Chm 222, Section 1
Spring 2017
Patterns in Organic Chemistry

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‘He took another sip as the clouds revealed themselves in a multitude of colors, from cherry and raspberry to peach and honeydew. Then, at last, Jean Perdu understood.” – Nina George
WWWHHHH
December 2, 2016
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Chapter 1

Introduction

1.1 Organic Chemistry

There are something of the order of 100 million organic compounds (those containing C, H, and sometimes other atoms) on the records of the Chemical Abstract Service. This course is concerned with the properties and reactivities of those molecules. Clearly in order to understand something of this subject requires the use of patterns of behavior gleamed from a small number of these molecules. It is the intent of this document to try to lead you to an appreciation of the use of such patterns. We have four major topics in this course: (1) An introduction to a simple bonding model of organic compounds, (2) methods of determination of the structure of molecules, (3) the stereochemistry—how the atoms are arranged in space—of molecules, and (4) reactivities of organic compounds. The last is the most extensive and the hardest for students to appreciate. It requires an appreciation of the polarization of bonds and the acidity of molecules. That these are the four topics does not mean we have to discuss to completion any one of them and then do the next. Generally, we will take what we need from each to move forward in a grand understanding of organic chemistry.

The bonding model that we use most extensively is the Lewis structure, which you should have learned about in an introductory courses. There are several extensions of the simple Lewis model that are important: polarization of bonds, hybridization, and resonance. Molecular orbital theory is a more sophisticated model of chemical bonding. Although not a major topic in this course, there are some features that we want to learn that are best understood with this model, so we will exert a little effort in understanding mo theory.

Structure determination is critical to understanding organic chemistry. The major tools to determine structure are infra-red spectroscopy (IR) and nuclear magnetic resonance (nmr). We will discuss these extensively, as well as spend a little effort on mass spectroscopy (mass spec).

Molecules have an architecture. The atoms are arranged in space in definite ways. These arrangements turn out to be quite important in determining properties and reactivities of
molecules. Some structural aspects of the shape of organic molecules is simple and needed early. Other aspects are quite sophisticated and will be discussed late in the semester.

The main thrust of this course is the reactivity of organic compounds. There are so many reactions that a student needs to learn that we must find some method of organizing the information. Many reactions are very similar to each other. It is the task of the pattern learner to find those similarities and to utilize them to help keep the kinds of reactions to a small enough set to remember. Much of the effort in this document will be devoted to such organizational skills. Most typical textbooks fail to organize except around compound types. We will try to do more. One method of organization is the concept of “oxidation level” or “carbon level.” A second useful tool is to recognize the kind of compound you have, or desire to synthesize, and to be able to see its relationship to other compounds. We will try to identify kinds of compounds, using both traditional words when they are suitable, but also by “making up” words when needed. The ability to suggest a synthesis of a given molecule is also a focus of the course. This is typically harder to do than to learn the reactions, but learning the reactions is certainly a prerequisite to doing a synthesis. Our aim is to learn how to do a synthesis (at least on paper!).

Underlying almost everything discussed in this course is the simple concept that things in nature have “charge.” Philosophically, that is just someone’s word to explain a property of the thing. Of course that property is that something with a “positive charge” will attract another object with “negative charge” and will repel another object with “positive charge.” Knowing and applying this concept will take you very far in understanding organic chemistry. Always think charge!

1.2 The Course

This document represents my attempt to organize the material in a way that seems efficient to me. Mostly this is a set of problems with introductory discussions. Those discussions are not meant to be the entire presentation of material. Both the readings and lecture will provide additional material. Rather, the introductory discussions are meant to highlight the major points and to give definite examples of approaches to the following problems. Doing those problems, and asking questions in class when confused, is highly important.

There are two feature in this document that I believe are important in education. Firstly, repetition. In my opinion, learning something more than once is necessary. We introduce topics early and then come back to them again, often with more sophistication. Another aspect of this: assignments in the regular text and discussion in class will sometimes be similar (repetition). Secondly, in a traditional approach to this subject (look at most organic textbooks) there is a bunch of preliminary stuff before any discussion of the heart of organic courses, reactions. We will try to introduce reactions as soon as possible in order to even out the material to be learned over the semester.

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2 The student must recognize these words that members of the class will know, but people outside the class may not; and act accordingly.
The actual mechanics of the class are worth discussing. I will assign readings in the text and sometimes use those as the starting point for discussion in class. If you don’t understand the reading, it is your responsibility to ask about your confusion. I will also assign readings in this document and use those as the starting point of discussion; same responsibility. There are required exercises after each assignment and you should do all of those. There are also lots of exercises labeled “additional” that you should attempt if you have time.

Traditionally, courses labeled “Organic Chemistry” do require time.
Chapter 2

Lewis Structures, Epwa, and a Few Reactions

2.1 Lewis Structures and Associated Issues

Read Klein, Sections 1.1-1.5 (1.1-1.5 in the first edition)

Remarks: (1) To conserve time, you should always draw your Lewis structures with “lines” for a pair of electrons rather than with “dots” to represent the individual electrons; this includes lone pairs. There are two counting schemes in Lewis structures that can be accomplished by drawing circles within the structure. The first is to determine if there is an “octet.” Draw a circle around an atom and include both electrons of any bond and any lone pairs. The total within the circle should be eight (except for H, and sometimes, heavier elements like P, S, Cl. Incidentally, past experience teaches me that those of you that are like me and draw sloppy Lewis structures are much more likely to be in the bottom half of the class than those of you that draw neat ones.

(2) Calculation of formal charge is important. If you forget charge on your Lewis structures, you will get into trouble. To get the formal charge requires drawing a different circle from that above. This circle should include all lone pairs and cut all bonding pairs in half. The formal charge is then the valence shell nuclear charge minus the number of electrons in the circle.

(3) Polarization of bonds is critical. The Lewis structure does not indicate polarization of bonds (although an molecular orbital scheme does). Polarization is the uneven sharing of electrons in a bond between the two nuclei. The periodic table is our guide to polarization. Elements to the upper right pull on electrons more strongly than those to the lower left because their valence shell nuclear charge is more positive and electrons move closer to the higher valence shell nuclear charge. This means that in a bond between carbon and fluorine, C-F, the carbon is partially positively charged and the fluorine is partially negatively charged. A polarization in a bond creates a “bond dipole,” which is the magnitude of the positive charge (or the negative) times the distance the two charges are separated.
that bond dipoles in molecules can cancel each other out so that the molecule as a whole
does not have a net dipole; consider CO$_2$.

(4) Isoelectronic materials are those with the same (“iso”) number of valence shell electrons. Thus C, N$^+$, and O$^{2+}$ are isoelectronic, as are C$^-$, N, and O$^+$. Another useful “iso”
concept involves the bonding characteristics of atoms or groups of atoms. As you will
convince yourself in the exercises, Cl atoms (when they obey the octet rule and have no
formal charge) always form one and only one bond in a Lewis structure because they have
a single lone electron to pair with one on another atom. An OH group is in exactly the
same condition, as is a CH$_3$ group. (Be sure to draw this to establish it to yourself; you
will need “dots” to indicate some of the electrons in these odd electron species.) So the
bonding properties of these three groups are the same. For instance, if they were to bond
to a hydrogen atom, we would get H-Cl, H-OH, and H-CH$_3$, where only the bond formed
we are discussing is indicated. Or, we could bind them to OH to get Cl-OH, HO-OH, and
HO-CH$_3$. This property, which we might call “valence shell isoelectronic” is very powerful
in drawing Lewis structures.

2.1.1 Required Exercises

2.1.1.1 Write Lewis structures for C$_2$H$_6$, CH$_3$OH, CH$_3$NH$_2$, CH$_2$O, C$_4$H$_8$O.

2.1.1.2 Draw Lewis structures of CH$_3$C(O)H, CH$_3$(CH$_3$)$_3$CH$_3$, CH$_3$CHCH$_2$, C$_2$NH$_3$
(cyclic), CH$_3$F, CH$_3$OCH$_3$, CH$_3$CH$_2$OH, CF$_3$C(O)OH, CH$_2$F$_2$, (CH$_3$)$_2$NH, (CH$_3$)$_3$N. Use
line structures. HINT: (X) means that group X is off the main chain; which in the first
molecule is taken to be, not uniquely, C-C-H.

2.1.1.3 Look at each structure in problems 2.1.1.1 and 2.1.1.2 and determine the number
of bonds to C, to N, to O, to F, to H. Formulate a rule for the number of bonds to these
atoms.

2.1.1.4 Use the pattern rule of problem 2.1.1.3 to build a Lewis structure for (CH$_3$)$_3$CCHC(CH$_3$)$_2$.

2.1.1.5 Draw Lewis structures of the charged compounds OH$^-$, NH$_2^-$, NH$_4^+$, and
H$_3$O$^+$. Note that charged compounds do not obey the rule that you have formulated
from problem 2.1.1.3. Use the concept of isoelectronic species to make sense of these and
formulate a rule for the number of bonds to charged atoms. NOTE: We will get an exception
to this rule at carbon where the positively charged species is, for instance, CH$_3^+$.

2.1.1.6 Until it becomes evident to you which atoms have formal charges and which
don’t, calculate the formal charge on each atom in every Lewis structure you draw. In
particular, try it on CH$_3$O$^-$, non-cyclic O$_3$, non-cyclic CH$_2$N$_2$, BH$_4^-$, NH$_4^+$.
2.1.1.7 Indicate the polarity of the bond (with the $\delta^+ / \delta^-$ notation) for each of the following: C-Cl, H-Cl, B-F, C-N, C-O, H-O, B-H, Mg-C, N-F, C-C-F. HINTS: (1) Use the periodic table. (2) What do you think I am getting at with the last example?

2.1.1.8 Here are a bunch of compounds containing a methyl group. Put them in order from the most positively charged methyl group to the most negatively charged methyl group. HINT: Li is generally a better polarizer than MgCl.

\[
\begin{align*}
\text{CH}_3\text{CH}_3 & \quad \text{CH}_3\text{OH} & \quad \text{CH}_3\text{Li} & \quad \text{CH}_3\text{MgCl} & \quad \text{CH}_3\text{F} & \quad \text{CH}_3\text{NH}_2 \\
\end{align*}
\]

2.1.1.9 Which of the following are isoelectronic with each other? $\text{O}^{2-}$, F, C, Si, N, N$^-$, N$^+$, F$^-$, Ne, O, S, O$^+$. 

2.1.1.10 Which of the following are valence shell isoelectronic with each other? OH$^-$, NH$_2^-$, F$^-$, OH, CH$_3$, NH$_2$, Cl, SiH$_3$, Br.

2.1.1.11 If a material X is valence shell isoelectronic with CH$_3$, what does that say about substituting X for CH$_3$ in a Lewis structure.

2.1.1.12 Show that CH$_2$ and O are valence shell isoelectronic and hence you can write the Lewis structure of CH$_3$CH$_2$CH$_3$ and know, absolutely positively, that you could replace that central “CH$_2$” with an “O” to give CH$_3$OCH$_3$.

2.1.1.13 Show that CH$_2$ and NH are isoelectronic and hence you can write the Lewis structure of CH$_3$CH$_2$CH$_3$ and know, absolutely positively, that you could write ____________.

2.1.2 Additional Exercises

2.1.2.1 Write the electron configuration for Li, Na, Mg, B, Al, C, Si, N, P, O, S, F, Cl, Br. Use a periodic table and appropriate abbreviations for inner shell electrons. This is not a busy work problem. You should learn to assign electronic configurations quickly and accurately, especially for the elements commonly used in organic chemistry.

2.1.2.2 How many valence electrons does each atom of problem [2.1.2.1] have? It should become second nature to you to know the number of valence electrons for a given atom. Use the periodic table, but work to make the answers resident in your brain. Look for isoelectronic (iso, from the Greek isos, equal, or same) systems.
2.1.2.3 Take some of the structures from problem 2.1.1 and replace one isoelectronic material with another. Convince yourself that this leads to an easy way to make new Lewis structures.

2.1.2.4 The dipole moment of HCl is 1.08 Debye and that of LiH is 6.0 Debye. For each molecule, which end of the molecule is positive and which is negative?

2.1.2.5 The dipole moment of FCl and ICl are both about 0.8 Debye. Why are they so similar when F and I differ so greatly in electronegativity?

2.1.2.6 To boil a liquid, to convert it into a gas, requires energy to break the bonds, often weak, between the closely spaced liquid molecules. These bonds form because of fluctuations of the positions of the electrons around atoms; generally, more electrons offers more possibility for significant fluctuations. Predict whether CH$_4$ or CH$_2$Cl$_2$ would have the higher boiling point. Incidentally, what physical property of liquids suggests that the molecules are closely spaced? HINT: Think about squeezing a full capped plastic soda bottle versus squeezing an empty capped one.

2.1.2.7 To boil a liquid, to convert it into a gas, requires energy to break the bonds, often weak, between the closely spaced liquid molecules. Predict whether CH$_4$ or CCl$_4$ would have the higher boiling point. HINT: Klein under “London ...”

2.1.2.8 Although CF$_3$ is not actually isoelectronic with CH$_3$, it is isolobal (has the same bonding characteristics). Use this to formulate a compound with fluorine in it from the Lewis structure of CH$_3$CH$_2$CH$_2$CH$_3$. HINT: Take advantage of this feature. Get to know what groups can replace what groups in organic structures.

2.1.2.9 Show that H has similar bonding characteristics as CH$_3$.

2.1.2.10 Show that OH has similar bonding characteristics as CH$_3$.

2.1.2.11 Show that NH$_2$ has similar bonding characteristics as CH$_3$.

2.2 A Shorthand For Lewis Structures

Writing out the carbon atoms and all those attached hydrogen atoms is very time consuming. Organic chemists use a shorthand to abbreviate this. The shorthand is a series of lines that join at points. Each point represents a carbon atom and as many hydrogen atoms as
are necessary to give a total of four bonds to the carbon atom. Note in order to see the points (and in order to approximate the real structure of organic compounds) we need to write the carbons in a chain of carbon atoms with a zig-zag pattern. In Figure 2.1 this concept is illustrated for three compounds. These representations are called skeletal or “line” structures. Learn to use this very efficient shorthand technique.

Notice how in the exercises I define the names of kinds of compounds. Pay attention; those names are important.

2.2.1 Required Exercises

2.2.1.1 If I were to say that you could draw a Lewis structure of C\textsubscript{4}H\textsubscript{9}Cl with two different connectivities, what would I mean? Do so. Use bond-line structures, hereafter, “line” or “skeletal” structures.

2.2.1.2 An aldehyde is a compound containing a carbon-oxygen double bond with a hydrogen and another carbon atom attached to the carbon of interest (except for formaldehyde, or methanal, which has two hydrogen atoms attached). Draw two skeletal (also called a “line”) structures for aldehydes with the formula C\textsubscript{4}H\textsubscript{8}O. HINT: There won’t be many of you, but there will be some that by the end of the semester still do not know what an aldehyde is: Don’t be one of them! Know what it is by yesterday.

2.2.1.3 A ketone is a compound containing a carbon-oxygen double bond with two carbon atoms attached to the carbon of interest. Draw a skeletal (also called a “line”) structure for at least four ketones with the formula C\textsubscript{6}H\textsubscript{12}O.

2.2.1.4 Is CH\textsubscript{3}C(O)Cl an aldehyde or ketone?

2.2.1.5 Draw a Lewis skeletal (or line) structure for C\textsubscript{5}H\textsubscript{12}, C\textsubscript{5}H\textsubscript{10}O, C\textsubscript{5}H\textsubscript{8}O\textsubscript{2}, C\textsubscript{5}H\textsubscript{6}O\textsubscript{3}, C\textsubscript{5}H\textsubscript{12}O, C\textsubscript{5}H\textsubscript{13}N, C\textsubscript{5}H\textsubscript{12}S, C\textsubscript{5}H\textsubscript{10}, and C\textsubscript{5}H\textsubscript{8}. HINT: Pay attention to make life easy for yourself: for example, once you have done the fifth, you have also done the seventh. Why?
2.2.2 Additional Exercises

2.2.2.1 Review: How many bonds are there to each C atom in the structures in problem 2.2.1.5?

2.2.2.2 Review: How many bonds are there to each O atom in the structures in problem 2.2.1.5?

2.2.2.3 Draw a skeletal structure for a compound of formula C\textsubscript{7}H\textsubscript{12}O, which is not a ketone.

2.2.2.4 **Carboxylic acid derivatives** are compounds with a carbon-oxygen double bond in which the carbon is attached to another electronegative element. Draw a skeletal structure for acetyl chloride, CH\textsubscript{3}C(O)Cl, which is a carboxylic acid derivative and ethyl acetate, CH\textsubscript{3}C(O)OC\textsubscript{2}H\textsubscript{5}, which is also a carboxylic acid derivative. Be sure you see that these two compounds have a common group in them, CH\textsubscript{3}C(O); that fragment has one carbon with three bonds. Be sure that you see that in each compound this carbon that needs one more bond and is attached to a group that also need one more bond.

2.2.2.5 An alkene is a compound with a carbon-carbon double bond. Draw a skeletal structure for an alkene with four carbon atoms.

2.2.2.6 Draw a skeletal structure for (CH\textsubscript{3}CH\textsubscript{2})\textsubscript{2}CHCH\textsubscript{2}OCH\textsubscript{3}. Try to analyze what this structure is telling you. The third typed C from the left is bonded to two C’s from the (CH\textsubscript{3}CH\textsubscript{2})\textsubscript{2}-, to the H, and to the fourth C, so it has all four of its bonds; etc.

2.2.2.7 Draw a skeletal structure for (CH\textsubscript{3}CH\textsubscript{2})\textsubscript{2}CCH\textsubscript{2}.

2.3 Resonance

Read Klein, pp. 68-85. (66-83 in the first edition)

The Lewis structure for molecules is a very simple concept; not surprisingly, there are molecules for which it fails. Consider the acetate anion, shown in Figure 2.2, part A. There is no reason why one of the oxygen atoms should be favored over the other for the double bond. The facts agree with this. Both of the carbon-oxygen bonds in the acetate anion are equal in length. Neither is a double bond; neither is a single bond, as the Lewis structure would imply. Rather, both bond lengths are intermediate between these values. This suggests that the real structure is between the two illustrated. Conventionally this is illustrated by a double headed arrow as shown in Figure 2.2, part B. A better
Figure 2.2: Drawing Resonance in the Acetate Anion. Note lone pairs are left out because in “ChemDraw” it is not easy to do so.
representation, in my opinion, is to write what you must do in your head, average the two structures. We shall use the averaging symbol to show resonance, as shown in Figure 2.2 part C. Resonance structures for the nitrite anion, NO$_2^-$, for benzene, C$_6$H$_6$, and for a 2-pentene cation are shown in Figure 2.3.

Resonance is very important in any chemistry that uses Lewis structures a lot, such as organic chemistry. It is important not only for an crude, but roughly correct picture of what electrons are doing in the molecules, but also, as we shall see, because resonance has a stabilizing effect on the energy of a molecule. Benzene is considerably more stable than the hypothetical cyclic molecule with three double bonds that do not resonate.

### 2.3.1 Required Exercises

**2.3.1.1** Do you need resonance to show the bonding in the carbonate dianion, CO$_3^{2-}$? If so, show the resonance structures.

**2.3.1.2** Show resonance and formal charge in the nitrate anion, NO$_3^-$

### 2.4 Curved Arrows, and, More Importantly, Epwa

Read Klein, Section 3.2. (Section 3.2 in first edition)

There is a convention to relate resonance structures to each other. It uses a curved arrow as discussed by Klein in the assigned reading. Figure 2.4 shows this for acetate anion. You should note that there is not really any motion of electrons in resonance structures: as stated above, resonance structures are really a breakdown of the Lewis structure picture and should be treated as the mental average of the collection of resonance structures. Electrons do not move in resonance structures; it is our inability to draw a single Lewis structure that is meaningful that causes us to use such pictures. You should note that the curved arrow starts at a pair of electrons in a double bond and goes to where that pair should be in the resonance structure. We will see a more important use of this method now.

There is in organic chemistry a real need to talk about the motion of electrons during a reaction. When methoxide ion reacts with ammonium ion,

$$\text{CH}_3\text{O}^- + \text{NH}_4^+ \rightarrow \text{CH}_3\text{OH} + \text{NH}_3$$

one of the pairs of electrons on the oxygen atom of the methoxide ion is forming a new bond with a hydrogen on the ammonium ion, which, in turn, is breaking a bond between that

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1 Using new symbols that are believed, by me, to be more instructive than conventional symbols sometimes upsets those with limited imagination: “Viva la revolución!” Do what you think helps you understand the most readily. And be prepared to find others that might not know what you are talking about. When you do, explain what you mean.
Figure 2.3: Drawing Resonance Structures. Note lone pairs are left out because in “ChemDraw” it is not easy to do so.

Figure 2.4: Example of Using Curved Arrows to Show Resonance Structures. Here lone pairs are very important, so they are added.
2.5 13

Figure 2.5: Epwa (Electron Pushing with Arrows) for the Reaction of Methoxide Ion with Ammonium Ion

hydrogen and the nitrogen. How to summarize all this action in a simple picture? The answer is to push electrons around, and the convention is to use an arrow to show this motion of electrons. We will use this device so frequently that it deserves a name. Others call this the “curved arrow formalism” or “electron pushing;” we shall use an acronym, “epwa,” or electron pushing with arrows. Figure 2.5 shows this process for the reaction above. Note that the start of the arrow is in the center of the pair of electrons that is going to “move.” These are generally the least tightly held electrons in the system–see the next section. The head of the arrow points to the middle of the new bond that is to be formed, which is usefully indicated by a dotted line. Often a single epwa will produce an atom that violates the “octet” and hence a second epwa is needed, as is the case in Figure 2.5. If you carefully build your epwa and think about what it means, you will have success in organic chemistry.

2.4.1 Required Exercises

2.4.1.1 An “epwa” arrow starts at what? Where does the arrow end? End of the arrow end?
REMARK: Isn’t English wonderful?

2.4.1.2 Draw a diagram using epwa that shows how H\(^+\) reacts with OH\(^-\) to form water, H\(_2\)O. HINT: This looks like busy work, but if you take your time and learn to do epwas clearly and carefully, you will do well in organic chemistry. Incidentally, most texts draw rather sloppy epwas. Make yours carefully because they really are trying to tell you something about what happens during a reaction. Don’t forget the dotted line.

2.4.1.3 Use epwa to show how H\(_3\)O\(^+\) is attacked by ammonia, NH\(_3\), to form a mole of water and a mole of ammonium ion. HINT: Where do epwas start?

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There is even an entire book devoted to the subject: "Pushing Electrons," Weeks, Cengage Press, 2014.

Here we go with one of our words. You can’t look epwa up on the web and find much except for the Warsaw airport. It is useful to us; if you must translate it for another, you need to say “electron-pushing with arrows.”

This dotted line device is seldom, if ever, used by others; like the averaging sign for resonance, I think it is very useful.
2.5 A Sampling of Organic Reactions

In this section we combine our knowledge of polarization and the epwa method of indicating motion of electrons to see how we go about analyzing the possibility of a reaction in organic chemistry. This is a five step process.

1. Let’s look at two molecules and understand their polarizations. First the methoxide ion, CH$_3$O$^-$. Draw the Lewis structure. The oxygen atom in methoxide ion is negatively charged. Is there any atom in methoxide ion that is likely to be positively polarized? The carbon, you say. OK.

Now consider a molecule called ethanoyl chloride, CH$_3$C(O)Cl. Draw the Lewis structure of this species, noting that the formula tells you the central chain of the molecule is C-C-Cl, and that O lies off the chain. Use the rule about the number of bonds to carbon, oxygen, and chlorine to do this efficiently. Is there any atom in this molecule that is polarized positively? Surely the carbon bonded to the electronegative oxygen and chlorine atoms is polarized positively and the oxygen atom and the chlorine atom are negatively polarized. An important nomenclature issue: A carbon atom double bonded to an oxygen atom is called a carbonyl group.

2. We want to identify the source of the beginning of the epwa, the electrons that are to move. These are generally the electrons that are most loosely held. In the case of our two molecules, the oxygen atom that is negatively charged in methoxide ion is likely to be the source of the electrons that move, the start of the epwa arrow.

3. To where will the arrow go? We want an epwa from the negative source to the positive site on the other molecule, in this case to the carbon attached to oxygen and chlorine in the ethanoyl chloride. So we draw a dotted line from the oxygen atom of the methoxide ion to the indicated carbon of ethanoyl chloride and put in our first epwa. See A of Figure 2.6.

4. Check to see if all atoms still obey the octet. As a result of A in Figure 2.6, we see that the central carbon atom now has five pairs of electrons around it, the original four
and the new pair that our epwa put to it. That is not acceptable. B is NOT acceptable: it violates the octet and puts negative charge on carbon; normally we would do both epwa at the same time, but for this learning experience, the step have been separated. We won’t make that mistake again! So we have to move some electrons away from that carbon. One option is to reverse our epwa, but that is seldom very interesting. Is there anything else we can do? How about moving the double part of the double bond onto the upper oxygen atom? See B in Figure 2.6.

(5) **Check the final product**, which is shown in C in Figure 2.6. There is negative charge on an oxygen atom. Is that an atom that “wants” negative charge? Yes. The net reaction took negative charge from an oxygen and put it on an oxygen. Not bad. If the process had taken negative charge on an oxygen and put it on a carbon, we might be worried that we had done something incorrect, because that is not the direction that charge would flow (according to electronegativity rules).

Now the species that we have made, C, turns out now to be very stable. Let me tell you something that is true about this molecule and then we will use our analysis steps to follow the process through. The rupture of a carbon-chloride bond in which a chloride ion is formed is a process that occurs readily. The words to describe this is “Chloride ion is a good leaving group.” Here is the analysis of what happens, as shown in Figure 2.7.

(1) Identify negatively and positively polarized atoms. We have only one molecule. The top oxygen atom is negative and the carbon in the center is very positive, as it is attached to three electronegative groups. (2 and 3) The source of the epwa is the negatively charged oxygen, which forms a double bond to the carbon. (4) That carbon atom now has five bonds, so we break the carbon-chlorine bond and give the electrons to the chlorine atom. (5) Net charge flow from oxygen to chlorine, OK, and we form a carbon-oxygen double bond, which is quite stable.

Clearly you could have done both the steps in the reaction at once, although for some compounds of this type there is strong evidence that the process does occur as we indicated.

### 2.5.1 Required Exercises

**2.5.1.1** Use epwa to show how this reaction occurs.

\[
\text{CH}_3\text{C}(O)\text{Cl} + \text{OH}^- \rightarrow \text{CH}_3\text{C}(O)\text{OH} + \text{Cl}^-
\]
HINT: In general terms, this is exactly like the description in the text. That, incidentally, is how to learn organic chemistry: X is just like Y.

2.5.1.2 Consider the molecule $\text{CH}_3\text{C(O)CH}_3$. Draw a Lewis structure and find the positively and negatively polarized atoms.

2.5.1.3 Consider the molecule NaH. Draw a Lewis structure and find the positively and negatively polarized atoms. HINT: Sodium atoms, like hydrogen atoms, take only a pair of electrons, not an octet. Their valence shell nuclear charges are too small to tolerate eight electrons. REMARK: We will call NaH an “H−” reagent because it is an example of a compound where the hydrogen atom is polarized negatively. “H−” reagents are important in this course.

2.5.1.4 Look at the last two exercises and determine which of the negatively polarized atoms is most likely to give up its electrons. Which negatively polarized atom, H or O, “wants” to be negative least?

2.5.1.5 The electrons you identified in the last problem are those bonding the sodium atom to the hydrogen atom. It is that single bond that is the source of electrons in the epwa. It is from that bond that the arrow begins. Draw the dotted line and finish the analysis of the reaction:

$$\text{CH}_3\text{C(O)CH}_3 + \text{NaH} = \text{CH}_3\text{CH(O−)CH}_3 + \text{Na}^+$$

Do products look OK? Does sodium want to be sodium ion? Does negative charge on an oxygen atom seem OK?

2.5.1.6 Use epwa to predict whether reaction will occur when CO$_2$ is mixed with OH$^−$.

2.5.1.7 When magnesium metal is treated with CH$_3$Cl in the presence of a catalyst, one forms CH$_3$MgCl (as you will do in the lab later this semester); this reaction is not easily analyzed by epwa, though it can be done. Ask if you are interested. Which atoms are polarized negatively in CH$_3$MgCl? Which positively? This reagent, CH$_3$MgCl, where the CH$_3$ group can be interchanged with other groups, is called a Grignard reagent. Grignard reagents are an example of a “C−” reagent; such reagents will be very useful to us in this course. Note that it creates a carbon-carbon bond, which means it can be used to build larger molecules.

2.5.1.8 Look at CH$_3$C(O)H. How are the atoms polarized?
2.5.1.9 Of all of the negatively polarized atoms in the last two exercises, which is least likely to want to keep negative charge? That is the start of the epwa; that is the atom on which the dotted line starts. Where should it end?

2.5.1.10 Complete the epwa for the reaction

\[ \text{CH}_3C(O)\text{H} + \text{CH}_3\text{MgCl} = \text{CH}_3C(\text{CH}_3)(O-)\text{H} + \text{MgCl}^+ \]

2.5.1.11 In the exercises of this section are two words we want to use extensively in this course. Be sure you know what is meant by a “C−” reagent and be a “H−” reagent.

2.5.2 Additional Exercises

2.5.2.1 Use epwa to describe the reaction:

\[ \text{CH}_3\text{I} + \text{Cl}^- = \text{CH}_3\text{Cl} + \text{I}^- \]

HINT: Iodide ion is a better leaving group than chloride.
Chapter 3

Bonding

3.1 Atomic Orbitals, Overlap, and Constructive and Destructive Interaction

Read Klein, Section 1.6-1.7. (1.6-1.7)

Remark: The three p orbitals point along the Cartesian axes. Where those axes are in space is up to you. Nature does not care.

Let’s consider two atoms, one located at the origin (x=0, y=0, z=0). The second is located at (0,0,1). If you draw an s orbital on each of those atoms and let the wave be positive on each, there will be a region of space between the two atoms where the two waves will add constructively. Convince yourself of that.

3.1.1 Required Exercises

3.1.1.1 Sketch the angular wave function for a 2s electron; a 2p_x electron; a 2p_z electron. Label your axes.

3.1.1.2 Show that a 2p_z orbital on one carbon atom overlaps (that is, shows either constructive or destructive interference) with a 2p_z orbital on another carbon if the z axis is the internuclear axis, the axis between the two carbon atoms.

3.1.1.3 Show that a 2p_z orbital on one carbon atom does not have net overlap with a 2p_x orbital on another carbon if the z axis is the internuclear axis.

3.1.1.4 Show that a 2p_x orbital on one carbon atom overlaps with a 2p_x orbital on another carbon if the z axis is the internuclear axis. What is the magnitude of this overlap?
compared to that of problem 3.1.1.2. HINT: Since the magnitude of bonding is generally related to the amount of overlap, this assessment is important. Do the orbitals “point at” each other?

3.1.1.5 Does a 2p\textsubscript{z} orbital on one carbon atom overlap with a 2s on another carbon atom if the z axis is the internuclear axis?

### 3.2 Diatomic MO Diagrams

Read Klein, Section 1.8. (1.8)

Let an 1s orbital on one hydrogen overlap constructively with a 1s orbital on another hydrogen atom. The region of constructive interaction produces a buildup of electron density between the nuclei, which attracts them to each other, and hence forms a bond. Since the wave functions are the only available descriptions of electrons, if you add two wave functions to produce a new one, you must subtract them to form a second. Subtraction of wave functions produces destructive interaction in the internuclear region, which lowers electron density, and hence makes an antibond. The diagram for these interactions are given in Figure 3.1. This is called a $\sigma$ bond because the overlap has a circular cross section when viewed down the internuclear axis.

Another important aspect occurs in molecules with two different atoms—see Figure 3.2. The bonding molecular orbital between these two atoms is bigger on the nuclear center with the larger valence shell nuclear charge and the antibonding orbital is bigger on the atom with the lower valence shell nuclear charge. This causes $\sigma$ bond to be polarized toward the atom of highest electronegativity; the antibonding molecular orbital is polarized toward the atom of lowest electronegativity.

You showed in the last section that a 2p\textsubscript{z} orbital on one atom will overlap constructively
Figure 3.2: MO diagram for HHe$^+$. Note polarization in mo theory is dictated by the relative size of the orbital.

with a 2p$_x$ orbital on another (if $z$ is the internuclear axis) to build up electron density right between the nuclei. There is also a buildup of electron density for a constructive interaction of 2p$_x$ with 2p$_x$ (if $z$ is the internuclear axis), but this build up is not as great as the overlap is not straight-on: see Figure 3.3. This interaction is called a $\pi$ interaction because it is not circular (but changes sign twice upon circling 360° about a circle perpendicular to the bond. This means that $\pi$ bonds are weaker than $\sigma$ bonds, a very important feature of organic chemistry.

3.2.1 Required Exercises

3.2.1.1 Imagine an atom with only three 2p orbitals, no others. Build a molecular orbital diagram like that in Figure 3.1 for two of these atoms bonding to each other.

3.2.1.2 For the mo diagram in the last exercise, find the number of bonds if 6 electrons are in the system. If 10 electrons are in the system.

3.2.1.3 On which atom, C or O, does the $\pi$ bond of 11 (in Figure 3.6) have the largest orbital contribution? Sketch it.
Figure 3.3: Overlap of two p orbitals perpendicular to the molecular axis. The line is the internuclear axis.

### 3.2.1.4
On which atom, C or O, does the $\pi^*$ bond of 11 (in Figure 3.6) have the largest orbital contribution? Sketch it.

### 3.2.1.5
Draw an mo diagram for the $\pi$ bonding in $\text{H}_2\text{CCH}_2$ and in $\text{H}_2\text{CO}$. How are they similar? How do they differ?

### 3.3 Hybridization

Read Klein, Section 1.9. (1.9)

Remarks: Of all the hybrids possible, the sp hybrid, made from one s orbital and one p, is the easiest to handle. This is because two orbitals can be “added” and “subtracted” to give the new orbitals. You will show this in the exercises.

### 3.3.1 Required Exercises

#### 3.3.1.1
Add the angular wave function for a 2s electron of C to that of a 2p$_z$ electron of the same carbon atom. Subtract one from the other. HINT: These statements are exactly what they say. A wave function is a wave, has sign in space. If two waves come together
and both are positive, then you get a bigger positive. If two waves come together and one is positive and the other negative, then you get a wave that is smaller in magnitude. Just look at the signs of the waves and do as instructed.

3.3.1.2 In the last exercise, in what direction do the sum and difference functions point? Give me an answer that involves the initial orbitals. Also, what orbitals are “left” unused on the C atom?

3.3.1.3 Add the angular wave function for a 2s electron of C to that of a 2p_y electron of the same carbon atom. Subtract one from the other. In what direction do the functions point? What orbitals are “left” unused on the C atom?

3.3.1.4 It is less easy (at this level of your knowledge) to determine directionality for sp^2 and sp^3 hybrids. Just use what was said in lecture (or can be found in any text) and memorize it. Where in space do sp^2 hybrids point? You can answer this next question without ambiguity. What orbital on the atom is “left” over after you make sp^2 hybrids? Articulate carefully your answer to this last question, recognizing that no axes were defined. Can you give an answer without specifically defining axes? Where does the “left over” orbital point relative to the sp^2 hybrids?

3.3.1.5 If two carbon atoms are hybridized sp^2 and are bonded to each other, how would you describe the total bonding between the two carbon atoms?

3.3.1.6 Where in space do sp^3 hybrids on a carbon atom point? What orbital on the atom is “left” over? HINT: The last question is a “trick” question.

3.3.1.7 In organic chemistry you need to make accurate drawings of molecules showing their three dimensional shapes. This is especially important for a tetrahedral molecule. Sketch a tetrahedral molecule, showing the three dimensional character, in at least three ways. HINTS: Use wedges and dotted lines to stress the third dimension. Also, and this is important, if one atom is in front of another, then the lines describing them should be close to each other; see Figure 3.4.

3.3.1.8 For the skeletal structures 10 (in Figure 3.6), indicate the hybridization of each C atom.

3.3.1.9 Given the number of atoms attached to each carbon atom of cyclopropane, what hybridization would you use to discuss the bonding? HINT: Upon answering this, the next problem should occur to you as well as to me.
3.3.1.10 What is wrong with using sp\(^3\) hybridization in cyclopropane?

3.3.1.11 Given the information in the last two exercises, would you like to predict anything about the stability of the C-C bonds in cyclopropane compared to those in propane? If so, do so. If not, maybe this is not the course for you.

3.3.2 Additional Exercises

3.3.2.1 A carbon atom is attached to four other groups. What hybridization would it use?

3.3.2.2 A carbon atom is sp\(^2\) hybridized. What bonding characteristics does it have (i.e., how many σ bonds? how many π?)

3.3.2.3 Consider the molecule HOOH. What happens to the overlap in the σ bond between the two oxygen atoms as one OH group is rotated in a clockwise fashion (looking down the O-O internuclear axis) relative to the other OH group? The result of this is that it is easy to “rotate” about a σ bond.

3.3.2.4 Is it easy to turn the left hand structure in Figure 3.5 into the right hand one? Why? HINT: This aspect will be important to us soon in nuclear magnetic resonance, and also later in our study of stereochemistry.

3.3.2.5 Imagine a π bond between two groups of atoms, say the C=C in C\(_2\)H\(_4\). What happens to the overlap in a π bond as one CH\(_2\) group is rotated in a clockwise fashion (looking down the C-C internuclear axis) relative to the other CH\(_2\) group?

3.3.2.6 For the skeletal structures 11-15 (in Figure 3.6), indicate the hybridization of each C atom.
Figure 3.5: Two Rotational Related Structures. The lighter colored spheres are one kind of atom, the darker, another. Also, atoms are made larger when they are closer to you, and smaller when further away. Be sure you see how this figure is conveying the same information as that in Figure 3.4.

Figure 3.6: Structures for Various Problems
3.3.2.7 Predict the approximate bond angles and the hybridization used in $\text{CH}_3\text{CH}_2\text{OH}$, non-cyclic $\text{C}_3\text{H}_6$, $\text{CH}_3\text{CN}$.

3.4 HOMO and LUMO

In a molecular orbital diagram the electrons have various stabilities; those lowest in the diagram being the most stable. The least stable electrons are to be found in the highest occupied molecular orbital, or the HOMO. These are the electrons that are likely to be used if the molecule in question is going to be the donor, is going to donate electrons to another molecule, the acceptor. Therefore identification of the HOMO is important.

Likewise, the acceptor will take electrons from the donor and put them in its most stable (empty) orbital. Hence identification of the lowest unoccupied molecular orbital, the LUMO, is also important. Since empty orbitals do not show up in Lewis structures, identification of the LUMO is more difficult than that of the HOMO. However, consider this as a guide. Since a $\pi$ bond is weaker than a $\sigma$ bond, a $\pi^*$ level is less high than a $\sigma^*$ level: If a molecule has a double bond in its Lewis structure, or more properly said, a $\pi$ bond, it is likely that the corresponding $\pi^*$ is the LUMO.

Generally then, orbitals range in energy from $\sigma$ bonding to $\pi$ bonding to lone pairs to $\pi^*$ to $\sigma^*$

3.4.1 Required Exercises

3.4.1.1 Try to identify the electrons that are least tightly held (that is, the highest occupied mo, the homo) in 16-20. For example, in the first compound they would be the lone pair on the nitrogen atom.
Chapter 4

Some Useful Organic Tools

4.1 Using Your Knowledge to Predict a Reaction

4.1.1 Required Exercises

4.1.1.1 Review: Would you expect the hydrogen in BH$_4^-$ to be more negative than that in HCl? More negative than that in NH$_3$? More negative than that in CH$_4$?

4.1.1.2 Might you think of BH$_4^-$ as a “H$^-$” reagent? You should.

4.1.1.3 We (everyone) uses the word “carbonyl” to describe the carbon-oxygen double bond. Review: Would you expect the carbon atom or the oxygen atom of the carbonyl group to be more positive?

4.1.1.4 If you brought a BH$_4^-$ ion up to a carbonyl group, what atoms would be attracted to each other? HINT: The boron atom in BH$_4^-$ is rather effectively shielded by the hydrogen atoms from the “outside” world.

4.1.1.5 If you brought a NaBH$_4$ molecule up to a carbonyl group, what atoms would be attracted to each other? HINTS: (1) How does this problem differ from the last one? (2) Remember, under most conditions, sodium ions do not bind well to anions.

4.1.1.6 Review: In the reaction

\[ \text{CH}_3\text{C}(\text{O})\text{CH}_3 + \text{BH}_4^- = \text{CH}_3\text{CH(O}^-)\text{CH}_3 + \text{BH}_3 \]

What happens to the hybridization of the central carbon atom? State what electrostatic interaction occurs between the reactants to facilitate this reaction.
4.1.1.7 Use epwa to describe what happens in the reaction in the last exercise. HINTS: (1) From where does the epwa start? (2) To what dotted line does it go? (3) Draw your epwa carefully.

4.1.1.8 We can complete the reaction of exercise 4.1.1.6 by adding dilute acid in a second step. Here then is both steps

\[
\begin{align*}
\text{CH}_3\text{C(O)CH}_3 + \text{BH}_4^- & = \text{CH}_3\text{CH(O}^-\text{)CH}_3 + \text{BH}_3 \\
\text{CH}_3\text{CH(O}^-\text{)CH}_3 + \text{H}^+ & = \text{CH}_3\text{CH(OH)CH}_3 
\end{align*}
\]

Use epwa to describe the second step.

4.1.2 Additional Exercises

4.1.2.1 Predict any reaction between BH\(_4^-\) and CH\(_3\)CH\(_2\)C(O)H. Use epwa to describe it. If reaction occurs, and we treat the product with H\(^+\), use epwa to predict the final product.

4.1.2.2 When we know the reaction of a pair of molecules, we can often predict what will happen if we make slight changes. What would you predict would happen if you reacted BH(CH\(_3\))\(_3\)\(^-\), which I am imagining is a hydride donor, with CH\(_3\)C(O)H? Use epwa to describe your reaction professionally.

4.1.2.3 Would you make a prediction about how effective BF\(_3\)H\(^-\) would be as a hydride donor to an aldehyde compared to BH\(_4^-\)? Give your reasons.

4.1.2.4 Review: In the molecule CH\(_3\)MgCl, which atom(s) are negative? Which positive?

4.1.2.5 Review: If you were to bring a molecule of CH\(_3\)MgCl up to a carbonyl group, which atoms would be attracted to each other? HINT: There are two general answers to this question, and two sub-answers to one of those. We are ultimately concerned with net reaction, so if you ask the question “Which negative group of the CH\(_3\)MgCl will most likely give up charge?” you will be on the right track.

4.1.2.6 Review: What might you expect for the immediate products of the reaction

\[
\text{CH}_3\text{C(O)CH}_3 + \text{CH}_3\text{MgCl} \rightarrow 
\]

As always, use epwa.
4.2 Functional Groups

Klein lists common functional groups on the frontispiece of the book. He gives 16 examples. Almost all of those will appear in this semester’s work.

4.2.1 Required Exercises

4.2.1.1 Distinguish between an amide and an amine; draw examples.

4.2.1.2 Distinguish between an amine and an imine; draw examples. HINT: An imine is a nitrogen with a double bond to a carbon.

4.2.1.3 Distinguish between an carboxylic acid and an alcohol; draw examples

4.2.1.4 Distinguish between an carboxylic acid and an aldehyde; draw examples.

4.2.1.5 Distinguish between a ketone and an aldehyde; draw examples.

4.2.1.6 Distinguish between an alkane and an alkene; draw examples.

4.2.2 Additional Exercises

4.2.2.1 Name the class of compound in compounds 32-38.

4.2.3 Nomenclature

Read Klein, Sections 4.2-4.3 (4.2-4.3) for the naming of alkanes, compounds of only carbon and hydrogen, with no double or triple bonds. These names always end in “-ane.”

Remarks. As you have already seen, we often just draw a compound rather than go through the rather laborious task of naming it. However, some familiarity with the naming scheme is necessary. Most compounds are named based on the carbon skeleton and Table 4.1 in Klein gives the code between number of carbons and the name. Some functional groups are named as substituents before the skeleton name and some are indicated by the ending of the skeleton name. Table 4.1 gives these features.
Table 4.1: Endings for Some Common Functional Groups.

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Name</th>
<th>Functional Group</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halides</td>
<td>As substituent before</td>
<td>Ketone</td>
<td>-one</td>
</tr>
<tr>
<td>Alkenes</td>
<td>-ene</td>
<td>Aldehyde</td>
<td>-al</td>
</tr>
<tr>
<td>Alkyne</td>
<td>-yne</td>
<td>Carboxylic Acid</td>
<td>-anoic</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-ol</td>
<td>Acid Halide</td>
<td>-anoyl halide</td>
</tr>
</tbody>
</table>

4.2.4 Required Exercises

4.2.4.1 Draw the line structure of 4-methyloctane.

4.2.4.2 Draw the line structure of 2,4-dimethyl-5-propyldecane.

4.2.4.3 Draw the line structure of 4-(1,1-dimethylethyl)decane.

4.2.4.4 The official names are called IUPAC (International Union of Pure and Applied Chemistry) names. Write the IUPAC name for 29-31.

4.2.4.5 Draw a line structure for 3-isobutylcyclopentanol.

4.2.4.6 Name 39-43.

4.2.4.7 If you have any doubts about how to understand using eqwa to predict a reaction, do exercises 4.2.5.6-4.2.5.11.

4.2.5 Additional Exercises

4.2.5.1 Name the class of compound (the functional group) in compounds 32-38. Then give the IUPAC name for the compounds.

4.2.5.2 The trivial name for a propyl group attached by the central carbon is “isopropyl”. Draw the line structure for 4-isopropyldecane.

4.2.5.3 The trivial name for a 1-methylpropyl group attached by carbon 1 is an “secondary butyl” group, usually abbreviated sec-butyl. Draw the line structure for 5-sec-butyldecane.
4.2.5.4 The trivial name for a 1,1-dimethylethyl group attached by carbon 1 is an “tertiary butyl” group, usually abbreviated tert-butyl or even t-butyl. Draw the line structure for 5-t-butyldecane.

4.2.5.5 Boniface Beebe, in his book, “A Grand View of Organic Chemistry”, published in 1896, described the preparation of a compound he called 4-ethyl-pentane. Although this conveys sufficient information for you to draw the compound, what should he have named it?

4.2.5.6 Consider CH$_3$Li and CH$_3$C(O)CH$_3$. Find the positively polarized and the negatively polarized atoms on each species. HINT: You have just been subtly introduced to a new “C−” reagent; do you recognize that?

4.2.5.7 Of the two negatively polarized atoms in the last exercise, which “wants” the negative charge least?

4.2.5.8 Draw a dotted line from the answer to the last exercise to the positively polarized atom of the other molecule.

4.2.5.9 Use epwa to move electrons.
4.2.5.10 What might you expect for the immediate products of the reaction
\[
\text{CH}_3\text{C(O)CH}_3 + \text{CH}_3\text{Li} \rightarrow
\]

4.2.5.11 Carry out the reaction in the last problem as step one of a two step process. The second step involves addition of H\(^+\). Use epwa to illustrate this second step. What is the net reaction?

4.3 Carbon Level

A useful concept for organizing reactions is carbon level or oxidation level. The carbon level of a given carbon atom is defined as the number of bonds from that carbon atom to electronegative elements. So a ketone has a carbon level 2 carbon atom in it. An alcohol has a carbon level 1 carbon in it.

4.3.1 Required Exercises

4.3.1.1 Give the carbon level in the compounds 39-43.

4.3.1.2 What is the carbon level of the carbons in acetone (propanone), ethanoic acid, ethanal, and carbon dioxide?

4.3.1.3 What are the carbon level of carbon atoms in CH\(_3\text{CH}_2\text{C(O)Cl}\), CH\(_3\text{C(O)H}\), CH\(_3\text{C(O)OCH}_3\)?

For reasons we will justify later in the course, the only odd issue with carbon level concerns compounds with double bonded carbon atoms. The carbon level in each carbon of a double bond is $\frac{1}{2}$ (or the pair has a carbon level of 1, sometimes called a delocalized carbon level 1 compound) and that of each carbon in a triple bond between two carbons, the carbon level of each carbon is 1 (or delocalized carbon level 2). What is the carbon level of each carbon in $\text{CH}_3\text{CHCHCl}$, $\text{HCCCH}_2\text{CH}_2\text{OH}$?

### 4.4 ihd

Search the index of Klein for “Hydrogen Deficiency Index” and read about it.

The concept of the “index of hydrogen deficiency,” what we will call, because we use it so often, $\text{ihd}$, is called by Klein the “Hydrogen Deficiency Index” or by Jones and Fleming the “degree of unsaturation.” It is a powerful tool to be used in structure determination from empirical formula. The formula looks a lot more complicated than its usage:

$$\text{ihd} = \frac{2n_C + 2 - n_H - n_F + n_N}{2}$$

where the $n_i$ are the number of atoms of the indicated elements or those valence shell isoelectronic with them. The answer must be an integer. For instance, $\text{CH}_3\text{CH}_2\text{F}$ has $n_C = 2$, $n_H = 5$, and $n_F = 1$, so the $\text{ihd}$ is zero; or $\text{C}_6\text{H}_6$ has $n_C = 6$ and $n_H = 6$, so $\text{ihd} = 4$.

What does $\text{ihd}$ tell us? It indicates the number of $\pi$ bonds and/or the number of rings in the compound. The first compound in the last paragraph has neither of either; on the other hand, $\text{C}_6\text{H}_6$ has 4 $\pi$ bonds, or 3 $\pi$ bonds and one ring, or ...

### 4.4.1 Required Exercises

4.4.1.1 Find the ihd for each compound in problem 4.3.1.2.

4.4.1.2 Find the ihd for each of the following compounds: $\text{C}_6\text{H}_{10}\text{Cl}_2$, $\text{C}_5\text{H}_{10}\text{O}$, $\text{C}_6\text{H}_{14}\text{O}_2$, $\text{C}_7\text{H}_{10}$. Use your result to draw appropriate Lewis structures. HINT: There is often more than one correct answer.

4.4.1.3 What is the ihd for a compound of formula $\text{C}_4\text{H}_9\text{N}$? Suggest a structure.

4.4.1.4 Find the ihd for each compound in problem 4.3.1.2.

---


CHM 222, SECTION 1 Patterns in Organic Chemistry
4.4.2 Additional Exercises

4.4.2.1 Boniface Beebe, the great natural philosopher from Searcy, Arkansas, looked at a compound with the formula $C_{24}H_{48}$. "Wow", he said, "as big as this is, it must contain a triple bond." Was Bonnie correct?

4.4.2.2 Suggest a possible structure for a compound of formula $C_6H_{12}O$.

4.4.2.3 Find the ihd and draw a structure for each of the following compounds: $C_3H_4$, $C_5H_9Cl$, $C_6H_{10}O$, $C_7H_{10}O_3$, $C_5H_5NH_2$, $C_4H_5N$, $C_6H_{12}S$, $C_5SiH_{14}$, $C_4H_{11}N$, $C_5H_5N$. HINT: What structure you draw and that another student draws may be very different, even though both of your could be correct. Life is hard!

4.4.2.4 Suggest a possible structure for a compound of formula $C_6H_{10}O$.

4.5 Nucleophiles and Electrophiles

Read Klein, Section 6.7. (6.7)

Remarks: We have not yet talked about acidity (or basicity); we soon will. But you have a general sense of this. An classic acid (usually called a Bronsted acid) is a substance that is capable of giving up $H^+$. A classic base is a substance capable of reacting with $H^+$. The property of a strong base is a substance that reacts efficiently with a proton, $H^+$. A nucleophile is a substance that reacts efficiently with another center, in our case, a carbon center. So a good classical base is usually a good nucleophile, but not always. An electrophile is an electron deficient atom that is capable of reacting with a pair of electrons (such as that provided by a nucleophile). These two words, nucleophile and electrophile, are simply the names we are giving to the centers that we identified as reactive centers when we set about determining reaction products using epwa–see problems 4.2.5.6-4.2.5.11. Another way to look at these terms: The atom on which a HOMO is most strongly concentrated is a nucleophilic center, as it is electron rich. The atom on which a LUMO is centered is a electrophilic center, as it is the position most likely to accept electrons.

4.5.1 Required Exercises

4.5.1.1 If you had a positively charged species, $E^+$, which is called an electrophile, and it came up to 39, what atom(s) would it likely attack? How about 40? How about 41? How about 2-butyne? HINT: Think where the homo is.
4.5.1.2 If you had a negatively charged species, \( \text{Nu}^- \), which is called a nucleophile, and it came up to 39, what atom(s) would it likely attack? How about 40-44?

4.5.1.3 From the name, what property does an “electrophile” have? HINT: Webster’s International Dictionary says: “Definition of -PHILE: lover: one having an affinity for or a strong attraction to, <acidophile > <Slavophile >.”

4.5.1.4 From the name, what property does a “nucleophile” have?

4.5.1.5 Would \( \text{H}^- \) be a nucleophile? Would \( \text{BH}_4^- \)? Which do you think would be “stronger?”

4.5.2 Additional Exercises

4.5.2.1 Guess the product of allowing \( \text{H}^- \) to attack butanal, followed by treatment with \( \text{H}^+ \). First identify the nucleophile, then the electrophile. Usually there two of each, maybe more; find the best of each. Then use epwa. Name the final product. HINT: Another issue with epwa. Most texts make the head of the arrow for an epwa that is making a bond go
to an atom. A few say this isn’t right, but do it anyway. You should not. You should have
the head of your epwa pointing to an atom only if a lone pair is being formed, in which case
that is where the electrons are going. If they are going to a new bond, then the head of
the arrow should point between the nuclei where the bond is forming, the infamous “dotted
line” that we, in this course, draw for a reason. See Figure 4.4

4.5.2.2 Guess why you have to do the two steps in problem 4.5.2.1 sequentially; that is,
why can you not add H\(^-\), the aldehyde, and H\(^+\) all together? HINTS: (1) Think electrostatic
attraction and write a balanced chemical reaction. (2) Most nucleophiles react with H\(^+\) (an
“acid/base” reaction) faster than with other electrophiles.

4.5.2.3 Would the hydrogen atom in AlH\(_4^-\) be more or less reactive than that in BH\(_4^-\)?
Why? HINT: As usual, think periodic position. REMARK: Oops, another “H^-” reagent!

4.5.2.4 If I told you that BH\(_4^-\) was not reactive enough to react with an ester (what
is an ester and what product am I looking for?), which it is not (at least in ethanol as a
solvent), would you throw your hands into the air or look for another reagent on the shelf?
What would it be? Why? HINT: Bonnie might throw up his hands, but perhaps you should
look at the last exercise.

4.6 Newman Projections and Single Bond Rotation

Read Klein, Sections 4.6-4.8. (4.6-4.8)

Remarks: Because there is no change in overlap with a rotation about a σ bond, this
is a relatively easy (energetically) thing to do. Be sure that you see the two features of
this rotation. Firstly, as one rotates about a carbon-carbon bond, there are two types of
conformations, the unstable eclipsed, and the more stable staggered. Each of these kinds is
influenced by the size of the substituents on the carbon atoms. The general idea is to keep
the large groups away from each other.

4.6.1 Required Exercises

4.6.1.1 Draw a Newman projection of ethane.

4.6.1.2 Draw a Newman projection of propane looking down the C\(_1\)-C\(_2\) bond.

4.6.1.3 Draw the gauche conformation of 1,2-dibromoethane.
4.6.1.4 Draw the anti conformation of 1,1,1-trifluorobutane looking down the appropriate bond.

4.6.1.5 How do isomers differ from conformers?

4.6.2 Additional Exercises

4.6.2.1 If you did Exercises 4.6.1.3 and 4.6.1.4 using Newman projections, draw the line structures. If you did those two problems using line structures, draw the Newman projections.

4.6.2.2 Draw Newman projections for each of the three minimum energies of 2-bromo-1,1-dichloroethane and indicate their relative stabilities.

4.6.2.3 Make a Newman projection for 3-methylpentane looking down the C₁-C₂ bond; down the C₂-C₃ bond. If there is more than one conformer, draw all of them.

4.6.2.4 Consider oxirane, a cyclic compound of formula C₂H₄O. Make a Newman projection looking down the C₁-C₂ bond. Can you see any reason why this structure might have some instability? NOTE: Oxiranes are also called epoxides, three membered rings with two carbon atoms and one oxygen atom. We shall learn how to synthesize them and how to open the ring to make interesting compounds.

4.7 Review: The Epwa Procedure and Reactions

We review again, by going through the steps, the critical thought process needed to make an intelligent guess about reactivity in some organic molecules. Consider AlH₄⁻ and ethanal, CH₃C(O)H. (1) Identify the positively and negatively polarized atoms in each of the molecules. In AlH₄⁻ the hydrogen atom is negatively polarized and the boron is positively polarized; in ethanal, the carbonyl carbon is positive and the carbonyl oxygen is negative. (3) Which negatively polarized atom is most likely to give up the negative charge? In the case of interest, it is between hydrogen and oxygen. Surely hydrogen will give up negative charge easiest. That is the start of the epwa, and since the only electrons available to hydrogen are those in one of the Al-H bonds, that is where the epwa starts. (4) The dotted line goes from that hydrogen to the positive atom of the other molecule, the carbonyl carbon. (5) Use epwa to move and you are then forced to break the carbon-oxygen π bond and move that electron pair to the oxygen atom. (6) Redraw what you have. The AlH₃ is not bonded and floats off. There is a new C-H bond and the oxygen atom carries the negative charge.
4.7.1 Required Exercises

4.7.1.1 Will $\text{H}_3\text{O}^+$ attack the oxygen atom or one of the carbon atoms of ethanal? Why? Use epwa to show the product.

4.7.1.2 If $\text{H}^+$ does attack the oxygen atom of ethanal, what happens to the electrophilicity of the carbonyl carbon? HINT: Read the question carefully.

4.7.1.3 Will $\text{OH}^-$ attack the carbon atom or oxygen atom of ethanal? Why? Use epwa to show the product.

4.7.2 Additional Exercises

4.7.2.1 Will $\text{OH}^-$ attack a carbon atom of CH$_3$C(O)Cl? Which carbon atom? Why? Use epwa to show the product. HINT: At the moment I don’t care too much if you plan a “substitution” or an “addition” although in this case it is rather obvious and we have discussed it. Later the question you should always ask is: Is there a group that can easily leave, that is, be stable when it leaves. If so, you have a “good leaving group;” the concept of acidity is the key to this analysis.

4.7.2.2 Use epwa to show the reaction of 45 with BH$_4^-$, followed by treatment of the immediate products with $\text{H}^+$.

4.7.2.3 Use the already stressed similarity between what happens with BH$_4^-$ and what should happen with CH$_3$MgCl to predict the product of the latter with 45. To finish the reaction, follow that first step with treatment with $\text{H}^+$.

4.7.2.4 Use epwa to show reaction of 46 with 47 followed by treatment with $\text{H}^+$. Make sure you keep track of charges.

4.7.2.5 Use epwa to show reaction of 46 with 48 followed by treatment with $\text{H}^+$.
4.7.2.6 What is the product of the reaction of the product of a Grignard reagent with acetone?

4.7.2.7 What happens if a Grignard reagent is treated with water? HINT: Think “C−” looking for something positive.

4.7.2.8 What happens if a Grignard reagent is treated with CO₂? HINT: Same as last exercise.

4.8 Synthesis

To be able to suggest how to prepare a compound is vital to understanding organic chemistry. This will be a recurring theme in this course. I think an efficient manner of solving synthesis problems is to identify the kind of the compound you are trying to make—usually a statement of the functional group—and then to ask yourself if you know of any way to make that kind of compound. At the moment the only kind of compound we really know how to make are alcohols, so the first step is easy. How do we make alcohols? An alcohol is a carbon level one compound and it is prepared from a carbon level two compound by adding something with loosely held electrons, H−, BH₄⁻, AlH₄⁻, Grignard reagent, or alkyl lithium reagent. The last two compounds put in a new carbon-carbon bond; the first three do not. So it would be good to know if you want to make a new carbon-carbon bond or not. Also, remember that the last two reagents in the list above are made from alkyl halides and either magnesium metal or lithium metal, respectively.

As an example: We want to synthesize 2-pentanol from 46. Both the starting molecule and the product have five carbon atoms, so we do not need any new carbon-carbon bonds. The starting material is a carbon level two compound, so we need an electron rich reagent to convert it down to carbon level one, the alcohol. Hence reaction of 46 with H−, BH₄⁻, or AlH₄⁻, followed by H⁺ would achieve our goal.

4.8.1 Required Exercises

4.8.1.1 What is the product of reaction of 2-iodopropane with Mg metal?

4.8.1.2 How would you synthesize 47 from chloroethane?

4.8.1.3 What kind of compound is 49?

4.8.1.4 You can make [answer to last exercise]s from what kind of compounds? And the answer is?
4.8.1.5 How would you synthesize 49 (also known as “Molecular Woman with Lopsided Hat”)? HINT: Can you really do it with BH\text{4}^-? Why or why not?

4.8.2 Additional Exercises

4.8.2.1 What is the product of reaction of 2-chlorobutane with Mg metal?

4.8.2.2 How would you synthesize 2-methyl-2-propanol from acetone? Write a mechanism using epwa.
Chapter 5

Mass Spectroscopy

5.1 Introduction

Read Klein, Section 15.8 (15.8)

We use mass spectroscopy only slightly in this course. The key to our usage involves the molecular radical ion which is the molecule with one electron knocked out. It is an ion, a cation to be precise, because of the loss of that electron. It is a radical because it has an odd number of electrons. We therefore symbolize this species as $M^+\cdot$. Since the mass of the electron is small compared to that of nuclei, the mass of the molecular radical ion is essentially the same as that of the unionized material from which it arose. Although modern spectrometers are capable of distinguishing more finely, we shall stick with “integer” mass units: $\text{CH}_4^+\cdot$ would have a peak at 16 mass units.

5.1.1 Required Exercises

5.1.1.1 Octane would have a molecular ion peak at what mass number?

5.1.1.2 At what mass numbers would the $M^+\cdot$ peaks be for the following compounds: $\text{C}_5\text{H}_{10}\text{O}$, $\text{C}_5\text{H}_8\text{F}_2$, $\text{C}_3\text{H}_6$?

5.2 Fragmentation

Read Klein, Section 15.8 (15.8)

After the electron is removed, the molecular radical ion can also break into smaller fragments. The ions of these fragments are also detected in the mass spectrum. Hence we have a number of peaks, one with the mass of the molecular radical ion and peaks of smaller
mass.

5.2.1 Required Exercises

5.2.1.1 In the mass spectrum of a compound there are major peaks at 27, 39, 41, 55, 56, 69, and 84. If the compound contains only C and H, what is the formula? HINT: Find the M^+ peak and use ihd.

5.3 Nitrogen Compounds

Read Klein, 15.9. (15.9)

Compounds with an odd number of nitrogen atoms in them exhibit molecular masses with an odd integral value. When you see this, it is highly suggestive of a nitrogen atom in the molecule.

5.3.1 Required Exercises

5.3.1.1 Why do compounds with an odd number of nitrogen atoms have an odd mass number for the molecular ion when the mass of N is 14. HINT: Think about typical groups that are isovalent with the NH_2 group.

5.4 Bromine and Chlorine Containing Compounds

Read Klein, Section 15.11. (15.11)

For Br, there are two common isotopes, ^79\text{Br} and ^81\text{Br}. These occur in nearly equal quantities in nature. A consequence of this is that compounds containing a bromine atom have two equally intense peaks at the high limit of peaks. These peaks are usually called the M^+ and (M+2)^+ peaks. Two peaks, two units apart, of equal intensity with no significant higher peaks above them (see, however, Section 5.5) means the molecule contains a bromine atom.

The common isotopes of Cl are ^35\text{Cl} and ^37\text{Cl}; the former is three times as abundant as the latter. Thus compounds containing a chlorine atom have two peaks at the high limit with a relative intensity of about 3:1.
5.4.1 Required Exercises

5.4.1.1 What would the masses of the molecular ions be for ethyl bromide and what are their relative intensities? HINT: Look carefully at the grammar of the question, especially the (correct) use of plurality.

5.4.1.2 A compound has molecular ion peaks (judged to be so because there is nothing at a higher mass number) of 136 and 138 of about equal intensity. Make an intelligent guess as to the identity of the compound.

5.4.1.3 A compound has “molecular” peaks in the mass spectrum at 135 and 137 of about equal intensity. What can you say about this compound? HINT: Think. There is more information here than what first meets the eye; try to find it all.

5.4.1.4 What would the masses of the “molecular ions” be for 3-chlorohexane and what are their relative intensities? HINT: Again, the use of a plural.

5.5 $^{13}$C Issues

Read Klein, Section 15.10. (15.10)

There is an isotope of carbon, $^{13}$C, which has an abundance of 1.1%. This means that for every 1000 carbon atoms, you will find 11 atoms with the heavier isotope. Compounds containing carbon with lots of carbon atoms often show a small peak one unit in mass higher than the molecular ion peak due to the 1.1% of carbon that is $^{13}$C. See if you can convince yourself that if you have a compound containing five carbons (each of which has a 1.1% chance of being a $^{13}$C) that the relative height of the (M+1)$^+$ peak relative to the M$^+$ peak will be 0.055/1.

The following formula gives the number of carbon atoms in a compound, $n_C$.

$$n_C = \frac{I_{M+1}}{I_M} \times \frac{0.011}{I_{M+1}}$$

where $I_M$ and $I_{M+1}$ are the intensities of the M$^+$ and (M+1)$^+$ peaks, respectively.

5.5.1 Required Exercises

5.5.1.1 A compound has “molecular” peaks in the mass spectrum at (mass, (intensity)) 76 (25.3); 77 (0.9); 78 (8.0); and 79 (0.3). What can you say about this compound? HINT: This course is trying to get you to put arguments together to arrive at a logical conclusion.
5.5.1.2 A substance of formula $C_8H_{16}O$ has a molecular ion peak in the mass spectrum with intensity of 24.3. What would you expect for the intensity of the peak at $M^+\cdot$ of 129?

5.5.1.3 A compound has a mass spectrum with peaks at 186 and 188 of equal intensity, say 100, and peaks at 187 and 189 of 7.8. What can you say about the compound?

5.5.2 Additional Exercises

5.5.2.1 The compound in the exercise 5.5.1.3 has additional peaks in the mass spectrum: at 171 (51 units), 172 (3.3 units), 173 (52 units), and 174 (3.4 units). Can you say anything about what fragment was lost from the original molecular ion?

5.5.2.2 Here are some “fudged” data, manipulated to make your analysis easier. A compound has mass spectrum peaks at 92 (intensity = 70.0) and 93 (5.5). How many carbons are in the material?

5.5.2.3 Here is the real data for the compound in the last problem. The peaks and intensities near the molecular ion peak are: 91 (100), 92 (77.7), and 93 (5.5). Figure out why and how I “fudged” the data. Be sure you see that because I “fudged” the data in the last problem, that problem was much easier than it might have been. HINT: Think about the number of carbons likely in that peak at 91 and the consequences for the peak at 92.
Chapter 6

Infrared Spectroscopy

6.1 General Considerations

Read Klein, 15.1-15.3. (15.1-15.3)

In contrast to mass spectroscopy, which does not involve quantum levels, most other spectroscopic tools in organic chemistry involve the transition from one allowed energy level to another. A system has its energy changed from one allowed motion to another by a photon whose energy exactly matches that of the energy gap. In infrared spectroscopy the energy levels are the various vibrations of the molecule, including bond stretching processes as well as bond bending motions. The gaps in infrared spectroscopy that we are interested in depend on the strength of the bond, as measured by a quantity called the force constant, generally symbolized with a “k”, and the reduced mass of the two atoms involved in the bond, $\mu$. The reduced mass is given by $\left(\frac{m_1 m_2}{m_1 + m_2}\right)$ where $m_i$ is the mass of the atom. The formula giving an approximation to the energy gap is given by:

$$\Delta E = h \sqrt{\frac{k}{\mu}}$$

Thus strong bonds involving small masses occur at high energies—see following sections.

The presentation of infrared data requires some comment. As opposed to most modern spectroscopic methods, IR data is usually presented as transmittance, not as absorbance. Hence, although we will continue to refer to peaks in the spectrum, they actual situation is that they are presented as valleys. Secondly, IR spectra are usually presented with an ordinate that goes from high energy (on the left) to low energy (on the right); the units are usually the reciprocal of the wavelength of the absorbance, or “wave number.”
6.1.1 Required Exercises

6.1.1.1 The frequency at which a peak occurs in the IR spectrum caused by a bond stretch is governed by the equation:

\[ \nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \]

where \( k \) is the force constant, a measure of the bond strength, and \( \mu \) is the reduced mass, equal to \( \frac{m_1 m_2}{(m_1 + m_2)} \). Why do C-H, O-H, and N-H bond stretches occur at higher \( \nu \) than C-C, O-C, or N-C stretches?

6.1.1.2 Why does a carbon-carbon double bonds stretch occur at higher \( \nu \) than a carbon-carbon single bond stretch?

6.1.2 Additional Exercises

6.1.2.1 Where would you expect double bonded carbon-oxygen (C=O) stretches to occur relative to single bonded C-O stretches?

6.1.2.2 Where would you expect the stretches of triple bonded carbon-carbon species to occur relative to double bonded carbon-carbon molecules?

6.1.2.3 Where would you expect double bonded carbon-sulfur stretches to occur relative to double bonded carbon-oxygen stretches? HINT: If there are multiple factors, and there are in this question, then you should examine all of them.

6.2 C-H Bond Stretches

Read Klein, Section 15.6. (15.6)

The strength of carbon-hydrogen bonds depends upon the hybridization of the carbon atom. Bonds with sp hybridized carbon-hydrogen bonds occur at higher energies than sp\(^2\) carbon-hydrogen bonds, which occur at higher energies than sp\(^3\) carbon-hydrogen bonds. The approximate values of the wave numbers for these three are given in Table 6.1. The aldehyde C-H bond absorbs in a unique position; this is also given in the table.

Important note. Remember when you are given a empirical formula in any exercise to apply the ihd rule to learn what is true of the compound in terms of the number of double bonds and rings.
6.2.1 Required Exercises

6.2.1.1 You have two compounds of formula C₆H₁₂. Compound A has peaks in the IR at 3016, 2861-2961, 1658 cm⁻¹ and a bunch of stuff in the region below 1500 cm⁻¹. Compound B has peaks at 2853-2928 cm⁻¹ and a bunch of stuff below 1500 cm⁻¹. Which is cyclohexane? Why do you reach this conclusion?

6.2.1.2 A compound is synthesized that could be either 1-pentene or 1-pentyne. How could you use IR to determine which it is?

6.3 E-H Stretches

There are a few other stretches involving a bond to a hydrogen atom that are of concern to us. Two of these are the O-H stretch in alcohols and carboxylic acids, and the N-H stretch in various compounds. These occur at slightly higher frequency (energy) than the sp³ C-H stretches, but, more importantly, in the liquid phase are almost always broad, strong peaks. The O-H stretch in alcohols occurs in the range from 3200-3500 cm⁻¹ and the O-H stretch in carboxylic acids occurs a little lower, near 3000 cm⁻¹. Again these are broad; the last can extend from 2500-3300 cm⁻¹. The N-H stretch occurs in a similar region to that of the O-H stretch and is also broad. They are difficult to distinguish, except when the group is an NH₂ group. This almost always has a pair of peaks: tip off!

6.3.1 Required Exercise

6.3.1.1 A compound has an IR peak in the region from 2800-3000 cm⁻¹. If you were given the choice of assigning the compound to diethylether or butanol, which would you choose?

6.3.1.2 Predict where you would expect 1-butanamine to absorb.
Table 6.2: C-E double and triple bond stretching frequencies

<table>
<thead>
<tr>
<th>Bond</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C double bond C</td>
<td>1600-1680 cm$^{-1}$</td>
</tr>
<tr>
<td>C double bond O</td>
<td>1690-1800 cm$^{-1}$</td>
</tr>
<tr>
<td>C double bond N (rare)</td>
<td>1640-1680 cm$^{-1}$</td>
</tr>
<tr>
<td>C triple bond C</td>
<td>2250-2300 cm$^{-1}$, weak</td>
</tr>
<tr>
<td>C triple bond N</td>
<td>about 2250 cm$^{-1}$, strong</td>
</tr>
</tbody>
</table>

6.4 Double and Triple Bonds to C

Double and triple bonds between a carbon atom and another element are strong; hence the force constant, $k$, is large, and the energy (frequency) of these bonds are reasonably large. Table 6.2 gives typical values. As an added note, the C triple bond C frequency is often quite weak; indeed, it sometimes does not show up.

6.4.1 Required Exercises

6.4.1.1 You are analyzing an IR and find a rather weak and narrow peak near 1675 cm$^{-1}$. Given the weakness, should you ignore it or instantly check elsewhere in the spectrum? HINTS: (1) Why would I ask if the answer wasn’t obvious? (2) Learn to “pursue” your analysis to conclusions that are certain. (First of many times this will be said.)

6.4.1.2 What can you say about the following compounds given their IR spectra in the functional group region (all reported in units of cm$^{-1}$). A 3410 sharp, 2900-3000, 2150 sharp, but weak; B 3400 broad, 2900-3020; C 2850-3000, 2710, 1725.

6.4.1.3 What carbon level is the carbon atom in CH$_2$O? What carbon level is the carbon atom in CH$_3$OH? How could you use IR to distinguish between the two?

6.4.2 Additional Exercises

6.4.2.1 What is the product when CH$_2$O is treated with 1) BH$_4^-$ followed by 2) H$^+$? How could you use IR to tell if the reaction occurred?

6.4.2.2 A student treats 3-hexanol with PCC (a Cr(VI) compound officially called pyridinium chlorochromate, C$_5$H$_5$NH$^+$CrClO$_3$ $^-$, which we will use extensively later in the semester; it is a good oxidizing agent) to try to form 3-hexanone. What should she look for in the IR to verify that reaction occurred? HINT: Remember a good scientist looks for confirmation of observations.
6.4.2.3 What is happening in this reaction?

\[ \text{CH}_3\text{C(O)CH}_3 \quad \xrightarrow{1.\text{BH}_4^-/2.\text{H}^+} \quad \text{CH}_3\text{CH(OH)CH}_3 \]

HINTS: (1) An answer in several different manners would be nice: carbon level; oxidation/reduction; kinds of compounds destroyed, formed. (2) Unless you are sure what you are seeing, write out the reaction in our normal line (zig-zag) form. How would you detect reaction using IR? HINT: The notation 1. blah blah, 2. yap yap means add the first reagent, wait for reaction, then add the second.

6.4.2.4 What is happening in this reaction?

\[ \text{CH}_3\text{C(O)CH}_3 \quad \xrightarrow{1.\text{CH}_3\text{MgI}/2.\text{H}^+} \quad (\text{CH}_3)_3\text{COH} \]

HINTS: (1) An answer in several different manners would be nice: carbon level; oxidation/reduction; kinds of compounds destroyed, formed. (2) Unless you are sure what you are seeing, write out the reaction in our normal line (zig-zag) form. How would you detect reaction using IR?

6.5 Practice with IR

Read Klein, Section 15.7. (15.7)

6.5.1 Required Exercises

6.5.1.1 What can you say about the compound whose IR is given in Figure 6.1?

6.5.1.2 What can you say about the compound whose IR has, in addition to the normal peaks, a broad peak at 3100 cm\(^{-1}\) and a intense, slightly broadened, peak near 1720 cm\(^{-1}\).

6.5.1.3 What can you say about the following compounds given their IR spectra in the functional group region (all reported in units of cm\(^{-1}\)). A 3450-3600, broad with some sharp peaks on top of it in the 2950-3000 region, 1723 intense; B 3450-3600, broad with some sharp peaks on top of it in the 2950-3000 region, 1700 intense, 1650 sharp; C broad peak centered at 3350, 3080 sharp,1650, sharp.

6.5.1.4 Figures 6.2 and 6.3 give two IR spectra, both of compounds of the formula C\(_5\)H\(_{10}\)O. Find a structure that is consistent with each spectrum.
Figure 6.1: IR for Problem 6.5.1.1
Figure 6.2: IR for Problem 6.5.1.4
Figure 6.3: IR for Problem 6.5.1.4
6.5.1.5 Propanal, whose IR spectrum has an interesting peak at 1740 cm$^{-1}$ reacts with a reagent to produce a compound whose spectrum no longer has the 1740 cm$^{-1}$ peak, but now has an interesting peak at 3350 cm$^{-1}$; this peak is broad and strong. What can you say happened in the reaction? HINT: By “interesting” I mean within the context of this problem.

6.5.2 Additional Exercises

6.5.2.1 Make a summary of the position, intensity, and broadness of peaks caused by various X-H stretches in the region between 2700 and 3600 cm$^{-1}$.

6.5.2.2 Make a summary of the position, intensity, and broadness of peaks caused by various stretches in the region between 1500 and 1800 cm$^{-1}$. HINT: I am looking for only two entries in your list.

6.5.2.3 The force constants for the C-H bond and the C-C bond are about the same. Yet the C-H bond stretch occurs at a much higher wave number than does the C-C stretch, which is buried in the “garbage” below 1500 cm$^{-1}$. Why?

6.5.2.4 Two isomers of C$_4$H$_6$O, A and B, are both symmetric. Isomer A has IR peaks at 3090 and 1620 cm$^{-1}$, whereas isomer B has peaks at <3000 and 1780 cm$^{-1}$. Neither material absorbs in the 3300-3700 cm$^{-1}$ region. Propose structures for the two isomers.

6.5.2.5 Without looking at any tables or books, at roughly what energy (units of wave number) do carbonyl compounds absorb in the IR?

6.5.2.6 Without looking at any tables or books, at roughly what energy (units of wave number) do alcohols compounds absorb in the IR?

6.5.2.7 Are 2-butanone and but-2-en-1-ol isomeric? Do they have the same ihd? How could you use IR to distinguish between 2-butanone and but-2-en-1-ol?

6.5.2.8 How would you distinguish between compounds 1 and 2 using IR?

6.5.2.9 Here are three IR spectra, A, B, and C. Spectrum A: <3000 including 2700; 1722 cm$^{-1}$; Spectrum B: Broad peak with two maxima 3200-3400, <3000, broad peak 1620-1680 cm$^{-1}$; Spectrum C: 3110, <3000, 1645 cm$^{-1}$. Assign each spectrum to one of the compounds 3-7.
6.5.2.10  Review. What would be the product of the reaction of 2-hexanone with BH$_4^-$, followed by H$^+$?

6.5.2.11  How could you use IR to tell when the reaction between 2-hexanone and BH$_4^-$, followed by H$^+$, was complete?

6.5.2.12  Review. What would be the product of the reaction of 2-hexanone with CH$_3$MgI, followed by H$^+$?

6.5.2.13  How could you use IR to tell when the reaction between 2-hexanone and CH$_3$MgI, followed by H$^+$, was complete?
Chapter 7

NMR

7.1 Introduction

Read Klein, Sections 16.1-16.2. (16.1-16.2)

The most powerful tool for assigning structure in nuclear magnetic resonance, almost always labeled nmr. This is a subject with some level of complication, and our approach will be to do the simple first and then introduce complication as we proceed.

Just as electrons have spin, so do certain nuclei. Spin is a quantum mechanical phenomenon of considerable importance. One way in which spin manifests itself is through the interaction of quantum particles with a magnetic field. Hydrogen nuclei (and later we will talk about $^{13}\text{C}$ also) have a spin of 1/2 and this can align either with or against a magnetic field. These two states have slightly different energies that depends on the strength of the field that the nuclei “sees,” being larger the larger that field.

7.2 Equivalent Hydrogen Atoms

Read Klein, Section 16.4. (16.4)

Hydrogen atoms in the same environment “see” the same magnetic field. It is critical that you be able to tell the number of different hydrogen atom environments in a molecule. To do this, always take into account the ease of rotation about a $\sigma$ bond. For instance, draw Newman projection of chloroethane. On the CH$_3$ group, there are two kinds of hydrogen atoms in your drawing. But, because of free rotation about the $\sigma$ bond, there is, on average (and the nmr experiment is “slow” so that average environments matter), there is only one average environment. Be sure you get used to this feature.
### 7.2.1 Required Exercises

#### 7.2.1.1
Are all the hydrogen atoms in the same environment in 10? in 11? in 12? in 13?

#### 7.2.1.2
How many different environments are there in the compounds of the last exercise that don’t have only one environment?

#### 7.2.1.3
How many $^1$H nmr signals will we see for each of the compounds 14-17? HINT: If you have heard of it, ignore spin-spin coupling.

### 7.2.2 Additional Exercises

#### 7.2.2.1
The $^1$H nmr spectrum of toluene shows a sharp peak at 2.28 δ and a broader peak at 7.1 δ. How many different peaks should be present in toluene (which is the trivial name for methylbenzene)? Account for the observed spectrum. HINT: You might use the words “accidentally equivalent” in your answer.

### 7.3 Shielding

Read Klein, pp. 743-747. (730-734)

One of the causes of a different field at the nucleus when all the hydrogen atoms are in the same external magnetic field is the presence of electrons around the nucleus. Under the influence of the external field, the electrons around the nucleus move in such a way as to create an “induced” field that is in the opposite direction to the external field. These two fields add as vectors to create a smaller net field at the nucleus, and hence the energy of the transition between the two spin states is decreased. The more electrons, the greater
Table 7.1: Chemical Shifts of Methine, Methylene, and Methyl Groups, δ, in ppm.

<table>
<thead>
<tr>
<th></th>
<th>X-CH-R$_2$</th>
<th>X-CH$_2$-R</th>
<th>X-CH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH$_2$-</td>
<td>1.5</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>F-</td>
<td>4.8</td>
<td>4.45</td>
<td>4.25</td>
</tr>
<tr>
<td>Cl-</td>
<td>4.05</td>
<td>3.45</td>
<td>3.05</td>
</tr>
<tr>
<td>ClCH$_2$-</td>
<td>1.95</td>
<td>1.80</td>
<td>1.50</td>
</tr>
<tr>
<td>HO-</td>
<td>3.95</td>
<td>3.55</td>
<td>3.2</td>
</tr>
<tr>
<td>RCC-</td>
<td>2.8</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>C$_6$H$_5$O-</td>
<td>4.5</td>
<td>4.05</td>
<td>3.85</td>
</tr>
<tr>
<td>RC(O)-</td>
<td>2.65</td>
<td>2.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

7.3.1 **Required Exercises**

7.3.1.1 All bare protons in a magnetic field of fixed strength have a transition between the two spin states (up and down) at the same energy (and that energy is calculated to be at about 40 ppm). Why do hydrogen atoms in different environments in molecules have signals at different energies?

7.3.1.2 Table 7.1 gives the chemical shift (δ in units of ppm) of compounds with methyl, methylene (-CCH$_2$-), and methine (C$_2$CH-) hydrogen atoms. For instance, the signal due to the methylene protons in CH$_3$CH$_2$OH would occur at approximately 3.55 δ. What do you learn about the relative chemical shift of methine versus methylene versus methyl hydrogen atoms when the X group on the carbon is the same?

7.3.1.3 What do you learn about the position of a CH$_3$C(O)R signal? HINT: When I see a signal at δ = 2.1 ppm, I hear “ding, (pause), ding, (pause) ding” and I burst into song: “It’s three o’clock in the morning, we’ve danced the whole night thru . . . ” written
Figure 7.1: Schematic plot of the energy levels of the two spin states of a hydrogen nucleus. The vertical scale on the left part of the diagram is energy, while the abscissa is the magnetic field strength. On the right side of A are shown the large shielding field from a hydrogen atom with lots of electrons, and the resulting net field, which generates a transition as indicated by the red arrow in A; this is a low energy transition. On the right side of B is shown a hydrogen atom with few electrons, and the resulting net field, which generates a transition as indicated by the green arrow in B; this is a high energy transition.
Table 7.2: Chemical Shifts of Various Fragments

<table>
<thead>
<tr>
<th>Fragment</th>
<th>δ</th>
<th>Fragment</th>
<th>δ, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkene-CH₃</td>
<td>1.7</td>
<td>C₆H₅-H</td>
<td>6.5-8.0</td>
</tr>
<tr>
<td>alkene-H</td>
<td>4.5-6.0</td>
<td>C₆H₅−CH₃</td>
<td>2.3</td>
</tr>
<tr>
<td>alkynyl-H</td>
<td>2.5</td>
<td>C(=O)−H</td>
<td>9.0-10.0</td>
</tr>
<tr>
<td>R−NH₂</td>
<td>1.5-4.0</td>
<td>RC(O)O−H</td>
<td>10-12</td>
</tr>
<tr>
<td>RCH₂O−H</td>
<td>2-5</td>
<td>C₆H₅O−H</td>
<td>4-7</td>
</tr>
</tbody>
</table>

by Theodora Morse (as Dorothy Terriss) and Julian Robledo in 1921.

7.3.1.4 From Table 7.1, what do you learn about a CH₃-C signal compared to a CH₃-O signal? HINT: The professional would use words like “deshielded” or “shielded.” What would you expect?

7.3.1.5 From Table 7.1, what do you learn about the methyl group signal in CH₃CH₂Cl compared to the methyl group signal in CH₃Cl? What would you predict for the methyl group signal in CH₃CH₂CH₂Cl?

7.3.1.6 Table 7.2 lists the chemical shift of some hydrogen atoms in compounds that you should know. NOTE: All data are approximate and will vary from molecule to molecule. Similar data is also available on the chemistry department web page under “Resources”. If you had a compound with a signal near δ = 5 ppm, what structural feature would you suspect was in your molecule?

7.3.2 Additional Exercises

7.3.2.1 Which of the following hydrogen nuclei would you expect to have a signal most shielded (near TMS, that is, (CH₃)₄Si, the zero of the hydrogen nmr scale), lower δ, and which least shielded (near CHCl₃), higher δ? a. R₂BCH₃, b. CH₂F₂, c. CCl₃CHClCCl₃,d. N(CH₃)₄⁺. HINTS: (1) “R” is just some unspecified collection of carbon and hydrogen atoms. (2) Be careful with the last compound; think about what causes chemical shifts.

7.3.2.2 Boniface Beebe, the highly admired natural philosopher of Searcy, Arkansas, wrote: “I have an proton with a signal at about δ 4.0. There must be an ‘H of an OH’ in my sample.” What would you say to Bonnie?

7.3.2.3 Which member of each pair would you expect to have the most deshielded signal? a. CH₃Cl or C₂H₆; b. CCl₃CH₃ or CF₃CH₃; c. CH₃R or CH₂ClR; d. RC(O)CH₃ or RCH₃. HINT: R is, as usual, a non-electronegative/non-electropositive group typically containing C and H atoms.
7.4 Area, or “Integration”

Read Klein, Section 16.6. (16.6)

Another useful tool in $^1$H nmr is the area under the curve for a signal. This is also called the “integration.” The area under a signal is proportional to the relative number of hydrogen atoms in that signal. In practice, these areas are only approximate, but the tool is useful. For instance, in the nmr of CH$_3$CH$_2$Cl we will see two signals, the deshielded signal (also known as the “downfield” signal) with an area that is $2/3$ of that of the more shielded signal.

7.4.1 Required Exercises

7.4.1.1 Predict the approximate positions of the signals and their relative areas in the $^1$H nmr spectrum of CH$_3$C(O)OCH$_3$.

7.4.1.2 Predict the approximate position of the signal(s) in the $^1$H nmr spectrum for compounds 18-20. Give integrations. HINTS: (1) You may treat all of the hydrogen atoms in a benzene rings as equivalent for now. (2) You should neglect spin-spin coupling in this problem.

7.4.1.3 How would you distinguish between 21 and 22 using $^1$H nmr (ignoring spin-spin coupling)?

7.4.1.4 A compound of formula C$_3$H$_6$O has only one peak in the nmr spectrum. Give a structural formula for this compound? HINT: Use ihd.

7.4.1.5 How would you, in principle, distinguish between 23 and 24 using $^1$H nmr (ignoring spin-spin coupling)?
7.4.1.6 How would you distinguish between 25 and 26 using $^1$H nmr (ignoring spin-spin coupling)?

7.4.1.7 Predict the approximate positions of the signals and their relative areas in the $^1$H nmr spectrum of 2-bromobutane.

7.4.1.8 A compound of formula $C_3H_6Cl_2$ has only one peak in the nmr spectrum. Give a structural formula for this compound?

7.4.1.9 Find the number of $^1$H signals, predict their positions, and state their relative areas for compounds 27-30. HINT: Treat all protons on the benzene ring as if they were “accidentally degenerate.”

7.4.1.10 How many $^1$H nmr signals in 31-33? HINTS: (1) If you think about the ring as being planar (it isn’t, but that works, as we will see), and consider hybridization for four coordinate carbons, you will find the first two molecules have a top and a bottom side. (2) This makes the first two problems somewhat challenging.

7.4.2 Additional Exercises

7.4.2.1 A compound of formula $C_4H_9Br$ has three $^1$H nmr signals, one at about $\delta = 1.0$ ppm (Area 3), a second at 2.0 ppm (0.5) and a third at 3.3 ppm (1). What is the compound? HINTS: (1) If you have heard of spin-spin splitting, ignore it for this problem. (2) As always, if given a formula, use ihd.

7.4.2.2 In the last exercise, articulate how you handled the relative areas given the total number of hydrogen atoms in the molecule was 9.
7.4.2.3 A compound with the formula $C_7H_{14}O$ has two $^1H$ nmr signals. What is the compound? HINT: If you have heard of spin-spin coupling, ignore it.

7.4.2.4 In the last exercise, articulate what you can conclude from the relative simplicity of the nmr spectrum and the complicated formula with 14 hydrogen atoms.

7.4.2.5 A compound with the formula $C_5H_{12}O$ has $^1H$ nmr signals at $\delta = 3.2$ ppm (20) and 1.2 ppm (59). What is the compound?

7.4.2.6 A compound with the formula $C_9H_{10}O_2$ has $^1H$ nmr signals at $\delta = 7.4$ ppm (108), 5.2 ppm (45) and 2.2 ppm (66). What is the compound? HINTS: (1) Last time: As always when given a formula, use ihd. (2) Ignore spin-spin coupling and treat all protons on a benzene ring as if they are in one environment.

7.4.2.7 How many $^1H$ nmr signals will the product of the reaction of 3-pentanone with ethylmagnesium Grignard have (after acidification) in the $^1H$ nmr spectrum? HINT: Ignore spin-spin coupling.

7.4.2.8 Bromomethyl-methyl ether has an $^1H$ nmr spectrum with signals at $\delta = 5.7$ ppm (2) and 3.2 ppm (3). Assign the peaks to hydrogen atoms in the structure.

7.4.2.9 1-Bromo-2-methylpropane has an $^1H$ nmr spectrum with signals (ignoring spin-spin coupling) at $\delta = 1.05$ ppm (6), 1.98 ppm (1) and 3.3 ppm (2). Assign the peaks to hydrogen atoms in the structure.

7.4.2.10 A compound of formula $C_7H_{14}O$ has the following $^1H$ nmr spectrum (with integration): $\delta = 1.0$ ppm (Area 18) 2.1 ppm (6), and 2.3 ppm (4). What is the compound?

7.4.2.11 A compound of formula $C_9H_{13}N$ has the following $^1H$ nmr spectrum (with integration): $\delta = 2.25$ ppm (3) 3.4 ppm (1), and 7.3 ppm (2.5). What is the compound? Be sure that you can account for the values of the various chemical shifts. HINT: You may need those “accidentally equivalent” words again.

7.4.2.12 How would you use chemical shift and integration to distinguish between HCCCH$_2$OH and H$_2$C=CHC(O)H? HINT: Make sure you have the Lewis structures before you answer.
7.4.2.13 A compound with the formula C\textsubscript{6}H\textsubscript{3}Cl\textsubscript{2}(NO\textsubscript{2}) has an \(^1\text{H}\) nmr spectrum (with integration): \(\delta = 7.63\) ppm (1) 8.09 ppm (1), and 8.36 ppm (1). What structures are not possible? HINTS: This compound has a benzene ring; and the signals in that ring are not accidentally degenerate. (2) The problem ignores spin-spin coupling. (3) The formula implies that the compound contains an -NO\textsubscript{2} group (isovalent with H) and not some other combination of N and O.

7.4.2.14 Using chemical shift and integration data only, how would you distinguish between 34 and 35?

7.5 Ring Current and Anisotropy

Read Klein, pp. 747-749. (734-736)

We have talked about a field that opposes the external field caused by electrons rotating about the hydrogen nucleus. If the molecule has the proper kinds of orbitals, there can also be rotation of electrons within the molecule as a whole that causes a field. This can occur in benzene, C\textsubscript{6}H\textsubscript{6}, where the electrons can rotate within the \(\pi\) framework of the molecule. See Figure 16.9. in Klein. Notice that this field “bites its own back” and although it is oriented downward at the center of the rotation, the center of the ring, it is going upward when it strikes the hydrogen nuclei. Hence this field supports the external field and causes the peak to occur at higher energy, de-shielded. The vector diagram for this is given in Figure 7.2.

The same process can occur with triple bonded carbon atoms, but now the rotation is about the bond axis and the hydrogen atoms above and below the axis see a ring current field that is opposed to the external field. This is shown schematically in Figure 7.3. The effect on the NMR signal of a hydrogen atom attached to a double bond is shown in Figure 7.4.

7.5.1 Required Exercises

7.5.1.1 Briefly indicate why the hydrogen atoms attached to an sp\textsuperscript{2} carbon on a benzene ring have signals that are de-shielded relative to that of an alkene.

7.5.1.2 Briefly indicate why the hydrogen atoms attached to an sp carbon of an alkyne have a signal that is shielded relative to that of an alkene.
Figure 7.2: Schematic plot of the the energy levels of the two spin states of a hydrogen nucleus. The vertical scale on the left part of the diagram is energy, while the abscissa is the magnetic field strength. On the right side of A are shown the large shielding field from a hydrogen atom with electrons, and the resulting net field, which generates a transition as indicated by the red arrow in A; this is a low energy transition. On the right side of B is shown a hydrogen atom with the same number of electrons (same “shielding field,” but on a benzene ring so that the “ring current field” supports the external field and causes a shift to higher energy (de-shielded). This is shown by the green arrow in B.
Figure 7.3: Schematic plot of the induced magnetic field caused by the $\pi$ electrons of a triple bond. Note both of the hydrogen atoms see a field that is pointed against the external field. This leads to a shielding effect of the induced field, in contrast to that found in the benzene case, see Figure 7.4.
Figure 7.4: Schematic plot of the energy levels of the two spin states of a hydrogen nucleus. The vertical scale on the left part of the diagram is energy, while the abscissa is the magnetic field strength. On the right side of A are shown the large shielding field from a hydrogen atom with electrons, and the resulting net field, which generates a transition as indicated by the red arrow in A; this is a low energy transition. On the right side of B is shown a hydrogen atom with the same number of electrons (same “shielding field,” but on a alkyne so that the “ring current field” works against the external field and causes a shift to lower energy (shielded). This is shown by the green arrow in B.
7.5.1.3 In summary, nmr signals have hydrogens on sp\(^3\) carbons shielded with respect to sp\(^2\) and those with respect (ideally) to sp. The hydrogens on sp carbons are shifted to the right, shielded, by ring current. Hydrogen atoms on benzene are shifted to the left, de-shielded, by ring currents. All of these are de-shielded by having an electronegative atom nearby. And then there are a few special cases. Think this general argument through.

7.5.2 Additional Exercises

7.5.2.1 In $^1$H nmr, where does the H atom in RC(O)OH absorb? HINT: “R” is some unspecified C, H group. HINT: There are two “odd ball” chemical shifts in $^1$H nmr; this is one of them.

7.5.2.2 In $^1$H nmr, where does the H atom in CH\(_3\)C(O)R absorb?

7.5.2.3 In $^1$H nmr, where does the H atom on an alkene absorb?

7.5.2.4 In $^1$H nmr, where do the H atoms in benzene-R absorb?

7.5.2.5 In $^1$H nmr, where does the H atom in CF\(_3\)C(O)H absorb? As they say in Beebe, Arkansas, which is right down the road from Searcy, “There ain’t no more bells in $^1$H spectroscopy,” than those you have discussed in this and the previous four exercises. HINT: This is the second “odd ball” chemical shift.

7.6 Simple Spin-Spin Splitting

Read Klein, Section 16.7. (16.7)

There is one additional, and very important, factor to consider in nmr. If two hydrogen atoms are close to each other, then the spin on one influences the spin on the other. This process is a through bond phenomenon between hydrogen atom A and hydrogen atom B and is illustrated schematically in Figure 7.5. Assume hydrogen atom A has up spin. This makes the electron in the C-H\(_A\) bond close to the hydrogen atom favor (let us say) a down spin. Therefore the up spin electron in that bond is pushed toward the carbon atom. This up spin electron influences the electrons in the C-C bond, pulling a down spin electron close to it and so on until we get to hydrogen atom B. The electron polarization next to it favors the nuclear spin on hydrogen atom B indicated in the Figure. We would say that the down spin of hydrogen atom B is stabilized (and hence the up spin will be destabilized). Figure 7.6 shows that this leads to a lower transition in the presence of hydrogen atom A than in it absence. If the spin of hydrogen atom A is reversed, everything in Figure 7.5 is reversed and now the up spin of hydrogen atom B is stabilized. This leads to the right hand diagram of Figure 7.6. Since the population of the two states at hydrogen atom A
Figure 7.5: Schematic illustration of spin-spin coupling. The blue circles are carbon atoms. If hydrogen atom A is up spin, that favors the electron spin polarizations indicated which in turn favors the nuclear spin of hydrogen atom B to be down spin.

If hydrogen atom A and B have spins that are about equal, the single signal of hydrogen atom B is split into a pair of signals, one higher in energy and one lower in energy than the position of the signal in the absence of hydrogen atom A. In the language of Figure 7.6, the black (dotted) arrows disappear and are replaced by the red and green arrows. The signal is split.

For future reference it is worth noting that the energy difference between the red transition and the green transition is called J, the spin-spin splitting constant.

If hydrogen atom B has two neighbors instead of just one, then the situation has slightly more complexity. The two neighbors could have both of their spins up, or one up and one down (two ways to do this), or both down. Hence there are three possible fields transmitted to hydrogen atom B: Strong up, nothing (two ways), or strong down. The signal at hydrogen atom B is split into a “triplet” with a ratio of peak heights of 1:2:1. This leads to the rule that the splitting of the peak is governed by the expression:

\[ n_{\text{peaks}} = n_{\text{neighbors}} + 1 \]

where \( n_{\text{peaks}} \) is the number of “split” peaks and \( n_{\text{neighbors}} \) is the number of neighboring hydrogen atoms.

There are cases where the number of equivalent neighbors on adjacent carbon atoms is greater than three. This occurs in the isopropyl group, \( 35A \), where the hydrogen on the central carbon has six equivalent neighbors. The \( n+1 \) rule holds for this situation. It would also hold in \( 35B \), where the hydrogen atoms on the central carbon atom are split by four neighboring (equivalent) hydrogen atoms. For cases where the the neighbors on the two sides are not equivalent, but appear to be, see Section 7.8.1.

Remarks: Hydrogen atoms in equivalent sites do not appear to split each other\(^1\). Generally they actually do, but the transitions do not appear in the spectrum because they are forbidden in the

\(^1\)They actually do, but the transitions do not appear in the spectrum because they are forbidden in the
Figure 7.6: Energy levels as a result of spin-spin coupling. The left hand picture of each pair (with black dotted arrow) gives the energy levels and the transition if hydrogen atom B has no neighbor. If the neighboring hydrogen atom A is of up spin then the down spin at hydrogen atom B is stabilized—see Figure 7.5—and the up spin is destabilized. This is shown in the left hand picture. The resulting transition, red arrow, is shifted from that of the no-neighbor picture. If the neighboring atom A is of down spin, the reverse stabilizations take place—right hand side—and the transition (green arrow) is now of higher energy.
ally hydrogen atoms on N, and especially O, do not contribute to splitting. They “exchange” too rapidly and this leads to an average spin of zero.

7.6.1 Required Exercises

7.6.1.1 A -CH$_3$ group has a neighboring C with one H atom. How many different spin orientations can that single neighboring hydrogen atom take?

7.6.1.2 Given your answer to the last exercise, how many different magnetic fields can the -CH$_3$ group that has one H atom on a neighboring carbon “see?” Into what kind of structure is the signal of the -CH$_3$ group split?

7.6.1.3 Complete the following sentence: “To determine the splitting of the hydrogens on a given carbon, you need to examine the . . . ”

7.6.1.4 A -CH$_3$ group has two equivalent H atoms on a neighboring carbon atom. How will the signal of the -CH$_3$ group be split? What will be the relative areas of the components of the signal?

7.6.1.5 A CH group has two neighboring equivalent -CH$_3$ groups. How is the CH group split?

7.6.1.6 Predict the spin splitting of the peak due to the hydrogen atom on the methyl group of CH$_3$CH(Cl)$_2$.

7.6.1.7 Predict the spin splitting of the peak due to the hydrogen atom on the methine group of CH$_3$CH(Cl)$_2$. REMARK: From the last two exercises, be sure that you see that if hydrogen atom A is split by hydrogen atom B, then hydrogen atom B must also be split by hydrogen atom A.

7.6.1.8 Predict the spin splitting of the peak due to the hydrogen atom on C-2 of 34. HINT: Structure is several pages back.

7.6.1.9 Predict the spin splitting of the peak due to the hydrogen atom on the methyl group of 35.

quantum mechanical sense.
7.6.1.10 Predict the spin-spin splitting pattern (i.e., triplet at 1.5 ppm, etc) for 1,1,2-tribromoethane.

7.6.1.11 A compound of formula C₄H₈O has three ¹H nmr signals: δ = 1.06 ppm (triplet J=7.6, 3), (ding) 2.14 ppm (s, 3) (ding), and 2.45 ppm (q, J=7.6, 2). What is the compound?

7.6.2 Additional Exercises

7.6.2.1 A -CH₂- group has one H atom on a neighboring carbon atom. How is the -CH₂- group split?

7.6.2.2 A -CH₃ group has two equivalent H atoms on a neighboring carbon atom. How many different spin orientations can those two neighboring hydrogen have? List them pictorially. What is the relative probability of each of the possible orientations? Do any of the possible orientations produce equivalent fields? How many different fields are possible? What is the probability of each? What is the splitting of the -CH₃ group?

7.6.2.3 A -CH₂- group has three equivalent H atoms on a neighboring carbon atom. How is the -CH₂- group split?

7.6.2.4 Imagine you have a -CH₃ group next to a -CH₂- group. From the point of view of the -CH₃ group, how many neighbors does it have? What splitting will you see at the -CH₃ group? From the point of view of the -CH₂- group, how many neighbors does it have? What splitting will you see at the -CH₂- group? Since the two interactions are modulated by the same electrons, they are completely reciprocal. If the -CH₂- group “splits” the -CH₃ group, the -CH₃ group will “split” the -CH₂- group. How will each be split?

7.6.2.5 Continuing with the scenario from the last exercise, the magnitude of the splitting, almost always called J, is exactly the same at both signals. If the -CH₃ group is split into a triplet with a separation between the peaks of J = 8.0 cps (in contrast to chemical shift, which is the same in magnitude in units of ppm independent of the strength of the magnet, the coupling constants depend on the magnet field strength, becoming smaller relative to the chemical shift in stronger fields), what will be the separation of the various peaks in the -CH₂- group?

7.7 Pursuing in NMR Problems

In solving nmr problems you should get all the information you can from a part of the data you have before you go on to other pieces of data. This leads to thoughtful results as
opposed to wild guesses. Here is an example exercise: “A compound of formula C₄H₈Br₂ has two ¹H nmr signals: $\delta = 1.97 \text{ ppm (s, 6)}$ and 3.89 ppm (s, 2). What is the compound?”

I am going to start, arbitrarily, at the 3.89 signal. It is de-shielded and hence must be next to one bromine atom and probably adjacent to another. Now to pursue: That same signal is a singlet so there is no hydrogen close to the hydrogens in the signal; incidentally, I know there are two in this signal from the integration. We have what is shown in Figure 7.7.

![Figure 7.7](image)

where the squiggly lines are NOT to hydrogens (because if they were, there would be a splitting of the 3.89 signal and there is not). One of the squiggly lines is probably to a bromine in order to give the de-shielding that the signal has. That means our structure has only two squiggly lines left, and they must go to two equivalent methyl groups to give us the four carbon atoms in the molecule and the six hydrogen atoms in the signal at 1.97 ppm.

Here is a second example of pursuit: A compound of formula C₈H₉Br has ¹H nmr signals: $\delta = 2.01 \text{ ppm (d, 3)}, 5.14 \text{ ppm (q, 1)}$ and 7.35 ppm (broad s, 5). What is the compound? I start (though there are other ways to start this problem) with ihd. This compound has an ihd of 4, which suggests a benzene ring. Pursue! Benzene signals absorb around 7-8 ppm and we have a signal there. Further, the integration on the signal is 5, suggesting a benzene ring with five hydrogen atoms and one other substituent. That lets me write the structure A in Figure 7.7. Moving to the 2.01 ppm signal. It has an integration of 3 so is most likely a CH₃ group. Pursue! It is a doublet so it has one neighbor, so I can write what I have in B where neither squiggle can be to a hydrogen atom. If the CH₃ is split, so must the thing that is splitting it. So the 5.14 ppm signal must be the single hydrogen atom in structure B; that it is split into a quartet is consistent with it being next to the methyl group. Pursue. How does the 5.14 ppm signal get so de-shielded? The hydrogen atom that makes up the 5.14 ppm signal must be next to the bromine atom, so the one of the two squiggles in B must be to a bromine atom, as indicated in C. Putting the two squiggles in A and C together gives us the structure. Pursue.

### 7.7.1 Required Exercises

#### 7.7.1.1
A compound of the formula C₅H₁₀O₂ has four ¹H nmr signals: $\delta = 1.14 \text{ ppm (t, J=7.7, 3)}, 1.26 \text{ ppm (t, J=7.2, 3)}, 2.32 \text{ ppm (q, J=7.7, 2)}, \text{ and } 4.13 \text{ ppm (q, J=7.2, 2)}$. What is the compound? HINTS: (1) Always use ihd. (2) In this problem we know who splits who because the J values are given.

#### 7.7.1.2
A compound of the formula C₇H₁₄O has ¹H nmr signals: $\delta = 1.06 \text{ ppm (s, 6)}, 2.15 \text{ ppm (s, 2)}, \text{ and } 2.33 \text{ ppm (s, 1.4)}$. What is the compound? HINTS: Use ihd. Watch
the integration; it is only relative.

7.7.1.3 A compound of the formula C_5H_{10}O_2 has two ¹H nmr signals: δ = 1.14 ppm (s, 9), 11.49 ppm (broad singlet, exchangeable, 1). What is the compound? HINT: “Exchangeable” means a hydrogen atom that rapidly comes on and off the site of the organic molecule; it usually means a -OH or a -NH₂.

7.8 Four Advanced Spin Rules

7.8.1 The (n+n′+1) rule

Imagine a situation where a -CH₂- has a methyl group on one side and a -CH- group on the other; these two sides cannot possibly be equivalent. However, under suitable circumstances, the four neighboring hydrogen atoms can act as if they are equivalent and split the signal on the central -CH₂- into a quintet. Our rule from problem 7.6 must be modified slightly in this case: it becomes (n+n′+1) where n is the number of neighboring hydrogen atoms on one side and n’ is the number on the other. In this case it would be (3+1+1), and we would see a quintet splitting pattern. What are the special circumstances? It is required that the splitting constant, J, between the CH₃ and the -CH₂- be close to that between the -CH- and the -CH₂-.

7.8.2 Required Exercises

7.8.2.1 What might be the splitting of a -CH₂- which had three hydrogen atom next to it on one side and one on the other side? HINT: The conditional “might,” and “can be,”

²WARNING: Unconventional use of words and the consequences thereof. My job is to help you learn to identify patterns that are meaningful. There are patterns that I see that no one else, as far as I know, has named. I intend to name those so that you and I can refer to them in an intelligent manner. You will not find these names outside of this course; and if you use them in polite company, others may look at you suspiciously. Do not use these words except with your classmates and me. The (n+n′+1) rule is the first of these “words.”
7.8.2.2 A compound of the formula $\text{C}_7\text{H}_{14}\text{O}$ has $^1\text{H}$ nmr signals: $\delta = 0.9$ ppm (t, 3), 1.1 ppm (d, 6), 1.6 ppm (sextet, 2), 2.42 ppm (t, 2), and 2.6 ppm (heptet, 1). What is the compound?

7.8.3 Multiplet Splitting

Our $(n+n'+1)$ rule, see Section 7.8.1, breaks down when the size of the coupling of the $n$ hydrogen atoms is not the same as the splitting of the $n'$ hydrogen atoms and the chemical shift difference is small. Under this circumstance, you get a multiplet (indicated by a “m”); which also can be a mess, for which “m” also serves as the abbreviation. You can learn little from the spin-spin coupling of such a peak except that it is coupled to two (or more) different hydrogen atoms. Hence with neighbors on two or more sides, we have two options (and will see a third): $(n+n'+1)$ rule or a multiplet are the first two. That is the meaning of the “can” in Section 7.8.1.

Here is an example of how to handle such situations. A compound of the formula $\text{C}_5\text{H}_{10}\text{O}_2$ has four $^1\text{H}$ nmr signals: $\delta = 0.99$ ppm (d, 6), 2.12 ppm (m, 1), 2.23 ppm (d, 2), and 11.9 ppm (broad singlet, exchangeable, 1). This is a beauty for pursuit. The 0.99 ppm peak is a doublet; hence coupled to one hydrogen atom. There are six hydrogen atoms in it, so it is probably two methyl groups. Pursue! Where is that one hydrogen atom that is splitting the two methyl groups? It must be the 2.12 ppm peak, as that is the only one with an integration of 1. Pursue! The 2.12 ppm peak is a multiplet, hence must be coupled to some other set of hydrogen atoms in addition to the two methyl groups. Those others must be the 2.23 ppm peak, as it is the only other peak that is split (and remember, if A splits B, B must split A). So we have what is shown in Figure 7.8. Where are we in solving this problem? We have used four of the five carbons, and have accounted for 9 of the 10 hydrogens. What we have left is a -C(O)OH group, which is consistent with the nmr signal at 11.9. So the final structure is shown in the right hand side of Figure 7.8. Pursue!
7.8.4 Required Exercises

7.8.4.1 A compound of the formula $C_9H_{11}Br$ has $^1H$ nmr signals: $\delta = 2.2$ ppm (quintet, 2), 2.75 ppm (t, 2), 3.35 ppm (t, 2), and 7.2-7.5 ppm (m, 5), What is the compound?

7.8.4.2 A compound of the formula $C_9H_8O_2$ has $^1H$ nmr signals: $\delta = 5.4$ ppm (d, 1, J=15), 7.2-7.5 ppm (m, 5), 7.8 ppm (d, 1, J=15), and 12.4 ppm (s, 1, exchanges with D$_2$O), What is the compound?

7.8.5 Additional Exercises

7.8.5.1 You have two compounds with the formula $C_{10}H_{12}O$. The first has $^1H$ nmr signals: $\delta = 1.18$ ppm (t, 1.5), 2.4 ppm (s, 1.5), 2.95 ppm (q, 1), 7.24 ppm (d, 1), and 7.8 ppm (d, 1). The second has $^1H$ nmr signals: 1.31 ppm (t, 3.1), 2.65 ppm (s, 2.9), 2.75 ppm (q, 2.0), 7.3 ppm (d, 1.95), and 7.8 ppm (d, 2.1). HINT: You will need to use Table 7.1 carefully to be successful in obtaining an answer.

7.8.6 The $(n+1)\,(n'+1)$ Rule

The previous two sections outlined two situations where spin-spin coupling occurs from more than one non-equivalent source. There is a third case. If the $n$ hydrogen atoms on one side of the site on which we are focussed and the $n'$ hydrogen atoms on the other side have sufficiently different $J$ values and the chemical shift is large enough, we then see an ($n+1)(n'+1)$ pattern. That is, we see, for instance, a doublet of triplets. A (d of t) means you have three major peaks, each of which is a doublet. The $(n+1)(n'+1)$ pattern often occurs when one of the couplings is long range (more than three bonds away), which is rare.

Here is an example: A compound of formula $C_5H_8$ has $^1H$ nmr signals: $\delta = 1.00$ ppm (t, 3), 1.55 ppm (sextet, 2), 1.94 ppm (t, 1), and 2.15 ppm (t of d, 2). What is the compound?

The signal at 2.15 is a triplet of doublets, so there are two neighbors on one side and one on the other. Since the doublet is the smaller splitting, there is presumably one hydrogen atom with a small coupling constant. The only signal in the spectrum with an integration of two is the 1.55 ppm signal, whose value is consistent with a single hydrogen atom on a triple bond. So we have the first picture in Figure 7.9. The other side of the 2.15 signal must have two neighbors and the only signal with an integration of two is the 1.94 ppm signal, so it must be next to the 2.15 hydrogen atom. That signal is a sextet, so it has a total number of neighbors of 5, 2 coming from the 2.15 hydrogen atom, the other three from the 1.00 ppm signal. The answer is in the second picture of Figure 7.9.

\footnote{WARNING. Another “linckism.” I am not aware that anyone else talks about this rule. I made up the name to aid in your education. Use it freely in this class. Outside this class, use with care.}
7.8.7 Required Exercises

7.8.7.1 Predict the $^1$H nmr spectrum for 4,4’-dimethyl-1-pentyne. HINTS: (1) This compound exhibits \((n+1)(n'+1)\) peaks through the triple bond. (2) See Section 7.8.6.

7.8.8 General Spectroscopic Problems

In this section are some problems using IR and \(^1\)H NMR together.

7.8.8.1 A compound of formula \(C_4H_8Br_2\) has IR, 2850-3000 cm\(^{-1}\) and a \(^1\)H nmr of \(\delta = 1.87\) ppm (s, 9.1), 3.86 ppm (s, 3.0). What is it?

7.8.8.2 A compound of formula \(C_9H_{18}O\) has IR, 1710 cm\(^{-1}\) and a \(^1\)H nmr of \(\delta = 1.2\) ppm. What is it?

7.8.8.3 A compound of formula \(C_2H_4Cl_2\) has IR, 2850-3000 cm\(^{-1}\) and a \(^1\)H nmr of \(\delta = 2.1\) ppm (d), 5.9 ppm (q). What is it? HINT: Use ihd and pursue.

7.8.8.4 A compound of formula \(C_8H_{12}O\) has a IR with prominent peaks at 1685 cm\(^{-1}\) (broad and strong), 1625 cm\(^{-1}\) (sharp), 3105 cm\(^{-1}\), and 2950-3000 cm\(^{-1}\). The \(^1\)H nmr has a doublets at 6.7 and 5.85 ppm, both with integrations of 1, triplets at 1.87 and 2.47 ppm, both with integrations of 2, and a singlet at 1.16 ppm with an integration of 6. Identify the compound.

7.8.9 Additional Exercises

7.8.9.1 A compound of formula \(C_3H_6Br_2\) has IR, 2850-3000 cm\(^{-1}\) and a \(^1\)H nmr of \(\delta = 2.4\) ppm (quintet), 3.5 ppm (t). What is it?
Table 7.3: $^{13}$C Chemical Shifts

<table>
<thead>
<tr>
<th>Environment</th>
<th>Chemical Shift, $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkanes</td>
<td>0 to 60</td>
</tr>
<tr>
<td>Alkenes and Aromatics</td>
<td>100 to 170</td>
</tr>
<tr>
<td>Alkynes</td>
<td>60 to 90</td>
</tr>
<tr>
<td>Carbonyl</td>
<td></td>
</tr>
<tr>
<td>Not aldehydes or ketones</td>
<td>160-190</td>
</tr>
<tr>
<td>Aldehydes and ketones</td>
<td>190-220</td>
</tr>
<tr>
<td>All downfield with Electronegative substituents</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.4: $^{13}$C Chemical Shifts

7.8.9.2 A compound of formula C$_5$H$_{10}$O$_2$ has IR, 1740 cm$^{-1}$ and a $^1$H nmr of $\delta = 1.15$ ppm (t, 3), 1.25 ppm (t, 3), 2.3 ppm (q, 2), and 4.32 ppm (q, 2). What is it? HINT: The 1.15 ppm (t, 3) signal must be next to one of the two signals with integration of 2. **Pursue!**

7.8.9.3 A compound of formula C$_6$H$_{14}$O has IR, 2850-3000 cm$^{-1}$ and a broad band at 3200 cm$^{-1}$. It has a $^1$H nmr of $\delta = 0.8$ ppm (t, 6), 1.0 ppm (s, 3), 1.5 ppm (q, 4), and 1.6 ppm (s, 1). What is it? HINT: The 0.8 ppm signal must be next to the 1.5 ppm signal, as they are the only things split. **Pursue!**

7.8.9.4 A compound of formula C$_6$H$_{14}$O has nothing of interest in the IR. The $^1$H nmr has peaks at $\delta = 1.1$ ppm (d, 30) and 3.6 ppm (heptet, 5). What is it?

7.9 $^{13}$C Chemical Shifts

Read Klein, Sections 16.1-16.2.

There is nucleus other than $^1$H that is useful in organic chemistry nmr; it is $^{13}$C. Like $^1$H, $^{13}$C has a spin of 1/2 and hence has a signal in the nmr when the transition from up spin to down spin takes place. The range of chemical shifts exhibited by $^{13}$C are given in Table 7.4. Note especially that these signals are also de-shielded by electronegative substituents. Also pay special attention to the two kinds of carbonyl signals, which are very useful in compound identification.

7.9.1 Required Exercises

7.9.1.1 Predict the decoupled $^{13}$C nmr of ethanal.

7.9.1.2 Predict the decoupled $^{13}$C nmr of 2-butanol.
7.10 Splitting and Integration in $^{13}$C Spectra

Since $^{13}$C occurs only to the extent of 1.1% of the carbon atoms, the likelihood of two $^{13}$C being neighbors is very slight. There is no $^{13}$C-$^{13}$C splitting. However, hydrogen atoms on a $^{13}$C will cause it to split. These are single bond splittings. As we learned in $^1$H spectra, spin-spin splitting commonly appear over three bonds. Thus not only would the hydrogens on the carbon (one bond away) split the $^{13}$C signal, so would those on the neighboring carbon (two bonds away), and those on the next carbon as well (three bonds away). The splitting is a mess! There are a number of ways (Off resonance decoupling, distortionless enhancement by polarization transfer, abbreviated DEPT$^4$) to simplify the splitting pattern so that all you see (or learn) is the splitting by the hydrogen atoms on the $^{13}$C, and not anything about splittings further away. Such information will be given in the problem that follow in the usual nomenclature of indicating the splitting pattern: singlet, doublet . . . .

Integration is not used in $^{13}$C spectra.

7.10.1 Required Exercises

7.10.1.1 A compound of the formula $C_4H_8O$ has four $^{13}$C nmr signals: $\delta = 7.87$ ppm (q), 29.43 ppm (q), 36.87 ppm (t), and 209.28 ppm (s) where the values in parenthesis are the off-resonance decoupled splittings. What is the compound?

7.10.1.2 A compound of the formula $C_6H_{12}$ has $^{13}$C nmr signals at $\delta = 17$ ppm, 25 ppm, and 138 ppm. What is the compound?

7.10.1.3 Predict the position and splitting of the $^{13}$C nmr peaks in 2-butanol with off resonance decoupling.

7.10.2 Additional Exercises

7.10.2.1 Review. How would you use $^1$H nmr to distinguish between cyclohexane and trans-2-hexene.

$^4$I did not make up that word!
7.10.2.2  Predict the decoupled $^{13}$C nmr of 3-butene-2-one.

7.10.2.3  A compound of the formula C$_7$H$_7$Br has seven decoupled $^{13}$C nmr signals: $\delta = 21.05$ ppm, 122.31 ppm, 127.65 ppm, 128.48 ppm, 129.70 ppm, 132.06 ppm, and 140.07 ppm. What are possible identifications of the compound?

7.11  Spectroscopic Identification

In this section are a number of problems for you to practice identification of compounds using the spectroscopic tools.

7.11.1  Required Exercises

7.11.1.1  Which method(s), IR, mass spectroscopy, $^1$H nmr, or $^{13}$C nmr would you use to distinguish between 61 and 62? Explain your answer.

7.11.1.2  Which method(s), IR, mass spectroscopy, $^1$H nmr, or $^{13}$C nmr would you use to distinguish between 63 and 64? Explain your answer.

7.11.1.3  A compound has five $^{13}$C nmr peaks: $\delta = 11.97$ ppm (q), 25.90 ppm, (t), 132.10 ppm (d), 160.24 ppm, (d) and 194.09 ppm (d) [splitting patterns from off-resonance decoupling] and five $^1$H nmr peaks: $\delta = 1.13$ ppm (t, 3), 2.38 ppm (quintet, 2), 6.12 ppm (d of d, 1), 6.942 ppm (d of t, 1), and 9.52 ppm (d, 1). What is the compound?

7.11.1.4  A compound has an IR with interesting peaks at 3082 and 3060 cm$^{-1}$ as well as 1621 cm$^{-1}$. The $^1$H nmr has peaks at 5.225, 5.737, 6.692, and between 7.1 and 7.5 ppm. The first two are doublets with an integration of 1, the third is a doublet of doublets with
an integration of 1, and the last is a mess (also called multiplet) with an integration of 5. The $^{13}$C nmr has 6 peaks at 113.7, 126.2, 127.8, 128.5, 137.0, and 137.6 ppm. What is the compound? How do we analyze this? The bunch of $^1$H nmr peaks in the region of 7.1 to 7.5 ppm catch my eye. Likely a benzene ring. Pursue! Area is 5 which suggests a monosubstituted benzene ring. Pursue! That would mean that there are four kinds of carbon in the ring, accounting for four of the $^{13}$C peaks. The two that are left (no matter which two you choose) are in the region of sp$^2$ hybrid carbon atoms, suggesting another double bond. Take it from there and pursue!

**7.11.1.5** A compound with formula C$_4$H$_8$O$_2$ has a $^1$H nmr with a broad singlet at $\delta = 12.2$ ppm, a heptet at 2.6 ppm, and a doublet at 1.21 ppm. What is the compound?

**7.11.1.6** A compound of formula C$_5$H$_8$O$_2$ has a $^1$H nmr with a triplet at $\delta = 1.1$ ppm, a singlet at 2.32 ppm, and a quartet at 2.78 ppm. The relative integrations are 3, 3, and 2, respectively. What is the compound?

**7.11.1.7** A compound of the empirical formula C$_4$H$_8$O has three $^1$H nmr signals: 1.06 ppm (d, 6); 2.39 ppm (m, 1), and 9.57 ppm (d,1). What is the compound?

**7.11.1.8** A compound has the formula C$_4$H$_8$O$_2$; IR 1730 cm$^{-1}$. The $^1$H nmr has peaks at 2.1 ppm (s, 31), 3.4 ppm (s, 30), and 3.9 ppm (s, 18.8). What is the compound?

**7.11.1.9** A compound with formula C$_7$H$_{14}$O has six $^{13}$C nmr peaks: 13.81 ppm, 17.24 ppm, 18.23 ppm, 40.80 ppm, 42.26 ppm and 214.77 ppm and five $^1$H nmr peaks: 0.96 ppm (t, 3), 1.09 ppm (d, 6), 1.59 ppm (sextet, 2), 2.42 ppm (t, 2), and 2.61 ppm (heptet, 1). What is the compound?

**7.11.1.10** A compound with formula C$_6$NO$_2$ClH$_4$ has an $^1$H nmr with two peaks, a doublet at 7.4 ppm and another doublet at 8.2 ppm. What is the compound?

### 7.11.2 Additional Exercises

**7.11.2.1** Which method(s), IR, mass spectroscopy, $^1$H nmr, or $^{13}$C nmr would you use to distinguish between 65 and 66? Explain your answer.

**7.11.2.2** A compound of formula C$_3$H$_6$O has IR, 1730 cm$^{-1}$ and a $^1$H nmr of $\delta = 1.11$ ppm (t), 2.46 ppm (m) and 9.79 ppm (t). What is it?
7.11.2.3 A compound with a formula C₇H₁₂O₂ has an IR band at 1746 cm⁻¹ and ¹H nmr peaks at δ = 1.8 ppm (m, 2), 2.12 ppm (d of t, 2), 2.41 ppm (t, 2), 3.76 ppm (s, 3), 4.9 ppm (m, 2) and 5.68 ppm (m, 1). The ¹³C nmr has peaks at 23, 34, 35 ppm, all decoupled triplets, 51 ppm (q), 115.9 ppm (t), 137 ppm (d), and 174.9 ppm (s). What is the compound? The ihd is 2 and the 1746 cm⁻¹ suggests a carbonyl. Pursue. This is verified by the 174.9 peak, which further demands it has an adjacent oxygen (it is too low in the ¹³C spectrum for a ketone or aldehyde). Continuing to pursue. The only peak in the hydrogen spectrum that could be attached to that -O- of the -C(O)O- group is the 3.76 ppm peak which is a methyl group. So we have a -C(O)COCH₃. That ends that pursuit. On to another. The 137 and 115.9 ppm peaks are an alkene, as are those (I pursue) at 4.9 and 5.68 ppm. The integration of the former indicates a terminal alkene. You can finish it.

7.11.2.4 A compound with the empirical formula C₄H₈O₂ has an ¹H nmr spectrum: triplet at 1.27 ppm (1.0), singlet at 2.03 ppm (1.05), quartet at 4.11 ppm (0.68). What is the compound?

7.11.2.5 A compound of formula C₉H₁₂ has IR, 2850-3150 cm⁻¹ and a ¹H nmr of 1.25 ppm (d, 6), 2.95 ppm (heptet, 1) and 7.3 ppm (m, 5). What is it?

7.11.2.6 A compound with formula C₄H₈O has four ¹³C nmr peaks: 37.11 ppm, (t), 61.61 ppm, (t), 117.21 ppm (t), and 135.02 ppm (d) [splitting patterns from off-resonance decoupling] and six ¹H nmr peaks: 2.318 ppm (g, 2), 2.76 ppm (broad, exchanges, 1), 3.65 ppm (t, 2), 5.10 ppm (d of d, 1), 5.13 ppm (d of d, 1), and 5.82 ppm (m, 1). What is the compound?

7.11.2.7 A compound with the formula C₉H₁₃N has an ¹H nmr spectrum as follows: 2.25 ppm (s, 6), 3.43 ppm, (s, 2), 7.32 ppm, (m, 5). What is the compound? The ihd is 4. I would first guess, therefore, a benzene ring. Pursue. That is consistent with the signal at 7.32 ppm, whose integration (pursuing) suggests a monosubstituted benzene ring. End of that pursuit. The signal at 2.25 ppm with integration of 6 suggests two methyl groups. Pursue. They are deshielded and hence probably on the N. You can take it from there.

7.11.2.8 A compound with formula C₅H₉N has four ¹³C nmr peaks: 21.79 ppm (q), 25.98 ppm, (d), 26.13 ppm (t), and 118.89 ppm (s) [off-resonance decoupled] and three ¹H nmr peaks: 1.07 ppm (d, 6), 2.02 ppm (nonet, 1), and 2.23 ppm (d, 2). What is the compound?

7.11.2.9 A compound of formula C₄H₁₀O has an IR with peaks between 2800-3000 cm⁻¹ and no other interesting peaks above 1500 cm⁻¹. The ¹H nmr has four peaks: 3.34 ppm (t, 2), 3.33 ppm (s, 3), 1.59 ppm (sextet, 2), and 0.93 ppm (t, 3). What is the compound?
7.11.2.10  A compound has a M⁺⁺ of 121, an IR as given in Figure 7.10, a $^{13}$C nmr with peaks at 151 ppm, 129 ppm, 117 ppm, 113 ppm, and 40.5 ppm, and a $^1$H nmr with peaks at 2.89 ppm (s, 1.7) and 6.6 to 7.4 ppm (m, 1.4). What is the compound?

7.11.2.11  A compound of formula C₄H₇ClO has an IR with peaks between 2800 and 3000 cm⁻¹ and at 1720 cm⁻¹. The $^1$H nmr has three peaks: 3.45 (t, 2), 3.07 (t, 2), and 2.14 (s, 3) ppm. What is the compound?

7.11.2.12  A compound has a mass spectrum with peaks at 120 and 122, intensities of 0.31 and 0.09, respectively, and an IR with peaks between 3000 and 2800 cm⁻¹. The $^{13}$C nmr has peaks at 18, 30, 40, and 75 ppm, and the $^1$H nmr has peaks at 1.02 (d, 18.3), 1.54 (s, 17.9), and 1.89 (heptet (septet), 3.1) ppm. What is the compound?

7.11.2.13  A compound of formula C₆H₁₂O₂ has the $^1$H and $^{13}$C spectra shown in Table 7.5. What is the compound?

7.11.2.14  A compound of has a mass spectrum with a molecular ion peak of 176. It has an IR peaks at 3101 cm⁻¹, 1725 cm⁻¹, and 1640 cm⁻¹. The nmr data is given in the Table 7.6. What is the compound? HINT: For partial credit you must give reasoning; and since you have lots of data, there is a lot of reasoning to be given.
Figure 7.10: IR for Exercise 7.11.2.10
### Table 7.6: Data for problem 7.11.2.14

<table>
<thead>
<tr>
<th>$^{13}$C $\delta$, ppm</th>
<th>$^1$H $\delta$, ppm</th>
<th>Splitting</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>1.3</td>
<td>t</td>
<td>6</td>
</tr>
<tr>
<td>30</td>
<td>2.4</td>
<td>s</td>
<td>6</td>
</tr>
<tr>
<td>32</td>
<td>2.7</td>
<td>q</td>
<td>4</td>
</tr>
<tr>
<td>135</td>
<td>7.0</td>
<td>d</td>
<td>4</td>
</tr>
<tr>
<td>137</td>
<td>7.2</td>
<td>d</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>206</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7.6: Data for problem 7.11.2.14
Chapter 8

Acids and Bases

8.1 Introduction

Read Klein, Section 3.1 and 3.3. (3.1 and 3.3)

If you have a good grasp of acids and bases, you have a good start on organic chemistry. This knowledge is critical.

We deal initially with Brønsted acids which are defined as materials that donate a proton, \( H^+ \). The corresponding base is the compound that accepts the proton. All reactions of acids require a base, as the bare proton is never seen. You will find chemical equations written as

\[
\text{HCl(aq)} = \text{H}^+(aq) + \text{Cl}^-(aq)
\]

as a shorthand for

\[
\text{HCl(aq) + H}_2\text{O} = \text{H}_3\text{O}^+(aq) + \text{Cl}^-(aq) \quad \text{or} \quad (8.1)
\]

\[
\text{HCl(aq) + 4H}_2\text{O} = \text{H(H}_2\text{O)}_4^+(aq) + \text{Cl}^-(aq) \quad (8.2)
\]

but it is better to use one of the latter forms. Notice in equations 8.1 or 8.2 that there is an acid and a base on the left hand side; and an acid and a base on the right hand side. The latter two are called the “conjugate” acid and conjugate base.

The strength of an acid is measured quantitatively by an equilibrium constant. You will recall this is an expression in which the concentrations of the products of a reaction (raised to their stoichiometric power) are divided by the concentrations of the reactants (raised to their stoichiometric power). For reaction 8.1 this would be written:

\[
K_a = \frac{[\text{H}_3\text{O}^+][\text{Cl}^-]}{[\text{HCl}][\text{H}_2\text{O}]} \quad (8.3)
\]

Usually the \([\text{H}_2\text{O}]\) is set equal to one. Since the range of \(K_a\) values is between \(10^{-10}\) and...
10^{50}, a very large range, the values are often expressed as a pK$_a$,

$$pK_a = -\log(K_a)$$  \hspace{1cm} (8.4)

Notice that a strong acid has a large $K_a$ but a less positive (more negative) pK$_a$; that pesky minus sign in the definition is the culprit.

From the definition of $K_a$ you can readily appreciate that a strong acid has a correspondingly weak conjugate base and a weak acid has a correspondingly strong conjugate acid: just invert $K_a$ to get the value for the reverse reaction.

### 8.1.1 Required Exercises

#### 8.1.1.1

For the reaction

$$\text{CH}_3\text{SH} + \text{OH}^- = \text{CH}_3\text{S}^- + \text{H}_2\text{O}$$

identify the acid, the base, the conjugate acid, and the conjugate base.

#### 8.1.1.2

What is the conjugate base of HBr, CH$_3$OH, NH$_4^+$?

#### 8.1.1.3

What is the conjugate acid of NH$_3$, NH$_2^-$, Cl$^-$, (CH$_3$)$_2$C(O)? Draw the Lewis structure for the last.

#### 8.1.1.4

Write the equilibrium constant in terms of concentrations for the reaction (in water)

$$\text{CH}_3\text{OH} = \text{CH}_3\text{O}^- + \text{H}^+$$

#### 8.1.1.5

What does a large value of an equilibrium constant mean? HINT: Give an answer in terms of concentrations of various species.

#### 8.1.1.6

What does a large value of an equilibrium constant mean? HINT: Give your answer in terms of “acid strength.”

#### 8.1.1.7

Consider the reaction

$$\text{CH}_3\text{C(O)OH} = \text{CH}_3\text{C(OO)}^- + \text{H}^+$$

for which we can write

$$K_a = \frac{[\text{CH}_3\text{C(OO)}^-][\text{H}^+]}{[\text{CH}_3\text{C(O)OH}]}$$

Show that this is equivalent to the expression

$$pK_a = pH - \log\left(\frac{[\text{CH}_3\text{C(OO)}^-]}{[\text{CH}_3\text{C(O)OH}]}\right)$$  \hspace{1cm} (8.5)
8.1.1.8 Will the conjugate base of an acid with a large \( pK_a \) react with another acid with a small \( pK_a \)? HINT: If the answer is not completely obvious to you, then write out the reactions and figure it out.

8.1.1.9 Will the conjugate base of an acid with a small \( pK_a \) react with another acid with a large \( pK_a \)? HINT: To do organic chemistry successfully, you have to use \( pK_a \) values like your toothbrush, without much thought.

8.1.2 Additional Exercises

8.1.2.1 Show that \( \text{NH}_3 \) can act as a base. Show that \( \text{NH}_3 \) can act as an acid.

8.1.2.2 If the \( pK_a \) of phenol, \( \text{C}_6\text{H}_5\text{OH} \), is 10, what is the ratio of phenoxide ion to phenol at equilibrium if the pH is 10? If the pH is 8? If the pH is 12? HINT: See equation 8.5.

8.1.2.3 Articulate what you learned in the last exercise. Something like: “If the pH is below the \( pK_a \), then the ratio of . . . If the pH is above the \( pK_a \), then the ratio . . .” Use general words like acid, conjugate base, base, conjugate acid.

8.1.2.4 Show that in the general case of an acid \( \text{HX} \), that if the \( \text{pH} = \text{pK}_a \), the ratio \([X^-]/[\text{HX}]\) is unity.

8.1.2.5 Ethanol has a \( pK_a \) of about 16. What is the dominant species, \( \text{CH}_3\text{CH}_2\text{OH} \) or \( \text{CH}_3\text{CH}_2\text{O}^- \) at a pH of 12? At a pH of 8?

8.1.2.6 The \( pK_a \) of \( \text{NH}_3 \) is 35. That of ethyne is 25. Will \( \text{NH}_2^- \) react with \( \text{HCCH} \) to produce ammonium ion and \( \text{HCC}^- \)? HINT: Write out the equation in terms of the two reactions defining the \( K_a \)’s.

8.1.2.7 Water and dichloromethane are immiscible. Butanoic acid has a \( pK_a \) of about 5. Butylammonium ion, \( \text{C}_4\text{H}_9\text{NH}_3^+ \) has a \( pK_a \) of about 11. We make a mixture of the two four-carbon species (butanoic acid and butyl amine) in water and adjust the pH as indicated in what follows. This aqueous solution is then shaken with dichloromethane. Determine: a. In what range of pH will both materials be found in the water layer? b. In what range of pH will butanoic acid be in the water layer while the butyl amine is in the \( \text{CH}_2\text{Cl}_2 \) layer? c. In what range of pH will butanoic acid be in the dichloromethane layer while the ammonium salt is in the water layer? HINTS: (1) Assume that ions are more soluble in water and neutral molecules are more soluble in the organic layer. (2) This is a simple problem using the relationship you derived in problem 8.1.1.7.
8.2 Acid Strength, Part I: Nature of Acid

Read Klein, pp 110-111. (108-109)

NOTES: (1) In this and the coming sections I am going to illustrate the role of the acidity issue being discussed by giving you examples of reactions where the acidity issue is important. These will be so extensive as to be in separate sections. This is an attempt to spread out the reactions we need to learn throughout the course. (2) I think in Figure 3.3 that Klein should have draw the arrow in the “electronegativity” figure as going from left to right, not bottom to top.

As indicated in the last section, acidities cover a large range. Look at Table 8.1 and get a sense for which substances are strong acids, which weak. We will work to refine that relationship in what follows. HINT: This table is trying to get you to classify acid strength with a broad brush. If you want details, there is a nice table of 600 acids at: www.chem.wisc.edu/courses/116/OtherDoc/pKas_of_Organic_Acids_and_Bases.pdf

The prediction of acidity is difficult as it involves concerns about bond strengths, electron affinities, and solvation. Our approach is to learn features that allow a reasonable guess about relative acidities by leaving some of the nuances of the subject unstated.

The first issue is the nature of the atom that looses the hydrogen ion. Consider first the series CH₄, NH₃, H₂O, and HF. The conjugate bases of these acids puts negative charge on C, N, O, and F, respectively. Which of these would prefer negative charge? The acid strength goes up across the series. Now consider the vertical trend, HF, HCl, HBr, and HI. Here the electron affinities do not vary much down the group, but the bond strengths of the H-X bond do, with the HI bond being the weakest. This latter is dominant and acidities go up as you move down the periodic table in any given column. So acidity (because of the nature of the atom that loses the hydrogen ion) goes up as you move to the right and down in the periodic table.

8.2.1 Required Exercises

8.2.1.1 Write out the reaction for HF acting as an acid. Write out the reaction for H₂O acting as an acid. Which anion is most easily able to accommodate the negative charge? HINT: Use periodic position.

8.2.1.2 Based on your answer to the last exercise, which material, HF or H₂O is the strongest acid?

8.2.1.3 Which is the strongest acid, NH₃ or H₂O?

8.2.1.4 Which is the strongest acid, NH₃ or PH₃?
### Table 8.1: Various pKₐ values for compounds. Note the labels “weak” etc. are subjective.

<table>
<thead>
<tr>
<th>pKₐ Range</th>
<th>C acids</th>
<th>N acids</th>
<th>O acids</th>
<th>Misc. acids</th>
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<tbody>
<tr>
<td>Strong acids</td>
<td></td>
<td>RCNH⁺, -10</td>
<td>HClO₄, -10</td>
<td>HI, -10</td>
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<tr>
<td>pKₐ below 0</td>
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<td>protonated ketone, -7</td>
<td>protonated acid, -6</td>
<td>HBr, -9</td>
</tr>
<tr>
<td>Weak acids</td>
<td>1,3-propanedial, 5</td>
<td>protonated aniline, 4.6</td>
<td>HCl, -7</td>
<td>RSH₂⁺, -7</td>
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<tr>
<td>pKₐ 0 to 10</td>
<td>2,4-pentadione, 9</td>
<td>protonated pyridine, 5.2</td>
<td>CF₃C(O)OH, 0.5</td>
<td>(Ph)₃PH⁺, 2.7</td>
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<td></td>
<td>HCN, 9.2</td>
<td>HONH₃⁺, 5.8</td>
<td>H₂PO₄, 2.2</td>
<td>HF, 3.2</td>
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<td></td>
<td></td>
<td>NH₄⁺, 9.2</td>
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<td>H₂Se, 3.9</td>
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<tr>
<td></td>
<td></td>
<td>succinimide, 9.6</td>
<td>CH₃C(O))H, 4.8</td>
<td>H₂S, 7.0</td>
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<tr>
<td>Very Weak</td>
<td>CH₃C(O)CH₂C(O)OC₂H₅, 10.7</td>
<td>(C₂H₅)_₂NH⁺, 10.7</td>
<td>H₂O₂, 11.6</td>
<td>C₂H₅SH, 10.6</td>
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<tr>
<td>pKₐ 10 to 20</td>
<td>C₂H₅OC(O)CH₂C(O)OC₂H₅, 13</td>
<td>(H₂N)₂CNH₂⁺, 13.6</td>
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<td>ketone, 19.2</td>
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<td>pKₐ 20 to 30</td>
<td>HCCCH, 25</td>
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<td>CH₄, 48</td>
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</table>
8.2.2 Additional Exercises

8.2.2.1 Which is the strongest acid, CH$_4$ or NH$_3$?

8.2.2.2 Which of the following can be significantly deprotonated by OH$^-$? H$_2$S, C$_6$H$_5$CH$_3$, CH$_3$NH$_2$

8.2.2.3 Rank each of the following sets in order of increasing acidity.

A. NH$_3$, H$_2$O, H$_2$S  
B. CH$_3$OH, CH$_3$NH$_2$, CH$_3$CH$_3$  
C. HBr, HF, NH$_3$

8.3 Nature of the Acid and Reactions

Recall that nucleophiles and bases are related. The former are efficient donors of electrons to, in this course, carbon atoms; the latter are efficient donors to the hydrogen ion. Generally (but not always) a good bases is a good nucleophile, and vice versa. This presents an critical feature in thinking about reactions. Consider the nucleophiles we have talked about so far in the course, Grignard reagents, “C−” reagents, and various hydrides, “H−” reagents. By our rules, these should both be good bases as well, and they are. Further, acid-base reactions are usually rapid compared to other reactions. Hence, if we attempted to react ethyl Grignard reagent with 311, the first thing that would happen is that the acidic -OH group would react with the ethyl Grignard reagent acting as a base to produce the products shown in 312 and 313. We would not get the desired product resulting from attack of the Grignard at the carbonyl carbon. Further, the negative charge on 312 would make it a poorer electrophile and perhaps stop attack at the carbonyl carbon even in the presence of excess Grignard reagent. The message: Check for acid-base reactions before you do nucleophilic attack.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Hybridization</th>
<th>$pK_a$</th>
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<tbody>
<tr>
<td>Ethane</td>
<td>$sp^3$</td>
<td>about 50</td>
</tr>
<tr>
<td>Ethylene</td>
<td>$sp^2$</td>
<td>44</td>
</tr>
<tr>
<td>Ethyne</td>
<td>$sp$</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 8.2: $pK_a$ for Various Hybridization at Carbon

8.3.1 Required Exercises

8.3.1.1 In an attempt to synthesize 1, Boniface Beebe, the esteemed natural philosopher from rural Arkansas, reacted one mole of ethyl Grignard with one mole of HC(O)C(O)OH, glyoxylic acid, then added acid. Can we be sure that his product was 1? What other possibility is there?

8.4 Acid Strength, Part IA: Hybridization

Read Klein, pp 117-118. (115-116)

The state of hybridization of a carbon atom affects the acidity of the C-H bond. This is a corollary of our nature of the atom rule. An $sp$ hybridized carbon atom after it loses the proton has the negative charge in an orbital that is 50% $s$ in character. This is a more stable situation than a carbon that is $sp^2$ hybridized, where the $s$ character is 33%, which in turn is better than the 25% in a $sp^3$ carbon. The effect is dramatic, covering 25 powers of ten, as shown in Table 8.2.

8.4.1 Required Exercises

8.4.1.1 In a carbon atom, what orbital is more stable, 2s or 2p? In which orbital would a free electron prefer to be?

8.4.1.2 What element tolerates negative charge best, F or C? What “kind” of C tolerates negative charge best?

8.4.1.3 Will butyl lithium react with propyne? To produce what?

8.4.1.4 Will methyl Grignard react with propyne? To produce what?
8.4.2 Additional Exercises

8.4.2.1 State the first rule of acidity and its corrollary.

8.5 Hybridization of the Acid and Reactions

The last section shows that it is much easier to make an “C−” reagent with an sp hybridized carbon that it is with an sp³ one. This means that we might be able to take advantage the fact that acetylene is a stronger acid that ethane to see some interesting chemistry. This is true.

The pKₐ of the conjugate acid of the NH₂⁻ group in NaNH₂ is about 35. That is capable of removing a proton from HCCH to form the HCC⁻ anion, which should be a reasonable nucleophile. Work your way through the exercises to show how this manifests itself.

8.5.1 Required Exercises

8.5.1.1 Propyne is mixed with NaNH₂ and the mixture is added to acetone; after some time, H⁺ is added. Use epwa to find the products. Show the mechanism.

8.5.1.2 Propyne is treated first with butyl lithium, then with 2-butanone, finally with dilute H⁺. Write a mechanism for the reaction and show final products. HINT: To be able to solve this kind of problem (albeit of increasing complexity) is the aim of organic chemistry courses.

8.5.1.3 Propyne is treated with butyl lithium. What kind of reagent have we made? This reagent that we produced is then added to oxirane (the epoxide of ethylene, a cyclic compound), C₂H₄O. Finally the solution is treated with H⁺ to neutralize charge. What is the product? Give a mechanism. HINT: Always make a Lewis structure of your reagents as you think about things. This is new chemistry, but should make sense to you based on the polarization arguments and epwa.

8.5.2 Additional Exercises

8.5.2.1 Let’s repeat the process in exercise 8.5.1.3. This time we do the same process but do not add acid. Instead, we add more butyl lithium and then more oxirane, C₂H₄O, and finally, after some time, dilute hydrogen ion. What now is the product? Give a mechanism with epwa. HINT: Look at what you can do with epwa!
Table 8.3: Reactions of the Alkyne Anion, CH₃CC⁻.

8.5.2.2 Propyne is treated with butyl lithium. The resulting nucleophile is added to CH₃I. See if you can use epwa to make a reasonable prediction about what might happen. This is more new chemistry. Note: You have a good nucleophile and a good leaving group, I⁻. Table 8.3 summarizes important reactions of alkyne anions.

8.6 Acid Strength. Part II: Charge

Klein does not discuss this important feature.

H₂S is an acid. It can lose a proton to produce HS⁻. However, HS⁻ still has a proton attached to it, so it too can act as an acid. Write those two reactions using the base NH₂⁻ to accept the proton. Which of the material, H₂S or HS⁻ do you think is the strongest acid? Is it easier for an positively charged proton to leave a one negative charge behind, or to leave a two negative charge behind? The pKₐ of H₂S and HS⁻ are approximately 7 and 14, respectively. Does that agree with your logic? Charge on or near a acidic site has a large influence on the strength of the acid. A negatively charged material is a weaker acid than the corresponding neutral compound and, conversely, a positively charged material is a stronger acid than the corresponding neutral compound.

8.6.1 Required Exercises

8.6.1.1 Which is the strongest acid, (C₂H₅)₂NH₂⁺ or (C₂H₅)₂NH?

8.6.1.2 Which of the two substances in the last exercise is the strongest base? HINT: Trick question.

8.6.1.3 Which is the strongest acid, HOC(O)C(O)OH or HOC(O)C(O)O⁻?

8.6.2 Additional Exercises

8.6.2.1 What are the first two rules for acidity?
8.6.2.2  NaH reacts with CH₃CH₂OH (to produce?) but not with CH₃CH₃. What is the order of base strength of H⁻, CH₃CH₂O⁻, and CH₃CH₂⁻? HINT: Write reactions.

8.6.2.3  Malonic acid is HOC(O)CH₂C(O)OH. It can give up two protons relatively readily; one has a pKₐ of 2.86, the second a value of 5.7. Comment.

8.7  Charge on the Acid and Reactions

In this section we discuss two important reactions that occur because of the charge on the acid. The first is understood by a comparison of P(CH₃)₃ and P(CH₃)₄⁺. Which would be the strongest acid? The second has a positive charge so a proton will leave it more readily than one would leave the first. The second comparison is between S(CH₃)₂ and S(CH₃)₃⁺. Which will be the stronger acid? Again, the positively charged material. Note in both cases it will, of necessity, be a C-H bond that is broken when the substance acts as an acid, and, therefore when those positively charged materials lose a proton, they generate a “C−” reagent.

8.7.1  The Wittig Reaction, Preparation of Reagent

Read Klein, pp 965-967. (951-953)

The actual reaction used to produce the positively charged materials in the last paragraph is analyzed, as usual, by looking for a nucleophile and an electrophile. The nucleophile in the phosphorous case is a phosphine, R₃P, where R is some carbon, hydrogen containing fragment; usually R is the phenyl group, C₆H₅-. (“Phenyl” is the name for C₆H₅⁻; so chlorobenzene, C₆H₅Cl could also be called phenyl chloride.) It is the lone pair of electrons on the phosphorus that act as the nucleophile. The other reagent is usually CH₃X, where X is a halogen (but not fluorine).

8.7.2  Required Exercises

8.7.2.1  Is there an position in the molecule CH₃I that is positively polarized? Let R₃P, acting as a nucleophile, attack CH₃I. This starts to form a new bond from the phosphorous atom to the carbon atom (draw the dotted line), but carbon cannot have five bonds, so at the same time, the electrons in the bond to the iodine atom must be leaving carbon and going to the iodine atom. Use epwa to show these motions of electrons. What is the net chemistry?

8.7.2.2  The attack described in the last exercise occurs with the phosphorous atom coming toward the CH₃I as far away from the iodine atom as possible. Why might this be true? NOTE: In addition to the obvious reason you just gave, it is also true that the
phosphorous lone pair are looking for an empty orbital on the CH$_3$I with which to bond. The lowest empty orbital is the σ* level of the C-I bond, which is more concentrated on the carbon. Processes such as this have “backside” attack and are sensitive to how easy it is to approach the carbon. Hence primary halides are preferred.

**8.7.2.3** The process you just described in exercise [8.7.2.1](#) requires that the C-I bond break. Hence these so-called S$_N$2 (S, substitution, N, nucleophilic, 2, bi-molecular; that is requiring both the phosphone and the CH$_3$I reagents) reactions are more facile when there is a good “leaving” group. Generally, as we shall see repeatedly later, good leaving groups are, generally, poor bases. Which would be the best leaving group, I$^-$ or Cl$^-$?

**8.7.2.4** Use epwa to show the reaction of triphenylphosphine with 1-butyl bromide; be sure to indicate the formal charges on the products.

**8.7.3 Additional Exercises**

**8.7.3.1** Which would you guess is the best leaving group, Cl$^-$ or OH$^-$?

**8.7.4 The Wittig Reaction: Nucleophilic carbon and Retrosynthetic Analysis**

If we treat the compound prepared in exercise [8.7.2.4](#) (C$_6$H$_5$)$_3$PCH$_2$CH$_2$CH$_2$CH$_3^+$, with a strong base, say butyl lithium, we can remove a proton from the CH$_2$ group next to the positive phosphorous atom. This generates a negative charged carbon atom next to a positive phosphorous. You can make that into a double bond to phosphorous if you like, but the chemistry is better understood leaving it as a zwitterion, a compound with both positive and negative charges.

**8.7.5 Required Exercises**

**8.7.5.1** In the result of exercise [8.7.2.4](#) the phosphorous atom carries a positive charge. What does that charge do to the acidity of a C-H bond next to it?

**8.7.5.2** Treatment of the product of the reaction in exercise [8.7.2.4](#) with a strong base gives a “C$^-$” reagent of sorts. Given that is true, deduce what the result is if that “C$^-$” reagent reacts with propanal? Use epwa.

**8.7.5.3** The product of the last exercise can rearrange to form the very stable (P$^+$-O$^-$, P=O) bond. No matter what pair of electrons you use to do this, sticking to the four bonds.
to carbon rule, you will end up with an alkene. Use epwa to show this. HINT: Again, you will get an alkene.

8.7.5.4 Take your product from the last problem and color the atoms that were originally in the aldehyde one color and those that were originally in the butyl bromide another. Draw a line between the two colors. That is how you determine what starting materials are necessary to make a given alkene.

8.7.5.5 From what compounds would you synthesize 3-methyl-2-pentene? HINT: Draw the structure of the desired product and draw the “retrosynthetic” line you established in the last exercise. What fragments do you have? Now note one fragment started as an aldehyde or ketone and the other as an alkyl bromide (or chloride or . . . ). Use epwa from those starting materials to establish everything is OK.

8.7.5.6 How would you synthesize 4-octene?

8.7.5.7 From what kind of compounds do you make alkenes?

8.7.6 Additional Exercises

8.7.6.1 When a carbon is charged positively, how many bonds does it make? When a carbon is charged negatively, how many bonds does it make? If the answers are not evident to you, draw Lewis structures and be sure.

8.7.6.2 How would you synthesize 2-ethyl-2-hexene? Use epwa. HINT: Generally, because the $S_N2$ reaction in the first step of this process occurs much more easily on a primary alkyl halide, that is the issue that determines which side of the retrosynthetic line is the original carbonyl and which side is the halide.

8.7.6.3 What is one way to make alkenes? HINT: Alas, there will be other methods we will learn.

8.7.7 The Sulfur Ylide. Another Charged Acid Example

Just as triphenylphosphine can utilize the lone pair of electrons to act as a nucleophile, so can $(CH_3)_2S$. If this nucleophile does an $S_N2$ attack on $CH_3I$ we will get a positively charged sulfur. Just as in the phosphorous case, this charge will increase the acidity of the neighboring carbon-hydrogen bonds, and allow a strong enough base to remove a proton from a carbon atom, generating what? If this is brought next to an electrophilic carbon,
say a ketone, reaction can occur. Note the steps to this stage are identical for both the phosphorous and sulfur reagents. The difference involves the decay of the intermediate. In the case of phosphorous, that involves attack of the negative oxygen on the phosphorous atom because phosphorous has high oxophilicity, “love for oxygen,” certainly higher than does sulfur. The intermediate in the sulfur case utilizes a different method to remove the (unfavorable) positive charge on the sulfur. The negatively charged oxygen, acting as a nucleophile, attacks the carbon adjacent to the sulfur, and the bonding pair of electrons between the carbon and the sulfur become a lone pair on the sulfur. The net effect is the formation of a three membered ring including an oxygen atom, an oxirane or epoxide.

8.7.8 Required Exercises

8.7.8.1 Which do you think is the better nucleophile, (CH₃)₃P or (CH₃)₂S? Why?

8.7.8.2 How would you prepare (CH₃)₃S⁺ from (CH₃)₂S and CH₃I?

8.7.8.3 Why is (CH₃)₃S⁺ a better acid than (CH₃)₂S?

8.7.8.4 A strong enough base will surely deprotonate (CH₃)₃S⁺. What base might you use?

8.7.8.5 Use epwa to write the chemical reaction of (CH₃)₃S⁺ with a strong base.

8.7.8.6 What kind of reagent have you made in the last exercise? HINT: We are mostly concerned with interesting carbon fragments in this course.

8.7.8.7 Write a mechanism for the reaction of the product of the last exercise with propanone.

8.7.8.8 The product of the last exercise is again a zwitterion, with the negative oxygen atom separated from the positive sulfur. Sulfur is not a good atom to be positive, but because the affinity of sulfur for an oxygen atom is considerably less than the affinity of phosphorous for oxygen, it turns out that we need to find another atom for the negative oxygen to attack that will still move charge to sulfur. Since epwa only occurs over short distances, there is only one choice. Do it.

8.7.8.9 Take the product from the last exercise and color the atoms that were originally in the propanone with one color and those that were originally in the CH₃I with another color. Draw a line between those two sets of color. That is how you figure out what molecules are needed to make the oxirane.

8.7.9 Additional Exercises

8.7.9.1 What starting materials would you use to make 1a (several pages previous)?

8.7.9.2 What starting materials would you use to make 1b (several pages previous)?

8.7.9.3 What acidity feature do we take advantage of in order to synthesize alkenes and oxiranes?

8.8 Acid Strength. Part III: Resonance

Read Klein, pp 113-114. (110-111)

On the basis of charge only, we would you expect ethanol (CH₃CH₂OH) to be a weaker acid than NH₄⁺ whereas on the basis of the nature of the atom that carries charge, we would expect the reverse. This then would be hard to predict. The pKₐ of the two materials are 15.9 and 9.2, respectively. Which is the stronger acid? We would conclude in this case that charge plays a greater role than the nature of the atom. Now examine the compound, acetic acid, CH₃C(O)OH and NH₄⁺. On the basis of the above analysis, if that is all there is, we would expect ammonium ion to be the strongest acid? It is not: The pKₐ of the these last two materials are 4.7 and 9.2, respectively. Something is making acid acetic a stronger acid than ethanol. That something is the resonance stability of the anion of acetic acid.

Consider the acidity of two arbitrary compounds HA and HB (that is NOT boron):

\[ HA = H^+ + A^- \]
\[ HB = H^+ + B^- \]

where we assume that the hydrogen atom is attached to the same element with the same charge (What does that say about acidity rules one and two?). If there is resonance stability in HB, but not in HA, then HB is stabilized. This is illustrated in Figure 8.1. Because of the stabilization of HB it releases less energy when it goes to its conjugate base, and hence is a weaker acid. Resonance stabilization of an acid makes it weaker.

On the other hand, consider the acidity of two arbitrary compounds HC (that is NOT
Figure 8.1: Reaction coordinate curves for two acids, HA and the resonance stabilized HB. B is NOT boron.

carbon) and HD (and that is NOT deuterium):

\[ HC = H^+ + C^- \]
\[ HD = H^+ + D^- \]

where we assume that the hydrogen atom is attached to the same element with the same charge (What does that say about acidity rules one and two?). If there is resonance stability in D\(^-\), but not in C\(^-\), then D\(^-\) is stabilized. Hence the energy release is greater when HD loses a proton and it is a stronger acid. This is illustrated in Figure 8.2. *Resonance stabilization of a conjugate base makes its acid a stronger acid.*

The trick to get it right, and students seem to get this wrong more often than any single subject that I can think of, is to write out the entire reaction for the acidity of a compound and ask where, if anywhere, is there resonance stability? In the acid, or in its conjugate base?

### 8.8.1 Required Exercises

**8.8.1.1** Articulate what you have to do to find out if an acid is stronger or weaker because of resonance. HINT: Many, many students look at a problem, see resonance, and say “That is the stronger acid.” To me, that sounds like something Boniface Beebe would say!
8.8.1.2 Which is the stronger acid, 315 or 316?

8.8.1.3 Which is the stronger acid, 317 or 318?

8.8.1.4 Which is the stronger acid, 319 or 320?

8.8.2 Additional Exercises

8.8.2.1 Consider the two compounds in Figure 8.1 If both HA and HB are resonance stabilized, what would you do to determine which is the stronger acid? HINT: Nothing beats thinking.

8.8.2.2 Consider the same two compounds in Figure 8.1 If both HA and A− are resonance stabilized (but neither HB or B− are), what would you do to determine whether HA or HB is the stronger acid? HINT: Same as last problem.

8.8.2.3 Diethyl malonate ester is CH₃CH₂OC(O)CH₂C(O)OCH₂CH₃. It can give up a proton with a pKₐ of about 9. Why should this “C” acid be so much stronger than, say, C₃H₈ with a pKₐ of about 50?
Nitromethane, (CH₃)NO₂, releases H⁺ to make (CH₃)NO₂⁻ with a pKₐ of 10. From the Lewis structure (which you drew, right?) the hydrogen ion had to come from the carbon atom. Is this more or less acidic than a “normal” C-H bond?

Why is this C-H bond in the molecule in the last exercise so acidic? HINT: You know what I am going to say; if not, it involves a pencil.

Many processes in organic chemistry are catalyzed by H⁺ and/or OH⁻. These generally involve acid/base reactions. See if you can provide a series of steps (a mechanism), with epwa, that account for the reaction below, which is catalyzed by OH⁻. HINT: Hydroxide ion is a base, which will react with an acidic hydrogen atom. Find a site in the molecule where you need to break a bond to hydrogen. Start there and then proceed.

8.9 Acid Strength. Part IV: Induction

Read Klein, pp 114-116. (112-114)

The least important (although students seem to look for it first, and Klein lists it before hybridization!) factor influencing acidity concerns whether neighboring atoms remove electrons from the atom that is to lose the proton. If electrons are removed, that atom is less negative and it is easier for the proton to leave. The material is a stronger acid.
CF₃C(O)OH is a stronger acid than CF₂HC(O)OH which is stronger than CFH₂C(O)OH which is stronger than CH₃C(O)OH.

Use this concept, called induction, last. If everything else is equal, it might be determining.

### 8.9.1 Required Exercises

**8.9.1.1** The $K_a$ of 2-chlorobutyric acid (2-chlorobutanoic acid) is $1.39 \times 10^{-3}$. Why is this value greater than the $K_a$ of butyric acid (butanoic acid)?

**8.9.1.2** Given the result in the last exercise, predict the $K_a$ of 3-chlorobutyric acid (3-chlorobutanoic acid). HINT: The p$K_a$ of butyric acid is 4.82.

### 8.10 Review of Acidity

**8.10.1 Required Exercises**

**8.10.1.1** What are the four factors (and the corollary) that influence acidity?

**8.10.1.2** What is the conjugate acid of 3? The conjugate base?

**8.10.1.3** Which of the following reactions takes place extensively to the right?

\[
\text{CH}_3\text{CC}^- + \text{CH}_3\text{CHCH}_2 = \text{CH}_3\text{CHCH}^- + \text{CH}_3\text{CCH}
\]
\[
\text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{C(O)O}^- = \text{CH}_3\text{CH}_2\text{O}^- + \text{CH}_3\text{C(O)OH}
\]

**8.10.1.4** Which is the stronger acid, 9 or 10? HINT: Go through the rules.

**8.10.1.5** Compound 11 is a stronger acid than a normal amine. Suggest a reason.

### 8.10.2 Additional Exercises

**8.10.2.1** The compound 7 is a stronger acid than 8 by a factor of about 40. Suggest a reason. HINT: It is not the electron withdrawal by the -OH group; but it is a favorite topic of biologists.
8.11 Three Strong Bases, Three Different Nucleophiles

As a reminder, weak acids have strong conjugate bases. In this section we talk about three carbon bases that have quite different nucleophilicities; that is, react with very different rates with electrophiles. In particular, we focus on a carbonyl carbon as the electrophile. The three bases (illustrated here as ethyl derivatives, although other fragments can be used) are the Grignard reagent with which you are already familiar, \( \text{CH}_3\text{CH}_2\text{MgCl} \), alkyl lithium compounds, \( \text{LiCH}_2\text{CH}_3 \), and the Gilman reagent, \( \text{CH}_3\text{CH}_2\text{CuCHCH}_3^- \), 4. All three of these species are strong bases and react readily with water to pull off a proton to form (in our example cases) \( \text{CH}_3\text{CH}_3 \) plus other products. Work your way through the required exercises to see the difference in these reagents.

8.11.1 Required Exercises

8.11.1.1 Order the following in terms of increasing \( \text{C}^- \) nucleophilicity: ethyl Grignard, ethyl lithium, and diethylcuprate(I) (Gilman reagent). HINT: Use the periodic table to
Nucleophile | Typical Example | Nucleophilicity | Reacts with
---|---|---|---
Alkyl lithium Grignard Reagent | CH₃CH₂CH₂CH₂Li, C₆H₅MgCl | High, Moderate | Almost everything, Not with negatively charged cmpds
Gilman Reagent | (CH₃CH₂)₂Cu⁻ | Poor | Very few reactive compounds

Table 8.4: Some Carbon Based Nucleophiles.

figure out which metal-carbon bond is polarized the most; the most negative carbon is likely the best nucleophile.

8.11.1.2 All three of our nucleophiles react with a carboxylic acid group (-C(O)OH or an alcohol, such as in 2, 3, 5, and 6 to remove a proton from an -OH group. With 6, the resultant negatively charged ion is not reactive to the weaker nucleophiles—see the last exercise—so reaction stops at an unproductive stage: we could deprotonate these acids with NaOH! Only alkyl lithium compounds react further. Use epwa to figure out what happens for alkyl lithium compounds.

8.11.1.3 The most reactive of carbonyl carbons are those with electronegative groups attached, such as CH₃C(O)Cl. This reagent reacts with even the weakest of the three nucleophiles. Use epwa to figure out the course of this reaction. Note for future reference that Gilman reagents react with normal ketones sluggishly, and hence a synthesis of a ketone can be accomplished from an acid chloride, RC(O)Cl, using this “C⁻” reagent.

8.11.1.4 Compound 6 is treated with ethyl Grignard, then acid. What are the products? HINT: Note the verb tense and that the noun is plural; in this case I really want all the products.

8.11.1.5 Look at Table 8.4 and appreciate the different nucleophilicities of the “C⁻” reagents.

8.11.2 Additional Exercises

8.11.2.1 Make an argument for what might happen if you react CH₃MgCl with 2. HINT: There is no right answer.

8.11.2.2 Make an argument for what might happen if you react CH₃MgCl with 5. HINT: There is no right answer.

8.11.2.3 Compound 5 is treated with excess ethyl lithium, then acid. What is the product?
8.11.2.4 Some of you will react a Grignard reagent with CO\textsubscript{2} in lab this semester. You should be able to figure out what the initial products of this reaction are. Do so. HINT: No water is added.

8.11.2.5 The reaction in the last exercise “stops” after this first step (at least in theory—some of you might find a small amount of product resulting from attack of two Grignard reagents on CO\textsubscript{2}). Why does this reaction “stop?”

8.11.2.6 What will happen if you react CH\textsubscript{3}CH\textsubscript{2}Li with 2?

8.11.2.7 What is the product of butanal with ethyl Grignard? HINT: No acid is added at the end.

8.11.2.8 What is the product of butyric acid with \textit{excess} methyl lithium? HINT: No acid is added at the end. HINT: Remember, methyl lithium, in contrast to methyl Grignard, is a very powerful C\textsuperscript{−} reagent.

8.12 Using Acid to Generate a Leaving Group

Read Klein, Sections 8.9-8.10 (8.9-8.10)

In this section we use our thinking about acidity to explore a reaction called an E1 elimination. This process generates a carbocation, which we discuss more thoroughly in the next chapter. In this section our interest is on the role of acid in reaction with alcohols.

If we brought a proton up to CH\textsubscript{3}CH\textsubscript{2}CH(OH)CH\textsubscript{3}, where would you expect it to “sit”? Since a proton is an electrophile, it must seek electrons. The only loosely held electrons on this molecule are the lone pair on the oxygen atom. This generates a positively charged oxygen atom which wants to find electrons. The only electrons readily available to it (besides taking them back from the hydrogen and reforming H\textsuperscript{+}) are those in the carbon-oxygen bond. If the oxygen takes those electrons it becomes water and is no longer bonded to the carbon atom, and hence is a good leaving group, with a carbocation, a positively charged carbon atom, left behind. This process is even more efficient if we devise a way to trap the water that is liberated. We say that the proton has changed a bad leaving group, OH\textsuperscript{−}, into a good leaving group, H\textsubscript{2}O.

The resultant carbocation is unstable (as we shall see in the next chapter) and must find some electrons from somewhere. If some nucleophile comes along and donates electrons a new bond to carbon can form (This is a topic in next semester’s organic course.), but we are more interested in the process if a base comes up and removes a hydrogen atom from a carbon atom that is a neighbor to the carbocation. This is shown in Figure 8.3. Strong acid with an alcohol can form an alkene.
8.12.1 Required Exercises

8.12.1.1 Why is $\text{H}_2\text{O}$ a better leaving group than $\text{OH}^-$?

8.12.1.2 How many ways do we know to form alkenes? Name them. In your mind (or, better, on paper) outline the important steps in those pathways.

8.12.1.3 Write the mechanism for the formation of 2-methylpropene from propanone and methyl iodide using a Grignard reaction and, at the end, strong acid. HINT: More than one step.
Chapter 9

Carbocations and Alkene Stability

Compounds in which carbon carries a largely negative charge, Grignards, alkyl lithium compounds, Wittig reagents, play an important role in organic chemistry. So do compounds in which carbon carries a positive charge. Both types of compound are reactive—carbon is difficult to make negative or positive. In this chapter we examine the nature of compounds in which carbon carries a positive charge and the closely related topic of alkene stability.

9.1 Simple Carbocations

If you imagine taking a bromoalkane, \((\text{CH}_3)_3\text{CBr}\) for instance, and letting the bromide ion leave with its pair of electrons, you will have left a cationic carbon, \((\text{CH}_3)_3\text{C}^+\). This cation, though very reactive, turns out to be more stable than others you can imagine. The stability order is \((\text{CH}_3)_3\text{C}^+ > \text{CH}_3\text{CHCH}_2\text{CH}_3^+ \) (where the positive charge is on carbon 2) > \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^+\) (where the positive charge is on carbon 4). In words, tertiary carbocations are more stable than secondary which are more stable than primary. The exercises allow you to establish why this order exists.

9.1.1 Required Exercises

9.1.1.1 Imagine \(\text{CH}_3^+\). How many atoms is the carbon bonded to? What hybridization would you invoke to explain the bonding? What orbital is left over? How many electrons are in that orbital? What is the shape of the molecule?

9.1.1.2 In the \(\text{CH}_3^+\) from the last exercise, what kind of orbital on the H is necessary to donate electrons to the empty orbital on the carbon atom? Is such an orbital available on a hydrogen atom?

1\(^{\text{Remember that you can make stability arguments only with isomeric compounds.}}\)
9.1.1.3 If you consider \( \text{CH}_2(\text{NH}_2)^+ \), a three-coordinate carbon compound, does the bonded -\( \text{NH}_2 \) group have an orbital of the correct symmetry to bond to the empty orbital on the carbon? Make a sketch showing this interaction. Draw the equivalent Lewis structure. This suggests a way to stabilize positive charge on carbon—see the next exercise. HINT: It makes no difference if you put the lone pair of the \( \text{NH}_2 \) group in a p orbital on the nitrogen or in an sp\(^3\) hybrid.

9.1.1.4 Given your answer to the last exercise, what is one way to stabilize a positive charge on a carbon atom?

9.1.1.5 If you consider \( \text{CH}_2(\text{CH}_3)^+ \), a compound with a carbon bonded to two hydrogen atoms and a -\( \text{CH}_3 \) group, does the bonded -\( \text{CH}_3 \) group have an orbital of the correct symmetry to bond to the empty orbital? Careful. This is a little tricky. Make a sketch showing this interaction (which clearly implies an answer to the last question). Draw the equivalent Lewis structure, which you will not like because it contains a “no-bond” structure. NOTE: This kind of stability of a carbocation is known as “hyperconjugation”.

9.1.2 Additional Exercises

9.1.2.1 In the following formulae, the “+” sign is inserted where the carbon atom is charged. Order the following in terms of stability: \( (\text{CH}_3)_2\text{CHC}^+\text{HCH}_2\text{CH}_3 \), \( (\text{CH}_3)_2\text{C}^+\text{CH}_2\text{CH}_2\text{CH}_3 \), \( (\text{CH}_3)_2\text{CHCH}_2\text{C}^+\text{HCH}_3 \), \( (\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{C}^+\text{H}_2 \).

9.1.2.2 Will this reaction proceed to the right?

\[
\text{CH}_3\text{CH}_2^+ + (\text{CH}_3)_2\text{CHCH}_3 \rightarrow \text{CH}_3\text{CH}_3 + (\text{CH}_3)_3\text{C}^+ 
\]
9.1.2.3 Which cation, 21 or 22 is most stable?

9.1.2.4 Which cation, 24 or 25 is most stable?

9.2 Resonance Stability of Carbocations

Carboncations are stabilized by hyperconjugation as shown in the last section. Also carboncations are more stable when the positive charged can be spread out over several carbon centers by resonance.

9.2.1 Required Exercises

9.2.1.1 Draw the Lewis structure of CH$_2$X$^+$ where X is a vinyl group, -CH=CH$_2$. Does the vinyl group have an orbital of the correct symmetry to bond to the empty orbital? Make a sketch showing this interaction. Draw the equivalent Lewis structure.

9.2.1.2 Which of the cations 18-20 are stabilized by adjacent double bonds? Use epwa to prove your point.

9.2.1.3 Which cation, 19 or 23 is most stable? HINT: Look carefully at the resonance structures that you drew. You did draw them, didn’t you?

9.2.1.4 What are three ways to stabilize a positive charge?

9.3 Stability of Alkenes by Hyperconjugation

Read Klein, Section 8.5 (8.5)

Draw the Lewis structure of propene. Now draw a minor resonance structure in which a pair of electrons in a C-H bond of the -CH$_3$ group makes a double bond between the -CH$_3$ carbon and one of the vinyl carbon atoms. HINT: Remember to keep all carbon atoms to four bonds or less. This resonance is not present when the double bond is attached only to hydrogen atom substituents; hence the stability of a double bond is higher when there is a substitution of a methyl group (or other alkyl group) for a hydrogen atom.

9.3.1 Required Exercises

9.3.1.1 Which alkene is more stable, CH$_3$CH=CHCH$_2$CH$_3$ or (CH$_3$)$_2$C=CHCH$_3$?
9.4 Stability of Alkenes by Resonance

The heat of hydrogenation of an alkene (heat absorbed by the compound at constant pressure when $H_2$ reacts with it) for 1,3–pentadiene is $-222.6$ kJ/mole and that of 1,4-pentadiene is $-253.1$ kJ/mole. Draw both alkenes. Which is most stable; by how much, and why? Think about these features: The negative sign means that heat is really released, not absorbed; that is, the products are more stable than the reactants. So if you make a diagram (which is always the safe thing to do in stability problems), the alkanes are below the alkenes. Note also the alkane is the same in both cases.

9.4.1 Required Exercises

9.4.1.1 The heat of combustion (heat absorbed by the system at constant pressure when the compound reacts with $O_2$ to produce $CO_2$ and $H_2O$) of 1,3–pentadiene is $-3010.7$ kJ/mole and that of 1,4-pentadiene is $-3041.2$ kJ/mole. Which is most stable; by how much, and why?

9.4.1.2 The heat of isomerization to spiropentane, 28, of 1,3–pentadiene is $109.3$ kJ/mole and that of 1,4-pentadiene is $78.8$ kJ/mole. Which of the dienes is most stable; by how much, and why? HINT: Are products up or down in energy?

9.4.1.3 Compare the resonance in benzene with that in butadiene. Which is most important? Why?
Chapter 10

A Review of some Old Syntheses and a New One

In this chapter we take a pause to review where we are with respect to syntheses. The reactions that we have learned are summarized in Table 10.1.

10.1 Old Syntheses

The reactions that we have learned are summarized in Table 10.1.

10.1.1 Required Exercises

10.1.1.1 What kind of compound is $29$? HINT: There are two answers.

10.1.1.2 From Table 10.1 how do you make the kind of compound that $29$ is?

10.1.1.3 Do we need to add carbons to acetone in order to make $29$ from it? How many?

<table>
<thead>
<tr>
<th>Cmpd to Synthesize</th>
<th>Starting Material</th>
<th>Reagent</th>
<th>New C-C bond?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Ketone/Aldehyde</td>
<td>Grignard, Alkyl lithium</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Ketone/Aldehyde</td>
<td>$\text{BH}_4^-$</td>
<td>No</td>
</tr>
<tr>
<td>Alkene</td>
<td>Ketone/Aldehyde</td>
<td>Wittig with RCl</td>
<td>Yes</td>
</tr>
<tr>
<td>Alkene</td>
<td>Alcohol</td>
<td>Strong acid with removal of water</td>
<td>No</td>
</tr>
<tr>
<td>Epoxide or Oxirane</td>
<td>Ketone/Aldehyde</td>
<td>Sulfur ylide with RCl</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 10.1: Synthetic Processes
10.1.1.4 How would you prepare 29 from 30 and acetone?

10.1.1.5 Compound 27 is treated first with ethyl magnesium bromide, then with acetic acid, a weak acid, but not as weak as NH\textsubscript{4}\textsuperscript{+}. What is the final product?

10.1.1.6 What kind of compound is 1-pentene?

10.1.1.7 From what kind of compound(s) do you prepare the kind of compound that 1-pentene is?

10.1.1.8 Do we have to add carbon atoms to butanal to make 1-pentene? How many?

10.1.1.9 How would you make 1-pentene from methyl iodide and butanal?

10.1.1.10 How would you make 4-methyl-2-pentene? HINT: Look at Table 10.1

10.1.2 Additional Exercises

10.1.2.1 Compound 26 is treated first with ethyl magnesium bromide, then with a weak acid. What is the final product?

10.1.2.2 Compound 26 is treated first with ethyl magnesium bromide, then with strong acid. What is the final product? HINT: Surely something is different here relative to the last exercise (or you are forced to the unmentionable alternative about my marbles).
10.1.2.3 Boniface Beebe, the famous chemist from rural Arkansas, reacted $(\text{C}_6\text{H}_5)_2(\text{CH}_3)\text{P}$ with ethyl iodide. He took the product of this reaction, treated it with butyl lithium, and then added acetone. Much to his surprise, he isolated two products containing only C and H. “Leapin’ lizards,” he shouted, “what are those products? Why are there two products?” And you would answer?

10.1.2.4 How would you prepare 32 from 2-bromopropane and 3-methyl-but-2-enal?

10.1.2.5 In the last exercise, there is are two possible routes in the last step. Why is the one you want the most efficient path?

10.1.2.6 Is there a synthesis of 32 other than that you suggested in exercise 10.1.2.4? If so, what is it? Which synthesis would you use? Why?

10.2 Synthetic Thinking

To think about making a given compound requires that you proceed down a list of questions. Here is the process using what we know already. Question: How would your prepare 2-pentene from compounds with less than five carbons? The first step is to identify what kind of compound we want to make. In this case, a alkene, a compound with a double bond, with five carbons and with the double bond in the “2” position. The second step is to review in your mind how to make that kind of compound, how to make alkenes in this case. We have two methods, lines 3 and 4 in Table 10.1. Any conditions on our synthesis? Yes, we need to start with less than five carbon atoms in our starting material. So do either of our methods make a new C-C bond? Yes, the Wittig process does. That is what we should use. So we draw the retrosynthetic line through the double bond and decide that propional and ethyl bromide would be good starting materials. Use epwa to convince yourself of this.

10.2.1 Required Exercises

10.2.1.1 We have (at this stage) two ways to make an alkene. Start with cyclohexanone and prepare alkenes with formula C$_7$H$_{12}$ by each of these methods. Use epwa. What is the difference between your products?

10.2.1.2 The ketone, 2-butanone, is reacted with methyl lithium and then with strong acid. What is the product? HINT: This exercise uses two of the reactions in Table 10.1.

10.2.1.3 Write a mechanism for the reactions in the last exercise, which is how you should have solved it in the first place.
10.2.2 Additional Exercises

10.2.2.1 The ketone, 2-butanone, is reacted with methyl lithium and then with strong acid. What is the product?

10.2.2.2 Give the carbon level of the carbon atoms in 34.

10.2.2.3 What happens to carbon levels when a Grignard reagent attacks a carbonyl compound to make an alcohol? Is there a “balance” among the changes in carbon levels?

10.3 Some Reactions are Reversible

Quite a number of the reactions that we will deal with this semester are reversible. That is, they can go either direction by applying the appropriate push. Grignard and alkyl lithium and borohydride ion reactions are not reversible because the leaving group would have to be a “C−” or an “H−”, both of which are strong bases and hence very poor leaving groups. The formation of an alkene by dehydration of an alcohol is reversible: you simply either remove water or provide water in the presence of the acid catalyst. Try the first exercise.

10.3.1 Required Exercises

10.3.1.1 How would you synthesize 2-methyl-2-butene from 2-methyl-2-butanol? To do so you would want conditions with low concentration of water to make it easier to remove that water molecule. How might you make the reverse reaction take place? Would you need water? Would you need H+? HINT: Think backwards, exactly backwards. There is even a name for that: microscopic reversibility.

10.4 A New Reaction: Opening Epoxides with Nucleophiles

Read Klein, pp 654-657. (643-646)

Epoxides are three membered ring compounds which have strain because the sp3 hybrids do not point in the direction of the atoms to which the carbon is bonded. Hence they are subject to “opening” of the ring. To open the oxirane ring requires that a new group come forward to bond to one of the two carbon atoms. This attack occurs as the oxygen atom leaves the carbon. Such a process requires both the oxirane and the incoming group to collide with sufficient energy to cause reaction. If both the oxygen atom and the incoming group are to be partially bonded to the carbon atom, we have to use one orbital on carbon to bond to two atoms. Since the 2p orbital on a carbon atom more easily extends away from the carbon atom, that is the orbital of preference. What would you imagine is the best
way for two atoms to *simultaneously* bond to a carbon atom? Make a rough sketch of this bonding situation. HINTS: (1) Here is a case where you *will* have five bonds, or at least five partial bonds, to a carbon atom: an unstable, high energy, transition state between two normal four-bonded carbon atoms. (2) We have done this reaction before in the Wittig reaction ($S_N2$ reaction); we are just looking at it in a slightly different way.

### 10.4.1 Required Exercises

#### 10.4.1.1
From your sketch made in response to my urging in the introduction, assess the difficulty in getting a nucleophile close to the oxirane carbon when it has two hydrogen atoms as its substituents versus the situation where it has two methyl groups as substituents. 

NOTE: This is called steric interference. HINT: This will play an important role in the study of $S_N1$ and $S_N2$ reactions next semester.

#### 10.4.1.2
Take methyl-oxirane and open it with $\text{SH}^-$, then treat the resultant material with dilute acid. Will the nucleophile attack one side preferentially?

#### 10.4.1.3
Look hard at the product from the last exercise. It contains an alcohol grouping from the original epoxide and the attacking nucleophile on the adjacent carbon, the so-called $\alpha$ carbon. This type of structure comes from opening of epoxides and it is important that you recognize it. I would like to name it so we can talk about it later. (WARNING: This name I am making up will not be found on the web or in books. This is disconcerting to some people. However, I believe it is pedagogically useful.) Let’s call this an $\alpha$-DIN, where “din” stands for “di-electronegative” reflecting the -OH and the -SH groups on adjacent carbon atoms. (WARNING continued: If you are dealing with a person that does not understand the words $\alpha$-DIN, you should use words like $\alpha$-thiol alcohol, or some such thing. We will find many compounds of this sort and need a general term. Hence the invention.) Be able to recognize that structure so that later you can synthesize it.
10.4.1.4 The compound 2-butanone is treated with the sulfur ylide, \((\text{CH}_3)_2\text{S}^+\text{CH}_2^-\) and product A is isolated. That material is reacted with ethyl Grignard, followed by dilute acid to give B. What are A and B? Give the mechanism and use epwa. HINT: Think about steric issues with this powerful nucleophile.

### 10.5 More of the New Reaction: Opening Epoxides in Acid

Read Klein, pp 657-662. (647-651)

Methyl-epoxide has only one site on which it can be protonated, the oxygen atom. Draw the Lewis structure of this material and consider a couple of possible resonance structures that move positive charge off of the oxygen. There are two resonance structures with positive charge on carbon; using your knowledge of the stability of a positive charge on carbon, decide which of these resonance structures is most important. Since the “average” of the resonance structures gives reality, which of the carbon atoms in protonated methyl-oxirane is most positive? If a nucleophile were to attack a protonated oxirane, it would do so at this site. Note that acid changes the attack site of an epoxide!

### 10.5.1 Required Exercises

10.5.1.1 Show that the result of opening an substituted oxirane depends on the acidity of the medium. Do two reaction epwas, one using \(\text{Br}^-\) as a good nucleophile for attack on neutral methyl-oxirane and another using \(\text{Br}^-\) as a nucleophile for attack on a protonated methyl-oxirane. Be sure to note the different products. Are both products \(\alpha\)-DINs?\(^1\)

10.5.1.2 The compound 2-pentanone is treated with the sulfur ylide, \((\text{CH}_3)_2\text{S}^+\text{CH}_2^-\) and product C is isolated. That material is reacted with bromide ion in the presence of acid to give D. What are C and D? Give the mechanism and use epwa. HINT: Think about the role of acid in opening an oxirane.

10.5.1.3 Do you recognized the structural features in 35? How do we make the kind of compound that 35 is?

10.5.1.4 To get 35 we have to open an epoxide the right way. Which way is that? And how do we open the oxirane that way?

10.5.1.5 Show how you could make 35 and 36 from propanal.

\(^1\)Warning: Use of the word “\(\alpha\)-DIN” is subject to questioning looks from many people. Explain yourself to them.
10.5.1.6 Prepare 39 from butanone and ethyl iodide. HINT: Several steps.

10.5.2 Additional Exercises

10.5.2.1 What is the product of the reaction of HBr with 37? HINT: HBr is a strong acid.

10.5.2.2 What is the product of the reaction of HS- with 37? HINT: HS- is a very weak acid.

10.5.2.3 What is the product of the reaction of ethanol with 38 under conditions of sulfuric acid catalysis?

10.5.2.4 What is the product of the reaction of methoxide ion with 38?

10.5.2.5 Review. What is the product when (1) methyl iodide is treated with (CH₃)₂S, (2) this product is treated with butyl lithium, and (3) that last product is added to acetone.

10.5.2.6 Prepare 40 from butanone and ethyl iodide. HINT: Several steps.

10.6 Several Step Syntheses

This section gives you the chance to practice multistep syntheses. Remember to (1) identify the kind of compound you are trying to make and (2) to determine what ways you have to make such a compound. At that stage ask if you need to form new C-C bonds. Work your way backwards to the starting materials (if given) slowly and patiently.

10.6.1 Required Exercises

10.6.1.1 How would you make 2,3-dihydroxypentane from propanal and ethyl bromide?

10.6.1.2 How would you synthesize 2-methyl-butan-2-ol from compounds with 2 carbon atoms or less.
10.6.2 Additonal Exercises

10.6.2.1 How would you prepare 4-methyl-2-pentene from substances with four or fewer carbon atoms?

10.6.2.2 How would you prepare 44 from 45 and other simple compounds? HINT: Think several steps.
Chapter 11

Reversible Addition to Aldehydes and Ketones

We are ready now to move to the next kind of reaction of aldehydes and ketones. The reactions we have looked at up to now have been irreversible because there is no good leaving group after a “C−” or “H−” reagent attacks a carbonyl. There are nucleophiles that do attack a carbonyl reversibly, and those are our current subject. There are many reactions of this type, but all of them are very similar. To appreciate that similarity makes this subject easy; if you neglect it, the subject becomes hard.

We shall also explore in this chapter two methods of making aldehydes and ketones from alcohols.

11.1 Reversible Addition of Nucleophiles to Aldehydes and Ketones

Read Klein, pp 937-941. (921-924)

Imagine a solution of OH− in water with an aldehyde, CH₃C(O)H. The hydroxide ion is a nucleophile and it can attack the positive carbon of the carbonyl (just as a “C−” reagent would). Draw the epwa for this process. This puts negative charge on what was the carbonyl oxygen, which, will react with a water molecule to remove a proton and generate an OH−. Draw the epwa for this second step. Thus the hydroxide ion is merely a catalyst for the reaction. The product is a diol, but rather than being an α-diol, it is a gem-diol, meaning both OH groups are on the same carbon atom. Though the word “gem-diol” is known to lots of people (and can be found on the web), this is one of a general class of compound that it is useful for you to recognize. WARNING: I am about to do it again! This compound has two electronegative elements attached to the same carbon, hence it would seem appropriate to call it a “gem-DIN.”¹

¹As usual, use this word to organize your thoughts, which is what it was designed to do. There are lots
What makes this reversible and the previous reactions with “C−” and ‘H−” reagents not? In a word, the leaving group. Do the reverse process from the last paragraph—remember it really is exactly the reverse. Take a proton off one of the bonded OH groups, making an “O−” which can push its electrons toward the carbon to form a double bond, but only if the carbon breaks the bond to the other oxygen atom. Because OH− is a much weaker base than “C−,” it is a much better leaving group. Do the epwa for the reverse process.

The process described here is just the addition of water to the carbonyl group, catalyzed by OH−. Besides the mechanism, the other important issue is which side, aldehyde/ketone or gem-diol, is favored at equilibrium? The answer is for aldehydes the equilibrium favors the diol form, whereas for ketones the carbonyl form is favored. (The rationalization for this is that the diol of a ketone has four large groups attached to the central carbon and is crowded; aldehydes have one small group, the hydrogen atom, and thus can adopt the diol form more readily.) The issue is a little more complex than that in that ketones with electron withdrawing substituents, such as CF3C(O)CF3 are also favored in the diol form.

11.1.1 Required Exercises

11.1.1.1 Use epwa to show the reaction of SH− to proponal in water. HINT: Two steps.

11.1.1.2 Butanal is treated with a mixture of HCN/CN−. Butanal has a peak at 1731 cm−1 which disappears and is replaced by peaks at 2247 cm−1 and a broad peak at 3340 cm−1. Use epwa to show what happens.

11.1.2 Additional Exercises

11.1.2.1 Chloral, CCl3CHO, is also known as the “knock-out” drops, is the famous “Mickey Finn” used by gin runners in prohibition to put the competition flat on their backs. To test for this in a glass of watered-down gin, the FBI asked Boniface Beebe, the natural philosopher of distinction from Searcy, Arkansas, which is just down the road from Beebe, AR, which is the town where the red-winged blackbirds plunged to their death on New Year’s Eve day in 2010 and 2011, to investigate (that folks, is a run-on sentence). He used nmr to look for the characteristic peak that occurs in aldehydes between 8 δ and 10 δ. He found no sign of a peak. Bonnie was joyful in his conclusion that chloral was not present? Was he right? Give your reasoning.

11.2 Acid Catalyzed Reversible Addition to Aldehydes and Ketones

Read Klein, pp 941-947. (925-931)

of people in this world, most, actually, that will look at you as if you are crazy if you utter this word. Keep it to yourself unless you are talking to students in this class.
By far the most significant reversible reaction with aldehydes and ketones are acid catalyzed. Let a proton approach a ketone. The site of protonation would be the oxygen atom, which would make it more positive, and hence, increase the positive charge on the carbonyl carbon, which makes it a much better electrophile. Now even a poor nucleophile, like water, would be able to attack the carbonyl carbon. Upon this attack, the double bond will shift to the carbonyl carbon, relieving the positive charge there, but the oxygen of the water molecule will be charged positive. If it loses a proton, we have the gem-diol (gem-DIN to us, and only us) formed by acid catalysis. Write out the epwa for these steps. You will see the same steps over and over again in this chapter.

**11.2.1 Required Exercises**

**11.2.1.1** Use epwa to show the mechanism of the reaction of water with 43 in the presence of acid.

**11.2.1.2** How does the reaction in the last problem differ from reaction of H\(^-\) (or BH\(_4^-\)) with 43? How is it the same? HINT: “Contrast and compare. Compare and contrast.”

**11.2.1.3** Use epwa to show the mechanism of the reverse reaction of exercise 11.2.1.1. HINT: If you recognize that this is a dumb question, don’t do it. If not, proceed and learn.

**11.2.1.4** Now let’s do just a minor modification. Write the mechanism for the acid catalyzed attack of one mole of an alcohol on acetone. HINT: This is just like water attacking, exactly, except on of the hydrogen atoms on the water has become an “R” group.

**11.2.1.5** Now two further modifications, one here and one in the next exercise. From the last exercise we have attached to the (old) carbonyl carbon, one HO- and one CH\(_3\)CH\(_2\)O-. Let a proton approach and sit on the second group. Which is the good leaving group? What will happen if a lone pair on the oxygen of the HO- group formed a double bond?

**11.2.1.6** Let a proton approach the molecule that started the last exercise and sit on the oxygen of the HO- group. Which is the good leaving group? What will happen if a lone pair on the oxygen of the CH\(_3\)CH\(_2\)O- group formed a double bond? Can the positive charge that results on this oxygen be resolved? Only by attack with another molecule of CH\(_3\)CH\(_2\)OH. Use epwa to show this. We have prepared what is called an acetal. Note water removal will favor the acetal products.

**11.2.1.7** WARNING: Do this problem only if you are willing to use words made up to make this course more understandable. Could the product of the last exercise, an acetal, be called a gem-DIN? Do you see why I want to use this name? Both gem-diols and acetals
are formed from aldehydes and ketones in exactly the same way; the single name, gem-DIN, reflects this.

11.2.1.8 Write the mechanism for the acid catalyzed decomposition of the ethanol acetal of acetone, that is the reverse of the reactions of the last several exercises. HINT: Duh.

11.2.1.9 Use epwa to show formation of the acetal of cyclopentanone with methanol in acid solution with water removal.

11.2.1.10 In your product of the last problem, color the carbon atoms that originated in the cyclopentanone one color and those that originated in the ethanol, and the oxygen atoms of the methanol, another. Draw a line between the two colors. Look hard at that sketch and be able to recognize how that structural form is synthesized. The same cleavage lines will be present in any gem-DIN, which is why we use the word.

11.2.2 Additional Exercises

11.2.2.1 Use epwa to show the acid catalyzed addition of water to cyclopentanone.

11.2.2.2 Use epwa to show hydrogen ion catalyzed acetal formation between cyclohexanone and propanol.

11.2.2.3 What kind of compound is 46? Answer both for the outside world and for this class.
11.2.2.4 From what kind(s) of compound(s) do we make compounds of the “kind” you specified in the last exercise?

11.2.2.5 What happens when you treat \(46\) with acidified water? Use epwa to write a mechanism. HINT: Do you recognize this as the reverse of something. If so, the question is trivial.

11.2.2.6 If one takes \(55\) and dissolves it in water containing catalytic amounts of acid, one finds the IR carbonyl peak disappears. What happens, and why, on the basis of bonding, does it happen?

11.3 Protection of Aldehydes and Ketones

Read Klein, p 945. (929)

We have seen that aldehydes and ketones react with alcohols under acid catalysis (sometimes with the removal of water) to yield acetals. These compounds lack the carbonyl double bond and hence are not subject to attack by the good nucleophiles such as Grignard reagents. Also, acetals are readily cleaved in acid solution (in the presence of water), hence are easily removed. Thus the formation of an acetal acts to protect that carbonyl from attack and then the carbonyl can be regenerated when the reaction is over. Since aldehydes form acetals much more readily than ketones, it is easy to protect an aldehyde in the presence of a ketone. (The other way around is more tedious.)
11.3.1 Required Exercises

11.3.1.1 How would you prepare 48 from 49? HINT: Two carbonyl groups: both would react with most reagents, unless . . . .

11.3.1.2 What do you obtain when you treat 54 with one equivalent of 1,3-propanediol in the presence of acid with removal of water, followed by reaction of that product with ethyl lithium, and then aqueous acid?

11.3.1.3 Multistriatin, a pheromone for the elm bark beetle, has the structure 53. What is the product when this material is treated with dilute aqueous acid?

11.4 Synthesis of Ketones and Aldehydes

We have not discussed synthesis of ketones and aldehydes (with one exception, in exercise 8.11.1.3). There are two other useful methods that are available to us at this point in the course. The first involves using the properties of aldehyde hydration to control the process.
11.4.1 Using H$_2$CrO$_4$ in Acid to Produce a Ketone

Read Klein, pp 609-612. (597-600)

Ketones can be prepared from alcohols using H$_2$CrO$_4$ in acid. The mechanism is shown in Figure 11.1. The alcohol attacks the Cr(VI) center and displaces a water molecule, made into a good leaving group with acid. Loss of a proton from the alcohol oxygen completes this first step, which is in equilibrium. The determining factor for net reaction is to get electrons to the Cr(VI), which occurs when a hydrogen atom is abstracted from the (incipient) carbonyl carbon by a base, and electrons can then flow to Cr(VI). That step is not reversible.

11.4.2 Required Exercises

11.4.2.1 Write the mechanism (use epwa) for the reaction of H$_2$CrO$_4$ in H$^+$/water with 3-pentanol.

11.4.2.2 Compound 41 is treated with CrO$_3$ in acid, the organic material is isolated and reacted with CH$_3$MgBr and then weak H$^+$. What is the product?

11.4.2.3 What side product may be formed in the process described in problem 11.4.2.2?

11.4.3 The Primary Alcohol Issue

A very similar reaction takes place with primary alcohols (but not tertiary—why not?). The initial product is an aldehyde. So why is this a separate section? Because we know what happens to aldehydes under acid conditions in the presence of water: they hydrate to the gem-diol, which, being an alcohol, can react with another mole of Cr(VI) in a very similar reaction to that given in Figure 11.1. The product is an carboxylic acid, a carbon level 3 compound. The next section solves our problem of oxidizing a primary alcohol to an aldehyde and stopping.

11.4.4 Required Exercises

11.4.4.1 Use epwa to show the oxidation of a primary alcohol, say ethanol, to an aldehyde with H$_2$CrO$_4$.

11.4.4.2 Use epwa to show the hydration of ethanal, the product of the last exercise.

11.4.4.3 Use epwa to show the oxidation of hydrated ethanal, a gem-diol, to acetic acid.
11.4.5 Primary Alcohols without Water, PCC

If we use H$_2$CrO$_4$ as the oxidizing agent (It might help your thinking here to recognize that an oxidizing agent raises the carbon level of a carbon atom on which it works,) for a primary alcohol, it is not feasible to stop at the aldehyde stage because of the formation of the gem-diol, the hydrate of the aldehyde, which then acts as an alcohol and reacts further with the H$_2$CrO$_4$. Organic chemists have designed a reagent that avoids this problem. It does so by reacting in a medium that is not aqueous so that there is no water around to react with the aldehyde. Since the aldehyde cannot bind well to the Cr(VI) center, the reaction stops. The reagent is called PCC, an abbreviation for pyridinium chlorochromate. This reagent is soluble in a non-aqueous solvent, say CH$_2$Cl$_2$ because of the large cation, the pyridinium ion, C$_5$H$_5$N$^+$. The Cr(VI) reagent has a chloride ion in the coordination sphere which acts as a good leaving group when the alcohol attacks. Other than those differences, the mechanism is exactly like that detailed in Figure 11.1.

11.4.6 Required Exercises

11.4.6.1 Write the mechanism (use epwa) for the reaction of PCC with 3-pentanol in CH$_2$Cl$_2$.

11.4.6.2 How would you prepare 43 from 2-methyl-1-propanol? Use epwa to describe.

11.4.7 Additional Exercises

11.4.7.1 Write the mechanism (use epwa) for the reaction of H$_2$CrO$_4$ in H$^+$/water with 3-pentanol.

11.4.7.2 Write the mechanism (use epwa) for the reaction of H$_2$CrO$_4$ in H$^+$/water with 1-pentanol.

11.4.7.3 What factor causes the difference in the mechanism (and products) of the reactions in problems 11.4.7.1 and 11.4.7.2?

11.4.8 Ozone Cleavage of Alkenes to Produce Aldehydes and Ketones

Read Klein, Section 9.11. (9.11)

A second method of preparing ketones and aldehydes using cleavage of an alkene with ozone, followed by treatment with metallic zinc. The alkene is cleaved at the double bond and each carbon of the double bond becomes a carbonyl carbon of an aldehyde or ketone with ozone providing the oxygen atoms. If one side of the double bond has two non-hydrogen
substituents, then that side becomes a ketone. If it has only one non-hydrogen substituent, it becomes an aldehyde. (And it if has none?) We will leave the detailed mechanism of this reaction until we talk about alkene chemistry.

11.4.9 Required Exercises

11.4.9.1 Predict the product of the reaction of ozone, \( O_3 \), with 2-hexene followed by treatment with Zn. What would you look for in the IR to identify the nature of the products?

11.4.10 Additional Exercises

11.4.10.1 Extrapolate your knowledge by predicting the product of the reaction of ozone, \( O_3 \), with 2-methyl-2-butene, followed by Zn. HINT: An H and a CH\(_3\) group are isovalent.

11.5 Reversible Addition of Nitrogen Nucleophiles

Read Klein, pp 947-954. (931-939)

The addition of \( \text{NH}_2X \), where X- can be R-, \( \text{H}_2\text{N}^- \), or HO- is exactly the same as addition of alcohols, and in each case we form, at least initially, a gem-DIN\(^2\). First the protonated carbonyl is prepared to make a better electrophile, then the amine nitrogen attacks, to form instead of a gem-diol, a gem-olamine. a gem-DIN. If a second mole of proton sits on the oxygen of the “-ol,” the resultant water becomes a good leaving group which the nitrogen long pair can “drive” out with the formation of a double bonded positively charged nitrogen atom. Loss of a proton from this completes the process to yield a carbon-nitrogen double bond, an \textit{imine}.

Again, this process close resembles acetal formation.

11.5.1 Required Exercises

11.5.1.1 Write the mechanism for the acid catalyzed attack of \( \text{NH}_3 \) on acetone to form what is officially called a hemi-aminal (NOT animal, but from amine and “al” because it works for aldehydes as well), but which we might recognize as a gem-DIN.

11.5.1.2 Aminals, see the last exercise, are generally not very stable. They undergo acid catalyzed dehydration. Use epwa to show this process. You should end up with an \textit{imine}, a “carbon double bonded nitrogen” compound.

\(^2\)As usual, warning!
11.5.1.3 What would happen to the aminal of exercise 11.5.1.1 if it underwent acid catalyzed loss of NH₃. Use epwa to describe.

11.5.1.4 Imines, see exercise 11.5.1.2, are also rather unstable and can revert back to the ketone (or aldehyde) under acid conditions. What would drive a mixture of NH₃, H⁺, and acetone to the imine form? What would drive it to the ketone form? Can you see a general picture here?

11.5.1.5 What do you see that is common among the compounds NH₂H, NH₂CH₃, NH₂OH, and NH₂NH₂, where I have written the first in an odd way to promote your recognition of the similarity. Draw Lewis structures of all these species.

11.5.1.6 Look at the last exercise and then show that if you understand how NH₃ reacts (under acid catalysis) with a ketone or aldehyde, you also know how any of the other NH₂X compounds do. Do you know how NH₃ reacts? If not, go back a few exercises and start again.

11.5.2 Additional Exercises

11.5.2.1 How would you prepare 47 from an ketone?

11.5.2.2 Repeat the general process for acid catalyzed reaction of NH₂X compounds with a ketone, see required exercises with a compound of the type NHX₂, for instance NH(CH₃)₂. HINT: You should be able to get almost to the end of the synthesis, but will be forced to stop before the final step. Why? Articulate your answer in less than eight words.

11.5.2.3 Examine the final material in your epwa from the last exercise, a species with a positive charge on a nitrogen atom double bonded to a carbon. There is a way to put a lone pair back on the nitrogen atom, and thereby relieve the positive charge. It involves using a C-H bond α to the carbonyl (or what was the carbonyl) carbon. See if you can produce this “enamine.”

11.6 Reactions of Nitrogen Containing Adducts

Read Klein, pp. 955-956. (939-940)

There are a number of interesting reactions of the adducts of carbonyl compounds with nitrogen nucleophiles that we discussed in the last section. The products formed with NH₂OH are called oximes and were used (before nmr) to identify carbonyls because of their crystalline nature and their sharp melting points. Oximes of aldehydes can also be
dehydration to form nitriles. Although not used very often, any of these adducts with carbon-nitrogen double bonds are susceptible to attack by “C−” and “H−” reagents.

Two reactions of these derivatives of carbonyl compounds are reasonably important: One is the Wolff-Kishner reaction. In this reaction of the hydrazone, for instance, \( \text{CH}_3\text{CH}_2\text{C(=NNH}_2\text{)}\text{CH}_2\text{CH}_3 \), strong base is used as a reagent. The base reacts with the most acidic site of the molecule (which is what?), the N-H bond, and removes a proton, which causes the reaction, as outlined by Klein, to proceed. The net chemistry is the removal of the functional group.

The second important reaction involves treating an aldehyde or ketone with an amine and dilute acid in the presence of cyanoborohydride ion, \( \text{BH}_3\text{CN}^- \). This hydride reagent is very weak because of the electron withdrawing ability of the cyanide group. It is not capable of reacting with an aldehyde or ketone, but can reduce an imine. The dilute acid and the amine set up an equilibrium between aldehyde or ketone and the corresponding imine, with the imine in low concentration. The cyanoborohydride reacts with imine, converting it to an amine, and removing it from the equilibrium system so the aldehyde or ketone reacts to form more imine, etc. Hence we have an efficient synthesis of amines.

11.6.1 Required Exercises

11.6.1.1 Close the book and try to do the Wolff-Kishner reaction from the very beginning using 3-pentanone as your ketone.

11.6.1.2 How would you prepare 65 from fragments with four carbons or less? HINT: There are only two ways we know to get rid of a functional groups from a molecule.

11.6.1.3 Use epwa to show how \( \text{BH}_3\text{CN}^- \) reacts with an imine in acid solution.

11.6.1.4 How would you prepare \( \text{CH}_3\text{CH(NHCH}_3\text{)CH}_3 \) from acetone and methyl amine?

11.7 Acid Catalyzed Addition of Sulfur Nucleophiles: Dithianes

A very useful reagent can be made by reaction of a thiol, a compound of with an -SH group. These react with aldehydes and ketones just like alcohols do under acid catalysis to form thioacetals (another example of a gem-DIN).\(^3\) When the carbonyl compound is formaldehyde, and the thiol is the dithiol, 1,3-propanedithiol, \( \text{HSCH}_2\text{CH}_2\text{CH}_2\text{SH} \), the product is also called a dithiane. The beauty of dithiane is that the carbon between the two sulfur atoms, the carbon that was a carbonyl carbon in the original formaldehyde, is somewhat acidic and can be deprotonated to form a “C−” reagent. This reagent can attack various

\(^3\)Beware! Only members of this class understand the term.
compounds, including alkyl halides, to form new carbon-carbon bonds. Work your way through the problems to convince yourself that you understand this. When the dithiane is then hydrolyzed back to a carbonyl compound with acid solution—but see exercise 11.7.1.4—a new aldehyde or ketone is formed. Dithiane offers a nice way to synthesize ketones and aldehydes.

### 11.7.1 Required Exercises

**11.7.1.1** Use epwa to show acid catalyzed (thio)acetal formation when formaldehyde, CH$_2$O, reacts with 1,3-propanedithiol. HINT: Use analogy with the corresponding oxygen derivative.

**11.7.1.2** A compound of the sort you made in the last exercise is called a **dithiane**. Dithiane is a weak acid at the carbon atom between the two sulfur atoms (Why?). Show using epwa what will happen if you deprotonate the dithiane with a strong base and then treat that anion with propyl bromide.

**11.7.1.3** What will happen if the product of the last exercise is treated with H$^+$? Use epwa to answer. HINT: Break one of the two C-S bonds with the proton, but do not allow a nucleophile to attack—see the next exercise.

**11.7.1.4** Compare your result for the intermediate in the last exercise with the corresponding intermediate involving oxygen derivatives. The resonance structure with the group VI atom becoming positive is favored for S by electronegativity, but by oxygen in terms of the better $\pi$ overlap between oxygen and carbon compared to sulfur and carbon. The net result (hard to predict) is that dithianes are a little harder to hydrolyze than the corresponding oxygen compounds. Mercuric ions are often added to aid in hydrolysis of the dithiane because they react strongly with -SH groups. For our purposes, you can go ahead and use the same kind of epwa that you used with the oxygen species to get rid of the sulfur atoms, to deprotect the old formaldehyde carbon, or just not do it at all and know that mercuric ions will achieve the end. Do the acid hydrolysis once for practice.

**11.7.1.5** Write an epwa to describe the mechanism of the following process. The dithiane of formaldehyde (exercise 11.7.1.1) is treated with strong base followed by methyl iodide. That product is treated with strong base followed by butyl bromide. That product is treated with aqueous acid and mercuric ion. What is the final product?

**11.7.1.6** How would you synthesize 5-methyl-3-hexanone from formaldehyde, ethyl bromide, and 1-bromo-2-methyl-propane using dithiane chemistry?
11.7.2 Additional Exercises

11.7.2.1 How would you synthesize cyclohexanone from 1,5-dibromopentane and formaldehyde using dithiane chemistry?
Chapter 12

Review of Reactions; Doing Paper Syntheses

This chapter contains review exercises covering the material in the course so far. You should spend some time thinking about the relationship between the reactions and hence the number of significantly different reactions we have covered. The reactions we have discussed in the course to date are given in a fashion that I organized in Table 12.1. You may want to organize them in a different fashion; that would be good. Also, I left off what is formed in all cases in order for you to engage with the table.

12.0.1 Required Exercises

12.0.1.1 How would you synthesize 56 from cyclohexanone and other carbon containing compounds?

12.0.1.2 How would you make 57 from compounds with four or fewer carbon atoms? Specify your reaction(s) with epwa.

12.0.1.3 Use epwa to show the formation of the imine formed from 2-propanone and ethyl amine.

12.0.1.4 Compare the reaction of acetone with, on the one hand, NH₃, and on the other with NH(CH₃)₂. How are they the same? How do they differ?

12.0.1.5 What kind of compound is 59?

12.0.1.6 How do you make the kind of compound that you specified in the last exercise?
1. Aldehydes and Ketones
   
   (a) Non-Reversible Reactions
      i. Reactions with “C⁻” and “H⁻” reagents.
      ii. Reactions with ylides.
      iii. Reactions with alkyne anions.
   
   (b) Reversible Reactions
      i. Diol Formation
      ii. Acetal Formation
      iii. Nitrogen Nucleophiles
         A. Wolff-Kishner reaction
   
   (c) Synthesis
      i. \( \text{H}_2\text{CrO}_4 \), PCC
      ii. \( \text{O}_3 \)
      iii. Dithiane
      iv. Gilman reagent on RC(O)Cl

2. Epoxides
   
   (a) Synthesis
   
   (b) Reactions
      i. In neutral solution
      ii. In acid solution

3. Alkenes
   
   (a) Synthesis
      i. Wittig
      ii. dehydration
   
   (b) Reactions
      i. In the future

---

Table 12.1: Reactions We Have Studied to Date
12.0.1.7 Do you need to make C-C bonds to make 59 from cyclohexanone and compounds with two or fewer carbon atoms?

12.0.1.8 How would you synthesize 59 from cyclohexanone and compounds with two or fewer carbon atoms?

12.0.1.9 How many ways do we have to make a ketone?

12.0.1.10 What is the product of the reaction of 64 with (1) N₂H₄ in dilute acid (too dilute to affect hydrolysis of the acetal!), (2) strong base with heat, followed by (3) H⁺/H₂O?

12.0.1.11 See if you can use the formation of an enamine as a guide to figure out how an enol, see 66, forms in acid solution from a ketone. Use epwa.

12.0.1.12 Enols, see the last problem, go back to ketones by the reverse mechanism of their formation. Use epwa to show this and learn once again that doing a reversible process is easy once you can do it in one direction.

12.0.1.13 A compound has the formula C₉H₁₀O₃. The IR features a broad peak at about 3000 cm⁻¹, and peaks at 1770 and 1680 cm⁻¹. The ¹H nmr has the following peaks: δ 1.41 ppm (t, 3), 4.09 ppm (q, 2), 6.9 ppm (d, 2), 7.9 ppm (d, 2), and 12.3 ppm (s, 1) and the ¹³C peaks are at δ 15 ppm, 63 ppm, 115 ppm, 128 ppm, 131 ppm, 163 ppm, and 167 ppm. What is the compound?
12.0.2 Additional Exercises

12.0.2.1 Use epwa to show the formation of the enamine from diethylamine and cyclohexanone.

12.0.2.2 What do you get if you treat 60 with CH₃MgBr followed by concentrated H₂SO₄? HINT: Be careful; acid/base chemistry is important in organic chemistry.

12.0.2.3 Compound 62 does not react with dilute aqueous acid, but compound 63 does. Account for this difference. HINT: What kinds of compounds would we, and only we call these two materials?

12.0.2.4 A compound has a ^{13}C nmr spectrum with peaks at δ 13.30 ppm, 19.04 ppm, 19.26 ppm, and 119.87 ppm. Its ^1H nmr spectrum has peaks at δ 1.081 ppm (t, 6), 1.699 ppm (hextet, 4), and 2.339 ppm (t, 4). The mass spectrum has a molecular ion peak at 110 with an intensity of 37.7 and an (M+1)^+ peak of intensity 3.5. What is the compound? HINT: This is a tricky question; you need to pursue and use logic.

12.0.2.5 Use epwa to show how an oxime is formed.

12.0.2.6 A variation of the Wittig reaction with aldehydes in the presence of formaldehyde takes place by the following steps. Let the Wittig reagent formed from propyl bromide and triphenylphosphine, after it is treated with butyl lithium, react with butanal to form a compound we call A. Now let A react with butyl lithium to form B. B then reacts with formaldehyde to form C, which in turn is treated with water to form 67. Identify A, B, and C. Use epwa to show mechanism. HINT: In the first step, don’t let triphenylphosphine oxide form.

12.0.2.7 Is there a second product that you might expect in the last exercise in addition to 67? What is it? If you can, give an explanation for why 67 might be the dominant product.

12.0.2.8 What kind of compound is 68?

12.0.2.9 Draw the cleavage lines to indicate the materials from which 68 can be made.

12.0.2.10 Starting with cyclohexanone, how would you make 68?
12.0.2.11 Use epwa to show how acid catalyzes the conversion of 69 into 70.

12.0.2.12 The ketone 71 in the presence of HCN and CN\(^{-}\) does NOT form very much of 72. Use epwa to show the mechanism of the small amount that does form.

12.0.2.13 Suggest an explanation for the lack of substantial product in the last problem?

12.0.2.14 What is the product when 73 is treated with H\(^{+}\) in water?

12.0.2.15 A compound has the formula C\(_9\)H\(_{10}\)O. The \(^1\)H nmr has the following peaks: \(\delta\) 1.2 ppm (t, 3), 2.75 ppm (q, 2), 7.3 ppm (d, 2), 7.8 ppm (d, 2), and 9.95 ppm (s, 1). What is the compound?

12.0.2.16 A compound has the formula C\(_6\)H\(_{10}\)O. The \(^1\)H nmr has the following peaks: \(\delta\) 1.1 ppm (t, 3), 1.9 ppm (d, 3), 2.53 ppm (q, 2), 6.15 ppm (d, 1), and 6.8 ppm (q of d, 1). What is the compound?

12.0.2.17 This exercise is not something that you have seen before, but you should be able to deduce it from what you have learned. Use epwa to show how the following process might take place. Compound 12 is an intermediate. HINT: As typically done, these reactions are NOT, and do not need to be, balanced. Also, count electrons on the sulfur species before you start.

12.0.2.18 What is driving the second step of the second reaction in the last exercise?
1. S\textsuperscript{+} + Br\textsuperscript{−} → 12
2. \text{alkyl Li} + 12 → \text{product}

\text{S\textsuperscript{+} + Br\textsuperscript{−} → 12}
\text{alkyl Li} + 12 → \text{product}
Chapter 13

Carbon Level Three Compounds

13.1 Substitutions

The organization of Klein and that used in class differ a lot. You should read Chapter 21 over the next several lectures.

Carbon level three compounds are more often called carboxylic acids and their derivatives. Clearly if we have a carbonyl carbon, and we want a carbon level three compound, there must be one other electronegative element bonded to the carbonyl carbon. This can range from halogens to -SH to -OH to -NH₂ with various replacements for the hydrogen atoms. Critical to our understanding is a hierarchy of compounds; this is given in Table 13.1 where compounds at the top of the list are more reactive.

This reactive difference applies in several ways, but the process of importance for this section is the substitution process by which X in CH₃CH₂C(O)X is replaced by Y⁻ in a nucleophilic attack on the carbonyl carbon to produce CH₃CH₂C(O)Y and X⁻. Generally speaking, a compound high on the hierarchal list can be used to make one below, but not the other way around. There are two factors that cause the order in the list. The first feature of reactivity difference is the leaving group ability. Acid chlorides are near the top of the list

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type of Cmpd</th>
<th>Ability of X to leave</th>
<th>Resonance Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC(O)Cl</td>
<td>Acid halide</td>
<td>Very good</td>
<td>Poor</td>
</tr>
<tr>
<td>RC(O)OC(O)R</td>
<td>Anhydride</td>
<td>Very good</td>
<td>Poor</td>
</tr>
<tr>
<td>RC(O)SR</td>
<td>Thioester</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>RC(O)SH</td>
<td>Thioacid</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>RC(O)OR</td>
<td>Ester</td>
<td>Poor</td>
<td>OK</td>
</tr>
<tr>
<td>RC(O)OH</td>
<td>Acid</td>
<td>Poor</td>
<td>OK</td>
</tr>
<tr>
<td>RC(O)NH₂</td>
<td>Amide</td>
<td>Rotten</td>
<td>Good</td>
</tr>
</tbody>
</table>

Table 13.1: Hierarchical Listing of Carbon Level 3 Compounds. The hierarchy of compounds in the same box is about the same.
partly because chloride ion is a good leaving group. Here’s the argument. The Y\(^-\) group is a nucleophile and attacks the electrophilic site at the carbonyl carbon to yield what is called the tetrahedral intermediate. This is shown in Figure 13.1 labeled I. What happens to the intermediate depends on whether X or Y is the better leaving group. If X is the better leaving group, we form products; reaction occurs. If Y is the better leaving group, it does just that, leaves, and we go back to reactants. Hence if we are to get the substitution process to occur, a poor leaving group must replace a good leaving group. We know how to approximate leaving group ability: it correlates roughly with basicity. A good leaving group is a poor base.

The second aspect to the hierarchal order of our list has to do with resonance stability of the starting material. When the X group is a good \(\pi\) donor, then there is more resonance stability to the starting material, it is more stable, and hence less reactive. An amine group is a better \(\pi\) donor than a hydroxy group (electronegativity), and sulfur and chlorine atoms are not too good at donation because their orbital overlap is poor: their orbitals are too big to overlap well with the \(p\) orbital of the carbonyl carbon.

To reiterate the key concept: Generally (there are some exceptions due to acid/base chemistry), any compound low on the hierarchal list can be prepared from one above it. Learn the hierarchal order and you will find carbon level three chemistry relatively easy.

13.1.1 Required Exercises

13.1.1.1 Write a line formula for hexanoic acid and for 2-hydroxybutanedioic acid.

13.1.1.2 Which is the weakest base, CH\(_3\)\(^-\) or Cl\(^-\)?
13.1.3 Which is the better leaving group, \( \text{CH}_3^- \) or \( \text{Cl}^- \)?

13.1.4 When a good nucleophile attacks a carbon level two compound to form an intermediate, is there any possible leaving group other than the nucleophile itself?

13.1.5 When a good nucleophile attacks a carbon level three compound to form an intermediate, is there any possible leaving group other than the nucleophile itself? NOTE: There you have it in the last two exercises, the difference, the only substantial difference, between carbon level 2 and carbon level 3 chemistry.

13.1.6 Acid chlorides absorb in the carbonyl region at about \( 1800 \text{ cm}^{-1} \), while esters absorb near \( 1740 \text{ cm}^{-1} \), and amides near \( 1650 \text{ cm}^{-1} \). Explain. HINT: Think about the C-O bond strength as shown in your resonance structures.

13.1.7 Boniface Beebe, the natural philosopher of great repute from rural Arkansas, wrote, in “Organic Thoughts: My Years in Synthesis,” Jones Brothers Printers, 1878, p. 544, “Acid chloride chemistry and ketone chemistry differ mostly because of the greater positive charge on the central carbon.” Comment.

13.1.8 Which ester, 18 or 19, is most reactive to attack by water? Why? HINT: Before you answer this question what should you determine? HINT to HINT: The leaving group is?

13.1.9 Use epwa to show how ethanoyl chloride is converted to an amide by reaction with methyl amine. For a change, pay attention to the net stoichiometry of the synthesis in the last problem and state why it is necessary to add two moles of the amine. HINT: Always be thinking about acids and bases in this course.

13.1.10 Can you prepare ethanoic trifluoroethanoic anhydride from ethanoic acid and trifluoroethanoic acid? Use epwa to reach your decision. If that reaction does not work, how would you prepare ethanoic trifluoroethanoic anhydride?

13.1.11 What kind of compound is 20? How would you synthesize 20 from 21?

13.1.2 Additional Exercises

13.1.2.1 State concisely the major difference between carbon level two and carbon level three chemistry.
13.1.2.2 Which electronegative group, Cl or NH$_2$, would give up the lone pair in a resonance structure with the carbonyl group most readily? In answering, draw the resonance structures.

13.1.2.3 Which compound, CH$_3$C(O)Cl or CH$_3$C(O)NH$_2$, would have the most resonance stability? What would that do to the reactivity of the two compounds?

13.1.2.4 Can you make acetyl bromide from acetic acid and HBr? Why or why not? Be specific. As always, write the reaction with epwa to guide you to an answer.

13.1.2.5 If you place acetic acid in water containing $^{18}$O, the “label” becomes incorporated in both oxygen sites of the acetic acid. Use epwa to explain.

13.1.2.6 What is the product if ethanoic trifluoroethanoic anhydride is reacted with methanol? Use epwa to explain.

13.1.2.7 How would you synthesize 22 from 23? Use epwa to describe. HINT: Go through the questions to ask yourself about a synthesis.

13.1.2.8 What would happen if you treated ethanoic anhydride with methyl amine? As usual, use epwa.
13.1.3 Additional Acid/Base Review Questions

Given the importance of acids and bases in this chemistry, here are some review problems if you need them.

13.1.3.1 Which is the strongest base, NH$_2^-$, OH$^-$, or F$^-$?

13.1.3.2 Which is the strongest base, hydroxide ion, acetate ion, or phenoxide ion? Give your reasons.

13.1.3.3 Which is the strongest base, methoxide ion, ammonium ion, or SH$^-$? Give your reasons.

13.1.3.4 Order the following in terms of increasing basicity: Br$^-$, CH$_3$C(O)O$^-$, O$^{2-}$, OH$^-$, H$_2$O, NH$_3$, NH$_2^-$, CH$_3^-$. 

13.1.3.5 Which is the strongest acid, ethanoic acid or ethanamide? Why?

13.1.3.6 Which is the stronger acid, 16 or 17? Or, are they the same. Why?

13.1.3.7 Which is the strongest acid, phenol or 4-nitrophenol?

13.1.3.8 Which is the strongest acid, 4-nitrobenzoic acid or benzoic acid (C$_7$H$_6$O$_2$)?
13.1.3.9  The numbers for the pKₐ values in the last two exercises are: phenol, 9.95; 4-nitrophenol, 7.08; benzoic acid, 4.2; 4-nitrobenzoic acid, 3.4. Explain, but pay attention to the magnitude of the two differences, almost three powers of ten versus a factor of about 6.

13.1.3.10  How many rules do we have for acid strength? What are they?

13.1.3.11  Which is the stronger acid, 24 or 25? Explain.

13.1.3.12  When heptane is treated with OH⁻, nothing happens. When 3,5-heptandione is treated with OH⁻, another base is formed. What is it? Why is it formed? Use epwa to explain.

13.2  Four Special Issues in Carboxylic Acid Substitution Chemistry

There are four issues that require attention. Three of these center around the fact that carboxylic acids themselves are the most common form of carbon level three compound. We need to be able to get from acids to other compounds. (1) If any other carboxylic acid derivative can be made from acid chlorides, how do we get acid chlorides? (2) There are acid/base problems in the synthesis of esters. And (3), it would be nice to have a method of getting from acids to amides, as that process is a critical step in protein synthesis. (4) The last concerns a carbon level three compound that differs in form from the others, nitriles.

Klein covers the preparation of acid chlorides from acids in mechanism 21.2 on p 1006 (p 992). The key to this process is to convert -OH, a crummy leaving group, into -OSOCl, a great leaving group. That allows attack at the carbonyl carbon by chloride ion to produce the acid chloride from a tetrahedral intermediate. We use this interesting reaction a lot; it also works nicely on alcohols, converting them to alkyl halides.

The second issue involves the formation and hydrolysis of esters. Esters react with water in either acid or basic solution, to form the acid or its conjugate base and liberate a mole of alcohol. But esters cannot be made from acids under basic conditions. The reason? If you try to react an acid with the anion of an alcohol, the first thing that happens, the fast thing, is deprotonation of the acid group. What does that turn the leaving group into? A rotten one! Hence the synthesis must take place in acid solution, catalyzed by a proton sitting on the carbonyl oxygen and converting the carbonyl into a more powerful electrophile which can react with the relatively poor nucleophile that an alcohol is.

Getting from acid to amides efficiently is the third issue. Since amides are below acids in the table, we should be able to just react the acid with an amine and make the amide. However, acid/base chemistry rears its ugly head again. Since an amine is a base, and a base will de-protonate the acid group, and turn it into a terrible leaving group, O²⁻, the
Figure 13.2: DCC and the mechanism of amide formation. Note in the mechanism “R” is used for the cyclohexyl group.
direct reaction is not efficient. We could convert the acid to an acid chloride and then react that with an amine, but that is an extra step and acid chlorides are hard to handle as they react with moisture in the atmosphere. It would be better if we could devise a trick to convert the poor leaving group, OH\(^-\) or O\(^2-\) into a better one. Dicyclohexylcarbodiimide, DCC for short, does this job; the molecular structure is shown in Figure 13.2 as 25A. Parts of the mechanism are indicated in that figure as well, and the questions in the exercises allow you to use your previous knowledge to follow through the steps.

Nitriles, for instance, CH\(_3\)CH\(_2\)CN, are formally carbon level three compounds. They represent an easy entry into other compounds since the nitrile can be formed (with one additional carbon atom—AH HA! a new way to make a C-C bond!) from an S\(_N\)2 attack of cyanide ion on an alkyl halide:

\[
\text{CH}_3\text{CH}_2\text{Cl} + \text{CN}^- \rightarrow \text{CH}_3\text{CH}_2\text{CN} + \text{Cl}^-
\]

Nitriles can be reacted with water under acid catalysis (forcing conditions—heat and time) to yield amides, though not in good yield, and then to yield acids. So nitriles are good compounds to make carboxylic acids. There is an exercise for you to work through this process.

13.2.1 Required Exercises

13.2.1.1 DCC is dicyclohexylcarbodiimide, shown in 25A. What can you say about the polarization of the central carbon atom? How would that be affected by protonation on the adjacent nitrogen as shown in the first reaction in Figure 13.2?

13.2.1.2 The anion of the carboxylic acid (second step in Figure 13.2) is a reasonable nucleophile and the central carbon of DCC protonated on the nitrogen is a decent electrophile. What should happen?

13.2.1.3 In the third step of the DCC mechanism, the amine attacks the carbonyl carbon to generate a tetrahedral intermediate. Draw that. Show why this is now a good leaving group when the imine nitrogen of it is protonated. Use epwa.

13.2.1.4 Often a good nucleophiles is a good base. What does a good base do to an carboxylic acid? Why is what it does important in reactions of carboxylic acids? Be specific and succinct.

13.2.1.5 How do you prepare an acid chloride? Use epwa to show the steps.

13.2.1.6 Articulate in just a few words the role SOCl\(_2\) plays in the synthesis of an acid chloride? HINT: It is the usual role of special reagents in carbon level three chemistry.
13.2.1.7 How would you prepare \((\text{CH}_3)\_2\text{CH}_2\text{CN}\) from compounds with four carbons or less?

13.2.1.8 Show that you can form an amide from a nitrile by reacting with water in the presence of acid. First step, what is the role of the acid? To which atom will it bond? What does that do to the carbon level 3 carbon? Continue to the amide.

13.2.1.9 Show that under conditions of acidified water, an amide, under forcing conditions, can be converted to an acid. What is the fundamental reason this “up the chart” reaction can occur? HINT: Think Le Chatelier.

13.2.2 Additional Exercises

13.2.2.1 What is the product of treating 3-methyl-butanoic acid with ethylamine in the presence of DCC? Use epwa.

13.2.2.2 An important experiment to prove the mechanism of substitution in esters involves the acid hydrolysis of the ester of ethyl benzoate labeled with \(^{18}\text{O}\) in the oxygen of the carbonyl group. Bender \((J. \text{ Amer. Chem. Soc, 1951, 73, 1626-1629.})\) established that the labeled oxygen was missing (had exchanged for normal \(^{16}\text{O}\) from the solvent water) from ethyl benzoate that had not hydrolyzed. Show how our mechanism of ester hydrolysis requires this.

13.2.3 Syntheses involving Carboxylic Acid Derivative Substitution

13.2.3.1 What would happen if you treated ethanoic anhydride with methyl amine? As usual, use epwa.

13.2.3.2 How would you prepare propionic anhydride from propanoyl chloride?

13.2.3.3 From what kinds of molecules are esters prepared?

13.2.3.4 One can use diazomethane to make methyl butyrate from butyric acid. Use epwa to show how this goes. HINTS: 1. Write the Lewis structure of \(\text{CH}_2\text{NN}\), with resonance structures. 2. Let the negative carbon remove a proton from the acid. 3. Now the negative oxygen of the original acid can act as a \(\text{S}_\text{N}2\) reagent on carbon; with what as a leaving group? Is it a good one?

13.2.3.5 What kind of functional groups are in compound 26?
13.3 Reduction of Carbon Level 3 Compounds: “H−” Reagents

Carboxylic acid and their derivatives, like aldehydes and ketones, are subject to reduction to a lower carbon level. If there is one general issue to apply to these reductions, it is this: they generally speaking do not stop at carbon level 2, but continue to carbon level 1. Very interesting exceptions occur, some because of the lack of a leaving group and others because of the surprising development of a better leaving group; yet others because of the weakness of a reductant. The former two can always be deduced. The latter have to be learned.

We deal first with hydride reagents. The most common reagent, NaBH₄, reduces only the more reactive of the carbon level three compounds. Thinking our way through this shows the general problem of stopping a reductive reaction at carbon level 2. Let BH₄ attack
an acid chloride. This forms a tetrahedral intermediate with a chloride attached; that good leaving group leaves, producing an aldehyde, which is then attacked again by BH$_4^-$, yielding an alcohol. Use epwa to work your way through this.

If the resonance stability of the carboxylic acid derivative is too much for BH$_4^-$ to overcome, how do we reduce the less reactive members of this group. Use a better “H−” reagent. We know one already: LiAlH$_4$. This substance will reduce all the carbon level 3 compounds. And will reduce them all the way to carbon level 1.

That last statement seems odd when you think about carboxylic acids themselves, for the first thing that AlH$_4^−$ will do to these is to act as a base and remove a proton from the acidic -OH. Then if AlH$_4^−$ attacks that compound it will form a tetrahedral intermediate with the four substituents being an R group, an H, and two O−. No good leaving group! So why doesn’t the process stop. Here we have a process where we turn one of those O− groups into a good leaving group. It uses the AlH$_3$ fragment left after the first reduction step. Aluminum is a better oxophile than even phosphorous. So it binds to one of the negative oxygen atoms of the tetrahedral intermediate, weakens the C-O bond, and turns the -OAlH$_2^-$ into a good leaving group. Then another mole of AlH$_4^−$ reacts with the aldehyde to reduce it to the carbon level 1. Use epwa to work your way through this.

How to stop at carbon level 2? A mild reducing agent, that reacts only with acid halides, and not with any other carbon level 3 or with carbon level 2 compounds, is Al(OBu$_3$)$_3$H−. It produces an aldehyde from an acid halide and stops.

A summary of reactivities of reducing agents is given in Table 13.2.

13.3.1 Required Exercises

13.3.1.1 Use epwa to show the mechanism of the reaction of 29 with BH$_4^−$ followed by acid in water with heat. HINT: Somewhat tricky. Look carefully at your initial product and remember that the solution is acidic.

13.3.1.2 Use epwa to show the mechanism of the reaction of 29 with AlH$_4^−$ followed by acid.

13.3.1.3 Predict the product of the reaction of 38 with excess LiAlH$_4$ followed by H$^+$. 

13.3.1.4 What is (are) the product(s) of the reaction of 44 with LiAlH$_4$? HINT: Remember the key to LiAlH$_4$: Al is oxophilic.

13.3.1.5 What is (are) the product(s) of the reaction of 45 with Al(tertiary butoxide)$_3$H$^-$?

13.3.1.6 What would be the product of the reaction of BH$_4^−$ with this compound:
13.3.1.7 What would be the product of the reaction of AlH$_4^-$ with the compound in the last exercise.

13.3.2 Additional Exercises

13.3.2.1 Why do you think Al(OBu$_t$)$_3$H$^-$ is a weak hydride donor?

13.3.2.2 Reductions with AlH$_4^-$ take place readily because of the great “H$^-$” character of the species, but also because Al ion is very oxophilic and coordinates strongly to negatively charged oxygen atoms. What would such a coordination do to the leaving group ability of oxygen?

13.3.2.3 It is especially important to turn O$^{2-}$ into a good leaving group when AlH$_4^-$ reacts with the conjugate base of an acid. Why?

13.3.2.4 What kind of molecule is 31?

13.3.2.5 How do you prepare the kind of molecule from the last exercise from a carbon level three compound? What’s so special about this synthesis?

13.3.2.6 How would you prepare 31 from 32? HINT: Think a couple of steps.

13.3.2.7 Predict the product of the reaction of 35 with excess LiAlH$_4$ followed by H$^+$. Use epwa.

13.4 Reduction of Carbon Level 3 Compounds: “C$^-$” Reagents

The presence of a leaving group on carbon level 3 compounds plays an important role when the reductant is a “C$^-$” reagent. Consider the reduction of CH$_3$C(O)SCH$_3$ with CH$_3$Li. The alkyl lithium will attack the carbonyl carbon of the thioester to form a four-coordinate intermediate with a good leaving group, the -SCH$_3$ group. The negatively charged carbonyl
Table 13.2: Hierarchical Listing of Carbon Level 3 Compounds and their Reducibility. A positive sign means reaction occurs efficiently; a negative sign means reaction is sluggish or does not occur. Reactions go to carbon level 1 compounds unless noted.

<table>
<thead>
<tr>
<th>Compound</th>
<th>AlH₄⁻</th>
<th>BH₄⁻</th>
<th>Al(OBu)₃H⁻</th>
<th>Alkyl Li</th>
<th>Grignard</th>
<th>Gilman</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC(O)Cl</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RC(O)OC(O)R</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>RC(O)SR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>RC(O)SH</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RC(O)OR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>RC(O)OH</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>RC(O)NH₂</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>R-CN</td>
<td>+²</td>
<td>-</td>
<td>-</td>
<td>+³</td>
<td>+³</td>
<td>-</td>
</tr>
</tbody>
</table>

¹ Stops at carbon level 2.
² To amines after acidification.
³ Imine or ketone.

Another case involves the reaction of a carboxylic acid with CH₃Li. This reagent will first act as a base and remove a proton from the carboxylic acid, leaving it negatively charged. As we have already established, if we had used a Grignard reagent instead of alkyl lithium, there would be no further reaction as the Grignard is not powerful enough to attack the negatively charged molecule. But an alkyl lithium is. It attacks at the carbonyl carbon to produce a tetrahedral intermediate with two negatively charged oxygen atoms: no leaving group. Hence it just sits there until the solution is acidified, in which case it becomes the gem-diol of a ketone which reverts to a ketone at equilibrium–recall Chapter 11. Here is a new synthesis of a ketone.

Finally, recall that Gilman reagents are reactive only toward acid halides and that they “stop” after production of a ketone. The reactivities are shown in Table 13.2.

13.4.1 Required Exercises

13.4.1.1 What happens if you try to reduce a carboxylic acid or an amide (with an N-H bond) with a Grignard reagent? HINT: Again, remember that acid/base reactions are generally fast compared to other reactions.

13.4.1.2 As Boniface Beebe has said, “Rules are meant to be broken, or at least carefully applied.” A Grignard reagent reacts smoothly with N,N-dimethyl-formamide to yield products with new C-C bonds. Why does this occur in violation of the statement in the last problem? What is the product of the reaction with methyl Grignard?
13.4.1.3 What kind of “C−” reagent is an alkyl lithium compared to a Grignard reagent? What happens if you try to reduce a carboxylic acid or an amide (with an N-H bond) with an alkyl lithium compound? Use epwa.

13.4.1.4 Predict the product of the reaction of 36 with (1) NaCN, (2) CH₃MgCl, (3) H⁺ in water.

13.5 Synthesis Using Carbon Level 3 Compounds

13.5.1 Required Exercises

13.5.1.1 What kind of molecule is 33? Do you have to make C-C bonds if you were to make 33 from molecule with four carbon atoms or less? HINT: DUH!, but then articulate why I asked the question. How would you prepare 33 from 1-butanol? HINT: Relative to some of our recent syntheses, a lots of steps.

13.5.1.2 Compound 34 is a compound that is used (with other materials) to impart apple flavor. How would you synthesize it from benzaldehyde and acetic acid?

13.5.1.3 Predict the product of the reaction of 37 with (1) C₂H₅MgBr, (2) H⁺ in water, (3) LiAlH₄, (4) H⁺.

13.5.1.4 An amine can be “protected” by reaction with 30. This compound is unusual in a way that will ultimately be to our advantage. To see why, determine the carbon level of the carbons in 30.

13.5.1.5 Use epwa to show how an amine attacks 30 and draw a Lewis structure of the protected amine.

13.5.1.6 The protected amine from exercise 13.5.1.5 is deprotected by treating with HBr. Use epwa to show how. HINTS: The hydrogen ion of the HBr serves to make the oxygen attached to the benzyl group a good leaving group (from the benzyl group!); and the resultant Br⁻ acts as a nucleophile to substitute for the oxygen on the benzyl carbon. The rest follows if you recognize that CO₂ can be liberated from the other product.

13.5.1.7 Would a compound with an ethyl group instead of the benzyl group (of 30) be useful in protecting amines? Why or why not?
13.5.1.8 Use epwa to show the product of 47 when it reacts with (1) BH₄⁻, (2) dilute H⁺.

13.5.1.9 Use epwa to show the product of 47 when it reacts with (1) AlH₄⁻, (2) dilute H⁺.

13.5.1.10 How would you prepare 48 from 49? HINT: Use retrosynthetic analysis and don’t be afraid of several steps.

13.5.1.11 What is (are) the product(s) when CH₃C(O)Cl is reacted with one mole of ethyl lithium? HINT: Carefully. We go to lots of trouble to get special reagents; why?

13.5.2 Additional Exercises

13.5.2.1 How can you convert 39 into 40?

13.5.2.2 How would you prepare 41 from butanedioic acid and methyl amine? HINT: Concentrated or dilute?

13.5.2.3 Show the mechanism of the reaction of 42 with ethyl lithium, followed by H⁺.

13.5.2.4 How would you convert benzaldehyde into 43?

13.5.2.5 Use your rapidly growing organic chemistry knowledge to predict the product after this sequence of reactions: triphenylphosphine reacts with (1) CH₃Br, (2) NaH, (3) benzylbromide, (4) NaH, (5) benzaldehyde. HINT: Patience.

13.5.2.6 The S ylide (CH₃)_2S⁺CH₂⁻ reacts with 1-bromobutane followed by treatment with a base (with heat). Dimethylsulfide is one product. Use epwa to predict the other. HINT: Base removal of a proton α to the sulfur is favored, but that product cannot do anything. What would be the next best proton to remove? Also, remember the ultimate trick is to get electrons to the sulfur.

13.5.2.7 How would you prepare 46 from compounds with three or fewer carbon atoms?
13.5.2.8 Starting with 43 and excess butyl lithium (only those two reagents except for treatment with acid at the end), show how to form 50. HINT: Think about butyl lithium acting as a base; find the acidic hydrogen; and, most importantly, note that ethene is a product of the reaction.

13.5.2.9 Show the product and the mechanism when a cyclopropyl Grignard reacts with 51, followed by H⁺. Anything ambiguous?

13.5.2.10 What happens when you react ethyl acetate with excess ethyl Grignard followed by acid? Use epwa to explain.

13.5.2.11 Starting with carbon compounds containing three or fewer carbon atoms, how would you make 3-methyl-3-hexanol?

13.5.2.12 Nmr review. A compound has a molecular mass of 83. The IR has a peak at 2268 cm⁻¹; the ¹H nmr has peaks at 0.8 (t, 3), 1.1-1.5 (m, 4), 2.2 (t, 2) ppm. The ¹³C nmr has peaks at 13.2, 16.8, 21.86, 27.42, and 119.84 ppm. What is the compound?

13.5.2.13 Nmr review. The ¹³C nmr of a compound of formula C₄H₆O₂ has peaks at 20.6, 97.54, 141.4 and 167.9 ppm. The ¹H nmr has peaks at 2.13 (s, 3), 4.563 (d of d, 1), 4.879 (d of d, 1), and 7.260 (d of d, 1) ppm. What is the compound?
13.5.2.14 Use epwa to show how 1,4-dibromobutane and $53$ can react to form $54$. HINTS: (1) You may use any inorganic reagent that you wish. (2) Look carefully at the lengths of the two carbon chains.

13.5.2.15 Use epwa to show how $55$ is interconverted into $56$. See if you can justify what must be true to keep this reaction from going in the reverse direction?

13.5.2.16 How would you prepare $57$ from materials with five carbons or less?
Chapter 14

The Chemistry of $\alpha,\beta$-Unsaturated Carbonyls

When a carbonyl group is “conjugated” with an alkene, interesting chemistry occurs. The alkene does not behave like an ordinary alkene because of the presence of the carbonyl. Further, in contrast to the situations we have dealt with, there are issues about the nature of the product, whether it is “kinetic” or “thermodynamic.” This chapter deals with these issues.

Read Klein, Section 22.6 (22.6)

14.1 $\beta$ Attack

The compound 63 is an $\alpha,\beta$-unsaturated carbonyl. The nomenclature refers to the double bond between the $\alpha$ and the $\beta$ carbon atoms. Because of the location of the alkene relative to the carbonyl, a nucleophile can attack the alkene at the $\beta$ position (usually, as we shall see, electrophiles attack alkenes), called $\beta$ attack or “conjugate addition,” and place the resultant charge from the attack on the carbonyl oxygen atom; the epwa cascade for this is shown in Figure 14.1. The initial product of the reaction is an enolate anion, which, in acid can be converted to an enol. Note also, the nucleophile could directly attack the carbonyl carbon. That is the issue that makes this chemistry fascinating.

14.1.1 Required Exercises

14.1.1.1 Which of the following are $\alpha,\beta$-unsaturated ketones? 3-penten-2-one; 5-hepten-3-one; 2-cyclohexeneone.

14.1.1.2 Show all the steps (epwa) for the reaction of an $\alpha,\beta$-unsaturated ketone with CH$_3$O$^-$ at the $\beta$-carbon. HINT: Be sure you get all the proton transfers correct.
14.2 Thermodynamic versus Kinetic Control

The issue of thermodynamic versus kinetic control is best illustrated with a “reaction coordinate diagrams.” Look at Figure 14.2. The substance \( R \) is a reactant and there are two possible products, \( P_1 \) and \( P_2 \). Does \( R \) produce \( P_1 \) or \( P_2 \) fastest? The answer depends on the height of the barrier between \( R \) and \( P_1 \), on the one hand, and between \( R \) and \( P_2 \) on the other. In this case, \( P_2 \) is formed fastest. But which compound, \( P_1 \) or \( P_2 \) is most stable? Thus if we let \( R \) react, it will form \( P_2 \) rapidly, but over time, if the barrier back from \( P_2 \) to \( R \) is not too large, over a long time, the ultimate product will be \( P_1 \). We say that \( P_2 \) is the kinetic product, the product found at short time, and \( P_1 \) is the thermodynamic product, that found at long time.

14.2.1 Required Exercises

14.2.1.1 Consider the energy surface in Figure 14.3. Reactant \( R' \), which, as indicated, can form both \( P_1' \) and \( P_2' \). Which compound, \( P_1' \) or \( P_2' \), is the kinetic product? Which product is the thermodynamic product?
Figure 14.2: Reaction Coordinate Diagram.

Figure 14.3: Reaction Coordinate Diagram for Exercise 14.2.1.1.
Table 14.1: Bonds broken and formed upon the two types of attacks at \( \alpha,\beta \)-unsaturated carbonyl compounds.

<table>
<thead>
<tr>
<th>Attack Site</th>
<th>Bonds Broken</th>
<th>Bonds Formed</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>( \text{NuH, } \pi \text{C-Nu, C-H} )</td>
<td>( \text{NuH, C-C} \pi \text{C-Nu, C-H} )</td>
</tr>
<tr>
<td>Carbonyl carbon</td>
<td>( \text{NuH, } \pi \text{C-Nu, O-H} )</td>
<td>( \text{NuH, C-O} \pi \text{C-Nu, O-H} )</td>
</tr>
</tbody>
</table>

\(^1\) Nu is the nucleophile.

14.4.2.1.2 We have two possibilities in the introduction and the last exercise: the “kinetic” product is different from the “thermodynamic” one; or they are the same. Is there another possibility?

14.3 The Thermodynamic Product

Let’s examine the products from attack at the \( \beta \) carbon versus attack at the carbonyl carbon. For the first attack, the ultimate product is addition across the double bond, meaning that the nucleophile ends up attached to the \( \beta \) carbon and a proton ends up on the \( \alpha \) carbon; the carbonyl functionality remains. If we imagine we start with the nucleophile attached to a hydrogen atom, the situation for bonds broken and bonds formed is shown in the first row of Table 14.1. If attack takes place at the carbonyl carbon, the results are shown in the second row of the table. As you will show in the exercises, the thermodynamic product is always that resulting from attack at the \( \beta \) position, leaving the very stable carbon-oxygen double bond intact.

14.3.1 Required Exercises

14.3.1.1 Verify the results in Table 14.1

14.3.1.2 Use the results in Table 14.1 and the following bond energies to establish that \( \beta \) attack always produces the thermodynamic product: C-C single bond, 83; C-H single bond, 99; C-O single bond, 86; O-H single bond, 111; C-C double bond, 146; C-O double bond, 179; all values in kcal/mole.

14.3.1.3 What is the thermodynamic product for the reaction of any \( \alpha,\beta \)-unsaturated ketone?
<table>
<thead>
<tr>
<th>Reversibility</th>
<th>Type of Reagent</th>
<th>Carbonyl Attack</th>
<th>β Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not</td>
<td>“H−”</td>
<td>BH₄⁻ with Ce³⁺</td>
<td>e⁻ in NH₃(l)</td>
</tr>
<tr>
<td></td>
<td>“C−”</td>
<td>Grignard, usually; LiR</td>
<td>Gilman</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>F⁻, OH⁻, CH₃O</td>
<td>RS⁻, R₃P, Br⁻</td>
</tr>
</tbody>
</table>

Table 14.2: Classification of Reagents for β attack and carbonyl attack on α,β-unsaturated compounds.

14.4 The Two Barriers

We have seen that attack at the β position is always thermodynamically favorable. We now need to deal with the kinetic issues. There are two questions to ask: (1) which reagents kinetically favor attack at the β position and which at the carbonyl; and (2) which reagents that attack the carbonyl are reversible so that ultimately the thermodynamic product can be formed. We know the answer to the last question from earlier in the course—see Chapter 11.

Generally substances that are small and whose electrons are not easily polarized favor attack at the carbonyl center. Nucleophiles that are large and polarizable favor attack at the β position, favor conjugate addition. Some cases are borderline; life is hard. Table 14.2 gives some examples.

14.4.1 Required Exercises

14.4.1.1 Give an example of a reaction involving an α,β-unsaturated ketone where the kinetic product is different from the thermodynamic one.

14.4.1.2 Draw a reaction coordinate diagram for your answer to the last exercise.

14.4.1.3 Give an example of a reaction involving an α,β-unsaturated ketone where the kinetic product is the same as the thermodynamic one.

14.4.1.4 Draw a reaction coordinate diagram for your answer to the last exercise.

14.4.1.5 How would you prepare 60 from 2-cyclohexenone?

14.4.1.6 How would you prepare 61 from 2-cyclohexenone?

14.4.1.7 How would you prepare 62 from 2-cyclohexenone?
14.4.2 Additional Exercises

14.4.2.1 When 52 is treated with HCN/NaCN at 5°C, a product is obtained; when treated with the same reagents at 80°C, a different product is obtained. What are these two products?

14.4.2.2 In principle, compound 63 could react with (CH₃)₂NH in two ways. What are they? How would you detect which reaction occurred using nmr?

14.4.2.3 Predict the product when 64 is warmed in ethanol (just a solvent).

14.4.2.4 If compound 64 is modified so that the nitrogen atom has two hydrogen atoms attached to it instead of the two methyl groups, predict the product when it is warmed in ethanol. What factors did you consider in formulating your answer?

14.4.2.5 When 2-cyclohexenone is treated with Ph₃P (where Ph is phenyl) in the presence of (CH₃)₃SiCl, 65 is the result. Suggest a mechanism. HINT: Remember that Si is
oxophilic and Cl is a [blank]?
Chapter 15

Review and Syntheses

15.1 NMR

15.1.1 Exercises

15.1.1.1 The $^{13}$C nmr signal of C2 and C3 in 2-butene-1-ol are 130 and 127.2 ppm. The $^{13}$C nmr signals for C2 and C3 in 2-butenal are at 134.6 and 154.3 ppm. Can you account for these features given the resonance structures of the $\alpha,\beta$-unsaturated aldehyde? HINT: Of course you can; I am asking you to do so.

15.1.1.2 A compound with formula C$_4$H$_6$O has a $^1$H nmr with the following signals: 2.27 (s, 3), 5.94 (d of d, 1), and 6.18-6.4 (m, 2) ppm. What is the compound?

15.1.1.3 From the following spectral data, find the structure of a compound with the formula C$_4$H$_7$ClO. IR: 1802 cm$^{-1}$. $^1$H nmr: 0.95 (t, 3), 1.67 (m, 2), and 2.90 (t, 2) ppm.

15.1.1.4 From the following spectral data, find the structure of a compound with the formula C$_4$H$_7$N. IR: 2250 cm$^{-1}$. $^1$H nmr: 1.08 (t, 3), 1.7 (m, 2), and 2.34 (t, 2) ppm.

15.2 Reactions and Syntheses

15.2.1 Exercises

15.2.1.1 How would you make 2-octanone from compounds with four carbons or less? HINT: Try to keep your number of steps small.
15.2.1.2 The active ingredient in one type of insect repellant is DEET, 66. How would you make this starting with 67 and N-ethyl-ethanamide. HINT: Several steps, with knowledge from earlier in the course.

15.2.1.3 One mole of compound 68 is reacted with one mole of 69. What do you find as final product(s)? HINT: I’m being very sneaky.

15.2.1.4 Use epwa to write a mechanism for the conversion of 70 and 71 to form 72.

15.2.1.5 How would you make pentanoic acid from bromobutane?

15.2.1.6 Compound 73 has been suggested as an intermediate in a reaction that produces a carboxylic acid, RC(O)OH, CO, CO₂, and HCl. Propose a mechanism. HINTS: (1) The intermediate reacts with water. (2) A classic case of one epwa demanding another.

15.2.1.7 Compound 74, known as Fmoc-Cl, is used as a protecting group for amines and alcohols. Use epwa to show how 74 reacts with an amine, NH₂R.

15.2.1.8 To remove Fmoc (see last exercise) from an amine or alcohol, one treats the adduct with a base. The base removes the hydrogen at position 9, which generates 75.
epwa to show this. Is the exocyclic double bond (the one to the right) in 75 conjugated? The other fragment (if you didn’t make it one grand epwa cascade) of the last problem (other than 75) readily decomposes to liberate CO₂. See if you can use epwa to figure out this process.

15.2.1.9 Show the mechanism for the reaction of benzoyl chloride with 1-butanol.

15.2.1.10 Starting with ethanol as your only organic compound, and any inorganic reagents that you wish, how would you prepare ethyl acetate?

15.2.1.11 What is the product of the reaction of (CH₃)₂CuLi with 76, followed by treatment with H⁺?

15.2.1.12 The rearrangement of 77 to 78 in the presence of a strong base is a reaction you have not seen previously. See if you can figure out how it happens (with epwa, of course). HINTS: (1) That’s a positive sulfur! (2) The base removes a proton from one of the methyl groups on sulfur, the anion of which then attacks the ring. (3) There is a weird looking intermediate.

15.2.1.13 What site in 79 is most acidic?

15.2.1.14 If you remove a proton from 79 with a base you make what is called an enolate anion. Why would it be called that? Why is it someone stable, even though the proton came from a carbon?

15.2.1.15 Enolate anions can act as nucleophiles at either of two sites, the negative oxygen atom or the negative carbon atom. What negative carbon atom? The latter site is a “C⁻” reagent (the focus of a lot of stuff next semester) and is a much better nucleophile. Predict what you might expect for a product if the enolate anion reacted with CH₃I.
Chapter 16

Ring Compounds

This and the following chapter deal with the broad subject of stereochemistry, how atoms are arranged in space. In this chapter we deal with the issue of cyclic, or ring, compounds.

16.1 Ring Size and Relative Energies

Read Klein, Section 4.9 (4.9)

We have already mentioned several times that three membered rings are unstable. To illustrate that look at Figure 16.1. In this Figure the blue points are for the heat of formation of alkanes running from propane, n=3, to heptane, n=7 and the red points are for the heat of formation of 1-alkenes, running from propene, n=3, to 1-heptene, n=7. It is clear that adding a -CH₂₂ group causes a change in the heat of formation by a constant amount of about -20.8 kJ/mole per -CH₂ group. Straight lines are drawn through each of these sets of points to demonstrate the constancy per addition of a -CH₂ group. The purple points are for the cycloalkanes. A fake curve has been drawn through the single point of cyclohexane, for reasons to be detailed below, with a slope identical to that of the two previously described curves. All the cycloalkanes are less stable than predicted as can be seen by comparing the purple points with the purple curve.

The reasons for the instability of rings (other than cyclohexane) are two: (1) angle strain that comes about because the atoms are not at the optimum position for the bonding orbitals, and (2) steric strain caused by the forced eclipsed arrangement of the hydrogens, especially in cyclopropane and cyclobutane.

Because cyclohexane, when in a chair conformation has no angle or steric strain, we presume that its enthalpy of formation is normal. Hence the line forced through the point for n=6 in Figure 16.1.
16.2 167

Figure 16.1: Stability of alkanes, 1-alkenes, and cycloalkanes from three carbons to seven. The blue curve is for alkanes, the red for 1-alkenes, and the purple dots are the corresponding cycloalkanes. See text for the justification of the purple line through cyclohexane point.

16.1.1 Required Exercises

16.1.1.1 What hybridization would you have a carbon atom in cyclopropane use? Is anything wrong with the bonding given your choice of hybridization and the structure of cyclopropane? HINT: Think angles.

16.1.1.2 Draw a cyclopropane ring looking down a C-C bond and comment on any obvious instability.

16.1.1.3 Draw a planar cyclohexane ring and then make a Newman projection looking down a C-C bond. Comment on any obvious instability.

16.2 The Structure of Cyclohexane, Axial and Equatorial Hydrogen Positions

Read Klein, Section 4.10-4.11 (4.10-4.11)

The cyclohexane structure can pucker so that all carbons are exactly tetrahedral and so there are no eclipsing hydrogen atoms. This leads to two kinds of positions for substituents, axial and equatorial. For substituents other than hydrogen atoms, the axial position is generally less stable. Work through the exercises.
16.2.1 Required Exercises

16.2.1.1 Draw a line structure representation of the cyclohexane ring in the chair form without any hydrogen atoms present.

16.2.1.2 Draw a cyclohexane ring in the chair form with axial hydrogen atoms.

16.2.1.3 Draw a cyclohexane ring in the chair form with equatorial hydrogen atoms.

16.3 Conformers of Cyclohexane

Read Klein, Section 4.12-4.13 (4.12-4.13)

If we put a substituent on the cyclohexane ring, we have two choices. We could replace an axial hydrogen atom or we could replace an equatorial one. It makes a difference.

16.3.1 Required Exercises

16.3.1.1 In Figure 16.2 is a Newman projection of a cyclohexane ring where each carbon is tetrahedrally coordinated. What is the relationship (gauche or antiperiplanar) of X and Y?
16.3.1.2 In Figure 16.2 is a Newman projection of a cyclohexane ring. What is the relationship (gauche or antiperiplanar) of X and the -CH$_2$ at the lower center (blue lines for those looking in color)?

16.3.1.3 In Figure 16.2 is a Newman projection of a cyclohexane ring. What is the relationship (gauche or antiperiplanar) of Y and the -CH$_2$ at the upper center (black lines for those looking in color)?

16.3.1.4 Again referencing Figure 16.2 if you were to put a large group at position X or Y, which would you choose for maximum stability? Why?

16.4 Flipping the Ring

Two carbons attached to each other via a single bond can easily “rotate” to convert a gauche form into an antiperiplanar form. A similar motion in the cyclohexane ring is called a “ring flip,” or for short, just “flip.” This occurs readily and interchanges the axial and equatorial positions with each other.

16.4.1 Required Exercises

16.4.1.1 Draw a “flipped” cyclohexane ring. This means, if the right hand carbon of your original drawing was “up,” make the right hand carbon now “down.”

16.4.1.2 Convince yourself with your diagrams of the last problem that upon “flipping” all the axial hydrogen atoms becomes equatorial and all the equatorial ones become axial. HINT: The easy way to do this, to follow a given hydrogen atom through a flip, is to note which hydrogen atom is on “top;” it will remain on top even after a flip.

16.5 Conformers in Cyclohexanes

The two conformers of a mono-substituted cyclohexane have different energies because of the interactions that you discovered in Section 16.3.1. Axial substitution causes a gauche interaction while equatorial substitution is antiperiplanar with respect to the $\beta$ carbon and its substituents.

16.5.1 Required Exercises

16.5.1.1 Sketch the stable conformation of each of the following.
Table 16.1: The A values ($\Delta G^\circ$ value) for the change from equatorial to axial conformer in kcal/mole for some $X$ groups in $C_6H_{11}X$.

<table>
<thead>
<tr>
<th>$X$</th>
<th>A (kcal/mole)</th>
<th>$X$</th>
<th>A (kcal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.15</td>
<td>CH$_3$</td>
<td>1.7</td>
</tr>
<tr>
<td>Cl</td>
<td>0.43</td>
<td>CF$_3$</td>
<td>2.1</td>
</tr>
<tr>
<td>Br</td>
<td>0.38</td>
<td>C$_2$H$_5$</td>
<td>1.75</td>
</tr>
<tr>
<td>CN</td>
<td>0.17</td>
<td>CCH</td>
<td>0.41</td>
</tr>
<tr>
<td>SH</td>
<td>0.9</td>
<td>SCH$_3$</td>
<td>0.7</td>
</tr>
</tbody>
</table>

16.5.1.2 Draw the most stable conformer of cis-1-t-butyl-3-methylcyclohexane.

16.5.1.3 A monosubstituted cyclohexane ring is more stable with the substituent in what position? Does that mean there is none of the other conformer? Explain.

16.5.1.4 The free energy difference, $G(\text{axial } C_6H_{11}X) - G(\text{eq } C_6H_{11}X)$ is 7.3 kJ/mole for $X = \text{CH}_3$. Calculate the ratio of equatorial species to axial at room temperature. HINT: $\Delta G = -RT \ln([\text{eq}]/[\text{ax}])$ where $R$ is the universal gas constant, 8.314 J/(K mole).

16.5.2 Additional Exercises

16.5.2.1 The ratio of the conformer of $C_6H_{11}X$, [eq]/[ax], when $X$ is a phenyl group, is 110. What is the free energy difference between the two conformers. Which is more stable? HINT: See exercise 16.5.1.3

16.5.2.2 Use Table 16.1, which gives cyclohexane stabilities, to guess (and draw) the stable conformation of trans-1-chloro-3-ethyl-cyclohexane.
16.5.2.3 Consider the two monosubstituted cyclohexane rings, $C_6H_{11}X$, where $X$ is $-CF_3$ in one and $-CCl_3$ in the other. Which would you predict has the largest fraction of material with the $X$ group axial? Explain.

16.5.2.4 Can you show the stable conformer of a substituted cyclohexane in a planar diagram? Why or why not?

16.6 Isomerization in Cyclohexanes

Read Klein, Section 4.14 (4.14)

Because the ring structure, disubstituted (and multi-substituted) cyclohexanes exhibit isomerization. You can appreciate the isomers by looking at a flat picture of cyclohexane and seeing if the two substituents are on the same side of the ring, or on opposite sides. You cannot assess the conformation from these “flat” pictures.

16.6.1 Required Exercises

16.6.1.1 Draw a cyclohexane ring with both the axial and equatorial hydrogen atoms on one of the carbons shown. Is one of those hydrogen atoms “on top”?

16.6.1.2 Draw trans-1,3-dichlorocyclohexane where the cyclohexane ring is drawn flat.

16.6.1.3 Draw trans-1,3-dichlorocyclohexane in its stable conformation (3D drawing required).

16.6.1.4 Draw the planar and 3D structures for cis-1,3-dichlorocyclohexane.

16.6.1.5 Is cis- or trans-1,2-dimethylcyclopropane more stable? Why?

16.6.1.6 Can you show axial and equatorial substituents in a planar cyclohexane structure? Why or why not?

16.6.1.7 Draw all of the isomers of dimethylcyclobutane.
16.6.1.8 Draw the isomer cis-2-isopropyl-cis-5-methyl-cyclohexanol in the planar representation. HINT: The stereochemistry designation is relative to the position of the hydroxy group.

16.6.1.9 Draw the stable conformer of the compounds in the last exercise.

16.6.2 Additional Exercises

16.6.2.1 Can you show a cis isomer in a 3D structure of cyclohexane? Why or why not?

16.7 Stability and Reactions in Cyclohexanes

16.7.1 Additional Exercises

16.7.1.1 The free energy change, $\Delta G^\circ$, for conversion of the axial form of a mono-substituted cyclohexane to the equatorial form is -1.92 kcal/mole when the substituent is COOH. What is the equilibrium constant for this conversion? HINT: See discussion in problem [16.5.1.4]

16.7.1.2 The value of $\Delta G^\circ$ (for a process such as described in the last exercise) for a phenyl substituent is -2.9 kcal/mole. What is the stable conformation of cis-4-phenylcyclohexanoic acid? HINT: You need data from problem [16.7.1.1]

16.7.1.3 Chemists have been able to synthesize (with difficulty) cubane, $C_8H_8$. This molecule has carbon atoms located at the corners of a cube, each carbon bonded also to one hydrogen atom. Why is this compound so unstable?

16.7.1.4 Here on the left is a planar perspective of a steroid ring. Put the substituents onto the proper positions with the proper geometric orientations in the chair form of that molecule, sketched without substituents on the right hand side.

16.7.1.5 Draw the conformers (with respect to the cyclohexane ring) of menthol, 7, and indicate which is the most stable.

16.7.1.6 How many kinds of hydrogen atoms are present in bornane, 8? How would each be split in $^1H$ nmr?
The difference in energy between the axial and equatorial conformers of the cyclohexylhalides ($E_{axial} - E_{equatorial}$) is F, 0.15; Cl, 0.43; Br, 0.38; I, 0.43, all in kcal/mole. Which of these data make sense to you on an initial look? Which don’t? Is there any way you can account for the similarity of the last three?

Progesterone, 9, is reacted with dimethylcuprate(I). Where will attack occur and what will be the stereochemistry of the product. Why?

Which is more stable, cis- or trans-1,3-dimethylcyclohexane? Why?

Which is more stable, cis-(1,5)-trans-(2,4)- or cis-(1,4)-trans-(2,5)-tetramethylcyclohexane? HINT: The nomenclature here means, in the first case, for instance, that the methyl groups on atoms 1 and 5 are on the same side, and opposite that of the methyl groups on atoms 2 and 4.
Chapter 17

Chirality

We have used terms like cis and trans to describe different isomeric structures. There is a more subtle kind of isomerization that is an important aspect to organic chemistry, and even more so, to biological chemistry. This involves a subtle difference in the arrangement in space of the groups around an atom.

17.1 Molecules with Chirality Centers; Mirror Images.

Read Klein, Section 5.2 (5.2)

A tetrahedral atom with four different groups attached to it has what is called a chirality center. The outstanding property of this environment is that such a molecule and its mirror image are not superimposable; cannot be made to look the same; are, therefore, different molecules. Do the exercises to check this.

The same issue occurs, although rarely, in some circumstances when the four groups are not all different. The rigorous definition of a chiral center is that it does not possess either a plane of symmetry or a center of inversion. A plane of symmetry, usually denoted \(\sigma\), is a plane that has exactly the same objects on both sides of the plane, at the same distance from the plane. For instance, a water molecule has a plane of symmetry in the plane of the molecule and another plane containing the line that bisects the H-O-H angle and perpendicular to the H-O-H plane. An illustration of a plane of symmetry is given in Figure 5.12 in Klein. A center of inversion is a symmetry operation that a object has if what is at the point \(x, y, z\) is also at the point \(-x, -y, -z\). A square planar molecule has a center of inversion, usually denoted \(i\); as does an octahedral one. Methane does not possess an \(i\).

The practice of using mirror images to work with chiral centers is not a good one. As soon

\[\text{This was decided in 1996, Klein tells us. At that time a group of guys (probably literally) got together and made up a word! Their word has the sanction of the IUPAC, the International Union of Pure and Applied Chemistry, so it has more force than the words that we make up! Older words for the same thing are also used in this document: chiral center, stereocenter, stereogenic center.}\]
as we have a nomenclature, as we soon will, we can (and will) completely avoid ever looking for a mirror image.

### 17.1.1 Required Exercises

**17.1.1.1** Which of the following have a “chiral” (or stereogenic) center?

![Chemical structures](image1)

**17.1.1.2** If it is possible, show how you would rotate $9A$ to yield $9B$. Specify the amount and your axes of rotation (i.e., $30^\circ$ about the C-Cl bond).

**17.1.1.3** If it is possible, show how you would rotate $9C$ to yield $9D$. Specify the amount and your axes of rotation (i.e., $30^\circ$ about the C-Cl bond).

**17.1.1.4** How do you rigorously define a chiral molecule? HINT: There are two ways to state this, one of which involves mirror images. In my view, that is the hard way, especially in practice. Think $i$ and $\sigma$.

**17.1.1.5** What works reasonably well (most of the time) to define a chiral molecule centered on a carbon atom?

### 17.1.2 Additional Exercises

**17.1.2.1** Consider three reactions: Ethyl Grignard reacts with 2-pentanone, 3-hexanone, and $10$, then with dilute acid, each separately. Which of these has a chiral center in the product?
What functional groups are in captopril, 11, a drug used to treat high blood pressure?

Identify the chiral centers in captopril, 11.

Here is a tricky question. Which of the following have a stereogenic center(s)? Which are chiral molecules?

A Nomenclature for Chiral Molecules

Read Klein, Section 5.3 (5.3)

We need to be able to describe which of the two mirror image molecules we have in any given situation. The method that has been developed relies on ranking of the four different substituents on the atom. The ranking is based on atomic number. If there is a tie, then you go further down the chain of atoms. For instance, in the molecule CHBrClF the ranking is Br > Cl > F > H. In the molecule HC(CH₂CH₃)(CH₂CH₂CH₃)Cl it is clear that Cl has the greatest rank and H the smallest. The two other substituents are “tied” at the C attached
to the chiral center. In both of these that C are two H’s and a C; still “tied.” Go out one
further C and we find three H in one case, a C and two H in the other. The “other” clearly
has the higher rank of the two. So the order is Cl >CH₂CH₂CH₃ >CH₂CH₃ >H.

Once we have the ranking, we orient the molecule so the group of lowest rank is pointing
away from us. We see the remaining three groups at the corners of a triangle. Move in
a circle from highest to middle to lowest rank; if you went clockwise, the name for the
compound starts with an “R;” if you went counterclockwise, the name starts with an “S.”
It is easy to remember the latter: counterclockwise is “sinister.”

17.2.1 Required Exercises

17.2.1.1 Rank the following groups: (1) -CH(CH₃)₂ versus -CH₂(CH₃); (2) -C(CH₃)(CH₂CH₃)(CH(CH₃)₂)
versus -C(CH₃)(CH₂CH₃)(C(CH₃)₃); (3) -CH₂(CH₂CH₂CH₂CH(CH₃)₂) versus -CH₂(C(CH₃)₂CH₃).

17.2.1.2 Determine whether each of the following is R or S.

17.2.1.3 In 21, 22, and 23 are drawings of 2-chlorobutane. For each compound, answer
the question: Is this a drawing of the R or S enantiomer of 2-chlorobutane?

17.3 Changing from R to S; Drawing the Enantiomer

The compounds that we named R and S in the section are called enantiomers. Klein shows
how to get one enantiomer from another by using a mirror plane. This is the hard way.
The easy way is to switch the relative positions of two groups around the chiral center. One
switch turns R to S (or vice versa); two switches reverts back to the original. Try it.

A common exercise is to request you to draw either the R or the S enantiomer of a given
compound. I think the easiest way to do this is to just draw the compound (in a three
dimensional sketch, because otherwise you cannot tell anything about stereochemistry),
find out what it is (R or S), and then be happy (50% of the time) or switch the groups if
you happened to be wrong (50% of the time).
17.3.1 Required Exercises

17.3.1.1 Draw a three-dimensional picture of CHClBrF. Determine if it is R or S. Switch two groups in your picture. Determine the name of the new compound.

17.3.1.2 Imagine BH₄⁻ attacking CH₃C(O)CF₃. Draw the ketone so it is in a plane perpendicular to the paper. Let the hydride attack from the top side and push the -CH₃ and the -CF₃ groups down as it forms a bond to the carbonyl carbon. Did you make the R or the S enantiomer?

17.3.1.3 Repeat the process in the last exercise, but attack from the bottom. R or S?

17.3.1.4 Lesson from the last two exercises: You cannot make a solution with net chirality from molecules that are not chiral. Why do the last two processes give identical yields?

17.3.1.5 Draw the enantiomer of 18 and 19. Also, determine whether the compound given is R or S.

17.3.2 Additional Exercises

17.3.2.1 Find all the chirality centers in 20, streptimidone, an antibiotic, and determine for each whether it is R or S.

17.3.2.2 Determine if 23A is R or S. How about 23B?

17.3.2.3 How would you convert 23A into 23B?
17.4  Multiple Chiral Centers

Read Klein, Sections 5.5-5.6 (5.5-5.6)

In many compounds there are multiple chiral centers. The easiest way to sort out the issues involved with these is to name the molecule’s chiral centers. Compounds in which all R centers become S centers and vice versa are enantiomers. Compounds in which there is a deviation from this are diastereomers. This is illustrated in Table 17.1 for two chiral centers.

There is a type of molecule with two chiral centers that is not chiral as a molecule because it has a mirror plane (or center of inversion) that converts one chiral center into another. Such compounds are called “meso” compounds.

To complete our classification, compounds that are not enantiomers or diastereomers, those that have a different connectivity, are constitutional isomers.

17.4.1  Required Exercises

17.4.1.1  Make a table similar to Table 17.1 for three chiral centers. HINTS: (1) There are eight possible species. (2) How many times can an “E” be in a row or column? (3) Is the upper right and lower left of the table the same?

17.4.1.2  Which of the following are chiral molecules? HINT: Remember, in cases where there are two (or more) chiral centers, you have to have 3D drawing to assess stereochemistry. When you don’t have it, you must generate it, even if you make assumptions in building your drawing.

17.4.1.3  For each of the pairs of compound, 12-17, classify them as a) identical, b) enantiomers, c) diastereomers, or d) constitutional isomers?

17.4.1.4  Draw all possible structures for 1,2-dihydroxycyclopentane. Are there any enantiomeric pairs. Is there a meso compound? Are there any diastereomers?
Table 17.1: Relationship between various molecules with two chiral centers. S means same molecule, E, enantiomers, and D, diastereomers.

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>SS</th>
<th>RS</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>S</td>
<td>E</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>SS</td>
<td>E</td>
<td>S</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>RS</td>
<td>D</td>
<td>D</td>
<td>S</td>
<td>E</td>
</tr>
<tr>
<td>SR</td>
<td>D</td>
<td>D</td>
<td>E</td>
<td>S</td>
</tr>
</tbody>
</table>

17.4.1.5 Is 24 chiral? HINT: Trick question.

17.4.1.6 Draw stereorepresentations for all stereoisomers of 24. Label those that are meso compounds and those that are enantiomers.

17.4.2 Additional Exercises

17.4.2.1 Is compound 25 R or S (or neither)?

17.4.2.2 Pretend those guys in Switzerland that developed the rules for R,S designation tried to name 27. Assume reasonable logic and decide if it is R or S. What is your “logic”?

17.4.2.3 Is 28 chiral?

17.4.2.4 Is 29 a meso compound? Why or why not?

17.4.2.5 Is 30 a meso compound? Why or why not?

17.4.2.6 Assign R or S to each chiral (stereogenic) center in 31. HINT: Remember N inversion is fast (although P is not).

17.5 Detecting an Enantiomer

Read Klein, Section 5.4 (5.4)

All of the physical and chemical properties of one enantiomer are the same as that of the other as long as neither the physical or chemical interaction we measure has “handedness,” being different for the right hand relative to the left. The major physical property that
The major chemical property, discussed in the next section, is the interaction of an enantiomer with a handed molecule.

Two features of light. First, light has an electric field that oscillates in a given direction. Second, the speed at which light moves through a medium depends on the nature of that medium; the ratio of the speed in a vacuum to that in a medium is called the index of refraction. Plane polarized light has the field oscillating in a single direction; let’s assume that direction is up and down. The up and down oscillation can be split into two vectors moving in a circle with equal velocity as shown in the lower part of Figure 17.1. In that figure, the purple vector is the sum of the blue and the red vectors. Both of these circularly rotating electric fields see the same molecular fragments when they pass through the molecule show in the top part of the figure, hence they move with equal velocities. When circularly polarized light encounters a chiral molecule, there is no longer equal velocity of the two components. In Figure 17.2 we show the red vector moving through the chlorine atom is slowed down relative to the blue vector moving through the fluorine atom. The resultant vector (just add the red and blue to each other) is now shifted. The plane polarized light has had its plane rotated. This process is called “optical activity” (and NOT just by us, but by everyone!). Chiral molecules rotate the plane of plane polarized light.
Figure 17.1: The breakdown of plane polarized light into two oppositely rotating circularly polarized beams. See text.

Figure 17.2: The difference in the circularly polarized beams upon encountering a chiral molecule. See text.
17.5.1 Required Exercise

17.5.1.1 Make an argument to convince yourself that if the R enantiomer rotates the plane by 12° that the S enantiomer will rotate the plane by −12°.

17.6 Isolation of One Enantiomer

Read Klein, Section 5.9 (5.9)

Unless they are interacting with something that is handed, is chiral, enantiomers have all the same physical and chemical properties. This statement has important practical application: You cannot get an excess of one enantiomer over another unless your reactants have an excess of one enantiomer over another. How then, can we ever isolate one enantiomer. To do so we take advantage of diastereomers, which do have different chemical properties.

We have an equal molar mixture of two enantiomers, call them (R)-X and (S)-X. Such a mixture is called a racemic mixture. We this racemic mixture with an enantiomer of compound Y, say (R)-Y. The resulting mixture contains (R,R)-XY and (S,R)-XY, which are diastereomers of each other. These can be separated by crystallization, or boiling points, or chromatographic properties. We isolate the (R,R)-XY molecule, say, and then undo the chemistry that made the adduct, throw away the Y solution and have a solution of pure (R)-X.

17.6.1 Required Exercises

17.6.1.1 A chemist makes 2-hydroxy-2-phenylacetic acid (2-hydroxy-2-phenylethanoic acid). She reacts this acid with the natural enantiomer of cinchonine, a base (formula
C_{19}H_{22}N_{20} isolated from cinchona bark (and used to treat malaria) and carefully crystallizes the solution. The very first material to precipitate is separated from that which is the last to precipitate. When acidified, she finds the first material is (R)-2-hydroxy-2-phenylacetic acid and the second is (S)-2-hydroxy-2-phenylacetic acid. Explain.

17.6.1.2 You have a racemic mixture of 2-methyl-1-butanol. Looking around the lab, you find that there is a bottle of (R)-2-chloro-butanoic acid. Draw all the compounds and indicate what kind of chemistry you might use to create diastereomers.

17.7 Review Exercises on Stereochemistry and, as always, some Reactions.

17.7.1 Required Exercises

17.7.1.1 Ibuprofen has the structure 26, but only the S enantiomer is active as an antinflammatory. Draw it.

17.7.1.2 Is it true or false to say “Every chiral compound has a diastereomer”? Explain your answer.

17.7.1.3 Let CH_3SC(H)(I)CH_3 be attacked in an S_N2 reaction with azide ion, N_3^−, as shown in 32. Is the product R or S? Did the configuration invert during the reaction? Did the name (that is, R or S) change? Why or why not?

17.7.1.4 Draw an accurate representation of the three dimensional shape of (S)-1,3-dichloropentane.

17.7.1.5 Treat 33 with AlH_4\(^-\) followed by H^+. What is the product? Pay attention to stereochemistry. HINT: The hydride attacks from the side of the molecule opposite the C-O bond; you can understand the stereochemistry of the reaction if you let the two substituents (methyl group and hydrogen atom) on the carbon of the ring go “up” upon attack (in the picture of 33).

17.7.1.6 Is 34 chiral?

17.7.1.7 What is the relationship between the pairs of compounds, 38, 39, and 40? Choices are “same molecule” (which includes conformers), “enantiomers,” or “diastereomers.” HINT: Remember the easy way to answer this kind of question is to name the compounds.
17.7.2 Additional Exercises

17.7.2.1 Does (1,3)-di-\textit{tert}-butyl allene have an enantiomeric pair? HINT: Allene is “C double bond C double bond C.”

17.7.2.2 Draw all possible structures of 2,3,4-tribromopentane and find the relationships between them. HINT: From a mathematical point of view, with all carbon atoms in the plane of the paper, the bromine atoms on C2, C3, and C4 can point either in or out: that gives $2^3$ possible arrangements, all of which may not be distinguishable.

17.7.2.3 Is it possible for that a substitution of X for Y in a molecule (where all other groups stay in the same absolute position) will lead to a change in name (R or S)? Is it possible for the name to not change with a change in configuration? Comment. HINT: Think about the rules for naming chiral centers.

17.7.2.4 Treat 33 with dilute H\textsuperscript{+} in ethanol. What is the product? Pay attention to stereochemistry. HINT: See hint to exercise 17.7.1.5

17.7.2.5 If (R)-1-bromo-1-deutero-ethane is treated with triphenylphosphine to form the Wittig cation, what is the configuration (R or S) of that cation? HINT: Remember this is an S\textsubscript{N}2 backside attack.

17.7.2.6 Is 35 chiral?

17.7.2.7 Is 36 chiral?
17.7.2.8 Is 37 chiral?
Chapter 18

Alkenes

18.1 Nomenclature and Review of Stability

Read Klein, Section 8.4 (8.4).

We discussed the stability of alkenes in sections 9.3 and 9.4. We have also used the trivial nomenclature system for alkenes from time to time, in which they are labeled cis when the two substituents are on the same side of the double bond, and trans when the substituents are on opposite sides. It is worth our time to be sure we communicate with the words “side” and “end” of a double bond. Figure 18.1 illustrates the meaning this class will associate with those words. Note also that an alkene has a “top,” which we are looking at in Figure 18.1 and a “bottom,” which you would be looking at from the back side of the paper in the figure. The words will be used extensively in what follows, both for nomenclature issues as well as to describe reactions.

The rigorous nomenclature is straight forward. First we assign a priority to the two groups on one end. The order for the priority is exactly the same as we used with chiral compounds. Then we assign a priority to the two groups on the other end. Now we ask: are the high priority groups on the two ends on the same side. If so, the compound is labeled the “Z” isomer. If the two high priority groups are on opposite sides, the isomer is labeled the “E” isomer.

If you are asked to draw a given isomer of an alkene, the easiest way is to just draw one, determine if it is Z or E, and switch two groups in the 50% of the cases that you get it wrong.

18.1.1 Required Exercises

Here is a list of alkenes along with their heat of formation: (E)-2-heptene, -74.2 kJ/mole; (Z)-2-heptene, -70.7; (E)-3-heptene, -73.2; (Z)-3-heptene, -69.4; (E)-3-methyl-3-hexene -76.9. For each, draw the Lewis structure and compute the heat of combustion.
Rationalize your results. HINT: The heat of formation of CO$_2$ is -393.5 kJ/mole and that of H$_2$O is -241.8 kJ/mole.

18.1.1.2 Order the alkenes 3, 4, and 5 in terms of increasing stability.

18.1.1.3 Name the alkenes 1 and 2.

18.1.1.4 Review. A compound of formula C$_3$H$_4$Cl$_2$ has a $^1$H nmr with peaks at 1.8 (d, 3) and 5.9 (q, 1) ppm. What is the compound? Name it.

18.1.1.5 Draw the isomers of 2-methyl-2,4-hexadiene and name them.

18.1.1.6 Is compound 6 (E) or (Z)?

18.1.2 Additional Exercises

18.1.2.1 What is the heat of formation? HINT: The name answers it all if you only know “formed from what”?

18.1.2.2 Give the structure of (Z)-1-bromo-1,2-difluoroethene and of (E)-1-chloro-3-ethyl-4-methyl-3-heptene.

18.1.2.3 Review. A compound of formula C$_{10}$H$_{20}$ has a $^1$H nmr with peaks at 5.30 (s, 1) and 0.97 (s, 9) ppm. What is a possible structure for the compound?
A compound of formula $C_5H_8O_2$ has a $^1H$ nmr with the following peaks at 2.08 (s, 3) and 4.57 (d, 2) ppm, and a collections of peaks in the region of 5.2 (m, 1) and 5.9 (m, 2) ppm. The former looks like four peaks of equal intensity; the exact positions are 5.18, 5.20, 5.22, and 5.25 ppm. The latter is a mess, but there is some hint that it is a collection of triplets, such as a doublet of triplets, or a doublet of doublet of triplets. What is the compound and how do you rationalize the peaks? HINT: It is relatively easy to get the compound’s structure. Understanding this relatively complicated nmr is more useful. Pay attention to Table 18.1.

Is compound 7 (E) or (Z)?

Which is more stable, 1-methylocyclohexene or 8?
18.2 Carbon Level of Alkenes and Hydrogenation

Read Klein pp 428-431 (418-422).

The argument is that alkenes are delocalized carbon level 1 compounds, or, if you prefer, each carbon that is double bonded to another carbon is a carbon level 1/2 carbon. The need for this device is to make carbon level a consistent concept, indicating the degree of oxidation of the carbon. One reason is this: we have seen that under acid conditions we can add water across a double bond (the reverse of a dehydration) to form an alcohol. The product has one carbon at carbon level 1 and the other at carbon level 0. So the alcohol has a total carbon level of 1. Water is neither an oxidizing or reducing agent, so the carbon level of the reactant must be the same as the carbon level of the product. Hence the alkene is net carbon level 1. Where to assign that? Each carbon of the double bond is carbon level 1/2 or we have a delocalized carbon level 1. A second argument: Alkenes react with H₂ under the right circumstances (see below) to form alkanes. Alkanes are carbon level 0 and dihydrogen is a reducing agent. The reactants must have had a higher carbon level. (You know the routine by now: “Each carbon of the double bond...”)

The reaction of an alkene with dihydrogen is normally very slow and requires a catalyst to occur at a reasonable rate. Metallic Pt, Pd, or Ni are such catalysts. The mechanism of these processes involves the bonding of the dihydrogen to the metal surface, which weakens the H-H bond. Then the alkene can attack and generate a cascade of epwas to give the products. This is shown in Figure 18.2. Note that both the hydrogen atoms end up on bottom of the alkene. This is called a “syn” attack.

18.2.1 Required Exercises

18.2.1.1 What is the product of the reaction of H₂ with cyclohexene? Use epwa to describe.

18.2.1.2 What is the product of the reaction of D₂ with cyclohexene? Specify stereochemistry. HINT: D₂ is a form of H₂ where both atoms of hydrogen have a mass of two instead of the normal of one for a hydrogen atom.
18.2.1.3 Find the product of hydrogenation over Pd of (Z)-3,4-dimethyl-1-heptene. Indicate the stereochemistry by describing the names of any chiral centers.

18.2.1.4 Will the product of the last exercise (as recovered from the vessel with no further workup) rotate the plane of plane polarized light? Why or why not?

18.3 The Addition of Halogens to Alkenes

Read Klein, Section 9.8 (9.8)

Although we have briefly discussed the addition of water to an alkene under acid catalyzed conditions, it turns out that the mechanism of this reaction is different from that of other additions. We choose to look at the general case first, then come back later to look at the acid catalyzed addition of water.

What species do we expect to react with alkenes? Unlike carbonyls, alkenes have only small polarizations. Also, unlike carbonyls, where the LUMO is localized more or less on the carbonyl carbon, alkenes do not have a localized LUMO. What alkenes do have is a loosely held pair of electrons in the π bond; they can act as nucleophiles. It is this pair of electrons that alkenes use to act as nucleophiles. Clearly they must find an electrophile, and that is the role of dihalogen compounds. Alkenes can form a bond to a dihalogen, which have a ready made good leaving group, a halide ion. The top row in Figure 18.3 shows the epwa. What is chemically (and structurally) interesting is the formation of a bridged intermediate, a way to stabilize the cationic charge on the molecule. This intermediate is called a bromonium ion. The second row in Figure 18.3 indicates the resonance structures of this bridged intermediate. The three structures have the positive charge on the bromine or on the two carbons of the original alkene. Note carefully that if the alkene is symmetrical, the last two resonance structures would have equal weight; in the case shown in the figure, the middle structure is more important than the last one because greater substitution stabilizes carbocations. We will see the importance of this shortly. The last row of Figure 18.3 pictorially indicates the two bonding interactions that are important in the bridged intermediate. The drawing A indicates that the electrons in the π bond of the alkene overlap with an empty orbital of Br⁺ and donate electrons to the bromine ion. In turn, a filled p orbital on the bromine ion donates electrons back to the carbon atoms through the empty π* level of the alkene. Inorganic chemists call this “back-bonding.” The occurrence of “bridging” is common to much of alkene chemistry. In fact, under appropriate conditions of extreme steric hindrance to stop attack on the bromonium ion, a bridged cation has been isolated and has been subject to x-ray analysis.

Careful inspection of the bridged intermediate in the bromination of alkenes reveals the chemistry of this species is chemistry that we already have seen. The bridged intermediate is isoelectronic with an epoxide! And because it is dominated by the positive charge, its chemistry is like that of a protonated epoxide. We have already studied that in Section 10.5. To review with reference to the bromonium ion. The positive charge is more localized on the more highly substituted carbon of the original alkene. It is that carbon that will be attacked
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Figure 18.3: The addition of a bromine to an alkene. Top row, epwa. Second row, resonance structures of bridged intermediate. Third row, the $\sigma$ donation from the $\pi$ bond of the alkene to an empty orbital on Br$^+$, and the back donation from a filled p orbital on the Br$^+$ to the empty antibonding $\pi$ orbital of the alkene.

by a nucleophile in order to remove the positive charge from bromine and/or carbon, neither of which “wants” positive charge. Further, the attack will take place on the bottom of the molecule (as drawn in Figure 18.3) because that is where the biggest part of the LUMO of the $\sigma$ bond is, and is the position away from the big bromine atom. This has stereochemical consequences that you will see in the exercises.

18.3.1 Required Exercises

18.3.1.1 What aspect of bonding allows alkenes to act as nucleophiles?

18.3.1.2 Use epwa to carry out the reaction of Br$_2$ with (Z)-3-methyl-3-hexene. Find the stereochemistry of the centers (R or S).
18.3.1.3 Use epwa to show that the addition of Br₂ to cyclohexene produces trans-1,2-dibromocyclohexane. What is the conformation of this material? Is it a chiral molecule? Is it a single enantiomer?

18.3.1.4 Determine the stereochemistry (R or S at each chiral center) of the addition of Cl₂ to (E)-2,3-difluoro-2-butene.

18.3.1.5 Is the product in the last exercise a racemic mixture, a diastereomeric mixture, or a meso compound?

18.3.1.6 How could you prepare a diastereomer of the product of problem 18.3.1.4?

18.3.2 Additional Exercises

18.3.2.1 Is it possible to produce a single enantiomer from a reaction between an alkene and Br₂? HINT: I am looking for the general answer but pay attention to a specific exception to it.

18.3.2.2 (E)-2-pentene is treated with Br₂. What is the product? Pay attention to stereochemistry.

18.4 Addition of Halogens to Alkenes with a Dominant Nucleophile

Still in Klein, section 9.8 (9.8)

A minor, but important, modification to the reaction in the last section is readily available. By having a large amount of some external nucleophile present to attack the bromonium ion, we can get substitution of a bromine atom on one carbon and another group on the adjacent carbon. For instance, adding dilute Br₂ to 2-methyl-2-butene in aqueous solution allows water to act effectively as a nucleophile for the bromonium ion, yielding an α-DIN (Whoops! Here we go again, using a word that no one but those in this class know. If you use it and someone looks at you weirdly, just have empathy and tell them what you mean.), 3-bromo-2-methyl-butan-2-ol. Other good nucleophiles to use in place of water are carboxylic acids, alcohols, and large amounts of chloride ions (but not iodide ions! Why not?).
18.4.1 Required Exercises

18.4.1.1 Find the products and determine the stereochemistry (R, S) when dilute Cl\textsubscript{2} is added to 2-methyl-2-butene in acetic acid solution.

18.4.1.2 Alkene 10 is treated with dilute Cl\textsubscript{2} in water. What is the product?

18.4.1.3 Compound 10 is treated with Br\textsubscript{2} in a non-aqueous solution in the presence of a large amount of tetraethylammonium chloride. What is (are) the product(s)? HINT: The tetraethylammonium cation is a spectator ion.

18.4.1.4 How would you prepare (4R),(5S)-4,5-dibromooctane?

18.4.1.5 In the last exercise, you should be worried about getting an (apparently) chiral compound from achiral starting materials. What is the answer to that worry?

18.4.2 Additional Exercises

18.4.2.1 What is the product of the reaction of propene with ICl? HINT: Think about the mechanism to get the right answer. However, before you go on, try to establish what issue I am worried about?

18.4.2.2 Compound 11 is treated with (dilute) Br\textsubscript{2} in ethanol. What is(are) the product(s)?
18.4.2.3  Show the mechanism and stereochemistry of the addition of (dilute) Br\(_2\) in methanol to 1-methylecyclohexene.

18.4.2.4  Thinking problem. You have available the 2-methyl-1,2-epoxypropane (In naming epoxides, the two atoms to which the oxygen is attached are given.) and 2-methyl-propene. How could you prepare 1-bromo-2-methyl-propan-2-ol from one and 2-bromo-2-methyl-propan-1-ol from the other?

18.4.2.5  When Br\(_2\) is added to trans-2-butene in CH\(_3\)OH saturated with LiCl, three products are found. Use epwa to show what they are. HINT: This is NOT a stereochemical problem.

18.4.2.6  What would be the product if you treated 8 (see page 190 with ICl?]

18.4.2.7  How would you prepare a racemic mixture of (4R),(5R)-4,5-dibromo-octane and (4S),(5S)-4,5-dibromo-octane?

18.5  Reaction of Acids with Alkenes

Read Klein, Section 9.3 (9.3)

What makes the reaction of alkenes with HX compounds different from reaction with Br\(_2\)? Both have a good leaving group for attack by the alkene, but they differ significantly. The bonding interaction shown in Figure 18.3 for Br\(^+\) does not hold for H\(^+\) because the hydrogen ion has no electrons to donate to the alkene in a back-bonding fashion. Thus the hydrogen ion does not bridge; it binds to the least substituted carbon and sends the other carbon off on its own as a carbocation. Being a pure carbocation, that carbon is free to rotate about the single bond and to be attached from either side. Stereochemistry is lost. Another problem also arises as discussed in the Section 18.8.

Just as with halogen addition, the presence of an abundance of a good nucleophile will allow that group to attack the carbocation rather than the anion of the acid. This is especially true if the anion of the acid is a poor nucleophile, such as perchlorate ion, ClO\(_4^−\) or bisulfate, HSO\(_4^−\).

Finally, a warning: If you write a mechanism which involves a primary carbocation, think again. Primary carbocations are very unstable!
18.5.1 Required Exercises

18.5.1.1 When alkenes act as nucleophiles, what is the difference between the process when the electrophile is $\text{H}^+$ and when the electrophile is anything else?

18.5.1.2 Show the product when $\text{HBr}$ is added to 1-phenyl-1-propene. Use epwa.

18.5.1.3 Predict the product if you react 2-methyl-1-pentene with $\text{HBr}$.

18.5.1.4 How would you prepare $\text{12}$ from an alkene?

18.5.1.5 Use epwa to show the mechanism of the reaction of 2-methyl-2-pentene with $\text{H}^+$ in methanol.

18.5.1.6 How would you convert cyclopentylmethanol to 1-methyl-cyclopentanol?

18.5.1.7 When $\text{36}$ (page 202) is treated with acid, it forms a cyclic compound. Show using epwa.

18.5.2 Additional Exercises

18.5.2.1 Review: The alcohol $\text{9}$ (page 190) is dehydrated in strong acid with removal of the product. What is the product? Why?

18.5.2.2 Review: Starting with 2-methyl-3-pentanone, how would you make 2-methyl-2-pentene?

18.5.2.3 Which alkenes can be used to produce 1-bromo-1-methylcyclopentane? HINT: Notice the tense of the first noun.

18.5.2.4 How would your answer to the last exercise differ if you used DBr and you wanted the D on the methyl group?

18.5.2.5 What is the product when $\text{13}$ is treated with acid (with removal of product or water)? Use epwa.
18.6 Alkenes and Acid without Nucleophiles

When an alkene is treated with an acid in the absence of any decent nucleophile, the first step, protonation of the alkene occurs. That intermediate carbocation can either give up a proton to a base to make the original alkene, or, if stability favors it, to form another alkene: Acid can migrate the position of the double bond.

18.6.1 Required Exercises

18.6.1.1 Use epwa to show the mechanism of reaction of 1-butene in aqueous acid where the anion of the acid is a poor nucleophile.

18.6.1.2 The natural philosopher of rural Arkansas, the wonderful Boniface Beebe, had a bottle of 2,3-dimethyl-1-butene; he ran the $^1$H nmr and found a rather complicated spectrum. Predict what he saw in that spectrum. Bonnie took the 2,3-dimethyl-1-butene and reacted it with $\text{H}^+$ in a dry medium without any good nucleophile. He was completely befuddled when he isolated a material with a single $^1$H nmr signal at 1.64 $\delta$ and $^{13}$C nmr signals at 123 $\delta$ and 18.9 $\delta$. Use epwa to show Bonnie what happened.

18.6.1.3 Boniface Beebe, the most famous of the natural philosophers from rural Arkansas, reacted cyclopentyl-ethene with HBr. The $^1$H nmr of the product clearly showed the presence of an ethyl group, and there were no signals indicating a proton strongly deshielded by a bromine atom. “Great leaping green iguana,” he bellowed. “What happened?” Indeed.

18.7 Alkenes as Nucleophiles, Not Once, but Twice or More

Read Klein, pp 1285-1286 (1274-1275)

We have seen that in the presence of acid, alkenes form carbocations which can be attacked by nucleophiles to produce “addition” products, or possibly to migrate the double bond to a more stable position. One nucleophile that is always present in a solution with an alkene is the alkene itself. A second molecule of the alkene can attack the carbocation formed from reaction of a first molecule of alkene with the acid to form a dimer of the alkene. If this continues, we have an acid catalyzed polymerization reaction. Look at the exercises.

18.7.1 Required Exercises

18.7.1.1 Styrene, phenylethene, is treated with $\text{H}_3\text{PO}_4$, an acid whose conjugate base is a poor nucleophile. The product has a M$^+$ of 208. Use epwa to show what happened.
18.7.1.2 When 19 is treated with formic acid, HC(O)OH, 20 is formed. Use epwa to suggest a mechanism for this reaction. HINT: A carboncation acts as an electrophile in the process.

18.7.1.3 When 33 is treated with acid, one isolates 34. Use epwa to suggest a mechanism.

18.8 The Trouble with HX Reactions

Read Klein, Section 6.11 (6.11)

There is an issue with all reactions of alkenes initiated with a proton. Because of the lack of bridging, the carbocation is of limited stability and will always seek a path toward greater stability. We know the ways to achieve greater stability from earlier: (1) Go from secondary to tertiary; (2) Move the charge to a position where it is alpha to a lone pair of electons; (3) Move the charge to a position where it is conjugated. Figure 18.4 shows these three cases. Pay attention to the dotted lines in the epwa for these migrations. No one else but our class does this, but here they are very helpful in indicating the new bond, which is not always completely clear in a migration.
Figure 18.4: Three cases of rearrangements to increase the stability of a carbocation. NOTE in all cases only the hydrogen of the acid and the one that is going to migrate (if any) are indicated. In the first case, migration of a hydrogen atom changes a secondary cation into a tertiary one. In the second case, migration of a methyl group changes a tertiary cation into one stabilized by a lone pair. In the third case, migration of a hydrogen atom changes a secondary cation into a benzylic cation. WARNING: No one draws the dotted lines indicated in these figures except members of this class.
18.8.1 Required Exercises

18.8.1.1 Which of the cations 70-73 are likely to show a proton migration? Why?

18.8.1.2 Which of the cations 70-73 are likely to show a methyl migration?

18.8.1.3 A compound with IR: 3211, 1643 cm$^{-1}$ and $^1$H nmr 1.011 (s, 4.5), 4.820 (m, 0.48), 4.926 (m, 0.51), and 5.834 (d of d, J values of 17.5 and 10.4, 0.5) ppm is treated with HBr. The product has no interesting IR peaks, but shows a $^1$H nmr of 1.08 (d, 12), 1.76 (s, 12), and 1.85 (heptet, 2) ppm. What are the molecules?

18.8.1.4 Use epwa to show the mechanism of the reaction in the last problem. HINT: Remember that hydrogen ion does not “bridge” effectively.

18.8.2 Additional Exercises

18.8.2.1 When HBr reacts with 35 one obtains a cyclohexane derivative. Use epwa to predict the product and to explain why it forms.

18.9 Putting an OH Where We Want It Without Rearrangement

Read Klein, 9.5-9.6 (9.5-9.6)

There are two problem with formation of an alcohol from an alkene as we have developed the process: (1) We have the possibility of rearrangement and (2) the alcohol group always ends up on the most substituted carbon of the alkene. Both of these difficulties can be overcome. The first uses Hg(CH$_3$C(O)O)$_2$ and the second uses BH$_3$·THF. Both obey exactly the same rules we have developed up to now. There is no new chemistry. What allows rearrangement to be thwarted is a bridged intermediate with mercuric ion; what allows the opposite direction with BH$_3$·THF is to use a form of “H$^-$” as the nucleophile for the second step of alkene reaction.
An alkene acts as a nucleophile toward the mercury ion in Hg(CH\(_3\)C(O)O\)_2 which has lost an acetate group to form the ion Hg(CH\(_3\)C(O)O\)^+. This behaves as usual with the nucleophilic alkene which attacks the positive mercury ion. This forms a bridged intermediate with the alkene, using the empty 6s orbital of the mercury as the acceptor orbital for the \(\pi\) bond of the alkene and the filled 5d orbital of the mercury ion as the donor orbital for back-bonding into the empty \(\pi^*\) of the alkene. Because it bridges, rearrangements are stopped. The species is then attacked by water as a nucleophile; and the water attacks the more positive of the carbons of the original alkene, as determined, as usual, by their substitution pattern. This is all just like the role of Br\(^+\) in bromination of an alkene discussed above and illustrated in Figure 18.3. The only issue remaining is to make an alcohol; this is done by cleavage of the carbon-mercury bond using, in a second step, BH\(_4^-\).

In BH\(_3\)·THF we have species that liberates BH\(_3\) when the THF, tetrahydrofuran, leaves. (The only role of THF is to stabilize the BH\(_3\).) Because BH\(_3\) has an empty p orbital on the boron, this is the site of attack by the nucleophilic alkene. This forms a from a carbon on the alkene to the boron. Since the formation of this bond leaves the other carbon positive, the bond to the boron will use the least substituted carbon, leaving the more highly substituted carbon slightly positive, and thus attracted to a negatively polarized hydrogen of the BH\(_3\). We get a transition state with a pseudo-four membered ring, C to C to B to H back to original C—see Figure 9.5 in Klein; and more importantly, we have a negatively polarized hydrogen ready to bond to the usual positively charged carbon. Our product from this step is a species with a hydrogen atom attached to the most substituted carbon and a -BH\(_2\) group attached to the least substituted carbon. (Incidental to our interest, this process occurs two more times because there are still two B-H bonds to react with further alkenes, giving us the boron attached to three (former) alkenes.) The challenge is to convert that -BH\(_2\) (or strickly speaking the -BR\(_2\)) group into an -OH (or, as we shall see, into an -NH\(_2\)).

This second step is accomplished by reaction of the -BR\(_2\) with a good nucleophile, taking advantage of the empty orbital on the boron. If we use the anion of hydrogen peroxide, HO\(_2^-\), we get a species that can rearrange to form a carbon oxygen bond, which then ultimately is cleaved by water to give the alcohol. The process is shown in Figure 18.3. The critical step, the rearrangement, shown in B is driven by the strength of a C-O bond, by the weakness of the O-O bond, and by the ability to move formal negative charge from boron to oxygen. With all those factors on our side, this rearrangement seems very reasonable, right?

### 18.9.1 Required Exercises

18.9.1.1 Use epwa to show what happens to 2-methyl-1-pentene when reacted with Hg(OAc)_2 followed by BH\(_4^-\). HINTS: (1) -OAc is an abbreviation for -CH\(_3\)C(O)O. (2) Do not epwa the BH\(_4^-\) step, just replace the mercuric ion with an H.

18.9.1.2 Show the product(s) of the reaction of 3-methyl-cyclopentene with Hg(OAc)_2 in methanol, followed by treatment of the product with BH\(_4^-\) in methanol.
18.9.1.3 Explain how 14 is converted to 15 (on page 195) by treatment with Hg(OAc)$_2$ in a non-nucleophilic solvent followed by treatment with BH$_4^\text{-}$.

18.9.1.4 What product is formed when 1-butene is treated with (1) BH$_3$·THF; (2) H$_2$O$_2$ in base; (3) H$^+$?

18.9.1.5 Compound 16 (page 199) is treated with (1) BH$_3$·THF; (2) H$_2$O$_2$ in base; (3) H$^+$. What is the product? Use epwa.

18.9.1.6 What property of H$_2$O$_2$ makes it very useful for removing a boron from a carbon skeleton?

18.9.1.7 Three hydration reactions of (E)-2-phenyl-3-methyl-3-hexene are carried out. The first with sulfuric acid in water; the second with Hg(OAc)$_2$ followed by BH$_4^-$; and the third with BH$_3$·THF followed by basic peroxide and then acid. Give the three products; use epwa to show details of the reactions, including the peroxide cleavage of the B-C bond.

18.9.1.8 How would you make the alcohols 29-32 from alkenes? HINT: See the next exercise.
18.9.1.9 Depending on your choice of method, you may have a difficulty with the last compound in the last exercise. What would that difficulty be? How could you make it efficiently from an alkene?

18.9.2 Additional Exercises

18.9.2.1 If we haven’t covered it in class, determine the structure of BBN (See Klein, page 485 (475)). This reagent is very good at putting a hydroxyl group on the terminal end of an alkene. Why?

18.9.2.2 BBN is reacted with 3-hexene and then treated with basic peroxide and acid. What is the product? HINT: BBN can be used (more conveniently) in place of BH$_3$·THF.

18.9.2.3 BBN is reacted with 18 (page 199) and then treated with basic peroxide and acid. What is the product? HINT: See last exercise.

18.9.2.4 Because of the weakness of the O-O bond in peroxide, OH$^-$ is a reasonable leaving group. After BH$_3$ has attacked an alkene, the C-B bond is ruptured after attack by H$_2$O$_2$ by a rearrangement driven the good leaving group. Use epwa to show this process.

18.9.2.5 Presumably any reagent that can act as a nucleophile and has a good leaving group can play the role of the H$_2$O$_2$ in the last exercise. Use epwa to show how NH$_2$Cl can do this. What is the good leaving group?

18.9.2.6 Use epwa to show how NH$_2$OSO$_3^-$, which is called hydroxylamine-O-sulfonic acid, can replace NH$_2$Cl of the last exercise. What is the good leaving group?

18.9.2.7 Show how to synthesize 3-cyclohexyl-propylamine from 17 (page 199). HINT: Last exercise.

18.9.2.8 Arkansas’s great natural philosopher, Boniface Beebe, better known to his friends as Bonnie, tried to make 22 from 21 (page 199). He used the three steps:

a. Treat 21 with Mg to give 23.
b. Treat 23 with pentanal followed by dilute acid to give 24.
c. Treat 24 with concentrated HCl to yield 22.

Use epwa to show the mechanism of what happens during these steps. The last failed to give what Bonnie wanted. What did happen? HINT: You are to figure out what 23 and 24 are.
18.9.2.9 Although somewhat slow, the addition of BH$_3$·THF is reversible. Use epwa to show how 5-decene allowed to stand in the presence BH$_3$·THF for a time might yield 4-decene.

18.9.2.10 Use epwa to show how 5-decene allowed to stand in the presence BH$_3$·THF for a long time might yield 1-decanol when treated with hydrogen peroxide. HINT: As always, think about what drives that reaction; in this case, those thoughts are a trivial exercise. HINT: See the last exercise.

18.9.2.11 When 36 (page 202) is treated with Hg(OAc)$_2$ and then BH$_4^-$ in a non-nucleophilic solvent one obtains a compound with no broad strong peak in the 3000-3500 cm$^{-1}$ region of the IR. The compound has a M$^+$ of 114 and contains only C, H, and O. Use epwa to account for these facts.

18.10 Two Possible $\alpha$-Diols

Read Klein, sections 9.9-9.10 (9.9-9.10)

We have already seen that epoxides open in an anti fashion. Thus if we attack an epoxide with OH$^-$, we will get a $\alpha$-diol with the two hydroxyl groups anti to each other, just as the two bromine atoms are anti to each other in the isoelectronic bromonation of an alkene. If we had a good way of making an epoxide from an alkene, we would have a way of making an anti-$\alpha$-diol from an alkene. Of course, we do have such a reaction. It uses a peracid, RC(O)OOH (be sure you do the Lewis structure of that) as the source of oxygen and occurs, again, because of the weakness of the O-O bond in the peracid. The process is shown in A of Figure 18.6, where the cascade of epwas is numbered to help in the logic: First the alkene acts, as usual, as a nucleophile to attack one of the oxygens of the weak O-O bond, which breaks (step 2) and shifts negative charge to what was the carbonyl oxygen (step 3), which removes the proton, creating a negative oxygen to react with the carbon of the alkene made positive by the initial nucleophilic attack (step 4).

A second reagent can carry achieve be used to synthesize an epoxide from an alkene, dimethyldioxirane, (CH$_3$)$_2$COO, a molecule with a C-O-O cyclic structure. This reagent forms the epoxide as shown in B of Figure 18.6. The initiation is again the alkene acting as a nucleophile, with the weak O-O bond driving the reaction.

The second variation of making $\alpha$-diols uses OsO$_4$ as the oxidizing agent. (Do you recognize that an alkene is a carbon level 1 (delocalized) compound, which, when converted into an $\alpha$-diol becomes a carbon level 2 compound--two carbon level 1 carbons, and hence is being oxidized?) The first step in the mechanism (to form the osmate ester) is clear and is given by Klein in Section 9.10. The breakdown of this ester is a little obscure (water or hydroxide attacks the osmium of the ester and cleaves the C-O-Os bond between the O and the Os) and we won’t worry about it. What is to be noted is that both oxygen atoms in the product diol come from the OsO$_4$ and hence for steric reasons, the addition to the alkene must occur
Figure 18.6: The epoxidation of an alkene by a peracid (A) or by dimethyldioxirane (B). In both cases the weak O-O bond is critical is causing net reaction.

*syn.* The syn-α-diol is formed.

### 18.10.1 Required Exercises

**18.10.1.1**

Review. Can you make an epoxide from an aldehyde or ketone? Show how.

**18.10.1.2**

Can you make an epoxide from an alkene? Show how.

**18.10.1.3**

Use epwa to show the product of reaction of 18 (page 199) with MCPBA (meta-chloro-perbenzoic acid, a peracid often used for expoxidations) followed by treatment with ethyl magnesium iodide and then weak acid.

**18.10.1.4**

How would you synthesize 25 from 18? (Structures on page 199)

**18.10.1.5**

Cyclohexene is treated with MCPBA to form A, which is isolated. The compound A is then treated with ethyl Grignard, followed by water and H⁺. Is the final product cis or trans? Use epwa to show the mechanism.

**18.10.1.6**

How would you prepare the *cis*-1,2-diol and the *trans*-1,2-diol of cyclohexane starting with cyclohexene.
18.10.2 Additional Exercises

18.10.2.1 How would you prepare 26 (page 199) from 27 (page 202) and other carbon containing compounds?

18.10.2.2 How would you prepare 26 (page 199) from 3-cyclohexyl-2-pentene and other carbon containing compounds?

18.10.2.3 How would you prepare 28 (page 202) from ethanoic acid?

18.10.2.4 See if you can use epwa to prepare dimethyldioxirane from acetone and peroxymonosulfuric acid, $O_3S$SOO$^2$$. Look for a good leaving group from the weak O-O bond after attack by the anion on the carbonyl carbon of acetone.

18.10.2.5 Use $O_2H^−$, the anion of hydrogen peroxide, to attack the $\beta$ position of an $\alpha,\beta$-unsaturated ketone. Show using epwa that the enolate anion product can produce an epoxide. HINT: Write the enolate anion in the “negative charge on carbon resonance form” and note that OOH$^−$ is a good leaving group from a peroxide linkage due to the weakness of the O-O bond.

18.10.2.6 Is 2,3-dimethyl-2-pentene chiral?

18.10.2.7 Show that formation of the epoxide of the alkene in the last exercise, followed by attack with AlH$_4^−$ gives a racemic mixture (as it must).

18.11 Ozonolysis

Read Klein, Section 9.11 (9.11)

Early in the course I stated that ozone could cleave an alkene to change each carbon of the double bond into a carbonyl group. The mechanism of that reaction is a little complicated, as it goes through a couple of intermediate compounds. This late in the course you are capable of following Klein’s arguments for the mechanism. Ozone is a molecule in which a formal positive charge exists on the central oxygen in all resonance structures. It is therefore an electrophile and can be attacked by a nucleophilic alkene. The resulting molozonide is unstable because of two O-O single bonds; it fragments and then recombines to an ozonide, which has removed one of those unstable bonds. If the ozonide is treated with Zn or dimethylsulfide, (CH$_3$)$_2$S, the rupture of the remaining O-O single bond occurs. A mechanism to help us make sense of this is shown in Figure 18.7 with numbers to indicate a logical order to think about the steps. (1) The lone pair on the sulfur attacks the oxygen
in order to rupture the O-O single bond (2). The epwa cascade, (2) and (3), produce the carbonyl functionality, and the final step (4) creates the sulfur-oxygen zwitteron.

If one uses $\text{H}_2\text{O}_2$ to decompose the ozonide rather than Zn or $(\text{CH}_3)_2\text{S}$, the products are carboxylic acids where possible. When is that?

**18.11.1 Required Exercises**

**18.11.1.1** What are the products of ozonolysis (followed by treatment with Zn) of 37 (page 202)?

**18.11.1.2** Compound 38 (page 202) is the result of ozonolysis (followed by $\text{H}_2\text{O}_2$ treatment). What is the original alkene?

**18.11.1.3** What is the product when 1-methyl-cyclopentene is treated with $\text{O}_3$ followed by $(\text{CH}_3)_2\text{S}$?

**18.11.1.4** What is the product when 1-methyl-cyclopentene is treated with $\text{O}_3$ followed by $\text{H}_2\text{O}_2$?

**18.12 HBr Addition to Alkenes, the Wrong Way**

Read Klein, Section 11.10 (11.10)

In the early days of organic chemistry experimentation there was some argument over the products of the reaction between HBr and an alkene. Take propene for example. Some groups reported that the product was 2-bromopropane, which is the product we would anticipate from what we have said thus far, and others argued that they found 1-bromopropane.
After considerable further experimentation it was found that when HBr (and only HBr; HCl and HI always add the “correct” way) was used under very clean conditions, it yielded, as expected, 2-bromopropane. But if the HBr was added to the alkene in the presence of a radical source, 1-bromopropane was found. Here is what happens using RO· radicals as the initiator:

\[
\begin{align*}
\text{HBr} & + \text{RO} & \text{= ROH} & + \text{Br} & \cdot \\
\text{Br} & \cdot & + \text{CH}_3\text{CHCH}_2 & \text{=} & \text{CH}_3\text{CH} & \cdot \text{CH}_2\text{Br} \\
\text{CH}_3\text{CH} & \cdot \text{CH}_2\text{Br} & + \text{HBr} & \text{=} & \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} & + \text{Br} & \cdot
\end{align*}
\]

In the second step the bromine radical adds to the end carbon so that the resultant radical is stabilized by the same features that stabilize the cation: it is more substituted. This extends across the entire set of possible radicals; their stability order is the same as the carbocation order. This radical abstracts a hydrogen from another HBr and the resultant bromine radical does it thing all over again. Once started this chain reaction is very efficient at producing product. It turns out that how bond energies are balanced in these steps is critical. This is the reason that this reaction works only with HBr and not with other acids.

### 18.12.1 Required Exercises

18.12.1.1 How would you make 1-bromo-3,3-dimethylbutane from 3,3-dimethyl-1-butene?

18.12.1.2 Will reaction of a benzyl radical with (CH₃)₃CBr to form benzyl bromide and (CH₃)₃C· take place?

18.12.1.3 What would be the product of the reaction of HBr with (CH₃)₂CCH(CH₃) in the presence of peroxide?

### 18.13 Review of Alkene Chemistry

Here are some exercises for you to review alkene chemistry.

### 18.13.1 Required Exercises

18.13.1.1 Where will the charge reside on the carbocation intermediate when HCl reacts with propene?

18.13.1.2 Which cation will be more stable, that formed on a tertiary carbon or that formed on a carbon attached to two other CH₃ groups and a bromine? Why?
18.13.1.3 What do you predict is the product of HCl reacting with 1-bromopropene? Use epwa to justify. REMARK: You have just learned something of use in alkyne chemistry.

18.13.1.4 Starting with propene and cyclopentanone, how would you prepare 45? HINT: Pay attention to regioselectivity in the steps.

18.13.1.5 What products would you find from treatment of 49 with O₃, followed by reaction with Zn?

18.13.1.6 A compound, Y, of formula C₁₀H₁₈O reacts with acid (with removal of water) to give two alkenes, both with formula C₁₀H₁₆. The major product, 48, is treated with ozone followed by Zn, to give only cyclopentanone. What is 48? What is its isomer? What is Y?

18.13.1.7 How would you prepare compound Y from the last problem starting with cyclopentene?

18.13.2 Additional Exercises

18.13.2.1 One can use D₂ instead of H₂ in hydrogenations. What would the product be if cyclohexene were treated with D₂ over Pd(C)? Specify stereochemistry.

18.13.2.2 What product(s) would you find if you treated 49 with H₂O₂ with OsO₄ catalyst? Specify stereochemistry. HINT: OsO₄ is expensive; the same reaction occurs with
the mixture given in this problem as with pure OsO₄.

18.13.2.3 Use epwa to see if you can figure out how 2-bromobutane might form 2-butene when treated with a base, (CH₃)₃CO⁻. HINT: This reaction requires specific stereochemistry that you will learn next semester.

18.13.2.4 A compound, X, that absorbs two moles of H₂ per mole of compound under catalytic hydrogenation conditions. The compound also reacts with O₃ followed by H₂O₂. One product that is isolated is oxalic acid. The other has the following nmr data: ¹H: 2.19 (s, 18) and 2.71 (s, 11.9) ppm. ¹³C: 29.76(q), 36.96(t), 206.87(s) ppm. What is X? Give your reasoning.

18.13.2.5 The great natural philosopher from Beebe, Arkansas, “jus’ down the road a little” from Conway, Boniface Beebe, tried to make 53 from 54. He used MCPBA followed by OH⁻ and then H⁺. Was he successful? Why or why not? If not, what did he obtain?

18.13.2.6 How would you prepare 53 from 54?

18.13.2.7 When 3-bromo-cyclopentene is reacted with HBr, the only product is trans-1,2- dibromo-cyclopentane (a racemic mixture, obviously). Account for this result.

18.13.2.8 The following reaction occurs. Use epwa to show the mechanism. Be sure that you indicate the role of the proton. Comment on why this process is efficient.
Chapter 19

Alkyne Chemistry

Alkyne chemistry appears to be a relatively simple extension of alkene chemistry, but there is more richness that is apparent. At the superficial level, alkyne reactions are what we expect given alkene chemistry. Often the products that are formed, with, for instance, addition of $X_2$, are difficult to stop at the alkene level and produce final products of a “double attack.”

Read Klein, Chapter 10 (10)

19.1 Addition of HX and $X_2$ to Alkynes

Reaction of alkynes with HX and $X_2$ give products expected from the arguments made with alkenes (although there are questions about the details of the mechanism as vinyl cations do not seem particularly stable). These reactions are difficult to stop and lead to disubstituted products as well.

19.1.1 Required Exercises

19.1.1.1 What is the product of reaction of 1-hexyne with excess HCl? HINT: Excess is the key word here.

19.1.1.2 Give the product of treatment of 3-heptyne with Br$_2$.

19.2 Hydration of Alkynes

The two reagents for producing stereospecific addition of water to alkenes can also be used with alkynes. Consider first Hg(CH$_3$C(O)O)$_2$. The alkyne attacks the mercuric ion to put
the positive charge on the most favorable site, which then reacts with water to produce A in Figure [19.1]. The double bond in this species attacks a second proton, putting positive charge in a position stabilized by the -OH group, and then the bond to the mercuric ion breaks, moving positive charge from carbon to mercury. We form an enol, which, as we saw earlier in the course, rearranges to a ketone. This process is most efficient (as a synthesis tool) if the alkyne is terminal, in which case the product is a methyl ketone.

The hydroboration of alkynes is the same as with alkenes, although usually the process uses a sterically hindered disubstituted borane, BHR₂, where R is a large group. The reason for this is to avoid having the boron reagent react with the alkene formed in the first step, which would generate a lot number of different products. This reagent is often BBN. The product is the enol of an aldehyde which can be converted into the aldehyde. Here is a nice way to make aldehydes.

19.2.1 Required Exercises

19.2.1.1 What is the product of reaction of 1-hexyne with excess HClO₄ in water? HINT: HClO₄ is a very strong acid. HINT: Use your chemical intuition.

19.2.1.2 What is the product when 3-cyclopentyl-1-propyne is treated first with BBN and subsequently with basic peroxide and then acid?

19.2.1.3 How would you prepare 46 from 47 (see page 211)?
19.3 Reduction of Alkynes

Read Klein, Section 10.4-10.5 (10.4-10.5)

Alkynes are delocalized carbon level 2 compounds that can be reduced. If the conditions used for alkenes (H₂ over Ni, Pd, or Pt—see Section 18.2—the alkyne is reduced to the alkane. More useful are two methods of reduction that stop at alkenes. If a “poisoned” catalyst is used, typically called “Lindlar’s catalyst,” the reduction stops at the alkene stage and, because of the surface reaction, the product is the Z isomer. On the other hand, if the reduction is carried out with electrons in liquid ammonia (see Klein, pp 476 (466)), the E isomer is produced. This is a clever way of making an alkene of the desired form, at least when two of the substituents are hydrogen atoms.

To complete a story, we should note that a good way to form an alkyne is to dehydrohalogenate a dihalide; this is a reaction that you will learn more about next semester, but let’s preview it here. If one takes either a gem-dihalide or an α-dihalide and treats it with strong base, a proton is removed from a carbon adjacent to halide, and the resultant lone pair of electrons form a double bond to drive out the good leaving group, X⁻. If that happens a second time, one gets an alkyne. Since an alkene can be used (with Br₂ to produce an α-dibromide alkane) that can then be converted to an alkyne, which can then be changed to an alkene of the desired type (E or Z), we have a way of changing the geometry around an alkene.

19.3.1 Required Exercises

19.3.1.1 What reagent would you use to convert 2-bromopropane to propene?

19.3.1.2 What reagent would you use to convert propene to 1,2-dichloropropane?

19.3.1.3 What reagent would you use to convert 1,2-dichloropropane to propyne?

19.3.1.4 What reagent would you use to convert propyne to 2-butyne?

19.3.1.5 What reagent would you use to convert 2-butyne to butanone?

19.3.1.6 How would you convert trans-5-decene to cis-5-decene. HINT: It takes more than one step.

19.3.1.7 What reagent would you use to convert 2-butyne to (Z)-2-butene?
19.3.1.8 What reagent would you use to convert 2-butyne to (E)-2-butene?

19.3.2 Additional Exercises

19.3.2.1 In this and the following three problems we work with the following acids: maleic acid, 50, fumaric acid, 51, and tartaric acid, 52. Show how to carry out the transformation of 50 to (2R,3S)-52, which is the same as (2S,3R)-52, i.e., a meso compound. HINT: See page 211.

19.3.2.2 How would you convert 50 to (2R,3R)-52 and (2S,3S)-52. HINT: See page 211.

19.3.2.3 How would you convert 51 to (2R,3S)-52, which is the same as (2S,3R)-52, a meso compound. HINT: See page 211.

19.3.2.4 How would you convert 51 to (2R,3R)-52 and (2S,3S)-52. HINT: See page 211.

19.3.2.5 Reaction of 2-hexyne with acidic water is a method of preparing 3-hexanone. Use epwa to show how.

19.3.2.6 The method used in the last exercise is not very efficient. Why not?
Chapter 20

Review Problem for Chm 222

In this chapter are a bunch of problems for you to use to review for exams or for the final in this course. Choose the section with which you want practice, although problems sometimes will cover more than one kind of problem.

Because I have organized the problems according to four areas, which is not the way they were originally organized, the figures are sometimes remote from the problem.

20.1 Reactions

20.1.1 Additional Exercises

20.1.1.1 A marine algae converts 55 into 56. The first step of this process involves an enzyme that adds “Br+” to a double bond of 55. Presumably, the enzyme has structural components that allow a specific double bond in 55 to be converted into a “bromonium ion”. Given that, outline the remaining steps that occur in the conversion.

20.1.1.2 Suggest a mechanism (use epwa) for the conversion of 57 into 58 when 57 is treated with Hg(OAc)$_2$. HINT: Don’t let a stable carbocation be replaced by an less stable one.

20.1.1.3 Use epwa to see if you can figure out how 2-bromobutane might form 2-butene when treated with a base, (CH$_3$)$_3$CO$^-$. HINT: This reaction requires specific stereochemistry that you will learn next semester.

20.1.1.4 DIBAL, shown in 10, is an “H−” reagent that reacts with esters once and then “stops.” Compound 11 is reacted first with DIBAL and then with aqueous acid; show using
epwa the net reaction and the final product. HINT: Think; there must be something here other than the first sentence.

20.1.1.5 Give the product when 2-methyl-2-butene is reacted with HBr in the presence of ROOR, where R is the tertiary butyl group.

20.1.1.6 Give the product when 2-methyl-2-butene is reacted with 1. BH₃·THF, 2. H₂O₂/OH⁻, 3. H⁺.

20.1.1.7 What will be the product of 1-methyl cyclohexene with MCPBA.

20.1.1.8 What happens to the product of the last exercise if it is reacted with HBr?

20.1.1.9 What happens to the product of exercise [20.1.1.7] if it is reacted with SCH₃⁻?

20.1.1.10 Give the product when 2-methyl-2-butene is reacted with MCPBA or dimethyl-dioxirane.

20.1.1.11 Give the product when 2-methyl-2-butene is reacted with 1. Ozone, 2. Zn.

20.1.1.12 What is (are) the product(s) of the attack of HBr on 3,3-dimethyl-1-butene?

20.1.1.13 Compound 12 is treated with methyl Grignard reagent, then dilute acid. What is the product?

20.1.1.14 Compound 13 is treated with CH₃O⁻ and then with dilute acid. What is the product?
20.1.1.15 Propanone, acetone, \( \text{CH}_3\text{C(O)CH}_3 \), is dissolved in water and treated with methyl Grignard. What is the product?

20.1.1.16 Compound 14 is treated with ethyl lithium and then with dilute acid. What is the product?

20.1.1.17 Compound 13 of Figure 20.7 (see page 237) is treated with acid in aqueous solution to produce 14. Explain.

20.1.1.18 Give a mechanism to produce 1 from 2—See Figure 20.7 on page 237.

20.1.1.19 Imagine you start with 3 of Figure 20.7 on page 237 and treat it as follows: 1. \( \text{SOCl}_2 \); 2. excess ethyl magnesium bromide; 3. strong \( \text{H}^+ \); 4. Mg metal; 5. acetone; 6. strong \( \text{H}^+ \); 7. HBr in \( \text{CH}_2\text{Cl}_2 \). Give the product of each reaction and the final product.

20.1.1.20 Give a mechanism by which 62 can be prepared from 61 using \( \text{Br}_2 \) in water. HINTS: (1) This is “new” chemistry in a sense, but you should be able to use your experience to do the problem. (2) Need I say this late in the course, “use epwa.”

20.1.1.21 Use epwa to show how 64 is converted to 65 in acid solution.
20.1.1.22  Show how addition of Br$_2$ to 66 can form 67.

20.1.1.23  Use epwa to show how you would convert 134 to 135. Account for stereochemistry

20.1.1.24  Use epwa to show how you would convert 136 to 137. Account for stereochemistry.

20.1.1.25  When 138 is treated with I$_2$, 139 results. Use epwa to account for the process. Pay attention to stereochemistry. HINT: There is an “I” on the top carbon of the six membered ring in 139 that is impossible to see.

20.1.1.26  The Swern oxidation of alcohols to aldehydes and ketones involves as the active reagent (CH$_3$)$_2$SCl$^+$, a S(IV) compound with a good leaving group, Cl$^-$. Show how this might be attacked by an alcohol. HINT: Remember PCC.

20.1.1.27  When the product of exercise 20.1.1.26 is treated with a base, often N(C$_2$H$_5$)$_3$, oxidation occurs. Use epwa to describe this step.

20.1.1.28  The original Swern reagent is made by reacting (CH$_3$)$_2$SO with oxalyl chloride, the di-acid chloride of oxalic acid. See if you can make sense of this with an epwa.
20.1.1.29 What is the product when 8 (page 232) is reacted with ethyl magnesium bromide followed by H⁺?

20.1.1.30 What is the product when 9 (page 232) is reacted with ethyl magnesium bromide followed by H⁺?

20.1.1.31 Cyclohexene, when treated with HBr in acetic acid solution, yields two products (I am not talking about stereochemistry here). See if you can figure out what they are. HINT: When water is a solvent in a bromination, it is not innocent; neither is the acetic acid.

20.1.1.32 When 10 (page 232) is treated with HCl, the product is 1-chloro-1,2-dimethylcyclohexane. Use epwa to account for this transformation.

20.1.1.33 When 1-cyclohexylcyclohexene is treated with Cl₂, the product is exclusively the one with chlorine atoms trans to each other. However, treatment of 1-phenylcyclohexene upon treatment with Cl₂ yields two products, one of which has the chlorine atoms trans to each other and the other of which has them cis. Explain both experiments.

20.1.1.34 Compound 82 is converted to 83 with H⁺ in water. Give a mechanism.
20.1.1.35 This is *really* going to get me into trouble with the word police! Thinking about the last exercise causes me to want to call \( \text{82} \) a gem-DIN of sorts. Care to comment on my thoughts?

20.1.1.36 Use epwa to show the mechanism for the formation of \( \text{94} \) from \( \text{95} \).

20.1.1.37 It is fairly easy to put a halogen \( \alpha \) to a ketone using, for example, \( \text{Br}_2 \). Suggest a mechanism using epwa. HINT: Use your knowledge of alkene chemistry and think about the enol form (in equilibrium with the ketone).

20.1.1.38 Suggest a mechanism for the transformation shown in \( \text{265} \), which is catalyzed by acid.

20.1.1.39 When 2,2-diphenylethanol is treated with aqueous HI, the main product is 1-iodo-1,1-diphenylethane. Account for this result with a detailed mechanism (use epwa).

20.1.1.40 What is the major product of the reaction of propanoyl chloride with two equivalents of ethylamine?

20.1.1.41 What is the major product of the reaction of ethanoic acid with propyl lithium followed by acidification?

20.1.1.42 What is the major product of the reaction of 4-chlorocyclopentene with \( \text{OsO}_4 \) followed by treatment with water and sulfite? Specify stereochemistry. HINT: The water and sulfite simply break the O-Os bonds.

20.1.1.43 What is the major product of the reaction of cyclopentene with \( \text{Cl}_2 \) in the non-nucleophilic solvent \( \text{CH}_2\text{Cl}_2 \)? Specify stereochemistry.
20.1.1.44 What is the major product of the reaction of 3-hexyne with 1. BBN; 2. H₂O₂, OH⁻; 3. dilute acid?

20.1.1.45 What is the product of the reaction of 1-pentyne with HBr?

20.1.1.46 What is the product of the reaction of 2-chloro-2-butene with HBr?

20.1.1.47 What is the product of the reaction of acetylene with 1. NaNH₂; 2. 2-chloropropane?

20.1.1.48 What is the product of the reaction of propyne with mercuric ion in acid solution?

20.1.1.49 Compound 33 is more reactive than most amides. Why?

20.1.1.50 What happens when 34 is treated (separately, that is, four different experiments) with each of the following: a. NaOH; b. NaCl; c. CH₃SH, H⁺; d. 1. SOCl₂, 2. isopropyl alcohol.
20.1.1.51 What will be the product of reacting ethyl lithium with propynitrile (followed by H⁺)?

20.1.1.52 Predict the product when 35 is reacted with H⁺ in water. HINT: The aldehyde ends up as a hemiacetal.

20.1.1.53 What alkene can be used to make 2-cyclohexyl-2-bromo-propane, bromocyclopentane, 2,3-dibromohexane, and 1-chloro-1-methylcyclopentane in good yield? HINT: Four questions.

20.1.1.54 Under dilute conditions in a non-nucleophilic solvent, what products might you expect from 40 when it reacts with Br₂?

20.1.1.55 An alkene reacts with O₃ followed by (CH₃)₂S, which gives the same results as Zn, and produces 41. What is the alkene?

20.1.1.56 An alkene reacts with O₃ followed by Zn and produces acetone, butanone, and 42. What is the alkene?

20.1.1.57 What products would you expect from the reaction of HCl (dilute) with cyclohexene in acetic acid solution?

20.1.1.58 Predict the product of the addition of CH₃SeCl to 21 (on page 238). HINT: Think about the polarization of the Se-Cl bond.

20.1.1.59 Give the product when 91 (on page 234) is treated with ozone followed by Zn.

20.1.1.60 What is the product of 411 (on page 234) with LiAlH₄ followed by H⁺.

20.1.1.61 It has been found that if CH₃C(O)SH is reacted with propene in the presence of light and ROOR, that CH₃C(O)SCH₂CH₂CH₃ is formed. Using your knowledge of stability of intermediates, predict the major product in the reaction of CH₃C(O)SH with 2-methyl-2-pentene under the same conditions of peroxide and light. Give your suggested mechanism in detail using epwa.

20.1.1.62 If CH₃C(O)SCH₂CH₂CH₃ is reacted with Cl⁻ in a non-nucleophilic solvent, what is (are) the major organic product(s)?
20.1.1.63 If CH$_3$C(O)SCH$_2$CH$_2$CH$_3$ is reacted with OH$^-$ in aqueous solution, what is (are) the major organic product(s)?

20.1.1.64 What is the product of the reaction of propyne with 1.BBN; 2. H$_2$O$_2$, OH$^-$, followed by H$^+$?

20.1.1.65 What is the product of the reaction of 2-hexyne with H$_2$ using Lindlar’s catalyst?

20.1.1.66 What is the product of the reaction of 2-hexyne with Li in liquid ammonia?

20.1.1.67 Give the product when a carboxylic acid reacts with SOCl$_2$.

20.1.1.68 Give the product when a ketone reacts with ethyl Grignard followed by acid.

20.1.1.69 Give the product when an aldehyde reacts with BH$_4^-$ followed by acid.

20.1.1.70 Give the product when a cyclic alkene reacts with OsO$_4$ followed by acid. Show and label (R, S?) stereochemistry.

20.1.1.71 Give the product(s) when an tri-substituted alkene reacts with dilute Br$_2$ in CH$_3$OH.

20.1.1.72 Give the product of the reaction of benzyl alcohol with PCC in CH$_2$Cl$_2$.

20.2 Spectroscopic Techniques

20.2.1 Additional Exercises

20.2.1.1 A compound of formula C$_7$H$_{12}$ has nmr data as follows: $^1$H: 0.903 (d, 6), 1.42 (q, 2), 1.65 (m, 1), 1.912 (t, 1), 2.18 (t of d, 2) ppm; $^{13}$C: 16.46, 22.14, 27.19, 37.56, 68.01, and 84.63 ppm. What is the compound? How would you prepare it from three carbons or less? HINT: This is a somewhat challenging question.
### Table 20.1: NMR of compound A for exercise 20.2.1.2

<table>
<thead>
<tr>
<th>$^1$H δ</th>
<th>Splitting</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.58</td>
<td>s</td>
<td>6.0</td>
</tr>
<tr>
<td>1.73</td>
<td>d</td>
<td>5.8</td>
</tr>
<tr>
<td>2.81</td>
<td>s</td>
<td>4.0</td>
</tr>
<tr>
<td>5.25</td>
<td>q</td>
<td>1.9</td>
</tr>
<tr>
<td>7.2-7.7</td>
<td>m</td>
<td>10.3</td>
</tr>
</tbody>
</table>

### Table 20.2: NMR of compound B for exercise 20.2.1.2

<table>
<thead>
<tr>
<th>$^{13}$C</th>
<th>DEPT</th>
<th>$^1$H δ</th>
<th>Splitting</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.7</td>
<td>q</td>
<td>0.97</td>
<td>t</td>
<td>1.49</td>
</tr>
<tr>
<td>20.2</td>
<td>t</td>
<td>1.32</td>
<td>d</td>
<td>1.52</td>
</tr>
<tr>
<td>25.3</td>
<td>q</td>
<td>1.42</td>
<td>quintet</td>
<td>1.0</td>
</tr>
<tr>
<td>28.3</td>
<td>d</td>
<td>1.84</td>
<td>m</td>
<td>0.51</td>
</tr>
<tr>
<td>46.4</td>
<td>d</td>
<td>4.43</td>
<td>d</td>
<td>0.48</td>
</tr>
<tr>
<td>128.7</td>
<td>s</td>
<td>7.2-7.7</td>
<td>m</td>
<td>2.4</td>
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<tr>
<td>128.8</td>
<td>d</td>
<td></td>
<td></td>
<td></td>
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<td>129.2</td>
<td>d</td>
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<tr>
<td>138</td>
<td>s</td>
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</tr>
</tbody>
</table>

#### 20.2.1.2
A compound, A, containing only carbon and hydrogen, has a M$^+$ of 146 and the $^1$H nmr as given in Table 20.1. Compound A is reacted with HBr under dilute conditions in a non-nucleophilic solvent and compound B results. The $^1$H and $^{13}$C (with off resonance decoupling) nmr are given for compound B in Table 20.2. What is compound A?

#### 20.2.1.3
What is compound B of the last exercise? Pursue.

#### 20.2.1.4
A compound with formula $C_6H_{10}$ has the following nmr: $^1$H: 5.66 (approximate t, 2), 2.0 (m, 4), and 1.6 (m, 4) ppm; $^{13}$C: 22.1, 24.5, and 126.2 ppm. It is treated as follows: $C_6H_{10}$ with Hg(OAc)$_2$ and NaBH$_4$ to give A; A with CrO$_3$ in H$_2$SO$_4$ to give B; B with R$_3$P=CH$_2$ to give C; C with BH$_3$ in THF followed by treatment with HO$_2^−$ to give D; D with CrO$_4^{2−}$ in aqueous sulfuric acid to give E. Compound E is treated with methanol in acid to give F. Identify all the compounds and use epwa to show the reactions coupling them.

#### 20.2.1.5
What is the compound of formula $C_{10}H_{12}O_2$ with the following spectral characteristics? IR: 1740 cm$^{-1}$. 1H nmr: 2.1 (s, 3), 2.95 (t, 2), 4.3 (t, 2), and 7.2-7.4 (m, 5) ppm.

#### 20.2.1.6
A compound with the formula $C_6H_{10}$ has an IR with no interesting peaks. The nmr has a triplet at 1 ppm, area 2.0, and a quartet at 2.03 ppm with an area of 1.3. What is the compound?
20.2.1.7 How would you use $^1$H nmr to distinguish between butanone and 2-butyne?

20.2.1.8 A compound with $M^+$ value of 60 has a $^1$H nmr with peaks: 1.2 (d, 14), 2.55 (s, 2.2), and 4.05 (heptet, 2.3) ppm. What is the compound?

20.2.1.9 What is the compound with $^1$H nmr of 0.96 (d, 3), 1.96 (m, 0.5), 3.96 (d, 1) and 8.08 (s, 0.5) ppm. The $^{13}$C has peaks at 19, 27.7, 70.0, and 161.1 ppm.

20.2.1.10 A compound with formula C$_6$H$_{12}$O$_2$ has $^1$H with peaks 1.21 (s, 6), 2.18 (s, 3), 2.62 (s, 2) and 3.82 (s, 1, exchangeable) ppm. When heated with acid, the nmr changes to 1.88 (s, 3); two peaks near 2.23 (6) and 6.12 (s, 1) ppm. What are the two compounds?

20.2.1.11 Somewhat challenging. Compound A has an $^1$H nmr with peaks at 1.28 (t, 12), 3.36 (s, 4), and 4.21 (q, 8) ppm. It is treated with AlH$_4$ and produces after acidification a molecule, B, with $^1$H of 1.75 (quintet, 2), 2.70 (exchangeable, 2), and 3.82 (t, 4) ppm. The $^{13}$C has peaks at 34.1 and 61.7 ppm. The IR of B is boring except for a broad peak centered at 3340 cm$^{-1}$. What are A and B?

20.2.1.12 A compound, C, has the following $^1$H nmr data: 4.10 (s, 5.9), 3.41 (s, 9.1), 2.43 (s, 3.1) ppm. The IR shows sharp peaks at 3300 and 2125 cm$^{-1}$. This compound is treated with acidic mercuric solution and produces D. Compound D has spectral data as follows: Molecular weight of 88. $^1$H nmr: 4.03 (s, 4.8), 3.42 (s, 7.4), and 2.15 (s, 7.5) ppm. $^{13}$C nmr: 206, 77.9, 59.2, and 26.1 ppm. IR: 2934, 1730, 1422, 1357, 1202, 1180, 1126, 933, 617 cm$^{-1}$. Identify C and D. Give the arguments to convince the reader of your identification.

20.2.1.13 This is a “box” problem without the boxes. We have three compounds, A, B, and C with the following information available about each: A has a mass spec with a molecular peak at 110; The IR shows a peak at 1703 cm$^{-1}$. The hydrogen nmr has peaks at 7.45 (d, 4.1), 5.98 (d, 4), 2.22 (s, 7.9), and 1.2 (s, 24.2) ppm. The carbon nmr has peaks at 11, 29, 34, 134, 165, and 209 ppm. Compound B is produced from A by using Cu(C$_3$H$_5$)$_2$ followed by acid and water. Compound B has an IR peak at 1724 cm$^{-1}$. Compound C is produced from B by treating it with a Wittig reagent formed from triphenylphosphine, methyl iodide, and butyl lithium. Compound C has an IR peak at 1630 cm$^{-1}$. Find A, B, and C.

20.2.1.14 A compound that I call A has a mass spectral molecular ion peak at 112 has a $^{13}$C nmr spectrum with peaks at 19.3, 19.5, 19.7, 29.0, 132, 137, and 206 ppm. The $^1$H nmr has four peaks, all singlets with equal areas, at 1.61, 1.63, 1.70, and 2.11 ppm. What is the compound?
A compound that I call B has a formula C\textsubscript{8}H\textsubscript{16}O and has a $^{13}$C nmr spectrum (with off-resonance decoupling listed in parenthesis) with peaks at 12.4 (q), 27.1 (q), 30.0 (s), 30.7 (q), 55.1 (d), and 212 (s) ppm. The $^1$H nmr has peaks at 0.91 (s, 9), 1.26 (d, 3), 2.65 (q, 1), and 2.13 (s, 3) ppm. What is the compound?

A compound has a M$^+$ peak at 240 and a (M+2)$^+$ peak at 242 of equal intensity and an IR with peaks at 1630, 1710, and 3120 cm$^{-1}$. The $^1$H and $^{13}$C (with off resonance decoupling) nmr have peaks as given in the Table. What is the compound?

## Synthesis

### Additional Exercises

How would you prepare 2,7-dimethyl-3-octanone from substances with four carbons or less?

How would you prepare 59 from 60 (on page 218)?

Give three different ways of making 2-bromo-3-methylbutane from substances with five carbons.

Give two different ways of making the epoxide of 1-methylcyclohexene. HINT: I think we only have two ways of making epoxides, so the issue here is really only one of what are the starting materials.

Give four different ways of making butanal.
20.3.1.6 How would you make N-methyl-N-butyl-amine from butyric acid and other compounds.

20.3.1.7 How would you prepare (E)-3-heptene from 3-heptyne?

20.3.1.8 How would you synthesize 63 (on page 220) from 1-butanol as your only source of carbon atoms? HINT: Remember, you can’t make a primary carbocation; see problem 20.1.1.3.

20.3.1.9 How would you prepare 68 (on page 220) starting with propene as your only source of carbon?

20.3.1.10 Synthesize compound 1.

20.3.1.11 Synthesize compound 2.

20.3.1.12 Synthesize compound 3.
20.3.1.13 Synthesize compound 4.

20.3.1.14 Synthesize compound 5.

20.3.1.15 Synthesize compound 6.

20.3.1.16 Synthesize compound 7.

20.3.1.17 Synthesize compound 8.

20.3.1.18 Synthesize compound 9.

20.3.1.19 Synthesize compound 15 from 16 and other carbon compounds containing three carbon atoms or less. You may use any “inorganic” reagents you wish.

20.3.1.20 Synthesize compound 17 from compounds containing three carbons or less. NOTE: The Z stereochemistry of the final product is important, but if you do not know how to generate that stereochemistry, just do the process without. HINT: The note.

20.3.1.21 How would you make 2 from 1? See Figure 20.7 on page 237.

20.3.1.22 Using only (E)-3-hexene, show how to prepare propyl propanoate. All carbons in the product must come from the hexene.

20.3.1.23 Starting with 4, 5, and 6 of Figure 20.1 on page 221 show how you would synthesize 7, moclobemide, an antidepressant.

20.3.1.24 How would you prepare 41 from 43?
20.3.1.25 How would you prepare 42 from 43?

20.3.1.26 The odor of honey is caused by 341 (on page 222). Outline a synthesis of this from bromobenzene and ethanol.

20.3.1.27 Suggest a synthesis for 28 (on page 222) starting from cyclohexanone.

20.3.1.28 How about a synthesis for the isomer, 29 (on page 222)?

20.3.1.29 How would you prepare 1-propylamine from propene?

20.3.1.30 Find a synthetic pathway to make 2-methyl-3-pentanone from propene as your only carbon source.

20.3.1.31 Here is a sneaky synthesis problem; one would never do it this way in real life, but it is instructive in terms of learning organic chemistry. How would you synthesize 4-chloroheptane from propene as your only carbon source?

20.3.1.32 How would you make trans-2-methyl-cyclohexanol from cyclohexene?

20.3.1.33 You can’t form 16 from 1-butene and dimethylamine, but you can form 17 from 18 and dimethylamine. Comment.

20.3.1.34 How can you make 16 from 17?
20.3.1.35 How else can you get 17 to 16?

20.3.1.36 From 4-octyne how would you make (E)-4-octene?

20.3.1.37 From 4-octyne how would you make (Z)-4-octene?

20.3.1.38 From 4-octyne how would you make octane?

20.3.1.39 How would you carry out transformation 43 of Figure 20.6? HINT: More than one step is required.

20.3.1.40 How would you convert 19 into 20?

20.3.1.41 How would you prepare 306 (on page 238) from acetylene?

20.3.1.42 How would you prepare 307 (on page 238) from acetylene?

20.3.1.43 Consider all of the products you get from the reactions in exercise 20.3.1.41 and exercise 20.3.1.42. Which are enantiomers and which are diastereomers?
20.3.1.44  How would you prepare 22 (on page 238) from cyclohexanone?

20.3.1.45  How would you prepare 88 from 89 (on page 238)?

20.3.1.46  How would you prepare 90 from 89 (on page 238)?

20.3.1.47  How would you synthesize 24 (on page 238) from an alkene (any alkene, \( \text{C}_n\text{H}_{2n} \)) as your only source of carbon atoms?

20.3.1.48  Outline the steps you would take to synthesize 25 from 26 and 27.

20.3.1.49  How would you prepare 92 from cyclohexanone?

20.3.1.50  How would you prepare 93 from cyclohexanone?

20.3.1.51  How would you synthesize 32 from 4-hydroxypentanal and one mole of methanol.

20.3.1.52  The antiviral drug rimantidine has the structure shown in 30. How would you make it from 31 and ethanol?
20.3.1.53  How would you synthesize 47 (on page 224) from compounds with two carbons or less?

20.3.1.54  How would you make 48 (on page 224) from cyclohexene and compounds with two carbons or less?

20.3.1.55  How would you synthesize 2-octanone from heptanal?

20.3.1.56  How would you prepare 252 from 253?

20.3.1.57  How would you prepare 254 from 255? HINT: We have done NO benzene chemistry this semester.

20.3.1.58  Compound 256 when treated with H⁺ in H₂O produces 257. Use epwa to show how.

20.3.1.59  Phosgene, COCl₂, is a highly poisonous compound that is a very useful synthetic reagent. Show by example what kind of chemistry phosgene is likely to undergo.
20.3.1.60 How would you prepare (Z)-2-butene (with the indicated stereochemistry) from compounds with two carbons or less?

20.3.1.61 How would you synthesize 1,2-dimethyl-cyclopentene starting with cyclopentene? Indicate reagents. HINT: Go backwards, slowly. Have patience.

20.3.1.62 How would you prepare 4-propyl-3-heptene from propene and CO$_2$ as your only carbon containing materials? HINT: Several steps, but not hard.

20.3.1.63 From what alkene and with what reagent would you prepare (3S,4S)-3-methyl-3,4-hexandiol?

20.4 Structure

20.4.0.1 Sketch the stable form of cis-1,3-dimethylcyclohexane.

20.4.0.2 Sketch a chiral molecule of 2,3,4-trichloropentane and indicate the R/S nature of each chiral center.

20.4.0.3 What is the product of treatment of 4-pentenoic acid with Br$_2$? Specify stereochemistry.

20.4.0.4 When 11 (Figure 20.7) is treated with Br$_2$ the product is 12. Account for this product and the stereochemistry.

20.4.0.5 A dilute solution of Cl$_2$ in CH$_3$OH reacts with cis-3-hexene to produce a pair of enantiomers. Make a perspective drawing of one of these enantiomers. (That is, make a drawing that reveals the three dimensional structure of the material.) If this material has a stereogenic center, give the R/S configuration.

20.4.0.6 Make a drawing of (S)-2-(1-fluoromethyl)-pentane.

20.4.0.7 Show the product, with stereochemistry (R,S) indicated, of the reaction of (E)-3-methyl-3-hexene with dilute Br$_2$ in water.

20.4.0.8 Show how the enantiomer of the product of the last exercise is formed.
20.4.0.9 Give the structure of (R)-2-bromobutane.

20.4.0.10 Draw the stable conformer of trans-1-chloro-2-methyl-cyclohexane.

20.4.0.11 Give the structure of (3-Z)-hexene.

20.4.0.12 Give the reaction product and the stereochemistry (R,S?) when 1 reacts with Cl₂.

20.4.0.13 Give the reaction product and the stereochemistry (R, S?) when 2 reacts first with dimethyldioxirane, 3, followed by reaction with Br⁻ in acid solution.
20.4.0.14 Treatment of α-pinene, 15 (on page 233), with BH$_3$ followed by HO$_2^-$, and then H$^+$ yields an alcohol. What is the regiochemistry of this reaction?

20.4.0.15 There are four possible cis/trans isomers of the product of exercise 20.4.0.14. Which do you think is predominant? Why?

20.4.0.16 Boniface Beebe, acclaimed by the Friends of the Natural Museum of Arkansas to be one of the world’s greatest natural philosophers, reacted 21 with HBr. He said, “The monobromo compound I isolate will be an enantiomeric pair so I will have difficulty separating them.” Is he right? Why? HINT: Given the source of the words, the first question is rather silly!

20.4.0.17 Boniface Beebe, perhaps a reasonable natural philosophers, tried again. He reacted 23 with phenyl magnesium bromide, then H$^+$. He said, “The compound I isolate will be an enantiomeric pair so I will have difficulty separating them.” Is he right? Why?

20.4.0.18 Addition of CH$_3$SeCl to cyclohexene produces only the trans product. Explain.
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