by using the enzyme alkaline phosphatase (EC 3.1.3.1), which catalyzes the dephosphorylation of many different organic phosphates, including 5'-phosphorylated DNA (recall that we discussed phosphatases in section 9.6).

Alkaline phosphatase reaction:



With the phosphate group removed, ligation is impossible - there is no way to make a new phosphodiester bond without a 5' phosphate group!

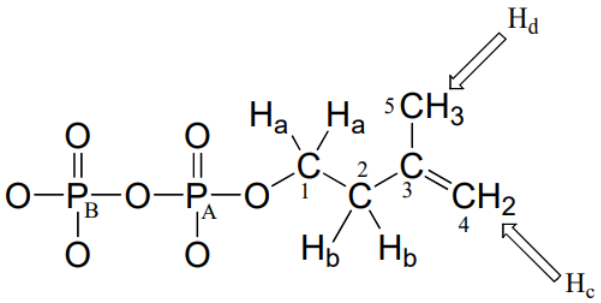
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9.9: NMR of phosphorylated compounds

Because so many biological molecules contain phosphoryl groups, it is worthwhile to look at how scientists use NMR to determine the structure of these molecules. Recall from section 5.1 that ^{31}P, the most abundant isotope of phosphorus, is NMR active: it can be directly observed by $^{31}P-NMR$, and indirectly observed in $^{1}H-NMR$ and $^{13}C-NMR$ through its spin-coupling interactions with neighboring protons and carbons, respectively.

Consider the case of isopentenyl diphosphate, the building block molecule used by cells to make 'isoprenoid' compounds such as cholesterol (in many animals), or β-carotene (in some plants). NMR spectra of this molecule were taken in a D_2O solvent, buffered with ND_4OD (the deuterium equivalent of aqueous ammonium hydroxide, NH_4OH) (J. Org. Chem. 1986, 51, 4768). In our discussion, carbon atoms are specified with numbers, protons with lower case letters, and phosphorus atoms with upper case letters.



First, let's look at the proton spectrum:

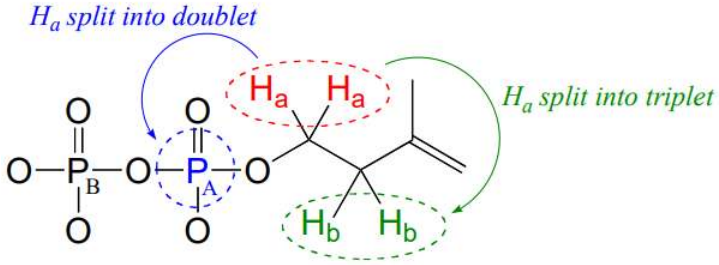
$^{1}H-NMR$

H_a : 4.05$ppm(t_d)$;$^{3}J_{H_a-H_b}$ = 6.6 Hz; $^{3}J_{H_a-P_A}$ = 3.3 Hz.

H_b : 2.39$ppm(t)$ $^{3}J_{H_a-H_b}$ = 6.6 Hz

H_c : 4.86$ppm(s)$

H_d : 1.77$ppm(s)$



The signals for H_b, H_c, and H_d look like we would expect from our discussion in chapter 5, with the exception of Hc which you will be invited to discuss in the exercise below. Why, though, is the signal for Ha split into a triplet of doublets (td)? First of all, as, expected, the two neighboring Hb protons split the Ha signal into a triplet, with 3JH-H = 6.6 Hz. Then, **the signal is further split into doublets ($^{3}J_{H-P}$ = 3.3 Hz) by \(P_A\), the closer of the two phosphorus atoms**. A phosphorus atom will

? Exercise 9.10.1

The signal for the two '\(H_c\)' protons in isopentenyl diphosphate is reported above as a singlet integrating to $2H$. Are these two protons really chemically equivalent, and, according to what you know about proton NMR, should this signal really be a singlet? If not, what kind of signal(s)

would you expect to see? Explain any discrepancies between what you would expect to see and the actual reported data.

Now, let's look at the ^{13}C spectrum of IPP:

$^{13}C-NMR$ (proton-decoupled)

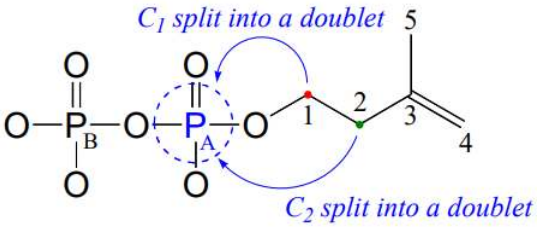
C_1 : 40.7$ppm(d)$;^{2} $J_{C_1-P_A}$ = 7.2 Hz

C_2 : 67.0$ppm(d)$;^{3} $J_{C_2-P_A}$ = 4.0 Hz

C_3 : 147.4ppm

C_4 : 114.6ppm

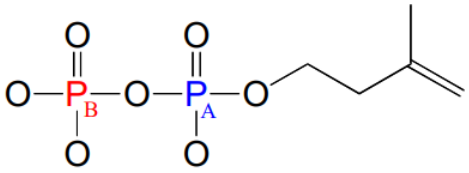
C_5 : 24.5ppm



Notice that the signals for both C_1 and C_2 are split into doublets by the magnetic field of P_A. Phosphorus atoms will spin-couple with ^{13}C nuclei up to three bonds away. Notice also that the 2-bond coupling between C_1 and P_A is larger than the 3-bond coupling between C_2 and P_A (7.2 Hz vs. 4.0 Hz). Finally, notice that we do not observe 4-bond $C-P$ coupling: C_3 is not spin-coupled to P_A, and P_B is not coupled to any of the ^{13}C or ^1H nuclei on the molecule.

Remember that when processing a typical $^{13}C-NMR$ spectrum, we electronically 'turn off' spin coupling between carbons and neighboring protons in order to simplify the spectrum (this is referred to as 'proton decoupling'). Proton decoupling does not turn off $C-P$ spin coupling.

Because ^{31}P is NMR-active, we can also, with an NMR spectrophotometer equipped with a phosphorus probe, directly observe the phosphorus NMR signals, just as we can directly observe the signals from protons and ^{13}C nuclei. On an NMR instrument where protons resonate at 300 MHz and ^{13}C nuclei resonate at 75 MHz, phosphorus resonates at 32 MHz. In $^{31}P-NMR$ experiments, the reference standard used to determine the 0 ppm point is usually phosphoric acid (tetramethylsilane, the standard 0 ppm point for ^1H - and $^{13}C-NMR$, doesn't have a phosphorus atom!). The $^{31}P-NMR$ spectrum of isopentenyl diphosphate has, as expected, two peaks, each of which is upfield of the phosphoric acid standard (negative chemical shifts!) and split into a doublet ($^2J_{P-P}$ = 20 Hz) due to 2-bond coupling between the two phosphorus nuclei.



P_A: (-)11.03 ppm (d, $^2J_{P-P}$ = 20 Hz)
P_B: (-)7.23 ppm (d, $^2J_{P-P}$ = 20 Hz)

Notice that although the C_1 and C_2 signals were split by P_A in our $^{13}C-NMR$ spectrum, in the $^{31}P-NMR$ spectrum the converse is not true: the P_A signal is not split by C_1 or C_2. Both of these carbons are NMR-inactive ^{12}C isotope in 99 out of 100 molecules. In addition, $P-H$ splitting is not observed in this ^{31}P spectrum, because proton decoupling is in effect.

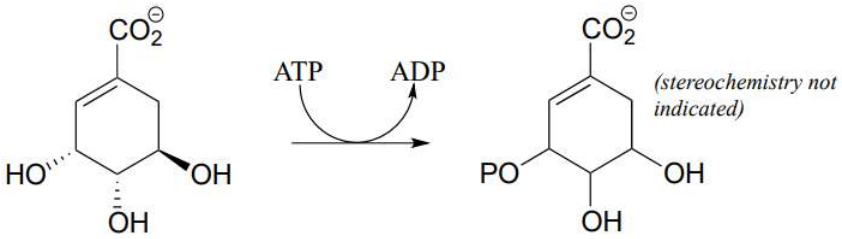
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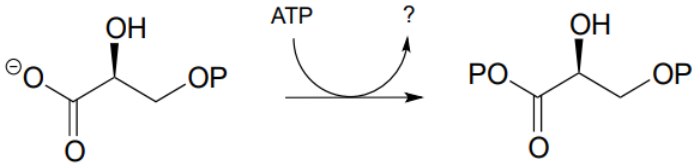
9.E: Phosphate Transfer Reactions (Exercise)

In all of the problems that follow, feel free to use appropriate abbreviations when drawing structures. However, always be sure not to abbreviate regions of a structure which are directly involved in bond-breaking or bond-forming events.

P9.1: Draw a likely mechanism for reaction catalyzed by shikimate kinase (EC 2.7.1.71) in the aromatic amino acid biosynthesis pathway). Stereochemistry of the product is not indicated in the figure below - in your mechanism, show the stereochemistry of the product, and explain how you are able to predict it from your knowledge of kinase reactions.

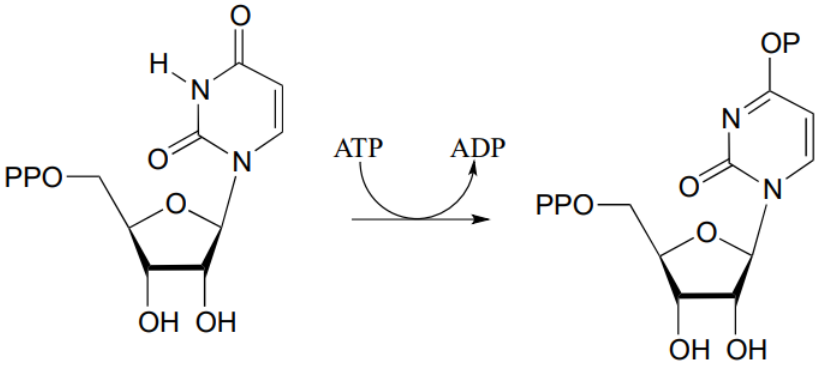


P9.2: Draw a likely mechanism for the following reaction (EC 2.7.2.3) in the gluconeogenesis pathway, and predict what compound is indicated by the question mark.

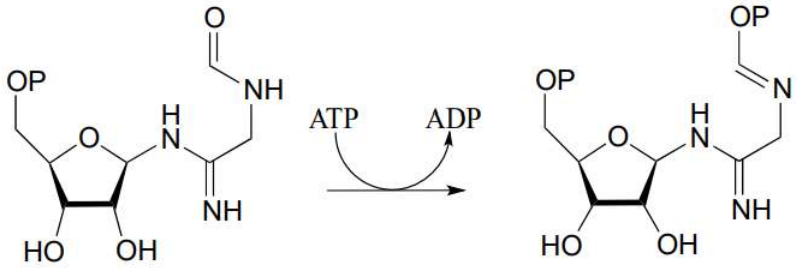


P9.3:

a. Draw a likely mechanism for the following reaction (EC 6.3.4.2) from ribonucleotide biosynthesis. Hint: what is the nucleophilic group? How could the enzyme increase it's nucleophilicity?

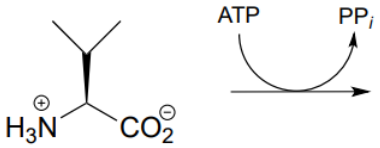


b. Draw a mechanism for the following reaction, also from ribonucleotide biosynthesis (EC 6.3.3.1):



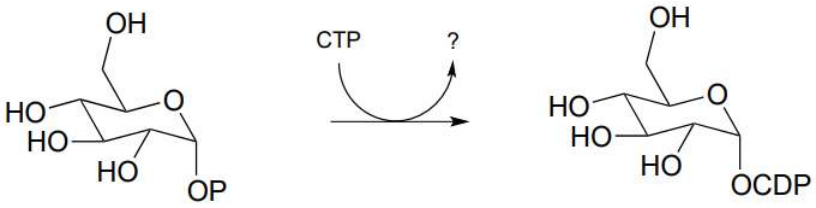
P9.4:

a. The carboxylate group on the amino acid valine is activated in an early step in the biosynthesis of the antibiotic penicillin. Predict the product of this reaction, and draw the likely intermediate of the phosphate group transfer reaction.



valine

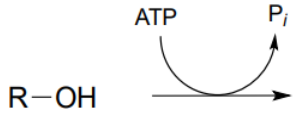
P9.5: The reaction below is an early step in the synthesis of tyvelose, a sugar found on the surface of some pathogenic bacteria. Notice that CTP plays the role of the phosphate group donor in this case, rather than ATP.



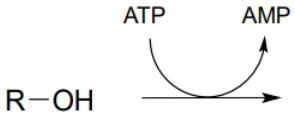
Draw a mechanism for the reaction, and indicate the second product that is released by the enzyme. (J. Biol. Chem. 2005, 280, 10774)

P9.6: Draw the likely product of the following hypothetical phosphate group transfer reactions. Specify which phosphate group of ATP is the electrophile in each case.

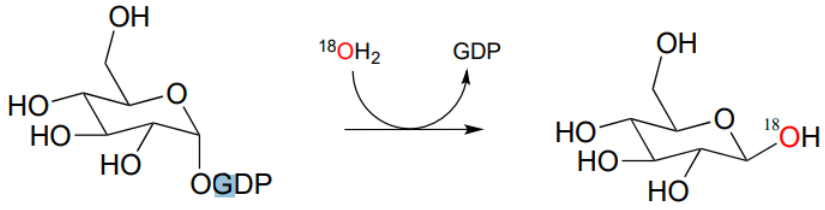
a.



b.



P9.7: The figure below illustrates an experiment in which a reaction catalyzed by an E. coli enzyme was run in isotopically labeled water.

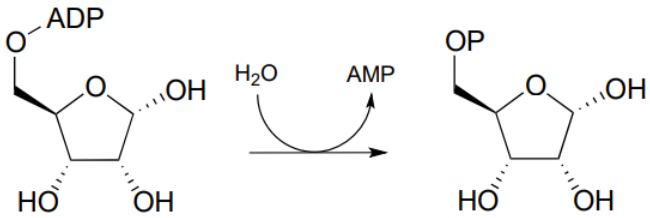


a. The researchers concluded that the reaction was not a phosphate group transfer. Explain their reasoning.
b. Draw the products that would be expected if the reaction actually did proceed by a phosphate transfer mechanism (be sure to show stereochemistry and the location of the ^{18}O atom).

P9.8: The reaction below proceeds with a direct attack by a water molecule on the substrate, but the hydrolysis could be expected to proceed through two possible mechanisms. Draw two possible mechanisms for the reaction run in $H_2^{18}O$. Trace the progress of

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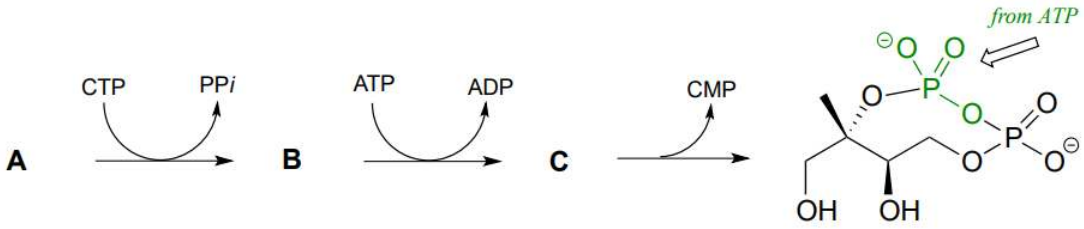
the ^{18}O 'label' throughout each mechanism to see where it ends up: this should indicate to you how the two mechanisms could be (and in fact were!) distinguished experimentally.



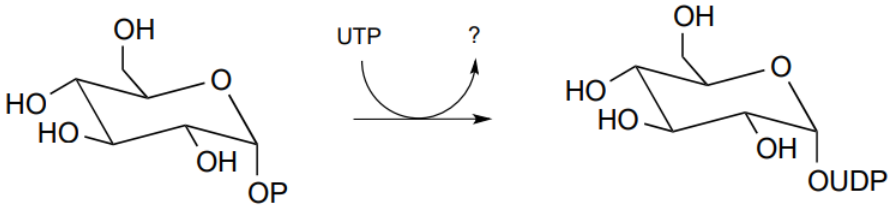
P9.9: Glucose-6-phosphate is dephosphorylated to glucose in the last step of the gluconeogenesis pathway (EC 5.3.1.9). The reaction is not a direct hydrolysis: like the phosphotyrosine phosphatase reaction we saw in this chapter it involves formation of a phosphoenzyme intermediate, but in this case the enzyme residue acting as the initial phosphate acceptor is an active site histidine rather than an asparate. Given this information, propose a likely mechanism for the reaction.

P9.10: (This question assumes a basic knowledge of DNA structure and the idea of supercoiling). DNA topoisomerase enzymes catalyze the temporary 'nicking' of one strand of double-stranded DNA, which allows supercoiled DNA to 'unwind' before the nicked strand is re-ligated. During the unwinding process, the 5' end of the nicked strand is transferred to a tyrosine in the enzyme's active site, effectively holding it in place while the 3' end rotates. Overall, the stereochemical configuration of the bridging phosphate is retained. Propose a likely mechanism for this nicking and re-ligating process. (Biochemistry 2005, 44, 11476.)

P9.11: Pictured below is a series of phosphate group transfer steps in the early part of isoprenoid biosynthesis in bacteria. With the knowledge that the atoms in green are derived from ATP, predict the structures of compounds A, B and C.

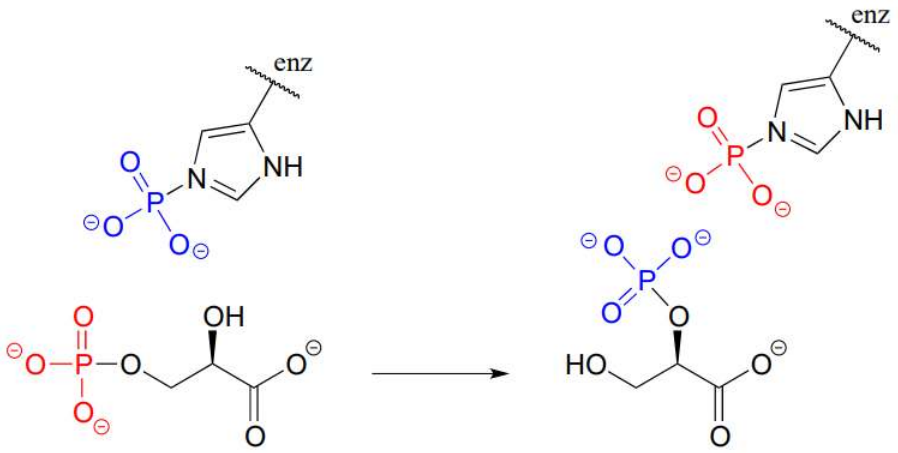


P9.12: The reaction below shows the synthesis of glucose-UDP, an important intermediate in carbohydrate biosynthesis. Notice that UTP (instead of ATP) is the phosphate donor. Identify the by-product denoted below by a question mark.

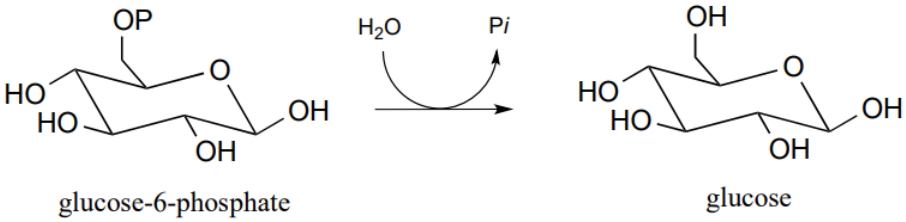


P9.13: Isomerization of 3-phosphoglycerate to 2-phosphoglycerate (EC 5.4.2.1, a reaction in glycolysis) has been shown to occur with the participation of a phosphohistidine residue in the enzyme's active site. The two phosphate groups are distinguished in the figure below by color. With this information, propose a mechanism for the reaction.

https://chem.libretexts.org/@go/page/393551



P9.14: The gluconeogenesis (sugar-building) pathway enzyme glucose-6-phosphatase catalyzes an indirect phosphate hydrolysis reaction with a phosphohistidine intermediate ('indirect hydrolysis' in this context means that a water molecule does not directly attack glucose-6-phosphate).



Researchers wanted to confirm that the hydrolysis in this reaction is indirect, rather than direct. It turns out that the same enzyme is also capable of catalyzing the transfer of the phosphate group from glucose-6-phosphate to the hydroxyl group on carbon #6 of another glucose molecule (instead of to water, which is the natural reaction). The enzyme-catalyzed transfer of phosphate between two glucose substrates is reversible.

The researchers incubated the enzyme with labeled glucose-6-phosphate, in which in the phosphate center was chiral (with the R configuration) due to the incorporation of ^{17}O and ^{18}O isotopes. They also included a high concentration of glucose in the reaction mixture, which ensured that the glucose-to-glucose transfer reaction predominated and hydrolysis (the 'natural' reaction) did not take place. After allowing the reaction to reach equilibrium, they isolated the glucose-6-phosphate and looked at the configuration of the phosphate group.

Given what you have just learned about the enzyme mechanism, predict what the researchers found in this experiment, explain your prediction, and draw the appropriate structure(s), including stereochemistry. Assume that the glucose-to-glucose mechanism is identical to the hydrolysis mechanism, aside from the identity of the ultimate phosphate acceptor.

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9.S: Phosphate Transfer Reactions (Summary)

All of the reactions detailed in this chapter involved the transfer of a phosphate group - usually a phosphate, diphosphate, or AMP group - from one molecule (the donor) to another (the acceptor). Your learning goal for this chapter is to recognize and understand what is happening in these phosphate group transfer reactions, and to gain a basic understanding of the chemistry of phosphate and other phosphate groups.

Be sure that you can identify and provide examples of the following terms:

inorganic phosphate	organic triphosphate
inorganic phosphate	phosphate (mono)ester
inorganic pyrophosphate	phosphate diester
organic (mono)phosphate	phosphate anhydride
organic diphosphate	bridging/non-bridging oxygen

- Also, make sure that you can recognize and use appropriately the various abbreviations introduced in this chapter:

P_i PP_i $R-OP$

$R-OPP$ $R-OAMP$ ATP

ADP AMP

. . . in addition to the various structural abbreviations for adenosine mono-, di-, and triphosphate.

- You should know the approximate pK_a values for phosphoric acid and an organic monophosphate, and be able to state the approximate net charge (to the nearest 0.5 charge unit) of these species in buffers of different pH levels.
- You should be able to describe, in words and pictures, the tetrahedral sp3d bonding picture for the phosphorus atom of a phosphate group. Even though the geometry is not always shown in every drawing, always keep in mind that the phosphate group is tetrahedral.
- You should be able to draw resonance contributors for different phosphate groups, identify major versus minor contributors, and explain why some are major and some are minor. Remember - charges are shared between non-bridging oxygens, even if they are not drawn that way!
- ***Absolutely critical to your success with this chapter is being able to picture and illustrate the mechanistic pattern which we refer to as a phosphate group transfer.***
- Though not usually included in reaction illustrations, always remember that charge-charge interactions with magnesium ions and hydrogen bonds to active site amino acids both serve to increase the electrophilicity of a phosphorus atom in donor compounds such as ATP.
- You should understand the distinctions between the three mechanistic models for phosphate transfer reactions - concerted, addition-elimination, and elimination-addition - and know that the concerted model probably most closely describes biochemical reactions.
- You should be able to identify the apical and equatorial positions in the pentavalent transition state of a phosphate transfer reaction, and recognize that the reaction results in inversion at the phosphorus center.
- You should be able to identify the a, b, and g phosphate groups of ATP, as well as the ribose and adenosine parts of the molecule.
- You should be able to explain how ATP acts as a phosphate group donor, and why such reactions are thermodynamically favorable.
- You should be able to draw a curved-arrow mechanism for reactions in which ATP acts as a phosphate group donor in the phosphorylation and/or diphosphorylation of an alcohol. You should be able to predict the result of nucleophilic attack at the α, β, or γ phosphates of ATP.
- In general, you should be able to propose a likely mechanism for any phosphate transfer reaction, given the starting compounds and products.

- Given information about the existence of a covalently linked enzyme-substrate complex in an enzyme mechanism, you should be able to propose a likely mechanism that accounts for such an intermediate. For example, after being told that the phosphotyrosine phosphatase reaction involves a phosphocysteine intermediate, you should be able to propose a mechanism.

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CHAPTER OVERVIEW

10: Nucleophilic Carbonyl Addition Reactions

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10.2: Hemiacetals, Hemiketals, and Hydrates
10.3: Acetals and Ketals
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10.0: Prelude to Nucleophilic Carbonyl Addition Reactions

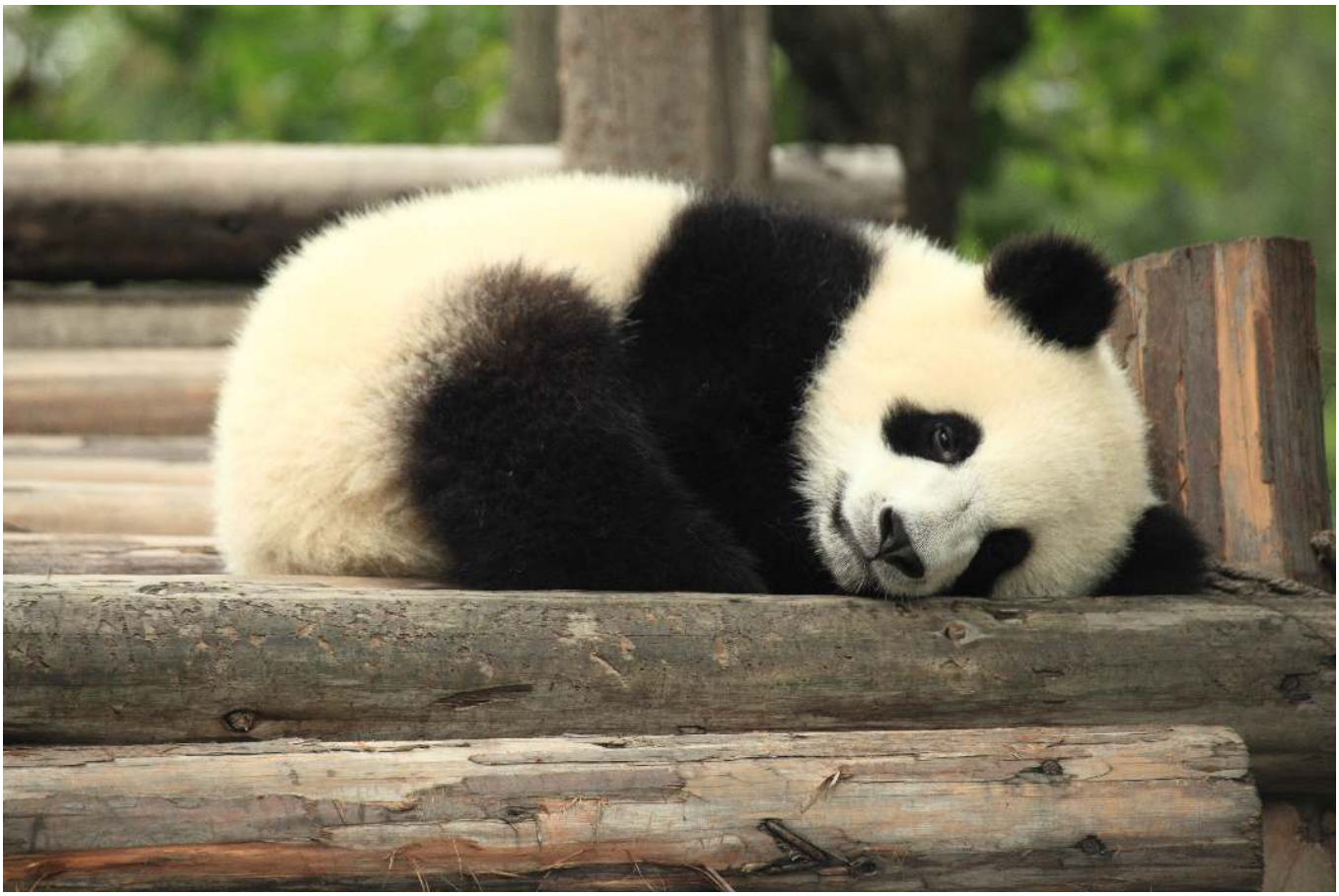


Figure 10.1.1 : Panda (photo credit: https://www.flickr.com/photos/gzlu/)

Introduction

It's possible that the fuel for the car you drive thirty years from now will come from the back end of a panda. Not literally, of course – but it just might turn out that future biofuel technology will be derived in part from the stuff that workers have to clean out of the enclosure housing Ya Ya and Le Le, the two resident pandas at the Memphis Zoo in . At least, that's the hope of Dr. Ashli Brown, a biochemistry professor at Tennessee State University.

First, a little background. If you are like most people in the United States, you are already burning ethanol every time you drive: in 2012, the U.S. Department of Energy reports that over 13 million gallons of ethanol were sold at gas stations nationwide, most often as a 10% mixture along with 90% conventional gasoline. The ethanol we burn today is made by fermenting the sugars present in edible corn. The use of corn ethanol, while a significant step forward in the effort to move away from petroleum fuels and towards carbon-neutral, renewable energy sources, is far from a permanent, sustainable solution to the world's ever-increasing energy needs. Growing corn crops requires a lot of energy and expense, from running the large equipment used to plow and harvest the fields, to manufacturing and applying pesticides and fertilizers, all the way to trucking the corn to the ethanol plant. In fact, some calculation methods suggest that more energy goes into producing a gallon of corn-based ethanol than is released when the ethanol is burned.

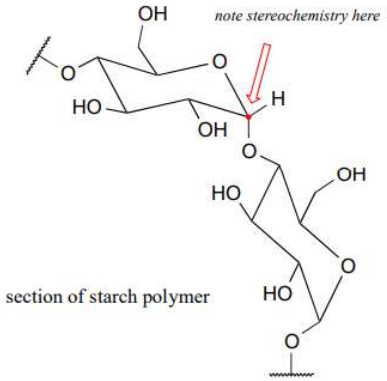
Moreover, growing corn requires a lot of water, and takes up land which otherwise could be used for growing food, or preserved as a natural habitat. A recent study by scientists in South Dakota reported that between 2006 and 2011, a full 1.3 million acres of wetland and prairie were plowed over and converted to biofuel crop production in five midwestern states.

What would be much better in the long run is if we could produce ethanol or other biofuels not from resource-intensive food crops like corn, but from non-edible plant materials: grasses, trees, and agricultural byproducts such as the cobs and stalks from corn

plants. Switchgrass, for example, is a native North American prairie grass that is thought to have high potential for biofuel production.

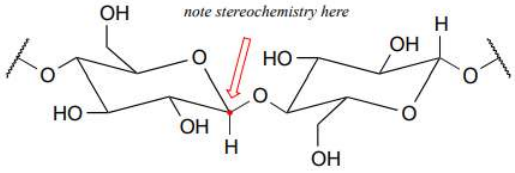
So if we can make ethanol from corn, couldn't we just change over to switchgrass using the same technology?

Unfortunately, it's not nearly that simple. Ethanol is made by 'feeding' glucose to living yeast cells, allowing them to break down the sugar into ethanol – a metabolic process called fermentation. Corn kernels contain sugar in the form of starch, a polysaccharide of linked glucose molecules. Enzymes called 'amylases' are used to break up the starch polymer into individual glucose molecules (as well as two-glucose units called cellobiose), which are then fermented by the yeast.



section of starch polymer

The rest of the corn plant – the stalks, leaves, and cobs – is composed in large part of another glucose polymer called cellulose.



section of cellulose polymer

Cellulose is a major component of plant cell walls, and is the most abundant organic compound on the planet - an enormous source of glucose for fermentation! The problem, from a renewable energy perspective, is how to get at the glucose monomers that make up the polymer. Look closely at the bond connecting two glucose monomers in starch, and then compare it to the same bond in cellulose. They both link the same two carbons of glucose, but with opposite stereochemistry. Recall that enzymes are very sensitive to the stereochemical configuration of their substrate molecules. It should come as no surprise, then, that the amylase enzymes which are so efficient at breaking apart starch are completely ineffective at breaking apart cellulose. Other enzymes, known as cellulases, are needed for this job. These enzymes do exist in nature: just think about what happens to tree branches, leaves, and other cellulose-rich plant matter that lies on the forest floor. These slowly rot away, the cellulose broken apart by cellulase enzymes in microscopic fungi.

The key word here, though, is 'slowly'. Fungi living on the forest floor are not in any great hurry to degrade the leaves and wood around them – the cellulose is not going anywhere. Fungal cellulases are, comparatively speaking, very slow, inefficient enzymes. Herein lies the biggest challenge to the development of economically viable production of ethanol from cellulosic sources such as switchgrass or wood. Breaking the glucose-glucose bonds in cellulose is the main bottleneck in the whole process.

This is where the pandas come in.

Pandas live primarily on a diet of bamboo, obtaining their energy from the cellulose in the plant. Like other plant-eaters such as cows, horses, and sheep, pandas do not make their own cellulase enzymes. Rather, they rely on a diverse population of symbiotic microbes inhabiting their digestive tracts to do the job of cellulose digestion for them. Unlike the microbes living the slow-paced lifestyle of the forest floor, though, the panda's microbes don't have a lot of time to spare - the food is moving through the system pretty quickly. In theory, evolutionary pressure should have resulted in panda-gut microbes with speedy cellulase enzymes, and that

is what Dr. Ashli Brown at Tennessee State was hoping to find as she and her research students analyzed panda feces from the Memphis Zoo. They have had some success: at the fall, 2013 meeting of the American Chemical Society, Dr. Brown announced that her group, working in cooperation with colleagues at the University of Wisconsin, had found over forty cellulose-digesting bacteria, courtesy of Ya Ya and Le Le. The next step is to clone the cellulase- encoding genes, use the DNA to produce recombinant enzyme, and see just how fast they are.

Other less cuddly and photogenic animals are also being studied with similar goals in mind. Dr. Falk Warnecke, working at the U.S. Department of Energy Joint Genome Institute in Northern California, has been investigating the microbes that live in the guts of wood-eating termites, and many other researchers around the world are interested in the symbiotic bugs which inhabit the rumen of cows and sheep.

The problematic chemical reaction catalyzed by cellulase enzymes is, in organic chemistry terminology, an 'acetal hydrolysis'. Acetals are derived from aldehydes. The reactions that occur at the carbonyl carbon of aldehydes and ketones is absolutely central to the chemistry of carbohydrates such as starch and cellulose, and it is this chemistry that is the subject of the chapter we are about to begin.

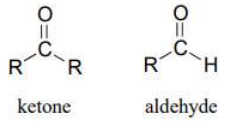
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10.1: Nucleophilic Additions to Aldehydes and Ketones - An Overview

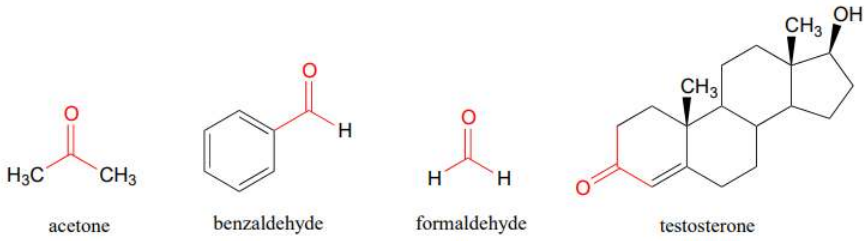
The aldehyde and ketone functional groups

Recall from chapter 1 that the ketone functional group is made up of a carbonyl bonded to two carbons, while in an aldehyde one (or both) of the neighboring atoms is a hydrogen.

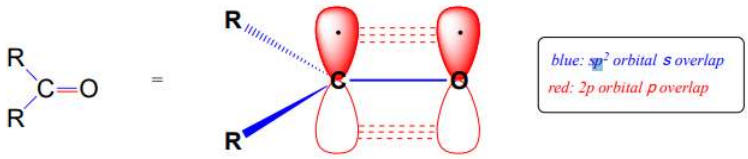


Organic Chemistry With a Biological Emphasis
Tim Soderberg

You probably are familiar with the examples shown below: acetone, the simplest ketone compound, is the solvent in nail polish remover, benzaldehyde is the flavoring in maraschino cherries, and formaldehyde (a special case in which the carbonyl carbon is bonded to hydrogens on both sides) is the nasty-smelling stuff that was used to preserve the unlucky frog that you dissected in high school biology class. The male sex hormone testosterone contains a ketone group in addition to alcohol and alkene groups.

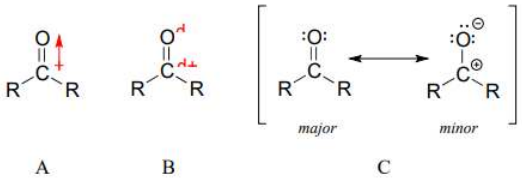


Recall from chapter 2 the bonding picture in a ketone or aldehyde: the carbonyl carbon is sp^2 hybridized, with its three trigonal planar sp^2 orbitals forming s bonds with orbitals on the oxygen and on the two carbon or hydrogen atoms. The remaining unhybridized $2p$ orbital is perpendicular to the plane formed by the sp^2 orbitals, and forms a p bond through a side-by-side overlap with a $2p$ orbital on the oxygen. The s and p bonds between the carbon and oxygen combine to make the $C=O$ double bond that defines the carbonyl functionality.



Nucleophilic addition

The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen end of the bond and lower on the carbon end. Recall that bond polarity can be depicted with a dipole arrow (A in the figure below), or by showing the oxygen as bearing a partial negative charge and the carbonyl carbon a partial positive charge (B).

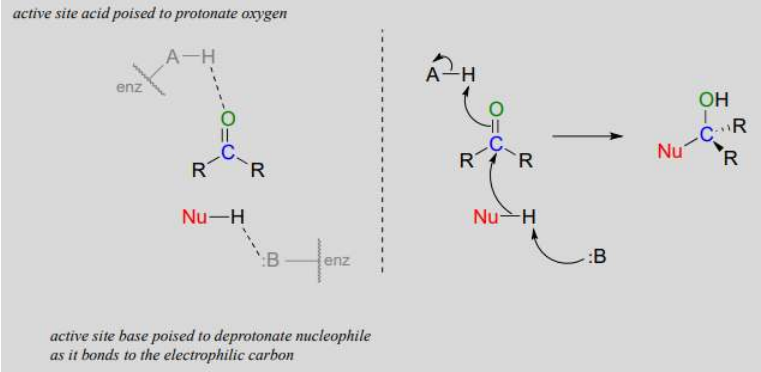


A third way to illustrate the carbon-oxygen dipole (C in the figure above) is to consider the two main resonance contributors: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both

electrons in the p bond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty $2p$ orbital and a full positive charge.

However the bond polarity is depicted, the end result is that the carbonyl carbon is electron-poor - in other words, it is an electrophile. In addition, the trigonal planar geometry means that the carbonyl group is unhindered). Thus, it is an excellent target for attack by an electron-rich nucleophilic group, a mechanistic step called nucleophilic addition:

Nucleophilic addition to an aldehyde or ketone (enzymatic)

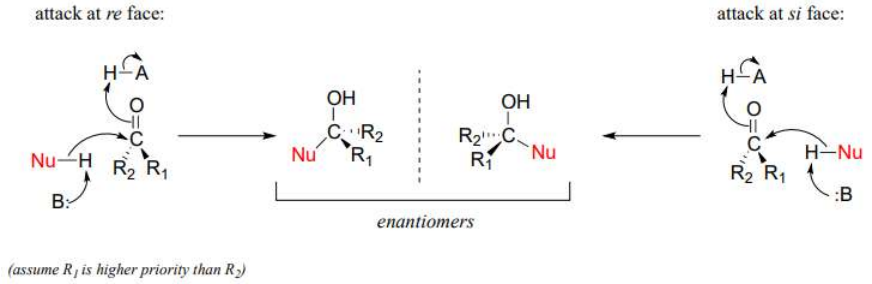


Notice the acid-base catalysis that is going on in this generalize mechanism: in the enzyme active site, a basic group is poised to deprotonate the nucleophile (thus enhancing its nucleophilicity) as begins to attack the carbonyl carbon, while at the same time an acidic proton on another active site group is poised just above the carbonyl oxygen (thus enhancing the electrophilicity of the carbon), ready to protonate the oxygen and neutralize any negative charge that builds up.

Stereochemistry of nucleophilic addition to a carbonyl

Recall from section 3.11B that when the two groups adjacent to a carbonyl are not the same, we can distinguish between the re and si 'faces' of the planar structure.

The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp2 to sp3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from.



If the reaction is catalyzed by an enzyme, the stereochemistry of addition is (as you would expect) tightly controlled, and leads to one stereoisomer exclusively- the nucleophilic and electrophilic substrates are bound in specific positions within the active site, so that attack must occur specifically from one side and not the other. Nonenzymatic reactions of this type often result in a 50:50 mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place. We'll see some examples of this phenomenon soon when we look at cyclic forms of sugar molecules.

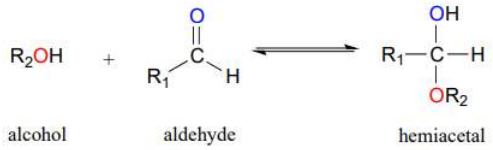
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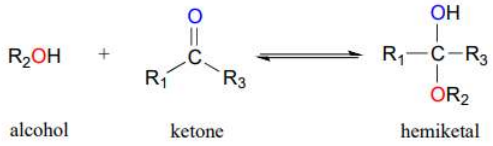
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10.2: Hemiacetals, Hemiketals, and Hydrates

Overview

One of the most important examples of a nucleophilic addition reaction in biochemistry, and in carbohydrate chemistry in particular, is the addition of an alcohol to a ketone or aldehyde. When an alcohol adds to an aldehyde, the result is called a hemiacetal; when an alcohol adds to a ketone the resulting product is a hemiketal.

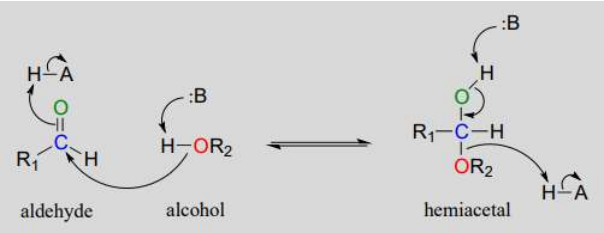




(The prefix ‘hemi’ (half) is used in each term because, as we shall soon see, addition of a second alcohol nucleophile can occur, resulting in species called acetals and ketals.)

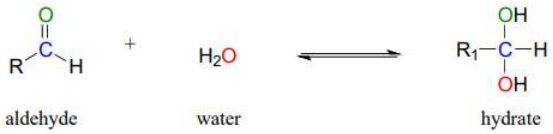
The conversion of an alcohol and aldehyde (or ketone) to a hemiacetal (or hemiketal) is a reversible process. The generalized mechanism for the process at physiological pH is shown below.

Biochemical mechanism of hemiacetal formation:



In general, hemiacetals (and hemiketals) are higher in energy than their aldehyde-alcohol components, so the equilibrium for the reaction lies to the left. As we will soon see in the context of glucose and other sugars, however, five- and six-membered cyclic hemiacetals are considerably lower in energy, and are favored at equilibrium: recall from chapter 3 the inherent stability of five- and six-membered rings.

Aldehydes and ketones, when in aqueous solution, exist in equilibrium with their hydrate form. A hydrate forms as the result of a water molecule adding to the carbonyl carbon of the aldehyde or ketone.

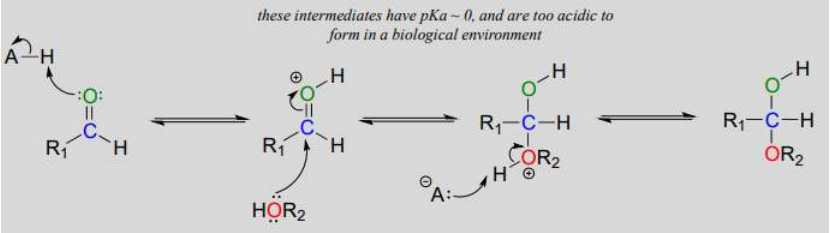


Although you should be aware that aldehyde and ketone groups may exist to a considerable extent in their hydrated forms when in aqueous solution (depending upon their structure), they are usually drawn in their non-hydrated form for the sake of simplicity.

The mechanism we just saw for hemiacetal formation applies to biochemical reactions occurring at physiological ***pH***. In the organic laboratory, however, hemiacetal and hemiketal formation usually takes place in the presence of a strong acid. The acid catalyzes the reaction by protonating the carbonyl oxygen, thus increasing the electrophilicity of the carbonyl carbon. Notice in the

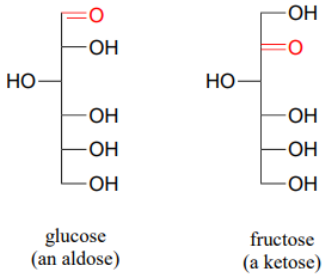
mechanism below that highly acidic intermediates are drawn which would be unreasonable to propose for the corresponding biochemical mechanisms occurring at physiological ***pH***.

Acid-catalyzed hemiacetal formation (non-biological):



Sugars as intramolecular hemiacetals and hemiketals

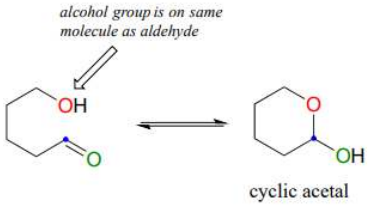
As stated above, the reactions of hemiacetals and hemiketals are central to the chemistry of carbohydrates. Recall that sugar molecules generally contain either an aldehyde or a ketone functional group, in addition to multiple alcohol groups. Aldehyde sugars are often referred to as aldoses; ketone sugars as ketoses. For example, glucose is an aldose, and fructose is a ketose - their structures are drawn below in Fischer projection:



? Exercise 10.3.1

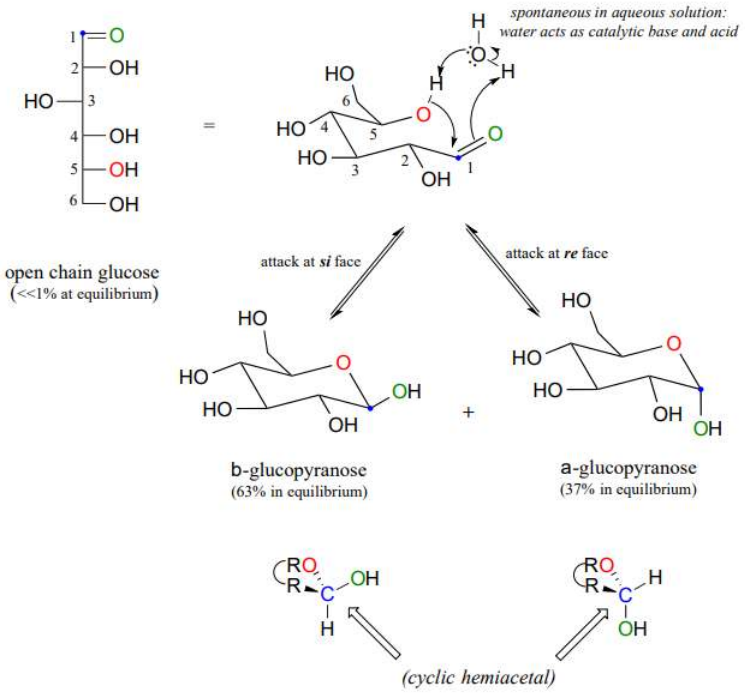
What term describes the relationship between glucose and fructose (in other words, what kind of isomers are they)?

Glucose and fructose are shown above in their open-chain form. However, recall from section 1.3 that in aqueous solution, glucose, fructose, and other sugars of five or six carbons rapidly interconvert between straight-chain and cyclic forms. This occurs through the formation of intramolecular hemiacetals and hemiketals. This simply means that the 'R' group of the alcohol is already covalently attached to the 'R 'group of the aldehyde (R1 in our general mechanism).



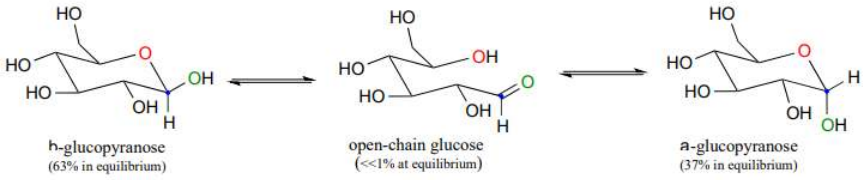
Unlike most of the biochemical reactions you will see in this text, sugar cyclization reactions are not catalyzed by enzymes: they occur spontaneously and reversibly in aqueous solution. For most five- and six-carbon sugars, the cyclic forms predominate in equilibrium.

The cyclic form of glucose is a six-membered ring, with an intramolecular hemiacetal formed by attack of the hydroxl on carbon #5 to the aldehyde carbon (carbon #1, also called the anomeric carbon in carbohydrate terminology).



The cyclic form of glucose is called glucopyranose. As was discussed above, nucleophilic attack on a planar carbonyl group can occur at either face of the plane, leading to two different stereochemical outcomes - in this case, to two different diastereomers. In carbohydrate nomenclature, these two diastereomers are referred to as the a and b anomers of glucopyranose.

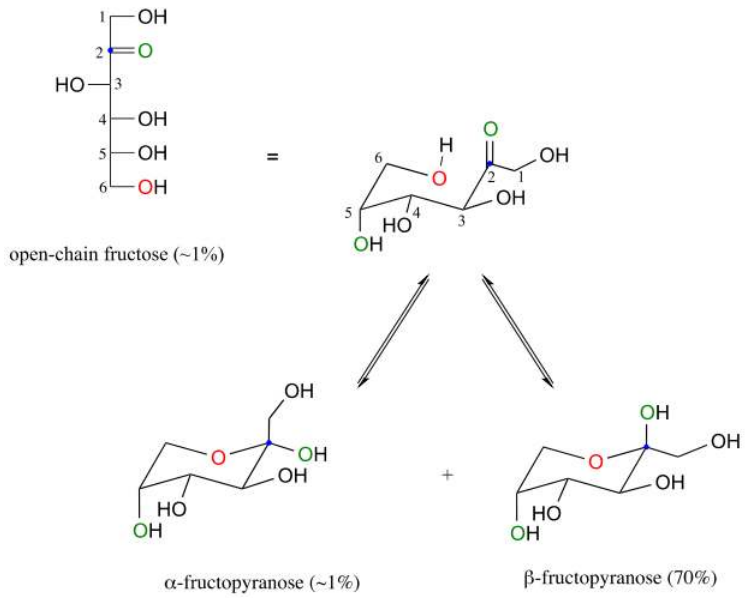
Because the formation of glucopyranose occurs spontaneously without enzyme catalysis, shouldn't equal amounts of these two anomers form? In fact, this does not happen: there is almost twice as much of one anomer than the other at equilibrium. Why is this? Remember (section 3.2) that six-membered rings exist predominantly in the chair conformation, and that the lower energy chair conformation is that in which unfavorable interactions between substituents are minimized – in most cases, this is the conformation in which larger substituents are in the equatorial position. In the lower-energy chair conformation of the major b anomer of glucopyranose, all of the hydroxyl groups are in the equatorial position, but in the minor a anomer one hydroxyl group is forced into the axial position. As a result, the a anomer is higher in energy, and less abundant at equilibrium.



? Exercise 10.3.2

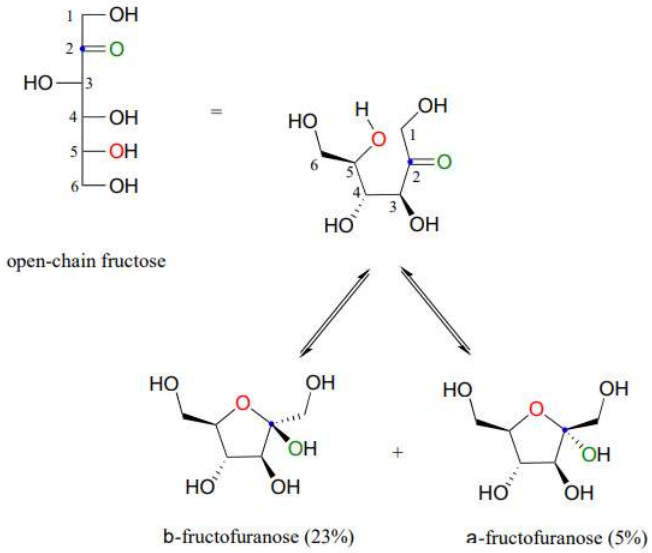
Draw a mechanism for the conversion of a-glucopyranose to open-chain glucose.

Fructose in aqueous solution forms a six-membered cyclic hemiketal called fructopyranose when the hydroxyl oxygen on carbon #6 attacks the ketone carbon (carbon #2, the anomeric carbon in fructose).



In this case, the b anomer is heavily favored in equilibrium by a ratio of 70:1, because in the minor a anomer the bulkier CH_2OH group occupies an axial position.

Notice in the above figure that the percentages of α and β anomers present at equilibrium do not add up to 100%. Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as fructofuranose. In the formation of fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.



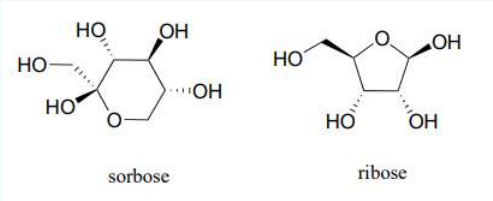
In aqueous solution, then, fructose exists as an equilibrium mixture of 70% β-fructopyranose, 23% β-fructofuranose, and smaller percentages of the open chain and cyclic α-anomers. The β-pyranose form of fructose is one of the sweetest compounds known, and is the main component of high-fructose corn syrup. The β-furanose form is much less sweet.

Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chais and cyclic hemiacetals and hemiketals. Shorter monosaccharides are unlikely to undergo analogous ring-forming reactions, however, due to the inherent instability of three and four-membered rings.

? Exercise 10.3.3

a. Identify the anomeric carbon of each of the sugars shown below, and specify whether the structure shown is a hemiacetal or hemiketal.

b. Draw mechanisms for cyclization of the open-chain forms to the cyclic forms shown.



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10.3: Acetals and Ketals

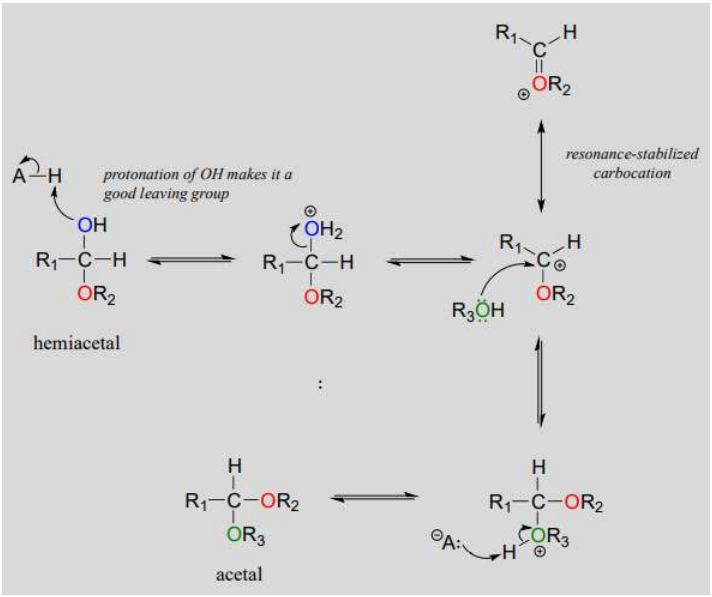
Overview

Hemiacetals and hemiketals can react with a second alcohol nucleophile to form an acetal or ketal. The second alcohol may be the same as the first (ie. if $R_2 = R_3$ in the scheme below), or different.



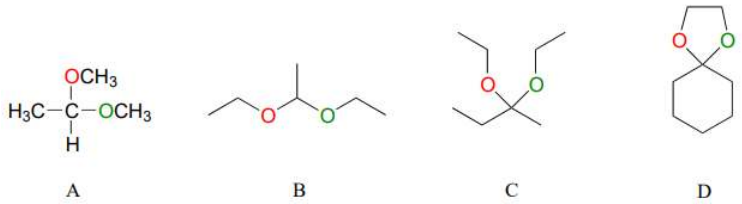
Although we focus here on biological reactions, it is instructive in this case to consider non-biological acetal-forming reactions before we look at their biochemical counterparts. In a non-enzymatic context, acetal/ketal formation - just like hemiacetal/hemiketal formation - is generally catalyzed by a strong acid.

Acid-catalyzed acetal formation (non-biological)



The role of the acid catalyst is to protonate the OH group of the acetal, thus making it a good leaving group (water). Notice something important here: the conversion of a hemiacetal to an acetal is simply an S_N1 reaction, with an alcohol nucleophile and water leaving group. The carbocation intermediate in this S_N1 mechanism is stabilized by resonance due to the oxygen atom already bound to the electrophilic carbon.

Below are some examples of simple, non-biological acetal and ketals.

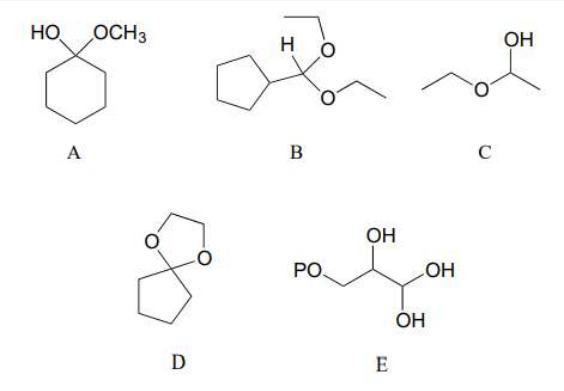


? Exercise 10.4.1

For each acetal/ketal A-D in the figure above, specify the required aldehyde/ketone and alcohol starting materials.

Exercise 10.4.2

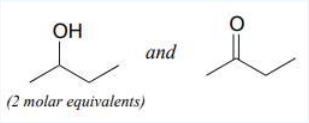
Categorize each of the following molecules as a hemiacetal, hemiketal, acetal, ketal, hydrate of an aldehyde, or hydrate of a ketone.



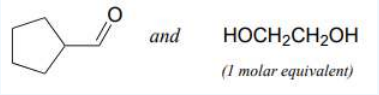
Exercise 10.4.3

Specify the acetal/ketal that would form from a reaction between the given starting compounds.

a.



b.

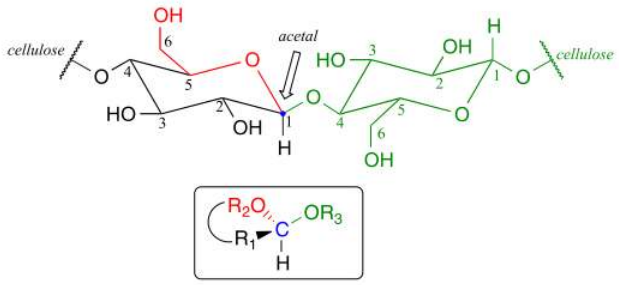


Exercise 10.4.4

Specify the aldehyde/ketone and alcohol combination that would be required to form the compounds in exercise 10.5.

Glycosidic bond formation

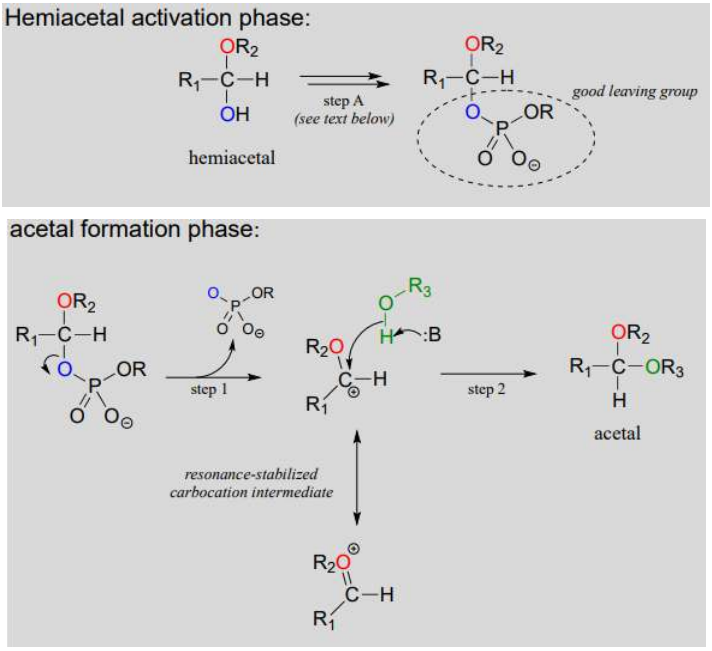
Now, let's consider acetal formation in a biochemical context. A very important example of the acetal/ketal group in biochemistry is the glycosidic bonds which link individual sugar monomers to form polysaccharides (see section 1.3 for a quick review). Look at the glycosidic bond between two glucose monomers in a cellulase chain:



If you look carefully, you should recognize that carbon #1, the anomeric carbon on the left-side glucose monomer, is the central carbon of an acetal group. Biochemists refer to this as a b-1,4 linkage, because the stereochemistry at carbon #1 is b in the specialized carbohydrate nomenclature system, and it is linked to carbon #4 of the next glucose on the chain. The vast structural diversity of carbohydrates stems in large part from the different linkages that are possible - both in terms of which two carbons are linked, and also the stereochemistry of the linkage. You will see many more variations of glycosidic bond linkage patterns if you study carbohydrate biochemistry in greater depth.

Reactions in which new glycosidic bonds are formed are catalyzed by enzymes called glycosyltransferases, and in organic chemistry terms these reactions represent the conversion of a hemiacetal to an acetal (remember that sugar monomers in their cyclic form are hemiacetals and hemiketals). The mechanism for glycosidic bond formation in a living cell parallels the acid-catalyzed (non-biological) acetal-forming mechanism, with an important difference: rather than being protonated, the ***OH*** group of the hemiacetal is converted to a good leaving group by phosphorylation (this is a pattern that we are familiar with from chapters 9 and 10). The specific identity of the activating phosphate group varies for different reactions, so it is generalized in the figure below.

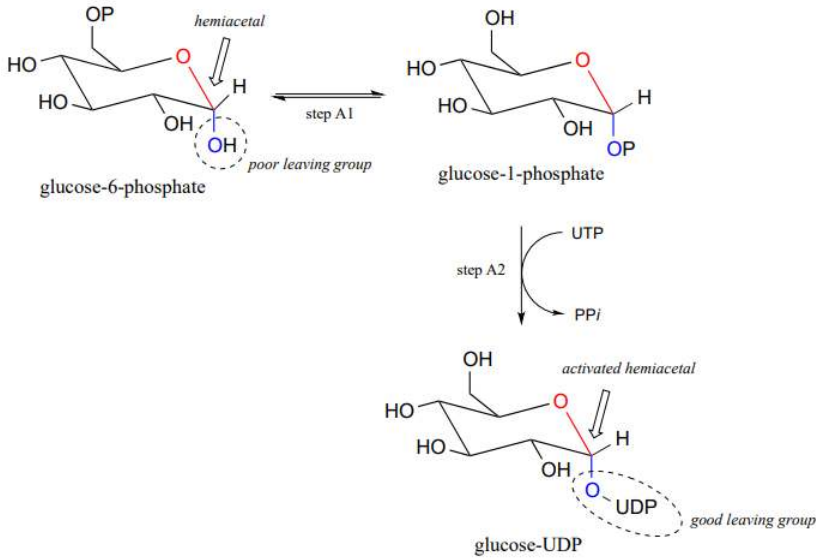
Mechanism for (biochemical) acetal formation:



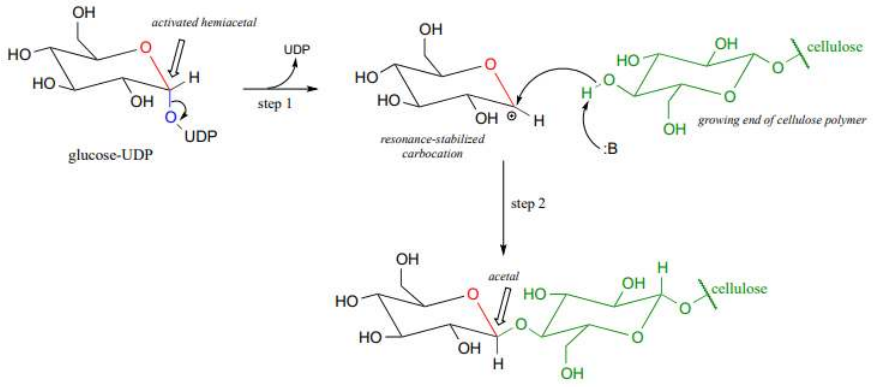
- Step A (Activation phase): This phase of the reaction varies according to the particular case, but always involves phosphate group transfer steps that are familiar from chapter 9. What is most important for our present discussion, however, is simply that the hydroxyl group on the hemiacetal has been activated - ie. made into a good leaving group - by phosphorylation.
- Step 1: Now that the leaving group has been activated, it does its job and leaves, resulting in a resonance stabilized carbocation.
- Step 2: A nucleophilic alcohol on the growing cellulose chain attacks the highly electrophilic carbocation to form an acetal. Here is where the stereochemistry of the new glycosidic bond is determined: depending on the reaction, the alcohol nucleophile could approach from either side of the planar carbocation.

To reiterate: it is important to recognize the familiar S_N1 mechanistic pattern in play here: in step A, a poor leaving group is converted into a good leaving group, in step 1 the leaving group leaves and a stabilized carbocation is left behind, and in step 2 a nucleophile attacks to form a new bond and complete the substitution process. Look back at the S_N1 reactions we saw in chapter 8 if you are having trouble making this mechanistic connection.

Now, let's look specifically at the glycosyl transferase reaction mechanism in which a new glycosidic bond is formed on a growing cellulose chain. Glucose (a hemiacetal) is first activated through two enzymatic phosphate transfer steps: step A1, a phosphate isomerization reaction with a mechanism similar to the reaction in problem P9.13, followed by a UTP-dependent step A2, for which you were invited to propose a mechanism in problem P9.12.

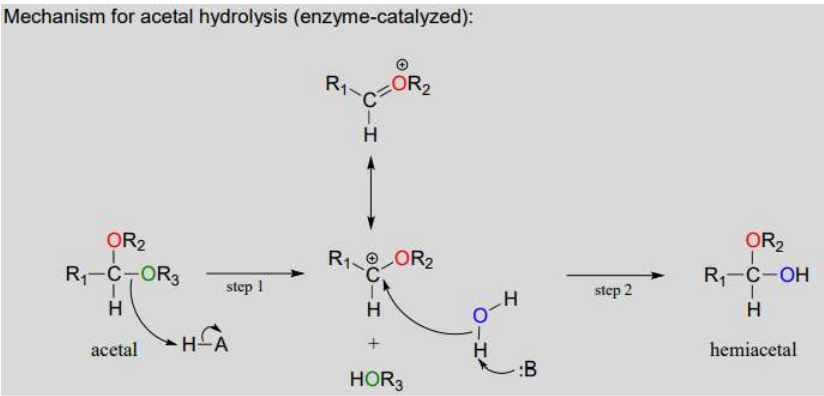


The UDP group on glucose-UDP then leaves (step 1 below), forming a resonance-stabilized carbocation intermediate. Attack by the alcohol group on the growing cellulose chain in step 2 forms the glycosidic (acetal) bond. Note the inversion of stereochemistry.



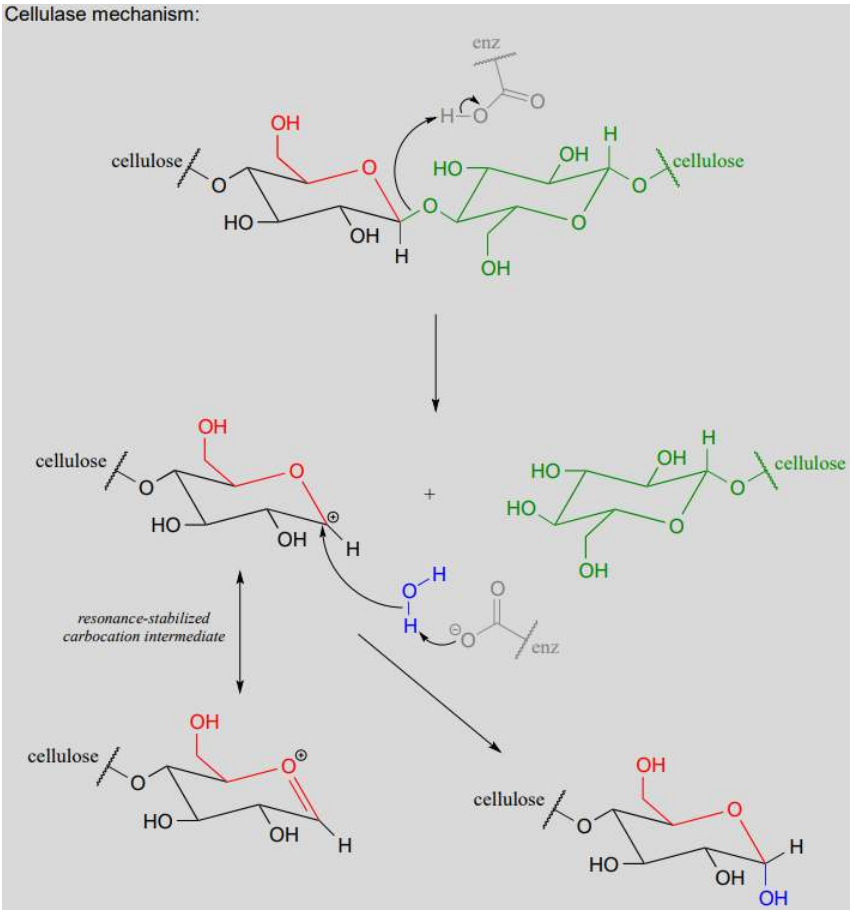
Glycosidic bond hydrolysis

Acetals can be hydrolyzed back to hemiacetals. Notice that an acetal to hemiacetal conversion is an S_N1-type reaction with a water nucleophile and an alcohol leaving group.



In step 1, an alcohol is protonated by a nearby acid group as it breaks away to form a resonance-stabilized carbocation intermediate. The carbocation is attacked by a nucleophilic water molecule in step 2 to form a hemiacetal.

The general mechanism above applies to reactions catalyzed by glycosidase enzymes, which catalyze the cleavage of glycosidic bonds in carbohydrates. In the introduction to this chapter, we learned about ongoing research in the field of cellulosic ethanol. Recall that the main bottleneck in the production of ethanol from sources such as switchgrass or wood is the cellulase-catalyzed step in which the glycosidic bonds in cellulose are cleaved. Cellulose-digesting microbes have several different but closely related forms of cellulase enzymes, all working in concert to cleave cellulose into smaller and smaller pieces until individual glucose molecules are free to be converted to ethanol by the fermentation process. Below is a representative mechanism for a cellulase reaction.



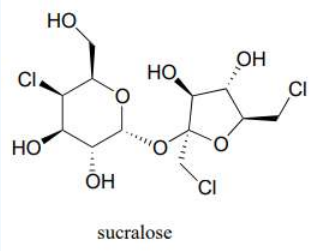
The starch-digesting amylase enzymes used in the corn ethanol production process catalyze similar glycoside hydrolysis reactions, the main difference being the opposite stereochemistry at the anomeric carbon of the substrate.

Exercise 10.4.5

Notice that the cellulose glycososide bond-forming reaction requires the cell to 'spend' a high-energy UTP molecule, but the cellulase glycoside bond-breaking reaction does not. Use your knowledge of chemical thermodynamics to explain this observation.

Exercise 10.4.6

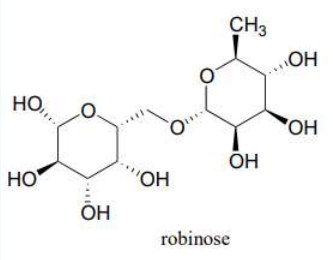
Below is the structure of the artificial sweetener sucralose. Identify the two anomeric carbons in the disaccharide.



sucralose

Exercise 10.4.7

Robinose is a disaccharide found in 'Chenille Plant', a flowering shrub native to the Pacific Islands.



robinose

a. Identify the two anomeric carbons and the glycosidic bond in robinose.
b. Using the same carbon numbering system as for glucose in the earlier figure, fill in in the carbon numbers (#1 through #6) for each of the monosaccharides that make up robinose.
c. Based on what you know of glycosidic bond-forming reactions in nature, propose a reasonable mechanism for the linking of the two monosaccharides, starting with the activated hemiacetal species, assuming that it is a UDP species as in the cellulose gycosidic bond-forming reaction.
d. Draw the open chain form of each of the monosaccharides

Exercise 10.4.8

Look again at the structures of the two-glucose fragments of cellulose and amylose shown the introduction to this chapter. A structural feature of the cellulose polymer makes it inherently more resistant to enzymatic hydrolysis compared to starch. Explain.

Hint

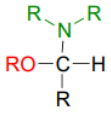
Think about intermolecular interactions.

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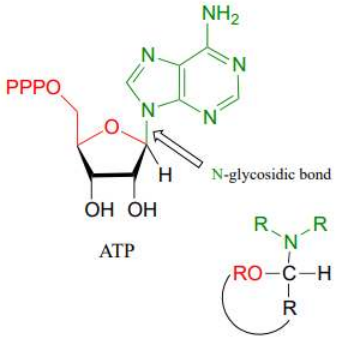
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10.4: N-glycosidic Bonds

We have just seen that when a second alcohol attacks a hemiacetal or hemiketal, the result is an acetal or ketal, with the glycosidic bonds in carbohydrates providing a biochemical example. But if a hemiacetal is attacked not by a second alcohol but by an amine, what results is a kind of 'mixed acetal' in which the anomeric carbon is bonded to one oxygen and one nitrogen.

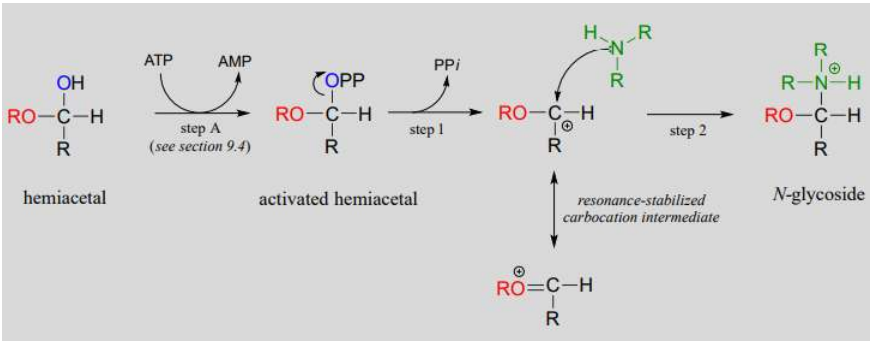


This arrangement is referred to by biochemists as an N-glycosidic bond. You may recognize these as the bonds in nucleosides and nucleotides that link the G, C, A, T, or U base to the sugar.



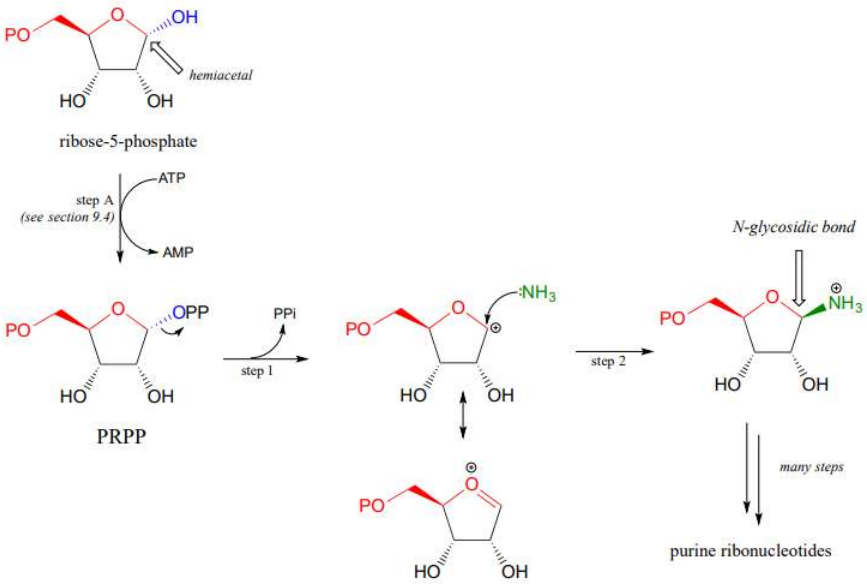
The formation of ***N***-glycosidic bonds in ribonucleotides is closely analogous to the formation of glycosidic bonds in carbohydrates – again, it is an S_N1-like process with an activated water leaving group. Typically, the hemiacetal is activated by diphosphorylation, as illustrated in step A of the general mechanism below.

Mechanism for formation of an ***N***-glycosidic bond:



The starting point for the biosynthesis of purine (G and A) ribonucleotides is a five-carbon sugar called ribose-5-phosphate, which in solution takes the form of a cyclic hemiacetal. The critical ***N***-glycosidic bond is established through substitution of NH_3 for OH at the anomeric carbon of the ribose. The anomeric OH group is first activated (step A below) to form an activated intermediate called phosphoribosylpyrophosphate (PRPP). The inorganic pyrophosphate then leaves to generate a resonance-stabilized carbocation (step 1) which is attacked by a nucleophilic ammonia in step 2 to establish the ***N***-glycosidic bond.

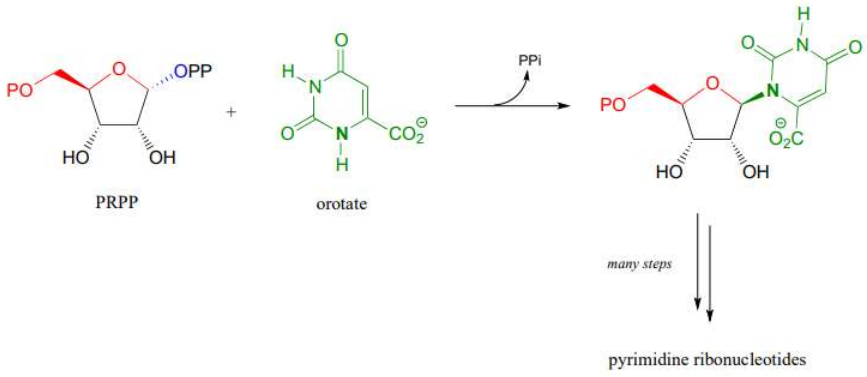
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With the ***N***-glycosidic bond in place, the rest of the purine base is assembled piece by piece by other biosynthetic enzymes.

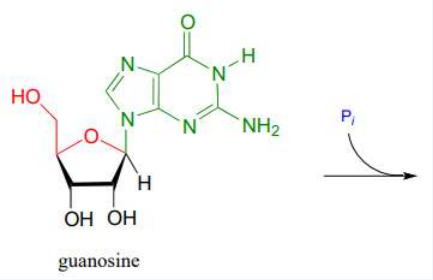
(The mechanism above should look familiar - we saw step A in chapter 9 as an example of alcohol diphosphorylation , and steps 1 and 2 in chapter 8 as an example of a biochemical S_N1 reaction).

Establishment of the ***N***-glycosidic bond in biosynthesis of the pyrimidine ribonucleotides and (U, C and T) also begins with PRPP, but here the ring structure of the nucleotide base part of the biomolecule has already been 'pre-fabricated' in the form of orotate:



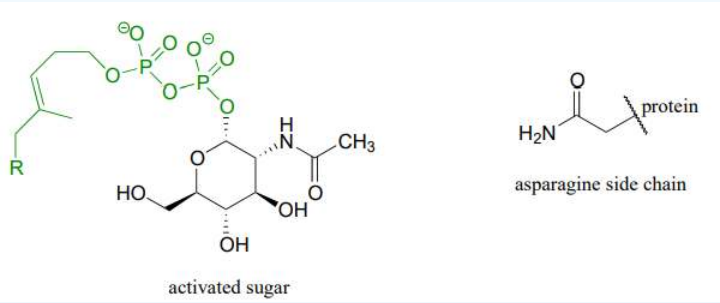
? Exercise 10.5.1

We have just seen an illustration of the formation of an N-glycosidic bond in a biosynthetic pathway. In the catabolic (degradative) direction, an N-glycosidic bond must be broken, in a process which is analogous to the hydrolysis of a glycosidic bond (illustrated earlier). In the catabolism of guanosine nucleoside, the N-glycosidic bond is broken by inorganic phosphate (not water!) apparently in a concerted (SN2-like) displacement reaction (Biochemistry 2011, 50, 9158). Predict the products of this reaction, and draw a likely mechanism.



Exercise 10.5.2

Glycoproteins are proteins that are linked, by glycosidic or *N*-glycosidic bonds, to sugars or carbohydrates through an asparagine, serine, or threonine side chain on the protein. As in other glycosylation and *N*-glycosylation reactions, the hemiacetal of the sugar must be activated prior to glycosidic bond formation. Below is the structure of the *activated* sugar hemiacetal substrate in an asparagine glycosylation reaction



Draw the product of the asparagine glycosylation reaction, assuming inversion of configuration of the anomeric carbon.

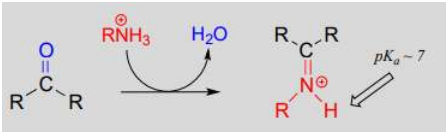
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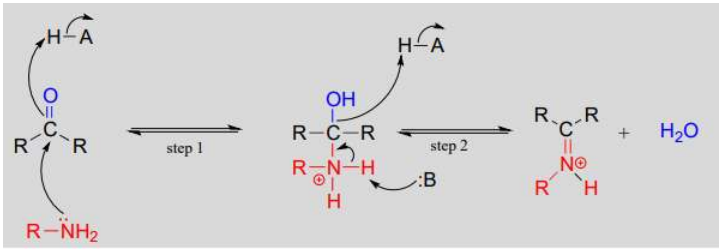
10.5: Imines

The electrophilic carbon atom of aldehydes and ketones can be the target of nucleophilic attack by amines as well as alcohols. The end result of attack by an amine nucleophile is a functional group in which the C=O double bond is replaced by a C=N double bond, and is known as an imine. (An equivalent term is 'Schiff base', but we will use 'imine' throughout this book). Recall from section 7.5B that imines have a pKa of approximately 7, so at physiological pH they can be accurately drawn as either protonated (iminium ion form) or neutral (imine).

Iminium ion formation:



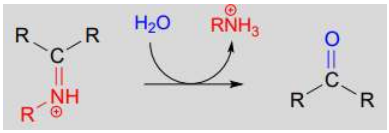
Mechanism (enzymatic):



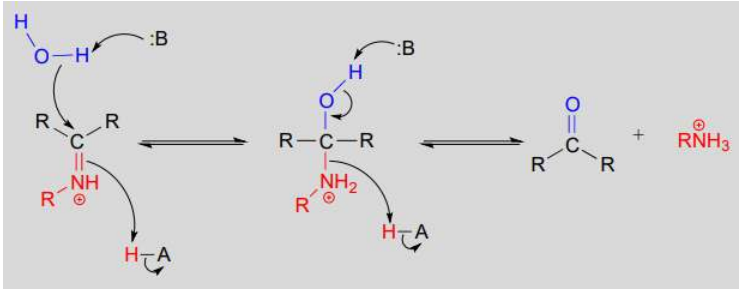
Mechanistically, the formation of an imine involves two steps. First, the amine nitrogen attacks the carbonyl carbon in a nucleophilic addition step (step 1) which is closely analogous to hemiacetal and hemiketal formation. Based on your knowledge of the mechanism of acetal and ketal formation, you might expect that the next step would be attack by a second amine to form a compound with a carbon bound to two amine groups – the nitrogen version of a ketal or acetal. Instead, what happens next (step 2 above) is that the nitrogen lone pair electrons 'push' the oxygen off of the carbon, forming a $C = N$ double bond (an iminium) and a displaced water molecule.

The conversion of an iminium back to an aldehyde or ketone is a hydrolytic process (bonds are broken by a water molecule), and mechanistically is simply the reverse of iminiom formation:

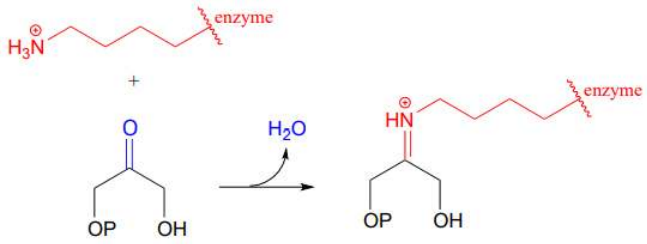
Hydrolysis of an iminium ion:



Mechanism (enzymatic):

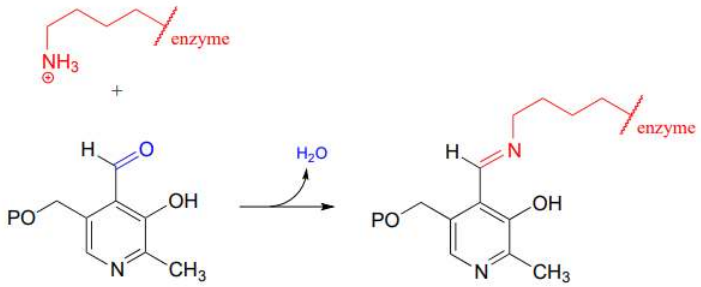


Carbon-carbon bond forming enzymes called aldolases (which we'll cover in detail in chapter 12) often form iminium links between a carbonyl carbon on a substrate and a lysine residue from the active site of the enzyme, as in this aldolase reaction from the Calvin Cycle:

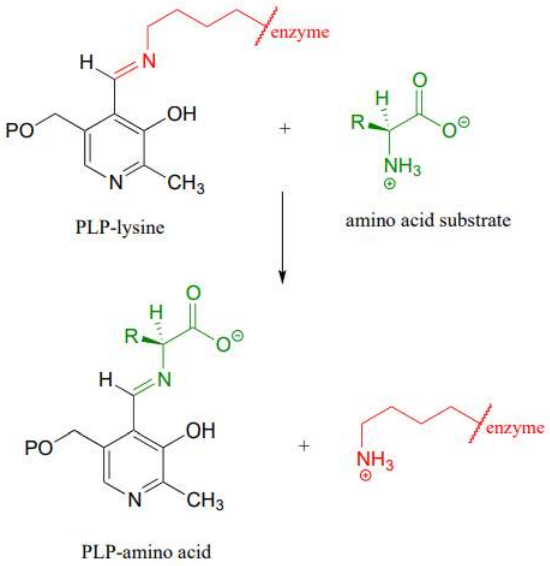


After the carbon-carbon bond forming part of an aldolase reaction is completed, the iminium linkage is hydrolyzed, freeing the product so that it can diffuse out of the active site and allow another catalytic cycle to begin.

In chapter 17, we will learn about reactions that are dependent upon a coenzyme called pyridoxal phosphate (***PLP***), also known as vitamin ***B6***. In these reactions, the aldehyde carbon of ***PLP*** links to an enzymatic lysine in the active site:

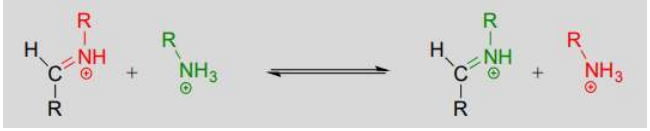


Then, the ***PLP***-lysine imine linkage is traded for an imine linkage between ***PLP*** and the amino group on the substrate, in what can be referred to as a transimination.

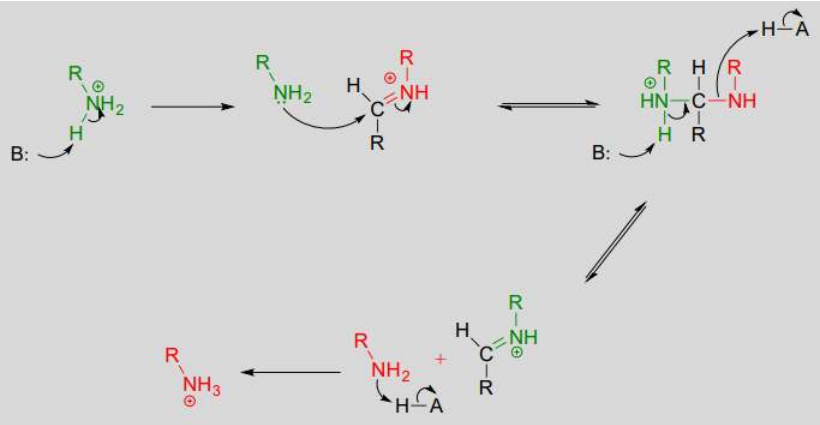


The mechanism for a transimination is very similar to that of imine formation:

Transimination reaction:



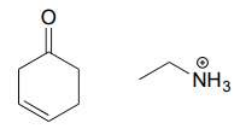
Mechanism:



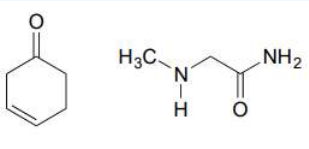
Exercise 10.6.1

Draw an imine that could be formed between each pair of compounds.

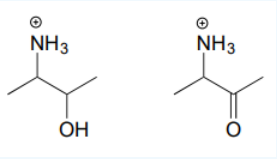
a.



b.

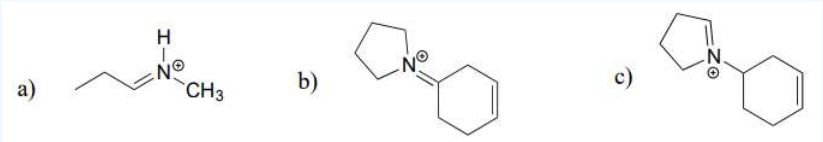


c.



Exercise 10.6.2

Draw the imminium hydrolysis product for each of the following compounds.

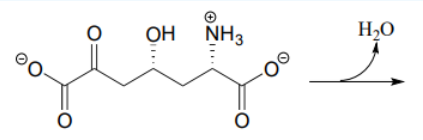


Answer

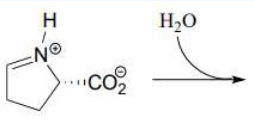
Add answer text here and it will automatically be hidden if you have a "AutoNum" template active on the page.

Exercise 10.6.3

a. The metabolic intermediate shown below undergoes an intramolecular imine formation as a step in the biosynthesis of lysine (EC 4.3.3.7). Draw the product of this intramolecular imine formation step.



b. Predict the product of this iminium hydrolysis step (EC 2.3.1.117) from the proline degradation pathway.

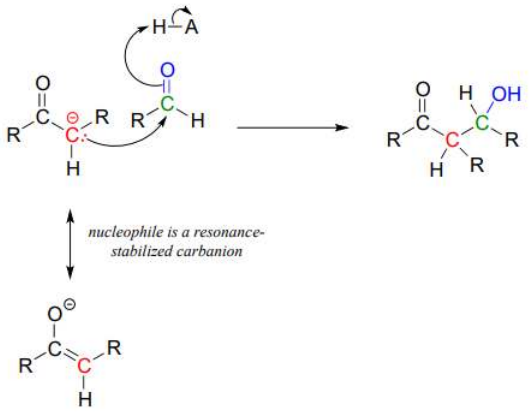


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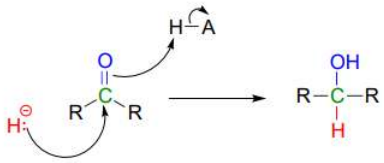
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10.6: A Look Ahead - Addition of Carbon and Hydride Nucleophiles to Carbonyls

We have seen in this chapter a number of reactions in which oxygen and nitrogen nucleophiles add to carbonyl groups. Other nucleophiles are possible in carbonyl addition mechanisms: in chapters 12 and 13, for example, we will examine in detail some enzyme-catalyzed reactions where the attacking nucleophile is a resonance stabilized carbanion (usually an enolate ion):



Then in chapter 15, we will see how the carbonyl groups on aldehydes and ketones can be converted to alcohols through the nucleophilic addition of what is essentially a hydride (H^-) ion.



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10.E: Nucleophilic Carbonyl Addition Reactions (Exercises)

P10.1: Draw a mechanism showing the formation of an imine linkage between a lysine side chain and a-ketobutyrate (this is the first step in the degradation of lysine, EC 1.5.1.8).

P10.2: Draw four possible cyclic hemiketal isomers of the compound below.

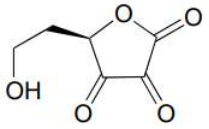
P10.3: A downstream intermediate in the lysine degradation pathway undergoes imine hydrolysis to release two amino acid products (EC 1.5.1.1). Draw a mechanism for this hydrolysis reaction, and show the structures of the two products formed.

P10.4: Below is the structure of lactose, the sugar found in dairy products.

Lactose is a disaccharide of galactose and glucose. People who are lactose intolerant do not produce enough lactase - the enzyme that hydrolyzes the glycosidic bond linking the two monosaccharides - to be able to fully digest dairy products.

a. Draw a likely stabilized carbocation intermediate in the hydrolysis reaction catalyzed by lactase.
b. Draw, in the chair conformation, the structure of what you predict would be the most abundant form of the galactose monosaccharide in aqueous solution.
c. Is galactose an aldose or a ketose?
d. Draw, showing sterochemistry, the open-chain form of galactose.

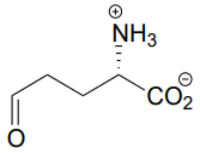
P10.5: You probably know that ascorbic acid (vitamin C) acts as an antioxidant in the body. When vitamin C does its job, it ends up being oxidized to dehydroascobate, which is usually drawn as shown below, in the so-called tricarbonyl form.



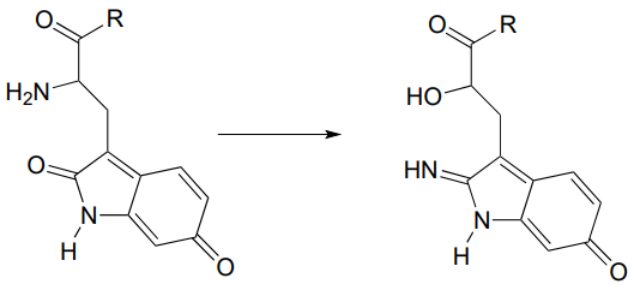
dehydroascorbate
(tricarbonyl form)

Evidence suggests, however, that the most important form of dehydroascorbate in a physiological context is one in which one of the ketone groups is in its hydrated form, and the other is an intramolecular hemiketal (see Chemical and Engineering News, Aug. 25, 2008, p. 36). Show the structure of this form of dehydroascorbic acid.

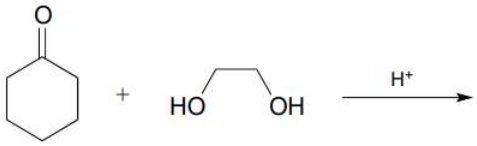
P10.6: The compound below is the product of a ring-opening imine hydrolysis step in the degradation pathway for proline, one of the amino acids. Draw the structure of the starting compound.



P10.7: The rearrangement below was proposed to proceed via imine formation followed by nucleophilic substitution. Propose a mechanism that fits this description. (J. Biol. Chem. 280, 12858, scheme 2 part 2) .

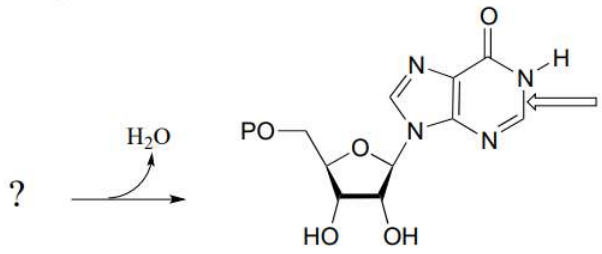


P10.8: The biochemical acetal-forming reactions we learned about in this chapter all require activation of the hemiacetal through phosphorylation. In the organic synthesis lab, non-enzymatic acetal-forming reactions are carried out with a catalytic amount of strong acid, which serves to activate the hemiacetal. Predict the product of the following acetal forming reaction, and propose a reasonable mechanism for the reaction. Remember that the reaction is carried out under acidic conditions, which means that the protonation state of intermediates will be different than biochemical reactions occurring at neutral ***pH***.



Problems 9-15 all involve variations on, and combinations of, the nucleophilic addition steps that we studied in this chapter. Although the reactants and/or products may look somewhat different from the simpler aldehydes, acetals, imines, etc. that we used as examples in the chapter, the key steps still involve essentially the same mechanistic patterns. Before attempting these problems, you may want to review tautomerization reactions in section 7.6.

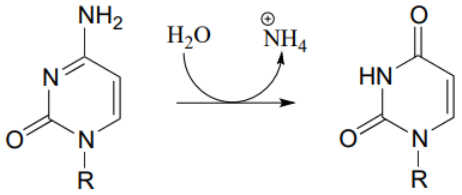
P10.9: The final step in the biosynthesis of inosine monophosphate (IMP, a precursor to both AMP and GMP), is a ring-closing reaction in which a new nitrogen-carbon bond (indicated by an arrow in the structure below) is formed. Predict the starting substrate for this reaction, and propose a mechanism that involves a slight variation on typical imine formation. (EC 3.5.4.10)



inosine monophosphate

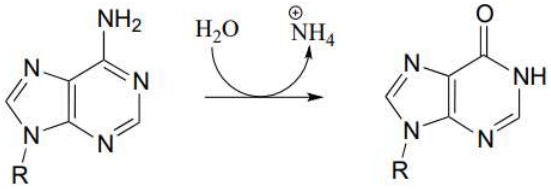
P10.10: Propose a mechanism for these steps in nucleotide metabolism:

a. (EC 3.5.4.5)



Cytidine Uridine

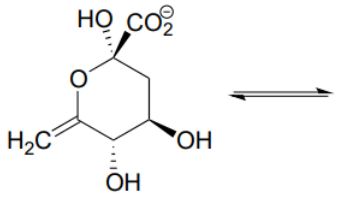
b. (EC 3.5.4.4)



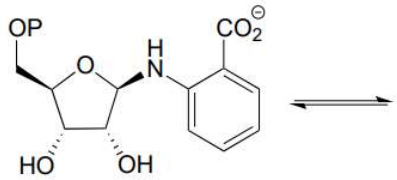
Adenosine Inosine

P10.11

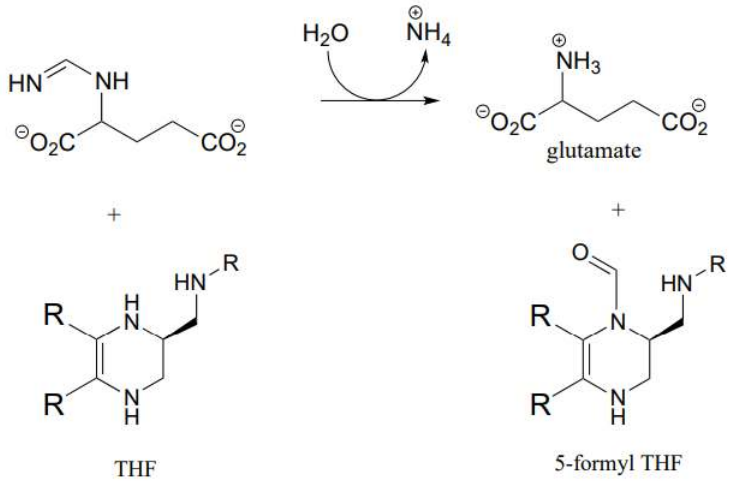
a. Draw the structure (including stereochemistry) of the compound that results when the cyclic hemiketal shown below coverts to an open-chain compound with two ketone groups.



b. The compound shown below undergoes a ring-opening reaction to form a species that can be described as both an enol and an enamine. Draw the structure (including stereochemistry) of this product, and a likely mechanism for its formation. (EC 5.3.1.24)



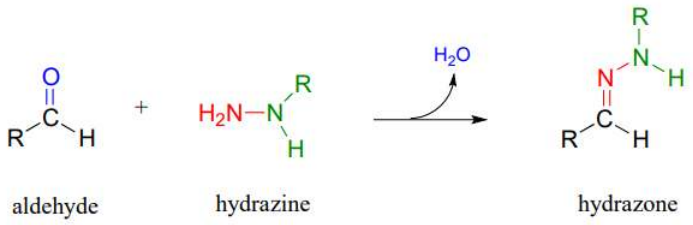
P10.12: Tetrahydrofolate (***THF***) is a coenzyme that serves as a single-carbon donor in many biochemical reactions. Unlike ***S***-adenosylmethionine (SAM, see section 8.8), the carbon being transferred in a ***THF***-dependent reaction is often part of a carbonyl. Below is a reaction in the histidine degradation pathway (EC 3.5.3.8). The mechanism involved is thought to be an transimination, followed by a imine-to-imine tautomerization, followed by an imine hydrolysis. Propose a reasonable mechanism that fits this description. Hint: first identify the carbon atom being transferred.

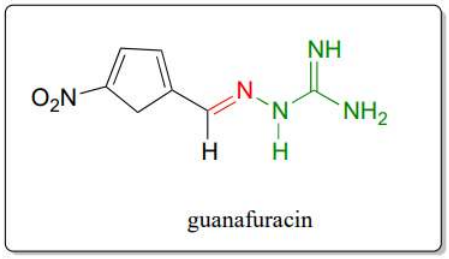


P10.13: Hydrazones are close relatives of imines, formed in reactions between aldehydes/ketones and hydrazines, a functional group containing a nitrogen-nitrogen bond. The mechanism for hydrazone formation is analogous to that of imine formation.

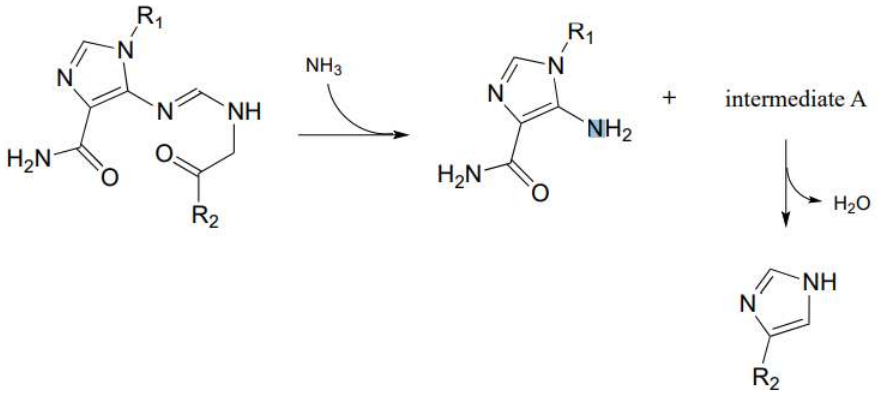
Guanafuracin, a known antibiotic compound, is a hydrazone, and can be prepared easily in the laboratory by combining equimolar amounts of the appropriate aldehyde and hydrazine in water (no heat or acid catalyst is required, and the reaction is complete in seconds).

Determine the starting materials required for the synthesis of guanafuracin, and propose a likely mechanism for the reaction.





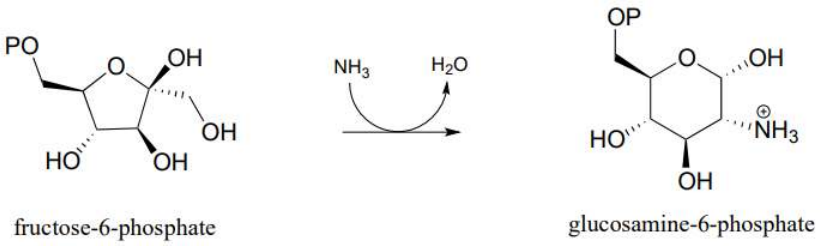
P10.14: Propose reasonable mechanisms for the following steps from the histidine biosynthesis pathway, and predict the structure of intermediate A (which is open-chain, not cyclic).



The last several problems are quite challenging!

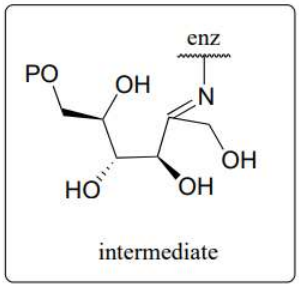
P10.15: Propose a likely mechanism for the synthesis of glucosamine 6-phosphate from fructose-6-phosphate. One of several intermediates is shown. (EC 2.6.1.16.)

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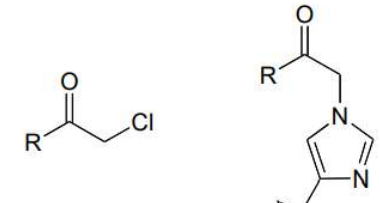
fructose-6-phosphate

glucosamine-6-phosphate



intermediate

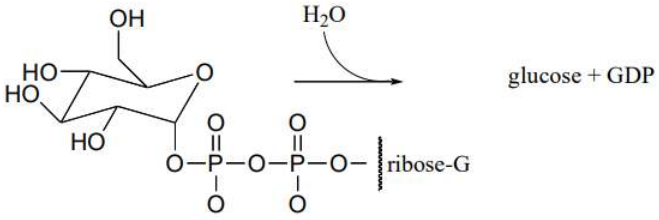
P10.16: α-chloromethyl ketones (structure below) are effective irreversible inhibitors of proteolytic (peptide-bond breaking) enzymes such as chymotrypsin. In these enzymes, a nucleophilic serine plays a key role in the reaction. The mechanism for inactivation of a-chymotrypsin is thought to involve, as a first step, nucleophilic attack by the active site serine on the carbonyl of the inhibitor. However, when the inactivated enzyme is analyzed, an active site histidine rather than the serine, is found to be covalently modified by the inhibitor. The structure of the modified histidine is shown below. The mechanism of inactivation is thought to involve an epoxide intermediate - with this in mind, propose a reasonable mechanism of inactivation.



-chloromethyl
ketone inhibitor

modified histidine

P10.17: An enzyme in E. coli bacteria catalyzes the hydrolysis of a-glucose-GDP to glucose.



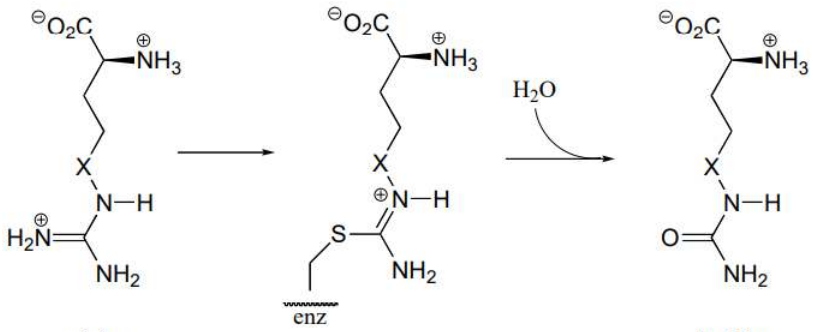
glucose + GDP

^1H-NMR analysis of the reaction in progress showed the initial appearance of a doublet at 4.64 ppm with J = 7.9 Hz (the spectrum contained other signals as well, of course). After 20 minutes (at which point the hydrolysis reaction has been complete for some time), another doublet began to appear slightly downfield, this one with J = 4.0 Hz. Over time, the strength of the downfield signal gradually increased and that of the upfield signal gradually decreased, until they stabilized at constant levels.

Draw a mechanism for the enzymatic hydrolysis reaction, and correlate your mechanism to the NMR data (including the appearance of the second doublet).

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P10.18: Arginine deaminase, an enzyme in the arginine degradation pathway, catalyzes the transformation of (***L***)-arginine to (***L***)-citrulline via a covalent substrate-cysteine intermediate.



This enzyme is the target for the development of drugs for cancer and immunological diseases such as arthritis. However, rather than completely and permanently shutting down the enzyme (eg. with an irreversible inhibitor), researchers are looking for a way to temporarily 'turn down' the activity of the enzyme. One strategy that has recently been reported involves the use of an oxygen-containing arginine analog, called canavanine, which reacts in the same way as arginine except that the second (hydrolysis) step is very slow. While the enzyme is covalently attached to the inhibitor (in the ***S***-alkyl thiuronium stage), it is inactivated.

a. Show a mechanism for the reaction catalyzed by arginine deaminase.
b. Explain how the electronic effect of the oxygen substituent would slow down the hydrolysis step of the reaction, and why the rate of the hydrolysis step is more affected by the oxygen substitution than the ***S***-alkylthiuronium-forming step.

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10.S: Nucleophilic Carbonyl Addition Reactions (Summary)

Before moving on to the next chapter, you should be confident in your ability to:

- Recognize aldehyde and ketone groups in organic biomolecules
- Draw/explain the bonding picture for aldehyde and ketone groups
- Explain why the carbonyl carbon in an aldehyde or ketone is electrophilic
- Draw complete curved arrow mechanisms for the following reaction types:
  - formation of a hemiacetal/hemiketal
  - collapse of a hemiacetal/hemiketal to revert to an aldehyde/ketone
  - formation and hydrolysis of an acetal/ketal
  - formation and hydrolysis of an N-glycosidic bond
  - formation and hydrolysis of an imine
  - transimination
- Explain how the carbocation intermediates in glycosidic bond formation and hydrolysis reactions are stabilized by resonance
- Explain the stereochemical considerations of a nucleophilic addition to an aldehyde/ketone, especially in the context of glycosidic bond formation. Be able to identify the re and si faces of an aldehyde, ketone, or imine.
- In addition to these fundamental skills, you should develop your confidence in working with end-of-chapter problems involving more challenging, multi-step biochemical reactions.

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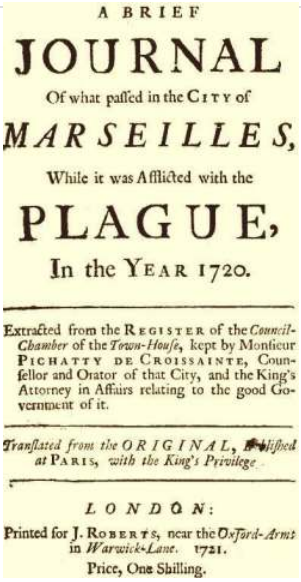
CHAPTER OVERVIEW

11: Nucleophilic Acyl Substitution Reactions

11.0: Prelude to Nucleophilic Acyl Substitution Reactions
11.1: Carboxylic Acid Derivatives
11.2: The Nucleophilic Acyl Substitution Mechanism
11.3: Acyl Phosphates
11.4: The Relative Reactivity of Carboxylic Acid Derivatives
11.5: Acyl Phosphates
11.6: Hydrolysis of Thioesters, Esters, and Amides
11.7: Protein Synthesis on the Ribosome
11.8: Nucleophilic Substitution at Activated Amides and Carbamides
11.9: Nucleophilic Acyl Substitution Reactions in the Laboratory
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11.0: Prelude to Nucleophilic Acyl Substitution Reactions



A BRIEF

JOURNAL

Of what paſſed in the CITY of

MARSEILLES,

While it was Afflicted with the

PLAGUE,

In the YEAR 1720.

Extracted from the REGISTER of the *Council-Chamber* of the *Town-Houſe*, kept by Monſieur PICHATTY DE CROISSAINTE, Counſellor and Orator of that City, and the King's Attorney in Affairs relating to the good Government of it.

Tranſlated from the ORIGINAL, Publiſhed at PARIS, *with the King's Privilege.*

LONDON:

Printed for J. ROBERTS, near the *Oxford-Arms* in *Warwick-Lane.* 1721.

Price, One Shilling.

Introduction

> *The 26th of July, Notice is given to the Sheriffs, that in the Street of Lescalle, a Part of the old Town inhabited only by poor People, Fifteen Persons are suddenly fallen sick: They dispatch thither Physicians and Surgeons; they examine into the Distemper, and make Report; some, that 'tis a Malignant Fever; others, a contagious or pestilential Fever, occasioned by bad Food, which Want had long forced those poor Creatures to live upon . . .*
>
> *The 27th, Eight of those Sick dye; the Sheriffs themselves go to their Houses to cause them to be searched; Buboes [swelling of the lymph nodes] are found on Two of them: The Physicians and Surgeons still hold the same Language, and impute the Cause of the Distemper to unwholsome Food. Notwithstanding which, as soon as Night comes, M. Moustier repairs to the Place, sends for Servants from the Infirmaries, makes them willingly or by Force, take up the Bodies, with all due Precautions; they are carried to the Infirmaries, where they are buried with Lime; and all the rest of the Night he causes the remaining Sick, and all those of their Houses, to be removed to the Infirmaries.*
>
> *The 28th, very early in the Morning, Search is made every where for those who had Communication with them, in order to confine them: Other Persons in the same Street fall sick, and some of those who first sicken'd dye. ..*
>
> *The People who love to deceive themselves, and will have it absolutely not to be the Plague, urge a Hundred false Reasons on that Side. Would the Plague, say they, attack none but such poor People? Would it operate so slowly?*
>
> *Let them have but a few Days Patience, and they will see all attacked without Distinction, with the swiftest Rage, and the most dreadful Havock, that ever was heard of.*

(source: Gutenberg Project http://www.gutenberg.org/files/45673...-h/45673-h.htm)

In late May of 1720, a ship arrived in the Mediterranean port city of Marseille, having recently departed from Cyprus and Tripoli. Although several crew members had fallen ill and died during the journey, the ship was allowed to unload after only a very brief quarantine, the result of political pressure on port authorities from local businessmen who wanted quick access to the valuable silk and cotton waiting in the ship's hold.

Along with silk and cotton, the hold carried rats. The rats, in turn, carried fleas. The fleas carried a microscopic mass murderer: Yersinia pestis, the species of bacteria that causes bubonic plague.

It is next to impossible to estimate how many people have died from bubonic plague over the course of human history. In the time of the 'Black Death' in the 14th century, it wiped out more than half the population of Europe. In the Great Plague of Marseille in 1720, over 100,000 people succumbed to Y. pestis infection in the city and surrounding provinces. At the height of the outbreak,

corpses piled up in city streets, and a fortified wall, the 'mur de la peste' was constructed in an attempt to prevent people from traveling north to the neighboring city of Aix.

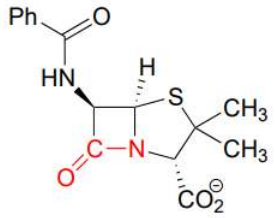
Throughout history, bacteria have been the cause of untold human death and suffering, making the threat posed by more obviously frightening species - lions and bears, spiders and snakes – seem inconsequential by comparison. As recently as the mid-1940s, a minor cut or cold could become a life-threatening event if a bacterial infection were to set in, and even in developed countries, one in twenty infants did not survive to celebrate their first birthday.

Since then, the infant mortality rate in developed countries has declined by a factor of ten. You probably don't worry very much when a small cut on your hand becomes infected. The idea of half of the population of the United States dying in a plague is, in most people's minds, the stuff of zombie movies, not reality. Bacteria are, for now at least, no longer public enemy #1.

How did this happen?

For an answer, we move to a September morning in 1928, in the laboratory of Alexander Fleming, a Scottish bacteriologist working at St. Mary's Hospital in London. As a young man serving in the British Medical Corps during World War I, Fleming saw first-hand how deadly bacteria could be, as he watched countless soldiers in his battlefield hospital die from infected wounds. After returning to civilian life, he began to study Staphylococci bacteria, a common source of life-threatening infections in humans, hoping to discover new antibacterial agents that were more effective than those he had used in the war. He spent a lot of his time growing Staphylococcus cultures in petri dishes for his experiments, and, notoriously untidy, he tended to leave piles of culture dishes lying around his lab. One morning, he returned from a short vacation to find that one of the cultures he had left out had some mold growing on it. He was about to throw it away, but happened to notice something curious: surrounding the small spot of mold was a circle of clear medium, where no bacteria were growing. He realized that the mold must be secreting something that killed bacteria.

As it turned out, the mold was a of strain called Penicillium notatum, and the 'something' killing the bacteria was an organic compound that came to be known as penicillin.



penicillin

Fleming published his findings in the British Journal of Experimental Pathology, but made only passing reference to the potential therapeutic value of penicillin. The paper received little attention.

Fast-forward now to early February 1941, with the world once again at war. One morning, a policeman named Albert Alexander living in Oxford, England, had an unfortunate gardening accident. While he was trimming some roses on his day off, his shears slipped and gave him a nasty cut on the side of his mouth. The cut became infected, and after a few days it appeared as if the infection would kill him. Then, he got a visit in his hospital room from some chemists at nearby Oxford University.

For the last few years, the chemists had been hard at work isolating pure penicillin from mold cultures, a tricky job because the compound tends to degrade during purification. It is a feat that Alexander Fleming -who, after all, was a bacteriologist, not a chemist - had never been able to accomplish, but the Oxford researchers had realized how valuable penicillin might be to the war effort, and had finally met with some success. They needed a human subject on whom to test the ability of their compound to treat infected wounds, and Albert was their man for the job. They injected him with penicillin, and within a day his infection cleared up. It was a new day in the history of medicine.

At the heart of a penicillin molecule is an amide functional group - more specifically, a cyclic amide, or 'lactam'. To understand how penicillin works at the molecular level as it prevents bacteria from multiplying, we first need to know more about the chemistry of amides and other carboxylic acid derivative functional groups, and a type of organic reaction mechanism called 'nucleophilic acyl substitution'. Understanding the reactivity of carboxylic acid derivative groups will also allow us to appreciate

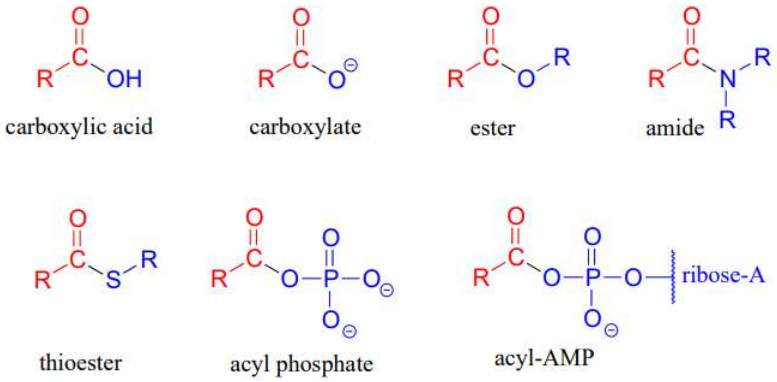
why penicillin is so prone to degradation, and why - very significantly for all of us - the era of not having to worry about bacterial infections may be near an end, as common toxic bacterial species such as Staphylococcus develop increasingly robust resistance to antibiotics.

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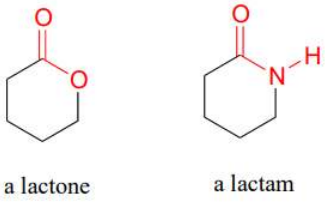
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11.1: Carboxylic Acid Derivatives

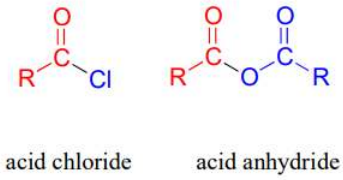
The functional groups at the heart of this chapter are called **carboxylic acid derivatives**: they include carboxylic acids themselves, carboxylates (deprotonated carboxylic acids), amides, esters, thioesters, and acyl phosphates.



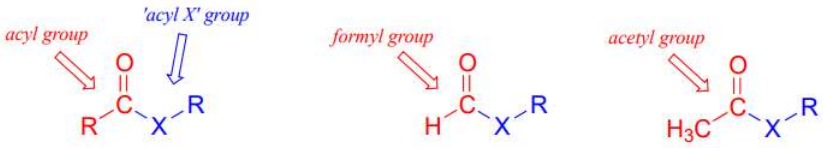
Cyclic esters and amides are referred to as **lactones** and **lactams**, respectively.



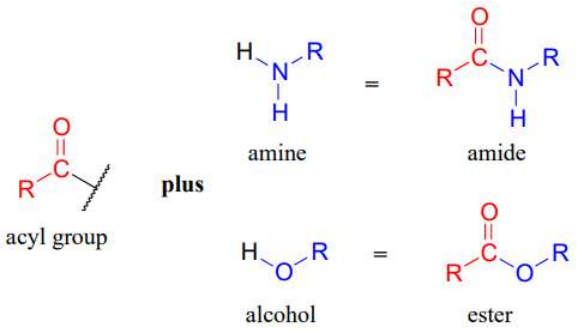
Carboxylic acid anyhydrides and acid chlorides, which also fall under the carboxylic acid derivative category, are not generally found in biomolecules but are useful intermediates in laboratory synthesis. They are discussed in a section on laboratory reactions at the end of this chapter.



Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, or sulfur – bonded directly to the carbonyl carbon. You can think of a carboxylic acid derivative as having two sides. One side is the acyl group, which is the carbonyl plus the attached alkyl (R) group. In the specific cases where R is a hydrogen or methyl, chemists use the terms formyl and acetyl group, respectively. One the other side is the heteroatom-linked group: in this text, we will sometimes refer to this component as the ‘acyl X' group (this, however, is not a standard term in organic chemistry).



Notice that the acyl X groups are simply deprotonated forms of other functional groups linked to the acyl group: in an amide, for example, the acyl X group is an amine, while in an ester the acyl X group is an alcohol.



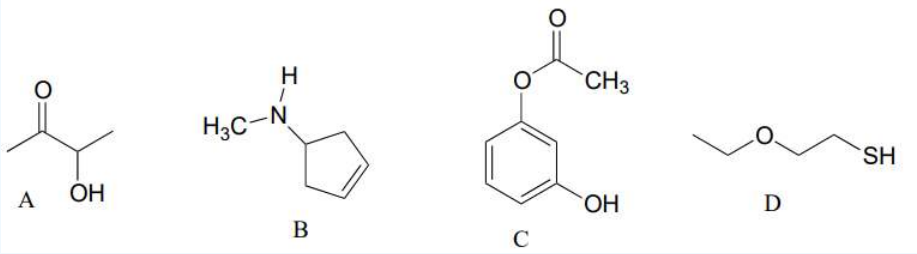
Exercise 11.2.1

What is the ‘acyl X’ group in:

a. an acid anhydride?
b. a thioester?
c. a carboxylic acid?
d. an acyl phosphate?

Exercise 11.2.2

Draw the structures indicated:

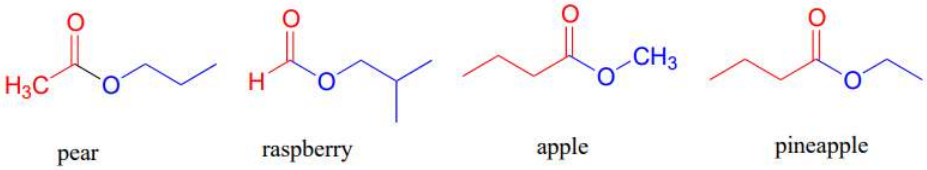


a. compound A after is has been acetylated (ie. an acetyl group added)
b. compound B after it has been formylated
c. compound C after it has been formylated
d. Compound D after it has been acetylated

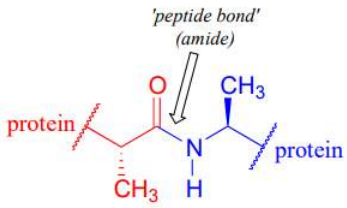
'Fatty acid' molecules such as stearate are carboxylates with long carbon chains for acyl groups.



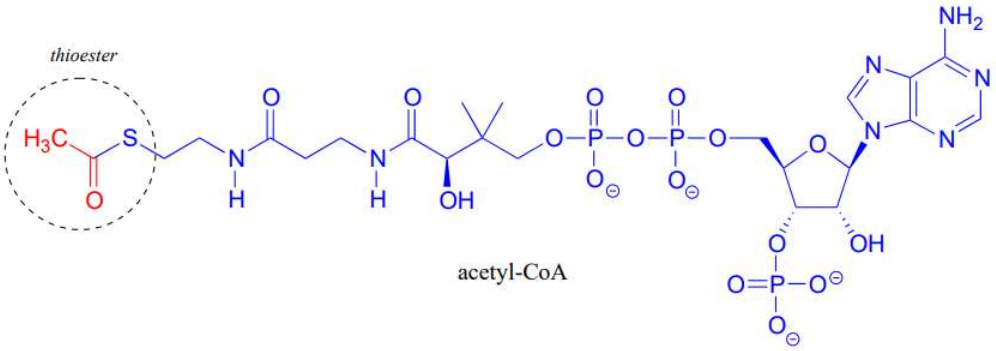
The aromas of many fruits come from small ester-containing molecules:



The 'peptide bonds' that link amino acids together in proteins are amides.



Acetyl-Coenzyme A, a very important two carbon (acetyl group) 'building block' molecule in metabolism, is characterized by reactions at its thioester functional group:

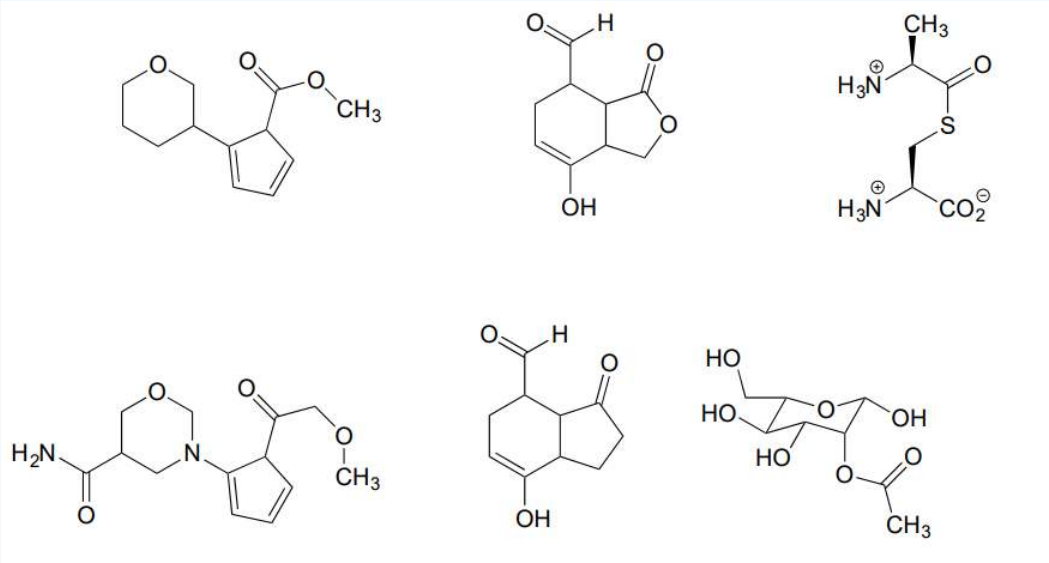


? Exercise 11.2.3

There are two amide groups in acetyl-CoA: identify them.

? Exercise 11.2.4

Name all carboxylic acid derivative groups in the molecules below.

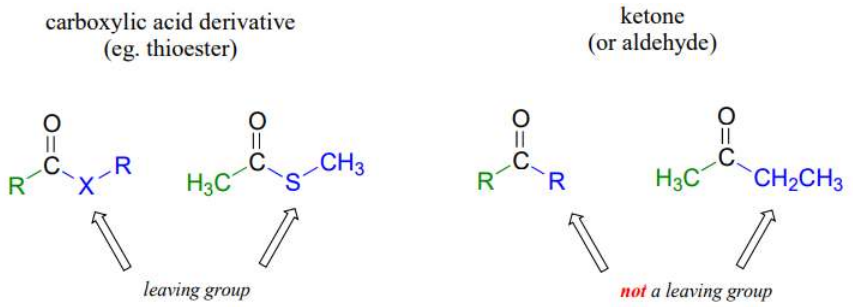


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11.2: The Nucleophilic Acyl Substitution Mechanism

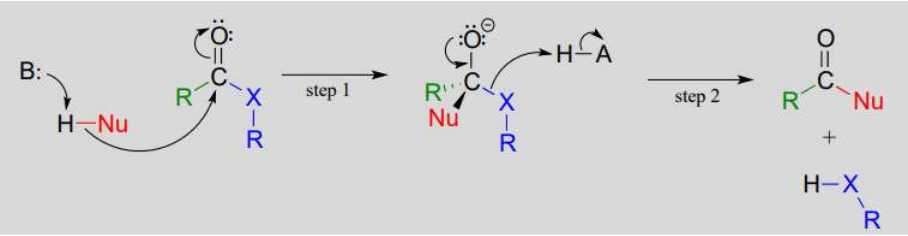
The fact that one of the atoms adjacent to the carbonyl carbon in carboxylic acid derivatives is an electronegative heteroatom – rather than a carbon like in ketones or a hydrogen like in aldehydes - is critical to understanding the reactivity of carboxylic acid derivatives. The most significant difference between a ketone/aldehyde and a carboxylic acid derivative is that the latter has a potential leaving group - what we are calling the 'acyl X group' - bonded to the carbonyl carbon.



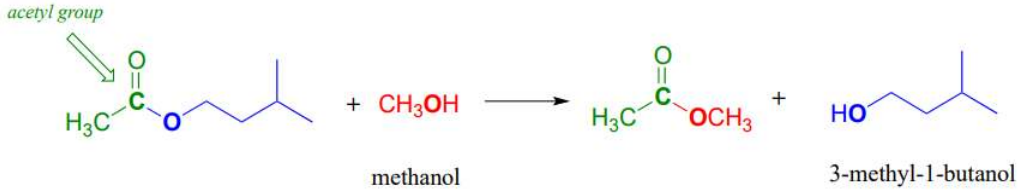
As a result, carboxylic acid derivatives undergo nucleophilic acyl substitution reactions, rather than nucleophilic additions like ketones and aldehydes.

A nucleophilic acyl substitution reaction starts with nucleophilic attack at the carbonyl, leading to a tetrahedral intermediate (step 1 below). In step 2, the tetrahedral intermediate collapses and the acyl X group is expelled, usually accepting a proton from an enzymatic acid in the process.

Mechanism for a nucleophilic acyl substitution reaction:



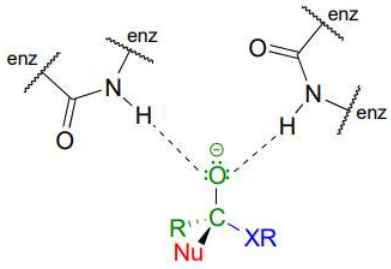
Notice that in the product, the nucleophile becomes the new acyl X group. This is why this reaction type is called a nucleophilic acyl substitution: one acyl X group is substituted for another. For example, in the reaction below, one alcohol 'X group' (methanol), substitutes for by another alcohol 'X group' (3-methyl-1-butanol) as one ester is converted to another.



Another way of looking at this reaction is to picture the acyl group being transferred from one acyl X group to another: in the example above, the acetyl group (in green) is transferred from 3-methyl-1-butanol (blue) to methanol (red). For this reason, nucleophilic acyl substitutions are also commonly referred to as acyl transfer reactions.

Enzymes catalyzing nucleophilic acyl substitution reactions have evolved ways to stabilize the negatively charged, tetrahedral intermediate, thus lowering the activation energy of the first, rate-determining step (nucleophilic attack). The late transition state of the first step resembles the tetrahedral intermediate that results: recall from chapter 6 that the Hammond postulate tells us that anything that stabilizes the tetrahedral intermediate will also stabilize the transition state. In many cases, for example, enzymatic amino acid residues are positioned in the active site so as to provide stabilizing hydrogen bond donating interactions with the

negatively-charged oxygen. This arrangement is sometimes referred to in the biochemistry literature as an oxanion hole. The figure below shows a tetrahedral intermediate stabilized by hydrogen bond donation from two main chain (amide) nitrogen atoms.

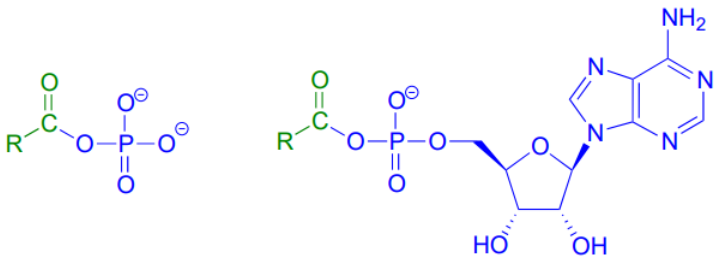


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11.3: Acyl Phosphates

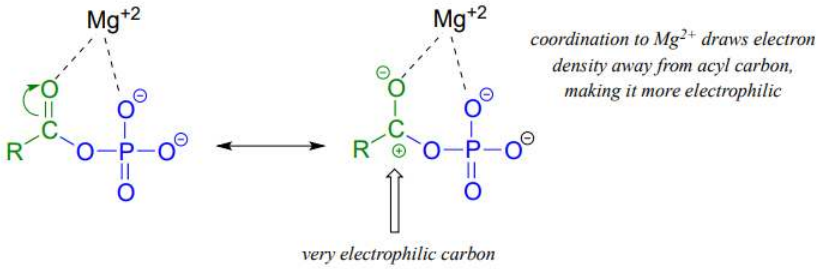
Acyl phosphates, because they are so reactive towards acyl substitutions, are generally seen as reaction intermediates rather than stable metabolites in biochemical pathways. Acyl phosphates usually take one of two forms: a simple acyl monophosphate, or acyl-adenosine monophosphate.



acyl monophosphate

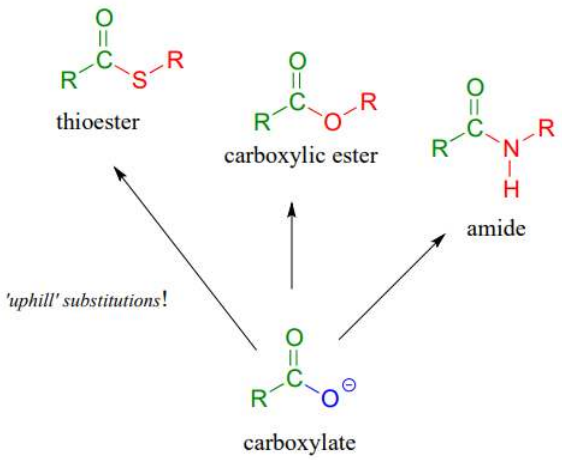
acyl adenosine monophosphate
(acyl AMP)

Both forms are highly reactive to acyl substitution reactions, and are often referred to as ‘activated acyl groups’ or ‘activated carboxylic acids’ for reasons that will become clear soon. The tendency of phosphates to form stabilizing complexes with one or more magnesium ions in an enzyme's active site contributes in a large way to the reactivity of acyl phosphates.



A magnesium ion acts as a Lewis acid, accepting electron density from the oxygen end of the acyl carbonyl bond, which greatly increases the degree of partial positive charge - and thus the electrophilicity - of the carbonyl carbon. The magnesium ion also balances negative charge on the phosphate, making it a weak base and excellent leaving group.

We have already learned that the carboxylate functional group is the least reactive substrate for an enzyme-catalyzed acyl substitution reactions. In biology, though, carboxylates are frequently transformed into thioesters, carboxylic esters, and amides, all of which are higher in energy, meaning that these transformations are thermodynamically 'uphill'.



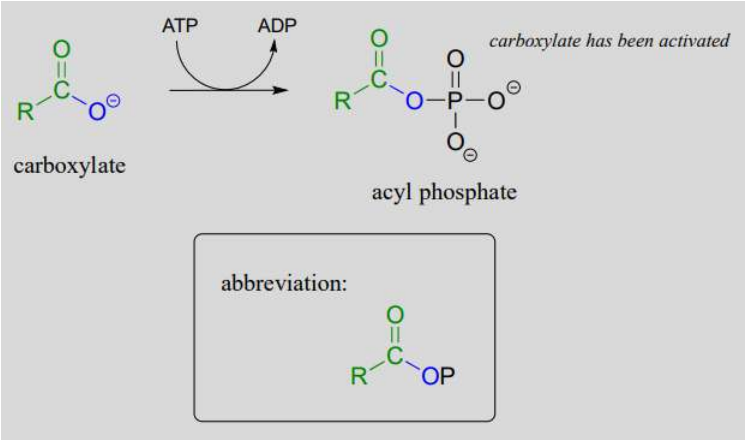
How are these uphill substitutions accomplished? They are not carried out directly:

like all thermodynamically unfavorable reactions in biochemistry, they are linked to an energy-releasing, 'downhill' reaction. In this case, (and many others), the linked reaction that 'pays for' the uphill reaction is hydrolysis of ATP.

In order to undergo an acyl substitution reaction, a carboxylate must first be activated by phosphorylation. You are already familiar with this phosphoryl group transfer process from chapter 9.

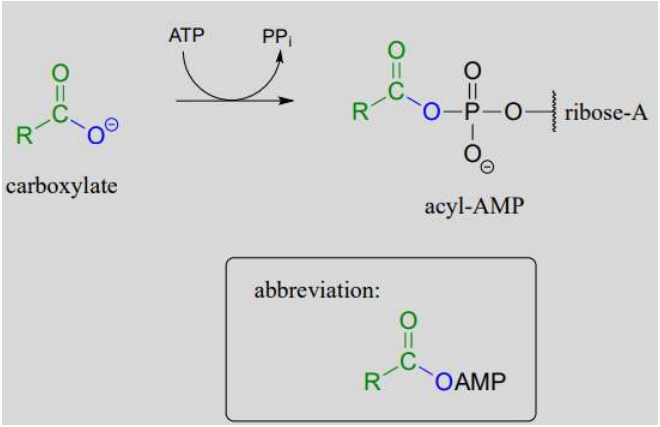
In many cases, enzymes activate a carboxylate group by converting it to an acyl phosphate (the most reactive of the carboxylic acid derivatives), at the expense of an ATP: the mechanism for this type of transformation is shown in Section 9.5.

Formation of an acyl phosphate (see section 9.5 for the complete mechanism):

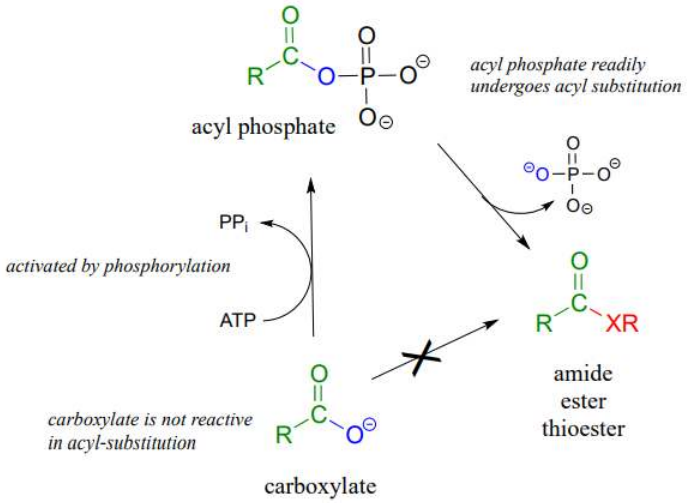


As a common alternative, some enzymatic reactions begin with the conversion of a carboxylate to an acyl-AMP intermediate:

Formation of an acyl -AMP (see section 9.5 for the complete mechanism):



In either case, once the carboxylate group has been activated, the reactive acyl phosphate/acyl-AMP intermediate can go on to act as the electrophile in an energetically favorable nucleophilic acyl substitution reaction.



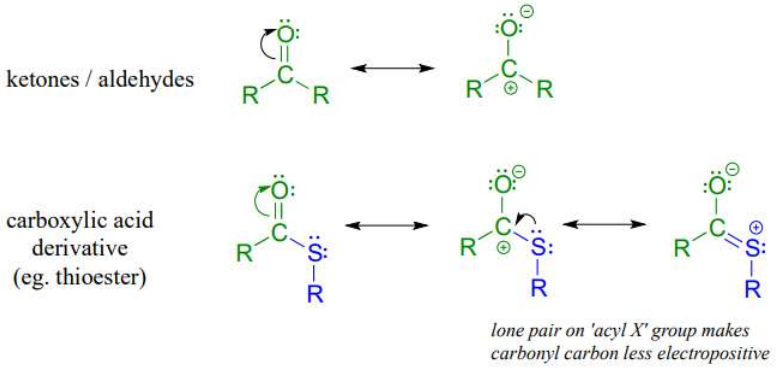
You have probably heard ATP referred to as the 'energy currency' molecule. The reactions in this section provide a more concrete illustration of that concept. A lower-energy group (a carboxylate) is converted to a higher-energy group (a thioester, for example) by 'spending' a high-energy ATP.

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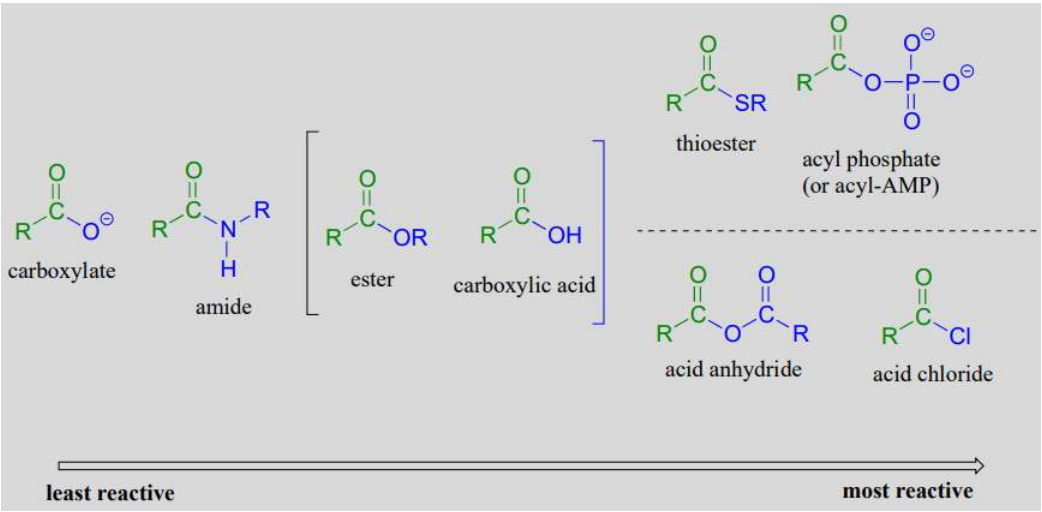
11.4: The Relative Reactivity of Carboxylic Acid Derivatives

In carboxylic acid derivatives, the partial positive charge on the carbonyl carbon is stabilized by electron donation from nonbonding electrons on the adjacent heteroatom, which has the effect of decreasing electrophilicity.



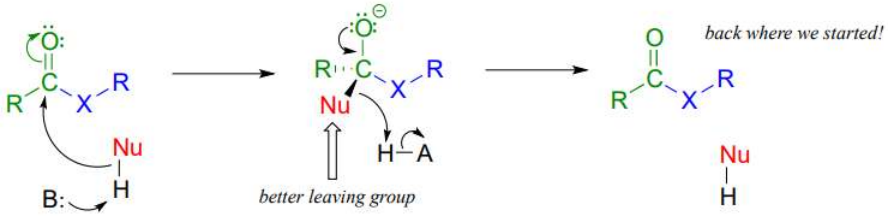
Among the carboxylic acid derivatives, carboxylate groups are the least reactive towards nucleophilic acyl substitution, followed by amides, then carboxylic esters and carboxylic acids, thioesters, and finally acyl phosphates, which are the most reactive among the biologically relevant acyl groups. Acid anhydrides and acid chlorides are laboratory reagents that are analogous to thioesters and acyl phosphates, in the sense that they too are highly reactive carboxylic acid derivatives. Section 11.8 near the end of this chapters includes information about the chemistry of these two reagents.

Relative reactivity of carboxylic acid derivatives:



The reactivity trend of the carboxylic acid derivatives can be understood by evaluating the basicity of the leaving group (acyl X group) - remember from section 8.4 that weaker bases are better leaving groups. A thioester is more reactive than an ester, for example, because a thiolate (RS-) is a weaker base and better leaving group than an alcoxide (*RO*-). Recall from chapter 7 that the pK_a of a thiol is about 10, while the pK_a of an alcohol is 15 or higher: a stronger conjugate acid means a weaker conjugate base.

In general, if the incoming nucleophile is a weaker base than the ‘acyl X’ group that is already there, it will also be the better leaving group, and thus the first nucleophilic step will simply reverse itself and we’ll get the starting materials back:



In general, acyl substitution reactions convert higher energy carboxylic acid derivatives into derivatives of lower energy. Thioesters, for example, are often converted directly into carboxylic esters in biochemical reactions, but not the other way around. To go 'uphill' - from a carboxylate to a thioester, for example, requires the 'coupling' of the uphill reaction to an energetically favorable reaction. We will see how this works in the next section.

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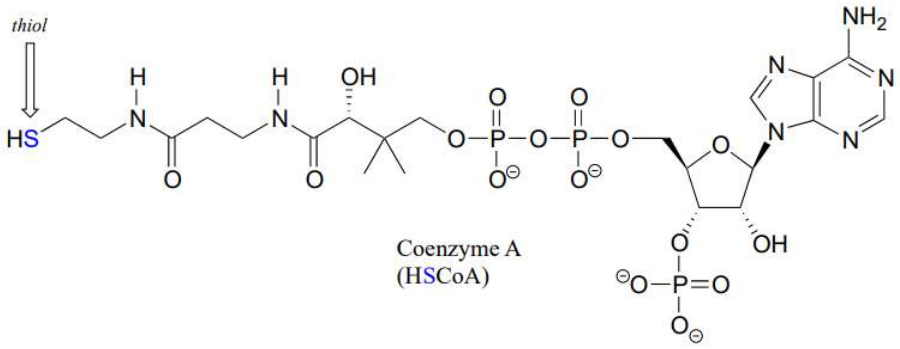
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11.5: Acyl Phosphates

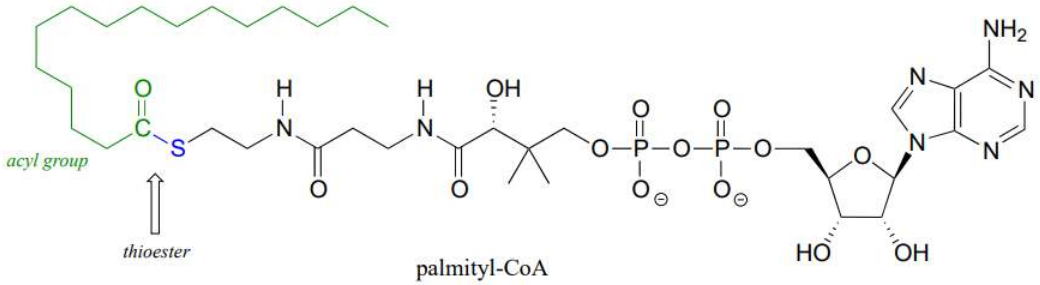
Thioester formation

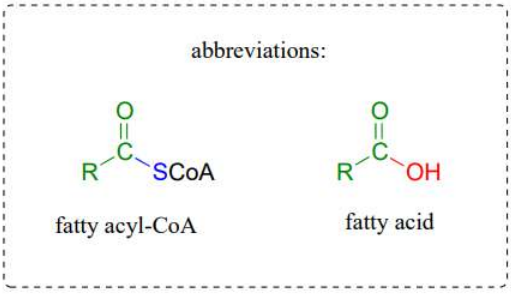
Thioesters, which are themselves quite reactive in acyl substitution reactions (but less so than acyl phosphates), play a crucial role in the metabolism of fatty acids The ‘acyl X group’ in a thioester is a thiol.

Coenzyme A is a thiol-containing coenzyme that plays a key role in metabolism. Coenzyme A is often abbreviated 'HSCoA' in order to emphasize the importance of the thiol functionality.

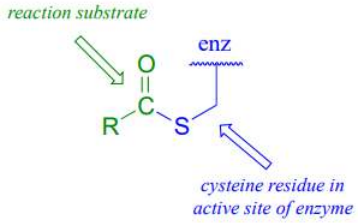


Coenzyme A serves as a 'carrier' group in lipid biosynthesis, and is attached by a thioester linkage to growing fatty acid chains. Palmityl is shown below as an example of a typical fatty acyl-CoA thioester.



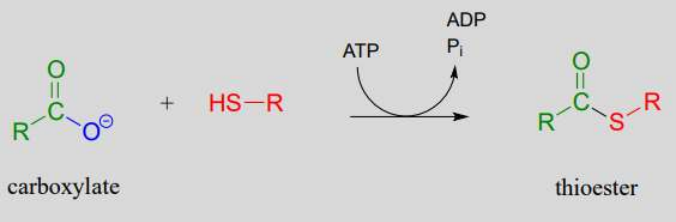


As we look at reactions involving thioesters in this and future sections, we will frequently see Coenzyme A playing a key role. We will also see the formation and breaking of thioester linkages between an acyl group and other thiol-containing species, such as a cysteine residue on the enzyme:



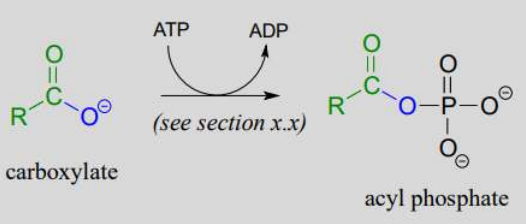
The term 'thioesterification' refers to the formation of a thioester functional group. In a typical biochemical thioesterification reaction, a carboxylate is first converted into an acyl phosphate (in other words, it is activated), then the acyl phosphate undergoes an acyl substitution reaction with a thiol nucleophile.

Thioesterification reaction:

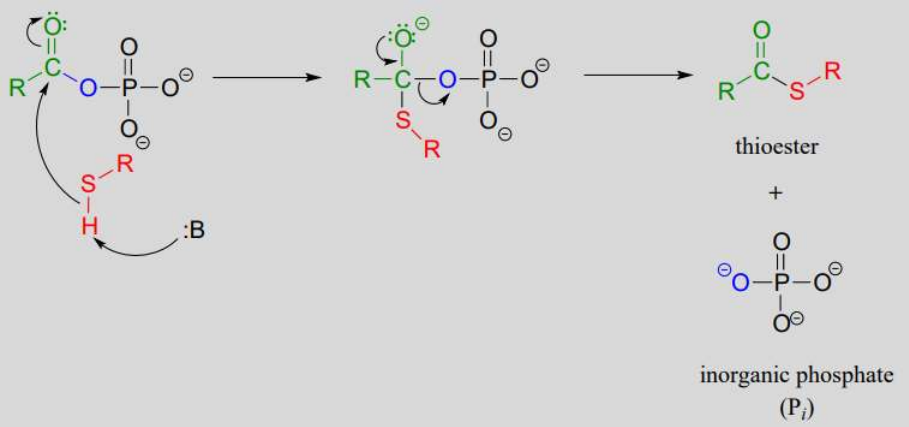


Mechanism:

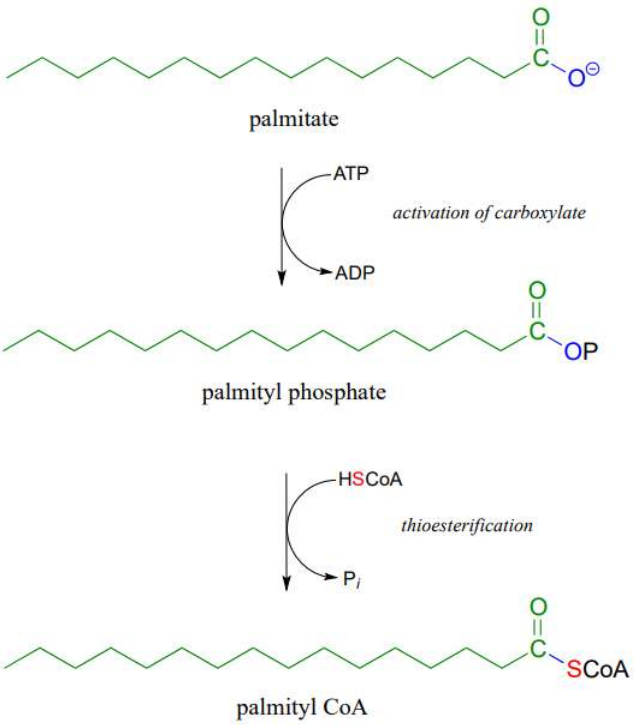
1. activation phase:



2. acyl substitution phase:

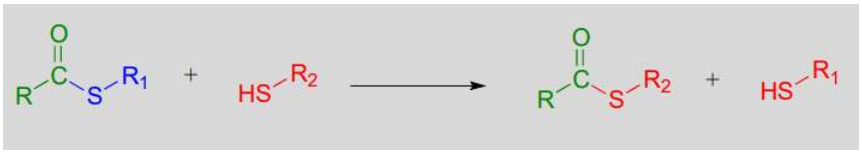


Fatty acids such as palmitate , from fats and oils in your food, are converted to a coenzyme A thioester prior to being broken down by the fatty acid degradation pathway.

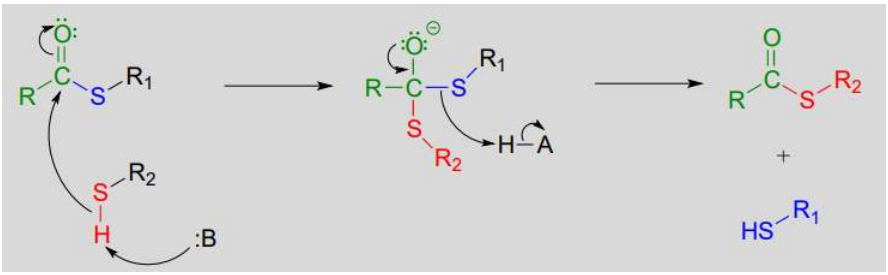


A transthioesterification reaction is a thioester to thioester conversion - in other words, an acyl group is transferred from one thiol to another.

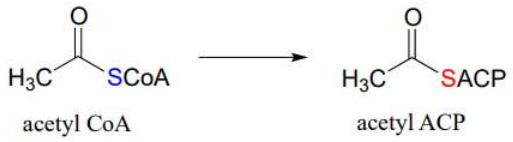
Transthioesterification:

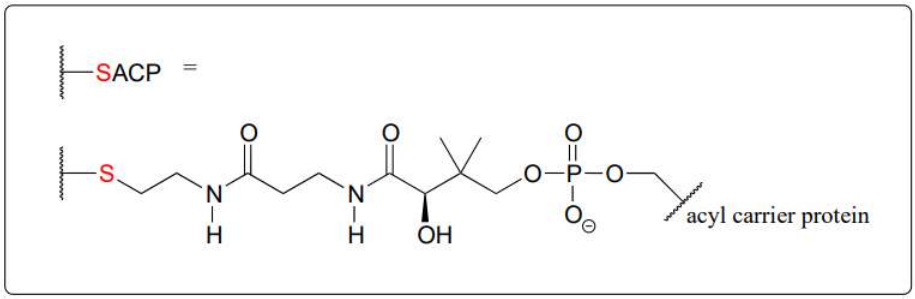


Mechanism:



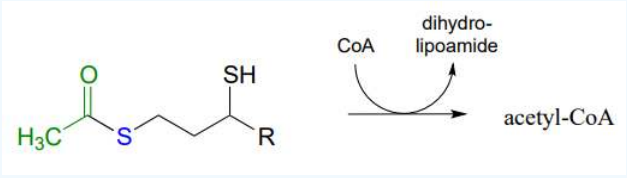
For example, when your body synthesizes fatty acids, the two-carbon fatty acid 'building block' acetyl CoA is first converted to acetyl ACP (EC 2.3.1.38). ACP is an abbreviation for 'Acyl Carrier Protein', a modified protein with a thiol-containing prosthetic group attached to one of its serine side chains. Throughout the fatty acid chain elongation process, the growing hydrocarbon chain remains linked to ACP.





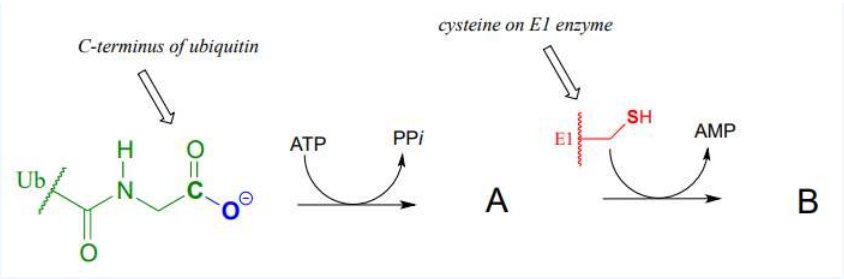
Exercise 11.6.1

The pyruvate dehydrogenase complex (EC 1.2.4.1) catalyzes one of the most central of all central metabolism reactions, the conversion of pyruvate to acetyl-CoA, which links the gycolytic pathway to the citric acid (Krebs) cycle. The reaction is quite complex, and we are not yet equipped to follow it through from start to finish (we will finally be ready to do this in section 17.3). The final step, however, we can understand: it is a transthioesterification, involving a dithiol coenzyme called dihydrolipoamide and coenzyme A. Given the information below, draw out a reasonable mechanism for the reaction.



Exercise 11.6.2

Ubiquitin is a protein which plays a key role in many cellular processes by reversibly attaching to other proteins, thus altering or regulating their function. Recently, a team of researchers uncovered details of the mechanism by which ubiquitin (abbreviated Ub) is transferred by the ubiquitin activating enzyme (abbreviated E1) to target proteins. In the first part of this process, the carboxy terminus of ubiquitin is linked to a cysteine side chain on E1, as shown in the incomplete reaction sequence below. Complete the figure by drawing the structures of species A and B.

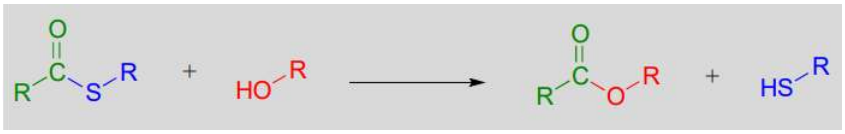


Formation of esters

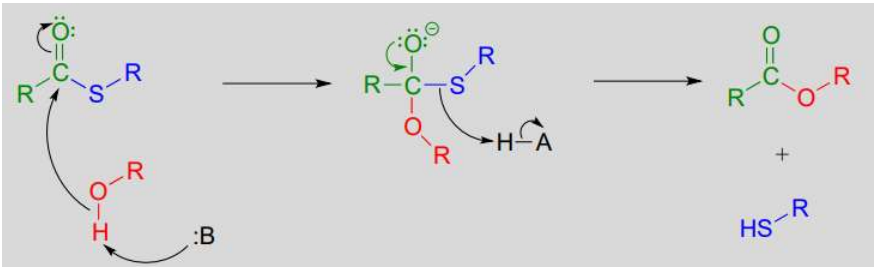
Esterification refers to the formation of a new ester functional group.

In a typical biochemical esterification, a thioester is subjected to nucleophilic attack from an alcohol, leading to the formation of an ester and a thiol.

Esterification reaction (from thioester):

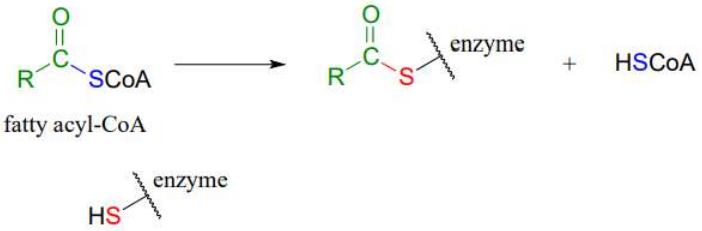


Mechanism:

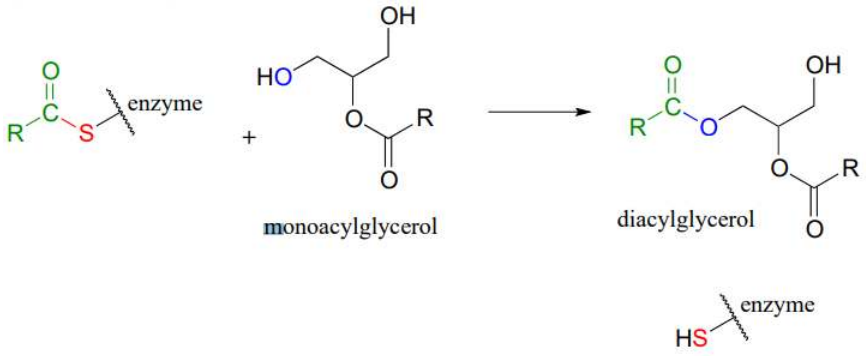


The reaction below is from the synthesis of triacylglycerol, the form in which fat is stored in our bodies.

Phase 1 (transthioesterification):



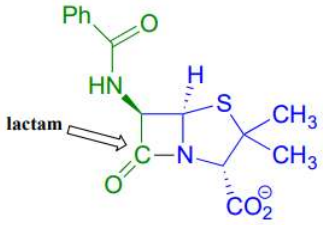
Phase 2 (esterification):



The reaction, catalyzed by monoacylglycerol acyltransferase (EC 2.3.1.22), begins (phase 1 above) with a preliminary transthioesterification step in which the fatty acyl group is transferred from coenzyme A to a cysteine residue in the active site of the enzyme. Recall that it is a common strategy for enzymes to first form a covalent link to one substrate before catalyzing the 'main' chemical reaction.

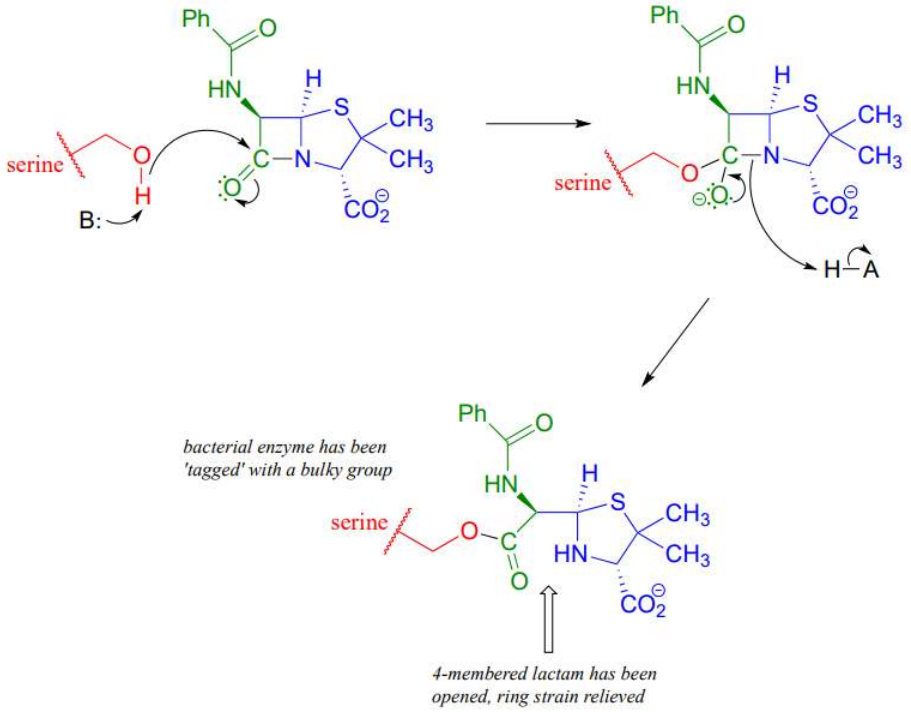
In phase 2 of the reaction, the fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol.

An esterification reaction has tremendous importance in the history of drug development, a story that we heard in the introduction to this chapter. The discovery of penicillin was arguably one of the most important events in the history of modern medicine. The key functional group in penicillin is the four-membered lactam (recall that a lactam is a cyclic amide).



benzyl penicillin

Penicillin, and later generations of antibiotic drugs, have saved countless lives from once-deadly bacterial infections. The elucidation of the chemical mechanism of penicillin action was also a milestone in our developing understanding of how drugs function on a molecular level. We now know that penicillin, and closely related drugs such as ampicillin and amoxycillin, work by inhibiting an enzyme that is involved in the construction of the peptide component bacterial cell walls. The details of the wall-building reaction itself are outside the scope of this discussion, but it is enough to know that the process involves the participation of a nucleophilic serine residue in the active site of the enzyme. The penicillin molecule is able to enter the active site, and once inside, the lactam group serves as an electrophilic 'bait' for the nucleophilic serine:



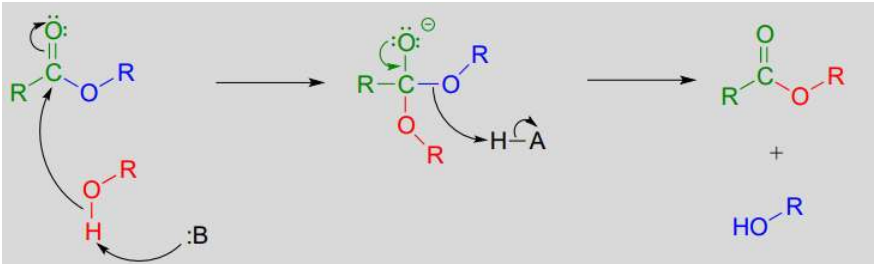
Although you might expect that an amide-to-ester conversion such as what is shown above would be energetically unfavorable based on the reactivity trends we have learned, this lactam is in fact much more reactive than an ordinary amide group due to the effect of ring strain: recall from section 3.2 that four-membered rings are highly strained, and considerable energy is released when they are opened.

Ring strain also accounts for why penicillin has a tendency to degrade: when in contact with water, the lactam will spontaneously hydrolyze over time, which opens the ring and forms a carboxylate group.

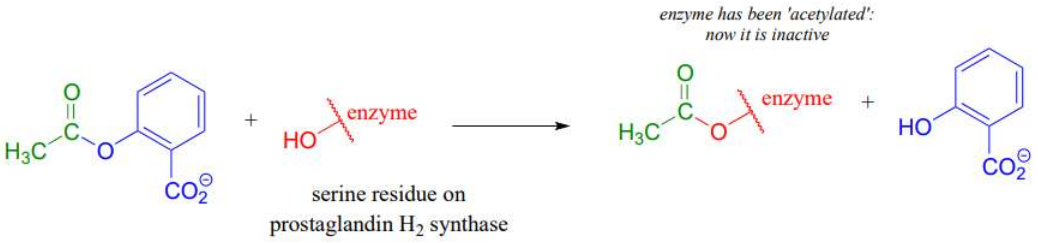
Unfortunately, many strains of bacteria have acquired an enzyme called β-lactamase (EC 3.5.2.6), that catalyzes rapid hydrolysis of the lactam ring in penicillin-based drugs, rendering them inactive. These bacteria are consequently resistant to penicillin and related antibiotics. As you are probably aware, the evolution of drug resistance in bacteria is a major, world-wide health problem, and scientists are engaged in a constant battle to develop new antibiotics as the older ones become less and less effective.

In a transesterification reaction, one ester is converted into another by an acyl substitution reaction.

Mechanism for a transesterification reaction:



If studying organic chemistry sometimes gives you a headache, you might want to turn to a transesterification reaction for help. Prostaglandins are a family of molecules that promote a wide range of biological processes, including inflammation. Acetylsalicylic acid, commonly known as aspirin, acts by transferring - through a transesterification reaction - an acetyl group to a serine residue on the enzyme responsible for the biosynthesis of prostaglandin H2 (one member of the prostaglandin family).



Acetylation of this serine blocks a channel leading to the active site, effectively shutting down the enzyme, impeding prostaglandin production, and inhibiting the inflammation process that causes headaches.

In section 11.8, we will see two laboratory acyl substitution reactions that lead to the formation of aspirin and ibuprofen.

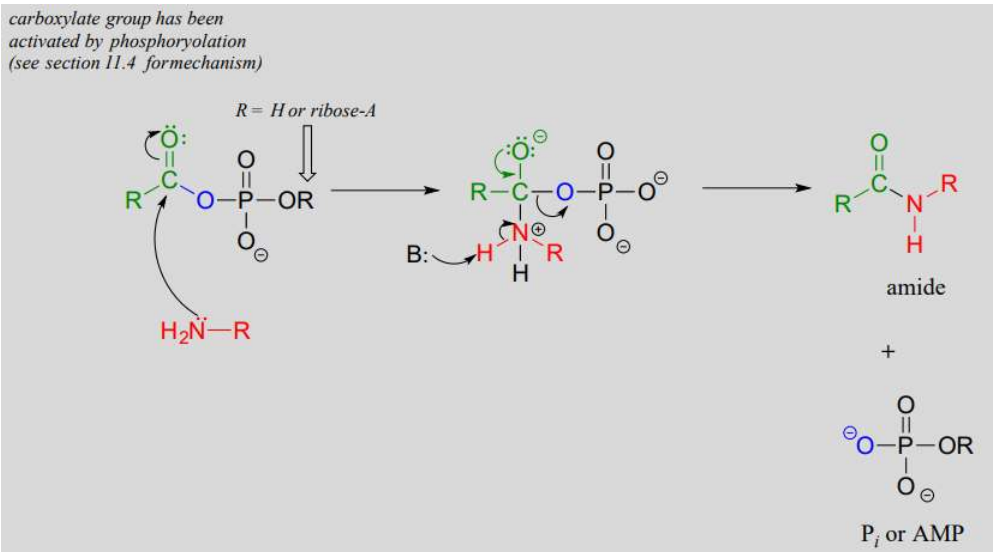
? Exercise 11.6.3

Discuss the key structural feature of aspirin that makes it so effective at transferring its acetyl group - in other words, why is the ester group in aspirin more reactive than a typical ester?

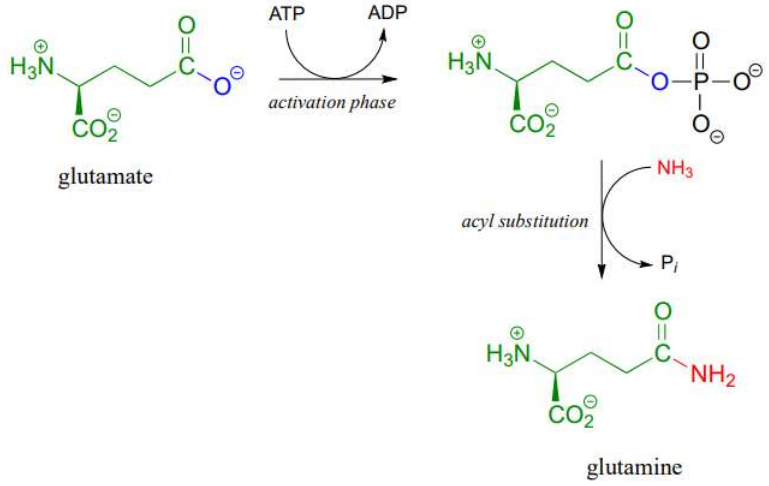
Amide formation

An activated carboxylate group (in other words, acyl phosphate or acyl-AMP) can be converted to an amide through nucleophilic attack by an amine.

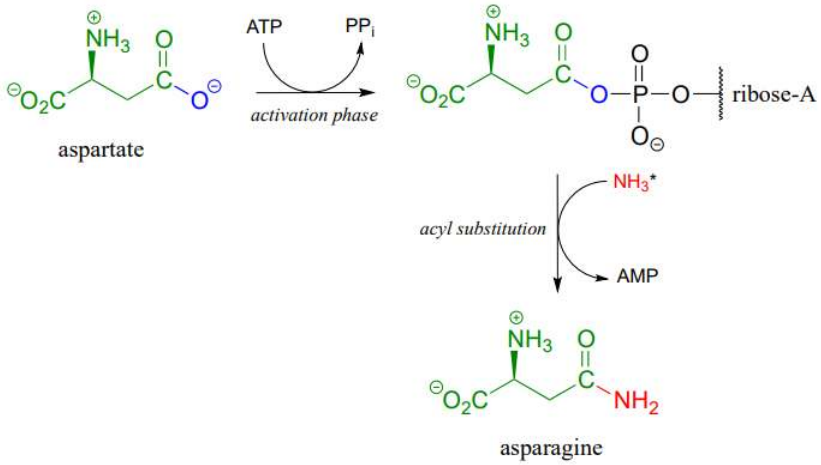
Mechanism for amide formation:



The amino acid biosynthesis pathways provide examples of amide formation in biology. The amino acid glutamine is synthesized in most species by converting the carboxylate side chain of glutamate (another amino acid) to an amide, after first activating the carboxylate by monophosphorylation: (EC 6.3.1.2)



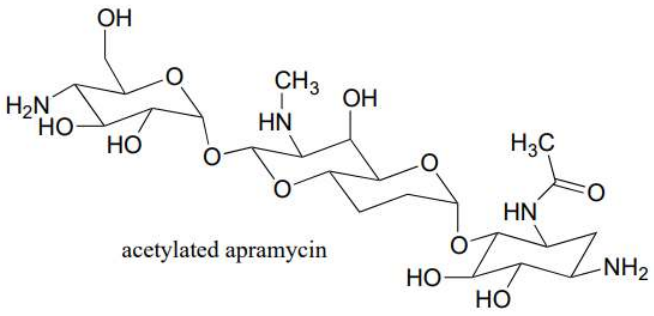
A similar process takes place in the synthesis of asparagine from aspartate, except that the activated carboxylate in this case is an acyl-AMP:



*In the asparagine synthesis reaction, the ammonia nucleophile actually comes from hydrolysis of a glutamine molecule.

? Exercise 11.6.4

A enzyme in bacteria is thought to be responsible for resistance to a class of antibiotics that includes apramycin, ribostamycin and paromomycin. The enzyme catalyzes acetylation of the antibiotic compound with acetyl-CoA as an additional substrate. The structure of acetylated apramycin is shown below.



acetylated apramycin

a. a) Identify the acetyl group that has been transferred to apramycin, (and thus inactivating it).
b. b) What functional group acts as an acetyl group donor? What functional group acts as an acetyl group?
c. c) What is the coproduct of the reaction?

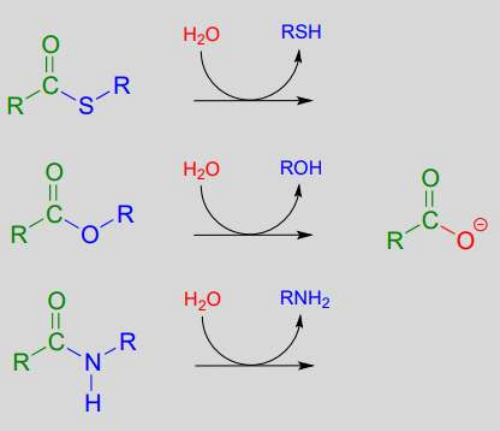
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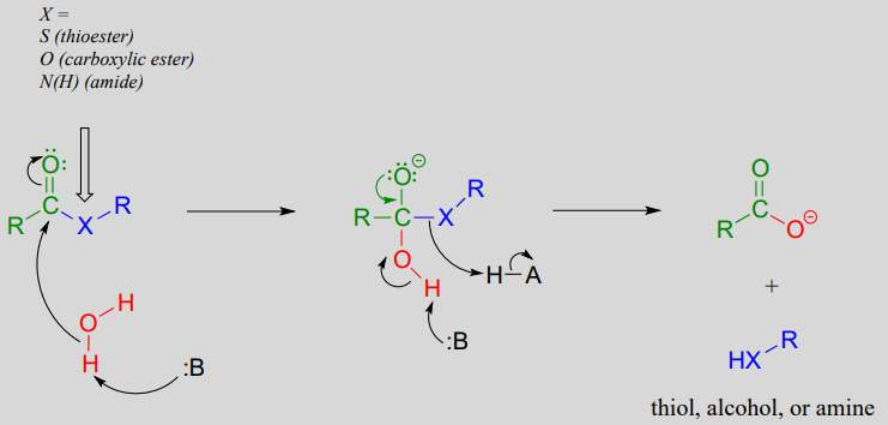
11.6: Hydrolysis of Thioesters, Esters, and Amides

So far we have been looking at the formation of thioesters, carboxylic esters, and amides, starting from carboxylates. In hydrolytic acyl substitution reactions, nucleophilic water is the incoming nucleophile and a carboxylate group is the final product. Because carboxylates are the least reactive among the carboxylic acid derivatives, these hydrolysis reactions are thermodynamically favorable, with thioester hydrolysis the most favorable of the three.

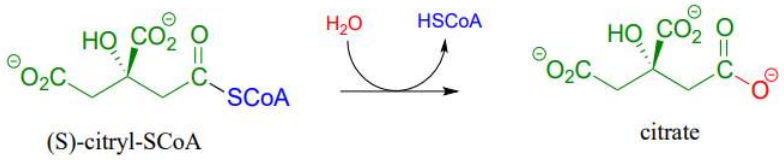
Thioester, carboxylic ester, and amide hydrolysis:



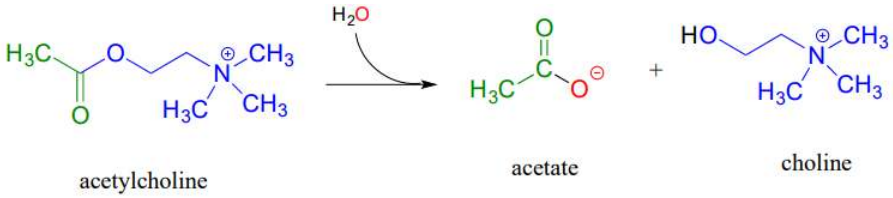
Mechanism:



In the citric acid (Krebs) cycle, (S)-citryl CoA is hydrolyzed to citrate (EC 2.3.3.8):



Acetylcholinesterase (EC 3.1.1.7), an enzyme present in the synapse, catalyzes hydrolysis of the ester group in acetylcholine, a neurotransmitter that triggers muscle contraction.



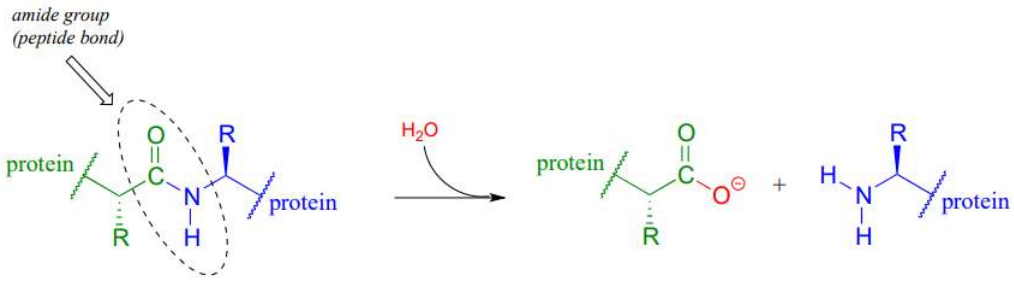
Like many other hydrolytic enzymes, the acetylcholinesterase reaction proceeds in two phases: first, a covalent enzyme-substrate intermediate is formed when the acyl group of acetylcholine is transferred to an active-site serine on the enzyme (a transesterification reaction). A water nucleophile then attacks this ester, driving off acetate and completing the hydrolysis.

? Exercise 11.7.1

Based on the above description, draw the structure of the covalent enzyme-substrate intermediate in the acetylcholinesterase reaction.

If the action of acetylcholinesterase is inhibited, acetylcholine in the synapse does not get hydrolyzed and thus accumulates, resulting in paralysis and death in severe cases. Sarin nerve gas is a potent inhibitor of acetylcholinasterase action. Some victims of the Tokyo subway sarin attack in 1995 who were exposed to low levels of the gas reported that they initially realized that something was wrong when they noticed how dark everything seemed around them. This was due to uncontrolled contraction of their pupils. You will be invited to consider the mechanism of inhibition by sarin in problem 11.6.4.

Peptide (amide) bonds in proteins and polypeptides are subject to spontaneous (nonenzymatic) hydrolysis in water.

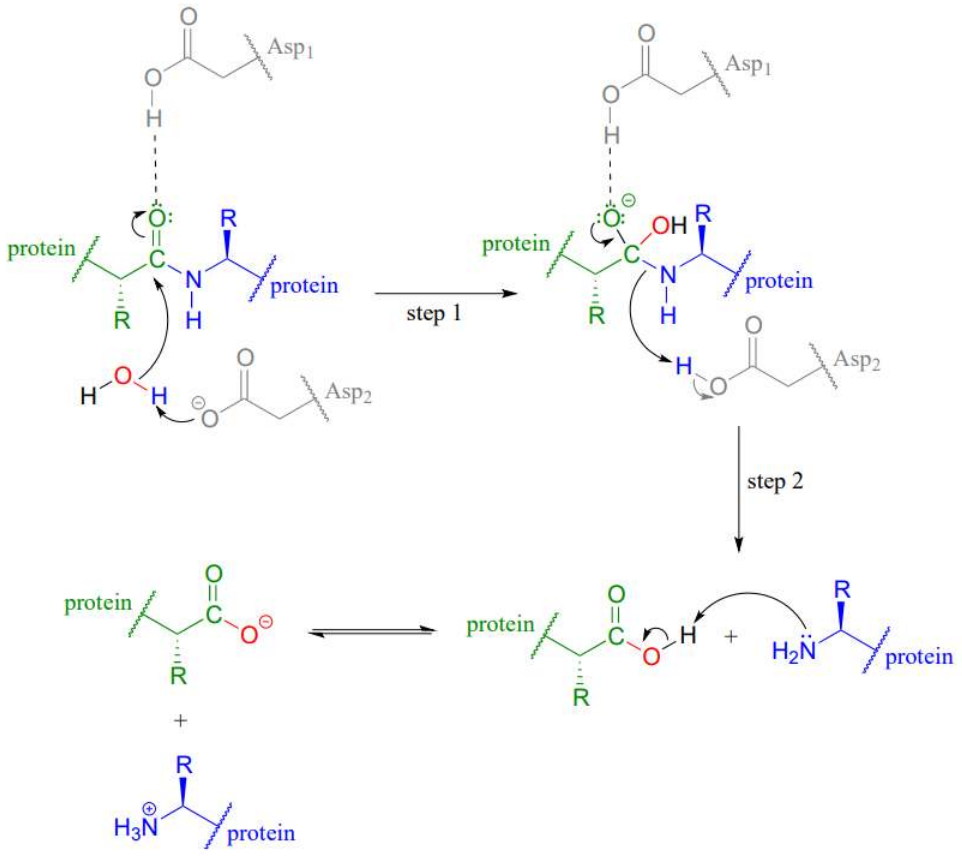


Although this amide to carboxylate conversion is thermodynamically a downhill reaction, peptide bonds are kinetically very stable (they react slowly) at neutral pH. In fact, the half-life for uncatalyzed hydrolysis of a peptide bond in pH 7 water is by some estimates as high as 1000 years. (Ann. Rev. Biochem. 2011, 80, 645.)

The stability of peptides bonds makes good physiological sense: we would all be in trouble if our enzymes, receptors, and structural proteins were hydrolyzing away while we slept! That being said, it is also true that controlled, specific hydrolysis of peptide bonds, catalyzed by a large, diverse class of enzymes called proteases, is a critical biochemical reaction type that can occur very rapidly, in many different biological contexts. For example, many proteins only become active after they have been ‘processed' - in other words, hydrolyzed at a specific amino acid location by a specific protease.

Although all proteases catalyze essentially the same reaction – amide hydrolysis - different protease subfamilies have evolved different catalytic strategies to accomplish the same result. HIV protease is the target of some the most recently-developed anti-HIV drugs. It plays a critical role in the life cycle if the HIV virus, hydrolyzing specific peptide bonds of essential viral proteins in order to convert them to their active forms. HIV protease is a member of the aspartyl protease subfamily, so-named because of the two aspartate residues located in the active sites of these enzymes. HIV protease is also, as you are probably aware, the target of HIV protease inhibitor drugs, which are a component of the most effective treatment currently available for HIV infection.

In HIV protease and other aspartyl proteases, the two enzymatic aspartates residues (shaded grey and abbreviated 'Asp1' and 'Asp2 'in the figure below) work in concert to activate the electrophile, nucleophile, and leaving group in the reaction.

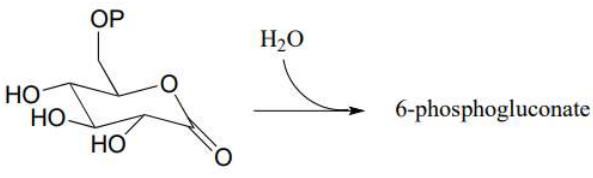


Exactly how this works is a subject of some debate and the details may well vary according to the enzyme in question, but one likely mechanism is illustrated in the figure above, where Asp1, which is initially in its protonated form, contributes a hydrogen bond to draw electron density away from the carbonyl carbon, making it more electrophilic. At the same time, Asp2, which begins the reaction cycle in its anionic form, deprotonates the water molecule to make it more nucelophilic. In step 2, Asp2 donates a proton back to the nitrogen, making it a better leaving group.

HIV protease inhibitors shut down this reaction, which prevents the virus from processing the proteins that it uses to bond to host cells.

Exercise 11.7.2

Lactonase (EC 3.1.1.17), the second enzyme in the oxidative branch of the pentose phosphate pathway, catalyzes hydrolysis of the lactone (cyclic ester) group in 6-phosphogluconolactone. Draw the structure of 6-phosphogluconate, the product of this reaction.



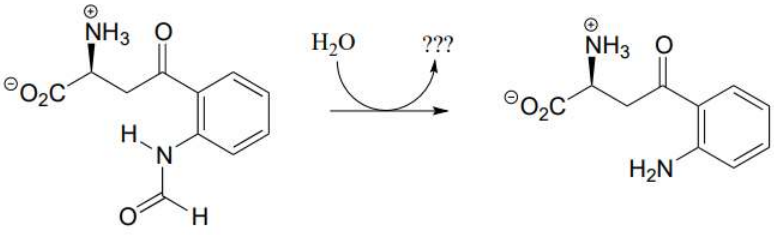
6-phosphogluconolactonate

Exercise 11.7.3

Draw the product of the β-lactamase-catalyzed hydrolysis of penicillin as described in section 11.6.

Exercise 11.7.4

What is the missing product (designated below by question marks) in the reaction below, which is part of degradation pathway for the amino acid tryptophan? How could you describe this reaction in organic chemistry terminology?



Answer

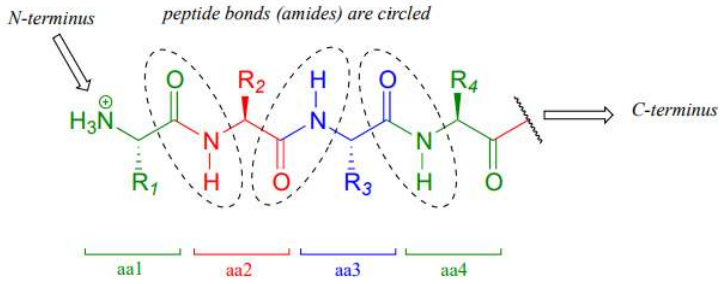
Add answer text here and it will automatically be hidden if you have a "AutoNum" template active on the page.

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11.7: Protein Synthesis on the Ribosome

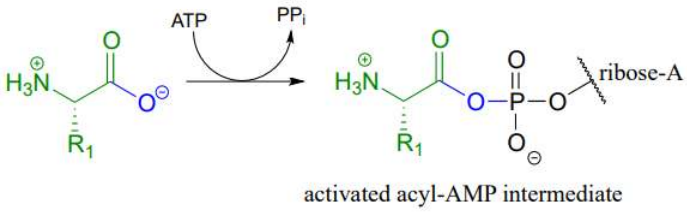
Recall from section 1.3D that the 'peptide bonds' which link amino acids to form polypeptides and proteins are in fact amide functional groups. The figure below shows the first four amino acid residues in a protein, starting at the amino terminus.



Let's take a look at the chemistry behind the formation of a new peptide bond between the first two amino acids - which we will call $aa-1$ and $aa-2$ - in a growing protein molecule. This process takes place on the ribosome, which is essentially a large biochemical 'factory' in the cell, composed up of many enzymes and RNA molecules, and dedicated to the assembly of proteins. You will learn more in a biochemistry or cell biology course about the complex but fascinating process of ribosomal protein synthesis. For now, we will concentrate on the enzyme-catalyzed organic transformation that is taking place: the formation of an amide from a carboxylate and an amine.

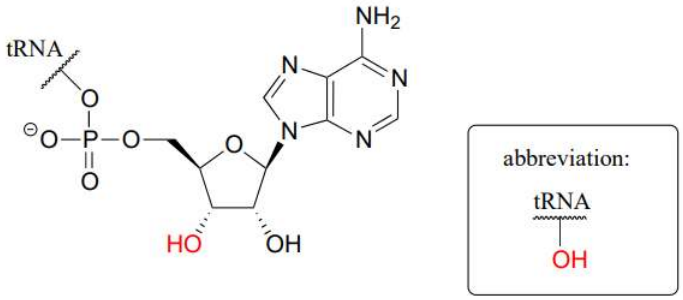
We have seen amide-forming reactions before – think back to the glutamine and asparagine synthetase reactions (section 11.5). The same ideas that we learned for those reactions hold true for peptide bond formation: the carboxylate group on a substrate amino acid must first be activated, and the energy for this activation comes from ATP.

The carboxylate group of aa-1 is first transformed to an acyl-AMP intermediate through a nucleophilic substitution reaction at the α -phosphate of ATP.

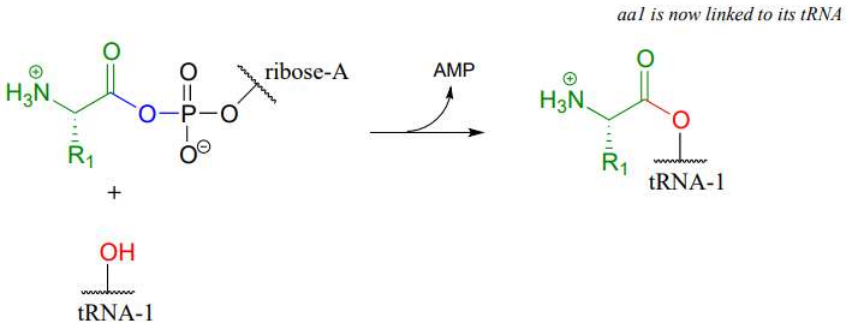


activated acyl-AMP intermediate

In the next step, the amino acid is transferred to a special kind of RNA polymer called transfer RNA, or $tRNA$ for short. We need not concern ourselves here with the structure of $tRNA$ molecules- all we need to know for now is that the nucleophile in this reaction is a hydroxyl group on the terminal adenosine of a $tRNA$ molecule. Because this $tRNA$ molecule is specific to $aa-1$, we will call it $tRNA-1$

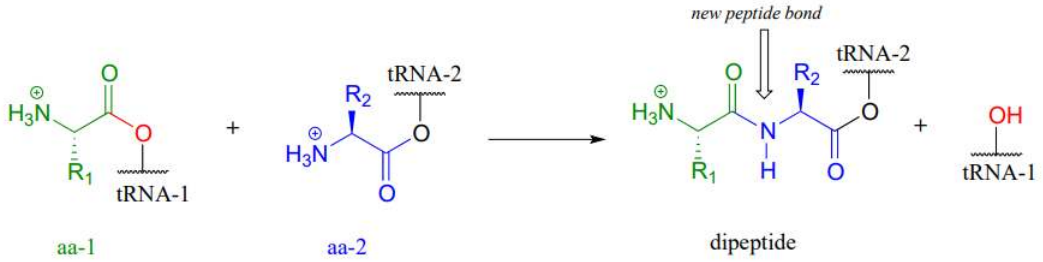


The incoming nucleophile is an alcohol, thus what we are seeing is an esterification: an acyl substitution reaction between the activated carboxylate of $aa-1$ and an alcohol on $tRNA-1$ to form an ester.

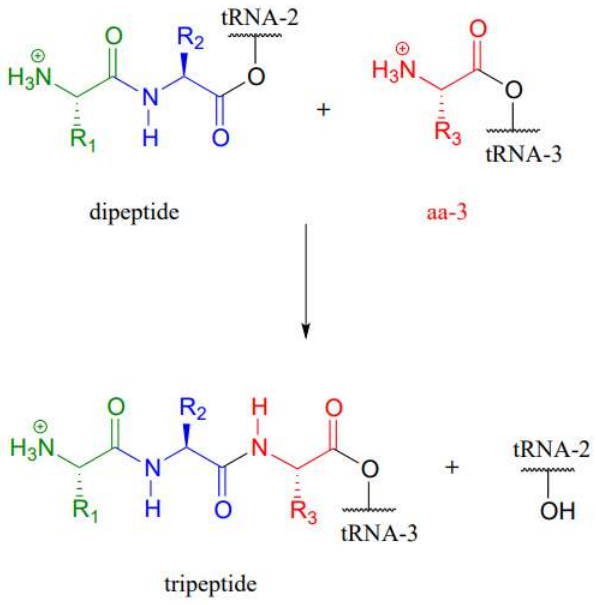


This reaction, starting with activation of the amino acid, is catalyzed by a class of enzymes called aminoacyl-$tRNA$ synthetases (there are many such enzymes in the cell, each one recognizing its own amino acid - $tRNA$ pair).

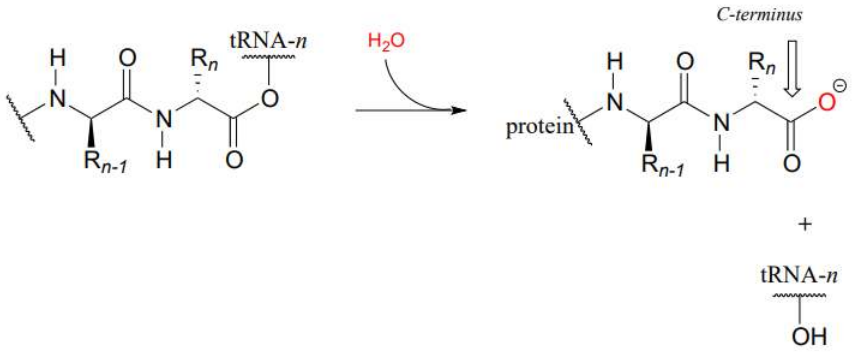
The first amino acid is now linked via an ester group to $tRNA-1$. The actual peptide bond-forming reaction occurs when a second amino acid (aa-2) also linked to its own $tRNA-2$ molecule, is positioned next to the first amino acid on the ribosome. In another acyl substitution reaction, catalyzed by an enzymatic component of the ribosome called peptidyl transferase (EC 2.3.2.12), the amino group on $aa-2$ displaces $tRNA1$: thus, an ester has been converted to an amide (thermodynamically downhill, so ATP is not required).



This process continues on the ribosome, as one amino acid after another is added to the growing protein chain:



When a genetically-coded signal indicates that the chain is complete, an ester hydrolysis reaction – as opposed to another amide formation - occurs on the last amino acid, which we will call $aa-n$. This reaction is catalyzed by proteins called release factors (RFs).



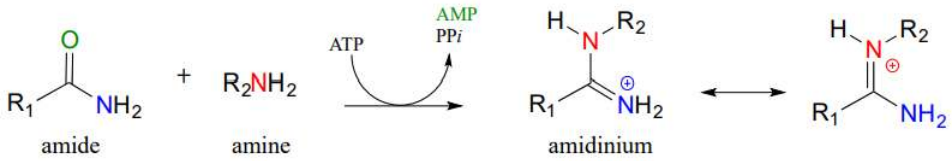
This hydrolysis event frees the mature protein from the ribosome, and results in the formation of a free carboxylate group at the end of the protein (this is called the carboxy-terminus, or *C*-terminus of the protein, while the other end – the 'starting' end – is called the *N*-terminus).

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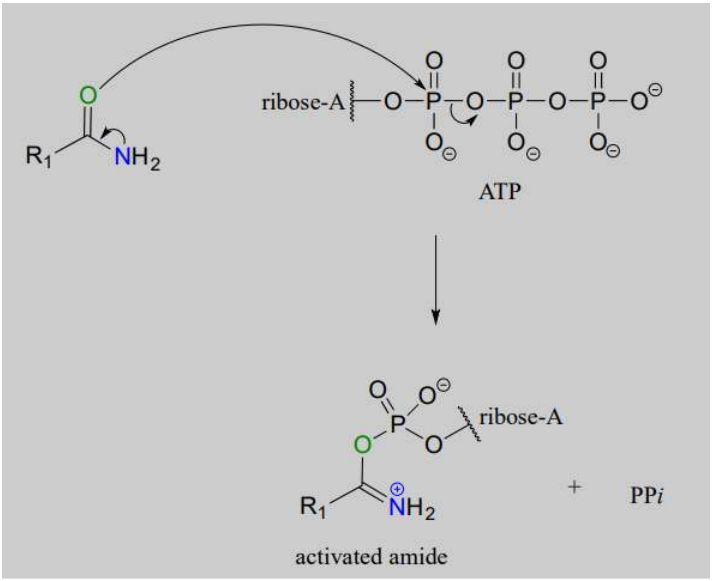
11.8: Nucleophilic Substitution at Activated Amides and Carbamides

In discussing the nucleophilic acyl substitution reactions of acyl phosphates, thioesters, esters, and amides, we have seen many slight variations on one overarching mechanistic theme. Let's now look at a reaction that can be thought of as a 'cousin' of the nucleophilic acyl substitution, one that follows the same general pattern but differs in several details. Below is a generic illustration of this reaction type:



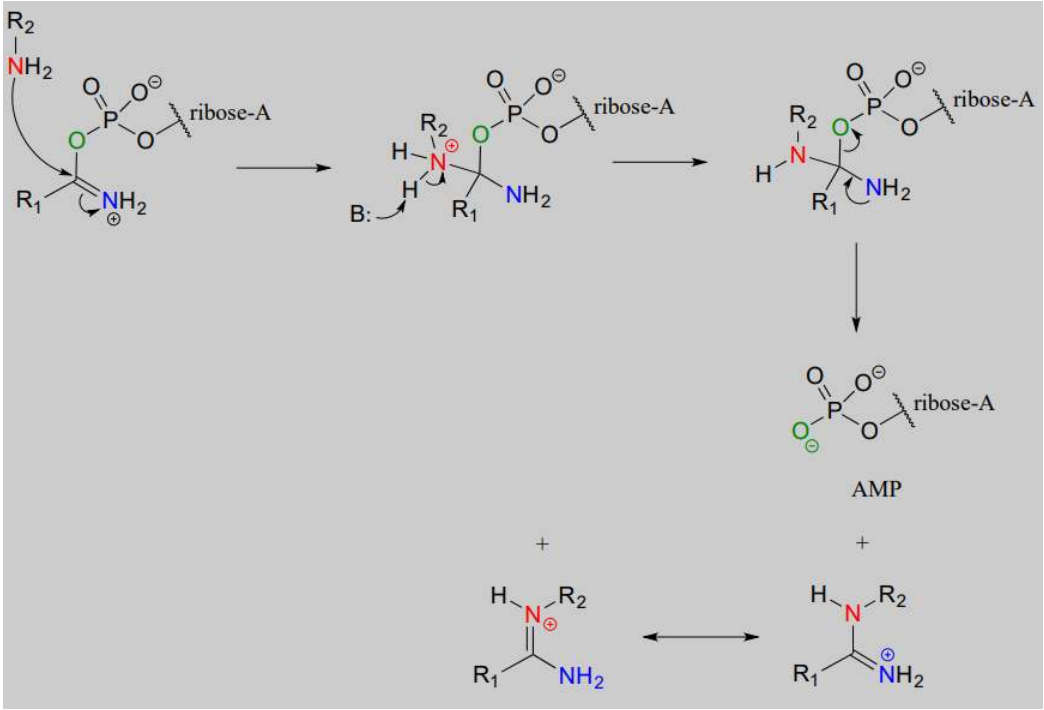
Looking at this reaction, you can see that substitution is occurring at an amide group, but the atom that gets expelled is the amide oxygen rather than the amide nitrogen. Also, we see that the substituting nucleophile is an amine, and the product is a functional group referred to as an amidinium ion (the uncharged conjugate base is called an amidine, and the pKa of the group is close enough to 7 that it can be shown in either protonated or deprotonated form in a biological context). As we learned previously in this chapter, amides are comparatively stable to nucleophilic substitution, and thus it stands to reason that the starting amide must be activated before the reaction can take place. This occurs, as you might predict, through the formation of an acyl phosphate intermediate at the expense of one ATP molecule. The amide oxygen acts as a nucleophile, attacking the a-phosphate of ATP to form the activated acyl-AMP intermediate:

Substitution at an activated amide, phase 1 (activation):

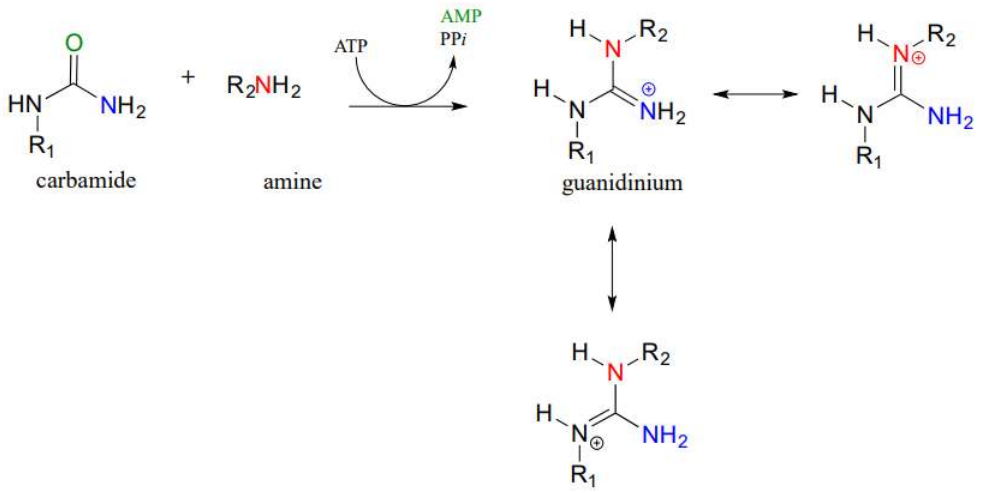


Next, a kind of acyl substitution occurs that we have not yet seen: an amine nitrogen attacks the electrophilic carbon of a carbon-nitrogen double bond, and the reaction proceeds through a tetrahedral intermediate before the AMP group is expelled, taking with it what was originally the carbonyl oxygen of the starting amide.

Substitution at an activated amide, phase 2:

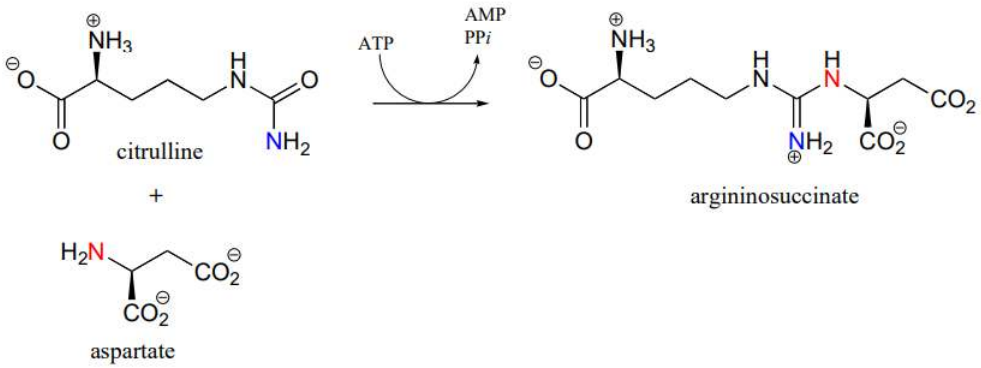


Carbamides, a kind of 'double amide' functional group in which a carbonyl oxygen is bonded to two nitrogens, also undergo this type of reaction, leading to the formation of a guanidinium/gaunidine functional group (look again at the structure of the amino acid arginine and you will see that it contains a guanidinium group on the side chain).



The reaction catalyzed by argininosuccinate synthetase (EC 6.3.4.5) is the second step in the urea cycle, a four-step series of reactions in which ammonia is converted into urea for elimination in urine. Note that the substitution takes place at the carbamide group of citrulline, the nucleophilic amine is on aspartate, and the product has a guanidinium functional group.

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Exercise 11.9.1

a. Draw the structure of the 'activated carbamide' intermediate in the reaction above.
b. Draw the structure of the cyclic product of a hypothetical intramolecular substitution reaction of citrulline (ie. aspartate is not involved).

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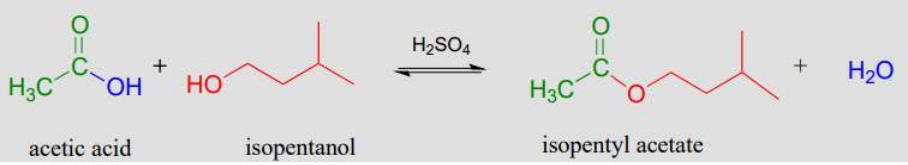
11.9: Nucleophilic Acyl Substitution Reactions in the Laboratory

All of the biological nucleophilic acyl substitution reactions we have seen so far have counterparts in laboratory organic synthesis. Mechanistically, one of the biggest differences between the biological and the lab versions is that the lab reactions usually are run with a strong acid or base as a catalyst, whereas biological reactions are of course taking place at physiological pH. When proposing mechanisms, then, care must be taken to draw intermediates in their reasonable protonation states: for example, a hydronium ion (H_3O^+) intermediate is reasonable to propose in an acidic reaction, but a hydroxide (OH^-) intermediate is not.

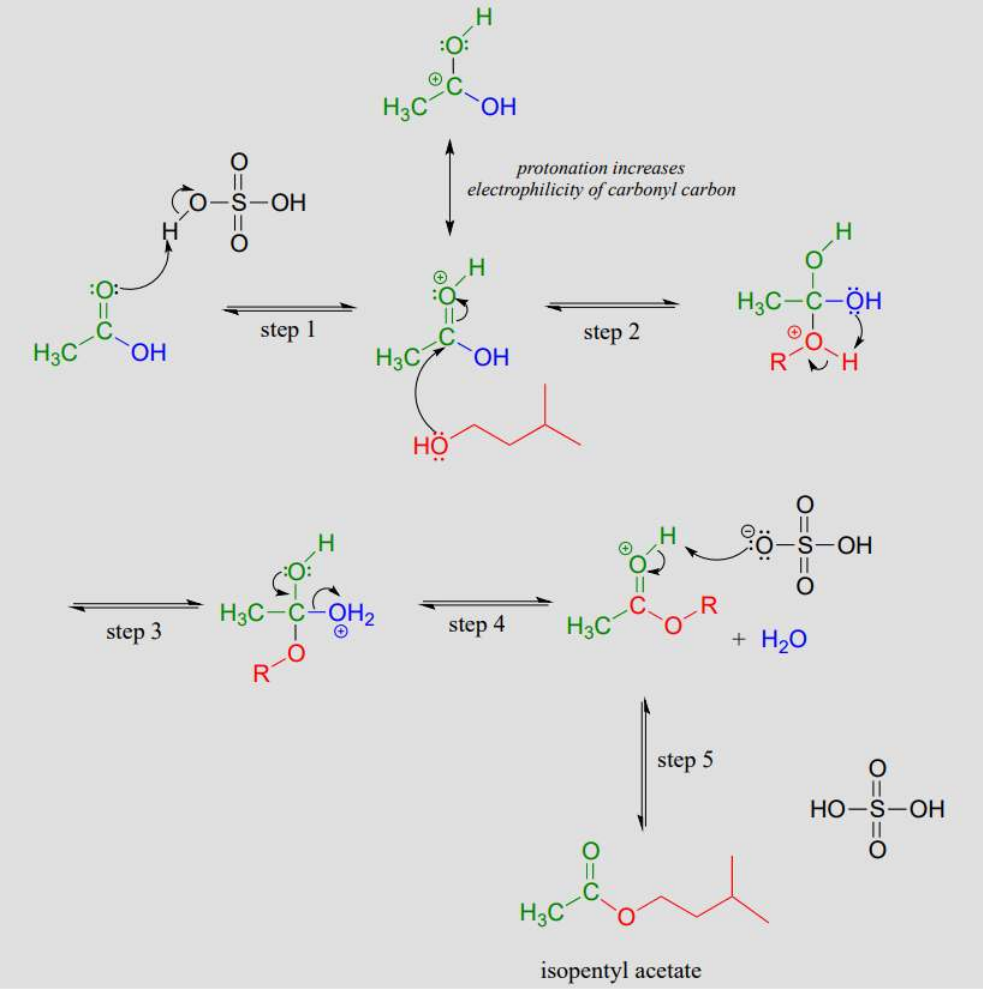
Ester reactions - bananas, soap and biodiesel

Acid-catalyzed synthesis of flavor compounds such as isopentyl acetate (an ester with the flavor of banana) is simple to carry out in the lab. In this esterification reaction, acetic acid is combined with isopentyl alcohol along with a catalytic amount of sulfuric acid.

Acid-catalyzed esterification (laboratory reaction):



Mechanism:



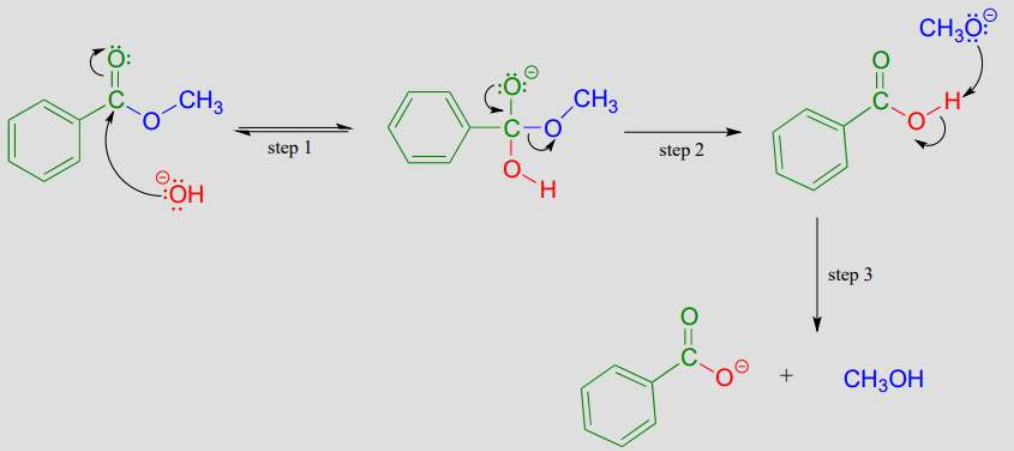
The carbonyl oxygen of acetic acid is first protonated (step 1), which draws electron density away from the carbon and increases its electrophilicity. In step 2, the alcohol nucleophile attacks: notice that under acidic conditions, the nucleophile is not deprotonated

simultaneously as it attacks (as we would show in a biochemical mechanism), and the tetrahedral intermediate is a cation rather than an anion. In step 3, a proton is transferred from one oxygen atom to another, creating a good leaving group (water) which is expelled in step 4. Finally (step 5), the carbonyl oxygen on the ester is deprotonated, regenerating the catalytic acid.

This reaction is highly reversible, because carboxylic acids are approximately as reactive as esters. In order to obtain good yields of the ester, an excess of acetic acid can be used, which by Le Chatelier's principle (see your General Chemistry textbook for a review) shifts the equilibrium toward the ester product.

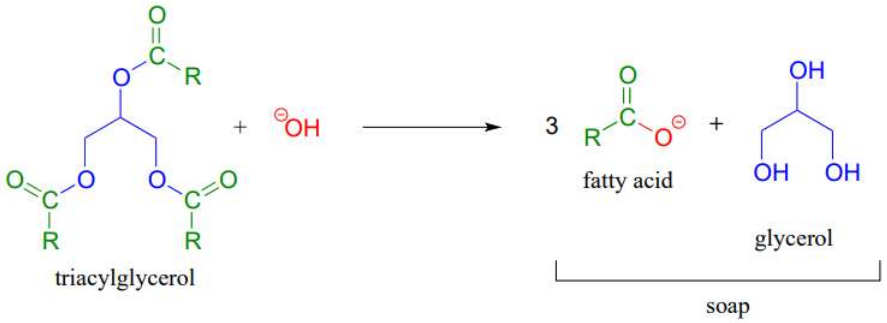
Saponification is a common term for base-induced hydrolysis of an ester. For example, methyl benzoate will hydrolize to benzoate and methanol when added to water with a catalytic amount of sodium hydroxide.

Mechanism of base-catalyzed ester hydrolysis (saponification):

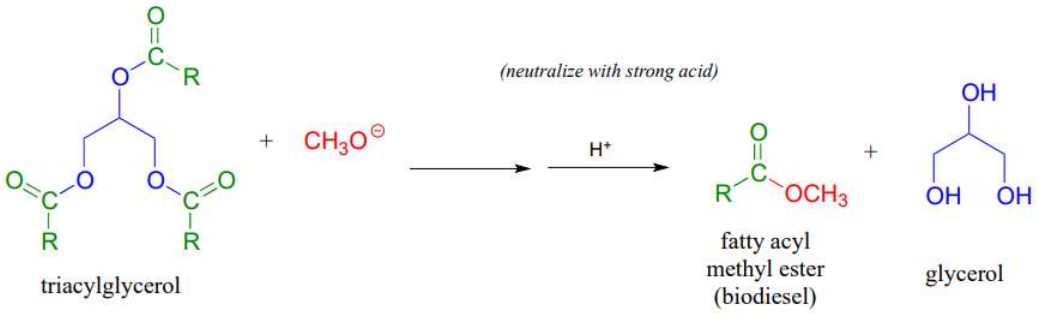


Addition of the base provides hydroxide ion to act as a nucleophile (hydroxide is of course a better nucleophile than water) in step 1. The tetrahedral intermediate (anionic in this case, because the reaction conditions are basic) then collapses in step 2, and the alkoxide (CH_3O^-) leaves. We are not used to seeing alkoxides or hydroxides as leaving groups in biochemical reactions, because they are strong bases - but in a basic solution, this is a reasonable chemical step. Step 3 is simply an acid-base reaction between the carboxylic acid and the alkoxide. Note that this is referred to as base-induced rather than base-catalyzed because hydroxide is not regenerated, and thus a full molar equivalent of base must be used.

The saponification process derives its name from the ancient craft of soap-making, in which the ester groups of triacylglycerols in animal fats are hydrolized under basic conditions to glycerol and fatty acyl anions (see section 2.5A for a reminder of how fatty acyl anions work as soap).



We learned earlier about transesterification reactions in the context of the chemical mechanism of aspirin. Transesterification also plays a key role in a technology that is already an important component in the overall effort to develop environmentally friendly, renewable energy sources: biodeisel. You may have heard stories about people running their cars on biodeisel from used french fry oil. To make biodeisel, triacylglycerols in fats and oils can be transesterified with methanol or ethanol under basic conditions. The fatty acyl methyl and ethyl ester products are viable motor fuels.



? Exercise 11.10.1

Draw structures of the carboxylic acid and alcohol starting materials that could be used to synthesize the fragrant fruit esters shown in section 11.1.

? Exercise 11.10.2

What would happen if you tried to synthesize isopentyl acetate (banana oil) with basic rather than acidic conditions? Would this work?

? Exercise 11.10.3

Consider the reverse direction of the acid-catalyzed esterification reaction. What would you call this reaction in organic chemistry terms?

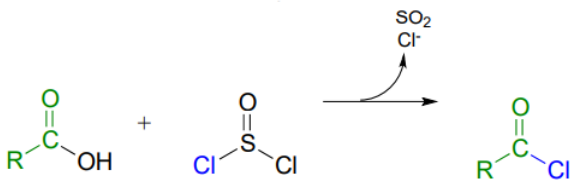
? Exercise 11.10.4

An alternative way to synthesize esters is to start with a carboxylate and an alkyl halide. Draw a mechanism for such a synthesis of methyl benzoate - what type of reaction mechanism is this?

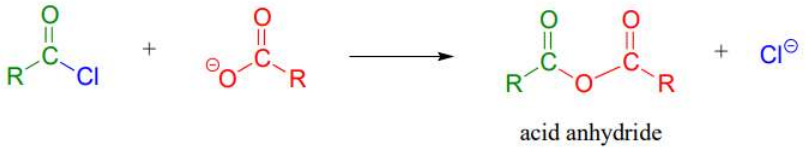
Acid chlorides and acid anhydrides

In the cell, acyl phosphates and thioesters are the most reactive of the carboxylic acid derivatives. In the organic synthesis lab, their counterparts are acid chlorides and acid anhydrides, respectively. Of the two, acid chlorides are the more reactive, because the chloride ion is a weaker base and better leaving group than the carboxylate ion (the pK_a of HCl is -7, while that of carboxylic acids is about 4.5: remember, a stronger conjugate acid means a weaker conjugate base).

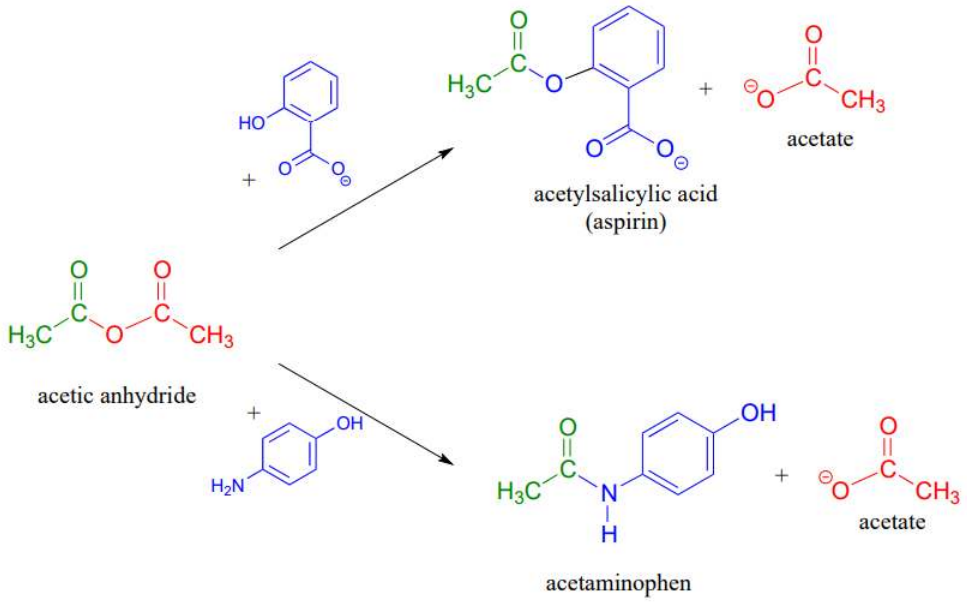
Acid chlorides can be prepared from carboxylic acids using $SOCl_2$:



Acid anhydrides can be prepared from carboxylic acids and an acid chloride under basic conditions:



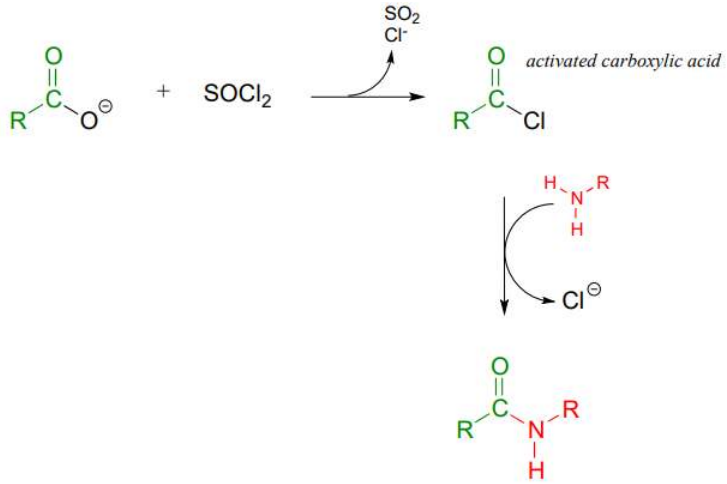
Acetic anhydride is often used to prepare acetate esters and amides from alcohols and amines, respectively. The synthesis of aspirin and acetaminophen are examples:



A carboxylic acid cannot be directly converted into an amide because the amine nucleophile would simply act as a base and deprotonate the carboxylic acid:



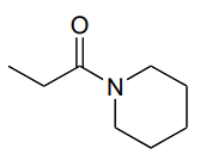
Instead, the carboxylic acid is first converted to an acid chloride (in other words, the carboxylic acid is activated), then the acid chloride is combined with an amine to make the amide.



This sequence of reactions is a direct parallel to the biochemical glutamine and asparagine synthase reactions we saw earlier in the chapter (section 11.5), except that the activated form of carboxylic acid is an acid chloride instead of an acyl phosphate or acyl-AMP.

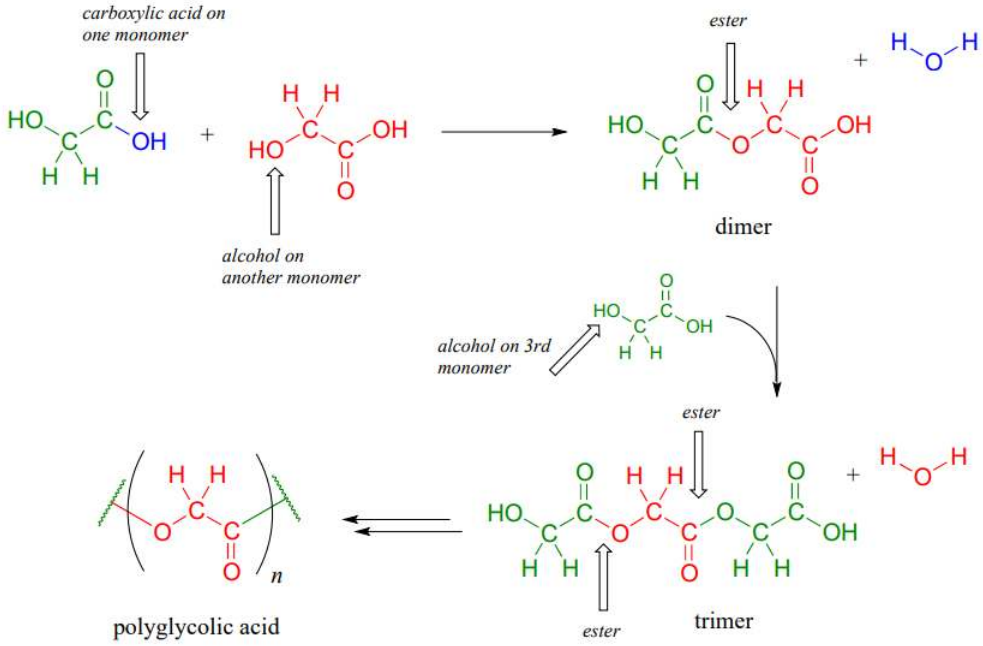
? Exercise 11.10.5

For the preparation of the amide below, show a starting carboxylate and amine and the intermediate acid chloride species.



Polyesters and polyamides

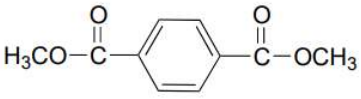
If you have ever had the misfortune of undergoing surgery or having to be stitched up after a bad cut, it is likely that you benefited from our increasing understanding of polymers and carboxylic ester chemistry. Polyglycolic acid is a material commonly used to make dissolving sutures. It is a polyester - a polymer linked together by ester groups - and is formed from successive acyl substitution reactions between the alcohol group on one end of a glycolic acid monomer and the carboxylic acid group on a second:



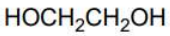
The resulting polymer - in which each strand is generally several hundred to a few thousand monomers long - is strong, flexible, and not irritating to body tissues. It is not, however, permanent: the ester groups are reactive to gradual, spontaneous hydrolysis at physiological ***pH***, which means that the threads will dissolve naturally over several weeks, eliminating the need for them to be cut out by a doctor.

? Exercise 11.10.6

Dacron, a polyester used in clothing fiber, is made of alternating dimethyl terephthalate and ethylene glycol monomers.



dimethyl terephthalate

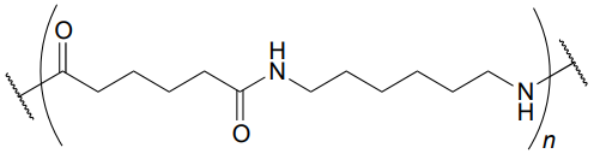


ethylene glycol

a. Draw the structure of a Dacron tetramer (in other words, four monomers linked together).
b. Water is a side product of glycolic acid polymerization. What is the equivalent side product in Dacron production?

Exercise 11.10.7

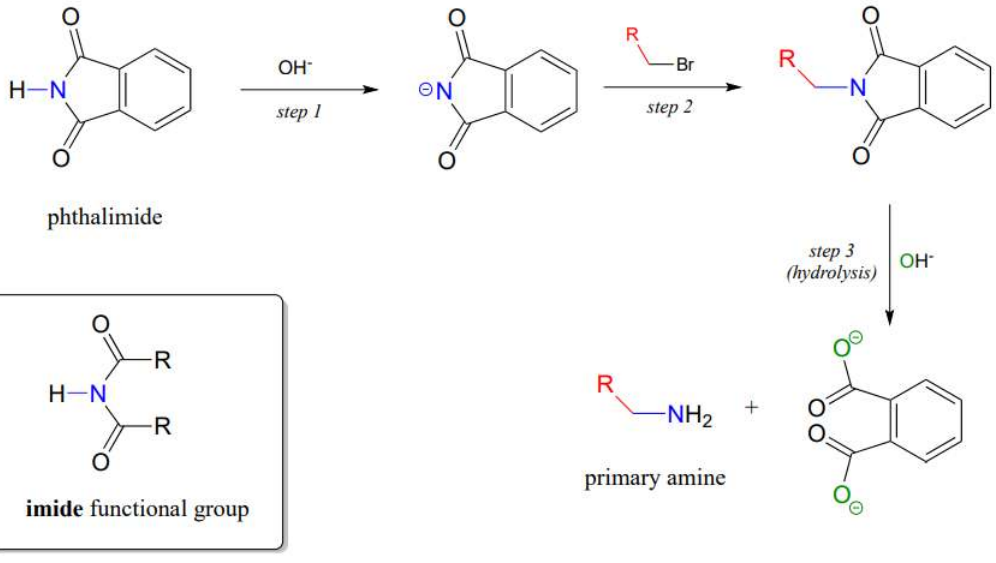
Nylon 6,6 is a widely used polyamide composed of alternating monomers. Nylon 6,6 has the structure shown below -the region within the parentheses is the repeating unit, with 'n' indicating a large number of repeats. Identify the two monomeric compounds used to make the polymer.



Nylon 66

The Gabriel synthesis of primary amines

The Gabriel synthesis, named after the 19th-century German chemist Siegmund Gabriel, is a useful way to convert alkyl halides to amines and another example of S_N2 and acyl substitution steps in the laboratory. The nitrogen in the newly introduced amine group comes from phthalimide. In the first step of the reaction, phthalimide is deprotonated by hydroxide, then in step 2 it acts as a nucleophile to displace a halide in an S_N2 reaction (phthalimide is not a very powerful nucleophile, so this reaction works only with unhindered primary or methyl halides).

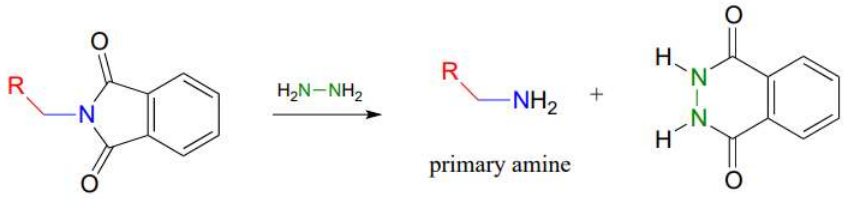


Step 3 is simply a pair of hydrolytic acyl substitution steps to release the primary amine, with an aromatic dicarboxylate by-product.

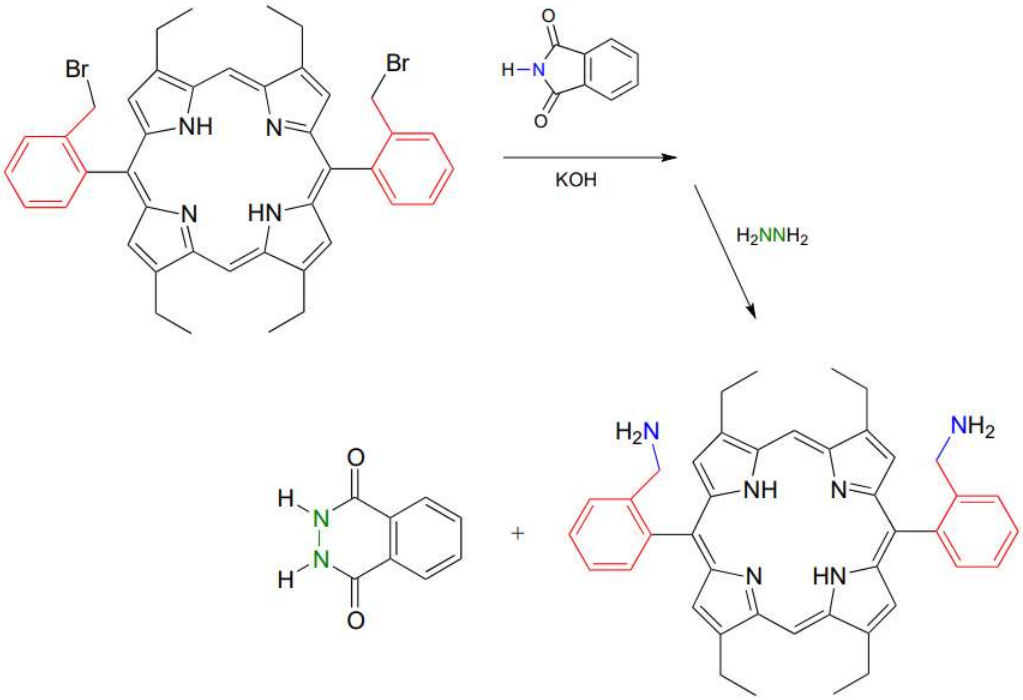
Exercise 11.10.8

Phthalimide contains an 'imide' functional group, and has a pK_a of approximately 10. What makes the imide group so much more acidic than an amide, which has a pK_a of approximately 17?

As an alternative procedure, release of the amine in step 3 can be carried out with hydrazine (H_2NNH_2) instead of hydroxide. Again, this occurs through two nucleophilic acyl substitution reactions.



In 2000, chemists at MIT synthesizing a porphyrin-containing molecule introduced two amine groups using the Gabriel synthesis with hydrazine. Porphyrins, which include the 'heme' in our red blood cells, are an important family of biomolecules with a variety of biochemical function (J. Org. Chem. 2000, 65, 5298).



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11.10: A Look Ahead - Acyl Substitution Reactions with a Carbanion or Hydride Ion Nucleophile

Although we have seen many different types of nucleophilic acyl substitutions in this chapter, we have not yet encountered a reaction in which the incoming nucleophile is a carbanion or a hydride. Recall that in the previous chapter on aldehydes and ketones, we also postponed discussion of nucleophilic carbonyl addition reactions in which a carbanion or a hydride is the nucleophile. The reason for putting off these discussions is that these topics are both important and diverse enough to warrant their own dedicated chapters.

In the next chapter, we will see many carbonyl addition and acyl substitution reactions where the nucleophilic species is a resonance-stabilized carbanion such as an enolate (section 7.6). Then in chapter 14, we will encounter nucleophilic addition and acyl substitution reactions in which a hydride ion (H^-) essentially plays the part of a nucleophile. In these chapters we will see how nucleophilic carbanion and hydride species are generated in a biochemical context. For now, see if you can predict the result of the following biochemical reactions.

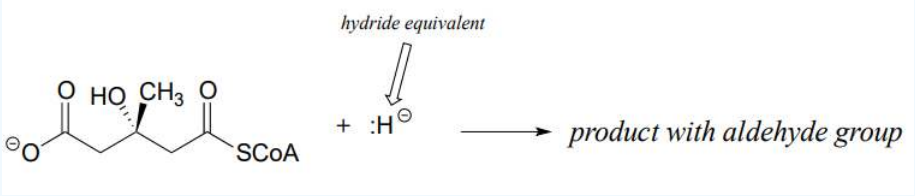
Exercise 11.11.1

Predict the products of the following nucleophilic acyl substitution reactions, both of which are part of the biosynthesis of isoprenoid compounds such as cholesterol and lycopene:

a. acetoacetyl CoA acetyltransferase reaction (enolate nucleophile)



b. HMG-CoA reductase reaction (to repeat, the nucleophile here is not literally an isolated hydride ion, which would be a very unlikely species in a physiological environment. We will learn in chapter 16 what is actually going on, but for the time being, just predict the result of an acyl substitution reaction with a "hydride ion" nucleophile.)

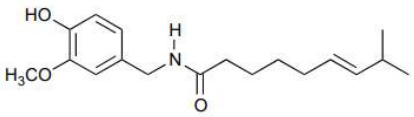


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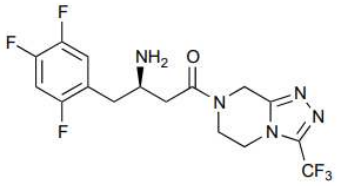
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11.E: Nucleophilic Acyl Substitution Reactions (Exercises)

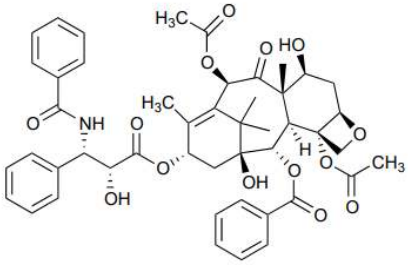
P11.1: Here is some practice in recognizing carboxylic acid derivative functional groups in large, complex biological molecules. There are seven amide and four ester groups in the molecules below - see if you can find them all.



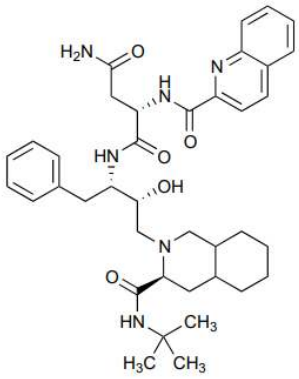
capsaicin
(the 'hot' molecule in hot peppers)



sitagliptin
(component of Janumet, a diabetes drug from Merck Pharmaceuticals)



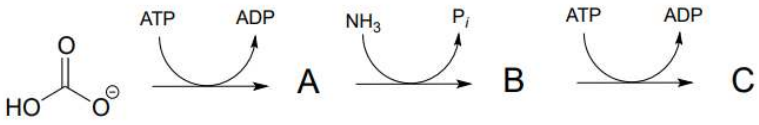
paclitaxel
(cancer drug Taxol from Bristol-Myers Squibb)



Saquinavir
(first HIV protease inhibitor to be approved by FDA)

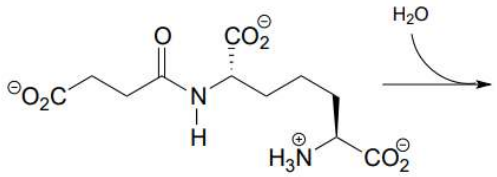
P11.2

a. a) Predict the structures of intermediate compounds A, B, and C in the reaction below (EC 6.3.4.16). Compound C contains an activated carboxylate functionality. Use abbreviations as appropriate.
b. Draw a reasonable mechanism for the A to B step



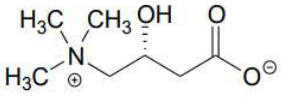
P11.3: Imagine that acetylcholine is combined with acetylcholinesterase (section 11.6) in a buffer made from ^{18}O-labeled water. Where would you expect to find the ^{18}O label in the products?

P11.4: Predict the products of this hydrolysis reaction (EC 3.5.1.18):



P11.5: The breakdown of fat in our bodies begins with the action of lipase enzymes, which catalyze the cleavage of fatty acids from t glycerol backbone of triacylglycerol (see section 1.3 for a reminder of the structure of triacylglycerol). A serine residue in the lipase acti site plays a key nucleophilic role in the reaction. Draw the single mechanistic step in which the covalent link between a fatty acid and t glyceryl backbone is broken, using curved arrow notation and appropriate abbreviation.

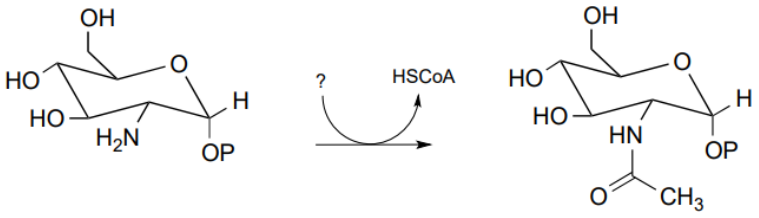
P11.6: Before long-chain fatty acids are transported across the inner mitochondrial membrane, they are temporarily transferred from Coenzyme A to a transport molecule called carnitine, to which they are linked by an ester group (EC 2.3.1.21).



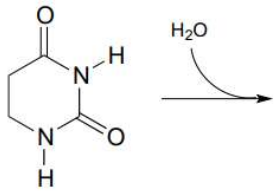
carnitine

Draw the structure of fatty acyl carnitine (use R to denote the hydrocarbon chain of the fatty acid)

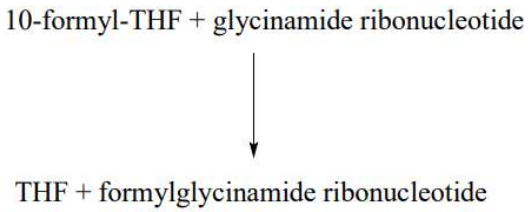
P11.7: Below is a reaction from carbohydrate metabolism (EC 2.3.1.157). Identify the compound designated with a question mark.

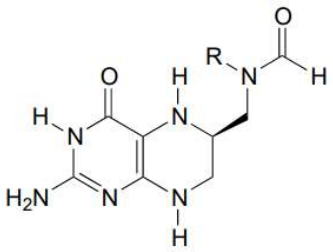


P11.8: Propose the most likely enzymatic hydrolysis product of the substrate below (hint - think about electrophilicity when consideri regiochemical outcomes!) (EC 3.5.2.2) J. Biol. Chem. 2006, 281, 13762 scheme 2)

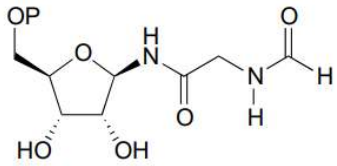


P11.9: The coenzyme tetrahydrofolate (***THF***) participates in single-carbon transfer reactions. One derivative of ***THF***, called 10-form ***THF*** (abbreviated structure shown below), transfers a formyl group early in purine ribonucleotide biosynthesis to glycinami ribonucleotide.





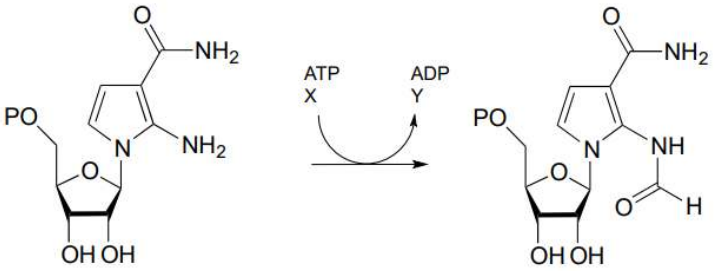
10-formyl-THF



formylglycinamide ribonucleotide

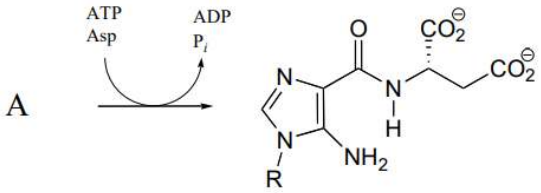
Draw a nucleophilic attack step for this reaction (assume that acyl transfer between the two substrates is direct, without any covalent enzyme-substrate intermediates being formed).

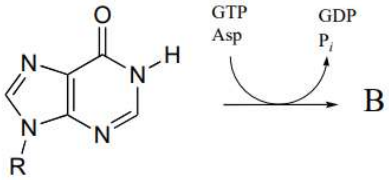
P11.10: One of the key steps in the biosynthesis of purine nucleotides (guanosine and adenosine) in archaea is shown below.



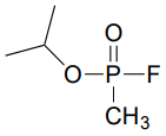
Identify the missing compounds X and Y in the figure above, and draw the structure of an acyl phosphate intermediate.

P11.11: The reactions below are part of nucleotide biosynthesis. Predict the structures of compounds A and B. Compound A contains a carboxylate group, and the reaction that forms compound B is of the type discussed in section 11.8, in which an amine group substitutes at an activated amide to form an amidine/amidinium group.



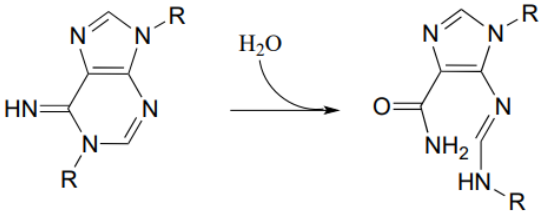


P11.12: Recall from section 11.6 that acetylcholinesterase catalyzes the hydrolysis of the ester group in acetylcholine, going through intermediate in which the acetyl group on the substrate is transferred to a serine on the enzyme by a transesterification reaction. The ner gas sarin acts by blocking this initial transesterification step: the drug enters the active site and attaches to the active site serine. Given t structure of sarin below, propose a mechanism for how this happens.

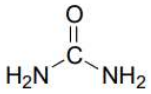


sarin

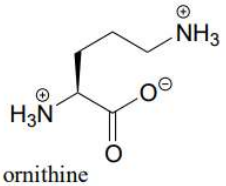
P11.13: Propose a mechanism for the following reaction from histidine biosynthesis (EC 3.5.4.19).



P11.14 (Challenging!) In the final step of the urea cycle (a phase of amino acid degradation pathways), the amino acid arginine hydrolyzed to urea and ornithine (EC 3.5.3.1). Propose a reasonable mechanism.

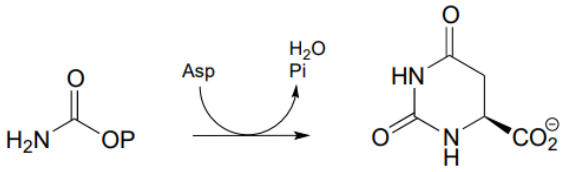


urea



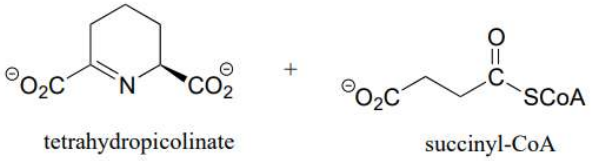
ornithine

P11.15: In the biosynthetic pathway for the DNA/RNA bases uridine and cytidine, a reaction occurs in which carbamoyl phospha condenses with aspartate, and the resulting intermediate cyclizes to form dihydroorotate. Propose a mechanism for this transformatic Hint: in a very unusual step, a carboxylate group is at one point in the process directly subjected to an acyl transfer reaction, without pr activation by phosphorylation. The enzyme accomplishes this with the help of two bo.und zinc ions, which serve to stabilize the negati charge on a hydroxide leaving group. (EC 3.5.2.3) (Biochemistry 2001, 40, 6989, Scheme 2)



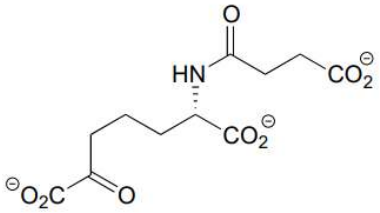
dihydroorotate

P11.16: Propose a reasonable mechanism for the reaction below (from lysine biosynthesis), and fill in the missing species indicated by question marks.



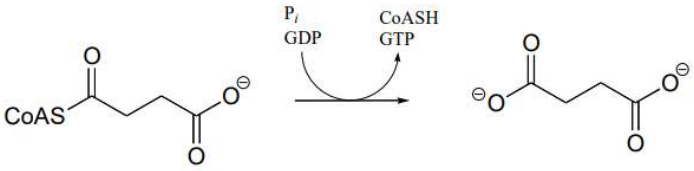
tetrahydropicolinate

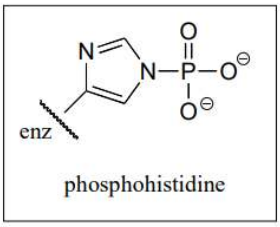
succinyl-CoA



P11.17: In a step in the citric acid cycle, hydrolysis of succinyl-***CoA*** is coupled to phosphorylation of GDP. The mechanism involves t transient phosphorylation of an active site histidine. Suggest a (multi-step) mechanism for this process (EC 6.2.1.4).

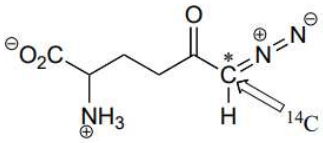
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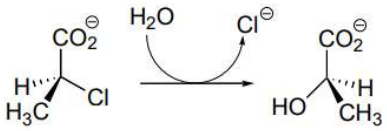
P11.18: A ^{14}C-labeled diazoketone compound (structure below) was used to irreversibly inactivate an enzyme called glutaminase Inactivation was shown to occur with ^{14}C labeling of an active site cysteine.

a)Propose a mechanism of inactivation and cysteine labeling.



b) To a lesser extent, inactivation of the enzyme and labeling of the cysteine was found to occur with release of a radioactive compou from the active site. Propose a mechanism for the mode of inactivation.

P11.19: Dehelogenase enzymes catalyze the cleavage of carbon-halogen bonds, and are of interest to scientists looking for new ways detoxify organohalogen pollutants that make their way into the environment. One such dehalogenase catalyzes the following reaction:



An active site aspartate is thought to carry out the initial nucleophilic attack that expels the chloride.

a. Draw a likely mechanism for the complete reaction shown above. Look carefully at the stereochemical progress!
b. When the active site aspartate was mutated to asparagine, the enzyme still maintained activity. Mass spectrometry analysis indicated that, at one point in the catalytic cycle of the mutant enzyme, the asparagine exists as a cyanoalanine. Draw a likely mechanism for the reaction as catalyzed by the mutant enzyme, including formation of the transient cyanoalanine residue and subsequent regeneration of the asparagine.

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11.S: Nucleophilic Acyl Substitution Reactions (Summary)

Before moving forward you should be able to:

- Recognize and draw examples of carboxylic acid derivative functional groups:
  - carboxylic acids/carboxylates
  - acyl phosphates (both acyl monophosphate and acyl-AMP)
  - thioesters
  - esters
  - amides
  - acid chlorides
  - carboxylic acid anhydrides
- Know the meaning of the terms 'acyl', 'acetyl', 'formyl', 'lactone', and 'lactam'.
- You need not memorize the structure of coenzyme A, but you should recognize that it contains a key thiol group and often forms thioester linkages, particularly in fatty acid metabolism.
- Understand what happens in a nucleophilic acyl substitution (also called acyl transfer reaction), and be able to draw mechanistic arrows for a generalized example.
- Know the trends in relative reactivity for the carboxylic acid derivatives:
  - in a biological context (acyl phosphates and thioesters as activated acyl groups)
  - in a laboratory context (acid chlorides and carboxylic acid anhydrides as activated acyl groups)
- Recognize and understand the most important types of nucleophilic acyl substitution reactions in biology:
  - How a carboxylate group, which is unreactive to nucleophilic acyl substitution reactions, is activated in the cell by ATP-dependent phosphorylation to either acyl monophosphate or acyl-AMP.
  - Conversion of an acyl phosphate to a thioester, a (carboxylic) ester, or an amide.
  - Transthioesterification, esterification, and transesterification reactions.
  - Conversion of a thioester or ester to an amide
  - Hydrolysis of a thioester, a (carboxylic) ester, or an amide to a carboxylate.
- Understand the energetics of the above reactions:
  - Carboxylate to acyl phosphate is 'uphill' energetically, paid for by coupling to hydrolysis of one ATP
  - Other conversions above are 'downhill': it is unlikely, for example, to see a direct conversion of an amide to an ester. (Notable exception: the lactam (cyclic amide) group in penicillin is very reactive due to ring strain, and forms an ester with an active site serine residue in the target protein)
- You need not memorize all of the details of peptide bond formation on the ribosome, but you should be able to follow the description in section 7 and recognize the nucleophilic acyl substitution reactions that are occuring.
- Be able to draw complete mechanisms for the following lab reactions:
  - acid-catalyzed esterification of a carboxylic acid
  - saponification (base-catalyzed hydrolysis of an ester), application to soap-making
  - base-catalyzed transesterification, application to biodiesel production
- Understand how acid chlorides and carboxylic acid anhydrides serve as activated acyl groups in laboratory synthesis. Be able to describe how an amide to ester conversion could be carried out in the laboratory.
- Understand how polyesters and polyamides are formed. Given the structure of a polymer be able to identify monomer(s), and vice-versa.
- Be able to recognize, predict products of, and draw mechanisms for the Gabriel synthesis of primary amines, using either hydroxide ion or hydrazine to release the amine product.

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CHAPTER OVERVIEW

12: Reactions at the α-Carbon, Part I

12.0: Prelude to Reactions at the α-carbon, part I

12.1: Review of Acidity at the α-Carbon

12.2: Isomerization at the α-Carbon

12.3: Aldol Addition

12.4: α-Carbon Reactions in the Synthesis Lab - Kinetic vs. Thermodynamic Alkylation Products

12.5: Nitrosation

12.E: Reactions at the α-Carbon, Part I (Exercises)

12.S: Reactions at the α-Carbon, Part I (Summary)

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12.0: Prelude to Reactions at the α-carbon, part I



Introduction

There are lots of things that can kill you in northern Australia. On land, there is the death adder, the tiger snake and the redback spider; in the water, you'd be well advised to give wide berth to the salt water crocodile, the stonefish, the great white shark, and of course, the duck-billed platypus.

The duck-billed platypus?

Consider this: in 1991, a man fishing a river in northern Queensland, Australia happened across a platypus sitting on a log. Thinking it was injured, he picked it up. For his trouble, he spent the next six days in a nearby hospital, suffering from two puncture wounds in his right hand that resulted in "immediate, sustained, and devastating" pain, against which the usual analgesic drugs were almost completely useless. His hand "remained painful, swollen and with little movement for three weeks. Significant functional impairment . . . persisted for three months".

Meanwhile, on the other side of the planet, deep in the rain forests that straddle the border between eastern Peru and Brazil, a young man of the Matses tribe prepares himself to receive the 'hunting magic'. He holds the end of a short wooden stick in a fire for a few minutes, then removes it and presses the red-hot end into the skin of his chest, holding it there for long enough for the skin to be burned. Then he scrapes the burned skin away, and rubs into the wound a paste made from saliva mixed with secretions taken from the skin of a giant leaf frog.

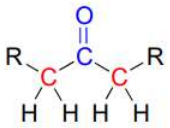
An American journalist named Peter Gorman, who reports having had the frog-skin paste administered in the same manner during a visit to a Matses village, describes what happens next:

> *Instantly my body began to heat up. In seconds I was burning from the inside . . . I began to sweat. My blood began to race. My heart pounded. I became acutely aware of every vein and artery in my body and could feel them opening to allow for the fantastic pulse of my blood. My stomach cramped and I vomited violently. I lost control of my bodily functions. . . (and) fell to the ground. Then, unexpectedly, I found myself growling and moving about on all fours. I felt as though animals were passing through me, trying to express themselves through my body.*

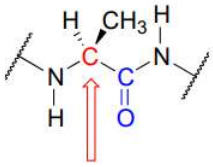
After the immediate violent effects pass, the Matses hunter is carried by his friends to a hammock to recover. After sleeping for a day, he awakens to find himself with what his people call the 'hunting magic': a state of heightened awareness, possessed of

tremendous energy and an abnormally keen sense of vision, hearing and smell. In the words of Mr. Gorman, "everything about me felt larger than life, and my body felt immensely strong... [I was] beginning to feel quite godlike".

There is a connection between the killer platypus in Australia and the 'hunting magic' in the Amazon, and it has to do with the structure and reactivity of what organic chemists refer to as the α-carbon: the carbon atom positioned adjacent to a carbonyl or imine group in an organic molecule:



α-carbons on a ketone



the α-carbon of an alanine amino acid residue in a protein

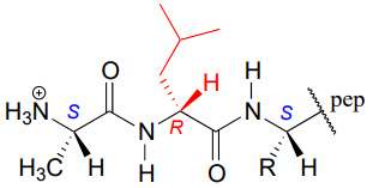
It is this chemistry that we are going to be studying for the next two chapters. But first, let's go back to that river in northern Australia and the fisherman who apparently didn't pay enough attention in his high school wildlife biology class.

The platypus, along with a few species of shrews and moles, is an example of a very rare phenomenon in nature: a venomous mammal. The male platypus possesses a pair of sharp spurs on each of his hind legs near the ankle. These spurs are hollow, and connected by a duct to a venom-producing gland in the thigh. The consensus among scientists who study the platypus is that males use their venomous barbs mainly when fighting each other over territory during mating season. Because healthy animals are often found with multiple scars from spur wounds, a platypus who gets spurred during a fight with a rival will not always die, but the experience is unpleasant enough that he will start looking for real estate a healthy distance down the river.

It is not easy to milk the venom from an angry, thrashing platypus, but there are scientists out there who have done it. It turns out that, like snake and spider venom, the venom from a platypus spur consists of a mixture of neuroactive peptides (peptides are very short proteins - less than 50 amino acids long). Recently, a team of biochemists from the Universities of Sydney, Queensland, and Adelaide reported that they were able to isolate from platypus venom two forms of a 39-amino acid peptide. Further analysis using NMR and mass spectrometry revealed that the two forms of the peptide differed in structure only at a single amino acid: the leucine at the #2 position. In one form, the leucine had the L configuration (or S if using the R/S system), just like the amino acids in virtually all other peptides and proteins found in nature. In the other form, this leucine had the unusual D, or R configuration.



peptide with L-Leu at position 2



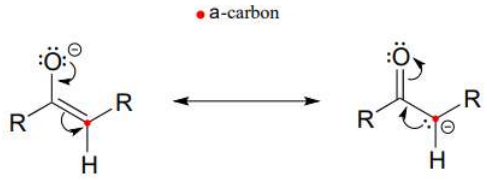
peptide with D-Leu at position 2

Peptides or proteins incorporating D-amino acids are not unheard of in nature, but this was the first time that one had been found in a mammal. Interestingly, the venom from certain marine cone snails and spiders - and, yes, the skin of the giant leaf frog in the Amazon rain forest - also contain neuroactive peptides with D-amino acids.

What is the advantage - to a platypus, cone snail, spider, or frog - of making a venomous peptide with D stereochemistry on one or more of its amino acids? It all has to do with generating diversity of shape and function. These are neuroactive peptides: each one interacts in a very specific way with a specific neural protein, thus exerting a specific neurological effect on the person or animal exposed to the venom. The different spatial arrangement of atoms about the α-carbon of D- and L-amino acids will cause a peptide with a D-leucine at position #2, for example, to fold into a different shape than its counterpart with an L-leucine at the same position. Thus, the two peptides may bind differently to one or more proteins in the nervous system, and ultimately may exert different neurological effects - such as intense pain in the case of playpus venom, or the 'hunting magic' effect in the case of the peptide from frog skin. The ability to incorporate D-amino acids greatly expands the potential structural and functional diversity of these short peptides.

The two stereoisomeric platypus venom peptides are encoded by the same gene. The peptides are initially synthesized using all L-amino acids, and then the leucine at position #2 undergoes a 'post-translational modification': in other words, a specific enzyme binds the all-L peptide after it has been synthesized on the ribosome and changes the leucine residue to the D configuration.

It is this reaction - a stereoisomerization reaction that takes place at the a-carbon of an amino acid - that brings us to the central topic of this chapter and the next: chemistry at the α-carbon. The key concept to recall from what we have learned about acidity and basicity in organic chemistry, and to keep in mind throughout this discussion, is that α-protons (in other words, protons on a-carbons) are weakly acidic. Loss of an α-proton forms an enolate - a species in which a negative formal charge is delocalized between a carbon and an oxygen. The 'enolate' term will be very important in the next two chapters, because most of the reactions we see will go through an enolate intermediate.



an enolate

In this chapter, we will first see several examples of isomerization reactions, in which an enzyme acts at the α-carbon of a substrate to catalyze the interconversion of two constitutional isomers or stereoisomers. Then, we will be introduced to a reaction type known as the 'aldol addition' and its reverse counterpart, the 'retro-aldol' cleavage reaction. Up to now, we have seen plenty of reactions where bonds were formed and broken between carbon and oxygen, nitrogen, or sulfur. Here, for the first time, we will see how enzymes can catalyze the formation or cleavage - again, at the a position - of *carbon-carbon* bonds: in other words, we will learn how an α-carbon can be either a nucleophile or a leaving group in an enzymatic reaction. This has clear importance for an understanding of metabolism in living things: the molecules of life, after all, are built upon a framework of carbon-carbon bonds, and metabolism is the process by which living cells build up and break down complex biomolecules.

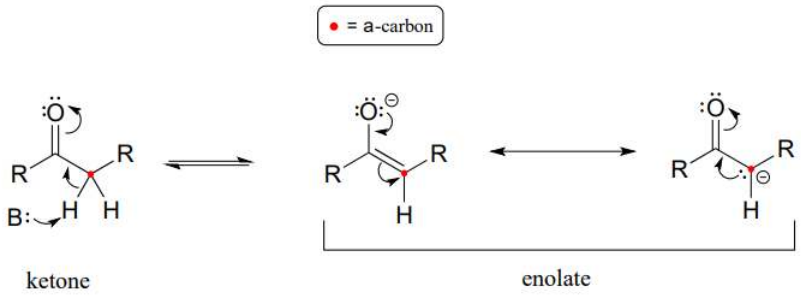
It all starts with the α-carbon - and as both the Australian fisherman and the Amazonian hunter could attest, what happens at the α-carbon can have some rather dramatic consequences.

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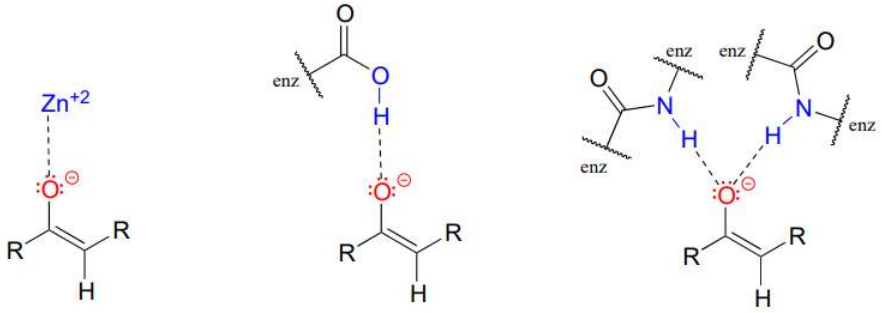
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12.1: Review of Acidity at the α-Carbon

Let's review what we learned in section 7.6 about the acidity of a proton on an a-carbon and the structure of the relevant conjugate base, the enolate ion. Remember that this acidity can be explained by the fact that the negative charge on the enolate conjugate base is delocalized by resonance to both the α-carbon and the carbonyl oxygen.



The α-carbon on the enolate is sp^2-hybridized with trigonal planar geometry, as are the carbonyl carbon and oxygen atoms (now would be a good time to go back to section 2.1, section 2.2, and section 2.3 to review, if necessary, the geometry of p-bonding in conjugated systems). pK_a of a typical a-proton in aqueous solution is approximately 18-20: acidic, but only weakly so. Recall from section 7.8, however, that the effective pK_a of a functional group on an enzyme-bound molecule can be altered dramatically by the 'microenvironment' of the active site. In order to lower the pK_a of an α-proton, an enzyme catalyzing a reaction that begins with an a-proton abstraction step must further stabilize the negative charge that develops on the oxygen atom of the (enolate) conjugate base. Different enzymes have evolved different strategies for accomplishing this task: in some cases, a metal cation (often Zn^{+2}) is bound in the active site to provide a stabilizing ion-ion interaction. In other cases, stabilization is provided by a proton-donating group positioned near the oxygen. As a third possibility, the active site architecture sometimes provides one or more stabilizing hydrogen bond donor groups.



In most of the mechanism illustrations in this chapter where an enolate intermediate is depicted, stabilizing metal ions or hydrogen bond interactions will not be explicitly drawn, for the sake of clarity. However, whenever you see an enolate intermediate in an enzyme-catalyzed reaction, you should remember that there are stabilizing interactions in play inside the active site.

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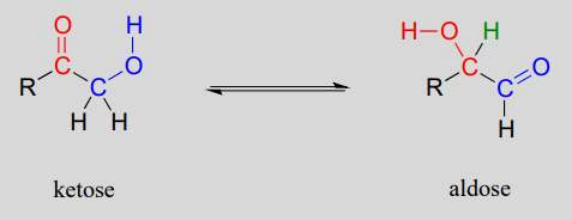
12.2: Isomerization at the α-Carbon

Enolate ions, as well as enols and enamines (section 7.6) are the key reactive intermediates in many biochemical isomerization reactions. Isomerizations can involve either the interconversion of constitutional isomers, in which bond connectivity is altered, or of stereoisomers, where the stereochemical configuration is changed. Enzymes that interconvert constitutional isomers are usually called isomerases, while those that interconvert the configuration of a chiral carbon are usually referred to as racemases or epimerases.

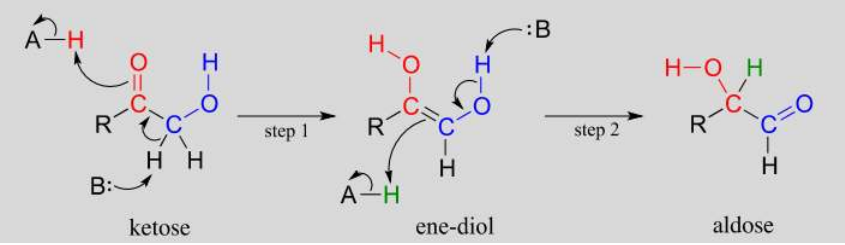
Carbonyl isomerization

One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose (recall that the terms ketose and aldolse refer to sugar molecules containing ketone and aldehyde groups, respectively).

Carbonyl isomerization:

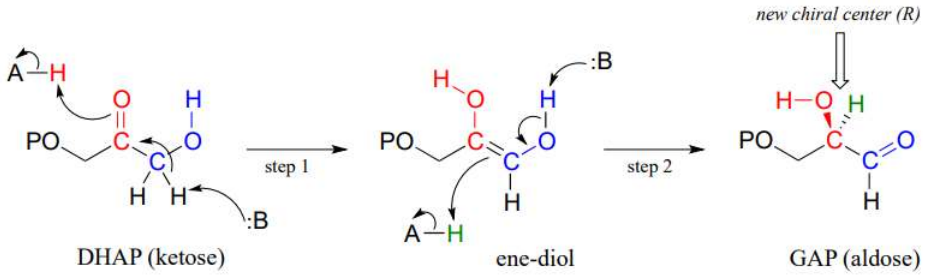


Mechanism:



The ketose species is first converted to its enol tautomer in step 1 (actually, this particular intermediate is known as an 'ene-diol' rather than an enol, because there are hydroxyl groups on both sides of the carbon-carbon double bond). Step 2 leads to the aldose, and is simply another tautomerization step. However, because there is a hydroxyl group on the adjacent (blue) carbon, a carbonyl can form there as well as at the red carbon.

An example is the glycolysis pathway reaction catalyzed by the enzyme triose phosphate isomerase (EC 5.3.1.1). Here, dihydroxyacetone phosphate (DHAP) is reversibly converted to glyceraldehyde phosphate (GAP).



Notice that DHAP is achiral while GAP is chiral, and that a new chiral center is introduced at the middle (red) carbon of GAP. As you should expect, the enzyme is stereoselective: in step 2 a proton is delivered to the red carbon, from behind the plane of the page, to yield the R enantiomer.

Also in the glycolysis pathway, glucose-6-phosphate (an aldose) and fructose-6-phosphate (a ketose) are interconverted through an ene-diol intermediate (EC 5.3.1.9) by an enzyme that is closely related to triose-phosphate isomerase.



glucose-6-phosphate fructose-6-phosphate

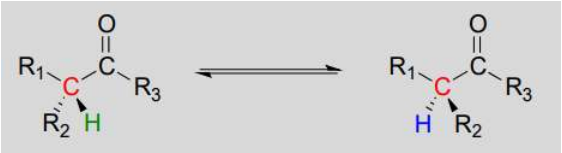
? Exercise 12.3.1

Draw the ene-diol intermediate in the phosphoglucose isomerase reaction.

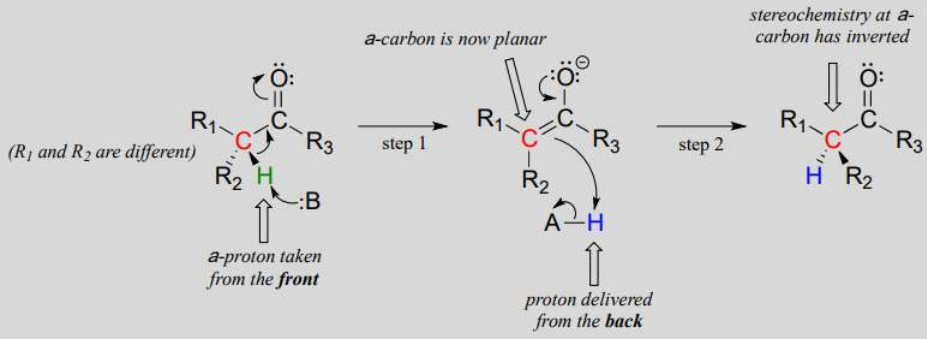
Stereoisomerization at the α-carbon

Enolates are a common intermediate in reactions where the stereochemical configuration of a chiral α-carbon is interconverted. These are commonly referred to as racemization or epimerization reactions, depending on whether the interconverted isomers are enantiomers or epimers (recall that the term 'epimer' refers to a pair of diastereomers that differ by a single chiral center).

Racemization/ epimerization:

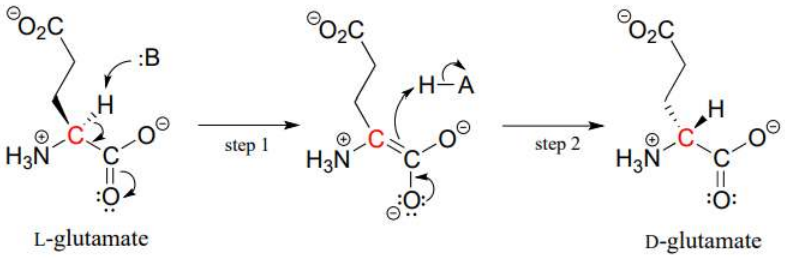


Mechanism:



These reactions proceed though a deprotonation-reprotonation mechanism, illustrated above. In step 1, the chiral a-carbon is deprotonated, leading to a planar, achiral enolate. In step 2, a proton is delivered back to the a-carbon, but from the opposite side from which the proton was taken in step 1, resulting in the opposite stereochemistry at this carbon. Two acid-base groups, positioned at opposing sides of the enzyme's active site, work in tandem to accomplish this feat.

The proteins and peptides in all known living things are constructed almost exclusively of L-amino acids, but in rare cases scientists have identified peptides which incorporate D-amino acids, which have the opposite stereochemistry at the a-carbon. Amino acid racemase enzymes catalyze the interconversion of L and D amino acids. As you may recall from the introductory section to this chapter, the venom of the male platypus contains a neurotoxic peptide in which an L-leucine amino acid has been converted by a racemase enzyme to D-leucine. In another example, the cell walls of bacteria are constructed in part of peptides containing D-glutamate, converted from L-glutamate by the enzyme glutamate racemase. (EC 5.1.1.3) (Biochemistry 2001, 40, 6199).



L-glutamate D-glutamate

A reaction (EC 5.1.3.1) in sugar metabolism involves the interconversion of the epimers ribulose-5-phosphate and xylulose-5-phosphate. The enzyme that catalyzes this reaction is called an 'epimerase'. (J. Mol. Biol. 2003, 326, 127).



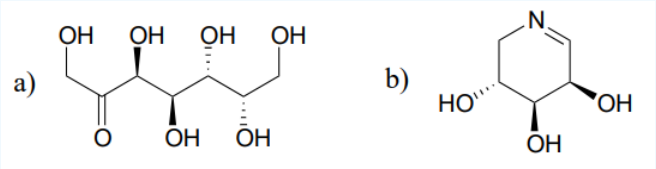
ribulose-5-phosphate xylulose-5-phosphate

? Exercise 12.3.2

Draw a reasonable mechanism for the ribulose-5-phosphate epimerization reaction above. Your mechanism should show an enolate intermediate and specify stereochemistry throughout.

? Exercise 12.3.3

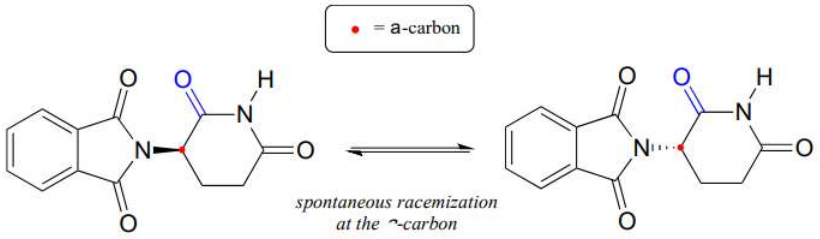
Predict the products of epimerization reactions starting with each of the substrates shown.



Hint

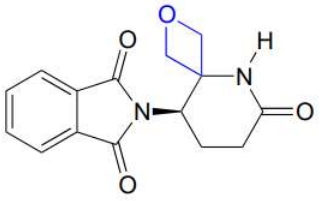
Carbons next to imine groups can also be considered α-carbons!

Recall from chapter 3 that a major issue with the drug thalidomide is the fact that the R enantiomer, which is an effective sedative, rapidly isomerizes in the body to the terotogenic (mutation-causing) S enantiomer. Note that the chiral center in thalidomide is an α -carbon!



(*R*)-thalidomide
(effective form)

(*S*)-thalidomide
(teratogenic form)



(*R*)-oxetano-thalidomide

Recently chemists reported the synthesis of a thalidomide derivative in which the carbonyl group is replaced by an 'oxetane' ring, with the aim of making an isotopically stable form of the drug (because the carbonyl group has been removed, racemization is no longer possible - there is no a-carbon!) (Org. Lett. 2013, 15, 4312.)

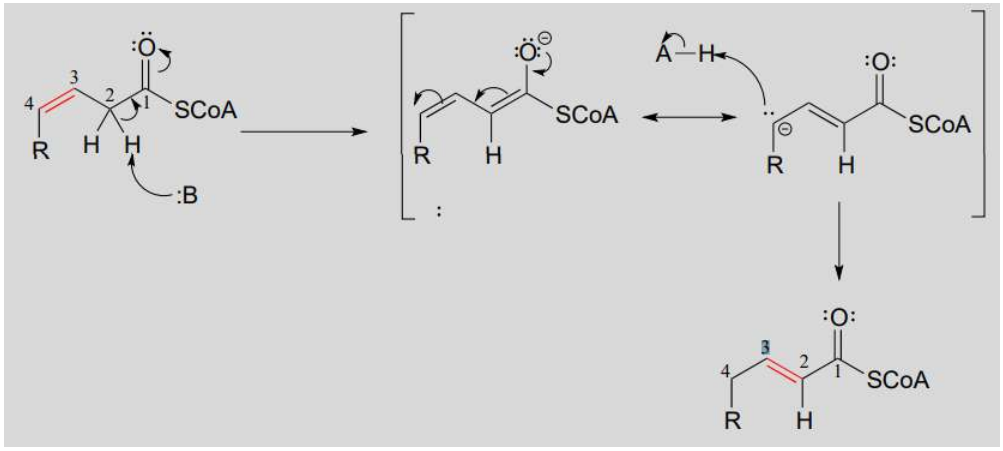
Alkene regioisomerization

The position of an alkene group can also be changed through a reaction in which the first step is abstraction of an α-proton and formation of an enolate intermediate. degradation pathway for unsaturated fatty acids (fatty acids whose hydrocarbon chains contain one or more double bonds) involves the 'shuffling' of the position of a carbon-carbon double bond, from a cis bond between carbon #3 and carbon #4 to a trans bond between carbon #2 and carbon #3. This is accomplished by the enzyme enoyl ***CoA*** isomerase (EC 5.3.3.8). (J. Biol Chem 2001, 276, 13622).

Alkene isomerization:



Mechanism:



? Exercise 12.3.4

Consider the structures of the substrate and product of the isomerization reaction above. What two factors contribute to the thermodynamic 'driving force' for the transformation?

? Exercise 12.3.5

The reaction below is part of the biosynthetic pathway for menthol. Suggest a mechanism that includes an enolate intermediate.

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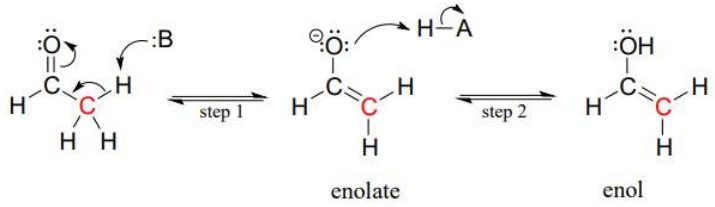
12.3: Aldol Addition

We arrive now at one of the most important mechanisms in metabolism: the aldol addition.

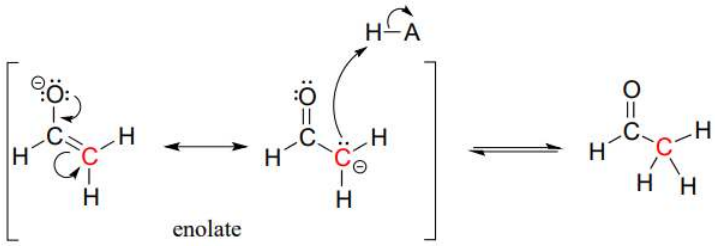
Along with Claisen condensation reactions, which we will study in the next chapter, aldol additions are responsible for most of the carbon-carbon bond forming events that occur in a living cell. Because biomolecules are built upon a framework of carbon-carbon bonds, it is difficult to overstate the importance of aldol addition and Claisen condensation reactions in the chemistry of living things!

Overview of the aldol addition reaction

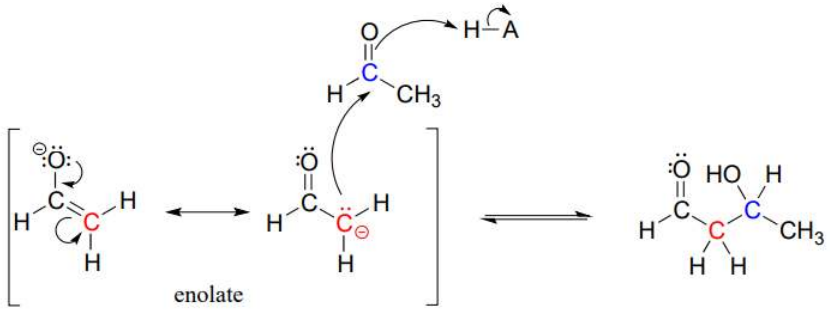
Consider the potential pathways available to a reactive enolate intermediate once the a-proton has been abstracted. We'll use acetaldehyde as a simple example. The oxygen, which bears most of the negative charge, could act as a base, (step 2 below) and the result would be an enol.



Alternatively, the enolate carbon, which bears a degree of negative charge, could act as a base, which is simply the reverse of the initial deprotonation step that formed the enolate in the first place. This of course just takes us right back to the starting aldehyde.

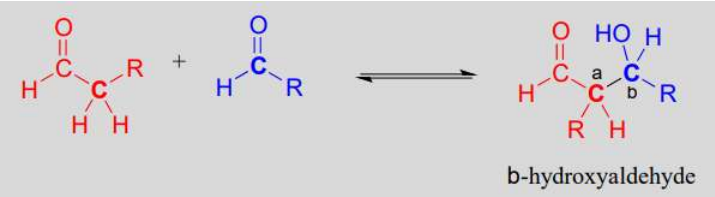


In both of these cases, the electron-poor species attacked by the enolate is an acidic proton. What if the electron-poor species - the electrophile - is not a proton but a carbonyl carbon? In other words, what if the enolate acts not as a base but rather as a nucleophile in a carbonyl addition reaction? For example, the enolate of acetaldehyde could attack the carbonyl group of a second acetaldehyde molecule. The result is the formation of a new carbon-carbon bond:

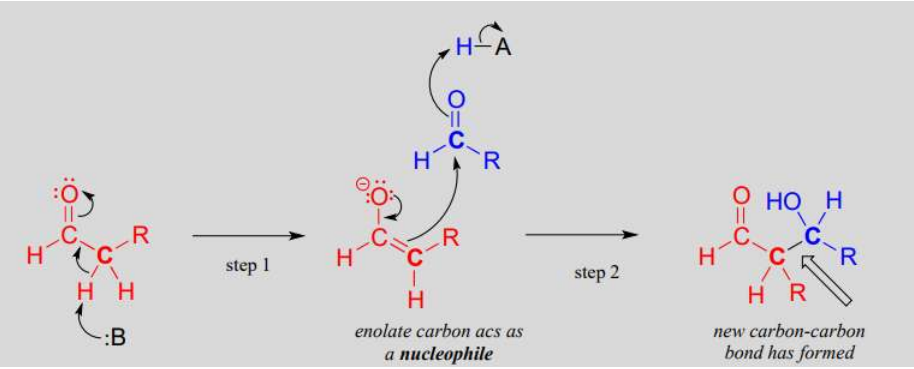


This type of reaction is called an aldol addition. It can be very helpful to think of an aldol addition reaction as simply a nucleophilic carbonyl addition (Chapter 10) reaction with an enolate a-carbon (rather than an alcohol oxygen or amine nitrogen) as the nucleophile.

An aldol addition reaction:



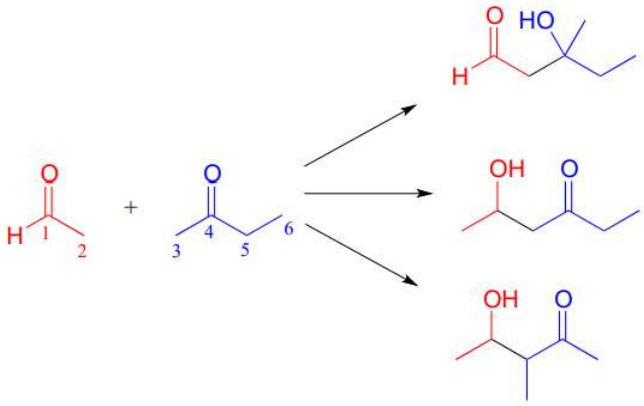
Mechanism:



Historically, the first examples of this mechanism type to be studied involved reactions very similar to what is shown above: an aldehyde reacting with itself. Because the resulting product contained both an aldehyde and an alcohol functional group, the reaction was referred to as an 'aldol' addition, a terminology that has become standard for reactions of this type, whether or not an aldehyde is involved. More generally, an aldol addition is characterized as a nucleophilic addition to an aldehyde, ketone, or imine electrophile where the nucleophile is the a-carbon in an aldehyde, ketone, imine, ester, or thioester. The enzymes that catalyze aldol reactions are called, not surprisingly, **aldolases**.

Note that the aldol reaction results in a product in which a hydroxide group is two carbons away from the carbonyl, in the β position. You can think of the β-hydroxy group as a kind of 'signature' for an aldol addition product.

Depending on the starting reactants, *nonenzyatic* aldol reactions can take more than one route to form different products. For example, a reaction between acetaldehyde and 2-butanone could potentially result in in three different aldol addition products, depending on which of the three a-carbons (carbons 2, 3, and 5 below) becomes the attacking nucleophile.



? Exercise 12.4.1

a. Fill in the appropriate carbon numbers for each of the three possible aldol addition products shown above.

b. Draw arrows for the carbon-carbon bond forming step that leads to each of the three products.

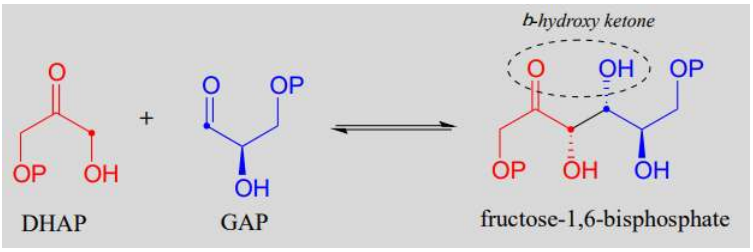
Hint

For each reaction, first identify the nucleophilic and electrophilic carbon atoms on the starting compounds!

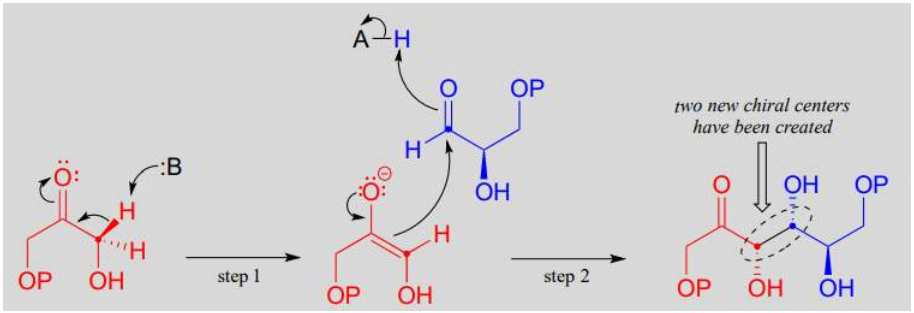
Biochemical aldol addition reactions

Fructose 1,6-bisphosphate aldolase (EC 4.1.2.13) is an enzyme that participates in both the glycolytic (sugar catabolism) and gluconeogenesis (sugar synthesis) biochemical pathways. The reaction catalyzed by fructose 1,6-bisphosphate aldolase links two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP, the electrophile in the reaction) and dihydroxyacetone phosphate (DHAP, the nucleophile), forming a 6-carbon product. In the figures below, the nucleophilic and electrophilic carbons are identified with dots.

The fructose 1,6-bisphosphate aldolase reaction



Mechanism:



In step 1 of the reaction, an a-carbon on DHAP is deprotonated, leading to an enolate intermediate. this and many other aldolase reactions, a zinc cation (Zn^{+2}) is positioned in the enzyme's active site so as to interact closely with - and stabilize - the negatively charged oxygen of the enolate intermediate. This is one important way in which the enzyme lowers the energy barrier to the reaction.

Next, (step 2), the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, leading to the fructose 1,6-bisphosphate product.

Notice that two new chiral centers are created in this reaction. This reaction, being enzyme-catalyzed, is highly stereoselective due to the precise position of the two substrates in the active site: only one of the four possible stereoisomeric products is observed. The enzyme also exhibits tight control of regiochemistry: GAP and DHAP could potentially form two other aldol products which are constitutional isomers of fructose 1,6-bisposphate.

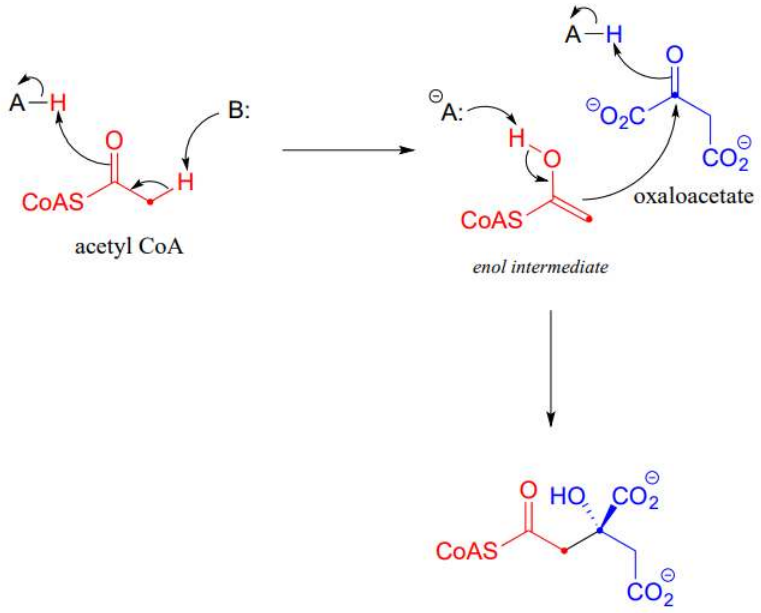
? Exercise 12.4.2

a. Fill in the blanks with the correct term: (pro-R, pro-S, re, si). You may want to review the terminology in section 3.11.

In the fructose 1,6-bisphosphate aldolase reaction, the _____ proton on the a-carbon of DHAP is abstracted, then the _____ face of the resulting enolate a-carbon attacks the _____ face of the aldehyde carbon of GAP.

b. Draw structures of the two other constitutional isomers that could hypothetically form in aldol addition reactions between GAP and DHAP. How many stereoisomers exist for these two alternative products?

Along with aldehydes and ketones, esters and thioesters can also act as the nucleophilic partners in aldol reactions. In the first step of the citric acid (Krebs) cycle, acetyl ***CoA*** (a thioester nucleophile) adds to oxaloacetate (a ketone electrophile) (EC 2.3.3.8).

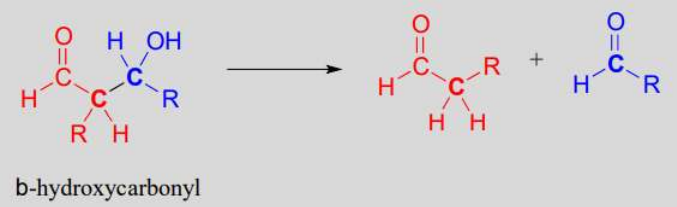


Notice that the nucleophilic intermediate is an enol, rather than a zinc-stabilized enolate as was the case with the fructose 1,6-bisphosphate aldolase reaction. An enol intermediate is often observed when the nucleophilic substrate is a thioester rather than a ketone or aldehyde.

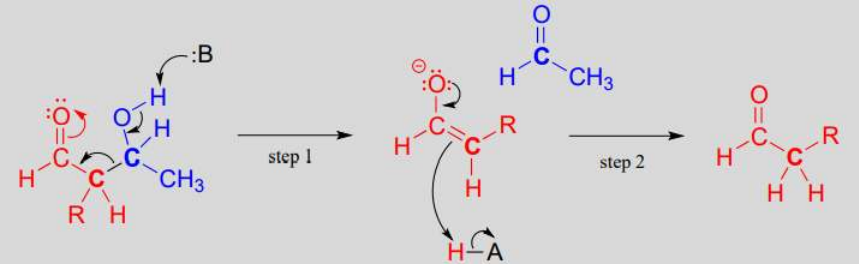
Going backwards: the retro-aldol cleavage reaction

Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they can also be reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze retro-aldol reactions: the reverse of aldol reactions, in which carbon-carbon bonds are broken.

A retro-aldol cleavage reaction:



Mechanism:

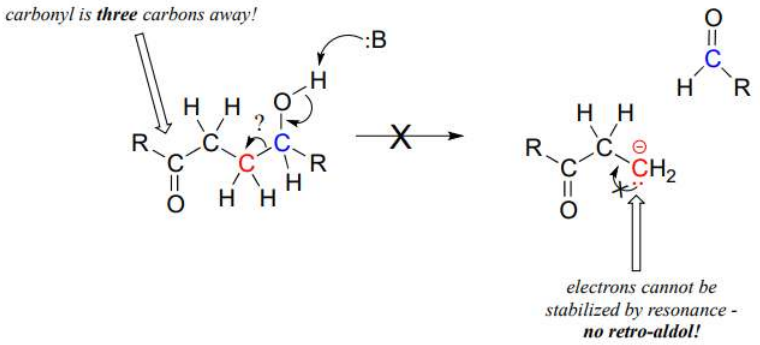


In the retro-aldol cleavage reaction the β-hydroxy group is deprotonated (step 1 above), to form a carbonyl, at the same time pushing off the enolate carbon, which is now a leaving group rather than a nucleophile.

Is an enolate a good enough leaving group for this step to be chemically reasonable? Sure it is: the same stabilizing factors that explain why it can form as an intermediate in the forward direction (resonance delocalization of the negative charge to the oxygen, interaction with a zinc cation) also explain why it is a relatively weak base, and therefore a relatively good leaving group (remember, weak base = good leaving group!). All we need to do to finish the reaction off is reprotonate the enolate (step 2) to yield the starting aldehyde, and we are back where we started.

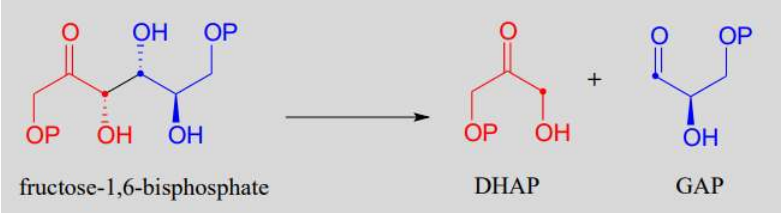
The key thing to keep in mind when looking at a retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have 'some place to go' where they will be stabilized by resonance. Most often, the substrate for a retro-aldol reaction is a β-hydroxy aldehyde, ketone, ester, or thioester.

If the leaving electrons cannot be stabilized, a retro-aldol cleavage step is highly unlikely.

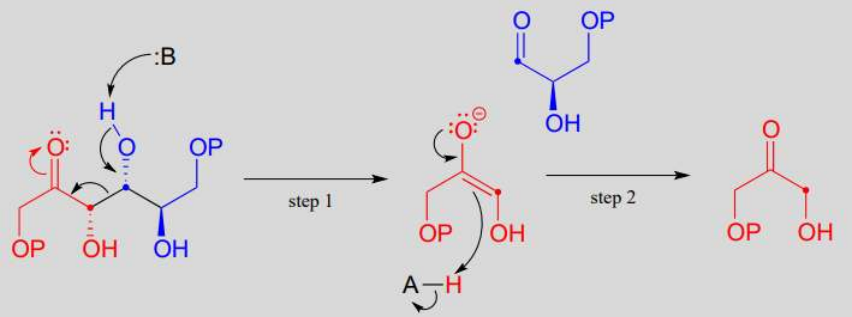


The fructose 1,6-bisphosphate aldolase reaction we saw in the previous section is an excellent example of an enzyme whose metabolic role is to catalyze both the forward and reverse (retro) directions of an aldol reaction. The same enzyme participates both as an aldolase in the sugar-building gluconeogenesis pathway, and as a retro-aldolase in the sugar breaking glycolysis pathway. We have already seen it in action as an aldolase in the gluconeogenesis pathway. Here it is in the glycolytic direction, catalyzing the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP:

The fructose 1,6-bisphosphate aldolase reaction (retro-aldol direction)

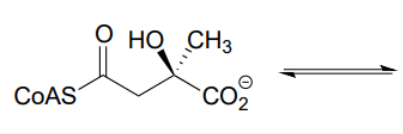


Mechanism:



? Exercise 12.4.3

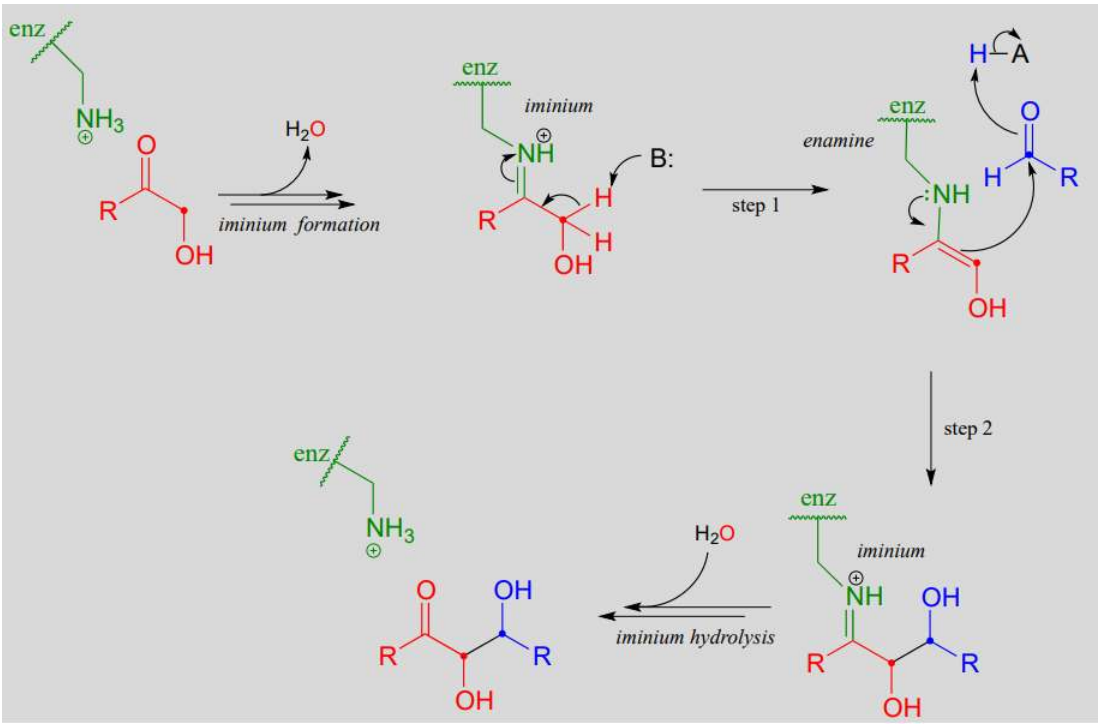
Predict the products of a retro-aldol reaction with the given substrate.



Aldol addition reactions with enzyme-linked enamine intermediates

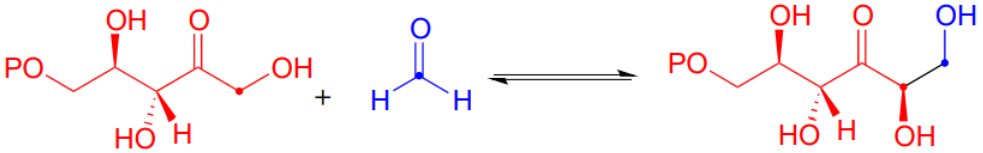
Earlier we looked at the mechanism for the fructose 1,6-bisphosphate aldolase reaction in bacteria. Interestingly, it appears that the enzyme catalyzing the exact same reaction in plants and animals evolved differently: instead of going through a zinc-stabilized enolate intermediate, in plants and animals the key intermediate is an enamine. The nucleophilic substrate is first linked to the enzyme through the formation of an iminium with a lysine residue in the enzyme's active site (refer to section 10.5 for the mechanism of iminium formation). This effectively forms an 'electron sink', in which the positively-charged iminium nitrogen plays the same role as the Zn^{+2} ion in the bacterial enzyme.

Mechanism for an aldol addition reaction with an enzyme-linked enamine intermediate



The α-proton, made more acidic by the electron-withdrawing effect of the imminium nitrogen, is then abstracted by an active site base to form an enamine (step 1). In step 2 , the α-carbon attacks the carbonyl carbon of an aldehyde, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the iminium is hydrolyzed back to a ketone group (see section 10.5 to review the imine/imminium hydrolysis mechanism).

There are many more examples of aldol/retroaldol reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by linking it to ribulose monophosphate. The reaction (EC 4.1.2.43) proceeds through imine and enamine intermediates.

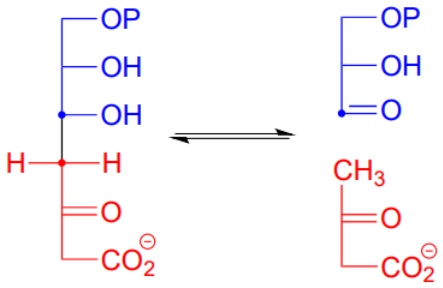


ribulose-5-phosphate formaldehyde hexulose-6-phosphate

Exercise 12.4.4

Draw the carbon-carbon bond-forming step for the hexulose-6-phosphate aldolase reaction shown above.

Here is an example of an enamine intermediate retro-aldol reaction from bacterial carbohydrate metabolism (EC 4.1.2.14). Notice that the structures are drawn here in the Fischer projection notation - it is important to practice working with this drawing convention, as biologists and biochemists use it extensively to illustrate carbohydrate chemistry. Proc. Natl. Acad. Sci. 2001, 98, 3679



Exercise 12.4.5

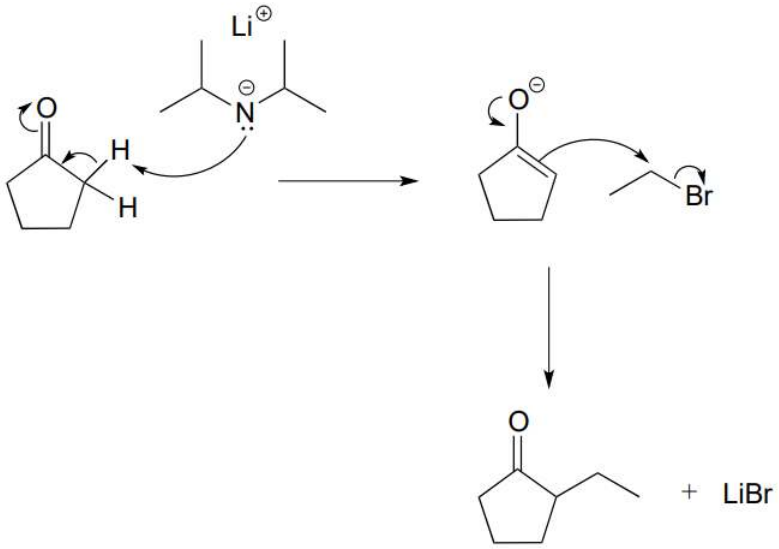
Draw the carbon-carbon bond breaking step in the reaction above. Use the Fischer projection notation.

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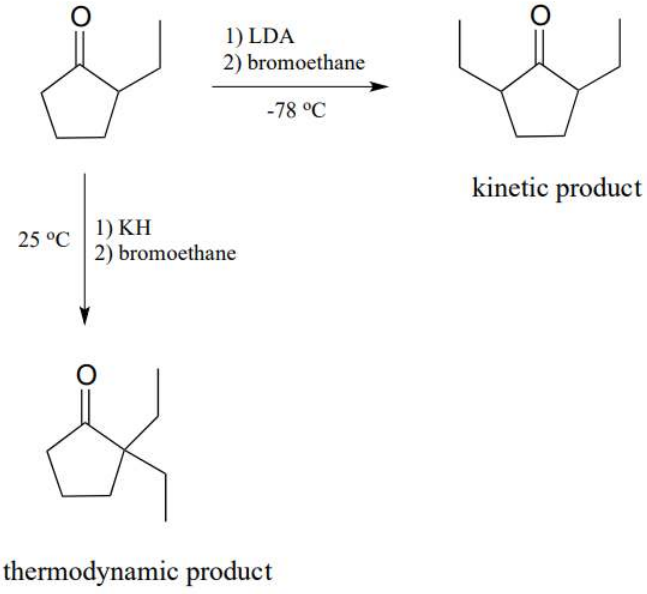
12.4: α-Carbon Reactions in the Synthesis Lab - Kinetic vs. Thermodynamic Alkylation Products

While aldol addition reactions are widespread in biochemical pathways as a way of forming carbon-carbon bonds, synthetic organic chemists working the lab also make use of aldol-like reactions for the same purpose. Consider this reaction:



Here, cyclopentanone is deprotonated at an α-carbon by lithium diisopropylamide (LDA), a very strong base commonly used in the synthesis lab. Addition to the reaction mixture of an electrophile in the form of a primary alkyl bromide results in formation of a new carbon-carbon bond. Notice that this is a kind of 'S_N2 variation' on the aldol addition reactions we saw above, because the enolate nucleophile is attacking in S_N2 fashion rather than in a carbonyl addition fashion.

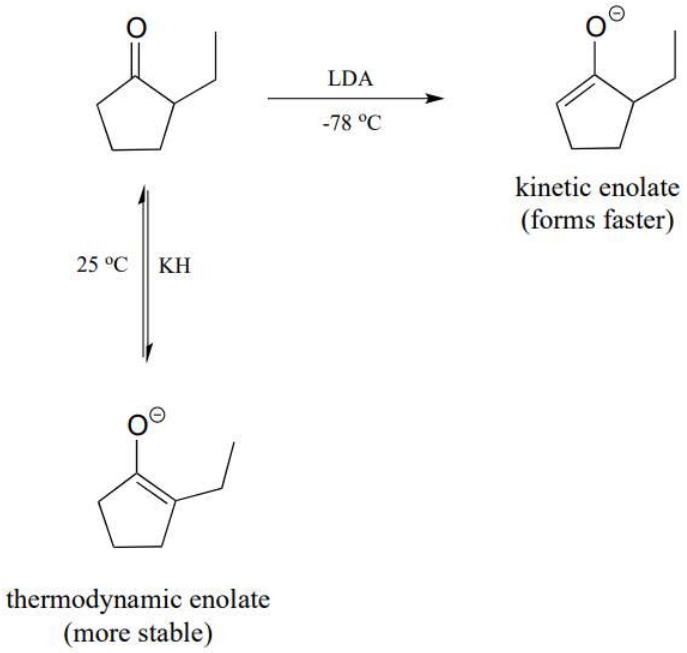
What would happen, though, if we started with 2-ethylcyclopentantone? Because the starting ketone is no longer symmetrical, we could hypothetically obtain two different products:



It turns out that we can control which product we get by selecting the base used in the reaction, and the reaction temperature. If we use LDA and immerse the reaction flask in a dry ice-acetone bath ($-78°C$), we get mainly 2,5-diethyl cyclopentanone. If we use

potassium hydride (***KH***) and run the reaction at room temperature, we get mainly 2,2-diethylcyclopentanone.

LDA is a very *hindered* base: the basic nitrogen atom is surrounded by two bulky isopropyl groups, and thus it is more difficult for it to come into contact with an ***α***-proton. The ***α***-protons on the less substituted side of 2-ethylcyclopentanone are less hindered and more accessible to the base. In addition, the cold reaction temperature means that the deprotonation step is irreversible: the system does not have enough energy to overcome the energy barrier for the reverse (reprotonation) reaction. The less substituted enolate forms faster, and once it forms it goes on to attack the bromoethane rather then reversing back to the ketone form. Because it is the rate of enolate formation that determines the major product under these conditions, we say that this reaction is under kinetic control, and the less substituted enolate intermediate is called the kinetic enolate.



If, on the other hand, we use ***KH*** as a base, hindrance is no longer an issue because the base is a hydride ion. We run this reaction at room temperature, so the system has enough energy to overcome the energy barrier for re-protonation, and enolate formation is reversible. The enolate in most abundance at equilibrium is therefore not the one that forms fastest, but the one that is more stable. The more substituted enolate is more stable (recall that alkenes are more stable when they are more substituted - the same idea applies here). The more substituted enolate leads to the 2,2-diethyl cyclopentanone product. Because it is the stability of the enolate intermediate that determines the major product under these conditions, we say that this reaction is under thermodynamic control, and the more substituted enolate intermediate is the thermodynamic enolate.

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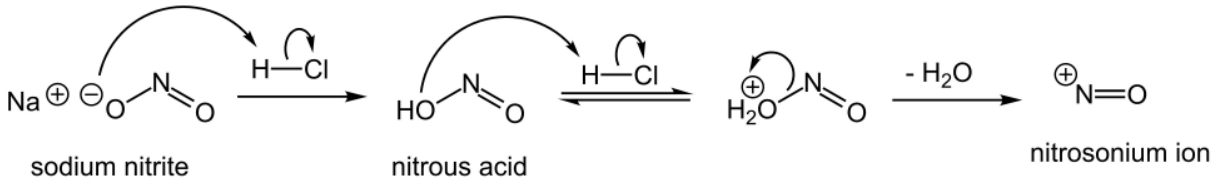
12.5: Nitrosation

Nitrosation - Nitroso Compounds

In organic chemistry, **nitrosamines** (or more formally ***N*-nitrosamines**) are organic compounds with the chemical structure $R_2N{-}N{=}O$, where R is usually an alkyl group. They feature a nitroso group (-N=O) bonded to a deprotonated amine.

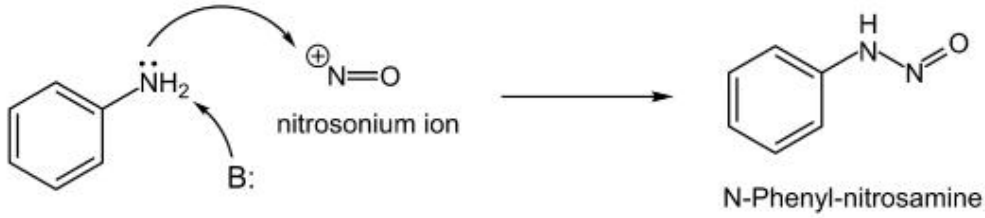
Most nitrosamines are carcinogenic. In foods, nitrosamines are produced from the reaction of nitrites and secondary amines, which are often present in proteins. Their formation can occur only under certain conditions, including strongly acidic conditions such as that of the human stomach. High temperatures, as in frying, can also enhance the formation of nitrosamines. There are significant levels of nitrosamines in many foodstuffs, especially meat and cheese products preserved with nitrite compounds. Tobacco specific nitrosamines (TSNAs) comprise one of the most important groups of carcinogens in tobacco products, particularly cigarettes and fermented dipping snuff.

Nitrosation reaction mechanisms begin with addition of a strong acid to sodium nitr**ite** ($NaNO_2$). Nitrous acid is formed, but it reacts further with acid to make water and the nitrosonium cation.



The nitrosonium cation is electron deficient. Its nitrogen has only three pairs of electrons in the valence shell, so it is a very good electrophile, very susceptible to attack by a nucleophile.

When the nucleophile is an amine, the product (after loss of an H^+ from the amine nitrogen) is called an *N*-nitrosoamine.



The nitrosonium ion can also be attacked by an enolate nucleophile, similar to other reactions earlier in this chapter. In this case, the nitroso group is attached to an alpha carbon, and the product is known as a nitrosoalkane.

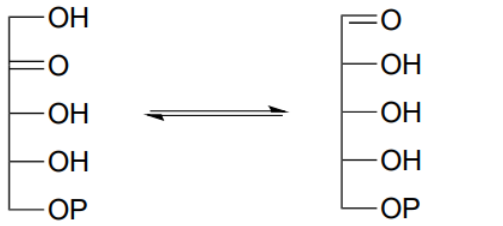
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12.E: Reactions at the α-Carbon, Part I (Exercises)

P12.1: The enzyme ribulose-5-phosphate isomerase (EC 5.3.1.6), which is active in both the Calvin cycle and the pentose phosphate pathway, catalyzes an aldehyde-to-ketone isomerization between two five-carbon sugars.

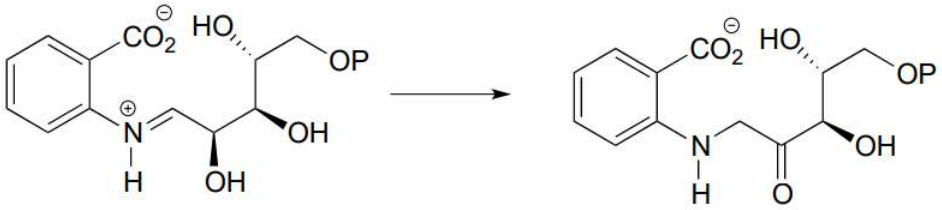
a. Draw a mechanism for this step.



ribulose 5-phosphate ribose 5-phosphate

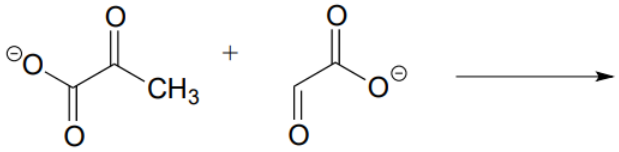
b. What ^1H-NMR signal would most clearly differentiate the aldose from the ketose in this reaction?

P12.2: Provide a likely mechanism for the reaction below, from tryptophan biosynthesis (EC 5.3.1.24) Hint: this is mechanistically very similar to a carbonyl isomerization reaction.



P12.3:

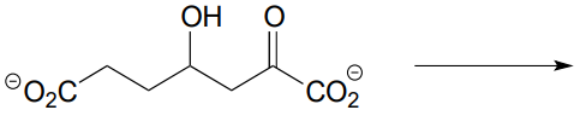
a. Draw the product of an aldol addition reaction between pyruvate and glyoxylate (EC 4.1.3.16):



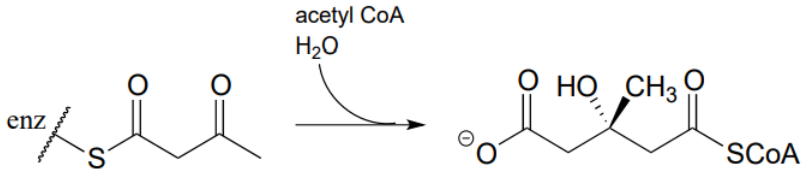
pyruvate glyoxylate

b. Draw the product of an aldol addition reaction between two molecules of pyruvate (EC 4.1.3.17).

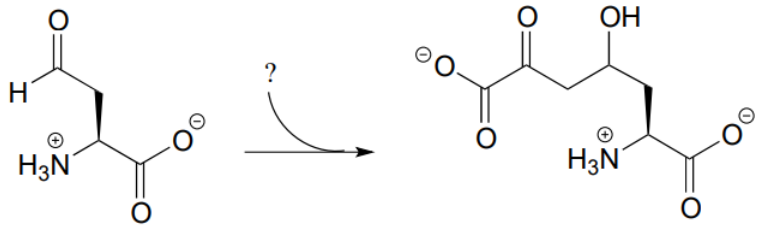
c. The molecule below undergoes a retroaldol cleavage reaction in E. coli (J. Biol. Chem. 2012, 287, 36208). Draw the structure of the products.



d. Propose a mechanism for this early reaction in the biosynthesis of isoprenoids (EC 2.3.3.10). Hint: this is an aldol reaction, followed by thioester hydrolysis.

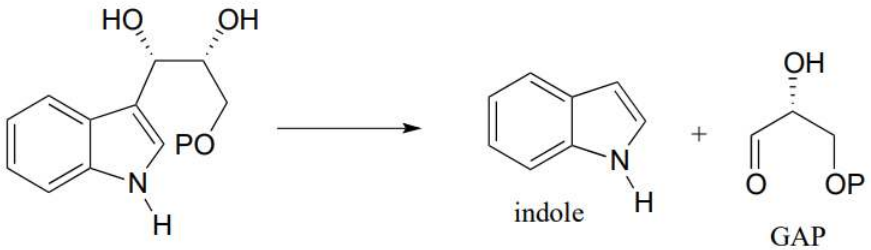


e. The carbon-carbon bond cleaving reaction below was reported to take place in many species of bacteria. Predict the structure of product X, and draw a mechanism for the reaction. Assume that an imine linkage to an enzymatic lysine residue does not play a part in the mechanism. (J. Bacteriol. 2009, 191, 4158).

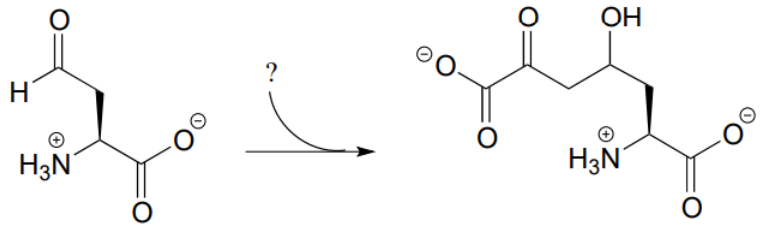


aspartate semialdehyde

P12.4: Below is a step in the biosynthesis of tryptophan. Draw a likely mechanism. Hint: you will need to show an enamine to imine tautomerization step first, then the carbon-carbon bond breaking step will become possible.



P12.5: The following step in the biosynthesis of lysine makes a connection between aspartate semialdehyde and a common metabolic intermediate. Identify the intermediate, and propose a mechanism for the reaction.



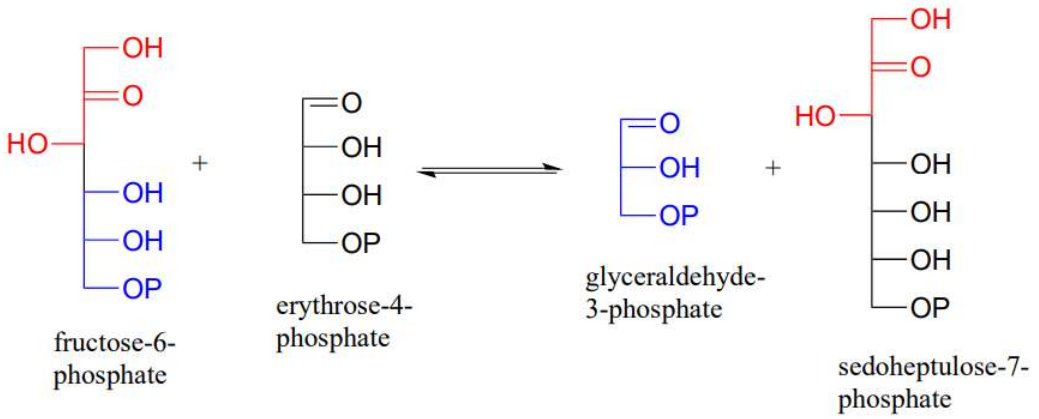
aspartate semialdehyde

P12.6: Sugar-interconverting transaldol reactions play an important role in sugar metabolism. In a transaldolase reaction, a ketose (e.g. fructose-6-phosphate) first breaks apart in a retro-aldol step to release an aldose (e.g. glyceraldehyde-3-phosphate) from the active site. Then, in a forward aldol step, a second aldose (e.g. erythrose-4-phosphate) enters the active site and connects to what remains from the original ketose (the red part in the figure below) to form a new ketose (e.g. sedoheptulose-7-phosphate). Transaldolase enzymes generally have a lysine in the active site that is covalently bound to the substrate throughout the reaction cycle.

Draw curved-arrow diagrams showing

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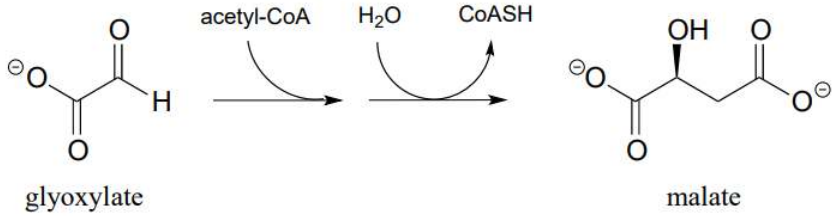
a. the carbon-carbon bond breaking step of the reaction cycle
b. he carbon-carbon bond forming step.



P12.7: Scientists are investigating the enzymatic reaction below, which is part of the biosynthesis of the outer membrane of gram-negative bacteria, as a potential target for new antibiotic drugs. Draw a likely mechanism for the reaction. (J. Biol. Chem. 2008, 283, 2835).

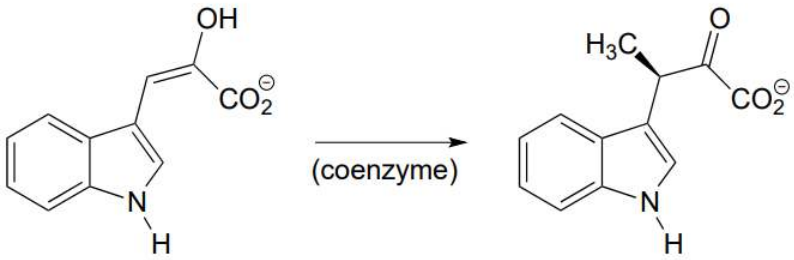


P12.8: The reaction below, catalyzed by the enzyme malate synthase, is part of the glyoxylate cycle of plants and some bacteria. It is the glyoxylate cycle that allows these organisms to convert acetyl CoA, derived from the metabolism of oils, into glucose.

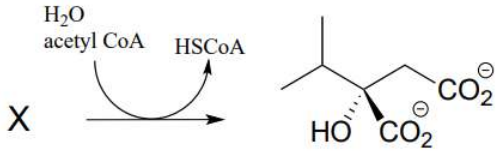


a. Propose a mechanism.
b. Predict the signals you would expect to see in a ^1H-NMR spectrum of malate.

P12.9: The reaction below, from the biosynthetic pathway for the amino acid tryptophan, is dependent upon a coenzyme that we learned about in an earlier chapter. Based on the reaction, identify this coenzyme and propose a mechanism.

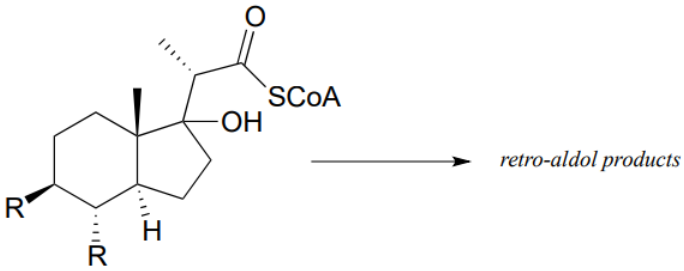


P12.10: In the biosynthesis of leucine, acetyl CoA condenses with another metabolic intermediate 'X" to form 1-isopropylmalate (EC 2.3.3.13). Give the structure for substrate X, and provide a mechanism for the reaction.

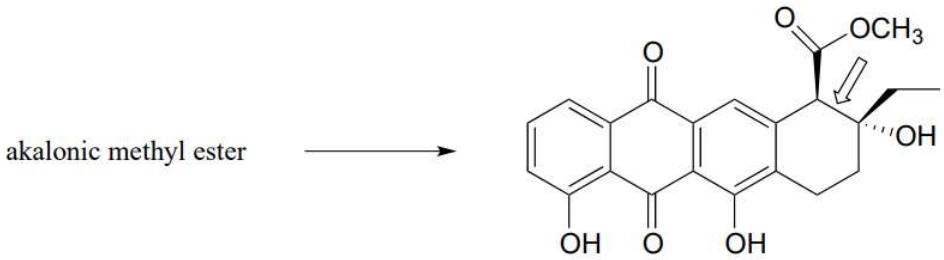


P12.11:

a. Mycobacterium tuberculosis, the microbe that causes tuberculosis, derives energy from the metabolism of cholesterol from infected patients. The compound below is predicted to be an intermediate in that metabolic pathway, and to undergo a retro-aldol cleavage reaction. Predict the retro-aldol products and show the mechanism involved. (Crit. Rev. Biochem. Mol. Biol. 2014, 49, 269, fig 5).

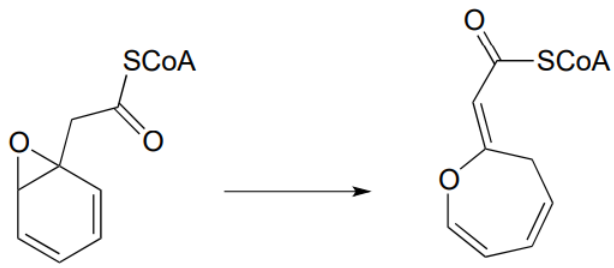


b. Polyketides are a structurally diverse class of biomolecules produced by almost all living things. Many drugs are derived from polyketide precursors. The cancer drug doxorubicin (trade name Adriamycin) is derived from a bacterial polyketide called rhodomycinone. Aklaviketone, an intermediate in the biosynthesis of rhodomycinone, is derived in a single enzymatic step from akalonic methyl ester, in a reaction in which the carbon-carbon bond indicated by an arrow is formed. Predict the structure of akalonic methyl ester.



aklaviketone

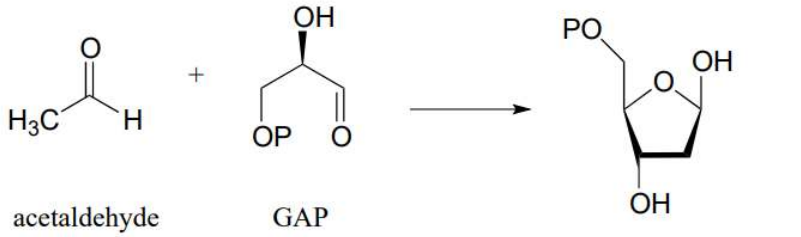
P12.12: The unusual isomerization reaction shown below has been reported recently to occur in some bacteria. Propose a mechanism that begins with formation of an enolate intermediate. (J. Biol. Chem. 2012, 287, 37986).



P12.13: The reactions in parts a) and b) below both proceed through lysine-linked enamine intermediates. Show the carbon-carbon bond forming step for each reaction. Hint: you will want to consider the straight-chain (ie. aldose/ketose) form of the sugars in both

cases.

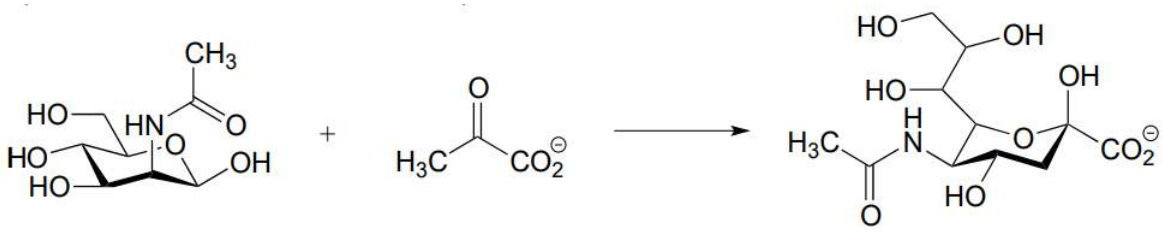
a. (J. Bacteriol. 2004, 186, 4185)



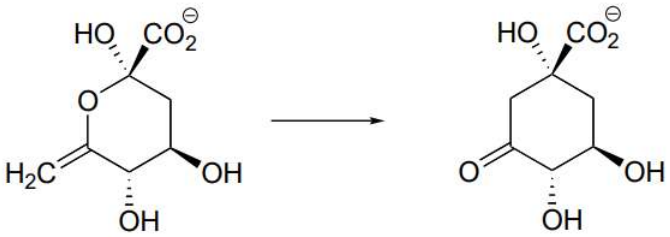
acetaldehyde GAP

deoxyribose 5-phosphate

b. (J. Biol. Chem. 2011, 286, 14057)



P12.14: Suggest a mechanism for the following transformation from aromatic amino acid biosynthesis (EC 4.2.3.4). Hint – only two mechanistic steps are required.



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12.S: Reactions at the α-Carbon, Part I (Summary)

Before moving on to the next chapter, you should:

- Understand what is meant by 'a and b positions' relative to a carbonyl group.
- Understand how an enzyme can increase the acidity of an a-proton through the active site microenvironment
- Understand the 3D bonding arrangement of an enolate ion
- Be able to recognize and draw reasonable mechanisms for the following reaction types:
  - tautomerizations: keto-enol, imine-enamine
  - racemization/epimerization
  - carbonyl isomerization (changing position of a carbonyl group)
  - alkene isomerization (changing position of an alkene relative to carbonyl)
  - aldol addition, retro-aldol cleavage (both enolate intermediate and enamine intermediate mechanisms)
- Be able to draw a mechanism for a laboratory alkylation reaction at the a-carbon of a ketone or aldehyde. Understand the difference between kinetic and thermodynamic control of this reaction type, and be able to predict the regiochemical outcome of the reaction based on reaction conditions.

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CHAPTER OVERVIEW

13: Reactions at the α-Carbon, Part II

13.0: Prelude to Reactions at the α-Carbon, Part II
13.1: Decarboxylation
13.2: An Overview of Fatty Acid Metabolism
13.3: Claisen Condensation
13.4: Conjugate Addition and Elimination
13.5: Carboxylation
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13.0: Prelude to Reactions at the α-Carbon, Part II



Introduction

We begin this chapter with the story of two men, and two chemical reactions.

The two men couldn't be more different. One was an acclaimed scientist who lived and continued to work productively into his eighties. The other was struck down as a young boy by what was assumed at the time to be a fatal disease. With the heroic support of his parents and caregivers, though, he lived to his thirtieth birthday and provided the inspiration for development of a medical treatment that could potentially save thousands of lives.

The two chemical reactions in this story are closely related, and both involve the metabolism of fats in the human body. One serves to build up fatty acid chains by repeatedly linking together two-carbon units, while the other does the reverse, progressively breaking off two-carbon pieces from a long chain fatty acid molecule. The life and work of the two men are inextricably linked to the two reactions, and while we will be learning all about the reactions in the main part of this chapter, we'll begin with the stories of the two men.

On a Saturday in January of 2007, Dr. Hugo Moser passed away in the Johns Hopkins Hospital in Baltimore, succumbing to pancreatic cancer. He was 82 years old. A neurologist who had taught and researched for much of his career at Johns Hopkins, he was well known for his workaholic nature: he had signed off on his last grant application while on the way to the hospital for major surgery just a few months previously. Two days after his death, his wife and colleague Ann Moser was back in their lab, because, she said, “He gave us all a mandate to continue with the work”. Dr. Moser was a highly esteemed scientist who had devoted his life to understanding and eventually curing a class of devastating neurodegenerative diseases, most notably adrenoleukodystrophy, or ALD. In his work he was careful, rational, painstaking, and relentless – a classic scientist. But in the minds of many movie fans, he became a Hollywood villain.

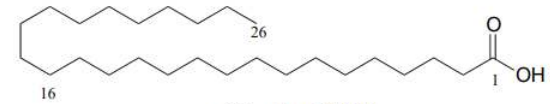
Only 17 months after the death of Dr. Moser, newspapers around the world published moving obituaries marking the passing, at age 30, of Lorenzo Odone. In one, written by his older sister and published in the British newspaper The Guardian, Lorenzo as a young boy is described as “lively and charming . . .he displayed a precocious gift for languages as he mastered English, Italian and French. He was funny, articulate and favored opera over nursery rhymes.” But for more than 20 years leading up to his death, he had been confined to a wheelchair, blind, paralyzed, and unable to communicate except by blinking his eyes. Because he was unable to swallow, he needed an attendant to be with him around the clock to suction saliva from his mouth so he wouldn't choke.

When he was he six years old, Lorenzo started to show changes in behavior: a shortening attention span, moodiness. More disturbing to his parents, Augusto and Michaela Odone, was their suspicion that he was having trouble hearing. They took him in to be examined, and although his hearing was fine, the doctors noticed other behavioral symptoms that concerned them, and so ordered more neurological tests. The results were a kick to the stomach: Lorenzo had a fatal neurodegenerative disease called adrenoleukodystrophy. There was no cure; his nervous system would continue to degenerate, and he would probably be dead within two years.

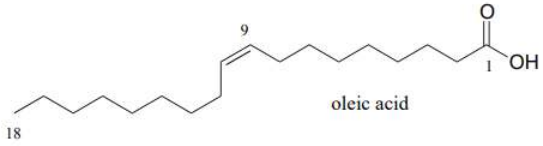
What happened next became such a compelling story that it was eventually retold by director George Miller in the 1992 movie Lorenzo's Oil, starring Nick Nolte and Susan Sarandon as Augusto and Michaela Odone and Peter Ustinov as a character based on Dr. Hugo Moser. The Odones were unwilling to accept the death sentence for their son and, despite having no scientific or medical training, set about to learn everything they could about ALD.

They found out that the cause of ALD is a mutation in a gene that plays an important role in the process by which saturated fatty acids of 26 or more carbons are broken down in the body. When these 'very long chain fatty acids' (VLCFAs) accumulate to excessive levels, they begin to disrupt the structure of the myelin sheath, a protective fatty coating around nerve axons, leading eventually to degradation of the nervous system.

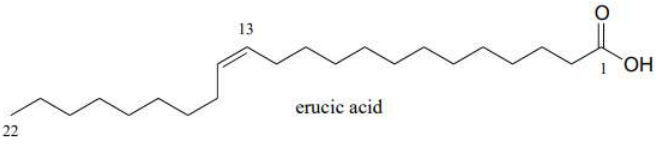
Researchers had found that restricting dietary intake of VLCFAs did not help – apparently much of the damage is done by the fats that are naturally synthesized by the body from shorter precursors. The Odones realized that the key to preventing destruction of the myelin sheath might be to somehow disrupt the synthesis of VLCFAs in Lorenzo's cells. The breakthrough came when they came across studies showing that the carbon chain-elongating enzyme responsible for producing VLCFAs is inhibited by oleic and erucic acids, which are monounsaturated fatty acids of 18 and 22 carbons, respectively and are found in vegetable oils.



a 26-carbon VLCFA



oleic acid



erucic acid

Administration of a mixture of these two oils, which eventually came to be known as 'Lorenzo's Oil' , was shown to lead to a marked decrease in levels of VLCFAs in ALD patients.

This was, however, a therapy rather than a miracle cure – and tragically for the Odones and the families of other children afflicted with ALD, the oil did not do anything to reverse the neurological damage that had already taken place in Lorenzo's brain. Although he was profoundly disabled, with round-the-clock care and a daily dosage of the oil Lorenzo was able to live until a day after his 30th birthday, 22 years longer than his doctors had predicted.

The story does not end there. Although the discovery of the treatment that bears his name came too late for Lorenzo Odone, might daily consumption of the oil by young children who are at a high genetic risk for ALD possibly prevent onset of the disease in the first place, allowing them to live normal lives? This proposal was not without a lot of controversy. Many ALD experts were very skeptical of the Lorenzo's oil treatment as there was no rigorous scientific evidence for its therapeutic effectiveness, and indeed erucic oil was thought to be potentially toxic in the quantities ingested by Lorenzo. Most doctors declined to prescribe the oil for their ALD patients until more studies could be carried out. The Hollywood version of Lorenzo's story cast the medical and scientific establishment, and Dr. Hugo Moser in particular, in a strikingly negative light – they were portrayed as rigid, callous technocrats who cared more about money and academic prestige than the lives of real people. Dr. Moser was not mentioned by name in the movie, but the character played by Peter Ustinov was based closely on him: as his obituary in the Washington Post recounts, Dr. Moser once told an interviewer "The good guys were given real names. The bad guys were given pseudonyms."

What Hugo Moser in fact did was what a good scientist should always do: he kept an open mind, set up and performed careful, rigorous experiments, and looked at what the evidence told him. In a 2005 paper, Moser was finally able to confidently report his

results: when young children at risk of developing ALD were given a daily dose of Lorenzo's oil, they had significantly better chance of avoiding the disease later on.

When he died, Dr. Moser was tantalizingly close to demonstrating conclusively that a simple and rapid blood test that he and his team had developed could reliably identify newborns at high risk of developing ALD – but it was not until after his death that his colleagues, including his wife, Ann Moser, were able to publish results showing that the test worked. The hope is that many lives might be saved by routinely screening newborns for ALD and responding with appropriate preventive treatments - possibly including Lorenzo's oil.

The biochemical reactions at the heart of the Lorenzo's oil story – the carbon-carbon bond forming and bond breaking steps in the synthesis and degradation of fatty acids - both involve chemistry at the α-carbon and proceed through enolate intermediates, much like the aldol and isomerization reactions we studied in chapter 11. They are known as 'Claisen condensation' and 'retro-Claisen cleavage' reactions, respectively, and represent another basic mechanistic pattern - in addition to the aldol reaction - that is ubiquitous in metabolism as a means of forming or breaking carbon-carbon bonds.

To begin this chapter, we will first learn about 'carboxylation' and 'decarboxylation' reactions, in which organic molecules gain or lose a bond to carbon dioxide, respectively, in a mechanism that is really just an extension of the aldol/retro-aldol reactions we learned about in the previous chapter. As part of this discussion, we will work through the mechanism of the carbon-fixing enzyme in plants commonly known as 'Rubisco', which is thought to be the most abundant enzyme on the planet. Then, we will move to the Claisen reactions that are so central to lipid metabolism and the story of Lorenzo Odone. Finally, we will study 'conjugate additions' and 'β-eliminations', common reaction patterns that involve double bonds in the $\alpha - \beta$ position relative to a carbonyl group, and which, again, proceed via enolate intermediates.

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13.1: Decarboxylation

Many carbon-carbon bond-forming and bond-breaking processes in biological chemistry involve the gain or loss, by an organic molecule, of a single carbon atom in the form of CO_2. You undoubtedly have seen this chemical equation before in an introductory biology or chemistry class:

$$CO_2\,(g) + 6\,H_2O\,(l) + \text{energy} \rightarrow C_6H_{12}O_6\,(aq) + 6\,O_2\,(g) \qquad (13.1.1)$$

This of course represents the photosynthetic process, by which plants (and some bacteria) harness energy from the sun to build glucose from individual carbon dioxide molecules. The key chemical step in plants in which a carbon dioxide molecule is 'fixed' (linked to a larger organic molecule) is a carboxylation reaction, and is catalyzed by the enzyme ribulose 1,5-bisphosphate carboxylase, commonly known as Rubisco.

The reverse chemical equation is also probably familiar to you:

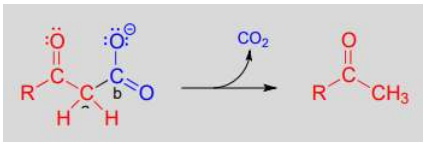
$$C_6H_{12}O_6\,(aq) + 6\,O_2\,(g) \rightarrow 6\,CO_2\,(g) + 6\,H_2O\,(l) + \text{energy} \qquad (13.1.2)$$

This equation expresses what happens in the process known as respiration: the oxidative breakdown of glucose to form carbon dioxide, water, and energy (in a non-biological setting, it is also the equation for the uncatalyzed combustion of glucose). In respiration, each of the carbon atoms of glucose is eventually converted to a CO_2 molecule. The process by which a carbon atom - in the form of carbon dioxide - breaks off from a larger organic molecule is called decarboxylation.

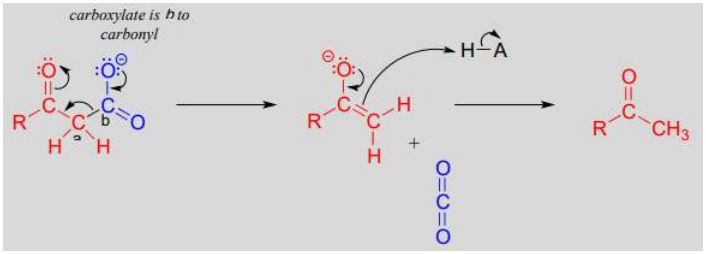
We will look now at the biochemical mechanism of decarboxylation reactions. Later in the chapter, we will look at the carboxylation reaction catalyzed by the Rubisco enzyme.

Decarboxylation steps occur at many points throughout central metabolism. Most often, the substrate for a decarboxylation step is a β-carboxy ketone or aldehyde.

Decarboxylation of a b-carboxy ketone or aldehyde:

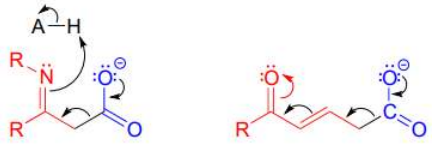


Mechanism:



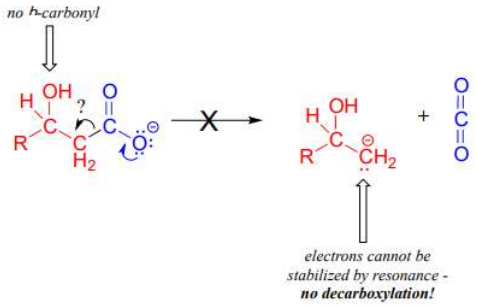
Just as in a retro-aldol reaction, a carbon-carbon bond is broken, and the electrons from the broken bond must be stabilized for the step to take place. Quite often, the electrons are stabilized by the formation of an enolate, as is the case in the general mechanism pictured above.

The electrons from the breaking carbon-carbon bond can also be stabilized by a conjugated imine group and/or by a more extensively conjugated carbonyl.

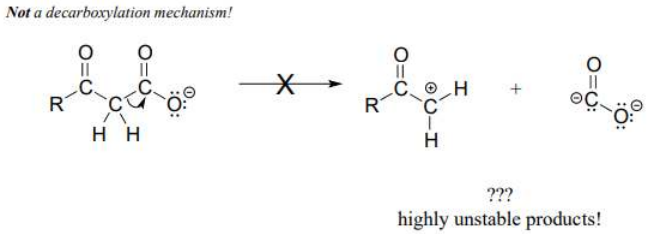


The key in understanding decarboxylation reactions is to first mentally 'push' the electrons away from the carboxylate group, then ask yourself: where do these electrons go? If the electrons cannot 'land' in a position where they are stabilized, usually by resonance with an oxygen or nitrogen, then a decarboxylation is very unlikely.

The compound below is not likely to undergo decarboxylation:



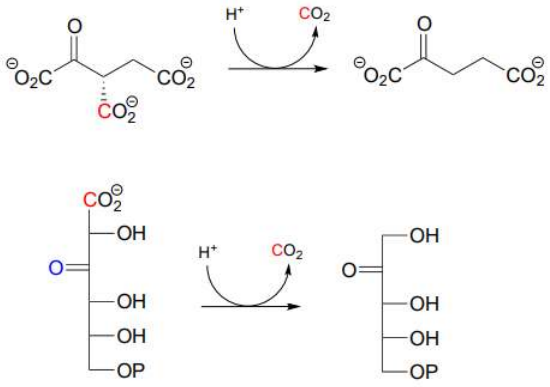
Be especially careful, when drawing decarboxylation mechanisms, to resist the temptation to treat the CO_2 molecule as the leaving group in a mechanistic sense:



The above is not what a decarboxylation looks like! (Many a point has been deducted from an organic chemistry exam for precisely this mistake!) Remember that in a decarboxylation step, it is the rest of the molecule that is, in fact, the leaving group, 'pushed off' by the electrons on the carboxylate.

Decarboxylation reactions are generally thermodynamically favorable due to the entropic factor: one molecule is converted into two, one of which is a gas - this represents an increase in disorder (entropy). Enzymatic decarboxylation steps in metabolic pathways are also generally irreversible.

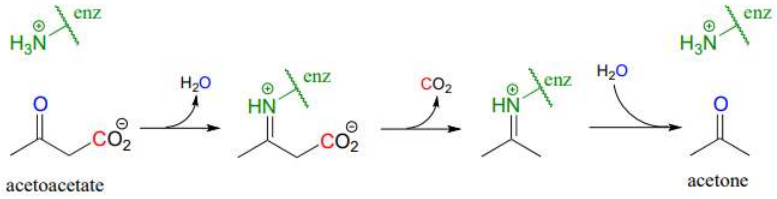
Below are two decarboxylation steps (EC 1.1.1.42; EC 1.1.1.43) in central catabolic metabolism (specifically the citric acid cycle and pentose phosphate pathway catabolism, respectively). Each step representing a point at which a carbon atom derived from the food we eat is released as carbon dioxide:



? Exercise 13.2.1

Draw mechanistic arrows showing the carbon-carbon bond breaking step in each of the reactions shown above.

The reaction catalyzed by acetoacetate decarboxylase (EC 4.1.1.4) relies on an imminium (protonated imine) link that forms temporarily between the substrate and a lysine residue in the active site, in a strategy that is similar to that of the enamine-intermediate aldolase reactions we saw in chapter 12. (Recall from section 7.5 that the pK_a of an imminium cation is approximately 7, so it is generally accurate to draw either the protonated imminium or the neutral imine in a biological organic mechanism).

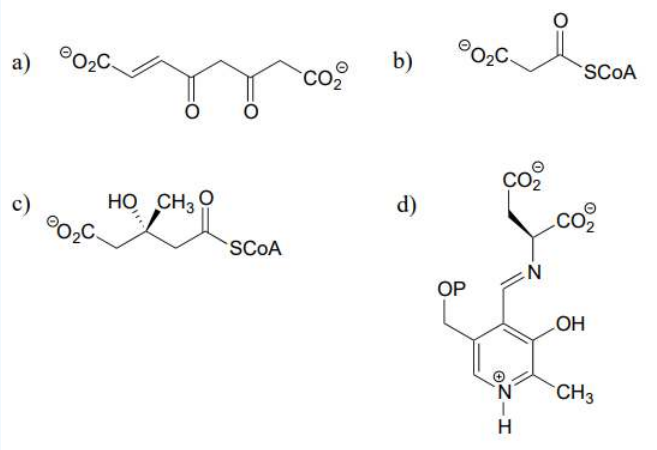


Exercise 13.2.2

Draw a mechanism for the carbon-carbon bond breaking step in the acetoacetate decarboxylase reaction.

Exercise 13.2.3

Which of the following compounds could be expected to potentially undergo decarboxylation? Draw the mechanistic arrows for the decarboxylation step of each one you choose, showing how the electrons from the breaking carbon-carbon bond can be stabilized by resonance.



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13.2: An Overview of Fatty Acid Metabolism

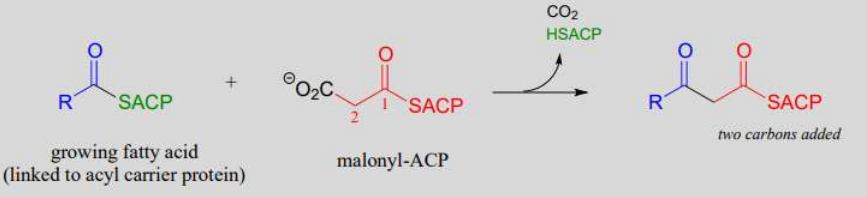
In the introduction to this chapter, we learned about a patient suffering from a rare disease affecting fatty acid metabolism. The reaction mechanisms that we are about to learn about in the next two sections are central to the process by which fatty acids are assembled (synthesis) and taken apart (degradation), so it is worth our time to go through a brief overview before diving into the chemical details.

Fatty acid metabolism is a two-carbon process: in the synthetic directions, two carbons are added at a time to a growing fatty acid chain, and in the degradative direction, two carbons are removed at a time. In each case, there is a four-step reaction cycle that gets repeated over and over. We will learn in this chapter about steps I and III in the synthesis direction, and steps II and IV in the degradative direction. The remaining reactions, and the roles played by the coenzymes involved, are the main topic of chapter 15.

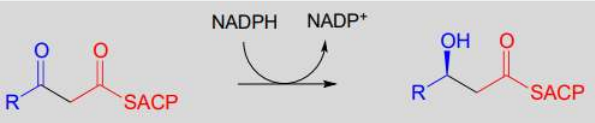
Fatty acid synthesis

'ACP' stands for 'acyl carrier protein', which is a protein that links to growing fatty acid chains through a thioester group (see section 11.5)

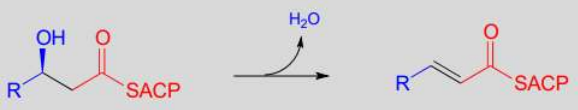
Step I: Condensation (covered in section 13.3)



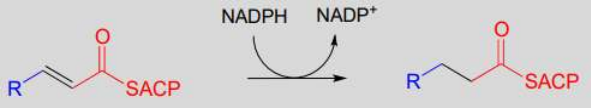
Step II: Ketone hydrogenation (covered in section 15.3)



Step III: Elimination (covered in section 13.4)



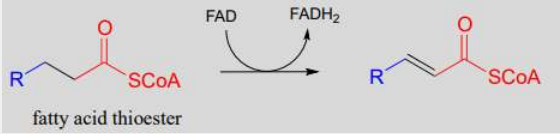
Step IV: Alkene hydrogenation (covered in section 15.4)



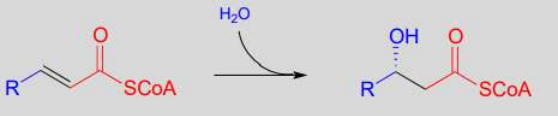
. . . back to step I, add another malonyl-ACP, repeat.

Fatty acid degradation

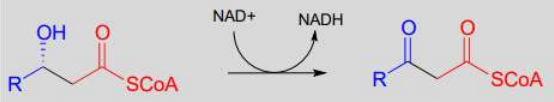
Step I: Alkane oxidation (covered in section 15.4)



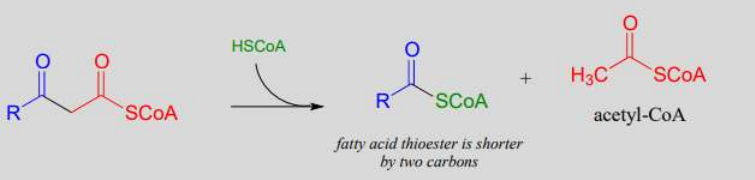
Step II: Addition of water (covered in section 13.4)



Step III: Oxidation of alcohol (covered in section 15.3)



Step IV: Cleavage (covered in section 13.3)



. . . back to step I

When looking at these two pathways, it is important to recognize that they are not the reverse of each other. Different coenzymes are in play, different thioesters are involved (coenzyme A in the degradative direction, acyl carrier protein in the synthetic direction), and even the stereochemistry is different (compare the alcohols in steps II/III of both pathways). As you will learn in more detail in a biochemistry course, metabolic pathways that work in opposite directions are generally not the exact reverse of each other. In some, like fatty acid biosynthesis, all of the steps are catalyzed by different enzymes in the synthetic and degradative directions. Other 'opposite direction' pathways, such as glycolysis/gluconeogenesis, contain mostly reversible reactions (each catalyzed by one enzyme working in both directions), and a few irreversible 'check points' where the reaction steps are different in the two directions. As you will learn when you study metabolism in biochemistry course, this has important implications in how two 'opposite direction' metabolic pathways can be regulated independently of one another.

Recall that in Chapter 12 we emphasized the importance of two reaction types - the aldol addition and the Claisen condensation - in their role in forming (and breaking) most of the carbon-carbon bonds in a living cell. We have already learned about the aldol addition, and its reverse, the retro-aldol cleavage. Now, we will study the Claisen condensation reaction, and its reverse, the retro-Claisen cleavage. Step I in fatty acid synthesis is a Claisen condensation, and step IV in fatty acid degradation is a retro-Claisen cleavage.

In section 13.4, we will look more closely at the reactions taking place in step III of fatty acid synthesis (an elimination) and step II of fatty acid degradation (a conjugate addition).

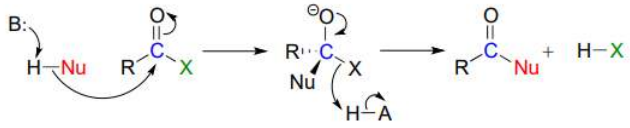
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13.3: Claisen Condensation

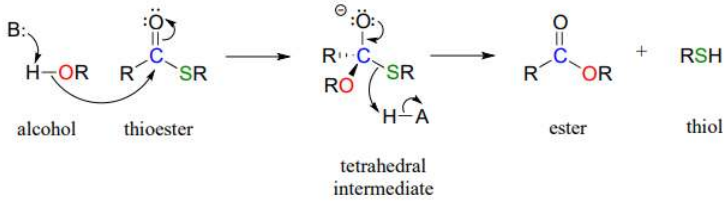
Claisen condensation - an overview

Recall the general mechanism for a nucleophilic acyl substitution mechanism, which we studied in chapter 10:



The major points to recall are that a nucleophile attacks a carboxylic acid derivative, leading to a tetrahedral intermediate, which then collapses to expel the leaving group (X). The whole process results in the formation of a different carboxylic acid derivative.

A typical nucleophilic acyl substitution reaction might have an alcohol nucleophile attacking a thioester, driving off a thiol and producing an ester.

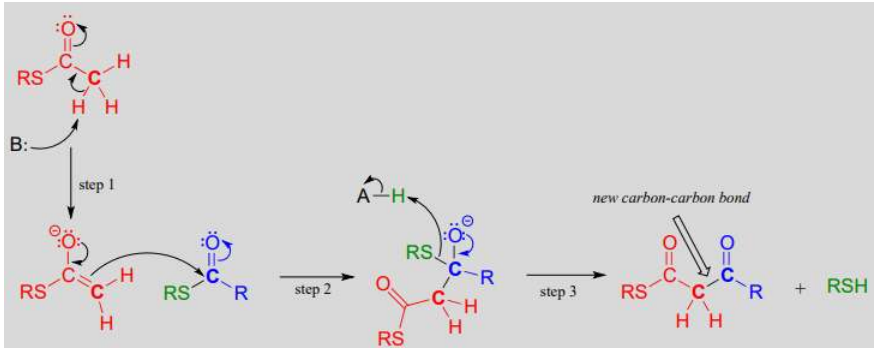


If, however, the attacking nucleophile in an acyl substitution reaction is the a-carbon of an enolate, a new carbon-carbon bond is formed. This type of reaction is called a **Claisen condensation**, after the German chemist Ludwig Claisen (1851-1930).

A Claisen condensation reaction



Mechanism:



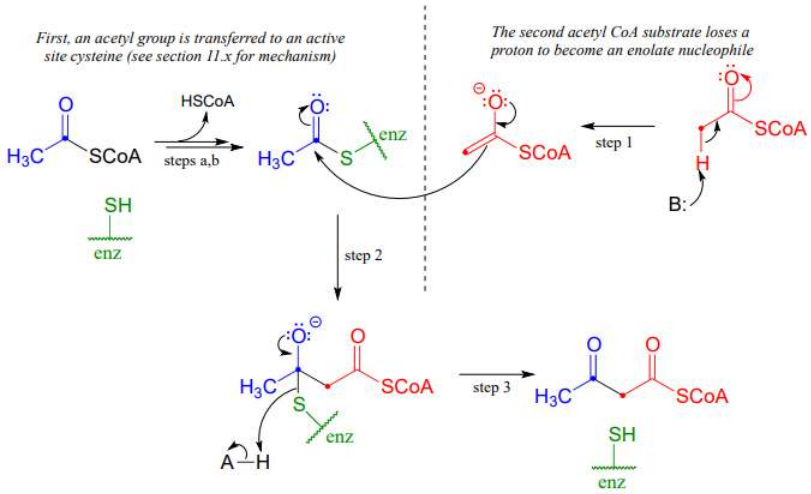
In step 1, the αcarbon of one thioester substrate is deprotonated to form an enolate, which then goes on to attack the second thioester substrate (step 2). Then the resulting tetrahedral intermediate collapses (step 3), expelling the thiol leaving group and leaving us with a β-keto thioester product (a thioester with a ketone group two carbons away).

To reiterate: *A Claisen condensation reaction is simply a nucleophilic acyl substitution (Chapter 11) reaction with an enolate carbon nucleophile.*

Biochemical Claisen condensation examples

A Claisen condensation between two acetyl ***CoA*** molecules (EC 2.3.1.9) serves as the first step in the biosynthesis of cholesterol and other isoprenoid compounds in humans (see section 1.3 for a reminder of what isoprenoids are). First, a transthioesterase reaction transfers the acetyl group of the first acetyl ***CoA*** to a cysteine side chain in the enzyme's active site (steps a, b). (This preliminary event is typical of many enzyme-catalyzed Claisen condensation reactions, and serves to link the electrophilic substrate covalently to the active site of the enzyme).

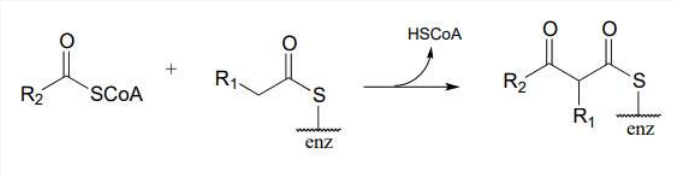
In the 'main' part of the Claisen condensation mechanism, the α-carbon of a second acetyl ***CoA*** is deprotonated (step 1), forming a nucleophilic enolate.



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (step 2) which collapses to expel the cysteine thiol (step 3).

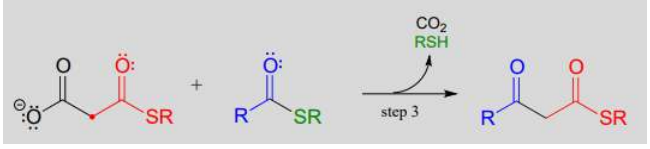
? Exercise 13.4.1

Draw curved arrows for the carbon-carbon bond-forming step in mechanism for this condensation reaction between two fatty acyl-thioester substrates. R1 and R2 can be hydrocarbon chains of various lengths. (J. Biol. Chem. 2011, 286, 10930.)

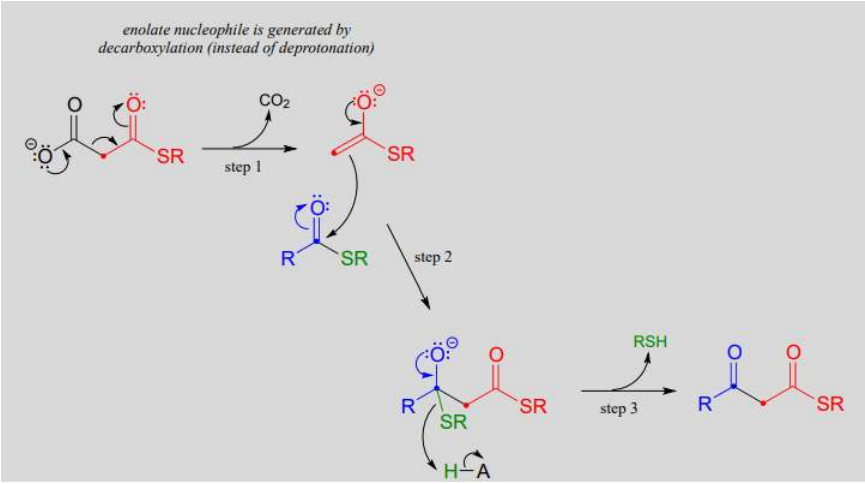


In an alternative mechanism, Claisen condensations in biology are often initiated by decarboxylation at the α-carbon of a thioester, rather than by deprotonation:

Decarboxylation/Claisen condensation:



Mechanism:

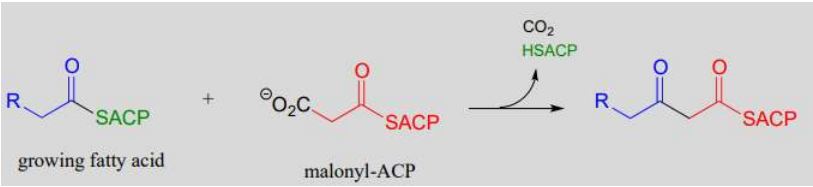


The thing to notice here is that the nucleophilic enolate (in red) is formed in the first step by decarboxylation, rather than by deprotonation of an α-carbon. Other than that, the reaction looks just like the Claisen condensation reactions we saw earlier.

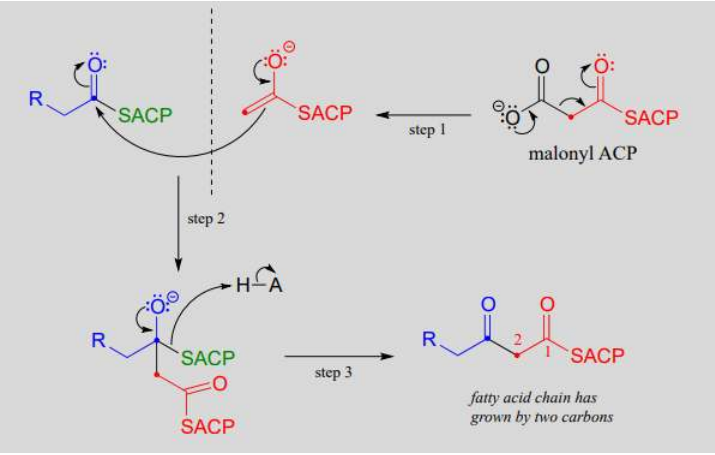
Now, we can finally understand the fatty acid chain-elongation step that we heard about in the chapter introduction in the context of the Lorenzo's oil story, which is a decarboxylation/Claisen condensation between malonyl-ACP (the donor of a two-carbon unit) and a growing fatty acyl CoA molecule. Notice that, again, the electrophilic acyl group is first transferred to an active site cysteine, which then serves as the leaving group in the carbon-carbon bond forming process.

Chain elongating (Claisen condensation) reaction in fatty acid biosynthesis

(step 1 in fatty acid synthesis cycle)

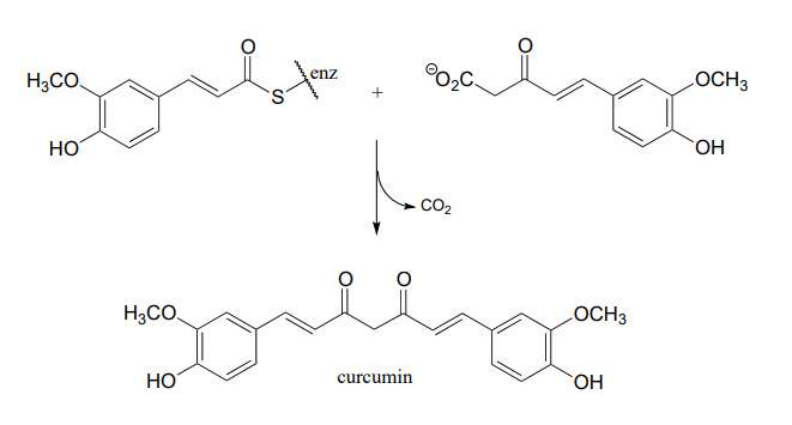


Mechanism:



? Exercise 13.4.2

Curcumin is the compound that is primarily responsible for the distinctive yellow color of turmeric, a spice used widely in Indian cuisine. The figure below shows the final step in the biosynthesis of curcumin. Draw a mechanism for this step.



Retro-Claisen cleavage

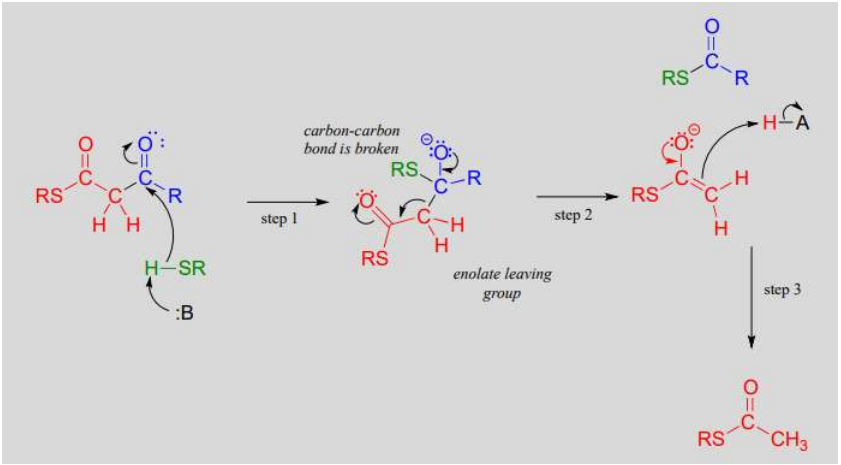
Just like the aldol mechanism, Claisen condensation reactions often proceed in the 'retro', bond-breaking direction in metabolic pathways.

A typical Retro-Claisen cleavage reaction

(thiol nucleophile)



Mechanism:



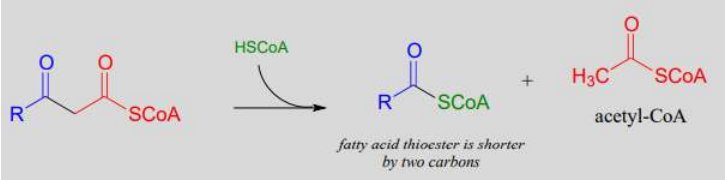
In a typical retro-Claisen reaction, a thiol (or other nucleophile such as water) attacks the carbonyl group of a β-thioester substrate (step 1), and then the resulting tetrahedral intermediate collapses to expel an enolate leaving group (step 2) - this is the key carbon-carbon bond-breaking step. The leaving enolate reprotonates (step 3) to bring us back to where we started, with two separate thioesters. You should look back at the general mechanism for a forward Claisen condensation and convince yourself that the retro-Claisen mechanism illustrated aboveis a step-by-step reverse process.

? Exercise 13.4.3

Is a decarboxylation/Claisen condensation step also likely to be metabolically relevant in the 'retro' direction? Explain.

When your body 'burns' fat to get energy, it is a retro-Claisen cleavage reaction (EC 2.3.1.16) that is responsible for breaking the carbon-carbon bonds in step IV of the fatty acid degradative pathway. A cysteine thiol on the enzyme serves as the incoming nucleophile (step 1 in the mechanism below), driving off the enolate leaving group as the tetrahedral intermediate collapses (step 2). The enolate is then protonated to become acetyl CoA (step 3), which goes on to enter the citric acid (Krebs) cycle. Meanwhile, a transthioesterification reaction occurs (steps a and b) to free the enzyme's cysteine residue, regenerating a fatty acyl CoA molecule which is two carbons shorter than the starting substrate.

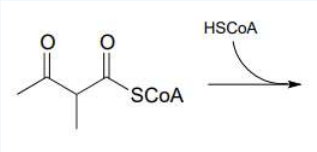
The retro-Claisen reaction (step IV) in fatty acid degradation



Mechanism:

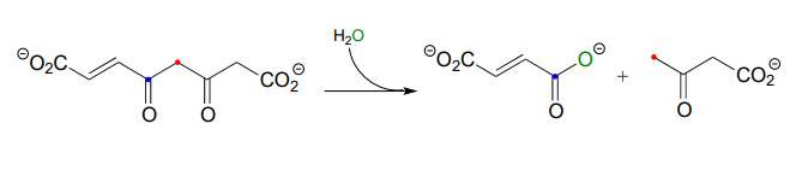
Exercise 13.4.4

In a step in the degradation if the amino acid isoleucine, the intermediate compound 2-methyl-3-keto-butyryl ***CoA*** undergoes a retro-Claisen cleavage. Predict the products.



Exercise 13.4.5

Many biochemical retro-Claisen steps are hydrolytic, meaning that water, rather than a thiol as in the example above, is the incoming nucleophile that cleaves the carbon-carbon bond. One example (EC 3.7.1.2) occurs in the degradation pathway for tyrosine and phenylalanine:



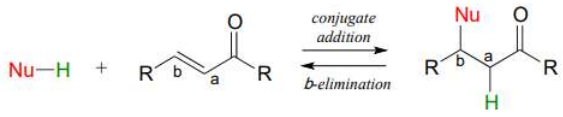
a. Propose a likely mechanism for the reaction shown.
b. The b-diketone substrate in the reaction above could hypothetically undergo a different retro-Claisen cleavage reaction in which the nucleophilic water attacks the other ketone group. Predict the products of this hypothetical reaction.

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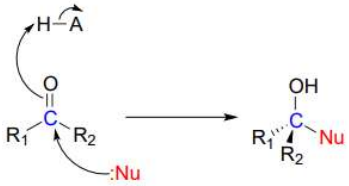
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13.4: Conjugate Addition and Elimination

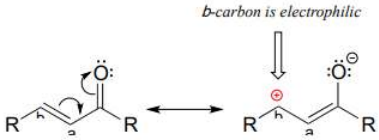
In this section, we will look at two more common biochemical reactions that proceed through enolate intermediates. In a typical **conjugate addition**, a nucleophile and a proton are 'added' to the two carbons of an alkene which is conjugated to a carbonyl (i.e. in the $\alpha - \beta$ position). an β-elimination step, the reverse process occurs:



In chapter 9 we learned about nucleophilic carbonyl addition reactions, including the formation of hemiacetals, hemiketals, and imines. In all of these reactions, a nucleophile directly attacks a carbonyl carbon.

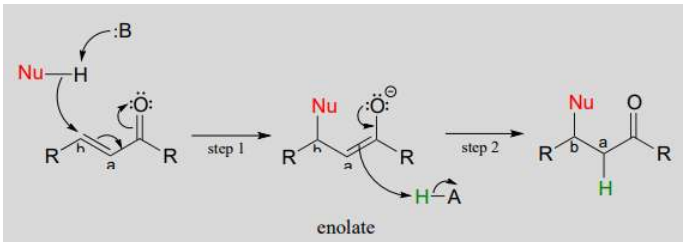


If, however, the electrophilic carbonyl is β-unsaturated - if, in other words, it contains a double bond conjugated to the carbonyl - a different reaction pathway is possible. A resonance structure can be drawn in which the β-carbon has a positive charge, meaning that the β-carbon also has the potential to be an electrophilic target.



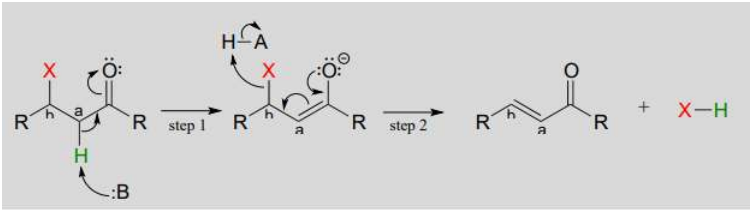
If a nucleophile attacks at the b-carbon, an enol or enolate intermediate results (step 1 below). In many cases this intermediate collapses and the a-carbon is protonated (step 2). This type of reaction is known as a **conjugate addition**.

Mechanism of a conjugate addition reaction



The reverse of a conjugate addition is a **β-elimination**, and is referred to mechanistically the abbreviation ***E*1*cb***.

Mechanism of an E1cB elimination

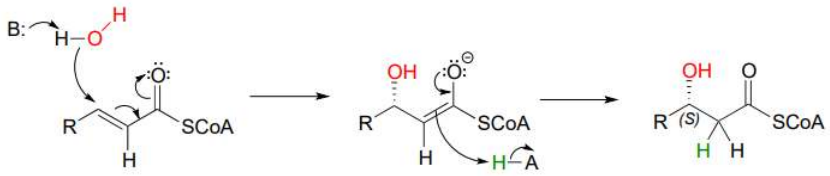


The ***E*** stands for 'elimination'; the numeral 1 refers to the fact that, like the S_N1 mechanism, it is a stepwise reaction with first order kinetics. '***cB***' designation refers to the intermediate, which is the **c**onjugate **b**ase of the starting compound. In step 1, an α-carbon is

deprotonated to produce an enolate, just like in aldol and Claisen reactions we have already seen. In step 2, the excess electron density on the enolate expels a leaving group at the β position (designated 'X' in the figure above). Notice that the α and β carbons change from sp^3 to sp^2 hybridization with the formation of a conjugated double bond.

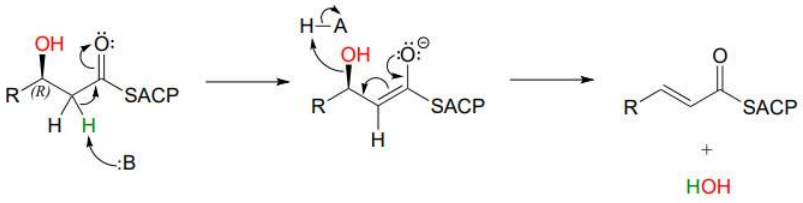
(In chapter 14 we will learn about alternate mechanisms for alkene addition and β-elimination reactions in which there is not an adjacent carbonyl (or imine) group, and in which the key intermediate species is a resonance-stabilized carbocation.)

Step II of fatty acid degradation is a conjugate addition of water, or hydration.



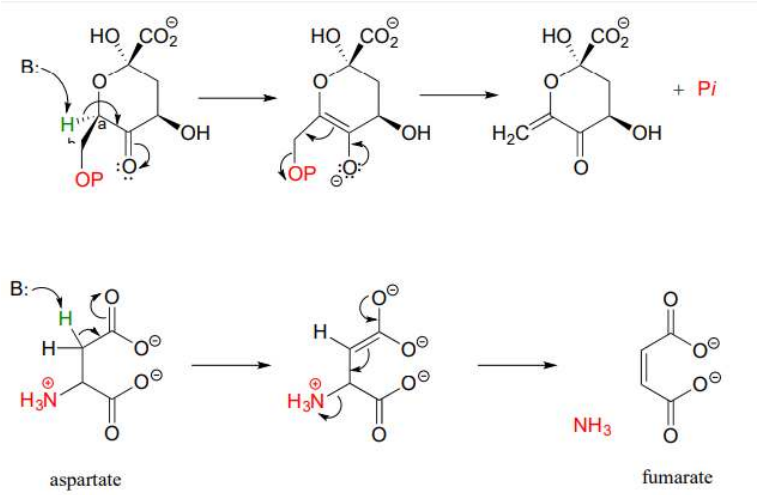
Note the specific stereochemical outcome: in the active site, the nucleophilic water is bound behind the plane of the conjugated system (as drawn in the figure above), and the result is S configuration in the β-hydroxy thioester product.

In step III of the fatty acid synthesis cycle we saw an $E1cb$ β-elimination of water (dehydration):



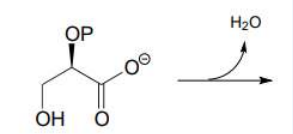
Notice that the stereochemistry at the β-carbon of the starting alcohol is R, whereas the hydration pathway (step II) reaction in the fatty acid degradation cycle pathway results in the S stereoisomer. These two reactions are not the reverse of one another!

Here are two more examples of β-elimination reactions, with phosphate and ammonium respectively, as leaving groups. The first, 3-dehydroquinate synthase (EC 4.2.3.4) is part of the biosynthesis of aromatic amino acids, the second, aspartate ammonia lyase (EC 4.3.1.1) is part of amino acid catabolism.



? Exercise 13.5.1

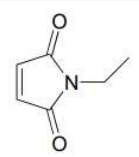
In the glycolysis pathway, the enzyme 'enolase' (EC 4.2.1.11) catalyzes the $E1cb$ dehydration of 2-phosphoglycerate. Predict the product of this enzymatic step.



2-phosphoglycerate

Exercise 13.5.2

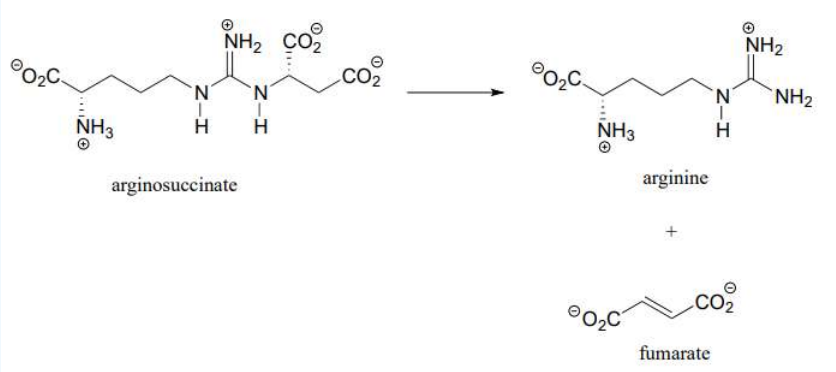
N-ethylmaleimide (NEM) is an irreversible inhibitor of many enzymes that contain active site cysteine residues. Inactivation occurs through conjugate addition of cysteine to NEM: show the structure of the labeled residue. (Michael addition)



NEM

Exercise 13.5.3

Argininosuccinate lyase (4.3.2.1), an enzyme in the metabolic pathway that serves to eliminate nitrogen from your body in the form of urea in urine, catalyzes this β-elimination step:



Propose a complete mechanism.

Hint

Don't be intimidated by the size or complexity of the substrate - review the β-elimination mechanism, then identify the leaving group and breaking bond, the α-carbon which loses a proton, the carbonyl that serves to stabilize the negatively-charged (enolate) intermediate, and the double bond that forms as a result of the elimination. You may want to designate an appropriate 'R' group to reduce the amount of drawing.

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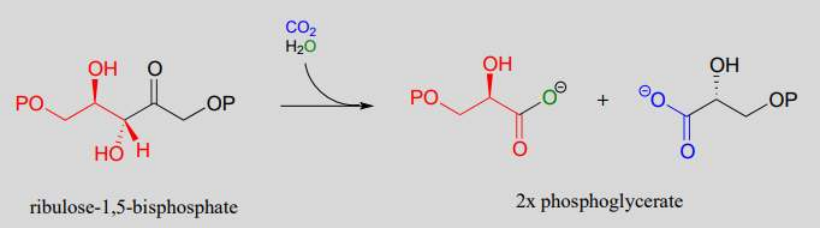
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13.5: Carboxylation

It is difficult to overstate the importance to biology and ecology of the enzymatic reaction we are going to see next: ribulose 1,5-bisphosphate carboxylase (Rubisco) plays a key role in closing the 'carbon cycle' in our biosphere, catalyzing the incorporation of a carbon atom - in the form of carbon dioxide from the atmosphere - into organic metabolites and eventually into carbohydrates, lipids, nucleic acids, and all of the other organic molecules in living things. Rubisco is probably the most abundant enzyme on the planet.

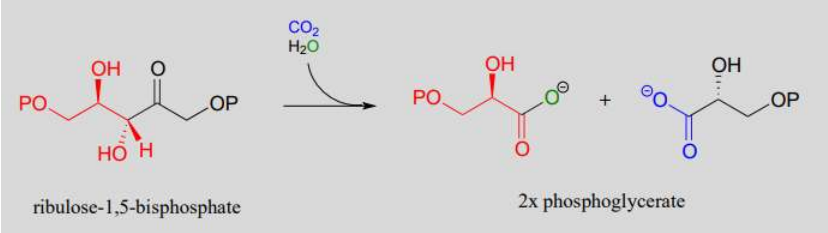
You can think of a carboxylation reaction as essentially a special kind of aldol reaction, except that the carbonyl electrophile being attacked by the enolate is CO_2 rather than a ketone or aldehyde:

Mechanism for carboxylation of an enolate

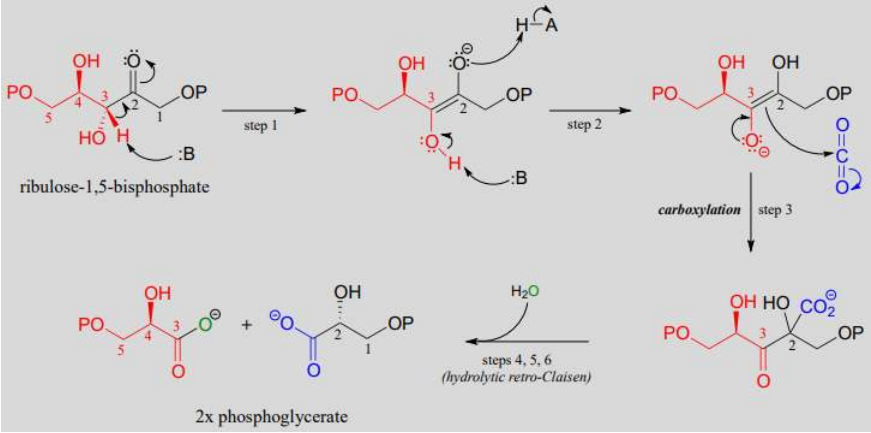


Here is the full Rubisco reaction. Notice that the carbon dioxide (in blue) becomes incorporated into one of the two phosphoglycerate products.

The Rubisco reaction:



Mechanism:



The mechanism for the Rubisco reaction is somewhat involved, but if we break it down into its individual steps, it is not terribly difficult to follow. In step 1, an α-carbon on ribulose 1,5-bisphosphate is deprotonated to form an enolate. In step 2, the oxygen at carbon #3 is deprotonated while the oxygen at carbon #2 is protonated: combined, these two steps have the effect of creating a different enolate intermediate and making carbon #2, rather than carbon #3, into the nucleophile for an aldol-like addition to CO_2 (step 3). Carbon dioxide has now been 'fixed' into organic form - it has become a carboxylate group on a six-carbon sugar derivative. Steps 4, 5, and 6 make up a hydrolytic retro-Claisen cleavage reaction (in other words, water is the bond-breaking

nucleophile) producing two molecules of 3-phosphoglycerate. Phosphoglycerate is channeled into the gluconeogenesis pathway to eventually become glucose.

? Exercise 13.6.1

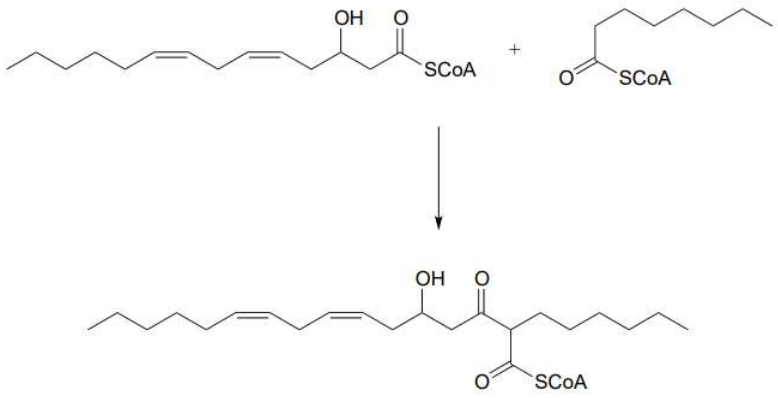
Draw out the full mechanism for steps 4-6 in the Rubisco reaction.

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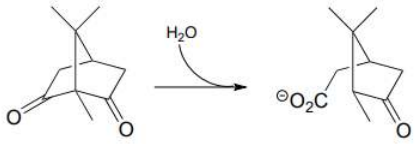
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13.E: Reactions at the α-Carbon, Part II (Exercises)

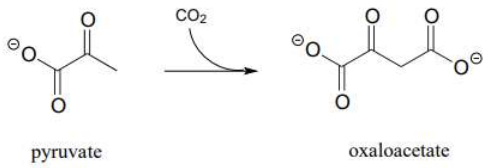
P13.1: Tetrahydrolipastatin, a potent inhibitor of lipase enzymes (see section 11.6) is being tested as a possible anti-obesity drug. Lipastatin, a close derivative, is synthesized by the bacterium Streptomyces toxytricini. The biosynthetic pathway involves the following step shown below - draw a likely mechanism. (J. Biol. Chem. 1997, 272, 867).



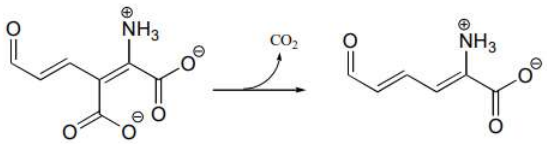
P13.2: The metabolism of camphor by some bacteria involves the step below. Draw a likely mechanism. (J. Biol. Chem 2004, 279, 31312)



P13.3: The glucogeogenesis pathway, by which glucose is synthesized from pyruvate, begins with a reaction catalyzed by pyruvate carboxylase. The enzyme requires the CO_2-carrying biotin to function, but the final step is thought to be the simple carboxylation of pyruvate by free carbon dioxide (Biochem. J. 2008, 413, 369). Draw a mechanism for this step.

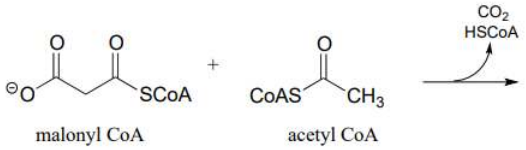


P13.4: Draw a reasonable mechanism for this decarboxylation step in tryptophan biosynthesis (EC 4.1.1.45). Hint: a tautomerization step precedes the decarboxylation.

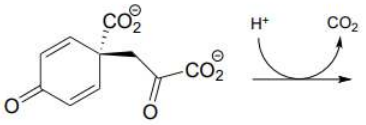


P13.5: The biosynthetic pathway for the antibiotic compound rabelomycin begins with the condensation of malonyl ***CoA*** and acetyl ***CoA***. Predict the product of this reaction, and propose a likely mechanism. (Org. Lett. 2010 12, 2814.)

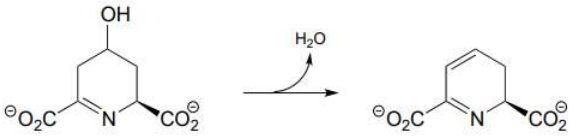
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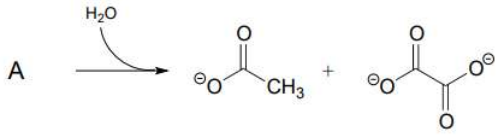
P13.6: Predict the product of this decarboxylation step in the biosynthesis of the amino acid tyrosine. Hint: think about comparative stability when you are considering where protonation will occur!



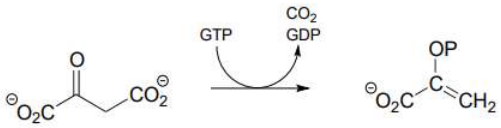
P13.7: Show a likely mechanism for this reaction from lysine biosynthesis:



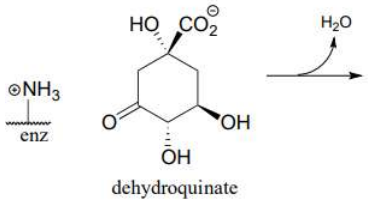
P13.8: Compound A undergoes hydrolytic cleavage in some fungi to form the products shown. Predict the structure of A. (J. Biol. Chem. 2007, 282, 9581)



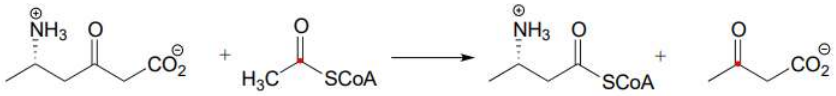
P13.9: Propose a mechanism for the following reaction from the gluconeogenesis pathway (EC 4.1.1.32):



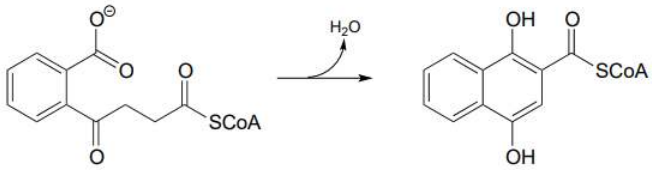
P13.10: Dehydroquinate undergoes dehydration (EC 4.2.1.10) in aromatic amino acid biosynthesis. Experimental and genomic evidence points to a lysine-linked iminium intermediate. More than one dehydration product is possible for dehydroquinate, but in this case the most stable product is the one that forms. Predict the structure of the product, explain why it is the more stable of the possible dehydration products, and draw a mechanism for its formation.



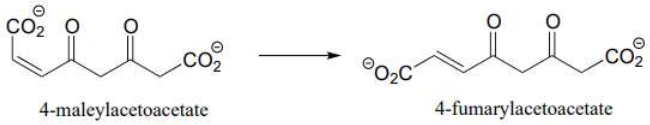
P13.11: The enzyme catalyzing the reaction below, thought to participate in the fermentation of lysine in bacteria, was recently identified and characterized (J. Biol. Chem. 2011, 286, 27399). Propose a likely mechanism. Hint: the mechanism involves two separate carbon-carbon bond forming and bond breaking steps. C_1 of acetyl ***CoA*** is identified with a red dot to help you trace it through to the product.



P13.12: Menaquinone (Vitamin K) biosynthesis in bacteria includes the following step:

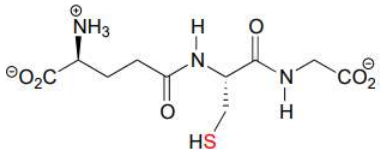


Propose a likely mechanism. Hint: the mechanism involves a Claisen condensation step which is unusual in that the electrophile is a carboxylic acid group rather than a thioester. What is the driving force that allows this unusual step to occur? (J. Biol. Chem. 2010, 285, 30159)



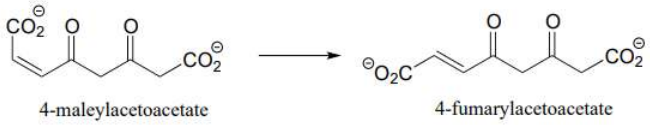
4-maleylacetoacetate

4-fumarylacetoacetate



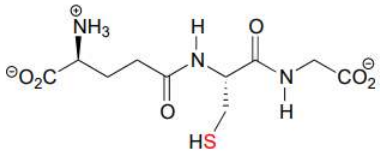
Glutathione
(GSH)

P13.13: 4-maleylacetoacetate isomerase (EC 5.2.1.2) catalyzes the following cis to trans alkene isomerization as part of the degradation of the aromatic amino acids phenylalanine and tyrosine.



4-maleylacetoacetate

4-fumarylacetoacetate



Glutathione
(GSH)

The enzyme uses the thiol-containing coenzyme glutathione, which is also involved in the formation of disulfide bonds in proteins, but in this case glutathione serves as a 'thiol group for hire'. The mechanism for the reaction is essentially a reversible conjugate addition of glutathione. Draw out the steps for this mechanism, showing how the cis-trans isomerization could be accomplished. Also, explain why the equilibrium for this reaction favors 4-fumarylacetoacetate. The structure of glutathione is shown, but you can use the abbreviation GSH in your mechanism.

P13.14: Based on the mechanistic patterns you have studied in this chapter, propose a likely mechanism for this final reaction in the degradation of the amino acid cysteine in mammals.

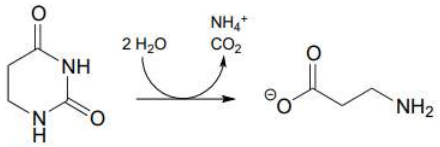


pyruvate

P13.15: Propose a mechanism for the following carboxylation reaction (EC 6.4.1.4) in the leucine degradation pathway. The complete reaction is dependent on the CO_2-carrying coenzyme biotin as well as ATP, but assume in your mechanism that the actual carboxylation step occurs with free CO_2 (you don't need to account for the role played by biotin or ATP).

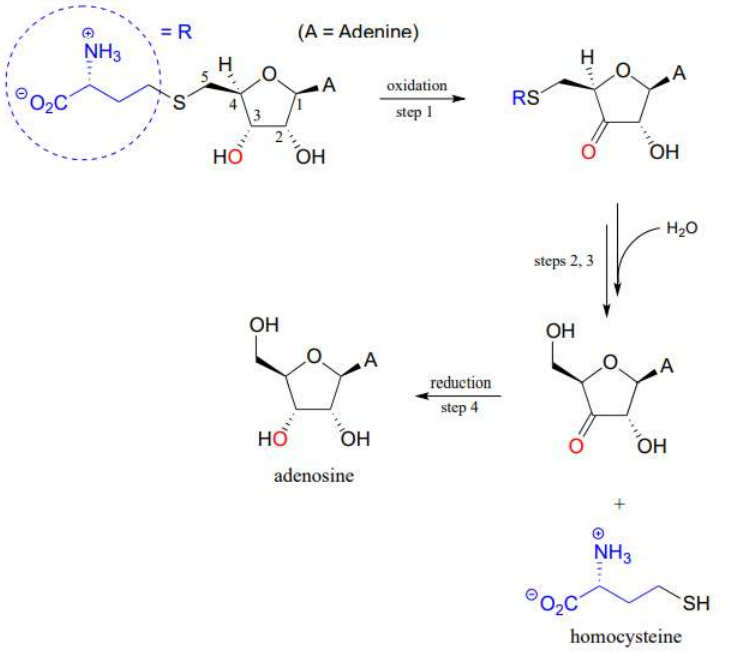


P13.16: Propose a mechanism for the following reaction, which is part of the degradation pathway for the nucleotide uridine.



P13.17: Illustrated below is a series of reactions in the degradation pathway for the amino acid methionine. In step 1, an alcohol group on C_3 is oxidized to a ketone, and in step 4 the ketone is reduced back to an alcohol - we will study these reactions in chapter X. In steps 2 and 3, the thiol (homocysteine) is replaced by water - but this does NOT involve a nucleophilic substitution process.

a. Draw a likely mechanism for step 2
b. Draw a likely mechanism for step 3
c. How does the involvement of the redox steps (steps 1 and 4) provide evidence that overall substitution of water for homocysteine is not a nucleophilic substitution?



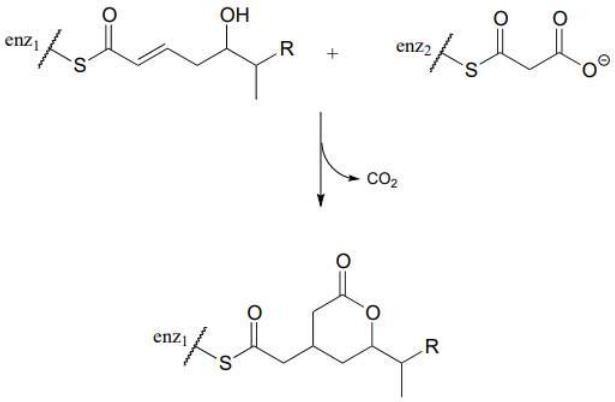
adenosine

homocysteine

P13.18: (Challenging!) A recently discovered reaction in the biosynthesis of rhizoxin, a potent virulence factor in the rice-seedling blight fungus Rhizopus microsporus, is illustrated below (Angewandte Chemie 2009, 48, 5001). The reaction takes place at the intersection of two 'modules' of a multi-enzyme complex, and provides an example of a biochemical conjugate addition step that

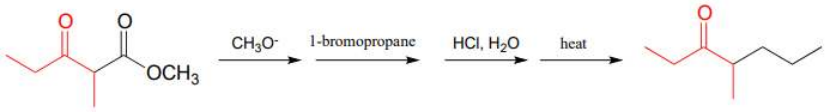
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results in the formation of a new carbon-carbon bond (conjugate addition of a carbon nucleophile is referred to as a Michael addition). Draw a likely mechanism.



P13.19:

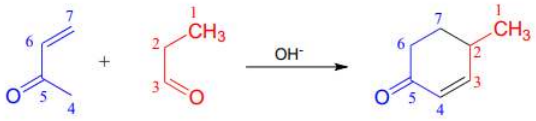
a. The 'acetoacetic ester synthesis' is a useful carbon-carbon bond-forming reaction in the laboratory. The reaction mechanism is described as a-carbon deprotonation to form an enolate, followed by SN2 alkylation, ester hydrolysis, and decarboxylation. Below is an example:



Draw out a reasonable mechanism, taking care to propose reactive intermediates that are appropriate given the basic or acidic conditions present (note that the reaction starts under basic conditions, then is later acidified).

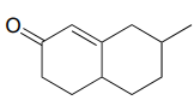
b. Suggest starting compounds for the synthesis of 4-phenyl-2-butanone by the acetoacetic ester reaction.

c. A very useful ring-forming reaction in laboratory synthesis is called 'Robinson annulation' (Sir Robert Robinson was an English chemist who won the 1947 Nobel Prize in Chemistry, and the term ‘annulation’ comes from the Latin annulus, meaning ‘ring’.) The reaction, which takes place in basic conditions, consists of a conjugate (Michael) addition step, followed by aldol addition and finally dehydration (*β*-elimination of water). A typical example is shown below, with carbons numbered to help you to follow the course of the reaction.



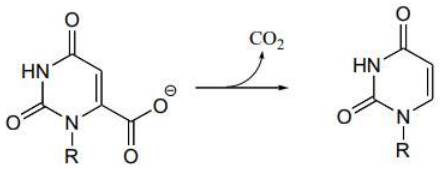
Draw a mechanism for this reaction (when proposing intermediate species, keep in mind that the reaction is occurring in a basic environment, and choose protonation states accordingly).

d. Propose starting compounds for the Robinson annulation synthesis of the following product:

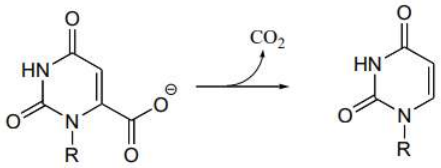


P13.20: The reaction shown below, catalyzed by orotidine monophosphate decarboxylase (EC 4.1.1.23), is one of the most extensively studied enzymatic transformations. It is known to occur without the participation of any coenzymes.

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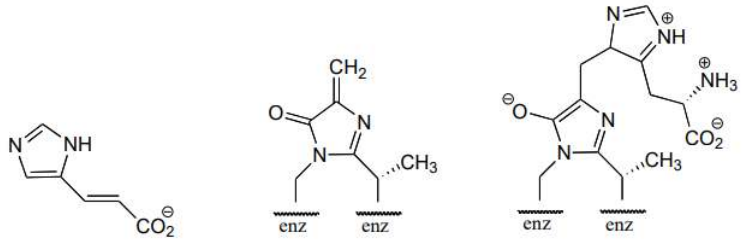


a. Look at the reaction closely: what is unique about it?
b. In 1997, a paper was published in which the authors predicted, based on theoretical calculations, that this reaction proceeded through a carbene intermediate (carbenes are not covered in this text – you may need to look them up). This was prior to the publication of an x-ray crystal structure. What kind of active site environment does this imply?
c. When the crystal structure was published a few years later, we learned that an aspartate residue (predicted to be negatively charged) is positioned very near the substrate carboxylate group, and a lysine residue (predicted to be positively charged) is positioned nearby on the opposite side (see figure below). What roles do you think were predicted for these two active site residues?



P13.21: In the histidine degradation pathway, histidine undergoes elimination of ammonia to form trans-urocanate. The enzyme catalyzing this reaction (E.C. 4.3.1.3) has been shown to use an unusual 'coenzyme', 4-methylideneimidazole-5-one (MIO), which is formed from the cyclization of an alanine-serine-glycine stretch of the enzyme itself.

A mechanism has been proposed in which the MIO coenzyme plays the role of electron sink, and the intermediate shown below forms.



Propose a full mechanism for this reaction according to this information.

P13.22: The product that forms in the reaction between benzaldehyde and acetophenone (along with a catalytic amount of sodium hydroxide) has a 1H-NMR spectrum in which all of the signals are between 7-8 ppm. Give the structure of product.

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13.S: Reactions at the α-Carbon, Part II (Summary)

Before moving on to the next chapter, you should:

- Be able to draw reasonable mechanisms for reactions of the following type:
  - Decarboxylation of a β-carboxy ketone or aldehyde
  - Claisen condensation and retro-Claisen cleavage
  - Hybrid decarboxylation-Claisen condensation
  - Conjugate addition
  - $E1cb$ elimination
- Understand (though not necessarily memorize) the fatty acid synthesis and degradation cycles, and how the Claisen. retro-Claisen, conjugate addition, and $E1cb$ elimination steps fit in.
- Be able to draw a complete mechanism for the Rubisco reaction.

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CHAPTER OVERVIEW

14: Electrophilic Reactions

14.0: Prelude to Electrophilic Reactions
14.1: Electrophilic Addition to Alkenes
14.2: Elimination by the E1 Mechanism
14.3: Electrophilic Isomerization
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14.5: Carbocation Rearrangements
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14.E: Electrophilic Reactions (Exercises)
14.S: Electrophilic Reactions (Summary)

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14.0: Prelude to Electrophilic Reactions



Introduction

Linnda Caporael probably should have paid a little more attention to the graduation requirements in her college catalog. Going through the graduation checklist during her senior year, she discovered to her dismay that she still needed to fulfill a social science requirement, so she promptly enrolled in an American History course. It was a decision that would in time lead to her authoring a paper in a prestigious scientific journal, being featured in a front page story in the New York Times, and changing our understanding of one of the most intriguing - and disturbing – episodes in American history.

Professor Caporael (Linnda went on to become a professor of Behavioral Psychology at Rensselaer Polytechnic Institute) recounted her story in an episode of the PBS documentary series Secrets of the Dead. Early in the semester, she learned that as part of her history course she would be required to complete a research paper on a topic of her own choosing. She had recently seen a performance of The Crucible, Arthur Miller's classic play about the Salem witch trials, and decided to do her research on Anne Putnam, one of the young Salem girls who accused several village women of bewitching them. The symptoms of 'bewitchment' that afflicted the girls were truly frightening: thrashing and convulsions, visions of snakes and ferocious beasts, a sudden inability to speak, and a feeling that ants were crawling under their skin.

> *These children were bitten and pinched by invisible agents: their arms, necks and backs turned this way and that way, and returned back again, so as it was, impossible for them to do of themselves, and beyond the power of any epileptick fits, or natural disease to effect. Sometimes they were taken dumb, their mouth flopped, their throats choaked, their limbs wracked and tormented. . .*

(From “A Modest Enquiry Into the Nature of Witchcraft” (1702) by Reverend John Hale. http://historyofmassachusetts.org/betty-parris-first-afflicted-girl-of-the-salem-witch-trials/)

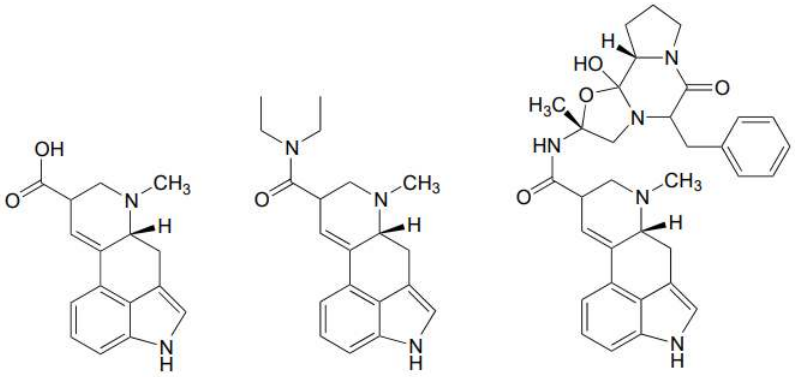
As Linnda continued to read accounts of the 'fits' afflicting the Salem girls, she was suddenly struck by the similarities to another, more recent episode that she had read about. In the summer of 1951, in the French village of Pont Saint Esprit, a number of local people were simultaneously seized by hallucinations, convulsions, and other symptoms very much like those described during the Salem witch trials hundreds of years earlier. Leon Armunier, a former postman in Pont Saint Esprit, described his experience to the BBC:

> *It was terrible. I had the sensation of shrinking and shrinking, and the fire and the serpents coiling around my arms . . .Some of my friends tried to get out of the window. They were thrashing wildly. . . screaming, and the sound of the metal beds and*

the jumping up and down... the noise was terrible. I'd prefer to die rather than go through that again.

There have been several explanations offered for what caused the Pont Saint Esprit outbreak (including that the CIA was experimenting with mass LSD poisoning as a form of chemical warfare), but the most widely accepted theory is that the hallucinations were caused by eating bread made from contaminated grain.

Claviceps purpurea, a fungus known to grow in rye and other grains, produces a class of hallucinogenic compounds called 'ergot alkaloids' which are derived from lysergic acid (the hallucinogenic drug LSD is a synthetic derivative of lysergic acid). Claviceps thrives in damp grain, and special care must be taken to avoid contamination when storing grain grown during warm, rainy summers.



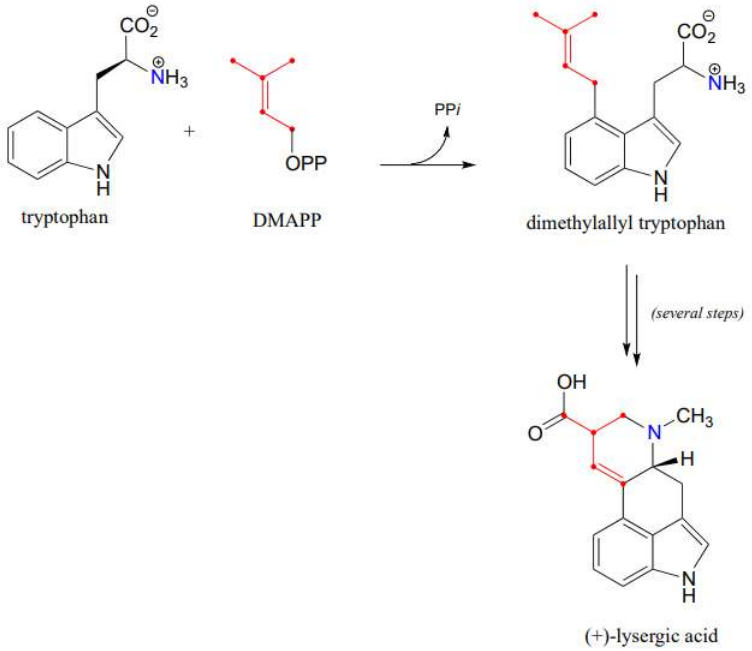
Digging deeper into the records of the Salem witchcraft episode, Linnda Caporael learned that the summer of 1691 was unusually damp. The first cases of 'bewitchment' in Salem village occurred in the winter of 1691-1692, when the villagers would have been consuming grain stored from the previous summer. Rye, the kind of grain most vulnerable to Claviceps contamination, was the staple crop in Salem at the time. Furthermore, nearly all of the affected girls lived on farms on the swampy western edge of the town, where Claviceps contamination would have been most likely to occur.

This was all circumstantial evidence, to be sure, but it was enough to convince Linnda that ergot poisoning was much more plausible as a root cause of the behavior of the afflicted girls than simply mass hysteria, which had long been the accepted theory. She summarized her findings in a paper that was later published in the journal Science, with the colorful title "Ergotism: The Satan Loosed in Salem?" (Science 1976, 192, 21). Her theory is still not universally accepted, but scientists and historians are for the most part in agreement that ergot poisoning was the cause of other outbreaks of convulsions and hallucinations, often called 'Saint Anthony's Fire', that have occurred throughout European history. It is possible that ergot poisoning may have played a role in literature as well: professor Caporael, in an interview with PBS, recounts how she was recently contacted by an historian with in intriguing idea. Is it possible that Caliban, the wild, half-human character in Shakespeare's The Tempest who is tormented by hallucinations inflicted upon him by the wizard Prospero, could be a literary manifestation of ergot poisoning episodes that occurred in England during Shakespeare's time?

For every trifle are they set upon me;
Sometime like apes that mow and chatter at me
And after bite me, then like hedgehogs which
Lie tumbling in my barefoot way and mount
Their pricks at my footfall; sometime am I
All wound with adders who with cloven tongues
Do hiss me into madness.

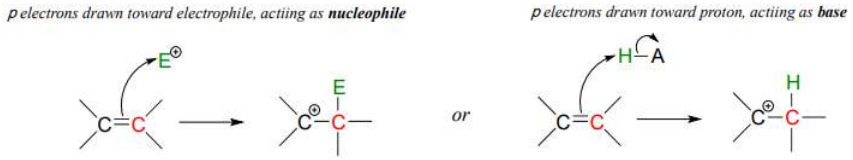
(William Shakespeare's The Tempest, Act II scene ii)

In this chapter, we will learn about a class of organic reaction that is central to the biosynthesis of ergot alkaloids in Claviceps. The key first step in the biosynthetic pathway is a reaction unlike any we have yet seen:



As you can see, the first step is condensation between the amino acid tryptophan and dimethylallyl diphosphate (DMAPP), the building block molecule for isoprenoids (section 1.3A). What you should also notice in the reaction figure above is that a new carbon-carbon bond is formed, and yet the chemistry involved is clearly very different from the carbon-carbon bonding forming aldol additions and Claisen condensations we learned about in the previous two chapters: there is no carbonyl to be found anywhere near the site of reaction, and one of the bond-forming carbons is part of an aromatic ring.

We will see later in this chapter that this reaction mechanism is classified as an 'electrophilic aromatic substitution', and is one of a broader family of organic reaction mechanisms that includes electrophilic additions, substitutions, and isomerizations. 'Electrophilic' is the key term here: in organic chemistry, an 'electrophilic' reaction mechanism is one in which the p-bonded electrons in a carbon-carbon double (or sometimes triple) bond are drawn towards an electron-poor species, often an acidic proton or carbocation. In essence, the p bond is acting as a nucleophile or base.



Notice above that, once the p bond breaks and a new σ bond forms, the second carbon that was part of the original p bond becomes a carbocation. Carbocation intermediates play a critical role in this chapter, because a carbocation is a highly reactive species and will quickly attract a pair of electrons. The stability of the carbocation intermediate (recall that we learned about carbocation stability in section 8.5), and the manner in which it accepts a pair of electrons, plays a key role in determining the outcome of the reaction.

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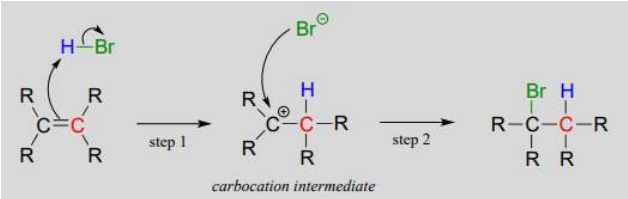
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14.1: Electrophilic Addition to Alkenes

Addition of HBr to alkenes

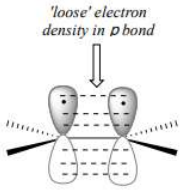
The simplest type of electrophilic reaction to visualize is the addition of a haloacid such as HBr to an isolated alkene. It is not a biological reaction, but nonetheless can serve as a convenient model to introduce some of the most important ideas about electrophilic reactions.

Electrophilic addition of HBr to an alkene:



Step 1 is an acid-base reaction: the π electrons of the alkene act as a base and extract the acidic proton of HBr. This leaves one of the carbons with a new bond to hydrogen, and the other with an incomplete octet and a positive formal charge. In step 2, the nucleophilic bromide anion attacks the electrophilic carbocation to form a new carbon-bromine bond. Overall, the HBr molecule - in the form of a proton and a bromide anion - has been added to the double bond.

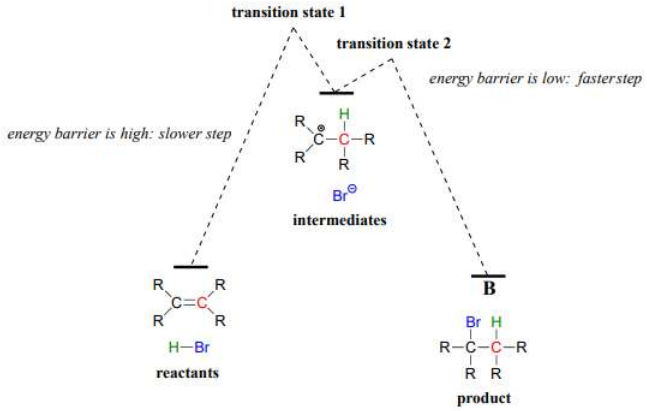
To understand how π-bonded electrons in an alkene could be basic, let's first review the bonding picture for alkenes. Recall (section 2.1) that the both of the carbons in an alkene group are sp^2 hybridized, meaning that each carbon has three sp^2 hybrid orbitals extending out in the same plane at $180°$ angles (trigonal planar geometry), and a single, unhybridized p orbital oriented perpendicular to that plane - one lobe above the plane, one lobe below.



The unhybridized p orbitals on the two alkene carbons overlap, in a side-by-side fashion, to form the pi bond, which extends above and below the plane formed by the s bonds. two electrons shared in this π bond are farther away from the carbon nuclei than the electrons in the carbon-carbon s bond, and thus are more accessible to the acidic proton. In addition, recall that molecular orbital (MO) theory tells us that p orbitals are higher in energy than s orbitals (section 2.2). As a consequence, it is easier to break the p bond of an alkene than it is to break the s bond: the p bond is more reactive.

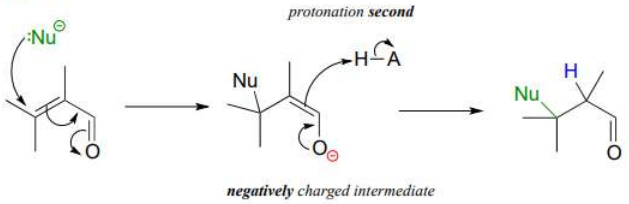
As the HBr molecule approaches the alkene, a new s bond is formed between one of the alkene carbons and the electron-poor proton from HBr. The carbon, which was sp^2 hybridized when it was part of the alkene, is now sp^3 hybridized. The other alkene carbon is still sp^2 hybridized, but it now bears a positive formal charge because it has only three bonds, and its p orbital is empty. But it won't stay empty for long: a carbocation is a very reactive, unstable intermediate. The bromide ion will rapidly act as a nucleophile, filling the orbital with a pair of electrons, and now with four s bonds the carbon is sp^3-hybridized.

The first step in the electrophilic addition reaction is much slower than the second step, because the intermediate carbocation species is higher in energy than either the reactants or the products, and as a result the energy barrier for the first step is also higher than for the second step. The slower first step is the rate-determining step: a change in the rate of the slow step will effect the rate of the overall reaction, while a change in the rate of the fast step will not.

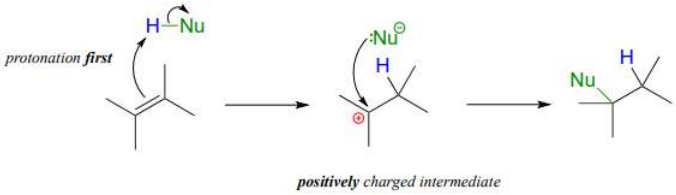


It is important to recognize the inherent difference between an electrophilic addition to an alkene and a conjugate addition to an alkene in the □□□ position, the latter of which we studied earlier in section 13.4. In both reactions, a proton and a nucleophile add to the double bond of an alkene. In a conjugate addition, the nucleophilic attack takes place first, resulting in a negatively charged intermediate (an enolate). Protonation is the second step. Also, of course, the alkene must be conjugated to a carbonyl or imine.

conjugate addition:



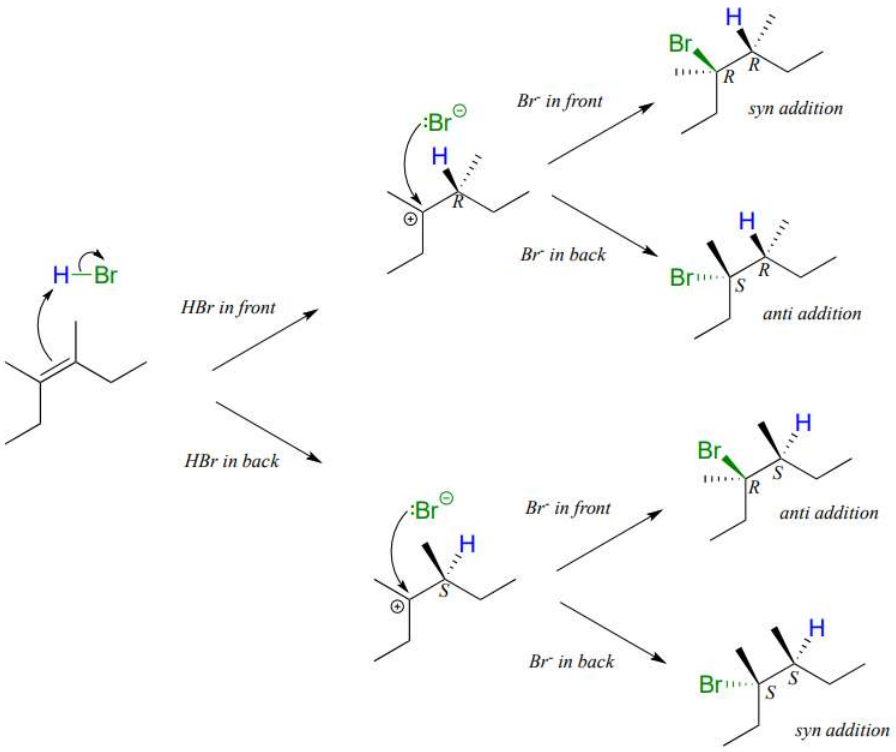
electrophilic addition:



In an electrophilic addition, proton abstraction occurs first, generating a positively-charged intermediate. Nucleophilic attack is the second step. No conjugated carbonyl or imine group is required: in fact a nearby carbonyl group would actually slow down a hypothetical electrophilic addition reaction down because a carbonyl is an electron withdrawing, carbocation-destabilized group.

The stereochemistry of electrophilic addition

Depending on the structure of the starting alkene, electrophilic addition has the potential to create two new chiral centers. Addition of HBr to an alkene is not stereoselective: the reaction results in racemization at both of the alkene carbons. Consider the addition of HBr to cis-3,4-dimethyl-3-hexene. The initial proton abstraction step creates a new chiral center, and because the acidic proton could be added to either side of the planar alkene carbon with equal probability, the center could have either S or R configuration.



Likewise, in the second step the nucleophilic bromide ion could attack from either side of the planar carbocation, leading to an equal mixture of ***S*** and ***R*** configuration at that carbon as well. Therefore, we expect the product mixture to consist of equal amounts of four different stereoisomers.

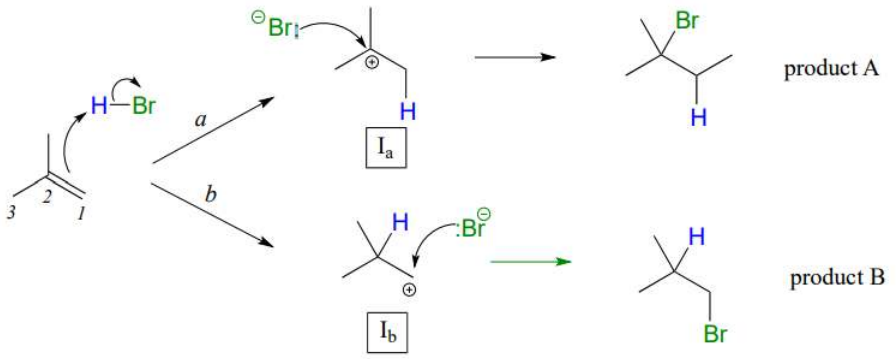
? Exercise 14.2.1

Predict the product(s) of electrophilic addition of ***HBr*** to the following alkenes. Draw all possible stereoisomers that could form, and take care not to draw identical structures twice.

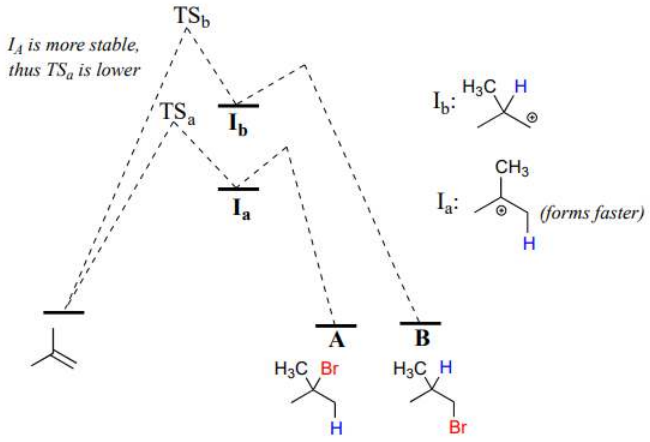
a. trans-2-butene
b. cis-3-hexene
c. cyclopentene

The regiochemistry of electrophilic addition

In many cases of electrophilic addition to an alkene, regiochemistry comes into play: the reaction can result in the formation of two different constitutional isomers. Consider the electrophilic addition of ***HBr*** to 2-methylpropene:



Note that carbon #1 and carbon #2 in the starting alkene are not the same - carbon #2 is bonded to two methyl groups, and carbon #1 to two hydrogen atoms. The initial protonation step could therefore go two different ways, resulting in two different carbocation intermediates. Notice how pathway '**a**' gives a tertiary carbocation intermediate (I_a), while pathway '**b**' gives a primary carbocation intermediate (I_b) We know from section 8.5 that the tertiary carbocation I_a is lower in energy. Consequently, the transition state $TS(a)$ leading to I_a is lower in energy than $TS(b)$, meaning that I_a forms faster than I_b.



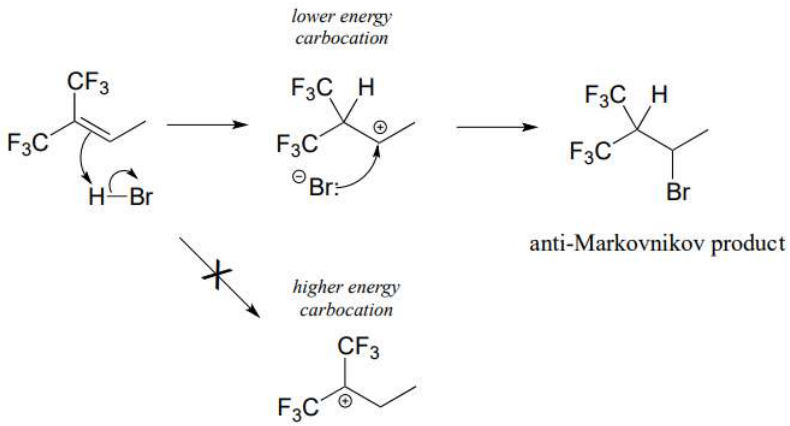
Because the protonation step is the rate determining step for the reaction, tertiary alkyl bromide A will form faster than the primary alkyl bromide B, and thus A will be the predominant product of the reaction. The electrophilic addition of HBr to 2-methylpropene is regioselective: more than one constitutional isomer can potentially form, but one isomer is favored over the other. It is generally observed that in electrophilic addition of haloacids to alkenes, the more substituted carbon is the one that ends up bonded to the heteroatom of the acid, while the less substituted carbon is protonated. This 'rule of thumb' is known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869.

While it is useful in many cases, Markovikov's rule does not apply to all electrophilic addition reactions. It is better to use a more general principle:

The regioselectivity of electrophilic addition

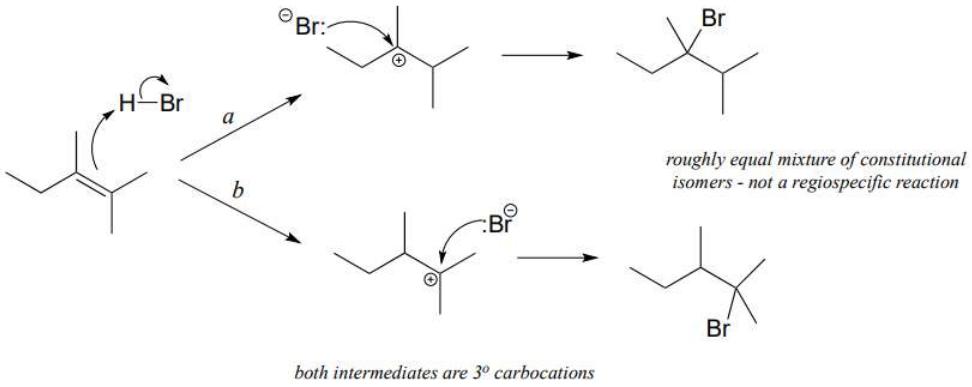
When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

How is this different from Markovnikov's original rule? Consider the following hypothetical reaction, in which the starting alkene incorporates two trifluoromethyl substituents:



Now when HBr is added, it is the less substituted carbocation that forms faster in the rate-determining protonation step, because in this intermediate the carbon bearing the positive charge is located further away from the electron-withdrawing, cation-destabilizing fluorines. As a result, the predominant product is the secondary rather than the tertiary bromoalkane. This is referred to as an anti-Markovnikov addition product, because it 'breaks' Markovnikov's rule.

If the two possible carbocation intermediates in an electrophilic addition reaction are of similar stability, the product will be a mixture of constitutional isomers.



Electrophilic addition of water and alcohol

The (non-biochemical) addition of water to an alkene is very similar mechanistically to the addition of a haloacid such as HBr or HCl, and the same stereochemical and regiochemical principles apply. A catalytic amount of a strong acid such as phosphoric or sulfuric acid is required, so that the acidic species in solution is actually H_3O^+. Note that H_3O^+ is regenerated in the course of the reaction.



Figure 14.2.10

If an alkene is treated with methanol and a catalytic amount of strong acid, the result is an ether:



Figure 14.2.11

? Exercise 14.2.2

Draw a mechanism for the ether-forming reaction above.

Addition to conjugated alkenes

Electrophilic addition to conjugated alkenes presents additional regiochemical possibilities, due to resonance delocalization of the allylic carbocation intermediate. Addition of one molar equivalent of HBr to 1,3-butadiene, for example, leads to a mixture of three

products, two of which are a pair of enantiomers due to the creation of a chiral center at carbon #2.



Figure 14.2.12

? Exercise 14.2.3

Explain why 4-bromo-1-butene is not a significant product of the reaction above.

? Exercise 14.2.4

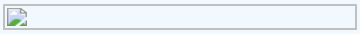
Predict the major product(s) of the following reactions. Draw all possible stereoisomers, and take care not to draw the same structure twice.

a. 

b. 

c. 

d. ***Hint*** - are the double bonds in an aromatic ring likely to undergo electrophilic addition?



e. 

Biochemical electrophilic addition reactions

Myrcene is an isoprenoid compound synthesized by many different kinds of plants and used in the preparation of perfumes. Recently an enzymatic pathway for the degradation of myrcene has been identified in bacteria (J. Biol. Chem 2010, 285, 30436). The first step of this pathway is electrophilic addition of water to a conjugated alkene system.



Figure 14.2.13

? Exercise 14.2.5

Draw a mechanism for the above reaction, showing two resonance contributors of the carbocation intermediate. How would you characterize the intermediate?

Although the hydration of myrcene above looks very familiar, many enzyme-catalyzed electrophilic addition reactions differ from what we have seen so far, in that the electron-poor species attacked by the p-bonded electrons in the initial step is a carbocation rather than an acidic proton:



Figure 14.2.14

□-terpineol, a major component in the sap of pine trees, is formed in an electrophilic addition reaction. The first thing that happens (which we will refer to below as 'step a', in order to keep the step numbering consistent what the addition mechanisms we have seen so far) is departure of a pyrophosphate leaving group, forming an allylic carbocation electrophile.



Figure 14.2.15

The actual electrophilic addition stage of the reaction begins with step 1, as the π electrons an alkene are drawn toward one of the two carbons that share the positive charge, effectively closing a six-membered ring. A water molecule then attacks the second carbocation intermediate (step 2), which completes the addition process.

Notice something important about the regiochemical course of the reaction: step 1 results in the formation of a six-membered ring and a tertiary carbocation. As we have stressed before, biochemical reactions tend to follow energetically favorable mechanistic pathways.

? Exercise 14.2.6

An alternate regiochemical course to step 1 shown above could result in a seven-membered ring and a secondary carbocation, a much less energetically favorable intermediate in terms of both carbocation stability and ring size. Draw a mechanism for this hypothetical alternate reaction, and show the product that would result after the addition of water in a hypothetical 'step 2'.

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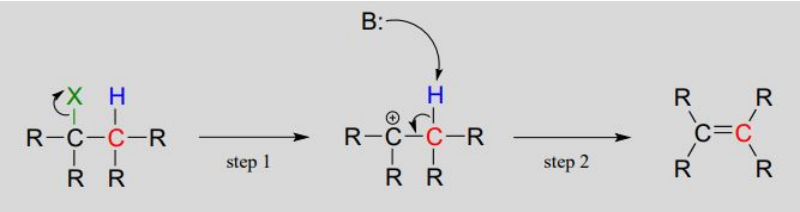
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14.2: Elimination by the E1 Mechanism

E1 elimination - An overview

The reverse of electrophilic addition is called E1 elimination. We will begin by looking at some non-biochemical E1 reactions, as the E1 mechanisms is actually somewhat unusual in biochemical pathways.

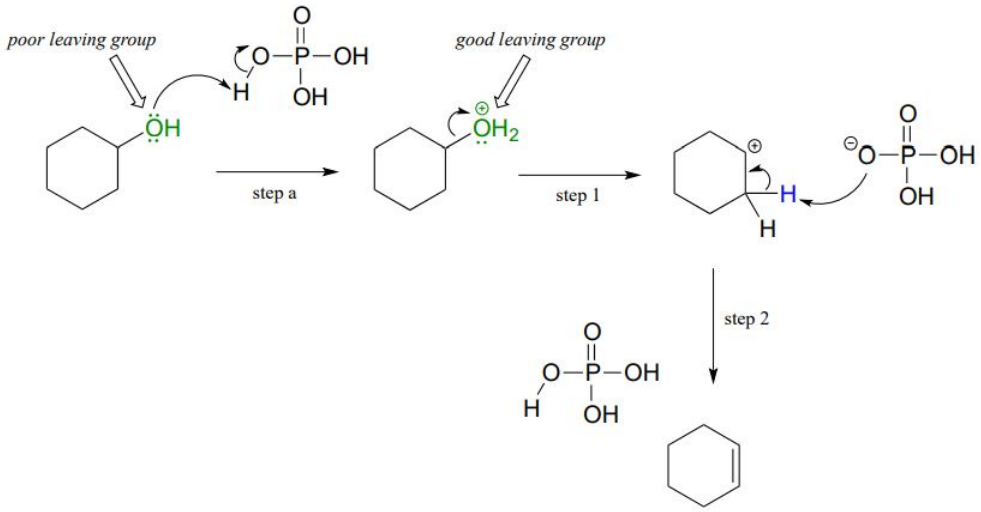
E1 elimination:



An E1 elimination begins with the departure of a leaving group (designated 'X' in the general figure above) and formation of a carbocation intermediate (step 1). Abstraction of a proton from an adjacent carbon (step 2) sends two electrons down to fill the empty p orbital of the carbocation, forming a new p bond. The base in this step may be the leaving group, or another basic species in solution.

E1 elimination does not occur when the leaving group is bonded to a primary carbon, unless the carbon is in the allylic or benzylic position. Recall that a primary carbocation, unless stabilized by resonance, is highly unstable and an unlikely reaction intermediate.

E1 eliminations can occur at secondary carbons, however. If cyclohexanol is heated with a catalytic amount of phosphoric acid, elimination of water (dehydration) results in cyclohexene as the product. The role of the phosphoric acid is to protonate the alcohol ('step a' below), making it a viable leaving group.



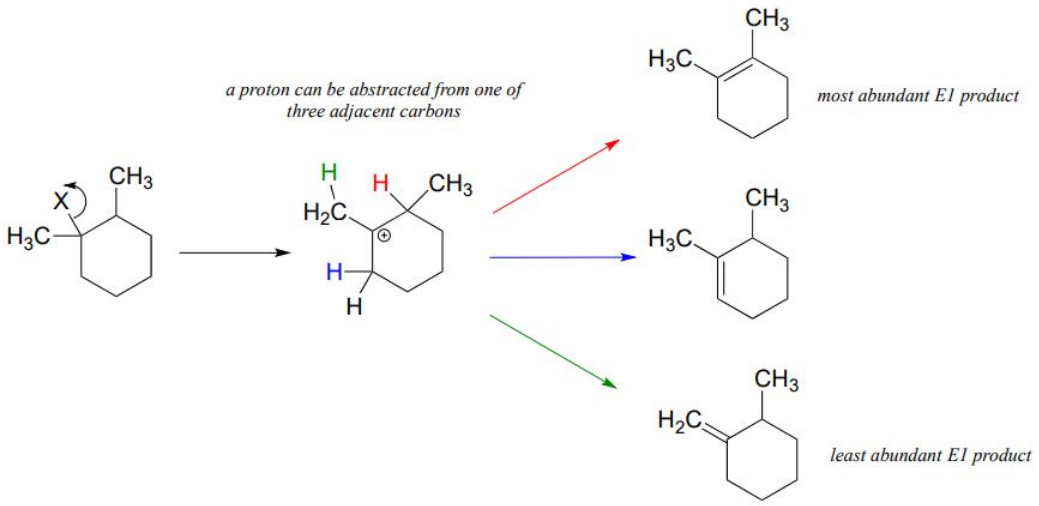
The reaction is reversible, but if cyclohexene is distilled away from the reaction mixture as it forms, the equilibrium can be driven towards product (you may want to review Le Chatelier's principle in your General Chemistry textbook). Separation of cyclohexene (boiling point **83°**) from cyclohexanol (boiling point **161°**) is simple because of the large difference in boiling points between the two liquids.

? Exercise 14.3.1

When the laboratory reaction described above is run to completion, a viscous 'goop' is usually left over in the distillation flask, which hardens upon cooling. Draw a mechanism showing how this 'goop' might form, and explain why it hardens upon cooling.

Regiochemistry of E1 elimination

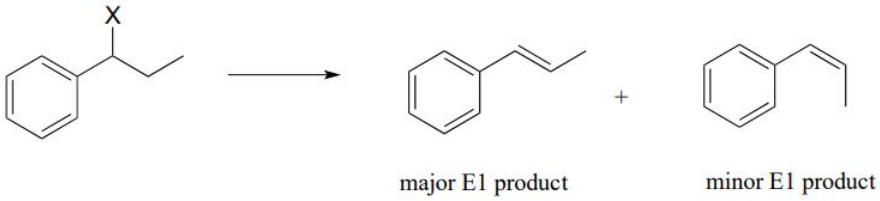
Nonenzymatic E1 reactions can often result in a mixture of more than one alkene product. Elimination of 'HX' from the following starting compound, for example, could yield three different possible alkene products.



Notice in the figure above that the three possible E1 products do not form in equal abundance. The most abundant alkene product is that which is most substituted: in other words, the alkene in which the two sp^2 carbons are bonded to the fewest hydrogen atoms. In this case, the most substituted alkene has zero hydrogen substituents. The least substituted - and least abundant - alkene product has two hydrogen substituents, while the middle alkene has one hydrogen substituent. This trend is observed generally with nonenzymatic E1 elimination reactions, and is known as Zaitsev's rule after the Russian chemist Alexander Zaitsev.

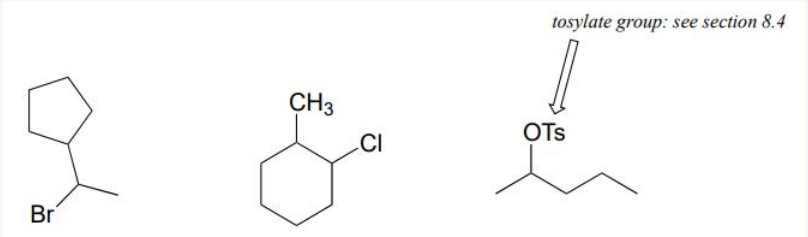
Stereochemistry of E1 elimination

Nonenzymatic E1 reactions can also result in both *cis* and *trans* alkenes. Keeping in mind that in general *trans* alkenes are more stable than *cis* alkenes, we can predict that trans alkenes will predominate in the product mixture.



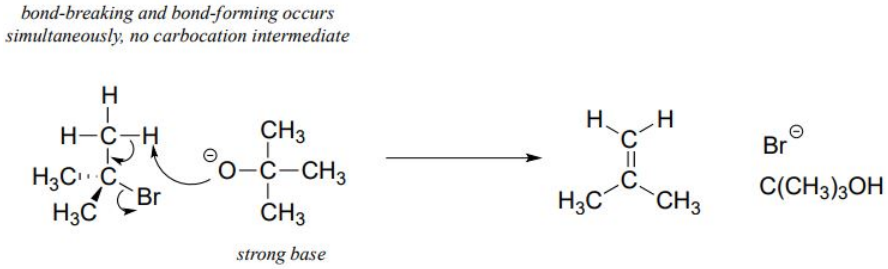
Exercise 14.3.2

Draw the structures of all possible E1 products starting with the compounds below, and rank them in order of highest to lowest abundance.



The E2 elimination mechanism

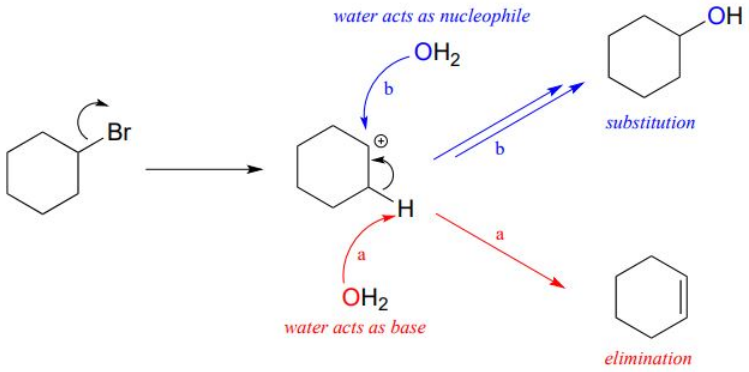
When a strong base is combined with an alkyl halide (or alkyl tosylate/mesylate), elimination generally occurs by the E2 pathway, in which proton abstraction and loss of the leaving group occur simultaneously, without an intervening carbocation intermediate:



Just like in the S_N2 mechanism, the '2' in the E2 designation refers to the idea that the rate-determining (and only) step of the reaction is a collision between the two reacting molecules, in this case bromocyclohexane and methoxide ion.

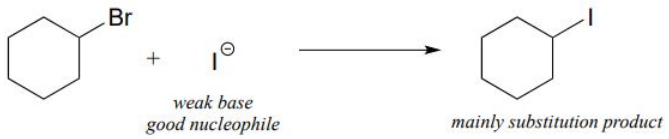
Competition between elimination and substitution

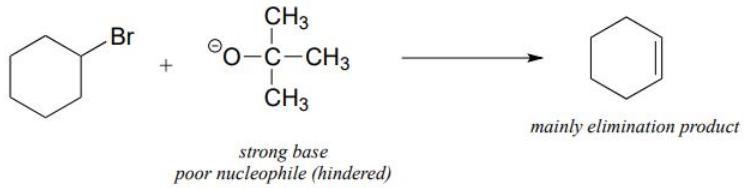
Consider a reaction between water and bromocyclohexane. Based on what we have just learned, a likely product would be the alkene formed from an E1 elimination reaction (pathway (a) in red below).

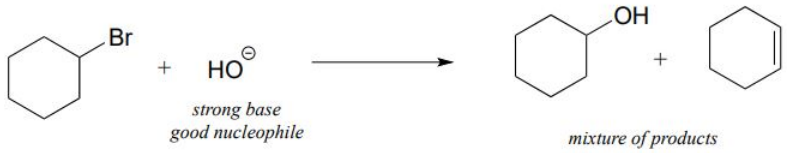


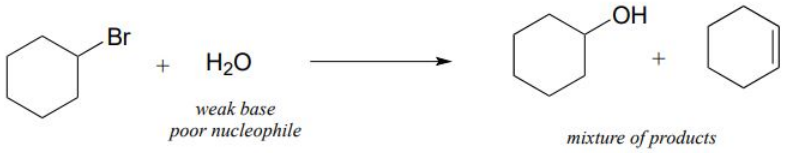
However, the reaction could take another course: what if the water molecule, instead of acting as a base, were to act as a nucleophile (pathway (b) in blue? This should look familiar - it is simply an S_N1 reaction (section 8.1). In fact, the reaction would result in a mixture of elimination (E1) and substitution (S_N1) products. This is a common theme: elimination and substitution often compete with each other.

When both elimination and substitution products are possible, however, we can often predict which reaction will predominate. In general, strong bases and hindered carbons favor elimination, while powerful nucleophiles and unhindered carbons favor substitution.



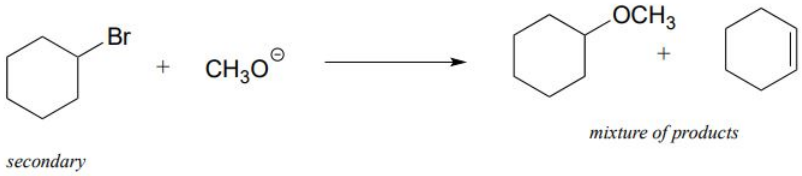






In addition, primary alkyl halides are much more likely to undergo substitution than elimination, even when the nucleophile is also a strong base, because the electrophilic carbon is unhindered and accessible to the nucleophile. Recall that the Williamson ether synthesis (section 8.8) is an efficient laboratory S_N2 reaction between a primary (or methyl) alkyl halide and an alkoxide. If a secondary alkyl halide is used, a substantial amount of elimination product will form (the electrophilic carbon is more hindered, and the alkoxide will act as a base as well as a nucleophile).





While competition between substitution and elimination pathways is an issue for chemists running reactions in the lab, the same cannot be said of biochemical reactions, as the architecture active site of enzymes have evolved to ensure the formation of only one product.

? Exercise 14.3.3

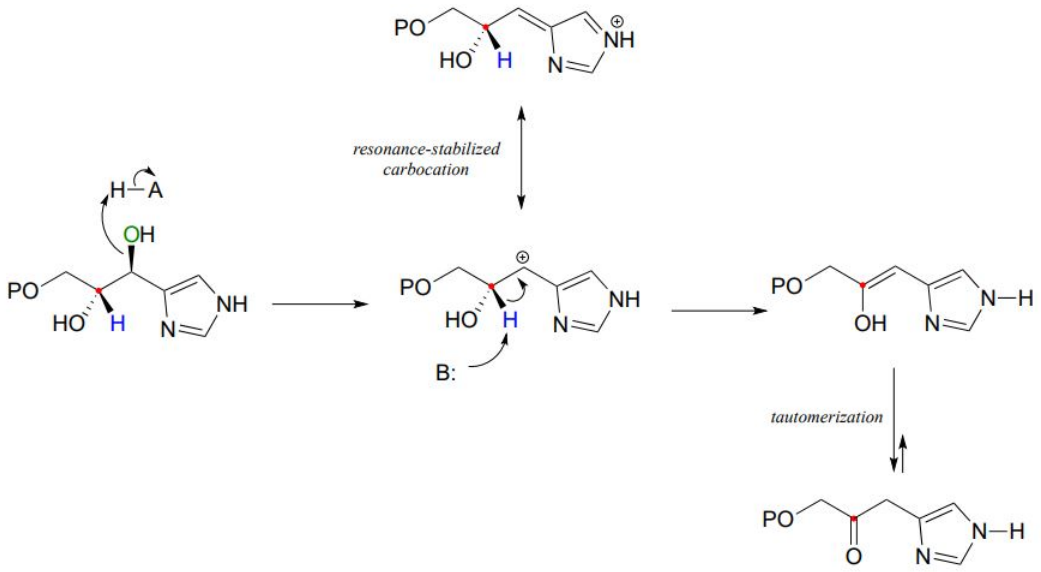
Predict the major organic product(s) of the following reactions. If the reaction is expected to result in a mixture of elimination and substitution product, show both.

a. bromocyclopentane plus ethoxide
b. 1-chlorohexane plus CH3S-
c. 2-iodo-2-methylpentane plus hydroxide

Biochemical E1 elimination reactions

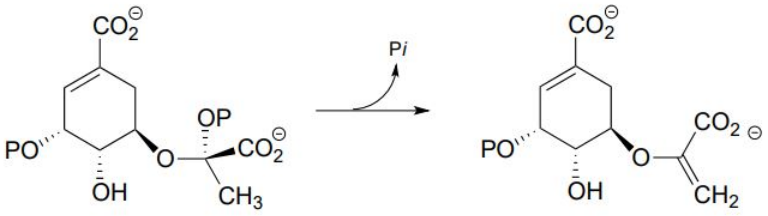
Looking through metabolic pathways in a biochemistry textbook, you'll see that almost all elimination reactions appear to be of the E1cb type, occurring on carbons in the □□□ position relative to a carbonyl or imine. A relatively small number of elimination steps, however, take place away from the electron-withdrawing influence of a carbonyl or imine, and these are of the carbocation-intermediate, E1 type. The E2 mechanism is veyr rare in biochemical pathways.

A reaction in the histidine biosynthetic pathway (EC 4.2.1.19) provides an example of a biological E1 dehydration step:



Notice that an E1cb mechanism is not possible here - there is no adjacent carbonyl or imine and thus no possibility for a stabilized anionic intermediate. Instead, the first step is loss of water to form a resonance-stabilized carbocation intermediate. Deprotonation completes the E1 phase of the reaction to form an enol, which rapidly tautomerizes to a ketone.

Another example of a biological E1 reaction is found in the biosynthesis pathway for aromatic amino acids (EC 2.5.1.19):

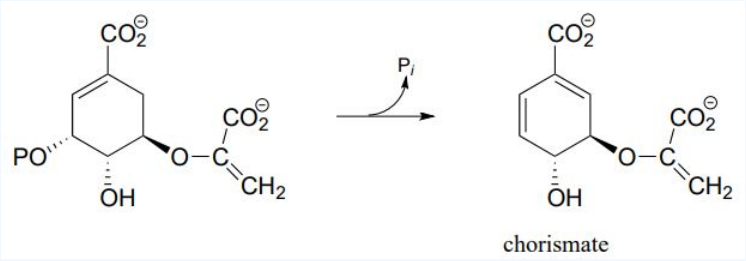


? Exercise 14.3.4

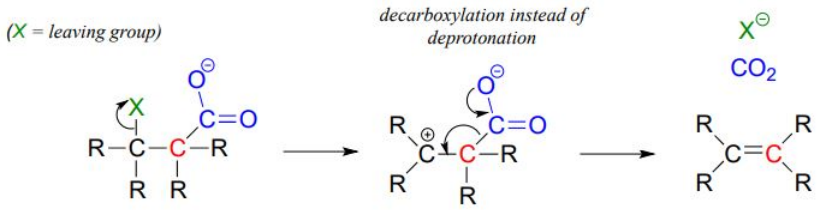
Draw a complete mechanism for the reaction above. Show how the carbocation intermediate is stabilized by resonance.

? Exercise 14.3.5

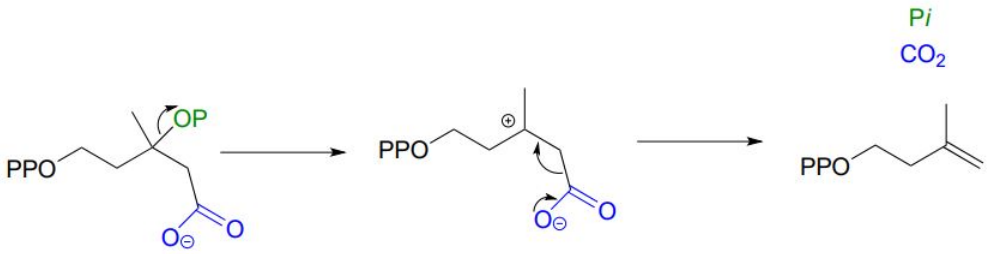
Another step (EC 4.2.3.5) in the aromatic acid biosynthesis pathway could be referred to as a conjugated E1 elimination of phosphate, the mechanistic reverse of electrophilic addition to a conjugated diene (section 14.1). Draw a complete mechanism for this reaction, showing two resonance contributors of the carbocation intermediate.



In section 13.3, we saw some Claisen condensation reactions in which the usual proton-abstracton step was replaced by decarboxylation. A similar thing can happen with E1 eliminations:

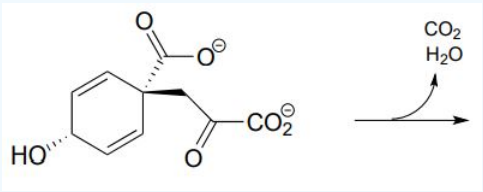


Isopentenyl diphosphate, the 'building block' for all isoprenoid compounds, is a product of this type of hybrid decarboxylation / elimination reaction (EC 4.1.1.33).



Exercise 14.3.6

A conjugated decarboxylation/E1 elimination reaction (EC 4.2.1.51) occurs in the phenylalanine biosynthesis pathway.



a. Predict the product, and draw a mechanism.
b. What two main factors contribute to the 'driving force' for this reaction?

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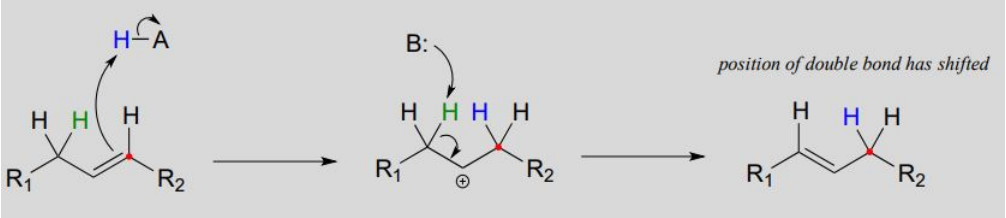
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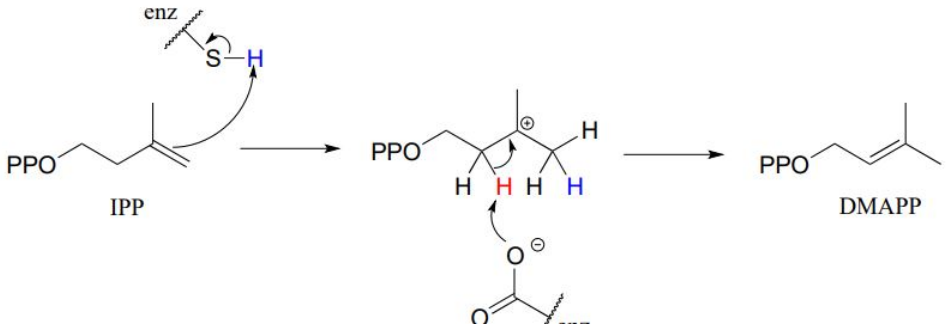
14.3: Electrophilic Isomerization

Electrophilic reactions in biochemistry are not limited to addition to alkene double bonds. The position of a double bond in an alkene can also be shifted through an electrophilic, carbocation-intermediate reaction. An electrophilic alkene isomerization occurs when an initial π bond protonation event (step 1 below) is followed by deprotonation of an adjacent carbon to re-form the π bond in a different location.

Electrophilic isomerization mechanism:



In a key early step in the biosynthesis of isoprenoid compounds, isopentenyl diphosphate (IPP), the isoprenoid 'building block' molecule, is isomerized to dimethylallyl diphosphate (DMAPP) (EC 5.3.3.2).



In the first step, the p bond between carbon #3 and carbon #4 is protonated by a cysteine residue in the active site. X-ray crystallography studies on the isomerase enzyme (EMBO J. 2001, 20, 1530) show that the carbocation intermediate is bound in a very deep, hydrophobic active site cavity that seals out any water molecules that could potentially attack the carbocation to form an undesired alcohol product. stead, a basic glutamate residue is positioned in the active site to abstract a proton from carbon #2 (step 2), serving to reestablish the double bond in a new position between carbons #2 and #3.

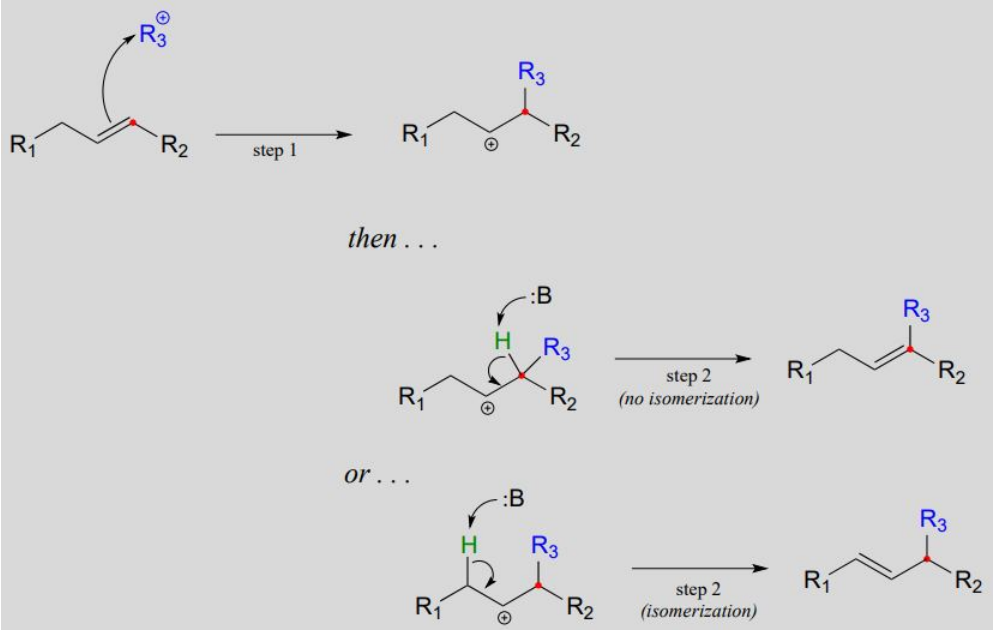
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14.4: Electrophilic Substitution

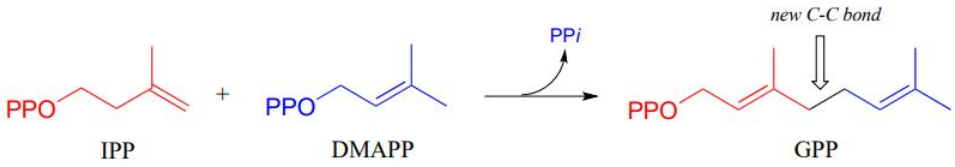
Until now, have already been introduced to electrophilic addition and electrophilic isomerization - now, let's move to the third variation on the electrophilic theme, that of electrophilic substitution. In an electrophilic substitution reaction, a pair of π-bonded electrons first attacks an electrophile - usually a carbocation species - and a proton is then abstracted from an adjacent carbon to reestablish the double bond, either in the original position or with isomerization.

Electrophilic substitution mechanism:

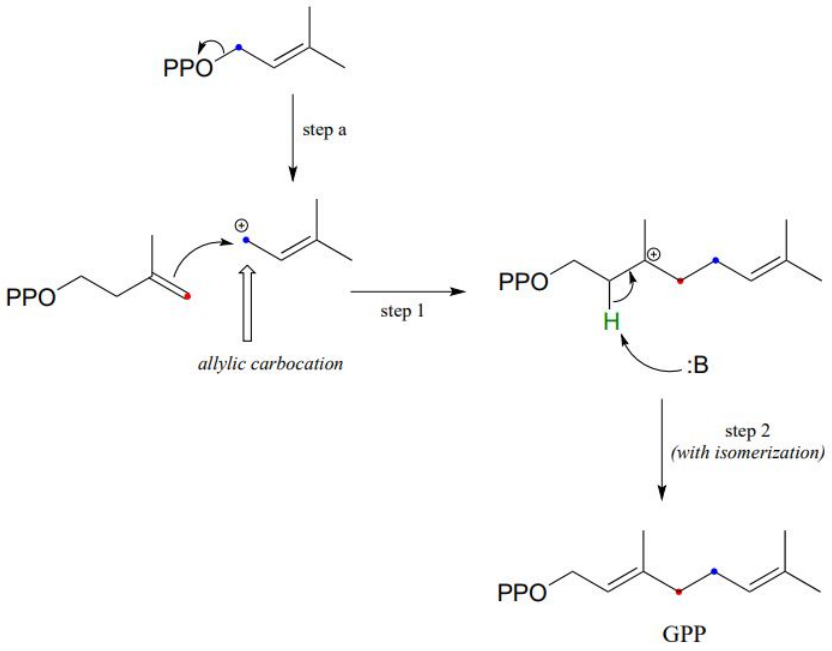


Electrophilic substitution reactions in isoprenoid biosynthesis

Electrophilic substitution steps are very important in the biosynthetic pathways if isoprenoid compounds. In an early, chain-elongating reaction (EC 2.5.1.1) of the pathways of many isoprenoids, building blocks IPP and DMAPP combine to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP):



In a preliminary step (step a below), the diphosphate group on DMAPP departs to form an allylic carbocation.



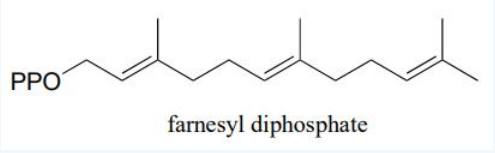
In step 1, the π electrons in IPP then attack the electrophilic carbocation from step a, resulting in a new carbon-carbon bond and a tertiary carbocation intermediate. Proton abstraction (step 2) leads to re-establishment of a double bond one carbon over from where it started out in IPP.

? Exercise 14.5.1

DMAPP is much more prone to spontaneous hydrolysis than IPP when they are dissolved in water. Explain why.

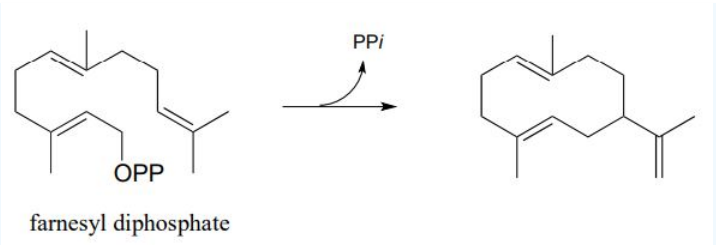
? Exercise 14.5.2

Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



? Exercise 14.5.3

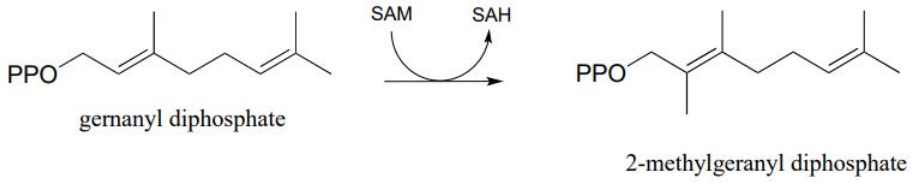
Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



farnesyl diphosphate

? Exercise 14.5.4

The electrophilic carbon in an electrophilic substitution reaction is often a carbocation, but it can also be the methyl group on S-adenosylmethionine (SAM - see section 8.8A). Propose a likely mechanism for this methylation reaction. (Biochemistry 2012, 51, 3003)



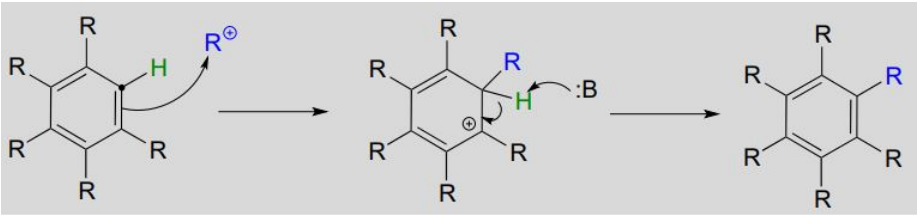
gernanyl diphosphate

2-methylgeranyl diphosphate

Electrophilic aromatic substitution

Until now, we have been focusing mostly on electrophilic reactions of alkenes. Recall from section 2.2 that π bonds in aromatic rings are substantially less reactive than those in alkenes. Aromatic systems, however, do in fact undergo electrophilic substitution reactions given a powerful electrophile such as a carbocation, and if the carbocation intermediate that forms can be sufficiently stabilized.

Electrophilic aromatic substitution (Friedel-Crafts alkylation) mechanism

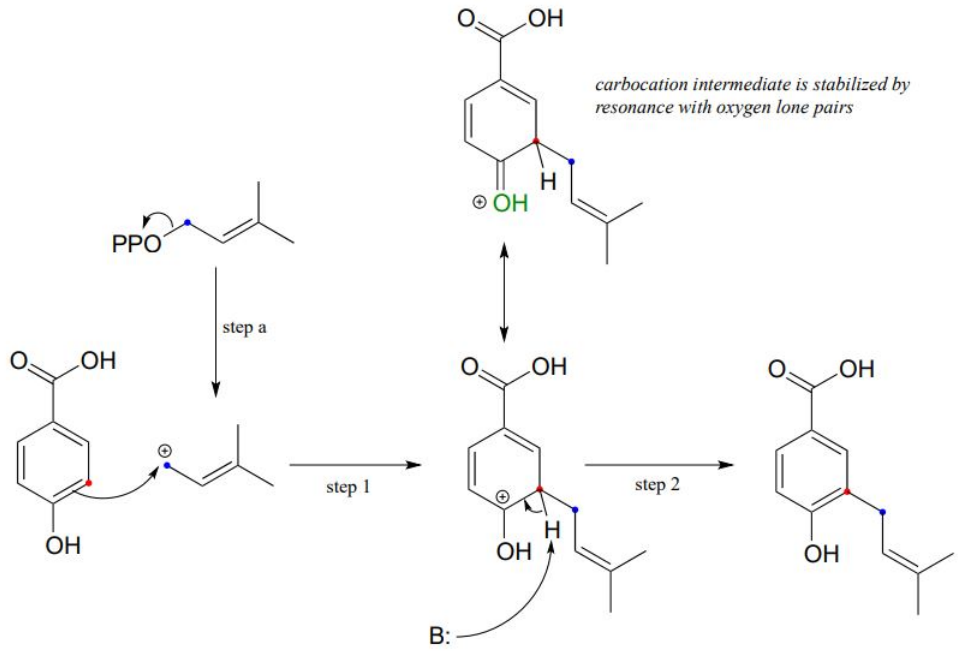


Organic chemists often refer to electrophilic aromatic substitution reactions with carbocation electrophiles as **Friedel-Crafts alkylation reactions**.

? Exercise 14.5.5

Aromatic rings generally do not undergo electrophilic *addition* reactions. Why not?

The Friedel-Crafts reaction below is part of the biosynthesis of vitamin K and related biomolecules.



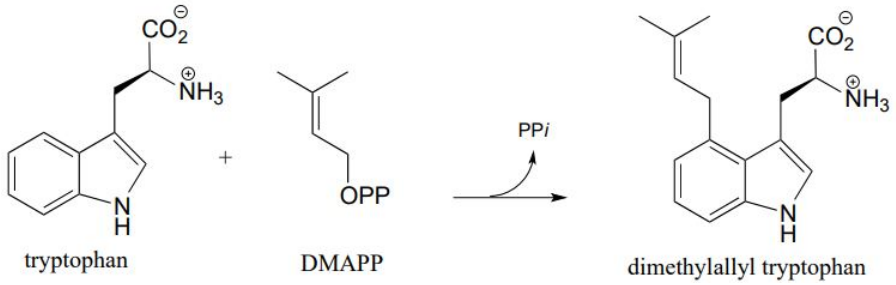
Loss of diphosphate creates a powerful carbocation electrophile (step a) which attracts the π electrons of the aromatic ring to form a carbocation intermediate with a new carbon-carbon bond (step 1). Substitution is completed by proton abstraction (step 2) which re-establishes the aromatic sextet.

An important point must be made here: because aromatic π bonds are substantially less reactive than alkene p bonds, the electrophilic must be VERY electrophilic - usually a carbocation. In addition, the carbocation intermediate that results from attack by aromatic π electrons is generally stabilized by resonance with lone pair electrons on a nearby oxygen or nitrogen (look at the resonance forms of the positively-charged intermediate that forms as the result of step 1 in the above figure).

Remember that stabilizing the intermediate formed in a rate-limiting step has the effect of lowering the activation energy for the step, and thus accelerating the reaction.

Organic chemists use the term ring activation to refer to the rate-accelerating effect of electron-donating heteroatoms in electrophilic aromatic substitution reactions. Aromatic rings lacking any activating oxygen or nitrogen atoms are less reactive towards electrophilic substitution.

An example of the ring-activating effect of the nitrogen atom on an aromatic ring can be found in the following Friedel-Crafts reaction (EC 2.5.1.34), which should be familiar from the introduction to this chapter:



Recall that this is a key early step in the biosynthetic pathway for the ergot alkaloids which are hypothesized to have been the root cause of the 'bewitchment' of several young girls in 17th century Salem, Massachusetts. (J. Am. Chem. Soc. 1992,114, 7354).

? Exercise 14.5.6

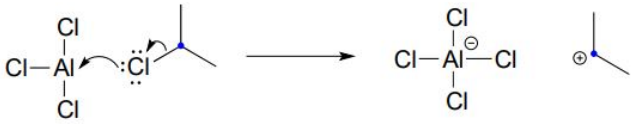
Draw a likely mechanism for the biosynthesis of dimethylallyl tryptophan, including a resonance structure showing how the carbocation intermediate in the rate determining step is stabilized by lone pair electrons on the ring nitrogen (in other words, show how the nitrogen serves to activate the ring).

Friedel-Crafts reactions, in addition to being important biochemical transformations, are commonly carried out in the laboratory. It is instructive to consider a few examples to see how the same principles of structure and reactivity apply to both biochemical and laboratory reactions.

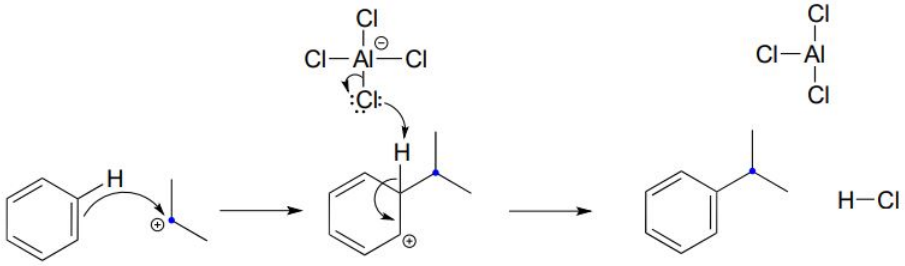
Below is an example of a laboratory Friedel-Crafts alkylation reaction:



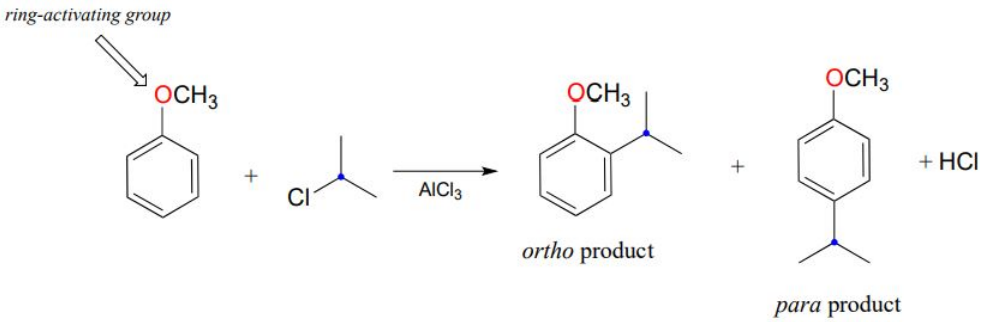
Recall that a powerful electrophile - such as a carbocation - is required for an electrophilic aromatic substitution to occur. The 2-chloropropane reactant is electrophilic, but not electrophilic enough to react with benzene. Here's where the aluminum trichloride catalyst comes in: it reacts as a Lewis acid with the alkyl chloride to generate a secondary carbocation:



The carbocation thus generated is sufficiently electrophilic to react with the aromatic π electrons, in a manner that should be familiar from the biochemical examples discussed above:



You may have noticed, however, that one element from the biochemical Friedel-Crafts reactions is missing here: there is no activating group to stabilize the ring carbocation intermediate. Indeed, the presence of an activating group - for example, the oxygen atom of a methoxy substituent - greatly increases the rate of a Friedel-Crafts alkylation.



Note in the example shown above that two products are formed: one is an ortho-disubstituted benzene and one is para-disubstituted. Note also that no meta-disubstituted product is formed. This phenomenon is referred to as the ortho-para directing effect, and you are led towards an explanation in the exercise below.

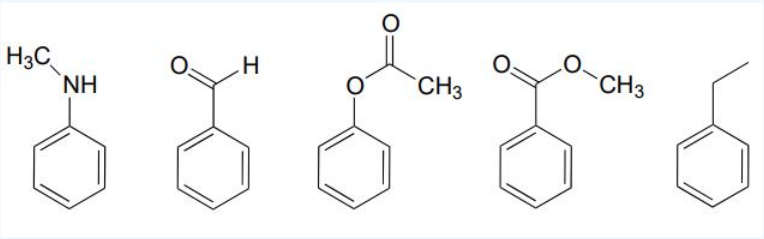
Exercise 14.5.7

a. Draw the lowest-energy resonance contributors of the carbocation intermediates leading to formation of the ortho and para products in the reaction above. Use resonance structures to illustrate how the methoxy substituent is a ring-activating group.

b. Draw the hypothetical carbocation intermediate in a reaction leading to formation of a meta-disubstituted product. Is this carbocation stabilized by the methoxy oxygen? Can you see why no meta product forms?

Exercise 14.5.8

a. a) Just as there are ring-activating groups in electrophilic aromatic substitutions, there are also ring-deactivating groups. For each of the substituted benzene reactants below, draw the carbocation intermediate leading to the ortho substitution product and decide whether the substituent is ring-activating or ring-deactivating in a Friedel-Crafts reaction with 2-chloropropane and AlCl3 (in other words, which compounds would react faster than benzene, and which would react slower?) Explain how the ring-deactivating effect works.



b. (challenging!) Ring-deactivating substituents are usually also meta-directing. Use one of your carbocation intermediate drawings from part (a) of this exercise, and the concept od resonance, to explain this observation.

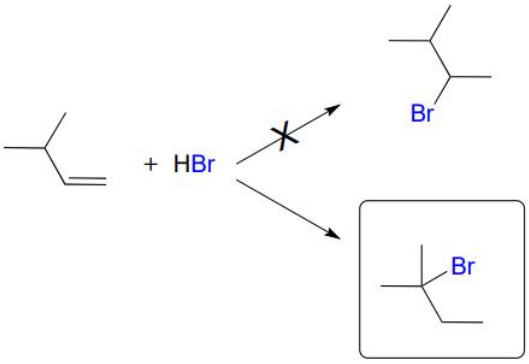
c. (answer part (b) first) Look again at the vitamin K biosynthesis reaction, and discuss the ring activating/directing effects of the two substituents on the substrate.

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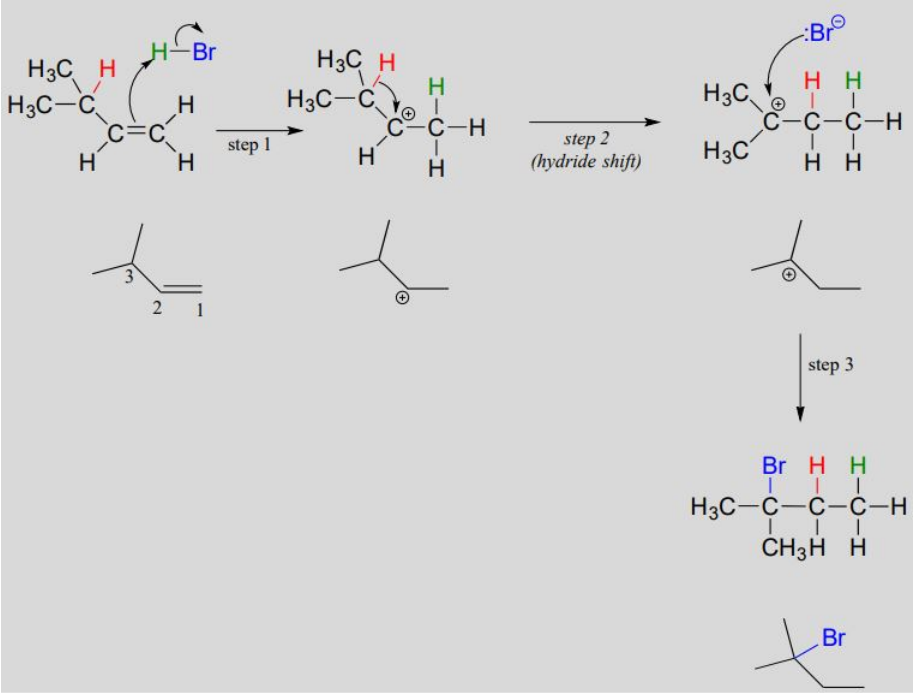
14.5: Carbocation Rearrangements

Earlier in this chapter we introduced the so-called 'Markovnikov rule', which can be used to predict the favored regiochemical outcome of electrophilic additions to asymmetric alkenes. According to what we have learned, addition of ***HBr*** to 3-methyl-1-butene should result in a secondary bromoalkane. However, the predominant product that is actually be observed in this reaction is a tertiary alkyl bromide! Little or no secondary alkyl bromide forms.



To explain this result, let's take a look at the mechanism for the reaction:

Electrophilic addition with a hydride shift:

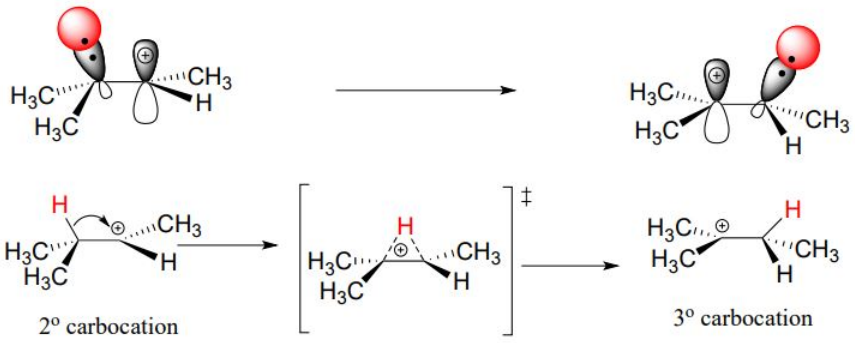


Protonation of the double bond results in a secondary carbocation (step 1). What happens next (step 2 above) is a process called a carbocation rearrangement, and more specifically, a hydride shift. The electrons in the bond between carbon #3 and a hydrogen are attracted by the positive charge on carbon #2, and they simply shift over to fill the empty ***p*** orbital, pulling the proton over with them. Notice that the hydride, in shifting, is not acting as an actual leaving group - a hydride ion is a very strong base and a very poor leaving group.

An important reminder

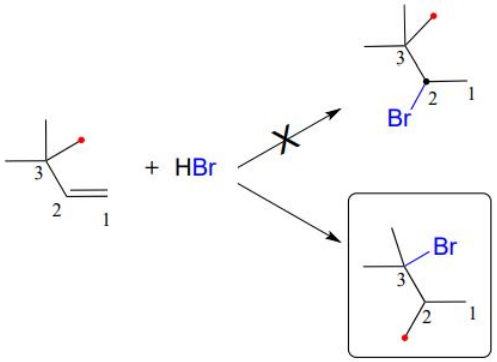
A hydride ion (H^-) is a proton plus two electrons. Be sure not to confuse a hydride ion with H^+, which is just a proton without any electrons.

As the shift proceeds, a new $C-H$ σ bond is formed at carbon #2, and carbon #3 is left with an empty p orbital and a positive charge.



What is the thermodynamic driving force for this process? Notice that the hydride shift results in the conversion of a secondary carbocation to a (more stable) tertiary carbocation - a thermodynamically downhill step. As it turns out, the shift occurs so quickly that it is accomplished before the bromide nucleophile has time to attack at carbon #2. Rather, the bromide will attack (step 3) at carbon #3 to complete the addition.

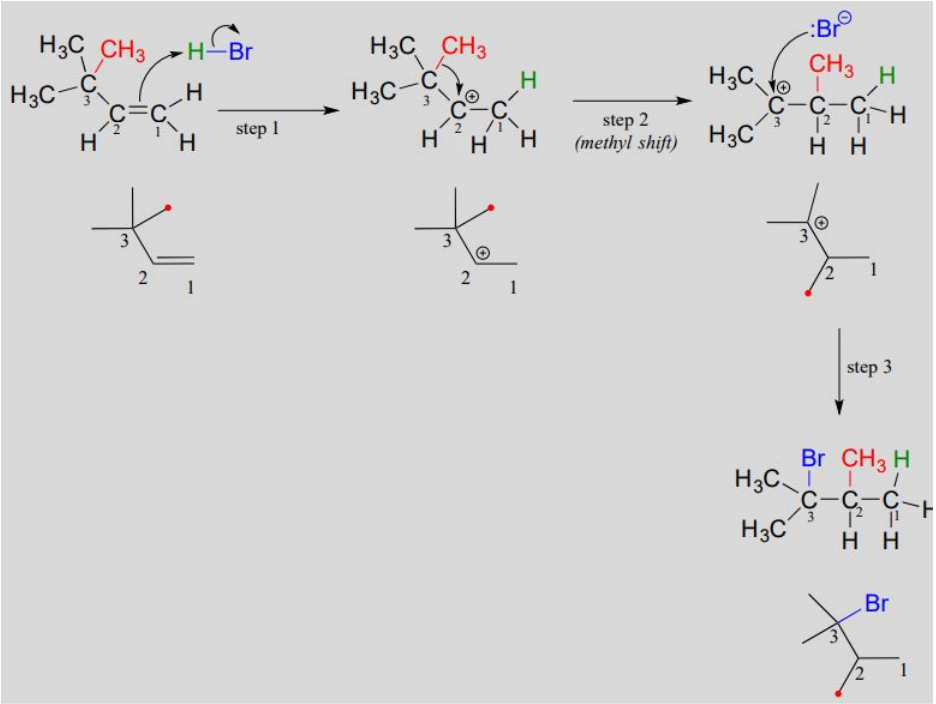
Consider another example. When HBr is added to 3,3-dimethyl-1-butene, the product is a tertiary - rather than a secondary - alkyl bromide.



Notice that in the observed product, the carbon framework has been rearranged: the methyl carbon indicated by a red dot has shifted from carbon #3 to carbon #2. This is an example of another type of carbocation rearrangement, called a methyl shift.

Below is the mechanism for the reaction. Once again a secondary carbocation intermediate is formed in step 1. In this case, there is no hydrogen on carbon #3 available to shift over create a more stable tertiary carbocation. Instead, it is a methyl group that does the shifting, as the electrons in the carbon-carbon σ bond move over to fill the empty orbital on carbon #2 (step 2 below).

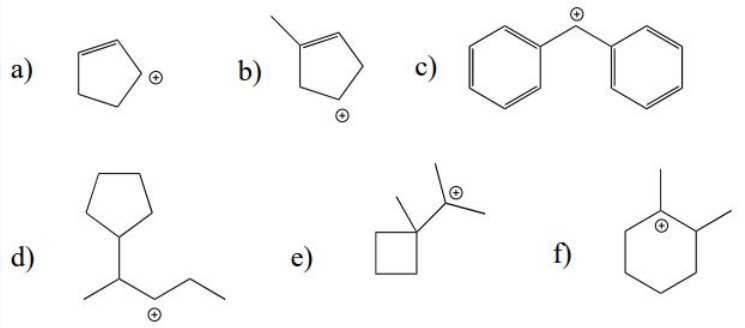
Electrophilic addition with methyl shift:



The methyl shift results in the conversion of a secondary carbocation to a more stable tertiary carbocation. The end result is a rearrangement of the carbon framework of the molecule.

Exercise 14.6.1

Which of the following carbocations are likely to undergo a shift? If a shift is likely, draw the new carbocation that would result.

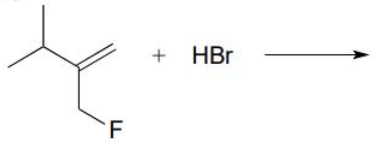


Exercise 14.6.2

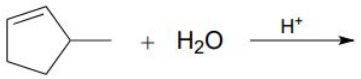
In the (non-biochemcial) reactions below, the major product forms as the result of a hydride or methyl shift from a carbocation intermediate. Predict the structure of the major product for each reaction, disregarding stereochemistry.

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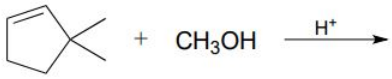
a)



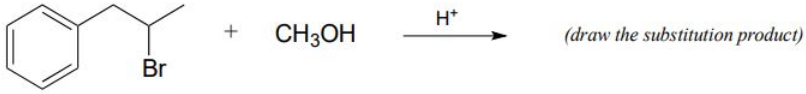
b)



c)

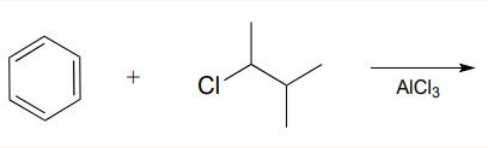


d)

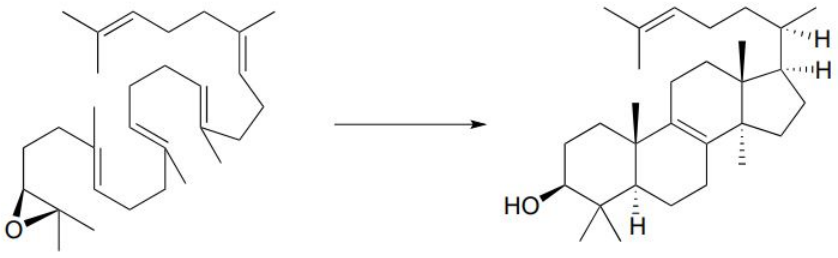


Exercise 14.6.3

Draw the most abundant product of this laboratory Friedel-Crafts reaction:



Carbocation rearrangements are involved in many known biochemical reactions. Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. For example, one of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol (E.C. 5.4.99.7).



(3S)-2,3-oxidosqualene lanosterol

This complex but fascinating reaction has two phases. The first phase is where the actual cyclization takes place, with the formation of four new carbon-carbon bonds and a carbocation intermediate. This phase is a 'cascade' of electrophilic alkene addition steps, beginning with addition of an electrophilic functional group called an 'epoxide'.

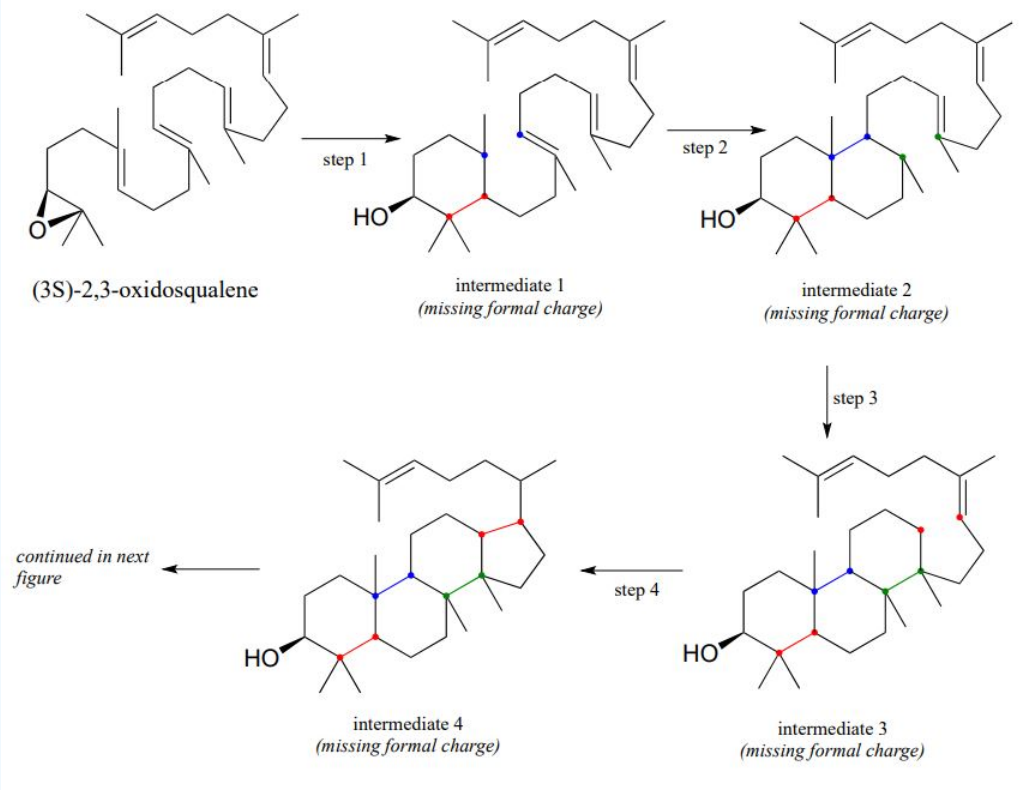
The epoxide functional group - composed of a three membered ring with two carbons and an oxygen - is relatively rare in biomolecules and biochemical reactions, and for this reason it is not discussed in detail in this book. However, epoxides are an important and versatile intermediate in laboratory organic synthesis, so you will learn much more about how they are made and how they react if you take a course in chemical synthesis. For now, it is sufficient to recognize that the carbon atoms of an epoxide are potent electrophiles, due to both the carbon-oxygen bond dipoles and the inherent strain of the three membered ring.

The second phase involves a series of hydride and methyl shifts culminating in a deprotonation. In the exercise below, you will have the opportunity to work through the entire cyclase reaction mechanism. In section 15.7, we will take a look at how the epoxide group of oxidosqualene is formed. Trends Pharm. Sci. 2005, 26, 335; J. Phys Chem B., 2012, 116, 13857.

Exercise 14.6.4

a. The figure below outlines the first, cyclizing phase of the reaction that converts oxidosqualene to lanosterol. However, the diagram is missing electron movement arrows, and intermediates 1-4 are all missing formal charges - fill these in.

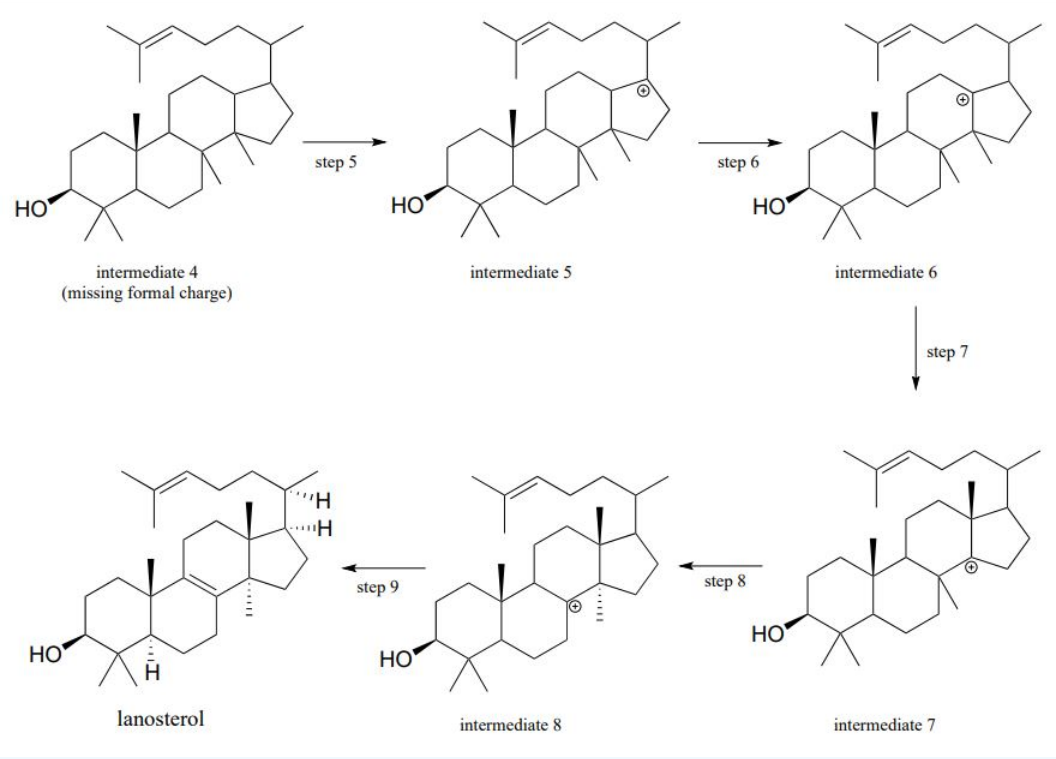
First phase (ring formation):



b. Next comes the 'shifting' phase of the reaction. Once again, supply the missing mechanistic arrows.

Second phase: rearrangement and deprotonation

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c. Look at the first and last steps of the entire process: overall, would you describe this as an electrophilic addition or substitution?

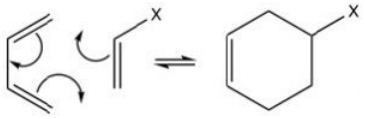
The oxidosqualene cyclization reaction and others like it are truly remarkable examples of the exquisite control exerted by enzymes over the course of a chemical reaction. Consider: an open-chain starting molecule is converted, by a single enzyme, into a complex multiple fused-ring structure with seven chiral centers. Oxidosqualene could potentially cyclize in many different ways, resulting in a great variety of different products. In order for the enzyme to catalyze the formation of a single product with the correct connectivity and stereochemistry, the enzyme must be able to maintain precise control of the conformation of the starting compound and all reactive intermediates in the active site, while also excluding water molecules which could attack at any of the positively charged carbons.

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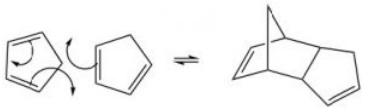
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14.6: Cycloaddition reactions

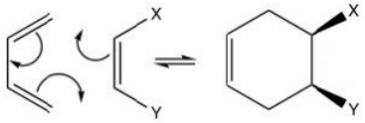
Diels-Alder Reactions:



Cylcoaddition reactions are addition reactions that form a ring. The best-known cycloaddition reaction is the Diels-Alder reaction. It typically occurs between a conjugated diene and another alkene known as the dienophile. This reaction is very useful in synthesis because it forms two new $\mathbf{C-C}$ bonds at the same time. It is also stereospecific and regiospecific. The simplest diene that can participate in a Diels-Alder is butadiene. Typically, butadiene tends to exist in the more stable s-trans[10] conformation—however, there is an equilibrium concentration of the s-cis conformation through which the reaction can occur. In fact, cyclopentadiene, in which the diene is permanently fused in the s-trans conformation, reacts rapidly with itself (it can be both diene and dienophile) in a reversible reaction.

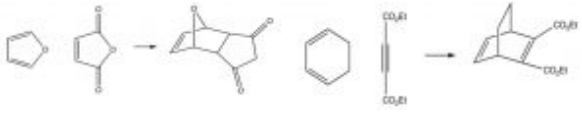


The "dienophile" can be a simple alkene, but the presence of an electron-withdrawing group (such as a carbonyl group) on the double bond improves yields. We can envision the reaction as taking place in a concerted fashion. Again, the reaction is reversible, and the reverse reaction is known as a retro Diels-Alder. We can use our knowledge of thermodynamics to predict the most appropriate conditions for the reaction. Recall that the extent of any reaction can be predicted from the Gibbs free-energy change $\mathbf{\Delta G = \Delta H – T\Delta S}$. Since the reaction produces two new $\mathbf{C-C}$ single bonds and one new $\mathbf{C-C}$ pi bond while breaking two $\mathbf{C-C}$ pi bonds, we can assume that the enthalpy change for this reaction is negative (bond formation releases energy and bond-breaking uses energy). Therefore, the $\mathbf{\Delta H}$ term is always favorable. We can also predict the sign of the entropy change for the system; since we are producing one molecule from two, we would expect $\mathbf{\Delta S}$ to be negative also. The entropy term is unfavorable. From this analysis, we can see that the temperature at which the reaction is carried out is crucial. High temperatures would favor the reverse reaction. Therefore Diels-Alder reactions are typically run at fairly moderate temperatures that are between room temperature and $\mathbf{150°C}$).

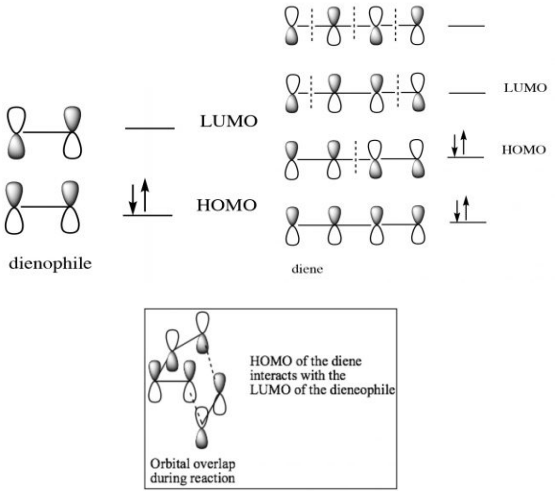


The possibilities for Diels-Alder reactions are quite extensive and since this is a concerted reaction, any stereochemistry in the starting materials is conserved in the products. For example, if the dienophile has cis or trans stereochemistry, this is conserved in the product. The cis dienophile gives the cis product (and vice versa for the trans).

Some examples of Diels-Alder reactions are given here.

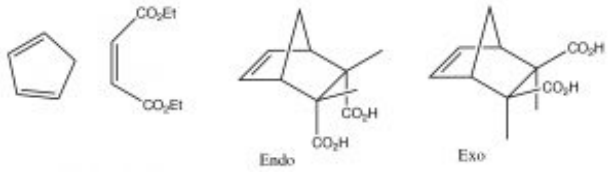


While we can draw mechanistic arrows for cycloaddition reactions such as Diels-Alder, they are best understood by using molecular orbital theory. In this treatment, we can consider the reaction as taking place between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile.



For our purposes, this treatment is too complex, but if you go on to further studies of cycloaddition reactions, MO theory will be the approach that will allow you to predict the outcome of many different reactions.

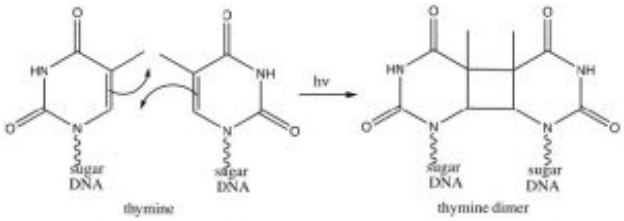
If a fused ring is formed during the reaction, there are two possibilities for the orientation of the substituents on the diene as shown below: exo and endo.



Because of the possibility of a stabilizing interaction in the endo position, (the pi system of the carboxylic acid can interact with the pi system of the diene), the endo product is usually produced.

As noted earlier, there are other types of cycloaddition reactions. All of the common reactions that occur simply by heating up the starting materials involve the cyclic movement of six electrons. The transition states for these reactions all involve molecular orbitals that extend throughout the system; these orbitals have considerably lower energy than one might expect. In some ways, this is analogous to the 6 pi electrons of aromatic systems, which are also stabilized in lower energy molecular orbitals.

Interestingly, these reactions do not occur in the same way if they are initiated by electromagnetic radiation (that is, if we shine light on them rather than heat them up). In this case the electrons that participate in the reaction are actually in higher energy orbitals (the electron absorbs a photon and is promoted to a higher energy level). Absorbing light leads to a completely different set of reactions and outcomes, something that could be explored in subsequent organic chemistry courses. There is, however, one particularly interesting (and biologically relevant) photochemically induced reaction, namely the reaction of adjacent thymine bases within a DNA molecule. Upon the absorption of a UV photon, such adjacent thymines can undergo a cycloaddition reaction that results in formation of a thymine dimer.



The presence of a thymine dimer results in conformational changes in the DNA that, unrepaired, can lead to mutations during DNA replication. Thymine dimers are recognized and repaired via two distinct cellular-repair mechanisms. Unrepaired damage can lead to skin cancer (a range of carcinomas and melanomas). This is one reason to limit skin exposure to the sun.

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14.E: Electrophilic Reactions (Exercises)

P14.1: Draw the major product(s) (including all stereoisomers) that would be expected to result from the nonenzymatic electrophilic addition reactions below. Your product(s) should result from the most stable possible carbocation intermediate. ***Hint***: consider the possibility of thermodynamically favorable rearrangement steps.

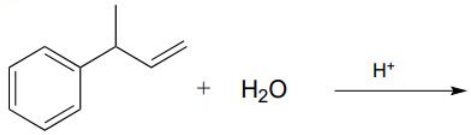
a)



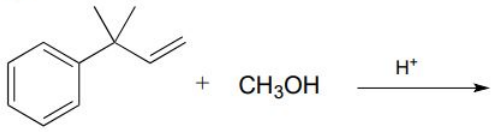
b)



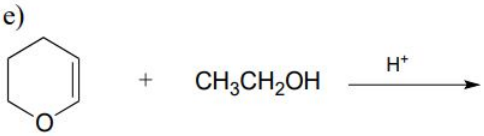
c)



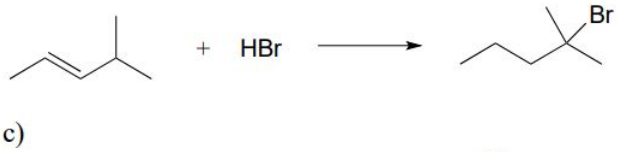
d)



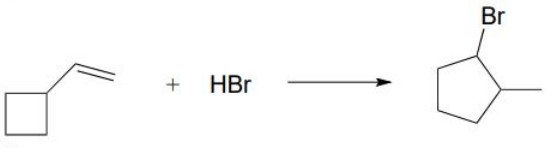
e)



P14.2: Draw likely mechanisms for the nonenzymatic reactions below. Products shown are not necessarily the most abundant for the reaction.



c)

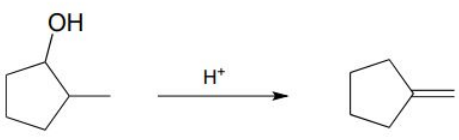


d)

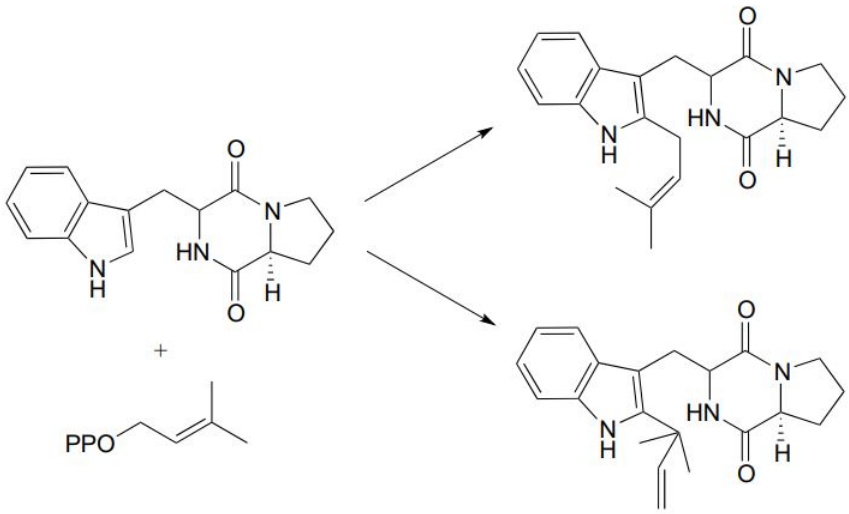
a)



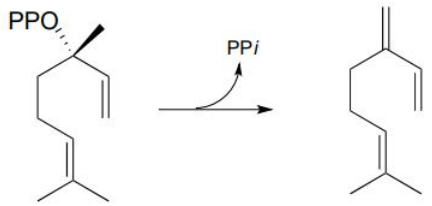
b)



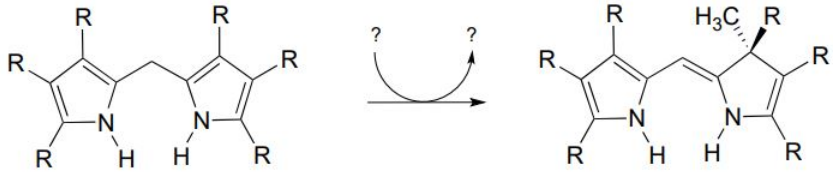
P14.3: Provide mechanisms for the following reactions, both of which are part of an alkaloid synthesis pathway in fungi. (Microbiol. 2005, 151, 2199)



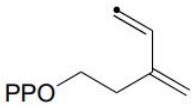
P14.4: Draw a likely mechanism for the reaction below. The product is myrcene, a compound produced by fir trees as a defense against insects. (J. Biol. Chem 1997, 272, 21784)



P14.5: Provide a mechanism for the following reaction from the vitamin B_{12} biosynthetic pathway, and identify the missing participants indicated by questions marks in the figure.



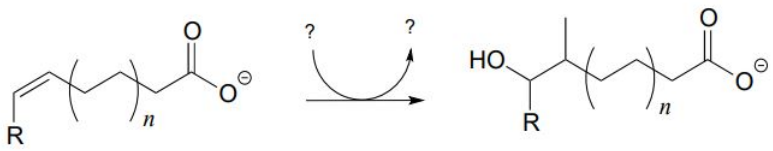
P14.6: A diene molecule synthesized in the laboratory was found to irreversibly inhibit the action of isopentenyl diphosphate isomerase (section 14.3) when the carbon indicated with a dot becomes covalently bonded to a cysteine residue in the enzyme's active site. Propose a mechanism showing how this could happen. (J. Am. Chem. Soc. 2005, 127, 17433)



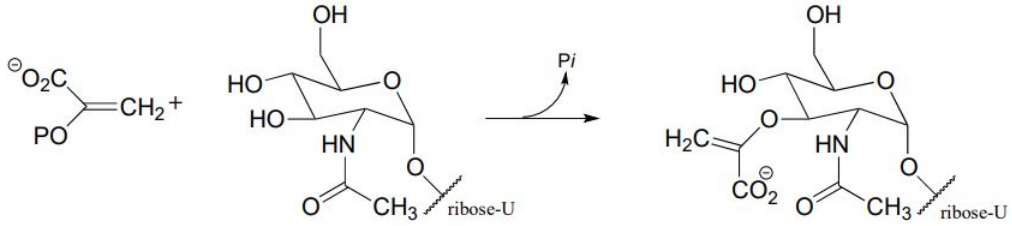
inhibitor

P14.7: Nonenzymatic electrophilic addition of water to alkynes results in the formation of a ketone or an aldehyde, depending on the starting alkyne. A vinylic carbocation is a key intermediate, and the reaction is accelerated with the use of a catalytic amount of strong acid. Predict the product the addition of water to propyne, and draw a mechanism for the reaction.

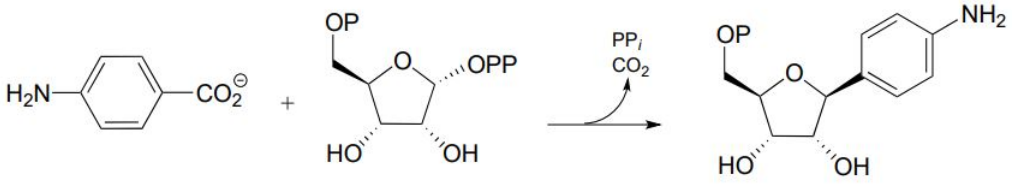
P14.8: The reaction below is part the pathway by which some bacteria -including the species which cause tuberculosis and leprosy - form distinctive branched-chain fatty acids for incorporation into their cell walls. This enzyme is of interest to scientists as possible targets for new antibiotic drugs. Propose a likely mechanism, and identify the missing participants denoted by questions marks. (J. Biol. Chem. 2006, 281, 4434)



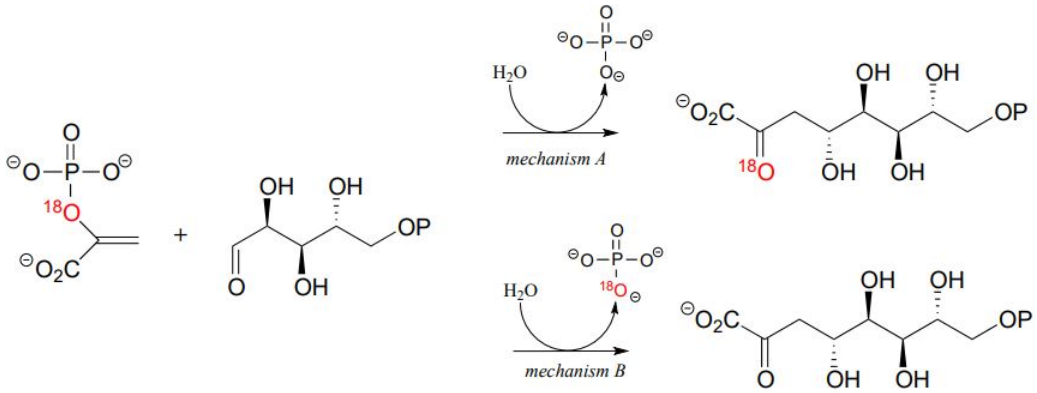
P14.9: Suggest a likely mechanism for this reaction, which is a key step in the synthesis of bacterial cell walls. Your mechanism should show an electrophilic addition, followed by an E1 elimination.



P14.10: Suggest a mechanism for the following reaction, which is part of the pathway by which many microbes synthesize methanopterin, a derivative of the vitamin folic acid. ***Hint***: the mechanism can be described as an electrophilic aromatic substitution with a final decarboxylation step in place of the usual deprotonation step. (J. Biol. Chem. 2004, 279, 39389.



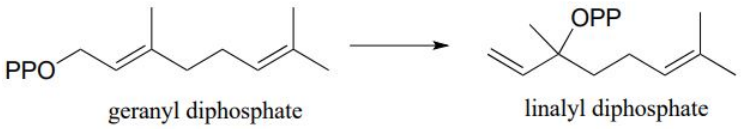
P14.11: Researchers investigated the mechanism of the enzyme 3-deoxy-D-manno-octulosonate-8-phosphate synthase by running the reaction with one of the substrates labeled with the 18O isotope (colored red in the scheme below). Consider the two hypothetical results shown below, each pointing to a different mechanism. Both mechanisms involve a carbocation intermediate. (Biochem. Biophys. Res. Commun. 1988, 157, 816)



a. Propose a mechanism that is consistent with result A, in which the \(^1$8$O \) label ends up in the ketone group of the organic product.
b. Propose a mechanism that is consistent with result B, in which the \(^18O \) label ends up in the inorganic phosphate by-product

P14.12: Consider the following isomerization reaction (J. Biol. Chem. 1989, 264, 2075):

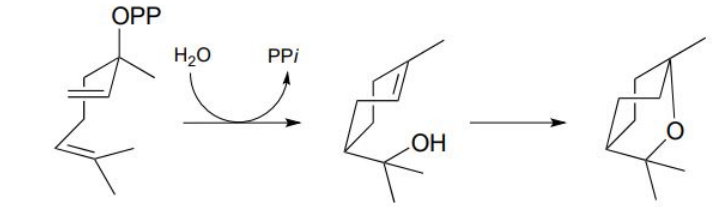
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geranyl diphosphate linalyl diphosphate

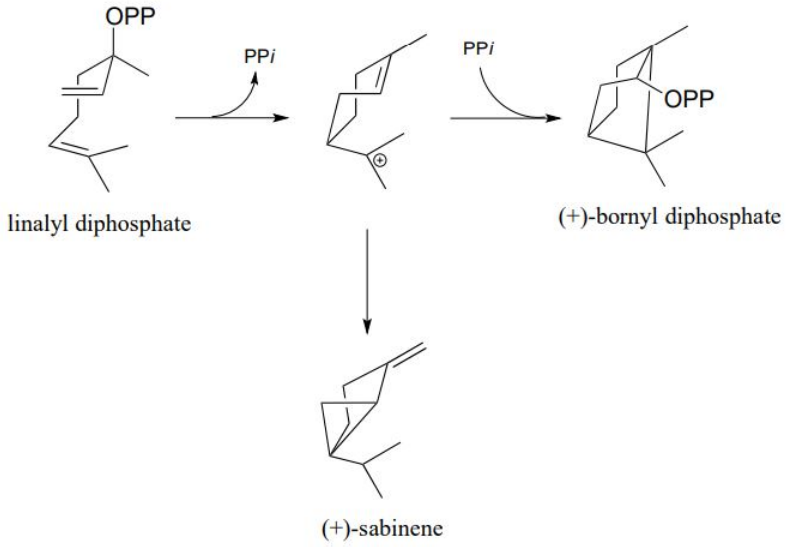
(JBC264, 2075)

a. Suggest a likely mechanism involving a carbocation intermediate.
b. Suggest an isotopic labeling experiment (using substrate labeled with ^{18}O) that could confirm or rule out a alternative, concerted isomerization mechanism (ie. one without formation of a carbocation intermediate). Explain your reasoning.
c. Propose a mechanism for the following reaction (notice that the starting compound is linalyl diphosphate from part (a), drawn in a different conformation). (Arch Biochem Biophys 2003, 417, 203)



linalyl diphosphate 1,8-cineole

For parts d-f, refer to the figure below:

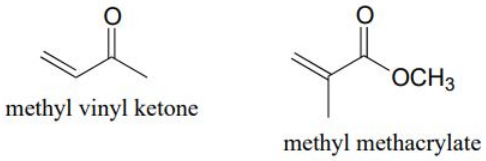


linalyl diphosphate (+)-bornyl diphosphate

(+)-sabinene

d. Provide mechanisms for the conversion of linalyl diphosphate to (+)-bornyl diphosphate.
e. Provide mechanisms for the conversion of linalyl diphosphate to (+)-sabinene.
f. Is the second step in the (+)-bornyl diphosphate pathway (addition of phosphate) a Markovnikov or anti-Markovnikov addition? Explain the regiochemistry of this step in terms of carbocation stability.

P14.13: The two compounds shown below were each treated with HBr, and the products isolated and analyzed by ^1HNMR. Use the NMR data provided to determine the structure of both products, then explain the observed regiochemistry of the addition reaction.



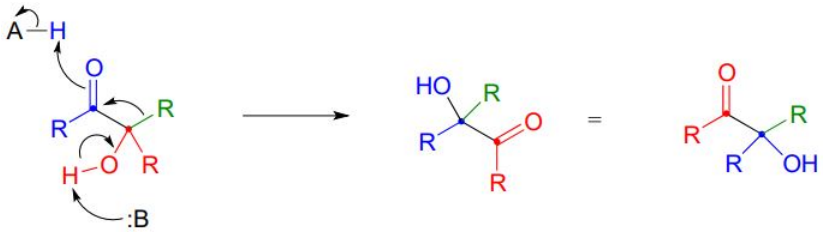
^1H-NMR data for product of HBr addition to methyl vinyl ketone:

δ□□□□□	Integration	Splitting
2.2	1.5	s
3.0	1	t
3.5	1	t

^1H-NMR data for product of HBr addition to methyl methacrylate:

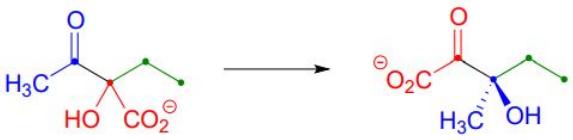
δ□□□□□	Integration	Splitting
1.3	3	d
2.3	1	sextet
3.5	2	d
3.7	3	s

P14.14: Ketones and aldehydes with a hydroxy group in the □ position are known to undergo an isomerization reaction known as an acyloin rearrangement:



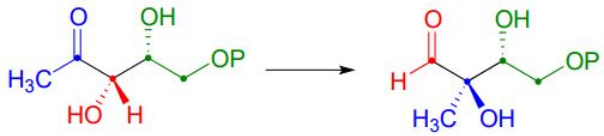
Notice in the general acyloin rearragnement mechanism below, the green alkyl group is shifting from the □ carbon (red) to the carbonyl carbon (blue). Notice also that this shift does not involve a carbocation intermediate, although a resonance contributor can be drawn in which the carbonyl carbon has a positive charge.

a. Draw a mechanism for this acyloin rearrangement step in the biosynthetic pathway for the amino acid leucine:



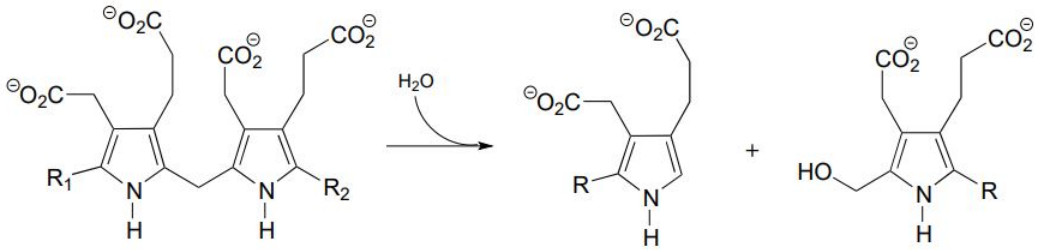
b. Draw a mechanism for this acyloin rearrangement step in the isoprenoid biosynthetic pathway in bacteria:

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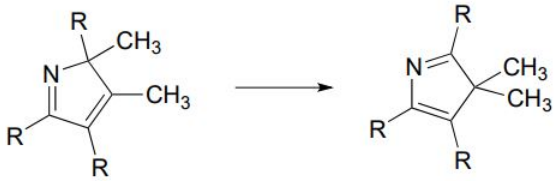


P14.15: Propose mechanisms for these reactions in the vitamin B_{12} biosynthetic pathway:

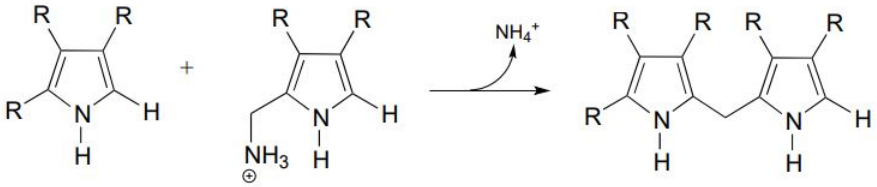
a)



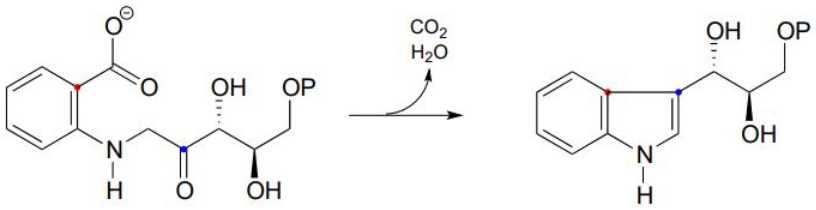
b)



c)

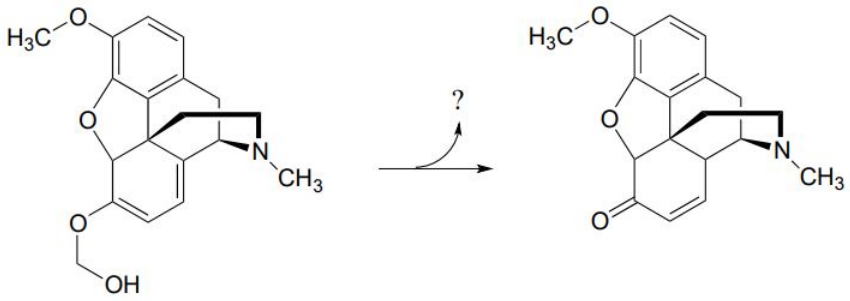


P14.16: An early reaction in the biosynthesis of tryptophan can be described as an intramolecular electrophilic aromatic substitution/decarboxylation hybrid, followed by an E1 dehydration (EC 4.1.1.48).



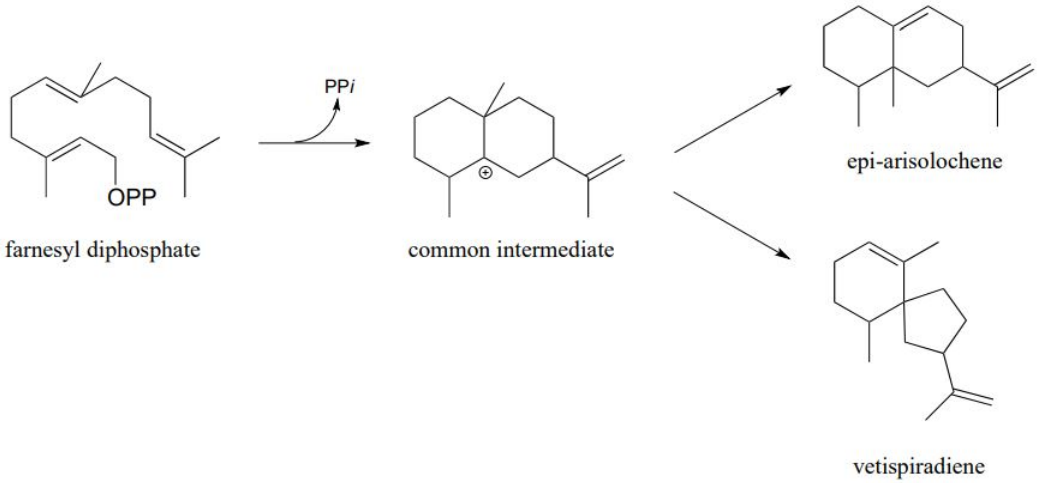
a. Draw a mechanism that corresponds to the verbal description given above. Use resonance structures to show how the nitrogen atom helps to stabilize the carbocation intermediate. ***Hint***: the electrophilic carbon in this case is a ketone rather than a carbocation.
b. What aspect of this reaction do you think helps to compensate for the energetic disadvantage of not having a powerful carbocation electrophile?
c. Again thinking in terms of energetics, what is the 'driving force' for the dehydration step?

P14.17: Propose a likely carbocation-intermediate mechanism for the following reaction in the biosynthesis of morphine, being sure to identify the structure of the organic compound released in the reaction.

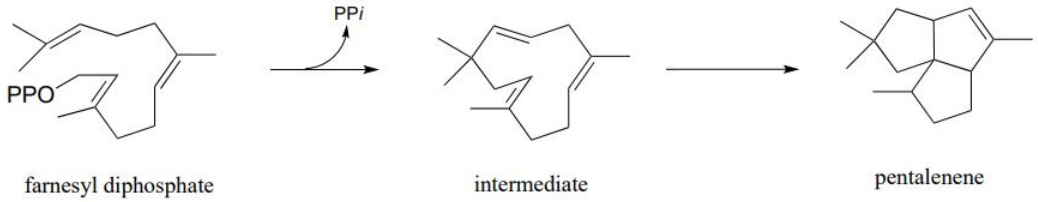


P14.18: Propose mechanisms for these three electrophilic cyclization reactions. Carbocation rearrangement steps are involved.

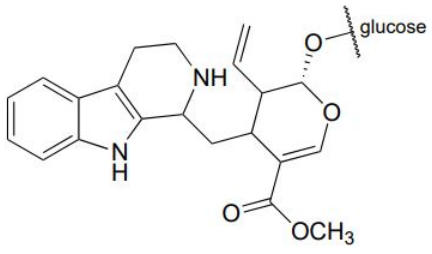
a. epi-arisolochene
b. vetispiradiene (Science 1997, 277, 1815)



c. pentalenene (Science 1997, 277, 1820)



P14.19: Strictosinide, an intermediate in the biosynthesis of the deadly poison strychnine, is formed from two steps: a) intermolecular imine formation, and b) an intramolecular, ring-forming electrophilic aromatic substitution with the imine carbon from step (a) as the electrophile.



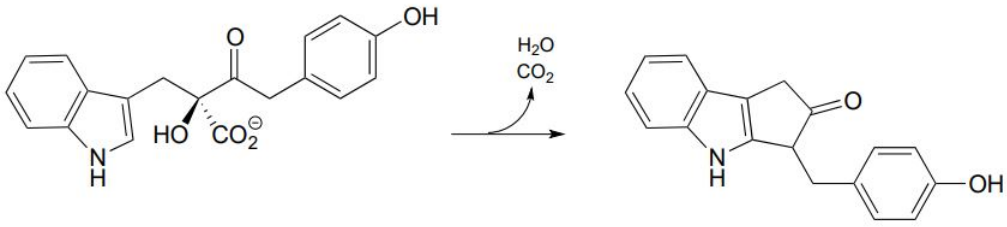
strictosinide

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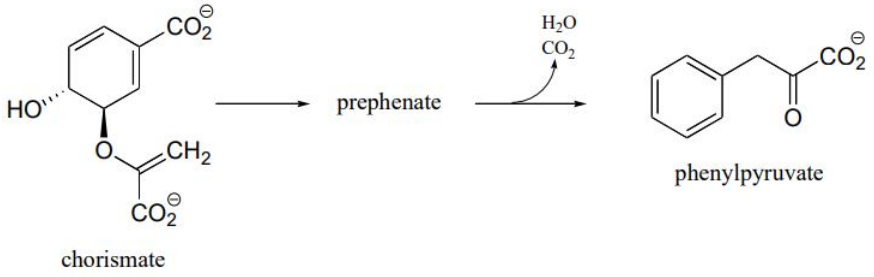
Given this information, predict the two precursors to strictosinide, and draw a mechanism for the reaction described. ***Hint***: use the 'retro' skills you developed in chapter 12 and chapter 13.

P14.20: In the introduction to chapter 8, we learned about reactions in which the cytosine and adenine bases in DNA are methylated. In the course of that chapter, we learned how adenine N-methylation occurs in bacteria, but we were not yet equipped to understand cytosine C-methylation, which was the more relevant reaction in terms of human health and development. Now we are: propose a reasonable mechanism for the C-methylation of cytosine.

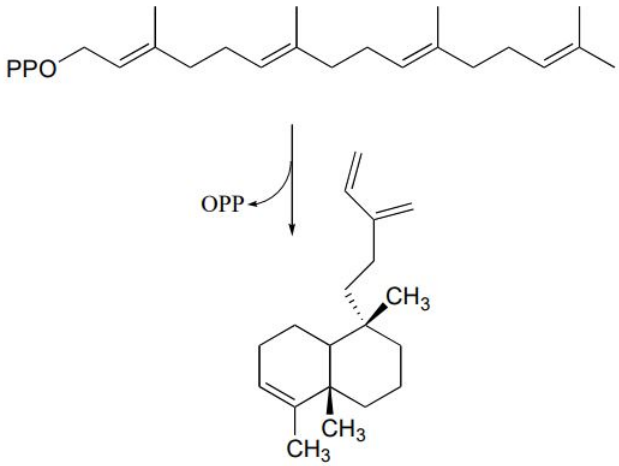
P14.21: The reaction below has been proposed to proceed via a cyclization step followed by an E1/decarboxylation step (in other words, an E1 mechanism where decarboxylation occurs instead of deprotonation). Draw a mechanism that fits this description, and show the most stable resonance contributors of the two key cationic intermediates.



P14.22: The conversion of chorismate to phenylpyruvate is a key transformation in the biosynthesis of phenylalanine. The first step is a concerted electrophilic rearrangement to form prephenate (this step involves a six-membered transition state). Deduce the structure of prephenate, and provide a complete mechanism for the transformation.



P14.23: Suggest likely a mechanism for the following reaction:



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Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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14.S: Electrophilic Reactions (Summary)

Understand why the π bond in a carbon-carbon double bond is more reactive than the σ bond.

Addition

- Be able to draw a mechanism for the electrophilic addition of a haloacid to an alkene.
  - Stereochemistry: understand why nonenzymatic electrophilic addition of a haloacid to an alkene occurs with racemization (both inversion and retention of configuration) at both alkene carbons. Be able to distinguish syn vs anti addition.
  - Regiochemistry: Be able to predict the regiochemical outcome of an electrophilic addition, based on the relative stability of the two possible carbocation intermediates. Be able to predict when anti-Markovnikov addition is likely to occur.
- Be able to predict the product of nonenzymatic addition of water/alcohol to an alkene, including regio- and stereo-chemistry when applicable. Be able to draw complete mechanisms.
- Be able to predict the products of nonenzymatic addition of water/alcohol to a conjugated diene or triene, including regio- and stereochemistry when applicable. Be able to draw complete mechanisms, including multiple resonance forms for carbocation intermediates.
- Be able to apply your understanding of nonenzymatic alkene addition reactions to draw mechanisms for enzymatic addition reactions. In particular, you should be able to draw mechanisms for biochemical electrophilic addition reactions in which a new carbon-carbon bond is formed.

Elimination

- Be able to draw a mechanism for an E1 elimination reaction.
- Be able to predict possible E1 reaction products from a common starting compound , taking into account both regiochemistry (Zaitsev's rule) and stereochemistry.
- Be able to recognize and draw a mechanism for biochemical E1 reactions in which
  - the second step is a deprotonation event
  - the second step is a decarboxylation event
- Be able to distinguish whether a biochemical elimination reaction is likely to proceed through a E1cb or E1 mechanism, based on the structure of the starting compound.

Isomerization/substitution

- Be able to recognize and draw mechanisms for a biochemical electrophilic isomerization reaction (shifting the location of the carbon-carbon double bond).
- Be able to recognize and draw mechanisms for a biochemical electrophilic substitution reaction.
- Be able to recognize and draw mechanisms for a biochemical electrophilic aromatic substitution reaction, and be able to explain the ring-activating effect (how the carbocation intermediate is stabilized by resonance, usually with lone-pair electrons on either an oxygen or a nitrogen atom).
- Be able to recognize when a hydride or alkyl shift is likely to occur with a carbocation reaction intermediate.
- Be able to draw a mechanism for a reaction that includes a carbocation rearrangement.

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CHAPTER OVERVIEW

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15.2: Oxidation and Reduction in the Context of Metabolism
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15.0: Prelude to Oxidation and Reduction Reactions



Introduction

Theo Ross was not doing very well at his summer job, and he was frustrated. His boss had given him specific instructions, and yet Theo kept botching the job, over and over again. Theo was not used to failure – he had achieved almost perfect scores on both the ACT and SAT college entrance exams, and was headed to Stanford University in the fall. Why couldn't he get it right? It wasn't brain surgery, after all.

Well, actually – it was brain surgery.

An April 17, 2014 article in Sports Illustrated tells Theo's story. Wanting to do something interesting over the summer of 2010 before he started college, Theo had applied for a research internship at the National Institutes of Health in Bethesda, Maryland. This was an extremely competitive program normally reserved for outstanding college students, but somehow Theo had managed to win a coveted spot in the program, working with Dr. Dorian McGavern, a neurologist studying how meningitis effects the brain. Dr. McGavern assigned Theo the task of performing 'skull-thinning' surgery on mice, part of which involved using a special saw to shave down a small section of the bone in order to gain access to the brain. It was a delicate procedure, something that even some experienced neurosurgeons who had tried it had found challenging. Any small slip resulted in a concussion to the mouse's brain, rendering it useless for the study. Theo just couldn't get the hang of it, and ended up concussing one mouse after another.

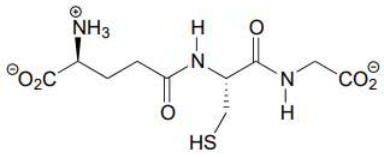
You have probably heard the old expression: “when life gives you lemons, make lemonade”. Theo made a lot of lemonade that summer.

Theo and Dr. McGavern eventually realized that his failure at the procedure actually presented an opportunity to observe what happens to a brain right after a concussive injury. Theo started doing more skull-thinning surgeries, but now the goal was to cause concussion, rather than to avoid it. The concussed mice (who had been anaesthetized prior to the surgery) were immediately strapped under a microscope so that Theo could observe how their brains responded to the injury. This was new, and very exciting stuff: most of what neurologists knew about concussions up to that point had come from MRI (magnetic resonance imaging – see chapter 5) or autopsies. Nobody knew very much about what happens at the cellular level in a brain in the minutes and hours after a concussion has occurred. In addition, the problem of traumatic head injuries and the long-lasting effects they cause was becoming an increasingly hot topic in the news, critically relevant to thousands of veterans returning from Iraq and Afghanistan as well as to football players and other athletes in contact sports– including Theo, who had been a competitive wrestler in high school. (You might have been wondering why Theo's story appeared in Sports Illustrated – now you know.)

Theo spent the rest of that summer, and every spring break and summer vacation over the next few years, working in McGavern's lab on the new project. He and McGavern found evidence that the 'hidden' damage to a concussed brain – that which went

undetected in MRI scans but could come back to haunt the victim years later in the form of recurring headaches, memory loss, and depression – may be caused by a type of molecule referred to as 'reactive oxygen species', or ROS, leaking from damaged tissues into the brain. ROS are potentially harmful byproducts of respiration such as hydrogen peroxide (H_2O_2) that are constantly being produced in our cells. Although ROS can cause serious oxidative damage if they are allowed to build up, our bodies have evolved ways to deal with them, using so-called 'ROS scavengers' to convert them to something innocuous like water.

With this new understanding, Theo and his mentor had another idea: what if they could prevent the ROS from causing further damage to a recently concussed brain by applying an scavenger to the injury? After some trial and error, they found that an ROS scavenger compound called glutathione, when applied directly to the skull of a concussed mouse within a few minutes to three hours after the injury, could permeate the bone and react with the ROS. Brain cells from these glutathione-treated mice appeared normal, with none of the signs of ROS damage Theo was used to seeing.



glutathione

The road from an initial scientific discovery to a safe and effective medical treatment is often a very long one, but Theo Roth and Dorian McGavern appear to have made a discovery that could eventually help prevent some of the most devastating and long-term damage caused by traumatic head injuries. In the end, it's a very good thing that Theo's hands were not cut out for brain surgery.

The chemistry of oxidation and reduction - often called 'redox' chemistry - is central to Theo Roth's discovery about what happens to a concussed brain at the molecular level. This chapter is dedicated to redox chemistry. We'll begin with a reminder of what you learned in General Chemistry about the fundamentals of redox reactions in the context of inorganic elements such as iron, copper and zinc: reduction is a gain of electrons, and oxidation is a loss of electrons. Then, we'll expand our understanding to include bioorganic redox reactivity, examining among other things how alcohols are converted to ketones and aldehydes, aldehydes are converted to carboxylic acids, and amines are converted to imines. We will also talk about redox reactions in the broader context of metabolism in living things.

A central player in some of the biochemical redox reactions we will see is the coenzyme called glutathione, Theo Roth's 'magic bullet' molecule that was able to rescue mouse brain cells from death by oxidation. We'll see how glutathione acts as a mediator in the formation and cleavage of disulfide bonds in proteins, and how it acts as an 'ROS scavenger' to turn hydrogen peroxide into water.

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15.1: Oxidation and Reduction of Organic Compounds - An Overview

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or element is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in tandem: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)} \tag{15.1.1}$$

Exercise 15.2.1

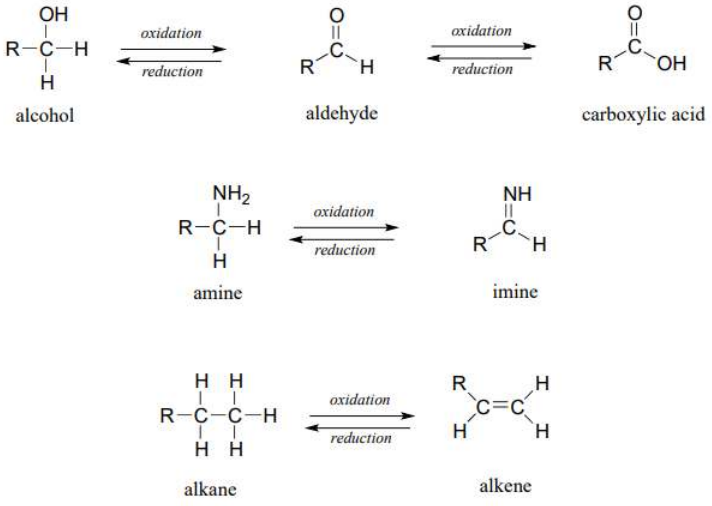
Reading the reaction above from left to right, which chemical species is being oxidized? Which is being reduced?

When we talk about the oxidation and reduction of organic compounds, what we are mainly concerned with is the number of carbon-heteroatom bonds in the compound compared to the number of carbon-hydrogen bonds. (Remember that the term 'heteroatom' in organic chemistry generally refers to oxygen, nitrogen, sulfur, or a halogen).

Note

- Oxidation of an organic compound results an increase in the number of carbon-heteroatom bonds, and/or a decrease in the number of carbon-hydrogen bonds.
- Reduction of an organic compound results in a decrease in the number of carbon-heteroatom bonds, and/or an increase in the number of carbon-hydrogen bonds.

Below are a number of common functional group transformations that are classified as redox.



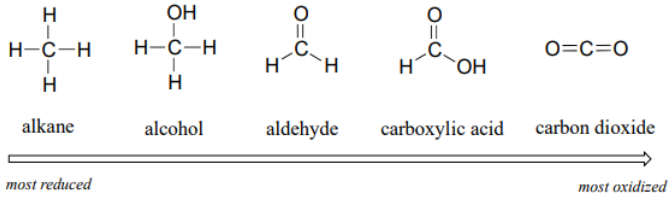
Heteroatoms such as oxygen and nitrogen are more electronegative than carbon, so when a carbon atom gains a bond to a heteroatom, it loses electron density and is thus being oxidized. Conversely, hydrogen is less electronegative than carbon, so when a carbon gains a bond to a hydrogen, it is gaining electron density, and thus being reduced.

Exercise 15.2.2

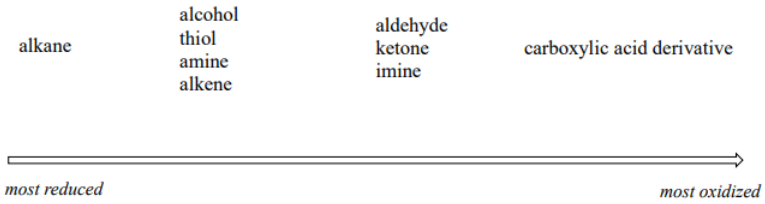
The hydration of an alkene to an alcohol is not classified as a redox reaction. Explain.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. The concept of oxidation state can be useful in this context. When a compound has lots of carbon-hydrogen bonds, it is said to be in a lower oxidation state, or a more reduced state. Conversely, if it contains a lot of carbon-heteroatom bonds, it is said to be in a higher oxidation state.

We'll start with a series of single carbon compounds as an example. Methane, in which the carbon has four bonds to hydrogen, is the most reduced member of the group. The compounds become increasingly oxidized as we move from left to right, with each step gaining a bond to oxygen and losing a bond to hydrogen. Carbon dioxide, in which all four bonds on the carbon are to oxygen, is in the highest oxidation state.

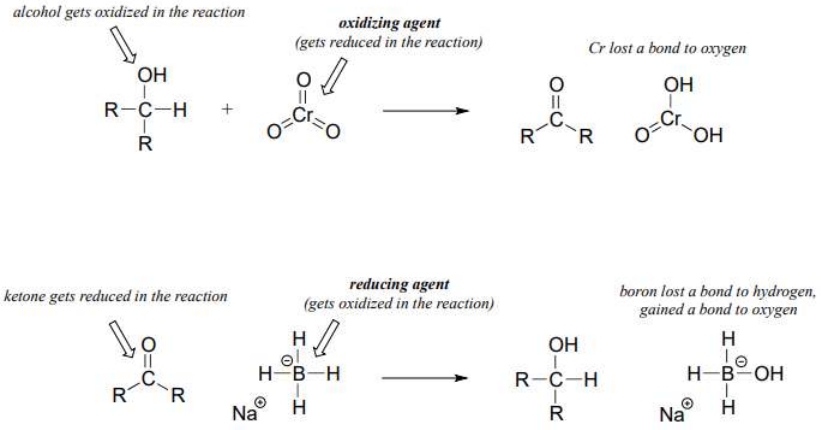


More generally, we can rank the oxidation state of common functional groups:



The alkane oxidation state is the most reduced. Alcohols, thiols, amines, and alkenes are all at the same oxidation state: therefore, a reaction converting one of these groups to another - an alcohol to alkene conversion, for example - is not a redox reaction. Aldehydes, however, are at a higher oxidation state than alcohols, so an alcohol to aldehyde conversion is an oxidation. Likewise, an imine to amine conversion is a reduction, but an imine to ketone conversion is not a redox reaction.

It is important to keep in mind that oxidation and reduction always occurs in tandem: when one compound is oxidized, another compound must be reduced. Often, organic chemists will use the terms oxidizing agent and reducing agent to refer to species that are commonly used, by human chemists or by nature, to achieve the oxidation or reduction of a variety of compounds. For example, chromium trioxide (CrO_3) is a laboratory oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone, in the process being reduced to H_2CrO_3. Sodium borohydride ($NaBH_4$) is a laboratory reducing agent used to reduce ketones (or aldehydes) to alcohols, in the process being oxidized to $NaBH_3OH$.



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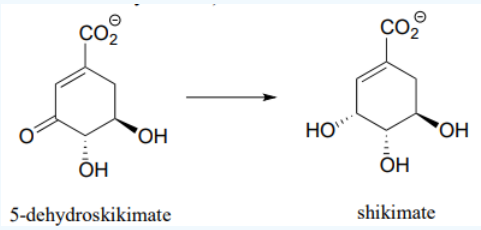
There is a wide selection of oxidizing and reducing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. For example, while sodium borohydride is very useful for reducing aldehyde and ketone groups to alcohols, it will not reduce esters and other carboxylic acid derivatives. If you take a course in synthetic organic chemistry, you will learn about the use of many of these agents.

In this book, of course, we are concerned primarily with the organic chemistry that occurs within a living cell. A large part of this chapter will be spent looking at the action of two very important classes of coenzymes - the nicotinamides and the flavins - that serve as biochemical oxidizing and reducing agents. We also consider the oxidation and reduction of sulfur atoms in thiol groups, especially the thiol group on the side chain of cysteine residues in proteins.

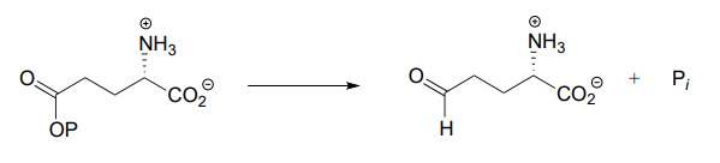
? Exercise 15.2.3

Each of the biochemical transformations shown below is a step in amino acid metabolism. For each, state whether the substrate is being oxidized, reduced, or neither oxidized nor reduced.

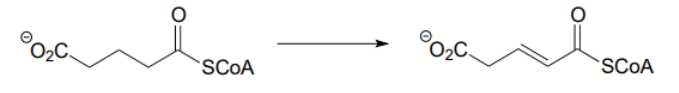
a. (from aromatic amino acid biosynthesis)



b. (from the biosynthesis of arginine and proline)



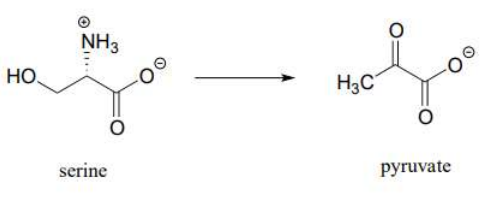
c. (from the catabolism of lysine)



d. (from the catabolism of tryptophan)



e. (from the catabolism of serine)

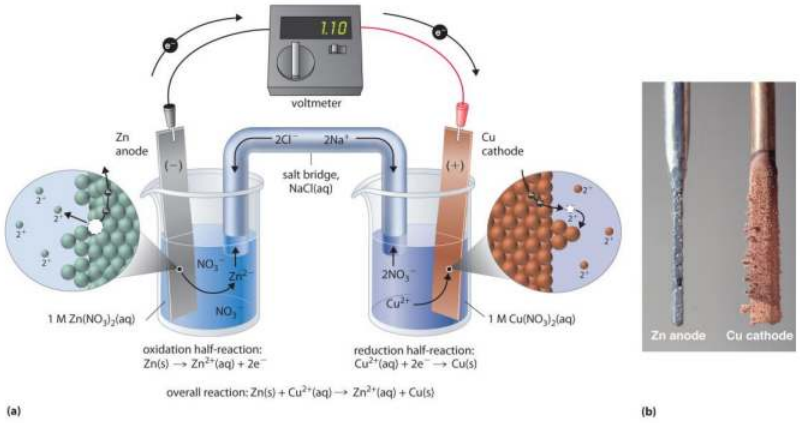


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15.2: Oxidation and Reduction in the Context of Metabolism

Think back again to the redox chemistry that you learned in your general chemistry course. A common experiment in a general chemistry lab is to set up a galvanic cell consisting of a copper electrode immersed in an aqueous copper nitrate solution, connected by a wire to a zinc electrode immersed in an aqueous zinc nitrate solution.



When the cell is completed with a salt bridge, an electrical current begins to flow - what we have is a simple battery (figure a above). Over time, the copper electrode gets heavier as metallic copper is deposited on the copper cathode, while the zinc anode slowly dissolves into solution (figure b above). The redox reaction occurring here is:

$$\mathrm{Cu^{+2}\,(aq) + Zn\,(s) \;\rightarrow Cu\,(s) + Zn^{+2}\,(aq) + energy} \tag{15.2.1}$$

Electrons flow from zinc metal to copper cations, creating zinc cations and copper metal: in other words, zinc metal is being oxidized to zinc cation and copper cation is being reduced to copper metal, as expressed by the two relevant half-cell reactions:

$$\mathrm{Cu^{+2}\,(aq) + 2\,e^{-} \;\rightarrow Cu^{0}\,(s)} \tag{15.2.2}$$

$$\mathrm{Zn^{0}\,(s) \;\rightarrow Zn^{+2}\,(aq) + 2\,e^{-}} \tag{15.2.3}$$

We can predict before we set up the cell that the spontaneous flow of electrons will go in the zinc to copper direction, just by looking at a table of standard reduction potentials (such a table was no doubt in your general chemistry text).

Table 15.3.1 : Standard reduction potentials at **25°**

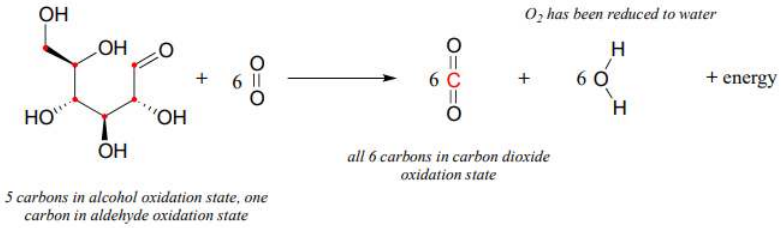
Reduction half-reaction	Reduction potential (volts)
$\mathrm{Ag^{+1}\,(aq) + e^{-} \;\rightarrow Ag^{0}\,(s)}$	0.800
$\mathrm{Cu^{+2}\,(aq) + 2\,e^{-} \;\rightarrow Cu^{0}\,(s)}$	0.337
$\mathrm{H^{+1}\,(aq) + 2\,e^{-} \;\rightarrow H_2\,(g)}$	0 (Standard)
$\mathrm{Pb^{+2}\,(aq) + 2\,e^{-} \;\rightarrow Pb^{0}\,(s)}$	-0.126
$\mathrm{Fe^{+2}\,(aq) + 2\,e^{-} \;\rightarrow Fe^{0}\,(s)}$	-0.441
$\mathrm{Zn^{+2}\,(aq) + 2\,e^{-} \;\rightarrow Zn^{0}\,(s)}$	-0.763

Copper ion (Cu^{+2}) has a higher standard reduction potential than zinc ion (Zn^{+2}), meaning that, under identical conditions, more energy is released by reducing one mole of Cu^{+2} ion to Cu^{0} metal than is released by reducing one mole of Zn^{+2} ion to Zn^{0} metal.. Another way to think about this is to imagine that the copper ion 'wants' to gain electrons more than the zinc ion does. Conversely, zinc metal 'wants' to lose electrons more than the copper metal does. Therefore, transfer of two electrons from zinc metal to Cu^{2+} is a thermodynamically downhill process, whereas the reverse process - transfer of two electrons from copper metal to Zn^{2+} - is thermodynamically uphill.

$$Cu^{+2}(aq) + Zn(s) \rightarrow Cu(s) + Zn^{+2}(aq) + energy \quad (15.2.4)$$

$$Cu(s) + Zn^{+2}(aq) + energy \rightarrow Cu^{+2}(aq) + Zn(s) \quad (15.2.5)$$

Let's now extend the idea of redox reactions to the context of metabolism in living things. When we 'burn' glucose for energy, we transfer (by a series of enzyme-catalyzed reactions) electrons from glucose to molecular oxygen (O_2), oxidizing the six carbon molecules in glucose to carbon dioxide and at the same time reducing the oxygen atoms in O_2 to water. The overall chemical equation is:



The transfer of electrons from glucose to O_2 is a thermodynamically downhill, energy-releasing process, just like the transfer of electrons from zinc metal to copper ion. And while you could have used the energy released by the zinc/copper redox reaction to light a small light bulb, your cells use the energy released by the glucose/oxygen redox process to carry out a wide variety of energy-requiring activities, such as walking to your organic chemistry lecture.

In your general chemistry copper/zinc experiment, was it possible to reverse the reaction so that it runs in the uphill direction - in other words, to oxidize copper and reduce zinc?

$$Zn^{+2}(aq) + Cu(s) + energy \rightarrow Zn(s) + Cu^{+2}(aq) \quad (15.2.6)$$

Just ask yourself the question: is it possible to get water to flow uphill? Of course it is - but only if you supply a pump and some energy!

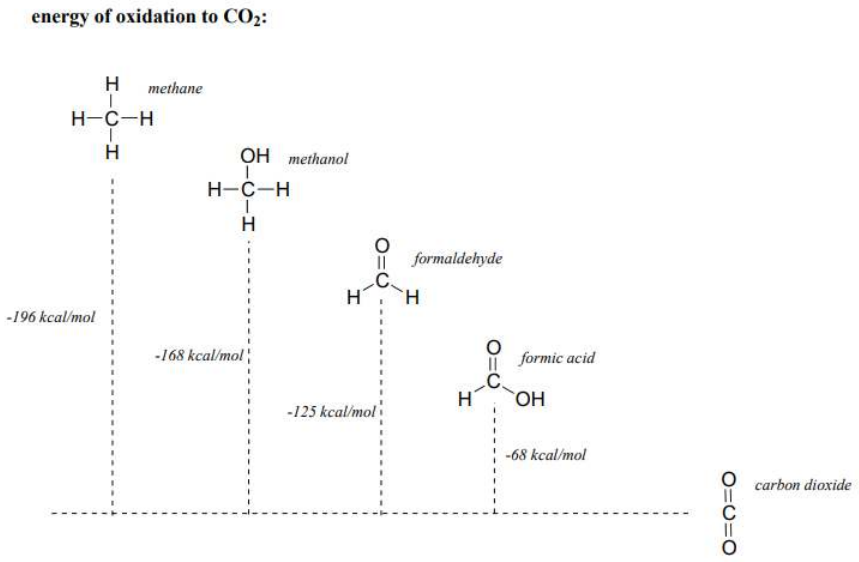
The same idea applies to 'pumping' electrons uphill in your copper-zinc electrochemical cell: all you need to do is to provide some energy in the form of an external electrical current in order to pump the electron flow in the uphill direction. You are recharging your battery.

Thinking again in a biochemical context: plants are able, by a process called photosynthesis, to reduce carbon dioxide and oxidize water to form glucose and molecular oxygen: essentially recharging the ecosystem's biochemical battery using energy from the sun.

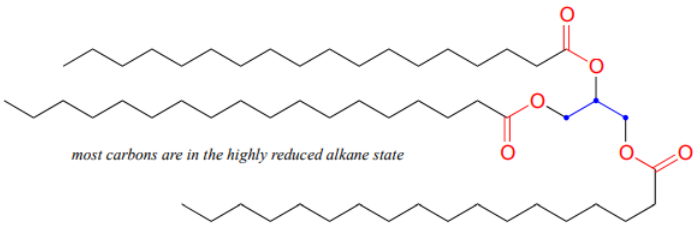
$$6\,CO_2 + 6\,H_2O + energy \rightarrow C_6H_{12}O_6 + 6\,O_2 \quad (15.2.7)$$

On a global scale, oxidation of the carbons in glucose to CO_2 by non-photosynthetic organisms (like people) and the subsequent reductive synthesis of glucose from CO_2 by plants is what ecologists refer to as the 'carbon cycle'.

In general the more reduced an organic molecule is, the more energy is released when it is oxidized to CO_2. Going back to our single-carbon examples, we see that methane, the most reduced compound, releases the most energy when oxidized to carbon dioxide, while formic acid releases the least:

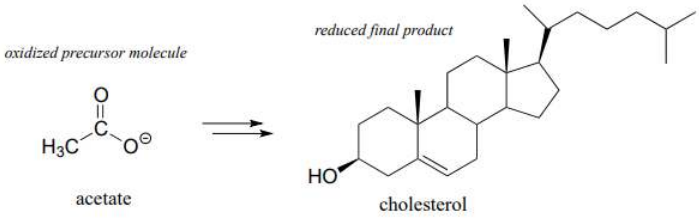


A lipid (fat) molecule, where most of the carbons are in the highly reduced alkane state, contains more energy per gram than glucose, where five of the six carbons are in the more oxidized alcohol state (look again at the glucose structure we saw just a couple of pages back).



a saturated fat molecule

After we break down and oxidize sugar and fat molecules to obtain energy, we use that energy to build large, complex molecules (like cholesterol, or DNA) out of small, simple precursors. Many biosynthetic pathways are reductive: the carbons in the large biomolecule products are in a reduced state compared to the small precursors. Look at the structure of cholesterol compared to that of acetate, the precursor molecule from which all of its carbon atoms are derived - you can see that cholesterol is overall a more reduced molecule.



While we are focusing here on the mechanistic details of the individual organic redox reactions involved in metabolism, if you take a course in biochemistry you will learn much more about the bigger picture of how all of these reactions fit together in living systems.

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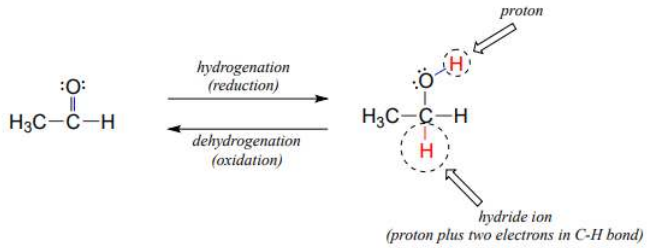
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15.3: Hydrogenation of Carbonyl and Imine Groups

Next, we'll go on to look at the actual chemical mechanisms involved in the enzyme-catalyzed oxidation and reduction of biomolecules.

An overview of hydrogenation and dehydrogenation

Many of the redox reactions that you will encounter when studying the central metabolic pathways are classified as hydrogenation or dehydrogenation reactions. Hydrogenation is simply the net addition of a hydrogen (H_2) molecule to a compound, in the form of a hydride ion (H^-, a proton plus a pair of electrons) and a proton. Hydrogenation corresponds to reduction. Dehydrogenation reactions are the reverse process: loss of a hydride and a proton. Dehydrogenation corresponds to oxidation.



Hydrogenation and dehydrogenation reactions can also be called hydride transfer reactions, because a hydride ion is transferred from the molecule being oxidized to the one being reduced. In the next few sections, we will learn about two important classes of coenzyme molecules that serve hydride ion acceptors (oxidizing agents) and hydride ion donors (reducing agents) in biochemical redox reactions.

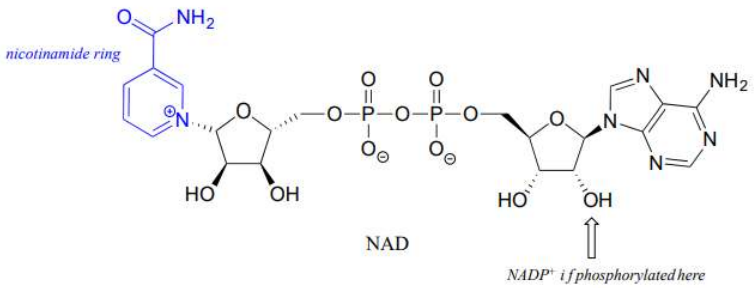
Note

Be careful not to confuse the terms *hydrogenation* and *dehydrogenation* with *hydration* and *dehydration* - the latter terms refer to the gain or loss of water, while the former terms refer to the gain or loss of hydrogen.

Many mechanistic patterns that we have already learned about in previous chapters will come into play again in this discussion, with the only variation being that here, a hydride ion will act as a nucleophile (in the hydrogenation direction) or as a leaving group (in the dehydrogenation direction). The key to understanding these reactions will be to understand how a hydride can act as a nucleophile or leaving group.

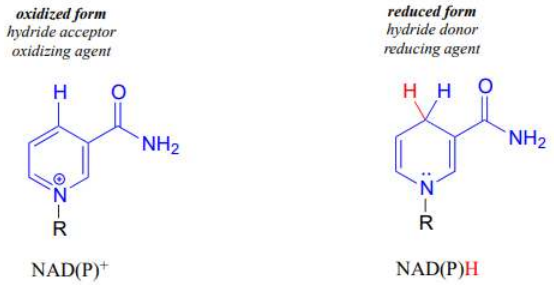
Nicotinamide adenine dinucleotide - a hydride transfer coenzyme

Although we are talking here about hydrides acting as nucleophiles and leaving groups, you already know that literal hydride ions are far too unstable to exist as discreet intermediates in the organic reactions of living cells (the pK_a of H_2, the conjugate acid of hydride, is about 35: a very weak acid, meaning hydride is a very strong base and not a reasonable species to propose for a biochemical reaction). As was alluded to earlier, biochemical hydrogenation/dehydrogenation steps require the participation of a specialized hydride transfer coenzyme. The most important of these is a molecule called **nicotinamide adenine dinucleotide**. The full structure of the oxidized form of this coenzyme, abbreviated NAD^+, is shown below, with the active nicotinamide group colored blue. Because the redox chemistry occurs specifically at the nicotinamide ring (in blue in the figure below), typically the rest of the molecule is simply designated as an 'R' group.



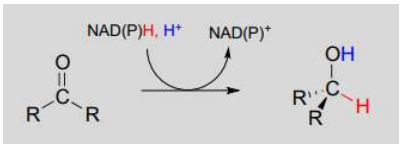
If the hydroxyl group indicated by the arrow is phosphorylated, the coenzyme is called $NADP^+$. The phosphate is located far from the nicotinamide ring and does not participate directly in the hydride transfer function of the cofactor. It is, however, important in a larger metabolic context: as a general rule, redox enzymes involved in catabolism (the breakdown of large molecules) typically use the non-phosphorylated coenzyme, while those involved in anabolism (biosynthesis of large molecules from small precursors) use the phosphorylated coenzyme.

NAD^+ and $NADP^+$ both function in biochemical redox reactions as hydride acceptors: that is, as oxidizing agents. The reduced forms of the coenzyme, abbreviated $NADH$ and $NADPH$, serve as hydride donors: that is, as reducing agents.

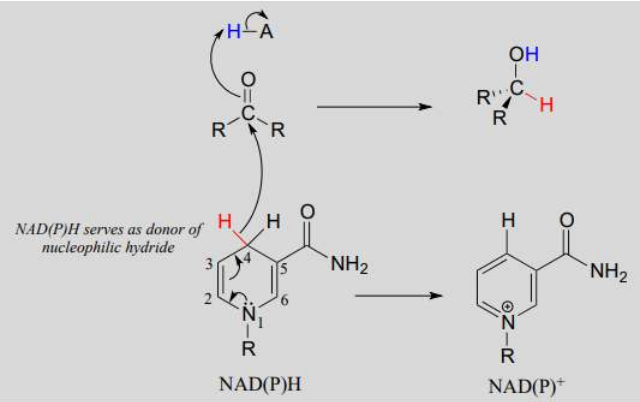


To understand how the nicotinamide coenzymes function in hydride transfer, let's look at a general picture of a reversible, redox conversion from a ketone to a secondary alcohol. Mechanistically, the reaction we are about to see can be described as a nucleophilic addition to a carbonyl - a mechanism type we studied in chapter 10 - with the twist that the nucleophilic species is a hydride ion. At the beginning of the reaction cycle, both the ketone substrate and the $NADH$ cofactor are bound in the enzyme's active site, and carbon #4 of the nicotinamide ring is positioned very close to the carbonyl carbon of the ketone.

$NAD(P)H$-dependent hydrogenation (reduction) of a ketone



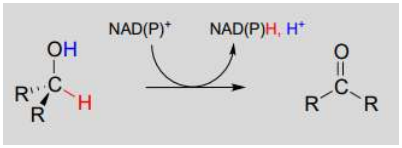
Mechanism:



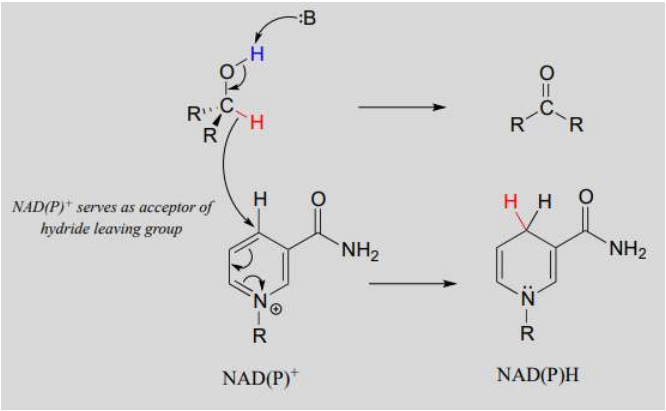
As an enzymatic group transfers a proton to the ketone oxygen, the carbonyl carbon loses electron density and becomes more electrophilic, and is attacked by a hydride from ***NADH***. Because carbon #4 of ***NADH*** is bound in such close proximity to the electrophile, this step can occur without generating a free hydride ion intermediate – the two hydride electrons can be pictured as shifting from one carbon to another. Note the products of this reaction: the ketone (which accepted a hydride and a proton) has been reduced to an alcohol, and the ***NADH*** cofactor (which donated a hydride) has been oxidized to NAD^+.

The dehydrogenation of an alcohol by NAD^+ is simply the reverse of a ketone hydrogenation:

$NAD(P)^+$-dependent dehydrogenation (oxidation) of an alcohol



Mechanism:



An enzymatic base positioned above the carbonyl removes a proton, and the electrons in the $O-H$ bond shift down and push out the hydride, which shifts over to carbon #4 of NAD^+. Note that the same process with a primary alcohol would yield an aldehyde instead of a ketone.

? Exercise 15.4.1

Draw general mechanisms for:

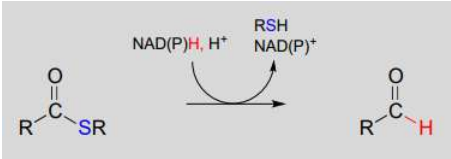
a. hydrogenation of an imine
b. dehydrogenation of an amine

? Exercise 15.4.2

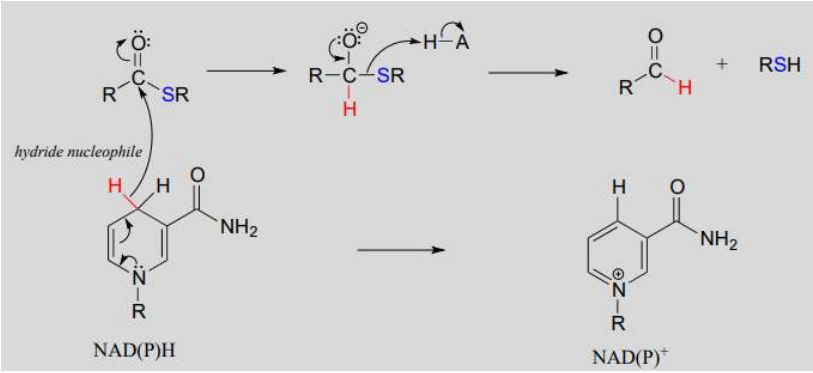
We just saw that when the nucleophile in a nucleophilic carbonyl addition step is a hydride ion from \(NADH\), the result is a ketone/aldehyde hydrogenation reaction. As a review: what kind of reaction step results when the nucleophile in this process is not a hydride ion but a) an alcohol, or b) an enolate carbon?

The nicotinamide coenzymes also serve as hydride donors/acceptors in the redox reactions interconverting carboxylic acid derivatives and aldehydes. Notice that these reactions can be thought of as nucleophilic acyl substitution reactions (chapter 11) in which the nucleophile or leaving group is a hydride ion.

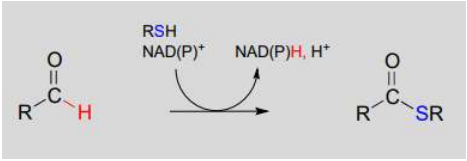
NAD(P)H-dependent hydrogenation (reduction) of a thioester to an aldehyde:



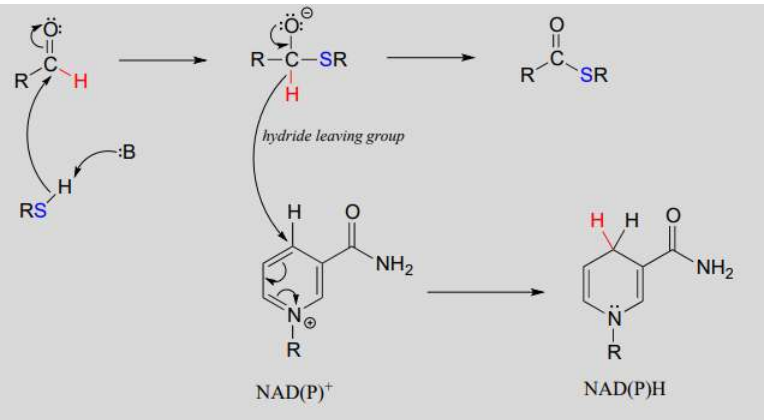
Mechanism:



$NAD(P)^+$-dependent dehydrogenation (oxidation) of an aldehyde to a thioester:

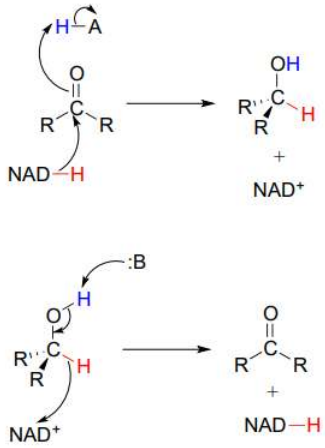


Mechanism:



https://chem.libretexts.org/@go/page/393659

To simplify figures, hydrogenation and dehydrogenation reactions are often drawn with the role of the coenzyme abbreviated:



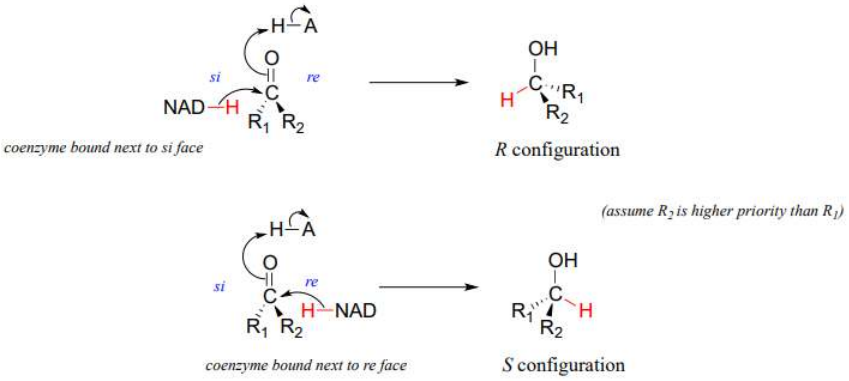
However, it is very important to make sure that you can remember and draw out the full mechanism, including the role of the coenzyme, in these types of reactions.

Caution

A very common error made by students learning how to draw biochemical redox mechanisms is to incorrectly show nicotinamide coenzymes acting as acids or bases. Remember: \(NADH\) and \(NADPH\) are hydride donors, **NOT** proton donors. \(NAD^+\) and \(NADP^+\) are hydride acceptors, **NOT** proton acceptors.

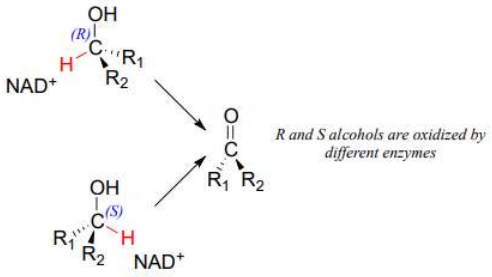
Stereochemistry of ketone hydrogenation

It should not surprise you that the stereochemical outcomes of enzymatic hydrogenation / dehydrogenation steps are very specific. Consider the hydrogenation of an asymmetric ketone: In the hydrogenation direction, attack by the hydride can occur from either the *re* or the *si* face of an asymmetric ketone (see section 10.1), leading specifically to the S or R alcohol.



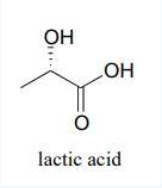
The stereochemical configuration of the product depends on which side of the ketone substrate the $NAD(P)H$ coenzyme is bound in the active site. Any given enzyme will catalyze its reaction with one of these two stereochemical outcomes, not both.

Stereochemical considerations apply in the dehydrogenase direction as well: in general, enzymes specifically catalyze the oxidation of either an R or S alcohol, but not both.



? Exercise 15.4.3

During an intense workout, lactic acid forms in muscle tissue as the result of enzymatic reduction of a ketone group in the precursor molecule (EC 1.1.1.27). It is the lactate that you can blame for the sore muscles you feel the day after a workout.



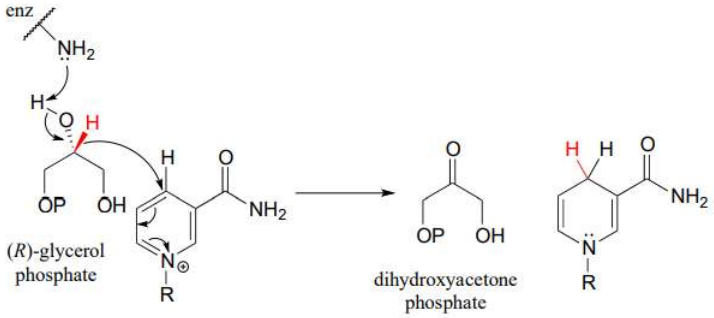
lactic acid

a. Which face of the ketone is the coenzyme positioned next to in the active site of the enzyme?

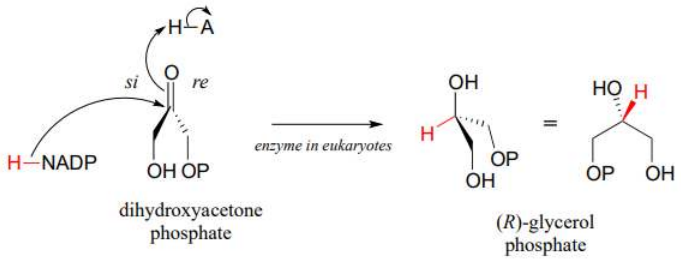
Examples of biochemical carbonyl/imine hydrogenation

Now that we have covered the basics, let's look at some real examples of hydrogenation and dehydrogenation reactions.

Glycerol phosphate dehydrogenase (EC 1.1.1.8) catalyzes one of the final chemical steps in the breakdown of fat molecules. The enzyme specifically oxidizes (R)-glycerol phosphate to dihydroxyacetone phosphate. (S)-glycerol phosphate is not a substrate for this enzyme. J. Mol. Biol. 200



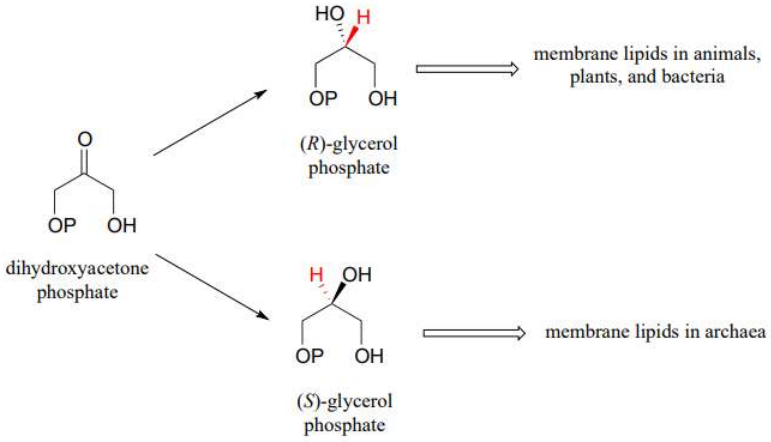
The reverse reaction (catalyzed by the same enzyme) converts dihydroxyacetone phosphate to (R)-glycerol phosphate, which serves as a starting point for the biosynthesis of membrane lipid molecules (see section 1.3).



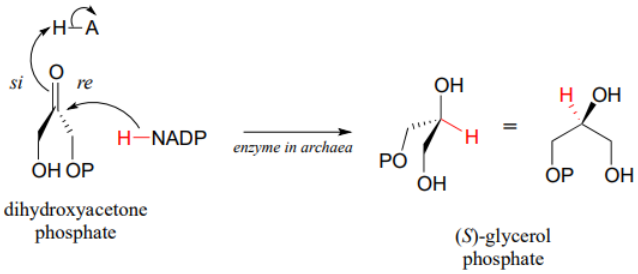
? Exercise 15.4.4

X-ray crystallography experiments reveal that in the active site of glycerol phosphate dehydrogenase, a zinc cation (Zn^{+2}) is coordinated to the oxygen atom of the carbonyl/alcohol group. How does this contribute to catalysis of the reaction?

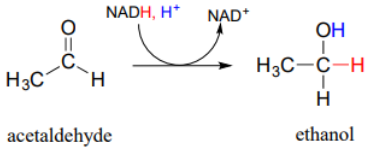
While the cell membranes of animals, plants, and bacteria are made from lipids with the R stereochemistry exclusively, archaeal microbes (the so-called 'third kingdom of life) are distinguished in part by the S stereochemistry of their membranes.



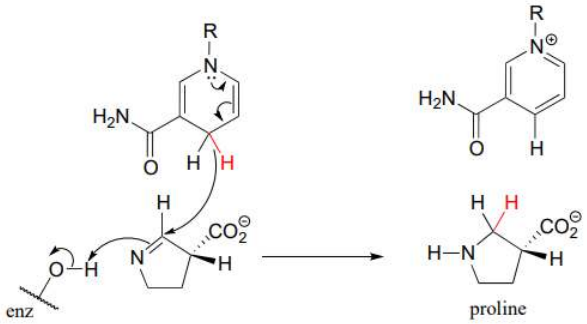
Archaea have an enzyme that catalyzes hydrogenation of dihydroxyacetone with the opposite stereochemistry compared to the analogous enzyme in bacteria and eukaryotes. This archaeal enzyme was identified and isolated in 1997.



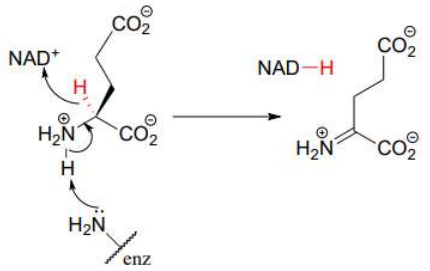
In a reaction that is relevant to people who enjoy the occasional 'adult beverage', an ***NADH***-dependent enzyme (EC 1.1.1.1) in brewer's yeast produces ethanol by reducing acetaldehyde. This is the final step in the process by which yeast ferment glucose to ethanol.



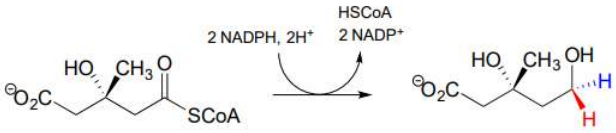
The reaction below, which is the final step in the biosynthesis of proline (EC 1.5.1.2), is an example of an enzymatic reduction of an imine to an amine. J. Mol. Biol. 2005, 354, 91.



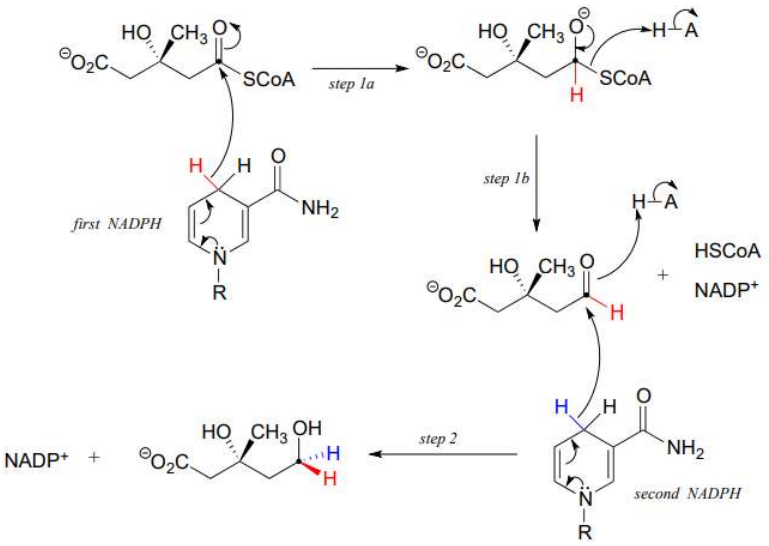
This step in the breakdown of the amino acids glutamate (EC 1.4.1.2) provides an example of the oxidation of an amine to an imine: Structure 1999, 7, 769.



The 'double reduction' reaction below (EC 1.1.1.34) is part of the isoprenoid biosynthetic pathway, which eventually leads to cholesterol in humans.

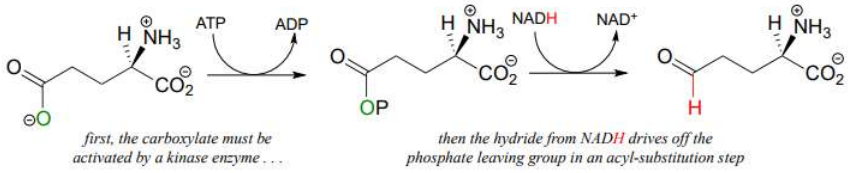


In this reaction, a thioester is first reduced to an aldehyde in steps 1a and 1b:

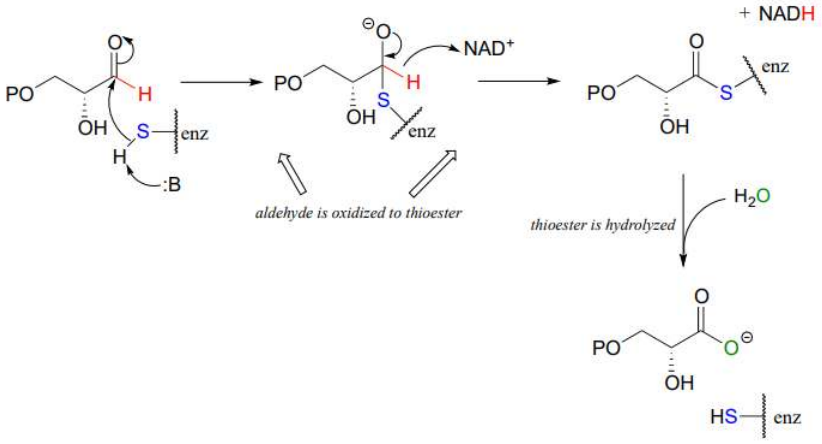


Then in step 2, the aldehyde is in turn reduced by the same enzyme (and a second ***NADPH*** that enters the active site) to a primary alcohol. This enzyme is inhibited by atorvastatin and other members of the statin family of cholesterol-lowering drugs. Atorvastatin, marketed under the trade name Lipitor by Pfizer, is one of the all-time best-selling prescription medications.

Recall from chapter 11 that carboxylates are not reactive in acyl substitution steps, so it follows that they cannot be directly reduced to aldehydes by an enzyme in the same way that thioesters can. However, a carboxylate can be converted to its 'activated' acyl phosphate form (section 11.4), which can then be hydrogenated. An example of this is found in a two-reaction sequence found in amino acid metabolism (EC 2.7.2.11; EC1.2.1.41).

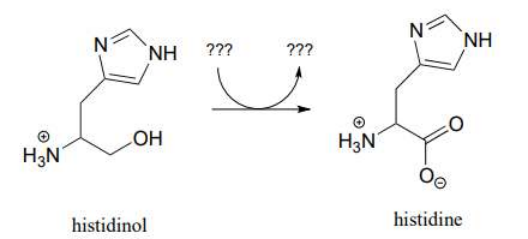


Glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12) , a key enzyme in the glycolysis pathway, provides an example of the oxidation of an aldehyde to a thioester, in this case a thioester linkage between the substrate and a cysteine residue in the enzyme's active site. In the second phase of the reaction, the thioester intermediate is hydrolyzed to free the carboxylate product.



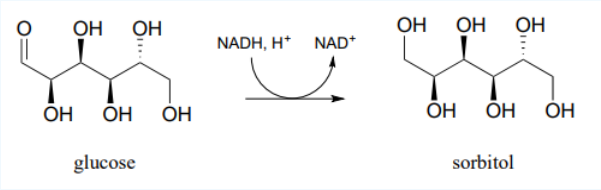
? Exercise 15.4.5

Below is the final step in the biosynthesis of the amino acid histidine (EC 1.1.1.23). Fill in the species that are indicated with question marks. Proc. Natl. Acad. Sci. U.S.A. 2002, 99, 1859



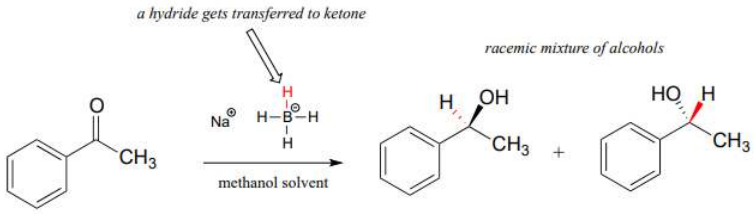
Exercise 15.4.6

Draw a likely mechanism for the conversion of glucose to sorbitol, a process that occurs in the liver. Do not abbreviate the nicotinamide ring structure.



Reduction of ketones and aldehydes in the laboratory

Although our focus in this book is biological organic reactions, it is interesting to note that synthetic organic chemists frequently perform hydrogenation reactions in the lab that are similar in many respects to the NAD(P)H-dependent reactions that we have just finished studying. A reagent called sodium borohydride ($NaBH_4$) is very commonly used, often in methanol solvent, to reduce ketones and aldehydes to alcohols. The reagent is essentially a laboratory equivalent of ***NADH*** (or ***NADPH***): it serves as a source of nucleophilic hydride ions. Sodium borohydride is a selective reagent in the sense that it will reduce ketones and aldehydes but not carboxylic acid derivatives such as esters (recall from section 11.2 and section 11.3 that the carbonyl carbons of carboxylic acid derivatives are less potent electrophiles than the carbonyl carbons of ketones and aldehydes). Unlike the enzymatic hydrogenation reactions we saw earlier, the reduction of asymmetric ketones with sodium borohydride usually results in a 50:50 racemic mixture of the R and S enantiomers of the alcohol product.



Synthetic organic chemists have at their disposal a wide range of other reducing and oxidizing reagents with varying specificities and properties, many of which you will learn about if you take a course in laboratory synthesis.

Exercise 15.4.7

Camphor can be easily reduced by sodium borohydride. However, the mixture of stereoisomeric alcohols that results is not 50:50.



camphor

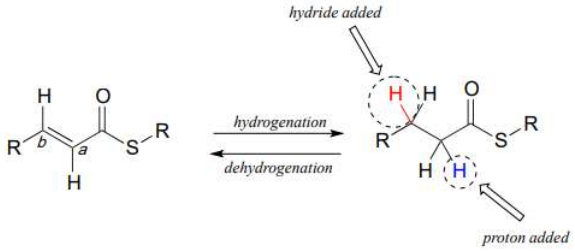
a. Draw the two stereoisomers of the alcohol products of this reaction, and explain why they are not formed in a 50:50 ratio.
b. Which analytical technique - ^1H-NMR, IR, UV, or MS - could best be used to determine the ratio of the stereoisomers in the product mix? Describe how this analysis could be accomplished.

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15.4: Hydrogenation of alkenes and Dehydrogenation of Alkanes

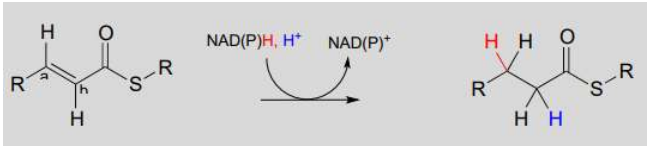
We turn next to reactions in which a hydrogen molecule is added to the double bond of an alkene, forming an alkane - and the reverse, in which H_2 is eliminated from an alkane to form an alkene. Many biochemical reactions of this type involve α, β-unsaturated thioesters.



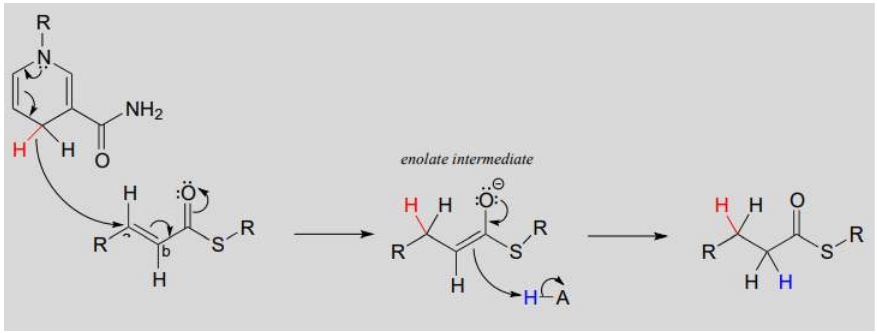
Alkene hydrogenation

In the cell, alkene hydrogenation most often occurs at the a and b position relative to a carbonyl. This type of alkene hydrogenation is essentially a conjugate addition (section 11.4) of hydrogen, with a hydride ion (often from $NAD(P)H$) acting as the nucleophile in the first step.

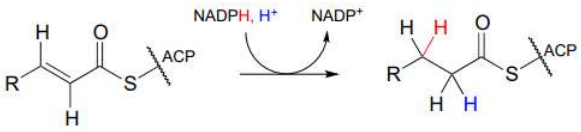
$NAD(P)H$-dependent hydrogenation (reduction) of an α, β-conjugated alkene:



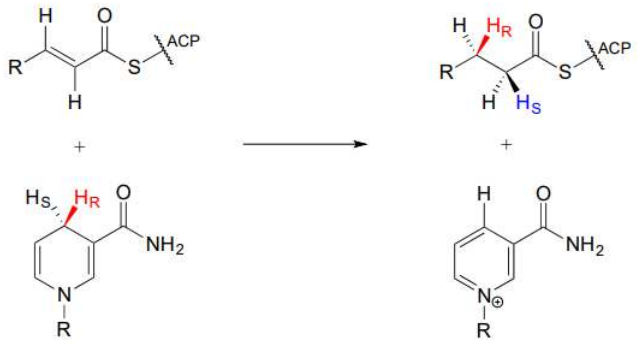
Mechanism:



As part of the fatty acid synthesis pathway, a double bond between the a and b carbons of a fatty acid is reduced to a single bond by hydrogenation (EC 1.3.1.10). The fatty acid is attached to an acyl-carrier protein via a thioester linkage (section 11.5).



It can be easy to forget but important to remember that there is a lot of stereospecificity inherent in biochemical reactions, including this one - even though no chiral centers are involved. First, notice that the substrate contains a trans (E) alkene. Next, let's add some new information about prochirality:

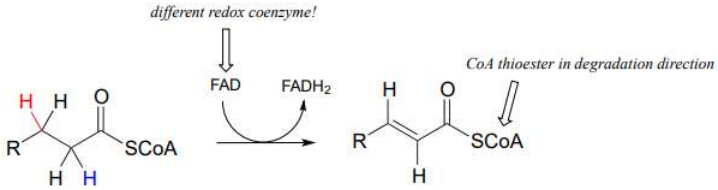


Notice that in this particular reaction it is specifically the pro-R hydride on ***NADPH*** that is delivered to the substrate. Also notice that the hydride and proton are added to the same side of the alkene, and become the pro-R and pro-S hydrogen atoms, respectively, on the substrate. This level of stereospecificity, you should recall from previous discussions, stems from the highly precise positioning of substrate and cofactor within the active site of the enzyme.

Other hydrogenase enzymes are known to deliver the pro-S hydride of ***NADH*** or ***NADPH*** to their substrate, and there are many examples of biochemical conjugate addition reactions in which the nucleophile and proton are added from opposite sides. Always keep in mind that stereochemistry is a key element in the amazing diversity of biological organic reactions.

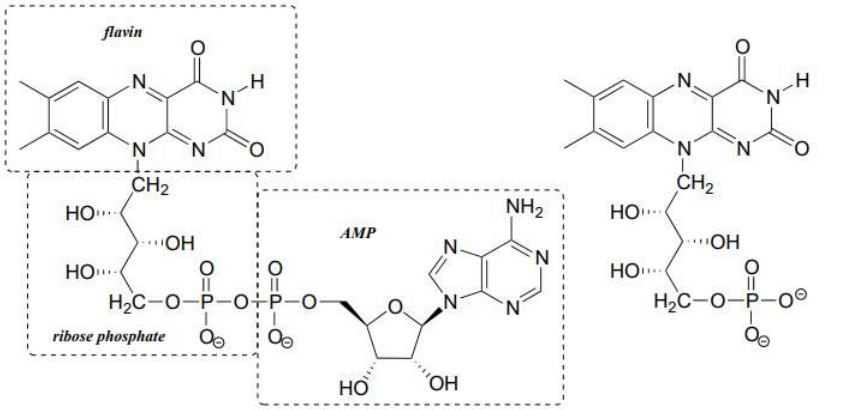
Flavin-dependent alkane dehydrogenation

Next let's consider an alkane dehydrogenation reaction (EC 1.3.99.3) in the fatty acid degradation pathway. Here, a double bond is introduced between the α and β carbons, with concurrent loss of a hydride ion and a proton.



This reaction is clearly not the reverse of the hydrogenation reaction we just saw from fatty acid biosynthesis. First of all, you should notice that the thioester linkage is to coenzyme A rather than acyl carrier protein (***ACP***). More importantly to this discussion, while the hydride donor in the biosynthetic hydrogenation reaction is ***NADPH***, the relevant coenzyme in the catabolic direction is not NAD^+ or $NADP^+$ - rather, it is a **flavin coenzyme**.

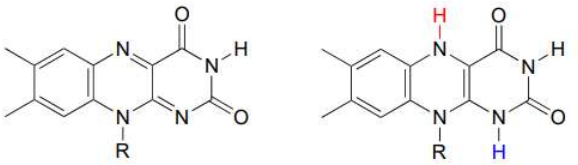
Flavin adenine dinucleotide (***FAD***) is composed of three components: the three-ring flavin system, ribose phosphate, and AMP. An alternate form, which is missing the AMP component, is called **flavin mononucleotide** (***FMN***).



flavin adenine dinucleotide (FAD) flavin mononucleotide (FMN)

The reactive part of the coenzyme is the flavin group, so usually the rest of the molecule is abbreviated with 'R'.

FAD and ***FMN*** are the oxidized form of flavin. The reduced (hydrogenated) forms of these cofactors are abbreviated $FADH_2$ and $FMNH_2$.

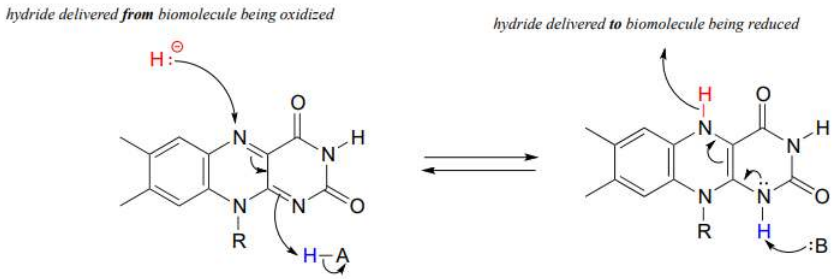


FAD or FMN
oxidized flavin
hydride acceptor
oxidizing agent

$FADH_2$ or $FMNH_2$
reduced flavin
hydride donor
reducing agent

The flavin coenzymes are synthesized in humans from riboflavin (vitamin B_2), which we obtain from our diet (the structure of riboflavin is the same as that of ***FMN***, except that riboflavin lacks the phosphate group). Notice the extended conjugated p system in the three fused rings: the flavin system absorbs light in the visible wavelengths and has a distinctive deep yellow color - it is riboflavin, and to some extent ***FAD*** and ***FMN***, that give urine its color.

Like the nicotinamide coenzymes, flavin serves as a hydride donor or acceptor. ***FAD*** and ***FMN*** are able to accept a hydride ion (and a proton), and $FADH_2$ and $FMNH_2$ in turn can serve as hydride donors in hydrogenation reactions.

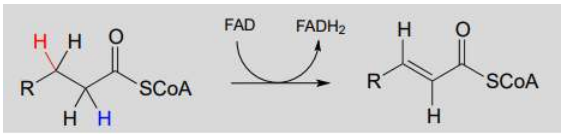


oxidized flavin
hydride acceptor
oxidizing agent

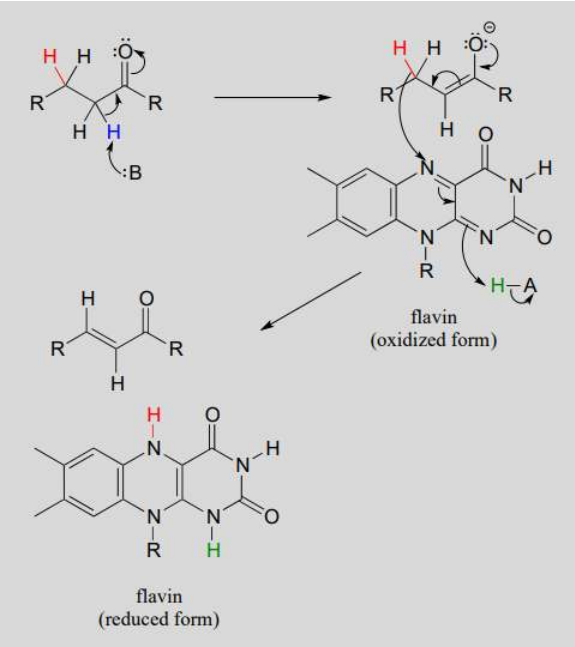
reduced flavin
hydride donor
reducing agent

Below is a general mechanism for the dehydration of an alkene at the α, β position - notice that it is mechanistically an E1cb elimination of H_2.

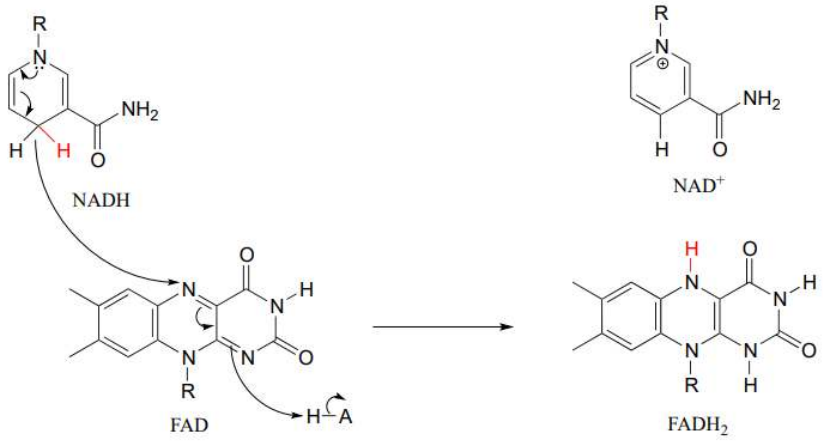
α, β dehydrogenation (oxidation) of an alkane:



Mechanism:



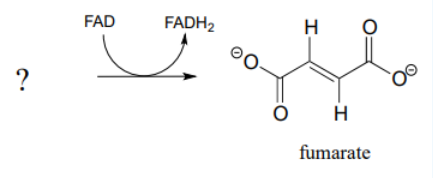
In many enzymatic reactions in which $FADH_2$ acts as the reducing agent, the reaction cycle is completed when FAD, rather than being released from the active site, is recycled back to $FADH_2$ with the concomitant oxidation of $NADH$.



Hydride ion transfer with flavin or nicotinamide coenzymes is a two electron redox process. However, unlike the nicotinamide cofactors, flavins are also able to function in single electron transfer (radical) mechanisms. We will come back to this idea briefly in the chapter 16.

? Exercise 15.5.1

Fumarate is formed in an alkane dehydrogenation reaction (EC 1.3.5.1) which is part of the citric acid cycle:



a. Predict the structure of the starting substrate in this reaction

b. Draw the structure of the enolate intermediate

Exercise 15.5.2

Reduced flavin can serve as the hydride donor in some hydrogenation reactions. Degradation of the RNA base uracil begins with hydrogenation of a conjugated alkene group by a flavin-dependent hydrogenase enzyme (EC 1.3.1.2). Predict the product of this step, and draw curved arrows for the first mechanistic step.

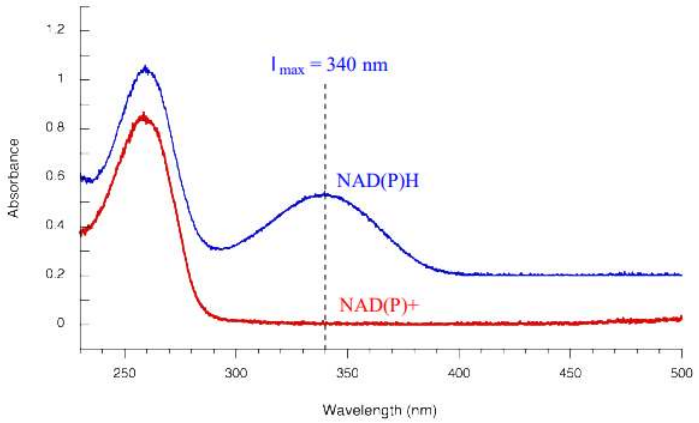
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15.5: Monitoring Hydrogenation and Dehydrogenation Reactions by UV Spectroscopy

In order to study any enzyme-catalyzed reaction, a researcher must have available some sort of test, or assay, in order to observe and measure the reaction's progress and measure its rate. In many cases, an assay simply involves running the reaction for a specified length of time, then isolating and quantifying the product using a separation technique such as high performance liquid chromatography (HPLC) or gas chromatography (GC). This type of assay can be extremely time-consuming, however, so it is to the researcher's great advantage if a more convenient assay can be found.

Redox reactions in which a nicotinamide coenzyme participates as a hydride donor or acceptor are generally quite convenient to assay. In fact, the progress of these reactions can usually be observed in real time, meaning that the researcher doesn't need to stop the reaction in order to see how far it has progressed. $NADPH$ and $NADH$ have distinctive $n - \pi^*$ UV absorbance bands centered at 340 nm, with a molar absorptivity of 6290 M-1 cm-1 (section 4.4). The oxidized coenzymes $NADP^+$ and NAD^+ do not absorb at this wavelength.



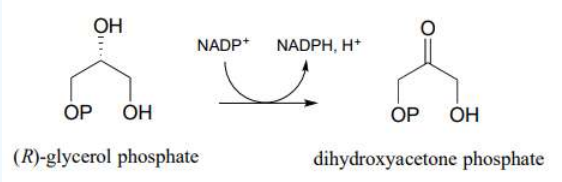
Therefore, the course of a hydrogenation reaction, in which $NAD(P)H$ is converted to $NAD(P)^+$, can be observed in real time if it is run in a quartz cuvette in a UV spectrometer. By observing the decrease in absorbance at 340 nm, the researcher can calculate how much $NAD(P)H$ has been oxidized to $NAD(P)^+$ at any given time point, and this number is the molar equivalent of the amount of organic substrate that has been reduced:



Likewise, a NAD^+-dependent dehydrogenase reaction can be followed in real time by monitoring the increase in absorbance at 340 nm as NAD^+ is converted to $NADH$.

? Exercise 15.6.1

You are observing the progress of the (R)-glycerol phosphate dehydrogenase reaction shown in the figure below.



You run the reaction in a quartz cuvette (path length 1 cm) in a total solution volume of 1 mL. start with 200 mM substrate and 100 mM $NADP^+$ in solution, zero the UV spectrophotometer, then add the enzyme to start the reaction. After 5 minutes, the A340 reading has climbed from 0.000 to 0.096. At this time point:

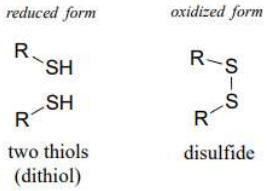
a. How many moles of substrate have been oxidized?
b. What is the solution concentration of $NADP^+$?
c. The enzyme has a mass of 25 kilodaltons (25,000 g/mol).You added 5 mL of a 2 ng/mL solution of pure enzyme to start the reaction. How many reactions does each enzyme molecule catalyze, on average, per second? (This number is referred to by biochemists as the 'turnover number').

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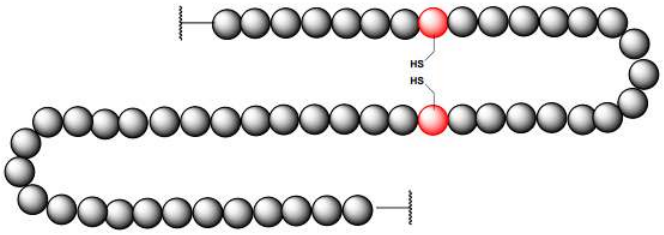
15.6: Redox Reactions of Thiols and Disulfides

A **disulfide bond** is a sulfur-sulfur bond, usually formed from two free thiol groups.

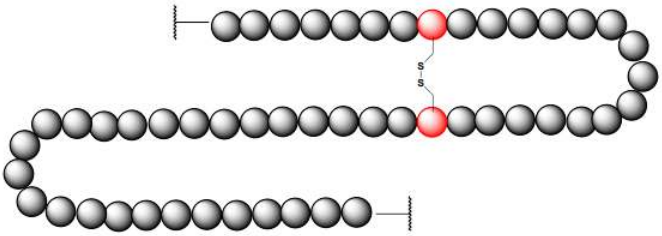


The interconversion between dithiol and disulfide groups is a redox reaction: the free dithiol form is in the reduced state, and the disulfide form is in the oxidized state. Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to sulfur.

As you should recall from your Biology courses, disulfide bonds between cysteine residues are an integral component of the three-dimensional structure of many extracellular proteins and signaling peptides.

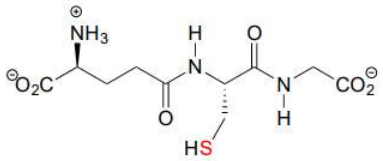


reduced protein (free cysteines)

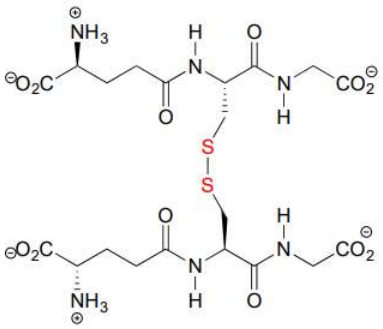


oxidized protein (disulfide)

A thiol-containing coenzyme called glutathione is integrally involved in many thiol-disulfide redox processes (recall that glutathione was a main player in this chapter's introductory story about concussion research). In its reduced (thiol) form, glutathione is abbreviated 'GSH'. In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.



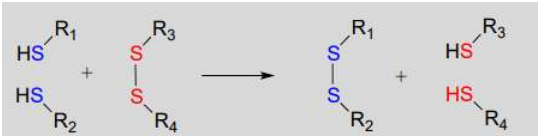
glutathione (GSH)
reduced state



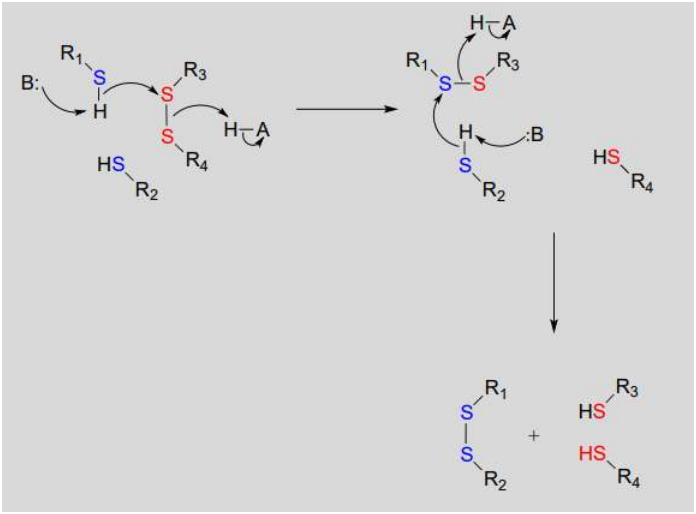
glutathione dimer (GSSG)
oxidized state

Disulfide bonds and free thiol groups in both proteins and smaller organic molecules like glutathione can 'trade places' through a disulfide exchange reaction. This process is essentially a combination of two direct displacement (S_N2-like) events, with sulfur atoms acting as nucleophile, electrophile and leaving group.

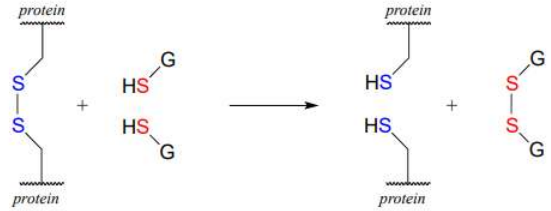
Disulfide exchange reaction



Mechanism:

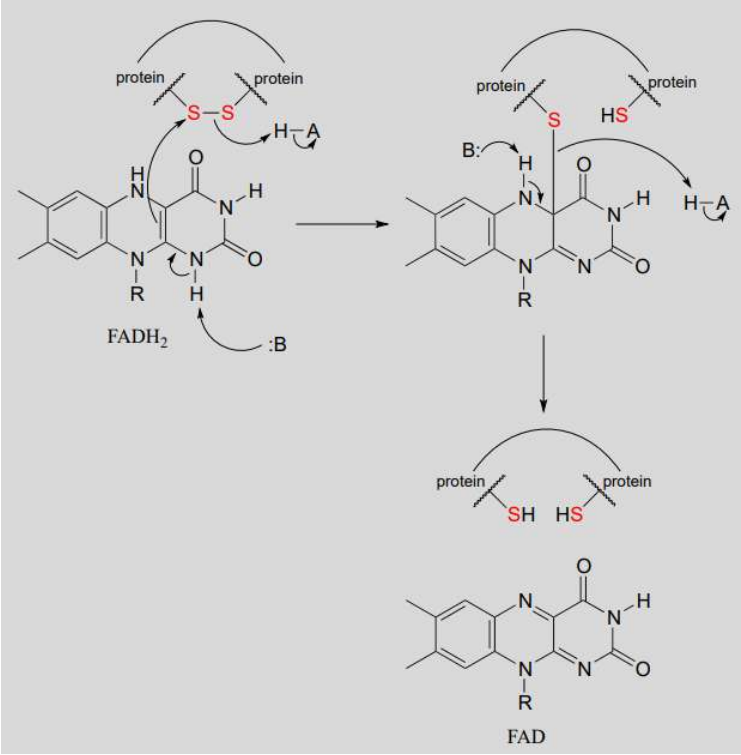


In eukaryotes, the cysteine side chains of intracellular (inside the cell) proteins are almost always in the free thiol (reduced) state due to the high concentration of reduced glutathione (GSH) in the intracellular environment. A disulfide bond in an intracellular protein will be rapidly reduced in a disulfide exchange reaction with excess glutathione.



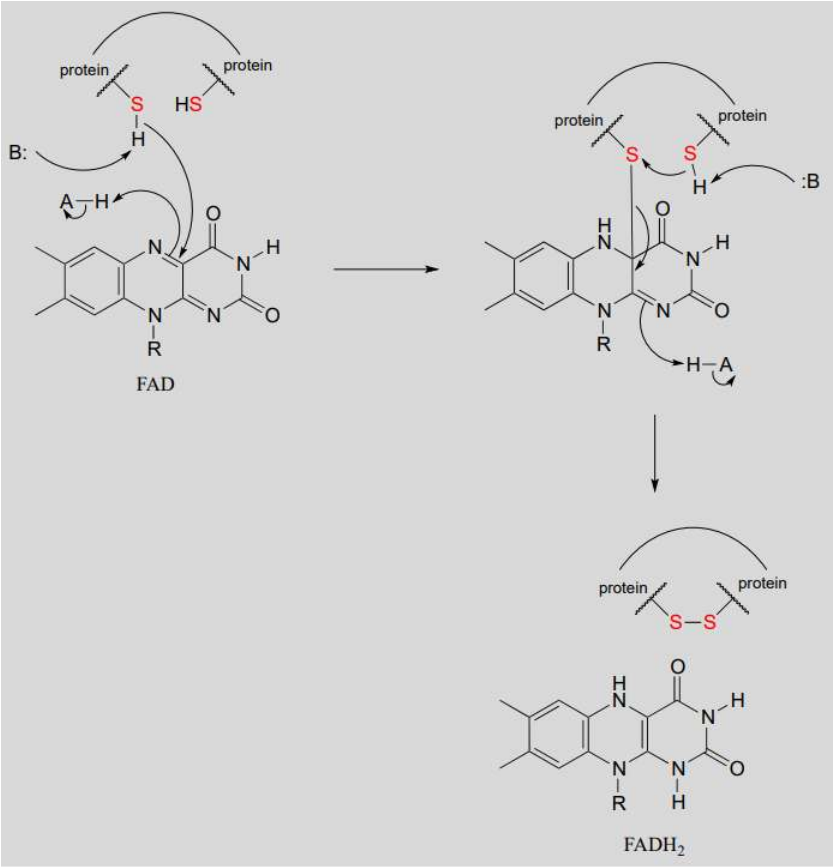
The interconversion of free thiols and disulfides is also mediated by flavin in some enzymes.

Flavin-mediated reduction of a protein disulfide bond



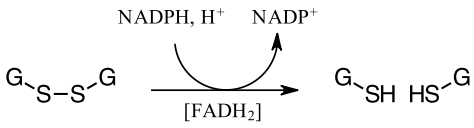
Flavin-mediated oxidation of a protein disulfide bond

https://chem.libretexts.org/@go/page/393662



As was stated earlier, a high intracellular concentration of reduced glutathione (GSH) serves to maintain proteins in the free thiol (reduced) state. An enzyme called glutathione reductase catalyzes the reduction of GSSG in a flavin-mediated process, with ***NADH*** acting as the ultimate hydride donor.

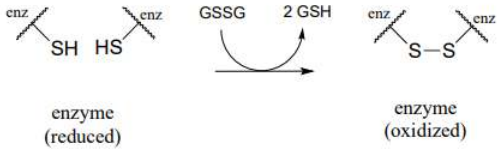
Gluthione reductase reaction:



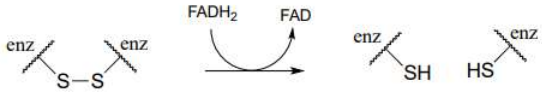
This figure shows oxidized glutathione converted to reduced glutathione by NADPH.

The mechanism for this and other similar reactions is not yet completely understood, but evidence points to an initial thiol-disulfide exchange reaction with a pair of cysteines from the enzyme, (phase 1 below) followed by flavin-dependent reduction of the cysteine-cysteine disulfide (phase 2). Finally, (phase 3) ***FAD*** is reduced back to ***$FADH_2$*** by ***NADH***. Frey and Hegeman, Enzymatic Reaction Mechanisms, p. 699

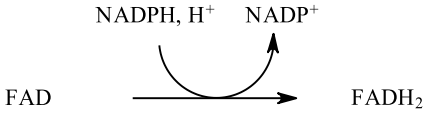
Phase 1: thiol-disulfide exchange (see earlier figure for mechanism):



Phase 2: Reduction of protein disulfide by ***$FADH_2$*** (see earlier figure for mechanism)



Phase 3: regeneration of $\boldsymbol{FADH_2}$ by $\boldsymbol{NADH}$ (see section 15.4B for mechanism)



In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of β-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, can form an intramolecular disulfide in its oxidized form.



b-mercaptoethanol (BME)

dithiothreitol (DTT)

? Exercise 15.7.1

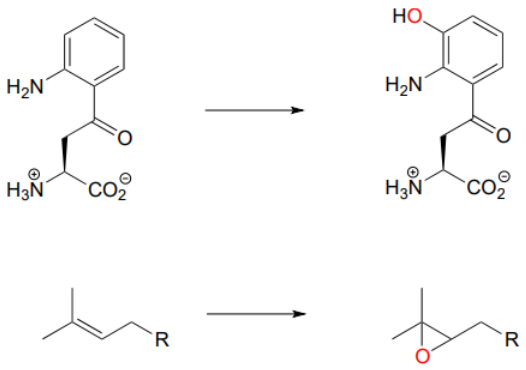
Draw structures of the oxidized (disulfide) forms of BME and DTT.

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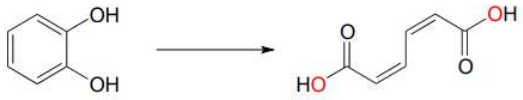
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15.7: Flavin-Dependent Monooxygenase Reactions - Hydroxylation, Epoxidation, and the Baeyer-Villiger Oxidation

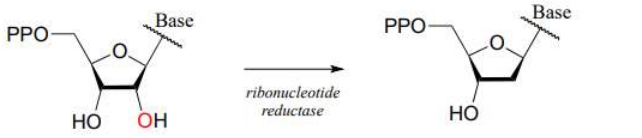
Up to now, the redox reaction examples we have seen have all been either hydrogenation/dehydrogenation transformations or interconversions between free thiols and disulfides. However, there are many important redox reactions in biological chemistry which do not fall under either of these descriptions. Oxygenase enzymes catalyze the insertion of one or two oxygen atoms from molecular oxygen (O_2) into an organic substrate molecule. Enzymes which insert a single oxygen atom are called monooxygenases. Below are two examples of biochemical transformations catalyzed by monooxygenase enzymes: one is a hydroxylation, the other is an epoxidation (an epoxide functional group is composed of a three-membered carbon-carbon-oxygen ring - epoxides are somewhat rare in biological organic chemistry but are very common and useful intermediates in laboratory organic synthesis).



Dioxygenase enzymes insert both oxygen atoms from O_2 into the substrate, and usually involve cleavage of an aromatic ring. Below is an example of a dioxygenase reaction, catalyzed by catechol dioxygenase:



In the reduction direction, reductases *remove* oxygen atoms, or sometimes other electronegative heteratoms such as nitrogen or halides. For example, DNA **deoxy**ribonucleosides are converted from their corresponding RNA ribonucleosides by the action of reductase enzymes:



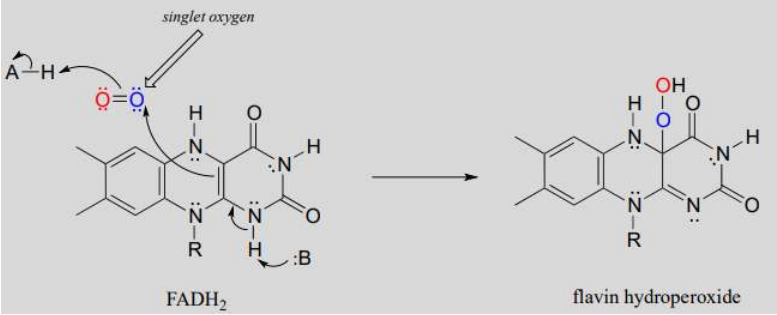
ribonucelotide diphosphate (RNA) — deoxyribonucleotide diphosphate (DNA)

Many oxygenase and reductase reactions involve the participation of enzyme-bound transition metals - such as iron or copper - and the mechanistic details of these reactions are outside the scope of our discussion. A variety of biochemical monooxygenase reactions, however, involve flavin as a redox cofactor, and we do have sufficient background knowledge at this point to understand these mechanisms. In flavin-dependent monooxygenase reactions, the key intermediate species is flavin hydroperoxide.

The term 'peroxide' refers to a functional group characterized by an oxygen-oxygen single bond. The simplest peroxide is hydrogen peroxide ($HOOH$) about which we will have more to say below. In flavin hydroperoxide, the peroxide group is linked to one of the carbons of the reactive triple-ring system of the coenzyme. A possible mechanism for the formation of flavin peroxide from $FADH_2$ and molecular oxygen is shown below.

Silverman, R.B. The Organic Chemistry of Enzyme-Catalyzed Reactions, p. 121-122, Scheme 3.33. 2000, Academic Press, San Diego.

Mechanism for the formation of flavin hydroperoxide:



(Note: Implicit in this mechanism is that the molecular oxygen first undergoes spin inversion from the triplet state to the higher energy 'singlet' state. You may recall from your general chemistry course that molecular oxygen exists in two states: 'singlet' oxygen has a double bond and no unpaired electrons, while 'triplet' oxygen has a single $O-O$ bond and two unpaired electrons - a kind of 'double radical'. Molecular orbital theory - and experimental evidence - show that the triplet state is lower in energy.

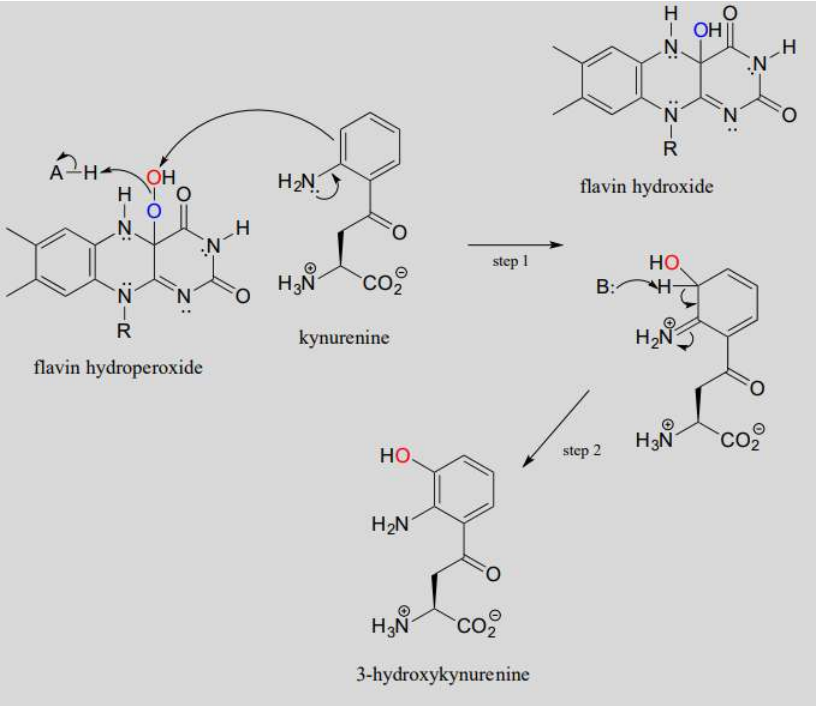


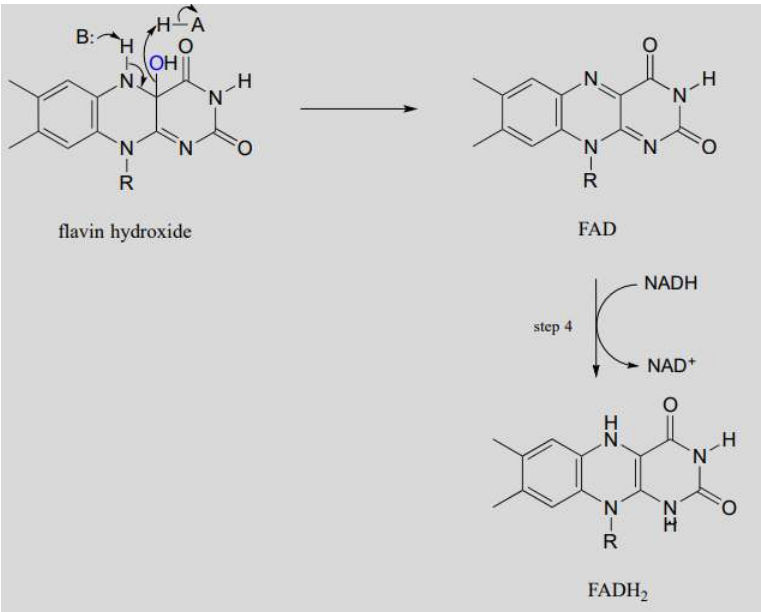
The mechanism shown above is one proposed mechanism, another proposal involves triplet oxygen reacting with flavin in a series of radical-intermediate, single-electron steps.)

Flavin hydroperoxide can be thought of as an activated form of molecular oxygen. Peroxides in general are potent oxidizing agents, because the oxygen-oxygen single bond is quite weak: only 138 kJ/mole, compared to 339 kJ/mol for a carbon-carbon bond, and 351 kJ/mol for a carbon-oxygen bond. When the 'outer' oxygen of flavin hydroperoxide (red in our figure above) comes into close proximity to the p-bonded electrons of an alkene or aromatic group, the $O-O$ bond will break, leaving an empty orbital on the outer oxygen to be filled by the p electrons - thus, a new carbon-oxygen bond is formed. This is what is happening in step 1 of a reaction in the tryptophan degradation pathway catalyzed by kynurenine 3-monooxygenase. Step 2 completes what is, mechanistically speaking, an electrophilic aromatic substitution reaction (section 14.4) with an peroxide oxygen electrophile.

Mechanism for the flavin hydroperoxide-dependent hydroxylation of kynurenine:

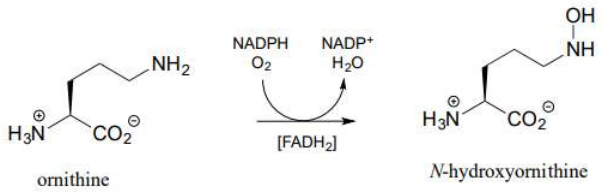
https://chem.libretexts.org/@go/page/393663





Elimination of water from the hydroxyflavin intermediate then leads to formation of ***FAD*** (step 3), which is subsequently reduced back to $FADH_2$ by ***NADH*** (step 4).

The ***N***-hydroxylation reaction below, which is part of the of the biosynthetic pathway of an iron-binding molecule in the pathogenic bacterium Pseudomonas aeruginosa, is mechanistically similar to the ***C***-hydroxylation reaction we just saw, except that the nucleophile is an amine nitrogen. Note that $FADH_2$ is shown in brackets below the reaction arrow, indicating that reduced flavin participates in the reaction but is not used up - rather it is regenerated in the active site at the end of the reaction cycle.



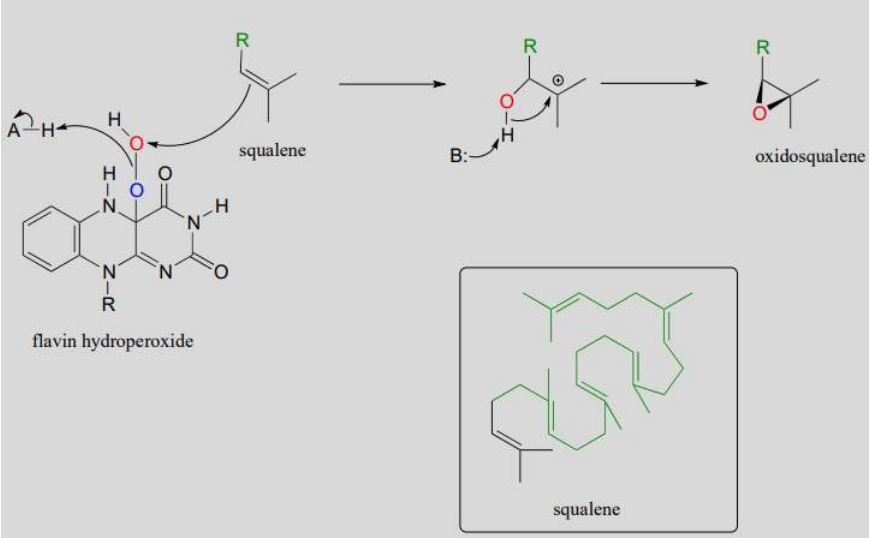
? Exercise 15.8.1

Draw arrows for the $N-O$ bond-forming step in the ornithine hydroxylation reaction above.

Epoxides, characterized by a three-membered ring composed of two carbons and one oxygen, are a very common and useful functional group employed in synthetic organic chemistry. Although rare, there are some interesting epoxide-forming reactions in biochemical pathways, catalyzed by flavin-dependent monooxygenase enzymes.

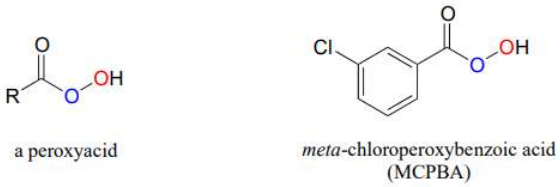
In a key step in the biosynthesis of cholesterol and other steroid compounds, an alkene is converted to an epoxide in a precursor molecule called squalene. Flavin hydroperoxide also serves as the direct oxidizing agent in this step:

Mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene:



Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which we discussed in section 14.5.

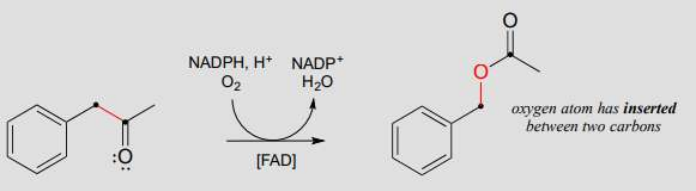
Epoxidation reactions have a parallel in the synthetic organic laboratory, and in fact are very important tools in organic synthesis. In laboratory epoxidations, peroxyacids are the counterpart to flavin hydroperoxide in biochemical epoxidations. meta-chloroperoxybenxoic acid (MCPBA) is a commonly used peroxyacid.



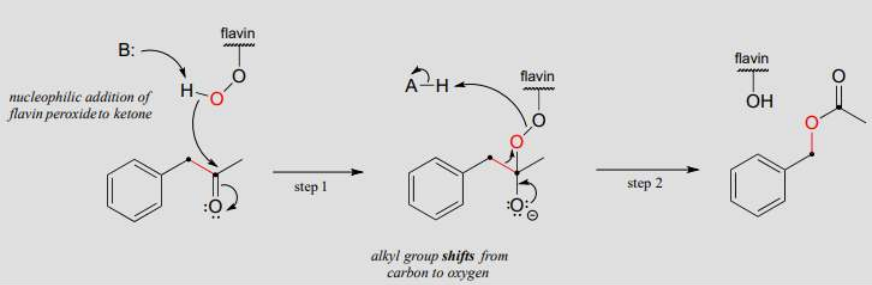
The Baeyer-Villiger oxidation, in which a ketone is converted to an ester through treatment with a peroxide reagent, is an extremely useful laboratory organic synthesis reaction discovered in the late 19th century. Recently, many biochemical examples of Baeyer-Villiger oxidations have been discovered: the reaction below, for example, is catalyzed by a monooxygenase in a thermophilic bacterium:

(Proc. Natl. Acad. Sci. U.S.A. 2004, 101, 13157)

A Baeyer-Villiger oxidation:



Mechanism:



The Baeyer-Villiger mechanism is differs significantly from the hydroxylation reactions we saw earlier, although flavin hydroperoxide (abbreviated in the above figure) still plays a key role. Here, the peroxide oxygen is a nucleophile, rather than an electrophile, attacking the ketone carbonyl in step 1. Step 2 is a rearrangement, similar in many ways to the hydride and alkyl shifts we learned about in section 14.5. The electrons in the red bond in the figure shift over one atom: from the carbonyl carbon to the outer peroxide oxygen. The end result is that an oxygen atom, from O_2 via flavin hydroperoxide, has been inserted between the carbonyl carbon and a neighboring methylene (CH_2) carbon, forming an ester.

Note that in the reaction mechanism above, the ketone substrate is asymmetric: on one side of the carbonyl there is a benzyl group (CH_2-phenyl), and on the other side a methyl group. Note also that it is the benzyl group, not the methyl, that shifts in step 2 of the mechanism. For reasons that are not yet well understood, in Baeyer-Villiger reactions the alkyl group with higher carbocation stability has a higher migratory aptitude: in other words, it has a lower energy barrier for the shifting step.

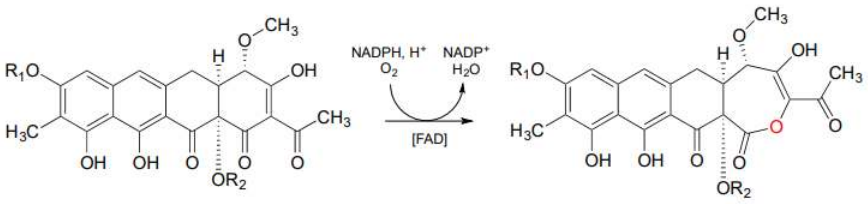
? Exercise 15.8.2

Draw the product of a hypothetical Baeyer-Villiger reaction involving the same substrate as the above figure, in which the methyl rather than the benzyl group shifts.

? Exercise 15.8.3

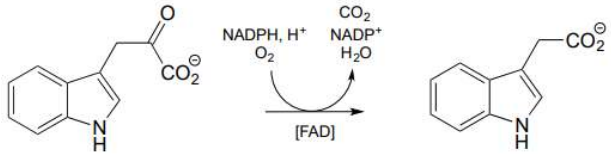
Draw the likely major product of a hypothetical Baeyer Villiger reaction starting with 2-methylcyclopentanone as the substrate. Take into account the idea of migratory aptitude.

Below is another example of a Baeyer-Villiger reaction in which a cyclic ketone is oxidized to a lactone (cyclic ester). Notice that oxygen insertion expands the ring from 6 to 7 atoms. This is the third-to-last step in the biosynthesis of the anti-cancer agent mithromycin in some bacterial species (ACS Chem. Biol. 2013, 8, 2466).



(R_1 and R_2 are triglycerides)

Yet another variety of flavin-dependent monooxygenase, which bears some mechanistic similarity to the Baeyer-Villiger oxidation, is the decarboxylative reaction below from biosynthesis of the plant hormone auxin: (J. Biol. Chem. 2013, 288, 1448)



auxin

? Exercise 15.8.4

Propose a mechanism for the above reaction, starting with flavin hydroperoxide.

This page titled 15.7: Flavin-Dependent Monooxygenase Reactions - Hydroxylation, Epoxidation, and the Baeyer-Villiger Oxidation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Tim Soderberg via source content that was edited to the style and standards of the LibreTexts platform.

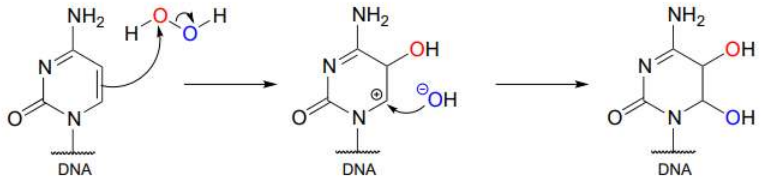
- **15.8: Flavin-Dependent Monooxygenase Reactions - Hydroxylation, Epoxidation, and the Baeyer-Villiger Oxidation** by Tim Soderberg is licensed CC BY-NC-SA 4.0. Original source: https://digitalcommons.morris.umn.edu/chem_facpubs/1/.

15.8: Hydrogen Peroxide is a Harmful - Reactive Oxygen Species

We get our energy from the oxidation of organic molecules such as fat and carbohydrates, as electrons from these reduced compounds are transferred to molecular oxygen, thereby reducing it to water. Reducing O_2, however, turns out to be a hazardous activity: harmful side products called reactive oxygen species (ROS) are inevitably formed in the process. Recall from the story introducing this chapter that ROS appear to play an important role in the damage that occurs to the brain immediately after a concussion.

Hydogen peroxide, $HOOH$, is an ROS. Recall peroxides are potent oxidizing agents due to the weakness of the $O-O$ single bond. It is this same weak bond that causes hydrogen peroxide to be dangerous when produced in our bodies, as it can react spontaneously with oxygen or nitrogen nucleophiles and p bonds.

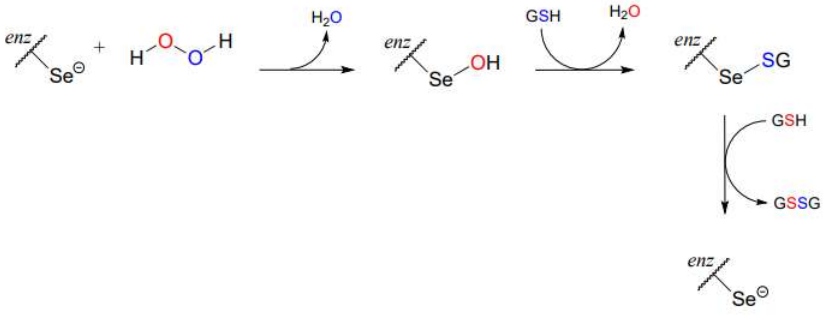
Peroxide formed as a by-product of our metabolism is particularly harmful when it oxidizes DNA bases. In just one of many known examples of oxidative damage, the DNA base cytosine is oxidized to thymine glycol in the presence of hydrogen peroxide. Although mechanistic details for reactions such as these are not yet well understood, one possibility is electrophilic addition:



cytosine thymine glycol

Our bodies have evolved ways to dispose of the harmful reactive oxygen species that are continuously being formed (the only way to stop the production of ROS is to stop breathing oxygen!). Glutathione peroxidase is a remarkable enzyme in that its active site contains selanocysteine, a modified cysteine residue in which the side chain sulfur is replaced by selenium (selenium is very toxic, but we do need a very small amount of it in our diet). Look at a periodic table: selenium is below oxygen and sulfur in the same column. If you think back to the vertical periodic trends in nucleophilicity (section 8.2), you'll recall that just as a thiol is a better nucleophile than an alcohol, a selanol (RSeH) is even more nucleophilic than a thiol. Moreover, the vertical periodic trend in acidity (section 7.3) tells us that a selenol should be more acidic than a thiol - in fact, the pKa of a selenocysteine is about 5.5, meaning that it is mostly in its deprotonated state at physiological pH, making it even more nucleophilic.

Glutathione peroxidase very efficiently catalyzes the reduction of hydrogen peroxide to water and the oxidation of glutathione (GSH) to GSSG, beginning with nucleophilic attack by the enzymatic selanocysteine on a peroxide oxygen. The intermediates in this process are shown below: each step can be thought of as a concerted nucleophilic displacement similar to those that take place in a disulfide exchange reaction.



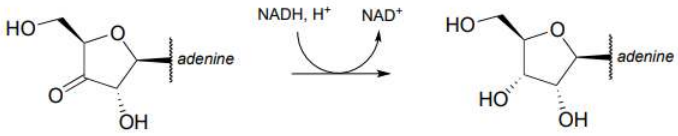
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15.E: Oxidation and Reduction Reactions (Exercises)

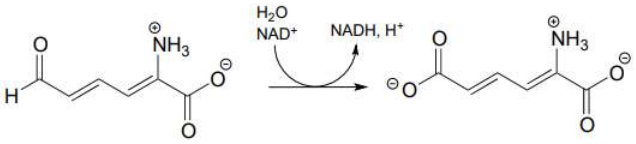
P15.1: Show a mechanism for each of the redox reactions below. Do not abbreviate the reactive parts of the redox coenzyme.

a)

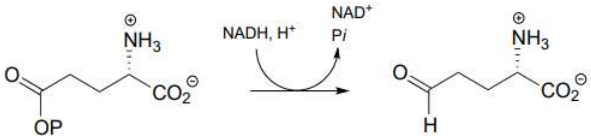


adenosine

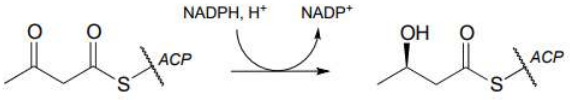
b)



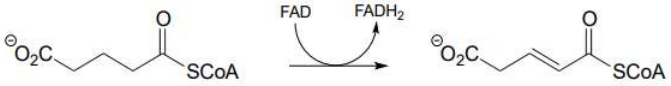
c)



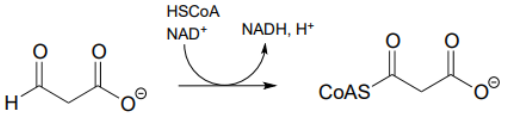
d)



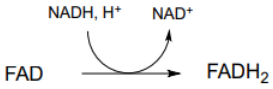
e)



f)



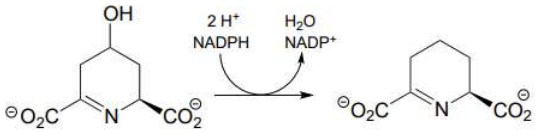
g) regeneration of reduced flavin by $NADH$):



h) In reaction (a), near which face of the substrate is the cofactor bound in the active site?

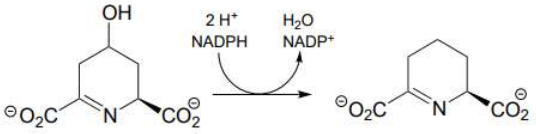
i) In reaction (d), near which face of the product is the cofactor bound in the active site?

P15.2: In the reactions below ((EC 2.7.2.4; EC 1.2.1.11) , the side chain of aspartate is altered, but the main peptide chain is not affected. Show the most probable structure of species A and B.

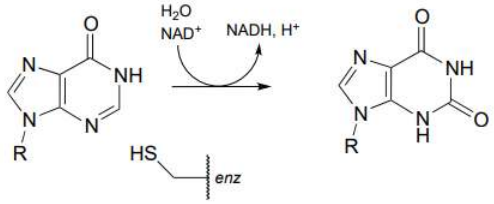


P15.3: Propose complete mechanisms for the following reactions.

a. (EC 1.3.1.26, from lysine biosynthesis)

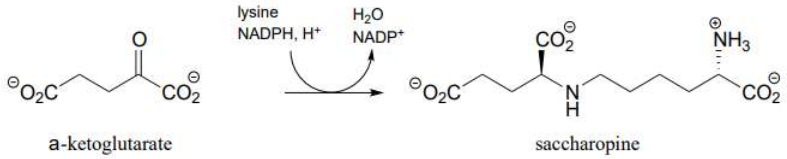


b. (EC 1.1.1.205, from guanosine ribonucleotide biosynthesis) The mechanism involves a covalent cysteine-linked enzyme-substrate intermediate.



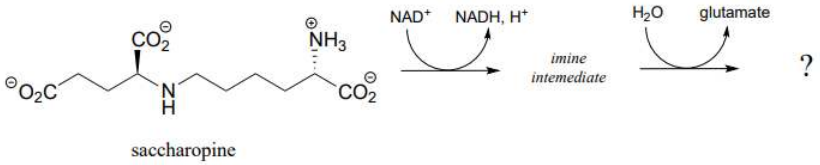
P15.4: The first step in the lysine degradation pathway is a reductive condensation with a-ketoglutarate to form an intermediate called saccharopine. (EC 1.5.1.8)

a. Propose a mechanism for this transformation.



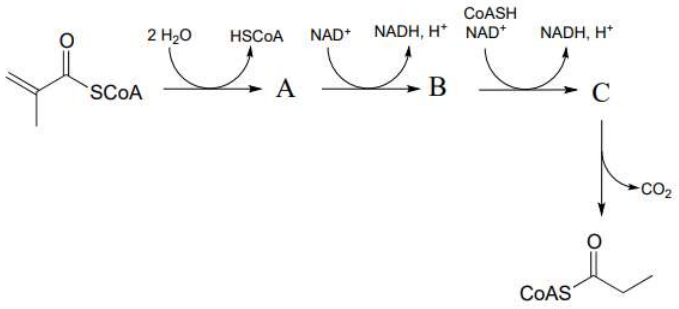
a-ketoglutarate saccharopine

b. Saccharopine (see part (a) above) is then broken up to yield glutamate and a second product that contains an aldehyde group. Predict the structure of this second product, and propose a likely mechanism for the reaction which involves and imine intermediate. (EC 1.5.1.10)

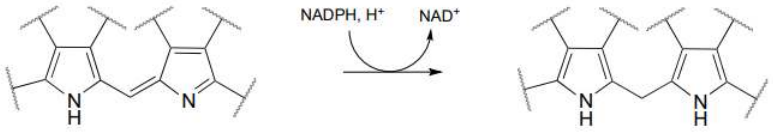


saccharopine

P15.5: Predict the structures of species A and B in the pathway below.



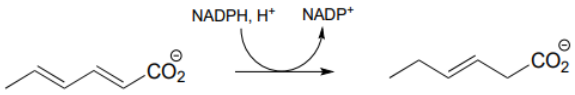
P15.6: Bilirubin, the molecule responsible for the yellowish color of bruises, is formed from the ***NADPH***-dependent hydrogenation of a double bond in biliverdin (EC 1.3.1.24), which is a product of heme degradation (heme is an iron-containing coenzyme in the oxygen-carrying blood protein hemoglobin). Draw a likely mechanism for this reaction.



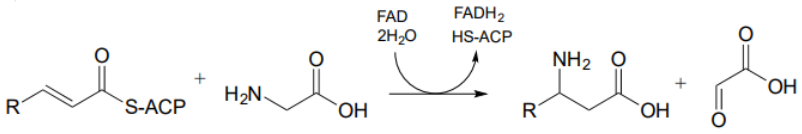
biliverdin bilirubin

P15.7: Draw a likely mechanism for each of the reactions below.

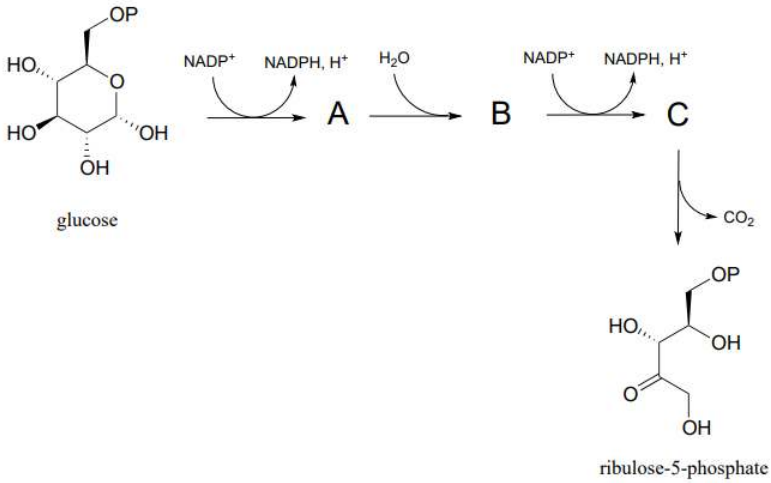
a. From the oxidation of polyunsaturated fatty acids:



b.

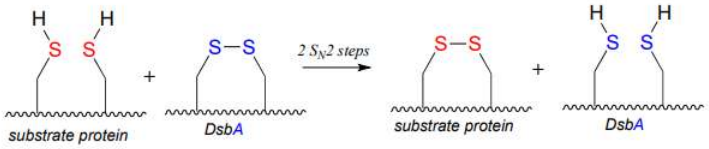


P15.8: Predict the structures of pathway intermediates A, B, and C:

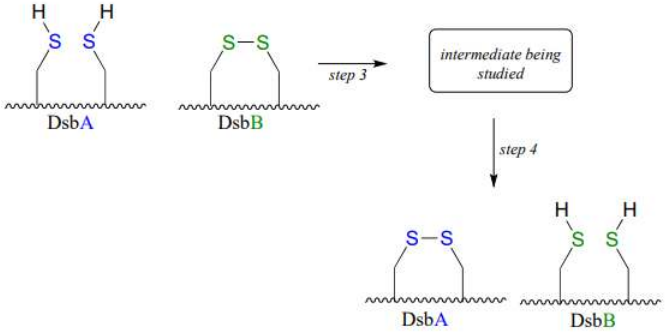


glucose ribulose-5-phosphate

P15.9: An enzyme called DsbA (EC1.8.4.2) is responsible for the formation of disulfide bonds in bacterial proteins. The process - which can be thought of as a 'disulfide exchange', involves the cleavage of a disulfide bond between two active site cysteines in DsbA. It is accomplished through two successive S_N2 displacements.



DsbA is then returned to it's starting (disulfide) state through a second disulfide exchange reaction with another protein called DsbB:

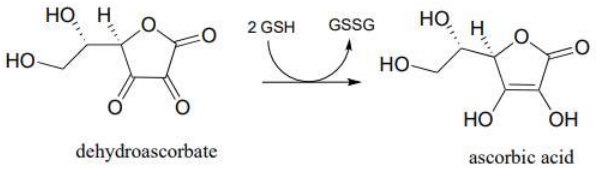


Scientists were interested in studying the intermediate species formed in step 3, but found that it is very short-lived and difficult to isolate. In order to address this problem, they ran the reaction with a synthetic analog of DsbB that contained an unnatural bromoalanine amino acid in place of one of the active site cysteines.

a. Draw a complete mechanism for the disulfide exchange reaction between DsbA and DsbB.
b. Show how the bromoalanine-containing DsbB analog allowed for the isolation of an intermediate that resembles the true, short-lived intermediate. (J. Am. Chem. Soc. 2004, 126, 15060; J. Nat. Prod. 2001, 64, 597).

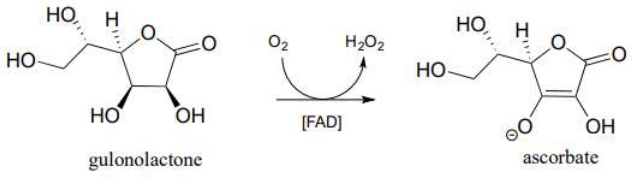
P15.10:

a. In chapter 16 we will learn how ascorbate (vitamin C) acts as a 'radical scavenger' antioxidant to protect our cells from damage by free radical species. When ascorbate scavenges a radical, it ends up being converted to dehydroascorbate . One possible metabolic fate of dehydroascorbate is to be recycled back to ascorbate through an enzyme-free reaction with glutathione. Biocemistry 1999, 38, 268.



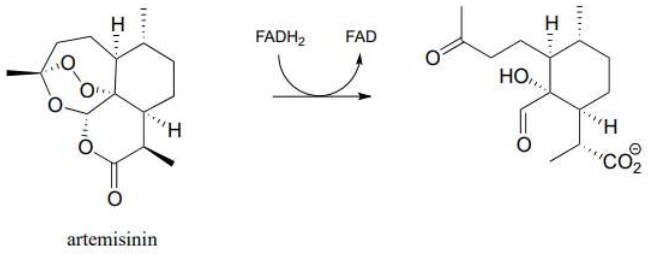
Suggest a likely mechanism for the enzyme-free reaction.

b. In the introduction to chapter 16, we will learn that most animals - but not humans - are able to synthesize their own ascorbate. Humans cannot synthesize vitamin C because we lack the enzyme for the final step in the biosynthetic pathway, gulonolactone oxidase:



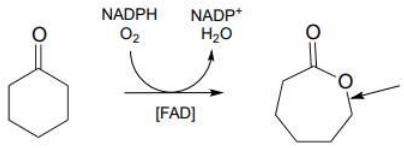
This enzyme uses FAD as an oxidizing agent, and $FADH_2$ is oxidized back to FAD at the end of the catalytic cycle by molecular oxygen, with hydrogen peroxide as a side product. Draw out a likely mechanism showing how gulonolactone is converted to ascorbate, and how FAD is regenerated.

c. Artemisinin is a naturally occurring compound with demonstrated antimalarial properties. It is thought to act by depleting the malaria-causing microbe's store of reduced flavin, thus disrupting the redox balance. The relevant reaction is shown below:



Draw mechanistic arrows for the step as shown above. (Molecules 2010, 15, 1705)

d. Draw the mechanistic step in the reaction below in which the C-O bond indicated by the arrow in the figure below is formed.



P15.11: Methanogens are a class of microorganisms in the domain archaea which inhabit a diversity of anaerobic (oxygen-lacking) environments, from the intestines of humans, to swamp mud, to the base of deep sea hot water vents. They obtain energy by reducing carbon dioxide to methane:

$$CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O + \text{energy} \tag{15.E.1}$$

Methanogenesis', like the oxidation of glucose in animals, is not accomplished in a single reaction - it requires a long series of enzymatic steps, and involves the participation of several unique coenzymes (if you are interested in learning more, see FEMS Microbiol. Rev. 1999, 23, 13 for a detailed review of the enzymatic reactions of methanogenesis).

The oxidation of methane to carbon dioxide when you burn natural gas for heating your house is obviously an exergonic process. How then is it possible that reducing carbon dioxide to methane could also be exergonic? Explain.

Multistep pathway prediction problems

In chapters 12 and 13, we were introduced to the challenge of mapping out potential multi-step transformations using the retrosynthesis approach, where we start with the more complex molecule and take it apart step be step. These problems have necessarily involved hypothetical, generalized transformations, because many of the reaction types involved in actual biochemical transformations were as-yet unfamiliar to us.

We have now reached a point in our study of organic reactivity where we can look at an actual metabolic pathway and probably recognize most of the reactions taking place - so were are ready to try our hand at mapping out real metabolic pathways.

Before we dive in, you may want to go back to the retrosynthesis interchapter and review the key elements of the retrosynthetic approach. You may (or may not) also need a little more practice with some simpler, shorter, hypothetical problems, similar to what

we worked on in the last three chapters but incorporating some of the redox reactions that we have just finished learning about. These are provided in problems 15.12 and 15.13 below.

As before, your job is to draw out a 'pathway diagram' for each transformation, using the 'arrow in - arrow out' convention to indicate the role of other necessary participants in each reaction, such as ATP, ***NADH***, water, or another organic molecule. An example for a simple two-step pathway is provided in problem 15.12 below. A three-step pathway would of course show two intermediate compounds.

Remember, it is most important that your proposed pathway be chemically reasonable - in other words, each hypothetical reaction that you propose should be very similar to a reaction pattern that we have seen in chapters 8-15. You should be able to put a name on each step: for example, 'step 1 is a Claisen condensation; step 2 is a ketone reduction', and so forth.

Also remember that there is usually no one correct way to approach problems like this - they are puzzles to solve, and success will be dependent in large part on having a solid grasp on the chemical 'tools' available to us: in other words, the biochemical reaction types that we have been studying, starting with nucleophilic substitutions in chapter 8.

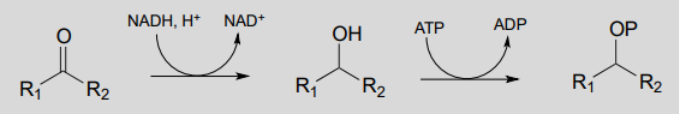
P15.12: Hypothetical 2-step transformations:

Each of the generalized transformations below would be expected to require two enzymatic steps. Draw a reasonable pathway diagram for each transformation.

Example:

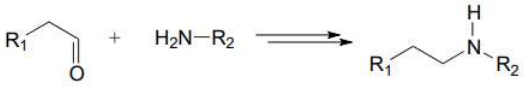


Diagram:

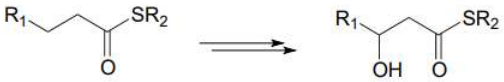


The first step is a nicotinamide-dependent ketone reduction/hydrogenation, and step 2 is ATP-dependent phosphorylation (ie. a kinase reaction). Note that the reducing agent in the first step could also be ***NADPH***)

a)



b)

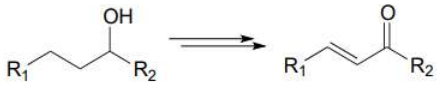


c)

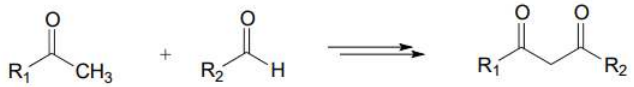


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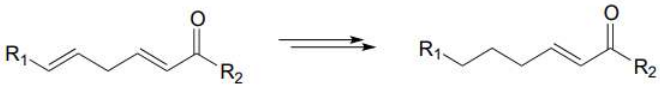
d)



e)



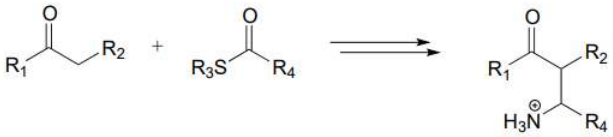
f)



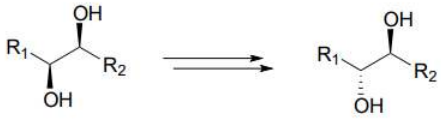
P15.13: Hypothetical 3-step transformations:

Each of the generalized transformations below would be expected to require three enzymatic steps. Draw a reasonable pathway diagram for each transformation.

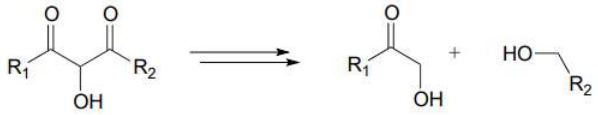
a)



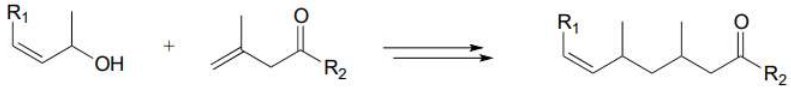
b)



c)



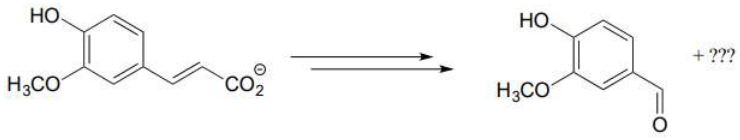
d)



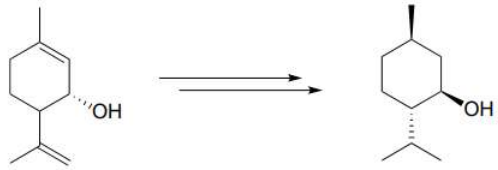
P15.14: Now, let's try our hand at predicting the steps of some actual metabolic pathways. For each, draw a complete pathway diagram. As needed, use any of the coenzymes we have studied, water, and ammonia.

Note: you will probably find these quite challenging! Do not expect to be able to figure them out in a few minutes - rather, think of them as puzzles to work on over a period of time, sharing ideas and strategies with classmates. Remember, if one side of the transformation is larger or more complex, start there and work towards the simpler molecules. It is also a good idea, when applicable, to start the process by a) counting carbons on each side of the transformation, and b) identifying the key bond being formed (or broken) in the transformation.

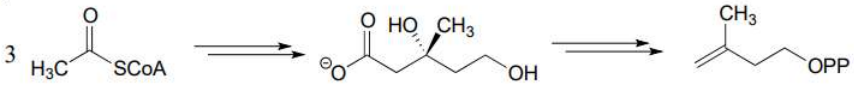
a)



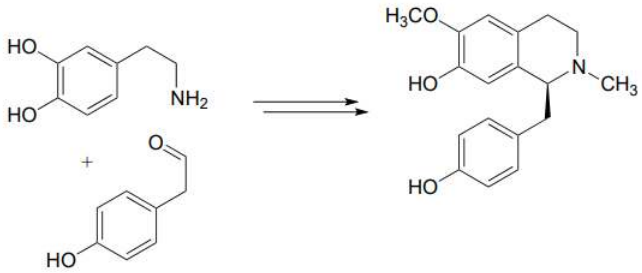
b)



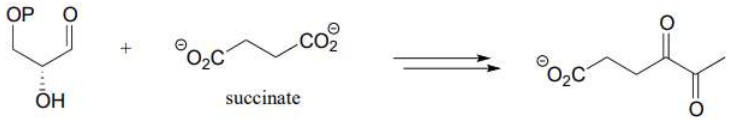
c)



e)



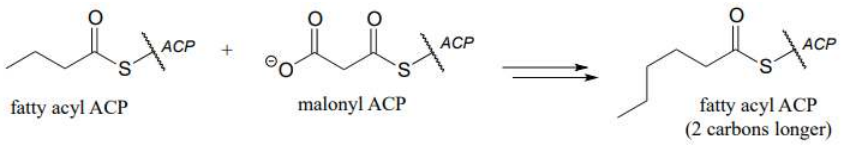
f)



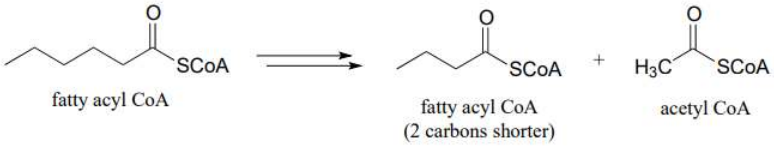
glyceraldehyde-3-phosphate

P15.15: Propose a pathway diagram for each of the metabolic pathways below. Note that some pathways contain steps that will be unfamiliar to you, and are therefore provided already.

a. one cycle of fatty acid biosynthesis:

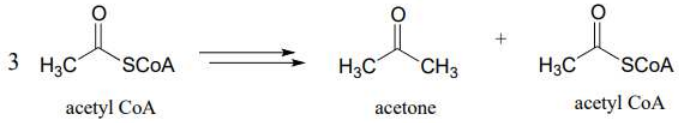


b. one cycle of fatty acid degradation:

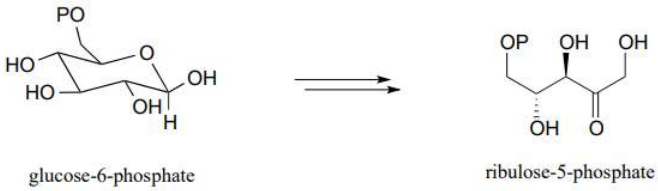


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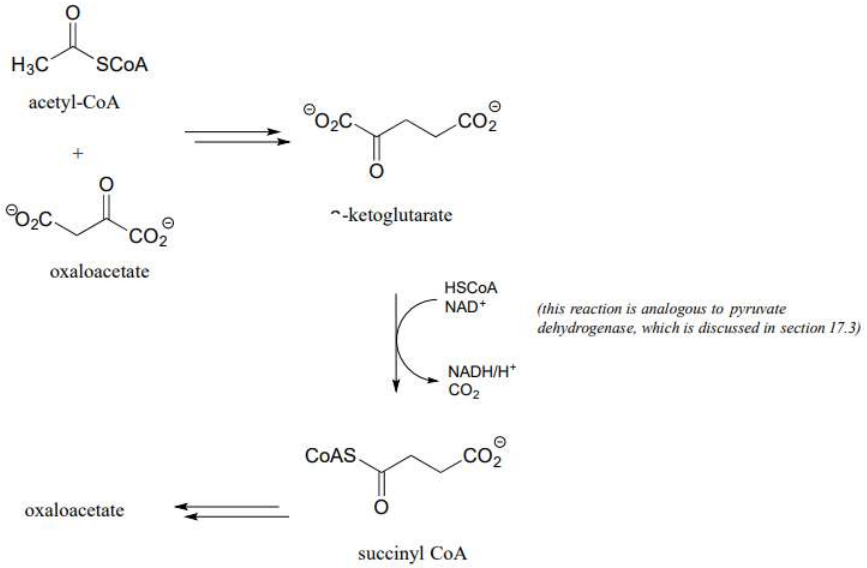
c. Diabetics and people who adopt an extreme low-carbohydrate diet sometimes have breath that smells like acetone, due to 'ketone body' formation that occurs when acetyl-***CoA*** from fatty acid oxidation (see part (b) above) is not able to enter into the citric acid cycle. Draw a pathway diagram showing how three molecules of excess acetyl ***CoA*** combine to form acetone (all three acetyl-***CoA*** molecules first link together, but one is left over at the end of the process).



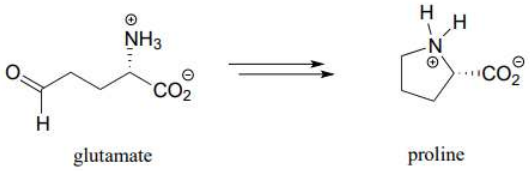
d. Pentose phosphate pathway (oxidative branch):



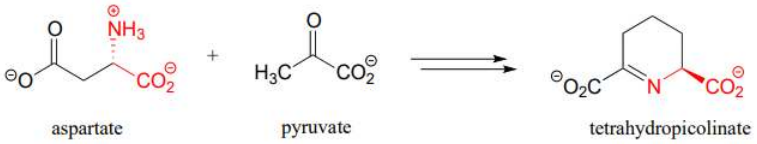
e. Citric acid (Krebs) cycle:



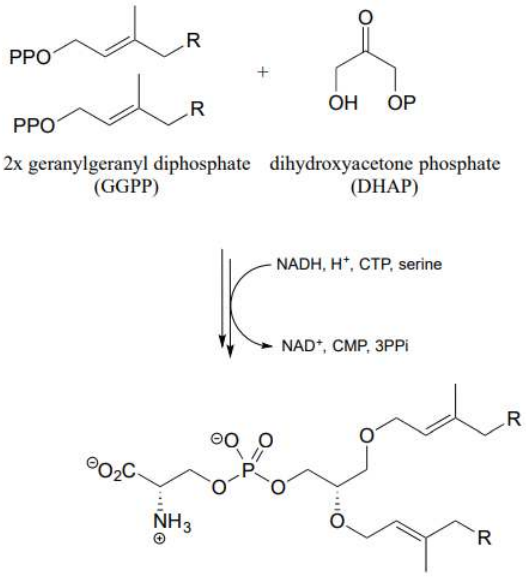
f. proline biosynthesis:



g. First half of lysine biosynthesis:



h. From the biosynthesis of membrane lipid in archaea: J. Bacteriol. 2003, 185, 1181



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15.S: Oxidation and Reduction Reactions (Summary)

Before moving on to the next chapter, you should be able to:

- Recognize when an organic molecule is being oxidized or reduced, and distinguish between redox and non-redox organic reactions.
- Draw complete mechanisms for the following reaction types, including the structure of the reactive part of the redox coenzyme (it is strongly recommended that you commit to memory the structures of the reactive parts of the nicotinamide and flavin coenzymes).
  - oxidation of an alcohol to an aldehyde or ketone
  - oxidation of an amine to an imine
  - oxidation of an aldehyde to a carboxylic acid derivative (usually a thioester or carboxylate)
  - oxidation of an alkane to an alkene at the a,b position relative to a carbonyl or imine
  - reduction of an aldehyde or ketone to an alcohol
  - reduction of an imine to an amine
  - reduction of a carboxylic acid derivative to an aldehyde
  - reduction of an α,β - conjugated alkene to an alkane
  - oxidation of two thiol groups to a disulfide in a disulfide-exchange type reaction
  - reduction of a disulfide group by flavin
  - flavin hydroperoxide-dependent hydroxylation, epoxidation, and Baeyer-Villiger reactions
  - reduction of FAD (or FMN) to $FADH_2$ (or $FMNH_2$) by $NAD(P)H$.
  - spontaneous oxidation of an alkene group in a biomolecule by hydrogen peroxide
  - reduction of hydrogen peroxide by glutathione peroxidase
- In addition, you should be able to draw complete mechanisms for hydrogenation-dehydrogenation and disulfide exchange reactions that we have not yet seen specific examples of, based on your understanding of the chemistry involved in these reaction types and organic reaction patterns in general. Several exercises and end-of-chapter problems provide opportunities practice with inferring and drawing mechanisms of less familiar redox reactions.
- Given a multistep pathway diagram, you should be able to recognize the transformations taking place and fill in missing intermediate compounds or reagents (problem 15.5 is an example of this type).
- You should be working on gaining proficiency at solving multi-step pathway elucidation problems, such as those at the end of this chapter's problem section.

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CHAPTER OVERVIEW

16: Radical Reactions

16.0: Prelude to Radical Reactions
16.1: Overview of Single-Electron Reactions and Free Radicals
16.2: Radical Chain Reactions
16.3: Useful Polymers formed by Radical Chain Reactions
16.4: Destruction of the Ozone Layer by a Radical Chain Reaction
16.5: Oxidative Damage to cells, Vitamin C, and Scurvy
16.6: Flavin as a One-Electron Carrier
16.E: Radical Reactions (Exercises)

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16.0: Prelude to Radical Reactions



Introduction

Imagine that you are an 18th century British sailor about set out with Commodore George Anson to raid Spanish shipping fleets in the Pacific. You know full well that you are signing up for a long and arduous ordeal, with months of constant seasickness, bad food, cramped, unsanitary conditions, and brutal warfare. You are mentally ready for these hardships, but what you are not prepared for is to watch your own body rot away – to literally fall apart.

Below is a description of the suffering endured by many sailors of the time:

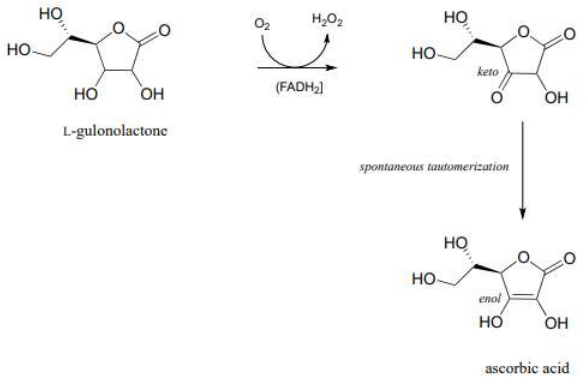
> *Some lost their very substance and their legs became swollen and puffed up while the sinews contracted and turned coal-black and, in some cases, all blotched with drops of purplish blood. Then the disease would creep up to the hips, thighs and shoulders, arms and neck. And all the sick had their mouths so tainted and their gums so decayed that the flesh peeled off down to the roots of their teeth, which almost all fell out. . .*

There were devastating neurological as well as physiological effects. Scurvy had the ability to inhibit a person's normal restraints on emotion: they became intensely homesick and nostalgic, wept at the slightest disappointment, and screamed in agony upon smelling the scent of flower blossoms drifting across the water from a nearby shore.

The disease afflicting the sailors was scurvy, which we now know is caused by a deficiency of vitamin C in the diet. European sea voyagers in the 18th century and earlier subsisted mainly on a diet of salted meat, hard biscuits, pea soup, oatmeal, and beer. After the first couple of weeks at sea, fresh fruits and vegetables - and the nutrients they contained – were all consumed or spoiled. The salted meat and hardtack diet provided salt and calories, but little else of nutritional value.

Although it is rare now, scurvy has plagued sailors for centuries, with records of its occurrence on ships going back as far as the 15th century voyages of Magellan and Vasco de Gama, both of whom lost up to three quarters of their crew to the disease on long ocean crossings. Various cultures made the connection between scurvy and diet, and learned effective preventative measures: sailors with the 16th century French explorer Jacques Cartier, for example, were cured of their scurvy upon arriving in Canada and taking the advice of native people to eat the leaves and bark of pine trees. These were lessons, unfortunately, that often had to be relearned time and again, as the knowledge gained by one culture was not effectively recorded and passed along to others.

Vitamin C, or ascorbic acid as it is known to chemists, plays an essential helping role in a variety of essential biochemical reactions. Most living things are able to synthesize ascorbic acid – the exceptions include humans and other higher primates, several species of bats, and some rodents such as guinea pigs and capybaras. Humans lack the last enzyme in the ascorbic acid biosynthetic pathway, L-gulonolactone oxidase. (EC 1.1.3.8) (You were invited to propose the mechanism for this redox reaction in problem 15.10).



Because we cannot make our own ascorbic acid, we need to get it in our diet. It is abundant in many plant-based foods, citrus fruits in particular. The traditional diet of the Inuit people of the arctic region contains virtually no plant products, but vitamin C is obtained from foods such as kelp, caribou livers, and whale skin. For a time in the 18th century, the observation that citrus fruits quickly cured scurvy led to the practice of including in a ship's stores a paste prepared from boiled lemon juice. Unfortunately, ascorbic acid did not survive the boiling process, rendering the paste ineffective against scurvy. Captain James Cook, the legendary explorer and the first European to make it to the east coast of Australia and the Hawaiian islands, brought along sourkraut (fermented cabbage), a somewhat more effective vitamin C supplement. According to his own account, Cook's sailors at first refused to eat the pungent preparation, so the captain engaged in a little psychological trickery: he declared that it would only be served to officers. The enlisted sailors quickly took offense, and demanded their own sourkraut ration. Later, the British navy famously adopted the practice of adding lemon or lime juice to their ships' rum rations, leading to the birth of the slang term 'Limey' used by European and American sailors to refer to their British counterparts.

The biochemical role of ascorbic acid is to facilitate the transfer of single electrons in a variety of redox reactions - note here the emphasis on single electrons, as opposed to the redox reactions we studied in chapter 15 in which electrons were transferred in pairs. The subject of this chapter is single-electron chemistry, and the free radical intermediates that are involved in single electron reaction steps.

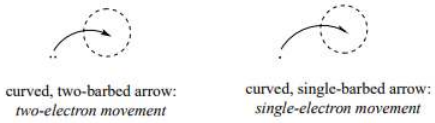
Later in this chapter we will learn the chemical details of why ascorbic acid deficiency causes scurvy, how the act of breathing makes you get old, how polystyrene packing foam is made, and other interesting applications of single-electron chemistry. But first we need to cover some basics ideas about single electron chemical steps, and the free radical intermediates that result from them.

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16.1: Overview of Single-Electron Reactions and Free Radicals

Beginning with acid-base reactions in chapter x and continuing though the chapters on nucleophilic substitution, carbonyl addition, acyl substitution, a-carbon chemistry, and electrophilic reactions , we have been studying reaction mechanisms in which both electrons in a covalent bond or lone pair move in the same direction. In this chapter, we learn about reactions in which the key steps involve the movement of single electrons. Single electron movement is depicted by single-barbed 'fish-hook' arrows (as opposed to the familiar double-barbed arrows that we have been using throughout the book to show two-electron movement).

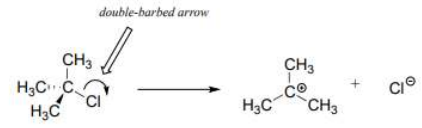


Single-electron mechanisms involve the formation and subsequent reaction of free radical species, highly unstable intermediates that contain an unpaired electron. Free radicals are often formed from homolytic cleavage, an event in which the two electrons in a breaking covalent bond move in opposite directions. The bond in molecular chlorine, for example, is subject to homolytic cleavage when chlorine is subjected to heat or light. The result is two chlorine radicals. Note that each radical has a formal charge of zero.



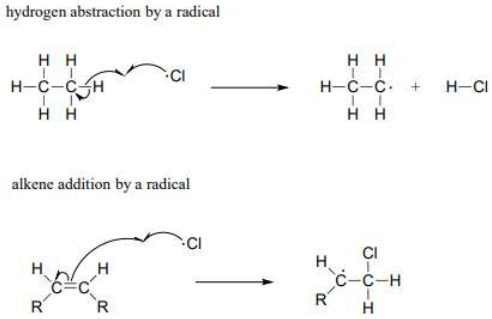
homolytic cleavage
(two electrons in breaking bond go with different atoms)

In contrast, essentially all of the reactions we have studied up to now involve bond-breaking events in which both electrons move in the same direction: this is called heterolytic cleavage.

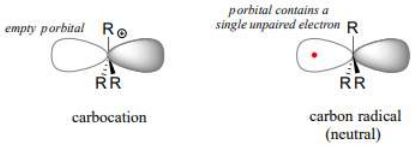


heterolytic cleavage
(both electrons in breaking bond go with the same atom)

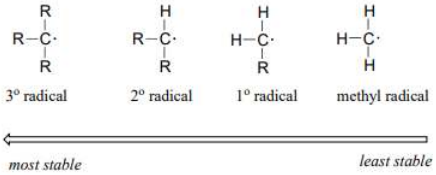
Two other homolytic cleavage reactions that we will see in this chapter can be described as 'radical hydrogen atom abstraction' and 'radical alkene addition':



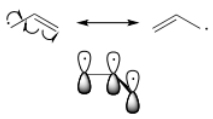
Single-electron reaction mechanisms involve the formation of radical species, and in organic reactions these are often carbon radicals. A carbon radical is sp^2 hybridized, with three s bonds arranged in trigonal planar geometry and the single unpaired electron occupying an unhybridized p orbital. Contrast this picture with a carbocation reactive intermediate, which is also sp^2 hybridized with trigonal planar geometry but with an empty p orbital.



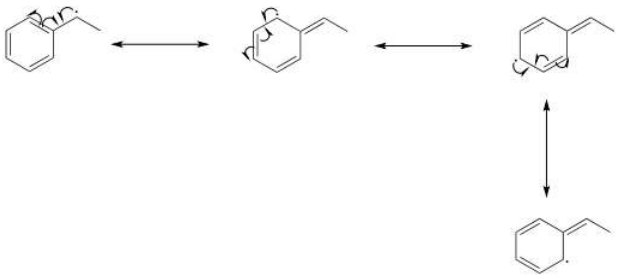
When we studied electrophilic reactions in chapter 14, a major concern when evaluating possible mechanisms was the stability of any carbocation intermediate(s). Likewise, the stability of proposed radical intermediates is of great importance when evaluating the likelihood of possible single-electron mechanisms. Fortunately, the trend in the stability of carbon radicals parallels that of carbocations (section 8.5): tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, are electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups.



Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron (just like a positive or negative charge) can be delocalized over a system of conjugated π bonds. An allylic radical, for example, can be pictured as a system of three parallel p orbitals sharing three electrons.

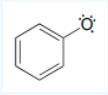


The drawing below shows how a benzylic radical is delocalized to three additional carbons around the aromatic ring:



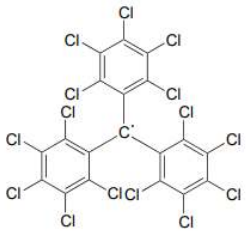
? Exercise 16.2.1

Just as phenolate ions are less reactive (less basic) than alkoxide ions, phenolic radicals are less reactive than alkoxide radicals. Draw one resonance contributor of a phenolic radical showing how the radical electron is delocalized to a ring carbon. Include electron-movement arrows.



While radical species are almost always very reactive and short-lived, in some extreme cases they can be unreactive. One example of an inert organic radical structure is shown below.

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The already extensive benzylic resonance stabilization is further enhanced by the fact that the large electron clouds on the chlorine atoms shield the radical center from external reagents. The radical is, in some sense, inside a protective 'cage'.

? Exercise 16.2.2

Draw a resonance contributor of the structure above in which the unpaired electron is formally located on a chlorine atom (include electron movement arrows)

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16.2: Radical Chain Reactions

Because of their high reactivity, free radicals have the potential to be extremely powerful chemical tools - but as we will see in this chapter, they can also be extremely harmful in a biological/environmental context. Key to understanding many types of radical reactions is the idea of a **radical chain reaction**.

Radical chain reactions have three distinct phases: initiation, propagation, and termination. We'll use a well-known example, the halogenation of an alkane such as ethane, to illustrate. The overall reaction is:

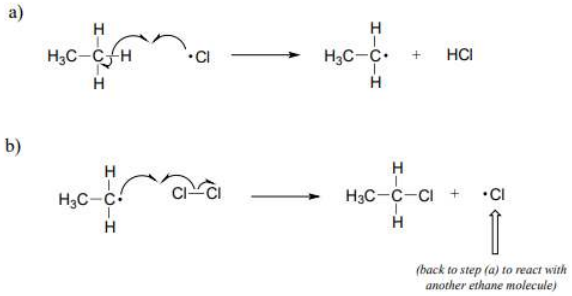
$$CH_3CH_3 + Cl_2 \underset{h\nu \text{ or } \Delta}{\rightarrow} CH_3CH_2Cl + HCl \cdots h\nu \text{ means light } \Delta \text{ means heat} \tag{16.2.1}$$

The initiation phase in a radical chain reaction involves the homolytic cleavage of a weak single bond in a non-radical compound, resulting in two radical species as products.

Often, heat or light provides the energy necessary to overcome an energy barrier for this type of event. The initiation step in alkane halogenation is homolysis of molecular chlorine (Cl_2) into two chlorine radicals. Keep in mind that that virtually all radical species, chlorine radicals included, are highly reactive.

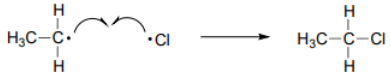
$$Cl \curvearrowright\!\curvearrowright Cl \rightarrow 2Cl \tag{16.2.2}$$

The **propagation** phase is the 'chain' part of chain reactions.



Once a reactive free radical (chlorine radical in our example) is generated in the initiation phase, it will react with relatively stable, non-radical compounds to form a new radical species. In ethane halogenation, a chlorine radical generated in the initiation step first reacts with ethane in a hydrogen abstraction step, generating HCl and an ethyl radical (part a above). Then, the ethyl radical reacts with another (non-radical) Cl_2 molecule, forming the chloroethane product and regenerating a chlorine radical (part b above). This process repeats itself again and again, as chlorine radicals formed in part (b) react with additional ethane molecules as in part (a).

The termination phase is a radical combination step, where two radical species happen to collide and react with each other to form a non-radical product and 'break the chain'. In our ethane chlorination example, one possible termination event is the reaction of a chlorine radical with an ethyl radical to form chloroethane.

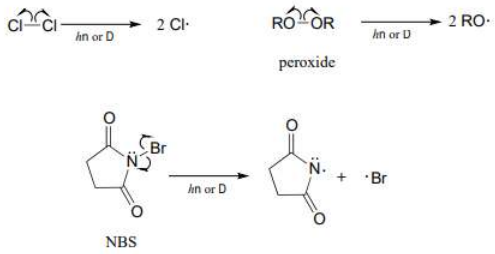


? Exercise 16.3.1

Draw two alternative chain termination steps in the ethane chlorination chain reaction. Which one leads to an undesired product?

Because radical species are so reactive and short-lived, their concentration in the reaction mixture at any given time is very low compared to the non-radical components such as ethane and Cl_2. Thus, many cycles of the chain typically occur before a termination event takes place. In other words, a single initiation event leads to the formation of many product molecules.

Compounds which readily undergo homolytic cleavage to generate radicals are called radical initiators. As we have just seen, molecular chlorine and bromine will readily undergo homolytic cleavage to form radicals when subjected to heat or light. Other commonly used as radical initiators are peroxides and ***N***-bromosuccinimide (NBS).

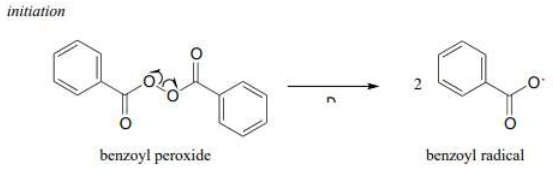


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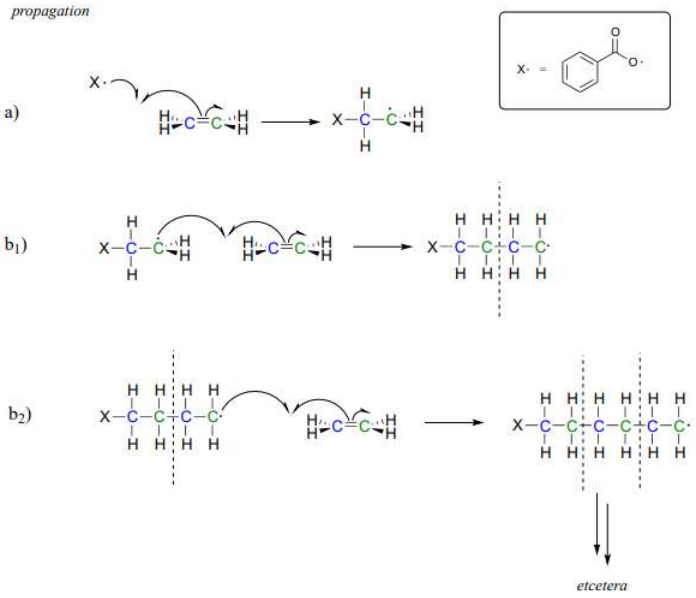
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16.3: Useful Polymers formed by Radical Chain Reactions

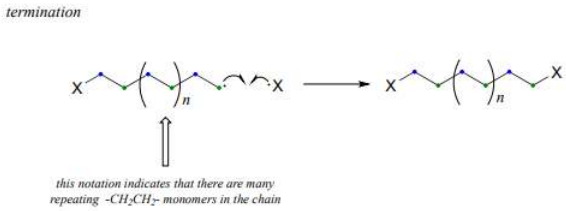
Many familiar household materials polymers made from radical chain reaction processes. Polyethylene (PET), the plastic material used to make soft drink bottles and many other kinds of packaging, is produced by the radical polymerization of ethylene (ethylene is a common name for what we call 'ethene' in IUPAC nomenclature). The process begins when a radical initiator such as benzoyl peroxide undergoes homolytic cleavage at high temperature:



In the propagation phase, the benzoyl radical (***X***· in the figure below) adds to the double bond of ethylene, generating a new organic radical.

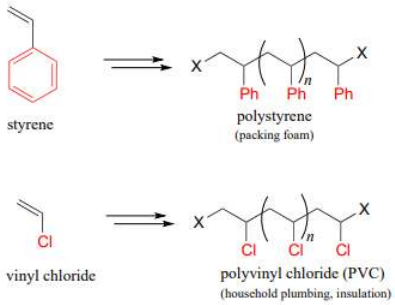


Successive ethylene molecules add to the growing polymer, until termination occurs when two radicals happen to collide.



The length of the polymer is governed by how long the propagation phase continues before termination, and can usually be controlled by adjusting reaction conditions.

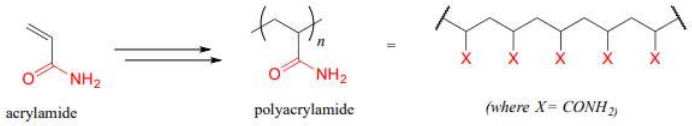
Other small substituted alkene monomers polymerize in a similar fashion to form familiar polymer materials. Two examples are given below.

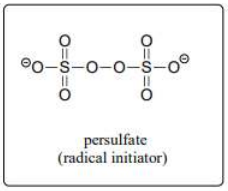


? Exercise 16.4.1

Show a mechanism for the formation of a 2-unit long section of polystyrene, starting with the monomer and benzoyl peroxide initiator. Keep in mind the relative stability of different radical intermediates.

A common way to separate proteins in the biochemistry lab is through a technique called polyacrylamide gel electrophoresis (**PAGE**). The polyacrylamide gel is formed through radical polymerization of acrylamide monomer, with the ammonium salt of persulfate used as the radical initiator.





In the end of chapter problems, you will be invited to propose a mechanism showing how a molecule called 'bis-acrylamide' serves as a 'crosslinker' between linear polyacrylamide chains to allow for formation of a net-like structure for the PAGE gel.

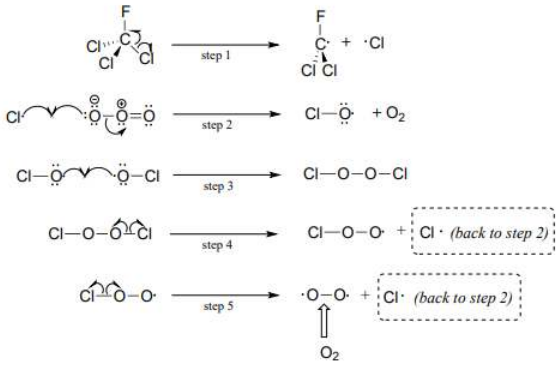
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16.4: Destruction of the Ozone Layer by a Radical Chain Reaction

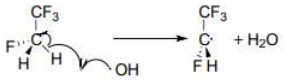
The high reactivity of free radicals and the multiplicative nature of radical chain reactions can be useful in the synthesis of materials such as polyethylene plastic - but these same factors can also result in dangerous consequences in a biological or ecological context. You are probably aware of the danger posed to the earth's protective stratospheric ozone layer by the use of chlorofluorocarbons (***CFCs***) as refrigerants and propellants in aerosol spray cans. Freon-11, or $CFCl_3$, is a typical ***CFC*** that was widely used until late in the 20th century. It can take months or years for a ***CFC*** molecule to drift up into the stratosphere from the surface of the earth, and of course the concentration of ***CFCs*** at this altitude is very low. Ozone, on the other hand, is continually being formed in the stratosphere. Why all the concern, then, about destruction of the ozone layer - how could such a small amount of ***CFCs*** possibly do significant damage? The problem lies in the fact that the process by which ozone is destroyed is a chain reaction, so that a single ***CFC*** molecule can initiate the destruction of many ozone molecules before a chain termination event occurs.

Although there are several different processes by which the ozone destruction process might occur, the most important is believed to be the chain reaction shown below.



First, a ***CFC*** molecule undergoes homolytic cleavage upon exposure to UV radiation, resulting in the formation of two radicals (step 1). The chlorine radical rapidly reacts with ozone (step 2) to form molecular oxygen and a chlorine monoxide radical. Step 3 appears to be a chain termination step, as two chlorine monoxide radicals combine. The Cl_2O_2 condensation product, however, is highly reactive and undergoes two successive homolytic cleavage events (steps 4 and 5) to form O_2 and two chlorine radicals, which propagates the chain.

To address the problem of ozone destruction, materials chemists have developed new hydrofluorocarbon refrigerant compounds. The newer compounds contain carbon-hydrogen bonds, which are weaker than the carbon-halogen bonds in ***CFCs***, and thus are susceptible to homolytic cleavage caused by small amounts of hydroxide radical present in the lower atmosphere:



This degradation occurs before the refrigerant molecules have a chance to drift higher up to the stratosphere where the ozone plays its important protective role. The degradation products are quite unstable and quickly degrade further into relatively harmless by-products. The hydroxide radical is sometimes referred to as an atmospheric 'detergent' due to its ability to degrade escaped refrigerants and other volatile organic pollutants.

Hydrofluorocarbons do, however, act as greenhouse gases, and are thought to contribute to climate change.

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16.5: Oxidative Damage to cells, Vitamin C, and Scurvy

While the hydroxide radical can be a beneficial 'detergent' in the atmosphere, it is harmful when present in a living cell. Hydroxide radical is one of the reactive oxygen species (ROS) that we learned about in chapter 15. Recall that ROS are continuously produced as minor but harmful side-products in the reduction of O_2 to H_2O in respiration.

You may recall from your general chemistry course that molecular oxygen exists in two states: 'singlet' oxygen has a double bond and no unpaired electrons, while 'triplet' oxygen has a single O-O bond and two unpaired electrons. Molecular orbital theory - and experimental evidence - show that the triplet state is lower in energy.



Figure 16.6.1

ROS are highly reactive oxidizing agents, capable of inflicting damage to DNA, proteins, and the lipids of cell membranes - they are thought to play a major role in the aging process. Hydroxide radical, for example, can initiate a radical chain reaction with the hydrocarbon chain of an unsaturated membrane lipid molecule, resulting in the formation of lipid hydroperoxide.

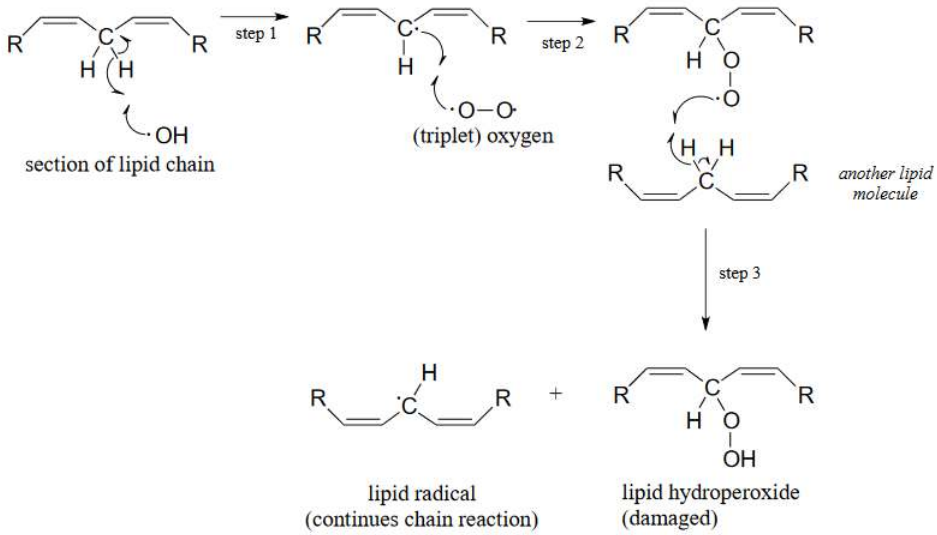


Figure 16.6.2

The allylic lipid radical formed as the result of homolytic hydrogen abstraction by hydroxide radical (step 1 above) reacts with one of the unpaired electrons in triplet oxygen (step 2) forming a peroxy radical. This radical species in turn homolytically abstracts a hydrogen from another lipid molecule (step 3), thus propagating the chain.

Many edible plants contain various antioxidant compounds, also known as 'free radical scavengers', which serve to protect cells from the oxidative effects of hydroxide radical and other harmful radical intermediates. Simply put, a free radical scavenger is a molecule that reacts with a potentially damaging free radical species, forming a more stable radical species which can be metabolized by the body before any damage is done to cell constituents.

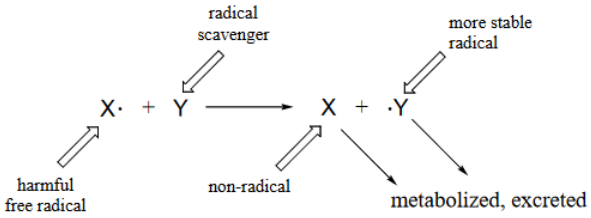


Figure 16.6.3

In the introduction to this chapter, we learned about scurvy, the disease long dreaded by sailors, and how it is caused by a deficiency of ascorbic acid (vitamin C) in the diet. We will soon get to the connection between ascorbic acid and scurvy, but first, let's look at how ascorbic acid functions as a free radical scavenger in your body.

The pK_a of ascorbic acid is about 4.1, so in a physiological environment it exists mainly as ascorbate anion, the conjugate base. When ascorbate encounters a hydroxide radical (or any other potentially damaging radical species), it donates a single electron, thus reducing the hydroxide radical to hydroxide ion and becoming itself an ascorbyl radical.

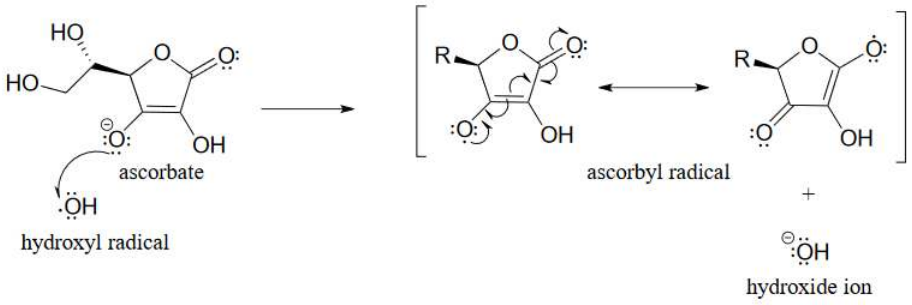


Figure 16.6.4

The ascorbyl radical is stabilized by resonance. The end result of this first step is that a very reactive, potentially harmful hydroxide radical has been 'quenched' to hydroxide ion and replaced by a much less reactive (and thus less harmful) ascorbyl radical.

The ascorbyl radical can then donate a second electron to quench a second hydroxide radical, resulting in the formation of dehydroascorbate, the oxidized form of ascorbate.

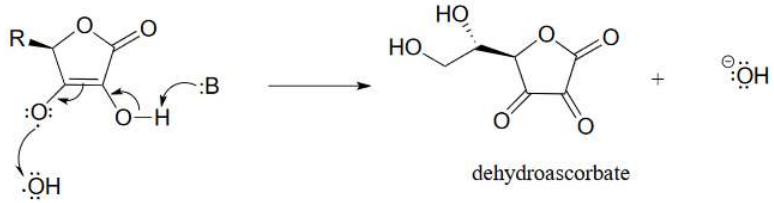


Figure 16.6.5

One ascorbate molecule is thus potentially able to scavenge two harmful radical species.

Dehydroascorbate is subsequently either broken down and excreted, or else enzymatically recycled (reduced) back to ascorbic acid. You were invited to propose a mechanism for the latter (redox) step in problem 15.10. J. Am. Coll. Nutr., 2003, 22, 18

We learned in the introduction to this chapter about the gruesome effects of long-term ascorbic acid deficiency. What, then, is the chemical connection between ascorbic acid and scurvy?

The symptoms association with scurvy are caused by the body's failure to properly synthesize collagen, the primary structural protein in our connective tissues. Essential to the stability of collagen is its ability to form a unique triple-helical structure, in which three protein strands coil around each other like a woven rope. Collagen strands are not able to pack together properly into their

triple helix structure unless certain of their proline amino acid residues are hydroxylated: the electronegative OH group on hydroxyproline causes the five-membered ring in the amino acid to favor a particular 'envelope' conformation (section 3.2) as well as the 'trans' peptide conformation, both of which are necessary for stable triple-helix formation.

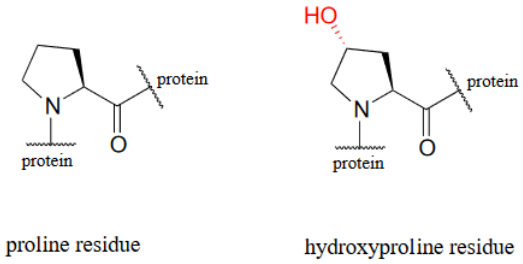


Figure 16.6.6

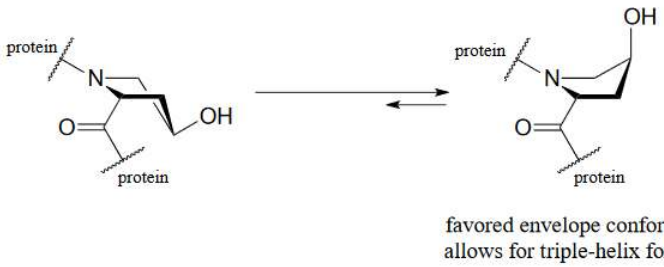


Figure 16.6.7

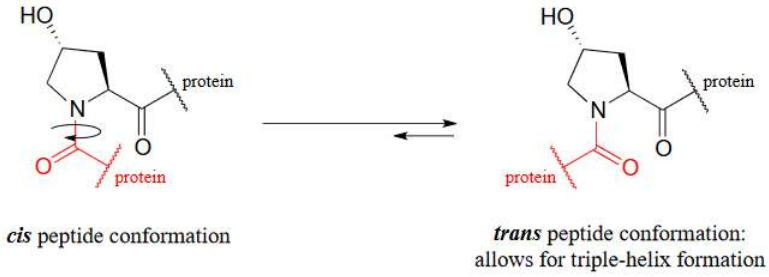


Figure 16.6.8

Proline hydroxylase, the enzyme responsible for this key modification reaction, depends in turn upon the presence of ascorbate. The hydroxylating reaction is complex, and involves electron-transfer steps with enzyme-bound iron - mechanistic details that are well outside of our scope here, but which you may learn about in a bioinorganic chemistry course. It is enough for us to know that iron starts out in the Fe^{+2} state, and during the course of the reaction it loses an electron to assume the Fe^{+3} state. In order for the enzyme to catalyze another reaction, the iron must be reduced back to its active Fe^{+2} state - it must accept a single electron. The donor of this single electron is ascorbate.

(For more information, see Crit. Rev. Biochem. Mol. Biol. 2010, 405, 106.)

So, to sum up: If we fail to get enough ascorbic acid in our diet (in other words, if we don't eat our fruits and vegetables!) the iron in our proline hydroxylase enzymes won't be returned to the active Fe^{+2} state, so the catalytic cycle is broken and we can't turn prolines into hydroxyprolines. Without the hydroxy group, the proline residues of our collagen proteins won't assume the proper conformation, and as a consequence the collagen triple helix structures will be unstable. At physiological temperature, our collagen will literally melt apart - and with it, our gums, our capillaries, and anything else held together by connective tissue. This is scurvy.

You have probably heard that many fruits and vegetables contain natural 'polyphenol' antioxidant compounds that are thought to be beneficial to our health. Apigenin, for example, is found in parsley and celery, while the skins of grapes used to produce red wine

are particularly rich in resveratrol, as well as many other polyphenols. Curcumin is the compound responsible for the distinctive yellow color of turmeric, a ubiquitous spice in Indian cuisine.

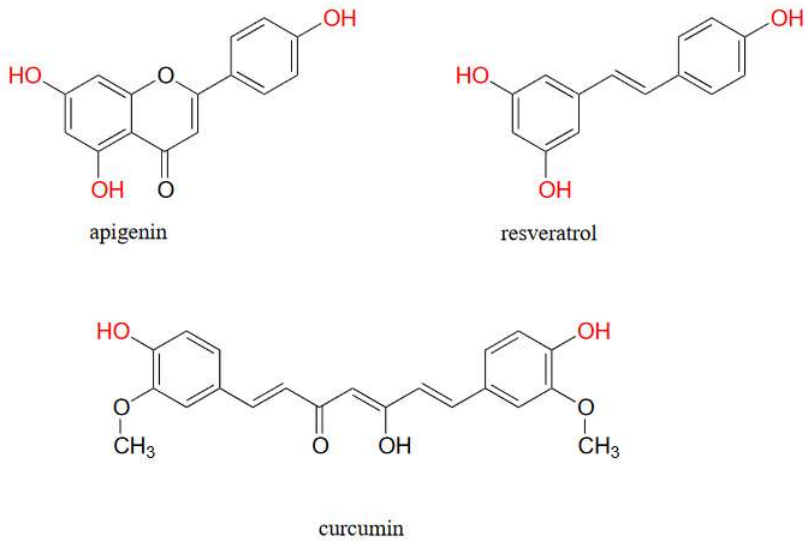


Figure 16.6.9

While much remains to be learned about exactly how these polyphenols exert their antioxidant effects, it is likely that they, like ascorbic acid, act as radical scavengers. For example, resveratrol could donate a single electron (and a proton) to hydroxide radical to reduce it to water. The phenolic radical that results is stabilized by resonance, and is much less likely than hydroxide radical to cause damage to important biomolecules in the cell.

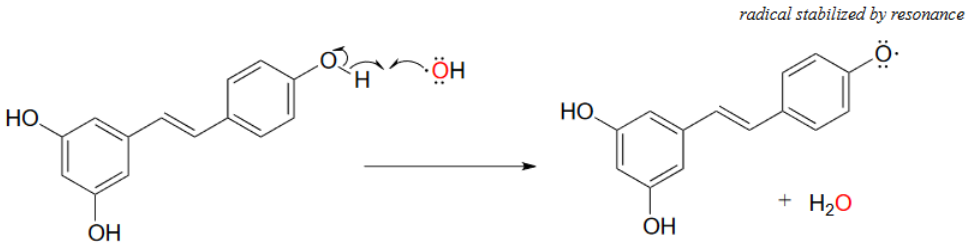


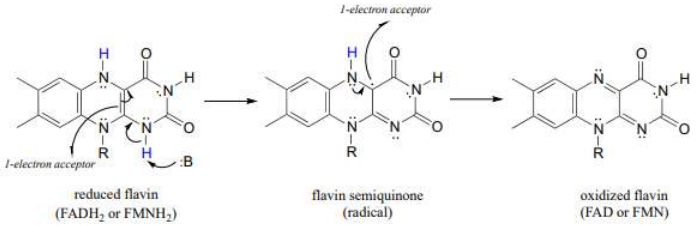
Figure 16.6.10

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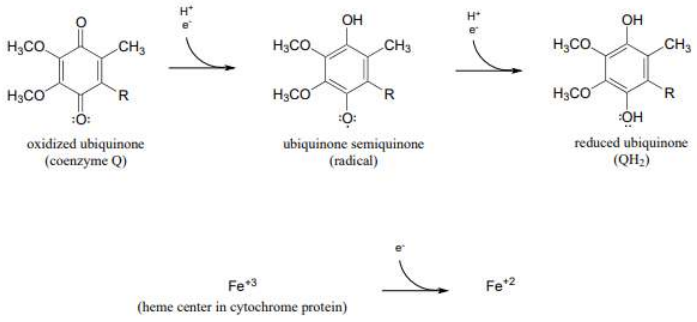
16.6: Flavin as a One-Electron Carrier

In chapter 15 we saw how a nicotinamide and flavin coenzymes can act as acceptors or donors of two electrons in hydride-transfer redox steps. Recall that it was mentioned that flavin, (but not nicotinamide) can also participate in single-electron transfer steps through a stabilized radical intermediate called a semiquinone.. Frey p. 162 fig 3-30; Silverman p. 122 sch. 3.34; J Phys Chem A. 2013, 117, 11136 fig 2)



Note in this reaction that overall, flavin loses or gains two electrons and two protons, just like in the flavin-dependent redox reactions we saw in chapter 15. The difference here is that the electrons are transferred one at a time, rather than paired in the form of a hydride ion.

Two important examples single-electron acceptor species in human metabolism are ubiquinone (coenzyme Q) and the oxidized form of cytochrome. Ubiquinone is a coenzyme that can transfer single electrons via a semiquinone state analogous to that of flavin, and cytochrome is a protein containing a 'heme' iron center which shuttles between the Fe^{+3} (oxidized) and Fe^{+2} (reduced) state.



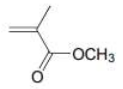
Further discussion of the mechanisms of single-electron flavin reactions is beyond our scope here, but when you study the 'respiratory chain' in a biochemistry course you will gain a deeper appreciation for the importance of flavin in single-electron transfer processes.

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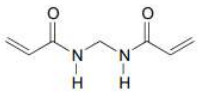
16.E: Radical Reactions (Exercises)

P16.1: Plexiglass is a polymer of methyl methacrylate. Show a mechanism for the first two propagation steps of polymerization (use $X\cdot$ to denote the radical initiator), and show a structure for the plexiglass polymer. Assume an alkene addition process similar to that shown in the text for polyethylene.



methyl methacrylate

P16.2: In section 16.3 we saw how acrylamide polymerizes to form the polyacrylamide used in PAGE protein gels. Polyacrylamide by itself is not sufficient by itself to form the gel - the long polyacrylamide chains simply slip against each other, like boiled spaghetti. To make a PAGE gel, with pores for the proteins to slip through, we need a crosslinker - something to tie the chains together, forming a three-dimensional web-like structure. Usually, a small amount of bis-acrylamide is added to the acrylamide in the polymerization mixture for this purpose.



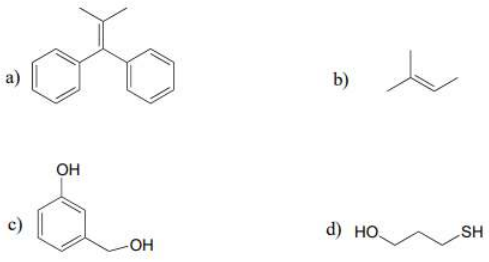
bis-acrylamide

Propose a radical mechanism showing how bis- acrylamide might form crosslinks between two polyacrylamide chains.

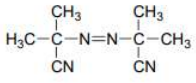
P16.3: Resveratrol is a natural antioxidant found in red wine (see section 16.5 for the structure).

a. Draw one resonance structure to illustrate how the resveratrol radical is delocalized by resonance.
b. Indicate all of the carbons on your structure to which the radical can be delocalized.
c. Draw an alternate resveratrol radical (one in which a hydrogen atom from one of the other two phenolic groups has been abstracted). To how many carbons can this radical be delocalized?
d. The curcumin structure is shown in the same figure as that of resveratrol, in section16.5. Draw two resonance contributors of a curcumin radical, one in which the unpaired electron is on a phenolic oxygen, and one in which the unpaired electron is on a ketone oxygen.

P16.4: Draw the radical intermediate species that you would expect to form when each of the compounds below reacts with a radical initiator.



P16.5: Azobis(isobutyronitrile) is a widely used radical initiator which rapidly undergoes homolytic decomposition when heated.



Azobis(isobutyronitrile)

Predict the products of this decomposition reaction, and show a likely mechanism. What is the thermodynamic driving force for homolytic cleavage?

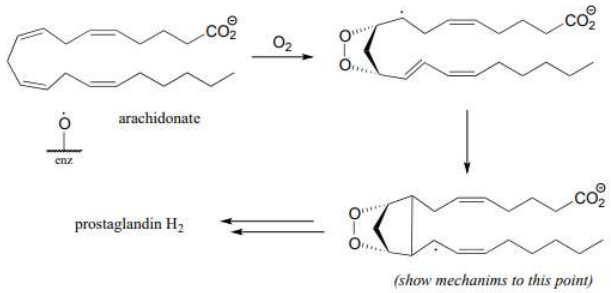
P16.6:

a. When 2-methylbutane is subjected to chlorine gas and heat, a number of isomeric chloroalkanes with the formula $C_5H_{11}Cl$ can form. Draw structures for these isomers, and for each draw the alkyl radical intermediate that led to its formation.
b. In part a), which is the most stable radical intermediate?
c. In the reaction in part a), the relative abundance of different isomers in the product is not exclusively a reflection of the relative stability of radical intermediates. Explain.

P16.7: We learned in chapter 14 that HBr will react with alkenes in electrophilic addition reactions with 'Markovnikov' regioselectivity. However, when the starting alkene contains even a small amount of contaminating peroxide (which happens when it is allowed to come into contact with air), a significant amount of 'anti-Markovnikov' product is often observed.

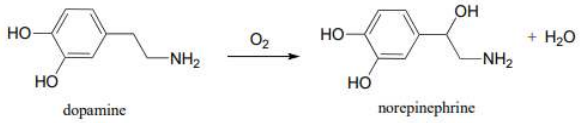
a. Propose a mechanism for formation of the anti-Markovnikov addition product when 1-butene reacts with HBr containing a small amount of benzoyl peroxide
b. Predict the product and propose a mechanism for the addition of ethanethiol to 1-butene in the presence of peroxide.

P16.8: In section 11.5 we learned that aspirin works by blocking the action of an enzyme that catalyzes a key step in the biosynthesis of prostaglandins, a class of biochemical signaling molecules. The enzyme in question, prostaglandin H synthase (EC 1.14.99.1) catalyzes the reaction via several single-electron steps. First, an iron-bound oxygen radical in the enzyme abstracts a hydrogen atom from arachidonate. The arachidonate radical intermediate then reacts with molecular oxygen to form a five-membered oxygen-containing ring, followed by closure of a cyclopentane ring to yield yet another radical intermediate. (Biochemistry 2002, 41, 15451.)

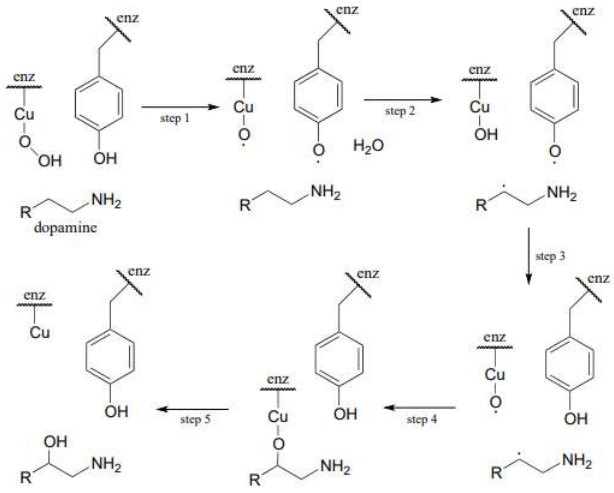


Propose a mechanism for the steps of the reaction that are shown in this figure.

P16.9: Some redox enzymes use copper to assist in electron transfer steps. One important example is dopamine b-monooxygenase (EC 1.14.1.1), which catalyzes the following reaction:



The following intermediates have been proposed: (see Biochemistry 1994, 33, 226) Silverman p. 222



Draw mechanistic arrows for steps 1-4.

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CHAPTER OVERVIEW

17: The Organic Chemistry of Vitamins

17.0: Prelude to the Organic Chemistry of Vitamins

17.1: Pyridoxal Phosphate (Vitamin B6)

17.2: Thiamine Diphosphate (Vitamin B1)

17.3: Thiamine Diphosphate, Lipoamide and the Pyruvate Dehydrogenase Reaction

17.4: Folate

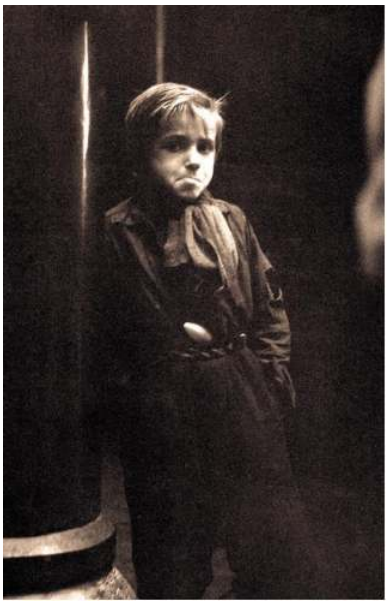
17.E: The Oganic Chemistry of Vitamins (Exercises)

17.S: The Oganic Chemistry of Vitamins (Summary)

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17.0: Prelude to the Organic Chemistry of Vitamins

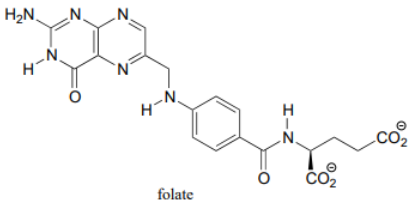
The old black and white photograph is haunting. A young boy, perhaps 10 or 11 years old, huddles against a wall outside a soup kitchen, his mouth in an odd twisted shape that could be expressing either pain or defiance, his eyes staring straight into those of the viewer. Tucked into his pants, almost like a pistol in a holster, is a metal spoon.



The photograph was taken in the Netherlands in 1945, at the height of what the Dutch people still refer to simply as "The Hunger Winter". With the western part of the country still occupied by the Nazis, the Dutch resistance government, based in London, had called for a railway strike with the aim of stopping German troop movements before a planned airborne invasion by Allied forces. In retaliation, the Germans cut off all food shipments to cities in the western Netherlands. The Allied invasion failed to liberate the country, and the winter of 1944-1945 turned out to be bitterly cold. With food supplies dwindling, rations were cut first to 1000 calories per day, then to 500. People resorted to eating grass and tulip bulbs just to stay alive. Over 20,000 people died of starvation before food shipments were restored in the spring.

As tragic as the Hunger Winter was for the Dutch people, some good did come from it. For medical scientists, the event became a unique 'social experiment': unlike most episodes of famine throughout human history, the Hunger Winter had a clearly defined beginning, end, and geographic boundary, and it occurred in a technologically advanced society that continued to keep thorough records before, during, and after the ordeal. Scientists knew exactly who suffered from famine and for precisely how long, and in the years that followed they were able to look at the long-term effects of famine, particularly on developing embryos. Researchers found that babies who had been conceived during the famine were born with a significantly higher incidence of neurological birth defects such as spina bifida, a condition in which a portion of the neural tube protrudes from between vertebrae which did not properly fuse together during fetal development. Later in life, members of this same cohort of 'famine babies' were more likely to be obese, and to suffer from schizophrenia.

These initial findings spurred interest in further research into the consequences of prenatal deprivation. In particular, carefully controlled studies later led to the recognition of the importance of the vitamin folate in ensuring proper neurological development in early-term fetuses.



folate

Folate - the conjugate base of folic acid - is an organic coenzyme: a helper molecule that binds in the active site of certain enzymes and plays a critical role in the biochemical reaction being catalyzed. Recall that we have seen coenzymes at work before: ***SAM***, ***ATP***, $NAD(P)^+$ and $NAD(P)H$, flavin and glutathione are all important coenzymes with which we are already familiar.

Because prenatal folate deficiency was found to be directly related to the incidence of spina bifida and other neural tube defects, health officials in the United States and many other countries changed their official guidelines to include a specific recommendation that women begin taking folate supplements as soon as they knew that they are pregnant, or better yet as soon as they begin trying to become pregnant. A number of studies conducted during the 1980s and early 1990s consistently showed that folate supplementation correlated with a 50-70% reduction in neural tube defects.

The molecular role of folate in prenatal neurological development is not understood in detail, but most researchers agree that it probably has a lot to do with DNA biosynthesis. Like ***S***-adenosyl methionine (***SAM***), folate functions in 1-carbon transfer reactions, including several critical steps in the nucleic acid biosynthesis pathways. The rapidly dividing cells of the developing brain of an early term fetus appear to be especially sensitive to folate deficiency in the mother's diet: insufficient folate leads to impaired DNA biosynthesis, which in turn leads to defects in brain development.

Folate also serves as a 1-carbon donor in the pathway by which ***SAM*** is regenerated after it donates a methyl group. You may recall from the introduction to chapter 8 that methylation of cytosine bases in DNA by ***SAM*** results in permanent changes to a individual's genome - this was the reason why the two 'identical' twin sisters in that introductory story turned out to be, as they grew older, not so identical after all. It is likely that the folate deprivation that afflicted expectant mothers during the Dutch Hunger Winter also caused epigenetic changes (in other words, changes in the extent of DNA methylation) in their developing fetuses, which decades later manifested in the form of an increased incidence of conditions such as obesity and schizophrenia. All the more reason, we now know, to make sure that women get plenty of folate in their diet early in the first trimester of pregnancy.

In this final chapter, we focus on the organic chemistry of folate, along with three other coenzymes: pyridoxal phosphate, thiamine diphosphate, and lipoamide. Humans can synthesize lipoamide, but we depend on dietary sources for the other three: pyridoxal phosphate is a form of vitamin B6, and thiamine diphosphate is a form of vitamin B1. In a mechanistic sense, there is really nothing new in this chapter. All of the reaction mechanism types that we will see are already familiar to us, ranging from nucleophilic substitutions (chapter 8) to disulfide exchanges (chapter 15). We will soon see, however, how each coenzyme plays its own specific and crucial role in assisting enzymes with the catalysis of key reactions of metabolism. We will begin with pyridoxal phosphate and its various roles in amino acid metabolism.

Additional reading:

http://www.naturalhistorymag.com/fea...na-epigenetics

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17.1: Pyridoxal Phosphate (Vitamin B6)

The coenzyme pyridoxal phosphate (commonly abbreviated PLP) is the active form of vitamin B_6, or pyridoxine.

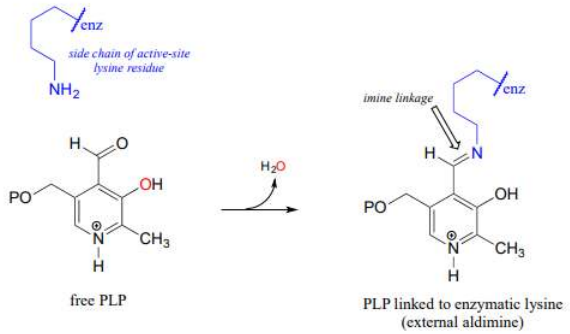


pyridoxine (vitamin B_6) pyridoxal phosphate (PLP)

PLP is required for over 100 different reactions in human metabolism, primarily in the various amino acid biosynthetic and degradation pathways. The essential function of PLP is to act as an 'electron sink', stabilizing a negative formal charge that develops on key reaction intermediates. Some of reactions will be familiar to you from chapter 12 and 13 we will see examples, for instance, of -dependent α-carbon racemization, as well as aldol- and Claisen-type reactions. Other reactions will be less familiar: for example, the participation of allows for decarboxylation of amino acids, a chemical step which would be highly unlikely without the coenzyme, and PLP is also required for a very important class of biochemical transformation called 'transamination', in which the amino group of an amino acid is transferred to an acceptor molecule. Before we dive into the reactions themselves, though, we need to begin by looking at a key preliminary step that is common to all of the PLP reactions we will see in this section.

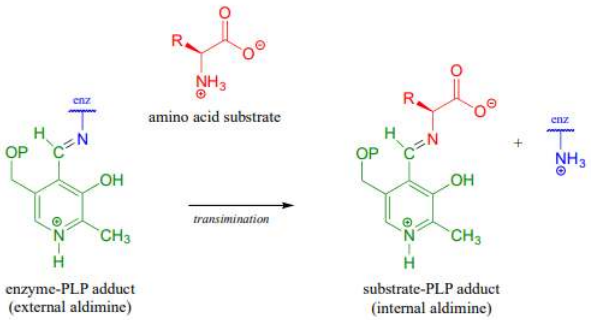
PLP in the active site: the imine linkage

The common catalytic cycle of a PLP-dependent enzyme begins and ends with the coenzyme covalently linked to the enzyme's active site through an imine linkage between the aldehyde carbon of PLP and the amine group of a lysine residue (see section 10.5 to review the mechanism for imine formation). For a PLP-dependent enzyme to become active, a PLP molecule must first enter the active site of an enzyme and form an imine link to the lysine. This state is often referred to as an **internal aldimine**.



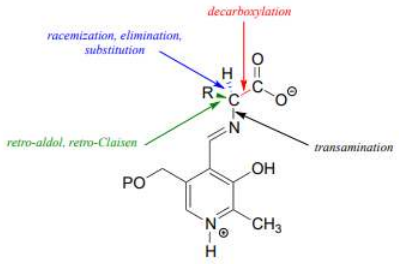
free PLP PLP linked to enzymatic lysine (external aldimine)

The first step of virtually all PLP-dependent reactions is transimination (section 10.5), as the amino group on the amino acid substrate displaces the amino group of the enzymatic lysine. This state - where the coenzyme is covalently linked to the substrate or product of the reaction - is often referred to as an **external aldimine**.



enzyme-PLP adduct (external aldimine) substrate-PLP adduct (internal aldimine)

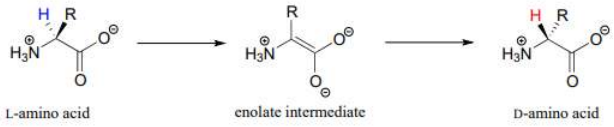
With the preliminary transimination accomplished, the real PLP chemistry is ready to start. The versatility of PLP in terms of its ability to assist with a wide variety of reaction types is illustrated by the figure below, showing how, depending upon the reaction/enzyme in question, PLP can assist in the cleavage of any one of the four bonds to the α-carbon of the amino acid substrate.



Let's look first at the reaction catalyzed by PLP-dependent alanine racemase. (EC 5.1.1.1).

PLP-dependent amino acid racemization

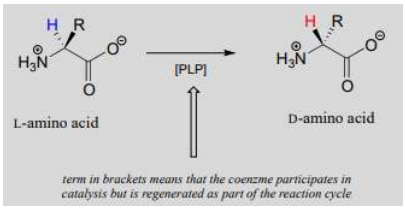
In section 12.2 we saw an example of a PLP-independent amino acid racemization reaction, in which the negatively-charged intermediate was simply the enolate form of a carboxylaten:



Many other amino acid racemase reactions, however, require the participation of PLP.

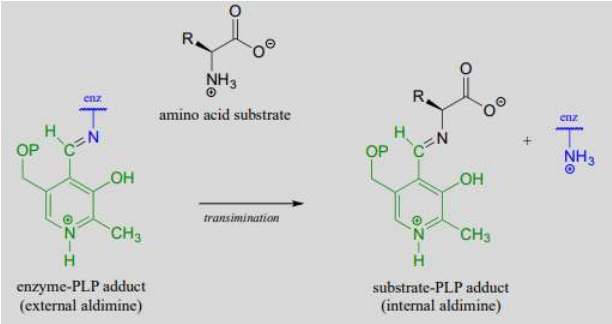
Like all other PLP-dependent reactions that we will see in this section, PLP-dependent amino acid racemization begins with a preliminary step in which the substrate becomes attached to the coenzyme through a transimination. Once it is linked to PLP in the active site, the a-proton of an amino acid substrate is abstracted by an active site base (step 1 below). The negative charge on the carbanion intermediate can, of course, be delocalized to the carboxylate group. The PLP coenzyme, however, provides an expanded network of conjugated π-bonds over which the electron density can be delocalized all the way down to the PLP nitrogen. This is what we mean when we say that the job of PLP is to act as an 'electron sink': the coenzyme is very efficient at absorbing, or delocalizing, the excess electron density on the deprotonated α-carbon of the reaction intermediate. PLP is helping the enzyme to increase the acidity of the α-hydrogen by stabilizing the conjugate base. A PLP-stabilized carbanion intermediate is commonly referred to as a quinonoid intermediate. Note that in the overall reaction equation below, PLP appears below the reaction arrow in brackets, indicating that it participates in the mechanism but is regenerated as part of the reaction cycle.

PLP-dependent amino acid racemization:

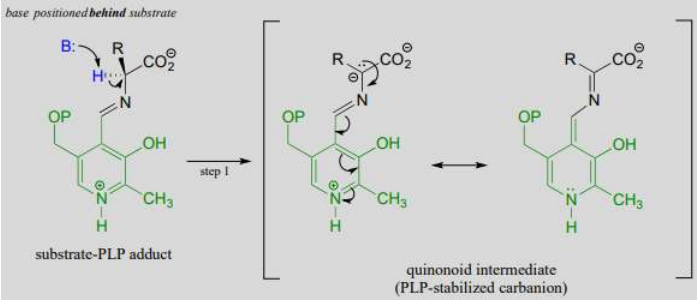


Mechanism:

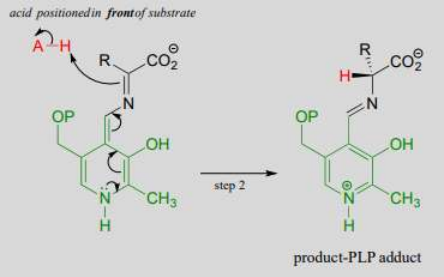
Preliminary step - transimination



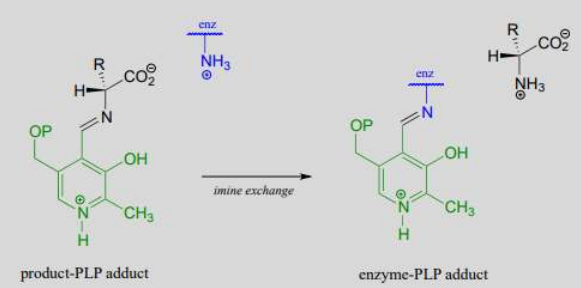
First step - deprotonation:



Second step - reprotonation from the opposite side:



Final step - transimination:



Just as in the PLP-independent racemase reactions, reprotonation occurs on the opposite side of the substrate (step 2), leading to the ***D***-amino acid product.

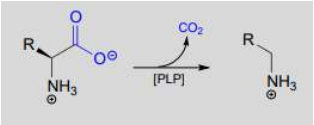
All that remains is the final imine exchange which frees the ***D***-amino acid product and re-attaches the coenzyme to the enzymatic lysine side-chain, ready to begin another catalytic cycle.

To simplify matters, from here on we will not include the preliminary and final transimination steps in our PLP reaction figures - we will only show mechanistic steps that occur while the substrate is attached to the coenzyme (the internal aldimine forms).

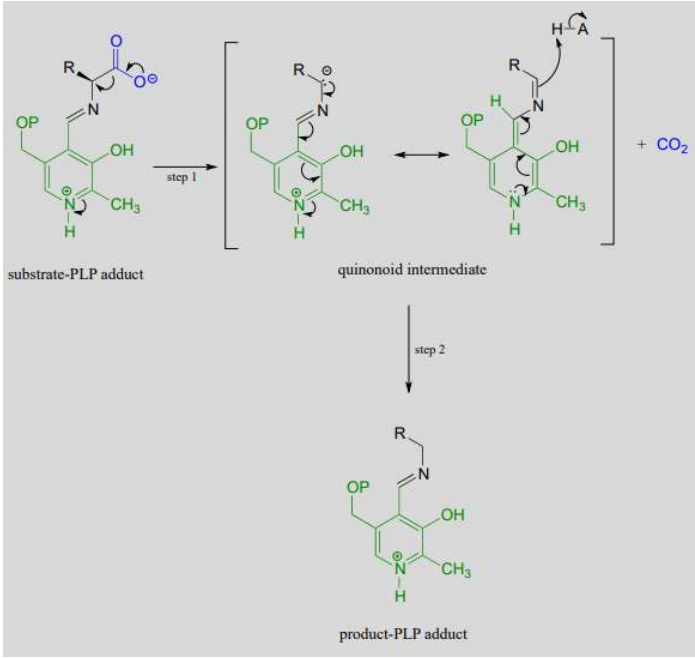
PLP-dependent decarboxylation

In the amino acid racemase reaction above, PLP assisted in breaking the α-carbon to α-proton bond of the amino acid. Other PLP-dependent enzymes can catalyze the breaking of the bond between the α-carbon and the carboxylate carbon by stabilizing the resulting carbanion intermediate: these are simply decarboxylation reactions.

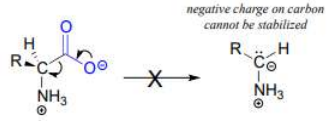
PLP-depended amino acid decarboxylation:



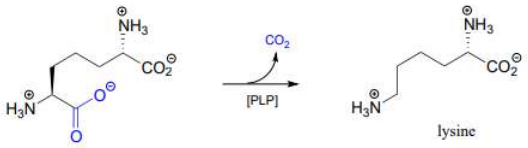
Mechanism:



Notice something very important here: while in racemization reactions the assistance of PLP can be seen as 'optional' (in the sense that some racemase enzyme use PLP and others do not), the coenzyme is essential for amino acid decarboxylation steps. Without PLP, there is no way to stabilize the carbanion intermediate, and decarboxylation is not a chemically reasonable step.



One example of a PLP-facilitated decarboxylation reaction is the final step in the lysine biosynthesis pathway: (EC 4.1.1.20).



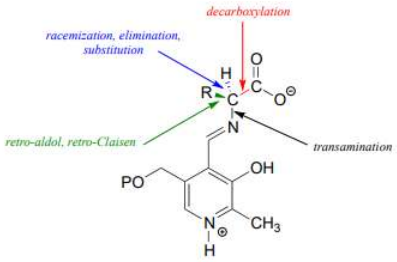
? Exercise 17.2.1

Draw mechanistic arrows for the carbon-carbon bond-breaking step of the PLP-dependent decarboxylation reaction above.

PLP-dependent retroaldol and retro-Claisen cleavage

(*It would be a good idea before reading this section to review aldol/retro-aldol and Claisen/retro-Claisen reaction mechanisms in sections 12.3 and 13.3, respectively*)

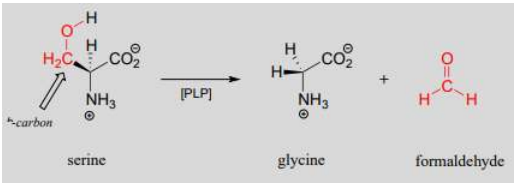
So far we have seen PLP playing a role in breaking the bond between the α-carbon and its α-proton (in the racemization reaction), and the bond between the α-carbon and carboxylate carbon (in the decarboxylation reaction).



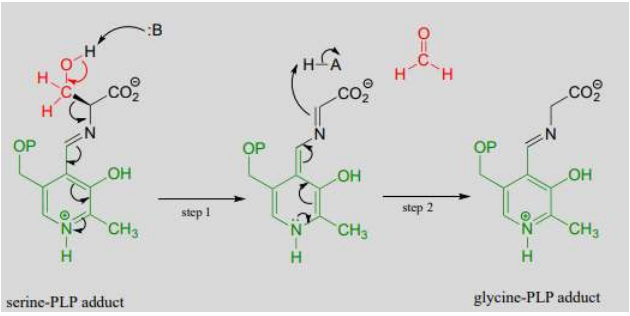
Other PLP-dependant enzymes catalyze cleavage of the bond between the α-carbon and the first carbon on the amino acid side chain, otherwise known as the β-carbon. In the serine degradation pathway, serine is first converted to glycine by a retro-aldol cleavage reaction. (). Although a reasonable mechanism could be proposed without the participation of PLP, this reaction in fact requires the coenzyme to assist in stabilization of the negative charge on the carbanion intermediate.

A PLP-dependent retro-aldol cleavage reaction

(serine hydroxymethyl transferase, EC 2.1.2.1)



Mechanism:

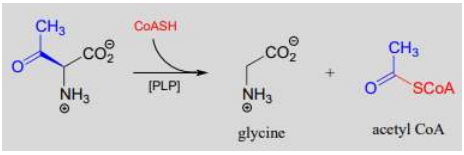


Note that, in this reaction just as in the racemase reaction described previously, the key intermediate is a PLP-stabilized carbanion, or quinonoid.

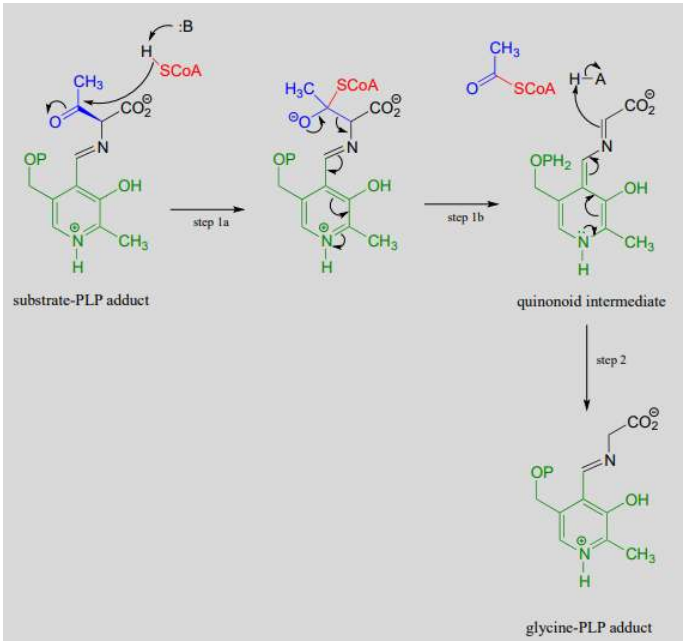
What happens to the (toxic!) formaldehyde produced in this reaction? We will see later in this chapter how the serine hydroxymethyltransferase enzyme goes on to use another coenzyme called tetrahydrofolate to prevent the formaldehyde from leaving the active site and causing damage to the cell.

PLP also assists in retro-Claisen cleavage reactions (section 13.3), such as this step in the degradation of threonine. (EC 2.3.1.29)

A PLP-dependent retro-Claisen reaction:



Mechanism:

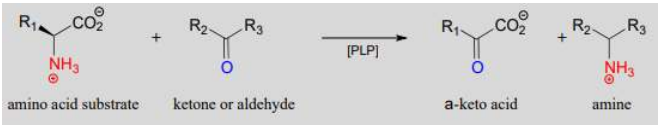


Notice how, like the retro-aldol reaction, the bond between the α-carbon and the β-carbon of the amino acid substrate is broken (in step 1b).

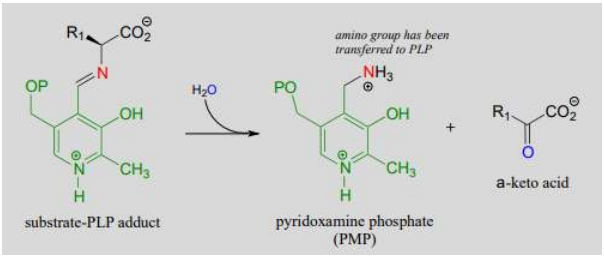
PLP-dependent transamination

One of the most important reaction types in amino acid metabolism is transamination, in which an amino group on a donor molecule (often an amino acid) is transferred to a ketone or aldehyde acceptor molecule.

A transamination reaction:

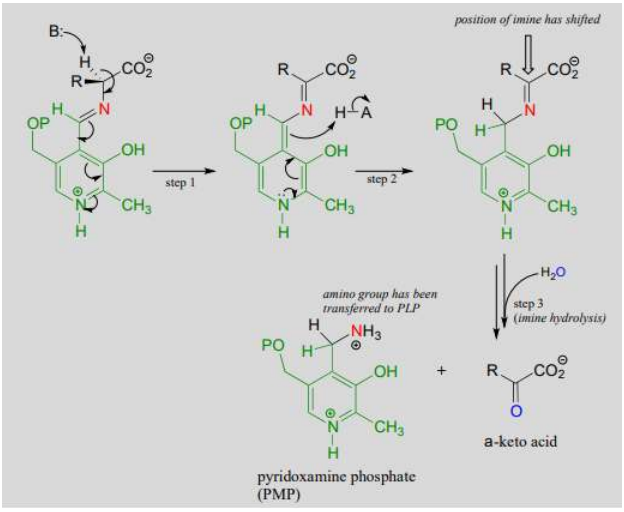


Transamination phase 1 (transfer of amino group from amino acid substrate to coenzyme)



Mechanism:

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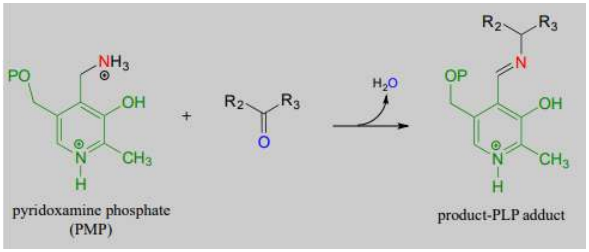


Once again, step 1 is abstraction of the α-proton from the PLP-substrate adduct. However, in a transaminase reaction this initial deprotonation step is immediately followed by reprotonation at what was originally the aldehyde carbon of PLP (step 2 above), which results in a new carbon-nitrogen double bond (in other words, an imine) between the α-carbon and the nitrogen atom of the original amino acid. The repositioned imine group is then hydrolyzed (step 3 above), breaking the carbon-nitrogen bond, transferring the amino group to the coenzyme, and releasing an α-keto acid.

The coenzyme, which now carries an amine group and is called pyridoxamine phospate (PMP), next transfers the amine group to α-ketoglutarate (to form glutamate) through a reversal of the whole process depicted above.

Transamination reaction, phase 2

(transfer of amino group from coenzyme to acceptor molecule)



Mechanism:

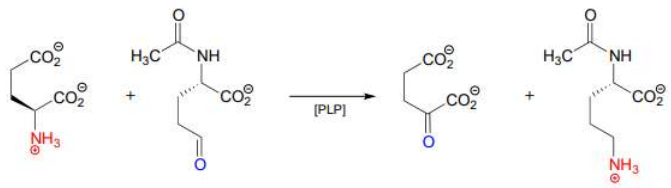
see exercise below

In a transamination reaction, the PLP coenzyme not only provides an electron sink, it also serves as a temporary 'parking place' for an amino group as it is transferred from donor to acceptor.

? Exercise 17.2.2

Show a complete, step-by-step mechanism for 'phase 2' of the transamination reaction above.

Here is an example of a transamination reaction in the arginine biosynthesis pathway: EC 2.6.1.11

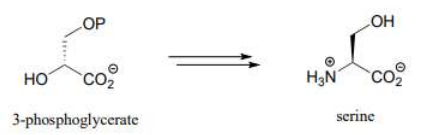


Exercise 17.2.3

a. Draw arrows for the first mechanistic step of 'phase 2' of the above transaminase reaction.
b. Which carbon on the substrate side of the reaction will eventually become the α-carbon of arginine?

Exercise 17.2.4

Propose a pathway, with three enzymatic steps, for the biosynthesis of serine from 3-phosphoglycerate. Include a generalized ('-ase') enzyme name for each step. Glutamate plays a role in the process as an amino group donor.



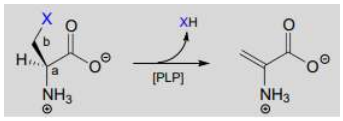
PLP-dependent *beta*-elimination and β-substitution

(*Before starting this section, it would be a good idea to review* ***E1cb*** *β-elimination and conjugate addition reaction mechanisms in section 13.4*)

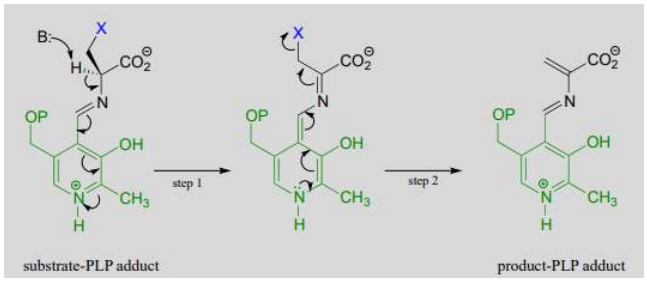
By now it should be pretty apparent that PLP is a pretty versatile coenzyme! Two more reaction types in the PLP toolbox are β-elimination and β-substitution on amino acid substrates.

In a PLP-dependent β-elimination reaction, the coenzyme simply helps to stabilize the carbanion intermediate of the ***E1cb*** mechanism:

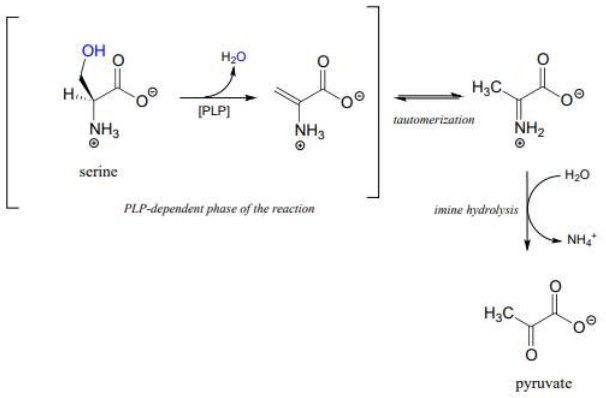
PLP-dependent β-elimination reaction



Mechanism:

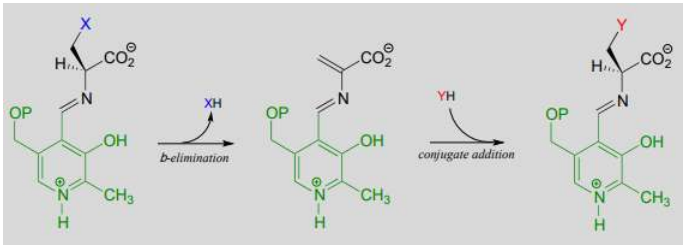


Serine dehydratase (EC 4.2.1.13) catalyzes a PLP-dependent β-elimination in the first step of the serine degradation pathway:

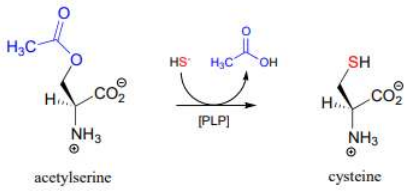


A β-substitution reaction is simply ***E1cb*** elimination followed directly by the reverse reaction (conjugate addition) with a different nucleophile (Y in the figure below):

A β-substitution reaction:



In many bacteria, the synthesis of cysteine from serine includes a PLP-dependent β-substitution step (EC 2.5.1.47).



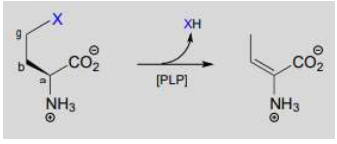
? Exercise 17.2.5

Draw a mechanism for the conjugate addition phase of the reaction above (end with the cysteine-PLP adduct).

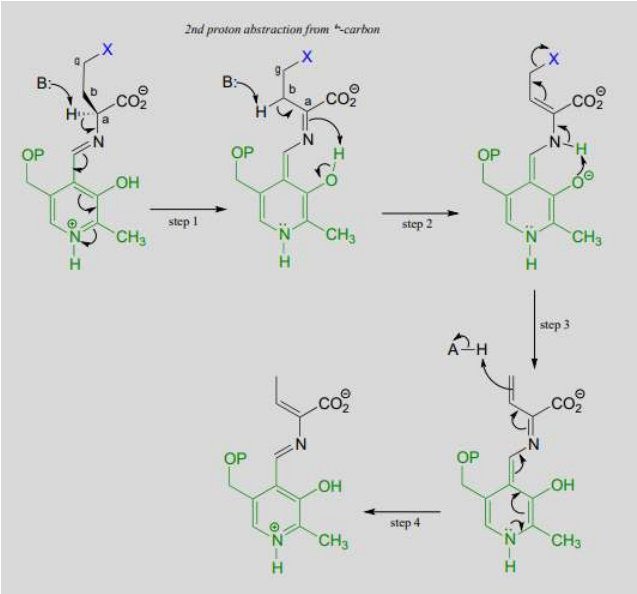
PLP-dependent γ-elimination and γ-substitution reactions

The electron sink capability of PLP allows some enzymes to catalyze eliminations at the γ-carbon of some amino acid side chains, rather than at the β-carbon. secret to understanding the mechanism of a γ-elimination is that PLP essentially acts as an electron sink twice - it absorbs the excess electron density from not one but two proton abstractions.

γ-elimination

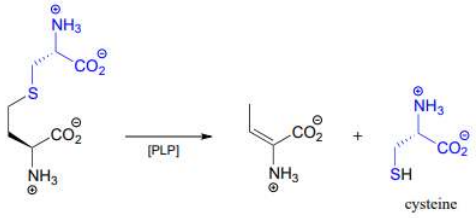


Mechanism:



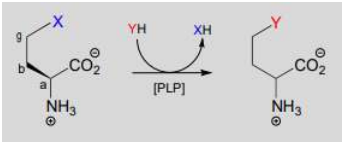
In a familiar first step, the α-proton of the amino acid is abstracted by an enzymatic base, and the electron density is absorbed by PLP. Next comes the new part - before anything happens to the electron density from the first proton abstraction, a second proton, this time from the β-carbon on the side chain, is abstracted, forming an enamine intermediate (step 2). The phenolic proton on the pyridoxal ring of PLP donates a proton to the nitrogen. step 3, the leaving is expelled and a new π-bond forms between the β and γ carbons (step 3). This π-bond is short-lived, however, as the electron density from the first proton abstraction, which has been 'stored' in PLP all this time, flows back up to protonate the α-carbon (step 4), leaving the γ-elimination product linked to PLP via the usual imine connection.

An example is the cystathionine γ-lyase reaction in the methionine degradation pathway (EC 4.4.1.1):

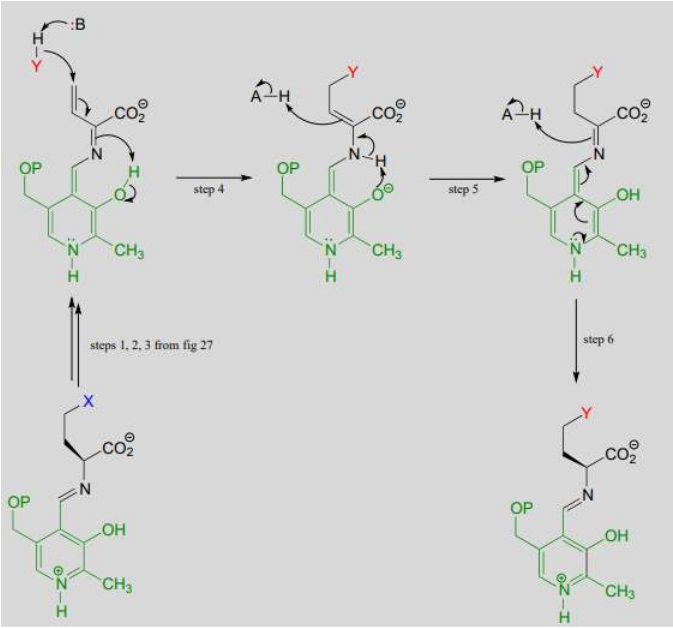


A related reaction is PLP-dependent γ-substitution, which again is simply γ-elimination of a leaving group (X in the figure below) followed directly by the reverse process (a γ-addition) with a different nucleophile ('Nu' in the figure below).

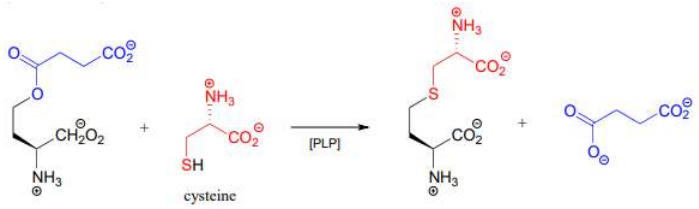
PLP-dependent γ-substitution:



Mechanism:



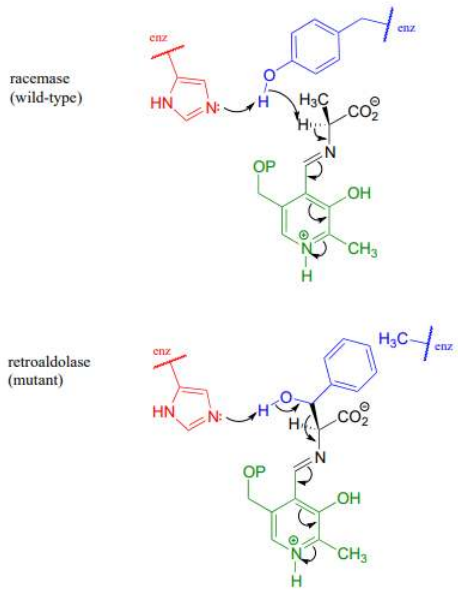
Below is a PLP-dependent γ-substitution reaction in the methionine degradation pathway (EC 4.2.1.22):



Racemase to aldolase: altering the course of a PLP reaction

We have seen how PLP-dependent enzymes catalyze a variety of reaction types - racemization, retroaldol/retro-Claisen cleavage, transaminination, elimination, and substitution - which, despite their apparent diversity, are all characterized by formation of a critical carbanion intermediate which is stabilized by the 'electron sink' property of the PLP coenzyme. Given this common mechanistic feature, it would be reasonable to propose that the active site architecture of these enzymes might also be quite close. This idea was nicely illustrated by an experiment in which researchers found that changing a single active site amino acid of PLP-dependent alanine racemase was sufficient to turn it into a retro-aldolase (J. Am. Chem. Soc. 2003, 125, 10158).

In the 'wild-type' (natural) alanine racemase reaction, an active site histidine (red in figure below) deprotonates a neighboring tyrosine residue (blue), which in turn acts as the catalytic base abstracting the α-proton of the substrate. When researchers changed the tyrosine to an alanine (using a technique called 'site-directed mutagenesis'), and substituted β-hydroxytyrosine for the alanine substrate, the new 'mutant' enzyme catalyzed a retro-aldol reaction.

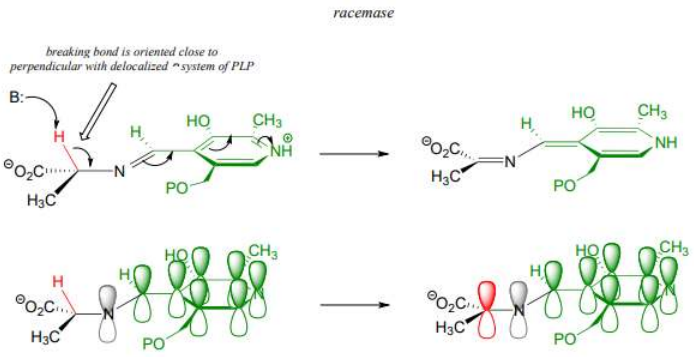


Notice what has happened here: the basic histidine, with no tyrosine to deprotonate because of the mutation, is instead positioned to abstract a proton from the β-hydroxyl group of the new substrate, setting up a retroaldol cleavage. That was all it took to change a racemase into a retroaldolase, because the necessary PLP electron sink system was all left in place. The researchers predicted correctly that the phenyl ring of β-hydroxy tyrosine would fit nicely in the space left empty due to the tyrosine to alanine change in the mutant enzyme's structure

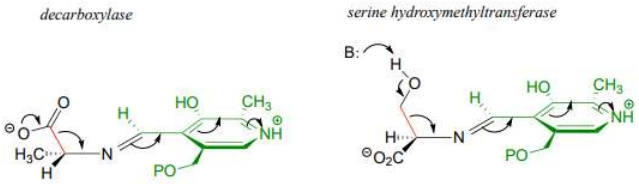
These results underline the close mechanistic relationship between two PLP-dependent reactions which, at first glance, appear to be quite different - and suggest that PLP-dependent racemases and aldolases may have evolved from a common 'ancestor' enzyme.

Stereoelectronic considerations of PLP-dependent reactions

Recall that all PLP-dependent reactions involve the cleavage of one of the bonds coming from the α-carbon of an amino acid substrate, with the coenzyme serving as an 'electron sink' to stabilize the intermediate that results. PLP-dependent enzymes accelerate this bond-breaking step by binding the substrate-PLP adduct in a conformation such that the bond being broken is close to perpendicular to the plane formed by the conjugated π system of PLP: this way, as the α-carbon transitions from sp^3 to sp^2 hybridization, the unhybridized π orbital is already oriented to overlap with the rest of the conjugated system. For example, in alanine racemase the first step is cleavage of the $C\alpha - H$ bond, so it must be that bond which is positioned near-perpendicular to the PLP plane:



Likewise, in an amino acid decarboxylase, the $C\alpha$-carboxylate bond is held near-perpendicular to the PLP plane, and in hydroxymethyltransferase, the $C\alpha - C\beta$ bond is in the perpendicular orientation:



These are all good examples of how enzymatic catalysis is achieved, in part, by the ability of the active site to bind the substrate molecule in a specific conformation which contributes to the lowering of the activation energy of a key reaction step.

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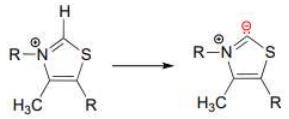
17.2: Thiamine Diphosphate (Vitamin B1)

Thiamine diphosphate (***ThDP***, sometimes also abbreviated ***TPP*** or ***ThPP***) is a coenzyme which, like PLP, acts as an electron sink to stabilize key carbanion intermediates. The most important part of the ***ThDP*** molecule from a catalytic standpoint is its thiazole ring.



thiamine diphosphate (ThDP)

The proton on the carbon between nitrogen and sulfur on the thiazole ring is weakly acidic, with a pK_a of about 18.



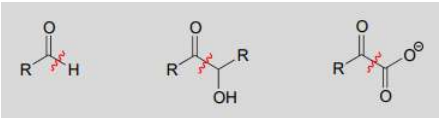
ThDP ylide

The reason for its acidity lies partly in the ability of the neighboring sulfur atom to accept, in its open ***d***-orbitals, some of the excess electron density of the conjugate base. Another reason is that the positive charge on the nitrogen helps to stabilize the negative charge on the conjugate base. The deprotonated thiazole is called an ylide, which is a general term for a species with adjacent positively and negatively charged atoms.

The negatively charged carbon on the ylide form of ***ThDP*** is nucleophilic, and as we shall soon see, the first step of most ***TPP***-dependent reactions is nucleophilic attack of the ylide carbon on a carbonyl group of the reaction substrate.

ThDP plays a key role in a variety of reaction types, but the common theme in all ***ThDP***-dependent reactions is cleavage of a bond adjacent to the carbonyl carbon of a ketone or aldehyde.

Thiamine diphosphate assists in breaking bonds next to a ketone or aldehyde:



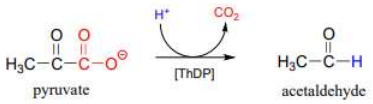
Consider this hypothetical decarboxylation step:



Hopefully, you can quickly recognize that this is not a chemically reasonable step, because the intermediate species which results from decarboxylation has a negative charge localized on the ketone carbon - a very unstable, unlikely intermediate indeed.

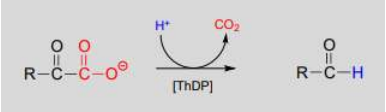
(Recall from section 13.1 that decarboxylation steps usually result in intermediates in which the negative formal charge is delocalized to an oxygen or nitrogen - in other words, enolates or enamines.)

Now consider, however, a reaction going on in your cells right now, catalyzed by the enzyme pyruvate decarboxylase (EC 4.1.1.1):

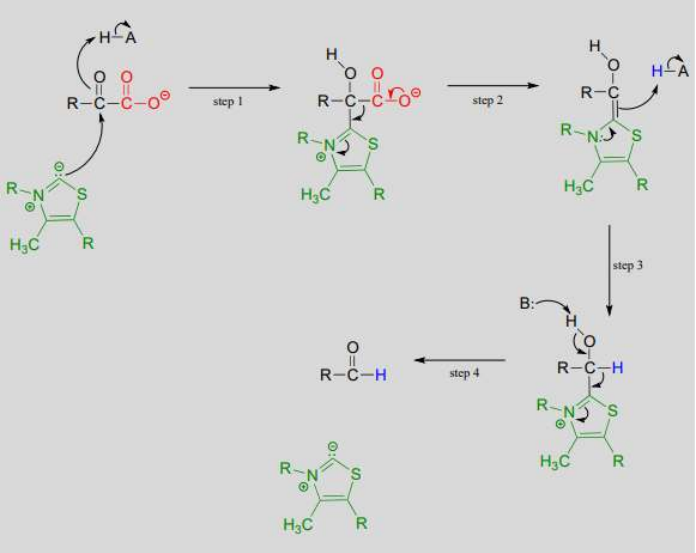


Somehow, the enzyme manages to accomplish this 'impossible' decarboxylation. How does this happen? Here is where the thiamine diphosphate coenzyme comes in.

A ***ThDP***-dependent decarboxylation reaction (pyruvate decarboxylase):



Mechanism:



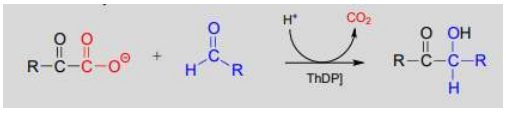
Upon binding to the enzyme's active site, ***ThDP*** quickly loses a proton. The nucleophilic ylide carbon then adds to the carbonyl carbon of pyruvate.

Look carefully at the intermediate that results from step 1 in the mechanism above. The thiazole ring of ***ThDP***, once it has added to the carbonyl of pyruvate, provides an 'electron sink' to absorb the electrons from decarboxylation (step 2). Note which bond is breaking in step 2 - as was mentioned earlier, the common function of ***ThDP*** is to make possible the cleavage of a bond to a carbonyl carbon.

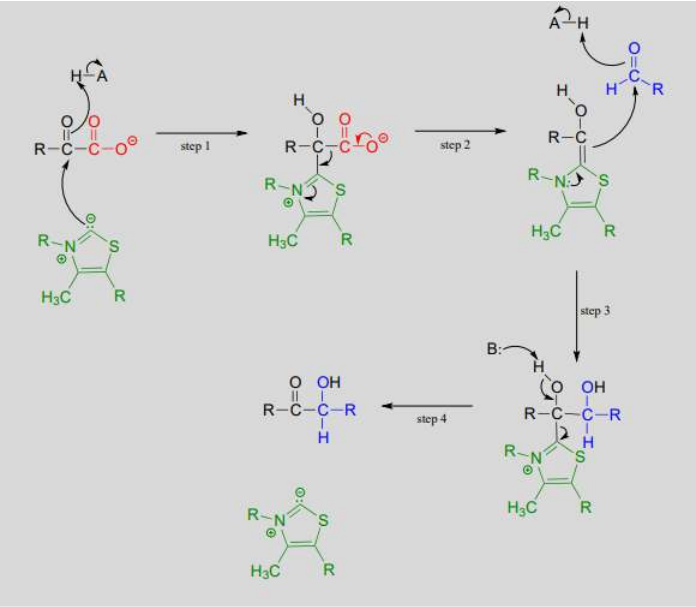
In step 3, the electrons from decarboxylation flow back to abstract a proton from an acidic group in the active site. All that remains is for the product to break free of thiamine in step 4.

Thiamine can also assist in decarboxylation-addition reactions:

ThDP-dependent decarboxylation-addition:

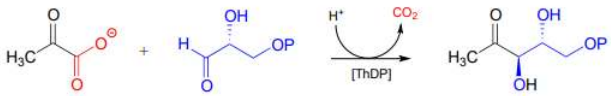


Mechanism:



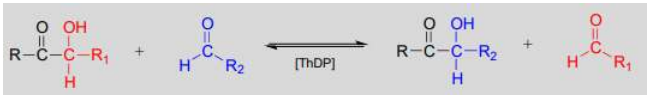
Here, the electron-rich intermediate formed from the decarboxylation step (step 2) simply goes on to act as a nucleophile rather than as a base, adding to the carbonyl group of an aldehyde or ketone (step 3). As before, the product breaks free of ***ThDP*** in step 4.

An example is the first step in the biosynthetic pathway for isoprenoid compounds in bacteria:

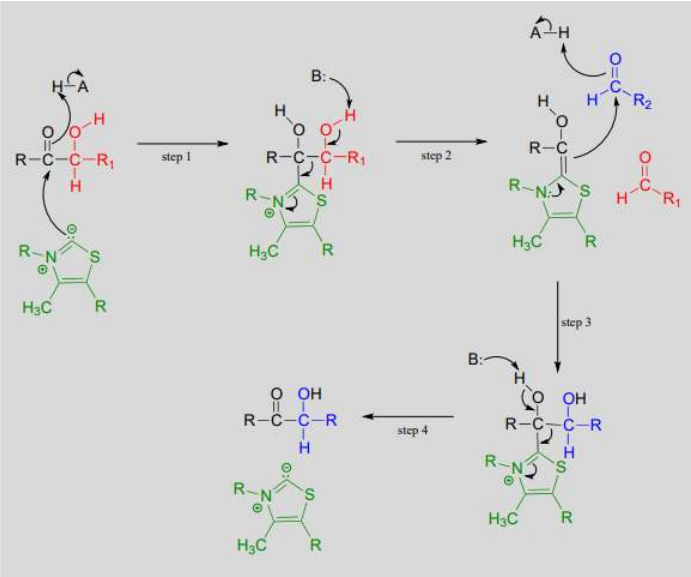


Transketolase, a ***ThDP***-dependent enzyme in the pentose phosphate pathway of sugar metabolism, catalyzes a carbon-carbon bond break step, followed by a carbon-carbon bond forming step. The substrates and products are at similar energy levels, so the reaction is completely reversible.

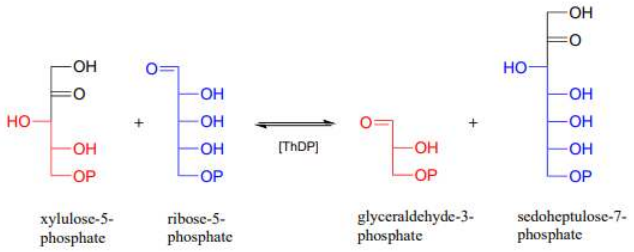
Transketolase reaction:



Mechanism:



Below is an actual example of a transketolase-catalyzed transformation from the pentose phosphate pathway (shown in Fischer projections, as is common for sugar structures).

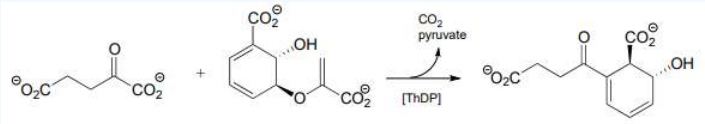


? Exercise 17.3.1

As was mentioned above, the transketolase reaction is highly reversible. Do you think the same can be said for the decarboxylation and decarboxylation-addition reactions we saw in this section? Why or why not?

? Exercise 17.3.2

(Challenging!) Propose a mechanism for the reaction below.

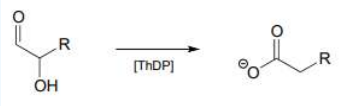


Hint

This is a *ThDP*-facilitated decarboxylation/ Michael addition, followed by \(E1cb\) elimination of pyruvate. A Michael addition is the name for a conjugate addition with a carbon nucleophile. (J. Mol. Biol. 2010, 401, 253).

Exercise 17.3.3

Propose a mechanism for the reaction below.



Hint

The mechanism can be described as a $ThDP$-facilitated dehydration step, followed by a tautomerization step, followed by a hydrolytic expulsion of $ThDP$ (a different kind of $ThDP$ expulsion from what we have seen so far!)

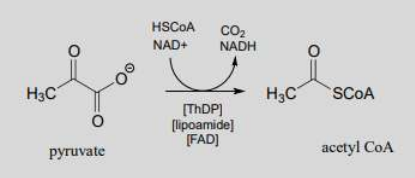
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17.3: Thiamine Diphosphate, Lipoamide and the Pyruvate Dehydrogenase Reaction

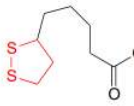
The enzyme pyruvate dehydrogenase is one of the most central of all the enzymes of central metabolism: by converting pyruvate to acetyl-***CoA***, it links glycolysis (where glucose is broken down into pyruvate) to the citric acid cycle, into which carbons enter in the form of acetyl-***CoA***. Five ceonzymes are involved: coenzyme A, nicotinamide, thiamine diphosphate, ***FAD***, and finally lipoamide, one which is new to us at this point.

Reaction catalyzed by pyruvate dehydrogenase:

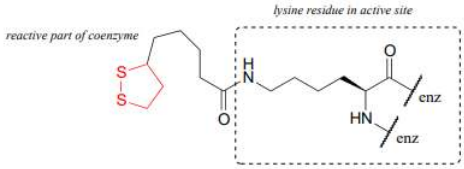


You will learn more about the structure and metabolic role of this complex and remarkable enzyme in a biochemistry course. Here, we will focus on the multi-step organic reaction it catalyzes, which we are at long last equipped to understand.

Looking at the reaction, you should recognize that, first of all, the pyruvate substrate is being oxidized - it starts out as a ketone, and ends up as a thioester, losing carbon dioxide in the process. Ultimately, the oxidizing agent in this reaction is ***NAD***$^+$, but the reduction of ***NAD***$^+$ is linked to the oxidative decarboxylation of pyruvate by ***FAD*** and a disulfide-containing coenzyme called lipoamide, which is lipoic acid attached by an amide linkage to a lysine residue on the enzyme.



lipoic acid

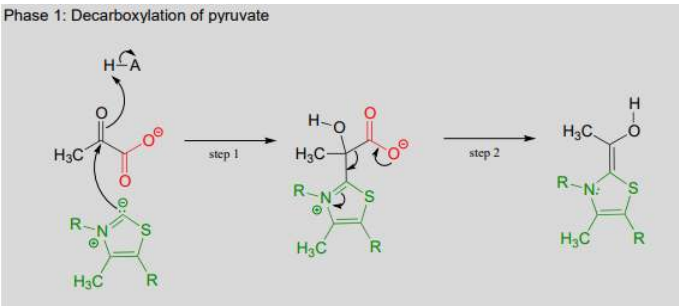


lipoamide
(linked to lysine residue in enzyme)

The second thing to notice is that, because the reaction involves breaking the bond between the ketone carbon and an adjacent carbon, thiamine diphosphate (***ThDP***) coenzyme is required. In fact, the first phase of the reaction (steps 1 and 2 below) is identical to that of pyruvate decarboxylase, an enzyme we discussed a few pages ago.

The pyruvate decarboxylase reaction mechanism

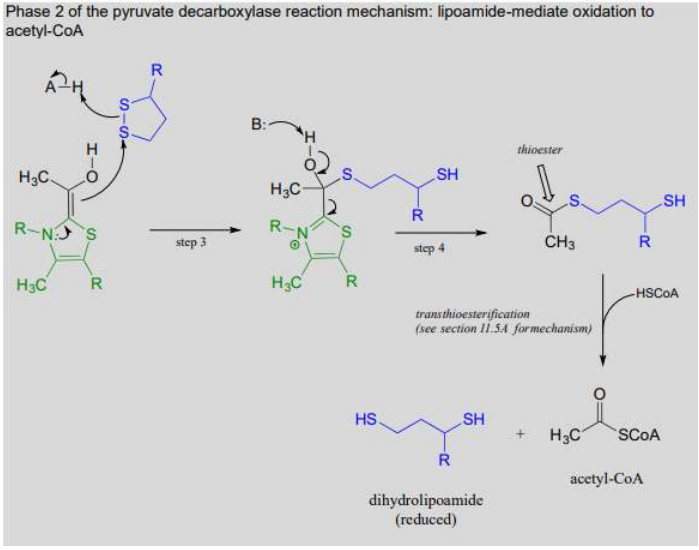
Phase 1: Decarboxylation of pyruvate



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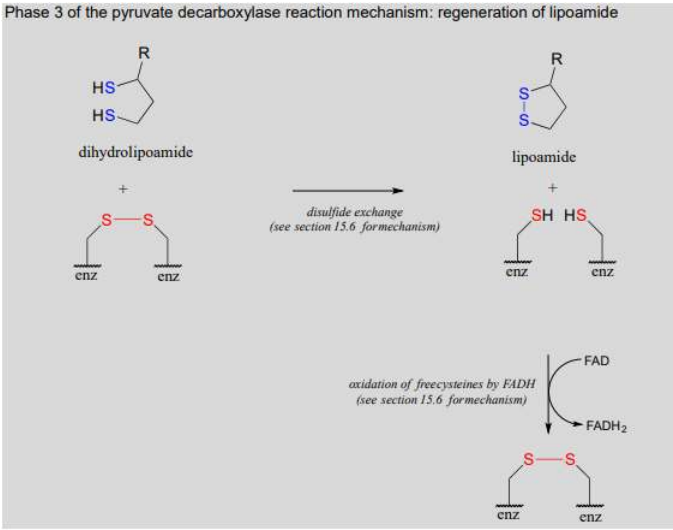
The ***ThDP***-stabilized carbanion then acts as a nucleophile, cleaving the disulfide bridge of lipoamide (step 3 below). It is in this step that oxidation of the substrate is actually occurring. After the resulting thioester product is released from ***ThDP*** (step 4 below), it undergoes transesterification form acetyl-***CoA***, the product of the reaction.

Phase 2 of the pyruvate decarboxylase reaction mechanism: lipoamide-mediate oxidation to acetyl-***CoA***



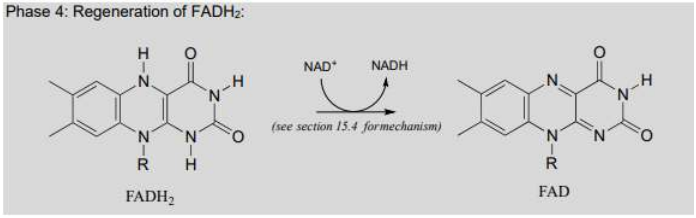
We are not done yet! In order for the catalytic cycle to be complete, the reduced dihydrolipoamide must be regenerated back to its oxidized state through disulfide exchange with a disulfide bond on the enzyme. The pair of enzymatic cysteines is then oxidized back to disulfide form by an ***FAD***-dependent reaction.

Phase 3 of the pyruvate decarboxylase reaction mechanism: regeneration of lipoamide



Finally, ***FAD*** is regenerated with concurrent reduction of NAD^+:

Phase 4: Regeneration of $FADH_2$:



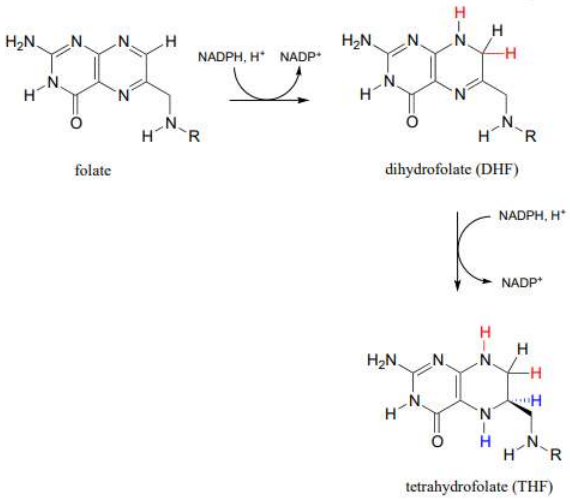
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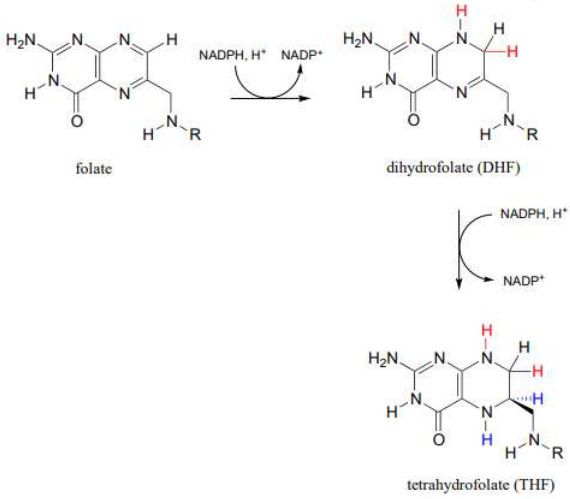
17.4: Folate

Folate, or vitamin B_9, is essential for a variety of important reactions in nucleotide and amino acid metabolism. The reactive part of folate is the **pterin** ring system, shown in red below. The conventional atom numbering system for folate is also indicated.

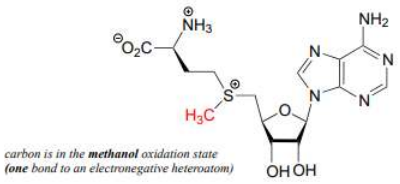


Active forms of folate

Folate is active as a coenzyme in its reduced forms, dihydrofolate and tetrahydrofolate, which are formed by $NADPH$–dependent imine hydrogenation steps (section 15.3).

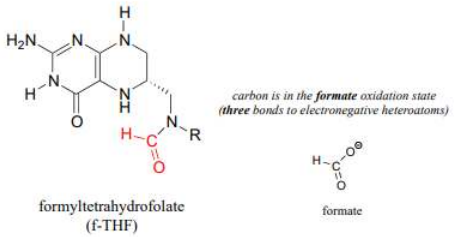


The metabolic role of folate is to serve as a donor or acceptor in single-carbon transfer reactions. How is folate different from S-adenosylmethionine (SAM, section 8.8) which also serves as a single-carbon donor? Recall that SAM donates a single carbon in the form of a methyl group: essentially, the single carbon of SAM is in the methanol (CH_3OH) oxidation state, because it has only one bond to a heteroatom (specifically, to sulfur). (Refer to section 15.1 for a review of oxidation states).



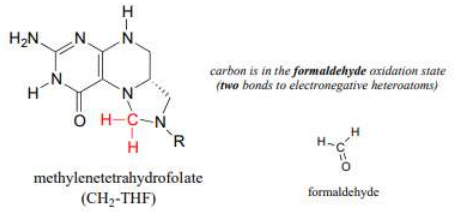
S-adenosylmethionine
(SAM)

Folate coenzymes, on the other hand, can carry a single carbon in the formaldehyde and formate oxidation states, in addition to the methanol oxidation state. By 'formaldehyde' and 'formate' oxidation state, we mean that the carbon has two and three bonds to heteroatoms, respectively.



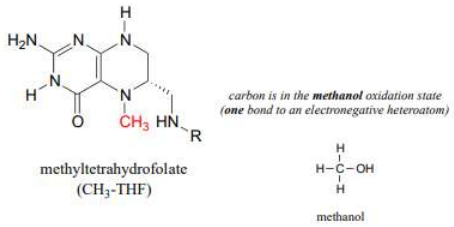
formyltetrahydrofolate
(f-THF)

formate



methylenetetrahydrofolate
(CH_2-THF)

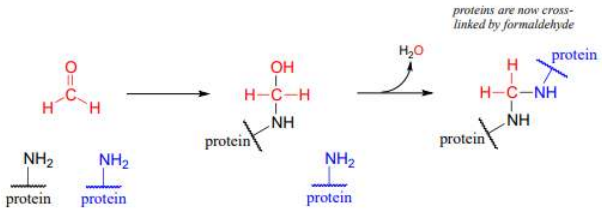
formaldehyde



methyltetrahydrofolate
(CH_3-THF)

methanol

Some key reactions in nucleic acid and amino acid metabolic pathways involve transfer of a single carbon in the formaldehyde or formate states. However, this could present problems. Formaldehyde by itself is very toxic: in particular, it tends to spontaneously form unwanted crosslinks between amine groups (eg. lysine side chains) in proteins.



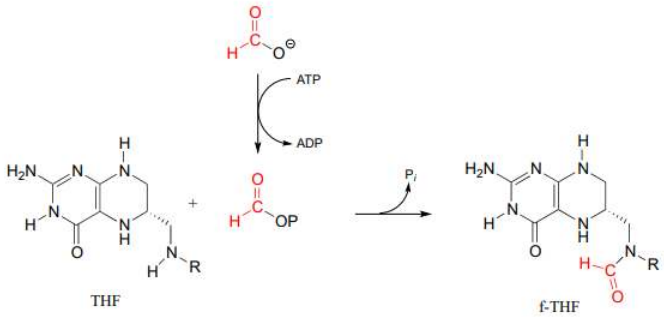
Free formaldehyde is too reactive, and would cause damage to a cell. The $\boldsymbol{CH_2-THF}$ coenzyme is stable in solution, but in the active site of certain enzymes it is reactive enough to serve as a formaldehyde donor, as we will see shortly.

Free formate, on the other hand, is a carboxylate, and we know from chapter 11 that carboxylates are not reactive in acyl substitution steps. Formate could be activated by phosphorylation, of course, but the resulting formyl phosphate would be too

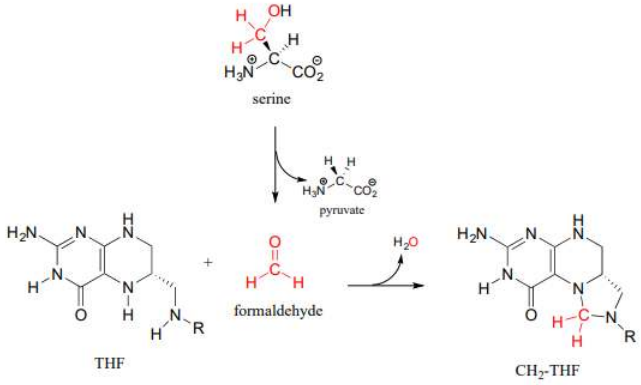
reactive in many enzyme active sites. A 'happy medium' has been found in which carbons in the formate oxidation state are carried by folate in the form of $f-THF$: once again, the carbon donor is stable in solution, but sufficiently reactive in certain enzyme active sites to accomplish controlled transfer of a formate group.

Formation of formyl-THF and methylene-THF

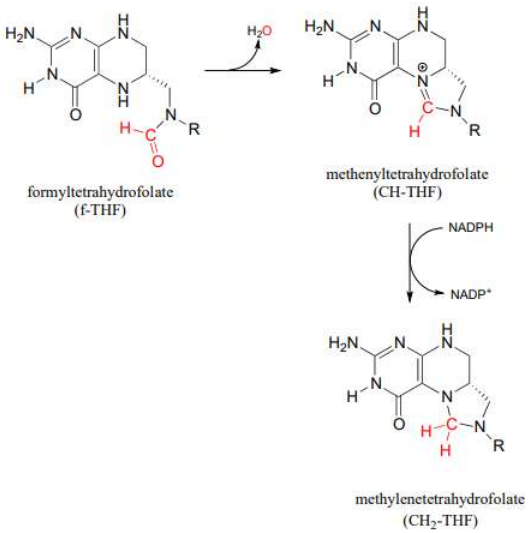
Formyltetrahydrofolate ($f-THF$) is formed from THF and a formate molecule which has been activated by phosphorylation (formyl phosphate, as stated in the paragraph above, is a high reactive intermediate, but is held inside the enzyme's active site for immediate reaction with the incoming amine group of THF).



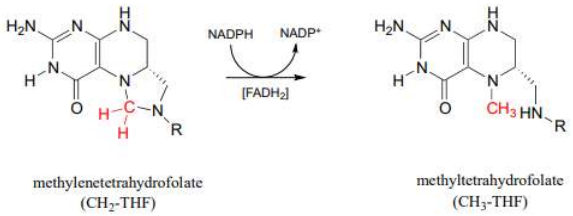
There are two main metabolic routes to CH_2-THF. One route is just the last step of the serine hydroxymethyltransferase reaction we have already seen in section 17.1: the formaldehyde formed in the PLP-dependent phase of the reaction stays in the active site, and the oxygen is displaced by successive attacks from the amine nucleophiles at the 5 and 10 positions of THF. (Notice the similarity to the formaldehyde-protein crosslinking reaction shown earlier in this section.)



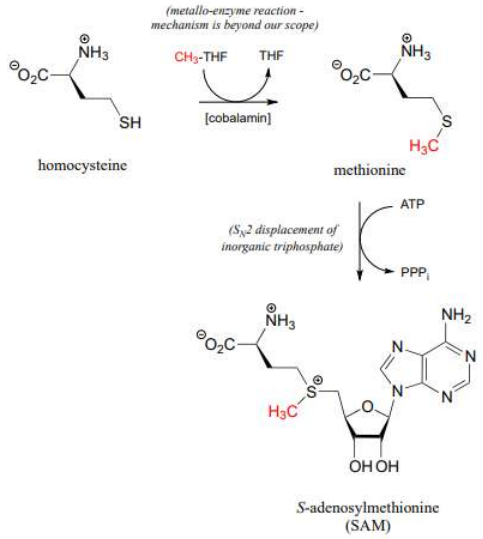
In the second route, $f-THF$ is dehydrated, then the resulting methenyl-THF intermediate is reduced by $NADPH$.



Methylene-THF (CH_2-THF) is reduced to methyl-THF (CH_3-THF) in a flavin-dependent reaction. *Biochemistry 2001, 40, 6216*



Recall from the introduction to this chapter that babies who were in the womb during the Dutch Hunger Winter faced a higher risk, when they reached adulthood, of conditions such as obesity and schizophrenia, most likely caused by disruptions in the S-adenosylmethionine-dependent methylation of their DNA, which was in turn caused by their mothers not getting enough folate. CH_3-THF is the source of the methyl group in methionine, which ultimately becomes the methyl group in SAM. The methylation of homocysteine to methionine (below) involves a cobalt-containing coenzyme called cobalamin, but the mechanism for this reaction is beyond the scope of our discussion. The second reaction below (formation of SAM) is simply an SN_2 displacement of the inorganic triphosphate leaving group on ATP by the nucleophilic sulfur in methionine.

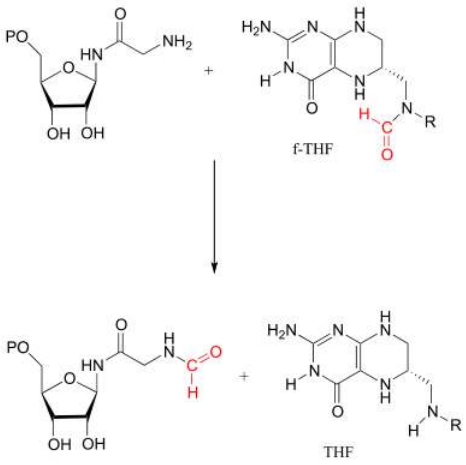


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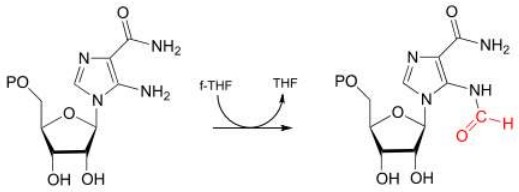
Single-carbon transfer with formyl-THF

There are two important $f-THF$-dependent formylation steps in the biosynthetic pathways for purine nucleophiles. Both are simply transamidation reactions: in other words, conversion by the nucleophilic acyl substitution mechanism (chapter 11) of one amide to another.

Glycinamide ribonucleotide transformylase reaction:



Aminoimidazole carboxamide transformylase reaction:

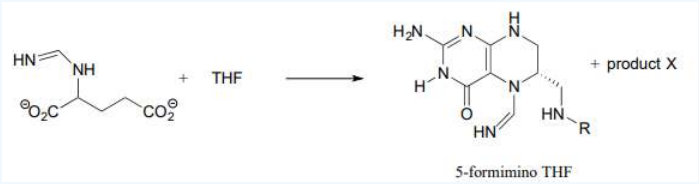


? Exercise 17.5.1

Which of the two transformylase reactions above would you expect to be more kinetically favorable? Explain your reasoning.

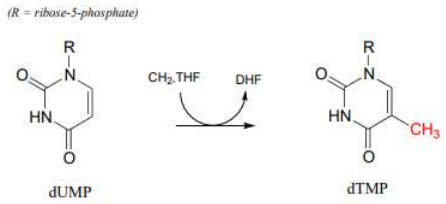
? Exercise 17.5.2

Predict the structure of 'product X' in the reaction below, from the histidine degradation pathway.

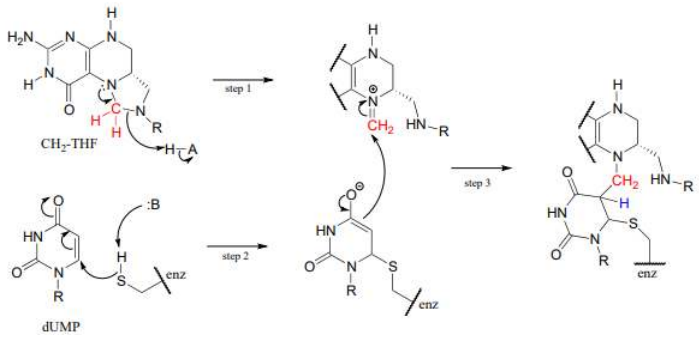


Single-carbon transfer with methylene-THF

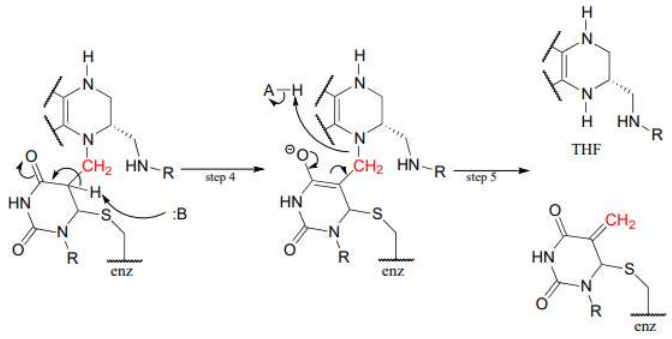
CH_2-THF serves as a single-carbon donor in a somewhat complicated reaction in the biosynthesis of the DNA monomer doexythymidine monophosphate ($dTMP$).



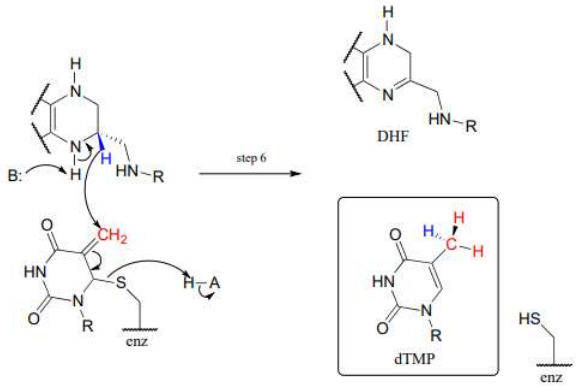
The reactions begins with the five-membered ring of CH_2-THF breaking apart to create an imine intermediate (step 1 below). The imine becomes an electrophile in a conjugate addition step (section 13.4, steps 2-3 below). Note that after step 1, the second ring in the pterin system of the coenzyme is abbreviated for clarity.



Next, tetrahydrofolate is eliminated in an $E1cb$ elimination mechanism (steps 4 and 5). Notice that this is where the single carbon is transferred from methyl-THF to dUMP.



The final step in the mechanism is where it gets really interesting: a hydride ion is transferred from the tetrahydrofolate coenzyme to the methylene (CH_2) group on the deoxynucleotide substrate. Essentially, this is a conjugated SN_2 step with hydride as the nucleophile and the active site cysteine as the leaving group.



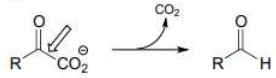
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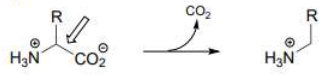
17.E: The Oganic Chemistry of Vitamins (Exercises)

P17.1: Here is a chance to test your ability to recognize reactions catalyzed by enzymes using three coenzymes - thiamine diphosphate, pyridoxal phosphate, and folate - that we have studied in this chapter. For each generalized reaction, look carefully at the transformation that is taking place, and decide which of the three coenzymes is likely to be required. Then, draw the single mechanistic step by which the bond identified by an arrow is broken or formed. In the cases where a double bond is indicated, show the mechanistic step in which the s bond is formed. In each case, your drawing should include the structure of the reactive part of the coenzyme, and should clearly show the role it plays in catalyzing the mechanistic step you are drawing.

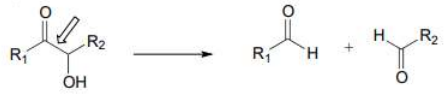
a)



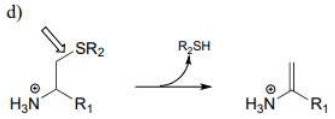
b)



c)



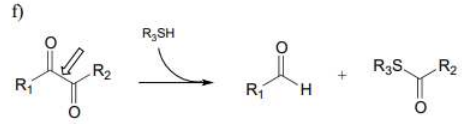
d)



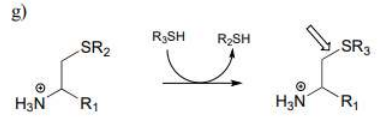
e)



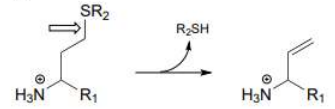
f)



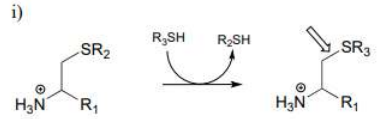
g)



h)

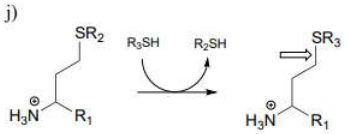


i)

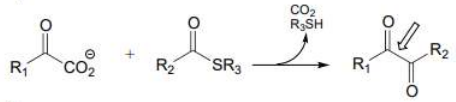


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j)



k)



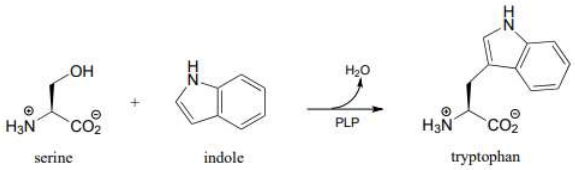
l)



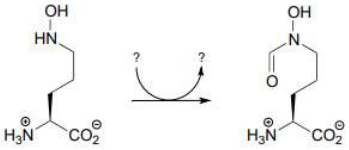
m)



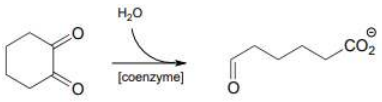
P17.2: The final step in the biosynthesis of the amino acid tryptophan is a PLP-dependent condensation between serine and indole, shown below (EC 4.2.1.20). The reaction mechanism involves steps that are familiar from this chapter, but also incorporates a reaction type we studied in chapter 14. Propose a mechanism.



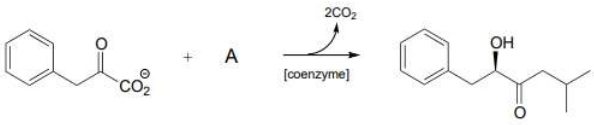
P17.3: Draw a reasonable mechanism for the following reaction, identifying the species denoted by questions marks. (Biochemistry 2012, 51, 3059)



P17.4: Propose a mechanism for the reaction below, which is part of the anaerobic catabolism of alcohols in some species of bacteria. (ChemBioChem 2014, 15, 389)

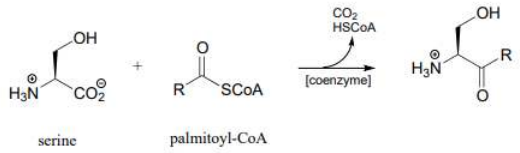


P17.5: Identify cosubstrate A and propose a mechanism for the reaction shown below, which was reported to occur in the thermophilic bacterium *Thermosporothrix hazakensis*. (ChemBioChem 2014 15, 527).



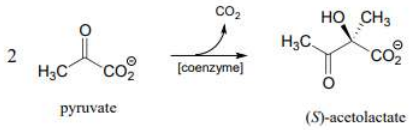
P17.6: Propose a mechanism for each of the reactions below, being sure to show the role played by the coenzyme (you need to determine which coenzyme is needed in each case).

a)



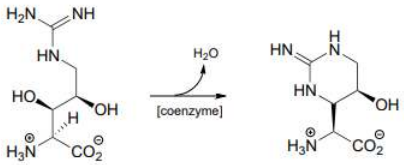
serine palmitoyl-CoA

b) (E.C. 2.2.1.6)



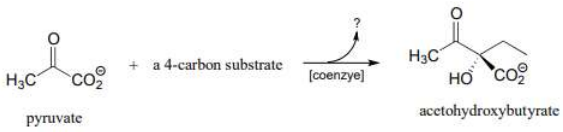
pyruvate (*S*)-acetolactate

c) *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 1943.



P17.7: Acetohydroxybutyrate is formed in a coenzyme-dependent reaction between pyruvate and a 4-carbon compound. What is a likely second substrate, coenzyme, and by-product (indicated below with a question mark)?

http://www.sciencedirect.com/science...67593105001043



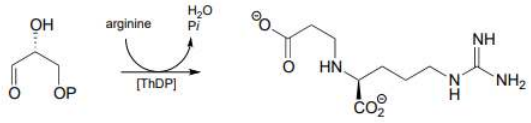
pyruvate acetohydroxybutyrate

P17.8: The 'benzoin condensation' reaction was discovered in the 19th century, and led eventually to a better understanding of ***ThDP***-dependent reactions in the cell. In a traditional benzoin condensation reaction, cyanide ion (instead of ThDP) plays the role of electron acceptor. Enzyme-catalyzed benzoin condensation reactions are also known to occur in some bacteria: Pseudomonas fluorescens, for example, contains an enzyme that catalyzes the synthesis of (R)-benzoin.



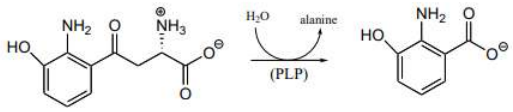
benzaldehyde benzoin

a. Draw a mechanism for the enzyme-catalyzed (***ThDP***-dependent) benzoin condensation reaction.
b. Draw a mechanism for the cyanide-catalyzed benzoin condensation reaction (non-enzymatic, basic conditions).
c. The following ***ThDP***-reaction was recently reported to be part of the biosynthetic pathway for clavulanic acid, a compound that inhibits the action of b-lactamases (b-lactamases are bacterial enzymes that hydrolyze penicillin-based antibiotic drugs, rendering them ineffective). As is typical for ***ThDP***-dependent reactions, the first step is addition of the ylide form of the coenzyme to the substrate carbonyl. The next steps are (in order): dehydration, tautomerization, elimination of phosphate, conjugate addition of arginine, and finally hydrolytic cleavage of the coenzyme-product bond. Draw out a complete mechanism that corresponds to this description.

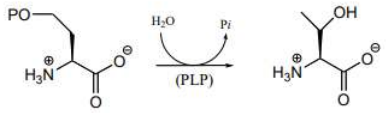


P17.9: Practice with PLP-dependent reactions:

a. Propose a mechanism for this reaction, which is part of the tryptophan degradation pathway (EC 3.7.1.3).

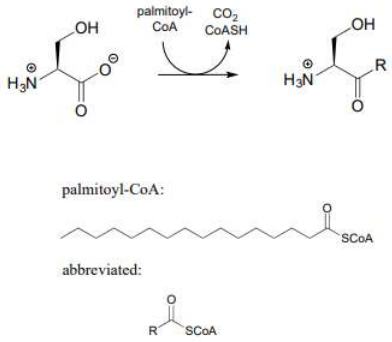


b. Propose a mechanism for the final step of the threonine biosynthesis pathway (EC 4.2.3.1).

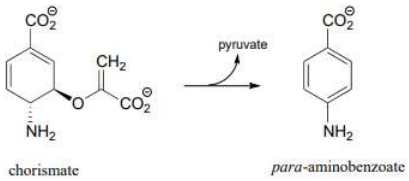


c. Propose a mechanism for the reaction catalyzed by aspartate β-decarboxylase (EC 4.1.1.12), which converts aspartate to alanine in a PLP-dependent reaction.

d. Sphingolipids are a type of membrane lipid found in the membranes of all eukaryotic cells, and are most abundant in the cells of central the central nervous system. Synthesis of sphingolipids involves the PLP-dependent reaction below, catalyzed by serine palmitoyl transferase (EC 2.3.1.50). Propose a mechanism.

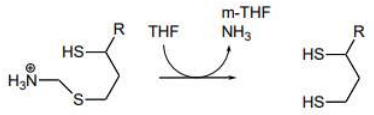


P17.10: As we saw in this chapter, PLP-dependent enzymes usually catalyze reactions involving amino acid substrates. Here is an exception, a PLP-dependent β-elimination reaction in the folate biosynthetic pathway (EC 4.1.3.38). Propose a mechanism for this reaction.

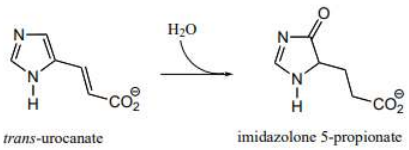


P17.11: The final step in the degradation pathway for the amino acid glycine (also known as the 'glycine cleavage system') is shown below. Propose a likely mechanism, given that evidence suggests that $CH_2NH_2^+$ is an intermediate.

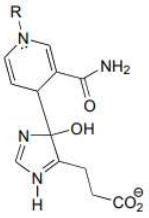
https://chem.libretexts.org/@go/page/393682



P17.12: As we saw in chapter 15, the usual biochemical role of NAD^+ is to act as a hydride acceptor in dehydrogenation reactions. An exception is the reaction catalyzed by the histidine degradation pathway enzyme urocanase (EC 4.2.1.49).



In this reaction, NAD^+ acts as a catalytic, electron-sink coenzyme - it temporarily accepts electrons from a pi bond in the substrate, resulting in a covalent substrate-NAD adduct. This allows a key isomerization step to occur on the substrate through a protonation-deprotonation mechanism, followed by addition of water, cleavage of the substrate-NAD adduct to regenerate NAD^+, and finally tautomerization to the product. Propose a mechanism that fits this description, and involves the intermediate below.



reaction intermediate

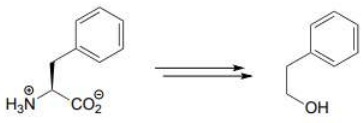
Pathway prediction problems

P17.13: Propose a multistep pathway for each of the following transformations. All involve at least one step requiring PLP, $ThDP$, or folate.

a. Below is portion of the biosynthesis of a modified membrane lipid in Salmonella and other pathogenic bacteria. The modified membrane confers antibiotic resistance to the bacterium.

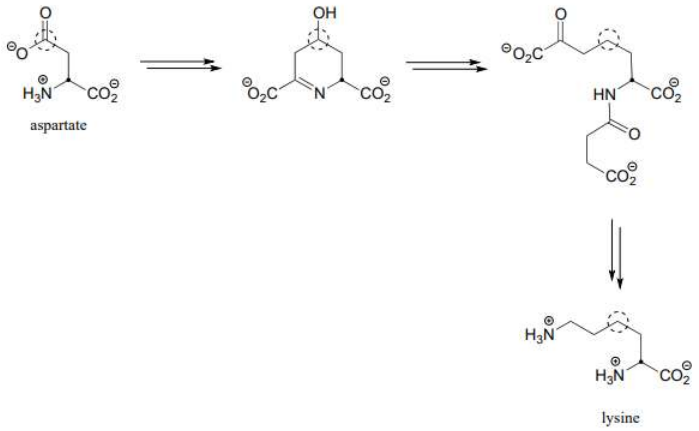


b. Below is the biosynthetic pathway for phenethanol in yeast. Phenethanol, which has a rose scent, is commonly used as a fragrance - this pathway has been proposed as a potential 'green' enzymatic synthesis to replace the traditional industrial synthesis, which uses toxic reagents.

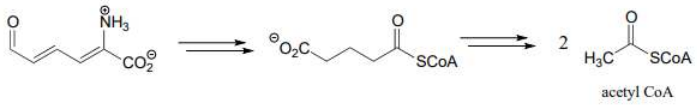


phenylalanine phenethanol

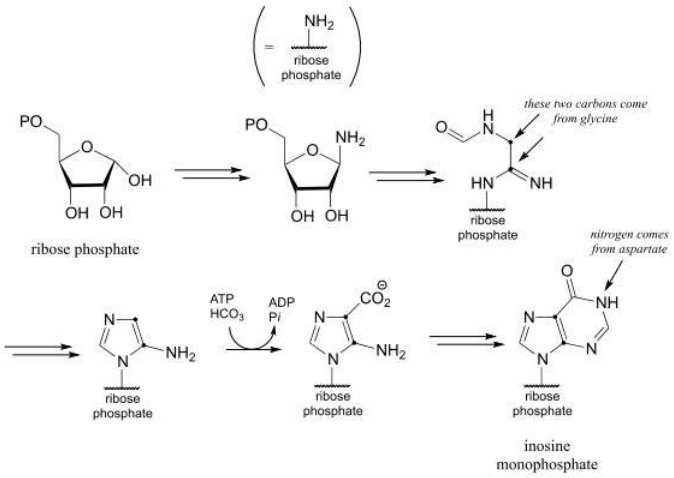
c. Below is an incomplete pathway diagram for the biosynthesis of the amino acid lysine, starting from aspartate. Fill in the missing steps and reactants/coenzymes to complete the diagram. The solid dot and dashed circle are provided to help you to trace two of the carbons from substrate to product.



d. Below is the second half of the tryptophan degradation pathway. Fill in the missing steps and reactants/coenzymes to complete the diagram.

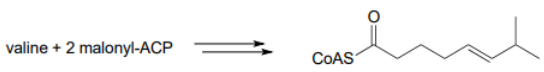


e. Below is an incomplete pathway diagram for the biosynthesis of inosine monophosphate, a precursor to the nucleotides adenosine monophosphate (***AMP***) and guanosine monophosphate (***GMP***). Fill in missing steps and reactants/coenzymes to complete the diagram. Note that one enzymatic step is provided (this is a carboxylation reaction of a type that we have not studied).

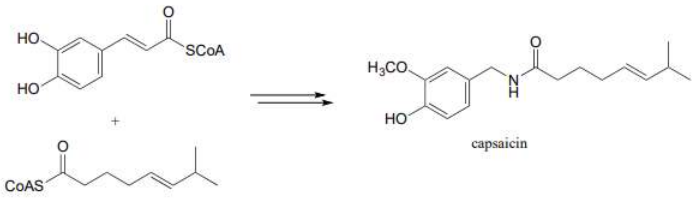


f. We begin our study of organic chemistry with a story about a hot pepper eating contest in Wisconsin (see the introduction the Chapter 1), and a compound called capsaicin which causes the 'hot' in hot peppers. As our last problem, let's try to predict some of the key steps in the biosynthesis of capsaicin.

Phase 1:



Phase 2:



Contributors and Attributions

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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17.S: The Oganic Chemistry of Vitamins (Summary)

After completing this chapter, you should be able to:

- Understand how pyridoxal phosphate (PLP) acts as an 'electron sink' in a variety of reactions in amino acid metabolism.
- Recognize and draw mechanisms for PLP-dependent transformations of the following types:
  - racemization
  - decarboxylation
  - transamination
  - retroaldol cleavage
  - retro-Claisen cleavage
  - β-elimination
  - β-substitution
  - γ-elimination
  - γ-substitution
- Recognize transformations - amino acid decarboxylation and transamination, for example - in which chemical steps occur that simply don't 'make sense' unless the electron sink role of PLP is taken into account.
- Understand how the orientation of the substrate in relation to the plane formed by the conjugated π system of PLP is a major factor in catalysis of PLP-dependent reactions.
- Understand how thiamine diphosphate ($ThDP$) acts as an 'electron sink' in a variety of reactions in which a bond to a carbonyl carbon is broken, and how these steps do not 'make sense' unless the electron sink role of $ThDP$ is taken into account.
- Recognize transformations for which $ThDP$ is likely required, and be able to draw reasonable mechanisms for them.
- Understand how $ThDP$ acts in tandem with lipoamide, flavin, and nicotinamide in the reaction catalyzed by pyruvate dehydrogenase.
- Recognize folate in its various forms - DHF, THF, $f-THF$, CH_2-THF, and CH_3-THF - functions in a variety of one-carbon transfer steps. Be able to recognize the oxidation state of the carbon being transferred in a folate-depenent step.

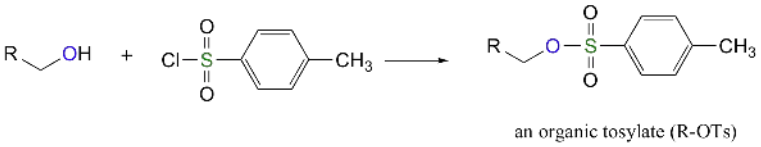
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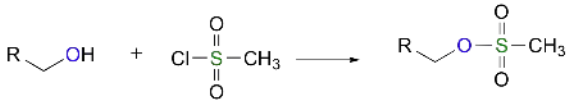
Appendix II: Review of laboratory synthesis reactions

While the focus of this textbook is on organic reactions occuring in living cells, if you are a chemistry major, or are planning to take a standardized exam such as the MCAT, you will need to be familiar with a number of laboratory synthesis reactions. Here, we review the lab synthesis reactions covered in this text, which include most of the reactions typically covered in traditional organic texts. Click on the chapter/section number for direct links to the section where these reactions are introduced.

Section 8.5B:

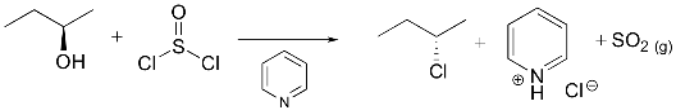


an organic tosylate (R-OTs)



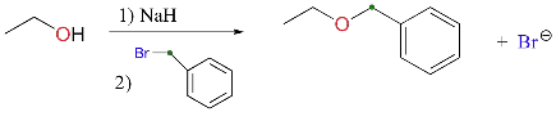
an organic mesylate (R-OMs)

alcohols converted into good leaving groups





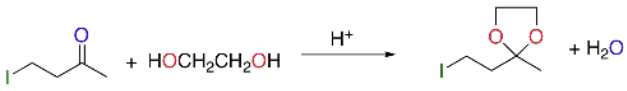
Section 9.1B:



Williamson ether synthesis

alkyl halide must be methyl or primary to avoid competing elimination

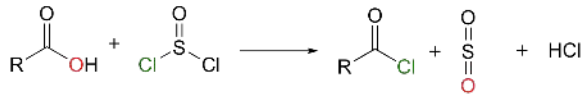
Section 11.4B:

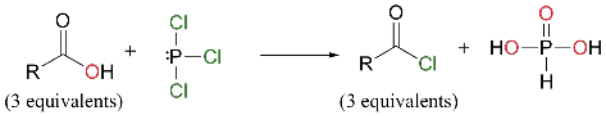


cyclic acetal 'protects' ketone/aldehyde group – stable to bases/nucleophiles

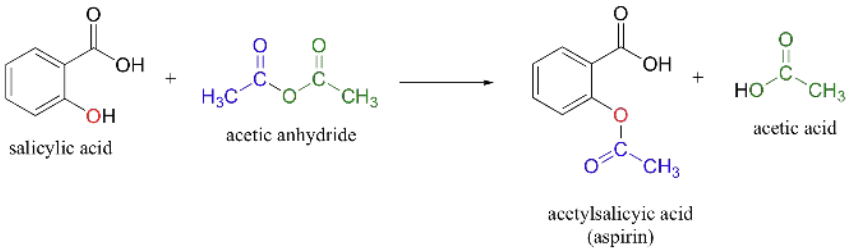
deprotect with aqueous acid

Section 12.2D:





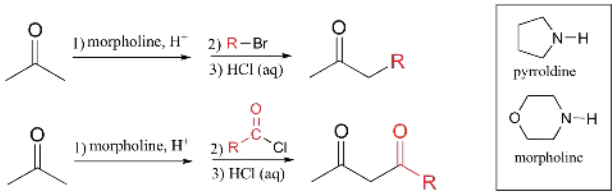
activates carboxylic acids



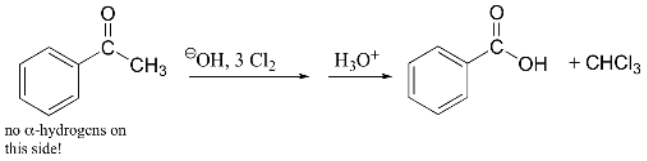
acetic anhydride is a good acetyl group donor (activated acetic acid)

adds acetyl group to acohols, amines

Section 13.6A

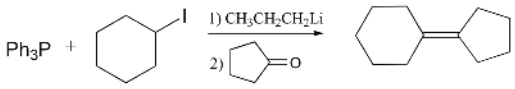


goes through enamine intermediate



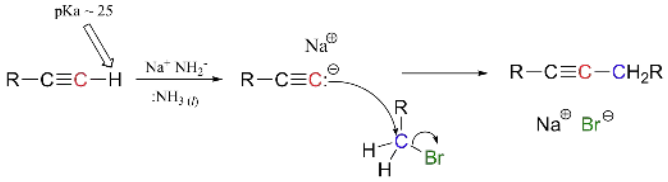
haloform reaction – also works with Br_2, I_2

Section 13.6B

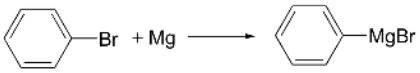


Wittig reaction

Section 13.6C



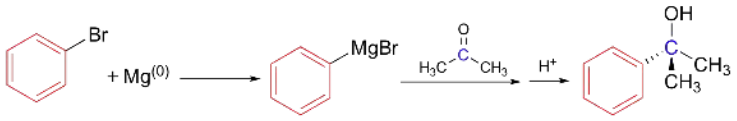
Section 13.6D

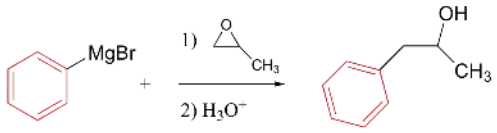


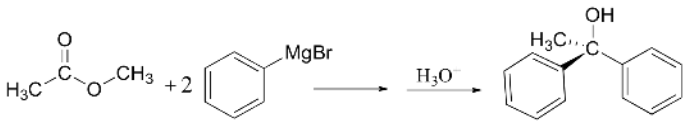
Grignard reagent – carbon nucleophile

No acidic protons can be present (it's a strong base)

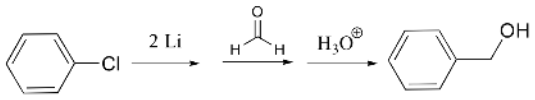
Can also use R-Cl



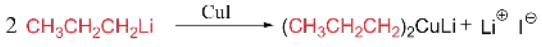




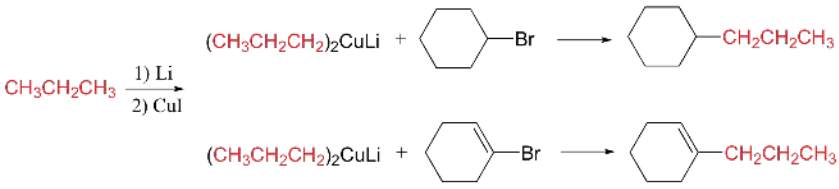
*Grignards add to esters, acid chlorides **twice***



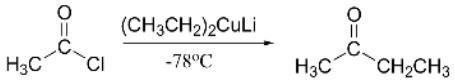
organolithium – similar to Grignard



Gilman reagent

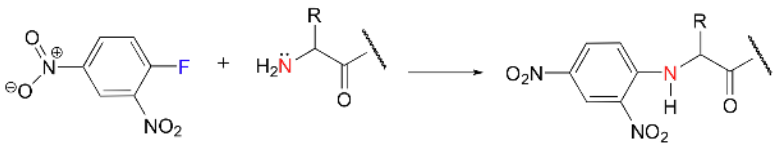


Gilman reagent will react with alkyl, vinyl halides as well as carbonyls



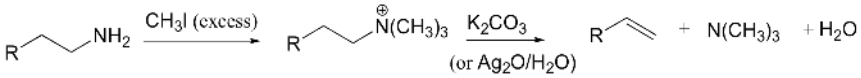
*Gilman reagent will add **once** to acid chlorides to make a ketone*

Section 14.2B

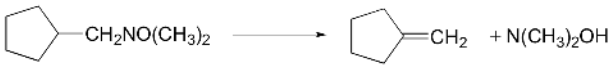


nucleophilic aromatic substitution

Section 14.3A

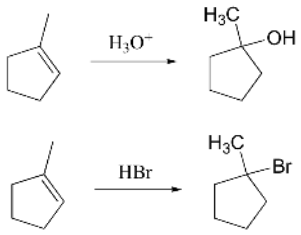


Hoffman elimination - least substituted alkene produced

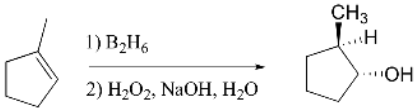


Cope elimination

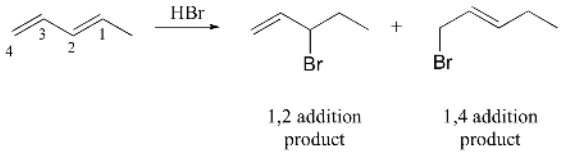
Section 15.2B

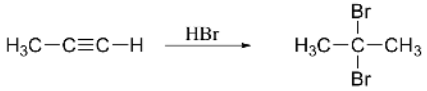


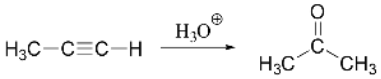
Section 15.2D

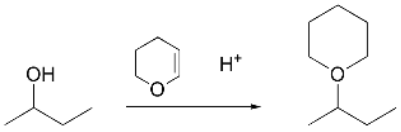


anti-Markovnikov addition of water to alkene. Notice syn addition!

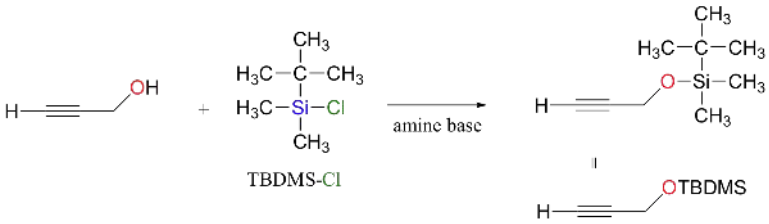






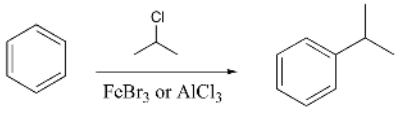


method to protect alcohol – remove with H_3O^+

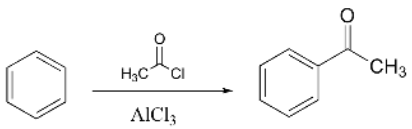


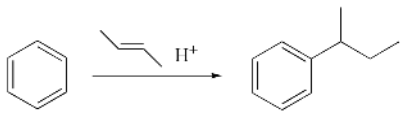
another alcohol protecting group: remove with F^- ion

Section 15.6A:

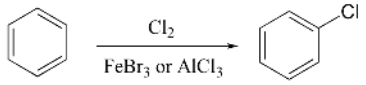


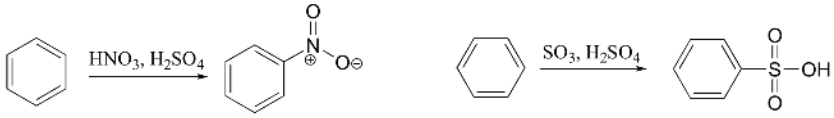
watch out for the possibility of carbocation rearrangements!





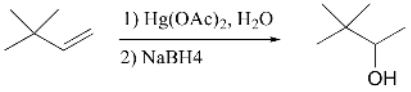
watch out for the possibility of carbocation rearrangements!





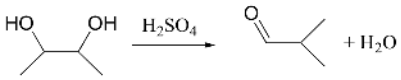
ortho-para directing vs. meta-directing groups

Section 15.7A:

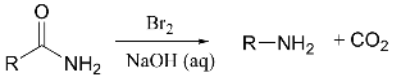


Markovnikov addition of water without possibility of carbocation shifting

Section 15.7C:

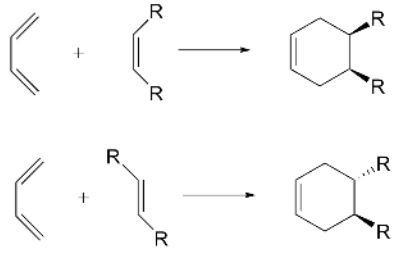


pinacol rearrangement

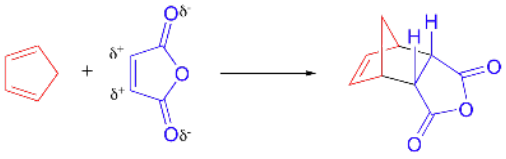


Hoffman rearrangement

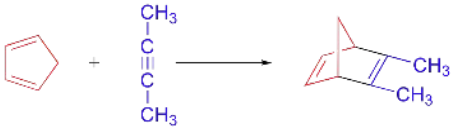
Section 15.10:



Diels-Alder: cis/trans stereoselectivity



bicyclic Diels-Alder product - no stereoselectivity



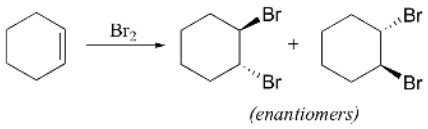


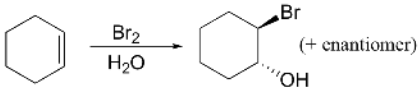
Cope rearrangement

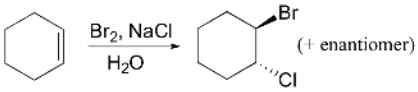


Claisen rearrangement

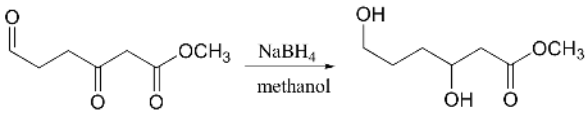
Section 16.11B:



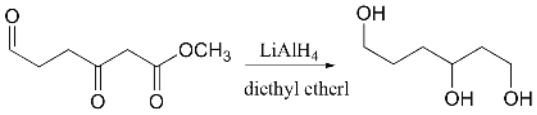




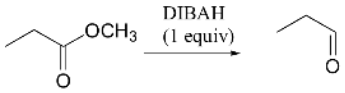
Section 16.13A:



reduces aldehydes/ketones, but not carboxylic acid derivatives

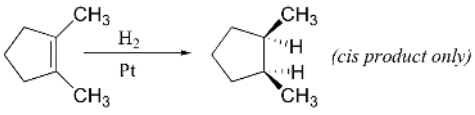


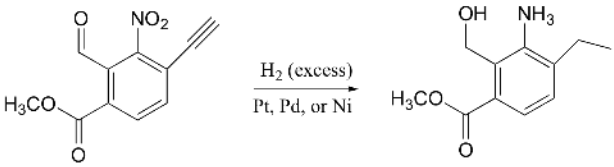
reduces aldehydes, ketones, carboxylic acid derivatives



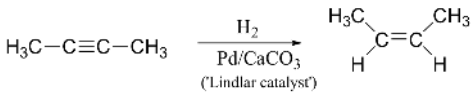
can reduce ester/amide to aldehyde ($LiAlH_4$ can't do this)

Section 16.13B:

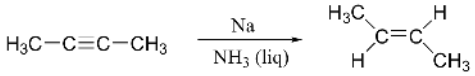




alkynes, aldehyde, ketones, nitro groups also reduced by H_2/Pt (but not acid derivatives!)

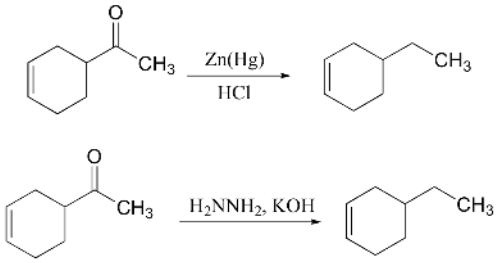


alkyne to cis-alkene

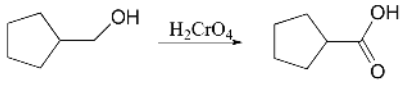


alkyne to trans-alkene

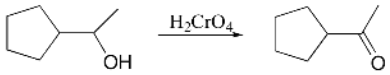
Section 16.13C:



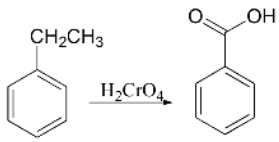
Section 16.13D:



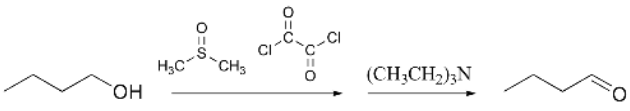
primary alcohol to acid



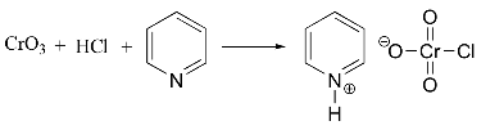
secondary alcohol to ketone



oxidation at the benzylic position

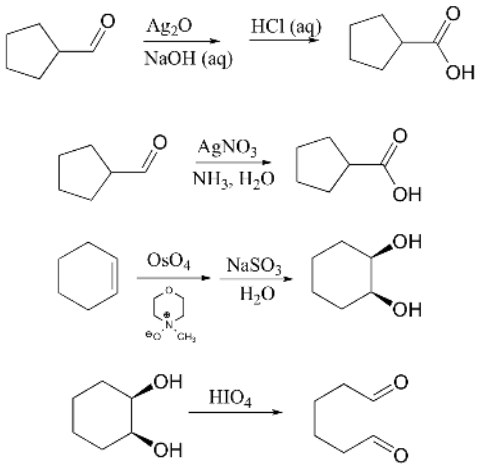


Swern oxidation

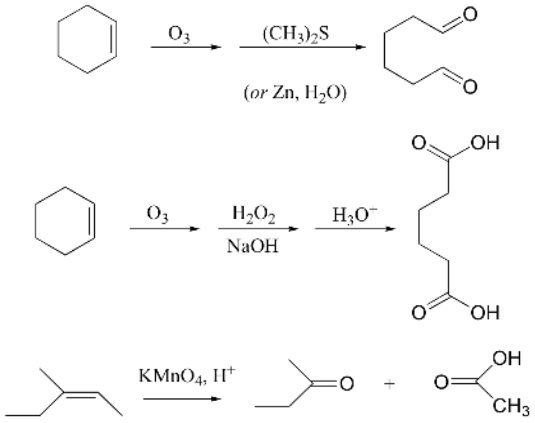


pyridinium chlorochromate
(oxidized alcohols to aldehydes/ketones)

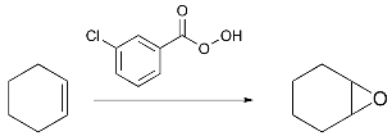
abbreviated PCC



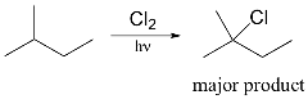
cis diols cleaved, not trans



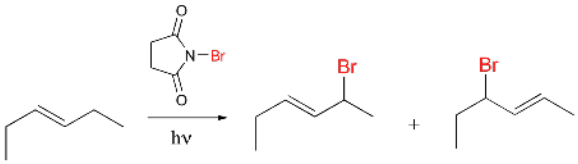
$KMnO_4$ also oxidizes primary alcohols and aldehydes to acids

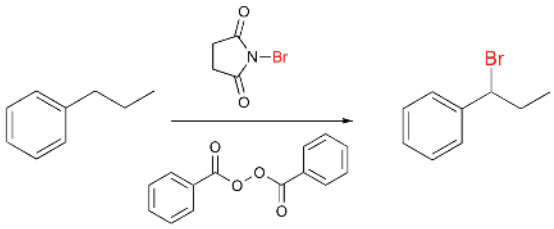


Section 17.2B:



radical halogenation is regiospecific – depends on stablity of radical intermediate





NBS can be source of Br in radical halogenation reactions

regiospecificity: benzylic / allylic

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CHAPTER OVERVIEW

Appendix I: Index of enzymatic reactions by pathway

While Organic Chemistry With a Biological Emphasis is organized, like most sophomore-level organic chemistry texts, around a structural and mechanistic framework, students of biochemistry may often want to clarify the mechanism of an enzymatic reaction which they encounter when studying the central metabolic pathways. An excellent resource for this purpose is John McMurry's The Organic Chemistry of Biological Pathways (Roberts and Company, 2005), but also helpful will be this index of enzymatic reactions organized by pathway, with links to sections/problems in this text where the reaction mechanism is addressed. Sections/problems listed with an asterisk (*) do not discuss the exact reaction indicated, but do discuss a closely related reaction.

EC numbers are provided whenever possible, with links to the corresponding page in the BRENDA database of enzymes. Clicking on the 'reaction flask' icon on a BRENDA page brings up the reaction diagram.

Pathways

- Amino acid biosynthesis
- Amino acid catabolism
- Citric Acid Cycle
- Fatty acid metabolism
- Glycolysis, Gluconeogenesis, Fermentation
- Isoprenoid biosynthesis
- Nucleoside biosynthesis
- Nucleotide catabolism
- Pentose Phosphate Pathway, Calvin Cycle

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Amino acid biosynthesis

Sections/problems listed with an asterisk (*) do not discuss the exact reaction indicated, but do discuss a closely related reaction.

Alanine (from pyruvate)

- Alanine aminotransferase (EC 2.6.1.2) Section 14.4E*

Aspartate (from oxaloacetate):

- Aspartate aminotransferase (EC 2.6.1.1) Section 14.4E

Glutamate (from *alpha*-ketoglutarate)

- Glutamate aminotransferase (EC 2.6.1.1) Section 14.4E

Glutamine (from glutamate)

- Glutamine synthase (EC 6.3.1.2) Section 10.2D, Section 12.2A

Asparagine (from aspartate)

- Asparagine synthase (EC 6.3.5.4) Section 10.2E, Section 12.2B

Arginine (from glutamate via ornithine, urea cycle)

- N-acetylglutamate synthase (EC 2.3.1.1) Section 12.3*
- Acetylglutamate kinase (EC 2.7.2.8) Section 10.2D*, Section 12.2*
- *N*-acetyl-*gamma*-glutamyl-phosphate reductase (1.2.1.38) Section 16.4D*
- Acetylornithine aminotransferase (EC 2.6.1.11) Section 14.4E*
- Acetylornithine deacetylase (EC 3.5.1.16) Chapter 12*

to arginine via urea cycle:

- Ornithine transcarbamylase (EC 2.1.3.3) Section 12.2A,B*
- Argininosuccinate synthetase (EC 6.3.4.5) Section 12.6, Section 14.1D
- Arginosuccinate lyase (EC 4.3.2.1) Section 14.1D
- Arginase (EC 3.5.3.1) P12.16

Proline (from glutamate)

- Glutamate-5-kinase (EC 2.7.2.11) Section 16.4D
- Glutamate-5-semialdehyde dehydrogenase (EC 1.2.1.41) Section 16.4D, reverse of P11.2
- Pyrroline-5-carboxylate reductase (EC 1.5.1.2) Section 16.4D

Serine (from 3-phosphoglycerate)

- Phosphoglycerate dehydrogenase (EC 1.1.1.95) Section 16.4*
- Phosphoserine transaminase (EC 2.6.1.52) Section 14.4E*
- Phosphoserine phosphatase (EC 3.1.3.3) Section 10.3*

Cysteine (from serine)

- Cystathionine *beta*-synthase (EC 4.2.1.22) Section 14.4G*
- Cystathionine *gamma*-lyase (EC 4.4.1.1) Section 14.4G

or, in bacteria:

- O-acetylserine sulfhydrolase (EC 2.5.1.47) Section 14.4F

Glycine (from serine)

- Serine hydroxymethyltransferase (EC 2.1.2.1) Section 14.4D

Lysine (from aspartate)

- Aspartate kinase (EC 2.7.2.4) P16.3; Section 10.2D*,
- Aspartate-semialdehyde dehydrogenase (EC 1.2.1.11) Section 16.4*; P16.3
- Dihydrodipicolinate synthase (EC 4.2.1.52) Section 13.3*, Section 11.6*, Section 14.1*; P11.7, C14.3
- Dihydrodipicolinate reductase (EC 1.3.1.26) Section 16.5*; P16.4a
- Tetrahydropyridine-2-carboxylate N-succinyltransferase (EC 2.3.1.117) P11.9
- Succinyldiaminopimelate transaminase (EC 2.6.1.17) Section 14.4E*
- Succinyl-diaminopimelate desuccinylase (EC 3.5.1.18) P12.8
- Diaminopimelate decarboxylase (EC 4.1.1.20) Section 14.4C

Methionine (from aspartate via homoserine)

- Aspartate kinase (EC 2.7.2.4) Section 10.2D*; P16.3
- Aspartate-semialdehyde dehydrogenase (EC 1.2.1.11) Section 16.4*; P16.3
- Homoserine dehydrogenase (EC 1.1.1.3) Section 16.4*
- Homoserine transsuccinylase (EC 2.3.1.46) Section 12.3*
- Cystathionine *gamma*-synthase (EC 4.2.1.22) Section 14.4G
- Cystathionine *beta*-lyase (EC 4.4.1.8) Section 14.4F*
- Methionine synthase (EC 2.1.1.13) P9.5

Threonine (from homoserine)

- Homoserine kinase (EC 2.7.1.39) Section 10.2*
- Threonine synthase (EC 4.2.3.1) P14.10c, Section 14.4G*

Isoleucine, leucine, and valine (from pyruvate):

- Acetolactate synthase (EC 2.2.1.6) P14.12 Section 14.5*
- Ketol acid reductoisomerase (EC 1.1.1.86) Section 15.7C
- Dihydroxyacid dehydratase (EC 4.2.1.9) P14.5

to isoleucine:

- Branched-chain-amino-acid aminotransferase (EC 2.6.1.42) Section 14.4E*

to valine:

- Valine—pyruvate aminotransferase (EC 2.6.1.66) Section 14.4E*

to leucine:

- 2-isopropylmalate synthase (EC 2.3.3.13) Section 13.3*
- Isopropylmalate isomerase (EC 4.2.1.33) P14.7
- 3-isopropylmalate dehydrogenase (EC 1.1.1.85) Section 16.4*
- Leucine aminotransferase (EC 2.6.1.6) Section 14.4E*

Aromatic amino acids

Erythrose-4-phosphate to chorismate:

- DAHP synthase (EC 2.5.1.54) Section 15.2C
- Dehydroquinate synthase (EC 4.2.3.4) C13.1, 14.1A
- Dehydroquinate dehydratase (EC 4.2.1.10) Section 14.1D
- Shikimate dehydrogenase (EC 1.1.1.25) Section 16.4*
- Shikimate kinase (EC 2.7.1.71) P10.2 Section 10.2*
- 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase (EC 2.5.1.19) Section 14.3B, Section 15.4
- Chorismate synthase (EC 4.2.3.5) Section 14.3B, Section 17.3C

chorismate to tryptophan:

- Anthranilate synthase (EC 4.1.3.27) P14.8a
- Anthranilate phosphoribosyltransferase (EC 2.4.2.18) Section 11.5*
- Phosphoribosyl anthranilate isomerase (EC 5.3.1.24) P11.12, P13.12
- Indole-3-glycerol phosphate synthase (EC 4.1.1.48) Section 15.5B
- Tryptophan synthase (EC 4.2.1.20) Section 13.3C, E13.7, Section 15.5B

chorismate to phenylalanine/tyrosine:

- Chorismate mutase (EC 5.4.99.5) Section 15.10
- Prephenate decarboxylase (EC 4.2.1.51) Section 14.3B
- Aromatic-amino-acid aminotransferase (EC 2.6.1.57) Section 14.4E*
- Tyrosine aminotransferase (EC 2.6.1.5) Section 14.4E*

Histidine

- ATP phosphoribosyltransferase (EC 2.4.2.17) Section 11.5*
- Phosphoribosyl-ATP diphosphatase (EC 3..6.1.31) Section 10.3*
- Phosphoribosyl-AMP cyclohydrolase (EC 3.5.4.19) P12.12
- 1-(5-phosphoribosyl)-5-[(5-phosphoribosylamino)methylideneamino]imidazole-4-carboxamide isomerase (EC 5.3.1.16) P14.8b
- Imidazole glycerol-phosphate synthase (no EC number assigned) Section 11.6*, C11.1
- Imidazoleglycerol-phosphate dehydratase (4.2.1.19) Section 14.3B
- Histidinol-phosphate transaminase (EC 2.6.1.9) Section 14.4E*
- Histidinol-phosphatase (EC 3.1.3.15) Section 10.3*
- Histidinol dehydrogenase (EC 1.1.1.23) Section 16.4D*

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Amino acid catabolism

Sections/problems listed with an asterisk (*) do not discuss the exact reaction indicated, but do discuss a closely related reaction.

- Transaminase (EC 2.6.1.1, EC 2.6.1.2) Section 14.4E
- Carbamoyl phosphate synthetase (EC 6.3.4.16) P12. 4

Urea cycle:

- Ornithine transcarbamylase (EC 2.1.3.3) Section 12.2A,B*
- Argininosuccinate synthetase (EC 6.3.4.5) Section 12.6, Section 14.1D
- Arginosuccinate lyase (EC 4.3.2.1) Section 14.1D
- Arginase (EC 3.5.3.1) P12.16

Glycine (glycine cleavage system)

- Glycine dehydrogenase (decarboxylating) (EC 1.4.4.2) P16.4b
- Aminomethyltransferase (EC 2.1.2.10) C11.5

Alanine (to pyruvate and glutamate):

- Alanine transaminase (EC 2.6.1.2) Section 14.4E

Serine

- (to pyruvate): Serine dehydratase (EC 4.3.1.17) Section 13.1B, Section 14.4F
- (to glycine): Serine hydroxymethyltransferase (EC 2.1.2.1) Section 11.6D, Section 14.4D

Cysteine (to pyruvate)

- Cysteine dioxygenase (EC 1.13.11.20) *not covered*
- Aspartate aminotransferase (2.6.1.1) Section 14.4E

Threonine

pathway 1 (to glycine and acetyl CoA):

- Threonine dehydrogenase (EC 1.1.1.103) Section 16.4D*
- Glycine *C*-acetyltransferase (EC 2.3.1.29) Section 14.4D

pathway 2 (to glycine and acetaldehyde):

- Threonine aldolase (EC 4.1.2.5) Section 14.4D*, P14.10a

pathway 3 (to succinyl-CoA via propionyl CoA):

- Threonine dehydratase (EC 4.3.1.19) P14.2
- 2-oxobutanoate dehydrogenase (EC 1.2.4.4) Section 16.12B*
- Propionyl-CoA carboxylase (EC 6.4.1.3) Section 13.5D*, P13.2*
- Methylmalonyl-CoA mutase (EC 5.4.99.2) *not covered*

Tryptophan (to glutaryl-CoA)

- Tryptophan 2,3-dioxygenase (EC 1.13.11.11) *not covered*
- Arylformamidase (EC 3.5.1.19) Chapter 12*
- Kynurenine 3-monooxygenase (EC 1.14.13.9) Section 16.10
- Kynurenimase (EC 3.7.1.3) P14.10b
- 3-hydroxyanthranilate 3,4-dioxygenase (EC 1.13.11.6) *not covered*
- Aminocarboxymuconate-semialdehyde decarboxylase (EC 4.1.1.45) Section 13.5C*, P13.5a
- 2-aminomuconate semialdehyde dehydrogenase (EC 1.2.1.32) Section 16.4D*, P16.2a
- 2-aminomuconate deaminase (EC 3.5.99.5) Section 11.6*, P11.1
- 2-oxoglutarate dehydrogenase (EC 1.2.4.2) Section 16.12B*

Asparagine (to aspartate)

- Asparaginase (EC 3.5.1.1) Chapter 12*

Aspartate

- (to oxaloacetate): Aspartate transaminase (EC 2.6.1.1) Section 14.4E
- (to fumarate): Aspartate-ammonia lyase (EC 4.3.1.1) P14.3

Glutamine (to glutamate)

- Glutaminase (EC 3.5.1.2) Chapter 12

Glutamate (to alpha-ketoglutarate):

- Glutamate dehydrogenase (EC 1.4.1.2) Section 16.4D

Arginine (to glutamate):

- Arginase (EC 3.5.3.1) P12.16b
- Ornithine transaminase (EC 2.6.1.13) Section 14.4E*
- Glutamate semialdehyde dehydrogenase (EC 1.2.1.41) Section 16.4D

Histidine (to glutamate):

- Histidine ammonia-lyase (EC 4.3.1.3) C14.5
- Urocanate hydratase (EC 4.2.1.49) C16.1
- Imidazolonepropionase (EC 3.5.2.7) Chapter 12*
- Formimidoylglutamase (EC 3.5.3.8) P11.13b

Valine, isoleucine, leucine:

- Branched chain amino acid transaminase (EC 2.6.1.42) Section 14.4E*
- Branched chain ketoacid dehydrogenase complex (EC 1.2.4.4) Section 16.12B*
- Acyl CoA dehydrogenase (eg. EC 1.3.99.13) Section 16.5C, Section 17.3C

valine (to succinyl CoA):

- Enoyl-CoA hydratase (EC 4.2.1.17) P16.9
- 3-hydroxyisobutyryl-CoA hydrolase (EC 3.1.2.4) P16.9
- 3-hydroxyisobutyrate dehydrogenase (EC 1.1.1.31) P16.9
- Methylmalonate-semialdehyde dehydrogenase (1.2.1.27) P16.9
- Propionyl-CoA carboxylase (EC 6.4.1.3) Section 13.5D*, P13.2*
- Methylmalonyl-CoA mutase (EC 5.4.99.2) *not covered*

isoleucine (to succinyl CoA and acetyl CoA):

- Enoyl-CoA hydratase (EC 4.2.1.17) P16.9
- Methyl-hydroxybutyryl CoA dehydrogenase (EC 1.1.1.178) Section 16.4*
- 3-ketoacyl-CoA thiolase (EC 2.3.1.16) Section 13.4B*
- Propionyl-CoA carboxylase (EC 6.4.1.3) Section 13.5D*, P13.2*
- Methylmalonyl-CoA mutase (EC 5.4.99.2) *not covered*

leucine (to acetyl CoA)

- Methylcrotonoyl-CoA carboxylase (EC 6.4.1.4) Section 13.5*
- Methylglutaconyl-CoA hydratase (EC 4.2.1.18) Section 14.1*
- Hydroxymethylglutaryl-CoA lyase (EC 4.1.3.4) Section 13.3C*

Methionine (to cysteine and succinyl-CoA):

- Methionine adenosyltransferase (EC 2.5.1.6) E9.1
- Methyltransferase (eg. 2.1.1.37) Section 9.1A

- Adenosylhomocysteinase (EC 3.3.1.1) Section 14.1A
- Cystathionine beta-synthase (EC 4.2.1.22) Section 14.4G*
- Cystathionine gamma-lyase (EC 4.4.1.1) Section 14.4G
- 2-oxobutanoate dehydrogenase (EC 1.2.4.4) Section 16.12B*
- Propionyl-CoA carboxylase (EC 6.4.1.3) Section 13.5D*, P13.2*
- Methylmalonyl-CoA mutase (EC 5.4.99.2) *not covered*

Lysine (to glutaryl-CoA)

- Saccharopine dehydrogenase (EC 1.5.1.8) P11.6, P16.7a
- Saccharopine reductase (EC 1.5.1.10) P11.7, P16.7b
- Aminoadipate-semialdehyde dehydrogenase (EC 1.2.1.31) Section 16.4D*
- 2-aminoadipate transaminase (EC2.6.1.39) Section 14.4E*
- 2-oxoglutarate dehydrogenase (EC 1.2.4.2) Section 16.12B*

Phenylalanine (to tyrosine):

- Phenylalanine hydroxylase (EC 1.14.16.1) *not covered*

Tyrosine (to fumarate and acetoacetate):

- Tyrosine transaminase (EC 2.6.1.5) Section 14.4E*
- 4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27) *not covered*
- Homogentisate 1,2-dioxygenase (EC 1.13.11.5) *not covered*
- Maleylacetoacetate isomerase (EC 5.2.1.2) Section 14.2A*
- Fumarylacetoacetase (EC 3.7.1.2) Section 13.4B*

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Citric Acid Cycle

Sections/problems listed with an asterisk (*) do not discuss the exact reaction indicated, but do discuss a closely related reaction.

- Pyruvate dehydrogenase complex (EC 1.2.4.1) Section 12.3D; Section 16.12B
- Citrate synthase (EC 2.3.3.8) Section 12.3E; Section 13.3B
- Aconitase (EC 4.2.1.3) Section 14.1D
- Isocitrate dehydrogenase (EC 1.1.1.42) Section 13.5C
- α-ketoglutarate dehydrogenase complex: Section 16.12B*; P16.8
    - Oxoglutarate dehydrogenase (EC 1.2.4.2)
    - Dihydrolipoyl succinyltransferase (EC 2.3.1.61)
    - Dihydrolipoyl dehydrogenase (EC 1.8.1.4)
- Succinyl CoA synthetase (EC 6.2.1.4) Section 12.3*; P12.2; C12.1
- Succinate dehydrogenase (EC 1.3.5.1) Section 15.5C
- Fumarase (EC 4.2.1.2) Section 14.1C
- Malate dehydrogenase (EC 1.1.1.37) Section 16.4*

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Fatty acid metabolism

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Fatty acid degradation

- Acyl CoA synthetase (EC 6.2.1.1) Section 12.3B*
- Carnitine acyltransferase (EC 2.3.1.21) Section 12.3C*
- Acyl CoA dehydrogenase (eg. EC 1.3.99.13) Section 16.5C, Section 17.3C
- Enoyl CoA hydratase (E.C. 4.2.1.74) Section 14.1B
- 3-hydroxyacyl CoA dehydrogenase (EC 1.1.1.35) Section 16.4B*
- *beta*-keto thiolase (EC 2.3.1.16) Section 13.4B
- *cis*-Enoyl-CoA isomerase (eg. EC 5.3.3.8) Section 13.2C
- 2,4-Dienoyl CoA reductase (EC 1.3.1.34) Section 16.5D
- Glycerol phosphate dehydrogenase (EC 1.1.1.8) Section 16.4D

Fatty acid biosynthesis

- acetyl CoA carboxylase (EC 6.4.1.2) P13.2
- acyl CoA synthetase(EC 6.2.1.1) Section 12.3B
- ACP transacylase (EC 2.3.1.38) Section 12.3D
- *beta*-ketoacyl-ACP synthase (EC 2.3.1.41) Section 13.5C
- *beta*-ketoacyl-ACP hydrogenase (EC 1.1.1.35) Section 16.4B*
- 3-hydroxyacyl dehydratase (EC 4.2.1.58) Section 14.1B
- enoyl-ACP reductase (EC 1.3.1.10) Section 16.5A

- acyl-CoA dehydrogenase (EC 1.3.99.3) Section 16.5A,B,C
- monoacylglycerolacyltransferase (EC 2.3.1.22) Section 12.3C

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Glycolysis, Gluconeogenesis, Fermentation

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Glycolysis

- Hexose kinase (EC 2.7.1.1) Section 10.2B
- Phosphoglucose isomerase (EC 5.3.1.9) Section 13.2A
- Phosphofructokinase (EC 2.7.1.56) Section 10.2B
- Fructose 1,6-bisphosphate aldolase (EC 4.1.2.13) Section 13.3B,C
- Triose phosphate isomerase (5.3.1.1) Section 13.2A
- Gyceraldehyde 3-phosphate dehydrogenase (EC 1.2.1.12) Section 16.4D
- Phosphoglycerate kinase (EC 2.7.2.3) Section 10.2F
- Phosphoglycerate mutase (EC 5.4.2.1) Section 10.1D*; C10.3
- Enolase (EC 4.2.1.11) Section 14.1*; P14.1
- Pyruvate kinase (EC 2.7.1.40) Section 10.2F, Section 13.1A
- 2-Keto-3-deoxy-6-phosphogluconate (KDPG) aldolase (EC 4.1.2.14) Section 13.3C

Gluconeogenesis

- Pyruvate carboxylase (EC 6.4.1.1) Section 13.5D
- Phosphoenolpyruvate carboxykinase (EC 4.1.1.32) P13.10
- Phosphoglycerate kinase (EC 2.7.2.3) Section 10.2D*; P10.1
- Fructose 1,6-bisphosphatase (EC 3.1.3.11) Section 10.3
- Glucose 6-phosphatase (EC 3.1.3.9) Section 10.3; P10.6

Fermentation

- Pyruvate decarboxylase (EC 4.1.1.1) Section 14.5C; E14.7
- Alcohol dehydrogenase (EC 1.1.1.1) Section 16.4D
- Lactate dehydrogenase (EC 1.1.1.27) Section 16.4*; P16.1

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Isoprenoid biosynthesis

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Synthesis of isopentenyl diphosphate building blocks

Mevalonate pathway

- Acetoacetyl CoA acetyltransferase (EC 2.3.1.9) Section 13.4A
- 3-hydroxy-3-methylglutaryl-CoA synthase (EC 2.3.3.10) P13.1
- HMG-CoA reductase (EC 1.1.1.34) Section 16.4D
- Mevalonate kinase (EC 2.7.1.36) Section 10.2C
- Phosphomevalonate kinase (EC 2.7.4.2) Section 10.2C
- Mevalonate diphosphate decarboxylase (EC 4.1.1.33) Section 14.3B

Deoxyxylulose phosphate pathway (bacteria, plant plastids)

- Deoxyxylulose phosphate synthase (EC 2.2.1.7) Section 14.5*; P14.5b
- Deoxyxylulose phosphate reductoisomerase (EC 1.1.1.267) P15.16
- MEP cytidylyltransferase (EC 2.7.7.60) Section 10.2E
- CDP-ME kinase (EC 2.7.1.148) Section 10.2E
- Methylerithritol 2,4-cyclodiphosphate synthase (EC 4.6.1.12) Section 10.2E

Chain elongation and prenyl transfer

- Isopentenyl diphosphate isomerase (EC 5.3.3.2) Section 15.3A
- Geranyl diphosphate synthase (EC 2.5.1.1) Section 15.3B
- Farnesyl diphosphate synthase (EC 2.5.1.10) Section 15.3B
- Squalene synthase (EC 2.5.1.21) Section 15.9, Section 16.6A
- Oxidosqualene cyclase (EC 5.4.99.7) Section 15.7B
- DMAPP-tryptophan synthase (EC 2.5.1.34) Section 15.5B
- protein prenyltransferase (EC 2.5.1.58) Section 9.3

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Nucleoside biosynthesis

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- PRPP synthetase (EC 2.7.6.1) Section 10.2C; P10.3

Uridine

- Carbamoyl phosphate synthase (EC 6.3.5.5) Section 12.2*
- Aspartate carbamoyltransferase (EC 2.1.3.2) Section 12.2*
- Dihydroorotase (EC 2.5.2.3) C12.4
- Dihydroorotate dehydrogenase (EC 1.3.3.1) P16.5
- Orotate phosphoribosyltransferase (EC 2.4.2.10) Section 10.2C
- Orotidine monophosphate decarboxylase (EC 4.1.1.23) C14.1

Thymine

- Thymidylate synthase (EC 2.1.1.45) C14.2

Cytosine

- CTP synthase (EC 6.3.4.2) P10.5a, P12.13

Inosine

- Glutamine phosphoribosyl amidotransferase (EC 2.4.2.14) Section 11.5
- Glycinamide ribonucleotide synthetase(EC 6.3.4.13) Section 12.2C
- GAR transformylase (EC 2.1.2.2) P12.14
- FGAM synthetase (EC 6.3.5.3) P12.16
- Aminoimidazole ribonucleotide synthetase (EC 6.3.3.1) P10.5b, P12.10
- Aminoimidazole ribonucleotide carboxylase (EC 4.2.1.1) Section 13.5*
- SAICAR synthetase (EC 6.3.2.6) Section 12.2C*; P12.17, C14.4
- Adenylosuccinate lyase (EC 4.3.2.2) Section 14.1*; P14.9
- AICAR transformylase (EC 2.1.2.3) P12.15
- IMP cyclohydrolase (EC 3.5.4.10) P11.3

Adenosine

- Adenylosuccinate synthetase (EC 6.3.4.4) P12.17
- Adenylosuccinate lyase (EC 4.3.2.2) Section 14.1*; P14.9

Guanosine

- IMP dehydrogenase (EC 1.1.1.205) Section 14.2B, Section 16.6B; P16.6
- GMP synthetase (EC 6.3.5.2) P10.5a, P12.13

Deoxynucleotides

- Ribonucleotide reductase (EC 1.17.4.1) Section 17.3B

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Nucleotide catabolism

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Cytidine (*to uridine*)

- Cytidine deaminase (EC 3.5.4.5) P11.4

Uridine

- Uridine phosphorylase (EC 2.4.2.3) Section 9.2*, Section 11.5; P9.1
- Dihydropyrimidine dehydrogenase (EC 1.3.1.2) Section 16.5D
- Dihydropyrimidase (EC 3.5.2.2) Section 12.5*; P12.11a
- *beta*-ureidopropionase (EC 3.5.1.6) P13.11

Thymidine

- Thymidine phosphorylase (EC 2.4.2.4) Section 9.2*
- Dihydropyrimidine dehydrogenase (EC 1.3.1.2) Section 16.5D
- Dihydropyrimidase (EC 3.5.2.2) Section 12.5*; P12.11a
- *beta*-ureidopropionase (EC 3.5.1.6) P13.11

Adenosine (*to uric acid via xanthine*)

- Adenosine deaminase (EC 3.5.4.4) P11.5
- Purine nucleoside phosphorylase (EC 2.4.2.1) Section 9.2*
- Xanthine oxidase (EC 1.17.1.4; EC 1.17.3.2) *not discussed*

Guanosine (*to uric acid via xanthine*)

- Purine nucleoside phosphorylase (EC 2.4.2.1) Section 9.2*
- Guanine deaminase (EC 3.5.4.3) P11.5*
- Xanthine oxidase (EC 1.17.1.4; EC 1.17.3.2) *not discussed*

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Pentose Phosphate Pathway, Calvin Cycle

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- Glucose 6-phosphate dehydrogenase (EC 1.1.1.49) Section 16.7B
- Gluconolactonase (EC 3.1.1.17) P12.3
- 6-Phosphogluconate dehydrogenase (EC 1.1.1.43) Section 13.5C, Section 16.7B
- Phosphopentose epimerase (EC 5.1.3.1) Section 13.2B
- Phosphopentose isomerase (EC 5.3.1.6) Section 13.2A
- Transketolase (EC 2.2.1.1) Section 14.5B
- Transaldolase (EC 2.2.1.2) Section 13.3D
- Rubisco (EC 4.1.1.39) Section 13.5B
- Aldolase (EC 4.1.2.13) Section 13.3B

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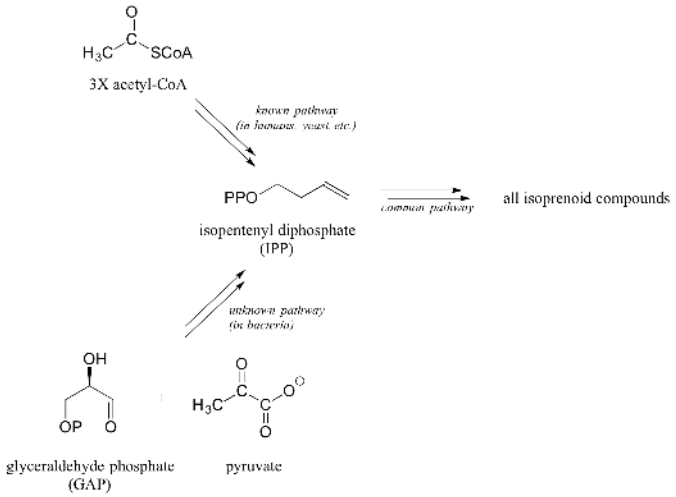
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Interchapter: Retrosynthetic analysis and metabolic pathway prediction

Imagine that you are a biological chemist doing research on bacterial metabolism. You and your colleagues isolate an interesting biomolecule from a bacterial culture, then use mass spectrometry, NMR, and other analytical techniques to determine its structure. Using your 'toolbox' of known organic reaction types - nucleophilic substitution, phosphorylation, aldol additions, and so forth - can you figure out a chemically reasonable pathway by which your compound might be enzymatically synthesized from simple metabolic precursors? In other words, can you fill in the missing biochemical steps (or at least some of them) to come up with a potential new metabolic pathway, which can then be used a hypothesis for future experimental work to try to find and study the actual enzymes involved?

An actual example approximating this scenario is shown below. A complete biosynthetic pathway for isopentenyl diphosphate (IPP), the building block molecule for all isoprenoid compounds, has been known since the 1960's. This pathway, which begins with acetyl-CoA, was shown to be active in yeast, plants, and many other species including humans. However, researchers in the late 1980s uncovered evidence indicating that the known pathway is *not* present in bacteria, although they clearly use IPP as a building block molecule just as other forms of life do.



Over the next several years, the researchers conducted a number of experiments in which bacteria were grown on a medium containing glucose 'labeled' with the ^{13}C isotope. With the results from these experiments, combined with their knowledge of common biological organic reaction types, the researchers were able to correctly predict that the bacterial pathway starts with *two* precursor molecules (pyruvate and glyceraldehyde phosphate instead of acetyl CoA) and they also correctly predicted the first two enzymatic steps of the newly discovered bacterial pathway. This accomplishment eventually led to elucidation of every step in the pathway, and isolation of the enzymes catalyzing them. (*Biochem J.* **1993**, *295*, 517; *J. Am. Chem. Soc.* **1996**, *118*, 2564; *Lipids* **2008**, *43*, 1095)

> Why weren't they able to predict the whole pathway? It turns out that several of the later steps were somewhat unusual, unfamiliar reaction types - but discovery of these reactions hinged upon the correct prediction of the more familiar first two steps.

Multi-step transformation problems of this type offer an unparalleled opportunity to use our knowledge of biological organic chemistry combined with creative reasoning to solve challenging, relevant scientific puzzles. At this point in your organic chemistry career, you have not yet accumulated quite enough tools in your reaction toolbox to tackle most real-life biochemical pathway problems such as the one addressed above - but by the time we finish with oxidation and reduction chemistry in chapter 15, you will be able to recognize most of the reaction types that you will encounter in real metabolism, and will be challenged to predict some real pathways in the end-of-chapter problems.

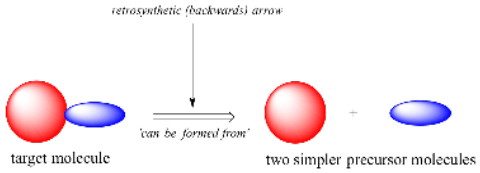
You do, however, have *right now* enough of a bioorganic repertoire to begin to learn how multi-step pathway problems can be approached, using for practice some generalized, hypothetical examples in which the reaction types involved are limited to those with which you are already familiar.

Imagine that you want to figure out how an old-fashioned mechanical clock is put together. One way to do this is to start with a working clock, and take it apart piece-by-piece. Alternatively, one could start with all of the disassembled pieces, plus a lot of other small parts from different clocks, and try to figure out how to put together the specific clock you are interested in. Which approach is easier? The answer is intuitively obvious - it's usually easier to take things apart than to put them back together.

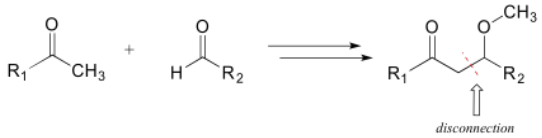
The same holds true for molecules. If we want to figure out the biosynthetic pathway by which a large, complex biomolecule might be made in a cell, it makes sense to start with the finished product and then mentally work backwards, taking it apart step-by-step using known, familiar reactions, until we get to simpler precursor molecules. Starting with a large collection of potential precursor molecules and trying to put the right ones together to make the target product would be a formidable task.

Retrosynthetic analysis - the concept of mentally dismantling a molecule step by step all the way back to smaller, simpler precursors using known reactions - is a powerful and widely-used intellectual tool first developed by synthetic organic chemists. The approach has also been adapted for use by biological chemists in efforts to predict pathways by which known biomolecules could be synthesized (or degraded) in living things.

In retrosynthesis, we think about a series of reactions in reverse. A backwards (retro) chemical step is symbolized by a 'thick' arrow, commonly referred to as a **retrosynthetic arrow**, and visually conveys the phrase '*can be formed from*'.

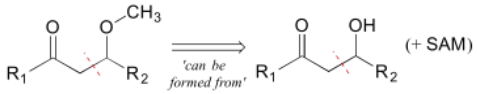


Consider a simple, hypothetical example: starting with the target molecule below, can we come up with a chemically reasonable pathway starting from the precursors indicated?

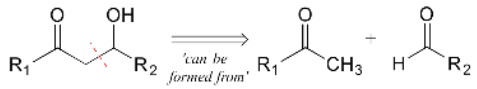


A first step is to identify the relevant **disconnection**: a key bond (usually a carbon-carbon bond) that must be formed to make the target product from smaller precursors. We search our mental 'toolbox' of common biochemical reaction types, and remember that the only way we know of (so far!) to make a new carbon-carbon bond is through an aldol addition reaction, which takes place at an alpha-carbon. Therefore, we can make a likely disconnection next to the alpha-carbon in the target molecule.

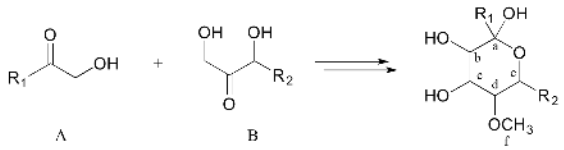
Next, we need to recognize that the aldol addition reaction results in a beta-hydroxy ketone. But our target molecule is beta-*methoxy* ketone! Working backwards, we realize that the beta-methoxy group could be formed from beta-hydroxy group by a SAM methylation reaction. This is our first retrosynthetic (backwards) step.



The second retro step (aldol) accounts for the disconnection we recognized earlier, and leads to the two precursor molecules.

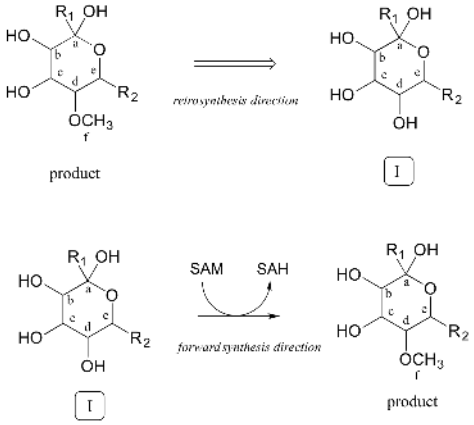


Now, consider the more involved (but still hypothetical) biochemical transformation below:



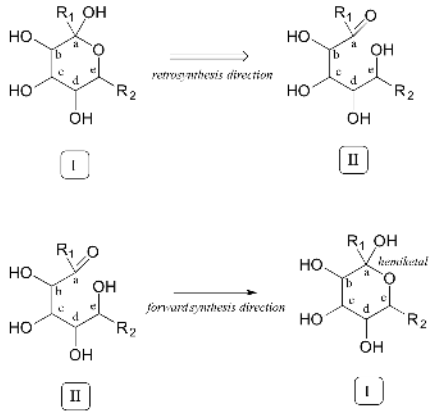
Often the best thing to do first in this type of problem is to count the carbons in the precursor compounds and product - this allows us to recognize when extra carbons on either side must at some point be accounted for in our solution. In this case, one carbon (labeled 'f") has been *gained* in the form of a methyl ether in the product. This is easy to account for: we know that the coenzyme *S*-adenosyl methionine (SAM) often serves as the methyl group donor in enzymatic *O*- or *N*-methylation reactions. So, we can propose our first backwards (retro) step: the product as shown could be derived from SAM-dependent methylation of an alcohol group on a proposed intermediate I.

Retrosynthetic step 1:

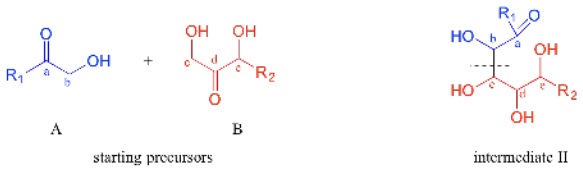


How do we know that the methylation step occurs last? We don't - remember, we are proposing a *potential* pathway, so the best we can do is propose steps that make chemical sense, and which hopefully can be confirmed or invalidated later through actual experimentation. For now, we'll stick with our initial choice to make the methylation step the last one.

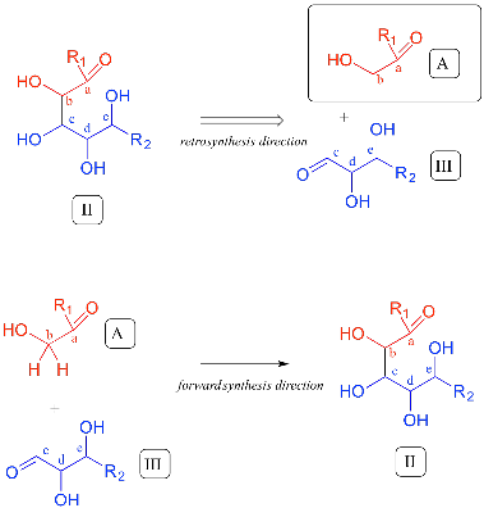
Now that we have accounted for the extra carbon, a key thing to recognize regarding the transformation in question is that two linear molecules are combining to form a cyclic product. Thus, *two* connections need to be made between reactants A and B, one to join the two, the other to close the circle. Our primary job in the retro direction, then, is to establish in the product the two points of *disconnection*: in other words, to find the two bonds in the product that need to be taken apart in our retrosynthetic analysis. Look closely at the product: what functional groups do you see? Hopefully, you can identify two alcohol groups, a methyl ether, and (critically) a *cyclic hemiketal*. We've already accounted for the methyl ether. Identifying the cyclic hemiketal is important because it allows us to make our next 'disconnection': we know how a hemiketal forms from a ketone and an alcohol, so we can mentally work backwards and predict the open-chain intermediate II that could cyclize to form our product.



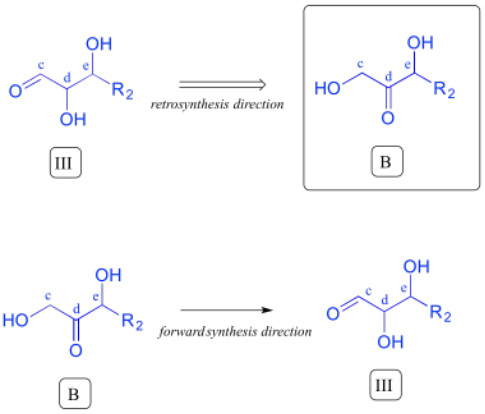
Now, starting with the R_1 group and working along the carbon chain, we can account for carbons a-e on the two precursors.



Thus, *the next disconnection is between carbons b and c.* Here's where our mastery of biological organic reactivity really comes into play: the OH at carbon c of intermediate II is in the beta position relative to carbonyl carbon a. Aldol addition reactions result in beta-hydroxy ketones or aldehydes. Therefore, we can work backward one more step and predict that our intermediate II was formed from an aldol addition reaction between intermediate III (as the nucleophile) and precursor molecule A (as the electrophile).

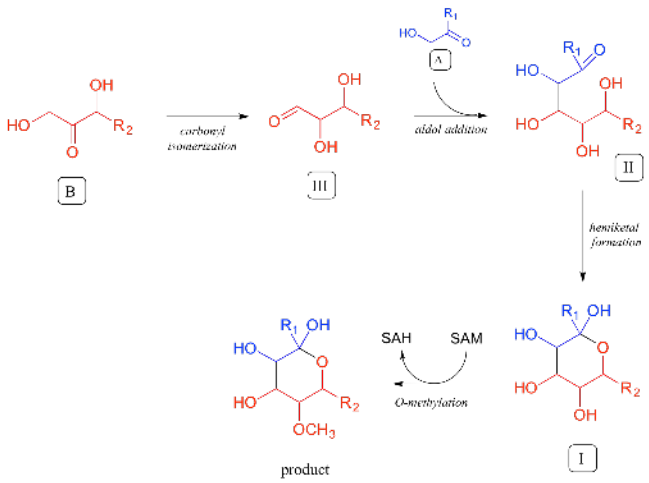


We are most of the way home - we have successfully accounted for given precursor A. Intermediate III, however, is *not* precursor B. What is different? Both III and B have a carbonyl and two alcohol groups, but the positioning is different: III is an aldehyde, while B is a ketone. Think back to earlier in this chapter: intermediate III could form from isomerization of the carbonyl group in compound B. We have now accounted for our second precursor - we are done!

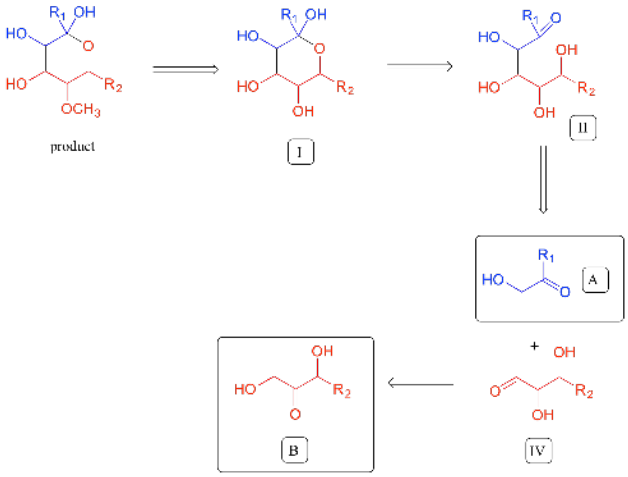


In the forward direction, a complete pathway diagram can be written as follows:

https://chem.libretexts.org/@go/page/395055



A full 'retrosynthesis' diagram for this problem looks like this:



Practice problems for retrosynthesis/pathway prediction

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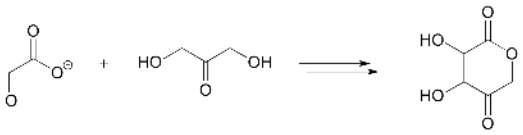
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Pathway prediction practice problems

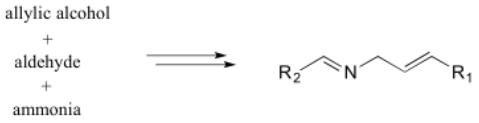
In the multi-step pathway prediction problems that you will be asked to solve below and in the remainder of this book, you will be instructed to present your solution in the form of a proposed 'forward' pathway diagram, showing the participation of all coenzymes and other species such as water. At first, we'll start with relatively simple, *hypothetical* (not real) biochemical transformations. As you learn more reaction types, the range and complexity of problems that you will be able to solve will expand correspondingly, and you will eventually be able to tackle real-life pathways.

For each transformation below, draw a pathway diagram illustrating a potential biosynthetic pathway. Indicate other molecules participating in the reaction but not shown below (eg. coenzymes, water, etc.). Each step should be recognizable as a reaction type that we have covered through the end of chapter 13. (Note - you are being asked to draw your pathways in the 'forward' direction, but you should attack each problem using a retrosynthetic analysis strategy).

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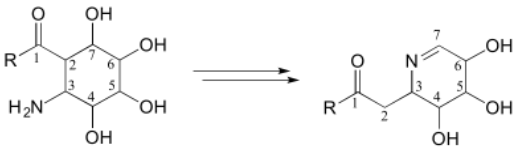
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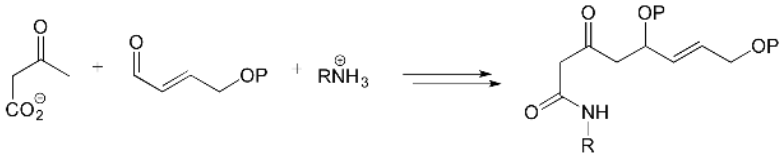
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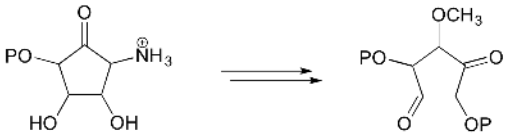
4:



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6:



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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