LECTURE TEXTBOOK



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Chem 221: Organic Chemistry I (Bennett)

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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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CHAPTER OVERVIEW

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University of Minnesota Morris

1: Introduction to Organic Structure and Bonding I

Tim Soderberg

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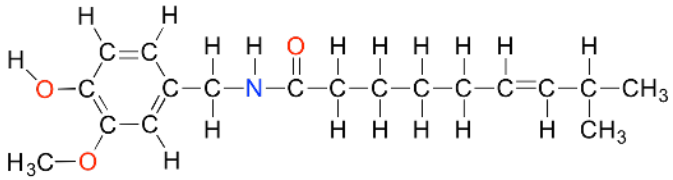
1.1: Prelude to Atoms, Electron Configurations, and Lewis Structures



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

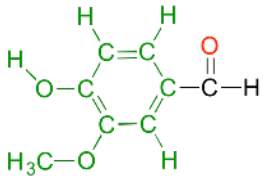
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Composed of the four elements carbon, hydrogen, oxygen and nitrogen, capsaicin is produced by the pepper plant for the purpose of warding off hungry mammals. The molecule binds to and activates a mammalian receptor protein called TrpV1, which in normal

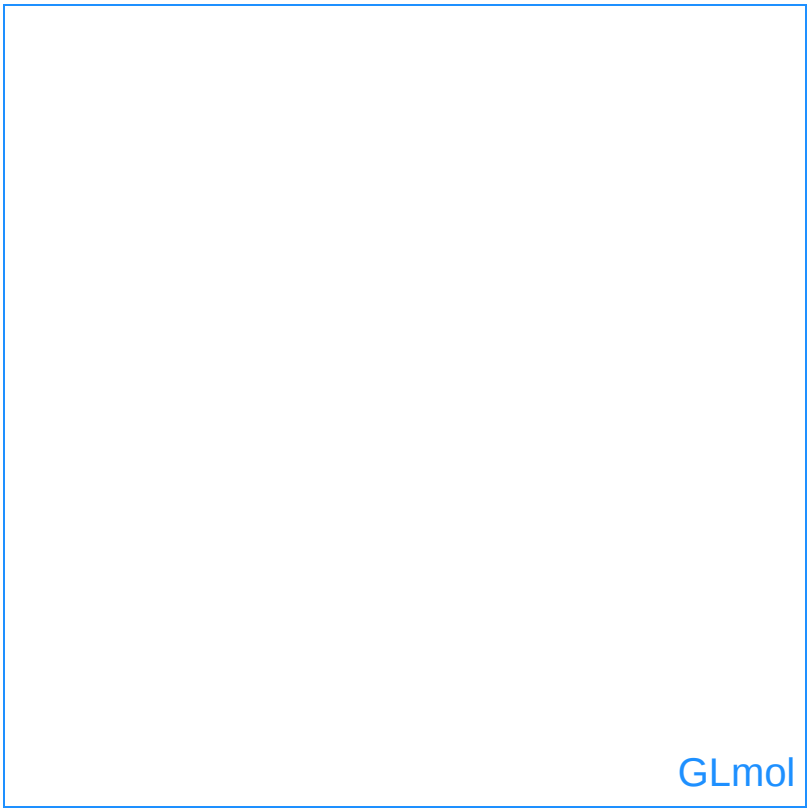
circumstances has the job of detecting high temperatures and sending a signal to the brain - 'it's hot, stay away!' This strategy works quite well on all mammalian species except one: we humans (some of us, at least) appear to be alone in our tendency to actually seek out the burn of the hot pepper in 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

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

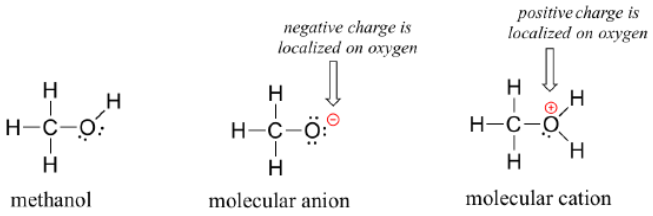
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1.2: Drawing organic structures

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.

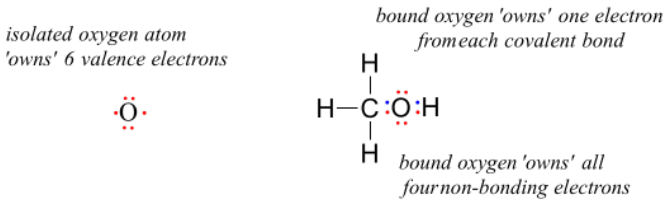
Organic molecules can also have positive or negative charges associated with them. Consider the Lewis structure of methanol, CH_3OH (methanol is the so-called 'wood alcohol' that unscrupulous bootleggers sometimes sold during the prohibition days in the 1920's, often causing the people who drank it to 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 =

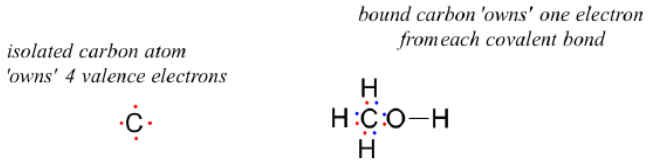
(6 valence electrons on isolated atom)

- (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 =

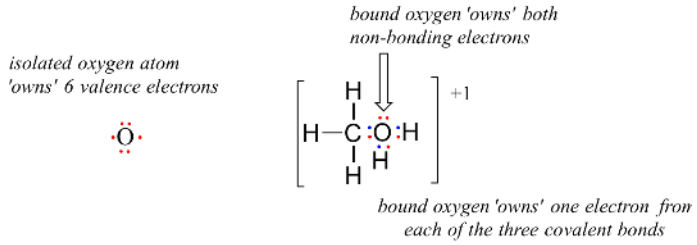
(1 valence electron on isolated atom)

- (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:

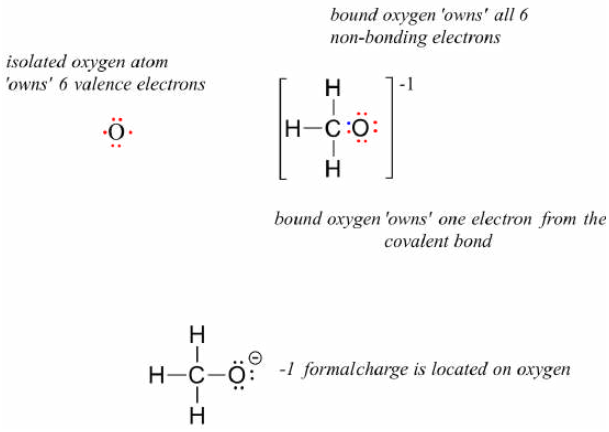
formal charge on oxygen =

(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.



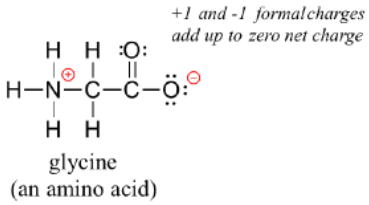
A very important rule to keep in mind is that *the sum of the formal charges on all atoms of a molecule must equal the net charge on the whole molecule.*

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:

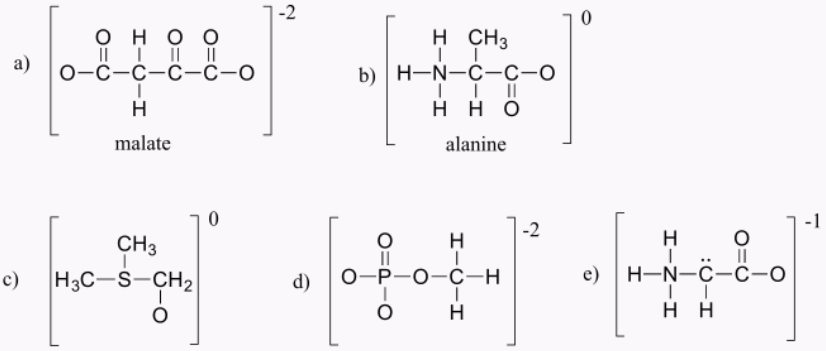


glycine
(an amino acid)

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

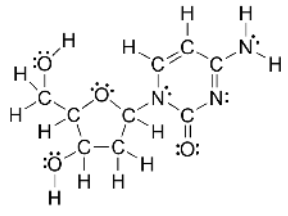
Fill in all missing lone pair electrons and formal charges in the structures below. Assume that all atoms have a complete valence shell of electrons. Net charges are shown outside the brackets.



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 well 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.

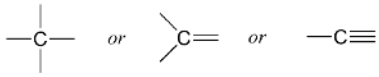


2'-deoxycytidine

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.

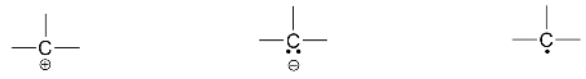
Let's start with carbon, the most important element for organic chemists. Carbon is said to be tetravalent, meaning that it tends to form four bonds. If you look at the simple structures of methane, methanol, ethane, ethene, and ethyne in the figures from the previous section, you should quickly recognize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

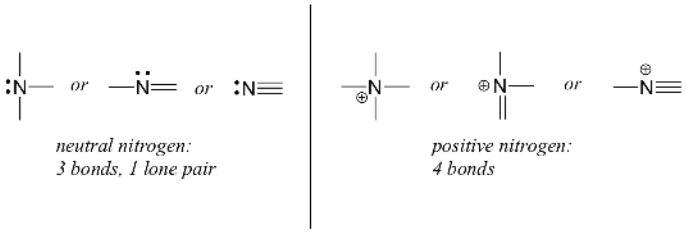
negative formal charge: 1 bond + 3 lone pairs

positive formal charge: 3 bonds + 1 lone pair

If an oxygen atom 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:

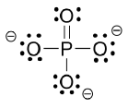


neutral nitrogen: 3 bonds, 1 lone pair

positive nitrogen: 4 bonds

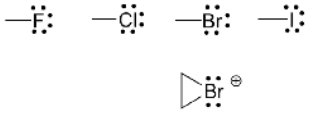
If a nitrogen has three bonds and a lone pair, it has a formal charge of zero. If it has four bonds (and no lone pair), it has a formal charge of +1. In a fairly uncommon bonding pattern, negatively charged nitrogen has two bonds and two lone pairs.

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.

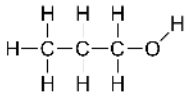
Exercise 1.5: Draw one structure that corresponds to each of the following molecular formulas, using the common bonding patters covered above. Be sure to include all lone pairs and formal charges where applicable, and assume that all atoms have a full valence shell of electrons. More than one correct answer is possible for each, so you will want to check your answers with your instructor or tutor.

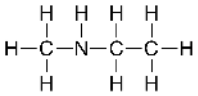
a) $C_5H_{10}O$ b) C_5H_8O c) $C_6H_8NO^+$ d) $C_4H_3O_2^-$

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:

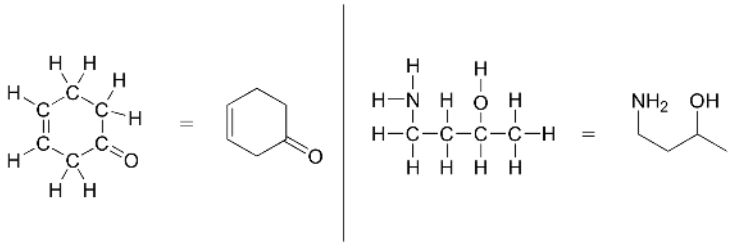




Lewis structures

$CH_3CH_2CH_2OH$ $CH_3NHCH_2CH_3$ Condensed structures

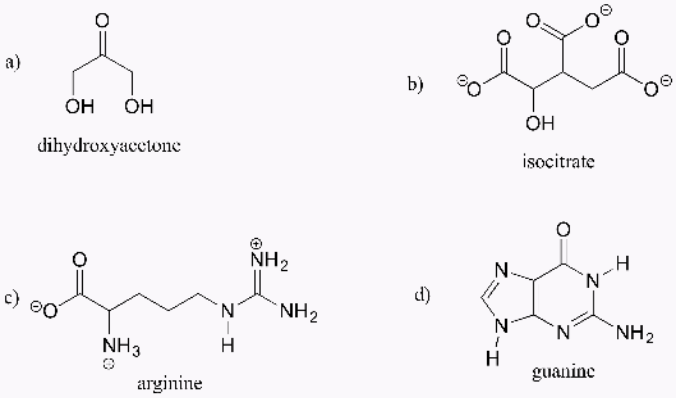
More commonly, organic and biological chemists use an abbreviated drawing convention called **line structures**. The convention is quite simple and makes it easier to draw molecules, but line structures do take a little bit of getting used to. Carbon atoms are depicted not by a capital C, but by a 'corner' 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.*

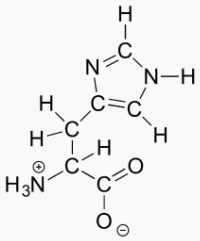
Exercise 1.6: A good way to test your understanding of the line structure convention is to determine the number of hydrogen atoms in a molecule from its line structure. Do this for the structures below.



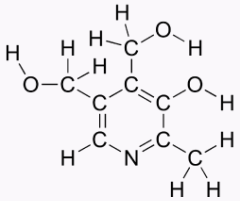
Exercise 1.7:

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).

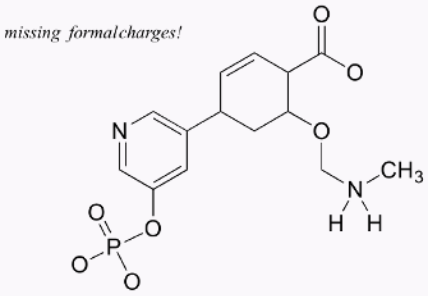


histidine



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

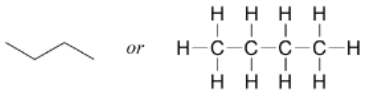
d) nitrogen with one double bond, two single bonds, and a +1 formal charge

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

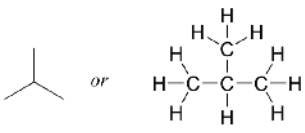
Solutions to exercises

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:

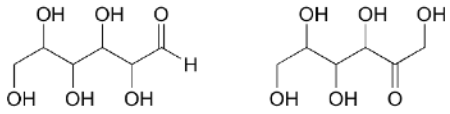


But when you compared your answer with that of a classmate, she may have drawn this structure:



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

Kahn Academy video tutorials:

Representing structures of organic molecules

Drawing Lewis Dot structures and determining formal charges

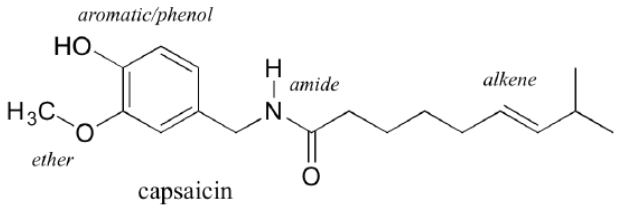
Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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1.3: Functional groups and organic nomenclature

Functional groups in organic compounds

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.

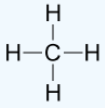


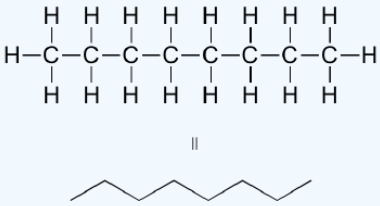
capsaicin

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.

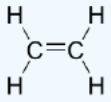
Alkanes

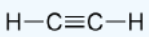

methane


octane

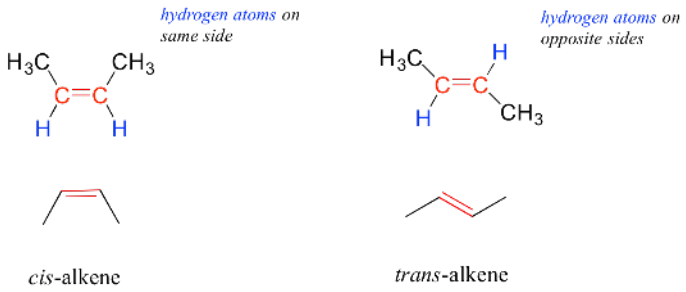
Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along 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 the bonding in alkenes is trigonal planar 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.

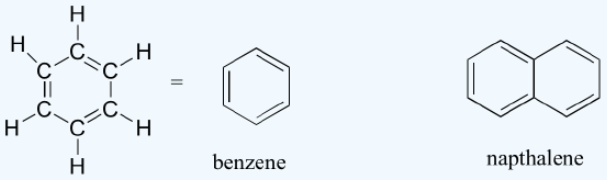


We will have more to say about the subject of *cis* and *trans* alkenes in chapter 3, and we will learn much more about the reactivity of alkenes in chapter 14.

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'.

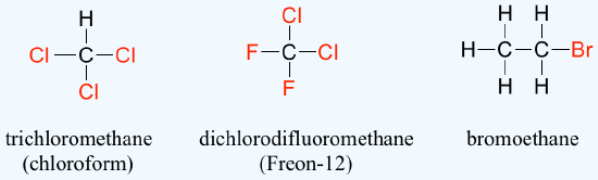
The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We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

Aromatics

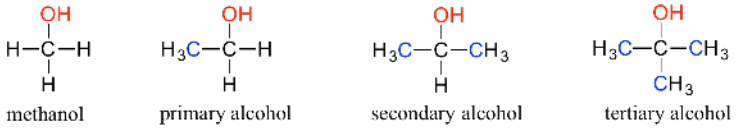


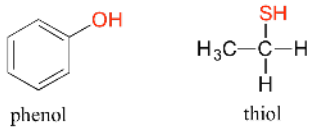
When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol 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

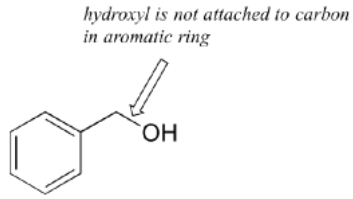


In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded 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).





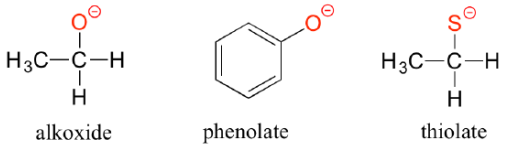
Note that the definition of a phenol states that the hydroxyl oxygen must be *directly* attached to one of the carbons of the aromatic ring. The compound below, therefore, is *not* a phenol - it is a primary alcohol.

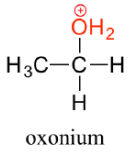


primary alcohol
(*not* a phenol)

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

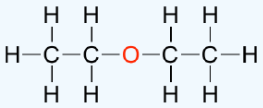
The deprotonated forms of alcohols, phenols, and thiols are called **alkoxides**, **phenolates**, and **thiolates**, respectively. A protonated alcohol is an **oxonium** ion.



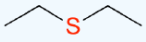


In an **ether** functional group, a central oxygen is bonded to two carbons. Below is the structure of diethyl ether, a common laboratory solvent and also one of the first compounds to be used as an anesthetic during operations. The sulfur analog of an ether is called a **thioether** or **sulfide**.

Ethers and sulfides



an ether

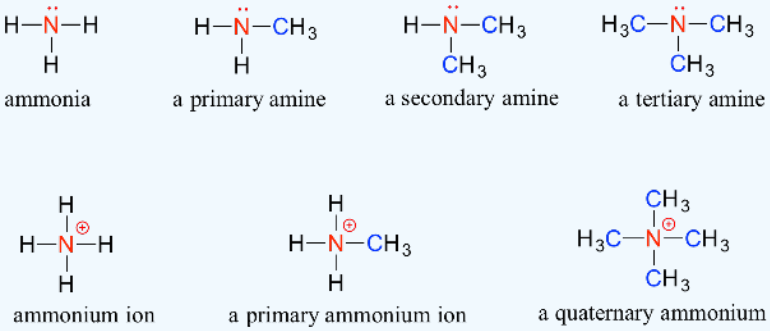


a sulfide

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

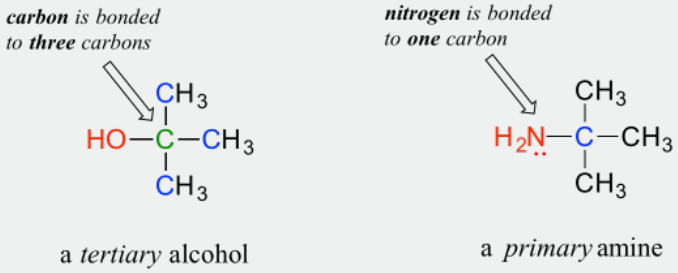


ammonia | a primary amine | a secondary amine | a tertiary amine

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

Note

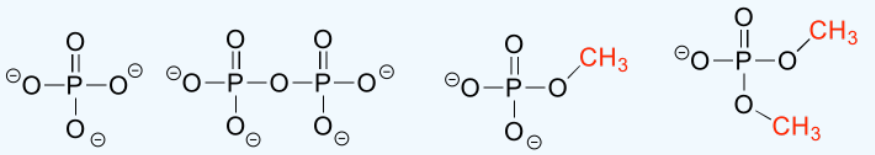
Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols versus amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is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

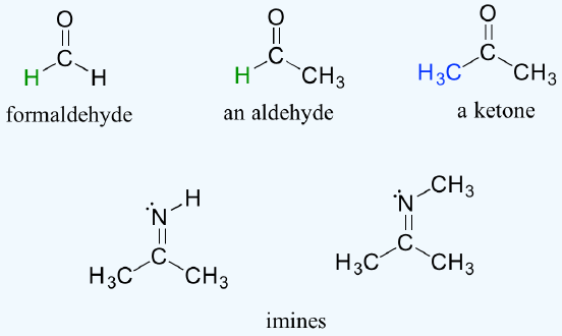


Chapter 9 of this book is devoted to the structure and reactivity of the phosphate group.

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.

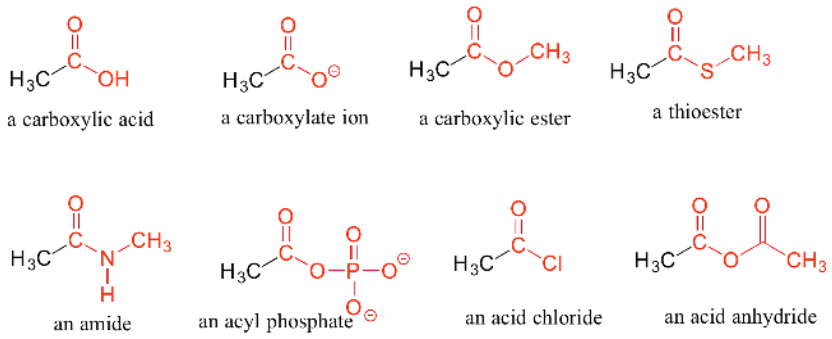
A group with a carbon-nitrogen double bond is called an **imine**, or sometimes a **Schiff base** (in this book we will use the term 'imine'). The chemistry of aldehydes, ketones, and imines will be covered in chapter 10.

Aldehydes, ketones, and imines



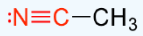
When a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to an oxygen, nitrogen, or sulfur, the functional group is considered to be one of the '**carboxylic acid derivatives**', a designation that describes a set of related functional groups. The eponymous member 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



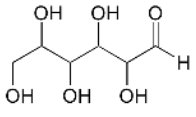
Finally, a **nitrile** group is characterized by a carbon triple-bonded to a nitrogen.

Nitriles

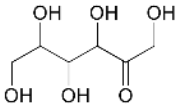


acetonitrile

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**').

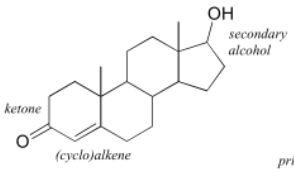


glucose

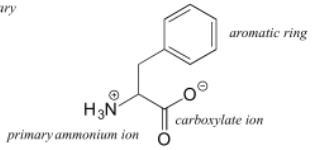


fructose

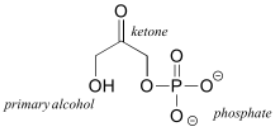
The hormone testosterone, the amino acid phenylalanine, and the glycolysis metabolite dihydroxyacetone phosphate all contain multiple functional groups, as labeled below.



testosterone



phenylalanine



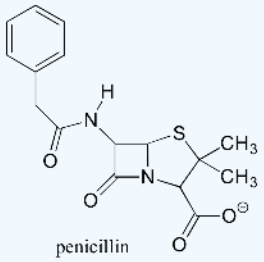
dihydroxyacetone phosphate (DHAP)

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

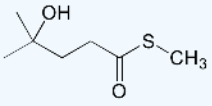
Identify the functional groups (other than alkanes) in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.

a)

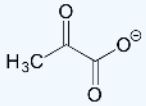


penicillin

b)

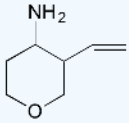


c)



pyruvate

d)



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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 identifying 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

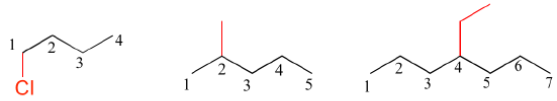
7 carbons: heptane

8 carbons: octane

9 carbons: nonane

10 carbons: decane

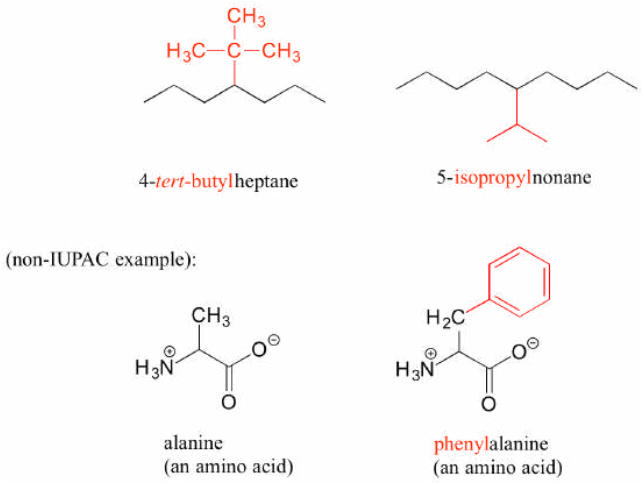
Substituents branching from the main parent chain are located by a carbon number, with *the lowest possible numbers* being used (for example, notice in the example below that the compound on the left is named 1-chlorobutane, *not* 4-chlorobutane). When the substituents are small alkyl groups, the terms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



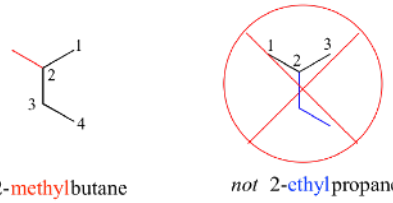
1-chlorobutane 2-methylpentane 4-ethylheptane

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

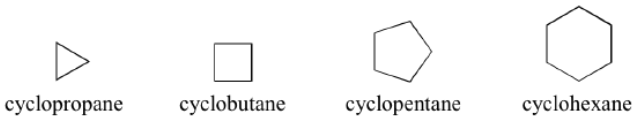
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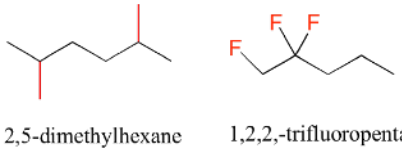
Notice in the example below, an 'ethyl group' (in blue) is not treated as a substituent, rather it is included as part of the parent chain, and the methyl group is treated as a substituent. The IUPAC name for straight-chain hydrocarbons is always based on the *longest possible parent chain*, which in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



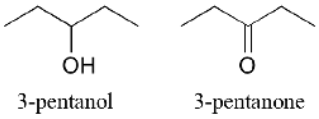
Cyclic alkanes are called cyclopropane, cyclobutane, cyclopentane, cyclohexane, and so on:



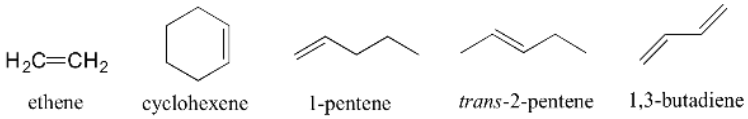
In the case of multiple substituents, the prefixes *di*, *tri*, and *tetra* are used.



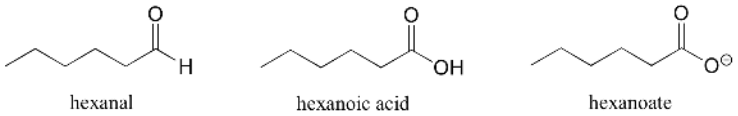
Functional groups have characteristic suffixes. Alcohols, for example, have '**ol**' appended to the parent chain name, along with a number designating the location of the hydroxyl group. Ketones are designated by '**one**'.



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.

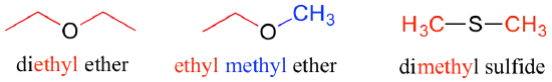


Some groups can only be present on a terminal carbon, and thus a locating number is not necessary: aldehydes end in ‘al’, carboxylic acids in ‘oic acid’, and carboxylates in ‘oate’.



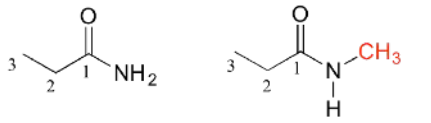
hexanal hexanoic acid hexanoate

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



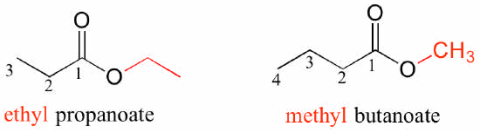
diethyl ether ethyl methyl ether dimethyl sulfide

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.



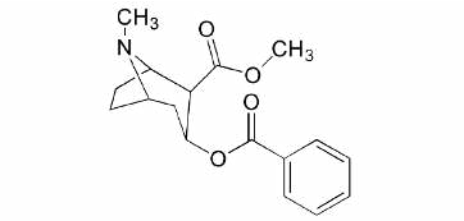
propanamide *N*-methylpropanamide

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



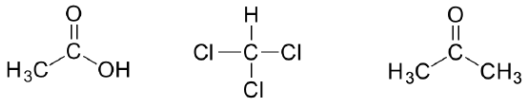
ethyl propanoate methyl butanoate

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

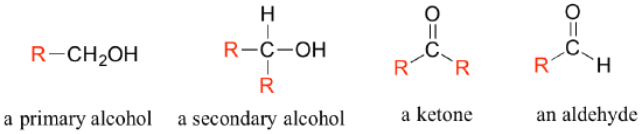
f) 4-penteneoic acid

g) *N*-ethyl-*N*-cyclopentylbutanamide

Solutions to exercises

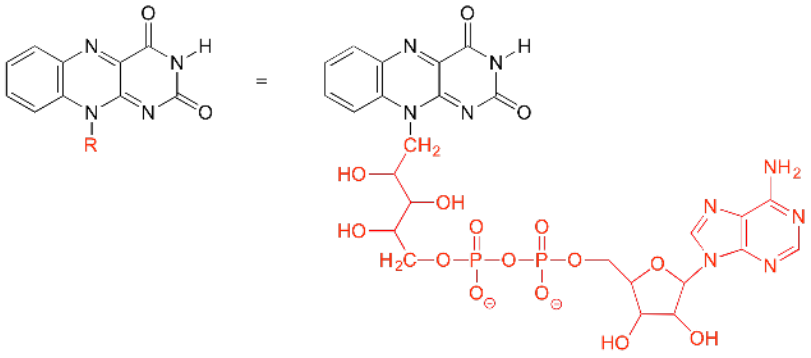
Drawing abbreviated organic structures

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:



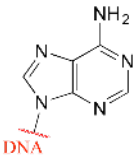
a primary alcohol a secondary alcohol a ketone an aldehyde

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:

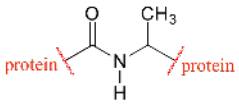


flavin adenine dinucleotide (FAD)

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.

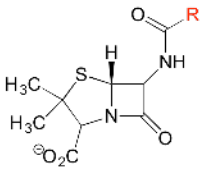


an adenine base in DNA

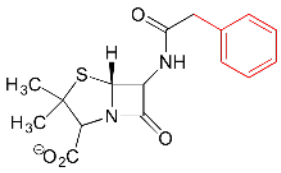


a small section of a protein

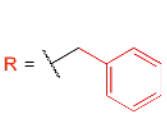
Finally, 'R' groups can be used to concisely illustrate a series of related compounds, such as the family of penicillin-based antibiotics.



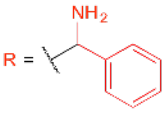
penicillin framework



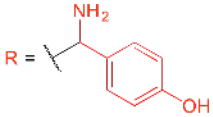
benzyl penicillin



benzyl penicillin



ampicillin

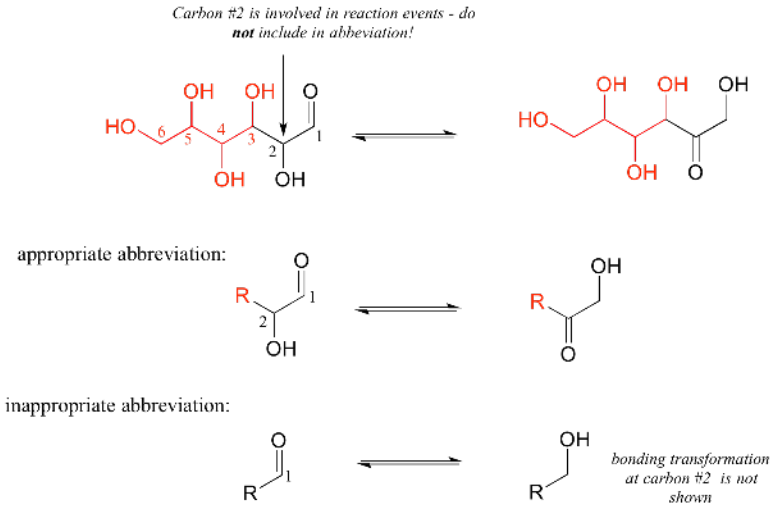


amoxicillin

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.

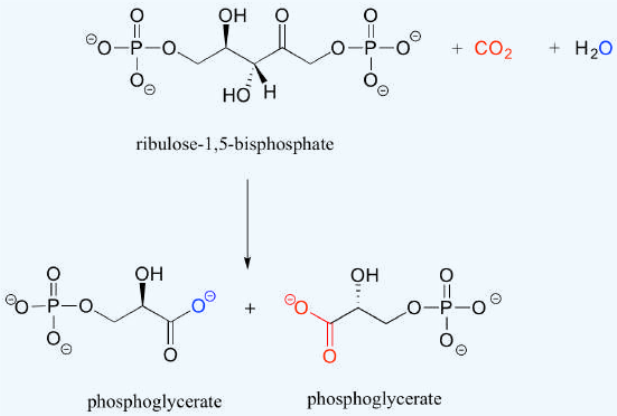


If you are unsure whether to draw out part of a structure or abbreviate it, the safest thing to do is to draw it out.

Exercise 1.16

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

Kahn Academy video tutorial on functional groups

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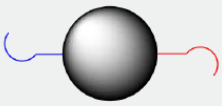
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1.4: Structures of some important biomolecules

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 about 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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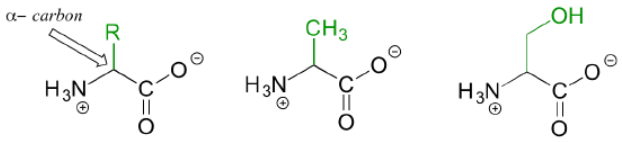
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1.4.1: Introduction to amino acids and proteins

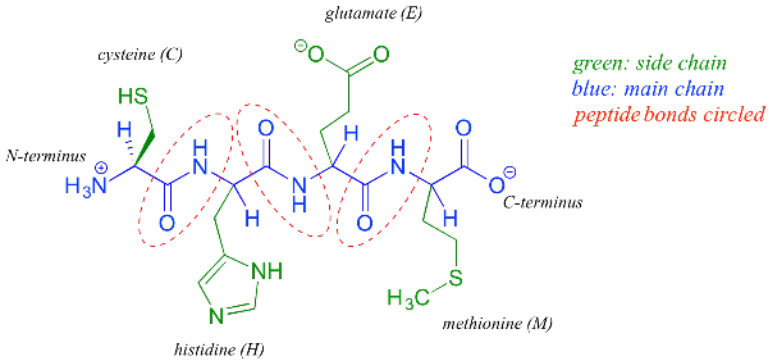
Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded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



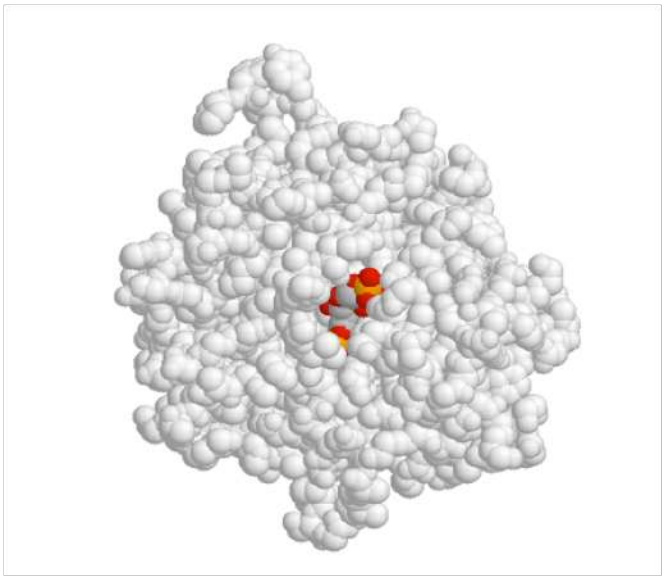
CHEM peptide

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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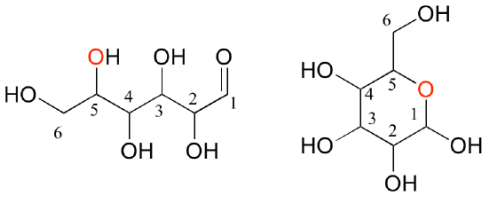
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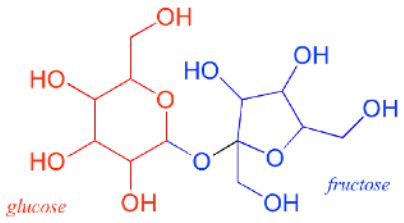
1.4.2: Introduction to carbohydrate structure

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.

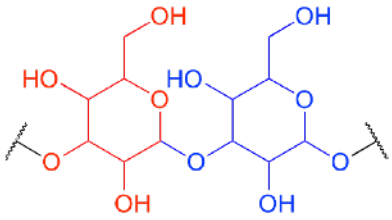


Disaccharides are two monosaccharides linked together: for example, sucrose, or table sugar, is a disaccharide of glucose and fructose.



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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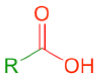
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1.4.3: Introduction to lipid structure

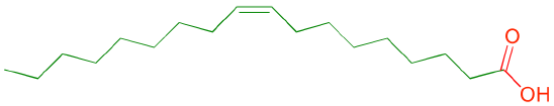
Lipids are a class of biomolecules which includes fats, oils, waxes, and compounds such as cholesterol that are referred to as 'isoprenoids'.. Fats, oils, and waxes all incorporate **fatty acids**, which are composed of hydrocarbon chains terminating in a carboxylic acid/carboxylate group (we will learn 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

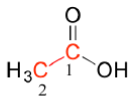


palmitic acid
(a 16-carbon saturated fatty acid)

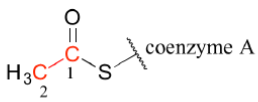


oleic acid
(an 18-carbon monounsaturated fatty acid)

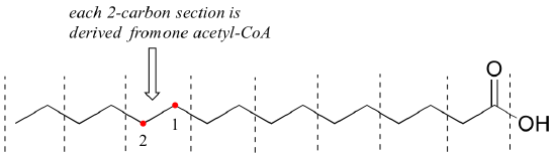
Fatty acids are synthesized in the body by a process in which the hydrocarbon chain is elongated two carbons at a time. Each two-carbon unit is derived from a metabolic intermediate called **acetyl-coA**, which is essentially an acetic acid (vinegar) molecule linked to a large 'carrier' molecule, called 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

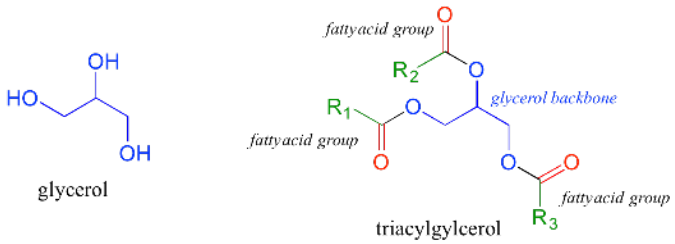


acetyl-coA



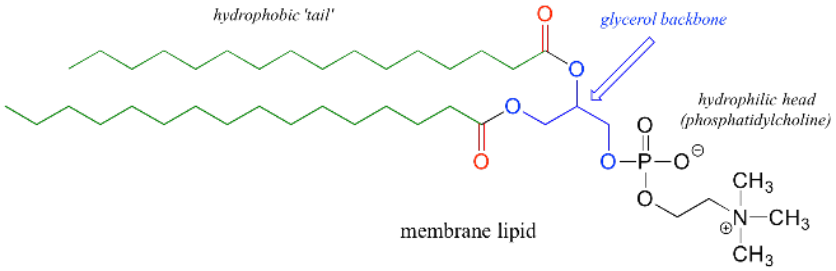
The breakdown of fatty acids in the body also occurs two carbons at a time, and the endpoint is again acetyl-coenzyme A. We will learn about the details of all of the reactions in these metabolic pathways at various places in this book. If you go on to take a biochemistry course, you will learn more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



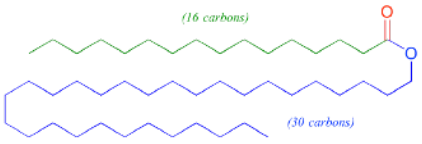
In chapter 2 we will see how these molecules come together to form a cell membrane.

Exercise 1.17

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

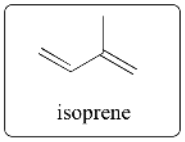
Solutions to exercises

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.

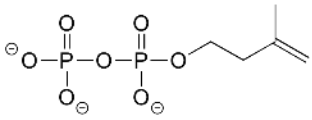


tricontanyl palmitate

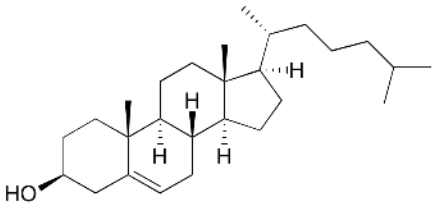
Isoprenoids, a broad class of lipids present in all forms of life, are based on a five-carbon, branched-chain building block called isoprene. In humans, cholesterol and hormones such as testosterone are examples of isoprenoid biomolecules. In plants, isoprenoids include the deeply colored compounds such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



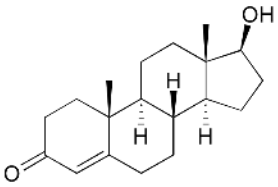
isoprene



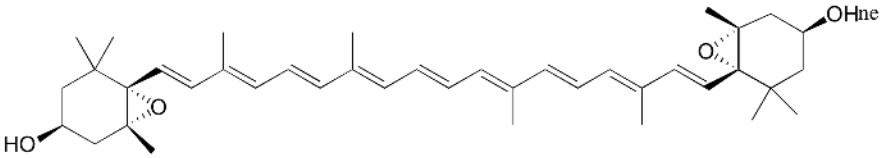
isopentenyl diphosphate



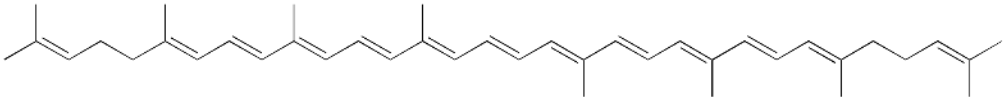
cholesterol



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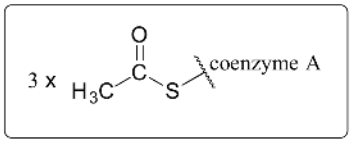


violaxanthin
(a carotenoid)



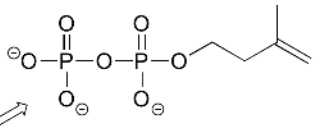
lycopene

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.



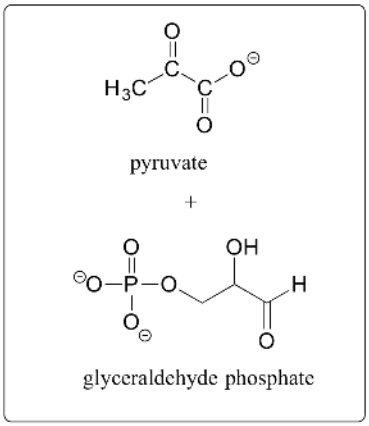
3 x coenzyme A

eukaryotes, archaea



isopentenyl diphosphate

bacteria



pyruvate

+

glyceraldehyde phosphate

isoprenoid compounds

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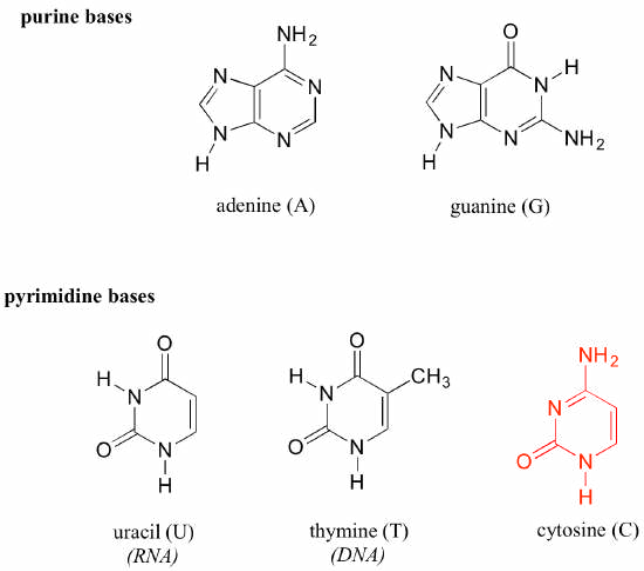
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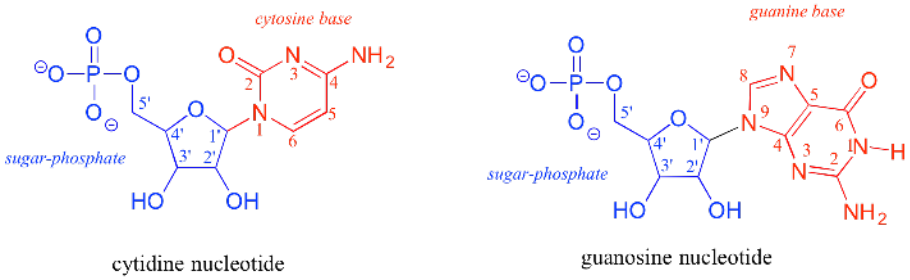
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1.4.4: Introduction to nucleic acid (DNA and RNA) structure

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).



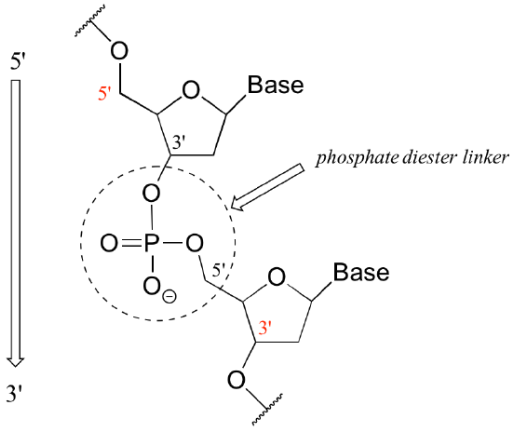


cytidine nucleotide

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.



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1.5: 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)

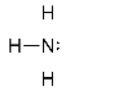
h) $1s^2 2s^2 2p^6 3s^2 3p^6$ (same as Argon atom)

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



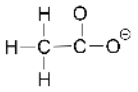
b) ammonium ion



c) amide ion



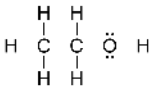
d) formaldehyde



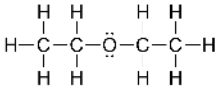
e) acetate ion



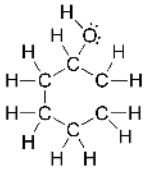
f) methylamine



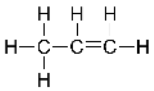
g) ethanol



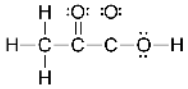
g) diethylether



i) cyclohexanol



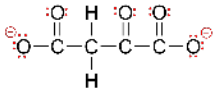
j) propene



k) pyruvic acid

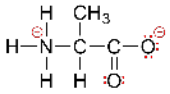
E1.4:

a)



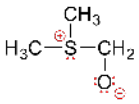
malate

b)

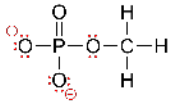


alanine

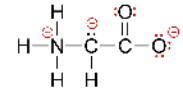
c)



d)



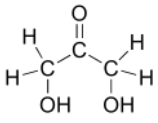
e)



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

6 hydrogens

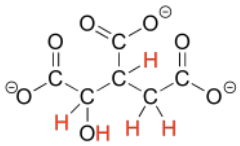
a)



dihydroxyacetone

5 hydrogens

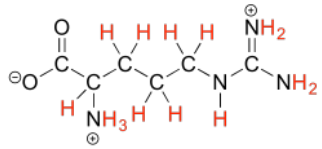
b)



isocitrate

15 hydrogens

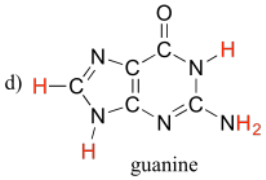
c)



arginine

5 hydrogens

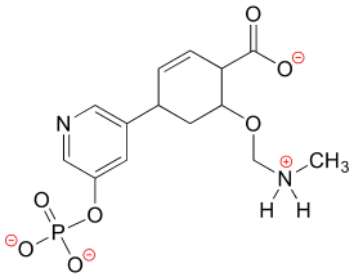
d)



guanine

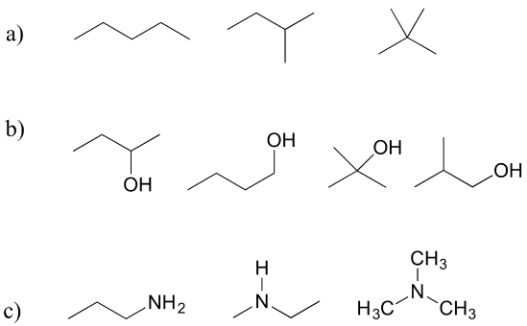
E1.8:

https://chem.libretexts.org/@go/page/234500



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

E1.11:



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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1.6: Problems for Chapter 1

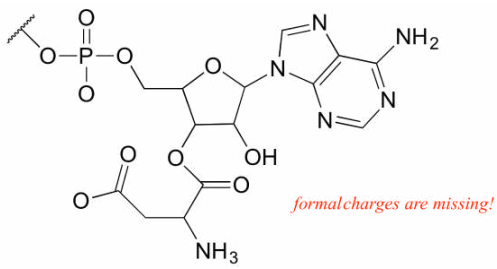
Solutions to selected Chapter 1 problems

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

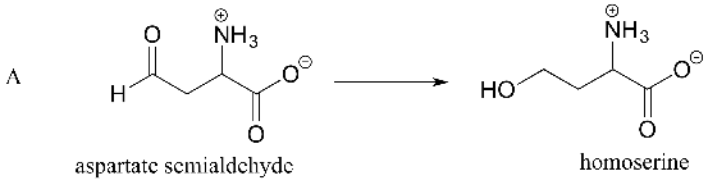
c) 6-methyl-2,5-cyclohexadienone d) 3-methylbutanenitrile

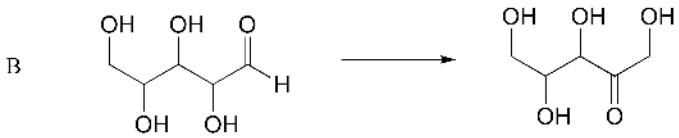
e) 2,6-dimethyldecane f) 2,2,5,5-tetramethyl-3-hexanol

g) methyl butanoate h) *N*-ethylhexanamide

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

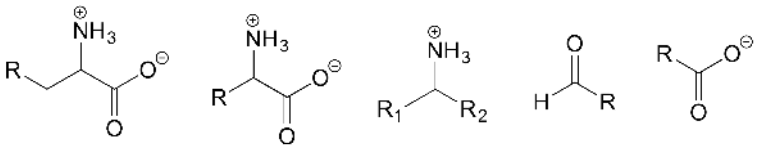
P1.4: Reaction A below is part of the biosynthetic pathway for the amino acid methionine, and reaction B is part of the pentose phosphate pathway of sugar metabolism.





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.

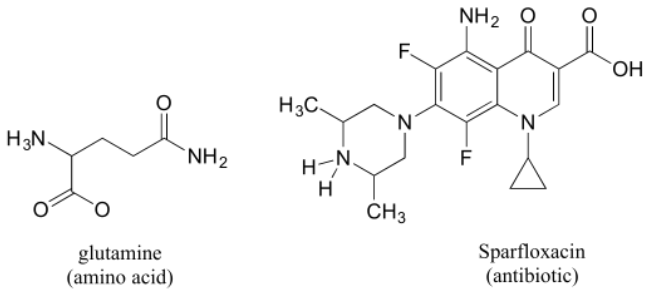
P1.7: Draw one example each of compounds fitting the descriptions below, using line structures. Be sure to include all non-zero formal charges. All atoms should fit one of the common bonding patters discussed in this chapter. There are many possible correct answers - be sure to check your drawings with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

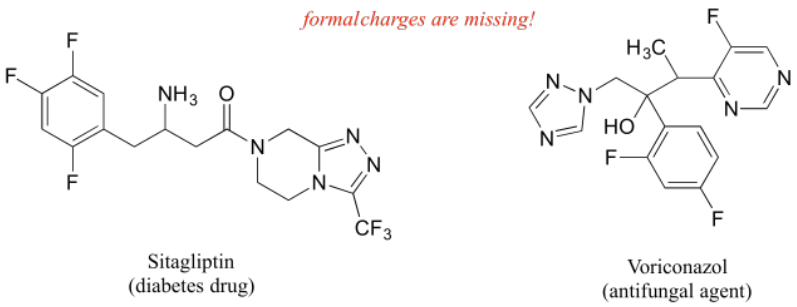
P1.8: Three of the four structures below are missing formal charges.



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.

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

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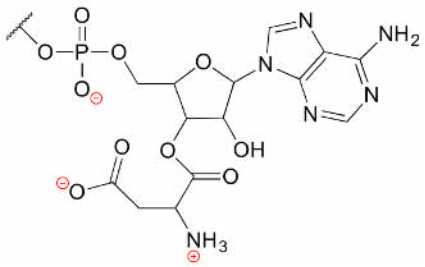
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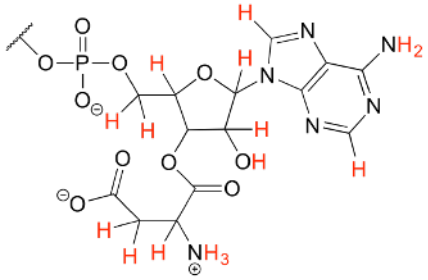
1.6.1: Solutions to selected Chapter 1 problems

P1.1:

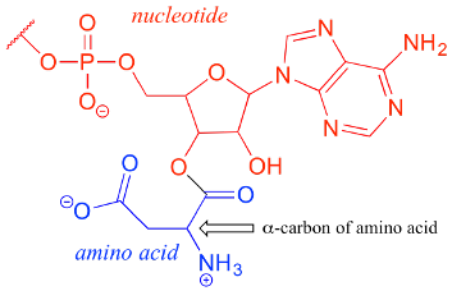
a) Formal charges are located as shown.



b) There are 16 hydrogen atoms:



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



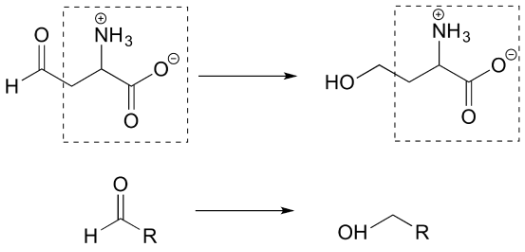
P1.4:

a)

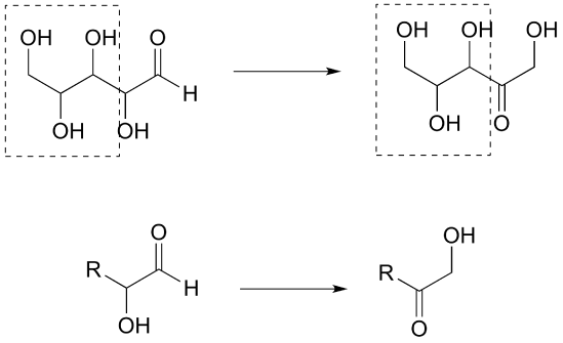
Reaction A: aldehyde to primary alcohol

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.

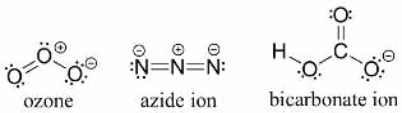
e) Tyrosine contains a phenol.

f) The lysine side chain contains a primary ammonium.

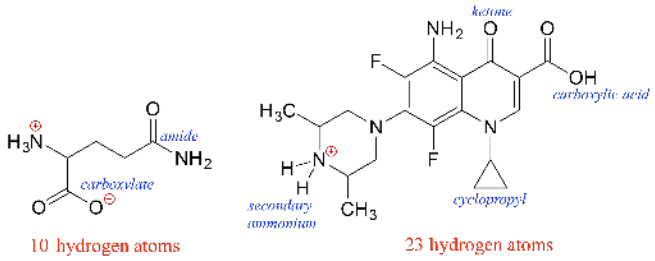
g) The glutamate and aspartate side chains contain carboxylates.

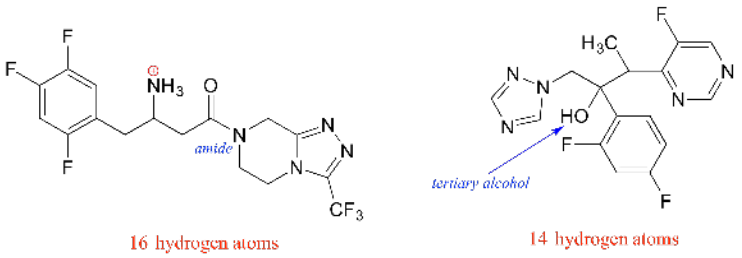
h) Proline contains a secondary amine.

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.

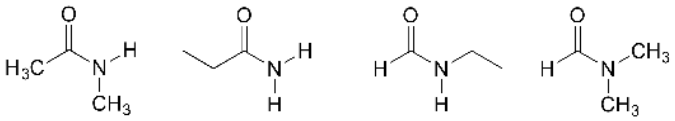


P1.8:





P1.10:



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CHAPTER OVERVIEW

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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.

2.1: Prelude to Organic Structure and Bonding II

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2.3: Molecular orbital theory- conjugation and aromaticity

2.4: Resonance

2.5: Non-covalent interactions

2.6: Physical properties of organic compounds

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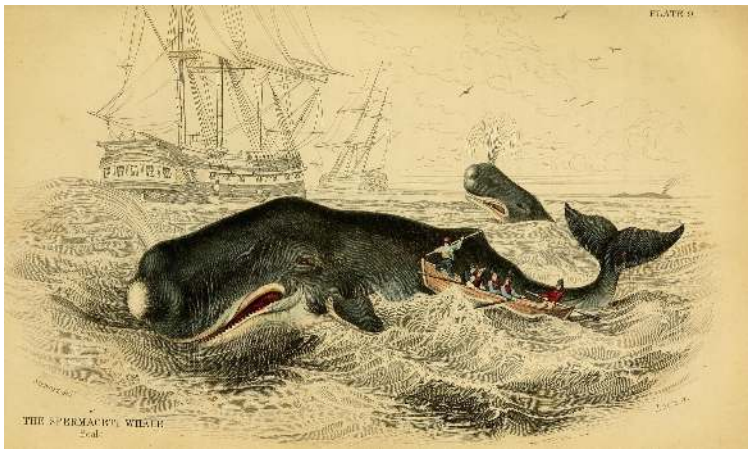
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2.1: Prelude to Organic Structure and Bonding II

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 Khan 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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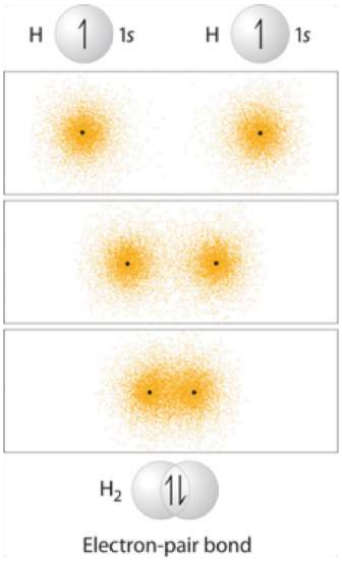
2.2: Valence Bond Theory

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

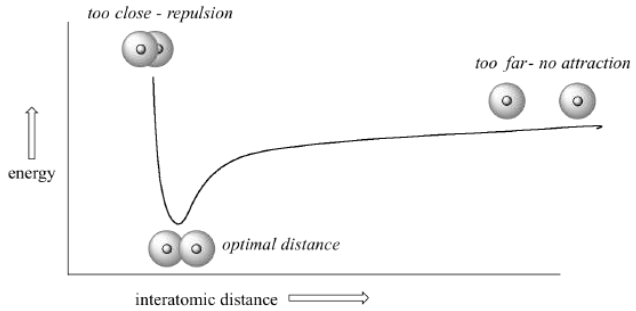
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two hydrogen nuclei share their electrons to form a covalent bond, what we mean in valence bond theory terms is that the two spherical 1*s* orbitals (the grey spheres in the figure below) overlap, and contain two electrons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



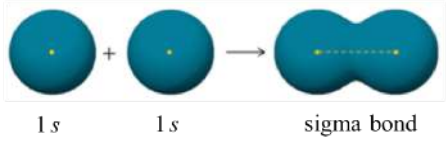
At first this repulsion is more than offset by the attraction between nuclei and electrons, but at a certain point, as the nuclei get even closer, the repulsive forces begin to overcome the attractive forces, and the potential energy of the system rises quickly. When the two nuclei are 'too close', we 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.

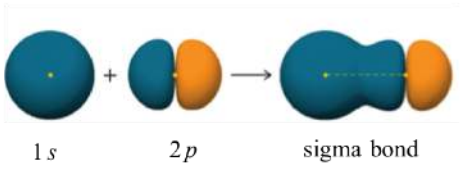
Table of bond lengths and bond energies

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.

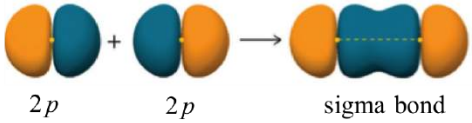
One more characteristic of the covalent bond in H_2 is important to consider at this point. The two overlapping 1*s* orbitals can be visualized as two spherical balloons being pressed together. This means that the bond has **cylindrical symmetry**: if we were to take a cross-sectional plane of the bond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

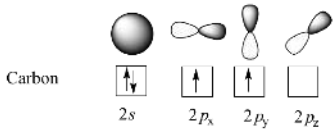


A sigma bond can also be formed by the overlap of two *p* orbitals. The covalent bond in molecular fluorine, F_2, is a sigma bond formed by the overlap of two half-filled 2*p* orbitals, one from each fluorine atom.

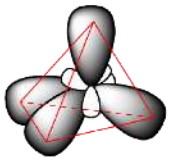


sp^3 hybrid orbitals and tetrahedral bonding

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.



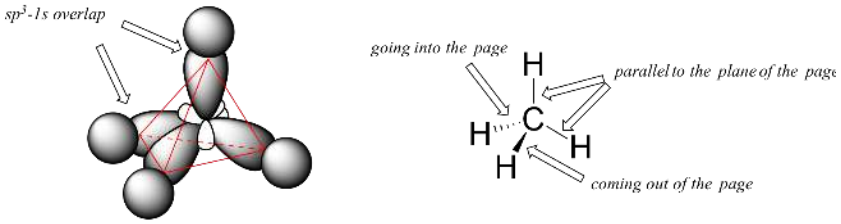
four sp^3 orbitals in tetrahedral orientation

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.



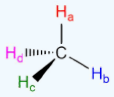
tetrahedral sp^3 bonding in methane

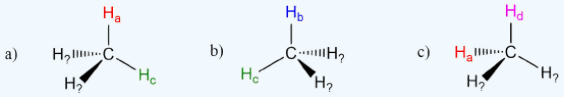
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: 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.)



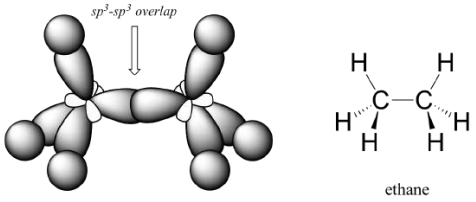


Exercise 2.2

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

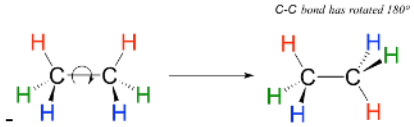
Solutions to exercises

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

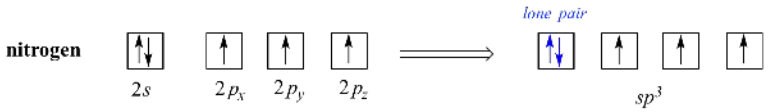
Because they are formed from the end-on-end overlap of two orbitals, *sigma bonds are free to rotate*. This means, in the case of ethane molecule, that the two methyl (CH_3) groups can be pictured as two wheels on an axle, each one able to rotate with respect to the other.

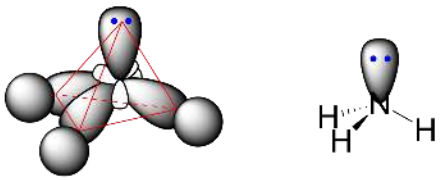


Video

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.



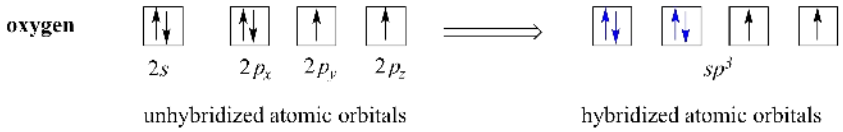


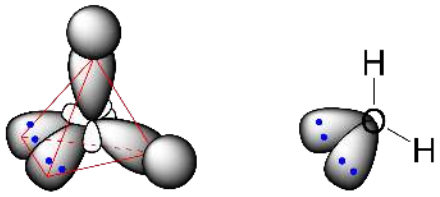
ammonia

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

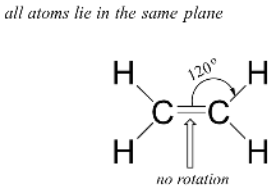
video tutorial on sp^3 orbitals and sigma bonds

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:

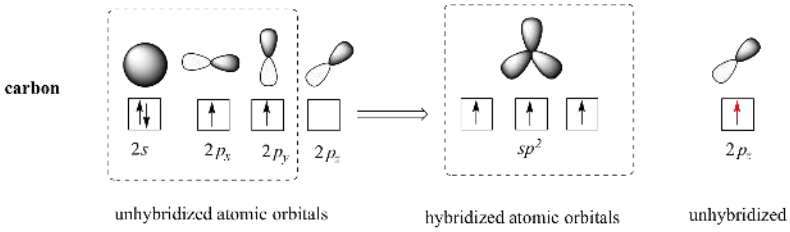
1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 134 pm, significantly shorter than the 154 pm single carbon-carbon bond in ethane.

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

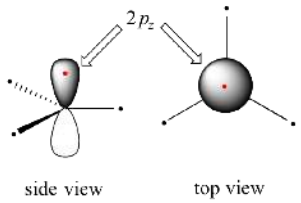


ethene

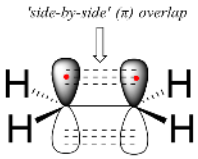
Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$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

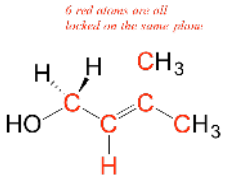


animation

video tutorial

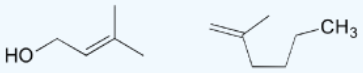
Interactive 3D model *(select 'show resulting pi orbital')*

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.



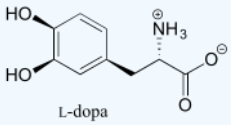
Exercise 2.4

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



Exercise 2.5

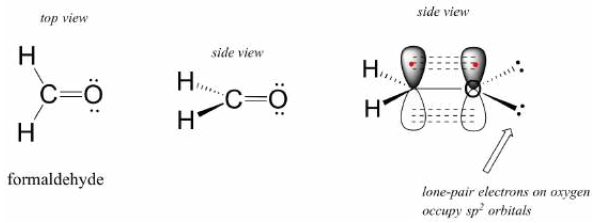
What is wrong with the way the following structure is drawn?



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

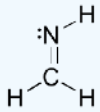
interactive 3D model

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.

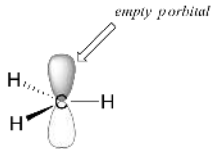
b: Draw a figure showing the bonding picture for the imine below.



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

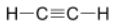
Solutions to exercises

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.



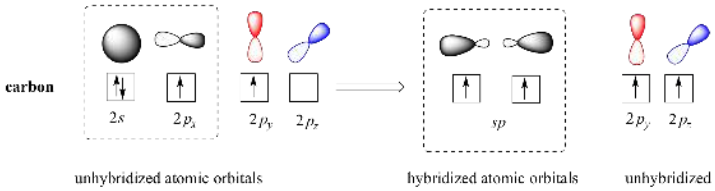
methyl carbocation, CH_3^-

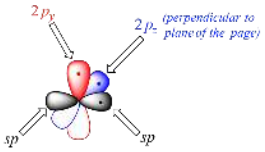
Finally, the hybrid orbital concept applies as well to triple-bonded groups, such as alkynes and nitriles. Consider, for example, the structure of ethyne (common name acetylene), the simplest alkyne.



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.

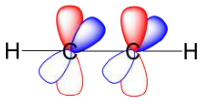




The carbon-carbon sigma bond, then, is formed by the overlap of one *sp* orbital from each of the carbons, while the two carbon-hydrogen sigma bonds are formed by the overlap of the second *sp* orbital on each carbon with a 1*s* orbital on a hydrogen. Each carbon atom still has two half-filled $2p_y$ 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

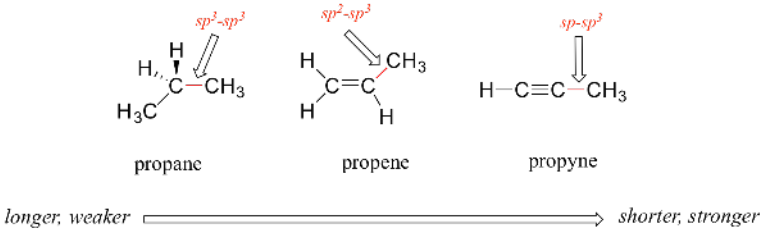
interactive 3D model

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.

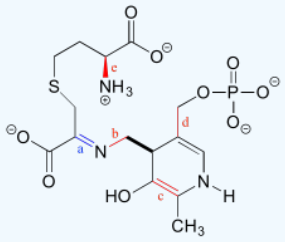


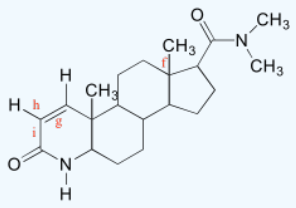
All three are single (sigma) bonds; the bond in propyne is shortest and strongest, while the bond in propane is longest and weakest. The explanation is relatively straightforward. An *sp* orbital is composed of one *s* orbital and one *p* orbital, and thus it has 50% *s* character and 50% *p* character. 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

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

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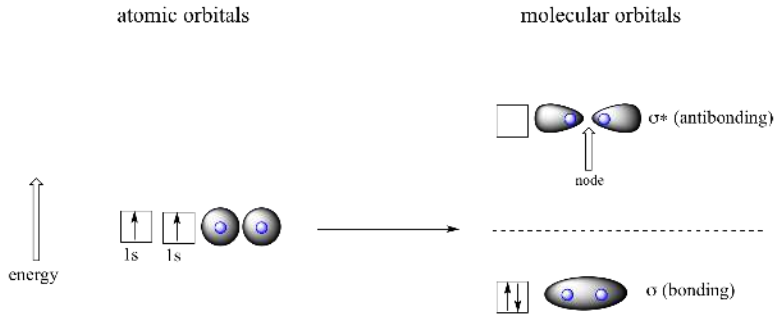
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2.3: Molecular orbital theory- conjugation and aromaticity

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.

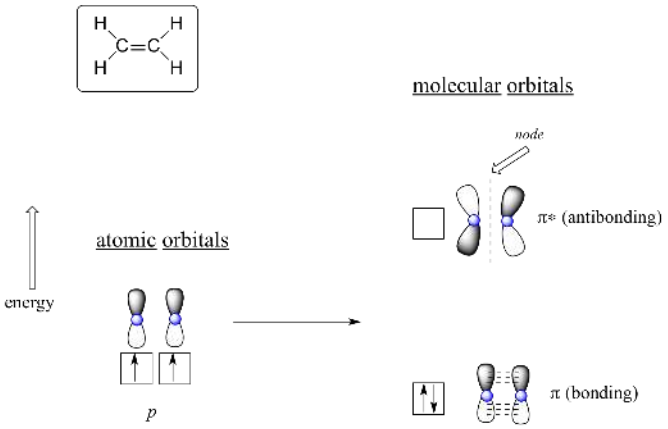
Remember that we are thinking here about electron behavior as *wave behavior*. When two separate waves combine, they can do so with **constructive interference**, where the two amplitudes build up and reinforce one another, or **destructive interference**, where the two amplitudes cancel one another 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.



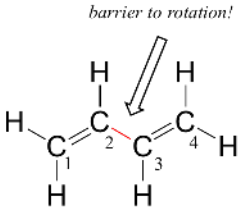
Molecular orbitals for ethene (ethylene)

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.

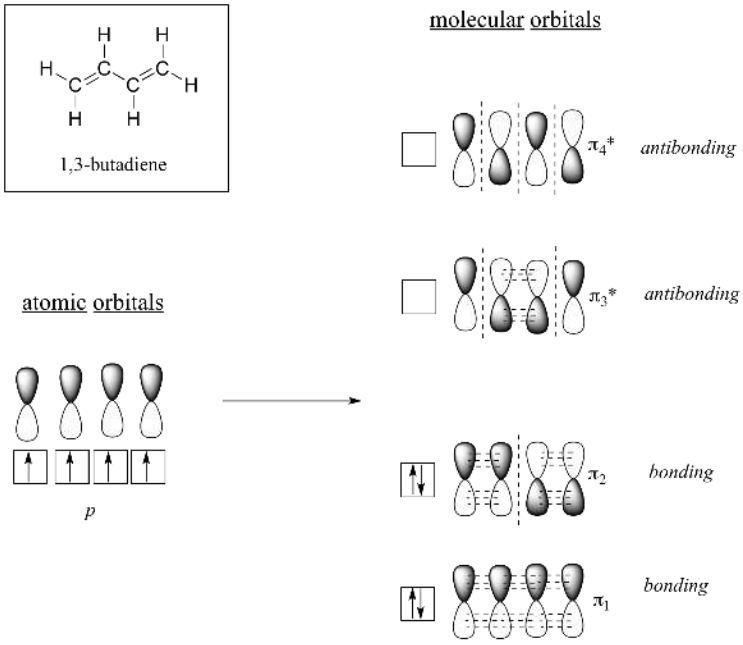
Again using the 'building up' principle, we place the two electrons in the lower-energy, bonding pi molecular orbital. The antibonding pi* orbital remains empty.

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.



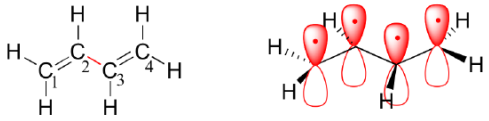
Experimentally, however, it is observed that there is a significant barrier to rotation about the C_2-C_3 bond, and that the entire molecule is planar. In addition, the C_2-C_3 bond is 148 pm long, shorter than a typical carbon-carbon single bond (about 154 pm), though longer than a typical double bond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

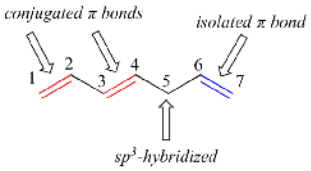
By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding pi_1 and pi_2 MO's. Because pi_1 includes constructive interaction between C_2 and C_3, there is a degree, in the 1,3-butadiene molecule, of pi-bonding interaction between these two carbons, 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

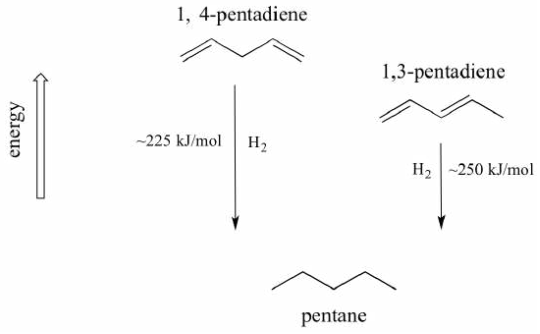
space-filling view

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.



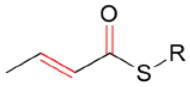
A very important concept to keep in mind is that *there is an inherent thermodynamic stability associated with conjugation.* This stability can be measured experimentally by comparing the **heat of hydrogenation** of two different dienes. (Hydrogenation is a reaction type that we will learn much more 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.

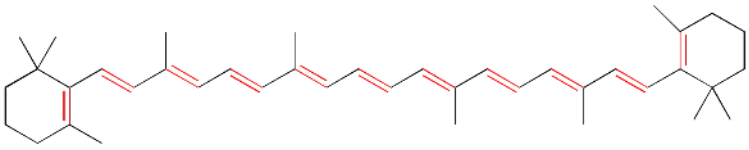


The conjugated diene is lower in energy: in other words, it is more stable. In general, conjugated pi bonds are more stable than isolated pi bonds.

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.



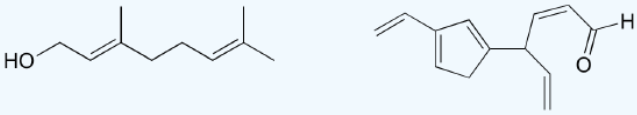
In chapter 4, we will see that MO theory is very useful in explaining why organic molecules that contain extended systems of conjugated pi bonds often have distinctive colors. beta-carotene, the compound responsible for the orange color of carrots, has an extended system of 11 conjugated pi bonds.



beta-carotene

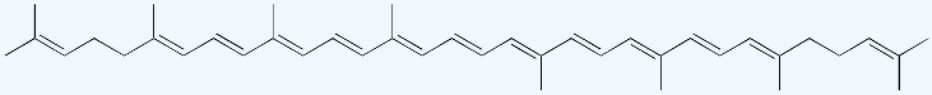
Exercise 2.9

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?

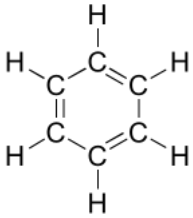


lycopene

Solutions to exercises

Aromaticity

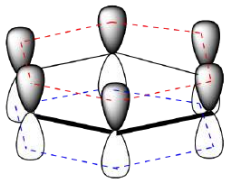
Molecular orbital theory is especially helpful in explaining the unique properties of **aromatic** compounds such as benzene:



3D interactive model of benzene

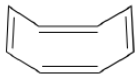
Although benzene is most often drawn with three double bonds and three single bonds, in fact all of the carbon-carbon bonds are exactly the same length (138 pm). In addition, the pi bonds in benzene are significantly less reactive than 'normal' pi bonds, either isolated or conjugated. Something about 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.



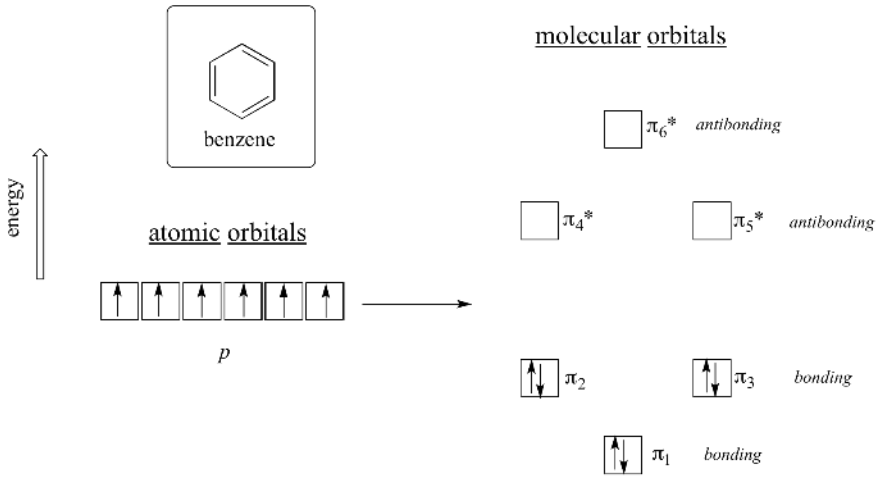
π electrons delocalized around the ring, above and below the plane

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



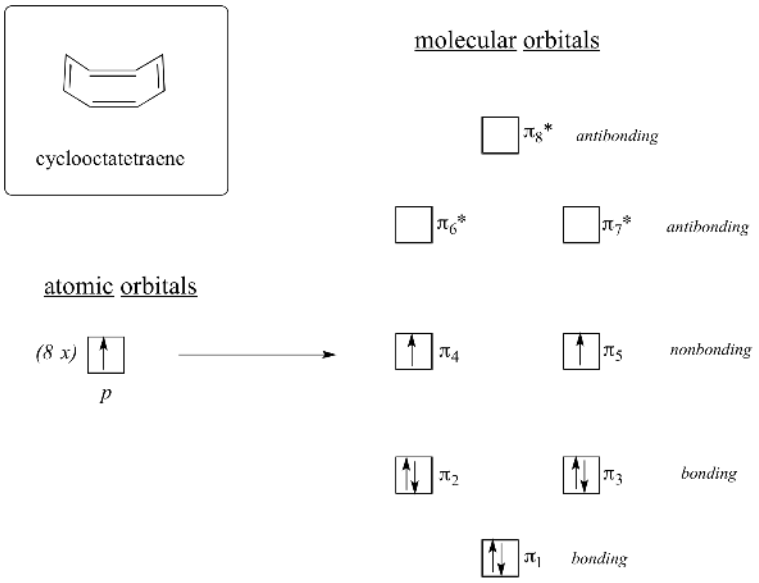
cyclooctatetraene
(not aromatic)

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.

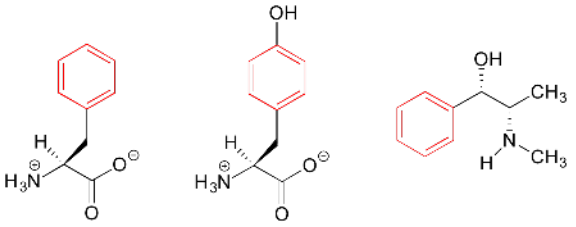
The ring must be planar.

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

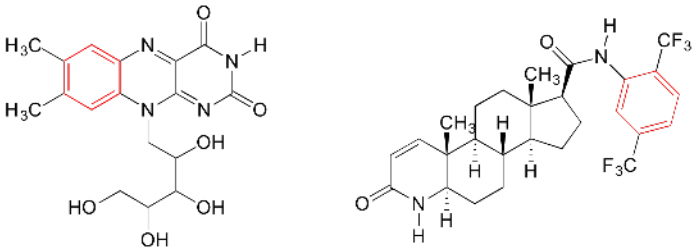
The number of pi electrons in the ring must equal $4n+2$, where n is any positive integer including zero.

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.



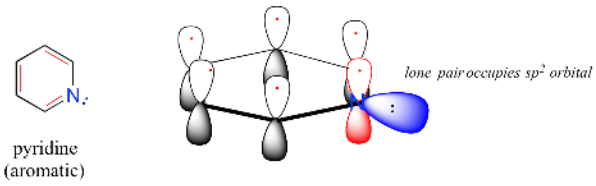
phenylalanine (an amino acid) | tyrosine (an amino acid) | pseudoephidrine (decongestant)



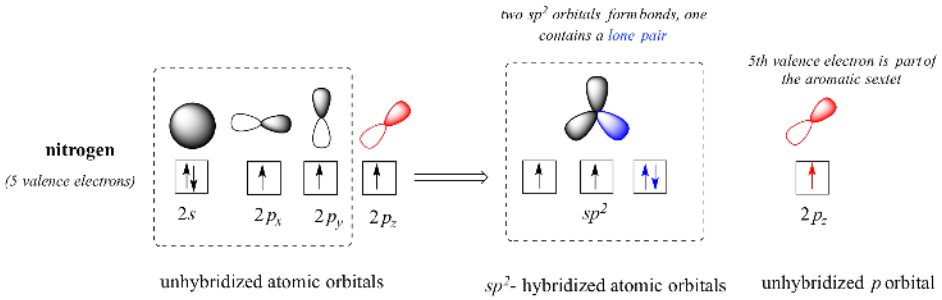
riboflavin (a vitamin) | dutasteride (GlaxoSmithKline drug for urinary condition in men)

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.



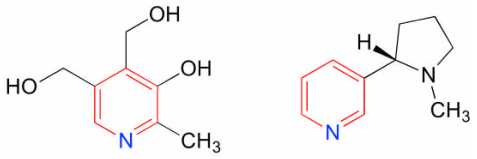
pyridine (aromatic)



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

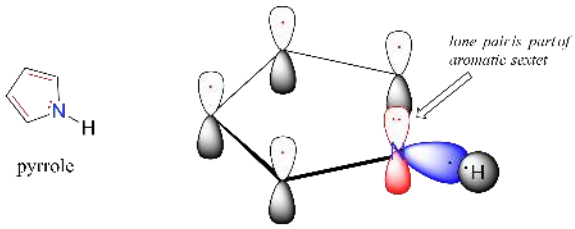
another image of orbitals in pyridine

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

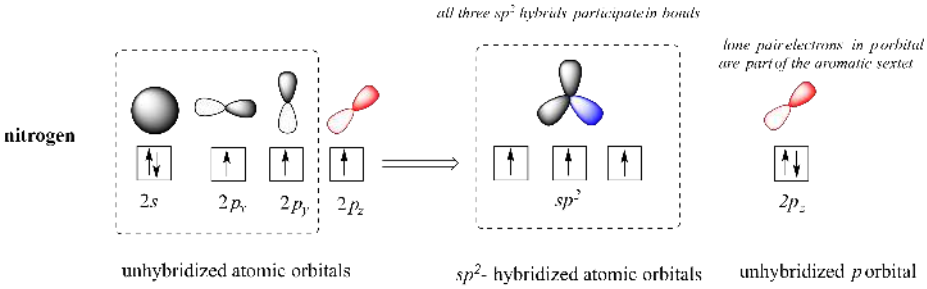


pyridoxine (vitamin B_6) nicotine

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).



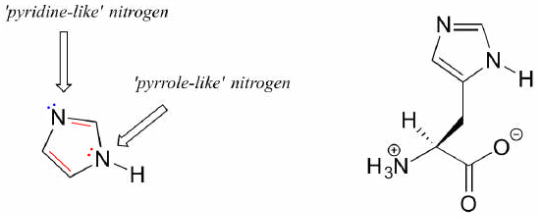
pyrrole



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.

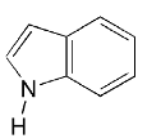
Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring.



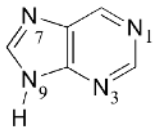
imidazole histidine

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.

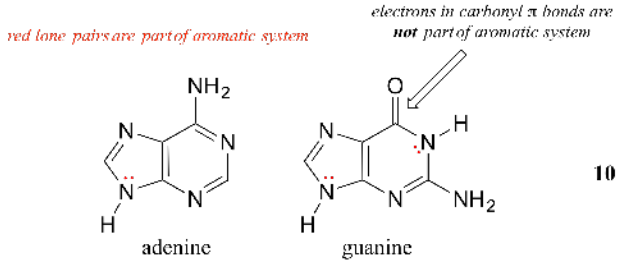


indole



purine

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.

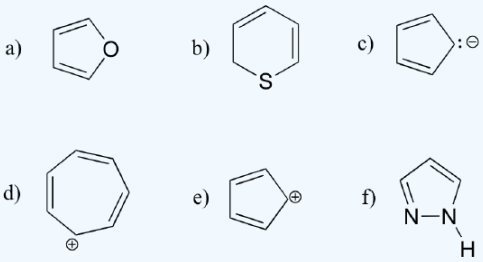


Exercise 2.11

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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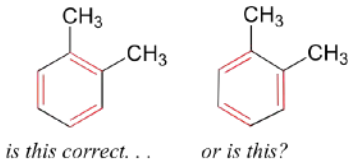
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2.4: Resonance

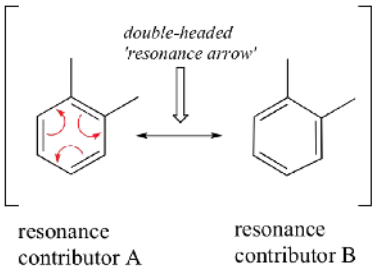
What is resonance?

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:

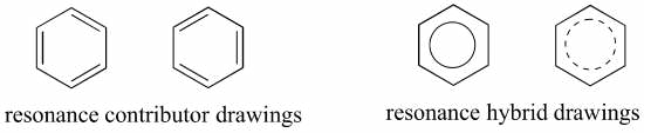


In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the ‘movement’ of two pi electrons. A few chapters from now when we begin to study organic reactions - a process in which electron density shifts 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.

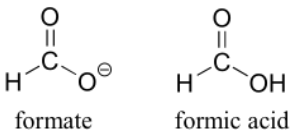
Caution! It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken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

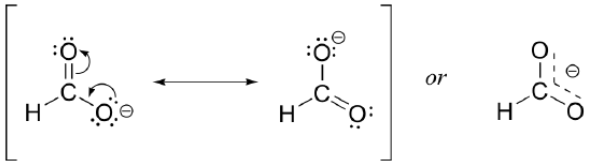


Resonance contributors for the carboxylate group

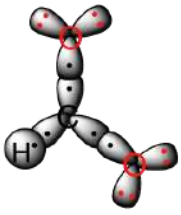
The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let's next consider 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.

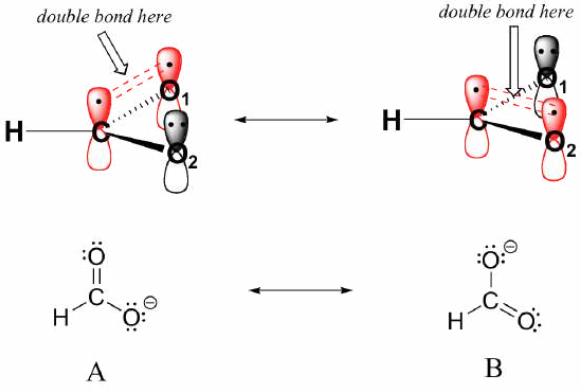


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as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

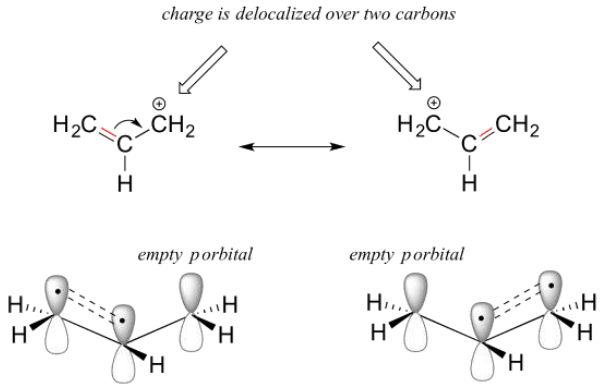


Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in 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

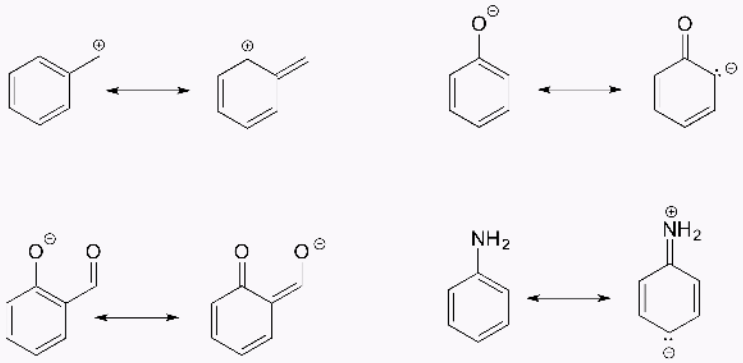
Exercise 2.14

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.

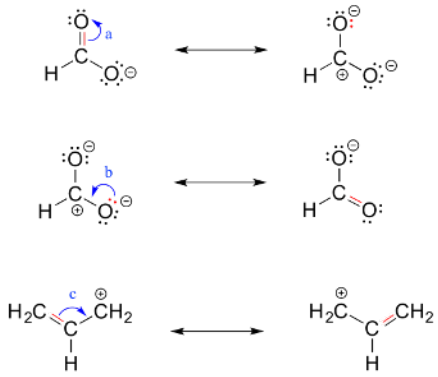
4) All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron movement' arrows that would lead to a situation where a second-row element (ie. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. 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').

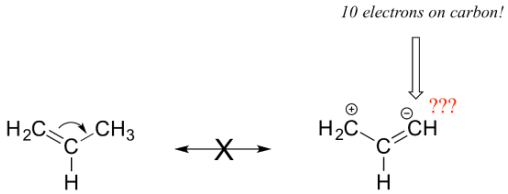
Third, we can shift a pi bond one position over (arrow c).



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

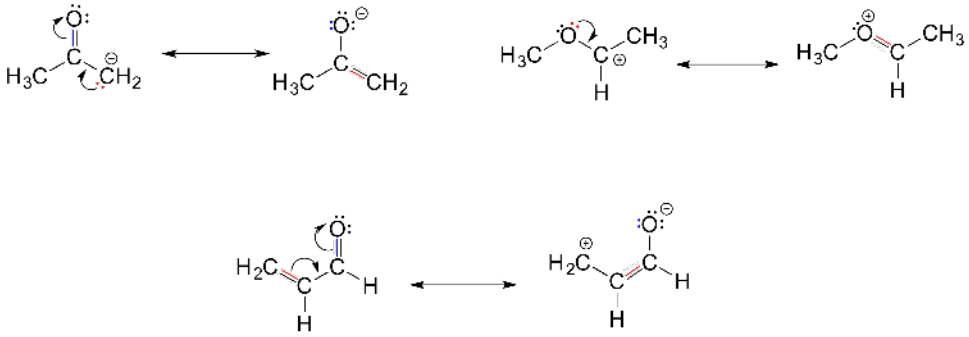


Notice that we do not exceed the octet rule on any atoms when we move electrons with arrows a, b and c. The resonance picture below shows an 'illegal' movement of electrons, because it would result in a carbon with five bonds, or 10 valence electrons (this would break the octet rule):



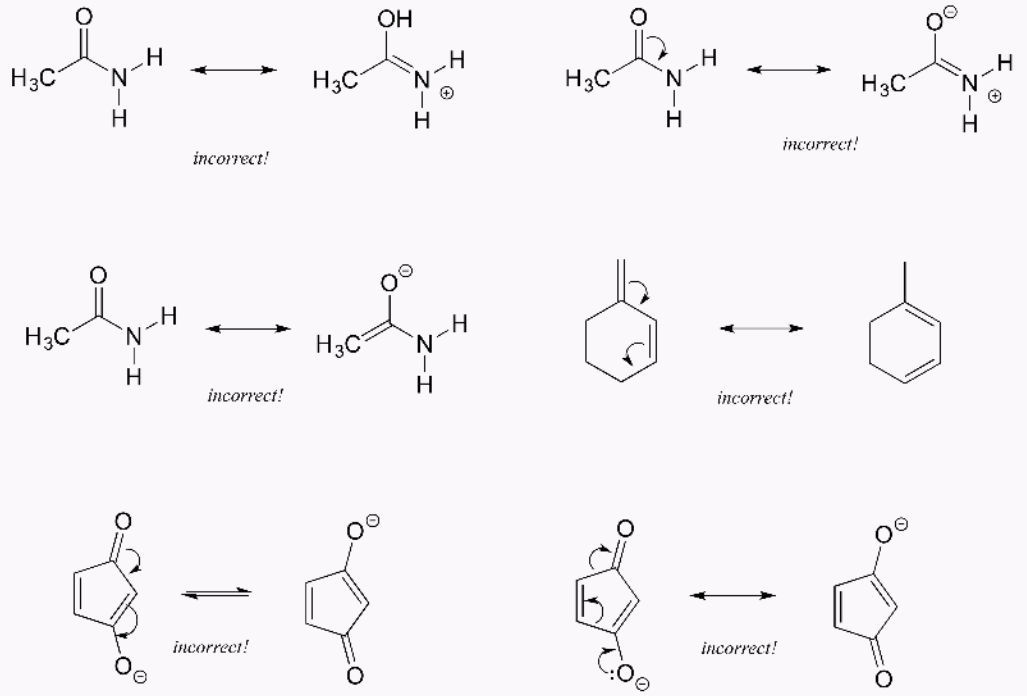
Always be very careful when drawing resonance structures that your arrows do ***only*** the three types of electron movement described above, and that you ***never*** exceed the octet rule on a second-row element. It is often helpful (but optional), to include all lone-pair electrons on oxygen and nitrogen 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

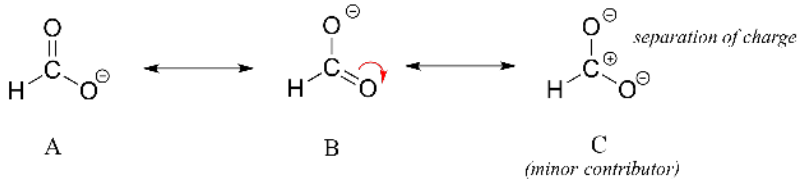
Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in each.



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:

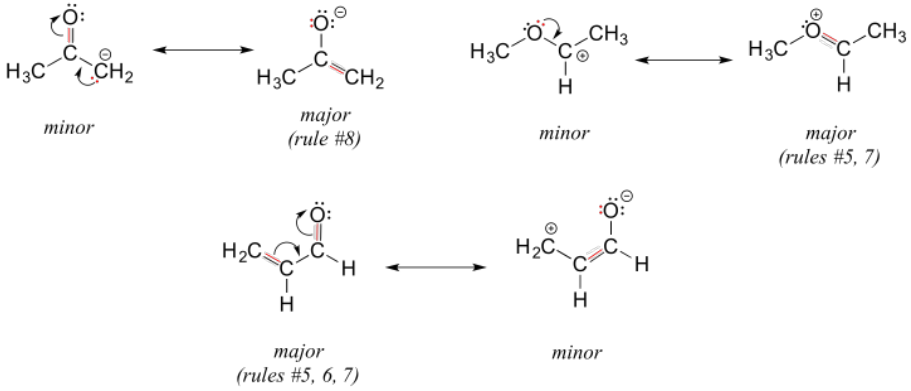
5) The carbon in contributor C does not have an octet – in general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important.

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.

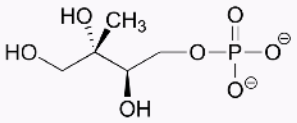
Exercise 2.17

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).



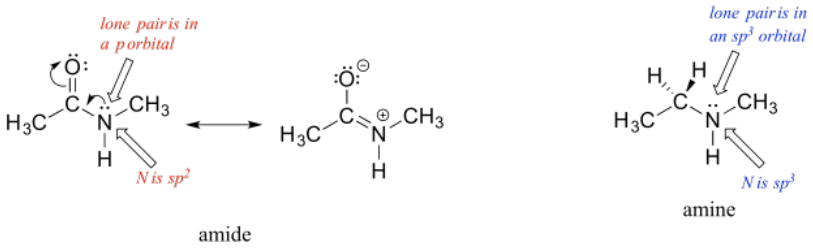
Exercise 2.19

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

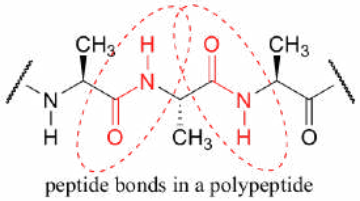
Resonance and peptide bonds

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.

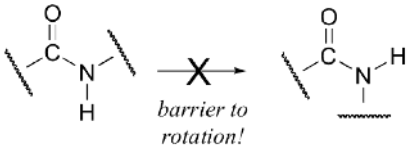


In fact, the latter picture is more accurate: the lone pair of electrons on an amide nitrogen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system, and the bonding geometry around the nitrogen is trigonal planar as expected for sp^2 hybridization. This 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.



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.



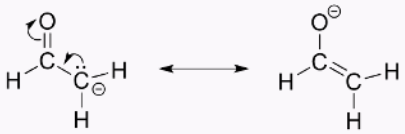
The barrier to rotation in peptide bonds is an integral part of protein structure, introducing more rigidity to the protein's backbone. If there were no barrier to rotation in a peptide bond, proteins would be much more 'floppy' and three dimensional folding would be very different.

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?

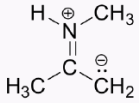
Exercise 2.21

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

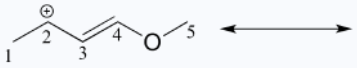
Below is a minor resonance contributor of a species known as an 'enamine', which we will study more in chapter 12. Draw the major resonance contributor for the enamine, and explain why your contributor is the major one (refer to resonance rules #5-8 from this section).



Solutions to exercises

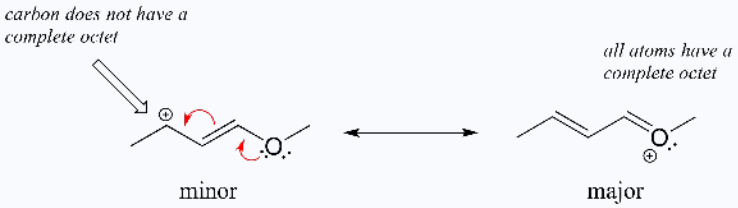
Solved example

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?



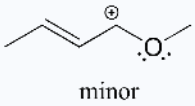
Solution

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).



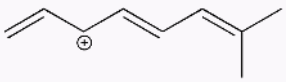
The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #5 and #7 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, 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

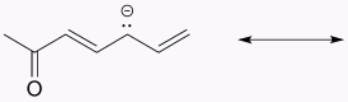
a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.

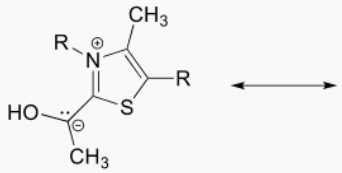


b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Exercise 2.24

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





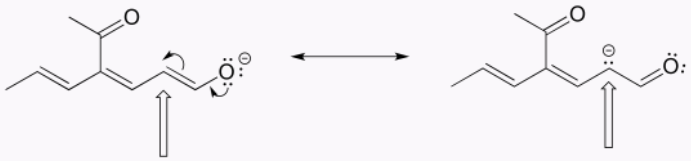
c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

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!

Kahn 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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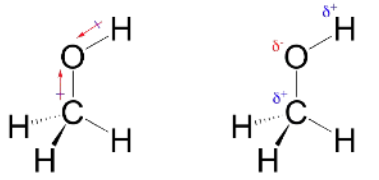
2.5: Non-covalent interactions

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.



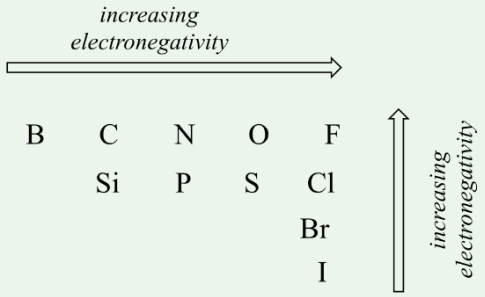
bond dipole arrows partial charge notation

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.

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Periodic trends in electronegativity

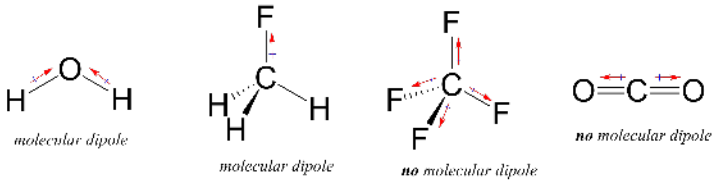


Exercise 2.26

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

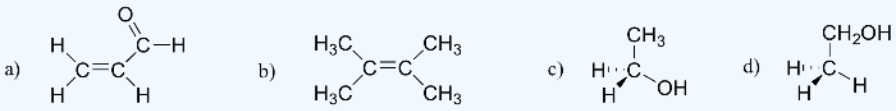
Most molecules contain both polar and nonpolar covalent bonds. Depending on the location of polar bonds and bonding geometry, molecules may posses a net polarity, called a **molecular dipole moment**. Water, as you probably recall, has a dipole moment that results from the combined dipoles of its two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

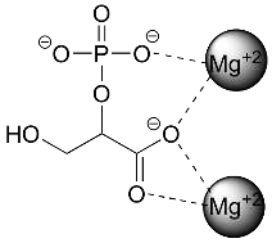
Which of the molecules below have molecular dipole moments?



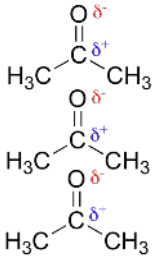
Solutions to exercises

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

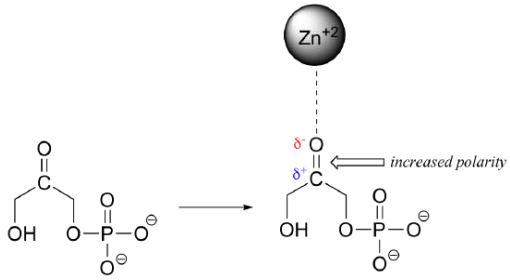
The strongest type of non-covalent interaction is between two ionic groups of opposite charge (an **ion-ion** or **charge-charge interaction**). You probably saw lots of examples of ionic bonds in inorganic compounds in your general chemistry course: for example, table salt is composed of sodium cations 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.



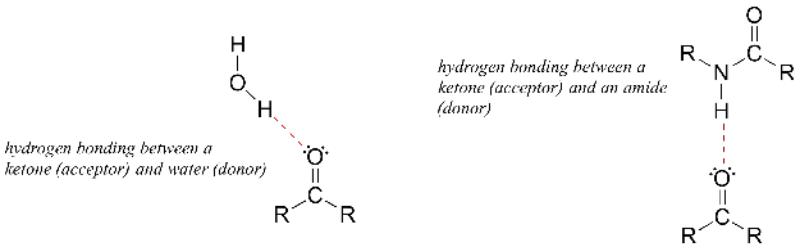
Because the metal cation is very electronegative, this interaction has the effect of pulling electron density in the carbonyl double bond even further toward the oxygen side, increasing the partial positive charge on carbon. As we shall later, this has important implications in terms of the reactivity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

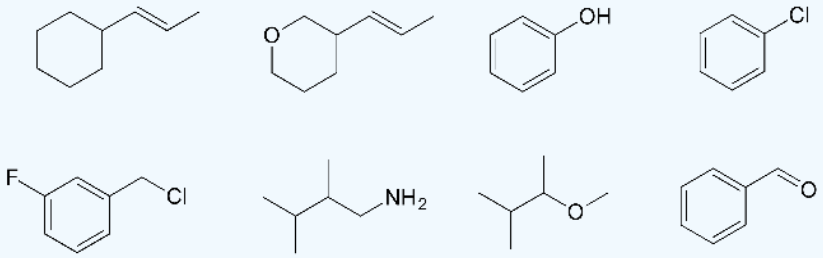


Hydrogen bonds are usually depicted with dotted lines in chemical structures. A group that provides a proton to a hydrogen bond is said to be acting as a **hydrogen bond donor**. A group that provides an oxygen or nitrogen lone pair is said to be acting as a **hydrogen bond acceptor**. Many common organic 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

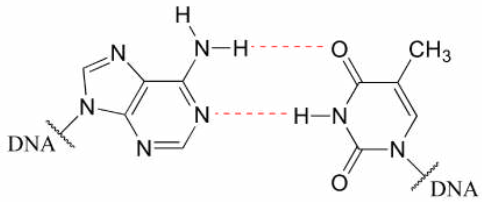
Draw figures that show the hydrogen bonds described below.

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.

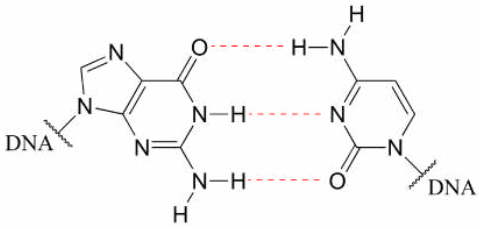
Solutions to exercises

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:

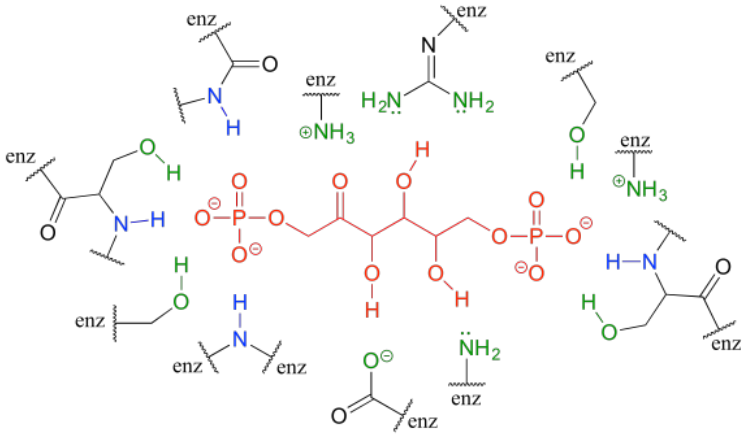
A-T base pair:



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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2.6: 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.

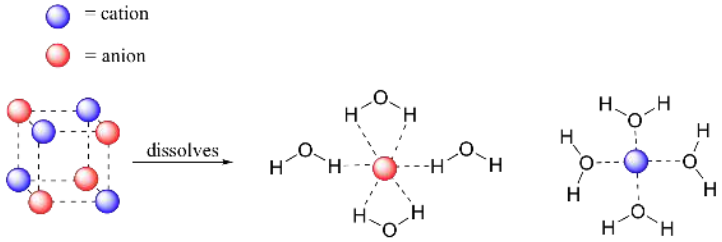
Solubility

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 diethyl ether. 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.

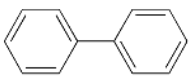
When considering the solubility of an organic compound in a given solvent, the most important question to ask ourselves is: how strong are the noncovalent interactions between the compound and the solvent molecules? If the solvent is polar, like water, then a smaller hydrocarbon component and/or more 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).

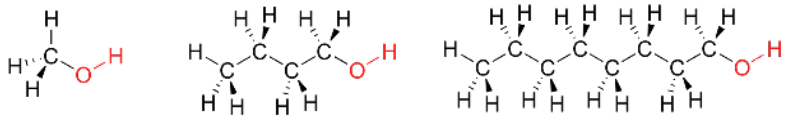
Now, we'll try a compound called biphenyl, which, like sodium chloride, is a colorless crystalline substance.



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

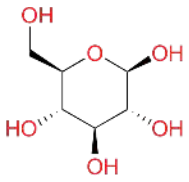
butanol
slightly soluble in water

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.

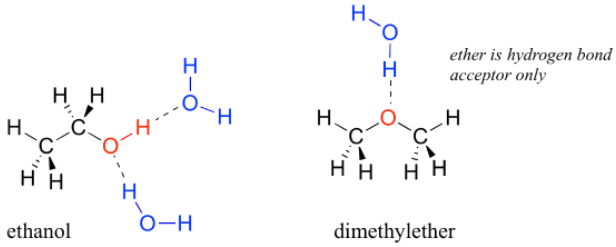
Now, try dissolving glucose in the water – even though it has six carbons just like hexanol, it also has five hydrogen-bonding, hydrophilic hydroxyl groups in addition to a sixth oxygen that is capable of being a hydrogen bond acceptor.



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 dimethyl 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.

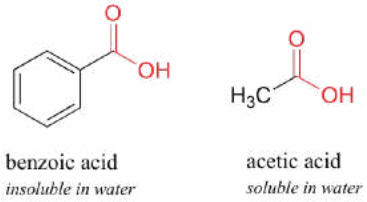


ethanol

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.

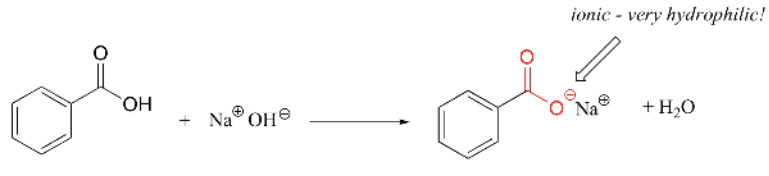


benzoic acid
insoluble in water

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

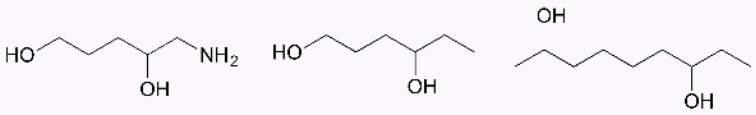
A: How many carbons? All else being equal, more carbons means more of a non-polar/hydrophobic character, and thus lower solubility in water.

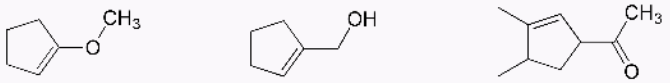
B: How many, and what kind of hydrophilic groups? The more, the greater the water solubility. In order of importance:

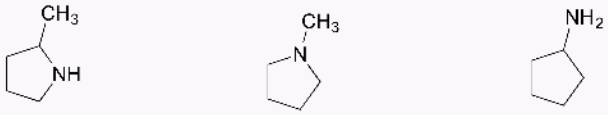
1. Anything with a **charged** group (eg. ammonium, carboxylate, phosphate) is almost certainly water soluble, unless has a vary large nonpolar group, in which case it will most likely be soluble in the form of micelles, like a soap or detergent (see next section).
2. Any functional group that can **donate 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 (e.g., 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):

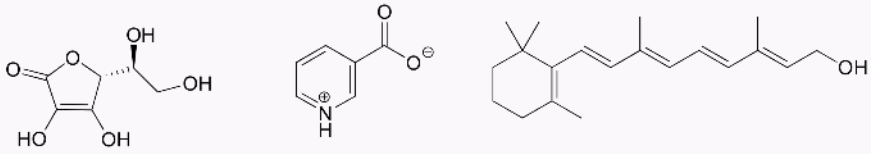
a) 

b) 

c) 

Exercise 2.31

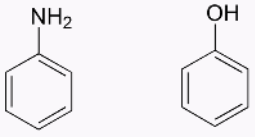
Vitamins can be classified as water-soluble or fat-soluble (consider fat to be a very non-polar 'solvent'). Decide on a classification for each of the vitamins shown below.



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.



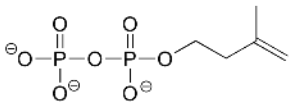
aniline | phenol

Exercise 2.33

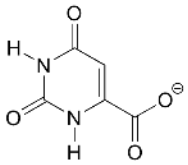
Would you predict methanol or 2-propanol (rubbing alcohol) to be a better solvent for cyclohexanone? Why?

Solutions to exercises

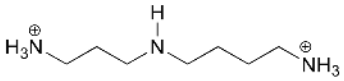
Because water is the biological solvent, most biological organic molecules, in order to maintain water-solubility, contain one or more charged functional groups: most often phosphate, ammonium or carboxylate.



ispentenyl diphosphate
an early precuror to cholesterol



orotate
a precursor to the RNA base uridine

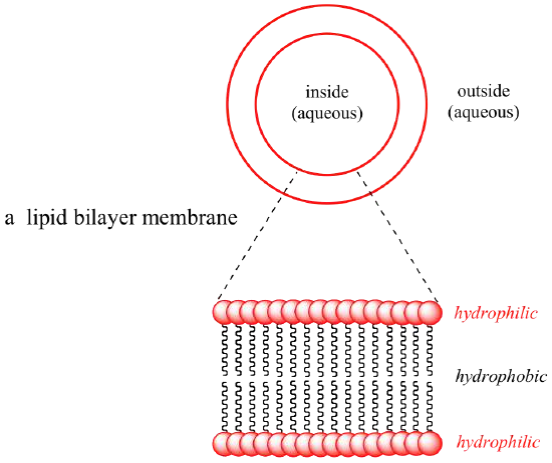


spermidine
binds tightly to DNA in rapidly dividing cells

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 6.

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.

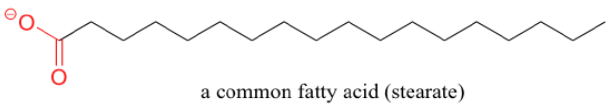
Some biomolecules, in contrast, contain distinctly hydrophobic components. Membrane lipids are **amphipathic**, meaning that they contain both hydrophobic and hydrophilic components. Cell membranes are composed of membrane lipids arranged in a 'bilayer', with the hydrophobic 'tails' pointing inward and 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)

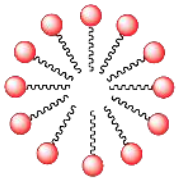
The nonpolar interior of the lipid bilayer is able to 'dissolve' hydrophobic biomolecules such as cholesterol. Polar and charged biomolecules, on the other hand, are not able to cross the membrane, because they are repelled by the hydrophobic environment of the bilayer's interior. The transport of water-soluble 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.

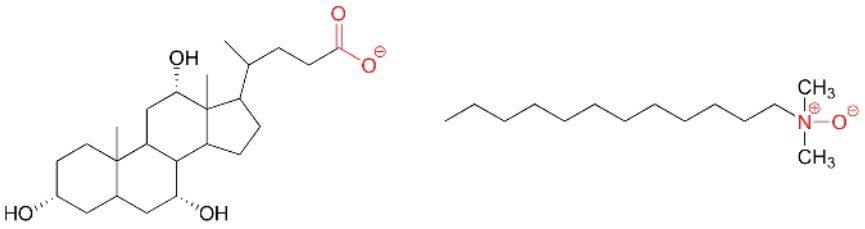


micelle

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.

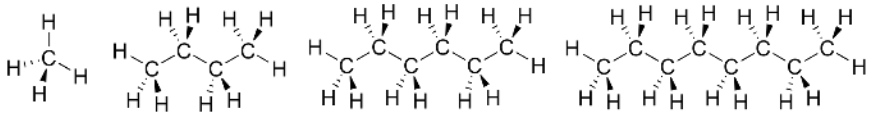


synthetic detergents

Boiling point and melting point

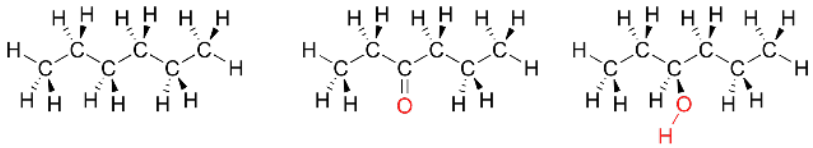
The observable melting and boiling points of different organic molecules provides an additional illustration of the effects of noncovalent interactions. The overarching principle involved is simple: *how well can a compound bind to itself*? Melting and boiling are processes in which noncovalent interactions 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°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.

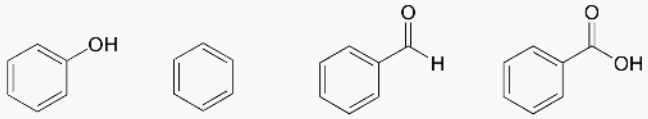


hexane bp = 69°C; 3-hexanone bp = 123 °C; 3-hexanol bp =135°C

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.

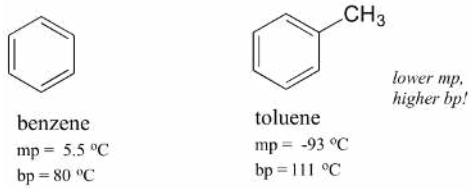


Solutions to exercises

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.

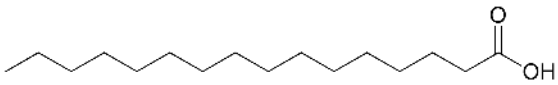
Exercise 2.35

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

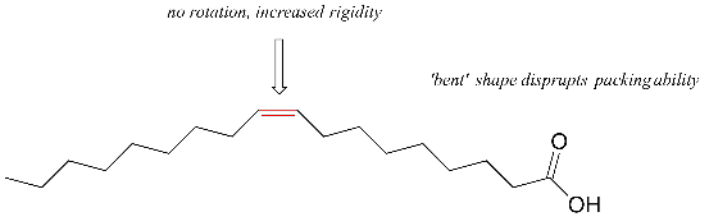
Physical properties of lipids and proteins

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.

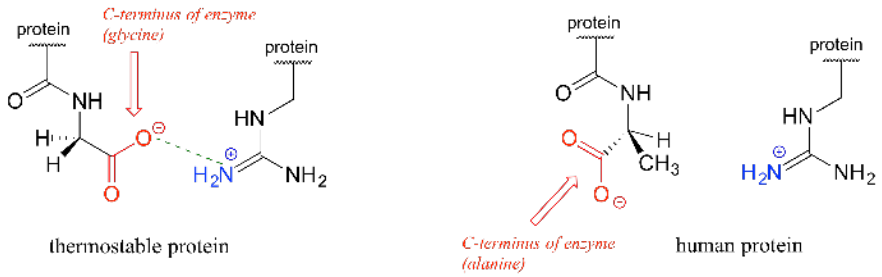
In a related context, the fluidity of a cell membrane (essentially, the melting point) is determined to a large extent by the length and degree of unsaturation of the fatty acid 'tails' on the membrane lipids. Longer and more saturated fatty acids make the membrane less fluid (they are able maximize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

Contributors

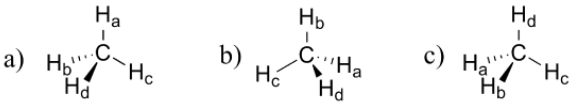
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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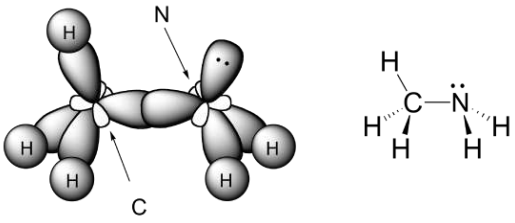
2.7: Solutions to Chapter 2 exercises

E2.1:

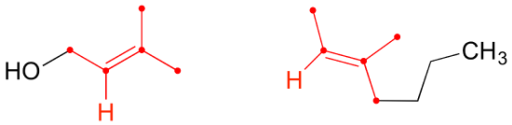


E2.2: sp^3 orbital on carbon overlapping with *3p* orbital on chlorine.

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.

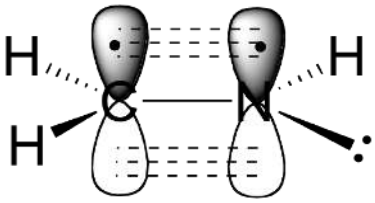


E2.5: The carbon atoms in an aromatic ring are sp^2 hybridized, thus bonding geometry is trigonal planar: in other words, the bonds coming out of the ring are in the same plane as the ring, *not* pointing above the plane of the ring as the wedges in the incorrect drawing indicate. A correct drawing should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



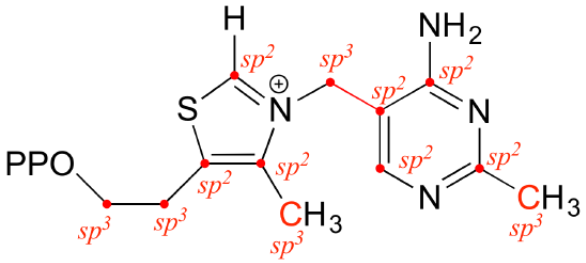
E2.6:

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

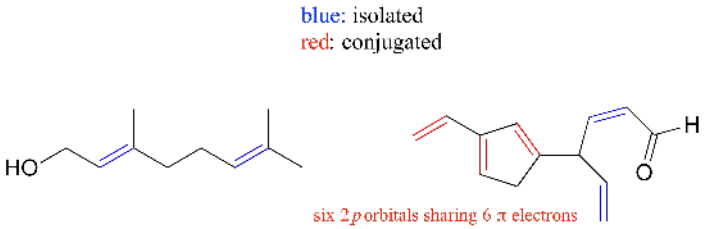
bond i: Csp^2-Csp^2

b)

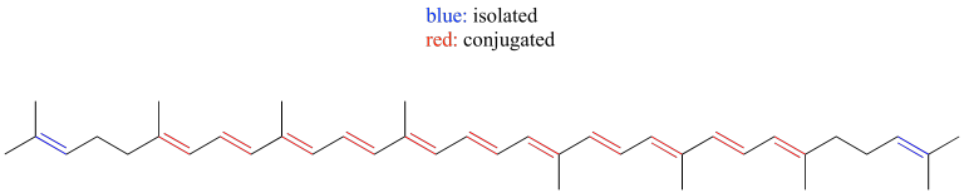
bond a: lone pair on N occupies an sp^2 orbital

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

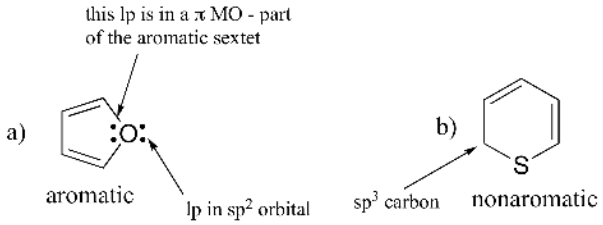


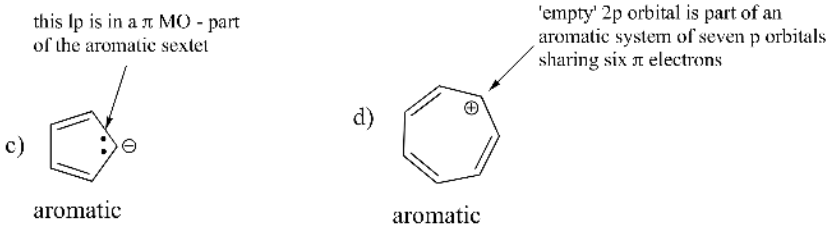
E2.11:

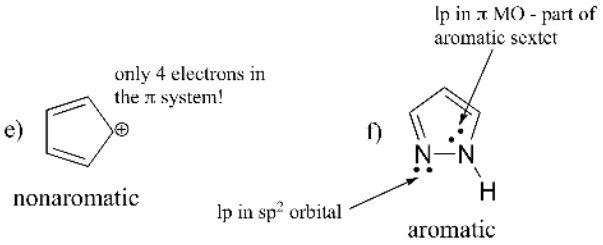
Indole: nitrogen is 'pyrrole-like' (lone pair is part of aromatic ring)

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

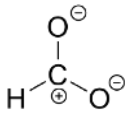
E2.12:



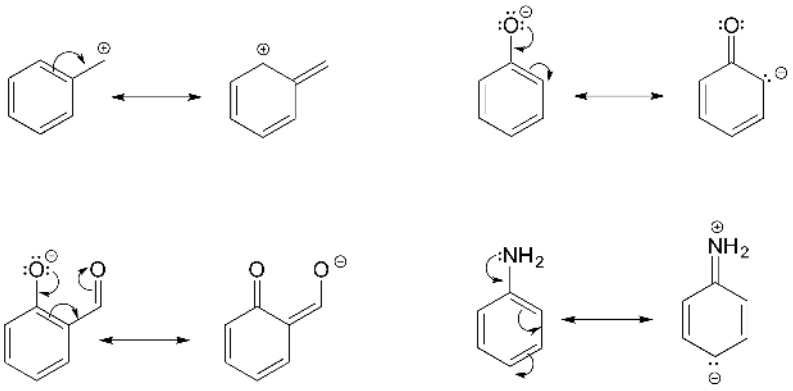




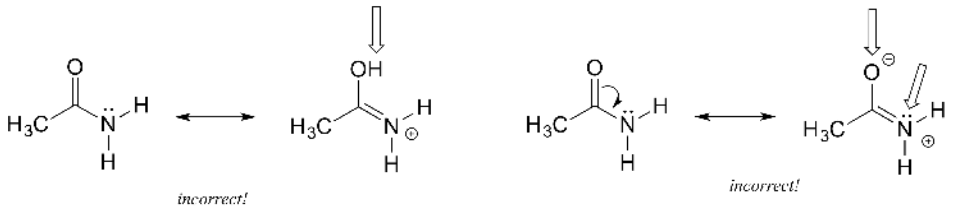
E2.13:



E2.15:

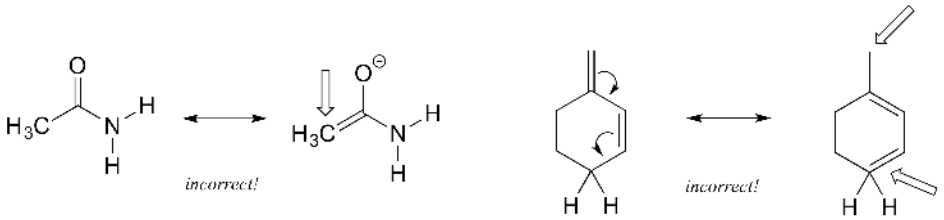


E2.16:



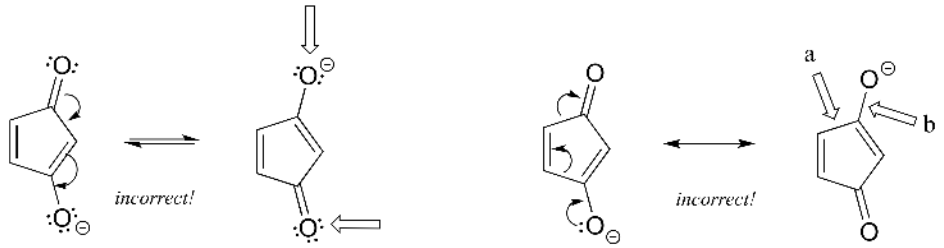
Left: an H atom has been added - in resonance contributors, only pi electrons and lone pairs are rearranged.

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!)

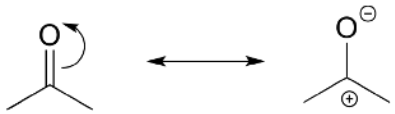


Left: One oxygen should have a positive formal charge, and one breaks the octet rule.

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:

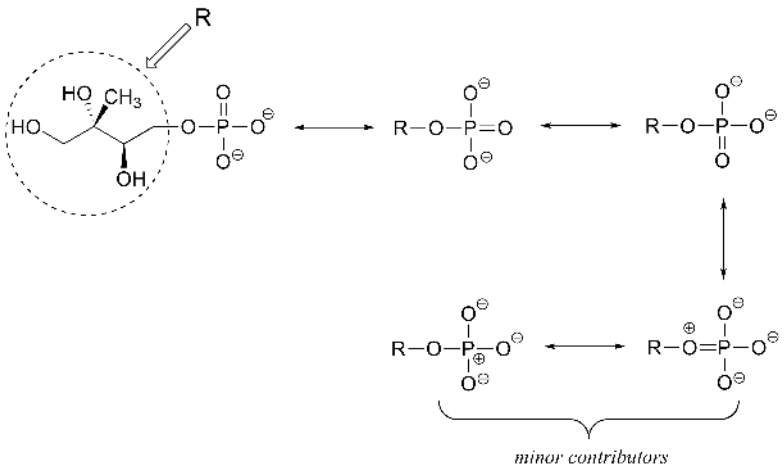
a)



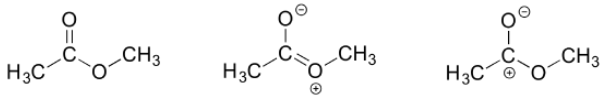
The contributor on the left is minor because it a) has a separation of charges, and b) the carbon has an incomplete octet.

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.

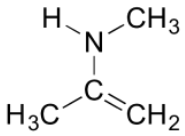
The contributor on the right is least stable: there are formal charges, and a carbon has an incomplete octet.

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.

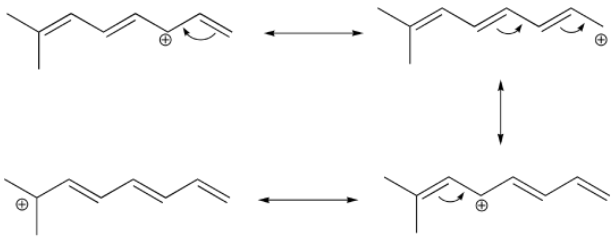
E2.21: Consult your instructor or tutor for an evaluation of your orbital drawings. Both contributors should show three overlapping *p* orbitals sharing four pi electrons.

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



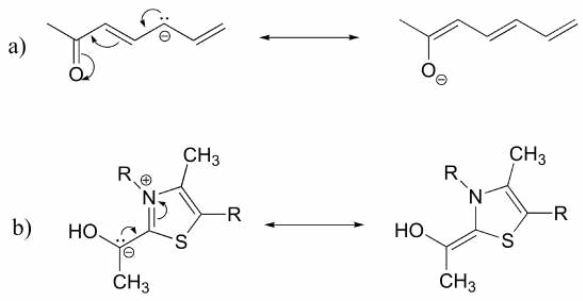
E2.23:

a)



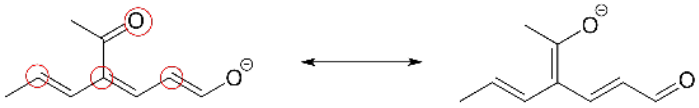
b) The conjugated pi system in this carbocation is composed of **seven** *2p* orbitals containing **six** delocalized pi electrons.

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.

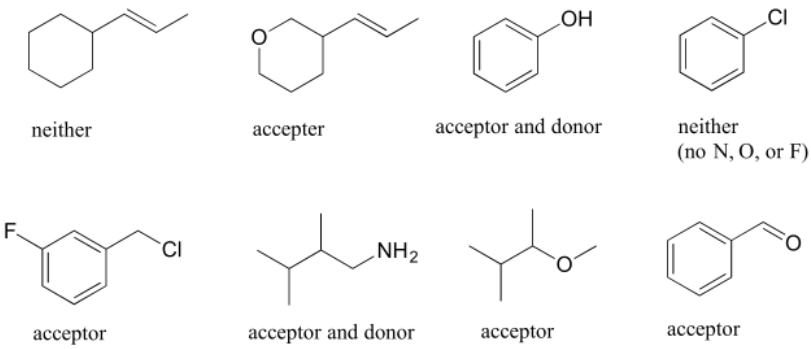


E2.26: The horizontal trend is based on atomic number (the number of protons in the nucleus). For example, fluorine is more electronegative than carbon, because the fluorine nucleus contains three more protons, the positive charges on which pull negatively-charged electrons closer to the nucleus.

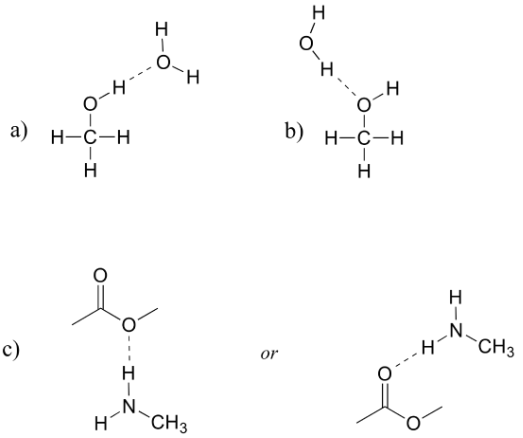
The vertical trend is based on atom size, specifically the size of the 'electron cloud' surrounding the nucleus. For example, fluorine is more electronegative than chlorine (even though chlorine contains more protons) because the outermost valence electrons on fluorine, which are in the n = 2 "shell", 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).

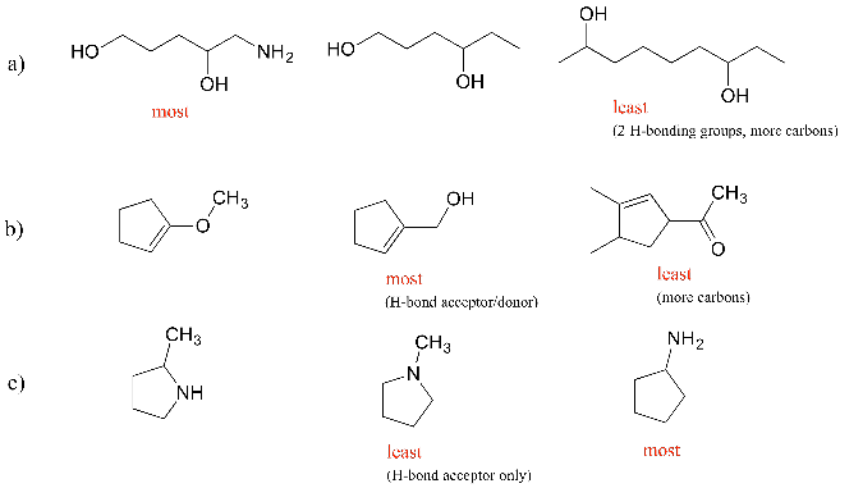
E2.28: To be a hydrogen bond donor, the molecule needs to have a hydrogen bound to N, O, or F. To be an acceptor, it merely needs an N, O, or F.



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.

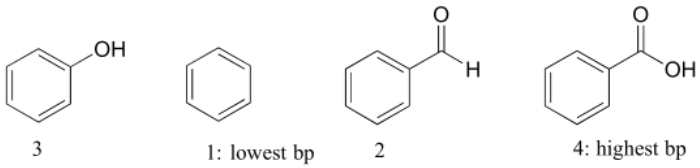


E2.31: Ascorbic acid and niacin are water soluble (lots of hydrophilic groups relative to the number of carbons). Retinol is fat-soluble (only one hydrophilic alcohol group, a large hydrophobic hydrocarbon group.

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

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

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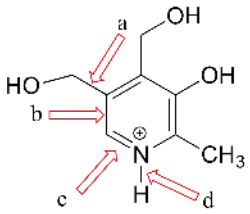
2.8: Problems for Chapter 2

Solutions to selected problems

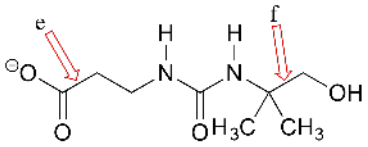
In questions involving drawing resonance contributors, assume that all second-row atoms should have a complete octet in all structures with the exception of positively-charged carbons.

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)

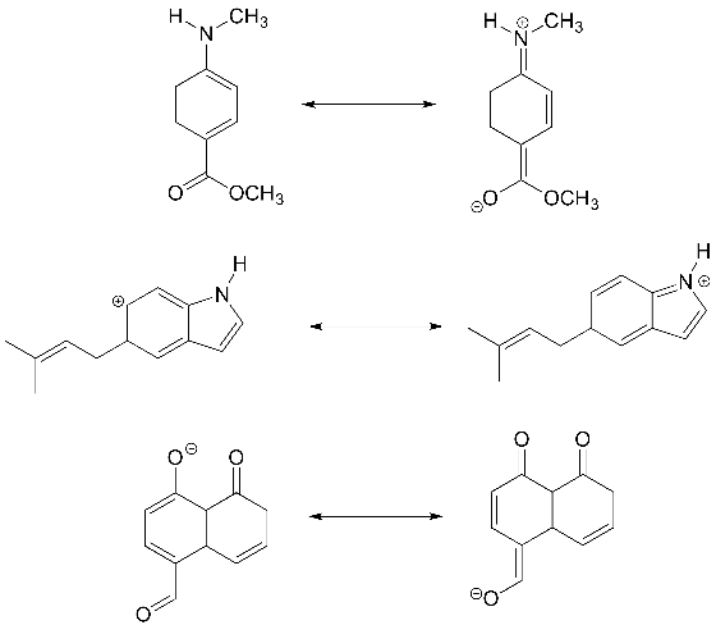


pantothenate
(vitamin B_5)

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.

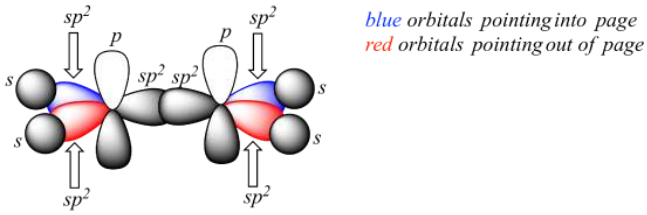
a) dimethyl ether (CH_3OCH_3)

b) ethanol (CH_3CH_2OH)

c) acetaldehyde (CH_3COH)

d) hydrogen cyanide (HCN)

An example is provided for ethene, CH_2CH_2:

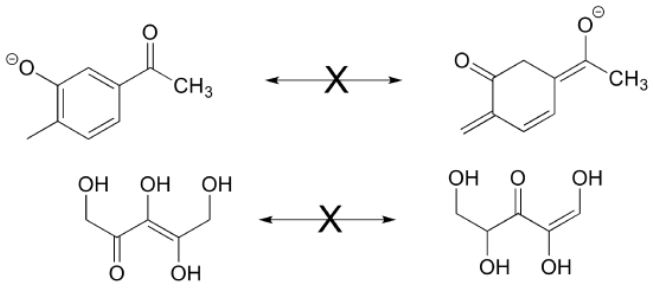


orbital overlap in ethene

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

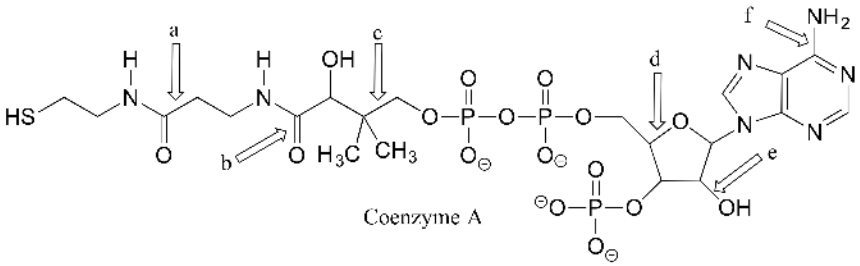
a) Explain why not.

b) What in fact is the relationship between them?

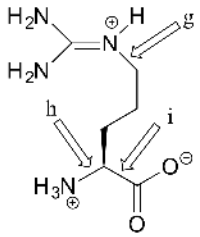


P2.5:

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



Coenzyme A



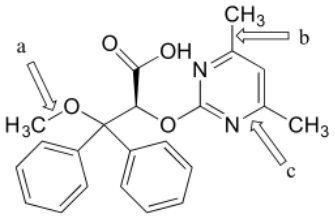
arginine

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

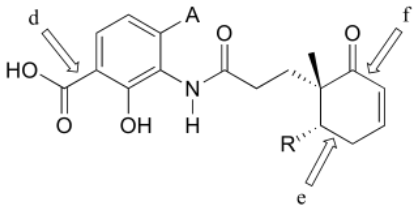
a-k) For each bond indicated by an arrow, specify the types of orbitals that are overlapping (for example, overlap between two *sp3*-hybridized carbons would be denoted C_{sp3}-C_{sp3})

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?)

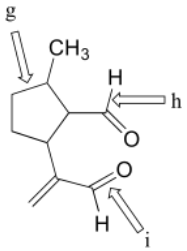
m) Give the molecular formula for the walking-stick compound



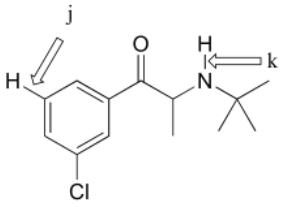
a hypertension drug



a newly-discovered antibiotic compound

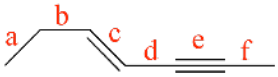


a defensive chemical extracted from a walking stick insect

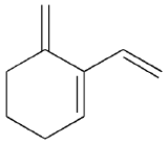


a drug for smoking cessation

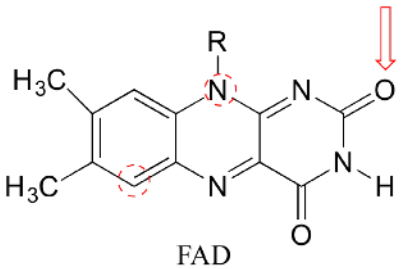
P2.7: Rank the bonds a-f below according to increasing bond length.



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

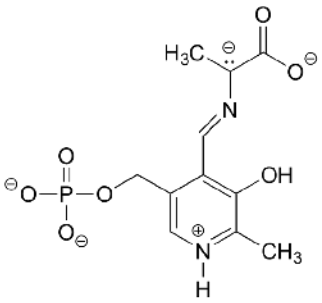


P2.9: Draw two different (minor) resonance contributors of the structure below (the flavin group of flavin adenine dinucleotide (FAD), a biochemical oxidation/reduction molecule) in which the oxygen indicated by an arrow bears a negative formal charge and one of the circled atoms bears a positive formal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



FAD

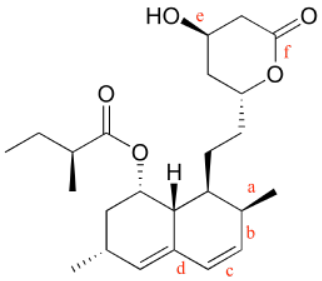
P2.10: The structure below shows an intermediate species in a reaction involving the amino acid alanine, attached to pyridoxal phosphate (vitamin B6). Draw a resonance contributor in which the only formal charges are on the oxygens.



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



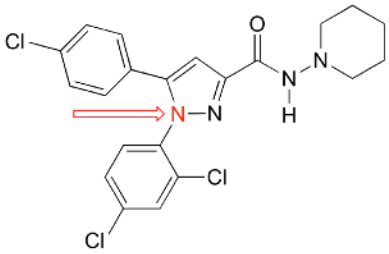
Lovastatin

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?

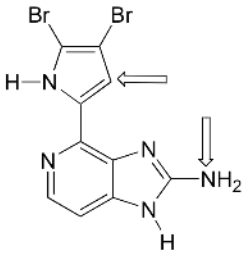
P2.13: Below is the structure of Rimonabant, a drug candidate which is being tested as a possible treatment for alcohol/tobacco dependence and obesity (see *Chemical and Engineering News*, October 15, 2006, p. 24). Draw minor resonance contributors in which

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

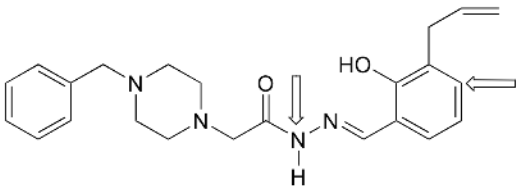
b) there is a separation of charge between a chlorine (positive) and one of the three nitrogens.



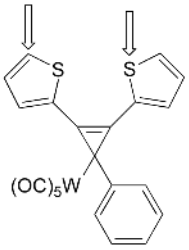
P2.14: For the molecules below, draw minor resonance contributors in which formal charges are placed on the atoms indicated by arrows. Use curved arrows to show how you are rearranging electrons between resonance contributors.



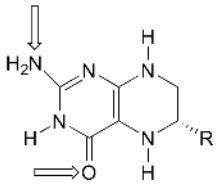
ageladine A, a potential cancer drug
Org. Lett. 2006, 8, 1443



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

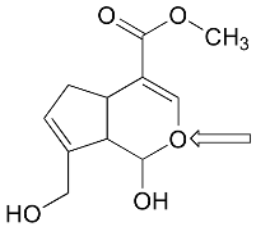


a new building block molecule for optoelectronic materials
Organometallics 2006, 25, 5176



tetrahydrofolate, a coenzyme

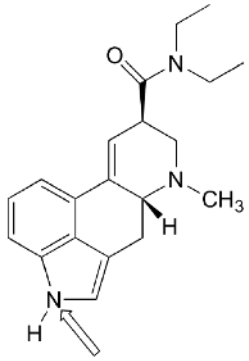
P2.15: Genipin was recently identified as the active compound in gardenia fruit extract, a traditional Chinese medicine for the treatment of diabetes (*Chemical and Engineering News* June 12, 2006, p. 34; *Cell Metab*. 2006, *3*, 417). Resonance contributors can be drawn in which the oxygen atom indicated 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

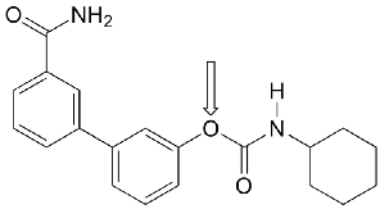
P2.16: Identify any *isolated* alkene groups in the PAC-1 structure in problem P2.14, and in the genipin structure in problem P2.15.

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.



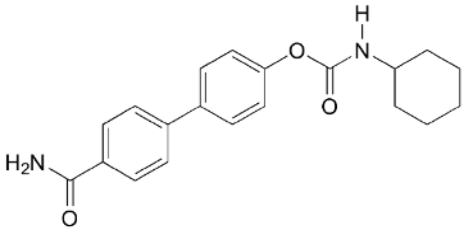
D-lysergic acid diethylamine (LSD)

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.)



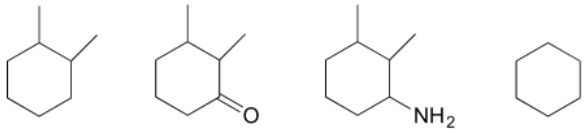
a) Several resonance contributors can be drawn in which the oxygen atom indicated by an arrow bears a positive formal charge. Indicate atoms where a corresponding negative formal charge could be located in these contributors.

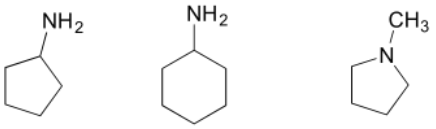
b) Answer the same question again, this time with the structural isomer shown below.

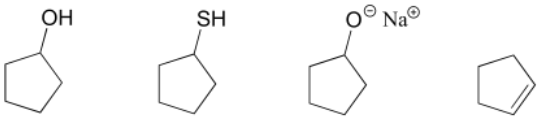


P2.19: Give the expected trend (lowest to highest) in boiling points for the following series of compounds.

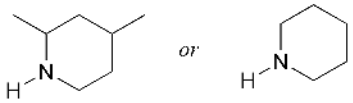
a) CH_3CHF_2 CH_2F_2 HF CH_3F

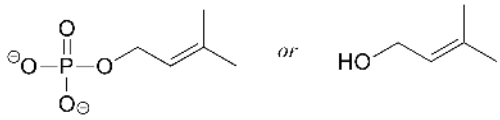
b) 

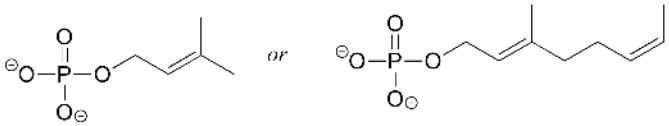
c) 

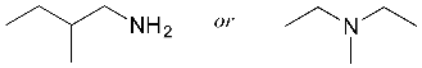
d) 

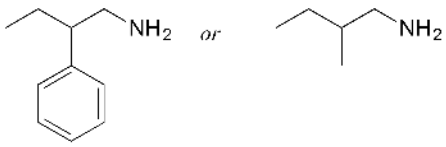
P2.20: For each pair of molecules below, choose the one that is more water-soluble, and explain your choice.

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.

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.

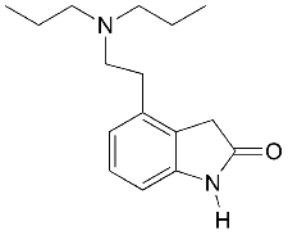
P2.24: Imagine that you hear a description of the bonding in water as being derived directly from the atomic orbital theory, without use of the hybrid orbital concept. In other words, the two bonds would be formed by the overlap of the half-filled $2p_y$ and $2p_z$ orbitals of oxygen with the 1s orbitals 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.

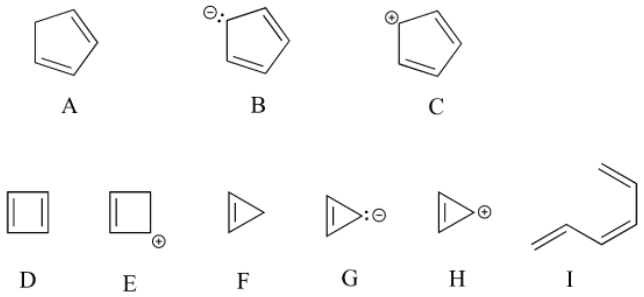
b) Draw a picture showing the geometry of the overlapping orbitals that form the bonding network in carbon dioxide.

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.

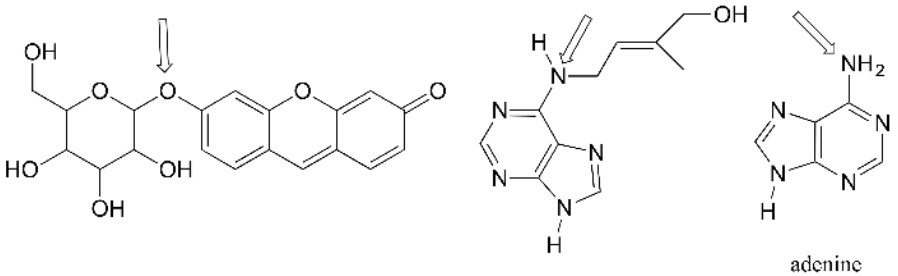


roprinol

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



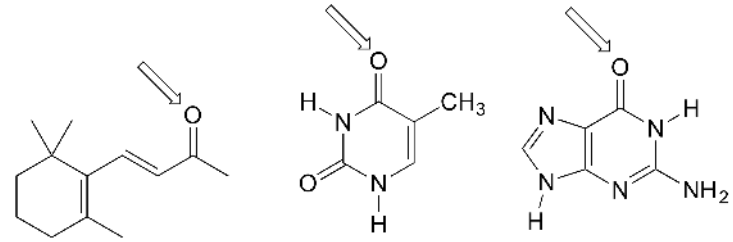
P2.28: For each of the compounds below, several minor resonance contributors can be drawn in which the atom indicated by an arrow bears a positive formal charge. Circle all atoms which could bear the corresponding negative formal charge.



zeatin, a plant ripening hormone

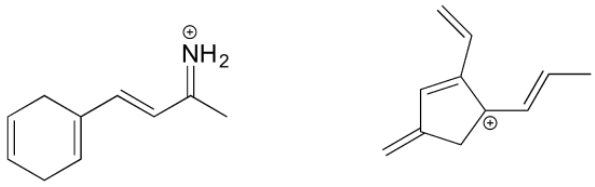
adenine

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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2.8.1: 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.

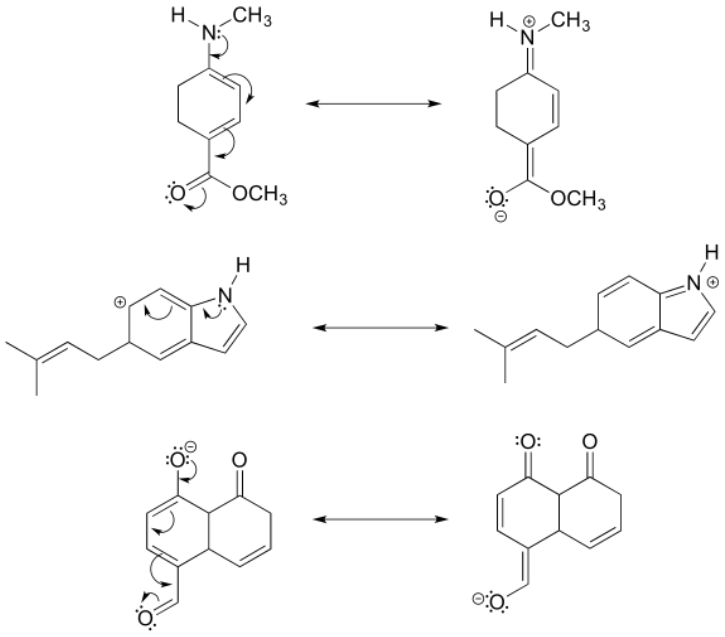
bond d is a sigma bond formed by the overlap of an sp^2 orbital on a nitrogen and a 1s orbital on a hydrogen.

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)

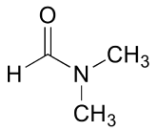
bond d (single bond between two sp^2 hybridized carbons)

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

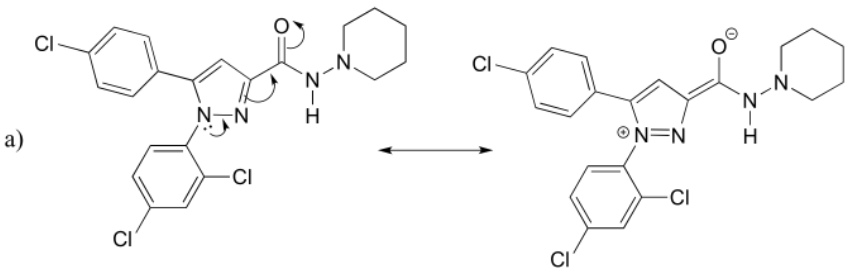
bond a (single bond between two sp^3 hybridized carbons)

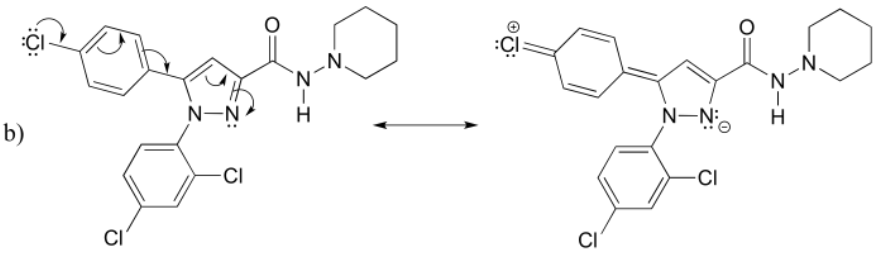
longest

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.

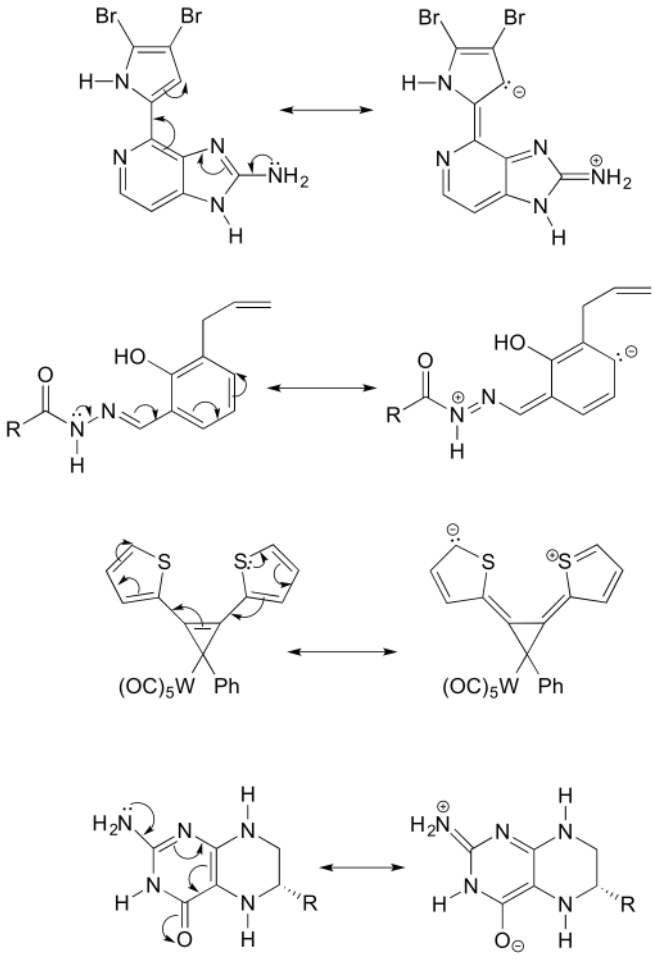


P2.13:

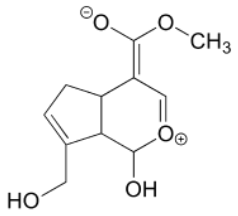

a)
Cl
O
N
H
Cl
Cl
Cl
O
N
N
H
Cl
Cl


b)
Cl
O
N
N
H
Cl
Cl
Cl
O
N
N
H
Cl
Cl

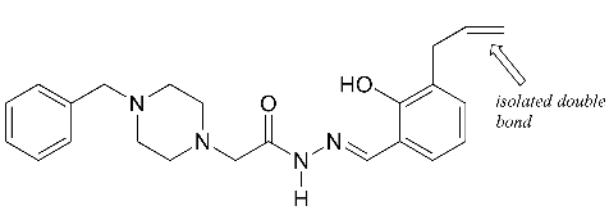
P2.14:


Br
Br
H
N
N
NH2
N
H
Br
Br
H
N
N
NH2
N
H
HO
O
R
N
N
H
HO
O
R
N
N
H
S
S
(OC)5W
Ph
S
S
(OC)5W
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N
H
N
R
O
H

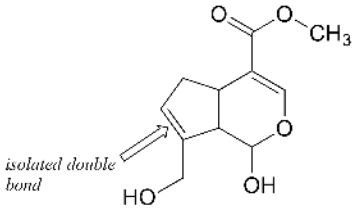
P2.15:



P2.16:

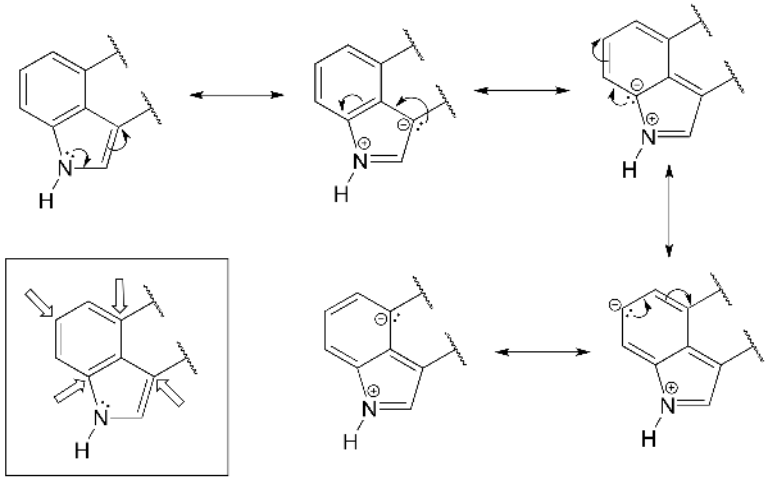


PAC-1

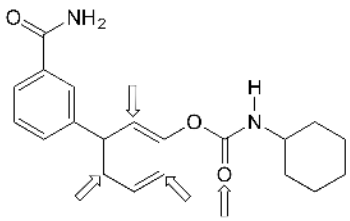


genipin

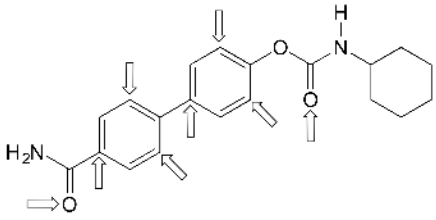
P2.17:



P2.18:



a)



b)

P2.19:

a)

1:CH_3F

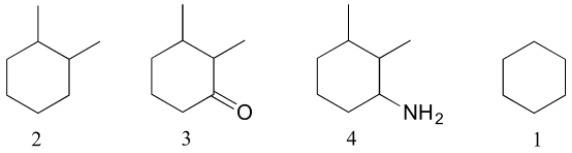
2: CH_2F_2

3: CH_3CHF_2

4: HF

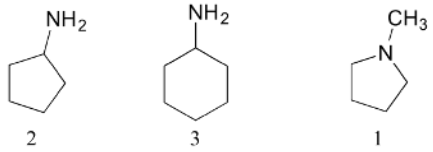
2 and 3 have two fluorines and are more polar than 1, so they have stronger intermolecular dipole-dipole interactions. 3 has one more carbon than 2, and therefore stronger van der Waals interactions. 4 is capable of hydrogen bonding, so it has the strongest intermolecular interactions and the highest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

b)



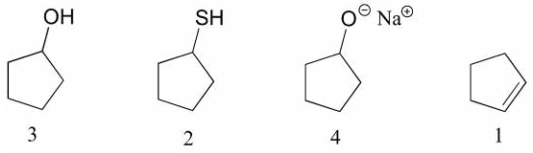
1 and 2 have only van der Waals interactions, but 2 has more carbons so these interactions are slightly stronger. 3 has a polar carbonyl group, and 4 is capable of hydrogen bonding.

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)

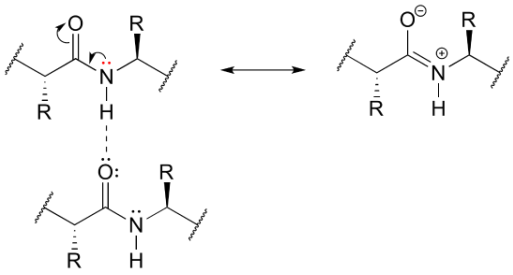
b) The compound on the left is more soluble (ionic phosphate group)

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)

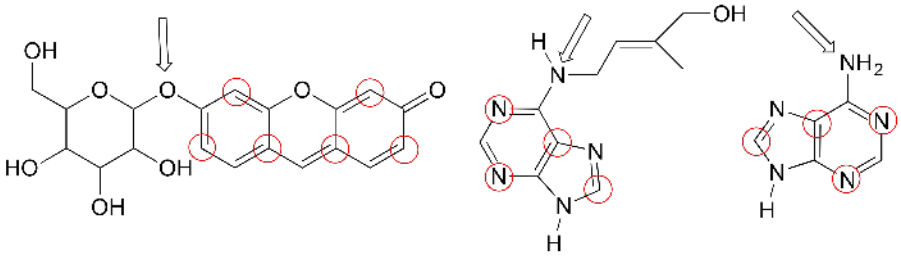
F is *not* aromatic (sp^3 hybridized carbon in the ring)

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.

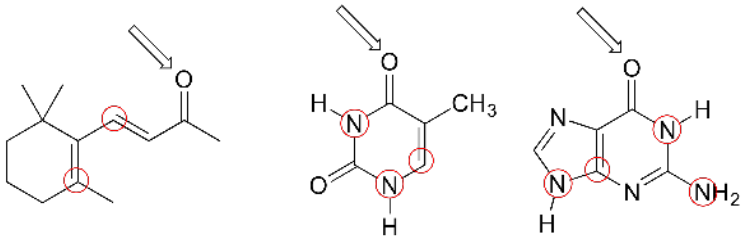
H is aromatic (carbocation is sp^2 hybridized, the 2*p* orbital is empty, so there are two pi electrons in the system, and 2 is a Huckel number)

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

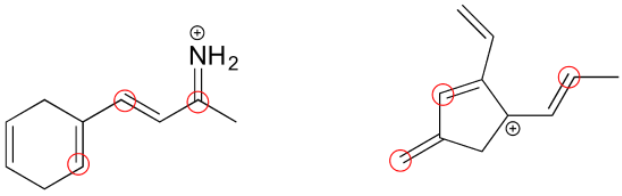
P2.28:



P2.29:



P2.30:



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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.

3.1: Prelude to Conformations and Stereochemistry
3.2: Conformations of open-chain organic molecules
3.3: Conformations of cyclic organic molecules
3.4: Chirality and stereoisomers
3.5: Naming chiral centers- the R and S system
3.6: Optical Activity
3.7: Compounds with multiple chiral centers
3.8: Meso Compounds
3.9: Fischer and Haworth projections
3.10: Stereochemistry of alkenes
3.11: Stereochemistry in biology and medicine
3.12: Prochirality
3.13: Solutions to Chapter 3 exercises
3.14: Problems for Chapter 3

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3.1: 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-Baptiste 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 so 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.

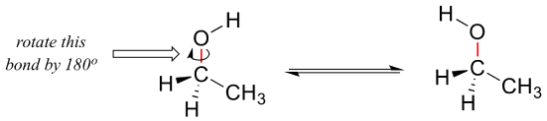
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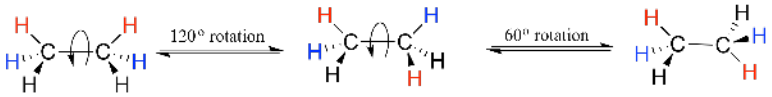
3.2: Conformations of open-chain organic molecules

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° rotation about this bond, the shape of the molecule would look quite different:

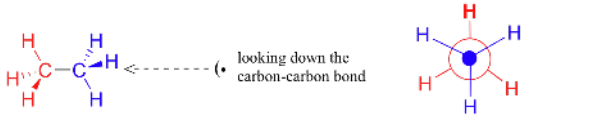


Or ethane: rotation about the carbon-carbon sigma bond results in many different possible three-dimensional arrangements of the atoms.



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)

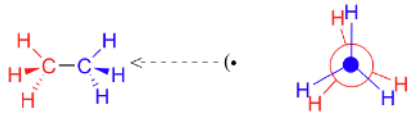
Interactive mode of ethane conformationsl

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° at noon, 90° 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°, 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° (we stagger the bonds slightly in our Newman projection drawing so that we can see them all).

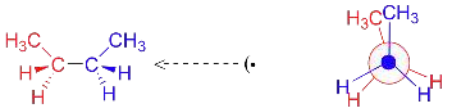


'eclipsed' conformation

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° 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

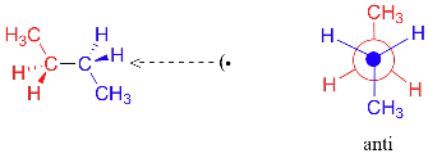
This is more specifically referred to as the **gauche** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be.

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)

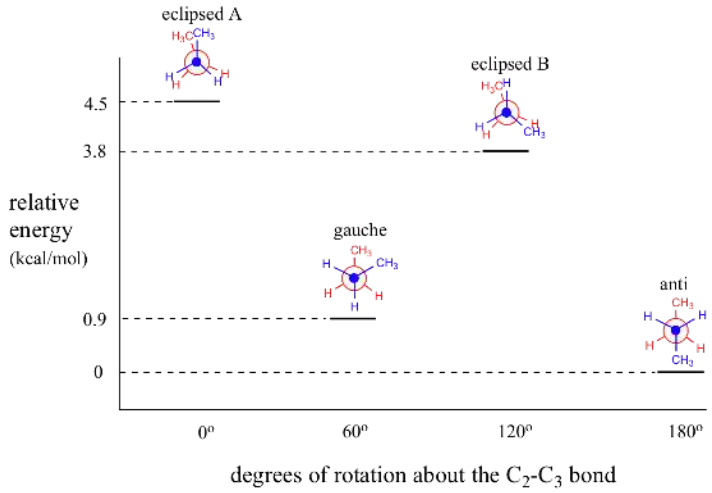
One more 60 rotation produces another staggered conformation called the **anti** conformation, where the two methyl groups are positioned opposite each other (a dihedral angle of 180°).



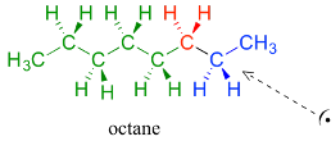
anti

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.



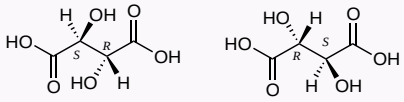
Because the anti conformation is lowest in energy (and also simply for ease of drawing), it is conventional to draw open-chain alkanes in a 'zigzag' form, which implies anti conformation at all carbon-carbon bonds. The figure below shows, as an example, a Newman projection looking down the C_2-C_3 bond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





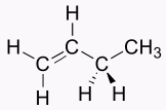
Exercise 3.1

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

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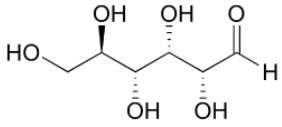
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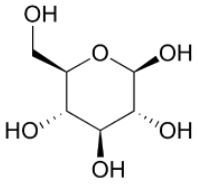
3.3: Conformations of cyclic organic molecules

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.

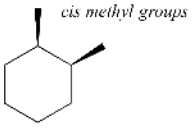


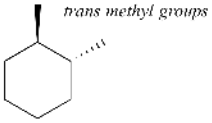
open-chain glucose

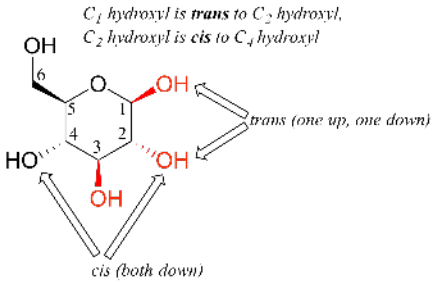


cyclic glucose (β-glucopyranose)

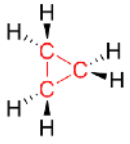
One thing that you should notice in the cyclic structure shown above is that atoms or groups bonded to tetrahedral ring carbons are either pointing up (out of the plane of the page) or down (into the plane of the page), as indicated by the use of dashed or solid wedge bonds. When two substituents on 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.



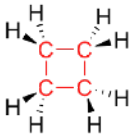




Ring structures in organic molecules are usually five-membered or six-membered. Three-and four-membered rings are occasionally found in nature, but are significantly higher in energy. The relative instability of these smaller ring structures can be explained by a concept called **angle strain**, in which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

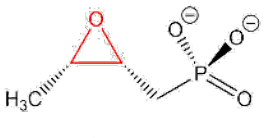


cyclopropane

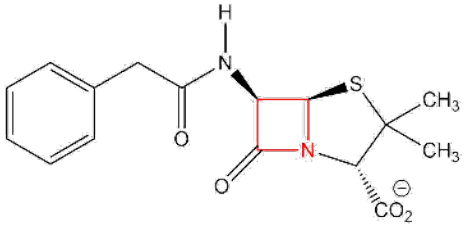


cyclobutane

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.

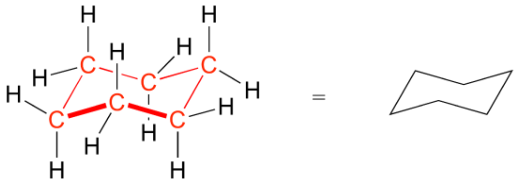


fosfomycin



penicillin G

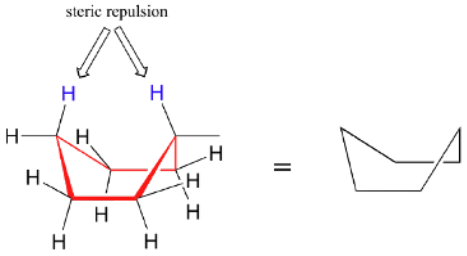
In six-membered cycloalkane structures, bonding angles are close to tetrahedral, and thus ring strain is not a factor – these rings are in fact very stable. However, the 'flat' drawings we have been using up to now do not accurately show the actual three-dimensional shape of a five- or six-membered ring. 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.

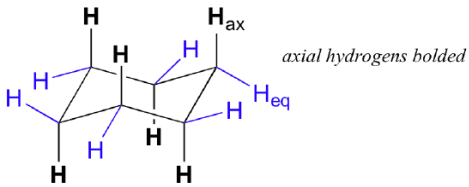
An alternate conformation for a six-membered ring is called the **'boat'**:



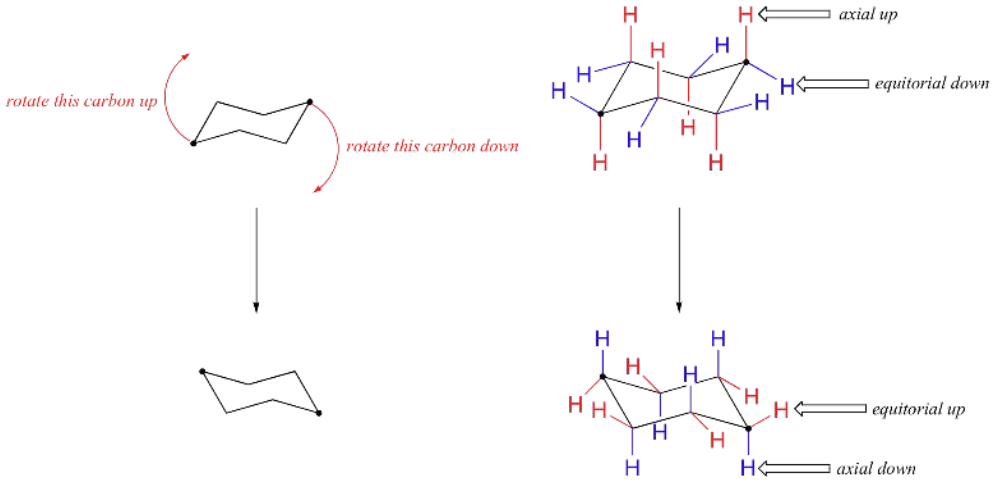
Interactive model of cyclohexane conformations

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).*



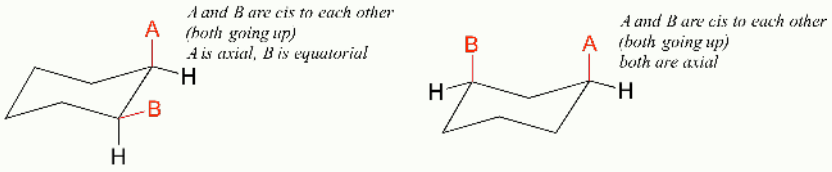
This is not the only possible chair conformation for cyclohexane. On your model, rotate one of the 'up' carbons down, and one of the 'down' carbons up. You now have a new, alternate chair conformation – this process is called **ring inversion**.



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*

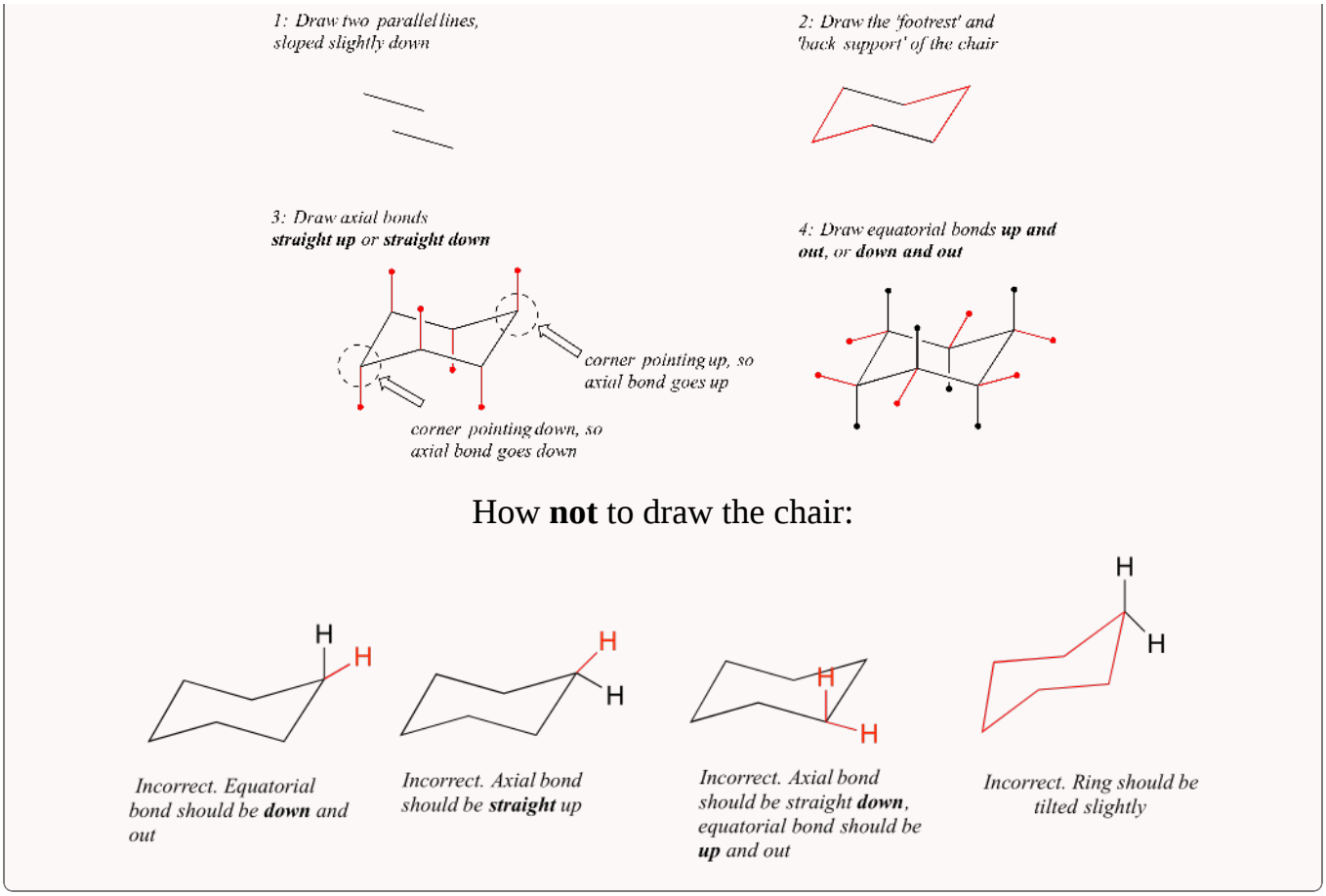
A very common error made by organic chemistry students as they begin to learn about chair conformations is to confuse the terms axial and equatorial with the terms *cis* and *trans*. **These are completely different things!** For example, when two substituents on a ring are *cis* in relation to one another, 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.



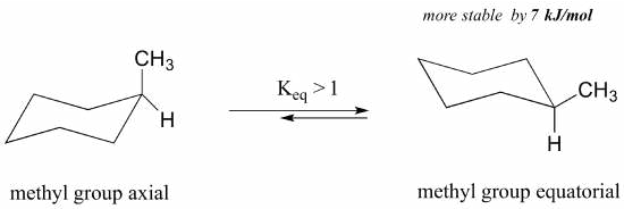
Do not make the mistake of calling two substituents *trans* to each other merely because one is equatorial and one is axial, or *cis* because the are both axial or both equatorial.

How to draw the cyclohexane chair conformation

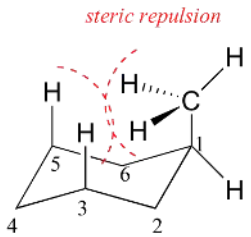
As an organic chemistry student, you will be expected to be able to draw an accurate representation of the chair conformations of six-membered cycloalkanes, which includes being able to draw axial and equatorial substituents with their correct orientations. Here, then, are some guidelines to follow:



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.



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**.



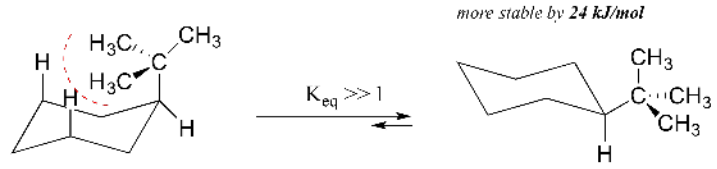
When in the equatorial position, the methyl group is pointing up and *away* from the rest of the ring, eliminating the unfavorable 1,3-diaxial interaction. As a consequence, the conformation in which the methyl group is in the equatorial position is more stable, by approximately 7 kJ/mol. At room temperature, 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?

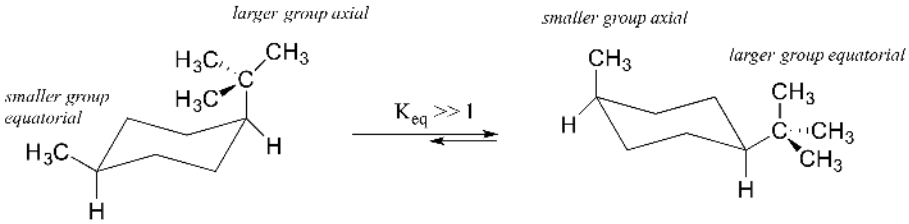
Solutions to exercises

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

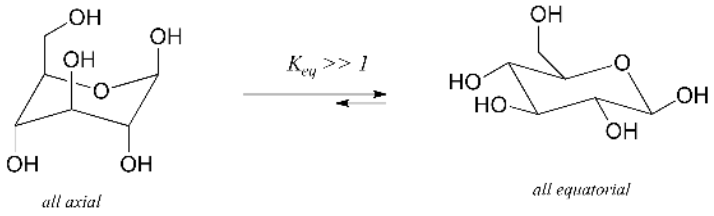
c) *trans*-1,2-dimethylcyclohexane or *trans*-1-isopropyl-2-methylcyclohexane

Exercise 3.6

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

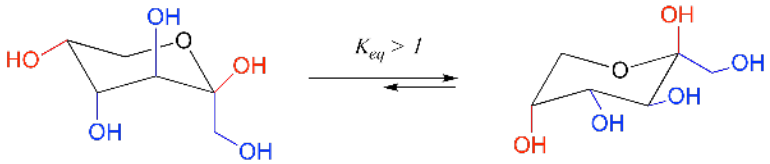
Solutions to exercises

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.

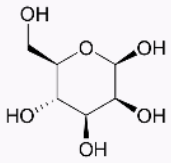


fructose
(β-fructopyranose form)

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

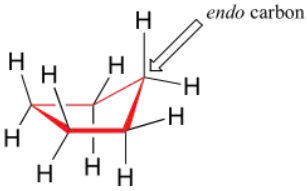
Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.



mannose

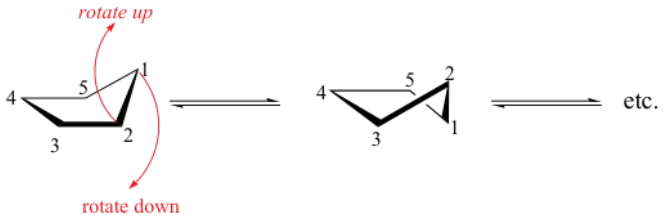
Solutions to exercises

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').

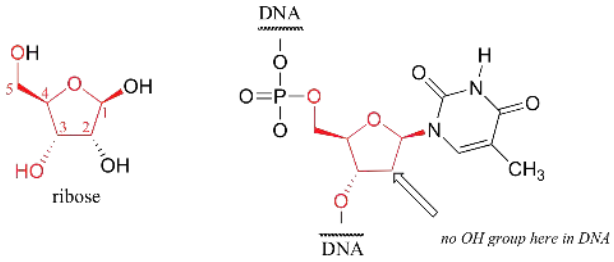


The 'equatorial' vs 'axial' distinction discussed in the context of 6-membered rings does not apply to five-membered rings.

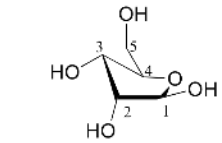
At room temperature, cyclopentane undergoes a rapid **pseudorotation** process in which each of the five carbons takes turns being in the *endo* position.



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

Contributors

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

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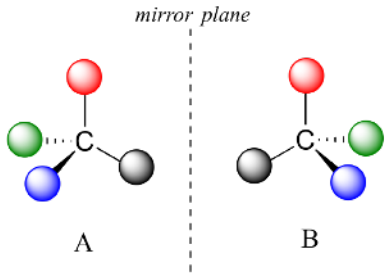
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3.4: Chirality and stereoisomers

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.

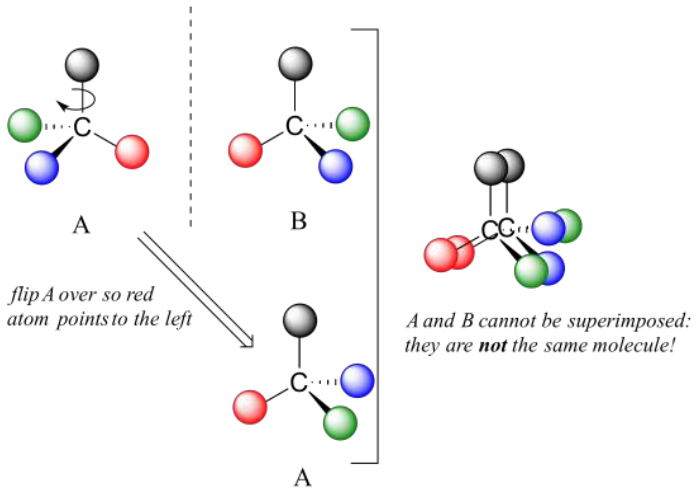
What Pasteur, Biot, and their contemporaries did not yet fully understand when Pasteur made his discovery of molecular chirality was the *source* of chirality at the molecular level. It stood to reason that a chiral molecule is one that does not contain a plane of symmetry, and thus cannot be superimposed 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.

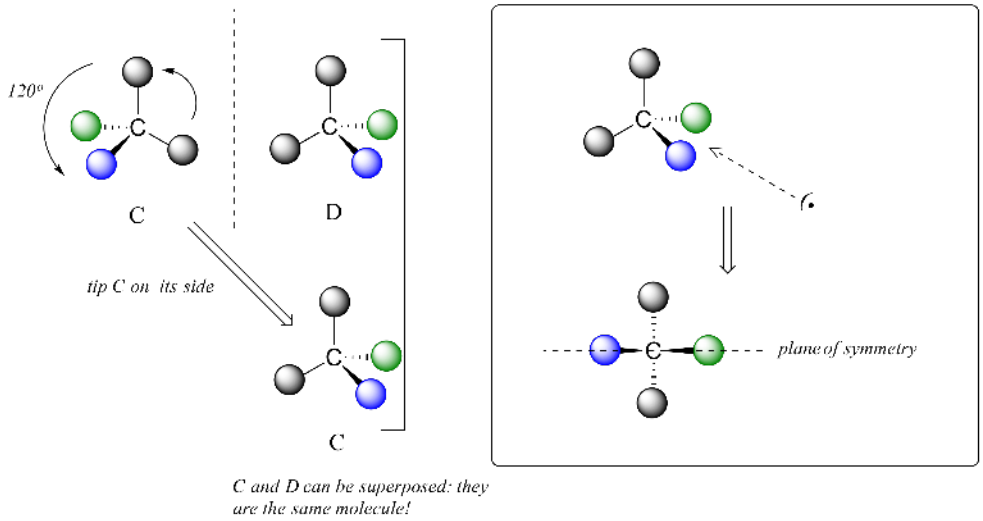


A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule. Also notice in the figure below (and convince yourself with models) that neither A nor B has an internal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

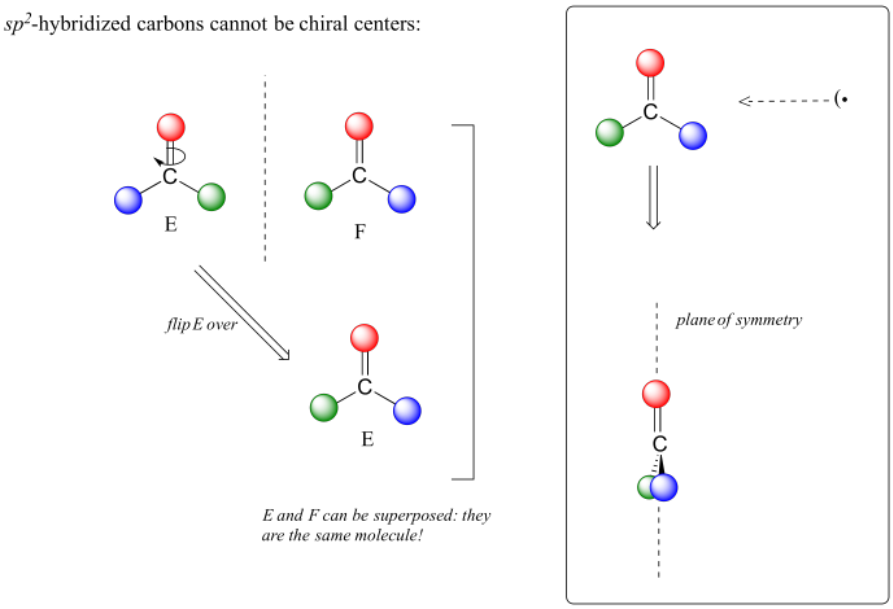
A and B are **stereoisomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. There are two types of stereoisomers: enantiomers and diastereomers. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: 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.



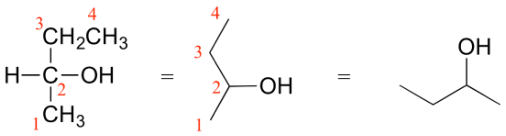
This molecule is **achiral** (lacking chirality). Using the same reasoning, we can see that a trigonal planar (sp^2-hybridized) carbon is also not a chiral center.



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.

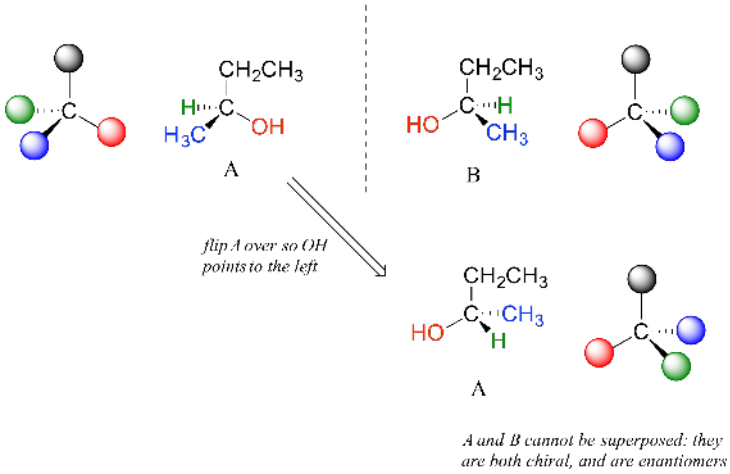
Let's apply our general discussion to real molecules. For now, we will limit our discussion to molecules with a single chiral center. It turns out that tartaric acid, the subject of our chapter introduction, has *two* chiral centers, so we will come back to it later.

Consider 2-butanol, drawn in two dimensions below.



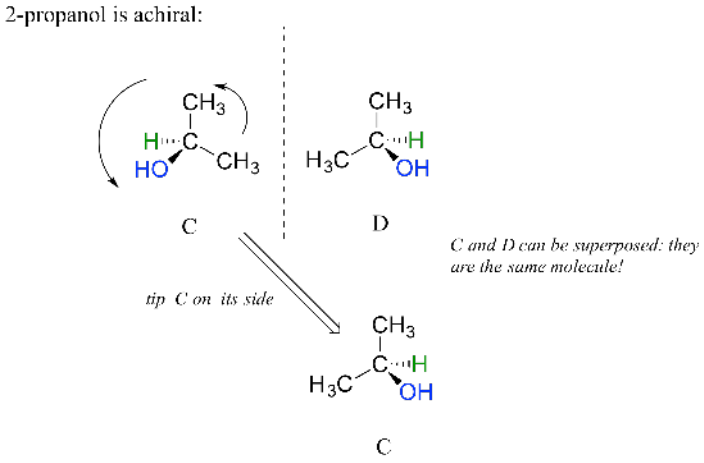
2-butanol
(drawn in 2D)

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 it 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.

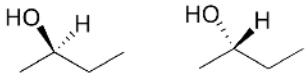
2-propanol, unlike 2-butanol, is *not* a chiral molecule. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral center.



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

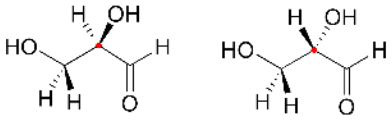
When we look at very simple molecules like 2-butanol, it is not difficult to draw out the mirror image and recognize that it is not superimposable. However, with larger, more complex molecules, this can be a daunting challenge in terms of drawing and three-dimensional visualization. The easy way to determine 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.

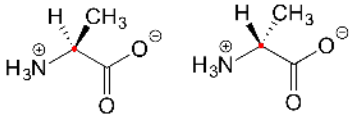


two enantiomers of 2-butanol

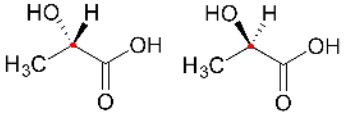
Here are four more examples of chiral biomolecules, each one shown as a pair of enantiomers, with chiral centers marked by red dots.



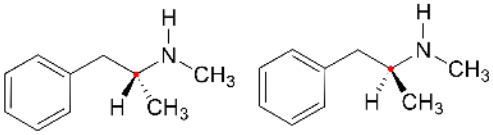
glyceraldehyde



alanine

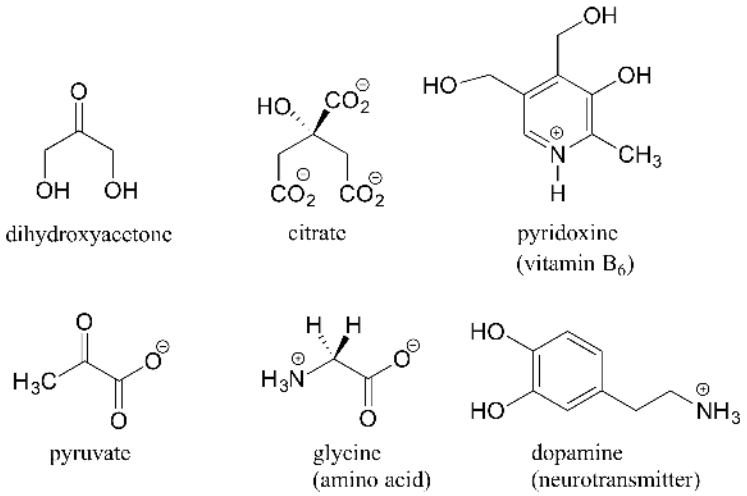


lactic acid



methamphetamine

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

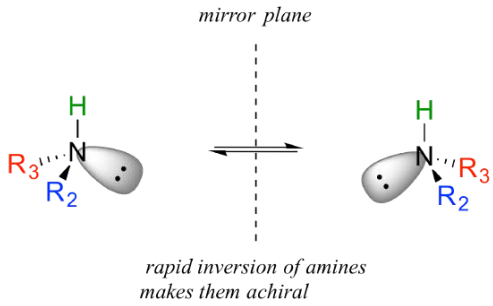


When looking for chiral centers, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). 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?

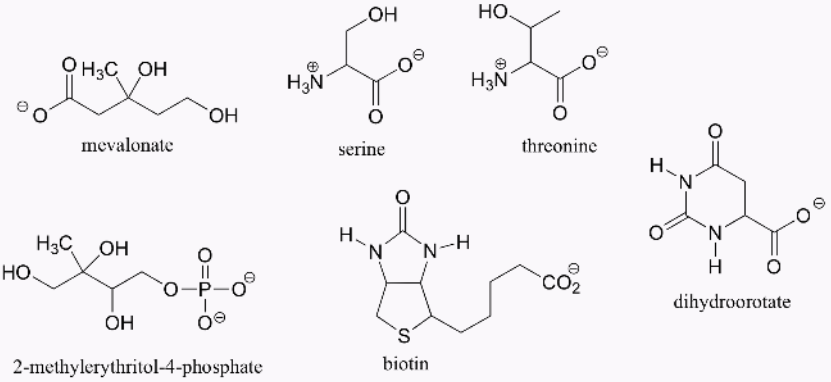
The answer: yes it is, in the static picture, but in reality, the nitrogen of an amine is rapidly and reversibly inverting, or turning inside out, at room temperature.



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

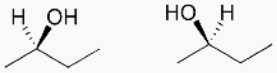
Locate all of the chiral centers (there may be more than one in a molecule). Remember, hydrogen atoms bonded to carbon usually are not drawn in the line structure convention - but they are still there!



Exercise 3.9

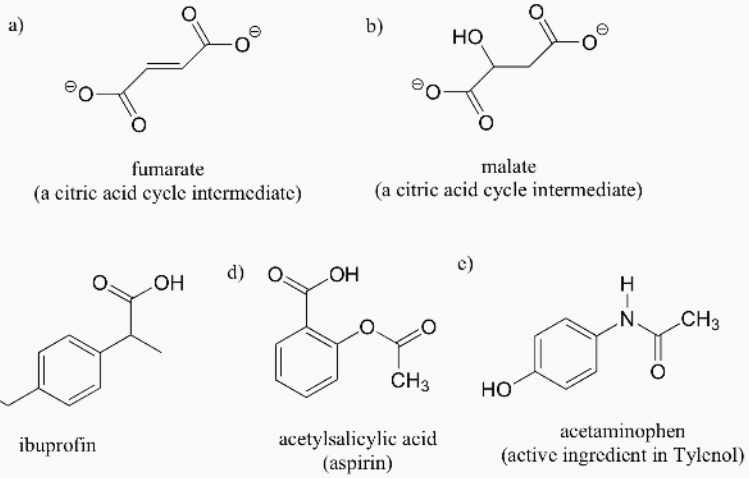
a) Draw two enantiomers of i) mevalonate and ii) serine.

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

Contributors

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

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3.5: 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.

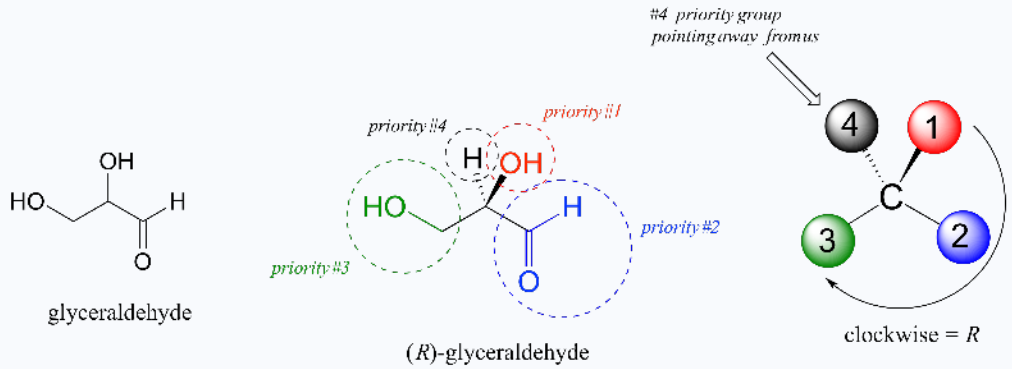
3: Determine the orientation of the #4 priority group. If it is oriented into the plane of the page (away from you), go to step 4a. If it is oriented out of the plane of the page (toward you) go to step 4b.

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).

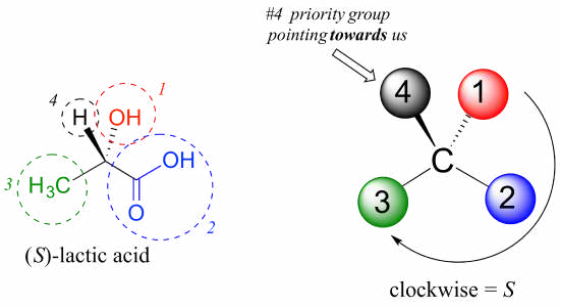
Assigning R/S configuration to glyceraldehyde



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.

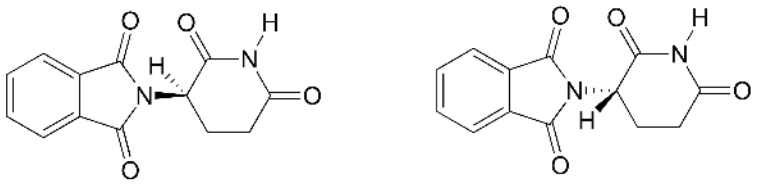
With our priorities assigned, we look next at the #4 priority group (the hydrogen) and see that it is pointed back away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The 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.



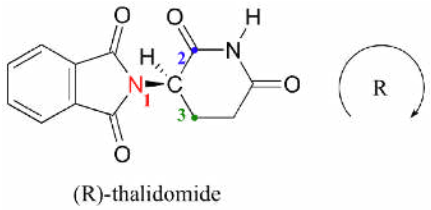
Interactive model of (S)-alanine

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.

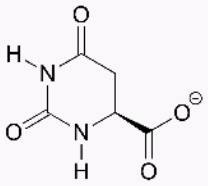
Although scientists are still unsure today how thalidomide works, experimental evidence suggests that it was actually the *R* enantiomer that had the desired medical effects, while the *S* enantiomer caused the birth defects. Even with this knowledge, however, pure (*R*)-thalidomide is not safe, because 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.

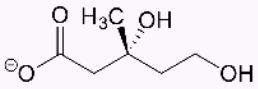
Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

Exercise 3.11

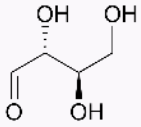
Determine the stereochemical configurations of the chiral centers in the biomolecules shown below.



dihydroorotate



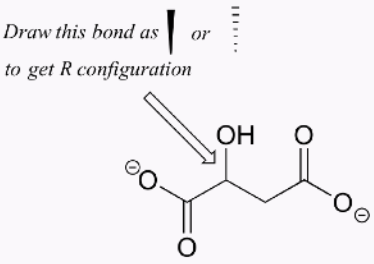
mevalonate



(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

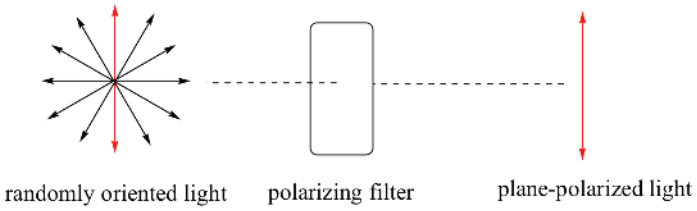
Contributors

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

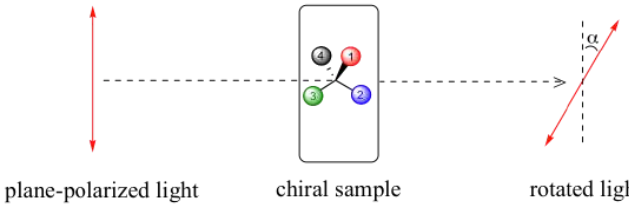
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3.6: Optical Activity

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**.



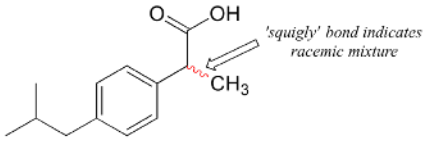
If a compound rotates plane polarized light in the clockwise (+) direction, it is said to be **dextrorotatory**, while if it rotates light in the counterclockwise (-) direction it is **levorotatory**. The magnitude of the observed optical activity is dependent on temperature, the wavelength of light 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:

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

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

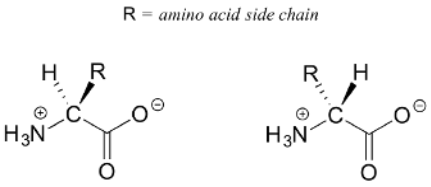
The specific rotation of (*R*)-limonene is +11.5º in ethanol. What is the expected observed rotation of a sample of 6.00 g (*S*)-limonene dissolved in ethanol to a total volume of 80.0 mL in a 1.00 dm (10.0 cm) pathlength cuvette?

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

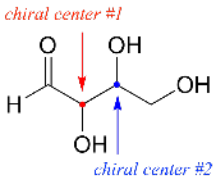
Khan Academy video tutorial on optical acitivity

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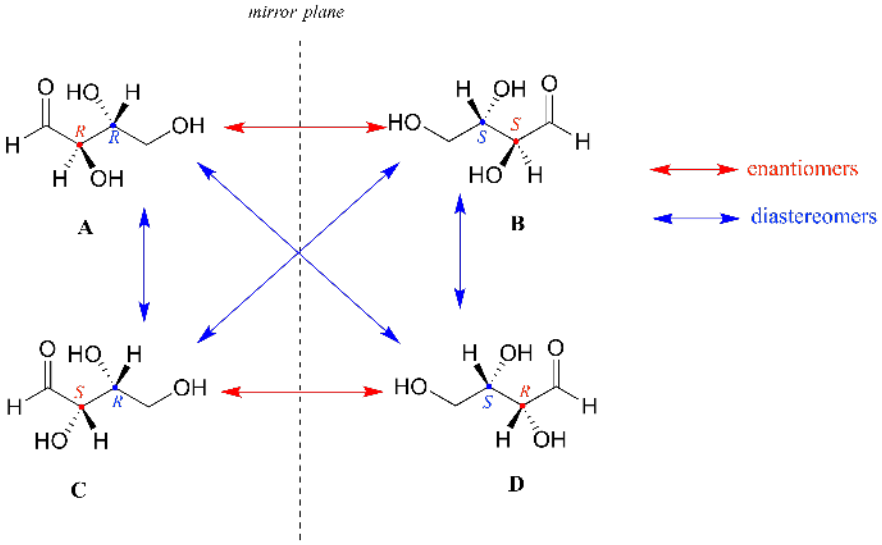
3.7: Compounds with multiple chiral centers

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:

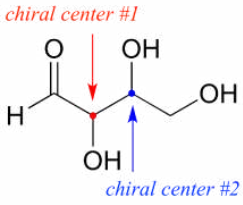
Stereoisomer shortcuts

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 do 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.

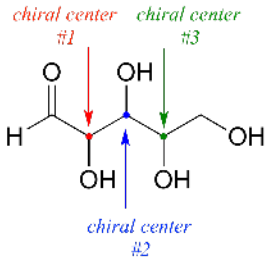


possible configurations:

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.

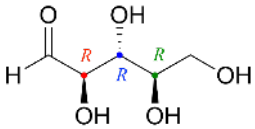
Now, let's extend our analysis to a sugar molecule with three chiral centers. Going through all the possible combinations, we come up with eight total stereoisomers - four pairs of enantiomers.



possible configurations:

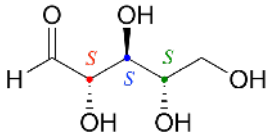
RRR RRS RSR RSS
SSS SSR SRS SRR

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

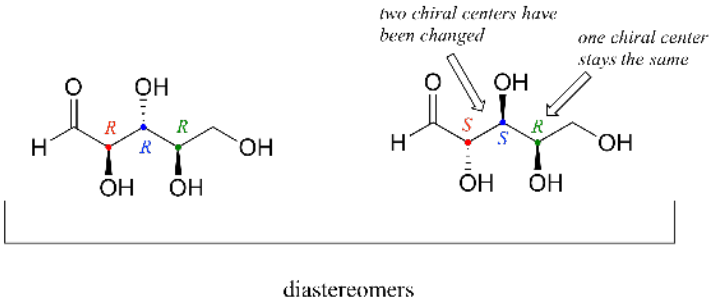
Now, using the above drawing as our model, drawing any other stereoisomer is easy. If we want to draw the enantiomer of *RRR*, we don't need to try to visualize the mirror image, we just start with the *RRR* structure and invert the configuration at *every* chiral center to get *SSS*.



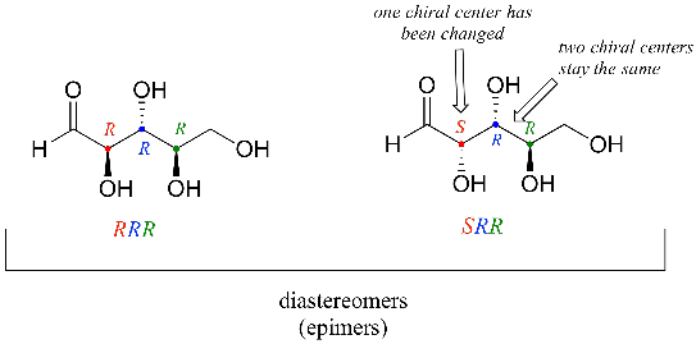
SSS stereoisomer

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*.

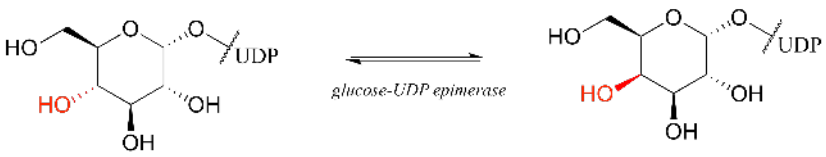
c) List all of the stereoisomers that are diastereomers, but not epimers, of *SRS*.

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

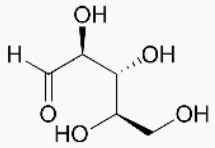


glucose-UDP galactose-UDP

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.



?

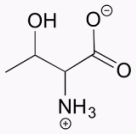
The only problem is, it is drawn with the carbon backbone in a different orientation from what we have seen. Determine the configuration at each chiral center to determine which stereoisomer it is.

Exercise 3.19

Draw the enantiomer of the xylulose-5-phosphate structure in the previous figure.

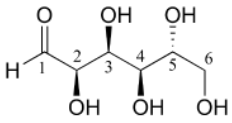
Exercise 3.20

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

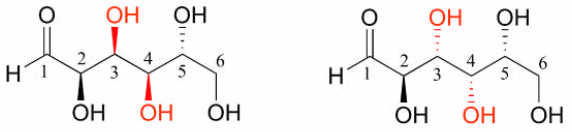
Here is some more practice in identifying isomeric relationships. D-glucose is the monosaccharide that serves as the entrance point for the glycolysis pathway and as a building block for the carbohydrate biopolymers starch and cellulose. The 'D' in D-glucose stands for *dextrarotatory* and is part of 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.

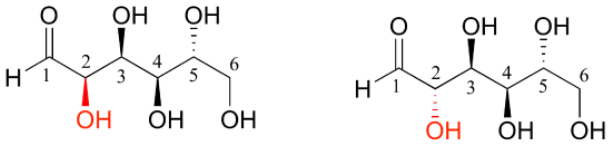


D-glucose D-gulose

(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.

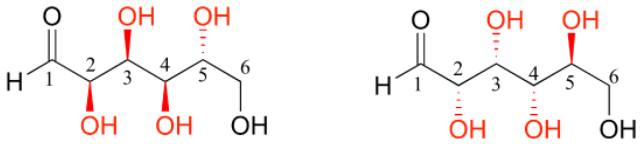


D-glucose D-mannose

(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.

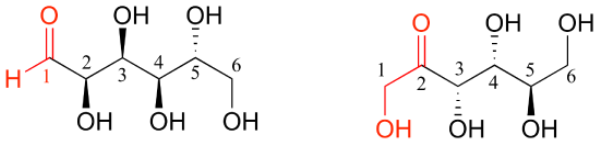


D-glucose L-glucose

(enantiomers)

D-glucose is the enantiomer commonly found in nature.

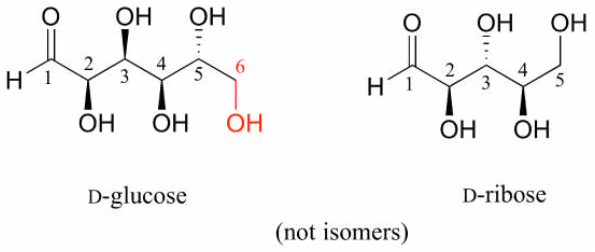
D-glucose and D-fructose are not stereoisomers, because they have different bonding connectivity: glucose has an aldehyde group, while fructose has a ketone. The two sugars do, however, have the same molecular formula, so by definition they are constitutional isomers.



D-glucose D-fructose

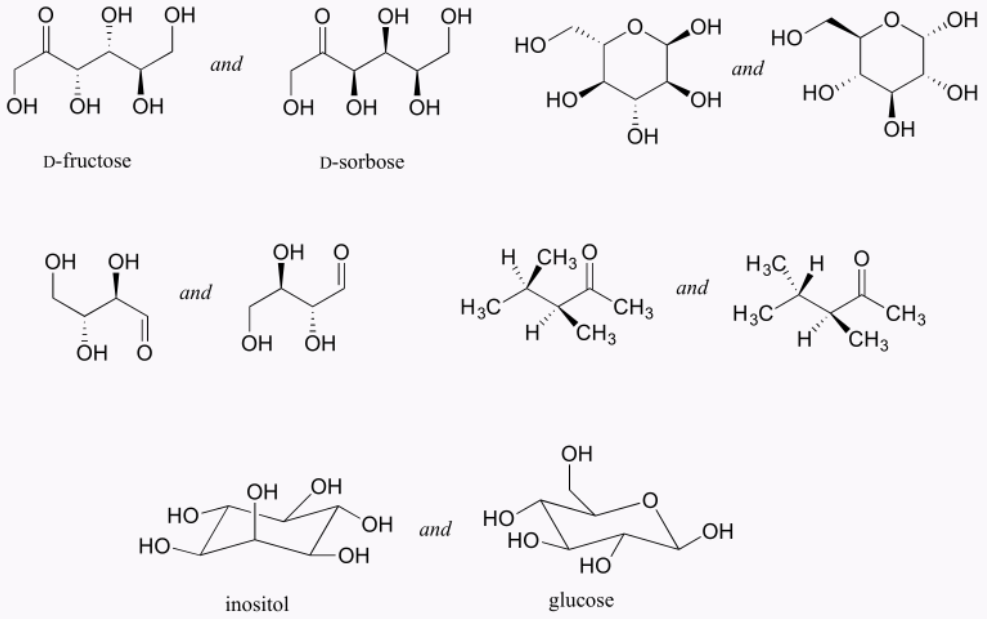
(constitutional isomers)

D-glucose and D-ribose are not isomers of any kind, because they have different molecular formulas.



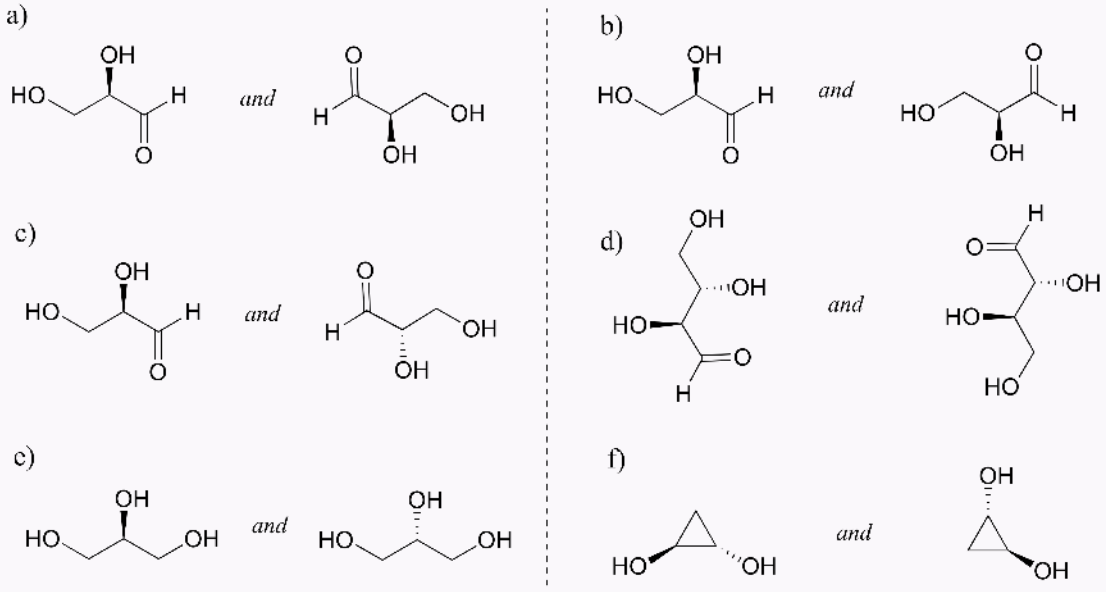
Exercise 3.21

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.



Khan Academy video tutorial on stereoisomeric relationships

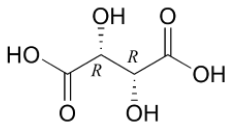
Contributors

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

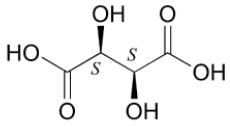
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3.8: Meso Compounds

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:



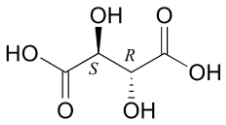
(*R*,*R*)-(+)-tartaric acid
('natural' isomer from grapes)



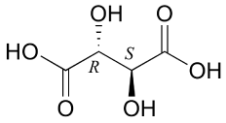
(*S*,*S*)-(-)-tartaric acid

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?



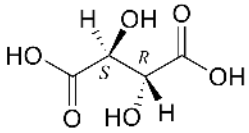
(*S*,*R*)-tartaric acid



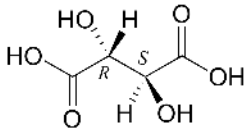
(*R*,*S*)-tartaric acid

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.

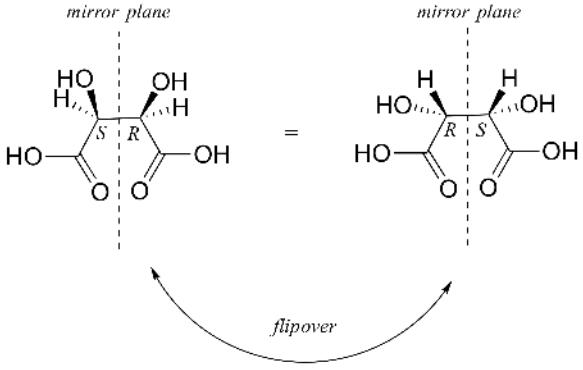
(*S*,*R*)-tartaric acid



(*R*,*S*)-tartaric acid



rotate right side down

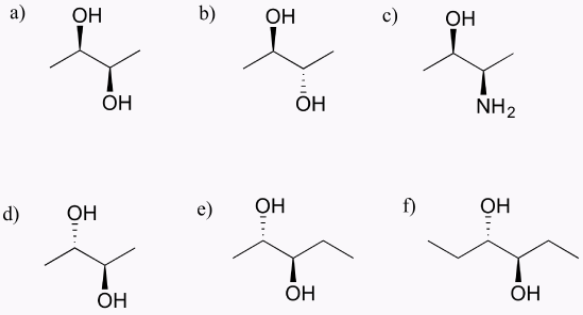


This tartaric acid isomer is an *achiral* diastereomer of the both the levorotatory and dextrorotatory isomers. It is a special case, called a ***meso*** compound: it has two apparent chiral centers but due to its internal symmetry it is not in fact chiral, and does not exhibit optical activity. Note 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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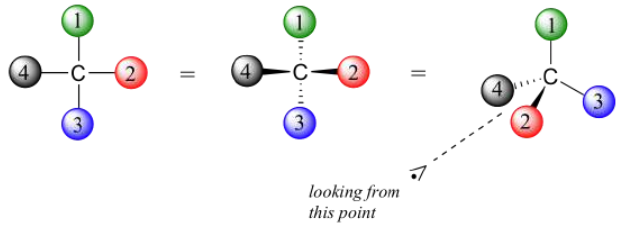
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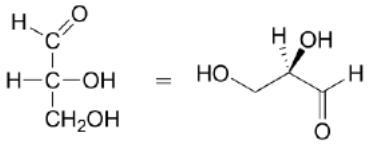
3.9: Fischer and Haworth projections

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.

Fischer 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.

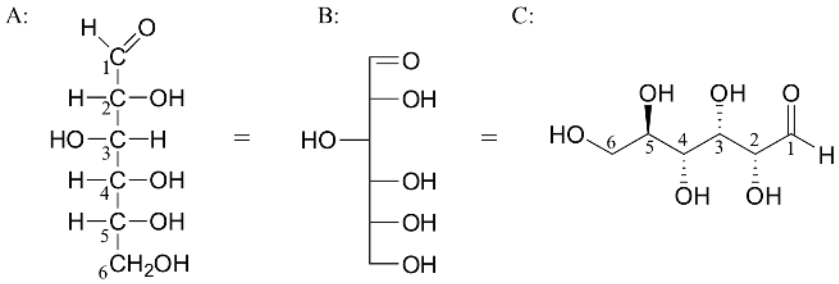


Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):

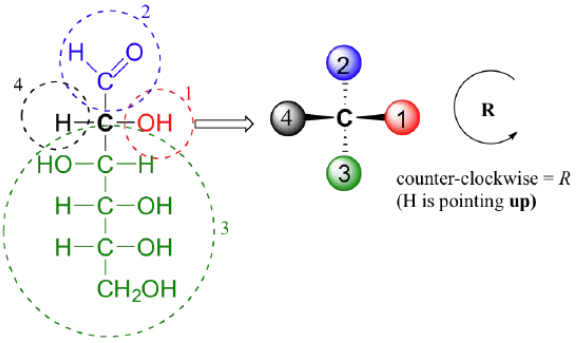


(R)-glyceraldehyde
(D-glyceraldehyde)

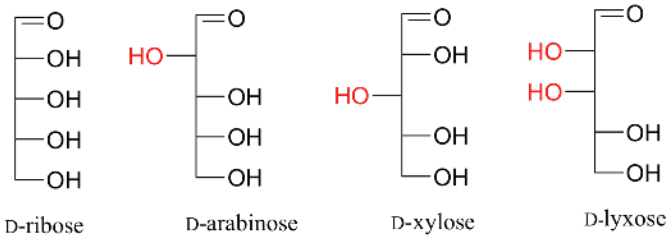
Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection (A), in the “line structure” variation of the Fischer projection in which carbons and hydrogens are not shown (B), and finally in the 'zigzag' style (C) that is preferred by organic chemists.



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).

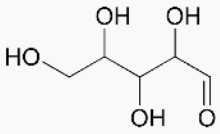


Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



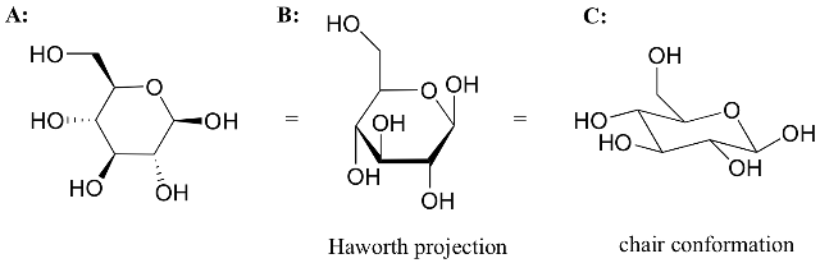
Exercise 3.24

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.

Contributors

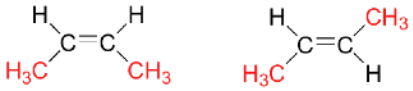
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3.10: Stereochemistry of alkenes

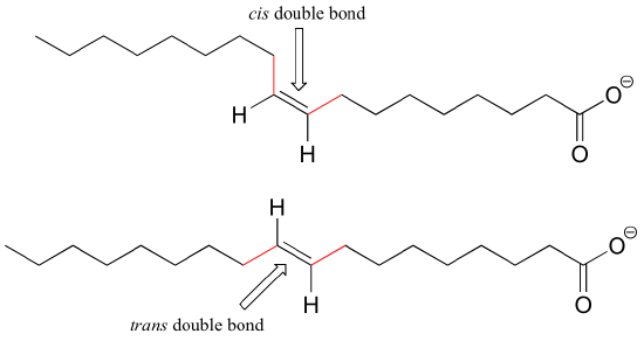
When we talk about stereochemistry, we are not always talking about chiral compounds and chiral centers. Consider *cis*- and *trans*-2-butene:



cis-2-butene *trans*-2-butene

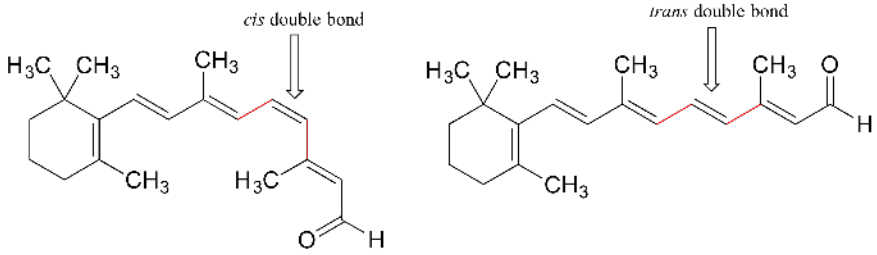
Each can be superimposed on its own mirror image, and neither is chiral (also, note the lack of a chiral center!) However, they both have the same molecular formula and the same bonding connectivity, so by definition they are stereoisomers of each other. Because they are not mirror images, they must 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.

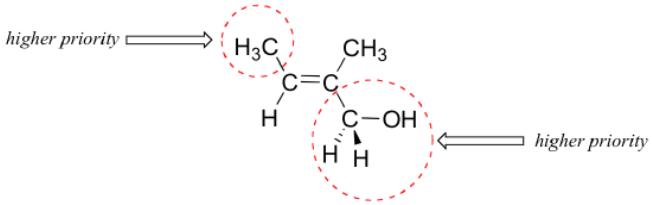


11-*cis*-retinal all-*trans*-retinal

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 on 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'*.

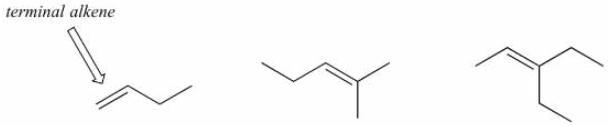
Shown below is an example of an *E*-alkene: notice that, although the two methyl groups are on the same side relative to one another, the alkene has *E* stereochemistry according to the rules of the *E/Z* system because one of the methyl groups takes a higher

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.



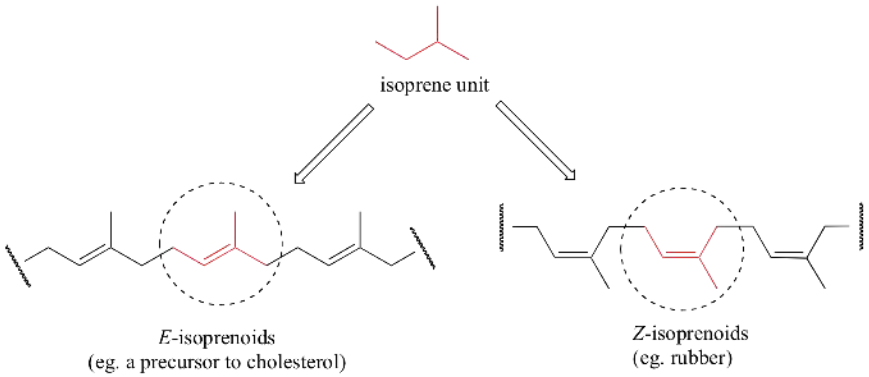
an *E*-alkene

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.



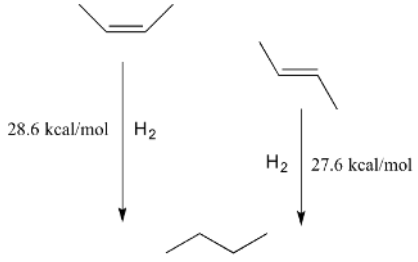
nonstereogenic alkenes (cannot be labelled *E* or *Z)*

Natural rubber is a polymer composed of five-carbon isoprenoid building blocks linked with *Z* stereochemistry. The same isoprenoid 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.



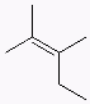
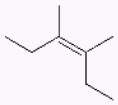
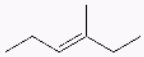
Alkenes located inside a five- or six-membered ring, such as in cyclohexene, are not generally labeled *E* or *Z*, simply because the closed geometry of the ring allows for only one stereochemical possibility. (*E*)-cyclohexene is not physically possible, so it is not necessary to include the (*Z*) designator 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'.)



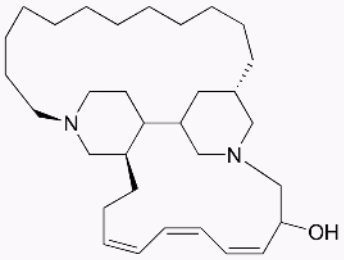
Exercise 3.25

Label the alkene groups below as *E*, *Z*, or *N* (for a nonstereogenic alkene).

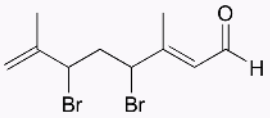
a)  b)  c)  d) 

Exercise 3.26

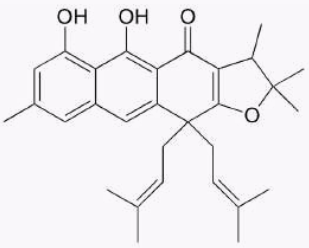
The compounds shown below were all isolated from natural sources and their structures reported in a 2007 issue of the *Journal of Natural Products*, an American Chemical Society publication. Label all alkene groups that are not inside 5- or 6-membered rings as *E*, *Z*, or *N* (for a nonstereogenic alkene).



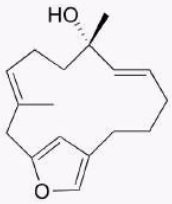
from marine sponge
J. Nat. Prod. **2007**, *70*, 538



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?

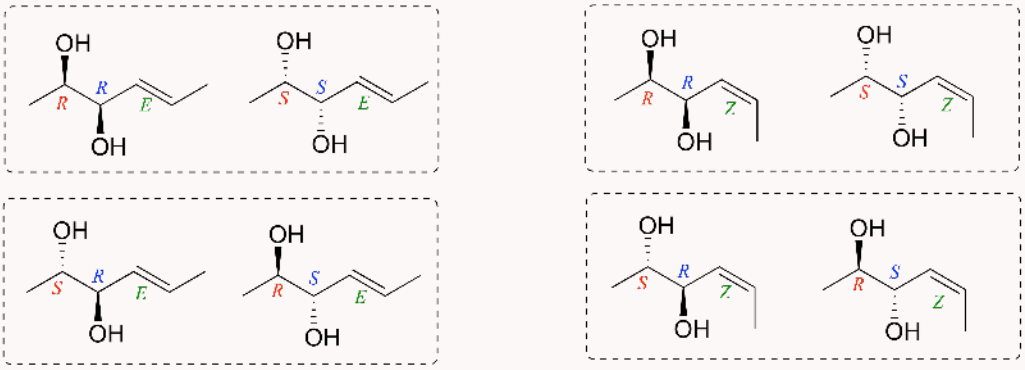
How do we know how many stereoisomers are possible for a given structure? There is actually a straightforward way to figure this out. All we need to do is count the number of chiral centers and stereogenic alkene groups, the use this following rule:

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:



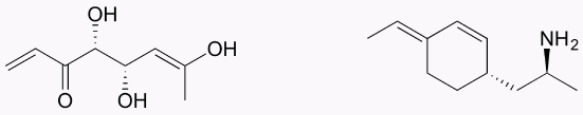
8 stereoisomers of a compound with two chiral centers plus one stereogenic alkene

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?



Contributors

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

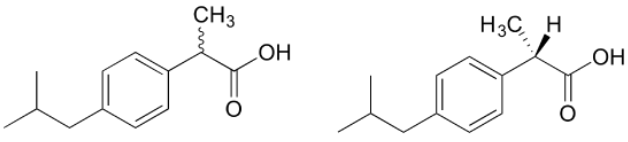
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3.11: Stereochemistry in biology and medicine

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.



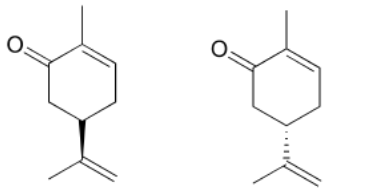
racemic ibuprofen

(*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.



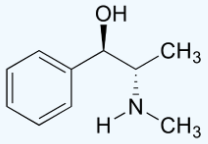
(*R*)-carvone
(spearmint odor)

(*S*)-carvone
(caraway odor)

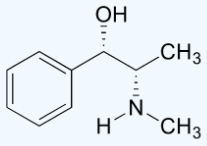
Although details are not known, the two enantiomers presumably interact differently with one or more smell receptor proteins in your nose, generating the transmission of different chemical signals to the olfactory center of your brain.

Exercise 3.28

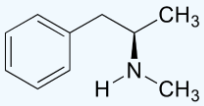
Ephedrine, found in the Chinese traditional medicine *ma huang*, is a stimulant and appetite suppressant. Both pseudoephedrine and levomethamphetamine are active ingredients in over-the-counter nasal decongestants. Methamphetamine is a highly addictive and illegal stimulant, and is usually prepared in illicit 'meth labs' using pseudoephedrine as a starting point.



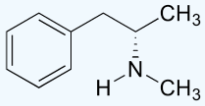
ephedrine



pseudoephedrine



methamphetamine



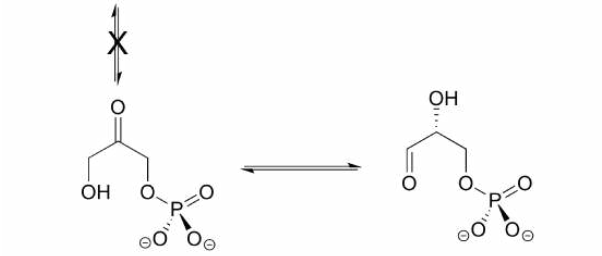
levomethamphetamine

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.

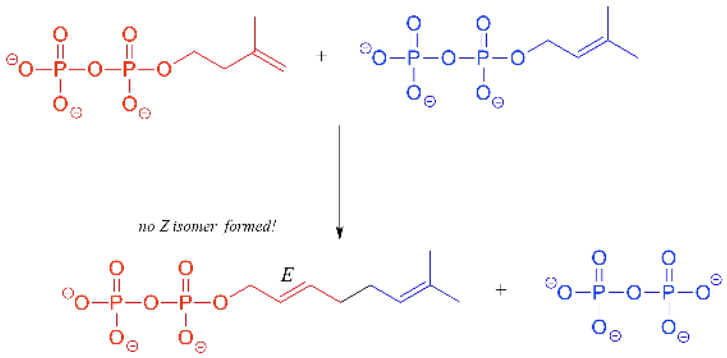
(*S*)-glyceraldehyde phosphate



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.

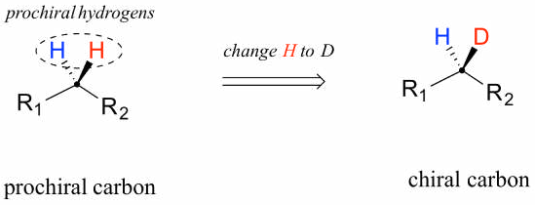
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3.12: Prochirality

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'.

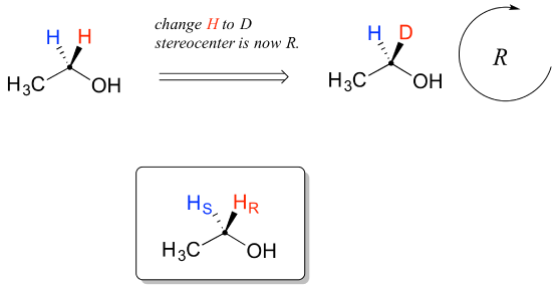


Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the ^{2}H isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

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).



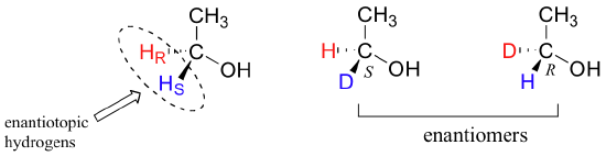
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it H_R. Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be *S*, so we can refer to blue H as the *pro-S* hydrogen of ethanol, and label it H_S.

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.



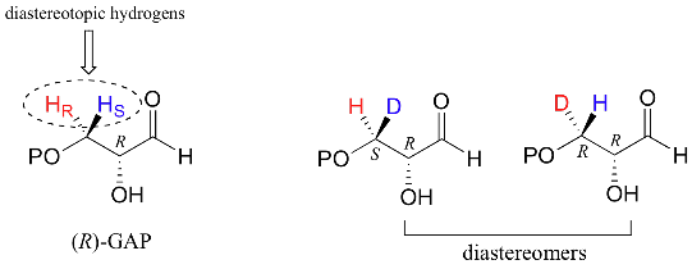
isopentenyl diphosphate dimethylallyl diphosphate

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).



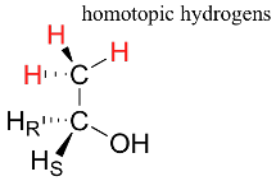
Thus, these two hydrogens are referred to as **enantiotopic**.

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.

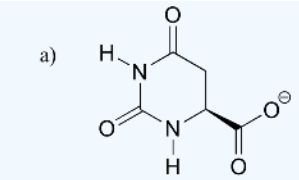
Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl (CH_3) group of ethanol (and on *any* methyl group) are homotopic.



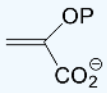
An enzyme cannot distinguish among homotopic hydrogens.

? Exercise 3.29

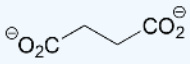
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as H_R or H_S.



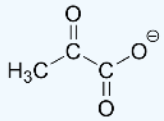
dihydroorotate
(a nucleotide biosynthesis intermediate)



phosphoenolpyruvate
(a glycolysis intermediate)



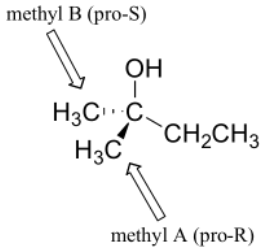
succinate
(a citric acid cycle intermediate)



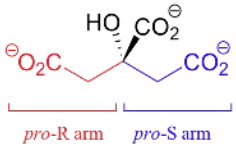
pyruvate
(endpoint of glycolysis)

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*.

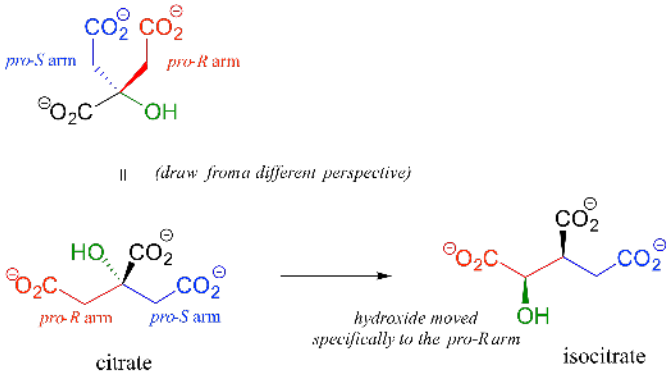


Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro-S*.



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).



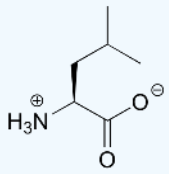
citrate

isocitrate

https://chem.libretexts.org/@go/page/234526

? Exercise 3.30

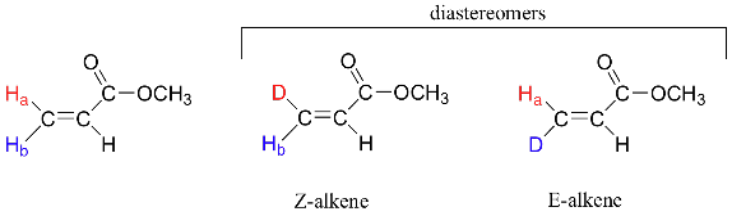
Assign *pro-R* and *pro-S* designations to all prochiral groups in the amino acid leucine. (*Hint*: there are two pairs of prochiral groups!). Are these prochiral groups diastereotopic or enantiotopic?



leucine

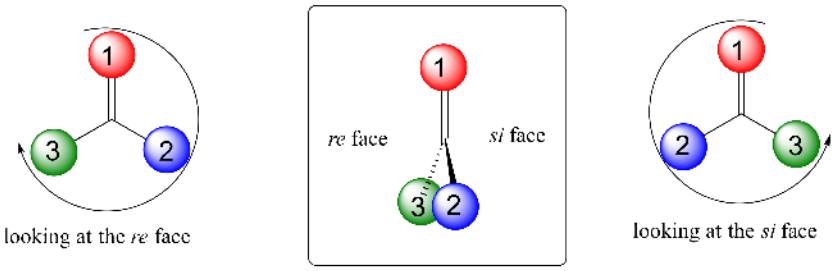
Solutions to exercises

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.

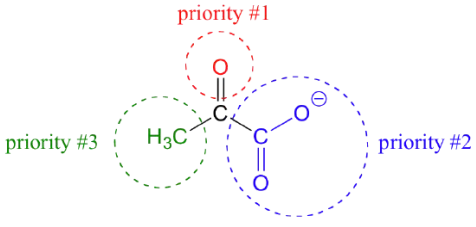


Prochiral carbonyl and imine groups

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.

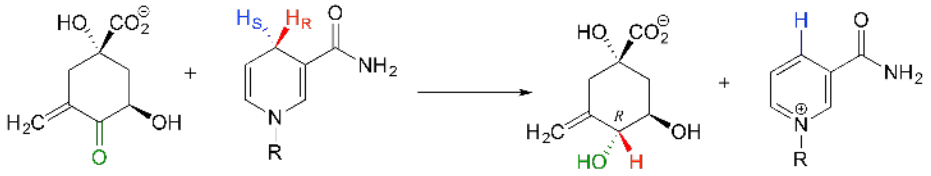


Below, for example, we are looking down on the *re* face of the ketone group in pyruvate:



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.

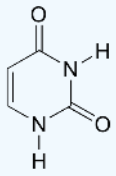


*we are looking at the **si** face of the ketone*

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

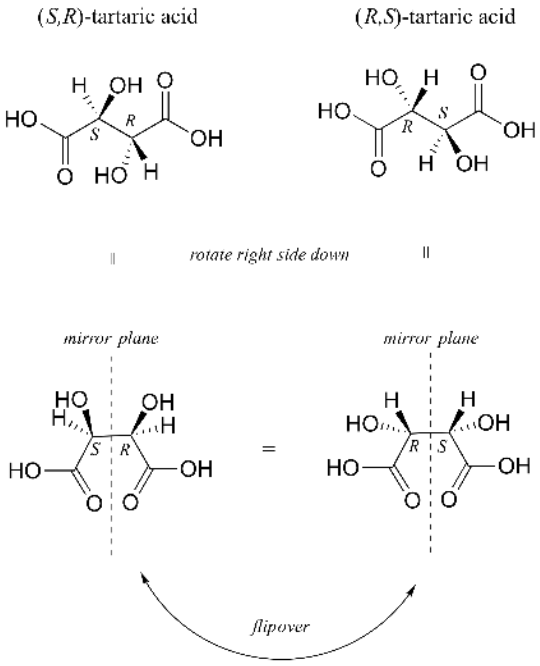
Solutions to exercises

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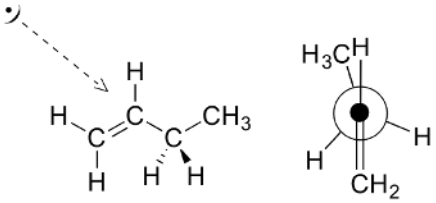
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3.13: Solutions to Chapter 3 exercises

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:

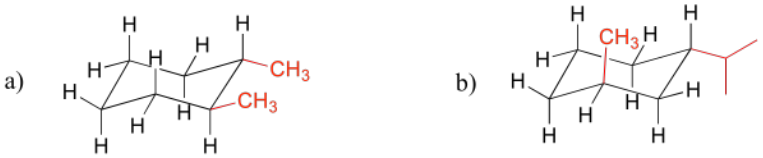
$\Delta G^0 = RT\ln K_{eq}$ *or* $K_{eq} = e^{\wedge}(-\Delta G^0/RT)$

. . . 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.

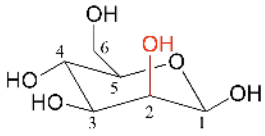
a) ***cis*-1,3-dimethylcyclohexane**: the two methyl groups are either both equatorial or both axial. In *cis*-1,4-dimethylcyclohexane, one methyl group is always axial and one equatorial, so the two conformations have the same energy.

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.

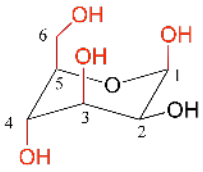
c) ***trans*-1-isopropyl-2-methylcyclohexane**: both compounds are either diaxial or diequatorial, but the larger isopropyl substituent means that the difference between the diaxial and diequatorial conformations is larger.

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:

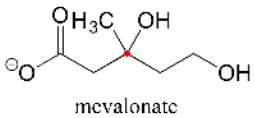


major chair form of mannose
(only one substituent axial)

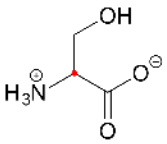


minor chair form of mannose
(four substituents axial)

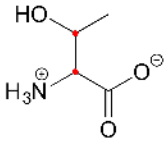
E3.8: Chiral centers are designated with a dot.



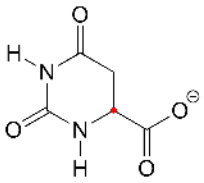
mevalonate



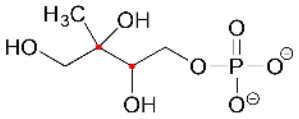
serine



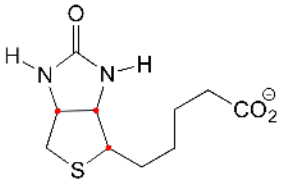
threonine



dihydroorotate



2-methylerythritol-4-phosphate



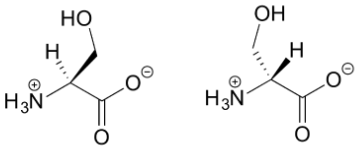
biotin

E3.9: (there are other ways that the two enantiomers can be drawn correctly - check your drawing with your instructor or tutor)

a)



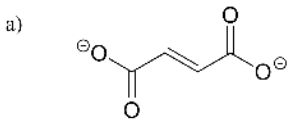
mevalonate



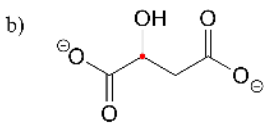
serine

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.

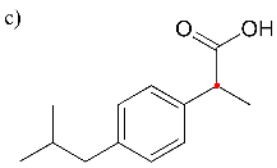
E3.10:



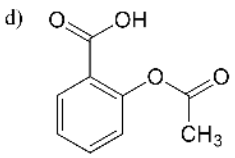
fumarate
(achiral)



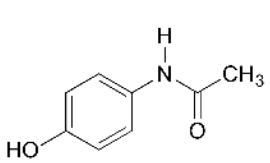
malate
(chiral)



ibuprofen
(chiral)

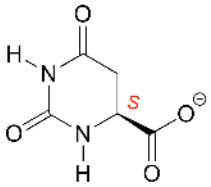


acetylsalicylic acid
(achiral)

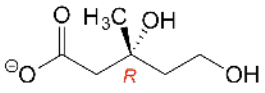


acetaminophen
(achiral)

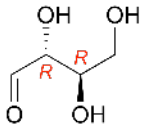
E3.11:



dihydroorotate



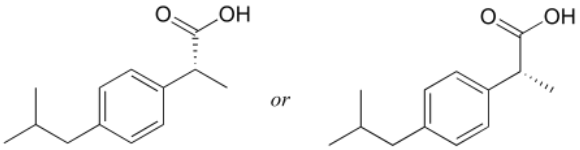
mevalonate



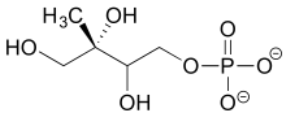
(D)-erythrose

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

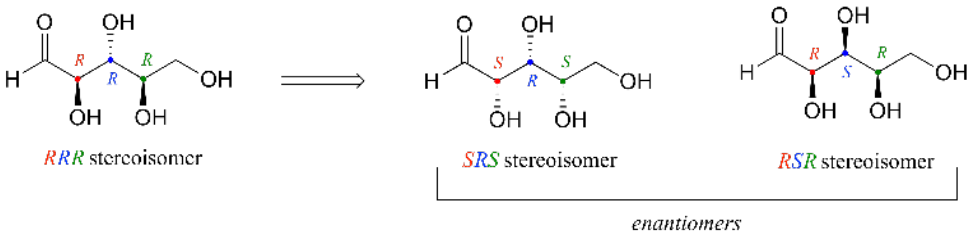
E3.14: The value of *c* is 7.50 g/100 mL, so using the definition of specific rotation, the observed rotation is expected to be (11.5)(7.5) = 86.3°.

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.

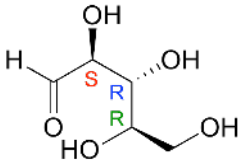


b) Epimers of the SRS stereoismer are RRS, SSS, and SRR (in each case, one of the three chiral centers has been flipped)

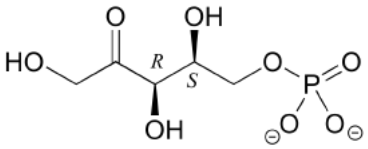
c) How to find the compounds that are diastereomers of the SRS stereoisomer, but not epimers? Start with the list of the eight possible stereoisomers given in the example. Cross out SRS itself, and its enantiomer RSR (determined in part (a) above). Then cross out the three epimers we found in part (b). 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

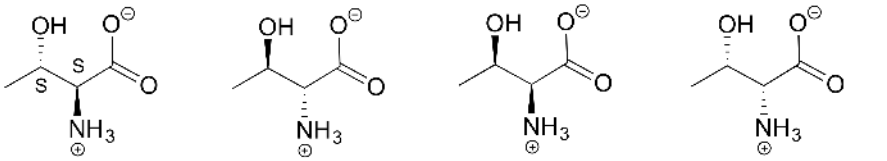
E3.18: This is the SRR stereoisomer:



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)

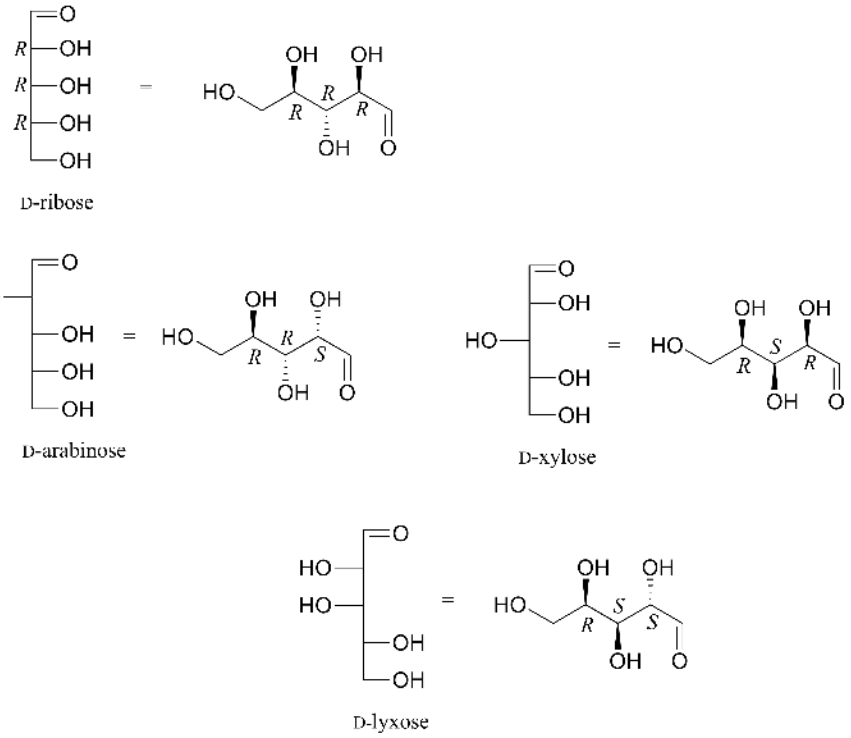
f) Identical. Both structures are *SS*. Also, notice that if you rotate the right-side structure 120 degrees clockwise, it becomes exactly the same as the left-side structure.

E3.23:

a) Not *meso* b) *Meso*. c) Not meso

d) *Meso* e) Not *meso* f) *Meso*

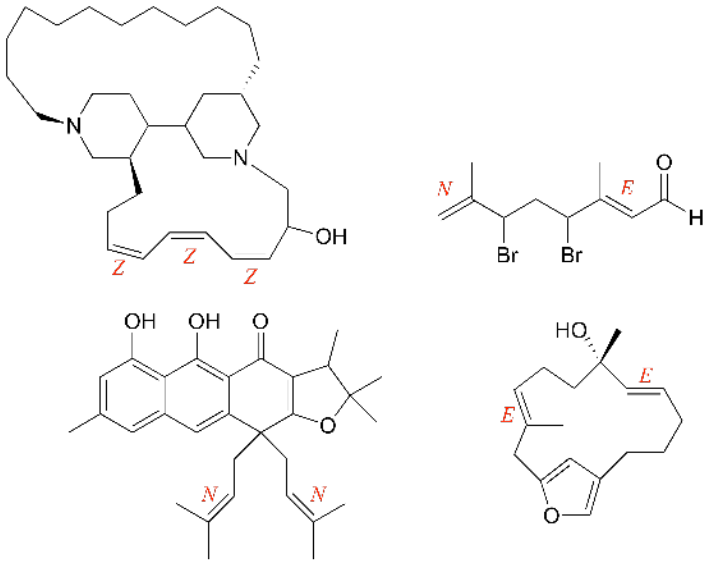
E3.24:



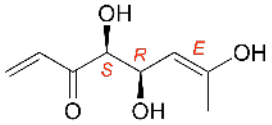
E3.25:

a) *E* b) *N* c) *Z* d) *E*

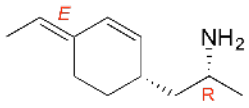
E3.26:



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).



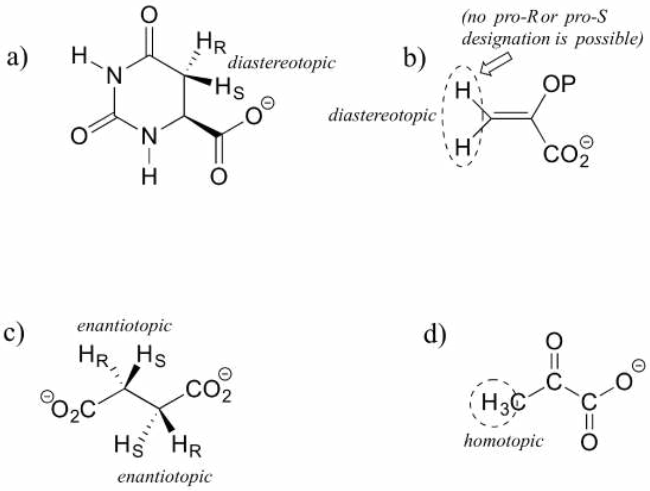
4 total stereoisomers possible (including this one).

E3.28:

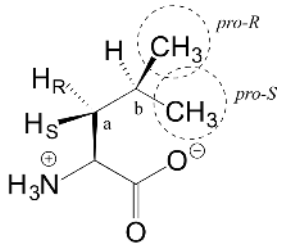
Ephedrine and pseudoephedrin are diastereomers (epimers). There are two chiral centers, and one of them (the OH) is flipped.

Methamphetamine and *levo*-methamphetamine are enantiomers (only one chiral center, and it is flipped). Methamphetamine technically should be called *dextro*-methamphetamine.

E3.29:

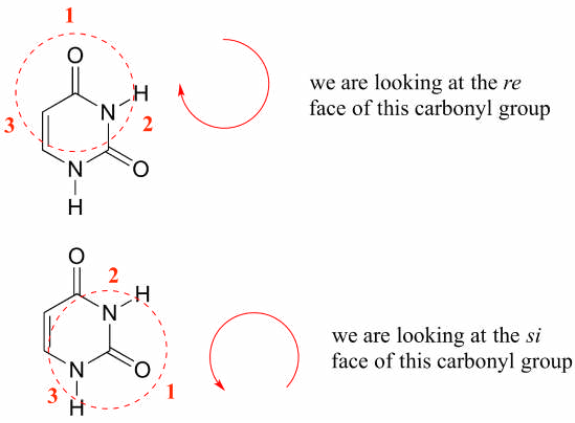


E3.30:



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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3.14: Problems for Chapter 3

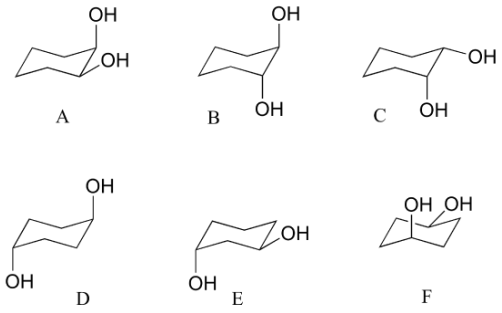
Solutions to selected problems

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.

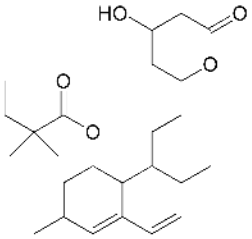
e) Draw a diastereomer of structure D (in two dimensions, as in part c).

f) Are structure D and its diastereomer chiral?

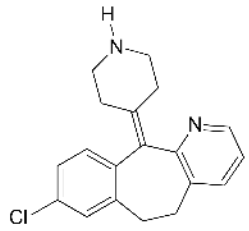
g) Assign R/S designations to the two chiral centers in structure B (hint: making a model will be *very* helpful!)

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.

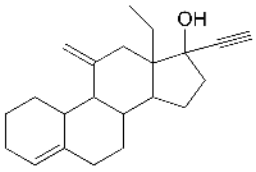
a) Circle all chiral centers. (Hint: *Don't panic*! Remember - you are looking for sp^3-hybridized carbons with four different substituents.)



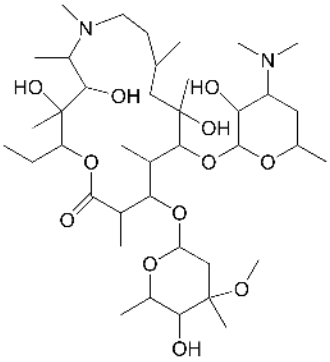
simvastatin
(active ingredient in Zocor, for high cholesterol



desloratadine
(Clarinex, for seasonal allergies)



desogestrel
(an active ingredient in Cyclessa, an oral contraceptive)

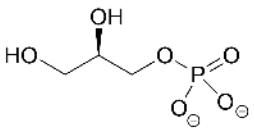


azithromycin
(an antibiotic in AzaSite, for conjunctivitis)

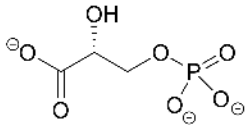
b) How many diastereomers are possible for desogestrel?

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.

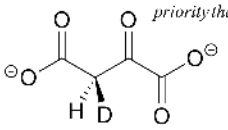


glycerol phosphate

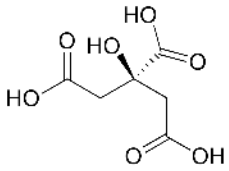


phosphoglycerate

D = deuterium, the ^2H isotope of hydrogen. D has a higher priority than H, lower priority than C.

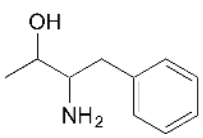


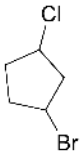
(^{2}H)-oxaloacetate

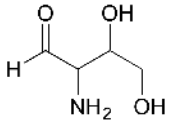


citric acid

P3.5: Draw the *R,R* stereoisomers of the structures below.

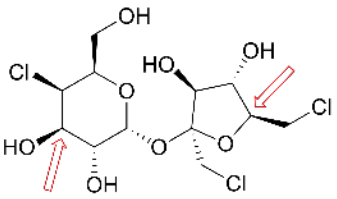




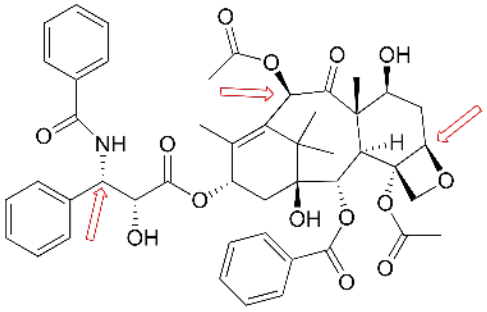


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P3.6: Below are the structures of sucralose, the artificial sweetener with the brand name Splenda (TM), and the cancer drug Paclitaxel. Give an *R* or *S* designation to chiral centers indicated with an arrow.



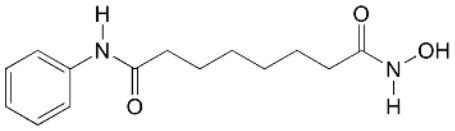
sucralose



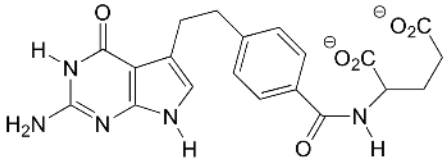
Paclitaxel

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.

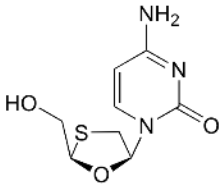
a) Identify each as chiral or achiral, and identify all stereocenters. Also, state how many possible stereoisomers exist for each structure.



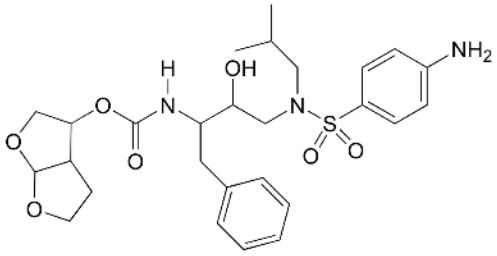
SAHA (suberoylanilide hydroxamic acid)



Alimta

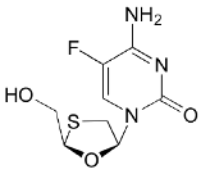


Epivir

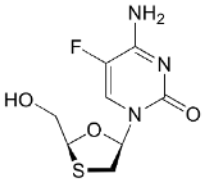


Darunavir

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)

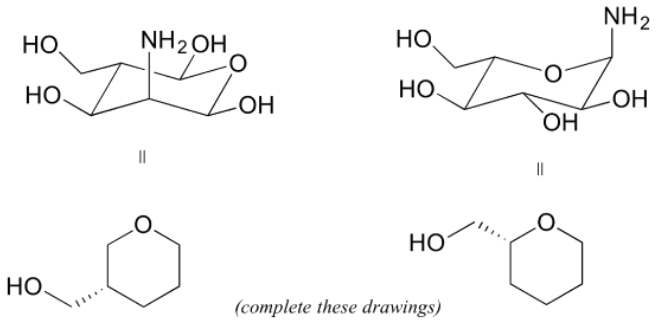


A



B

P3.8: Redraw the following structures in the flat ring, solid/dash wedge convention (the drawings have been started for you).

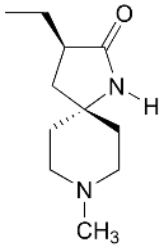


(complete these drawings)

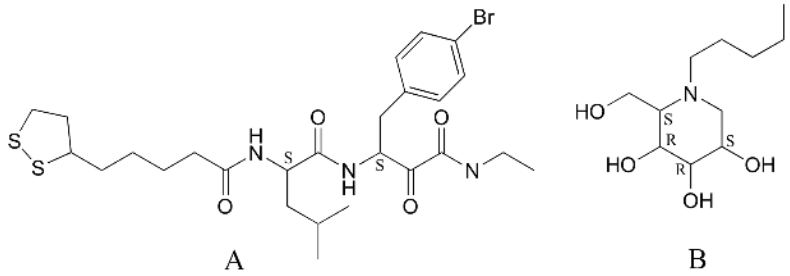
P3.9: Below is an experimental drug for Alzheimer's disease that was mentioned in the March 13, 2007 issue of *Chemical and Engineering News*.

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

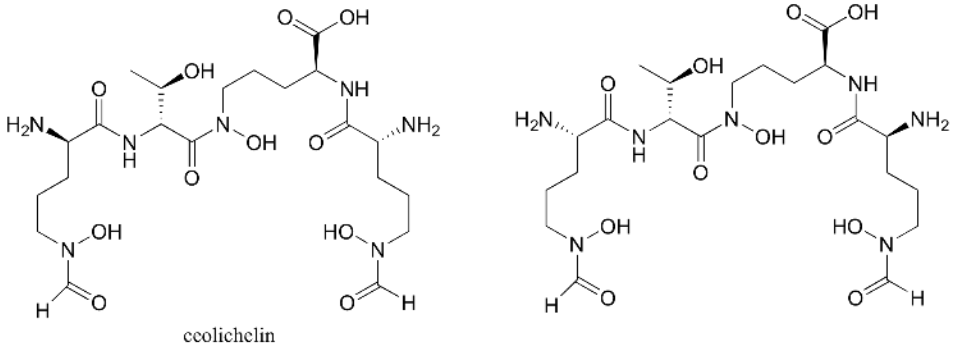
b) (*R*)-1-chloro-1-phenylethane

c) (2*R*, 3*R*)-2,3-dihydroxybutanedioic acid (tartaric acid)

d) (*S*)-(*E*)-4-chloro-3-ethyl-2-pentenoic acid

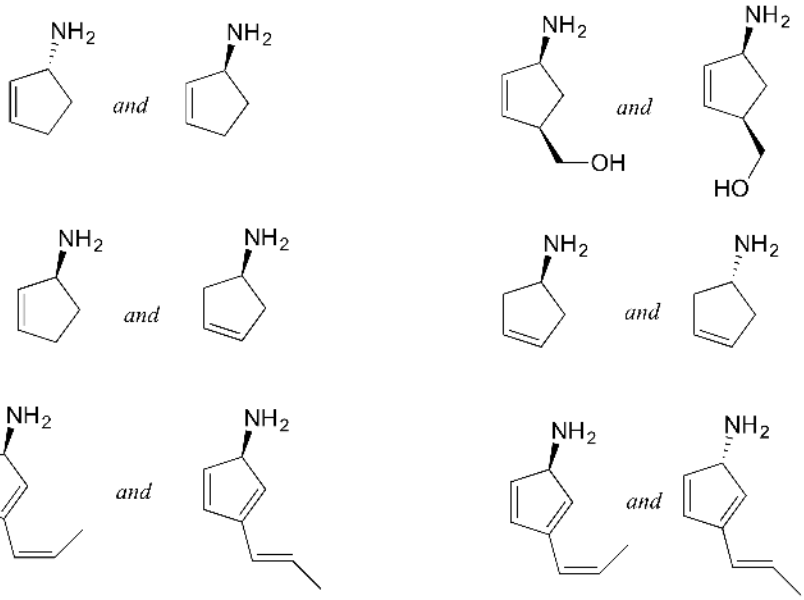
e) (1*S*, 3*R*)-1-chloro-3-ethylcyclohexane

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?

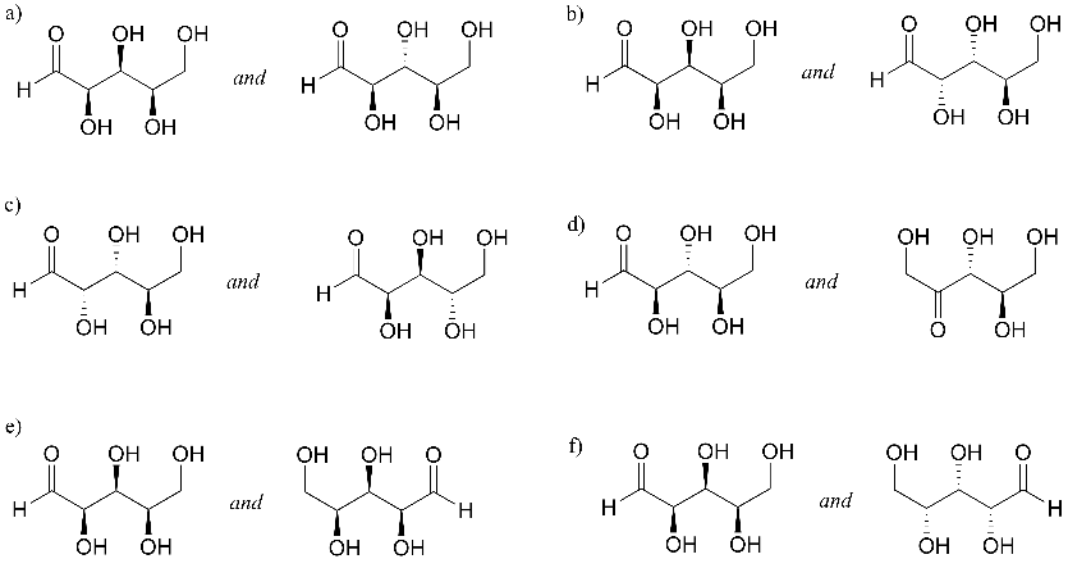


ecolichelin

P3.13: Identify the relationships between the following pairs of structures (Not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical)

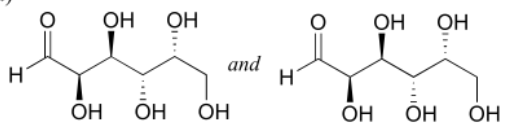


P3.14: Identify the relationships between each of the following pairs of pentose sugars (not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical).

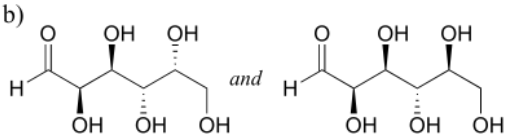


P3.15: Identify the relationships between each of the following pairs of hexose sugars (not isomers, constitutional isomers, diastereomers but *not* epimers, epimers, enantiomers, identical).

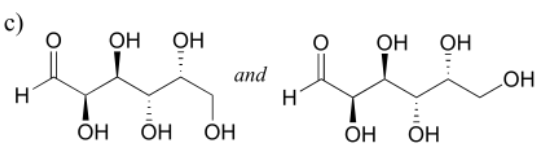
a)



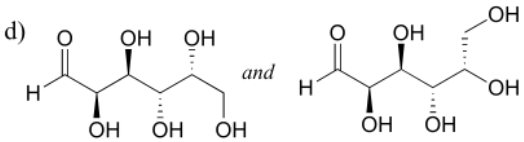
b)



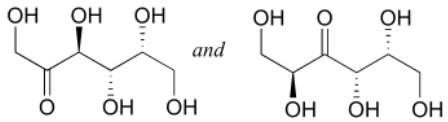
c)



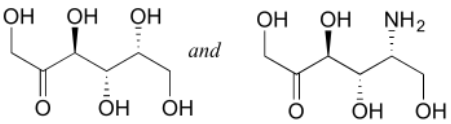
d)



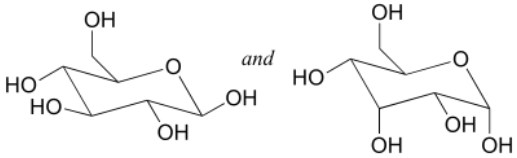
e)



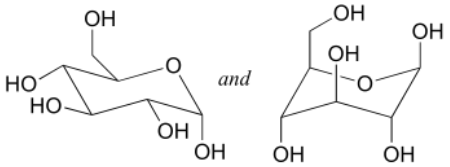
f)



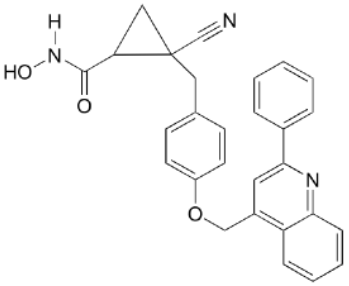
g)



h)



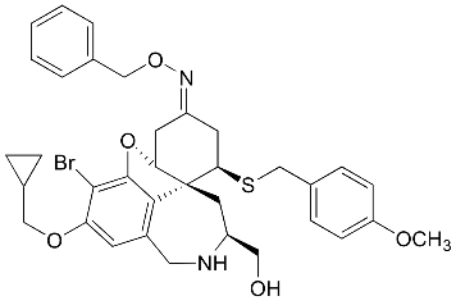
P3.16: The compound drawn below (not showing stereochemistry) has been identified as a potential anti-inflammatory agent by scientists at Schering-Plough a pharmaceutical company (see *Chemical and Engineering News* Nov. 28, 2005 p. 29). How many stereoisomers are possible for the compound?



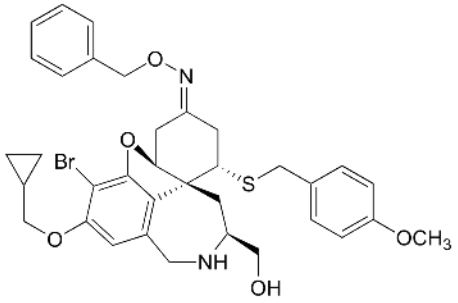
P3.17: Secramine is a synthetic compound that has been shown to interfere with the transport of newly synthesized proteins in the cell (see *Chemical and Engineering News* Nov. 28, 2005, p. 27). Also drawn below is a (hypothetical) isomer of secramine.

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.

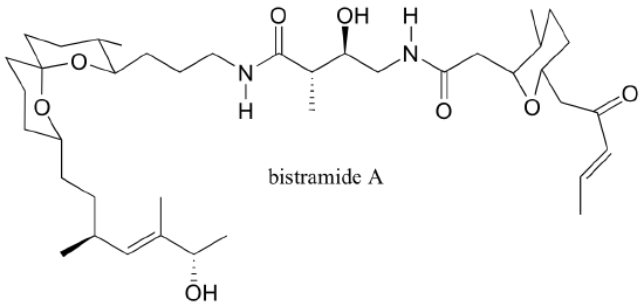


secramine



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.

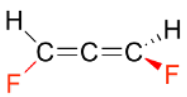
a) Label the stereochemical configuration at C_1 and C_2 for the structure you drew.

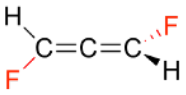
b) Build a model of your molecule, and try out different possible boat conformations. Can you find one in which there is a plane of symmetry?

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?*

4.1: Prelude to Structure Determination I

4.2: Introduction to molecular spectroscopy

4.3: Mass Spectrometry

4.4: Infrared spectroscopy

4.5: Ultraviolet and visible spectroscopy

4.6: Problems for Chapter 4

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

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4.1: Prelude to Structure Determination I



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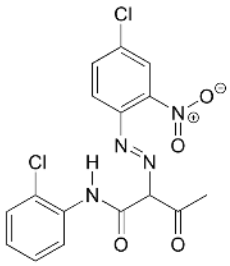
Introduction: a foiled forgery

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 9:

Nuclear magnetic resonance spectroscopy (NMR): What is the overall bonding framework of the molecule?

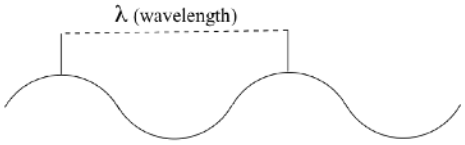
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4.2: Introduction to molecular spectroscopy

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:

$$E = \frac{hc}{\lambda} \tag{4.1.1}$$

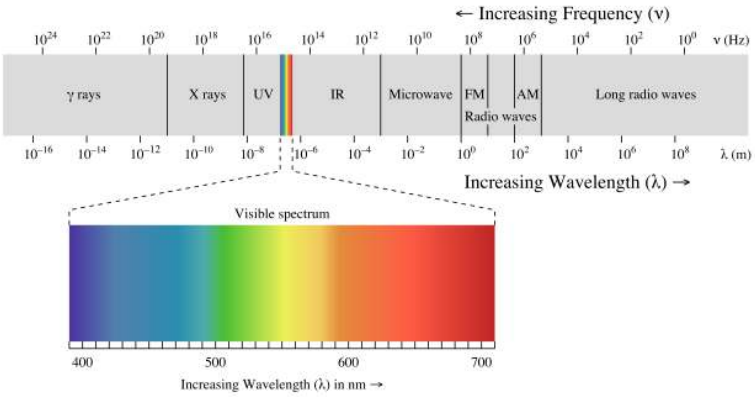
where E is energy in kJ/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^{8} m/s (the speed of light), and *h* is 3.99 x 10^{-13} kJ·s·mol^{-1}, a number known as **Planck's constant**.

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

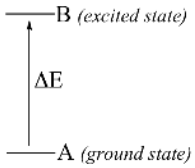
Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kJ/mol of photons?

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

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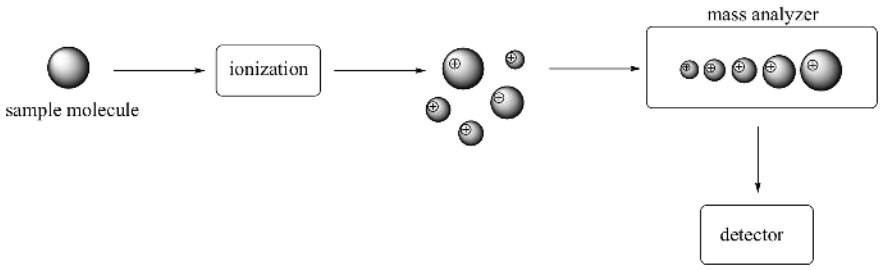
4.3: Mass Spectrometry

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

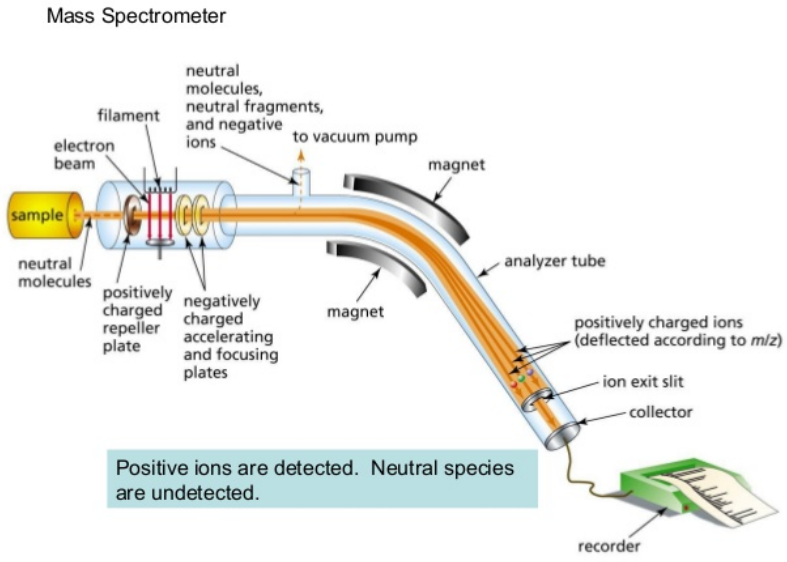
There are many different types of MS instruments, but they all have the same three essential components. First, there is an ionization source, where the molecule is given a positive electrical charge, either by removing an electron or by adding a proton. Depending on the ionization method used, the ionized 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.

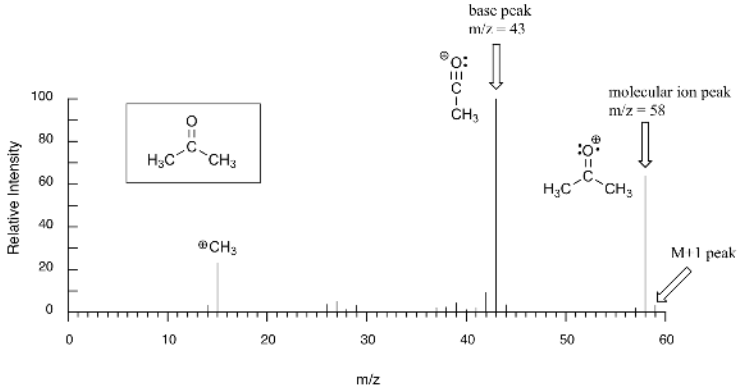


(Image from Wikipedia Commons)

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.

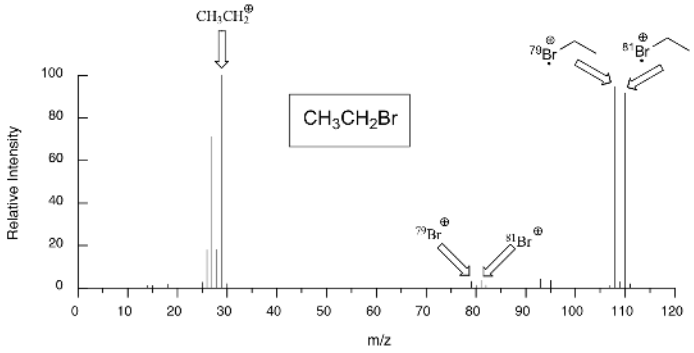
Looking at mass spectra

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.



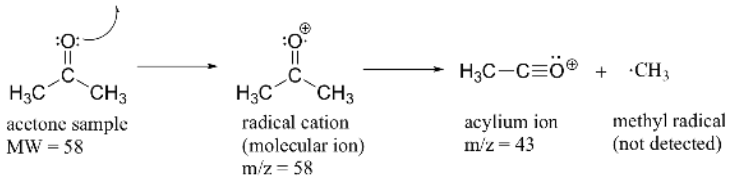
The sample is acetone. On the horizontal axis is the value for m/z (as we stated above, the charge z is almost always +1, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set 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:

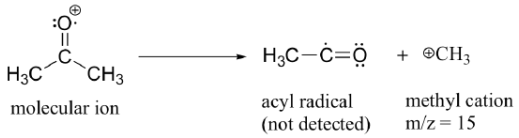


Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it 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

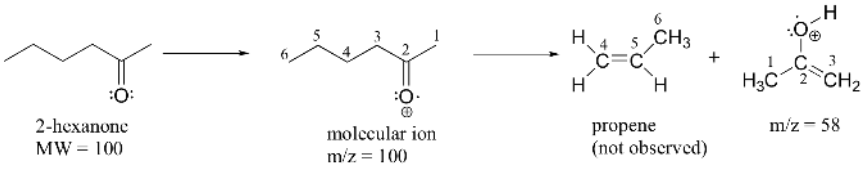
m/z = 43. This is the result of cleavage at the ‘alpha’ position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



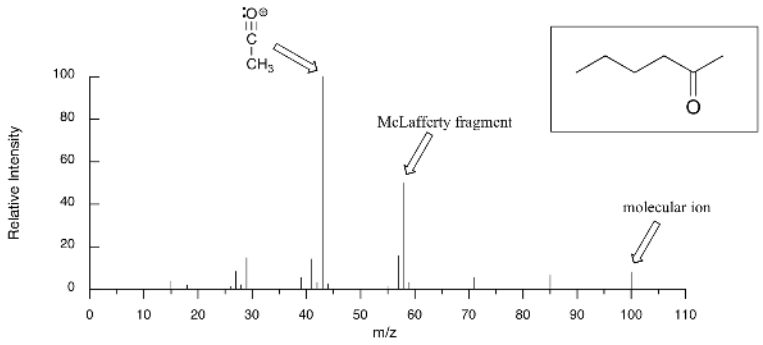
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



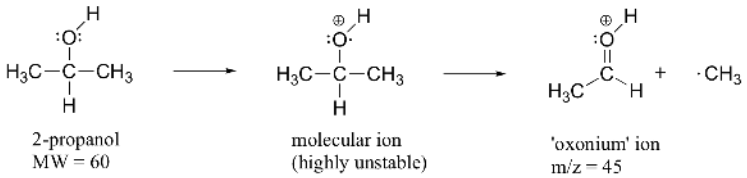
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

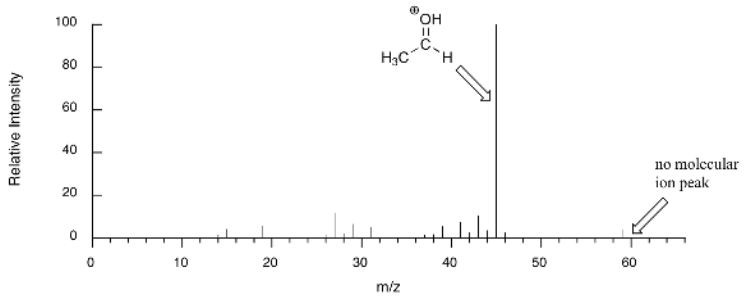


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



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 4.3.1

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 4.3.1

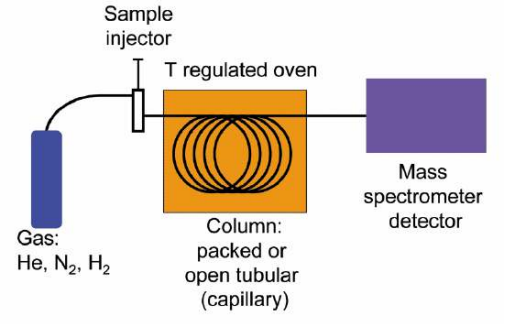
Predict some signals that you would expect to see in a mass spectrum of 2-chloropropane.

? Exercise 4.3.3

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)

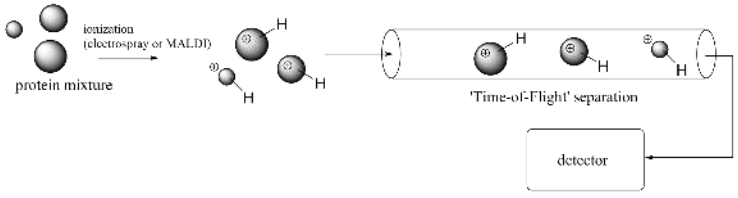
The extremely high sensitivity of modern GC-MS instrumentation makes it possible to detect and identify very small trace amounts of organic compounds. GC-MS is being used increasingly by environmental chemists to detect the presence of harmful organic contaminants in food and water samples. Airport security 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.

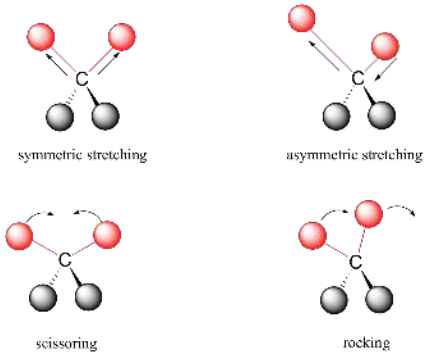
In a 2005 study, MALDI-TOF mass spectrometry was used to compare fluid samples from lung transplant recipients who had suffered from tissue rejection to samples from recipients who had not suffered rejection. Three peptides (short proteins) were found to be present at elevated levels specifically in 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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4.4: Infrared spectroscopy

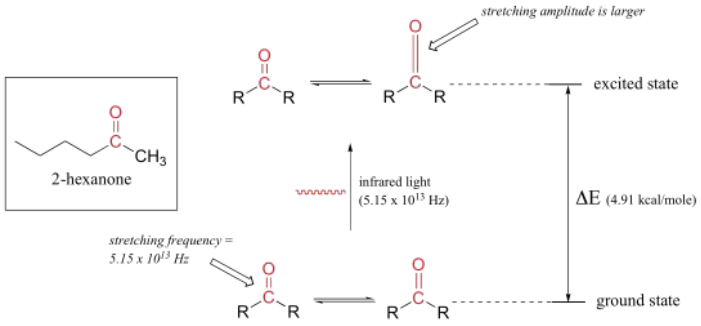
Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few 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.

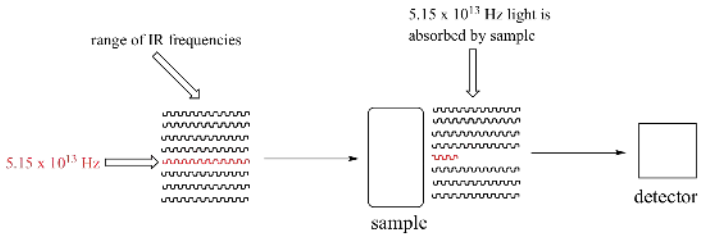
Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring that is constantly bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond. In the space of one second, the spring 'bounces' back and forth 5.15×10^{13} times - in other words, the ground-state frequency of carbonyl stretching for a the ketone group is about 5.15×10^{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 5.83×10^{-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.



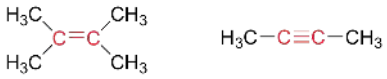
Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

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.

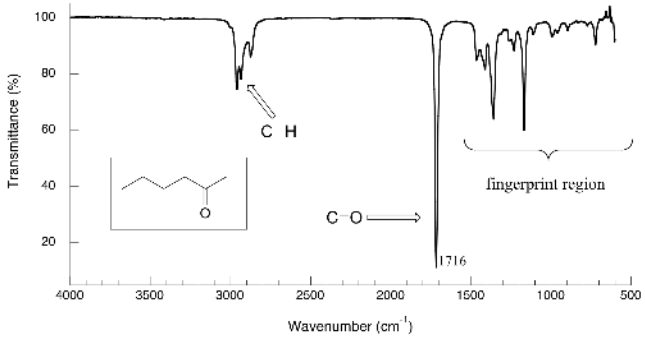
Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule*. Such vibrations are said to be **infrared active**. In general, the greater 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).

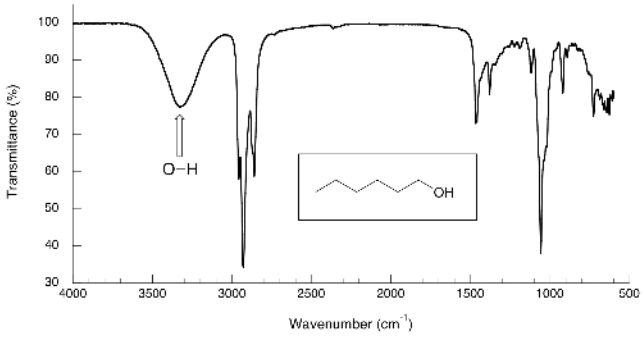
Solutions

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.

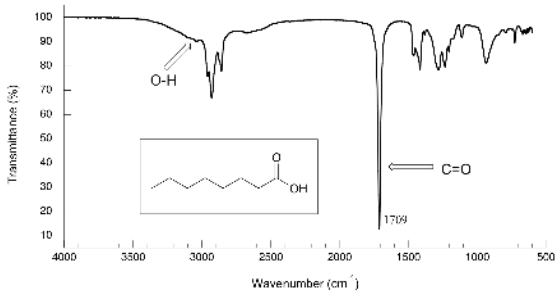
You will notice that there are many additional peaks in this spectrum in the longer-wavelength 400 -1400 cm^{-1} region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, 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.



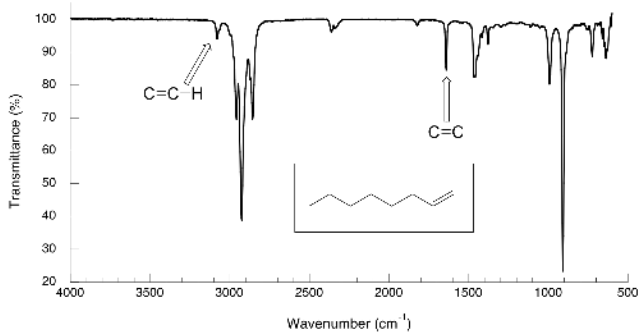
As you can see, the carbonyl peak is gone, and in its place is a very broad 'mountain' centered at about 3400 cm^{-1}. This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen 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-hexyn-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

Contributors

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

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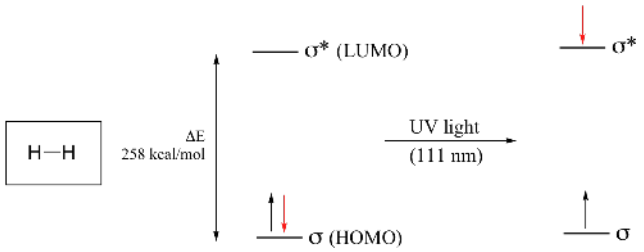
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4.5: Ultraviolet and visible spectroscopy

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.

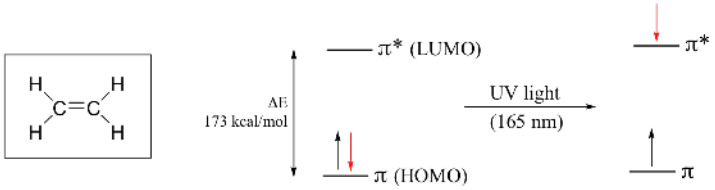
Electronic transitions

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).



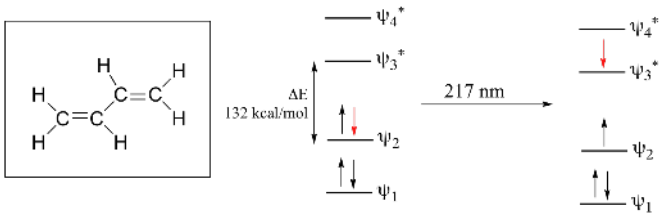
If the molecule is exposed to light of a wavelength with energy equal to **ΔE**, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. **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.



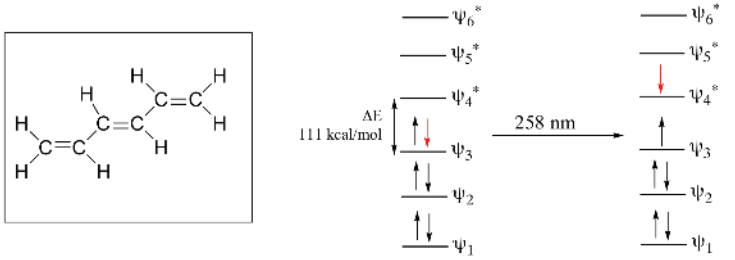
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with 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.

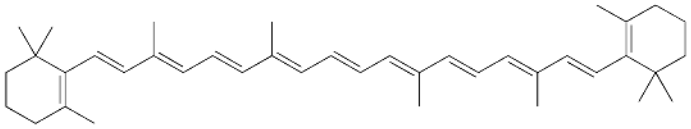


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

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.

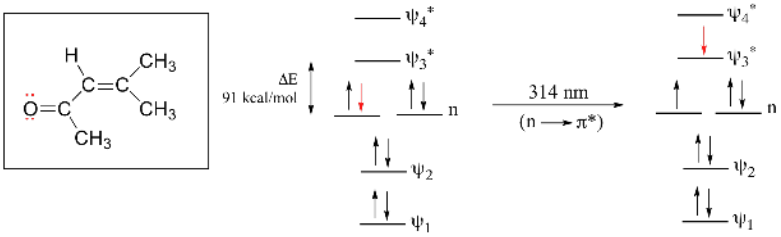


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather than the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible 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:



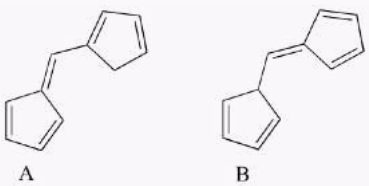
This is referred to as an **n - π* transition**. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n \rightarrow \pi^*$ transition is smaller than that of a π - π* transition – and thus the n - π* peak is at a longer wavelength. In general, n - 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.

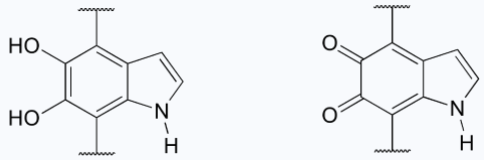


A B

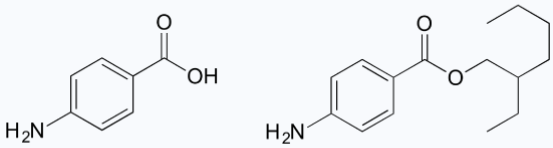
Solutions

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

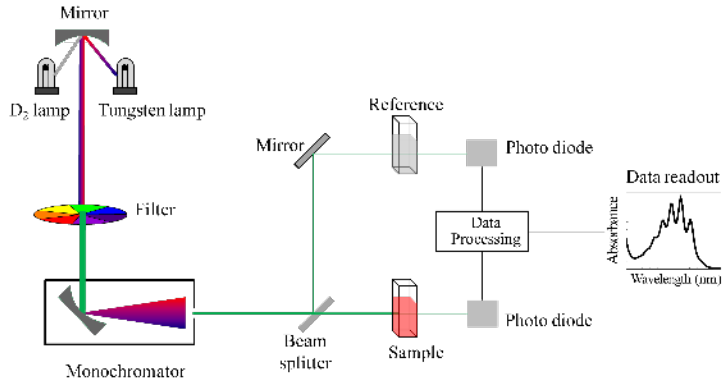


PABA Padimate-O

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

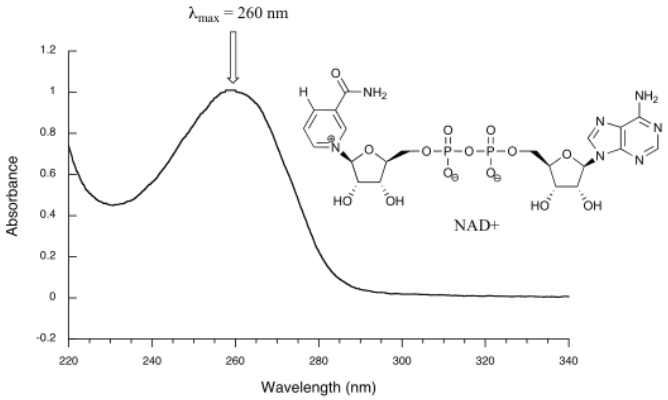
We have been talking in general terms about how molecules absorb UV and visible light – now let's look at some actual examples of data from a UV-vis absorbance spectrophotometer. The basic setup is the same as for IR spectroscopy: radiation with a range of wavelengths is directed through a sample of 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:

$$A = \log \frac{I_0}{I} \tag{4.3.1}$$

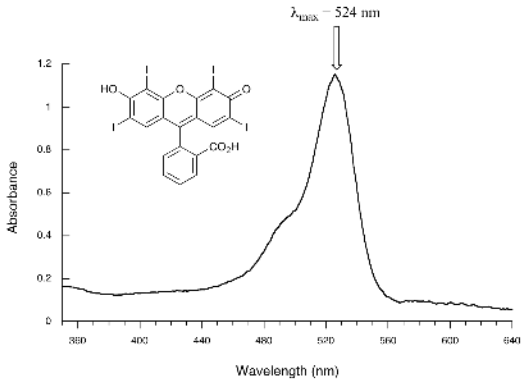
You can see that the absorbance value at 260 nm (A_{260}) is about 1.0 in this spectrum.

Exercise 4.11

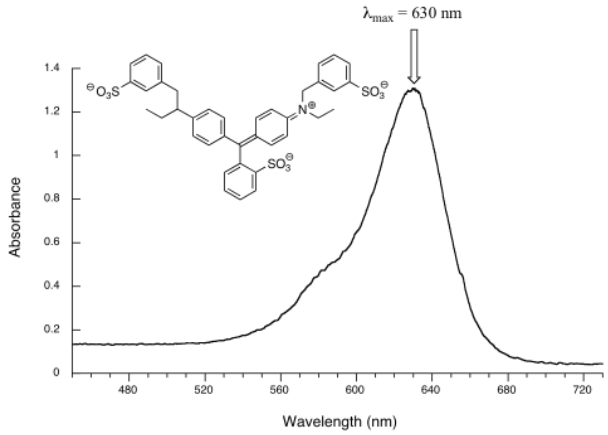
Express A = 1.0 in terms of percent transmittance (%T, the unit usually used in IR spectroscopy (and sometimes in UV-vis as well).

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

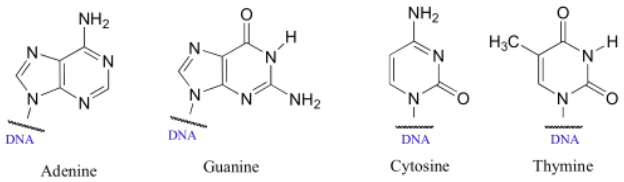
UV-vis spectroscopy has many different applications in organic and biological chemistry. One of the most basic of these applications is the use of the **Beer - Lambert Law** to determine the concentration of a chromophore. You most likely have performed a Beer – Lambert experiment in a previous chemistry 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 through 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:

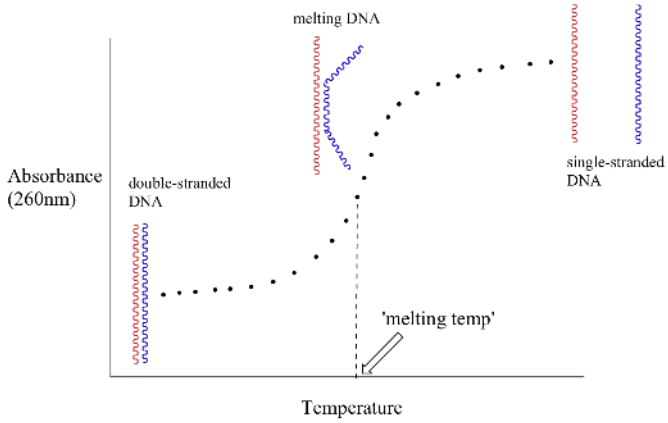


Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 $ng^{-1} \times mL$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Exercise 4.12

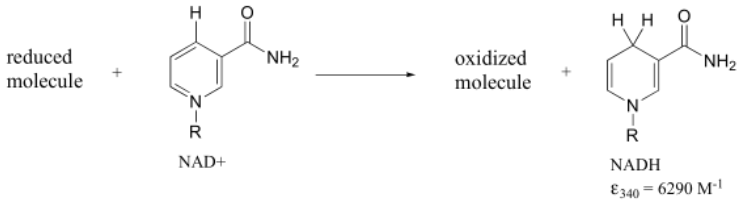
50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?

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').

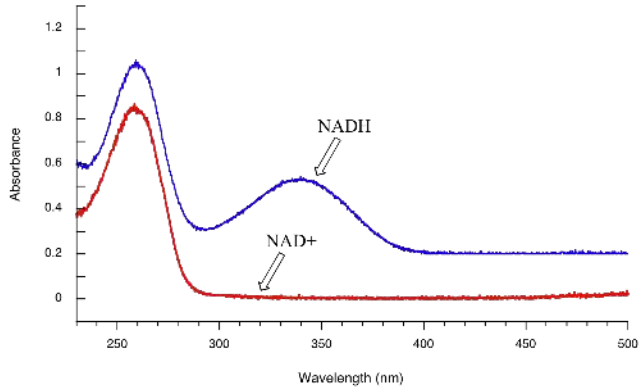


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or 'melts'. The mid-point of this process, called the 'melting temperature', provides a good indication of how tightly the two strands of DNA are able 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:

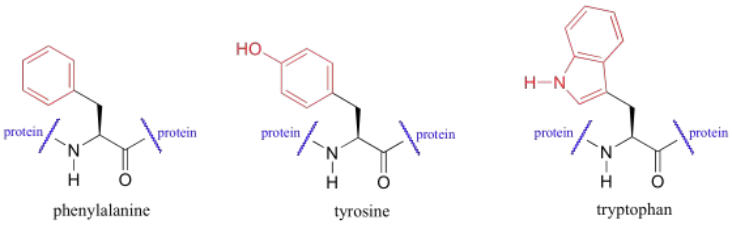


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L*mol^{-1}*cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:



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.

Kahn Academy video tutorials on UV-Vis spectroscopy

Contributors

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

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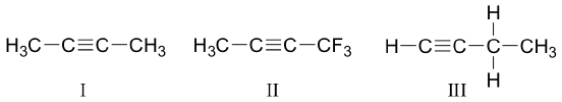
4.6: Problems for Chapter 4

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).

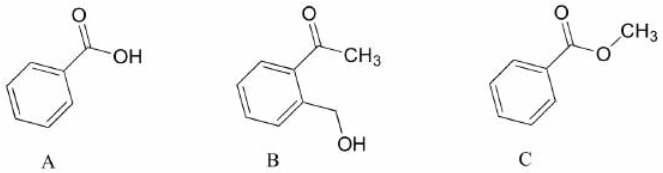
P4.2: Calculate the value, in kcal/mol, of the energy gap associated with a typical ketone carbonyl stretching transition at 1720 cm^{-1}.

P4.3: Explain how you could use IR spectroscopy to distinguish between compounds I, II, and III.



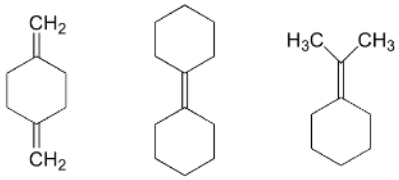
I II III

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.

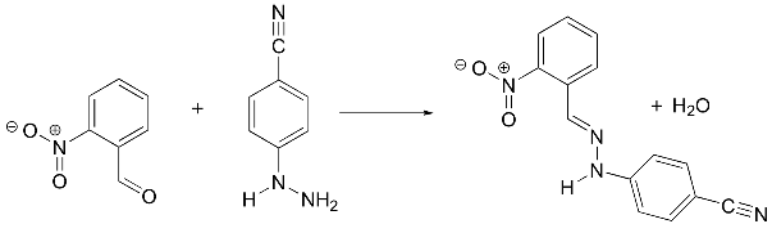


X Y Z

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?

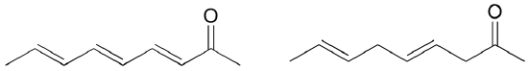
P4.8: The reaction below is of a type that we will study in Chapter 11. While the two starting materials are only slightly colored, the product is an intense orange-red. Account for this observation.



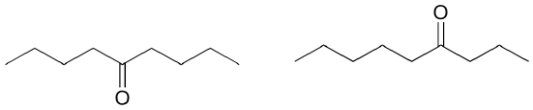
P4.9: Predict five fragments that you would expect to be evident in the mass spectrum of 3-methyl-2-pentanone.

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: Overview of Organic Reactivity

5.1: Prelude to Organic Reactivity
5.2: A First Look at Some Organic Reaction Mechanisms
5.3: A Quick Review of Thermodynamics and Kinetics
5.4: Catalysis
5.5: Comparing Biological Reactions to Laboratory Reactions
5.6: Overview of Organic Reactivity (Problems)
5.7: Overview of Organic Reactivity (Summary)

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5.1: 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 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 isolate 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 molecules 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.

$$\mathbf{N_2O_5\,(s) \longrightarrow 2\,NO_2\,(g) + \tfrac{1}{2}\,O_2\,(g)} \tag{5.1.1}$$

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.

Contributors

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5.2: A First Look at Some Organic Reaction Mechanisms

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:

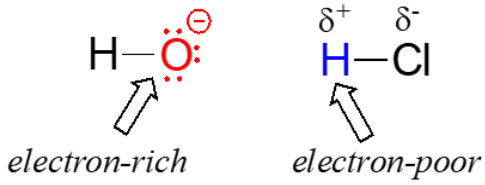


> **Note**
>
> A reaction such as the one above would of course include a spectator cation, such as sodium (Na^+) or potassium (K^+). In most of the reaction figures that we'll see throughout this book, the spectator ion is not shown in the interest of simplicity.

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**).

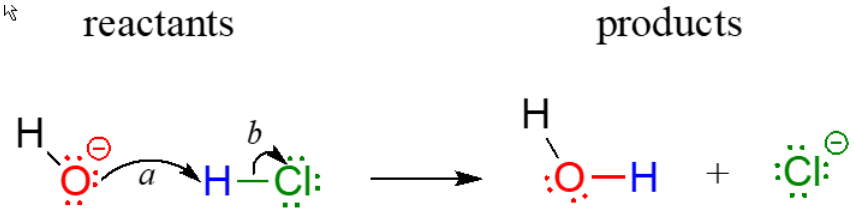
Despite its simplicity (and despite the fact that the reactants and products are inorganic rather than organic), this reaction allows us to consider for the first time many of the fundamental ideas of organic chemistry that we will be exploring in various contexts throughout this text.

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.

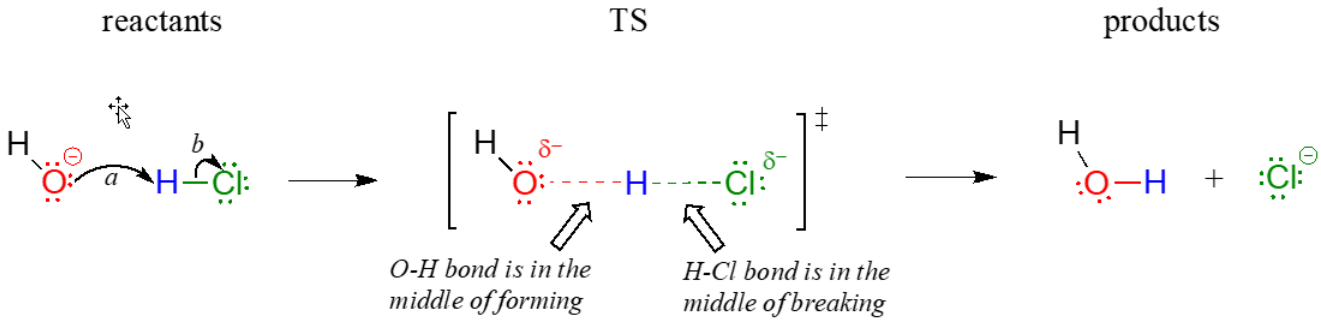
In organic chemistry terms, a reaction mechanism is a formalized description of how a reaction takes place - how we get, in other words, from reactants to products. Previously (section 2.3) , we saw how curved arrows were used to depict the 'imaginary' movement of two electrons when illustrating the 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 5.2.1

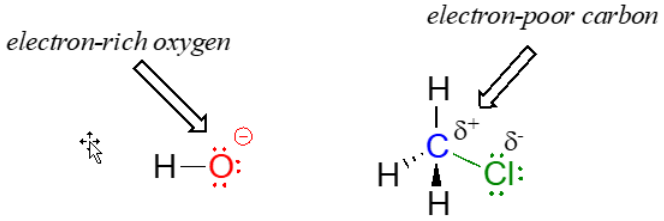
Draw electron movement arrows to illustrate mechanism of the acid-base reaction between acetic acid, CH_3CO_2H, and ammonia, NH_3. Draw out the Lewis structures of reactants and products, including all lone pairs and formal charges. Include a transition state drawing in your mechanism.

Exercise 5.2.2

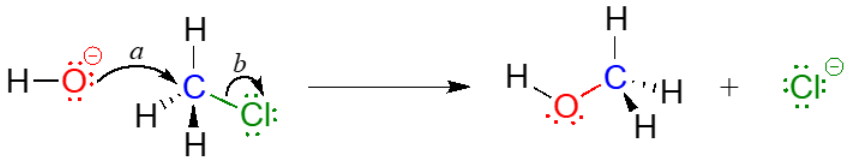
Draw electron movement arrows to illustrate the mechanism of the reverse of the reaction in Exercise **5.2.1**: the acid-base reaction between acetate ion ($CH_3CO_2^-$, acting as a base) and ammonium (NH_4^+), acting as an acid). Again, draw out the Lewis structures of reactants and products, including 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.



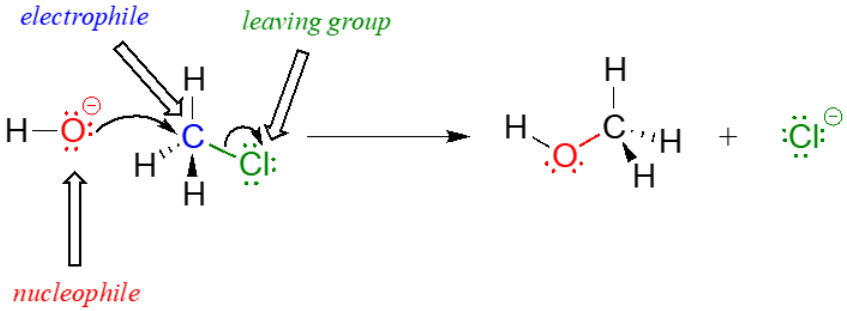
Due to the relative electronegativity of chlorine, the carbon-chlorine bond is polar. It stands to reason that a lone pair of electrons on the electron-rich hydroxide oxygen will be attracted to the electron-poor carbon nucleus.



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).

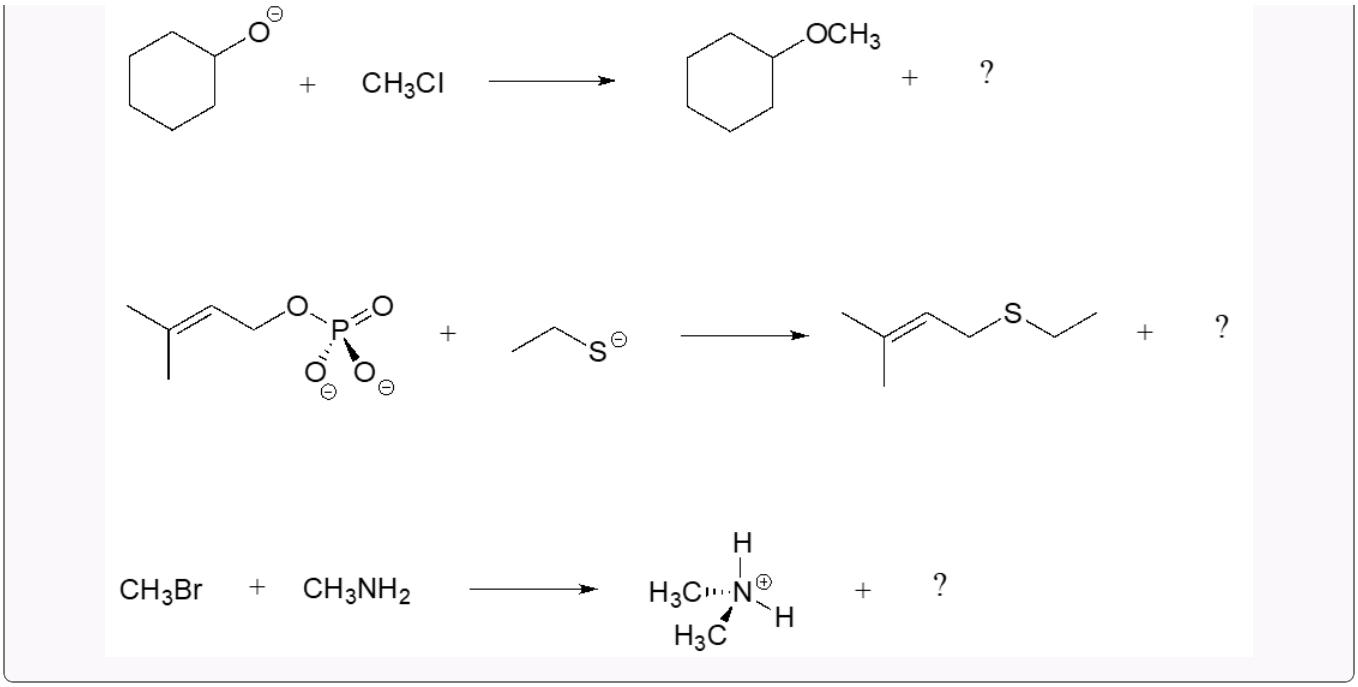
The reaction mechanism illustrated above called a nucleophilic substitution. The 'substitution' term is easy to understand: just recognize how hydroxide substitutes for chlorine as the fourth bond to the central carbon. The term 'nucleophilic' means 'nucleus-loving' and refers to the electron-rich species, 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.



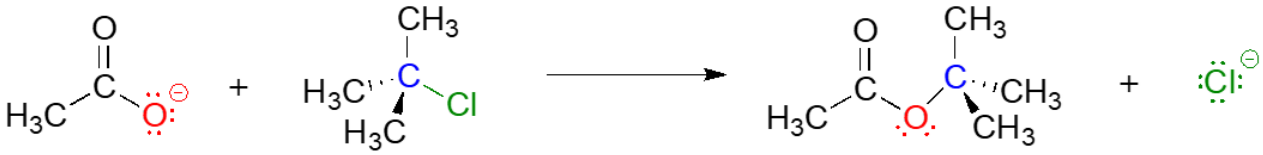
Exercise 5.2.3

In each of the nucleophilic substitution reactions below, identify the nucleophile, electrophile, and leaving group, and fill in the missing product.



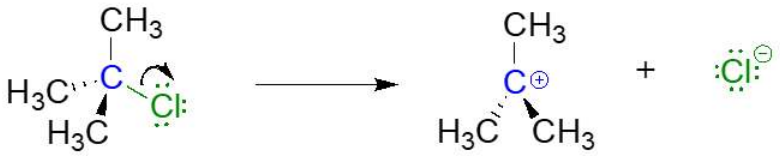
A Two-step Nucleophilic Substitution Mechanism

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).



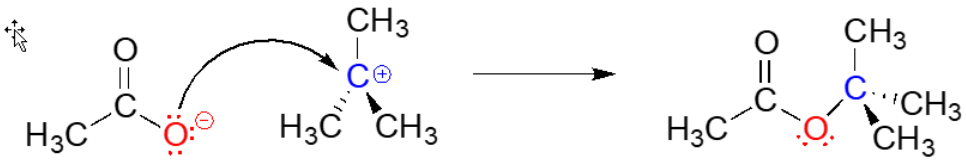
Unlike the chloromethane plus hydroxide reaction, in which the substitution process took place in a single, concerted step, it turns out that this mechanism involves two separate steps. The leaving group, chloride anion, leaves first, *before* the acetate nucleophile attacks.

Step 1: Loss of leaving group (slow)

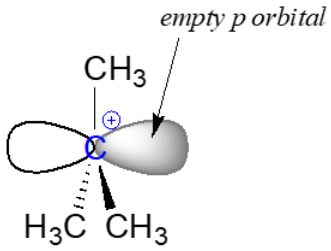


carbocation intermediate

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**.

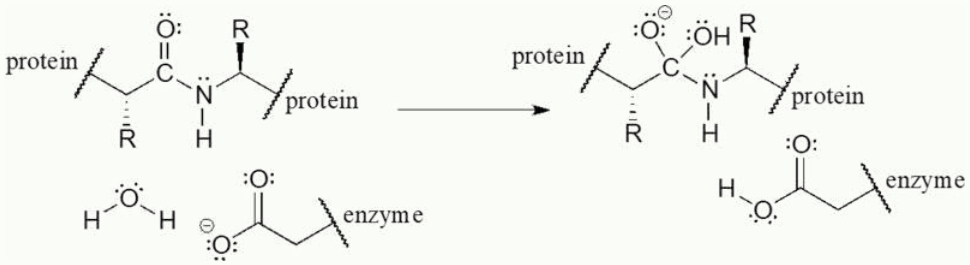
With its empty p orbital, the carbocation intermediate is clearly electron-poor, and thus is a powerful electrophile. The negatively charged acetate ion is electron dense and a nucleophile, and as such is strongly attracted to the carbocation electrophile. Attack by the nucleophile results in a new carbon-oxygen 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.

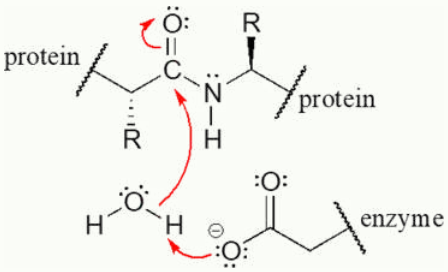
Curved Arrows

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.

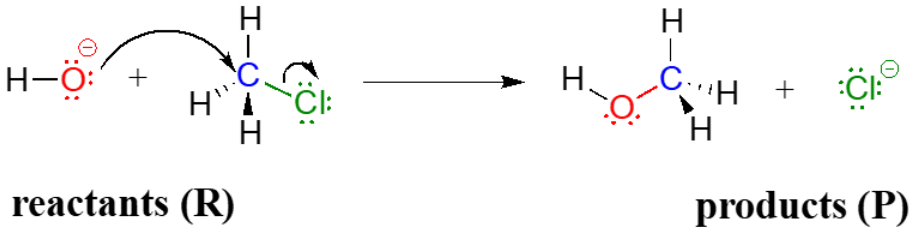
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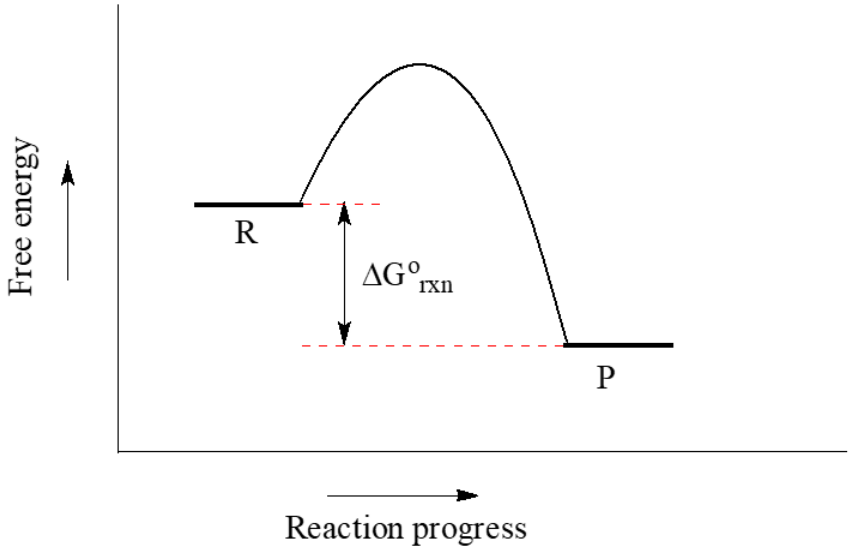
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5.3: A Quick Review of Thermodynamics and Kinetics

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):

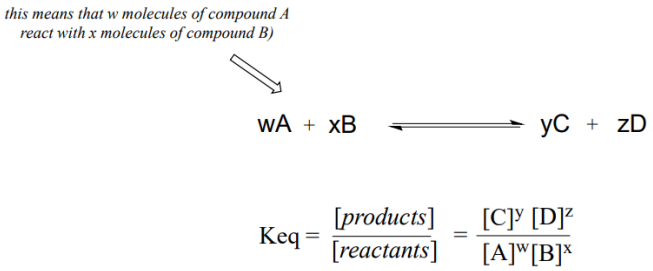
$$\Delta G = \Delta H^o - T\Delta S^o \tag{5.3.1}$$

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:



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'.

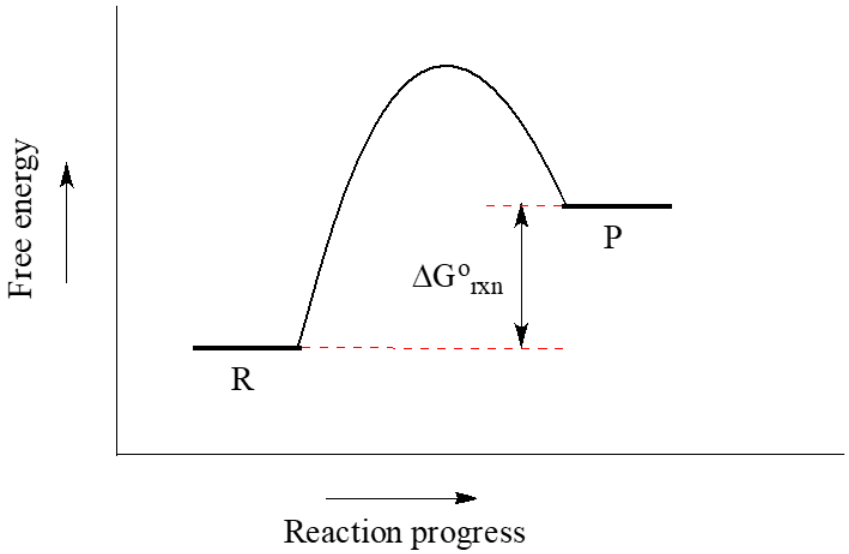
Recall from General Chemistry that the standard Gibbs free energy change for a reaction can be related to the reaction's equilibrium constant (Keq) by the equation:

$$\Delta G^o = -RT \ln K_{eq} \tag{5.3.2}$$

where R is the gas constant (8.314 J mol^{-1} K^{-1}) and T is the temperature in Kelvin (K).

If you do the math, you see that a negative value for ΔG_{rxn}° (an exergonic reaction) corresponds to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

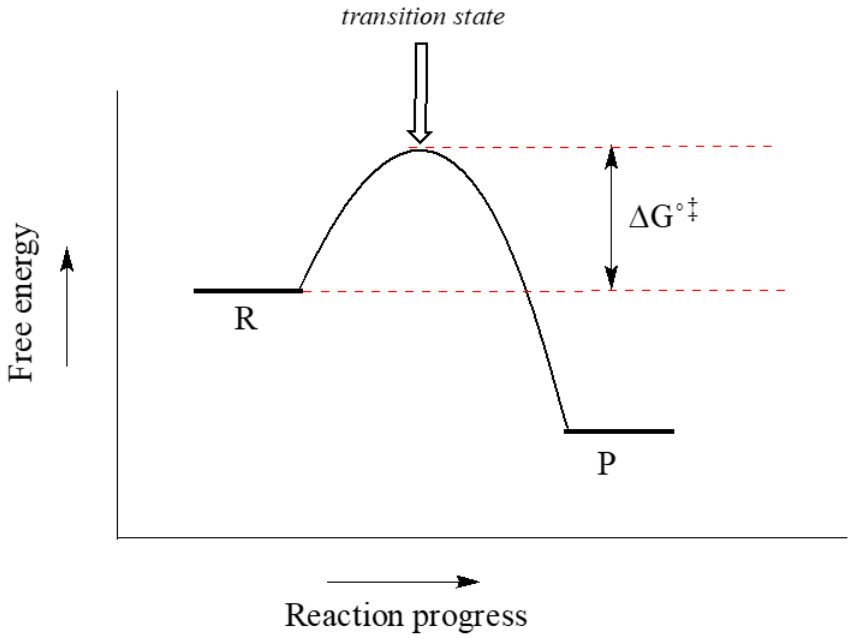
Conversely, an endergonic reaction is one in which the products are higher in energy than the reactants, and energy is absorbed. An endergonic reaction has a positive value of ΔG_{rxn}°, and a K_{eq} between 0 and 1.



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_{rxn}° is positive.

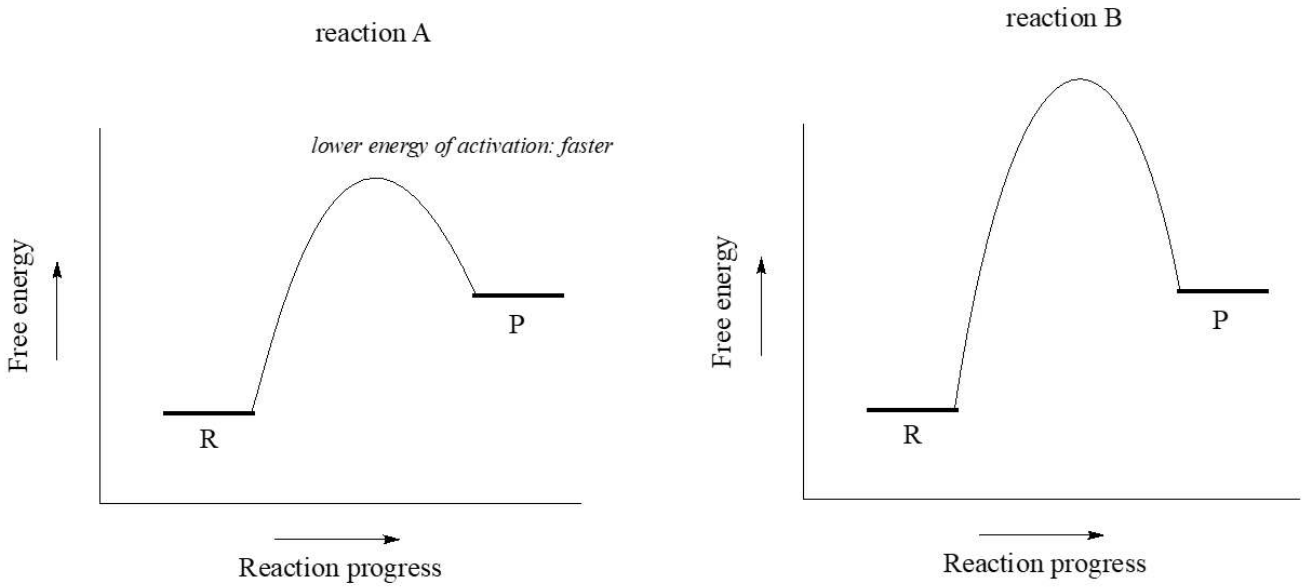
When talking about exergonic, or 'downhill' reactions, chemists sometimes use the term 'driving force' to describe the chemical factor or factors that drive the reaction from higher energy reactant to lower energy product. Using the 'downhill' analogy again, when water flows downhill, the driving force 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.

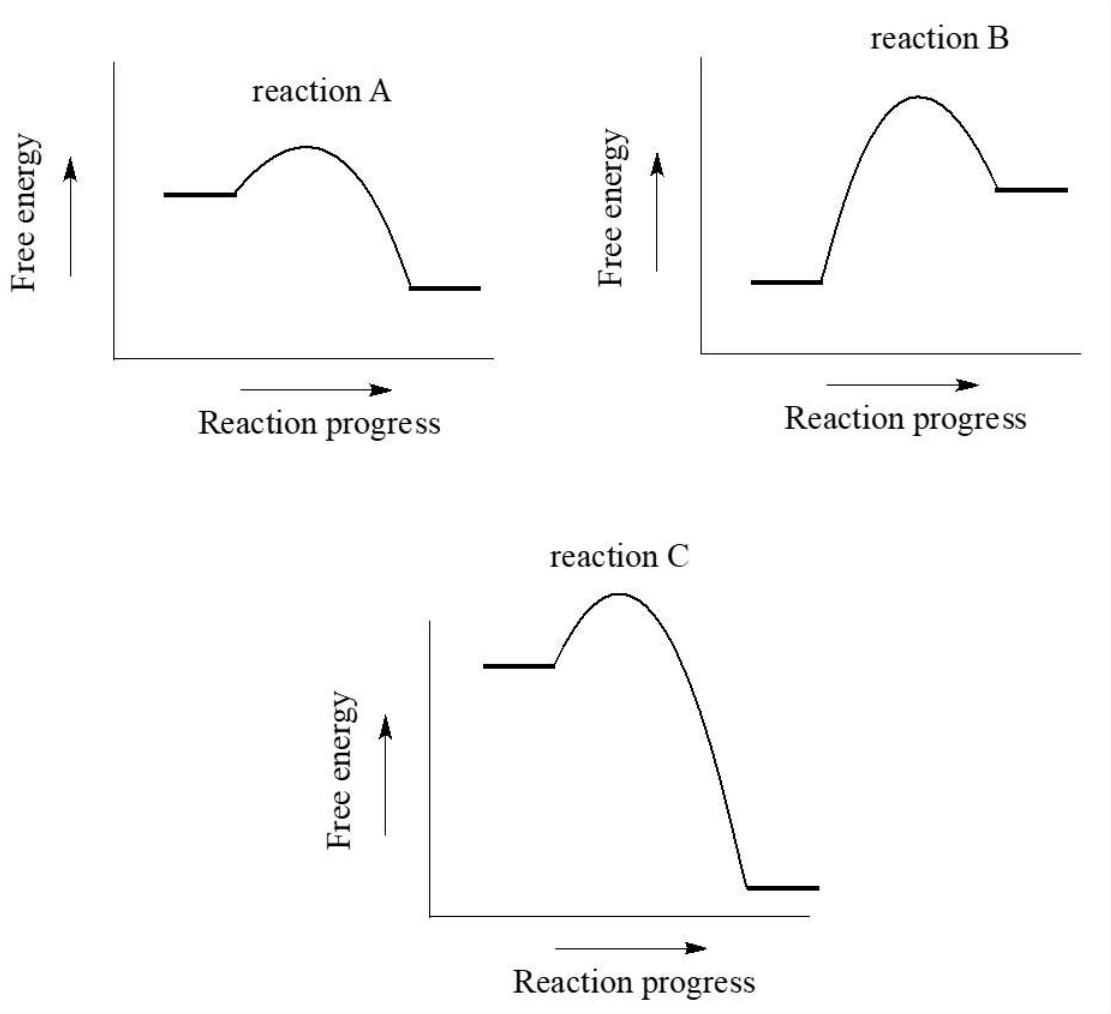
Consider the hypothetical reaction coordinate diagrams below.



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.

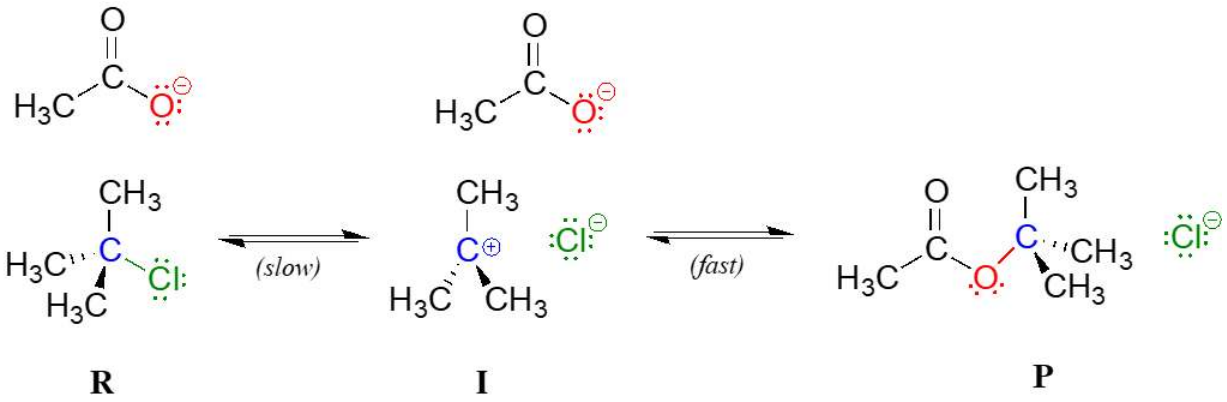
Exercise 5.3.1

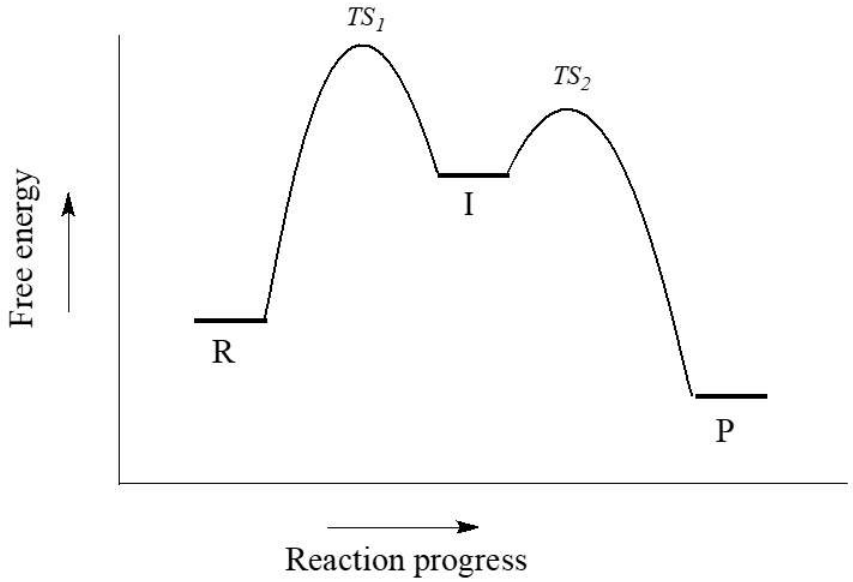
Consider the hypothetical reaction coordinate diagrams below, and assume that they are on the same scale.



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.

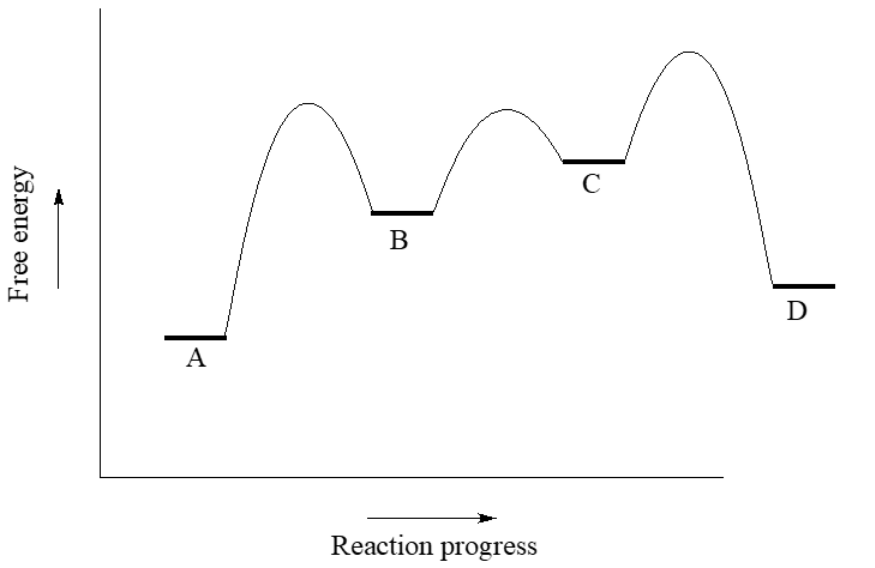
Exercise 5.3.2

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 5.3.3

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?

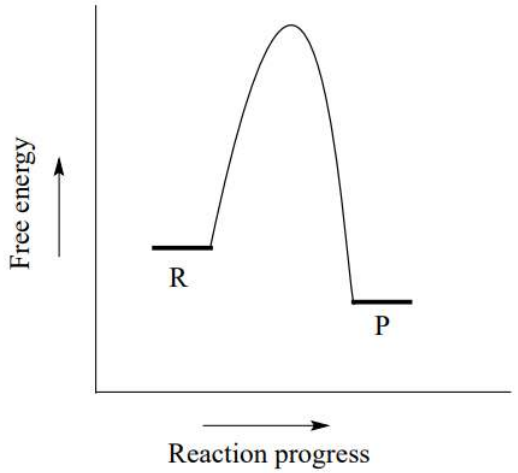
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5.4: Catalysis

Consider a hypothetical reaction $\mathbf{R} \rightarrow \mathbf{P}$ described by the diagram below.



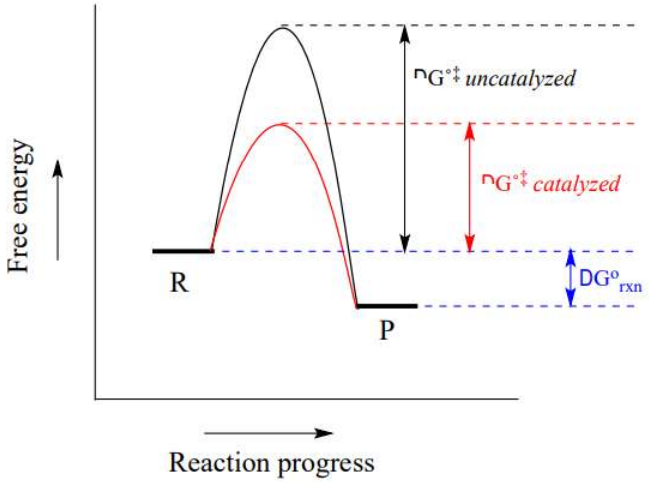
We notice two things about this reaction: it is exergonic, and it has a high activation energy. What this means is that although it is thermodynamically favorable, it is also slow: in other words, equilibrium favors product over reactants, but it will take a long time to reach equilibrium.

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:

$$\text{rate} = k[R] \tag{5.4.1}$$

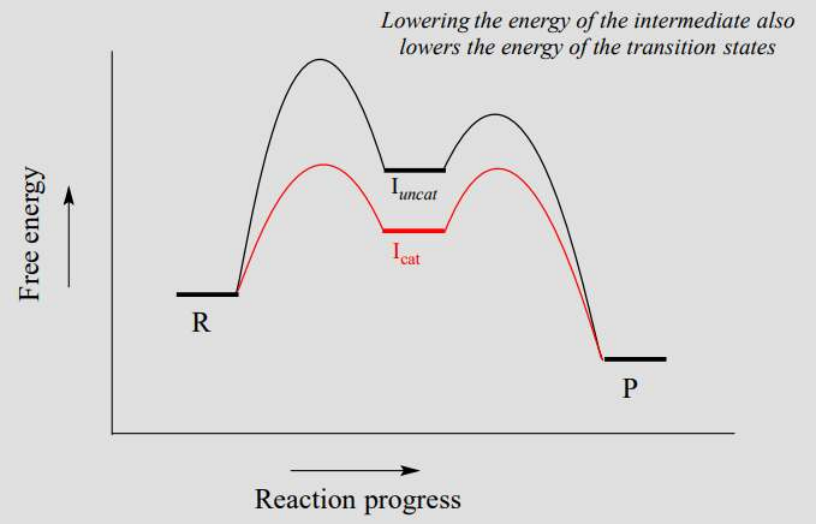
In the laboratory, many organic reactions are run at high temperatures for this very purpose. We could also increase the concentration of the reaction R, which would increase the rate of the reaction without increasing the value of k.

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 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 idea 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.

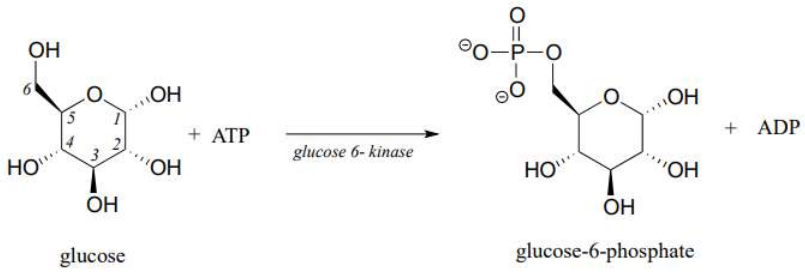
Enzymes are capable of truly amazing rate acceleration. Typical enzymes will speed up a reaction by anywhere from a million to a billion times, and the most efficient enzyme currently known to scientists is believed to accelerate its reaction by a factor of about 10^{17} over the uncatalyzed reaction (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 5.4.1

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 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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5.5: 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 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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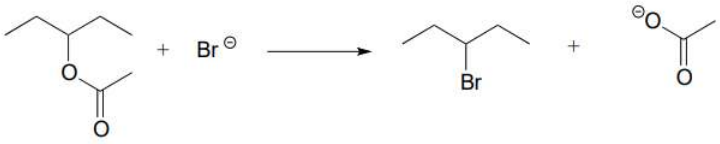
5.6: Overview of Organic Reactivity (Problems)

P5.1: 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.

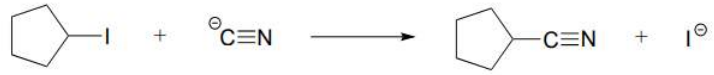
a.



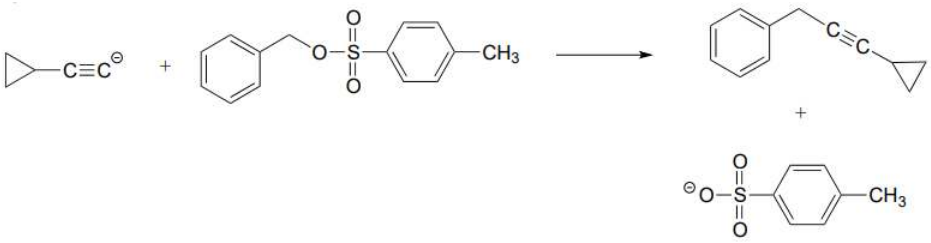
b.



c.

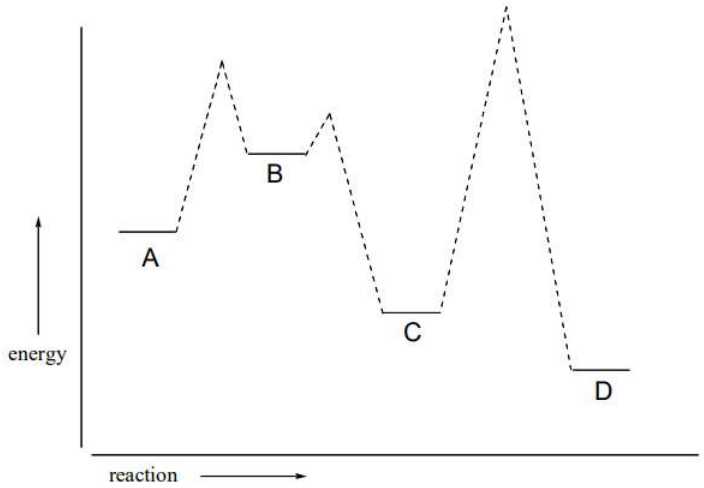


d.

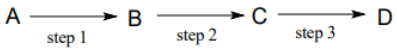


P5.2: Below is a reaction coordinate diagram for a hypothetical reaction.

a. What can you say about the value of $\mathbf{K_{eq}}$ 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?

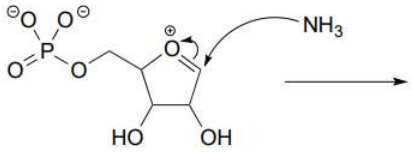


e. e) Below is a diagram of a hypothetical reaction. Step 2 is the rate-determining step, C is the least stable species, B is higher energy than D, and the overall reaction has an equilibrium constant $\mathbf{K_{eq} = 0.33}$. Draw a diagram that corresponds to all of this information.

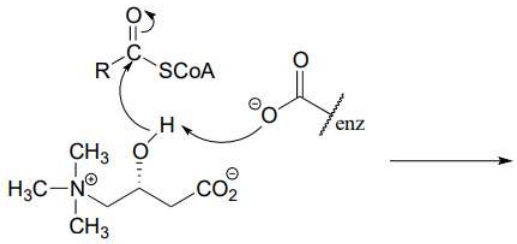


P5.3: Illustrated below are individual steps in some biochemical reaction mechanisms that we will be studying later. For each step, draw the products or intermediate species that would form according to the electron-movement arrows given. Be sure to include all formal charges. You do not need to show stereochemistry.

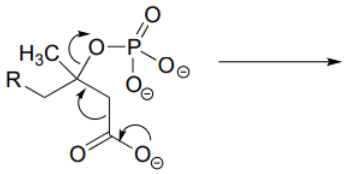
a.



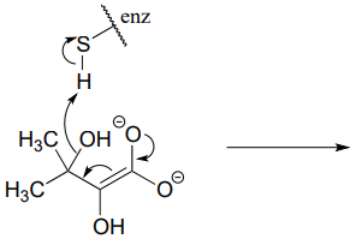
b.



c.

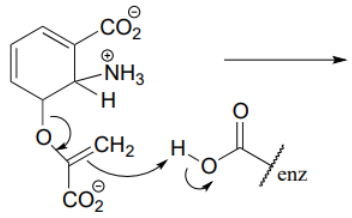


d.



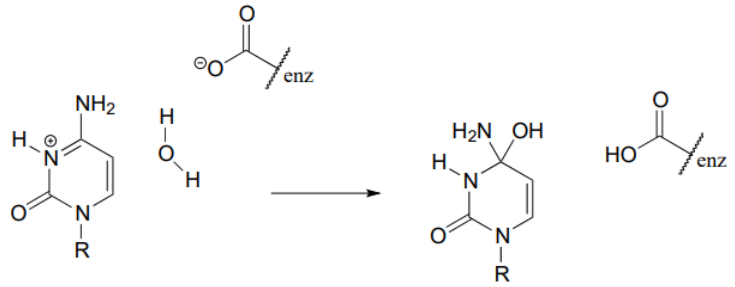
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e.

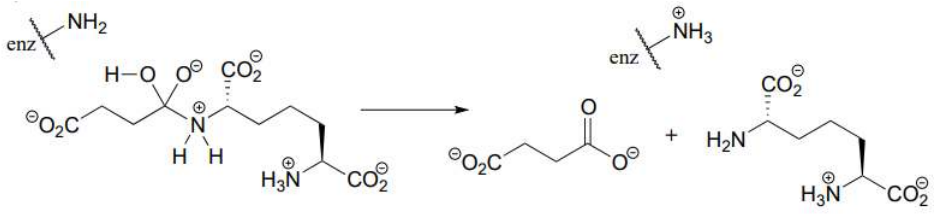


P5.4: Shown below are individual steps in some biochemical reaction mechanisms that we will be studying later. For each, draw curved arrows showing the electron movement taking place.

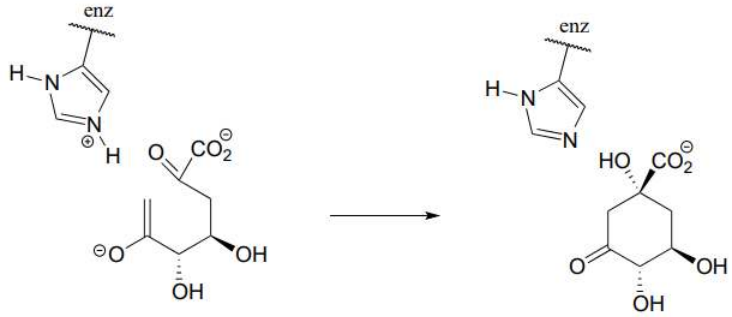
a.



b.



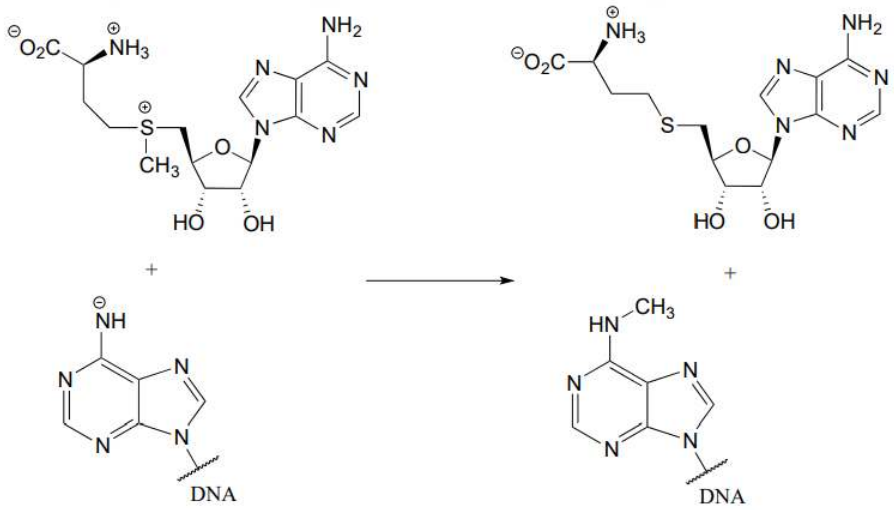
c.



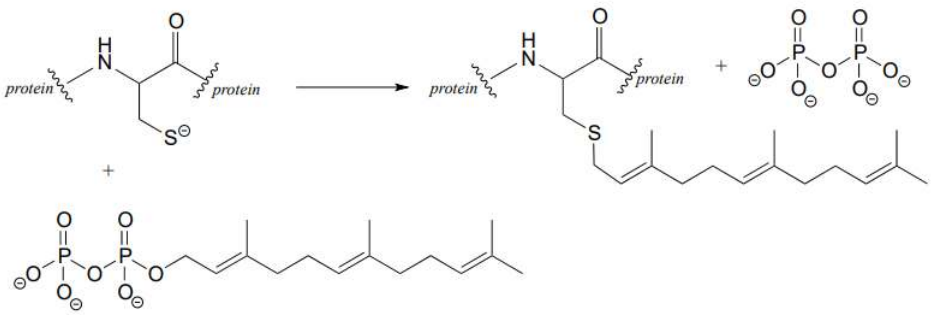
P5.5:

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.

Contributors

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

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5.7: 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

6: Acid-base Reactions

6.1: Prelude to Acid-base Reactions
6.2: Overview of Acid-Base Reactions
6.3: The Acidity Constant
6.4: Structural Effects on Acidity and Basicity
6.5: Acid-base Properties of Phenols
6.6: Acid-base properties of nitrogen-containing functional groups
6.7: Carbon Acids
6.8: Polyprotic Acids
6.9: Effects of enzyme microenvironment on acidity and basicity
6.P: Acid-base Reactions (Problems)
6.S: Acid-base Reactions (Summary)

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6.1: 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 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.

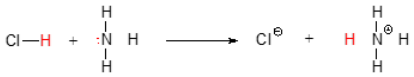
The paper gained some notice, especially from microbiologists, but did not have an immediate impact in clinical practice. Around the world, gastroenterologists continued to treat ulcers with acid blockers. Outside of the mainstream medical community, however, word was getting out that two Australian 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

Contributors

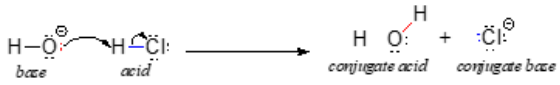
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.2: Overview of Acid-Base Reactions

The Brønsted-Lowry definition of acidity and basicity

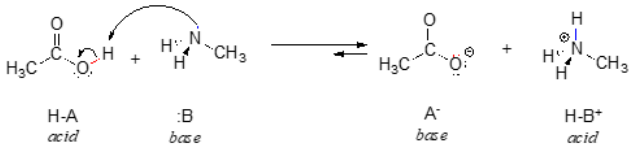
We'll begin our discussion of acid-base chemistry with a couple of essential definitions. The first of these was proposed in 1923 by the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry, and has come to be known as the Brønsted-Lowry definition of acidity and basicity. An acid, by 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:



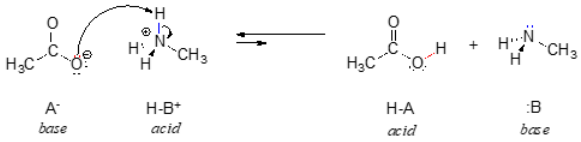
In this reaction, a proton is transferred from HCl (the acid, or proton donor) to hydroxide ion (the base, or proton acceptor). As we learned in the previous chapter, curved arrows depict the movement of electrons in this bond-breaking and bond-forming process.

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:



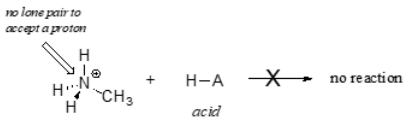
In the reverse of this reaction, acetate ion is the base and methylammonium ion (protonated methylamine) is the acid.



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.

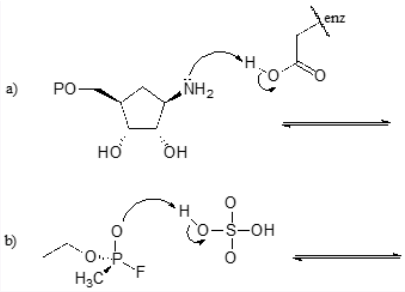


Later, in chapter 14, we will study reactions in which a pair of electrons in a bond of an alkene or aromatic ring act in a basic fashion - but for now, will concentrate on the basicity of non-bonding (lone pair) electrons.

Exercise 6.2.1

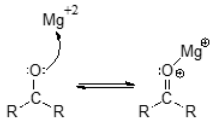
Complete the reactions below - in other words, draw structures for the missing conjugate acids and conjugate bases that result from the curved arrows provided.

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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.

Contributors

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

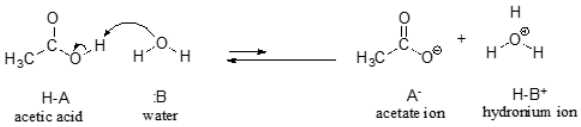
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6.3: The Acidity Constant

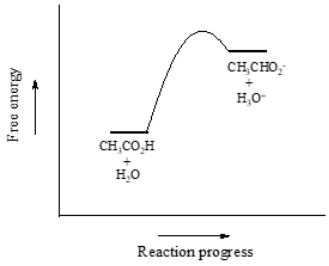
Defining the acidity constant

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:

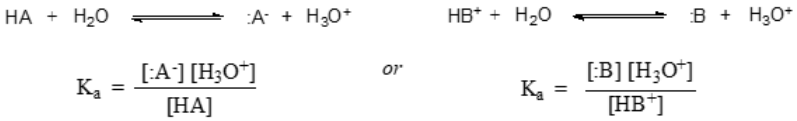
$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]} = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][H_2O]} \tag{6.3.1}$$

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:

$$K_a = K_{eq}[H_2O] = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} \tag{6.3.2}$$

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.

$$pK_a = -logK_a \qquad K_a = 10^{-pK_a} \tag{6.3.3}$$

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:

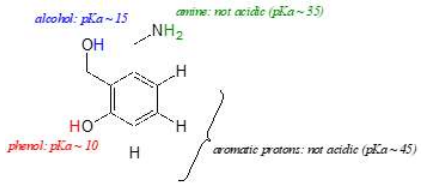
$$pH = -log[H_3O^+] \tag{6.3.4}$$

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 6.3.1

Which is the stronger base, CH_3O^- or CH_3S^-? Acetate ion or ammonia? Hydroxide ion or acetate ion?

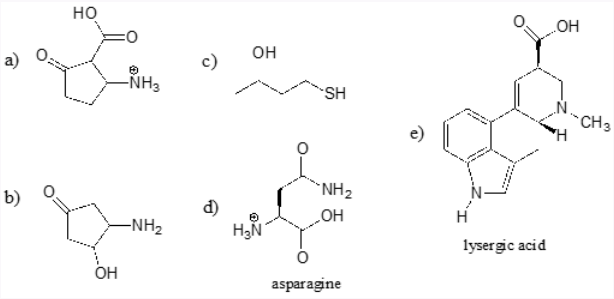
Let's put our understanding of the pK_a concept to use in the context of a more complex molecule. For example, what is the pK_a of the compound below?



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 6.3.2

Identify the most acidic functional group on each of the molecules below, and give its approximate pK_a.



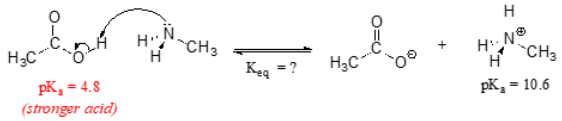
Using pK_a values to predict reaction equilibria

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:

$$K_{eq} = 10^{\Delta pK_a} \tag{6.3.5}$$

$$\Delta pK_a = (\text{pKa of product acid minus pKa of reactant acid}) \tag{6.3.6}$$

Consider a reaction between methylamine and acetic acid:

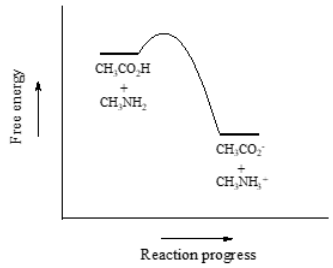


The first step is to identify the acid species on either side of the equation, and look up or estimate their pK_a values. On the left side, the acid is of course acetic acid while on the right side the acid is methyl ammonium ion (in other words, methyl ammonium ion is the acid in the reaction going 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

$$K_{eq} = 10^{\Delta pK_a} = 10^{(10.6-4.8)} = 10^{5.8} = 6.3 \times 10^5 \tag{6.3.7}$$

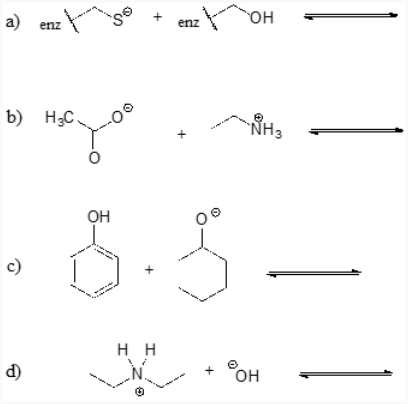
So K_{eq} is a very large number (much greater than 1) and the equilibrium for the reaction between acetic acid and methylamine lies far to the right-hand side of the equation, just as we had predicted. This also tells us that the reaction has a negative Gibbs free energy change, and is thermodynamically 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 6.3.3

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

$$pH = pK_a + \log\left(\frac{\text{concentration of conjugate base}}{\text{concentration of weak acid}}\right) \tag{6.3.8}$$

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 6.3.4

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

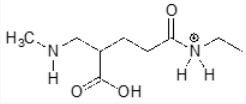
At physiological pH:

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 6.3.5

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 6.3.6

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 $pH2.8$? $pH3.8$? $pH4.8$? $pH5.8$? $pH6.8$?

Exercise 6.3.7

Would you expect phenol to be soluble in an aqueous solution buffered to $pH2$? $pH7$? $pH12$? Explain your answer.

Exercise 6.3.8

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 6.3.9

What is the approximate net charge on a tetrapeptide Cys-Asp-Lys-Glu in $pH 7$ buffer?

Contributors

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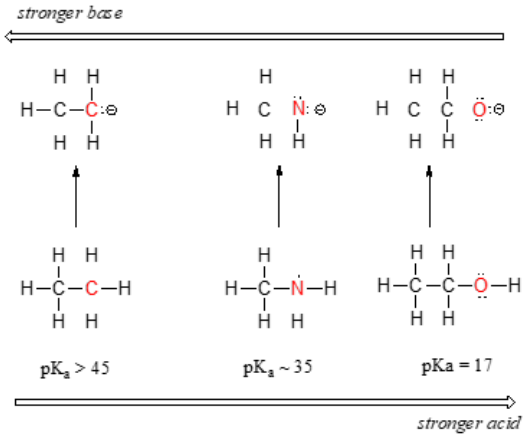
6.4: Structural Effects on Acidity and Basicity

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:



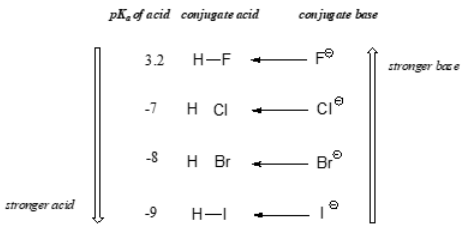
We can see a clear trend in acidity as we move from left to right along the second row of the periodic table from carbon to nitrogen to oxygen. The key to understanding this trend is to consider the hypothetical conjugate base in each case: the more stable (weaker) the conjugate base, the stronger the 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.

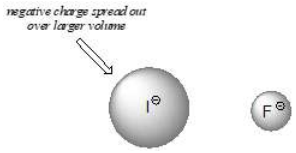
When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best illustrated with the haloacids and halides: basicity, like electronegativity, increases as we move up the column.

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:

$$HCl + F^- \rightarrow HF + Cl^- \tag{6.4.1}$$

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.

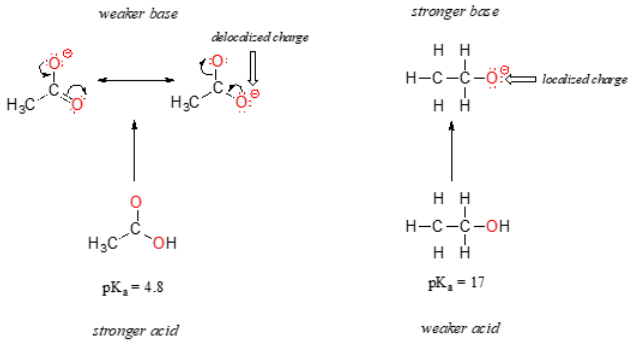
What about total bond energy, the other factor in driving force? If you consult a table of bond energies, you will see that the H-F bond on the product side is more energetic (stronger) than the H-Cl bond on the reactant side: 570 kJ/mol vs 432 kJ/mol, respectively). This also contributes to the driving 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.

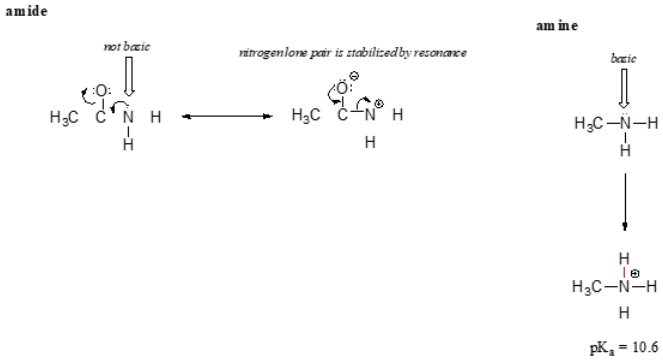


In both species, the negative charge on the conjugate base is located on oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: two resonance contributors can be drawn for the conjugate base, and the negative charge can be delocalized (shared) over two oxygen 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.

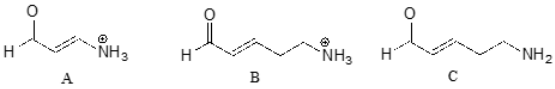
Exercise 6.4.1

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 6.4.2

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

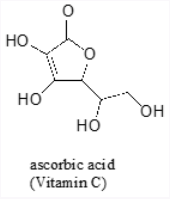


Exercise 6.4.3

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 of 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.

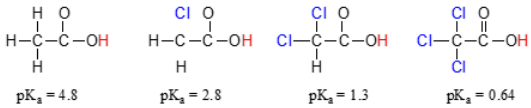
Hint

Try deprotonating each OH group in turn, then use your resonance drawing skills to figure out whether or not delocalization of charge can occur.



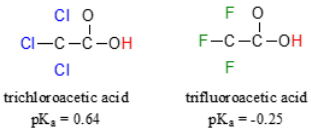
Inductive effects

Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:

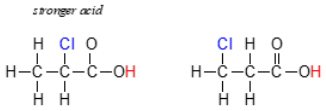


The presence of the chlorine atoms clearly increases the acidity of the carboxylic acid group, but the argument here does not have to do with resonance delocalization, because no additional resonance contributors can be drawn for the chlorinated molecules. Rather, the explanation for this phenomenon 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.

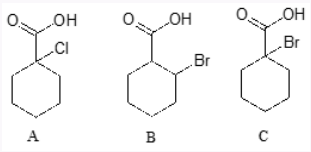


In addition, the inductive takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away.



Exercise 6.4.4

Rank the compounds below from most acidic to least acidic, and explain your reasoning.



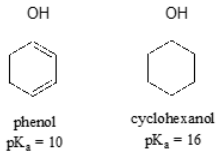
Contributors

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

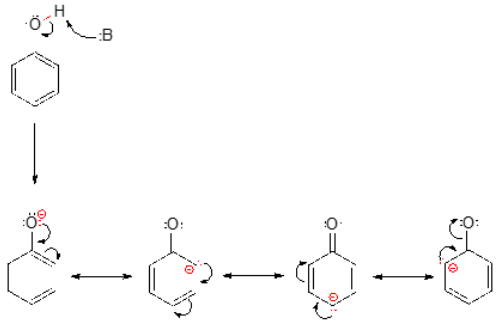
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6.5: Acid-base Properties of Phenols

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.

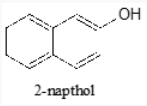


Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

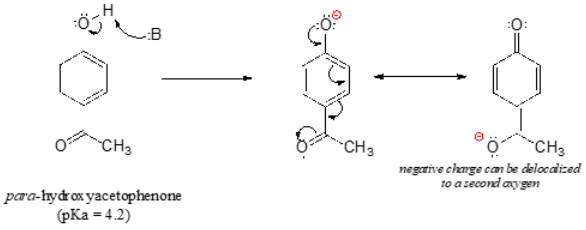
As we begin to study in detail the mechanisms of biological organic reactions, we'll see that the phenol side chain of the amino acid tyrosine (see table 5 at the back of the book), with its relatively acidic pK_a of 9-10, often acts as a catalytic proton donor/acceptor in enzyme active sites.

Exercise 6.5.1

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.

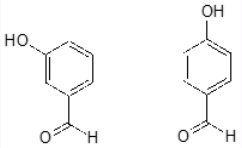


Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also

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.

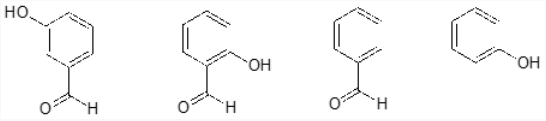
Exercise 6.5.2

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.



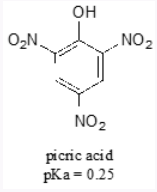
Exercise 6.5.3

Rank the four compounds below from most acidic to least.



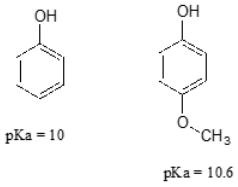
Exercise 6.5.4

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.

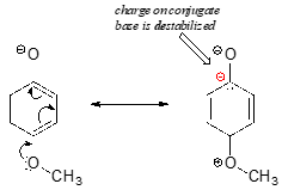


Use a resonance argument to explain why picric acid has such a low pKa.

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.



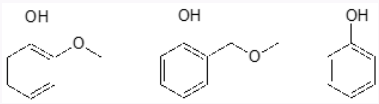
Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making it more basic. It may help to visualize the methoxy group ‘pushing’ electrons towards the lone pair electrons of the phenolate oxygen, causing them to be less 'comfortable' and more reactive.

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 6.5.5

Rank the three compounds below from lowest pKa to highest, and explain your reasoning. Hint - think about both resonance and inductive effects!



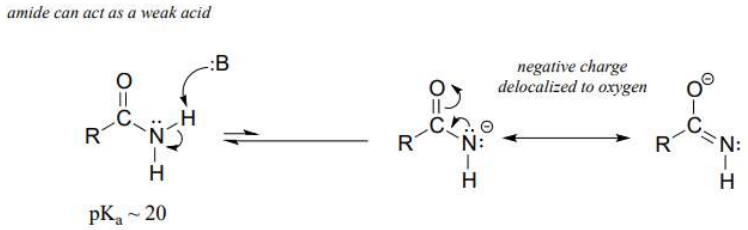
Contributors

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

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6.6: Acid-base properties of nitrogen-containing functional groups

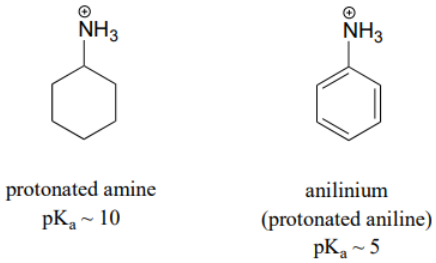
Many of the acid-base reactions we will see throughout our study of biological organic chemistry involve functional groups which contain nitrogen. In general, a nitrogen atom with three bonds and a lone pair of electrons can potentially act as a proton-acceptor (a base) - but basicity is reduced if the 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).



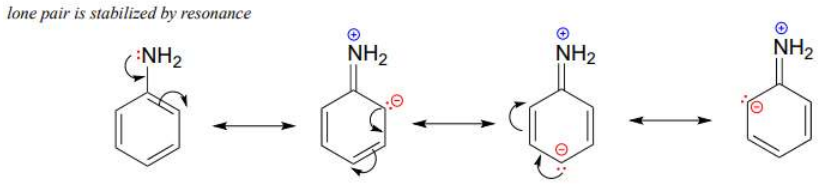
Next, let's consider the basicity of some other nitrogen-containing functional groups.

Anilines

Aniline, the amine analog of phenol, is substantially less basic than an amine.

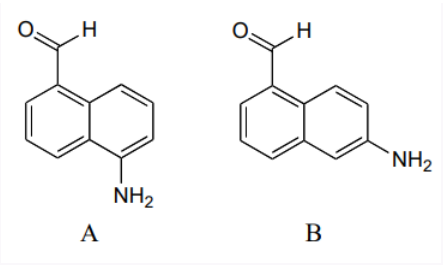


We can use the same reasoning that we used when comparing the acidity of a phenol to that of an alcohol. In aniline, the lone pair on the nitrogen atom is stabilized by resonance with the aromatic p system, making it less available for bonding and thus less basic.



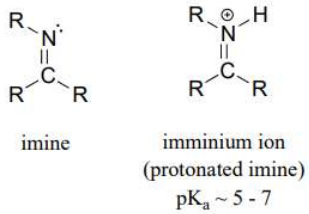
Exercise 6.6.1

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

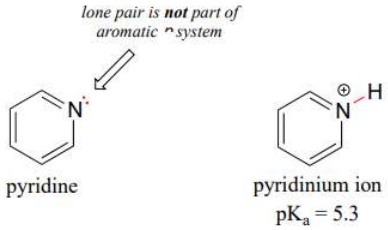
Imines are somewhat less basic than amines: pK_a for a protonated imine is in the neighborhood of 5-7, compared to ~10 for protonated amines. Recall that an imine functional group is characterized by an sp2-hybridized nitrogen double-bonded to a carbon.



The lower basicity of imines compared to amines can be explained in the following way:

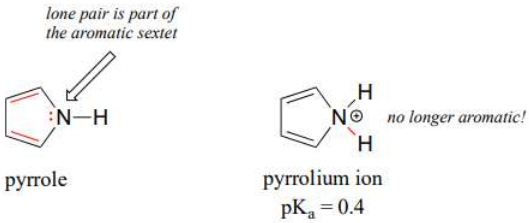
- The lone pair electrons on an imine nitrogen occupy an sp^2 hybrid orbital, while the lone pair electrons on an amine nitrogen occupy an sp^3 hybrid orbital.
- sp^2 orbitals are composed of one part s and two parts p atomic orbitals, meaning that they have about 33% s character. sp^3 orbitals, conversely, 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.

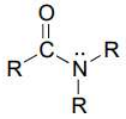
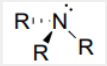
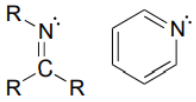
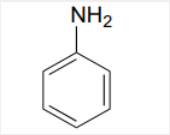
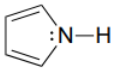


Pyrrole

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.

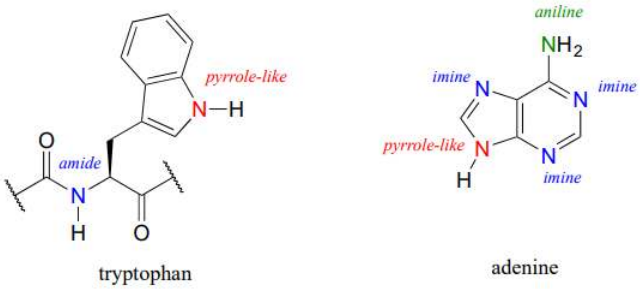


Below is a summary of the five common bonding arrangements for nitrogen and their relative basicity:

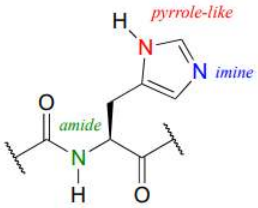
nitrogen group	structure	pK_a of conjugate acid
amide		NA (amide nitrogens are not basic)
amine		~ 10
imine		~ 5 - 7
aniline		~ 5
pyrrole		~ 0

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.

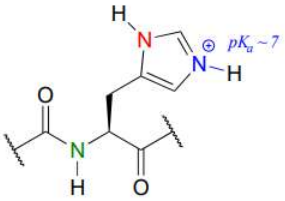
.



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.



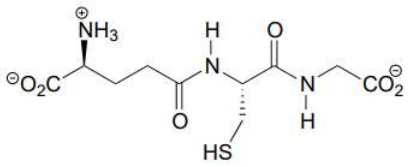
histidine
(deprotonated)



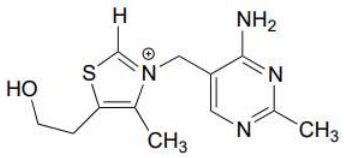
histidinium
(protonated)

Exercise 6.6.2

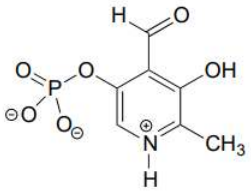
Below are the structures of four 'coenzyme' molecules necessary for human metabolism (we will study the function of all of these in chapter 17).



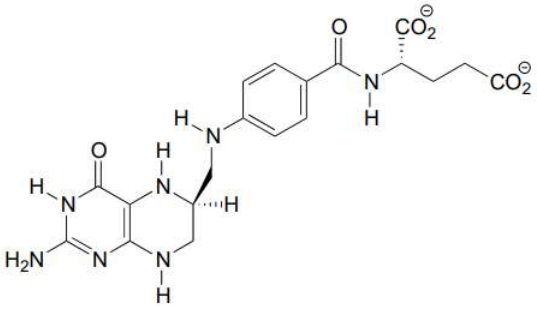
glutathione



thiamine
(vitamin B1)



pyridoxal phosphate
(derived from vitamin B6)



tetrahydrofolate
(derived from folic acid)

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?

Contributors

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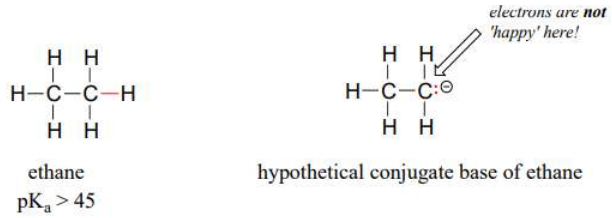
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6.7: Carbon Acids

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.

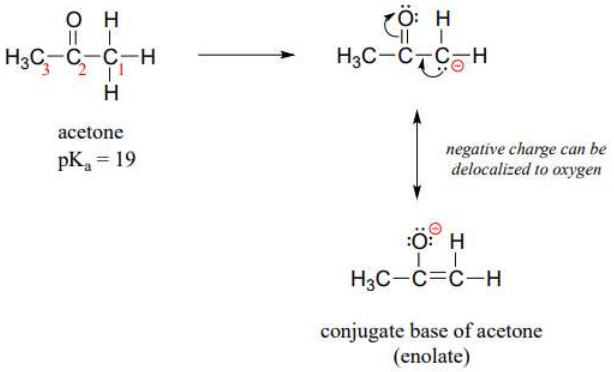
The acidity of α-protons

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.

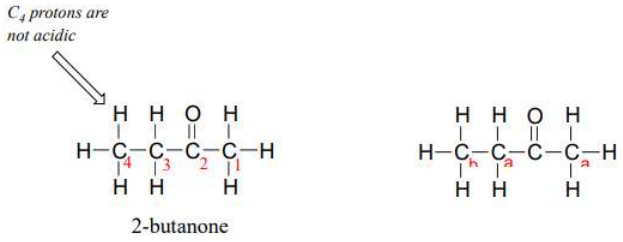


Because carbon is not electronegative and is terrible at holding a negative charge, such carbanion species are extremely unstable.

How, then, can a proton bonded to a carbon be acidic? Remember that an acid becomes stronger if the conjugate base is stabilized, and 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.

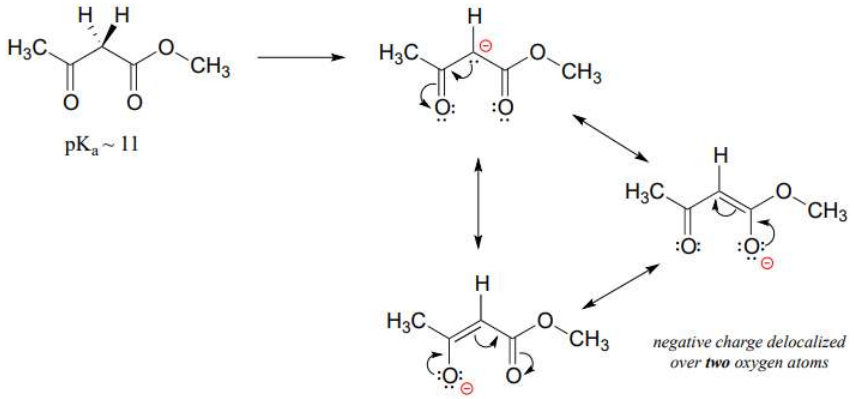


One resonance contributor puts the negative charge on the carbon #1. Due to the presence of the adjacent carbonyl group, however, a second resonance contributor can be drawn in which the negative charge is located on the carbonyl oxygen, where it is much more stable. This type of stabilized carbanion 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.

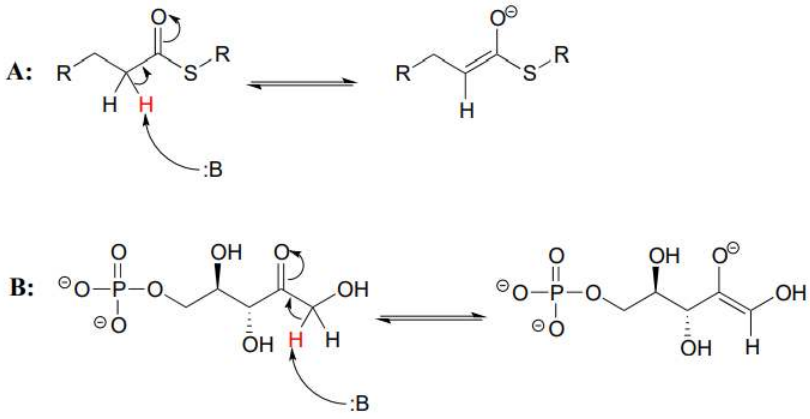


A carbon that is located next to a carbonyl group is referred to as an a-carbon, and any proton bound to it is an a-proton. In 2-butanone, carbons #1 and #3 are a-carbons, and their five protons are a-protons. Carbon #4 is a b-carbon, as it is two positions removed from the carbonyl carbon.

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.

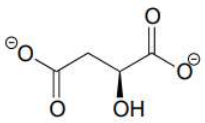


Exercise 6.7.1

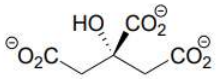
For each molecule shown below,

a. Show the location of all α-protons.

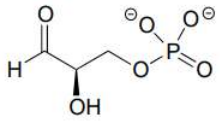
b. Draw the structure(s) of all possible enolate conjugate bases.



malate



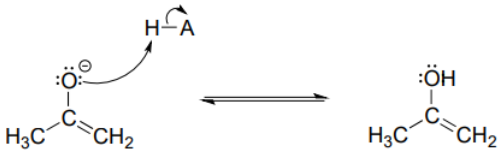
citrate



glyceraldehyde-3-phosphate

Keto-enol tautomers

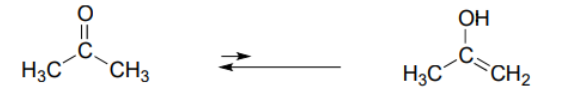
An enolate ion can, of course, be reprotonated at the α-carbon to return the molecule to the ketone or aldehyde form. An alternate possibility is that the oxygen atom, rather than the α-carbon, could be protonated. The species that results from this step is referred to as an enol (this term reflects the fact that an enol contains structural elements of both an alkene 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.

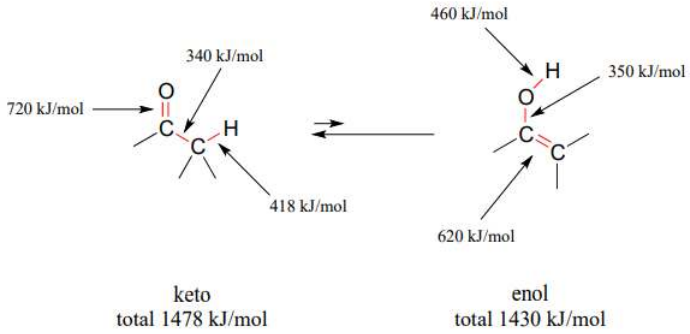
As a general rule, the keto form is lower in energy than the corresponding enol form, and thus the keto form predominates at equilibrium. Acetone, for example, is present at >99% keto form at equilibrium, and the enol form at less than 1%.



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.



Exercise 6.7.2

Draw all of the possible enol forms of the following aldehydes/ketones.

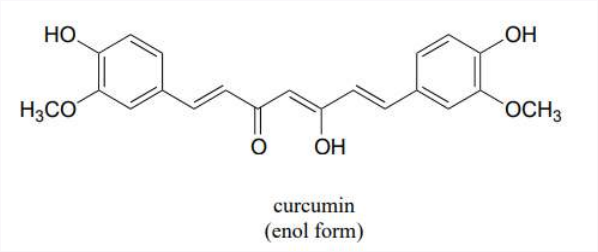
a. 3-pentanone
b. acetaldehyde (IUPAC name ethaldehyde)
c. cyclohexanone
d. 2-pentanone

Exercise 6.7.3

Draw three examples of aldehyde or ketone compounds for which there is no possible enol form.

Exercise 6.7.4

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.



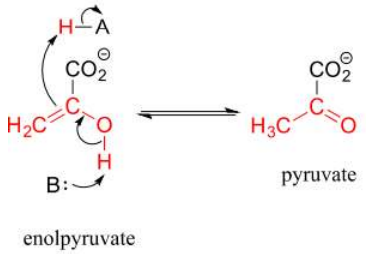
curcumin
(enol form)

Exercise 6.7.5

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.

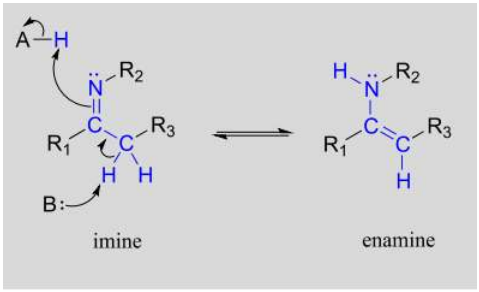


enolpyruvate

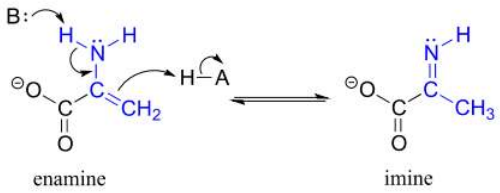
Imine-enamine tautomers

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

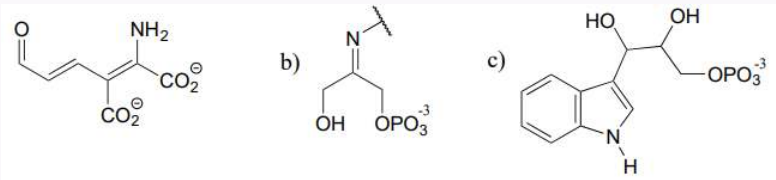


The degradation of serine, for example, involves an enamine to imine tautomerization step: (EC 4.2.1.13)



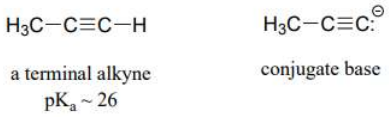
Exercise 6.7.6

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 6.7.7

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.

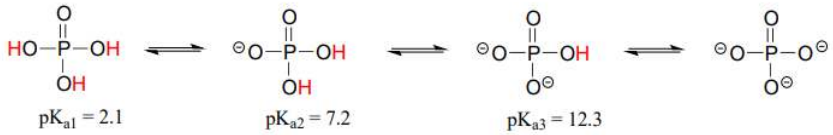
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6.8: Polyprotic Acids

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.



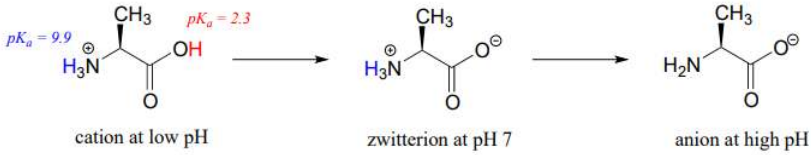
The pK_a values for any polyprotic acid always get progressively higher, because it becomes increasingly difficult to stabilize the additional electron density that results from each successive proton donation. H_3PO_4 is a strong acid because the (single) negative charge on its conjugate base $H_2PO_4^-$ 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 6.8.1

In a buffer at physiological pH, what form(s) of phosphoric acid predominate? What is the average net charge?

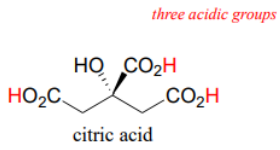
Free amino acids are polyprotic, with pK_a values of approximately 2 for the carboxylic acid group and 9-10 for the ammonium group. Alanine, for example, has the acid constants Double subscripts: use braces to clarify and Double subscripts: use braces to clarify.



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.



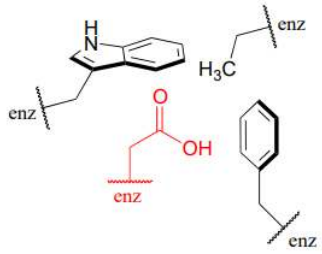
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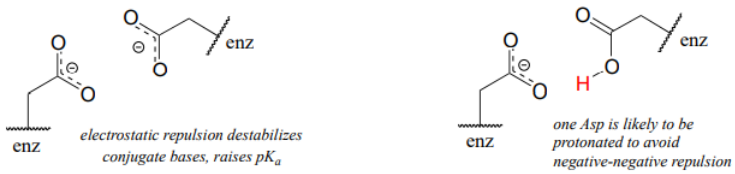
6.9: Effects of enzyme microenvironment on acidity and basicity

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.



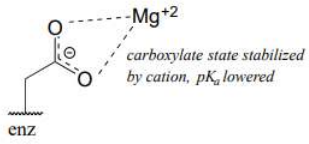
Cut off from the environment of the bulk solvent, the carboxylate group (red in the above figure) is now in a very nonpolar microenvironment, a situation in which the protonated, uncharged state is stabilized relative to the deprotonated, negatively charged state (this is simply another application of 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!)

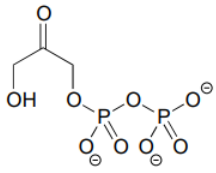
Exercise 6.9.1

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 6.9.2

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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6.P: Acid-base Reactions (Problems)

P6.1: For each pair of molecules below, choose the stronger acid, and explain your choice.

a.



b.



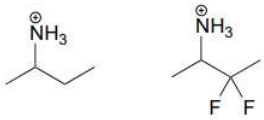
c.



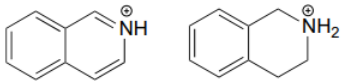
d.



e.



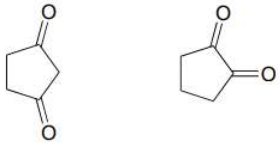
f.



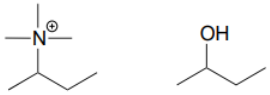
g.



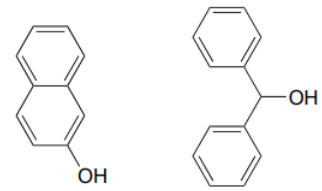
h.



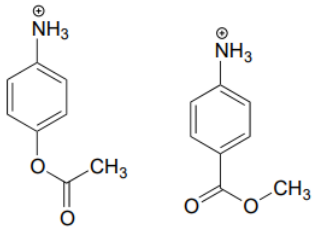
i.



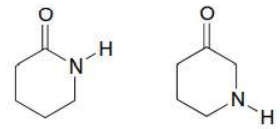
j.



k.

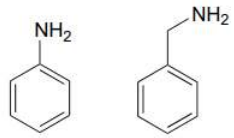


l.

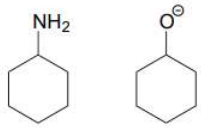


P6.2: For each pair of molecules below, choose the stronger base, and explain your choice.

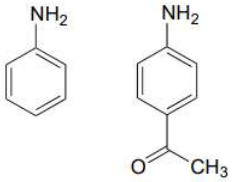
a.



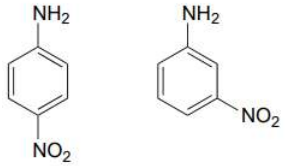
b.



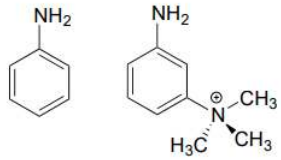
c.



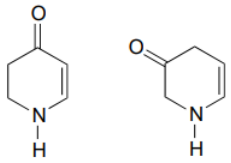
d.



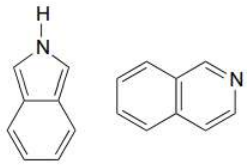
e.



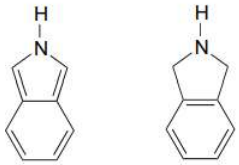
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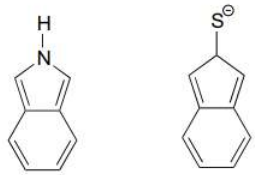
g.



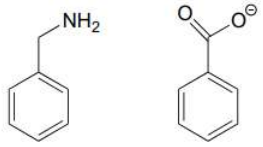
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i.



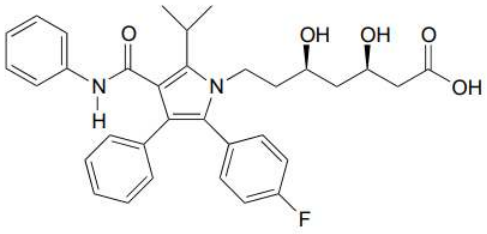
j.



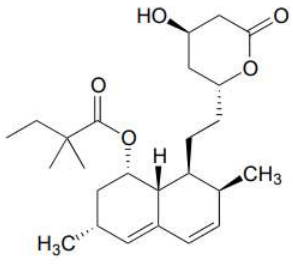
P6.3: Below are the structures of some well-known drugs.

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.)

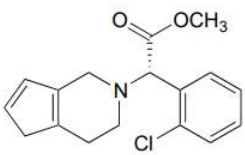
d. Identify the most acidic proton on methadone, and draw the conjugate base that would form if this proton were abstracted by a base. (Methadone is an opiate used in the treatment of heroin addiction.)



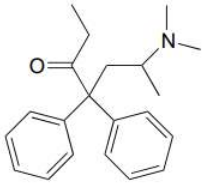
Lipitor



Zocor



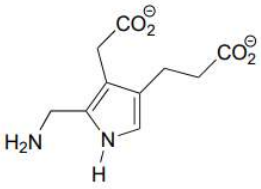
Plavix



methadone

P6.4:

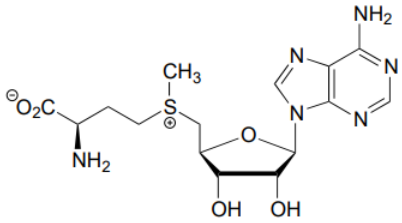
a. Porphobilinogen is a precuror to the biosynthesis of chlorophyll and many other biological molecules. Draw the form of the molecule with a +1 net charge. What would the net charge of the molecule be at physiological ***pH***?



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.

P6.5: 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?

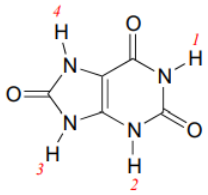


S-adenosylmethionine

P6.6: 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

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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

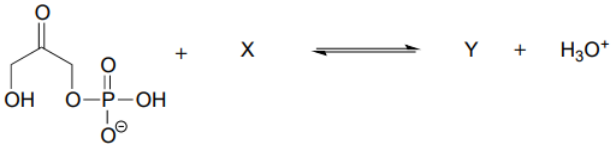
P6.7: Estimate the net charge on a peptide with the sequence P-E-P-T-I-D-E (single-letter amino acid code), when it is dissolved in a buffer with $pH = 7$ (don't forget to consider the terminal amino and carboxylate groups).

P6.8: Estimate the net charge on a dipeptide of sequence D-I.

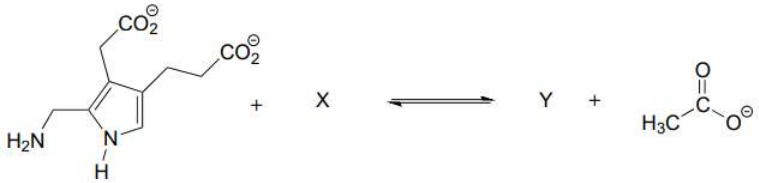
a. in a buffer with $pH = 4.0$
b. in a buffer with $pH = 7.3$
c. in a buffer with $pH = 9.6$

P6.9: 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.

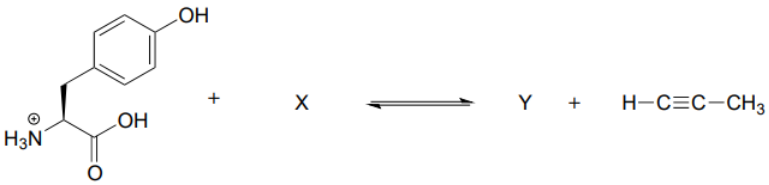
a.



b.



c.

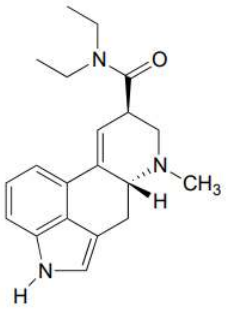


d.



P6.10: Locate the most basic site on the structure of the hallucinogenic drug known as LSD.

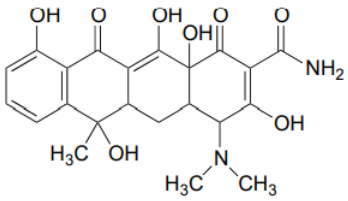
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lysergic acid diethylamide
(LSD)

P6.11:

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

P6.12: 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?

P6.13: (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.

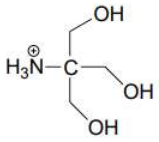
a. a glutamate residue
b. a lysine residue?
c. a histidine residue?
d. a tyrosine residue?
e. How would contact with a magnesium ion effect the pK_a of a bound water molecule in the interior of a protein?

P6.14: 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.

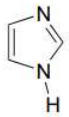
P6.15: The a-protons of ketones are, in general, significantly more acidic than those of esters. Account for this observation using structural arguments.

P6.16: 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.

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'Tris' buffer
$pK_a = 8.1$



imidazole
$pK_a = 7.0$

P6.17: 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.



$pK_a \sim 16$

Contributors

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

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6.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

7: Nucleophilic Substitution Reactions

7.1: Prelude to Nucleophilic Substitution Reactions
7.2: Two Mechanistic Models for Nucleophilic Substitution
7.3: Nucleophiles
7.4: Electrophiles
7.5: Leaving Groups
7.6: Regiochemistry of SN1 Reactions with Allylic Electrophiles
7.7: SN1 or SN2? Predicting the Mechanism
7.8: Biological Nucleophilic Substitution Reactions
7.9: Nucleophilic substitution in the Lab
7.10: Nucleophilic Substitution Reactions (Problems)
7.11: Nucleophilic Substitution Reactions (Summary)

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7.1: 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.

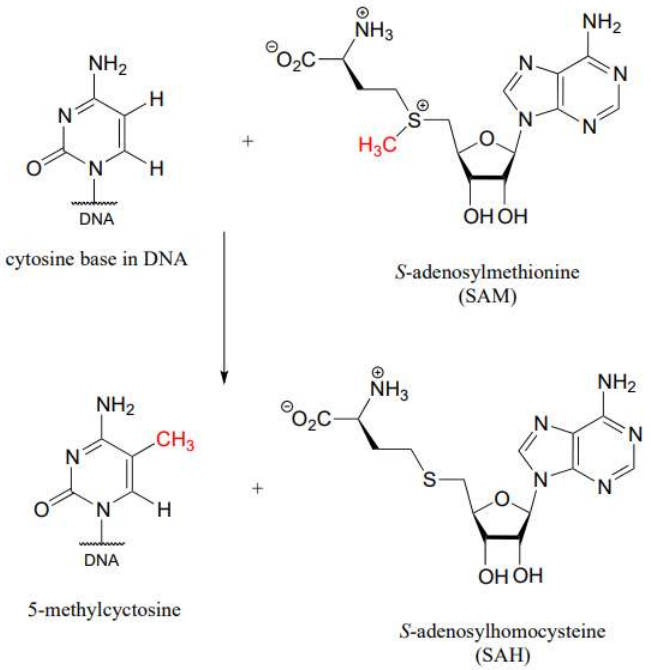


A recent article about Spector in the British newspaper The Guardian (June 1, 2013) begins with an introduction to two middle-aged twin sisters named Barbara and Christine, one of the pairs of twins in the Kings College study group. Although they were treated almost as a single person when growing up, 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.

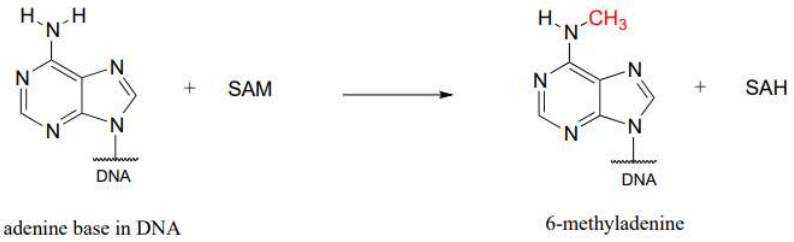
Given that they were born with the exact same DNA and were raised in the same home, where do these differences come from? In public debates about why people are the way they are, a catch phrase that often comes up is 'nature vs. nurture': people argue, in other words, about the relative influence of 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?

Contributors

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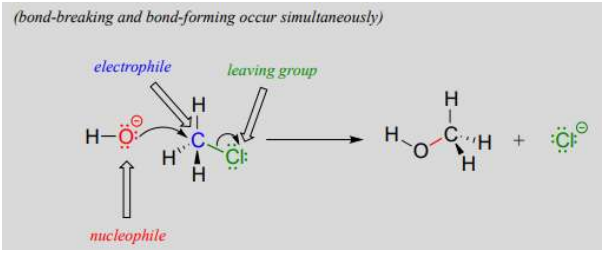
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7.2: Two Mechanistic Models for Nucleophilic Substitution

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.

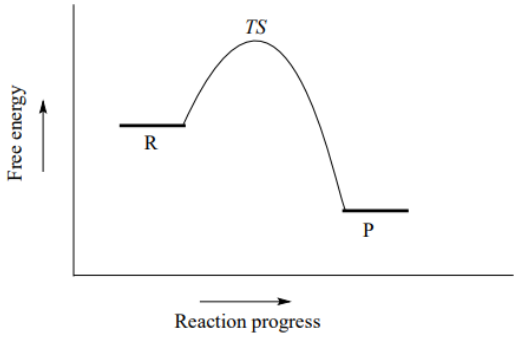
The S_N2 mechanism

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:

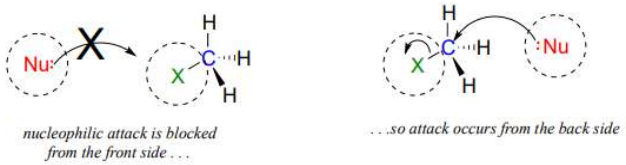


Recall that the hydroxide ion in this reaction is acting as a nucleophile (an electron-rich, nucleus-loving species), the carbon atom of chloromethane is acting as an electrophile (an electron-poor species which is attracted to electrons), and the chloride ion is the leaving group (where the name is self-evident).

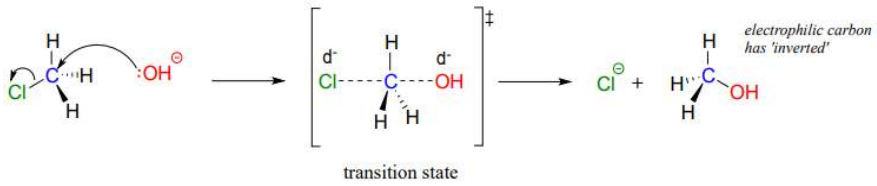
Organic chemists refer to this mechanism by the term 'S_N2', where S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a bimolecular reaction: the overall rate depends on a step in which two separate species collide. A potential energy 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.



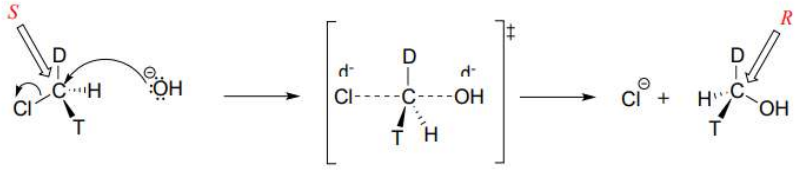
The transition state of the reaction is illustrated by drawing dotted lines to represent the covalent bonds that are in the process of breaking or forming. Because the formal charge on the oxygen nucleophile changes from negative one to zero as the reaction proceeds, and conversely the charge on the 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 7.2.1

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.

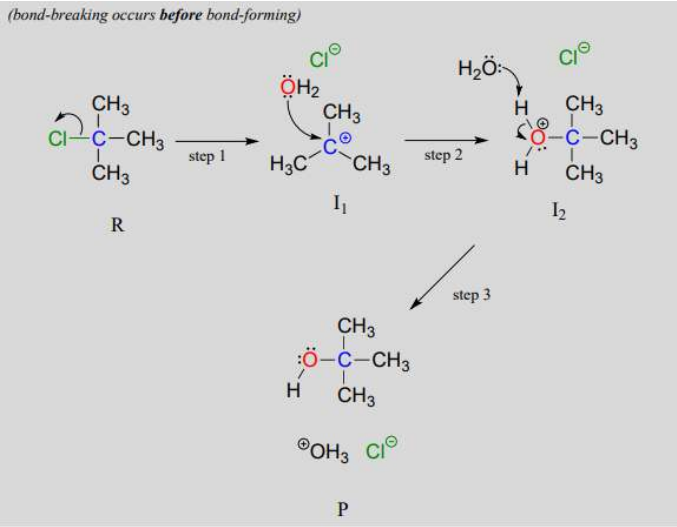
S_N2 reactions proceed with inversion of stereochemical configuration at the electrophilic carbon.

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.)

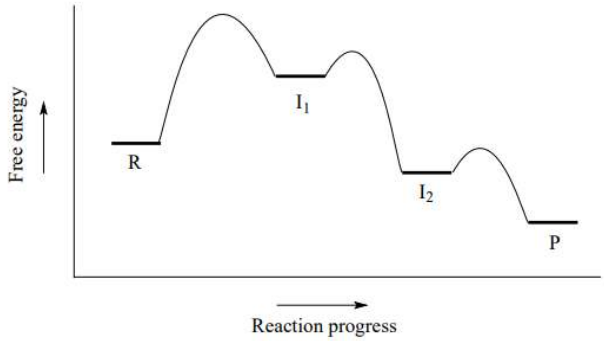
In an S_N1 mechanism the carbon-leaving group bond breaks first, before the nucleophile approaches, resulting in formation of a carbocation intermediate (step 1):



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

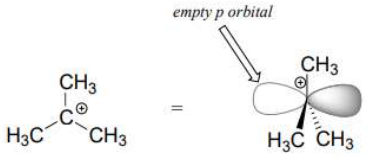
The nucleophilic substitution reactions we have seen so far are examples of hydrolysis. This term is one that you will encounter frequently in organic and biological chemistry. Hydrolysis means 'breaking with water': in a hydrolysis reaction, a water molecule (or hydroxide ion) participates in the breaking 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.

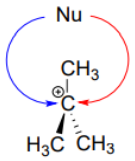
Exercise 7.2.2

Draw a mechanism for the S_N1 solvolysis of tert-butyl chloride in methanol. What new functional group has been formed?

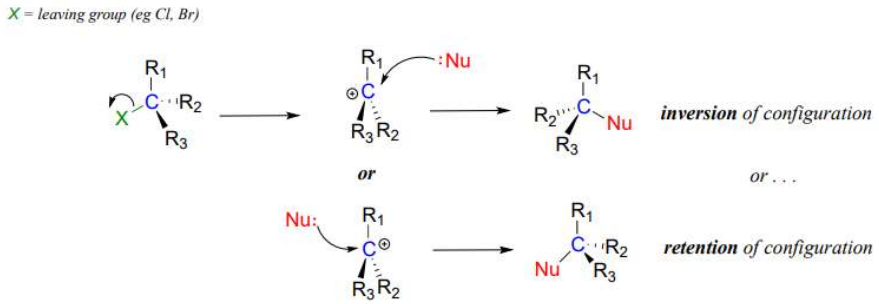
We saw that S_N2 reactions result in inversion of stereochemical configuration at the carbon center. What about the stereochemical outcome of S_N1 reactions? Recall that a carbocation is sp^2-hybridized, with an empty p orbital perpendicular to the plane formed by the three sigma bonds:



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).

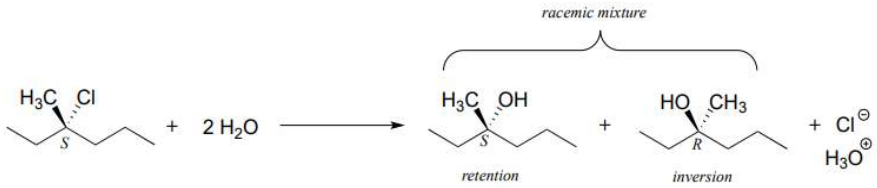


Consider an S_N1 reaction with a chiral tertiary alkyl chloride:



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 7.2.3

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 7.2.4

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)

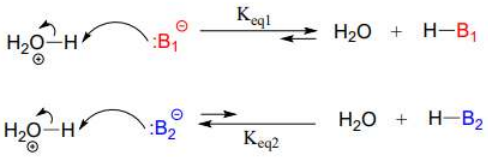
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7.3: Nucleophiles

What is a nucleophile?

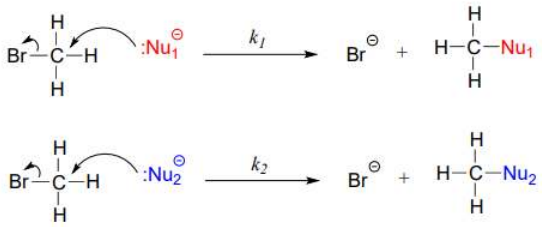
A nucleophile is an atom or functional group with a pair of electrons (usually a non-bonding, or lone pair) that can be shared. The same, however, can be said about a base: in fact, bases can act as nucleophiles, and nucleophiles can act as bases. What, then, is the difference between a base and a nucleophile?

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?

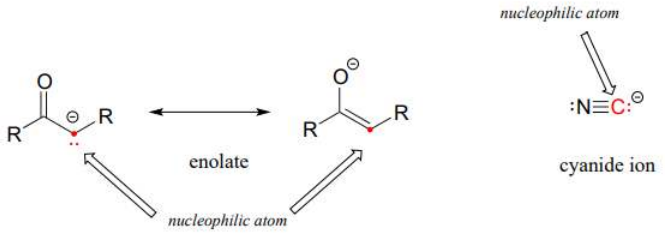


*$Nucleophile_1$ is more powerful than $Nucleophile_2$: reacts **faster** with a common electrophile.*
rate constant $k_1 > k_2$

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:

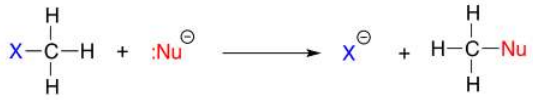
The horizontal periodic trend in nucleophilicity

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).

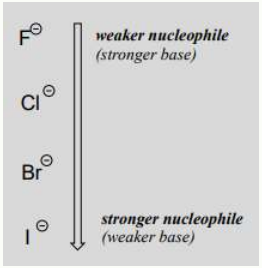
The vertical periodic trend for nucleophilicity is somewhat more complicated that for basicity, and depends on the solvent in which the reaction is taking place. Take the general example of the S_N2 reaction below:



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

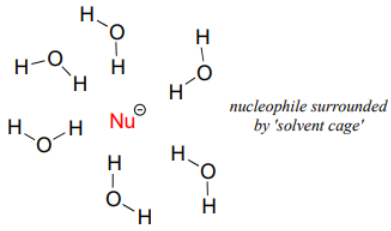
(opposite of the trend in basicity!)



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



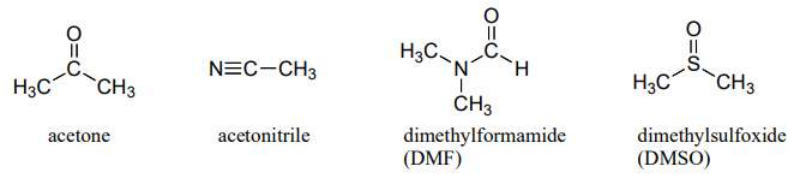
For the nucleophile to attack in an S_N2 reaction, the nucleophile-solvent hydrogen bonds must be disrupted - in other words, the nucleophilic electrons must 'escape through the bars' of the solvent cage. A weak base like iodide ion interacts weakly with the protons of the solvent, so these interactions 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.

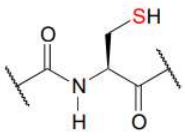
Note

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.

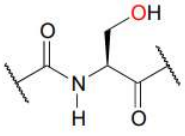
Structures of some of the most common polar aprotic solvents are shown below. These solvents are commonly used in laboratory nucleophilic substitution reactions.



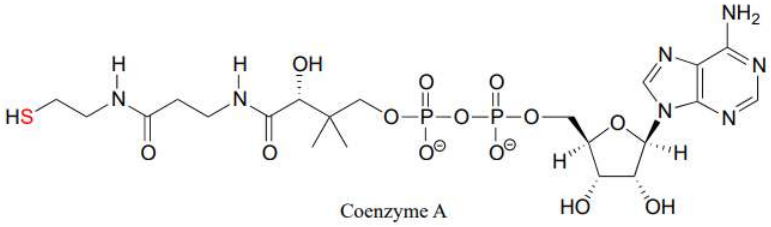
In biological chemistry, the most important implication of the vertical periodic trend in nucleophilicity is that thiols are more *nucleophilic* than alcohols. The thiol group in a cysteine amino acid residue, for example, is more nucleophilic than the alcohol group on a serine, and cysteine often acts 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



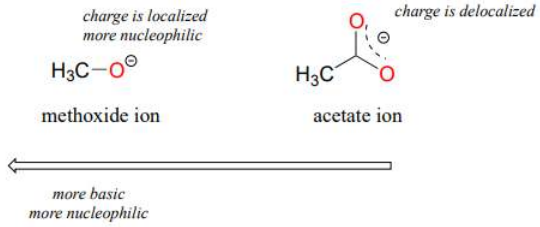
serine residue



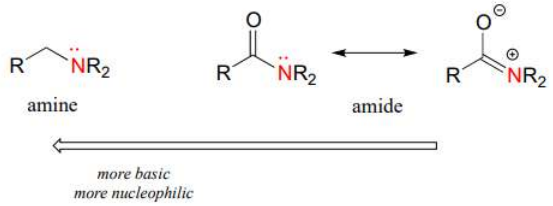
Coenzyme A

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.

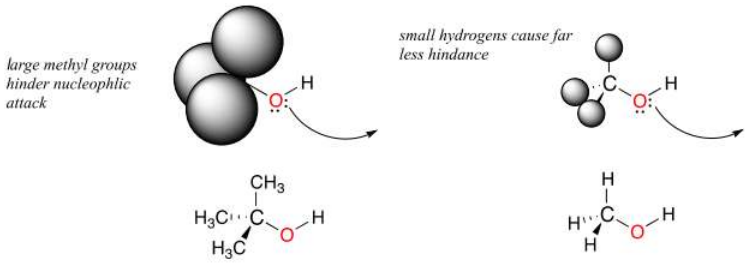


Exercise 7.3.1

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 7.3.2

Which is the better nucleophile - a cysteine side chain or a methionine side chain? A serine or a threonine? Explain.

Exercise 7.3.3

In each of the following pairs of molecules/ions, which is expected to react more rapidly with CH_3Cl in acetone solvent? Explain your choice.

a. phenolate ion (deprotonated phenol) or benzoate ion (deprotonated benzoic acid)?
b. water or hydronium ion?
c. trimethylamine or triethylamine?
d. chloride ion or iodide ion?
e. CH_3NH^- or $CH_3CH_2NH_2$?
f. acetate ion or trichloroacetate ion?
g. aniline or 4-methoxyaniline?
h. phenolate ion or 2,6-dimethylphenolate ion?

Contributors

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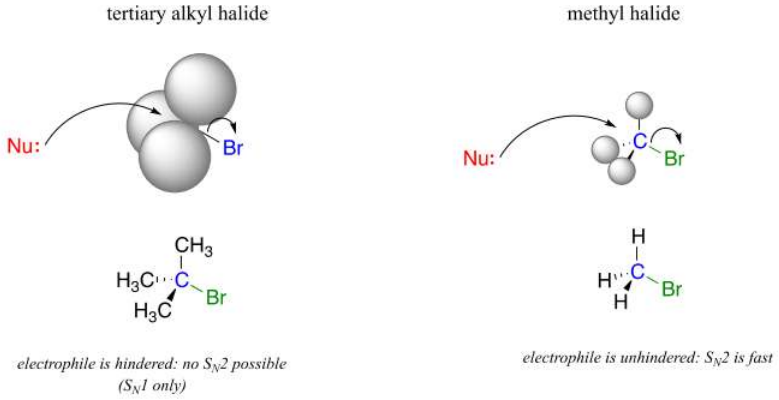
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7.4: Electrophiles

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.

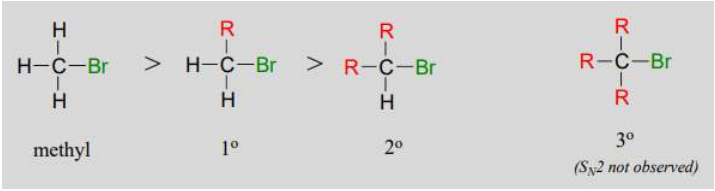
Steric hindrance at the electrophile

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.

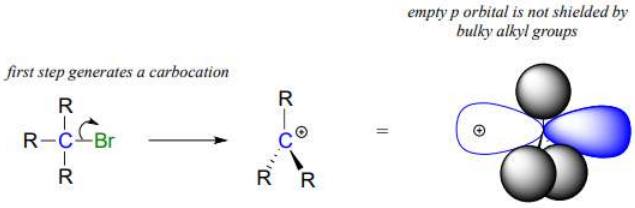


Exercise 7.4.1

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

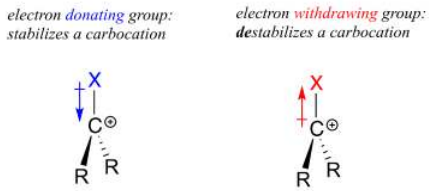
What, then, are the characteristics of an electrophile that favor an S_N1 reaction pathway as opposed to an S_N2 pathway? We know that the rate-limiting step of an S_N1 reaction is the first step: loss of the leaving group and formation of the carbocation intermediate. Accordingly, the rate of an S_N1 reaction depends to a large extent on the stability of the carbocation intermediate.

The critical question now becomes:

What stabilizes a carbocation?

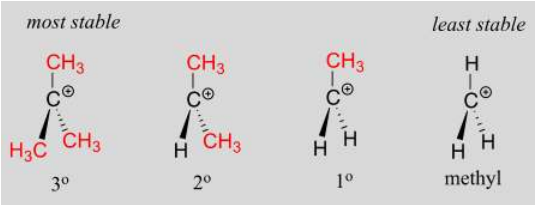
Think back to Chapter 7, when we were learning how to evaluate the strength of an acid. The critical question there was: “how stable is the conjugate base that results when this acid donates its proton”? In many cases, this conjugate base was an anion – a center of excess electron density. Anything that 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.

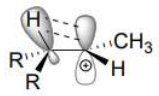


A positively charged species such as a carbocation is electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Alkyl groups, because of the electrons in their carbon-carbon and carbon-hydrogen bonds, are weak electron-donating groups, 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:



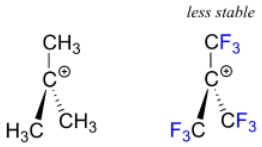
Another way to explain this trend in carbocation stability involves the phenomenon of hyperconjugation, in which the empty p orbital of a carbocation is stabilized by overlap with a σ bond on an adjacent carbon. This overlap effectively spreads the positive charge over a larger area. The figure below shows the empty p orbital of a secondary carbocation being stabilized by hyperconjugation with an adjacent $C-H$ σ bond.



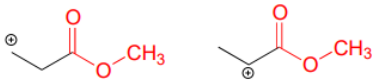
hyperconjugation

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.



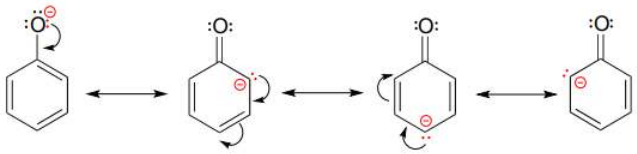
Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the $C=O$ double bond. It is possible to demonstrate in the laboratory (we'll see how in problem 14.x) that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.



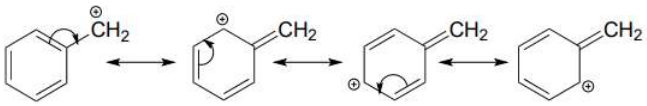
A: more stable **B**: less stable

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.



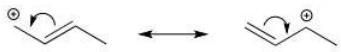
A positive charge is also stabilized when it can be delocalized over more than one atom. Consider a benzylic carbocation, where the positively-charged carbon is bonded directly to an aromatic ring. A benzylic carbocation is stabilized by the resonance electron-donating effect of the aromatic ring. Three additional resonance structures can be drawn for the carbocation in which the positive charge is located on one of three aromatic carbons:



Exercise 7.4.2

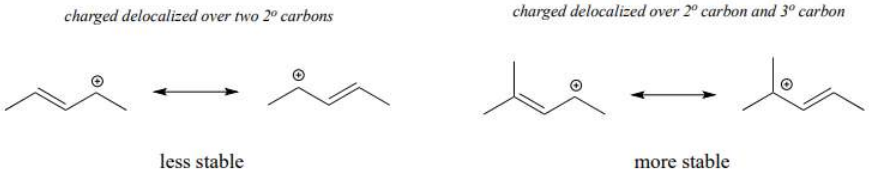
Fill in the missing numbers in this statement: The conjugated \(p\) system in the benzylic carbocation above is composed of _____ \(p\) orbitals overlapping to share _____ \(\pi \) electrons.

Allylic carbocations, where the positively charged carbon is adjacent to a double bond, are stabilized by resonance delocalization of the posive charge.



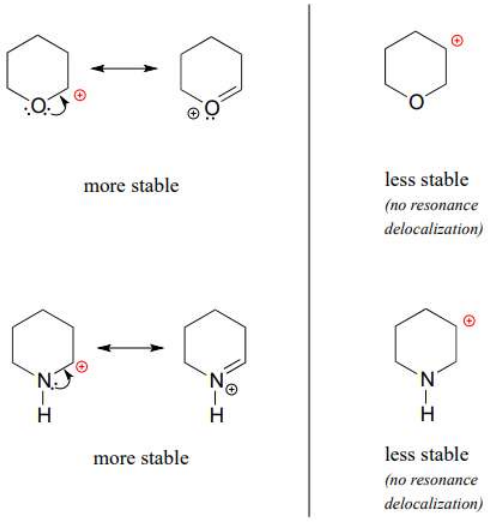
an allylic carbocation

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.



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.

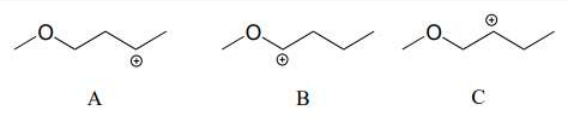
Consider the two pairs of carbocation species below:



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.

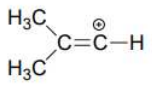
Exercise 7.4.3

Rank the following carbocations from most to least stable:



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Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are highly unstable.



a vinylic carbocation
(very unstable)

Exercise 7.4.4

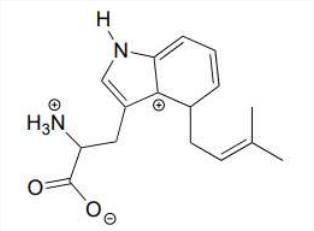
Explain why vinylic carbocations are unstable. (Hint:)

Hint

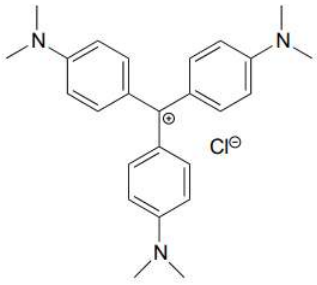
Think about hybridization and electronegativity.

Exercise 7.4.5

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

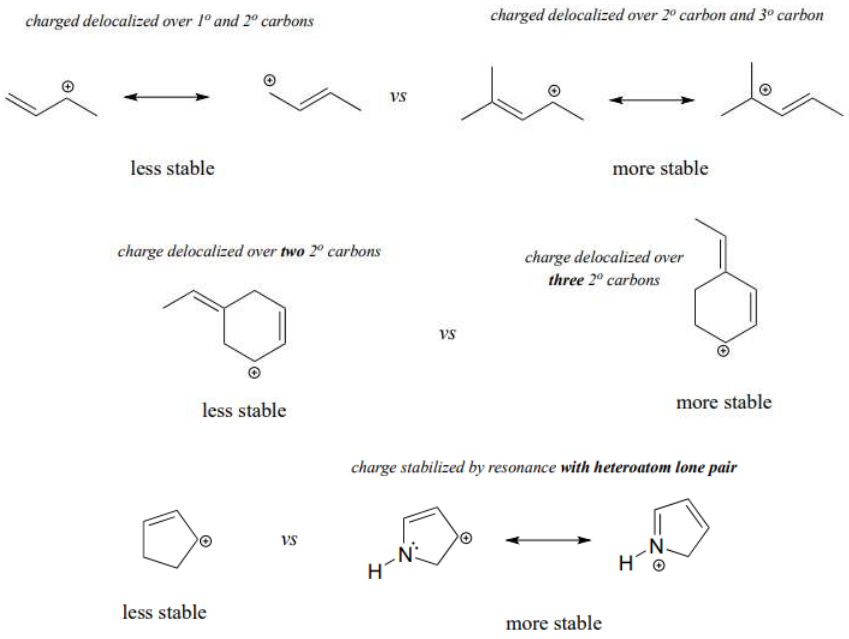
Exercise 7.4.6

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

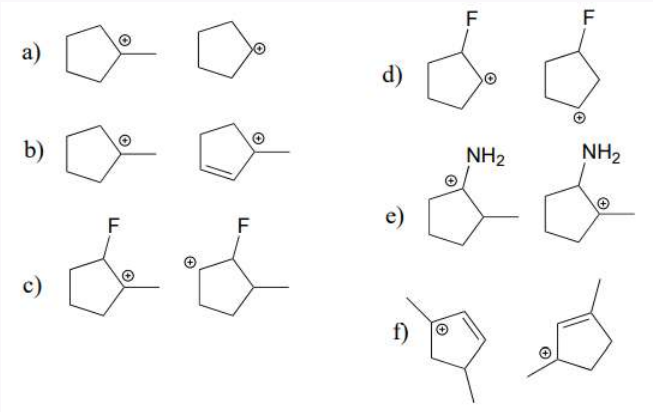
I. More substituted carbocations are more stable than less substituted carbocation (eg. tertiary carbocations are more stable than secondary carbocations).
II. Nearby electronegative atoms can decrease carbocation stability by the inductive effect.
III. Allylic and benzylic carbocations are stabilized 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 7.4.7

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.



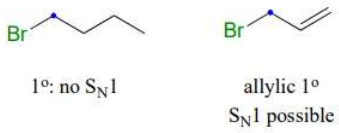
Now, back to our discussion of the electrophile in an S_N1 reaction:

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

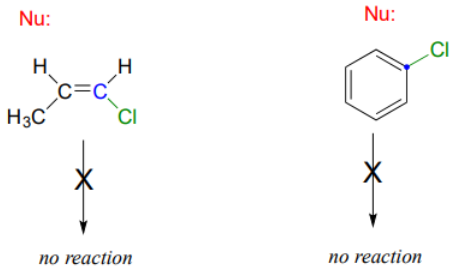
An allylic secondary alkyl bromide would undergo S_N1 substitution more rapidly than the allylic primary alkyl bromide, because the relevant carbocation is more substituted and thus more stable.



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.



no reaction | *no reaction*

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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7.5: 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

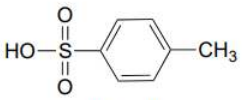
In our general discussion of nucleophilic substitution reactions, we have until now been using chloride ion as our common leaving group. Alkyl chlorides are indeed common reactants in laboratory nucleophilic substitution reactions, as are alkyl bromides and alkyl iodides. Iodide, which is the least basic 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*

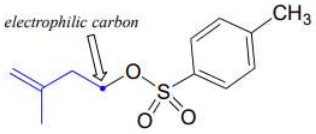
This trend is evident when you compare the relative rates of S_N2 reactions of four halomethanes with a common nucleophile and solvent: iodomethane reacts fastest, fluoromethane the slowest.

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.



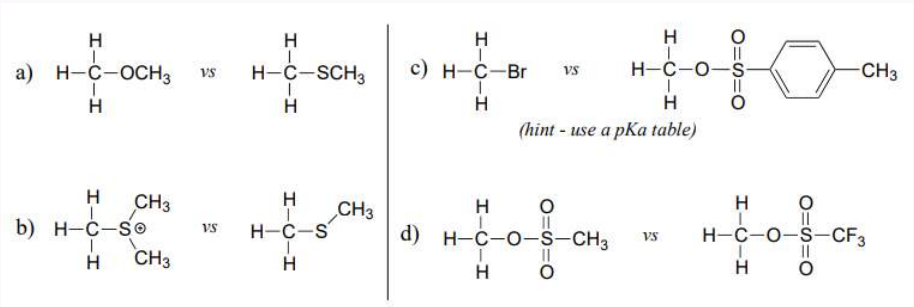
para-toluenesulfonic acid
(pKa -2.8)



organic electrophile with *para*-toluenesulfonate leaving group

Exercise 7.5.1

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.

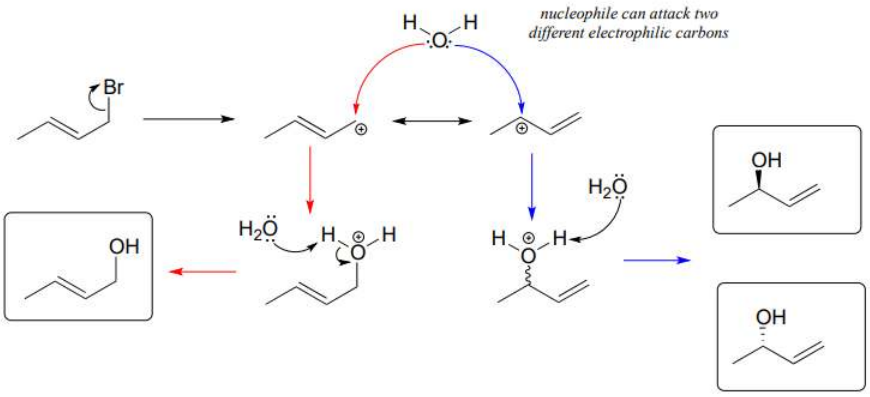
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7.6: Regiochemistry of SN1 Reactions with Allylic Electrophiles

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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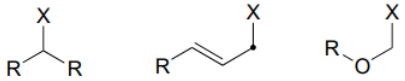
7.7: SN1 or SN2? Predicting the Mechanism

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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7.8: Biological Nucleophilic Substitution Reactions

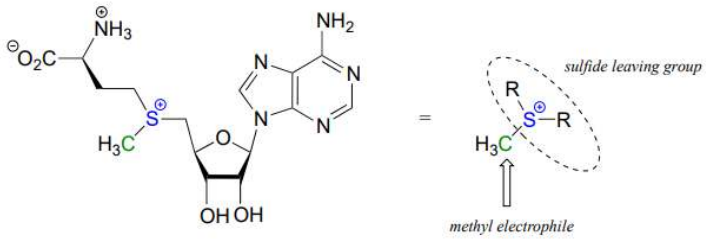
The nucleophilic substitution reactions we have seen so far have all been laboratory reactions, rather than biochemical ones. Now, finally, let's take a look at a few examples of nucleophilic substitutions in a biological context. All of the principles we have learned so far still apply to these biochemical 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.

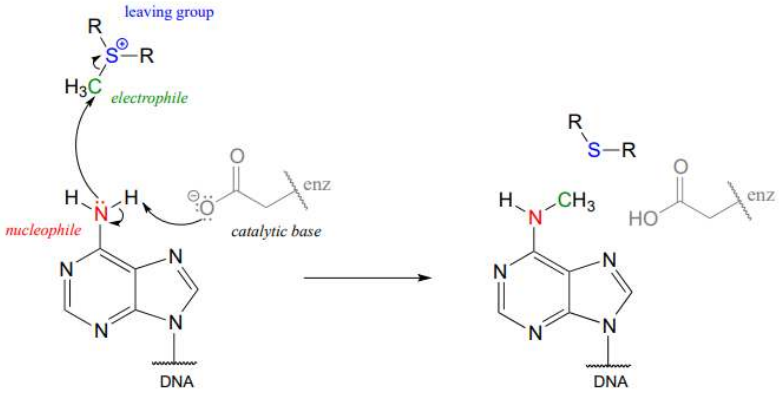
A biochemical S_N2 reaction

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.

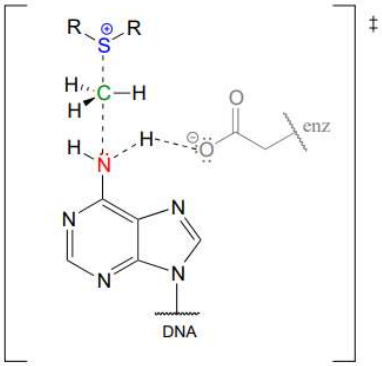


S-adenosylmethionine
(SAM)

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).

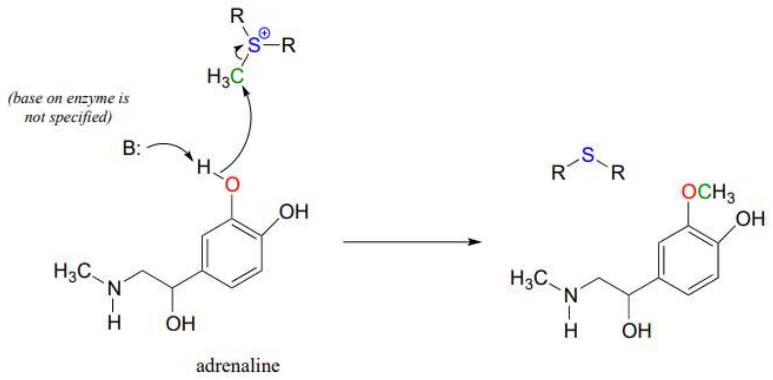
The electrophile is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The carbon is electrophilic (electron-poor) because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes 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 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 7.8.1

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.



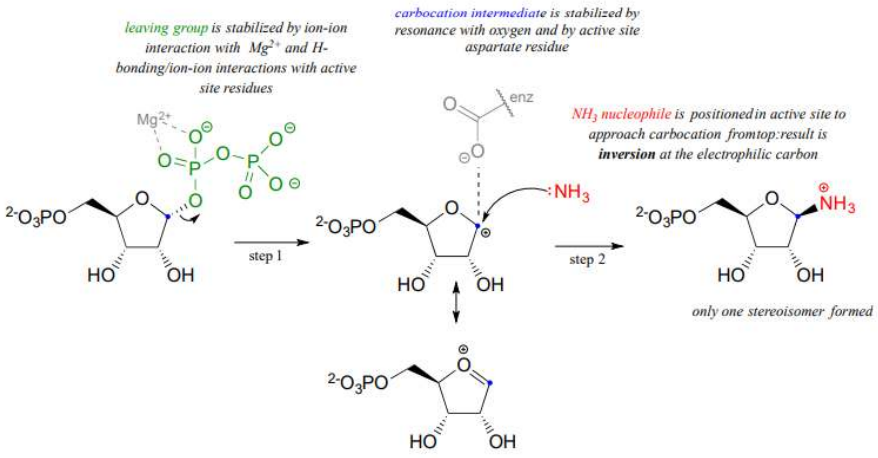
Notice that in this example, the attacking nucleophile is a phenol oxygen rather than a nitrogen (that's why the enzyme is called an *O*-methyltransferase). In many cases when drawing biochemical reaction mechanisms, we use the abbreviations B: for a catalytic base and $H-A$ for a catalytic acid, in 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 7.8.2

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.

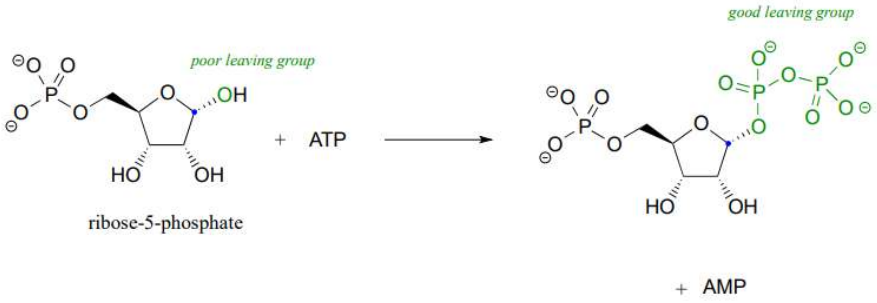
A biochemical S_N1 reaction

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 a 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 be stabilized through interactions with the active site of the enzyme catalyzing the S_N1 reaction.

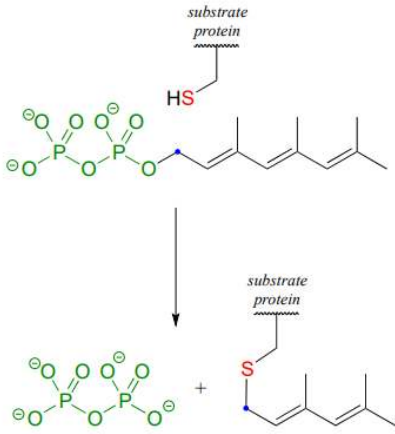


ribose-5-phosphate

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.

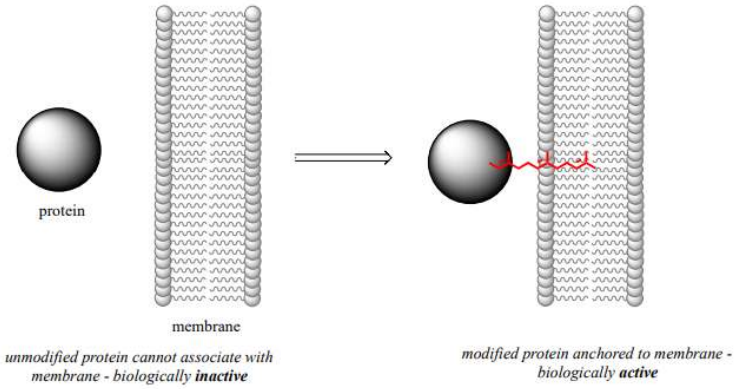
A biochemical S_N1/S_N2 hybrid reaction

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.



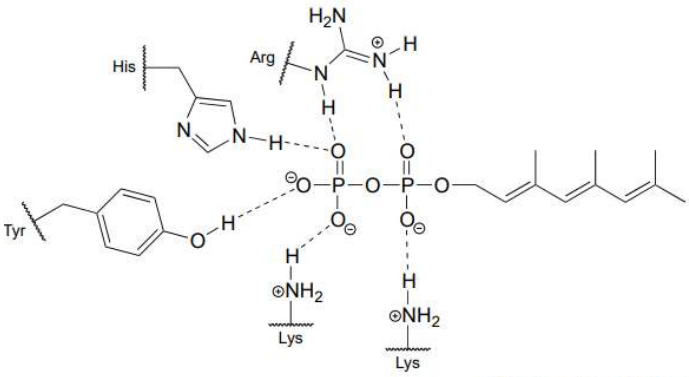
protein with modified cysteine side chain

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.

Contributors

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

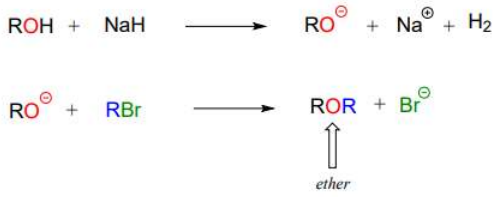
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7.9: Nucleophilic substitution in the Lab

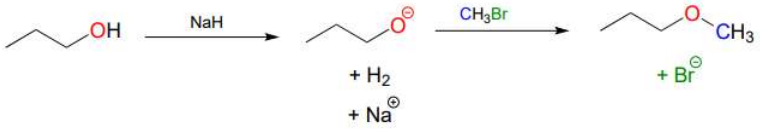
The Williamson ether synthesis

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.

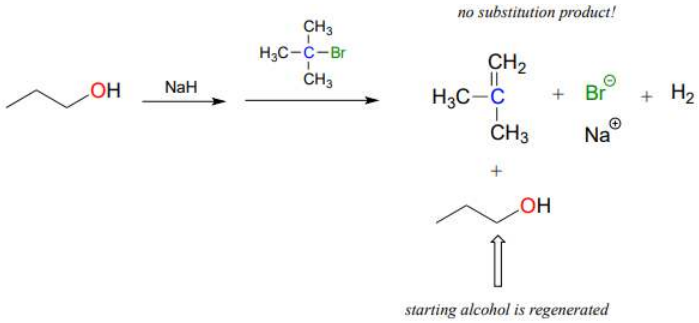


For example, below we see methyl bromide performing the role of methyl group donor, analogous to the role played by SAM in biochemical methylation reactions:



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.

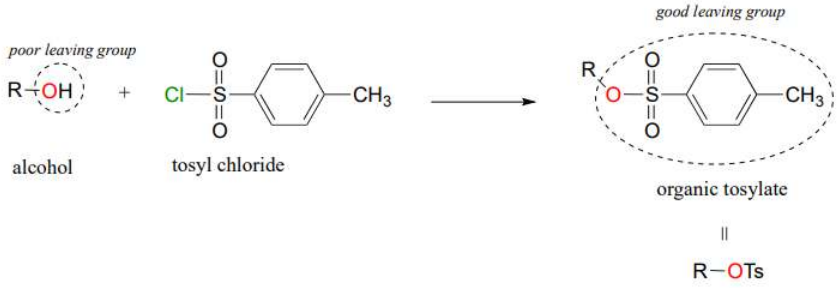
Exercise 7.9.1

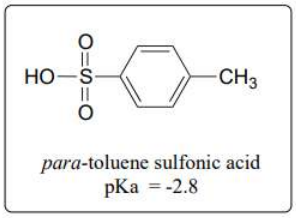
A rookie organic chemist ran the reaction shown above, hoping to synthesize an ether. Instead, he got the alkene shown. What alkyl halide/alcohol combination should he have used instead to get the ether product he was trying for?

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.





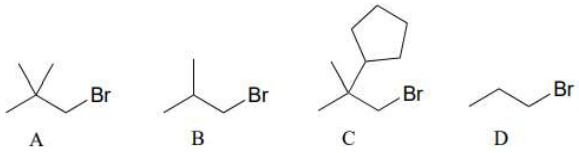
Contributors

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7.10: Nucleophilic Substitution Reactions (Problems)

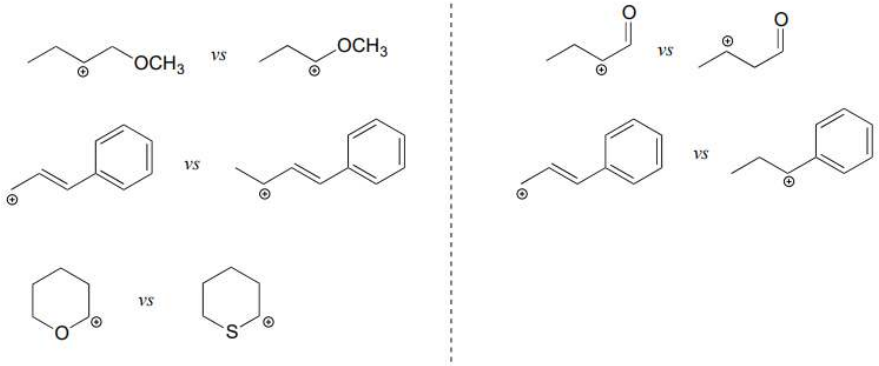
P7.1: Rank the following molecules in order of how fast they would be expected to react with CH_3SNa in acetone. (CH_3SNa is simply the sodium salt of CH_3S^-. Na^+ is a spectator ion.)



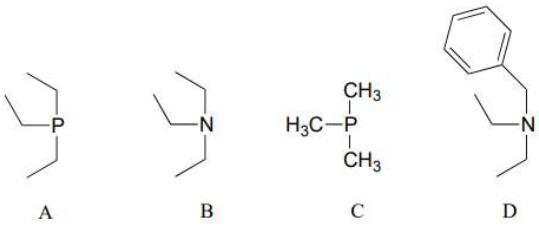
P7.2: Draw line structures representing the most stable cation with the given molecular formula:

a. $C_3H_7^+$
b. $C_4H_9^+$
c. $C_3H_8N^+$
d. $C_4H_7^+$

P7.3: For each pair of carbocations below, choose the one that is more stable, and explain your reasoning.

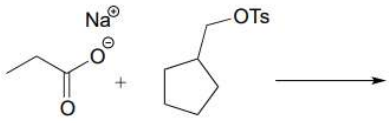


P7.4: Arrange the following species in order of increasing nucleophilicity in protic solvent:

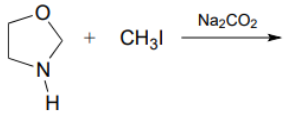


P7.5: Predict the organic products of the following nucleophilic substitution reactions, all of which are carried out in polar aprotic solvent. Show stereochemistry at chiral carbons. Hints: Na_2CO_3, sodium carbonate, is a weak base. For part (f): What is the conjugate acid of NH_2^-? What is the pK_a of this conjugate acid, and what is the pK_a of a terminal alkyne?

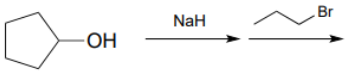
a.



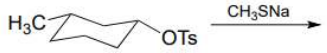
b.



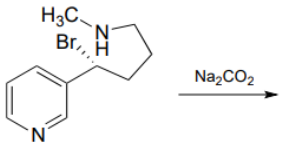
c.



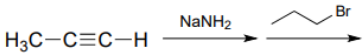
d.



e.



f.



P7.6: Which of the reactions in the previous problem has a unimolecular rate determining step? Explain.

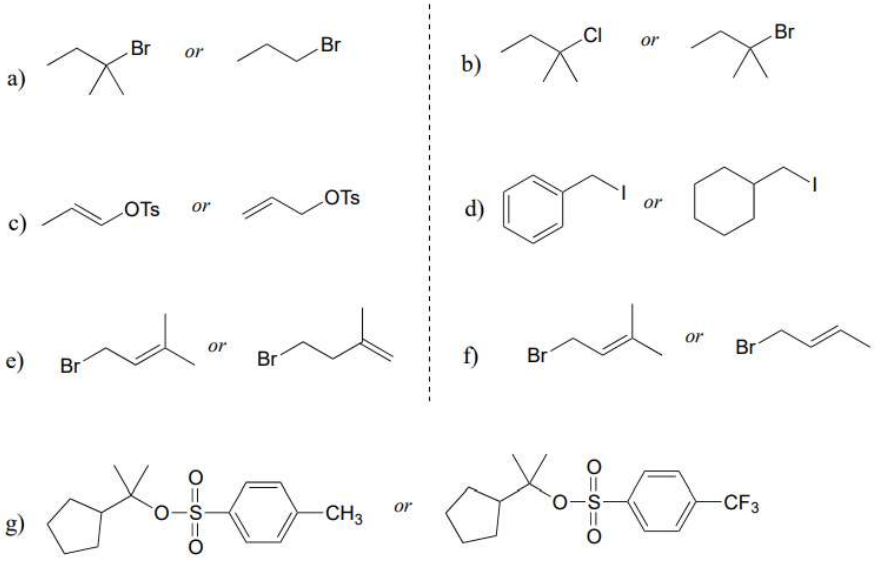
P7.7: From the following pairs, select the compound that would react more rapidly with bromomethane in acetone solvent.

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

P7.8: Methyl iodide (0.10 mole) is added to a solution that contains 0.10 mole $NaOCH_3$ and 0.10 mole $NaSCH_3$.

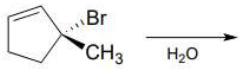
a. Predict the most abundant neutral organic product that would form, and explain your reasoning.
b. Assume that you isolate a mixture the major product (which you predicted in part) along with a smaller amount of a different nucleophilic substitution product. Explain briefly but specifically how you could use ^1H-NMR to determine the ratio of the two products in the mixture.

P7.9: For each pair of compounds, predict which will more rapidly undergo solvolysis in methanol solution.

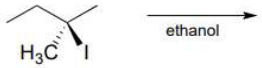


P7.10: Predict the solvolysis product(s) of each of the reactions below. Consider both regiochemistry and stereochemistry.

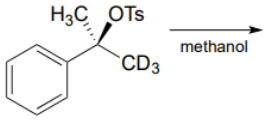
a.



b.



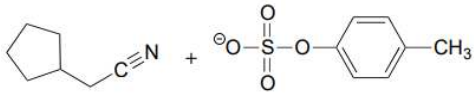
c.



e) Draw a complete curved-arrow mechanism for the formation of the secondary allylilc alcohol product in part (a).

P7.11: Show starting compounds that would lead to the following products through nucleophilic substitution reactions.

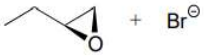
a.



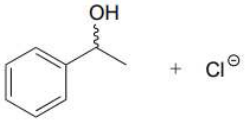
b.



c.



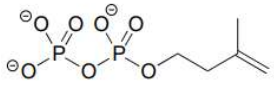
d.



P7.12: 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!)



P7.13 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

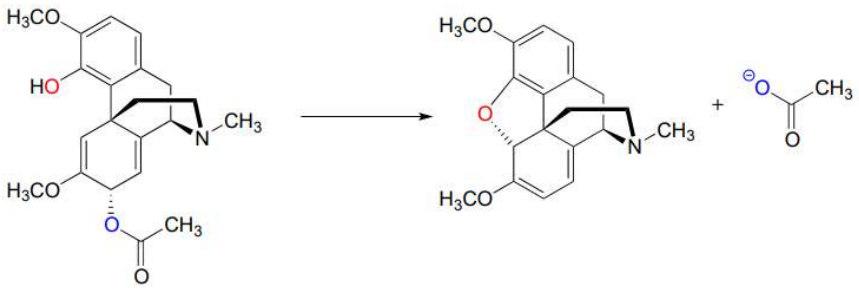
P7.14: Choline, an important neutotransmitter in the nervous system, is formed from 2-(N,N-dimethylamino)ethanol:

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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.

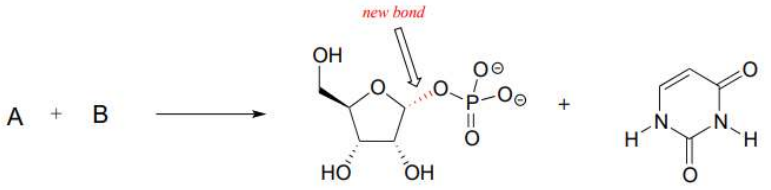
P7.15 The following is a reaction in the biosynthesis of morphine in opium poppies. (Science 1967, 155, 170; J. Biol. Chem 1995, 270, 31091).



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.

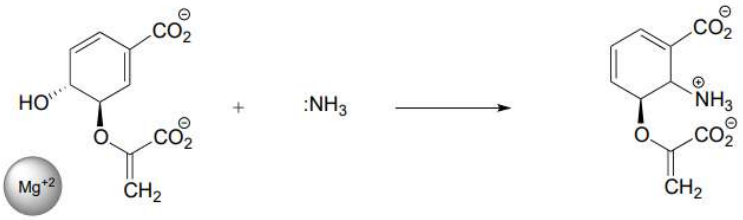
P7.16: The enzymatic reaction below, which is part of the metabolism of nucleic acids, proceeds by an S_N1 mechanism. The new bond formed in the substitution is indicated.

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.



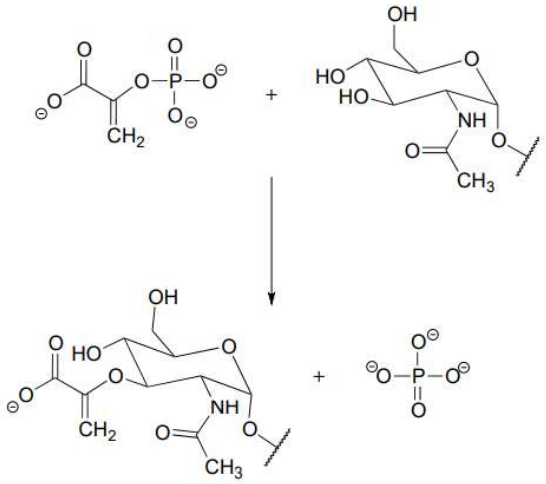
P7.17: Below is the first step of the reaction catalyzed by anthranilate synthase, an enzyme involved in biosynthesis of the amino acid tryptophan.

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.



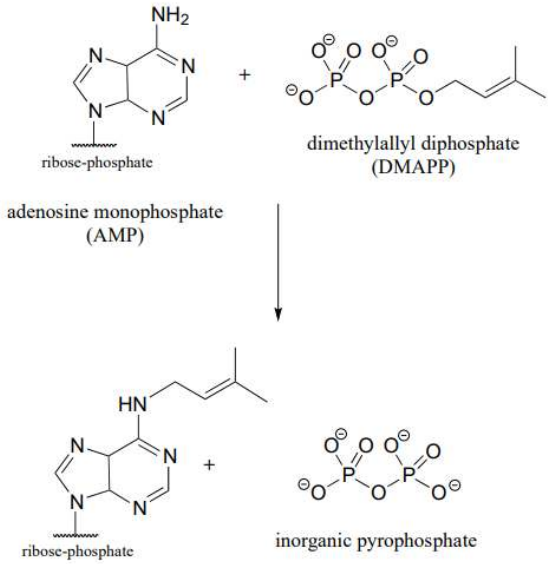
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P7.18: The reaction below is part of the biosynthesis of peptidoglycan, a major component of bacterial cell walls. Is it likely to proceed by a nucleophilic substitution mechanism? Explain.

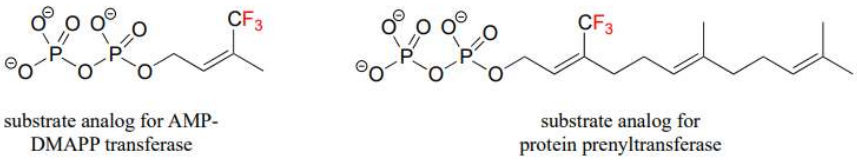


P7.19: Compare the reaction below, catalyzed by the enzyme AMP-DMAPP transferase, to the protein prenyltransferase reaction we learned about in section 8.8, the mechanism of which, as we discussed, is thought to be mostly S_N2-like with some S_N1-like character.

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.



P7.20: 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?

Contributors

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

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7.11: 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

8: Alkyl Halides and Elimination Reactions

	**UI Springfield CHE 267** **Organic Chemistry I** **Fall 2015: Prof. Morsch**	**Reading Assignments** **Homework Problems** **Homework Solutions** **Quizzes**

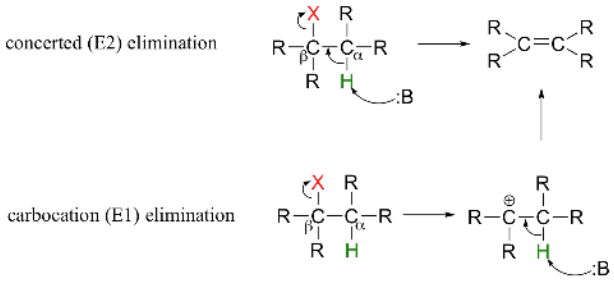
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8.1: General Features of Elimination
8.2: The Mechanisms of Elimination
8.3: The E2 Mechanism
8.4: The Zaitsev Rule
8.5: The E1 Mechanism
8.6: SN1 and E1 Reactions
8.7: Stereochemistry of the E2 Reaction
8.8: E2 Reactions and Alkyne Synthesis
8.9: Alkenes—The Products of Elimination Reactions
8.10: When Is the Reaction SN1, SN2, E1, or E2?
8.P: Nucleophilic Substitution and Elimination Reactions (Problems)

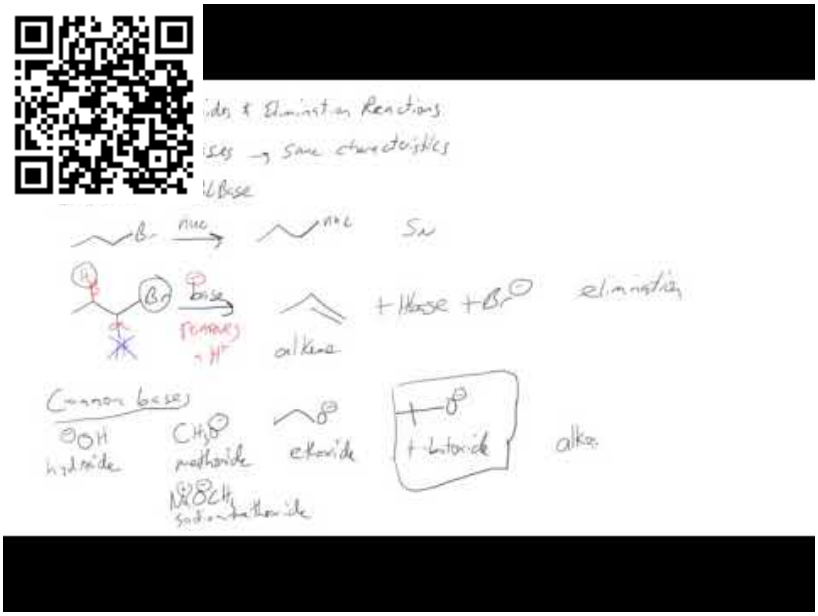
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8.1: General Features of Elimination

So far in this chapter, we have seen several examples of carbanion-intermediate (E1cb) beta-elimination reactions, in which the first step was proton abstraction at a carbon positioned at an electron-withdrawing carbonyl or imine. Elimination reactions are also possible at positions that are isolated from carbonyls or any other electron-withdrawing groups. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as Cβ-X bond cleavage), or in two steps (Cβ-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).

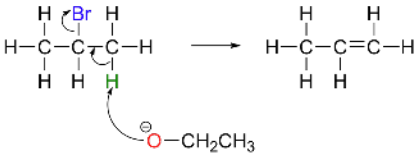


These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (ie., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.

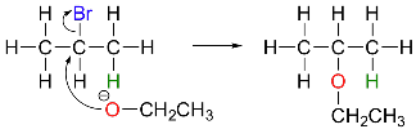


E1 and E2 reactions in the laboratory

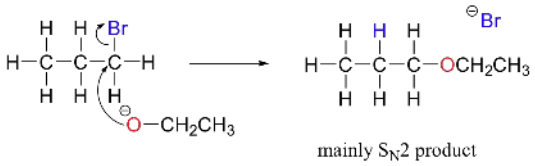
E2 elimination reactions in the laboratory are carried out with relatively strong bases, such as alkoxides (deprotonated alcohols). 2-bromopropane will react with ethoxide, for example, to give propene.



Propene is not the only product of this reaction, however - the ethoxide will also to some extent act as a nucleophile in an S_N2 reaction.

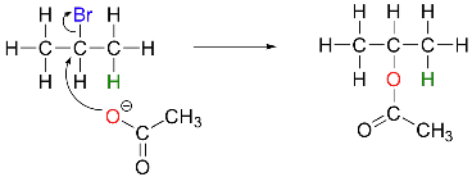


Chemists carrying out nonenzymatic nucleophilic substitution or elimination reactions always have to be aware of the competition between the two mechanisms, because bases can also be nucleophiles, and vice-versa. However, a chemist can tip the scales in one direction or another by carefully choosing reagents. Primary carbon electrophiles like 1-bromopropane, for example, are much more likely to undergo substitution (by the S_N2 mechanism) than elimination (by the E2 mechanism) – this is because the electrophilic carbon is unhindered and a good target for a nucleophile.

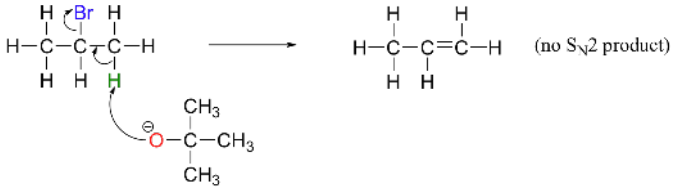


S_N1 and E1 mechanisms are unlikely with such compounds because of the relative instability of primary carbocations.

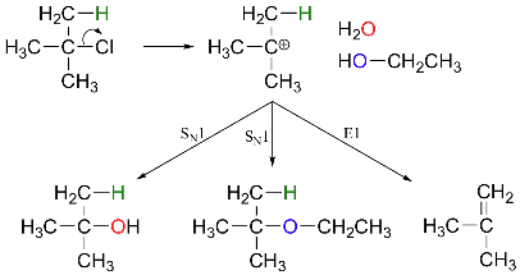
The nature of the electron-rich species is also critical. Acetate, for example, is a weak base but a reasonably good nucleophile, and will react with 2-bromopropane mainly as a nucleophile.



In order to direct the reaction towards elimination, a strong *hindered* base such as tert-butoxide can be used. The bulkiness of tert-butoxide makes it difficult for the oxygen to reach the carbon (in other words, to act as a nucleophile). It is more likely to pluck off a proton, which is much more accessible than the electrophilic carbon).



E1 reactions occur by the same kinds of carbocation-favoring conditions that have already been described for S_N1 reactions (section 9.4): a secondary or tertiary substrate, a protic solvent, and a relatively weak base/nucleophile. In fact, E1 and S_N1 reactions generally occur simultaneously, giving a mixture of substitution and elimination products after formation of a common carbocation intermediate. When tert-butyl chloride is stirred in a mixture of ethanol and water, for example, a mixture of S_N1 products (tert-butyl alcohol and tert-butyl ethyl ether) and E1 product (2-methylpropene) results.

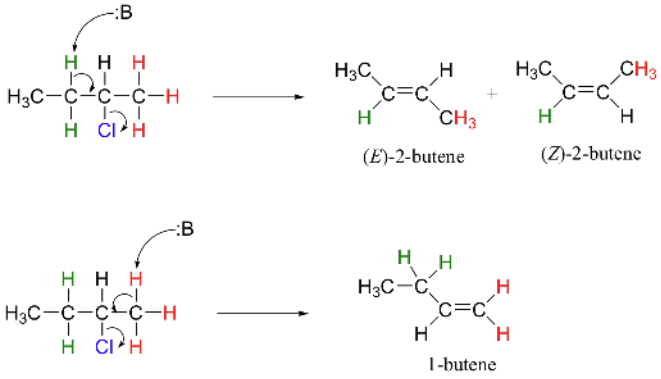


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Exercise 8.1: A straightforward functional group conversion that is often carried out in the undergraduate organic lab is the phosphoric acid-catalyzed dehydration of cyclohexanol to form cyclohexene. No solvent is necessary in this reaction - pure liquid cyclohexanol is simply stirred together with a few drops of concentrated phosphoric acid. In order to drive the equilibrium of this reversible reaction towards the desired product, cyclohexene is distilled out of the reaction mixture as it forms (the boiling point of cyclohexene is 83 ºC, significantly lower than that of anything else in the reaction solution). Any cyclohexyl phosphate that might form from the competing S_N1 reaction remains in the flask, and is eventually converted to cyclohexene over time. Draw a mechanism for the cyclohexene synthesis reaction described above. Also, draw a mechanism showing how the undesired cyclohexyl phosphate could form.

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Next, let's put aside the issue of competition between nucleophilic substitution and elimination, and focus on the regioselectivity of elimination reactions. In many cases an elimination reaction can result in more than one constitutional isomer or stereoisomer. The elimination products of 2-chloropentane provide a good example:

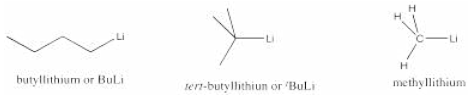


This reaction is both regiospecific and stereospecific. In general, *more substituted alkenes are more stable*, and as a result, the product mixture will contain less 1-butene than 2-butene (this is the regiochemical aspect of the outcome, and is often referred to as **Zaitsev's rule**). In addition, we already know that *trans* (*E*) alkenes are generally more stable than *cis* (*Z*) alkenes (section 3.7C), so we can predict that more of the *E* product will form compared to the *Z* product.

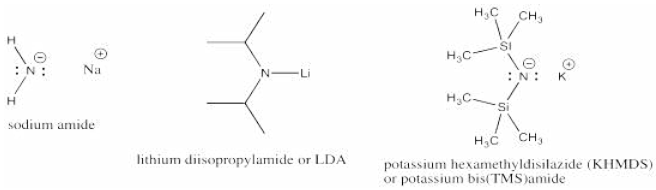
Why might a reaction undergo elimination rather than substitution? The most important reason concerns the nature of the nucleophile. The more basic the nucleophile, the more likely it will induce elimination.

- Basic nucleophiles lead to elimination.

Very strong bases include carbon and nitrogen anions and semi-anions. Examples include butyllithium and sodium amide. Very strong bases are highly likely to engage in elimination, rather than substitution.



Strong bases include non-stabilized oxygen anions. Examples include sodium hydroxide as well as alkoxides such as potassium tert-butoxide or sodium ethoxide. Strong bases favour elimination, too. Nevertheless, they can sometimes undergo either elimination or substitution, depending on other factors (see below).



Weak bases include cyanide, stabilized oxygen anions such as carboxylates and aryloxides, fluoride ion and neutral amines. Weak bases are much more likely to undergo substitution than elimination.



Very weak bases include heavy halides such as chloride, bromide or iodide, as well as phosphorus and sulfur nucleophiles. Very weak bases undergo elimination only rarely.

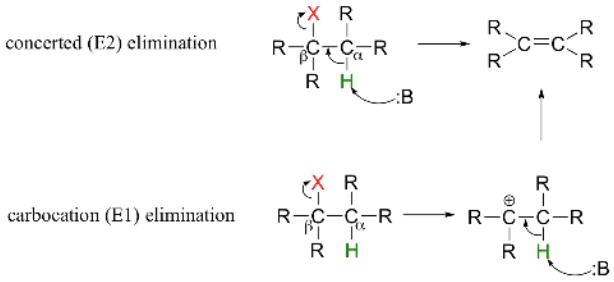
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- Prof. Steven Farmer (Sonoma State University)
- Layne A. Morsch (University of Illinois Springfield)

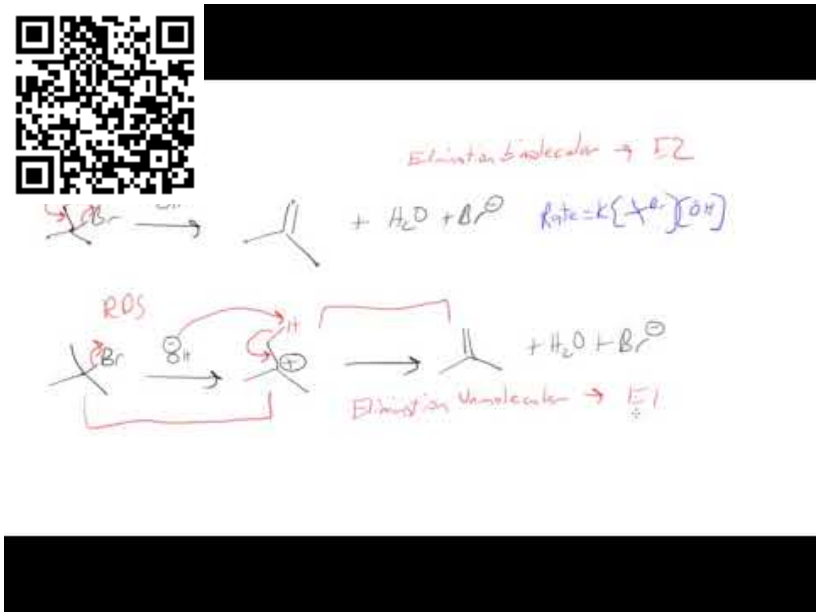
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8.2: The Mechanisms of Elimination

So far in this chapter, we have seen several examples of carbanion-intermediate (E1cb) beta-elimination reactions, in which the first step was proton abstraction at a carbon positioned ato an electron-withdrawing carbonyl or imine. Elimination reactions are also possible at positions that are isolated from carbonyls or any other electron-withdrawing groups. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as Cβ-X bond cleavage), or in two steps (Cβ-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).



These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (ie., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.



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- Layne A. Morsch (University of Illinois Springfield)

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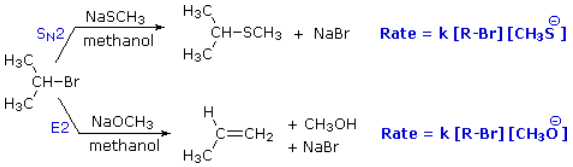
8.3: The E2 Mechanism

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. Unlike E1 reactions, E2 reactions remove two subsituents with the addition of a strong base, resulting in an alkene.

Introduction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

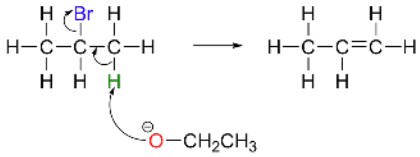
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.



General Reaction

Below is a mechanistic diagram of an elimination reaction by the E2 pathway:

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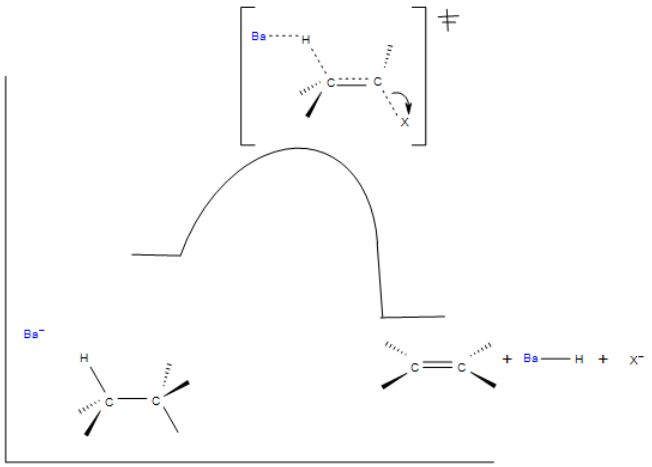


In this reaction Ba represents the base and Br representents a leaving group, typically a halogen. There is one transition state that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond. The product be both eclipse and staggered depending on the transition states. Eclipsed products have a synperiplanar transition states, while staggered products have antiperiplanar transition states. Staggered conformation is usually the major product because of its lower energy confirmation.

An E2 reaction has certain requirements to proceed:

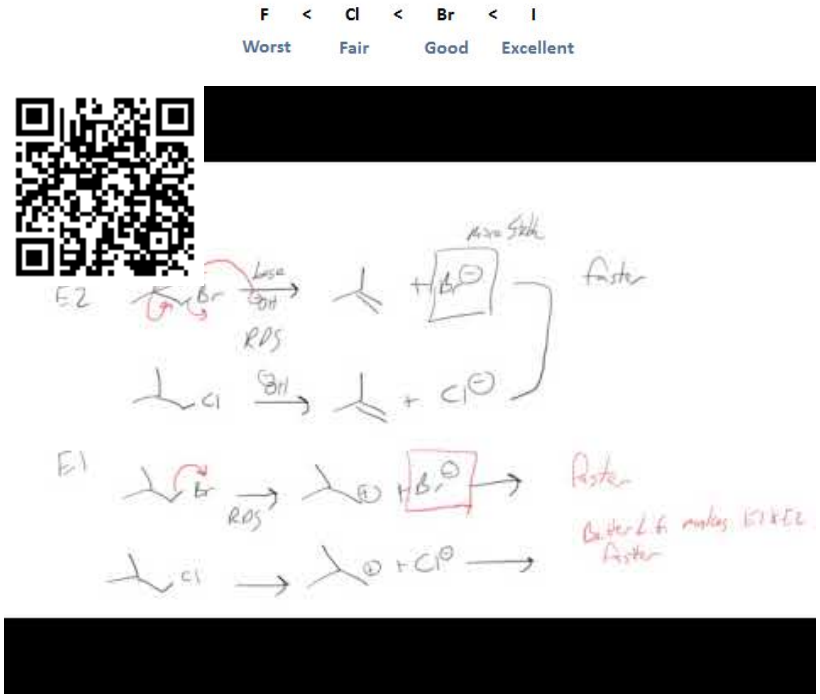
- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertirary primary halides will procede with E2 in the precesence of a base (OH-, RO-, R_2N-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
- Hoffman Rule, if a strically hindered base will result in the least substituted product.

E2 Reaction Coordinate



The Leaving Group Effect in E_2 Reactions

As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.



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

- Layne A. Morsch (University of Illinois Springfield)

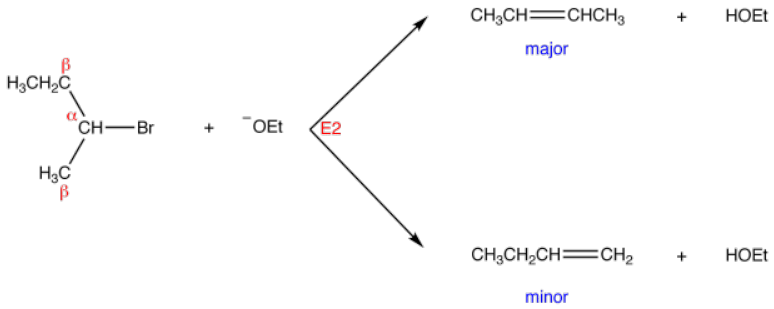
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8.4: The Zaitsev Rule

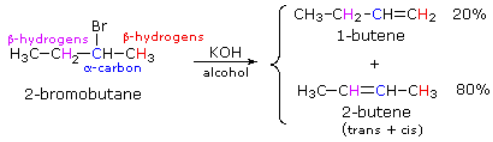
Zaitsev's Rule can be used to predict the regiochemistry of elimination reactions.

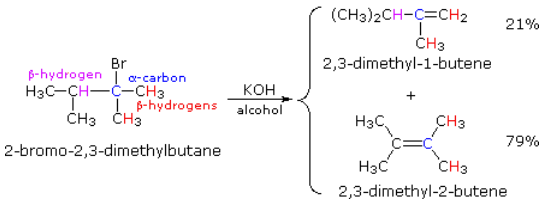
Introduction

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





By using the strongly basic hydroxide nucleophile, we direct these reactions toward elimination. In both cases there are two different sets of beta-hydrogens available to the elimination reaction (these are colored red and magenta and the alpha carbon is blue). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1°-hydrogens (red) and two 2°-hydrogens (magenta) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six 1°-beta-hydrogens compared with one 3°-hydrogen. These results point to a strong regioselectivity favoring the more highly substituted product double bond, an empirical statement generally called the **Zaitsev Rule**.

Contributors

- Gamini Gunawardena from the OChemPal site (Utah Valley University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

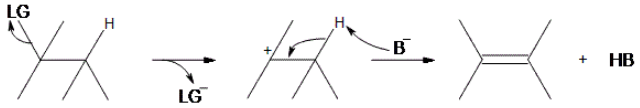
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8.5: The E1 Mechanism

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control. Although Elimination entails two types of reactions, E1 and E2, we will focus mainly on E1 reactions with some reference to E2.

General Reaction

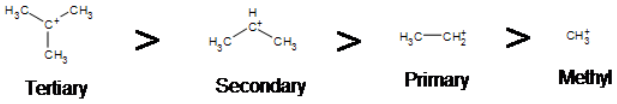
An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (B^-) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Reactivity

Due to the fact that E1 reactions create a carbocation intermediate, rules present in S_N1 reactions still apply.

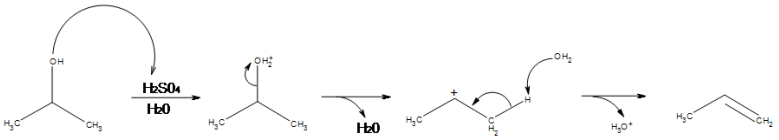


As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of *hyperconjugation*, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good / strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, *solvolysis* occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2 / S_n2 from occurring.

Acid catalyzed dehydration of secondary / tertiary alcohols

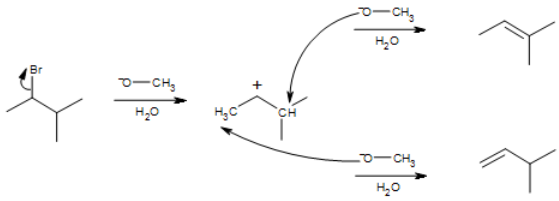
We'll take a look at a mechanism involving solvolysis during an E1 reaction of Propanol in Sulfuric Acid.



- Step 1: The OH group on the pentanol is hydrated by H_2SO_4. This allows the OH to become an H_2O, which is a better leaving group.
- Step 2: Once the OH has been hydrated, the H_2O molecule leaves, taking its electrons with it. This creates a carbocation intermediate on the attached carbon.
- Step 3: Another H_2O molecule comes in to deprotonate the beta carbon, which then donates its electrons to the neighboring C-C bond. The carbons are rehybridized from sp^3 to sp^2, and thus a pi bond is formed between them.

Mechanism for Alkyl Halides

This mechanism is a common application of E1 reactions in the synthesis of an alkene.



Once again, we see the basic 2 steps of the E1 mechanism.

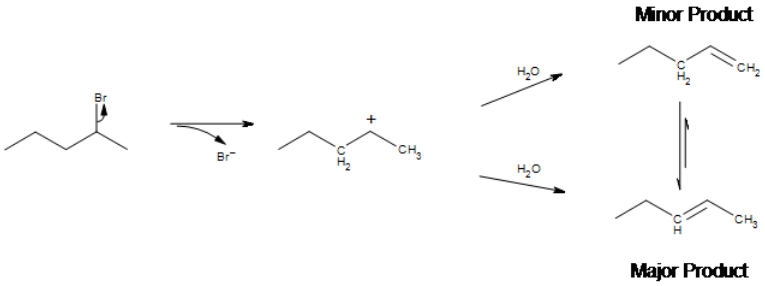
1. The leaving group leaves along with its electrons to form a carbocation intermediate.
2. A base deprotonates a beta carbon to form a pi bond.

In this case we see a mixture of products rather than one discrete one. This is the case because the carbocation has two nearby carbons that are capable of being deprotonated, but that only one forms a major product (more stable).

How are Regiochemistry & Stereochemistry involved?

In terms of regiochemistry, Zaitsev's rule states that although more than one product can be formed during alkene synthesis, the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

Unlike E2 reactions, E1 is not stereospecific. Thus, a hydrogen is not required to be anti-periplanar to the leaving group.



In this mechanism, we can see two possible pathways for the reaction. One in which the methyl on the right is deprotonated, and another in which the CH_2 on the left is deprotonated. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by **Zaitsev's rule**, deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.

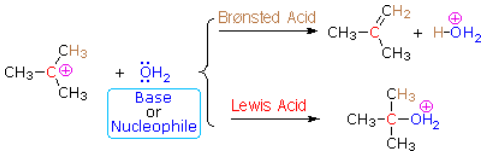
Contributors

- Satish Balasubramanian

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8.6: SN1 and E1 Reactions

The E1 mechanism is nearly identical to the S_N1 mechanism, differing only in the course of reaction taken by the carbocation intermediate. As shown by the following equations, a carbocation bearing beta-hydrogens may function either as a Lewis acid (electrophile), as in the S_N1 reaction, or a Brønsted acid, as in the E1 reaction.



Thus, hydrolysis of tert-butyl chloride in a mixed solvent of water and acetonitrile gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration. The alcohol is the product of an S_N1 reaction and the alkene is the product of the E1 reaction. The characteristics of these two reaction mechanisms are similar, as expected. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.

$$(CH_3)_3C–Cl + H_2O \longrightarrow [\ (CH_3)_3C(+)\ ] + Cl^{(-)} + H_2O \longrightarrow (CH_3)_3C–OH + (CH_3)_2C{=}CH_2 + HCl + H_2O$$

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a beta-proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

Since the S_N1 and E1 reactions proceed via the same carbocation intermediate, the product ratios are difficult to control and both substitution and elimination usually take place.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**. The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

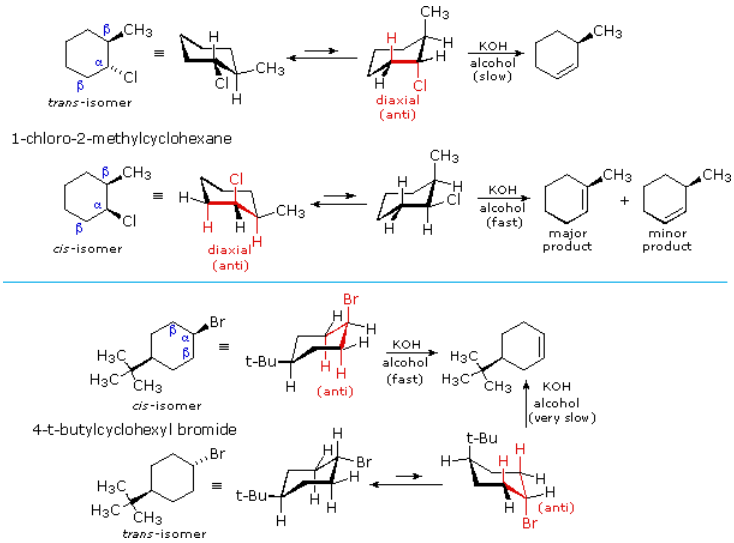
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8.7: Stereochemistry of the E2 Reaction

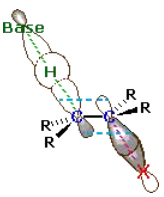
Stereochemistry of the E2 Reaction

E2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product. These differences are described by the first two equations in the following diagram.

Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. Consequently, reactions conducted on such substrates often provide us with information about the preferred orientation of reactant species in the transition state. Stereoisomers are particularly suitable in this respect, so the results shown here contain important information about the E2 transition state.



The most sensible interpretation of the elimination reactions of 2- and 4-substituted halocyclohexanes is that this reaction prefers an **anti orientation** of the halogen and the beta-hydrogen which is attacked by the base. These anti orientations are colored in red in the above equations. The compounds used here all have six-membered rings, so the anti orientation of groups requires that they assume a diaxial conformation. The observed differences in rate are the result of a steric preference for equatorial orientation of large substituents, which reduces the effective concentration of conformers having an axial halogen. In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that it will always assume an equatorial orientation, leaving the bromine to be axial in the cis-isomer and equatorial in the trans. Because of symmetry, the two axial beta-hydrogens in the cis-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the chlorine atom. To assume a conformation having an axial bromine the trans-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, substitution by hydroxide anion predominates.

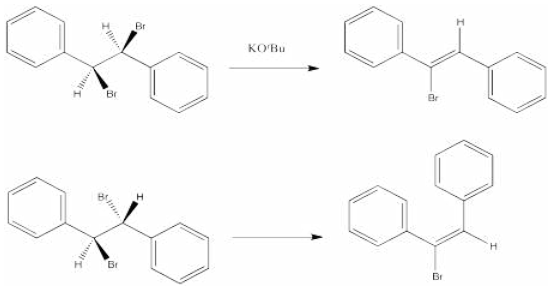


A similar analysis of the 1-chloro-2-methylcyclohexane isomers explains both the rate and regioselectivity differences. Both the chlorine and methyl groups may assume an equatorial orientation in a chair conformation of the trans-isomer, as shown in the top equation. The axial chlorine needed for the E2 elimination is present only in the less stable alternative chair conformer, but this structure has only one axial beta-hydrogen (colored red), and the resulting elimination gives 3-methylcyclohexene. In the cis-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two axial beta hydrogens. The more stable 1-methylcyclohexene is therefore the predominant product, and the overall rate of elimination is relatively fast.

An orbital drawing of the anti-transition state is shown on the right. Note that the base attacks the alkyl halide from the side opposite the halogen, just as in the S_N2 mechanism. In this drawing the α and β carbon atoms are undergoing a rehybridization from sp^3 to sp^2 and the developing π-bond is drawn as dashed light blue lines. The symbol **R** represents an alkyl group or hydrogen. Since both the base and the alkyl halide are present in this transition state, the reaction is bimolecular and should exhibit second order kinetics. We should note in passing that a syn-transition state would also provide good orbital overlap for elimination, and in some cases where an anti-orientation is prohibited by structural constraints *syn*-elimination has been observed.

Instead, in an E2 reaction, stereochemistry of the double bond -- that is, whether the *E* or *Z* isomer results -- is dictated by the stereochemistry of the starting material, if it is diastereomeric. In other words, if the carbon with the hydrogen and the carbon with the halogen are both chiral, then one diastereomer will lead to one product, and the other diastereomer will lead to the other product.

The following reactions of potassium ethoxide with dibromostilbene (1,2-dibromo-1,2-diphenylethane) both occurred via an E2 mechanism. Two different diastereomers were used. Two different stereoisomers (*E* vs. *Z*) resulted.



Contributors

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- Prof. Steven Farmer (Sonoma State University)

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8.8: E2 Reactions and Alkyne Synthesis

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

Introduction

One case in which elimination can occur is when a haloalkane is put in contact with a nucleophile. The table below is used to determine which situations will result in elimination and the formation of a π bond.

Elimination: Haloalkane-Nucleophile Reaction

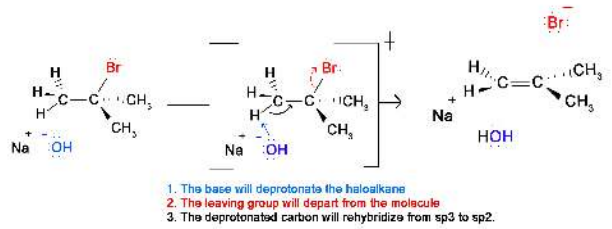
Type of Haloalkane	Weak Base, Poor Nucleophile	Weak Base, Good Nucleophile	Strong, Unhindered Base	Strong, Hindered Base
Primary				
Unhindered				E2
Branched			E2	E2
Secondary	E1		E2	E2
Tertiary	E1	E1	E2	E2

* Empty Box means no elimination or Pi bond forms

To synthesize alkynes from dihaloalkanes we use dehydrohalogenation. The majority of these reactions take place using alkoxide bases (other strong bases can also be used) with high temperatures. This combination results in the majority of the product being from the E2 mechanism.

E2 Mechanism

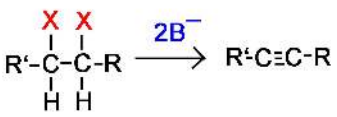
Recall that the E2 mechanism is a concerted reaction (occurs in 1 step). However, in this 1 step there are 3 different changes in the molecule. This is the reaction between 2-Bromo-2-methylpropane and Sodium Hyrdoxide.



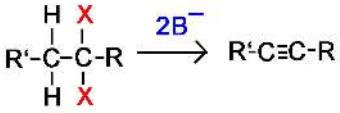
This is a brief review of the E2 reaction. For further information on why the reaction proceeds as it does visit the E2 reaction page. Now, if we apply this concept using 2 halides on vicinal or geminal carbons, the E2 reaction will take place twice resulting in the formation of 2 Pi bonds and thus an Alkyne.

Dihaloalkane Elimination

This is a general picture of the reaction taking place without any of the mechanisms shown.

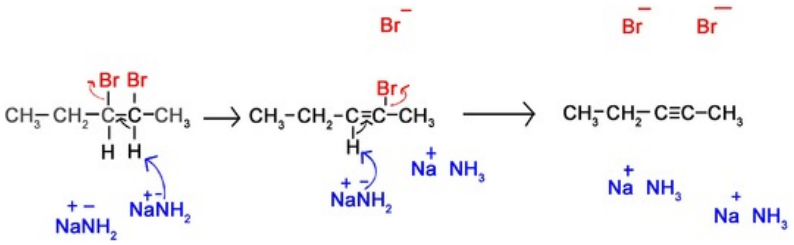


or



* With a terminal haloalkane the equation above is modified in that 3 equivalents of base will be used instead of 2.

Lets look at the mechanism of a reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia.

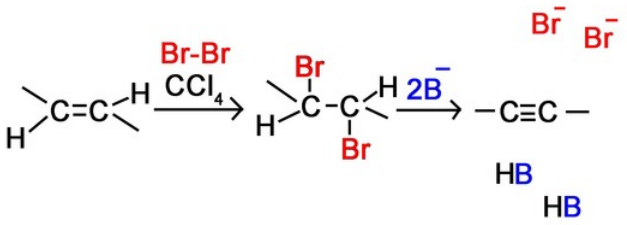


- Liquid ammonia is not part of the reaction, but is used as a solvent
- Notice the intermediate of the alkyne synthesis. It is stereospecifically in its anti form. Because the second proton and halogen are pulled off the molecule this is unimportant to the synthesis of alkynes. For more information on this see the page on preparation of alkenes from haloalkanes.

Preparation of Alkynes from Alkenes

Lastly, we will briefly look at how to prepare alkynes from alkenes. This is a simple process using first halogenation of the alkene bond to form the dihaloalkane, and next, using the double elimination process to protonate the alkane and from the 2 Pi bonds.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyene using double elimination, as covered previously on this page.

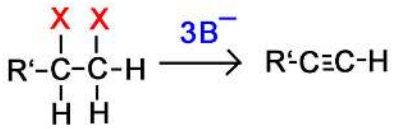


In The Lab

Due to the strong base and high temperatures needed for this reaction to take place, the triple bond may change positions. An example of this is when reactants that should form a terminal alkyne, form a 2-Alkyne instead. The use of $NaNH_2$ in liquid NH_3 is used in order to prevent this from happening due to its lower reacting temperature. Even so, most chemists will prefer to use nucleophilic substitution instead of elimination when trying to form a terminal alkyne.

Questions

Question 1: Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

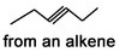


Question 2: What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide ($Na^+ {}^-O\text{-}CH_2CH_3$)

Question 3: What would be good starting molecules for the synthesis of the following molecules:

a.) 
from an alkene

b.) 
from a dihaloalkane

Question 4: Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answers

Answer 1: Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Answer 2:

a.) 1-Pentyne

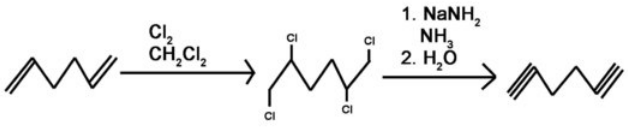
b.) 1-Pentyne

Answer 3:

a.) 

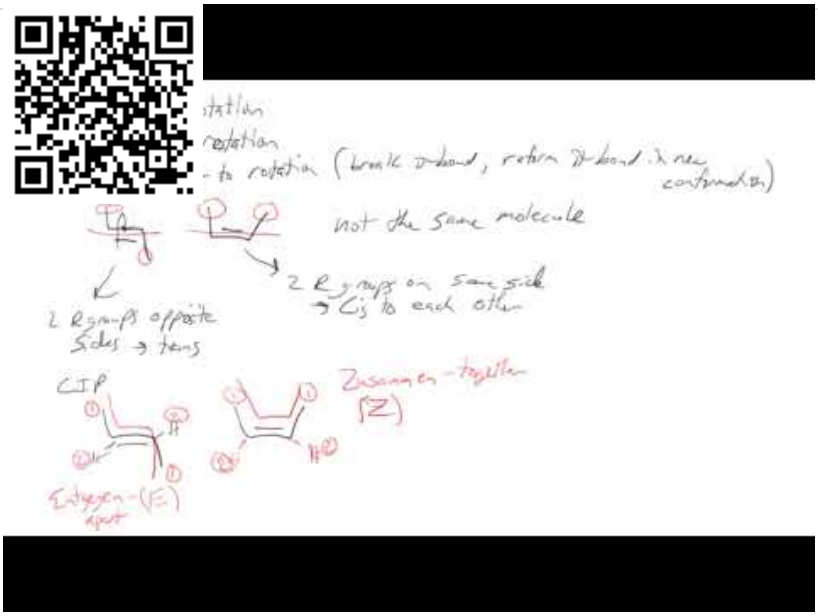
b.) 

Answer 4: Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.



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8.9: Alkenes—The Products of Elimination Reactions

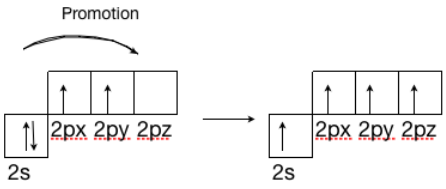


Ethene is the formal IUPAC name for $H_2C{=}CH_2$, but it also goes by a common name: Ethylene. The name Ethylene is used because it is like an ethyl group (CH_2CH_3) but there is a double bond between the two carbon atoms in it. Ethene has the formula C_2H_4 and is the simplest alkene because it has the fewest carbons (two) necessary for a carbon-carbon double bond.

Introduction

Bonding in carbon is covalent, containing either sigma or π bonds. Carbon can make single, double, or triple bonds. The number of bonds it makes determines the structure. With four single bonds, carbon has a tetrahedral structure, while with one double bond it's structure is trigonal planar, and with a triple bond it has a linear structure.

A solitary carbon atom has four electrons, two in the 2s orbital, and one in each of the $2p_x$ and $2p_y$ orbitals, leaving the $2p_z$ orbital empty. A single carbon atom can make up to four bonds, but by looking at its electron configuration this would not be possible because there are only two electrons available to bond with. The other two are in a lone pair state, making them much less reactive to another electron that is by itself. Well it is, in order to make the four bonds, the carbon atom promotes one of the 2s electrons into the empty $2p_z$ orbital, leaving the carbon with four unpaired electrons allowing it to now form four bonds. The electron is not promoted spontaneously. It becomes promoted when a photon of light with the correct wavelength hits the carbon atom. When this photon hits the carbon atom it gives the atom enough energy to promote one of the lone pair electrons to the $2p_z$ orbital.



Sigma and Pi Bonds

All the bonds in Ethene are covalent, meaning that they are all formed by two adjacent atoms sharing their valence electrons. As opposed to ionic bonds which hold atoms together through the attraction of two ions of opposite charges.

Sigma bonds are created when there is overlap of similar orbitals, orbitals that are aligned along the inter-nuclear axis. Common sigma bonds are $s+s$, p_z+p_z and $s+p_z$, z is the axis of the bond on the xyz-plane of the atom.

π bonds are created when there is adequate overlap of similar, adjacent p orbitals, such as p_x+p_x and p_y+p_y. Each p orbital has two lobes, one usually indicated by a + and the other indicated by a - (sometimes one may be shaded while the other is not). This + and

- (shaded, not shaded) are only meant to indicate the opposite phase ϕ the wave functions, they **do not** indicate any type of electrical charge. For a π bond to form both lobes of the p orbital must overlap, + with + and - with -. When a + lobe overlaps with a - lobe this creates an anti-bonding orbital interaction which is much higher in energy, and therefore not a desirable interaction.

Usually there can be no π bonds between two atoms without having at least one sigma bond present first. But there are special cases such as dicarbon (C_2) where the central bond is a π bond not a sigma bond, but in cases like these the two atoms want to have as much orbital overlap as possible so the bond lengths between the atoms are smaller than what is normally expected.

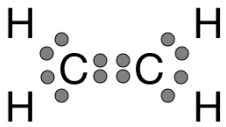
The π bond in ethene is weak compared to the sigma bond between the two carbons. This weakness makes the π bond and the overall molecule a site of comparatively high chemical reactivity to an array of different substances. This is due to the high electron density in the π bond, and because it is a weak bond with high electron density the π bond will easily break in order to form two separate sigma bonds. Sites such as these are referred to as functional groups or functionalities. These groups have characteristic properties and they control the reactivity of the molecule as a whole. How these functional groups and other reactants form various products are an important concept in organic chemistry.

Orbital Bonding in Ethene

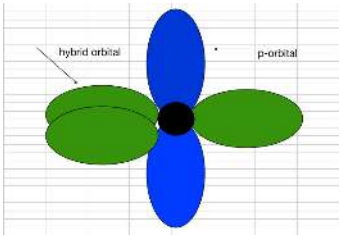
Ethene is made up of four $1s^1$ Hydrogen atoms and two $2s^2\ 2p_x^1\ 2p_y^2$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight in the valence shell. Having eight valence electrons around carbon gives the atom itself the same electron configuration as neon, a noble gas. Carbon wants to have the same configuration as Neon because when it has eight valence electrons carbon is at its most stable, lowest energy state, it has all of the electrons that it wants, so it is no longer reactive.

Structure of Ethene

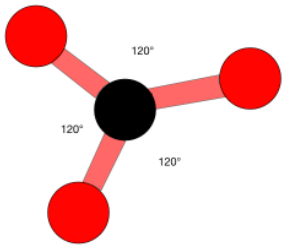
Ethene is not a very complicated molecule. It contains two carbon atoms that are double bonded to each other, with each of these atoms also bonded to two Hydrogen atoms.



This forms a total of three bonds to each carbon atom, giving them an sp^2 hybridization. Since the carbon atom is forming three sigma bonds instead of the four that it can, it only needs to hybridize three of its outer orbitals, instead of four. It does this by using the $2s$ electron and two of the $2p$ electrons, leaving the other unchanged. This new orbital is called an sp^2 hybrid because that's exactly what it is, it is made from one s orbital and two p orbitals.



When atoms are an sp^2 hybrid they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



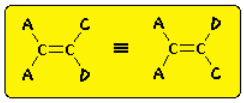
The H-C-H bond angle is 117°, which is very close to the ideal 120° of a carbon with sp^2 hybridization. The other two angles (H-C=C) are both 121.5°.

Rigidity in Ethene

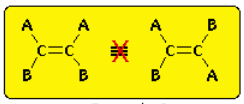
There is rigidity in the Ethene molecule due to the double-bonded carbons. In Ethane there are two carbons that share a single bond, this allows the two Methyl groups to rotate with respect to each other. These different conformations result in higher and lower energy forms of Ethane. In Ethene there is no free rotation about the carbon-carbon sigma bond. There is no rotation because there is also a π bond along with the sigma bond between the two carbons. A π bond is only formed when there is adequate overlap between both top and bottom p-orbitals. In order for there to be free rotation the p-orbitals would have to go through a phase where they are 90° from each other, which would break the π bond because there would be no overlap. Since the π bond is essential to the structure of Ethene it must not break, so there can be not free rotation about the carbon-carbon sigma bond.

Configurational Stereoisomers of Alkenes

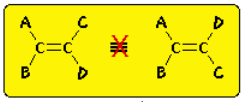
The carbon-carbon double bond is formed between two sp^2 hybridized carbons, and consists of two occupied molecular orbitals, a sigma orbital and a pi orbital. Rotation of the end groups of a double bond relative to each other destroys the p-orbital overlap that creates the pi orbital or bond. Because the pi bond has a bond energy of roughly 60 kcal/mole, this resistance to rotation stabilizes the planar configuration of this functional group. As a result, certain disubstituted alkenes may exist as a pair of configurational stereoisomers, often designated cis and trans. **The essential requirement for this stereoisomerism is that each carbon of the double bond must have two different substituent groups** (one may be hydrogen). This is illustrated by the following general formulas. In the first example, the left-hand double bond carbon has two identical substituents (**A**) so stereoisomerism about the double bond is not possible (reversing substituents on the right-hand carbon gives the same configuration). In the next two examples, each double bond carbon atom has two different substituent groups and stereoisomerism exists, regardless of whether the two substituents on one carbon are the same as those on the other.



Example 1

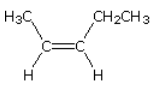


Example 2

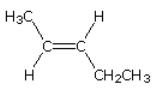


Example 3

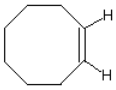
Some examples of this configurational stereoisomerism (sometimes called geometric isomerism) are shown below. Note that cycloalkenes smaller than eight carbons cannot exist in a stable trans configuration due to ring strain. A similar restriction holds against cycloalkynes smaller than ten carbons. Since alkynes are linear, there is no stereoisomerism associated with the carbon-carbon triple bond.



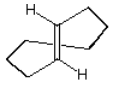
cis-2-pentene



trans-2-pentene



cis-cyclooctene

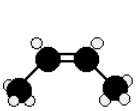


trans-cyclooctene

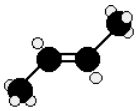
Geometric (cis-trans) isomerism

The carbon-carbon double bond doesn't allow any rotation about it. That means that it is possible to have the CH_3 groups on either end of the molecule locked either on one side of the molecule or opposite each other.

These are called cis-but-2-ene (where the groups are on the same side) or trans-but-2-ene (where they are on opposite sides).



cis-but-2-ene

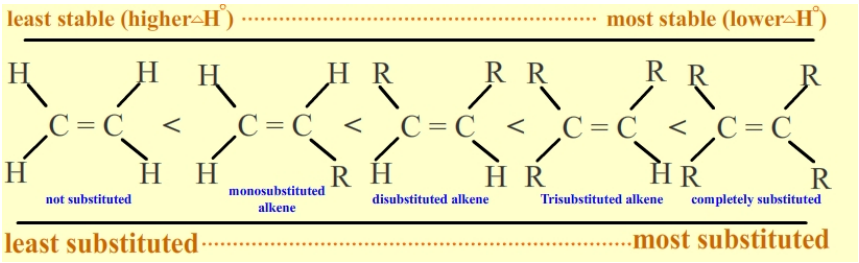


trans-but-2-ene

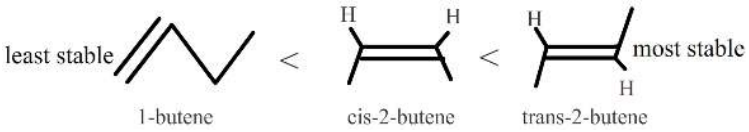
Cis-but-2-ene is also known as (Z)-but-2-ene; trans-but-2-ene is also known as (E)-but-2-ene. For an explanation of the two ways of naming these two compounds, follow the link in the box below.

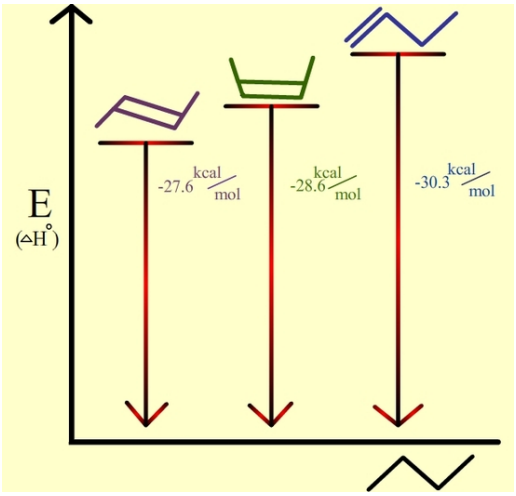
Stability of Alkenes

The stability of alkene can be determined by measuring the amount of energy associated with the hydrogenation of the molecule. Since the double bond is breaking in this reaction, the energy released in hydrogenation is proportional to the energy in the double bond of the molecule. This is a useful tool because heats of hydrogenation can be measured very accurately. The ?H° is usually around -30 kcal/mol for alkenes. Stability is simply a measure of energy. Lower energy molecules are more stable than higher energy molecules. More substituted alkenes are more stable than less substituted ones due to hyperconjugation. They have a lower heat of hydrogenation. The following illustrates stability of alkenes with various substituents:



In disubstituted alkenes, trans isomers are more stable than cis isomers due to steric hindrance. Also, internal alkenes are more stable than terminal ones. See the following isomers of butene:





Trans-2-butene is the most stable because it has the lowest heat of hydrogenation.

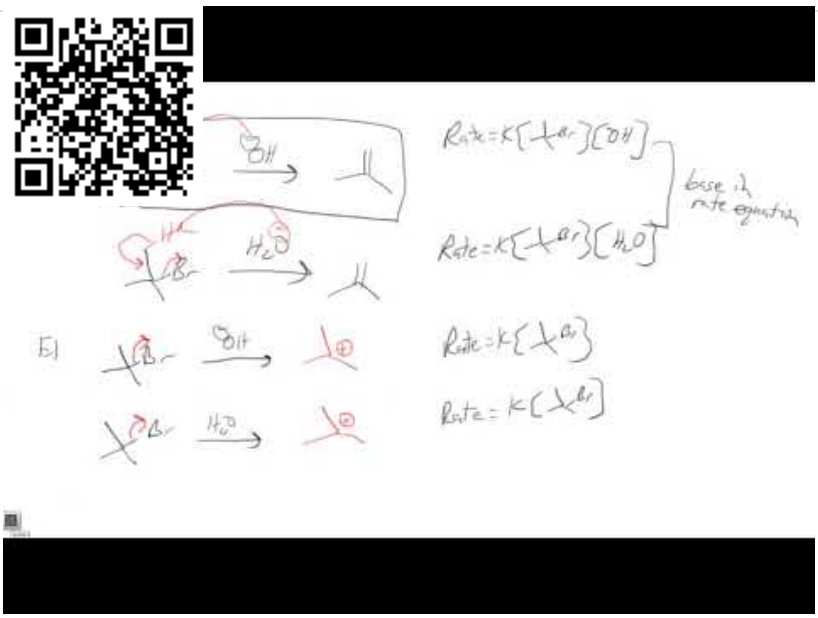
Note: In cycloalkenes smaller than cyclooctene, the cis isomers are more stable than the trans as a result of ring strain.

Contributors

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8.10: When Is the Reaction SN1, SN2, E1, or E2?



Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, several variables must be considered, **the most important being the structure of the alkyl group and the nature of the nucleophilic reactant**.In general, in order for an SN1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible; and that low dielectric solvents (e.g. acetone, ethanol, tetrahydrofuran & ethyl acetate) are used. When a high dielectric solvent would significantly influence the reaction this is noted in red. **Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents**.

Nucleophile	**Anionic Nucleophiles** (Weak Bases: I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^- etc.) pK_a's from -9 to 10 (left to right)	**Anionic Nucleophiles** (Strong Bases: HO^-, RO^-) pK_a's > 15	**Neutral Nucleophiles** (H_2O, ROH, RSH, R_3N) pK_a's ranging from -2 to 11

Alkyl Group			
Primary RCH_2–	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH \longrightarrow CH_2=CHCl$	S_N2 substitution. (N ≈ S >>O)
Secondary R_2CH–	S_N2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK_a = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S_N2 substitution. (N ≈ S >>O) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be formed slowly.
Tertiary R_3C–	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be expected.	E2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	E2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E1 products may be formed.
Allyl $H_2C=CHCH_2$–	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides. E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.
Benzyl $C_6H_5CH_2$–	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides (note there are no β hydrogens). E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.

Contributors

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8.P: Nucleophilic Substitution and Elimination Reactions (Problems)

Exercise 8-1 Write Lewis structures for each of the following reagents and classify them as either electrophilic, nucleophilic, both, or neither by evaluating whether they will react appreciably with hydroxide ion, $HO^{\ominus}$, or hydronium ion, $H_3O^{\oplus}$. Write equations for each of the reactions involved.

a. NH_3
b. NH_2^-
c. $Na^{\oplus}$
d. $Cl^{\ominus}$
e. Cl_2
f. CH_4
g. $CN^{\ominus}$
h. CH_3OH
i. $CH_3\overset{\oplus}{O}H_2$
j. BF_4^-
k. HBr
l. $HC \equiv C:^{\ominus}$
m. $:CH_2$
n. FSO_3H
o. SO_3

Exercise 8-2 Identify the electrophile and the nucleophile in each of the following reactions:

a. $CH_3I + \overset{\ominus}{O}CH_3 \rightarrow CH_3{-}O{-}CH_3 + I^{\ominus}$

b. $CH_2{=}CH_2 + Br_2 \rightarrow \overset{\oplus}{C}H_2{-}CH_2{-}Br + Br^{\ominus}$

c. $CH_3NH_2 + CH_3I \rightarrow (CH_3)_2NH + HI$

d. $Br^{\ominus} + CH_3 - \overset{\oplus}{O}H_2 \rightarrow CH_3Br + H_2O$

Exercise 8-3 Calculate ΔH^0 for the polar reaction of one mole of bromomethane with water in accord with the equation $CH_3Br + H_2O \rightarrow CH_3OH + HBr$ (a) in the gas phase and (b) with all of the participants in dilute aqueous solution. For Part (a) you will need the bond energies of Table 4-3 and for Part (b) you will require the bond energies and the following ΔH^0 values:

$$\begin{aligned} H_2O\,(g) &\rightarrow H_2O\,(l) & \Delta H^0 &= -10.8\text{ kcal} \\ HBr\,(g) &\rightarrow HBr\,(\text{dilute aq}) & \Delta H^0 &= -20\text{ kcal} \\ CH_3Br\,(g) &\rightarrow CH_3Br\,(aq) & \Delta H^0 &\cong -1\text{ kcal} \\ CH_2OH\,(g) &\rightarrow CH_3OH\,(aq) & \Delta H^0 &\cong -10\text{ kcal} \end{aligned} \qquad (8.P.1)$$

Exercise 8-4 Ethyl chloride (0.1 M) reacts with potassium iodide (0.1 M) in 2-propanone (acetone) solution at $60°$ to form ethyl iodide and potassium chloride at a rate (v) of $5.44 \times 10^{-7}\text{ mol L}^{-1}\text{ s}^{-1}$.

a. If the reaction proceeded by an S_N2 mechanism, what is the value of k (in proper units) and what would be the *rate* of the reaction in moles per liter per sec at 0.01 M concentrations of both reactants? Show your method of calculation.

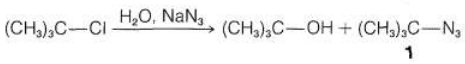
b. Suppose the rate were proportional to the square of the potassium iodide concentration and the first power of the ethyl chloride concentration. What would be the rate with 0.01 M reactants?

c. It one starts with solutions initially 0.1 M in both reactants, the rate of formation of ethyl iodide initially is $5.44 \times 10^{-7}\text{ mol L}^{-1}\text{ s}^{-1}$, but falls as the reaction proceeds and the reactants are used up. Plot the rate of formation of ethyl iodide against the concentration of ethyl chloride as the reaction proceeds (remembering that one molecule of ethyl chloride consumes one molecule of potassium iodide). Assume that the rate of reaction is proportional to the first power of the ethyl chloride concentration; and to (1) the zeroth power, (2) the first power, and (3) the second power of the potassium iodide concentration.

d. What kind of experimental data would one need to determine whether the rate of the reaction of ethyl chloride with potassium iodide is first order in each reactant or second order in ethyl chloride and zero order in potassium iodide?

e. Suppose the reaction is first order in both ethyl chloride and potassium iodide. Plot the rate of formation of ethyl iodide against the concentration of ethyl chloride, assuming one starts with $0.01\ \mathbf{M}$ ethyl chloride and $1\ \mathbf{M}$ potassium iodide. Compare this plot with the zeroth- and first-order plots you made in Part c.

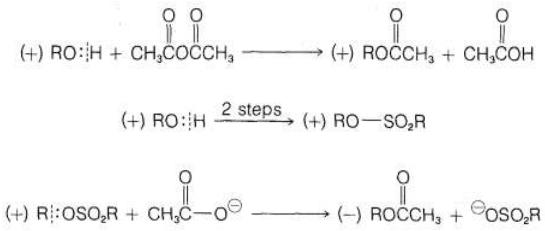
Exercise 8-5 The rate of solvolysis of *tert*-butyl chloride in aqueous solution is unaffected by having sodium azide, $\mathrm{Na\overset{\oplus}{\overset{\ominus}{N}}=\overset{\oplus}{N}=\overset{\oplus}{N}}$, in the solution, yet the products include both 2-azido-2-methylpropane, **1**, and *tert*-butyl alcohol:



Show how this information can be used to determine whether an S_N1 or an S_N2 mechanism occurs in the solvolysis of *tert*-butyl chloride in aqueous solution.

Exercise 8-6 What inference as to reaction mechanism might you make from the observation that the rate of hydrolysis of a certain alkyl chloride in aqueous 2-propanone is *retarded* by having a moderate concentration of lithium chloride in the solution?

Exercise 8-7 Equations 8-3 through 8-5 show how Kenyon and Phillips established that inversion of configuration accompanies what we now recognize to be S_N2 substitutions. For each reaction, we indicate whether $\mathbf{R{-}O}$ or $\mathbf{O{-}H}$ is broken by an appropriately placed vertical line. Explain how the sequence of steps shows that inversion occurs in the S_N2 reaction of Equation 8-5. The symbols $(+)$ or $(-)$ designate for each compounds the sign of the rotation α of the plane of polarized light that it produces.



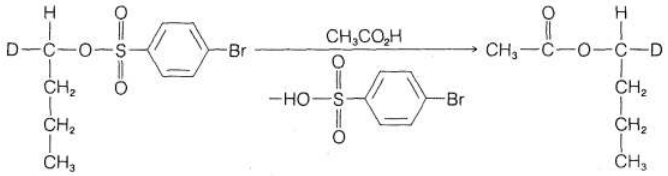
Exercise 8-8 Explain how, in the presence of bromide ion, either enantiomer of 2-bromobutane racemizes (Section 5-1B) in 2-propanone solution at a rate that is first order in $\mathbf{Br^{\ominus}}$ and first order in 2-bromobutane.

Exercise 8-9* When either of the enantiomers of 1-deuterio-1-bromobutane is heated with bromide ion in 2-propanone, it undergoes an S_N2 reaction that results in a slow loss of its optical activity. If radioactive bromide ion ($\mathbf{Br^{*\ominus}}$) is present in the solution, radioactive 1-deuterio-1-bromobutane is formed by the same S_N2 mechanism in accord with the following equation:

$$\mathbf{CH_3CH_2CH_2CHDBr + Br^{*\ominus} \xrightarrow{2\text{-propanone}} CH_3CH_2CH_2CHDBr^{*} + Br^{\ominus}} \qquad (8.P.2)$$

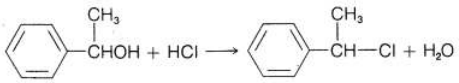
Within experimental error, the time required to lose 10% of the optical activity is just equal to the time required to have 5% of the $\mathbf{CH_3CH_2CH_2CHDBr}$ molecules converted to $\mathbf{CH_3CH_2CH_2CHDBr^{*}}$ with radioactive bromide ion. Explain what we can conclude from these results as to the degree to which the S_N2 reaction produces inversion of configuration of the primary carbon of 1-deuterio-1-bromobutane.

Exercise 8-10 What can be concluded about the mechanism of the solvolysis of 1-butyl derivatives in ethanoic acid from the projection formulas of the starting material and product of the following reaction?



Would you call this an S_N1 or S_N2 reaction?

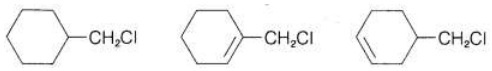
Exercise 8-11 In the reaction of 1-phenylethanol with concentrated $\mathbf{HCl}$, 1-phenylethyl chloride is formed:

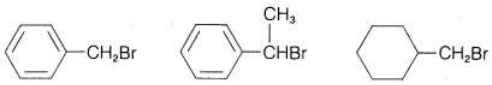


If the alcohol originally has the D configuration, what configuration would the resulting chloride have if formed (a) by the S_N2 mechanism and (b) by the S_N1 mechanism?

Exercise 8-12 Predict which compound in each of the following groups reacts most rapidly with potassium iodide in 2-propanone as solvent by the S_N2 mechanism. Give your reasoning and name the substitution product by the IUPAC system.

a. $(CH_3)_3CCH_2Cl$ $(CH_3)_3CCl$ $CH_3CH_2CH_2CH_2Cl$

b. 

c. 

Exercise 8-13 Which of the monobromine-substituted methylcyclohexanes would you judge to be the most reactive in (a) S_N2-type displacement and (b) S_N1-type displacement?

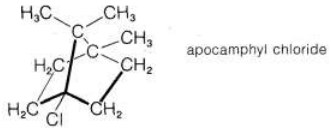
Exercise 8-14 Answer the question in the preceding exercise, but with the monobromine-substituted 1-methylcyclohexenes.

Exercise 8-15 Select the compounds from the following list that would be expected to hydrolyze *more rapidly* than phenylmethyl (benzyl) chloride by the S_N1 mechanism:

a. 2-phenylmethyl chloride
b. diphenylmethyl chloride
c. 1-phenylmethyl chloride
d. (chloromethyl)cyclohexane
e. 1-chloro-4-methylbenzene

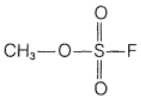
Exercise 8-16 Explain the following observations:

a. The tertiary chloride, apocamphyl chloride, is unreactive in either S_N1 or S_N2 reactions. For example, no reaction occurs when its solution in aqueous ethanol containing 30% potassium hydroxide is refluxed for 20 hours.



b. Chloromethyl alkyl (or aryl) ethers, $ROCH_2Cl$, are very reactive in S_N1 solvolysis reactions. Compared to chloromethane, the rate of hydrolysis of chloromethyl phenyl ether is about 10^{14}. Also, the rate of hydrolysis is retarded significantly by lithium chloride.

Exercise 8-17 Methyl sulfides are prepared conveniently by the S_N2 reaction of a CH_3X derivative with a sulfur nucleophile: $RS^{\ominus} + CH_3X \rightarrow RSCH_3 + X^{\ominus}$. The rate of the reaction with a given $RS^{\ominus}$. If you are uncertain of the pK_a of the acids HX, look them up in an appropriate reference, such as the *CRC Handbook of Physics and Chemistry*.

a. dimethyl sulfate, $(CH_3O)_2SO_2$
b. methyl nitrate, CH_3ONO_2
c. methyl cyanide (ethanenitrile), CH_3CN
d. methyl fluoride, CH_3F
e. methyl iodide, CH_3I
f. methyl fluorosulfonate, 

g. methyl acetate (ethanoate), $CH_3O\overset{\overset{O}{\|}}{C}CH_3$

h. methanol, CH_3OH

Exercise 8-18 Account for the following observations:

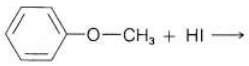
a. *tert*-Alkyl fluorides are unreactive in S_N1 solvolysis reactions *unless* a strong acid is present.

b. *D*-1-Phenylethyl chloride dissolved in *aqueous* 2-propanone containing mercuric chloride loses much of its optical activity before undergoing hydrolysis to give racemic 1-phenylethanol.

c. 1-Bromobutane can be prepared by heating 1-butanol with a mixture of sodium bromide and sulfuric acid. The reaction fails, however, if the sulfuric acid is omitted.

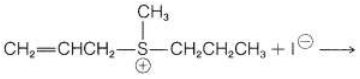
d. Benzenoxide (phenoxide) ion, $C_6H_5O^{\ominus}$, is a better leaving group than ethoxide, $C_2H_5O^{\ominus}$.

Exercise 8-19 Using the discussion in Section 8-7 of how the structure of R and X influence the S_N reactivity of RX, predict the favored course of each of the following reactions. Give your reasoning.

a. 

b. $(CH_3)_3C{-}O{-}CH_3 + HI \rightarrow$

c. $CF_3{-}O{-}CH_3 + HBr \rightarrow$

d. 

Exercise 8-20 Methyl ethers of the type $R{-}O{-}CH_3$ cannot be prepared by the reaction of the alcohol ROH with CH_3I, but if Ag_2O is present the following reaction occurs under mild conditions:

$$2R{-}OH + Ag_2O + 2CH_3I \rightarrow 2ROCH_3 + 2AgI + H_2O \tag{8.P.3}$$

Explain how Ag_2O promotes this reaction.

Exercise 8-21 Explain each of the following observations:

a. Methyl sulfide $(CH_3)_2S$ reacts with $C_6H_5COCH_2Cl$ in benzene to give the sulfonium salt, $C_6H_5COCH_2\overset{\oplus}{S}(CH_3)_2Cl^{\ominus}$, which precipitates as it is formed. Attempts to recrystallize the product from ethanol result in formation of methyl sulfide and $C_6H_5COCH_2Cl$.

b. S_N2 displacements of alkyl chlorides by $\overset{\ominus}{O}H$ often are catalyzed by iodide ion, $RCl + :\overset{\ominus}{O}H \xrightarrow{I^{\ominus}} ROH + Cl^{\ominus}$ and may result in a product with *less* than 100% of inverted configuration at the carbon carrying the chlorine.

c.* Tris(trifluoromethyl)amine, $(CF_3)_3N$, is completely nonnucleophilic, whereas trimethylamine is a good nucleophile.

Exercise 8-22 Classify the following solvents according to effectiveness for solvation of (i) cations and (ii) anions:

a. 2-propanone, CH_3COCH_3
b. tetrachloromethane, CCl_4
c. anhydrous hydrogen fluoride, HF
d. trichloromethane, $CHCl_3$
e. trimethylamine, $(CH_3)_3N$
f. trimethylamine oxide, $(CH_3)_3\overset{\oplus}{N}-\overset{\ominus}{O}$

Exercise 8-23* Would you expect the S_N2 reaction of sodium cyanide with methyl bromide to be faster, slower, or about the same with $(CH_3)_2S{=}O$ or ethanol as solvent? Explain.

Exercise 8-24 An alternative mechanism for $E2$ elimination is the following:

$$CH_3CH_2Cl + OH^{\ominus} \overset{\text{fast}}{\rightleftharpoons} {}^{\ominus}:CH_2CH_2Cl + H_2O \xrightarrow{\text{slow}} CH_2{=}CH_2 + Cl^{\ominus} \tag{8.P.4}$$

a. Would this mechanism lead to overall second-order kinetics with respect to the concentrations of $OH^{\ominus}$ and ethyl chloride? Explain.

b. This mechanism as written has been excluded for several halides by carrying out the reaction in deuterated solvents such as D_2O and C_2H_5OD. Explain how such experiments could be relevant to the reaction mechanism.

c. Does the test in Part b also rule out $CH_3CH_2Cl + \overset{\ominus}{O}H \xrightarrow{\text{slow}} :\overset{\ominus}{C}H_2CH_2Cl + H_2O \xrightarrow{\text{fast}} CH_2{=}CH_2 + Cl^{\ominus}$? Explain.

Exercise 8-25 Write equations and mechanisms for all the products that might reasonably be expected from the reaction of 2-chlorobutane with a solution of potassium hydroxide in ethanol.

Exercise 8-26

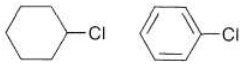
a. Why is potassium *tert*-butoxide, $\overset{\oplus\ominus}{K}OC(CH_3)_3$, an excellent base for promoting elimination reactions of alkyl halides, whereas ethylamine, $CH_3CH_2NH_2$, is relatively poor for the same purpose?

b. Potassium *tert*-butoxide is many powers of ten more effective a reagent for achieving *E*2 eliminations in methylsulfinylmethane (dimethyl sulfoxide) than in *tert*-butyl alcohol. Explain.

Exercise 8-27 Which one of the following groups of compounds would eliminate HCl most readily on reaction with potassium hydroxide? Draw the structure of the product and name it.

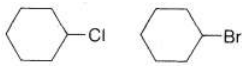
a. $(CH_3)_3CCl$ $CH_3CH_2CH_2CH_2Cl$ $CH_3CH(Cl)CH_2CH_3$

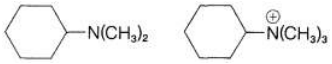
b. $(CH_3)_3CCH_2Cl$ $(CH_3)_2CHCH_2Cl$

c. 

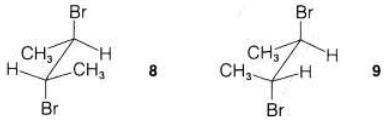
Exercise 8-28 Which one of each of the following pairs of compounds would react most rapidly with potassium hydroxide in an *E*2 -type elimination? Draw the structure of the product and name it.

a. $(CH_3)_3COH$ $(CH_3)_3CCl$

b. 

c. 

Exercise 8-29 Write all the possible staggered conformations for each of the isomers of 2,3-dibromobutane, **8** and **9**:



Show the structures of the alkenes that could be formed from each by antarafacial *E*2 elimination of one mole of hydrogen bromide with hydroxide ion. Which alkene should more readily eliminate further to form 2-butyne? Explain.

Exercise 8-30 For the reaction of Equation 8-7, would you expect the ratio of *tert*-butyl alcohol to 2-methylpropene to change significantly with changes in the nature of the leaving group [i.e., Cl, Br, I, or $\overset{\oplus}{S}(CH_3)_2$]? Give your reasoning.

Would you expect the same or different behavior as X is changed, if elimination were occurring by an *E*2 *mechanism* with the solvent acting as the base? Explain.

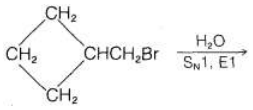
Exercise 8-31 The reaction of *tert*-butyl chloride with water is accelerated strongly by sodium hydroxide. How would the ratio of elimination to substitution products be affected thereby? Explain.

Exercise 8-32 Explain how $(CH_3)_2CDCHBrCH_3$ (where D is the hydrogen isotope of mass 2) might be used to determine whether 2-methyl-2-butene is formed directly from the bromide in an *E*1 reaction, or by rearrangement and elimination as shown in the preceding equations.

Exercise 8-33 Predict the products of the following reactions:

a. $CH_3CH_2CBr(CH_3)CH_2CH_3 \xrightarrow[S_N1,\ E1]{H_2O}$

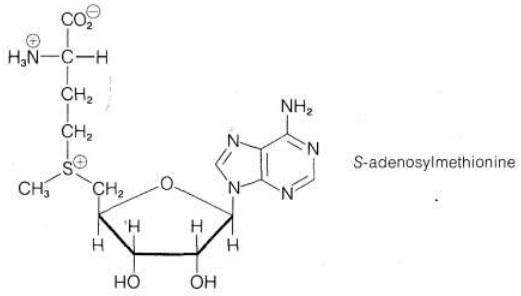
b. $(CH_3)_3CCH(CH_3)Cl \xrightarrow[S_N1,\ E1]{H_2O}$

c. 

Exercise 8-34 Write reaction sequences, using specific and appropriate compounds, that illustrate the following conversions:

a. alcohol → ether
b. alcohol → alkene
c. alcohol → alkyl chloride
d. alcohol → nitrile ($ROH \rightarrow RCN$)
e. alkyl chloride → sulfonium salt → alkene

Exercise 8-35 S-Adenosylmethionine is a biologically important compound that reacts in the S_N2 manner with the *amino group* of phosphorylated 2-aminoethanol, $NH_2CH_2CH_2OPO_3H_2$. Which carbon of S-adenosylmethionine would be most likely to undergo an S_N2 reaction with an RNH_2 compound? Give your reasoning and write the structures of the expected products.



S-adenosylmethionine

Exercise 8-36 Nitriles, RCN, can be prepared by S_N2 displacement of alkyl derivatives, RX, by using sodium or potassium cyanide:

$$RX + NaCN \rightarrow RCN + NaX \qquad (8.P.5)$$

a. Which of the following solvents would be most suitable for this reaction: water, 2-propanone, ethanol, benzene, $(CH_3)_2S{=}O$, or pentane? Give reasons for your choice.

b. Which of the six isomeric monobromoderivatives of 1-methylcyclohexane would you expect to react most rapidly with sodium cyanide? Why?

c. If you wished to make 2-phenylethanenitrile, $C_6H_5CH_2CN$, which of the following phenylmethyl compounds, RCH_2X, would you select to convert to the nitrile? $X = -F$, $-OH$, $-OCOCH_3$, $-H$, $-NH_2$, $-O_3SCH_3$, $-SO_3{-}CH_3$. Why?

Exercise 8-37 Give a plausible explanation for each of the following observations:

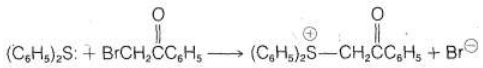
a. Aqueous sodium chloride will *not* convert *tert*-butyl alcohol to *tert*-butyl chloride but concentrated hydrochloric acid will.

b. Better yields are obtained in the synthesis of isopropyl methyl ether starting with methyl iodide rather than sodium methoxide:

$$CH_3I + (CH_3)_2CHO^{\ominus}Na^{\oplus} \rightarrow (CH_3)_2CHOCH_3 + Na^{\oplus}I^{\ominus} \qquad (8.P.6)$$

$$(CH_3)_2CHI + CH_3O^{\ominus}Na^{\oplus} \rightarrow (CH_3)_2CHOCH_3 + Na^{\oplus}I^{\ominus} \qquad (8.P.7)$$

c. The following reaction proceeds only if an equivalent amount of silver fluoroborate, $Ag^{\oplus}BF_4{}^{\ominus}$, is added to the reaction mixture:



d. 1-Bromo-2-butene reacts with water to give a mixture of 2-buten-1-ol, 3-buten-2-ol, and some 1,3-butadiene.

Exercise 8-38 Which compound in the following pairs would react faster under the reaction conditions? Draw the structures of the major products expected.

a. $C_6H_5CH_2CH_2Br$ or $C_6H_5C(CH_3)(Br)CH_3$ in ethanol-water solution.

b. Same as in Part a, but with potassium iodide in acetone.

c. Same as in Part a, but with potassium hydroxide in ethanol.

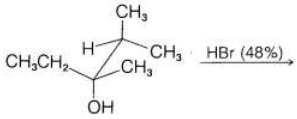
d. $CH_3CH_2\overset{\oplus}{N}(CH_3)_3\ \overset{\ominus}{B}F_4$ or $CH_3CH_2\overset{\oplus}{N}(CH_3)_3\ \overset{\ominus}{O}CH_3$ on heating in methanol solution.

Exercise 8-39 Show the products of the following reactions and indicate the stereochemistry where important.

a. *trans*-1-bromo-3-methylcyclopentane $\xrightarrow[\text{acetone}]{KI}$

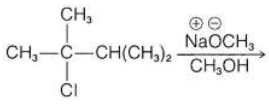
b. *trans*-1-chloro-2-methylcyclopentane $\xrightarrow[\textit{tert}\text{-butyl alcohol}]{{}^{\oplus}K^{\ominus}OC(CH_3)_3}$

c.



d. *D*-2-butanol $\xrightarrow{\text{potassium metal}}$ potassium salt $\xrightarrow{\textit{L}\text{-2-chlorobutane}}$

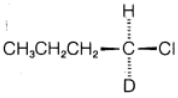
e.



f. *meso*-1,2-dibromo-1,2-diphenylethane $\xrightarrow{{}^{\oplus}K^{\ominus}OC(CH_3)_3}$

Exercise 8-40 The S_N1 reactions of many RX derivatives that form moderately stable carbocations are substantially retarded by adding $X^{\ominus}$ ions. However, such retardation is diminished, at given $X^{\ominus}$ concentrations, by adding another nucleophile such as $N_3{}^{\ominus}$. Explain.

Exercise 8-41 The reaction of 1-chlorobutane with sodium hydroxide to give 1-butanol is catalyzed by sodium iodide.



a. Work out the stereochemistry to be expected for both the catalyzed and the uncatalyzed reactions if (optically active) were used as the starting material. Show your reasoning.

b. Does retention of configuration, as the overall result of an S_N2, automatically preclude operation of the usual mechanism? Explain.

Exercise 8-42* Suppose a water solution was made up initially to be 0.01 M in methyl bromide and 1.0 M in sodium ethanoate at 50°. In water, the S_N2 rate constant for reaction of hydroxide ion with methyl bromide at 50° is 30×10^{-4} L mol^{-1} sec^{-1}, whereas that of ethanoate ion at 50° is 1.0×10^{-4} L mol^{-1} sec^{-1}. The ionization constant of ethanoic acid at 50° is 1.8×10^{-5}. In the following, neglect the rates of the reactions of methyl bromide with water or ethanoic acid and any further reactions of ethanoate:

a. Calculate the hydroxide-ion concentration in the initial solution.

b. Calculate the initial rates of formation of methyl ethanoate and methanol.

c. Compute the concentrations of the organic products when the reaction is complete. Show your reasoning and justify any assumptions.

d. What kind of information would be needed to predict what products would be expected from a solution of methyl bromide and sodium hydroxide in methanol? Explain.

Exercise 8-43 Indicate how you would synthesize each of the following substances from the given organic starting materials and any other necessary organic or inorganic reagents. Specify reagents and conditions. (You may have to use reactions discussed in

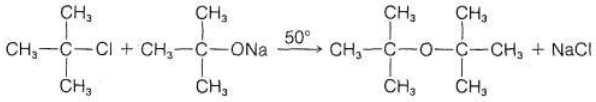
Chapter 4.)

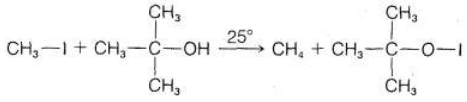
a. $CH_2{=}CH{-}CH_2OCOCH_3$ from propene
b. $CH_3{-}O{-}CH_2CH_3$ from ethanol
c. $CH_3{-}O{-}C(CH_3)_3$ from *tert*-butyl alcohol
d. cyclohexene from cyclohexane

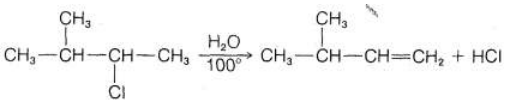
Exercise 8-44 Which compound in each of the following pairs would you expect to react more readily with (A) potassium iodide in 2-propanone, (B) concentrated sodium hydroxide in ethanol, and (C) silver nitrate in aqueous ethanol? Write equations for all the reactions involved and give your reasoning with respect to the predicted orders of reactivity.

a. methyl chloride and isobutyl chloride with A, B, and C
b. methyl chloride and *tert*-butyl chloride with A, B, and C
c. *tert*-butyl chloride and 1-fluoro-2-chloro-2-methylpropane with B and C
d. 1-chloro-2-butene and 4-chloro-1-butene with A, B, and C

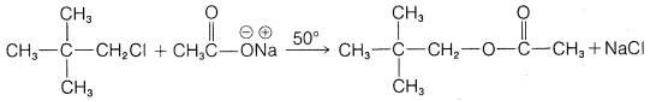
Exercise 8-45 Classify each of the following reactions from the standpoint of yield, side reactions, and reaction rate as good, fair, or bad synthetic procedures for preparation of the indicated products under the given conditions. Show your reasoning and designate any important side reactions.

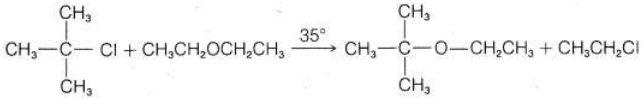
a.


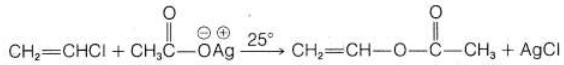
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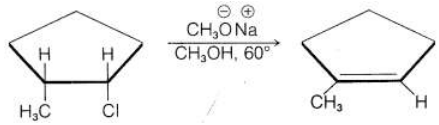
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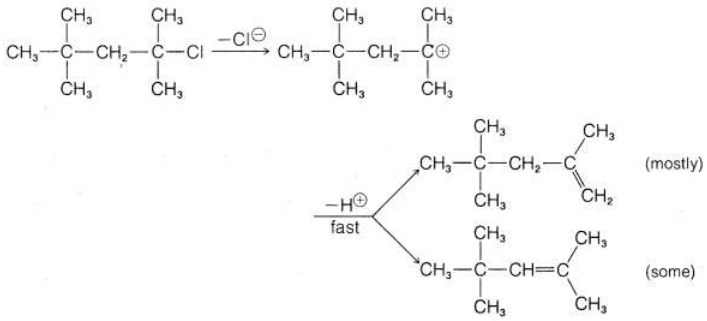
h.


Exercise 8-46 Consider each of the following compounds to be in unlabeled bottles in pairs as indicated. For each pair give a chemical test (preferably a test-tube reaction) that will distinguish between the two substances. Write equations for the reactions involved.

	Bottle A	*Bottle B*
a.	$(CH_3)_3CCH_2Cl$	$CH_3CH_2CH_2CH_2Cl$
b.	$BrCH{=}CHCH_2Cl$	$ClCH{=}CHCH_2Br$
c.	$(CH_3)_3CCl$	$(CH_3)_2CHCH_2Cl$
d.	$CH_3CH{=}CHCl$	$CH_2{=}CHCH_2Cl$
e.	$(CH_3)_2C{=}CHCl$	$CH_3CH_2CH{=}CHCl$
f.	$CH_3CH_2CH{=}CHCl$	$CH_2{=}CHCH_2CH_2Cl$

(8.P.8)

Exercise 8-47 Why does the following ***E*1** reaction give more of the least substituted alkene? (Use models.)



Contributors

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CHAPTER OVERVIEW

9: Structure Determination Part 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.

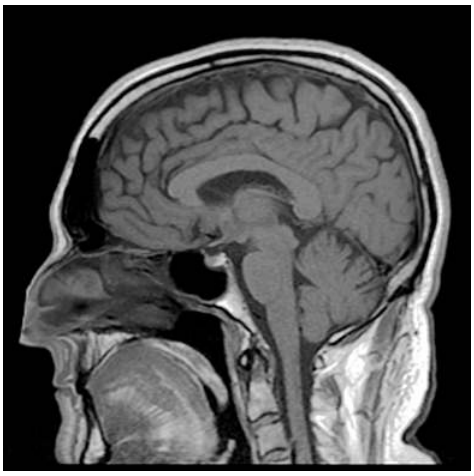
In NMR, the nuclei of hydrogen, carbon, and other important elements undergo transitions in their magnetic states, leading to the absorbance of radiation in the radio frequency range of the electromagnetic spectrum. By analyzing the signals from these transitions, we learn about the chemical environment 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.

9.1: Prelude to Structure Determination
9.2: The Origin of the NMR Signal
9.3: Chemical Equivalence
9.4: The 1H-NMR experiment
9.5: The Basis for Differences in Chemical Shift
9.6: Spin-Spin Coupling
9.7: 13C-NMR Spectroscopy
9.8: Solving Unknown Structures
9.9: Complex Coupling in Proton Spectra
9.10: Other Applications of NMR
9.11: Structure Determination (Problems)
9.12: Structure Determination (Summary)

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9.1: 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 to 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.

Contributors

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

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9.2: 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.

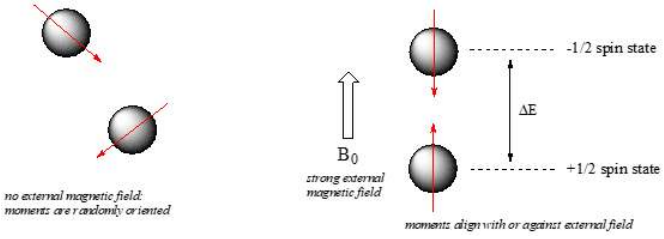
In practice it is ^1H and ^{13}C nuclei that are most commonly observed by NMR spectroscopy, and it is on those techniques that we will focus in this chapter, beginning with ^1H-NMR. The terms ‘proton’ and ‘hydrogen’ are used interchangeably when discussing because the ^1H nucleus is just a single proton.

Table **9.2.1**: 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

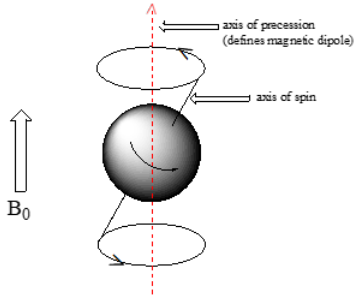
When a sample of an organic compound is sitting in a flask on a laboratory bench, the magnetic moments of all of its protons are randomly oriented. However, when the same sample is placed within the field of a very strong superconducting magnet (this field is referred to by NMR spectroscopists as the 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.

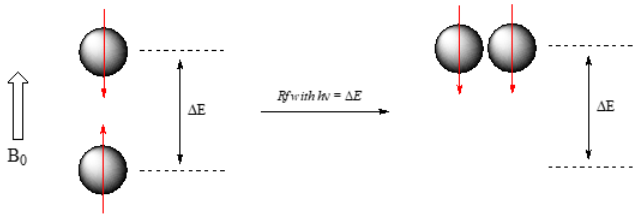


Watch the first minute or so of this video of spinning tops: look for the precessional motion

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 9.2.1

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?

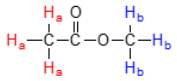
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9.3: Chemical Equivalence

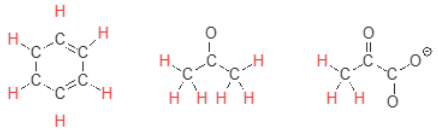
The frequency of radiation absorbed by a proton (or any other nucleus) during a spin transition in an NMR experiment is called its 'resonance frequency'. If all protons in all organic molecules had the same resonance frequency, NMR spectroscopy but would not be terribly useful for chemists. Fortunately 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

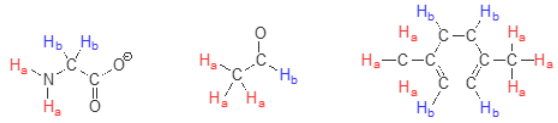
The three methyl acetate protons labeled Ha above have a different resonance frequency compared to the three Hb protons, because the two sets of protons are in non-identical electronic environments: the H_a protons are on a carbon next to a carbonyl carbon, while the H_b protons or on a carbon next to 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

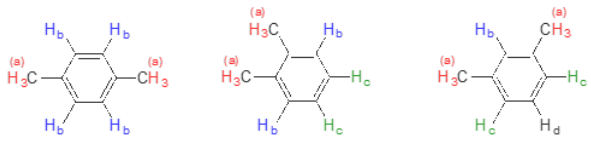
Each of the molecules in the next figure contains two sets of chemically equivalent protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



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.

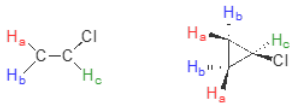


1,4-dimethylbenzene 1,2-dimethylbenzene 1,3-dimethylbenzene

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.

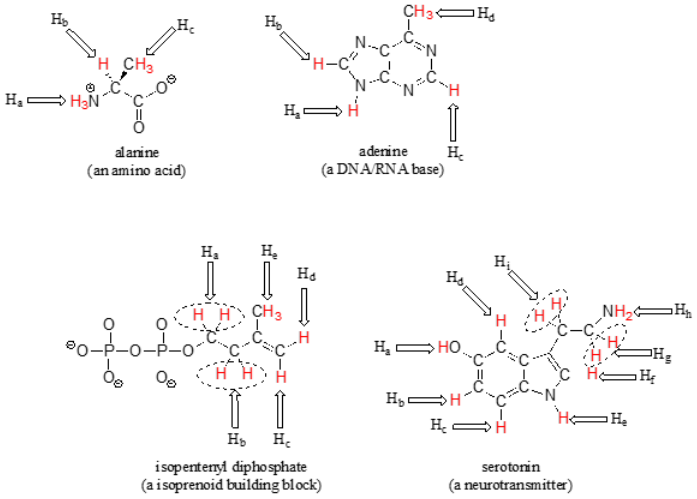
As you have probably already realized, chemical equivalence or non-equivalence in NMR is closely related to symmetry. Different planes of symmetry in the three isomers of dimethylbenzene lead to different patterns of equivalence.

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.



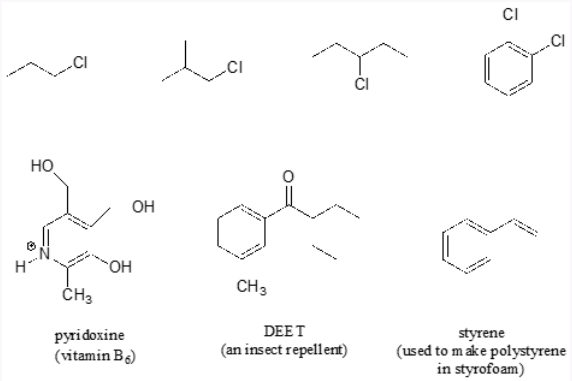
If you think back to our discussion of prochirality in section 3.11, you should recognize that the H_a and H_b protons in the examples above are diastereotopic pairs.

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 9.3.1

How many sets of equivalent protons do the following molecules contain?



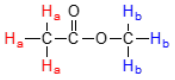
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9.4: The 1H-NMR experiment

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!)



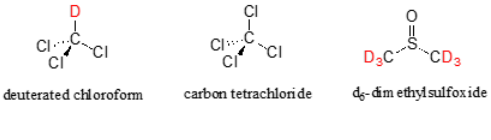
methyl acetate

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'.

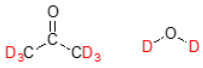
> **Note**
>
> The above description of an NMR experiment is an oversimplification of what is happening in a modern NMR instrument, but is adequate for our purpose here. If you take a more advanced course in molecular spectroscopy you will learn about the process is much greater detail.

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

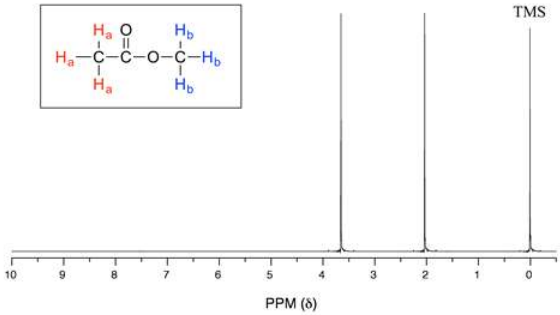


deuterated chloroform | carbon tetrachloride | d_6-dimethylsulfoxide

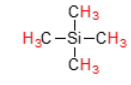


d_6-acetone | D_2O

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 9.4.1

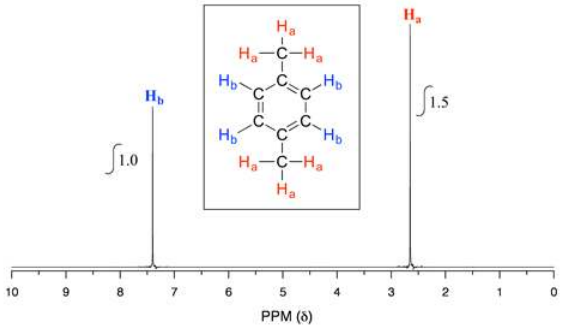
a. What is the chemical shift, expressed in Hz, of proton signals at 2.0 ppm and 3.6 ppm for an NMR instrument in which the TMS protons have a resonance frequency of exactly 500 MHz?

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 9.4.2

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 9.4.3

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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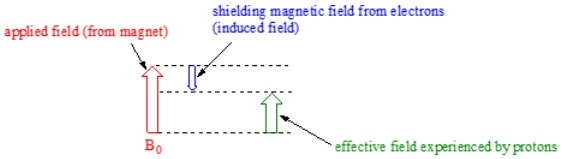
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9.5: The Basis for Differences in Chemical Shift

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.



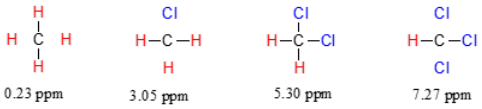
Because B_{eff} is slightly weaker than B0, the resonance frequency (and thus the chemical shift) of the methane proton is slightly lower than what it would be if it did not have electrons nearby and was feeling the full force of B_0. (You should note that the figure above is not to scale: the applied 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).

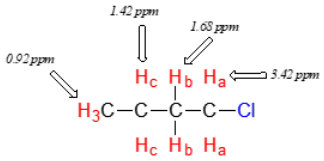


To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton.

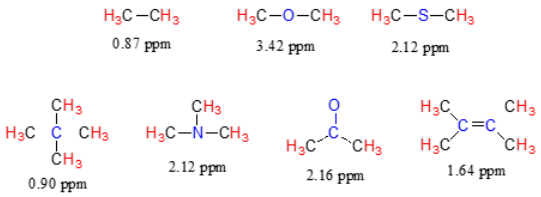
The chemical shift of trichloromethane (common name chloroform) is, as expected, higher than that of dichloromethane, which is in turn higher than that of chloromethane.



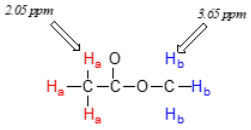
The deshielding effect of an electronegative substituent diminishes sharply with increasing distance:



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:

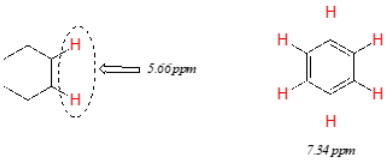


Now we can finally assign the two peaks in the the ^1H-NMR spectrum of methyl acetate. We can predict that the methyl ester protons (H_b), which are deshielded by the adjacent oxygen atom, will have a higher chemical shift than the acetate protons (H_a), which are deshielded to a lesser extent by the carbonyl group. Therefore, the signal at 3.7 must correspond to H_b, and the signal at 2.0 to H_a.



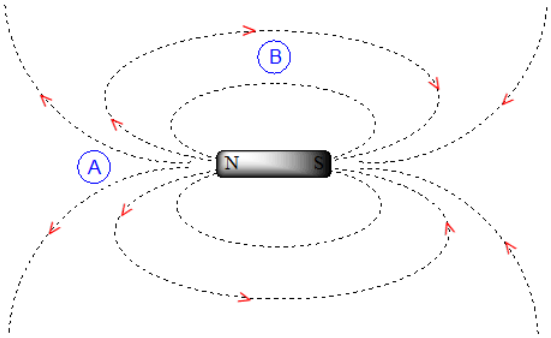
Diamagnetic anisotropy

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:



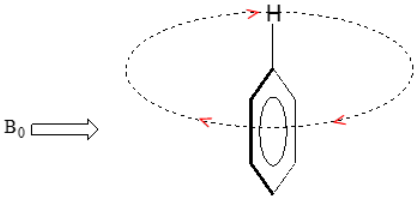
We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a ring current, generating their own induced magnetic field that opposes 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.



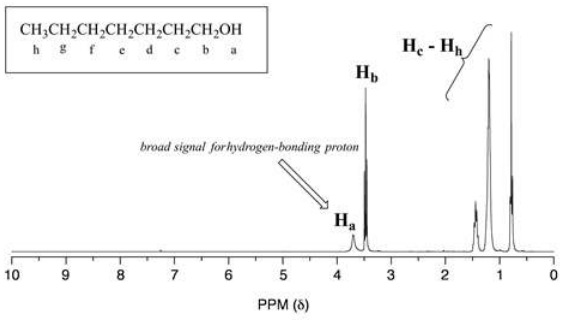
The end result is that aromatic protons, due to the anisotropy of the induced field generated by the *pi* ring current, appear to be highly deshielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

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.



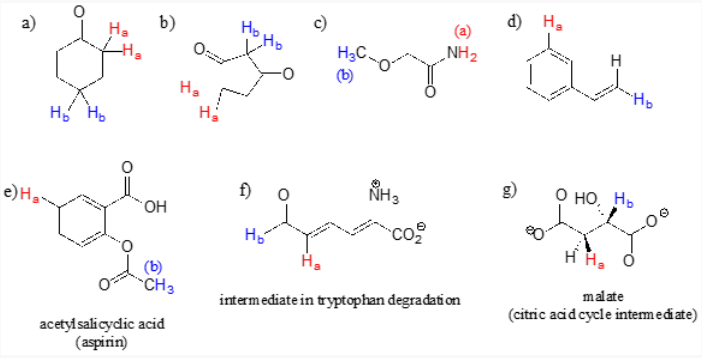
The table below provides a summary of approximate chemical shift ranges for protons in different bonding arrangements. A more detailed table can be found in the appendix.

Table 9.5.1: 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

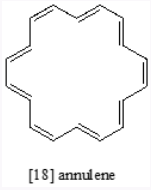
Exercise 9.5.1

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 9.5.2

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.



Contributors

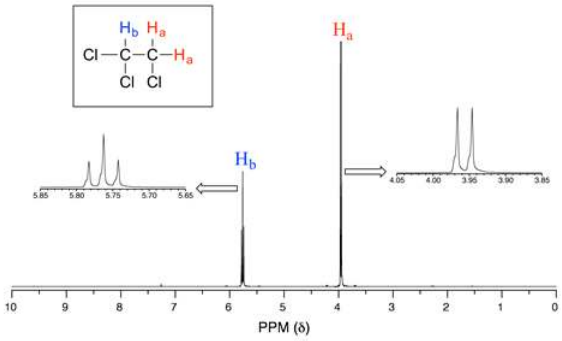
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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9.6: Spin-Spin Coupling

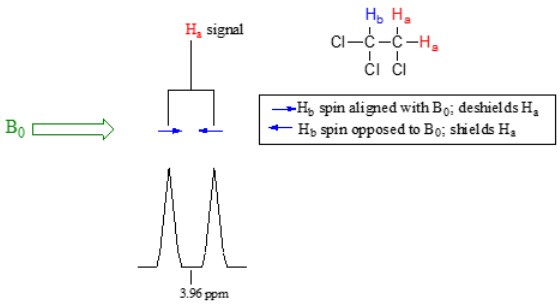
The ^1H-NMR spectra that we have seen so far (of methyl acetate and 1,4-dimethylbenzene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^1H-NMR spectra of most organic molecules contain proton signals that are 'split' 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.



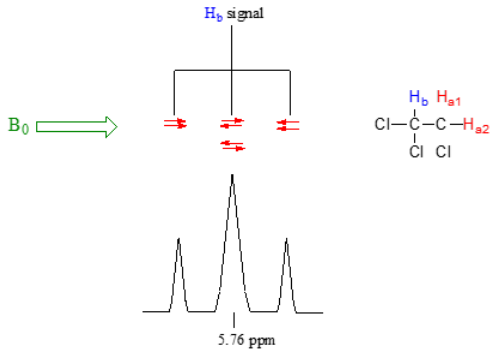
The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a doublet. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were to 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.



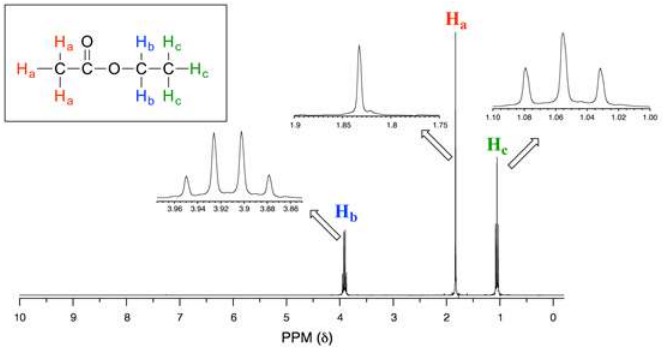
Now, let's think about the H_b signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_a1 and H_a2. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_a1 and H_a2 could 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 9.6.1

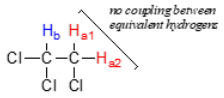
a. Explain, using a splitting diagram, the possible combinations of nuclear spin states for the H_c protons in ethyl acetate, and why the H_b signal is split into a quartet.

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.)

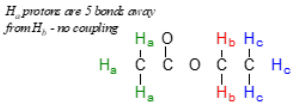
By now, you probably have recognized the pattern which is usually referred to as the n + 1 rule: if a set of protons has n neighboring, non-equivalent protons, it will be split into n + 1 subpeaks. Thus the two H_b protons in ethyl acetate split the H_c signal into a triplet, and the three H_c protons 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.



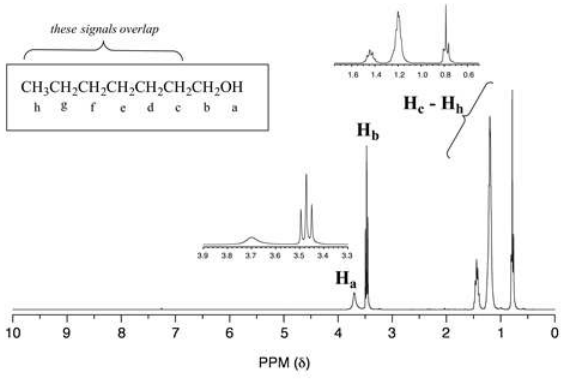
Second, splitting occurs primarily between protons that are separated by three or fewer bonds. This is why the H_a protons in ethyl acetate form a singlet– the nearest proton neighbors are five bonds away, too far for coupling to occur.



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.

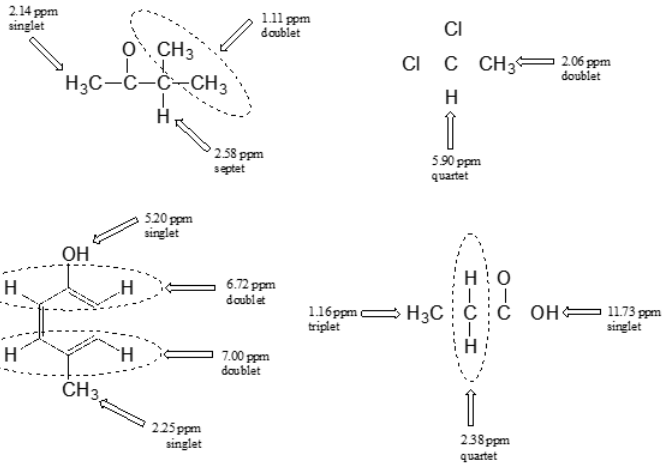
Third, protons that are bonded to oxygen or nitrogen generally do not split - and are not split by - adjacent protons. OH and NH protons are acidic enough to rapidly exchange between different molecules, so the neighboring protons never actually 'feels' their influence.

The spectrum of 1-heptanol has a characteristically broad alcohol proton signal at 3.7 ppm (labeled Ha below).



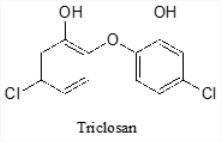
Notice in this spectrum that H_b is a triplet, coupled to the two H_c protons but not coupled to H_a. The signals corresponding to H_c through Hh are complex due to overlapping - when this happens (as it often does!), detailed analysis becomes more challenging.

Below are a few more examples of chemical shift and splitting pattern information for some relatively simple organic molecules.



Exercise 9.6.2

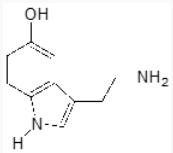
How many proton signals would you expect to see in the ^1H-NMR spectrum of triclosan (a common antimicrobial agent in soap)? For each of the proton signals, predict the splitting pattern, assuming that you can see only 3-bond splitting.



Triclosan

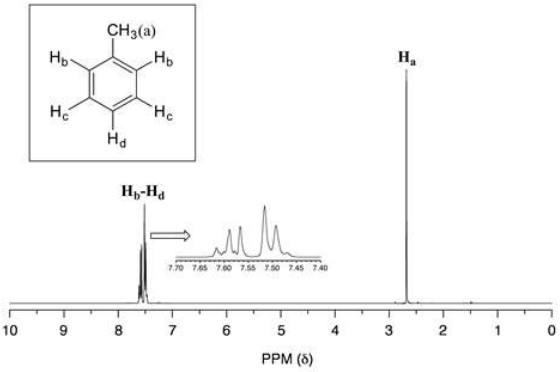
Exercise 9.6.3

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

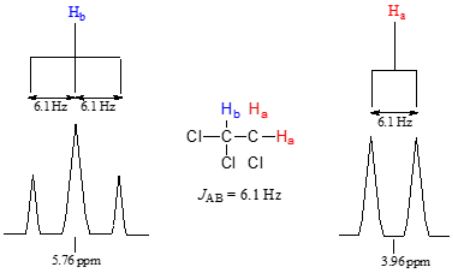
In an ideal world, all NMR spectra would be as easy to interpret as those we have seen so far: every peak would be separated from the others, the peak integration would be obvious, and the multiplicity (singlet, doublet, etc.) would be easy to recognize. The real world, unfortunately, is not always so 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 $^3J_{a-b} = 6.1Hz$.

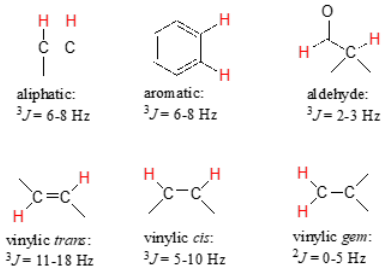


The superscript '3' tells us that this is a three-bond coupling interaction, and the 'a-b' subscript tells us that we are talking about coupling between H_a and H_b. Unlike the chemical shift value, the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR 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 9.6.4

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 **9.6.1**: ^1H-NMR spectrum of ethyl acetate

ppm	splitting	integration
3.92	q	1
1.83	s	1.5
1.06	t	1.5

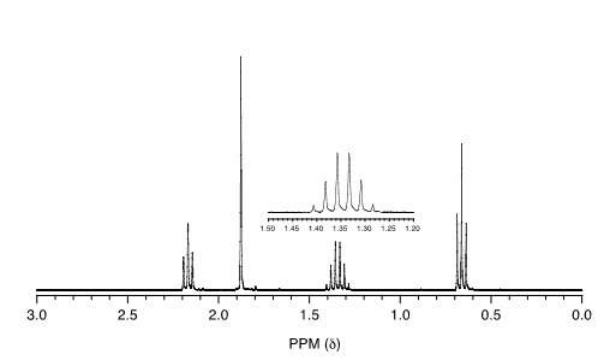
Table 9.6.2: ^1H-NMR spectrum of methylbenzene.

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 9.6.5

Match the ^1H-NMR spectrum below to its corresponding compound, and assign all of the signals.



a) cyclopentanone b) 3-pentanone c) butanal

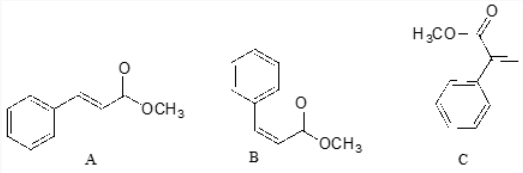
d) 2-pentanone e) 4-heptanone f) 1-butene

Exercise 9.6.6

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 9.6.7

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

Contributors

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

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9.7: 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.

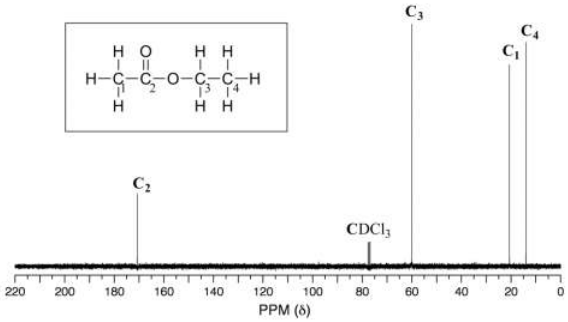
The magnetic moment of a ^{13}C nucleus is much weaker than that of a proton, meaning that NMR signals from ^{13}C nuclei are inherently much weaker than proton signals. This, combined with the low natural abundance of ^{13}C, means that it is much more difficult to observe carbon signals: more sample 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 9.15
How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 9.2?
Exercise 9.16
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)

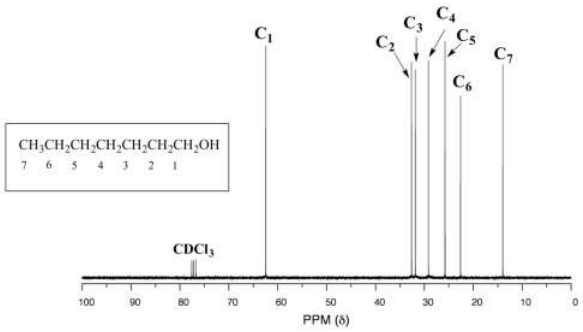
Because of the low natural abundance of ^{13}C nuclei, it is very unlikely to find two ^{13}C atoms near each other in the same molecule, and thus *we do not see spin-spin coupling between neighboring carbons in a ^{13}C-NMR spectrum*. ^{13}C nuclei are coupled to nearby protons, however, which results 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

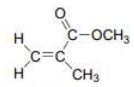
we can almost always distinguish separate peaks for each carbon, even in a relatively large compound containing carbons in very similar environments. In the proton spectrum of 1-heptanol we saw earlier only the broad singlet of the alcohol proton (H_a) and the triplet for (H_b) are easily analyzed. The 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 9.17

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.

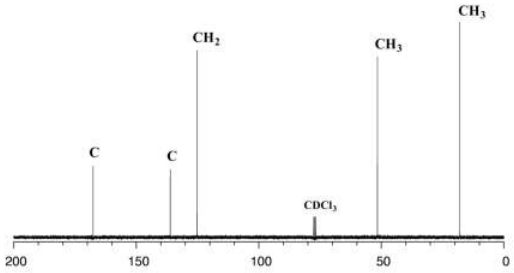


methyl methacrylate

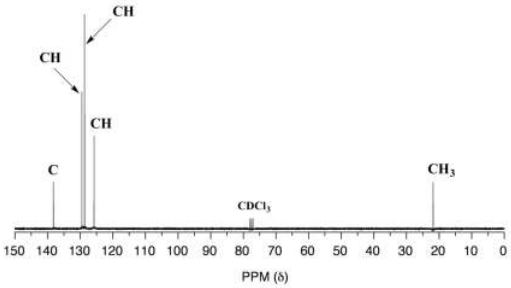


toluene

Spectrum A:



Spetrum B:



Exercise 9.18

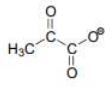
^{13}C-NMR data for some common biomolecules are shown below (data is from the Aldrich Library of ^{1}H and ^{13}C NMR). Match the NMR data to the correct structure, and make complete peak assignments.

spectrum a: 168.10 ppm (C), 159.91 ppm (C), 144.05 ppm (CH), 95.79 ppm (CH)

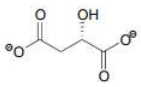
spectrum b: 207.85 ppm (C), 172.69 ppm (C), 29.29 ppm (CH_3)

spectrum c: 178.54 ppm (C), 53.25 ppm (CH), 18.95 ppm (CH_3)

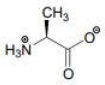
spectrum d: 183.81 ppm (C), 182. 63 ppm (C), 73.06 ppm (CH), 45.35 ppm (CH_2)



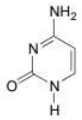
pyruvate



(S)-malate



alanine

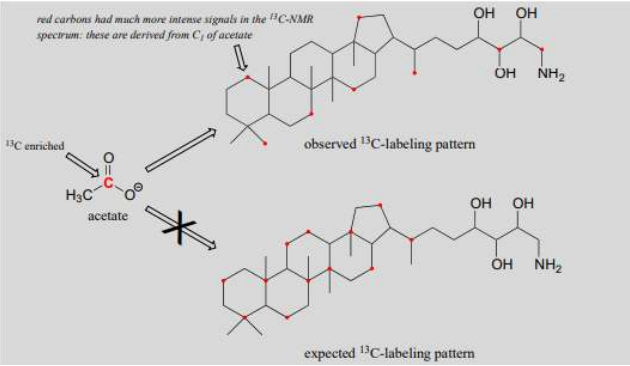


cytosine

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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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9.8: 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:

$$IHD = \frac{(2n+2) - A}{2} \tag{9.8.1}$$

where:

n = number of carbon atoms

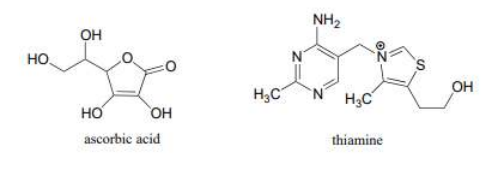
A = (number of hydrogen atoms) + (number of halogen atoms) - (number of nitrogen atoms) - (net charge)

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 9.8.1

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 $C_3H_8NO_2^+$ 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)

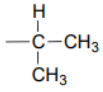
31.06 (CH)

20.08 (CH_3)

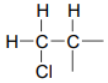
The process of piecing together an organic structure is very much like putting together a puzzle. In every case we start the same way, determining the molecular formula and the IHD value. After that,

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:

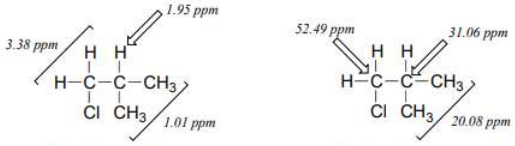


The ^1H-NMR signal at 3.38 ppm must be for protons bound to the carbon which is in turn bound to the chlorine (we infer this because this signal is the furthest downfield in the spectrum, due to the deshielding effect of the electronegative chlorine). This signal is for two protons and is a doublet, 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 9.8.1

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 9.8.2

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)

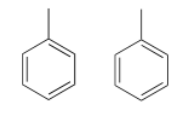
138.4 (C) 127.2 (CH)

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).

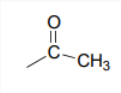


This accounts for 12 carbons, 10 hydrogens, and 8 IHD units. Notice that the carbon spectrum has only six peaks - and only four peaks in the aromatic region! This again indicates that the two phenyl groups are in chemically equivalent positions

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:

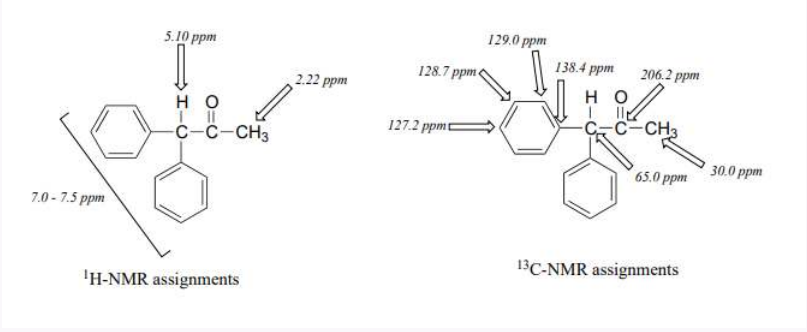


fig 43

Answer

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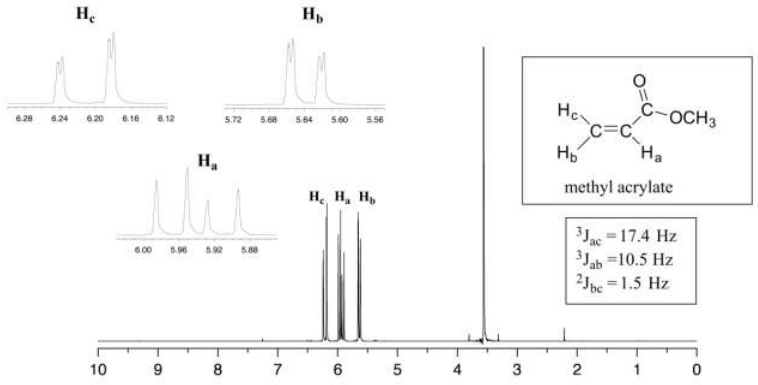
Contributors

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

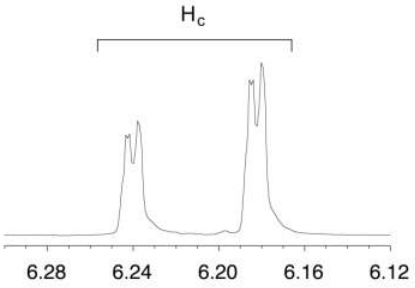
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9.9: Complex Coupling in Proton Spectra

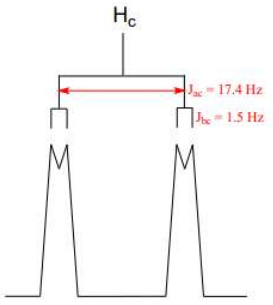
In all of the examples of spin-spin coupling we saw in our discussion of proton NMR, the observed splitting resulted from the coupling of one set of protons to just one neighboring set of protons. When a set of protons is coupled to two sets of nonequivalent neighbors, with significantly different coupling 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.



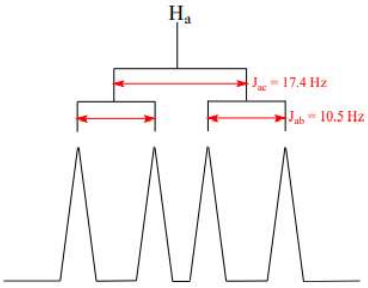
The result of this `double splitting` is a pattern referred to as a doublet of doublets, abbreviated `**dd**`.

The reported chemical shift of H_c is 6.210 ppm, the average of the four sub-peaks.

Exercise 9.9.1

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 9.9.2

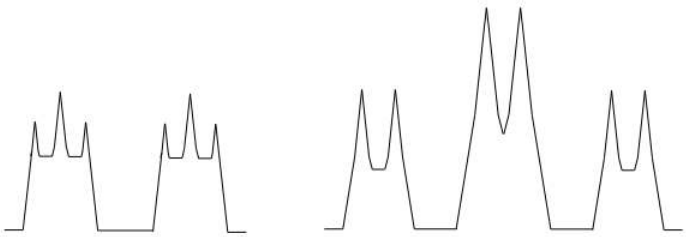
Construct a splitting diagram for the Hb signal in the ^1H-NMR spectrum of methyl acrylate. The chemical shift of H_b, in Hz, is 1691 Hz - label the chemical shifts (in Hz) of each of the four sub-peaks.

Exercise 9.9.3

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.

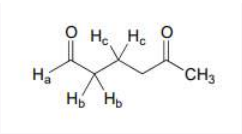


a doublet of triplets

a triplet of doublets

Exercise 9.9.4

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 9.9.5

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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9.10: 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.



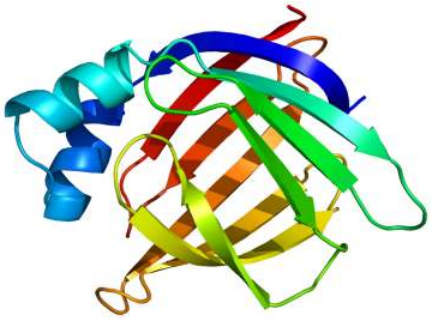
NMR of proteins and peptides

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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9.11: Structure Determination (Problems)

P9.1:

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.



P9.2: For each of the 20 common amino acids, predict the number of signals in the proton-decoupled $^{13}C-NMR$ spectrum.

P9.3: 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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9.12: 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

10: Electrophilic Reactions

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10.2: Electrophilic Addition to Alkenes
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10.4: Electrophilic Isomerization
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10.6: Carbocation Rearrangements
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10.1: 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/)

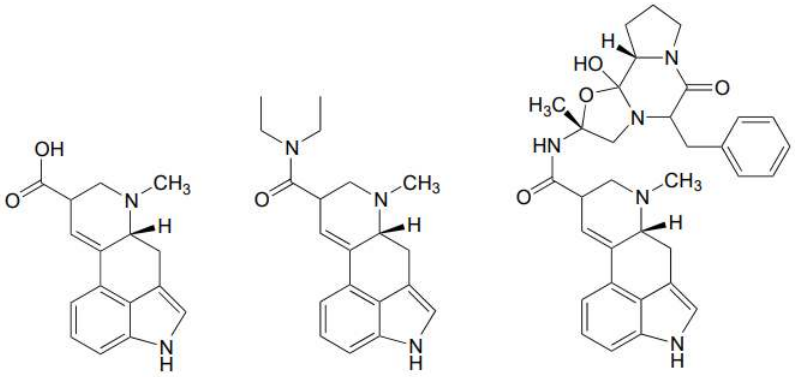
As Linnda continued to read accounts of the 'fits' afflicting the Salem girls, she was suddenly struck by the similarities to another, more recent episode that she had read about. In the summer of 1951, in the French village of Pont Saint Esprit, a number of local people were simultaneously seized by 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.



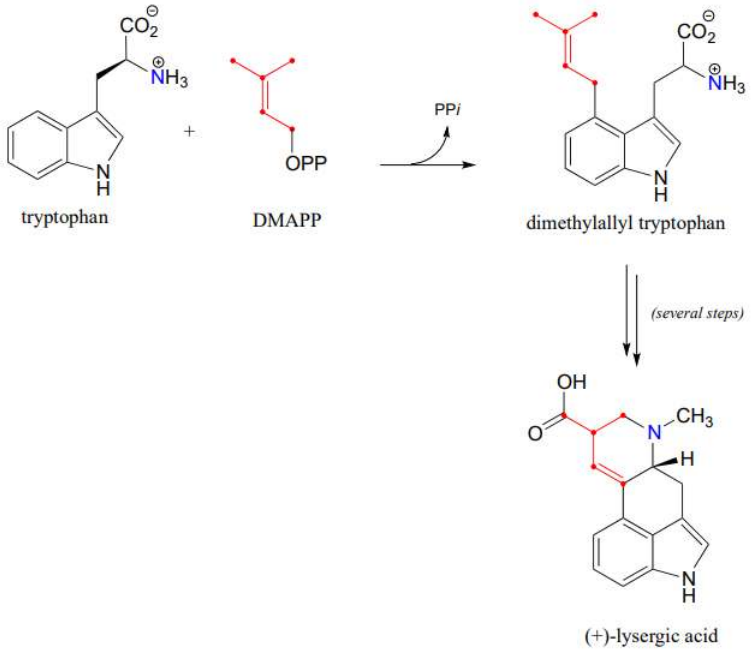
Digging deeper into the records of the Salem witchcraft episode, Linnda Caporael learned that the summer of 1691 was unusually damp. The first cases of 'bewitchment' in Salem village occurred in the winter of 1691-1692, when the villagers would have been consuming grain stored from the previous summer. 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.

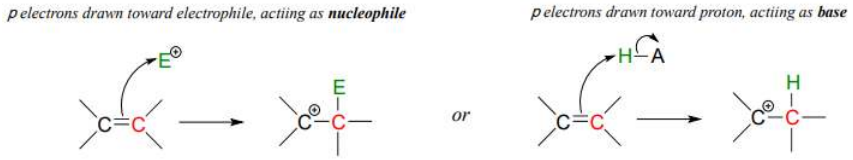
(William Shakespeare's The Tempest, Act II scene ii)

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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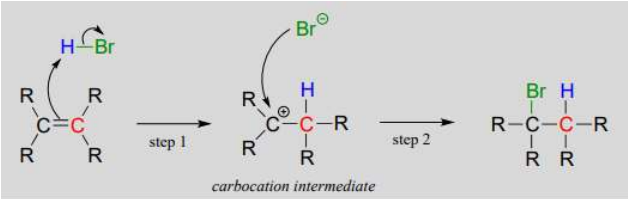
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10.2: Electrophilic Addition to Alkenes

Addition of HBr to alkenes

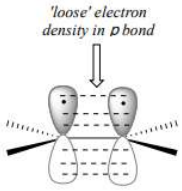
The simplest type of electrophilic reaction to visualize is the addition of a haloacid such as HBr to an isolated alkene. It is not a biological reaction, but nonetheless can serve as a convenient model to introduce some of the most important ideas about electrophilic reactions.

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.

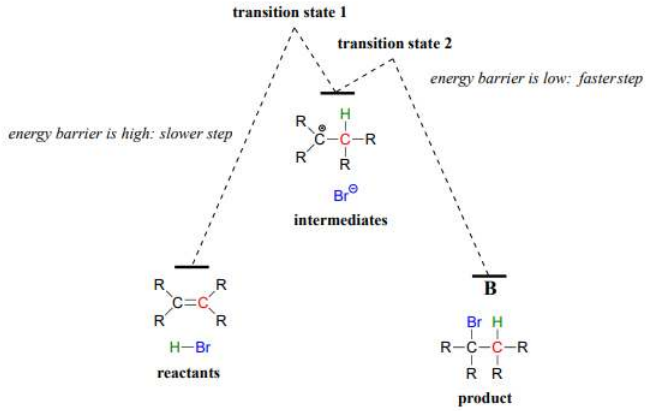
To understand how π-bonded electrons in an alkene could be basic, let's first review the bonding picture for alkenes. Recall (section 2.1) that both of the carbons in an alkene group are sp^2 hybridized, meaning that each carbon has three sp^2 hybrid orbitals extending out in the same plane at $180°$ 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.

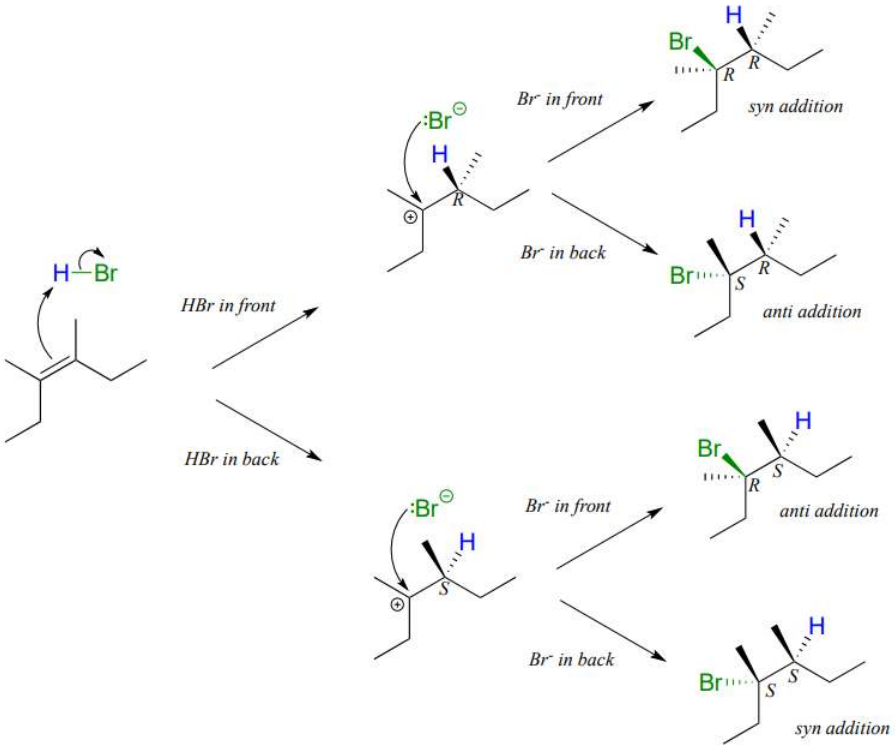
As the HBr molecule approaches the alkene, a new s bond is formed between one of the alkene carbons and the electron-poor proton from HBr. The carbon, which was sp^2 hybridized when it was part of the alkene, is now sp^3 hybridized. The other alkene carbon is still sp^2 hybridized, but it now bears a 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.



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.

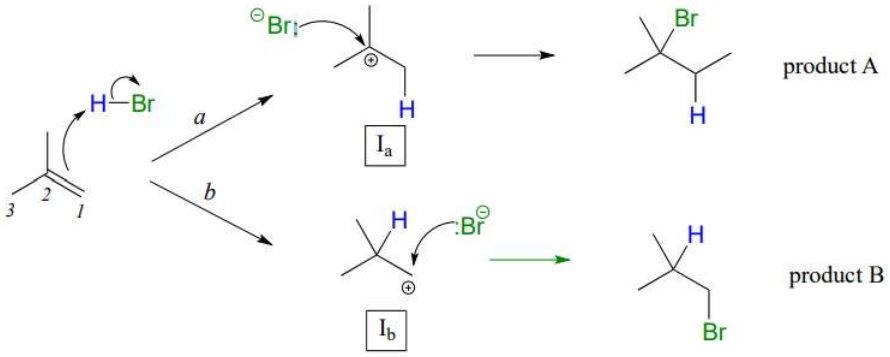
Exercise 10.2.1

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.

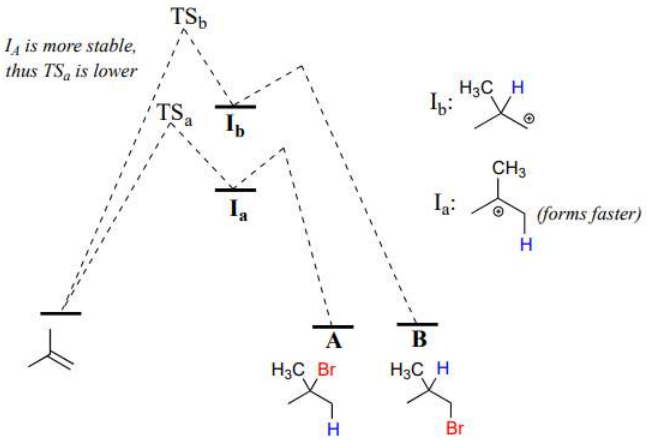
a. trans-2-butene
b. cis-3-hexene
c. cyclopentene

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.



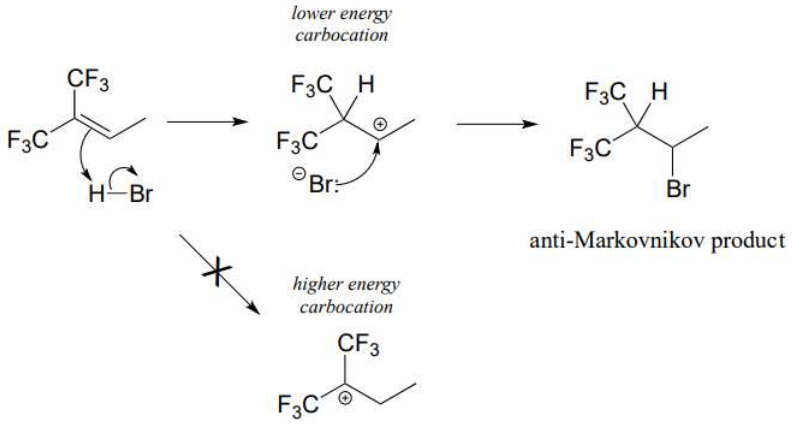
Because the protonation step is the rate determining step for the reaction, tertiary alkyl bromide A will form faster than the primary alkyl bromide B, and thus A will be the predominant product of the reaction. The electrophilic addition of HBr to 2-methylpropene is regioselective: more than one constitutional 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

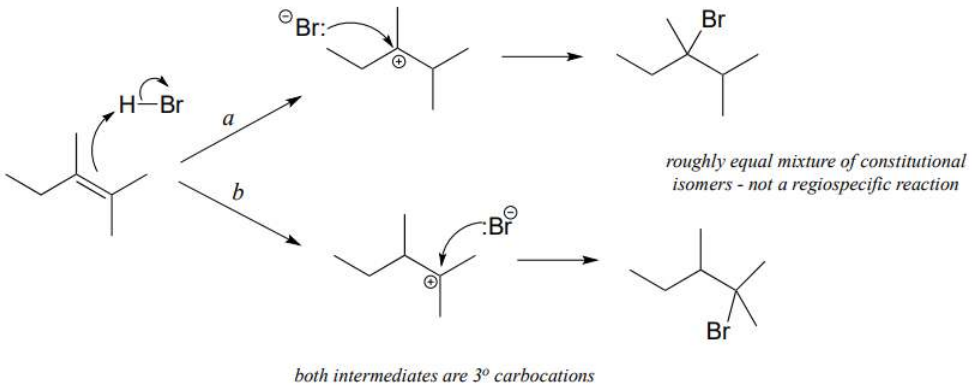
When an asymmetrical alkene undergoes electrophilic addition, the product that predominates is the one that results from the more stable of the two possible carbocation intermediates.

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.

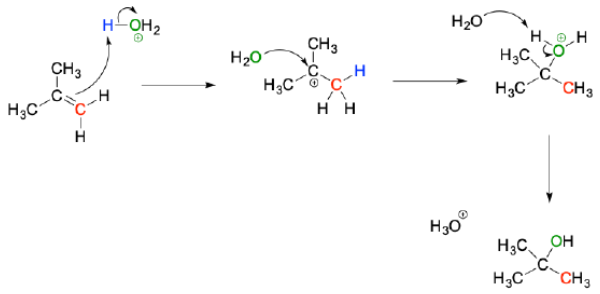


Figure **10.2.10**

If an alkene is treated with methanol and a catalytic amount of strong acid, the result is an ether:

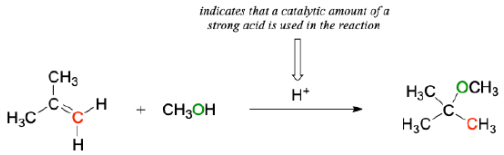


Figure **10.2.11**

Exercise 10.2.2

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.

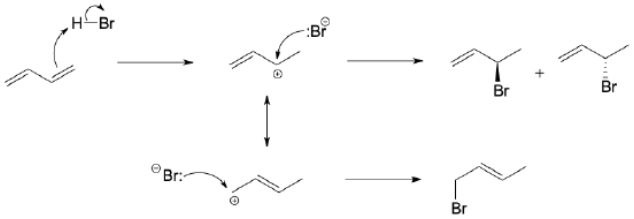


Figure **10.2.12**

Exercise 10.2.3

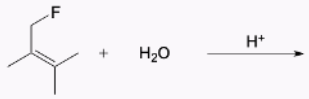
Explain why 4-bromo-1-butene is not a significant product of the reaction above.

Exercise 10.2.4

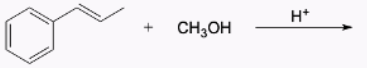
Predict the major product(s) of the following reactions. Draw all possible stereoisomers, and take care not to draw the same structure twice.

a. 

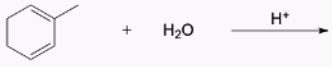
b. 

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.

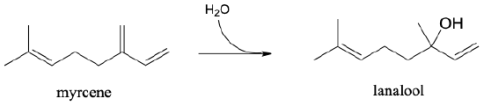


Figure **10.2.13**

Exercise 10.2.5

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:

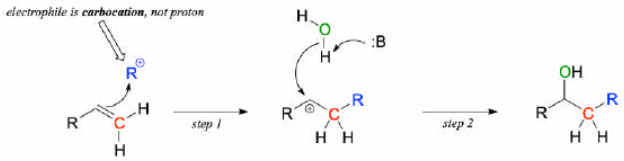


Figure **10.2.14**

□-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.

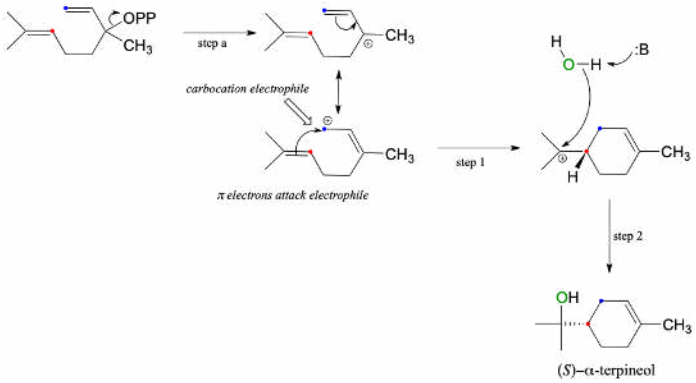


Figure **10.2.15**

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 10.2.6

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'.

Contributors

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

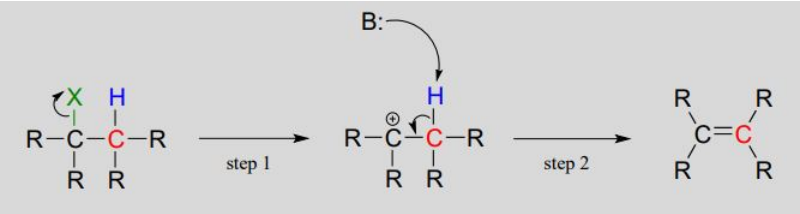
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10.3: Elimination by the E1 Mechanism

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.

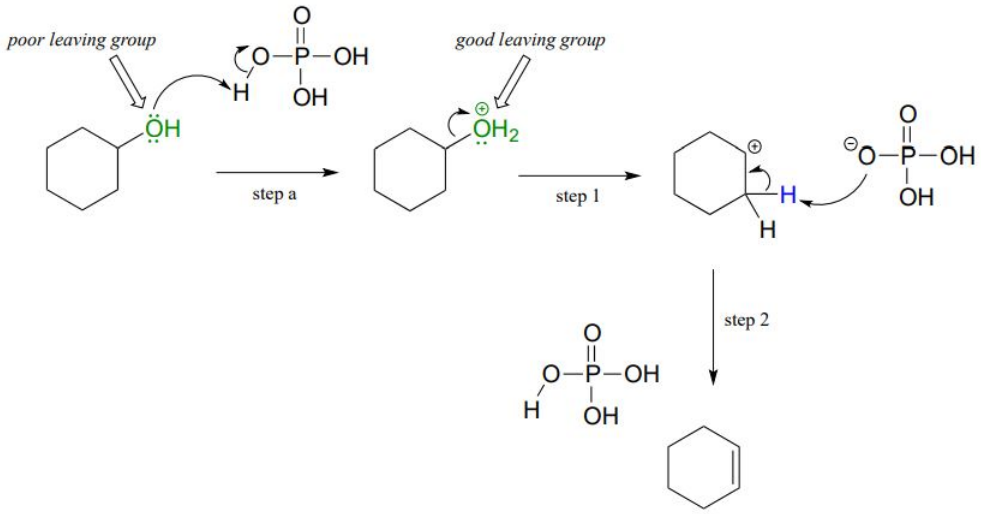
E1 elimination:



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.



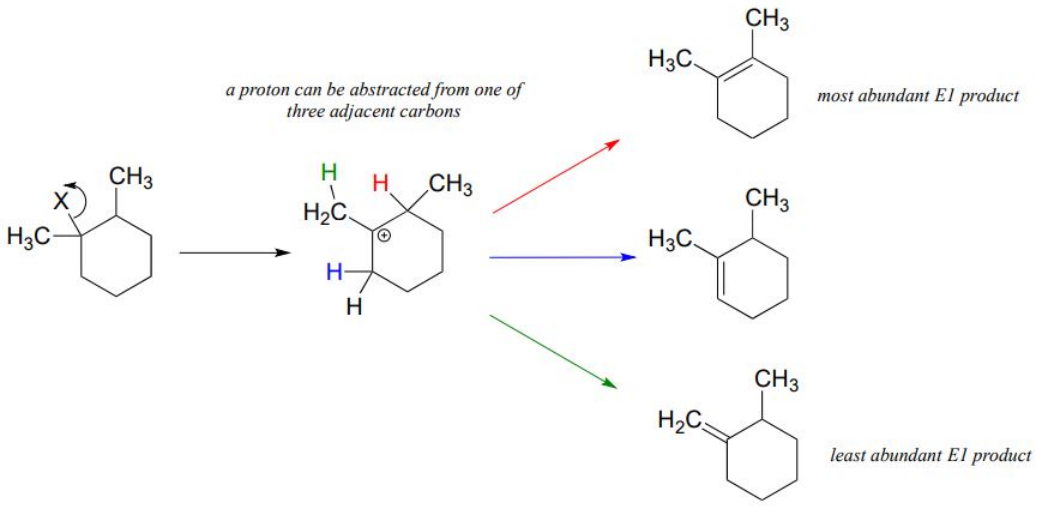
The reaction is reversible, but if cyclohexene is distilled away from the reaction mixture as it forms, the equilibrium can be driven towards product (you may want to review Le Chatelier's principle in your General Chemistry textbook). Separation of cyclohexene (boiling point **83°**) from cyclohexanol (boiling point **161°**) is simple because of the large difference in boiling points between the two liquids.

Exercise 10.3.1

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

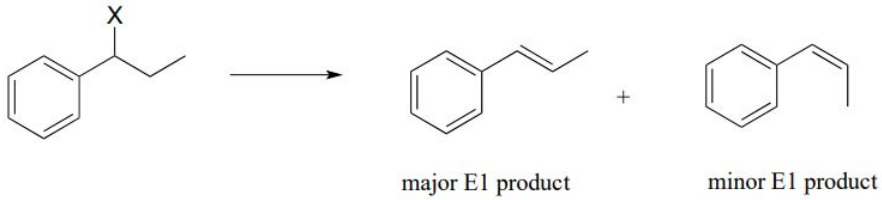
Nonenzymatic E1 reactions can often result in a mixture of more than one alkene product. Elimination of 'HX' from the following starting compound, for example, could yield three different possible alkene products.



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.

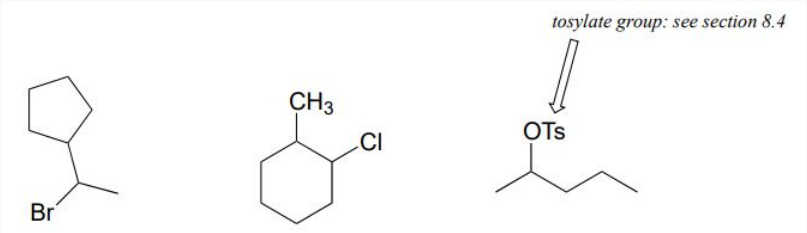
Stereochemistry of E1 elimination

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.



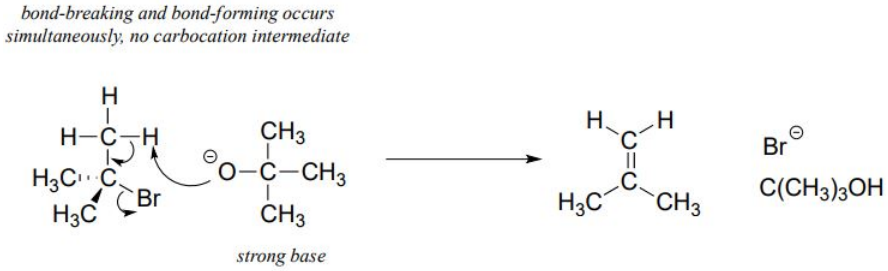
Exercise 10.3.2

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

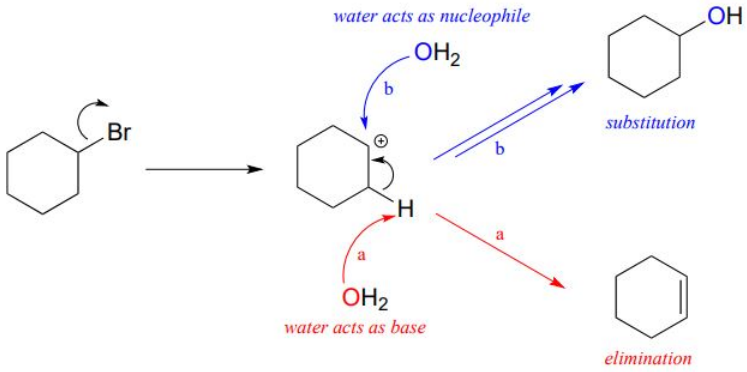
When a strong base is combined with an alkyl halide (or alkyl tosylate/mesylate), elimination generally occurs by the E2 pathway, in which proton abstraction and loss of the leaving group occur simultaneously, without an intervening carbocation intermediate:



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.

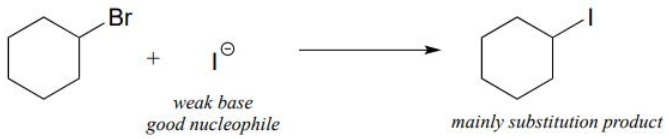
Competition between elimination and substitution

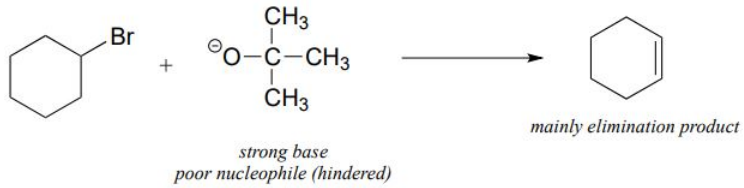
Consider a reaction between water and bromocyclohexane. Based on what we have just learned, a likely product would be the alkene formed from an E1 elimination reaction (pathway (a) in red below).

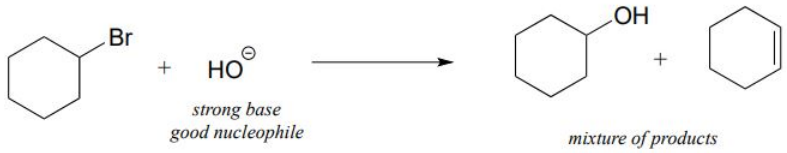


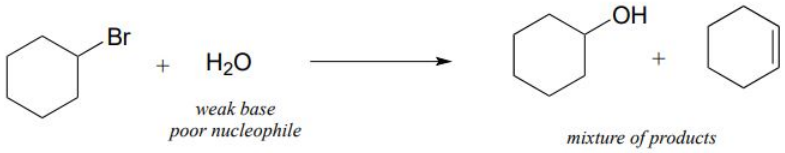
However, the reaction could take another course: what if the water molecule, instead of acting as a base, were to act as a nucleophile (pathway (b) in blue? This should look familiar - it is simply an S_N1 reaction (section 8.1). In fact, the reaction would result in a mixture of elimination (E1) and 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.



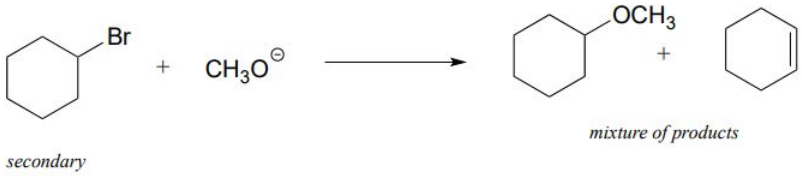






In addition, primary alkyl halides are much more likely to undergo substitution than elimination, even when the nucleophile is also a strong base, because the electrophilic carbon is unhindered and accessible to the nucleophile. Recall that the Williamson ether synthesis (section 8.8) is an efficient 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 10.3.3

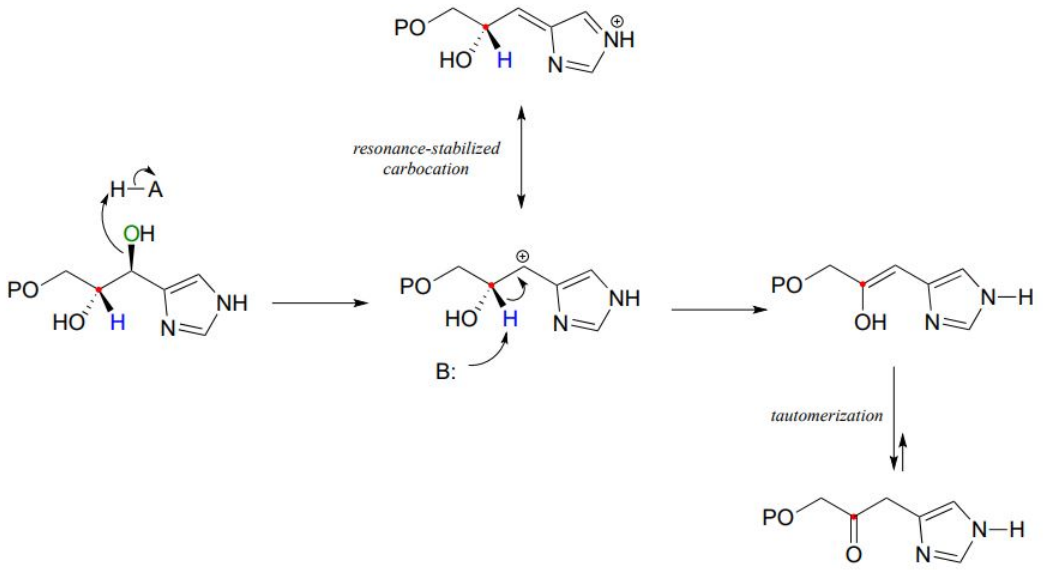
Predict the major organic product(s) of the following reactions. If the reaction is expected to result in a mixture of elimination and substitution product, show both.

a. bromocyclopentane plus ethoxide
b. 1-chlorohexane plus CH3S-
c. 2-iodo-2-methylpentane plus hydroxide

Biochemical E1 elimination reactions

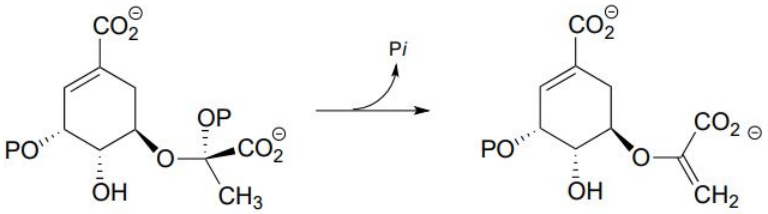
Looking through metabolic pathways in a biochemistry textbook, you'll see that almost all elimination reactions appear to be of the E1cb type, occurring on carbons in the □□□ position relative to a carbonyl or imine. A relatively small number of elimination steps, however, take place away from the electron-withdrawing 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):



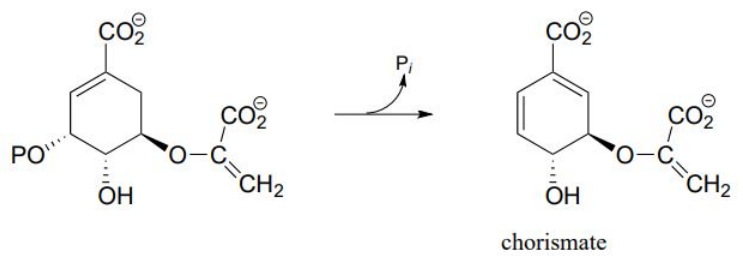
Exercise 10.3.4

Draw a complete mechanism for the reaction above. Show how the carbocation intermediate is stabilized by resonance.

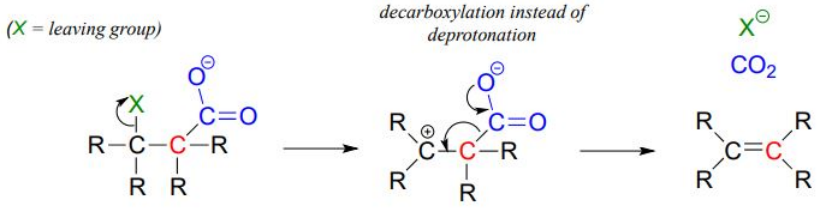
Exercise 10.3.5

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

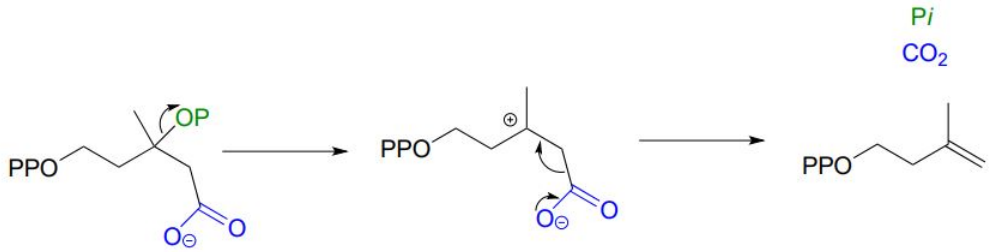
conjugated diene (section 14.1). Draw a complete mechanism for this reaction, showing two resonance contributors of the carbocation intermediate.



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:

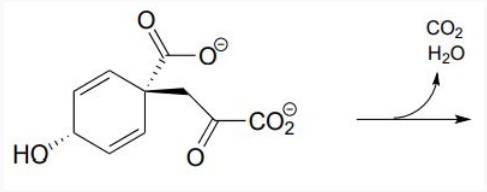


Isopentenyl diphosphate, the 'building block' for all isoprenoid compounds, is a product of this type of hybrid decarboxylation / elimination reaction (EC 4.1.1.33).



Exercise 10.3.6

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?

Contributors

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

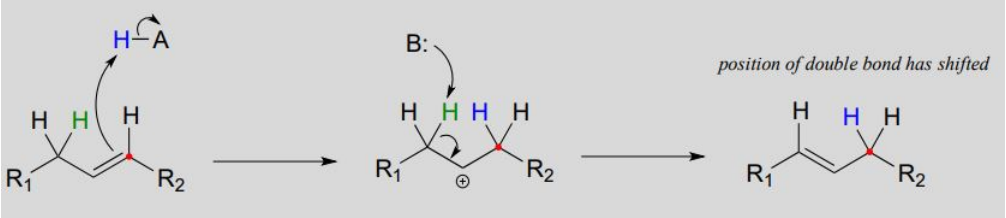
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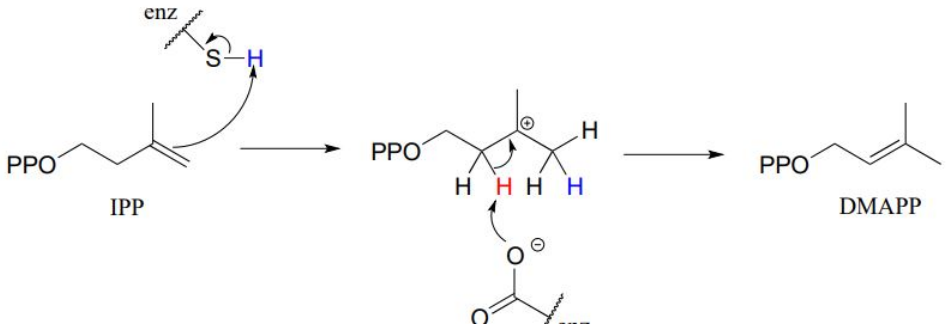
10.4: Electrophilic Isomerization

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.

Contributors

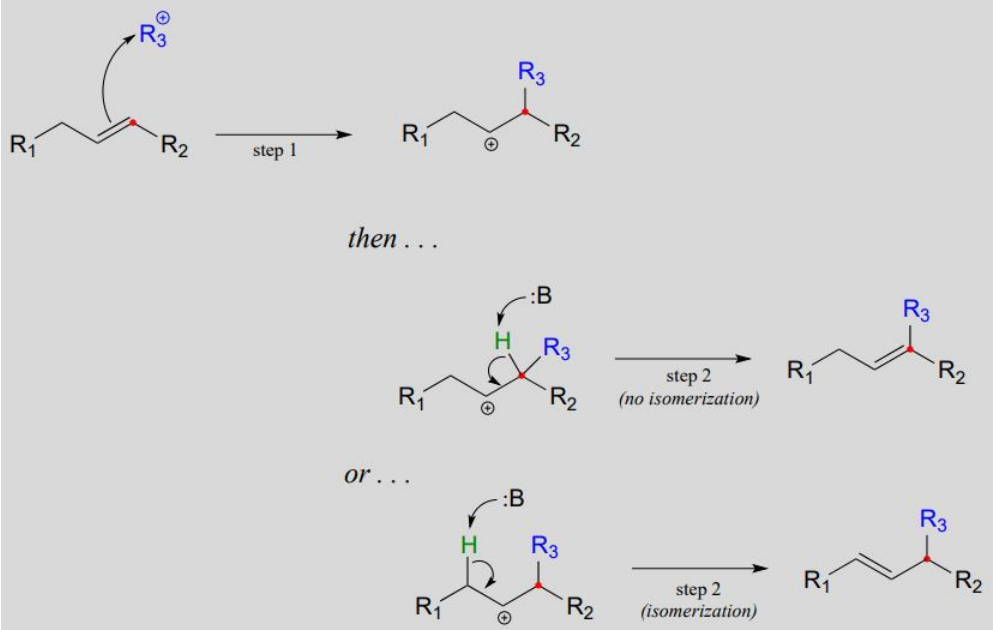
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10.5: Electrophilic Substitution

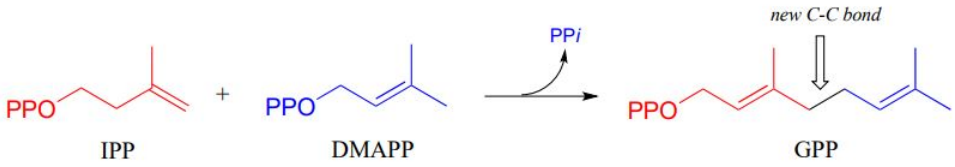
Until now, have already been introduced to electrophilic addition and electrophilic isomerization - now, let's move to the third variation on the electrophilic theme, that of electrophilic substitution. In an electrophilic substitution reaction, a pair of π-bonded electrons first attacks an electrophile - 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:

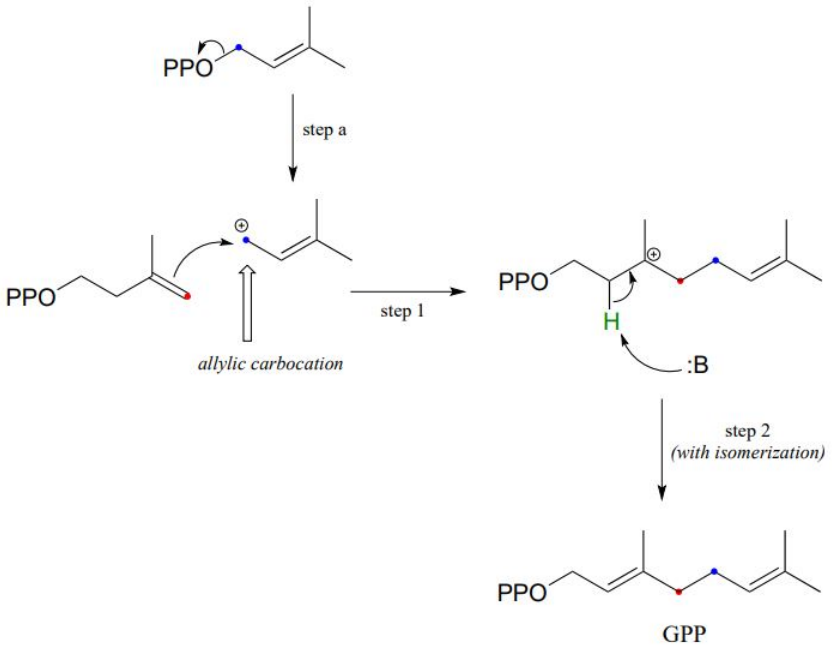


Electrophilic substitution reactions in isoprenoid biosynthesis

Electrophilic substitution steps are very important in the biosynthetic pathways of 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.



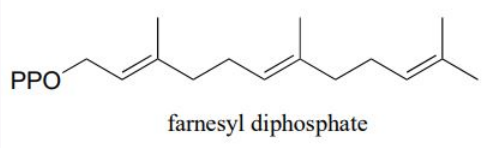
In step 1, the π electrons in IPP then attack the electrophilic carbocation from step a, resulting in a new carbon-carbon bond and a tertiary carbocation intermediate. Proton abstraction (step 2) leads to re-establishment of a double bond one carbon over from where it started out in IPP.

Exercise 10.5.1

DMAPP is much more prone to spontaneous hydrolysis than IPP when they are dissolved in water. Explain why.

Exercise 10.5.2

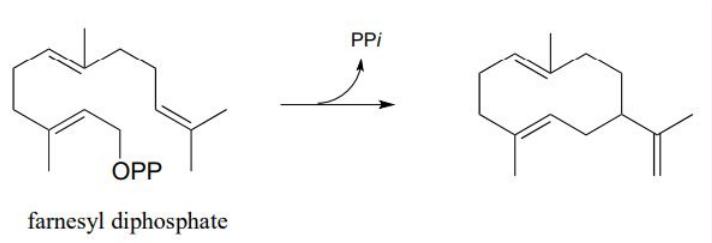
Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



farnesyl diphosphate

Exercise 10.5.3

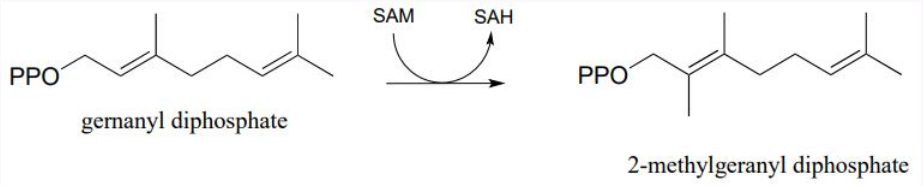
Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



farnesyl diphosphate

Exercise 10.5.4

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)



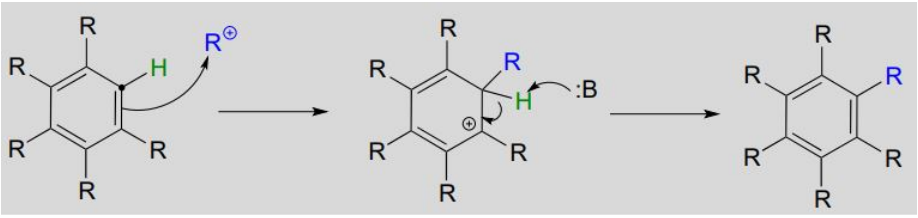
gernanyl diphosphate

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

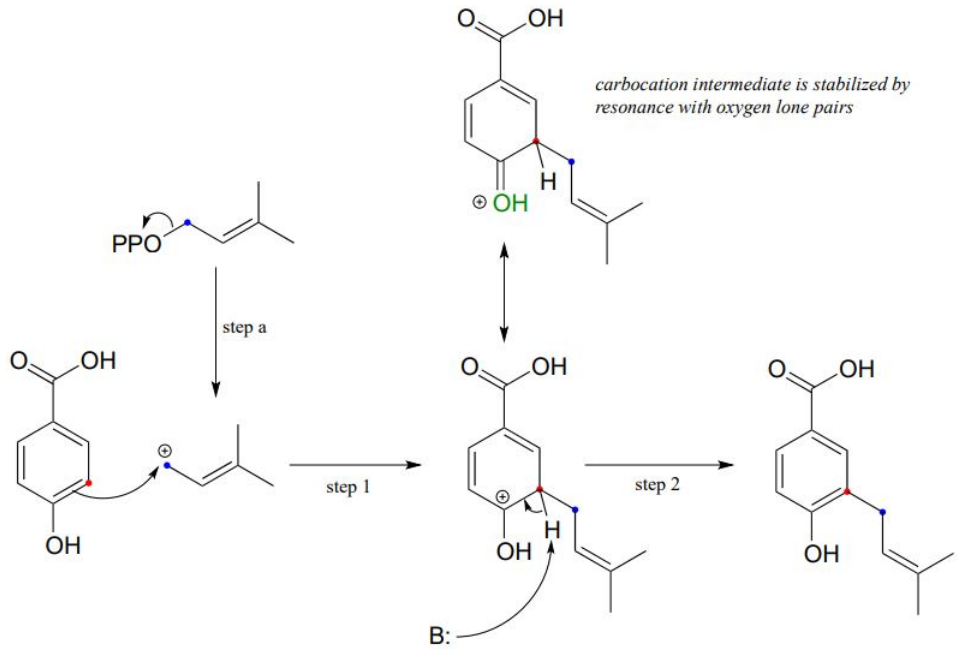


Organic chemists often refer to electrophilic aromatic substitution reactions with carbocation electrophiles as **Friedel-Crafts alkylation reactions**.

Exercise 10.5.5

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.



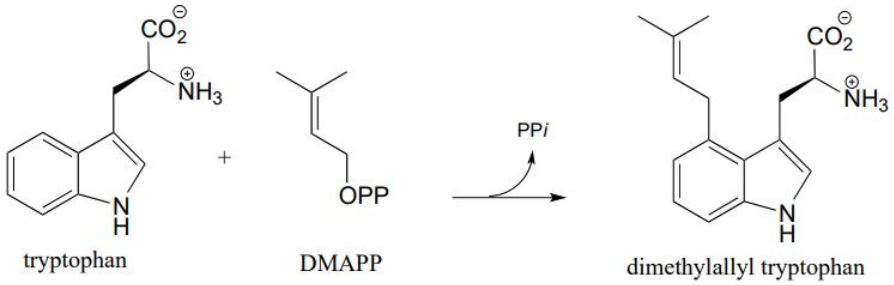
Loss of diphosphate creates a powerful carbocation electrophile (step a) which attracts the π electrons of the aromatic ring to form a carbocation intermediate with a new carbon-carbon bond (step 1). Substitution is completed by proton abstraction (step 2) which re-establishes the aromatic sextet.

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 10.5.6

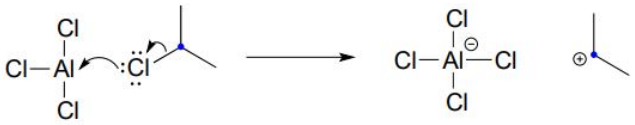
Draw a likely mechanism for the biosynthesis of dimethylallyl tryptophan, including a resonance structure showing how the carbocation intermediate in the rate determining step is stabilized by lone pair electrons on the ring nitrogen (in other words, show how the nitrogen serves to activate the ring).

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.

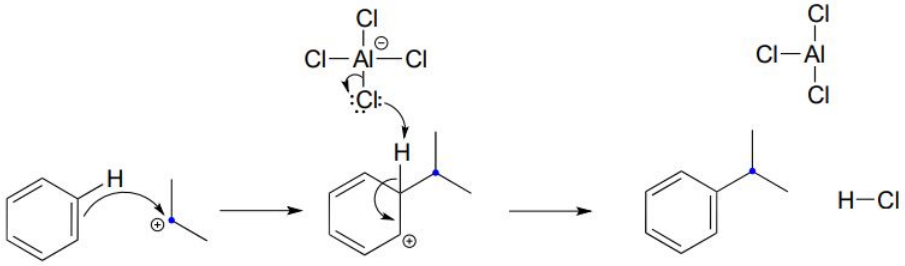
Below is an example of a laboratory Friedel-Crafts alkylation reaction:



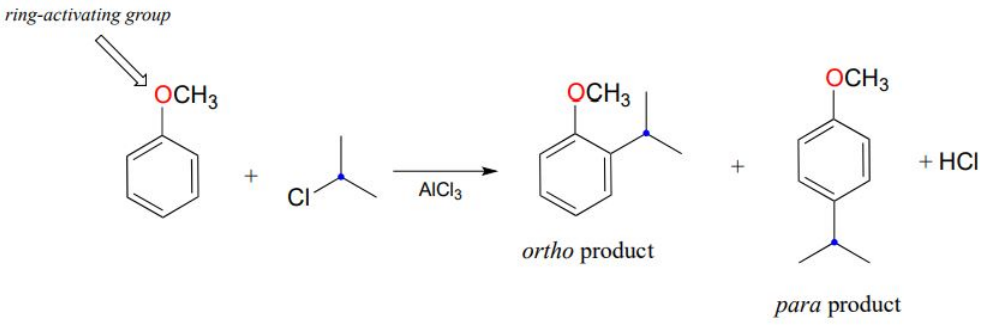
Recall that a powerful electrophile - such as a carbocation - is required for an electrophilic aromatic substitution to occur. The 2-chloropropane reactant is electrophilic, but not electrophilic enough to react with benzene. Here's where the aluminum trichloride catalyst comes in: it reacts as a Lewis 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.

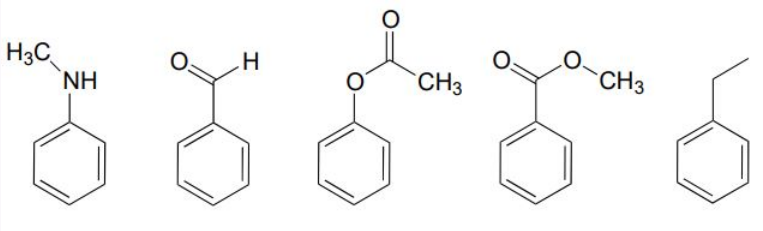
Exercise 10.5.7

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 10.5.8

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.

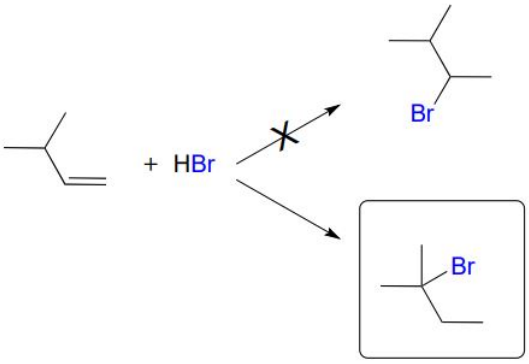
Contributors

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

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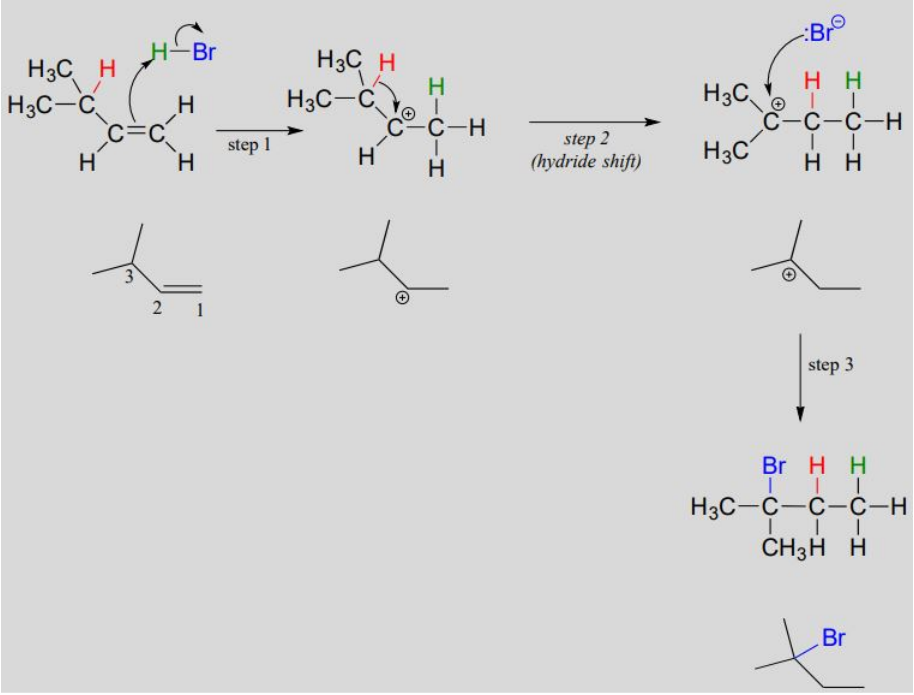
10.6: Carbocation Rearrangements

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:

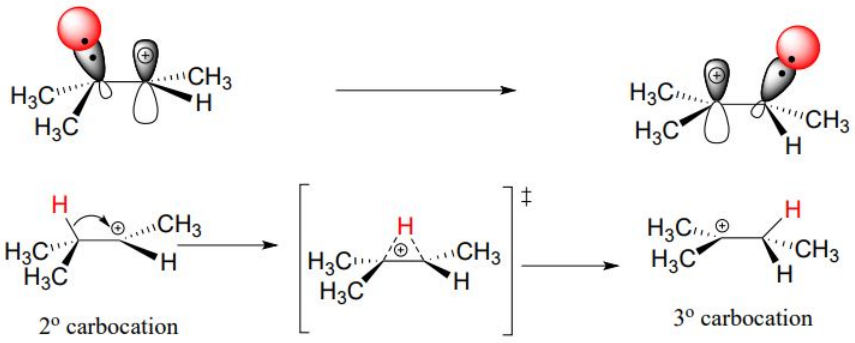


Protonation of the double bond results in a secondary carbocation (step 1). What happens next (step 2 above) is a process called a carbocation rearrangement, and more specifically, a hydride shift. The electrons in the bond between carbon #3 and a hydrogen are attracted by the positive charge on carbon #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

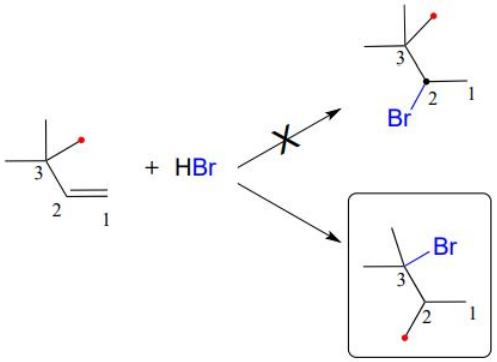
A hydride ion (H^-) is a proton plus two electrons. Be sure not to confuse a hydride ion with H^+, which is just a proton without any electrons.

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.

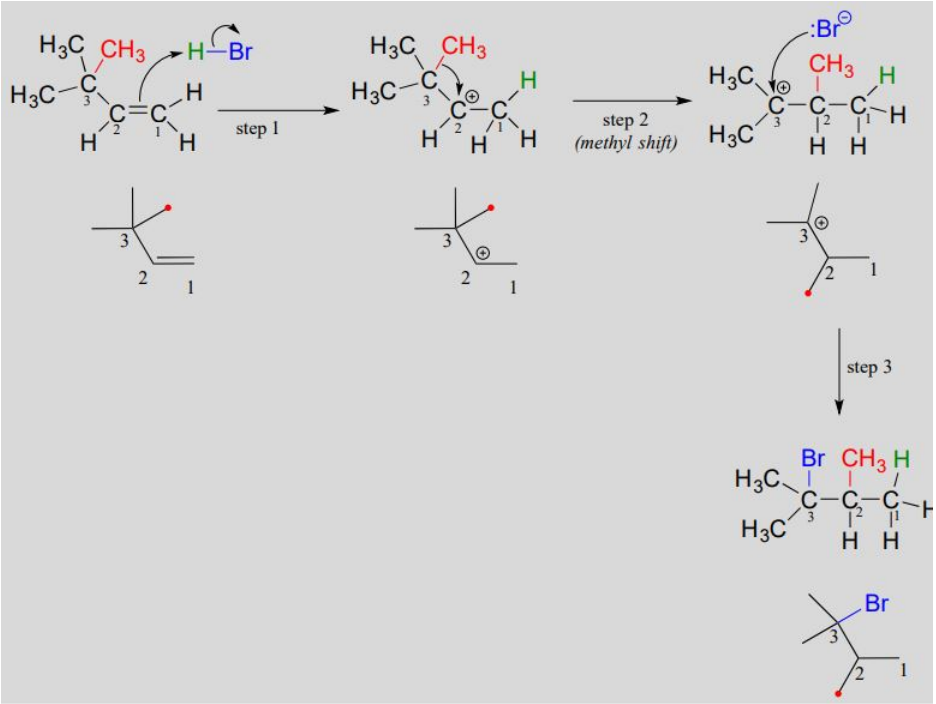
Consider another example. When HBr is added to 3,3-dimethyl-1-butene, the product is a tertiary - rather than a secondary - alkyl bromide.



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).

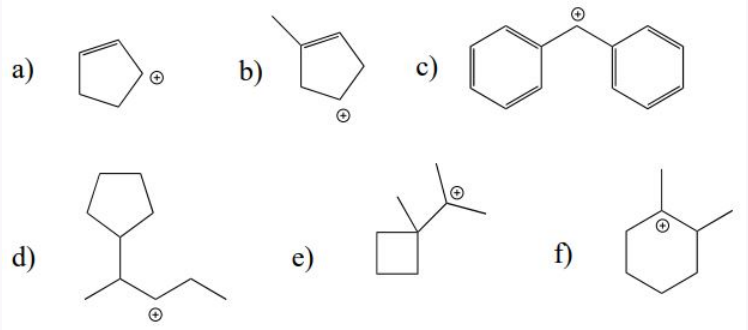
Electrophilic addition with methyl shift:



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 10.6.1

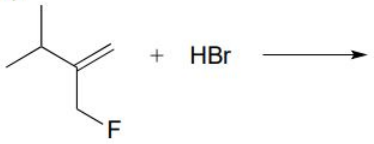
Which of the following carbocations are likely to undergo a shift? If a shift is likely, draw the new carbocation that would result.



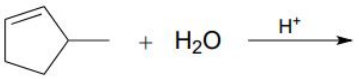
Exercise 10.6.2

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.

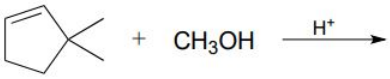
a)



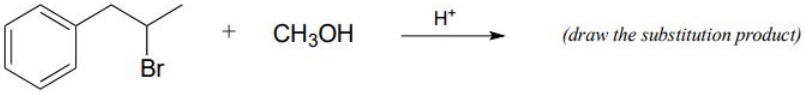
b)



c)

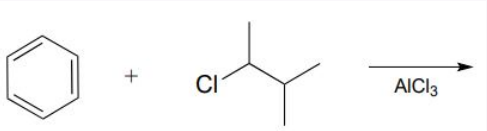


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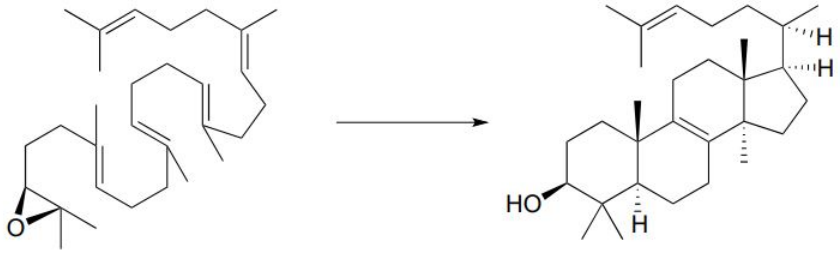


Exercise 10.6.3

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

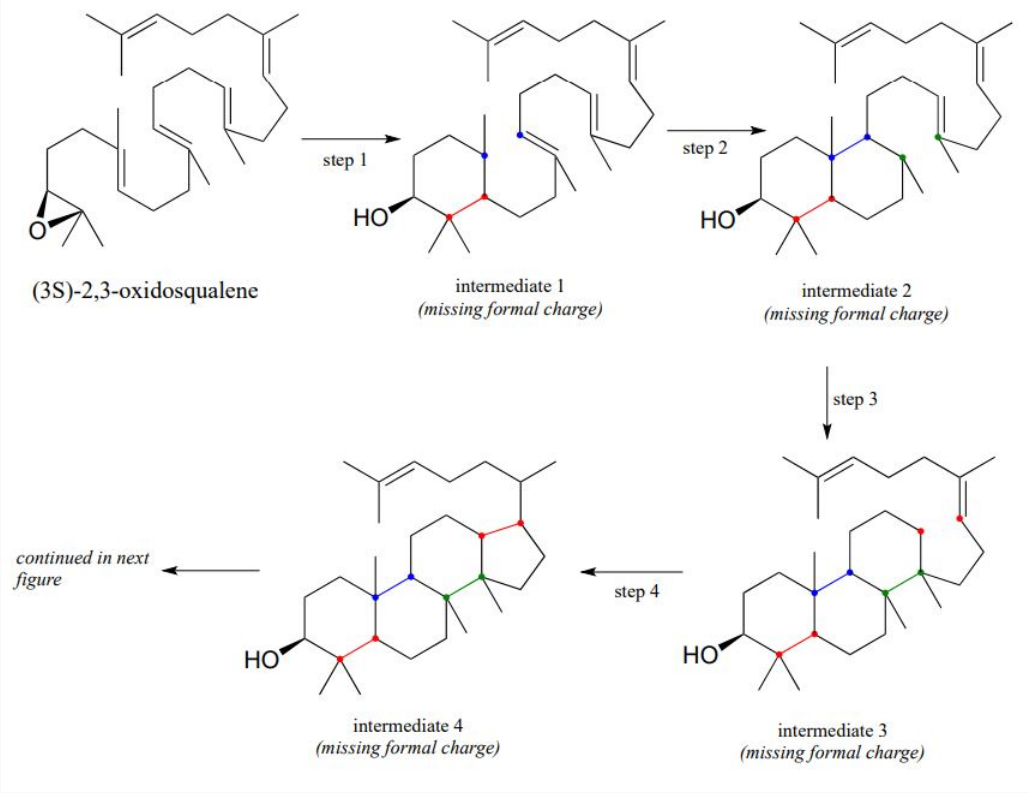
important and versatile intermediate in laboratory organic synthesis, so you will learn much more about how they are made and how they react if you take a course in chemical synthesis. For now, it is sufficient to recognize that the carbon atoms of an epoxide are potent electrophiles, due to both the 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 10.6.4

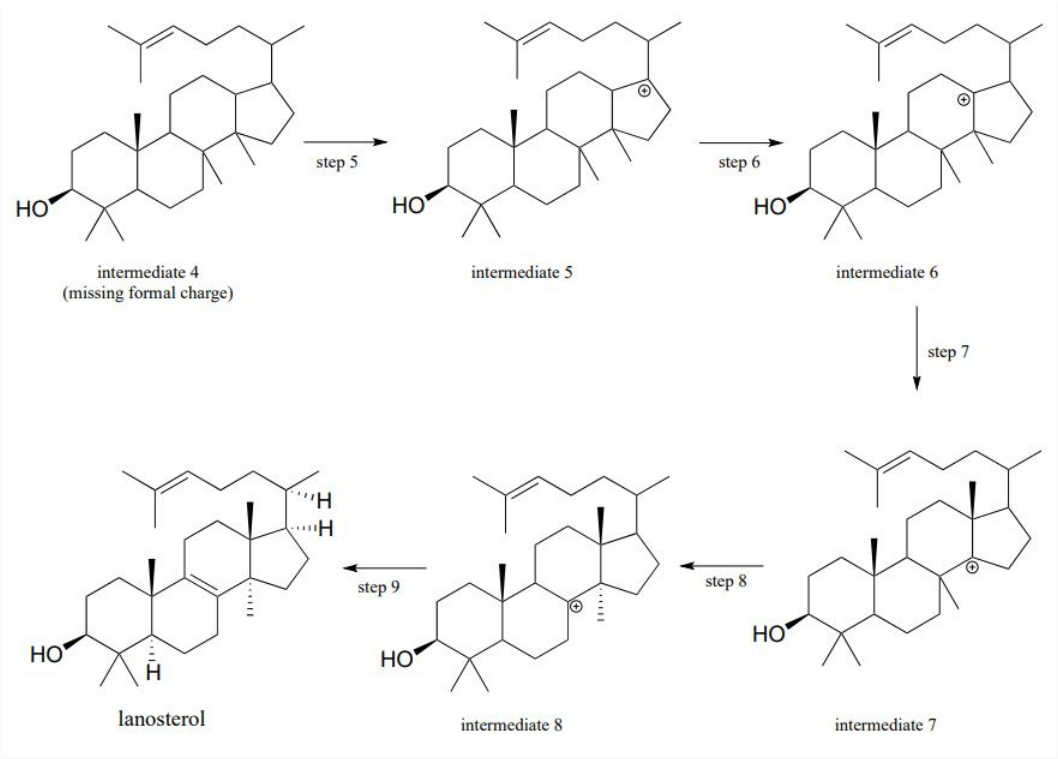
a. The figure below outlines the first, cyclizing phase of the reaction that converts oxidosqualene to lanosterol. However, the diagram is missing electron movement arrows, and intermediates 1-4 are all missing formal charges - fill these in.

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



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.

Contributors

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

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SECTION OVERVIEW

10.7: Alkenes

	UI Springfield CHE 267 **Organic Chemistry I** **Fall 2015: Prof. Morsch**	**Reading Assignments** **Homework Problems** **Homework Solutions** **Quizzes**

Template:HideTOC

Topic hierarchy

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10.P: Electrophilic Reactions (Problems)

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.

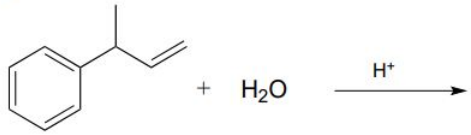
a)



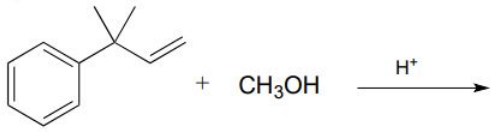
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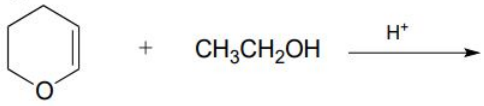
c)



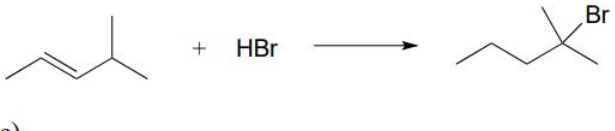
d)



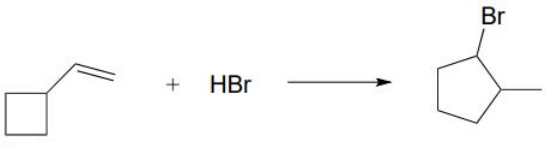
e)



P14.2: Draw likely mechanisms for the nonenzymatic reactions below. Products shown are not necessarily the most abundant for the reaction.



c)

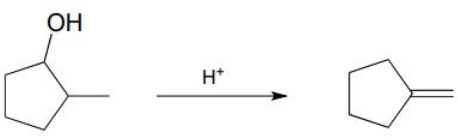


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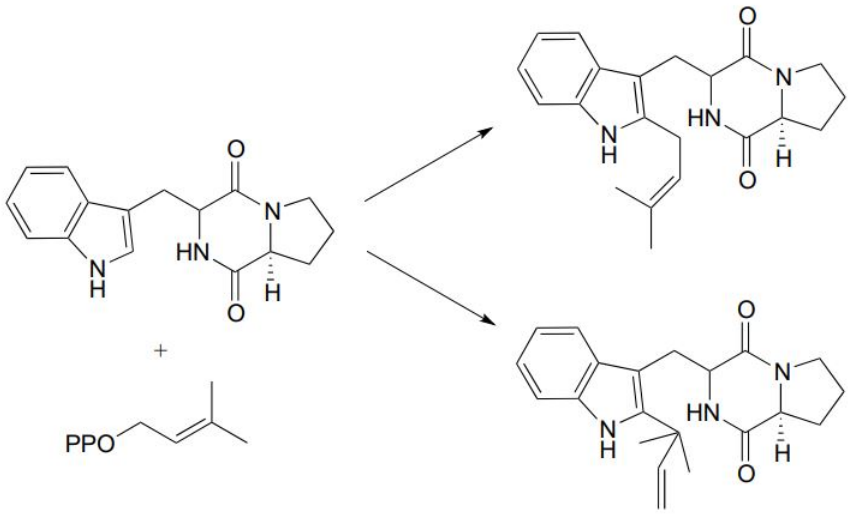
a)



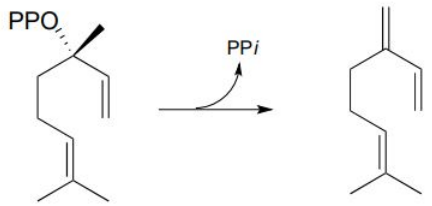
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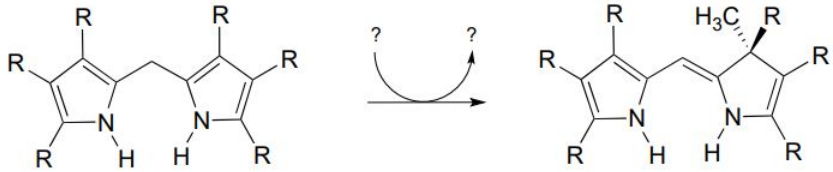
P14.3: Provide mechanisms for the following reactions, both of which are part of an alkaloid synthesis pathway in fungi. (Microbiol. 2005, 151, 2199)



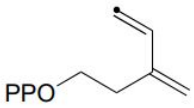
P14.4: Draw a likely mechanism for the reaction below. The product is myrcene, a compound produced by fir trees as a defense against insects. (J. Biol. Chem 1997, 272, 21784)



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.



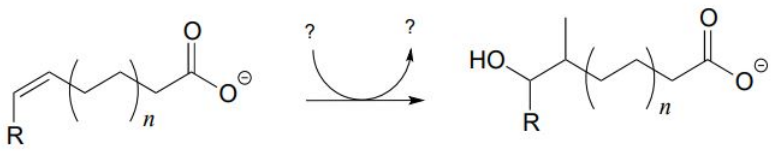
P14.6: A diene molecule synthesized in the laboratory was found to irreversibly inhibit the action of isopentenyl diphosphate isomerase (section 14.3) when the carbon indicated with a dot becomes covalently bonded to a cysteine residue in the enzyme's active site. Propose a mechanism showing how this could happen. (J. Am. Chem. Soc. 2005, 127, 17433)



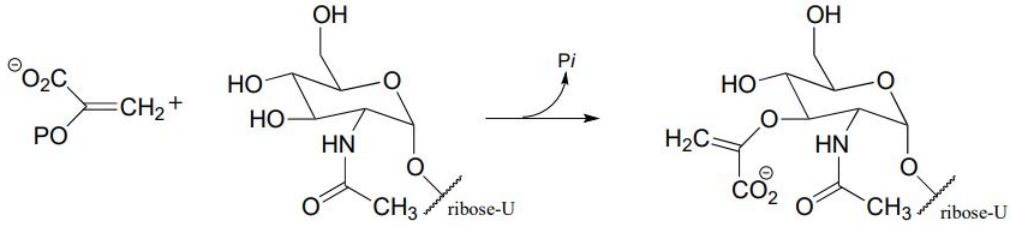
inhibitor

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.

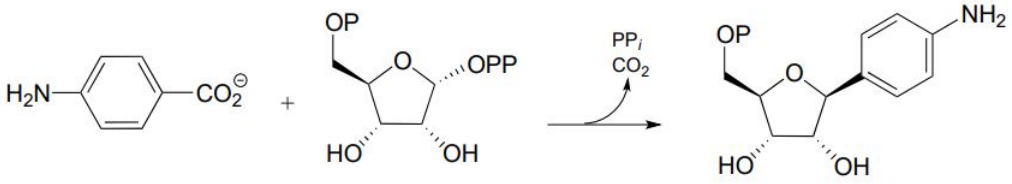
P14.8: The reaction below is part the pathway by which some bacteria -including the species which cause tuberculosis and leprosy - form distinctive branched-chain fatty acids for incorporation into their cell walls. This enzyme is of interest to scientists as possible targets for new antibiotic drugs. Propose a likely mechanism, and identify the missing participants denoted by questions marks. (J. Biol. Chem. 2006, 281, 4434)



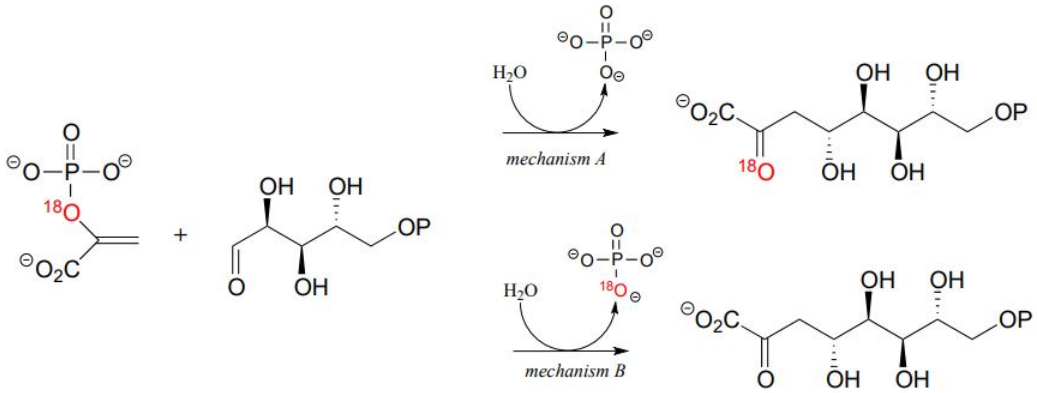
P14.9: Suggest a likely mechanism for this reaction, which is a key step in the synthesis of bacterial cell walls. Your mechanism should show an electrophilic addition, followed by an E1 elimination.



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.

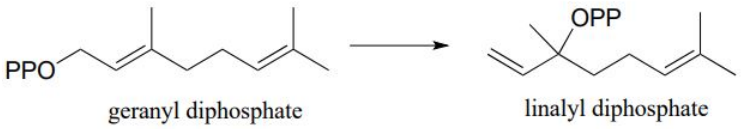


P14.11: Researchers investigated the mechanism of the enzyme 3-deoxy-D-manno-octulosonate-8-phosphate synthase by running the reaction with one of the substrates labeled with the 18O isotope (colored red in the scheme below). Consider the two hypothetical results shown below, each pointing to a different 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 \(^1$8O$ \) 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

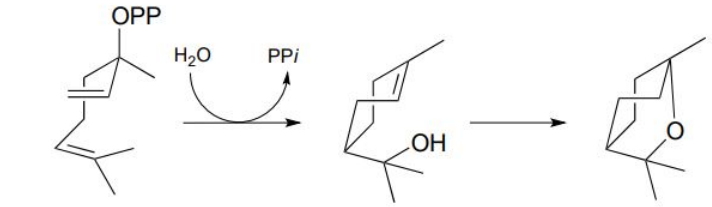
P14.12: Consider the following isomerization reaction (J. Biol. Chem. 1989, 264, 2075):



geranyl diphosphate linalyl diphosphate

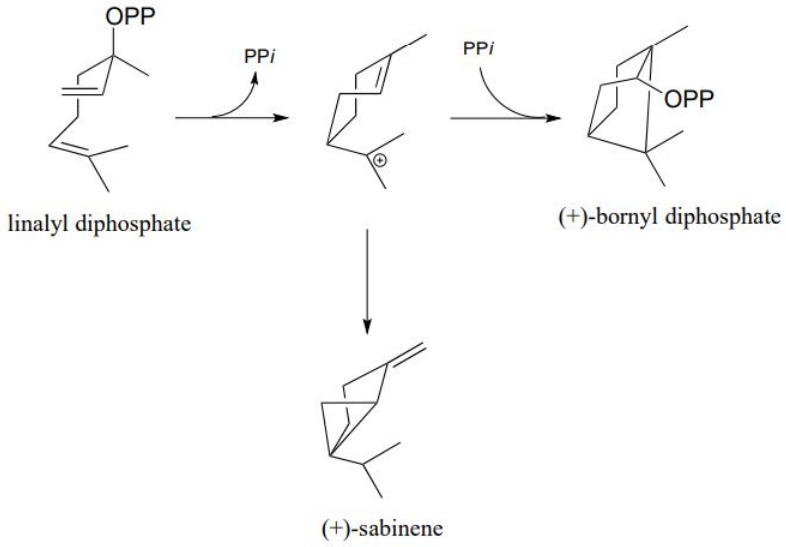
(JBC264, 2075)

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:

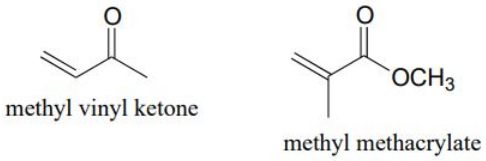


linalyl diphosphate (+)-bornyl diphosphate

(+)-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.



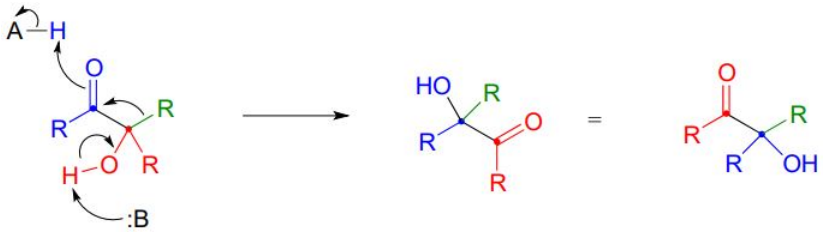
^1H-NMR data for product of HBr addition to methyl vinyl ketone:

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:

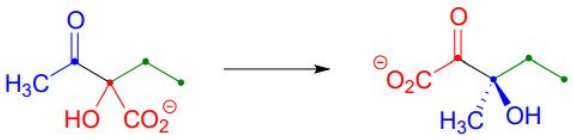
δ□□□□□	Integration	Splitting
1.3	3	d
2.3	1	sextet
3.5	2	d
3.7	3	s

P14.14: Ketones and aldehydes with a hydroxy group in the □ position are known to undergo an isomerization reaction known as an acyloin rearrangement:



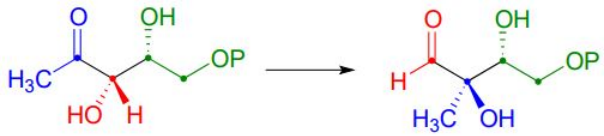
Notice in the general acyloin rearragnement mechanism below, the green alkyl group is shifting from the □ carbon (red) to the carbonyl carbon (blue). Notice also that this shift does not involve a carbocation intermediate, although a resonance contributor can be drawn in which the carbonyl carbon has a positive charge.

a. Draw a mechanism for this acyloin rearrangement step in the biosynthetic pathway for the amino acid leucine:



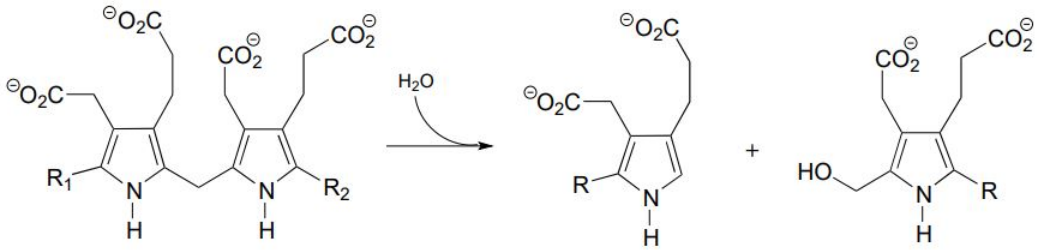
b. Draw a mechanism for this acyloin rearrangement step in the isoprenoid biosynthetic pathway in bacteria:

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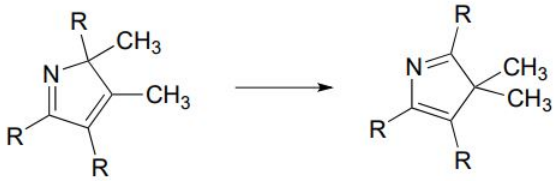


P14.15: Propose mechanisms for these reactions in the vitamin B_{12} biosynthetic pathway:

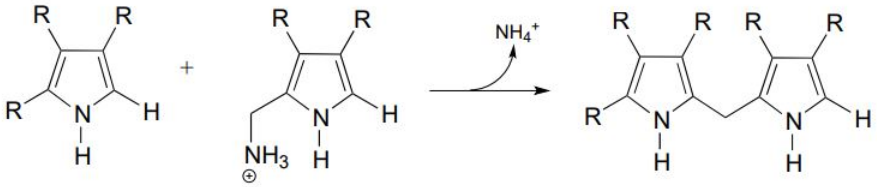
a)



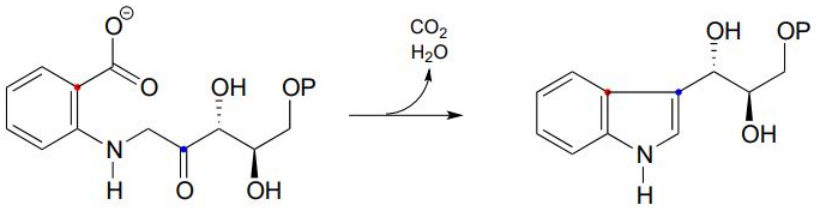
b)



c)

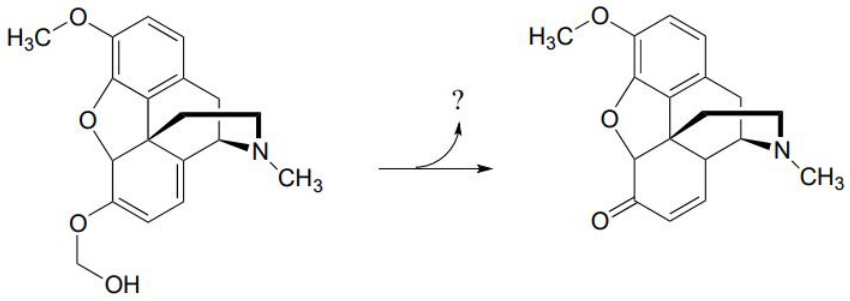


P14.16: An early reaction in the biosynthesis of tryptophan can be described as an intramolecular electrophilic aromatic substitution/decarboxylation hybrid, followed by an E1 dehydration (EC 4.1.1.48).



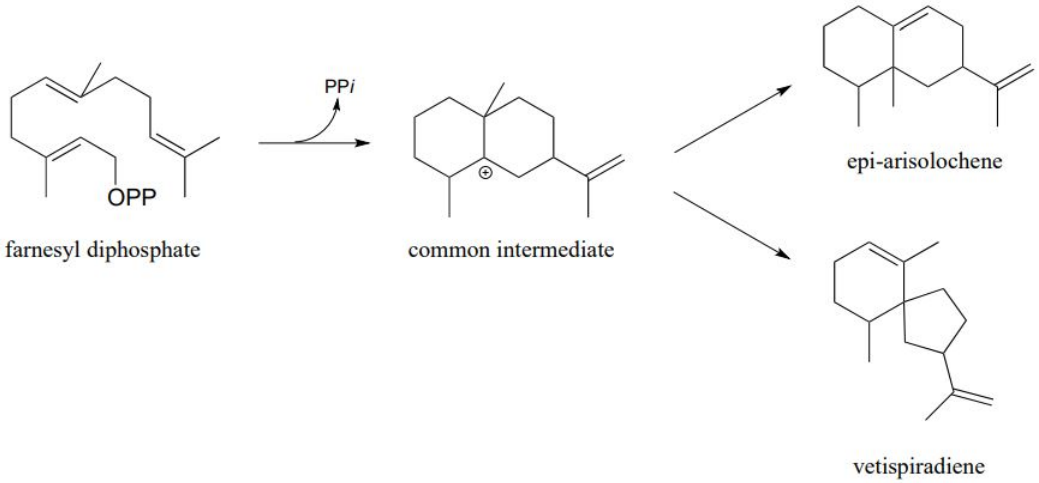
a. Draw a mechanism that corresponds to the verbal description given above. Use resonance structures to show how the nitrogen atom helps to stabilize the carbocation intermediate. ***Hint***: the electrophilic carbon in this case is a ketone rather than a carbocation.
b. What aspect of this reaction 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.

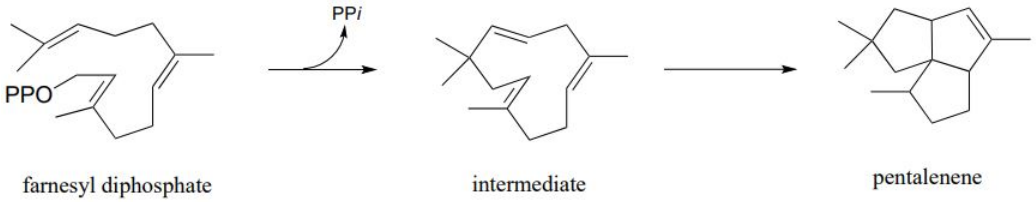


P14.18: Propose mechanisms for these three electrophilic cyclization reactions. Carbocation rearrangement steps are involved.

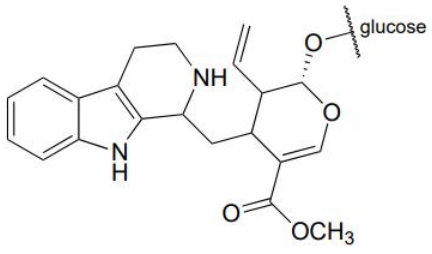
a. epi-arisolochene
b. vetispiradiene (Science 1997, 277, 1815)



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.



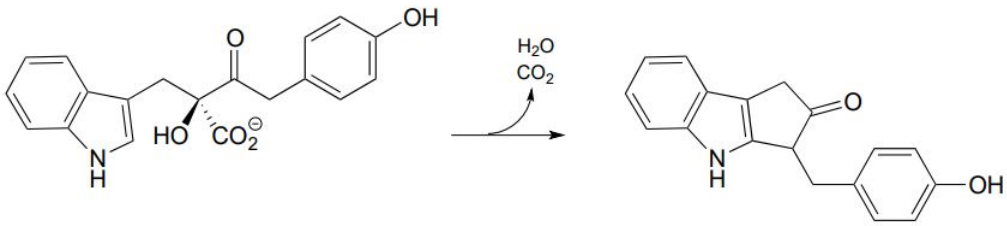
strictosinide

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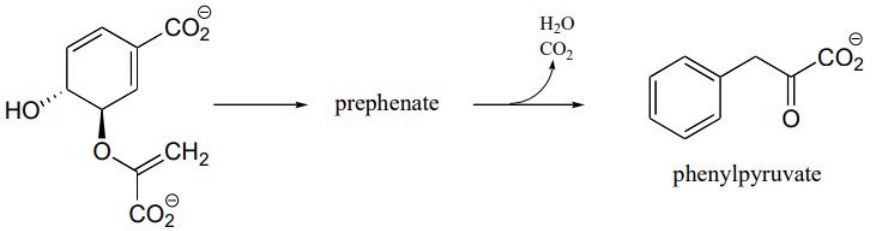
Given this information, predict the two precursors to strictosinide, and draw a mechanism for the reaction described. ***Hint***: use the 'retro' skills you developed in chapter 12 and chapter 13.

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.

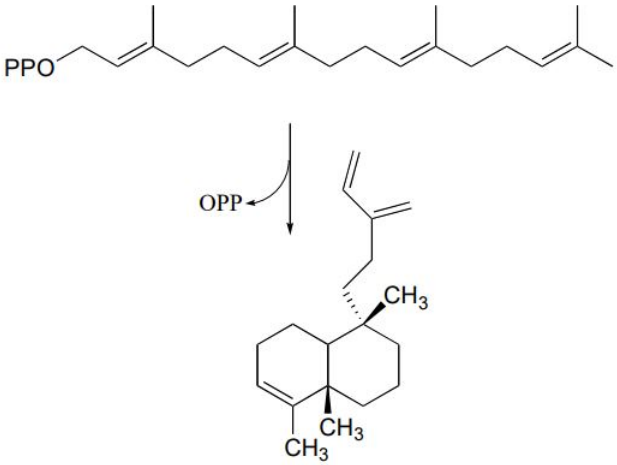
P14.21: The reaction below has been proposed to proceed via a cyclization step followed by an E1/decarboxylation step (in other words, an E1 mechanism where decarboxylation occurs instead of deprotonation). Draw a mechanism that fits this description, and show the most stable resonance contributors of 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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10.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

11: Alkenes

	**UI Springfield CHE 267** **Organic Chemistry I** **Fall 2015: Prof. Morsch**	**Reading Assignments** **Homework Problems** **Homework Solutions** **Quizzes**

Template:HideTOC

- 11.1: Preparation of Alkenes
- 11.2: Introduction to Addition Reactions
- 11.3: Stereochemistry of Electrophilic Addition of HX
- 11.4: Stereochemistry of Halogenation
- 11.5: Keeping Track of Reactions
- 11.6: Interesting Alkenes
- 11.7: Hydrohalogenation—Electrophilic Addition of HX
- 11.8: Markovnikov's Rule
- 11.9: Hydration—Electrophilic Addition of Water
- 11.10: Halogenation—Addition of Halogen
- 11.11: Hydroboration–Oxidation
- 11.12: Lipids—Part 2
- 11.13: Alkenes and Alkynes I (Problems)

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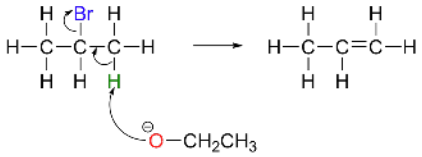
11.1: Preparation of Alkenes

E2 Reaction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

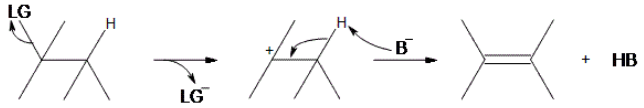
To get a clearer picture of the interplay of these factors involved in a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.

.



E1 Reaction

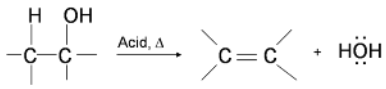
An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.



As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base ( ) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Dehydration

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



Primary alcohol dehydrates through the E2 mechanism

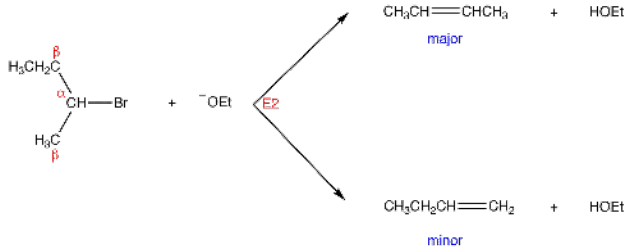
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.

Secondary and tertiary alcohols dehydrate through the E1 mechanism

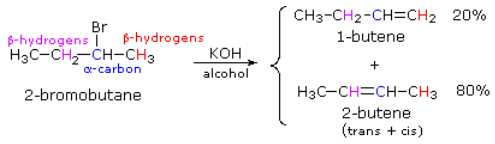
Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the alkene formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

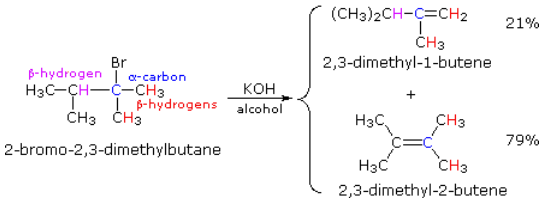
Zaitsev's Rule

Zaitsev's or Saytzev's (anglicized spelling) rule is an empirical rule used to predict regioselectivity of 1,2-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene, (i.e., the alkene with the more highly substituted double bond). For example:



If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.





Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

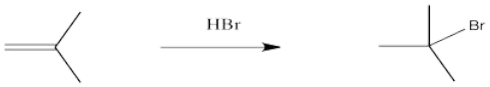
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11.2: Introduction to Addition Reactions

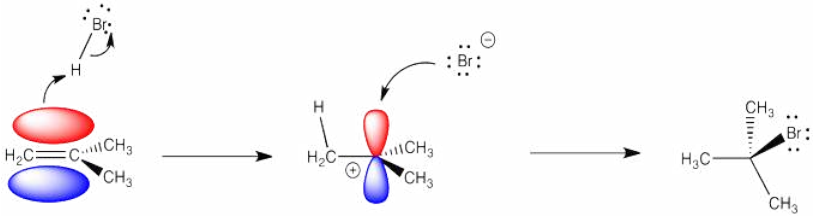
Alkenes are found throughout nature. They form the basis of many natural products, such as terpenes, which play a variety of roles in the lives of plants and insects. The C=C bonds of alkenes are very different from the C=O bonds that are also common in nature. The C=C bonds of alkenes are electron-rich and nucleophilic, in contrast to the electron-poor C=O bonds of carbohydrates, fatty acids and proteins. That difference plays a role in how terpenes form in nature.

Alkenes, or olefins, are also a major product of the petroleum industry. Reactions of alkenes form the basis for a significant porion of our manufacturing economy. Commonly used plastics such as polyethylene, polypropylene and polystyrene are all formed through the reactions of alkenes. These materials continue to find use in our society because of their valuable properties, such as high strength, flexibility and low weight.

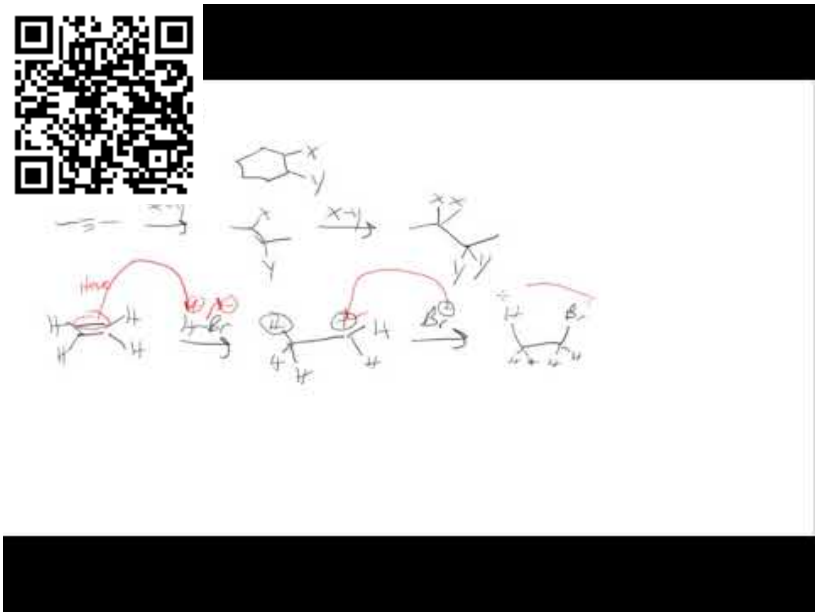
Alkenes undergo addition reactions like carbonyls do. Often, they add a proton to one end of the double bond and another group to the other end. These reactions happen in slightly different ways, however.



Alkenes are reactive because they have a high-lying pair of π-bonding electrons. These electrons are loosely held, being high in energy compared to σ-bonds. The fact that they are not located between the carbon nuclei, but are found above and below the plane of the double bond, also makes these electrons more accessible.



Alkenes can donate their electrons to strong electrophiles other than protons, too. Sometimes their reactivity pattern is a little different than the simple addition across the double bond, but that straightforward pattern is what we will focus on in this chapter.



Contributors

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11.3: Stereochemistry of Electrophilic Addition of HX

As illustrated in the drawing below, the pi-bond fixes the carbon-carbon double bond in a planar configuration, and does not permit free rotation about the double bond itself. We see then that addition reactions to this function might occur in three different ways, depending on the relative orientation of the atoms or groups that add to the carbons of the double bond: (i) they may bond from the same side, (ii) they may bond from opposite sides, or (iii) they may bond randomly from both sides. The first two possibilities are examples of stereoselectivity, the first being termed **syn-addition**, and the second **anti-addition**. Since initial electrophilic attack on the double bond may occur equally well from either side, it is in the second step (or stage) of the reaction (bonding of the nucleophile) that stereoselectivity may be imposed.

If the two-step mechanism described above is correct, and if the carbocation intermediate is sufficiently long-lived to freely-rotate about the sigma-bond component of the original double bond, we would expect to find random or non-stereoselective addition in the products. On the other hand, if the intermediate is short-lived and factors such as steric hindrance or neighboring group interactions favor one side in the second step, then stereoselectivity in product formation is likely. The following table summarizes the results obtained from many studies, the formula HX refers to all the strong Brønsted acids. The interesting differences in stereoselectivity noted here provide further insight into the mechanisms of these addition reactions.

Reagent	H–X	X_2	HO–X	RS–Cl	$Hg(OAc)_2$	BH_3
Stereoselectivity	mixed	anti	anti	anti	anti	syn

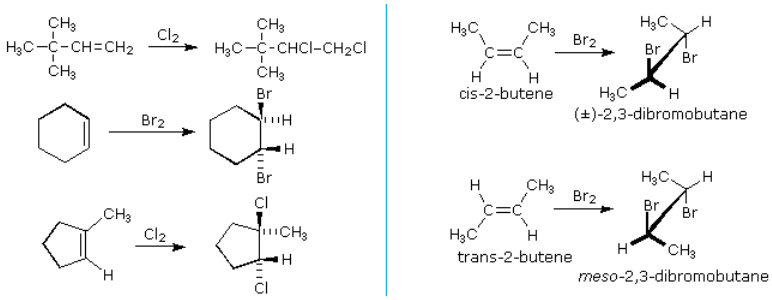
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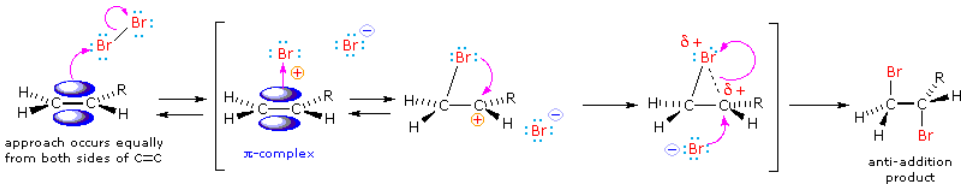
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11.4: Stereochemistry of Halogenation

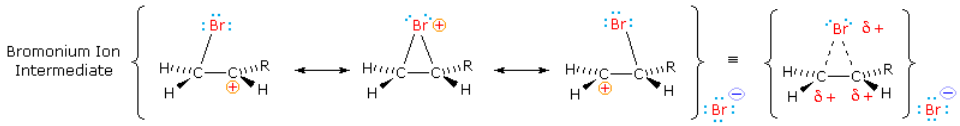
The halogens chlorine and bromine add rapidly to a wide variety of alkenes without inducing the kinds of structural rearrangements (carbocation shifts) noted for strong acids - this is because a discreet carbocation intermediate does not form in these reactions. The stereoselectivity of halogen additions is strongly anti, as shown in many of the following examples.



We can account both for the high stereoselectivity and the lack of rearrangement in these reactions by proposing a stabilizing interaction between the developing carbocation center and the electron rich halogen atom on the adjacent carbon. This interaction delocalizes the positive charge on the intermediate and blocks halide ion attack from the *syn*-location.



The stabilization provided by the halogen-carbocation bonding makes rearrangement unlikely, and in a few cases three-membered cyclic halonium cations have been isolated and identified as true intermediates. A resonance description of such a bromonium ion intermediate is shown below. The positive charge is delocalized over all the atoms of the ring, but should be concentrated at the more substituted carbon (where positive charge is more stable), and this is the site to which the nucleophile will bond.



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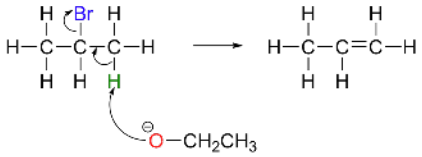
11.5: Keeping Track of Reactions

E2 Reaction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

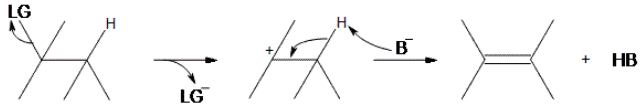
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.

.



E1 Reaction

An E1 reaction involves the deprotonation of a hydrogen nearby (usually one carbon away, or the beta position) the carbocation resulting in the formation of an alkene product. In order to accomplish this, a Lewis base is required. For a simplified model, we'll take B to be a Lewis base, and LG to be a halogen leaving group.

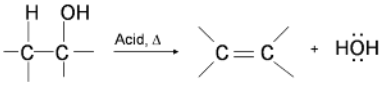


As can be seen above, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base ( ) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond, forming a double bond. Unlike E2 reactions, which require the proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has already left the molecule. The final product is an alkene along with the HB byproduct.

Dehydration

One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond.

The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



Primary alcohol dehydrates through the E2 mechanism

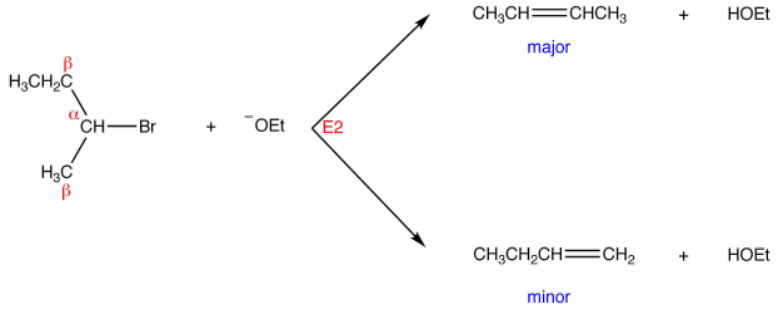
Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. Then the nucleophile HSO_4^- back-side attacks one adjacent hydrogen and the alkyloxonium ion leaves in a concerted process, making a double bond.

Secondary and tertiary alcohols dehydrate through the E1 mechanism

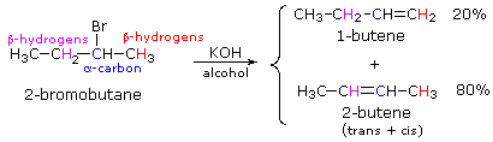
Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond. Notice in the mechanism below that the aleke formed depends on which proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.

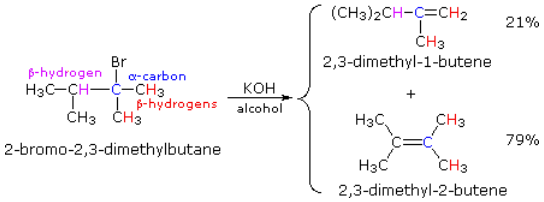
Zaitsev's Rule

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11.6: Interesting Alkenes

Ethene

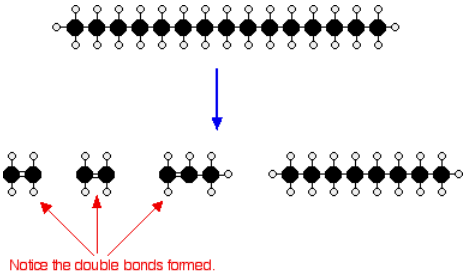
Cracking is the name given to breaking up large hydrocarbon molecules into smaller and more useful bits. This is achieved by using high pressures and temperatures without a catalyst, or lower temperatures and pressures in the presence of a catalyst. The source of the large hydrocarbon molecules is often the naphtha fraction or the gas oil fraction from the fractional distillation of crude oil (petroleum). These fractions are obtained from the distillation process as liquids, but are re-vaporized before cracking.

There is not any single unique reaction happening in the cracker. The hydrocarbon molecules are broken up in a fairly random way to produce mixtures of smaller hydrocarbons, some of which have carbon-carbon double bonds. One possible reaction involving the hydrocarbon $C_{15}H_{32}$ might be:

$$C_{15}H_{32} \longrightarrow 2C_2H_4 + C_3H_6 + C_8H_{18}$$

ethene propene octane

Or, showing more clearly what happens to the various atoms and bonds:

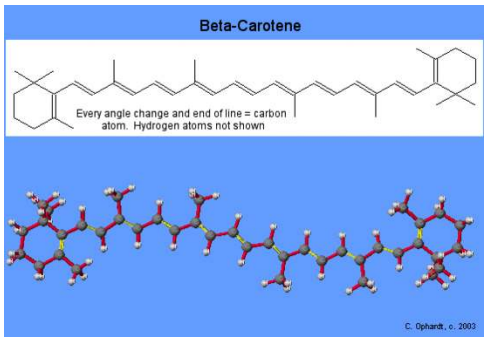


This is only one way in which this particular molecule might break up. The ethene and propene are important materials for making plastics or producing other organic chemicals. You will remember that during the polymeriation of ethene, thousands of ethene molecules join together to make poly(ethene) - commonly called polythene. The reaction is done at high pressures in the presence of a trace of oxygen as an initiator.

$$nCH_2{=}CH_2 \longrightarrow [\text{-}CH_2\text{-}CH_2\text{-}]_n$$

Beta-Carotene

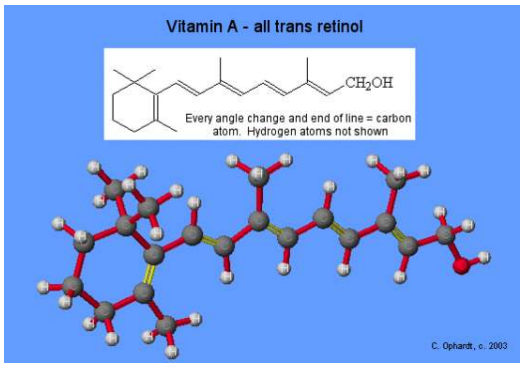
The long chain of alternating double bonds (conjugated) is responsible for the orange color of beta-carotene. The conjugated chain in carotenoids means that they absorb in the visible region - green/blue part of the spectrum. So β-carotene appears orange, because the red/yellow colors are reflected back to us.



Vitamin A

Vitamin A has several functions in the body. The most well known is its role in vision - hence carrots "make you able to see in the dark". The retinol is oxidized to its aldehyde, retinal, which complexes with a molecule in the eye called opsin. When a photon of

light hits the complex, the retinal changes from the 11-cis form to the all-trans form, initiating a chain of events which results in the transmission of an impulse up the optic nerve. A more detailed explanation is in Photochemical Events.



Other roles of vitamin A are much less well understood. It is known to be involved in the synthesis of certain glycoproteins, and that deficiency leads to abnormal bone development, disorders of the reproductive system, xerophthalmia (a drying condition of the cornea of the eye) and ultimately death.

Vitamin A is required for healthy skin and mucus membranes, and for night vision. Its absence from diet leads to a loss in weight and failure of growth in young animals, to the eye diseases; xerophthalmia, and night blindness, and to a general susceptibility to infections. It is thought to help prevent the development of cancer. Good sources of carotene, such as green vegetables are good potential sources of vitamin A. Vitamin A is also synthetically manufactured by extraction from fish-liver oil and by synthesis from beta-ionone.

Contributors

- Jim Clark (Chemguide.co.uk)
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11.7: Hydrohalogenation—Electrophilic Addition of HX

Objectives

After completing this section, you should be able to

1. use Markovnikov's rule to predict the product formed when a protic acid, HX, reacts with an alkene.
2. identify the protic acid, HX, and the alkene that must be reacted together to produce a given alkyl halide. [**Note:** Special conditions are needed if an alkyl iodide is to be produced.]
3. distinguish among primary, secondary and tertiary carbocations.

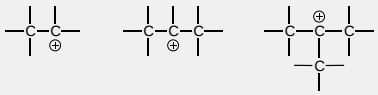
Key Terms

Make certain that you can define, and use in context, the key terms below.

- Markovnikov's rule
- regioselective (regiospecific)

Study Notes

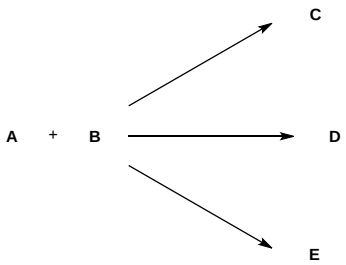
Recall the definitions of primary, secondary and tertiary hydrogen atoms given in Section 3.3. It follows that a "primary carbocation" is a carbocation in which the carbon atom carrying the positive charge is bonded to only one other carbon atom, a "secondary carbocation" is one in which the carbon atom carrying the positive charge is bonded to two other carbon atoms, and so on.



Regioselectivity

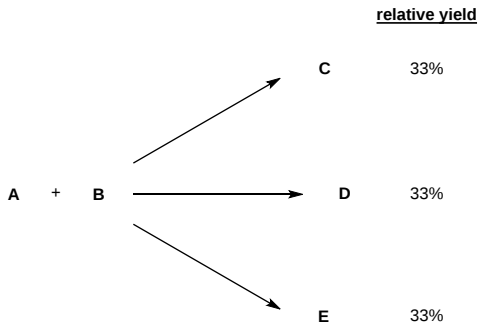
If more than one reaction could occur between a set of reactants under the same conditions giving products that are constitutional isomers and if one product forms in greater amounts than the others, the overall reaction is said to be regioselective.

Say three reactions could occur between the hypothetical reactants **A** and **B** under the same conditions giving the constitutionally isomeric products **C**, **D**, and **E**.



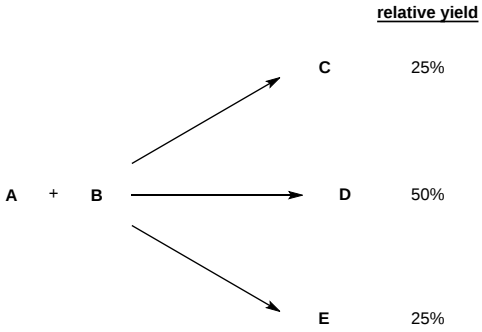
There are two possibilities:

1. The three products form in equal amounts, i.e., of the total product 33% is **C**, another 33% **D**, the remaining 33% **E**. (These percentages are called relative yields of the products.)



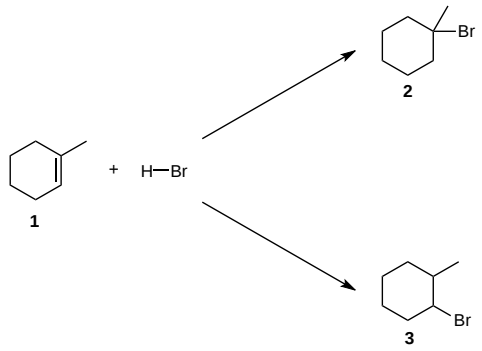
If this is what is observed, the overall reaction between **A** and **B** is not regioselective.

2. One product forms in greater amounts than the others. Say, for example, the relative yields of **C**, **D**, and **E** are 25%, 50%, and 25%, respectively.



If this is what is observed, the overall reaction between **A** and **B** is regioselective.

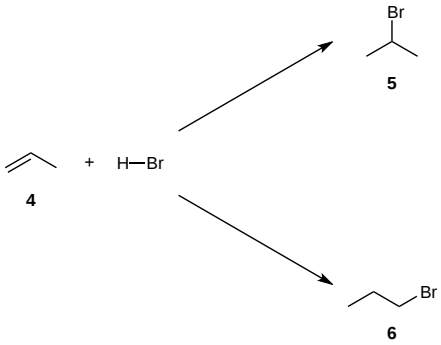
eg:



Experimentally, **2** is the major product; **3** is the minor product. Thus, the overall reaction between **1** and HBr is regioselective toward **2**.

If more than one reaction could occur between a set of reactants under the same conditions giving products that are constitutional isomers and if only one product is observed, the overall reaction is said to be 100% regioselective or regiospecific.

eg:

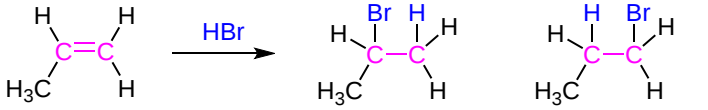


The only observed product is **5**. (Relative yields of **5** and **6** are 100% and 0%, respectively.) Thus the overall reaction between **4** and HBr is regiospecific toward **5**.

Regiospecificity is merely the limiting case of regioselectivity. All regiospecific reactions are regioselective, but not all regioselective reactions are regiospecific.

Addition to unsymmetrical alkenes

During the electrophilic addition of HX to an alkene, the halide (X) could attach to either carbon in the double bond producing two different isomers as products. But, when an unsymmertrically alkyl substituted alkene undergoes an electrophillic addition with HX a single isomer is typically produced. For example, if propene were reacted with HBr, two products could possibly form: 2-bromolpropane and 1-bromopropane. However, 2-bromopropane is produced as the reaction's only product. Reactions are called regiospecific when only one of multiple possible isomers is exclusively formed.

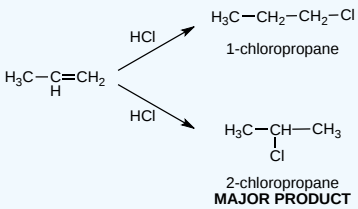


2-Propene | **2-Bromopropane** (Sole Product) | **1-Bromopropane** (Not Formed!)

Example 11.7.1

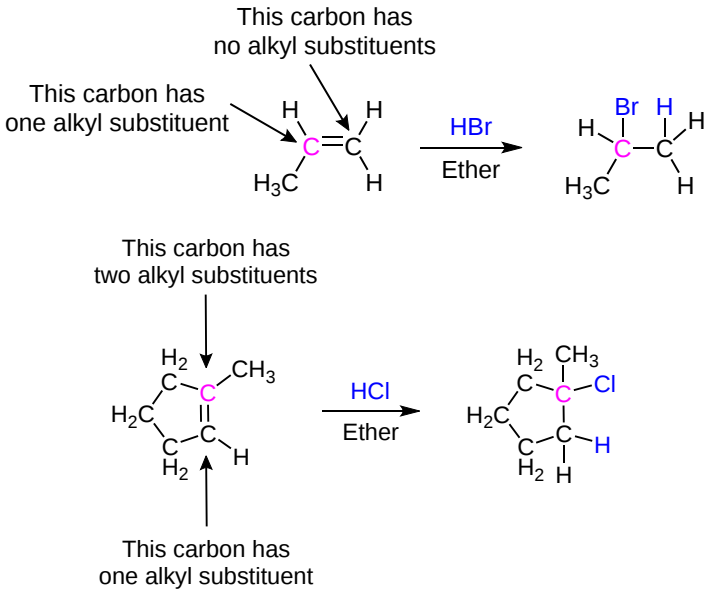
If HCl adds to an unsymmetrical alkene like propene what will the major product be?

Solution

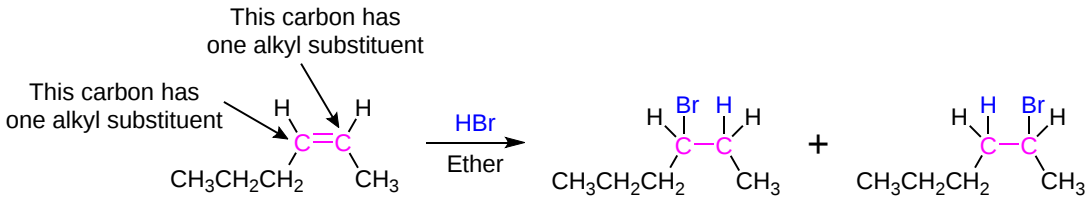


The regiospecificity of electrophilic additions to alkenes is commonly known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869. The electrophilic addition of HX to an alkene is said to follow Markovnikov's rule.

Markovnikov's rule: During the electrophilic addition of HX to an alkene, the H adds to the carbon of the double bond with the fewest number of alkyl substitutent. The halide (X) adds to the double bond carbon with the most alkyl substituents. Although Markovnikov's rule has been specifically stated for the electrophilic addition of HX, later in this chapter many more reaction will be shown to also follow Markovnikov's rule.

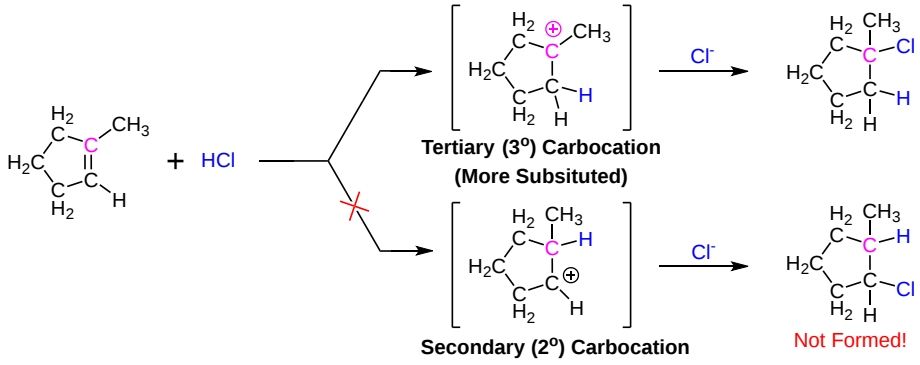


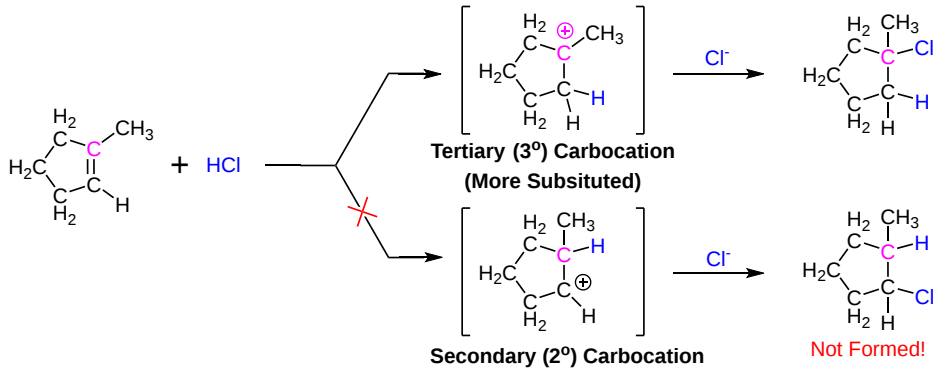
It is important to point out that Markovnikov's rule only truley applies when there is a difference between the number of alky groups attached to each carbon in the double bond. When both carbon of the double bond have the same degree of alkyl substitution, Markovnikovs's rule becomes void and a mixture of both possible isomers is produced.



To consider an explanation for why Markovnikov's rule holds true, the mechanism of the reaction needs to be considered. As seen in the previous section, the mechanism starts with the addition of H to a carbon in the double bond. This in turn caused the other double bond carbon to become a carbocation intermediate. In the second step of the mechanism the halide ion attacks the carbocation to form a C-X. Because Markovnikov's rule says that the halogen adds to the carbon in the double bond with the most alky substituents, it can be said the carbocation also prefers to form on the carbon with the most alkyl substituents. The reason for this holds the explaination for Markovnikov's rule. To simplify this idea, Markovnikov's rule can be restated in a different form.

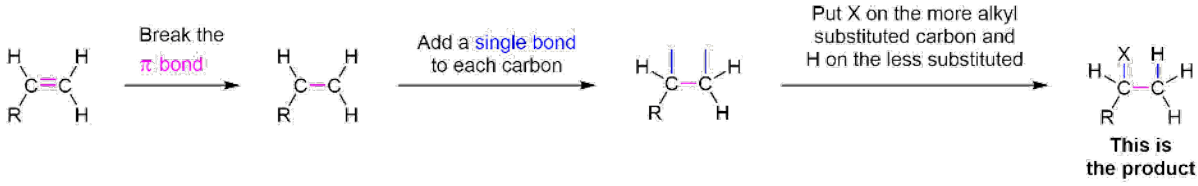
Markovnikov's rule: During the electrophilic addition of HX to an alkene, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents.





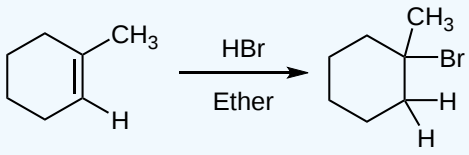
Predicting the Product of an Electrophilic Addition with HX

Overall, during the electrophilic addition of HX to an alkene there are two major changes in the bonding. First, the pi bond of the alkene is broken. Second, a single bond is formed on each carbon that was originally in the double bond. The two single bonds will become attached to and H and an X. If the alkene is unsymmertrically alkyl substituted, Markovnikov's rule is followed and the X will be bonded to the more alky substituted carbon and the H to the less substiuted. If the alkene is symmertrically alkyl substituted a mixture of isomers will be produced in the product.



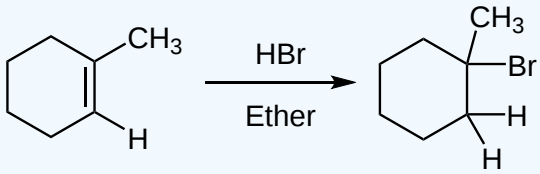
? Worked Example 11.7.1

Please draw the product of the following reaction:



Answer

In answering these types of questions it is always important to first determine which reaction is occurring. Because an alkene is the reactant and HBr is the product this reaction is an electrophilic addition. Overall, the double bond will be broken as H and Br are added. The next step is to determine if Markovnikov's rule needs to be applied. In the reactant's double bond the upper carbon has two alkyl substituents and the lower carbon has only two. Markovnikov's rule says that Br will attach to the upper carbon and H to the lower.

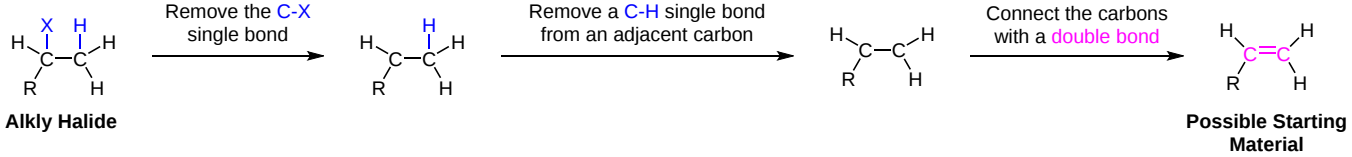


Planning the Synthesis of an Alkyl Halide using Electrophilic Addition

Understanding the starting material and reaction required for the synthesis a specific target molecule is an important concept in organic chemistry. The preferred method for answering these types of questions is to work backwards from the target molecule.

Often there will be multiple variations of reactions and starting materials capable synthesizing the target molecule. Further analysis of these variations can draw out strengths and weaknesses and lead to the pathway with the best chance of success.

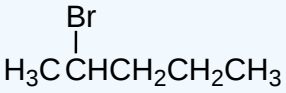
To create a possible starting material for a given alkyl halide simply reverse the bonding changes expected during an electrophilic addition. Remove the C-X single bond and a C-H bond from an adjacent carbon. Then connect these two carbons with a double bond.



Alkly Halide **Possible Starting Material**

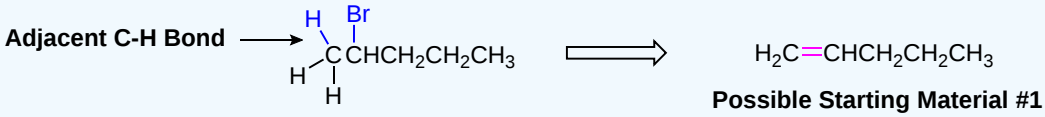
? Worked Example 11.7.1

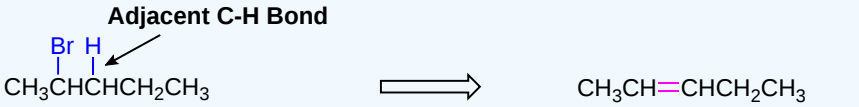
What alkene would be required to make the following 2-bromopentane using an electrophilic addition?



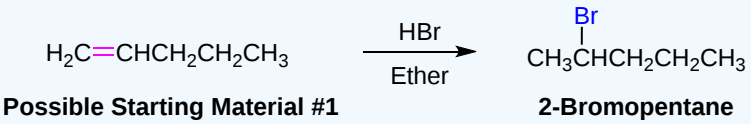
Answer

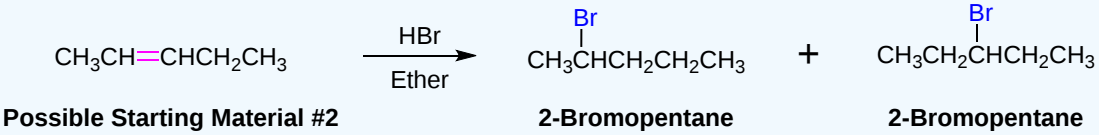
Analysis: Possible starting materials can be made by first removing the C-Br bond and an adjacent C-H bond. Then connecting the two carbons with a double bond. Because there are two different locations where an adjacent C-H bond can be removed there will be two possible starting material.





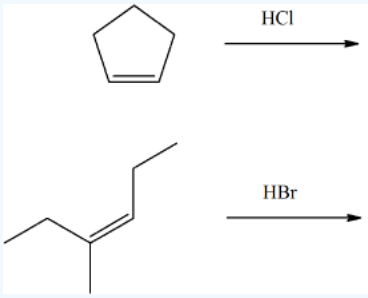
Solution: When comparing the the possible starting materials, #1 will follow Markovnikov's rule and produce 2-bromopentane as the sole product. Starting material #2 is symmertrically alkyl substituted, so Markovnikov's rule does not apply. A mixture of 2-bromopentane and 3-bromopentane would be produced. Between the two possible starting material #1 would be preferred because only one product is produced.



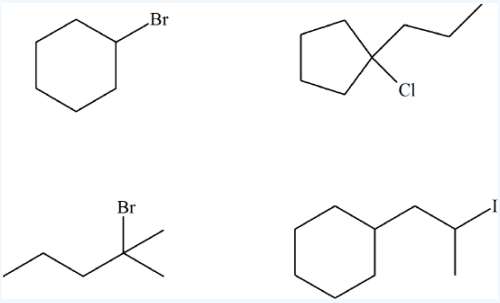


Exercise 11.7.1

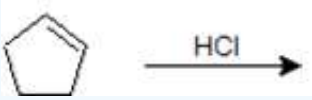
1) Predict the product(s) for the following reactions:



2) In each case, suggest an alkene that would give the product shown.

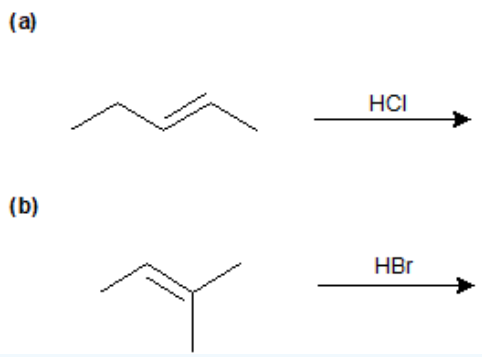


3) Give the IUPAC name for the product of the following reaction.



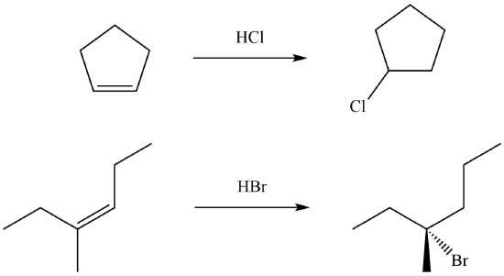
4) Draw the reaction mechanism of the previous problem **(3).**

5) Identify the products of the following reactions.

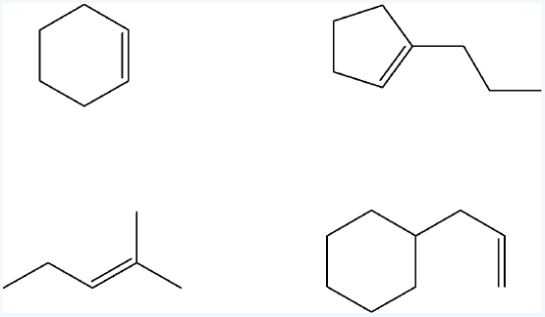


Answer

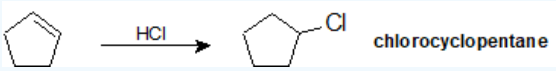
1)



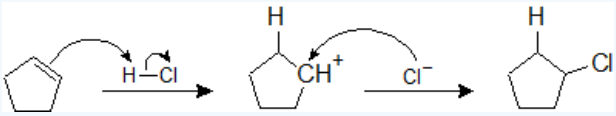
2)



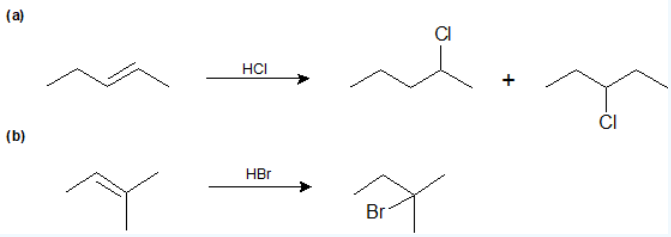
3)



4)



5)



Contributors and Attributions

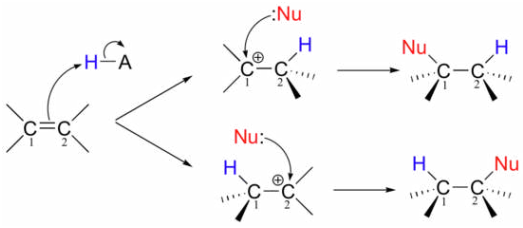
- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)
- Dr. Krista Cunningham

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- **7.9: Orientation of Electrophilic Additions - Markovnikov's Rule** by Dietmar Kennepohl, Gamini Gunawardena, Jim Clark, Krista Cunningham, Steven Farmer, Zachary Sharrett is licensed CC BY-SA 4.0.

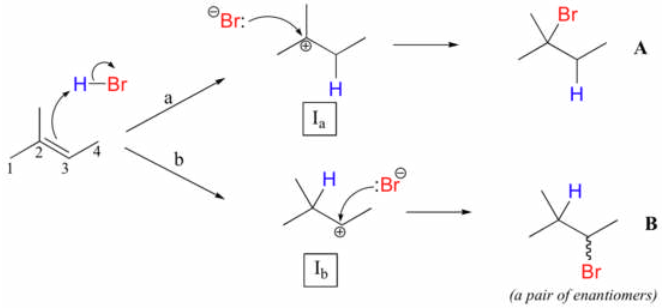
11.8: Markovnikov's Rule

A very important point with regard to electrophilic addition reactions is that if the starting alkene is asymmetrical, there are two possible courses that could be followed, depending on which of the two alkene carbons forms the new sigma bond in the first step.

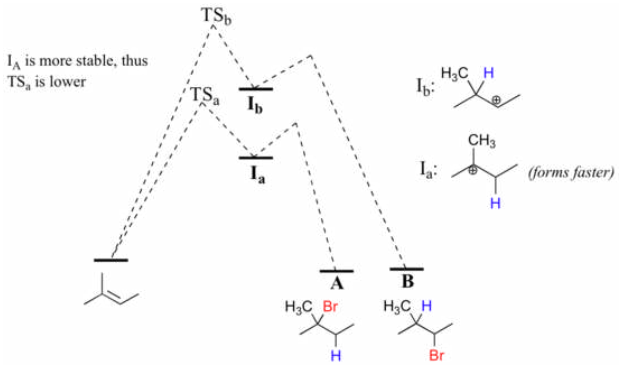


Of course, the two reaction courses involve two different carbocation intermediates, which may have different energy levels. Two different products are possible, and in general *the product which predominates will be the one that is derived from the lower-energy carbocation intermediate*.

This important regiochemical principle is nicely illustrated by a simple electrophilic addition that is commonly carried out in the organic laboratory: the conversion of an alkene to an alkyl bromide by electrophilic addition of HBr to the double bond. Let's look at a hypothetical addition of HBr to 2-methyl-2-butene, pictured below. Two different regiochemical outcomes are possible:



The initial protonation step could follow two different pathways, resulting in two different carbocation intermediates: pathway '**a**' gives a tertiary carbocation intermediate (I_a), while pathway '**b**' gives a secondary carbocation intermediate (I_b) We know already that the tertiary carbocation is more stable (in other words, lower in energy). According to the Hammond postulate, this implies that the activation energy for pathway **a** is lower than in pathway **b**, meaning in turn that I_a forms *faster*.



Because the protonation step is the rate determining step for the reaction, the tertiary alkyl bromide A will form much faster than the secondary alkyl halide B, and thus A will be the predominant product observed in this reaction. This is a good example of a non-enzymatic organic reaction that is highly regiospecific.

In the example above, the difference in carbocation stability can be accounted for by the electron-donating effects of the extra methyl group on one side of the double bond. It is generally observed that, in electrophilic addition of acids (including water) to asymmetrical 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.

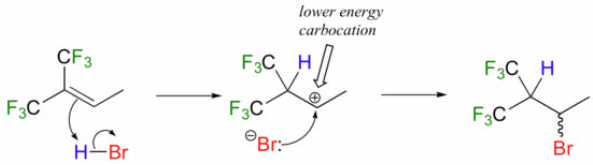


This rule of thumb is known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869.

While it is useful in many cases, Markovikov's rule does not apply to all possible electrophilic additions. It is more accurate to use the more general principle that has already been stated above:

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.

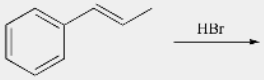
How is this different from Markovnikov's original rule? Consider the following hypothetical reaction, which is similar to the HBr addition shown above except that the six methyl hydrogens on the left side of the double bond have been replaced by highly electron-withdrawing fluorines.



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 would be referred to as an 'anti-Markovnikov' addition product, because it 'breaks' Markovnikov's rule.

Example

Predict the product of the following reaction:



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

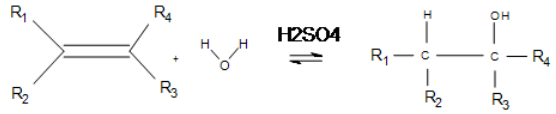
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11.9: Hydration—Electrophilic Addition of Water

Electrophilic hydration is the act of adding electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1º, 2º, or 3º alcohol on the alkane.

What Is Electrophilic Hydration?

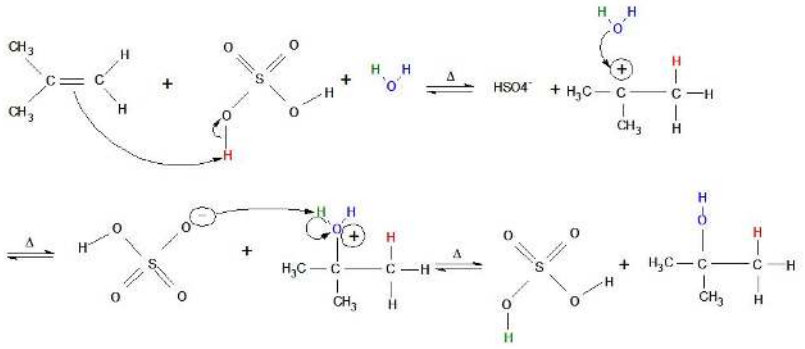
Electrophilic hydration is the reverse dehydration of alcohols and has practical application in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:

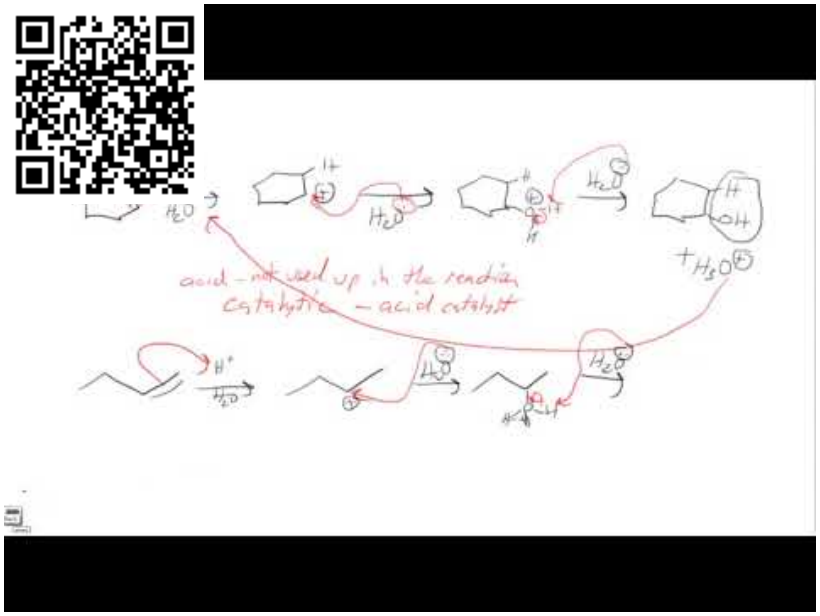


The phrase "electrophilic" literally means "electron loving" (whereas "nucleophilic" means "nucleus loving"). Electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electrons. Electrophilic hydrogen is commonly used to help break double bonds or restore catalysts (see S_N2 for more details).

How Does Electrophilic Hydration Work?

Mechanism for 3º Alcohol (1º and 2º mechanisms are similar):





Temperatures for Types of Alcohol Synthesis

Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

- Primary Alcohol: Less than 170ºC
- Secondary Alcohol: Less than 100ºC
- Tertiary Alcohol: Less than 25ºC

But...Why Does Electrophilic Hydration Work?

- An alkene placed in an aqueous non-nucleophilic strong acid immediately "reaches out" with its double bond and attacks one of the acid's hydrogen atoms (meanwhile, the bond between oxygen and hydrogen performs heterolytic cleavage toward the oxygen—in other words, both electrons from the oxygen/hydrogen single bond move onto the oxygen atom).
- A carbocation is formed on the original alkene (now alkane) in the more-substituted position, where the oxygen end of water attacks with its 4 non-bonded valence electrons (oxygen has 6 total valence electrons because it is found in Group 6 on the periodic table and the second row down: two electrons in a 2s-orbital and four in 2p-orbitals. Oxygen donates one valence electron to each bond it forms, leaving four 4 non-bonded valence electrons).
- After the blue oxygen atom forms its third bond with the more-substituted carbon, it develops a positive charge (3 bonds and 2 valence electrons give the blue oxygen atom a formal charge of +1).
- The bond between the green hydrogen and the blue oxygen undergoes heterolytic cleavage, and both the electrons from the bond move onto the blue oxygen. The now negatively-charged strong acid picks up the green electrophilic hydrogen.
- Now that the reaction is complete, the non-nucleophilic strong acid is regenerated as a catalyst and an alcohol forms on the most substituted carbon of the current alkane. At lower temperatures, more alcohol product can be formed.

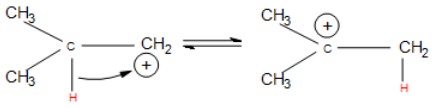
What is Regiochemistry and How Does It Apply?

Regiochemistry deals with where the substituent bonds on the product. **Zaitsev**'s and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bonds onto the product. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies. See the following for an in-depth explanation of regiochemistry Markovnikov explanation: Radical Additions--Anti-Markovnikov Product Formation

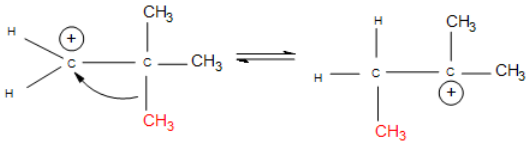
In the mechanism for a 3º alcohol shown above, the red H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3º carbon, causing it to be highly stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, **carbocations form on the most substituted carbon** connected to the double bond. Carbocations are also stabilized by resonance, but resonance is not a large factor in this case because any carbon-carbon double bonds are used to initiate the reaction, and other double bonded molecules can cause a completely different reaction.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

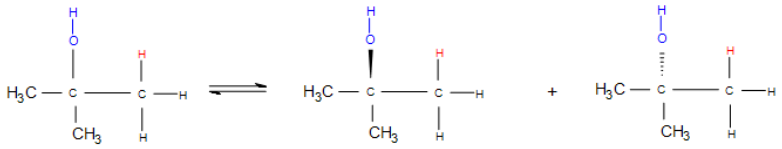


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3º alcohol shown above, water is the nucleophile. When the green H is removed from the water molecule, the alcohol attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

What is Stereochemistry and How Does It Apply?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that **the product is a racemic mixture**.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3º alcohol product could look like either of the following products:



Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

Is There a Better Way to Add Water to Synthesize an Alcohol From an Alkene?

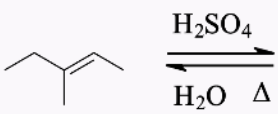
A more efficient pathway does exist: see Oxymercuration - Demercuration: A Special Electrophilic Addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (R)-enantiomer and an (S)-enantiomer)
- Using sulfuric or phosphoric acid

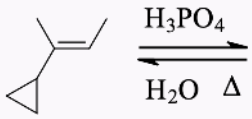
Exercise 11.9.1

Predict the product of each reaction.

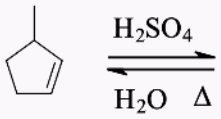
1)



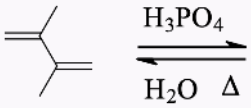
2) How does the cyclopropane group affect the reaction?



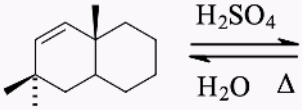
3) (Hint: What is different about this problem?)



4) (Hint: Consider stereochemistry.)

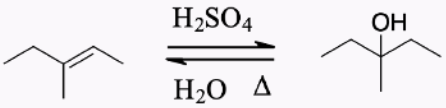


5) Indicate any shifts as well as the major product:

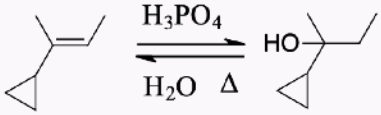


Answer

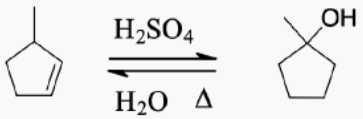
1) This is a simple electrophilic hydration.



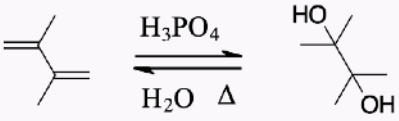
2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3º carbon will remain as such).



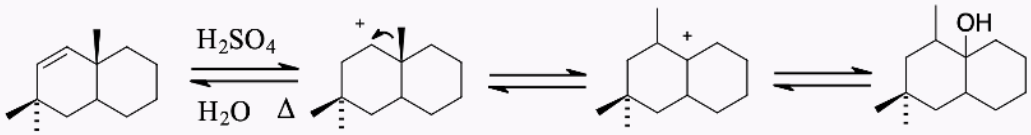
3) A hydride shift actually occurs from the 3 carbon of the 3-methylcyclopentene to where the carbocation had formed.



4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.



5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.



References

1. Vollhardt and Schore. Organic Chemistry, Structure and Function- Fifth Edition. New York: W. H. Freeman and Company, 2007.
2. Krow, Grant. "Sulfuric Acid." Encyclopedia of Reagents for Organic Synthesis. Philadelphia, Pennsylvania: John Wiley & Sons, 2001.

Outside Links

- http://en.wikipedia.org/wiki/Electrophile
- http://www.youtube.com/watch?v=Z7xskJnGDEM
- For more on Hyperconjugation: http://en.wikipedia.org/wiki/Hyperconjugation
- For more on Markovnikov's Rule: http://en.wikipedia.org/wiki/Markovnikov_rule
- For more on Zaitsev's Rule: http://en.wikipedia.org/wiki/Zaitsev%27s_rule

Contributors

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11.10: Halogenation—Addition of Halogen

Halogens can act as electrophiles to attack a double bond in alkene. Double bond represents a region of electron density and therefore functions as a nucleophile. How is it possible for a halogen to obtain positive charge to be an electrophile?

Introduction

As halogen molecule, for example Br_2, approaches a double bond of the alkene, electrons in the double bond repel electrons in bromine molecule causing polarization of the halogen bond. This creates a dipolar moment in the halogen molecule bond. Heterolytic bond cleavage occurs and one of the halogens obtains positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but stereoselective.Stereochemistry of this addition can be explained by the mechanism of the reaction.In the first step electrophilic halogen with a positive charge approaches the double carbon bond and 2 p orbitals of the halogen, bond with two carbon atoms and create a cyclic ion with a halogen as the intermediate step. In the second step, halogen with the negative charge attacks any of the two carbons in the cyclic ion from the back side of the cycle as in the S_N2 reaction. Therefore stereochemistry of the product is **vicinial dihalides through anti** addition.

$$\mathbf{R_2C{=}CR_2 + X_2 \rightarrow R_2CX{-}CR_2X} \tag{11.10.1}$$

Halogens that are commonly used in this type of the reaction are: ***Br*** and ***Cl***. In thermodynamical terms ***I*** is too slow for this reaction because of the size of its atom, and ***F*** is too vigorous and explosive.

Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl_4) can be used in this reaction.

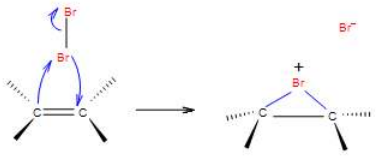
Because halogen with negative charge can attack any carbon from the opposite side of the cycle it creates a mixture of steric products.Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

Electrophilic addition mechanism consists of two steps.

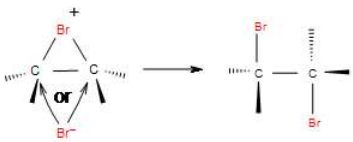
Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene.

Nucleophile	Double bond in alkene
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a intermediate cycle with the double bond.



Step 2: In the second step, bromide anion attacks any carbon of the bridged bromonium ion from the back side of the cycle. Cycle opens up and two halogens are in the position **anti**.



Summary

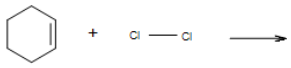
Hallogens can act as electrophiles due to polarizability of their covalent bond.Addition of halogens is stereospecific and produces vicinial dihalides with anti addition.Cis starting material will give mixture of enantiomers and trans produces a meso compound.

References

1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function.New Yourk: W.H.Freeman and Company 2007
2. Chemestry-A Europian Journal 9 (2003) :1036-1044

Problems

1.What is the mechanism of adding Cl_2 to the cyclohexene?

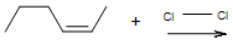


2.A reaction of Br_2 molecule in an inert solvent with alkene follows?

a) syn addition

b) anti addition

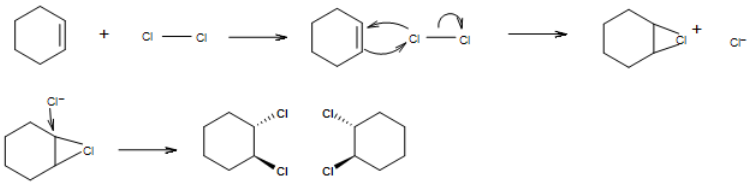
c) Morkovnikov rule

3) 

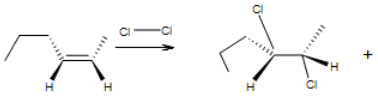
4) 

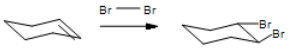
Key:

1.



2. b

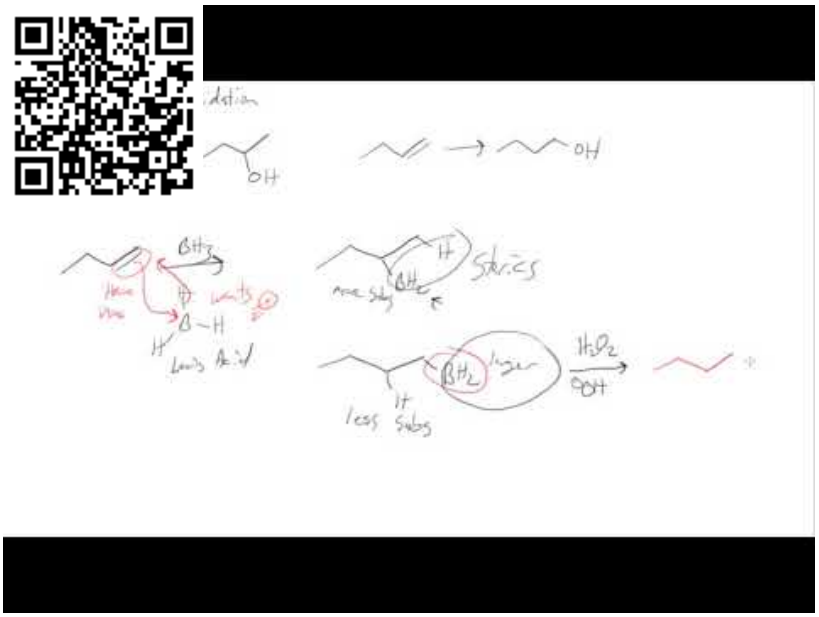
3.  enantiomer

4. 

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11.11: Hydroboration–Oxidation

Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. Furthermore, the borane acts as a lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The Hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

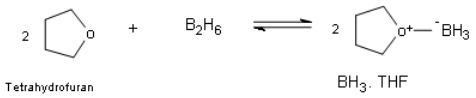


Introduction

Hydroboration-oxidation of alkenes has been a very valuable laboratory method for the stereoselectivity and regioselectivity of alkenes. An Additional feature of this reaction is that it occurs without rearrangement.

The Borane Complex

First off it is very imporatnt to understand a little bit about the structure and the properties of the borane molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula B_2H_6 (diborane). Additionally, the dimer B_2H_6 ignites spontaneously in air. Borane is commercially available in ether and tetrahydrofuran (THF), in these solutions the borane can exist as a lewis acid-base complex, which allows boron to have an electron octet.



Tetrahydrofuran (THF)

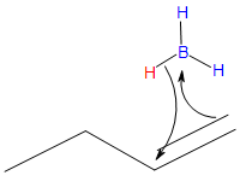
BH_3. THF

The Mechanism

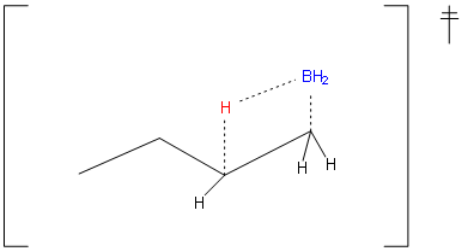
Step #1

- Part #1: Hydroboration of the alkene. In this first step the addittion of the borane to the alkene is initiated and prceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p

orbital of the boron electrophile pairing with the electron pair of the ? bond of the nucleophile.

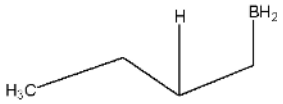


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

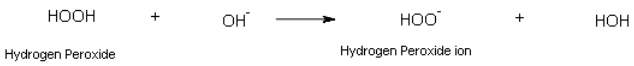
- Part #2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).

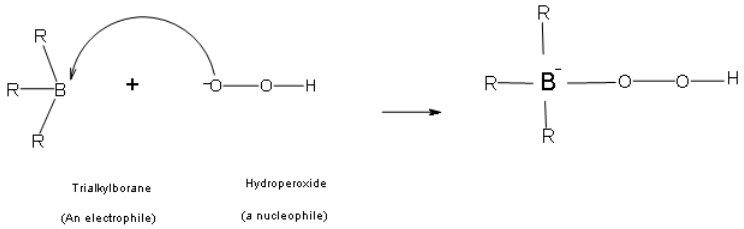


Oxidation of the Trialkylborane by Hydrogen Peroxide

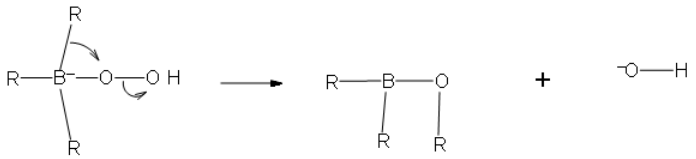
Step #2

- Part #1: the first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. The hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.

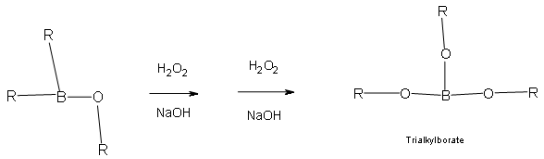




- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



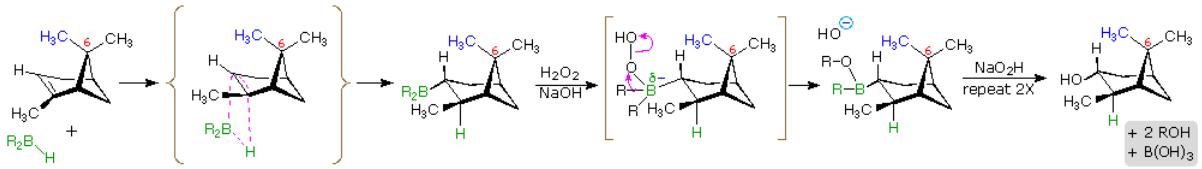
- Part 3: This is the final part of the Oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.



If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

Stereochemistry of hydroboration

The hydroboration reaction is among the few simple addition reactions that proceed cleanly in a *syn* fashion. As noted above, this is a single-step reaction. Since the bonding of the double bond carbons to boron and hydrogen is concerted, it follows that the geometry of this addition must be syn. Furthermore, rearrangements are unlikely inasmuch as a discrete carbocation intermediate is never formed. These features are illustrated for the hydroboration of α-pinene.



Since the hydroboration procedure is most commonly used to hydrate alkenes in an anti-Markovnikov fashion, we also need to know the stereoselectivity of the second oxidation reaction, which substitutes a hydroxyl group for the boron atom. Independent study has shown this reaction takes place with retention of configuration so the overall addition of water is also syn.

The hydroboration of α-pinene also provides a nice example of steric hindrance control in a chemical reaction. In the less complex alkenes used in earlier examples the plane of the double bond was often a plane of symmetry, and addition reagents could approach with equal ease from either side. In this case, one of the methyl groups bonded to C-6 (colored blue in the equation) covers one face of the double bond, blocking any approach from that side. All reagents that add to this double bond must therefore approach from the side opposite this methyl.

Outside links

- http://en.wikipedia.org/wiki/Hydroboration-oxidation
- http://bcs.whfreeman.com/vollhardtschore4e/cat_010/ch12/12010-03.htm
- http://www.chemhelper.com/hydroboration.html
- http://www.cartage.org.lb/en/themes/...roboration.htm
- http://www.organic-chemistry.org/nam...oboration.shtm

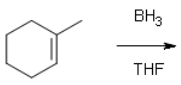
References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Foote, S. Christopher, and William H. Brown. Organic Chemistry. 5th. Belmont, CA: Brooks/Cole Cengage Learning, 2005.
3. Bruice, Paula Yurkanis. Oragnic Chemistry. 5th. CA. Prentice Hall, 2006.
4. Bergbreiter E. David , and David P. Rainville. Stereochemistry of hydroboration-oxidation of terminal alkenes. *J. Org. Chem.*, 1976, 41 (18), pp 3031–3033
5. Ilich, Predrag-Peter; Rickertsen, Lucas S., and Becker Erienne. Polar Addition to C=C Group: Why Is Anti-Markovnikov Hydroboration-Oxidation of Alkenes Not "Anti-"? Journal of Chemical Education., 2006, v83, n11, pg 1681-1685

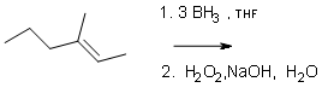
Problems

What are the products of these following reactions?

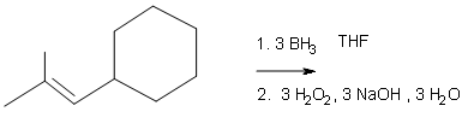
#1.



#2.

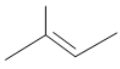


#3.



Draw the structural formulas for the alcohols that result from hydroboration-oxidation of the alkenes shown.

#4.

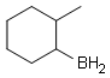


#5. (E)-3-methyl-2-pentene

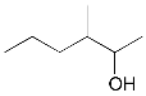
If you need clarification or a reminder on the nomenclature of alkenes refer to the link below on naming the alkenes.

Answers

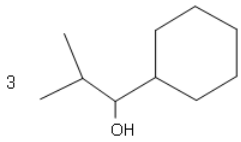
#1.



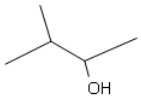
#2.



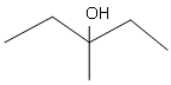
#3.



#4.



#5.



Contributors

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)
- Layne A. Morsch (University of Illinois Springfield)

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11.12: Lipids—Part 2

Fatty acids are merely carboxylic acids with long hydrocarbon chains. The hydrocarbon chain length may vary from 10-30 carbons (most usual is 12-18). The non-polar hydrocarbon alkane chain is an important counter balance to the polar acid functional group. In acids with only a few carbons, the acid functional group dominates and gives the whole molecule a polar character. However, in fatty acids, the non-polar hydrocarbon chain gives the molecule a non-polar character.

Introduction

The most common fatty acids are listed. Note that there are two groups of fatty acids--saturated and unsaturated. Recall that the term **unsaturated** refers to the presence of one or more double bonds between carbons as in alkenes. A **saturated fatty acid** has all bonding positions between carbons occupied by hydrogens.

The melting points for the saturated fatty acids follow the **boiling point principle** observed previously. Melting point principle: **as the molecular weight increases, the melting point increases.** This observed in the series lauric (C12), palmitic (C16), stearic (C18). Room temperature is 25ºC, Lauric acid which melts at 44º is still a solid, while arachidonic acid has long since melted at -50º, so it is a liquid at room temperature.

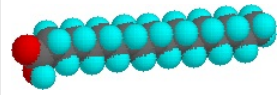
Table 1: Common Fatty Acids

Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

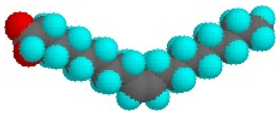
Unsaturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

Melting Points of Saturated vs. Unsaturated Fatty Acids

Note that as a group, the **unsaturated fatty acids have lower melting points than the saturated fatty acids**. The reason for this phenomenon can be found by a careful consideration of molecular geometries. The tetrahedral bond angles on carbon results in a molecular geometry for saturated fatty acids that is relatively linear although with zigzags.



Stearic acid



Oleic acid

This molecular structure allows many fatty acid molecules to be rather closely "stacked" together. As a result, close intermolecular interactions result in relatively high melting points.

On the other hand, the introduction of one or more double bonds in the hydrocarbon chain in unsaturated fatty acids results in one or more "bends" in the molecule. The geometry of the double bond is almost always a cis configuration in natural fatty acids. and these molecules do not "stack" very well. The intermolecular interactions are much weaker than saturated molecules. As a result, the melting points are much lower for unsaturated fatty acids.

Percent Fatty Acid Present in Triglycerides					
Fat or Oil	**Saturated**		**Unsaturated**		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegatable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

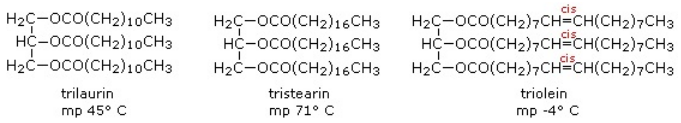
Saturated vs. Unsaturated Fatty Acids in Fats and Oils

The triesters of fatty acids with glycerol (1,2,3-trihydroxypropane) compose the class of lipids known as fats and oils. These **triglycerides** (or triacylglycerols) are found in both plants and animals, and compose one of the major food groups of our diet. Triglycerides that are solid or semisolid at room temperature are classified as fats, and occur predominantly in animals. Those

triglycerides that are liquid are called oils and originate chiefly in plants, although triglycerides from fish are also largely oils. Some examples of the composition of triglycerides from various sources are given in the following table.

	Saturated Acids (%)					Unsaturated Acids (%)		
Source	C_{10} & less	C_{12} lauric	C_{14} myristic	C_{16} palmitic	C_{18} stearic	C_{18} oleic	C_{18} linoleic	C_{18} unsaturated
Animal Fats								
butter	15	2	11	30	9	27	4	1
lard	-	-	1	27	15	48	6	2
human fat	-	1	3	25	8	46	10	3
herring oil	-	-	7	12	1	2	20	52
Plant Oils								
coconut	-	50	18	8	2	6	1	-
corn	-	-	1	10	3	50	34	-
olive	-	-	-	7	2	85	5	-
palm	-	-	2	41	5	43	7	-
peanut	-	-	-	8	3	56	26	7
safflower	-	-	-	3	3	19	76	-

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

The hydrogenation of vegetable oils to produce semisolid products has had unintended consequences. Although the hydrogenation imparts desirable features such as spreadability, texture, "mouth feel," and increased shelf life to naturally liquid vegetable oils, it introduces some serious health problems. These occur when the cis-double bonds in the fatty acid chains are not completely saturated in the hydrogenation process. The catalysts used to effect the addition of hydrogen isomerize the remaining double bonds to their trans configuration. These unnatural trans-fats appear to to be associated with increased heart disease, cancer, diabetes and obesity, as well as immune response and reproductive problems.

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11.13: Alkenes and Alkynes I (Problems)

Exercise 11-1 Deduce possible structures of the substances whose infrared spectra are shown in Figure 11-2. Assign as many of the bands as you can to *specific* stretching and bending vibrations by comparison with Figure 10-1. Be sure your structural assignments fit with the spectrum - that is, think twice about assigning a structure than has $-CH_2-$ groups if there are no $-CH_2-$ bands in the spectrum, or that has no $-CH_3$ groups when there appear to be strong $-CH_3$ absorptions.

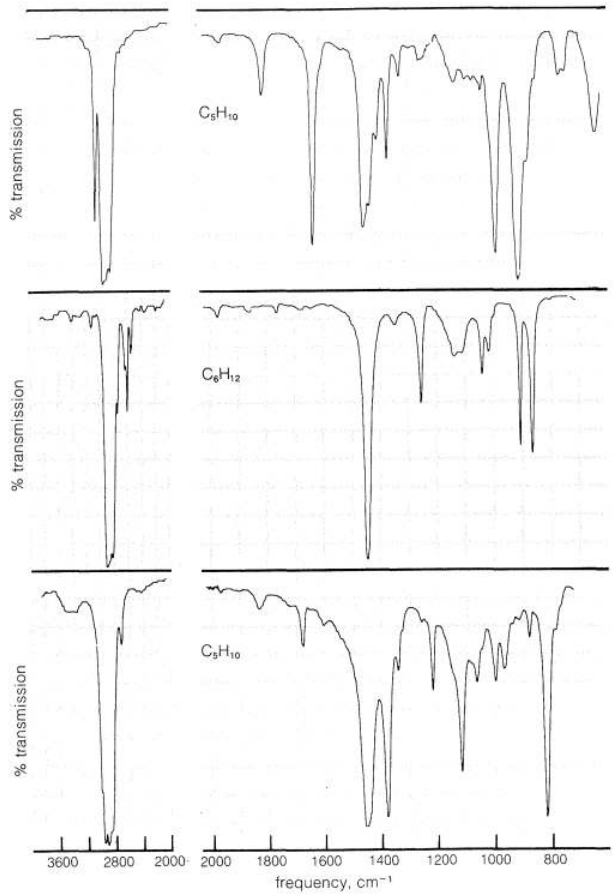


Figure 11-2: *Infrared spectra for Exercise 11-1.*

Exercise 11-2 Deduce the structures of the substances whose proton nmr spectra are shown in Figure 11-3. Analyze the spectra in as much detail as you can in terms of chemical shifts and spin-spin splitting.

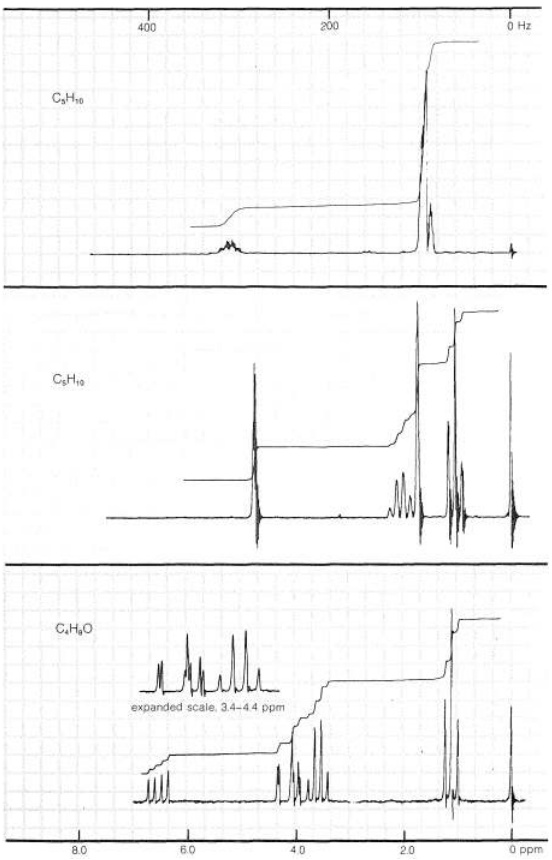


Figure 11-3: *Proton nmr spectra at* **60 MHz** *with TMS as the standard at* **0 ppm**. *See Exercise 11-2.*

Exercise 11-3 Sketch the principal features you would expect for the infrared and proton nmr spectra of each of the following substances. (It will be helpful to review Sections 9-7 and 9-10.)

a. $CH_3C \equiv CCH_3$
b. $CH_3C \equiv CH$ (expect a four-bond coupling of about **3 Hz**)
c. $CH_3CH_2C \equiv CCH_2CH_3$
d. $HC \equiv C{-}CH{=}C{-}C \equiv CH$ (cis and trans)

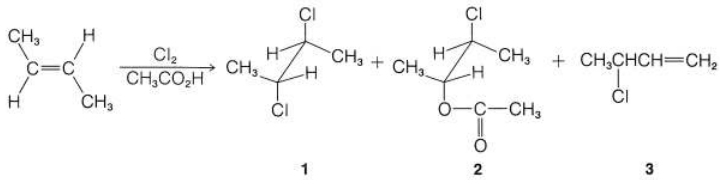
Exercise 11-4 Deduce the structure of a compound with the following spectral properties:

Mass spectrum	Infrared	Nmr
m/e 82 (highest mass number)	3320 cm^{-1} (s)	δ 0.93, area 3, triplet
m/e 39 (base peak)	2950 cm^{-1} (s)	1.18–1.65, 4, complex
	2120 cm^{-1} (m)	1.73, 1, closely spaced triplet
	1460 cm^{-1} (s)	
	1375 cm^{-1} (w)	2.16, 2, complex
	640 cm^{-1} (s)	

No electronic absorption was evident at wavelengths longer than **200 nm**.

Exercise 11-5 Use the bond energies (Table 4-3) to calculate ΔH^0 for the addition of Br_2, Cl_2, I_2, HOCl, HCl, HBr, HI, and H_2O to ethene in the gas phase. The addition of HCl, HBr, and HI is energetically unfavorable in dilute water solution. Why should this be so?

Exercise 11-6 Addition of chlorine to *trans*-2-butene in ethanoic acid (acetic acid, CH_3CO_2H as solvent gives **74%** *meso*-2,3-dichlorobutane, **1**, **24%** 2-chloro-1-methylpropyl ethanoate, **2**, and **2%** 3-chloro-1-butene, **3**. (*Note:* **2** is formed as a *D*,*L* pair, although only one enantiomer is shown here.)



Write a mechanism to show how all three products could be obtained from a common chloronium ion intermediate. Draw structures for the products expected from addition of chlorine to *cis*-2-butene in ethanoic acid. Show the configurations. If necessary, review Section 5-5 before working this problem.

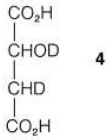
Exercise 11-7 In the formation of ethenebromonium ion from 1-bromo-2-fluoroethane and SbF_5 is SO_2, is the SbF_5 playing the role of an acid, a base, an electrophile, or a nucleophile? How strong a nucleophile do you judge SbF_6^- to be? Explain.

Exercise 11-8 Show the steps involved in the formation of ethyl hydrogen sulfate from ethene and sulfuric acid. Show how diethyl sulfate, $(CH_3CH_2O)_2SO_2$, could be formed from the same reagents.

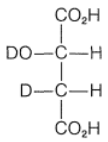
Exercise 11-9* Suppose we were gradually to add water to a solution of $C_3H_2^+—SbF_6^-$ and excess $HSbF_6$ in SO_2. What changes would you expect to take place? Write equations for the reactions you expect to occur.

Exercise 11-10* Assess the possibility of adding ammonia, NH_3, to 2-methylpropene with the aid of sulfuric acid as a catalyst.

Exercise 11-11* Show by projection formulas the stereochemical course you would expect for the *acid-catalyzed* addition of D_2O to fumaric acid to give the deuterated malic acid **4**. Be sure you consider the stereochemistry of the C—D bond relative to the C—O bond. Indicate your reasoning.



Exercise 11-12* The hydration of fumaric acid catalyzed by *fumarase* in D_2O leads to malic acid with only *one* C—D bonds, which is selectively removed when malic acid is enzymatically reconverted to fumaric acid. The configuration of deuteriomalic acid prepared in this way has been shown to correspond to the following projection formula:



Deduce the stereochemistry of both the forward and backward reactions (hydration and dehydration) from this information.

Exercise 11-13 Explain how Markownikoff's rule for orientation in electrophilic additions can be accounted for in terms of the modern view of how these reactions occur, using the reaction of HCl with 1-methylcyclohexene as an example.

Exercise 11-14 Predict the major product(s) of each of the following electrophilic addition reactions (under conditions of kinetic control):

a. 1-butene with concentrated H_2SO_4
b. 2-methylpropene in 10% aqueous H_2SO_4
c. 2-methyl-2-butene with Br_2 in methanol as solvent.

Exercise 11-15 Arrange ethene, propene, and 2-methylpropene in order of expected ease of hydration with aqueous acid. Show your reasoning.

Exercise 11-16 Use the electronegativity chart of Figure 10-11 and Table 10-2 to predict the products of the following additions under conditions of kinetic control. Indicate the configuration of the products where possible.

a. 2-methyl-2-butene with ICl, and with INO_2
b. a carbon-nitrogen double bond with water

c. N-bromosuccinimide and cyclohexene in aqueous medium

d. 2-methylpropene with HOF

e. 2-methylpropene with N-bromosuccinimide and 70% hydrogen fluoride in pyridine (Notice that the pyridine serves only to moderate the activity of the hydrogen fluoride.)

Exercise 11-17 Make atomic-orbital models of the 1- and 2-fluoroethyl carbocations (CH_3CHF^+ and $FCH_2CH_2^+$). Predict which should be formed more rapidly by the addition of H^+ to fluoroethene. Give your reasoning.

Exercise 11-18 Predict the predominant product from addition of hydrogen chloride to each of the following alkenes. Give your reasoning.

a. $CH_2{=}CCl_2$

b. $(CH_3)_2C{=}CCl_2$

c. $CF_3{-}CH{=}CH{-}CH_3$

d. $CH_3OCH{=}CHF$

Exercise 11-19 The ethenyl carbocation, $CH_2{-}CH^{\oplus}$, apparently is formed much more easily by addition of a proton from HCl to ethyne than it is by S_N1 reactions of ethenyl chloride. Deduce from bond energies why this should be so.

Exercise 11-20 Show how the rearrangement of ethenol to ethanal could take place in aqueous solution with water behaving as both a proton acceptor (base) and a proton donor (acid).

Exercise 11-21 Predict the predominant products in each of the following reactions. Show the expected configurations of the intermediates and products.

a. 2-butyne with mercuric ethanoate, $Hg(OCOCH_3)_2$, in ethanoic acid

b. ethenylbenzene with aqueous sulfuric acid containing mercuric sulfate, $HgSO_4$

c. ethyne with mercuric chloride in methanol

(*Note:* A mercuric salt of structure HgX_2 is a potential source of an electrophile, $HgX^{\oplus}$. Mercuric sulfate probably is a source of the electrophilic cation, $HgOSO_3H^{\oplus}$, in aqueous sulfuric acid.)

Exercise 11-22 Show the steps involved in the base-initiated addition of methanol to 2-hexen-4-yne (review Section 6-6).

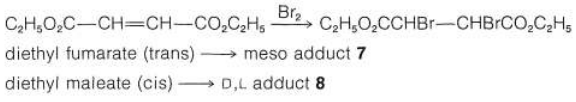
Exercise 11-23 Sodium chloride in the presence of $OH^{\ominus}$ with 2-hexen-4-yne does not yield $CH_3CCl{=}CH{-}CH{=}CHCH_3$. Explain.

Exercise 11-24 Write two different radical mechanisms for peroxide-initiated addition of hydrogen chloride to alkenes and consider the energetic feasibility for each.

Exercise 11-25 Calculate the ΔH^0 values for initiation and chain-propagation steps of radical addition of hydrogen fluoride, hydrogen chloride, and hydrogen iodide to an alkene. Would you expect these reagents to add easily to double bonds by such a mechanism?

Exercise 11-26

a. Bromine adds to diethyl fumarate (diethyl *trans*-butenedioate) to give the meso adduct **7**, and to diethyl maleate (diethyl *cis*-butenedioate) to give the ***D,L*** adduct **8**, provided that the reaction mixtures are kept at 25° or less and are carefully protected from light. Deduce whether the stereochemistry of the reaction is suprafacial or antarafacial under these conditions.



b.* Diethyl maleate rearranges rapidly to diethyl fumarate on irradiation with ultraviolet light, provided that a trace of bromine is present. Irradiation of *equimolar* amounts of bromine and diethyl maleate leads to a mixture of ***D,L*** and meso adducts. Under these conditions the fumarate ester gives only the meso adduct. Show the steps involved in these transformations and explain clearly why the light-induced addition to the cis ester is not stereospecific.

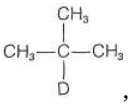
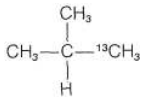
Exercise 11-27 A radical of structure $CH_3\dot{C}{=}CHBr$ is involved in the light-induced addition of HBr to propyne. What geometry would you expect it to have? Draw an atomic-orbital picture of the radical with particular attention to the hybridization of orbitals

at the radical center.

Exercise 11-28 Bromotrichloromethane, $BrCCl_3$, adds to 1-octene by a radical-chain mechanism on heating in the presence of a peroxide catalyst. Use the bond-energy tables to devise a feasible mechanism for this reaction and work out the most likely structure for the product. Show your reasoning. Show the most likely product of addition of $BrCCl_3$ to 1-octyne. [*Note:* Radical-chain reactions involve abstraction of atoms, not abstraction of groups.]

Exercise 11-29 Propenenitrile (acrylonitrile, $CH_2{=}CHCN$) will polymerize readily at $-50°$ in a polar solvent [e.g., dimethylmethanamide, $HCON(CH_3)_2$] under the influence of sodium cyanide, $NaCN$. Show the initiation and propagation steps of this reaction, and predict the structure of the polymer. Why is a polar solvent necessary? Why does this polymerization proceed but not that of propene under the same conditions?

Exercise 11-30 Write a reasonable mechanism for termination of ethene polymerization by disproportionation. Calculate ΔH^0 values for termination of the chain reaction by combination and disproportionation. Which is the more favorable process?

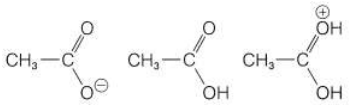
Exercise 11-31 It has been reported that a mixture of 2-methylpropane-2-D,  , and 2-methylpropane-1-^{13}C,  , (^{13}C is the stable carbon isotope of mass 13) is converted only very slowly by sulfuric acid to a mixture containing the two starting materials, ordinary 2-methylpropane and 2-methylpropane-1-^{13}C-2-D.

The reaction is speeded up greatly by addition of small amounts of 2-methylpropene. Explain. Would you expect any significant formation of D_2SO_4 when the reaction is carried out in the presence of 2-methylpropene? Why?

Exercise 11-32 For each of the following groups of substances designate which is the strongest electrophile and which is the strongest nucleophile. Give your reasoning.

a. H_2O $H_3O^{\oplus}$ $HO^{\ominus}$

b. I_2 $I^{\ominus}$ $H_2\overset{\oplus}{O}I$

c. 

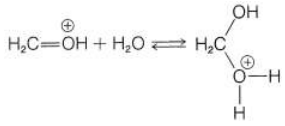
d. $CH_3\ddot{N}H_2$ $CH_3\ddot{N}H^{\ominus}$ $CH_3\overset{\oplus}{N}H_3$

e. $HO{-}NO_2$ $H_2\overset{\oplus}{O}{-}NO_2$ $^{\oplus}NO_2$ $^{\ominus}O{-}NO_2$

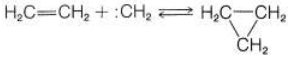
f. HF $HF + SbF_5$ SbF_6^- F^-

g. FSO_3H $ClSO_3H$ $HOSO_3^-$

Exercise 11-33 Identify the nucleophile and the electrophile in each of the following reactions:

a. 

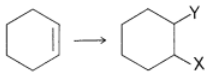
b. $H_2C{=}CH_2 + Br_2 \rightleftharpoons H_2C(Br)\overset{\oplus}{C}H_2 + Br^{\ominus}$

c. 

d. $CH_2{=}CHCN + NH_2^- \rightleftharpoons NH_2{-}CH_2 - \overset{\ominus}{C}HCN$

Exercise 11-34 Indicate what reagents and conditions would convert cyclohexane to the following derivatives:

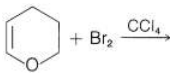
	X	Y
a.	Cl	H
b.	OH	H
c.	Cl	OH
d.	—OCCH$_3$ (O)	H
e.	F	Br



Exercise 11-35 Use the electronegativity chart (Figure 10-11) to predict how the indicated bond would be expected to be polarized for each of the following compounds:

a. H_3C-H
b. H_3Si-H
c. CH_3-Li
d. CH_3-MgCH_3
e. CH_3S-Cl
f. H_2N-SCH_3
g. H_2N-OH
h. H_2N-Br
i. H_2P-Cl
j. $(CH_3)_3Si-Cl$

Exercise 11-36 Draw structures for the major products of each of the following reactions. Indicate the stereochemistry of the product, where possible (D is deuterium, the hydrogen isotope of mass 2.)

a. 

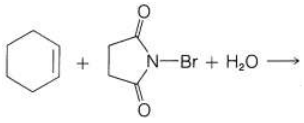
b. $CH_3CH{=}CH_2 + HF \rightarrow$

c. *cis*-1-phenylpropene $+DBr \xrightarrow{CH_2Cl_2}$

d. $C_6H_5C \equiv CCH_3 + HCl + CH_3COOH$ (solvent) $\rightarrow$

e. $CH_3C \equiv CH \xrightarrow{1.\ HgCl_2} \xrightarrow{2.\ DCl}$

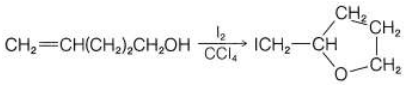
f. $C_6H_5CH{=}CH_2 + CH_3SCl \rightarrow$

g. 

Exercise 11-37 Why is molecular fluorine generally unsatisfactory as a reagent to convert alkenes to 1,2-difluoroalkanes?

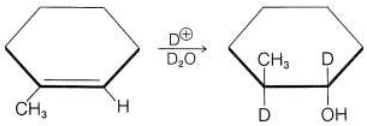
Exercise 11-38 Why does the addition of chlorine to 2-pentene in methanol give a mixture of the following products?
2,3-dichloropentane (16%)
2-chloro-3-methoxypentane (35%)
3-chloro-2-methoxypetane (49%)

Exercise 11-39 Suggest a mechanism to account for the following reaction:



Exercise 11-40 In Section 1-1I, the addition of bromine to tetrachloroethene was reported to be catalyzed by aluminum bromide. What is the function of aluminum bromide in this addition?

Exercise 11-41 Evaluate (show your reasoning) the possibility that the following reaction will give the indicated product.



If you do not think the indicated product would be important, write the structure(s) of the product(s) you think would be more likely to be found.

Exercise 11-42 2-Methylpropene reacts with ethene and hydrogen chloride under polar conditions to yield 1-chloro-3,3-dimethylbutane. Show a mechanism for this reaction that is consistent with the reactants, conditions, and product. Give your reasoning.

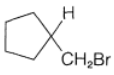
Exercise 11-43 2-Methylpropane (containing traces of 2-methylpropene) is converted by a *large* excess of deuteriosulfuric acid ($\mathbf{D_2SO_4}$) rather rapidly to 2-methylpropane with only nine deuteriums.

a. Write a polar mechanism for this hydrogen-exchange reaction that is in harmony with the known chemical properties of sulfuric acid and that predicts exchange of no more than nine of the ten hydrogens of 2-methylpropane.

b. Explain how 2-methylpropane-$\mathbf{D_9}$ can be formed more rapidly than 2-methylpropane-$\mathbf{D}_n$ with $n < 9$ in the early stages of the reaction.

Exercise 11-44 Suggest how each of the following compounds may be prepared. Assume any necessary starting hydrocarbons are available. Specify the reaction conditions as closely as possible and indicate when isomer separations may be necessary.

a. 

b. 

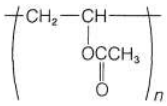
c. 1,1,1-trichloro-3-bromohexane

d. $\mathbf{C_6H_5COCH_2CH_3}$

e. $\mathbf{C_6H_5CH(OH)CH_3}$

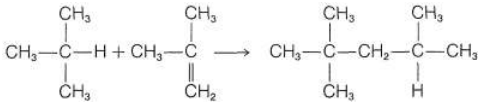
f. $\mathbf{Cl_2CHCHCl_2}$

g. $\mathbf{CH_2{=}CHOCOCH_3}$ (ethenyl ethanoate)

h. 

Exercise 11-45 Calculate ΔH^0 values for the following reactions in the gas phase per mole of the principal reactants, using the bond-energy table (Table 4-3).

a. $n \times \mathbf{CH_2{=}CH_2} \rightarrow \mathbf{-(CH_2{-}CH_2)_n-}$

b. 

Exercise 11-46 Use bond energies (Table 4-3) to investigate the possibility of adding water to propene, using peroxide ($\mathbf{ROOR}$) catalysts. It has been reported that γ rays, such as from a cobalt-60 source, decompose water into $\mathbf{H\cdot}$ and $\mathbf{HO\cdot}$. Could such radiation initiate a *chain*-addition reaction of water to propene? How about a nonchain mechanism (i.e., one γ-ray photon per molecule of reacting propene)? In a nonchain mechanism, would you expect to get 1-propanol or 2-propanol? What other products may be obtained in a nonchain reaction? Give your reasoning in detail.

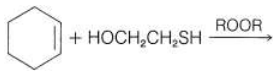
Exercise 11-47 Use bond energies (Table 4-3) to investigate the energetic feasibility of adding ammonia ($\mathbf{NH_3}$) to an alkene by a radical-chain mechanism with the aid of a peroxide ($\mathbf{ROOR}$) catalyst. What product would you expect to obtain from propene and

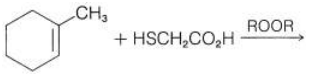
ammonia by a radical mechanism of addition?

Exercise 11-48 Draw an energy diagram similar to Figure 10-10 for the progress of a two-step reaction $\mathrm{A + BC \rightleftharpoons A{-}B{-}C \xrightarrow{D} A{-}B + C{-}D}$ in which the first step is a rapidly established equilibrium and the second step is the slow or rate-determining step. Label the diagram to show what part represents the transition state, reaction intermediate, overall energy of activation ($\Delta H'$), and overall standard enthalpy change (ΔH^0) for the process $\mathrm{A + BC + D \rightarrow AB + CD}$. Assume that the overall equilibrium constant, $K_{eq} > 1$.

Exercise 11-49 Complete the following equations showing the structures of the expected products under the reaction conditions:

a. $\mathrm{CH_2{=}CHCN + (C_2H_5)_3SiH \xrightarrow{ROOR}}$

b. 

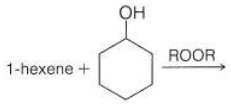
c. 

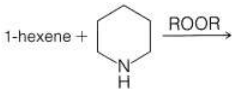
d. 1-octene $\mathrm{+ Cl_3SiH \xrightarrow{ROOR}}$

e. $\mathrm{(CH_3)_2C{=}CH_2 + CCl_4 \xrightarrow{ROOR}}$

f. $\mathrm{HC \equiv CCH_2OCOCH_3 + BrCCl_3 \xrightarrow{ROOR}}$

g. $\mathrm{CH_3C \equiv CH + CF_3I \xrightarrow{h\nu}}$

h. 

i. 

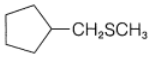
j. 1-hexene + $\mathrm{CH_3CO_2H \xrightarrow{ROOR}}$

Exercise 11-50 This problem illustrates one of the complications that can arise in radical-addition reactions.

Cyclohexene reacts with bromotrichloromethane at **40°** in the presence of small quantities of peroxides to give a mixture of products: 2-bromo-1-trichloromethylcyclohexane (**67%**) and 3-bromocyclohexene (**33%**). Account for the formation of both of these products under the reaction conditions.

Exercise 11-51 Describe how you would prepare each of the following compounds from the indicated starting materials. Specify the reagents and reaction conditions as closely as possible.

a. $\mathrm{HO_2CCH_2CH_2CH_2CH_2CO_2H}$ (hexanedioic acid) from $\mathrm{CH_3CO_2H}$ (ethanoic acid) and $\mathrm{HC \equiv CH}$ (ethyne) by a radical-chain addition

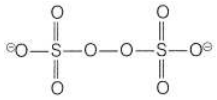
b. 

from methylenecyclopentane

c. $\mathrm{CH_3(CH_2)_7COCH_3}$ (2-decanone) from 1-octene

d. 2-decanone from 1-decyne

Exercise 11-52* The molecular weight of a polymer obtained by radical-addition polymerization can be reduced by addition of a thiol, **RSH**. For example, when propenoic acid (acrylic acid) is polymerized in the presence of potassium peroxodisulfate, $\mathrm{K_2S_2O_8}$, adding mercaptoethanoic acid, $\mathrm{HSCH_2CO_2H}$, causes the average molecular weight of the polymer molecule to become much smaller. Draw the structure of the polymer and explain how the thiol compound functions to reduce the molecular weight. Would an alcohol do as well? Show how the potassium peroxodisulfate could function as an initiator. Would you expect it to decompose more rapidly in alkaline or strongly acidic solution? Explain.



Exercise 11-53

a. 1-Bromocyclopentene adds hydrogen bromide on irradiation with ultraviolet light to give **94%** *cis*-1,2-dibromocyclopentane and **6%** of the trans isomer. Explain why 1,1-dibromocyclopentane is not obtained and why the cis isomer predominates.

b. From your answer to the questions in Part a, predict the structure and stereochemistry of the major products in the following reactions:

(i) $\mathrm{CH_3{-}C\equiv C{-}CH_3 + 2HBr \xrightarrow{ROOR}}$

(ii) $\mathrm{CH_3C\equiv CBr + HBr \xrightarrow{h\nu}}$

(iii) $\mathit{cis}\mathrm{{-}CH_3CH{=}CHCH_3 + DBr \xrightarrow{ROOR}}$

(iv) $\mathrm{HC\equiv CH + DCl \xrightarrow{HgCl_2}}$ (monoaddition product of DCl)

Contributors

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CHAPTER OVERVIEW

12: Alkynes

	**UI Springfield CHE 267** **Organic Chemistry I** **Fall 2015: Prof. Morsch**	**Reading Assignments** **Homework Problems** **Homework Solutions** **Quizzes**

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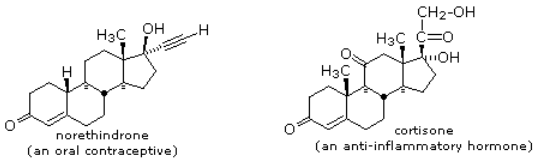
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12.3: Introduction to Alkyne Reactions
12.4: Addition of Hydrogen Halides to Alkynes
12.5: Addition of Halogen to Alkynes
12.6: Addition of Water to Alkynes
12.7: Reaction of Acetylide Anions
12.8: Synthesis
12.9: Hydroboration–Oxidation of Alkynes
12.10: Alkenes and Alkynes II (Problems)

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12.1: Interesting Alkynes

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring.

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.



Medicinally Useful Steroids

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12.2: Preparation of Alkynes

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

Introduction

One case in which elimination can occur is when a haloalkane is put in contact with a nucleophile. The table below is used to determine which situations will result in elimination and the formation of a π bond.

Elimination: Haloalkane-Nucleophile Reaction

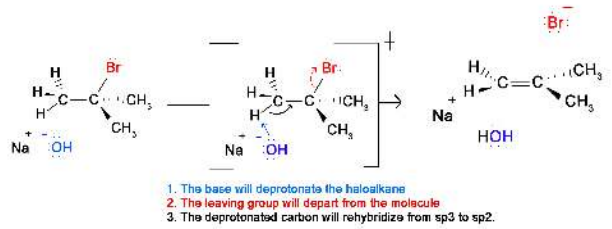
Type of Haloalkane	Weak Base, Poor Nucleophile	Weak Base, Good Nucleophile	Strong, Unhindered Base	Strong, Hindered Base
Primary				
Unhindered				E2
Branched			E2	E2
Secondary	E1		E2	E2
Tertiary	E1	E1	E2	E2

* Empty Box means no elimination or Pi bond forms

To synthesize alkynes from dihaloalkanes we use dehydrohalogenation. The majority of these reactions take place using alkoxide bases (other strong bases can also be used) with high temperatures. This combination results in the majority of the product being from the E2 mechanism.

E2 Mechanism

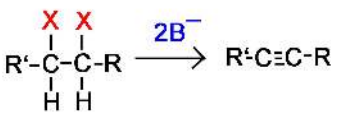
Recall that the E2 mechanism is a concerted reaction (occurs in 1 step). However, in this 1 step there are 3 different changes in the molecule. This is the reaction between 2-Bromo-2-methylpropane and Sodium Hyrdoxide.



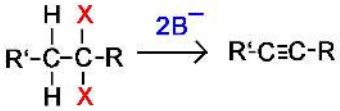
This is a brief review of the E2 reaction. For further information on why the reaction proceeds as it does visit the E2 reaction page. Now, if we apply this concept using 2 halides on vicinal or geminal carbons, the E2 reaction will take place twice resulting in the formation of 2 Pi bonds and thus an Alkyne.

Dihaloalkane Elimination

This is a general picture of the reaction taking place without any of the mechanisms shown.

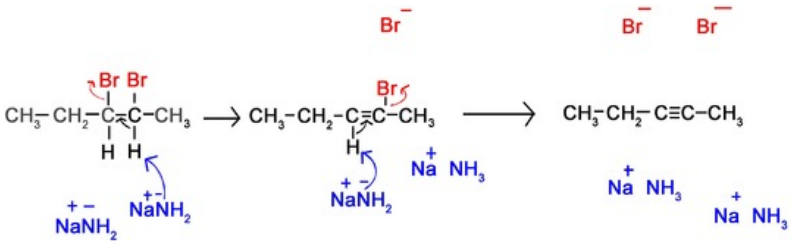


or



* With a terminal haloalkane the equation above is modified in that 3 equivalents of base will be used instead of 2.

Lets look at the mechanism of a reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia.

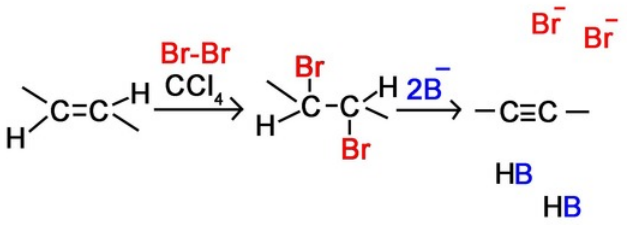


- Liquid ammonia is not part of the reaction, but is used as a solvent
- Notice the intermediate of the alkyne synthesis. It is stereospecifically in its anti form. Because the second proton and halogen are pulled off the molecule this is unimportant to the synthesis of alkynes. For more information on this see the page on preparation of alkenes from haloalkanes.

Preparation of Alkynes from Alkenes

Lastly, we will briefly look at how to prepare alkynes from alkenes. This is a simple process using first halogenation of the alkene bond to form the dihaloalkane, and next, using the double elimination process to protonate the alkane and from the 2 Pi bonds.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyene using double elimination, as covered previously on this page.

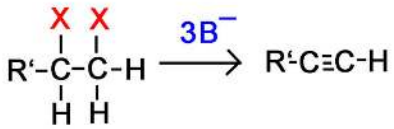


In The Lab

Due to the strong base and high temperatures needed for this reaction to take place, the triple bond may change positions. An example of this is when reactants that should form a terminal alkyne, form a 2-Alkyne instead. The use of $NaNH_2$ in liquid NH_3 is used in order to prevent this from happening due to its lower reacting temperature. Even so, most chemists will prefer to use nucleophilic substitution instead of elimination when trying to form a terminal alkyne.

Questions

Question 1: Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

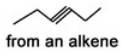


Question 2: What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide ($Na^+ {}^-O\text{-}CH_2CH_3$)

Question 3: What would be good starting molecules for the synthesis of the following molecules:

a.)

from an alkene

b.)

from a dihaloalkane

Question 4: Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answers

Answer 1: Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Answer 2:

a.) 1-Pentyne

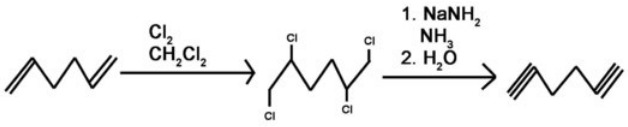
b.) 1-Pentyne

Answer 3:

a.)


b.)


Answer 4: Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.



Outside links

- http://en.wikipedia.org/wiki/Alkyne

References

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Daley, Richard, and Sally Daley. "13.8 Elimination of Organohalogens." Organic Chemistry. Daley. 5 July 2005. 21 Feb. 2009. <http://www.ochem4free.info/node/143>.

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12.3: Introduction to Alkyne Reactions

Alkanes are undoubtedly the weakest Brønsted acids commonly encountered in organic chemistry. It is difficult to measure such weak acids, but estimates put the pK_a of ethane at about 48. Hybridizing the carbon so as to increase the s-character of the C-H increases the acidity, with the greatest change occurring for the sp-C-H groups found in terminal alkynes. Thus, the pK_a of ethene is estimated at 44, and the pK_a of ethyne (acetylene) is found to be 25, making it 10^{23} times stronger an acid than ethane. This increase in acidity permits the isolation of insoluble silver and copper salts of such compounds.

$$RC{\equiv}C\text{-}H + Ag(NH_3)_2^{(+)} \text{ (in } NH_4OH) \rightarrow RC{\equiv}C\text{-}Ag \text{ (insoluble)} + NH_3 + NH_4^{(+)}$$

Despite the dramatic increase in acidity of terminal alkynes relative to other hydrocarbons, they are still very weak acids, especially when compared with water, which is roughly a billion times more acidic. If we wish to prepare nucleophilic salts of terminal alkynes for use in synthesis, it will therefore be necessary to use a much stronger base than hydroxide (or ethoxide) anion. Such a base is sodium amide ($NaNH_2$), discussed above, and its reactions with terminal alkynes may be conducted in liquid ammonia or ether as solvents. The products of this acid-base reaction are ammonia and a sodium acetylide salt. Because the acetylide anion is a powerful nucleophile it may displace halide ions from 1º-alkyl halides to give a more highly substituted alkyne as a product (S_N2 reaction). This synthesis application is described in the following equations. The first two equations show how acetylene can be converted to propyne; the last two equations present a synthesis of 2-pentyne from propyne.

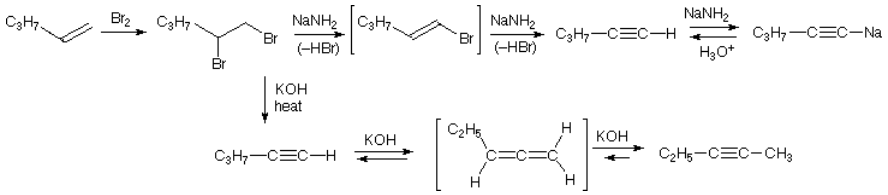
$H\text{-}C{\equiv}C\text{-}H + NaNH_2$ (in ammonia or ether) $\rightarrow H\text{-}C{\equiv}C\text{-}Na$ (sodium acetylide) $+ NH_3$
$H\text{-}C{\equiv}C\text{-}Na + CH_3\text{-}I \rightarrow H\text{-}C{\equiv}C\text{-}CH_3 + NaI$
$CH_3\text{-}C{\equiv}C\text{-}H + NaNH_2$ (in ammonia or ether) $\rightarrow CH_3\text{-}C{\equiv}C\text{-}Na$ (sodium propynylide) $+ NH_3$
$CH_3\text{-}C{\equiv}C\text{-}Na + C_2H_5\text{-}Br \rightarrow CH_3\text{-}C{\equiv}C\text{-}C_2H_5 + NaBr$

Because $RC{\equiv}C:^{(-)}\ Na^{(+)}$ is a very strong base (roughly a billion times stronger than NaOH), its use as a nucleophile in S_N2 reactions is limited to 1º-alkyl halides; 2º and 3º-alkyl halides undergo elimination by an E2 mechanism.

The enhanced acidity of terminal alkynes relative to alkanes also leads to metal exchange reactions when these compounds are treated with organolithium or Grignard reagents. This exchange, shown below in equation 1, can be interpreted as an acid-base reaction which, as expected, proceeds in the direction of the weaker acid and the weaker base. This factor clearly limits the usefulness of Grignard or lithium reagents when a terminal triple bond is present, as in equation 2.

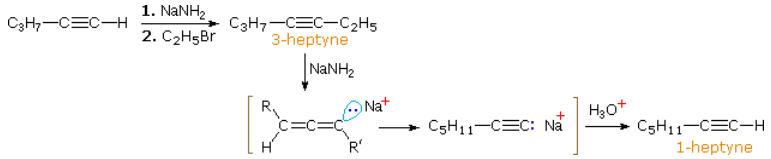
1) $RC{\equiv}C\text{-}H + C_2H_5MgBr$ (in ether) $\rightarrow RC{\equiv}C\text{-}MgBr + C_2H_6$
2) $HC{\equiv}C\text{-}CH_2CH_2Br + Mg$ (in ether) $\rightarrow [\ HC{\equiv}C\text{-}CH_2CH_2MgBr] \rightarrow BrMgC{\equiv}C\text{-}CH_2CH_2H$

The acidity of terminal alkynes also plays a role in product determination when vicinal (or geminal) dihalides undergo base induced bis-elimination reactions. The following example illustrates eliminations of this kind starting from 1,2-dibromopentane, prepared from 1-pentene by addition of bromine. The initial elimination presumably forms 1-bromo-1-pentene, since base attack at the more acidic and less hindered 1 º-carbon should be favored. The second elimination then produces 1-pentyne. If the very strong base sodium amide is used, the terminal alkyne is trapped as its sodium salt, from which it may be released by mild acid treatment. However, if the weaker base KOH is used for the elimination, the terminal alkyne salt is not formed, or is formed reversibly, and the initially generated 1-pentyne rearranges to the more stable 2-pentyne via an allene intermediate.



In the case of non-terminal alkynes, sodium and potassium amide, and related strong bases from 1 º-amines, are able to abstract protons from carbon atoms adjacent to the triple bond. The resulting allenic carbanions undergo rapid proton transfer equilibria, leading to the relatively stable terminal alkyne conjugate base. This isomerization may be used to prepare longer chain 1-alkynes,

as shown in the following conversion of 3-heptyne to 1-heptyne. The R and R' substituents on the allenic intermediate range from propyl to hydrogen, as the proton transfers proceed.



Conjugate base anions of terminal alkynes (acetylide anions) are nucleophiles, and can do both nucleophilic substitution and nucleophilic addition reactions.

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.4: Addition of Hydrogen Halides to Alkynes

Reaction 1: Addition of Hydrogen Halide to an Alkyne

Summary: Reactivity order of hydrogen halides: HI > HBr> HCl > HF.

Follows Markovnikov's rule:

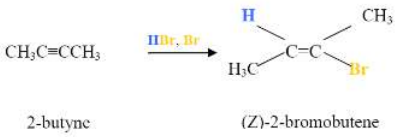
- Hydrogen adds to the carbon with the greatest number of hydrogens, the halogen adds to the carbon with fewest hydrogens.
- Protonation occurs on the more stable carbocation. With the addition of HX, haloalkenes form.
- With the addition of excess HX, you get *anti* addition forming a geminal dihaloalkane.

Addition of a HX to an Internal Alkyne

As described in Figure 1, the π electrons will attack the hydrogen of the HBr and because this is a symmetric molecule it does not matter which carbon it adds to, but in an asymmetric molecule the hydrogen will covalently bond to the carbon with the most hydrogens. Once the hydrogen is covalently bonded to one of the carbons, you will get a carbocation intermediate (not shown, but will look the same as depicted in Figure 1) on the other carbon. Again, this is a symmetric molecule and if it were asymmetric, which carbon would have the positive charge?

The final step is the addition of the Bromine, which is a good nucleophile because it has electrons to donate or share. Bromine, therefore attacks the carbocation intermediate placing it on the highly substituted carbon. As a result, you get 2-bromobutene from your 2-butyne reactant, as shown below.

Figure 2



2-butyne (Z)-2-bromobutene

Now, what if you have excess HBr?

Addition due to excess HX present ? yields a geminal dihaloalkane

Figure 3



(Z)-2-bromobutene 2,2-Dibromobutane

Here, the electrophilic addition proceeds with the same steps used to achieve the product in Addition of a HX to an Internal Alkyne. The π electrons attacked the hydrogen, adding it to the carbon on the left (shown in blue). Why was hydrogen added to the carbon on left and the one on the right bonded to the Bromine?

Now, you will have your carbocation intermediate, which is followed by the attack of the Bromine to the carbon on the right resulting in a haloalkane product.

Addition of HX to Terminal Alkyne

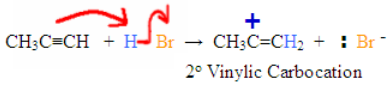
- Here is an addition of HBr to an asymmetric molecule.
- First, try to make sense of how the reactant went to product and then take a look at the mechanism.

Figure 4



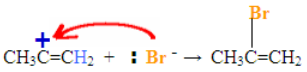
Propyne 2-Bromopropene

Mechanism:

1) 

2° Vinylic Carbocation

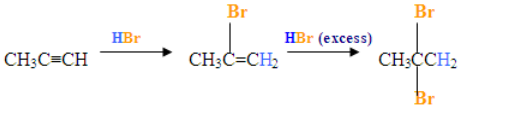
The π electrons are attacking the hydrogen, depicted by the electron pushing arrows and the Bromine gains a negative charge. The carbocation intermediate forms a positive charge on the left carbon after the hydrogen was added to the carbon with the most hydrogen substituents.

2) 

The Bromine, which has a negative charge, attacks the positively charged carbocation forming the final product with the nucleophile on the more substituted carbon.

Addition due to excess HBr present

Figure 5

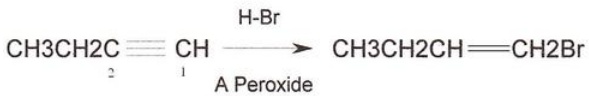


Propyne 2-Bromopropene 2,2-Dibromopropane

Most Hydrogen halide reactions with alkynes occur in a Markovnikov-manner in which the halide attaches to the most substituted carbon since it is the most positively polarized. A more substituted carbon has more bonds attached to 1) carbons or 2) electron-donating groups such as Fluorine and other halides. However, there are two specific reactions among alkynes where anti-Markovnikov reactions take place: the radical addition of HBr and Hydroboration Oxidation reactions. For alkynes, an anti-Markovnikov addition takes place on a terminal alkyne, an alkyne on the end of a chain.

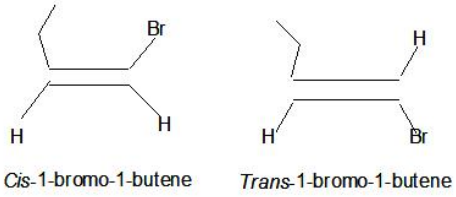
HBr Addition With Radical Yields 1-bromoalkene

The Br of the Hydrogen Bromide (H-Br) attaches to the less substituted 1-carbon of the terminal alkyne shown below in an anti-Markovnikov manner while the Hydrogen proton attaches to the second carbon. As mentioned above, the first carbon is the less substituted carbon since it has fewer bonds attached to carbons and other substituents. The H-Br reagent must also be reacted with heat or some other radicial initiator such as a peroxide in order for this reaction to proceed in this manner. This presence of the radical or heat leads to the anti-Markovnikov addition since it produces the most stable reaction. For more on Anti-Markovnikov additions:Radical Additions--Anti-Markovnikov Product Formation

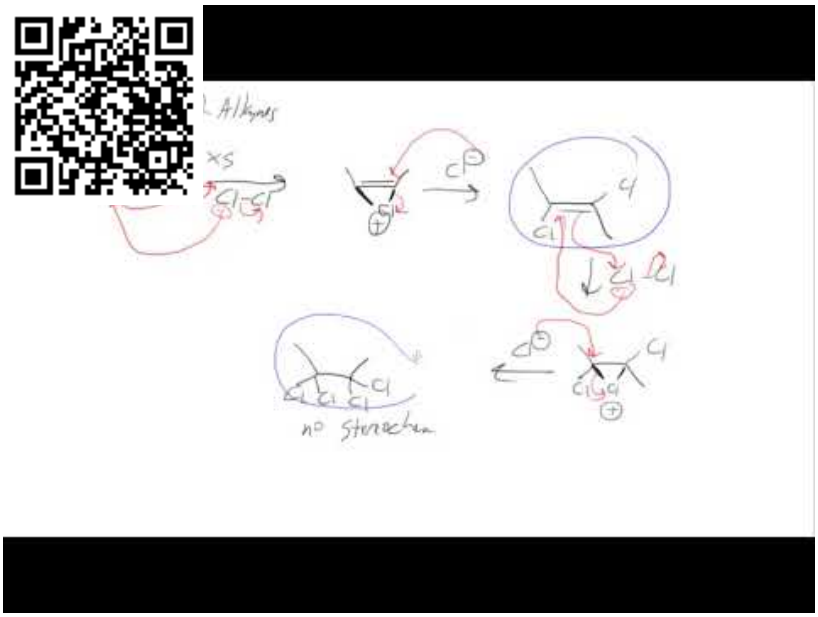


The product of a terminal alkyne that is reacted with a peroxide (or light) and H-Br is a 1-bromoalkene.

Regioselectivity: The Bromine can attach in a ***syn*** or ***anti*** manner which means the resulting alkene can be both ***cis*** and ***trans***. ***Syn*** addition is when both Hydrogens attach to the same face or side of the double bond (i.e. ***cis***) while the ***anti*** addition is when they attach on opposite sides of the bond (***trans***).



Cis-1-bromo-1-butene *Trans*-1-bromo-1-butene



Contributors

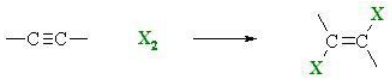
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12.5: Addition of Halogen to Alkynes

Reaction: Halogenation of Alkynes

Summary:

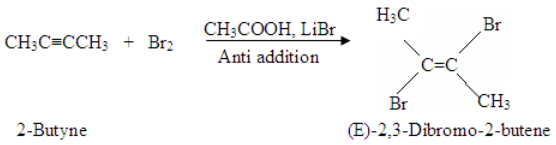


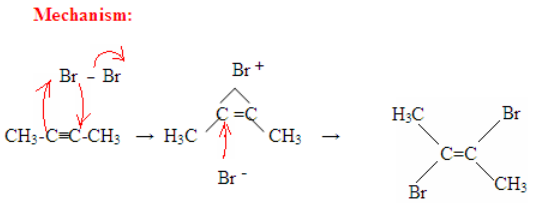
- Stereoslectivity: anti addition
- Reaction proceeds via cyclic halonium ion

Addition of Br_2

- The addition of Br_2 to an alkyne is analogous to adding Br_2 to an alkene.
- Once Br_2 approaches the nucleophilic alkyne, it becomes polarized.
- The π electrons, from the triple bond, can now attack the polarized bromine forming a C-Br bond and displacing the bromine ion.
- Now, you will get an intermediate electrophilic carbocation, which will immediately react with the bromine ion giving you the dibromo product.

Figure 6





First, you see the polarized Br_2 being attacked by the π electrons. Once you form the C-Br bond, the other bromine is released as a bromine ion. The intermediate here is a bromonium ion, which is electrophilic and reacts with the bromine ion giving you the dibromo product.

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12.6: Addition of Water to Alkynes

Objectives

After completing this section, you should be able to

1. write the equation for the reaction of water with an alkyne in the presence of sulfuric acid and mercury(II) sulfate.
2. describe keto-enol tautomerism.
3. predict the structure of the ketone formed when a given alkyne reacts with sulfuric acid in the presence of mercury(II) sulfate.
4. identify the reagents needed to convert a given alkyne to a given ketone.
5. identify the alkyne needed to prepare a given ketone by hydration of the triple bond.
6. write an equation for the reaction of an alkyne with borane.
7. write the equation for the reaction of a vinylic borane with basic hydrogen peroxide or hot acetic acid.
8. identify the reagents, the alkyne, or both, needed to prepare a given ketone or a given cis alkene through a vinylic borane intermediate.
9. identify the ketone produced when a given alkyne is reacted with borane followed by basic hydrogen peroxide.
10. identify the cis alkene produced when a given alkyne is reacted with borane followed by hot acetic acid.
11. explain why it is necessary to use a bulky, sterically hindered borane when preparing vinylic boranes from terminal alkynes.
12. predict the product formed when the vinylic borane produced from a terminal alkyne is treated with basic hydrogen peroxide.
13. identify the alkyne needed to prepare a given aldehyde by a vinylic borane.

Key Terms

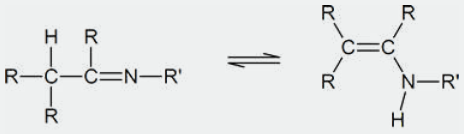
Make certain that you can define, and use in context, the key terms below.

- enol
- keto-enol tautomeric equilibrium
- tautomerism
- tautomers

Study Notes

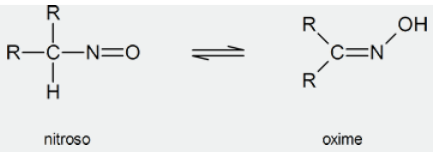
Rapid interconversion between tautomers is called *tautomerism*; however, as the two tautomers are in equilibrium, the term *tautomeric equilibrium* may be used. This section demonstrates the equilibrium between a ketone and an enol; hence, the term *keto-enol tautomeric equilibrium* is appropriate. The term “enol” indicates the presence of a carbon-carbon double bond and a hydroxyl (i.e., alcohol) group. Later in the course, you will see the importance of keto-enol tautomerism in discussions of the reactions of ketones, carbohydrates and nucleic acids.

It is important to note that tautomerism is not restricted to keto-enol systems. Other examples include imine-enamine tautomerism



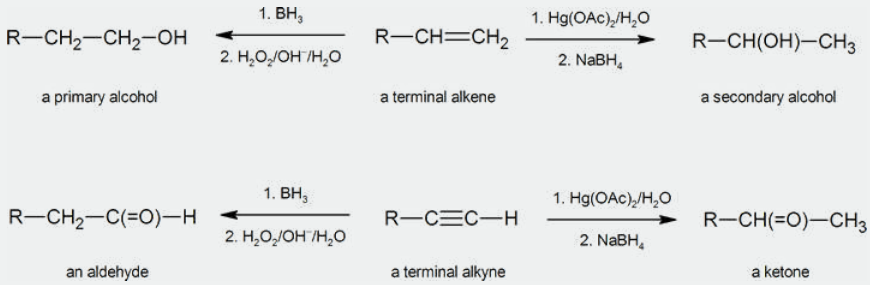
imine enamine

and nitroso-oxime tautomerism



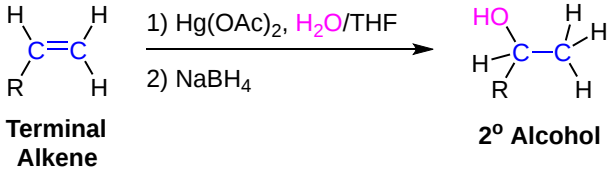
However, at the moment you need only concern yourself with keto-enol tautomerism.

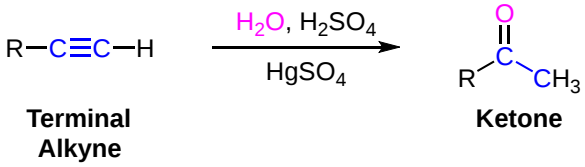
Notice how hydroboration complements hydration in the chemistry of both alkenes and alkynes.



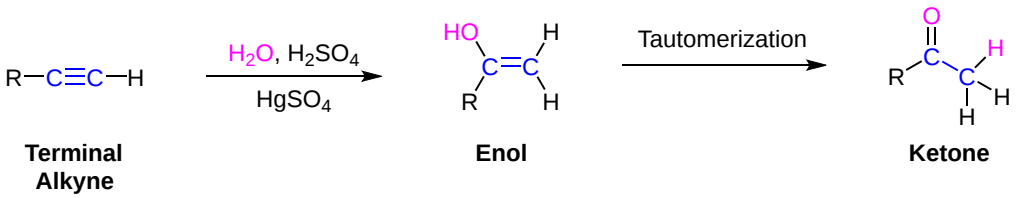
Mercury(II)-Catalyzed Hydration of Alkynes

As with alkenes, hydration (addition of water) of alkynes requires a strong acid, usually sulfuric acid, and is facilitated by the mercuric ion (Hg^{2+}). However, the hydration of alkynes gives ketone products while the hydration of alkenes gives alcohol products. Notice that the addition of oxygen in both reactions follows Markovnikov rule.

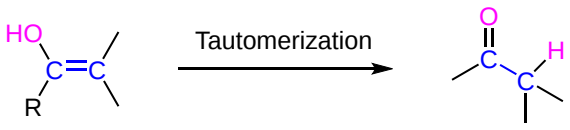




During the hydration of an alkyne, the initial product is an enol intermediate (a compound having a hydroxyl substituent attached to a double-bond), which immediately rearranges to the more stable ketone through a process called **enol-keto tautomerization**.



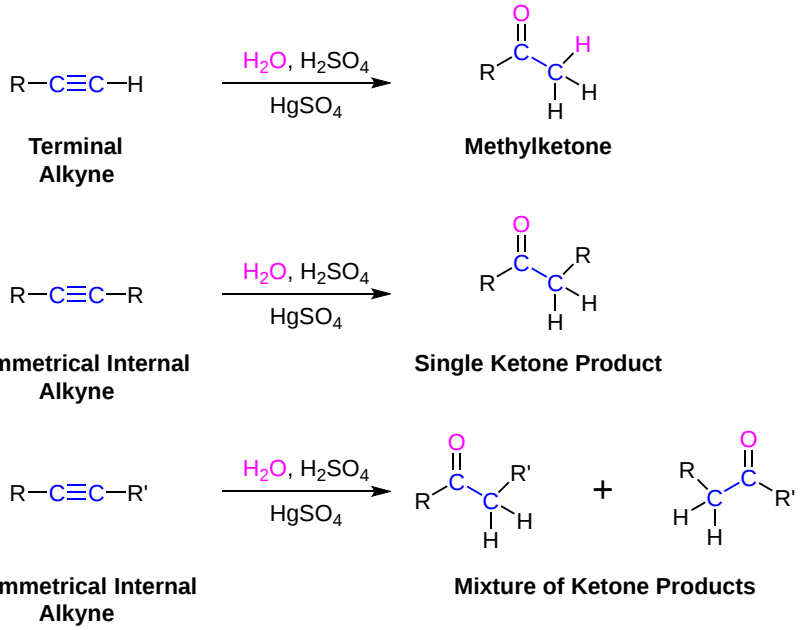
Tautomers are defined as rapidly inter-converted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The keto and enol tautomers are in equilibrium with each other and with few exceptions the keto tautomer is more thermodynamically stable and therefor favored by the equilibrium. This mechanism for tautomerization will be discussed in greater detail in **Section 22-1**.



Enol Tautomer | **Keto Tautomer (Favored)**

General Reaction

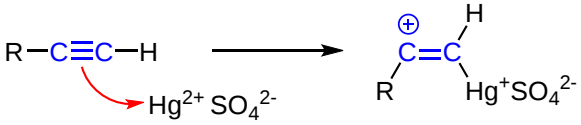
For terminal alkynes, the addition of water follows the Markovnikov rule, and the final product is a methyl ketone. For internal alkynes the addition of water is not regioselective. Hydration of symmetrical internal alkynes produces a single ketone product. However, hydration of asymmetrical alkynes, (i.e. if R & R' are not the same) produces two isomeric ketone products.



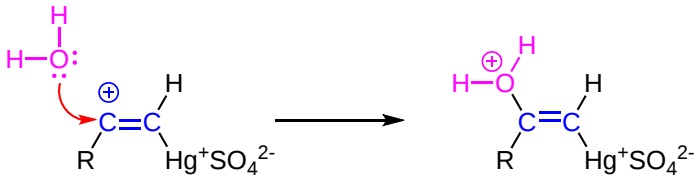
Mechanism

The mechanism starts with the eletrophilic addition of the mercuric ion (Hg^{2+}) to the alkyne producing a mercury-containing vinylic carbocation intermediate. Nucleophilic attack of water on the vinylic carbocation forms a C-O bond to produce a protonated enol. Deprotonation of the enol by water then produces a organomurcury enol. The murcury is substituted with H^+ to produced a neutral enol and regenerate the Hg^{2+} catalyst. The enol is converted to the ketone product through keto-enol tautomerization the mechanism of which is provided in **Section 22-1**.

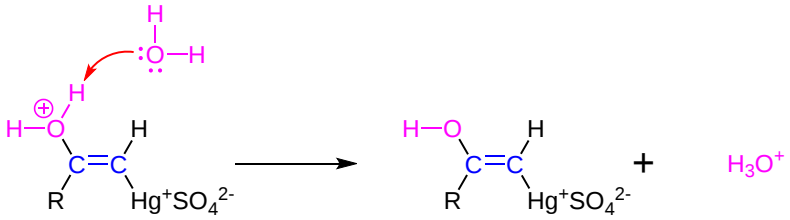
1) Electrophilic addition of Mg^{2+}



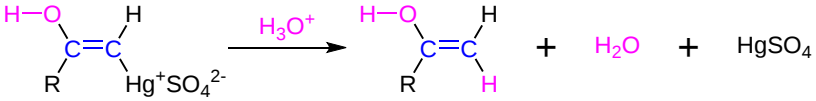
2) Nucleophilic attack by water



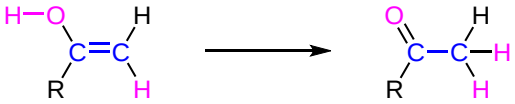
3) Deprotonation



4) Substitution

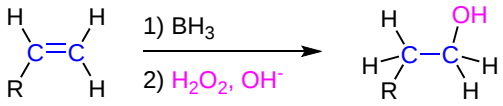


5) Tautomerization

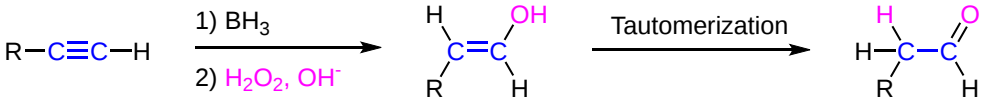


Hydroboration–Oxidation of Alkynes

The hydroboration-oxidation of alkynes is analagous to the reaction with alkenes. However, where alkenes for alcohol products, alkynes for aldehyde or ketone products. In both cases the addition is anti-Markovnikov and an oxygen is placed on the less alkyl substituted carbon. With the hydroboration of an alkyne the presences of a second pi bond allows the initial product to under tautomerization to become the final aldehyde product.

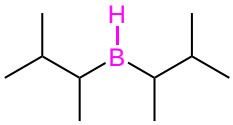


Terminal Alkene **1° Alcohol**

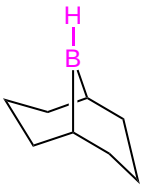


Terminal Alkyne **Enol** **Aldehyde**

Alkynes have two pi bonds both of which are capable of reacting with borane (BH_3). To limit the reactivity to only one alkyne pi bond, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance which enhances the anti-Markovnikov regioselective of the reaction. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for this hydroboration reaction. The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes.



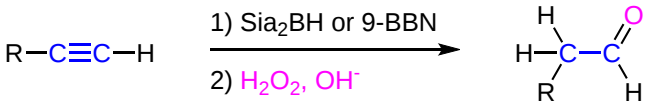
Disiamylborane
(Sia_2BH)



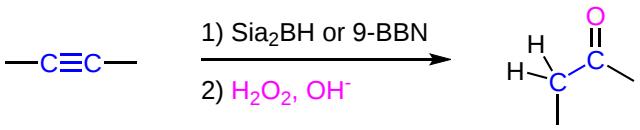
9-Borabicyclo[3.3.1]nonane
(9-BBN)

General Reaction

The hydroboration of terminal alkynes produces aldehyde products while internal alkynes produce ketone products. The hydroboration of symmetrical alkynes produces one ketone product and asymmetrical alkynes produce a mixture of product ketones.



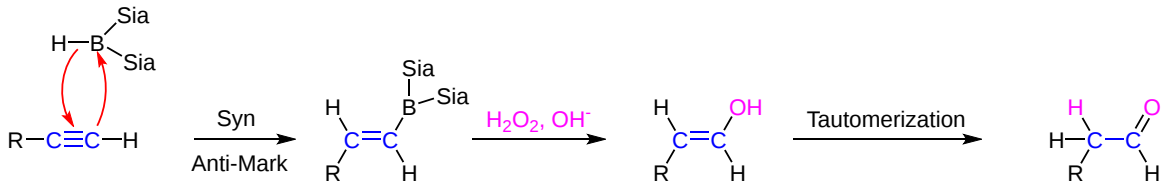
Terminal Alkyne → **Aldehyde**



Internal Alkyne → **Ketone**

Mechanism

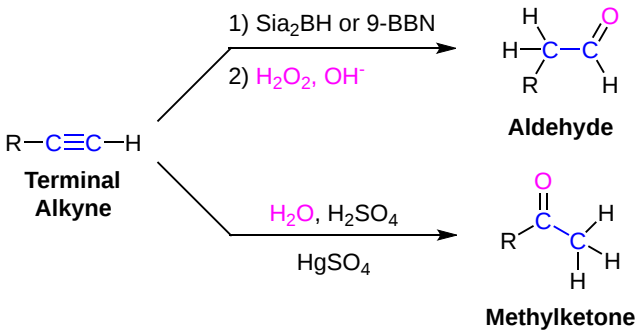
The mechanism starts with the electrophilic addition of the B-H bond of the borane. The hydrogen atom and the borane all on the same side of the alkyne creating a syn addition configuration in the alkene poduct. Also, the addition is anti-Markovnikov regioselective which means the borane adds to the less substituted carbon of the alkyne and the hydrogen atom adds to the more substituted. The oxidative work-up replaces the borane with a hydroxy group (-OH) creating an enol intermediate. The enol immediately tautomerizes to the product aldehyde for terminal alkynes and the product ketone for internal alkynes.



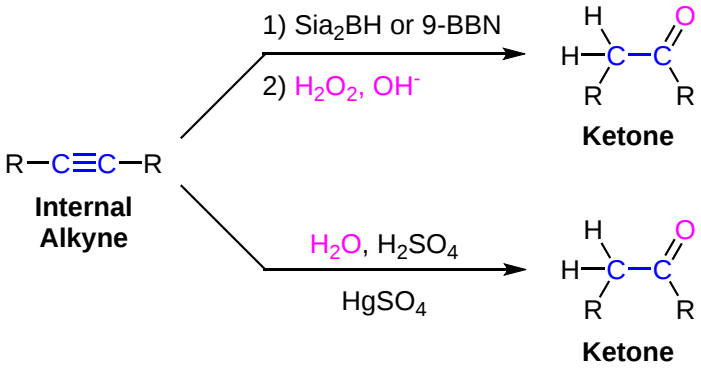
Alkyne → **Enol** → **Aldehyde**

Comparison of Mercury(II)-Catalyzed Hydration and Hydroboration–Oxidation of Alkynes

These two reactions are complementary for the reaction of a terminal alkyne because the produce distinctly different products. The mercury(II) catalyzed hydration of a terminal alkyne produces a methyl ketone, while the hydroboration-oxidation produces an aldehyde.



For internal alkynes, the regioslectivity of these reactions are rendered ineffective. The reactions are redundant in that they both produce the same ketone products.



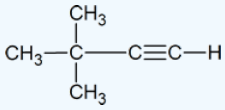
Exercise 12.6.1

1) Draw the structure of the product formed when each of the substances below is treated with H_2O/H_2SO_4 in the presence of $HgSO_4$.

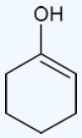
a)

$H_3CH_2CC{\equiv}CH$

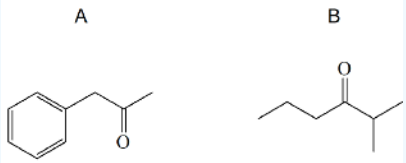
b)



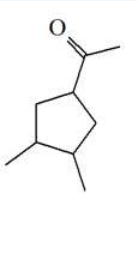
2) Draw the structure of the keto form of the compound shown below. Which form would you expect to be the most stable?



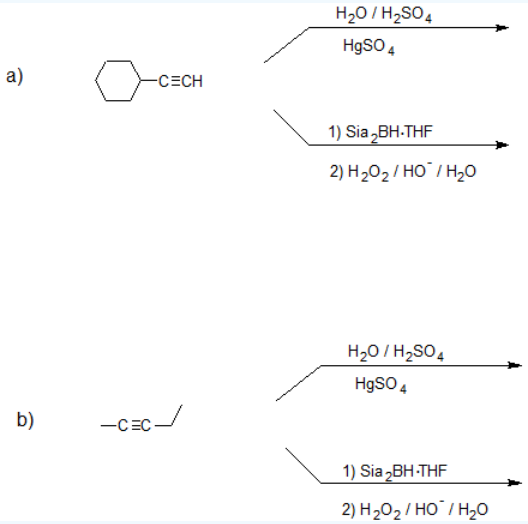
3) What alkyne would you start with to gain the following products?



4) What alkyne would you start with to gain the following product?



5) Draw the product(s) of the following reactions:

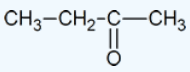


Answer

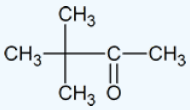
Answers:

1)

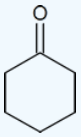
a)



b)

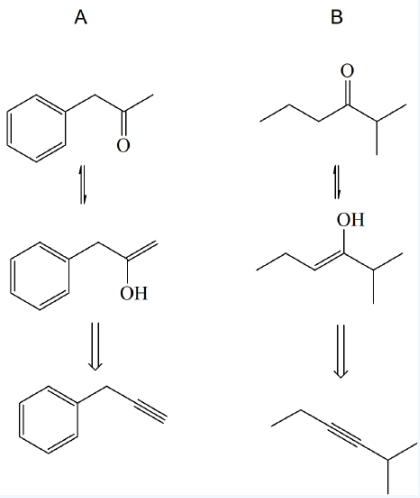


2.

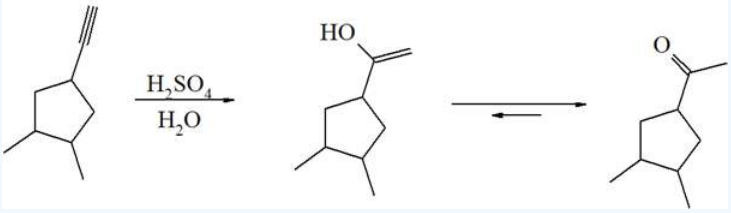


The keto form should be the most stable.

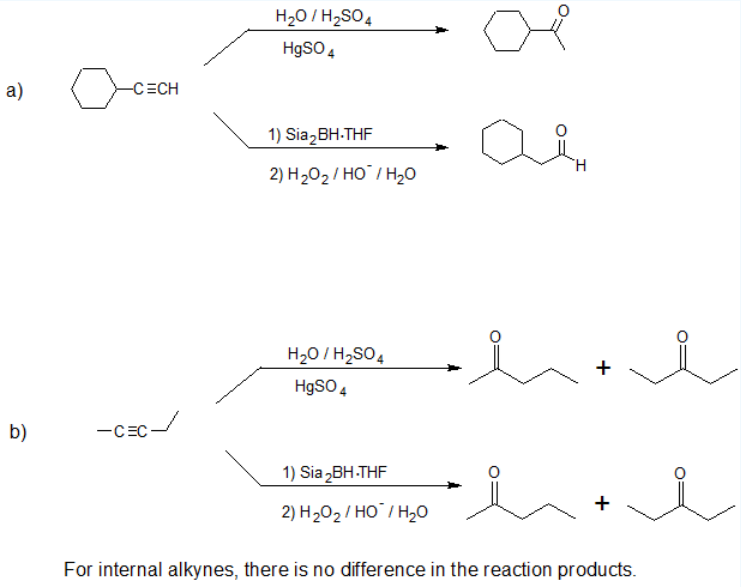
3)



4)



5)



For internal alkynes, there is no difference in the reaction products.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.7: Reaction of Acetylide Anions

Objectives

After completing this section, you should be able to

1. write an equation for the reaction that occurs between a terminal alkyne and a strong base, such as sodamide, $NaNH_2$.
2. rank a given list of compounds, including water, acetylene and ammonia, in order of increasing or decreasing acidity.
3. rank a given list of hydrocarbons, such as acetylene, ethylene and ethane, in order of increasing or decreasing acidity.
4. describe a general method for determining which of two given compounds is the stronger acid.
5. provide an acceptable explanation of why terminal alkynes are more acidic than alkanes or alkenes.
6. write an equation to describe the reaction of an acetylide ion with an alkyl halide.
7. discuss the importance of the reaction between acetylide ions and alkyl halides as a method of extending a carbon chain.
8. identify the alkyne (and hence the acetylide ion) and the alkyl halide needed to synthesize a given alkyne.
9. determine whether or not the reaction of an acetylide ion with a given alkyl halide will result in substitution or elimination, and draw the structure of the product formed in either case.

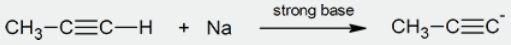
Key Terms

Make certain that you can define, and use in context, the key terms below.

- acetylide anion
- acidity order
- alkylation

Study Notes

An *acetylide anion* is an anion formed by removing the proton from the end carbon of a terminal alkyne:

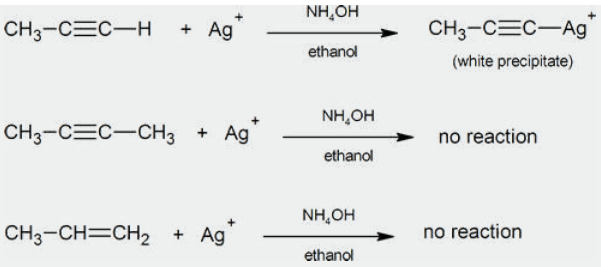


An *acidity order*is a list of compounds arranged in order of increasing or decreasing acidity.

The general ideas discussed in this section should already be familiar to you from your previous exposure to chemistry and from the review in Section 2.8. A slightly different account of why terminal alkynes are stronger acids than are alkenes or alkanes is given below. However, the argument is still based on the differences between *sp*-, sp^2- and sp^3-hybrid orbitals.

The carbons of a triple bond are *sp*-hybridized. An *sp*-hybrid orbital has a 50% *s* character and a 50% *p* character, whereas an sp^2-hybrid orbital is 33% *s* and 67% *p*, and an sp^3-hybrid orbital is 25% *s* and 75% *p*. The greater the *s* character of the orbital, the closer the electrons are to the nucleus. Thus in a C(*sp*)$\ce{-}$H bond, the bonding electrons are closer to the carbon nucleus than they are in a C(sp^2)$\ce{-}$H bond. In other words, compared to a C(sp^2)$\ce{-}$H bond (or a C(sp^3)$\ce{-}$H bond), a C(*sp*)$\ce{-}$H bond is very slightly polar: $C^{\delta-}$$\ce{-}$$H^{\delta+}$. This slight polarity makes it easier for a base to remove a proton from a terminal alkyne than from a less polar or non-polar alkene or alkane.

As you will appreciate, the reaction between sodium amide and a terminal alkyne is an acid-base reaction. The sodium acetylide product is, of course, a salt. Terminal alkynes can also form salts with certain heavy-metal cations, notably silver(I) and copper(I). In the laboratory component of this course, you will use the formation of an insoluble silver acetylide as a method for distinguishing terminal alkynes from alkenes and non-terminal alkynes:

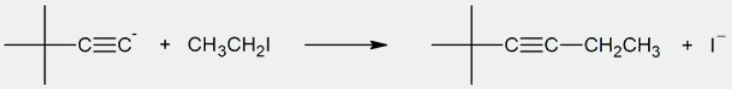


Metal acetylides are explosive when dry. They should be destroyed while still wet by warming with dilute nitric acid:

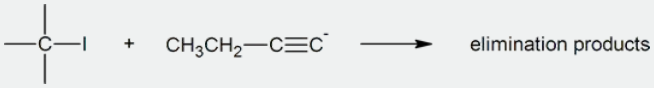


The alkylation of acetylide ions is important in organic synthesis because it is a reaction in which a new carbon-carbon bond is formed; hence, it can be used when an organic chemist is trying to build a complicated molecule from much simpler starting materials.

The alkyl halide used in this reaction must be primary. Thus, if you were asked for a suitable synthesis of 2,2-dimethyl-3-hexyne, you would choose to attack iodoethane with the anion of 3,3- dimethyl-1-butyne



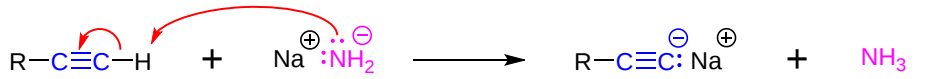
rather than to attack 2-iodo-2-methylpropane with the anion of 1-butyne.



The reasons will be made clear in Chapter 11.

Acidity of Terminal Alkynes: Formation of Acetylide Anions

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the terminal proton leads to the formation of an acetylide anion, $RC\equiv C:^-$.



Terminal Alkyne **Sodium Amide** **Acetylide Anion** **Ammonia**

As discussed in **Section 2.10**, acidity typically increases with the stability of the corresponding conjugate base. The origin of the enhanced acidity of terminal alkynes can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals increases as the percent s character increases and follows the order $sp > sp^2 > sp^3$. This trend indicates the sp hybridized orbitals of the acetylide anion are more electronegative and better able to stabilize a negative charge than sp^2 or sp^3 hybridized orbitals. There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The table below shows how orbital hybridization compares with the identity of the atom when predicting relative acidity. Remember that as the pK_a of a compound decreases its acidity increases.

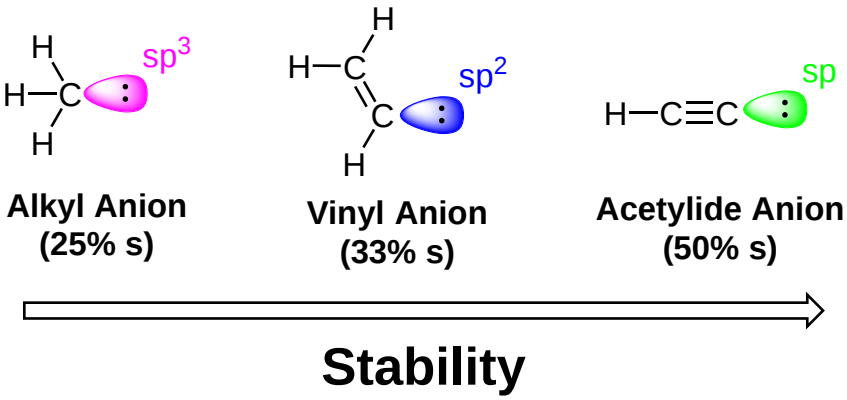
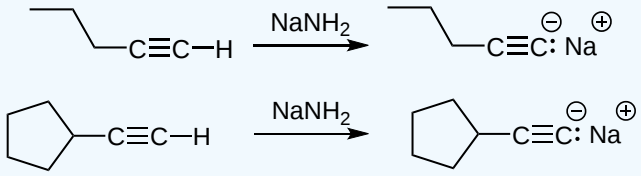


Table 9.7.1: Akynes

Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Acetylene, with a pK_a of 25 is shown to be much more acidic than ethylene (pK_a = 44) or ethane (pK_a = 50). Consequently, acetylide anions can be readily formed by deprotonation of a terminal alkynes with a sufficiently strong base. The amide anion (NH_2^-), in the form of sodium amide ($NaNH_2$) is commonly used for the formation of acetylide anions.

Example 12.7.1



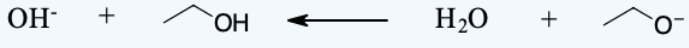
Exercise 12.7.1

1. Given that the p*K*a of water is 14.00, would you expect hydroxide ion to be capable of removing a proton from each of the substances listed below? Justify your answers, briefly.
   a. ethanol (p*K*a = 16)
   b. acetic acid (p*K*a = 4.72)
   c. acetylene (p*K*a = 25)

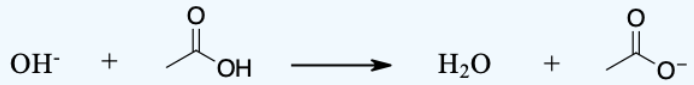
Answer

1.

a. No, not very well. The p*K*a of ethanol is greater than that of water, thus the equilibrium lies to the left rather than to the right.Add texts here. Do not delete this text first.



b. Yes, very well. There is a difference of 11 p*K*a units between the p*K*a of water and the p*K*a of acetic acid. The equilibrium lies well to the right.



c. No, hardly at all. The hydroxide ion is too weak a base to remove a proton from acetylene. The equilibrium lies well to the left.

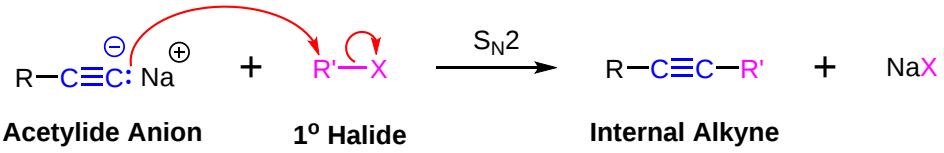


Nucleophilic Substitution Reactions of Acetylides

The presence of lone pair electrons and a negative charge on a carbon, makes acetylide anions are strong bases and strong nucleophiles. Therefore, acetylide anions can attack electrophiles such as alkyl halides to cause a substitution reaction. These substitution reactions will be discussed in detail in **Chapter 11**.

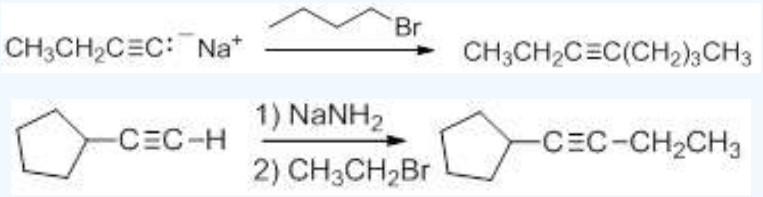
Mechanism

The C-X bonds in 1° alkyl halides are polarized due to the high electronegativity of the halogen. The electrons of the C-X sigma bond are shifted towards the halogen giving it a partial negative charge. This also causes electrons to be shifted away from the carbon giving it a partial positive and making it electrophilic. During this reaction, the lone pair electrons on the acetylide anion attack the electrophilic carbon in the 1° alkyl halide forming a new C-C bond. The formation of this new bond causes the expulsion of the halogen as what is called a leaving group. Overall, this reaction forms a C-C bond and converts a terminal alkyne into a internal alkyne. Because a new alkyl group is added to the alkyne during this reaction, it is commonly called an alkylation.

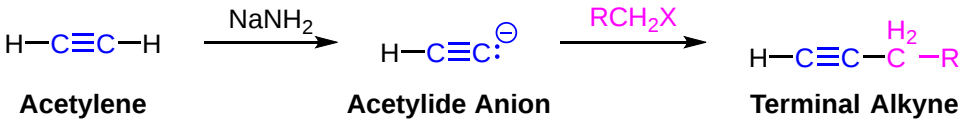


This substitution reaction is often coupled with the acetylide formation, discussed in the previous section, and shown as a single reaction.

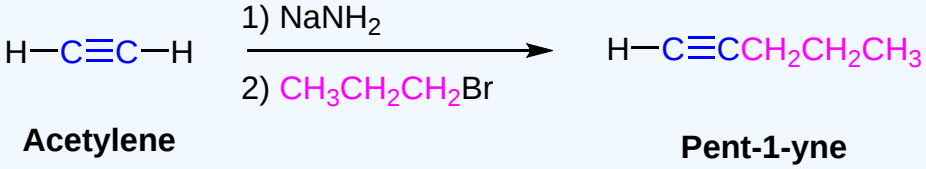
Example 12.7.2



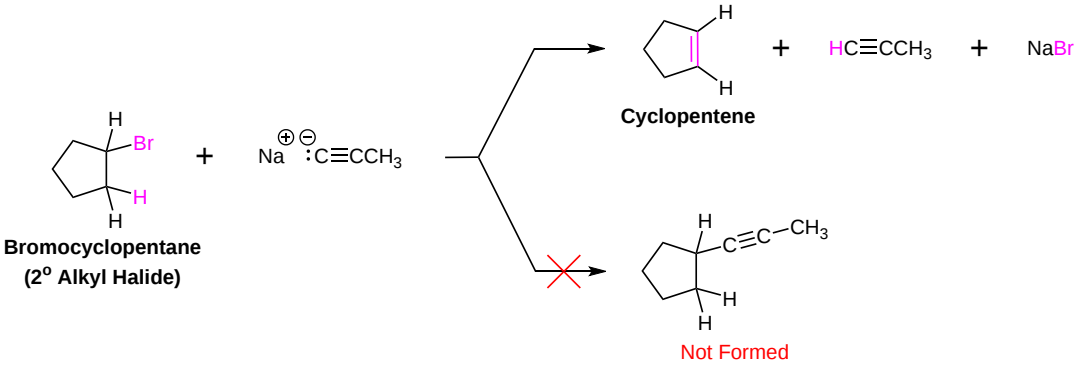
Terminal alkynes can be generated through the reaction of acetylene and a 1° alkyl halide.



Example 12.7.3

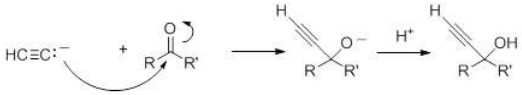


Because the acetylide anion is a very strong base, this substitution reaction is most efficient with methyl or primary halides. Secondary, tertiary, or even bulky primary halogens will give alkenes by the E2 elimination mechanism discussed in **Section 11.10**. An example of this effect is seen in the reaction of bromocyclopentane with a propyne anion. The reaction produces the elimination product cyclopentene rather than the substitution product 1-propynylcyclopentane.



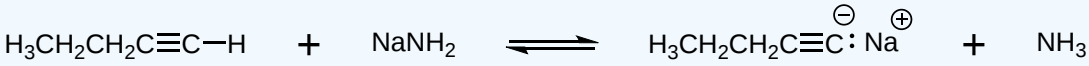
Nucleophilic Addition of Acetylides to Carbonyls

Acetylide anions also add to the electrophilic carbon in aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols. With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers. These types of reaction will be discussed in more detail in **Chapter 19**.

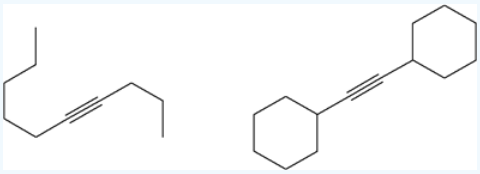


? Exercise 12.7.2

1) The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by sodium amide, as shown below.

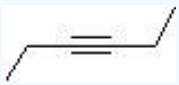


2) Give the possible reactants which could form the following molecules by an alkylation.

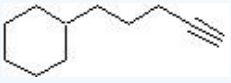


3) Propose a synthetic route to produce 2-pentene from propyne and an alkyl halide.

4) Using acetylene as the starting material, show how you would synthesize the following compounds

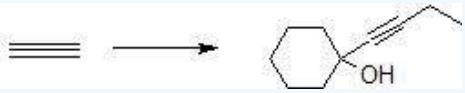
a) 

b) but-2-yne

c) 

d) 

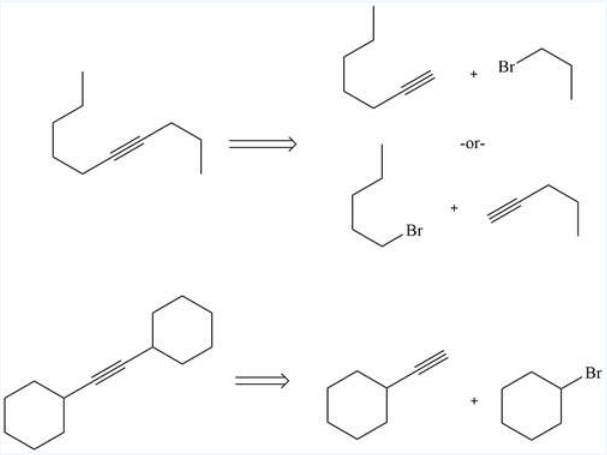
5) Show how you would accomplish the following synthetic transformation.



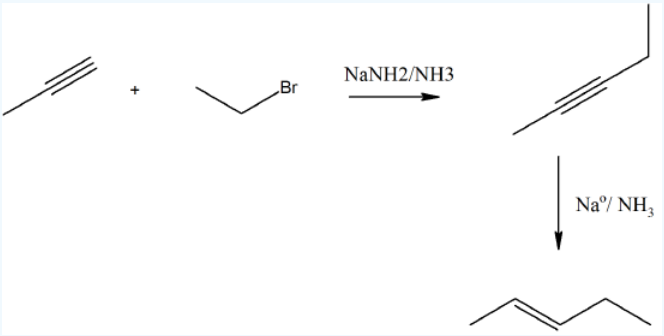
Answer

1) Assuming the pK_a of pent-1-yne is about 25, then the difference in pK_as is 10. Since pentyne is more acidic, the formation of the acetylide will be favored at equilibrium, so the equilibrium constant for the reaction is about 10^{10}.

2)

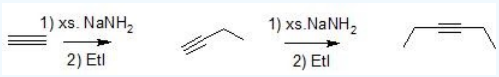


3)

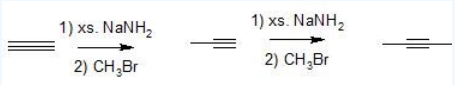


4)

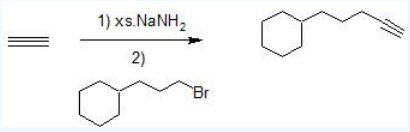
a)



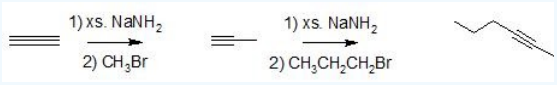
b)



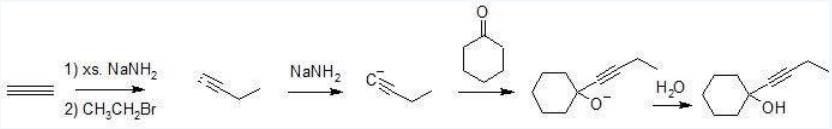
c)



d)



5)



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Paul G. Wenthold (Purdue University)
- Layne A. Morsch (University of Illinois Springfield)

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12.8: Synthesis

Read the section on synthesis at Dr. William Reusch's website. After you read that, skim through the section below up until Disconnection of Bonds, since there are images missing in that section.

'There could be ART in Organic Synthesis' declared the inimitable monarch of organic synthesis, Professor R.B. Woodward. His school unveiled several elegant approaches covering a variety of complex structures and broke new grounds to define the art of organic synthesis. 'If organic synthesis is a branch of science, what is the LOGIC of organic synthesis?' marveled several others. The development of the concept of logical approaches towards synthesis has been evolving over the past several decades. A few stalwarts focused their attention on this theme and attempted to evolve a pattern to define this logic. There is no doubt that all of us who dabble with synthesis contribute our small bit in the magnificent direction. A few names stand out in our minds for their outstanding contributions. Notable contributions came from the schools of J.A. Marshal, E.J. Wenkert, G. Stork, S Hanessian, E.E. van Tamalen, S. Masamune, R.B. Woodward, E.J. Corey and several others. More focused on this theme were the contributions from the school of E.J. Corey.

The period 1960 – 1990 witnessed the evolution of this thought and the concept bloomed into a full-fledged topic that now merits a separate space in college curriculum. Earlier developments focused on the idea of *ANTITHETIC APPROACHES* and perfected the art of DISCONNECTION via RETROSYNTHESIS. This led to logical approaches for the construction of *SYNTHETIC TREES* that summarized various possible approaches for the proposed Target structure. All disconnections may not lead to good routes for synthesis. Once the synthetic tree was constructed, the individual branches were analyzed critically. The reactions involved were looked into, to study their feasibility in the laboratory, their mechanistic pathways were analyzed to understand the conformational and stereochemical implications on the outcome of each step involved and the time / cost factors of the proposed routes were also estimated. The possible areas of pitfall were identified and the literature was critically scanned to make sure that the steps contemplated were already known or feasible on the basis of known chemistry. In some cases, model compounds were first constructed to study the feasibility of the particular reaction, before embarking on the synthesis of the complex molecular architecture. Thus a long process of logical planning is now put in place before the start of the actual synthetic project. In spite of all these careful and lengthy preparations, an experienced chemist is still weary of the Damocles Sword of synthesis viz., the likely failure of a critical step in the proposed route(s), resulting in total failure of the entire project. All achievements are 10% inspiration and 90% perspiration. For these brave molecular engineers, sometimes also called chemists, these long-drawn programs and possible perils of failures are still worth, for the perspiration is enough reward.

A sound knowledge of mechanistic organic chemistry, detailed information on the art and science of functional group transformations, bond formation and cleavage reactions, mastery over separation and purification techniques and a sound knowledge of spectroscopic analysis are all essential basics for the synthesis of molecules. A synthetic chemist should also be aware of developments in synthetic strategies generated over the years for different groups of compounds, which include Rules and guidelines governing synthesis. Since organic chemistry has a strong impact on the development of other sister disciplines like pharmacy, biochemistry and material science, an ability to understand one or more of these areas and interact with them using their terminologies is also an added virtue for a synthetic chemist. With achievements from synthesis of strained molecules (once considered difficult (if not impossible) to synthesize, to the synthesis of complex, highly functionalized and unstable molecules, an organic chemist could now confidently say that he could synthesize any molecule that is theoretically feasible. This is the current status of the power of organic synthesis. Based on the task assigned to the chemist, he would select a Target molecule for investigation and devise suitable routes for synthesis.

Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a 'ROUTE' based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 1.4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.



Fig 1.4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in **Fig 1.4.2.2**.



Fig 1.4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 1.4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.



Fig 1.4.2.3

Efficiency of a route

A route is said to be efficient when the 'overall yield' of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a 'linear syntheses' involving only consequential steps or a 'convergent syntheses' involving fewer consequential steps. **Fig 1.4.3.1** shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion



Fig 1.4.3.1

all the way to one set of starting materials (SM), the process is called a Linear Synthesis. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called Convergent Syntheses.

The flow charts shown below **(Fig 1.4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..



Contributors

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

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12.9: Hydroboration–Oxidation of Alkynes

Hydroboration Reactions

Diborane reacts readily with alkynes, but the formation of substituted alkene products leaves open the possibility of a second addition reaction. A clever technique for avoiding this event takes advantage of the fact that alkynes do not generally suffer from steric hindrance near the triple-bond (the configuration of this functional group is linear). Consequently, large or bulky electrophilic reagents add easily to the triple-bond, but the resulting alkene is necessarily more crowded or sterically hindered and resists further additions. The bulky hydroboration reagent needed for this strategy is prepared by reaction of diborane with 2-methyl-2-butene, a highly branched alkene. Because of the alkyl branching, only two alkenes add to a BH_3 moiety (steric hindrance again), leaving one B-H covalent bond available for reaction with an alkyne, as shown below. The resulting dialkyl borane is called disiamylborane, a contraction of di-secondary-isoamylborane (amyl is an old name for pentyl).

$$2\ (CH_3)_2C{=}CHCH_3 + BH_3 \text{ in ether} \longrightarrow [\ (CH_3)_2CH\text{-}CH(CH_3)\ ]_2B\text{-}H \textit{ disiamylborane}$$

An important application of disiamylborane is its addition reaction to terminal alkynes. As with alkenes, the B-H reagent group adds in an apparently anti-Markovnikov manner, due to the fact that the boron is the electrophile, not the hydrogen. Further addition to the resulting boron-substituted alkene does not occur, and the usual oxidative removal of boron by alkaline hydrogen peroxide gives an enol which rapidly rearranges to the aldehyde tautomer. Thus, by the proper choice of reagents, terminal alkynes may be converted either to methyl ketones (mercuric ion catalyzed hydration) or aldehydes (hydroboration followed by oxidation).

$$RC{\equiv}CH + (C_5H_{11})_2B\text{-}H \longrightarrow [\ RCH{=}CH\text{-}B(C_5H_{11})_2\ ] + H_2O_2\ \&\ NaOH \longrightarrow [\ RCH{=}CH\text{-}OH\ ] \longrightarrow RCH_2\text{-}CH{=}O$$

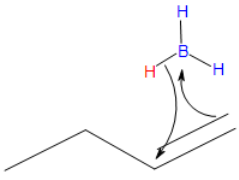
Hydroboration of internal alkynes is not a particularly useful procedure because a mixture of products will often be obtained, unless the triple-bond is symmetrically substituted. Mercuric ion catalyzed hydration gives similar results.

Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. Furthermore, the borane acts as a lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The Hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

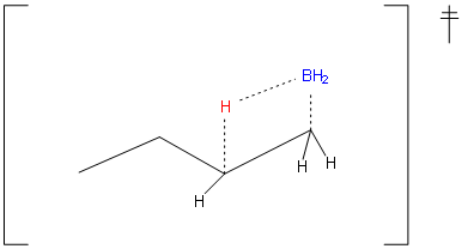
The Mechanism

Step #1

- Part #1: Hydroboration of the alkene. In this first step the addittion of the borane to the alkene is initiated and proceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p orbital of the boron electrophile pairing with the electron pair of the ? bond of the nucleophile.

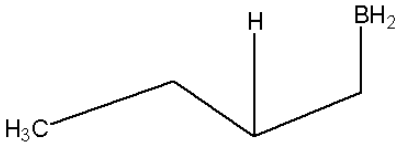


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

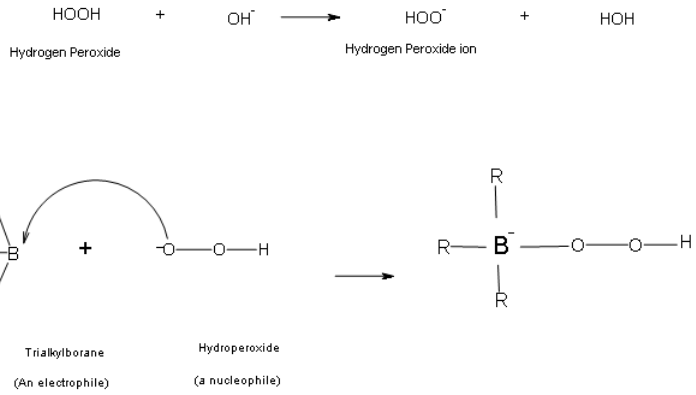
- Part #2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).



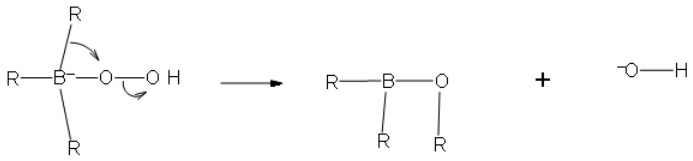
Oxidation of the Trialkylborane by Hydrogen Peroxide

Step #2

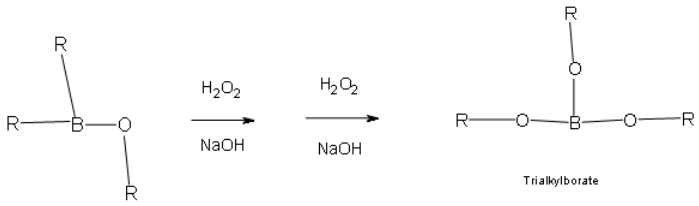
- Part #1: the first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. The hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.



- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



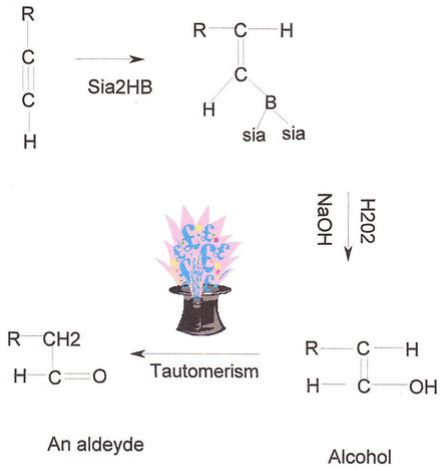
- Part 3: This is the final part of the Oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.



If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

Stereospecific Hydroboration Oxidation of Alkynes

Step 1: Hydroboration of terminal alkynes reacts in an anti-Markovnikov fashion in which the Boron attacks the less substituted carbon which is the least hindered. It is a stereospecific reaction where ***syn*** addition is observed as the hydroboration occurs on the same side of the alkyne and results in ***cis*** stereochemistry. However, a bulky borane reagent needs to be used to stop at the alkenyl-borane stage. Otherwise, a second hydroboration will occur. In this example, diisoamyl borane or $HBsia_2$, a fairly large and sterically-hindered borane reagent, is used. Both of the alkyne's pi bonds will undergo hydroboration if BH_3 (borane) is used by itself.



Step 2: Oxidation is the next step that occurs. The resulting alkylborane is oxidized to a vinyl alcohol due to the reaction with a hydroxide in a basic solution such as aqueous sodium hydroxide. A vinyl alcohol is an alcohol that has both an alkene and an -OH group. After the vinyl alcohol is formed, tautomerization takes place. Tautomerism is the interconversion of isomeric compounds due to the migration of a proton. The alcohol, which in this case is a terminal enol, **spontaneously and rapidly rearranges** due to tautomerism to become an aldehyde since the aldehyde form is much more stable than the enol.

For additional information on hydroboration oxidation: Hydroboration Oxidation

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Gilbert Torres (UCD)
- Ali Alvandi

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12.10: Alkenes and Alkynes II (Problems)

Exercise 12-1 For each of the following reactions determine the oxidation state of the carbons in the reactants and products and decide whether the overall changes involve oxidation, reduction, or neither.

a. $CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$

b. $CH_3CH{=}CH_2 + HCl \rightarrow CH_3CH(Cl)CH_3$

c. $CH_3CH{=}CH_2 + HOCl \rightarrow CH_3CH(OH)CH_2Cl$

d. $(CH_3)_2C{=}CH_2 + (CH_3)_3CH \rightarrow (CH_3)_2CHCH_2C(CH_3)_3$

e. $n(CH_2{=}CHCN) \rightarrow -(CH_2CH(CN))_n-$

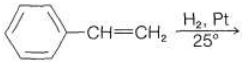
f. $CH_3OH \rightarrow CH_2{=}O + H_2$

Exercise 12-2 Balance each of the following equations. You may need to add H_2O to one side or the other of the equations.

a. $\overset{\oplus}{K}\overset{\ominus}{MnO_4} + RCH{=}CH_2 \rightarrow R\overset{\ominus}{C}O_2\overset{\oplus}{K} + CH_2{=}O + MnO_2$

b. $CrO_3 + C_6H_5CH_2CH_3 \rightarrow C_6H_5CH_2CO_2H + Cr^{3\oplus}$

Exercise 12-3 Draw structures for the products expected from the following reactions. Show configurations where significant.

a. 

b. *cis*-2-butene $\xrightarrow[25°]{D_2,\ Pt}$

c. $CH_2{=}CHCOCH_3 \xrightarrow[25°]{H_2,\ Pt}$

d. 1-penten-3-yne $\xrightarrow{H_2,\ Pd{-}Pb}$

e. $C_6H_5C \equiv CC_6H_5 \xrightarrow{H_2,\ Pd{-}Pb}$

f. 1,3-dimethylcyclopentene $\xrightarrow[25°]{H_2,\ Pt}$

Exercise 12-4* The conditions of catalytic hydrogenation sometimes lead to rearrangement of a double bond from one location to another. Using 1-butene as an example, show how operation of the *equilibria* shown in the mechanism of Figure 11-2 could lead to rearrangement of 1-butene to 2-butene over a hydrogenation catalyst in the presence of H_2. If D_2 were used for reduction of 1-butene under these circumstances, suggest where and how much deuterium might be introduced into the butane formed.

Exercise 12-5 Use bond energies to explain the following facts:

a. Ethyne is more easily hydrogenated catalytically than nitrogen.

b. Ethyne is more easily hydrogenated catalytically than ethene.

c. Ethene is more easily hydrogenated catalytically than methanal (CH_2O).

d. In the hydrogenation of nitrogen, ammonia is formed; in contrast, the hydrogenation of ethyne leads to ethane, not methane.

Exercise 12-6

a. Would you expect a carbon-nitrogen triple bond to be hydrogenated more, or less, easily than a carbon-carbon triple bond?

b. Why is it difficult to hydrogenate a tetrasubstituted alkene such as 2,3-dimethyl-2-butene?

Exercise 12-7* Accurate ΔH^0 and ΔG^0 values in kcal mol^{-1} for hydrogen addition to 1-butene, *cis*- and *trans*-2-butene in the gas phase at $25°$ follow:

	ΔH^0	ΔG^0 (25°)
$CH_2{=}CHCH_2CH_3$	−30.12	−12.94
$CH_3CH{=}CHCH_3$ (*cis*)	−28.48	−11.64
$CH_3CH{=}CHCH_3$ (*trans*)	−27.48	−10.95

a. From the data (and after reviewing Section 4-4B), calculate ΔS^0 for each of these reactions at 25° (298 K). Why is ΔS^0 so large for these reactions?

b. Calculate ΔH^0, ΔG^0, and ΔS^0 for $CH_2{=}CHCH_2CH_3 \rightarrow CH_3CH{=}CHCH_3$ (*trans*) and for $CH_3CH{=}CHCH_3$ (*cis*) $\rightarrow CH_3CH{=}CHCH_3$ (*trans*). Are the ΔS^0 values in accord with your expectations? What can you conclude as to how good a qualitative measure heats of hydrogenation are of relative alkene stabilities?

Exercise 12-8 Consider that it is necessary to synthesize pure samples of *D*,*L*-hexane-3,4-D_2 and *meso*-hexane-3,4-D_2. Show how this might be done both with diimide and catalytic-type reductions, assuming that any necessary deuterium-labeled reagents and six-carbon organic compounds are available.

Exercise 12-9

a. Show how 1 is formed by hydroboration of 1,5-cyclooctadiene.

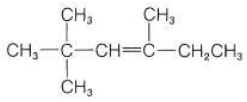
b. What product would you expect from the hydroboration of 2,4-dimethyl-1,4-pentadiene with BH_3?

c. Explain why diborane adds to methylcyclohexene to give tris-(*trans*-2-methylcyclohexyl)borane in preference to the cis isomer.

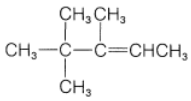
Exercise 12-10 What products would you expect from hydroboration of the following alkenes with a dialkylborane, R_2BH, followed by isomerization at 160°?

a. $CH_3CH{=}CHCH_3$

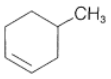
b.



c.

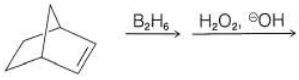


d.



Exercise 12-11 Predict the products in each step of the following reaction sequences:

a.



b. $(CH_3)_2C{=}CHCH_3 \xrightarrow{B_2H_6} \xrightarrow{C_2H_5C{\equiv}CC_2H_5} \xrightarrow{H_2O_2,\ {}^{\ominus}OH}$

c. $(CH_3)_2C{=}CHCH_3 \xrightarrow{B_2H_6} \xrightarrow{C_2H_5C{\equiv}CC_2H_5} \xrightarrow{CH_3CH_2CO_2D}$

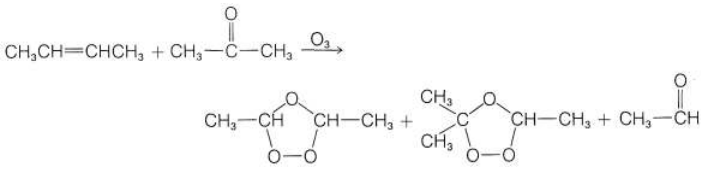
Exercise 12-12

a. Draw the structure and configuration of the product expected of the reaction between 1-bromo-1-hexyne and diethylborane, $(C_2H_5)_2BH$.

b. When the product is treated with sodium methoxide, $NaOCH_3$, then with propanoic acid, *trans*-3-octene is formed. Show the steps involved in forming this *trans*-alkene.

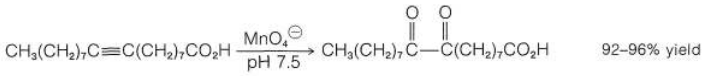
Exercise 12-13 A hydrocarbon of formula $C_{11}H_{18}$ on reaction with ozone in dichloromethane gave, after the addition of water and finely divided zinc, three products in equimolar amounts that were identified as 2-butanone ($CH_3COCH_2CH_3$), methanal (CH_2O), and cyclohexane-1,4-dione  . Draw the structure of the hydrocarbon $C_{11}H_{18}$.

Exercise 12-14* When 2-butene reacts with ozone in the presence of 2-propanone, two structurally different ozonides are obtained, as well as ethanal:



Suggest how these products can be formed from the molozonide(s) of 2-butene.

Exercise 12-15 Alkynes react more slowly than alkenes with permanganate and usually give dicarbonyl compounds. An example follows:



a. What is the change in oxidation state of carbon in this reaction?

b. If **Mn**(VII) is reduced to **Mn**(IV), how many moles of permanganate are required per mole of alkyne?

Exercise 12-16 Starting with cyclohexene, show how you could prepare each of the following compounds:

a. the epoxide of cyclohexene
b. *cis*-cyclohexane-1,2-diol
c. *trans*-cyclohexane-1,2-diol

Exercise 12-17 Suppose you were given four unlabeled bottles, each of which is known to contain one of the following compounds: pentane, 1-pentene, 2-pentyne, or 1-pentyne. Explain how you could use simple chemical tests (preferably test-tube reactions) to identify the contents of each bottle. (Notice that all four compounds are low-boiling liquids.)

Exercise 12-18* Show how the (\Delta H\) values of the following processes can be combined to calculate the heat of solution of $\mathbf{Na^{\oplus}}\,(g) + \mathbf{Cl^{\ominus}}\,(g)$ at **298°K**.

$$\begin{aligned}
&\mathbf{Na}\,(s) + \tfrac{1}{2}\mathbf{Cl_2}\,(g) \rightarrow \mathbf{Na^{\oplus}}\,(aq) + \mathbf{Cl^{\ominus}}\,(aq) && \Delta H^0 = -97\ \mathbf{kcal}\\
&\mathbf{Na}\,(g) \rightarrow \mathbf{Na^{\oplus}}\,(g) + \mathbf{e^-} && \Delta H^0 = +118\ \mathbf{kcal}\\
&\mathbf{Cl^{\ominus}}\,(g) \rightarrow \mathbf{Cl}\cdot\,(g) + \mathbf{e^-} && \Delta H^0 = +83\ \mathbf{kcal}\\
&\tfrac{1}{2}\mathbf{Cl_2}\,(g) \rightarrow \mathbf{Cl}\cdot\,(g) && \Delta H^0 = +29\ 29\\
&\mathbf{Na}\,(s) \rightarrow \mathbf{Na}\,(g) && \Delta H^0 = +26\ \mathbf{kcal}
\end{aligned} \qquad (12.10.1)$$

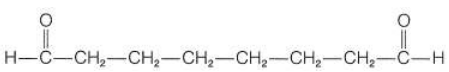
Exercise 12-19 A serious contamination in butenyne made by dimerization of ethyne with cuprous ion is 1,5-hexadien-3-yne. Show how this substance can be formed.

Exercise 12-20 The following physical properties and analytical data pertain to two isomeric hydrocarbons, **A** and **B**, isolated from a gasoline:

	bp, °C	mp, °C	%C	%H
A	68.6	−141	85.63	14.34
B	67.9	−133	85.63	14.34

Both ***A*** and ***B*** readily decolorize bromine and permanganate solutions and give the same products on ozonization. Suggest possible structures for ***A*** and ***B***. What experiments would you consider necessary to further establish the structures and configurations of ***A*** and ***B***?

Exercise 12-21 It is possible to synthesize two isomeric cycloalkenes of formula $\mathbf{C_8H_{14}}$. Both of these compounds react with hydrogen in the presence of platinum to give cyclooctane, and each, on ozonization followed by reduction, gives:



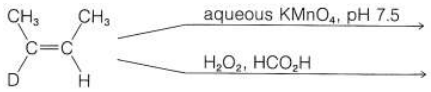
a. What are the structures of the two compounds?

b. Would the two substances give the same compound on hydroxylation with potassium permanganate?

Exercise 12-22 When 5-decyne is heated with diborane at **160°** and the product is oxidized with hydrogen peroxide in basic solution, 1,10-decanediol is obtained. Write equations to show the several reactions involved in these transformations. You need not show detailed mechanisms.

Exercise 12-23

a. Draw the structures and configurations of the products that will be formed by the following reactions of *cis*-2-butene-2-**D**:

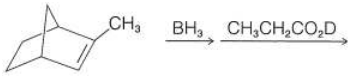


b. What is the stereochemical relationship between the products of the two reactions in Part a?

Exercise 12-24* Show the structures of the products expected in each step of the following sequences. Be sure to indicate the stereochemistry of reactions where this is important. Remember that **D** is the hydrogen isotope of mass 2.

a. *cis*-2-butene $\xrightarrow{C_2NND_2}$

b. 1-methylcyclohexene $\xrightarrow{BH_3}\xrightarrow{160^\circ}\xrightarrow{H_2O_2,\ ^{\ominus}OH}$

c. 

d. propyne $\xrightarrow{R_BD}\xrightarrow{CH_3CH_2CO_2H}\xrightarrow{O_3}\xrightarrow{H_2O,\ Zn}$

e. 2-butyne $\xrightarrow{R_2BH}\xrightarrow{H_2O_2,\ ^{\ominus}OH}$

f. $CH_3C\equiv CH \xrightarrow{R_2BD}\xrightarrow{CH_3CH_2CO_2D}$

g. 3-methylcyclopentene $\xrightarrow{BH_3}\xrightarrow{160^\circ}\xrightarrow[\text{(as trapping agent)}]{CH_3(CH_2)_7CH=CH_2}$

h. 1-pentene $\xrightarrow{HBr,\ ROOR}\xrightarrow{CH_3C\equiv CNa}\xrightarrow{H_2,\ Pd-Pb}\xrightarrow{O_3}\xrightarrow{Na_2SO_3}$

i. 1-pentene $\xrightarrow{BH_3}\xrightarrow{H_2N-OSO_3H}$

Exercise 12-25 Two stable compounds of formula C_6H_6 react with bromine and with $KMnO_4$. On hydrogenation with a platinum catalyst at **25°**, both absorb two moles of hydrogen and form cyclohexane. Write possible structures for these substances and explain how electronic spectra may be used to tell which compound is which.

Exercise 12-26 Suppose one added hydrogen as H_2 to the cyclopropene double bond of 1-methoxy-2-phenyl-3,3-dimethylcyclopropene. Explain how the proton nmr of the product can be used to infer whether the hydrogen added to the double bond in the suprafacial or antarafacial manner. (Review Section 9-10G and 9-10H.)

Exercise 12-27 In the hydrogenation of 1,2-dimethylcyclohexene over a platinum catalyst, the suprafacial addition product is formed. Assuming that the mechanism of this hydrogenation is as shown in Figure 11-2, what conditions must be put on the stereochemistry of each of the postulated steps in order that the overall reaction be suprafacial?

Exercise 12-28* When *optically active* 3-methylhexane is shaken with a nickel catalyst in the presence of deuterium gas $(D_2 = {}^2H_2)$ it, like other alkanes, undergoes slow exchange of hydrogen for deuterium at the various carbons. The key observation is that substitution of **D** for **H** at C_3 causes racemization (i.e., formation of equal amounts of deuterated 3-methylhexane with the two possible configurations at C_3). Assuming that racemization and deuterium exchange occur *only* by way of the steps shown in Figure 11-2, determine how many steps backward the reaction has to go to produce the racemized, exchanged 3-methylhexane. To work this problem you will need to determine whether, when one starts with optically active 3-methylhexane, the various possible intermediate structures in Figure 11-2 would be chiral or not and how many steps back one would have to go to get to an achiral system. If you are uncertain about chirality we suggest that you review Section 5-1B.

Figure 12-29 Calculate ΔH^0 for the reaction $CH_3{-}C \equiv C{-}H \rightarrow CH_2{=}C{=}CH_2$ from bond energies and also from ΔH^0 values for the following reactions:

$$\begin{aligned} CH_3C \equiv CH + 2H_2 &\rightarrow CH_3CH_2CH_2 \quad \Delta H^0 = -69.1 \text{ kcal} \\ CH_2{=}C{=}CH_2 + 2H_2 &\rightarrow CH_3CH_2CH_3 \quad \Delta H^0 = -71.3 \text{ kcal} \end{aligned} \tag{12.10.2}$$

Explain why the value of ΔH^0 calculated form bond energies might be unreliable for the last reaction.

Exercise 12-30

a. Write a mechanism for the sulfuric acid-induced dimerization of 2-methyl-2-butene, indicating the products you expect to be formed. (It will be helpful to review Section 10-8B.)

b. Ozonization of the actual alkene mixture that is formed gives (along with a mixture of aldehydes and ketones) substantial amounts of 2-butanone ($CH_3COCH_2CH_3$). Write a structure and reaction mechanism for formation of a C_{10}-olefin that reasonably might be formed in the dimerization reaction and that, on ozonization, would yield 2-butanone and a C_6-carbonyl compound. (Consider how sulfuric acid might cause the double bond in 2-methyl-2-butene to shift its position.)

Exercise 12-31 How would you distinguish between the components in each of the following pairs using chemical methods (preferably test-tube reactions)?

a. $CH_3CH_2C \equiv CH$ and $CH_3C \equiv CCH_3$
b. $CH_3CH_2C \equiv CH$ and $CH_2{=}CH{-}CH{=}CH_2$
c. $C_6H_5C \equiv CC_6H_5$ and $C_6H_5CH_2CH_2C_6H_5$

Exercise 12-32 How could you distinguish between the compounds in the previous exercise, using spectroscopic methods?

Contributors

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